convention 657794

AUSTRALIA

Patents Act 1990

REQUEST FOR A (b) STANDARD PATENT

~~I~~/We being the person(s) identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying Standard/ Complete Patent Specification.

~~I am~~/We are (not an opponent or eligible person described in Sections 33-36 of the Act.

[70.71] Applicant and Nominated Person:

MERRELL DOW PHARMACEUTICALS INC.

of
2110 East Galbraith Road
Cincinnati, Ohio 45215
United States of America

[54] Invention Title **NOVEL CARBOXYALKYL DERIVATIVES USEFUL AS INHIBITORS OF ENKEPHALINASE AND ACE**

[72] Names of Actual Inventors

ALAN M. WARSHAWSKY

GARY A. FLYNN

[74] Address for Service:

PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia 3000
Attorney Code: PO

(Note: *The following applies only to Convention applications)*
Basic Convention Application Details

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MERRELL DOW PHARMACEUTICALS INC.

By

Stephen L. Nesbitt
Corporate Patent Counsel

Signature of Applicant

28 July 1992

Date

M01607 AU

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trademark Attorneys
367 Collins Street
Melbourne, Australia

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NOTICE OF ENTITLEMENT

I, STEPHEN L. NESBITT

Corporate Patent Counsel

of MERRELL DOW PHARMACEUTICALS INC.

of 2110 East Galbraith Road
Cincinnati, Ohio 45215
United States of America

State the following:

1. The nominated person (applicant) is entitled to the grant of a patent

    (i) as assignee of the actual inventor(s)
    ~~(ii) by contract of employment of the actual inventor(s)~~

2. The basic convention application~~(s)~~ was/~~were~~ the first made in a Convention country in respect of the invention the subject of the application.

Date July 28, 1992

MERRELL DOW PHARMACEUTICALS INC.

By Stephen L Nesbitt
STEPHEN L. NESBITT
Corporate Patent Counsel

To: The Commissioner of Patents

M01607 AU

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trademark Attorneys
367 Collins Street
Melbourne, Australia

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(54) Title
NOVEL CARBOXYALKYL DERIVATIVES USEFUL AS INHIBITORS OF ENKEPHALINASE AND ACE

International Patent Classification(s)
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C07D 513/04

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(71) Applicant(s)
MERRELL DOW PHARMACEUTICALS INC.

(72) Inventor(s)
ALAN M. WARSHAWSKY; GARY A. FLYNN

(74) Attorney or Agent
PHILLIPS ORMONDE & FITZPATRICK , 367 Collins Street, MELBOURNE VIC 3000

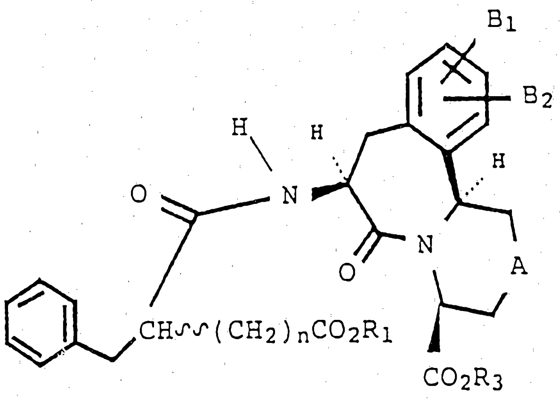
(56) Prior Art Documents
AU 89819/91 C07D 471/04
AU 85819/91 C07D 471/04

(57)

Compounds inhibit enkephalinase and ACE.

CLAIM

1. A compound of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_2$ wherein R_2 is a C_1-C_4 alkyl or an Ar-Y-group wherein Ar is aryl and Y is a ~~hydrogen~~ bond or C_1-C_4 alkyl; or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

A is a bond, methylene or oxygen, sulfur or NR_4 or $NCOR_5$ wherein R_4 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_5 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

R_3 is hydrogen or $-CH_2OC(O)C(CH_3)_3$;

R_1 is hydrogen, C_1-C_4 alkyl or $-CH_2OC(O)-C(CH_3)_3$; and

n is an integer 1 to 3.

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657794

COMPLETE SPECIFICATION
(ORIGINAL)

	Class	Int. Class
Application Number:		
Lodged:		

Complete Specification Lodged:
Accepted:
Published:

Priority

Related Art:

Name of Applicant:

Merrell Dow Pharmaceuticals Inc.

Actual Inventor(s):

Gary Alan Flynn
Alan M. Warshawsky

Address for Service:

PHILLIPS ORMONDE & FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne 3000 AUSTRALIA

Invention Title:

NOVEL CARBOXYALKYL DERIVATIVES USEFUL AS INHIBITORS OF ENKEPHALINASE AND ACE

Our Ref : 302120
POF Code: 1432/120371

The following statement is a full description of this invention, including the best method of performing it known to applicant(s):

NOVEL CARBOXYALKYL DERIVATIVES USEFUL AS INHIBITORS OF ENKEPHALINASE AND ACE

BACKGROUND OF THE INVENTION

Enkephalinase or, more specifically, endopeptidase-24.11, is a mammalian ectoenzyme which is involved in the metabolic degradation of certain circulating regulatory peptides. This enzyme, which is a Zn^{+2}-metallopeptidase, exerts its effect by cleaving the extracellular peptides at the amino group of hydrophobic residues and thus inactivates the peptides as regulatory messengers.

Enkephalinase is involved in the metabolic degradation of a variety of circulating regulatory peptides including endorphins, such as β-endorphin and the enkephalins, atrial natriuretic peptide (ANP), and other circulating regulatory peptides.

Endorphins are naturally-occurring polypeptides which bind to opiate receptors in various areas of the brain and thereby provide an analgesic effect by raising the pain threshold. Endorphins occur in various forms including α-endorphin, β-endorphin, γ-endorphin as well as the enkephalins. The enkephalins, i.e., Met-enkephalin and Leuenkephalin, are pentapeptides which occur in nerve endings of brain tissue, spinal cord and the gastrointestinal tract. Like the other endorphins, the enkephalins provide an analgesic effect by binding to the opiate receptors in the brain. By inhibiting enkephalinase, the metabolic degradation of the naturally-occurring endorphins and enkephalins are inhibited, thereby providing a potent endorphin- or enkephalin-mediated analgesic effect. Inhibition of enkephalinase would therefore be useful in a patient suffering from acute or chronic pain. Inhibition of enkephalinase would also be useful in providing an antidepressant effect and in providing a reduction in severity of withdrawal symptoms associated with termination of opiate or morphine administration.

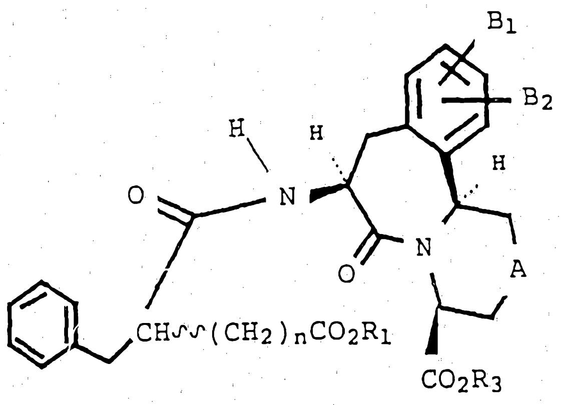
ANP refers to a family of naturally-occurring peptides which are involved in the homeostatic regulation of blood pressure, as well as sodium and water levels. ANP have been found to vary in length from about 21 to about 126 amino acids with a common structural feature being one or more disulfide-looped sequences of 17 amino acids with various amino- and carboxy-terminal sequences attached to the cystine moiety. ANP have been found to bind to specific binding sites in various tissues including kidney, adrenal, aorta, and vascular smooth muscle with affinities ranging from about 50 pico-molar (pM) to about 500 nano-molar (nM) [Needleman, *Hypertension* 7, 469 (1985)]. In addition, it is believed that ANP binds to specific receptors in the brain and possibly serves as a neuromodulator as well as a conventional peripheral hormone.

The biological properties of ANP involve potent diuretic/natriuretic and vasodilatory/hypotensive effects as well as an inhibitory effect on renin and aldosterone secretion [deBold, *Science* 230, 767 (1985)]. By inhibiting enkephalinase, the metabolic degradation of the naturally-occurring ANP are inhibited, thereby providing a potent ANP-mediated diuretic, natriuretic, hypotensive, hypoaldosteronemic effects. Inhibition of enkephalinase would therefore be useful in a patient suffering from disease states characterized by abnormalities in fluid, electrolyte, blood pressure, intraocular pressure, renin, or aldosterone homeostasis, such as, but not limited to, hypertension, renal diseases, hyperaldosteronemia, cardiac hypertrophy, glaucoma and congestive heart failure.

In addition, the compounds of the present invention are inhibitors of Angiotensin-Converting Enzyme (ACE). ACE is a peptidyl dipeptidase which catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II is a vasoconstrictor which also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE would therefore be useful in a patient suffering from disease states such as hypertension and congestive heart failure [See William W. Douglas, "Polypeptides - Angiotensin, Plasma Kinins, and Others", Chapter 27, in GOODMAN AND GILLMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 7th edition, 1985, pp. 652-3, MacMillan Publishing Co., New York, New York]. In addition, it has been disclosed that ACE inhibitors are useful in treating cognitive disorders [German Application No. 3901-291-A, published August 3, 1989].

SUMMARY OF THE INVENTION

The present invention provides novel compounds of the Formula (I)



(I)

wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_2$ wherein R_2 is a C_1-C_4 alkyl or an Ar-Y-group wherein Ar is aryl and Y is a ~~hydrogen~~ bond or C_1-C_4 alkyl; or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

A is a bond, methylene or oxygen, sulfur or NR_4 or $NCOR_5$ wherein R_4 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_5 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

R_3 is hydrogen or $-CH_2OC(O)C(CH_3)_3$;

R_1 is hydrogen, C_1-C_4 alkyl or $-CH_2OC(O)-C(CH_3)_3$; and

n is an integer 1 to 3.

The present invention further provides a method of inhibiting enkephalinase in a patient in need thereof ~~comprising~~ including administering to said patient an effective enkephalinase inhibitory amount of a compound of Formula (I). The present invention also provides a method of inhibiting ACE in a patient in need thereof including ~~comprising~~ administering to said patient an effective ACE inhibitory amount of a compound of Formula (I).

In addition, the present invention provides a composition ~~comprising~~ including an assayable amount of a compound of Formula (I) in admixture or otherwise in association with an inert carrier. The present invention also provides a pharmaceutical composition ~~comprising~~ including an effective inhibitory amount of a compound of Formula (I) in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

DETAILED DESCRIPTION OF THE INVENTION

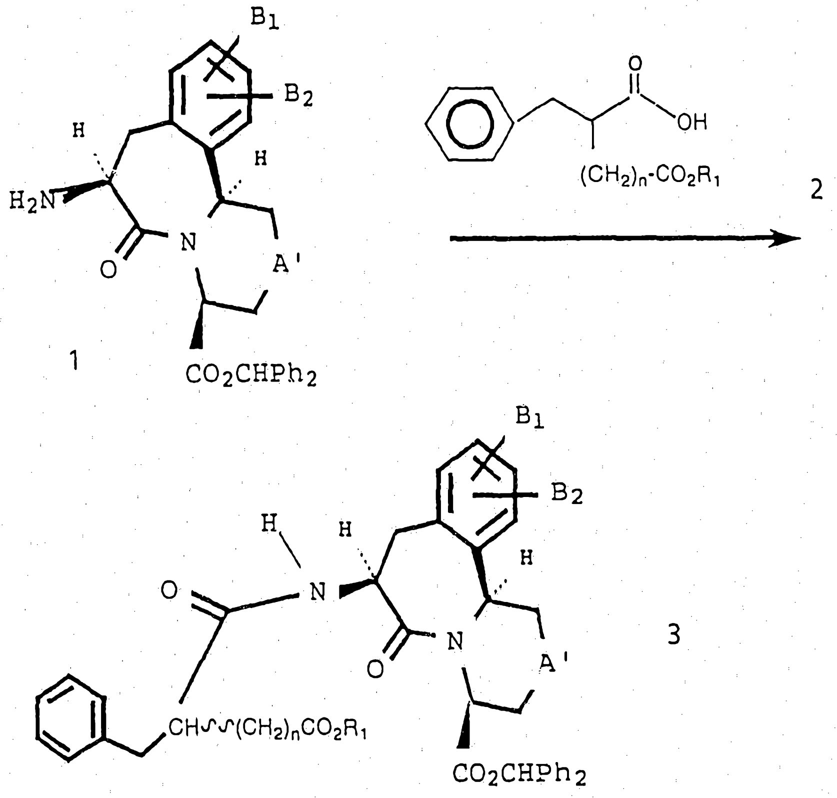
As used herein, the term "C_1-C_4 alkyl" refers to a saturated straight or branched chain hydrocarbyl radical of one to four carbon atoms and includes methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl and the like. The terms "C_1-C_8 alkyl" and "C_1-C_{10} alkyl" refer to saturated straight or branched chain hydrocarbyl radicals of one to eight and one to ten carbon atoms, respectively, including methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, pentyl, isopentyl, hexyl, 2,3-dimethyl-2-butyl, heptyl, 2,2-dimethyl-3-pentyl, 2-methyl-2-hexyl, octyl, 4-methyl-3-heptyl and the like. The term "halogen", "halo", "halide" or "X" refers to a chlorine, bromine, or iodine atom.

As used herein, the term "Ar-Y-" refers to a radical wherein Ar is an aryl group and Y is a C_0-C_4 alkyl. The term "Ar" refers to a phenyl or naphthyl group unsubstituted or substituted with from one to three substituents selected from the group consisting of methylenedioxy, hydroxy, C_1-C_4 alkoxy, fluoro and chloro. The term "C_0-C_4 alkyl" refers to a saturated straight or branched chain hydrocarbyl radical of zero to four carbon atoms and includes a bond, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl and the like. Specifically included within the scope of the term "Ar-Y-" are phenyl, naphthyl, phenylmethyl or benzyl, phenylethyl, p-methoxybenzyl, p-fluorobenzyl and p-chlorobenzyl.

As used herein, the designation "∿∿" refers to a bond to a chiral atom for which the stereochemistry is not designated and compounds of Formula I wherein A is a bond is understood to be a 5-membered ring.

The compounds of Formula I wherein A is methylene, oxygen, sulfur or NH, R_1 is t-butyl and R_3 is diphenylmethyl can be prepared by utilizing procedures and techniques well known and appreciated by one of ordinary skill in the art. A general synthetic scheme for preparing these compounds is set forth in Scheme A wherein all substituents, unless otherwise indicated, are previously defined.

Scheme A



A' = a bond, $-CH_2-$, O, S or NH

The compounds of Formula I wherein A is a bond, methylene, oxygen, sulfur or NH can be prepared by reacting the appropriate 3-phenyl-2-carbalkoxyalkylpropionic acid compound of structure 2 with the appropriate amino compound of structure 1. For example, the appropriate amino compound of structure 1 can be reacted with the appropriate 3-phenyl-2-carbalkoxyalkylpropionic acid compound of structure 2 in the presence of a coupling reagent such as EEDQ (1-

ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline), DCC (1,3-dicyclohexylcarbodiimide), or diethylcyanophosponate in a suitable aprotic solvent, such as methylene chloride to give the appropriate tricyclic compound of Formula I.

Alternatively, the 3-phenyl-2-carbalkoxyalkylpropionic acid compound of structure 2 can be converted to the corresponding 3-phenyl-2-carbalkoxyalkylpropionic acid, acid chloride, followed by reaction with the appropriate amino compound of structure 1 to give the appropriate compound of Formula I.

As summarized in Table 1, the R_1 and R_3 groups on the compounds of structure 3 can be manipulated using techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding compounds of structures 4 through 9.

For example, both the diphenylmethyl ester functionality and the t-butyl ester functionality of the appropriate compound of structure 3 can be removed using trifluoroacetic acid to give the appropriate dicarboxylic acid compound of structure 4.

For example, the appropriate tricyclic compound of structure 3, wherein R_1 is t-butyl and R_3 is diphenylmethyl, is contacted in an appropriate acidic solvent such as trifluoroacetic acid. The reactants are typically stirred together at om temperature for a period of time ranging from 1-24 hours. The carboxylic acid compound of structure 4 is recovered from the reaction zone by extractive methods as is known in the art. It can be purified by silica gel chromatography.

Both the carboxylic acid functionalities of the appropriate dicarboxylic acid compound of structure 4 can be reesterified using techniques and procedures well known and appreciated in the art. For example, a dipivaloyl methyl ether ester compound of structure 5 can be prepared by treating the dicarboxylic acid compound of structure 4 with 2 molar equivalents of chloromethyl pivalate in a suitable aprotic solvent, such as dimethylformamide along with a non-nucleophilic base, such as cesium carbonate.

The diphenylmethyl ester functionality of the appropriate tricyclic compound of structure 3, wherein R_1 is C_1-C_4 and R_3 is diphenylmethyl can be selectively removed using catalytic hydrogenation as is known in the art to give the appropriate C_1-C_4 alkyl ester/carboxylic acid compound of structure 6. For example, the C_1-C_4 alkyl ester/carboxylic acid compound of structure 6 can be prepared by treating the appropriate tricyclic compound of structure 3, wherein R_1 is C_1-C_4 and R_3 is diphenylmethyl with a catalytic amount of palladium/carbon and a molar excess of ammonium formate. The reactants are typically contacted in a suitable polar organic solvent such as methanol. The reactants are typically contacted at room temperature for a period of time ranging from 3 minutes to 24 hours. The C_1-C_4 alkyl ester/carboxylic acid compound of structure 6 can be recovered from the reaction zone by filtration and evaporation of the solvent.

The carboxylic acid functionality of the appropriate C_1-C_4 alkyl ester/carboxylic acid compound of structure 6 can be reesterified to give the appropriate C_1-C_4 alkyl ester/pivaloyl methyl ether ester of structure 7. For example, a C_1-C_4 alkyl ester/pivaloyloxymethyl ester compound of structure 7 can be prepared by treating the appropriate C_1-C_4 alkyl ester/carboxylic acid compound of structure 6 with 1 molar equivalent of chloromethyl pivalate in a suitable aprotic solvent, such as dimethylformamide along with a non-nucleophilic base, such as cesium carbonate.

The C_1-C_4 alkyl ester functionality of the appropriate C_1-C_4 alkyl ester/pivaloyl methyl ether ester of structure 7, wherein the C_1-C_4 alkyl ester is not t-butyl, can be hydrolyzed under basic conditions, such as lithium hydroxide in methanol, as is known in the art, to give the carboxylic acid/pivaloyl methyl ether ester of structure 8.

The compounds of Formula I wherein R_1 is pivaloyloxymethyl ester and R_3 is hydrogen can be prepared in a multi-step process.

For example, the C_1-C_4 alkyl ester functionality of the appropriate C_1-C_4 alkyl ester/diphenylmethyl ester of the appropriate tricyclic compound of structure 3, wherein the C_1-C_4 alkyl ester is not t-butyl can be hydrolyzed under basic conditions, such as lithium hydroxide in methanol, as is known in the art, to give the intermediate carboxylic acid/diphenylmethyl ester compound.

The carboxylic acid functionality of the appropriate intermediate carboxylic acid/diphenylmethyl ester compound can then be reesterified to give the intermediate pivaloyloxymethyl ester/diphenylmethyl ester compound. For example, an intermediate pivaloyloxymethyl/diphenylmethyl ester compound can be prepared by treating the appropriate intermediate carboxylic acid/diphenylmethyl ester compound with 1 molar equivalent of chloromethyl pivalate in a suitable aprotic solvent, such as dimethylformamide along with a non-nucleophilic base, such as cesium carbonate.

The diphenylmethyl ester functionality of the appropriate intermediate pivaloyloxymethyl/diphenylmethyl ester compound can be removed by hydrogenation as is known in the art to give the pivaloyloxymethyl/carboxylic acid compound of structure 9. For example, the pivaloyloxymethyl/carboxylic acid compound of structure 9 can be prepared by treating the appropriate intermediate pivaloyloxymethyl/diphenylmethyl ester compound with a catalytic amount of palladium/carbon and a molar excess of ammonium formate. The reactants are typically contacted in a suitable polar organic solvent such as methanol. The reactants are typically contacted at room temperature for a period of time ranging from 3 minutes to 24 hours. The pivaloyloxymethyl/carboxylic acid compound of structure 9 can be recovered from the reaction zone by filtration and evaporation of the solvent.

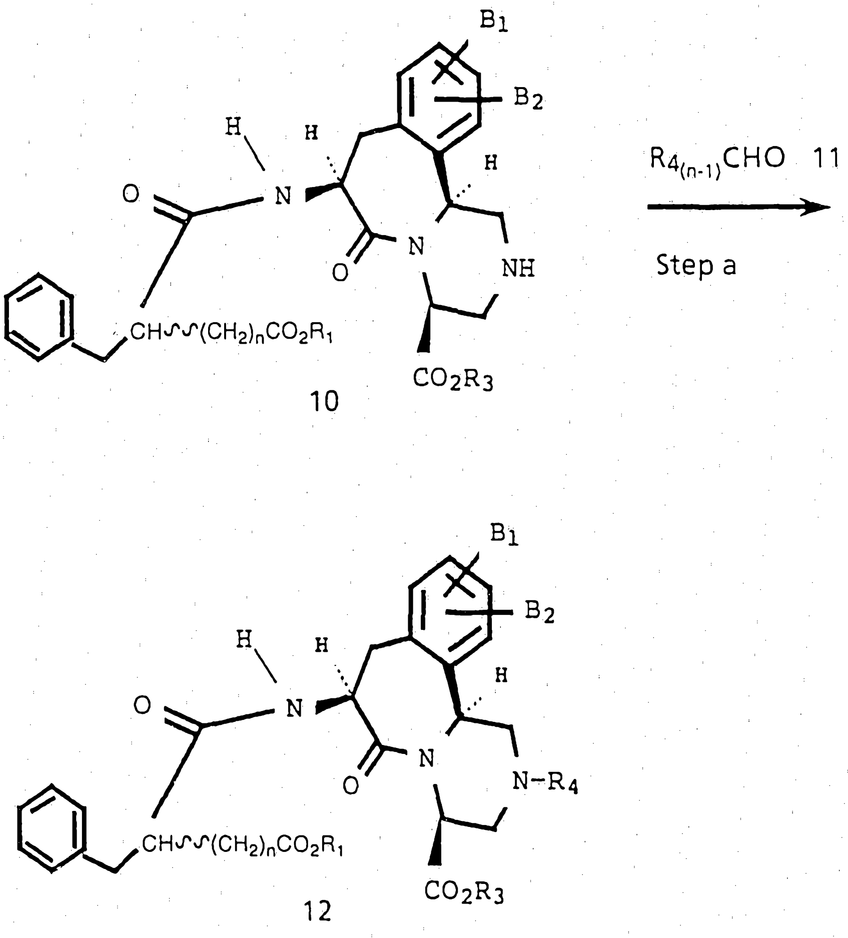
TABLE 1

MANIPULATION OF R_1 AND R_3

Compound	R_1	R_3
4	H	H
5	$CH_2OCOC(CH_3)_3$	$-CH_2OCOC(CH_3)_3$
6	C_1-C_4 alkyl-	H
7	C_1-C_4 alkyl	$-CH_2OCOC(CH_3)_3$
8	H	$-CH_2OCOC(CH_3)_3$
9	$-CH_2OCOC(CH_3)_3$	H

The compounds of Formula I wherein A is $-NR_4$ can be prepared by techniques and procedures well known and appreciated by one of ordinary skill in the art. A general synthetic procedure for preparing these compounds is set forth in Scheme B. In Scheme B, all substituents unless otherwise indicated are as previously defined.

Scheme B

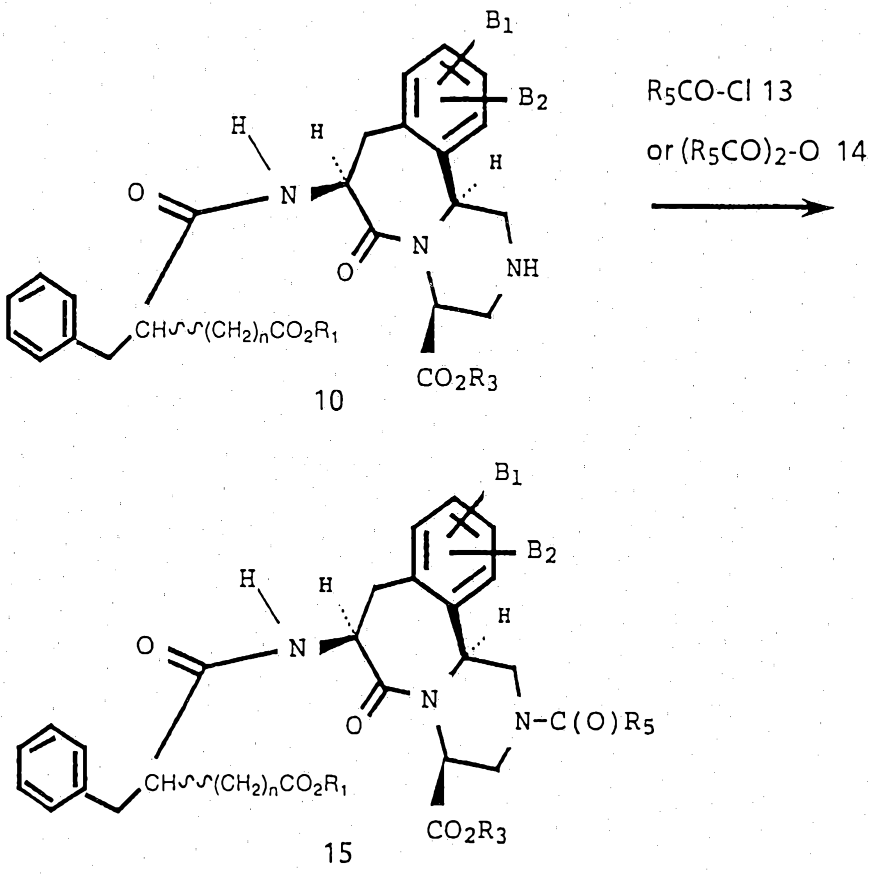


Scheme B provides a general synthetic procedure for preparing the compounds of Formula I wherein A is $-NR_4$. The amino functionality of the appropriate amino compound of structure <u>10</u> is subjected to reductive alkylation with the appropriate aldehyde of structure <u>11</u> using sodium cyanoborohydride, as is well known in the art, to give the corresponding N-alkylamino compound of structure <u>12</u>.

The R_1 and R_3 groups on the compounds Formula 1 wherein A is $-NR_4$ can be manipulated as described previously in Scheme A and Table 1.

The compounds of Formula I wherein A is $-NCOR_5$ can be prepared by techniques and procedures well known and appreciated by one of ordinary skill in the art. A general synthetic procedure for preparing these compounds is set forth in Scheme C. In Scheme C, all substituents unless otherwise indicated are as previously defined.

Scheme C



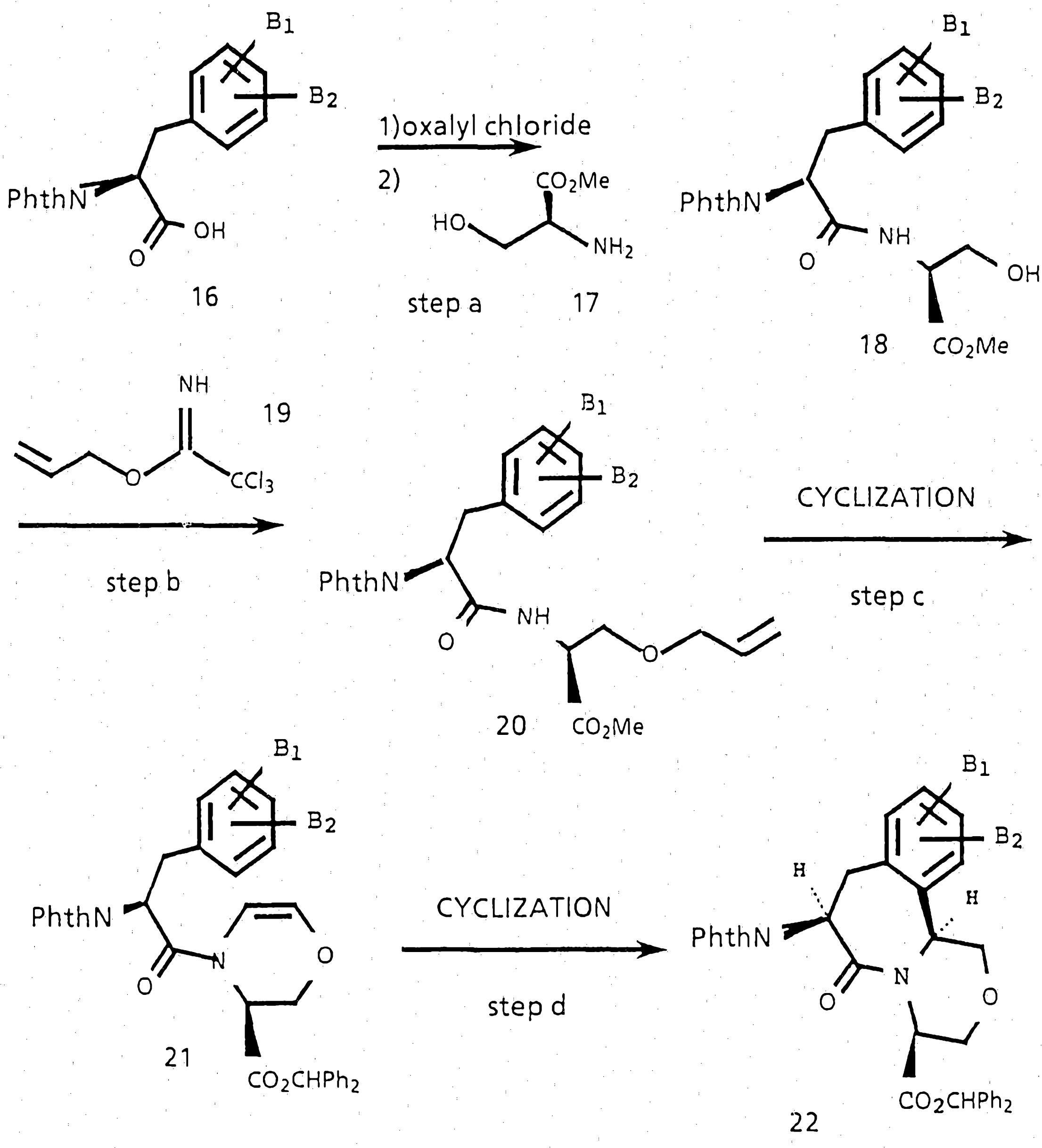
Scheme C provides a general synthetic procedure for preparing the compounds of Formula I wherein A is -NCOR$_5$. The appropriate amino compound of structure 10 is acylated using the appropriate acyl chloride of structure 13 or the appropriate anhydride of structure 14, as is well known in the art, to give the corresponding N-acylamino compound of structure 15.

The groups R_1 and R_3 may be manipulated by techniques and procedures well known and appreciated in the art and described previously in Scheme A and shown in Table 1.

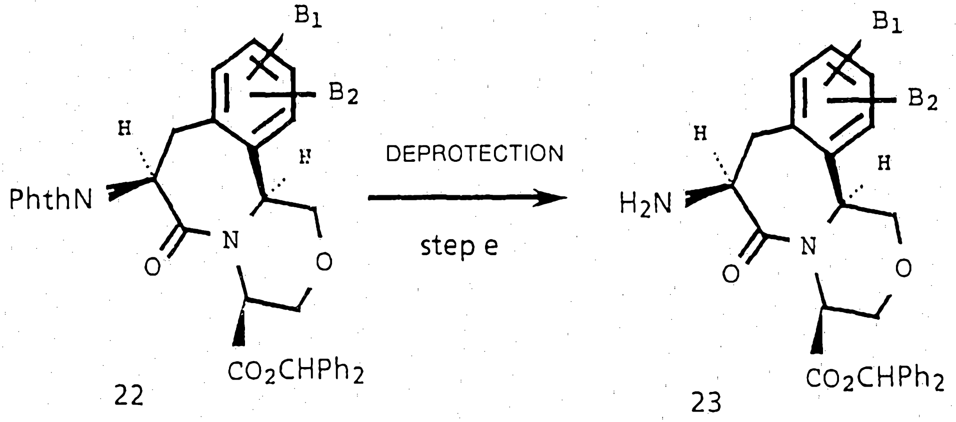
Starting materials for use in Scheme A through Scheme C are readily available to one of ordinary skill in the art. For example, certain tricyclic amino compounds of structure 1 wherein X is S are described in European Patent 0 249 223 (December 16, 1987) and certain other tricyclic amino compounds of structure 1 wherein A is methylene may be prepared as described in European Patent Application of Flynn and Beight, Application #34533A EP (June 11, 1987).

Tricyclic amino compounds of structure 1 wherein A is O may be prepared as described in Scheme D. In Scheme D, all substituents unless otherwise indicated are as previously defined.

Scheme D


B1
B2
PhthN
OH
O
16
1)oxalyl chloride
2)
CO2Me
HO
NH2
step a
17
PhthN
NH
OH
18
CO2Me
NH
19
O
CCl3
step b
PhthN
NH
O
20
CO2Me
CYCLIZATION
step c
PhthN
N
O
21
CO2CHPh2
CYCLIZATION
step d
H
PhthN
N
O
CO2CHPh2
22

Scheme D



Scheme D provides a general synthetic procedure for preparing amino compounds of structure 1 wherein A is O.

In step a, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure 16 is converted to the corresponding acid chloride, then reacted with the appropriate L-serine methyl ester of structure 17 to give the corresponding 1-oxo-3-phenylpropyl-L-serine methyl ester of structure 18.

For example, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure 16 can be reacted with oxalyl chloride in a suitable aprotic solvent, such as methylene chloride. The resulting acid chloride can then be coupled with the appropriate L-serine methyl ester of structure 17 using N-methylmorpholine in a suitable aprotic solvent, such as dimethylformamide, to give the appropriate 1-oxo-3-phenylpropyl-L-serine methyl ester of structure 18.

In step b, the hydroxy functionality of the appropriate 1-oxo-3-phenylpropyl-L-serine methyl ester of structure 18 is allylated with the allyl imidate of structure 19 to give the corresponding 1-oxo-3-phenylpropyl-L-serine-O-allyl methyl ester of structure 20.

For example, the appropriate 1-oxo-3-phenylpropyl-L-serine methyl ester of structure 18 is contacted with 2 molar equivalents of the allyl imidate of structure 19 and a molar equivalent of a suitable acid such as trifluoromethanesulfonic acid. The reactants are typically contacted in a suitable organic solvent mixture such as methylene chloride/cyclohexane. The reactants are typically stirred together at room temperature under an inert atmosphere for a period of time ranging from 2-24 hours. The 1-oxo-3-phenylpropyl-L-serine-O-allyl methyl ester of structure 20 is recovered from the reaction zone by extractive methods as is known in the art. It may be purified by silica gel chromatography or crystallization.

In step c, the appropriate 1-oxo-3-phenylpropyl-L-serine-O-allyl methyl ester of structure 20 is cyclized to give the corresponding (4S)-enamine of structure 21.

For example, the appropriate 1-oxo-3-phenylpropyl-L-serine-O-allyl methyl ester of structure 20 is first contacted with a molar excess of a mixture of ozone/oxygen. The reactants are typically contacted in a suitable organic solvent mixture such as methylene chloride/methanol. The reactants are typically stirred together for a period of time ranging from 5 minutes to 30 minutes or until a blue color persists and at a temperature range of from -78°C to -40°C. The reaction is quenched with an excess of methylsulfide and the intermediate aldehyde compound recovered from the reaction zone by extractive methods as is known in the art.

The intermediate aldehyde compound is then contacted with trifluoroacetic acid in a suitable aprotic solvent, such as methylene chloride to give the corresponding (4S)-enamine of structure <u>21</u>.

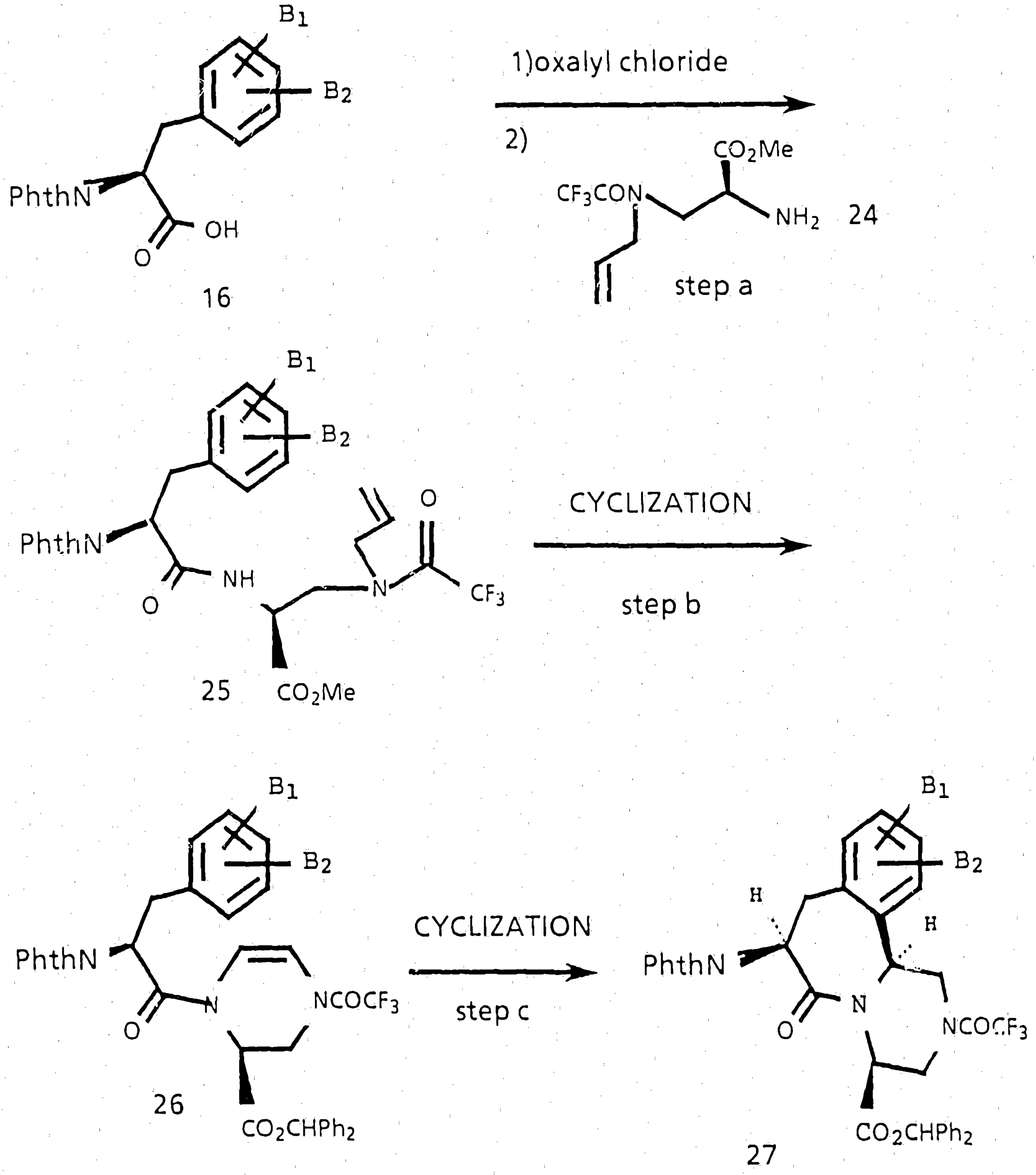
In step d, the appropriate and (4S)-enamine of structure <u>21</u> is cyclized to give the corresponding (4S)-tricyclic compound of structure <u>22</u> by an acid catalyzed Friedel-Crafts reaction. For example, the appropriate (4S)-enamine of structure <u>21</u> can be converted to the corresponding (4S)-tricyclic compound of structure <u>22</u> by treatment with a mixture of trifluoromethane sulfonic acid and trifluoroacetic anhydride in a suitable aprotic solvent, such as methylene chloride.

In step d, it may be necessary to reesterify the carboxy functionality due to the conditions of the work-up. For example, treatment of the crude product with bromodiphenylmethane in a suitable aprotic solvent, such as dimethylformamide along with a non-nucleophilic base, such as cesium carbonate, may be used to give the corresponding (4S)-diphenylmethyl ester.

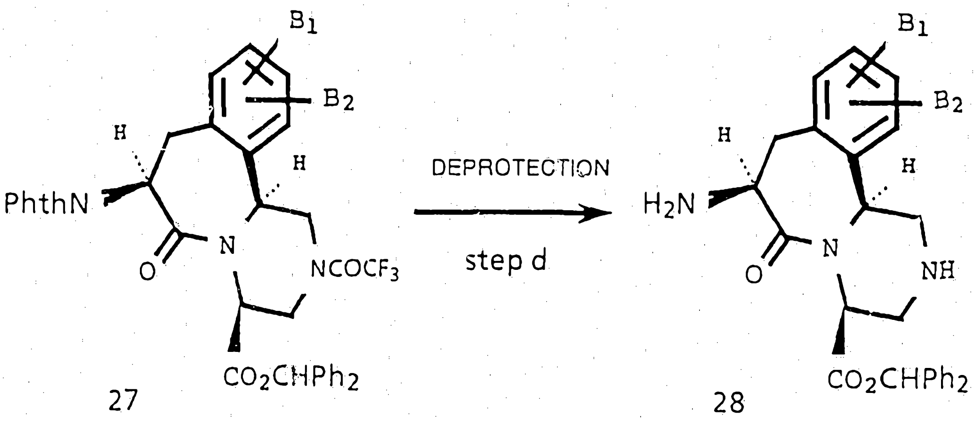
In step e, the phthalimide protecting group of the appropriate (4S)-tricyclic compound of structure <u>22</u> is removed to give the corresponding amino compound of structure <u>23</u> wherein X is O. For example, the phthalimide protecting group of the appropriate (4S)-tricyclic compound of structure <u>22</u> can be removed using hydrazine monohydrate in a suitable protic solvent such as methanol, to give the corresponding (4S)-tricyclic amino compound of structure 23.

Tricyclic amino compounds of structure 1 wherein A is NH may be prepared as described in Scheme E. In Scheme E, all substituents unless otherwise indicated are as previously defined.

Scheme E


B1
B2
PhthN
OH
O
16
1)oxalyl chloride
2)
CO2Me
CF3CON
NH2
24
step a
B1
B2
PhthN
NH
O
O
N
CF3
25
CO2Me
CYCLIZATION
step b
B1
B2
PhthN
O
N
NCOCF3
26
CO2CHPh2
CYCLIZATION
step c
B1
B2
H
H
PhthN
O
N
NCOCF3
CO2CHPh2
27

Scheme E



Scheme E provides an alternative general synthetic procedure for preparing amino compounds of structure 1 wherein A is NH.

In step a, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure 16 is converted to the corresponding acid chloride, then reacted with the appropriate 3-trifluoracetylamino-3-allyl-L-2-aminopropionic acid, methyl ester of structure 24 to give the corresponding 1-oxo-3-phenylpropyl-N-trifluoracetyl-N-allyl-L-amino acid, methyl ester of structure 25 as described previously in Scheme D, step a.

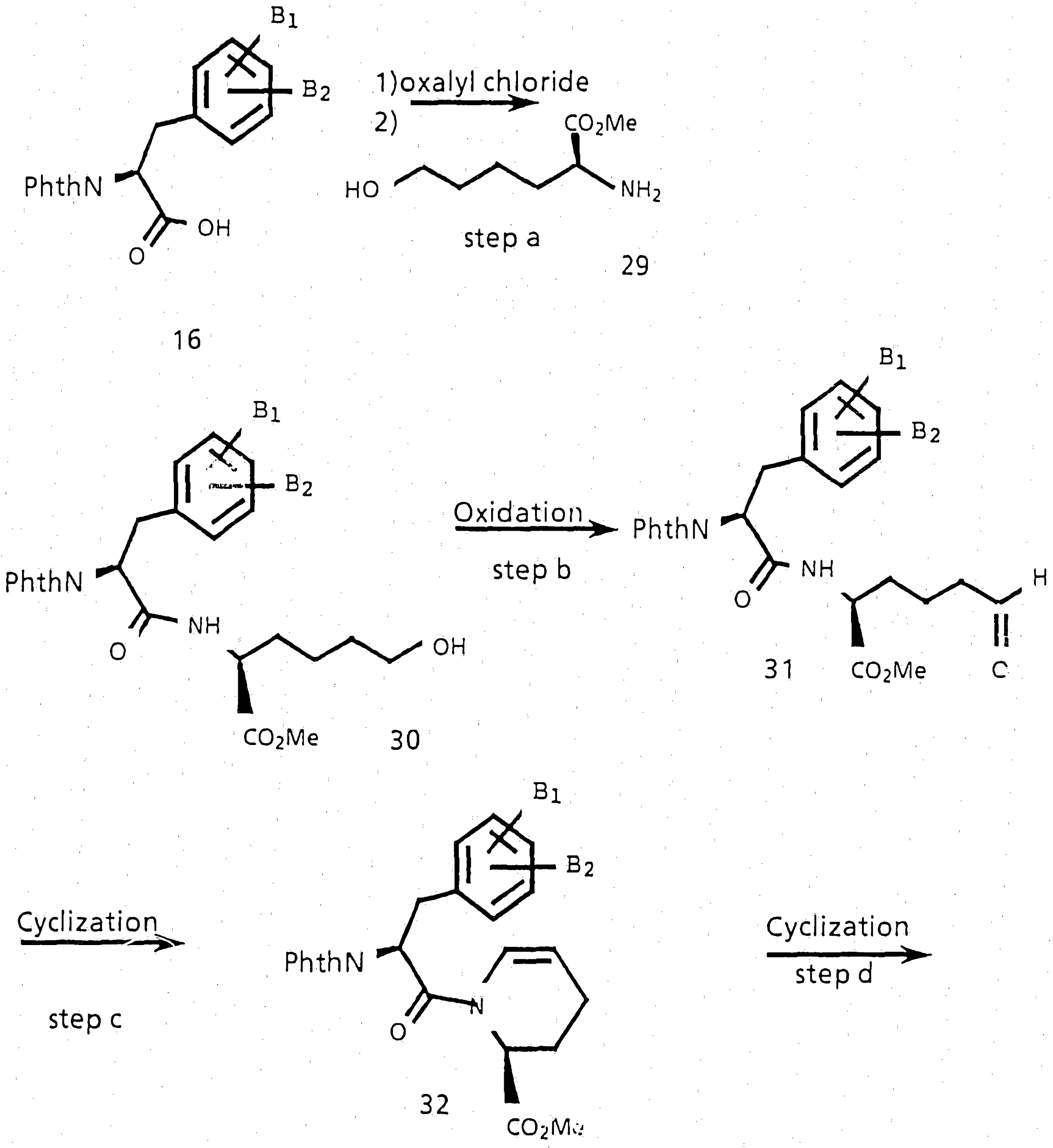
In step b, the appropriate 1-oxo-3-phenylpropyl-N-trifluoracetyl-N-allyl-L-amino acid methyl ester of structure 25 is cyclized to give the corresponding enamine of structure 26 as described previously in Scheme D, step c.

In step c, the appropriate (4S)-enamine of structure 26 is cyclized to give the corresponding (4S)-tricyclic compound of structure 27 as described previously in Scheme D, step d.

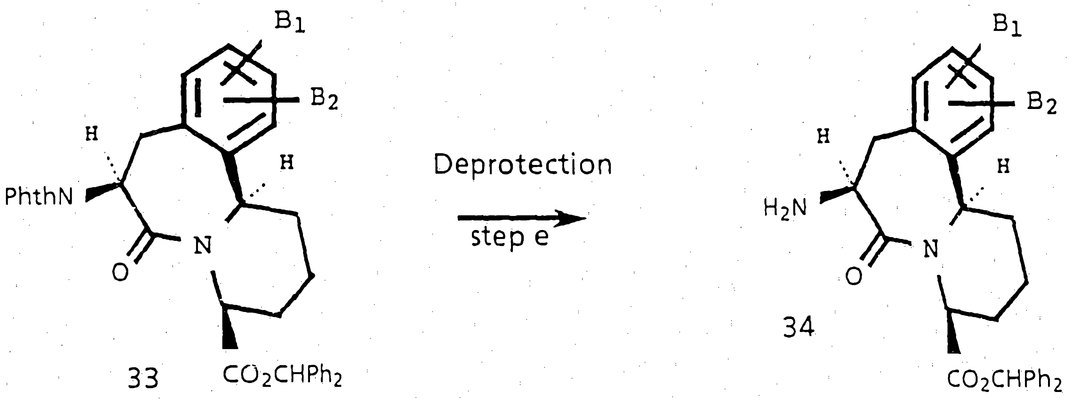
In step d, the phthalimide protecting group of the appropriate (4S)-tricyclic compound of structure 27 is removed to give the corresponding (4S)-amino compound of structure 28 wherein X is NH as described in Scheme D, step e.

Tricyclic amino compounds of structure 1 wherein A is methylene may be prepared as described in Scheme F. In Scheme F, all substituents unless otherwise indicated are as previously defined.

Scheme F


B1
B2
1)oxalyl chloride
2)
CO2Me
HO
NH2
PhthN
OH
O
step a
29
16
Oxidation
step b
NH
30
31
H
O
Cyclization
step c
N
32
Cyclization
step d

Scheme F cont.



Scheme F provides a general synthetic procedure for preparing the tricyclic amino compounds of structure <u>1</u> wherein A is methylene.

In step a, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure <u>16</u> can be converted to the corresponding acid chloride, then reacted with the appropriate amino acid methyl ester of structure <u>29</u> in a coupling reaction. For example, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure <u>16</u> can be reacted with oxalyl chloride in a suitable aprotic solvent, such as methylene chloride. The resulting acid chloride can then be coupled with the appropriate amino acid methyl ester of structure <u>29</u> using N-methylmorpholine in a suitable aprotic solvent, such as dimethylformamide, to give the appropriate 1-oxo-3-phenylpropyl-amino acid methyl ester derivative of structure <u>30</u>.

In step b, the hydroxymethylene functionality of the appropriate 1-oxo-3-phenylpropyl-amino acid methyl ester derivative of structure <u>30</u> can be oxidized to the appropriate aldehyde of structure <u>31</u> by oxidation techniques well known and appreciated in the art. For example, the hydroxymethylene functionality of the appropriate 1-oxo-3-phenylpropyl-amino acid methyl ester derivative of structure <u>30</u> can be oxidized to the appropriate aldehyde of structure <u>31</u> by means of a Swern oxidation using oxalyl chloride and dimethylsulfoxide in a suitable aprotic solvent, such as methylene chloride.

In step c, the appropriate aldehyde of structure <u>31</u> can be cyclized to the appropriate enamine of structure <u>32</u> by acid catalysis. For example, the appropriate aldehyde of structure <u>31</u> can be cyclized to the appropriate enamine of structure <u>32</u> by treatment with trifluroacetic acid in a suitable aprotic solvent, such as methylene chloride.

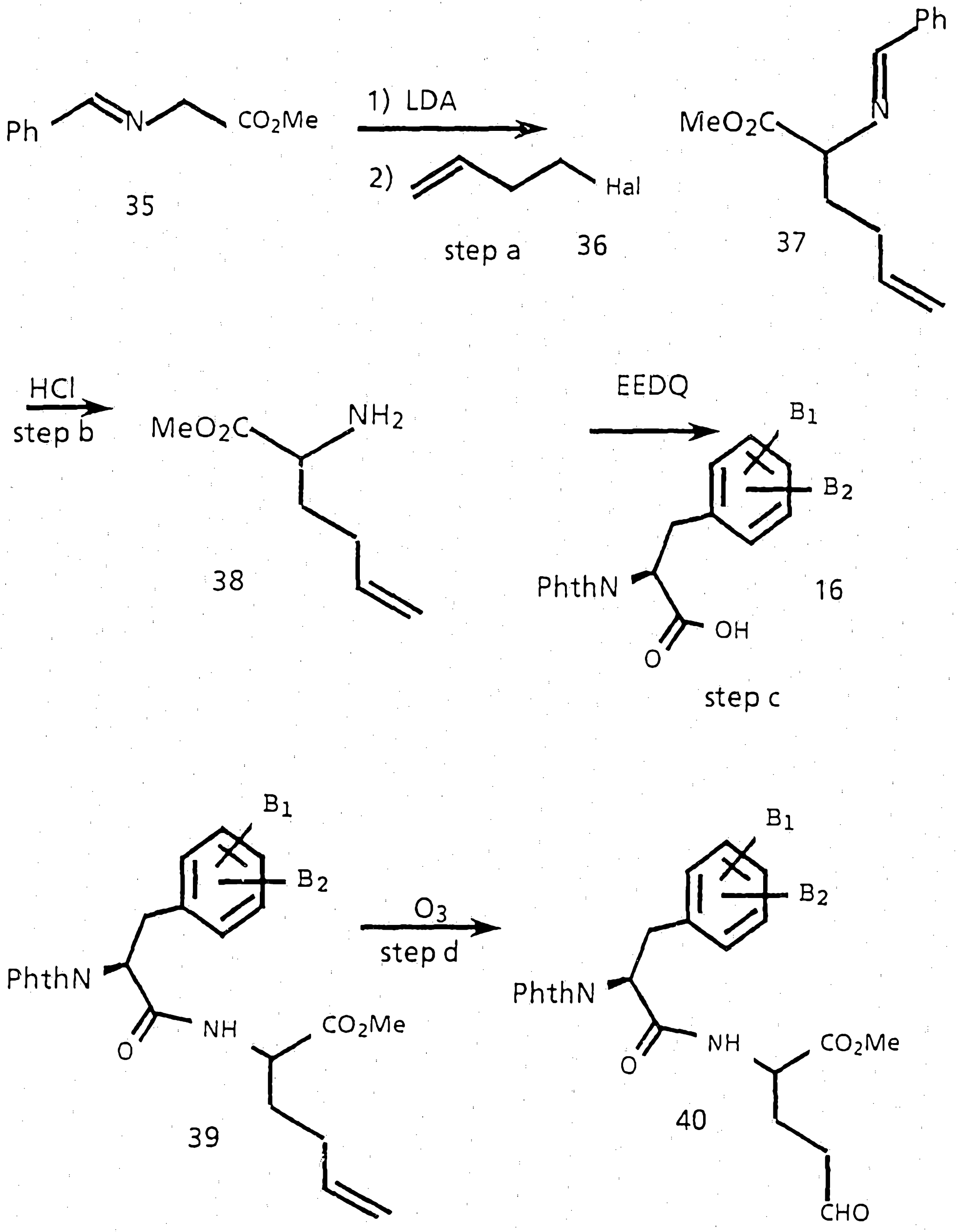
In step d, the appropriate enamine of structure <u>32</u> can be converted to the corresponding tricyclic compound of structure <u>33</u> by an acid catalyzed Friedel-Crafts reaction. For example, the appropriate enamine of structure <u>32</u> can be converted to the corresponding tricyclic compound of structure <u>33</u> by treatment with a mixture of trifluoromethane sulfonic acid and trifluoroacetic anhydride in a suitable aprotic solvent, such as methylene chloride.

In step d, it may be necessary to reesterify the carboxy functionality due to the conditions of the work-up. For example, treatment of the crude product with bromodiphenylmethane in a suitable aprotic solvent, such as dimethylformamide along with a non-nucleophilic base, such as cesium carbonate, may be used to give the corresponding diphenylmethyl ester.

In step e, the phthalimide protecting group of the appropriate tricyclic compound of structure <u>33</u> can be removed using techniques and procedures well known in the art. For example, the phthalimide protecting group of the appropriate tricyclic compound of structure 33 can be removed using hydrazine monohydrate in a suitable protic solvent such as methanol, to give the corresponding amino compound of structure 34.

The compounds of Formula I wherein A is a bond can be prepared by utilizing procedures and techniques well known and appreciated by one of ordinary skill in the art. A general synthetic scheme for preparing these compounds is set forth in Scheme G wherein all substituents, unless otherwise indicated, are previously defined.

Scheme G


Ph
CO2Me
35
1) LDA
2)
Hal
step a
36
MeO2C
N
Ph
37
HCl
step b
MeO2C
NH2
38
EEDQ
B1
B2
PhthN
OH
O
16
step c
B1
B2
PhthN
O
NH
CO2Me
39
O3
step d
B1
B2
PhthN
O
NH
CO2Me
40
CHO

Scheme G provides a general synthetic procedure for preparing compounds of Formula I wherein A is a bond.

In step a, the N-(phenylmethylene)glycine methyl ester of structure 35 can be treated with one equivalent of a non-nucleophilic base, such as lithium diisopropylamide, in a suitable aprotic solvent, such as tetrahydrofuran, followed by addition of a 4-halobutene of structure 36 to give 2-(3-butenyl)-N-(phenylmethylene)glycine methyl ester of structure 37.

In step b, the N-(phenylmethylene) functionality of 2-(3-butenyl)-N-(phenylmethylene)glycine methyl ester of structure 37 can be hydrolyzed under acidic conditions, such as with hydrochloric acid in a suitable aprotic solvent, such as ethyl ether to give 2-(3-butenyl)-glycine methyl ester of structure 38.

In step c, the appropriate amide compound of structure 38 can be prepared by reacting the appropriate phthalimide protected (S)-phenylalanine compound of structure 16 with 2-(3-butenyl)-glycine methyl ester of structure 39 under coupling reaction conditions, such as with EEDQ, in a suitable aprotic solvent, such as methylene chloride.

In step d, the olefin functionality of the appropriate amide compound of structure 39 can be converted to the appropriate aldehyde compound of structure 40 under conditions of oxidative cleavage, such as treatment with ozone in a suitable solvent mixture, such as methylene chloride and methanol.

The compounds of Formula I wherein A is a bond can be prepared from an appropriate aldehyde of structure 40 in a process as outlined previously in Scheme F, steps c-e and Scheme A.

The individual 3(S) and 3(R) esters of the compounds of Formula I wherein A is a bond can be prepared from an appropriate aldehyde of structure 40 in a process as outlined previously in Scheme F, step c, separating the 3(S) and 3(R) esters of the enamine compounds formed from the cyclization reaction described in Scheme F, step c and completing the process as outlined in Scheme F, steps d-e and Scheme A.

The groups R_1 and R_3 may be manipulated by techniques and procedures well known and appreciated in the art and described previously in Scheme A and Table 1.

Starting materials for use in the general synthetic procedures outlined in Schemes D and G are readily available to one of ordinary skill in the art. For example, Nα-(benzyloxycarbonyl)-β-(amino)-L-alanine is described in *J. Am.Chem.Soc.*, 107(24) 7105 1985, N-(phenylmethylene)glycine methyl ester is described in *J.Org.Chem.* 41, 3491 1976 and allyl trichloroacetimidate is described in *J.Chem.Soc.Perkin Trans.* 1(11) 2247 1985.

The following examples present typical syntheses as described in Schemes A through G. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to grams; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "mp" refers to melting point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "μL" refers to microliters; "µg" refers to micrograms; "nM" refers to nanomolar and "µM" refers to micromolar.

Example 1

Preparation of [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid-MDL 101,287

Scheme F, Step a: (S)-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-6-hydroxy-(S)-norleucine, methyl ester

Mix phthalic anhydride (1.82kgs, 12.3mole), (S)-phenylalanine (1.84kgs, 11.1 moles) and anhydrous dimethylformamide (2.26L). Stir at 115-120°C for 2 hours under a nitrogen atmosphere. Pour into rapidly stirring water (32.6L) and cool overnight at 0°C. Filter, wash with cold water (2X2L) and air dry. Dissolve in a mixture of 9A ethanol (8.05L) and water (8.05L) and heat at reflux temperature. Gravity filter, cool to ambient temperature and refrigerate overnight at about 0°C. Filter the crystallized product, wash with cold 50:50 9A ethanol/water (2X2L) and air dry to yield 2.96kg (90.3%) of N-phthaloyl-S)-phenylalanine; mp 177-179°C.(

Mix N-phthaloyl-(S)-phenylalanine (50.2g, 0.17mole), methylene chloride (660mL) and dimethylformamide (0.5mL) under a nitrogen atmosphere. Add oxalyl chloride (17.7mL, 0.2mole) over about 5 minutes with stirring. Stir at ambient temperature for 3 hours and evaporate the solvent *in vacuo* to leave N-phthaloyl-(S)-phenylalanine, acid chloride as a solid (54.3g, 101.9%).

Mix 6-hydroxy-(S)-norleucine, methyl ester, hydrochloride salt (33.5g, 0.1mole) and dimethylformamide (201mL), cool to about 0°C and place under nitrogen atmosphere. Add by dropwise addition, N-methylmorpholine (51mL, 0.46mole) with cooling so that the pot temperature stays at 0-5°C. Stir at 0-5°C for an additional 10 minutes, than add a solution of N-phthaloyl-(S)-phenylalanine, acid chloride (53.5g, 0.17mole) in methylene chloride (270mL) over 30 minutes with cooling so that the temperature stays at 0-5°C. Remove the cooling bath and stir at room temperature for 18 hours.

Evaporate the methylene chloride <u>in vacuo</u> and dilute the remaining residue with ethyl acetate (800mL). Extract the resulting mixture with water (800mL), separate the organic layer and extract with 1N hydrochloric acid (270mL), followed by water (3X500mL). Dry the organic layer ($MgSO_4$), filter and evaporate <u>in vacuo</u> to yield crude product (76g, 98%). Dissolve the crude product in hot toluene (223.5mL), cool to room temperature, than cool overnight at about 0°C. Filter the crystallized product, wash with cold toluene and air dry to yield 56.6g (76%) of the title compound; mp 128-130°C.

<u>Scheme F, Step b: 2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl-6-oxo-(S)-norleucine, methyl ester</u>

Mix oxalyl chloride (80mL, 0.92mole) and methylene chloride (2L) and place under nitrogen atmoxphere. Cool below -50°C and add a solution of dimethyl sulfoxide (65.4mL, 0.92mole) in methylene chloride (425mL). Stir for 15 minutes and add a solution of (S)-N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-6-hydroxy-(S)-norleucine, methyl ester (200g, 0.456mole) in methylene chloride (800mL) over about 45 minutes, keeping the pot temperature below -50°C for 30 minutes. Add triethylamine (420mL, 3.01mole) over 30 minutes. Stir while warming to 0°C over 1.25 hours. Transfer the reaction mixture to a 12-liter flask. Stir and cool while adding a solution of OXONE (potassium peroxymonosulfate) (566g) in water (6.74L) at such a rate that the pot temperature stays below 15°C. Stir for 5 minutes, separate the organic layer and extract the aqueous layer with methylene chloride (1L). Combine the organic phases, dry ($MgSO_4$) and filter to yield the title compound as a solution.

Scheme F, Step c: [S-(R*,R*)]-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-1,2,3,4-tetrahydro-2-pyridinecarboxylic acid, methyl ester

Transfer the solution of 2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-6-oxo-(S)-norleucine, methyl ester in methylene chloride (volume about 4.5L) to a 12-liter flask and place under nitrogen atmosphere. Stir and add trifluoroacetic acid (440mL, 5.71mole) in one portion. Stir the resulting mixture at room temperature for one hour, then rapidly cool to about 0°C. Add a solution of sodium hydroxide (240g, 6.0mole) in water (3.4L) in a slow stream to the vigorously stirred mixture at such a rate that the pot temperature stays at about 0°C. Separate the organic phase and extract the aqueous phase with methylene chloride (1L). Combine the organic phases and dry ($MgSO_4$). Filter and remove the solvent *in vacuo* to leave a residue (262g, 137%).

Dissolve the above residue in diethyl ether (1L) and wash with water (5X500mL). Evaporate the organic phase *in vacuo* to leave a residue of 229g. Dilute the residue with methylene chloride (200mL) and purify by silica gel chromatography (methylene chloride) to yield a viscous residue of 225g.

Dilute the above residue with diethyl ether (250mL) and allow to stand at room temperature for 24 hours. Filter the solid, wash with diethyl ether, and air dry to yield 123.2g; mp 140-142.5°C. Recrystallize (methylene chloride (125mL)/isopropanol (615mL)) by boiling off the solvent until the pot temperature reaches 75°C and allowing the resulting sample to stand at room temperature for 24 hours. Filter, wash with cold isopropanol and air dry to yield 101.5g of the title compound; mp 144-146°C.

Evaporate the filtrate from the 101.5g _in vacuo_ to yield 24g. Recrystallize (isopropanol) to yield an additional 3.5g of the title compound.

Evaporate the filtrate from the 123.2g _in vacuo_ to leave 62g of oil. Purify by silica gel chromatography (25% ethyl acetate/75% hexane), collecting 21-500mL fractions. Combine fractions 9-20 and evaporate _in vacuo_ to yield 35g of a viscous oil. Recrystallize three times (isopropanol/5mL/g) to yield an additional 11.9g of the title compound; mp 142.5-144.5°C. Total yield of useful material: 116.9g (61.3%).

Scheme F, Step d: [4S-[4α, 7α(R*), 12bβ]]-7-[(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester

Mix trifluoromethanesulfonic acid (500g, 3.33mole) and trifluoroacetic anhydride (74.8mL, 0.53mole) and place under nitrogen atmosphere. Stir and add a solution of [S-(R*,R*)]-N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-1,2,3,4-tetrahydro-2-pyridinecarboxylic acid, methyl ester (200g, 0.48mole) in methylene chloride (1L) with cooling at such a rate as to keep the pot temperature below 35°C. Stir at ambient temperature for 2 days. Pour into vigorously stirring ice water (5L) and stir for 30 minutes. Extract with ethyl acetate (3X1L), combine the organic phases and wash with water (3x500mL). Evaporate <u>in vacuo</u> to a residue. Dissolve the residue in ethyl acetate (4L) and extract with 1/4 saturated potassium hydrogen carbonate (1L), then 1/3 saturated potassium hydrogen carbonate (7X1L). Combine the aqueous extracts and dilute with ethyl acetate (2L). Stir the resulting mixture and cool to 5-10°C. Adjust to pH 2 using concentrated hydrochloric acid (about 750mL).

Separate the organic phase and extract the aqueous phase with ethyl acetate (3X1L). Combine the ethyl acetate extracts, wash with water (3X1L), then saturated sodium chloride (0.8L), and dry ($MgSO_4$). Filter and wash with ethyl acetate (3X200mL). Evaporate <u>in vacuo</u> to leave (188.3g, 101.5%) [4S-[4α, 7α(R*), 12bβ]]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid as a colorless foam.

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid (113.9g, 0.28mole) in methylene chloride (1.2L) and dry over anhydrous $MgSO_4$ (60g). Filter and wash with methylene chloride (3X200mL). Evaporate <u>in vacuo</u> to a residue. Dissolve the residue in anhydrous dimethylformamide (860mL) and place under nitrogen atmosphere. Add cesium carbonate (98.9g, 0.3mole) in one portion. Stir for 45 minutes at ambient temperature. Add bromodiphenylmethane (164.8g, 0.67mole). Stir the resulting mixture at ambient temperature for 18 hours. Quench the reaction with ethyl acetate (2.464L) and water (630mL). Separate the organic phase and wash with water (7X625mL), 1/4 saturated potassium hydrogen carbonate (625mL), water (625mL), and saturated sodium chloride (625mL). Dry ($MgSO_4$), filter and evaporate in vacuo to yield 214.4g of an oil. Extract the combined aqueous washings with ethyl acetate (3X500mL), wash with water (4X300mL) and dry ($MgSO_4$). Filter and evaporate in vacuo to yield an additional 20.2g of an oil.

Dissolve the crude product (234.6g) in methylene chloride (200mL) and plug filter through 213g of silica gel, eluting with methylene chloride (2L). Boil off the solvent and replace with hexane (3L), with the pot temperature reaching a maximum of 65°C. Cool to ambient temperature, decant off the precipitated oil and crystallize (9A ethanol) to yield 96.6g (60%) of the title compound; mp 153-155°C.

Scheme F, Step e: [4S-[4α, 7α(R*), 12bβ]]-7-(Amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester

Mix [4S-[4α, 7α(R*), 12bβ]]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (170.9g, 0.3mole), hydrazine monohydrate (34.4g, 0.68mole) and methanol (3.4L) under nitrogen atmosphere. Heat at reflux for 5 hours. Cool to ambient temperature and filter to remove phthaloyl hydrazide. Evaporate the filtrate in vacuo to a residue and slurry in chloroform (600mL). Remove insoluble phthaloyl hydrazide by filtration and wash with chloroform (4X210mL). Wash the filtrate with water (4X429mL), dry ($MgSO_4$), and filter. Evaporate the filtrate to a solid residue of the title compound weighing 142g (107.7%).

Scheme A: [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid

Dissolve diisopropylamine (3.5mL, 25mmol) in tetrahydrofuran (30mL). Add n-butyllithium (14mL of a 1.6M solution in hexane, 22.4mmol). Stir for 15 minutes and cool to -78°C. Add, by dropwise addition, ethyl dihydrocinnamate (3.5mL, 20mmol) and stir for 30 minutes. Add t-butyl bromoacetate (4.0mL, 25mmol) and gradually warm to room temperature overnight. Quench the solution with ammonium chloride solution (10mL) and partition between water (25mL) and ethyl ether (50mL). Separate the organic phase, dry ($MgSO_4$) and evaporate the solvent <u>in vacuo</u>. Purify by silica gel chromatography (5% ethyl acetate/hexane) to give 3-phenyl-2-t-butylcarboxymethylpropionic acid, ethyl ester as a pale yellow oil (2.68g, 46%).

Dissolve 3-phenyl-2-t-butylcarboxymethylpropionic acid, ethyl ester (2.68g, 9.17mmol) in ethanol (95%, 60mL) and water (30mL). Treat with potassium hydroxide (2.94g, 52mmol). Stir at room temperature for 3 hours. Add water (75mL) and extract with ethyl ether (2X50mL). Extract the combined ethereal phases with water (75mL) and acidify the combined aqueous phases with aqueous 1M tartaric acid (pH 2-3). Extract with ethyl acetate (2X125mL), dry (Na_2SO_4) and evaporate the solvent <u>in vacuo</u>. Take the residue up in methylene chloride and filter to give 3-phenyl-2-t-butylcarboxymethylpropionic acid as a pale yellow solid (1.96g, 81%).

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-(amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (250mg, 0.567mmol) in methylene chloride (6mL) and treat with 3-phenyl-2-t-butylcarboxymethylpropionic acid (226mg, 0.855mmol) and EEDQ (211mg, 0.853mmol). Stir at room temperature for 19 hours and evaporate the solvent in vacuo. Take the residue up in ethyl acetate (50mL) and wash with 5% sulfuric acid (20mL) then with saturated sodium hydrogen carbonate (20ml). Dry ($MgSO_4$) and evaporate the solvent in vacuo. Purify by silica gel chromatography (2.5:1 hexane/ethyl acetate to 1:1 hexane/ethyl acetate) to give a 1:1 diastereomeric mixture of [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-(t-butylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester as a white solid (266mg, 68%).

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-(t-butylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (266mg, 0.387mmol) in anhydrous methylene chloride (3mL) and treat with anisole (0.2mL, 1.8mmol). Cool in an ice-methanol bath, add trifluoroacetic acid (0.8mL, 10mmol) and stir with warming to room temperature over 20 hours. Partition between ethyl acetate (25mL) and brine (15mL). Separate the organic phase and wash with brine (15mL). Dry (Na_2SO_4), evaporate the solvent in vacuo and purify by silica gel chromatography to give the title compound as a diastereomeric mixture (150mg).

Example 2

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-(pivaloyloxymethylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, pivaloyloxymethyl ester

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid (30mg, 0.14mmol) in methylene chloride (1mL) and dry over anhydrous $MgSO_4$ (60mg). Filter and wash with methylene chloride (3X20mL). Evaporate *in vacuo* to a residue. Dissolve the residue in anhydrous dimethylformamide (10mL) and place under nitrogen atmosphere. Add cesium carbonate (100mg, 0.3mmol) in one portion. Stir for 45 minutes at ambient temperature. Add chloromethyl pivalate (42mg, 0.28mmol). Stir the resulting mixture at ambient temperature for 18 hours. Quench the reaction with ethyl acetate (3mL) and water (10mL). Separate the organic phase and wash with water (7X10mL), 1/4 saturated potassium hydrogen carbonate (10mL), water (10mL), and saturated sodium chloride (10mL). Dry ($MgSO_4$), filter and evaporate *in vacuo* to yield the title compound.

Example 3

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-(methylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid

Dissolve 3-phenylpropionic acid (1.5g, 10mmol) in dimethylformamide (5mL) and add t-butyldimethylsilyl chloride (7.5g, 50mmol) and imidazole (6.8g, 0.1mol). Stir for 48 hours at room temperature, pour into ethyl ether and water and separate the organic phase. Dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give 3-phenylpropionic acid, t-butyldimethylsilyl ester.

Dissolve diisopropylamine (0.88mL, 6.28mmol) in tetrahydrofuran (7.5mL). Cool in an ice bath and add, by dropwise addition, n-butyllithium (3.6mL of a 1.6M solution in hexanes, 5.75mmol). Stir for 15 minutes, then cool to -78°C. Add a solution of 3-phenylpropionic acid, t-butyldimethylsilyl ester (1.33g, 5.04mmol) in tetrahydrofuran (5mL). Stir for 45 minutes then add methyl bromoacetate (949mg, 6.2mmol). Stir for 3 hours, add saturated ammonium chloride (6mL) and warm to room temperature. Partition between ethyl ether (75mL) and water (10mL). Dry (Na_2SO_4), evaporate the solvent in vacuo and purify by silica gel chromatography to give 3-phenyl-2-methylcarboxymethylpropionic acid, t-butyldimethylsilyl ester.

Dissolve 3-phenyl-2-methylcarboxymethylpropionic acid, t-butyldimethylsilyl ester (3.07g, 9.13mmol) in tetrahydrofuran (11mL) and place under an argon atmosphere. Add, by dropwise addition, tetra-n-butylammonium fluoride (11mL of a 1M solution in tetrahydrofuran, 11mmol). Stir for 1 hour at room temperature and partition between ethyl ether and water. Separate the organic phase, wash with saturated aqueous sodium chloride, dry ($MgSO_4$), filter and evaporate the solvent in vacuo to give 3-phenyl-2-methylcarboxymethylpropionic acid.

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-(amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (150mg, 0.34mmol) and EDC (98mg, 0.50mmol) in tetrahydrofuran (5mL). Treat with 3-phenyl-2-methylcarboxymethylpropionic acid (89.5mg, 0.426mmol). Stir at room temperature for 15 hours and evaporate the solvent in vacuo. Partition the residue between ethyl acetate (35mL) and 1N hydrochloric acid (6ml). Wash the organic phase with saturated sodium hydrogen carbonate (6mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-(methylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester.

Suspend [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-(methylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (3.22g, 5mmol) in anhydrous methanol (10mL) and add 10% palladium/carbon (0.2-0.3g). Add anhydrous ammonium formate (23mmol) in a single portion under an argon atmosphere. Stir at room temperature for 3-40 minutes, remove the catalyst by filtration through filter aid and wash with dry methanol (10mL). Evaporate the solvent _in vacuo_, extract into ethyl acetate and dry (Na_2SO_4). Evaporate the solvent _in vacuo_ and purify by silica gel chromatography to give the title compound.

Example 4

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-(methylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, pivaloyloxymethyl ester

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-(methylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid (134mg, 0.28mmol) in methylene chloride (3mL) and dry over anhydrous $MgSO_4$ (60mg). Filter and wash with methylene chloride (3X20mL). Evaporate _in vacuo_ to a residue. Dissolve the residue in anhydrous dimethylformamide (10mL) and place under nitrogen atmosphere. Add cesium carbonate (100mg, 0.3mmol) in one portion. Stir for 45 minutes at ambient temperature. Add chloromethyl pivalate (42mg, 0.28mmol). Stir the resulting mixture at ambient temperature for 18 hours. Quench the reaction with ethyl acetate (3mL) and water (10mL). Separate the organic phase and wash with water (7X10mL), 1/4 saturated potassium hydrogen carbonate (10mL), water (10mL), and saturated sodium chloride (10mL). Dry ($MgSO_4$), filter and evaporate in vacuo to yield the title compound.

Example 5

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, pivaloyloxymethyl

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-(methylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, pivaloyloxymethyl ester (71mg, 0.12mmol) in methanol (3mL) and 1N aqueous lithium hydroxide (0.50mL, 0.50mmol). Stir for 30 minutes under an argon atmosphere at ambient temperature. Reduce in volume to 1.5mL in vacuo, then add, by dropwise addition, to a rapidly stirring solution of 2N hydrochloric acid (2mL). Collect the resulting precipitate, wash with water and dry in a vacuum dessicator for 1 hour. Dry at 35°C overnight to give the title compound.

Example 6

[4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-(pivaloyloxymethylcarboxymethyl carboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-(methylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (77.3mg, 0.12mmol) in methanol (3mL) and aqueous 1N lithium hydroxide (0.50mL, 0.50mmol). Stir for 30 minutes under an argon atmosphere at ambient temperature. Reduce in volume to 1.5mL in vacuo, then add, by dropwise addition, to a rapidly stirring solution of 2N hydrochloric acid (2mL). Collect the resulting precipitate, wash with water and dry in a vacuum dessicator for 1 hour. Dry at 35°C overnight to give [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-(carboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester.

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-(carboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (176mg, 0.28mmol) in methylene chloride (3mL) and dry over anhydrous $MgSO_4$ (60mg). Filter and wash with methylene chloride (3X20mL). Evaporate in vacuo to a residue. Dissolve the residue in anhydrous dimethylformamide (10mL) and place under a nitrogen atmosphere. Add cesium carbonate (100mg, 0.3mmol) in one portion. Stir for 45 minutes at ambient temperature. Add chloromethyl pivalate (42mg, 0.28mmol). Stir the resulting mixture at ambient temperature for 18 hours. Quench the reaction with ethyl acetate (3mL) and water (10mL). Separate the organic phase and wash with water (7X10mL), 1/4 saturated potassium hydrogen carbonate (10mL), water (10mL), and saturated sodium chloride (10mL). Dry ($MgSO_4$), filter and evaporate in vacuo to give [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-(pivaloyloxymethylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester.

Suspend [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-(pivaloyloxymethylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester

(3.72g, 5mmol) in anhydrous methanol (10mL) and add 10% palladium/carbon (0.2-0.3g). Add anhydrous ammonium formate (23mmol) in a single portion under an argon atmosphere. Stir at room temperature for 3-40 minutes, remove the catalyst by filtration through filter aid and wash with dry methanol (10mL). Evaporate the solvent *in vacuo*, extract into ethyl acetate and dry (Na_2SO_4). Evaporate the solvent *in vacuo* and purify by silica gel chromatography to give the title compound.

Example 7

Preparation of [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-~~hexahydro~~octahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid

Scheme D, step a: N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-L-serine, methyl ester

Slurry N-phthaloyl-(S)-phenylalanine (90g, 0.3mol) in methylene chloride (450mL) and add, by dropwise addition, oxalyl chloride (54mL, 0.62mol). Place under a dry atmosphere ($CaSO_4$ tube) and treat with dimethylformamide (10μL). Stir for 5 hours, filter and concentrate *in vacuo* to give N-phthaloyl-(S)-phenylalanine, acid chloride as an off white amorphous solid.

Dissolve serine methyl ester hydrochloride (56g, 0.36mol) in tetrahydrofuran (300mL) then cool to 0°C and add 4-methylmorpholine (88mL, 0.8mol). Add, by dropwise addition, a solution of the N-phthaloyl-(S)-phenylalanine, acid chloride in tetrahydrofuran (200mL). Allow to warm to room temperature and stir for 3 hours. Filter and concentrate the filtrate *in vacuo*. Dissolve the residue in ethyl acetate and separate the organic phase. Wash with water then saturated sodium chloride and dry ($MgSO_4$). Evaporate the solvent in vacuo to give an oil. Purify by silica gel chromatography (gradient 50% ethyl acetate/hexane to ethyl acetate) to give the title compound (80.8g, 67%) mp 129-132°C.

Scheme D, step b: N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-O-2-propenyl-L-serine, methyl ester

Dissolve N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-L-serine, methyl ester (25g, 63mmol) in methylene chloride/cyclohexane (1:1, 600mL). Add allyl trichloroacetimidate (26g, 128mmol) and trifluoromethanesulfonic acid (5mL), 56.6mmol). Stir at room temperature under a nitrogen atmosphere for 5 hours and dilute with methylene chloride. Wash with saturated aqueous sodium hydrogen carbonate, water, dry ($MgSO_4$) and evaporate the solvent in vacuo. Purify by silica gel chromatography (gradient 20% ethyl acetate/hexane to 35% ethyl acetate/hexane) to give the title compound; mp 95-97°C.

Scheme D, step c: [S-(R*, R*)]-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-3,4-dihydro-2H-1,4-oxazine-3-carboxylic acid, methyl ester

Dissolve N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-O-2-propenyl-L-serine, methyl ester (13g, 29.8mmol) in methylene chloride/methanol (10:1, 220mL). Cool to -78°C and sparge with a mixture of ozone/oxygen for approximately 10 minutes until a blue color persists. Sparge with nitrogen for 10 minutes at -78°C to remove excess ozone. Treat with methyl sulfide (60mL, 0.82mol) and allow to warm to room temperature. Stir at room temperature for 2.5 hours, evaporate the solvent in vacuo and dissolve the residue in ethyl acetate (200mL). Wash with water, saturated sodium chloride, dry ($MgSO_4$) and evaporate the solvent in vacuo to give the intermediate N-

[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-O-2-oxoethyl-L-serine, methyl ester as a foam (13.6g).

Dissolve N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-O-2-oxoethyl-L-serine, methyl ester (13.6g) in methylene chloride/trifluoroacetic acid (10:1/330mL). Stir at room temperature for 2.5 hours and evaporate the solvent in vacuo. Purify by silica gel chromatography (35% ethyl acetate/hexane) and recrystallize (ethyl acetate/hexane) to give the title compound (8.52g, 68%); mp 70-72°C.

Scheme D, step d: [4S-[4α, 7α(R*), 12bβ]]-7-[(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester

Dissolve [S-(R*, R*)]-N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-3,4-dihydro-2H-1,4-oxazine-3-carboxylic acid, methyl ester (2.5g, 5.9mmol) in methylene chloride (5mL) and add, by dropwise addition, to a previously prepared solution of trifluoromethanesulfonic acid (4.0mL, 45mmol) and trifluoroacetic anhydride (1.0mL, 7.1mmol). Place under a nitrogen atmosphere and stir at room temperature for 123 hours. Pour into a separatory funnel containing ice (200g) and ethyl acetate (200mL). Separate the organic phase, wash with water (3X200mL) and saturated aqueous sodium chloride (100mL). Extract the organic phase with 10% wt. potassium hydrogen carbonate (4X40mL) and water (40mL). Layer the combined basic aqueous phases with ethyl acetate (100mL) and cool in an ice bath. Add, by dropwise addition, 6N hydrochloric acid to adjust the pH to 1 while maintaining the temperature at 5-10°C. Separate the organic phase and extract the aqueous phase with ethyl acetate (3X200mL), wash with saturated sodium chloride and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and dry the residue under high vacuum at 56°C for 24 hours to give the intermediate [4S-[4α, 7α(R*), 12bβ]]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid (1.75g, 73%).

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid (500mg, 1.23mmol) in methylene chloride (12mL) and treat with diphenyldiazomethane (360mg, 1.86mmol). Stir for 5.5 hours and evaporate the solvent *in vacuo*. Purify by silica gel chromatography (gradient 20% ethyl acetate/hexane to 35% ethyl acetate/hexane) to give the title compound (563mg, 80%); mp 178-181°C (isopropanol).

Scheme D, step e: [4S-[4α, 7α(R*), 12bβ]]-7-(Amino)-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (296mg, 0.517mmol) in methanol (5mL) and treat with hydrazine monohydrate (1.1mL of a 1M solution in methanol, 1.1mmol). Stir at room temperature for 44 hours, evaporate the solvent *in vacuo* and slurry the residue in methylene chloride (10mL). Filter and evaporate the solvent *in vacuo* to give the title compound (218mg, 95%).

Scheme A: [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-~~hexahydro~~ octahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-(amino)-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (450mg, 1.018 mmol) and 3-phenyl-2-t-butylcarboxymethylpropionic acid (296mg, 1.12mmol) in methylene chloride (10mL). Add EEDQ (280mg, 1.13mmol) and stir at room temperature for 16 hours. Evaporate the solvent in vacuo and purify by silica gel chromatography to give [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-(t-butylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-~~hexahydro~~octahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester.

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-(t-butylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-~~hexahydro~~octahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (266mg, 0.387mmol) in anhydrous methylene chloride (3mL) and treat with anisole (0.2mL, 1.8mmol). Cool in an ice-methanol bath and add trifluoroacetic acid (0.8mL, 10mmol) and stir for 2.5 hours at 0°C. Partition between ethyl acetate (25mL) and brine (15mL). Separate the organic phase and wash with brine (15mL). Dry (Na_2SO_4), evaporate the solvent in vacuo and purify by silica gel chromatography to give the title compound as a diastereomeric mixture.

Example 8

Preparation of [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-~~hexahydro~~octahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine-4-carboxylic acid

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-(amino)-3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (466mg, 1.018 mmol) and 3-phenyl-2-t-butylcarboxymethylpropionic acid (296mg, 1.12mmol) in methylene chloride (10mL). Add EEDQ (280mg, 1.13mmol) and stir at room temperature for 16 hours. Evaporate the solvent in vacuo and purify by silica gel chromatography to give [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-(t-butyloxycarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-~~hexahydro~~octahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester.

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2(t-butylcarboxyl)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-~~hexahydro~~octahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (550mg, 0.78mmol) in methylene chloride (10mL) and treat with anisole (0.2mL, 1.8mmol) and trifluoroacetic acid (0.8mL, 10.4mmol). Stir for 3.25 hours at room temperature under a nitrogen atmosphere. Evaporate the solvent in vacuo and purify by silica gel chromatography to give the title compound.

Example 9

Preparation of [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-~~hexahydro~~octahydro-6-oxo-1H-~~[1,4]-azazino[3,4-a]~~pyrazino[2,1-a][2]benzazepine-4-carboxylic acid

Scheme E, step a: N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-(S)-3-[(trifluoroacetyl-2-propenyl)amino]-2-amino-propionic acid, methyl ester

Dissolve Nα-(benzyloxycarbonyl)-β-(amino)-L-alanine (47.6g, 0.2mol) in methanol (500mL) and treat with concentrated sulfuric acid (0.5mL). Heat to 60°C for 16 hours, cool and reduce the solvent by 50% in vacuo. Dilute with ethyl ether (500mL), wash with saturated sodium hydrogen carbonate, then brine. Dry ($MgSO_4$) and evaporate the solvent in vacuo to give N^{α}-(benzyloxycarbonyl)-β-(amino)-L-alanine, methyl ester.

Dissolve N^{α}-(benzyloxycarbonyl)-β-(amino)-L-alanine, methyl ester (15.9g, 63mmol) in methylene chloride/cyclohexane (1:1, 600mL). Add allyl trichloroacetimidate (26g, 128mmol) and trifluoromethanesulfonic acid (5mL, 56.6mmol). Stir at room temperature under a nitrogen atmosphere for 5 hours and dilute with methylene chloride. Wash with saturated aqueous sodium hydrogen carbonate, water, dry ($MgSO_4$) and evaporate the solvent <u>in vacuo</u>. Purify by silica gel chromatography to give N^{α}-(benzyloxycarbonyl)-β-(allylamino)-L-alanine, methyl ester.

Dissolve N^{α}-(benzyloxycarbonyl)-β-(allylamino)-L-alanine, methyl ester (663mg, 2.27mmol) in anhydrous tetrahydrofuran (15mL). Treat with pyridine (183μL, 2.27mmol) followed by trifluoroacetic anhydride (321μL, 2.27mmol) and stir at room temperature overnight. Partition between ethyl ether and water. Separate the organic phase, dry ($MgSO_4$) and evaporate the solvent <u>in vacuo</u>. Purify by silica gel chromatography to give N^{α}-(benzyloxycarbonyl)-β-(trifluoroacetyl-allylamino)-L-alanine, methyl ester.

Place boron tribromide (215mg, 0.86mmol) in a flask and cool to 0°C. Cautiously add trifluoroacetic acid (5mL) with stirring. Evaporate the solvent to give boron tris(trifluoroacetate).

Dissolve boron tris(trifluoroacetate) (0.3g, 0.86mmol) in trifluoroacetic acid (10mL) and add N^{α}-(benzyloxycarbonyl)-β-(trifluoroacetyl-allylamino)-L-alanine, methyl ester (105mg, 0.27mmol). Stir under an argon atmosphere for 1 hour then evaporate the solvent <u>in vacuo</u> at room temperature. Add methanol and evaporate repeatedly. Purify by silica gel chromatography to give β-(trifluoroacetyl-allylamino)-L-alanine, methyl ester, hydrochloride.

Dissolve β-(trifluoroacetyl-allylamino)-L-alanine, methyl ester, hydrochloride (104.8g, 0.36mol) in tetrahydrofuran (300mL) then cool to 0°C and add 4-methylmorpholine (88mL, 0.8mol). Add, by dropwise addition, a solution of the N-phthaloyl-(S)-phenylalanine, acid chloride (108.7g, 0.36mol) in tetrahydrofuran (200mL). Allow to warm to room temperature and stir for 3 hours. Filter and concentrate the filtrate <u>in vacuo</u>. Dissolve the residue in ethyl acetate and separate the organic phase. Wash with water then saturated sodium chloride and dry ($MgSO_4$). Evaporate the solvent <u>in vacuo</u> to give an oil. Purify by silica gel chromatography to give the title compound.

<u>Scheme E, step b: [S-(R*, R*)]-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-3,4-dihydro-2H-4-trifluoroacetyl-1,4-azazine-3-carboxylic acid, methyl ester</u>

Dissolve N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-(S)-3-[(trifluoroacetyl-2-propenyl)amino]-2-amino-propionic acid, methyl ester (15.8g, 29.8mmol) in methylene chloride/methanol (10:1, 220mL). Cool to -78°C and sparge with a mixture of ozone/oxygen for approximately 10 minutes until a blue color persists. Sparge with nitrogen for 10 minutes at -78°C to remove excess ozone. Treat with methyl sulfide (60mL, 0.82mol) and allow to warm to room temperature. Stir at room temperature for 2.5 hours, evaporate the solvent <u>in vacuo</u> and dissolve the residue in ethyl acetate (200mL). Wash with water, saturated sodium chloride, dry ($MgSO_4$) and evaporate the solvent <u>in vacuo</u> to give the intermediate N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-N-2-oxoethyl, methyl ester.

Dissolve N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-(S)-3-[(trifluoroacetyl-2-oxoethyl)amino]-2-amino-propionic acid, methyl ester (15.9g, 29.8mmol) in methylene chloride/trifluoroacetic acid (10:1/330mL). [illegible] at room temperature for 2.5 hours and evaporate the solvent <u>in vacuo</u>. Purify by silica gel chromatography to give the title compound.

<u>Scheme E, step c: [4S-[4α, 7α(R*), 12bβ]]-7-[(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo--4-trifluoroacetyl-pyrazino[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester</u>

Dissolve [S-(R*, R*)]-N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-3,4-dihydro-2H-4-trifluoracetyl-1,4-azazine-3-carboxylic acid, methyl ester (3.04g, 5.9mmol) in methylene chloride (5mL) and add, by dropwise addition, to a previously prepared solution of trifluoromethanesulfonic acid (4.0mL, 45mmol) and trifluoroacetic anhydride (1.0mL, 7.1mmol). Place under a nitrogen atmosphere and stir at room temperature for 123 hours. Pour into a separatory funnel containing ice (200g) and ethyl acetate (200mL). Separate the organic phase, wash with water (3X200mL) and saturated aqueous sodium chloride (100mL). Extract the organic phase with 10% wt. potassium hydrogen carbonate (4X40mL) and water (40mL). Layer the combined basic aqueous phases with ethyl acetate (100mL) and cool in an ice bath. Add, by dropwise addition, 6N hydrochloric acid to adjust the pH to 1 while maintaining the temperature at 5-10°C. Separate the organic phase and extract the aqueous phase with ethyl acetate (3X200mL), wash with saturated sodium chloride and dry ($MgSO_4$). Evaporate the solvent <u>in vacuo</u> and dry the residue under high vacuum at 56°C for 24 hours to give the intermediate [4S-[4α, 7α(R*), 12bβ]]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-

3,4,6,7,8,12b-hexahydro-6-oxo-1H-4-trifluoroacetyl-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid.

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-4-trifluoroacetyl-pyrazino[2,1-a][2]benzazepine-4-carboxylic acid (616mg, 1.23mmol) in methylene chloride (12mL) and treat with diphenyldiazomethane (360mg, 1.86mmol). Stir for 5.5 hours and evaporate the solvent *in vacuo*. Purify by silica gel chromatography to give the title compound.

Scheme E, step e: [4S-[4α, 7α(R*), 12bβ]]-7-(Amino)-3,4,6,7,8,12b-hexahydro-6-oxo-pyrazino[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-3,4,6,7,8,12b-hexahydro-6-oxo-4-trifluoroacetyl-pyrazino[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (345mg, 0.517mmol) in methanol (5mL) and treat with hydrazine monohydrate (1.1mL of a 1M solution in methanol, 1.1mmol). Stir at room temperature for 44 hours, evaporate the solvent *in vacuo* and slurry the residue in methylene chloride (10mL). Filter and evaporate the solvent *in vacuo* to give the title compound.

Scheme A: [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrazino[2,1-a][2]benzazepine-4-carboxylic acid

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-(amino)-3,4,6,7,8,12b-hexahydro-6-oxo-pyrazino[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (449mg, 1.018 mmol) and 3-phenyl-2-t-butylcarboxymethylpropionic acid (296mg, 1.12mmol) in methylene chloride (10mL). Add EEDQ (280mg, 1.13mmol) and stir at room temperature for 16 hours.

Evaporate the solvent in vacuo and purify by silica gel chromatography to give [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-(t-butylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrazino[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester.

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-(t-butylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrazino[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (536mg, 0.78mmol) in methylene chloride (10mL) and treat with anisole (0.2mL, 1.8mmol) and trifluoroacetic acid (0.8mL, 10.4mmol). Stir for 3.25 hours at room temperature under a nitrogen atmosphere. Evaporate the solvent in vacuo and purify by silica gel chromatography to give the title compound.

Example 10

Preparation of [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-N^2-trifluoroacetyl-pyrazino[2,1-a][2]benzazepine-4-carboxylic acid

Dissolve [4S-[4α, 7α(R*), 12bβ]]-7-[(1-oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrazino[2,1-a][2]benzazepine-4-carboxylic acid (1.06g, 2.27mmol) in anhydrous tetrahydrofuran (15mL). Treat with pyridine (183μL, 2.27mmol) followed by trifluoroacetic anhydride (321μL, 2.27mmol) and stir at room temperature overnight. Partition between ethyl ether and water. Separate the organic phase, dry ($MgSO_4$) and evaporate the solvent in vacuo. Purify by silica gel chromatography to give the title compound.

Example 11

[6α(R*), 11bβ]-6-[(S)-(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine-3(S)-carboxylic acid, methyl ester

Scheme G, step a: N-(Phenylmethylene)-2-(3-butenyl)glycine methyl ester

Dissolve diisopropylamine (15.4mL, 110mmol) in tetrahydrofuran (250mL), place under a nitrogen atmosphere and cool to -78°C. Add n-butyllithium (39mL of a 2.7M solution in hexane, 105mmol). Stir for 30 minutes and add, by dropwise addition, a solution of N-(phenylmethylene)glycine methyl ester (17.7g, 100mmol) in tetrahydrofuran (25mL). Stir for 15 minutes and add 4-bromobutene (13.5g, 100mmol) and allow to warm slowly to room temperature. Add hexamethylphosphoramide (20mL, 100mmol) and stir under a nitrogen atmosphere for 3 hours. Pour into water, extract into ethyl ether and wash with brine several times. Dry ($MgSO_4$) and evaporate the solvent in vacuo to give the title compound as an amber oil (25g).

Scheme G, step b: 2-(3-Butenyl)glycine methyl ester

Dissolve N-(phenylmethylene)-2-(3-butenyl)glycine methyl ester (25g) in ethyl ether (400mL) and stir with 1N hydrochloric acid (150mL) and water (150mL). Place under an argon atmosphere and stir for 2 hours. Separate the aqueous phase and adjust to pH 9, extract into chloroform, dry and evaporate the solvent in vacuo to give the title compound as a light oil (4.5g).

Scheme G, step c: (S)-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-2-(3-butenyl)-glycine, methyl esters

Dissolve N-phthaloyl-(S)-phenylalanine (2) (6.0g, 20mmol) and EEDQ (6.0g, 24mmol) in methylene chloride (30mL). Add 2-(3-butenyl)glycine methyl ester (3.0g, 21mmol) and stir for 18 hours. Pour into methylene chloride, wash with 10% hydrochloric acid (2X100mL) then saturated sodium hydrogen carbonate. Dry and evaporate the solvent in vacuo to give 8.3g yellow oil. Purify by silica gel chromatography (25% ethyl acetate/hexane) to give a diastereomeric mixture of the title compounds as a foam (5.2g).

Scheme G, step d: (S)-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)]-(S)-phenylalanyl]-2-(3-oxopropyl)glycine, methyl esters

Dissolve the diastereomeric mixture of (S)-N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-2-(3-butenyl)-glycine, methyl esters (4.2g, 10mmol) in methylene chloride (100mL) and absolute methanol (10mL). Cool to -78°C and treat with ozone until blue. Degas with with oxygen and add methyl sulfide (10mL) and pyridine (0.5mL). Allow to warm slowly to room temperature and stir for 18 hours. Wash with 10% hydrochloric acid then brine. Dry and evaporate the solvent in vacuo to give a diastereomeric mixture of the title compounds as an oil (4.5g).

Scheme F, step c: (S)-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)]-1-oxo-3-phenylpropyl-1,2,3-trihydro-2(S)-pyrrolecarboxylic acid, methyl ester and (S)-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)]-1-oxo-3-phenylpropyl-1,2,3-trihydro-2(R)-pyrrolecarboxylic acid, methyl ester

Dissolve the diastereomeric mixture of (S)-N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-(S)-phenylalanyl]-2-(3-oxopropyl)glycine, methyl esters (4.5g) in 1,1,1-trichloroethane (150mL) and treat with trifluoroacetic acid (0.5mL). Heat at reflux for 18 hours, evaporate the solvent and purify by silica gel chromatography (80% ethyl acetate/hexane) to give the 2(S)-title compound (700mg) and the 2(R)-title compound (600mg).

Scheme F, Step d: [6α(R*), 11bβ]-6-[(S)-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine-3(S)-carboxylic acid, methyl ester

Dissolve (S)-N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-1-oxo-3-phenylpropyl-1,2,3-trihydro-2(S)-pyrrolecarboxylic acid, methyl ester (338mg, 0.836mmol) in anhydrous methylene chloride (10mL) and add to trifluoromethanesulfonic acid (5mL). Stir for 3.5 hours, cool in an ice bath and carefully add water (25mL). Extract with ethyl acetate (75mL) and wash with saturated sodium hydrogen carbonate (25mL). Dry (Na_2SO_4) and evaporate the solvent in vacuo. Purify by silica gel chromatography (1:1 ethyl acetate/hexane to 2:1 ethyl acetate/hexane) to give the title compound as a white foam (314mg, 93%).

Scheme F, Step e: [6α(R*), 11bβ]-6-[(S)-Amino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine-3(S)-carboxylic acid, methyl ester

Dissolve [6α(R*), 11bβ]-6-[(S)-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine-3(S)-carboxylic acid, methyl ester (244mg, 0.603mmol) in methanol (3mL) and treat with hydrazine monohydrate (0.70mL of a 1M solution in methanol) and stir at room temperature for 24 hours. Add additional hydrazine monohydrate (0.3mL of a 1M solution in methanol) and stir for 48 hours. Filter through filter aid, evaporate the solvent *in vacuo* and add methylene chloride. Filter slowly through a mixture of filter aid and $MgSO_4$ then evaporate the solvent *in vacuo* to give the title compound as a yellow oil (181mg).

Scheme A: [6α(R*), 11bβ]-6-[(S)-(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine-3(S)-carboxylic acid, methyl ester

Dissolve 3-phenyl-2-t-butylcarboxymethylpropionic acid (223mg, 0.845mmol) in methylene chloride (6mL), cool in an ice-methanol bath and treat with oxalyl chloride (0.94mL, 11mmol). Stir for 1.5 hours, evaporate the solvent *in vacuo* at 0-5°C. Dilute the residue with methylene chloride (3mL) and add a solution of [6α(R*), 11bβ]-6-[(S)-amino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine-3(S)-carboxylic acid, methyl ester (155mg, 0.565mmol) in methylene chloride (6mL). Add pyridine (68μL, 0.85mmol) and stir for 2 hours. Dilute with ethyl acetate (60mL) and wash with 1N hydrochloric acid (30mL) and saturated sodium hydrogen carbonate (2X30mL). Dry ($MgSO_4$), evaporate the solvent *in vacuo* and purify by silica gel chromatography to give [6α(R*), 11bβ]-6-[(S)-(1-oxo-2-(t-butylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine-3(S)-carboxylic acid, methyl ester.

Dissolve [6α(R*), 11bβ]-6-[(S)-(1-oxo-2-(t-butylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine-3(S)-carboxylic acid, methyl ester (85mg, 0.163mmol) in methylene chloride (3mL) and treat with anisole (0.19mL, 1.7mmol). Cool in an ice-methanol bath and add trifluoroacetic acid (0.8mL, 10mmol) and stir for 2.5 hours at 0°C. Partition between ethyl acetate (25mL) and brine (15mL). Separate the organic phase and wash with brine (15mL). Dry (Na_2SO_4), evaporate the solvent in vacuo and purify by silica gel chromatography to give the title compound.

Example 12

Preparation of [6α(R*), 11bβ]-6-[(S)-(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine-3(S)-carboxylic acid

Dissolve [6α(R*), 11bβ]-6-[(S)-(1-oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine-3(S)-carboxylic acid, methyl ester (45mg, 0.098mmol) in methanol (1.5mL) and at 0°C and add 1N aqueous lithium hydroxide (0.6mL, 0.6mmol). Add tetrahydrofuran to obtain solution (4mL) and stir for 17 hours at room temperature, cool in an ice bath and add 1N hydrochloric acid (1mL). Partition between methylene chloride (30mL) and water (15mL) and separate the organic phase. Dry (Na_2SO_4), evaporate the solvent in vacuo and purify by silica gel chromatography to give the title compound.

In a further embodiment, the present invention provides a method of inhibiting enkephalinase in a patient in need thereof comprising administering to said patient an effective enkephalinase inhibitory amount of a compound of Formula (I).

As used herein, the term "patient" refers to warm-blooded animals or mammals, including mice, rats and humans. A patient is in need of treatment to inhibit enkephalinase when the patient is suffering from acute or chronic pain and is in need of an endorphin- or enkephalin-mediated analgesic effect. In addition, a patient is in need of treatment to inhibit enkephalinase when the patient is suffering from a disease state characterized by abnormalities in fluid, electrolyte, blood pressure, intraocular pressure, renin, or aldosterone homeostasis, such as, but not limited to, hypertension, renal diseases, hyperaldosteronemia, cardiac hypertrophy, glaucoma and congestive heart failure. In these instances the patient is in need of an ANP-mediated diuretic, natriuretic, hypotensive, hypoaldosteronemic effect. Inhibition of enkephalinase would provide an endorphin- or enkephalin-mediated analgesic effect by inhibiting the metabolic degradation of endorphins and enkephalins. Inhibition of enkephalinase would provide an ANP-mediated diuretic, natriuretic, hypotensive, hypoaldosteronemic effect by inhibiting the metabolic degradation of ANP.

In addition, a patient is in need of treatment to inhibit enkephalinase when the patient is in need of an antidepressant effect or a reduction in severity of withdrawal symptoms associated with termination of opiate or morphine administration.

The identification of those patients who are in need of treatment to inhibit enkephalinase is well within the ability and knowledge of one skilled in the art. A clinician skilled in the art can readily identify, by the use of clinical tests, physical examination and medical/family history, those patients who are in need of an endorphin- or enkephalin-mediated analgesic effect or who are in need of an ANP-mediated diuretic, natriuretic, hypotensive or hypoaldosteronemic effect.

An effective enkephalinase inhibitory amount of a compound of Formula (I) is an amount which is effective in inhibiting enkephalinase and in thus inhibiting the metabolic degradation of the naturally-occurring circulating regulatory peptides such as the endorphins, including enkephalins, and ANP. Successful treatment is also understood to include prophylaxis in treating a patient in those instances such as, for example, in a pre-operative procedure, where a patient will be suffering from acute or chronic pain in the near future.

An effective enkephalinase inhibitory amount of a compound of Formula (I) is an amount which is effective in inhibiting enkephalinase in a patient in need thereof which results, for example, in endorphin- or enkephalin-mediated analgesic effects or in ANP-mediated diuretic, natriuretic, hypotensive, hypoaldosteronemic effect.

An effective enkephalinase inhibitory dose can be readily determined by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the effective dose, a number of factors are considered including, but not limited to: the species of patient; its size, age, and general health; the specific disease involved; the degree of or involvement or the severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; and the use of concomitant medication.

An effective enkephalinase inhibitory amount of a compound of Formula (I) will generally vary from about 0.01 milligram per kilogram of body weight per day (mg/kg/day) to about 20 mg/kg/day. A daily dose of from about 0.1 mg/kg to about 10 mg/kg is preferred.

In addition, the present invention further provides a method of inhibiting ACE in a patient in need thereof comprising administering to said patient an effective ACE inhibitory amount of a compound of Formula (I). A patient is in need of treatment to inhibit ACE when the patient is suffering from hypertension, chronic congestive heart failure, hyperaldosteronemia or cognitive disorders. Inhibition of ACE reduces levels of angiotensin II and thus inhibits the vasopressor, hypertensive and hyperaldosteronemic effects caused thereby. An effective ACE inhibitory amount of a compound of Formula (I) is that amount which is effective in inhibiting ACE in a patient in need thereof which results, for example, in a hypotensive effect. An effective ACE inhibitory amount and an effective ACE inhibitory dose are the same as that described above for an effective enkephalinase inhibitory amount and dose.

In effecting treatment of a patient, compounds of Formula (I) can be administered in any form or mode which makes the compound bioavailable in effective amounts, including oral and parenteral routes. For example, the compound can be administered orally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, and the like. Oral administration is generally preferred. One skilled in the art of preparing Formulations can readily select the proper form and mode of administration depending upon the disease state to be treated, the stage of the disease, and other relevant circumstances.

Compounds of Formula (I) can be administered in the form of pharmaceutical compositions or medicaments which are made by combining the compounds of Formula (I) with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the chosen route of administration, and standard pharmaceutical practice.

In another embodiment, the present invention provides compositions comprising a compound of Formula (I) in admixture or otherwise in association with one or more inert carriers. These compositions are useful, for example, as assay standards, as convenient means of making bulk shipments, or as pharmaceutical compositions. An assayable amount of a compound of Formula (I) is an amount which is readily measurable by standard assay procedures and techniques as are well known and appreciated by those skilled in the art. Assayable amounts of a compound of Formula (I) will generally vary from about 0.001% to about 75% of the composition by weight. Inert carriers can be any material which does not degrade or otherwise covalently react with a compound of Formula (I). Examples of suitable inert carriers are water; aqueous buffers, such as those which are generally useful in High Performance Liquid Chromatography (HPLC) analysis; organic solvents, such as acetonitrile, ethyl acetate, hexane and the like; and pharmaceutically acceptable carriers or excipients.

More particularly, the present invention provides pharmaceutical compositions comprising an effective amount of a compound of Formula (I) in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

The pharmaceutical compositions or medicaments are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral or parenteral use and may be administered to the patient in the form of tablets, capsules, suppositories, solution, suspensions, or the like.

The pharmaceutical compositions may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds of Formula (I) may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of Formula (I), the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of the active ingredient present in compositions is such that a unit dosage form suitable for administration will be obtained.

The tablets, pills, capsules, troches and the like may also contain one or more of the following adjuvants: binders, such as microcrystalline cellulose, gum tragacanth or gelatin; excipients, such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants, such as magnesium stearate or Sterotex; glidants, such as colloidal silicon dioxide; and sweetening agents, such as sucrose or saccharin may be added or flavoring agents, such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active ingredient, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral administration, the compounds of Formula (I) may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of a compound of the invention, but may be varied to be between 0.1 and about 50% of the weight thereof. The amount of the active ingredient present in such compositions is such that a suitable dosage will be obtained.

The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of toxicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

As with any group of structurally related compounds which possess a particular generic utility, certain groups and configurations are preferred for compounds of Formula (I) in their end-use application.

The compounds of Formula (1) wherein B_1 is hydrogen or alkoxy are preferred. Compounds of Formula (1) wherein R_1 and R_3 are hydrogen are preferred.

It is, of course, understood that the compounds of Formula (I) may exist in a variety of isomeric configurations including structural as well as stereo isomers. It is further understood that the present invention encompasses those compounds of Formula (I) in each of their various structural and stereo isomeric configurations as individual isomers and as mixtures of isomers.

The following specific compounds of Formula (1) are particularly preferred in the end-use application of the compounds of the present invention: MDL 101,287.

The following studies illustrate the utility of the compounds of the present invention as enkephalinase inhibitors and as ACE inhibitors.

Enkephalinase is partially purified from rat kidney. The enzyme is extracted from the microvilli fraction by using Triton X-100 according to the method of Malfroy and Schwartz [*J. Biol. Chem.* 259, 14365-14370 (1984)] or by using a proteolytic treatment according to the method of Almenoff and Orlowski [*Biochem.* 22, 590-59 (1983)]. The enzyme is further purified by anion exchange chromatography (Mono Q™

column, Pharmacia) using a Pharmacia FPLC system. The enzyme activity may be measured by the fluorometric methods of Florentin et al. [*Anal. Biochem.* 141, 62-69 (1984)] or of Almenoff and Orlowski [*J. Neurochemistry* 42, 151-157 (1984)]. The enzyme is assayed in 50mM HEPES buffer (pH 7.4) in a 3.0 mL reaction volume containing 12 μM of the substrate dansyl-D-AlaGly(p-nitro)PheGly (K_m=40μM) at 25°C. The substrate (and inhibitor) is added from a concentrated stock solution in DMSO (up to 0.1 mL DMSO final volume). The enzyme in a small volume (approximately 0.1 μg of FPLC purified protein) is added to initiate the reaction and the rate of fluorecense increase is recorded continuously using a fluorometer (excitation at 339nm, emission at 562nm).

The enzymatic activity of ACE is monitored using the spectrophotometric substrate described by Holmquist et al. [*Anal. Biochem.* 95, 540-548 (1979)] and the buffer system described by Ryan [*Methods of Enzymatic Analysis*, 3rd ed., H. U. Bergmeyer, editor; vol. V, Verlag Chemie, Weinheim, 1983, pp. 20-34].

The results of the analysis of enzymatic activity as described in Table 1 indicate that the compounds of the present invention are inhibitors of enkephalinase as well as inhibitors of ACE.

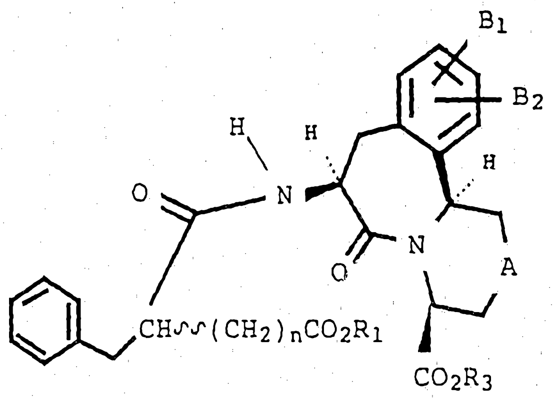
Table 1
K_i's of Compounds of Formula (1) as Inhibitors of Enkephalinase and of ACE

Compound of Formula (1)	Enkephalinase, K_i (nM)	ACE, K_i (nM)
101,287	5	

101,287 = [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid

~~WHAT IS CLAIMED IS:~~
The claims defining the invention are as follows:

1. A compound of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_2$ wherein R_2 is a C_1-C_4 alkyl or an Ar-Y-group wherein Ar is aryl and Y is a ~~hydrogen~~ bond or C_1-C_4 alkyl; or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

A is a bond, methylene or oxygen, sulfur or NR_4 or $NCOR_5$ wherein R_4 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_5 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

R_3 is hydrogen or $-CH_2OC(O)C(CH_3)_3$;

R_1 is hydrogen, C_1-C_4 alkyl or $-CH_2OC(O)-C(CH_3)_3$; and

n is an integer 1 to 3.

2. A compound according to Claim 1 wherein A is methylene.

3. A compound according to Claims 1 or 2 wherein n is 1.

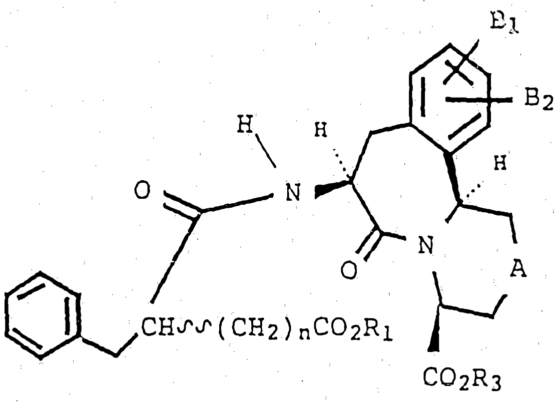
4. A compound according to any one of Claims 1-3 wherein R_1 and R_3 are hydrogen.

5. A compound according to any one of Claims 1-4 wherein A is -O-.

6. A compound according to any one of Claims 1-4 wherein A is -S-.

7. A compound according to any one of Claims 1-4 wherein A is -NH-.

8. A method of inhibiting enkephalinase in a patient in need thereof including administering to said patient an effective enkephalinase inhibitory amount of a compound of the formula.



wherein

B_1 and B_2 are each independently hydrogen; hydroxy;

$-OR_2$ wherein R_2 is a C_1-C_4 alkyl or an Ar-Y-group wherein Ar is aryl and Y is a ~~hydrogen~~ bond or C_1-C_4 alkyl; or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

A is a bond, methylene or oxygen, sulfur or NR_4 or $NCOR_5$ wherein R_4 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_5 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;
R_3 is hydrogen or $-CH_2OC(O)C(CH_3)_3$;
R_1 is hydrogen, C_1-C_4 alkyl or $-CH_2OC(O)-C(CH_3)_3$; and
n is an integer 1 to 3.

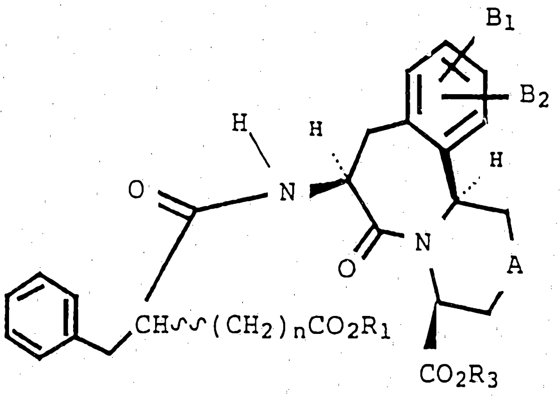
9. A method according to Claim 8 wherein the patient is in need of an endorphin- or enkephalin-mediated analgesic effect.

10. A method according to Claim 8 wherein the patient is in need of an ANP-mediated hypotensive effect.

11. A method according to Claim 8 wherein the patient is in need of an ANP-mediated diuretic effect.

12. A method according to Claim 8 wherein the patient is suffering from congestive heart failure.

13. A method of inhibiting ACE in a patient in need thereof ~~comprising~~ including administering to said patient an effective ACE inhibitory amount of a compound of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_2$ wherein R_2 is a C_1-C_4 alkyl or an Ar-Y-group wherein Ar is aryl and Y is a ~~hydrogen~~ bond or C_1-C_4 alkyl; or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

A is a bond, methylene or oxygen, sulfur or NR_4 or $NCOR_5$ wherein R_4 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_5 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

R_3 is hydrogen or $-CH_2OC(O)C(CH_3)_3$;

R_1 is hydrogen, C_1-C_4 alkyl or $-CH_2OC(O)-C(CH_3)_3$; and

n is an integer 1 to 3.

14. A method according to Claim 12 wherein the patient is in need of a hypotensive effect.

15. A method according to Claim 12 wherein the patient is in need of a a cognition enhancing effect.

16. A method according to Claim 12 wherein the patient is suffering from congestive heart failure.

17. A composition ~~comprising~~ including an assayable amount of a compound of Claim 1 in admixture or otherwise in association with an inert carrier.

18. A pharmaceutical composition ~~comprising~~ including an effective immunosuppressive amount of a compound of Claim 1 in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

19. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid.

20. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-(pivaloyloxymethylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, pivaloyloxymethyl ester.

21. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-(methylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid.

22. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-(methylcarboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, pivaloyloxymethyl ester.

23. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, pivaloyloxymethyl.

24. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-(pivaloyloxymethylcarboxymethyl carboxy)methyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid.

25. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid.

26. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine-4-carboxylic acid.

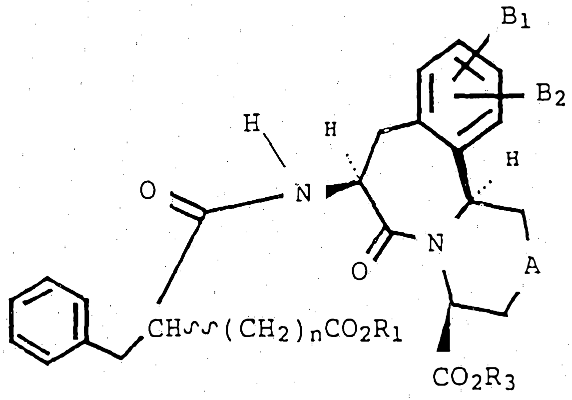
27. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrazino[2,1-a][2]benzazepine-4-carboxylic acid.

28. A compound of Claim 1 wherein the compound is [4S-[4α, 7α(R*), 12bβ]]-7-[(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-N^2-trifluoroacetyl-pyrazino[2,1-a][2]benzazepine-4-carboxylic acid.

29. A compound of Claim 1 wherein the compound is [6α(R*), 11bβ]-6-[(S)-(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine-3(S)-carboxylic acid, methyl ester.

30. A compound of Claim 1 wherein the compound is [6α(R*), 11bβ]-6-[(S)-(1-Oxo-2-carboxymethyl-3-phenylpropyl)amino]-1,2,3,5,6,7,11b-heptahydro-5-oxo-pyrrolo[2,1-a][2]benzazepine-3(S)-carboxylic acid.

31. A process for preparing the compounds of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_2$ wherein R_2 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a ~~hydrogen~~ bond or C_1-C_4 alkyl; or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

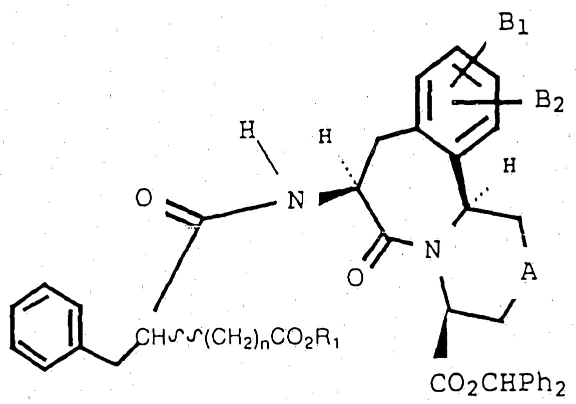
A is a bond, methylene or oxygen, sulfur or NR_4 or $NCOR_5$ wherein R_4 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_5 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

R_3 is hydrogen;

R_1 is hydrogen; and

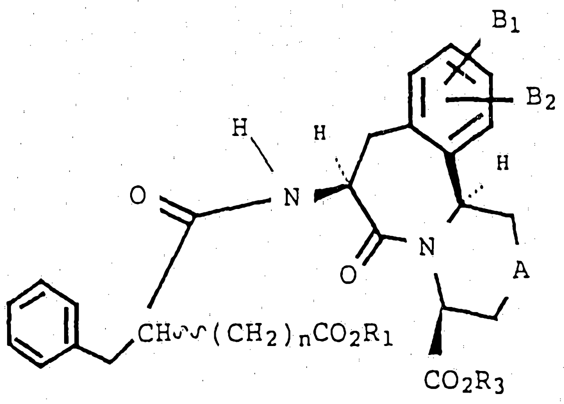
n is an integer 1 to 3,

~~comprising~~ including reacting a compound of the formula



wherein B_1, B_2, A and ~~m~~ n are as defined above and R_1 is t-butyl with an acid.

32. A process for preparing the compounds of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_2$ wherein R_2 is a C_1-C_4 alkyl or an Ar-Y-group wherein Ar is aryl and Y is a ~~hydrogen~~ bond or C_1-C_4 alkyl; or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

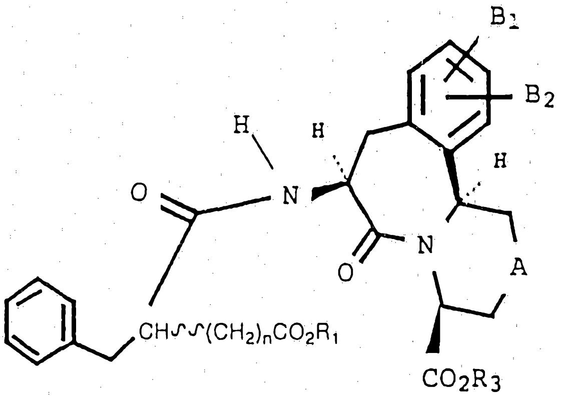
A is a bond, methylene or oxygen, sulfur or NR_4 or $NCOR_5$ wherein R_4 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_5 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

R_3 is $-CH_2OC(O)C(CH_3)_3$;

R_1 is $-CH_2OC(O)-C(CH_3)_3$; and

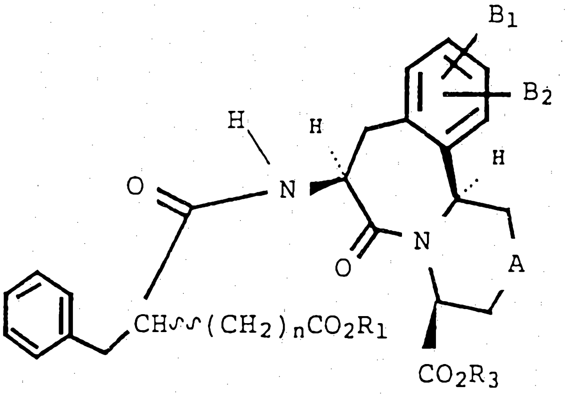
n is an integer 1 to 3,

~~comprising~~ including reacting a compound of the formula



wherein B_1, B_2, A and ~~m~~ n are as defined above and R_1 and R_3 are hydrogen with chloromethyl pivalate in the presence of a suitable base.

33. A process for preparing the compounds of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_2$ wherein R_2 is a C_1-C_4 alkyl or an Ar-Y-group wherein Ar is aryl and Y is a ~~hydrogen~~ bond or C_1-C_4 alkyl; or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

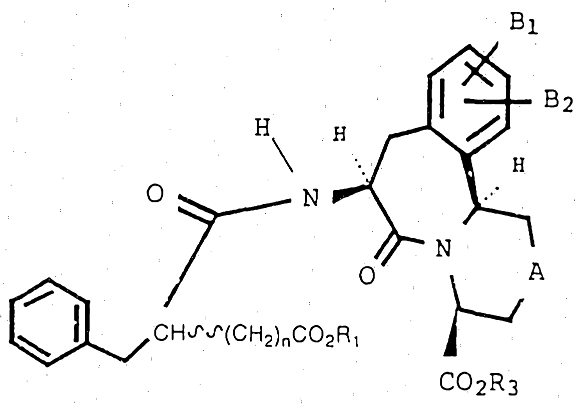
A is a bond, methylene or oxygen, sulfur or NR_4 or $NCOR_5$ wherein R_4 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_5 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

R_3 is hydrogen;

R_1 is C_1-C_4 alkyl; and

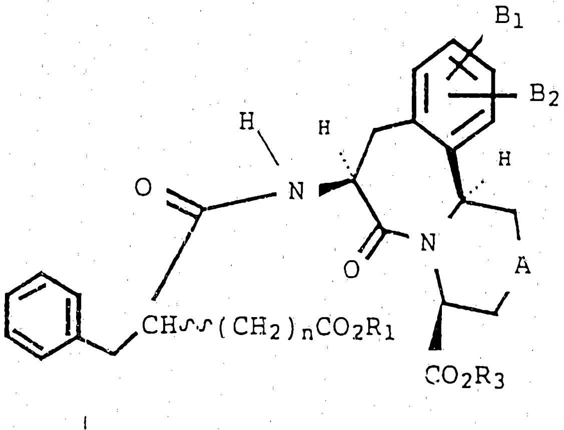
n is an integer 1 to 3,

~~comprising~~ including reacting a compound of the formula



wherein B_1, B_2, A and n are as defined above, R_1 is C_1-C_4 alkyl and R_3 is diphenylmethyl with palladium/carbon in the presence of hydrogen.

34. A process for preparing the compounds of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_2$ wherein R_2 is a C_1-C_4 alkyl or an Ar-Y-group wherein Ar is aryl and Y is a ~~hydrogen,~~ bond or C_1-C_4 alkyl; or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

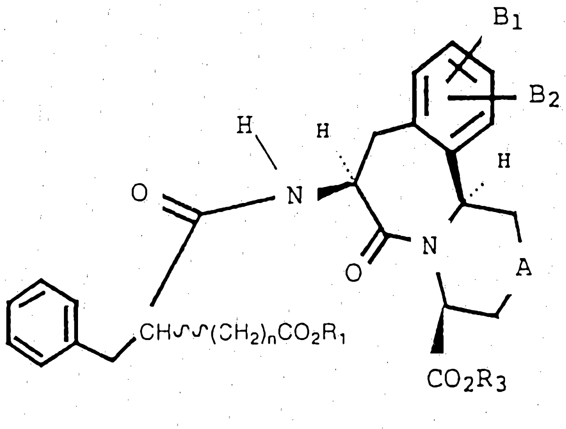
A is a bond, methylene or oxygen, sulfur or NR_4 or $NCOR_5$ wherein R_4 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_5 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

R_3 is $-CH_2OC(O)C(CH_3)_3$;

R_1 is C_1-C_4 alkyl; and

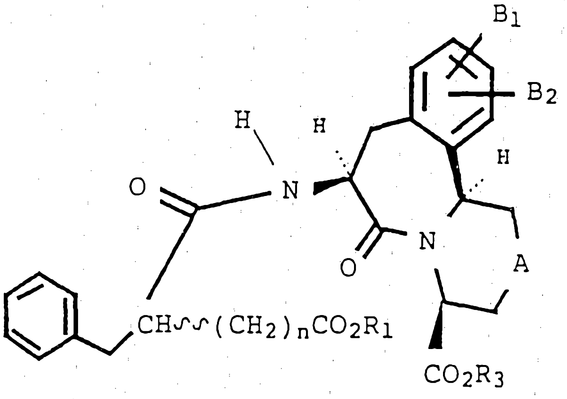
n is an integer 1 to 3,

~~comprising~~ including reacting a compound of the formula



wherein B_1, B_2, A, ~~m~~ n and R_1 are as defined above and R_3 is hydrogen with chloromethyl pivalate in the presence of a suitable base.

35. A process for preparing the compounds of the formula



wherein

B$_1$ and B$_2$ are each independently hydrogen; hydroxy; -OR$_2$ wherein R$_2$ is a C$_1$-C$_4$ alkyl or an Ar-Y-group wherein Ar is aryl and Y is a ~~hydrogen~~ bond or C$_1$-C$_4$ alkyl; or, where B$_1$ and B$_2$ are attached to adjacent carbon atoms, B$_1$ and B$_2$ can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

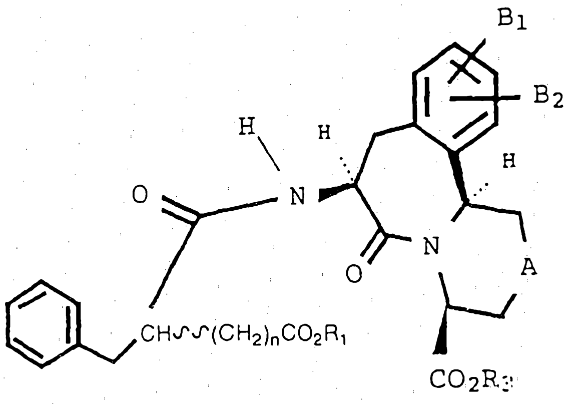
A is a bond, methylene or oxygen, sulfur or NR$_4$ or NCOR$_5$ wherein R$_4$ is hydrogen, a C$_1$-C$_4$ alkyl or an Ar-Y- group and R$_5$ is -CF$_3$, a C$_1$-C$_{10}$ alkyl or an Ar-Y- group;

R$_3$ is $-CH_2OC(O)C(CH_3)_3$;

R$_1$ is hydrogen; and

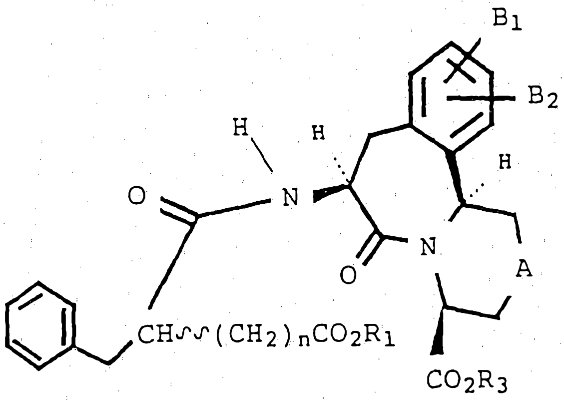
n is an integer 1 to 3,

~~comprising~~ including reacting a compound of the formula



wherein B_1, B_2, A, ~~m~~ n and R_3 are as defined above and R_1 is C_1-C_4 alkyl with a base.

36. A process for preparing the compounds of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_2$ wherein R_2 is a C_1-C_4 alkyl or an Ar-Y-group wherein Ar is aryl and Y is a ~~hydrogen~~ bond or C_1-C_4 alkyl; or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

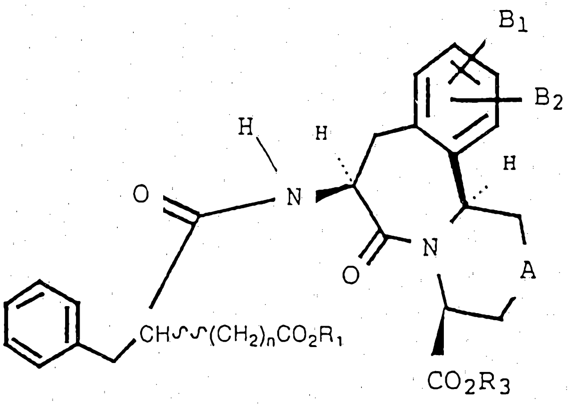
A is a bond, methylene or oxygen, sulfur or NR_4 or $NCOR_5$ wherein R_4 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_5 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

R_3 is hydrogen;

R_1 is $-CH_2OC(O)-C(CH_3)_3$; and

n is an integer 1 to 3,

including reacting a compound of the formula



wherein B_1, B_2, A and n are as defined above, R_1 is $CH_2OC(O)-C(CH_3)_3$ and R_3 is diphenylmethyl with palladium/carbon in the presence of hydrogen.

37. A compound according to claim 1 substantially as described herein with reference to any one of the examples.

DATED: 7 November, 1994

PHILLIPS ORMONDE & FITZPATRICK

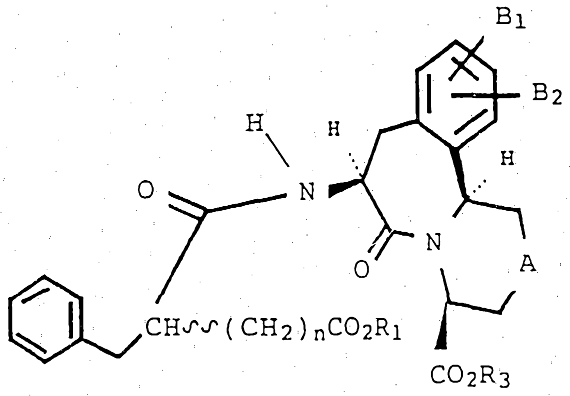
Attorneys for:

MERRELL DOW PHARMACEUTICALS INC.

David B Fitzpatrick

ABSTRACT OF THE DISCLOSURE

The present invention relates to compounds of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_2$ wherein R_2 is a C_1-C_4 alkyl or an Ar-Y group wherein Ar is aryl and Y is a hydrogen or C_1-C_4 alkyl; or, where B_1 and B_2 are attached to adjacent carbon atoms, B_1 and B_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

A is a bond, methylene or oxygen, sulfur or NR_4 or $NCOR_5$ wherein R_4 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_5 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

R_3 is hydrogen or $-CH_2OC(O)C(CH_3)_3$;

R_1 is hydrogen, C_1-C_4 alkyl or $-CH_2OC(O)-C(CH_3)_3$; and

n is an integer 1 to 3,

which are useful as inhibitors of enkephalinase and ACE.