

INSTRUCTIONS

(a) If Convention application insert "Convention"

(a) CONVENTION

AUSTRALIA

Patents Act

(b) Delete one

APPLICATION FOR A (b) STANDARD/~~PETTY~~ PATENT

(c) Insert FULL name(s) of applicant(s)

I/We (c) E.R. SQUIBB & SONS, INC.

603058

(d) Insert FULL address(es) of applicant(s)

of (d) Lawrenceville-Princeton Road,
Princeton, New Jersey 08543-4000
United States of America

(e) Delete one

hereby apply for the grant of a (e) Standard/~~Petty~~ Patent for an invention entitled

(f) Insert TITLE of invention

(f) 7-OXABICYCLOHEPTANE SUBSTITUTED DIAMIDE AND ITS CONGENER PROSTAGLANDIN ANALOGS

(g) Insert "complete" or "provisional" or "petty patent"

which is described in the accompanying (g) COMPLETE specification.

(Note: The following applies only to Convention applications)

Details of basic application(s)

(h) Insert number, country and filing date for the/or each basic application

	Application No.	Country	Filing Date
(h)	750,948	United States of America	1 July, 1985
	853,788	United States of America	18 April, 1986

LOGGED AT SUB-OFFICE

13 JUN 1986

Address for Service:

PATENT OFFICE

\$860

-- 000190

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

(i) Insert date of signing

Dated (i) 13 June, 1986

(j) Signature of applicant(s) (For body corporate see headnote*)

PHILLIPS ORMONDE & FITZPATRICK
Attorneys for

(j) E.R. SQUIBB & SONS, INC.

By

David B. Fitzpatrick

(k) Corporate seal if any

(k)

Note: No legalization or other witness required

ON ACCEPTED AND AMENDMENTS

APPROVED

15-8-90

PHILLIPS ORMONDE AND FITZPATRICK
Patent and Trade Mark Attorneys
367 Collins Street
Melbourne, Australia

DECLARATION FOR A PATENT APPLICATION

▼ INSTRUCTIONS

(a) Insert "Convention" if applicable
(b) Insert FULL name(s) of applicant(s)

(c) Insert "of addition" if applicable
(d) Insert TITLE of invention

(e) Insert FULL name(s) AND address(es) of declarant(s) (See headnote)

(f) Insert FULL name(s) AND address(es) of actual inventor(s)

(g) Recite how applicant(s) derive(s) title from actual inventor(s) (See headnote)

(h) Insert country, filing date, and basic applicant(s) for the/or EACH basic application

(i) Insert PLACE of signing

(j) Insert DATE of signing

(m) Signature(s) of Declarant(s)

Makes No legalization or other witness required

In support of the (a) convention application made by
(b) E.R. SQUIBB & SONS, INC., a corporation duly organized and existing under the laws of the State of Delaware, United States of America, having its offices at Lawrenceville-Princeton Road, Princeton, New Jersey, United States of America, (hereinafter called "applicant" for a patent (c) for an invention entitled (d)

(e) Insert FULL name(s) AND address(es) of declarant(s) (See headnote)
I Nicholas P. Malatestinic of Princeton, New Jersey, United States of America,

do solemnly and sincerely declare as follows:

1. I am authorized to make this declaration on behalf of the applicant(s).

2. (f) Joyce Ann Reid, H-11 Quincy Circle, Dayton, New Jersey, United States of America
Masami Nakane, 6-28-2C Kawanahonmachi, Showaku Nagoya, Aichi Japan

is/are the actual inventor(s) of the invention and the facts upon which the applicant is entitled to make the application are as follows:

(a) The said E.R. SQUIBB & SONS, INC., is the assignee of the said
Joyce Ann Reid and Masami Nakane by virtue of an assignment dated July 29, 1985

3. The basic application(s) for patent or similar protection on which the application is based is/are identified by country, filing date, and basic applicant(s) as follows:

(h)

In: United States of America on: July 1, 1985

By: Joyce Ann Reid and Masami Nakane

In: United States of America on: April 18, 1986

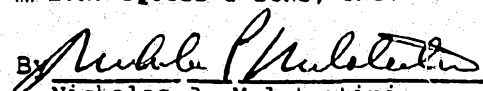
By: Joyce Ann Reid and Masami Nakane

4. The basic application(s) referred to in paragraph 3 hereof was/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at (k) Princeton, New Jersey, U.S.A.

Dated (l) June 2, 1986

(m) E.R. SQUIBB & SONS, INC.

By 
Nicholas P. Malatestinic
Assistant Secretary

To: The Commissioner of Patents

(SEAL)

PHILLIPS ORMONDE & FITZPATRICK

Patent and Trade Mark Attorneys

Melbourne, Australia

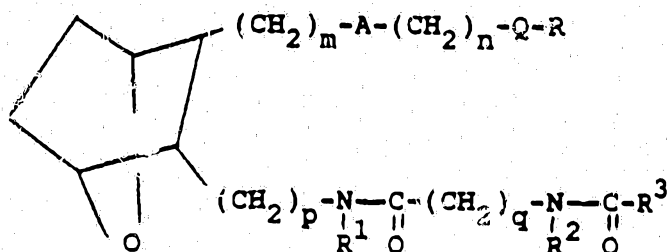
Patent Declaration

No legalization or other witness required

(12) PATENT ABRIDGMENT (11) Document No. AU-B-58715/86
 (19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 603058

- (54) Title
 7-OXABICYCLOHEPTANE SUBSTITUTED DIAMIDE AND ITS CONGENER
 PROSTAGLANDIN ANALOGUES
- International Patent Classification(s)
 (51)⁴ C07D 493/08 A61K 031/34 A61K 031/41
- (21) Application No. : 58715/86 (22) Application Date : 13.05.86
- (30) Priority Data
- (31) Number (32) Date (33) Country
 750948 01.07.85 US UNITED STATES OF AMERICA
 853788 18.04.86 US UNITED STATES OF AMERICA
- (43) Publication Date : 08.01.87
- (44) Publication Date of Accepted Application : 08.11.90
- (71) Applicant(s)
 E.R. SQUIBB & SONS, INC.
- (72) Inventor(s)
 JOYCE ANN REID; MASAMI NAKANÉ
- (74) Attorney or Agent
 PHILLIPS ORMONDE & FITZPATRICK, 367 Collins Street, MELBOURNE VIC 3000
- (56) Prior Art Documents
 AU 60139/86 C07D 493/08
 AU 40781/85 C07D 493/08
 AU 37717/85 C07D 493/08
- (57) Claim

1. A compound having the structure

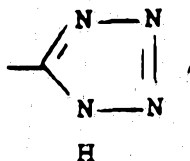


including all stereoisomers thereof, wherein m is 0 to 4; A is -CH=CH- or -CH₂-CH₂-; n is 1 to 5; Q is -CH=CH-,
 $\text{---CH}_2\text{---}$, $\text{---}\overset{\text{OH}}{\underset{|}{\text{CH}}}\text{---}$, $\text{---}\overset{\text{Halo}}{\underset{|}{\text{CH}}}\text{---}$, $\text{---}\overset{\text{Halo}}{\underset{|}{\text{C}}}\text{---}\overset{\text{Halo}}{\underset{|}{\text{C}}}\text{---}$, or a single bond; R is CO₂H, CO₂alkyl, CO₂ alkali metal, CO₂

(11) AU-B-58715/86
(10) 603058

-2-

polyhydroxyamine salt, $-\text{CH}_2\text{OH}$,



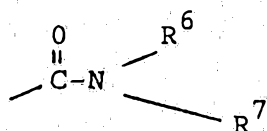
or $\text{C}(\text{O})\text{NR}^4\text{R}^5$ wherein R^4 and R^5 are the same or different and are H, alkyl, hydroxy, alkoxy or aryl, at least one of R^4 and R^5 being other than hydroxy and alkoxy; p is 1 to 4; R^1 is H or alkyl; q is 1 to 12; R^2 is H or alkyl; and R^3 is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, arylalkoxy, aryloxy, amino, alkylamino,

arylamino, arylalkylamino, alkyl-S-, aryl-S-,

arylalkyl-S-, aryl-S-alkyl-, alkyl-S-alkyl-,

arylalkyl-S-alkyl (wherein n is 0, 1 or 2), alkylaminoalkyl, arylaminoalkyl, arylalkylaminoalkyl, alkoxyalkyl, aryloxyalkyl or arylalkoxyalkyl wherein the alkyl groups, as such or as part of another group, contain 1 to 12 carbon atoms and may include a halo-substituent, an alkoxy substituent, an aryl substituent, an alkyl-aryl substituent, a haloaryl substituent, a cycloalkyl substituent, an alkylcycloalkyl substituent, hydroxy, an alkylamino substituent, an alkanoylamino substituent, an arylcarbonylamino substituent, a nitro substituent, a cyano substituent, a thiol substituent or an alkylthio substituent; the cycloalkyl groups, as such or as part of another group, contain 3 to 12 carbon atoms and may be substituted with 1 or 2 halogens, 1 or 2 alkyl groups, 1 or 2 alkoxy groups, 1 or 2 hydroxy groups, 1 or 2 alkylamino groups, 1 or 2 alkanoylamino groups, 1 or 2 arylcarbonylamino groups, 1 or 2 amino groups, 1 or 2 nitro groups, 1 or 2 cyano groups, 1 or 2 thiol groups, and/or 1 or 2 alkylthio groups; the aryl groups, as such or as part of another group, are monocyclic or bicyclic aromatic groups containing 6 to 10 carbon atoms in the ring portion and in the case of phenyl or naphthyl may be substituted with 1 or 2 alkyl

groups, halogens, 1 or 2 alkoxy groups, 1 or 2 hydroxy groups, 1 or 2 alkylamino groups, 1 or 2 alkanoylamino groups, 1 or 2 arylcarbonylamino groups, 1 or 2 amino groups, 1 or 2 nitro groups, 1 or 2 cyano groups, 1 or 2 thiol groups, and/or 1 or 2 alkylthio groups; the alkenyl groups, as such or as part of another group, contain 2 to 12 carbon atoms; the alkynyl groups, as such or as part of another group, contain 2 to 12 carbon atoms; the groups $(CH_2)_m$, $(CH_2)_n$ and $(CH_2)_p$ and contain 0 to 4 carbon atoms in the case of $(CH_2)_m$, 1 to 5 carbon atoms in the case of $(CH_2)_n$, 1 to 4 carbon atoms in the case of $(CH_2)_p$ and may contain one or more alkyl and/or halogen substituents; the group $(CH_2)_q$ contains 1 to 12 carbon atoms and may be substituted by one or more halo, hydroxy, alkoxy, amine, alkylamine, arylamine, amide, thioamide, thiol, alkylthio, arylthio, cyano or nitro groups; the amide group refers to



wherein R^6 and R^7 are independently hydrogen, alkyl or aryl; and polyhydroxyamine salt refers to glucamine salt or tris(hydroxymethyl)aminomethane salt.

29. A method of inhibiting platelet aggregation and/or bronchoconstriction, which comprises administering to the circulatory system of a mammalian host an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

• AUSTRALIA

• *Patents Act*

COMPLETE SPECIFICATION

(ORIGINAL)

Class

Int. Class

Application Number: 58 715/86.

Lodged:

60 30 58

Complete Specification Lodged:

Accepted:

Published:

Priority

Related Art:

This document contains amendments made under Section 49 and is correct for printing

APPLICANT'S REF: V-750,948-S

Name(s) of Applicant(s): E.R. SQUIBB & SONS, INC.

Address(es) of Applicant(s): Lawrenceville-Princeton Road,
Princeton, New Jersey 08543-4000,
United States of America

Actual Inventor(s): JOYCE ANN REID
and
MASAMI NAKANE

Address for Service is:

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

Complete Specification for the invention entitled:

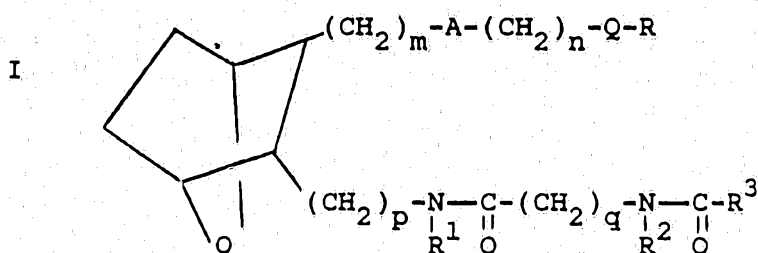
7-OXABICYCLOHEPTANE SUBSTITUTED DIAMIDE AND ITS CONGENER
PROSTAGLANDIN ANALOGS

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

-1^a-

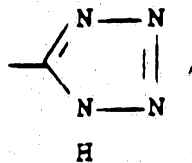
7-OXABICYCLOHEPTANE SUBSTITUTED DIAMIDE
AND ITS CONGENER PROSTAGLANDIN ANALOGS

The present invention relates to 7-oxabi-
 cycloheptane substituted diamide and congener
 prostaglandin analogs which are cardiovascular
 agents useful, for example, in the treatment of
 thrombotic disease. These compounds have the
 structural formula



including all stereoisomers thereof, wherein m is
 0 to 4; A is ---CH=CH--- or $\text{---CH}_2\text{---CH}_2\text{---}$; n is 1 to 5; Q
 is ---CH=CH--- , $\text{---CH}_2\text{---}$, $\text{---}\overset{\text{OH}}{\underset{|}{\text{CH}}}\text{---}$, $\text{---}\overset{\text{Halo}}{\underset{|}{\text{CH}}}\text{---}$, $\text{---}\overset{\text{Halo}}{\underset{|}{\text{C}}}\text{---}$, or a
 single bond; R is CO_2H , CO_2alkyl , $\text{CO}_2\text{ alkali}$

metal, CO₂polyhydroxyamine salt, -CH₂OH,

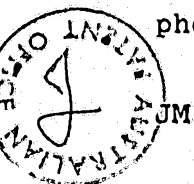


or CNR^4R^5 wherein R^4 and R^5 are the same or different and are H, alkyl, hydroxy, alkoxy or aryl, at least one of R^4 and R^5 being other than hydroxy and alkoxy; p is 1 to 4; R^1 is H or alkyl; q is 1 to 12; R^2 is H or alkyl; and R^3 is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, arylalkoxy, aryloxy, amino, alkylamino,

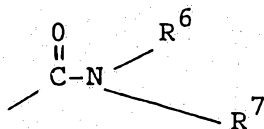
arylamino, arylalkylamino, alkyl-S-, aryl-S-,

arylalkyl-S-, aryl-S-alkyl-, alkyl-S-alkyl-,

arylalkyl-S-alkyl (wherein n' is 0, 1 or 2), alkylaminoalkyl, arylaminoalkyl, arylalkylaminoalkyl, alkoxyalkyl, aryloxyalkyl or arylalkoxyalkyl wherein the alkyl groups, as such or as part of another group, contain 1 to 12 carbon atoms and may include a halo-substituent, an alkoxy substituent, an aryl substituent, an alkyl-aryl substituent, a haloaryl substituent, a cycloalkyl substituent, an alkylcycloalkyl substituent, hydroxy, an alkylamino substituent, an alkanoylamino substituent, an arylcarbonylamino substituent, a nitro substituent, a cyano substituent, a thiol substituent or an alkylthio substituent; the cycloalkyl groups, as such or as part of another group, contain 3 to 12 carbon atoms and may be substituted with 1 or 2 halogens, 1 or 2 alkyl groups, 1 or 2 alkoxy groups, 1 or 2 hydroxy groups, 1 or 2 alkylamino groups, 1 or 2 alkanoylamino groups, 1 or 2 arylcarbonylamino groups, 1 or 2 amino groups, 1 or 2 nitro groups, 1 or 2 cyano groups, 1 or 2 thiol groups, and/or 1 or 2 alkylthio groups; the aryl groups, as such or as part of another group, are monocyclic or bicyclic aromatic groups containing 6 to 10 carbon atoms in the ring portion and in the case of phenyl or naphthyl may be substituted with 1 or 2 alkyl

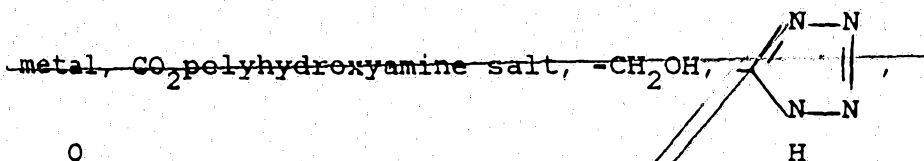


groups, halogens, 1 or 2 alkoxy groups, 1 or 2 hydroxy groups, 1 or 2 alkylamino groups, 1 or 2 alkanoylamino groups, 1 or 2 arylcarbonylamino groups, 1 or 2 amino groups, 1 or 2 nitro groups, 1 or 2 cyano groups, 1 or 2 thiol groups, and/or 1 or 2 alkylthio groups; the alkenyl groups, as such or as part of another group, contain 2 to 12 carbon atoms; the alkynyl groups, as such or as part of another group, contain 2 to 12 carbon atoms; the groups $(CH_2)_m$, $(CH_2)_n$ and $(CH_2)_p$ and contain 0 to 4 carbon atoms in the case of $(CH_2)_m$, 1 to 5 carbon atoms in the case of $(CH_2)_n$, 1 to 4 carbon atoms in the case of $(CH_2)_p$ and may contain one or more alkyl and/or halogen substituents; the group $(CH_2)_q$ contains 1 to 12 carbon atoms and may be substituted by one or more halo, hydroxy, alkoxy, amine, alkylamine, arylamine, amide, thioamide, thiol, alkylthio, arylthio, cyano or nitro groups; the amide group refers to



wherein R^6 and R^7 are independently hydrogen, alkyl or aryl; and polyhydroxyamine salt refers to glucamine salt or tris(hydroxymethyl)aminomethane salt.





- 5 or CNR^4R^5 wherein R^4 and R^5 are the same or different and are H, lower alkyl, hydroxy, lower alkoxy or aryl at least one of R^4 and R^5 being other than hydroxy and lower alkoxy; p is 1 to 4; R^1 is H or lower alkyl; q is 1 to 12; R^2 is H or
- 10 lower alkyl; and R^3 is H, lower alkyl, lower alkenyl, lower alkynyl, aryl, arylalkyl, lower alkoxy, arylalkyloxy, aryloxy, amino, alkylamino, arylalkylamino, arylamino, lower alkyl-S-, aryl-S-,
- 15 arylalkyl-S-, aryl-S-alkyl-, alkyl-S-alkyl-, arylalkyl-S-alkyl (wherein n' is 0, 1 or 2), alkylaminoalkyl, arylaminoalkyl, arylalkylamino-
- 20 ~~alkyl, alkoxyalkyl, aryloxyalkyl or arylalkoxyalkyl.~~

- The term "lower alkyl" or "alkyl" as employed herein alone or as part of another group ~~includes~~ means both straight and branched chain carbons, containing 1 to 12 carbons in the normal chain, preferably
- 25 1 to 7 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the
- 30 like as well as such groups including a halo-substituent, such as F, Br, Cl or I or CF_3 , an alkoxy substituent, an aryl substituent, an alkyl-aryl substituent, a haloaryl substituent, a cycloalkyl substituent, an alkylcycloalkyl substituent,
- 35 hydroxy, and alkylamino substituent, an

alkanoylamino substituent, an arylcarbonylamino substituent, a nitro substituent, a cyano substituent, a thiol substituent or an alkylthio substituent.

5 The term "cycloalkyl" as employed herein alone or as part of another group ~~includes~~ means saturated cyclic hydrocarbon groups containing 3 to 12 carbons, preferably 3 to 8 carbons, which include cyclopropyl, cyclobutyl, cyclopentyl, 10 cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, any of which groups may be substituted with 1 or 2 halogens, 1 or 2 lower alkyl groups 1 or 2 lower alkoxy groups. 1 or 2 hydroxy groups, 1 or 2 alkylamino groups, 1 or 2 alkanoyl- 15 amino groups, 1 or 2 arylcarbonylamino groups, 1 or 2 amino groups, 1 or 2 nitro groups, 1 or 2 cyano groups, 1 or 2 thiol groups and/or 1 or 2 alkylthio groups.

20 The term "aryl" or "Ar" as employed herein refers to monocyclic or bicyclic aromatic groups containing from 6 to 10 carbons in the ring portion, such as phenyl, naphthyl, substituted phenyl or substituted naphthyl wherein the 25 substituent on either the phenyl or naphthyl may be 1 or 2 lower alkyl groups, halogens (Cl, Br or F), 1 or 2 lower alkoxy groups, 1 or 2 hydroxy groups, 1 or 2 alkylamino groups, 1 or 2 alkanoyl- amino groups, 1 or 2 arylcarbonylamino groups, 1 or 2 amino groups, 1 or 2 nitro groups, 1 or 2 cyano 30 groups, 1 or 2 thiol groups, and/or 1 or 2 alkylthio groups.

 The term "aralkyl", "aryl-alkyl" or "aryl-lower alkyl" as used herein alone or as part of another group refers to lower alkyl groups as



discussed above having an aryl substituent, such as benzyl.

The term "lower alkoxy", "alkoxy", or "aryloxy" or "aralkoxy" as employed herein alone or as part of another group ^{means} includes any of the above lower alkyl, alkyl, aralkyl or aryl groups linked to an oxygen atom.

The term "lower alkylthio", "alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group ^{means} includes any of the above lower alkyl, alkyl, aralkyl or aryl groups linked to a sulfur atom.

The term "lower alkylamino", "alkylamino", "arylamino", "arylalkylamino" as employed herein alone or as part of another group ^{means} includes any of the above lower alkyl, alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

The term "alkanoyl" as used herein as part of another group refers to lower alkyl linked to a carbonyl group.

The term "lower alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 12 carbons, preferably 2 to 6 carbons in the normal chain, which include one double bond in the normal chain, such as 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl and the like.

The term "lower alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 12 carbons, preferably 2 to 6 carbons in the normal chain, which include one triple bond in the normal



chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like.

The terms $(CH_2)_m$, $(CH_2)_n$ and $(CH_2)_p$ ^{refer to} ~~includes~~ straight or branched chain radicals having from 0 to 4 carbons in the normal chain in the case of $(CH_2)_m$, from 1 to 5 carbons in the normal chain in the case of $(CH_2)_n$ and from 1 to 4 carbons in the normal chain in the case of $(CH_2)_p$ and may contain one or more lower alkyl and/or halogen substituents. Examples of $(CH_2)_m$, $(CH_2)_n$ and $(CH_2)_p$

groups include CH_2 , $\begin{array}{c} CH_3 \\ | \\ CH- \end{array}$, $\begin{array}{c} CH_3 \\ | \\ -CH- \end{array}$, $\begin{array}{c} CH_3 \\ | \\ -C- \end{array}$, $(CH_2)_2-\begin{array}{c} CH_3 \\ | \\ -C- \end{array}$, CH_2CH_2 , $\begin{array}{c} CH_3 \\ | \\ -CH_2CH- \end{array}$, $\begin{array}{c} CH_3 \\ | \\ -CH_2CH- \end{array}$, $\begin{array}{c} CH_3 \\ | \\ -CHCH_2- \end{array}$, $\begin{array}{c} CH_3 \\ | \\ -CHCH_2- \end{array}$, $\begin{array}{c} CH_3 \\ | \\ -CHCH- \end{array}$

$\begin{array}{c} CH_3 \\ | \\ -C-CH_2- \end{array}$, $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$, $-(CH_2)-\begin{array}{c} F \\ | \\ -C- \\ | \\ F \end{array}$

$\begin{array}{c} Cl \\ | \\ -CH_2-CH- \end{array}$, $-(CH_2)_2-\begin{array}{c} CH_3 \\ | \\ -CH- \end{array}$, $\begin{array}{c} CH_3 \\ | \\ -CH_2-C- \end{array}$, $\begin{array}{c} CH_3 \\ | \\ -CH_2-CH-CH-CH_2- \end{array}$, $\begin{array}{c} CH_3 \\ | \\ -CH_2-CH-CH_2-CH- \end{array}$, and the like.

The term $(CH_2)_q$ ^{refers to} ~~includes~~ straight or branched chain radicals having from 1 to 12 carbons in the normal chain and includes any of the above examples of $(CH_2)_m$, $(CH_2)_n$ and $(CH_2)_p$ groups as well as $(CH_2)_6$, $(CH_2)_7$, $(CH_2)_8$, $(CH_2)_9$, $(CH_2)_{10}$, $(CH_2)_{11}$, $(CH_2)_{12}$, and may be unsubstituted or substituted by one or more halo, hydroxy,

alkoxy, amine, alkylamine, arylamine, amide, thioamide, thiol, alkylthio, arylthio, cyano or nitro groups.

5 The term "amide" refers to the group $\begin{array}{c} \text{O} \\ \parallel \\ \text{CN} \end{array} \begin{array}{l} \text{R}^6 \\ \text{R}^7 \end{array}$

wherein R^6 and R^7 are independently hydrogen, lower alkyl or aryl.

10 The term "polyhydroxyamine salt" refers to glucamine salt or tris(hydroxymethyl)aminomethane.

The term "halogen" or "halo" as used herein refers to chlorine, bromine, fluorine, iodine and CF_3 , with chlorine or fluorine being preferred.

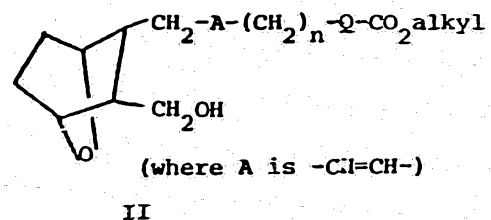
15 Preferred are those compounds of formula I wherein m is 1 or 2, A is a $-\text{CH}=\text{CH}-$, n is 1 or 4,

20 Q is a single bond or $-\text{C}(\text{F}_2)-$, $\begin{array}{c} \text{OH} \\ | \\ -\text{CH}- \end{array}$, $(\text{CH}_2)_2$, or $-\text{CH}=\text{CH}$, R is CO_2H or CH_2OH ; p is 1, R^1 is H, $(\text{CH}_2)_q$ is $-\text{CH}_2-$; R^2 is H or CH_3 , and R^3 is lower alkyl, such as pentyl, hexyl, or heptyl or lower alkoxy, such as pentoxy, lower alkylamino such as pentylamino or arylthioalkyl, such as phenylthiomethyl.

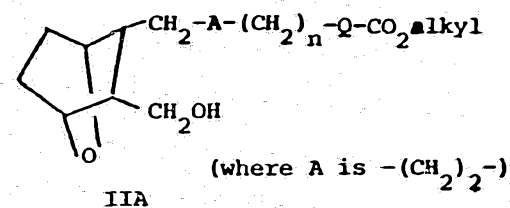
25 The compounds of formula I of the invention may be prepared as described below.

13 8 8 58713

A. p is 1, m is 1, Q is $-\text{CH}_2-$ or a single bond and R^1 is H

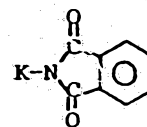
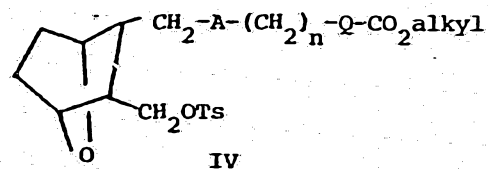


Reduction
 $\xrightarrow{\text{H}_2/\text{Pd/C}}$

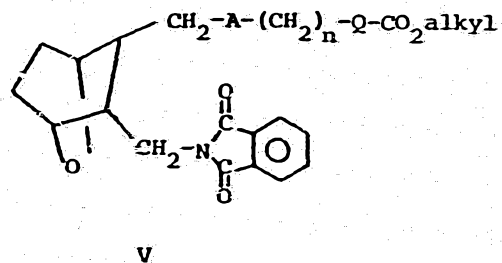


II
or
IIA

Tosylation
 $\xrightarrow{\text{TsCl/pyridine}}$



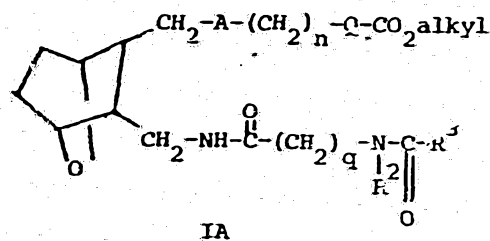
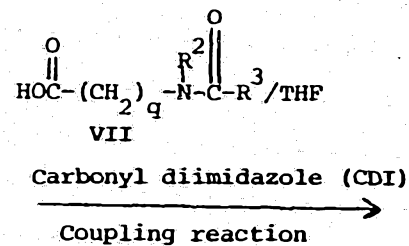
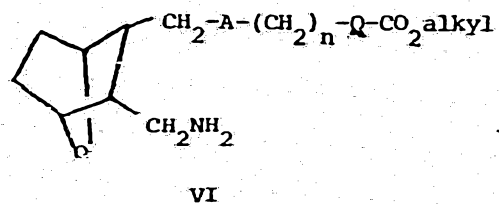
Displacement reaction
 $\xrightarrow{\text{DMSO } 90-100^\circ\text{C}}$



HA356 a

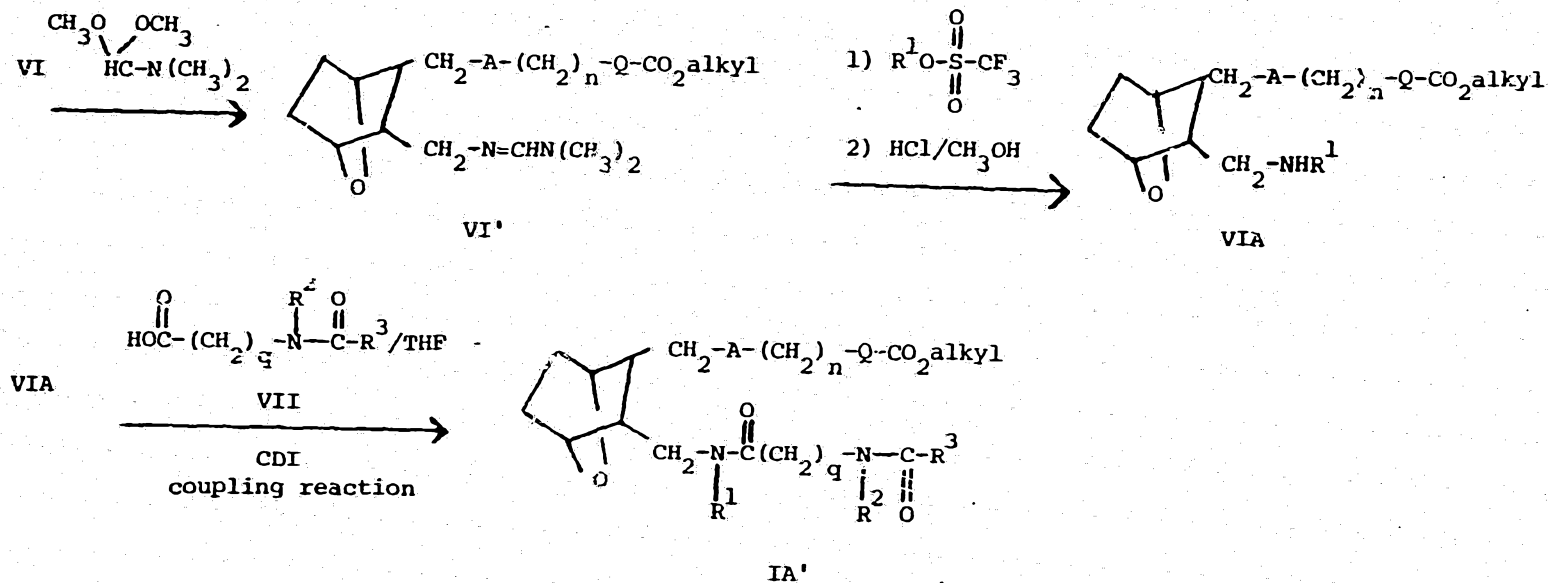
12 8 15 0018

V
Selective
Hydrolysis
 $\xrightarrow[\text{C}_2\text{H}_5\text{OH/CH}_2\text{Cl}_2]{\text{H}_2\text{NNH}_2}$



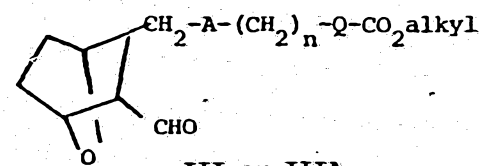
13 8 88 50715

A'. Where p is 1, m is 1, Q is -CH₂- or a single bond and R¹ is alkyl



B. Where Q is CH₂ or a single bond, p is 2 to 5, m is 1 and R¹ is H

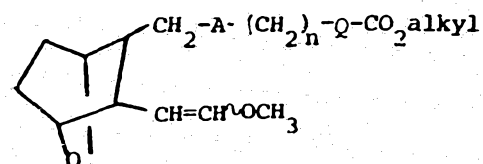
II
or
IIA
Collins oxidation
→



III (where A is -CH=CH-)

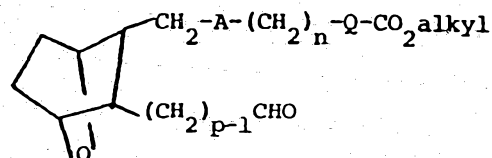
IIIA (where A is -(CH₂)₂-)

Wittig
→
(C₆H₅)₃P=CHCCH₃



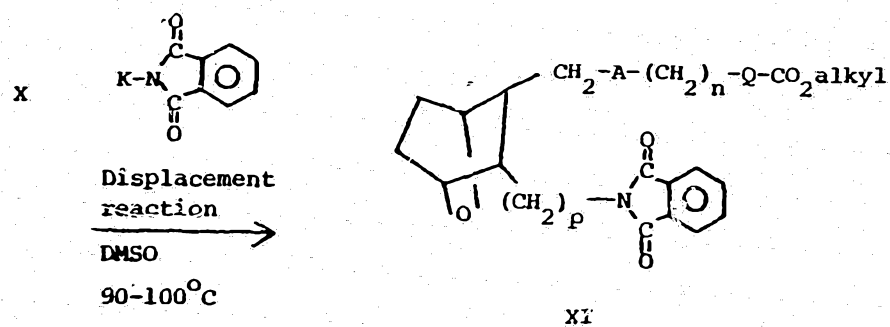
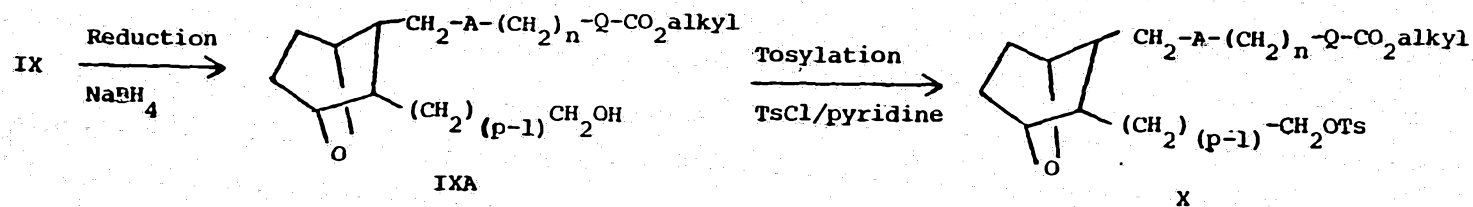
VIII

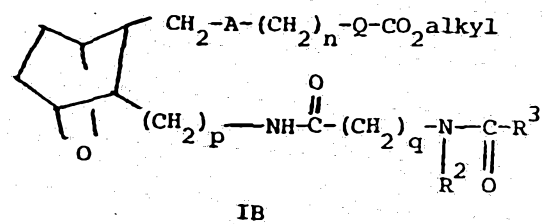
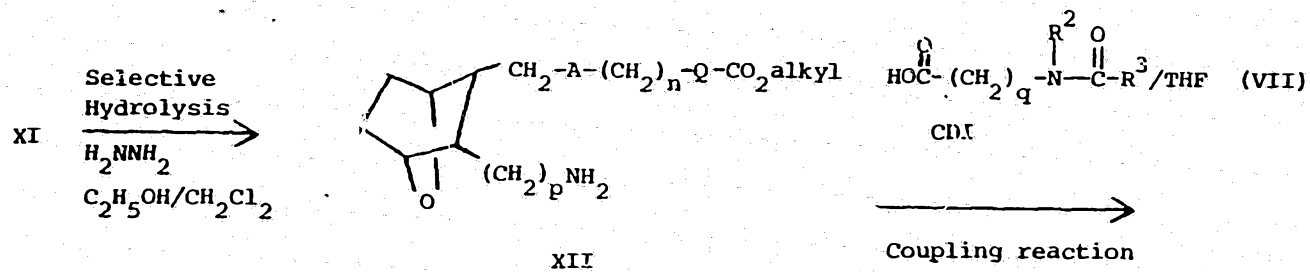
H₃O⁺
→



(repeat
p-1 times)

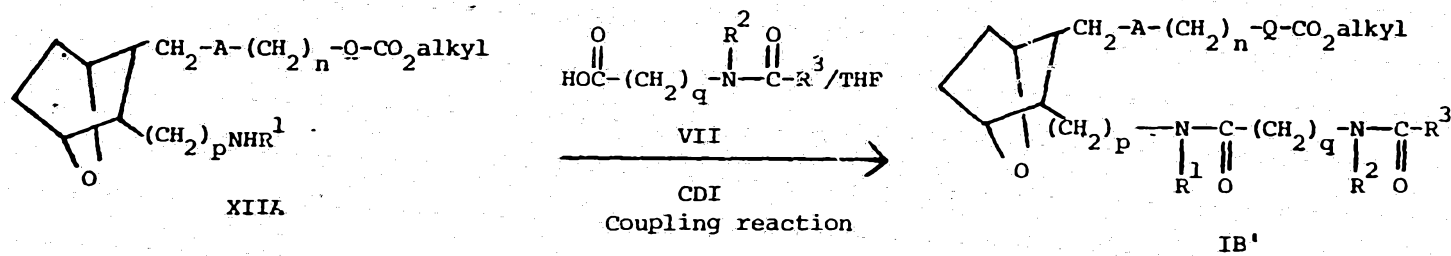
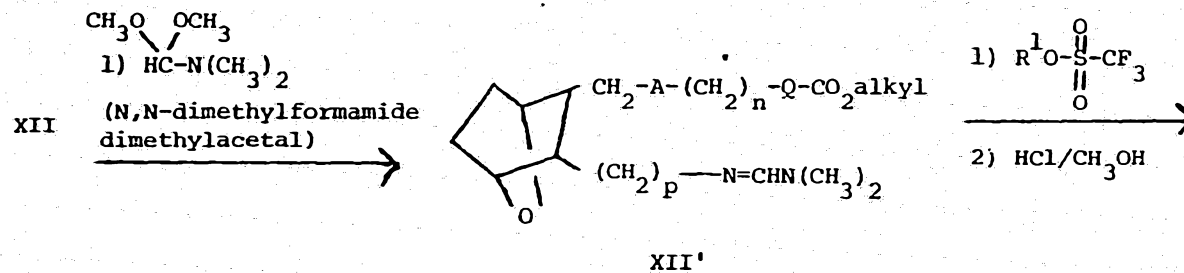
13 006 50715





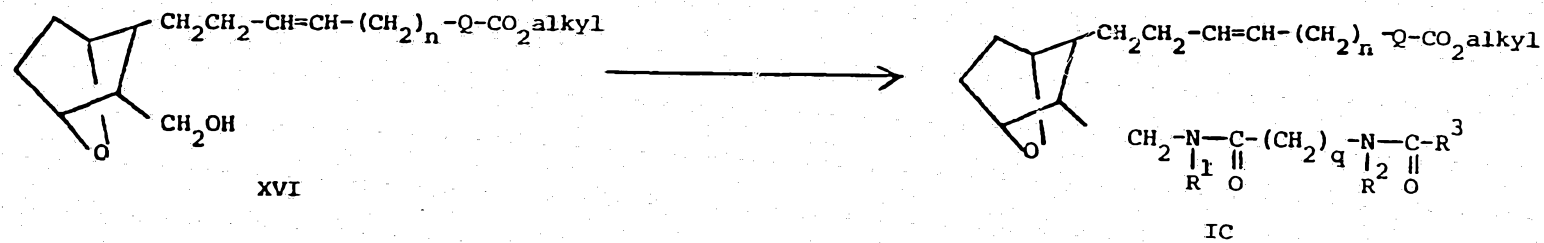
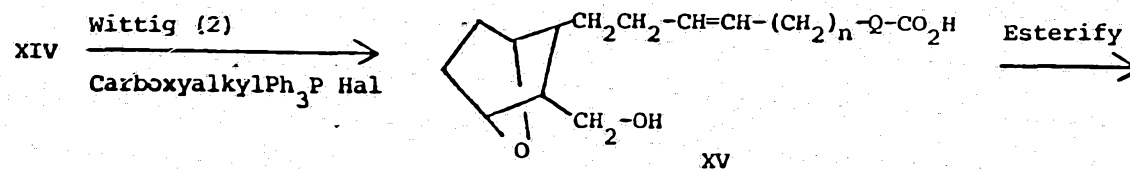
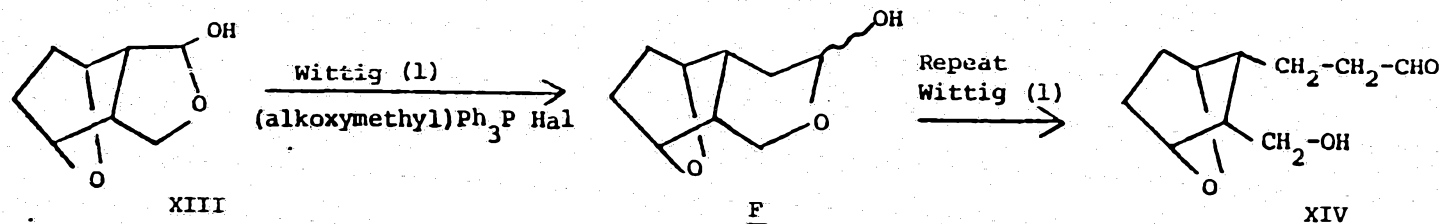
13 6 88 50715

B'. Where Q is CH₂ or a single bond, p is 2 to 5, m is 1 and R¹ is alkyl



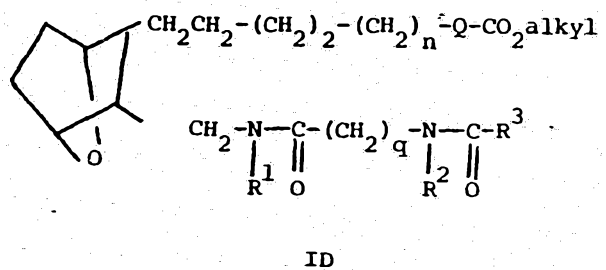
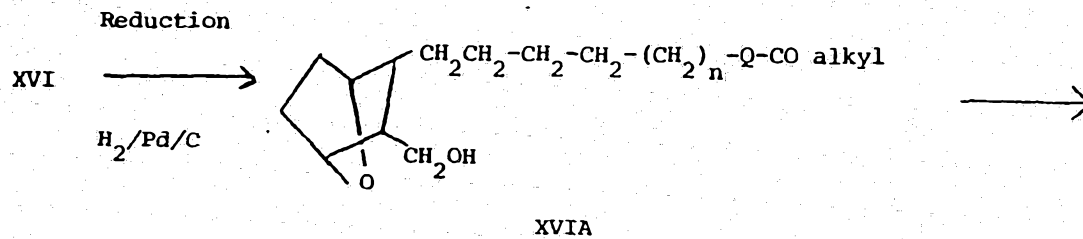
13 0 05 50715

C₂ Where m is 2, p is 1, A is -CH=CH- and Q is CH₂ or a single bond



13 0 00 50715

D. m is 2, p is 1, A is $-\text{CH}_2-\text{CH}_2-$ and Q is CH_2 or a single bond

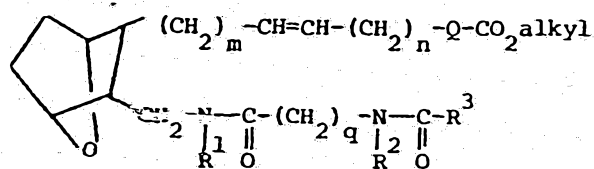
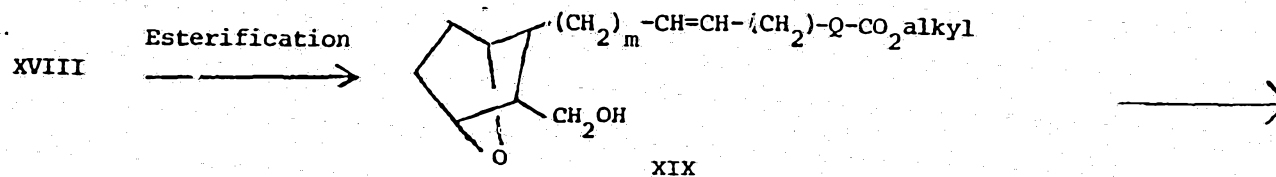
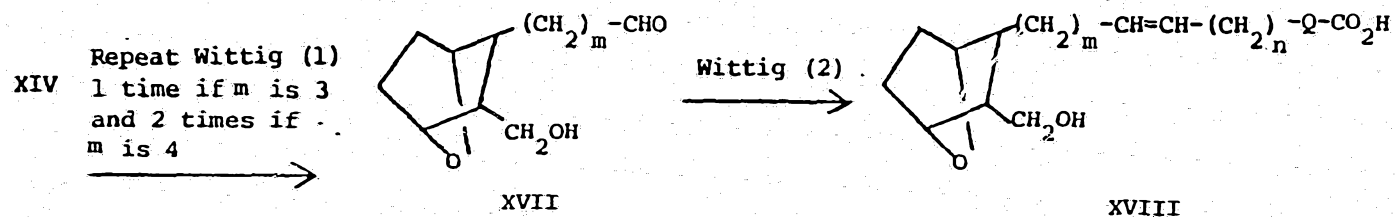


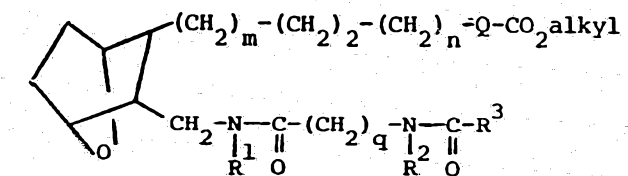
- 15 -

HA356a

13 5 88 50715

E. Where m is 3 or 4, p is 1, A is $-\text{CH}=\text{CH}-$ and Q is CH_2 or a single bond

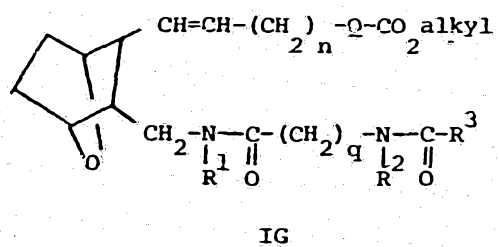
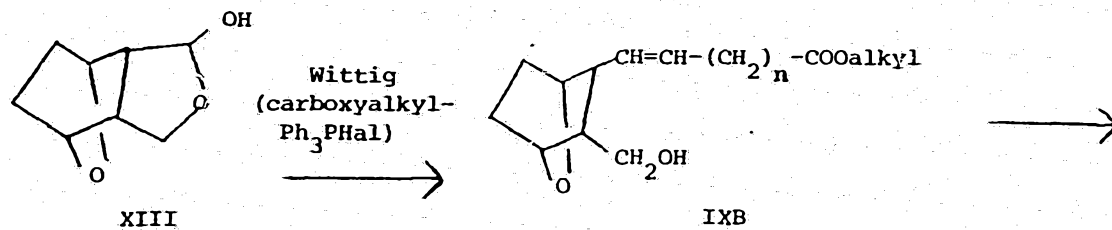




- 17 -

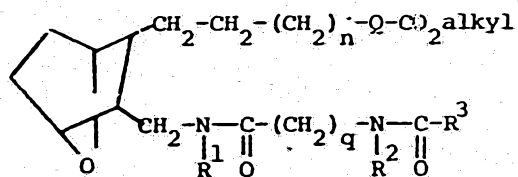
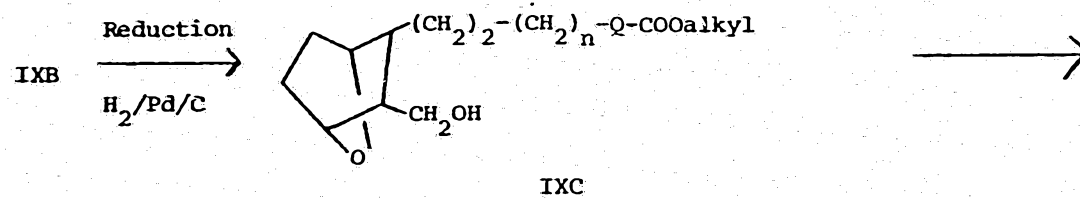
HA356 a

G. Where $m=0$, A is $-\text{CH}=\text{CH}-$, p is 1, Q is CH_2 or a single bond



13 0 00 50713

H. Where $m=0$, A is $-(CH_2)_2-$, p is 1, Q is CH_2 or a single bond



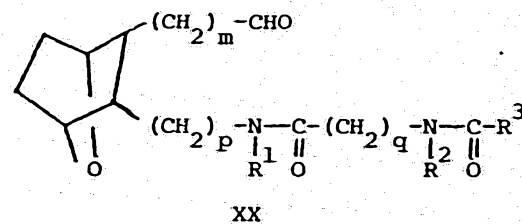
IH

13 000 50715

I. Where Q is -CH=CH-

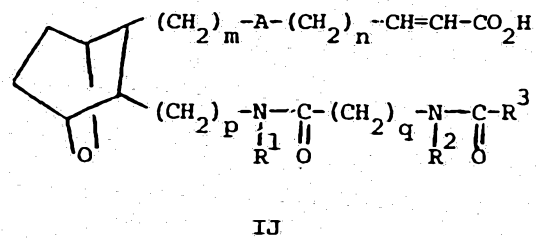
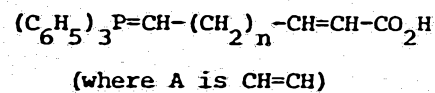
IA,
IB,
IC,
IE,
IG

Ozonolysis
→
O₃



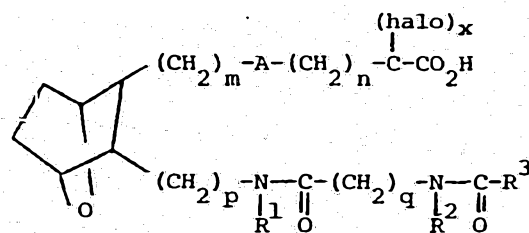
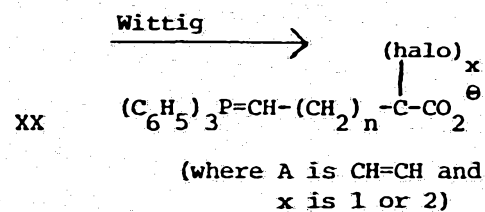
Wittig

XX



13 006 50715

J. Where Q is $\begin{array}{c} \text{halo} \\ | \\ -\text{CH}- \end{array}$ or $\begin{array}{c} \text{halo} \quad \text{halo} \\ \diagdown \quad \diagup \\ -\text{C}- \end{array}$

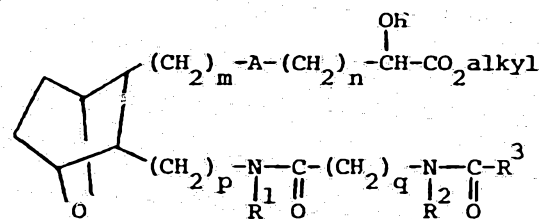
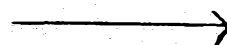


13 8 86 50715

K. Where Q is $\begin{array}{c} \text{OH} \\ | \\ -\text{CH}- \end{array}$

IA,
IB,
IC,
ID,
IE,
IF,
IG,
IH

- 1) $\text{LiN}(\text{i-C}_3\text{H}_7)_2$
- 2) $\text{MoO}_5\text{PyHMPA}$

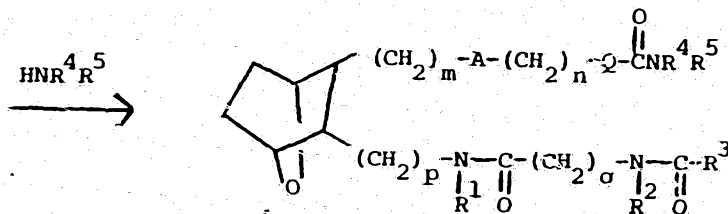


IL

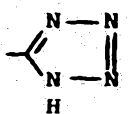
13 006 53713

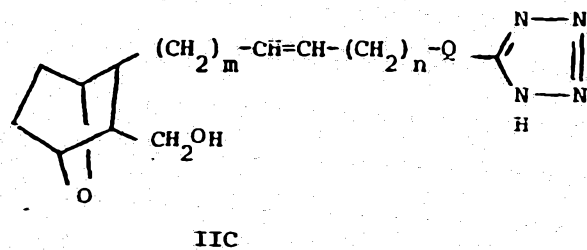
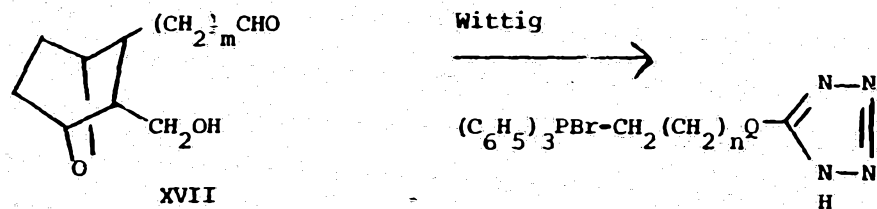
L. Where R is $\text{C}(=\text{O})\text{NR}^4\text{R}^5$ (wherein R^4 and R^5 are other than hydroxy or alkoxy)

IA,
IB,
IC,
ID,
IE,
IF,
IG,
IH,
or IL
or esters of
IJ or IK

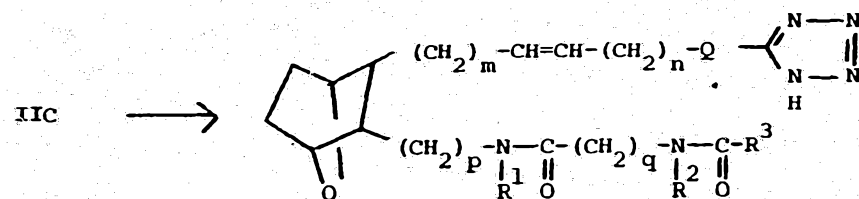


IM

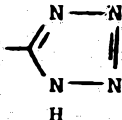
M. Where R is  and A is CH=CH

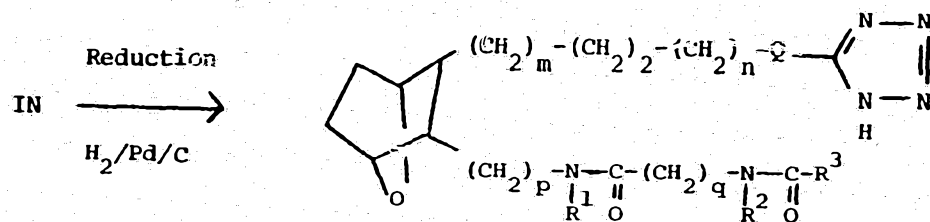


13 6 06 50715



IN

N. Where R is  and A is $(CH_2)_2$

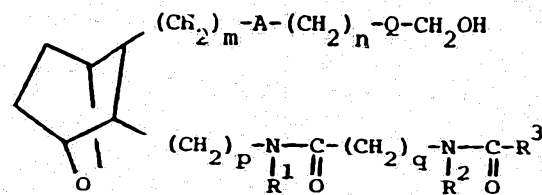
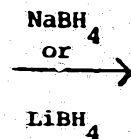


IO

13 00 5815

O. Where R is CH_2OH

IA to IH,
IL,
or
esters of
IJ and IK



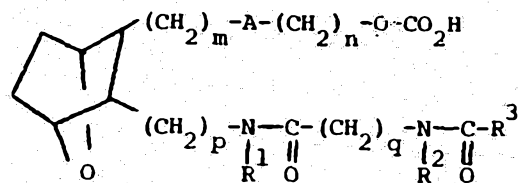
IP

13 00 5015

P. Where R is CO₂H

IA to IH,
IL

Hydrolysis
LiOH, HCl



(IQ where A is CH=CH)

(IR where A is (CH₂)₂)

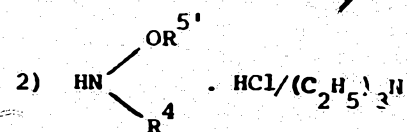
12 6 03 56715

Q. Where R is $\begin{array}{c} \text{O} \\ \parallel \\ \text{CN-OR}^{5'} \\ | \\ \text{R}^4 \end{array}$

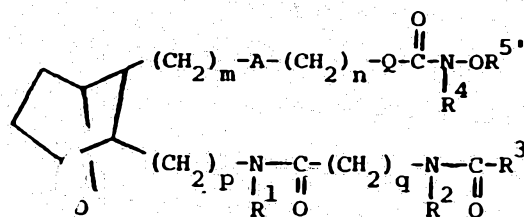
IQ Hydroxamate Formation

or 1) ClCOCOC1, benzene, N₂, R.T.

IR $\xrightarrow{\text{cat. DMF}}$



(wherein R^{5'} is H or alkyl)

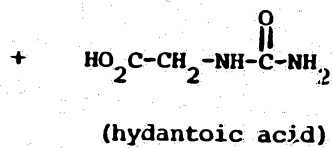


IS

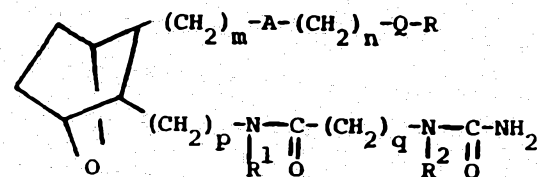
13 8 45 5015

R. Where R^3 is NH_2

VI,
VIA
or XII

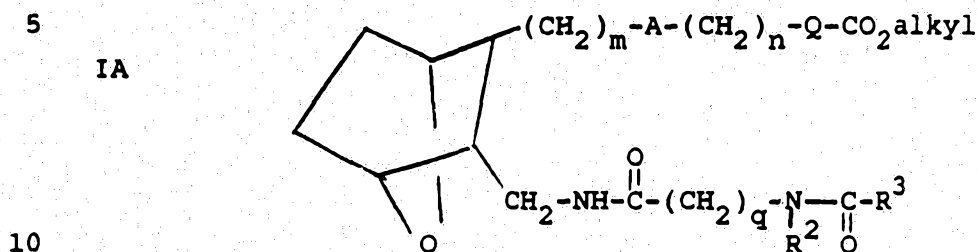


1) carbonyldiimidazole
2) hydrolysis



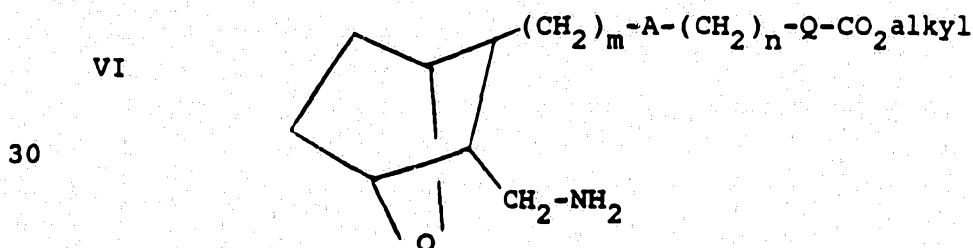
IT

As seen in reaction sequence "A", compounds of the invention where Q is $-\text{CH}_2-$ or a single bond, p is 1, R is CO_2 alkyl, and R^1 is H, that is

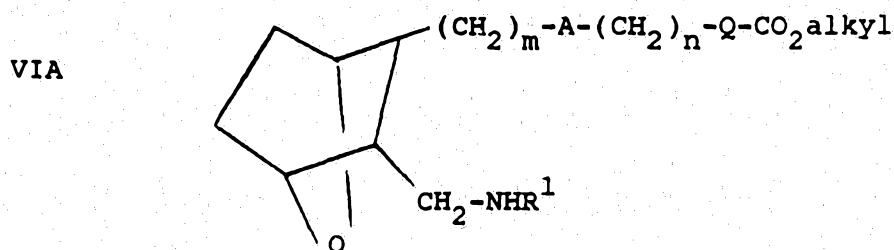


are prepared by tosylating the lower alkyl ester containing the hydroxymethyl group, that is, compound II or IIA, (prepared as described in U. S. Patent No. 4,143,054) by reacting II or IIA with tosyl chloride in the presence of pyridine to form the corresponding tosylate IV which is subjected to a displacement reaction by dissolving IV in dimethylsulfoxide and heating to 90 to 100°C in the presence of potassium phthalimide to form the phthalimide V. The phthalimide V is then made to undergo selective hydrolysis by dissolving V in methylene chloride and ethanol under an inert atmosphere such as argon and reacting with anhydrous hydrazine to form the amine VI

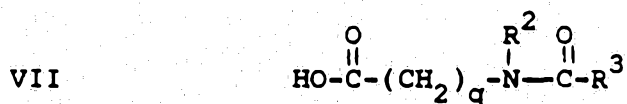
15
20
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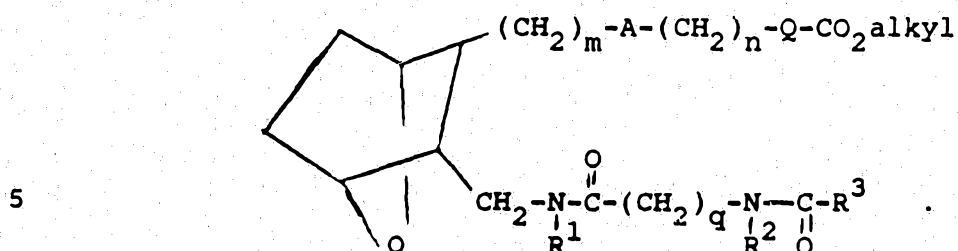
As seen in reaction sequence " A' ", where R^1 is lower alkyl, an alkylation reaction is carried out as in the reference M. J. O'Donnell et al., Tetrahedron Lett. (1984), 25, 3651-3654 to give VIA



The amine VI or VIA is then subjected to a CDI coupling reaction by reacting VI or VIA with acid VII



in the presence of an inert organic solvent such as tetrahydrofuran and carbonyl diimidazole under an inert atmosphere, such as argon, employing a molar ratio of VI:VII of within the range of from about 1:1 to about 1:1.2, to form the amide ester compound of the invention IA or IA'



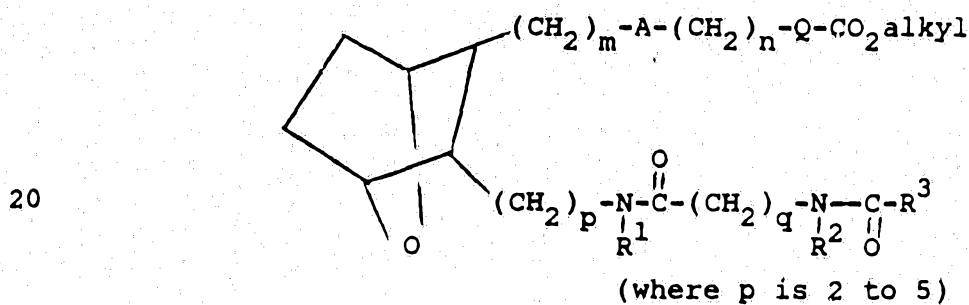
(IA - where R^1 is H

IA' - where R^1 is lower alkyl)

10

The reaction sequences identified as "B" and "B'" are employed to prepare compounds of the invention wherein Q is $-\text{CH}_2-$ or a single bond, p is 2 to 5, and R is CO_2alkyl , that is,

15



25

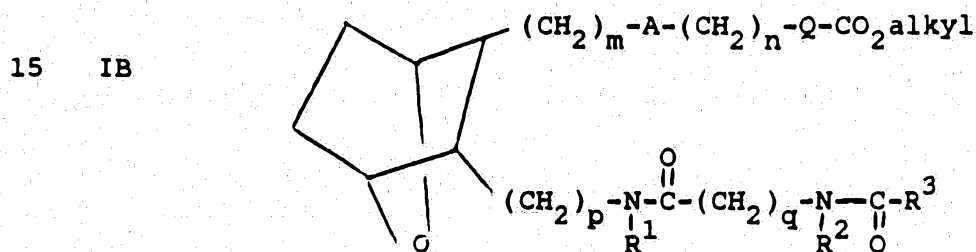
(IB - where R^1 is H

IB' - where R^1 is alkyl)

30

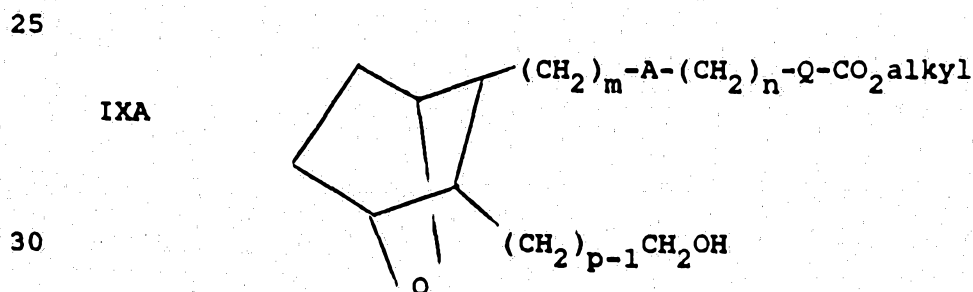
Compound II or IIA is used to form the aldehyde III (where A is $-\text{CH}=\text{CH}-$) or IIIA (where A is $-(\text{CH}_2)_2$). Thus, to form aldehyde III where A is $-\text{CH}=\text{CH}-$, compound II is subjected to a Collins oxidation, for example, by reacting II with chromium trioxide in pyridine. To form the aldehyde IIIA (where A is $(\text{CH}_2)_2$)

compound II is reduced, for example, with hydrogen over a palladium on carbon catalyst, to form hydroxymethyl compound IIA (where A is $(CH_2)_2$) and compound IIA is subjected to a Collins oxidation to form aldehyde IIIA (where A is $(CH_2)_2$). The aldehyde III or IIIA is used to prepare aldehyde IX (where p is 2-5) by carrying out a homologation sequence, such as a Wittig reaction with $(C_6H_5)_3P=CHOME$ followed by hydrolysis, (p-1) times. The aldehyde IX (where p is 2-5) is then carried on to compounds of this invention where p is 2-5, that is

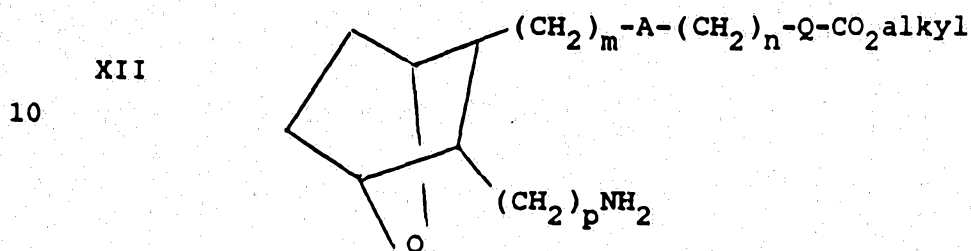


(where p is 2 to 5)

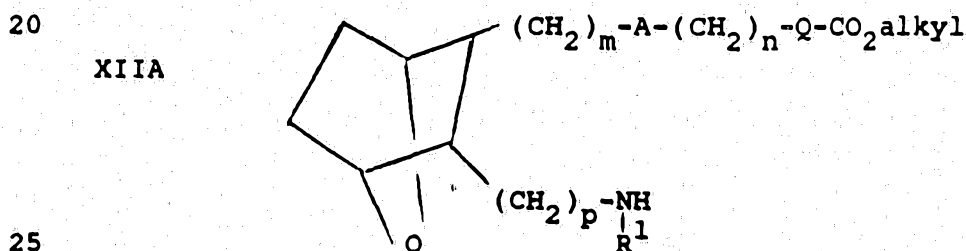
by reducing aldehyde IX by reacting with a reducing agent such as sodium borohydride to form alcohol IXA



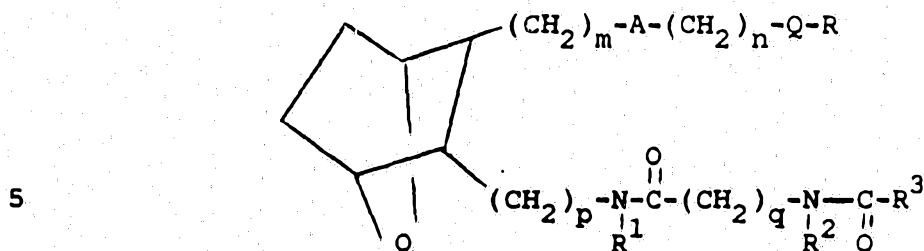
tosylating alcohol IXA as described above to form the tosylate X which is subjected to a displacement reaction with potassium phthalimide as described above to form the phthalimide XI. Phthalimide XI
 5 is then made to undergo selective hydrolysis as described above to form the amine XII



15 As seen in reaction sequence " B' ", where R^1 is lower alkyl, an alkylation reaction is carried out as in O'Donnell et al, supra to give
 XIIA



The amine XII or XIIA is then reacted with acid VII in a CDI coupling reaction as described above to form the amide ester compound of the invention IB
 30 or IB'



(IB - where R^1 is H

IB' - where R^1 is lower alkyl)

10

Compounds of the invention wherein m is 2, A is $-\text{CH}=\text{CH}-$, p is 1 and Q is CH_2 or a single bond may be prepared as outlined in reaction sequence "C" by subjecting starting compound XIII to a

15 Wittig reaction, referred to as Wittig (1), by reacting XIII with an alkoxymethyltriphenyl phosphonium halide, such as (methoxymethyl)-triphenylphosphonium chloride, for example, as described in Example 4 of U. S. Patent No.

20 4,143,054, to form compound F. The Wittig (1) procedure is repeated on compound F to form aldehyde compound XIV. Aldehyde XIV is then subjected to a Wittig (2) procedure wherein XIV is reacted with a carboxyalkyltriphenylphosphonium

25 halide, such as carboxypentyltriphenylphosphonium bromide, to form hydroxymethyl compound XV. Compound XV is esterified, for example, by reacting with diazomethane, to form ester XVI which is then employed in place of compound II in reaction

30 scheme "A" to form compound IC of the invention.

As seen in reaction sequence "D", compounds of the invention wherein m is 2, A is $-\text{CH}_2-\text{CH}_2-$, p is 1 and Q is CH_2 or a single bond may be prepared

as outlined in reaction sequence "D" by reducing hydroxymethyl compound XVI to form compound XVIA which is then employed in place of compound IIA in reaction sequence "A" to form compound ID of the invention.

Referring to reaction sequence "E", compounds of the invention wherein m is 3 or 4, A is $-\text{CH}=\text{CH}-$, p is 1 and Q is CH_2 or a single bond may be prepared by subjecting aldehyde XIV to the Wittig (1) procedure one time in the case where m is 5 and a second time in the case where m is 4, to form the aldehyde XVII. Aldehyde XVII is then subjected to the Wittig (2) procedure to form acid XVIII which is esterified to form ester XIX which is then employed in place of compound II in reaction scheme "A" to form compound IE of the invention.

As seen in reaction sequence "F", compounds of the invention wherein m is 3 or 4, A is CH_2CH_2 , p is 1 and Q is CH_2 or a single bond may be prepared by reducing hydroxymethyl compound XIX to form compound XIXA which is then employed in place of compound II in reaction scheme "A" to form compound IF of the invention.

Thus, compounds of the invention wherein m is 0, 2, 3 or 4 and p is 2, 3 or 4 may be prepared by substituting hydroxymethyl compound XVI, XVIA, XIX, or XIXA in place of hydroxymethyl compound II or IIA in reaction sequences A and B.

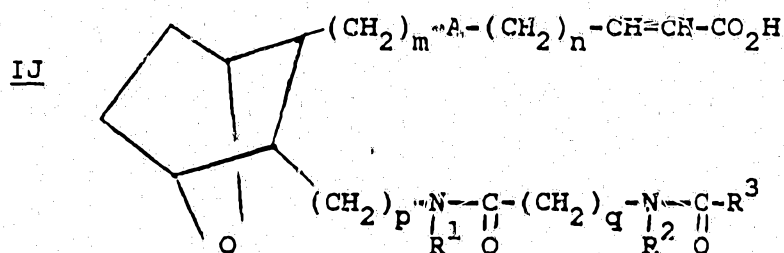
Referring now to reaction sequence "G", compounds of the invention wherein m is 0, A is $\text{CH}=\text{CH}$, p is 1 and Q is CH_2 or a single bond, that is, compound IG may be prepared by subjecting compound XIII (prepared as described in Example 3 of

U. S. Patent No. 4,143,054) to a Wittig reaction, for example, as described in Example 6(c) of U. S. Patent No. 4,143,054, by reacting B with a carboxyalkyltriphenyl phosphonium halide, such as carboxypentyltriphenyl phosphonium bromide to form the hydroxymethyl compound IXB which may then be used to form the ester IG which, in turn, may be hydrolyzed to the corresponding acid.

As seen in reaction sequence "H", where it is desired to prepare compounds of the invention wherein m is 0 and A is $(CH_2)_2$, the hydroxymethyl compound IXB is reduced by treatment with hydrogen in the presence of a palladium on carbon catalyst to form hydroxymethyl compound IXC which may then be used to form ester IH which then may be hydrolyzed to the corresponding acid.

Referring to reaction sequence "I", compounds of formula I of the invention wherein Q is $-CH=CH-$, that is IJ

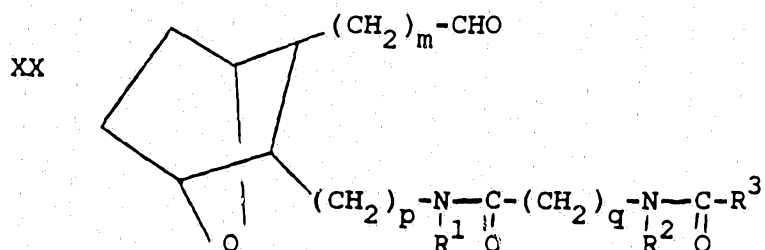
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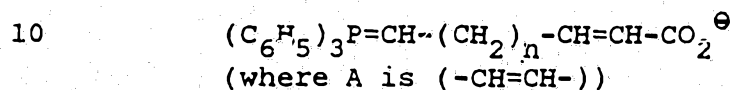
25

may be prepared by subjecting ester IA, IB, IA', IB', IC, IE and IG to ozonolysis by treating IA, IB, IA', IB', IC, IE and IG with ozone at $-78^\circ C$ in methylene chloride and methanol to form aldehyde XX.

30



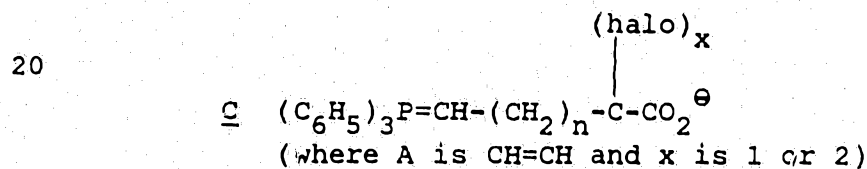
which is then treated with Wittig reagent



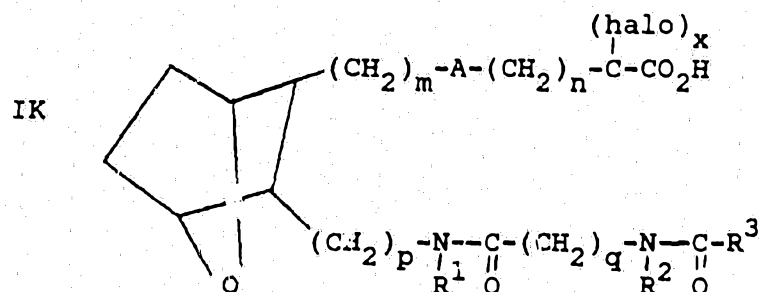
to form IJ.

15 In reaction sequence "J" compounds wherein

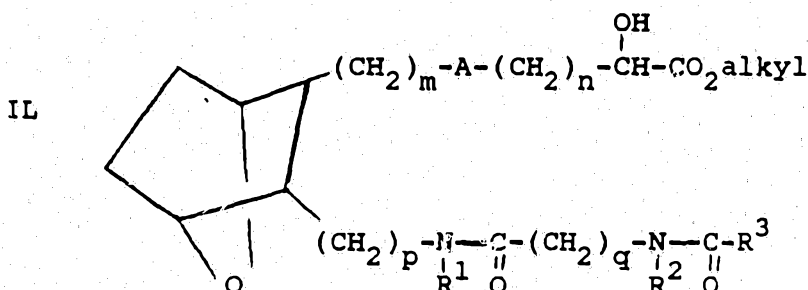
Q is $\begin{array}{c} \text{hal} \\ | \\ -CH- \end{array}$ or $\begin{array}{c} \text{halo} \quad \text{halo} \\ \diagdown \quad \diagup \\ -C- \end{array}$ are prepared by subjecting aldehyde XX to a Wittig reaction with



to form compounds of the invention IK

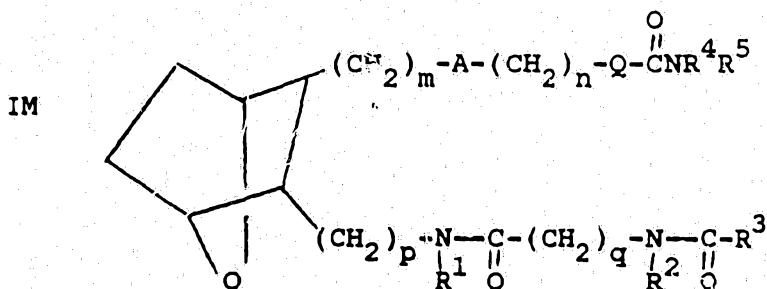


As seen in reaction sequence "K" compounds
 of the invention wherein Q is $\begin{array}{c} \text{OH} \\ | \\ -\text{CH}- \end{array}$, that is, IL

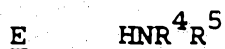


are formed by reacting ester IA to IH with lithium
 diisopropylamide in the presence of an inert
 15 solvent such as tetrahydrofuran at reduced
 temperatures of lower than about -50°C and then
 with oxodiperoxymolybdenum(pyridine)(hexamethyl-
 phosphoric triamide) ($\text{MoO}_5\text{PyHMPA}$).

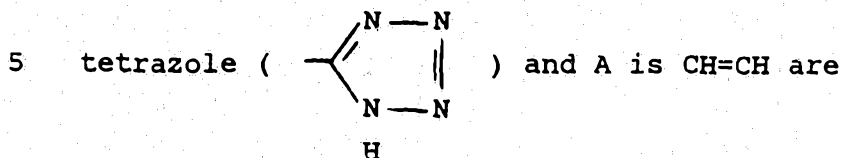
In reaction sequence "L", amides of the
 20 invention of structure IM



wherein R^4 and R^5 are independently H, alkyl or
 aryl are prepared by treating ester IA to IH or IL
 or esters of IJ or IK with an amine of the
 structure

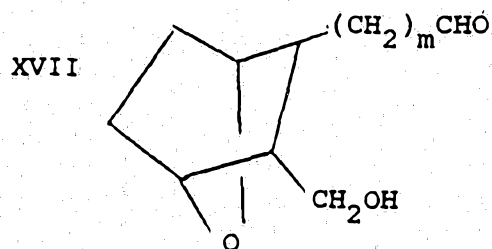


Compounds of the invention wherein R is



prepared as described in reaction sequence "M"
wherein alcohol XVII

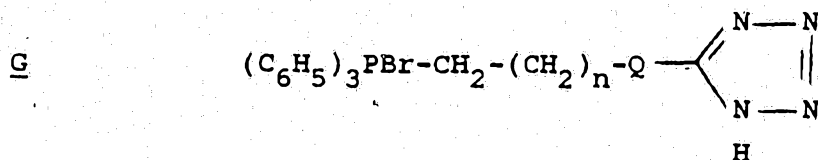
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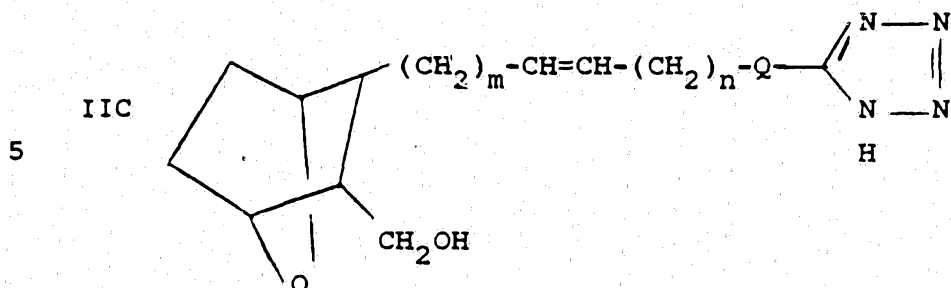
(prepared as described in U. S. Patent No.
4,143,054) is reacted with a Wittig reagent of the
20 structure G

20

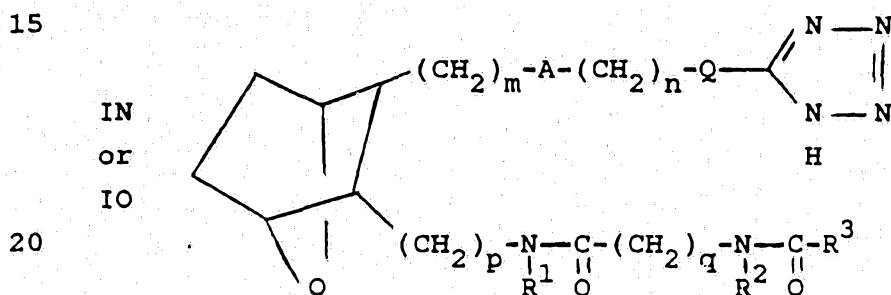


25

in the presence of a base, such as potassium
t-butoxide or sodium hydride-dimethyl sulfoxide
employing a molar ratio of XVII:G of within the range
30 of from about 1:1 to about 0.2:1 to form the
hydroxymethyl compound IIC



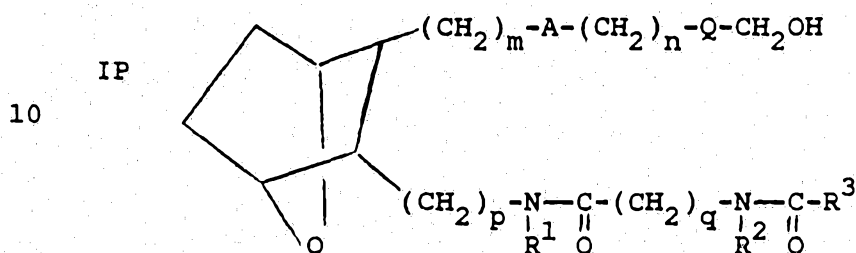
10 which may then be employed in reaction sequences
 "A" and "B" in place of compounds II or IIA to
 form compounds of the invention IN where A is
 $-\text{CH}=\text{CH}-$ or IO where A is $(\text{CH}_2)_2$



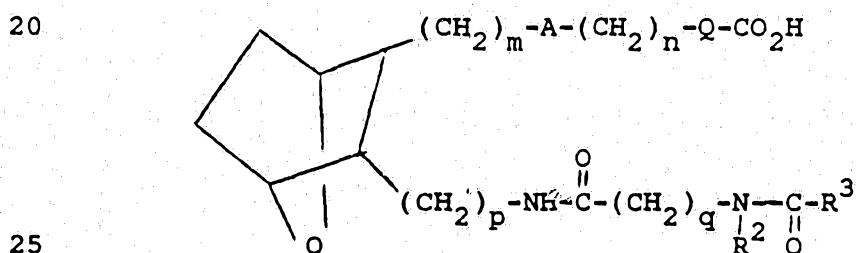
Alternatively, compound IO may be prepared by
 reducing compound IN by treating with H_2 in the
 25 presence of palladium on charcoal.

Compounds of the invention wherein R is
 tetrazole and A is $\text{CH}=\text{CH}$ may also be prepared by
 reacting aldehyde XX in the reaction sequence "I"
 with a Wittig reagent of the structure G in the
 30 presence of base such as potassium t-butoxide or
 sodium hydride-dimethyl sulfoxide as described
 above.

As seen in reaction sequence "O", compounds of the invention wherein R is CH_2OH may be prepared by reducing esters IA to IH, and IL and esters of J and K by treatment with sodium borohydride or lithium borohydride to form compounds of the invention IP



Referring to reaction sequence "P", the esters IA, IA', IB, IB' to IH and IL can be converted to the free acid, that is, to



by treating the esters with a base, such as lithium hydroxide, sodium hydroxide or potassium hydroxide to form the corresponding alkali metal salt, followed by neutralization with an acid, such as

dilute hydrochloric acid or oxalic acid to form the acid compounds of the invention IQ and IR.

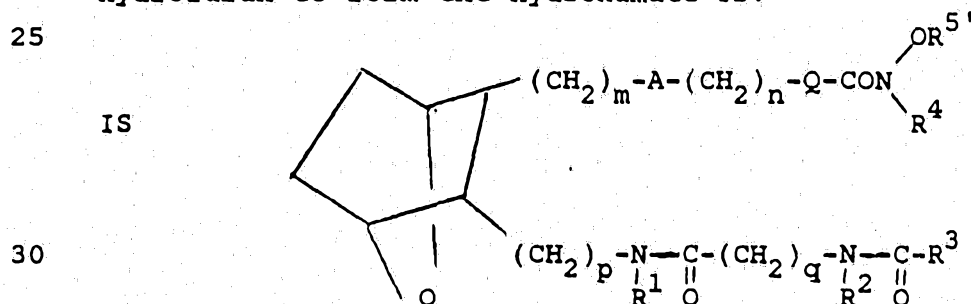
In the reaction sequence identified as "Q"

5 where in Formula I, R is $\begin{array}{c} \text{O} \\ \parallel \\ \text{CN} \end{array} \begin{array}{l} \text{OR}^{5'} \\ \text{R}^4 \end{array}$, wherein $\text{R}^{5'}$ is H

or alkyl, a solution of acid dissolved in an inert organic solvent such as benzene is treated with oxalyl chloride and a catalytic amount of
10 dimethylformamide (DMF) and the mixture is stirred at room temperature under nitrogen. The resulting acid chloride is dissolved in an inert organic solvent such as tetrahydrofuran and the so-formed solution is added dropwise into a cold solution of
15 amine hydrochloride H



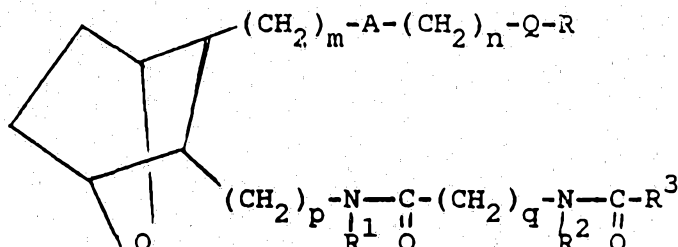
20 (wherein $\text{R}^{5'}$ is H or alkyl, employing a molar ratio of acid chloride:H of within the range of from about 0.3:1 to about 1:1 and preferably from about 0.5:1) and triethylamine in aqueous tetrahydrofuran to form the hydroxamate IS.



In reaction sequence "R" compounds of the invention wherein R^3 is NH_2 , that is IT

IT

5



may be prepared by reacting amine VI, VIA or XII
with hydantoic acid in the presence of carbonyl-
diimidazole and then hydrolyzing the resulting
product to form IT.

10

The tris(hydroxymethyl)aminomethane salt of
any of the acids of formula I of the present
invention is formed by reacting a solution of such
acid in an inert solvent such as methanol with
tri(hydroxymethyl)aminomethane and thereafter the
solvent is removed by evaporation to leave the
desired salt.

15

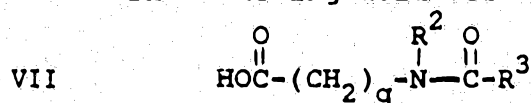
To form the sulfinyl and/or sulfonyl
analogs of compounds of formula I wherein R^3 is
-S-alkyl, -S-aryl, -S-alkylaryl, -alkyl-S-aryl,
alkyl-S-alkyl, or -alkyl-S-alkylaryl, such formula
I compounds are subjected to oxidation, for
example, by reacting same with sodium periodate or
potassium monopersulfate (oxone) in the presence
of methanol to form the sulfinyl derivative and/or
sulfonyl derivative. Mixtures thereof may be
separated by chromatography or other conventional
separation procedures.

20

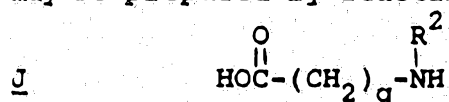
25

The starting acid VII

30



may be prepared by reacting the amino acid J



35

or its acid chloride with acid chloride K



5 (or its acid if the acid chloride of J is employed)
in the presence of a strong base such as NaOH and
water.

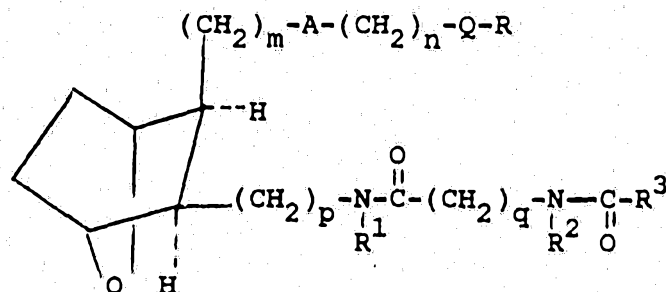
The compounds of this invention have four
centers of asymmetry as indicated by the asterisks
10 in formula I. However, it will be apparent that
each of the formulae set out above which do not
include asterisks still represent all of the
possible stereoisomers thereof. All of the various
stereoisomeric forms are within the scope of the
15 invention.

The various stereoisomeric forms of the
compounds of the invention, namely, cis-exo, cis-
endo and all trans forms and stereoisomeric pairs
may be prepared as shown in the working Examples
20 which follow and by employing starting materials
following the procedures as outlined in U. S.
Patent No. 4,143,054. Examples of such
stereoisomers are set out below.

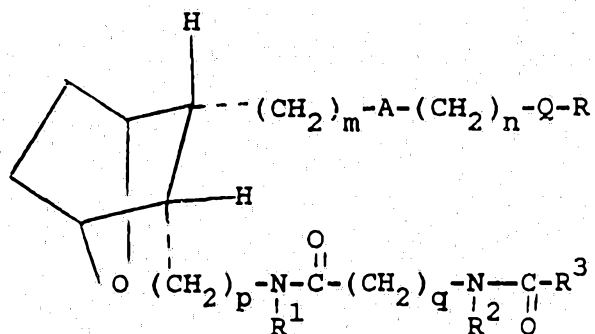
25

Ia

30

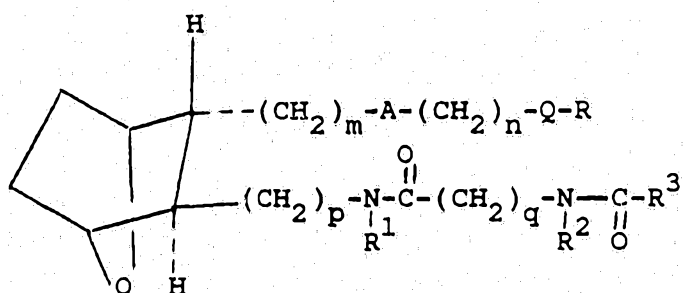


Ib



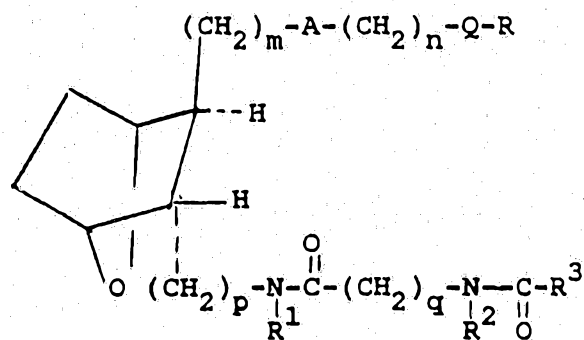
(cis-exo)

Ic



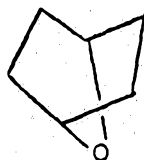
(trans)

Id

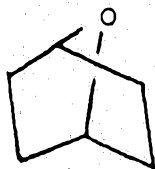


(trans)

The nucleus in each of the compounds of the invention is depicted as



for matter of convenience; it will also be appreciated that the nucleus in the compounds of the invention may be depicted as



The compounds of this invention are cardiovascular agents useful as platelet aggregation inhibitors, such as in inhibiting arachidonic acid-induced platelet aggregation, e.g., for treatment of thrombotic disease such as coronary or cerebral thromboses, and in inhibiting bronchoconstriction. They are also selective thromboxane A_2 receptor antagonists and synthetase inhibitors, e.g., having a vasodilatory effect for treatment of myocardial ischemic disease, such as angina pectoris.

The compounds of this invention may also be used in combination with a cyclic AMP phosphodiesterase (PDE) inhibitor such as theophylline or papaverine in the preparation and storage of platelet concentrates.

The compounds of the invention can be administered orally or parenterally to various mammalian species known to be subject to such maladies, e.g., humans, cats, dogs, and the like in
5 an effective amount within the dosage range of about 1 to 100 mg/kg, preferably about 1 to 50 mg/kg and especially about 2 to 25 mg/kg on a regimen in single or 2 to 4 divided daily doses.

The active substance can be utilized in a
10 composition such as tablet, capsule, solution or suspension containing about 5 to about 500 mg per unit of dosage of a compound or mixture of compounds of formula I. They may be compounded in conventional matter with a physiologically
15 acceptable vehicle or carrier, excipient, binder, preservative, stabilizer, flavor, etc. as called for by accepted pharmaceutical practice. Also as indicated in the discussion above, certain members additionally serve as intermediates for other
20 members of the group.

The compounds of the invention may also be administered topically to treat peripheral vascular diseases and as such may be formulated as a cream or ointment.

The following Examples represent preferred embodiments of the present invention. Unless otherwise indicated, all temperatures are expressed in degrees Centigrade.

5

Example 1

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxohexyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

10

A. N-Hexanoylglycine

Glycine (7.5 g, 100 mmol) was dissolved in NaOH solution (NaOH:8 g, H₂O:50 ml) and cooled to 0°C. Et₂O (50 ml) was added and n-hexanoyl chloride (13.4 g, 100 mmol) was then added dropwise over 60 minutes at 0°C under vigorous stirring. The reaction was allowed to warm to room temperature and was stirred for 1 hour. 1N-NaOH (10 ml) was added and the layers were separated. The water layer was washed with Et₂O (20 ml x 2). The combined Et₂O layers were extracted with 1N-NaOH (20 ml). The combined water layers were acidified with concentrated HCl to pH 2 and the products were extracted with Et₂O (100 ml x 3). The combined Et₂O layers were washed with brine (50 ml) and dried over MgSO₄. Filtration and evaporation of solvent gave a colorless solid (16.2 g), which was crystallized from EtOAc (60 ml) to give colorless needle crystals (10.9 g, 63 mmol, 63%); m.p. 93-96°.

TLC: silica gel, MeOH, CH₂Cl₂, HCOOH; 10, 89.5, 0.5, PMA R_f=0.45.

30

B. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-(Tosyloxy-
methyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-
heptenoic acid, methyl ester

Tosyl chloride (4.256 g, 22.4 mmol) dissolved
5 in CH₂Cl₂ (30 ml) was added dropwise to a
magnetically stirred solution of
[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-(hydroxymethyl)-7-
oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid,
methyl ester (prepared as described in U. S. Patent
10 No. 4,143,054 (3 g, 11.2 mmol) in pyridine (30 ml)
at 0°C. After completion of the addition, the
reaction was warmed to room temperature and stirred
overnight. The reaction was poured into ice/H₂O
and stirred for 30 minutes. The products were
15 extracted with EtOAc (80 ml x 3). The combined
EtOAc layers were washed with 3N-HCl (40 ml x 3),
saturated NaHCO₃, brine and dried over MgSO₄.
Filtration and evaporation of solvent gave a white
solid, which was crystallized from isopropyl ether
20 to give the corresponding title tosylate in the
form of needle crystals (4.23 g, 89%), m.p.
68-70°C.

C. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[(3-(Amino-
methyl)-7-oxabicyclo[2.2.1]hept-2-yl]-
25 5-heptenoic acid, methyl ester

The title B tosylate was subjected to a
Gabriel synthesis to form the corresponding amino
compound as described below.

30 The potassium phthalimide used was purified
prior to use by boiling 5 g thereof with 9 ml
acetone for 15 minutes, filtering while hot and
washing with 5 ml acetone. The remaining solid

was dried in vacuo for 6 hours at 100°C prior to use.

5 The title B tosylate (8.11 g, 19.2 mmol) and purified potassium phthalimide (6.4 g, 34.6 mmol, 1.8 equiv.) in dimethylsulfoxide (70 ml, Burdick & Jackson) were heated at 90-100°C for 2½ hours (checked by TLC Et₂O-pet ether 2:1, no tosylate remaining). After cooling to room temperature, water (90 ml) was added. Material
10 began precipitating. The mixture was poured into ice water (~350 ml) and stirred 30 minutes. The straw colored solid was harvested by filtration and washed with more water. The solid was dissolved in warm ethyl acetate (150 ml), washed
15 with water (3 x 50 ml), dried (MgSO₄), filtered and freed of solvent in vacuo. The remaining solid (7.88 g) was recrystallized from isopropyl ether (~150 ml) to give corresponding phthalimide (6.35 g, 83%) TLC. Et₂O-hexane 2:1, UV + vanillin
20 R_f = 0.38, trace 0.09.

The above phthalimide (5.05 g, 13.8 mmol) was dissolved in distilled CH₂Cl₂ (24 ml) and distilled ethanol (104 ml) in an argon atmosphere. Anhydrous hydrazine (0.73 ml, 25.6 mmol) was added.
25 The mixture was stirred at room temperature. After 8 hours an additional 0.2 ml of hydrazine was added and the mixture was stirred an additional 15 hours at room temperature. A white solid was removed by filtration and washed with more CH₂Cl₂. The
30 filtrate was taken to dryness in vacuo (on the pump at end). Cold 0.5 N HCl solution (80 ml) was added. A small amount of white solid was removed by filtration and washed with additional 0.5 N HCl

solution (80 ml). The acidic solution was washed with ether (2 x 100 ml) and then basified with solid K_2CO_3 . The amine was extracted into $CHCl_3$ (3 x 100 ml), dried ($MgSO_4$) and freed of solvent
5 in vacuo leaving a yellow oil. Ether (100 ml) was added to this oil. Some solid was insoluble. After cooling in an ice bath, the solid was removed by filtration. The solvent was removed from the filtrate in vacuo leaving title amine as a pale
10 yellow oil (2.441 g, 71%). NMR spectra and TLC indicated some minor impurities. The material was used without further purification.

15 D. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxoheptyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

Part A compound (260 mg, 1.5 mmol) was dissolved in distilled THF (12 ml) in an argon
20 atmosphere. After cooling in an ice bath carbonyldiimidazole (CDI) (243 mg, 1.5 mmol) was added. The mixture was stirred cold for 1 hour and then at room temperature for 1 hour. The solution was cooled to 0°C and a solution of Part C amine
25 (401 mg, 1.5 mmol) in THF (3 ml) was added. The mixture was left stirring overnight at room temperature. The solvent was removed in vacuo and the residue was dissolved in $CHCl_3$ (50 ml). This was washed with 1N HCl (20 ml), 1N NaOH (20 ml) and
30 H_2O (20 ml), dried ($MgSO_4$) and freed of solvent in vacuo leaving a viscous oil. The oil was chromatographed on silica gel (30 g, Baker for flash chromatography), eluting with EtOAc and 1%

MeOH in EtOAc to give title compound as an oil (425 mg, 67%). TLC: silica gel, 10% MeOH in CH_2Cl_2 , vanillin $R_f = 0.48$.

5

Example 2

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxohexyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

10 The Example 1 methyl ester (420 mg, 0.994 mmol) was dissolved in distilled THF (40 ml) and water (8 ml) in an argon atmosphere. 1N LiOH solution (9.5 ml) was added and the mixture was stirred at room temperature for 3-3/4 hours. After neutralization with 1N HCl (9.5 ml), solid 15 KCl was added and the layers were separated. The aqueous layer was reextracted with CHCl_3 (3 x 50 ml). The combined organic layers (THF + CHCl_3) were washed with saturated NaCl solution (2 x 25 ml), dried (MgSO_4), and freed of solvent in vacuo 20 leaving a very viscous oil. This was chromatographed on silica gel (30 g, Baker for flash chromatography) eluting with 4% MeOH in CH_2Cl_2 to give material which crystallized, (358 mg, 88%). This was recrystallized from 25 acetonitrile (~10 ml) to give title acid, 248 mg, 61%, m.p. 119-121°C). TLC: silica gel, 10% MeOH in CH_2Cl_2 , vanillin, $R_f=0.37$.

30

Anal Calcd for $\text{C}_{22}\text{H}_{36}\text{O}_5\text{N}_2$: C, 64.68; H, 8.88;
N, 6.86

Found: C, 64.67; H, 8.87;
N, 6.86

Example 3

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[[(Butylamino)-
carbonyl]amino]acetyl]amino]methyl]-7-oxabicyclo-
[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

5 A. N-[(Butylamino)carbonyl]glycine,
 ethyl ester

Glycine ethyl ester•HCl (5.58 g, 40 mmol)
was suspended in distilled CH₂Cl₂ (20 ml). After
cooling in an ice bath, distilled Et₃N (6.13 ml,
10 44 mmol) was added. Distilled n-butyl isocyanate
(4.95 ml, 44 mmol) was added. The cooling bath
was removed and the mixture was left stirring
overnight at room temperature. Additional Et₃N
(3.05 ml) was added and the mixture was stirred 3
15 more hours. After diluting with more CH₂Cl₂, the
solution was washed with water (50 ml), 1N HCl (50
ml), saturated NaHCO₃ solution (50 ml) and water
(50 ml). After drying (MgSO₄), the solvent was
removed in vacuo leaving the title compound (7.641
20 g, 94%) which slowly crystallized. This was
used without further purification.

 B. N-[(Butylamino)carbonyl]glycine

Part A ethyl ester (3.378 g, 16.7 mmol) was
25 dissolved in distilled THF (100 ml) and treated
with 1N LiOH solution (40 ml). After stirring
overnight at room temperature and acidifying with
concentrated HCl, solid KCl was added. The layers
were separated. The aqueous layer was reextracted
30 with EtOAc (3 x 50 ml). The combined organic
layers (THF and EtOAc) were washed with saturated
NaCl solution (25 ml), dried (MgSO₄), and freed of

Example 3

[1S-[1 β , 2 α (5Z), 3 α , 4 β]]-7-[3-[[[[(Butylamino)-
carbonyl]amino]acetyl]amino]methyl]-7-oxabicyclo-
[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

5 A. N-[(Butylamino)carbonyl]glycine,
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was removed and the mixture was left stirring
overnight at room temperature. Additional Et₃N
(3.05 ml) was added and the mixture was stirred 3
15 more hours. After diluting with more CH₂Cl₂, the
solution was washed with water (50 ml), 1N HCl (50
ml), saturated NaHCO₃ solution (50 ml) and water
(50 ml). After drying (MgSO₄), the solvent was
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25 dissolved in distilled THF (100 ml) and treated
with 1N LiOH solution (40 ml). After stirring
overnight at room temperature and acidifying with
concentrated HCl, solid KCl was added. The layers
were separated. The aqueous layer was reextracted
30 with EtOAc (3 x 50 ml). The combined organic
layers (THF and EtOAc) were washed with saturated
NaCl solution (25 ml), dried (MgSO₄), and freed of

solvent in vacuo leaving the title compound, as a white solid (2.81 g, 97%).

5 C. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[[(Butyl-
amino)carbonyl]amino]acetyl]amino]-
methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-
5-heptenoic acid, methyl ester

Part B compound (174.2 mg, 1 mmol) was partially dissolved in distilled THF (8 ml) in an argon atmosphere. After cooling in an ice bath, carbonyl diimidazole (CDI) (162 mg, 1 mmol) was added. The mixture was stirred cold 1 hour and at room temperature 1½ hours (became a clear solution near the end of this time). The solution was cooled in an ice bath and a solution of chiral amine prepared in Example 1 Part C (267 mg, 1 mmol) in THF (3 ml) was added. The cooling bath was removed and the mixture was left stirring overnight at room temperature. The solvent was removed in vacuo. CHCl₃ (35 ml) was added to the residue. The solution was washed with 1N HCl (15 ml), 1N NaOH (15 ml) and H₂O (15 ml), dried (MgSO₄) and freed of solvent in vacuo leaving a very viscous oil (340 mg). This was chromatographed on silica gel (20 g, Baker for flash chromatography), eluting with EtOAc and 5% MeOH in EtOAc to give the title compound as a viscous oil (212 mg, 50%). TLC: silica gel, 5% MeOH in EtOAc, vanillin, R_f=0.23.

30

Example 4

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[[(Butylamino)-
carbonyl]amino]acetyl]amino]methyl]-7-oxabicyclo-
[2.2.1]hept-2-yl]-5-heptenoic acid

Example 3 methyl ester (208 mg, 0.491 mmol) was dissolved in distilled THF (20 ml) and water (4.8 ml) in an argon atmosphere. 1N LiOH solution (4.9 ml) was added and the mixture was stirred at
5 room temperature 5 hours. The mixture was neutralized with 1N HCl solution (4.9 ml) and solid KCl was added. The layers were separated. The aqueous layer was reextracted with CHCl_3 (3 x 25 ml). The combined organic layers (THF and
10 CHCl_3) were washed with saturated NaCl solution (15 ml), dried (MgSO_4) and freed of solvent in vacuo leaving an oil. This was chromatographed on silica gel (18 g), eluting with 4% MeOH in CH_2Cl_2 to give the title compound (158 mg, 78.2%)
15 as a white foam. TLC: silica gel, 10% MeOH in CH_2Cl_2 , vanillin, $R_f=0.28$.

Anal Calcd for $\text{C}_{21}\text{H}_{35}\text{O}_5\text{N}_3 \cdot 0.1 \text{H}_2\text{O}$: C, 61.32;
H, 8.63; N, 10.21

20 Found: C, 61.15; H, 8.74; N, 10.23

Example 5

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[Methyl(1-oxohexyl)-
amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]-
25 hept-2-yl]-5-heptenoic acid, methyl ester

A. N-Hexanoyl-N-methylglycine

Sarcosine (1.78 g, 20 mmol) was dissolved in 1N NaOH solution (40 ml) and Et_2O (40 ml) was added. After cooling in an ice bath a solution of
30 hexanoyl chloride (3.1 ml, 22 mmol) in Et_2O (10 ml) was added dropwise. The mixture was stirred cold for 1 hour. The pH was then adjusted to about 8 by adding 1N NaOH solution (about 3 ml) and

the mixture was stirred at room temperature 45 minutes. NaOH solution was added to about pH 9-10. The layers were separated and the aqueous layer was washed with Et₂O (50 ml). After acidification of
5 the aqueous layer with concentrated HCl and saturation with solid KCl, the product was extracted into CHCl₃ (3 x 70 ml). The combined CHCl₃ extracts were washed with saturated NaCl solution (25 ml), dried (MgSO₄), and freed of
10 solvent leaving the title compound as an oil (3.78 g, quant.) which was used without further purification.

B. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[Methyl-
15 (1-oxohexyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-
heptenoic acid, methyl ester

Part A compound (187 mg, 1 mmol) was dissolved in distilled THF (8 ml) in an argon atmosphere and cooled in an ice bath. Carbonyl-diimidazole (CDI) (162 mg, 1 mmol) was added and
20 the mixture was stirred cold for 1 hour and then for 1 hour at room temperature. After cooling in an ice bath, a solution of chiral amine prepared in Example 1 part C (267 mg, 1 mmol) in THF (3 ml) was
25 added. The ice bath was removed and the mixture was stirred overnight at room temperature. The solvent was removed in vacuo. CHCl₃ (35 ml) was added to the residue. The solution was washed
30 with 1N HCl (15 ml), 1N NaOH solution (15 ml) and H₂O (15 ml), dried (MgSO₄) and freed of solvent in vacuo leaving an oil (424 mg). This was chromatographed on silica gel (20 g, Baker for

flash chromatography), eluting with EtOAc and 2% MeOH in EtOAc to give the title compound as an oil (252 mg, 57.7%). TLC: silica gel, 5% MeOH in EtOAc, vanillin; $R_f=0.46$.

5

Example 6

[1S-[1 β , 2 α (5Z), 3 α , 4 β]]-7-[3-[[[Methyl(1-oxohexyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic acid

10 The Example 5 methyl ester (248 mg, 0.568 mmol) was dissolved in distilled THF (25 ml) and water (5 ml) in an argon atmosphere. 1N LiOH solution was added and the mixture was stirred at room temperature 4 hours. After neutralizing with
15 1N HCl solution (5.6 ml) and addition of solid KCl, the layers were separated. The aqueous layer was extracted with CHCl_3 (3 x 25 ml). The combined organic layers (THF + CHCl_3) were washed with saturated NaCl solution (15 ml), dried (MgSO_4) and
20 freed of solvent in vacuo leaving an oil (242 mg). This was chromatographed on silica gel (20 g, Baker for flash chromatography) eluting with 4% MeOH in CH_2Cl_2 to give the title compound (191.8 mg, 79.9%) as a viscous oil. TLC: silica gel, 10%
25 MeOH in CH_2Cl_2 , vanillin, $R_f=0.46$.

Anal Calcd for $\text{C}_{23}\text{H}_{38}\text{O}_5\text{N}_2$; C, 65.37; H, 9.06;
N, 6.63

Found: C, 65.50; H, 9.10; N, 6.74

30

Example 7

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(Butoxycarbonyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic acid, methyl ester

5 A. N-(Butoxycarbonyl)glycine ethyl ester

Glycine ethyl ester•HCl (3.5 g, 25 mmol) was suspended in distilled CH₂Cl₂ (25 ml) in an argon atmosphere. After cooling to -40°C distilled Et₃N (7.65 ml, 55 mmol) was added
10 followed by dropwise addition of a solution of distilled n-butyl chloroformate (3.2 ml, ~25 mmol) in CH₂Cl₂ (10 ml). After stirring at -40° for 1 hour the mixture was left in a freezer (-5°C) overnight. The mixture was stirred at -5 to -10°
15 for 1 hour. More CH₂Cl₂ was added followed by water (50 ml). The layers were separated. The organic layer was washed with 1N HCl (50 ml), saturated NaHCO₃ solution (50 ml) and water (50 ml), dried (MgSO₄), and freed of solvent in vacuo
20 leaving 3.129 g of material. This was combined with material from a 5 mmol run and chromatographed on silica gel (100 g, Baker for flash chromatography), eluting with ether-hexane 1:1 to give the title compound as an oil (3.196 g,
25 52.5%). TLC: silica gel, Et₂O-hexane 1:1, PMA, R_f=0.34.

B. N-(Butoxycarbonyl)glycine

The ethyl ester prepared in part A (3.141 g, 15.47 mmol) was dissolved in 100 ml distilled THF and treated with 1N LiOH solution (40 ml). The mixture was left stirring overnight at room temperature. After acidification with

concentrated HCl and addition of solid KCl, the layers were separated. The aqueous layer was reextracted with EtOAc (3 x 50 ml). The combined organic layers (THF + EtOAc) were washed with
5 saturated NaCl solution (25 ml), dried (MgSO₄) and freed of solvent in vacuo leaving the title compound (2.78 g, quant.) which slowly crystallized.

10 C. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(Butoxy-carbonyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

The acid prepared in part B (175.2 mg, 1
15 mmol) was dissolved in distilled THF (8 ml) in an argon atmosphere. After cooling in an ice bath carbonyldiimidazole (CDI) (162 mg, 1 mmol) was added. The mixture was stirred cold 1 hour and at room temperature 1 hour. The mixture was again
20 cooled in an ice bath and a solution of chiral amine (prepared in Example I part C, 267 mg, 1 mmol) in THF (3 ml) was added. The cooling bath was removed and the mixture was left stirring overnight at room temperature. The solvent was
25 removed in vacuo. CHCl₃ (35 ml) was added. The solution was washed with 1N HCl (15 ml), 1N NaOH (15 ml) and H₂O (15 ml), dried (MgSO₄) and freed of solvent in vacuo. The remaining oil (433 mg) was chromatographed on silica gel (20 g of Baker for
30 flash chromatography) eluting with EtOAc to give partially purified material (291 mg). This was rechromatographed on silica gel (20 g), eluting with Et₂O and 2% MeOH in Et₂O to give the title

compound (172 mg, 40.5%) as an oil. Additional material (57 mg, 13.4%) was contaminated with a small amount of slower moving material. TLC: silica gel, 5% MeOH in Et₂O, vanillin, R_f=0.32.

5

Example 8

[1S-[1β,2α(5Z),3α,4β]]-7-[3-[[[(Butoxycarbonyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

10 The methyl ester prepared in Example 7 (168 mg, 0.396 mmol) was dissolved in distilled THF (16 ml) and water (3.8 ml) in an argon atmosphere and 1N LiOH solution (3.9 ml) was added. The mixture was stirred at room temperature 5½ hours, then
15 neutralized with 1N HCl solution (3.8 ml). After adding solid KCl the layers were separated. The aqueous layer was reextracted with CHCl₃ (3 x 25 ml). The combined organic layers (THF + CHCl₃) were washed with saturated NaCl solution (15 ml),
20 dried (MgSO₄) and freed of solvent in vacuo leaving an oil (150 mg). This was chromatographed on silica gel (10 g, Baker for flash chromatography) eluting with 4% MeOH in CH₂Cl₂ to give 77 mg of material which appeared clean by
25 TLC: silica gel, 10% MeOH in CH₂Cl₂, vanillin, R_f= 0.43. The material became partially crystalline on standing several days in the cold room. Trituration with Et₂O gave the title compound as a white solid (58.5 mg, 36%) m.p. 104-106°C.

30

Anal Calcd for C₂₁H₃₄O₆N₂: C, 61.44; H, 8.35;
N, 6.82

Found: C, 61.50; H, 8.37; N, 6.98

Example 9

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-2,2-Difluoro-7-[3-[[[(1-Oxo-
Oxohexyl)amino]acetyl]amino]methyl]-7-oxabicyclo-
[2.2.1]hept-2-yl]-5-heptenoic acid

- 5 A. [1S-[1 β ,2 α ,3 α ,4 β]]-2-[3-[[[(1-Oxo-
hexyl)amino]acetyl]amino]methyl]-
7-oxabicyclo[2.2.1]hept-2-yl]-
acetaldehyde

10 O₃ is bubbled through a magnetically
stirred solution of [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-
[3-[[[(1-oxohexyl)amino]acetyl]amino]methyl]-
7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid,
methyl ester (211 mg, 0.5 mmol) (prepared as
described in Example 1) in CH₂Cl₂/MeOH (10 ml/10
15 ml) at -78°C, until the solution becomes blue.
Excess O₃ is then purged by a stream of N₂ and
(CH₃)₂S (1 ml) is added. The reaction is allowed
to warm to room temperature and poured into CH₂Cl₂
(50 ml), H₂O (10 ml). The products are extracted
20 into CH₂Cl₂ layers. The H₂O layer separated is
re-extracted with CH₂Cl₂ (30 ml). The combined
CH₂Cl₂ layers are washed with brine (10 ml) and
dried over MgSO₄. Filtration and evaporation of
solvent gives a crude product which is purified by
25 silica gel column chromatography to afford the
title compound.

- B. (4-Carboxy-3,3-difluorobutyl)triphenyl-
phosphonium bromide

- 30 1) Methyl tetrahydrofuroate

Methyl furoate (75 g, 0.595 mole) was
dissolved in MeOH (150 ml), and poured into a Parr
bottle. Air was replaced with argon, and then 10%

Pd/C (2.5 g) was added. The atmosphere was replaced with H_2 and methyl furoate was hydrogenated at 40 psi for 48 hours. The reaction was filtered through celite pad, and the pad was washed with ether. The filtrate and the wash were combined and distilled to give the title compound (71 g, 0.546 mole, $59^\circ C/5.1$ mmHg, 92%) as a colorless liquid.

2) Methyl 2-acetoxy-5-bromopentanoate
HBr gas was bubbled into Ac_2O (200 ml) at $0^\circ C$ for 2 hours. The specific gravity became 1.4. Part 1) methyl tetrahydrofuroate (70 g, 0.538 mole) was added dropwise under magnetic stirring at $0^\circ C$ and the reaction was allowed to warm to room temperature. After stirring overnight, the reaction was poured into ice (~ 1200 ml) carefully, and left for 30 minutes with occasional swirling. The products were extracted with Et_2O (600 ml x 2 and 300 ml). The combined Et_2O layers were washed with dilute NaOH ($\sim 0.5\%$) solution, until the wash became basic. The Et_2O layer was further washed with H_2O , dried over Na_2SO_4 , and filtered. The filtrate was concentrated and distilled to give the title compound (116 g, 0.458 mole, $108^\circ C/1$ mmHg, 85%) as a colorless liquid.

3) Methyl 5-bromo-2-hydroxypentanoate
MeOH (100 ml, distilled over $Mg(OMe)_2$) was saturated with HBr gas at $0^\circ C$. This was added to Part 2) compound (60 g, 0.237 mole) in MeOH (200 ml distilled over $Mg(OMe)_2$). The reaction was allowed to warm to room temperature and stirred

overnight. The reaction was concentrated
in vacuo. Toluene (200 ml) was added to the
resulting liquid, and the reaction was
concentrated. The same process was repeated
5 twice. The resulting liquid was dissolved in
EtOAc (2000 ml) and washed with 0.5% NaOH, brine,
and dried over MgSO_4 . Filtration and evaporation
of solvent gave a straw colored oil (44.8 g).
This was distilled to give the title compound (34
10 g, 0.161 mole, 68%) as a colorless liquid.

4) Methyl 5-bromo-2-oxopentanoate

Jones' reagent (CrO_3 : 9.58 g, H_2SO_4 : 8.47
ml, H_2O : 36.8 ml) was added to a magnetically
15 stirred solution of Part 3) compound (12.53 g,
59.3 mmole) in acetone (150 ml) at room
temperature. The addition was controlled to
maintain the temperature below 35°C . After the
completion of the addition, the reaction was
20 stirred at room temperature for 45 minutes.
Isopropyl alcohol (30 ml) was added dropwise and
stirred for 30 minutes. The reaction was then
diluted with H_2O (500 ml) and the products were
extracted with CH_2Cl_2 (1 l.). The CH_2Cl_2 layer
25 was washed with brine (100 ml x 3) and dried over
 MgSO_4 . Filtration and evaporation of solvents
gave the title compound (11.4 g, 54.5 mmole, 92%)
as a colorless liquid.

30 5) Methyl 5-bromo-2,2-difluoropentanoate

Part 4) compound (11.4 g, 54.5 mmole) was
added dropwise to $(\text{C}_2\text{H}_5)_2\text{NSF}_3$ (DAST) (6.8 ml,
55.7 mmole) at room temperature. The container of

Part 4) was rinsed with CH_2Cl_2 (20 ml), which was added to the reaction. The reaction was stirred at room temperature for 1 hour and poured into H_2O (80 ml). The products were extracted with CH_2Cl_2 (40 ml x 3). The combined CH_2Cl_2 layers were washed with H_2O (20 ml x 3) and dried over MgSO_4 . Filtration and evaporation of solvent gave a straw colored liquid (10.8 g). This was distilled to give the title compound (8.4 g, 36.3 mmole, 67%, 41°C/0.015 mmHg) as a colorless liquid.

6) 5-Bromo-2,2-difluoropentanoic acid

HBr gas was introduced into 48% HBr in H_2O (100 ml) with occasional cooling in an ice bath until the weight became 180 g. The HBr solution was then added to Part 5) compound (8.4 g, 36.3 mmole) at room temperature and the reaction was stirred for 5 hours at room temperature. The reaction was cooled to 0°C and poured into Et_2O (900 ml) in an ice bath. The products were extracted into the Et_2O layer. The water layer was further extracted with Et_2O (200 ml and 100 ml). The combined ether layers were washed with H_2O (200 ml). The H_2O wash was backwashed with Et_2O (100 ml). The Et_2O layers were combined and dried over MgSO_4 . Filtration and evaporation of solvent gave the title compound (7.8 g, quant.) as a colorless liquid.

7) (4-Carboxy-3,3-difluorobutyl)triphenylphosphonium bromide

Acetonitrile (23 ml) was added to a mixture of triphenylphosphine (6.7 g, 25.7 mmole) and Part

6) compound (4.6 g, 21.2 mmole). The solution was heated at gentle reflux under magnetic stirring for 30 hours. Toluene (46 ml) was then added and the reaction was brought to reflux for a brief period. The reaction was allowed to cool to 5°C and kept overnight. The resulting white precipitates were collected, washed with cold acetonitrile/toluene (1/2), and dried in a heated vacuum oven (60°C ~ 5 mmHg) to give the title bromide (9.8 g, 20.4 mmole, 96.5%) as white solid.

C. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-2,2-Difluoro-7-[3-[[[(1-oxohexyl)amino]acetyl]amino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

(4-Carboxy-3,3-difluorobutyl)triphenylphosphonium bromide (1.27 g) (prepared in Part B) is suspended in THF (15 ml). KOT-Amylate (1.7 M in toluene, 3 ml) is added at room temperature. The reaction is stirred for 4 hours. The resulting solution is transferred dropwise to aldehyde obtained in Part A, (177.1 mg) in THF (10 ml) at 0°C. The reaction is warmed to room temperature and stirred for 15 hours. Saturated NH₄Cl (25 ml) is added and the products are extracted with EtOAc (40 ml x 3). The combined organic layers are washed with brine (30 ml) and dried over MgSO₄. Filtration and evaporation of solvents afford a brown colored oil, which is purified by silica gel column to give the title compound.

Example 10

[1S-[1 β ,2 α (2E,5Z),3 α ,4 β]]-7-[3-[[[(1-Oxohexyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-2,5-heptadienoic acid

- 5 (4-Carboxy-2-butenyl)triphenylphosphonium bromide (1.13 g) is suspended in THF (15 ml). KOT Amylate (1.7 M in toluene, 3 ml) is added at room temperature. The reaction is stirred for 4 hours. The resulting solution is transferred
- 10 dropwise to aldehyde obtained in Example 9 Part A, (177.1 mg) in THF (10 ml) at 0°C. The reaction is warmed to room temperature and stirred for 15 hours. Saturated NH₄Cl (25 ml) is added and the products are extracted with EtOAc (40 ml x 3).
- 15 The combined organic layers are washed with brine (30 ml) and dried over MgSO₄. Filtration and evaporation of solvents afford a crude product, which is purified by silica gel column to give the title compound.

20

Example 11

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-2-Hydroxy-7-[3-[[[(1-Oxohexyl)amino]acetyl]amino]methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

- 25 Lithium diisopropylamine (LDA) is prepared in an argon atmosphere, by dissolving diisopropylamine (0.89 ml, 644 mg, 6.36 mmol) in THF (30 ml) at 0°C and adding dropwise a solution of 2N-n-BuLi in hexane (2.55 ml, 5.1 mmol). After stirring at
- 30 0°C for 30 minutes, the LDA solution was cooled at -78°C. Ester prepared in Example 1 (767 mg, 1.8 mmol) dissolved in THF (10 ml) is added to LDA at -78°C. The reaction is stirred at -78°C for 1

hour. Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) (MoOPH) (2.76 g, 6.36 mmol) is added in one portion. The mixture is stirred at -78°C for 30 minutes and at -30°C to -40°C for 1
5 hour. The reaction is quenched by adding saturated NaHSO₃ (20 ml), and allowed to warm to room temperature. After stirring at room temperature for 30 minutes, H₂O (0 ml) is added to give two layers which are separated. The aqueous layer is
10 extracted with EtOAc (100 ml x 3). The combined organic layers are washed with 1N-HCl (50 ml x 2), brine (20 ml x 2) and dried over MgSO₄. Filtration and evaporation of solvents affords a crude product which is purified by silica gel column to give the
15 title compound.

Example 12

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-2-Hydroxy-7-[3-[[[(1-Oxoheptyl)amino]acetyl]amino]methyl]-7-oxabicyclo-
20 [2.2.1]hept-2-yl]-5-heptenoic acid

Following the procedure of Example 2 except substituting the Example 11 ester for the Example 1 ester, the title compound is obtained.

25 Example 13

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxoheptyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-
5-heptene-1,2-diol

NaBH₄ (185 mg) is added to a magnetically
30 stirred solution of hydroxy ester prepared in Example 11 (438 mg) at 0°C. After hydrogen evolution has subsided, the reaction is allowed to warm to room temperature and stirred overnight (16

hours). Saturated NH_4Cl (10 ml) is added and stirred for 1 hour. Most of MeOH is removed in vacuo and the residue is partitioned between EtOAc (50 ml) and brine (10 ml). The water layer is reextracted with EtOAc (40 ml x 2). The combined organic layers are washed with brine (30 ml) and dried over MgSO_4 . Filtration and evaporation of solvent give a crude product, which is purified by silica gel column. The title compound is thus obtained.

Example 14

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-N-Methyl-7-[3-[[[(1-Oxo-hexyl)amino]acetyl]amino]methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenamide

40% MeNH_2 in H_2O (2 ml) is added to a magnetically stirred solution of ester prepared in Example 1 (153 mg) in THF (14 ml) at room temperature. Stirring is continued overnight (17 hours) at room temperature. The reaction is concentrated in vacuo to give a crude product which is purified by silica gel column. The title compound is then obtained.

Example 15

[1S-[1 β ,2 α (5Z),3 α (R),4 β]]-7-[3-[[[1-Oxo-2-[(1-Oxo-hexyl)amino]propyl]amino]methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

A. (2R)-2-(Hexanoylamino)propionic acid

D-alanine (20 mmol) and hexanoyl chloride (22 mmol) were reacted using the method as described in Example 5 Part A to give the title compound as a white crystalline material (2.45 g,

65.5%) after recrystallization from isopropyl ether (20 ml), m.p. 82-95°C.

5 B. [1S-[1 β ,2 α (5Z),3 α (R),4 β]]-7-[3-[[[1-Oxo-2-[(1-Oxohexyl)amino]propyl]amino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

10 Part A acid compound (1 mmol) and chiral amine prepared as described in Example 1 Part C (1 mmol) were coupled using CDI (1 mmol) as described in Example 5 Part B. The crude product was chromatographed on silica gel (Baker for flash chromatography) eluting with 2-4% MeOH in Et₂O. The eluted product was triturated with Et₂O to
15 give the title methyl ester as a white solid (217 mg, 50%).

TLC: silica gel, 5% MeOH in Et₂O, vanillin R_f=0.47.

20 Example 16
[1S-[1 β ,2 α (5Z),3 α (R),4 β]]-7-[3-[[[1-Oxo-2-[(1-Oxohexyl)amino]propyl]amino]methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic acid

25 The Example 15 methyl ester (215 mg, 0.49 mmol) was hydrolyzed with LiOH solution in a THF-water mixture as described in Example 6. The viscous product was dissolved in EtOAc (~2-3ml). On standing crystalline material was deposited. This was harvested by filtration and washed with
30 Et₂O to give title acid (166.6 mg, 80%), m.p. 101-103°.

Anal Calcd for $C_{23}H_{38}O_5N_2$: C, 65.37; H, 9.06;
N, 6.63

Found: C, 65.30; H, 9.16; N, 6.46

5 TLC: Silica gel, 10% MeOH in CH_2Cl_2 , vanillin,
 $R_f=0.48$.

$[\alpha]_D^{25}=+25.5^\circ$ ($c=1.37$, MeOH).

10

Example 17

[1S-[1 β ,2 α (5Z),3 α (S),4 β]]-7-[3-[[[1-Oxo-2-[(1-oxohexyl)amino]propyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

15

A. (2S)-2-(Hexanoylamino)propionic acid

L-Alanine (10 mmol) and hexanoyl chloride (11 mmol) were reacted using the method described in Example 5 Part A to give the title compound as a white crystalline material (1.091 g, 58%) after recrystallization from isopropyl ether (~6 ml).

20

B. [1S-[1 β ,2 α (5Z),3 α (S),4 β]]-7-[3-[[[1-Oxo-2-[(1-oxohexyl)amino]propyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

25

Part A compound (1 mmol) and chiral amine (prepared as described in Example 1 Part C) (1 mmol) were coupled using CDI (1 mmol) as described in Example 5 Part B. The crude product was chromatographed on silica gel (Baker for flash chromatography) eluting with 2% MeOH in Et_2O to give clean title methyl ester (178 mg, 41%) and additional material (129 mg, 29%) contaminated with material moving slower on TLC. TLC: silica

30

gel, 5% MeOH in Et₂O, vanillin, R_f=0.55. Slower moving contaminant R_f=0.34.

Example 18

5 [1S-[1 β ,2 α (5Z),3 α (S),4 β]]-7-[3-[[[1-Oxo-2-[(1-oxohexyl)amino]propyl]amino]methyl]-7-oxabicyclo-
[2.2.1]hept-2-yl]-5-heptenoic acid

The Example 17 methyl ester (175 mg, 0.40 mmol) was hydrolyzed with LiOH in a THF-water
10 mixture as described in Example 6. The viscous product was dissolved in EtOAc (2 ml). Crystalline material was deposited on standing. This was harvested by filtration and washed with cold Et₂O to give the title compound (129 mg, 76%),
15 m.p. 104-106°C.

Anal Calcd for C₂₃H₃₈O₅N₂: C, 65.37; H, 9.06;
N, 6.63

Found: C, 65.53; H, 9.26; N, 6.50

20 TLC: silica gel, 10% MeOH in CH₂Cl₂, vanillin, R_f=0.48.

[α]_D = -40° (C=1.29, MeOH)

25

Example 19

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[2-Methyl-2-[(1-oxohexyl)amino]-1-oxopropyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid,
30 methyl ester

A. 2-(Hexanoylamino)-2-methylpropionic acid

2-Aminoisobutyric acid (2.0 g, 19.4 mmol) and n-hexanoyl chloride (3.0 g, 22.4 mmol) were reacted in the presence of NaOH (1.6 g, 40 mmol) in a mixture of ether and water using the method described in Example 5, Part A. The title compound (1.90 g, 49%) was obtained after crystallization from benzene, m.p. 141-143°C.

10 B. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[2-Methyl-2-[(1-Oxohexyl)amino]-1-oxopropyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

15 Part A compound (1 mmol) was reacted with CDI (1 mmol) and then with chiral amine prepared as described in Example 1 Part C (1 mmol) employing the method described in Example 1 Part D. The crude product was chromatographed on silica gel (25 g, Baker for flash chromatography), eluting
20 with 2% MeOH in Et₂O to give title ester (235 mg, 52%) as white crystalline material.

TLC: silica gel, 5% MeOH in Et₂O, vanillin, R_f=0.46.

25

Example 20

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[2-Methyl-2-[(1-oxohexyl)amino]-1-oxopropyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

30 The Example 19 methyl ester (231 mg, 0.51 mmol) was hydrolyzed with LiOH in a water-THF mixture as described in Example 6. The product

was crystallized from ethyl acetate (~4 ml) to give title acid (154.2 mg, 69%), m.p. 81-87°C.

TLC: silica gel, 10% MeOH in CH₂Cl₂, vanillin,

5 $R_f=0.42$.

$[\alpha]_D = -10.1^\circ$ (c=1.63, MeOH)

Anal Calcd for C₂₄H₄₀O₅N₂: C, 66.02; H, 9.24;
N, 6.42

10 Found: C, 65.92; H, 9.37; N, 6.46

Example 21

15 [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-oxoheptyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic acid, methyl ester

A. 2-(Heptanoylamino)acetic acid

Glycine (1.5 g, 20 mmol) and heptanoyl chloride (22 mmol) were reacted in the presence of NaOH (40 mmol) in a mixture of water and ether
20 using the method described in Example 5. The crude product was recrystallized from EtOAc (30 ml) to give title compound (2.71 g, 72%), m.p. 98-100°C.

25 B. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-oxoheptyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

Part A compound (1 mmol) was reacted with
30 CDI (1 mmol) and then with chiral amine (1 mmole) prepared as described in Example 1 Part C employing the method described in Example 5 Part B. The crude product was chromatographed on silica gel (25

g, Baker for flash chromatography) eluting with EtOAc and 2% MeOH in EtOAc to give title ester (270 mg, 62%) as an oil. TLC: silica gel, 5% MeOH in EtOAc, vanillin, $R_f=0.45$.

5

Example 22

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxoheptyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic acid

10 The Example 21 methyl ester (265 mg, 0.607 mmol) was hydrolyzed with LiOH in a water-THF mixture as described in Example 6. The crude crystalline product was recrystallized from EtOAc (4 ml) to give title acid (204 mg, 80%), m.p. 15 114-116°C.

TLC:Silica gel, 10% MeOH in CH₂Cl₂, vanillin, $R_f=0.40$

[α]_D = -6.6° (C=1.15, MeOH).

20

Anal Calcd for C₂₃H₃₈O₅N₂: C, 65.37; H, 9.06; N, 6.42

Found: C, 65.38; H, 9.01; N, 6.64

25

Example 23

[1S-(1 β ,2 α ,3 α ,4 β)]-7-[3-[[[(1-Oxohexyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-heptanoic acid, methyl ester

30

A. [1S-(1 β ,2 α ,3 α ,4 β)]-7-[3-(Hydroxymethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-heptanoic acid, methyl ester

To 800 mg (3.0 mmole) of the [1S-(1 β ,2 α (Z),-3 α ,4 β)]-7-[3-(hydroxymethyl)-7-oxabicyclo[2.2.1]-

5 positive pressure of hydrogen and the reaction was stirred for 8 hours at 25°, filtered through a celite plug and evaporated to provide 730 mg (90%) of the title A compound.

1.0 B. [1S-(1 β ,2 α ,3 α ,4 β)]-7-[3-[[[(1-Oxohexyl)-amino]acetyl]amino]methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]heptanoic acid, methyl ester

Following the procedure of Example 1 except
15 substituting the Part A alcohol-ester for the
alcohol ester employing in Example 1 Part B, the
title product is obtained.

Example 24

20 [1S-[1 β , 2 α (5Z), 3 α , 4 β]]-7-[3-[[[(1-Oxo-3-[(1-oxo-
pentyl)amino]propyl)amino]methyl]-7-oxabicyclo-
[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

A. 3-(Pentamethylamino)propionic acid

25 β -Alanine (20 mmol) was reacted with
valeryl chloride (22 mmol) in the presence of NaOH
(40 mmol) in a mixture of H_2O and ether using the
method described in Example 5. The crude
crystalline product (2.75 g, 79%) was
recrystallized from a mixture of isopropyl ether
30 (150 ml) and ethyl acetate (10 ml) to give title
acid (1.51 g, 44%), m.p. 73-76°C.

B. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxo-3-[(1-oxopentyl)amino]propyl]amino)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester]

5 Part A acid (1 mmol) was reacted with carbonyl diimidazole (1 mmol) followed by [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-(aminomethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester (prepared as described in Example 1
10 Part C (1 mmol)). The crude product was chromatographed on silica gel (25 g, Baker for flash chromatography) eluting with 5-10% MeOH in Et₂O to give title product as a white solid (304 mg, 72%).

15 TLC: silica gel, 10% MeOH in Et₂O, vanillin, R_f=0.47.

Example 25

20 [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxo-3-[(1-oxopentyl)amino]propyl]amino)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid]

The Example 24 methyl ester (301 mg, 0.71 mmol) was hydrolyzed with LiOH in a THF-H₂O
25 mixture as described in Example 6 to give a white solid (249 mg). This was recrystallized from EtOAc (~4 ml) to give title acid (218 mg, 75%), m.p. 113-115°.

30 TLC: silica gel, 10% MeOH in CH₂Cl₂, vanillin, R_f=0.28

Anal Calcd for $C_{22}H_{36}O_5N_2$: C, 64.68; H, 8.88;
N, 6.86

Found: C, 64.65; H, 8.85; N, 6.87

5 $[\alpha]_D = -8.4^\circ$ (c=1.0, MeOH)

Example 26

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(4-Phenylbenzoyl)-
amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]-
10 hept-2-yl]-5-heptenoic acid, methyl ester

A. 2-[(4-Phenylbenzoyl)amino]acetic acid

Glycine (5 mmol) was reacted with
4-biphenylcarbonyl chloride (about 5 mmol) in the
presence of 1N NaOH solution (10 ml), ether (21
15 ml) and THF (2 ml) using the procedure described
in Example 5. Most of the product precipitated as
a solid on acidification of the aqueous layer
during the work up. This was found to be quite
insoluble in $CHCl_3$ and EtOAc. It was largely
20 dissolved in CH_3CN (~35 ml) and filtered to remove
insoluble material. Crystalline acid (0.81 g,
63%) was deposited on cooling, m.p. 207-218°C
decomp.

25 B. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(4-
Phenylbenzoyl)amino]acetyl]amino]-
methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-
5-heptenoic acid, methyl ester

Part A acid (1 mmol) was reacted with
30 carbonyldiimidazole (1 mmole) followed by
[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-(aminomethyl)-7-oxa-
bicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl
ester (1 mmole) as in Example 1, Part C. After

stirring overnight at room temperature, a large amount of solid was still out of solution and TLC indicated the reaction was not complete. DMF (3 ml) was added to give a nearly clear reaction mixture and the mixture was left stirring an additional 24 hours. After the usual work up, the viscous product was chromatographed on silica gel (30 g of Baker for flash chromatography), eluting with 2% MeOH in CH_2Cl_2 . The material obtained from the column was crystallized from ethyl acetate (2 ml) to give title ester (143 mg, 28%) as a white solid.

TLC: silica gel, 10% MeOH in CH_2Cl_2 , UV + vanillin, $R_f=0.51$.

Example 27

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7- β -[[[(4-Phenylbenzoyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic acid

The Example 26 methyl ester (141 mg, 0.279 mmol) was hydrolyzed with LiOH as described in Example 6 to give a white solid. This was triturated with EtOAc to give title acid (118 mg, 86%), m.p. 227-229°dec.

Anal Calcd for $\text{C}_{29}\text{H}_{34}\text{O}_5\text{N}_2$: C, 71.00; H, 6.99;
N, 5.71

Found: C, 70.90; H, 6.91; N, 5.65

Example 27A

[1S-(1 β , 2 α , 3 α , 4 β)]-7-[3-[[[2-Methyl-2-[(1-oxohexyl)amino]-1-oxopropyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]heptanoic acid

- 5 Following the procedure of Example 2 except substituting the Example 19 Part A acid for the Example 1 Part A acid, the title acid is obtained.

Example 28

10 [1S-[1 β , 2 α (5Z), 3 α , 4 β)]-7-[3-[[[[(1-Oxopropyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

- 15 Following the procedure of Examples 1 and 2 except substituting propanoyl chloride for hexanoyl chloride, the title compound is obtained.

Example 28A

20 [1S-[1 β , 2 α (5Z), 3 α , 4 β)]-7-[3-[[[[(1-Oxoethyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

 Following the procedure of Examples 1 and 2 except substituting acetyl chloride for 6-hexanoyl chloride, the title compound is obtained.

25 Example 29

[1S-[1 β , 2 α (5Z), 3 α , 4 β)]-7-[3-[[[[(1-Oxo-2-butenyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

- 30 Following the procedure of Examples 1 and 2 except substituting 2-butenoyl chloride for hexanoyl chloride, the title compound is obtained.

Example 29A

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxo-3-butynyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

5 Following the procedure of Examples 1 and 2 except substituting 3-butynoyl chloride for hexanoyl chloride, the title compound is obtained.

Example 30

10 [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(Pentylamino)-carbonyl]amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

15 Following the procedure of Examples 3 and 4 except substituting n-pentyl isocyanate for n-butyl isocyanate, the title compound is obtained.

Example 30A

20 [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(Phenylamino)-carbonyl]amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

 Following the procedure of Examples 3 and 4 except substituting phenyl isocyanate for n-butyl isocyanate, the title compound is obtained.

25 Example 31

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(Phenylcarbonyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

30 Following the procedure of Examples 1 and 2 except substituting benzoyl chloride for hexanoyl chloride, the title compound is obtained.

Example 32

[1S-[1 β , 2 α (5Z), 3 α , 4 β]]-7-[3-[[[1-Oxo-3-[ethyl-(phenylcarbonyl)amino]propyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

- 5 Following the procedure of Examples 5 and 6 except substituting 3-(ethylamino)propionic acid for sarcosine and benzoyl chloride for hexanoyl chloride, the title compound is obtained.

Example 33

[1S-[1 β , 2 α (5Z), 3 α , 4 β]]-7-[3-[[[[(Benzyloxycarbonyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

- 10
15 Following the procedure of Examples 7 and 8 except substituting benzyl chloroformate for n-butyl chloroformate, the title compound is obtained.

Example 34

[1S-(1 β , 2 α , 3 α , 4 β)]-7-[3-[[[[(1-Oxobutyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-heptanoic acid

- 20
25 Following the procedure of Example 23 except substituting butanoyl chloride for hexanoyl chloride, the title compound is obtained.

Example 35

[1S-(1 β , 2 α , 3 α , 4 β)]-7-[3-[[[[(1-Oxo-2-propenyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]heptanoic acid

- 30 Following the procedure of Example 23 except substituting propenyl chloride for hexanoyl chloride, the title compound is obtained.

Example 36

[1S-(1 β ,2 α ,3 α ,4 β)]-7-[3-[[[(1-Oxo-4-pentynyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]heptanoic acid

- 5 Following the procedure of Example 23 except substituting 4-pentynoyl chloride for hexanoyl chloride, the title compound is obtained.

Example 37

- 10 [1S-(1 β ,2 α ,3 α ,4 β)]-7-[3-[[[(Phenylamino)carbonyl]-amino]acetyl]amino]methyl]-7-oxabicyclo-
[2.2.1]hept-2-yl]heptanoic acid

- 15 Following the procedure of Examples 23 and 3 except substituting phenyl isocyanate for n-butyl isocyanate in Example 3 Part A, the title compound is obtained.

Example 38

- 20 [1S-(1 β ,2 α ,3 α ,4 β)]-7-[3-[[[1-Oxo-4-[propyl(1-oxo-benzyl)amino]butyl]amino]methyl]-7-oxabicyclo-
[2.2.1]hept-2-yl]heptanoic acid

- 25 Following the procedure of Examples 23 and 5 except substituting 4-(propylamino)butanoic acid for sarcosine in Example 5 Part A, the title compound is obtained.

Example 39

- 30 [1S-(1 β ,2 α ,3 α ,4 β)]-7-[3-[[[Benzyloxycarbonyl]-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-
2-yl]heptanoic acid

 Following the procedure of Examples 23 and 7 except substituting benzyl chloroformate for

n-butyl chloroformate, the title compound is obtained.

Example 40

5 [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[2-[[[(1-Oxohexyl)amino]-
acetyl]amino]ethyl]-7-oxabicyclo[2.2.1]hept-2-yl]-
5-heptenoic acid

10 A. [1S-[1 β ,2 α (Z),3 α ,4 β]]-7-[3-(2-Oxo)ethyl-
7-oxabicyclo[2.2.1]hept-2-yl]-5-
heptenoic acid, methyl ester

Into a dry 100 ml round bottom 3-necked flask containing a stir bar was added dried 12.9 g (37.7 mmol) methoxymethyltriphenylphosphonium chloride ((C₆H₅)₃P⁺-CH₂OCH₃Cl⁻) and 235 ml
15 distilled toluene (stored over molecular sieves). The resulting suspension was stirred in an ice-bath, under argon, until cold and then a 1.55 M solution of 18.3 ml (28.3 mmol) of potassium t-amylate in toluene was added dropwise. A bright
20 red solution formed which was stirred at 0°C for an additional 35 minutes. Thereafter, a solution of 4.97 g (18.8 mmol) [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-formyl-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester in 60 ml toluene was added by
25 means of a dropping funnel over a 35 minute period with the ice-bath still in place. The reaction was then quenched by addition of 2.3 g (39 mmol) acetic acid in 5 ml ether. The reaction mixture immediately turned pale yellow and was immediately poured
30 into 200 ml saturated NH₄Cl, and extracted with ether (4 x 200 ml). The combined ether phases were washed with NaCl, saturated solution, and dried (MgSO₄) and concentrated to yield a yellow oil in a

white crystalline solid (phosphine oxide). The white solid was triturated with EtOAc and the mother liquor was purified by chromatography on an LPS-1 silica column. The fractions obtained were

5 (A) [1S-[1 β ,2 α (Z),3 α ,4 β]]-7-[3-(2-oxo)ethyl-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester, (B) [1S-[1 β ,2 α (Z),3 α ,4 β]]-7-[3-(2-methoxy)-ethenyl-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester, and (C) [1S-[1 β ,2 α (Z),3 α ,4 β]]-

10 7-[3-(2,2-dimethoxy)ethyl-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester.

Compounds (B) and (C) are each treated with trifluoroacetic acid to convert each to compound (A).

15 B. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-(2-Hydroxyethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

The aldehyde (1.4 g, 5 mmol) from part A in

20 methanol (50 ml) is treated with NaBH₄ (0.19 g, 5 mmol) in an argon atmosphere at 0°C. After stirring at 0° for 1 hour, the reaction is quenched by addition of 2N HCl (to pH 2). The methanol is removed in vacuo and the reaction mixture is taken

25 up in ether. The ether solution is washed with saturated KHCO₃, saturated NaCl and dried (MgSO₄). The ether is evaporated to yield the title B compound.

5 Following the procedure of Examples 1 and 2 except substituting the above part B alcohol for the alcohol used in Example 1 Part B, the title compound is obtained.

[1S-(1 β ,2 α ,3 α ,4 β)]-7-[3-[2-[[[(1-Oxohexyl)amino]-acetyl]amino]ethyl]-7-oxabicyclo[2.2.1]hept-2-yl]-heptanoic acid

Following the procedure of Examples 40 and 15 except substituting [1S-(1 β ,2 α ,3 α ,4 β)]-7-[3-formyl-7-oxabicyclo[2.2.1]hept-2-yl]heptanoic acid, methyl ester for [1S-[1 β ,2 α (2),3 α ,4 β)]-7-[3-formyl-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester, the title compound is obtained.

[1S-[1 β ,2 α (5Z),3 α ,4 β]-7-[3-[2-[[[(1-Oxopropyl)amino]-acetyl]amino]ethyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

25 Following the procedure of Example 40
except substituting propionoyl chloride for
hexanoyl chloride, the title compound is obtained.

Example 43

30 (1 β , 2 α , 3 α , 4 β)-7-[3-[2-[[[(1-Oxo-2-butenyl)amino]-acetyl]amino]ethyl]-7-oxabicyclo[2.2.1]hept-2-yl]-heptanoic acid

Following the procedure of Examples 40 and 23 except substituting 2-butenoyl chloride for hexanoyl chloride, the title compound is obtained.

5 Example 44

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[2-[[[(Phenylamino)-
carbonyl]amino]acetyl]amino]ethyl]-7-oxabicyclo-
[2.2.1]hept-2-yl]-5-heptenoic acid

10 Following the procedure of Examples 40 and 3
except substituting phenyl isocyanate for
n-butyl isocyanate, the title compound is obtained.

Example 45

15 [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[2-[[1-Oxo-3-[ethyl(1-
oxophenylmethyl)amino]propyl]amino]ethyl]-7-
oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

20 Following the procedure of Examples 40 and 5
except substituting 3-(ethylamino)propionic acid for
sarcosine and benzoyl chloride for hexanoyl
chloride, the title compound is obtained.

Example 46

25 [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[4-[[[(1-Oxohexyl)-
amino]acetyl]amino]butyl]-7-oxabicyclo[2.2.1]-
hept-2-yl]-5-heptenoic acid

A. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-(3-Oxo)-
propyl-7-oxabicyclo[2.2.1]hept-2-yl]-
5-heptenoic acid, methyl ester

30 Following the procedure of Example 40 Part A
except substituting [1S-[1 β ,2 α (Z),3 α ,4 β]]-7-[3-(2-oxo)-
ethyl-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic
acid, methyl ester for [1S-[1 β ,2 α (Z),3 α ,4 β]]-7-[3-
formyl-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic

acid, methyl ester, the title A compound is obtained.

- 5 B. [1S-[1 β ,2 α (Z),3 α ,4 β]]-7-[3-(4-Oxo)-
butyl-7-oxabicyclo[2.2.1]hept-2-yl]-
5-heptenoic acid, methyl ester

Following the procedure of Example 40 Part A except substituting the aldehyde from Part A above for [1S-[1 β ,2 α (Z),3 α ,4 β]]-7-[3-formyl-7-oxabicyclo-
10 [2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester, the title B compound is obtained.

- 15 C. [1S-[1 β ,2 α (Z),3 α ,4 β]]-7-[3-(4-Hydroxy-
butyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-
heptenoic acid, methyl ester

Following the procedure of Example 40 Part B except substituting the title B aldehyde for [1S-[1 β ,2 α (Z),3 α ,4 β]]-7-[3-(2-oxo)ethyl-7-oxabi-
cyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl
20 ester, the title C alcohol is obtained.

- 25 D. [1S-[1 β ,2 α (Z),3 α ,4 β]]-7-[3-[4-[[[(1-
Oxohexyl)amino]acetyl]amino]butyl]-7-
oxabicyclo[2.2.1]hept-2-yl]-5-
heptenoic acid

Following the procedure of Examples 1 and 2 except substituting the above Part C alcohol for the alcohol used in Example 1, the title compound is obtained.

Example 47

[1S-[1 β , 2 α (5Z), 3 α , 4 β]]-8-[3-[[[(1-Oxohexyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]-hept-2-yl]-5-octenoic acid

- 5 A. [1S-(1 β , 2 α , 3 α , 4 β)]-3-[3-(Hydroxymethyl)-7-oxabicyclo[2.2.1]hept-2-yl]propionaldehyde

 A slurry of methoxymethyltriphenylphosphonium chloride (1.09 kg, 3.18 mol) in Burdick and Jackson
10 sieve-dried tetrahydrofuran (3 liters) was chilled to 0°C and treated dropwise with 1.4M potassium t-amylate in toluene (1910 ml, 2.67 mol) over 20 minutes. The resultant dark red solution was
15 stirred at 0°C for 1 hour. The mixture was then treated slowly over 5 minutes with solid hemiacetal (XIII in reaction sequence C) prepared as described in Example 3 of U. S. Patent No.
4,143,054 (200 g, 1.28 mol). The temperature gradually rose to 23°C. The mixture was stirred
20 vigorously at room temperature for 90 minutes. The reaction mixture was then chilled to 0°C and treated slowly with acetaldehyde (124 ml, 2.2 mol) over 10 minutes. The mixture was diluted with
25 water (2500 ml) and treated with 10% hydrochloric acid to pH 7. The mixture was then extracted with ether (7x2 liters). The combined ether extracts were dried over magnesium sulfate, filtered, and the filtrates concentrated in vacuo. The resultant mixture was treated with isopropyl ether (4 liters)
30 and stirred overnight. The mixture was chilled to -10°C for 90 minutes then filtered. The solids were washed thoroughly with isopropyl ether. The filtrate was concentrated in vacuo to an oily

residue (460 g). This oily residue was treated with water (4000 ml) and stirred vigorously for 2 hours. The aqueous layer was decanted and the oily residue treated two additional times with water (2x1 liter). After the third wash, the residue solidified and was filtered. The combined aqueous triturations were concentrated in vacuo to 3.5 liters. The cloudy mixture was filtered through a bed of Celite. The filtrate was concentrated again to a volume of 2.3 liters. The cloudy solution was chilled in an ice bath and treated slowly with concentrated hydrochloric acid (683 ml). The mixture was then stirred at room temperature for 3 hours. After this time the solution was neutralized by the slow addition of solid sodium bicarbonate (720 g). The mixture was filtered through a bed of Celite then extracted with hexane (4 x 2 liters) then ethyl acetate (10 x 2 liters). The combined ethyl acetate extracts were dried over MgSO_4 and concentrated in vacuo. The solid residue was trituated with hexane (1 liter), filtered, and dried in vacuo to yield 220 g (100%) of desired compound (hemiacetal F in reaction sequence C), m.p. 104-105°C, $[\alpha]_D^{25} = +27^\circ$ c=1 MeOH.

25

TLC: silica gel; EtOAc; $R_f=0.3$; $\text{Ce}(\text{SO}_4)_2$.

The above Wittig procedure was repeated on the hemiacetal F used in place of hemiacetal XIII to form the title aldehyde.

30

B. [1S-[1 β ,2 α (Z),3 α ,4 β]]-8-[3-(Hydroxy-methyl)-7-oxabicyclo[2.2.1]hept-2-yl]-5-octenoic acid, methyl ester

A Wittig reagent was prepared in
5 dimethyl sulfoxide (dried over calcium hydride) by
adding a solution of sodium methylsulfinylmethide
(prepared by heating 600 mg of sodium hydride in
60 ml of dimethyl sulfoxide at 75° until hydrogen
evolution stops) dropwise to a solution of 5.32 g
10 (12 mmole) of 4-carboxybutyl triphenylphosphonium
bromide in 100 ml of dimethyl sulfoxide. After
the first orange color lasting more than 10 seconds
formed, an equivalent amount of base was added to
form the ylide. To this deep orange solution was
15 added a solution of Part A aldehyde 1.02 g (6
mmole) in 20 ml of dimethyl sulfoxide and the
resulting mixture stirred at room temperature for
45 minutes. The reaction was quenched by addition
of 24 mmole of acetic acid and the mixture poured
20 into brine (300 ml) and extracted with ether (3 x
200 ml). Concentration of these extracts gave an
oil which was stirred with saturated sodium
bicarbonate solution until crystalline triphenyl-
phosphine oxide formed in the mixture. This
25 mixture was washed with benzene and acidified with
10% hydrochloric acid. The aqueous layer was
saturated with salt and extracted with ether which
on drying (sodium sulfate) and concentration gave
2.43 g of crude product. The mixture was stirred
30 24 hours with 10% aqueous sodium hydroxide and
reisolated by acidification and ether extraction.
The product was purified on 70 g of silica gel
with 50/50 ethyl acetate-hexane as the eluant which

gave 1.1 g of acid. This was treated with diazomethane (CH_2N_2) in Et_2O to give the title compound.

- 5 C. [1S-[1 β ,2 α (Z),3 α ,4 β]]-8-[3-[[[(1-Oxohexyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-octenoic acid

Following the procedure of Examples 1 and 2
10 except substituting the title B ester for the ester used in Example 1 Part B, the title compound is obtained.

Example 48

- 15 [1S-[1 β ,2 α (Z),3 α ,4 β]]-6-[3-[[[(1-Oxohexyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-1-(1H-tetrazol-5-yl)-4-hexene

- 20 A. [1S-[1 β ,2 α (Z),3 α ,4 β]]-6-[3-Hydroxy-methyl-7-oxabicyclo[2.2.1]hept-2-yl]-1-(1H-tetrazol-5-yl)-4-hexene

To 5.5 g (11.8 mmole) of triphenyl-4-(1H-tetrazol-5-yl)butyl phosphonium bromide in 100 ml of tetrahydrofuran (THF) at 0° is added 2.78 g (23.6 mmole) potassium t-butoxide. The reaction
25 is stirred at 25° for 30 minutes and (exo)octahydro-5,8-epoxy-1H-benzopyran-3-ol, (2 g, 11.8 mmole, prepared as described in U. S. Patent No. 4,143,054) is added in 30 ml of THF. The reaction is stirred for 2 hours and quenched with dilute
30 aqueous HCl. The aqueous layer is extracted with 250 ml of ethyl acetate. The combined organic solutions are evaporated in vacuo, diluted with 500 ml of a 5% NaHCO_3 solution, washed with 100 ml

of ether, acidified with dilute HCl to pH 3, and extracted with three 500 ml portions of ethyl acetate. The combined organic solutions are dried over anhydrous MgSO_4 , and purified by silica chromatography using a 5% methanol in methylene chloride eluant to provide 2 g of title A compound.

10 B. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-6-[3-[[[(1-Oxoheptyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-1-(1H-tetrazol-5-yl)-4-hexene

15 Following the procedure of Examples 1 and 2 except substituting the Part A compound for the hydroxymethyl compound used in Example 1 Part B, the title compound is obtained.

Example 49

20 [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxoheptyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-N-hydroxy-N-methyl-5-heptenamide

A solution of Example 2 acid (0.82 mmole) in dry benzene (5.0 ml) is treated with oxalyl chloride (1 ml; 11.24 mmole or 13.7 eq.) and a drop of DMF, and stirred at room temperature under nitrogen for 2 hours. The excess oxalyl chloride and solvent are blown off by a stream of nitrogen while heating the reaction flask in a warm water bath and the oil obtained dried in vacuo (oil pump) for 1 hour. The residual acid chloride is dissolved in dry tetrahydrofuran (1.5 ml) and added dropwise into a cold solution (0°, ice-water) of 98% methylhydroxylamine hydrochloride (139.8 mg; 1.64

mmole; 2 eq.) and triethylamine (0.34 ml; 2.46 mmole; 3 eq.) in tetrahydrofuran (2 ml) and water (2.0 ml). The mixture is stirred at 0° under nitrogen for 30 minutes and at room temperature for 5.5 hours, diluted with water (10 ml) and extracted twice with dichloromethane (50 ml). The organic extract is washed with 1N HCl (10 ml), 5% NaHCO₃ (5 ml) and water (10 ml), dried (anhydrous MgSO₄), filtered and evaporated to dryness giving the crude product, which is purified by silica gel column to afford the title compound.

Example 50

[1S-[1 β ,2 α (6Z),3 α ,4 β]]-7-[3-[[[(1-Oxohexyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-6-heptenoic acid

A. [1S-[1 β ,2 α (6Z),3 α ,4 β]]-7-[3-(Hydroxymethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-heptenoic acid, methyl ester

A slurry of carboxypentyl triphenylphosphonium bromide in THF is cooled in an ice bath and treated dropwise with 1.4 M KOT-amylate in toluene. After completion of this addition, the reaction mixture is allowed to warm to room temperature and is stirred for 6 hours. To this stirred solution is then added a solution of hemiacetal XIII (reaction sequence G) (prepared as described in Example 3 of U. S. Patent No. 4,143,054) in THF dropwise over 30 minutes. The reaction mixture is then stirred overnight (15 hours). The mixture is cooled in an ice bath and quenched with HOAc. The solvent is removed in vacuo and the resulting residue is dissolved in

saturated NaCl solution. This is extracted with chloroform. The chloroform layers are then extracted with saturated NaHCO₃ solution. The aqueous extracts are acidified to pH~3.5 by addition of aqueous HCl solution, and then are extracted with several portions of chloroform. The combined chloroform extracts are concentrated in vacuo to afford the crude product. The crude acid is esterified with excess ethereal diazomethane at 0°C and then is purified by chromatography on silica gel to afford the title ester.

B. [1S-[1 β ,2 α (6Z),3 α ,4 β]]-7-[3-[[[(1-Oxohexyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-6-heptenoic acid

Following the procedure of Example 1 except substituting the Part A ester for the hydroxymethyl compound used in Example 1 Part B, the title compound is obtained.

Example 51

[1S-[1 β ,2 α (2E),3 α ,4 β]]-7-[3-[[[(1-Oxohexyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-2-heptenoic acid

A. [1S-(1 β ,2 α ,3 α ,4 β)]-5-[3-(Hydroxymethyl)-7-oxabicyclo[2.2.1]hept-2-yl]pentanal

Following the procedure of Example 47 Part A, except substituting [1S-(1 β ,2 α ,3 α ,4 β)]-3-[3-(hydroxymethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-propionaldehyde for the hemiacetal XIII (see reaction sequence C or E), [1S-(1 β ,2 α ,3 α ,4 β)]-4-[3-

(hydroxymethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-butanal is obtained. Then by repeating the procedure of Example 47 Part A on [1S-(1 β ,2 α ,3 α ,4 β)]-4-[3-(hydroxymethyl)-7-oxabicyclo[2.2.1]hept-2-yl]butanal, the title A aldehyde is produced.

10 B. [1S-[1 β ,2 α (2E),3 α ,4 β)]-7-[3-(Hydroxymethyl)-7-oxabicyclo[2.2.1]hept-2-yl]-2-heptenoic acid, methyl ester

To a stirred solution of the title A aldehyde in MeOH is added carbomethoxymethylene triphenylphosphorane. The resulting solution is stirred under argon at room temperature for 24
15 hours. The solvent is then removed in vacuo and the resultant viscous oil is triturated with ether. The precipitated triphenylphosphine oxide is removed by filtration and the filtrate is concentrated in vacuo to afford a mixture of the
20 (E) and (Z) esters. Purification is affected by chromatography to afford the pure title ester.

25 C. [1S-[1 β ,2 α (2E),3 α ,4 β)]-7-[3-[[[(1-Oxoheptyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-2-heptenoic acid

Following the procedure of Example 1 except substituting the Part B ester for the ester used in Example 1 Part B, the title compound is
30 obtained.

Example 52

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[(Methylamino)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

- 5 Chiral amine from Example 1, Part C, (1 mmole) and N,N-dimethylformamide dimethylacetal (1.5 mmole) are dissolved in CH₂Cl₂ (6 ml). The reaction is stirred at room temperature overnight. The solvent and the excess reagent are
- 10 evaporated to give crude amidine, which is dissolved in CH₂Cl₂ (5 ml). Methyl triflate (2 mmole) is added into the reaction at room temperature and the reaction is stirred for 1 hour at room temperature. The organic solvent and the
- 15 excess reagent are evaporated off in vacuo and the residue is treated with methanolic hydrogen chloride at room temperature overnight. The reaction is concentrated in vacuo and the resulting crude product is dissolved in 1N HCl.
- 20 The water layer is washed with ethyl ether and basified with saturated NaHCO₃. The water layer is extracted with ethyl ether, which is dried over MgSO₄. Filtration and evaporation of the solvent leave a crude product, which is purified by silica
- 25 gel column to give the title compound.

The title compound is then employed in place of the chiral amine from Example 1 Part C to prepare compounds of the invention wherein R¹ is CH₃.

Example 53

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxononyl)amino]-
acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-
5-heptenoic acid, methyl ester

5 A. N-Nonanoyl glycine

Glycine (20 mmol) was reacted with nonanoyl
chloride (22 ml) in the presence of NaOH (40 mmol)
in a mixture of water and ether as described in
Example 1 Part A. The crude crystalline product
10 (4.25 g) was recrystallized from ethyl acetate
(40-50 ml) to give the title compound (3.42 g,
79.5%), m.p. 106-109°C.

15 B. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-
Oxononyl)amino]acetyl]amino]methyl]-7-
oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic
acid, methyl ester

Part A compound (1 mmol) was reacted with
carbonyldiimidazole (1 mmol) followed by Example 1
20 Part C chiral amine as described in Example 1
Part D. The crude product was chromatographed on
silica gel (30 g, Baker for flash chromatography)
eluting with EtOAc and 2% MeOH in EtOAc to give
the title ester (305 mg, 65.6%) as a colorless oil.

25 TLC: silica gel, 2% MeOH in EtOAc, vanillin,
R_f=0.39.

Example 54

30 [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxononyl)amino]-
acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-
2-yl]-5-heptenoic acid

The Example 53 methyl ester (302 mg, 6.5 mmol) was hydrolyzed with LiOH in a THF-H₂O mixture as described in Example 2 to give crystalline material. This was recrystallized from EtOAc (about 8 ml) to give title acid (233 mg, 79.5%), m.p. 121-127°C.

TLC: silica gel, 10% MeOH in CH₂Cl₂, vanillin, R_f=0.44

10 $[\alpha]_D = -6.0^\circ$ (c=1, MeOH)

Anal Calcd for C₂₅H₄₂O₅N₂: C, 66.64; H, 9.39; N, 6.22

Found: C, 66.27; H, 9.32; N, 6.28

15

Example 55

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxo-octyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

20

A. N-Octanoylglycine

Glycine (20 mmol) was reacted with octanoyl chloride (22 mmol) in the presence of NaOH (40 mmol) in a mixture of water and ether using the method described in Example 1 Part A. The crude crystalline product (3.06 g, 76%) was recrystallized from EtOAc (15 ml) to give the title compound (1.11 g, 28%), m.p. 105-107°C.

25

B. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxo-octyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

30

Part A compound (1 mmol) was reacted with carbonyldiimidazole (1 mmol), followed by Example 1 Part C chiral amine (1 mmol) as described in Example 1 Part D. The crude product was chromatographed on silica gel (30 g, Baker for flash chromatography), eluting with EtOAc and 2% MeOH in EtOAc to give title ester as a colorless oil (330 mg, 73%).

TLC: silica gel, 2% MeOH in EtOAc, vanillin, $R_f=0.26$

Example 55A

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxo-octyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

The Example 55 methyl ester (327 mg, 0.726 mmol) was hydrolyzed with LiOH in a THF-H₂O mixture as described in Example 2 to give a white solid (306 mg). This was recrystallized from EtOAc (10 ml) to give title acid (262 mg, 83%), m.p. 129-131°C.

TLC: silica gel, 10% MeOH in CH₂Cl₂, vanillin, $R_f = 0.44$.
 $[\alpha]_D = -6.0$ (c=0.96, MeOH)

Anal Calcd for C₂₄H₄₀O₅N₂: C, 66.02; H, 9.24;
N, 6.42

Found: C, 66.02; H, 9.16; N, 6.39

Example 56

[1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxo-4-phenyl)-butyl]amino]acetyl]amino]methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic acid

5 A. 4-Phenylbutanoyl glycine ethyl ester

4-Phenylbutyric acid (2.46 g, 15 mmol) was dissolved in distilled THF (70 ml) in an argon atmosphere. After cooling in an ice bath, carbonyldiimidazole (CDI) (2.43 g, 1.5 mmol) was
10 added and the mixture was stirred cold 1 hour and at room temperature 1 hour. The mixture was then cooled and glycine ethyl ester•HCl (2.09 g, 15 mmol) and distilled Et₃N (2.1 ml, 15 mmol) were added. The mixture was left stirring overnight at
15 room temperature. After removal of the solvent in vacuo, Et₂O (200 ml) was added. The solution was washed with 1N HCl (70 ml), 0.5 N NaOH (70 ml) and saturated NaCl solution (70 ml), dried (MgSO₄) and freed of solvent in vacuo leaving title
20 compound (3.13 g, 84%) as white crystalline material. TLC: silica gel, Et₂O, UV; R_f: 0.58.

B. 4-Phenylbutanoyl glycine

The Part A ester (3.07 g, 12.3 mmol) was
25 hydrolyzed with NaOH (5 g, 125 mmol) in water (60 ml). After stirring at room temperature 6 hours, neutral material was removed by washing with Et₂O (2 x 50 ml). The aqueous solution was then acidified with concentrated HCl solution. The

product was extracted into CHCl_3 (3 x 60 ml), dried (MgSO_4) and freed of solvent in vacuo leaving a white solid. This was recrystallized from EtOAc (10 ml) to give title compound (2.18 g, 80%), m.p. 99-101°C.

C. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxo-4-phenyl)butyl]amino]acetyl]amino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

Part B acid (1 mmol) was reacted with CDI (1 mmol) and then with Example 1 Part C chiral amine (1 mmol) as described in Example 5 Part B. The crude product was chromatographed on silica gel (26 g, Baker for flash chromatography) eluting with EtOAc and 2% MeOH in EtOAc to give title compound (337 mg, 72%) as an oil. TLC: silica gel, 2% CH_3OH in EtOAc, $\text{Ce}(\text{SO}_4)_2$, $R_f=0.40$.

D. [1S-[1 β ,2 α (5Z),3 α ,4 β]]-7-[3-[[[(1-Oxo-4-phenyl)butyl]amino]acetyl]amino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

The Part C methyl ester (336 mg, 0.71 mmol) was hydrolyzed with LiOH in a water-THF mixture as described in Example 6. The crude crystalline product (300 mg) was recrystallized from a mixture of MeOH and EtOAc to give title compound (247.8 mg, 76%), m.p. 114-116°C, TLC: silica gel, 2% CH_3OH in EtOAc, $\text{Ce}(\text{SO}_4)_2$, $R_f 0.20$ $[\alpha]_D = -5.8$ ($C=1.7$, CH_3OH)

Anal calcd for $C_{26}H_{36}N_2O_5$: C, 68.40; H, 7.95;
N, 6.14

Found: C, 68.45; H, 8.03; N, 6.11

5

Example 57

[1S-[1 α ,2 β (2),3 β ,4 α]]-7-[3-[[[[(Phenylthio)acetyl]-
amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-
2-yl]-5-heptenoic acid

10

A. (Phenylthio)acetyl glycine ethyl ester

The title ethyl ester was prepared from
thiophenoxy acetic acid (15 mmol) and the ethyl
ester of glycine•HCl using carbonyldiimidazole
(CDI) as described in Example 56, Part A giving
2.95 g (78%) of solid.

15

B. (Phenylthio)acetyl glycine

The Part A ethyl ester was hydrolyzed with
aqueous NaOH as described in Example 56 Part B to
give the title acid (1.041 g, 92%) as a
crystalline material.

20

C. [1S-[1 α ,2 β (2),3 β ,4 α]]-7-[3-[[[[(Phenyl-
thio)acetyl]amino]acetyl]amino]methyl]-
7-oxobicyclo[2.2.1]hept-2-yl]-5-
heptenoic acid, methyl ester

25

The Part B acid (1.5 mmol) was reacted with
CDI (1.5 mmol) followed by Example 1 Part C chiral
amine (1.5 mmol) as described in Example 5 Part
B. The crude product was chromatographed on

silica gel (30g, Baker for flash chromatography) eluting with EtOAc and 2% MeOH in EtOAc to give title ester as a solid, 523 mg, 73%. TLC: silica gel, 5% MeOH in EtOAc, UV + vanillin, R_f : 0.48.

5

D. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[(Phenylthio)acetyl]amino]acetyl]amino]methyl]-7-oxobicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

10 The Part C methyl ester (467 mg, 0.98 mmol) was hydrolyzed with 1N LiOH (2 equivalents) as described in Example 6. The crude product was recrystallized from EtOAc (10 ml) to give title acid (419 mg, 93%), m.p. 126-128°C. $[\alpha]_D = -5.4^\circ$
 15 (c=0.8, MeOH). TLC: silica gel, 10% MeOH in CH_2Cl_2 + HOAc (3 drops/10 ml), UV + vanillin, R_f 0.51.

Anal Calcd for $C_{24}H_{32}O_5N_2S$: C, 62.58; H, 7.00;
 20 N, 6.08; S, 6.96

Found: C, 62.49; H, 7.14; N, 6.02; S, 6.91

Example 58

25 [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[(3-(4-Hydroxyphenyl)-1-oxopropyl]amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

A. 3-(4-Hydroxyphenyl)propanoyl glycine ethyl ester

30 3-(4-Hydroxyphenyl)propionic acid (2.49 g, 15 mmol) was reacted with glycine ethyl ester hydrochloride in the presence of CDI and Et_3N as described in Example 56 Part A. After removal of

the solvent the residue was dissolved in CHCl_3 and washed with 1N HCl, saturated NaHCO_3 solution and saturated NaCl solution. After drying (MgSO_4) and removal of the solvent in vacuo crude title ester
5 remained (2.44 g) as a viscous oil. NMR indicated this contained a major impurity but it was used without further purification.

B. 3-(4-Hydroxyphenyl)propanoyl glycine

10 Crude Part A ethyl ester was hydrolyzed with NaOH in water as described in Example 56 Part B to give a white solid (1.37 g). This was recrystallized from $\text{EtOAc} \cdot \text{MeOH}$ to give the title solid (0.98 g, 29% from starting acid).

15 C. [1S-[1 α ,2 β (2),3 β ,4 α]]-7-[3-[[[[3-(4-Hydroxyphenyl)-1-oxopropyl]amino]-acetyl]amino]methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

20 Example 1, Part C chiral amine (401 mg, 1.5 mmol) was dissolved in distilled THF (20 ml) in an argon atmosphere. Part B acid (346 mg, 1.55 mmol) was added and the mixture was cooled in an ice
25 bath. Dicyclohexylcarbodiimide (DCC) (319 mg, 1.55 mmol) was added and the mixture was stirred cold 20 minutes and at room temperature overnight. 1N HCl (4 drops) was added and after stirring 10 minutes the solvent was removed in vacuo. EtOAc
30 (8 ml) was added to the residue. After cooling in an ice bath the solid was removed by filtration

and washed with cold EtOAc (~10 ml). The filtrate was freed of solvent in vacuo and the remaining material was chromatographed on silica gel (35 g, Baker for flash chromatography) eluting with EtOAc and 3% MeOH in EtOAc to give title ester (243 mg, 34%) as a viscous material. TLC: silica gel, 8% MeOH in EtOAc, UV + vanillin, $R_f = 0.45$.

10 D. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[3-(4-Hydroxyphenyl)-1-oxopropyl]amino]acetyl]-amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

15 The Part C methyl ester (243 mg, 0.51 mmol) was dissolved in distilled THF (20 ml) and water (2 ml) in an argon atmosphere and treated with 1N LiOH solution (3 ml). The reaction appeared complete by TLC in 1 hour and at 2 hours was worked up as described in Example 6. The product (212 mg, 90%) was a brittle foam which failed to
20 crystallize. $[\alpha]_D = -5.7^\circ$ (c=0.65, MeOH).

TLC: silica gel, 10% MeOH in CH_2Cl_2 + HOAc (3 drops/10ml), UV + vanillin. $R_f = 0.32$.

25 Anal Calcd for $\text{C}_{25}\text{H}_{34}\text{O}_6\text{N}_2$: C, 65.48; H, 7.47;
N, 6.11

Found: C, 65.34; H, 7.59; N, 6.09

Example 59

[1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[(Phenoxyacetyl)-
amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]-
hept-2-yl]-5-heptenoic acid

5 A. Phenoxyacetyl glycine

Glycine (20 mmol) was reacted with
distilled phenoxyacetyl chloride (22 mmol) in the
presence of NaOH (40 mmol) in a mixture of water
and ether as described in Example 5 Part A. The
10 crude product was recrystallized from EtOAc (15
ml) to give title acid (2.38 gm, 57%).

15 B. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[(Phenoxy-
acetyl)amino]acetyl]amino]methyl]-7-
oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic
acid, methyl ester

Part A acid (1.5 mmol) was reacted with CDI
(1.5 mmol), followed by Example 1 Part C chiral
amine (1.5 mmol) as described in Example 5, Part
20 B. The crude product was chromatographed on
silica gel (25 g, Baker for flash chromatography)
eluting with EtOAc and 2% MeOH in EtOAc to give
title ester as a white solid (463 mg, 67%). TLC:
silica gel, 5% MeOH in EtOAc, UV + vanillin, R_f =
25 0.53.

30 C. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[(Phenoxy-
acetyl)amino]acetyl]amino]methyl]-7-
oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic
acid

The Part B methyl ester (463 mg, 1.01 mmol) was hydrolyzed with 1N LiOH (2 equivalents) in a THF-H₂O mixture as described in Example 6 to give a white solid. This was recrystallized from EtOAc (20 ml) containing a few drops of MeOH to give title acid (380 mg, 84.6%). $[\alpha]_D = -5.9^\circ$ (c=0.68, MeOH). TLC: Silica gel, 10% MeOH in CH₂Cl₂ + HOAc (3 drops/10 ml), UV + vanillin, $R_f = 0.57$.

- 10 Anal Calcd for C₂₄H₃₂O₆N₂: C, 64.85; H, 7.26;
N, 6.30
Found: C, 64.94; H, 7.34; N, 6.26

Example 60

- 15 [1S-[1 α ,2 β (5Z),3 β ,4 α]]-7-[3-[[[(1-Oxo-3-phenyl-propyl)amino]acetyl]amino]methyl]-7-oxabicyclo-[2.2.1]hept-2-yl]-5-heptenoic acid

A. 3-Phenylpropanoyl glycine

- Glycine (1.5 g, 20 mmol) and hydrocinnamoyl chloride (3.37 g, 22 mmol) were reacted in the presence of NaOH (40 mmol) in a mixture of water and ether using the method described in Example 5 Part A. The crude product was extracted into chloroform, dried (MgSO₄) and freed of solvent in vacuo leaving a near white solid (3.53 g, 85%). This was recrystallized from EtOAc (13 ml) to give title compound (2.66 g, 64%) m.p. 112-114°C.

B. [1S-[1 α ,2 β (5Z),3 β ,4 α]]-7-[3-[[[(1-Oxo-3-phenylpropyl)amino]acetyl]amino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

5 Part A acid (1 mmol) was reacted with CDI (1 mmol) and then with Example 1 Part C chiral amine (1 mmol) as described in Example 5 Part B. The crude product was chromatographed on silica gel (25 g, Baker for flash chromatography),
10 eluting with 2% MeOH in EtOAc to give title compound (330 mg, 72%) as an oil. TLC: silica gel, 2% MeOH in EtOAc, vanillin R_f = 0.29.

15 C. [1S-[1 α ,2 β (5Z),3 β ,4 α]]-7-[3-[[[(1-Oxo-3-phenylpropyl)amino]acetyl]amino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

The Part B methyl ester (330 mg, 0.72 mmol) was hydrolyzed with LiOH in a water-THF mixture as
20 described in Example 6. The crude crystalline product was recrystallized from EtOAc (12 ml) to give title compound (264 mg, 82.8%) m.p. 119-122°C. TLC: silica gel, 8% MeOH in CH₂Cl₂, UV and vanillin, R_f = 0.29. $[\alpha]_D$ = -5.9 (c=1.1,
25 MeOH).

Anal Calcd for C₂₅H₃₄O₅N₂: C, 67.85; H, 7.74;
N, 6.33

Found: C, 67.62; H, 7.65; N, 6.22

Example 61

[1S-[1 α ,2 β (5Z),3 β ,4 α]]-7-[3-[[[(1-Oxo-5-phenylpentyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

- 5 A. 5-Phenylpentanoyl glycine ethyl ester
5-Phenylvaleric acid (2.67 g, 15 mmol) in distilled THF was reacted with CDI (15 mmol) followed by glycine ethyl ester•HCl (15 mmol) and (C₂H₅)₃N (15 mmol) as described in Example 56 Part
10 A. The crude material (3.25 g, 82%) was used without purification.

- B. 5-Phenylpentanoyl glycine
The Part A ester (12.34 mmol) was
15 hydrolyzed with NaOH in water as described in Example 56 Part B. The crude product was recrystallized from EtOAc (12 ml) to give title compound (2.39 g, 82%), m.p. 93-96°C.

- 20 C. [1S-[1 α ,2 β (5Z);3 β ,4 α]]-7-[3-[[[(1-Oxa-5-phenylpentyl)amino]acetyl]amino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester
Part B compound (1 mmol) was reacted with
25 CDI (1 mmol) and then with Example 1 Part C chiral amine (1 mmol) as described in Example 5 Part B. The crude product was chromatographed on silica gel (25 g, Baker for flash chromatography) eluting with 2% MeOH in EtOAc to give title compound (363 mg,
30 75%) as an oil.

TLC: silica gel, 2% MeOH in EtOAc, vanillin R_f = 0.33.

5 D. [1S-[1 α ,2 β (5Z),3 β ,4 α]]-7-[3-[[[(1-Oxa-5-phenylpentyl)amino]acetyl]amino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

10 The Part C methyl ester (362 mg, 0.749 mmol) was hydrolyzed with LiOH in a water-THF mixture as described in Example 6. The crude crystalline product was recrystallized from EtOAc (10 ml) containing a few drops of MeOH to give title compound (278 mg, 79%), m.p. 129-131°C.
 15 TLC: silica gel, 8% MeOH in CH_2Cl_2 , vanillin, R_f = 0.31
 $[\alpha]_D = -5.5$ (c=0.9, CH_3OH)

Anal Calcd for $\text{C}_{27}\text{H}_{38}\text{O}_5\text{N}_2$: C, 68.91; H, 8.14;
 N, 5.95

20 Found: C, 68.82; H, 8.02; N, 5.88

Example 62

25 [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[(4-Cyclohexyl-1-oxobutyl)amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

A. 4-Cyclohexylbutanoic acid

4-Phenylbutanoic acid prepared as described in Example 56, Part A was dissolved in glacial acetic acid (25 ml). Platinum oxide
 30 (0.1 g) was added and the solution was hydrogenated in the Paar shaker at up to 55 p.s.i. until hydrogen uptake ceased (6.5 hours). The catalyst was removed by filtration and the acetic acid was removed in vacuo. The product

crystallized and was recrystallized from Et₂O (20 ml) to give title compound (1.18 g, 77%), m.p. 85-88°C.

- 5 B. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[(4-Cyclohexyl-1-oxobutyl)amino]acetyl]-amino]methyl]-7-oxabicyclo[2.2.1]-hept-2-yl]-5-heptenoic acid, methyl ester

10 The Part A acid (341 mg, 1.5 mmol) was dissolved in CHCl₃ (10 ml) in an argon atmosphere. The solution was cooled in an ice bath and carbonyldiimidazole (2.43 mg, 1.5 mmol) was added. The mixture was stirred cold 30
15 minutes and at room temperature 1 hour. The hydrochloride of the chiral amine (prepared as described in Example 1 Part C) (456 mg, 1.5 mmol) was added. The solution was cooled in an ice bath and tri-n-butylamine (0.36 ml, 278 mg, 1.5 mmol)
20 was added and the mixture was left stirring overnight at room temperature. More CHCl₃ (40 ml) was added and the solution was washed with 1N HCl (20 ml), saturated NaHCO₃ solution (20 ml) and saturated NaCl solution (20 ml). After drying
25 (MgSO₄), the solvent was removed in vacuo. The product was purified by chromatography on silica gel (30 g of Baker for flash chromatography) eluting with 1% MeOH in EtOAc to give the title methyl ester (661 mg, 92.5%) as an oil which
30 slowly became crystalline. TLC: silica gel, 2% MeOH in EtOAc, vanillin, R_f = 0.26.

5 The Part B methyl ester (661 mg, 1.39 mmol)
was hydrolyzed with LiOH as described in Example
6. The crude crystalline product was
recrystallized from EtOAc (15 ml) and MeOH (1 ml)
to give title acid compound (542 mg, 84%), m.p.
0 141-143°C. $[\alpha]_D^{25} = -6.0^\circ$ (C=0.96, MeOH)

15 Anal Calcd for $C_{26}H_{42}O_5N_2$: C, 67.50; H, 9.15;
N, 6.06
Found: C, 67.58; H, 9.24; N, 6.05

20 [1S-[1 α , 2 β (Z), 3 β , 4 α]]-7-[3-[[[[[1-Oxo-3-(phenylthio)propyl]amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

25 Thiophenol (440 mg, 4 mmol) and Et_3N (70
 μl , 0.5 mmol) were dissolved in CH_2Cl_2 (5 ml).
 Methyl acrylate (412 mg, 4.8 mmol) was added
 dropwise. The reaction was exothermic. After
 stirring at room temperature for 30 minutes, the
 30 excess methyl acrylate was removed in vacuo. TLC:
 silica gel, Et_2O -hexane 1:2, UV R_f = 0.58. The

crude title ester was used without further purification.

B. 3-(Phenylthio)propanoic acid

5 The crude Part A methyl ester (~4 mmole)
was treated with 10 ml 1N NaOH and THF (5 ml).
After stirring at room temperature 3 hours, ether
(30 ml) was added. The layers were separated and
the ether layer was reextracted with 1N NaOH
10 solution (10 ml). The combined aqueous layers were
washed with Et₂O (20 ml) and then acidified with
concentrated HCl. The product was extracted with
CHCl₃ (2 x 30 ml). The chloroform extracts were
15 washed with saturated NaCl solution (2 x 20 ml),
dried (MgSO₄) and freed of solvent in vacuo
leaving title acid as a white solid (quant.).
This was used without further purification.

C. 3-(Phenylthio)propanoyl glycine ethyl
ester

20 Part B acid (0.740 g, 4.06 mmol) was reacted
with carbonyldiimidazole (4.06 mmol) followed by
glycine ethyl ester•HCl (4.06 mmol) as described
in Example 56 Part A to give the title ester (1.00
25 g, 92%) as crystalline material.

D. 3-(Phenylthio)propanoyl glycine

The Part C ethyl ester (0.96 g, 3.6 mmol) was hydrolyzed with NaOH solution as described in Example 56 Part B to give a white solid which was triturated with Et₂O to give title acid (0.75 g, 87%).

E. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[1-Oxo-3-(phenylthio)propyl]amino]acetyl]-amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

The Part D acid (359 mg, 1.5 mmol) was reacted with carbonyldiimidazole (1.5 mmol) followed by the hydrochloride of Example 1 Part C chiral amine by the procedure described in Example 62 Part B. The crude product was chromatographed on silica gel (30 g, Baker for flash chromatography), eluting with 1% MeOH in EtOAc to give the title methyl ester (623 mg, 85%) as an oil. TLC: silica gel, 2% MeOH in EtOAc, UV and vanillin R_f = 0.21.

F. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[1-Oxo-3-(phenylthio)propyl]amino]acetyl]-amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

The Part E methyl ester (623 mg, 1.285 mmol) was dissolved in THF (25 ml) and H₂O (2.5 ml) in an argon atmosphere and treated with 1N LiOH solution (2.6 ml). The mixture was stirred at room temperature for 5 hours and then worked up as described in Example 6. The crude product was chromatographed on silica gel (20 g, Baker for flash chromatography) eluting with 5% MeOH in

CH₂Cl₂ to give an oil (436 mg, 71%) which crystallized on standing. This was recrystallized from EtOAc (10 ml) to give title acid (136.5 mg, 22%), m.p. 95-97°C. TLC: silica gel, 10% MeOH in CH₂Cl₂, R_f = 0.50. [α]_D = -5.3° (c=0.88, MeOH)

Anal Calcd for C₂₅H₃₄O₅N₂S: C, 63.27; H, 7.22;
N, 5.90; S, 6.76

Found: C, 63.41; H, 7.28; N, 5.94; S, 6.63

Example 64

[1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[(Phenylmethyl)-thio]acetyl]amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

A. Chloroacetyl glycine

Glycine (1.5 g, 20 mmol) was dissolved in 2N NaOH (25 ml, 50 mmol) and ether (20 ml) was added. Chloroacetyl chloride (2.26 g) dissolved in Et₂O (20 ml) was added dropwise at 0°C. The mixture was stirred at 0° for 30 minutes and at room temperature 1 hour. The layers were separated and the water layer was washed with Et₂O (2 x 20 ml). The water layer was then acidified to pH 2 with concentrated HCl and the product was extracted into EtOAc (3 x 50 ml). The combined EtOAc extracts were washed with brine, dried (MgSO₄), and freed of solvent in vacuo to give title acid compound as a solid (2.56 g, 84%) which was used without further purification.

B. (Benzylthio)acetyl glycine

Part A acid (1.28 g, 8.4 mmol) was dissolved in methanol (10 ml) and cooled in an ice bath. Sodium methoxide (1.08 g, 20 mmol) was added followed by dropwise addition of benzyl mercaptan (1.25 g, 10.08 mmol). After stirring overnight at room temperature, 1N NaOH solution (10 ml) was added. Ether washes (2 x 40 ml) removed neutral material. The aqueous layer was then acidified to pH 2 with concentrated HCl. The product was extracted with Et₂O (3 x 50 ml), washed with brine, dried (MgSO₄) and freed of solvent in vacuo leaving a white solid. This was recrystallized from benzene to give title acid compound (1.28 g, 64%).

C. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[(Phenyl-methyl)thio]acetyl]amino]acetyl]amino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

Part B acid (359 mg, 1.5 mmol) was reacted with carbonyldiimidazole (1.5 mmol) followed by Example 1 Part C chiral amine•HCl 3 (1.5 mmol) using the procedure described in Example 62. The crude product was chromatographed on silica gel (30 g, Baker for flash chromatography) eluting with 1% MeOH in EtOAc to give title ester as an oil (625 mg, 85%). TLC: silica gel 2% MeOH in EtOAc, UV + vanillin, R_f = 0.30.

D. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[(Phenyl-methyl)thio]acetyl]amino]acetyl]amino]-methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

5 The Part C methyl ester (625 mg, 1.28 mmol) was hydrolyzed with 1N LiOH solution (2.6 ml) in a THF-water mixture as described in Example 5 Part B. The reaction mixture was worked up at 5 hours 20 minutes. The crude product was recrystallized
10 from EtOAc (15 ml) to give title product (427 mg, 77.7%), m.p. 98-101°C. $[\alpha]_D = -5.7^\circ$ (c=0.95, MeOH) TLC: silica gel, 10% MeOH in CH₂Cl₂, UV + vanillin, R_f = 0.4.

15 Anal Calcd for C₂₅H₃₄O₅N₂S: C, 63.27; H, 7.22; N, 5.90; S, 6.76
Found: C, 63.53; H, 7.42; N, 5.91; S, 6.77

Example 65

20 [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[(Butylthio)acetyl]-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

A. (Butanethio)acetyl glycine

25 Example 64 Part A acid compound (1.28 g, 8.4 mmol) was reacted with 1-butanethiol using the procedure described in Example 64. The crude product was crystallized with diisopropylether (~10 ml) to give title acid (0.55 g, 32%).

B. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[(Butyl-thio)acetyl]amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

5 Part A acid (308 mg, 1.5 mmol) was reacted with carbonyldiimidazole (1.5 mmol) followed by Example 1 Part C chiral amine hydrochloride (1.5 mmol) using the procedure described in Example 62. The crude product was chromatographed on
10 silica gel (30 g, Baker for flash chromatography) eluting with 1% MeOH in EtOAc to give title compound (538 mg, 79%) as an oil. TLC: silica gel, 2% MeOH in EtOAc, UV + vanillin, R_f = 0.29.

15 C. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[(Butyl-thio)acetyl]amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

The Part B methyl ester (538 mg, 1.18 mmol) was hydrolyzed with 1N LiOH solution (2.4 ml) in a tetrahydrofuran-water mixture using the procedure described in Example 5 Part B. The reaction mixture was worked up in 5 hours. The crude product was crystallized from EtOAc (20 ml) to
25 give title product (444 mg, 85.4%), m.p. 114-116°. $[\alpha]_D = -6.0^\circ$ (c=0.9, MeOH) TLC: silica gel, 10% MeOH in CH₂Cl₂, UV + vanillin, R_f = 0.3.

Anal calcd for C₂₂H₃₆O₅N₂S: C, 59.97; H, 8.24;
30 N, 6.36; S, 7.28
Found: C, 59.77; H, 8.31; N, 6.30; S, 7.27

Example 66

[1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[(Cyclohexylmethyl)-thio]acetyl]amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

5 A. Cyclohexylmethylthiol acetate

Cyclohexylmethyl mesylate (1.92 g, 10 mol) and KSCOCH₃ (1.25 g) were suspended in distilled tetrahydrofuran (THF). The reaction mixture was heated under reflux for 3 hours. Additional
10 KSCOCH₃ (1.25 g) and THF (9 ml) were added and the mixture was heated under reflux an additional 3 hours. Et₂O (100 ml) was added and the mixture was washed with brine (30 ml). The aqueous layer was reextracted with Et₂O (30 ml). The combined
15 organic layers were washed with brine (15 ml), dried (MgSO₄) and freed of solvent to give a straw colored oil (1.8 g). This was chromatographed on silica gel (50 g, Baker for flash chromatography) eluting with 2% Et₂O in hexane to give title
20 compound (1.189 g, 69%) as an oil. TLC: silica gel, 10% Et₂O in hexane, UV and I₂, R_f = 0.48.

B. [(Cyclohexylmethyl)thio]acetyl glycine

Part A compound (6 mmol) and the Example 64
25 Part A acid (6 mmol) were reacted in the presence of NaOMe (17 mmol) as described in Example 64 Part B. The crude product was

crystallized from diisopropyl ether to give title compound (516 mg, 35%).

5 C. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[(Cyclohexylmethyl)thio]acetyl]amino]acetyl]-amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid, methyl ester

Part B compound (368 mg, 1.5 mmol) was coupled with Example 1 Part C chiral amine•HCl (456 mg, 1.5 mmol) in the presence of carbonyl diimidazole (CDI) (1.5 mmol) as described in Example 62 Part B. The crude product was chromatographed on silica gel (30 g, Baker for flash chromatography) eluting with 1% MeOH in EtOAc to give title compound (542 mg, 73%) as an oil. TLC: silica gel, 2% MeOH in EtOAc, UV + vanillin, R_f = 0.38.

20 D. [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[(Cyclohexylmethyl)thio]acetyl]amino]acetyl]-amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid

The Part C methyl ester (542 mg, 1.09 mmol) was hydrolyzed with 1N LiOH (4 ml) in a mixture of THF and water as described in Example 6. The crude product was recrystallized from EtOAc (30 ml) to give title acid (439 mg, 83%), m.p. 131-133°C. TLC: silica gel, 10% MeOH in CH₂Cl₂, UV + vanillin, R_f = 0.56. $[\alpha]_D = -5.0^\circ$ (c=0.95, MeOH).

Anal Calcd for $C_{25}H_{40}N_2O_5S$: C, 62.47; H, 8.39;

N, 5.83; S, 6.67

Found: C, 62.37; H, 8.46; N, 5.77; S, 6.60

5

Example 67

[1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[(Phenylsulfinyl)-
acetyl]amino]acetyl]amino]methyl]-7-oxabicyclo-
[2.2.1]hept-2-yl]-5-heptenoic acid

10 Powdered $NaIO_4$ (385 mg, 1.8 mmol) was
dissolved in water (12 ml). A solution of Example
57 acid compound (276 mg, 0.6 mmol) in methanol
(20 ml) was added. The mixture was stirred
overnight at room temperature. Most of the
methanol was removed in vacuo. Saturated NaCl
15 solution (50 ml) was added. The product was
extracted with $CHCl_3$ (3 x 50 ml). The combined
chloroform extracts were washed with NaCl solution
(20 ml), dried ($MgSO_4$), and freed of solvent
in vacuo leaving an oil. This was chromatographed
20 on silica gel (4 g, Baker for flash chromatography)
eluting with 5% MeOH in CH_2Cl_2 to give a foam (254
mg) which gave very broad peaks in ^1H NMR. The
material was dissolved in $CHCl_3$ (100 ml) and
washed with 1N HCl solution (2 x 25 ml) and
25 saturated NaCl solution (2 x 20 ml), dried ($MgSO_4$)
and freed of solvent in vacuo leaving title acid
(213 mg, 74%) as a white solid foam. TLC: silica
gel, 10% MeOH in CH_2Cl_2 , UV + vanillin, $R_f=0.14$.

30 Anal calcd for $C_{24}H_{32}N_2O_6S \cdot 0.2 H_2O$: C, 60.02;

H, 6.80; N, 5.83; S, 6.68

Found: C, 59.95; H, 6.83; N, 5.78; S, 6.53

$[\alpha]_D = -9.7^\circ$ (c=0.7, MeOH)

Example 68

5 [1S-[1 α , 2 β (Z), 3 β , 4 α]]-7-[3-[[[[(Phenylsulfonyl)-
acetyl]amino]acetyl]amino]methyl]-7-oxabicyclo-
[2.2.1]hept-2-yl]-5-heptenoic acid

Example 57 acid compound (44.5 mg, 0.9 mmol) was dissolved in methanol (10 ml) and cooled in an ice bath. Oxone (810 mg ~2.7 mmol)
10 dissolved in water (10 ml) was added. The mixture was stirred at room temperature 4 hours, then diluted with water (30 ml). The product was extracted into CHCl₃ (3 x 35 ml). The combined CHCl₃ extracts were washed with saturated NaCl
15 solution (2 x 20 ml), dried (MgSO₄), and freed of solvent in vacuo leaving an oil (430 mg). This was chromatographed on silica gel (10 g, Baker for flash chromatography) eluting with 5% MeOH in CH₂Cl₂ to give title acid, 165 mg (37%). TLC:
20 silica gel, 10% MeOH/CH₂Cl₂, UV + vanillin. R_f = 0.27.

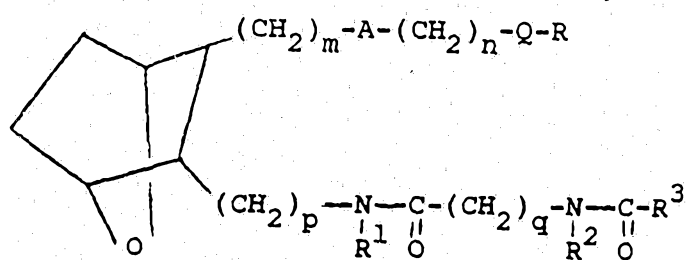
Anal Calcd for C₂₄H₃₂O₇N₂S•0.5 H₂O: C, 57.46;
H, 6.63; N, 5.59

25 Found: C, 57.27; H, 6.44; N, 5.55

Examples 69 to 104

Following the procedures outlined in the specification and described in the above working
30 Examples, the following compounds may be prepared.

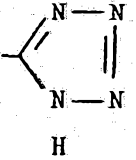
5



10 000 0015

35	30	25	20	15	10	5				
Ex.										
No.	m	A	(CH ₂) _n	Q	R	p	R ¹	(CH ₂) _q	R ²	R ³
69.	2	CH=CH	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}- \end{array}$	CH=CH	$\begin{array}{c} \text{O} \\ \\ \text{CN-OCH}_3 \\ \text{H} \end{array}$	3	C ₂ H ₅	(CH ₂) ₇	C ₃ H ₇	$\begin{array}{c} \text{H} \text{ H} \\ \quad \\ -\text{CH}_2-\text{C}=\text{C}-\text{CH}_3- \end{array}$
70.	3	(CH ₂) ₂	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{C}- \\ \\ \text{CH}_3 \end{array}$	CH ₂	$\begin{array}{c} \text{O} \\ \\ \text{CN-OC}_2\text{H}_5 \\ \\ \text{CH}_3 \end{array}$	4	H	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}- \end{array}$	C ₄ H ₉	OC ₆ H ₅
71.	4	(CH ₂) ₂	(CH ₂) ₄	$\begin{array}{c} \text{OH} \\ \\ -\text{CH}- \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{CNHC}_6\text{H}_5 \end{array}$	1	C ₃ H ₇	-CH ₂ -	C ₅ H ₁₁	C ₆ H ₅
72.	1	CH=CH	$\begin{array}{c} \text{CH}_3 \text{ CH}_3 \\ \diagdown \quad / \\ -\text{C}-\text{CH}_2- \end{array}$	$\begin{array}{c} \text{F} \\ \\ -\text{CH}- \end{array}$	CO ₂ Li	2	H	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}_2-\text{CH}- \end{array}$	H	CH ₂ C ₆ H ₅
73.	0	CH=CH	$\begin{array}{c} \text{CH}_3 \text{ CH}_3 \\ \quad \\ -\text{CH}-\text{CH} \end{array}$	$\begin{array}{c} \text{F} \text{ F} \\ \diagdown \quad / \\ -\text{C}- \end{array}$	CO ₂ N _a	3	CH ₃	$\begin{array}{c} \text{CH}_3 \text{ CH}_3 \\ \diagdown \quad / \\ -\text{CH}_2-\text{C}- \end{array}$	H	-(CH ₂) ₇ C ₆ H ₅
74.	1	(CH ₂) ₂	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{C}-\text{CH}_2- \\ \\ \text{F} \end{array}$	CH=CH	CO ₂ glucamine salt	4	C ₂ H ₅	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}_2-\text{CH}-\text{CH}_2- \end{array}$	H	-C ₆ H ₄ -p-CH ₃

13 0 45 55 13

35	30	25	20	15	10	5				
Ex.										
No.	m	A	(CH ₂) _n	Q	R	P	R ¹	(CH ₂) _q	R ²	R ³
75.	2	CH=CH	$\begin{array}{c} \text{F} \quad \text{F} \\ \quad \\ -\text{CH}-\text{CH}- \end{array}$	CH ₂	CO ₂ tris salt	1	H	-(CH ₂) ₃ -	CH ₃	-C ₆ H ₄ -p-OH
76.	3	(CH ₂) ₂	$\begin{array}{c} \text{F} \quad \text{F} \\ \diagdown \quad \diagup \\ -\text{C}-\text{CH}_2- \end{array}$	$\begin{array}{c} \text{OH} \\ \\ -\text{CH}- \end{array}$	CH ₂ OH	2	C ₄ H ₉	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \\ -\text{CH}_2-\text{CH}- \end{array}$	CH ₃	-OCH ₂ C ₆ H ₅
77.	4	(CH ₂) ₂	-(CH ₂) ₅	$\begin{array}{c} \text{F} \\ \\ -\text{CH}- \end{array}$		3	H	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}_2-\text{C}-\text{CH}_2- \\ \\ \text{H} \end{array}$	CH ₃	-SC ₂ H ₅
78.	0	CH=CH	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}_2-\text{CH}-\text{CH}_2- \end{array}$	$\begin{array}{c} \text{F} \quad \text{F} \\ \diagdown \quad \diagup \\ -\text{C}- \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{CNH}_2 \end{array}$	4	CH ₂	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{C}-\text{CH}_2- \\ \\ \text{CH}_3 \end{array}$	C ₂ H ₅	-OC ₆ H ₅
79.	0	(CH ₂) ₂	$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \diagdown \quad \diagup \\ -\text{CH}_2-\text{C}- \end{array}$	--	$\begin{array}{c} \text{O} \\ \\ \text{CNOH} \\ \text{H} \end{array}$	1	C ₂ H ₅	(CH ₂) ₂	CH ₃	-NH ₂
80.	1	CH=CH	CH ₂	--	$\begin{array}{c} \text{O} \\ \\ \text{CN}(\text{CH}_3)_2 \end{array}$	2	C ₂ H ₅	-CH ₂ -	H	-NHCH ₃
81.	2	(CH ₂) ₂	(CH ₂) ₂	CH ₂	$\begin{array}{c} \text{O} \\ \\ \text{CN}-\text{CH}_3 \\ \\ \text{OH} \end{array}$	3	CH ₃	$\begin{array}{c} \text{CH}_3 \\ \\ -\text{CH}_2-\text{C}- \\ \\ \text{CH}_3 \end{array}$	C ₄ H ₉	-NHC ₆ H ₅

13 6 8 6 5 6 7 1 5

35	30	25	20	15	10	5				
Ex.										
No.	m	A	(CH ₂) _n	Q	R	P	R ¹	(CH ₂) _q	R ²	R ³
82.	3	CH=CH	(CH ₂) ₃	--	CO ₂ H	4	C ₂ H ₅	$\begin{array}{c} \text{CH}_3\text{CH}_3 \\ \quad \\ -\text{CH}_2-\text{CH}-\text{CH}-\text{CH}_2- \end{array}$	CH ₃	NCH ₃ (C ₂ H ₅)
83.	4	(CH ₂) ₂	(CH ₂) ₄	CH=CH	CH ₂ OH	1	C ₃ H ₇	(CH ₂) ₂	C ₂ H ₅	-N(CH ₃) ₂
84.	0	CH=CH	$\begin{array}{c} \text{F} \quad \text{F} \\ \diagdown \quad / \\ -\text{CH}_2-\text{C}- \end{array}$	CH ₂	$\begin{array}{c} \text{N} \quad \text{N} \\ // \quad \backslash \\ \text{C} \quad \text{C} \\ \backslash \quad // \\ \text{N} \quad \text{N} \\ \\ \text{H} \end{array}$	2	C ₄ H ₉	(CH ₂) ₃	CH ₃	H
85.	1	(CH ₂) ₂	$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \quad \\ -\text{CH}_2-\text{C}- \end{array}$	$\begin{array}{c} \text{OH} \\ \\ -\text{CH}- \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{CN}(\text{C}_2\text{H}_5)_2 \end{array}$	3	C ₅ H ₁₁	$\begin{array}{c} \text{F} \\ \\ -\text{CH}-\text{CH}_2- \end{array}$	C ₃ H ₇	-NH-CH ₂ -C ₆ H ₅
86.	2	CH=CH	(CH ₂) ₅	$\begin{array}{c} \text{F} \\ \\ -\text{CH}- \end{array}$	$\begin{array}{c} \text{O} \\ \\ \text{CNHC}_6\text{H}_5 \end{array}$	4	H	$\begin{array}{c} \text{F} \quad \text{F} \\ \diagdown \quad / \\ -\text{C}-\text{CH}_2 \end{array}$	CH ₄ H ₉	-(CH ₂) ₂ CH=CHCH ₂
87.	3	(CH ₂) ₂	$\begin{array}{c} \text{CH}_3 \quad \text{F} \\ \quad \\ -\text{CH}-\text{CH}- \end{array}$	$\begin{array}{c} \text{F} \quad \text{F} \\ \diagdown \quad / \\ -\text{C}- \end{array}$	CH ₂ OH	1	H	(CH ₂) ₂	H	C ₆ H ₅
88.	4	(CH ₂) ₂	(CH ₂) ₂	CH=CH	$\begin{array}{c} \text{N} \quad \text{N} \\ // \quad \backslash \\ \text{C} \quad \text{C} \\ \backslash \quad // \\ \text{N} \quad \text{N} \\ \\ \text{H} \end{array}$	2	H	CH ₂	H	-CH ₂ C ₆ H ₅
89.	0	CH=CH	(CH ₂) ₃	$\begin{array}{c} \text{OH} \\ \\ -\text{CH}- \end{array}$	CO ₂ CH ₃	3	CH ₃	(CH ₂) ₃	C ₃ H ₇	-SC ₄ H ₉
90.	2	(CH ₂) ₂	(CH ₂) ₄	CH ₂	CO ₂ CH ₃	4	CH ₃	(CH ₂) ₈	H	-SC ₆ H ₅

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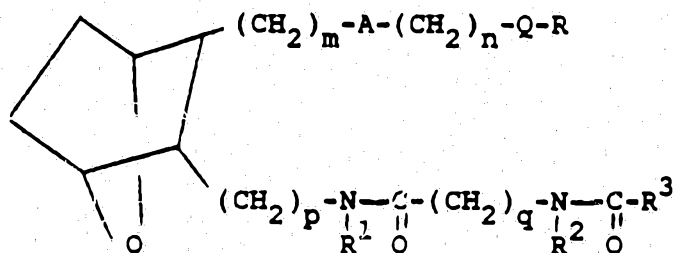
35	30	25	20	15	10	5					
Ex.	No.	m	A	(CH ₂) _n	Q	R	P	R ¹	(CH ₂) _q	R ²	R ³
91.	3	CH=CH	(CH ₂) ₅	--	CO ₂ H	1	CH ₃	(CH ₂) ₁₀	H	-NCH ₃ (C ₆ H ₅)	
92.	2	CH=CH	CH ₂	CH=CH	CO ₂ H	1	H	(CH ₂) ₂	CH ₃	H	
93.	3	(CH ₂) ₂	(CH ₂) ₂	CH ₂	CH ₂ OH	2	C ₂ H ₅	(CH ₂) ₃	H	CH ₃	
94.	4	CH=CH	(CH ₂) ₃	OH -CH- N-N N-N H	3	H	(CH ₂) ₄	H	-CH=CH-CH ₃		
95.	1	(CH ₂) ₂	(CH ₂) ₄	F -CH-	O CN(CH₃)C₂H₅	1	CH ₃	(CH ₂) ₅	CH ₃	-C≡C-CH ₃	
96.	0	CH=CH	(CH ₂) ₅	F F \ / -C-	O CN-OH CH₃	2	H	(CH ₂) ₆	C ₂ H ₅	-CH ₂ -C≡C-CH ₃	
97.	1	CH=CH	(CH ₂) ₃	--	CO ₂ H	1	H	CH ₂	H	O -SC₆H₅	
98.	1	CH=CH	CH ₂	--	CO ₂ H	1	H	CH ₂	O -SC₂H₅ O		
99.	2	(CH ₂) ₂	(CH ₂) ₃	CH ₂	CH ₂ OH	2	CH ₃	(CH ₂) ₂	-SCH ₂ C ₆ H ₅		

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35	30	25	20	15	10	5				
Ex.										
No.	n	A	$(CH_2)_n$	Q	R	p	R^1	$(CH_2)_q$	R^2	R^3
100.	3	CH=CH	$(CH_2)_3$	CH=CH	CO ₂ H	3	H	$(CH_2)_3$	H	-CH ₂ -S-C ₂ H ₅
101.	4	$(CH_2)_2$	$(CH_2)_3$	--	$\begin{matrix} O \\ \\ -CNH_2O \end{matrix}$	1	CH ₅	CH ₂	CH ₃	-CH ₂ -S-CH ₂ -C ₆ H ₅
102.	2	CH=CH	$(CH_2)_3$	CH ₂	CO ₂ H	2	H	CH ₂	H	-CH ₂ -O-CH ₂ -C ₆ H ₅
103.	3	CH=CH	CH ₂	--	CO ₂ H	1	CH ₃	CH ₂	H	-CH ₂ -N-CH ₂ -C ₆ H ₅
104.	2	$(CH_2)_2$	$(CH_2)_3$	CH ₂	CO ₂ CH ₃	1	H	$(CH_2)_2$	CH ₃	$\begin{matrix} H \\ -CH_2-S-C_4H_9 \end{matrix}$

The claims defining the invention are as follows:-

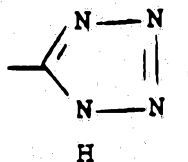
1. A compound having the structure



including all stereoisomers thereof, wherein m is 0 to 4; A is -CH=CH- or -CH₂-CH₂-; n is 1 to 5; Q is -CH=CH-,

-CH₂-, $\begin{matrix} \text{OH} \\ | \\ -\text{CH}- \end{matrix}$, $\begin{matrix} \text{Halo} \\ | \\ -\text{CH}- \end{matrix}$, $\begin{matrix} \text{Halo} & & \text{Halo} \\ & \diagdown & / \\ & \text{C} & \end{matrix}$, or a single bond; R is CO₂H, CO₂alkyl, CO₂ alkali metal, CO₂

polyhydroxyamine salt, -CH₂OH,



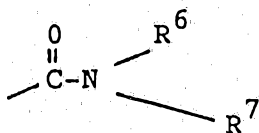
or $\begin{matrix} \text{O} \\ || \\ \text{CNR}^4\text{R}^5 \end{matrix}$ wherein R⁴ and R⁵ are the same or different and are H, alkyl, hydroxy, alkoxy or aryl, at least one of R⁴ and R⁵ being other than hydroxy and alkoxy; p is 1 to 4; R¹ is H or alkyl; q is 1 to 12; R² is H or alkyl; and R³ is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkoxy, arylalkoxy, aryloxy, amino, alkylamino,

aryl-amino, arylalkyl-amino, alkyl-S-, aryl-S-,

$\begin{matrix} \text{(O)}_{n'} \\ || \\ \text{arylalkyl-S-} \end{matrix}$, $\begin{matrix} \text{(O)}_{n'} \\ || \\ \text{aryl-S-alkyl-} \end{matrix}$, $\begin{matrix} \text{(O)}_{n'} \\ || \\ \text{alkyl-S-alkyl-} \end{matrix}$,

$\begin{matrix} \text{(O)}_{n'} \\ || \\ \text{arylalkyl-S-alkyl} \end{matrix}$ (wherein n' is 0, 1 or 2), alkylaminoalkyl, arylaminoalkyl, arylalkylaminoalkyl, alkoxyalkyl, aryloxyalkyl or arylalkoxyalkyl wherein the alkyl groups, as such or as part of another group, contain 1 to 12 carbon atoms and may include a halo-substituent, an

alkoxy substituent, an aryl substituent, an alkyl-aryl substituent, a haloaryl substituent, a cycloalkyl substituent, an alkylcycloalkyl substituent, hydroxy, an alkylamino substituent, an alkanoylamino substituent, an arylcarbonylamino substituent, a nitro substituent, a cyano substituent, a thiol substituent or an alkylthio substituent; the cycloalkyl groups, as such or as part of another group, contain 3 to 12 carbon atoms and may be substituted with 1 or 2 halogens, 1 or 2 alkyl groups, 1 or 2 alkoxy groups, 1 or 2 hydroxy groups, 1 or 2 alkylamino groups, 1 or 2 alkanoylamino groups, 1 or 2 arylcarbonylamino groups, 1 or 2 amino groups, 1 or 2 nitro groups, 1 or 2 cyano groups, 1 or 2 thiol groups, and/or 1 or 2 alkylthio groups; the aryl groups, as such or as part of another group, are monocyclic or bicyclic aromatic groups containing 6 to 10 carbon atoms in the ring portion and in the case of phenyl or naphthyl may be substituted with 1 or 2 alkyl groups, halogens, 1 or 2 alkoxy groups, 1 or 2 hydroxy groups, 1 or 2 alkylamino groups, 1 or 2 alkanoylamino groups, 1 or 2 arylcarbonylamino groups, 1 or 2 amino groups, 1 or 2 nitro groups, 1 or 2 cyano groups, 1 or 2 thiol groups, and/or 1 or 2 alkylthio groups; the alkenyl groups, as such or as part of another group, contain 2 to 12 carbon atoms; the alkynyl groups, as such or as part of another group, contain 2 to 12 carbon atoms; the groups $(CH_2)_m$, $(CH_2)_n$ and $(CH_2)_p$ and contain 0 to 4 carbon atoms in the case of $(CH_2)_m$, 1 to 5 carbon atoms in the case of $(CH_2)_n$, 1 to 4 carbon atoms in the case of $(CH_2)_p$ and may contain one or more alkyl and/or halogen substituents; the group $(CH_2)_q$ contains 1 to 12 carbon atoms and may be substituted by one or more halo, hydroxy, alkoxy, amine, alkylamine, arylamine, amide, thioamide, thiol, alkylthio, arylthio, cyano or nitro groups; the amide group refers to



wherein R^6 and R^7 are independently hydrogen, alkyl or aryl; and polyhydroxyamine salt refers to glucamine salt or tris(hydroxymethyl)aminomethane salt.

2. A compound according to Claim 1 wherein R^3 is alkyl, alkoxy or arylthioalkyl.

3. A compound according to Claim 1 or Claim 2 wherein A is $CH=CH$.

4. A compound according to any one of Claims 1 to 3 wherein m is 1 and n is 1 to 4.

10 5. A compound according to any one of Claims 1 to 4 wherein p is 1 and q is 1.

6. A compound according to any one of Claims 1 to 5 wherein Q is a single bond or CH_2 .

7. A compound according to any one of Claims 1 to 6 wherein R is CO_2 alkyl or CO_2H .

8. A compound according to any one of Claims 1 to 7 wherein R^1 is H and R^2 is H or CH_3 .

9. A compound according to any one of Claims 1 to 8 wherein m is 1, n is 2 to 4, Q is CH_2 , a single bond,

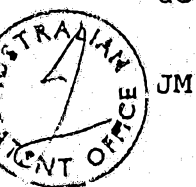
$CH=CH$, $\begin{array}{c} OH \\ | \\ -CH- \end{array}$ or $\begin{array}{c} halo \quad halo \\ \diagdown \quad / \\ -C- \end{array}$, R is CO_2 alkyl,

CO_2H , CH_2OH , or $\begin{array}{c} O \\ || \\ CNR^4R^5 \end{array}$, p is 1, R^1 is H, q is 1, R^2 is H or alkyl and R^3 is alkyl, alkoxy or phenylthiomethyl.

10. A compound according to Claim 1 having the name [1S-[1B,2 α (5Z),3 α ,4B]]-7-[3-[[[(1-oxohexyl)amino]acetyl]-amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof, including all stereoisomers thereof.

11. A compound according to Claim 1 having the name [1S-[1B,2 α (5Z),3 α ,4B]]-7-[3-[[[[(butylamino)carbonyl]-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof, including all stereoisomers thereof.

12. A compound according to Claim 1 having the name [1S-[1B,2 α (5Z),3 α ,4B]]-7-[3-[[[[(methyl-(1-oxohexyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof, including all



stereoisomers thereof.

13. A compound according to Claim 1 having the name [1S-[1B,2α(5Z),3α,4B]]-7-[3-[[[(butoxycarbonyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof, including all stereoisomers thereof.

14. A compound according to Claim 1 having the name [1S-[1B,2α(5Z),3α(R),4B]]-7-[3-[[[1-Oxo-2-[(1-oxohexyl)amino]-propyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof, including all stereoisomers thereof.

15. A compound according to Claim 1 having the name [1S-[1B,2α(5Z),3α(S),4B]]-7-[3-[[[1-Oxo-2-[(1-oxohexyl)amino]-propyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof, including all stereoisomers thereof.

16. A compound according to Claim 1 having the name [1S-[1B,2α(5Z),3α,4B]]-7-[3-[[[(1-oxo-4-phenyl)butyl]amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof, including all stereoisomers thereof.

17. A compound according to Claim 1 having the name [1S-[1α,2B(Z),3B,4α]]-7-[3-[[[(phenylthio)-acetyl]amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof, including all stereoisomers thereof.

18. A compound according to Claim 1 having the name [1S-[1α,2B(Z),3B,4α]]-7-[3-[[[3-(4-hydroxyphenyl)-1-oxopropyl]amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof including all stereoisomers thereof.

19. A compound according to Claim 1 having the name [1S-[1α,2B(Z),3B,4α]]-7-[3-[[[(phenoxyacetyl)amino]acetyl]-amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof including all stereoisomers thereof.

20. A compound according to Claim 1 having the name [1S-[1α,2B(5Z),3B,4α]]-7-[3-[[[(1-oxo-3-phenylpropyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic



acid or an alkyl ester thereof including all stereoisomers thereof.

21. A compound according to Claim 1 having the name [1S-[1 α ,2 β (5Z),3 β ,4 α]]-7-[3-[[[(1-oxo-5-phenylpentyl)amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof including all stereoisomers thereof.

22. A compound according to Claim 1 having the name [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[(4-cyclohexyl-1-oxobutyl)-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof including all stereoisomers thereof.

23. A compound according to Claim 1 having the name [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[1-oxo-3-(phenylthio)propyl]-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof including all stereoisomers thereof.

24. A compound according to Claim 1 having the name [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[(phenylmethyl)thio]-acetyl]amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof including all stereoisomers thereof.

25. A compound according to Claim 1 having the name [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[(butylthio)acetyl]amino]-acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof including all stereoisomers thereof.

26. A compound according to Claim 1 having the name [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[(cyclohexylmethyl)thio]-acetyl]amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof including all stereoisomers thereof.

27. A compound according to Claim 1 having the name [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[(Phenylsulfinyl)acetyl]-amino]acetyl]amino]methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof including all stereoisomers thereof.

28. A compound according to Claim 1 having the name [1S-[1 α ,2 β (Z),3 β ,4 α]]-7-[3-[[[[[(phenylsulfonyl)acetyl]-

aminolacetyl]amino[methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid or the alkyl esters thereof including all stereoisomers thereof.

29. A method of inhibiting platelet aggregation and/or bronchoconstriction, which comprises administering to the circulatory system of a mammalian host an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

30. A method according to Claim 29 wherein said compound is administered in an amount within the range of from 1 to 100 mg/kg.

31. A composition for inhibiting platelet aggregation and/or bronchoconstriction comprising an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier therefor.

32. A method of treating peripheral vascular diseases, which comprises topically or systemically administering to a mammalian host an effective amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

33. A compound according to Claim 1 substantially as hereinbefore described with reference to any one of the examples.

DATED: 1 August, 1990

E.R. SQUIBB & SONS, INC.

Bu their Patent Attorneys:

PHILLIPS ORMONDE & FITZPATRICK

David B Fitzpatrick

5327m

