S. MAJUMDAR & CO.
PATENT & TRADEMARK ATTORNEYS

Undertakings : Intellectual Property Laws,
Patents, Trademarks, Designs, Copyrights.
Licencing, Investigations, Litigations
DOMESTIC AND INTERNATIONAL

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February 11, 2011

The Controller of Patents
The Patent Office
Mumbai

2996

Dear Sir,

Pre-grant

Re: Opposition under Section 25(1) against
Patent Application No: **IN/PCT/2001/00018/MUM** filed on
January 3rd, 2001
Applicant: **ABBOTT LABORATORIES**
Opponent: **Matrix Laboratories Limited.**
Our Ref: **PII-0423**

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1. Sending herewith a representation under Section 25(1) and Evidence in support of opposition in duplicate. Please take the documents on record and take necessary action.
2. Power of Attorney.
3. Please grant a hearing in due course.

We request you to kindly take the opposition on record under intimation to us.

Yours faithfully,

Mythili

Mythili Venkatesh
Of S. Majumdar & Co.
Opponent's Attorney

Encl: a/a.

Head office. : 5, Harish Mukherjee Road, Kolkata - 700 025, India, Tel. : 91-33-2455 7484/85/86,
Fax : 91-33-2455 7487/88, e-mail : cal@patentindia.com

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The Patents Act, 1970

IN THE MATTER OF:

A representation under section 25(1) of The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005 ("the Act") and Rule 55 of The Patents Rules, 2003 as amended by the Patents Rules, 2006 ("the Rules")

by
M/s Matrix Laboratories Limited
... ("The Opponent")

And

IN THE MATTER OF:

Indian Patent Application IN/PCT/2001/00018/MUM *filed on* 03/Jan/2001by Abbott Laboratories
... ("The Applicant")

STATEMENT OF OPPOSITION

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1. **The Opposition in brief:**

The Opponent hereby files a pre-grant opposition under Section 25(1) of the Patent Act 1970, as amended by the Patents (Amendment) Act, 2005 against the application entitled:

"*Polymorph of a Pharmaceutical*", *filed by Abbott Laboratories, on* 03/Jan/2001, bearing No. IN/PCT/2001/00018/MUM (the "Application").

The bibliographic details of the Application were published in the Official Journal of the Patent Office dated 15/Sep/2001.

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Maintainability of the present Opposition:

2.1 The Act states:

> "25. Opposition to the patent:
> (1) Where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the ground --..."

Thus, the Act clearly allows any person to oppose a published application for patent that has not matured into a patent.

2.2 Matrix Laboratories Limited ("Matrix") is a key player and has significant commercial interests on a global level in the anti-retro viral drugs arena [field to which the Application pertains]. It is a leading supplier of generic anti-retro viral drug compositions in the global market such as the US President's Emergency Plan for AIDS Relief [PEPFAR] as well as other national tenders issued by governments and hence may be directly impacted by the Application.

2.3 The Opponent believes that the Application is still under examination and has not matured into a granted patent. The Opponent further states that in its search of the Patent Office Gazette [for Gazette published through 07/January/2011], no patent was advertised as granted for this Application. Hence the current pre-grant opposition is covered within the framework envisaged in the Act and the Rules made there under.

3. Jurisdiction of the Patent Office:

The Application was filed at the Patent Office in Mumbai. Therefore the Mumbai Patent Office has the jurisdiction to hear and deliberate upon this pre-grant Opposition.

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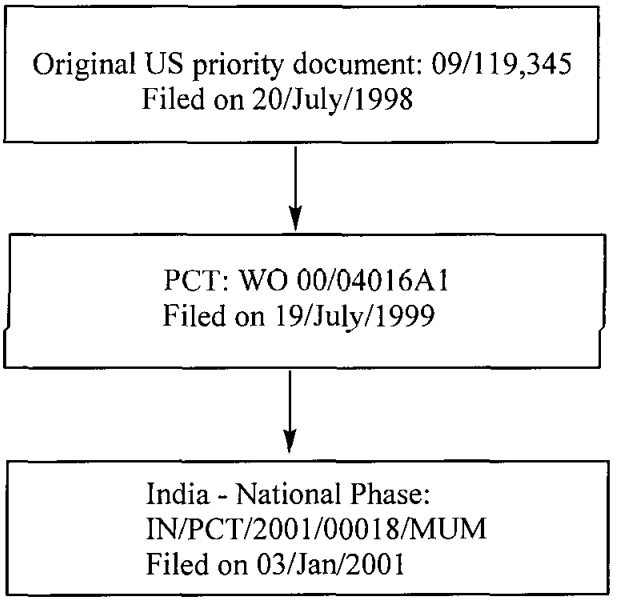
Ritonavir: In Brief

Ritonavir is a chiral molecule having the following chemical name: (2S,3S,5S)-5-(N-(N-4N-methyl-N-((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) -L-valinyl)amino)-2-(N-((5thiazolyl) -methoxycarbonyl)amino)-1, 6-diphenyl-3-hydroxyhexane

One of the early patents disclosing Ritonavir was US 5541206, published on 30/July/1996 **[Exhibit 1].** US patent 5567823, published on 22/Oct/1996 disclosed processes to make Ritonavir **[Exhibit 2].** The United States Food and Drug Administration (US FDA) first approved Ritonavir as an oral solution in March 1996 and later approved a capsule dosage form of Ritonavir in June 1999. The Applicant sells it commercially under the brand name Norvir™.

The Application-Filing details

The Application was filed as a national phase filing from a PCT application. Its genesis is graphically represented below:



In view of the above, publications or public use prior to 20/July/1998 will be considered as prior art against the Application and the invention[s] claimed therein.

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4. **Analysis of the Applicant's specification.**

4.1 The present Application relates to new crystalline polymorphs of ritonavir and the method for the preparation thereof.

4.2 The Applicant has further provided in the background on page 2 that US5541206 and US5567823 provide crystalline Form I of Ritonavir and the PXRD data with regards to the same.

4.3 Page 4 of the present Application specifically mentions the unexpected discovery of crystalline form II of Ritonavir as the subject matter of the present invention. The Opponent states that by the Applicant's own contention, the Applicant has only discovered the Form II of Ritonavir in the process of characterization of earlier available Ritonavir.

4.4 Page 5-8 discuss the various techniques for the preparation of Ritonavir Form II from Amorphous Ritonavir/ Ritonavir Form I as well as the preparation of Ritonavir Form I from Ritonavir Form II and also the preparation of Amorphous Ritonavir from Form I/Form II of Ritonavir.

4.5 Page 9-15 provide examples with regards to the formation of Ritonavir Form II, Amorphous form of Ritonavir and Form I of Ritonavir.

4.6 Page 17 defines the term "substantially pure" in reference to a polymorph of Ritonavir as greater than about 90% pure wherein it is stated that "substantially pure" means that the polymorph of Ritonavir does not contain more than about 10% of any other compound. The Opponent states that though an Applicant can be a lexicographer for his application, he cannot change the meaning of a well defined terminology especially for pharmaceutical substances where the purity of the pharmaceutical substance is of paramount importance, as any compromise on the purity can have adverse effects.

5. **Brief review of Applicant's claims**

5.1 The as filed Application had 30 claims. The Applicant in response to the First Examination Report (FER) issued on October 11, 2006, submitted a response in two parts i.e. October 11, 2007 and October 18, 2007.

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5.2 The Applicant in response to the FER had amended the claims and restricted it to 10 claims specifically pertaining to Form II of Ritonavir thereby deleting other claims relating to Amorphous Ritonavir and Form I Ritonavir. The Opponent would like to point out that the Applicant has acknowledged and voluntarily deleted some of the claims due to lack of novelty and inventive step in view of the objections raised by the examiner. This goes on to show that the Applicant is aware of non-patentability of his claims and has submitted a modified set of claims, restricting to 10 claims.

5.3 The amended claims are annexed hereto as Annexure A. A brief analysis of the finally amended claims as available on the IPAIRS site is given below:

The present Application, with 10 claims, is focused on the following components:

Group	Coverage	Claims
A	Crystalline polymorphic form of Ritonavir Form II / Substantially pure crystalline polymorphic form of Ritonavir Form II. Note: Claim 2 is dependent on claim 1, and Claim 4 is dependent on claim 3.	1 to 4
B	Process for the preparation of substantially pure crystalline polymorph of Ritonavir II by using seed crystals of (2S)-N-((1S)-1-Benzyl-2-(4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-(((2-isopropyl-1,3-thiazol-4-yl)methyl)amino-carbonyl)amino-3-methylbutanamide. Note: Claims 5 and 6 are dependent on claim 3. ➢ Claim 7 is dependent on claim 6.	5,6 and 7
C	Process for the preparation of substantially pure crystalline polymorph of Ritonavir II by using seed crystals of Ritonavir form II, followed by addition of anti-solvent. Note: Claims 8 to 10 are dependent on claim 3.	8 to 10

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5.4 Claim 1 claims the crystalline polymorph Form II of Ritonavir with the characteristic 2 theta values and claim 2 is dependent on claim 1, wherein further characteristic data is provided.

5.5 Claim 3 claims substantially pure crystalline polymorph with characteristic PXRD data. The Opponent states that substance intended to be used as a pharmaceutical substance needs to be very high purity. Hence the Applicants cannot claim a crystalline substance and subsequently pure crystalline form of the same as both are the same substances and the Applicant has not provided any data as to the purity of the material claimed in claim 1 as compared to the substantially pure material of claim 3. Further none of the claims define as to what the term substantial pure refers to. Claim 4 is dependent on claim 3 wherein further characteristic data is provided.

5.6 Claim 5 claims a process for the preparation of substantially pure crystalline polymorph wherein the process involves seeding a saturated solution of Ritonavir with seed crystals. The Opponent states that claim 5 is very broadly claimed as it does not specify the solution in which Ritonavir is dissolved.

5.7 Claim 6 claims a process for the preparation of substantially pure crystalline polymorph wherein the process involves seeding a saturated solution of Ritonavir with seed crystals wherein the solution is C1-C3 alcohol. The Opponent states that does not specify the amount of unseeded crystals to be used. Claim 7 claims the alcohol to be ethanol.

5.8 Claim 8 claims a process for the preparation of substantially pure crystalline polymorph wherein the process involves seeding a solution of Ritonavir with seed crystals followed by addition of an anti-solvent. The Opponent states that claim 8 is very broadly claimed as it does not specify the solution/anti-solvent or the amount of seed crystals to be used.

5.9 Claim 9 claims a process for the preparation of substantially pure crystalline polymorph wherein the process involves seeding a solution (ethyl acetate) of Ritonavir with seed crystals (Ritonavir Form II) followed by addition of an anti-solvent (heptane). Claim 10 further claims the reaction parameters involved in the preparation of substantially pure crystalline polymorph.

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6. **General discussions of the art relating to the invention of the Application under opposition**

Polymorphism is often characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and / or conformations of the molecules in the crystal lattices. The physical and chemical properties of the two solid forms of a drug can sometimes vary dramatically and have great impact on pharmacokinetics, ease of manufacturing and dosage form stability. Properties that can differ among solid forms of a substance include color, solubility, crystal shape, water sorption and desorption properties, particle size, hardness, drying characteristics, flow and filterability, compressibility, and density. Different solid forms can have different melting points, spectral properties, and thermodynamic stability.

Manufacturing processes involve the presence of various solvents such as water and other organic solvents. Furthermore, due to varying climatic conditions drug substances and drug products are subject to different temperatures and relative humidity, giving rise to unexpected hydration or dehydration aging phenomena. Upon dehydration crystal hydrates may retain more or less their original crystal structure, they can lose crystallinity and give an amorphous phase, they can transform to crystalline less hydrated forms or to crystalline anhydrous forms. Therefore the manufacture and the characterization of solvates such as hydrates is almost always a part of the study of the physical properties of drug substances during the pre-formulation studies.

The proper understanding of the complex polyphasic system hydrates–polymorphs–amorphous state is achieved with several analytical methods by the use of techniques such as DSC-TG, TG-MS, sorption-desorption isotherms, sub-ambient experiments, X-ray diffraction combined with temperature or moisture changes as well as crystal structure and crystal modeling in addition to solubility and dissolution experiments. They form the routine experimentation of any active

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pharmaceutical moiety, as the properties of a solid important to its efficacy as a drug or excipient are highly dependent on the form of the solid.

Therefore the selection of the specific form is done using a tried approach to rationally select the optimal physical form of the specific drug. This approach includes salt selection, polymorph and co-crystal screening, and comparative property determinations.

7. **Grounds for Opposition:**

7.1 The Opponent hereby oppose the grant of a patent to the present application on the following grounds as provided under Section 25(1) of the Patents Act, 1970:

> (1) Where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the ground –
>
> (b) that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim –
> ....
> 2) in India or elsewhere, in any other document: provided that the ground specified in sub clause II shall not be available where such publication does not constitute an anticipation of the invention by virtue of sub section (2) or sub section (3) of section 29;
>
> d) that the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of that claim.
>
> (e) that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b);
> or
> having regard to what was; used in India before the priority date of the applicant's claim;
>
> (f) that the subject of any claim of the complete specification is not an invention within the meaning of this act, or is not patentable under this act;
>
> (g) that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;

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(h) that the applicant has failed to disclose to the controller the information required by Section 8 or has furnished the information which in any material particular was false to his knowledge.

7.2 The present Opposition is based on the above (amended) 10 claims as available on the IPAIR web-site. The Opponent opposes present claims 1 through 4 and 8 through 10. Should the Applicant amend his claims from the above version, the Opponent reserves his right to file a fresh pre-grant opposition or amend the present pre-grant opposition. The grounds stated above are distinct and independent of each other. Each ground, individually, provides sufficient reason to bar the issuance of a patent from an Application filed under the Act.

8. The present claims can be divided into following key segments:

- Segment A covering Crystalline polymorphic form of Ritonavir Form II and substantially pure crystalline polymorphic form of Ritonavir Form II (product claims 1 to 4)
- Segment B covering Process for the preparation of substantially pure crystalline polymorph of Ritonavir II by using seed crystals of (2S)-N-((1S)-1-Benzyl-2-(4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-(((2-isopropyl-1,3-thiazol-4-yl)methyl)amino-carbonyl)amino-3-methylbutanamide.(process dependent claims 5 to 7)
- Segment C covering Process for the preparation of substantially pure crystalline polymorph of Ritonavir II by using seed crystals of Ritonavir form II, followed by addition of anti-solvent. .(process dependent claims 8 to 10)

9. The Opponent Opposes claims 1 through 4 and 8 through 10 on following grounds:

9.1 The Opponent respectfully submits that claims 1 to 4 of Segment A and claims 8 to 10 of Segment C are not-patentable under Section 25(1) (b),25(1)(d), 25(1) (e), 25(1) (f), 25(1) (g) and 3(d) of the Patent Act, 1970.

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a) Segment A and Segment C are not patentable under Section 25(1)(b): Prior publication/ {anticipation}:

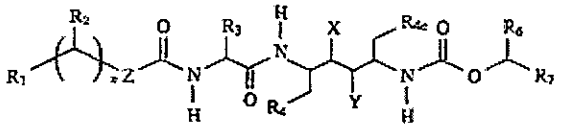
Section 25(1)(b) states:

> that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim –
>
> .....
>
> 2) in India or elsewhere, in any other document: provided that the ground specified in sub clause II shall not be available where such publication does not constitute an anticipation of the invention by virtue of sub section (2) or sub section (3) of section 29;

The following definitions from the Act, are important for the present argument:

> 'Section 2(1)(j) "invention" means a new product or process involving an inventive step and capable of industrial application;
> Section 2(1)(ja) "inventive step" means a feature of an invention that involves technical advance as compared to existing knowledge or having economic significance or both and makes the invention not obvious to a person skilled in the art; '
> Section 2(1)(l) "new invention" means any invention or technology which has not been anticipated by publication in any document or used in the country or elsewhere in the world before the date of filing of patent application with complete specification, i.e. the subject matter has not fallen in public domain or that it does not form part of the state of the art;'

9.2.1 US5541206 entitled "Retroviral Protease Inhibiting Compounds" published on July 30, 1996 annexed hereto as Exhibit 1 discloses compounds of the formula



and column 8 Lines 31-33 specifically discloses the compound *(2S, 3S, 5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane* (Ritonavir).

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Further examples 69 and 71 specifically disclose the preparation of the above compound. Example 69 C also discloses that Ritonavir was crystallized using 42 ml Ethyl acetate and 21 ml Hexane. Example 71 discloses the preparation of Ritonavir which undergoes crystallization twice. The relevant portion with regards to crystallization is reproduced here for ready reference:

The residue was dissolved in a 1:1 ethyl acetate/heptane mixture (200 mL) at 70^{0}C. The solution was allowed to cool slowly and stirred overnight at room temperature to provide a thick slurry. The product was collected by filtration and washed with 1:1 ethyl acetate/heptane (20 mL). The product was dried briefly at 55^{0}C in a vacuum oven to obtain an approximate weight prior to the second crystallization (12.85 g, 83%). A second crystallization from 144 mL of 2:1 ethyl acetate/heptane (dissolved at about 70^{0}C., then stirred at room temperature 12 hours) produced a thick slurry of fine white solid. The product was collected by filtration and washed with 15 mL 2:1 ethyl acetate/heptane, then dried in a vacuum oven at 55^{0}C for 2 days to give the desired product.

The Opponent states that while Exhibit 1 discloses the formation of crystalline Ritonavir, it does not specifically disclose the characteristic PXRD data of the crystal form obtained therein.

9.2.2 The Opponent states that the impugned Application on page 8 states that when a mixture containing Form I and Form II of Ritonavir is crystallized from Ethyl acetate: Heptane (1:1) and stirred for at least 12 hours at about 25°C, than the product obtained is Ritonavir Form II and when it is stirred for at least 3 hours at 20°C, than the product obtained is Ritonavir Form I.

9.2.3 The Opponent therefore states that in view of the similar process parameter as disclosed in Exhibit 1 with regards to crystallization, it is implied that the crystallized product claimed in the impugned application is the same as those obtained in Exhibit 1 and therefore is anticipated by Exhibit 1.

9.3 US5567823 entitled "Process for the preparation of an HIV Protease Inhibiting Compound" published on October 22, 1996 annexed hereto as Exhibit 2 discloses

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process for the preparation of (2S,3S,5S)-5-(N-(N-((N-methyl-N-(2-isopropyl-4-thiazolyl)methyl)amino) carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxy carbonyl) amino)-1,6-diphenyl-3-hydroxy-hexane.

Further example 4 specifically discloses the preparation of the above compounds via crystallization. Example 4 also discloses that Ritonavir was crystallized from 1:1 Heptane: Ethyl acetate. Example 5 discloses the preparation of Ritonavir which undergoes crystallization through seeding. The relevant portion with regards to crystallization is reproduced here for ready reference:

The resulting solid was recrystallized by dissolving in hot ethyl acetate (2 L), diluting with hot hexane (1 L), addition of seed crystals, stirring until cool and letting stand at room temperature overnight to provide the desired product as a white solid. m.p. 122°C.

The Opponent states that though Exhibit 2 discloses the formation of crystalline Ritonavir, it does not specifically disclose the characteristic PXRD data of the crystal form obtained therein.

9.3.3 The Opponent therefore states that in view of the similar process parameter as disclosed in Exhibit 2 with regards to crystallization, it is implied that the crystallized product claimed in the impugned application is the same as those obtained in Exhibit 2 and therefore is anticipated by Exhibit 2.

9.4 The Opponent submits that claims 1 to 4 are anticipated by Exhibit 1 and Exhibit 2.

9.5 The Opponent states that claim 8 to 10 of segment C relating to a process for the preparation of the substantially pure crystalline Ritonavir polymorphic form II involving a solution of Ritonavir, seeding and addition of antisolvent.

9.6 The Opponent states that Example 5 of Exhibit 2 discloses the preparation of Ritonavir which undergoes crystallization through seeding. The relevant portion with regards to crystallization is reproduced here for ready reference:

The resulting solid was recrystallized by dissolving in hot ethyl acetate (2 L), diluting with hot hexane (1 L), addition of seed crystals, stirring until cool and letting stand at room temperature overnight to provide the desired product as a white solid. m.p. 122°C.

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9.7 The Opponent therefore states that the process as claimed in claim 8-10 is anticipated by Exhibit 2.

9.8 The Opponent therefore submits that the crystalline form II of Ritonavir as claimed in claims 1-4 and the processes as claimed in claim 8-10 are anticipated by Exhibit 1 and Exhibit 2.

Segment A and Segment C are not patentable under Section 25(1)(d): {Publicly known}

10.1 The Opponent respectfully submits that claims 1 to 4 of Segment A and claims 8 to 10 of Segment C are not-patentable under Section 25(1)(d) of the Patent Act, 1970.

U/S 25 (1) (d)-that the invention so far as claimed in any claim of the complete specification was publicly known or publicly used in India before the priority date of that claim.

The Opponent strongly states that the Segment A and Segment C set of claims of the impugned application are known from Exhibit 1 and Exhibit 2 as has been discussed in paragraph 9 of the representation. The arguments have not been reproduced here for the sake of repetition. Thus the claimed invention was publicly known in India before priority data of the current application [filing date: July 20, 1998]. Hence the Opponent reaffirms that Segment A and Segment C are not patentable under section 25(1) (d).

11. **Segment A and Segment C are not patentable under Section 25(1)(e);**

11.1 U/S 25(1)(e)states that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b);
or
having regard to what was; used in India before the priority date of the Applicant's claim.

11.2 It is a well established principle of patent law that inventive step is assessed by first establishing the closest state of the art, determining the technical problem to be

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solved and thereafter to assess the claimed solution to the problem in view of the prior art. The Opponent states that the common general knowledge of a person skilled in the art before the priority date of the alleged invention stated that purification process of a pharmaceutically active compound may lead to many polymorphic/ pseudo polymorphic forms which exhibit improved properties in terms of stability and enhanced bioavailability. Hence it is but obvious to a person skilled in the art to purify a pharmaceutically active compound with different techniques such as seeding, addition of solvent/ antisolvent so as to obtain the most stable form of that compound.

11.3 The Opponent states that the impugned Application does not provide any drawbacks associated with the prior art nor has the Applicant provided any improvement in the functioning/ characteristics of Ritonavir due to the preparation of Form II. The Opponent therefore states that in view of the para 9 of the representation, the Form II is clearly anticipated by Exhibit 1 and Exhibit 2. The Opponent states that even if arguably, the Application satisfies the criteria of novelty, the impugned Application would lack inventive merit and be obvious to a person skilled in the art, in view of the absence of any technical advancement over the known form of Ritonavir nor there being any difference in the process employed by the Applicant to arrive at the product claimed in the impugned Application.

11.4 The Applicant has acknowledged that crystalline form of Ritonavir is known from Examples 1, 69 and 71 of US 5541206 **[Exhibit 1]** and Examples 2, 4 and 5 of US 5567823 **[Exhibit 2]**. The Applicant has stated in the impugned Application that Exhibit 1 and Exhibit 2 provide crystalline form I of Ritonavir and has also acknowledged in the background information of the impugned application that it has been unexpectedly discovered that ritonavir can be prepared as a new crystalline polymorph termed as Form II.

11.5 In the present situation, Exhibit 1 uses ethyl acetate/ heptane for crystallization and Exhibit 2 uses ethyl acetate/hexane followed by addition of seed crystals. The relevant paragraphs from Exhibit 1 and Exhibit 2 have been reproduced in para 9 of the representation.

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11.6 The Opponent further states that in view of the similarity in the processes as disclosed in Exhibit 1 and Exhibit 2, the Opponent had carried out the experiments as disclosed in Exhibit 1 and Exhibit 2 with the help of an expert to identify the product formed therein. The Opponent further relies upon the opinion of the expert - Affidavit annexed hereto and referred to hereinafter as Exhibit 3.

11.7 The Opponent states that repetition of process exemplified in example 71 of Exhibit 1 gives the same PXRD as that of the claimed ritonavir form II of the impugned invention without seeding, hence present claims are also obvious over Exhibit 2, example 5 wherein seeding methodology is used for crystallization.

11.8 The Opponent states that the claims while anticipated by prior art are also obvious and lack an inventive step on the face of Exhibit 1 and Exhibit 2, when seen through the eyes of a person skilled in the art. The results obtained by the expert clearly indicate that the product obtained in Exhibit 1 is Form II as may be noted from the PXRD data provided by the expert in Exhibit 3.

11.9 The Opponent therefore states that the product claims (Claim 1-4) of the impugned Application are obvious to a person skilled in the art in view of Exhibit 1 and Exhibit 2.

11.10 The Opponent further brings about the fact that exhibit 1 discloses in Example 71, the crystallization of Ritonavir by dissolving Ritonavir in Ethyl acetate at higher temperature, followed by addition of heptane in 1:1 ratio followed by slow cooling which is then stirred at room temperature for 12 hours to obtain crystalline form of Ritonavir. The Opponent states that in view of the Applicant's statement on page 8 of the impugned Specification, it is implied that when a mixture of Form I and Form II when stirred for not less than 12 hours, then Form II is obtained and if it is stirred for less than 12 hours but more than 3 hours, then Form I is obtained. The Opponent therefore states that Form II as claimed in the impugned application is arrived at by routine trial and error techniques which are obvious to a person skilled in the art in view of Exhibit1 and hence lack inventive merit.

11.11 Further Exhibit 2 also discloses in Example 2, the formation of crystals of Ritonavir by the usage of solvent/ anti-solvent technique. The relevant paras are reproduced for ready reference.

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The residue was dissolved in ethyl acetate (500 kg, 556 L) and warmed to about 60^{0}C until a clear solution was obtained. The solution was filtered into a clean 300 gallon reactor and a rinse of ethyl acetate (77 kg, 86 L) was also filtered into the 300 gallon reactor. Heptane (218 kg, 320 L) was charged to the ethyl acetate solution in the 300 gallon reactor. The mixture was heated to about 80°C until a clear solution was obtained. The solution was cooled at a rate of less than 25°C. per hour to a final temperature of 22°C and was stirred for another 12 hours after the product began to crystallize. The thick slurry was centrifuged in four separate loads to isolate the product. Each isolated load was washed with approximately 45 kg of a 2:1 (v/v) solution of ethyl acetate/heptane. The last wash was used to also rinse the reactor. The product was dried in a blender drier under vacuum at 55°C. for about 24 hours to provide 101.9 kg of the desired product. m.p. 121°-123°C.

11.12 Further, Example 5 discloses the preparation of crystalline form of ritonavir through the addition of seeded crystals, though the anti-solvent used herein is not heptane but another hydrocarbon i.e. Hexane.

11.13 The Opponent hence states that the Exhibit 1 and Exhibit 2 provide the following teachings for the preparation of crystal form of Ritonavir.

- Ritonavir solution is prepared normally in Ethyl acetate by dissolving it at higher temperatures.
- An anti-solvent selected from the group of hydrocarbons such as heptane, hexane is added to the dissolved Ritonavir solution.
- Optionally, seeded crystals are added to the solution.
- Slow cooling to room temperature.
- Stirring for another 12 hours at room temperature after the product starts crystallizing.
- Centrifugation of the thick slurry to isolate the product.

The Opponent states that the Applicant has used a combination of the above teachings in the impugned application.

11.14 The Opponent therefore states that the Applicant has not made any technical advance over the prior art Exhibit 1 and 2 and has merely combined the teachings of Exhibit 1and

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2 individually or in combination with each other so as to arrive at the processes claimed in the impugned application. The Applicant has also not disclosed the inventive merits of the current process versus the process disclosed in these prior documents. This clearly shows the impugned Application lacks inventive step. Hence, the Opponent strongly states that the invention claimed in claims 1 through 4 and 8 through 10 of the impugned application are obvious over the prior art Exhibits 1 and 2, and hence liable for rejection in entirety.

12. **Segment A and Segment C are not patentable under Section 25(1)(f):**

12.1 U/S – **25 (1) (f)** - states that the subject of any claim of the complete specification is not an invention within the meaning of this act, or is not patentable under this act;

12.2 The Opponent reiterates that the impugned applications lacks novelty and does not involve inventive step which are the basic requirements for an invention to be eligible for grant of a patent. The claimed invention of the impugned application does not involve any new solvent or new technology over Exhibit 1 and Exhibit 2. All the parameters of the impugned application are already disclosed in the prior publications. Hence it lacks novelty.

12.3 The Applicant in the impugned application has said that they discovered new and stable polymorphic form II of ritonavir (for which alleged stability, no data has been adduced). But from the examples 71 of Exhibit 1and example 5 of Exhibit 2 is it clearly evident that Applicant has only used the known solvents already used in the prior art patents and thus lack inventive merit.

12.4 **Segment A and Segment C are not patentable under Section 3(d):**

(3d) the mere discovery of a new form of a known substance which does not result in increased efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such process results in a new product or employs at least one new reactant.

Explanation: For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of

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isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy."

12.5 The Opponent respectfully submits that the Applicant himself has acknowledged about the crystalline ritonavir form I in the background part of the impugned application. Now, the impugned Application claims crystalline ritonavir polymorph form II without providing any efficacy or stability data relating to form II (generally) or substantially pure crystalline form II (specifically). Nor does it give any comparative efficacy data showing enhanced efficacy comparing Form II with prior art Form I. As per section 3(d), mere discovery of a new form of a known substance which does not result in an increased efficacy of that substance or the mere discovery of a new property or new use of a known substance is not an invention unless such process results in a new product or employs at least one new reactant. As it is already said above, that the crystalline ritonavir form II is obtained by example 71 of US' 206 [proved by experimentation carried out by the Opponent], it cannot be considered as a new product. Even though the response made to the FER mentions that the claimed ritonavir form II is thermodynamically stable but no absolute or comparative data is provided showing the stability in the impugned invention vis-à-vis the prior art Form I. Moreover, the stability data shows the quality of the product but not the therapeutic efficacy as required under section 3(d). The Opponent further states that any data with regards to the efficacy needs to be provided on the date of filing and not after the date of filing.

12.6 Further, in the response to FER, the Applicant has admitted that "presence of form II has made the production of form I from saturated solutions extremely difficult. This makes impractical the production of form I at a form II exposed facility and therefore the use of form I as a starting material to make Norvir formulations".

12.7 Further in the response to FER, Applicant stated that ritonavir is isolated from a solvent mixture of ethyl acetate/ heptane by centrifugation. This is not enabled by present Specification. Here the Applicant has tried to hoodwink the examiner by showing some 'difficult' production parameter which is not discussed in the

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Specification and may or may not be even true or relevant to the present Specification and process claimed therein. The Applicant states that because of the shape and size of the crystals, the time to complete the centrifugation step for ritonavir form II is reduced by about 35 – 50% when compared to ritonavir form I, this aspect again is not enabled by the Specification. The Applicant also mentioned in the response to FER that the centrifugation step is more complete for ritonavir form II than for ritonavir form I crystals wherein the residual solvent present after the centrifugation of ritonavir form II is unexpectedly reduced to 30-50%. Hence the current impugned invention lacks enablement. This clearly indicates that the Applicant, to overcome the section 3(d) objection raised by the examiner, has tried to convince the examiner by showing the unsubstantiated benefits of ritonavir form II, without the reflection of these benefits in the Specification.

12.8 There is no new reactant involved in the preparation of Ritonavir crystalline form II. All the components of process for the preparation of form II are already disclosed in US' 206 and US' 823. Hence the Opponent states that the claimed invention of the impugned applications is not patentable U/S 3(d).

12.9 Additionally, the Patent Office has consistently held that crystal form of known substances is patentable only when they pass the enhanced efficacy criterion.

> "In the recent Gleevec case, the controller has held that the patent specification does not bring any improvement in the efficacy of any new crystalline form over the known crystalline form....."
>
> Patent Office decision [IN 1602/MAS/1998]

For instance, the Controller has held:

> ".. there has to be an improvement in the therapeutic content or capacity in a same amount of drug compound of the present invention vis-à-vis prior art compound.
> ...
> (the present application) claims only a new form of a already known compound without any significant enhancement in the known

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therapeutic efficacy and therefore the said new form is not patentable under section 3(d) of the Patents (Amendment) Act 2005."

Patent Office decision [1577/DEL/1996]

In another case, the Controller has noted:

"A mere difference in physical property is a well known conventional variation of the same pure substance not showing any unobvious properties. Therefore the change alleged by the applicant is in the physical properties and not in the therapeutic efficacy. I therefore conclude that the instant invention claim 1&2 are not patentable under section 3(d) of the Patent (Amendment) Act."

Patent Office decision [IN/PCT/2002/507/DEL]

12.10 The Opponent states that as has been established by the Patent Office in many decisions, the enhancement of efficacy should be in terms of therapeutic efficacy and should have an improvement in the treatment as compared to the main compound i.e. Ritonavir. The Opponent states that in absence of data regarding enhanced therapeutic efficacy for any of the crystalline forms of Ritonavir, all the claims pertaining to the impugned application are unpatentable and liable to be rejected in their entirety.

13. **Segment A and Segment C are not patentable under Section 25(1) (g)**

(g) that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;

13.1 The examiner in the FER has raised the objection on the term "substantially". The Applicant in his response has mentioned that the term substantially is defined in the specification. Opponent states that the written description of impugned invention has nowhere clearly defined the term "substantially" thus making this term vague and unclear. This shows that the Applicant has not sufficiently and clearly described the invention. The Opponent states that the impugned Application has neither described the invention sufficiently nor provided any preferred embodiments and specific examples to overcome the enablement issue, especially when seen while keeping the response to FER in view. Thus Opponent states that

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the claimed invention of the impugned application is not sufficiently described and hence not patentable under section 25(1) (g).

13.2 Further on the objection raised on the inventive step in the FER, the Applicant has simply mentioned that the polymorphic ritonavir form II is technically advanced as compared to ritonavir form I in terms of stability, processibility and isolation. This is a vague reply which doesn't have a written support in the Specification. None of these parameters were sufficiently disclosed in the Specification, thus making the specification insufficient and unclear In essence, these are after-thoughts.

13.3 Claim 8 claims a process for the preparation of substantially pure crystalline polymorph wherein the process involves seeding a solution of Ritonavir with seed crystals followed by addition of an anti-solvent. The Opponent states that claim 8 is very broadly claimed as it does not specify the technical parameters like solvent/anti-solvent or amount of seed crystals to be used.

13.4 Claim 9 claims a process for the preparation of substantially pure crystalline polymorph wherein the process involves seeding a solution (ethyl acetate) of Ritonavir with seed crystals (Ritonavir Form II) followed by addition of an anti-solvent (heptane). The Opponent states that specific ratio with regards to the usage of solvent: antisolvent, the reaction parameters such as temperature and the addition of amount of seeded crystals is not specifically claimed in the process claims thereby broadening the scope of the process claims.

14. Segment A and Segment C are not patentable under Section 25 (1) (h)

25(1) (h) Non-intimation of information under Section 8 to the Controller:

The Opponent also opposes the present impugned Application, in its entirety, under Section 25(1) (h) pertaining to non-disclosure of information required under Section 8 of the Act. The section states:

> (h) that the Applicant has failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge;

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Section 8(1)(a) and (b) makes it an obligation on the Applicant to keep the Controller informed of an application which is being prosecuted in another country and which is considered to be the same invention, or substantially the same invention, as the patent applied for in India. The Applicants in their response to FER has acknowledged in para 9 that they failed to submit the required information to the IPO within the stipulated timelines, hence filed a petition under rules 137 and 138. The Opponent reiterates that Applicant's failure to inform Indian Patent Office on the foreign filings of the same or substantially same invention with in the given time lines itself is a ground for opposing the impugned application hence pray that the impugned application is not eligible for grant of a patent. The Opponent in his search has found that the Applicant has filed the same or substantially same application in the following jurisdiction(s).

S.NO	Publication number	Country name
1.	AR0059764	Argentina
2.	AT0261947	Austria
3.	BR9912010	Brazil
4.	CO5090830	Colombia
5.	HU0103823	Hungary
6.	ID0027996	Indonesia
7.	IL0187181	Israel
8.	JP2002520410	Japan
9.	PT1097148	Portugal
10.	SI1097148	Slovenia
11.	TR0100171	Turkey

15. PRAYERS:

The Opponents' arguments are based on the revised set of claims on record filed on 3rd Jan 2001. The Opponent now prays for the following:

- That the Controller take the present Opposition on record;
- Reject the claims 1-4 and 8-10 of the Application, *in toto*;

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- Revert with arguments, additional evidence and additional grounds, should the Applicant choose to amend / add to the present claims;
- Grant of hearing to the Opponent, should the Controller deem that the present Opposition lacks merit or decides in favour of proceeding with grant of patent on the Application;
- Leave to file further evidence and additional grounds, if necessary; and
- Grant such additional relief as the Controller may deem fit.

Dated this the 11th day of February 2011

Mythili Venkatesh
Of S. MAJUMDAR & CO.
Opponent's Agent

The Controller of Patents
The Patent Office Branch
Mumbai.

Enclosures:

Annexure A

Exhibit 1: US 5541206

Exhibit 2: US 5567823

Exhibit 3: PXRD pattern corroborating the experimental verification conducted by the Opponent in the form of an Expert Affidavit.

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Annexure - A

24 Amended page

We claim:

1. The crystalline polymorph of (2S, 3S, 5S) -5- (N- (N- ((N-methyl-N- ((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) -L-valinyl) amino) -2- (N- ((5-thiazolyl) methoxycarbonyl) amino) -1,6-diphenyl-3-hydroxyhexane with characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.88° ± 0.1°, 16.11 ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0. 1°. 18.93° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.71° ± 0.1° and 25.38° ± 0.1°.

2. The crystalline polymorph as claimed in Claim 1 with characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.51° ± 0.1°, 9.88° ± 0.1°, 10.97° ± 0.1°, 13.74° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18. 40° ± 0.1°, 18. 93° ± 0.1°, 19.52° ± 0.1°, 19.80° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.49° ± 0.1°, 21.71° ± 0.1°, 22.23° ± 0.1°, 25.38° ± 0.1°, 26.15° ± 0.1° and 28.62° ± 0.1°.

3. The substantially pure crystalline polymorph of (2S, 3S, 5S) -5- (N- (N- ((N-methyl-N- ((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) -L-valinyl) amino) -2- (N- ((5-thiazolyl) methoxycarbonyl) amino) -1,6-diphenyl-3-hydroxyhexane with characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.88° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.71° ± 0.1°and 25.38° ± 0.1°.

4. The substantially pure crystalline polymorph as claimed in Claim 3 with characteristic peaks in the powder X-ray diffraction pattern at values of two theta of 8.67° ± 0.1°, 9.51° ± 0.1°, 9.88° ± 0.1°, 10.97° ± 0.1°, 13.74° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1 °, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°.

3)1|01

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19.52° ± 0.1°, 19.80° ± 0. 1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.49° ± 0.1°, 21.71 ° ± 0.1°, 22.23° ± 0.1°, 25.38° ± 0.1°, 26.15° ± 0.1° and 28.62° ± 0. 1°

5. A process for the preparation of the substantially pure crystalline polymorph as claimed in Claim 3, wherein a solution of ritonavir is seeded with seed crystals of (2S) -N- ((1 S) -1 -Benzyl-2- ((4S, 5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl) -2- ((((2-isopropyl-1,3-thiazol-4-yl) methyl) amino) -carbonyl) amino) -3- methylbutanamide in an amount such that there are undissolved seed crystals in the solution of ritonavir.

6. A process for the preparation of the substantially pure crystalline polymorph as claimed in Claim 3, wherein a solution of ritonavir in a C1-C3 alcohol is seeded with seed crystals of (2S) -N- ((1 S) -1-Benzyl-2- ((4S, 5S) -4-benzyl-2-oxo-1, 3-oxazolidin-5-yl) ethyl) -2- ((((2-isopropyl-1, 3-thiazol-4-yl) methyl) amino) -carbonyl) amino) -3-methylbutanamide in an amount such that there are undissolved seed crystals in the solution of ritonavir.

7. The process as claimed in Claim 6, wherein the C1-C3 alcohol is ethanol.

8. A process for the preparation of the substantially pure crystalline polymorph as claimed in Claim 3, wherein a solution of ritonavir is seeded with seed crystals of ritonavir Form II, followed by addition of an anti-solvent.

9. A process for the preparation of the substantially pure crystalline polymorph as claimed in Claim 3, wherein a solution of ritonavir in ethyl acetate is seeded with seed crystals of ritonavir Form II, followed by addition of heptane.

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10. A process for the preparation of the substantially pure crystalline polymorph as claimed in Claim 3, wherein a solution of ritonavir in ethyl acetate at from about 50°C to about 55°C is seeded with seed crystals of ritonavir Form II, followed by addition of heptane and cooling to about 25°C.

Dated 3rd day of January 2001

Archana Shanker
Anand and Anand, Advocates
Attorneys for the applicants

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Exhibit-1

US005541206A

United States Patent [19]

Kempf et al.

[11] **Patent Number: 5,541,206**

[45] **Date of Patent: Jul. 30, 1996**

[54] **RETROVIRAL PROTEASE INHIBITING COMPOUNDS**

[75] Inventors: **Dale J. Kempf**, Libertyville; **Daniel W. Norbeck**, Crystal Lake; **Hing Leung Sham**; **Chen Zhao**, both of Gurnee, all of Ill.

[73] Assignee: **Abbott Laboratories**, Abbott Park, Ill.

[21] Appl. No.: **423,387**

[22] Filed: **Apr. 25, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 158,587, Dec. 2, 1993, abandoned, which is a continuation-in-part of Ser. No. 998,114, Dec. 29, 1992, abandoned, which is a continuation-in-part of Ser. No. 777,626, Oct. 23, 1991, abandoned, which is a continuation-in-part of Ser. No. 746,020, Aug. 15, 1991, abandoned, which is a continuation-in-part of Ser. No. 616,170, Nov. 20, 1990, abandoned, which is a continuation-in-part of Ser. No. 518,730, May 9, 1990, Pat. No. 5,142,056, which is a continuation-in-part of Ser. No. 456,124, Dec. 22, 1989, abandoned, which is a continuation-in-part of Ser. No. 405,604, Sep. 8, 1989, abandoned, which is a continuation-in-part of Ser. No. 355,945, May 23, 1989, abandoned.

[51] **Int. Cl.**[6] **A61K 31/425**; C07D 413/12; C07D 417/12

[52] **U.S. Cl.** **514/365**; 548/204; 548/194; 548/187; 548/235; 548/227; 548/228; 548/229; 514/374; 514/369; 514/370; 514/376; 514/377

[58] **Field of Search** 514/365, 374, 514/369, 370, 376, 377; 548/204, 194, 187, 235, 227, 228, 229

[56] **References Cited**

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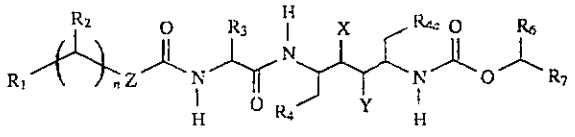
Primary Examiner—Jane Fan

Attorney, Agent, or Firm—Steven R. Crowley

[57] **ABSTRACT**

A retroviral protease inhibiting compound of the formula:



is disclosed.

19 Claims, No Drawings

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RETROVIRAL PROTEASE INHIBITING COMPOUNDS

This invention was made with Government support under contract number AI27220 awarded by the National Institute of Allergy and Infectious Diseases. The Government has certain rights in this invention.

This is a continuation of U.S. patent application Ser. No. 08/158,587, filed Dec. 2, 1993 now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 998,114, filed Dec. 29, 1992, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 777,626, filed Oct. 23, 1991, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 746,020, filed Aug. 15, 1991, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 616,170, now abandoned filed Nov. 20, 1990, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 518,730, filed May 9, 1990, now U.S. Pat. No. 5,142,056 which is a continuation-in-part of U.S. patent application Ser. No. 456,124, filed Dec. 22, 1989, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 405,604, filed Sep. 8, 1989, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 355,945, filed May 23, 1989 now abandoned.

TECHNICAL FIELD

The present invention relates to novel compounds and a composition and method for inhibiting retroviral proteases and in particular for inhibiting human immunodeficiency virus (HIV) protease, a composition and method for treating a retroviral infection and in particular an HIV infection, processes for making such compounds and synthetic intermediates employed in these processes.

BACKGROUND OF THE INVENTION

Retroviruses are those viruses which utilize a ribonucleic acid (RNA) intermediate and a RNA-dependent deoxyribonucleic acid (DNA) polymerase, reverse transcriptase, during their life cycle. Retroviruses include, but are not limited to, the RNA viruses of the Retroviridae family, and also the DNA viruses of the Hepadnavirus and Caulimovirus families. Retroviruses cause a variety of disease states in man, animals and plants. Some of the more important retroviruses from a pathological standpoint include human immunodeficiency viruses (HIV-1 and HIV-2), which cause acquired immune deficiency syndrome (AIDS) in man, hepatitis B virus, which causes hepatitis and hepatic carcinomas in man, human T-cell lymphotrophic viruses I, II, IV and V, which cause human acute cell leukemia, and bovine and feline leukemia viruses which cause leukemia in domestic animals.

Proteases are enzymes which cleave proteins at specific peptide bonds. Many biological functions are controlled or mediated by proteases and their complementary protease inhibitors. For example, the protease renin cleaves the peptide angiotensinogen to produce the peptide angiotensin I. Angiotensin I is further cleaved by the protease angiotensin converting enzyme (ACE) to form the hypotensive peptide angiotensin II. Inhibitors of renin and ACE are known to reduce high blood pressure in vivo. An inhibitor of a retroviral protease will provide a therapeutic agent for diseases caused by the retrovirus.

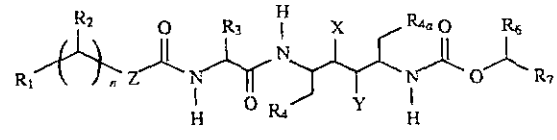
The genomes of retroviruses encode a protease that is responsible for the proteolytic processing of one or more polyprotein precursors such as the pol and gag gene products. See Wellink, Arch. Virol. 98 1 (1988). Retroviral proteases most commonly process the gag precursor into core proteins, and also process the pol precursor into reverse transcriptase and retroviral protease. In addition, retroviral proteases are sequence specific. See Pearl, Nature 328 482 (1987).

The correct processing of the precursor polyproteins by the retroviral protease is necessary for the assembly of infectious virions. It has been shown that in vitro mutagenesis that produces protease-defective virus leads to the production of immature core forms which lack infectivity. See Crawford, J. Virol. 53 899 (1985); Katoh, et al., Virology 145 280 (1985). Therefore, retroviral protease inhibition provides an attractive target for antiviral therapy. See Mitsuya, Nature 325 775 (1987).

Current treatments for viral diseases usually involve administration of compounds that inhibit viral DNA synthesis. Current treatments for AIDS involve administration of compounds such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxycytidine (DDC) and 2',3'-dideoxyinosine (DDI) and compounds which treat the opportunistic infections caused by the immunosuppression resulting from HIV infection. None of the current AIDS treatments have proven to be totally effective in treating and/or reversing the disease. In addition, many of the compounds currently used to treat AIDS cause adverse side effects including low platelet count, renal toxicity and bone marrow cytopenia.

DISCLOSURE OF THE INVENTION

In accordance with the present invention, there are retroviral protease inhibiting compounds of the formula A:



A

wherein

R_1 is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi) cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy;

n is 1,2 or 3;

R_2 is hydrogen or loweralkyl;

R_3 is loweralkyl;

R_4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a

substituent selected from (i) halo, (ii)loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy;

R_6 is hydrogen or loweralkyl;

R_7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl;

X is hydrogen and Y is —OH or X is —OH and Y is hydrogen, *with the proviso that X is hydrogen and Y is* —OH when Z is —N(R_8)— and R_7 is unsubstituted and with the proviso that X is hydrogen and Y is —OH when R_3 is methyl and R_7 is unsubstituted; and

Z is absent, —O—, —S—, —CH_2— or —N(R_8)— wherein R_8 is loweralkyl, cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen, loweralkyl or an N-protecting group; or a pharmaceutically acceptable salt, ester or prodrug thereof.

Preferred compounds of the formula A are those wherein R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl or thiazolyl; R_{4a} is phenyl; R_6 is hydrogen and R_7 is thiazolyl, oxazolyl, isothiazolyl or isoxazolyl.

More preferred compounds of the formula A are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen and R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl.

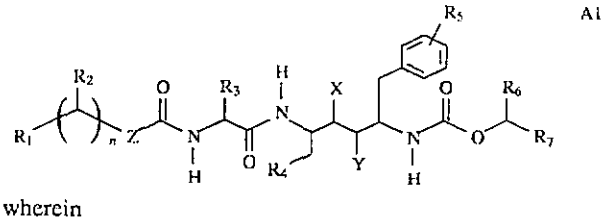
Even more preferred compounds of the formula A are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is loweralkyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O— or —N(R_8)— wherein R_8 is loweralkyl.

Most preferred compounds of the formula A are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1; R_2 is hydrogen; R_3 is methyl or isopropyl; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O—.

Most preferred compounds of the formula A are also those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1; R_2 is hydrogen; R_3 is isopropyl; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —N(R_8)— wherein R_8 is methyl.

Most preferred compounds of the formula A are also those wherein the configuration of the carbon atom bearing —CH_2R_4 is "S" and the configuration of the carbon bearing X is "S" when X is —OH and the configuration of the carbon atom bearing Y is "S" when Y is —OH and the configuration of the carbon atom bearing —CH_2(R_5-substituted phenyl)is "S".

Preferred compounds of the invention are compounds of the formula A1:



A1

wherein

R_1 is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi)cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, pipcridinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy;

n is 1,2 or 3;

R_2 is hydrogen or loweralkyl;

R_3 is loweralkyl;

R_4 is phenyl, thiazolyl or oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii)loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy;

R_5 is hydrogen, halo, loweralkyl, hydroxy, alkoxy or thioalkoxy;

R_6 is hydrogen or loweralkyl;

R_7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl;

X is hydrogen and Y is—OH or X is —OH and Y is hydrogen, with the proviso that X is hydrogen and Y is —OH when Z is —N(R_8)— and R_7 is unsubstituted and with the proviso that X is hydrogen and Y is —OH when R_3 is methyl and R_7 is unsubstituted;

Z is absent, —O—, —S—, —CH_2— or —N(R_8)— wherein R_8 is loweralkyl, cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen, loweralkyl or an N-protecting group; or a pharmaceutically acceptable salt, ester or prodrug thereof.

Preferred compounds of the formula A1 are those wherein R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl or thiazolyl; R_5 is hydrogen; R_6 is hydrogen and R_7 is thiazolyl, oxazolyl, isothiazolyl or isoxazolyl.

More preferred compounds of the formula A1 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen and R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl.

Even more preferred compounds of the formula A1 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is loweralkyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O— or —N(R_8)— wherein R_8 is loweralkyl.

Most preferred compounds of the formula A1 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1; R_2 is hydrogen; R_3 is methyl or isopropyl; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O—.

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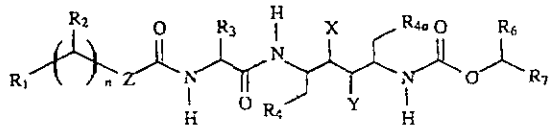
Most preferred compounds of the formula A1 are also those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1; R_2 is hydrogen; R_3 is isopropyl; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —N(R_8)— wherein R_8 is methyl.

Most preferred compounds of the formula A1 are also those wherein X is hydrogen and Y is —OH.

Most preferred compounds of the formula A1 are also those wherein the configuration of the carbon atom bearing —CH_2R_4 is "S" and the configuration of the carbon bearing X is "S" when X is —OH and the configuration of the carbon atom bearing Y is "S" when Y is —OH and the configuration of the carbon atom bearing —CH_2(R_5-substituted phenyl)is "S".

In accordance with the present invention, there are also retroviral protease inhibiting compounds of the formula A2:



A2

wherein

R_1 is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi)cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy;

n is 1,2 or 3;

R_2 is hydrogen or loweralkyl;

R_3 is loweralkyl;

R_4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii)loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy;

R_6 is hydrogen or loweralkyl;

R_7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl;

X is —OH and Y is —OH; and

Z is absent, —O—, —S—, —CH_2— or —N(R_8)— wherein R_8 is loweralkyl, cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen, loweralkyl or an N-protecting group; or a pharmaceutically acceptable salt, ester or prodrug thereof.

Preferred compounds of the formula A2 are those wherein R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl or thiazolyl; R_{4a} is phenyl; R_6 is hydrogen and R_7 is thiazolyl, oxazolyl, isothiazolyl or isoxazolyl.

More preferred compounds of the formula A2 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen and R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl.

Even more preferred compounds of the formula A2 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is loweralkyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O— or —N(R_8)— wherein R_8 is loweralkyl.

Preferred compounds of the formula A2 are also those wherein the configuration of the carbon atom bearing —CH_2R_4 is "S" and the configuration of the carbon atom bearing —CH_2(R_5-substituted phenyl) is "S".

The compounds of the invention comprise asymmetrically substituted centers (i.e., asymmetrically substituted carbon atoms). The present invention is intended to include all stereoisomeric forms of the compounds, including racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention. The terms "S" and "R" configuration are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13–30.

The terms "Val" and "Ala" as used herein refer to valine and alanine, respectively. Unless otherwise noted, when "Val" and "Ala" are used herein they refer to the L-isomer. In general, the amino acid abbreviations used herein follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature for amino acids and peptides (Eur. J. Biochem. 1984, 158, 9–31).

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis,"(John Wiley & Sons, New York (1981)), which is hereby incorporated by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, ben-

zoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "O-protecting group" as used herein refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures such as those O-protecting groups disclosed in Greene, "Protective Groups In Organic Synthesis,"(John Wiley & Sons, New York (1981)). O-protecting groups comprise substituted methyl ethers, for example, methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, t-butyl, benzyl and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl; silyl ethers, for example, trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl; and esters prepared by reacting the hydroxyl group with a carboxylic acid, for example, acetate, propionate, benzoate and the like.

The term "loweralkyl" as used herein refers to straight or branched chain alkyl radicals containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "loweralkenyl" as used herein refers to a straight or branched chain alkyl radical containing from 2 to 6 carbon atoms and also having one carbon-carbon double bond including, but not limited to, vinyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl and the like.

The term "phenyl" as used herein refers to a phenyl group which is unsubstituted or substituted with a substituent selected from loweralkyl, alkoxy, thioalkoxy, hydroxy and halo.

The term "phenylalkyl" as used herein refers to an phenyl group appended to a loweralkyl radical including, but not limited to, benzyl, 4-hydroxybenzyl, 4-chlorobenzyl, 1-naphthylmethyl and the like.

The term "alkylamino" as used herein refers to a loweralkyl radical appended to an —NH radical.

The term "cycloalkyl" as used herein refers to an aliphatic ring having 3 to 7 carbon atoms including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl and the like. A preferred cycloalkyl group is cyclopropyl

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical, including but not limited to cyclohexylmethyl.

The term "cycloalkenyl" as used herein refers to an aliphatic ring having 5 to 7 carbon atoms and also having one carbon-carbon double bond including, but not limited to, cyclopentenyl, cyclohexenyl and the like.

The term "cycloalkenyalkyl" as used herein refers to a cycloalkenyl group appended to a loweralkyl radical including, but not limited to, cyclopentenylmethyl, cyclohexenylmethyl and the like.

The terms "alkoxy" and "thioalkoxy" as used herein refer to $R_{15}O$— and $R_{15}S$—, respectively, wherein R_{15} is a loweralkyl group or benzyl.

The term "alkoxyalkyl" as used herein refers to an alkoxy group appended to a loweralkyl radical.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group appended to a loweralkyl radical.

The term "dialkylamino" as used herein refers to $—NR_{16}R_{17}$ wherein R_{16} and R_{17} are independently selected from loweralkyl groups.

The term "dialkylaminoalkyl" as used herein refers to $—NR_{18}R_{19}$ which is appended to a loweralkyl radical wherein R_{18} and R_{19} are independently selected from loweralkyl.

The term "halo" or "halogen" as used herein refers to —Cl,—Br,—I or —F.

The term "heterocyclic" as used herein refers to a heterocyclic group selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group appended to a loweralkyl radical including, but not limited to, pyrrolidinylmethyl and morpholinylmethyl.

The term "activated ester derivative" as used herein refer to acid halides such as acid chlorides, and activated esters including, but not limited to, formic and acetic acid derived anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinimide derived esters, N-hydroxyphthalimide derived esters, N-hydroxybenzotriazole derived esters, N-hydroxy-5-norbornene-2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters and the like.

In the compounds of the invention, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. As used herein, the term "stable compound" refers to a compound that is sufficiently stable to survive isolation to a useful degree of purity from a reaction mixture and formulation into a therapeutic dosage form suitable for administration.

Preferred compounds of the invention are selected from the group consisting of:

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)-amino)-5-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-2-(N-((5-methoxycarbonyl)amino-1,6-diphenyl-3-hydroxyhexane;

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(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino-1,6-diphenyl-3-hydroxyhexane;

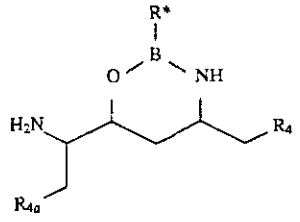
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; and

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; or a pharmaceutically acceptable salt, ester or prodrug thereof.

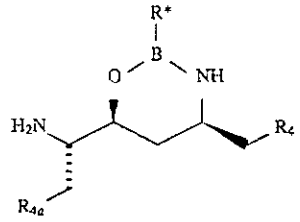
Compounds useful as intermediates for the preparation of the compound of formula A and A1 include the compound of the formula A3:



A3

wherein R_4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy; and R* is phenyl, halo-substituted phenyl, dihalo-substituted phenyl, alkoxy-substituted phenyl, loweralkyl-substituted phenyl, bis-trifluormethyl-substituted phenyl or naphthyl or loweralkyl; or an acid addition salt thereof.

Preferred intermediates are compounds of the formula A4:



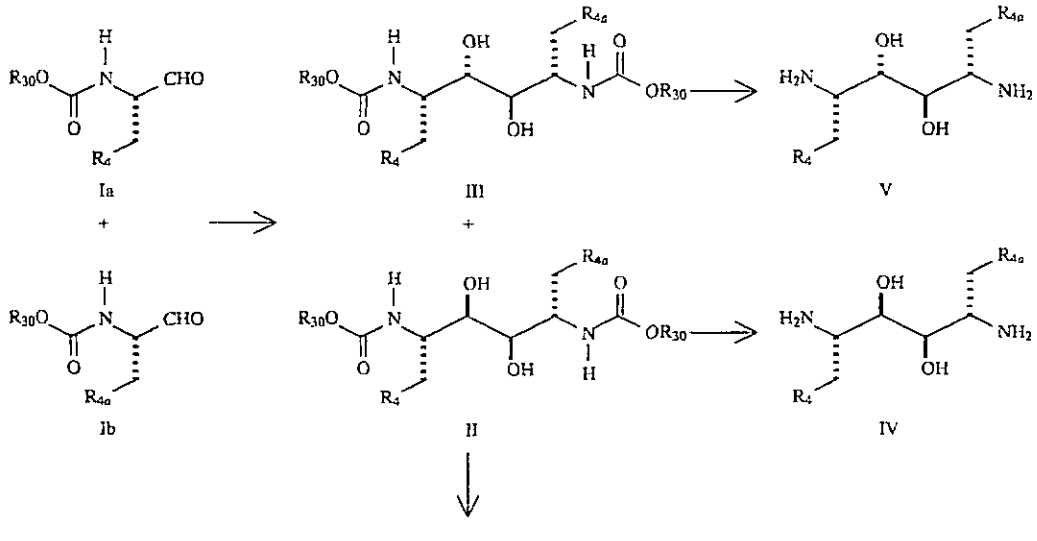
A4

wherein R_4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii)loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy; and R* is phenyl, halo-substituted phenyl, dihalo-substituted phenyl, alkoxy-substituted phenyl, loweralkyl-substituted phenyl, bis-trifluormethyl-substituted phenyl or naphthyl or loweralkyl; or an acid addition salt thereof.

Preferred compounds of the formula A4 are those wherein R_{4a} is phenyl and R* is phenyl. Most preferred compounds of the formula A4 are those wherein R_4 and R_{4a} are phenyl and R* is phenyl.

The compounds of the invention can be prepared as shown in Schemes 1–9. As outlined in Scheme 1, coupling of protected α-aminoaldehyde Ia and Ib (R_{30} is loweralkyl or benzyl) with VCl_3(tetrahydrofuran)$_3$ and Zn produces a mixture of diols, out of which compounds II and III can be isolated. Hydrolysis of II and III with barium hydroxide leads, respectively, to diaminodiols IV and V. Alternately, treatment of II with α-acetoxyisobutyryl bromide in acetonitrile leads to compound VI, which upon hydrolysis with barium hydroxide, produces diaminodiol VII. In a preferred embodiment, R_4 and R_{4a} are each phenyl and the first reaction in Scheme 1 is a dimerization.

Scheme 1



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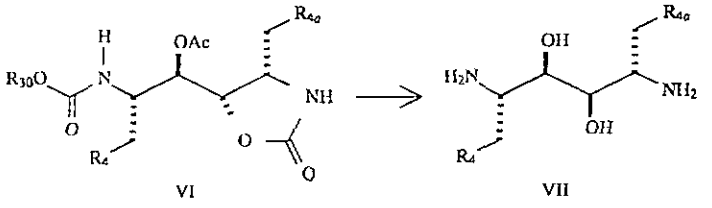
Scheme 1

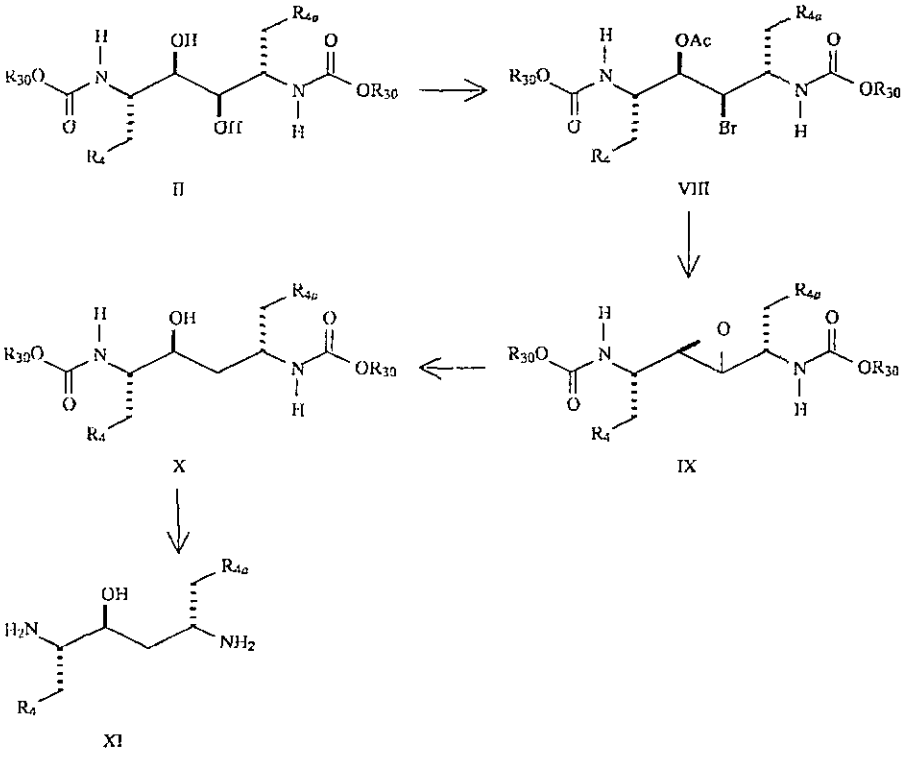


VI VII

As outlined in Scheme 2, treatment of compound II with *α-acetoxy-isobutyryl bromide in hexane/dichloromethane* produces bromoacetate VIII. Hydrolysis of VIII with concommitant cyclization produces epoxide IX, which is reduced with sodium borohydride and trifluoroacetic acid to produce compound X. Barium hydroxide hydrolysis of X leads to diamine XI.

is hydrolyzed and decarboxylated to lactone XV. Hydrolysis of XV and protection of the hydroxyl group leads to compound XVI, which, upon treatment with diphenylphosphoryl azide undergoes a Curtius rearrangement. The intermediate isocyanate is trapped with benzyl alcohol to produce compound XVII. Desilylation of XVII with tetrabutylammonium

Scheme 2



II VIII IX X XI

As outlined in Scheme 3, acylation of the enolate derived from compound XII with ethyl chloroformate gives compound XIII. Subsequent alkylation of the enolate prepared from XIII provides compound XIV (R_{4a} is thiazolyl), which *fluoride provides compound XVIII, which is deprotected* with HBr to give diamine XIX.

In a preferred embodiment of the process shown in Scheme 3, R_4 is phenyl.

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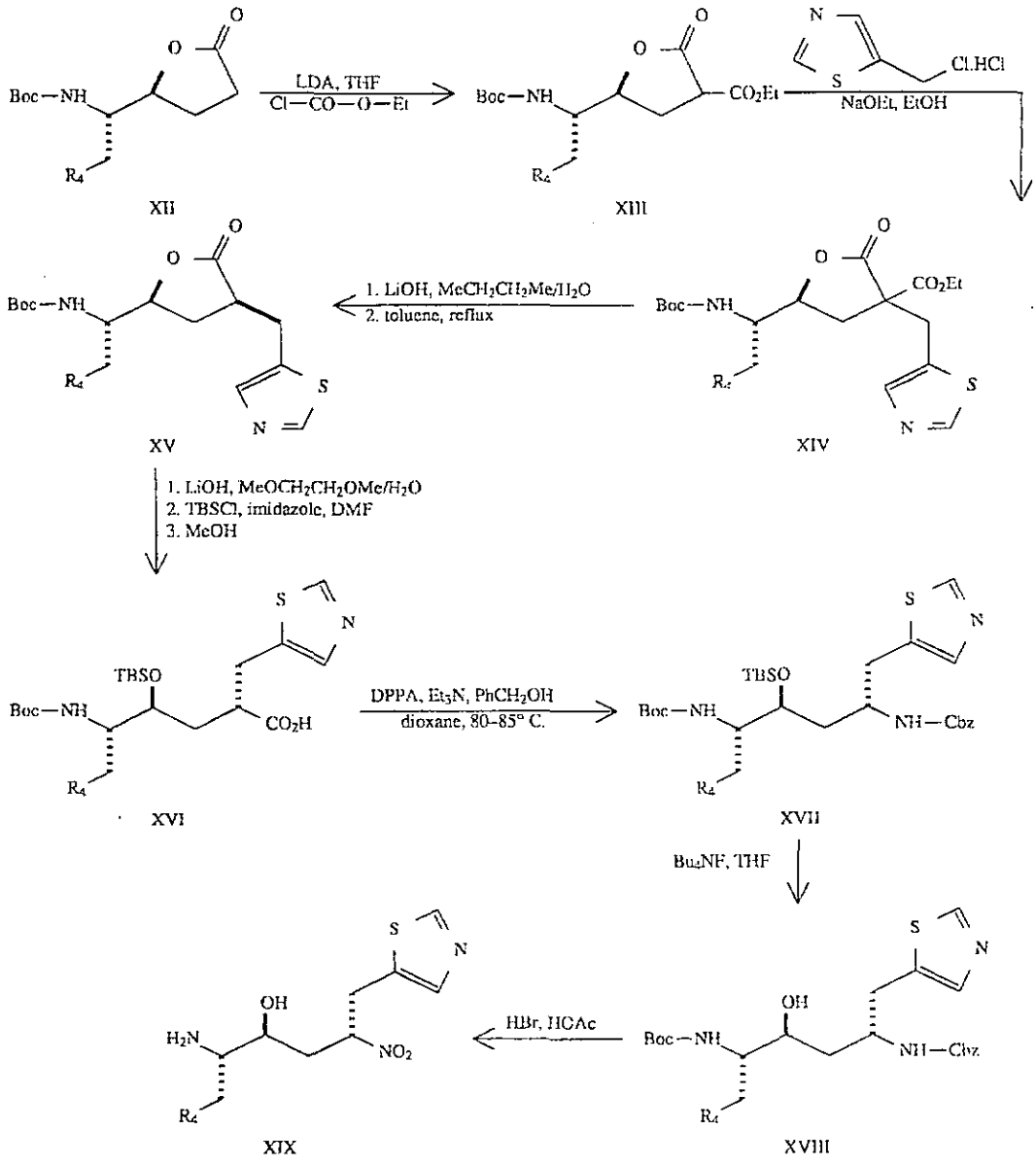
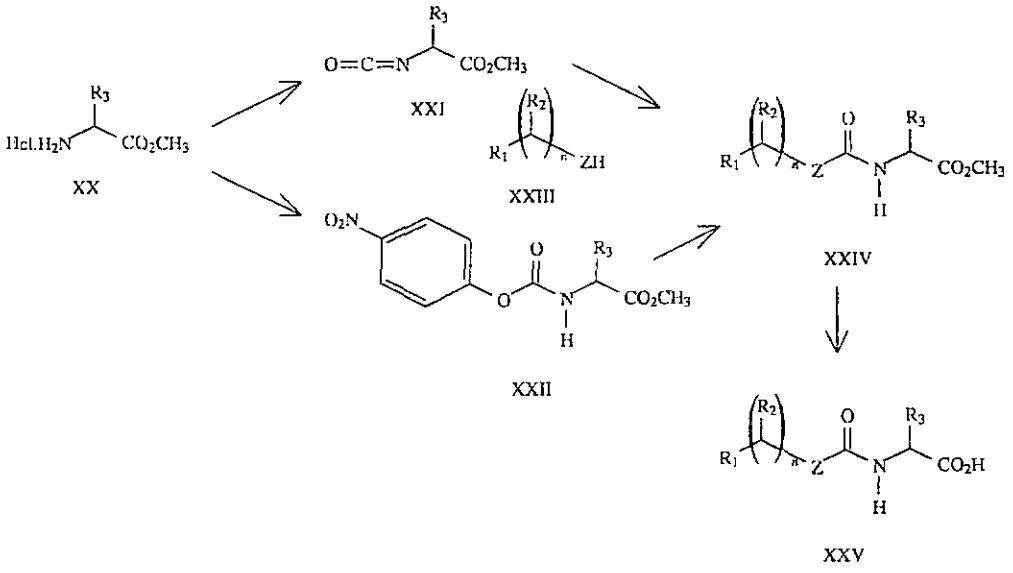
Scheme 3



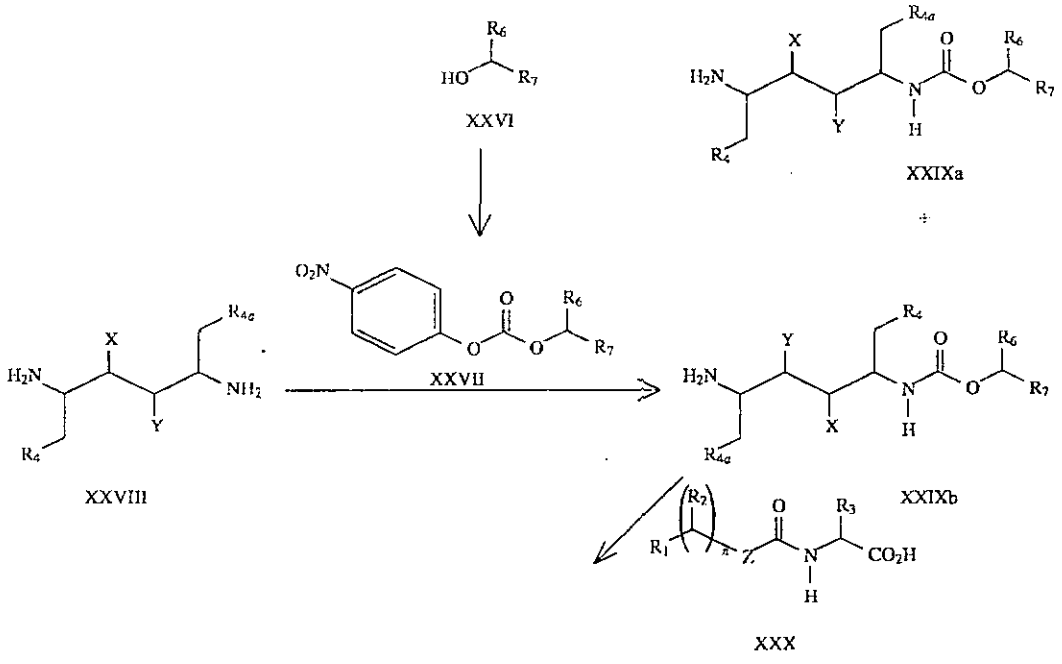
As outlined in Scheme 4, compound XX (R_3 is lower-alkyl) is converted to isocyanate XXI by treatment with phosgene. Alternatively, treatment of XX with 4-nitrophenyl chloroformate produces carbamate XXII. Condensation of either XXI or XXII with compound XXIII wherein Z is O, S or N(R_8), with catalytic 4-dimethylaminopyridine as needed, provides compound XXIV. Lithium hydroxide hydrolysis of XXIV produces compound XXV. In a preferred embodiment of the process shown in Scheme 4, n is 1.

Scheme 4



As outlined in Scheme 5, compound XXVIII, which represents diamines IV, V, VII, XI and XIX, is acylated with an activated derivative of XXVI having the formula $(R_6)(R_7)CHOC(O)OL$ wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII, which is prepared by reacting XXVI with 4-nitrophenyl chloroformate) to provide a mixture of compounds XXIXa and XXIXb or an acid addition salt thereof. Coupling of XXIXa or XXIXb to compound XXX by treatment with a carbodiimide (or by reaction with an activated ester of XXX) produces compound XXXIa or XXXIb, respectively. In a preferred embodiment of the process shown in Scheme 5, n is 1, R_4 and R_{4a} are each phenyl, X is H and Y is OH.

Scheme 5



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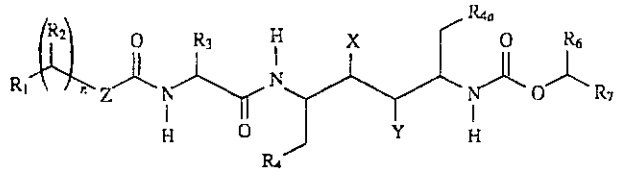
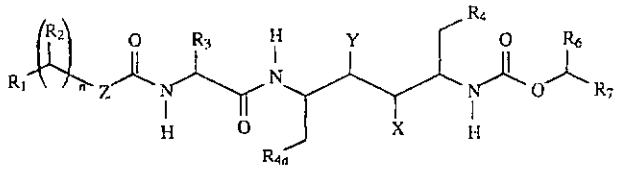
-continued

Scheme 5



XXXIa

+

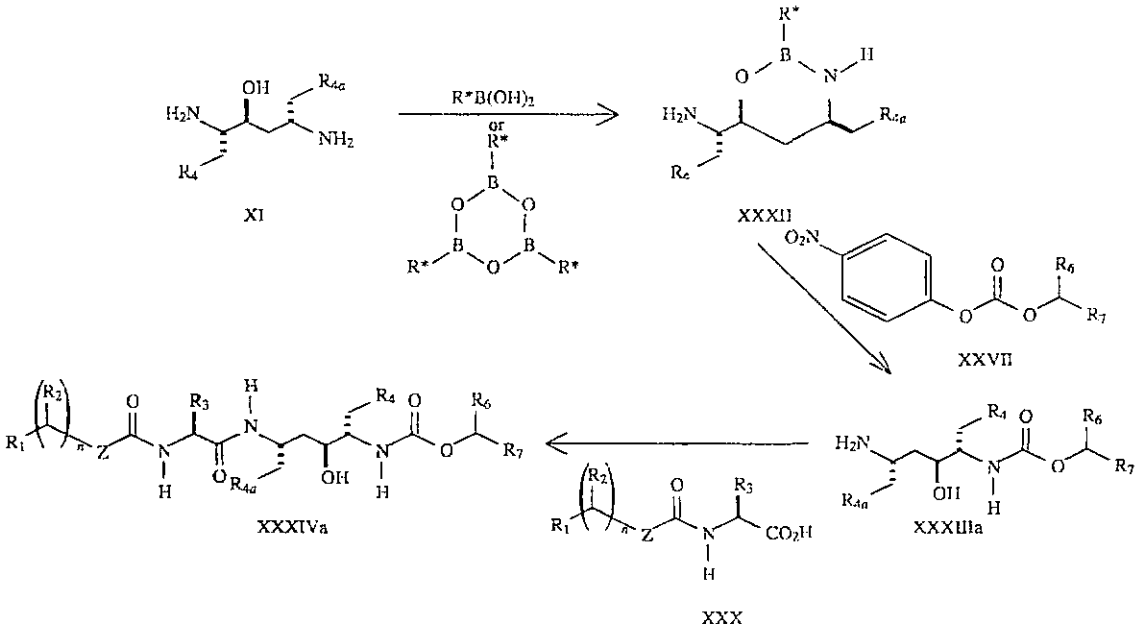


XXXIb

As outlined in Scheme 6A, treatment of diamine XI with a boronic acid (preferably, phenylboronic acid) or a boroxine produces compound XXXII, which is selectively acylated with an activated derivative of XXVI having the formula $(R_6)(R_7)CHOC(O)OL$ wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII) to provide compound XXXIIIa or an acid addition salt thereof. Carbodiimide-mediated coupling of XXXIIIa to compound XXX (:or reaction of XXXIIIa with an activated ester of XXX) leads to compound XXXIVa. In a preferred embodiment of the process shown in Scheme 6A, n is 1, R_4 and R_{4a} are each phenyl and R* is phenyl.

Alternatively, compound XXXII can be acylated with compound XXX (or an activated ester thereof) to provide compound XXXIIIb or an acid addition salt thereof. Acylation of compound XXXIIIb with an activated derivative of XXVI having the formula $(R_6)(R_7)CHOC(O)OL$ wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII) provides compound XXXIVb.

Scheme 6A



XI

XXXII

XXVII

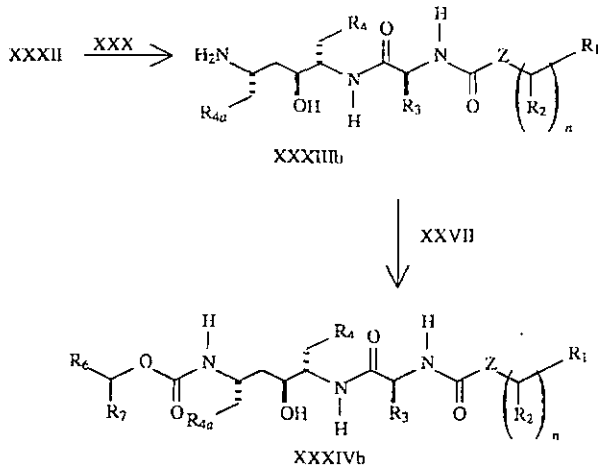
XXXIVa

XXXIIIa

XXX

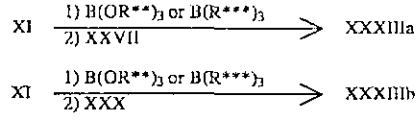
-continued

Scheme 6A



Scheme 6B outlines an alternative preparation of XXXIIIa or XXXIIIb. Reaction of compound XI with (i) two equivalents of $B(OR^{**})_3$ wherein R** is loweralkyl (preferably, isopropyl) or (ii) two equivalents of $B(R^{***})_3$ *wherein R*** *is halo (preferably, fluoro) and four equiva*lents of an amine such as triethylamine in an inert solvent such as tetrahydrofuran, followed by reaction with an activated derivative of XXVI having the formula $(R_6)(R_7)CHOC(O)OL$ wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII), gives compound XXXIIIa or an acid addition salt thereof. Similarly, reaction of compound XI with two equivalents of $B(OR^{**})_3$ wherein R** is loweralkyl (preferably, isopropyl) or two equivalents of $B(R^{***})_3$ wherein R*** is halo (preferably, fluoro), followed by reaction with compound XXX (or an activated ester derivative thereof), gives compound XXXIIIb or an acid addition salt thereof. In the preferred embodiment of the process shown in Scheme 6B, n is 1, R_4 and R_{4a} are each phenyl and R** is isopropyl or R*** is fluoro.

Scheme 6B



Scheme 6C outlines an alternative preparation of XXXIVa and XXXIVb. Reaction of compound XI with two molar equivalents of $Ti(OR^{****})_4$ wherein R_4 is loweralkyl (preferably, isopropyl), followed by reaction with an activated derivative of XXVI having the formula $(R_6)(R_7)CHOC(O)OL$ wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII), provides compound XLII or an acid addition salt thereof. Reaction of compound XLII with compound XXX (or an activated ester derivative thereof) gives compound XXXIVb. Similarly, reaction of compound XI with two molar equivalents of $Ti(OR^{****})_4$ wherein R_4 is loweralkyl (preferably, isopropyl), followed by reaction with compound XXX (or an activated ester derivative thereof), provides compound XLIII or an acid addition salt thereof. Reaction of compound XL. III with an activated derivative of XXVI having the formula $(R_6)(R_7)CHOC(O)OL$ wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII) gives compound XXXIVa. In the preferred embodiment of the process shown in Scheme 6C, n is 1, R_4 and R_{4a} are each phenyl and R**** is isopropyl.

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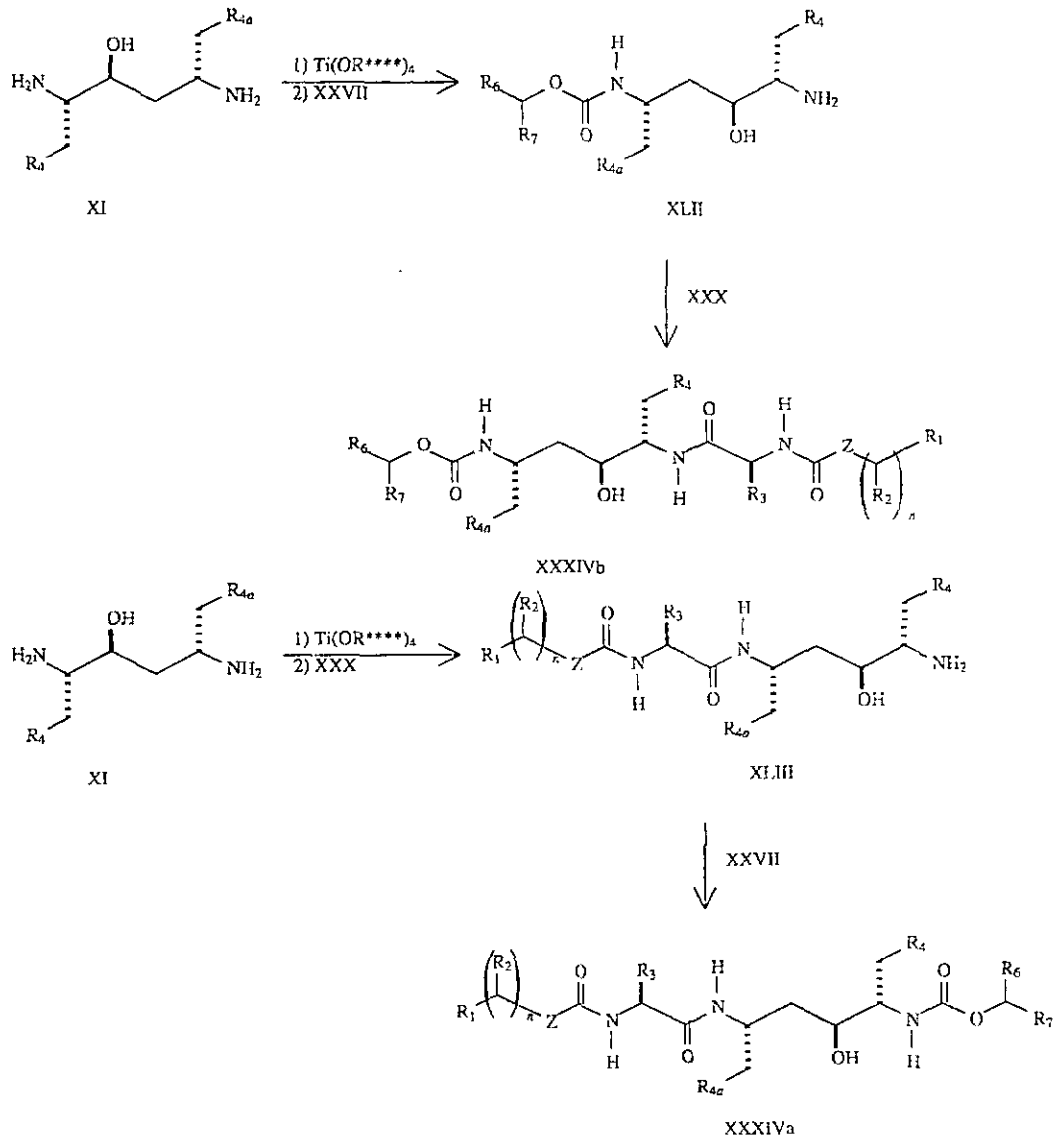
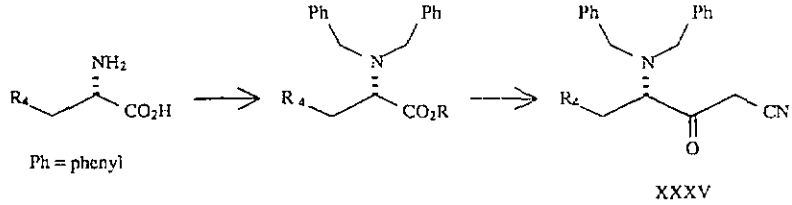
Scheme 6C



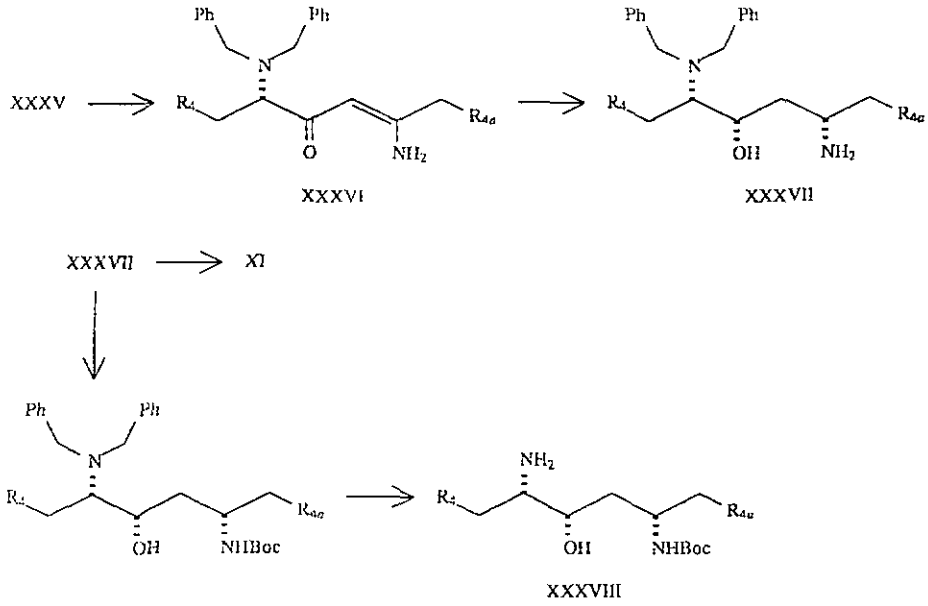
Scheme 7 shows an alternative preparation of diamino-mono-ol XI. Reaction of ketonitrile XXXV with Grignard reagent $R_{4a}CH_2MgX$ provides ketoenamine XXXVI. Reaction of the ketoenamine with $NaBH_4/CH_3SO_3H$, followed by reaction of the resulting intermediate (without isolation) with $NaBH_4/CF_3CO_2H$, provides XXXVII. Hydrogenation of the benzyl groups gives XI. Alternatively, protection of the free amino group of XXXVII as the t-butyloxycarbonylamino group, followed by hydrogenation of the benzyl groups, gives XXXVIII. In a preferred embodiment, R_4 and R_{4a} are each phenyl.

Scheme 7



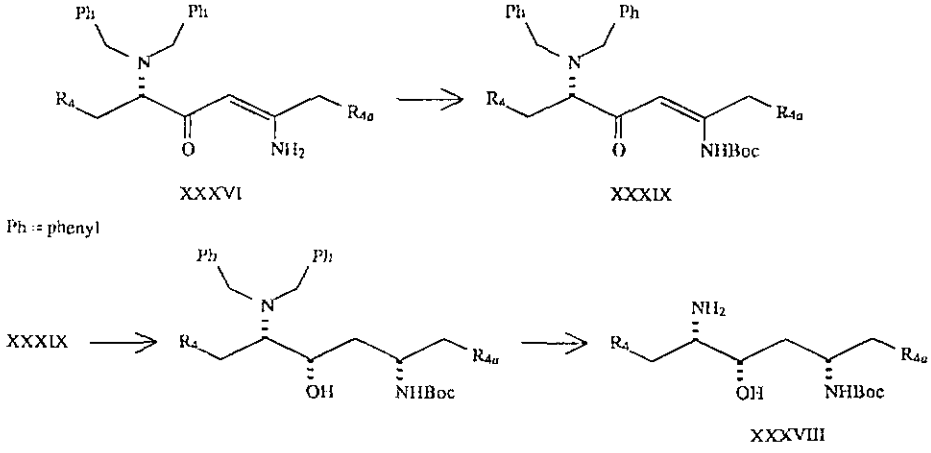
-continued

Scheme 7



Scheme 8 shows an alternative preparation of XXXVIII. N-protection of XXXVI gives XXXIX. Reaction of XXXIX with borane-tetrahydrofuran complex, followed by reaction of the resulting product with $LiAlH_4$ or KBH_4, provides the N,N-dibenzyl precursor to XXXVIII.

Scheme 8



Ph = phenyl

Scheme 9 shows how the selectively protected diamine XXXIX can be used to prepare compounds of the invention XL and XLI.

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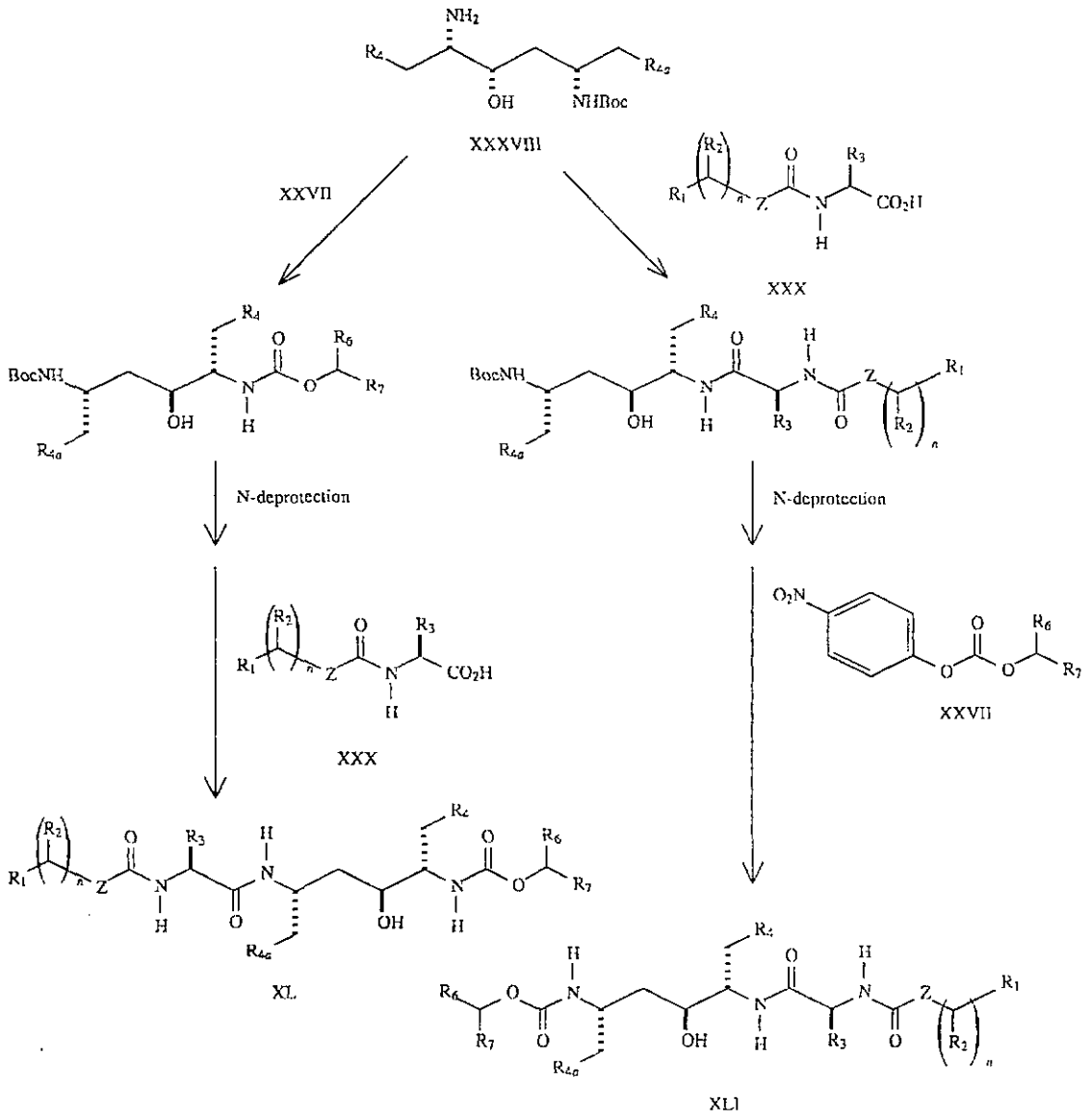
Scheme 9



The following examples will serve to further illustrate the preparation of the novel compounds of the invention.

EXAMPLE 1

A. N-(((Benzyl)oxy)carbonyl)-L-phenylalaninal.

A solution of 24.5 ml of anhydrous dimethyl sulfoxide in 870 ml of anhydrous dichloromethane was cooled under N_2 atmosphere to −60° C. and treated over a period of 15 min with 131 ml of a 2M solution of oxalyl chloride in dichloromethane in order that the internal temperature remained below −50° C. After addition, the solution was stirred at −60° C. for 15 min and treated over a period of 20 min with a solution of 50 g (0.175 mol) of N-(((benzyl)oxy)-carbonyl)-L-phenylalaninol in 200 ml of dichloromethane. The resulting solution was stirred at −60° C. for 1 h, then treated over a period of 15 min with 97 ml of triethylamine in order that the internal temperature remained below −50° C. After addition the solution was stirred at −60° C. for 15 min, then, with the cooling bath in place, was treated rapidly (over a period of 1 min) with a solution of 163 g of citric acid in 550 ml of water. The resulting slurry was stirred vigorously for 10 min, allowed to warm, diluted to 1 liter with water, and separated. The organic layer was washed with 700 ml of water followed by a mixture of 550 ml of water and 150 ml of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo at 20° C. to give the crude desired compound as a light yellow solid.

B. (2S,3R,4R,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane and (2S,3S,4S,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

A suspension of 78.5 g of VCl_3.(tetrahydrofuran)$_3$ and 16 g of zinc dust in 400 ml of dry dichloromethane was stirred under N_2 atmosphere for 1 h at 25° C. A solution of 0.175 mol of N-(((benzyl)oxy)carbonyl)-L-phenylalaninal in 200 ml of dichloromethane was then added in one portion, and the resulting mixture was stirred at ambient temperature under N_2 atmosphere for 16 h. The resulting mixture was added to 500 ml of 1M aqueous HCl, diluted with 500 ml of hot chloroform, and shaked vigorously for 2 min. The layers were separated, and the organic layer was washed with 1M

aqueous HCl and separated. Filtration of the organic phase provided the crude desired product as a solid residue. The residue was slurried in 1.25 liters of acetone, treated with 5 ml of concentrated H_2SO_4, and stirred for 16 h at ambient temperature. The resulting mixture was filtered, and the residue (residue A) was washed with 50 ml of acetone. The combined filtrate was concentrated to a volume of 250 ml, diluted with 1000 ml of dichloromethane, washed three times with water and once with saturated brine, dried over $MgSO_4$, and concentrated to give a viscous oil. The oil was taken up in 1000 ml of 1M HCl in methanol (prepared from 71 ml of acetyl chloride and 1000 ml of methanol) and stirred at ambient temperature for 2 h. The resulting precipitate was filtered, washed with methanol, and air-dried on the filter to provide 26.7 g of the desired compound as a white solid. The filtrate was concentrated and filtered to give a second crop (8.3 g) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane. ^1H NMR (d_6-DMSO) δ2.59 (dd, J=13, 5 Hz, 2H), 2.74 (dd, J=13, 9 Hz, 2H), 3.26 (br, 2H), 4.19 (m, 2H), 4.54 (m, 2H), 4.92 (m, 4H), 6.82 (d, J=9 Hz, 2H), 7.0–7.35 (m, 20H). Mass spectrum: $(M+H)^+$=569.

Residue A (above, 2.65 g) was suspended in 75 ml of tetrahydrofuran (THF) and 75 ml of 1M aqueous HCl and heated at reflux for 24 h. After concentration of the resulting solution in vacuo, the residue was taken up in 10% methanol in chloroform, washed two times with water, dried over Na_2SO_4, and concentrated in vacuo to provide (2S,3S,4S,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane as a white solid. ^1H NMR (d_6-DMSO) δ2.64(m, 2H), 3.04(m, 2H), 3.49(m, 2H), 3.78 (m, 2H), 4.70 (d, J=7 Hz, 2H), 4.93 (AA', 4H), 7.1–7.4 (m, 20H). Mass spectrum: $(M+H)^+$=569.

C. (2S,3R,4S,5S)-3-Acetoxy-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3-bromo-1,6-diphenylhexane.

A suspension of 25 g (44 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane in 500 ml of 2:1 dichloromethane/hexane was treated with 23 g of α-acetoxyisobutyryl bromide. The resulting mixture was stirred at ambient temperature until the reaction clarified, washed with two 200 ml portions of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to give 30.8 g of the crude desired compound. A portion was purified by silica gel chromatography using 9:1 dichloromethane:ethyl acetate to provide the pure desired compound as a white solid. ^1H NMR ($CDCl_3$), δ2.21 (s, 3H), 2.62 (dd, J=13, 11Hz, 1H), 2.75 (d, J=7 Hz, 2H), 2.95 (br d, J=15 Hz, 1H), 4.03 (br t, J=10 Hz, 1 h), 4.40 (br d, J=10 Hz, 1H), 4.6–5.0 (m, 6H), 5.12 (br d, J=13Hz, 1H), 5.33 (br d, J=11Hz, 1H), 7.0–7.4 (m, 10H). Mass spectrum: $(M+NH_4)^+$=690,692.

D. (2S,3R,4R,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-epoxy-1.6-diphenylhexane.

A solution of 35.56 g (52.8 mmol) of (2S,3R,4S,5S)-3-acetoxy-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3-bromo-1,6-diphenylhexane in 375 ml of dioxane was treated with 255 ml of 1N aqueous sodium hydroxide and stirred at ambient temperature for 16 h, during which the desired compound precipitated. The resulting mixture was filtered, and the residue was washed with water and dried to provide 22.23 g (76%) of the desired compound as a white solid. ^1H NMR ($CDCl_3$) δ2.7–2.9 (m, 6H), 3.9–4.0 (m, 2H), 4.6–4.7 (m, 2H), 5.03 (m, 4H), 7.1–7.4 (m, 10H).

E. (2S,3S,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)1,6-diphenyl-3-hydroxyhexane.

A mixture of 39.2 g (71.2 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-epoxy-1,6-diphenylhexane in 600 ml of THF was treated under N_2 atmosphere with 13 g (0.36 mol) of sodium borohydride. The resulting mixture was treated dropwise with 27.7 ml (0.36 mol) of trifluoroacetic acid. After being stirred for 3.5 h at ambient temperature, the resulting mixture was quenched with 1N aqueous HCl, diluted with water, and stirred for 16 h. The resulting mixture was filtered, washed with water, and dried to provide 22.85 g (58%) of the desired compound as a white solid.

F. (2S,3S,5S)-2,5-Diamino-1,6-diphenyl-3-hydroxyhexane.

A suspension of 32 g of the crude resultant compound of Example 1E and 55.5 g (176 mmol) of barium hydroxide octahydrate in 400 ml of 1,4-dioxane and 400 ml of water was heated at reflux for 4 h. The resulting mixture was filtered, and the residue was rinsed with dioxane. The combined filtrates were concentrated to a volume of approximately 200 ml and extracted with four 400 ml portions of chloroform. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography using first 2% isopropylamine in chloroform and then 2% isopropylamine/2% methanol in chloroform to provide 10.1 g (81%) of the pure desired compound as a white solid. ^1H NMR ($CDCl_3$) δ1.54 (dt, J=14, 10 Hz, 1H), 1.67 (dt, J=14, 3 Hz, 1H), 2.50 (dd, J=13, 8 Hz, 1H), 2.58 (dd, J=13, 8Hz, 1H), 2.8 (m, 2H) 2.91 (dd, J=13,5 Hz, 1H), 3.10(m, 1H), 3.72(ddd, J=11,3,2 Hz, 1H), 7.1–7.4 (m, 10H). Mass spectrum: $(M+H)^+$=285.

G. (4S,6S, 1'S)-6-(1-Amino-2-phenylethyl)-4-benzyl-2-phenyl-3-aza-2-bora-1-oxacyclohexane.

A solution of 131 g (460 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane in 1.2 L of toluene was treated under N_2 atmosphere with 56.16 g (460 mmol) of phenylboric acid. The resulting solution was heated at reflux (bath temperature 135° C.) and water azeotropically removed with the aid of a Dean Stark trap until the distillate was clear and the theoretical amount of water (15.6 ml) was collected (ca 1.5h). After being allowed to cool, the solution was concentrated in vacuo to provide 176 g of the crude desired compound as a resin. H^1 NMR ($CDCl_3$) δ7.59 (m, 2H), 7.47–7.07 (m, 13H, 3.92 (m, 1H), 3.78 (s br, 1H), 3.52 (m, 1H)3.50 (m, 2H), 2.87 (dd, 1H, J=13.5, 5.7 Hz), 2.72 (m, 1H), 2.58 (dd, 1H , J=13.5, 8.7 Hz), 1.92 (m, 1H), 1.68 (m, 1H), 1.60–1.30 (s-very broad, 2H). CIMS m/z 371 (M+H)

H. Thioformamide,

To a cooled (0° C.) 2 L three neck round bottom flask equipped with an overhead stirrer charged with a solution of formamide (30.5 mL, 0.76 mol) in 1 L of diethyl ether was added 89 g (0.19 mol) of phosphorous pentasulfide in small portions. The reaction mixture was allowed to warm to ambient temperature, stirred for 2 h, filtered, and concentrated in vacuo to afford thioformamide as a yellow offensive smelling oil which was used without purification.

I. Ethyl 2-Chloro-2-formylacetate.

To a three neck 2 L round bottom flask charged with potassium t-butoxide (0.5 mol, 500 mL of a 1M solution in THF) and 500 mL of dry THF cooled to 0° C. was added dropwise from an addition funnel a solution of ethyl chloroacetate (0.5 mol, 53.5 mL) and ethyl formate (0.5 mol, 40.4 mL), in 200 mL of THF over 3 hours. After completion of addition, the reaction mixture was stirred for 1 hour and allowed to stand overnight. The resulting solid was diluted with diethyl ether and cooled in an ice bath. Then, the pH was lowered to approximately 3 using 6N HCl. The organic phase was separated, and the aqueous layer was washed 3 times with diethyl ether. The combined ethereal portions were dried over $NaSO_4$, and concentrated in vacuo. The

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crude desired compound was stored at −30° C. and used without further purification.

J. Ethyl Thiazole-5-carboxylate.

To a round bottom flask was added 250 mL of dry acetone, 7.5 g (0.123 mol) of thioformamide, and 18.54 g (0.123 mol) of ethyl 2-chloro-2-formylacetate. The reaction was heated at reflux for 2 hours. The solvent was removed in vacuo, and the residue was purified by chromatography (SiO_2, 6 cm o.d. column, 100% $CHCl_3$, R_f=0.25) to provide 11.6 g (60%) of the desired compound as a light yellow oil. NMR ($CDCl_3$) δ1.39 (t, J=7Hz, 3H), 4.38 (q, J=7 Hz, 2H), 8.50 (s, 1H), 8.95 (s, 1H).

K. 5-(Hydroxymethyl)thiazole.

To a precooled (ice bath) three neck 500 mL flask containing lithium aluminum hydride (76 mmol) in 250 mL of THF was added ethyl thiazole-5-carboxylate (11.82 g, 75.68 mmol) in 100 mL of THF dropwise over 1.5 hours to avoid excess foaming. The reaction was stirred for an additional hour, and treated cautiously with 2.9 mL of water, 2.9 mL of 15% NaOH, and 8.7 mL of water. The solid salts were filtered, and the filtrate set aside. The crude salts were heated at reflux in 100 mL of ethyl acetate for 30 min. The resulting mixture was filtered, and the two filtrates were combined, dried over Na_2SO_4, and concentrated in vacuo. The product was purified by silica gel chromatography eluting sequentially with 0%–2%–4% methanol in chloroform, to provide the desired compound, Rf=0.3 (4% methanol in chloroform), which solidified upon standing in 75% yield. NMR ($CDCl_3$) δ4.92 (s, 2H), 7.78 (s, 1H), 8.77 (s, 1H). Mass spectrum: $(M+H)^+$=116.

L. ((5-Thiazolyl)methyl)-(4-nitrophenyl)carbonate.

A solution of 3.11 g (27 mmol) of 5-(hydroxymethyl)thiazole and excess N-methyl morpholine in 100 ml of methylene chloride was cooled to 0° C. and treated with 8.2 g (41 mmol) of 4-nitrophenyl chloroformate. After being stirred for 1 h, the reaction mixture was diluted with $CHCl_3$, washed successively with 1N HCl, saturated aqueous $NaHCO_3$, and saturated brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (SiO2, 1–2% MeOH/$CHCl_3$, Rf=0.5 in 4% MeOH/$CHCl_3$) to yield 5.9 g (78%) of the desired compound as a yellow solid. NMR ($CDCl_3$) δ5.53 (s, 2H), 7.39 (dt, J=9, 3 Hz, 2H), 8.01 (s, 1H), 8.29 (dt, J=9, 3 Hz, 2H), 8.90 (s, 1H). Mass spectrum: $(M+H)^+$=281.

M. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and (2S,3S,5S)-2-Amino-5-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 500 mg (1.76 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 480 mg (1.71 mmol) of ((5-thiazolyl)methyl)-4-nitrophenyl)carbonate in 20 ml of THF was stirred at ambient temperature for 4 h. After removal of the solvent in vacuo, the residue was purified by silica gel chromatography using first 2% then 5% methanol in chloroform to provide a mixture of the two desired compounds. Silica gel chromatography of the mixture using a gradient of 0–1–2% methanol in 93:2 isopropylamine: chloroform provided 110 mg (16%) of (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (R_f0.48, 96:2:2 chloroform:methanol:isopropylamine) and 185 mg (28%) of (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (R_f0.44, 96:2:2 chloroform :methanol:isopropylamine).

(2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane: NMR ($CDCl_3$) δ1.3–1.6 (m, 2H), 2.40 (dd, J=14, 8 Hz, 1H), 2.78 (dd, J=5 Hz, 1H), 2.88 (d, J=7Hz, 2H), 3.01 (m, 1H), 3.72 (br q, 1H), 3.81 (br d, J=10 Hz, 1H), 5.28 (s, 2H), 5.34 (br d, J=9 Hz, 1H), 7.07 (br d, J=7 Hz, 2H), 7.15–7.35 (m, 8H), 7.87 (s, 1H), 8.80 (s, 1H). Mass spectrum: $(M+H)^+$=426.

(2S,3S,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane: NMR ($CDCl_3$) δ1.55 (dt, J=14, 8 Hz, 1H), 1.74 (m, 1H), 2.44 (dd, J=15, 1 Hz, 1H), 2.75–3.0 (m, 4H), 3.44 (m, 1H), 4.00(br t, 1H), 5.28 (m, 3H), 7.1–7.4 (m, 10H), 7.86 (s, 1H), 8.80 (s, 1H). Mass spectrum: $(M+H)^+$=426.

N. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 40 mmol of crude (4S,6S,1'S)-6-(1-amino-2-phenylethyl)-4-benzyl-2-phenyl-3-aza-2-bora-1-oxacyclohexane in 700 ml of anhydrous THF was cooled to −40° C. and treated dropwise over a period of 1 h with a solution of 7.83 g (27.9 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 300 ml of dry THF. The resulting solution was allowed to warm to 0° C. for 3 h, then to ambient temperature for 16 h. The solvent was removed in vacuo, and the residue was taken up in 700 ml of ethyl acetate, washed with three 150 ml portions of 1N aqueous NaOH and one 150 ml portion of brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography using methanol/chloroform mixtures provided the desired compound mixed with its regioisomer. A second chromatography using 1–3% isopropylamine in chloroform provided 5.21 g of the desired compound which solidified upon standing.

O. 2-Methylpropane-thioamide.

A suspension of 100 g (1.15 mol) of isobutyramide in 4 L of diethyl ether was stirred vigorously and treated in portions with 51 g (0.115 mol) of P_4S_{10}. The resulting mixture was stirred at ambient temperature for 2 h, filtered, and concentrated in vacuo to provide 94.2 g (80%) of the crude desired compound. ^1H NMR (DMSO-d_6) δ1.08 (d, J=7 Hz, 6H), 2.78(heptet, J=7 Hz, 1H), 9.06 (br, 1H), 9.30 (br, 1H). Mass spectrum: $(M+H)^+$=104.

P. 4-(Chloromethyl)-2-isopropylthiazole hydrochloride.

A mixture of 94.0 g (0.91 mol) of 2-methylpropane-thioamide, 115.7 g (0.91 mol) of 1,3-dichloroacetone, and 109.7 g (0.91 mol) of $MgSO_4$ in 1.6 liters of acetone was heated at reflux for 3.5 h. The resulting mixture was allowed to cool, filtered, and the solvent was removed in vacuo to provide the crude desired compound as a yellow oil. ^1H NMR (DMSO-d_6) δ1.32 (d, J=7 Hz, 6H), 3.27 (heptet, J=7 Hz, 1H), 4.78 (s, 2H), 7.61 (s, 1H). Mass spectrum: $(M+H)^+$ =176.

Q. 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole.

A solution of 40 g of 4-(chloromethyl)-2-isopropylthiazole hydrochloride in 100 ml of water was added dropwise with stirring to 400 ml of 40% aqueous methylamine. The resulting solution was stirred for 1 h, then concentrated in vacuo. The residue was taken up in chloroform, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel chromatography using 10% methanol in chloroform provided 21.35 g (55%) of the desired compound. ^1H NMR (DMSO-d_6) δ1.34 (d, J=7 Hz, 6H), 2.56 (s, 3H), 3.30 (heptet, J=7 Hz, 1H), 4.16 (s, 2H), 7.63 (s, 1H). Mass spectrum: $(M+H)^+$=171.

R. N-(((4-Nitrophenyl)oxy)carbonyl)-L-valine Methyl Ester.

A solution of 66.1 g (0.328 mol) of 4-nitrophenyl chloroformate in 1.2 liters of CH_2Cl_2 was cooled to 0° C. and treated with L-valine methyl ester hydrochloride. The resulting mixture was treated slowly, with stirring, with 68.9 ml (0.626 mol) of 4-methylmorpholine. The resulting solution

was allowed to slowly warm to ambient temperature and was stirred overnight. After washing with 3 portions of 10% aqueous $NaHCO_3$, the solution was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography by eluting with chloroform to provide the desired compound. ^1H NMR (DMSO-d_6) δ0.94 (d, J=7 Hz, 3H), 0.95 (d, J=7 Hz, 3H), 2.12 (octet, J=7 Hz, 1H), 3.69 (s, 3H), 4.01 (dd, J=8, 6 Hz, 1H), 7.41(dt, J=9, 3 Hz, 2H), 8.27 (dt, J=9, 3 Hz, 2H), 8.53 (d, J=8 Hz, 1H). Mass spectrum: $(M+NH_4)^+$=314.

S. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

A solution of 15.7 g (92 mmol) of 2-isopropyl-4-(((N-methyl)amino)-methyl)thiazole in 200 ml of THF was combined with a solution of 20.5 g (69 mmol) of N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester. The resulting solution was treated with 1.6 g of 4-dimethylaminopyridine and 12.9 ml (92 mmol) of triethylamine, heated at reflux for 2 h, allowed to cool, and concentrated in vacuo. The residue was taken up in CH_2Cl_2, washed extensively with 5% aqueous K_2CO_3, dried over Na_2SO_4, and concentrated in vacuo. The resulting product mixture was purified by silica gel chromatography using chloroform as an eluent to provide 16.3 g (54%) of the desired compound. ^1H NMR (DMSO-d_6) δ0.88 (d, J=7 Hz, 3H), 0.92 (d, J=7 Hz, 3H), 1.32 (d, J=7 Hz, 3H), 2.05 (octet, J=7 Hz, 1H), 2.86(s,3H), 3.25 (heptet, J=7 Hz, 1H), 3.61 (s, 3H), 3.96 (dd, J=8, 7 Hz, 1H), 4.4 (AA', 2H), 6.58 (d, J=8 Hz, 1H), 7.24 (s, 1H). Mass spectrum: $(M+H)^+$=328.

T. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

A solution of 1.42 g (4.3 mmol) of the resultant compound of Example 1S in 17 ml of dioxane was treated with 17.3 ml of 0.50M aqueous LiOH. The resulting solution was stirred at ambient temperature for 30 min, treated with 8.7 ml of 1M HCl, and concentrated in vacuo. The residue was taken up in dichloromethane, washed with water, dried over Na_2SO_4, and concentrated in vacuo to provide 1.1 g (81%) of the desired compound. Mass spectrum: $(M+H)^+$=314.

U. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 70 mg (0.223 mmol) of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine, 79 mg (0.186 mmol) of (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane, 30 mg (0.223 mmol) of 1-hydroxybenzotriazole hydrate, and 51 mg (0.266 mmol) of N-ethyl-N'-dimethylaminopropyl carbodiimide in 2 ml of THF was stirred at ambient temperature for 16 h. The resulting solution was concentrated in vacuo, and the residue was purified by silica gel chromatography using 97:3 CH_2Cl_2:CH_3OH to provide 100 mg (74%) of the desired compound (R_f0.4, 95:5 CH_2Cl_2:CH_3OH) as a solid. ^1H NMR (d_6-DMSO) δ0.73 (d, J=7 Hz, 6H), 1.30 (d, J=7 Hz, 6H), 1.45 (m, 2H), 1.87 (m, 1H), 2.5–2.7 (m, 4H), 2.87 (s, 3H), 3.23 (heptet, J=7 Hz, 1H), 3.57 (m, 1H), 3.81 (m, 1H), 3.93 (m, 1H), 4.15 (m, 1H), 4.44 (AA', 2H), 4.62 (d, J=6 Hz, 1H), 5.13 (AA', 2H), 6.01 (d, J=9 Hz, 1H), 6.89 (d, J=9 Hz, 1H), 7.1–7.2 (m, 11H), 7.68 (d, J=9 Hz, 1H 7.85 (s, 1H), 9.05 (s, 1H). Mass spectrum: $(M+H)^+$=721. Anal. Calcd for $C_{37}H_{48}N_6O_5S_2.0.5H_2O$: C, 60.88; H, 6.77; N, 11.51. Found: C, 60.68;H , 6.53; N, 11.36.

EXAMPLE 2

Following the procedures of Example 1, the following compounds can be prepared:

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl-)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

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(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl-)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

EXAMPLE 3

A. N-(((4-nitrophenyl)oxy)carbonyl)-L-alanine Methyl Ester.

Using the procedure of Example 1R, but replacing L-valine methyl ester hydrochloride with L-alanine methyl ester hydrochloride provided the desired compound (R_f0.25, dichloromethane)in 95% yield.

B. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-alanine Methyl Ester.

Using the procedure of Example 1S, but replacing N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester with the resultant compound of Example 3A provided, after silica gel chromatography using 97:3 CH_2Cl_2:CH_3OH, the desired compound (R_f0.55, 95:5 CH_2Cl_2: CH_3OH) in 24% yield. ^1H NMR ($CDCl_3$) δ1.39 (d, J=7 Hz, 6H), 1.43 (d, J=7 Hz, 3H), 2.98 (s, 3H), 3.28 (heptet, J=7 Hz, 1H), 3.74 (s, 3H), 4.46 (s, 2H), 4.49 (q, J=7 Hz, 1H), 6.12 (br, 1H), 6.98 (s, 1H). Mass spectrum: $(M+H)^+$=300.

C. N-((N-Methyl-N((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-alanine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 3B provided the desired compound.

D. (2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-isopropyl-4-thiazolylmethyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 3C provided, after silica gel chromatography using 97:3 CH_2Cl_2:CH_3OH, 70 mg (35%) of the desired compound (R_f 0.36, 95:5 CH_2Cl_2:CH_3OH), mp. 56°–58° C. Mass spectrum: $(M+H)^+$=693. Anal. Calcd for $C_{35}H_{44}N_6O_5S_2.0.5H_2O$: C, 59.89; H, 6.46; N, 11.97. Found: C, 60.07; H, 6.39; N, 12.00.

EXAMPLE 4

A. 2-Isopropyl-4-(((N-ethyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 40% aqueous methylamine with 70% aqueous ethylamine provided the crude desired compound. ^1H NMR (DMSO-d_6) δ1.12 (t, J=7 Hz, 3H), 1.32 (d, J=7Hz, 6H), 2.78 (q, J=7 Hz, 2H), 3.27 (q, J=7 Hz, 1H), 3.97 (s, 2H), 7.44 (s, 1H)

B. N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-(((N-ethyl)amino)methyl)-thiazole provided, after silica gel chromatography using 98:2 $CHCl_3$:CH_3OH, the desired compound (R_f0.5, 95:3 CH_2Cl_2:CH_3OH) in 54% yield. ^1H NMR ($CDCl_3$) δ0.94 (d, J=7Hz, 3H), 0.98 (d, J=7 Hz, 3H), 1.16 (t, J=7 Hz, 3H), 1.39 (d, J=7 Hz, 6H), 2.16 (m, 1H), 3.25–3.50 (m, 3H), 3.71 (s, 3H), 4.38 (dd, J=8, 6 Hz, 1H), 4.46 (AA', 2H), 6.13 (br, 1H), 7.00 (s, 1H). Mass spectrum: $(M+H)^+$=342.

C. N-((N-Ethyl-N-((2.-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 4B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2,isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 4C provided, after silica gel chromatography using 98:2 $CHCl_3$:CH_3OH, 60 mg (35%) of the desired compound (R_f 0.4, 95;5 CH_2Cl_2:CH_3OH), mp. 58°–60° C. Mass spectrum: $(M+H)^+$=735.

EXAMPLE 5

A. Ethyl 2–1-isopropylthiazole-4-carboxylate.

A solution of 2.35 g (23 mmol) of 2-methylpropanethioamide and 2.89 ml (23 mmol) of ethyl bromopyruvate in 75 ml of acetone was treated with excess $MgSO_4$ and heated at reflux for 2.5 h. The resulting mixture was allowed to cool, filtered, and concentrated in vacuo to an oil, which was taken up in chloroform, washed sequentially with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel using chloroform as an eluent to provide 3.96 g (86%) of the desired compound, R_f0.21 (chloroform) as an oil. ^1H NMR ($CDCl_3$) δ1.41 (t, J=8 Hz, 3H), 1.42 (d, J=7 Hz, 6H), 3.43 (heptet, J=7 Hz, 1H), 4.41 (q, J=8 Hz, 2H), 8.05 (s, 1H). Mass spectrum: $(M+H)^+$=200.

B. 4-(Hydroxymethyl)-2-isopropylthiazole.

A solution of 10 ml (10 mmol) of lithium aluminum hydride in toluene was diluted in a dry flask under N_2 atmosphere with 75 ml of THF. The resulting mixture was cooled to 0° C. and treated dropwise with a solution of 3.96 g (20 mmol) of ethyl 2-isopropyl-4-thiazolecarboxylate in 10 ml of THF. After addition, the solution was stirred at 0° C. for 3 h, diluted with ether, and treated with a small amount of aqueous Rochelle's salt. After stirring, the slurry was filtered, washed with ethyl acetate, and the combined filtrates were concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 2.18 g (69%) of the desired compound, R_f0.58 (4% methanol in chloroform). ^1H NMR ($CDCl_3$) δ1.39 (d, J=7 Hz, 6H), 2.94 (br, 1H), 3.31 (heptet, J=7 Hz, 1H 4.74 (s, 2H), 7.04 (s, 1H). Mass spectrum: $(M+H)^+$=158.

C. α-Isocyanato-valine Methyl Ester.

A suspension of L-valine methyl ester hydrochloride (49 g, 0.29 mol) in toluene (700 ml) was heated to 100° C. and phosgene gas was bubbled into the reaction mixture. After approximately 6 h, the mixture became homogeneous. The bubbling of phosgene was continued for 10 more min, then the solution was cooled with the bubbling of N_2 gas. The solvent was then evaporated and the residue chased with toluene two times. Evaporation of solvent gave 40.8 g (89%) of the crude desired compound.

D. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

A solution of 2.18 g (15 mmol) of 4-(hydroxymethyl)-2-isopropylthiazole, 15.8 mmol of α-isocyanato-valine methyl ester and 1.5 mmol of 4-dimethylaminopyridine in 75 ml of dichloromethane was heated at reflux for 5 h. The resulting solution was washed successively with 10% citric acid, aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography of the residue using 5% ethyl acetate in chloroform provided 2.67 g (57%) of the pure desired compound, R_f0.46 (4% methanol in chloroform). NMR^1H NMR (DMSO-d_6) δ1.26 (d, J=8 Hz, 3H), 1.32 (d, J=7 Hz, 6H), 3.27 (heptet, J=7 Hz, 1H), 3.63 (s, 3H), 4.10 (pentet, J=8 Hz, 1H), 5.02 (s, 2H), 7.47 (s, 1H), 7.81 d), J=8 Hz, 1H). Mass spectrum: $(M+H)^+$=287.

E. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 5D provided the desired compound.

F. (2S,3S,5S),5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 5E provided, after silica gel chromatography using 2% methanol in chloroform, 110 mg (58%) of the desired compound (R_f0.44, 10% methanol in chloroform), mp. 142°–145° C. Mass spectrum: $(M+H)^+$=708.

EXAMPLE 6

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl) methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 5E and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 105 mg (55%) of the desired compound (R_f0.33, 10% methanol in chloroform), mp. 172°–174° C. Mass spectrum: $(M+H)^+$=708.

EXAMPLE 7

A. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alanine Methyl Ester.

A solution of 1.12 g (5.56 mmol) of 4-nitrophenyl chloroformate in 20 ml of CH_2Cl_2 was cooled to 0° C. and treated sequentially with 0.8 g (5.1 mmol) of 4-(hydroxymethyl)-2-isopropylthiazole and 0.6 ml (5.6 mmol) of 4-methylmorpholine. The resulting solution was stirred at 0° C. for 1 h, diluted with CH_2Cl_2, washed with three portions of aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to give crude 2-isopropyl-4-(p-nitrophenyloxycarbonyloxymethyl)thiazole. A portion (0.53 g, 1.65 mmol) of the residue was taken up in 20 ml of chloroform, treated with 0.23 g (1.67 mmol) of L-alanine methyl ester hydrochloride and 0.36 ml (3.3 mmol) of 4-methylmorpholine, and heated at reflux for 16 h. After being allowed to cool, the solvent was removed in vacuo, and the residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 0.45 g (94%) of the desired compound, R_f0.43 (5% methanol in CH_2Cl_2). ^1H NMR (DMSO-d_6) δ1.26 (d, J=8 Hz, 3H), 1.32 (d, J=7 Hz, 6H), 3.27 (heptet, J=7 Hz, 1H), 3.63 (s, 3H), 4.10 (p, J=8 Hz, 1H), 5.02 (s, 2H), 7.47 (s, 1H), 7.81 (d, J=8 Hz, 1H). Mass spectrum: $(M+H)^+$=287.

B. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alanine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 7A provided the desired compound.

C. (2S,3S,5S,)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbo-

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nyl)-L-valine with the resultant compound of Example 7B provided, after silica gel chromatography using 1% methanol in chloroform, 110 mg (69%) of the desired compound (R_f0.4, 5% methanol in CH_2Cl_2), mp. 59°–61° C. Mass spectrum: $(M+H)^+$=680. Anal. Calcd for $C_{34}H_{41}N_5O_6S_2.0.5H_2O$: C, 59.28; H, 6.15; N, 10.17. Found: C, 59.37;H, 5.96; N, 10.18.

EXAMPLE 8

A. (5S, 1'S)-5-(1-(tert-Butyloxycarbonylamino),2-phenylethyl)-dihydrofuran-2(3H)-one.

Prepared from commercially available ethyl-3-bromopropionate by using the procedure of A.E.DeCamp, et al., (*Tetrahedron Lett.* 1991, 32, 1867H).

B. (5S, 1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-3-carboethoxy-dihydrofuran-2(3H)-one.

Lithium diisopropylamide (LDA) was prepared by dropwise addition of 16.5 ml (41.2 mmol) of 2.5 M n-BuLi to a solution of 5.8 ml (41.2 mmol) of diisopropyl amine in 30 ml of dry tetrahydrofuran at −78° C. The LDA solution was stirred for 30 min at −78° C. and 6.0 g (19.6 mmol) of the resultant compound of Example 8A in 30 ml of dry tetrahydrofuran was added dropwise. The reaction mixture was stirred for 30 min at −78° C. and 4.7 ml (49.1 mmol) of ethyl chloroformate was then added. After being stirred at −78° C. for 5 h, the reaction was quenched with saturated aqueous NH_4Cl, extracted with three 60 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the residue was purified by silica gel chromatography using 25% ethyl acetate in hexane to provide 4.73 g (64%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+$=378.

C. 5S,1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-3-carboethoxy-3-((5-thiazolyl)methyl)dihydrofuran-2(3H)-one.

Sodium metal (536 mg, 23.3 mmol) was dissolved in 10 ml of absolute ethanol. A solution of 4.0 g (10.6 mmol) of the resultant compound of Example 8B in 50 ml of absolute ethanol was added dropwise. The mixture was stirred at ambient temperature for 20 min and 5-chloromethylthiazole hydrochloride was then added. After being stirred at ambient temperature for 60 h, the reaction was cooled in an ice bath, neutralized with 10% citric acid to pH ~6 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 3.88 g (78%) of the desired compound as a white foamy solid. Mass spectrum: $(M+H)^+$=475.

D. (3S,5S, 1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-3-((5-thiazolyl)methyl)dihydrofuran-2(3H)-one.

A solution of 3.88 g (8.18 mmol) of the resultant compound of Example 8C in 65 ml of dimethoxyethane was treated with 32.7 ml (32.7 mmol) of 1M aqueous lithium hydroxide. After being stirred at ambient temperature for 4 h, the bulk of the 1,2-dimethoxyethane was removed in vacuo. The remaining mixture was treated with 10% citric acid to pH 4~5 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give the crude acid. The acid was dissolved in 50 ml of toluene, heated at reflux for 15 h. The solvent was removed in vacuo, and the residue was separated by silica gel chromatography using 50% ethyl acetate in hexane to provide 0.86 g (26%) of 3R isomer and 1.58 g (48%) of the desired compound as a white solid. ^1H NMR ($CDCl_3H$) δ1.40 (s, 9H), 1.84 (m, 1H), 2.21 (ddd, 1H), 2.82–2.99 (m, 3H), 3.07 (dd, 1H), 3.43 (dd, 1H), 3.97 (br q, 1H), 4.36 (ddd, 1H), 4.55 (br d, 1H), 7.21–7.33 (m, 5H), 7.63 (s, 1H), 8.69 (s, 1H). Mass spectrum: $(M+H)^+$ =403.

E. (2S,4S,5S)-4-(tert-Butyldimethylsilyloxy)-5-(tert-Butyldimethylsilyloxy)-5-(tert-butyloxycarbonylamino-6-phenyl-2-((5-thiazolyl)-methyl)hexanoic acid.

A solution of 1.50 g (3.73 mmol) of the resultant compound of Example 8D in 80 ml of a 2:1 mixture of 1,2-dimethoxyethane and water was treated with 14.9 ml (14.9 mmol) of 1M aqueous lithium hydroxide. After being stirred at ambient temperature for 1.5 h, the bulk of the 1,2-dimethoxyethane was removed in vacuo. The remaining mixture was treated with 10% citric acid to pH 4~5 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give 1.48 g of the crude hydroxy acid. This hydroxy acid was dissolved in 14 ml of dry DMF and 2.64 g (17.5 mmol) of tert-butyldimethylsilyl chloride and 2.23 g (32.8 mmol) of imidazole were added. After being stirred at ambient temperature for 18 h, 28 ml of methanol was added to the mixture. Stirring was continued for 4 h and the solvents were then removed in vacuo. The residue was treated with 10% citric acid to pH 4~5 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 1.70 g (85%) of the desired compound as a white foamy solid. Mass spectrum: $(M+H)^+$=529.

Anal. Calcd for $C_{27}H_{42}N_2O_5SSi.0.5H_2O$: C,59.64;H, 7.97; N, 5.15; Found: C, 59.71;H, 7.83; N, 5.31.

F. (2S,3S,5S)-5-((((Benzyl)oxy)carbonyl)amino)-3-(tert-Butyldimethylsilyloxy)-2-(tert-butyloxycarbonylamino)-1-phenyl-6-(5-thiazolyl)hexane.

A solution of 500.0 mg (0.935 mmol) of the resultant compound of Example 8E, 402 μl (1.87 mmol) of diphenylphosphoryl azide and 326 μl (2.38 mmol) of triethylamine in 5 ml of dioxane was heated at 70° C. for 1 h. Benzyl alcohol (483 μl, 4.67 mmol) was subsequently added. The mixture was stirred at 80° C. for 24 h. The solvents were removed in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 598.1 mg (100%) of the desired compound as a white foamy solid. Mass spectrum: $(M+H)^+$=640.

G. (2S,3S,5S)-5-((((Benzyl)oxy)carbonyl)amino)-2-(tert-butyloxycarbonylamino)-1-phenyl-6-(5-thiazolyl)-3-hydroxyhexane.

A solution of 570.6 mg (0.892 mmol) of the resultant compound of Example 8F in 25 ml of tetrahydrofuran was treated with 0.89 ml of 1M solution of tetrabutylammonium fluoride in tetrahydrofuran. After being stirred at ambient temperature for 20 h, the solvent was removed in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 295.6 mg (63%) of the desired compound as a white solid. ^1H NMR ($CDCl_3H$) δ1.39 (s, 9H), 1.54 (m, 2H), 2.87 (m, 2H), 3.08 (m, 2H), 3.69 (m, 2H), 3.96 (m, 1H), 4.77 (br d, 1H), 5.08 (s, 2H), 5.11 (br s, 1H), 7.18–7.36 (m, 10H), 7.53 (s, 1H), 8.67 (s, 1H). Mass spectrum: $(M+H)^+$=526.

H. (2S,3S,5S)-2,5-Diamino-1-phenyl-6-(5-thiazolyl)-3-hydroxyhexane.

The resultant compound of Example 8G (201.2 mg, 0.383 mmol) was dissolved in 1 ml of acetic acid saturated with hydrogen bromide and stirred at ambient temperature for 1 h. The solvent was removed in vacuo. The residue was treated with 2 ml of saturated aqueous $NaHCO_3$, extracted

with five 5 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to provide 99.3 mg (89%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+$=292.

I. (4S,6S,1'S)-6-(1-Amino-2-phenylethyl)-2-phenyl-4-((5-thiazolyl)methyl)-3-aza-2-bora-1-oxacyclohexane.

A solution of 95.7 mg (0.328 mmol) of the resultant compound of Example 8H and 40.0 mg (0.328 mmol) of phenylboric acid in 5 ml of toluene was heated at reflux and the water azeotropically removed with the aid of a Dean Stark trap until the distillate was clear. The solvent was then removed in vacuo to provided 124.3 mg (100%) of the desired compound as a resin. Mass spectrum: $(M+H)^+$=378.

J. (2S,3S,5S)-5-Amino-1-phenyl-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

A solution of 100.0 mg (0.265 mmol) of the resultant compound of Example 8I and 74.0 mg (0.265 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 5 ml of tetrahydrofuran was stirred at ambient temperature for 24 h. The solvent was then removed in vacuo. The residue was dissolved in 20 ml of dichloromethane, washed with three 5 ml portions of 0.5N NaOH and two 5 ml portions of water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol and 2% isopropylamine in chloroform to provide 22.8 mg (20%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+$=433.

K. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-1-phenyl-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 8J provided 16.7 mg (47%) of the desired compound as a white solid. ^1H NMR ($CDCl_3$H) δ0.90 (d, 3H), 0.94 (d, 3H), 1.38 (d, 6H), 1.63 (m, 2H), 2.32 (m, 1H), 2.85 (m, 2H), 2.97 (s, 3H), 3.04 (m, 2H), 3.31 (m, 1H), 3.68 (m, 1H), 3.77 (m, 1H), 3.96 (m, 1H), 4.16 (m, 1H), 4.39 (s, 2H), 5.22 (m, 4H), 6.40 (br s, 1H), 6.80 (br d, 1H), 7.04 (s, 1H), 7.18–7.28 (m, 5H), 7.55 (s, 1H), 7.83 (s, 1H), 8.58 (s, 1H), 8.80 (s, 1H). Mass spectrum: $(M+H)^+$=728.

EXAMPLE 9

A. 4-(Chloromethyl)-2-(dimethylamino)thiazole.

A mixture of 15 g (144 mmol) of N,N-dimethylthiourea and excess $MgSO_4$ in 350 ml of acetone was heated to reflux and treated dropwise with a solution of 18.3 g (144 mmol) of 1,3-dichloroacetone in 35 ml of acetone. The resulting mixture was heated at reflux for 1.5 h, allowed to cool, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography using 20% ethyl acetate in hexane to provide 14.0 g (70%) of the desired compound.

B. 2-(N,N-Dimethylamino)-4-(hydroxymethyl)thiazole.

A solution of 5.186 g (29 mmol) of 4-(chloromethyl)-2-(dimethylamino)thiazole in 100 ml of 1:1 THF/H_2O was cooled to 0° C. and treated dropwise with a solution of 5.73 g (29 mmol) of silver tetrafluoroborate in 50 ml of 1:1 THF/H_2O. After being stirred for 1 h, the mixture was filtered, the solid mass was washed with ethyl acetate, and the combined filtrates were concentrated in vacuo. The black residue was purified by silica gel chromatography to provide 0.80 g (17%) of the desired compound (R_f0.24, 6% methanol in chloroform) as an oil. ^1H NMR ($CDCl_3$) δ2.67 (br, 1H), 3.09 (s, 6H), 4.54 (s, 2H), 6.35 (s, 1H). Mass spectrum: $(M+H)^+$=159.

C. N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

A solution of 505 mg (3.19 mmol) of 2-(N,N-dimethylamino)-4-(hydroxymethyl)thiazole, 3.19 mmol of α-isocyanato-L-valine methyl ester, and 100 mg of 4-dimethylaminopyridine in 30 ml of dichloromethane was heated at reflux for 3 h. The resulting solution was allowed to cool, diluted with dichloromethane, washed sequentially with 10% citric acid, aqueous Na_2CO_3, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 0.95 g (95%) of the desired compound, R_f0.42 (4% methanol in chloroform). ^1H NMR ($CDCl_3$) δ0.84 (d, J=7Hz, 3H), 0.93 (d, J=7 Hz, 3H), 2.12 (m, 1H), 3.11 (s, 6H), 3.73 (s, 3H), 4.24 (dd, J=8,4 Hz, 1H), 4.99 (s, 2H), 5.26 (br d, 1H), 6.49 (s, 1H). Mass spectrum: $(M+H)^+$=316.

D. N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 9C provided the desired compound. Mass spectrum: $(M+H)^+$=302.

E. (2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 9D provided, after silica gel chromatography using 2% methanol in chloroform, 100 mg of the desired compound (R_f0.49, 10% methanol in chloroform), mp. 162°–165° C. Mass spectrum: $(M+H)^+$=709.

EXAMPLE 10

(2S,3S,5S)-2-(N-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 9D and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 25 mg (10%) of the desired compound (R_f0.49, 10% methanol in chloroform), mp. 157°–159° C. Mass spectrum: $(M+H)^+$=709.

EXAMPLE 11

A. 4-((Amino)thiocarbonyl)morpholine.

A solution of 3.35 g (18.8 mmol) of thiocarbonyl diimidazole in 100 ml of THF was treated with 0.82 ml (9.4 mmol) of morpholine. After being stirred at ambient temperature for 3.5 h, an additional 0.82 ml portion of morpholine was added, and stirring was continued. After 6 h, the solution was treated with excess concentrated aqueous ammonia, and stirred overnight. The resulting solution was concentrated in vacuo, taken up in chloroform, separated from the aqueous phase, dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel chromatography using ethyl acetate provided 1.85 g (76%) of the desired compound, R_f0.17 (10% methanol in chloroform), as a white solid. ^1H NMR ($CDCl_3$) δ3.76 (m, 4H), 3.83 (m, 4H), 5.75 (br, 2H). Mass spectrum: $(M+H)^+$=147.

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B. Ethyl 2-(4-Morpholinyl)thiazole-4-carboxylate.

A mixture of 1.85 g (12.7 mmol) of 4-((amino)thiocarbonyl)morpholine, 1.59 ml (12.7 mmol) of ethyl bromopyruvate, and excess $MgSO_4$ in 50 ml of acetone was heated at reflux for 2 h. The resulting mixture was allowed to cool, filtered, and concentrated in vacuo. The residue was taken up in chloroform, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Silica gel chromatography using 1% methanol in chloroform provided 1.7 g (55%) of the desired compound, R_f 0.70 (ethyl acetate). Mass spectrum: $(M+H)^+$=243.

C. 2-(4-Morpholinyl)-4-(hydroxymethyl)thiazole.

A solution of 7.0 ml (7.0 mmol) of lithium aluminum hydride in toluene was diluted with 10 ml of THF, cooled to 0° C., and treated with a solution of 1.7 g (7.0 mmol) of ethyl 2-(4-morpholinyl)thiazole-4-carboxylate in 25 ml of THF. The resulting solution was stirred for 1 h, quenched cautiously with aqueous Rochelle's salts, diluted with chloroform, filtered, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography using 2–4% methanol in chloroform provided 856 mg (61%) of the desired compound, R_f 0.16 (4% methanol in chloroform). ^1H NMR ($CDCl_3$) δ2.44 (br, 1H), 3.46 (t, J=5 Hz, 4H), 3.81 (t, J=5 Hz, 1H), 4.55 (br s, 2H), 6.45 (s, 1H). Mass spectrum: $(M+H)^+$ =200.

D. N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 9C but replacing 2-(N, N-dimethylamino)-4-(hydroxymethyl)thiazole with 2-(4-morpholinyl)-4-(hydroxymethyl)thiazole provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound, R_f 0.54 (4% methanol in chloroform), in 65% yield. ^1H NMR ($CDCl_3$) δ0.97 (d, J=7Hz, 3H), 1.00 (d, J=7 Hz, 3H), 2.25 (m, 1H), 3.50 (dd, J=5, 4 Hz, 2H), 3.76 (s, 3H), 3.84 (dd, J=5, 4 Hz, 2H), 4.67 (dd, J=9, 5 Hz, 1H), 7.63 (br d, 1H), 8.02 (s, 1H).

E. N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 11D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 11E provided, after silica gel chromatography using 2% methanol in chloroform, 201 mg (92%) of the desired compound (R_f 0.19, 4% methanol in chloroform), mp. 169°–170° C. Mass spectrum: $(M+H)^+$=751.

EXAMPLE 12

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 11E and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 196 mg (90%) of the desired compound (R_f 0.19, 4% methanol in chloroform), mp. 146°–148° C. Mass spectrum: $(M+H)^+$=751.

EXAMPLE 13

A. 1-((Amino)thiocarbonyl)pyrrolidine.

Using the procedure of Example 11A but replacing morpholine with pyrrolidine, and stirring the solution for six days after addition of aqueous ammonia provided the desired compound. ^1H NMR ($CDCl_3$) δ1.97 (m, 2H), 2.11 (m, 2H), 3.38 (br t, 2H), 3.85 (br t, 2H), 5.56 (br, 2H). Mass spectrum: $(M+H)^+$=131.

B. Ethyl 2-(1-Pyrrolidinyl)thiazole-4-carboxylate.

Using the procedure of Example 11B but replacing 4-((amino)thiocarbonyl)morpholine with 1-((amino)thiocarbonyl)pyrrolidine provided the desired compound. ^1H NMR ($CDCl_3$) δ1.37 (t, J=7Hz, 3H), 2.04 (m, 4H), 3.51 (m, 4H), 4.35 (q, J=7Hz, 2H), 7.37 (s, 1H). Mass spectrum: $(M+H)^+$ =227.

C. 2-(1-Pyrrolidinyl)-4-(hydroxymethyl)thiazole.

Using the procedure of Example 11C but replacing ethyl 2-(4-morpholinyl)thiazole-4-carboxylate with ethyl 2-(1-pyrrolidinyl)thiazole-4-carboxylate provided, after silica gel chromatography using 2–4% methanol in chloroform, the desired compound (R_f 0.26, 4% methanol in chloroform) in 53% yield. ^1H NMR ($CDCl_3$) δ2.04 (m, 4H), 2.75 (br, 1H), 3.45 (m, 4H), 4.56 (s, 2H), 6.32 (s, 1H). Mass spectrum: $(M+H)^+$=185.

D. N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 9C but replacing 2-(N, N-dimethylamino)-4-(hydroxymethyl)thiazole with 2-(1-pyrrolidinyl)-4-(hydroxymethyl)thiazole provided, after silica gel chromatography using 1.5% methanol in chloroform, the desired compound (R_f 0.34). ^1H NMR ($CDCl_3$) δ0.89 (d, J=7 Hz, 6H), 2.04 (m, 4H), 2.14 (m, 1H), 3.46 (m, 4H), 3.74 (s, 3H), 4.30 (dd, J=9, 4 Hz, 1H), 5.01 (s, 2H), 5.33 (br d, 1H), 6.44 (s, 1H). Mass spectrum: $(M+H)^+$=342.

E. N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 13D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 13E provided, after silica gel chromatography using 1–3% methanol in chloroform, 120 mg (53%) of the desired compound, mp. 146°–148° C. Mass spectrum: $(M+H)^+$= 735.

EXAMPLE 14

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 13E and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 89 mg (39%) of the desired compound (R_f 0.16, 4% methanol in chloroform), mp. 165°–167° C. Mass spectrum: $(M+H)^+$=735.

EXAMPLE 15

A. 2-Isopropyl-4-(((N-cyclopropyl)amino)methyl)thiazole.

A solution of 1.8 g (10.2 mmol) of 4-(chloromethyl)-2-isopropylthiazole hydrochloride in 10 ml of chloroform was added dropwise with stirring to 10 ml of cyclopropylamine. The resulting solution was stirred at ambient temperature for 16 h, concentrated in vacuo, and purified by silica gel chromatography using 5% methanol in chloroform to provide 0.39 g (19%) of the desired compound. ^{1}H NMR (DMSO-d_6) δ0.24 (m, 2H), 0.35 (m, 2H),1.30 (d, J=7 Hz, 6H), 2.10 (tt, J=12, 3Hz, 1H), 3.23 (heptet, J=7 Hz, 1H), 3.77 (s, 2H), 7.21 (s, 1H). Mass spectrum: $(M+H)^+$=197.

B. N-((N-Cyclopropyl-N-((2-isopropyl -thiazolyl)methyl)amino)carbonyl)-L-alanine Methyl Ester.

Using the procedure of Example 1S, but replacing N-(((4-nitrophenyl)-oxy)carbonyl)-L-valine methyl ester with N-(((4-nitrophenyl)oxy)carbonyl)-L-alanine methyl ester and replacing 2-isopropyl-4-(((N-methyl)amino)methyl)-thiazole with the resultant compound of Example 15A provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound (R_f 0.54, 5% methanol in chloroform) in 56% yield. ^{1}H NMR (DMSO-d_6H) δ0.70 (m, 2H), 0.80 (m, 2H), 1.30 (d, J=7 Hz, 6H), 1.34 (d, J=7 Hz, 3H), 2.57 (m, 1H), 3.22 (heptet, J=7Hz, 1H), 3.62 (s, 3H), 4.23 (pentet, J=7 Hz, 1H), 4.44 (AA', 2H), 6.54 (d, J=7Hz, 1H), 7.05 (s, 1H). Mass spectrum: $(M+H)^+$=326.

C. N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino }carbonyl)-L-alanine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 15B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-*((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hy*droxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 15C provided, after silica gel chromatography using 1% methanol in chloroform, 74 mg (40%) of the desired compound (R_f 0.25, 5% methanol in chloroform), mp. 65°–67° C. Mass spectrum: $(M+H)^+$=719. Anal. Calcd for $C_{37}H_{46}N_6O_5S_2.0.5H_2O$: C, 61.05;H, 6.51; N, 11.54. Found: C, 61.08;H, 6.32; N, 11.44.

EXAMPLE 16

A. 2-Isopropylthiazole-4-carboxaldehyde.

A solution of ethyl 2-isopropylthiazole-4-carboxylate (1 mmol) in 50 ml of dry dichloromethane was cooled to –78° C. under N_2 atmosphere and treated dropwise with 1.2 mmol of diisobutylaluminum hydride (1.5M in toluene). The resulting solution was stirred for 0.5 h, quenched with aqueous Rochelle salts, extracted with dichloromethane, dried over Na_2SO_4, and concentrated in vacuo to provide the crude desired compound.

B. 4-(1-Hydroxyethyl)-2-isopropylthiazole.

A solution of the resultant compound of Example 16A (0.5 mmol) in 25 ml of dry THF was cooled to –20° C. under Ar atmosphere, treated with 0.5 mmol of methylmagnesium chloride (3.0M in THF), stirred for 15 min, and quenched with water. The mixture was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated in vacuo to provide the crude desired compound.

C. N-(1-(2-propyl-4-thiazolyl)ethoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 4-(1-hydroxyethyl)-2-isopropylthiazole provided the desired compound.

D. N-(1-(2-Isopropyl-4-thiazolyl)ethoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 16C provided the desired compound.

E. (2S,3S,5S)-5-N-(N-(1-(2-Isopropyl-4-thiazolyl)ethoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl)N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 16D provided the desired compound.

EXAMPLE 17

A. N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with the resultant compound of Example 15A provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound (R_f 0.64, 5% methanol in chloroform) in 91% yield. ^{1}H NMR (DMSO-d_6H) δ0.73 (m, 2H), 0.82 (m, 2H), 0.90 (d, J=7 Hz, 6H), 1.30 (d, J=7 Hz, 6H), 2.10 (octet, J=7 Hz, 1H), 2.62 (m, 1H), 3.23 (heptet, J=7 Hz, 1H), 3.64 (s, 3H), 4.10 (dd, J=9, 6 Hz, 1H), 4.45 (AA', 2H), 6.29 (d, J=9Hz, 1H), 7.06 (s, 1H). Mass spectrum: $(M+H)^+$=354.

B. N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 17A provided the desired compound.

C. (2S,3S,5S)-5-(N-(N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 17B provided, after silica gel chromatography using 1% methanol in chloroform, 85 mg (48%) of the desired compound (R_f 0.30, 5% methanol in chloroform), mp. 65°–66° C. Mass spectrum: $(M+H)^+$=747. Anal. Calcd for $C_{39}H_{50}N_6O_5S_2$: C, 62.71;H, 6.75; N, 11.25. Found: C, 62.74;H, 6.61;N, 11.03.

EXAMPLE 18

A. 4-Chloromethyl-4-hydroxy-2-isopropyloxazoline.

To a solution of isobutyramide (9.876 g, 0.1122 mol) in acetone (130 mL) was added 1,3-dichloroacetone (10.0 g, 0.0748 mol), $NaHCO_3$ (9.429 g, 0.1122 mol), and $MgSO_4$ (18.01 g, 0.1496 mol). The mixture was heated at reflux under argon for 63 hrs, then cooled to room temperature, vacuum filtered, and concentrated in vacuo to a dark brown semi-solid. The residue was purified by SiO_2 flash chromatography using a gradient of EtOAc/CH_2Cl_2 (5%, 10%, 20%, 40%) to obtain the desired product as an orange liquid (6.06 g, 0.0341 mol, 46%): ^{1}H NMR ($CDCl_3$) δ1.20–1.28 (m, 6H), 2.56–2.72 (m, 1H), 3.70 (s, 2H), 4.18 (d, J=9.6 Hz, 1H), 4.38 (d, J=9.6 Hz, 1H). Mass spectrum: $(M+H)^+$=178, 180.

B. 4-Chloromethyl-2-isopropyloxazole.

A solution of 4-chloromethyl-4-hydroxy-2-isopropyloxazoline (4.88 g, 0.0275 mol) in 1,2-dichloroethane (20 mL) was added to a solution of $SOCl_2$ (2.40 mL, 0.0329 mol) in 1,2-dichloroethane (80 mL) at 0° C. under argon, and the solution was heated to 70° C. After 15 min at 70° C, the reaction was cooled to room temperature and the solvent removed by rotary evaporation in vacuo. Drying the residue

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on high vacuum gave the desired compound as a brown semi-solid (4.20 g, 0.0263 mol, 96%): ^{1}H NMR ($CDCl_3$) δ1.36 (d, J=7.5 Hz, 6H), 3.03–3.18 (m, 1H), 4.50 (s, 2H), 7.56 (s, 1H). Mass spectrum: $(M+H)^+$=160, 162.

C. 2-Isopropyl-4-(((N-methyl)amino)methyl)oxazole

To 40% aqueous methylamine (100 mL) was added dropwise a suspension of 4-chloromethyl-2-isopropyloxazole (4.20 g, 0.0263 mol)in p-dioxane/H_2O (1:1 (v/v), 20 mL) over a 25 min period. After stirring for 45 min at ambient temperature, the volume was reduced to ca. 50 mL by rotary evaporation in vacuo, and NaCl was added. The aqueous was extracted with $CHCl_3$ (4×100 mL), and the combined extract was dried over Na_2SO_4 and concentrated in vacuo. The resulting brown liquid was chromatographed on a 200 g SiO_2 flash column with 2% $iPrNH_2/CH_2Cl_2$ followed by a gradient of $iPrNH_2$/MeOH/CH_2Cl_2 (0.5:2:97.5, 0.5:4:95.5). Concentration in vacuo of the product-containing fractions afforded the desired compound as a golden oil (2.89 g, 0.0187 mol, 71%): ^{1}H NMR ($CDCl_3$) δ1.33 (d, J=6.9 Hz, 6H), 2.46 (s, 3H), 2.99–3.14 (m, 1H), 3.64 (s, 2H), 7.42 (s, 1H). Mass spectrum: $(M+H)^+$=155, $(M+NH_4)^+$=172.

D. N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

A solution of N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester (0.903 g, 0.00305 mol) in anhydrous DMF (6 mL) was added to a solution of 2-isopropyl-4-(((N-methyl)amino)methyl)oxazole (9, 0.470 g, 0.00305 mol) in anhydrous DMF (6 mL) under argon, and the yellow solution was stirred at room temperature for 30 min. Solvent was removed by rotary evaporation in vacuo and the resulting oil dried on high vacuum for 1 hr. The residue was applied to a 150 g SiO_2 flash column and eluted with 20% EtOAc/CH_2Cl_2 and 3% MeOH/CH_2Cl_2. The material obtained after concentration of the product fractions was repurified on a 100 g SiO_2 flash column with a gradient of MeOH/CH_2Cl_2 (1%, 2%, 3%) to obtain the desired compound as an oil (0.515 g, 0.00165 mol, 54 %): ^{1}H NMR ($CDCl_3$) δ0.97 (dd, J=9 Hz, J_2=6.9 Hz, 6H), 1.33 (d, J=6.9 Hz, 6H), 2.11–2.23 (m, 1H), 2.98 (s, 3H),300–3.13 (m, 1H), 3.77 (s, 3H), 4.23–4.36 (m, 2H), 4.36–4.42 (m, 1H), 5.79–5.86 (br d, 1H), 7.46 (s, 1H). Mass spectrum: $(M+H)^+$=312.

E. N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine.

To a solution of the resultant compound of Example 18D 10 (0.511 g, 0.00164 mol)in p-dioxane (10 mL) and H_2O(5 mL) was added LiOH monohydrate (0.103 g, 0.00246 mol). After stirring at room temperature for 1 hr, the p-dioxane was removed by rotary evaporation in vacuo, and the remaining aqueous solution was treated with 1N aq HCl (2.46 mL) and extracted with ethyl acetate (4×100 mL). The combined organic extract was washed with saturated brine and dried for 15 mins over Na_2SO_4. Concentration in vacuo followed by CH_2Cl_2 chases (2×) afforded the desired compound as a white solid (0.480 g, 0.00161 mol, 98%): ^{1}H NMR (DMSO-d_6) δ0.90 (dd, J_1=6.9 Hz, J_2=2.4 Hz, 6H), 1.24 (d, J=6.9 Hz, 6H), 1.99–2.12 (m, 1H), 2.83 (s, 3H), 2.96–3.10 (m, 1H), 3.96 (dd, J_1=8.4 Hz, J_2=6 Hz, 1H), 4.19–4.32 (m, 2H), 6.26 (d, J=8.4Hz, 1H), 7.80 (s, 1H). Mass spectrum: $(M+H)^+$=298

F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using 3–5–7% methanol in chloroform, 70 mg. (53%) of the desired compound. ^{1}H NMR (DMSO-d_6) δ0.74 (d, J=6.3 Hz, 6H), 1.23 (d, J=6.9 Hz, 6H), 1.38–1.51 (m, 2H), 1.80–1.94 (m, 1H), 2.54–2.74 (m, 5H), 2.83 (s, 3H), 2.94–3.09 (m, 1H), 3.53–3.63 (m, 1H), 3.76–3.97 (m,2H),4.08–4.35 (m, 3H), 4.63 (d, J=6 Hz, 1H), 5.08–5.19 (m, 2H), 5.90 (d, J=8.7 Hz, 1H), 6.89 (d, J=9 Hz, 1H), 7.07–7.25 (m, 12H), 7.68 (d, J=8.7 Hz, 1H), 7.77 (s, 1H), 7.86 (s, 1H), 9.05 (s, 1H). High resolution mass spectrum: calcd for $C_{37}H_{49}N_6O_6S$: 705.3434. Found: 705.3431 $(M+H)^+$. Anal. Calcd for $C_{37}H_{48}N_6O_6S.0.5H_2O$: C, 62.25;H , 6.92; N, 11.77. Found: C, 62.35;H, 6.86; N, 11.34.

EXAMPLE 19

A. Methyl Isocyanide.

A 100 mL 3-neck flask (equipped with septum, stopper, and a short path mini distillation head with cow collector cooled to −78° C.) was charged with p-toluenesulfonyl chloride (36.25 g, 0.1901 mol) and quinoline (60 mL). The vigorously stirred solution was heated to 75° C. with the system under vacuum (H_2 O aspirator with trap cooled to −40° C). Neat N-methylformamide (7.50 g, 0.127 mol) was added via syringe in small portions over 15 mins. The increasingly viscous solution was heated for 10 mins. at which time gas evolution had ceased. Material in the cow collector and in the vacuum trap were combined and vacuum distilled to provide the compound as a colorless liquid (2.06 g, 0.0502 mol, 39%).

B. 5-((Diethoxy)methyl)oxazole.

Prepared according to the procedure of Schöllkopf (*J. Am. Chem. Soc.* 112 (10) 4070 (1990)). To a solution of methyl isocyanide (2.88 g, 0.0702 mol) in THF (50 mL) under argon at −78° C. was added dropwise n-butyllithium solution (1.6M in hexanes, 44 mL) over 15 mins. After stirring for an additional 20 mins at −78° C., a solution of ethyl diethoxyacetate (12.62 g, 0.0702 mol) in THF (15 mL) was added dropwise over 20 mins. The bath was allowed to warm to −30° C. over the next 2 hrs and the reaction was then stirred at 0° C. for 30 mins. The reaction was quenched at 0° C. with glacial HOAc (4.22 g, 0.0702 mol) and the solvent was removed by rotary evaporation in vacuo. The golden solid was partitioned with H_2O (45 mL) and EtOAc (200 mL), and the aqueous extracted with EtOAc (2×200 mL). The combined organic was washed with satd aq NaCl, dried over Na_2SO_4, and concentrated in vacuo to a brown oil. Chromatography on a 300 g SiO_2 flash column with a gradient of EtOAc/hexane (10%, 15%, 20%) afforded the desired compound as a colorless liquid (7.46 g, 0.0436 mol, 62%): ^{1}H NMR ($CDCl_3$) δ1.25 (t, J=6.9 Hz, 6H), 3.56–3.70 (m, 4H), 5.62 (s, 1H), 7.26 (s, 1H), 7.86 (s, 1H). Mass spectrum: $(M+H)^+$=172.

C. 5-Oxazolecarboxaldehyde

A flask was charged with 5-((diethoxy)methyl)oxazole (1.02 g, 0.00596 mol) and cooled to 0° C. A solution of trifluoroacetic acid/CH_2Cl_2 (1:1 (v/v), 6.7 mL) and H_2O (0.39 mL) was added and the solution stirred at 0° C. for 10 min. The solvent was removed in vacuo, and the residue was treated with toluene and concentrated. Chromatography on a 100 g SiO_2 flash column with a gradient of EtOAc/hexane (20%, 30%, 40%) afforded the desired compound as a colorless liquid (0.344 g, 0.00354 mol, 59%): ^{1}H NMR ($CDCl_3$) δ7.89 (s, 1H), 8.12 (s, 1H), 9.87 (s, 1H). Mass spectrum: $(M+H)^+$=98.

D. 5-(Hydroxymethyl)oxazole

A solution of 5-oxazolecarboxaldehyde (0.627 g, 0.00646 mol) in MeOH (10 mL) under argon at 0° C. was treated

with $NaBH_4$ (0.247 g, 0.00646 mol). After 5 mins the reaction was quenched with acetone and the solvent removed by rotary evaporation in vacuo. Chromatography on a 100 g SiO_2 flash column with a gradient of MeOH/CH_2Cl_2 (5%, 10%) afforded the desired compound as a colorless oil (0.408 g, 0.00412 mol, 64%): ^1H NMR ($CDCl_3$) δ2.03 (t, J=6.0 Hz, 1H), 4.70 (d, J=6.0Hz, 2H), 7.04 (s, 1H), 7.87 (s, 1H). MS (Cl/NH_3)m/e 117 (m+NH_4), 100 (m+H).

E. ((5-Oxazolyl)methyl)-4-nitrophenyl)carbonate.

A solution of 5-(hydroxymethyl)oxazole (1.31 g, 0.0132 mol)in CH_2Cl_2 (70 mL) under argon at 0° C. was treated with triethylamine (1.90 mL, 0.0139 mol) and 4-nitrophenyl *chloroformate (2.75 g, 0.0132 mol). After stirring at* 0° C. for 2.5 hrs, solvent was removed by rotary evaporation in vacuo and the yellow solid was dried on vacuum pump to provide the crude desired compound.

F. (2S,3S,5S)-2-Amino-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1, 6-diphenyl-3-hydroxyhexane.

A solution of crude ((5-oxazolyl)methyl)-(4-nitrophenyl-)carbonate (made from 0.0132 mol 5-(hydroxymethyl)oxazole)in THF (110 mL) under argon was treated with a *solution of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hy*droxyhexane (3.76 g, 0.0132 mol) in THF (20 mL), and the reaction stirred at room temperature for 16 hrs. Solvent was removed by rotary evaporation in vacuo and the yellow foam dried on a vacuum pump. Chromatography on a 200 g SiO_2 flash column with 5% MeOH/CH_2Cl_2, 2% $iPrNH_2$/CH_2Cl_2, and a gradient of $iPrNH_2$/MeOH/CH_2Cl_2 (2:2:96, 2:5:93H) afforded a mixture (1.74 g) of the desired compound and (2S,3S,5S)-5-amino-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane. The mixture was applied to a 150 g SiO_2 flash column (deactivated with 2% $iPrNH_2$/CH_2Cl_2) and eluted with 2% $iPrNH_2$/CH_2Cl_2 to afford the desired compound as a gummy light yellow solid (0.382 g, 0.933 mmol, 7%): ^1H NMR (DMSO-d6) δ1.16–1.30 (m, 1H), 1.36–1.47 (m, 1H), 2.56–2.66 (m, 2H), 2.75–2.85 (m, 1H), 2.89–3.01 (m, 1H), 3.53–3.71 (m, 3H), 4.97 (d, J=2.4 Hz, 2H), 7.01 (d, J=9 Hz, 1H), 7.11–7.32 (m, 14H), 8.36 (s, 1H). Mass spectrum: $(M+H)^+$=410.

G. (2S,3S,5S}-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2,(N-((5-oxazolyl)methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S, 3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and replacing N(-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using a gradient of 1–4% methanol in dichloromethane, 145 mg (80%) of the desired compound. ^1H NMR ($CDCl_3$) δ0.74 (d, J=6.9 Hz, 6H), 1.23 (d, J=6.9 Hz, 6H), 1.39–1.50 (m, 2H), 1.80–1.94 (m, 1H), 2.56–2.74 (m, 4H), 2.83 (s, 3H), 2.94–3.09 (m, 1H), 3.52–3.62 (m, 1H), 3.72–3.84 (m, 1H), 3.88–3.92 (m, 1H), 4.08–4.35 (m, 3H), 4.62 (d, J=6 Hz, 1H), 4.94 (s, 2H), 5.91 (d, J=8.4Hz, 1H), 6.89 (d, J=9Hz, 1H),7.06–7.26 (m, 11H), 7.69 (d, J=9 Hz, 1H), 7.77 (s, 1H), 8.35 (s, 1H). Mass spectrum: $(M+NH_4H)^+$ 706;$(M+H)^+$=689. Anal. Calcd for $C_{37}H_{48}N_6O_7 0.5H_2O$: C, 63.68;H , 7.08; N, 12.04. Found: C, 63.50;H, 7.13; N, 11.60.

EXAMPLE 20

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino) -2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S, 3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-oxazolyl)methoxycarbonyl)amino)1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 1% methanol in chloroform, 88 mg (55%) of the desired compound (R_f 0.4, 5% methanol in chloroform), mp. 59°–61° C. Mass spectrum: $(M+H)^+$=705. *Anal. Calcd for* $C_{37}H_{48}N_6O_6S.0.5H_2O$: *C, 62.25;H, 6.92; N,* 11.77. Found: C, 62.23;H, 6.55; N, 11.57.

EXAMPLE 21

A. *Methyl 4-isopropylthiazole-2-carboxylate.*

A mixture of 2.11 g (12.8 mmol) of 1-bromo-3-methylbutan-2-one (Gaudry and Marquet, Tetrahedron, 26, 5661 (1970)), 1.0 g (12.8 mmol) of ethyl thiooxamate, and 1.70 g (14 mmol) of $MgSO_4$ in 50 ml of acetone was heated at reflux for 3 h. After being allowed to cool, the mixture was filtered, concentrated in vacuo, and purified by silica gel chromatography using chloroform to provide 0.29 g (11%) of the desired compound (R_f 0.9, 4% methanol in chloroform). ^1H NMR (DMSO-d_6) δ1.27 (d, J=7 Hz, 6H), 1.32 (t, J=7 Hz, 3H), 3.12 (heptet, J=7 Hz, 1H), 4.37 (q, J=7 Hz, 2H), 7.73 (s, 1H). Mass spectrum: $(M+H)^+$=200.

B. 2–1Hydroxymethyl)-4-isopropylthiazole.

Using the procedure of Example 5B, but replacing ethyl 2-isopropyl-4-thiazolecarboxylate with methyl 4-isopropylthiazole-2-carboxylate provided, after silica gel chromatography using 2% methanol in chloroform, the desired compound (R_f 0.3, 5% methanol in chloroform) in 96% yield.

C. N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl)valine Methyl Ester.

A solution of 1.4 mmol of α-isocyanato-valine methyl ester and 0.22 g (1.4 mmol) of 2-(hydroxymethyl)-4-isopropylthiazole in 10 ml of chloroform was heated at reflux for 3 h. After being allowed to cool, the solvent was removed in vacuo, and the residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 0.23 g (52%) of the desired compound (R_f 0.54, 5% methanol in dichloromethane). NMR ^1H NMR (DMSO-d6) δ0.87 (d, J=7 Hz, 3H), 0.88 (d, J=7 Hz, 3H), 1.23 (d, J=7 Hz, 6H), 2.04 (octet, J=7 Hz, 1H), 3.01 (heptet, J=7 Hz, 1H), 3.73 (s, 3 H), 3.94 (dd, J=8, 6 Hz, 1H), 5.26 (AA', 2H), 7.28 (s, 1H), 7.92 (d, J=8 Hz, 1H). Mass spectrum: $(M+H)^+$=315.

D. N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 21C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 21D provided, after silica gel chromatography using 1% methanol in chloroform, 123 mg (61%) of the desired compound (R_f 0.4, 5% methanol in chloroform), mp. 62°–64° C. Mass spectrum: $(M+H)^+$=708.

EXAMPLE 22

A. N,N-Diethylthiourea

A mixture of 6.24 g (35 mmol) of thiocarbonyl diimidazole and 3.6 ml (35 mmol) of diethylamine in 50 ml of THF was stirred at ambient temperature for 5 h. The resulting solution was treated with 20 ml of 2M aqueous NH_3 and stirred for 24 h. After removal of the solvent the residue was

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purified by chromatography on silica gel to provide N,N-diethylthiourea (R_f 0.28, 4% methanol in chloroform).

B. Ethyl 2-(N,N-Diethylamino)thiazole-4-carboxylate.

A solution of 0.972 g (7.36 mmol) of N,N-diethylthiourea and 1.02 ml (8.1 mmol) of ethyl bromopyruvate in 25 ml of acetone was treated with excess solid $MgSO_4$ and heated at reflux for 1 h. The resulting mixture was filtered, and concentrated in vacuo. Silica gel chromatography using $CHCl_3$ provided 2.36 g (38%) of the desired compound as an oil. Mass spectrum: $(M+H)^+$=229.

C. 2-(N,N-Diethylamino)-4-hydroxymethyl)thiazole.

A solution of 3.14 ml of lithium aluminum hydride in toluene was diluted in a dry flask under N_2 atmosphere with 30 ml of THF. The resulting mixture was cooled to 0° C. and treated dropwise with a solution of 1.43 g (6.28 mmol) of ethyl 2-(N,N-diethylamino)thiazole-4-carboxylate in 5 ml of THF. After addition, the solution was allowed to warm slowly to ambient temperature, stirred for 1 h, recooled to 0° C., and treated with a small amount of aqueous Rochelle's salt followed by ethyl acetate. After stirring, the slurry was filtered, washed with additional ethyl acetate, and the combined filtrates were concentrated in vacuo. The residue was purified by silica gel chromatography using methanol in chloroform to provide 0.864 g (73%) of the desired compound, R_f 0.17 (4% methanol in chloroform). Mass spectrum: $(M+H)^+$=187.

D. N-((2-(N,N-Diethylamino)-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

A solution of 5.11 mmol of α-isocyanato-valine methyl ester in 10 ml of dichloromethane was treated with 0.864 g (4.65 mmol) of 2-(N,N-diethylamino)-4-(hydroxymethyl)thiazole and 0.46 mmol of 4dimethylaminopyridine. The resulting solution was stirred at ambient temperature for 16 h, after which it was diluted with 200 ml of chloroform, washed successively with 10% citric acid, aqueous $NaHCO_3$, and saturated brine. After drying over Na_2SO_4, the solvent was removed in vacuo, and the residue was chromatographed on silica gel using 1–2% methanol in chloroform to provide 1.31 g (82%) of the desired compound, R_f 0.51 (4% methanol in chloroform) as an oil. ^1H NMR ($CDCl_3$) δ0.89 (d, J=7 Hz, 3H), 0.96 (d, J=7 Hz, 3H), 1.24 (t, J=7 Hz, 6H), 2.15 (m, 1H), 3.51 (q, J=7 Hz, 4H), 3.74 (s, 3H), 4.29 (dd, J=8, 4 Hz, 1H), 5.03 (s, 2H), 5.34 (br d, J=8 Hz, 1H), 6.42 (s, 1H). Mass spectrum: $(M+H)^+$=344.

E. N-((2-(N,N-Diethylamino)-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 22D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((2,-(N,N-Diethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 22E provided the desired compound.

EXAMPLE 23

A. 2-(N,N-Dimethylamino)-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-(dimethylamino)thiazole dihydrochloride provided, after silica gel chromatography using first 10% methanol in chloroform followed by 4% methanol/2% isopropylamine in chloroform, the desired compound, R_f 0.05 (10% methanol in chloroform). ^1H NMR ($CDCl_3$) δ2.46 (s, 3H), 3.08 (s, 6H), 3.66 (s, 2H), 6.30 (s, 1H). Mass spectrum: $(M+H)^+$=172.

B. N-((N-Methyl-N-(((N,N-dimethylamino)-4-thiazolyl/methylaminocarbonyl)-L-valine Methyl Ester.

A solution of 741 mg (4.42 mmol) of α-isocyanato-L-valine in 5 ml of dichloromethane was added to a solution of 720 mg (4.21 mmol) of 2-(N,N-dimethylamino)-4-(((N-methyl)amino)methyl)thiazole in 25 ml of dichloromethane. The resulting solution was stirred at ambient temperature for 16 h, partitioned between chloroform and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 463 mg (34%) of the desired compound, R_f 0.25 (2% methanol in chloroform). NMR ($CDCl_3$) δ0.96 (d, J=7 Hz, 3H), 0.98 (d, J=7 Hz, 3H), 2.13 (m, 1H),2.97 (s, 3H), 3.11 (s, 6H), 3.71 (s, 3H), 4.07 (br d, J=16Hz, 1H), 4.34 (dd, J=9, 5 Hz, 1H), 4.42 (d, J=16 Hz, 1H), 6.29 (s, 1H), 6.37 (br, 1H). Mass spectrum: $(M+H)^+$=329.

C. N-((N-Methyl-N-(((N,N-dimethylamino)-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 23B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-(((N,N-dimethylamino)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 23C provided, after silica gel chromatography, the desired compound.

EXAMPLE 24

A. Ethyl 2-Isopropylthiazole-5-carboxylate.

Using the procedure of Example 1J but replacing thioformamide with 2-methylpropane-thioamide provided, after silica gel chromatography using 9:1 ethyl acetate:hexane, the desired compound, R_f 0.8, (5% methanol in chloroform) in 83% yield.

B. 5-(Hydroxymethyl)-2-isopropylthiazole.

Using the procedure of Example 5B, but replacing ethyl 2-isopropyl-4-thiazolecarboxylate with ethyl 2-isopropylthiazole-5-carboxylate provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.3, (5% methanol in chloroform) in 25% yield. ^1H NMR (d_6-DMSO) δ1.30 (d, J=7 Hz, 6H), 3.22 (heptet, J=7 Hz, 1H), 4.61 (dd, J=6, 1Hz, 2H), 5.45 (t, J=6 Hz, 1H), 7.48 (br s, 1H).

C. N-((2-Isopropyl-5-thiazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 5-(hydroxymethyl)-2-isopropylthiazole provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.8, (5% methanol in chloroform) in 29% yield. ^1H NMR δ0.89 (d, J=7 Hz, 6H), 0.95 (d, J=7 Hz, 3H), 0.97 (d, J=7Hz, 3 H), 2.14 (m, 1H), 3.33 (heptet, J=7 Hz, 1H), 3.74 (s, 3H), 4.30 (dd, J=9, 5 Hz, 1H), 5.23 (s, 2H), 5.25 (br d, 1H), 7.63 (s, 1H). Mass spectrum: $(M+H)^+$=315.

D. N-((2-Isopropyl-5.thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 24C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 24D provided the desired compound.

EXAMPLE 25

A. 2-Methoxythioacetamide.

Using the procedure of Example 1O but replacing isobutyramide *with 2-methoxyacetamide provided the desired* compound in 52% yield.

B. 4-(Chloromethyl)-2-(methoxymethyl)thiazole hydrochloride.

Using the procedure of Example 1P but replacing 2-methylpropanethioamide with 2-methoxythioacetamide provided the crude desired compound in 41% yield.

C. 2-(Methoxymethyl)-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-(methoxymethyl)thiazole hydrochloride provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.1, (5% *methanol in chloroform) in 73% yield.*

D. N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S but replacing 2-isopropyl-4-(((N-methyl)amino)-methyl)thiazole with 2-(methoxymethyl)-4-(((N-methyl)amino)-methyl)thiazole provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.5, (5% methanol in chloroform) in 23% yield.

E. N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 25D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-*(methoxymethyl)*-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1.,6.-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 25E provided the desired compound.

EXAMPLE 26

A. 1,-Diethoxy-4-((3,4,5,6-tetrahydro-2H-pyran-2-yl)oxy)-2-butyne.

A 1M solution of ethylmagnesium bromide in THF (200 ml, 0.2 mol) was treated with 29 ml (0.2 mol) of a solution of 3,4,5,6-tetrahydro-2-(2-propynyloxy)-2H-pyran in toluene, while maintaining ambient temperature through use of a cool water bath. The resulting solution was stirred for 4 h and treated with 47 ml (0.28 mol) of a solution of triethylorthoformate in toluene, while maintaining ambient temperature with a cool water bath. The resulting solution was heated to 85° C. for 8 h, allowing the removal of THF by distillation. After being allowed to cool, the resulting solution was poured into 500 ml of ice-water containing 29 g of NH_4OAc, extracted with two portions of ether, dried over K_2CO_3, and concentrated in vacuo. The residue was distilled at ca. 0.5 mm Hg pressure (b.p. 103°–108° C.) to provide 39.5 g (79%) of the desired compound. ^1H NMR ($CDCl_3$) δ1.24 (t, J=7 Hz, 6H), 1.5–1.9 (m, 6H), 3.5–3.65 (m, 3H), 3.7–3.9 (m, 3H), 4.32 (AA', 2H), 4.81 (m, 1H), 5.31 (m, 1H). Mass spectrum: $(M+NH_4)^+$=260.

B. 5-(Hydroxymethyl)isoxazole.

A solution of 39.28 g (161 mmol) of the resultant compound of Example 26A and 26 g (376 mmol) of hydroxylamine hydrochloride in 168 ml of ethanol and 34 ml of water was heated at reflux under N_2 atmosphere for 1 h. *After being allowed to cool, the resulting solution was* concentrated in vacuo to ⅓ the original volume, diluted with 50 ml of water, and extracted with 2 portions, of ether. The combined extracts were concentrated to an oil. The crude product (7.04 g, 44%) was obtained after distillation (79°–84° C., 0.5 mm Hg). Silica gel chromatography using 0–3% methanol in dichloromethane provided 4.9 g of the desired compound contaminated with 5-hydroxypentanal oxime. ^1H NMR ($CDCl_3$) δ1.95 (br, 1H), 4.81 (s, 2H), 6.27 (d, J=1 Hz, 1H), 8.23 (d, J=1 Hz, 1H). Mass spectrum: $(M+NH_4)^+$=117.

C. ((5-Isoxazolyl)methyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L, but replacing 5-(hydroxymethyl)thiazole with 5-(hydroxymethyl)isoxazole provided, after silica gel chromatography using 8:2 dichloromethane:hexane, the desired compound. ^1H NMR ($CDCl_3$) δ5.41 (s, 2H), 6.46 (d, J=1 Hz, 1H), 7.40 (m, 2H), 8.30 (m, 3H). Mass spectrum: $(M+NH_4)^+$=282.

D. (2S,3.S,5S)-5-Amino-2-(N-((5-isoxazolyl)methoxycarbonyl)amino-1,6-diphenyl-3hydroxyhexane.

A mixture of 1.54 g (5.41 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 0.673 g (5.41 mmol) of phenylboric acid in anhydrous toluene (130 mL) was heated at reflux under argon for 2 hrs with removal of H_2O by a Dean-Stark trap. The resulting yellow solution was allowed to cool and the solvent was removed in vacuo to give an oil which solidified upon standing. The residue was taken up in 90 ml of THF, cooled to −40° C., and treated dropwise under Ar atmosphere over a period of 1 h with 1.11 g (3.78 mmol) of ((5-isoxazolyl)methyl)-(4-nitrophenyl)carbonate in 40 ml of THF. The solution was allowed to warm to −20° C. over the next 0.5 hr, then was stirred at 0° C. for 2.5 hrs and at room temperature for 1 hr. After removal of the solvent in vacuo, the residue was taken up in ethyl acetate (200 mL), washed sequentially with 5% aqueous K_2CO_3 (4×25 *mL) and saturated brine (25 mL), dried over* Na_2SO_4 and concentrated in vacuo. Silica gel chromatography of the residue using a gradient of methanol in chloroform (2%, 4%, 6%) afforded a mixture of the desired product and its regioisomer. Purification of the mixture on two consecutive 250 g SiO_2 columns (deactivated with 1% isopropylamine/CH_2Cl_2) with a gradient of isopropylamine/CH_2Cl_2 (0.5%, 1%) afforded the desired compound as a sticky solid (0.730 g, 1.78 mmol, 33%): ^1H NMR (DMSO-d_6) δ1.17–1.57 (m, 5H), 2.56–2.69 (m, 2H), 2.75–2.86 (m, 1H), 2.89–3.00 (m, 2H), 3.53–3.71 (m, 3H), 5.06 (s, 2H), 6.32 (d, J=2.4 Hz, 1H), 7.11–7.30 (m, 10H), 8.54 (d, J=2.4 Hz, 1H). Mass spectrum: $(M+H)^+$=410.

E. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 1% methanol in chloroform, 120 mg (70%) of the desired compound, R_f 0.3, (5% methanol in

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chloroform), as a solid, mp 60°–62° C. Mass spectrum: $(M+H)^+$=705. Anal. Calcd for $C_{37}H_{48}N_6O_6S$: C, 63.05;H, 6.86; N, 11.92. Found: C, 2.68;H, 7.00; N, 11.65.

EXAMPLE 27

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino/-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino--(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using a gradient of 1–4% methanol in dichloromethane, 225 mg (80%) of the desired compound. ^1H NMR (DMSO-d_6),5 0.74 (d, J=6.9 Hz, 6H), 1.23 (d, J=6.9 Hz, 6H), 1.35–1.54 (m, 2H), 1.80–1.95 (m, 1H), 2.55–2.73 (m, 4H), 2.83 (s, 3H), 2.94–3.09 (m, 1H), 3.53–3.63 (m, 1H), 3.73–3.86 (m, 1H),3.92 (t, J=8.4 Hz, 1H), 4.08–4.34 (m, 3H), 4.65 (d, J=6 Hz, 1H), 5.04 (s, 2H),5.91 (d, J=9 Hz, 1H), 6.29 (d, J=2.4 Hz, 1H), 7.01 (d, J=9 Hz, 1H), 7.06–7.27 (m,10H), 7.69 (d, J=9 Hz, 1H), 7.77 (s, 1H), 8.52 (d, J=2.4 Hz, 1H). Mass spectrum: $(M+H)^+$=689; $(M+NH_4)^+$=706. Anal. Calcd for $C_{37}H_{48}N_6O_7$: C, 64.52;H, 7.02; N, 12.20. Found: C, 64.52;H, 7.14; N, 12.06.

EXAMPLE 28

A. Ethyl 2-Methylthiazole-5-carboxylate.

Using the procedure of Example 1J, but replacing thioformamide with thioacetamide provided the crude desired compound.

B. 5-(Hydroxymethyl)-8-methylthiazole.

Using the procedure of Example 1K, but replacing ethyl thiazole-5-carboxylate with crude ethyl 2-methylthiazole-5-carboxylate provided, after silica gel chromatography using 3% then 5% methanol in chloroform, the desired compound, R_f 0.27, (4% methanol in chloroform) in 78% yield. ^1H NMR ($CDCl_3$) δ2.32 (br, 1H), 2.70 (s, 3H), 4.80 (s, 2H), 7.46 (s, 1H). Mass spectrum: $(M+H)^+$=130.

C. ((2-Methyl-5-thiazolyl)methyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L, but replacing 5-(hydroxymethyl)-thiazole with 5-(hydroxymethyl)-2-methylthiazole provided, after silica gel chromatography using first 1:5 chloroform:hexane, then 4% methanol in chloroform, the desired compound, R_f 0.46 (20% ethyl acetate in chloroform) in 97% yield.

D. (2S,3S,5S)-5-Amino-2-(N-((2-methyl-5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and (2S,3S,5S)-2-Amino-5-(N-((2-methyl-5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1M, but replacing ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate with ((2-methyl-5-thiazolyl)methyl)-(4-nitrophenyl)-carbonate provided, after silica gel chromatography using 4% methanol in chloroform, a mixture of the desired compounds. A second chromatography using 1% –3% isopropylamine in chloroform provided pure (2S,3S,5S)-5-amino-2-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane and (2S,3S,5S)-2-amino-5-(N-((2-methyl-5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

E. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl.)valinyl)amino)-2-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 210 mg (84%) of the desired compound, R_f 0.18, (4% methanol in chloroform). Mass spectrum: $(M+H)^+$=735. Anal. Calcd for $C_{38}H_{50}N_6O_5S_2.2H_2O$: C, 59.20;H, 7.06; N, 10.90. Found: C, 58.92;H, 6.37; N, 10.71.

EXAMPLE 29

A. 5-Methyl-1-((3,4,5,6-tetrahydro-2H-pyran-2-yl)oxy)-2-hexyn-4-one.

The desired compound was prepared from isobutyryl chloride and 3,4,5,6-tetrahydro-2-(2-propynyloxy)-2H-pyran by analogy to the procedure of Tohda, et. al. (Synthesis, 777 (1977)).

B. 5-(Hydroxymethyl)-3-isopropylisoxazole.

Using the procedure of Example 26B but replacing the resultant compound of Example 26A with the resultant compound of Example 29A provided the desired compound.

C. N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 5-(hydroxymethyl)-3-isopropylisoxazole provided the desired compound.

D. N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 29C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 29D provided the desired compound.

EXAMPLE 30

A. 2-Isopropyl-4-(methanesulfonyloxymethyl)thiazole.

A solution of 1.2 mmol of 4-(hydroxymethyl)-2-isopropylthiazole and 1.3 mmol of diisopropylethylamine in 20 ml of dichloromethane was cooled to −20° C. and treated dropwise with 1.3 mmol of methanesulfonyl chloride. The resulting mixture was stirred for 1 h, quenched with aqueous citric acid, separated, dried over Na_2SO_4, and concentrated in vacuo to provide the desired compound.

B. 2-Isopropyl-4-(mercaptomethyl)thiazole.

A mixture of 0.8 mmol of the resultant compound of Example 30A and 1.0 mmol of sodium hydrosulfide hydrate in 20 ml of THF was heated at reflux until analysis by thin layer chromatography indicated consumption of starting material. The resulting mixture was allowed to cool, concentrated in vacuo, partitioned between dichloromethane and water, dried over Na_2SO_4, and concentrated to provide the crude desired compound.

C. N-((2-Isopropyl-4-thiazolyl)thiomethoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D, but replacing 4-(hydroxymethyl)-2-isopropylthiazole with the resultant com-

pound of Example 30B provided, after chromatography on silica gel, the desired compound.

D. N-((2-Isopropyl-4-thiazolyl)thiomethoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 30C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)thiomethoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 30D provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 31

A. 2-Isopropylthiazole-4-carboxaldehyde.

A solution of 3.1 g (15.6 mmol) of ethyl 2-isopropylthiazole-4-carboxylate in 50 ml of dichloromethane was cooled under N_2 atmosphere to −78° C. and treated dropwise with 15.6 ml (23.4 mmol) of a 1.5M solution of diisobutylaluminum hydride in toluene over a period of 1.5 h. After being stirred for an additional 0.5 h, the solution was quenched with 5 ml of methanol followed by 15 ml of aqueous Rochelle's salt. The resulting mixture was partitioned between chloroform and aqueous Rochelle's salt, dried over Na_2SO_4, and concentrated to provide 1.37 g (56%) of the crude desired compound, R_f 0.47 (20% ethyl acetate in *hexane*). ^1H *NMR* ($CDCl_3$) *δ1.45 (d, J=7 Hz, 6H), 3.39* (heptet, J=7Hz, 1H), 8.07 (s, 1H), 10.00 (s, 1H). Mass spectrum: $(M+H)^+$156.

B. (E)-Ethyl 3-(2-Isopropyl-4-thiazolyl)propenoate.

A slurry of 60% NaH (18 mmol) in mineral oil was washed with hexane, decante under N_2 atmosphere, and diluted with 25 ml of THF. The resulting mixture was cooled to 0° C., treated portionwise with 3.24 ml (16.4 mmol) of triethylphosphonoacetate. After addition, the solution was stirred for 10 min, treated with 1.37 g (8.84 mmol) of 2-isopropylthiazole-4-carboxaldehyde in 25 ml of THF, allowed to warm to ambient temperature for 25 min, and quenched with 100 ml of saturated aqueous NH_4Cl. The mixture was extracted with three 100 ml portions of ethyl acetate, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography of the residue using 5–10% ethyl acetate in hexane provided 1.61 g (81%) of the desired compound, R_f 0.64 (20% ethyl acetate in hexane). ^1H NMR ($CDCl_3$) δ1.33 (t, J=7 Hz, 3H), 1.42 (d, J=7 Hz, 6H), 3.32 (heptet, J=7 Hz, 1H), 4.26 (q, J=7 Hz, 2H), 6.75 (d, J=15 Hz, 1H), 7.29 (s, 1H), 7.57 (d, J=15 Hz, 1H).

C. Methyl 3-(2-Isopropyl-4-thiazolyl)propanoate.

A solution of 225 mg (1 mmol) of (E)-ethyl 3-(2-isopropyl-4-thiazolyl)-propenoate in 10 ml of freshly distilled (from calcium hydride) methanol and 1 ml of dry THF was treated with 49 mg (2 mmol) of magnesium turnings. The mixture was stirred for 20 min, during which the magnesium was consumed. The resulting solution was poured over cold aqueous HCl, basified to pH 8 with $NaHCO_3$, extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. Silica gel chromatography using 10% ethyl acetate in hexane provided a mixture of the desired compound and methyl 3-(2-isopropyl-4-thiazolinyl)propanoate.

D. 3-(2-Isopropyl-4-thiazolyl))propanoic Acid.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 31C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-(tert-Butyloxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-(tert-butyloxycarbonyl)-L-valine provided, after purification by silica gel chromatography, the desired compound.

F. (2S,3S,5S)-5-(N-(Valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 0.1 mmol of the resultant compound of Example 31E was treated with 10 ml of 4N HCl in dioxane, stirred at 0° C. for 1 h, concentrated in vacuo, partitioned between chloroform and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated to provide the crude desired compound.

G. (2S,3S,5S)-5-(N-(N-(3-(2-Isopropyl-4-thiazolyl)propanoyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 31D and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 31F provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 32

A. Thiazole-5-carboxaldehyde.

Using the procedure of Example 16A but replacing ethyl 2-isopropyl-4-thiazole carboxylate with ethyl thiazole-5-carboxylate provided the desired compound.

B. 5-(1-Hydroxyethyl)thiazole.

Using the procedure of Example 16B but replacing the resultant compound of Example 16A with the resultant compound of Example 32A provided the desired compound.

C. (1-(5-Thiazolyl)ethyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L but replacing 5-(hydroxymethyl)-thiazole with the resultant compound of Example 32B provided the desired compound.

D. (2S,3S,5S)-5-Amino-2-(N-(1-(5-thiazolyl)ethoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 19F but replacing ((5-oxazolyl)methyl)-(4-nitrophenyl)carbonate with (1-(5-thiazolyl)ethyl)-(4-nitrophenyl)carbonate provided, after purification by silica gel chromatography, the desired compound.

E. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)Valinyl)amino)-2-(N-(1-(5-thiazolyl)ethoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 32D provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 33

A. ((5-Isothiazolyl)methyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L but replacing 5-(hydroxymethyl)-thiazole with 5-(hydroxymethyl)isothiazole (Bennett, et. al., *J. Chem. Soc.*, 3834 (1965)) provided the desired compound.

B. (2S,3S,5S)-5-Amino-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 19F but replacing ((5-oxazolyl)methyl)-(4-nitrophenyl)carbonate with ((5-isothiazolyl)methyl)-(4nitrophenyl)carbonate provided, after puri-

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fication by silica gel chromatography, the desired compound.

C. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-16-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 33B provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 34

A. (2S,3R,4R,5S)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1F but replacing the resultant compound of Example 1E with (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)-carbonyl)amino)- 3,4-dihydroxy-1,6-diphenylhexane provided the crude desired compound mixed with benzyl alcohol in 92% yield. Purification of a sample was achieved by silica gel chromatography using 2% isopropylamine in chloroform. ^{1}H NMR ($CDCl_3$) δ2.71 (dd, J=13, 9 Hz, 2H), 2.92 (dd, J=13, 5 Hz, 2H), 3.03 (dd, J=9, 5Hz, 2H), 3.68 (s, 2H), 7.15–7.35 (m, 10H). Mass spectrum: $(M+H)^+$301.

B, (2S,3R,4, R,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1M but replacing (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane with (2S,3R,4R,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography, the desired compound.

C. (2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 34B provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 35

A. (2S,3S,4S,5S)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1F but replacing the resultant compound of Example 1E with (2S,3S,4S,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino-3,4-dihydroxy-1,6-diphenylhexane provided the desired compound. ^{1}H NMR ($CDCl_3$) δ2.63 (dd, J=14, 11 Hz, 2H), 2.85 (dd, J=14, 4 Hz, 2H), 3.60 (dt, J=11,4 Hz, 2H), 3.92 (d, J=3Hz, 2H), 7.2–7.4 (m, 10H). Mass spectrum: $(M+H)^+$=301.

B. (2S,3S,4S,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1M but replacing (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane with (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography, the desired compound.

C. (2S,3S,4S,5S,)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 35B provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 36

A. (4S,5S, 1'R,2'S)-5-(1-Acetoxy-2-(N-((((benzyl)oxy)carbonyl)amino))-3-phenylpropyl)-4-benzyl-oxazolidin-2-one.

A suspension of 5.02 g (8.80 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane in 400 ml of acetonitrile was treated dropwise with 3 ml (20 mmol) of α-acetoxyisobutyryl bromide. The resulting solution was stirred under N_2 atmosphere at ambient temperature for 2 h, filtered to remove traces of solid starting material, quenched cautiously with 100 ml of aqueous $NaHCO_3$, and concentrated in vacuo to a volume of 100 ml. The resulting mixture was extracted with two 100 ml portions of dichloromethane, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using first 10% then 25% ethyl acetate in dichloromethane to provide 3.15 g (71%) of the desired compound as a white foam. ^{1}H NMR ($CDCl_3$) δ2.09 (s, 3H), 2.53 (br t, J=12 Hz, 1H), 2.72 (dd, J=13, 3 Hz, 1H), 2.83 (dd, J=14, 8 Hz, 1H), 2.95 (dd, J=14, 7 Hz, 1H), 3.95 (m, 1H), 4.45 (m, 1H), 4.8 (m, 2H), 5.0–5.1 (m, 3H), 5.29 (dd, J=9, 3 Hz, 1H), 7.0–7.4 (m, 10H). Mass spectrum: $(M+NH_4)^+$=520.

B. (2S,3R,4S,5S)-2,5-Diamino-3,4,dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1F but replacing the resultant compound of Example 1E with (4S,5S,1'R,2'S)-5-(1-acetoxy-2-(N-(benzyloxycarbonylamino))-3-phenylpropyl)-4-benzyl-oxazolidin-2-one provided the desired compound mixed with benzyl alcohol. Purification of a small portion by silica gel chromatography using 5% methanol/2% isopropylamine in chloroform provided the pure desired compound., m.p. 115°–119° C. ^{1}H NMR ($CDCl_3$) δ2.46 (dd, J=14, 9 Hz, 1H), 2.61 (dd, J=14, 11 Hz, 1H), 3.02 (td, J=9, 3 Hz, 1H), 3.19 (dd, J=14, 4Hz, 1H), 3.35–3.4 (m, 2H),3.51 (t, J=9 Hz, 1H), 3.76 (dd, J=9, 3 Hz, 1H), 7.2–7.4 (m, 10H).

C. (2S,3R,4S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

A solution of 0.133 mmol of (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane and 0.147 mmol of ((5-thiazolyl)methyl)-(4-nitrophenyl)-carbonate in 10 ml of tetrahydrofuran was stirred at ambient temperature for 16 h. The resulting solution was diluted with 50 ml of chloroform, washed with several portions of 3N aqueous NaOH, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography of the residue provided the desired compound.

D.(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 36C provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 37

A. (2S,3R,4S,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane

provided, after purification by silica gel chromatography, the desired compound.

B. (2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 36C but replacing (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane with the resultant compound of Example 37A provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 38

A. 5-(Hydroxymethyl)-3-isopropylisothiazole.

The desired compound was prepared from the resultant compound of Example 29A using the procedure of Lucchesini, et. al. (Heterocycles, 29, 97 (1989)).

B. N-((3-Isopropyl-5-isothiazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 5-(hydroxymethyl)-3-isopropylisothiazole provided the desired compound.

C. N-((3-Isopropyl-5-isothiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 38B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isothiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 38C provided the desired compound.

EXAMPLE 39

(2S,3 8,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 20 mg (80%) of the desired compound, R_f 0.23, (4% methanol in chloroform). Mass spectrum: $(M+H)^+$=735. Anal. Calcd for $C_{38}H_{50}N_6O_5S_2.2H_2O$: C, 59.20;H, 7.06; N, 10.90. Found: C, 59.13;H, 6.42; N, 10.82.

EXAMPLE 40

Following the procedures of the above Examples, the following compounds can be prepared.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl-)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S, 3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4ox-azolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)-5-(N-((5-isothiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

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(2S,3R,4R,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N -((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4 R,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl-)methoxycarbonyl)alaninyl)amino)-2-(N-((5thiazolyl-)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-*thiazolyl)methoxycarbonyl)amino*)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxy*carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycar*bonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazoyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-*isothiazolyl)methoxycarbonyl)amino*)-3,4-*dihydroxy*-1,6-diphenylhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl)ethyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl) methoxycarbonyl)amino)1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)m*ethyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-ox*azolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl-)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl) valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl) amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl-)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl-)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl) methyl) amino)-carbonyl) valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

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(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Meth yl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl-)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

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(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

EXAMPLE 41

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedures of Example 18A - F, but replacing *isobutyramide with propionamide, provided the desired* compound. ^{1}H NMR (DMSO-d_6H) δ0.74 (d, J=6 Hz, 6H), 1.19 (t, J=7 Hz, 3H), 1.38–1.51 (m, 2H), 1.80–1.94 (m, 1H), 2.54–2.74 (m, 5H), 2.83 (s, 3H), 3.53–3.63 (m, 1H), 3.82 (br q, 1H), 3.92 (t, J=8 Hz, 1H), 4.13, (m, 1H), 4.26 (AA', 2H), 4.63 (d, J=6 Hz, 1H), 5.13 (AA', 2H), 5.90 (d, J=9 Hz, 1H), 6.89 (d, J=9 Hz, 1H), 7.07–7.25 (m, 12H), 7.68 (d, J=8.7 Hz, 1H), 7.77 (s, 1H), 7.86 (s, 1H), 9.05 (s, 1H). Mass spectrum: $(M+H)^+$=691. Anal. Calcd for $C_{36}H_{46}N_6O_6S.0.3H_2O$: C, 62.10;H, 6.75; N, 12.07. Found: C, 62.42;H, 6.68; N, 11.69.

EXAMPLE 42

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methyl-4-oxazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedures of Example 18A - F, but replacing isobutyramide with acetamide, provided the desired compound. Mass spectrum: $(M+H)^+$=677.

EXAMPLE 43

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-1-phenyl-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-oxazolyl)-3-hydroxyhexane.

Using the procedures of Example 8C–8K, but replacing 5-chloromethylthiazole hydrochloride with 5-chloromethyloxazole hydrochloride provided the desired compound.

EXAMPLE 44

A. 2-Ethylbutanamide.

A solution of 21.5 ml of oxalyl chloride (2M, 43 mmol) in dichloromethane was treated with 5.0 g (43 mmol) of 2-ethylbutyric acid followed by 0.1 ml of dimethylformamide. The resulting solution was stirred at ambient temperature for 1 h, during which gas evolution was observed. After the termination of gas evolution, the solution was concentrated in vacuo to give crude 2-ethylbutyryl chloride. The crude acid chloride was taken up in 200 ml of acetone and treated with 4.6 g (60 mmol) of ammonium acetate. The resulting mixture was stirred at ambient temperature for 1 h, filtered, and concentrated in vacuo to provide 4.2 g (85%) of the desired compound. ^{1}H NMR (d_6-DMSO) δ0.80 (t, J=7 Hz, 6H), 1.32 (m, 2H), 1.45 (m, 2H), 1.93 (m, 1H), 6.71 (br, 1H), 7.23 (br, 1H).

B. 2-Ethylbutane-thioamide.

Using the procedure of Example 1O, but replacing isobutyramide with 2-ethylbutanamide provided 1.6 g (25%) of the crude desired compound.

C. 4-(Chloromethyl)-2-(3-pentyl)thiazole hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with 2-ethylbutane-thioamide provided the crude desired compound as a yellow oil.

D. 2-(3-Pentyl)-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-(isopropylthiazole hydrochloride with 4-(chloromethyl)-2-(3-pentyl)thiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 5% methanol in chloroform, 1.5 g (71%) of the desired compound.

E. N-((N-Methyl-N-((2-(3-pentyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-(3-pentyl)-4-(((N-methyl)amino)methyl)thiazole provided, after purification by silica gel chromatography using 3% methanol in chloroform as an eluent, 1.6 g (61%) of the desired compound.

F. N-((N-Methyl-N-(2-(3-pentyl)-4-thiazolyl)methyl)amino/carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 44E provided 0.4 g (52%) of the desired compound.

G. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-pentyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-(3-pentyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 99:1 $CHCl_3$:CH_3OH, 72 mg (41%) of the desired compound (R_f 0.3, 95:5 $CHCl_3$:CH_3OH) as a solid, mp 64°–66° C. Mass spectrum: $(M+H)^+$=749. Anal. calcd for $C_{39}H_{52}N_6O_5S_2$: C, 62.54;H, 7.00; N, 11.22;S, 8.56. Found: C, 62.67;H, 6.85; N, 11.06;S, 8.45.

EXAMPLE 45

A. (((2-Isopropyl)-5-thiazolyl)methyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L, but replacing 5-(hydroxymethyl) thiazole with 5-(hydroxymethyl)-2-isopropylthiazole provided, after purification by silica gel chromatography using 1% MeOH/$CHCl_3$, 0.7 g (78%) of the desired compound, Rf=0.8 (5% MeOH/$CHCl_3$H).

B. (2S,3S,5S)-5-Amino-2-(N-(((2-isopropyl)-5-thiazolyl-)*methoxycarbonyl)amino*)-1,6-*diphenyl*,3-*hydroxyhexane*.

Using the procedure of Example 1N, but replacing ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate with (((2-isopropyl)-5-thiazolyl)methyl)-(4-nitrophenyl)carbonate provided, after purification by silica gel chromatography using *99:2:1 $CHCl_3$:isopropylamine:CH_3OH, Rf=0.2 , 0.17* g (18%) of the desired compound, (1% isopropylamine in $CHCl_3$H). ^{1}H NMR (d_6-DMSO) δ1.38 (d, J=7 Hz, 6H), 1.43 (m, 1H), 1.64 (m, 1H), 2.46 (dd, J=14, 8 Hz, 1H), 2.63 (m, 2H), 2.80 (dd, J=14, 5 Hz, 1H), 2.94 (m, 1H), 3.21 (m, 1H), *3.64 (m, 2H), 5.09 (AA', 2H), 6.98* (d, J=9 Hz, 1H), 7.1–7.3 (m, 10H), 7.60 (s, 1H). Mass spectrum: $(M+H)^+$=468.

C. (2S,3S,5S)-5-(N-(N-((N-Methyl-N,((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-(((2-isopropyl)-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing (2S, 3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-(((2-isopropyl)-5-*thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl*-3-hydroxyhexane provided, after purification by silica gel chromatography using 99:1 $CHCl_3$:CH_3OH, 50 mg (61%) of the desired compound (R_f 0.28, 95:5 $CHCl_3$:CH_3OH) as a solid, mp 64°–66° C. Mass spectrum: $(M+H)^+$=764. Anal. *calcd for $C_{40}H_{54}N_6O_5S_2$: C, 62.97;H, 7.13; N, 11.01. Found:* C, 62.91; H, 7.11; N, 10.81.

EXAMPLE 46

A. 1-(Aminothiocarbonyl)pyrrolidine.

A solution of 1.0 g (14 mmol) of pyrrolidine in 70 ml of tetrahydrofuran was treated dropwise with 2.0 ml of trimethylsilylisocyanate. The resulting solution was stirred at ambient temperature for two days, and concentrated in vacuo. Purification of the residue by silica gel chromatography *using 4% methanol in chloroform provided the* desired compound (R_f 0.5, 10% methanol in chloroform).

B. 4-(Chloromethyl)-2-(1-pyrrolidinyl)thiazole hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide *with 1-(aminothiocarbonyl)pyrroli*dine provided the crude desired compound.

C. 2-(1-Pyrrolidinyl)-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with *4-(chloromethyl)-2-(1-pyrrolidinyl)thiazole hydrochloride* provided, after purification of the residue by silica gel chromatography using 2% isopropylamine/2% methanol in chloroform, 0.89 g (30%) of the desired compound. ^{1}H NMR ($CDCl_3$H) δ2.02 (m, 4H), 2.61 (s, 3H), 3.44 (m, 4H), 3.90 (s, 2H), 4.84 (br, 1H), 6.51 (s, 1H). Mass *spectrum*: $(M+H)^+$=198.

D. N-((N-Methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-(1-pyrrolidinyl)-4-(((N-methyl)amino)methyl)thiazole provided, after purification by silica gel chromatography using 4% methanol in chloroform as an eluent, 0.63 g (39%) of the desired compound. ^{1}H NMR ($CDCl_3$H) δ0.96 (t, J=7 Hz, 3H), 0.98 (t, J=7 Hz, 3H), 2.04 (m, 4H), 2.14 (heptet, J=7 Hz, 1H), 2.97 (s, 3H), 3.45 (m, 4H), 3.71 (s, 3H), 4.10 (m, 1H), 4.33 (dd, J=9, 6 Hz, 1H), 4.42 (br d, J=16 Hz, 1H), 6.26 (s, 1H), 6.45 (br, 1H). Mass spectrum: $(M+H)^+$=355.

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E. N-((N-Methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 46D provided 0.24 g (96%) of the desired compound.

F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl) amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 2% methanol in chloroform, the desired compound (R_f 0.29, 4% methanol in chloroform). Mass spectrum: $(M+H)^+$=748.

EXAMPLE 47

A. Ethyl 2-(2-Isopropyl-4-thiazolyl)acetate.

Using the procedure of Example 1P, but replacing 1,3-dichloroacetone with ethyl 4-chloroacetoacetate provided, after purification by silica gel chromatography using $CHCl_3$, the desired compound in 34% yield. ^1H NMR (d_6-DMSO) δ1.18 (t, J=7 Hz, 3H), 1.30 (d, J=7 Hz, 6H), 3.24 (heptet, J=7 Hz, 1H), 3.76 (s, 2H), 4.09 (q, J=7 Hz, 2H), 7.31 (s, 1H). Mass spectrum: $(M+H)^+$=214.

B. 4-(2-Hydroxyethyl-2-isopropylthiazole.

Using the procedure of Example 5B, but replacing ethyl 2-isopropyl-4-thiazolecarboxylate with ethyl 2-(2-isopropyl-4-thiazolyl)acetate provided, after purification of the residue by silica gel chromatography using 2% methanol in chloroform, 0.9 g (47%) of the desired compound. ^1H NMR ($CDCl_3H$) δ1.40 (d, J=7 Hz, 6H), 2.95 (t, J=6 Hz, 2H), 3.30 (heptet, J=7 Hz, 1H), 3.92 (t, J=6 Hz, 2H), 6.83 (s, 1H). Mass spectrum: $(M+H)^+$=172.

C. N-((2-(2-Isopropyl-4-thiazolyl)ethoxy)carbonyl)valine Methyl Ester.

Using the procedure of Example 5D, but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 4-(2-hydroxyethyl)-2-isopropylthiazole provided, after purification by silica gel chromatography using 3% methanol in chloroform as an eluent, 0.8 g (52%) of the desired compound.

D. N-((2-(2-Isopropyl-4-thiazolyl)ethoxy)carbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 47C provided 0.17 g (82%) of the desired compound.

E. (2S,3S,5S)-5-(N-(N,((2,-(2-Isopropyl-4-thiazolyl)ethoxy)carbonyl)valinyl)amino)-2-(N-((5-thiazolylmethoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((2-(2-isopropyl-4-thiazolyl)ethoxy)carbonyl)valine provided, after purification by silica gel chromatography using 99:1 $CHCl_3$: CH_3OH, 80 mg (47%) of the desired compound (R_f 0.3, 95:5 $CHCl_3$: CH_3OH) as a solid, mp 146°–147° C. Mass spectrum: $(M+H)^+$=722. Anal. calcd for $C_{37}H_{47}N_5O_6S_2$:C, 61.56; H, 6.56; N, 9.70. Found: C, 61.24;H, 6.48; N, 9.53.

EXAMPLE 48

E. (2S,3S,5S)-2-(N-(N-((2-(2-Isopropyl-4-thiazolyl)ethoxy)carbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((2-(2-isopropyl-4-thiazolyl)ethoxy)carbonyl)valine and replacing (2S,3S,5S)-5-amino- 2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after purification by silica gel chromatography using 99:1 $CHCl_3$: CH_3OH, 50 mg (30%) of the desired compound (R_f 0.3, 95:5 $CHCl_3$: CH_3OH) as a solid, mp 159°–160° C. Mass spectrum: $(M+H)^+$=722 HRMS. Exact mass calcd for $C_{37}H_{47}N_5O_6S_2$: 722.3046. Found: 722.3036.

EXAMPLE 49

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-(2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-isoxazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after purification by silica gel chromatography using 2% methanol in chloroform, the desired compound (R_f 0.30, 4% methanol in chloroform).

EXAMPLE 50

A. (2S,3S,5S)-5-(N-(N-(t-Butyloxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-(t-butyloxycarbonyl)valine provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound (R_f 0.31, 4% methanol in chloroform).

B. (2S,3S,5S)-5-(N-(Valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane Hydrochloride.

To 135 mg (0.27 mmol) of (2S,3S,5S)-5-(N-(N-(t-butyloxycarbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane was added 8 ml of 4M HCl in dioxane. The resulting mixture was stirred at ambient temperature for 1 h and concentrated in vacuo to provide the crude desired compound.

G. 2-(2-Isopropyl-4-thiazolyl)acetic Acid.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 47A provided 0.24 g (55%) of the desired compound. ^1H NMR ($CDCl_3H$) δ1.93 (d, J=7 Hz, 6H), 3.35 (heptet, J=7 Hz, 1H), 3.85 (s, 2H), 7.00 (s, 1H) Mass spectrum: $(M+H)^+$=186.

D. (2S,3S,5S)-5-(N-(N-((2-Isopropyl,4-thiazolyl)acetyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with 2-(2-isopropyl-4-thiazolyl)acetic acid provided, after purification by silica gel chromatography using 99:1 $CHCl_3$: CH_3OH, 120 mg (80%) of the desired compound (R_f 0.6, 95:5 $CHCl_3$: CH_3OH) as a solid, mp

153°–155° C. Mass spectrum: $(M+H)^+$=692. Anal. calcd for $C_{36}H_{45}N_5O_5S_2.0.5H_2O$: C, 61.69; H, 6.62; N, 9.99; S, 9.15. Found: C, 61.92; H, 6.49; N, 10.06; S, 8.81.

EXAMPLE 51

A. Cyclopropanecarboxamide.

Using the procedure of Example 44A but replacing 2-ethylbutyric acid with cyclopropanecarboxylic acid provided 6.4 g (50%) of the crude desired compound.

B. Cyclopropanethiocarboxamide.

Using the procedure of Example 1O, but replacing isobutyramide with cyclopropanecarboxamide provided 7.2 g (96%) of the crude desired compound.

C. 4-(Chloromethyl)-2-cyclopropylthiazole-hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with cyclopropanethiocarboxamide provided the crude desired compound as a yellow oil.

D. 2-(Cyclopropyl-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-cyclopropylthiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 5% methanol in chloroform, 0.5 g (25%) of the desired compound.

E. N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-cyclopropyl-4-(((N-methyl)amino)methyl)thiazole provided, after purification by silica gel chromatography using 1% methanol/chloroform as an eluent, 0.4 g (48%) of the desired compound.

F. N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 51E provided 0.16 g (70%) of the desired compound.

G. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane,

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 90 mg (54%) of the desired compound (R_f 0.2, 95:5 $CHCl_3CH_3OH$) as a solid, mp 70°–71° C. Mass spectrum: $(M+H)^+$=719. Anal. calcd for $C_{37}H_{46}N_6O_5S_2$: C, 61.82; H, 6.45; N, 11.69. Found: C, 61.50; H, 6.46; N, 11.41.

EXAMPLE 52

A. Cyclobutanecarboxamide.

Using the procedure of Example 44A but replacing 2-ethylbutyric acid with cyclobutanecarboxylic acid provided 7.5 g (76%) of the crude desired compound.

B. Cyclobutanethiocarboxamide.

Using the procedure of Example 1O, but replacing isobutyramide with cyclobutanecarboxamide provided 6.9 g (80%) of the crude desired compound.

C. 4-(Chloromethyl)-2-cyclobutylthiazole hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with cyclobutanethiocarboxamide provided the crude desired compound as a yellow oil.

D. 2-Cyclobutyl-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-cyclobutylthiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 5% methanol in chloroform, 1.0 g (36%) of the desired compound.

E. N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-cyclobutyl-4-(((N-methyl)amino)methyl)-thiazole provided, after purification by silica gel chromatography using 1% methanol in chloroform as an eluent, 0.54 g (31%) of the desired compound. Mass spectrum: $(M+H)^+$=340.

F. N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 52E provided 0.2 g (42%) of the desired compound.

G. (2S,3S,5S)-5-(N-(N-((N-Methyl-N,((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl))valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl,3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 110 mg (64%) of the desired compound (R_f 0.17, 95:5 CH_2Cl_2: CH_3OH) as a solid, mp 74°–76° C. Mass spectrum: $(M+H)^+$=733. Anal. calcd for $C_{38}H_{48}N_6O_5S_2$: C, 62.27; H, 6.60; N, 11.47; S, 8.75. Found, C, 62.02; H, 6.73; N, 11.33; S, 8.51.

EXAMPLE 53

A. Propanethioamide.

Using the procedure of Example 1O, but replacing isobutyramide with propionamide provided 4.6 g (38%) of the crude desired compound. H NMR ($CDCl_3H$) δ1.33 (t, J=7 Hz, 3H), 2.70 (q, J=7 Hz, 2H), 6.9 (br, 1H), 7.6 (br, 1H). Mass spectrum: $(M+H)^+$=90.

B. 4-(Chloromethyl)-2-ethylthiazole hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with propanethioamide provided the crude desired compound as a yellow oil.

C. 2-Ethyl-(((N-methyl)amino)methyl)thiazole. Using the procedure of Example 1Q, but replacing 4-(chloromethyl)--isopropylthiazole hydrochloride with 4-(chloromethyl)-2-ethylthiazole hydrochloride provided 1.0 g (52%) of the desired compound.

D. N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-ethyl-4-(((N-methyl)amino)methyl)thiazole provided, after purification by silica gel chromatography using 1% methanol in chloroform as an eluent, 0.7 g (35%) of the desired compound.

E. N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 53D provided 0.28 g (43%) of the desired compound.

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F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-ethyl-4-thiazolyl-)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 60 mg (40%) of the desired compound (R_f 0.14, 95:5 CH_2Cl_2: CH_3OH) as a solid, mp 70°–71° C. Mass spectrum: $(M+H)^+$=707. Anal. calcd for $C_{36}N_{46}N_6O_5S_2.H_2O$:C, 59.65; H, 6.67; N, 11.59. Found: C, 59.64; H, 6.59; N, 11.88.

EXAMPLE 54

A. 2-Isopropyl-4-(((N-(1-propyl))amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 40% aqueous methylamine with 1-aminopropane provided the crude desired compound. ^1H NMR ($CDCl_3H$) δ0.94 (t, J=7 Hz, 3H), 1.39 (d, J=7 Hz, 6H), 1.54(sextet, J=7 Hz, 2H), 2.62 (t, J=7 Hz, 2H), 3.30 (heptet, J=7 Hz, 1H), 3.87 (d, J=1 Hz, 2H), 6.93 (s, 1H). Mass spectrum: $(M+H)^+$=199.

B. N-((N-(1-Propyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-(((N-(1-propyl))amino)methyl)thiazole provided, after silica gel chromatography using 1% methanol in chloroform as an eluent, 1.55 g (63%) of the desired compound. ^1H NMR ($CDCl_3$) δ0.86 (t, J=7 Hz, 3H), 1.38 (d, J=7 Hz. 6H), 1.41 (d, J=7 Hz, 6H), 1.56 (m, 1H), 1.57 (sextet, J=7 Hz, 2H), 3.27 (heptet, J=7 Hz, 1H), 3.29 (t, J=7 Hz, 2H), 3.71 (s, 3H), 4.45 (m, 3H) 6.31 (br, 1H), 6.98 (s, 1H). Mass spectrum: $(M+H)^+$=328.

C. N-((N-(1-Propyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 54B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-(1-Propyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-(1-propyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using 1% methanol in chloroform, 60 mg (44%) of the desired compound (R_f 0.3, 95:5 $CHCl_3$: CH_3OH) as a solid, mp 62°–64° C. Mass spectrum: $(M+H)^+$=721. Anal. calcd for $C_{37}H_{48}N_6O_5S_2.0.5H_2$: C, 60.88; H, 6.77; N, 11.51. Found: C, 60.66; H, 6.95; N, 11.45

EXAMPLE 55

A. 2-Isopropyl-4-((N-(isobutyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 40% aqueous methylamine with isobutylamine provided the crude desired compound. Mass spectrum: $(M+H)^+$=213.

B. N-((N-(isobutyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-(((N-(isobutyl))amino)-methyl)thiazole provided, after silica gel chromatography using 1% methanol in chloroform as an eluent, 0.7 g (41%) of the desired compound. ^1H NMR (DMSO-d_6H) δ0.78 (d, J=7 Hz, 3H), 0.79 (d, J=7 Hz, 3H), 1.30 (m, 12H), 1.89 (m, 2H), 3.05 (d, J=8 Hz, 2H), 3.22 (m, 1H), 3.58 (s, 3H), 4.13 (m, 1H), 4.44 (AA', 2H), 6.87 (br d, 1H), 7.23 (s, 1H). Mass spectrum: $(M+H)^+$=3.42.

C. N-((N-(isobutyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl))-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 55B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-(Isobutyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-(isobutyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using 1% methanol in chloroform, 70 mg (50%) of the desired compound (R_f 0.3, 5% methanol in chloroform) as a solid, mp 60°–61° C. Mass spectrum: $(M+H)^+$=735. Anal. calcd for $C_{38}H_{50}N_6O_5S_2$: C, 62.10; H, 6.86; N, 11.43; S, 8.72. Found: C, 61.74; H, 7.16; N, 11.36; S, 8.48.

EXAMPLE 56

A. N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alanine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-(((N-methyl)amino)methyl)-oxazole and replacing N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester with N-(((4-nitrophenyl)oxy)carbonyl)-L-alanine methyl ester provided the desired compound in 66 % yield. ^1H NMR ($CDCl_3H$) δ1.32 (d, 6H), 1.42 (d, 3H), 2.96 (s, 3H), 3.05 (m, 1H), 3.75 (s, 3H), 4.30 (s, 2H), 4.47 (m, 1H), 5.80 (br d, 1H), 7.46 (s, 1H). Mass spectrum: $(M+H)^+$=284.

B. N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alanine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 56A provided the desired compound.

C. (2S,3S,5S)-5-(N,(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alanine provided, after silica gel chromatography using 92:8 CH_2Cl_2: CH_3OH, the desired compound (R_f 0.49, 92:8 CH_2Cl_2: CH_3OH) in 75% yield. Mass spectrum: $(M+H)^+$=677.

EXAMPLE 57

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alaninyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alanine and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-isoxazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 92:8 CH_2Cl_2: CH_3OH, the desired

compound (R_f 0.48, 92:8 CH_2Cl_2: CH_3OH)in 64% yield. ^1H NMR (DMSO-d_6) δ1.08 (d, 3H), 1.24 (d, 6H), 1.50 (m, 2H), 2.82 (s, 3H), 3.0(m, 1H), 4.25 (s, 2H), 4.60 (d, 1H), 5.05 (s, 2H), 6.20 (br d, 1H), 6.32 (d, 1H), 7.20 (m, 11H), 7.50 (br d, 1H), 7.78 (s, 1H), 8.51 (d, 1H). Mass spectrum: $(M+H)^+$ =661.

EXAMPLE 58

A. Cyclopentanecarboxamide.

Using the procedure of Example 44A but replacing 2-ethylbutyric acid with cyclopentanecarboxylic acid provided 2.6 g (100%) of the crude desired compound.

B. Cyclopentanethiocarboxamide.

Using the procedure of Example 1O, but replacing isobutyramide with cyclopentanecarboxamide provided 2.4 g (83%) of the crude desired compound.

C. 4-(Chloromethyl)-2-cyclopentylthiazole hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with cyclopentanethiocarboxamide provided the crude desired compound as a yellow oil.

D. 2- Cyclopentyl-4-((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-cyclopentylthiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 3% methanol in chloroform, 0.83 g (43%) of the desired compound.

E. N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)-methyl)thiazole with 2-cyclopentyl-4-(((N-methyl)amino)methyl)-thiazole provided, after purification by silica gel chromatography using 1% methanol in chloroform as an eluent, 0.77 g (51%) of the desired compound. ^1H NMR ($CDCl_3$) δ0.93 (d, J=7 Hz, 3H), 0.97 (d, J=7 Hz, 3H), 1.6–1.9 (m, 6H), 2.2 (m, 3H), 2.99 (s, 3H), 3.40 (m, 1H), 3.71 (s, 3H), 4.37 (dd, J=9, 5 Hz, 1H), 4.45 (AA', 2H), 5.99 (br d, 1H) 6.95 (s, 1H). Mass spectrum: $(M+H)^+$=354.

F. N-((N-Methyl-N-(2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 58E provided 0.64 g (87%) of the desired compound.

G.(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 50 mg (36%) of the desired compound (R_f 0.40, 5% methanol in chloroform) as a solid, mp 70°–71° C. Mass spectrum: $(M+H)^+$=747. Anal. calcd for $C_{39}H_{50}N_6O_5S_2$: C, 62.71; H, 6.75; N, 11.25. Found: C, 63.16; H, 6.80; N, 10.84.

EXAMPLE 59

A. 3-Methylbutanamide.

Using the procedure of Example 44A but replacing 2-ethylbutyric acid with 3-methylbutyric acid provided 4.2 g (100%) of the crude desired compound.

B. 3-Methylpropanethiocarboxamide.

Using the procedure of Example 1O, but replacing isobutyramide with 3-methylbutanamide provided the crude desired compound.

C. 4-(Chloromethyl)-2-isobutylthiazole hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with 3-methylpropanethiocarboxamide provided the crude desired compound as a yellow oil.

D. 2-Isobutyl-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-isobutylthiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 10% methanol in chloroform, 0.61 g (31%) of the desired compound.

E. N-((N-Methyl-N-((2-isobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isobutyl-4-(((N-methyl)amino)methyl)thiazole provided, after purification by silica gel chromatography using 1% methanon in chloroform as an eluent, 0.40 g (32%) of the desired compound. Mass spectrum: $(M+H)^+$=342.

F. N-((N-Methyl-N-((2-isobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 59E provided 0.13 g (70%) of the desired compound.

G. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isobutyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5 -thiazolyl)methoxycarbonyl))amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 50 mg (33%) of the desired compound (R_f 0.65, 10% methanol in chloroform). Mass spectrum: $(M+H)^+$=735.

EXAMPLE 60

A. 2- Cyclopentyl-4-(((N-ethyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-cyclopentylthiazole hydrochloride and replacing 40% aqueous methylamine with 70% aqueous ethylamine provided, after purification of the residue by silica gel chromatography using 5% methanol in chloroform, 1.08 g (50%) of the desired compound.

B. N-((N-Ethyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-cyclopentyl-4-(((N-ethyl)amino)methyl)-thiazole provided, after purification by silica gel chromatography using 1% methanol in chloroform as an eluent, 0.40 g (46%) of the desired compound. ^1H NMR (DMSO-d_6H), δ1.00 (t, J=7 Hz, 3H), 1.29 (d, J=7 Hz, 3H), 1.6–1.8 (m, 9H), 2.1 (m, 3H), 3.27 (m, 2H), 3.37 (m, 1H), 3.60 (s, 3H), 4.17 (pentet, J=7 Hz, 1H), 4.41 (AA', 2H), 6.80 (d, J=7 Hz, 1H), 7.20 (s, 1H). Mass spectrum: $(M+H)^+$=340.

C. N-((N-Ethyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant com-

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pound of Example 60B provided 0.13 g (69%) of the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Ethyl-N-[(2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl))amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-ethyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1.5% methanol in chloroform, 50 mg (34%) of the desired compound (R_f 0.63, 10% methanol in chloroform) as a solid, mp 67°–69°

C. Mass spectrum: $(M+H)^+$=733. Anal. calcd for $C_{38}H_{48}N_6O_5S_2$: C, 62.27; H, 6.60; N, 11.47. Found: C, 62.02; H, 6.74; N, 10.98.

EXAMPLE 61

A. 2-Isopropyl-4-(2-((N-methyl)amino)ethyl)thiazole.

A solution of 2.0 g (12 mmol) of 2-isopropyl-4-(hydroxyethyl)thiazole in 50 ml of tetrahydrofuran was treated with 1.34 g (12 mmol) of methanesulfonyl chloride. The resulting solution was treated dropwise with 3.4 ml (24 mmol) of triethylamine and stirred at ambient temperature for 1 h. A portion (25 ml) of the resulting solution was added to 50 ml of aqueous ethylamine (70% in H_2O) with rapid stirring. After addition, the mixture was heated to reflux for 2 h, allowed to cool, diluted with ethyl acetate, washed with aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO_4, and concentrated in vacuo to provide the crude desired compound. Purification of the residue by silica gel chromatography using 5% methanol in chloroform, 0.52 g (48%) of the desired compound. ^1H NMR ($CDCl_3$) δ1.38 (d, J=7 Hz, 3H), 2.46 (s, 3H), 2.93 (s, 4H), 3.30 (heptet, J=7 Hz, 1H) 6.79 (s, 1H). Mass spectrum: $(M+H)^+$=185.

B. N-((N-Methyl-N-(2-(2-isopropyl-4-thiazolyl)ethyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-(2-((N-methyl)amino)ethyl)-thiazole provided, after purification by silica gel chromatography using 1% methanol in chloroform as an eluent, 0.16 g (35%) of the desired compound. ^1H NMR ($CDCl_3H$) δ0.91 (d, J=7 Hz, 3H), 0.98 (d, J=7 Hz, 3H), 1.48 (d, J=7 Hz, 3H), 1.49 (d, J=7 Hz, 3H), 2.11 (heptet of doublets, J=7, 5 Hz, 1H), 2.85 (s, 3H), 2.99 (t, J=7 Hz, 2H), 3.30 (heptet, J=7 Hz, 1H), 3.63 (t, J=7 Hz, 2H), 3.73 (s, 3H), 4.42 (dd, J=8, 5 Hz, 1H), 4.93 (br d, J=8 Hz, 1H), 6.83 (s, 1H). Mass spectrum: $(M+H)^+$=342.

C. N-((N-Methyl-N-(2-(2-isopropyl-4-thiazolyl)ethyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 61B provided 0.074 g (64%) of the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-(2-(2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl))amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-(2-(2-isopropyl-4-thiazolyl)ethyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 90 mg (54%) of the desired compound (R_f 0.44, 10% methanol in chloroform) as a solid, mp 62°–63°

C. Mass spectrum: $(M+H)^+$=735. Anal. calcd for $C_{38}H_{50}N_6O_5S_2$: C, 62.10; H, 6.86; N, 11.43; S, 8.72. Found: C, 61.72; H, 6.78; , N, 11.34; S, 8.89.

EXAMPLE 62

A. 2-Isopropyl-4-((N-(tert-butyloxycarbonylamino)amino)methyl)thiazole.

A solution of 7.5 g (57 mmol) to t-butylcarbazate in 200 ml of isopropyl alcohol was treated with a solution of 1.0 g (57 mmol) of 4-(chloromethyl)-2-isopropylthiazole hydrochloride in 10 ml of isopropyl alcohol. The resulting solution was heated at reflux for 16 h, allowed to cool, and concentrated in vacuo. The residue was diluted with 1N HCl, washed with three portions of ethyl acetate, basified to pH 12 with aqueous NaOH, and extracted with three portion of ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by silica gel chromatography using 20% ethyl acetate in hexane provided 0.32 g (21%) of the desired compound (R_f 0.4, 5% methanol in chloroform). ^1H NMR ($CDCl_3H$) δ1.40 (d, J=7 Hz, 6H), 1.47 (s, 9H), 2.53 (br, 1H), 3.33 (heptet, J=7 Hz, 1H), 4.11 (s, 2H), 6.22 (br, 1H), 7.01 (s, 1H). Mass spectrum: $(M+H)^+$=272.

B. N-((N-(tert-Butyloxycarbonylamino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-((N-(tert-butyloxycarbonylamino)amino)methyl)thiazole provided, after silica gel chromatography using 1% methanol in chloroform as an eluent, 0.30 g (95%) of the desired compound. ^1H NMR (DMSO-d_6H) δ0.84 (d, J=7 Hz, 3H), 0.87 (d, J=7 Hz, 3H), 1.31 (d, J=7 Hz, 6H), 1.39 (s, 9H), 2.05 (m, 1H), 3.24 (m, 1H), 3.64 (s, 3H), 4.09 (dd, J=9, 6 Hz, 1H), 6.35 (br, 1H), 7.24 (s, 1H). Mass spectrum: $(M+H)^+$=429.

C. N-((N-(tert-Butyloxycarbonylamino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl))-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 62B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-(tert-Butyloxycarbonyl)amino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-(tert-butyloxycarbonylamino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using 1% methanol in chloroform, 80 mg (41%) of the desired compound (R_f 0.35, 5% methanol in chloroform). Mass spectrum: $(M+H)^+$ =822. HRMS. Exact mass calcd for $C_{41}H_{56}N_7O_7S_2$: 822.3683. Found: 822.3682.

EXAMPLE 63

(2S,3S,5S)-5-(N-(N-((N-(Amino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane Hydrochloride.

To 60 mg (0.073 mmol) of (2S,3S,5S)-5-(N-(N-((N-(tert-butyloxycarbonyl-amino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane was added 5 ml of 4M HCl in dioxane. The resulting solution was stirred at ambient temperature for 2 h. After concentration of the solution in vacuo, the residue was taken up in 0.5 ml of methanol, added to 20 ml of diethyl ether, and

filtered to provide 40 mg (77%) of the desired compound (R_f 0.60, 10% methanol in chloroform). Mass spectrum: $(M+H)^+$=722.

EXAMPLE 64

(2S,3S,5S)-5-(N-{N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-1-phenyl-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-1-phenyl-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane and replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((2-isopropyl-4-thiazolyl)methoxycarbonyl)valine provided, after silica gel chromatography using 10% methanol in dichloromethane, 25 mg (76%) of the desired compound (R_f 0.47, 10% methanol in dichloromethane). Mass spectrum: $(M+H)^+$=715.

EXAMPLE 65

A. (2S,3S,5S)-3-(tert-Butyldimethylsilyloxy)-2-(tert-butyloxycarbonylamino)-1-phenyl-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)hexane.

Using the procedure of Example 8F, but replacing benzyl alcohol with 5-(hydroxymethyl)thiazole provided, after silica gel chromatography using 10% methanol in dichloromethane, 261 mg (67%) of the desired compound. ^{1}H NMR ($CDCl_3$H) δ0.05 (s, 6H), 0.91 (s, 9H), 1.34 (s, 9H), 1.70 (m, 2H), 2.72 (m, 2H), 3.03 (m, 2H), 3.74 (m, 1H), 3.91 (m, 1H), 4.02 (m, 1H), 4.63 (br d, 1H), 5.24 (s, 2H), 7.19–7.35 (m, 5H), 7.52 (s, 1H), 7.86 (s,1H), 8.66 (s, 1H), 8.79 (s, 1H). Mass spectrum: $(M+H)^+$=647.

B. (2S,3S,5S)-2-(tert-Butyloxycarbonylamino)-1-phenyl-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

Using the procedure of Example 8G, but replacing the resultant compound of Example 8F with the resultant compound of Example 65A provided, after silica gel chromatography using 10% methanol in dichloromethane, 74 mg (35%) of the desired compound. ^{1}H NMR ($CDCl_3$H) δ1.39 (s, 9H), 1,65 (m, 2H), 2.87 (m, 2H), 3.09 (m, 2H), 3.68 (m, 2H), 3.96 (m, 2H), 4.74 (br d, 1H), 5.26 (dd, 2H), 7.17–7.32 (m, 5H), 7.52 (s, 1H), 7.86 (s, 1H), 8.66 (s, 1H), 8.81 (s, 1H). Mass spectrum: $(M+H)^+$=533

C. (2S,3S,5S)-2-Amino-1-phenyl-5-(N-((5-thiazolyl-)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

A solution of 70 mg (0.13 mmol) of the resultant compound of Example 65B in 2.1 ml of CH_2Cl_2 was treated with 0.7 ml of trifluoroacetic acid, stirred for 1.5 h, and concentrated in vacuo. The residue was treated with 3 ml of aqueous $NaHCO_3$, extracted with three portions of 95:5 CH_2Cl_2:$CHCl_3$, dried over Na_2SO_4, and concentrated in vacuo to provide 55 mg (97%) of the desired compound as a white foamy solid. ^{1}H NMR ($CDCl_3$H) δ1.72 (m, 2H), 1.86 (br, 2H), 2.46 (dd, 1H), 2.84 (m, 2H), 3.20 (m, 2H), 3.45 (m, 1H), 4.02 (m, 1H), 5.30 (dd, 2H), 5.52 (br d, 1H), 7.14–7.34 (m, 5H), 7.59 (s, 1H), 7.88 (s, 1H), 8.67 (s, 1H), 8.80 (s, 1H). Mass spectrum: $(M+H)^+$=433.

D. (2S,3S,5S)-2,(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl))valine)amino)-1-phenyl-5-(N-((5-thiazolyl-)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((2-isopropyl-4-thiazolyl)methoxycarbonyl)valine and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-1-phenyl-5-(N-((5- thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane provided, after silica gel chromatography using 1% methanol in chloroform, 54 mg (66%) of the desired compound (R_f 0.6, 10% methanol in CH_2Cl_2H). ^{1}H NMR (DMSO-d_6H) δ0.69 (d, 3H), 0.74 (d, 3H), 1.31 (d, 6H), 1.47 (m, 2H), 1.85 (m, 1H), 2.75 (m, 4H), 2.95 (m, 1H), 3.57 (m, 1H), 3.80 (m, 2H), 4.08 (m, 1H), 4.95 (d, 1H), 5.03 (s, 2H), 5.19 (s, 2H), 7.12–7.29 (m), 7.45 (s,1H), 7.47 (s, 1H). Mass spectrum: $(M+H)^+$=715.

EXAMPLE 66

(2S,3S,5S)-2,5-Diamino-3-hydroxy-1,6-diphenylhexane dihydrochloride

EXAMPLE 66A

(L)-N,N-Dibenzylphenylalanine benzyl ester

A solution containing L-phenylalanine (11 kg, 66.7 moles), potassium carbonate (29 kg, 210 moles), and water (66 L), and benzyl chloride (27 kg, 213 moles) was heated to 90°±15° C. for 10–24 hours. The reaction mixture was cooled to room temperature and heptane (29 L) and tap water (27 L) was added. The layers were separated and the organics washed one to two times with 22 L of a methanol/water solution (1/2 v/v). The organics were then stripped to give the desired product as an oil. IR (neat) 3090, 3050, 3030, 1730, 1495, 1450, 1160 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$H) δ7.5–7.0 (m, 20H), 5.3 (d, 1H, J=13.5 Hz), 5.2 (d, 1H, J=13.5 Hz), 4.0 (d, 2H, J=15 Hz), 3.8 (t, 2H, J=8.4 Hz), 3.6 (d, 2H, J=15 Hz), 3.2 (dd, 1H, J=8.4, 14.4 Hz), ^{13}C NMR (300 MHz, $CDCl_3$H) δ172.0, 139.2, 138.0, 135.9, 129.4, 128.6, 128.5, 128.4, 128.2, 128.1, 128.1, 126.9, 126.2, 66.0, 62.3, 54.3, 35.6. $[\alpha]_D$–79° (c=0.9, DMF).

EXAMPLE 66B

(4S)-4-(N,N-Dibenzylamino)-3-oxo-5-phenyl-pentanonitrile

A solution containing the product of Example 66A (i.e., benzyl ester) (approx. 0.45 moles) in 520 mL tetrahydrofuran and 420 mL acetonitrile was cooled to –40° C. under nitrogen. A second solution containing sodium amide (48.7 g, 1.25 moles) in 850 mL tetrahydrofuran was cooled to –40° C. To the sodium amide solution was slowly added 75 mL acetonitrile and the resulting solution was stirred at –40° C. for more than 15 minutes. The sodium amide/acetonitrile solution was then slowly added to the benzyl ester solution at –40° C. The combined solution was stirred at –40° C. for one hour and then quenched with 1150 mL of a 25% (w/v) citric acid solution. The resulting slurry was warmed to ambient temperature and the organics separated. The organics were then washed with 350 mL of a 25% (w/v) sodium chloride solution, then diluted with 900 mL heptane. The organics were then washed three times with 900 mL of a 5% (w/v) sodium chloride solution, two times with 900 mL of a 10% methanolic water solution, one time with 900 mL of a 15% methanolic water solution, and then one time with 900 mL of a 20% methanolic water solution. The organic solvent was removed in vacuo and the resulting material dissolved into 700 mL of hot ethanol. Upon cooling to room temperature, the desired product precipitated. Filtration gave the

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desired product in 59% yield from the L-phenylalanine. IR ($CHCl_3$H) 3090, 3050, 3030, 2250, 1735, 1600, 1490, 1450, 1370, 1300, 1215 cm^{-1}, ^1H NMR ($CDCl_3$H) δ7.3 (m, 15H), 3.9 (d, 1H, J=19.5 Hz), 3.8 (d, 2H, J=13.5 Hz), 3.6 (d, 2H, J=13.5 Hz), 3.5 (dd, 1H , J=4.0, 10.5 Hz), 3.2 (dd, 1H, J=10.5, 13.5 Hz), 3.0 (dd, 1H, J=4.0, 13.5 Hz), 3.0 (d, 1H, J=19.5 Hz), ^{13}C NMR (300 MHz, $CDCl_3$H) δ197.0, 138.4, 138.0, 129.5, 129.0, 128.8, 128.6, 127.8, 126.4, 68.6, 54.8, 30.0, 28.4. $[\alpha]_D$–95° (c=0.5, DMF).

EXAMPLE 66C

Alternate preparation of (4S)-4-(N,N-Dibenzylamino)-3-oxo-5-phenyl-pentanonitrile

To a flask was charged sodium amide (5.8 g, 134 mmol) under nitrogen followed by 100 mL of methyl t-butyl ether (MTBE). The stirred solution was cooled to 0° C. Acetonitrile (8.6 mL, 165 mmol) was added over 1 minute. This solution was stirred at 5°±5° C. for 30 minutes. A solution of (L)-N,N-dibenzylphenylalanine benzyl ester (25 g, 90% pure, 51,6 mmol) in 125 mL of MTBE was added over 15 minutes and the resulting heterogeneous mixture was stirred at 5°±5° C. until the reaction was complete (approx. 3 hours). The reaction was quenched with 100 mL of 25% w/v aqueous citric acid and warmed to 25° C. before separating the layers. The organics were then washed with 100 mL of H_2O. The aqueous layer was separated and the organics filtered and concentrated in vacuo. The residue was crystallized from 50 mL of ethanol to afford 13.8 g of the desired product as a white solid.

EXAMPLE 66D

(5S)-2-Amino-5-(N,N-(dibenzylamino)-4-oxo-1,6-diphenylhex-2-ene

To a 5° C. solution of the product of Example 66B (20 Kg, 29 moles) in 29 L tetrahydrofuran was added benzylmagnesium chloride (45 Kg, 2M in THF, 84.5 moles). The solution was warmed to ambient temperature and stirred until analysis showed no starting material. The solution was then recooled to 5° C. and 54 L of a 15% citric acid solution was slowly added to quench excess benzylmagnesium chloride. The organics were separated and washed with 27 L 10% sodium chloride and stripped to a solid. The product was stripped again from 27 L ethanol (200 proof) and then dissolved in 67 L hot ethanol (200 proof). After cooling to room temperature and stirring for 12 hours, the resulting product was filtered and dried in a vacuum oven at 30° C. to give 24 kg of the desired product. mp 101°–102° C., IR ($CDCl_3$) 3630, 3500, 3110, 3060, 3030, 2230, 1620, 1595, 1520, 1495, 1450 cm^{-1}, ^1H NMR (300 MHZ, $CDCl_3$H) d 9.8 (br s, 1H), 7.2 (m, 20H), 5.1 (s, 1H), 4.9 (br s, 1H), 3.8 (d, 2H, J=14.7 Hz),3.6 (d, 2H, J=14.7 Hz), 3.5 (m, 3H), 3.2 (dd, 1H, J=7.5, 14.4 Hz), 3.0 (dd, 1H, J=6.6, 14.4 Hz), ^{13}C NMR ($CDCl_3$) d 198.0, 162.8, 140.2, 140.1, 136.0, 129.5, 129.3, 128.9, 128.7, 128.1, 128.0, 127.3, 126.7, 125.6, 96.9, 66.5, 54.3, 42.3, 32.4. $[\alpha]_D$ –147° (c=0.5, DMF).

EXAMPLE 66E

(2S, 3S, 5S)-5-Amino-2-(N,N-dibenzylamino)-3-hydroxy-1,6-diphenyl-hexane

(i). A suspension of sodium borohydride (6.6 kg, 175 moles) in tetrahydrofuran (157 L) was cooled to less than –10°±5° C. Methanesulfonic acid (41,6 kg, 433 moles) was slowly added and the temperature kept below 0° C. during the addition. Once the addition was complete, a solution of water (6 L, 333 moles), the product of Example 66D (20 kg, 43 moles) and tetrahydrofuran (61 L) was slowly added while maintaining the temperature below 0° C. during the addition. The mixture was stirred for not less than 19 h at 0°±5° C.

(ii). To a separate flask was added sodium borohydride (6.6 kg, 175 moles) and tetrahydrofuran (157 L). After cooling to –5°±5° C., trifluoroacetic acid (24.8 kg, 218 moles) was added while maintaining the temperature below 15° C. The solution was stirred 30 min at 15°±5° C. and was then added to the reaction mixture resulting from step (i), keeping the temperature at less than 20° C. This was stirred at 20°±5° C. until reaction was complete. The solution was then cooled to 10°±5° C. and quenched with 3N NaOH (195 kg). After agitating with tert-butyl methyl ether (162 L), the organic layer was separated and washed one time with 0.5N NaOH (200 kg), one time with 20% w/v aqueous ammonium chloride (195 kg), and two times with 25% aqueous sodium chloride (160 kg). The organics were stripped to give the desired product as an oil which was used directly in the next step.

IR ($CHCl_3$) 3510, 3400, 3110, 3060, 3030, 1630, ^1H NMR (300 MHz, $CDCl_3$) δ7.2 (m, 20H), 4.1 (d, 2H, J=13.5 Hz), 3.65 (m, 1H), 3.5 (d, 2H, J=13.5 Hz), 3.1 (m, 2H), 2.8 (m, 1H), 2.65 (m, 3H), 1.55 (m, 1H), 1.30 (m, 1H), ^{13}C NMR (300 MHz, $CDCl_3$) δ140.8, 140.1, 138.2, 129.4, 129.4, 128.6, 128.4, 128.3, 128.2, 126.8, 126.3, 125.7, 72.0, 63.6, 54.9, 53.3, 46.2, 40.1, 30.2.

EXAMPLE 66F

(2S, 3S, 5S)-2,5-Diamino-3-hydroxy-1,6-diphenylhexane Dihydrochloride

To a stirred solution of [2S,3S,5S]-2-(N,N-dibenzylamino)-3-hydroxy-5-amino-1,6-diphenylhexane (20 kg, 43.1 mol)in methanol (250 kg) was added an aqueous solution of ammonium formate (13.6 kg, 215 mol) in water (23 kg) and an aqueous suspension of 5% wet palladium on carbon (4.0 kg, Degussa catalyst, E101 NE/W, approximately 50–60% water by weight). The suspension which resulted was heated to reflux (70°±10° C.) for 6 hours and then cooled to room temperature. The suspension was filtered through a bed of diatomaceous earth and the cake was washed with methanol (2×30 kg). The filtrate was concentrated via vacuum distillation to an aqueous oil. The aqueous residue was taken up in 1N NaOH (200 liters) and extracted with ethyl acetate (155 kg). The organic product layer was washed with a 20% aqueous sodium chloride solution (194 kg) and then with water (97 kg). The ethyl acetate product solution was then concentrated to an oil under vacuum distillation. Isopropanol (40 kg) was then charged to the residue and again the solution was concentrated to an oil with vacuum distillation. To the oil was charged isopropanol (160 kg) and concentrated aqueous hydrochloric acid (20.0 kg). The suspension/solution was then heated to reflux for 1 hour and then slowly cooled to room temperature. The slurry was then stirred for 12–16 hours. The slurry was filtered and the cake was washed with ethyl acetate (30 kg). The wet cake was resuspended in isopropanol (93 kg) and water (6.25 kg) and heated to reflux for 1 hour with stirring. The reaction mixture was then slowly cooled to room temperature and stirred for 12–16 hours. The reaction mixture was filtered and the wet cake was washed with isopropanol (12 kg). The solid was dried in a vacuum oven at 45° C. for approximately 24 hours to provide 7.5 kg of the desired product. ^1H NMR (300 MHz, CD_3OD) δ7.40–7.15 (m, 10H), 3.8 (ddd, 1H, J=11.4, 3.7, 3.7 Hz), 3.68–3.58 (m, 1H), 3.37 (ddd, 1H, J=7.5, 7.5, 3.5 Hz), 3.05–2.80 (m, 4H), 1.95–1.70 (m, 2H), ^{13}C NMR (300 MHz, CD_3OD) δ135.3,

135.1, 129.0, 128.9, 128.7, 128.7, 127.12, 127.07, 67.4, 57.1, 51,6, 38.4, 35.5, 35.2.

EXAMPLE 67

(2S,3S,5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

EXAMPLE 67A

(2S,3S,5S)-2-(N,N-dibenzylamino)-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

To a stirred solution of (2S,3S,5S)-2-(N,N-dibenzylamino)-3-hydroxy-5-amino-1,6-diphenylhexane (10.0 g, 21,6 mmol)in tetrahydrofuran (200 mL) was added potassium carbonate (6.0 g, 43.2 mmol)in H_2O (200 mL). To this solution was added di-t-butyldicarbonate (5.64 g, 25.9 mmol) in tetrahydrofuran (10 mL). The solution which resulted was stirred at room temperature for 3 hours. N,N-dimethylethylenediamine (1 mL, 8.6 mmol) was added and the reaction mixture was stirred at room temperature for an additional hour. Ethyl acetate (400 mL) was added and the organic layer was separated and washed with 5% KH_2PO_4 (2×200 mL), water (1×200 mL), saturated $NaHCO_3$ (2×200 mL) and water (1×200 mL). The organic solution was then dried over sodium sulfate and concentrated under reduced pressure to provide the desired product as a light yellow oil. 300 MHz ^1H NMR ($CDCl_3$) δ1.40 (s,9H), 1.58 (s, 2H), 2.45–2.85 (m, 4H), 3.05 (m, 1H), 3.38 (d, 2H), 3.6 (m, 1H), 3.79 (m, 1H), 3.87 (d, 2H), 4.35 (s, 1H), 4.85 (s, broad, 1H), 7.0–7.38 (m, 20H).

EXAMPLE 67B

(2S,8S,5S)-2-amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

To a stirred solution of (2S,3S,5S)-2-(N,N-dibenzylamino)-3-hydroxy-5-(t-butyloxycarbonylamino)1,6-diphenylhexane (12 g, 21.3 mmol)in methanol (350 mL) was charged ammonium formate (8.05 g, 128 mmol, 6.0 eq) and 10% palladium on carbon (2.4 g). The solution was stirred under nitrogen at 60° C. for three hours and then at 75° C. for 12 hours. An additional amount of ammonium formate (6 g) and 10% palladium on carbon (1.5 g) was added as well as 1 mL of glacial acetic acid. The reaction was driven to completion within 2 hours at a reflux temperature. The reaction mixture was then cooled to room temperature and then filtered through a bed of celite. The filter cake was washed with methanol (75 mL) and the combined filtrates were concentrated under reduced pressure. The residue was taken up in 1N NaOH (300 mL) and extracted into methylene chloride (2×200 mL). The combined organic layers were washed with brine (250 mL) and dried over sodium sulfate. Concentration of the solution under reduced pressure provided the desired product as a light colored oil which slowly crystallized upon standing (5 g). Further purification of the product could be accomplished by flash chromatography (silica gel, 5% methanol in methylene chloride). 300 MHz ^1H NMR ($CDCl_3$) δ1.42 (s, 9H), 1.58 (m, 1H), 1.70 (m, 1H), 2.20 (s, broad, 2H), 2.52 (m, 1H), 2.76–2.95 (m, 4H), 3.50 (m, 1H), 3.95 (m, 1H), 4.80 (d, broad, 1H), 7.15–7.30 (m, 10H).

EXAMPLE 68

Alternative Preparation of (2S,3S,5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

EXAMPLE 68A

(5S)-2-(t-Butyloxycarbonylamino)-5-(N,N-dibenzylamino)-1,6-diphenyl-4-oxo-2-hexene

To 9.21 gm (20 mmol) of the resultant compound of Example 66D and 0.37 gm (3 mmol) 4-N,N-dimethylaminopyridine in 100 ml of methyl tert-butylether was added via syringe pump a solution containing 4.80 gm (22 mmol) di-tert-butyl dicarbonate in the same solvent (25 ml) over a period of 6 h. An additional amount (3 ml) of methyl tert-butylether was then added to complete the addition. After stirring at room temperature for 18 h the reaction mixture was cooled with the aid of an ice water bath. The resultant solid was collected by suction filtration and washed with cold (0° C.) methyl tert-butylether and hexane and dried under vacuum to give 9.9 gm of crude material as a white solid. The material thus isolated was dissolved in a minimal amount of dichloromethane and purified by flash chromatography on silica gel. Elution of the column with a mixture of hexane-ethyl acetate-dichloromethane (8:1:1) gave, after concentration of the appropriate fractions, 8.1 gm (72%) of the desired compound. Mp. 191°–193° C. $[\alpha]_D$183.7° (C=1.05, $CHCl_3$). ^1H NMR ($CDCl_3$, δH): 11,68 (bs, 1H), 7.05–7.47 (m, 20H), 5.28 (s,1H), 4.27 (d, J=16 Hz, 1H), 4.02 (d, J=16 Hz, 1H), 3.58 (m, 4H), 3.40 (m, 1H), 3.11 (m, 1H), 2.90 (m, 1H), 1.48 (s, 9H).

EXAMPLE 68B

Alternate preparation of (5S)-2-(t-Butyloxycarbonylamino)-5-(N,N-dibenzylamino)-1,6-diphenyl-4oxo-2-hexene

A suspension of (S)-2-amino-5-(N,N-dibenzylamino)1,6-diphenyl-4-oxo-2-hexene (100.0 g, 0.217 mol) in 15% ethyl acetate/hexanes (2 liters) under N_2 was warmed to about 40° C. The resulting solution was cooled to room temperature before adding 4.0 g (33 mmol) of N,N-dimethyl-4-aminopyridine and 49.7 g (0.228 mol) of di-tert-butyl dicarbonate. The reaction mixture was allowed to stir overnight at room temperature. (After approximately one hour, a white precipitate began to form.) The suspension was filtered and the precipitate was washed with hexanes to afford the desired product as colorless crystals. TLC: 25% ethyl acetate/hexanes R_f 0.38.

EXAMPLE 68C

(2S,3S,5S)-2-(N,N-Dibenzylamino)-5-(t-butyloxycarbonylamino)-3-hydroxyl-1,6-diphenylhexane.

A solution of the product of Example 68A (5 g, 8.9 mmol) in dichloromethane (1 00ml) and 1,4-dioxolane (100ml) was cooled to between −10° and −15° C. and treated dropwise with 1M BH_3THF (26.7ml, 26.7 mmol). The solution was stirred at this temperature for 3 hr. The clear solution was quenched with excess methanol (20ml) and stirred at room temperature for 30 min. The solvent was removed in vacuo.

The resulting white foam was dissolved in THF (75ml) and cooled to −40° C. A solution of LAH (9ml, 1M in THF, 9 mmol) was added dropwise. After 10 min. the solution was quenched with water followed by dilute aqueous HCl. The organics were removed and the aqueous layer extracted with ethyl acetate (3×20 ml). The combined organics were washed (saturated aqueous bicarbonate followed by brine), dried (Na_2SO_4H), filtered and evaporated to afford 4.9 g (99%) of the desired product as a white foam.

Alternatively, the white foam resulting from the BH_3THF reaction step was dissolved in MeOH (45ml), cooled to ±3° C. and treated portionwise with KBH_4 (1.44 g, 26.7 mmol). After addition of the last portion of KBH_4 the reaction was

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stirred for an additional 4 hours at +4° to +5° C. The solution was concentrated by 1/2 the volume in vacuo, diluted with 1/1 hexane-EtOAc (70 ml) and quenched (with cooling, maintain temp. <30° C.) by adding a 10% solution of $KHSO_4$ to pH=about 5. NaOH (15% aqueous) was added to pH=12–13. The insoluble salts were removed by filtration, and the filter cake washed 3 times with 7 ml 1/1 hexane/EtOAc. The filtrate and washes were transferred to a separatory funnel, diluted with 15 ml hexane and 15 ml H_2O. The organics were removed and the aqueous layer was extracted once with 20 ml (1/1H) hexane-EtOAc. The combined organics were washed (saturated brine), dried (Na_2SO_4H), filtered, and evaporated to afford 5.2 g of the desired product which was used without further purification in subsequent reactions. R_f 0.5 (25% EtOAc/hexane) ^1H NMR ($CDCl_3$) δ7.37–7.10 (m 20H); 6.78 (br, s, 1H); 4.62 (d, 1H); 4.50 (s, 1H); 4.18 (dd, 1H); 3.9 (d, 2H); 3.65 (dd, 2H); 3.40 (d, 2H); 3.00 (m, 2H); 2.77 (m, 1H); 1.39 (s, 9H). MS (El) m/e565 (M+H).

EXAMPLE 68D

(2S,3S,5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonyl)amino)-1,6-diphenylhexane.

A solution of the product from Example 68C (150 gm, 250 mmol) dissolved in absolute EtOH (2 liters) was treated with 10% Pd/C (18 gm, pre-wetted), followed by addition of ammonium formate (78.6 gms, 1.25 moles) dissolved in H_2O (200ml). The resulting mixture was stirred at reflux for 2.5 hours. The mixture was cooled to room temperature and filtered through a pad of infusorial earth (20 g). The filter cake was washed 3 times with EtOH (70ml each). The filtrate was concentrated in vacuo. The residue was dissolved into EtOAc (1 L) and washed (1N NaOH, followed by H_2O, followed by brine), dried (Na_2SO_4H), filtered and concentrated/n vacuo. to a constant weight of 95 gms. (99.2% of theory). The light yellow solid (91.5 gm of the 95 gm) was slurried in hot heptane (600 ml) (steam bath) and treated with isopropanol (45ml), and swirled to effect solution. The solution was allowed to slowly cool to room temperature over 3 hours, kept at room temperature for 2 more hours and filtered. The filter cake was washed 10 times with 9/1 hexane-isopropanol (30ml each) to give the desired product as an off-white finely crystalline solid which was dried to constant weight of 57.5 gm.

The crude product (20 gm) was recrystallized from hot 140 ml heptane/17 ml isopropanol. After letting the solution cool slowly to room temperature, the mixture was let stand at room temperature for 2 hours and then filtered. The filter cake was rinsed (5×15 ml (8/1) heptane/isopropanol) and dried to a constant weight of 18.5 gm.

EXAMPLE 69

Alternative Preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

EXAMPLE 69A

(2S,3S,5S)-5-(t-Butyloxycarbonylamino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

The product of Example 68D (6.0 g, 15.6 mmoles) was dissolved in 60 mL of DMF under nitrogen atmosphere. To this stirred solution at room temperature was added 5-(p-nitrophenyloxycarbonyloxymethyl)thiazole (4.67 g, 15.6 mmole) and the resulting solution was stirred for 4 h. The solvent was removed under reduced pressure by rotary evaporation and the residue dissolved in 150 mL EtOAc. This solution was washed with 5×75 mL 1N NaOH solution, 100 mL brine, dried over Na_2SO_4. The solvent was removed to afford 8.02 g of a slightly yellowish oil. This material was crystallized from 30 mL EtOAc and 40 mL hexane to afford 6.53 g (80%) of the desired product as a white solid. mp 118°–120° C. H ^{1}NMR ($CDCl_3$) δ8.79 (s, 1H), 7.83 (s, 1H), 7.30–7.15 (m, 8H), 7.08 (m, 2H), 5.23 (s, 2H),5.14 (d, 1H, J=9 Hz), 4.52 (m, 1H), 3.92–3.72 (m, 3H), 3.65 (m, 1H), 2.85 (d-apparent,2H, J=7.5 Hz), 2.72 (d-apparent, 2H, J=7 Hz), 1,61 (m, 2H), 1.38 (s, 9H). CIMS m/z (526) $(M+H)^+$, 543 $(M+18H)^+$.

EXAMPLE 69B

(2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

The product of Example 69A (6.43 g, 12.23 mmoles) was dissolved in 25 mL dioxane at room temperature under nitrogen atmosphere. To this stirred solution was added 20.25 mL of 4N HCl in dioxane, and after approximately 10 min a thick precipitate formed. An additional 10 mL of dioxane was added to loosen up the slurry. This mixture was stirred for 1 h and then filtered. The filter cake of the product bis-HCl salt was washed with 20 mL dioxane, air dried, and then dissolved in 175 mL water. To this solution was added 175 mL ethyl acetate and the two phase mixture rapidly stirred. The pH of this mixture was adjusted to pH=10 by the dropwise addition of 3N NaOH to the rapidly stirred mixture. The organic layer was isolated, washed with brine (150 mL), and dried over Na_2SO_4. The solvent was removed to afford 5.18 g (99%) of the desired product as a clear oil. H^{1}NMR ($CDCl_3$) δ8.81 (s, 1H), 7.87 (s, 1H), 7.35–7.05 (m, 10H), 5.33 (d, 1H, J=9.3 Hz), 5.28 (m,2H), 3.81 (m, 1H), 3.72 (m, 1H), 3.01 (m, 1H), 2.88 (m, 2H) 2.78 (dd, 1H, J=13.5, 5.1 Hz), 2.39 (dd, 1H, J=9.0, 4.5 Hz), 1.57–1.30 (m, 2H). CIMS m/z 426 $(M+H)^+$.

EXAMPLE 69C

(2S,3S,5S)-5-(N-(N-((N-Methyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl))amino)-1,6-diphenyl-3-hydroxyhexane

N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine (4.13 g, 13.18 mmole) and hydroxybenztriazole (2.23 g, 16.48 mmoles) were dissolved in 70 mL THF and then dicyclohexyl-carbodiimide(2.71 g, 13.18 mmoles) was added in one portion to the stirred solution under nitrogen atmosphere. This mixture was stirred for 4h at room temperature and then filtered to remove dicyclohexylurea precipitate. The product of Example 69B (5.1 g, 11.99 mmoles) was dissolved in 100 mL THF under nitrogen atmosphere. To this stirred solution was added the filtrate of HOBT-active ester and the resulting solution was stirred at room temperature for 4 h, and the solvent removed via rotary evaporation. The residue was dissolved in 150 mL ethyl acetate and washed with 2×100 mL 1N NaOH, 100 mL brine, 100 mL of 1% w/w aqueous $KHSO_4$ and the solvent was removed by rotary evaporation to afford a residue. The residue was dissolved in 175 mL 1N HCL, and the solution filtered to remove the small quantity of dicyclohexylurea. The filtrate solution was added to 175 mL ethyl acetate and the two phase mixture rapidly mixed. The pH of this rapidly stirred mixture was adjusted to pH=7 by dropwise addition of cold 3N NaOH. The organic layer was isolated, washed

with 100 mL brine, dried over Na_2SO_4, filtered, and the solvent was removed to afford 8.6 g of a colorless foam. This material was crystallized from 42 mL EtOAc and 21 mL hexane to give 7.85 g of the desired product as a white solid. mp=122°–123° C. CIMS m/z 721 $(M+H)^+$.

EXAMPLE 70

Alternative Preparation of (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Alternative A

The product of Example 66F (9.5 g, 33.4 mmol) and phenylboronic acid (4.1 g, 33.6 mmol) were combined in toluene (150 mL) and refluxed for 2.5 hours with azeotropic water removal (Dean-Stark trap). Toluene (100 mL) was distilled out at atmospheric pressure, then the remaining toluene was removed under vacuum, to provide a yellow syrup which was dissolved in DMF (50 mL) and cooled to –60° C. A solution of 5-(p-nitrophenyloxycarbonyloxy-methyl)thiazole (9.5 g, 33.5 mmol) in DMF (50 mL) was added over 45 minutes. The resulting mixture was stirred for 8 hours at –55±5° C., then 14 hours at –25° C., then was allowed to warm to room temperature. The reaction mixture was diluted with 1N HCl (250 mL) and washed with CH_2Cl_2 (2×80 mL). The combined organic layers were back-extracted with 1N HCl (60 mL). The combined aqueous HCl layers were cooled in an ice-bath to 2° C, and conc. (37%) HCL (30 mL) was added over 5 minutes. The desired product (bis HCl salt) began to precipitate within 30 minutes. The slurry was stirred 3 hours at 2°–5° C., then the product (bis HCl salt) was collected by filtration and dried in a vacuum oven at 55°–60° C. Yield 11.4 g (68%).

Second crop recovery:

The HCl mother liquors were stirred with ethyl acetate (190 mL) and neutralized to pH 9–10 with aqueous K_2CO_3 (200–300 g of 25% w/w K_2CO_3 was required). The ethyl acetate layer was concentrated under vacuum to an oil which was redissolved in 1N HCl (90 mL) and washed with methylene chloride (45 mL). The aqueous layer was cooled to 2° C. Conc. (37%) HCl (9.0 mL) was added to precipitate a second crop. After stirring for 1–3 hours at 2°–5° C., the solid was collected by filtration and dried in a vacuum oven at 55°–60° C. Yield 2.1 g (12.6%).

Neutralization of Bis HCl Salt:

The bis HCl salt (10.66 g, 21.4 mmol, mixture of first and second crops) was stirred with CH_2Cl_2 (110 mL) and 5% aqueous $NaHCO_3$ (110 mL) until all solids dissolved (2 hours). The aqueous layer was separated and extracted with another 50 mL CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 (10 g), filtered and concentrated under vacuum at <40° C. to an oil. The oil was dried on a vacuum pump to give the title compound as a yellow foam, 9.1 g (100%).

Alternative B

The product of Example 66F (15.0 g, 0.053 mole) was dissolved in DMF (75 mL). Triisopropylborate (24.4 mL, 0.105 mole) was added and stirred at ambient temperature for approximately 1.5 hours. The solution was cooled to –10° C. and a solution of 5-(p-nitrophenyloxycarbonyloxymethyl)thiazole (15.0 g, 0.054 mole)in DMF (75 mL) was added over 80 minutes. The reaction was stirred for approximately 1 hour at –10° C., then was diluted with methylene chloride (250 mL) and quenched with a mixture of triethanolamine (24.8 g) and 5% aqueous sodium bicarbonate (300 mL). The biphasic mixture was stirred for 1 hour, then the layers were separated and the aqueous was extracted with another portion of methylene chloride (50 mL). The combined organic layers were extracted with 1N HCl (1×390 mL, then 1×95 mL). The acid layers were combined, cooled in an ice-bath, and further acidified with conc. HCl (50 mL) which produced a white slurry of product. The slurry was stirred for approximately 1 hour at 2° C. The desired product bis HCl salt) was collected by filtration and dried at 55° C. in a vacuum oven. Yield 18.5 g (70%).

EXAMPLE 71

Alternative Preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

To a solution of the product of Example70 (9.1 g, 21.4 mmol), HOBT (3.6 g, 23.5 mmol) and N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)-L-valine (7.37 g, 23.5 mmol)in THF (170 mL) was added DCC (4.85 g, 23.5 mmol). The solution was stirred at ambient temperature for 16 hours (DCU precipitates). THF was removed under vacuum and the resulting paste was stirred with cold 1N HCl (106 mL at 5° C.) for 3 hours to dissolve the crude product. The DCU was removed by filtration and the filter cake was washed with 1N HCl (30 mL). KH_2PO_4 (3.2 g) was dissolved in the combined HCl filtrates. The solution was mixed with ethyl acetate (80 mL) and neutralized to pH 7 with aqueous NaOH (60.3 g of 10% w/w NaOH). The aqueous layer was extracted with another 25 mL ethyl acetate and the combined ethyl acetate extracts were washed with aqueous $NaHCO_3$ (2×37 mL of 5% w/w $NaHCO_3H$). The organic layer was dried with Na_2SO_4 (13 g), filtered, and concentrated under vacuum at ≦45° C. The residue was dissolved in a 1:1 ethyl acetate/heptane mixture (200 mL) at 70° C. The solution was allowed to cool slowly and stirred overnight at room temperature to provide a thick slurry. The product was collected by filtration and washed with 1:1 ethyl acetate/heptane (20 mL). The product was dried briefly at 55° C. in a vacuum oven to obtain an approximate weight prior to the second crystallization (12.85 g, 83%). A second crystallization from 144 mL of 2:1 ethyl acetate/heptane (dissolved at ~70° C., then stirred at room temperature 12 hours) produced a thick slurry of fine white solid. The product was collected by filtration and washed with 15 mL 2:1 ethyl acetate/heptane, then dried in a vacuum oven at 55° C. for 2 days to give the desired product. Yield 11.9 g (77%).

EXAMPLE 72

Alternate Preparation of ((5-Thiazolyl)methyl)-(4-nitrophenyl)carbonate

EXAMPLE 72A

2-Amino-5-(ethoxycarbonyl)thiazole Hydrochloride

To a –10° C. solution of potassium tert-butoxide (110 g, 0.98 mol) in THF (1.9 L) was added a solution of ethyl chloroacetate (100 mL, 0.934 mol) and ethyl formate (75 mL, 0.928 mol)in THF (400 mL) dropwise over 2 hours, with good mechanical stirring. The thick solution was stirred another 2 hours at ca. –1° C. then the reaction was quenched by addition of a solution of NaCl (150 g) in 1N HCL (750 mL). The mixture was allowed to warm to 20° C. and the lower aqueous layer (containing some precipitated salt) was separated. The organic layer was stripped under vacuum on a rotary evaporator. The oil was redissolved in 500 mL ethyl acetate, dried with 75 g Na_2SO_4 for 1 hour, filtered and

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concentrated under vacuum (40°–50° C. bath temperature) to an oil. The resulting crude chloroaldehyde (161 g) and thiourea (70 g, 0.92 mol) were dissolved in THF (2 L) and warmed to gentle reflux (60° C.). The thiourea dissolved during warming, and within 20 minutes, product precipitated from solution. After 100 minutes the suspension was allowed to cool to room temperature, then was cooled in an ice-bath for 1 hour. The product was collected on a fritted Buchner funnel and washed with 2×100 mL cold THF, then dried overnight in a vacuum oven at 50° C. Yield: 122 g of title compound as a tan-colored solid, m.p. 182°–185° C. (dec.). ^{1}H NMR (DMSO-d_6H) δ7.86 (s, 1H), 4.19 (q, 2H), 1.21 (t, 3H). ^{13}C NMR (DMSO-d_6) δ171.9, 160.4, 140.4, 114.4, 61.1, 14.2.

EXAMPLE 72B

2-Amino-5-(ethoxycarbonyl)thiazole

To a −10° C. solution of potassium tert-butoxide (150 g, 1.3 mol) in THF (1.35 L) was added a solution of ethyl chloroacetate (139 mL, 1.3 mol) and ethyl formate (103 mL, 1.27 mol) in THF (150 mL) dropwise over 75 minutes, with good mechanical stirring. A THF rinse (25 mL) was added over 5 minutes. The thick solution was stirred another 3 hours at ca. −5° to 0° C., then the reaction was quenched by addition of a solution of NaCl (240 g) and conc. HCl (90 mL) in water (960 mL). The mixture was allowed to warm to 15° C. and the lower aqueous layer was discarded. Thiourea (97 g, 1.27 mol) was dissolved in the crude THF solution of chloroaldehyde. The solution was warmed to 65° C. and refluxed for 1 hour, then cooled to 30° C. Addition of a solution of K_2CO_3 (88 g, 0.64 mol) in 1500 mL water produced two layers (aqueous pH=7H). The THF was removed under vacuum at ≦45° C., causing the product to precipitate as a yellow solid. The slurry was cooled to 15° C., and the product was collected on a fritted Buchner funnel and washed with 3×200 mL water, then dried 24 hours in a vacuum oven at 55° C. to provide 151 g of title compound as a yellow solid, m.p. 155°–158° C. ^{1}H NMR (DMSO-d_6) δ7.8 (br s, 2H, NH_2H), 7.62 (s, 1H), 4.13 (q, 2H), 1.18 (t, 3H). ^{13}C NMR (DMSO-d_6) δ173.4, 161.3, 147.9, 114.5, 60.1, 14.3.

EXAMPLE 72C

5-(Ethoxycarbonyl)thiazole

A solution of 2-amino-5-(ethoxycarbonyl)thiazole (50 g, 0.29 mmol) in a mixture of DMF (83 mL) and THF (31 7 mL) was added dropwise over 87 minutes to a stirred 41° C. solution of isoamyl nitrite (59 mL, 0.44 mol) in DMF (130 mL). A maximum temperature of 60° C. was observed during the exothermic addition. After another 40 minutes the THF was removed under vacuum at 45° C. The concentrated DMF solution was cooled to 25° C. and diluted with toluene (420 mL) and water (440 mL). The toluene layer was extracted with 3×120 mL water, then dried with Na_2SO_4 (50 g) for 1 hour. After filtration the toluene layer was stripped on a rotary evaporater at 50° C. bath temperature, then on a vacuum pump at 21° C. The crude residue containing the title compound weighed 65.6 g. This material was used directly in the next step. A sample of similarly prepared material was purified by column chromatography to give a yellow oil. ^{1}H NMR ($CDCl_3$) δ8.95 (s, 1H), 8.51 (s, 1H), 4.39 (q, 2H), 1.40 (t, 3H). ^{13} NMR ($CDCl_3$) δ161.0, 157.9, 148.6, 129.8, 61,6, 14.1.

EXAMPLE 72D

5-(Hydroxymethyl)thiazole

To a slurry of lithium aluminum hydride (9.0 g) in THF (633 mL) was added a solution of crude 5-(ethoxycarbonyl)thiazole (65.6 g from Example 72C) in THF (540 mL) over 95 minutes at 0°–5° C. After an additional 25 minutes, the reaction was quenched at 5° C. by sequential addition of water (8.1 mL), 15% NaOH (8.1 mL), and water (24.3 mL). After drying with Na_2SO_4 (44 g) for 2 hours, the slurry was filtered, and the filter cake was washed with 100 mL THF. The combined filtrates were concentrated under vacuum at 45° C. to a brown oil (39 g). The oil was fractionally distilled through a short-path apparatus. The product fractions distilled at 97°–104° C. vapor temperature at 3–5 mm, providing 20.5 g of the title compound as a turbid orange oil. ^{1}H NMR ($CDCl_3$) δ8.74 (s, 1H), 7.72 (s, 1H), 4.89 (s, 2H), 3.4 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ153.4, 140.0, 139.5, 56.6.

EXAMPLE 72E

5-(p-Nitrophenyoxycarbonyloxymethyl)thiazole Hydrochloride

Distilled 5-(hydroxymethyl)thiazole (14.1 g, 123 mmol) and triethylamine (17.9 mL, 129 mmol) were dissolved in ethyl acetate (141 mL) and cooled to −1° C. (ice/salt bath). A solution of 4-nitrophenyl chloroformate (26.0 g, 129 mmol) dissolved in ethyl acetate (106 mL) was added dropwise over 50 minutes at an internal temperature of 0°–4° C. An ethyl acetate flask rinse (20 mL) was also added. Salts precipitated from solution throughout the addition. The yellow mixture was stirred another 1 hour 45 minutes at 0°–2° C., then a solution of dilute HCl (3.1 g, 31 mmol of conc. HCl in 103 mL water) was added at once. The mixture was stirred for 0.5 hours while warming to 15° C., then stirring was stopped. The organic layer was washed twice with aqueous 5% K_2CO_3 solution (2×70 mL), then dried with Na_2SO_4 (30 g). After filtration the solution was concentrated under vacuum on a rotary evaporater (bath temperature of 41° C.) to a brown oil (38 g). The crude 5-(p-nitrophenyoxycarbonyloxymethyl)-thiazole was dissolved in ethyl acetate (282 mL), then cooled in an ice bath to 2° C. Dry HCl gas (7.1 g, 195 mmol) was bubbled in slowly over 50 minutes (temperature 2°–4° C.). After stirring for another 1 hour 45 minutes at 2°–4° C., the solid precipitate was collected on a sintered glass funnel under a nitrogen blanket and the flask was washed out with 50 mL cold ethyl acetate which was used to rinse the filter cake. The cake was dried on the funnel under strong nitrogen purge for 15 minutes then dried in a vacuum oven at 50° C. with a nitrogen purge to provide 29.05 g of the title compound as tan powder, m.p. 131°–135° C. (dec.). ^{1}H NMR (DMSO-d_6) δ9.21 (d, 1H), 8.27 (m, 2H), 8.06 (d, 1H), 7.52 (m, 2H), 5.54 (s, 2H). ^{13}C NMR (DMSO-d_6) δ157.3, 155.2, 151.8, 145.3, 143.7, 131.9, 125.5, 122.7, 62.1.

EXAMPLE 72F

5-(p-Nitrophenyoxycarbonyloxymethyl)thiazole

5-(p-Nitrophenoxycarbonyloxymethyl)thiazole hydrochloride (3.0 g) was slurried in ethyl acetate (30 mL) and cooled to 10°–15° C. A solution of 5% aqueous potassium carbonate (30 mL) was added with rapid stirring. After 15 minutes, stirring was stopped and the aqueous layer was separated. The organic layer was dried with Na_2SO_4 (3 g), filtered, and solvent was distilled under vacuum to give 2.49 g of the title compound as a brown syrup which slowly

solidified, m.p. 62°–64° C. ^{1}H NMR ($CDCl_3$) δ8.90 (d, 1H), 8.29 (m, 2H), 8.01 (d, 1H), 7.39 (m, 2H), 5.52 (s, 2H). ^{13}C NMR ($CDCl_3$) δ155.4, 155.2, 152.2, 145.4, 144.9, 130.6, 125.3, 121,6, 61.9.

EXAMPLE 73

Alternative Preparation of N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine

EXAMPLE 73A

Thioisobutyramide

To a 1 liter three neck round bottom flask equipped with mechanical stirrer, nitrogen atmosphere, condensor, thermocouple and 15° C. water bath was charged (26.0 g, 0.298 mols)isobutyramide followed by (19.9 g, 0.045 mols) phosphorous pentasulfide and 375 mls THF. This solution was stirred at 20°±5° C. for 3 hours, then was warmed to 60° C. and stirred an additional 3 hours. The THF was removed under vacuum with a 50° C. bath temperature to afford a yellow oil. This oil was neutralized with a solution of 5 g NaOH, 10 g NaCl and 90 g water. Next the product was extracted into EtOAc (2×250 mls) and the combined organics reduced under vacuum to an oil. The oil was dissolved in 50 mls THF and again the solvent was removed under vacuum to give the desired product as a yellow oil. (yield approx. 27 grams, 88%).

EXAMPLE 73B

2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole

The thioisobutyramide resulting from Example 73A was dissolved in 70 mls THF and added slowly to a solution of (34.1 g, 0.27 mols) 1,3-dichloracetone in 40 mls THF. A 10 ml rinse of THF was used to completely transfer the thioamide. The reaction was carried out in a 250 ml flask with mechanical stirring under nitrogen atmosphere. The reaction temperature was maintained below 25° C. during addition with a 15°±5° C. bath. The bath was kept in place for 1 hour after which it was removed and the reaction stirred for 18 hours. Next this stirred chloromethyl-thiazole solution was added to 376 mls (4.37 mols) 40% aqueous methylamine solution at 15° C. in a 1 liter flask. The temperature was maintained below 25° C. during addition. After half an hour the bath was removed and the reaction stirred for 3 hours at ambient temperature. The solvent was removed under vacuum with a 50° C. bath to an end volume of 310 mls. The residue was then basified with 50 g 10% NaOH to pH 12 and extracted into methylene chloride (2×160 mls). The combined organics were then washed with 1×150 g of 20% ammonium chloride followed by 1×90 g of 20% ammonium chloride. The combined aqueous washes were then back extracted with 150 mls methylene chloride. The combined product methylene chloride layers were then extracted with 100 g of a solution of 25 g conc. HCl and 75 g water. This acidic product solution was then washed with 135 mls methylene chloride. Next the acidic product solution was cooled, then neutralized with 100 g 20% NaOH solution. The product was extracted from this mixture with methylene chloride (2×135 mls). The solvent was removed under vacuum to afford the desired product as an amber oil. (yield approx. 28 grams)

EXAMPLE 73C

N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino/carbonyl)-L-valine Methyl Ester

Into a 500 ml 3-neck round bottom flask equipped with mechanical stirrer, nitrogen atmosphere, thermocouple, heating mantle and condensor was charged the product of Example 73B (28.1 g, 0.165 mols), phenoxycarbonyl-(L)-valine (41.5 g, 0.165 mol) and 155 ml toluene. This solution was warmed to reflux (110° C.) and stirred for three hours, then cooled to 20°±5° C. and washed with 2×69 ml 10% citric acid followed by 1×69 ml water, 1×116 mls 4% sodium hydroxide, 1×58 ml 4% sodium hydroxide and finally 1×58 ml water. The organic product solution was then treated with 3 grams of activated carbon at reflux for 15 minutes, filtered through infusorial earth to remove carbon, and the carbon/infusorial earth cake was washed with 25 ml hot toluene. Next the solvent was removed to afford a brown oil which solidified upon cooling. This brown solid was dissolved with warming in 31 ml EtOAc and 257 ml heptane at 60°±5° C. This solution was slowly cooled to 25° C., stirred 12 hours, cooled further to 0° C., and stirred 3 hours. The crystals were collected by filtration and washed with 50 ml 1:9 EtOAc/Heptane. The solid was dried in a 50° C. vacuum oven for 12 hours to afford 41.5 grams of the desired product as a tan-colored solid (76.9%).

EXAMPLE 73D

N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine

To a one liter three neck flask was charged the product of Example 73C (50 g, 0.153 mol), lithium hydroxide monohydrate (13 g, 0.310 mol), 200 ml THF and 190 ml water. This hazy solution was stirred for 2 hours. The reaction was quenched with a solution of conc. HCl (32.4 g, 0.329 mol) in 65 mL water, the THF was removed under vacuum and the product extracted into methylene chloride (3×210 ml). (NOTE: If necessary, the pH of the aqueous layer should be adjusted to maintain pH 1–4 during the extractions.) The combined organics were then dried with 50 g sodium sulfate, filtered with a 150 ml methylene chloride rinse of the sodium sulfate, and the solvent was removed under vacuum. The product was dissolved in 450 ml THF and again the solvent was removed. Next the product was dissolved in 475 ml THF containing 0.12 g butylated hydroxytoluene (BHT) for storage. If desired, the solvent can be removed under vacuum and the residual syrup dried in a vacuum oven at 55° C. to provide a glassy solid.

Fluorogenic Assay for Screening Inhibitors of HIV Protease

The inhibitory potency of the compounds of the invention can be determined by the following method.

A compound of the invention is dissolved in DMSO and a small aliquot further diluted with DMSO to 100 times the final concentration desired for testing. The reaction is carried out in a 6×50 mm tube in a total volume of 300 microliters. The final concentrations of the components in the reaction buffer are: 125 mM sodium acetate, 1M sodium chloride, 5 mM dithiothreitol, 0.5 mg/ml bovine serum albumin, 1.3 μM fluorogenic substrate, 2% (v/v) dimethylsulfoxide, pH 4.5. After addition of inhibitor, the reaction mixture is placed in the fluorometer cell holder and incubated at 30° C. for several minutes. The reaction is initiated by the addition of a small aliquot of cold HIV protease. The fluorescence intensity (excitation 340 nM, emmision 490 nM) is recorded as a function of time. The reaction rate is determined for the first six to eight minutes. The observed rate is directly proportional to the moles of substrate cleaved per unit time. The percent inhibition is 100×(1-(rate in presence of inhibitor)/(rate in absence of inhibitor)).

Fluorogenic substrate: Dabcyl-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-EDANS wherein DABCYL=4-(4-dimethylaminophenyl)azobenzoic acid and EDANS=5-((2-aminoethyl)amino)-naphthalene-1-sulfonic acid.

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Table 1 shows the inhibitory potencies of compounds of the invention against HIV-1 protease.

TABLE 1

Compound of Example	Percent Inhibition	Inhibitor Concentration (nanomolar)
1	79	0.5
3	70	0.5
4	72	0.5
5	79	0.5
6	75	0.5
7	74	0.5
9	64	0.5
10	56	0.5
11	71	0.5
12	72	0.5
13	46	0.5
14	61	0.5
15	57	0.5
17	66	0.5
18	80	0.5
19	70	0.5
20	86	0.5
26	71	0.5
27	82	0.5
28	68	0.5
39	63	0.5
41	75	0.5
42	70	0.5
44	68	0.5
45	50	0.5
46	46	0.5
47	73	0.5
48	69	0.5
49	55	0.5
50	61	0.5
51	69	0.5
52	71	0.5
53	75	0.5
54	50	0.5
55	54	0.5
56	66	0.5
57	64	0.5
58	49	0.5
59	39	0.5
60	44	0.5
61	69	0.5
62	54	0.5
63	61	0.5
64	52	0.5
65	70	0.5

Antiviral Activity

The anti-HIV activity of the compounds of the invention can be determined in MT4 cells according to the procedure of Kempf, et. al. (*Antimicrob. Agents Chemother.* 1991, 35, 2209H). The IC_{50} is the concentration of compound that gives 50% inhibition of the cytopathic effect of HIV. The LC_{50} is the concentration of compound at which 50% of the cells remain viable.

Table 2 shows the inhibitory potencies of compounds of the invention against HIV-1_{3B} in MT4 cells.

TABLE 2

Compound of Example	IC_{50} (micromolar)	LC_{50} (micromolar)
1	0.025–0.040	55
3	0.041–0.075	52
4	0.17–0.32	29
5	0.003–0.009	51
6	0.006–0.014	100
7	0.076–0.131	56
8	0.057–0.095	97

TABLE 2-continued

Compound of Example	IC_{50} (micromolar)	LC_{50} (micromolar)
9	0.080–0.10	62
10	0.054–0.071	55
11	0.017–0.132	60
12	0.053–0.106	>100
13	0.056–0.088	56
14	0.14–0.22	>100
15	0.43–0.67	41
17	0.23–0.31	19
18	0.039–0.046	62
19	0.022–0.048	87
20	0.011–0.014	55
26	0.007–0.011	28
27	0.011–0.012	57
28	0.11–0.12	18
39	0.073–0.077	22
41	0.015–0.02	100
42	0.073–0.08	>100
44	0.12–0.16	19
45	0.036–0.040	19
46	0.10–0.17	61
47	0.009–0.024	25
48	0.09–0.11	>100
49	0.081–0.13	38
50	0.15–0.27	>100
51	0.045–0.049	48
52	0.025–0.042	26
53	0.032–0.073	59
54	0.11–0.17	19
55	0.14–0.22	17
56	0.05–0.067	100
57	0.035–0.048	>100
58	0.03–0.046	18
59	0.11–0.13	18
60	0.34–0.51	17
61	0.15–0.22	25
62	0.69–1.0	17
63	0.13–0.18	45
64	0.10–0.13	>100
65	0.12–0.20	>100

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate (isethionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

Preferred salts of the compounds of the invention include hydrochloride, methanesulfonate, sulfonate, phosphonate and isethionate.

The compounds of the present invention can also be used in the form of esters. Examples of such esters include a hydroxyl-substituted compound of formula A or A1 or A2 which has been acylated with a blocked or unblocked amino acid residue, a phosphate function, a hemisuccinate residue, an acyl residue of the formula R*C(O)— or R*C(S)— wherein R* is hydrogen, loweralkyl, haloalkyl, alkoxy, thioalkoxy, alkoxyalkyl, thioalkoxyalkyl or haloalkoxy, or an acyl residue of the formula R_a—C(R_bH)(R_dH)—C(O)— or R_a—C(R_bH)(R_dH)—C(S)— wherein R_b and R_d are independently selected from hydrogen or loweralkyl and R_a is —N—(R_eH)(R_fH), OR_e or —SR_e wherein R_e and R_f are independently selected from hydrogen, loweralkyl and haloalkyl, or an amino-acyl residue of the formula $R_{180}NH(CH_2H)_2NHCH_2C(O)$— or $R_{180}NH(CH_2H)2OCH_2C(O)$— wherein R_{180} is hydrogen, loweralkyl, arylalkyl, cycloalkylalkyl, alkanoyl, benzoyl or an a-amino acyl group. The amino acid esters of particular interest are glycine and lysine; however, other amino acid residues can also be used, including those wherein the amino acyl group is —$C(O)CH_2NR_{200}R_{201}$ wherein R_{200} and R_{201} are independently selected from hydrogen and loweralkyl or the group —$NR_{200}R_{201}$ forms a nitrogen containing heterocyclic ring. These esters serve as pro-drugs of the compounds of the present invention and serve to increase the solubility of these substances in the gastrointestinal tract. These esters also serve to increase solubility for intravenous administration of the compounds. Other prodrugs include a hydroxyl-substituted compound of formula A or A1 or A2 wherein the hydroxyl group is functionalized with a substituent of the formula —CH(R_gH)OC(O)R_{181} or —CH(R_gH)OC(S)R_{181} wherein R_{181} is loweralkyl, haloalkyl, alkoxy, thioalkoxy or haloalkoxy and R_g is hydrogen, loweralkyl, haloalkyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl or dialkylaminocarbonyl. Such prodrugs can be prepared according to the procedure of Schreiber (Tetrahedron Lett. 1983, 24, 2363H) by ozonolysis of the corresponding methallyl ether in methanol followed by treatment with acetic anhydride.

The prodrugs of this invention are metabolized in vivo to provide the hydroxyl-substituted compound of formula A or A1 or A2. The preparation of the prodrug esters is carried out by reacting a hydroxyl-substituted compound of formula A or A1 or A2 with an activated amino acyl, phosphoryl, hemisuccinyl or acyl derivative as defined above. The resulting product is then deprotected to provide the desired pro-drug ester. Prodrugs of the invention can also be prepared by alkylation of the hydroxyl group with (haloalkyl)esters, transacetalization with bis-(alkanoyl)acetals or condensation of the hydroxyl group with an activated aldehyde followed by acylation of the intermediate hemiacetal.

The compounds of the invention are useful for inhibiting retroviral protease, in particular HIV protease, in Vitro or in vivo (especially in mammals and in particular in humans). The compounds of the present invention are also useful for the inhibition of retroviruses in vivo, especially human immunodeficiency virus (HIV). The compounds of the present invention are also useful for the treatment or prophylaxis of diseases caused by retroviruses, especially acquired immune deficiency syndrome or an HIV infection in a human or other mammal.

Total daily dose administered to a human or other mammal host in single or divided doses may be in amounts, for example, from 0.001 to 300 mg/kg body weight daily and more usually 0.1 to 10 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically accept-

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able and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976H), p. 33 et seq.

One preferred dosage form for the compounds of the invention comprises a solid dosage form for oral administration comprising a pharmaceutically acceptable adsorbent to which is adsorbed a mixture of (1H) a pharmaceutically acceptable organic solvent or a mixture of two or more pharmaceutically acceptable organic solvents, (2H) a compound of the invention in the amount of from about 10% to about 40% by weight and (3) a total of from about 0.2 molar equivalents to about 2 molar equivalents (based on the compound of the invention) of a pharmaceutically acceptable acid. This composition is filled into hard gelatin capsules for administration. The preparation of a specific example of this type of dosage form is described below.

Solid-filled capsule Dosage Form Preparation

Propylene glycol (USP, 139 mL) and ethanol (dehydrated, USP, 200 proof, 139 mL) were mixed in a stainless steel or glass container. Hydrochloric acid (reagent grade, 20 mL) was added and mixed well. To this solution was added ascorbic acid (21 g) and the mixture was stirred until it was clear. The product of Example 1U (200 g) was slowly added to the solution and mixing was continued until the solution was clear. Cremophore® EL (polyoxyethyleneglycerol oxystearate, 41 g) and polysorbate 80, NF (41 g) were added with mixing.

Microcrystalline cellulose, NF (139 g) and silicon dioxide, NF (Syloid 244, pharmaceutical grade, 209 g) were charged into a Hobart mixer and mixed for 3–5 minutes. The above solution was added dropwise to the dry mixture in the Hobart mixer while mixing at slow speed. This mixture was massed until granular.

The wet granulation was screened through an 8 mesh screen. The screened granulation was spread on paper-lined trays and dried in a tray dryer or a fluidbed dryer (20°–35° C.) until the loss on drying was not more than 12%.

The concentration of the product of Example 1U (mg/g of granulation) in the granulation was determined by HPLC analysis. Capsules (gelatin, No. 00, iron gray opaque) were filled with the appropriate amount of the dried granulation to provide the desired dose per capsule.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents, other antiinfective agents or vaccines. Other antiviral agents to be administered in combination with a compound of the present invention include AU721, beta interferon, polymannoacetate, reverse transcriptase inhibitors (for example, dideoxycytidine (DDC), dideoxyinosine (DDI), BCH-189, AzdU, carbovir, DDA, D4C, D4T, DP-AZT, FLT (fluorothymidine), BCH-189, 5-halo-3'-thiadideoxycytidine, PMEA, zidovudine (AZT) and the like), non-nucleoside reverse transcriptase inhibitors (for example, R_{82193}, L-697,661, BI-RG-587 (nevirapine), retroviral protease inhibitors (for example, HIV protease inhibitors such as Ro 31-8959, SC-52151, KNI-227, KNI-272 and the like), HEPT compounds, L,697,639, R_{82150}, U-87201E and the like), TAT inhibitors (for example, RO-24–7429 and the like), trisodium phosphonoformate, HPA-23, eflonithine, Peptide T, Reticulose (nucleophosphoprotein), ansamycin LM 427, trimetrexate, UA001, ribavirin, alpha interferon, oxetanocin, oxetanocin-G, cylobut-G, cyclobut-A, ara-M, BW882C87, foscarnet, BW256U87, BW348U87, L-693,989, BV ara-U, CMV triclonal antibodies, FIAC, HOE-602,HPMPC, MSL-109, TI-23, trifluridine, vidarabine, famciclovir, penciclovir, acyclovir, ganciclovir, castanospermine, rCD4/CD4-IgG, CD4-PE40, butyl-DNJ, hypericin, oxamyristic acid, dextran sulfate and pentosan polysulfate. Immunomodulators that can be administered in combination with a compound of the present invention include bropirimine, Ampligen, anti-human alpha interferon antibody, colony stimulating factor, CL246,738, Imreg-1, Imreg-2, diethydithiocarbamate, interleukin-2, alpha-interferon, inosine pranobex, methionine enkephalin, muramyltripeptide, TP-5, erythropoietin, naltrexone, tumor necrosis facator, beta interferon, gamma interferon, interleukin-3, interleukin-4, autologous CD8+ infusion, alpha interferon immunoglobulin, IGF-1, anti-Leu-3A, autovaccination, biostimulation, extracorporeal photophoresis, FK-565, FK-506, G-CSF, GM-CSF, hyperthermia, isopinosine, IVIG, HIVIG, passive immunotherapy and polio vaccine hyperimmunization. Other antiinfective agents that can be administered in combination with a compound of the present invention include pentamidine isethionate. Any of a variety of HIV or AIDS vaccines (for example, gp120 (recombinant), Env 2–3 (gp120H), HIVAC-1e (gp120H), gp160 (recombinant), VaxSyn HIV-1 (gp160H), Immuno-Ag (gp160H), HGP-30,HIV-Immunogen, p24 (recombinant), VaxSyn HIV-1 (p24H) can be used in combination with a compound of the present invention.

Other agents that can be used in combination with the compounds of this invention are ansamycin LM 427, apurinic acid, ABPP, AI-721, carrisyn, AS-101, avarol, azimexon, colchicine, compound Q, CS-85, N-acetyl cysteine, (2-oxothiazolidine-4-carboxylate), D-penicillamine, diphenylhydantoin, EL-10, erythropoieten, fusidic acid, glucan, HPA-23, human growth hormone, hydroxchloroquine, iscador, L-ofloxacin or other quinolone antibiotics, lentinan, lithium carbonate, MM-1, monolaurin, MTP-PE, naltrexone, neurotropin, ozone, PAI, panax ginseng, pentofylline, pentoxifylline, Peptide T, pine cone extract, polymannoacetate, reticulose, retrogen, ribavirin, ribozymes, RS-47, Sdc-28, silicotungstate, THA, thymic humoral factor, thymopentin, thymosin fraction 5, thymosin alpha one, thymostimulin, UA001, uridine, vitamin B12 and wobemugos.

Other agents that can be used in combination with the compounds of this invention are antifungals such as amphotericin B, clotrimazole, flucytosine, fluconazole, itraconazole, ketoconazole and nystatin and the like.

Other agents that can be used in combination with the compounds of this invention are antibacterials such as amikacin sulfate, azithromycin, ciprofloxacin, tosufloxacin, clarithromycin, clofazimine, ethambutol, isoniazid, pyrazinamide, rifabutin, rifampin, streptomycin and TLC G-65 and the like.

Other agents that can be used in combination with the compounds of this invention are anti-neoplastics such as alpha interferon, COMP (cyclophosphamide, vincristine, methotrexate and prednisone), etoposide, mBACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone), PRO-MACE/MOPP(prednisone, methotrexate (w/leucovin rescue), doxorubicin, cyclophosphamide, etoposide/mechlorethamine, vincristine, prednisone and procarbazine), vincristine, vinblastine, angioinhibins, pentosan polysulfate, platelet factor 4 and SP-PG and the like.

Other agents that can be used in combination with the compounds of this invention are drugs for treating neuro-

logical disease such as peptide T, ritalin, lithium, elavil, phenytoin, carbamazipine, mexitetine, heparin and cytosine arabinoside and the like.

Other agents that can be used in combination with the compounds of this invention are anti-protozoals such as albendazole, azithromycin, clarithromycin, clindamycin, corticosteroids, dapsone, DIMP, eflornithine, 566C80, fansidar, furazolidone, L,671,329, letrazuril, metronidazole, paromycin, pefloxacin, pentamidine, piritrexim, primaquine, pyrimethamine, somatostatin, spiramycin, sulfadiazine, trimethoprim, TMP/SMX, trimetrexate and WR6026 and the like.

Among the preferred agents for treatment of HIV or AIDS in combination with the compounds of this invention are reverse transcriptase inhibitors.

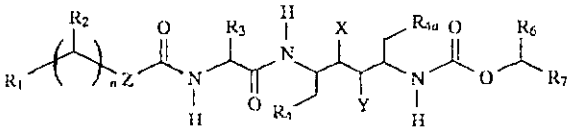
It will be understood that agents which can be combined with the compounds of the present invention for the treatment or prophylaxis of *AIDS* or an *HIV infection* are not limited to those listed above, but include in principle any agents useful for the treatment or prophylaxis of AIDS or an HIV infection.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

What is claimed is:

1. A compound of the formula:



wherein

R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl wherein the substituent is selected from (i) C_1–C_6-loweralkyl, (ii) C_2–C_6-loweralkenyl, (iii) C_3–C_7-cycloalkyl, (iv) C_3–C_7-cycloalkyl-C_1–C_6-alkyl, (v) C_5–C_7-cycloalkenyl, (vi) C_5–C_7-cycloalkyl-C_1–C_6-alkyl, (vii) C_1–C_6-alkoxy-C_1–C_6-alkyl or benzyloxy-C_1–C_6-alkyl, (viii) C_1–C_6-thioalkoxy-C_1–C_6-alkyl or benzyl- S—C_1–C_6-alkyl, (ix) C_1–C_6-alkylamino, (x) di-C_1–C_6-alkylamino, (xi) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, C_1–C_6-loweralkyl, hydroxy, C_1–C_6-alkoxy, benzyloxy, C_1–C_6-thioalkoxy and benzyl-S—, (xii) phenyl-C_1–C_6-alkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xiii) di-C_1–C_6-alkylamino-C_1–C_6-alkyl, (xiv) C_1–C_6-alkoxy or benzyloxy and (xv) C_1–C_6-thioalkoxy or benzyl-S—;

n is 1,2or 3;

R_2 is hydrogen or C_1–C_6-loweralkyl;

R_3 is C_1–C_6-loweralkyl;

R_4 and R_{4a} are independently selected from phenyl and substituted phenyl wherein the phenyl ring is substituted with a substituent selected from (i) halo, (ii) C_1–C_6-loweralkyl, (iii) hydroxy, (iv) C_1–C_6-alkoxy or benzyloxy and (v) C_1–C_6-thioalkoxy or benzyl-S—;

R_6 is hydrogen or C_1–C_6-loweralkyl;

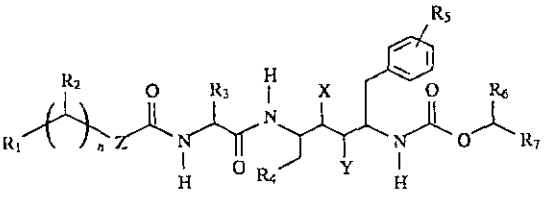
R_7 is thiazolyl or oxazolyl wherein the thiazolyl or oxazolyl ring is unsubstituted or substituted with C_1–C_6-loweralkyl;

X is hydrogen and Y is —OH ; and

Z is absent, —O—, —S—, —CH_2— or —$N(R_8)$— wherein R_8 is C_1–C_6-loweralkyl, C_3–C_7-cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen, C_1–C_6-loweralkyl or an N-protecting group selected from the group consisting of formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, benzenesulfonyl, p-toluenesulfonyl, benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, αα-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, benzyl, triphenylmethyl, benzyloxymethyl and trimethylsilyl;

or a *pharmaceutically acceptable salt thereof.*

2. A compound of the formula:



wherein

R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl wherein the substituent is selected from (i) C_1–C_6-loweralkyl, (ii) C_2–C_6-loweralkenyl, (iii) C_3–C_7-cycloalkyl, (iv) C_3–C_7-cycloalkyl-C_1–C_6-alkyl, (v) C_5–C_7-cycloalkenyl, (vi) C_5–C_7-cycloalkenyl-C_1–C_6-alkyl, (vii) C_1–C_6-alkoxy -C_1–C_6-alkyl or benzyloxy-C_1–C_6-alkyl, (viii) C_1–C_6-thioalkoxy-C_1–C_6-alkyl or benzyl-S—C_1–C_6-alkyl, (ix) C_1–C_6-alkylamino, (x) di-C_1–C_6-alkylamino, (xi) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, C_1–C_6-loweralkyl, hydroxy, C_1–C_6-alkoxy, benzyloxy, C_1–C_6-thioalkoxy and benzyl-S—, (xii) phenyl -C_1–C_6-alkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xiii) di-C_1–C_6-alkylamino -C_1–C_6-alkyl, (xiv) C_1–C_6-alkoxy or benzyloxy and (xv) C_1–C_6-thioalkoxy or benzyl-S—;

n is 1;

R_2 is hydrogen or C_1–C_6-loweralkyl;

R_3 is C_1–C_6-loweralkyl;

R_4 is phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii) C_1–C_6-loweralkyl, (iii) hydroxy, (iv) C_1–C_6-alkoxy or benzyloxy and (v) C_1–C_6-thioalkoxy or benzyl-S—:

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R_5 is hydrogen, halo, C_1–C_6-loweralkyl, hydroxy, C_1–C_6-alkoxy, benzyloxy, C_1–C_6-thioalkoxy or benzyl-S—;

R_6 is hydrogen or C_1–C_6-loweralkyl;

R_7 is thiazolyl or oxazolyl wherein the thiazolyl or oxazolyl ring is unsubstituted or substituted with C_1–C_6-loweralkyl;

X is hydrogen and Y is —OH;

Z is absent, —O—, —S—, —CH_2— or —N(R_8)-wherein R_8 is C_1–C_6-loweralkyl, C_3–C_7-cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen or C_1–C_6-loweralkyl; or a pharmaceutically acceptable salt thereof.

3. The compound of claim **2** wherein R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen and R_7 is thiazolyl or oxazolyl.

4. The compound of claim **3** wherein R_7 is 5-thiazolyl or 5-oxazolyl.

5. The compound of claim **2** wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is C_1–C_6-loweralkyl; ; R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl or 5-oxazolyl; and Z is —O— or —N-(R_8)— wherein R_8 is C_1–C_6-loweralkyl.

6. The compound of claim **2** wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; R_2 is hydrogen; R_3 is methyl or isopropyl; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl or 5-oxazolyl; and Z is —O—.

7. The compound of claim **2** wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; R_2 is hydrogen; R_3 is isopropyl; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl or 5-oxazolyl; and Z is —N-(R_8)— wherein R_8 is methyl.

8. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; or a pharmaceutically acceptable salt thereof.

9. A compound selected from the group consisting of:

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl)-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

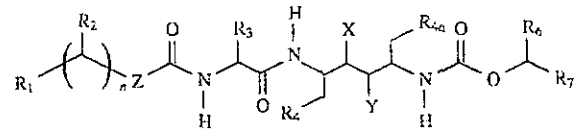
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; and

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

or a pharmaceutically acceptable salt thereof.

10. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; or a pharmaceutically acceptable salt thereof.

11. A compound of the formula:



wherein

R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl wherein the substituent is selected from (i) C_1–C_6-loweralkyl, (ii) C_2–C_6-loweralkenyl, (iii) C_3–C_7-cycloalkyl, (iv) C_3–C_7-cycloalkyl-C_1–C_6-alkyl, (v) C_5–C_7-cycloalkenyl, (vi) C_5–C_7-cycloalkenyl-C_1–C_6-alkyl, (vii) C_1–C_6-alkoxy-C_1–C_6-alkyl or benzyloxy-C_1–C_6-alkyl, (viii) C_1–C_6-thioalkoxy -C_1–C_6-alkyl or benzyl-S—C_1–C_6-alkyl, (ix) C_1–C_6-alkylamino, (x) di-C_1–C_6-alkylamino, (xi) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, C_1–C_6loweralkyl, hydroxy, C_1–C_6-alkoxy, benzyloxy, C_1–C_6-thioalkoxy and benzyl-S—, (xii) phenyl -C_1–C_6-alkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xiii) di-C_1–C_6-alkylamino-C_1–C_6-alkyl, (xiv) C_1–C_6-alkoxy or benzyloxy and (xv) C_1–C_6-thioalkoxy or benzyl-S—;

n is 1,2 or 3;

R_2 is hydrogen or C_1–C_6-loweralkyl;

R_4 and R_{4a} are independently selected from phenyl and substituted phenyl wherein the phenyl ring is substituted with a substituent selected from (i) halo, (ii) C_1–C_6-loweralkyl, (iii) hydroxy, (iv) C_1–C_6-alkoxy or benzyloxy and (v) C_1–C_6-thioalkoxy or benzyl-S—;

R_6 is hydrogen or C_1–C_6-loweralkyl;

R_7 is thiazolyl or oxazolyl wherein the thiazolyl or oxazolyl ring is unsubstituted and R_3 is C_2–C_6-loweralkyl and Z is absent, —O—, —S— or —CH_2—; or

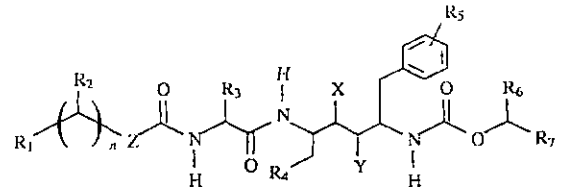
R_7 is thiazolyl or oxazolyl wherein the thiazolyl or oxazolyl ring is substituted with C_1–C_6-loweralkyl and R_3 is C_1–C_6-loweralkyl and Z is absent, —O—, —S—, —CH_2—Nor —(R_8)— wherein R_8 is C_1–C_6-loweralkyl, C_3–C_7-cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen, C_1–C_6-loweralkyl or an N-protecting group selected from the group consisting of formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, benzenesulfonyl, p-toluenesulfonyl, benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p- nitrobenzyloxycarbonyl, 2- nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl,

benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, benzyl, triphenylmethyl, benzyloxymethyl and trimethylsilyl; and

X is —OH and Y is hydrogen;

or a pharmaceutically acceptable salt thereof.

12. A compound of the formula:



wherein

R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl wherein the substituent is selected from (i) C_1–C_6-loweralkyl, (ii) C_2–C_6-loweralkenyl, (iii) C_3–C_7-cycloalkyl, (iv) C_3–C_7-cycloalkyl-C_1–C_6-alkyl, (v) C_5–C_7-cycloalkenyl, (vi) C_5–C_7-cycloalkenyl-C_1–C_6-alkyl, (vii) C_1–C_6-alkoxy-C_1–C_6-alkyl or benzyloxy-C_1–C_6-alkyl, (viii) C_1–C_6-thioalkoxy-C_1–C_6-alkyl or benzyl-S—C_1–C_6-alkyl, (ix) C_1–C_6-alkylamino, (x) di-C_1–C_6-alkylamino, (xi) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, C_1–C_6-loweralkyl, hydroxy, C_1–C_6-alkoxy, benzyloxy, C_1–C_6-thioalkoxy and benzyl-S—, (xii) phenyl -C_1–C_6-alkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xiii) di-C_1–C_6-alkylamino -C_1–C_6-alkyl, (xiv) C_1–C_6-alkoxy or benzyloxy and (xv) C_1–C_6-thioalkoxy or benzyl-S—;

n is 1;

R_2 is hydrogen or C_1–C_6-loweralkyl;

R_4 is phenyl or substituted phenyl wherein the phenyl ring is substituted with a substituent selected from (i) halo, (ii) C_1–C_6-loweralkyl, (iii) hydroxy, (iv) C_1–C_6-alkoxy or benzyloxy and (v) C_1–C_6-thioalkoxy or benzyl-S—;

R_5 is hydrogen or C_1–C_6-loweralkyl;

R_7 is thiazolyl or oxazolyl wherein the thiazolyl or oxazolyl ring is unsubstituted and R_3 is C_2–C_6-loweralkyl and Z is absent, —O—, —S— or —CH_2—; or

R_7 is thiazolyl or oxazolyl wherein the thiazolyl or oxazolyl ring is substituted with C_1–C_6-loweralkyl and R_3 is C_1–C_6-loweralkyl and Z is absent, —O—, —S—, —CH_2— or —N(R_8)— wherein R_8 is C_1–C_6-loweralkyl, C_3–C_7-cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen or C_1–C_6-loweralkyl; and

X is —OH and Y is hydrogen;

or a pharmaceutically acceptable salt thereof.

13. A compound selected from the group consisting of:

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S, 5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl-)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-(cyclopentenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-2-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-(cyclopentyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-(4-fluoro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

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(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methoxy)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isoproploxy-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S,)-5-(N-(N-(N-Methyl-N-((2-(methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)analinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-Isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-(1-(2-Isopropyl-4-thiazolyl)ethoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S, 3S, 5S) -5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(N,N-Diethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-(((N,N-dimethylamino)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((2-Isopropyl-4-thiazolyl)thiomethoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-(3-(2-Isopropyl-4-thiazolyl)propanoyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-(1-(5-thiazolyl)ethoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl-)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-ethyl-4-thiazolyl-)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane:

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-2-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-pentyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-(((2-isopropyl)-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(2-Isopropyl-4-thiazolyl)ethoxy)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(2-Isopropyl-4-thiazolyl)ethoxy)carbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)acetyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-(1-Propyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-(Isobutyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isobutyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Ethyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-((N-Methyl-N-(2-(2-isopropyl-4-thiazolyl)ethyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-(tert-Butyloxycarbonylamino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; and

(2S,3S,5S)-5-(N-(N-((N-(Amino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane Hydrochloride;

or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition for inhibiting HIV protease comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim **1**.

15. A pharmaceutical composition for inhibiting HIV protease comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim **2**.

16. A pharmaceutical composition for inhibiting HIV protease comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim **10**.

17. A pharmaceutical composition for inhibiting an HIV infection comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim **10**.

18. A method for inhibiting HIV protease comprising administering to a human in need thereof a therapeutically effective amount of a compound of claim **10**.

19. A method for inhibiting an HIV infection comprising administering to a human in need thereof a therapeutically effective amount of a compound of claim **10**.

* * * * *

Exhibit-2

US005567823A

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United States Patent [19]

Tien et al.

[11] Patent Number: 5,567,823

[45] Date of Patent: Oct. 22, 1996

[54] **PROCESS FOR THE PREPARATION OF AN HIV PROTEASE INHIBITING COMPOUND**

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[21] Appl. No.: **469,965**

[22] Filed: **Jun. 6, 1995**

[51] **Int. Cl.**[6] **C07D 417/12**

[52] **U.S. Cl.** **548/204**

[58] **Field of Search** 548/204

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[57] **ABSTRACT**

Processes are disclosed for the preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl) amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane or an acid addition salt thereof and (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl) methyl)amino)carbonyl)-D-valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane or an acid addition salt thereof.

8 Claims, No Drawings

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PROCESS FOR THE PREPARATION OF AN HIV PROTEASE INHIBITING COMPOUND

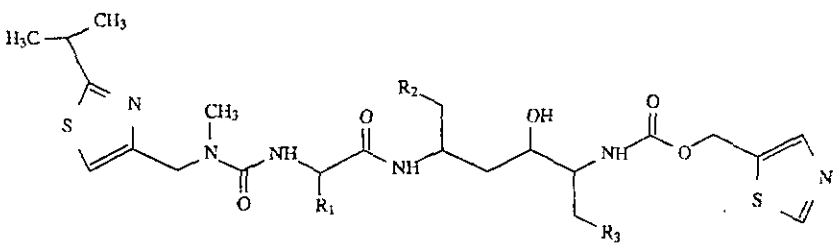
TECHNICAL FIELD

The present invention relates to a process for the preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

BACKGROUND OF THE INVENTION

It has recently been determined that HIV protease inhibiting compounds are useful for inhibiting HIV protease in vitro and in vivo and are also useful for inhibiting an HIV (human immunodeficiency virus) infection.

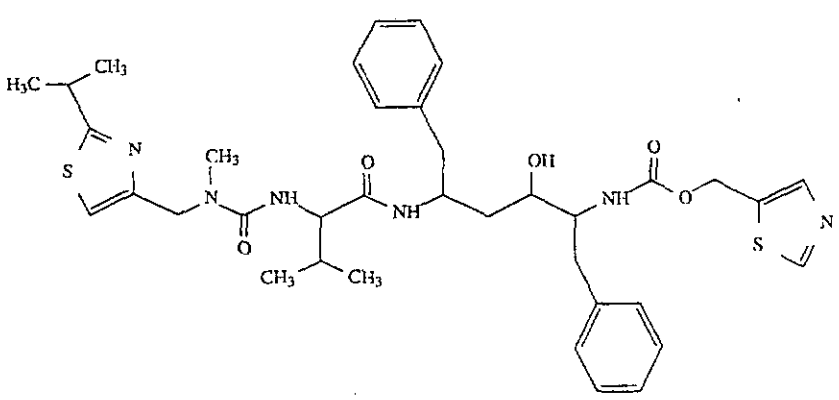
It has also recently been determined that compounds of the formula I:



I

wherein R_1 is lower alkyl and R_2 and R_3 are phenyl are particularly useful as inhibitors of HIV-1 and HIV-2 protease and are useful for inhibiting HIV protease in vitro and in vivo and are also useful to inhibit HIV infections.

In particular, the compound of formula II, has been found to be especially effective as an inhibitor of HIV-1 and HIV-2 protease.



II

The most preferred compounds of formula II are (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)- 1,6-diphenyl-3-hydroxyhexane (compound III) or an acid addition salt

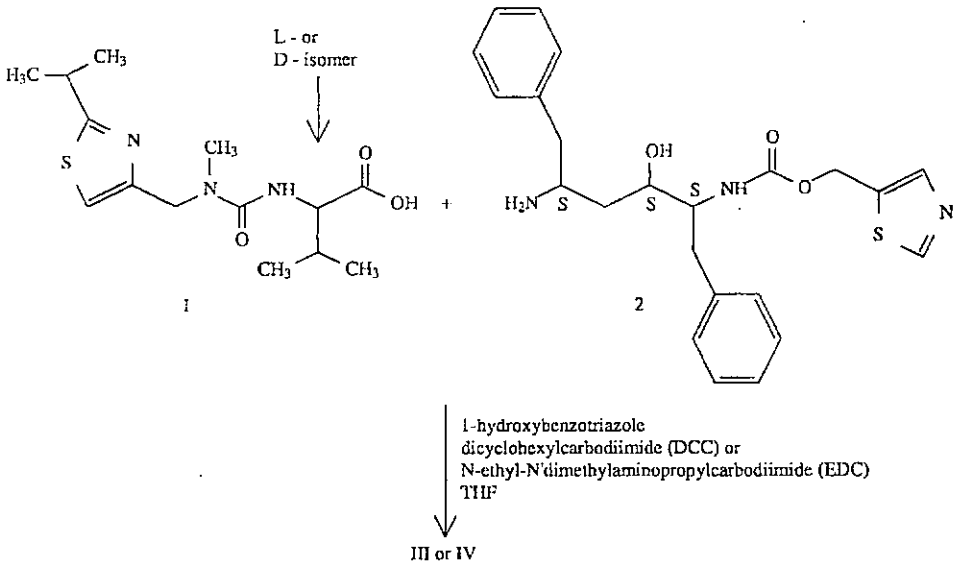
thereof and (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-D-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (compound IV) or an acid addition salt thereof.

The preparation of compound III and its use as an inhibitor of HIV protease are disclosed in PCT Patent Application No. WO94/14436, published Jul. 7, 1994, which is incorporated herein by reference. The method disclosed for preparing compound III is shown in Scheme I. This method involves an amide bond forming coupling reaction of intermediates 1 and 2 in the presence of 1-hydroxybenzotriazole and diimide such as dicyclohexylcarbodiimide (DCC) or N-ethyl-N'-dimethylaminopropyl carbodiimide (EDC) and the like. Such a process is not suitable for manufacturing scale production of III or IV because the diimides are toxic, they are sensitizers and they present a variety of other handling and workup problems.

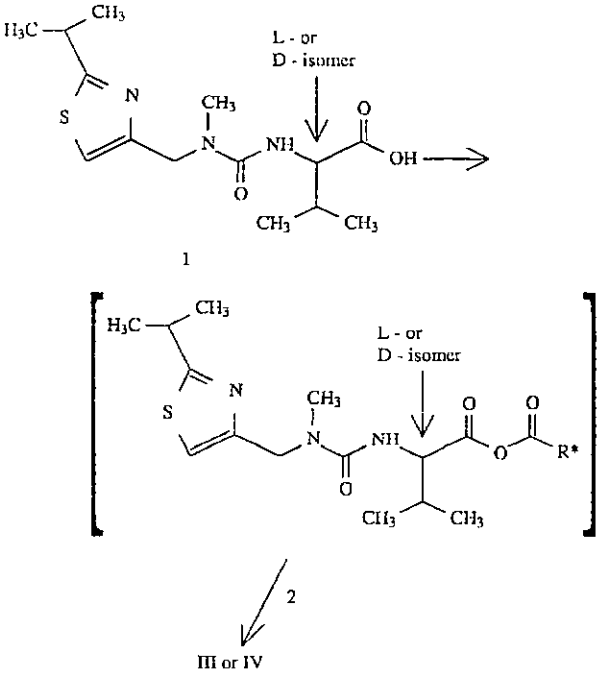
An alternative process is shown in Scheme II. In this process, intermediate 1 is converted to a mixed anhydride (wherein R* is loweralkyl, for example, by reaction with an alkyl chloroformate such as isobutylchloroformate and the like or by reaction with an alkanoyl chloride such as pivaloylchloride and the like). The mixed anhydride is then reacted (without isolation) with intermediate 2. Because of the high reactivity of the intermediate mixed anhydride, this process often leads to unacceptable amounts of undesired side products.

Therefore, there is a continuing need for an improved coupling process for the preparation of III and IV.

SCHEME I



SCHEME II



DISCLOSURE OF THE INVENTION

The present invention relates to processes for the preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (compound III) and (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-D-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (compound IV). The process is shown in Scheme 3. The process comprises three steps carried out without isolation of the intermediates. The first step comprises formation of an intermediate mixed anhydride derivative 3 (R* is loweralkyl or alkoxy).

In the second step, the mixed anhydride (without isolation) is converted to an intermediate activated ester derivative 4 (R** is selected from the group consisting of succinimid-1-yl, benzotriazol-1-yl, phthalimid-1-yl, 5-norbornene-2,3-dicarboximidyl, quinolin-8-yl, 1,2,3-benzotrazin-4(3H)-on-3-yl, piperidin-1-yl, pentachlorophenyl, 2,4,5-trichlorophenyl, 2-nitrophenyl, 4-nitrophenyl, pentafluorophenyl and the like).

In the third step, the activated ester (without isolation) is reacted with intermediate 2 to give the desired product. This process results in the preparation of highly pure III or IV on a manufacturing scale without complex purification procedures and without exposure to highly toxic or corrosive reagents.

In particular, the process of this invention comprises reacting intermediate 1 with a loweralkylchloroformate (for example, isobutylchloroformate or ethylchloroformate or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) or 2-isobutoxy-2-isobutoxycarbonyl-1,2-dihyroquinoline (IIDQ) and the like) or with a loweralkyl acid chloride (for example, pivaloylchloride and the like) to provide intermediate mixed anhydride 3. This reaction is carried out by reacting compound 1 with from about 0.9 molar equivalent to about 1.0 molar equivalents (based on the amount of compound 1) of the chloroformate or the acid chloride or like reagent in an inert solvent such as ethyl acetate or THF or acetonitrile or toluene and the like at a temperature of from about −20° C. to about 30° C. This reaction is preferably carried out in the presence of from about 1.0 molar equivalents to about 3.0 molar equivalents (based on the amount of compound 1) of an acid scavenger such as N-methylmorpholine or triethylamine or pyridine and the like.

To the resulting solution is added from about 1.0 molar equivalent to about 2.0 molar equivalents (based on the amount of compound 1) of R**OH, maintaining the temperature of the solution at from about −20° C. to about 30° C. to provide the activated ester. To the resulting solution of activated ester is added a solution of intermediate compound 2 in an inert solvent such as ethyl acetate or THF or DMF

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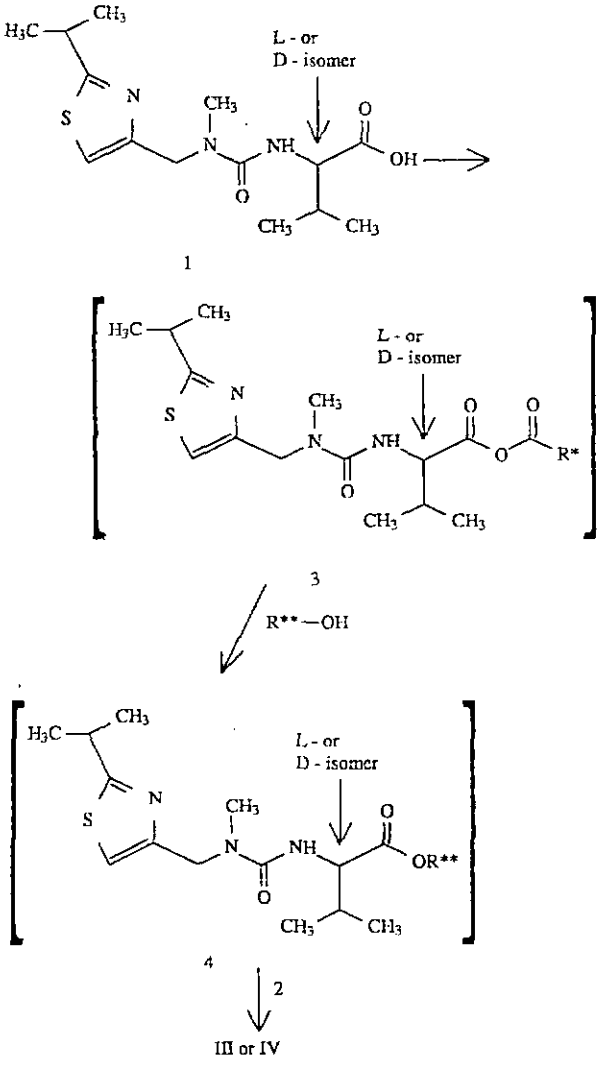
or acetonitrile or toluene and the like at a temperature of from about −20° C. to about 60° C. The resulting product III or IV can then be purified by recrystallization.

The first step of the process is preferably carried out by reacting intermediate compound 1 with about 1.0 molar equivalents of isobutyl chloroformate in ethyl acetate at about −15° C. in the presence of about 1.5 molar equivalents of N-methylmorpholine.

The second step of the process is preferably carried out by adding about 1.0 molar equivalent of N-hydroxysuccinimide to the solution of the mixed anhydride resulting from step one and maintaining the temperature of the solution at about 0° C.

The third step of the process is preferably carried out by adding to the solution of the activated ester resulting from step two a solution of from about 0.9 to about 1.0 molar equivalent of compound 2 in ethyl acetate at a temperature of about 0° C. This mixture is allowed to warm to about room temperature and is stirred for about 24 hours. The crude product can be purified by recrystallization from heptane/ethyl acetate.

SCHEME III



Acid addition salts of the compounds of the invention can be derived from reaction of an amine-containing compound of the invention with an inorganic or organic acid. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate (isethionate), lactate, maleate, malonate, glutarate, malate, mandelate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate.

Examples of acids which may be employed to form acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid, as well as the other acids mentioned above.

The term "loweralkyl" as used herein refers to a straight or branched chain alkyl radical containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "alkoxy" as used herein refers to RO- wherein R is a loweralkyl group.

The term "alkanoyl" as used herein refers to R'C(O)- wherein R' is a loweralkyl group.

As used herein, the terms "S" and "R" configuration are as defined by the IUPAC 1974 Recommendations for section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13 −30.

The following examples will serve to further illustrate the processes of the invention.

EXAMPLE 1

(2S,3S,5S)-5-amino-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

To a 750 gallon glass lined reactor were charged (2S, 3S, 5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane—0.5succinic acid salt (75.0 kg, 169 moles), 5-(p-nitrophenyloxycarbonyloxymethyl)thiazole hydrochloride (65.0 kg, 205 moles) and sodium bicarbonate (70.0 kg, 833 moles). Ethyl acetate (826 kg, 918 L) was added and the agitator was started. Tap water (788 kg) was added and the mixture was warmed to 30° C. and stirred for 2.5 hours until all of the solids were dissolved. After settling for 30 minutes, the aqueous layer was separated and discarded. The organic layer was warmed to 60° C. and stirred for 12 hours. The solution was then cooled to 30° C. and 28% ammonia water (9.0 kg, 148 moles) was added. The mixture was stirred for 3 hours at 25°–30° C. The mixture was washed three times with aqueous 10% potassium carbonate solution (903 kg each time). The aqueous layers were drained and discarded after each wash. Concentrated hydrochloric acid (59.0 kg, 600 moles) was added to the ethyl acetate solution and warmed to 50° C. with stirring for 3 hours.

The mixture was then cooled to 40° C. and the resulting precipitate was isolated by centrifugation. Five separate batches of 26 to 51 kg wet weight were obtained and each batch was rinsed with 50 kg of ethyl acetate. The wet solids were combined and charged back into the reactor and slurried in ethyl acetate (723 kg, 803 L). Dilute ammonia water (about 9.4% ammonia, about 190 L) was charged to

give a final aqueous pH of about 10.5. The aqueous layer was drained and discarded. The organic layer was washed with 25% sodium chloride solution (513 kg) and the aqueous layer was drained and discarded. The organic layer was filtered into a 300 gallon glass lined reactor and the, solvent was distilled under vacuum at an internal temperature of 40° C. or less. The residue was dissolved in ethyl acetate (576 kg, 640 L) and the solvent was distilled under vacuum until a volume of approximately 290 L was reached.

EXAMPLE 2

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

To a 750 gallon glass lined reactor was charged N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine (57.0 kg, 182 moles) and ethyl acetate (916 kg, 1018 L). The mixture was stirred until everything was in solution and then N-methylmorpholine (28.0 kg, 277 moles) was charged to the reactor and the resulting solution was cooled to −18° C. A solution of isobutyl chloroformate (24.4 kg, 180 moles) in ethyl acetate (101 kg, 112 L) was prepared in a separate reactor. The isobutyl chloroformate solution was charged (over about 50 minutes) into the cold solution of the valine derivative and N-methylmorpholine prepared above, maintaining the temperature at between −18° C. and −14° C. After stirring at −14° C. for about 30 minutes, N-hydroxysuccinimide (21.2 kg, 184 moles) was added to the mixture. After stirring for an additional 30 minutes, the mixture was warmed to about 0° C. and stirred for about one hour.

The resulting solution from Example 1 was cooled to about 0° C and charged slowly into the above solution. A rinse of the 300 gallon reactor with ethyl acetate (50 kg, 56L) was also added. The reaction mixture was warmed to 25 ° C. and was stirred for 24 hours. The reaction mixture was washed twice with 10% potassium carbonate solution (2×711 kg), once with 10% citric acid solution (1025 kg) and once with water (640 kg). The aqueous layers were drained and discarded after each separation. The solvent was distilled under vacuum at an internal temperature of about 50° C. or less. The residue was dissolved in ethyl acetate (576 kg, 640 L) and the solvent was distilled once more. The residue was dissolved in ethyl acetate (500 kg, 556 L) and warmed to about 60° C. until a clear solution was obtained. The solution was filtered into a clean 300 gallon reactor and a rinse of ethyl acetate (77 kg, 86 L) was also filtered into the 300 gallon reactor. Heptane (218 kg, 320 L) was charged to the ethyl acetate solution in the 300 gallon reactor. The mixture was heated to about 80° C. until a clear solution was obtained. The solution was cooled at a rate of less than 25° C. per hour to a final temperature of 22° C. and was stirred for another 12 hours after the product began to crystallize. The thick slurry was centrifuged in four separate loads to isolate the product. Each isolated load was washed with approximately 45 kg of a 2:1 (v/v) solution of ethyl acetate/heptane. The last wash was used to also rinse the reactor. The product was dried in a blender drier under vacuum at 55° C. for about 24 hours to provide 101.9 kg of the desired product.

m.p. 121°–123° C. ^{1}H NMR: (CD_3OD, 300 MHz) δ 7.78–7.96(m, 1H), 7.85 (s, 1H), 7.07–7.33 (m, 11H), 6.68–6.75 (m, 1H), 6.17–6.28 (m, 1H), 5.22 (s, 2H), 4.47–4.67 (m, 2H), 4.32–4.45 (m, 1H), 3.98–4.10 (m, 2H), 3.72–3.82 (m, 1H), 3.28–3.40 (m,1H), 3.02 (s, 3H), 2.67–2.92 (m, 4H), 1.92–2.08 (m, 1H), 1,56–1.80 (m, 2H), 1.37–1.46 (m, 6H), 0.84–0.96 (m, 6H). ^{13}C NMR; (CD_3OD, 75 MHz) δ 176.0, 169.8, 155.7, 153.7, 152.4, 149.3, 139.3, 139.2, 135.8, 135.2, 126.3, 126.0, 124.9, 124.8, 122.9, 122.8, 111.2, 111.1,66.5, 57.6, 57.5, 54.5, 52.9, 52.8, 45.4, 37.3, 35.7, 34.9, 30.9, 30.0, 27.7, 19.3, 19.2, 15.7, 14.5.

EXAMPLE 3

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-D-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino-1,6-diphenyl-3-hydroxyhexane

The title compound is prepared following the procedure of Example 2 with replacement of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-D-valine.

m.p.68°–69° C. ^{1}H NMR (DMSO-d_6) δ 0.56 (d, J=6Hz, 3H), 0.63 (d, J=6Hz, 3H), 1.28 (d, J=7Hz, 6H), 1.47 (m, 2H), 1.77 (octet, J=6Hz, 1H), 2.5–2.7 (m, 4H), 2.85 (s, 3H), 3.20 (heptet, J=7Hz, 1H), 3.4 (m, 1H), 3.6 (m, 1H),3.90 (dd, J=8, 6Hz, 1H), 3.93 (m, 1H), 4.43 (AA', 2H), 4.65 (d, J=6Hz, 1H), 5.15 (AA', 2H), 6.02 (br d, J=9Hz, 1H), 6.90 (br d, J=9Hz, 1H), 7.1–7.2 (m,11H), 7.70 (br d, J=9Hz, 1H), 7.85 (s, 1H). 9.04 (s, 1H). Mass spectrum: $(M+H)^+$ =721.

EXAMPLE 4

Alternative Preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

To a 250 mL 4-neck round bottom flask equipped with a mechanical stirrer, nitrogen atmosphere, 60 mL side arm addition funnel and a thermocouple was charged N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine (5.03 g, 16 mmoles) and ethyl acetate (93 mL). The mixture was stirred until all of the solids were dissolved and was then cooled to −15° C. To the cooled solution was added N-methylmorpholine (1.77 ML, 16 mmoles). The mixture was cooled to −18° C. Isobutyl chloroformate (2.08 mL, 16 mmoles) in ethyl acetate (8 mL) was added, maintaining the temperature of the reaction mixture below −14.5° C. After stirring for 1 hour at −17° C., 1-hydroxybenzotriazole (2.46 g, 16 mmoles) was added in one portion. The resulting slurry was warmed to 0° C. and was maintained at or below 0° C. as (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (6.4 g, 15 mmoles) in ethyl acetate (25 mL) was added. The resulting mixture was stirred at 0° C. for 1 hour and then allowed to warm to room temperature and stirred for 15 hours. To the reaction mixture was added 75 mL of 5% aqueous sodium bicarbonate. The organic layer was separated and washed again with 75 mL of 5% aqueous sodium bicarbonate, followed by washing twice with 75 mL of 10% aqueous citric acid each time and, finally, with 75 mL of water. The solvent was removed under vacuum and the residue crystallized from 270 mL of heptane/ethyl acetate 1:1 to provide 9.25 g of the desired product.

EXAMPLE 5

Alternative Preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

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In a three liter flask, N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valine (196.6 g, 0.627 moles) and 1-hydroxybenzotriazole (107 g, 0.701 moles) and THF (1.6 L) were mixed. A solution of dicyclohexylcarbodiimide (129.4 g, 0.627 moles)in THF (200 mL) was added in one portion. The resulting mixture was stirred overnight at room temperature.

The reaction mixture was filtered and the filter cake was washed with THF (500 mL). The filtrate was added to a solution of (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (238.9 g, 561 moles) dissolved in THF (3.5 L) at room temperature. After stirring for 4 hours, the THF was evaporated under reduced pressure. The residue was dissolved in methylene chloride (2L) and washed 0.5 M aqueous NaOH (1.25 L) and then with ½ saturated aqueous sodium bicarbonate (1L). The organic solution was then washed with 1% aqueous KH_2SO_4 (1 L). The resulting mixture was filtered and the phases separated. The organic solution was washed with 1 L of a 1:1 mixture of ½ saturated aqueous sodium chloride and ½ saturated pH 7 aqueous phosphate buffer. The organic solution was then dried over Na_2SO_4 and the solvent evaporated to give a tan foam.

The crude product was dissolved in methylene chloride (1.1 L) and the solvent evaporated to provide a brittle foam. This foam was dissolved in 1M aqueous HCl (3 L) at 10° C. The resulting insoluble material was filtered and the filter cake was washed with 1M aqueous HCl (100 mL). In a 12 L Morton flask, the filtrate was combined with KH_2PO_4 (100 g) and methylene chloride (2.2 L). With rapid stirring, the solution was neutralized to pH 6 with 2M aqueous NaOH. The bottom layer was drained and the aqueous layer was extracted with methylene chloride (2×500 mL). The combined organic layers were dried over Na_2SO_4, diluted with ethyl acetate (1 L) and concentrated to a colorless foam.

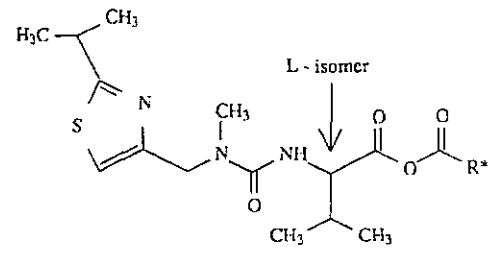
The resulting solid was recrystallized by dissolving in hot ethyl acetate (2 L), diluting with hot hexane (1 L), addition of seed crystals, stirring until cool and letting stand at room temperature overnight to provide the desired product as a white solid. m.p. 122° C.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed embodiments. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

What is claimed is:

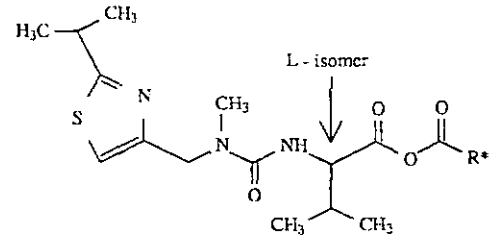
1. A process for the preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane or an acid addition salt thereof comprising converting a mixed anhydride derivative of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine to an activated ester derivative of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine, followed by reacting the activated ester with (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

2. The process of claim 1 comprising converting a compound of the formula:

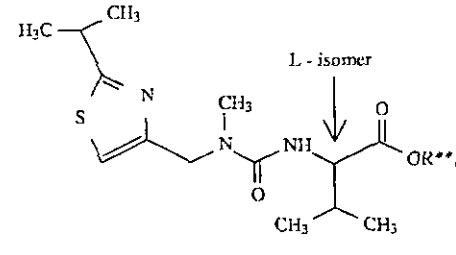


wherein R* is loweralkyl or alkoxy to an activated ester derivative of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine, followed by reacting the activated ester with (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

3. The process of claim 1 comprising reacting a compound of the formula:

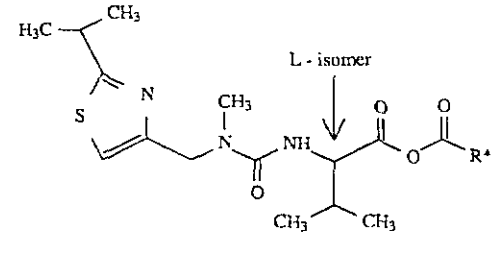


wherein R* is loweralkyl or alkoxy with R**OH wherein R** is selected from the group consisting of succinimid-1-yl, benzotriazol-1-yl, phthalimid-1-yl, 5-norbornene-2,3-dicarboximidyl, quinolin-8-yl, 1,2,3-benzotrazin-4(3H)-on-3-yl, piperidin-1-yl, pentachlorophenyl, 2,4,5-trichlorophenyl, 2-nitrophenyl, 4-nitrophenyl and pentafluorophenyl to provide an activated ester of the formula:

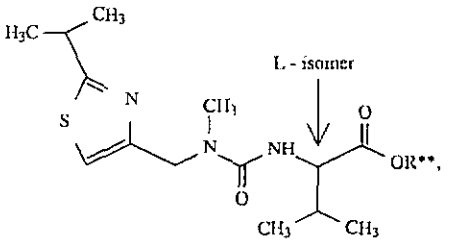


followed by reacting the activated ester with (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

4. A process for the preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane or an acid addition salt thereof comprising reacting a compound of the formula:



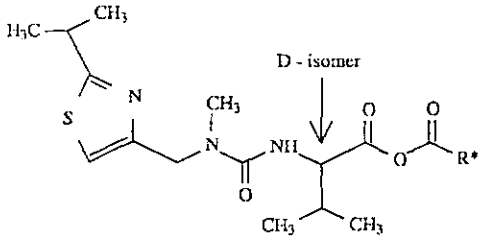
wherein R* is isobutoxy with R**OH wherein R** is succinimid-1-yl to provide an activated ester of the formula:



followed by reacting the activated ester with (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

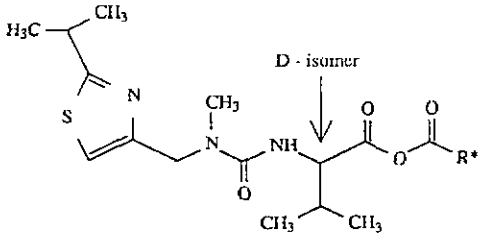
5. A process for the preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-D-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane or an acid addition salt thereof comprising converting a mixed anhydride derivative of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-D-valine to an activated ester derivative of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-D-valine, followed by reacting the activated ester with (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

6. The process of claim 5 comprising converting a compound of the formula:

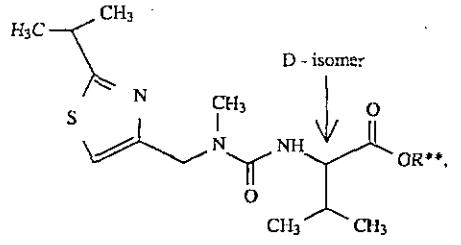


wherein R* is loweralkyl or alkoxy to an activated ester derivative of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-D-valine, followed by reacting the activated ester with (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

7. The process of claim 5 comprising reacting a compound of the formula:

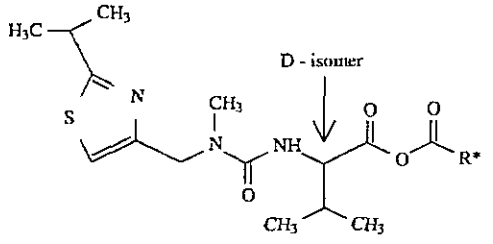


wherein R* is loweralkyl or alkoxy with R**OH wherein R** is selected from the group consisting of succinimid-1-yl, benzotriazol-1-yl, phthalimid-1-yl, 5-norbornene-2,3-dicarboximidyl, quinolin-8yl, 1,2,3-benzotrazin-4(3H)-on-3-yl, piperidin-1-yl, pentachlorophenyl, 2,4,5-trichlorophenyl, 2-nitrophenyl, 4-nitrophenyl and pentafluorophenyl to provide an activated ester of the formula:

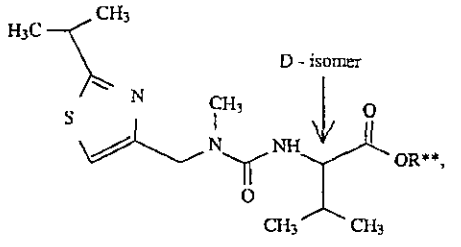


followed by reacting the activated ester with (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

8. A process for the preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-D-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane or an acid addition salt thereof comprising reacting a compound of the formula:



wherein R* is isobutoxy with R**OH wherein R** is succinimid-1-yl to provide an activated ester of the formula:



followed by reacting the activated ester with (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)- 1,6-diphenyl-3-hydroxyhexane.

* * * * *

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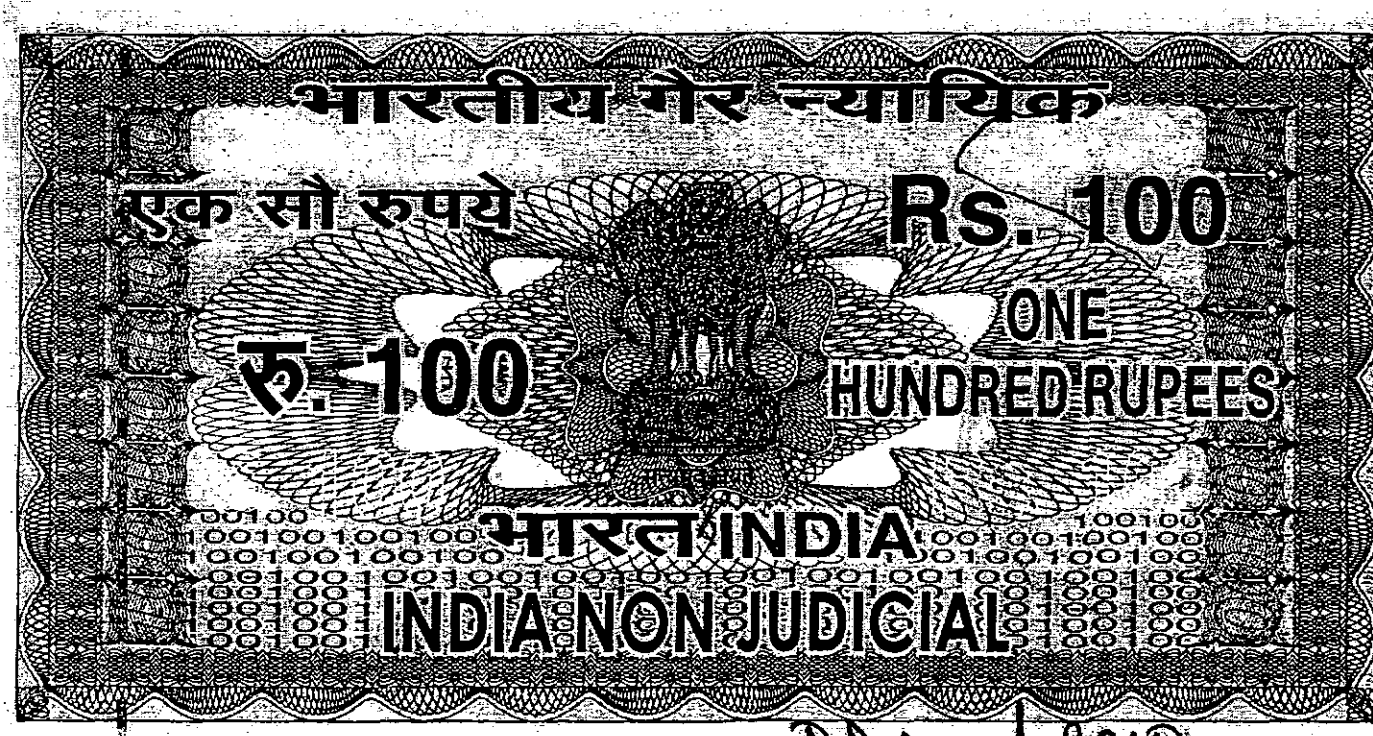

आंध्रप्रदेश आन्ध्र प्रदेश ANDHRA PRADESH P. Prasad Rao AM 348281

S.No. 325 Date 13/09/2010 Rs. 100/-

Name A. Venkatesh

S/o.W/o.D/o Badraiah

For Whom M/s Matrix Laboratories

P. PRASAD RAO
STAMP VENDOR
S.V.L.No.03/07 R.No.11/2010
H.No.6-3-1185/164,
Rebumpet, HYDERABAD

POWER OF ATTORNEY

In the matter of The Patents Act, 1970 *as amended by* The Patents (Amendment) Act of 1999 and 2002, and The Patents Amendment Act, 2005,

And

In the matter of The Patents Rules, 2003 *as amended by* The Patents (Amendment) Rules of 2006,

And

In the matter of Matrix Laboratories Limited, 1-1-151/1, 4th Floor, Sai Ram Towers, Alexander Road, Secunderabad – 500 003.

K. PARVATHI, Advocate
NOTARY
Appointed by the Govt. of A.P.
SECUNDERABAD

K. PARVATHI
Advocate & Notary
Flat No. 215, IIIrd Floor,
"Alliance House",
Beside Natraj Theatre, S.D.Road,
SECUNDERABAD.
(Res) 27803860

11 FEB 2011

original submitted with opposition U/Sec. 25(1) against 259/MUMNP/2003

TRUE COPY

11/02/2011.

We, the above named Matrix Laboratories Limited, do hereby retain, constitute and appoint S. MAJUMDAR, M. MAJUMDAR, DR. SANCHITA GANGULI, ABHISHEK SEN, AMIT CHAKRABORTY, A. MUKHERJEE, MYTHILI VENKATESH, N. R. SETH, MRIGANKI DUTTA, SULTANA SHAIKH, AMRITA MAJUMDAR, MD. IRFAN SHAIKH, DOMINIC ALVARES, RAJESHWARI HARIHARAN representatives of the Firm of S. MAJUMDAR & CO., 5, Harish Mukherjee Road, Calcutta – 700 025, India, all of Indian nationality, jointly and severally to be our Agents and Attorneys for the purpose of all acts under the Patents Act, 1970 (as amended by the Patents (Amendment) Act, 2005 or as may be amended hereafter) for all matters in which the name of the said firm of S MAJUMDAR & CO., appears in the address for service in the respective matters and we authorize any of them to sign our name and on our behalf on all applications and other papers and writings and do such acts, as may be necessary or expedient and lastly we request that all official communications now or hereafter relating to the same may be addressed to them at their office in Calcutta and that they be recognized as our authorized Agents in all proceedings incidental thereto.

We authorize them to appoint agents, advocates and attorneys. We hereby confirm all actions, if any, already taken by them in this matter. This Power of Attorney supercedes all previous Powers of Attorney given in favour of said firm of S. MAJUMDAR & CO.

Dated this 07th day of October, 2010

MATRIX LABORATORIES LIMITED

Sandeep K. Rathod

Associate Vice President -IP

K. PARVATHI, Advocate

7/10/10

K. PARVATHI
Advocate/Notary
Flat No. 213, Third Floor,
"Alliance House",
Beside Natraj Theatre, S.D.Road,
SECUNDERABAD
(Res) 27803860

11 FEB 2011

(92)

भारतीय गैर न्यायिक

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सत्यमेव जयते

भारत INDIA

INDIA NON JUDICIAL

आंध्रप्रदेश आन्ध्र प्रदेश ANDHRA PRADESH AE 238451

3631 29/10/2010

J. SRINIVAS
STAMP VENDOR
S.V.L.No.01/2010
H.No.4-4-75, Attapur,
Rajendra Nagar, R.R. Dist.

S.No.....Date.....Rs.100/-
Name: Venkatesh
S/o. W/o. D/o. Badraiah
For Whom: M/s matrix Lab Ltd

BEFORE THE CONTROLLER OF PATENTS

PATENT OFFICE, MUMBAI

In the matter of The Patents Act, 1970 *as amended by* The Patents (Amendment) Act 2005,

-And-

In the matter of The Patents Rules, 2003 as amended by The Patents (Amendment) Rules 2006,

-And-

NOTARY ★ GANJI YADAGIRI Advocate Secunderabad.A.P. Regd.No.6903 ★ APPOINTED BY THE GOVT. OF INDIA ★

ATTESTED

GANJI YADAGIRI
B.A.LL.M. (Osm)
ADVOCATE & NOTARY
H.No.12-1-1640/1, Shanti Nagar,
Nerth Lallaguda, Sec'bad-A.P.India
Mobile: 9963431448

V. S. A. Prasad

A. Sivalakshmi

11 FEB 2011

93

IN THE MATTER of Patents Application No. IN/PCT/20001/0018/MUM dated January 3, 2001 made by Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6050, U.S.A.

.....Applicant

-And-

IN THE MATTER of opposition of the grant of a patent thereto by Matrix Laboratories Ltd, 1-1-151/1, 4th Floor, Sai Ram Towers, Alexander Road, Secunderabad-500 003 Andhra Pradesh, India.

.....Opponent

EVIDENCE IN SUPPORT OF OPPOSITION

1. We, Dr. Vellanki Siva Rama Prasad and Mrs. Arikatla Sivalakshmi Devi, both working for gain at Matrix Laboratories Limited; referred to hereinafter as the Deponents. solemnly affirm and declare as under:

2. I, Dr. Vellanki Siva Rama Prasad, (referred to hereinafter as the Deponent No. 1) state as under:

   (a) I have been working with Matrix Laboratories Limited, since 2003 and my current position is Associate Vice President.

   (b) Details of my qualifications and experience in the field of Active Pharmaceutical Ingredients and intermediates are outlined below.

NOTARY ★ APPOINTED BY THE GOVT. OF INDIA ★
GANJI YADAGIRI
Advocate
Secunderabad.A.P.
Regd.No.6903

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GANJI YADAGIRI
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ADVOCATE & NOTARY
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North Lallaguda, Secunderabad-A.P.India

11 FEB 2011

(c) Academic Qualifications:

Degree	University	Year
Ph.D	Osmania university	1985-90
MSc.,	Osmania university	1982-84

(d) Industrial Experience:

Sr. No	Company	Designation	Year.
1	SIRIS Laboratories limited	**Chemist to Senior Chemist**	**1990-1992**
2	Voltas Limited	**Research Officer to Senior Research Officer**	**1992-2000**
3	Vani Chemicals Limited	**Manager to Chief Manager**	**2000-2003**
4	Matrix Laboratories Ltd.	**Asst. Gen. Manager to Associate Vice President**	**2003 onwards**

(e) Work profile:

I head a part of R & D group and my team consists of 40 members. My area of expertise involves process development and process improvements of generic molecules. Further, I take care of plant trouble shooting also.

(f) Achievements:

Received 'Junior and Senior Research fellowship' (1985&1988) award from Council of Scientific and Industrial Research of India.

(g) List of Publications:

1. Formation of Pyrolosis of 1(2'-thiazolo (5, 4-b) pyridyl)-5-aryltetrazoles.
   V.S.R Prasad, T. Sambaiah and K.Kondal Reddy
   Synth. Commun. , 20(13), 1983-88 (1990).

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11 FEB 2011

2. Synthesis of 2-aryl-1, 2, 4-triazolo (1, 5-a) pyrimidines

V.S.R Prasad and K.Kondal Reddy
Synth. Commun. , 20(17), 2617-2622(1990.)

3. Synthesis of 2,6-diaryl-1,2,4-triazolo(5,1-b)-1,3,4-thiadiazoles.

V.S.R Prasad and K.Kondal Reddy
Ind. Jou. Chem., 30B, 435-36 (1991).

4. Versatile Synthesis of 2-aryl(1,2,4) triazolo(3',2' : 2, 3)thiazolo (5,4-b) pyridines.

V.S.R Prasad, T. Sambaiah and K.Kondal Reddy
Ind. Jou. Chem., 30B, 517-18 (1991).

(h) Patent Publications:

S.No	TITLE	Application Number
1	An improved process for the preparation of ambrisentan	560/CHE/2009
2	Novel polymorphic forms of (3S,8S,9S,12S)-3,12-Bis(1,1-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl] methyl]-2,5,6,10,13-pentaazatetradecanedioic acid dimethyl ester and process for the preparation thereof	1264/CHE/2010
3	Process For The Preparation Of 4-Hydroxy Atomoxetine And Novel Intermediates In The Manufacture Thereof	1800/CHE/2009
4	Novel Polymorphs of 4-hydroxy Atomoxetine Hydrochloride.	2321/CHE/2010
5	Processes For Preparation Of Amorphous Darunavir	2257/CHE/2009
6	An Improved process for the preparation of Darunavir	54/CHE/2010

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7	An improved process for the preparation of darunavir	939/CHE/2010
8	Process For The Preparation Of (3r, 3as, 6ar)-Hexahydrofuro [2, 3-B] Furan-3-ol	3518/CHE/2010
9	Novel Polymorph of Didanosine	1677/CHE/2007
10	Novel polymorphic forms of Elvitegravir and its pharmaceutically acceptable salts	1114/CHE/2009
11	A Process for the Preparation of 6-(5-chloropyrid-2-yl)-5-(4-methylpiperazin-1-yl)-carbonyloxy-7-oxo-5,6-dihydropyrrolo-[3,4-B]-pyridine	782/CHE/2007
12	Process for the preparation of Elvetegravir and novel intermediates in the manufacture there of	1435/CHE/2009
13	Improved Process For The Preparation Of Elvitegravir And Intermediates In The Synthesis Thereof	2558/CHE/2009
14	A process for producing 5-(Fluoro-1-(2R,5S)-[2-9hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine	2929/CHE/2007
15	Novel Process For The Preparation Of Emtricitabine	3005/CHE/2009
16	Process for Preparation of 4-[4-(4-(Hydroxydiphenylmethyl)-1-Piperidinyl]-1-Oxobutyl]-α,α-Dimethylbenzene Acetic Acid Methyl Ester and Use Thereof	1027/CHE/2008 PCT/IN2009/000250
17	An Improved Process For The Preparation Of 2-Arylthiazole Derivatives	2387/CHE/2010
18	An Improved Process For The Preparation Of 2-Arylthiazole Derivatives	3312/CHE/2010

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11 FEB 2011

19	Amorphous form of (3S)-tetrahydrofuran-3-yl (1S,2R)-3-[[(4-aminophenyl) sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy) propylcarbamate monocalcium salt and process for the preparation thereof	1376/CHE/2010
20	Novel process for the preparation of (3S)-tetrahydrofuran-3-yl (1S, 2R)-3-[[(4-aminophenyl) sulfonyl] (isobutyl) amino]-1-benzyl-2-(phosphonooxy) propylcarbamate and pharmaceutically acceptable salts thereof	1703/CHE/2010
21	Process for the preparation of Lamivudine form-I and novel salts in the manufacture thereof	2492/CHE/2009
22	Process For Preparing An Amorphous Form of (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)-Amino-3-Hydroxy-5-(2-(1-Tetrahydropyrimid-2-Only)-3-Methylbutanoyl)-Amino-1,6-Diphenyl Hexane And Product Thereof	1438/CHE/2007
23	A Process for the Preparation of 2n-butyl-4-chloro-1-{[2-(2-triphenylmethyl-2H-tetrazole-5-yl)-1,1'-biphenyl-4-yl]methyl}-1H-imidazole-5-methanol	1032/CHE/2004 PCT/IN05/000308
24	Novel Crystalline forms of Nelfinavir Mesylate	439/CHE/NP/2007 PCT/IN04/000255
25	An improved process for preparing Nevirapine	1244/CHE/2009
26	Novel Crystalline forms of Paliperidone	2247/CHE/2007

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27	Improved Process for the Preparation of Paliperidone	2254/CHE/2007
28	Process For The Preparation Of Pure Paliperidone	903/CHE/2009
29	Novel Process For The Preparation Of Rilpivirine	2340/CHE/2009
30	Novel polymorph of Rilpivirne Hydrochloride.	3871/CHE/2010
31	Improved process for the synthesis of Rosiglitazone and its salts thereof	1192/CHE/2009
32	An Improved Process For The Preparation Of Rotigotine And Its Pharmaceutically Acceptable Salts	795/CHE/2009
33	Improved Process For The Preparation Of Sevelamer And Its Pharmaceutically Acceptable Salts	1897/CHE/2010
34	Improved Process For The Preparation Of Sevelamer And Its Pharmaceutically Acceptable Salts	3639/CHE/2010
35	Method of Dealkylation in Phosphonate esters Crystalline base of Tenofovir disoproxil Novel Tenofovir disoproxil hemifumarate salt and preparation methods there of	1218/CHE/2006 484/CHE/2007 1352/CHE/2006
36	Improved Process for the Preparation of Tenofovir Disoproxil and its Pharmaceutically Acceptable Salts	2169/CHE/2008
37	An Improved Process For The Preparation Of Tenofovir Disoproxil Fumarate	1050/CHE/2010
38	Process for the Preparation of Novel Amorphous Valsartan	14/CHE/2005

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11 FEB 2011

3. I, Mrs. Arikatla Sivalakshmi Devi (hereinafter referred as the Deponent No. 2) have been working with Matrix Laboratories Limited since 2003, state as under.

(a) I have been working with Matrix Laboratories Limited, since 2003 and my *current position is Deputy General Manager.*

(b) Details of my qualifications and experience in the field of Active Pharmaceutical Ingredients and intermediates are outlined below.

(c) Academic Qualifications:

Degree	University	Year
MSc	Osmania University	1993-1995

(d) Experience:

Sr. No	**Company**	**Designation**	**Year.**
1	Dr. Reddy's Research Foundation	**Chemist to Senior Research Associate**	**1995-2003**
2	Matrix laboratories	**Deputy Manager to Deputy General Manager**	**2003 onwards**

e) Work profile:

I head the solid sate and structural elucidation group at Matrix. This group comprises of 15 members. My area of expertise involves analysis of polymorphs and related solid state characterization. Further I take care of Molecular structure characterization by spectroscopic techniques such as NMR, Single crystal XRD, LC-MS, FTIR also.

NOTARY GANJI YADAGIRI Advocate Secunderabad.A.P. Regd.No.6903 APPOINTED BY THE GOVT. OF INDIA

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11 FEB 2011

f) ACHIEVEMENTS:

1. Received 'Excellent Performance' award (two times) in Dr. Reddys Research Foundation.

2. Received best poster presentation in IPC-USP 7th Annual Scientific Meeting, February 6 - 7, 2008

g) PUBLICATIONS:

1. Crystal Structure of 9-Ethyl-7-methyl-8-(2-chlorophenyl)-6-methyl-3,4,8,9-tetrahydropyrido[2,1-c][1,4]oxazine-7,9-dicarboxylate (Amlodipine degradation product)
A. Siva Lakshmi Devi, Y. Srinivasa RAO, M. SATISH, G. JYOTHI, K. Babu RAO and T. OMDUTT
Analytical Sciences: X-ray Structure Analysis Online, Vol. 23 (2007) p.x91

2. Structure elucidation of thermal degradation products of amlodipine
A. Siva Lakshmi Devi *, Y. Srinivasa Rao , M. Satish , G. Jyothi , K. Babu Rao , T. Omdutt
Magnetic Resonance in Chemistry, 2007, Vol-48,Issue 8, Pages 688-691

3. Structural confirmation of regioisomers of Lopinavir impurities using MS and gradient COSY (1H and 13C NMR assignment of Lopinavir impurities)
A.Sivalakshmi Devi , Y. Srinivasa Rao , Y. Suresh , M. Yogeswar Reddy , G. Jyothi , B. Rajababu , V. S. R. Prasad , V. Umamaheswar Rao
Magnetic Resonance in Chemistry, 2007, Vol-45,Issue 5, Pages 424-429

4. Modified reaction conditions to acieve high regioselectivity in the component synthesis of 1,5-diarylpyrazoles.
Sunil K.Singh, M.Srinivasa Reddy, S. Shivarama - krishna, D.KavithaR.Vasudev, J.Moses Babu, **A.Sivalakshmidevi** and Y. Koteswara Rao.
ChemInform Volume 36, Issue 4, 2005

5. Synthesis and conformational Studies of Novel Cyclic Peptides Constrained into A 310 Helical Structure by a Heterochiral D-Pro-L-Pro Dipeptide Template.
I.Nageswara Rao, Anima Boruah, S.Kiran Kumar, A.C.Kunwar, **A.Sivalakshmi** Devi, K.Vyas, Krishnan Ravikumar and Javed Iqbal.
J.Organic Chemistry, 2004, 69, 2181-2184.

6. Synthesis and structure-activity relationships of andrographolide analogues as novel cytotoxic agents
N.Srinivas, N. Vijaykumar, T. Sivasanjeeva Rao , K. Sridevi; P.Mahesh Kumar, P.Sairam, S. Rajagopal, R. Ajayakumar, R. Rajagopalan, J.Moses babu, K.Vyas, **A.Sivalakshmidevi**, G.Omreddy , A. Venkateswarlu.
Bioorganic& medicinal chemistry letters 2004, vol. 14, no18, pp. 4711-4717

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11 FEB 2011

7. 5-[5-(4-Methoxyphenyl)-3-trifluoromethyl-1H-pyrazol-1-yl]-2-sulfamoyl benzyl propionate: a novel 1,5-diraylpyrazole class of COX-2 inhibitor.
K. Vyas, **A.Sivalakshmi Devi**, S.K.Singh, Y.Koteswar Rao and G.Om Reddy.Acta ***Cryst. (2003). E59, o1731 - o1732***

8. Gemcitabine Hydrochloride.
A.Sivalakshmi Devi, K.Vyas, G.Om Reddy,S.D.V.N.Sivaram, Ramchandra Puranik and P.Sairam
Acta Crystallographica Section E, 2003, E59, o1435 - o1437.

9. 6-Nitro-1,2,3a,4-tetrahydrobenzo[b][1,3]oxazolo[3,2-d]oxazine.
K. Vyas, S. Vishnu Vardhan Reddy, **A. Sivalakshmidevi**, V.Venugopal Rao, Y. Koteswar Rao, A. Venkateswarlu and P. K. Dubey.
Acta Cryst. Section E (2003). E59, o360 - o362

10. A monoclinic polymorph of Venlafaxine Hydrochloride.
Sivalakshmidevi, A., Vyas.K, Mahender Rao.S, and Om Reddy.G
Acta Crystallographica Section E, 2002, E58, o1734 - o1735.

11. Lansoprazole, an antiulcerative drug.
Vyas, K., Sivalakshmidevi, A. & Om Reddy, G.
Acta Crystallographica Section C, 2000, C56, e572 - e573

12. Sparfloxacin, an antibacterial drug .
Sivalakshmidevi, A., Vyas, K. & Om Reddy, G.
Acta Crystallographica Section C, 2000, C56, e115 - e116

13 Process research and structural studies on Nabumetone.
C. Prabhakar, G.Bakki Reddy,Ch.Madhusudan, D.Nageswar, **A.Sivalakshmi Devi**, J. Moses Babu, K. Vyas, , M. R. Sarma and G. Om Reddy.
Organic process and research development 1999, 3,121-125.

14. Troglitazone an euglycemic antidiagetic agent
K. Vyas , **A.Sivalakshmi Devi**, C. Prabhakar and G. Om Reddy
Acta Crystallographica Section C, 1999, C55,411 - 413.

h) PATENT PUBLICATION(S):

Patents	Inventors	Publication number
NOVEL CRYSTALLINE POLYMORPHIC FORMS OF VENLAFAXINE HYDROCHLORIDE AND A PROCESS FOR THEIR PREPARION	Rao,S.M., Vyas,K., **Sivalakshmi Devi,** A., & Reddy,G.O.	WO02/46140 A1; 13 June 2002

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i) SEMINARS AND CONFERENCES:

Crystal structure of 9-deoxo-9-[2"-oxopropyl]Podophyllotoxin.
Y.Ravindra Kumar,. **A.Sivalakshmi Devi**, K. Vyas, G. Om Reddy, B.Renuka, and D.Subramanayam
XVIII th International union of Crystallography congress and general assembly, Aug. 4-13, 1999, Glasgow, Scotland, U.K

j) NATIONAL CONFERENCES

1. Crystal Structure of Troglitazone an euglycemic antidiagetic agent
K. Vyas , **A.Sivalakshmi Devi**, C. Prabhakar and G. Om Reddy.
XXVIII th National Seminar on Crystallography, Sept. 24-26, 1997, Kottayam, Kerala.

2. Crystal Structure of 2-(1-hydroxy cyclohexyl)-2-(4-methoxy phenyl)ethyl cyanide.
K. Vyas , **A.Sivalakshmi Devi**, C. Naveen Reddy ,S.Mahender Rao,M.R.Sharma and G. Om Reddy.
XXIX th National Seminar on Crystallography, Dec. 21-23, 1998, Channai

3. Crystal structure of Nabumetone
A.Sivalakshmi Devi, G.Bakki Reddy, C.Prabhakar, K.Vyas, M.R.Sharma and G. Om Reddy.
XXIX th National Seminar on Crystallography, Dec. 21-23, 1998, Channai

4. Crystal structure of Lovastatin.- Redetermination
K. Vyas , **A.Sivalakshmi Devi**, G. Om Reddy,M.Kumaraswamy and K.Venkateswara Rao.
XXIX th National Seminar on Crystallography, Dec. 21-23, 1998, Channai

5. Crystal structure of Fluorinated quinolones:Sparfloxacin and Enrofloxacin. .
K. Vyas , **A.Sivalakshmi Devi** and G. Om Reddy.
XXIX th National Seminar on Crystallography, Dec. 21-23, 1998, Channai

6. Crystal Structure of Troglitazone-another polymorph.
K. Vyas , **A.Sivalakshmi Devi**, C. Prabhakar and G. Om Reddy
XXIX th National Seminar on Crystallography, Dec. 21-23, 1998, Channai

7. Crystal structure of taxotere
A.Sivalkshmi Devi, P.Veerabhadra swamy, Prasada Rao Lingam, P.Sairam, K.Vyas and G. Om Reddy
XXX th National Seminar on Crystallography, Jun. 28-30, 2000, Tirupati

8. Crystal structure of 2-(1-hydroxy cyclohexyl)-2-(4-methoxy phenyl) ethyl cyanide.
K.Vyas, **A.Sivalkshmi Devi**, C.Naveen Kumar Reddy, S.Mahender Rao,M.R.Sarma and G. Om Reddy
XXX th National Seminar on Crystallography, Jun. 28-30, 2000, Tirupati

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9. Crystal structure of C-8 spiroepoxy andrographolide-tri-acetate
J. Moses Babu1, K. Vyas1, **A. Sivalakshmi Devi**, G.Om Reddy2, T. Siva Sanjeeva Rao1, N. Vijayakumar1, N. Srinivas1, P. Sai Ram1 and A. Venkateswarlu1
XXXII th National Seminar on Crystallography, Oct. 22-24, 2002, Jammu

10. Crystal structure of a novel 1,5-diaryl pyrazole class of COX-2 inhibitor
K. Vyas1, **A. Sivalakshmi Devi**1, S. K. Singh1, Y. Koteswar Rao1 and G.Om Reddy2, Discovery Resaerch1, Custom Chemical Synthesis2,
XXXII th National Seminar on Crystallography, Oct. 22-24, 2002, Jammu

11. Crystal structure of Gemcitabine Hydrochloride
J.Moses Babu1, K. Vyas1, **A. Sivalakshmi Devi1**, G.Om Reddy2, P.Veerabhadra Swamy3, S.D.V.N. Sivaram3, Ramachandra Puranik3 and P. Sai Ram3,
XXXII th National Seminar on Crystallography, Oct. 22-24, 2002, Jammu

12. 7-Nitro-1,2,3a,4-tetrahydrobenzo[b][1,3]oxazolo[3,2-d]oxazine
K. Vyas1, S. Vishnu Vardhan Reddy, **A. Sivalakshmi Devi1**, V.Venugopal Rao1, Y. Koteswar Rao1, A. Venkateswarlu1 and P. K. Dubey2.
XXXII th National Seminar on Crystallography, Oct. 22-24, 2002, Jammu

13. Identification and confirmation of new impurity of Efavirenz,
P. Praveen Kumar, **A. SivalakshmiDevi**, G.Jyothi, K. Ravi, V. Umamaheshwar Rao, Debashish Datta, B. Hari Babu.
IPC-USP 7th Annual Scientific Meeting February 6 - 7, 2008 Hyderabad

14. Solid state and spectral study on Tenofovir Disoproxil Fumarate and Hemifumarate.,
A.Sivalakshmi Devi, Ruchira M. Sarbajna,A.Preetam, Y. Srinivasa Rao, G. Jyothi, B.Rajababu,V.S.R.Prasad, Debashish Dutta, B.Haribabu.
IPC-USP 7th Annual Scientific Meeting February 6 - 7, 2008 Hyderabad

15. Structural Studies of Ritonavir Oxidation Impurity using NMR Spectroscopy, Y.Srinivasa Rao, **A. Sivalakshmi Devi**, Y.Suresh, M.Yogeswar Reddy, G.Jyothi, N.Madhu Murthy, Santosh Richhariya, V.S.R.Prasad, Debashish Datta, B.Hari Babu.
IPC-USP 7th Annual Scientific Meeting February 6 - 7, 2008 Hyderabad

k) TRAINING AND WORKSHOPS ATTENDED

a. Training on TOPAZ SOFTWARE on profile analysis and Rietveld methods in Bruker powder x-ray diffractometer .Bruker AXS GmbH, Karlsruhe, GERMANY (2004).

b. Training on Bruker NMR-AVANCE experimental methods, Fällanden, Switzerland (2006).

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c. First Workshop on X-Ray Crystallography;(Nov 15- Dec. 07 1997) Department of Studies in Physics, University of Mysore, Mysore-570 006; INDIA.

4. This affidavit is jointly deposed by Dr. Vellenki Siva Rama Prasad an expert in the field of Process R&D (Research & Development) and Mrs. Arikatla Sivalakshmi Devi an expert in the field of Analytical Research; referred to hereinafter, as Deponent No. 1 and Deponent No. 2 respectively.

5. The Deponents have been informed that the Opponent has opposed the application for the grant of patent application no. IN/PCT/2001/00018/MUM dated January 3, 2001. A copy of the complete specification of the aforesaid patent application and the Opponent's representation together with the various prior art documents relied upon have been provided to us.

6. The Deponents have carefully gone through the complete specification of the Applicant, the documents to be filed in the present proceedings including the written statement of opposition of the Opponent and the following Exhibits:

Sr. No.	Document	Publication Date
Exhibit 1	US5541206	July 30, 1996
Exhibit 2	US5567823	October 22, 1996

The Deponents herein have understood the invention claimed by the Applicant and have also understood the case made out by the Opponent.

7. In view of the Deponents' qualifications, experience and knowledge in the respective fields of API; Intermediates thereof and their Analysis, the Deponents are competent to depose this affidavit as experts.

8. The Deponents say that the Applicant's invention is directed to crystalline Form II of *(2S,3S,5S)-5-(N-(N-4N-methyl-N-((2-isopropyl-4-thiazolyl) methyl) amino) carbonyl) -L-valinyl)amino)-2-(N-((5-thiazolyl) -methoxycarbonyl)amino)-1, 6-diphenyl-3-hydroxyhexane* characterized by powder X-ray diffraction pattern.

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9. The Deponents say that the Applicant's invention relates to form II of known active agent viz. Ritonavir and specifically claims substantially pure crystalline form II of Ritonavir.

10. The Deponents shall first summarize the knowledge existing within the state of the art at the priority date of the Applicant's invention as regards to Ritonavir, which will form the background against which the inventive step of the applicant's invention will be assessed.

11. The Deponents note the Applicant has admitted that the crystalline form of the title compound is well known from US5541206, issued July 30, 1996. The aforesaid assertion of the Applicant establishes the fact that crystalline form of title compound is well known but is not specifically identified in literature as on the date of priority of the Application under opposition. The Deponents also note that page 3, line 7-8 of the complete specification reads as "It has now been unexpectedly ***discovered that*** *ritonavir can be prepared as a new crystalline polymorph which is termed crystalline form II.*" The Deponents are experts in the field of pharmaceutical chemistry and are well aware of the fact that the conditions adopted for crystallization of a substrate plays a key role in attaining the desired polymorphic form.

The Deponent further states that the impugned Application provides two processes for the preparation of form II of Ritonavir involving the following steps:

Process 1 (as demonstrated in ex. 4 of IN/PCT/2001/00018/MUM):

Intermediate obtained from example 3c is added to a solution of ritonavir Form 1 in ethanol.

Mixture is then allowed to stand at about 5°C for 24 hours.

The resulting crystals are then isolated. These purportedly are the form II crystals.

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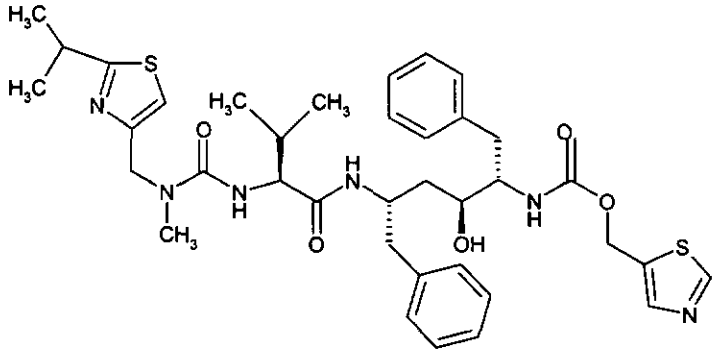
Process 2 (as demonstrated in ex. 5 of IN/PCT/2001/00018/MUM):

- Preparing a solution of Ritonavir (Form I or a mixture of Form I and Form II) in Ethyl acetate.
- Heating to 70°C under stirring until all solids dissolve.
- Adding Form II seed crystals such that all the seed crystals do not dissolve.
- Adding Heptane to the above solution.
- Allowing the mixture to cool slowly to 25°C
- Stirring the mixture for not less than 12 hours at 25°C.
- Isolation of the product through filtration by using a centrifuge.
- Drying the product.

With this background, the Deponents proceed to highlight certain key aspects in the Opponent's representation and the documents relied upon in the said representation. The Deponents, in the latter part of the affidavit, will discuss an experiment and analysis of the product obtained thereof, in support of the aforesaid statements.

12. The Deponents say that Ritonavir is a well known compound represented by the following structural formula was first disclosed in US5541206.



The Opponent has relied on US5541206 in its representation and referred to the same as Exhibit 1. The Deponents have gone through Exhibit 1 provided to them by the Opponent. The Deponents say that Exhibit 1 discloses retroviral protease inhibiting compounds including Ritonavir - which is the basic drug molecule whose crystalline form II is allegedly claimed by the Applicant in the present Specification (IN/PCT/2001/00018/MUM).

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13. The Deponents thus say that Exhibit 1 is one of the earliest literatures which teach the methods for the purification of Ritonavir so as to obtain the crystal form(s) of Ritonavir. The Deponents further say that any attempt by the Applicant to claim these forms requires a mere manipulation of solvents; drying conditions so as to physically isolate and characterize said forms. The Deponents also say that such routine laboratory experimentation is generally conducted by all process chemists so as to aid the pharmacist to employ the most suitable physical form of the drug while formulating a pharmaceutical composition.

14. The Deponents say that Exhibit 1 relates to Ritonavir and also provides for the crystalline form of Ritonavir and intermediates thereof. The Deponents have specifically studied Example 71 of Exhibit 1 which teaches the preparation of Ritonavir and is reproduced herein for ready reference.

"EXAMPLE 71
Alternative Preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxy carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

- *To a solution of the product of Example 70 (9.1 g, 21.4 mmol), HOBT (3.6 g, 23.5 mmol) and N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)-L-valine (7.37 g, 23.5 mmol)in THF (170 mL) was added DCC (4.85 g, 23.5 mmol).*
- *The solution was stirred at ambient temperature for 16 hours (DCU precipitates). THF was removed under vacuum and the resulting paste was stirred with cold 1N HCl (106 mL at 5^0C) for 3 hours to dissolve the crude product.*
- *The DCU was removed by filtration and the filter cake was washed with 1N HCl (30 mL). KH2 PO4 (3.2 g) was dissolved in the combined HCl filtrates.*
- *The solution was mixed with ethyl acetate (80 mL) and neutralized to pH 7 with aqueous NaOH (60.3 g of 10% w/w NaOH).*
- *The aqueous layer was extracted with another 25 mL ethyl acetate and the combined ethyl acetate extracts were washed with aqueous NaHCO3 (2.times.37 mL of 5% w/w NaHCO3 H).*
- *The organic layer was dried with Na2 SO4 (13 g), filtered, and concentrated under vacuum at $\leq 45^0$C.*

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- *The residue was dissolved in a 1:1 ethyl acetate/heptane mixture (200 mL) at 70^{0}C.*
- *The solution was allowed to cool slowly and stirred overnight at room temperature to provide a thick slurry.*
- *The product was collected by filtration and washed with 1:1 ethyl acetate/heptane (20 mL).*
- *The product was dried briefly at 55^{0}C. in a vacuum oven to obtain an approximate weight prior to the second crystallization (12.85 g, 83%).*
- *A second crystallization from 144 mL of 2:1 ethyl acetate/heptane (dissolved at about 70^{0}C, then stirred at room temperature 12 hours) produced a thick slurry of fine white solid.*
- *The product was collected by filtration and washed with 15 mL 2:1 ethyl acetate/heptane, then dried in a vacuum oven at 55^{0}C for 2 days to give the desired product.*
- *Yield 11.9 g (77%).*

15. The Deponents note that Exhibit 1 does not make any reference to the characteristics of the final product resulting from Example 71. Deponent No. 1, who is an expert in the field of process research, has supervised repetition of aforesaid experiment 71, thrice - with utmost care and precision, at Matrix Laboratories and the product thus obtained has been examined, under supervision of Deponent 2, for specific physical properties characteristic to polymorphic forms, so as to ascertain the physical form of the product of example 71 of Exhibit 1.

    The details of the thrice repeated experiment supervised by Deponent No. 1 and the analysis pertaining to the said product supervised by Deponent No. 2 are discussed hereinafter with special emphasis on the interpretation of analytical results. The Powder X-ray diffraction analysis of each of the three repetitions, is attached hereto as ET1.

16. The Deponent No. 1 says that to assess the polymorphic form of the molecule, it was synthesized as per reported process **(Example 71 of US5541206)**. Resultant product was evaluated for PXRD.

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17. Method of Synthesis of Sample used in Study

Deponent No. 1 says that Ritonavir was synthesized at Process Research Laboratory of Matrix Laboratories Ltd by using following process, under his direct supervision:

- *To a solution of the product of RIT-II (10 g, 23.5 mmol), HOBT (3.95 g, 25.8 mmol) and N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)-L-valine (8.1 g, 25.8 mmol)in THF (187 mL) was added DCC (5.33 g, 25.8 mmol).*
- *The solution was stirred at ambient temperature for 16 hours (DCU precipitates). THF was removed under vacuum and the resulting paste was stirred with cold 1N HCl (116 mL at 5^0C) for 3 hours to dissolve the crude product.*
- *The DCU was removed by filtration and the filter cake was washed with 1N HCl (33 mL). KH2 PO4 (3.5 g) was dissolved in the combined HCl filtrates.*
- *The solution was mixed with ethyl acetate (88 mL) and neutralized to pH 7 with aqueous NaOH (6.8g of 10% w/w NaOH).*
- *The aqueous layer was extracted with another 29 mL ethyl acetate and the combined ethyl acetate extracts were washed with aqueous NaHCO3 (2.times.41 mL of 5% w/w NaHCO3 H).*
- *The organic layer was dried with Na2 SO4 (14.3 g), filtered, and concentrated under vacuum at $\leq 45^0$C.*
- *The residue was dissolved in a 1:1 ethyl acetate/heptane mixture (220 mL) at 70^0C.*
- *The solution was allowed to cool slowly and stirred overnight at room temperature to provide a thick slurry.*
- *The product was collected by filtration and washed with 1:1 ethyl acetate/heptane (22 mL).*
- *The product was dried briefly at 55^0C. in a vacuum oven to obtain an approximate weight prior to the second crystallization (14.4 g, 85%).*
- *A second crystallization from 150 mL of 2:1 ethyl acetate/heptane (dissolved at about 70^0C, then stirred at room temperature 12 hours) produced a thick slurry of fine white solid.*
- *The product was collected by filtration and washed with 16 mL 2:1 ethyl acetate/heptane, then dried in a vacuum oven at 55^0C for 2 days to give the desired product.*
- *Yield 12.6 g (79%).*

The above mentioned process is same as the process mentioned in Example 71 of US5541206 (Exhibit 1).

18. The Deponent No. 2 has supervised the analysis of the product obtained from all the three batches and assessed the polymorphic forms of the products resulting

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from the above process, using pXRD technique. ***The X-ray powder diffraction data was collected on Bruker axs D8 ADVANCE powder diffractometer. The Copper anode was used as radiation source with scintillation counter as detector.*** The Deponent No. 2 says the pXRD results so obtained, are specified in ET1.

19. The Deponent No. 2 would now proceed to discuss and interpret the results obtained in the analysis. The powder-XRD of test sample shows a characteristic peak at **d-spacing 4.11 Å** and 2θ value 21.6 with 100% relative intensity. A comparison of 2 θ values for the data from IN/PCT/2001/00018/MUM versus data obtained from experiment conducted at Matrix is presented in Table-A.

Table A

IN/PCT/2001/00018/MUM Claim 2 (FORM II) 2Θ Values	**Prior art US '206; (Example 71) 2Θ Values – data from Matrix (Exhibit 3)**
8.67°±.0.1°	8.57°±.0.1°
9.51°±.0.1°	9.41°±.0.1°
9.88°±.0.1°	9.77°±.0.1°
10.97°±.0.1°	10.87°±.0.1°
13.74°±.0.1°	13.68°±.0.1°
16.11°±.0.1°	16.0°±.0.1°
16.70°±.0.1°	16.59°±.0.1°
17.36°±.0.1°	17.25°±.0.1°
17.78°±.0.1°	17.68°±.0.1°
18.40°±.0.1°	18.29°±.0.1°
18.93°±.0.1°	18.83°±.0.1°
19.52°±.0.1°	19.41°±.0.1°
19.80°±.0.1°	19.73°±.0.1°

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20.07°±.0.1°	19.97°±.0.1°
20.65°±.0.1°	20.55°±.0.1°
21.49°±.0.1°	21.38°±.0.1°
21.71°±.0.1°	21.60°±.0.1°
22.23°±.0.1°	22.11°±.0.1°
25.38°±.0.1°	25.28°±.0.1°
26.15°±.0.1°	26.04°±.0.1°
28.62°± 0.1°	28.53°±.0.1°

20. The Deponent No. 2 says that from the above data, it is clear that the PXRD data obtained with regards to example 71 of Exhibit 1 (three repetitions) completely overlaps with the PXRD data of form II as claimed by the applicant in the impugned application.

21. The Deponents therefore say that the form II of Ritonavir as discussed in IN/PCT/2001/00018/MUM is the same as product obtained from example 71 of Exhibit 1. The Deponents further say that the Applicant who is actively involved in the research of Retroviral Protease Inhibiting compounds and their processes was aware of the teachings of Exhibit 1 since Exhibit 1 also is assigned to the applicant itself. Though Exhibit 1 did not specifically disclose the characteristics of the crystals formed therein or did not identify the compound of example 71 as the Form II of Ritonavir, the same already existed in the state of the art. The Applicant has merely employed the use of Form II as seeding agents for the preparation of Ritonavir form II to achieve the same results and is trying to obtain a patent for a prior known and used compound. Deponent 1 states that use of seed crystals (preferably of the same substance) for purification purposes and for regeneration of the crystal molecules is well known in the art.

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22. The statements in paragraph Nos. 16 & 17 made herein are true to knowledge of the Deponent No. 1. The statements in paragraph Nos. 18, 19 & 20 made herein are true to knowledge of the Deponent No. 2. The statements in paragraph Nos. 1 to 21 made herein are true to knowledge of the Deponents.

Declared on this tenth (10th) Day of February 2011 at Hyderabad.

V.S.R.Prasad

Dr. Vellanki Siva Rama Prasad.
The Deponent No. 1

A.Sivalakshmi Devi

A. Sivalakshmi Devi
The Deponent No. 2

Enclosures:

- ET1;
- Exhibit 1.

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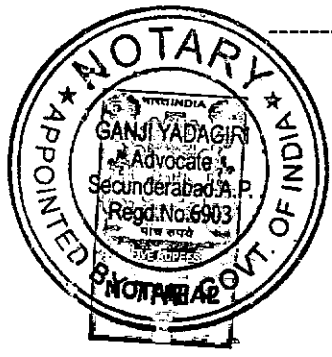
This is ET 1 referred to in the affidavit of Deponents 1 & 2
sworn before me on this the 10th day of February 2011



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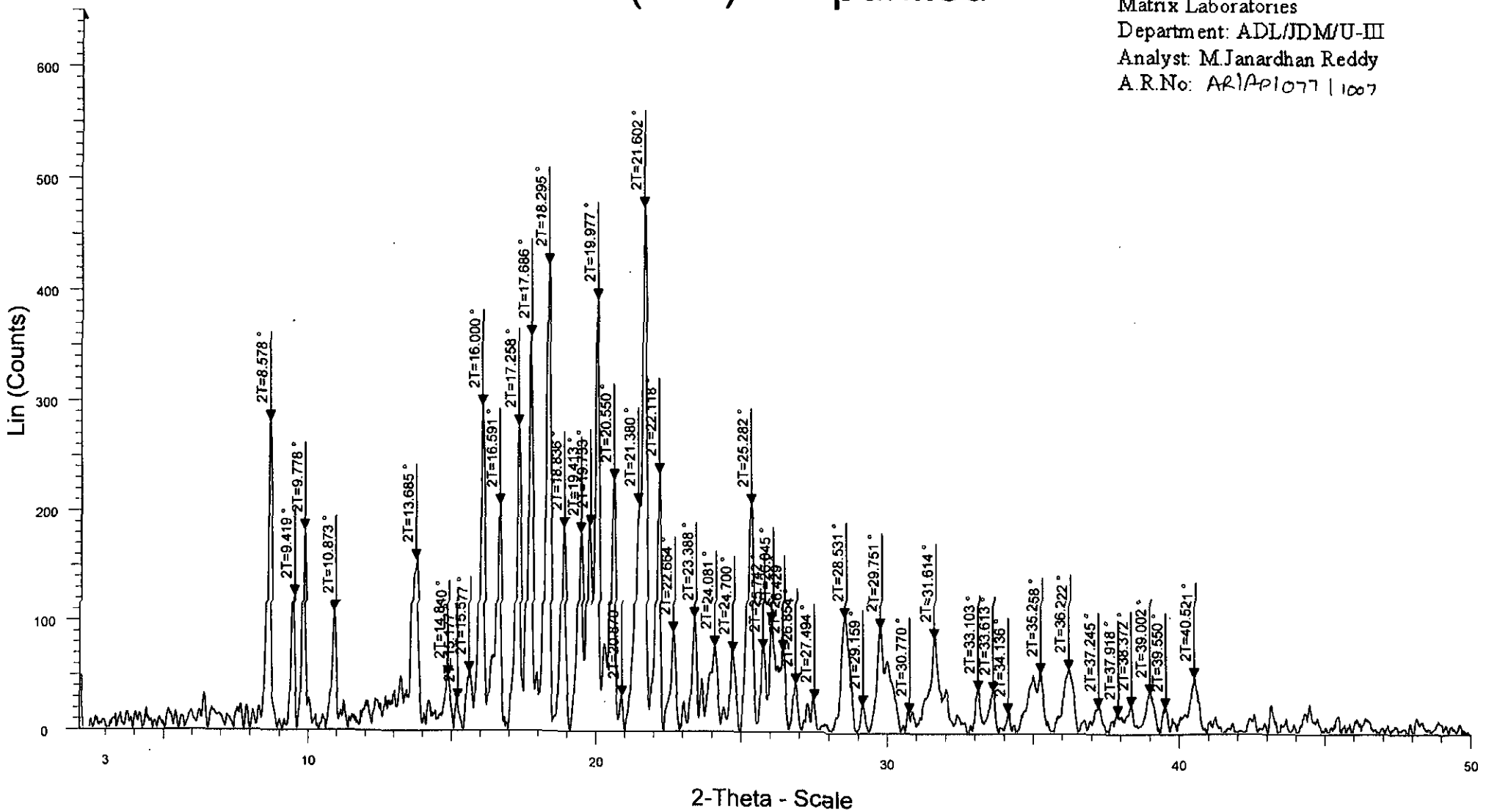
11 FEB 2011

RIT-III (854)103 purified

Matrix Laboratories
Department: ADL/JDM/U-III
Analyst: M.Janardhan Reddy
A.R.No: AR/AP1077 | 1007



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Operations: Background 1.000,3.000 | Smooth 0.100 | Import

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RIT-III (854)103 purified

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
8.578	10.29992	283	59.2
9.419	9.38197	123	25.7
9.778	9.03852	183	38.3
10.873	8.13019	108	22.7
13.685	6.46543	157	32.8
14.84	5.96493	50	10.5
15.177	5.83288	28.7	6
15.577	5.68433	53.4	11.2
16	5.53482	298	62.4
16.591	5.33893	207	43.3
17.258	5.13424	280	58.5
17.686	5.01072	361	75.5
18.295	4.84529	426	89.3
18.836	4.70748	187	39.2
19.413	4.56867	182	38.1
19.733	4.49541	189	39.6
19.977	4.44096	395	82.7
20.55	4.31848	231	48.3
20.87	4.25298	32.3	6.8
21.38	4.15267	209	43.8
21.602	4.11055	478	100
22.118	4.01566	236	49.5
22.664	3.92025	91	19.1
23.388	3.8005	104	21.8
24.081	3.69272	77.9	16.3
24.7	3.60157	72.8	15.2
25.282	3.51992	209	43.7
25.742	3.45798	75.7	15.8
26.045	3.4185	100	21
26.429	3.36973	74.3	15.6
26.854	3.31734	43.9	9.2
27.494	3.2415	29.1	6.1
28.531	3.12604	105	22.1
29.159	3.06007	25.3	5.3
29.751	3.00053	95.8	20.1
30.77	2.90345	18.3	3.8
31.614	2.82783	86.7	18.2
33.103	2.70396	39.6	8.3
33.613	2.66411	38.3	8
34.136	2.62446	18.5	3.9
35.258	2.54351	55.1	11.5
36.222	2.478	58.2	12.2
37.245	2.41226	23.5	4.9
37.918	2.37095	16.6	3.5
38.372	2.34395	25.1	5.3
39.002	2.30749	36.7	7.7
39.55	2.27677	23.5	4.9
40.521	2.22443	51.3	10.7

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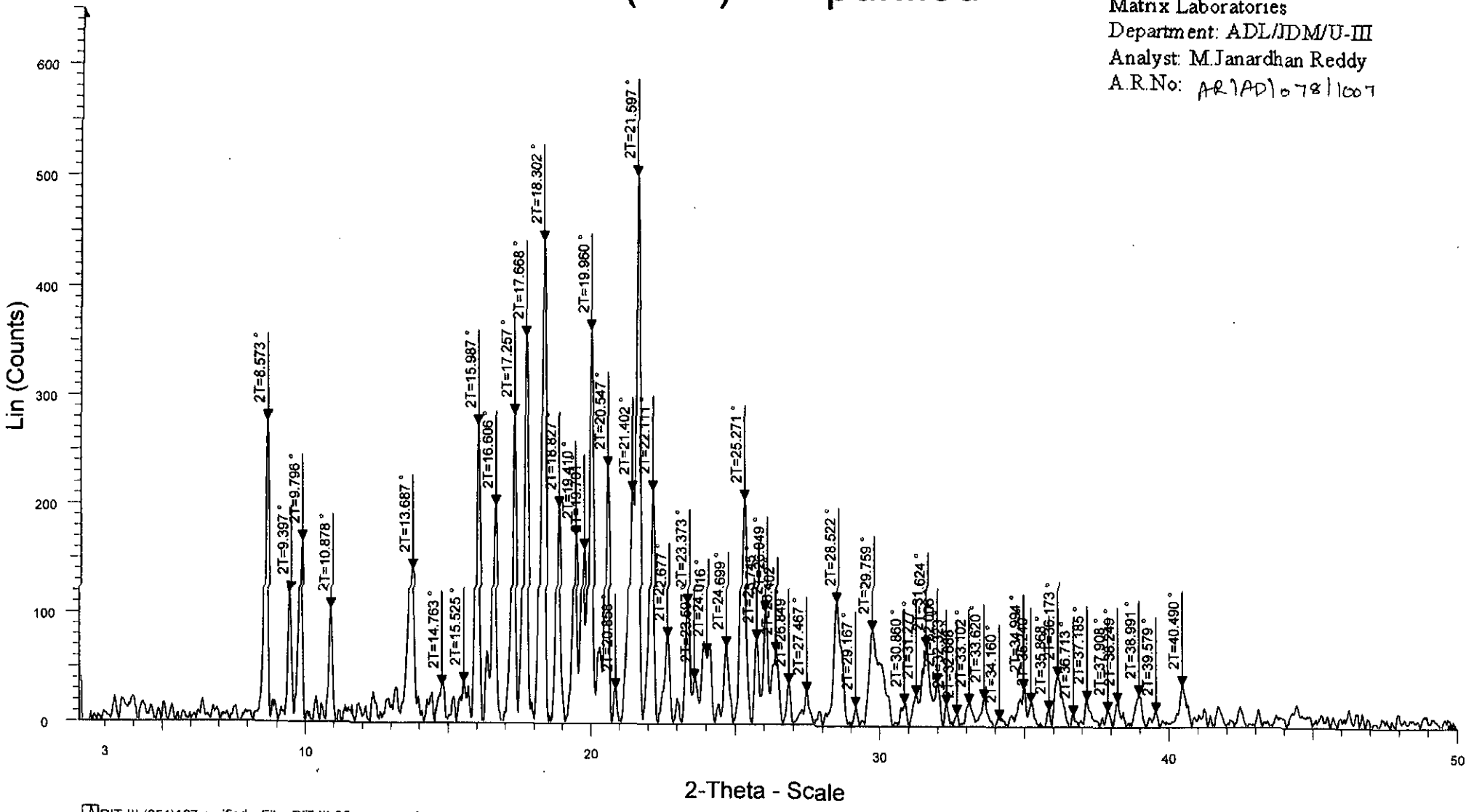
Compiled by : MP
Date : 03/10/07

Checked by : A. Prasad
Date : 03/10/07

11 FEB 2011

RIT-III (854)107 purified

Matrix Laboratories
Department: ADL/JDM/U-III
Analyst: M.Janardhan Reddy
A.R.No: ARIADI078/1007



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Operations: Background 3.162,0.000 | Smooth 0.100 | Import

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RIT-III (854)107 purified

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
8.573	10.3056	277	55
9.397	9.40393	119	23.6
9.796	9.02137	167	33.1
10.878	8.12665	104	20.6
13.687	6.46457	141	28
14.763	5.99551	34.1	6.8
15.525	5.70298	36.8	7.3
15.987	5.53925	275	54.6
16.606	5.33415	201	39.8
17.257	5.13446	285	56.5
17.668	5.01587	357	70.9
18.302	4.84351	445	88.3
18.827	4.70952	200	39.7
19.41	4.56953	173	34.4
19.701	4.50262	161	31.9
19.96	4.44473	364	72.1
20.547	4.31912	237	47.1
20.858	4.25544	32	6.3
21.597	4.11151	504	100
22.111	4.01693	215	42.8
22.677	3.91798	79.8	15.8
23.373	3.80288	111	22
23.597	3.7673	41.4	8.2
24.016	3.70254	64.9	12.9
24.699	3.60166	71.5	14.2
25.271	3.52135	207	41.1
25.745	3.45764	77.5	15.4
26.049	3.41798	104	20.7
26.402	3.37301	66.5	13.2
26.849	3.31797	37.2	7.4
27.467	3.24467	29.7	5.9
28.522	3.12701	114	22.6
29.167	3.05927	17.8	3.5
29.759	2.99978	87.9	17.4
30.86	2.89519	20.6	4.1
31.277	2.85755	28.5	5.6
31.624	2.82695	72.7	14.4
32.006	2.79409	39.6	7.8
32.323	2.76743	19.9	4
32.688	2.73738	10.6	2.1
33.102	2.70405	20.6	4.1
33.62	2.6636	24.9	4.9
34.16	2.62269	6.83	1.4
34.994	2.56205	34.7	6.9
35.24	2.54473	22.3	4.4
35.868	2.50163	15.1	3
36.173	2.48123	46.4	9.2
36.713	2.44593	10.7	2.1
37.185	2.41596	24.2	4.8
37.908	2.37157	14.4	2.9
38.249	2.35118	22.9	4.5
38.991	2.30814	29.6	5.9
39.579	2.27516	14	2.8
40.49	2.22606	38.1	7.6
21.402	4.14842	214	42.5

Compiled by :
Date : 03/10/07

Checked by :
Date : 03/10/07

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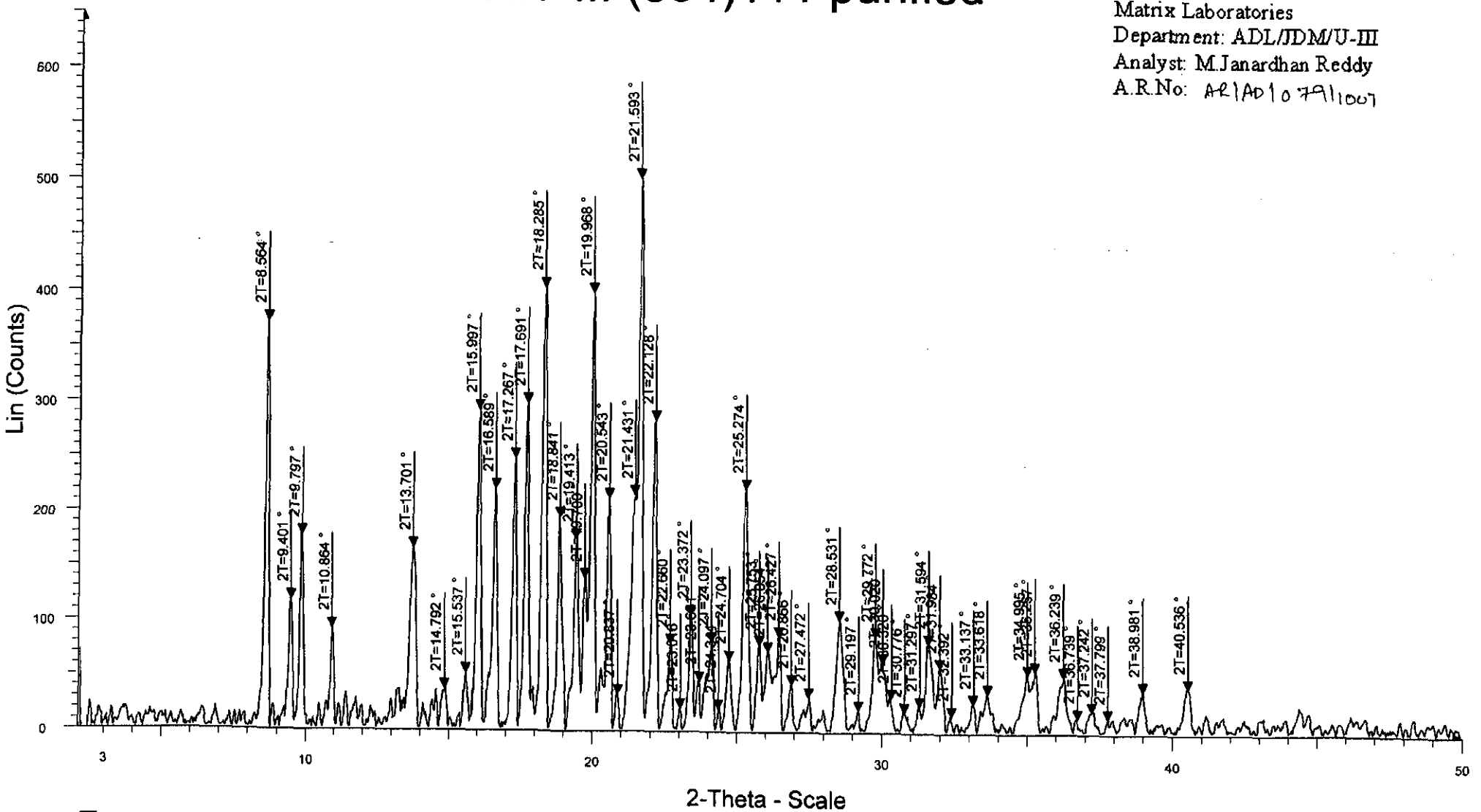
RIT-III (854)111 purified

Matrix Laboratories
Department: ADL/JDM/U-III
Analyst: M.Janardhan Reddy
A.R.No: AR/AD/0791/1007



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Operations: Background 3.162,0.000 | Smooth 0.100 | Import

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03/10/07

RIT-III (854)111 purified

Angle 2-Theta °	d value Angstrom	Intensity Count	Intensity %
8.564	10.31729	373	73.9
9.401	9.40013	118	23.3
9.797	9.02092	178	35.2
10.864	8.13699	91.4	18.1
13.701	6.45804	166	33
14.792	5.98413	36.2	7.2
15.537	5.69889	50.6	10
15.997	5.53581	293	58.1
16.589	5.33957	221	43.8
17.267	5.13147	249	49.4
17.691	5.00948	300	59.4
18.285	4.84792	405	80.4
18.841	4.70617	195	38.8
19.413	4.56888	176	34.9
19.7	4.50285	139	27.6
19.968	4.44311	401	79.5
20.543	4.31991	213	42.3
20.837	4.25968	32.3	6.4
21.431	4.14288	216	42.8
21.593	4.11218	504	100
22.128	4.01396	285	56.5
22.66	3.92085	79.2	15.7
23.016	3.86111	19.7	3.9
23.372	3.80298	105	20.9
23.661	3.75726	44.7	8.9
24.097	3.69019	80.8	16
24.344	3.65329	19.2	3.8
24.704	3.60091	64.4	12.8
25.274	3.52106	222	44.1
25.753	3.45656	78.2	15.5
26.054	3.41734	72.3	14.3
26.427	3.36995	86.4	17.1
26.866	3.31586	42.1	8.4
27.472	3.24411	30.1	6
28.531	3.12603	101	20.1
29.197	3.05619	18.7	3.7
29.772	2.9985	86	17
30.02	2.97427	62.1	12.3
30.32	2.94552	29.4	5.8
30.776	2.90291	16.7	3.3
31.297	2.85576	22.4	4.4
31.594	2.82957	80	15.9
31.984	2.79598	58.2	11.5
32.392	2.76166	14.2	2.8
33.137	2.70124	25.2	5
33.618	2.66371	34.2	6.8
34.995	2.56203	52	10.3
35.257	2.54353	55.5	11
36.239	2.47686	50.5	10
36.739	2.44425	12.5	2.5
37.242	2.41242	18.9	3.8
37.799	2.37813	12.6	2.5
38.981	2.3087	37.8	7.5
40.536	2.22363	40.9	8.1

Compiled by :
Date : 03/10/07

Checked by :
Date : 03/10/07

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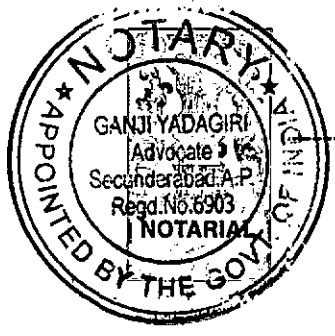
11 FEB 2011

120

This is Exhibit 1 referred to in the affidavit of Deponents 1 & 2
sworn before me on this the 10th day of February 2011



---------- Notary

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11 FEB 2011

US005541206A

United States Patent [19]

Kempf et al.

[11] Patent Number: 5,541,206

[45] Date of Patent: Jul. 30, 1996

[54] **RETROVIRAL PROTEASE INHIBITING COMPOUNDS**

[75] Inventors: **Dale J. Kempf**, Libertyville; **Daniel W. Norbeck**, Crystal Lake; **Hing Leung Sham**; **Chen Zhao**, both of Gurnee, all of Ill.

[73] Assignee: **Abbott Laboratories**, Abbott Park, Ill.

[21] Appl. No.: **423,387**

[22] Filed: **Apr. 25, 1995**

Related U.S. Application Data

[63] Continuation of Ser. No. 158,587, Dec. 2, 1993, abandoned, which is a continuation-in-part of Ser. No. 998,114, Dec. 29, 1992, abandoned, which is a continuation-in-part of Ser. No. 777,626, Oct. 23, 1991, abandoned, which is a continuation-in-part of Ser. No. 746,020, Aug. 15, 1991, abandoned, which is a continuation-in-part of Ser. No. 616,170, Nov. 20, 1990, abandoned, which is a continuation-in-part of Ser. No. 518,730, May 9, 1990, Pat. No. 5,142,056, which is a continuation-in-part of Ser. No. 456,124, Dec. 22, 1989, abandoned, which is a continuation-in-part of Ser. No. 405,604, Sep. 8, 1989, abandoned, which is a continuation-in-part of Ser. No. 355,945, May 23, 1989, abandoned.

[51] **Int. Cl.**[6] **A61K 31/425**; C07D 413/12; C07D 417/12

[52] **U.S. Cl.** **514/365**; 548/204; 548/194; 548/187; 548/235; 548/227; 548/228; 548/229; 514/374; 514/369; 514/370; 514/376; 514/377

[58] **Field of Search** 514/365, 374, 514/369, 370, 376, 377; 548/204, 194, 187, 235, 227, 228, 229

[56] **References Cited**

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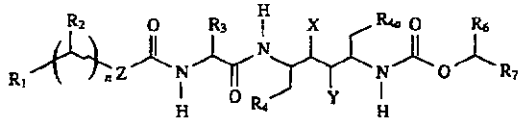
Primary Examiner—Jane Fan

Attorney, Agent, or Firm—Steven R. Crowley

[57] **ABSTRACT**

A retroviral protease inhibiting compound of the formula:



is disclosed.

19 Claims, No Drawings

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RETROVIRAL PROTEASE INHIBITING COMPOUNDS

This invention was made with Government support under contract number AI27220 awarded by the National Institute of Allergy and Infectious Diseases. The Government has certain rights in this invention.

This is a continuation of U.S. patent application Ser. No. 08/158,587, filed Dec. 2, 1993 now abandoned, which is a continuation-in-part of U.S. patent application Ser. No. 998,114, filed Dec. 29, 1992, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 777,626, filed Oct. 23, 1991, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 746,020, filed Aug. 15, 1991, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 616,170, now abandoned filed Nov. 20, 1990, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 518,730, filed May 9, 1990, now U.S. Pat. No. 5,142,056 which is a continuation-in-part of U.S. patent application Ser. No. 456,124, filed Dec. 22, 1989, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 405,604, filed Sep. 8, 1989, now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 355,945, filed May 23, 1989 now abandoned.

TECHNICAL FIELD

The present invention relates to novel compounds and a composition and method for inhibiting retroviral proteases and in particular for inhibiting human immunodeficiency virus (HIV) protease, a composition and method for treating a retroviral infection and in particular an HIV infection, processes for making such compounds and synthetic intermediates employed in these processes.

BACKGROUND OF THE INVENTION

Retroviruses are those viruses which utilize a ribonucleic acid (RNA) intermediate and a RNA-dependent deoxyribonucleic acid (DNA) polymerase, reverse transcriptase, during their life cycle. Retroviruses include, but are not limited to, the RNA viruses of the Retroviridae family, and also the DNA viruses of the Hepadnavirus and Caulimovirus families. Retroviruses cause a variety of disease states in man, animals and plants. Some of the more important retroviruses from a pathological standpoint include human immunodeficiency viruses (HIV-1 and HIV-2), which cause acquired immune deficiency syndrome (AIDS) in man, hepatitis B virus, which causes hepatitis and hepatic carcinomas in man, human T-cell lymphotrophic viruses I, II, IV and V, which cause human acute cell leukemia, and bovine and feline leukemia viruses which cause leukemia in domestic animals.

Proteases are enzymes which cleave proteins at specific peptide bonds. Many biological functions are controlled or mediated by proteases and their complementary protease inhibitors. For example, the protease renin cleaves the peptide angiotensinogen to produce the peptide angiotensin I. Angiotensin I is further cleaved by the protease angiotensin converting enzyme (ACE) to form the hypotensive peptide angiotensin II. Inhibitors of renin and ACE are known to reduce high blood pressure in vivo. An inhibitor of a retroviral protease will provide a therapeutic agent for diseases caused by the retrovirus.

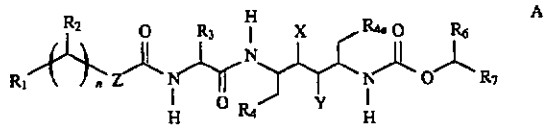
The genomes of retroviruses encode a protease that is responsible for the proteolytic processing of one or more polyprotein precursors such as the pol and gag gene products. See Wellink, Arch. Virol. 98 1 (1988). Retroviral proteases most commonly process the gag precursor into core proteins, and also process the pol precursor into reverse transcriptase and retroviral protease. In addition, retroviral proteases are sequence specific. See Pearl, Nature 328 482 (1987).

The correct processing of the precursor polyproteins by the retroviral protease is necessary for the assembly of infectious virions. It has been shown that in vitro mutagenesis that produces protease-defective virus leads to the production of immature core forms which lack infectivity. See Crawford, J. Virol. 53 899 (1985); Katoh, et al., Virology 145 280 (1985). Therefore, retroviral protease inhibition provides an attractive target for antiviral therapy. See Mitsuya, Nature 325 775 (1987).

Current treatments for viral diseases usually involve administration of compounds that inhibit viral DNA synthesis. Current treatments for AIDS involve administration of compounds such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxycytidine (DDC) and 2',3'-dideoxyinosine (DDI) and compounds which treat the opportunistic infections caused by the immunosuppression resulting from HIV infection. None of the current AIDS treatments have proven to be totally effective in treating and/or reversing the disease. In addition, many of the compounds currently used to treat AIDS cause adverse side effects including low platelet count, renal toxicity and bone marrow cytopenia.

DISCLOSURE OF THE INVENTION

In accordance with the present invention, there are retroviral protease inhibiting compounds of the formula A:



A

wherein

R_1 is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi) cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy;

n is 1,2 or 3;

R_2 is hydrogen or loweralkyl;

R_3 is loweralkyl;

R_4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a

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substituent selected from (i) halo, (ii)loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy;

R_6 is hydrogen or loweralkyl;

R_7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl;

X is hydrogen and Y is —OH or X is —OH and Y is hydrogen, with the proviso that X is hydrogen and Y is —OH when Z is —N(R_8)— and R_7 is unsubstituted and with the proviso that X is hydrogen and Y is —OH when R_3 is methyl and R_7 is unsubstituted; and

Z is absent, —O—, —S—, —CH_2— or —N(R_8)— wherein R_8 is loweralkyl, cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen, loweralkyl or an N-protecting group; or a pharmaceutically acceptable salt, ester or prodrug thereof.

Preferred compounds of the formula A are those wherein R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl or thiazolyl; R_{4a} is phenyl; R_6 is hydrogen and R_7 is thiazolyl, oxazolyl, isothiazolyl or isoxazolyl.

More preferred compounds of the formula A are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen and R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl.

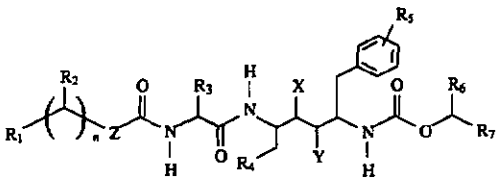
Even more preferred compounds of the formula A are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is loweralkyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O— or —N(R_8)— wherein R_8 is loweralkyl.

Most preferred compounds of the formula A are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1; R_2 is hydrogen; R_3 is methyl or isopropyl; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O—.

Most preferred compounds of the formula A are also those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1; R_2 is hydrogen; R_3 is isopropyl; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —N(R_8)— wherein R_8 is methyl.

Most preferred compounds of the formula A are also those wherein the configuration of the carbon atom bearing —CH_2R_4 is "S" and the configuration of the carbon bearing X is "S" when X is —OH and the configuration of the carbon atom bearing Y is "S" when Y is —OH and the configuration of the carbon atom bearing —CH_2(R_5-substituted phenyl)is "S".

Preferred compounds of the invention are compounds of the formula AI:



A1

wherein

R_1 is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi)cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy;

n is 1,2 or 3;

R_2 is hydrogen or loweralkyl;

R_3 is loweralkyl;

R_4 is phenyl, thiazolyl or oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii)loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy;

R_5 is hydrogen, halo, loweralkyl, hydroxy, alkoxy or thioalkoxy;

R_6 is hydrogen or loweralkyl;

R_7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl;

X is hydrogen and Y is—OH or X is —OH and Y is hydrogen, with the proviso that X is hydrogen and Y is —OH when Z is —N(R_8)— and R_7 is unsubstituted and with the proviso that X is hydrogen and Y is —OH when R_3 is methyl and R_7 is unsubstituted;

Z is absent, —O—, —S—, —CH_2— or —N(R_8)— wherein R_8 is loweralkyl, cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen, loweralkyl or an N-protecting group; or a pharmaceutically acceptable salt, ester or prodrug thereof.

Preferred compounds of the formula A1 are those wherein R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl or thiazolyl; R_5 is hydrogen; R_6 is hydrogen and R_7 is thiazolyl, oxazolyl, isothiazolyl or isoxazolyl.

More preferred compounds of the formula A1 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen and R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl.

Even more preferred compounds of the formula A1 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is loweralkyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O— or —N(R_8)— wherein R_8 is loweralkyl.

Most preferred compounds of the formula A1 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1; R_2 is hydrogen; R_3 is methyl or isopropyl; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O—.

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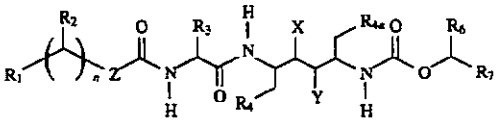
Most preferred compounds of the formula A1 are also those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; n is 1; R_2 is hydrogen; R_3 is isopropyl; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —N(R_8)— wherein R_8 is methyl.

Most preferred compounds of the formula A1 are also those wherein X is hydrogen and Y is —OH.

Most preferred compounds of the formula A1 are also those wherein the configuration of the carbon atom bearing —CH_2R_4 is "S" and the configuration of the carbon bearing X is "S" when X is —OH and the configuration of the carbon atom bearing Y is "S" when Y is —OH and the configuration of the carbon atom bearing —CH_2(R_5-substituted phenyl)is "S".

In accordance with the present invention, there are also retroviral protease inhibiting compounds of the formula A2:



A2

wherein

R_1 is monosubstituted thiazolyl, monosubstituted oxazolyl, monosubstituted isoxazolyl or monosubstituted isothiazolyl wherein the substituent is selected from (i) loweralkyl, (ii) loweralkenyl, (iii) cycloalkyl, (iv) cycloalkylalkyl, (v) cycloalkenyl, (vi)cycloalkenylalkyl, (vii) heterocyclic wherein the heterocyclic is selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (viii) (heterocyclic)alkyl wherein heterocyclic is defined as above, (ix) alkoxyalkyl, (x) thioalkoxyalkyl, (xi) alkylamino, (xii) dialkylamino, (xiii) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy, (xiv) phenylalkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xv) dialkylaminoalkyl, (xvi) alkoxy and (xvii) thioalkoxy;

n is 1,2 or 3;

R_2 is hydrogen or loweralkyl;

R_3 is loweralkyl;

R_4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii)loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy;

R_6 is hydrogen or loweralkyl;

R_7 is thiazolyl, oxazolyl, isoxazolyl or isothiazolyl wherein the thiazolyl, oxazolyl, isoxazolyl or isothiazolyl ring is unsubstituted or substituted with loweralkyl;

X is —OH and Y is —OH; and

Z is absent, —O—, —S—, —CH_2— or —N(R_8)— wherein R_8 is loweralkyl, cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen, loweralkyl or an N-protecting group; or a pharmaceutically acceptable salt, ester or prodrug thereof.

Preferred compounds of the formula A2 are those wherein R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl or thiazolyl; R_{4a} is phenyl; R_6 is hydrogen and R_7 is thiazolyl, oxazolyl, isothiazolyl or isoxazolyl.

More preferred compounds of the formula A2 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen and R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl.

Even more preferred compounds of the formula A2 are those wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is loweralkyl; n is 1; R_2 is hydrogen; R_4 is phenyl; R_{4a} is phenyl; R_6 is hydrogen; R_7 is 5-thiazolyl, 5-oxazolyl, 5-isothiazolyl or 5-isoxazolyl; and Z is —O— or —N(R_8)— wherein R_8 is loweralkyl.

Preferred compounds of the formula A2 are also those wherein the configuration of the carbon atom bearing —CH_2R_4 is "S" and the configuration of the carbon atom bearing —CH_2(R_5-substituted phenyl) is "S".

The compounds of the invention comprise asymmetrically substituted centers (i.e., asymmetrically substituted carbon atoms). The present invention is intended to include all stereoisomeric forms of the compounds, including racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention. The terms "S" and "R" configuration are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13–30.

The terms "Val" and "Ala" as used herein refer to valine and alanine, respectively. Unless otherwise noted, when "Val" and "Ala" are used herein they refer to the L-isomer. In general, the amino acid abbreviations used herein follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature for amino acids and peptides (Eur. J. Biochem. 1984, 158, 9–31).

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis,"(John Wiley & Sons, New York (1981)), which is hereby incorporated by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, ben-

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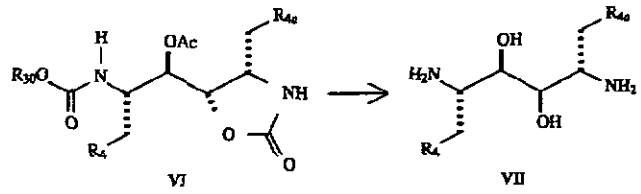
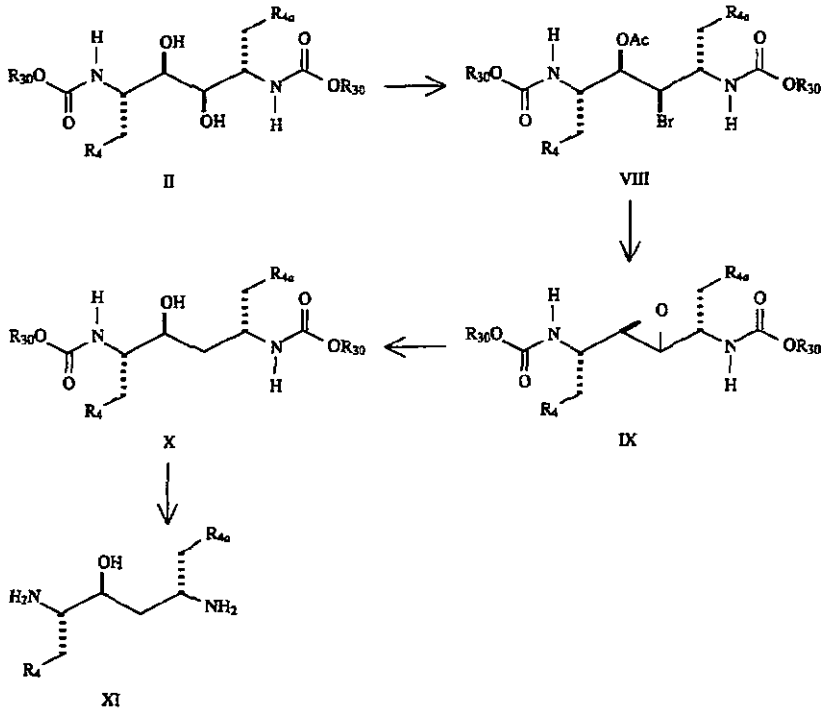
Scheme 1



VI VII

As outlined in Scheme 2, treatment of compound II with α-acetoxy-isobutyryl bromide in hexane/dichloromethane produces bromoacetate VIII. Hydrolysis of VIII with concommitant cyclization produces epoxide IX, which is reduced with sodium borohydride and trifluoroacetic acid to produce compound X. Barium hydroxide hydrolysis of X leads to diamine XI. is hydrolyzed and decarboxylated to lactone XV. Hydrolysis of XV and protection of the hydroxyl group leads to compound XVI, which, upon treatment with diphenylphosphoryl azide undergoes a Curtius rearrangement. The intermediate isocyanate is trapped with benzyl alcohol to produce compound XVII. Desilylation of XVII with tetrabutylammonium

Scheme 2



II VIII IX X XI

As outlined in Scheme 3, acylation of the enolate derived from compound XII with ethyl chloroformate gives compound XIII. Subsequent alkylation of the enolate prepared from XIII provides compound XIV (R_{4a} is thiazolyl), which fluoride provides compound XVIII, which is deprotected with HBr to give diamine XIX.

In a preferred embodiment of the process shown in Scheme 3, R_4 is phenyl.

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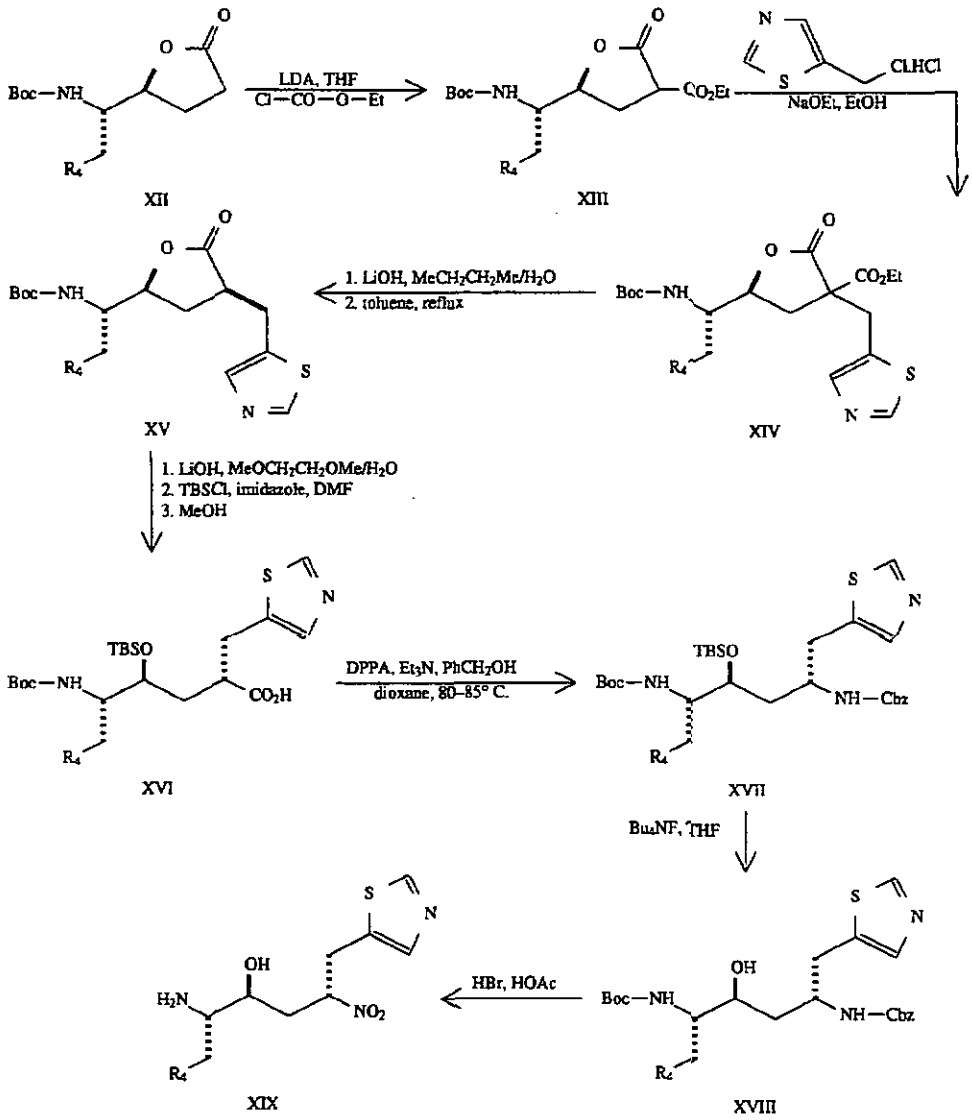
Scheme 3



XII XIII XIV XV XVI XVII XVIII XIX

As outlined in Scheme 4, compound XX (R_3 is lower-alkyl) is converted to isocyanate XXI by treatment with phosgene. Alternatively, treatment of XX with 4-nitrophenyl chloroformate produces carbamate XXII. Condensation of either XXI or XXII with compound XXIII wherein Z is O, S or N(R_8), with catalytic 4-dimethylaminopyridine as needed, provides compound XXIV. Lithium hydroxide hydrolysis of XXIV produces compound XXV. In a preferred embodiment of the process shown in Scheme 4, n is 1.

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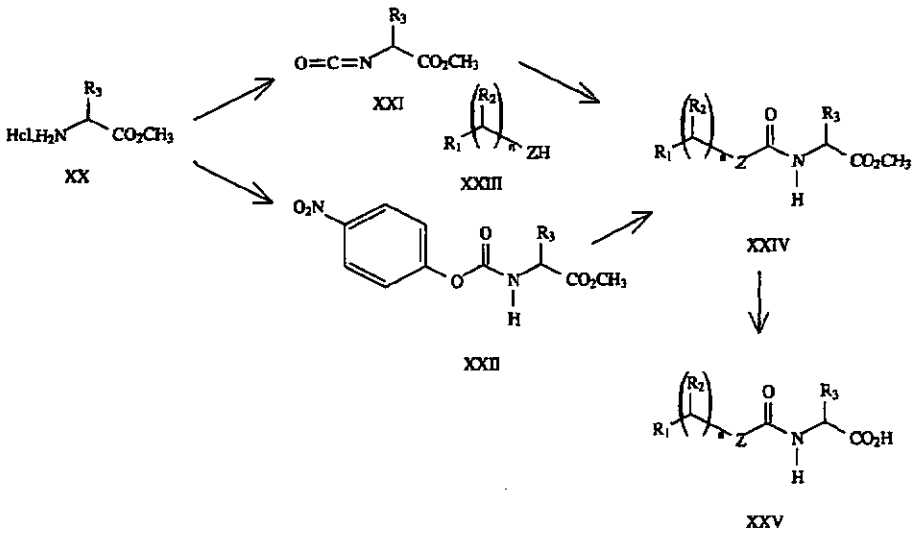
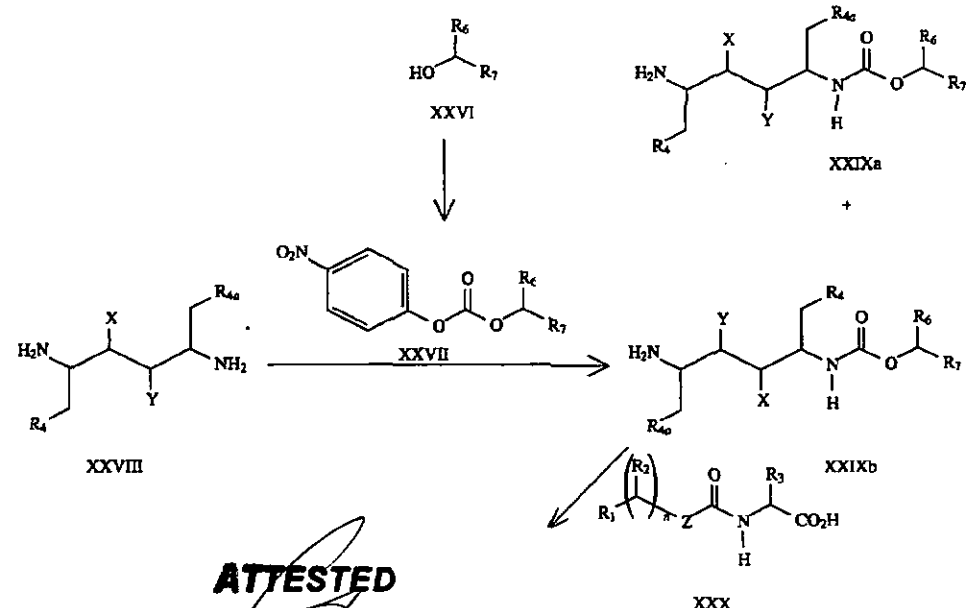
Scheme 4



As outlined in Scheme 5, compound XXVIII, which represents diamines IV, V, VII, XI and XIX, is acylated with an activated derivative of XXVI having the formula $(R_6)(R_7)CHOC(O)OL$ wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII, which is prepared by reacting XXVI with 4-nitrophenyl chloroformate) to provide a mixture of compounds XXIXa and XXIXb or an acid addition salt thereof. Coupling of XXIXa or XXIXb to compound XXX by treatment with a carbodiimide (or by reaction with an activated ester of XXX) produces compound XXXIa or XXXIb, respectively. In a preferred embodiment of the process shown in Scheme 5, n is 1, R_4 and R_{4a} are each phenyl, X is H and Y is OH.

Scheme 5



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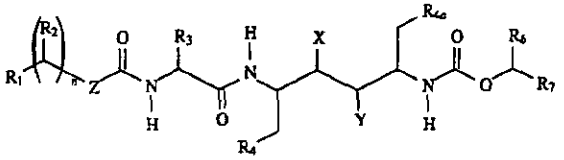
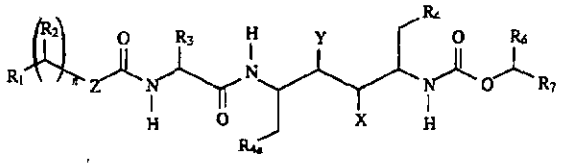
Scheme 5



XXXIa

+

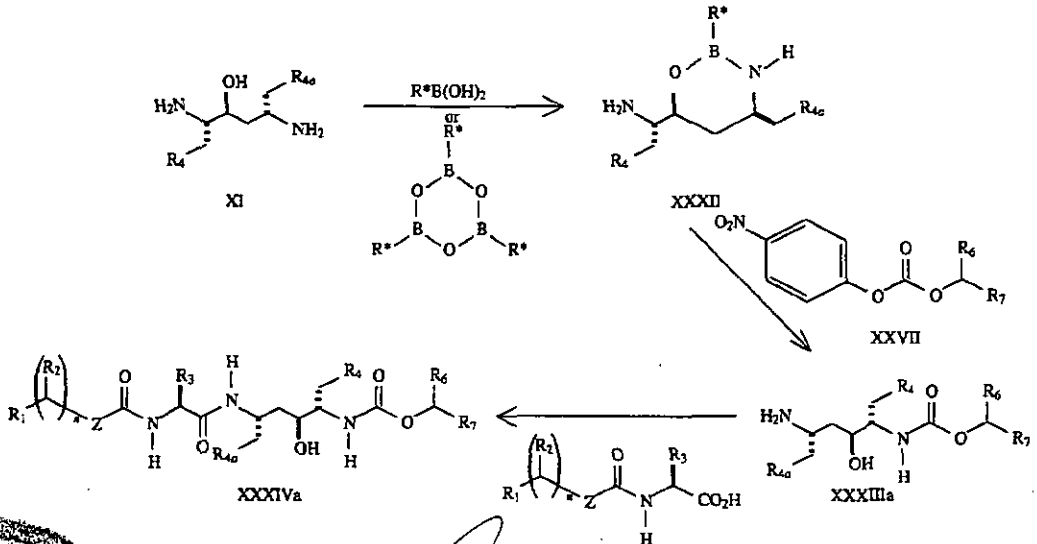


XXXIb

As outlined in Scheme 6A, treatment of diamine XI with a boronic acid (preferably, phenylboronic acid) or a boroxine produces compound XXXII, which is selectively acylated with an activated derivative of XXVI having the formula $(R_6)(R_7)CHOC(O)OL$ wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII) to provide compound XXXIIIa or an acid addition salt thereof. Carbodiimide-mediated coupling of XXXIIIa to compound XXX (:or reaction of XXXIIIa with an activated ester of XXX) leads to compound XXXIVa. In a preferred embodiment of the process shown in Scheme 6A, n is 1, R_4 and R_{4a} are each phenyl and R* is phenyl.

Alternatively, compound XXXII can be acylated with compound XXX (or an activated ester thereof) to provide compound XXXIIIb or an acid addition salt thereof. Acylation of compound XXXIIIb with an activated derivative of XXVI having the formula $(R_6)(R_7)CHOC(O)OL$ wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII) provides compound XXXIVb.

Scheme 6A



XI

XXXII

XXVII

XXXIVa

XXXIIIa

XXX

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zoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "O-protecting group" as used herein refers to a substituent which protects hydroxyl groups against undesirable reactions during synthetic procedures such as those O-protecting groups disclosed in Greene, "Protective Groups In Organic Synthesis,"(John Wiley & Sons, New York (1981)). O-protecting groups comprise substituted methyl ethers, for example, methoxymethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, t-butyl, benzyl and triphenylmethyl; tetrahydropyranyl ethers; substituted ethyl ethers, for example, 2,2,2-trichloroethyl; silyl ethers, for example, trimethylsilyl, t-butyldimethylsilyl and t-butyldiphenylsilyl; and esters prepared by reacting the hydroxyl group with a carboxylic acid, for example, acetate, propionate, benzoate and the like.

The term "loweralkyl" as used herein refers to straight or branched chain alkyl radicals containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "loweralkenyl" as used herein refers to a straight or branched chain alkyl radical containing from 2 to 6 carbon atoms and also having one carbon-carbon double bond including, but not limited to, vinyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl and the like.

The term "phenyl" as used herein refers to a phenyl group which is unsubstituted or substituted with a substituent selected from loweralkyl, alkoxy, thioalkoxy, hydroxy and halo.

The term "phenylalkyl" as used herein refers to an phenyl group appended to a loweralkyl radical including, but not limited to, benzyl, 4-hydroxybenzyl, 4-chlorobenzyl, 1-naphthylmethyl and the like.

The term "alkylamino" as used herein refers to a loweralkyl radical appended to an —NH radical.

The term "cycloalkyl" as used herein refers to an aliphatic ring having 3 to 7 carbon atoms including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl and the like. A preferred cycloalkyl group is cyclopropyl

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical, including but not limited to cyclohexylmethyl.

The term "cycloalkenyl" as used herein refers to an aliphatic ring having 5 to 7 carbon atoms and also having one carbon-carbon double bond including, but not limited to, cyclopentenyl, cyclohexenyl and the like.

The term "cycloalkenyalkyl" as used herein refers to a cycloalkenyl group appended to a loweralkyl radical including, but not limited to, cyclopentenylmethyl, cyclohexenylmethyl and the like.

The terms "alkoxy" and "thioalkoxy" as used herein refer to $R_{15}O$— and $R_{15}S$—, respectively, wherein R_{15} is a loweralkyl group or benzyl.

The term "alkoxyalkyl" as used herein refers to an alkoxy group appended to a loweralkyl radical.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group appended to a loweralkyl radical.

The term "dialkylamino" as used herein refers to $—NR_{16}R_{17}$ wherein R_{16} and R_{17} are independently selected from loweralkyl groups.

The term "dialkylaminoalkyl" as used herein refers to $—NR_{18}R_{19}$ which is appended to a loweralkyl radical wherein R_{18} and R_{19} are independently selected from loweralkyl.

The term "halo" or "halogen" as used herein refers to —Cl,—Br,—I or —F.

The term "heterocyclic" as used herein refers to a heterocyclic group selected from aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyridazinyl and pyrazinyl and wherein the heterocyclic is unsubstituted or substituted with a substituent selected from halo, loweralkyl, hydroxy, alkoxy and thioalkoxy.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group appended to a loweralkyl radical including, but not limited to, pyrrolidinylmethyl and morpholinylmethyl.

The term "activated ester derivative" as used herein refer to acid halides such as acid chlorides, and activated esters including, but not limited to, formic and acetic acid derived anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinimide derived esters, N-hydroxyphthalimide derived esters, N-hydroxybenzotriazole derived esters, N-hydroxy-5-norbornene-2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters and the like.

In the compounds of the invention, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. As used herein, the term "stable compound" refers to a compound that is sufficiently stable to survive isolation to a useful degree of purity from a reaction mixture and formulation into a therapeutic dosage form suitable for administration.

Preferred compounds of the invention are selected from the group consisting of:

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)-amino)-5-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-2-(N-((5-methoxycarbonyl)amino-1,6-diphenyl-3-hydroxyhexane;

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(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino-1,6-diphenyl-3-hydroxyhexane;

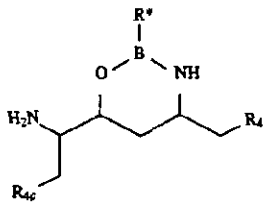
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; and

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; or a pharmaceutically acceptable salt, ester or prodrug thereof.

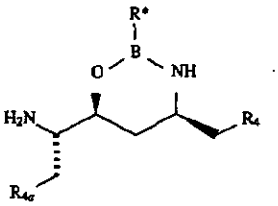
Compounds useful as intermediates for the preparation of the compound of formula A and A1 include the compound of the formula A3:



A3

wherein R_4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii) loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy; and R* is phenyl, halo-substituted phenyl, dihalo-substituted phenyl, alkoxy-substituted phenyl, loweralkyl-substituted phenyl, bis-trifluormethyl-substituted phenyl or naphthyl or loweralkyl; or an acid addition salt thereof.

Preferred intermediates are compounds of the formula A4:



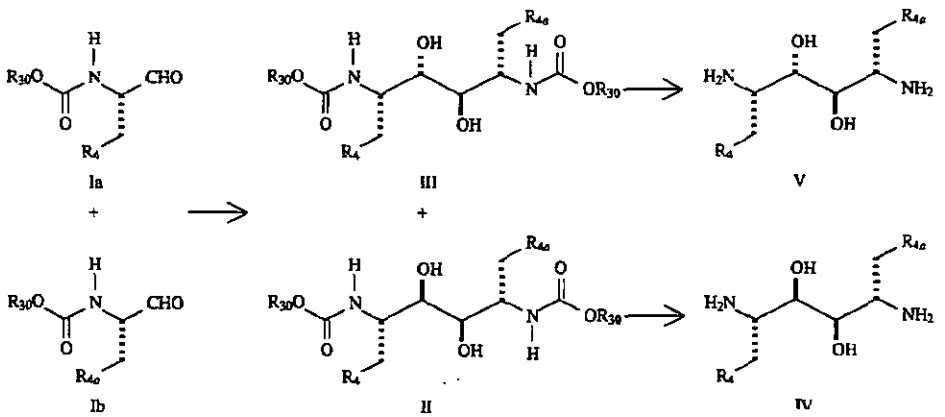
A4

wherein R_4 and R_{4a} are independently selected from phenyl, thiazolyl and oxazolyl wherein the phenyl, thiazolyl or oxazolyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii)loweralkyl, (iii) hydroxy, (iv) alkoxy and (v) thioalkoxy; and R* is phenyl, halo-substituted phenyl, dihalo-substituted phenyl, alkoxy-substituted phenyl, loweralkyl-substituted phenyl, bis-trifluormethyl-substituted phenyl or naphthyl or loweralkyl; or an acid addition salt thereof.

Preferred compounds of the formula A4 are those wherein R_{4a} is phenyl and R* is phenyl. Most preferred compounds of the formula A4 are those wherein R_4 and R_{4a} are phenyl and R* is phenyl.

The compounds of the invention can be prepared as shown in Schemes 1–9. As outlined in Scheme 1, coupling of protected α-aminoaldehyde Ia and Ib (R_{30} is loweralkyl or benzyl) with VCl_3(tetrahydrofuran)$_3$ and Zn produces a mixture of diols, out of which compounds II and III can be isolated. Hydrolysis of II and III with barium hydroxide leads, respectively, to diaminodiols IV and V. Alternately, treatment of II with α-acetoxyisobutyryl bromide in acetonitrile leads to compound VI, which upon hydrolysis with barium hydroxide, produces diaminodiol VII. In a preferred embodiment, R_4 and R_{4a} are each phenyl and the first reaction in Scheme 1 is a dimerization.

Scheme 1



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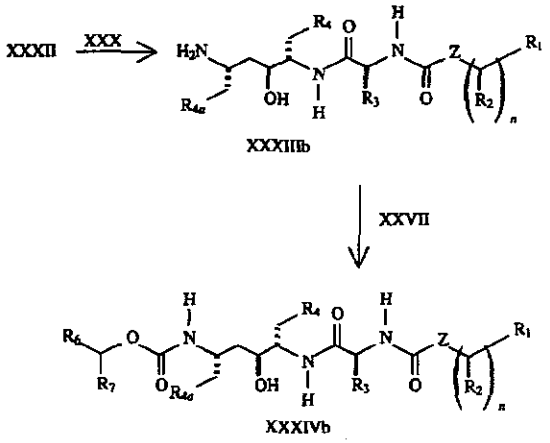
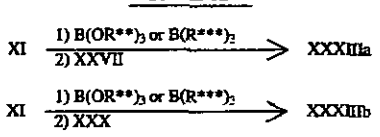
Scheme 6A



Scheme 6B outlines an alternative preparation of XXXIIIa or XXXIIIb. Reaction of compound XI with (i) *two equivalents of B(OR**)$_3$ wherein R** is loweralkyl* (preferably, isopropyl) or (ii) two equivalents of B(R***)$_3$ wherein R*** is halo (preferably, fluoro) and four equivalents of an amine such as triethylamine in an inert solvent such as tetrahydrofuran, followed by reaction with an activated derivative of XXVI having the formula $(R_6)(R_7)$CHOC(O)OL wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII), gives compound XXXIIIa or an acid addition salt thereof. Similarly, reaction of compound XI with two equivalents of B(OR**)$_3$ wherein R** is loweralkyl (preferably, isopropyl) or two equivalents of B(R***)$_3$ wherein R*** is halo (preferably, fluoro), followed by reaction with compound XXX (or an activated ester derivative thereof), gives compound XXXIIIb or an acid addition salt thereof. In the preferred embodiment of the process shown in Scheme 6B, n is 1, R_4 and R_{4a} are each phenyl and R** is isopropyl or R*** is fluoro.

Scheme 6B



Scheme 6C outlines an alternative preparation of XXXIVa and XXXIVb. Reaction of compound XI with two molar equivalents of Ti(OR****)$_4$ wherein R_4 is loweralkyl (preferably, isopropyl), followed by reaction with an activated derivative of XXVI having the formula $(R_6)(R_7)$CHOC(O)OL wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII), provides compound XLII or an acid addition salt thereof. Reaction of compound XLII with compound XXX (or an activated ester derivative thereof) gives compound XXXIVb. Similarly, reaction of compound XI with two molar equivalents of Ti(OR****)$_4$ wherein R_4 is loweralkyl (preferably, isopropyl), followed by reaction with compound XXX (or an activated ester derivative thereof), provides compound XLIII or an acid addition salt thereof. Reaction of compound XLIII with an activated derivative of XXVI having the formula $(R_6)(R_7)$CHOC(O)OL wherein L is an activating group for the acylation reaction such as p-nitrophenyl, phenyl, N-succinimidyl, N-phthalimidyl, N-benzotriazolyl, N-5-norbornene-2,3-carboxamidyl or 2,4,5-trichlorophenyl and the like (for example, XXVII) gives compound XXXIVa. In the preferred embodiment of the process shown in Scheme 6C, n is 1, R_4 and R_{4a} are each phenyl and R**** is isopropyl.

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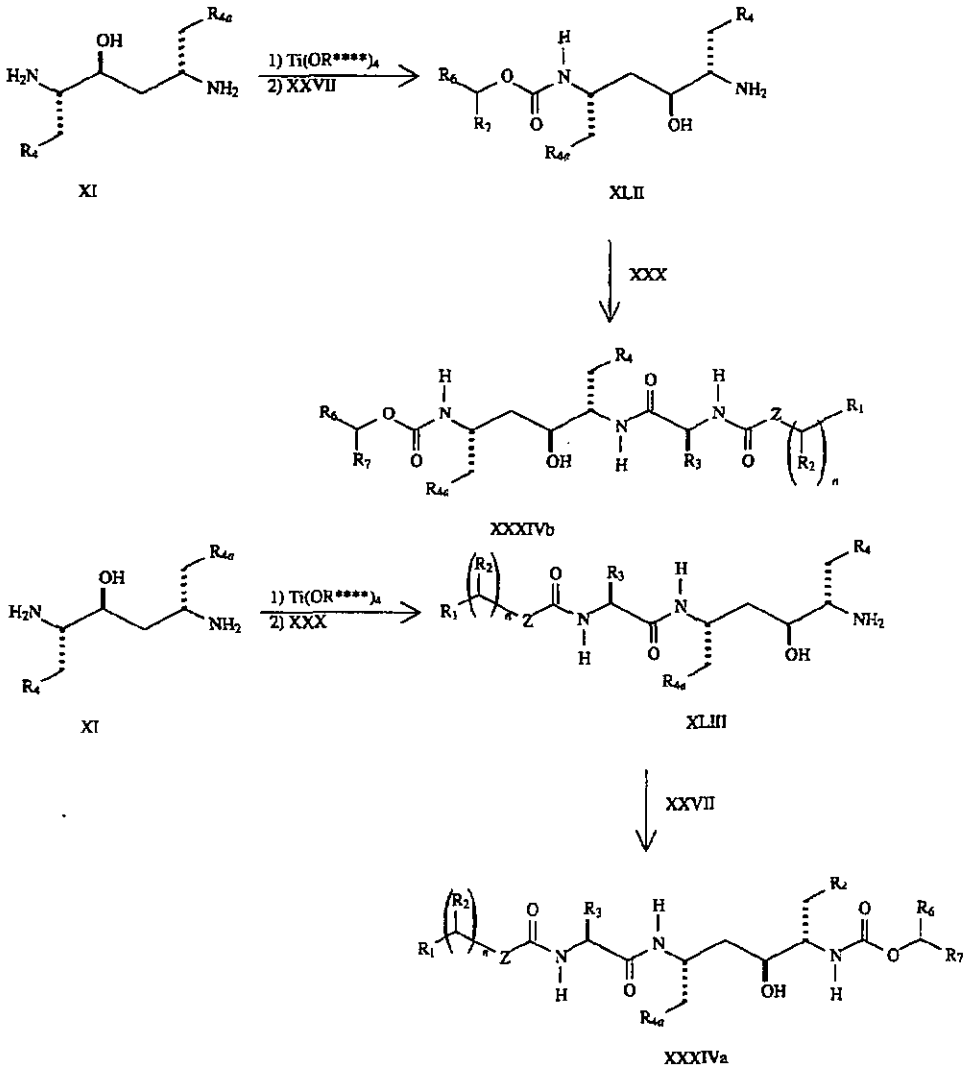
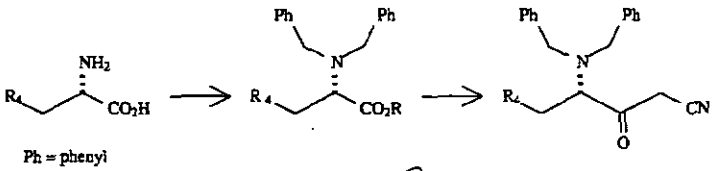
Scheme 6C



Scheme 7 shows an alternative preparation of diamino-mono-ol XI. Reaction of ketonitrile XXXV with Grignard reagent R_{4a} CH_2MgX provides ketoenamine XXXVI. Reaction of the ketoenamine with $NaBH_4/CH_3SO_3H$, followed by reaction of the resulting intermediate (without isolation) with $NaBH_4/CF_3CO_2H$, provides XXXVII. Hydrogenation of the benzyl groups gives XI. Alternatively, protection of the free amino group of XXXVII as the t-butyloxycarbonylamino group, followed by hydrogenation of the benzyl groups, gives XXXVIII. In a preferred embodiment, R_4 and R_{4a} are each phenyl.

Scheme 7



Ph = phenyl

XXXV

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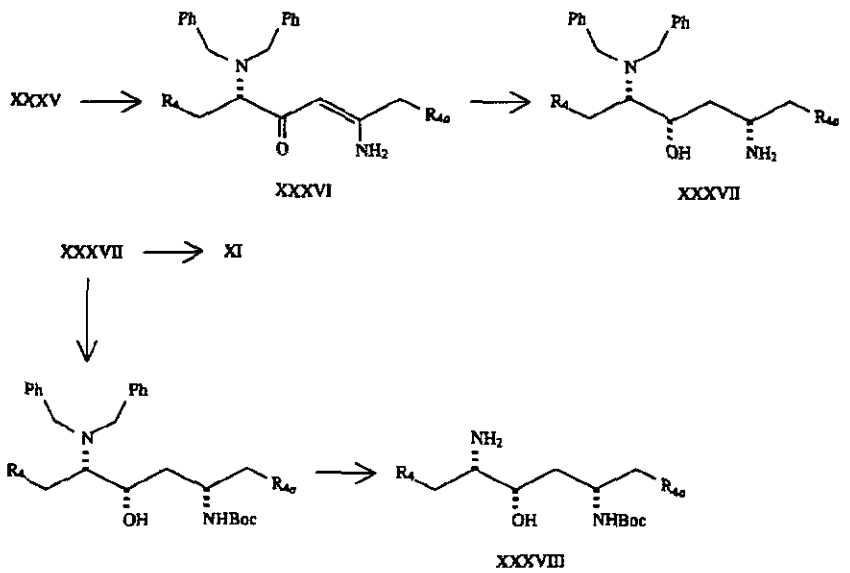
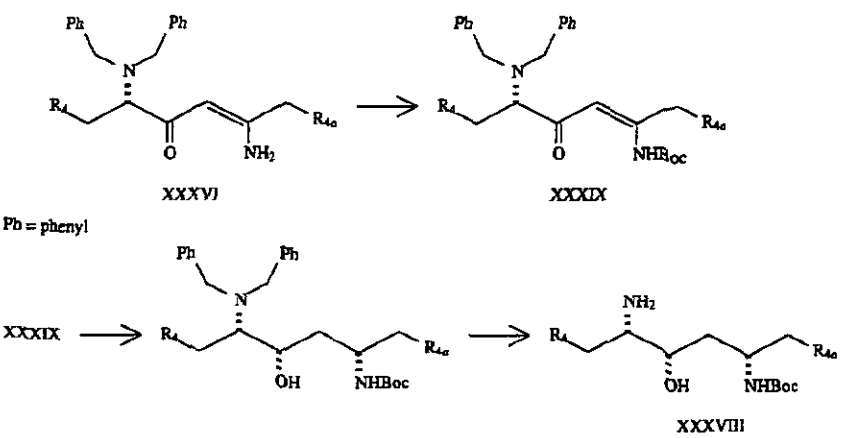
Scheme 7



Scheme 8 shows an alternative preparation of XXXVIII. N-protection of XXXVI gives XXXIX. Reaction of XXXIX with borane-tetrahydrofuran complex, followed by reaction of the resulting product with $LiAlH_4$ or KBH_4, provides the N,N-dibenzyl precursor to XXXVIII.

Scheme 8



Ph = phenyl

Scheme 9 shows how the selectively protected diamine XXXIX can be used to prepare compounds of the invention XL and XLI.

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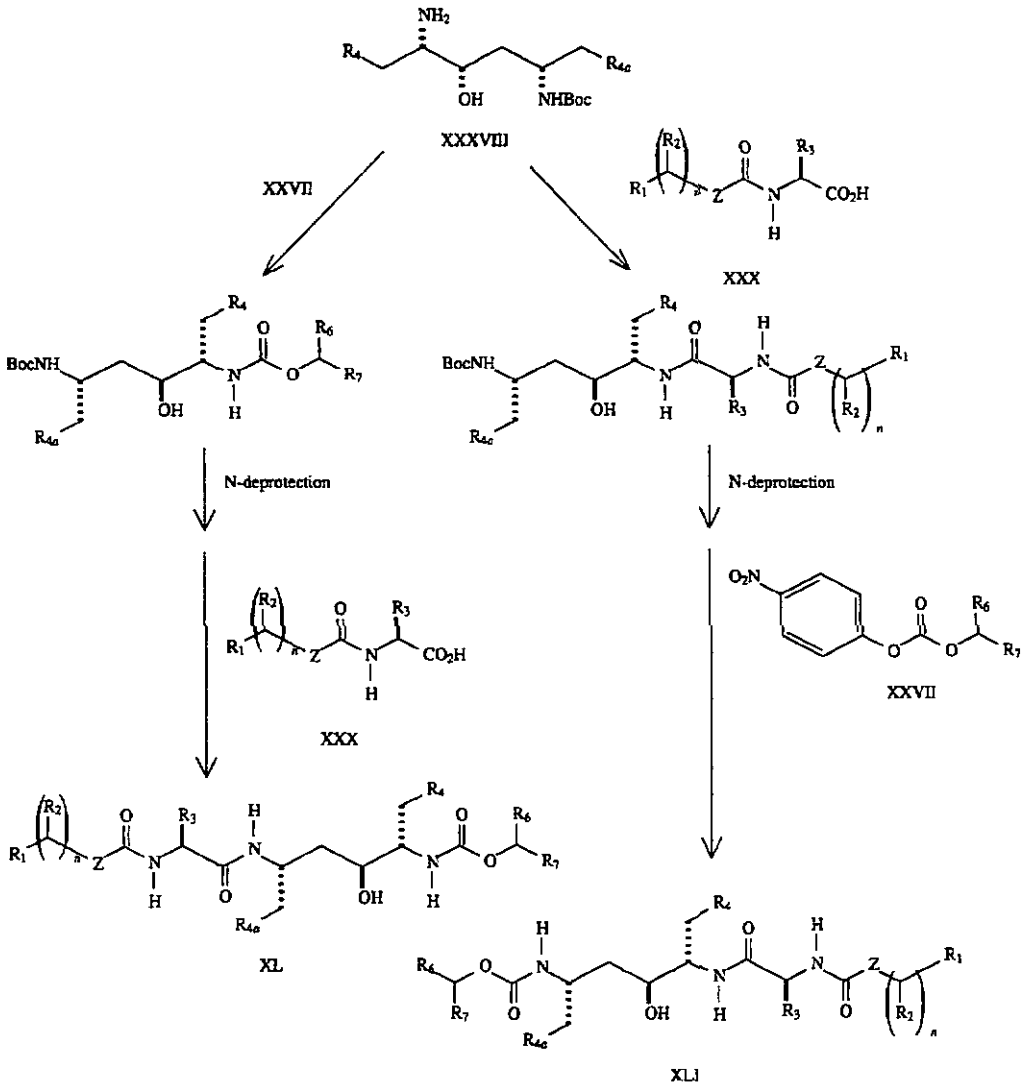
Scheme 9



The following examples will serve to further illustrate the preparation of the novel compounds of the invention.

EXAMPLE 1

A. N-(((Benzyl)oxy)carbonyl)-L-phenylalaninal.

A solution of 24.5 ml of anhydrous dimethyl sulfoxide in 870 ml of anhydrous dichloromethane was cooled under N_2 atmosphere to −60° C. and treated over a period of 15 min with 131 ml of a 2M solution of oxalyl chloride in dichloromethane in order that the internal temperature remained below −50° C. After addition, the solution was stirred at −60° C. for 15 min and treated over a period of 20 min with a solution of 50 g (0.175 mol) of N-(((benzyl)oxy)-carbonyl)-L-phenylalaninol in 200 ml of dichloromethane. The resulting solution was stirred at −60° C. for 1 h, then treated over a period of 15 min with 97 ml of triethylamine in order that the internal temperature remained below −50° C. After addition the solution was stirred at −60° C. for 15 min, then, with the cooling bath in place, was treated rapidly (over a period of 1 min) with a solution of 163 g of citric acid in 550 ml of water. The resulting slurry was stirred vigorously for 10 min, allowed to warm, diluted to 1 liter with water, and separated. The organic layer was washed with 700 ml of water followed by a mixture of 550 ml of water and 150 ml of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo at 20° C. to give the crude desired compound as a light yellow solid.

B. (2S,3R,4R,5S)-2.5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3.4-dihydroxy-1.6-diphenylhexane and (2S,3S,4S,5S)-2.5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3.4-dihydroxy-1.6-diphenylhexane.

A suspension of 78.5 g of VCl_3.(tetrahydrofuran)$_3$ and 16 g of zinc dust in 400 ml of dry dichloromethane was stirred under N_2 atmosphere for 1 h at 25° C. A solution of 0.175 mol of N-(((benzyl)oxy)carbonyl)-L-phenylalaninal in 200 ml of dichloromethane was then added in one portion, and the resulting mixture was stirred at ambient temperature under N_2 atmosphere for 16 h. The resulting mixture was added to 500 ml of 1M aqueous HCl, diluted with 500 ml of hot chloroform, and shaked vigorously for 2 min. The layers were separated, and the organic layer was washed with 1M

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aqueous HCl and separated. Filtration of the organic phase provided the crude desired product as a solid residue. The residue was slurried in 1.25 liters of acetone, treated with 5 ml of concentrated H_2SO_4, and stirred for 16 h at ambient temperature. The resulting mixture was filtered, and the residue (residue A) was washed with 50 ml of acetone. The combined filtrate was concentrated to a volume of 250 ml, diluted with 1000 ml of dichloromethane, washed three times with water and once with saturated brine, dried over $MgSO_4$, and concentrated to give a viscous oil. The oil was taken up in 1000 ml of 1M HCl in methanol (prepared from 71 ml of acetyl chloride and 1000 ml of methanol) and stirred at ambient temperature for 2 h. The resulting precipitate was filtered, washed with methanol, and air-dried on the filter to provide 26.7 g of the desired compound as a white solid. The filtrate was concentrated and filtered to give a second crop (8.3 g) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane. ^1H NMR (d_6-DMSO) δ2.59 (dd, J=13, 5 Hz, 2H), 2.74 (dd, J=13, 9 Hz, 2H), 3.26 (br, 2H), 4.19 (m, 2H), 4.54 (m, 2H), 4.92 (m, 4H), 6.82 (d, J=9 Hz, 2H), 7.0–7.35 (m, 20H). Mass spectrum: $(M+H)^+$=569.

Residue A (above, 2.65 g) was suspended in 75 ml of tetrahydrofuran (THF) and 75 ml of 1M aqueous HCl and heated at reflux for 24 h. After concentration of the resulting solution in vacuo, the residue was taken up in 10% methanol in chloroform, washed two times with water, dried over Na_2SO_4, and concentrated in vacuo to provide (2S,3S,4S,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane as a white solid. ^1H NMR (d_6-DMSO) δ2.64(m, 2H), 3.04(m, 2H), 3.49(m, 2H), 3.78 (m, 2H), 4.70 (d, J=7 Hz, 2H), 4.93 (AA', 4H), 7.1–7.4 (m, 20H). Mass spectrum: $(M+H)^+$=569.

C. (2S,3R,4S,5S)-3-Acetoxy-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3-bromo-1,6-diphenylhexane.

A suspension of 25 g (44 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane in 500 ml of 2:1 dichloromethane/hexane was treated with 23 g of α-acetoxyisobutyryl bromide. The resulting mixture was stirred at ambient temperature until the reaction clarified, washed with two 200 ml portions of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to give 30.8 g of the crude desired compound. A portion was purified by silica gel chromatography using 9:1 dichloromethane:ethyl acetate to provide the pure desired compound as a white solid. ^1H NMR ($CDCl_3$), δ2.21 (s, 3H), 2.62 (dd, J=13, 11Hz, 1H), 2.75 (d, J=7 Hz, 2H), 2.95 (br d, J=15 Hz, 1H), 4.03 (br t, J=10 Hz, 1 h), 4.40 (br d, J=10 Hz, 1H), 4.6–5.0 (m, 6H), 5.12 (br d, J=13Hz, 1H), 5.33 (br d, J=11Hz, 1H), 7.0–7.4 (m, 10H). Mass spectrum: $(M+NH_4)^+$=690,692.

D. (2S,3R,4R,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-epoxy-1.6-diphenylhexane.

A solution of 35.56 g (52.8 mmol) of (2S,3R,4S,5S)-3-acetoxy-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3-bromo-1,6-diphenylhexane in 375 ml of dioxane was treated with 255 ml of 1N aqueous sodium hydroxide and stirred at ambient temperature for 16 h, during which the desired compound precipitated. The resulting mixture was filtered, and the residue was washed with water and dried to provide 22.23 g (76%) of the desired compound as a white solid. ^1H NMR ($CDCl_3$) δ2.7–2.9 (m, 6H), 3.9–4.0 (m, 2H), 4.6–4.7 (m, 2H), 5.03 (m, 4H), 7.1–7.4 (m, 10H).

E. (2S,3S,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)1,6-diphenyl-3-hydroxyhexane.

A mixture of 39.2 g (71.2 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-epoxy-1,6-diphenylhexane in 600 ml of THF was treated under N_2 atmosphere with 13 g (0.36 mol) of sodium borohydride. The resulting mixture was treated dropwise with 27.7 ml (0.36 mol) of trifluoroacetic acid. After being stirred for 3.5 h at ambient temperature, the resulting mixture was quenched with 1N aqueous HCl, diluted with water, and stirred for 16 h. The resulting mixture was filtered, washed with water, and dried to provide 22.85 g (58%) of the desired compound as a white solid.

F. (2S,3S,5S)-2.5-Diamino-1,6-diphenyl-3-hydroxyhexane.

A suspension of 32 g of the crude resultant compound of Example 1E and 55.5 g (176 mmol) of barium hydroxide octahydrate in 400 ml of 1,4-dioxane and 400 ml of water was heated at reflux for 4 h. The resulting mixture was filtered, and the residue was rinsed with dioxane. The combined filtrates were concentrated to a volume of approximately 200 ml and extracted with four 400 ml portions of chloroform. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography using first 2% isopropylamine in chloroform and then 2% isopropylamine/2% methanol in chloroform to provide 10.1 g (81%) of the pure desired compound as a white solid. ^1H NMR ($CDCl_3$) δ1.54 (dt, J=14, 10 Hz, 1H), 1.67 (dt, J=14, 3 Hz, 1H), 2.50 (dd, J=13, 8 Hz, 1H), 2.58 (dd, J=13, 8Hz, 1H), 2.8 (m, 2H) 2.91 (dd, J=13,5 Hz, 1H), 3.10(m, 1H), 3.72(ddd, J=11,3,2 Hz, 1H), 7.1–7.4 (m, 10H). Mass spectrum: $(M+H)^+$=285.

G. (4S,6S, 1'S)-6-(1-Amino-2-phenylethyl)-4-benzyl-2-phenyl-3-aza-2-bora-1-oxacyclohexane.

A solution of 131 g (460 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane in 1.2 L of toluene was treated under N_2 atmosphere with 56.16 g (460 mmol) of phenylboric acid. The resulting solution was heated at reflux (bath temperature 135° C.) and water azeotropically removed with the aid of a Dean Stark trap until the distillate was clear and the theoretical amount of water (15.6 ml) was collected (ca 1.5h). After being allowed to cool, the solution was concentrated in vacuo to provide 176 g of the crude desired compound as a resin. H^1 NMR ($CDCl_3$) δ7.59 (m, 2H), 7.47–7.07 (m, 13H, 3.92 (m, 1H), 3.78 (s br, 1H), 3.52 (m, 1H)3.50 (m, 2H), 2.87 (dd, 1H, J=13.5, 5.7 Hz), 2.72 (m, 1H), 2.58 (dd, 1H , J=13.5, 8.7 Hz), 1.92 (m, 1H), 1.68 (m, 1H), 1.60–1.30 (s-very broad, 2H). CIMS m/z 371 (M+H)

H. Thioformamide,

To a cooled (0° C.) 2 L three neck round bottom flask equipped with an overhead stirrer charged with a solution of formamide (30.5 mL, 0.76 mol) in 1 L of diethyl ether was added 89 g (0.19 mol) of phosphorous pentasulfide in small portions. The reaction mixture was allowed to warm to ambient temperature, stirred for 2 h, filtered, and concentrated in vacuo to afford thioformamide as a yellow offensive smelling oil which was used without purification.

I. Ethyl 2-Chloro-2-formylacetate.

To a three neck 2 L round bottom flask charged with potassium t-butoxide (0.5 mol, 500 mL of a 1M solution in THF) and 500 mL of dry THF cooled to 0° C. was added dropwise from an addition funnel a solution of ethyl chloroacetate (0.5 mol, 53.5 mL) and ethyl formate (0.5 mol, 40.4 mL), in 200 mL of THF over 3 hours. After completion of addition, the reaction mixture was stirred for 1 hour and allowed to stand overnight. The resulting solid was diluted with diethyl ether and cooled in an ice bath. Then, the pH was lowered to approximately 3 using 6N HCl. The organic phase was separated, and the aqueous layer was washed 3 times with diethyl ether. The combined ethereal portions were dried over $NaSO_4$, and concentrated in vacuo. The

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crude desired compound was stored at –30° C. and used without further purification.

J. Ethyl Thiazole-5-carboxylate.

To a round bottom flask was added 250 mL of dry acetone, 7.5 g (0.123 mol) of thioformamide, and 18.54 g (0.123 mol) of ethyl 2-chloro-2-formylacetate. The reaction was heated at reflux for 2 hours. The solvent was removed in vacuo, and the residue was purified by chromatography (SiO_2, 6 cm o.d. column, 100% $CHCl_3$, R_f=0.25) to provide 11.6 g (60%) of the desired compound as a light yellow oil. NMR ($CDCl_3$) δ1.39 (t, J=7Hz, 3H), 4.38 (q, J=7 Hz, 2H), 8.50 (s, 1H), 8.95 (s, 1H).

K. 5-(Hydroxymethyl)thiazole.

To a precooled (ice bath) three neck 500 mL flask containing lithium aluminum hydride (76 mmol) in 250 mL of THF was added ethyl thiazole-5-carboxylate (11.82 g, 75.68 mmol) in 100 mL of THF dropwise over 1.5 hours to avoid excess foaming. The reaction was stirred for an additional hour, and treated cautiously with 2.9 mL of water, 2.9 mL of 15% NaOH, and 8.7 mL of water. The solid salts were filtered, and the filtrate set aside. The crude salts were heated at reflux in 100 mL of ethyl acetate for 30 min. The resulting mixture was filtered, and the two filtrates were combined, dried over Na_2SO_4, and concentrated in vacuo. The product was purified by silica gel chromatography eluting sequentially with 0%–2%–4% methanol in chloroform, to provide the desired compound, Rf=0.3 (4% methanol in chloroform), which solidified upon standing in 75% yield. NMR ($CDCl_3$) δ4.92 (s, 2H), 7.78 (s, 1H), 8.77 (s, 1H). Mass spectrum: $(M+H)^+$=116.

L. ((5-Thiazolyl)methyl)-(4-nitrophenyl)carbonate.

A solution of 3.11 g (27 mmol) of 5-(hydroxymethyl)thiazole and excess N-methyl morpholine in 100 ml of methylene chloride was cooled to 0° C. and treated with 8.2 g (41 mmol) of 4-nitrophenyl chloroformate. After being stirred for 1 h, the reaction mixture was diluted with $CHCl_3$, washed successively with 1N HCl, saturated aqueous $NaHCO_3$, and saturated brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (SiO2, 1–2% MeOH/$CHCl_3$, Rf=0.5 in 4% MeOH/$CHCl_3$) to yield 5.9 g (78%) of the desired compound as a yellow solid. NMR ($CDCl_3$) δ5.53 (s, 2H), 7.39 (dt, J=9, 3 Hz, 2H), 8.01 (s, 1H), 8.29 (dt, J=9, 3 Hz, 2H), 8.90 (s, 1H). Mass spectrum: $(M+H)^+$=281.

M. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and (2S,3S,5S)-2-Amino-5-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 500 mg (1.76 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 480 mg (1.71 mmol) of ((5-thiazolyl)methyl)-4-nitrophenyl)carbonate in 20 ml of THF was stirred at ambient temperature for 4 h. After removal of the solvent in vacuo, the residue was purified by silica gel chromatography using first 2% then 5% methanol in chloroform to provide a mixture of the two desired compounds. Silica gel chromatography of the mixture using a gradient of 0–1–2% methanol in 93:2 isopropylamine: chloroform provided 110 mg (16%) of (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (R_f0.48, 96:2:2 chloroform:methanol:isopropylamine) and 185 mg (28%) of (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (R_f0.44, 96:2:2 chloroform :methanol:isopropylamine).

(2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane: NMR ($CDCl_3$) δ1.3–1.6 (m, 2H), 2.40 (dd, J=14, 8 Hz, 1H), 2.78 (dd, J=5 Hz, 1H), 2.88 (d, J=7Hz, 2H), 3.01 (m, 1H), 3.72 (br q, 1H), 3.81 (br d, J=10 Hz, 1H), 5.28 (s, 2H), 5.34 (br d, J=9 Hz, 1H), 7.07 (br d, J=7 Hz, 2H), 7.15–7.35 (m, 8H), 7.87 (s, 1H), 8.80 (s, 1H). Mass spectrum: $(M+H)^+$=426.

(2S,3S,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane: NMR ($CDCl_3$) δ1.55 (dt, J=14, 8 Hz, 1H), 1.74 (m, 1H), 2.44 (dd, J=15, 1 Hz, 1H), 2.75–3.0 (m, 4H), 3.44 (m, 1H), 4.00(br t, 1H), 5.28 (m, 3H), 7.1–7.4 (m, 10H), 7.86 (s, 1H), 8.80 (s, 1H). Mass spectrum: $(M+H)^+$=426.

N. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 40 mmol of crude (4S,6S,1'S)-6-(1-amino-2-phenylethyl)-4-benzyl-2-phenyl-3-aza-2-bora-1-oxacyclohexane in 700 ml of anhydrous THF was cooled to –40° C. and treated dropwise over a period of 1 h with a solution of 7.83 g (27.9 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 300 ml of dry THF. The resulting solution was allowed to warm to 0° C. for 3 h, then to ambient temperature for 16 h. The solvent was removed in vacuo, and the residue was taken up in 700 ml of ethyl acetate, washed with three 150 ml portions of 1N aqueous NaOH and one 150 ml portion of brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography using methanol/chloroform mixtures provided the desired compound mixed with its regioisomer. A second chromatography using 1–3% isopropylamine in chloroform provided 5.21 g of the desired compound which solidified upon standing.

O. 2-Methylpropane-thioamide.

A suspension of 100 g (1.15 mol) of isobutyramide in 4 L of diethyl ether was stirred vigorously and treated in portions with 51 g (0.115 mol) of P_4S_{10}. The resulting mixture was stirred at ambient temperature for 2 h, filtered, and concentrated in vacuo to provide 94.2 g (80%) of the crude desired compound. ^1H NMR (DMSO-d_6) δ1.08 (d, J=7 Hz, 6H), 2.78(heptet, J=7 Hz, 1H), 9.06 (br, 1H), 9.30 (br, 1H). Mass spectrum: $(M+H)^+$=104.

P. 4-(Chloromethyl)-2-isopropylthiazole hydrochloride.

A mixture of 94.0 g (0.91 mol) of 2-methylpropane-thioamide, 115.7 g (0.91 mol) of 1,3-dichloroacetone, and 109.7 g (0.91 mol) of $MgSO_4$ in 1.6 liters of acetone was heated at reflux for 3.5 h. The resulting mixture was allowed to cool, filtered, and the solvent was removed in vacuo to provide the crude desired compound as a yellow oil. ^1H NMR (DMSO-d_6) δ1.32 (d, J=7 Hz, 6H), 3.27 (heptet, J=7 Hz, 1H), 4.78 (s, 2H), 7.61 (s, 1H). Mass spectrum: $(M+H)^+$ =176.

Q. 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole.

A solution of 40 g of 4-(chloromethyl)-2-isopropylthiazole hydrochloride in 100 ml of water was added dropwise with stirring to 400 ml of 40% aqueous methylamine. The resulting solution was stirred for 1 h, then concentrated in vacuo. The residue was taken up in chloroform, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel chromatography using 10% methanol in chloroform provided 21.35 g (55%) of the desired compound. ^1H NMR (DMSO-d_6) δ1.34 (d, J=7 Hz, 6H), 2.56 (s, 3H), 3.30 (heptet, J=7 Hz, 1H), 4.16 (s, 2H), 7.63 (s, 1H). Mass spectrum: $(M+H)^+$=171.

R. N-(((4-Nitrophenyl)oxy)carbonyl)-L-valine Methyl Ester.

A solution of 66.1 g (0.328 mol) of 4-nitrophenyl chloroformate in 1.2 liters of CH_2Cl_2 was cooled to 0° C. and treated with L-valine methyl ester hydrochloride. The resulting mixture was treated slowly, with stirring, with 68.9 ml (0.626 mol) of 4-methylmorpholine. The resulting solution

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was allowed to slowly warm to ambient temperature and was stirred overnight. After washing with 3 portions of 10% aqueous $NaHCO_3$, the solution was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography by eluting with chloroform to provide the desired compound. ^1H NMR (DMSO-d_6) δ0.94 (d, J=7 Hz, 3H), 0.95 (d, J=7 Hz, 3H), 2.12 (octet, J=7 Hz, 1H), 3.69 (s, 3H), 4.01 (dd, J=8, 6 Hz, 1H), 7.41(dt, J=9, 3 Hz, 2H), 8.27 (dt, J=9, 3 Hz, 2H), 8.53 (d, J=8 Hz, 1H). Mass spectrum: $(M+NH_4)^+$=314.

S. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

A solution of 15.7 g (92 mmol) of 2-isopropyl-4-(((N-methyl)amino)-methyl)thiazole in 200 ml of THF was combined with a solution of 20.5 g (69 mmol) of N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester. The resulting solution was treated with 1.6 g of 4-dimethylaminopyridine and 12.9 ml (92 mmol) of triethylamine, heated *at reflux for 2 h, allowed to cool, and concentrated in vacuo.* The residue was taken up in CH_2Cl_2, washed extensively with 5% aqueous K_2CO_3, dried over Na_2SO_4, and concentrated in vacuo. The resulting product mixture was purified by silica gel chromatography using chloroform as an eluent to provide 16.3 g (54%) of the desired compound. ^1H NMR (DMSO-d_6) δ0.88 (d, J=7 Hz, 3H), 0.92 (d, J=7 Hz, 3H), 1.32 (d, J=7 Hz, 3H), 2.05 (octet, J=7 Hz, 1H), 2.86(s,3H), 3.25 (heptet, J=7 Hz, 1H), 3.61 (s, 3H), 3.96 (dd, J=8, 7 Hz, 1H), 4.4 (AA', 2H), 6.58 (d, J=8 Hz, 1H), 7.24 (s, 1H). Mass spectrum: $(M+H)^+$=328.

T. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

A solution of 1.42 g (4.3 mmol) of the resultant compound of Example 1S in 17 ml of dioxane was treated with 17.3 ml of 0.50M aqueous LiOH. The resulting solution was stirred at ambient temperature for 30 min, treated with 8.7 ml of 1M HCl, and concentrated in vacuo. The residue was taken up in dichloromethane, washed with water, dried over Na_2SO_4, and concentrated in vacuo to provide 1.1 g (81%) of the desired compound. Mass spectrum: $(M+H)^+$=314.

U. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexane.

A solution of 70 mg (0.223 mmol) of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine, 79 mg (0.186 mmol) of (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane, 30 mg (0.223 mmol) of 1-hydroxybenzotriazole hydrate, and 51 mg (0.266 mmol) of N-ethyl-N'-dimethylaminopropyl carbodiimide in 2 ml of THF was stirred at ambient temperature for 16 h. The resulting solution was concentrated in vacuo, and the residue was purified by silica gel chromatography using 97:3 CH_2Cl_2:CH_3OH to provide 100 mg (74%) of the desired compound (R_f0.4, 95:5 CH_2Cl_2:CH_3OH) as a solid. ^1H NMR (d_6-DMSO) δ0.73 (d, J=7 Hz, 6H), 1.30 (d, J=7 Hz, 6H), 1.45 (m, 2H), 1.87 (m, 1H), 2.5–2.7 (m, 4H), 2.87 (s, 3H), 3.23 (heptet, J=7 Hz, 1H), 3.57 (m, 1H), 3.81 (m, 1H), 3.93 (m, 1H), 4.15 (m, 1H), 4.44 (AA', 2H), 4.62 (d, J=6 Hz, 1H), 5.13 (AA', 2H), 6.01 (d, J=9 Hz, 1H), 6.89 (d, J=9 Hz, 1H), 7.1–7.2 (m, 11H), 7.68 (d, J=9 Hz, 1H 7.85 (s, 1H), 9.05 (s, 1H). Mass spectrum: $(M+H)^+$=721. Anal. Calcd for $C_{37}H_{48}N_6O_5S_2.0.5H_2O$: C, 60.88; H, 6.77; N, 11.51. *Found:* C, 60.68;H , 6.53; N, 11.36.

EXAMPLE 2

Following the procedures of Example 1, the following compounds can be prepared:

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl-)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

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(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl-)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

EXAMPLE 3

A. N-(((4-nitrophenyl)oxy)carbonyl)-L-alanine Methyl Ester.

Using the procedure of Example 1R, but replacing L-valine methyl ester hydrochloride with L-alanine methyl ester hydrochloride provided the desired compound (R_f0.25, dichloromethane)in 95% yield.

B. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-alanine Methyl Ester.

Using the procedure of Example 1S, but replacing N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester with the resultant compound of Example 3A provided, after silica gel chromatography using 97:3 CH_2Cl_2:CH_3OH, the desired compound (R_f0.55, 95:5 CH_2Cl_2: CH_3OH) in 24% yield. ^1H NMR ($CDCl_3$) δ1.39 (d, J=7 Hz, 6H), 1.43 (d, J=7 Hz, 3H), 2.98 (s, 3H), 3.28 (heptet, J=7 Hz, 1H), 3.74 (s, 3H), 4.46 (s, 2H), 4.49 (q, J=7 Hz, 1H), 6.12 (br, 1H), 6.98 (s, 1H). Mass spectrum: $(M+H)^+$=300.

C. N-((N-Methyl-N((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-alanine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 3B provided the desired compound.

D. (2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-isopropyl-4-thiazolylmethyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 3C provided, after silica gel chromatography using 97:3 CH_2Cl_2:CH_3OH, 70 mg (35%) of the desired compound (R_f 0.36, 95:5 CH_2Cl_2:CH_3OH), mp. 56°–58° C. Mass spectrum: $(M+H)^+$=693. Anal. Calcd for $C_{35}H_{44}N_6O_5S_2.0.5H_2O$: C, 59.89; H, 6.46; N, 11.97. Found: C, 60.07; H, 6.39; N, 12.00.

EXAMPLE 4

A. 2-Isopropyl-4-(((N-ethyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 40% aqueous methylamine with 70% aqueous ethylamine provided the crude desired compound. ^1H NMR (DMSO-d_6) δ1.12 (t, J=7 Hz, 3H), 1.32 (d, J=7Hz, 6H), 2.78 (q, J=7 Hz, 2H), 3.27 (q, J=7 Hz, 1H), 3.97 (s, 2H), 7.44 (s, 1H)

B. N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-(((N-ethyl)amino)methyl)-thiazole provided, after silica gel chromatography using 98:2 $CHCl_3$:CH_3OH, the desired compound (R_f0.5, 95:3 CH_2Cl_2:CH_3OH) in 54% yield. ^1H NMR ($CDCl_3$) δ0.94 (d, J=7Hz, 3H), 0.98 (d, J=7 Hz, 3H), 1.16 (t, J=7 Hz, 3H), 1.39 (d, J=7 Hz, 6H), 2.16 (m, 1H), 3.25–3.50 (m, 3H), 3.71 (s, 3H), 4.38 (dd, J=8, 6 Hz, 1H), 4.46 (AA', 2H), 6.13 (br, 1H), 7.00 (s, 1H). Mass spectrum: $(M+H)^+$=342.

C. N-((N-Ethyl-N-((2.-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 4B provided the desired compound.

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D. (2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2,isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 4C provided, after silica gel chromatography using 98:2 $CHCl_3$:CH_3OH, 60 mg (35%) of the desired compound (R_f 0.4, 95:5 CH_2Cl_2:CH_3OH), mp. 58°–60° C. Mass spectrum: $(M+H)^+$=735.

EXAMPLE 5

A. Ethyl 2-1-isopropylthiazole-4-carboxylate.

A solution of 2.35 g (23 mmol) of 2-methylpropanethioamide and 2.89 ml (23 mmol) of ethyl bromopyruvate in 75 ml of acetone was treated with excess $MgSO_4$ and heated at reflux for 2.5 h. The resulting mixture was allowed to cool, filtered, and concentrated in vacuo to an oil, which was taken up in chloroform, washed sequentially with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel using chloroform as an eluent to provide 3.96 g (86%) of the desired compound, R_f0.21 (chloroform) as an oil. ^1H NMR ($CDCl_3$) δ1.41 (t, J=8 Hz, 3H), 1.42 (d, J=7 Hz, 6H), 3.43 (heptet, J=7 Hz, 1H), 4.41 (q, J=8 Hz, 2H), 8.05 (s, 1H). Mass spectrum: $(M+H)^+$=200.

B. 4-(Hydroxymethyl)-2-isopropylthiazole.

A solution of 10 ml (10 mmol) of lithium aluminum hydride in toluene was diluted in a dry flask under N_2 atmosphere with 75 ml of THF. The resulting mixture was cooled to 0° C. and treated dropwise with a solution of 3.96 g (20 mmol) of ethyl 2-isopropyl-4-thiazolecarboxylate in 10 ml of THF. After addition, the solution was stirred at 0° C. for 3 h, diluted with ether, and treated with a small amount of aqueous Rochelle's salt. After stirring, the slurry was filtered, washed with ethyl acetate, and the combined filtrates were concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 2.18 g (69%) of the desired compound, R_f0.58 (4% methanol in chloroform). ^1H NMR ($CDCl_3$) δ1.39 (d, J=7 Hz, 6H), 2.94 (br, 1H), 3.31 (heptet, J=7 Hz, 1H 4.74 (s, 2H), 7.04 (s, 1H). Mass spectrum: $(M+H)^+$=158.

C. α-Isocyanato-valine Methyl Ester.

A suspension of L-valine methyl ester hydrochloride (49 g, 0.29 mol) in toluene (700 ml) was heated to 100° C. and phosgene gas was bubbled into the reaction mixture. After approximately 6 h, the mixture became homogeneous. The bubbling of phosgene was continued for 10 more min, then the solution was cooled with the bubbling of N_2 gas. The solvent was then evaporated and the residue chased with toluene two times. Evaporation of solvent gave 40.8 g (89%) of the crude desired compound.

D. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

A solution of 2.18 g (15 mmol) of 4-(hydroxymethyl)-2-isopropylthiazole, 15.8 mmol of α-isocyanato-valine methyl ester and 1.5 mmol of 4-dimethylaminopyridine in 75 ml of dichloromethane was heated at reflux for 5 h. The resulting solution was washed successively with 10% citric acid, aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography of the residue using 5% ethyl acetate in chloroform provided 2.67 g (57%) of the pure desired compound, R_f0.46 (4% methanol in chloroform). NMR^1H NMR (DMSO-d_6) δ1.26 (d, J=8 Hz, 3H), 1.32 (d, J=7 Hz, 6H), 3.27 (heptet, J=7 Hz, 1H), 3.63 (s, 3H), 4.10 (pentet, J=8 Hz, 1H), 5.02 (s, 2H), 7.47 (s, 1H), 7.81 d), J=8 Hz, 1H). Mass spectrum: $(M+H)^+$=287.

E. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 5D provided the desired compound.

F. (2S,3S,5S),5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexanc.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 5E provided, after silica gel chromatography using 2% methanol in chloroform, 110 mg (58%) of the desired compound (R_f0.44, 10% methanol in chloroform), mp. 142°–145° C. Mass spectrum: $(M+H)^+$=708.

EXAMPLE 6

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl) methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 5E and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 105 mg (55%) of the desired compound (R_f0.33, 10% methanol in chloroform), mp. 172°–174° C. Mass spectrum: $(M+H)^+$=708.

EXAMPLE 7

A. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alanine Methyl Ester.

A solution of 1.12 g (5.56 mmol) of 4-nitrophenyl chloroformate in 20 ml of CH_2Cl_2 was cooled to 0° C. and treated sequentially with 0.8 g (5.1 mmol) of 4-(hydroxymethyl)-2-isopropylthiazole and 0.6 ml (5.6 mmol) of 4-methylmorpholine. The resulting solution was stirred at 0° C. for 1 h, diluted with CH_2Cl_2, washed with three portions of aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to give crude 2-isopropyl-4-(p-nitrophenyloxycarbonyloxymethyl)thiazole. A portion (0.53 g, 1.65 mmol) of the residue was taken up in 20 ml of chloroform, treated with 0.23 g (1.67 mmol) of L-alanine methyl ester hydrochloride and 0.36 ml (3.3 mmol) of 4-methylmorpholine, and heated at reflux for 16 h. After being allowed to cool, the solvent was removed in vacuo, and the residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 0.45 g (94%) of the desired compound, R_f0.43 (5% methanol in CH_2Cl_2). ^1H NMR (DMSO-d_6) δ1.26 (d, J=8 Hz, 3H), 1.32 (d, J=7 Hz, 6H), 3.27 (heptet, J=7 Hz, 1H), 3.63 (s, 3H), 4.10 (p, J=8 Hz, 1H), 5.02 (s, 2H), 7.47 (s, 1H), 7.81 (d, J=8 Hz, 1H). Mass spectrum: $(M+H)^+$=287.

B. N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alanine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 7A provided the desired compound.

C. (2S,3S,5S,)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbo-

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nyl)-L-valine with the resultant compound of Example 7B provided, after silica gel chromatography using 1% methanol in chloroform, 110 mg (69%) of the desired compound (R_f0.4, 5% methanol in CH_2Cl_2), mp. 59°–61° C. Mass spectrum: $(M+H)^+$=680. Anal. Calcd for $C_{34}H_{41}N_5O_6S_2.0.5H_2O$: C, 59.28; H, 6.15; N, 10.17. Found: C, 59.37;H, 5.96; N, 10.18.

EXAMPLE 8

A. (5S, 1'S)-5-(1-(tert-Butyloxycarbonylamino),2-phenylethyl)-dihydrofuran-2(3H)-one.

Prepared from commercially available ethyl-3-bromopropionate by using the procedure of A.E.DeCamp, et al., (*Tetrahedron Lett.* 1991, 32, 1867H).

B. (5S, 1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-3-carboethoxy-dihydrofuran-2(3H)-one.

Lithium diisopropylamide (LDA) was prepared by dropwise addition of 16.5 ml (41.2 mmol) of 2.5 M n-BuLi to a solution of 5.8 ml (41.2 mmol) of diisopropyl amine in 30 ml of dry tetrahydrofuran at –78° C. The LDA solution was stirred for 30 min at –78° C. and 6.0 g (19.6 mmol) of the resultant compound of Example 8A in 30 ml of dry tetrahydrofuran was added dropwise. The reaction mixture was stirred for 30 min at –78° C. and 4.7 ml (49.1 mmol) of ethyl chloroformate was then added. After being stirred at –78° C. for 5 h, the reaction was quenched with saturated aqueous NH_4Cl, extracted with three 60 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the residue was purified by silica gel chromatography using 25% ethyl acetate in hexane to provide 4.73 g (64%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+$=378.

C. 5S,1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-3-carboethoxy-3-((5-thiazolyl)methyl)dihydrofuran-2(3H)-one.

Sodium metal (536 mg, 23.3 mmol) was dissolved in 10 ml of absolute ethanol. A solution of 4.0 g (10.6 mmol) of the resultant compound of Example 8B in 50 ml of absolute ethanol was added dropwise. The mixture was stirred at ambient temperature for 20 min and 5-chloromethylthiazole hydrochloride was then added. After being stirred at ambient temperature for 60 h, the reaction was cooled in an ice bath, neutralized with 10% citric acid to pH –6 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 3.88 g (78%) of the desired compound as a white foamy solid. Mass spectrum: $(M+H)^+$=475.

D. (3S,5S, 1'S)-5-(1-(tert-Butyloxycarbonylamino)-2-phenylethyl)-3-((5-thiazolyl)methyl)dihydrofuran-2(3H)-one.

A solution of 3.88 g (8.18 mmol) of the resultant compound of Example 8C in 65 ml of dimethoxyethane was treated with 32.7 ml (32.7 mmol) of 1M aqueous lithium hydroxide. After being stirred at ambient temperature for 4 h, the bulk of the 1,2-dimethoxycthane was removed in vacuo. The remaining mixture was treated with 10% citric acid to pH 4–5 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give the crude acid. The acid was dissolved in 50 ml of toluene, heated at reflux for 15 h. The solvent was removed in vacuo, and the residue was separated by silica gel chromatography using 50% ethyl acetate in hexane to provide 0.86 g (26%) of 3R isomer and 1.58 g (48%) of the desired compound as a white solid. ^1H NMR ($CDCl_3H$) δ1.40 (s, 9H), 1.84 (m, 1H), 2.21 (ddd, 1H), 2.82–2.99 (m, 3H), 3.07 (dd, 1H), 3.43 (dd, 1H), 3.97 (br q, 1H), 4.36 (ddd, 1H), 4.55 (br d, 1H), 7.21–7.33 (m, 5H), 7.63 (s, 1H), 8.69 (s, 1H). Mass spectrum: $(M+H)^+$=403.

E. (2S,4S,5S)-4-(tert-Butyldimethylsilyloxy)-5-(tert-Butyldimethylsilyloxy)-5-(tert-butyloxycarbonylamino-6-phenyl-2-((5-thiazolyl)-methyl)hexanoic acid.

A solution of 1.50 g (3.73 mmol) of the resultant compound of Example 8D in 80 ml of a 2:1 mixture of 1,2-dimethoxyethane and water was treated with 14.9 ml (14.9 mmol) of 1M aqueous lithium hydroxide. After being stirred at ambient temperature for 1.5 h, the bulk of the 1,2-dimethoxyethane was removed in vacuo. The remaining mixture was treated with 10% citric acid to pH 4–5 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give 1.48 g of the crude hydroxy acid. This hydroxy acid was dissolved in 14 ml of dry DMF and 2.64 g (17.5 mmol) of tert-butyldimethylsilyl chloride and 2.23 g (32.8 mmol) of imidazole were added. After being stirred at ambient temperature for 18 h, 28 ml of methanol was added to the mixture. Stirring was continued for 4 h and the solvents were then removed in vacuo. The residue was treated with 10% citric acid to pH 4–5 and extracted with four 50 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 1.70 g (85%) of the desired compound as a white foamy solid. Mass spectrum: $(M+H)^+$=529.

Anal. Calcd for $C_{27}H_{42}N_2O_5SSi.0.5H_2O$: C,59.64;H, 7.97; N, 5.15; Found: C, 59.71;H, 7.83; N, 5.31.

F. (2S,3S,5S)-5-((((Benzyl)oxy)carbonyl)amino)-3-(tert-Butyldimethylsilyloxy)-2-(tert-butyloxycarbonylamino)-1-phenyl-6-(5-thiazolyl)hexane.

A solution of 500.0 mg (0.935 mmol) of the resultant compound of Example 8E, 402 µl (1.87 mmol) of diphenylphosphoryl azide and 326 µl (2.38 mmol) of triethylamine in 5 ml of dioxane was heated at 70° C. for 1 h. Benzyl alcohol (483 µl, 4.67 mmol) was subsequently added. The mixture was stirred at 80° C. for 24 h. The solvents were removed in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 598.1 mg (100%) of the desired compound as a white foamy solid. Mass spectrum: $(M+H)^+$=640.

G. (2S,3S,5S)-5-((((Benzyl)oxy)carbonyl)amino)-2-(tert-butyloxycarbonylamino)-1-phenyl-6-(5-thiazolyl)-3-hydroxyhexane.

A solution of 570.6 mg (0.892 mmol) of the resultant compound of Example 8F in 25 ml of tetrahydrofuran was treated with 0.89 ml of 1M solution of tetrabutylammonium fluoride in tetrahydrofuran. After being stirred at ambient temperature for 20 h, the solvent was removed in vacuo and the residue was purified by silica gel chromatography using 10% methanol in dichloromethane to provide 295.6 mg (63%) of the desired compound as a white solid. ^1H NMR ($CDCl_3H$) δ1.39 (s, 9H), 1.54 (m, 2H), 2.87 (m, 2H), 3.08 (m, 2H), 3.69 (m, 2H), 3.96 (m, 1H), 4.77 (br d, 1H), 5.08 (s, 2H), 5.11 (br s, 1H), 7.18–7.36 (m, 10H), 7.53 (s, 1H), 8.67 (s, 1H). Mass spectrum: $(M+H)^+$=526.

H. (2S,3S,5S)-2,5-Diamino-1-phenyl-6-(5-thiazolyl)-3-hydroxyhexane.

The resultant compound of Example 8G (201.2 mg, 0.383 mmol) was dissolved in 1 ml of acetic acid saturated with hydrogen bromide and stirred at ambient temperature for 1 h. The solvent was removed in vacuo. The residue was treated with 2 ml of saturated aqueous $NaHCO_3$, extracted

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with five 5 ml portions of dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to provide 99.3 mg (89%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+$=292.

I. (4S,6S,1'S)-6-(1-Amino-2-phenylethyl)-2-phenyl-4-((5-thiazolyl)methyl)-3-aza-2-bora-1-oxacyclohexane.

A solution of 95.7 mg (0.328 mmol) of the resultant compound of Example 8H and 40.0 mg (0.328 mmol) of phenylboric acid in 5 ml of toluene was heated at reflux and the water azeotropically removed with the aid of a Dean Stark trap until the distillate was clear. The solvent was then removed in vacuo to provided 124.3 mg (100%) of the desired compound as a resin. Mass spectrum: $(M+H)^+$=378.

J. (2S,3S,5S)-5-Amino-1-phenyl-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

A solution of 100.0 mg (0.265 mmol) of the resultant compound of Example 8I and 74.0 mg (0.265 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 5 ml of tetrahydrofuran was stirred at ambient temperature for 24 h. The solvent was then removed in vacuo. The residue was dissolved in 20 ml of dichloromethane, washed with three 5 ml portions of 0.5N NaOH and two 5 ml portions of water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol and 2% isopropylamine in chloroform to provide 22.8 mg (20%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+$=433.

K. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-1-phenyl-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 8J provided 16.7 mg (47%) of the desired compound as a white solid. ^1H NMR ($CDCl_3$,H) δ0.90 (d, 3H), 0.94 (d, 3H), 1.38 (d, 6H), 1.63 (m, 2H), 2.32 (m, 1H), 2.85 (m, 2H), 2.97 (s, 3H), 3.04 (m, 2H), 3.31 (m, 1H), 3.68 (m, 1H), 3.77 (m, 1H), 3.96 (m, 1H), 4.16 (m, 1H), 4.39 (s, 2H), 5.22 (m, 4H), 6.40 (br s, 1H), 6.80 (br d, 1H), 7.04 (s, 1H), 7.18–7.28 (m, 5H), 7.55 (s, 1H), 7.83 (s, 1H), 8.58 (s, 1H), 8.80 (s, 1H). Mass spectrum: $(M+H)^+$=728.

EXAMPLE 9

A. 4-(Chloromethyl)-2-(dimethylamino)thiazole.

A mixture of 15 g (144 mmol) of N,N-dimethylthiourea *and excess $MgSO_4$ in 350 ml of acetone was heated to reflux* and treated dropwise with a solution of 18.3 g (144 mmol) of 1,3-dichloroacetone in 35 ml of acetone. The resulting mixture was heated at reflux for 1.5 h, allowed to cool, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography using 20% ethyl acetate in hexane to provide 14.0 g (70%) of the desired compound.

B. 2-(N,N-Dimethylamino)-4-(hydroxymethyl)thiazole.

A solution of 5.186 g (29 mmol) of 4-(chloromethyl)-2-(dimethylamino)thiazole in 100 ml of 1:1 THF/H_2O was cooled to 0° C. and treated dropwise with a solution of 5.73 g (29 mmol) of silver tetrafluoroborate in 50 ml of 1:1 THF/H_2O. After being stirred for 1 h, the mixture was filtered, the solid mass was washed with ethyl acetate, and the combined filtrates were concentrated in vacuo. The black residue was purified by silica gel chromatography to provide 0.80 g (17%) of the desired compound (R_f0.24, 6% methanol in chloroform) as an oil. ^1H NMR ($CDCl_3$) δ2.67 (br, 1H), 3.09 (s, 6H), 4.54 (s, 2H), 6.35 (s, 1H). Mass spectrum: $(M+H)^+$=159.

C. N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

A solution of 505 mg (3.19 mmol) of 2-(N,N-dimethylamino)-4-(hydroxymethyl)thiazole, 3.19 mmol of α-isocyanato-L-valine methyl ester, and 100 mg of 4-dimethylaminopyridine in 30 ml of dichloromethane was heated at reflux for 3 h. The resulting solution was allowed to cool, diluted with dichloromethane, washed sequentially with 10% citric acid, aqueous Na_2CO_3, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 0.95 g (95%) of the desired compound, R_f0.42 (4% methanol in chloroform). ^1H NMR ($CDCl_3$) δ0.84 (d, *J=7Hz, 3H), 0.93 (d, J=7 Hz, 3H),* 2.12 *(m, 1H),* 3.11 *(s, 6H),* 3.73 (s, 3H), 4.24 (dd, J=8,4 Hz, 1H), 4.99 (s, 2H), 5.26 (br d, 1H), 6.49 (s, 1H). Mass spectrum: $(M+H)^+$=316.

D. N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 9C provided the desired compound. Mass spectrum: $(M+H)^+$=302.

E. (2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 9D provided, after silica gel chromatography using 2% methanol in chloroform, 100 mg of the desired compound (R_f0.49, 10% methanol in chloroform), mp. 162°–165° C. Mass spectrum: $(M+H)^+$=709.

EXAMPLE 10

(2S,3S,5S)-2-(N-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 9D and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 25 mg (10%) of the desired compound (R_f0.49, 10% *methanol in chloroform), mp. 157°–159° C. Mass spectrum:* $(M+H)^+$=709.

EXAMPLE 11

A. 4-((Amino)thiocarbonyl)morpholine.

A solution of 3.35 g (18.8 mmol) of thiocarbonyl diimi*dazole in 100 ml of THF was treated with 0.82 ml (9.4* mmol) of morpholine. After being stirred at ambient temperature for 3.5 h, an additional 0.82 ml portion of morpholine was added, and stirring was continued. After 6 h, the solution was treated with excess concentrated aqueous ammonia, and stirred overnight. The resulting solution was concentrated in vacuo, taken up in chloroform, separated from the aqueous phase, dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel chromatography using ethyl acetate provided 1.85 g (76%) of the desired compound, R_f0.17 (10% methanol in chloroform), as a white solid. ^1H NMR ($CDCl_3$) δ3.76 (m, 4H), 3.83 (m, 4H), 5.75 (br, 2H). Mass spectrum: $(M+H)^+$=147.

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B. Ethyl 2-(4-Morpholinyl)thiazole-4-carboxylate.

A mixture of 1.85 g (12.7 mmol) of 4-((amino)thiocarbonyl)morpholine, 1.59 ml (12.7 mmol) of ethyl bromopyruvate, and excess $MgSO_4$ in 50 ml of acetone was heated at reflux for 2 h. The resulting mixture was allowed to cool, filtered, and concentrated in vacuo. The residue was taken up in chloroform, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Silica gel chromatography using 1% methanol in chloroform provided 1.7 g (55%) of the desired compound, R_f0.70 (ethyl acetate). Mass spectrum: $(M+H)^+$=243.

C. 2-(4-Morpholinyl)-4-(hydroxymethyl)thiazole.

A solution of 7.0 ml (7.0 mmol) of lithium aluminum hydride in toluene was diluted with 10 ml of THF, cooled to 0° C., and treated with a solution of 1.7 g (7.0 mmol) of ethyl 2-(4-morpholinyl)thiazole-4-carboxylate in 25 ml of THF. The resulting solution was stirred for 1 h, quenched cautiously with aqueous Rochelle's salts, diluted with chloroform, filtered, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography using 2–4% methanol in chloroform provided 856 mg (61%) of the desired compound, R_f 0.16 (4% methanol in chloroform). ^1H NMR ($CDCl_3$) δ2.44 (br, 1H), 3.46 (t, J=5 Hz, 4H), 3.81 (t, J=5 Hz, 1H), 4.55 (br s, 2H), 6.45 (s, 1H). Mass spectrum: $(M+H)^+$ =200.

D. N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 9C but replacing 2-(N, N-dimethylamino)-4-(hydroxymethyl)thiazole with 2-(4-morpholinyl)-4-(hydroxymethyl)thiazole provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound, R_f0.54 (4% methanol in chloroform), in 65% yield. ^1H NMR ($CDCl_3$) δ0.97 (d, J=7Hz, 3H), 1.00 (d, J=7 Hz, 3H), 2.25 (m, 1H), 3.50 (dd, J=5, 4 Hz, 2H), 3.76 (s, 3H), 3.84 (dd, J=5, 4 Hz, 2H), 4.67 (dd, J=9, 5 Hz, 1H), 7.63 (br d, 1H), 8.02 (s, 1H).

E. N-((2-(4-Morpholinyl)-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 11D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 11E provided, after silica gel chromatography using 2% methanol in chloroform, 201 mg (92%) of the desired compound (R_f0.19, 4% methanol in chloroform), mp. 169°–170° C. Mass spectrum: $(M+H)^+$=751.

EXAMPLE 12

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 11E and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 196 mg (90%) of the desired compound (R_f0.19, 4% methanol in chloroform), mp. 146°–148° C. Mass spectrum: $(M+H)^+$=751.

EXAMPLE 13

A. 1-((Amino)thiocarbonyl)pyrrolidine.

Using the procedure of Example 11A but replacing morpholine with pyrrolidine, and stirring the solution for six days after addition of aqueous ammonia provided the desired compound. ^1H NMR ($CDCl_3$) δ1.97 (m, 2H), 2.11 (m, 2H), 3.38 (br t, 2H), 3.85 (br t, 2H), 5.56 (br, 2H). Mass spectrum: $(M+H)^+$=131.

B. Ethyl 2-(1-Pyrrolidinyl)thiazole-4-carboxylate.

Using the procedure of Example 11B but replacing 4-((amino)thiocarbonyl)morpholine with 1-((amino)thiocarbonyl)pyrrolidine provided the desired compound. ^1H NMR ($CDCl_3$) δ1.37 (t, J=7Hz, 3H), 2.04 (m, 4H), 3.51 (m, 4H), 4.35 (q, J=7Hz, 2H), 7.37 (s, 1H). Mass spectrum: $(M+H)^+$ =227.

C. 2-(1-Pyrrolidinyl)-4-(hydroxymethyl)thiazole.

Using the procedure of Example 11C but replacing ethyl 2-(4-morpholinyl)thiazole-4-carboxylate with ethyl 2-(1-pyrrolidinyl)thiazole-4-carboxylate provided, after silica gel chromatography using 2–4% methanol in chloroform, the desired compound (R_f 0.26, 4% methanol in chloroform) in 53% yield. ^1H NMR ($CDCl_3$) δ2.04 (m, 4H), 2.75 (br, 1H), 3.45 (m, 4H), 4.56 (s, 2H), 6.32 (s, 1H). Mass spectrum: $(M+H)^+$=185.

D. N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 9C but replacing 2-(N, N-dimethylamino)-4-(hydroxymethyl)thiazole with 2-(1-pyrrolidinyl)-4-(hydroxymethyl)thiazole provided, after silica gel chromatography using 1.5% methanol in chloroform, the desired compound (R_f 0.34). ^1H NMR ($CDCl_3$) δ0.89 (d, J=7 Hz, 6H), 2.04 (m, 4H), 2.14 (m, 1H), 3.46 (m, 4H), 3.74 (s, 3H), 4.30 (dd, J=9, 4 Hz, 1H), 5.01 (s, 2H), 5.33 (br d, 1H), 6.44 (s, 1H). Mass spectrum: $(M+H)^+$=342.

E. N-((2-(1-Pyrrolidinyl)-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 13D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 13E provided, after silica gel chromatography using 1–3% methanol in chloroform, 120 mg (53%) of the desired compound, mp. 146°–148° C. Mass spectrum: $(M+H)^+$= 735.

EXAMPLE 14

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 13E and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 89 mg (39%) of the desired compound (R_f 0.16, 4% methanol in chloroform), mp. 165°–167° C. Mass spectrum: $(M+H)^+$=735.

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EXAMPLE 15

A. 2-Isopropyl-4-(((N-cyclopropyl)amino)methyl)thiazole.

A solution of 1.8 g (10.2 mmol) of 4-(chloromethyl)-2-isopropylthiazole hydrochloride in 10 ml of chloroform was added dropwise with stirring to 10 ml of cyclopropylamine. The resulting solution was stirred at ambient temperature for 16 h, concentrated in vacuo, and purified by silica gel chromatography using 5% methanol in chloroform to provide 0.39 g (19%) of the desired compound. ^{1}H NMR (DMSO-d_6) δ0.24 (m, 2H), 0.35 (m, 2H),1.30 (d, J=7 Hz, 6H), 2.10 (tt, J=12, 3Hz, 1H), 3.23 (heptet, J=7 Hz, 1H), 3.77 (s, 2H), 7.21 (s, 1H). Mass spectrum: $(M+H)^+$=197.

B. N-((N-Cyclopropyl-N-((2-isopropyl -thiazolyl)methyl)amino)carbonyl)-L-alanine Methyl Ester.

Using the procedure of Example 1S, but replacing N-(((4-nitrophenyl)-oxy)carbonyl)-L-valine methyl ester with N-(((4-nitrophenyl)oxy)carbonyl)-L-alanine methyl ester and replacing 2-isopropyl-4-(((N-methyl)amino)methyl)-thiazole with the resultant compound of Example 15A provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound (R_f 0.54, 5% methanol in chloroform) in 56% yield. ^{1}H NMR (DMSO-d_6H) δ0.70 (m, 2H), 0.80 (m, 2H), 1.30 (d, J=7 Hz, 6H), 1.34 (d, J=7 Hz, 3H), 2.57 (m, 1H), 3.22 (heptet, J=7Hz, 1H), 3.62 (s, 3H), 4.23 (pentet, J=7 Hz, 1H), 4.44 (AA', 2H), 6.54 (d, J=7Hz, 1H), 7.05 (s, 1H). Mass spectrum: $(M+H)^+$=326.

C. N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino }carbonyl)-L-alanine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 15B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 15C provided, after silica gel chromatography using 1% methanol in chloroform, 74 mg (40%) of the desired compound (R_f 0.25, 5% methanol in chloroform), mp. 65°–67° C. Mass spectrum: $(M+H)^+$=719. Anal. Calcd for $C_{37}H_{46}N_6O_5S_2.0.5H_2O$: C, 61.05;H, 6.51; N, 11.54. Found: C, 61.08;H, 6.32; N, 11.44.

EXAMPLE 16

A. 2-Isopropylthiazole-4-carboxaldehyde.

A solution of ethyl 2-isopropylthiazole-4-carboxylate (1 mmol) in 50 ml of dry dichloromethane was cooled to −78° C. under N_2 atmosphere and treated dropwise with 1.2 mmol of diisobutylaluminum hydride (1.5M in toluene). The resulting solution was stirred for 0.5 h, quenched with aqueous Rochelle salts, extracted with dichloromethane, dried over Na_2SO_4, and concentrated in vacuo to provide the crude desired compound.

B. 4-(1-Hydroxyethyl)-2-isopropylthiazole.

A solution of the resultant compound of Example 16A (0.5 mmol) in 25 ml of dry THF was cooled to −20° C. under Ar atmosphere, treated with 0.5 mmol of methylmagnesium chloride (3.0M in THF), stirred for 15 min, and quenched with water. The mixture was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated in vacuo to provide the crude desired compound.

C. N-(1-(2-propyl-4-thiazolyl)ethoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 4-(1-hydroxyethyl)-2-isopropylthiazole provided the desired compound.

D. N-(1-(2-Isopropyl-4-thiazolyl)ethoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 16C provided the desired compound.

E. (2S,3S,5S)-5-N-(N-(1-(2-Isopropyl-4-thiazolyl)ethoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl)N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 16D provided the desired compound.

EXAMPLE 17

A. N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with the resultant compound of Example 15A provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound (R_f 0.64, 5% methanol in chloroform) in 91% yield. ^{1}H NMR (DMSO-d_6H) δ0.73 (m, 2H), 0.82 (m, 2H), 0.90 (d, J=7 Hz, 6H), 1.30 (d, J=7 Hz, 6H), 2.10 (octet, J=7 Hz, 1H), 2.62 (m, 1H), 3.23 (heptet, J=7 Hz, 1H), 3.64 (s, 3H), 4.10 (dd, J=9, 6 Hz, 1H), 4.45 (AA', 2H), 6.29 (d, J=9Hz, 1H), 7.06 (s, 1H). Mass spectrum: $(M+H)^+$=354.

B. N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 17A provided the desired compound.

C. (2S,3S,5S)-5-(N-(N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 17B provided, after silica gel chromatography using 1% methanol in chloroform, 85 mg (48%) of the desired compound (R_f 0.30, 5% methanol in chloroform), mp. 65°–66° C. Mass spectrum: $(M+H)^+$=747. Anal. Calcd for $C_{39}H_{50}N_6O_5S_2$: C, 62.71;H, 6.75; N, 11.25. Found: C, 62.74;H, 6.61;N, 11.03.

EXAMPLE 18

A. 4-Chloromethyl-4-hydroxy-2-isopropyloxazoline.

To a solution of isobutyramide (9.876 g, 0.1122 mol) in acetone (130 mL) was added 1,3-dichloroacetone (10.0 g, 0.0748 mol), $NaHCO_3$ (9.429 g, 0.1122 mol), and $MgSO_4$ (18.01 g, 0.1496 mol). The mixture was heated at reflux under argon for 63 hrs, then cooled to room temperature, vacuum filtered, and concentrated in vacuo to a dark brown semi-solid. The residue was purified by SiO_2 flash chromatography using a gradient of EtOAc/CH_2Cl_2 (5%, 10%, 20%, 40%) to obtain the desired product as an orange liquid (6.06 g, 0.0341 mol, 46%): ^{1}H NMR ($CDCl_3$) δ1.20–1.28 (m, 6H), 2.56–2.72 (m, 1H), 3.70 (s, 2H), 4.18 (d, J=9.6 Hz, 1H), 4.38 (d, J=9.6 Hz, 1H). Mass spectrum: $(M+H)^+$=178, 180.

B. 4-Chloromethyl-2-isopropyloxazole.

A solution of 4-chloromethyl-4-hydroxy-2-isopropyloxazoline (4.88 g, 0.0275 mol) in 1,2-dichloroethane (20 mL) was added to a solution of $SOCl_2$ (2.40 mL, 0.0329 mol) in 1,2-dichloroethane (80 mL) at 0° C. under argon, and the solution was heated to 70° C. After 15 min at 70° C, the reaction was cooled to room temperature and the solvent removed by rotary evaporation in vacuo. Drying the residue

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on high vacuum gave the desired compound as a brown semi-solid (4.20 g, 0.0263 mol, 96%): ^{1}H NMR ($CDCl_3$) δ1.36 (d, J=7.5 Hz, 6H), 3.03–3.18 (m, 1H), 4.50 (s, 2H), 7.56 (s, 1H). Mass spectrum: $(M+H)^+$=160, 162.

C. 2-Isopropyl-4-(((N-methyl)amino)methyl)oxazole

To 40% aqueous methylamine (100 mL) was added dropwise a suspension of 4-chloromethyl-2-isopropyloxazole (4.20 g, 0.0263 mol)in p-dioxane/H_2O (1:1 (v/v), 20 mL) over a 25 min period. After stirring for 45 min at ambient temperature, the volume was reduced to ca. 50 mL by rotary evaporation in vacuo, and NaCl was added. The aqueous was extracted with $CHCl_3$ (4×100 mL), and the combined extract was dried over Na_2SO_4 and concentrated in vacuo. The resulting brown liquid was chromatographed on a 200 g SiO_2 flash column with 2% $iPrNH_2/CH_2Cl_2$ followed by a gradient of $iPrNH_2$/MeOH/CH_2Cl_2 (0.5:2:97.5, 0.5:4:95.5). Concentration in vacuo of the product-containing fractions afforded the desired compound as a golden oil (2.89 g, 0.0187 mol, 71%): ^{1}H NMR ($CDCl_3$) δ1.33 (d, J=6.9 Hz, 6H), 2.46 (s, 3H), 2.99–3.14 (m, 1H), 3.64 (s, 2H), 7.42 (s, 1H). Mass spectrum: $(M+H)^+$=155, $(M+NH_4)^+$=172.

D. N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

A solution of N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester (0.903 g, 0.00305 mol) in anhydrous DMF (6 mL) was added to a solution of 2-isopropyl-4-(((N-methyl)amino)methyl)oxazole (9, 0.470 g, 0.00305 mol) in anhydrous DMF (6 mL) under argon, and the yellow solution was stirred at room temperature for 30 min. Solvent was removed by rotary evaporation in vacuo and the resulting oil dried on high vacuum for 1 hr. The residue was applied to a 150 g SiO_2 flash column and eluted with 20% EtOAc/CH_2Cl_2 and 3% MeOH/CH_2Cl_2. The material obtained after concentration of the product fractions was repurified on a 100 g SiO_2 flash column with a gradient of MeOH/CH_2Cl_2 (1%, 2%, 3%) to obtain the desired compound as an oil (0.515 g, 0.00165 mol, 54 %): ^{1}H NMR ($CDCl_3$) δ0.97 (dd, J=9 Hz, J_2=6.9 Hz, 6H), 1.33 (d, J=6.9 Hz, 6H), 2.11–2.23 (m, 1H), 2.98 (s, 3H),300–3.13 (m, 1H), 3.77 (s, 3H), 4.23–4.36 (m, 2H), 4.36–4.42 (m, 1H), 5.79–5.86 (br d, 1H), 7.46 (s, 1H). Mass spectrum: $(M+H)^+$=312.

E. N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine.

To a solution of the resultant compound of Example 18D 10 (0.511 g, 0.00164 mol)in p-dioxane (10 mL) and H_2O(5 mL) was added LiOH monohydrate (0.103 g, 0.00246 mol). After stirring at room temperature for 1 hr, the p-dioxane was removed by rotary evaporation in vacuo, and the remaining aqueous solution was treated with 1N aq HCl (2.46 mL) and extracted with ethyl acetate (4×100 mL). The combined organic extract was washed with saturated brine and dried for 15 mins over Na_2SO_4. Concentration in vacuo followed by CH_2Cl_2 chases (2×) afforded the desired compound as a white solid (0.480 g, 0.00161 mol, 98%): ^{1}H NMR (DMSO-d_6) δ0.90 (dd, J_1=6.9 Hz, J_2=2.4 Hz, 6H), 1.24 (d, J=6.9 Hz, 6H), 1.99–2.12 (m, 1H), 2.83 (s, 3H), 2.96–3.10 (m, 1H), 3.96 (dd, J_1=8.4 Hz, J_2=6 Hz, 1H), 4.19–4.32 (m, 2H), 6.26 (d, J=8.4Hz, 1H), 7.80 (s, 1H). Mass spectrum: $(M+H)^+$=298

F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using 3–5–7% methanol in chloroform, 70 mg, (53%) of the desired compound. ^{1}H NMR (DMSO-d_6) δ0.74 (d, J=6.3 Hz, 6H), 1.23 (d, J=6.9 Hz, 6H), 1.38–1.51 (m, 2H), 1.80–1.94 (m, 1H), 2.54–2.74 (m, 5H), 2.83 (s, 3H), 2.94–3.09 (m, 1H), 3.53–3.63 (m, 1H), 3.76–3.97 (m,2H),4.08–4.35 (m, 3H), 4.63 (d, J=6 Hz, 1H), 5.08–5.19 (m, 2H), 5.90 (d, J=8.7 Hz, 1H), 6.89 (d, J=9 Hz, 1H), 7.07–7.25 (m, 12H), 7.68 (d, J=8.7 Hz, 1H), 7.77 (s, 1H), 7.86 (s, 1H), 9.05 (s, 1H). High resolution mass spectrum: calcd for $C_{37}H_{49}N_6O_6S$: 705.3434. Found: 705.3431 $(M+H)^+$. Anal. Calcd for $C_{37}H_{48}N_6O_6S.0.5H_2O$: C, 62.25;H , 6.92; N, 11.77. Found: C, 62.35;H, 6.86; N, 11.34.

EXAMPLE 19

A. Methyl Isocyanide.

A 100 mL 3-neck flask (equipped with septum, stopper, and a short path mini distillation head with cow collector cooled to −78° C.) was charged with p-toluenesulfonyl chloride (36.25 g, 0.1901 mol) and quinoline (60 mL). The vigorously stirred solution was heated to 75° C. with the system under vacuum (H_2 O aspirator with trap cooled to −40° C). Neat N-methylformamide (7.50 g, 0.127 mol) was added via syringe in small portions over 15 mins. The increasingly viscous solution was heated for 10 mins, at which time gas evolution had ceased. Material in the cow collector and in the vacuum trap were combined and vacuum distilled to provide the compound as a colorless liquid (2.06 g, 0.0502 mol, 39%).

B. 5-((Diethoxy)methyl)oxazole.

Prepared according to the procedure of Schöllkopf (*J. Am. Chem. Soc.* 112 (10) 4070 (1990)). To a solution of methyl isocyanide (2.88 g, 0.0702 mol) in THF (50 mL) under argon at −78° C. was added dropwise n-butyllithium solution (1.6M in hexanes, 44 mL) over 15 mins. After stirring for an additional 20 mins at −78° C., a solution of ethyl diethoxyacetate (12.62 g, 0.0702 mol) in THF (15 mL) was added dropwise over 20 mins. The bath was allowed to warm to −30° C. over the next 2 hrs and the reaction was then stirred at 0° C. for 30 mins. The reaction was quenched at 0° C. with glacial HOAc (4.22 g, 0.0702 mol) and the solvent was removed by rotary evaporation in vacuo. The golden solid was partitioned with H_2O (45 mL) and EtOAc (200 mL), and the aqueous extracted with EtOAc (2×200 mL). The combined organic was washed with satd aq NaCl, dried over Na_2SO_4, and concentrated in vacuo to a brown oil. Chromatography on a 300 g SiO_2 flash column with a gradient of EtOAc/hexane (10%, 15%, 20%) afforded the desired compound as a colorless liquid (7.46 g, 0.0436 mol, 62%): ^{1}H NMR ($CDCl_3$) δ1.25 (t, J=6.9 Hz, 6H), 3.56–3.70 (m, 4H), 5.62 (s, 1H), 7.26 (s, 1H), 7.86 (s, 1H). Mass spectrum: $(M+H)^+$=172.

C. 5-Oxazolecarboxaldehyde

A flask was charged with 5-((diethoxy)methyl)oxazole (1.02 g, 0.00596 mol) and cooled to 0° C. A solution of trifluoroacetic acid/CH_2Cl_2 (1:1 (v/v), 6.7 mL) and H_2O (0.39 mL) was added and the solution stirred at 0° C. for 10 min. The solvent was removed in vacuo, and the residue was treated with toluene and concentrated. Chromatography on a 100 g SiO_2 flash column with a gradient of EtOAc/hexane (20%, 30%, 40%) afforded the desired compound as a colorless liquid (0.344 g, 0.00354 mol, 59%): ^{1}H NMR ($CDCl_3$) δ7.89 (s, 1H), 8.12 (s, 1H), 9.87 (s, 1H). Mass spectrum: $(M+H)^+$=98.

D. 5-(Hydroxymethyl)oxazole

A solution of 5-oxazolecarboxaldehyde (0.627 g, 0.00646 mol) in MeOH (10 mL) under argon at 0° C. was treated

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with $NaBH_4$ (0.247 g, 0.00646 mol). After 5 mins the reaction was quenched with acetone and the solvent removed by rotary evaporation in vacuo. Chromatography on a 100 g SiO_2 flash column with a gradient of MeOH/CH_2Cl_2 (5%, 10%) afforded the desired compound as a colorless oil (0.408 g, 0.00412 mol, 64%): ^1H NMR ($CDCl_3$) δ2.03 (t, J=6.0 Hz, 1H), 4.70 (d, J=6.0Hz, 2H), 7.04 (s, 1H), 7.87 (s, 1H). MS (Cl/NH_3)m/e 117 (m+NH_4), 100 (m+H).

E. ((5-Oxazolyl)methyl)-4-nitrophenyl)carbonate.

A solution of 5-(hydroxymethyl)oxazole (1.31 g, 0.0132 mol)in CH_2Cl_2 (70 mL) under argon at 0° C. was treated with triethylamine (1.90 mL, 0.0139 mol) and 4-nitrophenyl chloroformate (2.75 g, 0.0132 mol). After stirring at 0° C. for 2.5 hrs, solvent was removed by rotary evaporation in vacuo and the yellow solid was dried on vacuum pump to provide the crude desired compound.

F. (2S,3S,5S)-2-Amino-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1, 6-diphenyl-3-hydroxyhexane.

A solution of crude ((5-oxazolyl)methyl)-(4-nitrophenyl-)carbonate (made from 0.0132 mol 5-(hydroxymethyl)oxazole)in THF (110 mL) under argon was treated with a solution of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane (3.76 g, 0.0132 mol) in THF (20 mL), and the reaction stirred at room temperature for 16 hrs. Solvent was removed by rotary evaporation in vacuo and the yellow foam dried on a vacuum pump. Chromatography on a 200 g SiO_2 flash column with 5% MeOH/CH_2Cl_2, 2% $iPrNH_2$/CH_2Cl_2, and a gradient of $iPrNH_2$/MeOH/CH_2Cl_2 (2:2:96, 2:5:93H) afforded a mixture (1.74 g) of the desired compound and (2S,3S,5S)-5-amino-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane. The mixture was applied to a 150 g SiO_2 flash column (deactivated with 2% $iPrNH_2$/CH_2Cl_2) and eluted with 2% $iPrNH_2$/CH_2Cl_2 to afford the desired compound as a gummy light yellow solid (0.382 g, 0.933 *mmol*, 7%): ^1H NMR (DMSO-d6) δ1.16–1.30 (m, 1H), 1.36–1.47 (m, 1H), 2.56–2.66 (m, 2H), 2.75–2.85 (m, 1H), 2.89–3.01 (m, 1H), 3.53–3.71 (m, 3H), 4.97 (d, J=2.4 Hz, 2H), 7.01 (d, J=9 Hz, 1H), 7.11–7.32 (m, 14H), 8.36 (s, 1H). Mass spectrum: (M+H)$^+$=410.

G. (2S,3S,5S}-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2,(N-((5-oxazolyl)methoxycarbonyl)amino)-1.6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S, 3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and replacing N(-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using a gradient of 1–4% methanol in dichloromethane, 145 mg (80%) of the desired compound. ^1H NMR ($CDCl_3$) δ0.74 (d, J=6.9 Hz, 6H), 1.23 (d, J=6.9 Hz, 6H), 1.39–1.50 (m, 2H), 1.80–1.94 (m, 1H), 2.56–2.74 (m, 4H), 2.83 (s, 3H), 2.94–3.09 (m, 1H), 3.52–3.62 (m, 1H), 3.72–3.84 (m, 1H), 3.88–3.92 (m, 1H), 4.08–4.35 (m, 3H), 4.62 (d, J=6 Hz, 1H), 4.94 (s, 2H), 5.91 (d, J=8.4Hz, 1H), 6.89 (d, J=9Hz, 1H),7.06–7.26 (m, 11H), 7.69 (d, J=9 Hz, 1H), 7.77 (s, 1H), 8.35 (s, 1H). Mass spectrum: (M+NH_4H)$^+$ 706;(M+H)$^+$=689. Anal. Calcd for $C_{37}H_{48}N_6O_7$.0.5H_2O: C, 63.68;H , 7.08; N, 12.04. Found: C, 63.50;H, 7.13; N, 11.60.

EXAMPLE 20

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino) -2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S, 3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-oxazolyl)methoxycarbonyl)amino)1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 1% methanol in chloroform, 88 mg (55%) of the desired compound (R_f 0.4, 5% methanol in chloroform), mp. 59°–61° C. Mass spectrum: (M+H)$^+$=705. Anal. Calcd for $C_{37}H_{48}N_6O_6S$.0.5H_2O: C, 62.25;H, 6.92; N, 11.77. Found: C, 62.23;H, 6.55; N, 11.57.

EXAMPLE 21

A. Methyl 4-isopropylthiazole-2-carboxylate.

A mixture of 2.11 g (12.8 mmol) of 1-bromo-3-methylbutan-2-one (Gaudry and Marquet, Tetrahedron, 26, 5661 (1970)), 1.0 g (12.8 mmol) of ethyl thiooxamate, and 1.70 g (14 mmol) of $MgSO_4$ in 50 ml of acetone was heated at reflux for 3 h. After being allowed to cool, the mixture was filtered, concentrated in vacuo, and purified by silica gel chromatography using chloroform to provide 0.29 g (11%) of the desired compound (R_f 0.9, 4% methanol in chloroform). ^1H NMR (DMSO-d_6) δ1.27 (d, J=7 Hz, 6H), 1.32 (t, J=7 Hz, 3H), 3.12 (heptet, J=7 Hz, 1H), 4.37 (q, J=7 Hz, 2H), 7.73 (s, 1H). Mass spectrum: (M+H)$^+$=200.

B. 2–1Hydroxymethyl)-4-isopropylthiazole.

Using the procedure of Example 5B, but replacing ethyl 2-isopropyl-4-thiazolecarboxylate with methyl 4-isopropylthiazole-2-carboxylate provided, after silica gel chromatography using 2% methanol in chloroform, the desired compound (R_f 0.3, 5% methanol in chloroform) in 96% yield.

C. N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl)valine Methyl Ester.

A solution of 1.4 mmol of α-isocyanato-valine methyl *ester and 0.22 g (1.4 mmol) of 2-(hydroxymethyl)-4-isopro*pylthiazole in 10 ml of chloroform was heated at reflux for 3 h. After being allowed to cool, the solvent was removed in vacuo, and the residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 0.23 g (52%) of the desired compound (R_f 0.54, 5% methanol in dichloromethane). NMR ^1H NMR (DMSO-d6) δ0.87 (d, J=7 Hz, 3H), 0.88 (d, J=7 Hz, 3H), 1.23 (d, J=7 Hz, 6H), 2.04 (octet, J=7 Hz, 1H), 3.01 (heptet, J=7 Hz, 1H), 3.73 (s, 3 H), 3.94 (dd, J=8, 6 Hz, 1H), 5.26 (AA', 2H), 7.28 (s, 1H), 7.92 (d, J=8 Hz, 1H). Mass spectrum: (M+H)$^+$=315.

D. N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 21C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 21D provided, after silica gel chromatography using 1% methanol in chloroform, 123 mg (61%) of the desired compound (R_f 0.4, 5% methanol in chloroform), mp. 62°–64° C. Mass spectrum: (M+H)$^+$=708.

EXAMPLE 22

A. N,N-Diethylthiourea

A mixture of 6.24 g (35 mmol) of thiocarbonyl diimidazole and 3.6 ml (35 mmol) of diethylamine in 50 ml of THF was stirred at ambient temperature for 5 h. The resulting solution was treated with 20 ml of 2M aqueous NH_3 and stirred for 24 h. After removal of the solvent the residue was

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purified by chromatography on silica gel to provide N,N-diethylthiourea (R_f 0.28, 4% methanol in chloroform).

B. Ethyl 2-(N,N-Diethylamino)thiazole-4-carboxylate.

A solution of 0.972 g (7.36 mmol) of N,N-diethylthiourea and 1.02 ml (8.1 mmol) of ethyl bromopyruvate in 25 ml of acetone was treated with excess solid $MgSO_4$ and heated at reflux for 1 h. The resulting mixture was filtered, and concentrated in vacuo. Silica gel chromatography using $CHCl_3$ provided 2.36 g (38%) of the desired compound as an oil. Mass spectrum: $(M+H)^+$=229.

C. 2-(N,N-Diethylamino)-4-hydroxymethyl)thiazole.

A solution of 3.14 ml of lithium aluminum hydride in toluene was diluted in a dry flask under N_2 atmosphere with 30 ml of THF. The resulting mixture was cooled to 0° C. and treated dropwise with a solution of 1.43 g (6.28 mmol) of ethyl 2-(N,N-diethylamino)thiazole-4-carboxylate in 5 ml of THF. After addition, the solution was allowed to warm slowly to ambient temperature, stirred for 1 h, recooled to 0° C., and treated with a small amount of aqueous Rochelle's salt followed by ethyl acetate. After stirring, the slurry was filtered, washed with additional ethyl acetate, and the combined filtrates were concentrated in vacuo. The residue was purified by silica gel chromatography using methanol in chloroform to provide 0.864 g (73%) of the desired compound, R_f 0.17 (4% methanol in chloroform). Mass spectrum: $(M+H)^+$=187.

D. N-((2-(N,N-Diethylamino)-4-thiazolyl)methoxycarbonyl)valine Methyl Ester.

A solution of 5.11 mmol of α-isocyanato-valine methyl ester in 10 ml of dichloromethane was treated with 0.864 g (4.65 mmol) of 2-(N,N-diethylamino)-4-(hydroxymethyl)thiazole and 0.46 mmol of 4dimethylaminopyridine. The resulting solution was stirred at ambient temperature for 16 h, after which it was diluted with 200 ml of chloroform, washed successively with 10% citric acid, aqueous $NaHCO_3$, and saturated brine. After drying over Na_2SO_4, the solvent was removed in vacuo, and the residue was chromatographed on silica gel using 1–2% methanol in chloroform to provide 1.31 g (82%) of the desired compound, R_f 0.51 (4% methanol in chloroform) as an oil. ^1H NMR ($CDCl_3$) δ0.89 (d, J=7 Hz, 3H), 0.96 (d, J=7 Hz, 3H), 1.24 (t, J=7 Hz, 6H), 2.15 (m, 1H), 3.51 (q, J=7 Hz, 4H), 3.74 (s, 3H), 4.29 (dd, J=8, 4 Hz, 1H), 5.03 (s, 2H), 5.34 (br d, J=8 Hz, 1H), 6.42 (s, 1H). Mass spectrum: $(M+H)^+$=344.

E. N-((2-(N,N-Diethylamino)-4-thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 22D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((2,-(N,N-Diethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 22E provided the desired compound.

EXAMPLE 23

A. 2-(N,N-Dimethylamino)-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-(dimethylamino)thiazole dihydrochloride provided, after silica gel chromatography using first 10% methanol in chloroform followed by 4% methanol/2% isopropylamine in chloroform, the desired compound, R_f 0.05 (10% methanol in chloroform). ^1H NMR ($CDCl_3$) δ2.46 (s, 3H), 3.08 (s, 6H), 3.66 (s, 2H), 6.30 (s, 1H). Mass spectrum: $(M+H)^+$=172.

B. N-((N-Methyl-N-(((N,N-dimethylamino)-4-thiazolyl/methylaminocarbonyl)-L-valine Methyl Ester.

A solution of 741 mg (4.42 mmol) of α-isocyanato-L-valine in 5 ml of dichloromethane was added to a solution of 720 mg (4.21 mmol) of 2-(N,N-dimethylamino)-4-(((N-methyl)amino)methyl)thiazole in 25 ml of dichloromethane. The resulting solution was stirred at ambient temperature for 16 h, partitioned between chloroform and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using 2% methanol in chloroform to provide 463 mg (34%) of the desired compound, R_f 0.25 (2% methanol in chloroform). NMR ($CDCl_3$) δ0.96 (d, J=7 Hz, 3H), 0.98 (d, J=7 Hz, 3H), 2.13 (m, 1H),2.97 (s, 3H), 3.11 (s, 6H), 3.71 (s, 3H), 4.07 (br d, J=16Hz, 1H), 4.34 (dd, J=9, 5 Hz, 1H), 4.42 (d, J=16 Hz, 1H), 6.29 (s, 1H), 6.37 (br, 1H). Mass spectrum: $(M+H)^+$= 329.

C. N-((N-Methyl-N-(((N,N-dimethylamino)-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 23B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-(((N,N-dimethylamino)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 23C provided, after silica gel chromatography, the desired compound.

EXAMPLE 24

A. Ethyl 2-Isopropylthiazole-5-carboxylate.

Using the procedure of Example 1J but replacing thioformamide with 2-methylpropane-thioamide provided, after silica gel chromatography using 9:1 ethyl acetate:hexane, the desired compound, R_f 0.8, (5% methanol in chloroform) in 83% yield.

B. 5-(Hydroxymethyl)-2-isopropylthiazole.

Using the procedure of Example 5B, but replacing ethyl 2-isopropyl-4-thiazolecarboxylate with ethyl 2-isopropylthiazole-5-carboxylate provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.3, (5% methanol in chloroform) in 25% yield. ^1H NMR (d_6-DMSO) δ1.30 (d, J=7 Hz, 6H), 3.22 (heptet, J=7 Hz, 1H), 4.61 (dd, J=6, 1Hz, 2H), 5.45 (t, J=6 Hz, 1H), 7.48 (br s, 1H).

C. N-((2-Isopropyl-5-thiazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 5-(hydroxymethyl)-2-isopropylthiazole provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.8, (5% methanol in chloroform) in 29% yield. ^1H NMR δ0.89 (d, J=7 Hz, 6H), 0.95 (d, J=7 Hz, 3H), 0.97 (d, J=7Hz, 3 H), 2.14 (m, 1H), 3.33 (heptet, J=7 Hz, 1H), 3.74 (s, 3H), 4.30 (dd, J=9, 5 Hz, 1H), 5.23 (s, 2H), 5.25 (br d, 1H), 7.63 (s, 1H). Mass spectrum: $(M+H)^+$=315.

D. N-((2-Isopropyl-5.thiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 24C provided the desired compound.

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E. (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 24D provided the desired compound.

EXAMPLE 25

A. 2-Methoxythioacetamide.

Using the procedure of Example 1O but replacing isobutyramide with 2-methoxyacetamide provided the desired compound in 52% yield.

B. 4-(Chloromethyl)-2-(methoxymethyl)thiazole hydrochloride.

Using the procedure of Example 1P but replacing 2-methylpropanethioamide with 2-methoxythioacetamide provided the crude desired compound in 41% yield.

C. 2-(Methoxymethyl)-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-(methoxymethyl)thiazole hydrochloride provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.1, (5% methanol in chloroform) in 73% yield.

D. N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S but replacing 2-isopropyl-4-(((N-methyl)amino)-methyl)thiazole with 2-(methoxymethyl)-4-(((N-methyl)amino)-methyl)thiazole provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound, R_f 0.5, (5% methanol in chloroform) in 23% yield.

E. N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 25D provided the desired compound.

F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1.,6.-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 25E provided the desired compound.

EXAMPLE 26

A. 1,-Diethoxy-4-((3,4,5,6-tetrahydro-2H-pyran-2-yl)oxy)-2-butyne.

A 1M solution of ethylmagnesium bromide in THF (200 ml, 0.2 mol) was treated with 29 ml (0.2 mol) of a solution of 3,4,5,6-tetrahydro-2-(2-propynyloxy)-2H-pyran in toluene, while maintaining ambient temperature through use of a cool water bath. The resulting solution was stirred for 4 h and treated with 47 ml (0.28 mol) of a solution of triethylorthoformate in toluene, while maintaining ambient temperature with a cool water bath. The resulting solution was heated to 85° C. for 8 h, allowing the removal of THF by distillation. After being allowed to cool, the resulting solution was poured into 500 ml of ice-water containing 29 g of NH_4OAc, extracted with two portions of ether, dried over K_2CO_3, and concentrated in vacuo. The residue was distilled at ca. 0.5 mm Hg pressure (b.p. 103°–108° C.) to provide 59.5 g (79%) of the desired compound, ^1H NMR ($CDCl_3$) δ1.24 (t, J=7 Hz, 6H), 1.5–1.9 (m, 6H), 3.5–3.65 (m, 3H), 3.7–3.9 (m, 3H), 4.32 (AA', 2H), 4.81 (m, 1H), 5.31 (m, 1H). Mass spectrum: $(M+NH_4)^+$=260.

B. 5-(Hydroxymethyl)isoxazole.

A solution of 39.28 g (161 mmol) of the resultant compound of Example 26A and 26 g (376 mmol) of hydroxylamine hydrochloride in 168 ml of ethanol and 34 ml of water was heated at reflux under N_2 atmosphere for 1 h. After being allowed to cool, the resulting solution was concentrated in vacuo to ½ the original volume, diluted with 50 ml of water, and extracted with 2 portions, of ether. The combined extracts were concentrated to an oil. The crude product (7.04 g, 44%) was obtained after distillation (79°–84° C., 0.5 mm Hg). Silica gel chromatography using 0–3% methanol in dichloromethane provided 4.9 g of the desired compound contaminated with 5-hydroxypentanal oxime. ^1H NMR ($CDCl_3$) δ1.95 (br, 1H), 4.81 (s, 2H), 6.27 (d, J=1 Hz, 1H), 8.23 (d, J=1 Hz, 1H). Mass spectrum: $(M+NH_4)^+$=117.

C. ((5-Isoxazolyl)methyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L, but replacing 5-(hydroxymethyl)thiazole with 5-(hydroxymethyl)isoxazole provided, after silica gel chromatography using 8:2 dichloromethane:hexane, the desired compound. ^1H NMR ($CDCl_3$) δ5.41 (s, 2H), 6.46 (d, J=1 Hz, 1H), 7.40 (m, 2H), 8.30 (m, 3H). Mass spectrum: $(M+NH_4)^+$=282.

D. (2S,3.S,5S)-5-Amino-2-(N-((5-isoxazolyl)methoxycarbonyl)amino-1,6-diphenyl-3hydroxyhexane.

A mixture of 1.54 g (5.41 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 0.673 g (5.41 mmol) of phenylboric acid in anhydrous toluene (130 mL) was heated at reflux under argon for 2 hrs with removal of H_2O by a Dean-Stark trap. The resulting yellow solution was allowed to cool and the solvent was removed in vacuo to give an oil which solidified upon standing. The residue was taken up in 90 ml of THF, cooled to −40° C., and treated dropwise under Ar atmosphere over a period of 1 h with 1.11 g (3.78 mmol) of ((5-isoxazolyl)methyl)-(4-nitrophenyl)carbonate in 40 ml of THF. The solution was allowed to warm to −20° C. over the next 0.5 hr, then was stirred at 0° C. for 2.5 hrs and at room temperature for 1 hr. After removal of the solvent in vacuo, the residue was taken up in ethyl acetate (200 mL), washed sequentially with 5% aqueous K_2CO_3 (4×25 mL) and saturated brine (25 mL), dried over Na_2SO_4 and concentrated in vacuo. Silica gel chromatography of the residue using a gradient of methanol in chloroform (2%, 4%, 6%) afforded a mixture of the desired product and its regioisomer. Purification of the mixture on two consecutive 250 g SiO_2 columns (deactivated with 1% isopropylamine/CH_2Cl_2) with a gradient of isopropylamine/CH_2Cl_2 (0.5%, 1%) afforded the desired compound as a sticky solid (0.730 g, 1.78 mmol, 33%): ^1H NMR (DMSO-d_6) δ1.17–1.57 (m, 5H), 2.56–2.69 (m, 2H), 2.75–2.86 (m, 1H), 2.89–3.00 (m, 2H), 3.53–3.71 (m, 3H), 5.06 (s, 2H), 6.32 (d, J=2.4 Hz, 1H), 7.11–7.30 (m, 10H), 8.54 (d, J=2.4 Hz, 1H). Mass spectrum: $(M+H)^+$=410.

E. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 1% methanol in chloroform, 120 mg (70%) of the desired compound, R_f 0.3, (5% methanol in

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chloroform), as a solid, mp 60°–62° C. Mass spectrum: $(M+H)^+$=705. Anal. Calcd for $C_{37}H_{48}N_6O_6S$: C, 63.05;H , 6.86; N, 11.92. Found: C, 2.68;H, 7.00; N, 11.65.

EXAMPLE 27

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino/-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino--(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using a gradient of 1–4% methanol in dichloromethane, 225 mg (80%) of the desired compound. ^1H NMR (DMSO-d_6),5 0.74 (d, J=6.9 Hz, 6H), 1.23 (d, J=6.9 Hz, 6H), 1.35–1.54 (m, 2H), 1.80–1.95 (m, 1H), 2.55–2.73 (m, 4H), 2.83 (s, 3H), 2.94–3.09 (m, 1H), 3.53–3.63 (m, 1H), 3.73–3.86 (m, 1H),3.92 (t, J=8.4 Hz, 1H), 4.08–4.34 (m, 3H), 4.65 (d, J=6 Hz, 1H), 5.04 (s, 2H),5.91 (d, J=9 Hz, 1H), 6.29 (d, J=2.4 Hz, 1H), 7.01 (d, J=9 Hz, 1H), 7.06–7.27 (m,10H), 7.69 (d, J=9 Hz, 1H), 7.77 (s, 1H), 8.52 (d, J=2.4 Hz, 1H). Mass spectrum: $(M+H)^+$=689; $(M+NH_4)^+$=706. Anal. Calcd for $C_{37}H_{48}N_6O_7$: C, 64.52;H, 7.02; N, 12.20. Found: C, 64.52;H, 7.14; N, 12.06.

EXAMPLE 28

A. Ethyl 2-Methylthiazole-5-carboxylate.

Using the procedure of Example 1J, but replacing thioformamide with thioacetamide provided the crude desired compound.

B. 5-(Hydroxymethyl)-8-methylthiazole.

Using the procedure of Example 1K, but replacing ethyl thiazole-5-carboxylate with crude ethyl 2-methylthiazole-5-carboxylate provided, after silica gel chromatography using 3% then 5% methanol in chloroform, the desired compound, R_f 0.27, (4% methanol in chloroform) in 78% yield. ^1H NMR ($CDCl_3$) δ2.32 (br, 1H), 2.70 (s, 3H), 4.80 (s, 2H), 7.46 (s, 1H). Mass spectrum: $(M+H)^+$=130.

C. ((2-Methyl-5-thiazolyl)methyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L, but replacing 5-(hydroxymethyl)-thiazole with 5-(hydroxymethyl)-2-methylthiazole provided, after silica gel chromatography using first 1:5 chloroform:hexane, then 4% methanol in chloroform, the desired compound, R_f 0.46 (20% ethyl acetate in chloroform) in 97% yield.

D. (2S,3S,5S)-5-Amino-2-(N-((2-methyl-5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and (2S,3S,5S)-2-Amino-5-(N-((2-methyl-5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1M, but replacing ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate with ((2-methyl-5-thiazolyl)methyl)-(4-nitrophenyl)-carbonate provided, after silica gel chromatography using 4% methanol in chloroform, a mixture of the desired compounds. A second chromatography using 1% –3% isopropylamine in chloroform provided pure (2S,3S,5S)-5-amino-2-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane and (2S,3S,5S)-2-amino-5-(N-((2-methyl-5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

E. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl.)valinyl)amino)-2-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 210 mg (84%) of the desired compound, R_f 0.18, (4% methanol in chloroform). Mass spectrum: $(M+H)^+$=735. Anal. Calcd for $C_{38}H_{50}N_6O_5S_2.2H_2O$: C, 59.20;H, 7.06; N, 10.90. Found: C, 58.92;H, 6.37; N, 10.71.

EXAMPLE 29

A. 5-Methyl-1-((3,4,5,6-tetrahydro-2H-pyran-2-yl)oxy)-2-hexyn-4-one.

The desired compound was prepared from isobutyryl chloride and 3,4,5,6-tetrahydro-2-(2-propynyloxy)-2H-pyran by analogy to the procedure of Tohda, et. al. (Synthesis, 777 (1977)).

B. 5-(Hydroxymethyl)-3-isopropylisoxazole.

Using the procedure of Example 26B but replacing the resultant compound of Example 26A with the resultant compound of Example 29A provided the desired compound.

C. N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 5-(hydroxymethyl)-3-isopropylisoxazole provided the desired compound.

D. N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 29C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 29D provided the desired compound.

EXAMPLE 30

A. 2-Isopropyl-4-(methanesulfonyloxymethyl)thiazole.

A solution of 1.2 mmol of 4-(hydroxymethyl)-2-isopropylthiazole and 1.3 mmol of diisopropylethylamine in 20 ml of dichloromethane was cooled to –20° C. and treated dropwise with 1.3 mmol of methanesulfonyl chloride. The resulting mixture was stirred for 1 h, quenched with aqueous citric acid, separated, dried over Na_2SO_4, and concentrated in vacuo to provide the desired compound.

B. 2-Isopropyl-4-(mercaptomethyl)thiazole.

A mixture of 0.8 mmol of the resultant compound of Example 30A and 1.0 mmol of sodium hydrosulfide hydrate in 20 ml of THF was heated at reflux until analysis by thin layer chromatography indicated consumption of starting material. The resulting mixture was allowed to cool, concentrated in vacuo, partitioned between dichloromethane and water, dried over Na_2SO_4, and concentrated to provide the crude desired compound.

C. N-((2-Isopropyl-4-thiazolyl)thiomethoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D, but replacing 4-(hydroxymethyl)-2-isopropylthiazole with the resultant com-

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pound of Example 30B provided, after chromatography on silica gel, the desired compound.

D. N-((2-Isopropyl-4-thiazolyl)thiomethoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 30C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)thiomethoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 30D provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 31

A. 2-Isopropylthiazole-4-carboxaldehyde.

A solution of 3.1 g (15.6 mmol) of ethyl 2-isopropylthiazole-4-carboxylate in 50 ml of dichloromethane was cooled under N_2 atmosphere to −78° C. and treated dropwise with 15.6 ml (23.4 mmol) of a 1.5M solution of diisobutylaluminum hydride in toluene over a period of 1.5 h. After being stirred for an additional 0.5 h, the solution was quenched with 5 ml of methanol followed by 15 ml of aqueous Rochelle's salt. The resulting mixture was partitioned between chloroform and aqueous Rochelle's salt, dried over Na_2SO_4, and concentrated to provide 1.37 g (56%) of the crude desired compound, R_f 0.47 (20% ethyl acetate in hexane). ^1H NMR ($CDCl_3$) δ1.45 (d, J=7 Hz, 6H), 3.39 (heptet, J=7Hz, 1H), 8.07 (s, 1H), 10.00 (s, 1H). Mass spectrum: $(M+H)^+$156.

B. (E)-Ethyl 3-(2-Isopropyl-4-thiazolyl)propenoate.

A slurry of 60% NaH (18 mmol) in mineral oil was washed with hexane, decante under N_2 atmosphere, and diluted with 25 ml of THF. The resulting mixture was cooled to 0° C., treated portionwise with 3.24 ml (16.4 mmol) of triethylphosphonoacetate. After addition, the solution was stirred for 10 min, treated with 1.37 g (8.84 mmol) of 2-isopropylthiazole-4-carboxaldehyde in 25 ml of THF, allowed to warm to ambient temperature for 25 min, and quenched with 100 ml of saturated aqueous NH_4Cl. The mixture was extracted with three 100 ml portions of ethyl acetate, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography of the residue using 5–10% ethyl acetate in hexane provided 1.61 g (81%) of the desired compound, R_f 0.64 (20% ethyl acetate in hexane). ^1H NMR ($CDCl_3$) δ1.33 (t, J=7 Hz, 3H), 1.42 (d, J=7 Hz, 6H), 3.32 (heptet, J=7 Hz, 1H), 4.26 (q, J=7 Hz, 2H), 6.75 (d, J=15 Hz, 1H), 7.29 (s, 1H), 7.57 (d, J=15 Hz, 1H).

C. Methyl 3-(2-Isopropyl-4-thiazolyl)propanoate.

A solution of 225 mg (1 mmol) of (E)-ethyl 3-(2-isopropyl-4-thiazolyl)-propenoate in 10 ml of freshly distilled (from calcium hydride) methanol and 1 ml of dry THF was treated with 49 mg (2 mmol) of magnesium turnings. The mixture was stirred for 20 min, during which the magnesium was consumed. The resulting solution was poured over cold aqueous HCl, basified to pH 8 with $NaHCO_3$, extracted with ethyl acetate, dried over Na_2SO_4, and concentrated. Silica gel chromatography using 10% ethyl acetate in hexane provided a mixture of the desired compound and methyl 3-(2-isopropyl-4-thiazolinyl)propanoate.

D. 3-(2-Isopropyl-4-thiazolyl)propanoic Acid.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 31C provided the desired compound.

E. (2S,3S,5S)-5-(N-(N-(tert-Butyloxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-(tert-butyloxycarbonyl)-L-valine provided, after purification by silica gel chromatography, the desired compound.

F. (2S,3S,5S)-5-(N-(Valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 0.1 mmol of the resultant compound of Example 31E was treated with 10 ml of 4N HCl in dioxane, stirred at 0° C. for 1 h, concentrated in vacuo, partitioned between chloroform and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated to provide the crude desired compound.

G. (2S,3S,5S)-5-(N-(N-(3-(2-Isopropyl-4-thiazolyl)propanoyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 31D and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 31F provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 32

A. Thiazole-5-carboxaldehyde.

Using the procedure of Example 16A but replacing ethyl 2-isopropyl-4-thiazole carboxylate with ethyl thiazole-5-carboxylate provided the desired compound.

B. 5-(1-Hydroxyethyl)thiazole.

Using the procedure of Example 16B but replacing the resultant compound of Example 16A with the resultant compound of Example 32A provided the desired compound.

C. (1-(5-Thiazolyl)ethyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L but replacing 5-(hydroxymethyl)-thiazole with the resultant compound of Example 32B provided the desired compound.

D. (2S,3S,5S)-5-Amino-2-(N-(1-(5-thiazolyl)ethoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 19F but replacing ((5-oxazolyl)methyl)-(4-nitrophenyl)carbonate with (1-(5-thiazolyl)ethyl)-(4-nitrophenyl)carbonate provided, after purification by silica gel chromatography, the desired compound.

E. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)Valinyl)amino)-2-(N-(1-(5-thiazolyl)ethoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 32D provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 33

A. ((5-Isothiazolyl)methyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L but replacing 5-(hydroxymethyl)-thiazole with 5-(hydroxymethyl)isothiazole (Bennett, et. al., *J. Chem. Soc.*, 3834 (1965)) provided the desired compound.

B. (2S,3S,5S)-5-Amino-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 19F but replacing ((5-oxazolyl)methyl)-(4-nitrophenyl)carbonate with ((5-isothiazolyl)methyl)-(4nitrophenyl)carbonate provided, after puri-

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fication by silica gel chromatography, the desired compound.

C. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazoiyl)methoxycarbonyl)amino)-16-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 33B provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 34

A. (2S,3R,4R,5S)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1F but replacing the resultant compound of Example 1E with (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)-carbonyl)amino)- 3,4-dihydroxy-1,6-diphenylhexane provided the crude desired compound mixed with benzyl alcohol in 92% yield. Purification of a sample was achieved by silica gel chromatography using 2% isopropylamine in chloroform. ^{1}H NMR ($CDCl_3$) δ2.71 (dd, J=13, 9 Hz, 2H), 2.92 (dd, J=13, 5 Hz, 2H), 3.03 (dd, J=9, 5Hz, 2H), 3.68 (s, 2H), 7.15–7.35 (m, 10H). Mass spectrum: $(M+H)^+$301.

B, (2S,3R,4, R,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1M but replacing (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane with (2S,3R,4R,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography, the desired compound.

C. (2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 34B provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 35

A. (2S,3S,4S,5S)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1F but replacing the resultant compound of Example 1E with (2S,3S,4S,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino-3,4-dihydroxy-1,6-diphenylhexane provided the desired compound. ^{1}H NMR ($CDCl_3$) δ2.63 (dd, J=14, 11 Hz, 2H), 2.85 (dd, J=14, 4 Hz, 2H), 3.60 (dt, J=11,4 Hz, 2H), 3.92 (d, J=3Hz, 2H), 7.2–7.4 (m, 10H). Mass spectrum: $(M+H)^+$=301.

B. (2S,3S,4S,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1M but replacing (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane with (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography, the desired compound.

C. (2S,3S,4S,5S,)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 35B provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 36

A. (4S,5S, 1'R,2'S)-5-(1-Acetoxy-2-(N-((((benzyl)oxy)carbonyl)amino))-3-phenylpropyl)-4-benzyl-oxazolidin-2-one.

A suspension of 5.02 g (8.80 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane in 400 ml of acetonitrile was treated dropwise with 3 ml (20 mmol) of α-acetoxyisobutyryl bromide. The resulting solution was stirred under N_2 atmosphere at ambient temperature for 2 h, filtered to remove traces of solid starting material, quenched cautiously with 100 ml of aqueous $NaHCO_3$, and concentrated in vacuo to a volume of 100 ml. The resulting mixture was extracted with two 100 ml portions of dichloromethane, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using first 10% then 25% ethyl acetate in dichloromethane to provide 3.15 g (71%) of the desired compound as a white foam. ^{1}H NMR ($CDCl_3$) δ2.09 (s, 3H), 2.53 (br t, J=12 Hz, 1H), 2.72 (dd, J=13, 3 Hz, 1H), 2.83 (dd, J=14, 8 Hz, 1H), 2.95 (dd, J=14, 7 Hz, 1H), 3.95 (m, 1H), 4.45 (m, 1H), 4.8 (m, 2H), 5.0–5.1 (m, 3H), 5.29 (dd, J=9, 3 Hz, 1H), 7.0–7.4 (m, 10H). Mass spectrum: $(M+NH_4)^+$=520.

B. (2S,3R,4S,5S)-2,5-Diamino-3,4,dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1F but replacing the resultant compound of Example 1E with (4S,5S,1'R,2'S)-5-(1-acetoxy-2-(N-(benzyloxycarbonylamino))-3-phenylpropyl)-4-benzyl-oxazolidin-2-one provided the desired compound mixed with benzyl alcohol. Purification of a small portion by silica gel chromatography using 5% methanol/2% isopropylamine in chloroform provided the pure desired compound., m.p. 115°–119° C. ^{1}H NMR ($CDCl_3$) δ2.46 (dd, J=14, 9 Hz, 1H), 2.61 (dd, J=14, 11 Hz, 1H), 3.02 (td, J=9, 3 Hz, 1H), 3.19 (dd, J=14, 4Hz, 1H), 3.35–3.4 (m, 2H),3.51 (t, J=9 Hz, 1H), 3.76 (dd, J=9, 3 Hz, 1H), 7.2–7.4 (m, 10H).

C. (2S,3R,4S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

A solution of 0.133 mmol of (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane and 0.147 mmol of ((5-thiazolyl)methyl)-(4-nitrophenyl)-carbonate in 10 ml of tetrahydrofuran was stirred at ambient temperature for 16 h. The resulting solution was diluted with 50 ml of chloroform, washed with several portions of 3N aqueous NaOH, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography of the residue provided the desired compound.

D.(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with the resultant compound of Example 36C provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 37

A. (2S,3R,4S,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane

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provided, after purification by silica gel chromatography, the desired compound.

B. (2S,3R,4S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 36C but replacing (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane with the resultant compound of Example 37A provided, after purification by silica gel chromatography, the desired compound.

EXAMPLE 38

A. 5-(Hydroxymethyl)-3-isopropylisothiazole.

The desired compound was prepared from the resultant compound of Example 29A using the procedure of Lucchesini, et. al. (Heterocycles, 29, 97 (1989)).

B. N-((3-Isopropyl-5-isothiazolyl)methoxycarbonyl)valine Methyl Ester.

Using the procedure of Example 5D but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 5-(hydroxymethyl)-3-isopropylisothiazole provided the desired compound.

C. N-((3-Isopropyl-5-isothiazolyl)methoxycarbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 38B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isothiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with the resultant compound of Example 38C provided the desired compound.

EXAMPLE 39

(2S,3 8,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((2-methyl-5-*thiazolyl)methoxycarbonyl)amino)*-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 2% methanol in chloroform, 20 mg (80%) of the desired compound, R_f 0.23, (4% methanol in chloroform). Mass spectrum: $(M+H)^+$=735. Anal. Calcd for $C_{38}H_{50}N_6O_5S_2.2H_2O$: C, 59.20;H, 7.06; N, 10.90. Found: C, 59.13;H, 6.42; N, 10.82.

EXAMPLE 40

Following the procedures of the above Examples, the following compounds can be prepared.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

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(2S,3R,4R,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N -((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4 R,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl-)methoxycarbonyl)alaninyl)amino)-2-(N-((5thiazolyl-)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4ox-azolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4ox-azolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,4S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl)ethyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl) methoxycarbonyl)amino)1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl-)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl) valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl) amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

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(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl-)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl-)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl) methyl) amino)-carbonyl) valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

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(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexanc.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl-)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexanc.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexanc.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

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(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Meth yl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)-methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)methyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl-)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

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(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl)-methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-isoxazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((Ethyl-N-((2-isopropyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(4-Morpholinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-2-(N-(N-((2-(1-Pyrrolidinyl)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-5-(N-((5-isothiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((3-Isopropyl-5-isoxazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isothiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

EXAMPLE 41

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedures of Example 18A - F, but replacing isobutyramide with propionamide, provided the desired compound. ^{1}H NMR (DMSO-d_6H) δ0.74 (d, J=6 Hz, 6H), 1.19 (t, J=7 Hz, 3H), 1.38–1.51 (m, 2H), 1.80–1.94 (m, 1H), 2.54–2.74 (m, 5H), 2.83 (s, 3H), 3.53–3.63 (m, 1H), 3.82 (br q, 1H), 3.92 (t, J=8 Hz. 1H), 4.13, (m, 1H), 4.26 (AA', 2H), 4.63 (d, J=6 Hz, 1H), 5.13 (AA', 2H), 5.90 (d, J=9 Hz, 1H), 6.89 (d, J=9 Hz, 1H), 7.07–7.25 (m, 12H), 7.68 (d, J=8.7 Hz, 1H), 7.77 (s, 1H), 7.86 (s, 1H), 9.05 (s, 1H). Mass spectrum: $(M+H)^+$=691. Anal. Calcd for $C_{36}H_{46}N_6O_6S.0.3H_2O$: C, 62.10;H, 6.75; N, 12.07. Found: C, 62.42;H, 6.68; N, 11.69.

EXAMPLE 42

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methyl-4-oxazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedures of Example 18A - F, but replacing isobutyramide with acetamide, provided the desired compound. Mass spectrum: $(M+H)^+$=677.

EXAMPLE 43

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-1-phenyl-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-oxazolyl)-3-hydroxyhexane.

Using the procedures of Example 8C–8K, but replacing 5-chloromethylthiazole hydrochloride with 5-chloromethyloxazole hydrochloride provided the desired compound.

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EXAMPLE 44

A. 2-Ethylbutanamide.

A solution of 21.5 ml of oxalyl chloride (2M, 43 mmol) in dichloromethane was treated with 5.0 g (43 mmol) of 2-ethylbutyric acid followed by 0.1 ml of dimethylformamide. The resulting solution was stirred at ambient temperature for 1 h, during which gas evolution was observed. After the termination of gas evolution, the solution was concentrated in vacuo to give crude 2-ethylbutyryl chloride. The crude acid chloride was taken up in 200 ml of acetone and treated with 4.6 g (60 mmol) of ammonium acetate. The resulting mixture was stirred at ambient temperature for 1 h, filtered, and concentrated in vacuo to provide 4.2 g (85%) of the desired compound. ^{1}H NMR (d_6-DMSO) δ0.80 (t, J=7 Hz, 6H), 1.32 (m, 2H), 1.45 (m, 2H), 1.93 (m, 1H), 6.71 (br, 1H), 7.23 (br, 1H).

B. 2-Ethylbutane-thioamide.

Using the procedure of Example 1O, but replacing isobutyramide with 2-ethylbutanamide provided 1.6 g (25%) of the crude desired compound.

C. 4-(Chloromethyl)-2-(3-pentyl)thiazole hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with 2-ethylbutane-thioamide provided the crude desired compound as a yellow oil.

D. 2-(3-Pentyl)-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-(isopropylthiazole hydrochloride with 4-(chloromethyl)-2-(3-pentyl)thiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 5% methanol in chloroform, 1.5 g (71%) of the desired compound.

E. N-((N-Methyl-N-((2-(3-pentyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-(3-pentyl)-4-(((N-methyl)amino)methyl)thiazole provided, after purification by silica gel chromatography using 3% methanol in chloroform as an eluent, 1.6 g (61%) of the desired compound.

F. N-((N-Methyl-N-(2-(3-pentyl)-4-thiazolyl)methyl)amino/carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 44E provided 0.4 g (52%) of the desired compound.

G. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-pentyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-(3-pentyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 99:1 $CHCl_3$:CH_3OH, 72 mg (41%) of the desired compound (R_f 0.3, 95:5 $CHCl_3$:CH_3OH) as a solid, mp 64°–66° C. Mass spectrum: $(M+H)^+$=749. Anal. calcd for $C_{39}H_{52}N_6O_5S_2$: C, 62.54;H, 7.00; N, 11.22;S, 8.56. Found: C, 62.67;H, 6.85; N, 11.06;S, 8.45.

EXAMPLE 45

A. (((2-Isopropyl)-5-thiazolyl)methyl)-(4-nitrophenyl)carbonate.

Using the procedure of Example 1L, but replacing 5-(hydroxymethyl) thiazole with 5-(hydroxymethyl)-2-isopropylthiazole provided, after purification by silica gel chromatography using 1% MeOH/$CHCl_3$, 0.7 g (78%) of the desired compound, Rf=0.8 (5% MeOH/$CHCl_3$H).

B. (2S,3S,5S)-5-Amino-2-(N-(((2-isopropyl)-5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl,3-hydroxyhexane.

Using the procedure of Example 1N, but replacing ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate with (((2-isopropyl)-5-thiazolyl)methyl)-(4-nitrophenyl)carbonate provided, after purification by silica gel chromatography using 99:2:1 $CHCl_3$:isopropylamine:CH_3OH, Rf=0.2 , 0.17 g (18%) of the desired compound, (1% isopropylamine in $CHCl_3$H). ^{1}H NMR (d_6-DMSO) δ1.38 (d, J=7 Hz, 6H), 1.43 (m, 1H), 1.64 (m, 1H), 2.46 (dd, J=14, 8 Hz, 1H), 2.63 (m, 2H), 2.80 (dd, J=14, 5 Hz, 1H), 2.94 (m, 1H), 3.21 (m, 1H), 3.64 (m, 2H), 5.09 (AA', 2H), 6.98 (d, J=9 Hz, 1H), 7.1–7.3 (m, 10H), 7.60 (s, 1H). Mass spectrum: $(M+H)^+$=468.

C. (2S,3S,5S)-5-(N-(N-((N-Methyl-N,((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-(((2-isopropyl)-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing (2S, 3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-(((2-isopropyl)-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after purification by silica gel chromatography using 99:1 $CHCl_3$:CH_3OH, 50 mg (61%) of the desired compound (R_f 0.28, 95:5 $CHCl_3$:CH_3OH) as a solid, mp 64°–66° C. Mass spectrum: $(M+H)^+$=764. Anal. calcd for $C_{40}H_{54}N_6O_5S_2$: C, 62.97;H, 7.13; N, 11.01. Found: C, 62.91; H, 7.11; N, 10.81.

EXAMPLE 46

A. 1-(Aminothiocarbonyl)pyrrolidine.

A solution of 1.0 g (14 mmol) of pyrrolidine in 70 ml of tetrahydrofuran was treated dropwise with 2.0 ml of trimethylsilylisocyanate. The resulting solution was stirred at ambient temperature for two days, and concentrated in vacuo. Purification of the residue by silica gel chromatography using 4% methanol in chloroform provided the desired compound (R_f 0.5, 10% methanol in chloroform).

B. 4-(Chloromethyl)-2-(1-pyrrolidinyl)thiazole hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with 1-(aminothiocarbonyl)pyrrolidine provided the crude desired compound.

C. 2-(1-Pyrrolidinyl)-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-(1-pyrrolidinyl)thiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 2% isopropylamine/2% methanol in chloroform, 0.89 g (30%) of the desired compound. ^{1}H NMR ($CDCl_3$H) δ2.02 (m, 4H), 2.61 (s, 3H), 3.44 (m, 4H), 3.90 (s, 2H), 4.84 (br, 1H), 6.51 (s, 1H). Mass spectrum: $(M+H)^+$=198.

D. N-((N-Methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-(1-pyrrolidinyl)-4-(((N-methyl)amino)methyl)thiazole provided, after purification by silica gel chromatography using 4% methanol in chloroform as an eluent, 0.63 g (39%) of the desired compound. ^{1}H NMR ($CDCl_3$H) δ0.96 (t, J=7 Hz, 3H), 0.98 (t, J=7 Hz, 3H), 2.04 (m, 4H), 2.14 (heptet, J=7 Hz, 1H), 2.97 (s, 3H), 3.45 (m, 4H), 3.71 (s, 3H), 4.10 (m, 1H), 4.33 (dd, J=9, 6 Hz, 1H), 4.42 (br d, J=16 Hz, 1H), 6.26 (s, 1H), 6.45 (br, 1H). Mass spectrum: $(M+H)^+$=355.

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E. N-((N-Methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 46D provided 0.24 g (96%) of the desired compound.

F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl) amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 2% methanol in chloroform, the desired compound (R_f 0.29, 4% methanol in chloroform). Mass spectrum: $(M+H)^+$=748.

EXAMPLE 47

A. Ethyl 2-(2-Isopropyl-4-thiazolyl)acetate.

Using the procedure of Example 1P, but replacing 1,3-dichloroacetone with ethyl 4-chloroacetoacetate provided, after purification by silica gel chromatography using $CHCl_3$, the desired compound in 34% yield. ^1H NMR (d_6-DMSO) δ1.18 (t, J=7 Hz, 3H), 1.30 (d, J=7 Hz, 6H), 3.24 (heptet, J=7 Hz, 1H), 3.76 (s, 2H), 4.09 (q, J=7 Hz, 2H), 7.31 (s, 1H). Mass spectrum: $(M+H)^+$=214.

B. 4-(2-Hydroxyethyl-2-isopropylthiazole.

Using the procedure of Example 5B, but replacing ethyl 2-isopropyl-4-thiazolecarboxylate with ethyl 2-(2-isopropyl-4-thiazolyl)acetate provided, after purification of the residue by silica gel chromatography using 2% methanol in chloroform, 0.9 g (47%) of the desired compound. ^1H NMR ($CDCl_3H$) δ1.40 (d, J=7 Hz, 6H), 2.95 (t, J=6 Hz, 2H), 3.30 (heptet, J=7 Hz, 1H), 3.92 (t, J=6 Hz, 2H), 6.83 (s, 1H). Mass spectrum: $(M+H)^+$=172.

C. N-((2-(2-Isopropyl-4-thiazolyl)ethoxy)carbonyl)valine Methyl Ester.

Using the procedure of Example 5D, but replacing 4-(hydroxymethyl)-2-isopropylthiazole with 4-(2-hydroxyethyl)-2-isopropylthiazole provided, after purification by silica gel chromatography using 3% methanol in chloroform as an eluent, 0.8 g (52%) of the desired compound.

D. N-((2-(2-Isopropyl-4-thiazolyl)ethoxy)carbonyl)valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 47C provided 0.17 g (82%) of the desired compound.

E. (2S,3S,5S)-5-(N-(N,((2,-(2-Isopropyl-4-thiazolyl)ethoxy)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((2-(2-isopropyl-4-thiazolyl)ethoxy-)carbonyl)valine provided, after purification by silica gel chromatography using 99:1 $CHCl_3$: CH_3OH, 80 mg (47%) of the desired compound (R_f 0.3, 95:5 $CHCl_3$: CH_3OH) as a solid, mp 146°–147° C. Mass spectrum: $(M+H)^+$=722. Anal. calcd for $C_{37}H_{47}N_5O_6S_2$:C, 61.56; H, 6.56; N, 9.70. Found: C, 61.24;H, 6.48; N, 9.53.

EXAMPLE 48

E. (2S,3S,5S)-2-(N-(N-((2-(2-Isopropyl-4-thiazolyl)ethoxy-carbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((2-(2-isopropyl-4-thiazolyl)ethoxy-)carbonyl)valine and replacing (2S,3S,5S)-5-amino- 2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after purification by silica gel chromatography using 99:1 $CHCl_3$: CH_3OH, 50 mg (30%) of the desired compound (R_f 0.3, 95:5 $CHCl_3$: CH_3OH) as a solid, mp 159°–160° C. Mass spectrum: $(M+H)^+$=722 HRMS. Exact mass calcd for $C_{37}H_{47}N_5O_6S_2$: 722.3046. Found: 722.3036.

EXAMPLE 49

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-(2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-(1-pyrrolidinyl)-4-thiazolyl)methyl)amino)carbonyl)-L-valine and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-isoxazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after purification by silica gel chromatography using 2% methanol in chloroform, the desired compound (R_f 0.30, 4% methanol in chloroform).

EXAMPLE 50

A. (2S,3S,5S)-5-(N-(N-(t-Butyloxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-(t-butyloxycarbonyl)valine provided, after silica gel chromatography using 1% methanol in chloroform, the desired compound (R_f 0.31, 4% methanol in chloroform).

B. (2S,3S,5S)-5-(N-(Valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane Hydrochloride.

To 135 mg (0.27 mmol) of (2S,3S,5S)-5-(N-(N-(t-butyloxycarbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane was added 8 ml of 4M HCl in dioxane. The resulting mixture was stirred at ambient temperature for 1 h and concentrated in vacuo to provide the crude desired compound.

G. 2-(2-Isopropyl-4-thiazolyl)acetic Acid.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 47A provided 0.24 g (55%) of the desired compound. ^1H NMR ($CDCl_3H$) δ1.93 (d, J=7 Hz, 6H), 3.35 (heptet, J=7 Hz, 1H), 3.85 (s, 2H), 7.00 (s, 1H) Mass spectrum: $(M+H)^+$=186.

D. (2S,3S,5S)-5-(N-(N-((2-Isopropyl,4-thiazolyl)acetyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with 2-(2-isopropyl-4-thiazolyl)acetic acid provided, after purification by silica gel chromatography using 99:1 $CHCl_3$: CH_3OH, 120 mg (80%) of the desired compound (R_f 0.6, 95:5 $CHCl_3$: CH_3OH) as a solid, mp

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153°–155° C. Mass spectrum: $(M+H)^+$=692. Anal. calcd for $C_{36}H_{45}N_5O_5S_2.0.5H_2O$: C, 61.69; H, 6.62; N, 9.99; S, 9.15. Found: C, 61.92; H, 6.49; N, 10.06; S, 8.81.

EXAMPLE 51

A. Cyclopropanecarboxamide.

Using the procedure of Example 44A but replacing 2-ethylbutyric acid with cyclopropanecarboxylic acid provided 6.4 g (50%) of the crude desired compound.

B. Cyclopropanethiocarboxamide.

Using the procedure of Example 1O, but replacing isobutyramide with cyclopropanecarboxamide provided 7.2 g (96%) of the crude desired compound.

C. 4-(Chloromethyl)-2-cyclopropylthiazole-hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with cyclopropanethiocarboxamide provided the crude desired compound as a yellow oil.

D. 2-(Cyclopropyl-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-cyclopropylthiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 5% methanol in chloroform, 0.5 g (25%) of the desired compound.

E. N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-cyclopropyl-4-(((N-methyl)amino)methyl)thiazole provided, after purification by silica gel chromatography using 1% methanol/chloroform as an eluent, 0.4 g (48%) of the desired compound.

F. N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 51E provided 0.16 g (70%) of the desired compound.

G. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane,

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 90 mg (54%) of the desired compound (R_f 0.2, 95:5 $CHCl_3CH_3OH$) as a solid, mp 70°–71° C. Mass spectrum: $(M+H)^+$=719. Anal. calcd for $C_{37}H_{46}N_6O_5S_2$: C, 61.82; H, 6.45; N, 11.69. Found: C, 61.50; H, 6.46; N, 11.41.

EXAMPLE 52

A. Cyclobutanecarboxamide.

Using the procedure of Example 44A but replacing 2-ethylbutyric acid with cyclobutanecarboxylic acid provided 7.5 g (76%) of the crude desired compound.

B. *Cyclobutanethiocarboxamide.*

Using the procedure of Example 1O, but replacing isobutyramide with cyclobutanecarboxamide provided 6.9 g (80%) of the crude desired compound.

C. 4-(Chloromethyl)-2-cyclobutylthiazole hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with cyclobutanethiocarboxamide provided the crude desired compound as a yellow oil.

D. 2-Cyclobutyl-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-cyclobutylthiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 5% methanol in chloroform, 1.0 g (36%) of the desired compound.

E. N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-cyclobutyl-4-(((N-methyl)amino)methyl)-thiazole provided, after purification by silica gel chromatography using 1% methanol in chloroform as an eluent, 0.54 g (31%) of the desired compound. Mass spectrum: $(M+H)^+$=340.

F. N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 52E provided 0.2 g (42%) of the desired compound.

G. (2S,3S,5S)-5-(N-(N-((N-Methyl-N,((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl))valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl,3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine *with N-((N-methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine* provided, after purification by silica gel chromatography using 1% methanol in chloroform, 110 mg (64%) of the desired compound (R_f 0.17, 95:5 CH_2Cl_2: CH_3OH) as a solid, mp 74°–76° C. Mass spectrum: $(M+H)^+$=733. Anal. calcd for $C_{38}H_{48}N_6O_5S_2$: C, 62.27; H, 6.60; N, 11.47; S, 8.75. Found, C, 62.02; H, 6.73; N, 11.33; S, 8.51.

EXAMPLE 53

A. Propanethioamide.

Using the procedure of Example 10, but replacing isobutyramide with propionamide provided 4.6 g (38%) of the crude desired compound. H NMR ($CDCl_3H$) δ1.33 (t, J=7 Hz, 3H), 2.70 (q, J=7 Hz, 2H), 6.9 (br, 1H), 7.6 (br, 1H). Mass spectrum: $(M+H)^+$=90.

B. 4-(Chloromethyl)-2-ethylthiazole hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with propanethioamide provided the crude desired compound as a yellow oil.

C. 2-Ethyl-(((N-methyl)amino)methyl)thiazole. Using the procedure of Example 1Q, but replacing 4-(chloromethyl)--isopropylthiazole hydrochloride with 4-(chloromethyl)-2-ethylthiazole hydrochloride provided 1.0 g (52%) of the desired compound.

D. N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-ethyl-4-(((N-methyl)amino)methyl)thiazole provided, after purification by silica gel chromatography using 1% methanol in chloroform as an eluent, 0.7 g (35%) of the desired compound.

E. N-((N-Methyl-N-((2-ethyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 53D provided 0.28 g (43%) of the desired compound.

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F. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-ethyl-4-thiazolyl-)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 60 mg (40%) of the desired compound (R_f 0.14, 95:5 CH_2Cl_2: CH_3OH) as a solid, mp 70°–71° C. Mass spectrum: $(M+H)^+$=707. Anal. calcd for $C_{36}N_{46}N_6O_5S_2.H_2O$:C, 59.65; H, 6.67; N, 11.59. Found: C, 59.64; H, 6.59; N, 11.88.

EXAMPLE 54

A. 2-Isopropyl-4-(((N-(1-propyl))amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 40% aqueous methylamine with 1-aminopropane provided the crude desired compound. ^1H NMR ($CDCl_3H$) δ0.94 (t, J=7 Hz, 3H), 1.39 (d, J=7 Hz, 6H), 1.54(sextet, J=7 Hz, 2H), 2.62 (t, J=7 Hz, 2H), 3.30 (heptet, J=7 Hz, 1H), 3.87 (d, J=1 Hz, 2H), 6.93 (s, 1H). Mass spectrum: $(M+H)^+$=199.

B. N-((N-(1-Propyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-(((N-(1-propyl))amino)methyl)thiazole provided, after silica gel chromatography using 1% methanol in chloroform as an eluent, 1.55 g (63%) of the desired compound. ^1H NMR ($CDCl_3$) δ0.86 (t, J=7 Hz, 3H), 1.38 (d, J=7 Hz, 6H), 1.41 (d, J=7 Hz, 6H), 1.56 (m, 1H), 1.57 (sextet, J=7 Hz, 2H), 3.27 (heptet, J=7 Hz, 1H), 3.29 (t, J=7 Hz, 2H), 3.71 (s, 3H), 4.45 (m, 3H) 6.31 (br, 1H), 6.98 (s, 1H). Mass spectrum: $(M+H)^+$=328.

C. N-((N-(1-Propyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 54B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-(1-Propyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-(1-propyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using 1% methanol in chloroform, 60 mg (44%) of the desired compound (R_f 0.3, 95:5 $CHCl_3$: CH_3OH) as a solid, mp 62°–64° C. Mass spectrum: $(M+H)^+$=721. Anal. calcd for $C_{37}H_{48}N_6O_5S_2.0.5H_2$: C, 60.88; H, 6.77; N, 11.51. Found: C, 60.66; H, 6.95; N, 11.45

EXAMPLE 55

A. 2-Isopropyl-4-((N-(isobutyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 40% aqueous methylamine with isobutylamine provided the crude desired compound. Mass spectrum: $(M+H)^+$=213.

B. N-((N-(isobutyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-(((N-(isobutyl))amino)-methyl)thiazole provided, after silica gel chromatography using 1% methanol in chloroform as an eluent, 0.7 g (41%) of the desired compound. ^1H NMR (DMSO-d_6H) δ0.78 (d, J=7 Hz, 3H), 0.79 (d, J=7 Hz, 3H), 1.30 (m, 12H), 1.89 (m, 2H), 3.05 (d, J=8 Hz, 2H), 3.22 (m, 1H), 3.58 (s, 3H), 4.13 (m, 1H), 4.44 (AA', 2H), 6.87 (br d, 1H), 7.23 (s, 1H). Mass spectrum: $(M+H)^+$=3.42.

C. N-((N-(isobutyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl))-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 55B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-(Isobutyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-(isobutyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using 1% methanol in chloroform, 70 mg (50%) of the desired compound (R_f 0.3, 5% methanol in chloroform) as a solid, mp 60°–61° C. Mass spectrum: $(M+H)^+$=735. Anal. calcd for $C_{38}H_{50}N_6O_5S_2$: C, 62.10; H, 6.86; N, 11.43; S, 8.72. Found: C, 61.74; H, 7.16; N, 11.36; S, 8.48.

EXAMPLE 56

A. N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alanine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-(((N-methyl)amino)methyl)-oxazole and replacing N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester with N-(((4-nitrophenyl)oxy)carbonyl)-L-alanine methyl ester provided the desired compound in 66 % yield. ^1H NMR ($CDCl_3H$) δ1.32 (d, 6H), 1.42 (d, 3H), 2.96 (s, 3H), 3.05 (m, 1H), 3.75 (s, 3H), 4.30 (s, 2H), 4.47 (m, 1H), 5.80 (br d, 1H), 7.46 (s, 1H). Mass spectrum: $(M+H)^+$=284.

B. N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alanine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 56A provided the desired compound.

C. (2S,3S,5S)-5-(N,(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alanine provided, after silica gel chromatography using 92:8 CH_2Cl_2: CH_3OH, the desired compound (R_f 0.49, 92:8 CH_2Cl_2: CH_3OH) in 75% yield. Mass spectrum: $(M+H)^+$=677.

EXAMPLE 57

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alaninyl)amino)-2-(N-((5-isoxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alanine and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-2-(N-((5-isoxazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane provided, after silica gel chromatography using 92:8 CH_2Cl_2: CH_3OH, the desired

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compound (R_f 0.48, 92:8 CH_2Cl_2: CH_3OH)in 64% yield. ^1H NMR (DMSO-d_6) δ1.08 (d, 3H), 1.24 (d, 6H), 1.50 (m, 2H), 2.82 (s, 3H), 3.0(m, 1H), 4.25 (s, 2H), 4.60 (d, 1H), 5.05 (s, 2H), 6.20 (br d, 1H), 6.32 (d, 1H), 7.20 (m, 11H), 7.50 (br d, 1H), 7.78 (s, 1H), 8.51 (d, 1H). Mass spectrum: $(M+H)^+$ =661.

EXAMPLE 58

A. Cyclopentanecarboxamide.

Using the procedure of Example 44A but replacing 2-ethylbutyric acid with cyclopentanecarboxylic acid provided 2.6 g (100%) of the crude desired compound.

B. Cyclopentanethiocarboxamide.

Using the procedure of Example 1O, but replacing isobutyramide with cyclopentanecarboxamide provided 2.4 g (83%) of the crude desired compound.

C. 4-(Chloromethyl)-2-cyclopentylthiazole hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with cyclopentanethiocarboxamide provided the crude desired compound as a yellow oil.

D. 2- Cyclopentyl-4-((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-cyclopentylthiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 3% methanol in chloroform, 0.83 g (43%) of the desired compound.

E. N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)-methyl)thiazole with 2-cyclopentyl-4-(((N-methyl)amino)methyl)-thiazole provided, after purification by silica gel chromatography using 1% methanol in chloroform as an eluent, 0.77 g (51%) of the desired compound. ^1H NMR ($CDCl_3$) δ0.93 (d, J=7 Hz, 3H), 0.97 (d, J=7 Hz, 3H), 1.6–1.9 (m, 6H), 2.2 (m, 3H), 2.99 (s, 3H), 3.40 (m, 1H), 3.71 (s, 3H), 4.37 (dd, J=9, 5 Hz, 1H), 4.45 (AA', 2H), 5.99 (br d, 1H) 6.95 (s, 1H). Mass spectrum: $(M+H)^+$=354.

F. N-((N-Methyl-N-(2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 58E provided 0.64 g (87%) of the desired compound.

G.(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 50 mg (36%) of the desired compound (R_f 0.40, 5% methanol in chloroform) as a solid, mp 70°–71° C. Mass spectrum: $(M+H)^+$=747. Anal. calcd for $C_{39}H_{50}N_6O_5S_2$: C, 62.71; H, 6.75; N, 11.25. Found: C, 63.16; H, 6.80; N, 10.84.

EXAMPLE 59

A. 3-Methylbutanamide.

Using the procedure of Example 44A but replacing 2-ethylbutyric acid with 3-methylbutyric acid provided 4.2 g (100%) of the crude desired compound.

B. 3-Methylpropanethiocarboxamide.

Using the procedure of Example 1O, but replacing isobutyramide with 3-methylbutanamide provided the crude desired compound.

C. 4-(Chloromethyl)-2-isobutylthiazole hydrochloride.

Using the procedure of Example 1P, but replacing 2-methylpropanethioamide with 3-methylpropanethiocarboxamide provided the crude desired compound as a yellow oil.

D. 2-Isobutyl-4-(((N-methyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-isobutylthiazole hydrochloride provided, after purification of the residue by silica gel chromatography using 10% methanol in chloroform, 0.61 g (31%) of the desired compound.

E. N-((N-Methyl-N-((2-isobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isobutyl-4-(((N-methyl)amino)methyl)thiazole provided, after purification by silica gel chromatography using 1% methanon in chloroform as an eluent, 0.40 g (32%) of the desired compound. Mass spectrum: $(M+H)^+$=342.

F. N-((N-Methyl-N-((2-isobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 59E provided 0.13 g (70%) of the desired compound.

G. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isobutyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5 -thiazolyl)methoxycarbonyl))amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-((2-isobutyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 50 mg (33%) of the desired compound (R_f 0.65, 10% methanol in chloroform). Mass spectrum: $(M+H)^+$=735.

EXAMPLE 60

A. 2- Cyclopentyl-4-(((N-ethyl)amino)methyl)thiazole.

Using the procedure of Example 1Q, but replacing 4-(chloromethyl)-2-isopropylthiazole hydrochloride with 4-(chloromethyl)-2-cyclopentylthiazole hydrochloride and replacing 40% aqueous methylamine with 70% aqueous ethylamine provided, after purification of the residue by silica gel chromatography using 5% methanol in chloroform, 1.08 g (50%) of the desired compound.

B. N-((N-Ethyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-cyclopentyl-4-(((N-ethyl)amino)methyl)-thiazole provided, after purification by silica gel chromatography using 1% methanol in chloroform as an eluent, 0.40 g (46%) of the desired compound. ^1H NMR (DMSO-d_6H), δ1.00 (t, J=7 Hz, 3H), 1.29 (d, J=7 Hz, 3H), 1.6–1.8 (m, 9H), 2.1 (m, 3H), 3.27 (m, 2H), 3.37 (m, 1H), 3.60 (s, 3H), 4.17 (pentet, J=7 Hz, 1H), 4.41 (AA', 2H), 6.80 (d, J=7 Hz, 1H), 7.20 (s, 1H). Mass spectrum: $(M+H)^+$=340.

C. N-((N-Ethyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant com-

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pound of Example 60B provided 0.13 g (69%) of the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Ethyl-N-[(2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl))amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-ethyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1.5% methanol in chloroform, 50 mg (34%) of the desired compound (R_f 0.63, 10% methanol in chloroform) as a solid, mp 67°–69°

C. Mass spectrum: $(M+H)^+$=733. Anal. calcd for $C_{38}H_{48}N_6O_5S_2$: C, 62.27; H, 6.60; N, 11.47. Found: C, 62.02; H, 6.74; N, 10.98.

EXAMPLE 61

A. 2-Isopropyl-4-(2-((N-methyl)amino)ethyl)thiazole.

A solution of 2.0 g (12 mmol) of 2-isopropyl-4-(hydroxyethyl)thiazole in 50 ml of tetrahydrofuran was treated with 1.34 g (12 mmol) of methanesulfonyl chloride. The resulting solution was treated dropwise with 3.4 ml (24 mmol) of triethylamine and stirred at ambient temperature for 1 h. A portion (25 ml) of the resulting solution was added to 50 ml of aqueous ethylamine (70% in H_2O) with rapid stirring. After addition, the mixture was heated to reflux for 2 h, allowed to cool, diluted with ethyl acetate, washed with aqueous $NaHCO_3$ and saturated brine, dried over Na_2SO_4, and concentrated in vacuo to provide the crude desired compound. Purification of the residue by silica gel chromatography using 5% methanol in chloroform, 0.52 g (48%) of the desired compound. ^1H NMR ($CDCl_3$) δ1.38 (d, J=7 Hz, 3H), 2.46 (s, 3H), 2.93 (s, 4H), 3.30 (heptet, J=7 Hz, 1H) 6.79 (s, 1H). Mass spectrum: $(M+H)^+$=185.

B. N-((N-Methyl-N-(2-(2-isopropyl-4-thiazolyl)ethyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-(2-((N-methyl)amino)ethyl)-thiazole provided, after purification by silica gel chromatography using 1% methanol in chloroform as an eluent, 0.16 g (35%) of the desired compound. ^1H NMR ($CDCl_3H$) δ0.91 (d, J=7 Hz, 3H), 0.98 (d, J=7 Hz, 3H), 1.48 (d, J=7 Hz, 3H), 1.49 (d, J=7 Hz, 3H), 2.11 (heptet of doublets, J=7, 5 Hz, 1H), 2.85 (s, 3H), 2.99 (t, J=7 Hz, 2H), 3.30 (heptet, J=7 Hz, 1H), 3.63 (t, J=7 Hz, 2H), 3.73 (s, 3H), 4.42 (dd, J=8, 5 Hz, 1H), 4.93 (br d, J=8 Hz, 1H), 6.83 (s, 1H). Mass spectrum: $(M+H)^+$=342.

C. N-((N-Methyl-N-(2-(2-isopropyl-4-thiazolyl)ethyl)amino)carbonyl)-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 61B provided 0.074 g (64%) of the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-(2-(2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl))amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U, but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-methyl-N-(2-(2-isopropyl-4-thiazolyl)ethyl)amino)carbonyl)-L-valine provided, after purification by silica gel chromatography using 1% methanol in chloroform, 90 mg (54%) of the desired compound (R_f 0.44, 10% methanol in chloroform) as a solid, mp 62°–63°

C. Mass spectrum: $(M+H)^+$=735. Anal. calcd for $C_{38}H_{50}N_6O_5S_2$: C, 62.10; H, 6.86; N, 11.43; S, 8.72. Found: C, 61.72; H, 6.78; , N, 11.34; S, 8.89.

EXAMPLE 62

A. 2-Isopropyl-4-((N-(tert-butyloxycarbonylamino)amino)methyl)thiazole.

A solution of 7.5 g (57 mmol) to t-butylcarbazate in 200 ml of isopropyl alcohol was treated with a solution of 1.0 g (57 mmol) of 4-(chloromethyl)-2-isopropylthiazole hydrochloride in 10 ml of isopropyl alcohol. The resulting solution was heated at reflux for 16 h, allowed to cool, and concentrated in vacuo. The residue was diluted with 1N HCl, washed with three portions of ethyl acetate, basified to pH 12 with aqueous NaOH, and extracted with three portion of ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by silica gel chromatography using 20% ethyl acetate in hexane provided 0.32 g (21%) of the desired compound (R_f 0.4, 5% methanol in chloroform). ^1H NMR ($CDCl_3H$) δ1.40 (d, J=7 Hz, 6H), 1.47 (s, 9H), 2.53 (br, 1H), 3.33 (heptet, J=7 Hz, 1H), 4.11 (s, 2H), 6.22 (br, 1H), 7.01 (s, 1H). Mass spectrum: $(M+H)^+$=272.

B. N-((N-(tert-Butyloxycarbonylamino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

Using the procedure of Example 1S, but replacing 2-isopropyl-4-(((N-methyl)amino)methyl)thiazole with 2-isopropyl-4-((N-(tert-butyloxycarbonylamino)amino)methyl)thiazole provided, after silica gel chromatography using 1% methanol in chloroform as an eluent, 0.30 g (95%) of the desired compound. ^1H NMR (DMSO-d_6H) δ0.84 (d, J=7 Hz, 3H), 0.87 (d, J=7 Hz, 3H), 1.31 (d, J=7 Hz, 6H), 1.39 (s, 9H), 2.05 (m, 1H), 3.24 (m, 1H), 3.64 (s, 3H), 4.09 (dd, J=9, 6 Hz, 1H), 6.35 (br, 1H), 7.24 (s, 1H). Mass spectrum: $(M+H)^+$=429.

C. N-((N-(tert-Butyloxycarbonylamino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl))-L-valine.

Using the procedure of Example 1T, but replacing the resultant compound of Example 1S with the resultant compound of Example 62B provided the desired compound.

D. (2S,3S,5S)-5-(N-(N-((N-(tert-Butyloxycarbonyl)amino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((N-(tert-butyloxycarbonylamino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine provided, after silica gel chromatography using 1% methanol in chloroform, 80 mg (41%) of the desired compound (R_f 0.35, 5% methanol in chloroform). Mass spectrum: $(M+H)^+$ =822. HRMS. Exact mass calcd for $C_{41}H_{56}N_7O_7S_2$: 822.3683. Found: 822.3682.

EXAMPLE 63

(2S,3S,5S)-5-(N-(N-((N-(Amino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane Hydrochloride.

To 60 mg (0.073 mmol) of (2S,3S,5S)-5-(N-(N-((N-(tert-butyloxycarbonyl-amino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane was added 5 ml of 4M HCl in dioxane. The resulting solution was stirred at ambient temperature for 2 h. After concentration of the solution in vacuo, the residue was taken up in 0.5 ml of methanol, added to 20 ml of diethyl ether, and

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filtered to provide 40 mg (77%) of the desired compound (R_f 0.60, 10% methanol in chloroform). Mass spectrum: $(M+H)^+$=722.

EXAMPLE 64

(2S,3S,5S)-5-(N-{N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-1-phenyl-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

Using the procedure of Example 1U but replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-5-amino-1-phenyl-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane and replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((2-isopropyl-4-thiazolyl)methoxycarbonyl)valine provided, after silica gel chromatography using 10% methanol in dichloromethane, 25 mg (76%) of the desired compound (R_f 0.47, 10% methanol in dichloromethane). Mass spectrum: $(M+H)^+$=715.

EXAMPLE 65

A. (2S,3S,5S)-3-(tert-Butyldimethylsilyloxy)-2-(tert-butyloxycarbonylamino)-1-phenyl-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)hexane.

Using the procedure of Example 8F, but replacing benzyl alcohol with 5-(hydroxymethyl)thiazole provided, after silica gel chromatography using 10% methanol in dichloromethane, 261 mg (67%) of the desired compound. ^1H NMR ($CDCl_3H$) δ0.05 (s, 6H), 0.91 (s, 9H), 1.34 (s, 9H), 1.70 (m, 2H), 2.72 (m, 2H), 3.03 (m, 2H), 3.74 (m, 1H), 3.91 (m, 1H), 4.02 (m, 1H), 4.63 (br d, 1H), 5.24 (s, 2H), 7.19–7.35 (m, 5H), 7.52 (s, 1H), 7.86 (s,1H), 8.66 (s, 1H), 8.79 (s, 1H). Mass spectrum: $(M+H)^+$=647.

B. (2S,3S,5S)-2-(tert-Butyloxycarbonylamino)-1-phenyl-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

Using the procedure of Example 8G, but replacing the resultant compound of Example 8F with the resultant compound of Example 65A provided, after silica gel chromatography using 10% methanol in dichloromethane, 74 mg (35%) of the desired compound. ^1H NMR ($CDCl_3H$) δ1.39 (s, 9H), 1.65 (m, 2H), 2.87 (m, 2H), 3.09 (m, 2H), 3.68 (m, 2H), 3.96 (m, 2H), 4.74 (br d, 1H), 5.26 (dd, 2H), 7.17–7.32 (m, 5H), 7.52 (s, 1H), 7.86 (s, 1H), 8.66 (s, 1H), 8.81 (s, 1H). Mass spectrum: $(M+H)^+$=533

C. (2S,3S,5S)-2-Amino-1-phenyl-5-(N-((5-thiazolyl-)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

A solution of 70 mg (0.13 mmol) of the resultant compound of Example 65B in 2.1 ml of CH_2Cl_2 was treated with 0.7 ml of trifluoroacetic acid, stirred for 1.5 h, and concentrated in vacuo. The residue was treated with 3 ml of aqueous $NaHCO_3$, extracted with three portions of 95:5 CH_2Cl_2:$CHCl_3$, dried over Na_2SO_4, and concentrated in vacuo to provide 55 mg (97%) of the desired compound as a white foamy solid. ^1H NMR ($CDCl_3H$) δ1.72 (m, 2H), 1.86 (br, 2H), 2.46 (dd, 1H), 2.84 (m, 2H), 3.20 (m, 2H), 3.45 (m, 1H), 4.02 (m, 1H), 5.30 (dd, 2H), 5.52 (br d, 1H), 7.14–7.34 (m, 5H), 7.59 (s, 1H), 7.88 (s, 1H), 8.67 (s, 1H), 8.80 (s, 1H). Mass spectrum: $(M+H)^+$=433.

D. (2S,3S,5S)-2,(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl))valine)amino)-1-phenyl-5-(N-((5-thiazolyl-)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane.

Using the procedure of Example 1U but replacing N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine with N-((2-isopropyl-4-thiazolyl)methoxycarbonyl)valine and replacing (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane with (2S,3S,5S)-2-amino-1-phenyl-5-(N-((5- thiazolyl)methoxycarbonyl)amino)-6-(5-thiazolyl)-3-hydroxyhexane provided, after silica gel chromatography using 1% methanol in chloroform, 54 mg (66%) of the desired compound (R_f 0.6, 10% methanol in CH_2Cl_2H). ^1H NMR (DMSO-d_6H) δ0.69 (d, 3H), 0.74 (d, 3H), 1.31 (d, 6H), 1.47 (m, 2H), 1.85 (m, 1H), 2.75 (m, 4H), 2.95 (m, 1H), 3.57 (m, 1H), 3.80 (m, 2H), 4.08 (m, 1H), 4.95 (d, 1H), 5.03 (s, 2H), 5.19 (s, 2H), 7.12–7.29 (m), 7.45 (s,1H), 7.47 (s, 1H). Mass spectrum: $(M+H)^+$=715.

EXAMPLE 66

(2S,3S,5S)-2,5-Diamino-3-hydroxy-1,6-diphenylhexane dihydrochloride

EXAMPLE 66A

(L)-N,N-Dibenzylphenylalanine benzyl ester

A solution containing L-phenylalanine (11 kg, 66.7 moles), potassium carbonate (29 kg, 210 moles), and water (66 L), and benzyl chloride (27 kg, 213 moles) was heated to 90°±15° C. for 10–24 hours. The reaction mixture was cooled to room temperature and heptane (29 L) and tap water (27 L) was added. The layers were separated and the organics washed one to two times with 22 L of a methanol/water solution (1/2 v/v). The organics were then stripped to give the desired product as an oil. IR (neat) 3090, 3050, 3030, 1730, 1495, 1450, 1160 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3H$) δ7.5–7.0 (m, 20H), 5.3 (d, 1H, J=13.5 Hz), 5.2 (d, 1H, J=13.5 Hz), 4.0 (d, 2H, J=15 Hz), 3.8 (t, 2H, J=8.4 Hz), 3.6 (d, 2H, J=15 Hz), 3.2 (dd, 1H, J=8.4, 14.4 Hz), ^{13}C NMR (300 MHz, $CDCl_3H$) δ172.0, 139.2, 138.0, 135.9, 129.4, 128.6, 128.5, 128.4, 128.2, 128.1, 128.1, 126.9, 126.2, 66.0, 62.3, 54.3, 35.6. $[\alpha]_D$–79° (c=0.9, DMF).

EXAMPLE 66B

(4S)-4-(N,N-Dibenzylamino)-3-oxo-5-phenyl-pentanonitrile

A solution containing the product of Example 66A (i.e., benzyl ester) (approx. 0.45 moles) in 520 mL tetrahydrofuran and 420 mL acetonitrile was cooled to –40° C. under nitrogen. A second solution containing sodium amide (48.7 g, 1.25 moles) in 850 mL tetrahydrofuran was cooled to –40° C. To the sodium amide solution was slowly added 75 mL acetonitrile and the resulting solution was stirred at –40° C. for more than 15 minutes. The sodium amide/acetonitrile solution was then slowly added to the benzyl ester solution at –40° C. The combined solution was stirred at –40° C. for one hour and then quenched with 1150 mL of a 25% (w/v) citric acid solution. The resulting slurry was warmed to ambient temperature and the organics separated. The organics were then washed with 350 mL of a 25% (w/v) sodium chloride solution, then diluted with 900 mL heptane. The organics were then washed three times with 900 mL of a 5% (w/v) sodium chloride solution, two times with 900 mL of a 10% methanolic water solution, one time with 900 mL of a 15% methanolic water solution, and then one time with 900 mL of a 20% methanolic water solution. The organic solvent was removed in vacuo and the resulting material dissolved into 700 mL of hot ethanol. Upon cooling to room temperature, the desired product precipitated. Filtration gave the

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desired product in 59% yield from the L-phenylalanine. IR ($CHCl_3$H) 3090, 3050, 3030, 2250, 1735, 1600, 1490, 1450, 1370, 1300, 1215 cm^{-1}, ^1H NMR ($CDCl_3$H) δ7.3 (m, 15H), 3.9 (d, 1H, J=19.5 Hz), 3.8 (d, 2H, J=13.5 Hz), 3.6 (d, 2H, J=13.5 Hz), 3.5 (dd, 1H , J=4.0, 10.5 Hz), 3.2 (dd, 1H, J=10.5, 13.5 Hz), 3.0 (dd, 1H, J=4.0, 13.5 Hz), 3.0 (d, 1H, J=19.5 Hz), ^{13}C NMR (300 MHz, $CDCl_3$H) δ197.0, 138.4, 138.0, 129.5, 129.0, 128.8, 128.6, 127.8, 126.4, 68.6, 54.8, 30.0, 28.4. $[\alpha]_D$–95° (c=0.5, DMF).

EXAMPLE 66C

Alternate preparation of (4S)-4-(N,N-Dibenzylamino)-3-oxo-5-phenyl-pentanonitrile

To a flask was charged sodium amide (5.8 g, 134 mmol) under nitrogen followed by 100 mL of methyl t-butyl ether (MTBE). The stirred solution was cooled to 0° C. Acetonitrile (8.6 mL, 165 mmol) was added over 1 minute. This solution was stirred at 5°±5° C. for 30 minutes. A solution of (L)-N,N-dibenzylphenylalanine benzyl ester (25 g, 90% pure, 51.6 mmol) in 125 mL of MTBE was added over 15 minutes and the resulting heterogeneous mixture was stirred at 5°±5° C. until the reaction was complete (approx. 3 hours). The reaction was quenched with 100 mL of 25% w/v aqueous citric acid and warmed to 25° C. before separating the layers. The organics were then washed with 100 mL of H_2O. The aqueous layer was separated and the organics filtered and concentrated in vacuo. The residue was crystallized from 50 mL of ethanol to afford 13.8 g of the desired product as a white solid.

EXAMPLE 66D

(5S)-2-Amino-5-(N,N-(dibenzylamino)-4-oxo-1,6-diphenylhex-2-ene

To a 5° C. solution of the product of Example 66B (20 Kg, 29 moles) in 29 L tetrahydrofuran was added benzylmagnesium chloride (45 Kg, 2M in THF, 84.5 moles). The solution was warmed to ambient temperature and stirred until analysis showed no starting material. The solution was then recooled to 5° C. and 54 L of a 15% citric acid solution was slowly added to quench excess benzylmagnesium chloride. The organics were separated and washed with 27 L 10% sodium chloride and stripped to a solid. The product was stripped again from 27 L ethanol (200 proof) and then dissolved in 67 L hot ethanol (200 proof). After cooling to room temperature and stirring for 12 hours, the resulting product was filtered and dried in a vacuum oven at 30° C. to give 24 kg of the desired product. mp 101°–102° C., IR ($CDCl_3$) 3630, 3500, 3110, 3060, 3030, 2230, 1620, 1595, 1520, 1495, 1450 cm^{-1}, ^1H NMR (300 MHZ, $CDCl_3$H) d 9.8 (br s, 1H), 7.2 (m, 20H), 5.1 (s, 1H), 4.9 (br s, 1H), 3.8 (d, 2H, J=14.7 Hz),3.6 (d, 2H, J=14.7 Hz), 3.5 (m, 3H), 3.2 (dd, 1H, J=7.5, 14.4 Hz), 3.0 (dd, 1H, J=6.6, 14.4 Hz), ^{13}C NMR ($CDCl_3$) d 198.0, 162.8, 140.2, 140.1, 136.0, 129.5, 129.3, 128.9, 128.7, 128.1, 128.0, 127.3, 126.7, 125.6, 96.9, 66.5, 54.3, 42.3, 32.4. $[\alpha]_D$ –147° (c=0.5, DMF).

EXAMPLE 66E

(2S, 3S, 5S)-5-Amino-2-(N,N-dibenzylamino)-3-hydroxy-1,6-diphenyl-hexane

(i). A suspension of sodium borohydride (6.6 kg, 175 moles) in tetrahydrofuran (157 L) was cooled to less than –10°±5° C. Methanesulfonic acid (41,6 kg, 433 moles) was slowly added and the temperature kept below 0° C. during the addition. Once the addition was complete, a solution of water (6 L, 333 moles), the product of Example 66D (20 kg, 43 moles) and tetrahydrofuran (61 L) was slowly added while maintaining the temperature below 0° C. during the addition. The mixture was stirred for not less than 19 h at 0°±5° C.

(ii). To a separate flask was added sodium borohydride (6.6 kg, 175 moles) and tetrahydrofuran (157 L). After cooling to –5°±5° C., trifluoroacetic acid (24.8 kg, 218 moles) was added while maintaining the temperature below 15° C. The solution was stirred 30 min at 15°±5° C. and was then added to the reaction mixture resulting from step (i), keeping the temperature at less than 20° C. This was stirred at 20°±5° C. until reaction was complete. The solution was then cooled to 10°±5° C. and quenched with 3N NaOH (195 kg). After agitating with tert-butyl methyl ether (162 L), the organic layer was separated and washed one time with 0.5N NaOH (200 kg), one time with 20% w/v aqueous ammonium chloride (195 kg), and two times with 25% aqueous sodium chloride (160 kg). The organics were stripped to give the desired product as an oil which was used directly in the next step.

IR ($CHCl_3$) 3510, 3400, 3110, 3060, 3030, 1630, ^1H NMR (300 MHz, $CDCl_3$) δ7.2 (m, 20H), 4.1 (d, 2H, J=13.5 Hz), 3.65 (m, 1H), 3.5 (d, 2H, J=13.5 Hz), 3.1 (m, 2H), 2.8 (m, 1H), 2.65 (m, 3H), 1.55 (m, 1H), 1.30 (m, 1H), ^{13}C NMR (300 MHz, $CDCl_3$) δ140.8, 140.1, 138.2, 129.4, 129.4, 128.6, 128.4, 128.3, 128.2, 126.8, 126.3, 125.7, 72.0, 63.6, 54.9, 53.3, 46.2, 40.1, 30.2.

EXAMPLE 66F

(2S, 3S, 5S)-2,5-Diamino-3-hydroxy-1,6-diphenylhexane Dihydrochloride

To a stirred solution of [2S,3S,5S]-2-(N,N-dibenzylamino)-3-hydroxy-5-amino-1,6-diphenylhexane (20 kg, 43.1 mol)in methanol (250 kg) was added an aqueous solution of ammonium formate (13.6 kg, 215 mol) in water (23 kg) and an aqueous suspension of 5% wet palladium on carbon (4.0 kg, Degussa catalyst, E101 NE/W, approximately 50–60% water by weight). The suspension which resulted was heated to reflux (70°±10° C.) for 6 hours and then cooled to room temperature. The suspension was filtered through a bed of diatomaceous earth and the cake was washed with methanol (2×30 kg). The filtrate was concentrated via vacuum distillation to an aqueous oil. The aqueous residue was taken up in 1N NaOH (200 liters) and extracted with ethyl acetate (155 kg). The organic product layer was washed with a 20% aqueous sodium chloride solution (194 kg) and then with water (97 kg). The ethyl acetate product solution was then concentrated to an oil under vacuum distillation. Isopropanol (40 kg) was then charged to the residue and again the solution was concentrated to an oil with vacuum distillation. To the oil was charged isopropanol (160 kg) and concentrated aqueous hydrochloric acid (20.0 kg). The suspension/solution was then heated to reflux for 1 hour and then slowly cooled to room temperature. The slurry was then stirred for 12–16 hours. The slurry was filtered and the cake was washed with ethyl acetate (30 kg). The wet cake was resuspended in isopropanol (93 kg) and water (6.25 kg) and heated to reflux for 1 hour with stirring. The reaction mixture was then slowly cooled to room temperature and stirred for 12–16 hours. The reaction mixture was filtered and the wet cake was washed with isopropanol (12 kg). The solid was dried in a vacuum oven at 45° C. for approximately 24 hours to provide 7.5 kg of the desired product. ^1H NMR (300 MHz, CD_3OD) δ7.40–7.15 (m, 10H), 3.8 (ddd, 1H, J=11.4, 3.7, 3.7 Hz), 3.68–3.58 (m, 1H), 3.37 (ddd, 1H, J=7.5, 7.5, 3.5 Hz), 3.05–2.80 (m, 4H), 1.95–1.70 (m, 2H), ^{13}C NMR (300 MHz, CD_3OD) δ135.3,

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135.1, 129.0, 128.9, 128.7, 128.7, 127.12, 127.07, 67.4, 57.1, 51,6, 38.4, 35.5, 35.2.

EXAMPLE 67

(2S,3S,5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

EXAMPLE 67A

(2S,3S,5S)-2-(N,N-dibenzylamino)-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

To a stirred solution of (2S,3S,5S)-2-(N,N-dibenzylamino)-3-hydroxy-5-amino-1,6-diphenylhexane (10.0 g, 21,6 mmol)in tetrahydrofuran (200 mL) was added potassium carbonate (6.0 g, 43.2 mmol)in H_2O (200 mL). To this solution was added di-t-butyldicarbonate (5.64 g, 25.9 mmol) in tetrahydrofuran (10 mL). The solution which resulted was stirred at room temperature for 3 hours. N,N-dimethylethylenediamine (1 mL, 8.6 mmol) was added and the reaction mixture was stirred at room temperature for an additional hour. Ethyl acetate (400 mL) was added and the organic layer was separated and washed with 5% KH_2PO_4 (2×200 mL), water (1×200 mL), saturated $NaHCO_3$ (2×200 mL) and water (1×200 mL). The organic solution was then dried over sodium sulfate and concentrated under reduced pressure to provide the desired product as a light yellow oil. 300 MHz ^1H NMR ($CDCl_3$) δ1.40 (s,9H), 1.58 (s, 2H), 2.45–2.85 (m, 4H), 3.05 (m, 1H), 3.38 (d, 2H), 3.6 (m, 1H), 3.79 (m, 1H), 3.87 (d, 2H), 4.35 (s, 1H), 4.85 (s, broad, 1H), 7.0–7.38 (m, 20H).

EXAMPLE 67B

(2S,8S,5S)-2-amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

To a stirred solution of (2S,3S,5S)-2-(N,N-dibenzylamino)-3-hydroxy-5-(t-butyloxycarbonylamino)1,6-diphenylhexane (12 g, 21.3 mmol)in methanol (350 mL) was charged ammonium formate (8.05 g, 128 mmol, 6.0 eq) and 10% palladium on carbon (2.4 g). The solution was stirred under nitrogen at 60° C. for three hours and then at 75° C. for 12 hours. An additional amount of ammonium formate (6 g) and 10% palladium on carbon (1.5 g) was added as well as 1 mL of glacial acetic acid. The reaction was driven to completion within 2 hours at a reflux temperature. The reaction mixture was then cooled to room temperature and then filtered through a bed of celite. The filter cake was washed with methanol (75 mL) and the combined filtrates were concentrated under reduced pressure. The residue was taken up in 1N NaOH (300 mL) and extracted into methylene chloride (2×200 mL). The combined organic layers were washed with brine (250 mL) and dried over sodium sulfate. Concentration of the solution under reduced pressure provided the desired product as a light colored oil which slowly crystallized upon standing (5 g). Further purification of the product could be accomplished by flash chromatography (silica gel, 5% methanol in methylene chloride). 300 MHz ^1H NMR ($CDCl_3$) δ1.42 (s, 9H), 1.58 (m, 1H), 1.70 (m, 1H), 2.20 (s, broad, 2H), 2.52 (m, 1H), 2.76–2.95 (m, 4H), 3.50 (m, 1H), 3.95 (m, 1H), 4.80 (d, broad, 1H), 7.15–7.30 (m, 10H).

EXAMPLE 68

Alternative Preparation of (2S,3S,5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

EXAMPLE 68A

(5S)-2-(t-Butyloxycarbonylamino)-5-(N,N-dibenzylamino)-1,6-diphenyl-4-oxo-2-hexene

To 9.21 gm (20 mmol) of the resultant compound of Example 66D and 0.37 gm (3 mmol) 4-N,N-dimethylaminopyridine in 100 ml of methyl tert-butylether was added via syringe pump a solution containing 4.80 gm (22 mmol) di-tert-butyl dicarbonate in the same solvent (25 ml) over a period of 6 h. An additional amount (3 ml) of methyl tert-butylether was then added to complete the addition. After stirring at room temperature for 18 h the reaction mixture was cooled with the aid of an ice water bath. The resultant solid was collected by suction filtration and washed with cold (0° C.) methyl tert-butylether and hexane and dried under vacuum to give 9.9 gm of crude material as a white solid. The material thus isolated was dissolved in a minimal amount of dichloromethane and purified by flash chromatography on silica gel. Elution of the column with a mixture of hexane-ethyl acetate-dichloromethane (8:1:1) gave, after concentration of the appropriate fractions, 8.1 gm (72%) of the desired compound. Mp. 191°–193° C. $[\alpha]_D$183.7° (C=1.05, $CHCl_3$). ^1H NMR ($CDCl_3$, δH): 11,68 (bs, 1H), 7.05–7.47 (m, 20H), 5.28 (s,1H), 4.27 (d, J=16 Hz, 1H), 4.02 (d, J=16 Hz, 1H), 3.58 (m, 4H), 3.40 (m, 1H), 3.11 (m, 1H), 2.90 (m, 1H), 1.48 (s, 9H).

EXAMPLE 68B

Alternate preparation of (5S)-2-(t-Butyloxycarbonylamino)-5-(N,N-dibenzylamino)-1,6-diphenyl-4oxo-2-hexene

A suspension of (S)-2-amino-5-(N,N-dibenzylamino)1,6-diphenyl-4-oxo-2-hexene (100.0 g, 0.217 mol) in 15% ethyl acetate/hexanes (2 liters) under N_2 was warmed to about 40° C. The resulting solution was cooled to room temperature before adding 4.0 g (33 mmol) of N,N-dimethyl-4-aminopyridine and 49.7 g (0.228 mol) of di-tert-butyl dicarbonate. The reaction mixture was allowed to stir overnight at room temperature. (After approximately one hour, a white precipitate began to form.) The suspension was filtered and the precipitate was washed with hexanes to afford the desired product as colorless crystals. TLC: 25% ethyl acetate/hexanes R_f 0.38.

EXAMPLE 68C

(2S,3S,5S)-2-(N,N-Dibenzylamino)-5-(t-butyloxycarbonylamino)-3-hydroxyl-1,6-diphenylhexane.

A solution of the product of Example 68A (5 g, 8.9 mmol) in dichloromethane (1 00ml) and 1,4-dioxolane (100ml) was cooled to between −10° and −15° C. and treated dropwise with 1M BH_3THF (26.7ml, 26.7 mmol). The solution was stirred at this temperature for 3 hr. The clear solution was quenched with excess methanol (20ml) and stirred at room temperature for 30 min. The solvent was removed in vacuo.

The resulting white foam was dissolved in THF (75ml) and cooled to −40° C. A solution of LAH (9ml, 1M in THF, 9 mmol) was added dropwise. After 10 min. the solution was quenched with water followed by dilute aqueous HCl. The organics were removed and the aqueous layer extracted with ethyl acetate (3×20 ml). The combined organics were washed (saturated aqueous bicarbonate followed by brine), dried (Na_2SO_4H), filtered and evaporated to afford 4.9 g (99%) of the desired product as a white foam.

Alternatively, the white foam resulting from the BH_3THF reaction step was dissolved in MeOH (45ml), cooled to ±3° C. and treated portionwise with KBH_4 (1.44 g, 26.7 mmol). After addition of the last portion of KBH_4 the reaction was

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stirred for an additional 4 hours at +4° to +5° C. The solution was concentrated by 1/2 the volume in vacuo, diluted with 1/1 hexane-EtOAc (70 ml) and quenched (with cooling, maintain temp. <30° C.) by adding a 10% solution of $KHSO_4$ to pH=about 5. NaOH (15% aqueous) was added to pH=12–13. The insoluble salts were removed by filtration, and the filter cake washed 3 times with 7 ml 1/1 hexane/EtOAc. The filtrate and washes were transferred to a separatory funnel, diluted with 15 ml hexane and 15 ml H_2O. The organics were removed and the aqueous layer was extracted once with 20 ml (1/1H) hexane-EtOAc. The combined organics were washed (saturated brine), dried (Na_2SO_4H), filtered, and evaporated to afford 5.2 g of the desired product which was used without further purification in subsequent reactions. R_f 0.5 (25% EtOAc/hexane) ^1H NMR ($CDCl_3$) δ7.37–7.10 (m 20H); 6.78 (br, s, 1H); 4.62 (d, 1H); 4.50 (s, 1H); 4.18 (dd, 1H); 3.9 (d, 2H); 3.65 (dd, 2H); 3.40 (d, 2H); 3.00 (m, 2H); 2.77 (m, 1H); 1.39 (s, 9H). MS (El) m/e565 (M+H).

EXAMPLE 68D

(2S,3S,5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonyl)amino)-1,6-diphenylhexane.

A solution of the product from Example 68C (150 gm, 250 mmol) dissolved in absolute EtOH (2 liters) was treated with 10% Pd/C (18 gm, pre-wetted), followed by addition of ammonium formate (78.6 gms, 1.25 moles) dissolved in H_2O (200ml). The resulting mixture was stirred at reflux for 2.5 hours. The mixture was cooled to room temperature and filtered through a pad of infusorial earth (20 g). The filter cake was washed 3 times with EtOH (70ml each). The filtrate was concentrated in vacuo. The residue was dissolved into EtOAc (1 L) and washed (1N NaOH, followed by H_2O, followed by brine), dried (Na_2SO_4H), filtered and concentrated/n vacuo. to a constant weight of 95 gms. (99.2% of theory). The light yellow solid (91.5 gm of the 95 gm) was slurried in hot heptane (600 ml) (steam bath) and treated with isopropanol (45ml), and swirled to effect solution. The solution was allowed to slowly cool to room temperature over 3 hours, kept at room temperature for 2 more hours and filtered. The filter cake was washed 10 times with 9/1 hexane-isopropanol (30ml each) to give the desired product as an off-white finely crystalline solid which was dried to constant weight of 57.5 gm.

The crude product (20 gm) was recrystallized from hot 140 ml heptane/17 ml isopropanol. After letting the solution cool slowly to room temperature, the mixture was let stand at room temperature for 2 hours and then filtered. The filter cake was rinsed (5×15 ml (8/1) heptane/isopropanol) and dried to a constant weight of 18.5 gm.

EXAMPLE 69

Alternative Preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

EXAMPLE 69A

(2S,3S,5S)-5-(t-Butyloxycarbonylamino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

The product of Example 68D (6.0 g, 15.6 mmoles) was dissolved in 60 mL of DMF under nitrogen atmosphere. To this stirred solution at room temperature was added 5-(p-nitrophenyloxycarbonyloxymethyl)thiazole (4.67 g, 15.6 mmole) and the resulting solution was stirred for 4 h. The solvent was removed under reduced pressure by rotary evaporation and the residue dissolved in 150 mL EtOAc. This solution was washed with 5×75 mL 1N NaOH solution, 100 mL brine, dried over Na_2SO_4. The solvent was removed to afford 8.02 g of a slightly yellowish oil. This material was crystallized from 30 mL EtOAc and 40 mL hexane to afford 6.53 g (80%) of the desired product as a white solid. mp 118°–120° C. H ^{1}NMR ($CDCl_3$) δ8.79 (s, 1H), 7.83 (s, 1H), 7.30–7.15 (m, 8H), 7.08 (m, 2H), 5.23 (s, 2H),5.14 (d, 1H, J=9 Hz), 4.52 (m, 1H), 3.92–3.72 (m, 3H), 3.65 (m, 1H), 2.85 (d-apparent,2H, J=7.5 Hz), 2.72 (d-apparent, 2H, J=7 Hz), 1,61 (m, 2H), 1.38 (s, 9H). CIMS m/z (526) $(M+H)^+$, 543 $(M+18H)^+$.

EXAMPLE 69B

(2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

The product of Example 69A (6.43 g, 12.23 mmoles) was dissolved in 25 mL dioxane at room temperature under nitrogen atmosphere. To this stirred solution was added 20.25 mL of 4N HCl in dioxane, and after approximately 10 min a thick precipitate formed. An additional 10 mL of dioxane was added to loosen up the slurry. This mixture was stirred for 1 h and then filtered. The filter cake of the product bis-HCl salt was washed with 20 mL dioxane, air dried, and then dissolved in 175 mL water. To this solution was added 175 mL ethyl acetate and the two phase mixture rapidly stirred. The pH of this mixture was adjusted to pH=10 by the dropwise addition of 3N NaOH to the rapidly stirred mixture. The organic layer was isolated, washed with brine (150 mL), and dried over Na_2SO_4. The solvent was removed to afford 5.18 g (99%) of the desired product as a clear oil. H^{1}NMR ($CDCl_3$) δ8.81 (s, 1H), 7.87 (s, 1H), 7.35–7.05 (m, 10H), 5.33 (d, 1H, J=9.3 Hz), 5.28 (m,2H), 3.81 (m, 1H), 3.72 (m, 1H), 3.01 (m, 1H), 2.88 (m, 2H) 2.78 (dd, 1H, J=13.5, 5.1 Hz), 2.39 (dd, 1H, J=9.0, 4.5 Hz), 1.57–1.30 (m, 2H). CIMS m/z 426 $(M+H)^+$.

EXAMPLE 69C

(2S,3S,5S)-5-(N-(N-((N-Methyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl))amino)-1,6-diphenyl-3-hydroxyhexane

N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine (4.13 g, 13.18 mmole) and hydroxybenztriazole (2.23 g, 16.48 mmoles) were dissolved in 70 mL THF and then dicyclohexyl-carbodiimide(2.71 g, 13.18 mmoles) was added in one portion to the stirred solution under nitrogen atmosphere. This mixture was stirred for 4h at room temperature and then filtered to remove dicyclohexylurea precipitate. The product of Example 69B (5.1 g, 11.99 mmoles) was dissolved in 100 mL THF under nitrogen atmosphere. To this stirred solution was added the filtrate of HOBT-active ester and the resulting solution was stirred at room temperature for 4 h, and the solvent removed via rotary evaporation. The residue was dissolved in 150 mL ethyl acetate and washed with 2×100 mL 1N NaOH, 100 mL brine, 100 mL of 1% w/w aqueous $KHSO_4$ and the solvent was removed by rotary evaporation to afford a residue. The residue was dissolved in 175 mL 1N HCL, and the solution filtered to remove the small quantity of dicyclohexylurea. The filtrate solution was added to 175 mL ethyl acetate and the two phase mixture rapidly mixed. The pH of this rapidly stirred mixture was adjusted to pH=7 by dropwise addition of cold 3N NaOH. The organic layer was isolated, washed

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with 100 mL brine, dried over Na_2SO_4, filtered, and the solvent was removed to afford 8.6 g of a colorless foam. This material was crystallized from 42 mL EtOAc and 21 mL hexane to give 7.85 g of the desired product as a white solid. mp=122°–123° C. CIMS m/z 721 $(M+H)^+$.

EXAMPLE 70

Alternative Preparation of (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Alternative A

The product of Example 66F (9.5 g, 33.4 mmol) and phenylboronic acid (4.1 g, 33.6 mmol) were combined in toluene (150 mL) and refluxed for 2.5 hours with azeotropic water removal (Dean-Stark trap). Toluene (100 mL) was distilled out at atmospheric pressure, then the remaining toluene was removed under vacuum, to provide a yellow syrup which was dissolved in DMF (50 mL) and cooled to –60° C. A solution of 5-(p-nitrophenyloxycarbonyloxy-methyl)thiazole (9.5 g, 33.5 mmol) in DMF (50 mL) was added over 45 minutes. The resulting mixture was stirred for 8 hours at –55±5° C., then 14 hours at –25° C., then was allowed to warm to room temperature. The reaction mixture was diluted with 1N HCl (250 mL) and washed with CH_2Cl_2 (2×80 mL). The combined organic layers were back-extracted with 1N HCl (60 mL). The combined aqueous HCl layers were cooled in an ice-bath to 2° C, and conc. (37%) HCL (30 mL) was added over 5 minutes. The desired product (bis HCl salt) began to precipitate within 30 minutes. The slurry was stirred 3 hours at 2°–5° C., then the product (bis HCl salt) was collected by filtration and dried in a vacuum oven at 55°–60° C. Yield 11.4 g (68%).

Second crop recovery:

The HCl mother liquors were stirred with ethyl acetate (190 mL) and neutralized to pH 9–10 with aqueous K_2CO_3 (200–300 g of 25% w/w K_2CO_3 was required). The ethyl acetate layer was concentrated under vacuum to an oil which was redissolved in 1N HCl (90 mL) and washed with methylene chloride (45 mL). The aqueous layer was cooled to 2° C. Conc. (37%) HCl (9.0 mL) was added to precipitate a second crop. After stirring for 1–3 hours at 2°–5° C., the solid was collected by filtration and dried in a vacuum oven at 55°–60° C. Yield 2.1 g (12.6%).

Neutralization of Bis HCl Salt:

The bis HCl salt (10.66 g, 21.4 mmol, mixture of first and second crops) was stirred with CH_2Cl_2 (110 mL) and 5% aqueous $NaHCO_3$ (110 mL) until all solids dissolved (2 hours). The aqueous layer was separated and extracted with another 50 mL CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 (10 g), filtered and concentrated under vacuum at <40° C. to an oil. The oil was dried on a vacuum pump to give the title compound as a yellow foam, 9.1 g (100%).

Alternative B

The product of Example 66F (15.0 g, 0.053 mole) was dissolved in DMF (75 mL). Triisopropylborate (24.4 mL, 0.105 mole) was added and stirred at ambient temperature for approximately 1.5 hours. The solution was cooled to –10° C. and a solution of 5-(p-nitrophenyloxycarbonyloxymethyl)thiazole (15.0 g, 0.054 mole)in DMF (75 mL) was added over 80 minutes. The reaction was stirred for approximately 1 hour at –10° C., then was diluted with methylene chloride (250 mL) and quenched with a mixture of triethanolamine (24.8 g) and 5% aqueous sodium bicarbonate (300 mL). The biphasic mixture was stirred for 1 hour, then the layers were separated and the aqueous was extracted with another portion of methylene chloride (50 mL). The combined organic layers were extracted with 1N HCl (1×390 mL, then 1×95 mL). The acid layers were combined, cooled in an ice-bath, and further acidified with conc. HCl (50 mL) which produced a white slurry of product. The slurry was stirred for approximately 1 hour at 2° C. The desired product bis HCl salt) was collected by filtration and dried at 55° C. in a vacuum oven. Yield 18.5 g (70%).

EXAMPLE 71

Alternative Preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

To a solution of the product of Example70 (9.1 g, 21.4 mmol), HOBT (3.6 g, 23.5 mmol) and N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)-L-valine (7.37 g, 23.5 mmol)in THF (170 mL) was added DCC (4.85 g, 23.5 mmol). The solution was stirred at ambient temperature for 16 hours (DCU precipitates). THF was removed under vacuum and the resulting paste was stirred with cold 1N HCl (106 mL at 5° C.) for 3 hours to dissolve the crude product. The DCU was removed by filtration and the filter cake was washed with 1N HCl (30 mL). KH_2PO_4 (3.2 g) was dissolved in the combined HCl filtrates. The solution was mixed with ethyl acetate (80 mL) and neutralized to pH 7 with aqueous NaOH (60.3 g of 10% w/w NaOH). The aqueous layer was extracted with another 25 mL ethyl acetate and the combined ethyl acetate extracts were washed with aqueous $NaHCO_3$ (2×37 mL of 5% w/w $NaHCO_3H$). The organic layer was dried with Na_2SO_4 (13 g), filtered, and concentrated under vacuum at ≦45° C. The residue was dissolved in a 1:1 ethyl acetate/heptane mixture (200 mL) at 70° C. The solution was allowed to cool slowly and stirred overnight at room temperature to provide a thick slurry. The product was collected by filtration and washed with 1:1 ethyl acetate/heptane (20 mL). The product was dried briefly at 55° C. in a vacuum oven to obtain an approximate weight prior to the second crystallization (12.85 g, 83%). A second crystallization from 144 mL of 2:1 ethyl acetate/heptane (dissolved at ~70° C., then stirred at room temperature 12 hours) produced a thick slurry of fine white solid. The product was collected by filtration and washed with 15 mL 2:1 ethyl acetate/heptane, then dried in a vacuum oven at 55° C. for 2 days to give the desired product. Yield 11.9 g (77%).

EXAMPLE 72

Alternate Preparation of ((5-Thiazolyl)methyl)-(4-nitrophenyl)carbonate

EXAMPLE 72A

2-Amino-5-(ethoxycarbonyl)thiazole Hydrochloride

To a –10° C. solution of potassium tert-butoxide (110 g, 0.98 mol) in THF (1.9 L) was added a solution of ethyl chloroacetate (100 mL, 0.934 mol) and ethyl formate (75 mL, 0.928 mol)in THF (400 mL) dropwise over 2 hours, with good mechanical stirring. The thick solution was stirred another 2 hours at ca. –1° C. then the reaction was quenched by addition of a solution of NaCl (150 g) in 1N HCL (750 mL). The mixture was allowed to warm to 20° C. and the lower aqueous layer (containing some precipitated salt) was separated. The organic layer was stripped under vacuum on a rotary evaporator. The oil was redissolved in 500 mL ethyl acetate, dried with 75 g Na_2SO_4 for 1 hour, filtered and

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concentrated under vacuum (40°–50° C. bath temperature) to an oil. The resulting crude chloroaldehyde (161 g) and thiourea (70 g, 0.92 mol) were dissolved in THF (2 L) and warmed to gentle reflux (60° C.). The thiourea dissolved during warming, and within 20 minutes, product precipitated from solution. After 100 minutes the suspension was allowed to cool to room temperature, then was cooled in an ice-bath for 1 hour. The product was collected on a fritted Buchner funnel and washed with 2×100 mL cold THF, then dried overnight in a vacuum oven at 50° C. Yield: 122 g of title compound as a tan-colored solid, m.p. 182°–185° C. (dec.). ^{1}H NMR (DMSO-d_6H) δ7.86 (s, 1H), 4.19 (q, 2H), 1.21 (t, 3H). ^{13}C NMR (DMSO-d_6) δ171.9, 160.4, 140.4, 114.4, 61.1, 14.2.

EXAMPLE 72B

2-Amino-5-(ethoxycarbonyl)thiazole

To a −10° C. solution of potassium tert-butoxide (150 g, 1.3 mol) in THF (1.35 L) was added a solution of ethyl chloroacetate (139 mL, 1.3 mol) and ethyl formate (103 mL, 1.27 mol) in THF (150 mL) dropwise over 75 minutes, with good mechanical stirring. A THF rinse (25 mL) was added over 5 minutes. The thick solution was stirred another 3 hours at ca. −5° to 0° C., then the reaction was quenched by addition of a solution of NaCl (240 g) and conc. HCl (90 mL) in water (960 mL). The mixture was allowed to warm to 15° C. and the lower aqueous layer was discarded. Thiourea (97 g, 1.27 mol) was dissolved in the crude THF solution of chloroaldehyde. The solution was warmed to 65° C. and refluxed for 1 hour, then cooled to 30° C. Addition of a solution of K_2CO_3 (88 g, 0.64 mol) in 1500 mL water produced two layers (aqueous pH=7H). The THF was removed under vacuum at ≦45° C., causing the product to precipitate as a yellow solid. The slurry was cooled to 15° C., and the product was collected on a fritted Buchner funnel and washed with 3×200 mL water, then dried 24 hours in a vacuum oven at 55° C. to provide 151 g of title compound as a yellow solid, m.p. 155°–158° C. ^{1}H NMR (DMSO-d_6) δ7.8 (br s, 2H, NH_2H), 7.62 (s, 1H), 4.13 (q, 2H), 1.18 (t, 3H). ^{13}C NMR (DMSO-d_6) δ173.4, 161.3, 147.9, 114.5, 60.1, 14.3..

EXAMPLE 72C

5-(Ethoxycarbonyl)thiazole

A solution of 2-amino-5-(ethoxycarbonyl)thiazole (50 g, 0.29 mmol) in a mixture of DMF (83 mL) and THF (31 7 mL) was added dropwise over 87 minutes to a stirred 41° C. solution of isoamyl nitrite (59 mL, 0.44 mol) in DMF (130 mL). A maximum temperature of 60° C. was observed during the exothermic addition. After another 40 minutes the THF was removed under vacuum at 45° C. The concentrated DMF solution was cooled to 25° C. and diluted with toluene (420 mL) and water (440 mL). The toluene layer was extracted with 3×120 mL water, then dried with Na_2SO_4 (50 g) for 1 hour. After filtration the toluene layer was stripped on a rotary evaporater at 50° C. bath temperature, then on a vacuum pump at 21° C. The crude residue containing the title compound weighed 65.6 g. This material was used directly in the next step. A sample of similarly prepared material was purified by column chromatography to give a yellow oil. ^{1}H NMR ($CDCl_3$) δ8.95 (s, 1H), 8.51 (s, 1H), 4.39 (q, 2H), 1.40 (t, 3H). ^{13} NMR ($CDCl_3$) δ161.0, 157.9, 148.6, 129.8, 61,6, 14.1.

EXAMPLE 72D

5-(Hydroxymethyl)thiazole

To a slurry of lithium aluminum hydride (9.0 g) in THF (633 mL) was added a solution of crude 5-(ethoxycarbonyl)thiazole (65.6 g from Example 72C) in THF (540 mL) over 95 minutes at 0°–5° C. After an additional 25 minutes, the reaction was quenched at 5° C. by sequential addition of water (8.1 mL), 15% NaOH (8.1 mL), and water (24.3 mL). After drying with Na_2SO_4 (44 g) for 2 hours, the slurry was filtered, and the filter cake was washed with 100 mL THF. The combined filtrates were concentrated under vacuum at 45° C. to a brown oil (39 g). The oil was fractionally distilled through a short-path apparatus. The product fractions distilled at 97°–104° C. vapor temperature at 3–5 mm, providing 20.5 g of the title compound as a turbid orange oil. ^{1}H NMR ($CDCl_3$) δ8.74 (s, 1H), 7.72 (s, 1H), 4.89 (s, 2H), 3.4 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ153.4, 140.0, 139.5, 56.6.

EXAMPLE 72E

5-(p-Nitrophenyoxycarbonyloxymethyl)thiazole Hydrochloride

Distilled 5-(hydroxymethyl)thiazole (14.1 g, 123 mmol) and triethylamine (17.9 mL, 129 mmol) were dissolved in ethyl acetate (141 mL) and cooled to −1° C. (ice/salt bath). A solution of 4-nitrophenyl chloroformate (26.0 g, 129 mmol) dissolved in ethyl acetate (106 mL) was added dropwise over 50 minutes at an internal temperature of 0°–4° C. An ethyl acetate flask rinse (20 mL) was also added. Salts precipitated from solution throughout the addition. The yellow mixture was stirred another 1 hour 45 minutes at 0°–2° C., then a solution of dilute HCl (3.1 g, 31 mmol of conc. HCl in 103 mL water) was added at once. The mixture was stirred for 0.5 hours while warming to 15° C., then stirring was stopped. The organic layer was washed twice with aqueous 5% K_2CO_3 solution (2×70 mL), then dried with Na_2SO_4 (30 g). After filtration the solution was concentrated under vacuum on a rotary evaporater (bath temperature of 41° C.) to a brown oil (38 g). The crude 5-(p-nitrophenyoxycarbonyloxymethyl)-thiazole was dissolved in ethyl acetate (282 mL), then cooled in an ice bath to 2° C. Dry HCl gas (7.1 g, 195 mmol) was bubbled in slowly over 50 minutes (temperature 2°–4° C.). After stirring for another 1 hour 45 minutes at 2°–4° C., the solid precipitate was collected on a sintered glass funnel under a nitrogen blanket and the flask was washed out with 50 mL cold ethyl acetate which was used to rinse the filter cake. The cake was dried on the funnel under strong nitrogen purge for 15 minutes then dried in a vacuum oven at 50° C. with a nitrogen purge to provide 29.05 g of the title compound as tan powder, m.p. 131°–135° C. (dec.). ^{1}H NMR (DMSO-d_6) δ9.21 (d, 1H), 8.27 (m, 2H), 8.06 (d, 1H), 7.52 (m, 2H), 5.54 (s, 2H). ^{13}C NMR (DMSO-d_6) δ157.3, 155.2, 151.8, 145.3, 143.7, 131.9, 125.5, 122.7, 62.1.

EXAMPLE 72F

5-(p-Nitrophenyoxycarbonyloxymethyl)thiazole

5-(p-Nitrophenoxycarbonyloxymethyl)thiazole hydrochloride (3.0 g) was slurried in ethyl acetate (30 mL) and cooled to 10°–15° C. A solution of 5% aqueous potassium carbonate (30 mL) was added with rapid stirring. After 15 minutes, stirring was stopped and the aqueous layer was separated. The organic layer was dried with Na_2SO_4 (3 g), filtered, and solvent was distilled under vacuum to give 2.49 g of the title compound as a brown syrup which slowly

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solidified, m.p. 62°–64° C. ^{1}H NMR ($CDCl_3$) δ8.90 (d, 1H), 8.29 (m, 2H), 8.01 (d, 1H), 7.39 (m, 2H), 5.52 (s, 2H). ^{13}C NMR ($CDCl_3$) δ155.4, 155.2, 152.2, 145.4, 144.9, 130.6, 125.3, 121,6, 61.9.

EXAMPLE 73

Alternative Preparation of N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine

EXAMPLE 73A

Thioisobutyramide

To a 1 liter three neck round bottom flask equipped with mechanical stirrer, nitrogen atmosphere, condensor, thermocouple and 15° C. water bath was charged (26.0 g, 0.298 mols)isobutyramide followed by (19.9 g, 0.045 mols) phosphorous pentasulfide and 375 mls THF. This solution was stirred at 20°±5° C. for 3 hours, then was warmed to 60° C. and stirred an additional 3 hours. The THF was removed under vacuum with a 50° C. bath temperature to afford a yellow oil. This oil was neutralized with a solution of 5 g NaOH, 10 g NaCl and 90 g water. Next the product was extracted into EtOAc (2×250 mls) and the combined organics reduced under vacuum to an oil. The oil was dissolved in 50 mls THF and again the solvent was removed under vacuum to give the desired product as a yellow oil. (yield approx. 27 grams, 88%).

EXAMPLE 73B

2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole

The thioisobutyramide resulting from Example 73A was dissolved in 70 mls THF and added slowly to a solution of (34.1 g, 0.27 mols) 1,3-dichloracetone in 40 mls THF. A 10 ml rinse of THF was used to completely transfer the thioamide. The reaction was carried out in a 250 ml flask with mechanical stirring under nitrogen atmosphere. The reaction temperature was maintained below 25° C. during addition with a 15°±5° C. bath. The bath was kept in place for 1 hour after which it was removed and the reaction stirred for 18 hours. Next this stirred chloromethyl-thiazole solution was added to 376 mls (4.37 mols) 40% aqueous methylamine solution at 15° C. in a 1 liter flask. The temperature was maintained below 25° C. during addition. After half an hour the bath was removed and the reaction stirred for 3 hours at ambient temperature. The solvent was removed under vacuum with a 50° C. bath to an end volume of 310 mls. The residue was then basified with 50 g 10% NaOH to pH 12 and extracted into methylene chloride (2×160 mls). The combined organics were then washed with 1×150 g of 20% ammonium chloride followed by 1×90 g of 20% ammonium chloride. The combined aqueous washes were then back extracted with 150 mls methylene chloride. The combined product methylene chloride layers were then extracted with 100 g of a solution of 25 g conc. HCl and 75 g water. This acidic product solution was then washed with 135 mls methylene chloride. Next the acidic product solution was cooled, then neutralized with 100 g 20% NaOH solution. The product was extracted from this mixture with methylene chloride (2×135 mls). The solvent was removed under vacuum to afford the desired product as an amber oil. (yield approx. 28 grams)

EXAMPLE 73C

N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino/carbonyl)-L-valine Methyl Ester

Into a 500 ml 3-neck round bottom flask equipped with mechanical stirrer, nitrogen atmosphere, thermocouple, heating mantle and condenser was charged the product of Example 73B (28.1 g, 0.165 mols), phenoxycarbonyl-(L)-valine (41.5 g, 0.165 mol) and 155 ml toluene. This solution was warmed to reflux (110° C.) and stirred for three hours, then cooled to 20°±5° C. and washed with 2×69 ml 10% citric acid followed by 1×69 ml water, 1×116 mls 4% sodium hydroxide, 1×58 ml 4% sodium hydroxide and finally 1×58 ml water. The organic product solution was then treated with 3 grams of activated carbon at reflux for 15 minutes, filtered through infusorial earth to remove carbon, and the carbon/infusorial earth cake was washed with 25 ml hot toluene. Next the solvent was removed to afford a brown oil which solidified upon cooling. This brown solid was dissolved with warming in 31 ml EtOAc and 257 ml heptane at 60°±5° C. This solution was slowly cooled to 25° C., stirred 12 hours, cooled further to 0° C., and stirred 3 hours. The crystals were collected by filtration and washed with 50 ml 1:9 EtOAc/Heptane. The solid was dried in a 50° C. vacuum oven for 12 hours to afford 41.5 grams of the desired product as a tan-colored solid (76.9%).

EXAMPLE 73D

N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine

To a one liter three neck flask was charged the product of Example 73C (50 g, 0.153 mol), lithium hydroxide monohydrate (13 g, 0.310 mol), 200 ml THF and 190 ml water. This hazy solution was stirred for 2 hours. The reaction was quenched with a solution of conc. HCl (32.4 g, 0.329 mol) in 65 mL water, the THF was removed under vacuum and the product extracted into methylene chloride (3×210 ml). (NOTE: If necessary, the pH of the aqueous layer should be adjusted to maintain pH 1–4 during the extractions.) The combined organics were then dried with 50 g sodium sulfate, filtered with a 150 ml methylene chloride rinse of the sodium sulfate, and the solvent was removed under vacuum. The product was dissolved in 450 ml THF and again the solvent was removed. Next the product was dissolved in 475 ml THF containing 0.12 g butylated hydroxytoluene (BHT) for storage. If desired, the solvent can be removed under vacuum and the residual syrup dried in a vacuum oven at 55° C. to provide a glassy solid.

Fluorogenic Assay for Screening Inhibitors of HIV Protease

The inhibitory potency of the compounds of the invention can be determined by the following method.

A compound of the invention is dissolved in DMSO and a small aliquot further diluted with DMSO to 100 times the final concentration desired for testing. The reaction is carried out in a 6×50 mm tube in a total volume of 300 microliters. The final concentrations of the components in the reaction buffer are: 125 mM sodium acetate, 1M sodium chloride, 5 mM dithiothreitol, 0.5 mg/ml bovine serum albumin, 1.3 μM fluorogenic substrate, 2% (v/v) dimethylsulfoxide, pH 4.5. After addition of inhibitor, the reaction mixture is placed in the fluorometer cell holder and incubated at 30° C. for several minutes. The reaction is initiated by the addition of a small aliquot of cold HIV protease. The fluorescence intensity (excitation 340 nM, emmision 490 nM) is recorded as a function of time. The reaction rate is determined for the first six to eight minutes. The observed rate is directly proportional to the moles of substrate cleaved per unit time. The percent inhibition is 100×(1-(rate in presence of inhibitor)/(rate in absence of inhibitor)).

Fluorogenic substrate: Dabcyl-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gin-EDANS wherein DABCYL=4-(4-dimethylaminophenyl)azobenzoic acid and EDANS=5-((2-aminoethyl)amino)-naphthalene-1-sulfonic acid.

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Table 1 shows the inhibitory potencies of compounds of the invention against HIV-1 protease.

TABLE 1

Compound of Example	Percent Inhibition	Inhibitor Concentration (nanomolar)
1	79	0.5
3	70	0.5
4	72	0.5
5	79	0.5
6	75	0.5
7	74	0.5
9	64	0.5
10	56	0.5
11	71	0.5
12	72	0.5
13	46	0.5
14	61	0.5
15	57	0.5
17	66	0.5
18	80	0.5
19	70	0.5
20	86	0.5
26	71	0.5
27	82	0.5
28	68	0.5
39	63	0.5
41	75	0.5
42	70	0.5
44	68	0.5
45	50	0.5
46	46	0.5
47	73	0.5
48	69	0.5
49	55	0.5
50	61	0.5
51	69	0.5
52	71	0.5
53	75	0.5
54	50	0.5
55	54	0.5
56	66	0.5
57	64	0.5
58	49	0.5
59	39	0.5
60	44	0.5
61	69	0.5
62	54	0.5
63	61	0.5
64	52	0.5
65	70	0.5

Antiviral Activity

The anti-HIV activity of the compounds of the invention can be determined in MT4 cells according to the procedure of Kempf, et. al. (*Antimicrob. Agents Chemother.* 1991, 35, 2209H). The IC_{50} is the concentration of compound that gives 50% inhibition of the cytopathic effect of HIV. The LC_{50} is the concentration of compound at which 50% of the cells remain viable.

Table 2 shows the inhibitory potencies of compounds of the invention against HIV-1_{3B} in MT4 cells.

TABLE 2

Compound of Example	IC_{50} (micromolar)	LC_{50} (micromolar)
1	0.025–0.040	55
3	0.041–0.075	52
4	0.17–0.32	29
5	0.003–0.009	51
6	0.006–0.014	100
7	0.076–0.131	56
8	0.057–0.095	97

TABLE 2-continued

Compound of Example	IC_{50} (micromolar)	LC_{50} (micromolar)
9	0.080–0.10	62
10	0.054–0.071	55
11	0.017–0.132	60
12	0.053–0.106	>100
13	0.056–0.088	56
14	0.14–0.22	>100
15	0..43–0.67	41
17	0.23–0.31	19
18	0.039–0.046	62
19	0.022–0.048	87
20	0.011–0.014	55
26	0.007–0.011	28
27	0.011–0.012	57
28	0.11–0.12	18
39	0.073–0.077	22
41	0.015–0.02	100
42	0.073–0.08	>100
44	0.12–0.16	19
45	0.036–0.040	19
46	0.10–0.17	61
47	0.009–0.024	25
48	0.09–0.11	>100
49	0.081–0.13	38
50	0.15–0.27	>100
51	0.045–0.049	48
52	0.035–0.042	26
53	0.032–0.073	59
54	0.11–0.17	19
55	0.14–0.22	17
56	0.05–0.067	100
57	0.035–0.048	>100
58	0.03–0.046	18
59	0.11–0.13	18
60	0.34–0.51	17
61	0.15–0.22	25
62	0.69–1.0	17
63	0.13–0.18	45
64	0.10–0.13	>100
65	0.12–0.20	>100

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate (isethionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic

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Preferred salts of the compounds of the invention include hydrochloride, methanesulfonate, sulfonate, phosphonate and isethionate.

The compounds of the present invention can also be used in the form of esters. Examples of such esters include a hydroxyl-substituted compound of formula A or A1 or A2 which has been acylated with a blocked or unblocked amino acid residue, a phosphate function, a hemisuccinate residue, an acyl residue of the formula R*C(O)— or R*C(S)— wherein R* is hydrogen, loweralkyl, haloalkyl, alkoxy, thioalkoxy, alkoxyalkyl, thioalkoxyalkyl or haloalkoxy, or *an acyl residue of the formula* R_a—$C(R_bH)(R_dH)$—$C(O)$— or R_a—$C(R_bH)(R_dH)$—C(S)— wherein R_b and R_d are independently selected from hydrogen or loweralkyl and R_a is —N—$(R_eH)(R_fH)$, OR_e or —SR_e wherein R_e and R_f are independently selected from hydrogen, loweralkyl and haloalkyl, or an amino-acyl residue of the formula $R_{180}NH(CH_2H)_2NHCH_2C(O)$— or $R_{180}NH(CH_2H)2OCH_2C(O)$— wherein R_{180} is hydrogen, loweralkyl, arylalkyl, cycloalkylalkyl, alkanoyl, benzoyl or an a-amino acyl group. The amino acid esters of particular interest are glycine and lysine; however, other amino acid residues can also be used, including those wherein the amino acyl group is —$C(O)CH_2NR_{200}R_{201}$ wherein R_{200} and R_{201} are independently selected from hydrogen and loweralkyl or the group —$NR_{200}R_{201}$ forms a nitrogen containing heterocyclic ring. These esters serve as pro-drugs of the compounds of the present invention and serve to increase the solubility of these substances in the gastrointestinal tract. These esters also serve to increase solubility for intravenous administration of the compounds. Other prodrugs include a hydroxyl-substituted compound of formula A or A1 or A2 wherein the hydroxyl group is functionalized with a substituent of the formula —$CH(R_gH)OC(O)R_{181}$ or —$CH(R_gH)OC(S)R_{181}$ wherein R_{181} is loweralkyl, haloalkyl, alkoxy, thioalkoxy or haloalkoxy and R_g is hydrogen, loweralkyl, *haloalkyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl* or dialkylaminocarbonyl. Such prodrugs can be prepared according to the procedure of Schreiber (Tetrahedron Lett. 1983, 24, 2363H) by ozonolysis of the corresponding methallyl ether in methanol followed by treatment with acetic anhydride.

The prodrugs of this invention are metabolized in vivo to provide the hydroxyl-substituted compound of formula A or A1 or A2. The preparation of the prodrug esters is carried out by reacting a hydroxyl-substituted compound of formula A or A1 or A2 with an activated amino acyl, phosphoryl, hemisuccinyl or acyl derivative as defined above. The resulting product is then deprotected to provide the desired pro-drug ester. Prodrugs of the invention can also be prepared by alkylation of the hydroxyl group with (haloalkyl)esters, transacetalization with bis-(alkanoyl)acetals or condensation of the hydroxyl group with an activated aldehyde followed by acylation of the intermediate hemiacetal.

The compounds of the invention are useful for inhibiting retroviral protease, in particular HIV protease, in Vitro or in vivo (especially in mammals and in particular in humans). The compounds of the present invention are also useful for the inhibition of retroviruses in vivo, especially human immunodeficiency virus (HIV). The compounds of the present invention are also useful for the treatment or prophylaxis of diseases caused by retroviruses, especially acquired immune deficiency syndrome or an HIV infection in a human or other mammal.

Total daily dose administered to a human or other mammal host in single or divided doses may be in amounts, for example, from 0.001 to 300 mg/kg body weight daily and more usually 0.1 to 10 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, *time of administration, route of administration,* rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. *In addition, fatty acids* such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically accept-

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able and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976H), p. 33 et seq.

One preferred dosage form for the compounds of the invention comprises a solid dosage form for oral administration comprising a pharmaceutically acceptable adsorbent to which is adsorbed a mixture of (1H) a pharmaceutically acceptable organic solvent or a mixture of two or more pharmaceutically acceptable organic solvents, (2H) a compound of the invention in the amount of from about 10% to about 40% by weight and (3) a total of from about 0.2 molar equivalents to about 2 molar equivalents (based on the compound of the invention) of a pharmaceutically acceptable acid. This composition is filled into hard gelatin capsules for administration. The preparation of a specific example of this type of dosage form is described below.

Solid-filled capsule Dosage Form Preparation

Propylene glycol (USP, 139 mL) and ethanol (dehydrated, USP, 200 proof, 139 mL) were mixed in a stainless steel or glass container. Hydrochloric acid (reagent grade, 20 mL) was added and mixed well. To this solution was added ascorbic acid (21 g) and the mixture was stirred until it was clear. The product of Example 1U (200 g) was slowly added to the solution and mixing was continued until the solution was clear. Cremophore® EL (polyoxyethyleneglycerol oxystearate, 41 g) and polysorbate 80, NF (41 g) were added with mixing.

Microcrystalline cellulose, NF (139 g) and silicon dioxide, NF (Syloid 244, pharmaceutical grade, 209 g) were charged into a Hobart mixer and mixed for 3–5 minutes. The above solution was added dropwise to the dry mixture in the Hobart mixer while mixing at slow speed. This mixture was massed until granular.

The wet granulation was screened through an 8 mesh screen. The screened granulation was spread on paper-lined trays and dried in a tray dryer or a fluidbed dryer (20°–35° C.) until the loss on drying was not more than 12%.

The concentration of the product of Example 1U (mg/g of granulation) in the granulation was determined by HPLC analysis. Capsules (gelatin, No. 00, iron gray opaque) were filled with the appropriate amount of the dried granulation to provide the desired dose per capsule.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents, other antiinfective agents or vaccines. Other antiviral agents to be administered in combination with a compound of the present invention include AU721, beta interferon, polymannoacetate, reverse transcriptase inhibitors (for example, dideoxycytidine (DDC), dideoxyinosine (DDI), BCH-189, AzdU, carbovir, DDA, D4C, D4T, DP-AZT, FLT (fluorothymidine), BCH-189, 5-halo-3'-thiadideoxycytidine, PMEA, zidovudine (AZT) and the like), non-nucleoside reverse transcriptase inhibitors (for example, R_{82193}, L-697,661, BI-RG-587 (nevirapine), retroviral protease inhibitors (for example, HIV protease inhibitors such as Ro 31-8959, SC-52151, KNI-227, KNI-272 and the like), HEPT compounds, L,697,639, R_{82150}, U-87201E and the like), TAT inhibitors (for example, RO-24–7429 and the like), trisodium phosphonoformate, HPA-23, eflonithine, Peptide T, Reticulose (nucleophosphoprotein), ansamycin LM 427, trimetrexate, UA001, ribavirin, alpha interferon, oxetanocin, oxetanocin-G, cylobut-G, cyclobut-A, ara-M, BW882C87, foscarnet, BW256U87, BW348U87, L-693,989, BV ara-U, CMV triclonal antibodies, FIAC, HOE-602,HPMPC, MSL-109, TI-23, trifluridine, vidarabine, famciclovir, penciclovir, acyclovir, ganciclovir, castanospermine, rCD4/CD4-IgG, CD4-PE40, butyl-DNJ, hypericin, oxamyristic acid, dextran sulfate and pentosan polysulfate. Immunomodulators that can be administered in combination with a compound of the present invention include bropirimine, Ampligen, anti-human alpha interferon antibody, colony stimulating factor, CL246,738, Imreg-1, Imreg-2, diethydithiocarbamate, interleukin-2, alpha-interferon, inosine pranobex, methionine enkephalin, muramyltripeptide, TP-5, erythropoietin, naltrexone, tumor necrosis facator, beta interferon, gamma interferon, interleukin-3, interleukin-4, autologous CD8+ infusion, alpha interferon immunoglobulin, IGF-1, anti-Leu-3A, autovaccination, biostimulation, extracorporeal photophoresis, FK-565, FK-506, G-CSF, GM-CSF, hyperthermia, isopinosine, IVIG, HIVIG, passive immunotherapy and polio vaccine hyperimmunization. Other antiinfective agents that can be administered in combination with a compound of the present invention include pentamidine isethionate. Any of a variety of HIV or AIDS vaccines (for example, gp120 (recombinant), Env 2–3 (gp120H), HIVAC-1e (gp120H), gp160 (recombinant), VaxSyn HIV-1 (gp160H), Immuno-Ag (gp160H), HGP-30,HIV-Immunogen, p24 (recombinant), VaxSyn HIV-1 (p24H) can be used in combination with a compound of the present invention.

Other agents that can be used in combination with the compounds of this invention are ansamycin LM 427, apurinic acid, ABPP, AI-721, carrisyn, AS-101, avarol, azimexon, colchicine, compound Q, CS-85, N-acetyl cysteine, (2-oxothiazolidine-4-carboxylate), D-penicillamine, diphenylhydantoin, EL-10, erythropoieten, fusidic acid, glucan, HPA-23, human growth hormone, hydroxchloroquine, iscador, L-ofloxacin or other quinolone antibiotics, lentinan, lithium carbonate, MM-1, monolaurin, MTP-PE, naltrexone, neurotropin, ozone, PAI, panax ginseng, pentofylline, pentoxifylline, Peptide T, pine cone extract, polymannoacetate, reticulose, retrogen, ribavirin, ribozymes, RS-47, Sdc-28, silicotungstate, THA, thymic humoral factor, thymopentin, thymosin fraction 5, thymosin alpha one, thymostimulin, UA001, uridine, vitamin B12 and wobemugos.

Other agents that can be used in combination with the compounds of this invention are antifungals such as amphotericin B, clotrimazole, flucytosine, fluconazole, itraconazole, ketoconazole and nystatin and the like.

Other agents that can be used in combination with the compounds of this invention are antibacterials such as amikacin sulfate, azithromycin, ciprofloxacin, tosufloxacin, clarithromycin, clofazimine, ethambutol, isoniazid, pyrazinamide, rifabutin, rifampin, streptomycin and TLC G-65 and the like.

Other agents that can be used in combination with the compounds of this invention are anti-neoplastics such as alpha interferon, COMP (cyclophosphamide, vincristine, methotrexate and prednisone), etoposide, mBACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone), PRO-MACE/MOPP(prednisone, methotrexate (w/leucovin rescue), doxorubicin, cyclophosphamide, etoposide/mechlorethamine, vincristine, prednisone and procarbazine), vincristine, vinblastine, angioinhibins, pentosan polysulfate, platelet factor 4 and SP-PG and the like.

Other agents that can be used in combination with the compounds of this invention are drugs for treating neuro-

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logical disease such as peptide T, ritalin, lithium, elavil, phenytoin, carbamazipine, mexitetine, heparin and cytosine arabinoside and the like.

Other agents that can be used in combination with the compounds of this invention are anti-protozoals such as albendazole, azithromycin, clarithromycin, clindamycin, corticosteroids, dapsone, DIMP, eflornithine, 566C80, fansidar, furazolidone, L,671,329, letrazuril, metronidazole, paromycin, pefloxacin, pentamidine, piritrexim, primaquine, pyrimethamine, somatostatin, spiramycin, sulfadiazine, trimethoprim, TMP/SMX, trimetrexate and WR6026 and the like.

Among the preferred agents for treatment of HIV or AIDS in combination with the compounds of this invention are reverse transcriptase inhibitors.

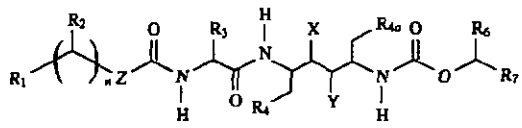
It will be understood that agents which can be combined with the compounds of the present invention for the treatment or prophylaxis of AIDS or an HIV infection are not limited to those listed above, but include in principle any agents useful for the treatment or prophylaxis of AIDS or an HIV infection.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

What is claimed is:

1. A compound of the formula:



wherein

R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl wherein the substituent is selected from (i) C_1–C_6-loweralkyl, (ii) C_2–C_6-loweralkenyl, (iii) C_3–C_7-cycloalkyl, (iv) C_3–C_7-cycloalkyl-C_1–C_6-alkyl, (v) C_5–C_7-cycloalkenyl, (vi) C_5–C_7-cycloalkyl-C_1–C_6-alkyl, (vii) C_1–C_6-alkoxy-C_1–C_6-alkyl or benzyloxy-C_1–C_6-alkyl, (viii) C_1–C_6-thioalkoxy-C_1–C_6-alkyl or benzyl- S—C_1–C_6-alkyl, (ix) C_1–C_6-alkylamino, (x) di-C_1–C_6-alkylamino, (xi) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, C_1–C_6-loweralkyl, hydroxy, C_1–C_6-alkoxy, benzyloxy, C_1–C_6-thioalkoxy and benzyl-S—, (xii) phenyl-C_1–C_6-alkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xiii) di-C_1–C_6-alkylamino-C_1–C_6-alkyl, (xiv) C_1–C_6-alkoxy or benzyloxy and (xv) C_1–C_6-thioalkoxy or benzyl-S—;

n is 1,2or 3;

R_2 is hydrogen or C_1–C_6-loweralkyl;

R_3 is C_1–C_6-loweralkyl;

R_4 and R_{4a} are independently selected from phenyl and substituted phenyl wherein the phenyl ring is substituted with a substituent selected from (i) halo, (ii) C_1–C_6-loweralkyl, (iii) hydroxy, (iv) C_1–C_6-alkoxy or benzyloxy and (v) C_1–C_6-thioalkoxy or benzyl-S—;

R_6 is hydrogen or C_1–C_6-loweralkyl;

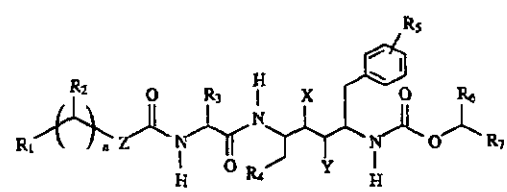
R_7 is thiazolyl or oxazolyl wherein the thiazolyl or oxazolyl ring is unsubstituted or substituted with C_1–C_6-loweralkyl;

X is hydrogen and Y is —OH ; and

Z is absent, —O—, —S—, —CH_2— or —$N(R_8)$— wherein R_8 is C_1–C_6-loweralkyl, C_3–C_7-cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen, C_1–C_6-loweralkyl or an N-protecting group selected from the group consisting of formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, benzenesulfonyl, p-toluenesulfonyl, benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, αα-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, benzyl, triphenylmethyl, benzyloxymethyl and trimethylsilyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of the formula:



wherein

R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl wherein the substituent is selected from (i) C_1–C_6-loweralkyl, (ii) C_2–C_6-loweralkenyl, (iii) C_3–C_7-cycloalkyl, (iv) C_3–C_7-cycloalkyl-C_1–C_6-alkyl, (v) C_5–C_7-cycloalkenyl, (vi) C_5–C_7-cycloalkenyl-C_1–C_6-alkyl, (vii) C_1–C_6-alkoxy -C_1–C_6-alkyl or benzyloxy-C_1–C_6-alkyl, (viii) C_1–C_6-thioalkoxy-C_1–C_6-alkyl or benzyl-S—C_1–C_6-alkyl, (ix) C_1–C_6-alkylamino, (x) di-C_1–C_6-alkylamino, (xi) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, C_1–C_6-loweralkyl, hydroxy, C_1–C_6-alkoxy, benzyloxy, C_1–C_6-thioalkoxy and benzyl-S—, (xii) phenyl -C_1–C_6-alkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xiii) di-C_1–C_6-alkylamino -C_1–C_6-alkyl, (xiv) C_1–C_6-alkoxy or benzyloxy and (xv) C_1–C_6-thioalkoxy or benzyl-S—;

n is 1;

R_2 is hydrogen or C_1–C_6-loweralkyl;

R_3 is C_1–C_6-loweralkyl;

R_4 is phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from (i) halo, (ii) C_1–C_6-loweralkyl, (iii) hydroxy, (iv) C_1–C_6-alkoxy or benzyloxy and (v) C_1–C_6-thioalkoxy or benzyl-S—;

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R_5 is hydrogen, halo, C_1–C_6-loweralkyl, hydroxy, C_1–C_6-alkoxy, benzyloxy, C_1–C_6-thioalkoxy or benzyl-S—;

R_6 is hydrogen or C_1–C_6-loweralkyl;

R_7 is thiazolyl or oxazolyl wherein the thiazolyl or oxazolyl ring is unsubstituted or substituted with C_1–C_6-loweralkyl;

X is hydrogen and Y is —OH;

Z is absent, —O—, —S—, —CH_2— or —N(R_8)-wherein R_8 is C_1–C_6-loweralkyl, C_3–C_7-cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen or C_1–C_6-loweralkyl; or a pharmaceutically acceptable salt thereof.

3. The compound of claim **2** wherein R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen and R_7 is thiazolyl or oxazolyl.

4. The compound of claim **3** wherein R_7 is 5-thiazolyl or 5-oxazolyl.

5. The compound of claim **2** wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is C_1–C_6-loweralkyl; ; R_2 is hydrogen; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl or 5-oxazolyl; and Z is —O— or —N-(R_8)— wherein R_8 is C_1–C_6-loweralkyl.

6. The compound of claim **2** wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; R_2 is hydrogen; R_3 is methyl or isopropyl; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl or 5-oxazolyl; and Z is —O—.

7. The compound of claim **2** wherein R_1 is 2-monosubstituted-4-thiazolyl or 2-monosubstituted-4-oxazolyl wherein the substituent is ethyl or isopropyl; R_2 is hydrogen; R_3 is isopropyl; R_4 is phenyl; R_5 is hydrogen; R_6 is hydrogen; R_7 is 5-thiazolyl or 5-oxazolyl; and Z is —N-(R_8)— wherein R_8 is methyl.

8. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; or a pharmaceutically acceptable salt thereof.

9. A compound selected from the group consisting of:

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl)-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)-valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

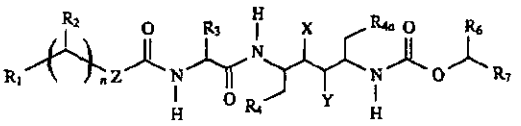
(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; and

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

or a pharmaceutically acceptable salt thereof.

10. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; or a pharmaceutically acceptable salt thereof.

11. A compound of the formula:



wherein

R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl wherein the substituent is selected from (i) C_1–C_6-loweralkyl, (ii) C_2–C_6-loweralkenyl, (iii) C_3–C_7-cycloalkyl, (iv) C_3–C_7-cycloalkyl-C_1–C_6-alkyl, (v) C_5–C_7-cycloalkenyl, (vi) C_5–C_7-cycloalkenyl-C_1–C_6-alkyl, (vii) C_1–C_6-alkoxy-C_1–C_6-alkyl or benzyloxy-C_1–C_6-alkyl, (viii) C_1–C_6-thioalkoxy -C_1–C_6-alkyl or benzyl-S—C_1–C_6-alkyl, (ix) C_1–C_6-alkylamino, (x) di-C_1–C_6-alkylamino, (xi) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, C_1–C_6loweralkyl, hydroxy, C_1–C_6-alkoxy, benzyloxy, C_1–C_6-thioalkoxy and benzyl-S—, (xii) phenyl -C_1–C_6-alkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xiii) di-C_1–C_6-alkylamino-C_1–C_6-alkyl, (xiv) C_1–C_6-alkoxy or benzyloxy and (xv) C_1–C_6-thioalkoxy or benzyl-S—;

n is 1,2 or 3;

R_2 is hydrogen or C_1–C_6-loweralkyl;

R_4 and R_{4a} are independently selected from phenyl and substituted phenyl wherein the phenyl ring is substituted with a substituent selected from (i) halo, (ii) C_1–C_6-loweralkyl, (iii) hydroxy, (iv) C_1–C_6-alkoxy or benzyloxy and (v) C_1–C_6-thioalkoxy or benzyl-S—;

R_6 is hydrogen or C_1–C_6-loweralkyl;

R_7 is thiazolyl or oxazolyl wherein the thiazolyl or oxazolyl ring is unsubstituted and R_3 is C_2–C_6-loweralkyl and Z is absent, —O—, —S— or —CH_2—; or

R_7 is thiazolyl or oxazolyl wherein the thiazolyl or oxazolyl ring is substituted with C_1–C_6-loweralkyl and R_3 is C_1–C_6-loweralkyl and Z is absent, —O—, —S—, —CH_2—Nor —(R_8)— wherein R_8 is C_1–C_6-loweralkyl, C_3–C_7-cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen, C_1–C_6-loweralkyl or an N-protecting group selected from the group consisting of formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacctyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, benzenesulfonyl, p-toluenesulfonyl, benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p- nitrobenzyloxycarbonyl, 2- nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl,

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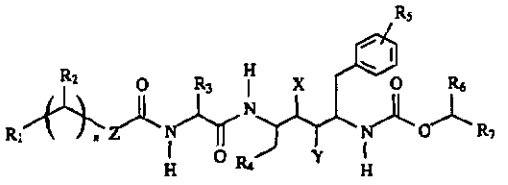
benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, benzyl, triphenylmethyl, benzyloxymethyl and trimethylsilyl; and

X is —OH and Y is hydrogen;

or a pharmaceutically acceptable salt thereof.

12. A compound of the formula:



wherein

R_1 is monosubstituted thiazolyl or monosubstituted oxazolyl wherein the substituent is selected from (i) C_1–C_6-loweralkyl, (ii) C_2–C_6-loweralkenyl, (iii) C_3–C_7-cycloalkyl, (iv) C_3–C_7-cycloalkyl-C_1–C_6-alkyl, (v) C_5–C_7-cycloalkenyl, (vi) C_5–C_7-cycloalkenyl-C_1–C_6-alkyl, (vii) C_1–C_6-alkoxy-C_1–C_6-alkyl or benzyloxy-C_1–C_6-alkyl, (viii) C_1–C_6-thioalkoxy-C_1–C_6-alkyl or benzyl-S—C_1–C_6-alkyl, (ix) C_1–C_6-alkylamino, (x) di-C_1–C_6-alkylamino, (xi) phenyl wherein the phenyl ring is unsubstituted or substituted with a substituent selected from halo, C_1–C_6-loweralkyl, hydroxy, C_1–C_6-alkoxy, benzyloxy, C_1–C_6-thioalkoxy and benzyl-S—, (xii) phenyl -C_1–C_6-alkyl wherein the phenyl ring is unsubstituted or substituted as defined above, (xiii) di-C_1–C_6-alkylamino -C_1–C_6-alkyl, (xiv) C_1–C_6-alkoxy or benzyloxy and (xv) C_1–C_6-thioalkoxy or benzyl-S—;

n is 1;

R_2 is hydrogen or C_1–C_6-loweralkyl;

R_4 is phenyl or substituted phenyl wherein the phenyl ring is substituted with a substituent selected from (i) halo, (ii) C_1–C_6-loweralkyl, (iii) hydroxy, (iv) C_1–C_6-alkoxy or benzyloxy and (v) C_1–C_6-thioalkoxy or benzyl-S—;

R_6 is hydrogen or C_1–C_6-loweralkyl;

R_7 is thiazolyl or oxazolyl wherein the thiazolyl or oxazolyl ring is unsubstituted and R_3 is C_2–C_6-loweralkyl and Z is absent, —O—, —S— or —CH_2—; or

R_7 is thiazolyl or oxazolyl wherein the thiazolyl or oxazolyl ring is substituted with C_1–C_6-loweralkyl and R_3 is C_1–C_6-loweralkyl and Z is absent, —O—, —S—, —CH_2— or —N(R_8)— wherein R_8 is C_1–C_6-loweralkyl, C_3–C_7-cycloalkyl, —OH or —NHR_{8a} wherein R_{8a} is hydrogen or C_1–C_6-loweralkyl; and

X is —OH and Y is hydrogen;

or a pharmaceutically acceptable salt thereof.

13. A compound selected from the group consisting of:

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S, 5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl-)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-(cyclopentenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-2-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-(cyclopentyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-(4-fluoro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

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(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methoxy)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropoxy-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S,)-5-(N-(N-(N-Methyl-N-((2-(methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)analinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-Isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl]amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-(1-(2-Isopropyl-4-thiazolyl)ethoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Cyclopropyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S, 3S, 5S) -5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((4-Isopropyl-2-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(N,N-Diethylamino)-4-thiazolyl-)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-(((N,N-dimethylamino)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(methoxymethyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((2-Isopropyl-4-thiazolyl)thiomethoxycarbonyl)valinyl)amino)-2-(N-((5-thiazolyl-)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-(3-(2-Isopropyl-4-thiazolyl)propanoyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-(1-(5-thiazolyl)ethoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-5-(N-((2-methyl-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

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(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-cyclohexyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,1-dimethyl-)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-ethyl-4-thiazolyl-)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane:

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-ethenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclopentenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-cyclohexenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclopentenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((4-cyclohexenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1,2-dimethyl-1-propenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclopentyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(cyclohexyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-phenyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-benzyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl)ethyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-phenyl-1-ethenyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino-2-(N-((5-oxazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(4-fluoro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-chloro)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-methoxy)phenyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-thiazolyl)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethoxy-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyloxy-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(N,N-dimethylamino)methyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-propyl-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

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(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(2-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-methyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(1-ethyl)propyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Ethyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl)methoxycarbonyl)alaninyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-2-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(N,N-Dimethylamino)-4-thiazolyl)methoxycarbonyl)valinyl)amino)-5-(N-((5-oxazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-oxazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-methyl-4-oxazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-pentyl)-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-(((2-isopropyl)-5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-(2-Isopropyl-4-thiazolyl)ethoxy-)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-2-(N-(N-((2-(2-Isopropyl-4-thiazolyl)ethoxy-)carbonyl)valinyl)amino)-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((2-Isopropyl-4-thiazolyl-1)acetyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Methyl-N-((2-cyclopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclobutyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-ethyl-4-thiazolyl-)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-(1-Propyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-([N-(Isobutyl)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-oxazolyl)methyl)amino)carbonyl)-L-alaninyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isobutyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N,N-((N-Ethyl-N-((2-cyclopentyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-((N-Methyl-N-((2-(2-isopropyl-4-thiazolyl)ethyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane;

(2S,3S,5S)-5-(N-(N-((N-(tert-Butyloxycarbonylamino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; and

(2S,3S,5S)-5-(N-(N-((N-(Amino)-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane Hydrochloride;

or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition for inhibiting HIV protease comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim **1**.

15. A pharmaceutical composition for inhibiting HIV protease comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim **2**.

16. A pharmaceutical composition for inhibiting HIV protease comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim **10**.

17. A pharmaceutical composition for inhibiting an HIV infection comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of claim **10**.

18. A method for inhibiting HIV protease comprising administering to a human in need thereof a therapeutically effective amount of a compound of claim **10**.

19. A method for inhibiting an HIV infection comprising administering to a human in need thereof a therapeutically effective amount of a compound of claim **10**.

* * * * *

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(179)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 3, line 55, change "AI" to --A1--.

Column 8, line 46, change "4 thiazolyl" to --4-thiazolyl--.

Column 8, line 58, change "valinyl" to -- -valinyl--.

Column 8, line 66, change "valinyl" to -- -valinyl--.

Column 8, line 66, change "methoxycarbonyl)amino" to --thiazolyl)methoxycarbonyl)amino--.

Column 9, line 2, change "amino)carbonyl" to --amino)-carbonyl--.

Column 9, line 3, change "amino-" to --amino)- --.

Column 9, line 6, change "amino)carbonyl)" to --amino)-carbonyl)--.

Column 9, line 7, change "amino)1" to --amino-1--.

Column 9, line 14, change "amino)carbonyl)" to --amino)-carbonyl)--.

Column 9, line 18, change "amino)carbonyl)" to --amino)-carbonyl)--.

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(180)

UNITED STATES PATENT AND TRADEMARK OFFICE

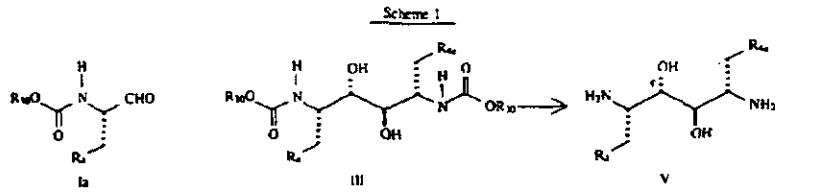
CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206 Page 2 of 22
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

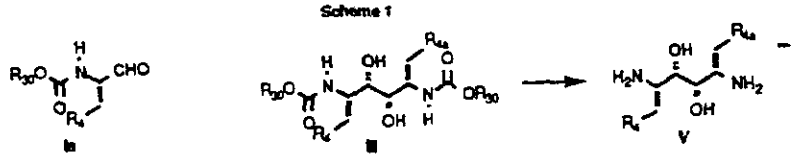
It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Columns 9 and 10, scheme 1, lines 50-55, change

"



to --



Columns 13 and 14, scheme 3, line 43, change "NO_2" to --NH_2--.

Column 17, line 34, change "(:or" to --(or--.

Column 20, line 42, change "XL. III" to --XLIII--.

Column 26, line 54, change "2.5" to --2,5--.

Column 26, line 55, change "3.4" to --3,4--.

Column 26, line 55, change "1.6" to --1,6--.

Column 26, line 56, change "2.5" to --2,5--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 26, line 56, change "3.4" to --3,4--.

Column 26, line 57, change "1.6" to --1,6--.

Column 27, line 53, change "1.6" to --1,6--.

Column 27, line 64, change "amino)1," to --amino)-1,--.

Column 28, line 10, change "2.5" to --2,5--.

Column 28, line 45, change "Thioformamide," to --Thioformamide.--.

Column 31, line 41, change "1.6" to --1,6--.

Column 31, line 60, change "1H 7.85" to --1H), 7.85--.

Column 33, line 6, change "4thiazolyl" to --4-thiazolyl--.

Column 33, line 27, change "-amino)" to -- amino)--.

Column 34, lines 29-30, change "thiazolylmethyl" to --thiazolyl)methyl--.

Column 34, line 31, change "1.6" to --1,6--.

Column 35, line 2, change "amino-2" to --amino)-2--.

Column 35, line 3, change "amino)-6" to --amino)-1,6--.

Column 35, line 15, change "2-1-isopropylthiazole" to --2-Isopropylthiazole--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 35, line 44, change "1H" to --1H),--.

Column 36, line 3, change "d)," to --(d,--.

Column 36, line 8, change ",5-" to -- -5- --.

Column 36, line 10, change "1.6" to --1,6--.

Column 36, line 22, change "1.6" to --1,6--.

Column 37, line 11, change ",2-" to -- -2- --.

Column 37, line 15, change "1867H)." to --1867).--.

Column 38, lines 5 and 6, delete "-5-(tert-Butyldimethylsilyloxy)"

Column 38, line 6, change "butyloxycarbonylamino-" to –butyloxycarbonylamino)- --.

Column 38, line 57, change "($CDCl_3H$)" to --($CDCl_3$)--.

Column 39, line 36, change "($CDCl_3H$)" to --($CDCl_3$)--.

Column 40, line 36, change "(N,N-Dimethylamino)" to --(N-((2-(N,N-Dimethylamino--.

Column 43, line 13, change "-thiazolyl)" to -- -4-thiazolyl)--.

Column 43, lines 21 and 22, change "(DMSO-d_6H)" to --(DMSO-d_6)--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206 Page 5 of 22
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Column 43, line 27, change "amino}" to --amino)--.

Column 43, line 33, change "1.6" to --1,6--.

Column 43, line 63, change "propyl" to --Isopropyl--.

Column 44, line 5, change "N" to --(N--.

Column 44, line 7, change "1.6" to --1,6--.

Column 44, line 9, change "methyl)N-" to --methyl-N- --.

Column 44, line 22, change "(DMSO-d_6H)" to --(DMSO-d_6)--.

Column 47, line 10, change "-4-nitrophenyl)" to -- -(4-nitrophenyl)--.

Column 47, line 39, change "(2S,3S,5S}" to --(2S,3S,5S)--.

Column 47, line 40, change "-2," to -- -2- --.

Column 47, line 41, change "1.6" to --1,6--.

Column 47, line 47, change "N(-" to –N- --.

Column 47, line 58, change "(M+NH_4H)+" to --(M+NH_4)+--.

Column 48, line 4, change "amino)1," to --amino)-1,--.

Column 48, line 25, change "1Hydroxymethyl)" to --(Hydroxymethyl)--.

Column 48, line 41, change "(DMSO-d6)" to --(DMSO-d_6)--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 49, line 32, change "4dimethylaminopyridinc" to --4-dimethylaminopyridine--.

Column 50, line 4, change "thiazolyl/" to --thiazolyl)--.

Column 50, line 5, change "methylaminocarbonyl)" to --methyl)amino)carbonyl)--.

Column 51, line 42, change "1.,6" to --1,6--.

Column 51, line 51, change "1,-Diethoxy" to --1,1-Diethoxy--.

Column 51, line 23, change "(methoxymethyl)thiazole" to --(methoxymethyl)-thiazole--.

Column 52, line 28, change "-3hydroxyhexane" to -- -3-hydroxyhexane--.

Column 53, line 3, change "2.68;" to --62.68;--.

Column 53, line 8, change "-6-diphenyl" to -- -1,6-diphenyl--.

Column 53, line 11, change "amino--" to --amino-2- --.

Column 53, line 20, change "(DMSO-d_6),5" to --(DMSO-d_6) δ--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 53, line 37, change "-8-" to -- -2- --.

Column 54, line 2, change "carbonyl.)" to --carbonyl)--.

Column 57, line 5, change "-16-diphenyl" to --1,6-diphenyl--.

Column 57, line 26, change "(2S,3R,4, R,5S)" to --(2S,3R,4R,5S)--.

Column 58, line 27, change "4,dihydroxy" to --4-dihydroxy--.

Column 59, line 29, change "1.6" to --1,6--.

Column 59, line 37, change "(2S,3 8,5S)" to --(2S,3S,5S)--.

Column 59, line 63, change "5thiazolyl" to --5-thiazolyl--.

Column 60, line 45, change "-4oxazolyl" to -- -4-oxazolyl)--.

Column 60, line 61, change "valinyl)-5-" to --valinyl)amino)-5- --.

Column 61, line 52, change "-4oxazolyl)" to -- -4-oxazolyl)--.

Column 61, line 56, change "4thiazolyl)" to --4-thiazolyl)--.

Column 61, line 64, change "4oxazolyl)" to --4-oxazolyl--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 61, line 66, change "5isoxazolyl)" to --5-isoxazolyl)--.

Column 62, line 1, change "4thiazolyl)" to --4-thiazolyl)--.

Column 62, line 6, change "carbonyl)" to -- -carbonyl)--.

Column 62, line 10, change "carbonyl)" to -- -carbonyl)--.

Column 62, line 15, change "amino)1" to --amino)-1--.

Column 62, line 21, change "carbonyl)" to -- -carbonyl)--.

Column 62, line 41, change "valinyl)-2-" to --valinyl)amino)-2- --.

Column 63, line 1, change "4thiazolyl)" to --4-thiazolyl)--.

Column 63, line 14, change "carbonyl)" to -- -carbonyl)--.

Column 63, line 37, change "amino)" to -- -amino)--.

Column 63, line 41, change "carbonyl)" to -- -carbonyl)--.

Column 64, line 2, change "carbonyl)" to -- -carbonyl)--.

Column 64, line 6, change "amino)" to -- -amino)--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 64, line 14, change "4thiazolyl)" to --4-thiazolyl)--.

Column 64, line 18, change "carbonyl)" to -- -carbonyl)--.

Column 64, line 21, change "carbonyl)" to -- -carbonyl)--.

Column 64, line 24, change "amino)" to -- -amino)--.

Column 64, line 29, change "carbonyl)" to -- -carbonyl)--.

Column 64, line 33, change "carbonyl)" to -- -carbonyl)--.

Column 64, line 37, change "carbonyl)" to -- -carbonyl)--.

Column 64, line 41, change "carbonyl)" to -- -carbonyl)--.

Column 64, line 49, change "methyl)" to -- -methyl)--.

Column 64, line 53, change "amino)" to -- -amino)--.

Column 65, line 10, change "methyl)" to -- -methyl)--.

Column 65, line 25, change "carbonyl)" to -- -carbonyl)--.

Column 65, line 42, change "amino)1," to --amino)-1,--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 66, line 14, change "carbonyl)" to -- -carbonyl)--.

Column 66, line 29, change "carbonyl)" to -- -carbonyl)--.

Column 66, line 33, change "carbonyl)" to -- -carbonyl)--.

Column 66, line 37, change "amino)" to -- -amino)--.

Column 66, line 41, change "carbonyl)" to -- -carbonyl)--.

Column 66, line 65, change "amino)" to -- -amino)--.

Column 67, line 57, change "amino)" to -- -amino)--.

Column 67, line 61, change "amino)" to -- -amino)--.

Column 68, line 2, change "amino)" to -- -amino)--.

Column 68, line 10, change "carbonyl)" to -- -carbonyl)--.

Column 68, line 32, change "amino)" to -- -amino)--.

Column 70, line 41, change "(DMSO-d_6H)" to --(DMSO-d_6)--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 71, line 28, change "(isopropylthiazole" to --isopropylthiazole--.

Column 71, line 35, change "methyl)" to -- -methyl)--.

Column 71, line 40, change "(2" to --((2--.

Column 71, line 41, change "amino/" to --amino)--.

Column 72, line 2, change "$CHCl_3H$)." to --$CHCl_3$).--.

Column 72, line 4, change "diphenyl,3" to --diphenyl-3--.

Column 72, line 11, change "$CHCl_3H$)." to --$CHCl_3$).--.

Column 72, line 16, change "-N," to -- -N- --.

Column 72, line 53, change "($CDCl_3H$)" to --($CDCl_3$)--.

Column 72, line 60, change "methyl)" to -- -methyl)--.

Column 72, line 63, change "($CDCl_3H$)" to --($CDCl_3$)--.

Column 73, line 29, change "Hydroxyethyl-" to --Hydroxyethyl)- --.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 73, line 35, change "($CDCl_3H$)" to --($CDCl_3$)--.

Column 73, line 50, change "N,((2,-" to --N-((2- --.

Column 74, line 3, change "ethoxy-)" to --ethoxy)--.

Column 74, line 52, change "G." to --C.--.

Column 74, line 56, change "($CDCl_3H$)" to --($CDCl_3$)--.

Column 74, line 59, change "Isopropyl," to --Isopropyl- --.

Column 75, line 18, change "(Cyclopropyl" to --Cyclopropyl--.

Column 76, line 2, change "isopropylthiazole" to --2-isopropylthiazole--.

Column 76, line 21, change "N," to --N- --.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 76, line 23, change "diphenyl," to --diphenyl- --.

Column 76, line 42, change "H" to --^{1}H--.

Column 76, line 42, change "($CDCl_3H$)" to --($CDCl_3$)--.

Column 76, line 49, change "Ethyl-" to --Ethyl-4- --.

Column 76, line 50, change "(chloromethyl)" to --(chloromethyl)-2- --.

Column 77, line 19, change "($CDCl_3H$)" to --($CDCl_3$)--.

Column 77, line 27, change "methyl" to -- -methyl--.

Column 77, line 42, change "amino)-6" to --amino)-1,6--.

Column 77, line 52, change "H_2" to --H_2O--.

Column 77, line 67, change "(DMSO-d_6H)" to --(DMSO-d_6)--.

Column 78, line 33, change "($CDCl_3H$)" to --($CDCl_3$)--.

Column 78, line 41, change "N," to --N- --.

Column 80, line 19, change "thiazole" to -- -thiazole--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : July 30, 1996
DATED : Kempf et al.
INVENTOR(S) :

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 80, line 59, change "(DMSO-d_6H)" to --(DMSO-d_6)--.

Column 81, line 3, change "[(2-" to --((2- --.

Column 81, line 44, change "^{1}H NMR ($CDCl_3$H" to ^{11}H NMR ($CDCl_3$)

Column 82, line 19, change "($CDCl_3$H)" to --($CDCl_3$)--.

Column 82, line 30, change "(DMSO-d_6H)" to --(DMSO-d_6)--.

Column 82, line 40, change "Butyloxycarbonyl)amino)" to --Butyloxycarbonylamino)--.

Column 83, line 6, change "{N" to --(N--.

Column 83, line 32, change "($CDCl_3$H)" to --($CDCl_3$)--.

Column 83, line 44, change "($CDCl_3$H)" to --($CDCl_3$)--.

Column 83, line 45, change "1.65" to --1.65--.

Column 83, line 59, change "($CDCl_3$H)" to --($CDCl_3$)--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206 Page 15 of 22
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 83, line 64, change "2." to --2- --.

Column 84, line 10, change "CH_2Cl_2H)." to --CH_2Cl_2).--.

Column 84, line 11, change "(DMSO-d_6H)" to --(DMSO-d_6)--.

Column 84, line 34, change "$CDCl_3H$)" to --$CDCl_3$)--.

Column 84, line 37, change "$CDCl_3H$)" to --$CDCl_3$)--.

Column 85, line 2, change "($CHCl_3H$)" to --($CHCl_3$)--.

Column 85, line 3, change "($CDCl_3H$)" to --($CDCl_3$)--.

Column 85, line 7, change "$CDCl_3H$)" to --$CDCl_3$)--.

Column 85, line 19, change "51,6" to --51.6--.

Column 85, line 31, change "(dibenzylamino)" to --dibenzylamino)--.

Column 85, line 49, change "$CDCl_3H$)" to --$CDCl_3$)--.

Column 85, line 63, change "41,6" to --41.6--.

Column 87, line 2, change "51,6" to --51.6--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 87, line 15, change "21,6" to --21.6--.

Column 87, line 35, change "(2S,8S,5S)" to --(2S,3S,5S)--.

Column 88, line 23, change "183.7°" to -- -183.7°--.

Column 88, line 23, change "$CDCl_3$,δH):" to --$CDCl_3$,δ):--.

Column 88, line 23, change "11,68" to --11.68--.

Column 88, line 30, change "4oxo" to --4-oxo--.

Column 88, line 31, change "1," to -- -1--.

Column 88, line 47, change "hydroxyl" to --hydroxy--.

Column 88, line 63, change "(Na_2SO_4H)" to --(Na_2SO_4)--.

Column 89, line 11, change "(1/1H)" to --(1/1)--.

Column 89, line 12, change "(Na_2SO_4H)" to --(Na_2SO_4)--.

Column 89, line 34, change "(Na_2SO_4H)" to --(Na_2SO_4)--.

Column 89, line 35, change "concentrated/n" to --concentrated in--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 90, line 15, change "$(M+18H)^+$" to --$(M+18)^+$--.

Column 90, line 40, change "Methyl)-N-" to --Methyl-N- --.

Column 92, line 32, change "$NaHCO_3H$)." to --$NaHCO_3$).--.

Column 93, line 12, change "(DMSO-d_6H)" to --(DMSO-d_6)--.

Column 93, line 34, change "(aqueous pH+7H)" to --(aqueous pH=7)--.

Column 93, line 41, change "NH_2H)" to --NH_2)--.

Column 93, line 67, change "61,6" to --61.6--.

Column 95, line 4, change "121,6," to --121.6,--.

Column 95, line 63, change "amino/" to --amino)--.

Column 96, line 65, change "Gin" to --Gln--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 99, line 12, change "(R_bH)(R_dH)" to --(R_b)(R_d)--.

Column 99, line 13, change "(R_bH)(R_dH)" to --(R_b)(R_d)--.

Column 99, line 15, change "-N-(R_cH)(R_fH)," to ---N(R_c)(R_f),--.

Column 99, line 18, change "(CH_2H)" to --(CH_2)--.

Column 99, line 19, change "(CH_2H)2OCH" to --(CH_2)$_2$OCH--.

Column 99, line 34, change "(R_gH)" to --(R_g)--.

Column 99, lines 34 and 35, change "(R_gH)" to --(R_g)--.

Column 99, line 40, change "2363H)" to --2363)--.

Column 101, line 9, change "(1976H)" to --(1976)--.

Column 101, line 13, change "(1H)" to --(1)--.

Column 101, line 15, change "(2H)" to --(2)--.

Column 101, line 54, change "AU721," to --AL-721,--.

Column 101, line 61, change "R_{82193}," to --R82193,--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206 Page 19 of 22
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 101, line 64, change "R_{82150}," to --R82150,--.

Column 102, line 25, change "(gp120H)" to --(gp120)--.

Column 102, line 25, change "(gp120H)" to --(gp120)--.

Column 102, line 26, change "(gp160H)" to --(gp160)--.

Column 102, line 26, change "(gp160H)" to --(gp160)--.

Column 102, line 27, change "(p24H)" to --(p24)--.

Column 105, line 32, change "-N-(R_8)-" to -- -N(R_8)- --.

Column 105, lines 48 and 49, change "(N-methoxycarbonyl)" to --(N-((5-thiazolyl)methoxycarbonyl)--.

Column 105, line 50, change "Isopropyl)-4" to --Isopropyl-4--.

Column 106, line 49, change "-CH_2-Nor-(R_8)-" to ---CH_2 or -N(R_8)---.

Column 107, line 54, change "NHR_8a" to --NHR_{8a}--.

Column 108, line 12, change "3hydroxyhexane;" to --3-hydroxyhexane--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206 Page 20 of 22
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 108, line 17, change "4-(cyclopentenyl" to --4-cyclopentenyl--.

Column 108, between lines 25 and 26 , insert --(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-(3-propenyl)-4-thiazolyl)methyl)amino)-carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino-1,6-diphenyl-3-hydroxyhexane;--.

Column 108, line 35, change "1-methyl-2" to --2-methyl-1--.

Column 108, line 42, change "3hydroxyhexane;" to --3-hydroxyhexane;--.

Column 108, lines 43 and 44, change "(1,2-(cyclopentyl)" to --(cyclopentyl)--.

Column 108, line 64, change "(2-(4-fluoro)" to --(4-fluoro)--.

Column 109, line 5, change "(2-methoxy)" to --(3-methoxy)--.

Column 109, line 29, change "2-(methyl)" to --(2-methyl)--.

Column 109, line 36, change "3hydroxyhexane;" to --3-hydroxyhexane;--.

Column 109, line 46, change "N-Methyl" to --N-Ethyl--.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 110, line 44, change "(N,N-" to --(N-(N- --.

Column 110, line 48, change "(N,N-" to --(N-(N- --.

Column 111, line 1, change "(N,N-" to --(N-(N- --.

Column 111, line 9, change "(N,N-" to --(N-(N- --.

Column 111, line 13, change "(N,N-" to --(N-(N- --.

Column 111, line 18, change "(N,N-" to --(N-(N- --.

Column 111, line 22, change "(N,N-" to --(N-(N- --.

Column 112, line 9, change "(N,N-" to --(N-(N- --.

Column 112, line 13, change "(N,N-" to --(N-(N- --.

Column 112, lines 39 and 40, change "methyl)" to -- -4-thiazolyl)methyl)--.

Column 113, line 24, change "-2(N-" to -- -2-(N- --.

Column 113, line 63, change "(N,N-" to --(N-(N- --.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 114, line 13, change "(N,N-" to --(N-(N- --.

Column 114, line 30, change "(N,N-" to --(N-(N- --.

Column 114, line 35, change "-5-(N-" to -- -5-(N-(N- --.

Signed and Sealed this

Twenty-first Day of July, 1998

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,541,206
DATED : July 30, 1996
INVENTOR(S) : Kempf *et al.*

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 103, line 45, change "C_5-C_7-cycloalkyl-C_1-C_6" to --C_5-C_7-cycloalkenyl-C_1-C_6--.

Column 109, line 43, change "olyl)methyl)amino)carbonyl)analinyl)amino)-2-(N-" to --olyl)methyl)amino)carbonyl)alaninyl)amino)-2-(N- --.

Signed and Sealed this

Ninth Day of March, 1999

Attest:

Q. TODD DICKINSON

Attesting Officer

Acting Commissioner of Patents and Trademarks

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MATRIX

Matrix Laboratories Limited

RESEARCH AND DEVELOPMENT CENTRE
LOCATION

Lab Note Book No. 854

Finished on

11 FEB 2011

203

Lab note book no: 854

Project: RITO NAVIR

Issue to: N. MADHUMURTHY

Team members:

1. M. Rajendar Reddy.
2. M. Nagesh babu
3. R. Revathi Srinivas
4. Nadeem.

From: 25.07.2007 To: 23.11.2007.

11 FEB 2011

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27/09/07 RST-III

Aim:- preparation of Ritonavir Stage-III as per

US 5541206 ex.no: 71

Inputs:-

SNO	Raw material name	units	Qty	mwt	moles	m/moles
1	RST-II (free base)	gm	10.0	425	0.0235	1.00
2	MTV-III (free acid)	gm	8.1	313	0.0258	1.10
3	Hydroxybenzotriazole monohydrate	gm	3.95	153	0.0258	1.10
4	Dicyclohexyl carbodiimide	gm	5.33	206	0.0258	1.10
5	Tetrahydrofuran	ml	187	-	-	-
6	Ethyl acetate	ml	346	-	-	-
7	Sodium hydroxide	gm	6.8	40	0.17	7.23
8	potassium dihydrogen phosphate	gm	3.5	135	-	-
9	1N Hydrochloric acid	ml	149	-	-	-
10	Sodium bicarbonate	gm	4.1	8.4	0.047	2.02
11	Heptane	ml	176	-	-	-
12	purified water	ml	150	-	-	-
13	Sodium sulfate	gm	14.3	-	-	-

procedure:-

SNO	unit operation	Qty	Time	Time From	Time To	Temp From	Temp To	
1	charged Tetrahydrofuran	187 ml	1 hr	9:30		26	26	
	U/nitrogen atmosphere							
2	charged RST-II free base	10.0 gm		9:32		26	26	
3	charged Hydroxybenzotriazole	3.95 gm		9:33		26	26	
	mono hydrate							
4	charged MTV-III free acid	8.1 gm		9:35		26	26	
5	stirred to get clear sol^n		10'	9:35	9:45	26	26	(clear sol^n obtained)
6	charged Dicyclohexyl carbo	5.33 gm		9:46		26	26	
	diimide							
7	stirred the rxn mass		16 hrs	9:47	1:27	26	29	
	(mass temp raised to 29°c &							
	solids emitted.)							

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Sno	unit operation	Qty	Time	Time From	Time To	Temp°C From	Temp°C To
8	Distill the solvent under to get residue		1 hr	9:20	10:20	26	39
9	cooled the rxn mass		20"	10:20	10:40	39	20
10	added chilled 1N HCl (5°c)	116 ml	15"	10:40	10:55	20	15
11	further cooled		20'	10:55	11:15	15	0
12	Stirred the rxn mass		3 hrs	11:15	14:15	0	5
13	Filter the rxn mass to remove off solids			14:15	14:20	3	
14	washed the cake with chilled (5°c) 1N HCl	33 ml		14:20	14:22		
15	filtrate charged to RBF			14:30		5	
16	Charged potassium dihydrogen phosphate	3.5 gm	10"	14:35		0	5
17	Stirred to get dissolution (clear sol" obtained)		10'	14:35	14:45	0	5
18	Charged Ethyl acetate	88 ml		14:45		0	5
19	adjusted the rxn mass pH to 7.0 with 10% w/w Sodium hydroxide solution (a) pH : 0.90 (b) pH : 7.06)	68 ml	30"	14:50	15:20	0	5
20	Raised the rxn mass temp		35'	15:20	15:55	4	25
21	Stirred the rxn mass		30"	15:55	16:25	25	27
22	Settled the rxn mass		15'	16:25	16:40	27	27
23	Separated the layers			16:40	16:45		
24	Charged Ethyl acetate to the aqeous layer	29 ml		16:46		26	
25	Stirred the rxn mass		30"	16:46	17:15	26	26
26	Settled the mass		15'	17:15	17:30	26	
27	Separate the layers			17:30	17:55	26	
28	Charged 5% w/w Sodium	41 ml		17:40		26	26

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Sr.no	unit operation	qty	Time	Time From	Time To	Temp(°c) From	Temp(°c) To	
	bicarbonate solution							
29	Stirred the rxn mass		30"	17:40	18:10	26	26	
30	Settled the rxn mass		15'	18:10	18:25	26	26	
31	Separated the layers			18:25	18:30			
32	Charged 5% w/w Sodium bicarbonate	41 kg		18:35		26	26	
	solution to the organic layer							
33	Stirred the rxn mass		30"	18:35	19:05	26	26	
34	Settled the rxn mass		15'	19:05	19:20	26	26	
35	Separated the layers			19:20	19:25	26	26	
36	Charged Sodium sulfate	14.3 kg		9:20		26	26	
	to the organic layer							
37	Stirred the rxn mass		10"	9:20	9:30	26	26	
38	filtered the Sodium sulfate			9:30	9:40	26	26	
39	distilled the solvent Under		45"	10:00	10:45	26	39	
	to get residue							
40	Charged Ethylacetate/Heptane	220 kg		10:50		35		
	(1:1) mixture							
41	heated the rxn mass		25'	10:50	11:15	35	70	
42	Maintained to get clear soln		1 hr	11:15	12:15	70	75	(Clear soln obtained)
43	Allow the mass to cool		55'	12:15	13:10	75	30	
	(hazy soln obtained at 70°,							
	thick mass obtained at 64°)							
44	Stirred the rxn mass		12 hrs	13:10	1:10	30	26	
45	filter the rxn mass			9:30	9:40	26		
46	washed the cake with	22 kg		9:40	9:45			
	Ethylacetate / Heptane (1:1)							
	mixture							
47	Dried the wet material		12 hrs	11:30	23:30	50	55	
	Under							
	wet wt = 17.1 gm							

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Sr.No	unit operation	Qty	Due	Time From	Time To	Temp°c From	Temp°c To
	Dry wt : 14.4 gm						
	Recrystallisation :-						
48	Charged above dried product	13.4gm	-	9:30		26	26
49	charged ethyl acetate/Heptane	150 ml	1hr	9:35		26	26
	(2:1) mixture						
50	heated the reaction mass		35"	9:35	10:10	26	70
51	observed the reaction mass to		1 hr	10:10	11:10	70	75
	get clear sol"						
	(at 75°c, 4/5 min clear sol"						
	obtained.)						
52	Allowed to cool		1 hr	11:10	12:10	25	30
	(4/30' at 55°c hazy sol" &						
	at 48°c thick mass obtained)						
53	Stirred		12 hrs	12:10	00:10	30	26
54	filtered			9:30	9:40		
55	washed the cake with	16 ml		9:40	9:45		
	Ethyl Acetate/Heptane (2:1) mixture						
56	Dried u/vac.		48 hr	11:00		50	55
	Wet wt : 14.9 gm						
	Dry wt : 12.6 gm						

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27/09/07 RST-III

Aim: preparation of Ritonavir Stage-III as per patent US 5541208 ex. 71

Input:

S.no	Raw material name	unit	Qty	mwt	moles	m/moles
1	RST-II (free base)	gm	10.0	425	0.0235	1.00
2	MTV-III (free acid)	gm	8.1	313	0.0258	1.10
3	Hydroxy benzo triazole mono hydrate	gm	3.95	153	0.0258	1.10
4	Dicyclohexyl carbodiimide	gm	5.33	206	0.0258	1.10
5	Tetrahydrofuran	ml	187	-	-	-
6	Ethyl acetate	ml	346	-	-	-
7	Sodium hydroxide	gm	6.6	40		
8	potassium dihydrogen phosphate	gm	3.5	135	-	-
9	1 N Hydrochloric acid	ml	149	-	-	-
10	Sodium bicarbonate	gm	4.1	84	0.047	2.02
11	Heptane	ml	196	-	-	-
12	purified water	ml	150	-	-	-
13	Sodium sulfate	gm	14.3	-	-	-

Procedure:-

S.No	unit operation	Qty	Time	Time From	Time To	Temp (°C) From	Temp (°C) To
1	Charged Tetrahydrofuran	187 ml		9:40		26	26
	Nitrogen atm.						
2	charged RST-II (free base)	10.0 gm		9:41		26	26
3	Charged Hydroxy benzo triazole	3.95 gm		9:43		26	26
	mono hydrate						
4	Charged MTV-III free acid	8.1 gm		9:45		26	26
5	Stirred to get clear sol"		10"	9:45	9:55	26	26
	(clear sol" obtained)						
6	charged Dicyclohexyl Carbo	5.33 gm		9:57			
	diimide						
7	Stirred the reaction mass		16 h	9:58	2:00	26	29
	(mass temp raised to 29°C)						

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S.No	unit operation	Qty	Time	Time From	Time To	Temp°c From	Temp°c To
	Solids emitted)						
8	Distilled the solvent under		1 hr	9:30	10:30	26	39
	to get residue						
9	Cooled the mass mass		20"	10:30	10:50	39	20
10	added chilled (5°c) 1N HCl	116 ml	15"	10:50	11:05	20	16
11	further cooled		20"	11:05	11:25	16	0
12	Stirred the mass mass		3 hr	11:25	14:25	0	5
13	filtered the mass mass			14:25	14:30		
	to remove off solids						
14	washed the cake with	33 ml		14:35			
	Chilled (5°c) 1N HCl						
15	Checked the filtrate is a aq			14:50			
16	Charged potassium dihydrogen	3.5 gm		14:50		0	3
	phosphate						
17	stirred to get dissolution		10'	14:50	15:00	0	3
	(clear soln obtained)						
18	Charged Ethyl acetate	88 ml		15:01		0	3
19	adjusted the mass mass pH	66 ml	30"	15:01	15:30	0	4
	to 7.0 with 10% w/v Sodium						
	hydroxide solution						
	(initial pH = 0.98 ; final pH = 7.03)						
20	raised the mass mass temp		30'	15:30	16:00	4	25
21	stirred		30"	16:00	16:30	25	27
22	settled		15"	16:30	16:45	27	
23	Separated the layers			16:45	16:50		
24	Charged Ethyl acetate to	29 ml		16:55		26	26
	the aq. layer						
			30'	16:55	17:25	26	26

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Entry	unit operation &	Qty	Time	Time From	Time To	Temp °C From	Temp °C To
28	Charged 5% w/v Sodium bi carbonate 50ml	41 ml		17:50		26	
29	Stirred		30"	17:50	18:20	26	26
30	Settled		15'	18:20	18:35	26	26
31	Separated the layers			18:35	18:40		
32	Charged 5% w/v Sodium bi carbonate 50ml	41 ml		18:50			
33	Stirred		30'	18:50	19:20	26	26
34	Settled		15'	19:20	19:35	26	26
35	separated the layers			19:35	19:40		
36	Charged sodium sulfate to the organic layer	14.3 gr		9:15			
37	Stirred		10'	9:15	9:25	26	26
38	filtered the sodium sulfate			9:25	9:35	26	26
39	distilled the solvent under reduced pressure		45'	9:50	10:35	26	39
40	Charged Ethylacetate / Heptane (1:1) mixture	220 ml		10:40		35	
41	heated the reaction mass (Clear 50° obtained)		30'	10:40	11:10	35	40
42	Maintained		1 h	11:10	12:10	40	45
43	Allow the mass to cool (Hazy 50° obtained at 48°c thick mass obtained at 60°c)		1 h	12:10	18:10	45	30
44	Stirred		12 h	13:10	1:10	30	26
45	Filtered			9:50	10:00	26	
46	washed the cake with Ethylacetate / Heptane (1:1) mixture	22 ml		10:00	10:05		
47	Dried under		12 h	11:30	23:30	50	55

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Sr No	unit operation	Qty	Time	Time From	Time To	Temp°C From	Temp°C To
	Wet wt : 17.6 gm						
	Dry wt : 14.6 gm						
	Recrystallisation :						
48	Charged above dried product	13.4 g		9:50		26	
49	Charged Ethylacetate/Heptane	150 ml		9:52		26	26
	(2:1) mixture						
50	heated the mass mass		40'	9:52	10:30	26	70
51	Stirred to get clear sol"		1 h	10:30	11:30	70	75
	(Clear sol" obtained at 74°c)						
52	Allowed to cool		1 h	11:30	12:30	75	30
53	(at 52°c hazy sol" & at 45°c						
	thick mass obtained)						
53	Stirred		12 h			30	26
54	filtered					26	
55	washed the cake with	16 ml					
	Ethylacetate/Heptane (2:1)						
	mixture						
56	Dried u/vac		48 h			50	55°
	Wet wt : 15.0 gm						
	Dry wt : 12.5 gm						

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27/09/07 RIT-III

Aim:- Preparation of Ritonavir - Stage-III as per US patent 5541206. ex. no: 71

Inputs :-

Sr.no	Raw material name	units	Qty	mwt	Moles	M/ratio
1	RIT-II (free base)	gm	10.0	425	0.0235	1.00
2	MTV-III (free acid)	gm	8.1	313	0.0258	1.10
3	Hydroxybenzotriazole monohydrate	gm	3.95	153	0.0258	1.10
4	Dicyclohexyl carbodiimide	gm	5.33	206	0.0258	1.10
5	Tetrahydrofuran	ml	187	-	-	-
6	Ethylacetate	ml	346	-	-	-
7	Sodium hydroxide	gm	6.8	40	0.17	7.23
8	potassiumdihydrogen phosphate	gm	3.5	135	-	-
9	1N Hydrochloric acid	ml	149	-	-	-
10	Sodium bicarbonate	gm	4.1	84	0.047	2.02
11	Heptane	ml	176	-	-	-
12	purified water	ml	150	-	-	-
13	Sodium sulfate	gm	14.3	-	-	-

Procedure :-

Sr.no	unit operation	Qty	Time	Time From	Time To	Temp(°C) From	Temp(°C) To
1	charged Tetrahydro furan	187 ml	1hour	10:00		26	26
	U/N atm						
2	charged RIT-II (free base)	10.0 g		10:02		26	26
3	charged Hydroxy benzotriazole monohydrate	3.95 g		10:04		26	26
4	charged MTV-III free acid			10:05		26	26
5	Stirred to get clear soln		10'	10:05	10:15	26	26
	(clear soln obtained)						
6	Charged Dicyclohexyl carbo -diimide	5.33 g		10:16		26	26
7.	stirred the reaction mass		16 hrs	10:16	2:15	26	29
	(mass temp raised to						

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Sno	unit operation	Qty	Time	Time From	Time To	Temp°C From	Temp°C To
	ope until solid emission)						
8	distilled solvent completely		1hr	10:00	11:00	26	38
	under to get residue						
9	cooled the mass		20'	11.00	11:20	38	20
10	added chilled (5°c) 1N HCl	116ml	15"	11:20	11:35	20	16
11	further cooled		20'	11:35	11:55	16	0
12	stirred the mass		3hr	11:55	14:55	0	5
13	filtered to remove off			14:55	15:00		
	solids						
14	washed the cake with	33ml		15:00	15:05		
	chilled 1N HCl						
15	charged the filtrate to a flask			15:15			
16	charged potassium dihydrogen	3.5gr		15:20		0	3
	phosphate						
17	stirred to get dissolution		10'	15:20	15:30	0	3
	(c: clear sol^n obtained)						
18	charged Ethyl acetate	88ml		15:30		0	3
19	adjusted pH to 7.0 with	69ml	25'	15:35	16:00	0	4
	10% w/w sodium hydroxide						
	solution.						
	(initial pH = 0.81, final pH = 7.08)						
20	cooled the mass temp		25'	16:00	16:25	4	25
21	stirred		30'	16:25	16:55	25	22
22	~~filtered~~ settled		15'	16:55	17:10	29	
23	separated the layers			17:10	17:15		
24	charged Ethyl acetate to the	29ml		17:20		22	
	aqeous layer						
			30"	17:20	17:50	22	26

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Sno	unit operation	Qty	Time	Time From	Time To	Temp°c From	Temp°c To
28	charged 5% w/w sodium bi carbonate soln	41 kg		18:15		26	26
29	Stirred		30'	18:15	18:45	26	26
30	Settled		15'	18:45	19:00	26	
31	separated the layers			19:00	19:03	26	
32	charged 5% w/w sodium bi carbonate soln	41 kg		19:10		26	26
33	Stirred		30'	19:10	19:40	26	26
34	Settled		15'	19:40	19:55	26	26
35	separated the layers			19:55	20:00	26	26
36	charged sodium sulfate to the organic layer	14.3 kg		9:45		26	26
37	Stirred		10'	9:45	9:55	26	26
38	filtered the sodium sulfate			9:55	10:00	26	
39	distilled solvent under to get residue		50'	10:20	11:10	26	39
40	charged Ethyl acetate / Heptane (1:1) mixture	220 kg		11:15		35	
41	heated the mass (clear soln obtained)		55"	11:15	11:40	35	70
42	Stirred		1 hr	11:40	12:40	70	35
43	Allowed the mass to cool to 25-30°c (after 30" at 65°c hazy soln & at 65°c thick mass obtained)		1 hr	12:40	13:40	35	30
44	Stirred		12 hr	13:40	1:40	30	26
45	filtered					26	
46	washed the cake with Ethyl acetate / Heptane (1:1) mixture	22 kg					

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Sno	unit operation	Qty	Time	Time From	Time To	Temp From	Temp To
48	Dried ulva		12h			50	55
	Wet wt : 13.2 gm						
	Dry wt : 11.3 gm						
	RECRYSTALISATION :-						
48	charged above dried product	13.4 gm				26	26
49	charged Ethyl acetate / Heptane	150 ml				26	26
	(2:1) mixture						
50	heated the iron mass		40°			26	70
51	Stirred to get dissolution		1h			70	75
	(4/5" clear sol" obtained						
	at 75°c)						
52	Allowed to cool		1h			75	30
	(at 55°c - hazy sol" & at						
	48°c thick mass obtained)						
53	stirred		12h			30	26
54	filtered					26	26
55	washed the cake with	16 ml				26	26
	Ethyl acetate / Heptane (2:1)						
	mixture						
56	Dried ulva		48h			50	55
	wet wt : 15.1 gm						
	Dry wt : 12.4 gm						