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(54) **DERIVES AMINOACETYLMERCAPTO AYANT DES PROPRIETES HYPOCHOLESTEROLEMIQUES, ANTIATHEROSCLEREUSES ET HYPOTRIGLYCERIDEMIQUES**

(54) **HYPOCHOLESTEROLEMIC, ANTIATHEROSCLEROTIC AND HYPOTRIGLYCERIDEMIC AMINOACETYLMERCAPTO DERIVATIVES**

(57) La présente invention concerne l'utilisation de certains dérivés aminoacétylmercapto pour le traitement de patients atteints d'hypertriglycéridémie, d'athérosclérose et d'hypercholestérolémie.

(57) The present invention relates to the use of certain aminoacetylmercapto derivatives in treating patients suffering from hypertriglyceridemia, atherosclerosis and hypercholesterolemia.

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(54) Title: HYPOCHOLESTEROLEMIC, ANTIATHEROSCLEROTIC AND HYPOTRIGLYCERIDEMIC AMINOACETYLMERCAPTO DERIVATIVES

(57) Abstract

The present invention relates to the use of certain aminoacetylmercapto derivatives in treating patients suffering from hypertriglyceridemia, atherosclerosis and hypercholesterolemia.

HYPOCHOLESTEROLEMIC, ANTIATHEROSCLEROTIC AND HYPOTRIGLYCERIDEMIC AMINOACETYLMERCAPTO DERIVATIVES

BACKGROUND OF THE INVENTION

Coronary heart disease (CHD) remains the leading cause of death in the industrialized countries. Despite recent declines in CHD mortality, CHD is still responsible for more than 500,000 deaths in the U.S. annually. It is estimated that CHD, directly and indirectly, costs the U.S. more than $100 billion a year. The primary cause of CHD is atherosclerosis, a disease characterized by the deposition of lipid (cholesterol and triglycerides) in the arterial vessel wall, resulting in a narrowing of the arterial lumen and ultimately hardening of the arteries.

Atherosclerosis as manifested in its major clinical complication, coronary heart disease (CHD) or ischaemic heart disease, continues to be a major cause of death in industrialized countries. It is now well accepted that atherosclerosis can begin with local injury to the arterial endothelium followed by the penetration of circulatory monocytes into the intima of the arterial wall where they become loaded with lipoprotein derived lipids. At about the same time there seems to be a migration of arterial smooth muscle cells from the medial layer to the intimal layer and their proliferation there along with the deposition of lipid and accumulation of foam cells in the lesion. As the atherosclerotic plaque develops it progressively occludes

more and more of the affected blood vessel and can eventually lead to ischaemia, thrombosis or infarction. Therefore, it is desirable to provide methods of inhibiting the progression of atherosclerosis in patients in need thereof.

National Institutes of Health Consensus Development Conference Panel concluded that lowering plasma cholesterol levels (specifically blood levels of low-density lipoprotein cholesterol) will definitely reduce the risk of heart attacks due to CHD. Serum lipoproteins are the carriers for lipids in the circulation. They are classified according to their density; i.e., chylomicrons, very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL) and high-density lipoproteins (HDL). About 50% to 70% of the cholesterol circulating in the blood is carried as LDL. In contrast, about 25% of total cholesterol is found in HDL, while VLDL carries most of the plasma triglycerides and only about 10% to 15% of the total cholesterol.

Chylomicrons are assembled in the intestinal wall from products of lipid digestion and are then transported into the peripheral circulation via the thoracicolymphatic system. In the circulation, they are broken down by lipoprotein lipase (LPL) into free fatty acids and triglycerides which are primarily used by muscles for energy or stored in adipose tissue. The other serum lipoproteins are involved in the transport of endogenously synthesized lipid. Endogenous lipid transport begins when the liver secretes triglycerides and cholesterol into the plasma as VLDL. The triglycerides of VLDL are cleaved in the capillaries by LPL to IDL and finally LDL. Some of these particles are cleared rapidly by the liver by receptor-mediated endocytosis. The remainder circulate mainly as LDL.

As cells die and cell membranes turn over, cholesterol is continously released into the plasma and becomes HDL. HDL promotes the removal of cholesterol from peripheral cells and facilitates its transport back to the liver.

Arterial wall cholesterol is derived almost exclusively from LDL [Brown and Goldstein, Ann. Rev. Biochem. 52, 223 (1983); Miller, Ann. Rev. Med. 31, 97 (1980)]. Framingham investigators found the higher the levels of LDL, the higher the risk of devloping CHD [Am. J. Med. 80 (Suppl. 2A) 23-32, 1986]. In patients with low levels of LDL, the development of atheroschlerosis is rare [Patton et. al, Clin. Chem. 29, 1890 (1983)]. Accordingly, it is desirable to provide a method for reducing plasma cholesterol in patients with hypercholesterolemia or at risk of developing hypercholesterolemia.

Elevated cholesterol levels are also associated with a number of disease states, including coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis, and xanthoma. It is desirable to provide a method for reducing plasma cholesterol in patients with, or at risk of developing disease states associated with elevated cholesterol levels.

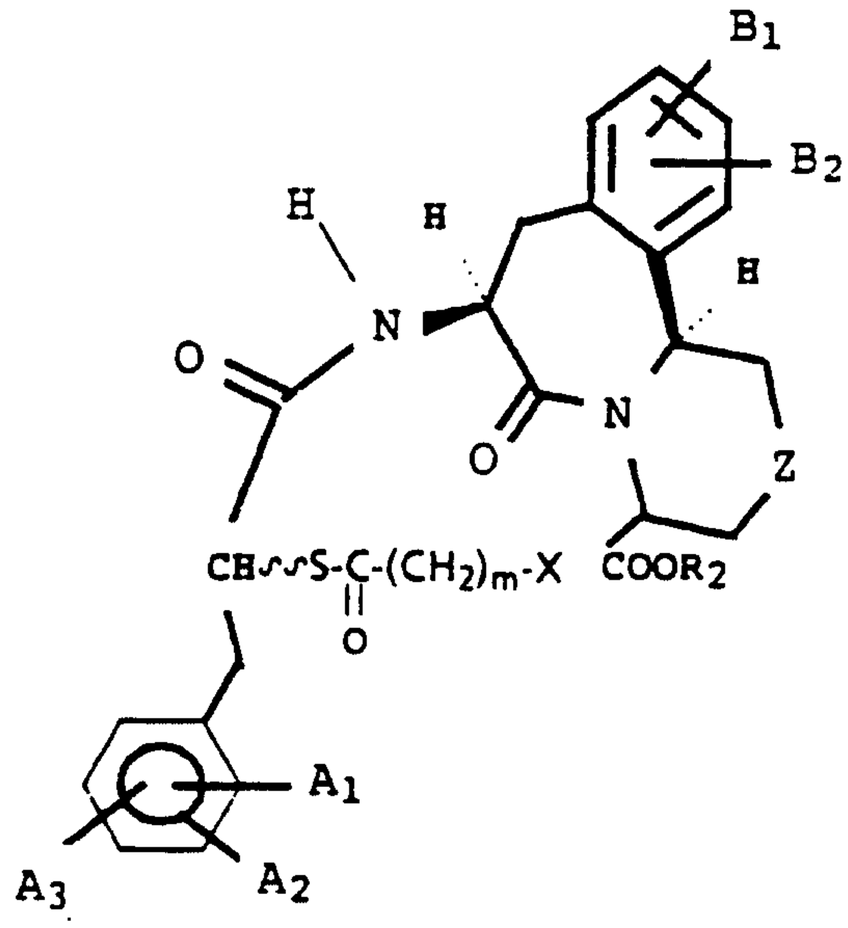
Hypertriglyceridemia is a condition in which there is an excessive amount of triglyceride (>500mg/dl) in the plasma. It may play a role in atherogenesis and the development of coronary heart disease [Vega and Grundy, Adv. Exp. Med. 243, 311 (1989)]. In addition, severe hypertriglyceridemia (>1000mg/dl) is associated with chylomicronemia and causes acute pancreatitis [See K. Soergel, ACUTE PANCREATITIS, in *Gastrointestinal Disease* 91, 3rd ed. (Sleisenger, M. H., and Fordtran, J. S., eds.), W. B. Saunders Company, Philadelphia, Pa., 1983, pp. 1462-1485; and See Brown, M. S., and Goldstein, J. L., DRUGS USED IN THE TREATMENT OF HYPERLIPOPROTEINEMIAS, in *Goodman and Gillman's, The*

Pharmacological Basis of Therapeutics 34, 7th edition, (Macmillan Publishing Co., New York, 1985, pp. 827-845]. Severe elevations in chylomicrons directly induce pancreatitis, and it can be prevented by triglyceride reduction [U.S. Department of Health and Human Services, NIH Publication No. 89-2925, pp. 74-77, January 1989, "Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults"] It is therefore desirable to provide a method for reducing plasma triglycerides in patients with hypertriglyceridemia.

The present invention relates to the use of certain mercaptoacetylamide derivatives in treating patients suffering from hypertriglyceridemia, atherosclerosis and hypercholesterolemia.

SUMMARY OF THE INVENTION

The present invention provides a method of treating hypercholesterolemia, atheroscherosis and hypertriglyceridemia in a patient in need thereof comprising administering to said patient an effective hypocholesterolemic, antiatherosclerotic or hypotriglyceridemic amount of a compound of the Formula (I)



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_1$ wherein R_1 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-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_1, A_2 and A_3 are each independently hydrogen; hydroxy; nitro; amino; fluoro, chloro, $-OR_1$ or an Ar-Y group; or, where A_1 and A_2 are attached to adjacent carbon atoms, A_1 and A_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

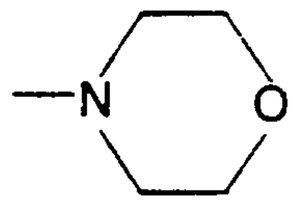
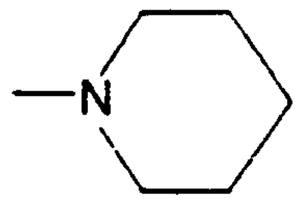
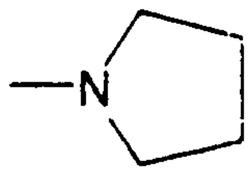
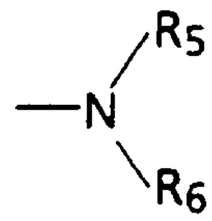
R_2 is hydrogen, a C_1-C_4 alkyl, an Ar-Y- group or $-CH_2O-C(O)C(CH_3)_3$;

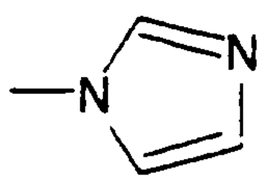
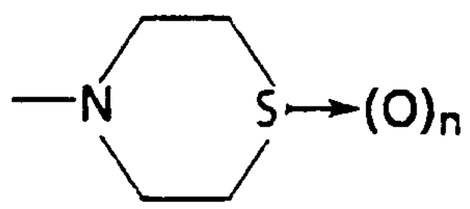
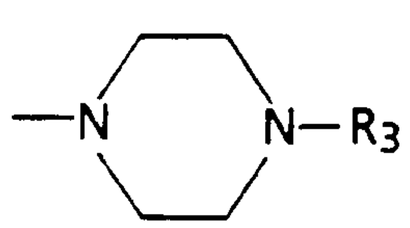
Z is $-CH_2-$, $-O-$, $-S-$, $-N(R_3)-$ or $-N(C(=O)R_4)-$ or a bond

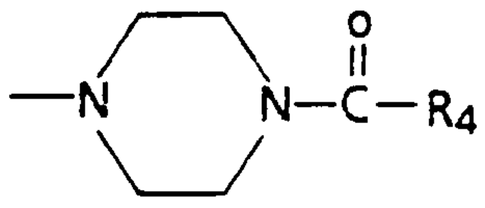
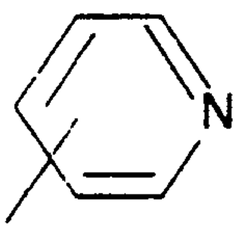
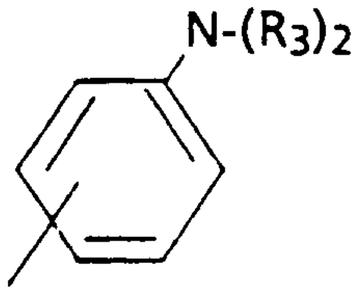
wherein R_3 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_4 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

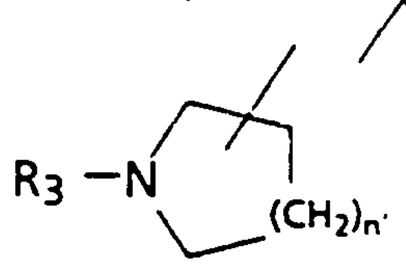
m is an integer 0 to 5;

X is selected from the group consisting of

and 

wherein R_5 and R_6 are each independently a C_1-C_4 alkyl or an Ar-Y- group and n is an integer 0-2; n' is an integer 1-2; and the pharmaceutically acceptable salts thereof.

The present invention further provides a method of treating hypercholesterolemia, antheroscherosis and hypertriglyceridemia in a patient in need thereof comprising administering to said patient an effective hypocholesterolemic, antiatherosclerotic or hypotriglyceridemic amount of a compound of the Formula (I).

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 term "C_1-C_{10} alkyl" refer to saturated straight or

branched chain hydrocarbyl radicals of 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, octyl, nonyl, or decyl and the like. The term "halogen", "halo", "halide" or "Hal" refers to a chlorine, bromine, or iodine atom. The term "BOC" refers to t-butyloxycarbonyl. The term "C_1-C_4 alkoxy" refers to a saturated straight or branched chain hydrocarboxy radical of one to four carbon atoms and includes methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, tertiary butoxy and the like.

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.

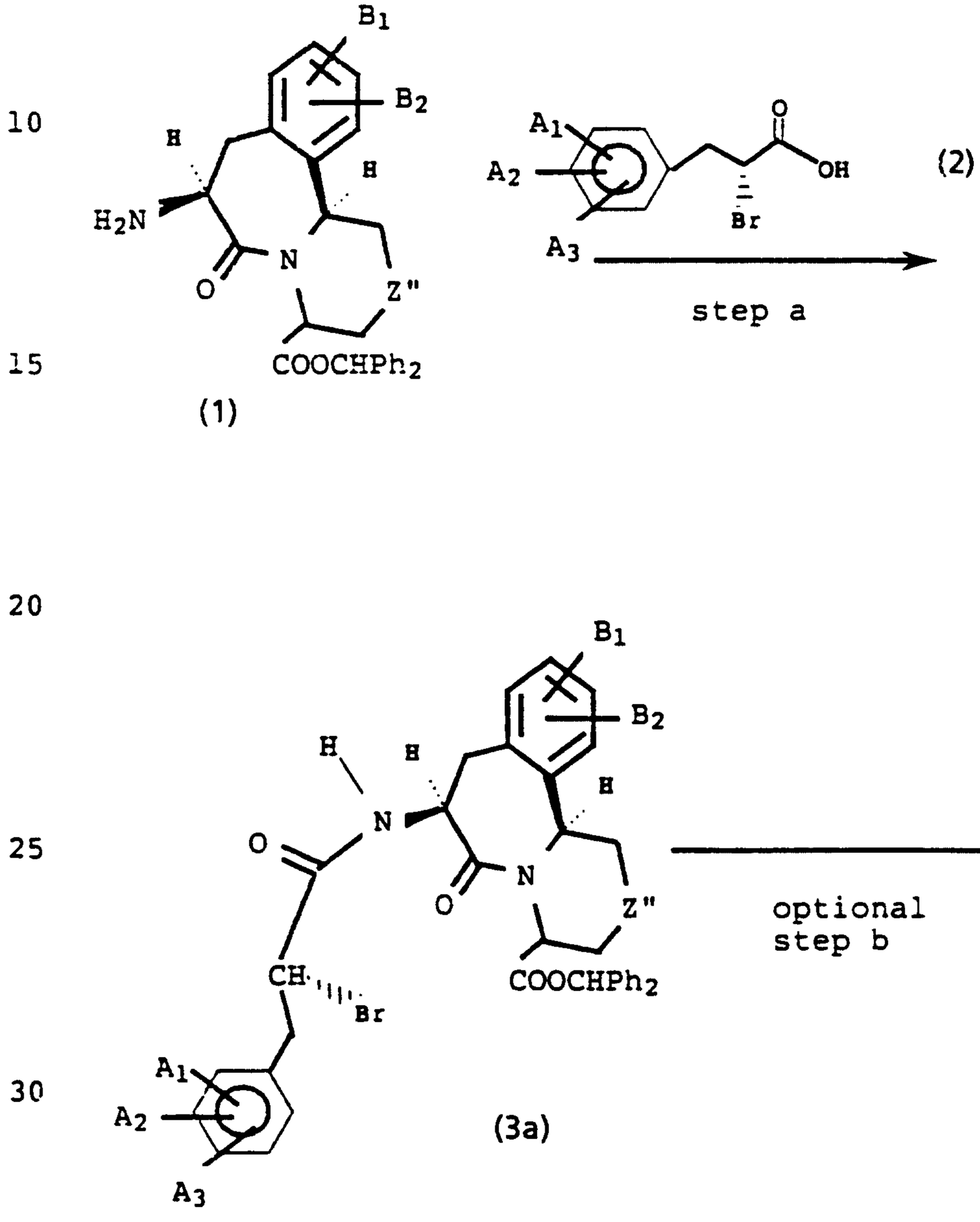
As used herein, the designation "$\sim$" refers to a bond to a chiral atom for which the stereochemistry is not designated.

Compounds of Formula (I) can form pharmaceutically acceptable salts with any non-toxic, organic or inorganic acid. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric and phosphoric acid and acid metals salts such as sodium

monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono, di and tricarboxylic acids. Illustrative of such acids are, for example, acetic, trifluoroacetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salacylic, 2-phenoxybenzoic and sulfonic acids such as methane sulfonic, trifluoromethane sulfonic, 2-hydroxyethane sulfonic acid and p-toluenesulfonic acid.

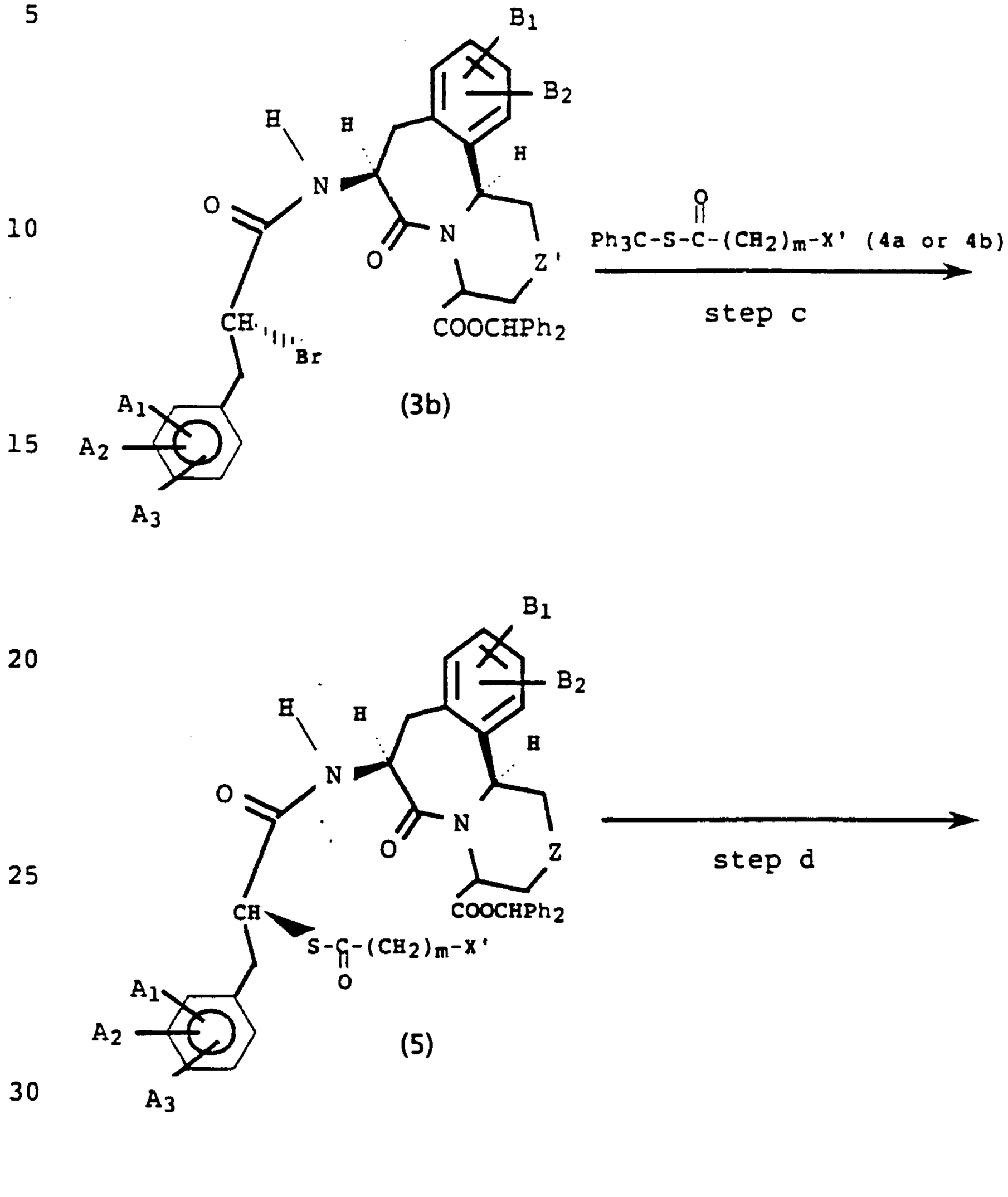
The compounds of Formula (I) can be prepared by utilizing procedures and techniques well known and appreciated by one of ordinary skill in the art. A general synthetic scheme for preparing these compounds is set forth in Scheme A wherein all substituents are as previously defined unless otherwise defined.

Scheme A



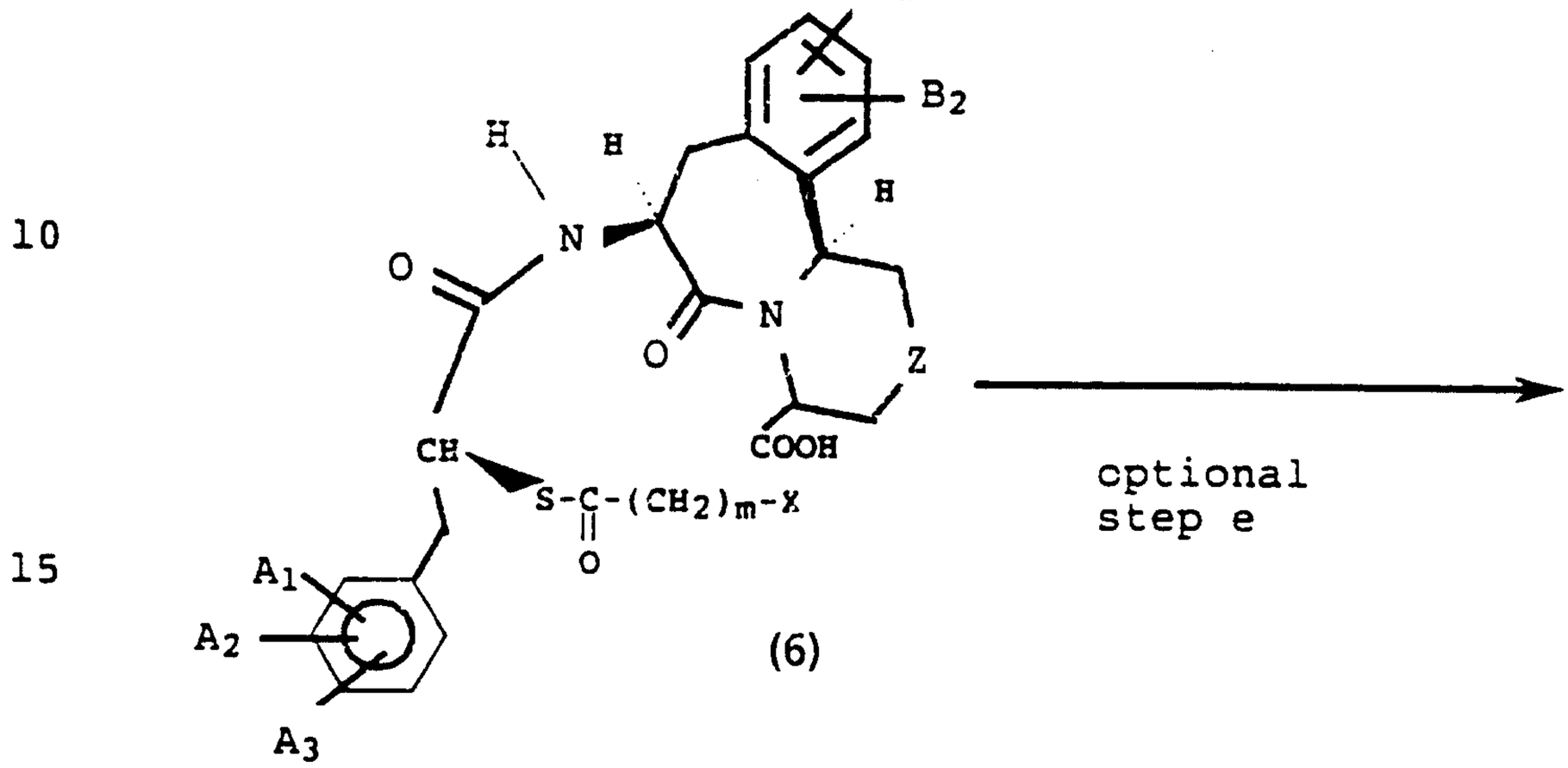
In step a, the appropriate (R)-bromotricyclic compound of structure (3a) can be prepared by reacting the appropriate amino tricyclic compound of structure (1) with

Scheme A Cont.



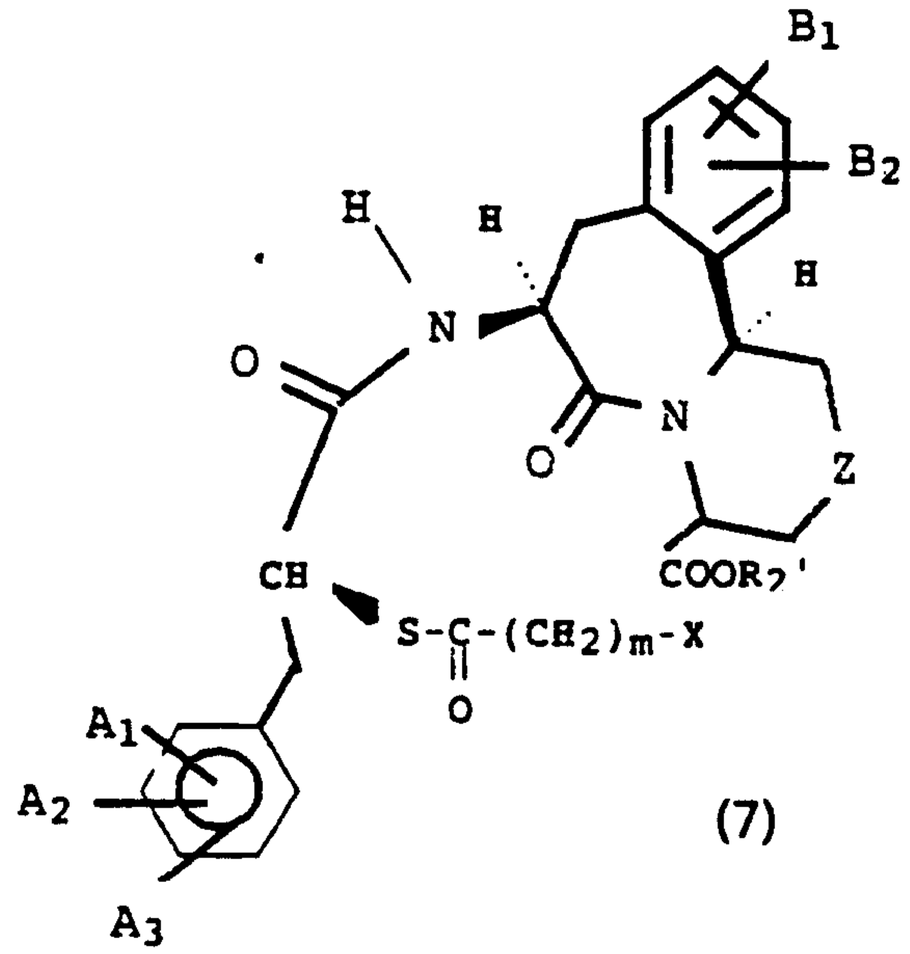
the appropriate (R)-bromo acid compound of structure (2). For example, the appropriate amino tricyclic compound of structure (1) can be reacted with the appropriate (R)-bromo

Scheme A Cont.



(6)

optional step e



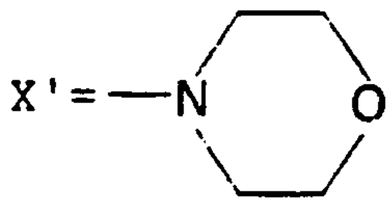
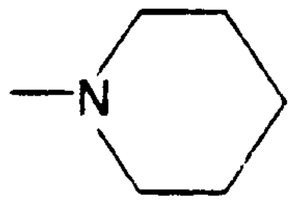
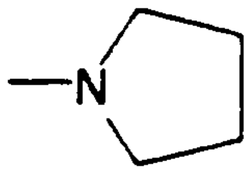
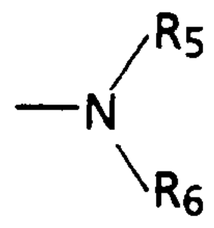
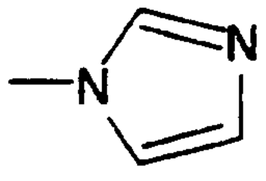
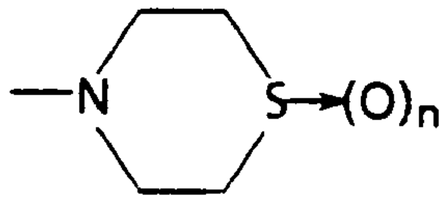
(7)

acid compound of structure (2) in the presence of a coupling reagent such as EEDQ (2-ethoxy-2-ethoxycarbonyl-1,2-dihydro-quinoline), DCC (1,3-dicyclohexylcarbodiimide),

Scheme A Cont.

Z'' = $-CH_2-$, $-O-$, $-S-$, $-NH-$ or a bond
Z' = $-NR_3'-$ or $-NC(O)R_4-$

R_2' = a C_1-C_4 alkyl, an Ar-Y- group or $-CH_2O-C(O)C(CH_3)_3$

X' = 
, 
, 
, 
, 
, 
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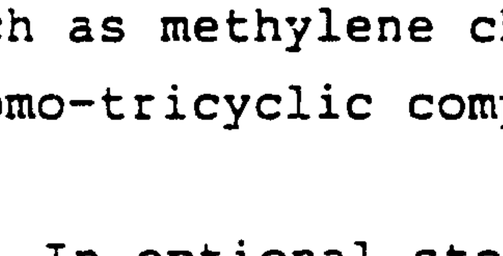
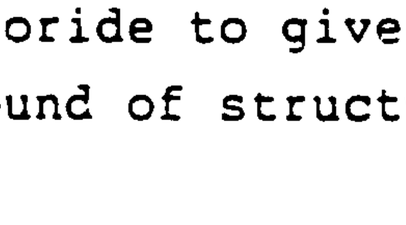
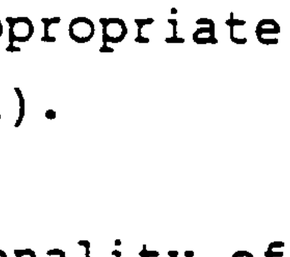

, 
, 
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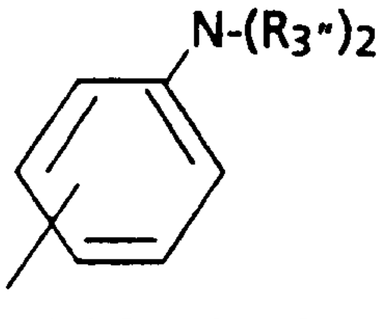
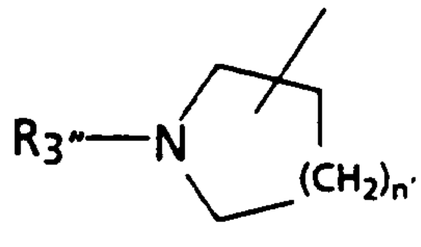

or 

R_3'' = BOC, C_1-C_4 alkyl or an Ar-Y- group

or diethylcyanophosphonate in a suitable aprotic solvent, such as methylene chloride to give the appropriate (R)-bromo-tricyclic compound of structure (3a).

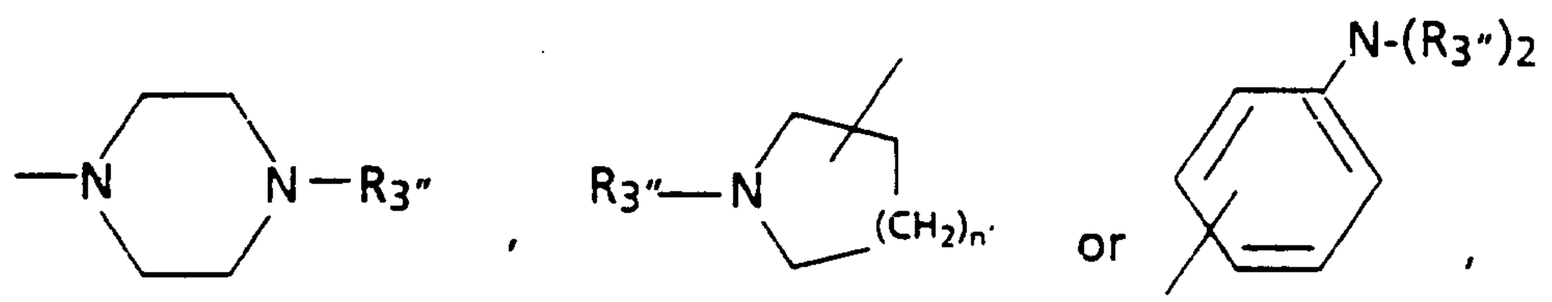
In optional step b, the amino functionality of those (R)-bromotricyclic compounds of structure (3a) wherein Z is NH can be subjected to reductive alkylation with an appropriate aldehyde of structure $R_3'_{(n-1)}CHO$ using sodium cyanoborohydride as is known in the art to give the corresponding (R)-bromotricyclic compound of structure (3b) wherein Z is NR_3', wherein R_3' is C_1-C_4 alkyl or an Ar-Y group.

Alternatively, the amino functionality of those (R)-bromotricyclic compounds of structure (3a) wherein Z is NH can be acylated using the appropriate acyl chloride of structure R_4CO-Cl or the appropriate anhydride of structure $(R_4CO)_2-O$ as is well known in the art to give the corresponding (R)-bromotricyclic compound of structure (3b) wherein Z is $N-C(O)R_4$.

In step c, the appropriate (S)-aminoacetylthiotricyclic compound of structure (5) can be prepared by reacting the appropriate (R)-bromotricyclic compound of structure (3a or 3b) with the appropriate triphenylmethyl aminothiolacetate of structure (4a or 4b) under basic conditions such as sodium hydride, hydrogen sulfide in a suitable aprotic solvent such as dimethylformamide.

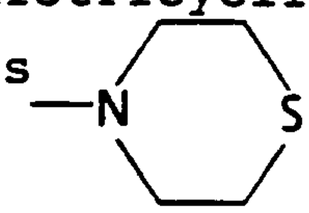
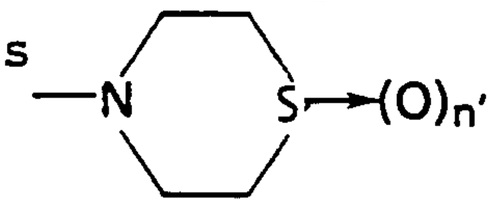
In step d, the diphenylmethyl ester functionality of the appropriate (S)-aminoacetylthiotricyclic compound of structure (5) can be removed using trifluoroacetic acid to give the corresponding (S)-aminoacetylthiotricyclic compound of structure (6).

For those (S)-aminoacetylthiotricyclic compounds of structure (5) wherein X' is



wherein $R_{3''}$ is BOC, the BOC protecting group is also removed during the diphenylmethyl ester removal of step d.

In optional step e, the carboxylic acid functionality of the appropriate (S)-aminoacetylthiotricyclic compound of structure (6) can be reesterified by techniques well known in the art to give the corresponding (S)-aminoacetylthiotricyclic compound of structure (7).

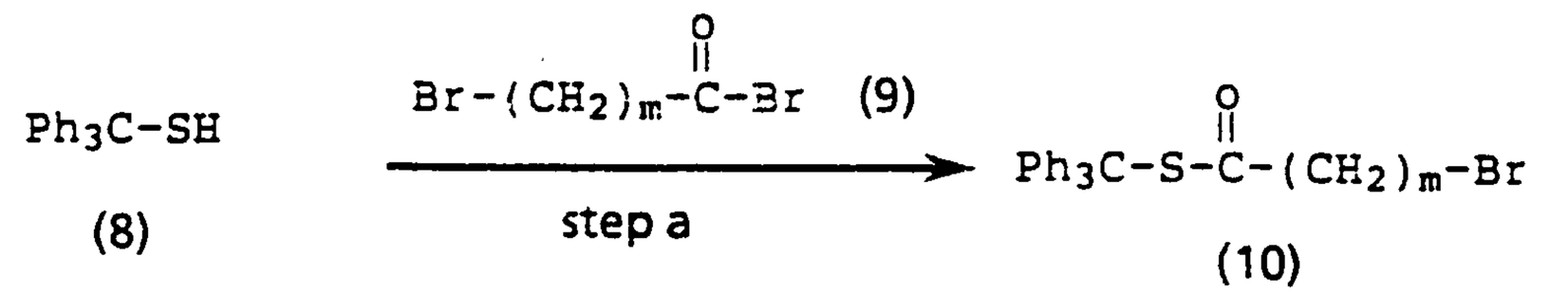
In addition, the sulfide functionality of those (S)-aminothiotricyclic compounds of structure (6) wherein X is  may be oxidized by techniques and procedures well known in the art, such as magnesium monoperoxyphthalic acid hexahydrate to give the (S)-aminothiotricyclic compounds of structure (6) wherein X is  wherein n' is 1 or 2.

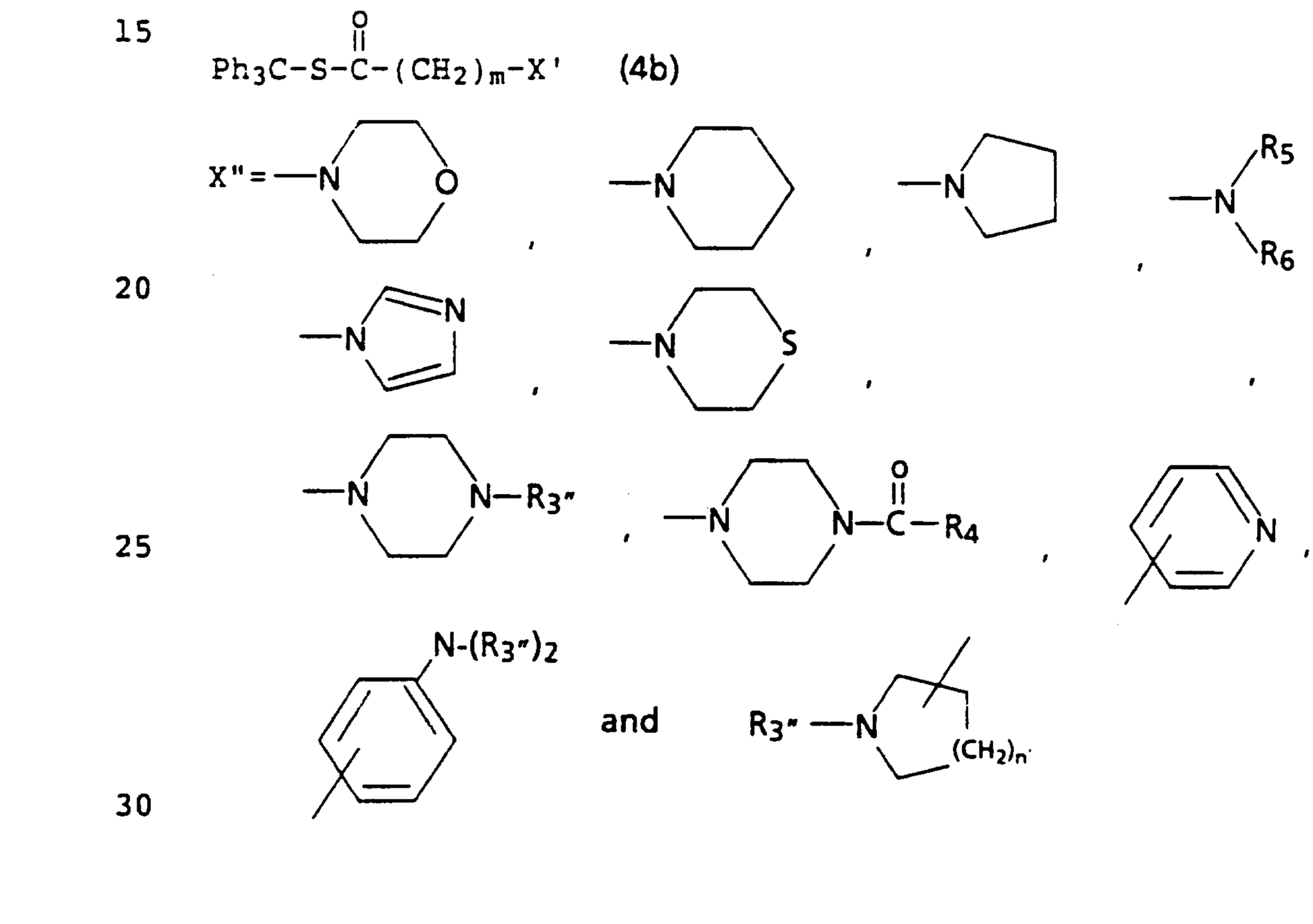
In addition, the nitro functionality of those (S)-aminothiotricylic compounds of structure (6) wherein A_1, A_2, or A_3 is a nitro group, can be reduced by techniques and procedures well known in the art, such as zinc/acetic acid, to give the (S)-aminothiotricylic compounds of structure (6) wherein A_1, A_2, or A_3 is an amino group.

Although Scheme A provides for the preparation of compounds of Formula (I) wherein the thioacetate functionality is of the (S)-configuration, the compounds of Formula I wherein the thioacetate functionality is of the (R)-configuration may be prepared by substituting the appropriate (R)-bromo compound of structure (2) with the corresponding (S)-bromo compound.

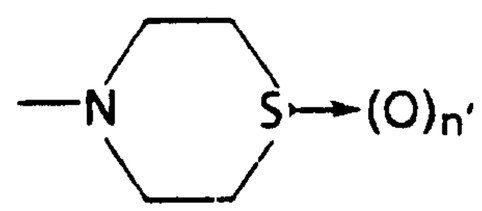
Scheme B provides a general synthetic scheme for preparing the triphenylmethyl aminothiolacetates of structures (4a and 4b).

Scheme B


Ph3C-SH
(8)
Br-(CH2)m-C-Br (9)
step a
Ph3C-S-C-(CH2)m-Br
(10)
X"H (11)
step b
Ph3C-S-C-(CH2)m-X"
(4a)
optional
step c


Ph3C-S-C-(CH2)m-X' (4b)
X"=
N
O
R5
R6
N-(R3")2
and
R3"
(CH2)n

Scheme B Cont.

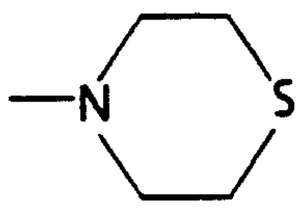
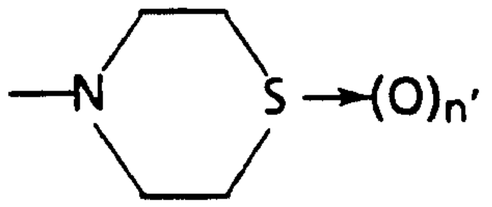
X' = 

n' = 1 or 2

R_3" = BOC, C_1-C_4 alkyl or an Ar-Y group

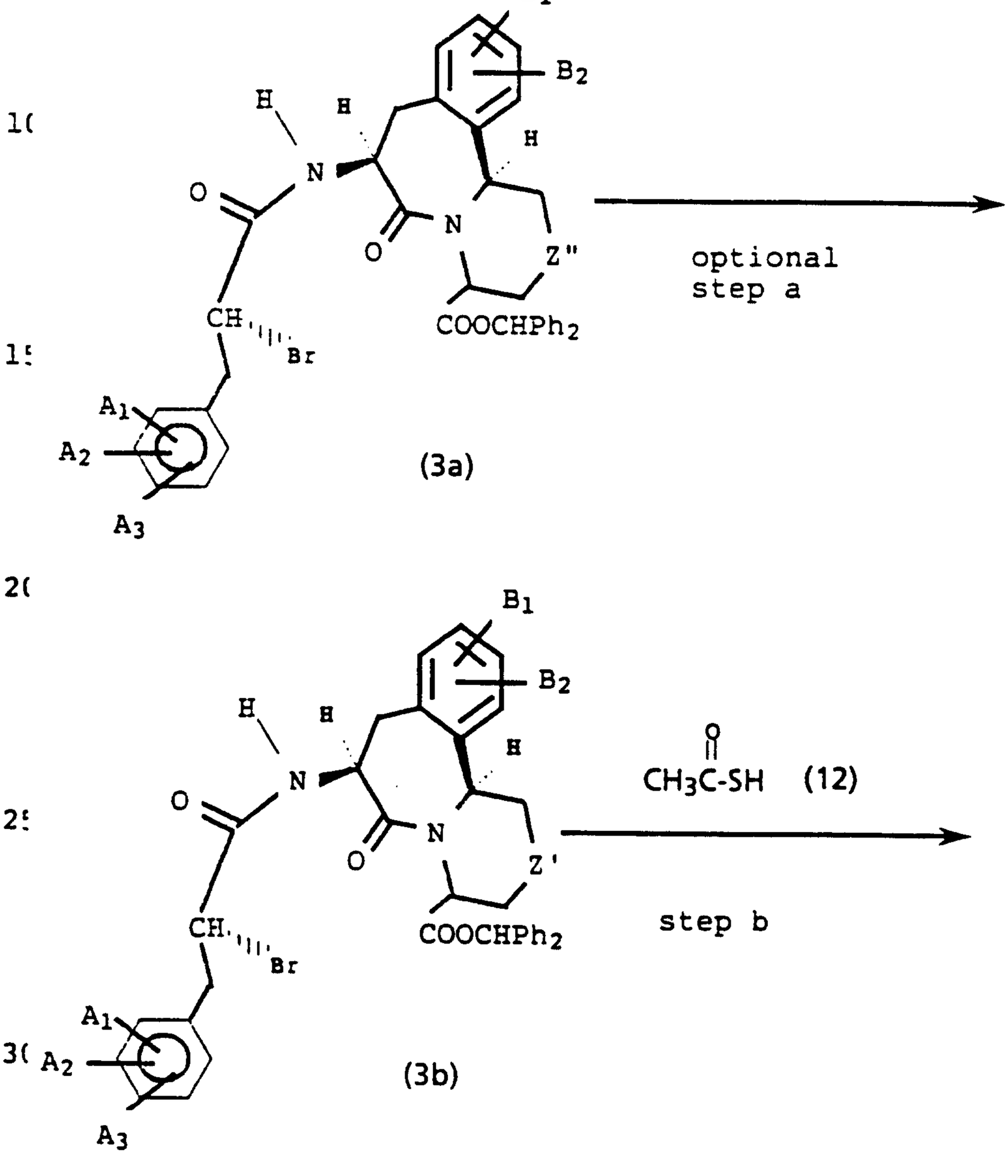
In step a, triphenylmethyl mercaptan (8) and bromoacetyl bromide (9) are reacted under basic conditions, such as pyridine, in an aprotic solvent such as methylene chloride to give triphenylmethyl bromothiolacetate of structure (10).

In step b, triphenylmethyl bromothiolacetate of structure (10) is reacted with the appropriate amino compound of structure (11) under basic conditions, such as pyridine, in an aprotic solvent such as methylene chloride to give the appropriate triphenylmethyl aminothiolacetate compound of structure (4a).

In optional step c, the sulfide functionality of those triphenylmethyl aminothiolacetate compounds of structure (4a) wherein X is represented by  may by oxidized by techniques and procedures well known in the art, such as metachloroperbenzoic acid, to give the triphenylmethyl aminothiolacetate compounds of structure (4b) wherein X is represented by  wherein n' is an 1 or 2.

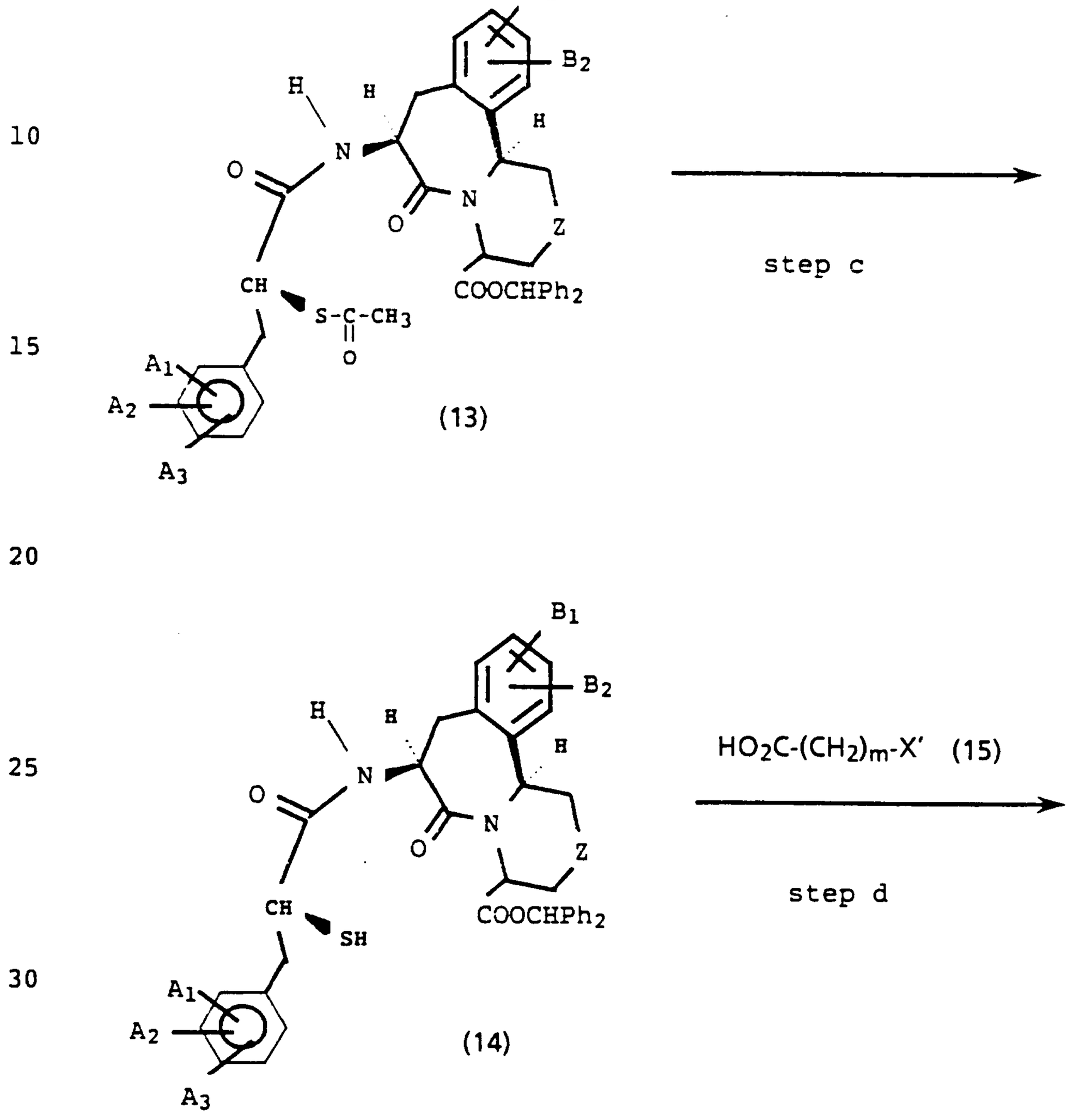
Alternatively, the compounds of Formula (I) may be prepared as described in Scheme C. In Scheme C, all substituents are as previously defined unless otherwise indicated.

Scheme C



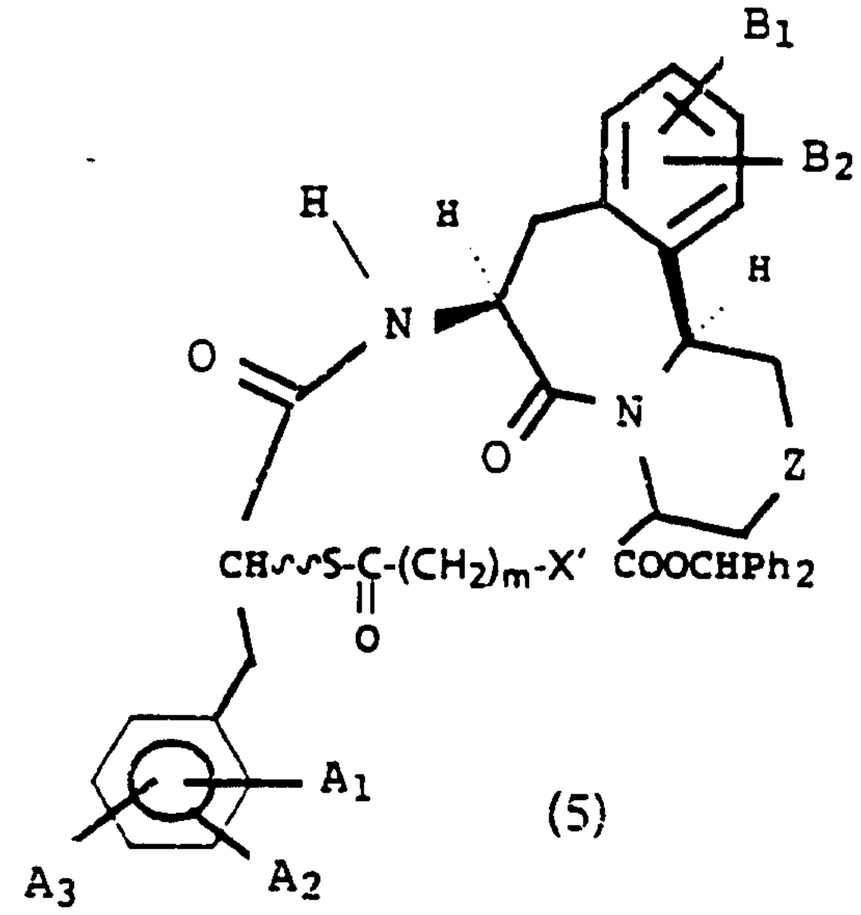
In optional step a, the amino functionality of those (R)-bromotricyclic compounds of structure (3a) wherein Z is

Scheme C Cont.



NH can be subjected to reductive alkylation with an appropriate aldehyde of structure $R_{3'(n-1)}CHO$ as described previously in Scheme A, optional step b to give the

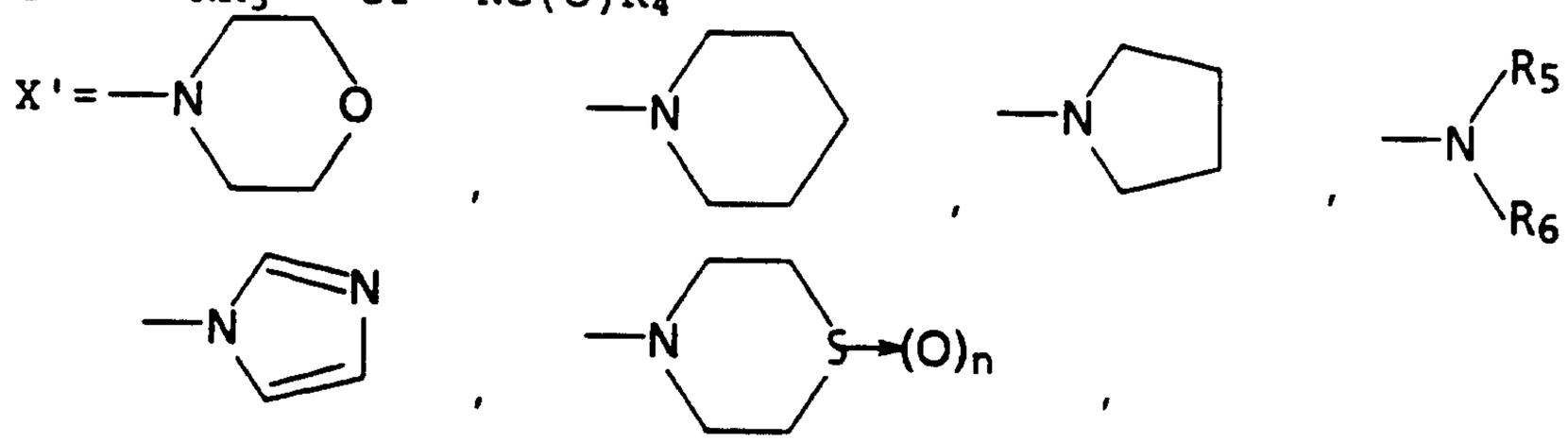
Scheme C Cont.

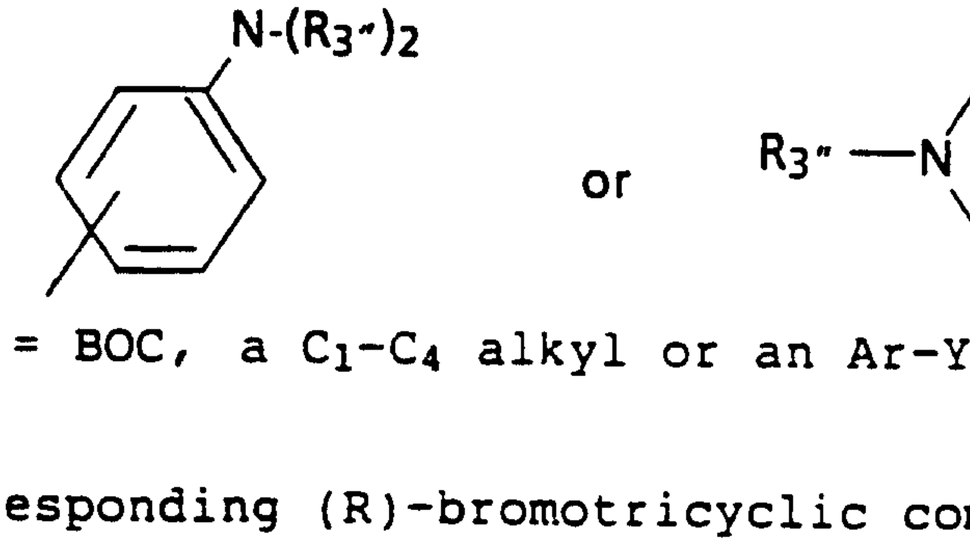


(5)

Z" = $-CH_2-$, $-O-$, $-S-$, $-NH-$ or a bond

Z' = $-NR_3'-$ or $-NC(O)R_4-$

X' = 



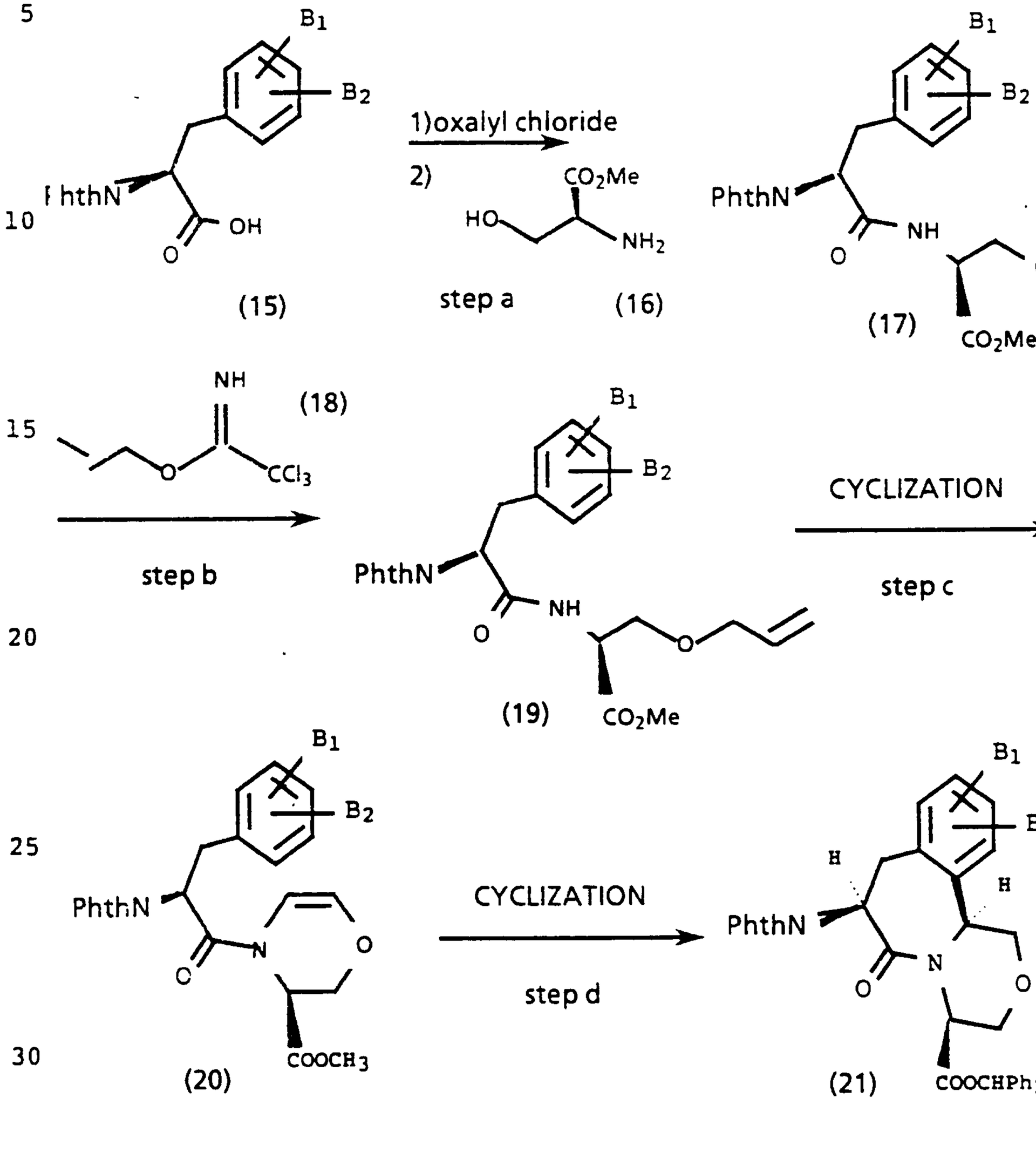
In step b, the appropriate (S)-acetylthiotricyclic compound of structure (13) can be prepared by reacting the appropriate (R)-bromotricyclic compound of structure (3a or 3b) with thiolacetic acid (12) in the presence of a base, such as cesium carbonate. The reactants are typically contacted in a suitable organic solvent such as dimethylformamide. The reactants are typically stirred together at room temperature for a period of time ranging from 1 to 8 hours. The resulting (S)-thioacetate of structure (13) is recovered from the reaction zone by extractive methods as is known in the art. It may be purified by chromatography.

In step c, the (S)-thioacetate functionality of the appropriate (S)-acetylthiotricyclic compound of structure (13) is hydrolyzed to the corresponding (S)-thiol compound of structure (14) with ammonia in a suitable protic solvent such as ethanol.

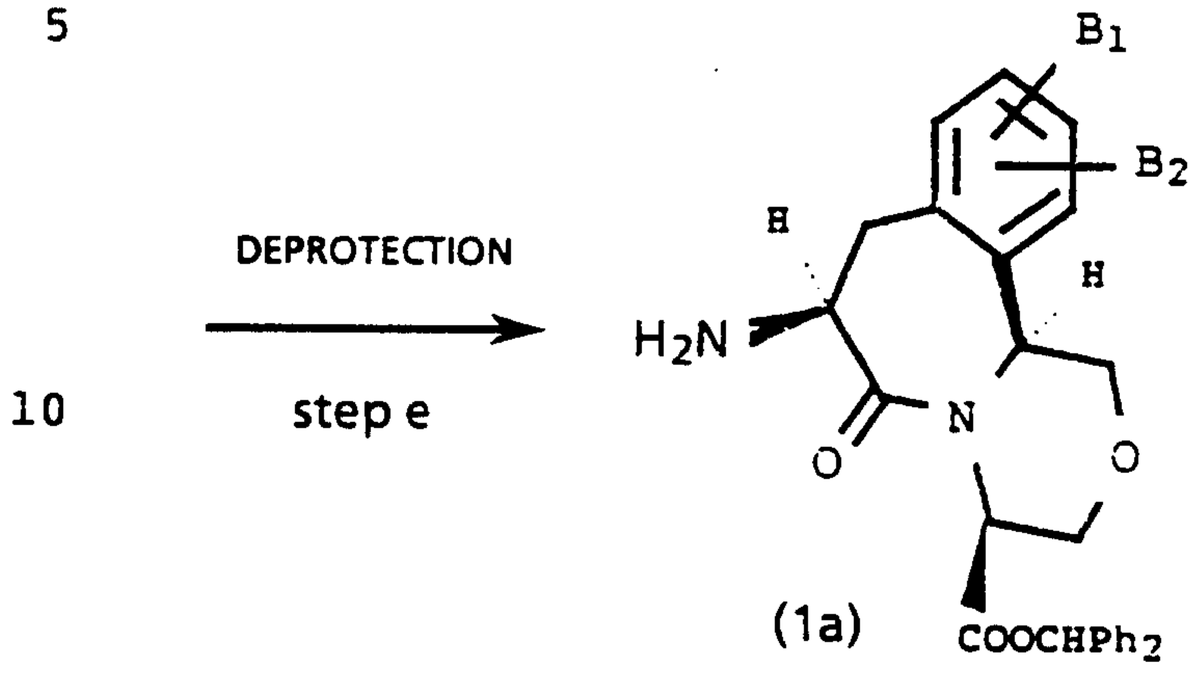
In step d, the thiol functionality of the appropriate (S)-thiol compound of structure (14) is coupled with the appropriate acid of structure (15) in the presence of a suitable coupling agent to give the appropriate (S)-aminoacetylthioltricyclic compound of structure (5). For example, the appropriate (S)-thiol compound of structure (14) can be reacted with the appropriate acid of structure (15) in the presence of a coupling reagent such as 2-fluoro-1-methylpyridinium p-toluenesulfate, EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), carbonyldiimidazole, EEDQ (1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, DCC (1,3-dicyclohexylcarbodiimide) or diethylcyanophosphonate in a suitable aprotic solvent such as methylene chloride to give the appropriate (S)-aminoacetyl-thiotricyclic compound of structure (5) which may be used as described previously in Scheme A, step d.

Amino tricyclic compounds of structure (1) wherein Z 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
(15)
1)oxalyl chloride
2)
CO2Me
HO
NH2
step a
(16)
PhthN
NH
O
OH
(17)
CO2Me
NH
(18)
CCl3
O
step b
B1
B2
PhthN
NH
O
O
(19)
CO2Me
CYCLIZATION
step c
B1
B2
PhthN
O
N
O
COOCH3
(20)
CYCLIZATION
step d
B1
B2
H
H
PhthN
O
N
O
(21)
COOCHPh2

Scheme D Cont.



Scheme D provides a general synthetic procedure for preparing amino tricyclic compounds of structure (1) wherein Z is -O-.

In step a, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure (15) is converted to the corresponding acid chloride, then reacted with the appropriate L-serine methyl ester of structure (16) to give the corresponding 1-oxo-3-phenylpropyl-L-serine methyl ester of structure (17).

For example, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure (15) 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 (16) 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 (17).

In step b, the hydroxy functionality of the appropriate 1-oxo-3-phenylpropyl-L-serine methyl ester of structure (17)

is allylated with the allyl imidate of structure (18) to give the corresponding 1-oxo-3-phenylpropyl-L-serine-O-allyl methyl ester of structure (19).

For example, appropriate 1-oxo-3-phenylpropyl-L-serine methyl ester of structure (17) is contacted with 2 molar equivalents of the allyl imidate of structure (18) 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 (19) 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 (19) is cyclized to give the corresponding (4S)-enamine of structure (20).

For example, the appropriate 1-oxo-3-phenylpropyl-L-serine-O-allyl methyl ester of structure (19) 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 (20).

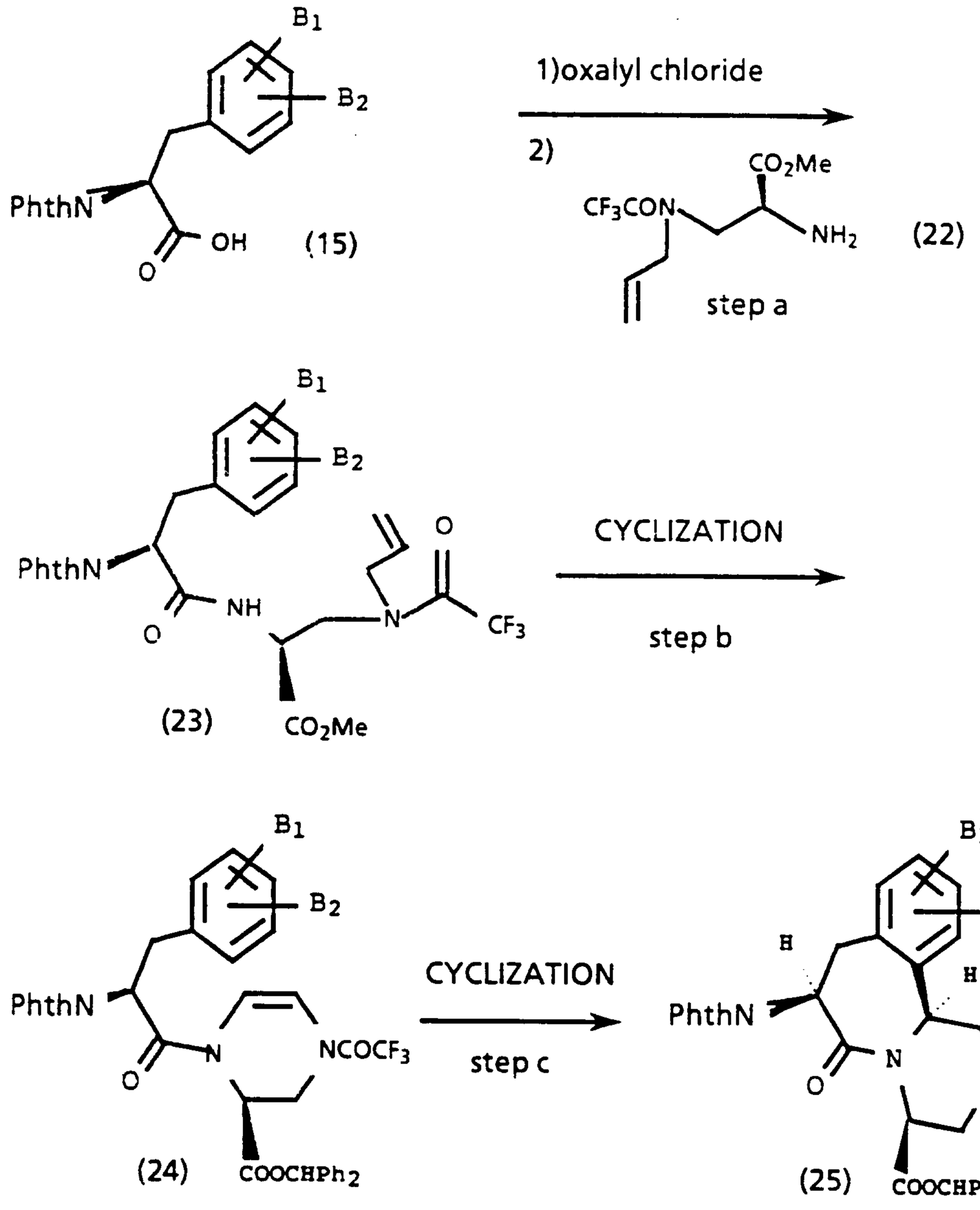
In step d, the appropriate (4S)-enamine of structure (20) is cyclized to give the corresponding (4S)-tricyclic compound of structure (21) by an acid catalyzed Friedel-Crafts reaction. For example, the appropriate (4S)-enamine of structure (20) can be converted to the corresponding (4S)-tricyclic compound of structure (21) 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 (21) is removed to give the corresponding amino tricyclic compound of structure (1) wherein X is -O-. For example, the phthalimide protecting group of the appropriate (4S)-tricyclic compound of structure (21) can be removed using hydrazine monohydrate in a suitable protic solvent such as methanol, to give the corresponding amino tricyclic compound of structure (1a).

Amino tricyclic compounds of structure (1) wherein Z is -NH- may be prepared as described in Scheme E. In Scheme E, all substituents unless otherwise indicated are as previously defined.

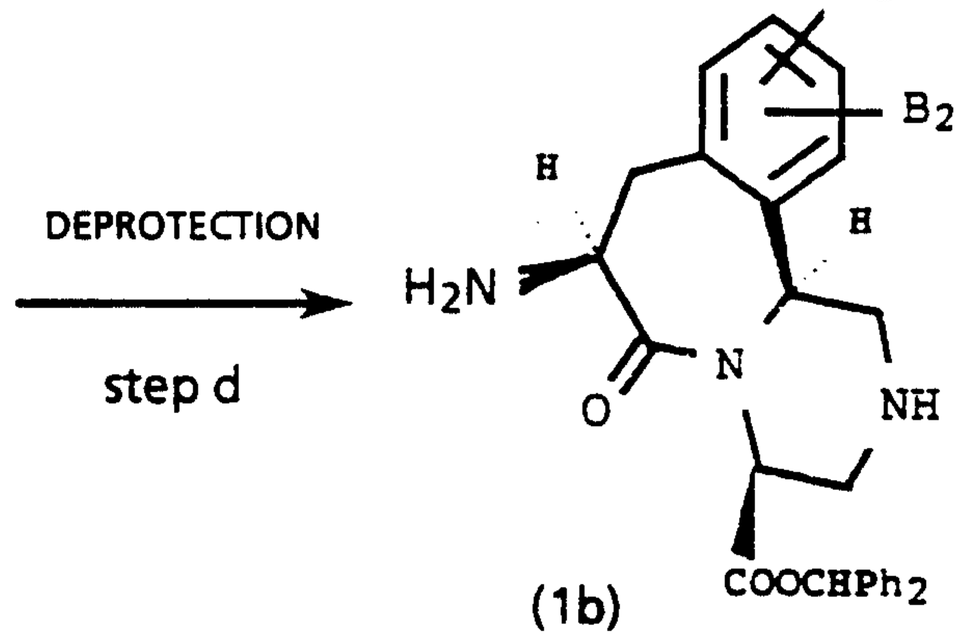
Scheme E



Scheme E provides an general synthetic procedure for preparing amino tricyclic compounds of structure (1) wherein Z is -NH-.

In step a, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure (15) is converted to the corresponding acid chloride, then reacted with the appropriate 3-trifluoracetylamino-3-allyl-L-2-aminopropionic

Scheme E Cont.



acid, methyl ester of structure (22) to give the corresponding 1-oxo-3-phenylpropyl-N-trifluoracetyl-N-allyl-L-amino acid, methyl ester of structure (23) as described previously in Scheme D, step a.

3-Trifluoracetylamino-3-allyl-L-2-aminopropionic acid, methyl ester of structure (22) may be prepared from Nα-(benzyloxycarbonyl)-β-(amino)-L-alanine in a 4-step process.

Nα-(Benzyloxycarbonyl)-β-(amino)-L-alanine is first converted to Nα-(benzyloxycarbonyl)-β-(amino)-L-alanine, methyl ester by techniques and procedures well known and appreciated by one of ordinary skill in the art, such as methanol/sulfuric acid esterification.

The β-amino functionality of Nα-(benzyloxycarbonyl)-β-(amino)-L-alanine, methyl ester is then allylated with allyl trichloroacetimidate to give the corresponding Nα-(benzyloxycarbonyl)-β-(allylamino)-L-alanine, methyl ester using conditions described previously in Scheme D, step b.

The B-allylamino functionality of Nα-(benzyloxycarbonyl)-β-(allylamino)-L-alanine, methyl ester is then acylated with trifluoroacetic anhydride as is known in the art to give Nα-(benzyloxycarbonyl)-β-(trifluoroacetyl-allylamino)-L-alanine, methyl ester.

The Nα-(benzyloxycarbonyl) protecting group is then removed using boron tris(trifluoroacetate)/trifluoroacetic acid as is known in the art to give 3-trifluoracetylamino-3-allyl-L-2-aminopropionic acid, methyl ester of structure (22).

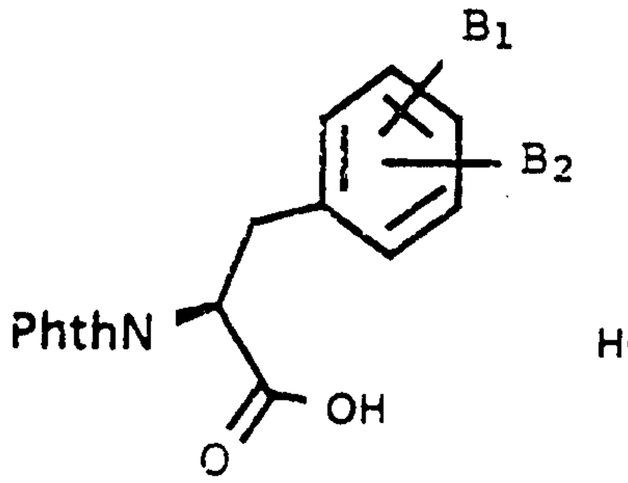
In step b, the appropriate 1-oxo-3-phenylpropyl-N-trifluoracetyl-N-allyl-L-amino acid methyl ester of structure (23) is cyclized to give the corresponding enamine of structure (24) as described previously in Scheme D, step c.

In step c, the appropriate (4S)-enamine of structure (24) is cyclized to give the corresponding (4S)-tricyclic compound of structure (25) as described previously in Scheme D, step d.

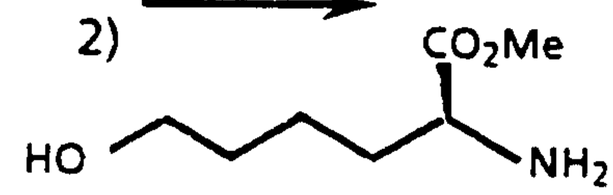
In step d, the phthalimide protecting group of the appropriate (4S)-tricyclic compound of structure (25) is removed to give the corresponding amino tricyclic compound of structure (1b) as described in Scheme D, step e.

Amino tricyclic compounds of structure (1) wherein Z is $-CH_2-$ may be prepared as described in Scheme F. In Scheme F, all substituents unless otherwise indicated are as previously defined.

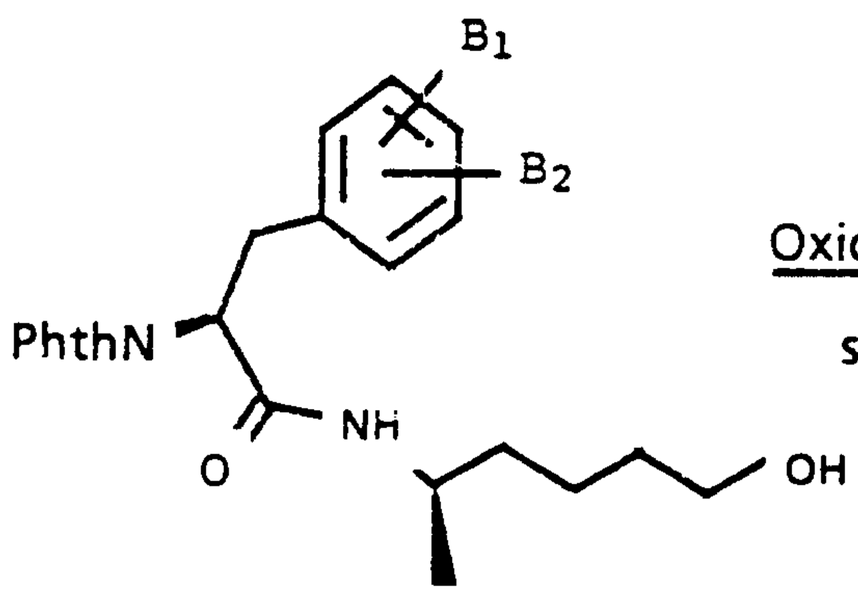
Scheme F



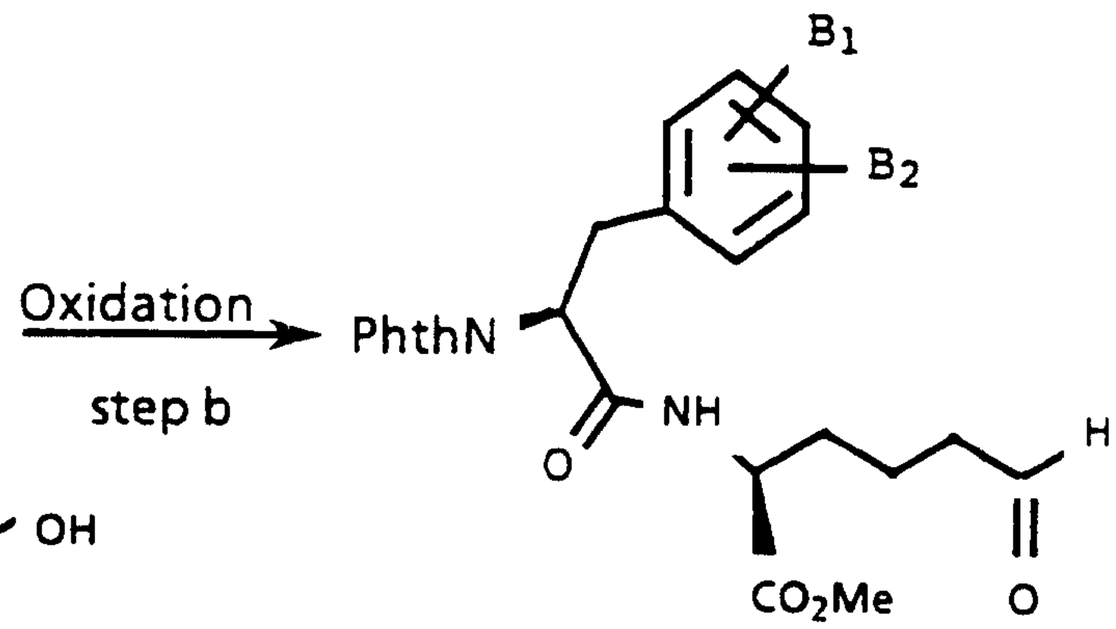
(15)



step a

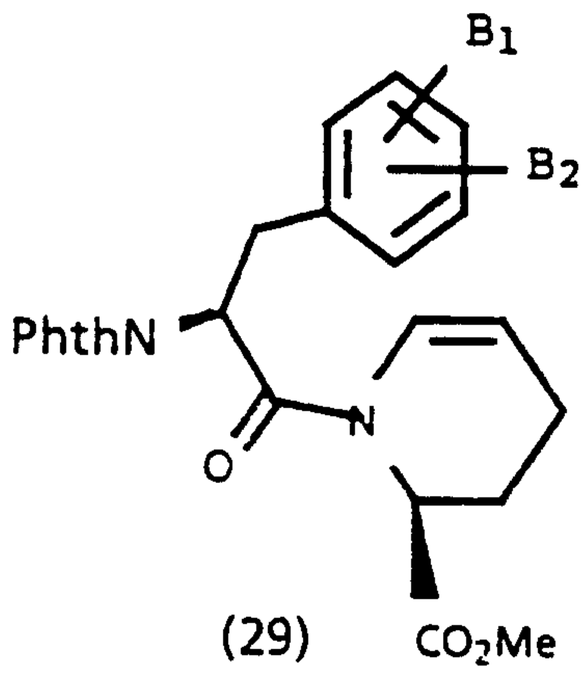


(27)



(28)

step b

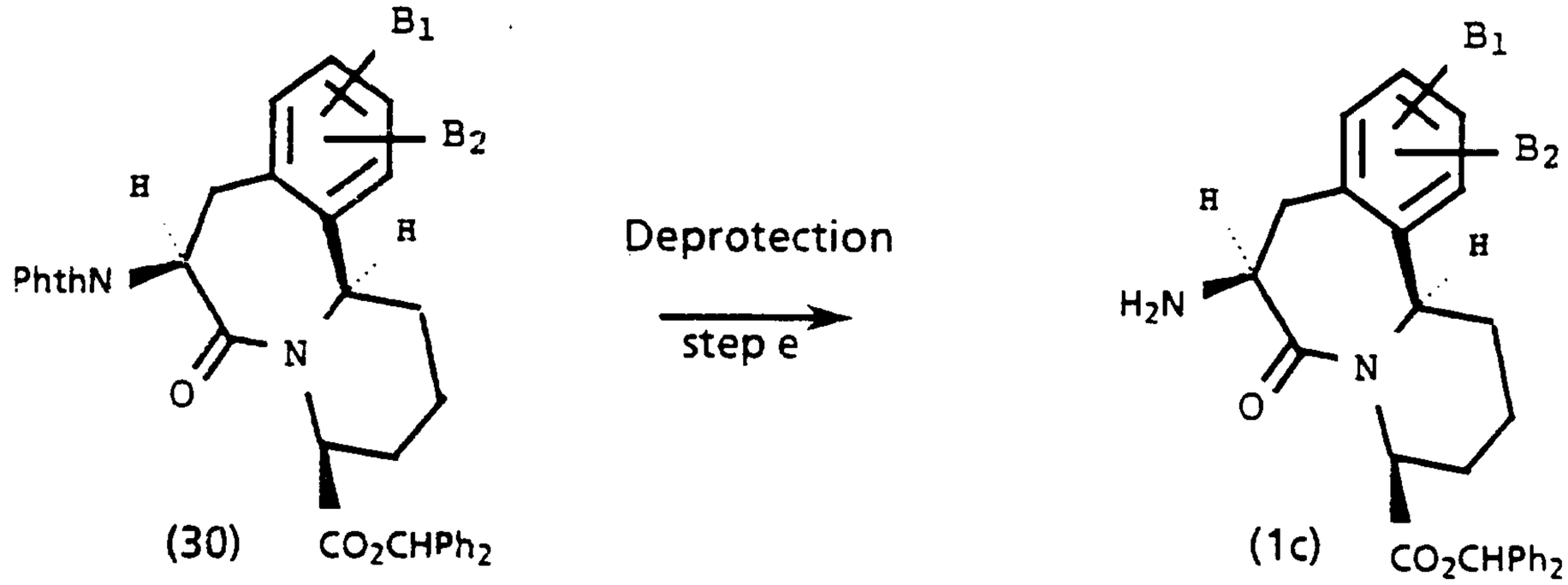


(29)

step c

step d

Scheme F cont.



Scheme F provides a general synthetic procedure for preparing the amino tricyclic compounds of structure (1) wherein Z is $-CH_2-$.

In step a, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure (15) can be converted to the corresponding acid chloride, then reacted with the appropriate amino acid methyl ester of structure (26) in a coupling reaction. For example, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure (15) 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 (26) 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 (27).

In step b, the hydroxymethylene functionality of the appropriate 1-oxo-3-phenylpropyl-amino acid methyl ester derivative of structure (27) can be oxidized to the appropriate aldehyde of structure (28) 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 (27) can be oxidized to the appropriate aldehyde of structure (28) by means of a Swern oxidation using oxalyl chloride and dimethylsulfoxide in a suitable aprotic solvent, such as methylene chloride.

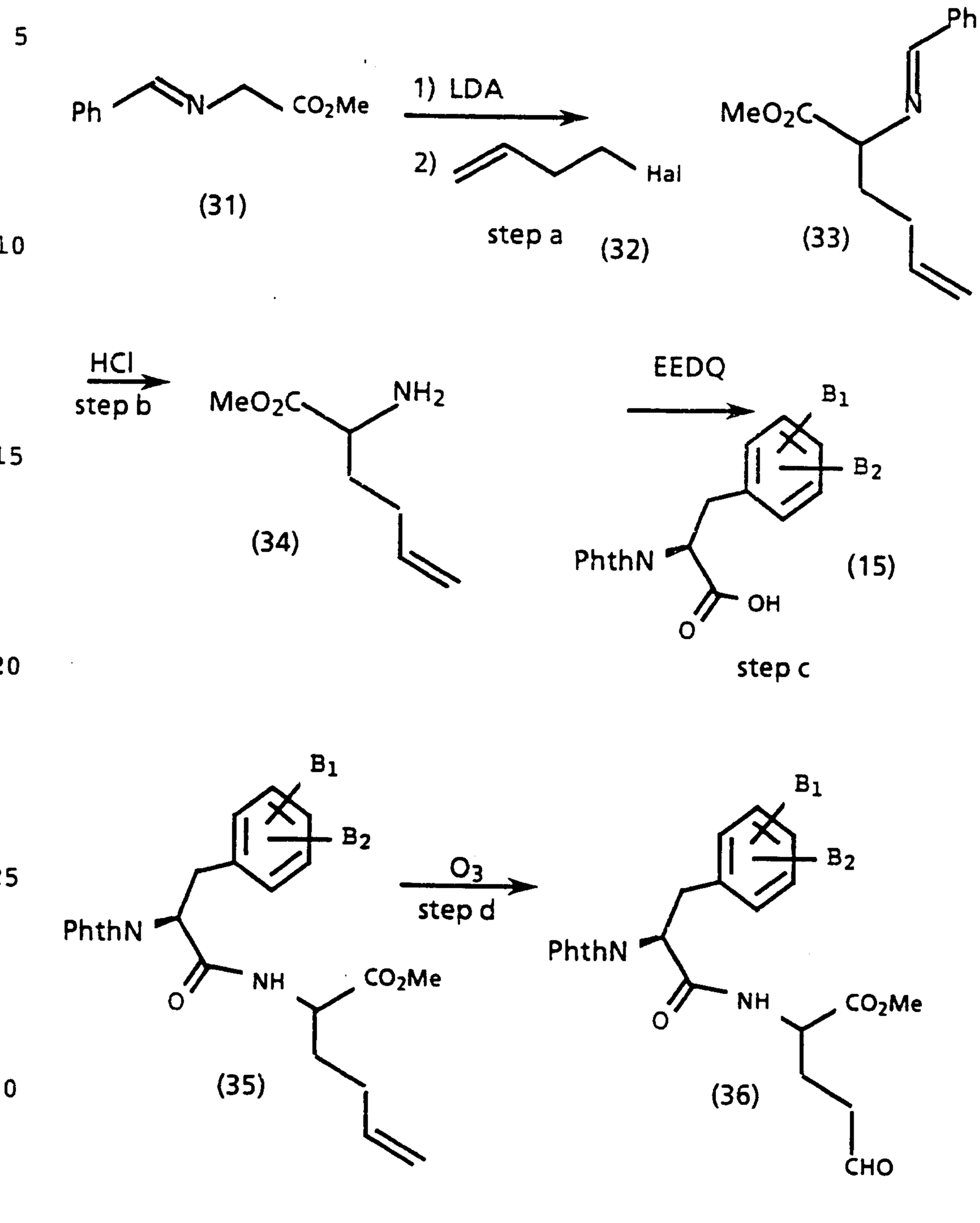
In step c, the appropriate aldehyde of structure (28) can be cyclized to the appropriate enamine of structure (29) by acid catalysis. For example, the appropriate aldehyde of structure (28) can be cyclized to the appropriate enamine of structure (29) by treatment with trifluroacetic acid in a suitable aprotic solvent, such as methylene chloride.

In step d, the appropriate enamine of structure (29) can be converted to the corresponding tricyclic compound of structure (30) by an acid catalyzed Friedel-Crafts reaction as described previously in Scheme D, step d.

In step e, the phthalimide protecting group of the appropriate tricyclic compound of structure (30) 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 (30) can be removed using hydrazine monohydrate in a suitable protic solvent such as methanol, to give the corresponding amino tricyclic compound of structure (1c).

Amino tricyclic compounds of structure (1) wherein Z is a bond may be prepared as described in Scheme G. In Scheme G, all substituents unless otherwise indicated are as previously defined.

Scheme G



Scheme G provides a general synthetic procedure for preparing the amino tricyclic compounds of structure (1) wherein Z is a bond.

In step a, the N-(phenylmethylene)glycine methyl ester of structure (31) 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 (32) to give 2-(3-butenyl)-N-(phenylmethylene)glycine methyl ester of structure (33).

In step b, the N-(phenylmethylene) functionality of 2-(3-butenyl)-N-(phenylmethylene)glycine methyl ester of structure (33) 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 (34).

In step c, the appropriate amide compound of structure (35) can be prepared by reacting the appropriate phthalimide protected (S)-phenylalanine compound of structure (15) with 2-(3-butenyl)-glycine methyl ester of structure (34) 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 (35) can be converted to the appropriate aldehyde compound of structure (36) under conditions of oxidative cleavage, such as treatment with ozone in a suitable solvent mixture, such as methylene chloride and methanol.

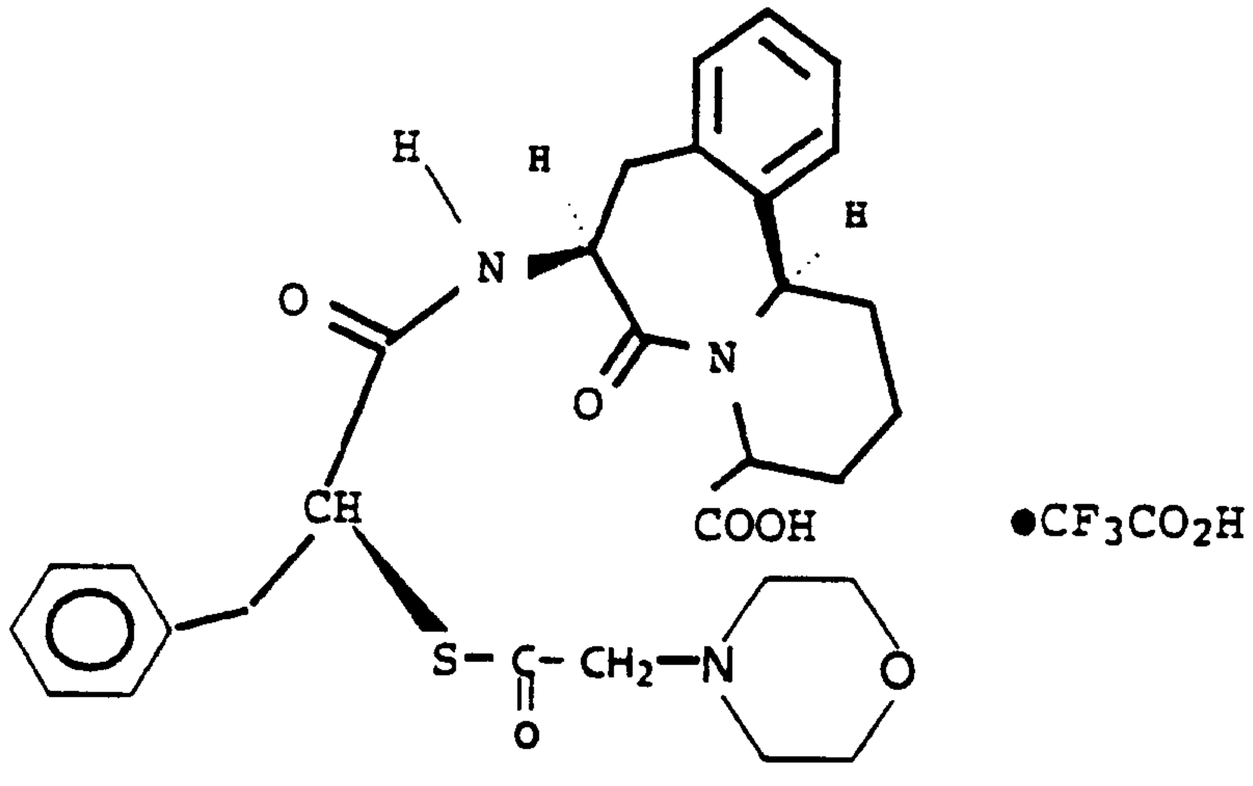
The amino tricyclic compounds of structure (1) wherein Z is a bond can be prepared from an appropriate aldehyde of structure (36) in a process as outlined previously in Scheme F, steps c-e.

Starting materials for use in Schemes A through G are readily available to one of ordinary skill in the art. For example, certain tricyclic compounds of structure (1) may be prepared as described in European Patent 0 249 223 (December 16, 1987). 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; and "µM" refers to micromolar.

Example 1

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluoroacetate salt--MDL 101,264



•CF_3CO_2H

Method A

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 a 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 in vacuo 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 in vacuo to yield crude product (76g, 98%). Dissolve the crude product in hot toluene (223.5mL), cool to room temperature, then 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.

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

Mix oxalyl chloride (80mL, 0.92mole) and methylene chloride (2L) and place under a nitrogen atmosphere. 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 a 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 a 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 in vacuo 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 in vacuo 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 in vacuo to a residue. Dissolve the residue in anhydrous dimethylformamide (860mL) and place under a 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 filter through a plug of silica gel (213g), 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 a 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 B, steps a and b: Triphenylmethyl 4-morpholinethiolacetate

Dissolve triphenylmethyl mercaptan (27.6g, 100mmol) and pyridine (10mL) in methylene chloride (120mL). Cool to -50°C, add bromoacetyl bromide (8.7mL, 100mmol) and stir for 20 minutes while warming to room temperature. Add morpholine (27mL, 300mmol) and cool as necessary to maintain ambient temperature. Stir for 3 hours, filter and pour into methylene chloride. Wash with water and brine and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by chromatography and crystallization to give the title compound as a crystalline solid.

Scheme A, step a: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(R)-bromo-3-phenylpropyl)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-amino-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (10mmol), (R)-3-phenyl-2-bromopropionic acid (2.75g, 12mmol), 2-ethoxy-2-ethoxycarbonyl-1,2-dihydro-quinoline (EEDQ) (3.0g, 12mmol) and methylene chloride (25mL). Stir at room temperature for 4 hours, dilute with methylene chloride, wash with 10% hydrochloric acid, saturated sodium hydrogen carbonate and brine. Dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by recrystallization (25% ethyl acetate/hexane) to give the title compound as a white solid (6.1g, 94%); mp 167-168°C.

Scheme A, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-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 sodium hydride (175mg of a 60% suspension, 4.0mmol) in anhydrous dimethylformamide (4mL) and place under a nitrogen atmosphere. Bubble hydrogen sulfide gas into the suspension until solution occurs. Add triphenylmethyl 4-morpholinethiolacetate (1.61g, 4.0mmol) and heat gently for 1.5 hours while bubbling nitrogen through the solution to facilitate removal of excess hydrogen sulfide gas. Add [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.3g, 2.0mmol) and stir for 2 hours. Pour into water, extract into ethyl acetate, wash with brine and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by chromatography (30→60% ethyl acetate/hexane) to give the title compound as a colorless foam (1.3g, 89%).

Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluroracetate--MDL 101,264

Mix [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.46g, 2.0mmol), anisole (0.5mL) and methylene chloride (6mL). Place under a nitrogen atmosphere and cool to -50°C. Add trifluroracetic acid (3.0mL) over 1 minutes and allow to warm to room temperature over 2 hours while stirring. Evaporate the solvent *in vacuo*, triturate with hexane and methylene chloride and dry under high vacuum to give the title compound as a light tan foam (1.47g).

Method B

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

Add thiolacetic acid (1.1mL, 15.4mmol) to a solution of cesium carbonate (2.51g, 7.7mmol) in methanol (30mL). Stir the reaction mixture at room temperature for 30 minutes, evaporate the solvent *in vacuo* and dry *in vacuo* for 2 hours. Dissolve the orange solid residue in dimethylformamide (40mL) and slowly add to a solution of [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (5.0g. 7.7mmol) in dimethylformamide (60mL). Stir the reaction mixture at room temperature for 1 hour, dilute with ethyl acetate, wash with water and brine, dry over $MgSO_4$ and evaporate the solvent *in vacuo*. Purify by silica

gel chromotography (hexane:ethyl acetate/6:4) to give the title compound as a foam (3.74g, 75%).

^{1}H NMR ($CDCl_3$) δ 7.46 (d, 1, J=9Hz), 7.18-7.37 (m, 12), 6.89-7.13 (m, 6), 6.62 (m, 1), 6.26 (s, 1), 5.56 (m, 1), 5.37 (m, 2), 4.39 (t, 1, J=7.5Hz), 3.28-3.43 (m, 2), 3.06 (dd, 1, J=7.5, 15Hz), 2.58-2.27 (m, 3), 2.40 (s, 3), 2.02-1.86 (m, 1), 1.62-1.84 (m, 3).

Scheme C, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-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(S)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (3.85g, 5.95mmol) in absolute ethanol (100mL) and add saturated ethanolic ammonia (100mL). Stir the reaction mixture at room temperature for 1.5 hours, evaporate the solvent and dissolve the residue in methylene chloride. Wash with water and brine, dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound as a glassy solid (3.38g, 94%).

IR (KBr) 3429, 3393, 3061, 3030, 2943, 1734, 1649, 1495, 1439, 1283, 1250, 747, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.61 (d, 1, J=6.6Hz), 7.14-7.37 (m, 12), 6.88-7.12 (m, 6), 6.63 (m, 1), 6.28 (s, 1), 5.58 (m, 1), 5.29-5.44 (m, 2), 3.65 (q, 1, J=8.1Hz), 3.38 (dd, 1, J=6, 17.4Hz), 3.05 (dd, 1, J=5.4, 15Hz), 2.54 (dd, 1, J=12, 17.4Hz), 2.34-2.47 (m, 2), 2.07 (d, 1, J=8.7Hz), 1.85-2.01 (m, 1), 1.61-1.85 (m, 3); ^{13}C NMR ($CDCl_3$) δ 171.74, 170.94, 169.61, 139.89, 138.97, 137,47, 136.50, 135.29, 130.81, 129.39, 128.39, 128.27, 128.19, 127.79, 127.71, 127.39, 126.95, 126.91, 126.80, 125.42, 124.66, 78.29, 51.14, 51.03, 48.51, 44.57, 41.34, 36.45, 24.92, 17.10; MS (FAB) m/z 605 [M^++H], 393, 167.

Anal. Calcd for $C_{37}H_{36}N_2O_4S \cdot 0.5H_2O$: C, 72,40; H, 6.08; N, 4.56; Found: C, 72.49; H, 6.11; N, 4.40.

Scheme C, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-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 t-butyl bromoacetate (1eq) in tetrahydrofuran and add morpholine (2.2eq) via syringe. Stir the reaction mixture at room temperature for 2 hours, filter and wash the filter cake with ethyl acetate. Combine the organic filtrates and wash with saturated sodium bicarbonate (2X), water (2X) and brine. Dry (Na_2SO_4), filter and evaporate the solvent *in vacuo*. Take up the oily residue in ethyl acetate, cool in ice and bubble hydrogen chloride gas into the solution. Stir at room temperature overnight, cool and filter to give morpholinoacetic acid (85%); mp 169-170°C; ^1H NMR (D_2O) δ 3.75-4.29 (br m, 6), 3.59 (br s, 2), 3.28 (br s, 2).

Suspend morpholinoacetic acid (4.9mmol) in degassed dimethylformamide (40mL) and add carbonyldiimidazole (0.477g, 2.94mmol). Stir the reaction mixture at room temperature for 1.5 hours. Add a solution of [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.45mmol) in degassed tetrahydrofuran and stir at room temperature overnight. Dilute with ethyl acetate, wash with water (2X) and brine, dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by silica gel chromatography (hexane:ethyl acetate/1:1 to 3:7) to give the title compound (86%).

^1H NMR ($CDCl_3$) δ7.44, (d, 1, J=9Hz), 7.15-7.35 (m, 12), 6.91-7.12 (m, 6), 6.63 (m, 1), 6.28 (s, 1), 5.57 (m, 1), 5.30-5.43 (m, 2), 4.30 (t, 1, J=7.5Hz), 3.74 (t, 4,

J=4.5Hz), 3.17-3.46 (m, 4), 2.33-2.68 (m, 7), 1.52-2.04 (m, 4).

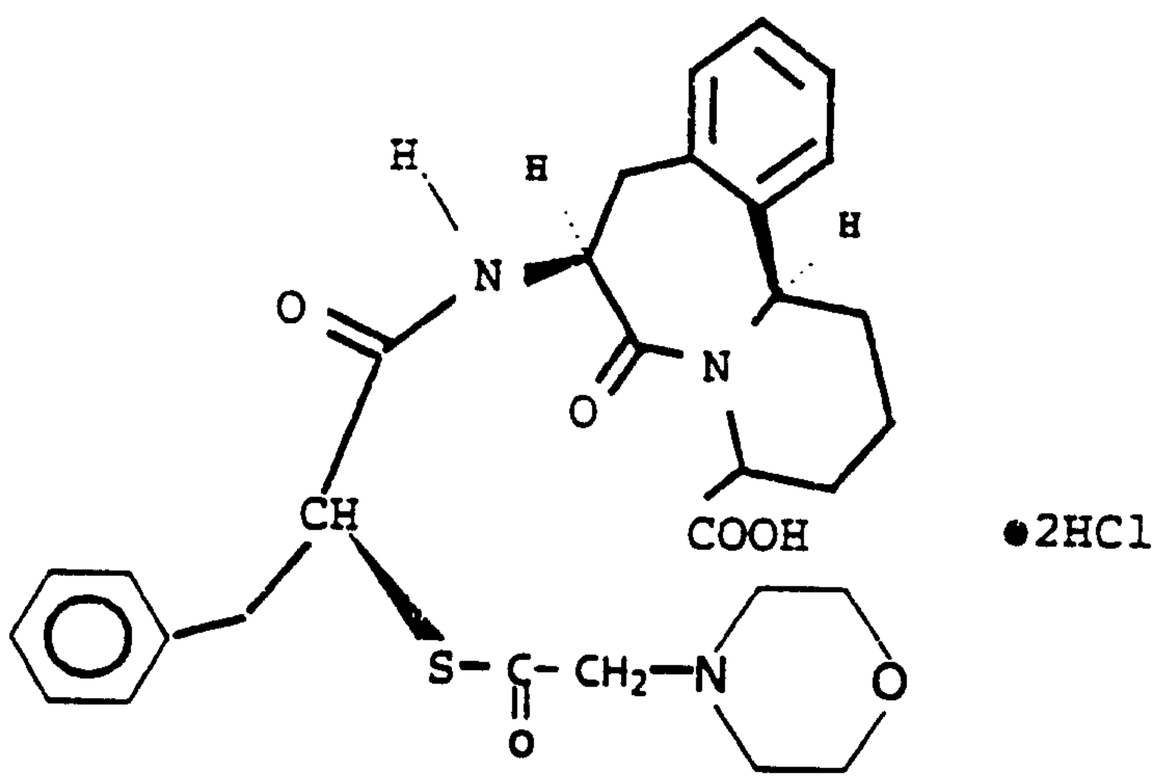
Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluoroacetate salt

Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.86mmol) and anisole (1.5mL, excess) in methylene chloride (20mL), cool to -50°C and add trifluoroacetic acid (3mL). Stir the reaction mixture at -50°C for 2.5 hours, evaporate the solvent *in vacuo* and triturate with hexane (4X). Take up the residue in a minimal amount of methylene chloride and precipitate from hexane (3X) to give the title compound (68%).

^{1}H NMR ($CDCl_3$) δ 7.66 (d, 1, J=7.5Hz), 6.97-7.39 (m, 9), 5.60-5.74 (m, 1), 5.39-5.48 (m, 1), 5.03-5.12 (m, 1), 4.54 (dd, 1, J=7.5, 9Hz), 4.00 (s, 2), 3.88 (t, 4, J=3Hz), 2.99-3.51 (m, 7), 2.85 (dd, 1, J=12, 18Hz), 2.43-2.57 (m, 1), 2.26-2.39 (m, 1), 1.66-2.06 (m, 4); ^{19}F NMR ($CDCl_3$) δ -74.0; MS (CI, 70eV) m/z 566 [M^++H].

Example 2

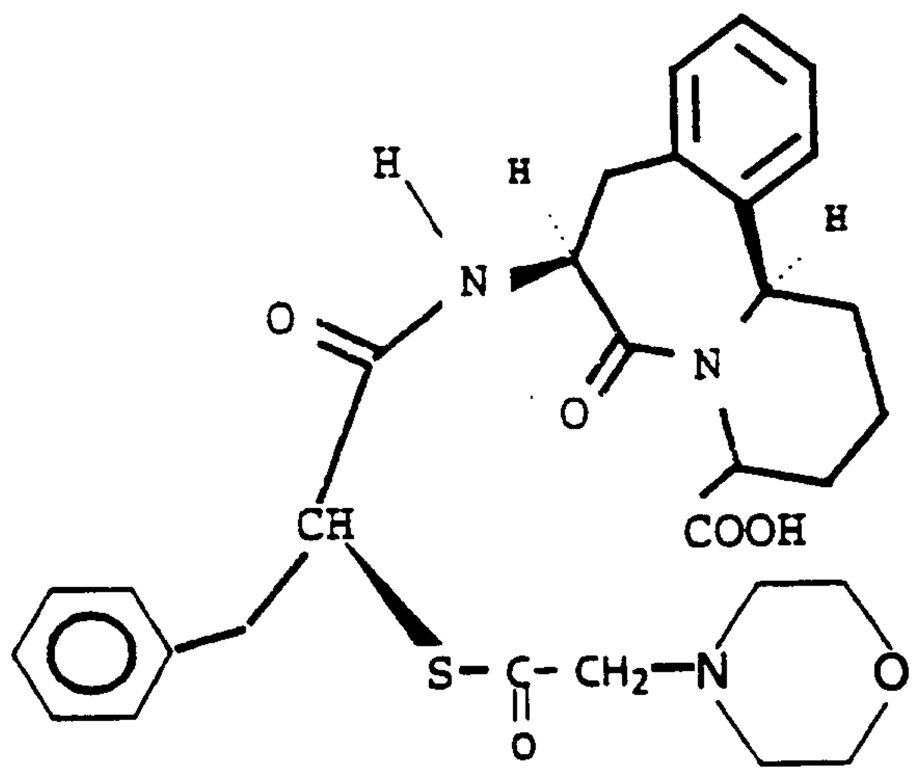
[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•dihydrochloride salt



Slurry [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluroacetate salt (900mg) in diethyl ether (50mL). Pass HCl gas through the slurry and stir for 30 minutes. Evaporate the solvent *in vacuo* and take the residue up in pentane. Filter to give the title compound as a white powder (695mg).

Example 3

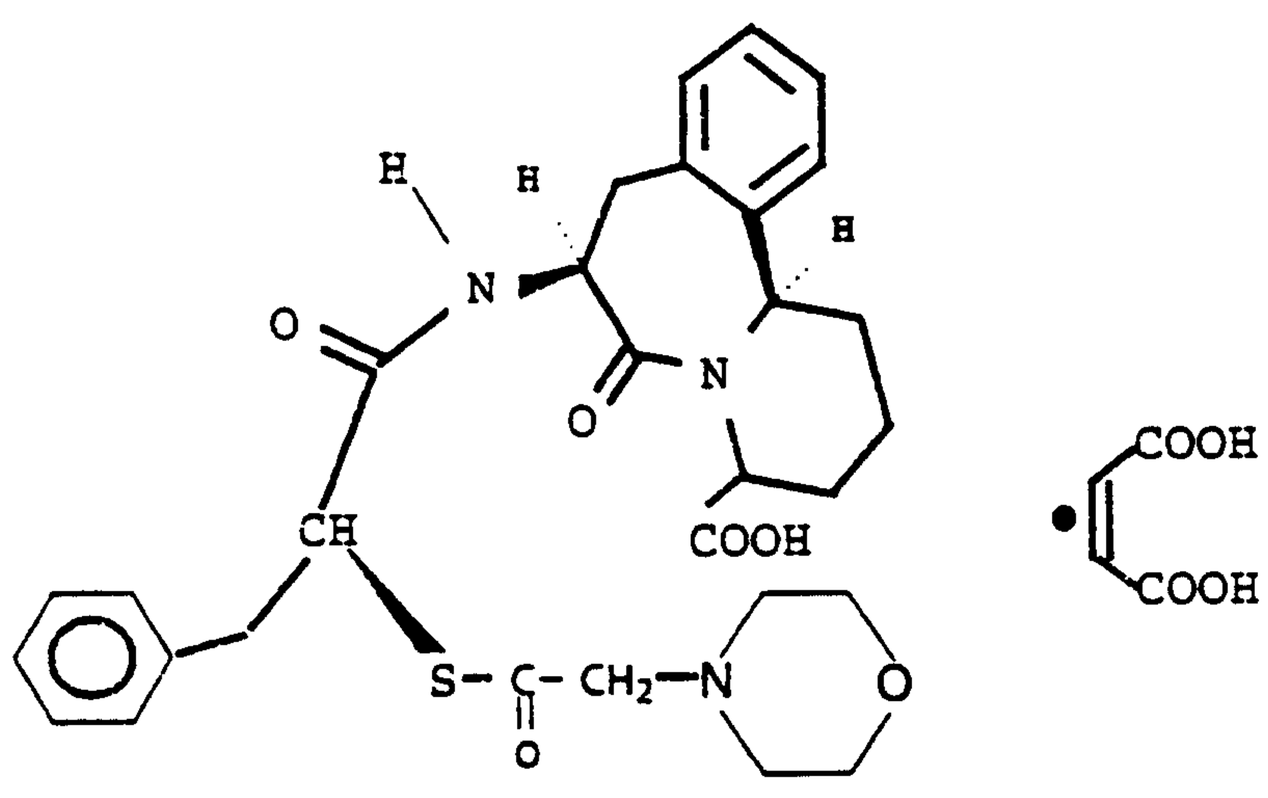
[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid



Suspend [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•dihydrochloride salt (5.01g, 8.86mmol) in 1M sodium hydrogen carbonate (50mL) and add methylene chloride (200mL). Stir at room temperature for 1 hour, separate the organic layer and extract the aqueous layer with methylene chloride (2X100mL). Combine the extraces, wash with water (50mL) and brine (50mL), evaporate the solvent *in vacuo* and dry *in vacuo* to give the title compound as a white solid (4.23g, 86%).

Example 4

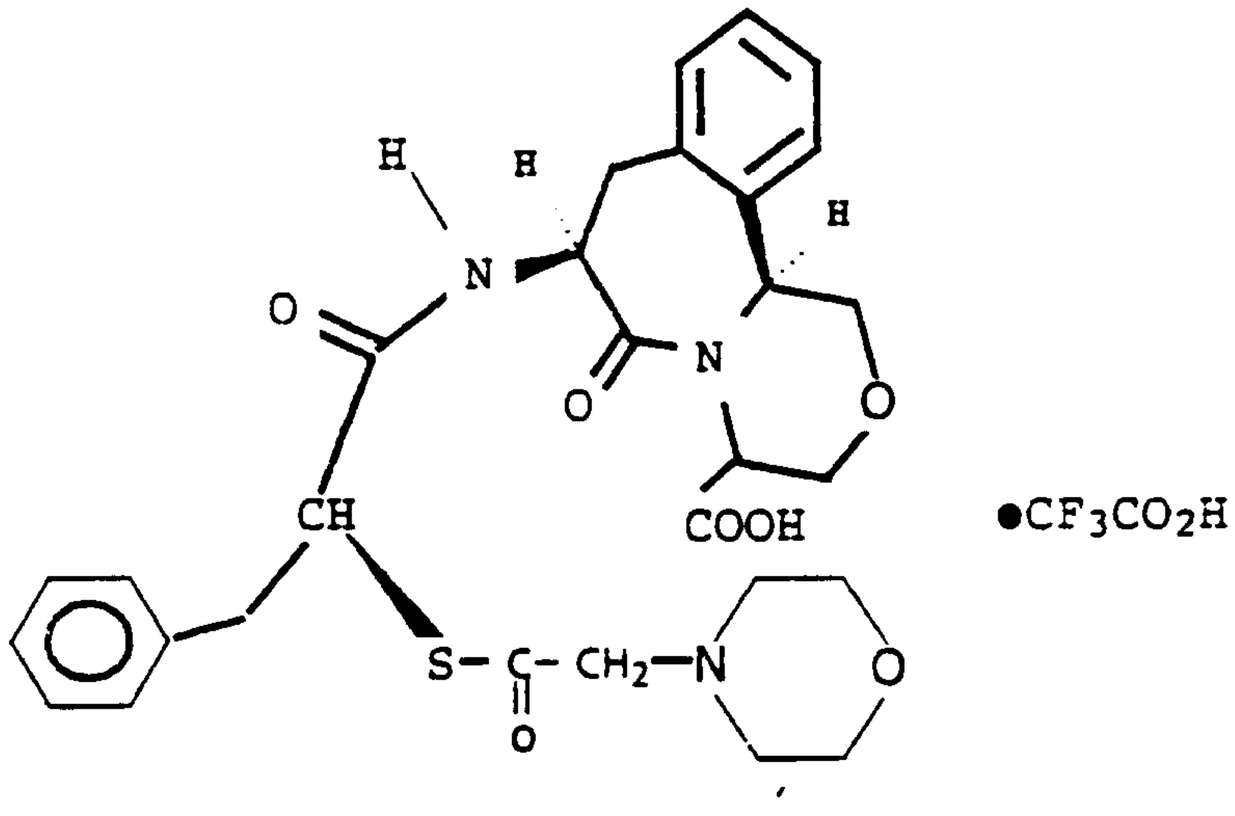
[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•maleate salt



Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid (1.87g, 3.31mmol) in tetrahydrofuran (8mL). Add a solution of maleic acid (392mg, 3.38mmol) in tetrahydrofuran (2mL). Reduce the volume of solvent to 9mL with a stream of argon and keep at room temperature for 15 minutes. Cool at -25°C overnight and filter the crystalline solid under nitrogen. Wash with cold (-25°C) tetrahydrofuran, dry briefly under argon and vacuum dry under a nitrogen atmosphere at room temperature for 120 hours to give the title compound as a crystalline solid (1.64g).

Example 5

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



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, step a: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(R)-bromo-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, diphenylmethyl ester

Mix [4S-[4α-7α(R*), 12bβ]]-7-amino-1,2,3,4,6,7,8,12b-octahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (10mmol), (R)-3-phenyl-2-bromopropionic acid (2.75g, 12mmol), 2-ethoxy-2-ethoxycarbonyl-1,2-dihydro-quinoline (EEDQ) (3.0g, 12mmol) and methylene chloride (25mL). Stir at room temperature

for 4 hours, dilute with methylene chloride, wash with 10% hydrochloric acid, saturated sodium hydrogen carbonate and brine. Dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by chromatography to give the title compound.

Scheme A, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-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, diphenylmethyl ester

Suspend sodium hydride (175mg of a 60% suspension, 4.0mmol) in anhydrous dimethylformamide (4mL) and place under a nitrogen atmosphere. Bubble hydrogen sulfide gas into the suspension until solution occurs. Add triphenylmethyl 4-morpholinethiolacetate (1.61g, 4.0mmol) and heat gently for 1.5 hours while bubbling nitrogen through the solution to facilitate removal of excess hydrogen sulfide gas. Add [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-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, diphenylmethyl ester (2.0mmol) and stir for 2 hours. Pour into water, extract into ethyl acetate, wash with brine and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

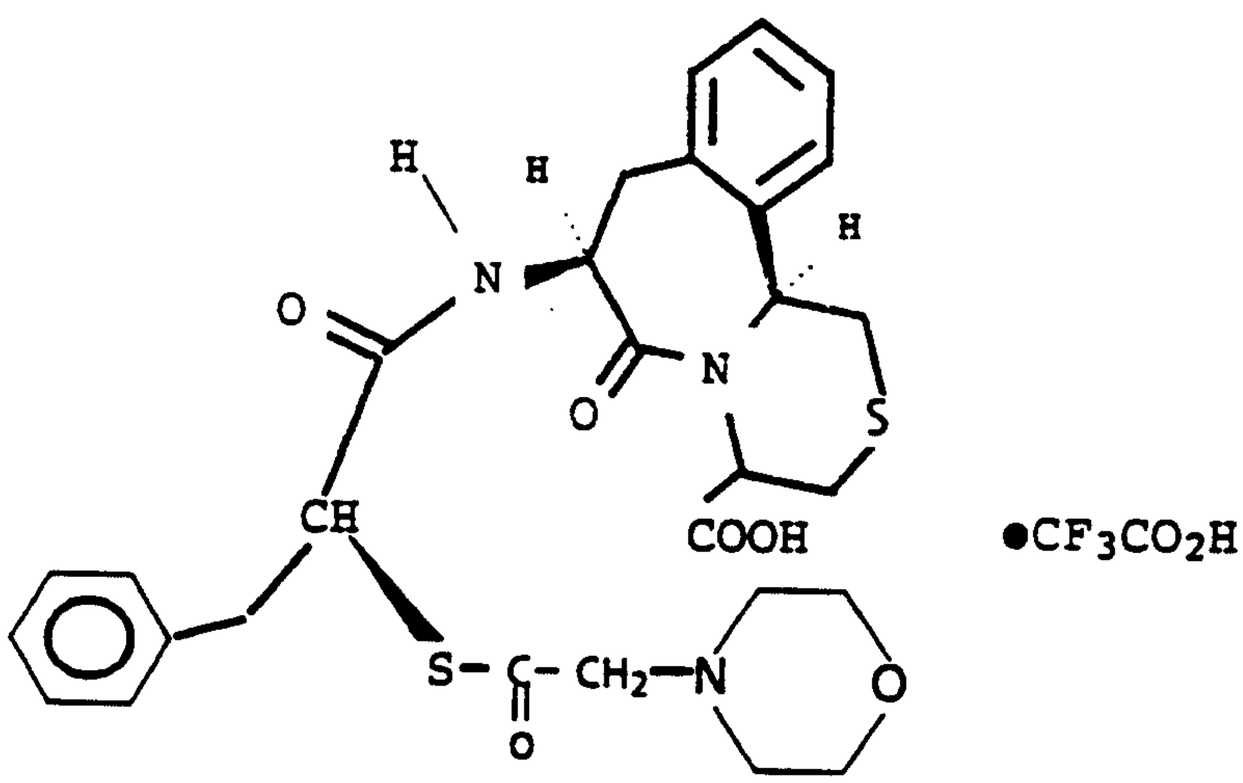
Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid•trifluoroacetate

Mix [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-morpholino)-acetylthio-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, diphenylmethyl ester (2.0mmol), anisole (0.5mL) and methylene chloride (6mL). Place under a nitrogen atmosphere and cool to -50°C. Add trifluroracetic acid (3.0mL) over 1 minutes and allow to warm to room temperature over 2 hours while stirring. Evaporate the solvent *in vacuo*, triturate with hexane and methylene

chloride and dry under high vacuum to give the title compound.

Example 6

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



Scheme A, step a: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(R)-bromo-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, diphenylmethyl ester

Mix [4S-[4α-7α(R*), 12bβ]]-7-amino-1,2,3,4,6,7,8,12b-octahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (10mmol), (R)-3-phenyl-2-bromopropionic acid (2.75g, 12mmol), 2-ethoxy-2-ethoxycarbonyl-1,2-dihydro-quinoline (EEDQ) (3.0g, 12mmol) and methylene chloride (25mL). Stir at room temperature for 4 hours, dilute with methylene chloride, wash with 10% hydrochloric acid, saturated sodium hydrogen carbonate and brine. Dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by chromatography to give the title compound.

Scheme A, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-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, diphenylmethyl ester

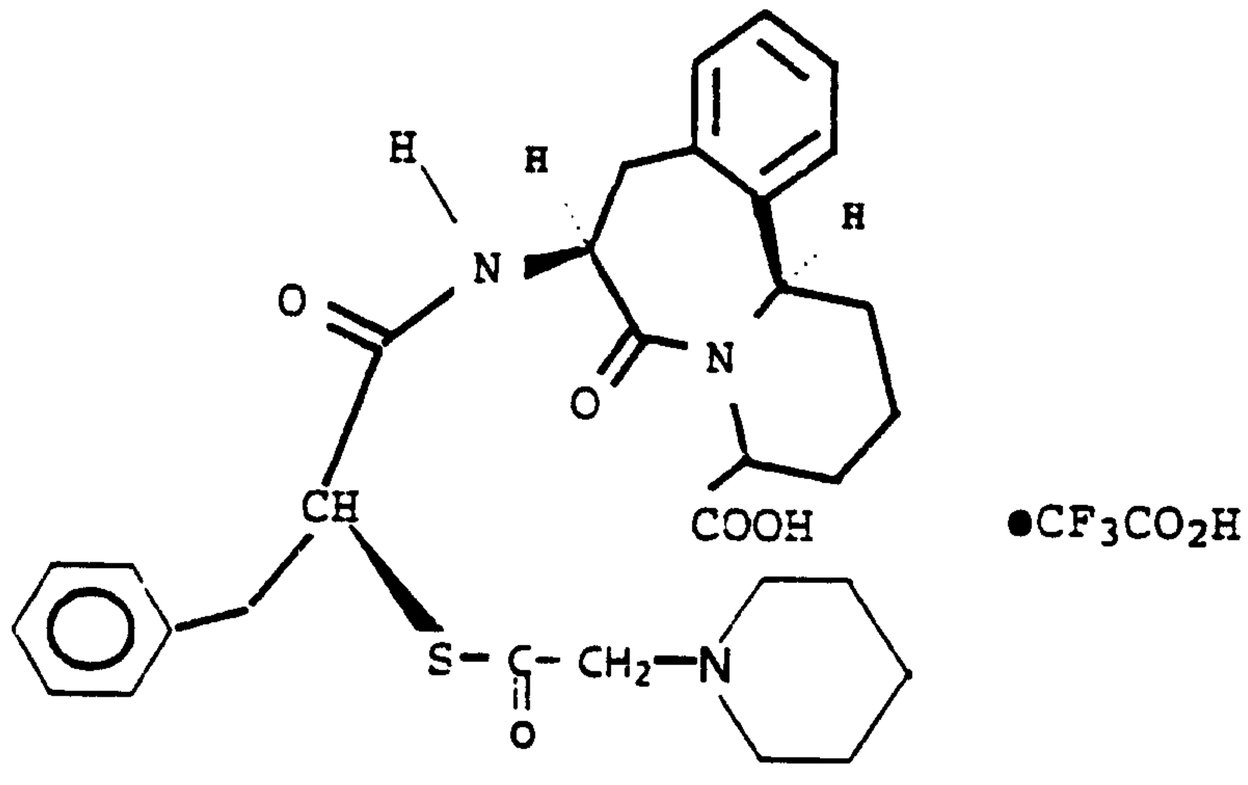
Suspend sodium hydride (175mg of a 60% suspension, 4.0mmol) in anhydrous dimethylformamide (4mL) and place under a nitrogen atmosphere. Bubble hydrogen sulfide gas into the suspension until solution occurs. Add triphenylmethyl 4-morpholinethiolacetate (1.61g, 4.0mmol) and heat gently for 1.5 hours while bubbling nitrogen through the solution to facilitate removal of excess hydrogen sulfide gas. Add [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-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, diphenylmethyl ester (2.0mmol) and stir for 2 hours. Pour into water, extract into ethyl acetate, wash with brine and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-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•trifluoroacetate

Mix [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-morpholino)-acetylthio-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, diphenylmethyl ester (2.0mmol), anisole (0.5mL) and methylene chloride (6mL). Place under a nitrogen atmosphere and cool to -50°C. Add trifluoroacetic acid (3.0mL) over 1 minute and allow to warm to room temperature over 2 hours while stirring. Evaporate the solvent *in vacuo*, triturate with hexane and methylene chloride and dry under high vacuum to give the title compound.

Example 7

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-piperidino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



•CF_3CO_2H

Scheme C, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-piperidino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester

Dissolve t-butyl bromoacetate (1eq) in tetrahydrofuran and add piperidine (2.2eq) via syringe. Stir the reaction mixture at room temperature for 2 hours, filter and wash the filter cake with ethyl acetate. Combine the organic filtrates and wash with saturated sodium bicarbonate (2X), water (2X) and brine. Dry (Na_2SO_4), filter and evaporate the solvent *in vacuo*. Take up the oily residue in ethyl acetate, cool in ice and bubble hydrogen chloride gas into the solution. Stir at room temperature overnight, cool and filter to give 1-piperidinoacetic acid hydrochloride salt (56%); mp 215-217°C; ^1H NMR (D_2O) δ 3.84 (s, 2), 3.41-3.51 (m, 2), 2.83-2.97 (m, 2), 1.56-1.87 (m, 5), 1.25-1.45 (m, 1).

Suspend 1-piperidinoacetic acid hydrochloride salt (4.9mmol) in degassed dimethylformamide (40mL) and add carbonyldiimidazole (0.477g, 2.94mmol). Stir the reaction mixture at room temperature for 1.5 hours. Add a solution of [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.45mmol) in degassed tetrahydrofuran and stir at room temperature overnight. Dilute with ethyl acetate, wash with water (2X) and brine, dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound (96%).

^1H NMR ($CDCl_3$) δ7.42 (d, 1, J=9Hz), 7.17-7.38 (m, 12), 6.90-7.15 (m, 6), 6.60 (m, 1), 6.28 (s, 1), 5.56 (m, 1), 5.31-5.44 (m, 2), 4.29 (t, 1, J=6Hz), 3.14-3.42 (m, 4), 2.85-3.08 (m, 3), 2.30-2.58 (m, 7), 1.54-2.05 (m, 6), 1.37-1.52 (m, 2).

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

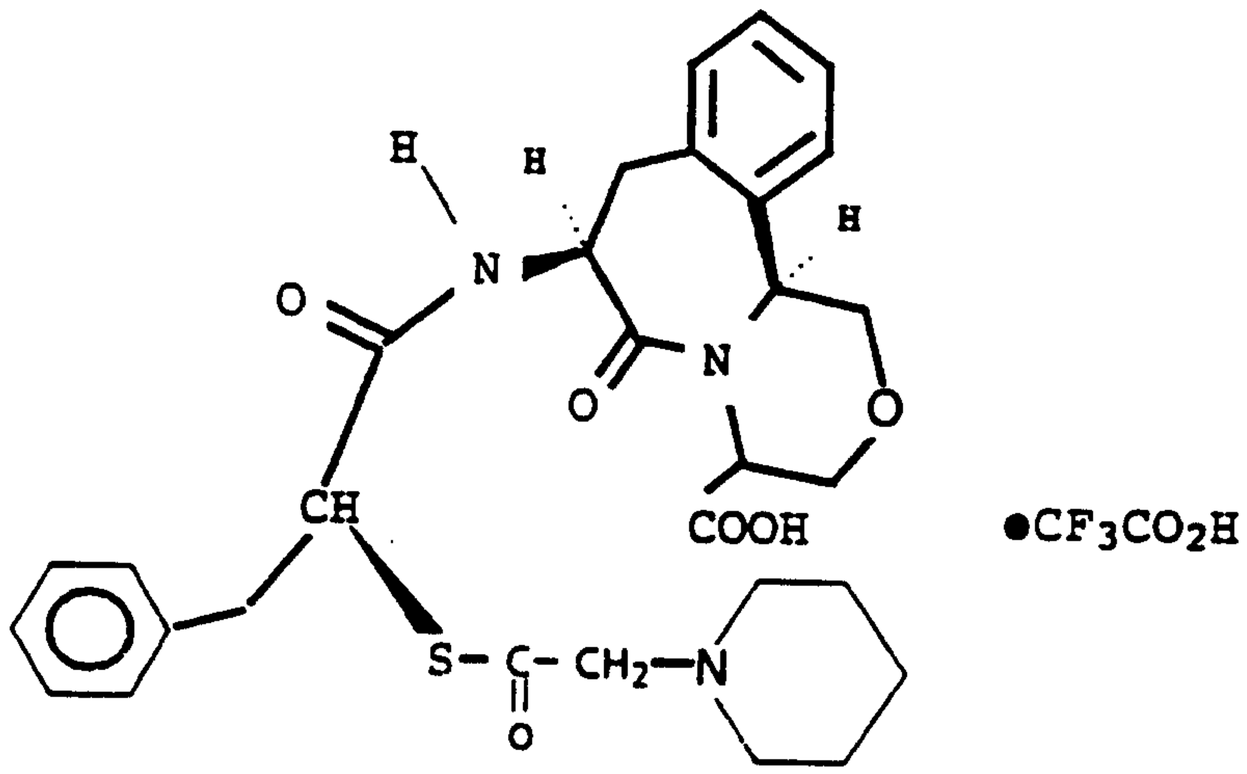
Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-piperidino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.86mmol) and anisole (1.5mL, excess) in methylene chloride (20mL), cool to -50°C and add trifluoroacetic acid (3mL). Stir the reaction mixture at -50°C for 2.5 hours, evaporate the solvent *in vacuo* and triturate with hexane (4X). Take up the residue in a minimal amount of methylene chloride and precipitate from hexane (3X) to give the title compound (40%).

IR (KBr) 3389, 3064, 3029, 2949, 2872, 1672, 1496, 1442, 1342, 1277, 1199, 1136 cm^{-1}, ^1H NMR ($CDCl_3$) δ 7.83 (d, 1,

J=7.5Hz), 6.89-7.41 (m, 9), 5.63-5.79 (m, 1), 5.39-5.50 (m, 1), 5.03-5.16 (m, 1), 4.60 (dd, 1, J=6, 7.5Hz), 3.98 (s, 2), 3.28-3.67 (m, 4), 2.66-3.12 (m, 4), 2.25-2.67 (m, 2), 1.62-2.08 (m, 10); ^{19}F NMR (DMSO-d6) δ -73.3; ^{13}C NMR (DMSO-d6) δ 171.8, 171..3, 168.5, 137.4, 136.8, 136.6, 130.1, 129.3, 128.2, 126.8, 126.7, 125.4, 124.9, 119.3, 53.0, 50.6, 49.9, 48.3, 37.5, 35.9, 25.0, 24.7, 22.5, 21.3, 16.9; MS (CI, 70eV) m/z 564 [M^++H], 144.

Example 8

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-piperidino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



Scheme A, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-piperidino)-acetylthio-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, diphenylmethyl ester

Suspend sodium hydride (175mg of a 60% suspension, 4.0mmol) in anhydrous dimethylformamide (4mL) and place under a nitrogen atmosphere. Bubble hydrogen sulfide gas into the suspension until solution occurs. Add triphenylmethyl 4-piperidinethiolacetate (4.0mmol) and heat gently for 1.5 hours while bubbling nitrogen through the solution to

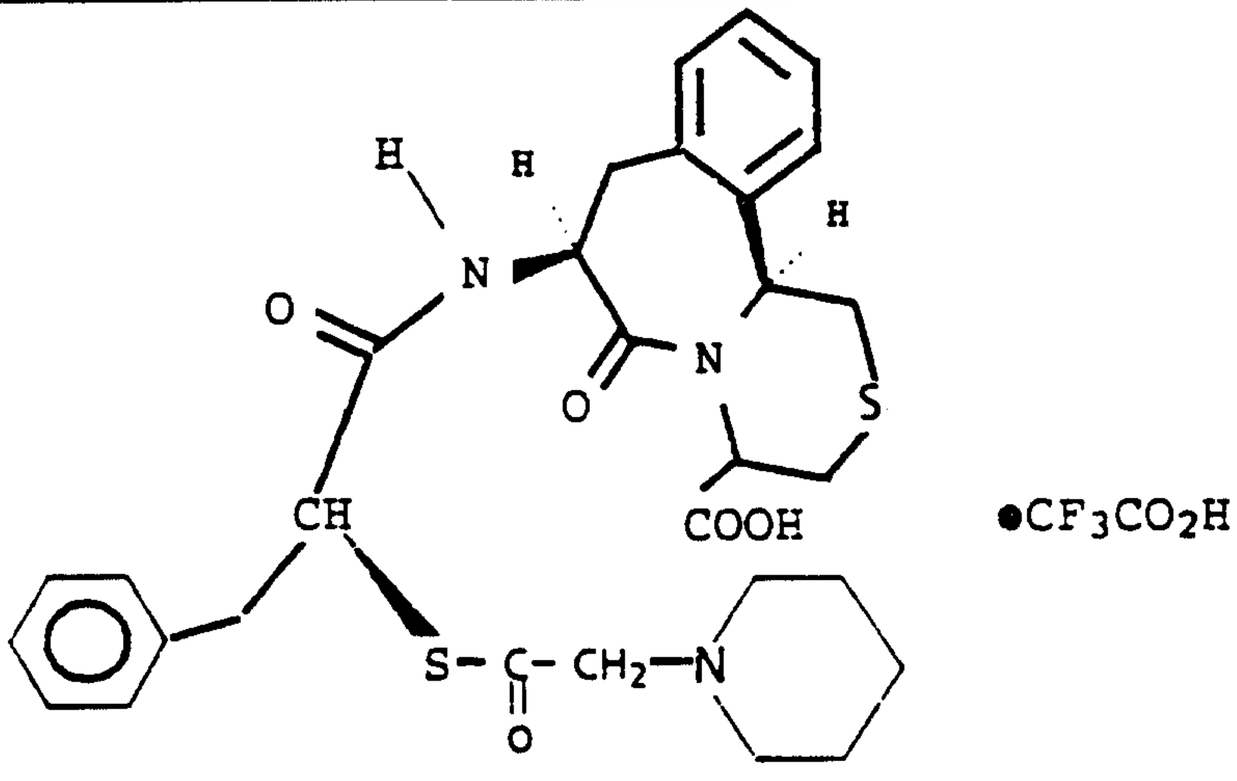
facilitate removal of excess hydrogen sulfide gas. Add [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.0mmol) and stir for 2 hours. Pour into water, extract into ethyl acetate, wash with brine and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-piperidino)-acetylthio-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

Mix [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(1-piperidino)-acetylthio-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, diphenylmethyl ester (2.0mmol), anisole (0.5mL) and methylene chloride (6mL). Place under a nitrogen atmosphere and cool to -50°C. Add trifluoroacetic acid (3.0mL) over 1 minute and allow to warm to room temperature over 2 hours while stirring. Evaporate the solvent *in vacuo*, triturate with hexane and methylene chloride and dry under high vacuum to give the title compound.

Example 9

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-piperidino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



Scheme A, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-piperidino)-acetylthio-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, diphenylmethyl ester

Suspend sodium hydride (175mg of a 60% suspension, 4.0mmol) in anhydrous dimethylformamide (4mL) and place under a nitrogen atmosphere. Bubble hydrogen sulfide gas into the suspension until solution occurs. Add triphenylmethyl 4-piperidinethiolacetate (4.0mmol) and heat gently for 1.5 hours while bubbling nitrogen through the solution to facilitate removal of excess hydrogen sulfide gas. Add [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-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, diphenylmethyl ester (2.0mmol) and stir for 2 hours. Pour into water, extract into ethyl acetate, wash with brine and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

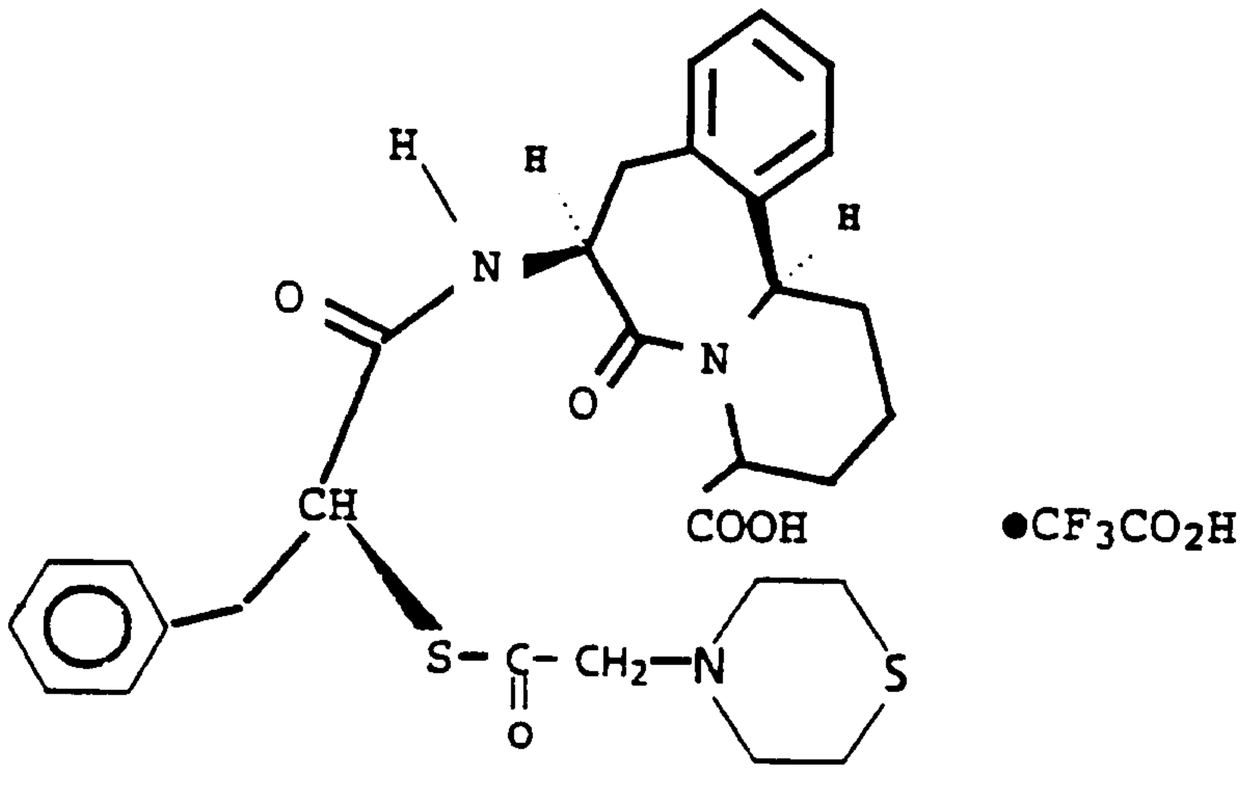
Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-piperidino)-acetylthio-3-phenylpropyl)amino]-

1,2,3,4,6,7,8,12b-octahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine-4-carboxylic acid•trifluoroacetate

Mix [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(1-piperidino)-acetylthio-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, diphenylmethyl ester (2.0mmol), anisole (0.5mL) and methylene chloride (6mL). Place under a nitrogen atmosphere and cool to -50°C. Add trifluoroacetic acid (3.0mL) over 1 minute and allow to warm to room temperature over 2 hours while stirring. Evaporate the solvent *in vacuo*, triturate with hexane and methylene chloride and dry under high vacuum to give the title compound.

Example 10

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



Scheme B, steps a and b: Triphenylmethyl 4-thiomorpholinethiolacetate

Dissolve triphenylmethyl mercaptan (9.2g, 33.3mmol) in methylene chloride (50mL) and add pyridine (4mL). Cool to -50°C and add bromoacetyl bromide (2.9mL) and stir vigorously for 20 minutes. Remove the ice bath and allow

to warm to room temperature. Add, by dropwise addition, thiomorpholine (10g, 96.9mmol) at such a rate that the temperature does not rise above 25°C. Stir for 2.5 hours, pour into methylene chloride and wash with water. Dry ($MgSO_4$), filter, evaporate the solvent *in vacuo* and purify by silica gel chromatography (hexane: ethyl acetate/4:1) to give the title compound as a solid (5.38g, 41%).

^1H NMR ($CDCl_3$) δ7.28 (m, 5), 3.21 (s, 2), 2.62-2.88 (m, 4).

Scheme A, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino)-acetylthio-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 sodium hydride (0.32g of a 60% suspension, 8.0mmol) in anhydrous dimethylformamide (8mL) and place under a nitrogen atmosphere. Bubble hydrogen sulfide gas into the suspension until solution occurs. Stir for 10 minutes and add triphenylmethyl 4-thiomorpholinethiolacetate (3.35g, 8.0mmol) and bubbling nitrogen through the solution to facilitate removal of excess hydrogen sulfide gas for 1.5 hours. Add, by slow addition, a solution of [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.6g, 3.99mmol) in dimethylformamide (8mL). Stir at room temperature for 3 hours, pour into water and extract into ethyl acetate, (3X). Wash with brine, dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by chromatography (hexane:ethyl acetate/9:1 to 4:1 to 1:1) to give the title compound.

^1H NMR ($CDCl_3$) δ7.44 (d, 1, J=7.5Hz), 7.16-7.37 (m, 10), 6.89-7.14 (m, 8), 6.59-6.68 (m, 1), 6.30 (s, 1), 5.51-5.63 (m, 1), 5.30-5.42 (m, 2), 4.28 (t, 1, J=6.0Hz), 3.17-3.45 (m, 4), 3.03 (dd, 1, J=7.5, 12Hz), 2.63-2.88 (m, 8), 2.32-

2.61 (m, 3), 1.61-2.03 (m, 4); MS (CI, 70eV) m/z 748 [M+H], 572, 178, 167, 116.

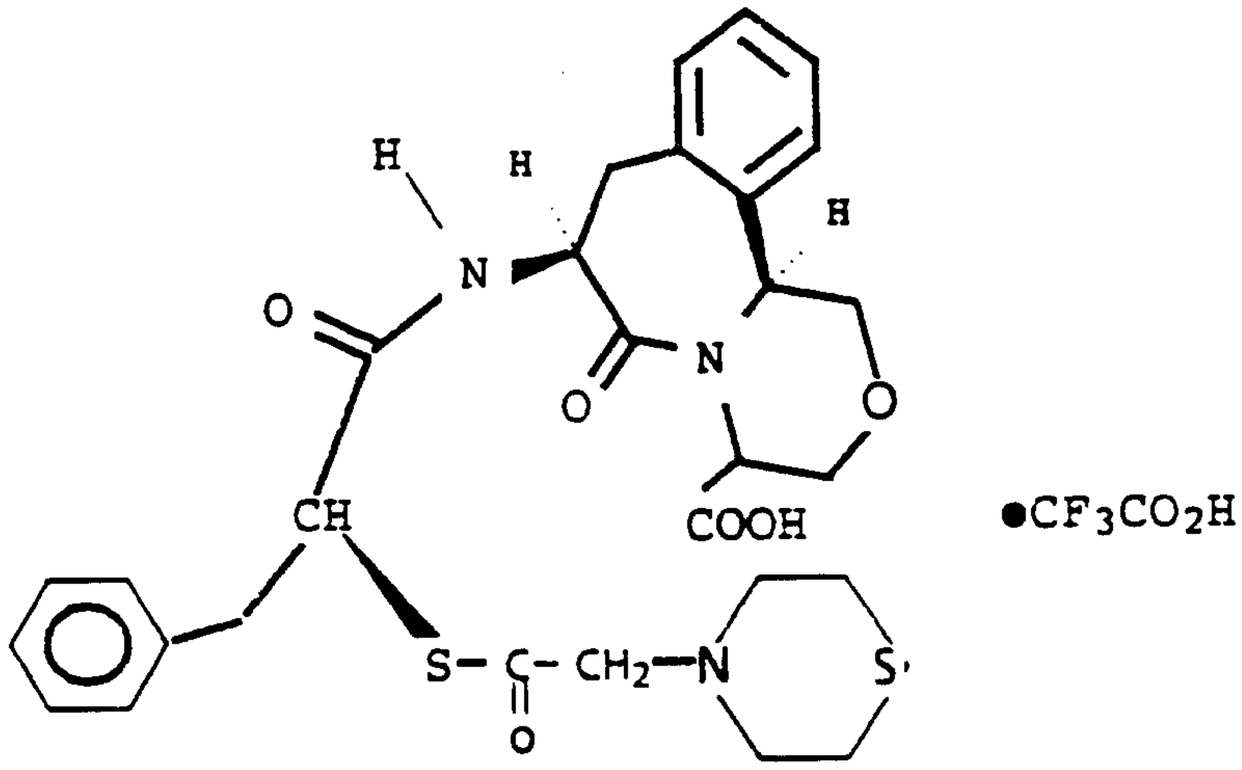
Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluoroacetate

Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-thiomorpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.86mmol) and anisole (1.5mL, excess) in methylene chloride (20mL), cool to -50°C and add trifluoroacetic acid (3mL). Stir the reaction mixture at -50°C for 2.5 hours, evaporate the solvent *in vacuo* and triturate with hexane (4X). Take up the residue in a minimal amount of methylene chloride and precipitate from hexane (3X) to give the title compound (75%).

^{1}H NMR ($CDCl_3$) δ7.63 (d, 1, J=7.5Hz), 6.93-7.42 (m, 9), 5.58-6.74 (m, 1), 5.38-5.50 (m, 1), 5.00-5.12 (m, 1), 4.51 (dd, 1, J=6, 9Hz), 3.90 (s, 2), 3.16-3.51 (m, 6), 3.06 (dd, 1, J=9, 15Hz), 2.68-2.95 (m, 6), 2.12-2.57 (m, 2), 1.60-2.05 (m, 4); ^{19}F NMR ($CDCl_3$) δ-76.3; MS (CI, 70eV) m/z 582 [M+H], 178, 162, 116.

Example 11

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



•CF_3CO_2H

Scheme A, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino)-acetylthio-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, diphenylmethyl ester

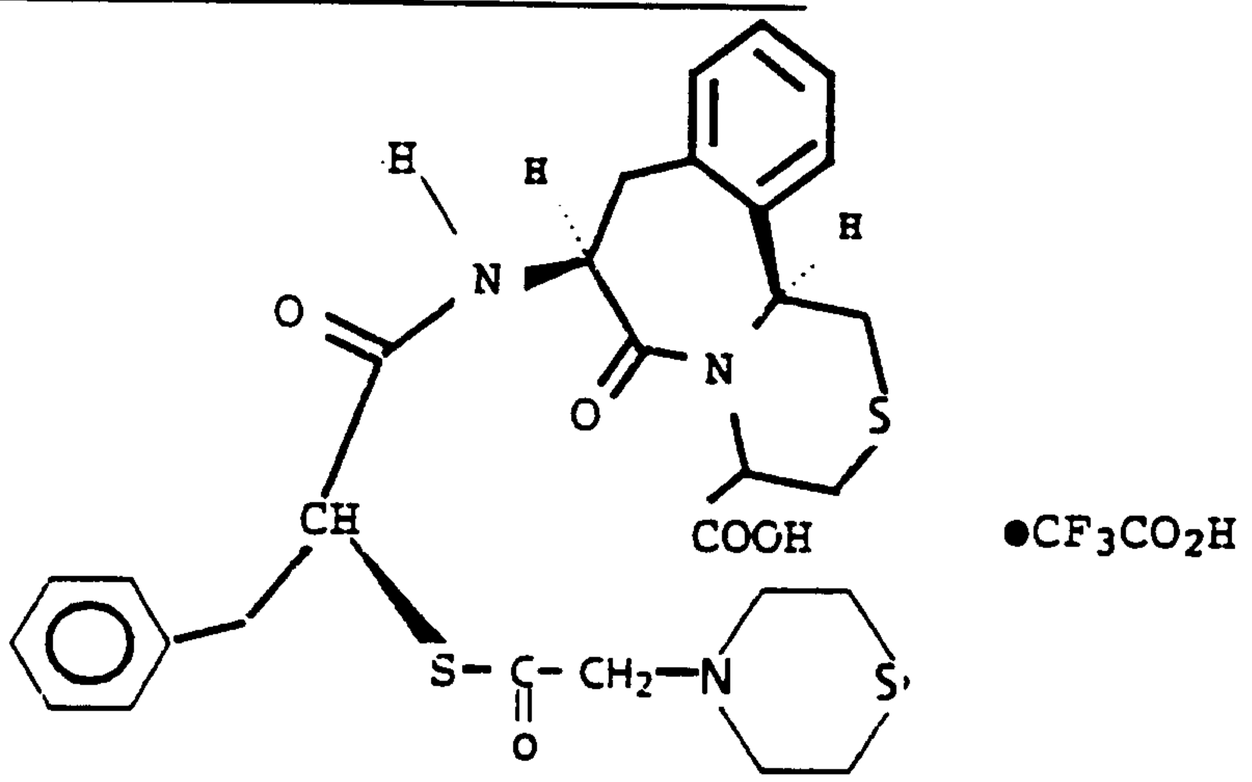
Suspend sodium hydride (175mg of a 60% suspension, 4.0mmol) in anhydrous dimethylformamide (4mL) and place under a nitrogen atmosphere. Bubble hydrogen sulfide gas into the suspension until solution occurs. Add triphenylmethyl 4-thiomorpholinethiolacetate (4.0mmol) and heat gently for 1.5 hours while bubbling nitrogen through the solution to facilitate removal of excess hydrogen sulfide gas. Add [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-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,diphenylmethyl ester (2.0mmol) and stir for 2 hours. Pour into water, extract into ethyl acetate, wash with brine and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino)-acetylthio-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•trifluoroacetate

Mix [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-thiomorpholino)-acetylthio-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, diphenylmethyl ester (2.0mmol), anisole (0.5mL) and methylene chloride (6mL). Place under a nitrogen atmosphere and cool to -50°C. Add trifluroracetic acid (3.0mL) over 1 minutes and allow to warm to room temperature over 2 hours while stirring. Evaporate the solvent *in vacuo*, triturate with hexane and methylene chloride and dry under high vacuum to give the title compound.

Example 12

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



Scheme A, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino)-acetylthio-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, diphenylmethyl ester

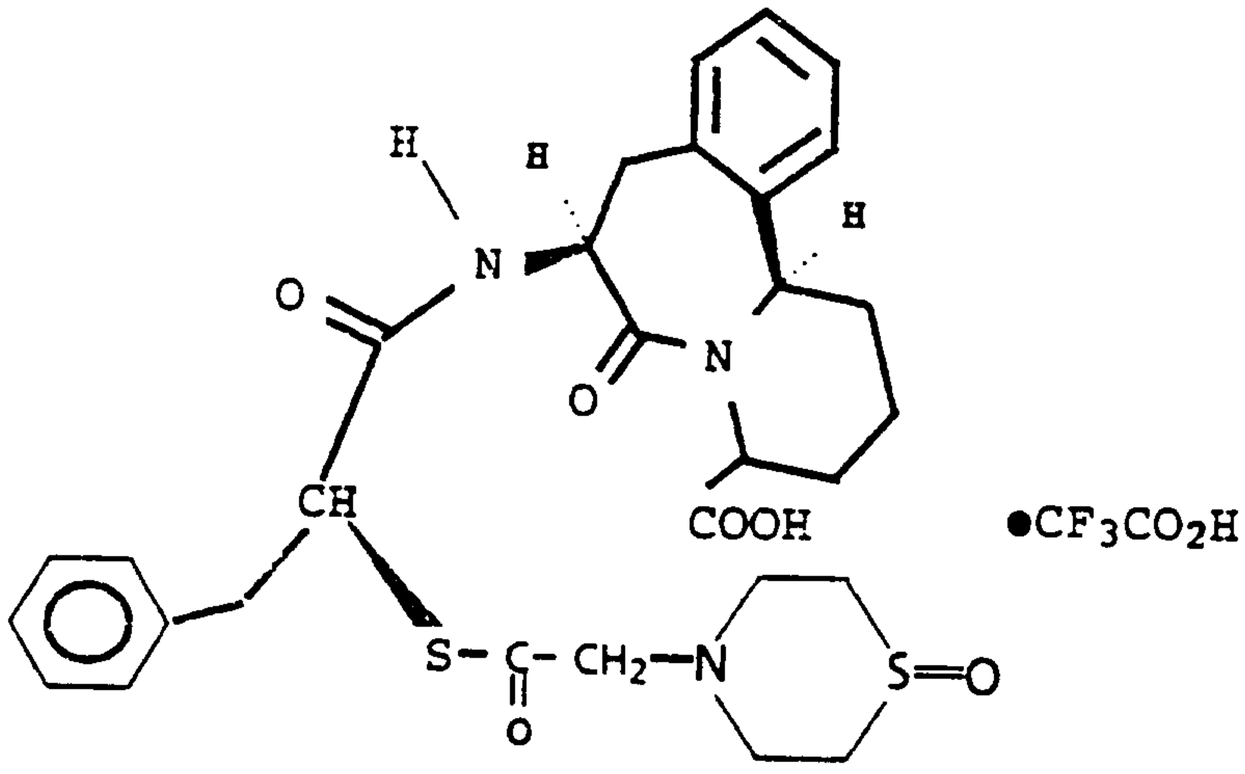
Suspend sodium hydride (175mg of a 60% suspension, 4.0mmol) in anhydrous dimethylformamide (4mL) and place under a nitrogen atmosphere. Bubble hydrogen sulfide gas into the suspension until solution occurs. Add triphenylmethyl 4-thiomorpholinethiolacetate (4.0mmol) and heat gently for 1.5 hours while bubbling nitrogen through the solution to facilitate removal of excess hydrogen sulfide gas. Add [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-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, diphenylmethyl ester (2.0mmol) and stir for 2 hours. Pour into water, extract into ethyl acetate, wash with brine and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino)-acetylthio-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•trifluoracetate

Mix [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-thiomorpholino)-acetylthio-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, diphenylmethyl ester (2.0mmol), anisole (0.5mL) and methylene chloride (6mL). Place under a nitrogen atmosphere and cool to -50°C. Add trifluoroacetic acid (3.0mL) over 1 minute and allow to warm to room temperature over 2 hours while stirring. Evaporate the solvent *in vacuo*, triturate with hexane and methylene chloride and dry under high vacuum to give the title compound.

Example 13

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino-1-oxide)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



Method A

Scheme B, optional step c: Triphenylmethyl 4-thiomorpholine-1-oxide-thiolacetate

Dissolve triphenylmethyl 4-thiomorpholinethiolacetate (5.39mmol) in methylene chloride (25mL), place under nitrogen atmosphere and cool to -20°C. Add, by dropwise addition, a solution of meta-chloroperbenzoic acid (930mg, 5.39mmol) in methylene chloride (25mL). Stir overnight atroom temperature. Filter and treat with aqueous sodium metabisulfite (until negative starch-iodide test) and separate the layers. Wash the organic phase with 5N sodium hydroxide until basic and dry ($MgSO_4$). Evaporate the solvent *in vacuo* to give the title compound.

Scheme A, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino-1-oxide)-acetylthio-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 sodium hydride (175mg of a 60% suspension, 4.0mmol) in anhydrous dimethylformamide (4mL) and place under a nitrogen atmosphere. Bubble hydrogen sulfide gas into the

suspension until solution occurs. Add triphenylmethyl 4-thiomorpholine-1-oxide-thiolacetate (4.0mmol) and heat gently for 1.5 hours while bubbling nitrogen through the solution to facilitate removal of excess hydrogen sulfide gas. Add [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.3g, 2.0mmol) and stir for 2 hours. Pour into water, extract into ethyl acetate, wash with brine and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

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

Mix [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-thiomorpholino-1-oxide)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.0mmol), anisole (0.5mL) and methylene chloride (6mL). Place under a nitrogen atmosphere and cool to -50°C. Add trifluoroacetic acid (3.0mL) over 1 minute and allow to warm to room temperature over 2 hours while stirring. Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Method B

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

Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-

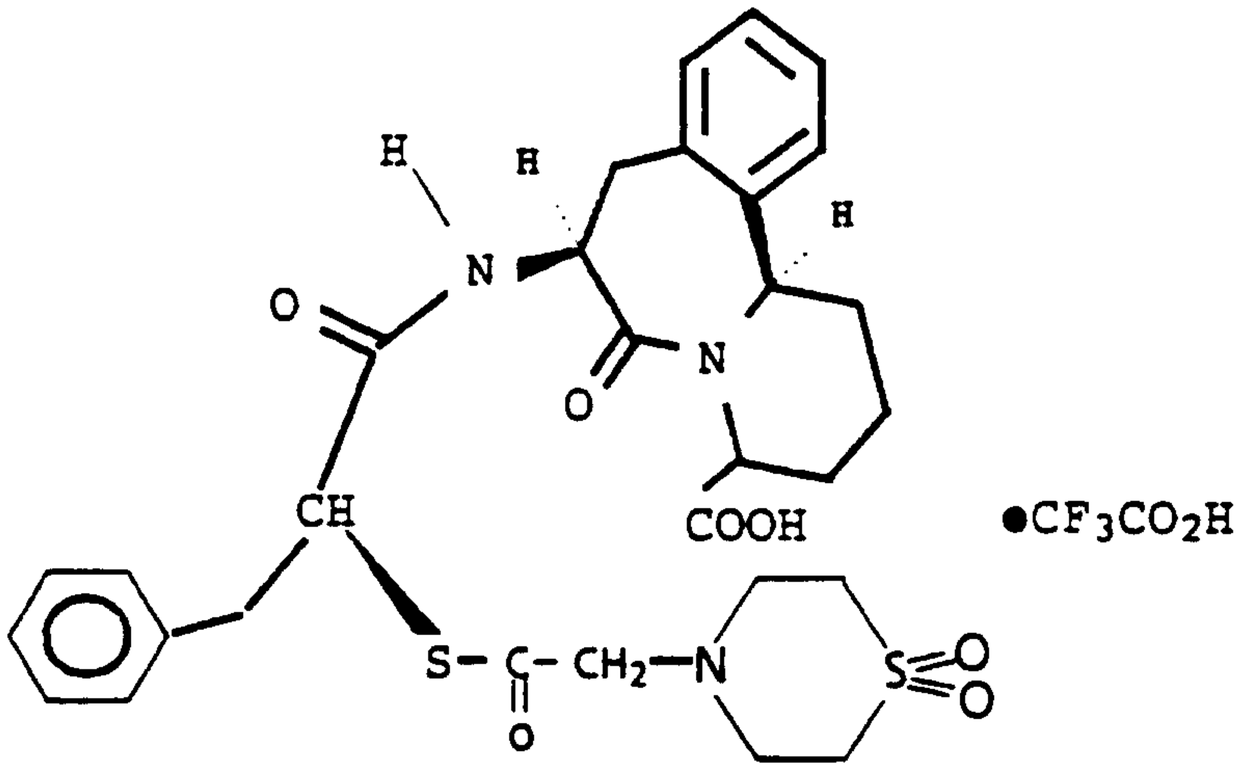
a][2]benzazepine-4-carboxylic acid (1.52g, 2.19mmol) in ethanol/water (40mL/10mL) and add magnesium monoperoxyphthalic acid hexahydrate (0.603g, 1.22mmol). Stir the reaction mixture at room temperature for 30 minutes, evaporate the solvent *in vacuo* at 40°C and take up the residue in methylene chloride. Dry ($MgSO_4$), evaporate the solvent *in vacuo* and purify by silica gel chromatography (methylene chloride:isopropanol/8:2 to 6:4) to give the title compound as a glassy solid (0.53g, 41%).

IR (KBr) 3384, 3029, 2936, 2871, 1651, 1495, 1440, 1054, 1015, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ7.51 (d, 1, J=4.8Hz), 6.91-7.40 (m, 9), 5.58 (m, 1), 5.36-5.48 (m, 1), 5.08-5.20 (m, 1), 4.30 (t, 1, J=7.8Hz), 3.51 (dd, 1, J=6, 16.5Hz), 3.25-3.44 (m, 3), 3.09-3.25 (m, 2), 3.02 (dd, 1, J=8.4, 14.1Hz), 2.65-2.94 (m, 6), 2.28-2.65 (m, 3), 1.52-2.04 (m, 3); ^{19}F NMR ($CDCl_3$) δ -75.8; ^{13}C NMR ($CDCl_3$) δ 199.2, 172.8, 171.9, 169.7, 137.6, 136.8, 135.6, 130.5, 129.4, 128.4, 127.4, 126.9, 125.6, 125.0, 66.6, 51.2, 51.1, 48.7, 47.7, 45.9, 44.2, 36.9, 36.7, 25.1, 17.2; MS (FAB) m/z 598 [M+-H], 580, 552, 232.

Anal. Calcd for $C_{30}H_{35}N_3O_6S_2 \bullet CF_3CO_2H$: C, 53.95; H, 5.09; N, 5.90; Found: C, 53.98, H, 5.29; N, 5.78.

Example 14

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino-1,1-dioxide)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



Method A

Scheme B, optional step c: Triphenylmethyl 4-thiomorpholine-1,1-dioxide-thiolacetate

Dissolve triphenylmethyl 4-thiomorpholinethiolacetate (4.43mmol) in methylene chloride (25mL) and place under a nitrogen atmosphere. Add a solution of meta-chloroperbenzoic acid (1.53g, 8.85mmol) in methylene chloride (25mL). Stir at room temperature overnight. Treat with aqueous sodium metabisulfite (until negative starch-iodide test) and separate the layers. Wash the organic phase with 5N sodium hydroxide until basic and dry ($MgSO_4$). Evaporate the solvent *in vacuo* to give the title compound.

Scheme A, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino-1,1-dioxide)-acetylthio-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 sodium hydride (175mg of a 60% suspension, 4.0mmol) in anhydrous dimethylformamide (4mL) and place under a nitrogen atmosphere. Bubble hydrogen sulfide gas into the suspension until solution occurs. Add triphenylmethyl 4-thiomorpholine-1,1-dioxide-thiolacetate (4.0mmol) and heat gently for 1.5 hours while bubbling nitrogen through the solution to facilitate removal of excess hydrogen sulfide gas. Add [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.3g, 2.0mmol) and stir for 2 hours. Pour into water, extract into ethyl acetate, wash with brine and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

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

Mix [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-thiomorpholino-1,1-dioxide)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.0mmol), anisole (0.5mL) and methylene chloride (6mL). Place under a nitrogen atmosphere and cool to -50°C. Add trifluoroacetic acid (3.0mL) over 1 minute and allow to warm to room temperature over 2 hours while stirring. Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Method B

Scheme C, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino-1,1-dioxide)-acetylthio-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 glycine (20g, 0.266mol) in water (50mL) and add divinyl sulfone (26.7mL, 0.2664mol). Heat at 100°C for 1.5 hours and cool to room temperature. Collect the precipitate by suction filtration, wash thoroughly with water and dry *in vacuo* at 50°C overnight to give thiomorpholino-1,1-dioxide acetic acid (26.1g, 51%); mp 177-180°C; IR (KBr) 3587, 3367, 3252, 3026, 2994, 1725, 1640, 1451, 1408, 1366, 1343, 1312, 1277, 1180, 1160, 1138, 1123, 1071, 1061 cm^{-1}; ^1H NMR (DMSO-d6) δ3.36 (s, 2), 3.05 (s, 4); ^{13}C NMR (DMSO-d6) δ171.7, 56.8, 50.7, 49.6; MS (EI, 70eV) m/z 193 (M^+), 175, 148.

Anal. Calcd for $C_6H_{11}NO_4S \cdot H_2O$: C, 34.12; H, 6.20; N, 6.63; Found: C, 34.09; H, 6.21; N, 6.70.

Suspend thiomorpholino-1,1-dioxide acetic acid (0.947g, 4.9mmol) in degassed dimethylformamide (40mL) and add carbonyldiimidazole (0.477g, 2.94mmol). Stir the reaction mixture at room temperature for 1.5 hours. Add a solution of [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.483g, 2.45mmol) in degassed tetrahydrofuran and stir the reaction mixture at room temperature overnight. Dilute with ethyl acetate, wash with water (2X) and brine, dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by silica gel chromatography (hexane:ethyl acetate/1:1 to 3:7) to give the title compound as a glassy solid (1.52g, 80%).

IR ($CHCl_3$) 3381, 3032, 3011, 1736, 1651, 1497, 1439, 1308, 1128 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (d, 1, J=6.6Hz), 7.17-7.38 (m, 12), 6.92-7.12 (m, 6), 6.68 (d, 1, J=6.9Hz), 6.33 (s, 1), 5.57 (m, 1), 5.39 (m, 1), 5.32 (m, 1), 4.31 (dd, 1, J=6.3, 8.7Hz), 3.39 (m, 4), 2.96-3.28 (m, 9), 2.59 (dd, 1, J=15, 18Hz), 2.36-2.51 (m, 1), 1.88-2.03 (m, 1), 1.58-1.88 (m, 3); ^{13}C NMR ($CDCl_3$) δ198.5, 171.7, 169.5, 169.4, 139.9, 139.1, 137.4, 136.4, 135.4, 130.7, 129.3, 128.4, 128.3, 128.2, 127.8, 127.7, 127.4, 127.0, 126.9, 126.8, 125.5, 124.7, 78.2, 65.7, 51.6, 51.4, 51.2, 51.1, 48.6, 48.1, 37.0, 36.6, 25.1, 25.0, 17.2; MS (FAB) m/z 780 [M++H], 752, 614, 572, 406, 167, 148; HRMS calcd for $C_{43}H_{45}N_3O_7S_2$ [M++H] 780.2777, Found: 780.2764.

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

Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-thiomorpholino-1,1-dioxide)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.45g, 1.86mmol) and anisole (1.5mL, excess) in methylene chloride (20mL). Add trifluoroacetic acid (3mL) and stir at room temperature for 2.5 hours. Evaporate the solvent *in vacuo* and triturate with hexane (4X). Take the residue up in a minimal amount of methylene chloride and precipitate from hexane (3X) to give the title compound as a beige powder (1.29g, 95%).

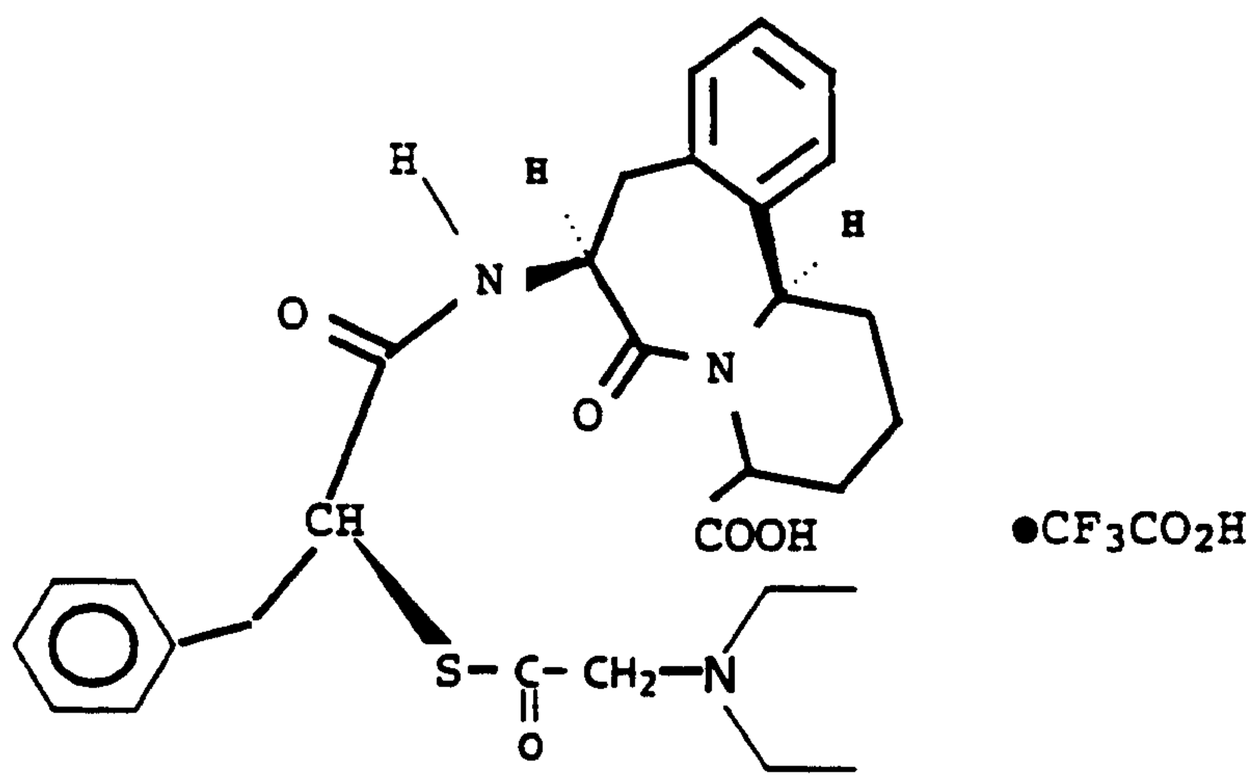
IR ($CHCl_3$) 3370, 3065, 3032, 2953, 1782, 1759, 1653, 1495, 1443, 1325, 1308, 1170, 1128 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (d, 1, J=6.6Hz), 6.91-7.39 (m, 9), 5.67 (m, 1), 5.45 (m, 1), 5.13 (m, 1), 4.36 (dd, 1, J=6.6, 8.4Hz), 3.29-3.60 (m, 4), 2.97-3.29 (m, 9), 2.82 (dd, 1, J=12.9, 17.1Hz), 2.44-2.60 (m, 1), 2.27-2.44 (m, 1), 1.67-2.09 (m, 4); ^{19}F NMR ($CDCl_3$)

δ -76.3; ^{13}C NMR ($CDCl_3$) δ 197.6, 174.4, 172.1, 170.8, 136.7, 136.1, 135.1, 130.6, 129.2, 128.6, 127.7, 127.2, 125.8, 125.0, 64.9, 51.3, 51.2, 48.9, 48.4, 36.8, 36.4, 25.0, 24.9, 17.0; MS (FAB) m/z 614 [M^++H], 596, 568.

Anal. Calcd for $C_{30}H_{35}N_3O_7S_2 \bullet CF_3CO_2H$: C, 52.81; H, 4.99; N, 5.77; Found: C, 53.09; H, 5.29; N, 5.77.

Example 15

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(diethylamino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



•CF_3CO_2H

Scheme C, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(diethylamino)-acetylthio-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 t-butyl bromoacetate (1eq) in tetrahydrofuran and add diethylamine (2.2eq) via syringe. Stir the reaction mixture at room temperature for 2 hours, filter and wash the filter cake with ethyl acetate. Combine the organic filtrates and wash with saturated sodium bicarbonate (2X), water (2X) and brine. Dry (Na_2SO_4), filter and evaporate the solvent *in vacuo*. Take up the oily residue in ethyl

acetate, cool in ice and bubble hydrogen chloride gas into the solution. Stir at room temperature overnight, cool and filter to give diethylaminoacetic acid hydrochloride salt as an oil (88%); ^{1}H NMR (D_2O) δ 3.86 (s, 2), 3.17 (q, 4, J=9Hz), 1.17 (t, 6, J=9Hz).

Suspend diethylaminoacetic acid hydrochloride salt (4.9mmol) in degassed dimethylformamide (40mL) and add carbonyldiimidazole (0.477g, 2.94mmol). Stir the reaction mixture at room temperature for 1.5 hours. Add a solution of [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.45mmol) in degassed tetrahydrofuran and stir at room temperature overnight. Dilute with ethyl acetate, wash with water (2X) and brine, dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound (77%).

^{1}H NMR ($CDCl_3$) δ7.43, (d, 1, J=6Hz), 7.16-7.35 (m, 12), 6.90-7.30 (m, 6), 6.59 (m, 1), 6.27 (s, 1), 6.19 (m, 1), 5.33-5.43 (m, 2), 4.28 (t, 1, J=7.5Hz), 3.25-3.42 (m, 3), 2.87-3.08 (m, 2), 2.31-2.70 (m, 7), 1.54-2.02 (m, 4). 1.07 (t, 6, J=9Hz); MS (CI, 70eV) m/z 718 [M^++H], 622, 605.

<u>Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(diethylamino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluoroacetate</u>

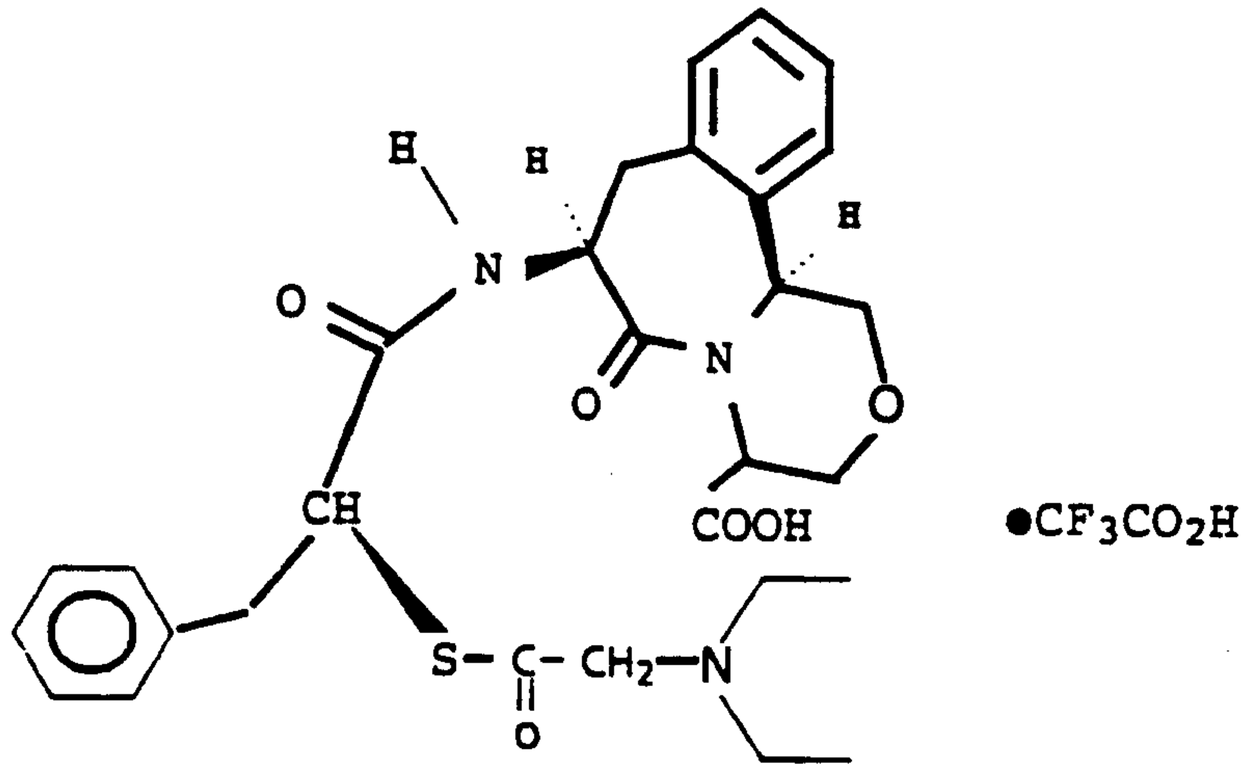
Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(diethylamino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester(1.86mmol) and anisole (1.5mL, excess) in methylene chloride (20mL), cool to -50°C and add trifluoroacetic acid (3mL). Stir the reaction mixture at -50°C for 2.5 hours, evaporate the solvent *in vacuo* and triturate with hexane

(4X). Take up the residue in a minimal amount of methylene chloride and precipitate from hexane (3X) to give the title compound (59%).

^{1}H NMR ($CDCl_3$) δ 7.85 (d, 1, J=9Hz), 6.90-7.35 (m, 9), 5.64-5.80 (m, 1), 5.39-5.51 (m, 1), 5.08-5.18 (m, 1), 4.61 (dd, 1, J=6, 10.5Hz), 3.87-4.06 (m, 2), 3.32-3.48 (m, 2), 2.81-3.24 (m, 6), 2.28-2.56 (m, 2), 1.62-2.03 (m, 4), 1.18 (t, 6, J=7.5Hz); ^{19}F NMR ($CDCl_3$) δ -76.3; MS (CI, 70eV) m/z 552 [M$^+$+H], 439.

Example 16

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(diethylamino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



Scheme A, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(diethylamino)-acetylthio-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, diphenylmethyl ester

Suspend sodium hydride (175mg of a 60% suspension, 4.0mmol) in anhydrous dimethylformamide (4mL) and place under a nitrogen atmosphere. Bubble hydrogen sulfide gas into the suspension until solution occurs. Add triphenylmethyl diethylaminethiolacetate (4.0mmol) and heat gently for 1.5

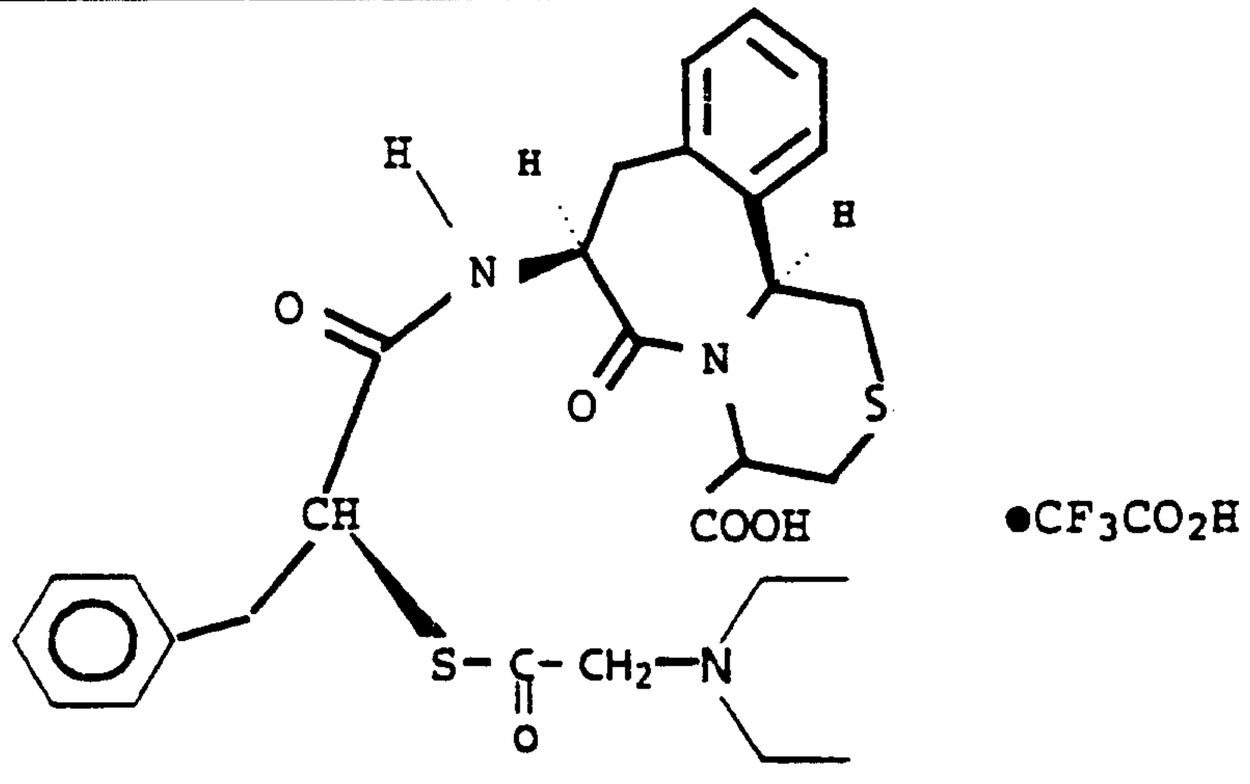
hours while bubbling nitrogen through the solution to facilitate removal of excess hydrogen sulfide gas. Add [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-1H-[1,4]-oxazino[3,4-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.0mmol) and stir for 2 hours. Pour into water, extract into ethyl acetate, wash with brine and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(diethylamino)-acetylthio-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•trifluoroacetate

Mix [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(diethylamino)-acetylthio-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, diphenylmethyl ester (2.0mmol), anisole (0.5mL) and methylene chloride (6mL). Place under a nitrogen atmosphere and cool to -50°C. Add trifluoroacetic acid (3.0mL) over 1 minute and allow to warm to room temperature over 2 hours while stirring. Evaporate the solvent *in vacuo*, triturate with hexane and methylene chloride and dry under high vacuum to give the title compound.

Example 17

[4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(diethylamino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-hexahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



Scheme A, step c: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(diethylamino)-acetylthio-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, diphenylmethyl ester

Suspend sodium hydride (175mg of a 60% suspension, 4.0mmol) in anhydrous dimethylformamide (4mL) and place under a nitrogen atmosphere. Bubble hydrogen sulfide gas into the suspension until solution occurs. Add triphenylmethyl diethylaminethiolacetate (4.0mmol) and heat gently for 1.5 hours while bubbling nitrogen through the solution to facilitate removal of excess hydrogen sulfide gas. Add [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(R)-bromo-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, diphenylmethyl ester (2.0mmol) and stir for 2 hours. Pour into water, extract into ethyl acetate, wash with brine and dry ($MgSO_4$). Evaporate the solvent *in vacuo* and purify by chromatography to give the title compound.

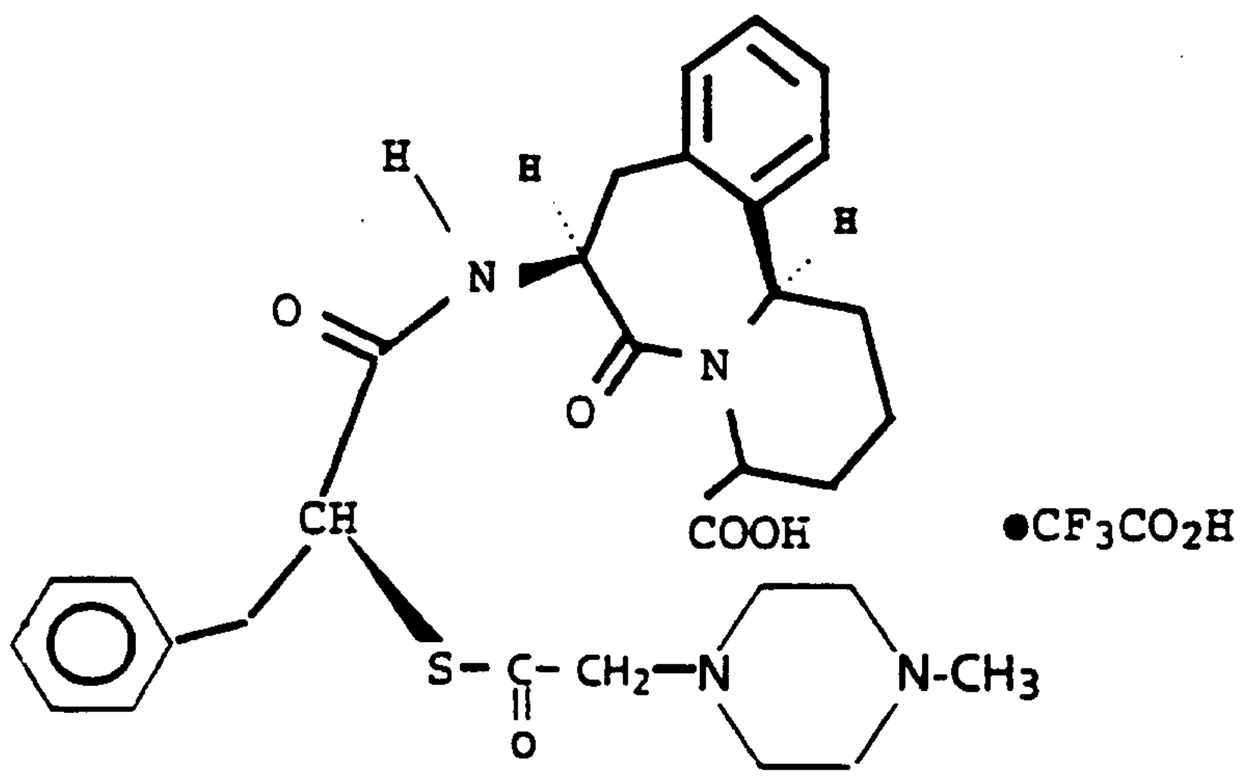
Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(diethylamino)-acetylthio-3-phenylpropyl)amino]-

1,2,3,4,6,7,8,12b-octahydro-6-oxo-1H-[1,4]-thiazino[3,4-a][2]benzazepine-4-carboxylic acid•trifluoroacetate

Mix [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(diethylamino)-acetylthio-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, diphenylmethyl ester (2.0mmol), anisole (0.5mL) and methylene chloride (6mL). Place under a nitrogen atmosphere and cool to -50°C. Add trifluoroacetic acid (3.0mL) over 1 minute and allow to warm to room temperature over 2 hours while stirring. Evaporate the solvent *in vacuo*, triturate with hexane and methylene chloride and dry under high vacuum to give the title compound.

Example 18

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



Scheme C, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-methyl-1,4-piperazino)-acetylthio-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 N-methylpiperazine (5.0mL, 45.09mmol) in diethyl ether in a stoppered flask and treat with neat ethyl bromoacetate (3.012g, 18.036mmol). Stir the reaction mixture at room temperature overnight, filter and wash the filter cake with diethyl ether. Combine the organic filtrates and evaporate the solvent *in vacuo* to give a light yellow oil. Take up in water (60mL) and heat at 95°C for 4 hours, allow to cool to room temperature and stir overnight. Evaporate the solvent *in vacuo* and dissolve the residue in acetonitrile and evaporate the solvent *in vacuo* (twice) to azeotrope residual water. Dissolve in a minimal amount of methanol, dilute with diethyl ether and place in the freezer. Isolate the crystals which form by decanting the supernatant and wash with diethyl ether. Obtain two more crops of crystals from the mother liquor to give 4-methylpiperazine-1-acetic acid (2.345g, 82%); mp 158-160°C (lit 159.5-161°C), ^{1}H NMR (D_2O) δ 3.98 (s, 2), 3.81-3.32 (m, 8), 2.89 (s, 3).

Suspend 4-methylpiperazine-1-acetic acid (4.9mmol) in degassed dimethylformamide (40mL) and add carbonyldiimidazole (0.477g, 2.94mmol). Stir the reaction mixture at room temperature for 1.5 hours. Add a solution of [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.45mmol) in degassed tetrahydrofuran and stir at room temperature overnight. Dilute with ethyl acetate, wash with water (2X) and brine, dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound (90%).

^{1}H NMR ($CDCl_3$) δ 7.41, (d, 1, J=6.7Hz), 7.33-6.92 (m, 17), 6.61 (m, 1), 6.27 (s, 1), 5.56 (quint, 1, J=6.3Hz), 5.37 (m, 2), 4.29 (t, 1, J=7.6Hz), 3.41-3.22 (m, 4), 3.02 (dd, 1, J=7.8, 13.8Hz), 2.66-2.34 (m, 10), 2.32 (s, 3), 2.03-1.66 (m, 6) ^{13}C NMR ($CDCl_3$) δ 171.67, 169.76, 169.68, 158.79,

141.38, 139.92, 139.77, 139.71, 139.01, 136.48, 135.38, 130.75, 130.21, 129.00, 128.25, 128.16, 127.76, 127.71, 127.31, 126.94, 126.86, 126.80, 125.35, 124.63, 124.12, 123.78, 123.02, 122.14, 114.00, 78.22, 55.20, 53.40, 51.05, 51.02, 49.95, 48.43, 36.79, 35.74, 33.41, 25.02, 24.91, 17.12; MS (CI/CH_4) m/z 745 [M^++H, base peak], 605, 572, 405, 203, 187, 175, 159, 113.

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

Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-methyl-1,4-piperazino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (500mg, 0.690mmol) and anisole (0.5mL) in methylene chloride (15mL). Add trifluoroacetic acid (1.0mL) and stir at room temperature for 2 hours. Evaporate the volatiles under a stream of nitrogen at ca. 35°C. Dissolve the residue in methylene chloride and evaporate again in the same way. Take the material up in methylene chloride and dilute with ca. 4 volumes of diethyl ether. Allow the resulting precipitate to settle overnight, decant the supernatant and wash the solid 4 times with diethyl ether, decanting the supernatant each time. Dry, first in air and then under high vacuum to give the title compound (382mg, 69%).

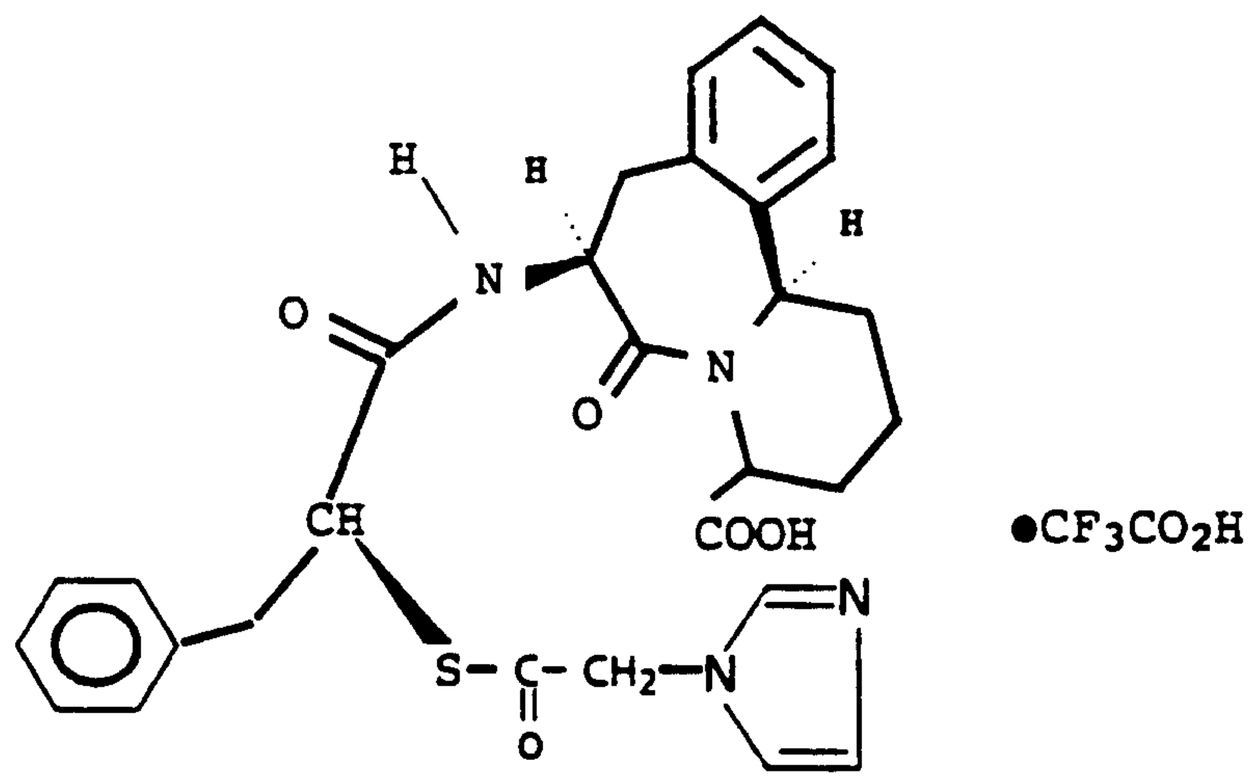
^{1}H NMR ($CDCl_3$) δ 7.56 (d, 1, J=8.6Hz), 7.37-6.98 (m, 7), 5.51 (m, 1), 5.38 (m, 1), 5.04 (m, 1), 4.33 (t, 1, J=8.4Hz), 3.55 (dd, 1, J=6.2, 16.9Hz), 3.49-3.25 (m, 3), 3.02 (dd, 1, J=9.3, 13.8Hz), 2.94- 2.79 (m, 8), 2.67 (s, 3), 2.59-2.30 (m, 2), 2.01-1.70 (m, 6); ^{13}C NMR ($CDCl_3$) δ 196.49, 173.44, 171.94, 170.13, 136.88, 136.28, 135.72, 130.51, 129.33, 129.18, 128.53, 128.46, 127.52, 127.17, 125.82, 125.14, 64.56, 53.07, 51.90, 51.31, 49.54, 49.49,

48.87, 48.18, 43.26, 36.67, 36.32, 25.18, 25.13, 17.13; ^{19}F NMR ($CDCl_3$) δ -76.1; MS (CI/CH_4) m/z 579 [M^++H], 517, 439, 406, 377, 343, 296, 257, 199, 187, 175, 159 (base peak), 115.

Anal. Calcd for $C_{31}H_{38}N_4O_5S \bullet CF_3CO_2H$: C, 57.22; H, 5.67; N, 8.09; Found: C, 57.15; H, 5.83, N, 7.73.

Example 19

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



Scheme C, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-imidazolino)-acetylthio-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 t-butyl bromoacetate (1eq) in tetrahydrofuran and add imidazole (2.2eq). Stir the reaction mixture at room temperature for 2 hours, filter and wash the filter cake with ethyl acetate. Combine the organic filtrates and wash with saturated sodium bicarbonate (2X), water (2X) and brine. Dry (Na_2SO_4), filter and evaporate the solvent *in vacuo*. Take up the oily residue in ethyl acetate, cool in

ice and bubble hydrogen chloride gas into the solution. Stir at room temperature overnight, cool and filter to give 1-imidazolinoacetic acid hydrochloride salt (57%); mp 195-205°C (dec) (lit 193-195°C, EtOH); ^{1}H NMR (D_2O) δ 8.66 (s, 1), 7.37 (d, 2, J=3.9Hz), 4.99 (s, 2).

Suspend 1-imidazolinoacetic acid hydrochloride salt (4.9mmol) in degassed dimethylformamide (40mL) and add carbonyldiimidazole (0.477g, 2.94mmol). Stir the reaction mixture at room temperature for 1.5 hours. Add a solution of [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.45mmol) in degassed tetrahydrofuran and stir at room temperature overnight. Dilute with ethyl acetate, wash with water (2X) and brine, dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound (99%).

^{1}H NMR ($CDCl_3$) δ7.52 (s, 1), 7.42 (d, 1, J=8.1Hz), 7.34-6.91 (m, 19), 6.66 (m, 1), 6.32 (s, 1), 5.54 (quint, 1, J=6.9Hz), 5.36 (m, 2), 4.82 (s, 2, 4.37 (t, 1, J=8.4Hz), 3.38-3.28 (m, 2), 3.03 (dd, 1, J=8.9, 13.8Hz), 2.54 (dd, 1, J=13.1, 16.9Hz), 2.97-2.86 (m, 2), 2.03-1.68 (m, 5); ^{13}C NMR ($CDCl_3$) δ 193.80, 171.56, 169.55, 168.35, 139.88, 139.01, 138.23, 136.80, 136.35, 135.31, 130.76, 130.18, 129.23, 128.51, 128.31, 128.25, 127.82, 127.77, 127.43, 127.15, 126.99, 126.84, 125.51, 124.69, 120.21, 78.26, 55.23, 51.16, 51.08, 49.08, 48.58, 37.05, 36.54, 25.02, 24.94, 17.13; MS (CI/CH_4) m/z 713 [M^++H], 605, 545, 501, 437, 406, 393, 359, 257, 217, 184, 167 (base peak), 155, 127.

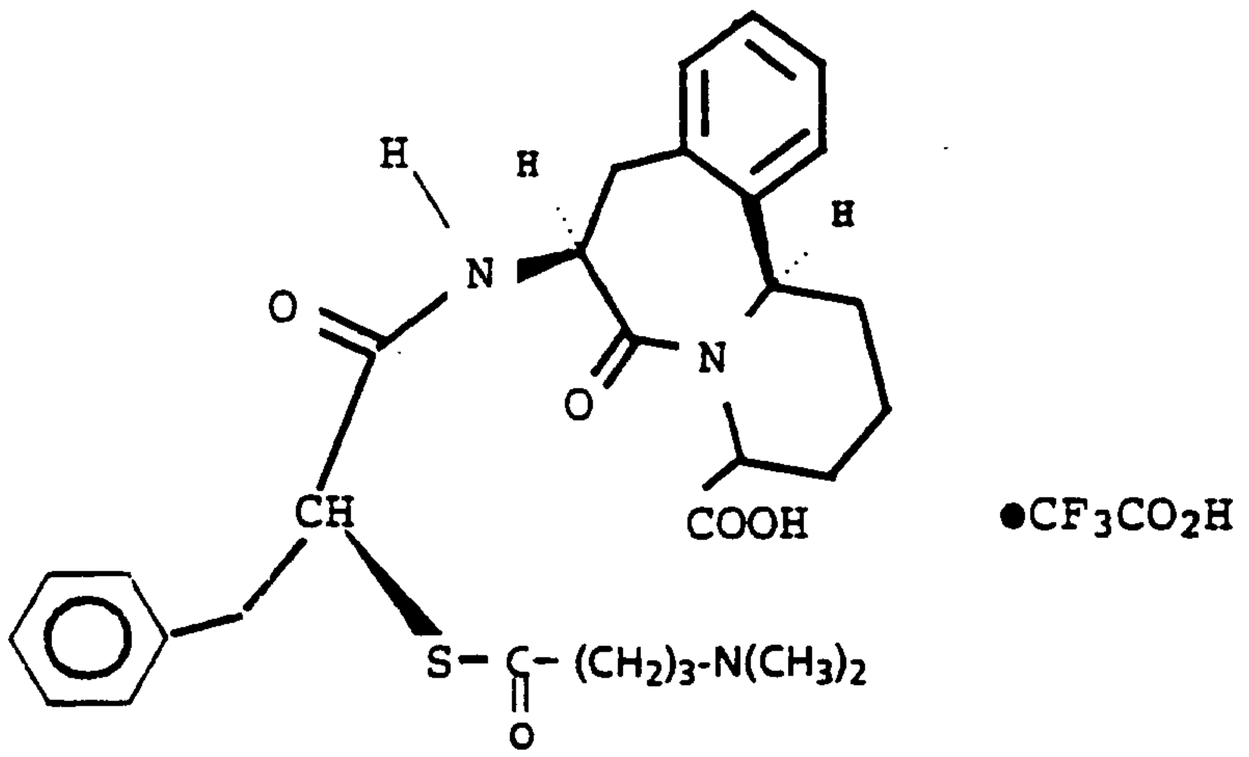
Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-imidazolino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluoroacetate

Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-imidazolino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (685mg, 0.962mmol) and anisole (0.5mL) in methylene chloride (15mL). Add trifluoroacetic acid (1.0mL) and stir at room temperature for 2 hours. Evaporate the volatiles under a stream of nitrogen at ca. 35°C. Dissolve the residue in methylene chloride and evaporate again in the same way. Take the material up in methylene chloride and dilute with ca. 4 volumes of diethyl ether. Allow the resulting precipitate to settle overnight, decant the supernatant and wash the solid 4 times with diethyl ether, decanting the supernatant each time. Dry, first in air and them under high vacuum to give the title compound as a white powder (518mg, 82%).

^{1}H NMR ($CDCl_3$) δ 8.67 (br s, 1), 7.59 (br s, 1), 7.33-6.99 (m, 10), 5.55 (m, 1), 5.38 (m, 1), 5.11 (br d, 1, J=18.4Hz), 4.99 (br d, 1, J=18.4Hz), 4.94 (m, 1), 4.47 (br t, 1, J=8.1Hz), 3.44-3.30 (m, 2), 3.06 (br dd, 1, J=10.8, 14.5Hz), 2.81 (m, 1), 2.49 (m, 1), 2.28 (m, 1), 2.01-1.68 (m, 5); ^{13}C NMR ($CDCl_3$) δ 198.44, 172.87, 171.71, 169.62, 137.50, 136.78, 136.20, 130.40, 129.21, 128.43, 127,28, 126.94, 125.68, 125.18, 65.60, 53.49, 52.12, 51.43, 49.74, 48.80, 47.65, 43.06, 36.71, 36.69, 25.34, 17.34,; ^{19}F NMR ($CDCl_3$) δ -75.9; MS (CI/CH_4) m/z 547 [M$^+$+H],529, 485, 449, 439, 421, 405, 377, 376, 343, 301, 274, 239, 227, 167, 155, 127, 115 (base peak).

Example 20

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



Suspend 4-dimethylaminobutyric acid (4.9mmol) in degassed dimethylformamide (40mL) and add carbonyldiimidazole (0.477g, 2.94mmol). Stir the reaction mixture at room temperature for 1.5 hours. Add a solution of [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.45mmol) in degassed tetrahydrofuran and stir at room temperature overnight. Dilute with ethyl acetate, wash with water (2X) and brine, dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by silica gel chromatography (hexane:ethyl acetate/1:1 to 3:7) to give the title compound (60%).

IR (KBr) 3384, 3062, 3030, 2942, 2868, 1735, 1680, 1651, 1495, 1438, 1421, 1199, 1185, 1154, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ7.44, (d, 1, J=6.3Hz), 7.15-7.36 (m, 12), 6.87-7.13 (m, 6), 6.62 (m, 1), 6.28 (s, 1), 5.57 (m, 1), 5.31-5.43 (m, 2), 4.38 (t, 1, J=7.5Hz), 3.29-3.44 (m, 2), 3.05 (dd, 1, J=10.5, 14.1Hz), 2.65 (t, 2, J=7.8Hz), 2.54 (dd, 1, J=12, 18Hz), 2.43 (m, 2), 2.29 (t, 2, J=7.2Hz), 2.21 (s, 6), 1.63-2.02 (m, 6); ^{13}C NMR ($CDCl_3$) δ 197.9, 171.6, 169.7, 169.4, 140.0, 139.1, 137.5, 136.6, 135.4, 130.8, 129.3, 128.4, 128.3, 128.2, 127.8, 127.7, 127.4, 127.0, 126.9, 125.4, 124.7, 78.2, 58.2, 51.1, 51.0, 48.5, 48.0, 45.1, 41.7, 36.9, 36.5, 25.0, 24.9, 23.2, 17.1; MS (FAB) m/z

718[M$^+$+H], 267, 167; HRMS calcd for $C_{43}H_{48}N_3O_5S$ [M$^+$+H]: 718.3315, Found: 718.3317.

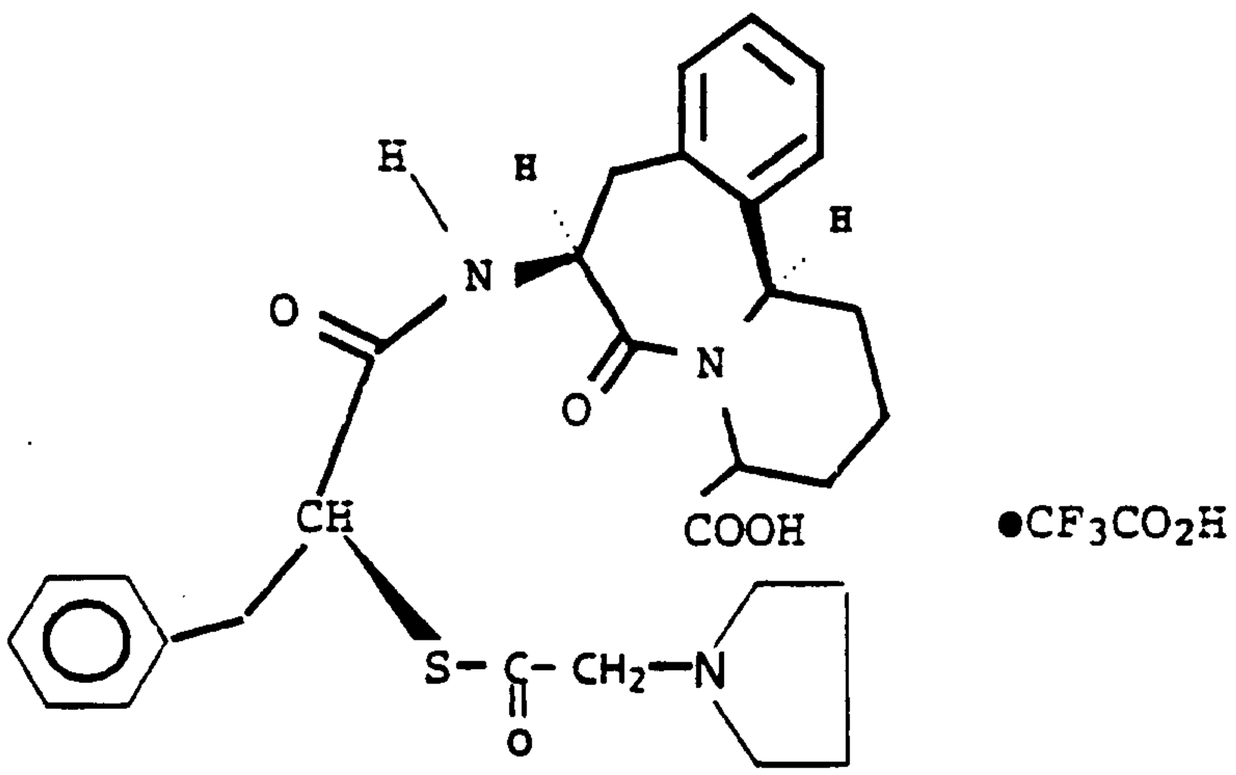
Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-dimethylaminobutyrylthio)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, trifluoroacetate salt

Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-dimethylaminobutyrylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.86mmol) and anisole (1.5mL, excess) in methylene chloride (20mL) and add trifluoroacetic acid (3mL). Stir the reaction mixture for 2.5 hours, evaporate the solvent *in vacuo* and triturate with hexane (4X). Take up the residue in a minimal amount of methylene chloride and precipitate from hexane (3X) to give the title compound (79%).

IR (KBr) 3394, 3061, 3030, 2951, 1731, 1678, 1651, 1495, 1441, 1199, 1141 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 10.68 (br s, 1) 7.59 (m, 1), 6.89-7.60 (m, 9), 5.58 (m, 1), 5.42 (m, 1), 5.02 (s, 1), 4.39 (m, 1), 3.26-3.67 (m, 2), 2.88-3.22 (m, 3), 2.20-2.88 (m, 11), 1.54-2.19 (m, 6); ^{19}F NMR ($CDCl_3$) δ -76.2; ^{13}C NMR ($CDCl_3$) δ 197.2, 173.1, 172.0, 169.5, 137.2, 136.4, 130.5, 129.3, 128.5, 127.5, 127.1, 125.8, 125.1, 56.3, 51.9, 51.2, 48.8, 48.2, 43.0, 42.6, 39.8, 36.4, 36.1, 25.3, 25.2, 19.8, 17.1; MS (FAB) m/z 552 [M$^+$+H].

Example 21

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



Scheme C, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-pyrrolidino)-acetylthio-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 t-butyl bromoacetate (1eq) in tetrahydrofuran and add pyrrolidine (2.2eq) via syringe. Stir the reaction mixture at room temperature for 2 hours, filter and wash the filter cake with ethyl acetate. Combine the organic filtrates and wash with saturated sodium bicarbonate (2X), water (2X) and brine. Dry (Na_2SO_4), filter and evaporate the solvent *in vacuo*. Take up the oily residue in ethyl acetate, cool in ice and bubble hydrogen chloride gas into the solution. Stir at room temperature overnight, cool and filter to give 1-pyrrolidinoacetic acid (86%); mp 188-190°C; ^1H NMR (D_2O) δ 3.93 (s, 2), 3.50-3.64 (m, 2), 2.97-3.04 (m, 2), 1.74-2.03 (m, 4).

Suspend 1-pyrrolidinoacetic acid (4.9mmol) in degassed dimethylformamide (40mL) and add carbonyldiimidazole (0.477g, 2.94mmol). Stir the reaction mixture at room temperature for 1.5 hours. Add a solution of [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.45mmol) in degassed tetrahydrofuran and stir at room temperature overnight. Dilute with ethyl acetate, wash with water (2X) and brine, dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give the title compound (60%).

^1H NMR ($CDCl_3$) δ 7.42 (d, 1, J=7.5Hz), 7.16-7.38 (m, 12), 6.90-7.12 (m, 6), 6.59 (m, 1), 6.26 (s, 1), 5.56 (m, 1), 5.32-5.42 (m, 2), 4.31 (t, 1, J=7.5Hz), 3.28-3.45 (m, 4), 3.03 (dd, 1, J=7.5, 12Hz), 3.60-3.76 (m, 4), 2.32-2.69 (m, 9), 1.57-2.02 (m, 10).

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

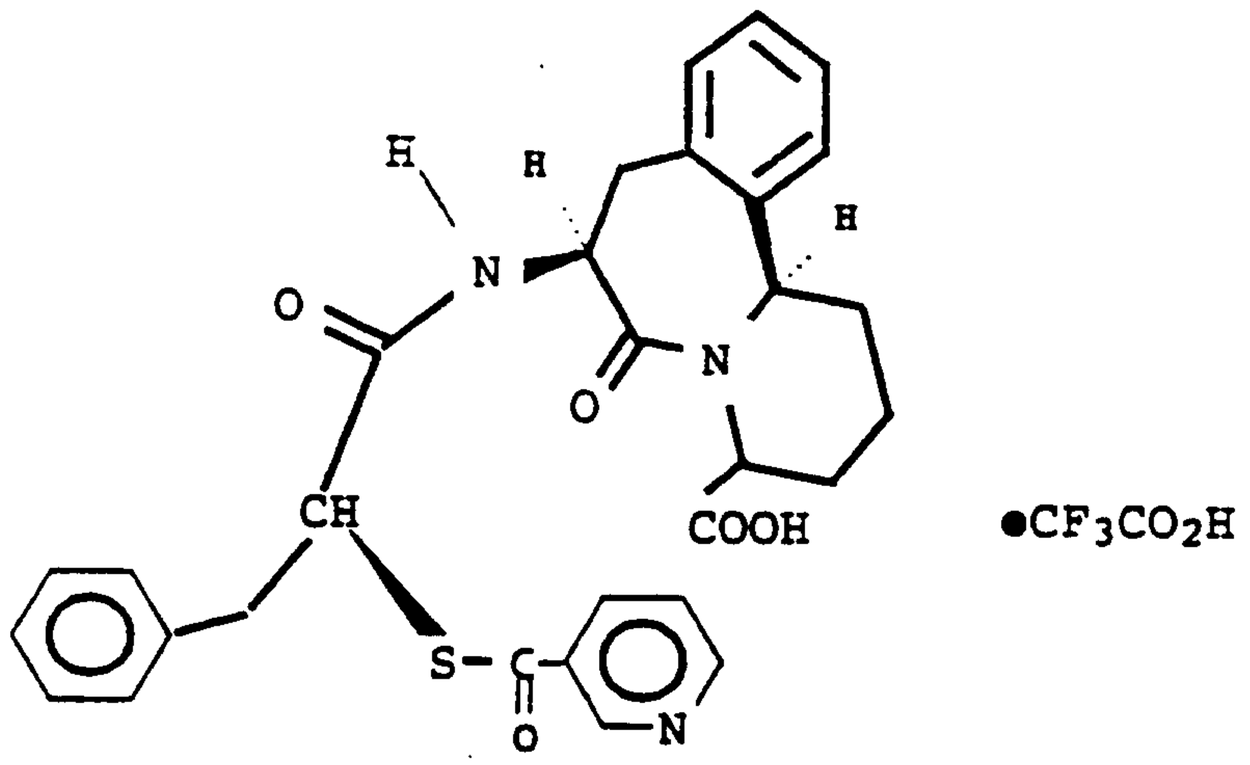
Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(1-pyrrolidino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.86mmol) and anisole (1.5mL), excess) in methylene chloride (20mL), cool to -50°C and add trifluoroacetic acid (3mL). Stir the reaction mixture at -50°C for 2.5 hours, evaporate the solvent *in vacuo* and triturate with hexane (4X). Take up the residue in a minimal amount of methylene chloride and precipitate from hexane (3X) to give the title compound (86%).

^1H NMR ($CDCl_3$) δ 7.85 (d, 1, J=7.5Hz), 6.87-7.39 (m, 9), 5.65-5.80 (m, 1), 5.38-5.49 (m, 1), 4.98-5.11 (m, 1), 4.63 (dd, 1, J=7.5, 9Hz), 3.95-4.11 (m, 2), 3.29-3.48 (m, 4),

2.76-3.11 (m, 4), 2.23-2.54 (m, 2), 1.59-2.09 (m, 8); ^{19}F NMR ($CDCl_3$) δ -76.1; ^{13}C NMR ($CDCl_3$) δ190.5, 172.8, 172.1, 168.6, 136.6, 136.5, 135.7, 130.6, 129.4, 128.5, 127.3, 127.2, 125.7, 125.0, 55.9, 51.5, 51.1, 49.5, 48.8, 37.2, 36.6, 25.4, 25.2, 17.2; MS (FAB) m/z 550 [M+H].

Example 22

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



Suspend [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.20g, 1.98mmol) and nicotinic acid (0.244g, 1.98mmol) in methylene chloride (50mL). Add EDCI (0.418g, 2.18mmol). Stir the reaction mixture at room temperature overnight. Dilute with methylene chloride, wash with saturated sodium bicarbonate, water, 0.5M hydrochloric acid, water and brine. Dry ($MgSO_4$) and evaporate the solvent *in vacuo*. Purify by silica gel chromatography (ethyl acetate) to give the title compound as a glassy solid (0.93g, 63%).

IR (KBr) 3430, 3062, 3031, 2943, 1736, 1656, 1584, 1495, 1438, 1419, 1219, 1155, 912 cm^{-1}; ^1H NMR ($CDCl_3$) δ9.21 (d, 1, J=1.8Hz), 8.82 (dd, 1, J=1.8, 5.1Hz), 8.23 (m, 1), 7.55 (d, 1, J=6.6Hz), 7.42 (m, 1), 7.20-7.37 (m, 12), 6.83-7.20 (m, 6), 6.57 (m, 1), 6.24 (s, 1), 5.59 (m, 1), 5.32-5.43 (m, 2), 4.63 (t, 1, J=7.8Hz), 3.46 (dd, 1, J=7.8, 14.4Hz), 3.38 (dd, 1, J=6.3, 18Hz), 3.18 (dd, 1, J=7.8, 14.4 Hz), 2.35-2.63 (m, 3), 1.59-2.07 (m, 4); ^{13}C NMR ($CDCl_3$) δ 189.8, 171.8, 170.0, 169.4, 154.5, 148.9, 140.1, 139.2, 137.5, 136.7, 135.5, 135.0, 132.1, 131.0, 129.5, 128.7, 128.5, 128.4, 127.9, 127.8, 127.6, 127.2, 127.1, 127.0, 125.6, 124.9, 123.8, 78.3, 51.0, 50.9, 48.5, 48.1, 36.8, 36.2, 24.8, 16.9; MS (CI, 70eV) m/z 710[M^++H], 542, 498, 167, 140, 106; HRMS calcd for $C_{43}H_{40}N_3O_5S$: 710.2689, Found: 710.2680.

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

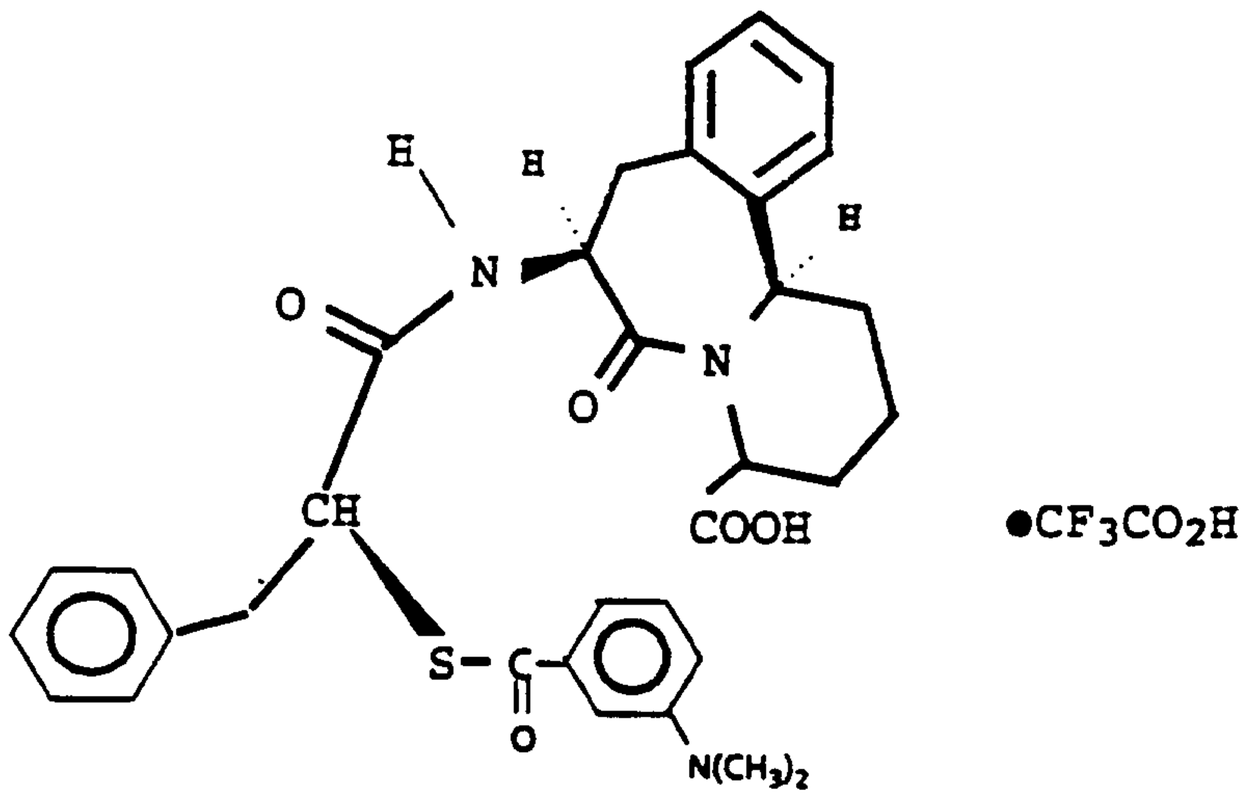
Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-3-pyridinylacetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.86mmol) and anisole (1.5mL, excess) in methylene chloride (20mL) and add trifluoroacetic acid (3mL). Stir the reaction mixture for 2.5 hours, evaporate the solvent *in vacuo* and triturate with hexane (4X). Take up the residue in a minimal amount of methylene chloride and precipitate from hexane (3X) to give the title compound (96%).

IR (KBr) 3394, 3064, 3033, 2950, 1729, 1669, 1517, 1496, 1444, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.14 (s, 1), 8.87 (dd, 1, J=1.2, 4.5Hz), 8.51 (d, 1, J=3.9Hz), 7.73 (m, 2), 6.79-7.46 (m, 9), 5.63 (m, 1) 5.43 (m, 1), 5.15 (m, 1), 4.66 (t, 1, J=7.5Hz), 3.33-3.58 (m, 2), 3.17 (dd, 1, J=8.4, 14.1Hz), 2.73-2.91 (m, 1), 2.24-2.58 (m, 1), 1.64-2.08 (m, 4); ^{19}F NMR ($CDCl_3$) δ -76.9; ^{13}C NMR ($CDCl_3$) δ 187.6, 173.9, 171.9,

169.2, 149.3, 144.5, 139.0, 136.6, 136.3, 135.3, 133.6, 130.5, 129.2, 128.6, 127.4, 127.3, 125.6, 125.5, 124.9, 51.1, 51.0, 49.2, 48.8, 36.9, 36.5, 25.0, 24.9, 17.1; MS (FAB)• m/z 544 [M+•H], 498; HRMS calcd for $C_{30}H_{30}N_3O_5S$ [M^++H]: 544.1906, Found: 544.1889.

Example 23

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



Scheme C, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-3-dimethylaminobenzoylthio-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 3-dimethylaminobenzoic acid (0.451g, 2.73mmol) and triethylamine (0.38mL) in methylene chloride (50mL) and cool to -20°C. Add 2-fluoro-1-methylpyridinium p-toluenesulfonate (0.773g, 2.73mmol). Stir the reaction mixture at -20°C for 1 hour, add solid [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.5g, 2.48mmol) and triethylamine (0.38mL, 2.73mmol).

Remove the cooling bath and stir at room temperature for 2.5 hours, dilute with methylene chloride, wash with water (2X) and brine. Dry ($MgSO_4$), evaporate the solvent *in vacuo* and purify by silica gel chromatography (hexane/ethyl acetate: 7:3 to 6.5:3.5) to give the title compound (1.38g, 70%).

IR ($CHCl_3$) 3385, 3067, 3034, 3011, 2949, 1734, 1655, 1601, 1497, 1437, 1356, 1198, 1157, 922 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (d, 1, J=9Hz), 6.85-7.42 (m, 18), 6.48 (d, 1, J=12Hz), 6.19 (s, 1), 5.58 (m, 1), 5.37 (m, 2), 4.59 (t, 1, J=7.5Hz), 3.45 (dd, 1, J=9, 15Hz), 3.34 (dd, 1, J=6, 16.5Hz), 3.15 (dd, 1, J=7.5, 13.5Hz), 2.98 (s, 6), 2.35-2.49 (m, 3), 1.63-2.02 (m, 4); ^{13}C NMR ($CDCl_3$) δ 191.5, 171.5, 169.8, 169.7, 150.5, 140.0, 139.0, 137.8, 137.1, 136.7, 135.3, 130.8, 129.3, 129.2, 128.4, 128.3, 128.2, 127.7, 127.6, 127.3, 126.9, 126.8, 125.3, 124.6, 117.5, 115.6, 110.4, 78.4, 51.0, 50.9, 48.5, 47.6, 40.4, 36.8, 36.2, 25.0, 17.1; MS (FAB) m/z 752 [M^++H], 587, 167.

Anal. Calcd for $C_{46}H_{45}N_3O_5S \cdot 0.3H_2O$: C, 72.95; H, 6.07; N, 5.55; Found: C, 72.61, H, 6.07; N, 5.32.

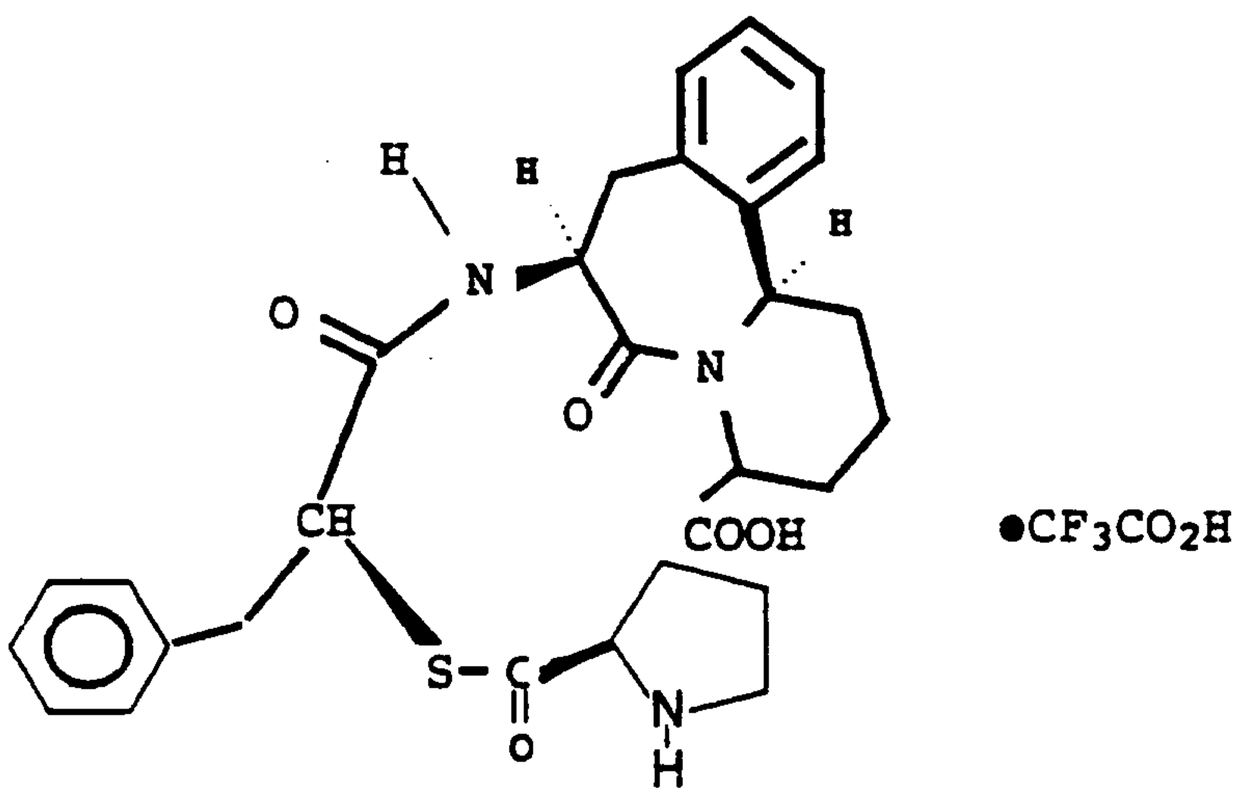
<u>Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-3-dimethylaminobenzoylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluoroacetate</u>

Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-3-dimethylaminobenzoylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.86mmol) and anisole (1.5mL, excess) in methylene chloride (20mL) and add trifluoroacetic acid (3mL). Stir the reaction mixture for 2.5 hours, evaporate the solvent *in vacuo* and triturate with hexane (4X). Take up the residue in a minimal amount of methylene chloride and precipitate from hexane (3X) to give the title compound (94%).

IR ($CDCl_3$) 3374, 3065, 3032, 2953, 1780, 1759, 1721, 1657, 1601, 1497, 1441, 1233, 1169 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71-7.83 (m, 2), 7.66 (d, 1, J=6.6Hz), 7.42-7.59 (m, 2), 7.17-7.40 (m, 5), 6.85-7.17 (m, 4), 5.63 (m, 1), 5.41 (m, 1), 5.12 (m, 1), 4.57 (t, 1, J=7.5Hz), 3.35-3.55 (m, 2), 3.17 (m, 1), 3.09 (s, 6), 2.74 (dd, 1, J=12.9, 17.1Hz), 2.21-2.55 (m, 2), 1.62-2.05 (m, 4); ^{19}F NMR ($CDCl_3$) δ -76.18; ^{13}C NMR ($CDCl_3$) δ 190.2, 173.9, 171.9, 169.8, 146.3, 137.8, 137.1, 136.4, 135.3, 130.6, 130.5, 129.3, 128.6, 127.4, 127.1, 125.6, 124.9, 124.1, 123.4 115.7, 51.0, 48.7, 48.5, 44.2, 36.8, 36.5, 25.1, 25.0, 17.1; MS (CI, 70eV) m/z 586 [M^++H], 182, 166.

Example 24

Scheme C, step d and Scheme A, step d: [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(2-pyrrolidino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid•trifluoroacetate



•CF_3CO_2H

Suspend N-t-butyloxycarbonylproline (4.9mmol) in degassed dimethylformamide (40mL) and add carbonyldiimidazole (0.477g, 2.94mmol). Stir the reaction mixture at room temperature for 1.5 hours. Add a solution of [4S-[4α-

7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (2.45mmol) in degassed tetrahydrofuran and stir at room temperature overnight. Dilute with ethyl acetate, wash with water (2X) and brine, dry ($MgSO_4$) and evaporate the solvent *in vacuo* to give [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(2-(1-t-butyloxycarbonyl)pyrrolidino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (65%).

^1H NMR ($CDCl_3$) δ 7.16-7.46 (m, 10), 6.89 (m, 10), 6.56-6.68 (m, 1), 6.24-6.38 (m, 1), 5.51-5.69 (m, 1), 5.33-5.47 (m, 2), 4.25-4.56 (m, 2), 3.23-3.59 (m, 4), 2.94-3.11 (m, 1), 2.51-2.71 (m, 1), 2.28-2.51 (m, 2), 2.05-2.23 (m, 1), 1.55-2.03 (m, 7), 1.38-1.52 (m, 9); MS (FAB) m/z 802 [M^++H], 746, 702, 605, 167, 113.

Dissolve [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(2-(1-t-butyloxycarbonyl)pyrrolidino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (1.86mmol) and anisole (1.5mL, excess) in methylene chloride (20mL), cool to -50°C and add trifluoroacetic acid (3mL). Stir the reaction mixture at -50°C for 2.5 hours, evaporate the solvent *in vacuo* and triturate with hexane (4X). Take up the residue in a minimal amount of methylene chloride and precipitate from hexane (3X) to give the title compound (73%).

^1H NMR ($CDCl_3$) δ 7.59-7.69 (m, 1), 6.90-7.40 (m, 9), 5.63-5.69 (m, 1), 5.38-5.51 (m, 1), 5.08-5.19 (m, 1), 4.55-4.68 (m, 1), 4.36-4.48 (m, 1), 3.22-3.49 (m, 2), 3.01-3.15 (m, 1), 2.34-2.95 (m, 5), 1.65-2.16 (m, 8); ^{19}F NMR ($CDCl_3$) δ -76.0; ^{13}C NMR ($CDCl_3$) δ 195.5, 173.0, 172.3, 168.8, 136.7, 136.6, 136.0, 130.6, 129.3, 128.6, 127.2, 127.1, 125.8,

125.3, 65.9, 51.7, 51.1, 48.4, 48.2, 45.5, 36.4, 35.9, 28.8, 25.5, 25.3, 23.2, 17.3; MS (FAB) m/z 536 [M^++H].

As used herein, the term "patient" refers to warm-blooded animals or mammals, including rabbits, rodents, monkeys and humans, who are in need of treatment for hypertriglyceridemia atherosclerosis or hypercholesterolemia, such as, for example, in the case of a patient suffering from familial hyperlipidemia. Patients are in need of treatment for hypertriglyceridemia, for example, in the case of a patient suffering from Type IV Hyperlipoproteinemia (indicating elevated VLDL) according to the Fredrickson classification [Fredrickson and Levy, FAMILIAL HYPERLIPOPROTEINEMIA, in *The Metabolic Basis of Inherited Disease*, 3rd ed. (Stanbury, J. B.; Wyngaarden, J. B.; and Fredrickson, D. S.; eds.) McGraw-Hill Book Co., New York, 1972, pp. 545-614].

Hypercholesterolemia is a disease state characterized by levels of serum cholesterol or of LDL cholesterol which are elevated by a clinically significant amount over that considered normal by those of ordinary skill in the art. The identification of those patients who are in need of treatment for hypercholesterolemia is well within the ability and knowledge of one skilled in the art. For example, individuals who have serum cholesterol levels or LDL cholesterol levels, as determined by clinical laboratory tests, which are substantially and chronically elevated over that considered normal by those of ordinary skill in the art, are patients in need of treatment for hypercholesterolemia. By way of further example, individuals who are at risk of developing hypercholesterolemia can also be patients in need of treatment for hypercholesterolemia. 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 suffering from hypercholesterolemia and

those who are at risk of developing hypercholesterolemia and thus readily determine if an individual is a patient in need of treatment for hypercholesterolemia.

An effective hypocholesterolemic amount of a compound of Formula (I) is an amount which is effective in reducing serum cholesterol levels or LDL cholesterol levels in a patient in need thereof. As such, successful treatment of a patient for hypercholesterolemia is understood to include reducing a patient's serum cholesterol or LDL cholesterol levels. Successful treatment for hypercholesterolemia is also understood to include prophylaxis in preventing clinically significant elevations in serum cholesterol or in LDL cholesterol levels in a patient who is at risk of the development of hypercholesterolemia.

Atherosclerosis is a disease state characterized by the development and growth of atherosclerotic lesions or plaque. The identification of those patients who are in need of treatment for atherosclerosis is well within the ability and knowledge of one skilled in the art. For example, individuals who are either suffering from clinically significant atherosclerosis or who are at risk of developing clinically significant atherosclerosis are patients in need of treatment for atherosclerosis. A clinician skilled in the art can readily determine, by the use of clinical tests, physical examination and medical/family history, if an individual is a patient in need of treatment for atherosclerosis.

An effective antiatherosclerotic amount of a compound of Formula (I) is an amount which is effective in inhibiting development or growth of atherosclerosis in a patient in need thereof. As such, successful treatment of a patient for atherosclerosis is understood to include effectively slowing, interrupting, arresting, or stopping atherosclerotic lesion or plaque development or growth and

does not necessarily indicate a total elimination of the atherosclerosis. It is further understood and appreciated by those skilled in the art that successful treatment for atherosclerosis can include prophylaxis in preventing atherosclerotic lesion or plaque formation.

An effective antiatherosclerotic or hypocholesterolemic 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 antiatherosclerotic or hypocholesterolemic amount of a compound of Formula (I) will generally vary from about 1 milligram per kilogram of body weight per day (mg/kg/day) to about 1000 milligrams per kilogram of body weight per day (1.0 gm/kg/day). A daily dose of from about 1 mg/kg to about 200 mg/kg is preferred.

In effecting treatment of a patient, a compound 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 compound 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.

Hypertriglyceridemia is a disease state characterized by levels of plasma triglycerides which are elevated by a clinically significant amount over that considered normal by those of ordinary skill in the art. The identification of those patients who are in need of treatment for hypertriglyceridemia is well within the ability and knowledge of one skilled in the art. For example, individuals who have plasma triglyceride levels, as determined by clinical laboratory tests, which are substantially and chronically elevated over that considered normal by those of ordinary skill in the art, are patients in need of treatment for hypertriglyceridemia. By way of further example, individuals who are at risk of developing hypertriglyceridemia can also represent patients in need of treatment for hypertriglyceridemia. 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 suffering from hypertriglyceridemia and those who are at risk of developing hypertriglyceridemia and thus readily determine if an individual is a patient in need of treatment for hypertriglyceridemia.

An effective hypotriglyceridemic amount of a compound of Formula (1) is an amount which is effective in reducing plasma triglyceride levels in a patient in need thereof. As such, successful treatment of a patient for

hypertriglyceridemia is understood to include reducing a patient's plasma triglyceride levels. Successful treatment for hypertriglyceridemia is also understood to include prophylaxis in preventing clinically significant elevations in plasma triglyceride levels in a patient who is at risk of the development of hypertriglyceridemia.

An effective hypotriglyceridemic 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 hypotriglyceridemic amount of a compound of Formula (1) will generally vary from about 1 milligram per kilogram of body weight per day (mg/kg/day) to about 1000 milligrams per kilogram of body weight per day (1.0 gm/kg/day). A daily dose of from about 1 mg/kg to about 200 mg/kg is preferred.

In effecting treatment of a patient, a compound of Formula (1) 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.

A compound of Formula (1) can be administered in the form of pharmaceutical compositions or medicaments which are made by combining a compound of Formula (1) with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the chosen route of administration, and standard pharmaceutical practice.

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, a compound Formula (1) 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 (1), 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, a compound of Formula (1) 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.

The compounds of Formula (I) can be prepared as described in European Patent Application, Publication Number 0 481 522 A1, published April 22, 1992.

The following example illustrates the utility of the mercaptoacetylamide derivatives of the present invention as hypocholesterolemic, antiatherosclerotic and hypocholesterolemic agents. This example is understood to be illustrative only and is not intended to limit the scope of the present invention in any way.

Example 1

Rabbit Test for Hypocholesterolemic, Antiatherosclerotic and Hypotriglyceridemic Activities

Feed rabbits a high cholesterol (1%) diet for eight weeks, supplementing the diets of certain rabbits with the agent of interest. At the end of eight weeks, sacrifice the rabbits, collect the serum and determine cholesterol and triglyceride levels by standard methods [Hypertension 15:327-331, 1990].

Dissect the aorta of each rabbit from the ascending arch to the iliac bifurcation, clean and prepare for staining with Sudan IV to determine areas of atherosclerotic lesion with the use of image analysis.

Make statistical comparisons between the control and drug-treated groups to determine the activity of the agent of interest.

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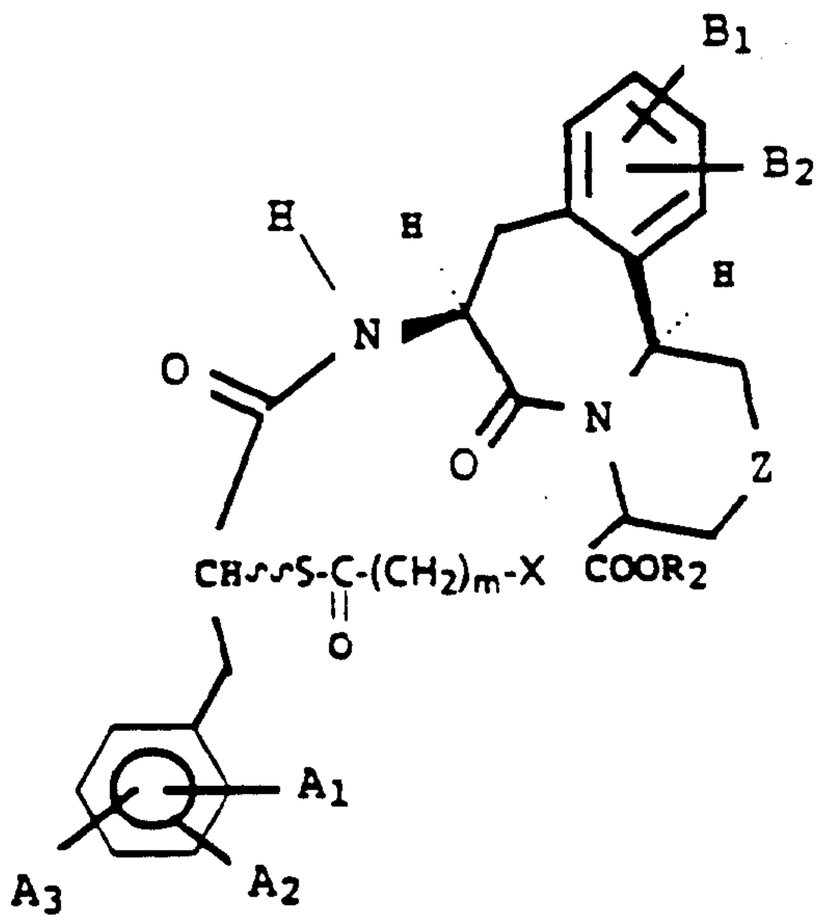
WHAT IS CLAIMED IS:

1. A use of a therapeutically effective hypocholesterolemic amount of a compound of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_1$ wherein R_1 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-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_1, A_2 and A_3 are each independently hydrogen; hydroxy; nitro; amino; fluoro, chloro, $-OR_1$ or an Ar-Y group; or, where A_1 and A_2 are attached to adjacent carbon atoms, A_1 and A_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R_2 is hydrogen, a C_1-C_4 alkyl, an Ar-Y- group or $-CH_2O-C(O)C(CH_3)_3$;

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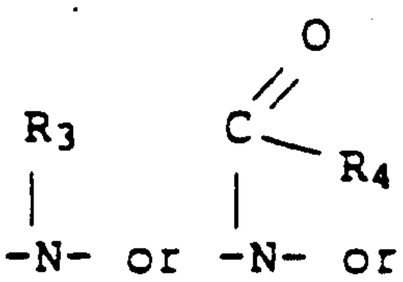
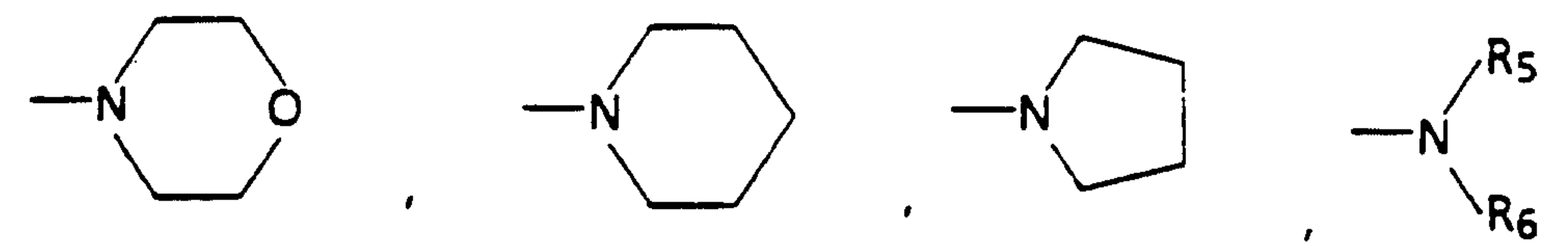


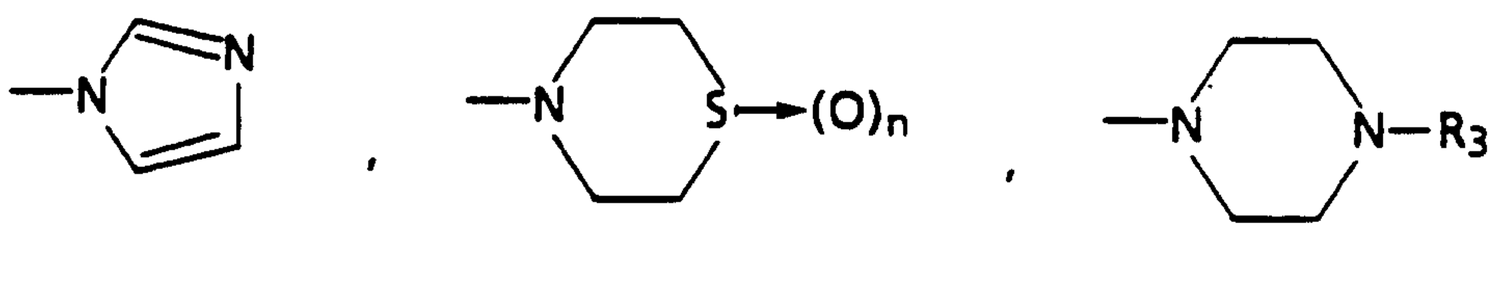
Z is $-CH_2-$, $-O-$, $-S-$, $-N(R_3)-$ or $-N(C(=O)R_4)-$ or a bond

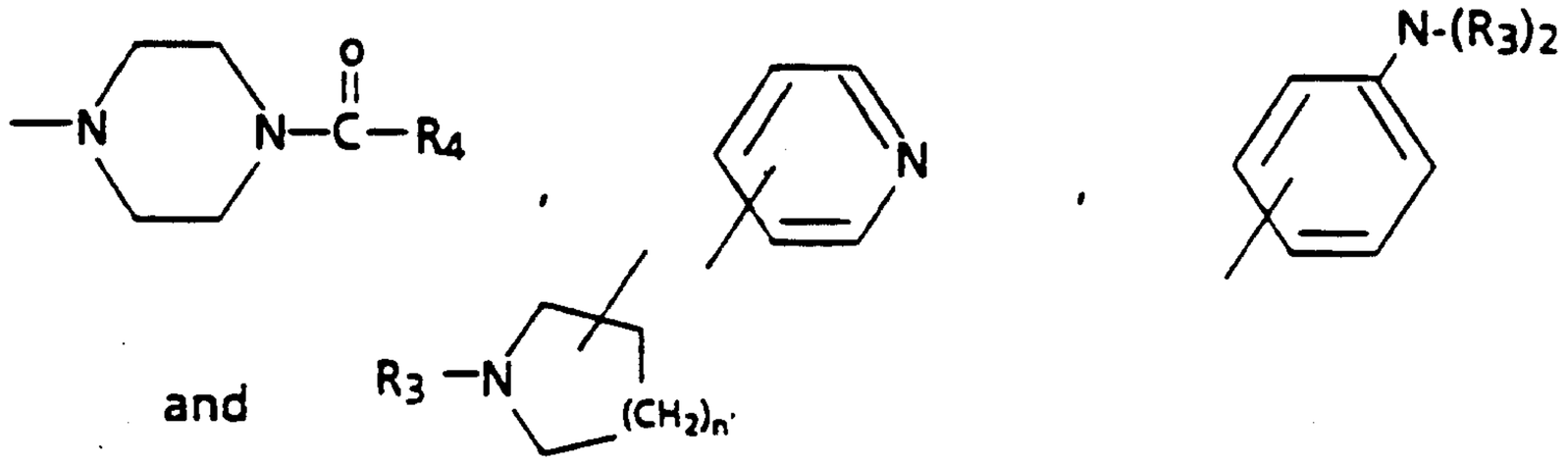
wherein R_3 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_4 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

m is an integer 0 to 5;

X is selected from the group consisting of







and

wherein R_5 and R_6 are each independently a C_1-C_4 alkyl or an Ar-Y- group and n is an integer 0-2; n' is an integer 1-2; and the pharmaceutically acceptable salts thereof;

for lowering total serum cholesterol in a patient in need thereof.

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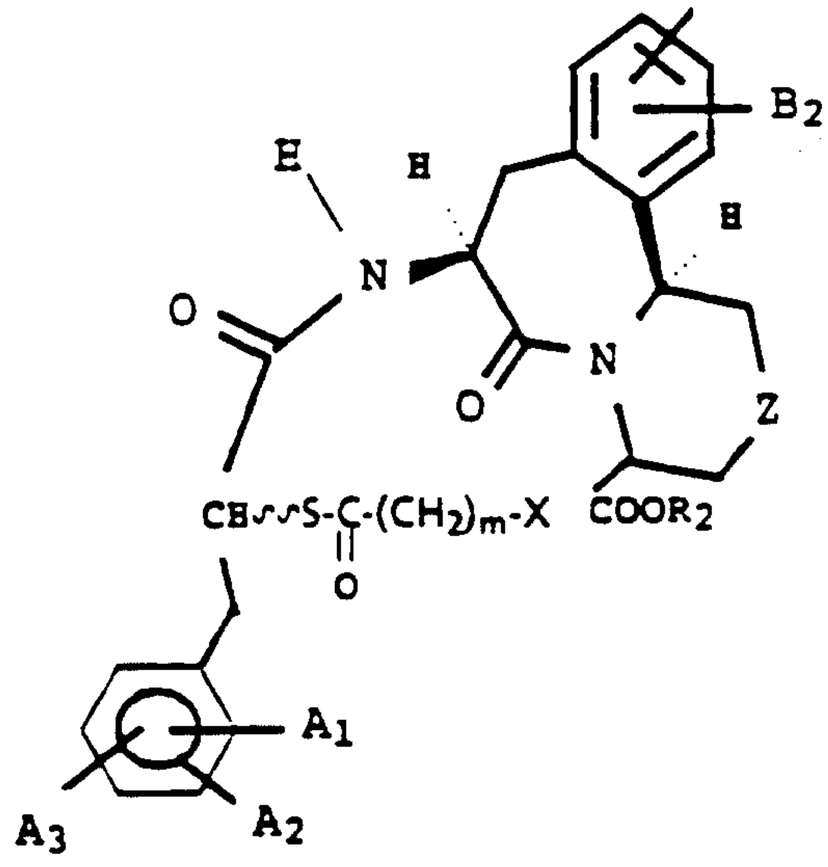
2. A use of a therapeutically effective hypocholesterolemic amount of a compound of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_1$ wherein R_1 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-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_1, A_2 and A_3 are each independently hydrogen; hydroxy; nitro; amino; fluoro, chloro, $-OR_1$ or an Ar-Y group; or, where A_1 and A_2 are attached to adjacent carbon atoms, A_1 and A_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R_2 is hydrogen, a C_1-C_4 alkyl, an Ar-Y- group or $-CH_2O-C(O)C(CH_3)_3$;

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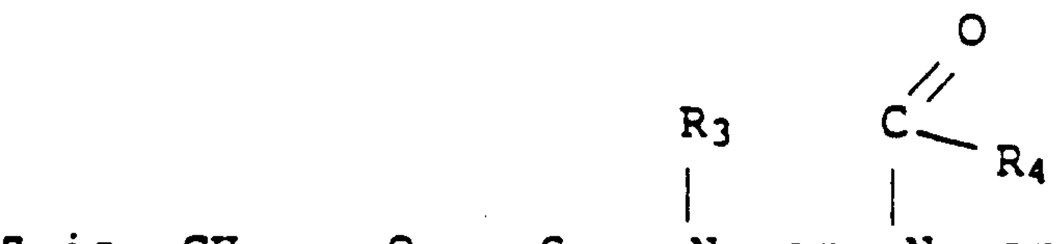
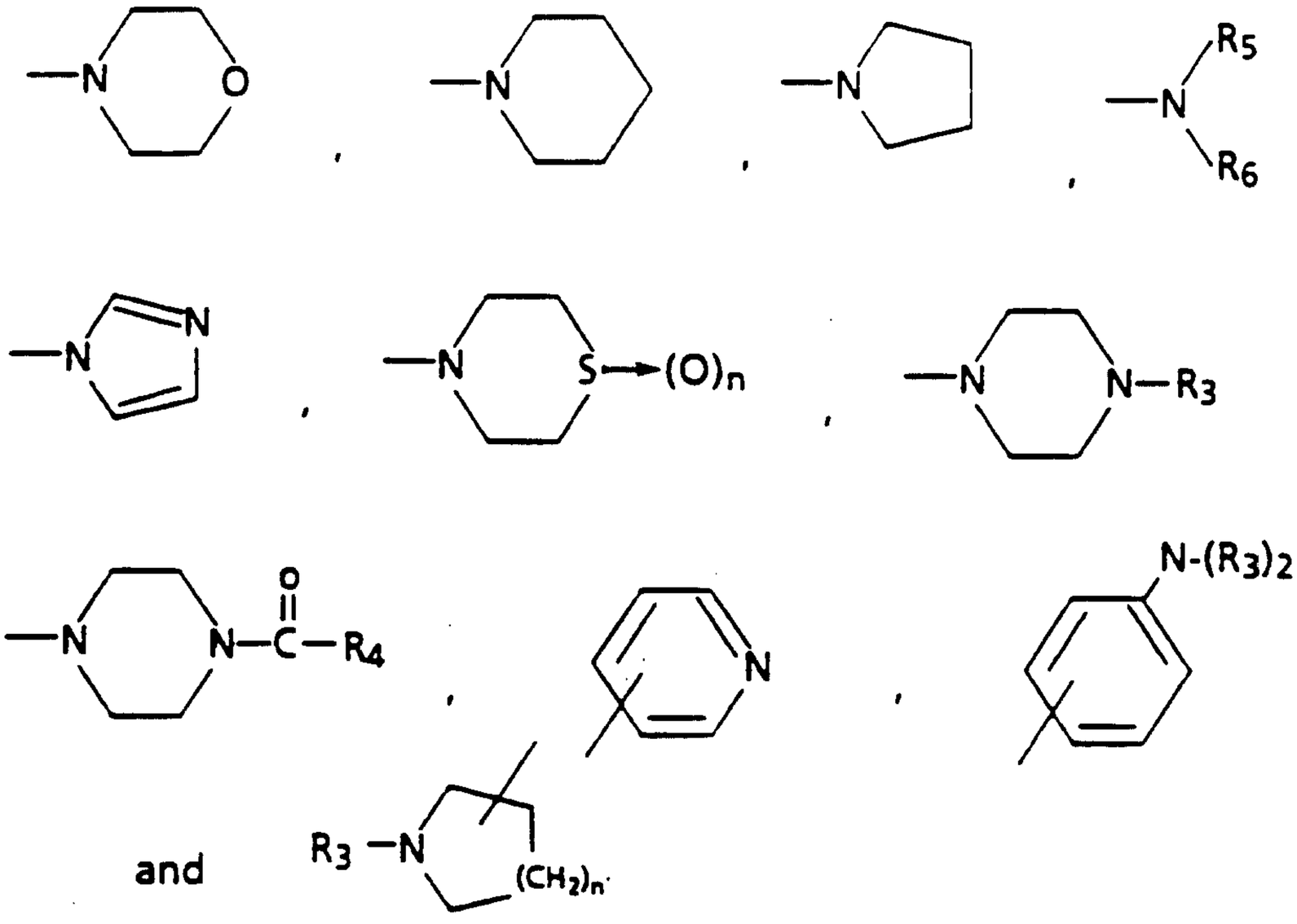


Z is $-CH_2-$, $-O-$, $-S-$, $-N-$ or $-N-$ or a bond

wherein R_3 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_4 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

m is an integer 0 to 5;

X is selected from the group consisting of

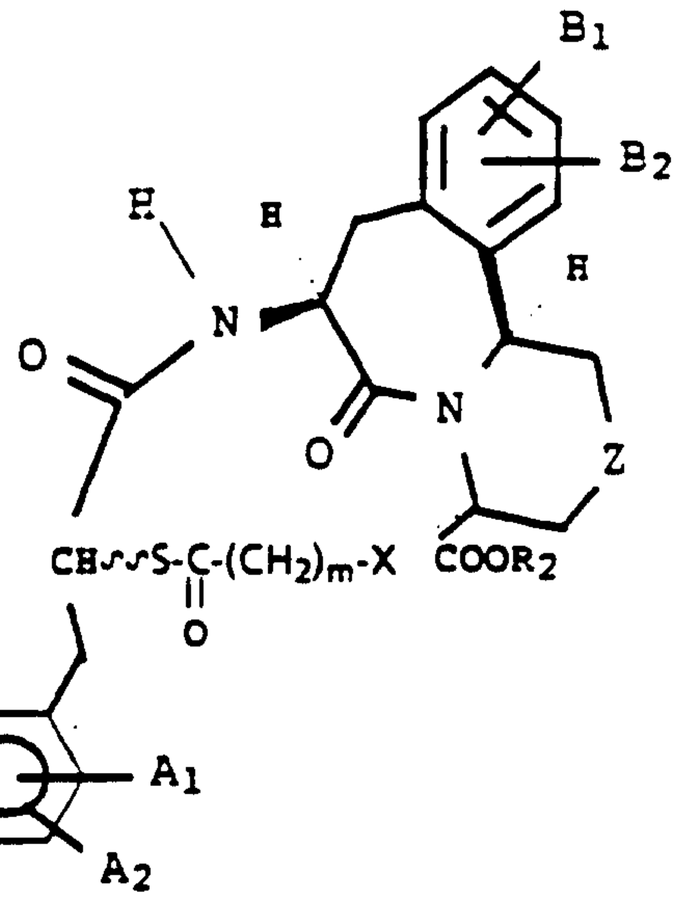


and

wherein R_5 and R_6 are each independently a C_1-C_4 alkyl or an Ar-Y- group and n is an integer 0-2; n' is an integer 1-2; and the pharmaceutically acceptable salts thereof;

for treating a patient for hypercholesterolemia.

3. A use of a therapeutically effective hypotriglyceridemic amount of a compound of the formula

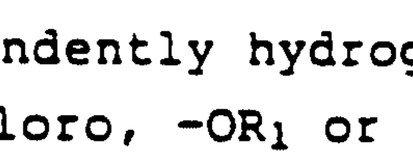


wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_1$ wherein R_1 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-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_1, A_2 and A_3 are each independently hydrogen; hydroxy; nitro; amino; fluoro, chloro, $-OR_1$ or an Ar-Y group; or, where A_1 and A_2 are attached to adjacent carbon atoms, A_1 and A_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R_2 is hydrogen, a C_1-C_4 alkyl, an Ar-Y- group or $-CH_2O-C(O)C(CH_3)_3$;



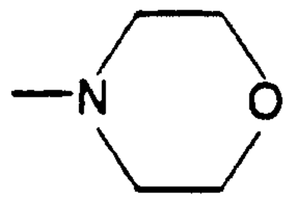
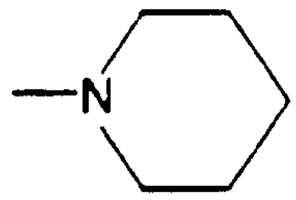
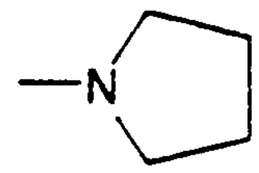
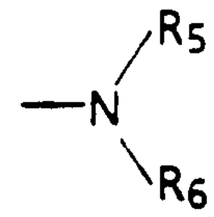
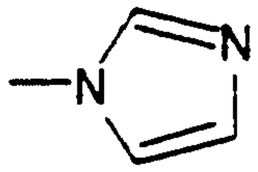
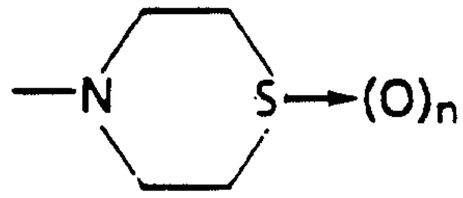
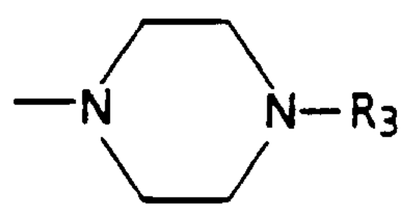
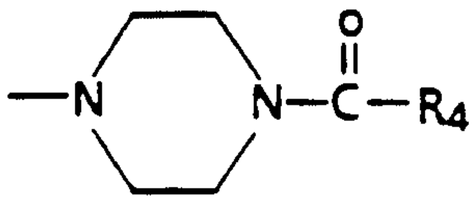
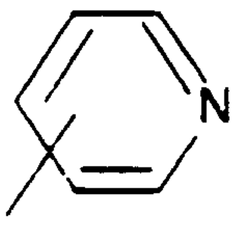
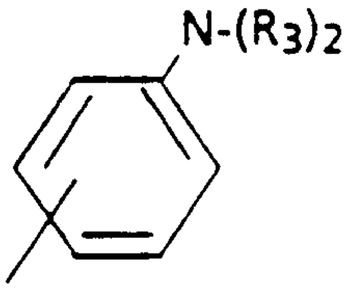
Z is $-CH_2-$, $-O-$, $-S-$, $-N-$ or $-N-$ or a bond

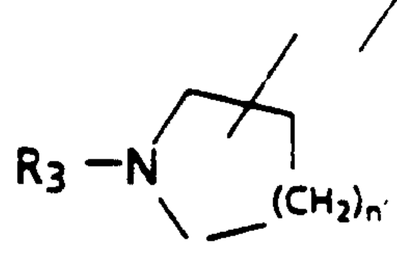
wherein R_3 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_4 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

m is an integer 0 to 5;

A

X is selected from the group consisting of

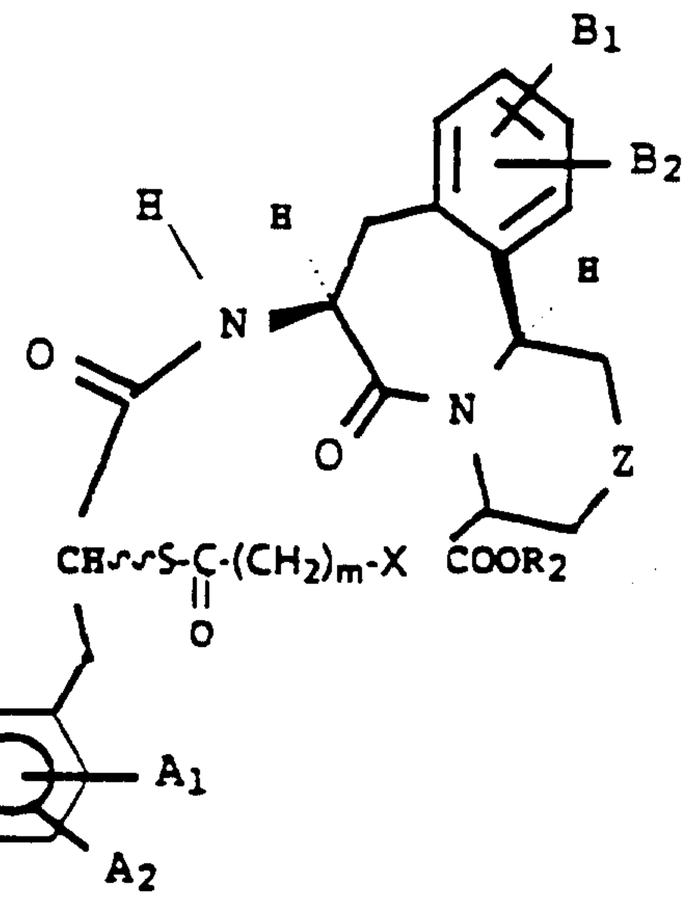
and 

wherein R_5 and R_6 are each independently a C_1-C_4 alkyl or an Ar-Y- group and n is an integer 0-2; n' is an integer 1-2; and the pharmaceutically acceptable salts thereof;

for lowering plasma triglycerides in a patient in need thereof.

4. A use of a therapeutically effective hypotriglyceridemic amount of a compound of the formula

A

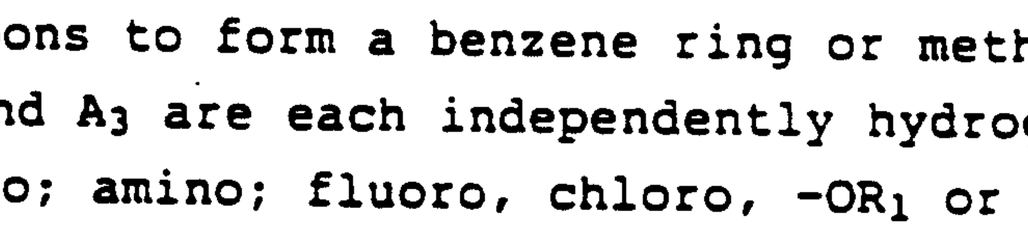


wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_1$ wherein R_1 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-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_1, A_2 and A_3 are each independently hydrogen; hydroxy; nitro; amino; fluoro, chloro, $-OR_1$ or an Ar-Y group; or, where A_1 and A_2 are attached to adjacent carbon atoms, A_1 and A_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R_2 is hydrogen, a C_1-C_4 alkyl, an Ar-Y- group or $-CH_2O-C(O)C(CH_3)_3$;



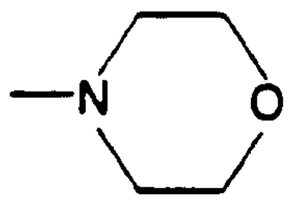
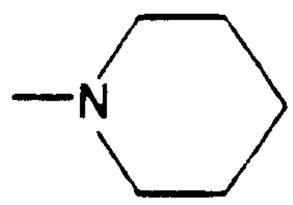
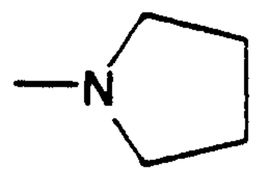
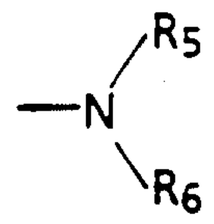
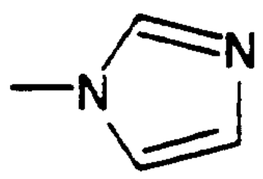
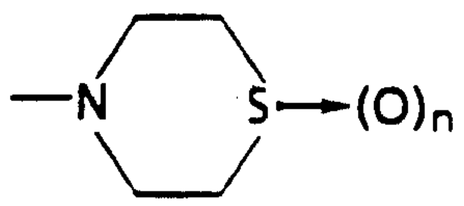
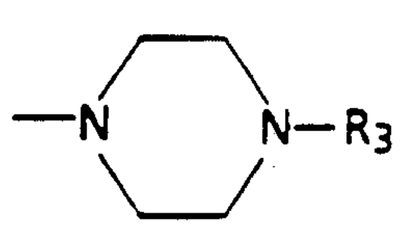
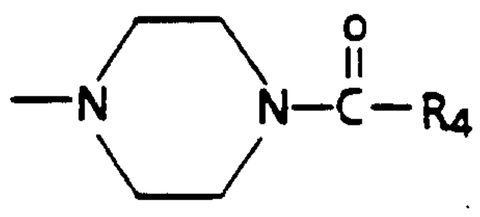
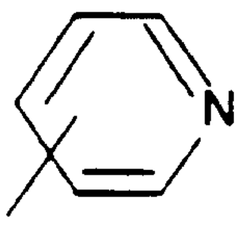
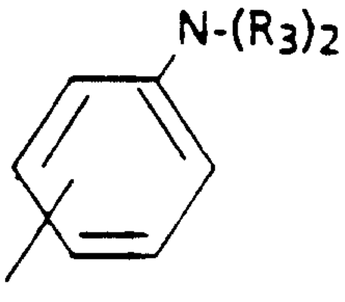
Z is $-CH_2-$, $-O-$, $-S-$, $-N-$ or $-N-$ or a bond

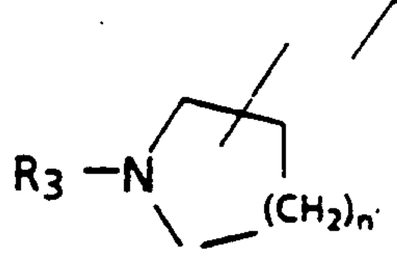
wherein R_3 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_4 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

m is an integer 0 to 5;

A

X is selected from the group consisting of

and 

wherein R_5 and R_6 are each independently a C_1-C_4 alkyl or an Ar-Y- group and n is an integer 0-2; n' is an integer 1-2; and the pharmaceutically acceptable salts thereof;

for treating a patient suffering from hypertriglyceridemia.

5. A use according to any of Claims 1-4 wherein the compound is [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid.

6. A use according to any of Claims 1-4 wherein the compound is [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, maleate salt.

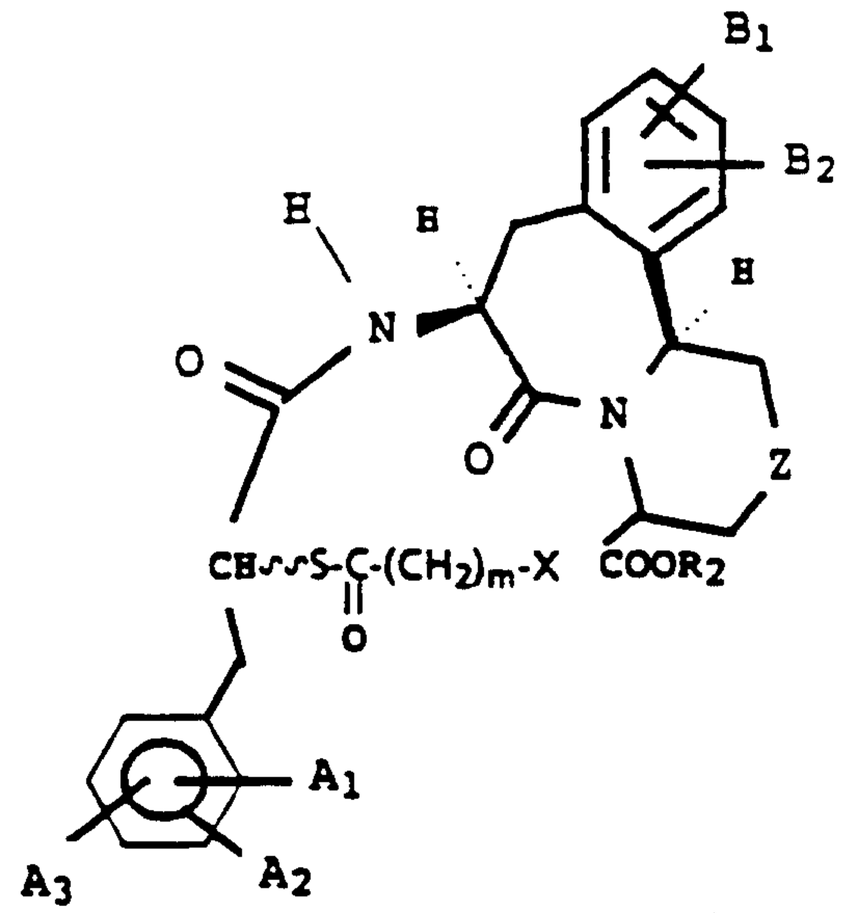
7. A use according to any of Claims 1-4 wherein the compound is [4S-[4α-7α(R*), 12bβ]]-7-[(1-oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-

A

1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, dihydrochloride salt.

8. A use according to any of Claims 1-4 wherein the compound is [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, citrate salt.

9. The use of a compound of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_1$ wherein R_1 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-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_1, A_2 and A_3 are each independently hydrogen; hydroxy; nitro; amino; fluoro, chloro, $-OR_1$ or an Ar-Y group; or, where A_1 and A_2 are attached to adjacent carbon atoms, A_1 and A_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

A

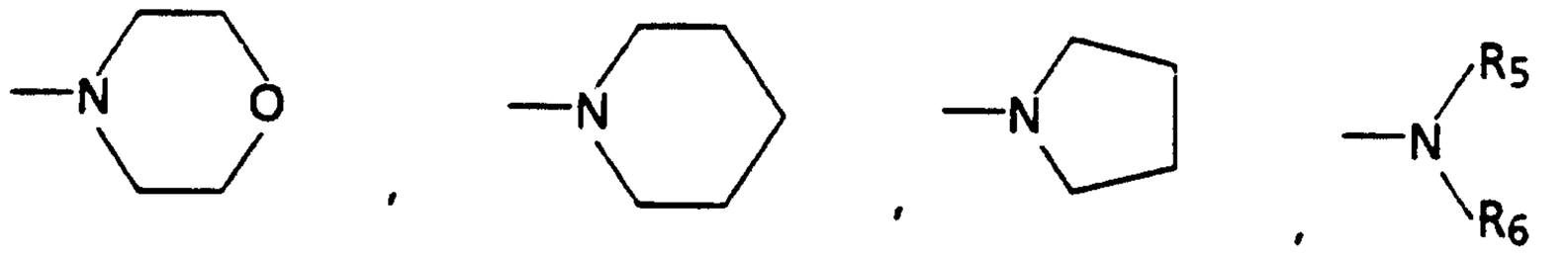
R_2 is hydrogen, a C_1-C_4 alkyl, an Ar-Y- group or $-CH_2O-C(O)C(CH_3)_3$;

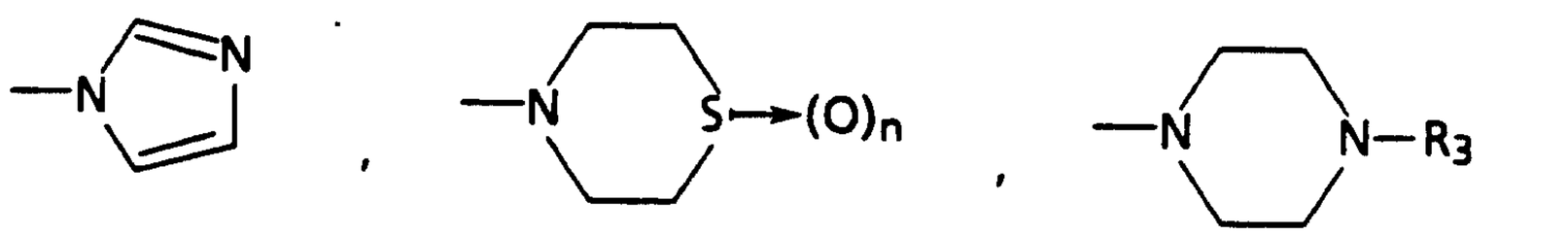
Z is $-CH_2-$, $-O-$, $-S-$, $-N(R_3)-$ or $-N(C(=O)R_4)-$ or a bond

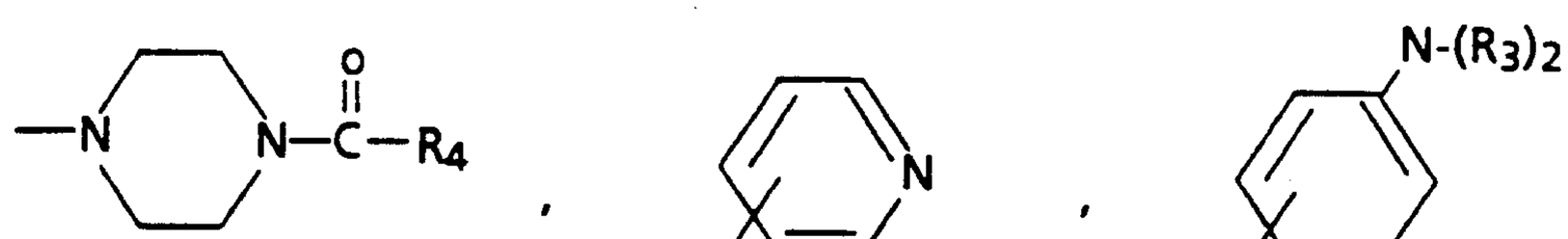
wherein R_3 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_4 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

m is an integer 0 to 5;

X is selected from the group consisting of







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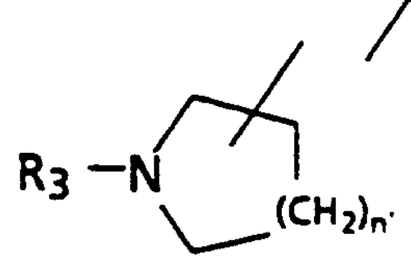
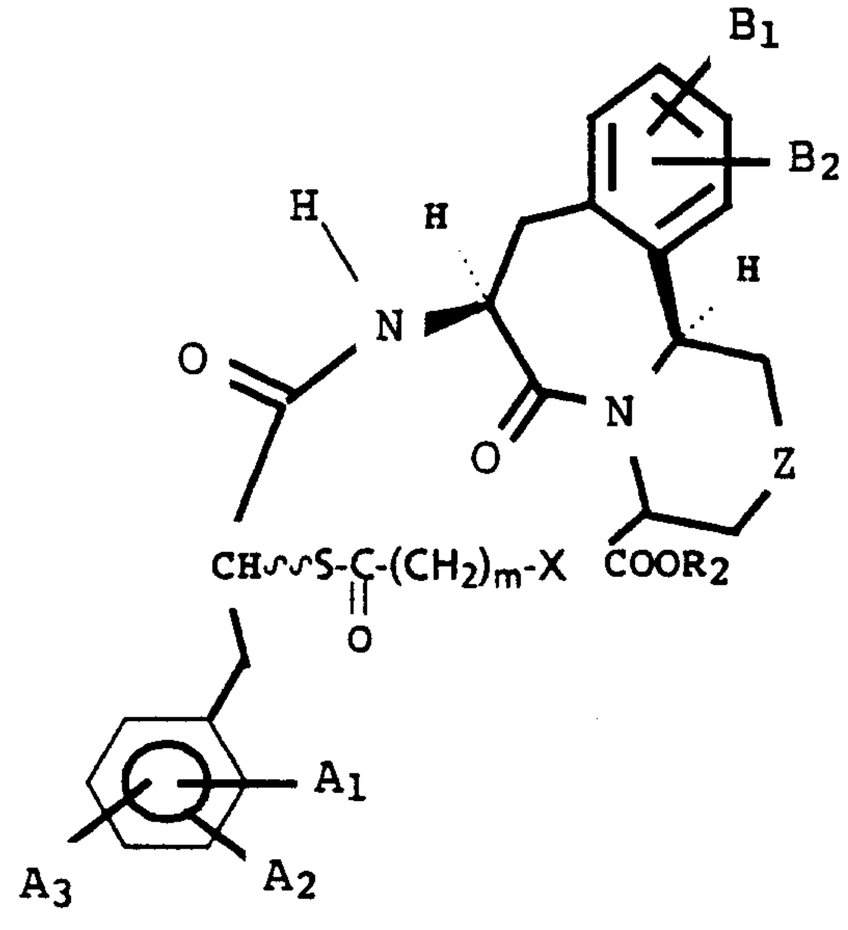


wherein R_5 and R_6 are each independently a C_1-C_4 alkyl or an Ar-Y- group and n is an integer 0-2; n' is an integer 1-2; and the pharmaceutically acceptable salts thereof,

optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a pharmaceutical composition

for the treatment of hypercholesterolemia, hypertriglyceridemia, or atherosclerosis by virtue of the lowering of cholesterol and/or triglycerides.

10. The use of a compound of the formula



wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_1$ wherein R_1 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-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_1, A_2 and A_3 are each independently hydrogen; hydroxy; nitro; amino; fluoro, chloro, $-OR_1$ or an Ar-Y group; or, where A_1 and A_2 are attached to adjacent carbon atoms, A_1 and A_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

R_2 is hydrogen, a C_1-C_4 alkyl, an Ar-Y- group or $-CH_2O-C(O)C(CH_3)_3$;

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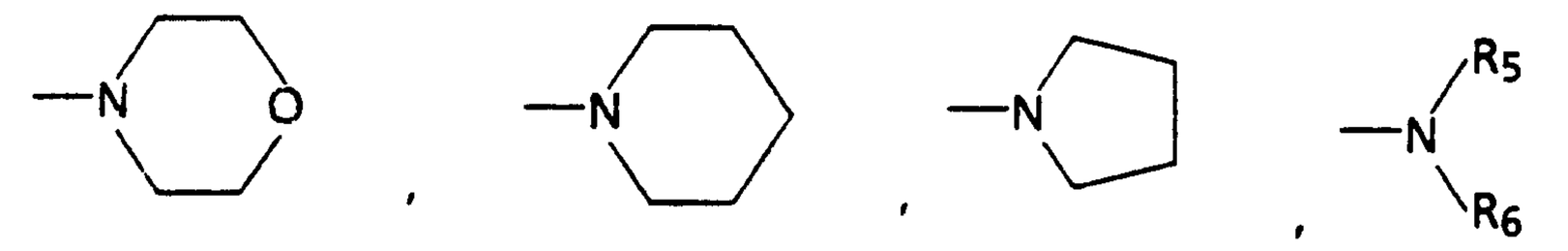
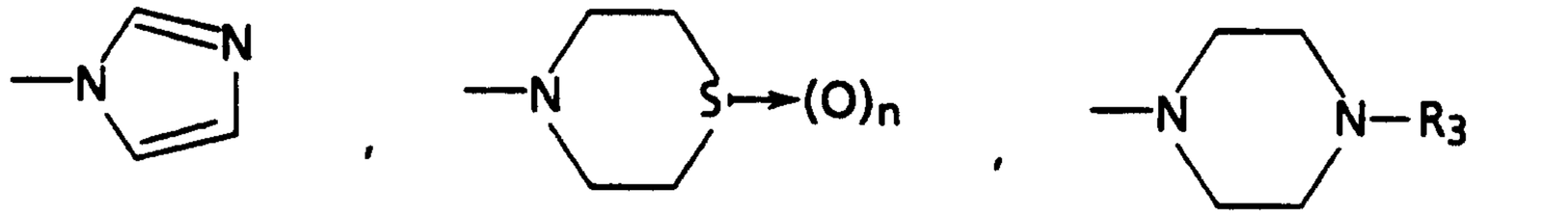
Z is $-CH_2-$, $-O-$, $-S-$, $-N-$ or $-N-$ or a bond

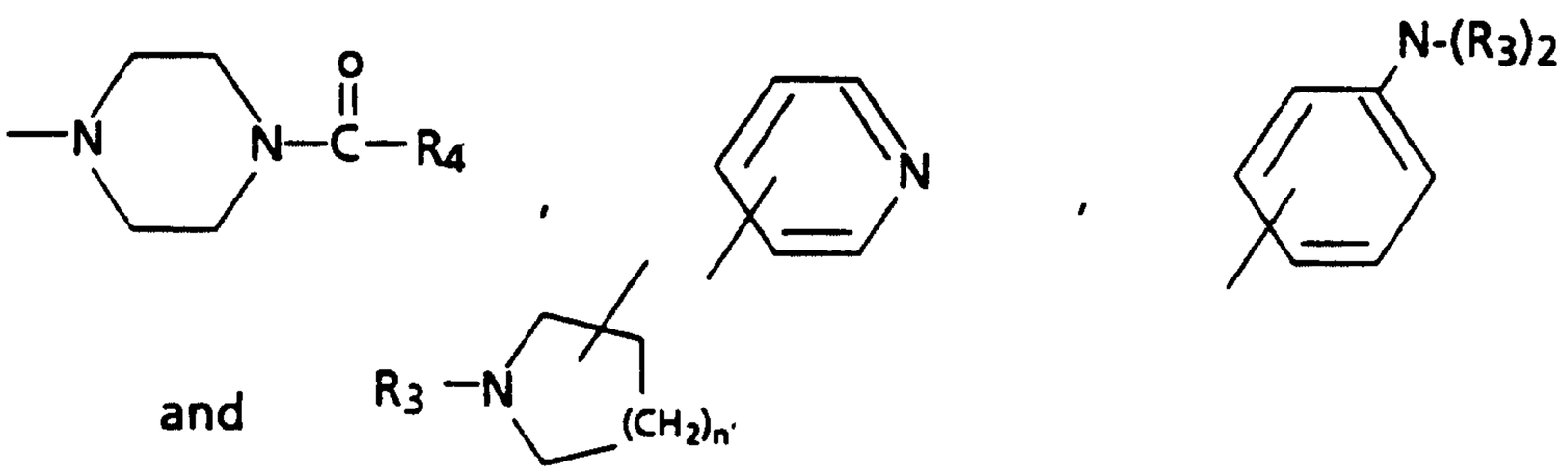
wherein R_3 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_4 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

m is an integer 0 to 5;

X is selected from the group consisting of





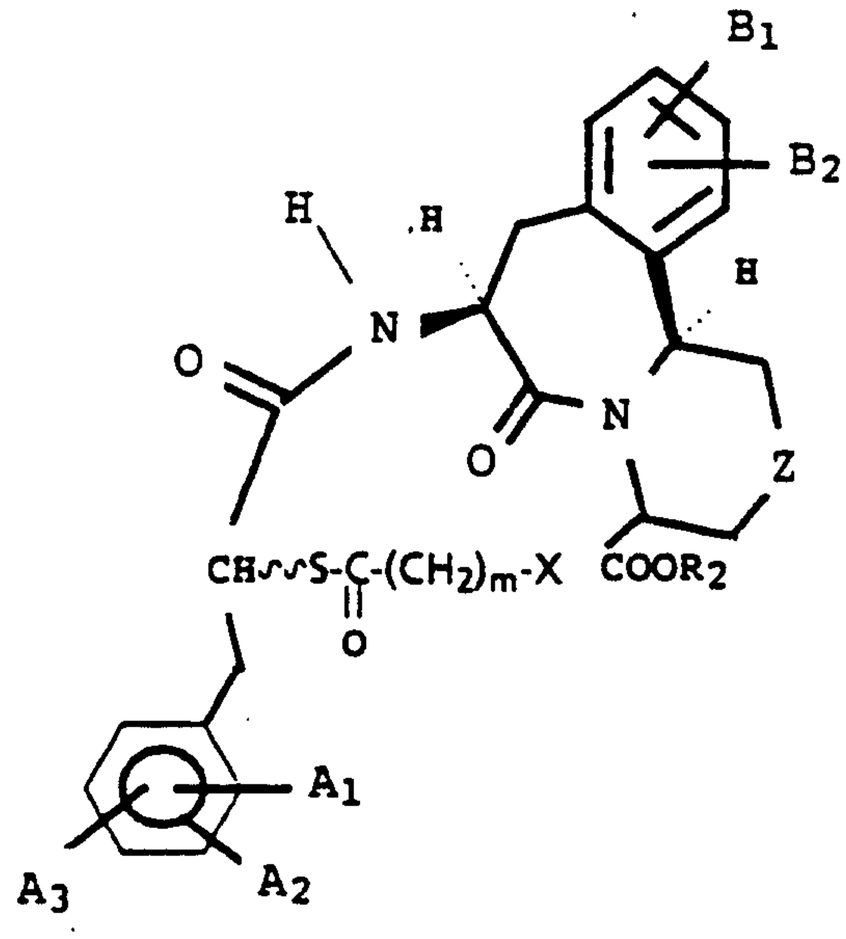


and

wherein R_5 and R_6 are each independently a C_1-C_4 alkyl or an Ar-Y- group and n is an integer 0-2; n' is an integer 1-2; and the pharmaceutically acceptable salts thereof,

optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a plasma triglyceride lowering agent.

11. The use of a compound of the formula

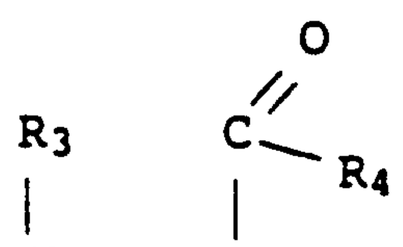


wherein

B_1 and B_2 are each independently hydrogen; hydroxy; $-OR_1$ wherein R_1 is a C_1-C_4 alkyl or an Ar-Y- group wherein Ar is aryl and Y is a C_0-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_1, A_2 and A_3 are each independently hydrogen; hydroxy; nitro; amino; fluoro, chloro, $-OR_1$ or an Ar-Y group; or, where A_1 and A_2 are attached to adjacent carbon atoms, A_1 and A_2 can be taken together with said adjacent carbons to form a benzene ring or methylenedioxy;

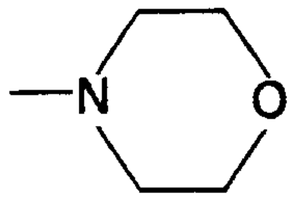
R_2 is hydrogen, a C_1-C_4 alkyl, an Ar-Y- group or $-CH_2O-C(O)C(CH_3)_3$;

Z is $-CH_2-$, $-O-$, $-S-$,  or a bond

wherein R_3 is hydrogen, a C_1-C_4 alkyl or an Ar-Y- group and R_4 is $-CF_3$, a C_1-C_{10} alkyl or an Ar-Y- group;

m is an integer 0 to 5;

X is selected from the group consisting of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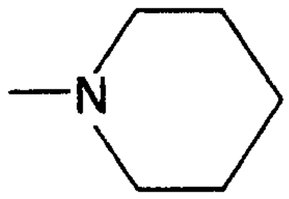
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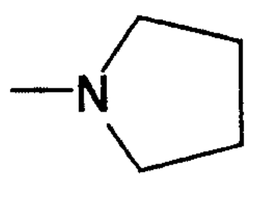
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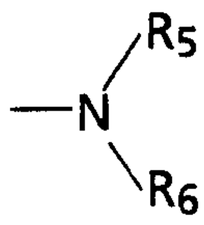
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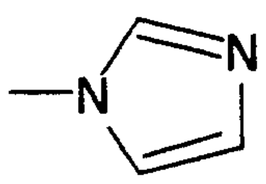
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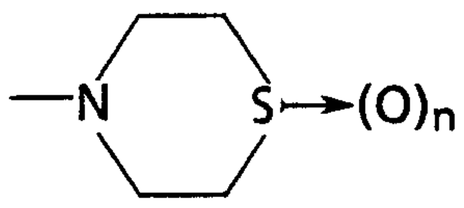
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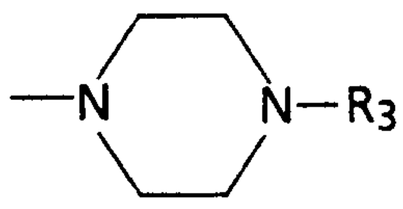
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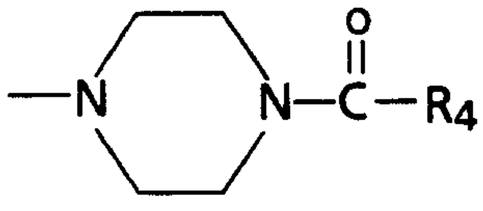
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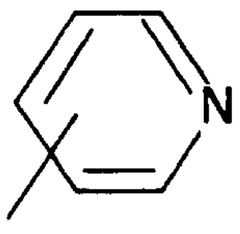
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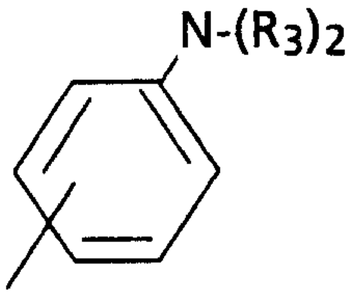
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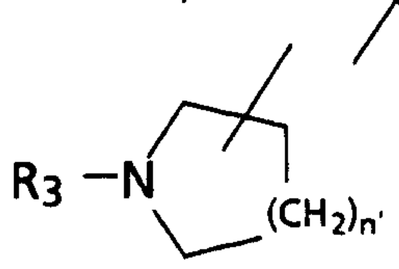

wherein R_5 and R_6 are each independently a C_1-C_4 alkyl or an Ar-Y- group and n is an integer 0-2; n' is an integer 1-2; and the pharmaceutically acceptable salts thereof,

optionally in combination with a pharmaceutically acceptable carrier, for the preparation of a serum cholesterol lowering agent.

12. The use of a compound [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, optionally in combination with a pharmaceutical accpetable carrier, for the preparation of a pharmaceutical composition for the treatment of hypercholesterolemia, hypertriglyceridemia, or

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atherosclerosis by virtue of the lowering of cholesterol and/or triglycerides.

13. The use of a compound [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, maleate salt, optionally in combination with a pharmaceutically accpetable carrier, for the preparation of a pharmaceutical composition for the treatment of hypercholesterolemia, hypertriglyceridemia, or atherosclerosis by virtue of the lowering of cholesterol and/or triglycerides.

14. The use of a compound [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, dihydrochloride salt, optionally in combination with a pharmaceutically accpetable carrier, for the preparation of a pharmaceutical composition for the treatment of hypercholesterolemia, hypertriglyceridemia, or atherosclerosis by virtue of the lowering of cholesterol and/or triglycerides.

15. The use of a compound [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, citrate salt, optionally in combination with a pharmaceutically accpetable carrier, for the preparation of a pharmaceutical composition for the treatment of hypercholesterolemia, hypertriglyceridemia, or atherosclerosis by virtue of the lowering of cholesterol and/or triglycerides.

16. The use of a compound [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, optionally in

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combination with a pharmaceutically accpetable carrier, for the preparation of a plasma triglyceride lowering agent.

17. The use of a compound [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, maleate salt, optionally in combination with a pharmaceutically accpetable carrier, for the preparation of a plasma triglyceride lowering agent.

18. The use of a compound [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, dihydrochloride salt, optionally in combination with a pharmaceutically accpetable carrier, for the preparation of a plasma triglyceride lowering agent.

19. The use of a compound [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, citrate salt, optionally in combination with a pharmaceutically accpetable carrier, for the preparation of a plasma triglyceride lowering agent.

20. The use of a compound of the formula [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, optionally in combination with a pharmaceutically accpetable carrier, for the preparation of a serum cholesterol lowering agent.

21. The use of a compound [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, maleate salt, optionally

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in combination with a pharmaceutically accpetable carrier, for the preparation of a serum cholesterol lowering agent.

22. The use of a compound [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, dihydrochloride salt, optionally in combination with a pharmaceutically accpetable carrier, for the preparation of a serum cholesterol lowering agent.

23. The use of a compound [4S-[4α-7α(R*), 12bβ]]-7-[(1-Oxo-2(S)-(4-morpholino)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, citrate salt, optionally in combination with a pharmaceutically accpetable carrier, for the preparation of a serum cholesterol lowering agent.

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