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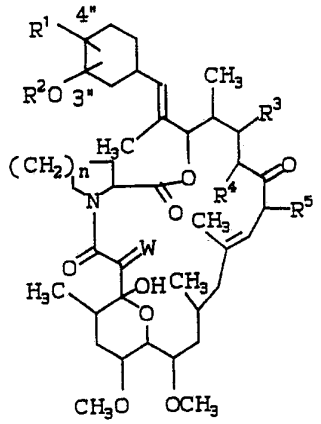

(I)

(57) Abstract

Amino O-aryl, O-alkyl, O-alkenyl and O-alkynyl macrolides of general structural formula (I) have been prepared from suitable precursors by arylation or alkylation and amination at C-3″/C-4″ of the cyclohexyl ring. These macrolide immunosuppressants are useful in a mammalian host for the treatment of autoimmune diseases, infectious diseases and/or the prevention of rejection of foreign organ transplants. In addition, these macrolide immunosuppressants are useful in the topical treatment of inflammatory and hyperproliferative skin diseases and cutaneous manifestations of immunologically-mediated illnesses. Also, these macrolides are useful in the treatment of reversible obstructive airways disease, particularly asthma; as hair revitalizing agents, especially in the treatment of male pattern alopecia or alopecia senilis; in the reversal of multidrug resistance of tumor cells; in treatment of inflammation of mucosa and blood vessels, gastric ulcers, vascular damage, ischemic bowel disease, inflammatory bowel disease, necrotizing enterocolitis, intestinal lesions associated with thermal burns; in the treatment of cytomegalovirus infection; and in the treatment of idiopathic thrombocytopenic purpura and Basedow's disease.

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TITLE OF THE INVENTION

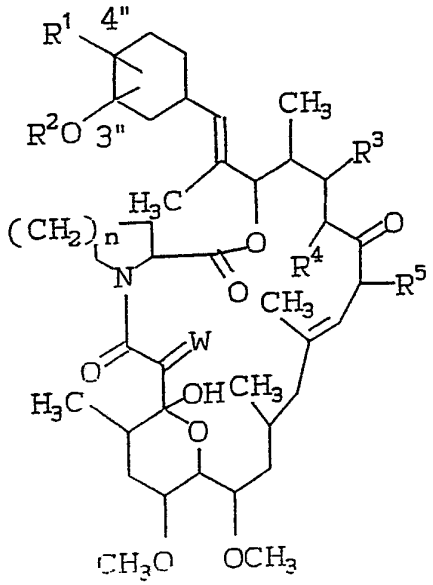
AMINO O-ARYL, O-ALKYL, O-ALKENYL AND O-ALKYNL MACROLIDES

SUMMARY OF THE INVENTION

The present invention is related to amino O-aryl, O-alkyl, O-alkenyl and O-alkynyl macrolides and derivatives which are useful in a mammalian host for the treatment of autoimmune diseases (such as juvenile-onset or recent-onset diabetes mellitus, multiple sclerosis, rheumatoid arthritis, liver disease, posterior uveitis, allergic encephalomyelitis, and glomerulonephritis), infectious diseases and/or the prevention of rejection of foreign organ transplants, e.g. bone marrow, kidney, liver, heart, skin,

small-bowel, and pancreatic-islet-cell transplants, the topical treatment of inflammatory and hyperproliferative skin diseases and cutaneous manifestations of immunologically-mediated illnesses (such as psoriasis, atopical dermatitiis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus or Alopecia areata), reversible obstructive airways disease, particularly asthma, and/or hepatic injury assoicated with ischemia.

More particularly, this invention relates to compounds of the general structural Formula I:



I

wherein R^1, R^2, R^3, R^4, R^5, W and n are hereinafter defined.

This invention also relates to pharmaceutical compositions containing the compounds, and to a method of use of the present compounds and other agents for the treatment and prevention of certain afflictions, diseases and illnesses.

BRIEF DESCRIPTION OF DISCLOSURES IN THE ART

Fujisawa United States, European and Japanese patents and applications (U.S. Patent No. 4,894,366, issued January 16, 1990, EPO Publication No. 0,184,162 and PBJ Disclosure 63-17884) and publications (J. Am. Chem. Soc., 1987, 109, 5031 and J. Antibiotics 1987, 40, 1249) disclose 17-allyl-1,14-dihydroxy-12-[2'-(4''-hydroxy-3''-methoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,-21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (FR-900506), (FK-506), (L-679,934), 17-ethyl-1,14-dihydroxy-12-[2'-(4''-hydroxy-3''-methoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone (FR-900520) and related compounds which are the starting materials for the preparation of the compounds described. The synthetic preparation of the aforementioned starting material (FR-900506) has recently been reported (J. Am. Chem. Soc., 1989, 111, 1157). A Sandoz European patent application (EPO Publication No. 0,356,399) discloses stereoisomers of FR-900506 and derivatives at the 17-position. Fisons European and WIPO patent (EPO Publication No. 0,323,042 and PCT Publication No.

WO89/05304) disclose various derivatives of FR-900506, FR-900520 and related compounds. A Sandoz European patent application (EPO Publication No. 0,437,680) discloses chloro, bromo, iodo and azido derivatives of FR-900506, FR-900520 and related compounds. A Merck European patent application (EPO Publication No. 0,428,365) discloses various amino derivatives of FR-900506, FR-900520 and related compounds. A Fujisawa UK patent application (UK Publication No. GB 2,245,891A) discloses various aryl(lower alkyl) and heteroaryl derivatives of FR-900506, FR-900520 and related compounds.

Fujisawa United States patents (U.S. Patent No. 4,929,611, issued May 29, 1990 and U.S. Patent No. 4,956,352 issued Sept 11, 1990) disclose the use of FK-506-type compounds in treating resistance to transplantation. A Sandoz European patent (EPO Publication No. 0,315,978) discloses the use of FR-900506 and related compounds in the topical treatment of inflammatory and hyperproliferative skin diseases and of cutaneous manifestations of immunologically-mediated illness. A Fisons WIPO patent application (PCT Publication WO 90/14826) discloses the use of FR-900506 and related compounds in the treatment of reversible obstructive airways disease, particularly asthma. A Fujisawa European patent application (EPO Publication No. 0,423,714) discloses the use of FK-506 and derivatives as hair revitalizing agents. Various studies have suggested the efficacy of FK-506 in the treatment of a number of ailments, including rheumatoid arthitis (C. Arita, et al., Clincial exp. Immunol., 1990, 82, 456-461; N. Inamura, et al., Clin. Immunol.

Immunopathol. 1988, 46, 82-90), recent-onset diabetes (N. Murase, et al., Diabetes, 1990, 39, 1584-86; N. Murase, et al., Lancet, 1990, 336, 373-74), posterior uveitis (H. Kawashima, Invest. Ophthalmul. Vis. Sci., 1988, 29, 1265-71), hepatic injury associated with ischemia (M. Sakr, et al., Life Sci., 1990, 47, 687-91) allergic encephalomyelitis (K, Deguchi, et al., Brain Nerve, 1990, 42, 391-97), glomerulonephritis (J. McCauley, et al., Lancet, 1990, 335, 674), systemic lupus erythematosus (K. Takabayashi, et al., Clin. Immunol. Immunopathol., 1989, 51, 110-117), multidrug resistance (M. Naito, et al., Cancer Chemother. Pharmacol., 1992, 29, 195-200), inflammation of mucosa and blood vessels (PCT Publication WO 91/17754), cytomegalovirus infection (UK Publication GB 2,247,620A), and idiopathic thrombocytophenic purpura and Basedow's disease (PCT Publication WO 91/19495).

BACKGROUND OF THE INVENTION

Immunoregulatory abnormalities have been shown to exist in a wide variety of "autoimmune" and chronic inflammatory diseases, including systemic lupus erythematosis, chronic rheumatoid arthritis, type 1 diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis and other disorders such as Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, ichthyosis, and Graves ophthalmopathy. Although the underlying pathogenesis of each of these conditions may be quite different, they have in common the appearance of a variety of autoantibodies and self-reactive lymphocytes. Such self-reactivity may be due, in part,

to a loss of the homeostatic controls under which the normal immune system operates.

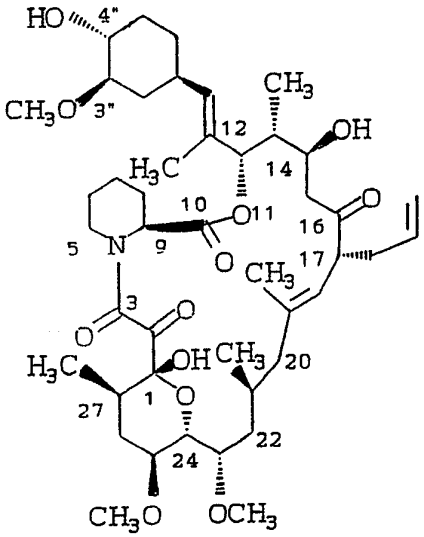
Similarly, following a bone-marrow or an organ transplantation, the host lymphocytes recognize the foreign tissue antigens and begin to produce antibodies which lead to graft rejection.

One end result of an autoimmune or a rejection process is tissue destruction caused by inflammatory cells and the mediators they release. Antiinflammatory agents such as NSAID's and corticosteroids act principally by blocking the effect or secretion of these mediators but do nothing to modify the immunologic basis of the disease. On the other hand, cytotoxic agents such as cyclophosphamide, act in such a nonspecific fashion that both the normal and autoimmune responses are shut off. Indeed, patients treated with such nonspecific immunosuppressive agents are as likely to succumb from infection as they are from their autoimmune disease.

Cyclosporin A which was approved by the US FDA in 1983 is currently the leading drug used to prevent rejection of transplanted organs. The drug acts by inhibiting the body's immune system from mobilizing its vast arsenal of natural protecting agents to reject the transplant's foreign protein. Though cyclosporin A is effective in fighting transplant rejection, it is nephrotoxic and is known to cause several undesirable side effects including kidney failure, abnormal liver function and gastrointestinal discomfort.

Newer, safer drugs exhibiting less side effects are constantly being searched for in the field.

The 23-membered tricyclo-macrolide immunosuppressant, FR-900506,



(17-allyl-1,14-dihydroxy-12-[2'-(4''-hydroxy-3''-methoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone) and related compounds which were isolated and characterized by Tanaka, Kuroda, and co-workers at Fujisawa Pharmaceutical Co. in Japan, see J. Am. Chem. Soc., 1987, 109, 5031, and U.S. Patent No. 4,894,366, issued January 16, 1990) have been shown to possess exceptional immunosuppressive activity. A Fujisawa United States patents (U.S. Patent No. 4,929,611, issued May 29, 1990 and U.S. Patent No. 4,956,352, issued Sept 11, 1990) disclose the use of FK-506-type compounds in treating resistance to transplantation. In particular, the compound FR-900506 has been reported

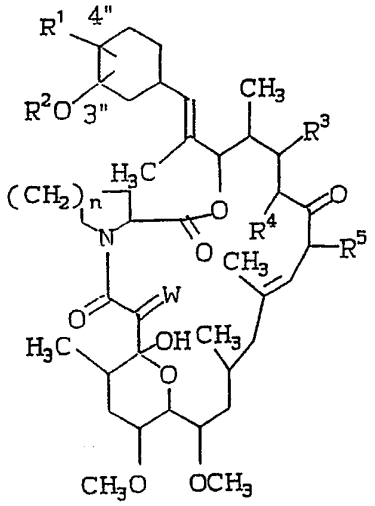
to be 100 times more effective than cyclosporin in the supression of in vitro immune systems (J. Antibiotics 1987, 40, 1256). In addition, these compounds are reputed to possess topical activity in the treatment of inflammatory and hyperproliferative skin diseases and cutaneous manifestations of immunologically-mediated illnesses (EPO Pub. No. 0,315,978).

The compound FK-506 and related compounds further have been suggested to be useful in the treatment of obstructive airways disease, particularly asthma (PCT Publication WO 90/14826), rheumatoid arthitis (C. Arita, et al., Clincial exp. Immunol., 1990, 82, 456-461; N. Inamura, et al., Clin. Immunol. Immunopathol. 1988, 46, 82-90), recent-onset diabetes (N. Murase, et al., Diabetes, 1990, 39, 1584-86; N. Murase, et al. Lancet, 1990, 336, 373-74), posterior uveitis (H. Kawashima, Invest. Ophthalmol. Vis. Sci., 1988, 29, 1265-71), hepatic injury associated with ischemia (M. Sakr, et al., Life Sci., 1990, 47, 687-91) allergic encephalomyelitis (K, Deguchi, et al., Brain Nerve, 1990, 42, 391-97), glomerulonephritis (J. McCauley, et al., Lancet, 1990, 335, 674), systemic lupus erythematosus (K. Takabayashi, et al., Clin. Immunol. Immunopathol., 1989, 51, 110-117), multidrug resistance (M. Naito, et al., Cancer Chemother. Pharmacol., 1992, 29, 195-200), inflammation of mucosa and blood vessels (PCT Publication WO 92/17754), cytomegalovirus infection (UK Publication GB 2,247,620A), and idiopathic thrombocytophenic purpura and Basedow's disease (PCT Publication WO 91/19495).

DETAILED DESCRIPTION OF THE INVENTION

A. Scope of the Invention

The novel compound of this invention has structural Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from:

1) $-N_3$;
2) -NHCN;
3) $-NR^6R^7$, wherein R^6 and R^7 independently, are,
   a) hydrogen,
   b) C_1-C_{12} alkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are independently selected from the group consisting of:

i) hydrogen,
ii) -OH,
iii) C_1-C_6alkoxy,
iv) -O-CO-C_1-C_6alkyl,
v) $-NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently, hydrogen, or C_1-C_6alkyl, unsubstituted or substituted with phenyl
vi) $-CONR^{10}R^{11}$,
vii) $-CO_2H$,
viii) -CO-O-C_1-C_6alkyl,
ix) -S-C_1-C_6alkyl,
x) -SO-C_1-C_6alkyl,
xi) $-SO_2$-C_1-C_6alkyl,
xii) halo, such as Cl, Br, F or I,
xiii) -C_3-C_7-cycloalkyl,
xiv) phenyl, unsubstituted or substituted with X, Y and Z,
xv) naphthyl, unsubstituted or substituted with X, Y and Z,
xvi) $-CF_3$,

c) C_3-C_{12} alkenyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above,

d) C_3-C_7 cycloalkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above,

e) phenyl, unsubstituted or substituted with X, Y and Z,

f) naphthyl, unsubstituted or substituted with X, Y and Z,

g) $-SO_2$-phenyl, wherein phenyl is unsubstituted or substituted with with X, Y and Z,

h) $-SO_2-C_1-C_6$alkyl,

i) or where R^6 and R^7 and the N to which they are attached may form an unsubstituted or substituted 3- to 7-membered heterocyclic ring which may include one or two additional heteroatoms independently selected from the group consisting of O, S, or NR^{10}, wherein R^{10} is as defined above, such as morpholine, thiomorpholine, piperidine, piperizine, and where the substituent(s), attached to the carbon atom(s) in the heterocyclic ring is/are independently selected from the group consisting of:

i) hydrogen,

ii) -OH,

iii) C_1-C_6 alkoxy,

iv) $-O-CO-C_1-C_6$ alkyl,

v) $-NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently, hydrogen, or C_1-C_6alkyl, unsubstituted or substituted with phenyl,

vi) $-CONR^{10}R^{11}$,
vii) $-CO_2H$,
viii) $-CO-O-C_1-C_6$ alkyl,
ix) -SH,
x) halo, such as Cl, Br, F or I,
xi) phenyl, unsubstituted or substituted with X, Y and Z,
xii) naphthyl, unsubstituted or substituted with X, Y and Z,
xiii) $-CF_3$;

4) $-N(R^6)CO-O-R^{12}$, wherein R^6 is as defined above and R^{12} is
C_1-C_{12} alkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above;

5) $-N(R^6)CO-R^{13}$, wherein R^6 is as defined above and R^{13} is
a) hydrogen,
b) C_1-C_{12} alkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above,
c) C_3-C_{12} cycloalkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above,

d) phenyl, unsubstituted or substituted with X, Y and Z,

e) naphthyl, unsubstituted or substituted with X, Y and Z, or

f) where R^6 and R^{13} and the -NCO- to which they are attached may form an unsubstituted or substituted 5- to 7-membered heterocyclic ring which may include one or two additional heteroatoms independently selected from the group consisting of O, S, or NR^{10}, wherein R^{10} is as defined above, such as pyrrolidone, or piperidinone;

6) $-N(R^{14})COCH(R^{22})NR^6R^7$ wherein R^6 and R^7 are as defined above, R^{14} is selected from the definitions of R^6, and R^{22} is

a) hydrogen,

b) C_1-C_4alkyl, unsubstituted or substituted with R^{23} wherein R^{23} is selected from the group consisting of:

i) -OH,

ii) C_1-C_6alkoxy,

iii) -O-CO-C_1-C_6alkyl,

iv) -SH,

v) -S-C_1-C_6alkyl,

vi) $-NR^{10}R^{11}$, wherein R^{10} and R^{11} are as defined above,

vii) $-CO_2H$,
viii) $-CONH_2$,
ix) imidazolyl,
x) indolyl,
xi) phenyl, and
xii) p-hydroxyphenyl,

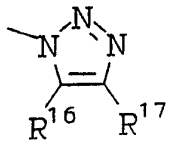
c) phenyl;

7) $-N(R^{14})CO(CH_2)_mNR^6R^7$, wherein m is 0 or 2-6, R^6 and R^7 are as defined above, and R^{14} is selected from the definitions of R^6, or
where R^{14} and R^6 and the $-NCO(CH_2)_mN-$ to which they are attached may form an unsubstituted or substituted 5- to 7-membered heterocyclic ring, such as 2-imidazolidone;

8) $-N=C(R^{14})-NR^6R^7$, wherein R^6 and R^7 are as defined above, and R^{14} is selected from the definitions of R^6, and wherein if either R^6 or R^7 are hydrogen, the tautomeric structure $-NHC(R^{14})=NR^{6or7}$ is also possible;

9) $-N(R^{15})_3^+ A^-$, wherein R^{15} is C_1-C_6 alkyl, unsubstituted or substituted with phenyl or naphthyl. and wherein A^- is a counterion:

10)



wherein R^{16} and R^{17} are independently,

a) hydrogen,
b) phenyl, unsubstituted or substituted with X, Y and Z,
c) naphthyl, unsubstituted or substituted with X, Y and Z,
d) -CN,
e) $-CF_3$,
f) $-CO-C_1-C_6$alkyl, or
g) $-CO-O-C_1-C_6$alkyl;

R^2 is selected from:

1) phenyl;
2) substituted phenyl in which the substituents are X, Y and Z;
3) 1- or 2- naphthyl;
4) substituted 1-or 2- naphthyl in which the substituents are X, Y and Z;
5) biphenyl;
6) substituted biphenyl in which the substituents are X, Y and Z;
7) substituted C_{1-10} alkyl in which one or more substituent(s) is(are) selected from:
   a) hydroxy,

b) C_{1-6} alkoxy,
c) phenyl C_{1-3} alkoxy,
d) substituted phenyl C_{1-3} alkoxy, in which the substituents on phenyl are X, Y and Z,
e) $-OCOC_{1-6}$ alkyl,
f) $-NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently hydrogen, or C_{1-6} alkyl unsubstituted or substituted with phenyl, which may be substituted with X, Y and Z,
g) $-NR^{6}CO-C_{1-6}$ alkyl, wherein R^{6} is as defined above,
h) $-COOR^{6}$, wherein R^{6} is as defined above,
i) -CHO,
j) phenyl,
k) substituted phenyl in which the substituents are X, Y and Z,
l) phenyloxy,
m) substituted phenyloxy in which the substituents are X, Y and Z,
n) 1- or 2- naphthyl,
o) substituted 1- or 2- naphthyl in which the substituents are X, Y and Z,
p) biphenyl, and
q) substituted biphenyl in which the substituents are X, Y and Z;

8) C_{3-10} alkenyl:
9) substituted C_{3-10} alkenyl in which one or more substituent(s) is(are) selected from:
a) hydroxy,
b) C_{1-6} alkoxy,

c) $-OCO-C_{1-6}$ alkyl,
d) C_{2-8} alkenyl,
e) phenyl,
f) substituted phenyl in which the substituents are X, Y and Z,
g) 1- or 2- naphthyl,
h) substituted 1- or 2- naphthyl in which the substituents are X, Y and Z,
i) biphenyl, and
j) substituted biphenyl in which the substituents are X, Y and Z;

10) C_{3-10} alkynyl; and
11) substituted C_{3-10} alkynyl in which one or more substituent(s) is(are) selected from:
a) hydroxy,
b) C_{1-6} alkoxy,
c) $-OCO-C_{1-6}$ alkyl,
d) phenyl,
e) substituted phenyl in which the substituents are X, Y and Z,
f) 1- or 2- naphthyl,
g) substituted 1- or 2- naphthyl in which the substituents are X, Y and Z,
h) biphenyl, and
i) substituted biphenyl in which the substituents are X, Y and Z;

R^3 is hydrogen, hydroxy, or C_1-C_6 alkoxy;
R^4 is hydrogen, or R^3 and R^4 taken together form a double bond;
R^5 is methyl, ethyl, propyl or allyl;
W is O or (H, OH);

X, Y and Z independently are selected from:

a) hydrogen,

b) C_{1-7} alkyl,

c) C_{2-6} alkenyl,

d) halo, such as Cl, Br, F or I,

e) $-(CH_2)_p-NR^{10}R^{11}$, wherein R^{10} and R^{11} are, as defined above and p is 0 to 2,

f) -CN,

g) -CHO,

h) $-CF_3$,

i) $-SR^{18}$, wherein R^{18} is hydrogen, C_{1-6}alkyl, or phenyl,

j) $-SOR^{18}$, wherein R^{18} is as defined above,

k) $-SO_2R^{18}$, wherein R^{18} is as defined above,

l) $-CONR^{10}R^{11}$, wherein R^{10} and R^{11} are as defined above,

m) $R^{19}O(CH_2)_p-$ wherein R^{19} is hydrogen, C_{1-3} alkyl, hydroxy-C_{2-3}alkyl, phenyl or naphthyl and p is as defined above,

n) $-CH(OR^{20})(OR^{21})$ wherein R^{20} and R^{21} are C_{1-3}alkyl or taken together form an ethyl or propyl bridge,

o) $R^{19}\overset{O}{\overset{\|}{C}}O(CH_2)_p-$ wherein R^{19} and p are as defined above; and

p) $R^{19}O\overset{O}{\overset{\|}{C}}(CH_2)_p-$ wherein R^{19} and p are as defined above;

or any two of X, Y and Z may be joined to form a saturated ring having 5, 6 or 7 ring atoms, said ring atoms comprising 0, 1 or 2 oxygen atoms, the remaining ring atoms being carbon, such as dioxolanyl or dioxanyl; and

n is 1 or 2.

The compounds of the present invention have asymmetric centers and this invention includes all of the optical isomers and mixtures thereof.

In addition compounds with carbon-carbon double bonds may occur in Z- and E- forms with all isomeric forms of the compounds being included in the present invention.

When any variable (e.g., alkyl, aryl, R^6, R^7, R^8, R^9, etc.) occurs more than one time in any variable or in Formula I, its definition on each ocurrence is independent of its definition at every other occurrence.

As used herein, the term "alkyl" includes those saturated hydrocarbon groups of a specified number of carbon atoms of either a straight, branched, or cyclic configuration. Representative examples of "alkyl" include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like. "Alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

"Alkanoyl" is intended to include those alkylcarbonyl groups of specified number of carbon atoms, which are exemplified by formyl, acetyl, propanoyl and butanoyl; "alkanoyloxy" is intended to include those alkylcarbonyl groups of specified number of carbon atoms attached through an oxygen bridge, which are exemplified by formyloxy, acetoxy, propionoyloxy, and butyryloxy. "Alkenyl" is intended

to include hydrocarbon chains of either a straight- or branched- configuration and at least one unsaturation, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, dimethylpentyl, and the like, and includes E and Z forms, where applicable; and "arylalkyl" represents aryl groups as herein defined which are attached through a straight or branched chain alkyl group of from one to six carbon atoms, such as, for example, benzyl, phenethyl, 3,3-diphenylpropyl, and the like. "Halogen", as used herein, means fluoro, chloro, bromo and iodo, and "counterion" is used to represent a small negatively-charged species, such as chloride, bromide, iodide, hydroxide, nitrate, acetate, citrate, benzoate, perchlorate, benzene sulfonate, tartrate, hemitartrate, maleate, and the like.

In the present invention it is preferred that in compounds of Formula I:

R^1 is selected from:

1) $-N_3$;
2) $-NR^6R^7$, wherein R^6 and R^7 independently, are,
   a) hydrogen,
   b) C_1-C_{12} alkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are independently selected from the group consisting of:
      i) hydrogen,
      ii) -OH,
      iii) $-O-CO-C_1-C_6$alkyl,
      iv) $-NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently,

hydrogen, or C_1-C_6alkyl, unsubstituted or substituted with phenyl

v) $-CONR^{10}R^{11}$,

vi) $-CO_2H$,

vii) $-CO-O-C_1-C_6$alkyl,

viii) phenyl, unsubstituted or substituted with X, Y and Z,

c) C_3-C_{12} alkenyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above;

3) $-N(R^6)CO-O-R^{12}$, wherein R^6 is as defined above and R^{12} is

C_1-C_{12} alkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above;

4) $-N(R^6)CO-R^{13}$, wherein R^6 is as defined above and R^{13} is

a) hydrogen,

b) C_1-C_{12} alkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above,

c) C_3-C_{12} cycloalkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above.

d) phenyl, unsubstituted or substituted with X, Y and Z,

5) $-N(R^{14})COCH(R^{22})NR^6R^7$ wherein R^6 and R^7 are as defined above, R^{14} is selected from the definitions of R^6, and R^{22} is

a) hydrogen,

b) C_1-C_4alkyl, unsubstituted or substituted with R^{23} wherein R^{23} is selected from the group consisting of:

i) -OH,

ii) C_1-C_6alkoxy,

iii) $-O-CO-C_1-C_6$alkyl,

iv) -SH,

v) $-S-C_1-C_6$alkyl,

vi) $-NR^{10}R^{11}$, wherein R^{10} and R^{11} are as defined above,

vii) $-CO_2H$,

viii) $-CONH_2$,

ix) imidazolyl,

x) indolyl,

xi) phenyl, and

xii) p-hydroxyphenyl, or

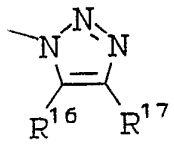
c) phenyl;

6) $-N(R^{14})CO(CH_2)_mNR^6R^7$, wherein m is 0 or 2-6, R^6 and R^7 are as defined above, and R^{14} is selected from the definitions of R^6, or where R^{14} and R^6 and the $-NCO(CH_2)_mN-$ to which they are attached may form an unsubstituted or substituted 5- to 7-membered heterocyclic ring, such as 2-imidazolidone;

7) $-N=C(R^{14})-NR^6R^7$, wherein R^6 and R^7 are as defined above, and R^{14} is selected from the definitions of R^6, and wherein if either R^6 or R^7 are hydrogen, the tautomeric structure $-NHC(R^{14})=NR^{6or7}$ is also possible;

8) $-N(R^{15})_3^+ A^-$, wherein R^{15} is C_1-C_6 alkyl, unsubstituted or substituted with phenyl or naphthyl, and wherein A^- is a counterion;

9)



wherein R^{16} and R^{17} are independently,

a) hydrogen,
b) phenyl, unsubstituted or substituted with X, Y and Z,
c) naphthyl, unsubstituted or substituted with X, Y and Z,
d) -CN,
e) $-CF_3$,
f) $-CO-C_1-C_6$alkyl, or
g) $-CO-O-C_1-C_6$alkyl;

R^2 is selected from:

1) phenyl;
2) substituted phenyl in which the substituents are X, Y and Z;
3) 1- or 2- naphthyl;
4) substituted 1- or 2- naphthyl in which the substituents are X, Y and Z;
5) substituted C_{1-10} alkyl in which one or more substituent(s) is(are) selected from:
   a) hydroxy,
   b) C_{1-6} alkoxy,
   c) phenyl C_{1-3} alkoxy,
   d) substituted phenyl C_{1-3} alkoxy, in which the substituents on phenyl are X, Y and Z,
   e) $-OCOC_{1-6}$ alkyl,
   f) $-NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently hydrogen, or C_{1-6} alkyl unsubstituted or substituted with phenyl, which may be substituted with X, Y and Z,
   g) $-NR^6CO-C_{1-6}$ alkyl, wherein R^6 is as defined above,
   h) $-COOR^6$, wherein R^6 is as defined above,
   i) -CHO,
   j) phenyl,
   k) substituted phenyl in which the substituents are X. Y and Z.
   l) phenyloxy, and
   m) substituted phenyloxy in which the substituents are X, Y and Z;
6) C_{3-10} alkenyl;

7) substituted C_{3-10} alkenyl in which one or more substituent(s) is(are) selected from:
   a) hydroxy,
   b) C_{1-6} alkoxy,
   c) $-OCO-C_{1-6}$ alkyl,
   d) C_{2-8} alkenyl,
   e) phenyl, and
   f) substituted phenyl in which the substituents are X, Y and Z;

8) C_{3-10} alkynyl; and

9) substituted C_{3-10} alkynyl in which one or more substituent(s) is(are) selected from:
   a) hydroxy,
   b) C_{1-6} alkoxy,
   c) $-OCO-C_{1-6}$ alkyl,
   d) phenyl, and
   e) substituted phenyl in which the substituents are X, Y and Z;

R^3 is hydrogen or hydroxy;

R^4 is hydrogen;

R^5 is ethyl, propyl or allyl;

W is O or (H, OH);

X, Y and Z independently are selected from:
   a) hydrogen,
   b) C_{1-7} alkyl,
   c) halo,
   d) -CN,
   e) -CHO,
   h) $-CF_3$,
   f) $-SR^{18}$, wherein R^{18} is hydrogen, C_{1-6}alkyl, or phenyl,

g) $-CONR^{10}R^{11}$, wherein R^{10} and R^{11} are as defined above,

h) $R^{19}O(CH_2)_p-$ wherein R^{19} is hydrogen, C_{1-3} alkyl, hydroxy-C_{2-3}alkyl, phenyl or naphthyl and p is 0 to 2;

i) $-CH(OR^{20})(OR^{21})$, wherein R^{20} and R^{21} are C_{1-3}alkyl or taken together form an ethyl or propyl bridge,

j) $R^{19}\overset{O}{\overset{\|}{C}}O(CH_2)_p-$ wherein R^{19} and p are as defined above; and

k) $R^{19}O\overset{O}{\overset{\|}{C}}(CH_2)_p-$ wherein R^{19} and p are as defined above;

or any two of X, Y and Z may be joined to form a saturated ring having 5, 6 or 7 ring atoms, said ring atoms comprising 0, 1 or 2 oxygen atoms, the remaining ring atoms being carbon; and

n is 1 or 2;

and pharmaceutically acceptable salts thereof.

Preferred compounds of the present invention are the compounds identified as follows:

17-allyl-1,14-dihydroxy-12-[2'-(4''-amino-3''-phenoxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-allyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-phenoxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-phenoxy-3"-amino-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-dimethylamino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4'''-methoxy-phenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11.28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3.10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4'''-hydroxy-phenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-acetylamino-3"-phenoxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4'''-fluoro-phenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(4'''-carboxyphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4'''-trifluoromethylphenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3''',4'''-dimethoxyphenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-allyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(4'''-methoxyphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4'''-methylphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(4'''-methylphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3'''-methoxyphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3'''-hydroxyphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-N-(2-propenyl)amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone; and

17-ethyl-1-hydroxy-12-[2'-(4"-(acetylamino-3"-(4'''-methoxyphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2"'R-hydroxypropyl)-amino-3"-phenyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,-16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2"'S-hydroxypropyl)-amino-3"-phenyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,-16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2""R-hydroxypropyl)-amino-3"-(4"'-methyl)phenyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2""S-hydroxypropyl)-amino-3"-(4"'-methyl)phenyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2""R-hydroxypropyl)-amino-3"-(4"'-methoxy)phenyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2""S-hydroxypropyl)-amino-3"-(4"'-methoxy)phenyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2"'R-hydroxypropyl)-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2"'S-hydroxypropyl)-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-dimethylamino-3"-(3"'-methoxy)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(4"'-dimethylamino)-phenyloxy-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-hydroxy-3"-(4"'-dimethylamino)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-azido-3"-(4"'-dimethylamino)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-dimethylamino)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-methyl)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxy-methyl)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-methoxy)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3"'-methoxy)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxy)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-formyl)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"allyloxy-3"-aminocyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$] octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-cinnamyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-cinnamyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Allyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-cinnamyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(3"'-phenylpropyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3"'-phenyl-propyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(2"'-benzyloxyethoxy)-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(2"'-benzyloxy-ethoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxycinnamyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxy-cinnamyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Allyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxycinnamyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Allyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxy-cinnamyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-acetylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-acetylamino-3"-allyl-oxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-N-(2-propenyl)amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(L-phenylalanine)-amido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(D-phenylalanine)-amido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-cyclopropanecarboxamido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-formamido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(4"',5"'-dicarboethoxy-1"',2"',3"'-triazole)-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-benzylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-dimethylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-trimethylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone iodide;

17-Ethyl-1,2,14-trihydroxy-12-[2'-(4"-acetylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-trione;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(N-phenylaminocarbonyl)amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(ethoxycarbonyl)-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-sec-butenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-sec-butenyl-oxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(3-methyl-2-butenyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3-methyl-2-butenyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(2-methyl-propenyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(2-methylpropenyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-methoxy-cinnamyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

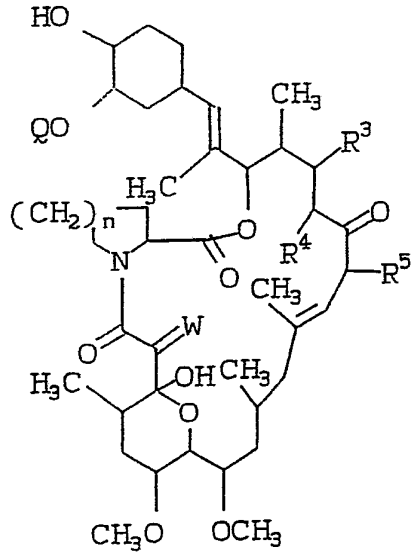
17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-fluorocinnamyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone; and

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(2-butynyloxy)-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

and pharmaceutically acceptable salts thereof.

B. Preparation of Compounds Within the Scope of the Present Invention

The starting materials for the preparation of the compounds of this invention are represented by Formula II:



II

wherein:
Q is hydrogen or methyl;
W is O or (H, OH);
R^3 is hydrogen, hydroxy, or C_1-C_6 alkoxy;
R^4 is hydrogen, or R^3 and R^4 taken together form a double bond;
R^5 is methyl, ethyl, propyl or allyl; and
n is 1 or 2.

The production and characterization of compounds of Formula II is well known in the literature (see U.S. Patent No. 4,894,366 issued January 16, 1990; U.S. Patent No. 4,929,611 issued May 29, 1990; U.S. Patent No. 3,244,592 issued April 15, 1966; EPO Publication No. 0,323,042; EPO Publication No. 0,356,399; PBJ Disclosure 63-17884; J. Am. Chem. Soc., 1987, 109, 5031; and J. Antibiotics, 1987, 40, 1249). Both biological fermentation and synthetic processes may be found. A synthetic route to compounds of Formula II can involve modifications of a route described in J. Am. Chem. Soc., 1989, 111, 1157.

Biological fermentation followed by synthetic modification is presently favored in the art as the method to produce compounds of Formula II. Organisms belonging to the genus Streptomyces such as Streptomyces tsukubaensis, No. 9993 and Streptomyces hygroscopicus, No. 7238 placed in an aqueous nutrient medium will produce desired compounds in isolable amounts. The nutrient medium contains sources of assimilable carbon and nitrogen, preferably under aerobic conditions. Produced in fermentation are four compounds of Formula II, (A) where Q is methyl, W is O, R^3 is hydroxyl, R^4 is hydrogen, R^5 is allyl and n is 2; (B) where Q is methyl, W is O, R^3 is hydroxyl, R^4 is hydrogen, R^5 is ethyl and n is 2; (C) where Q is methyl, W is O, R^3 is hydroxyl, R^4 is hydrogen, R^5 is methyl and n is 2; and (D) where Q is methyl, W is O, R^3 is hydroxyl, R^4 is hydrogen, R^5 is allyl and n is 1.

A lyophilized sample of the isolated Streptomyces tsukubaensis, No. 9993 was deposited with the Fermentation Research Institute, Agency of

Industrial Science and Technology (No. 1-3, Higashi 1-chome, Yatabemachi Tsukuba-gun, Ibaraki Prefecture, Japan) under the deposit number of FERM P-7886 (deposit date: October 5th, 1984), and then converted to Budapest Treaty route of the same depository on October 19, 1985 under the new deposit number of FERM BP-927.

Using the four compounds produced in fermentation above, the remaining compounds of Formula II may be easily produced. The allyl of R^5 may be conveniently reduced to propyl by well known methods, for example as described in U.S. Patent No. 4,894,366. The hydroxy of R^3 may be protected by well known methods, for example as disclosed in EPO Publication No. 0,323,042. Likewise, the hydroxyl at C-4'' may also be protected. In addition, the hydroxy of R^3 may be reduced to a hydrogen or eliminated to form a double bond with R^4 (by methods disclosed in U.S. Patent No. 4,894,366 or EPO Publication No. 0,323,042). The carbonyl of W may be reduced to the alcohol by methods disclosed in EPO Publication No. 0, 323,042 or by methods disclosed in U.S. Patent No. 5,064,835.

The methyl of Q as produced may be replaced with hydrogen or demethylated and subsequently protected as desired, if necessary. This demethylation of compounds wherein Q is methyl may be carried out in a fermentation reaction using the compounds of Formula II as a feedstock. For instance, compound A named under Formula II above may be demethylated at Q above by using the microorganism Actinomycetales ATCC No. 53771 (described in U.S. Patent No. 4,981,792, issued January 1, 1991). Similarly, compound B named under Formula II above may be demethylated at Q above using the microorganism Actinoplanacete sp. ATCC No. 53771

(described in EPO Publication No. 0,349,061). In addition the compound of Formula II wherein Q is H, W is O, R^3 is hydroxy, R^4 is hydrogen, R^5 is ethyl and n is 2 may be produced directly by fermentation using the mutant microorganism Streptomyces hygroscopicus sup. ascomyceticus, No. 53855 (being a blocked mutant of Streptomyces hygroscopicus sup. ascomyceticus, No. 14891) (as described in EPO Publication No. 0,388,152). Similarly, the compound of Formula II wherein Q is hydrogen, W is O, R^3 is hydroxy, R^4 is hydrogen, R^5 is methyl and n is 2 may be produced directly by fermentation using the mutant microorganism Streptomyces hygroscopicus sup. ascomyceticus, No. 53855 (being a blocked mutant of Streptomyces hygroscopicus sup. ascomyceticus, No. 14891) (as described in EPO Publication No. 0,388,153). Also, the compound of Formula II wherein Q is hydrogen, R^3 is hydroxy, R^4 is hydrogen, R^5 is allyl, W is O and n is 2 and the compound of Formula II wherein the C-3" position is keto, R^3 is hydroxy, R^4 is hydrogen, R is allyl, W is O and n is 2 may be produced directly by fermentation using the microorganism Streptomyces tsukubaensis, No. 9993 (described in EPO Publication No. 0,353,678). The hydroxy of C-3" may be protected by methods similar to those known for the protection of the hydroxy's of R^3 and/or C-4", for example as disclosed in U.S. Patent No. 4,894,366.

Suitable protecting groups for hydroxyl include those groups well known in the art which are:

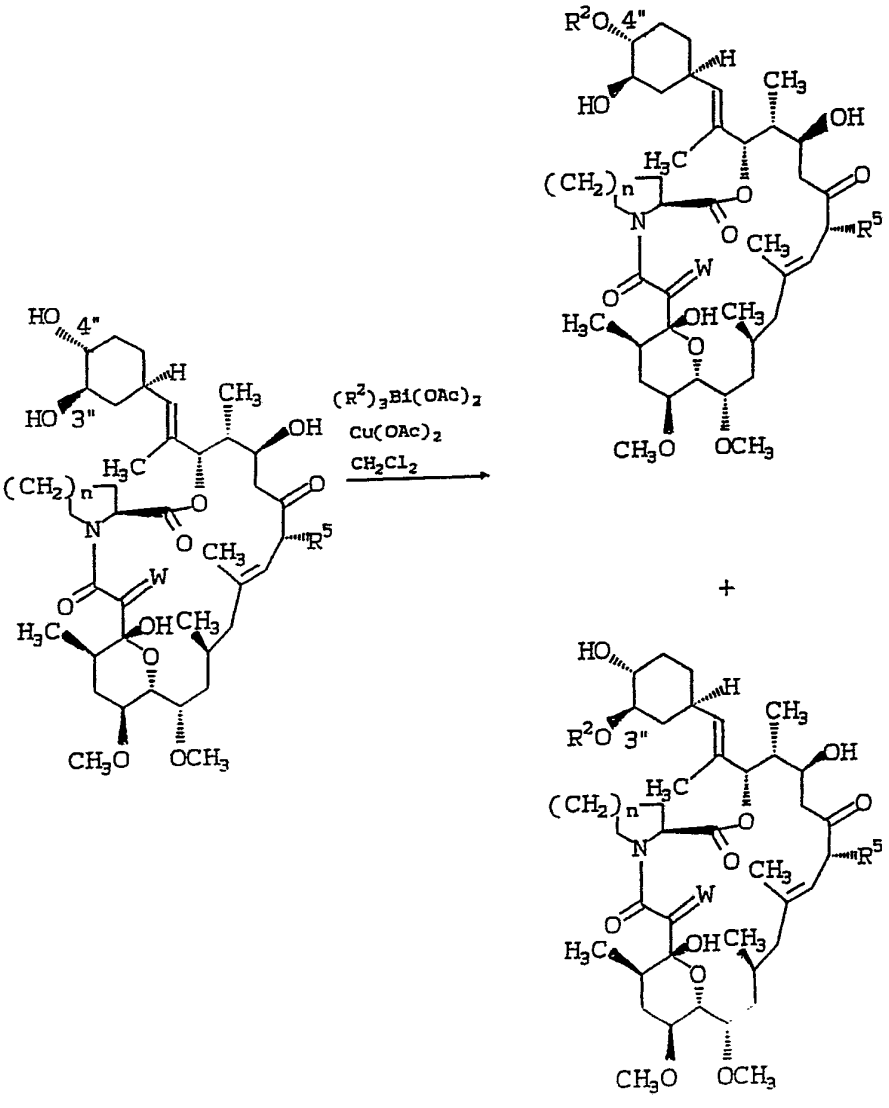
1-(lower alkylthio)(lower)alkyl, wherein "lower alkyl" indicates a straight, cyclic or branched chain of one to six carbon atoms,

such as lower alkylthiomethyl (e.g. methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), and the like, in which the preferred one may be C_1-C_4 alkylthiomethyl and the most preferred one may be methylthiomethyl; trisubstituted silyl such as tri(lower)alkylsilyl (e.g. trimethylsilyl, triethylsilyl, tributysilyl, tri-i-propylsilyl, t-butyldimethylsilyl, tri-t-butylsilyl, etc.), lower alkyldiarylsilyl (e.g. methyl-diphenylsilyl, ethyl-diphenylsilyl, propyl-diphenylsilyl, t-butyldiphenylsilyl, etc.), and the like, in which the preferred one may be tri(C_1-C_4)alkylsilyl and C_1-C_4 alkyl- diphenylsilyl, and the most preferred one may be tert-butyl-dimethylsilyl, tri-i-propylsilyl and tert-butyl-diphenylsilyl; acyl such as aliphatic acyl, aromatic acyl and aliphatic acyl substituted with aromatic group, which are derived from carboxylic acids; and the like.

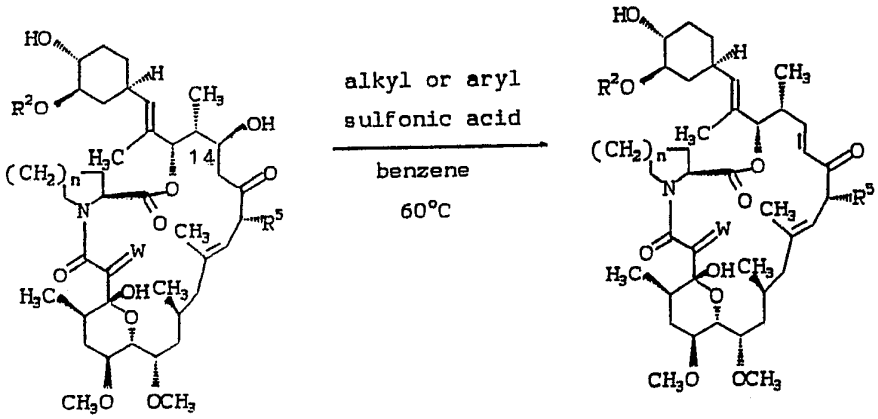
Compounds A, B, C and D of Formula II, organisms to produce the same, conditions of fermentation, separation techniques, and chemical modification of the products are fully described in U.S. Patent No. 4,894,366, issued January 16, 1990, and U.S. Patent No. 4,929,611, issued May 29, 1990.

The novel processes for preparing the novel compounds of the present invention are illustrated as follows, R^1, R^2, R^3, R^5, Q, W and n are as defined above unless otherwise indicated.

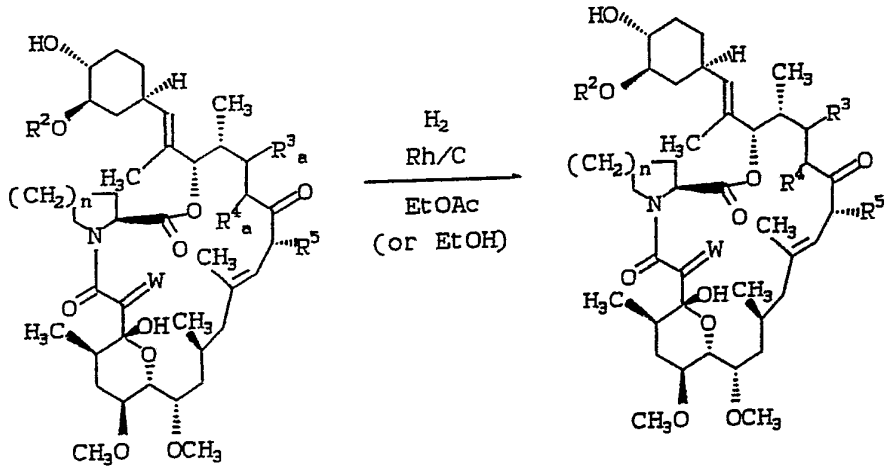
REACTION SCHEME A



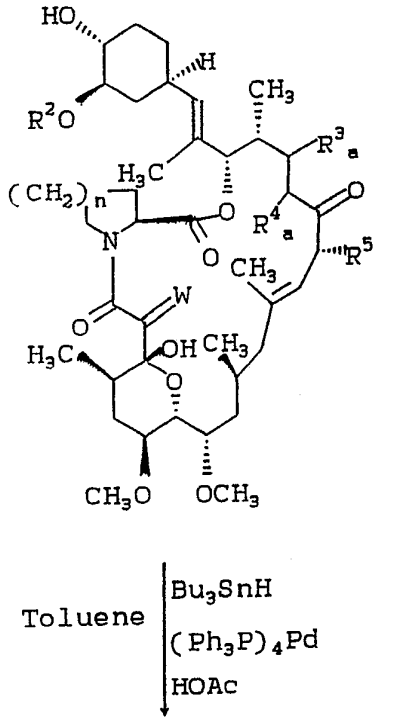
REACTION SCHEME B



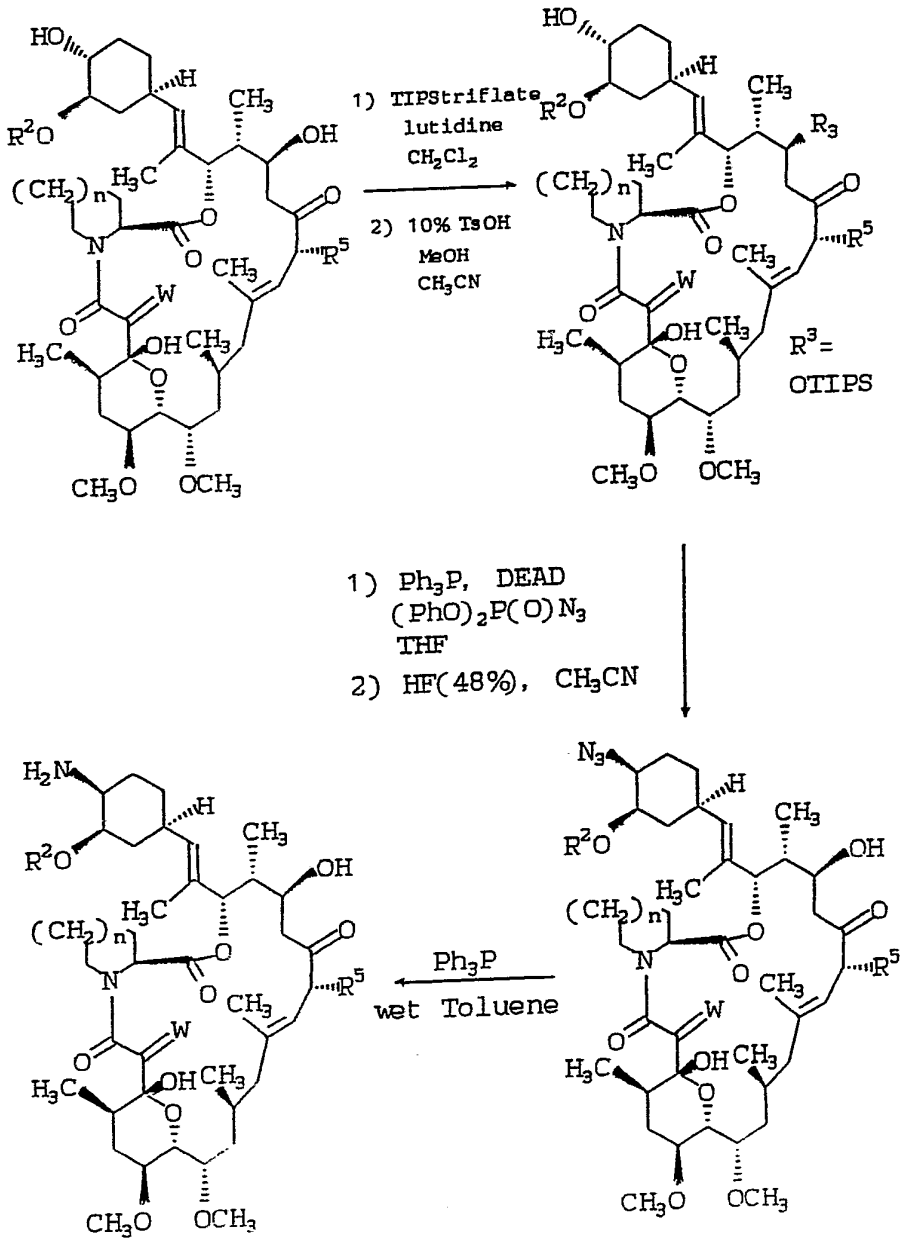
REACTION SCHEME C



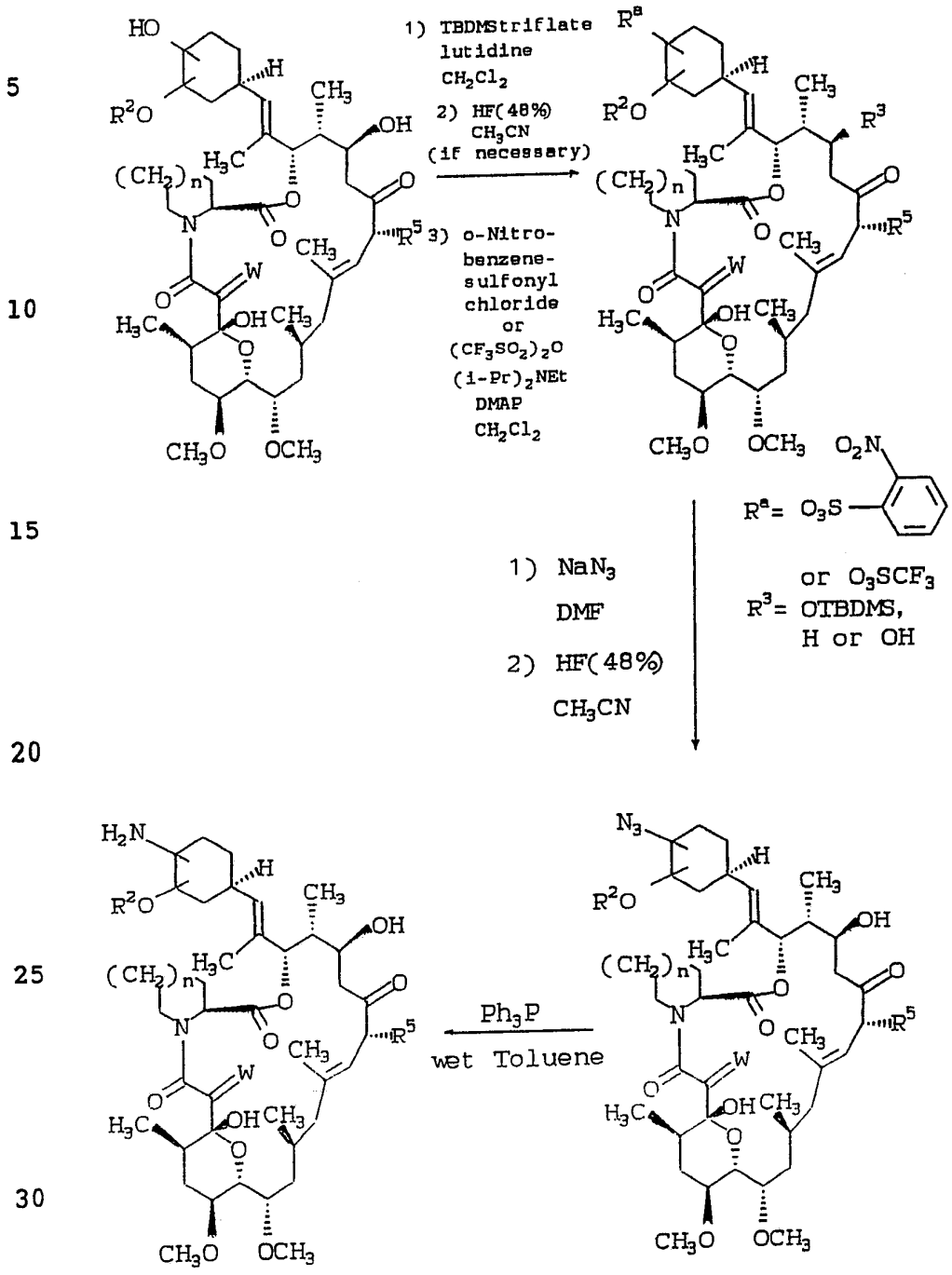
REACTION SCHEME D



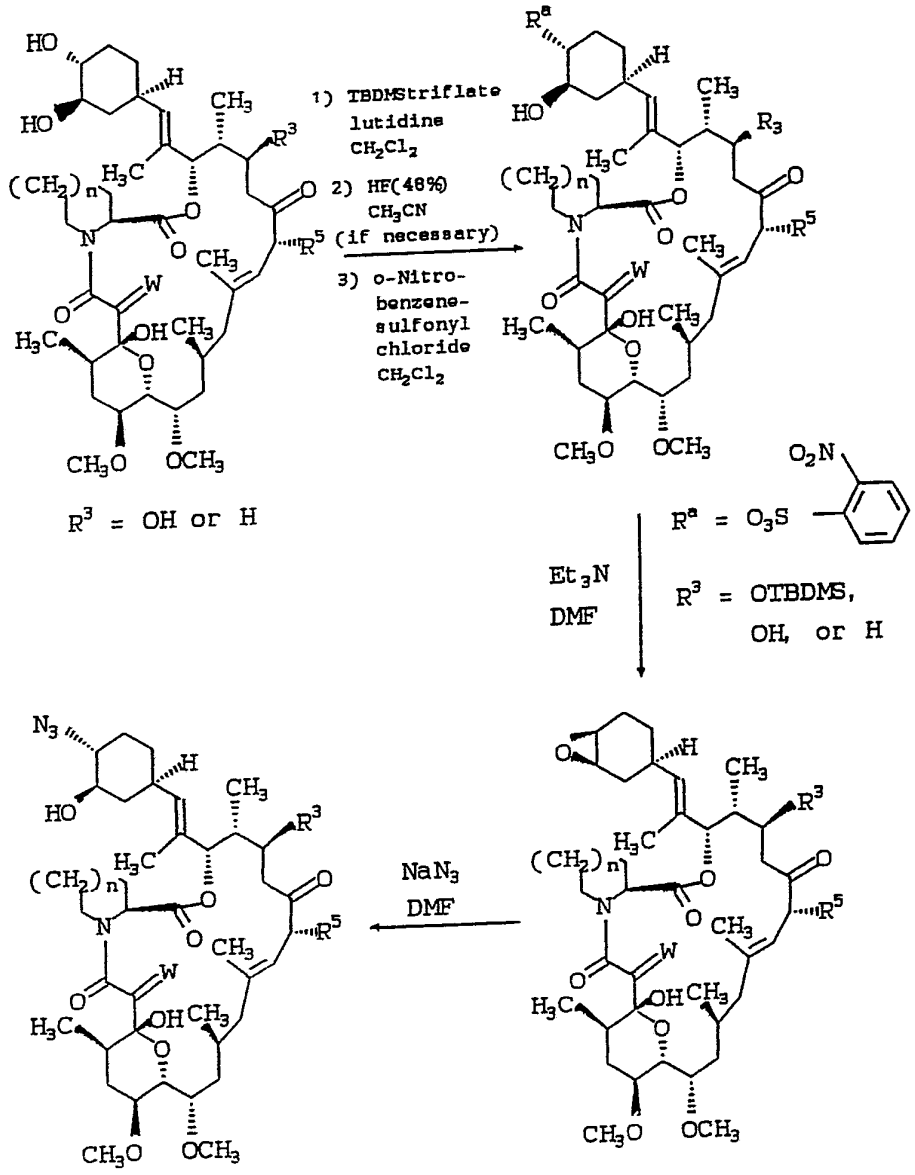
REACTION SCHEME E



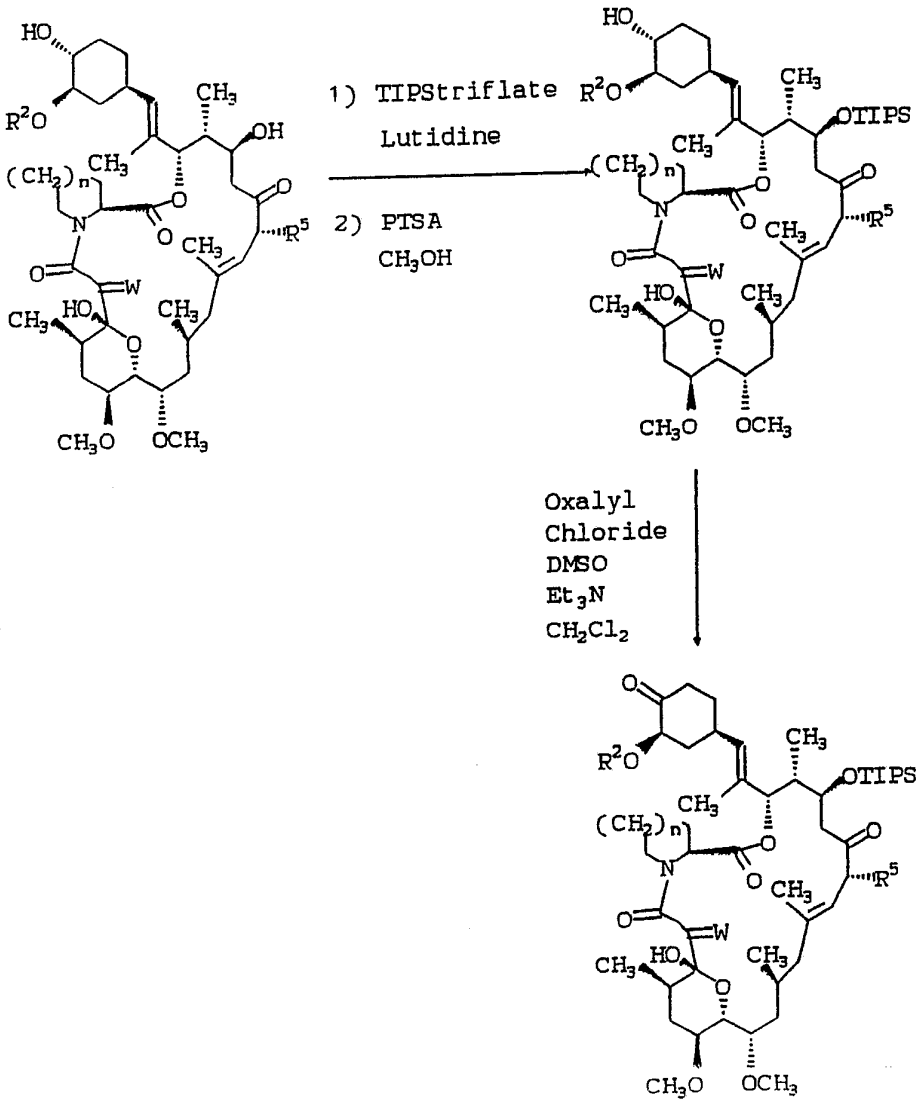
REACTION SCHEME F



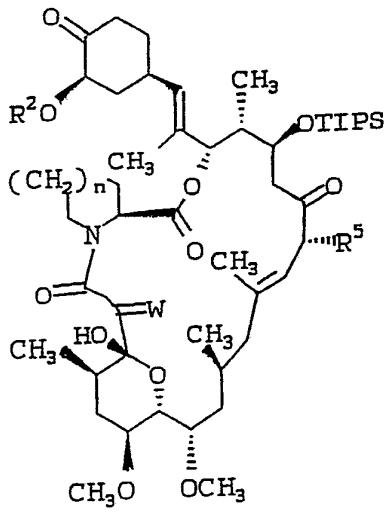
REACTION SCHEME G



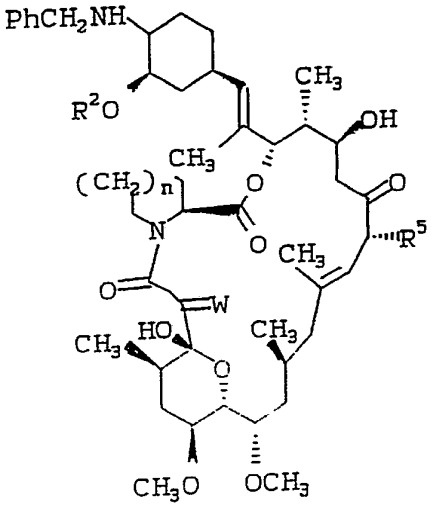
REACTION SCHEME H



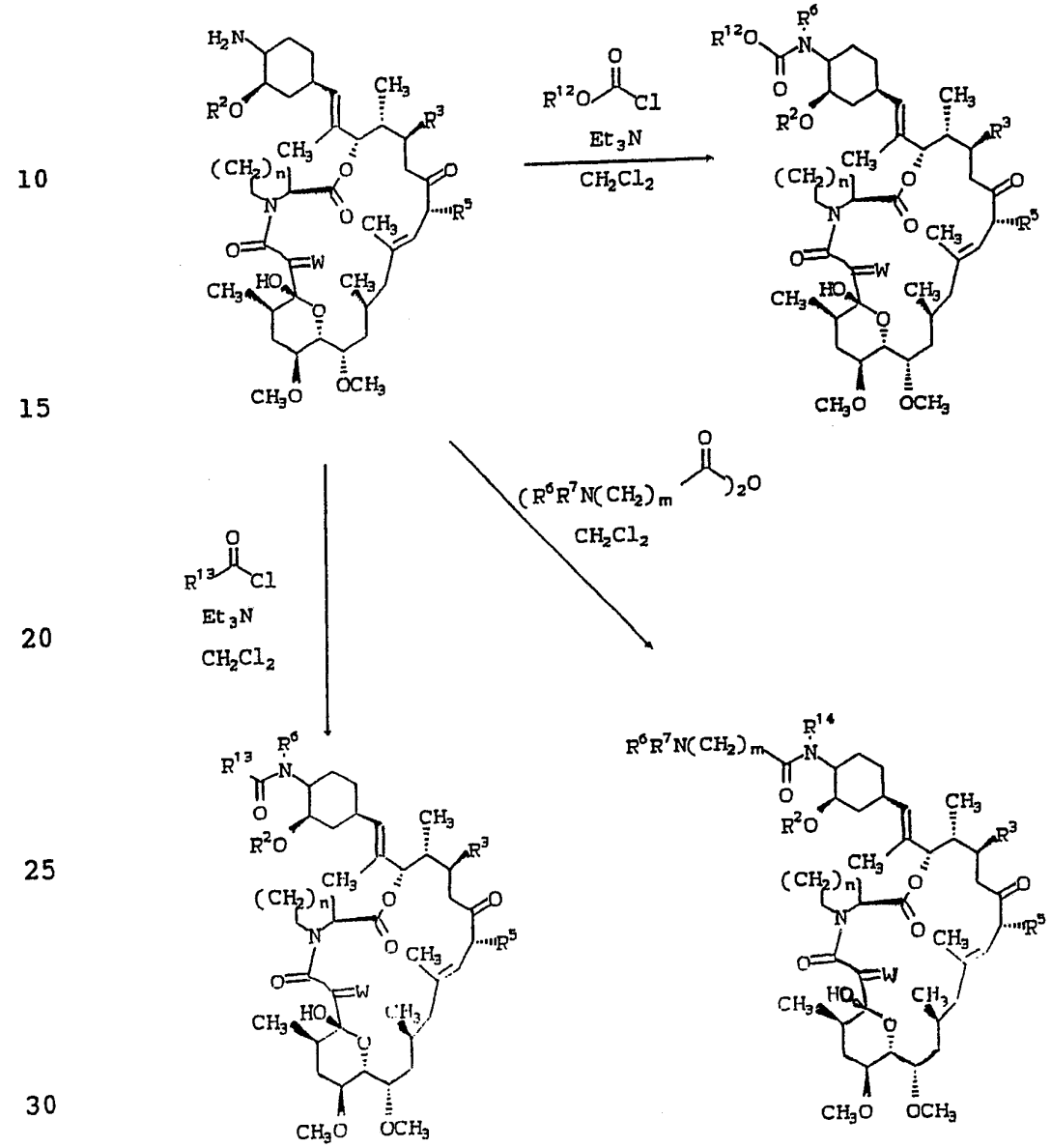
REACTION SCHEME H (CONT.)



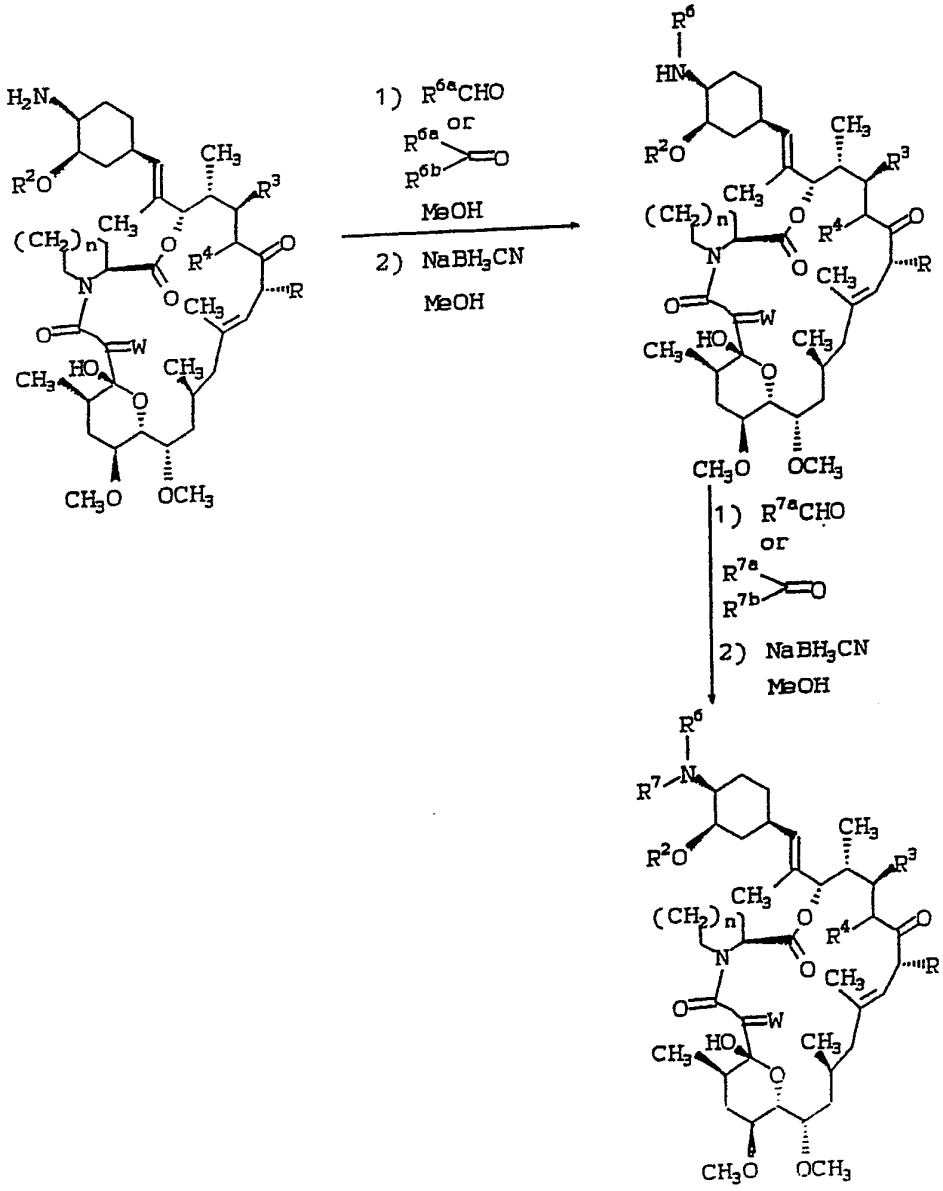
1) HF(48%) CH_3CN
2) $PhCH_2NH_2$
3) $NaCNBH_3$



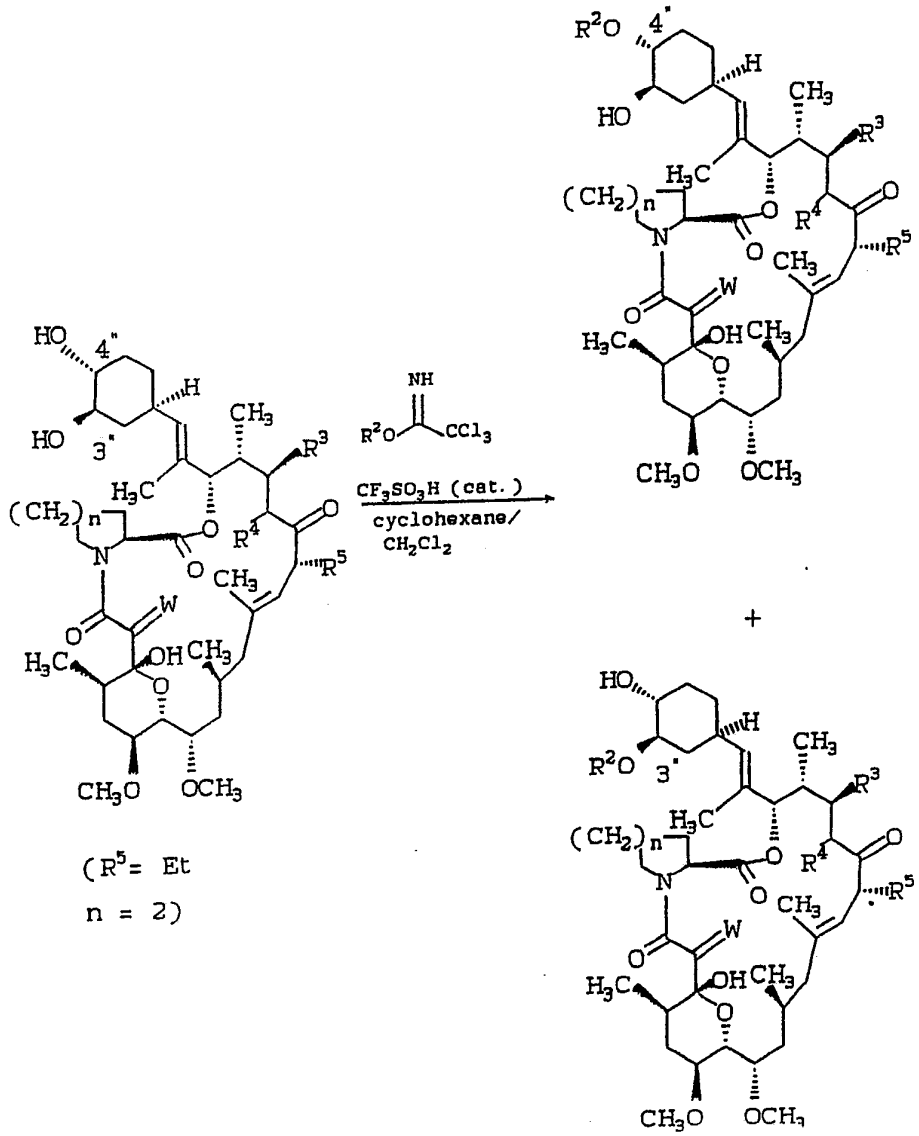
REACTION SCHEME I



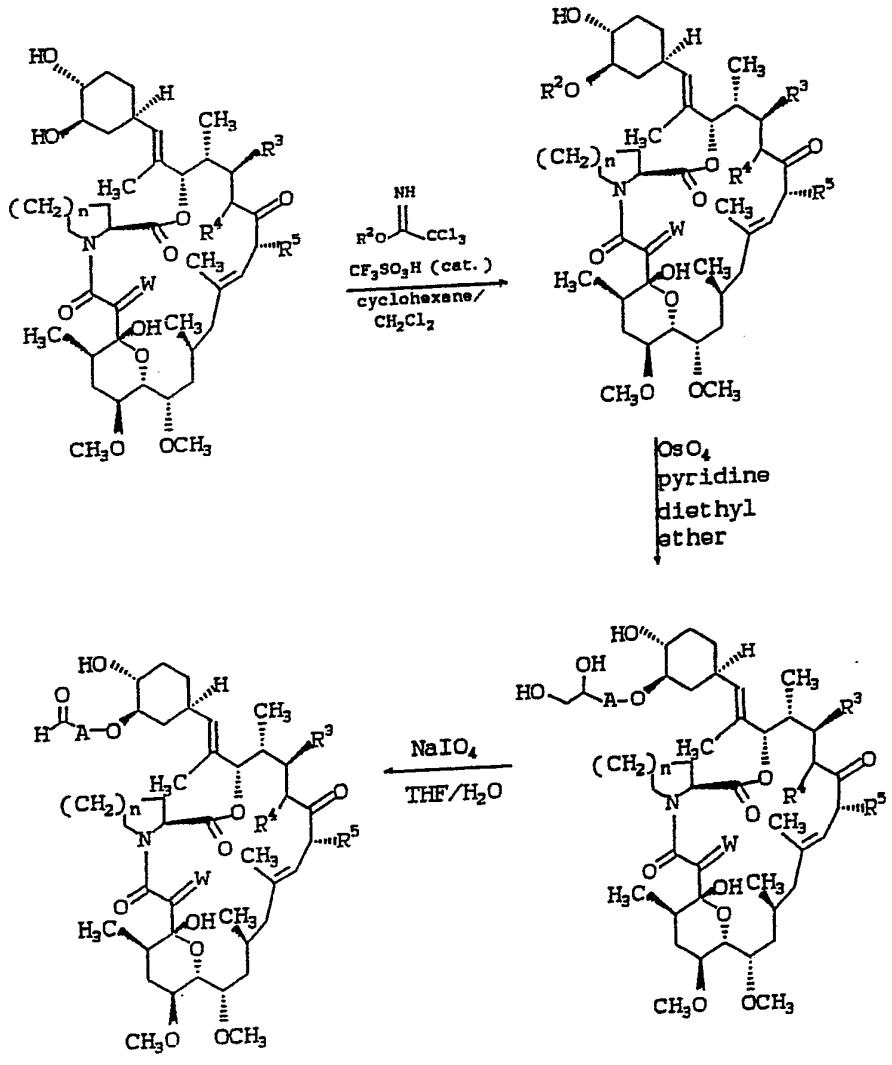
REACTION SCHEME J



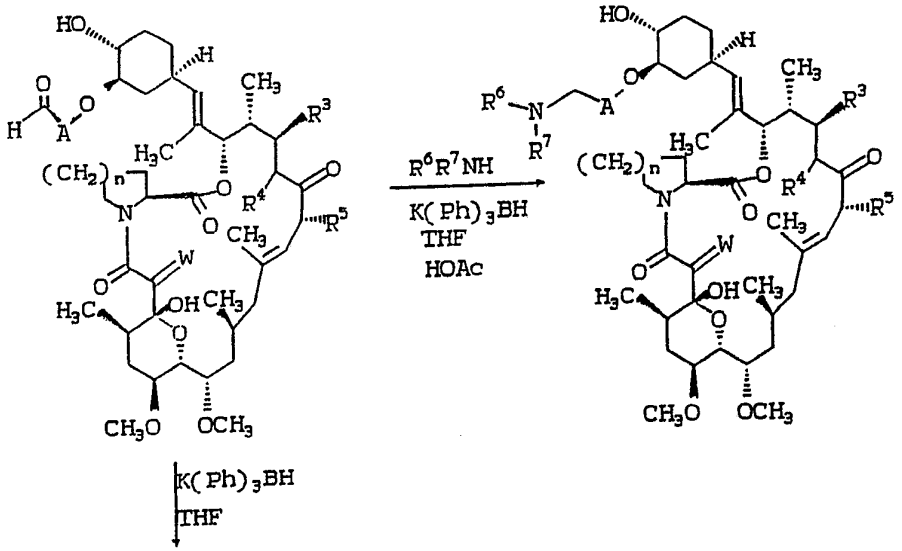
REACTION SCHEME K



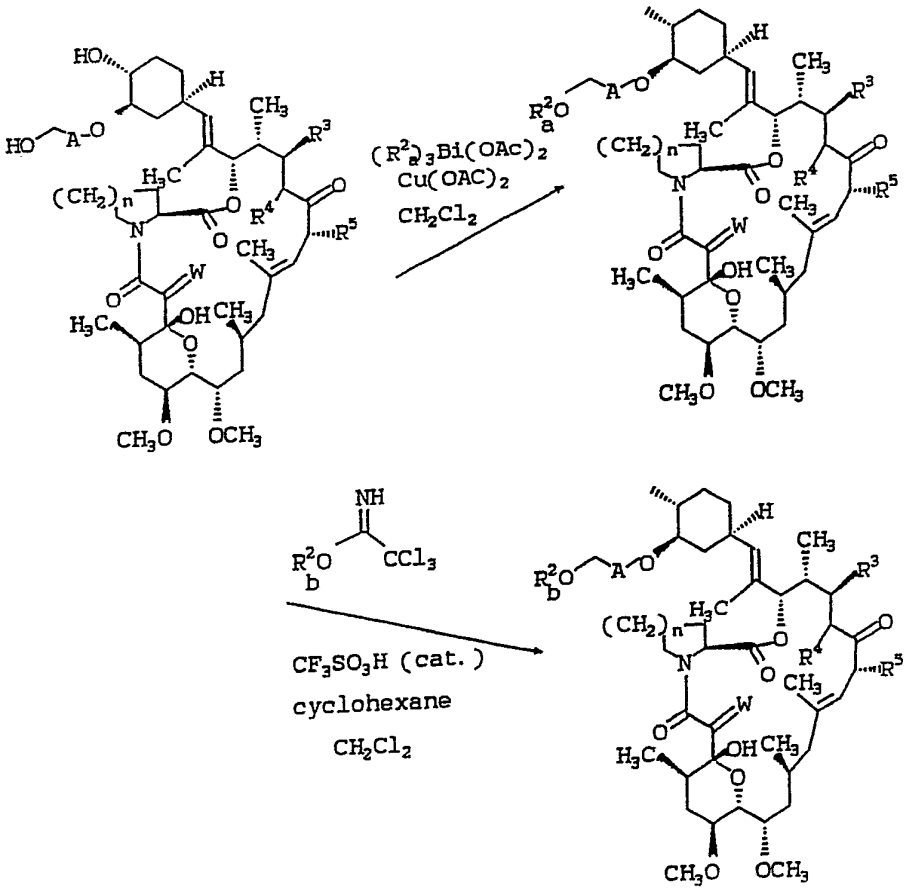
REACTION SCHEME L



REACTION SCHEME M



REACTION SCHEME M (CONT.)



As shown in Reaction Scheme A, a solution of the 3",4"-dihydroxy macrolide in an inert organic solvent such as methylene chloride, benzene, toluene, chloroform, or the like or mixtures thereof is treated with a triarylbismuth diacetate reagent (wherein R^2 is aryl) (prepared immediately prior to use by the addition of acetic acid to a suspension of a triarylbismuth carbonate in an inert organic solvent such as methylene chloride, chloroform or the like or mixtures thereof) in the presence of a catalytic amount of copper(II) acetate at a temperature of 20-50°C, preferably room temperature, for a period of one hour to seven days, preferably one day, to give a mixture of the 4"-O-aryl 3"-hydroxy macrolide and the 3"-O-aryl-4"-hydroxy macrolide. Alternatively, the triarylbismuth(V) reagent can be prepared by treatment of a triarylbismuthine with a suitable oxidant such as peracetic acid, iodobenzene diacetate, bis(trifluoroacetoxy)iodobenzene and the like in an inert solvent such as methylene chloride, chloroform, benzene, toluene and the like. The triarylbismuth(V) reagent can be used without purification or can be purified by silica gel chromatography. Triarylbismuthines may be prepared by the reaction of an appropriate aryl Grignard reagent with bismuth trichloride in an inert organic solvent such as tetrahydrofuran, diethyl ether, or 1,4-dioxane, or mixtures thereof, at or near room temperature for a period of 1 to 48 hours. General procedures for the preparation and use of triarylbismuth reagents may

be found in Barton, D.H.E., et al., J. Chem. Soc. Chem. Commun., 1986, 65 and references cited therein. The 4"-O-aryl 3"-hydroxy macrolide and the 3"-O-aryl 4"-hydroxy macrolide may be separated and purified in a conventional manner, for example, fractional crystallization, recrystallization, chromatography, and the like.

As shown in Reaction Scheme B the 14-hydroxy group of a macrolide (wherein R^1, R^2, R^5 and n are as defined above) may be eliminated by treatment with p-toluenesulfonic acid, benzenesulfonic acid, methanesulfonic acid, p-nitrobenzenesulfonic acid, p-bromobenzenesulfonic acid, p-chlorobenzenesulfonic acid, or p-methoxybenzenesulfonic acid, or mixtures thereof, in an inert organic solvent such as benzene, or toluene or the like at a temperature of 40°C to solvent reflux temperature, preferably 60°C, for about 0.5 to 6 hours, or a sufficient period of time to eliminate the 14-hydroxy group. Neutralization with an aqueous solution of a weak base such as aqueous saturated sodium bicarbonate gives the 14,15-dehydro macrolide. The 14-hydroxy group may also be eliminated by activation followed by basic elimination, as described in U.S. Patent No. 4,894,366.

As shown in Reaction Scheme C the macrolide (wherein $R^3{}_a$ and $R^4{}_a$ taken together form a double bond) is reduced under an atmosphere of hydrogen in the presence of a noble metal catalyst, such as rhodium on carbon catalyst or rhodium on alumina catalyst, at a pressure of atmospheric pressure to 40 psig, at or near room temperature in an organic

solvent such as ethyl acetate or ethanol for about 1 to 24 hours, or until the requisite amount of hydrogen is absorbed to reduce the olefin and give the reduced macrolide. Alternatively, the procedures described in Reaction Scheme D may be performed.

In Reaction Scheme D the macrolide (wherein R^3_a and R^4_a taken together form a double bond) is reduced with tri-n-butyltin hydride in the presence of tetrakis (triphenylphosphine)palladium(0) catalyst and acetic acid in an organic solvent such as toluene or tetrahydrofuran at or near room temperature for about 2 to 10 hours to give the reduced macrolide. By changing the sequence of synthetic steps, all possible variations in substitution may be obtained. For example, the C-14 hydroxy can be eliminated and the resultant olefin reduced prior to the introduction of substituents at C-3 "and/or C-4".

Protection of the C-3" and/or the C-4" hydroxy group may be accomplished by methods known in the prior art for compounds of Formula II such as by treatment with: 2,6-lutidine and triisopropylsilyl trifluoromethane sulfonate in a solution of methylene chloride; 2,6-lutidine and t-butyldimethylsilyl trifluoromethanesulfonate in a solution of methylene chloride; pyridine and acetic anhydride in a solution of methylene chloride; pyridine and benzoyl chloride in a solution of methylene chloride; pyridine and p-nitrobenzoyl chloride in a solution of methylene chloride; imidazole and t-butyldiphenylsilyl chloride in a solution of methylene chloride; and the like.

As shown in Reaction Scheme E the C-14-OTIPS protected macrolide is prepared from the 4",14-dihydroxy macrolide and reacted with diphenyl phosphoryl azide in the presence of triphenyl phosphine and diethyl azodicarboxylate to introduce the azide substituent at the C-4" position. The protecting group at C-14 is removed and reduction of the azide with triphenylphosphine/water gives the C-4" amino compound.

An alternate route to C-3"/C-4" amino substituted compounds is shown in Reaction Scheme F. The macrolide is protected if necessary and reacted with o-nitrobenzenesulfonyl chloride or trifluoromethanesulfonyl anhydride in the presence of an amine base to give the mono- C-3"/C-4" o-nitrobenzenesulfonyl or trifluoromethanesulfonyl derivative. The activated leaving group group is displaced by treatment with sodium azide (or an alternative nucleophillic amine), the protecting group is removed, if necessary, by treatment with hydrogen fluoride and, if necessary, the azide is reduced with triphenyl phosphine/water to give the amino compound. Azides can be reduced with other reagents known in the art, such as with hydrogen sulfide, propane-1,3-dithol, or thioacetic acid or by catalytic hydrogenation over a suitable catalyst.

As shown in Reaction Scheme G, the opposite stereochemistry of the resultant amino compound can be obtained by proceeding thru an epoxide as a synthetic intermediate. Reaction of the C-3"-beta, C-4"-alpha dihydroxy macrolide (wherein R^3 is hydrogen or protected hydroxy) with o-nitrobenzene-

sulfonyl chloride followed by separation of the isomers and treatment with a tertiary amine base, such as triethylamine, gives the two possible epoxides. The beta-epoxide may be opened by treatment with azide to give the C-3"-beta-hydroxy C-4"-alpha-azido macrolide. The C-3"-hydroxyl group may be arylated, prior to reduction of the azide to the amine (by the methods of Reaction Scheme E), and the resultant amine may be further modified by methods described in Reaction Scheme I.

An amino substituent may also be introduced at C-4" by reductive amination of a keto-substituted macrolide as shown in Reaction Scheme H. The ketone at C-4" is prepared by Swern oxidation of a suitably protected hydroxy-macrolide. Reductive amination of the ketone with an appropriate amine gives the corresponding amino-macrolide as a mixture of epimers at C-4".

Compounds bearing a C-4" amino substituent may be further modified by methods which are known in the art as exemplified in Reaction Scheme I. These method include, but are not limited to such methods as: acylation with an appropriate acid halide or acid anhydride in the presence of an amine base to give the corresponding amide, coupling with an appropriate carboxylic acid to give the corresponding amide, reaction with an isocyanate to give the urea derivative, treatment with an ethyl chloroformate equivalent to give the corresponding urethane or alkylation with an appropriate alkyl halide to give the corresponding secondary, tertiary or quarternary alkyl amine.

An amino substituent may also be modified at C-3" and/or C-4" by reductive amination of an amino-substituted macrolide as shown in Reaction Scheme J (wherein R^{6a} or R^{6b} and R^{7a} or R^{7b} are respectively equivalent to R^6 and R^7 absent one methyl group). The imine is prepared by reaction of the amine with an appropriate aldehyde or ketone. Reduction of the imine with sodium cyanoborohydride or similar reducing agent gives the corresponding amino-macrolide. The reductive amination may be repeated to give mixed-disubstituted amino macrolides.

As shown in Reaction Scheme K, (wherein R^2 is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl) a solution of the 3",4"-dihydroxy macrolide in an inert organic solvent such as methylene chloride, chloroform, pentane, hexane, cyclohexane, heptane or the like or mixtures thereof is treated with a trichloroacetimidate (prepared by the reaction of an appropriate sodium alkoxide with trichloroacetonitrile, such as described by Wessel, H.P., Iversen, T., Bundle, D.R., J. Chem. Soc., Perkin Trans. I, 1985, 2247) in the presence of a mild acid catalyst such as trifluoromethanesulfonic acid, p-toluene-sulfonic acid, methanesulfonic acid, benzenesulfonic acid, p-nitrobenzenesulfonic acid, p-bromobenzenesulfonic acid, p-chlorobenzenesulfonic acid, or p-methoxybenzenesulfonic acid, or mixtures thereof at a temperature of 20-50°C, preferably 25°C, for a period of one hour to seven days, preferably 6 hours, to give a mixture of the 3"-O-alkyl, -alkenyl or -alkynyl 4"-hydroxy macrolide and the 3"-hydroxy 4"-O-alkyl, -alkenyl or -alkynyl macrolide.

As shown in Reaction Scheme L, the 3",4"-dihydroxy macrolide (wherein R^3 is protected hydroxy or hydrogen) may be reacted with an alkenyl trichloroacetimidate (wherein R^2 is C_{3-8} alkenyl) under conditions described in Reaction Scheme E to give the C-3"-O-alkenyl macrolide. Treatment with a stochiometric amount of osmium tetraoxide in an inert organic solvent, such or tetrahydrofuran, in the presence of an amine base, such as pyridine at or near room temperature gives the corresponding glycol. Treatment with sodium metaperiodate in a solution of tetrahydrofuran/water gives the aldehyde. Alternatively, the C-3"-O-alkenyl macrolide may be treated with sodium metaperiodate in the presence of a catalytic amount of osmium tetraoxide in an organic solvent to give the aldehyde directly. In an analogous manner, the C-4"-derivatives may also be prepared.

A variety of compounds may be prepared from the corresponding aldehyde as illustrated in Reaction Scheme M. The aldehyde may be reacted with a primary or secondary amine (wherein R^6 and R^7 are as defined above) in an organic solvent such as tetrahydrofuran to give an imine which is reduced <u>in situ</u> with a hydride reducing agent, such as potassium triphenyl borohydride or sodium cyanoborohydride, to give the macrolide bearing an amino alkoxy functionality at C-3". The aldehyde may also be reduced to the corresponding alcohol by treatment with a hydride reducing agent, such as potassium triphenyl borohydride or sodium cyanoborohydride in an organic solvent such as tetrahydrofuran. The alcohol may be further modified by utilizing the methods of Reaction

Scheme B (wherein $R^2{}_b$ is unsubstituted or substituted alkyl, alkenyl or alkynyl) or by treatment with a triarylbismuth diacetate reagent (wherein $R^2{}_a$ is aryl or substituted aryl) (prepared immediately prior to use by the addition of acetic acid to a suspension of a triarylbismuth carbonate in an inert organic solvent such as methylene chloride, choroform or the like or mixtures thereof) in the presence of a catalytic amount of copper(II) acetate at a temperature of 20-50°C, preferably room temperature, for a period of one hour to seven days, preferably one day, to give the desired macrolide. Alternatively, the triarylbismuth(V) reagent can be prepared by treatment of a triarylbismuthine with a suitable oxidant such as peracetic acid, iodobenzene diacetate, bis(trifluoroacetoxy)iodobenzene and the like in an inert solvent such as methylene chloride, chloroform, benzene, toluene and the like. The triarylbismuth(V) reagent can be used without purification or can be purified by silica gel chromatography. Triarylbismuthines may be prepared by the reaction of an appropriate aryl Grignard reagent with bismuth trichloride in an inert organic solvent such as tetrahydrofuran, diethyl ether, or 1,4-dioxane, or mixtures thereof, at or near room temperature for a period of 1 to 48 hours. General procedures for the preparation and use of triaryl bismuth reagents may be found in Barton, D.H.E., et al., J. Chem. Soc. Chem. Commun., 1986, 65 and references cited therein. The procedures described in Reaction Scheme M are readily applicable to the preparation of compounds bearing an ether functionality at C-4".

The procedures described in Reaction Schemes E-M may optionally be conducted prior to the procedures of Reaction Schemes A-D. Additionally, the procedures described in Reaction Schemes B and C may be conducted subsequent to the procedures of Reaction Schemes E-M. In general, however, it is preferred that the O-aryl, alkyl, alkenyl or alkynyl group be introduced prior to the introduction of the amino functionality.

The object compounds of Formula I obtained according to the reactions as explained above can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

It is to be noted that in the aforementioned reactions and the post-treatment of the reaction mixture therein, the stereoisomer(s) of starting and object compounds due to asymmetric carbon atom(s) or double bond(s) of the object compounds of Formula I may occasionally be transformed into the other stereo isomer(s), and such cases are also included within the scope of the present invention.

In the present invention, compounds with asymmetric centers may occur as racemates, diastereomeric mixtures and as individual diastereomers. with all isomeric forms of the compounds being included in the present invention. These may be prepared by methods such as those disclosed in publications which describe synthetic routes to fragments of the macrolide FR-900506 and the total synthesis of the macrolide FR-900506 itself (see for example, J. Am. Chem. Soc. 1989, 111, 1157;

J. Am. Chem. Soc. 1990, 112, 2998; J. Org. Chem. 1990, 55, 2786; J. Am. Chem. Soc. 1990, 112, 5583. Tetrahedron Lett. 1988, 29, 277; Tetrahedron Lett. 1988, 29, 281; Tetrahedron Lett. 1988, 29, 3895; J. Org. Chem. 1988, 53, 4643; Tetrahedron Lett. 1988, 29, 4245; Tetrahedron Lett. 1988, 29, 4481; J. Org. Chem. 1989, 54, 9; J. Org. Chem. 1989, 54, 11; J. Org. Chem. 1989, 54, 12; J. Org. Chem. 1989, 54, 15; J. Org. Chem. 1989, 54, 17; Tetrahedron Lett. 1989, 30, 919; Tetrahedron Lett. 1989, 30, 1037; J. Org. Chem. 1989, 54, 2785; J. Org. Chem. 1989, 54, 4267; Tetrahedron Lett. 1989, 30, 5235; Tetrahedron Lett. 1989, 30, 6611; Tetrahedron Lett. 1989, 30, 6963; Synlett 1990, 38; J. Org. Chem. 1990, 55, 2284; J. Org. Chem. 1990, 55, 2771; J. Org. Chem. 1990, 55, 2776; Tetrahedron Lett. 1990, 31, 1439; Tetrahedron Lett. 1990, 31, 1443; Tetrahedron Lett. 1990, 31, 3007; Tetrahedron Lett. 1990, 31, 3283, 3287).

The compounds of the present invention are capable of forming salts with various inorganic and organic acids and bases and such salts are also within the scope of this invention. Examples of such acid addition salts include acetate, adipate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, ethanesulfonate, fumarate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, methanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, oxalate, pamoate, persulfate, picrate, pivalate, propionate, succinate, tartrate, toluenesulfonate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as

calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; aralkyl halides like benzyl bromide and others. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, such as in isolating or purifying the product.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed in vacuo or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

C. Utility of the compounds within the scope of the invention

The compounds of Formula I may be employed as immunosuppressants or antimicrobial compounds by methods and in dosages known in the prior art for compounds of Formula II. These compounds possess pharmacological activity such as immunosuppressive activity, antimicrobial activity, and the like, and therefore are useful for the treatment and prevention of the resistance to transplantation or transplan-

tation rejection of organs or tissues such as heart, kidney, liver, duodenum, small-bowel, medulla ossium, skin, pancreatic islet-cell, etc., graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosis, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis, allergic encephalomyelitis, glomerulonephritis, etc., and infectious diseases caused by pathogenic microorganisms.

The compounds of Formula I are also useful for treating or preventing inflammatory and hyperproliferative skin diseases and cutaneous manifestations of immunologically-mediated illnesses such as: psoriasis, atopical dermatitiis, contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, acne, cutaneous eosinophilias or Alopecia areata. More particularly, the compounds of Formula I are useful in hair revitalizing, such as in the treatment or prevention of male pattern alopecia or alopecia senilis, by providing epilation prevention, hair germination, and/or a promotion of hair generation and hair growth.

The compounds of Formula I are further useful for treating or preventing reversible obstructive airways disease, including conditions such as asthma, including bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma, particularly chronic or inveterate asthma (for example late asthma and airway hyper-responsiveness), bronchitis and the like. The

compounds of Formula I may also be useful for treating hepatic injury associated with ischemia.

The compounds of Formula I are also useful for treating multidrug resistance of tumor cells, (i.e. enhancing the activity and/or sensitivity of chemotherapeutic agents), preventing or treating inflammation of mucosa or blood vessels, LTB_4-mediated diseases, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel disease, inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) necrotizing enterocolitis, or intestinal lesions associated with thermal burns, cytomegalovirus infection, particularly HCMV infection, idiopathic thrombocytopenic purpura and Basedow's disease.

Further, the compounds of Formula I are also useful for treating or preventing renal diseases selected from interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome and diabetic nephropathy; nervous diseases selected from multiple myositis, Guillain-Barre syndrome, Meniere's disease and radiculopathy; endocrine diseases selected from hyperthyroidism; hematic diseases selected from pure red cell aplasia, aplastic anemia, hypoplastic anemia, autoimmune hemolytic anemia, agranulocytosis and anerythroplasia; bone diseases such as osteoporosis; respiratory diseases selected from sarcoidosis, fibroid lung and idiopathic interstitial pneumonia; eye diseases selected from herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukmas, ocular pemphigus, Mooren's ulcer, scleritis and Grave's ophthalmopathy; skin diseases selected from dermatomyositis, leukoderma

vulgaris, ichthyosis vulgaris, photoallergic sensitivity and cutaneous T cell lymphoma; circulatory diseases selected from arteriosclerosis, aortitis syndrome, polyarteritis nodosa and myocardosis; collagen diseases selected from scleroderma, Wegener's granuloma and Sjogren's syndrome; adiposis; eosinophilic fasciitis; periodontal disease; and muscular dystrophy.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. For example, the compounds of Formula I may be utilized with hydroxypropyl methylcellulose essentially as described in U.S Patent No. 4,916,138, issued April 10, 1990, or with a surfactant essentially as described in EPO Publication

0,428,169. Oral dosage forms may be prepared essentially as described by T. Hondo, et al., Transplantation Proceedings, 1987, XIX, Supp. 6, 17-22. Dosage forms for external application may be prepared essentially as described in EPO Publication 0,423,714. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of diseases.

For the treatment of these conditions and diseases caused by immmunoirregularity a compound of formula I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Dosage levels of the compounds of the present invention are of the order from about 0.005 mg to about 50 mg per kilogram of body weight per day, preferably from about 0.1 mg to about 10 mg per kilogram of body weight per day, are useful in the treatment of the above-indicated conditions (from about 0.7 mg to about 3.5 g per patient per day, assuming a 70 kg patient). In addition, the compounds of the present invention may be administered on an intermittent basis; i.e. at daily, semiweekly, weekly, semi-monthly or monthly intervals.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host

treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 gm of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain from about 0.5 mg to about 500 mg of active ingredient, and preferably about 0.5 mg to about 100 mg of active ingredient. For external administration the compound of Formula I may be formulated within the range of, for example, 0.0001% to 60% by weight, preferably from 0.001 to 10% by weight, and most preferably from about 0.005 to 0.8% by weight.

It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following examples are given for the purpose of illustrating the present invention and shall not be construed as being limitation on the scope or spirit of the instant invention.

EXAMPLE 1

General procedure for the preparation of triaryl-bismuthines

To a stirred suspension of magnesium (486 mg, 20 mmol) in dry tetrahydrofuran (10 mL) is added slowly a solution of aryl halide (20 mmol) in dry tetrahydrofuran (10 mL). If necessary the mixture is warmed gently to effect grignard formation. To the stirred solution of the grignard reagent is added a solution of bismuth trichloride (1.9 g, 6 mmol) dissolved in dry tetrahydrofuran (20 mL). The resulting mixture is stirred for 24 hours. The reaction mixture is poured into a separatory funnel containing brine and extracted 4x with CH_2Cl_2. The organic extracts were combined and dried over anhydrous Na_2SO_4. The mixture was filtered and concentrated in vacuo. The triarylbismuthine is isolated and purified by flash column chromatography on silica gel.

EXAMPLE 2

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-phenyloxy-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,-27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-phenyloxy-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,-27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (500 mg, 0.644 mmol, 1 eq) and $Cu(OAc)_2$ (12 mg, 0.064 mmol, 0.1 eq) in CH_2Cl_2 (10 ml) in a 25 ml recovery flask equipped with a magnetic stir-bar was added triphenyl bismuth diacetate [prepared immediately prior to use by addition of acetic acid (0.220 ml, 3.860 mmol, 6 eq) to a suspension of triphenyl bismuth carbonate (483 mg., 0.965 mmol, 1.5 eq) in CH_2Cl_2 (10 ml)]. The reaction flask was capped and the mixture stirred at room temperature for 6 hours. The flask was then fitted with a condenser and the mixture was warmed to 40°C. After 40 hours the reaction mixture was cooled, diluted with saturated aqueous $NaHCO_3$ and extracted 4 times with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The products were separated and purified by flash column chromatography on silica gel [eluted with 4:1 hexanes/acetone followed by preparative TLC on silica gel (eluted with 2:1 hexanes/acetone] yielding 94 mg ethyl-1,14-dihydroxy-12-[2'-(4"-phenyloxy-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and 110 mg 17-ethyl-1,14-

dihydroxy-12-[2'-(3"-phenyloxy-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone. (^{1}H NMR, ^{13}C NMR and mass spectral analysis were consistent with the desired structure).

EXAMPLE 3

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-methylphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-di-methoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-methyl-phenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatri-cyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred mixture of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,-10,16-tetraone (200 mg, 0.257 mmol, 1 eq) and $Cu(OAc)_2$ (10 mg, 0.055 mmol, 0.2 eq) in CH_2Cl_2 (2 ml) in a round bottom flask equipped with a magnetic stir-bar was added tri(4-tolyl)bismuth diacetate [prepared immediately prior to use by addition of acetic acid (0.075 ml, 1.31 mmol, 5.1 eq) to a suspension of tri(4-tolyl) bismuth carbonate (300 mg, 0.553 mmol, 2.1 eq) in CH_2Cl_2 (2 ml)]. The reaction flask was fitted with a reflux condenser and the

mixture warmed to 40°C for 5 hours then stirred without heating. After 18 hours the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted times with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated in <u>in vacuo</u>. The products were separated and purified by preparative TLC on silica gel (eluted with 2:1 hexanes/acetone) affording 31 mg 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-methylphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and 42 mg 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-methylphenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,-10,16-tetraone. (^1H NMR and ^{13}C NMR analysis were consistent with the desired structure).

<u>EXAMPLE 4</u>

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-phenoxyphenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-phenoxyphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone

To a stirred mixture of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (150 mg, 0.19 mmol, 1 eq) and $Cu(OAc)_2$ (7 mg, 0.039 mmol, 0.21 eq) in CH_2Cl_2 (2 mL) in a round bottom flask equipped with a magnetic stir-bar was added tri(4-phenoxyphenyl)bismuth diacetate [prepared immediately prior to use by addition of acetic acid (0.070 ml, 1.22 mmol, 6.4 eq) to a suspension of tri(4-phenoxyphenyl) bismuth carbonate (230 mg, 0.30 mmol, 1.58 eq) in CH_2Cl_2 (2 mL)]. The reaction flask was fitted with a reflux condenser and the mixture warmed to 40°C. After 4 hours the mixture was cooled, diluted with saturated aqueous $NaHCO_3$, and extracted 2 times with CH_2Cl_2 the extracts were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The products were separated and purified 3x by preparative TLC on silica gel (eluted with 3:2 hexanes/acetone) affording 35 mg 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-phenoxyphenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and 42 mg 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-phenoxyphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone. (^1H NMR, ^{13}C NMR, and mass spectral analysis were consistent with the desired structures).

EXAMPLE 5

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(naphth-1-yloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(naphth-1-yl-oxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred mixture of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,-10,16-tetraone (250 mg, 0.32 mmol, 1 eq) and $Cu(OAc)_2$ (15 mg, 0.08 mmol, 0.25 eq) in CH_2Cl_2 (5 ml) in a round bottom flask equipped with a magnetic stir/bar was added tri(1-naphthyl) bismuth diacetate [prepared immediately prior to use by addition of acetic acid (0.100 ml, 1.75 mmol, 5.46 eq) to a suspension of tri(1-naphthyl) bismuth carbonate (350 mg, 0.54 mmol, 1.69 eq) in CH_2Cl_2 (5 ml)]. The reaction flask was fitted with a reflux condensor and the mixture warmed to 40°C for 5 hours then stirred at room temperature. After 16 hours the mixture was diluted with saturated aqueous $NaHCO_3$ and extracted 2 times with CH_2Cl_2. The extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The products were separated and purified by preparative TLC on silica gel (eluted with 3:1 hexanes/acetone)

yielding 49 mg 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(naphth-1-yloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and 39 mg 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(naphth-1-yloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone. (^{1}H NMR analysis were consistent with the desired structures).

EXAMPLE 6

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(naphth-2-yloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(napth-2-yloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred mixture of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,-10,16-tetraone (250 mg, 0.32 mmol, 1 eq) and $Cu(OAc)_2$ (10 mg, 0.055 mmol, 0.17 eq) in CH_2Cl_2 (5.5 ml) in a round bottom flask equipped with a magnetic stir-bar was added tri(2-naphthyl) bismuth diacetate [prepared immediately prior to use by addition of acetic acid (0.100 mL, 1.75 mmol, 5.46 eq) to a

suspension of tri(2-naphthyl) bismuth carbonate (350 mg, 0.538 mmol, 1.7 eq) in CH_2Cl_2 (5.5 ml)]. The reaction flask was fitted with a reflux condenser and the mixture warmed to 40°C for 4 hours then stirred at room temperature. After 3 days the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted 3 times with CH_2Cl_2. The extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The products were separated and purified by preparative TLC on silica gel (eluted with 3:1 hexanes/acetone) to give 63 mg of 17-ethyl-1,14-dihydroxy-12-[2'-(3''-(napth-2-yloxy)-4''-hydroxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,-27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone and 49 mg of 17-ethyl-1,14-dihydroxy-12-[2'-(4''-(naphth-2-yloxy)-3''-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone. (^1H NMR were consistent with the desired structures).

EXAMPLE 7

Tri(6-Methoxy-2-naphthyl)bismuth diacetate

To a stirred solution of tri(6-methoxy-naphth-2-yl)bismuthine (100 mg, 0.158 mmol) in CH_2Cl_2 (8 mL) was added iodobenzene diacetate (200 mg, 0.621 mmol). The CH_2Cl_2 was removed in vacuo and the residue was dissolved in several milliliters of 4:1 hexanes/acetone plus small amount of CH_2Cl_2. The solution was passed through a silica gel plug and

eluted with 4:1 hexanes/acetone. The filtrate was concentrated in vacuo. The residue was dissolved in 4:1 hexanes/acetone plus small amount of CH_2Cl_2 and passed through a second silica gel plug and eluted with 4:1 hexanes/acetone. The filtrate was concentrated in vacuo leaving 52 mg yellow residue that was used without further purification.

EXAMPLE 8

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(6'''-methoxy-naphth-2-yloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$] octacos-18-ene-2,3,10,16-tetraone and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(6'''-methoxynaphth-2-yloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone

To a solution of tri-(6-methoxy-2-naphthyl) bismuth diacetate (22 mg, 0.028 mmol, 1 eq) in methylene chloride (2 ml) in a 10 mL round bottom flask equipped with a stir bar was added 17-ethyl-1, 14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (22 mg, 0.028 mmol, 1 eq). To the reaction mixture was added a catalytic amount of $Cu(OAc)_2$ (approximately 20 mg). The reaction flask

was fitted with a reflux condenser and the mixture was warmed to 40°C. After 1 hour the mixture was cooled, diluted with saturated aqueous $NaHCO_3$ and extracted 4 times with CH_2Cl_2. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The product was isolated by preparative thin layer chromatography on silica gel (eluted with 2:1 hexanes/acetone) giving 7.1 mg 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(6'''-methoxy-naphth-2-yloxy)-3"-hydroxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,-10,16-tetraone (R_f= 0.35) and 9 mg 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(6'''-methoxy-naphth-2-yloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (R_f= 0.28). (^1H NMR and mass spectral analysis were consistent with the desired structures).

EXAMPLE 9

17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-fluorophenyl-oxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred mixture of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxy-3"-methoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone (100 mg, 0.126

mmol, 1 eq) and $Cu(OAc)_2$ (3 mg, 0.0165 mmol, 0.13 eq) in CH_2Cl_2 (1 ml) in a 4 mL screw-cap vial equipped with a magnetic stir-bar is added tri(4-fluoro) bismuth diacetate [prepared immediately prior to use by addition of acetic acid (0.030 mL, 0.504 mmol, 4 eq) to a suspension of tri(4-fluorophenyl) bismuth carbonate (100 mg, 0.181 mmol, 1.4 eq) in CH_2Cl_2 (1 mL)]. The reaction vessel is capped and the mixture stirred for sufficieny time. The reaction mixture is diluted with several milliliters of saturated aqueous $NaHCO_3$ and extracted 2 times with CH_2Cl_2. The organic extracts are combined, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The product is isolated by preparative TLC on silica gel to afford 17-ethyl-1,14-dihydroxy-12-[2'-(3''-(4'''-fluorophenyloxy)-4''-hydroxycyclohexyl)-1'-methyl-vinyl]23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone.

EXAMPLE 10

17-Ethyl-1,14-dihydroxy-12-[2'-(4''-(3'''-chlorophenyl-oxy)-4''-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred mixture of 17-ethyl-1,14-dihydroxy-12-[2'-(3'',4''-dihydroxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-

2,3,10,16-tetraone (150 mg, 0.189 mmol, 1 eq) and $Cu(OAc)_2$ (6.1 mg, 0.033 mmol, 0.17 eq) in CH_2Cl_2 (2.5 ml) in a round bottom flask equipped with a magnetic stir-bar is added tri(4-chlorophenyl) bismuth diacetate [prepared immediately prior to use by addition of acetic acid (0.075 ml, 1.3 mmol, 6.9 eq) to a suspension of tri(4-chlorophenyl) bismuth carbonate (200 mg, 0.331 mmol, 1.75 eq) in CH_2Cl_2 (2.5 ml)]. The reaction flask is then fitted with a reflux condensor and the mixture warmed to 40°C. After sufficient time the reaction mixture is cooled, diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted times with CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The product is separated and purified by preparative TLC on silica gel to give 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-chloro-phenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone.

EXAMPLE 11

17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(3''',4'''-dimethylphenyloxy)-4"-hydroxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of tris(3,4-dimethyl-phenyl)bismuthine (200 mg, 0.381 mmol) in CH_2Cl_2 (3 mL.) is added bis(trifluoroacetoxy)iodobenzene (165 mg, 0.383 mmol). One mL of this solution was

transferred to a 10 mL flask. To this solution is added 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (100 mg, 0.128 mmol) and $Cu(OAc)_2$ (catalytic). The mixture is stirred overnight. The reaction mixture is quenched with saturated aqueous $NaHCO_3$ and extracted 4x with CH_2Cl_2. The organic extracts are combined and dried over anhydrous Na_2SO_4. The mixture is filtered and concentrated in vacuo. The products are isolated by first by radial chromatography on silica gel affording 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(3''',4'''-dimethylphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,-27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone.

EXAMPLE 12

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-methoxyphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-methoxyphenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of tri(4-methoxy-

phenyl)bismuthine (136 mg., 0.257 mmol., 2 eq.) in methylene chloride (4 mL.) was added peracetic acid (0.054 mL., 0.257 mmol., 2 eq., 32% solution in dilute acetic acid). To this stirred solution was added 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (100 mg., 0.126 mmol., 1 eq.), THF (0.5 mL.), and copper (II) acetate (7 mg., 0.038 mmol., 0.3 eq.). The mixture was allowed to stir for 7 days. The reaction was quenched with saturated aqueous NaCl plus 2 drops 2N HCl and extracted 4x with methylene chloride. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated <u>in vacuo</u>. The products were separated by preparative TLC on silica gel (2:1 hexanes/acetone). Each compound was repurified 2x by preparative TLC on silica gel (3:1 hexanes/acetone then 3.5% MeOH/CH_2Cl_2) affording 23.4 mg of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-methoxyphenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and 28.4 mg of 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-methoxyphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone. (^{1}H NMR and mass spectral analysis were consistent with the desired structures).

EXAMPLE 13

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(3'''-methoxyphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(3'''-methoxyphenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of tri(3-methoxyphenyl)bismuthine (136 mg., 0.257 mmol., 2 eq.) in methylene chloride (4 mL.) was added peracetic acid (.054 mL., 0.257 mmol., 2 eq., 32% solution in dilute acetic acid). To this stirred solution was added 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (100 mg., 0.126 mmol., 1 eq.), THF (0.5 mL.), and copper (II) acetate (7 mg., 0.038 mmol., 0.3 eq.). The mixture was allowed to stir for 7 days. The reaction was quenched with saturated aqueous NaCl plus 2 drops 2N HCl and extracted 4x with methylene chloride. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The products were separated by preparative TLC on silica gel (2:1 hexanes/acetone). Each compound was repurified 2x by preparative TLC on silica gel (2:1 hexanes/acetone then 3.5% MeOH/CH_2Cl_2) affording 27

mg of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(3'''-methoxyphenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and 35 mg of 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(3'''-methoxyphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone. (^{1}H NMR and mass spectral analysis were consistent with the desired structures).

EXAMPLE 14

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-tert-butyldimethylsilyloxyphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-tert-butyldimethylsilyloxyphenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of tri(4-tert-butyldimethylsilyloxyphenyl)bismuthine (213 mg., 0.257 mmol., 2 eq.) in methylene chloride (4 mL.) was added peracetic acid (.054 mL., 0.257 mmol., 2 eq., 32% solution in dilute acetic acid). To this stirred solution was added 17-ethyl-1,14-dihydroxy-12-[2'-

(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (100 mg., 0.126 mmol., 1 eq.), THF (0.5 mL.), and copper (II) acetate (7 mg., 0.038 mmol., 0.3 eq.). The mixture was allowed to stir for 7 days. The reaction was quenched with saturated aqueous NaCl plus 2 drops 2N HCl and extracted 4x with methylene chloride. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated <u>in vacuo</u>. The products were separated by preparative TLC on silica gel (2:1 hexanes/acetone) affording 41.9 mg. of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-tert-butyldimethylsilyloxy-phenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and 42.5 mg. of 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-tert-butyldimethylsilyloxyphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone. (^{1}H NMR and mass spectral analysis were consistent with the desired structures).

EXAMPLE 15

17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-hydroxyphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-tert-butyldimethylsilyloxyphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (42.5 mg) in CH_2Cl_2 (1.5 mL.) at 0°C was added a solution of p-toluenesulfonic acid in methanol (1.5 mL. of a 10% w/v solution). The mixture was stirred 3H at 0°C and then 3H at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted 4x with CH_2Cl_2. The organic extracts were combined and dried over anhydrous Na_2SO_4. The mixture was filtered and concentrated in vacuo. The product was isolated by preparative TLC on silica gel (eluted with 2:1 hexanes/acetone) affording 25.7 mg of 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(4'''-hydroxyphenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone. (^{1}H NMR and mass spectral analysis were consistent with the desired structure).

EXAMPLE 16

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-hydroxyphenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-tert-butyldimethylsilyloxyphenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (41.9 mg) in CH_2Cl_2 (1.5 mL.) at 0°C was added a solution of p-toluenesulfonic acid in methanol (1.5 mL. of a 10% w/v solution). The mixture was stirred 3H at 0°C and then 3H at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted 4x with CH_2Cl_2. The organic extracts were combined and dried over anhydrous Na_2SO_4. The mixture was filtered and concentrated in vacuo. The product was isolated by preparative TLC on silica gel (eluted with 2:1 hexanes/acetone) affording 23.9 mg of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-hydroxyphenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone. (^{1}H NMR and mass spectral analysis are consistent with the desired structure).

EXAMPLE 17

A. 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(6'''-tert-butyldimethylsilyloxynaphth-2-yloxy)-4"-hydroxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-tert-butyldimethylsilyloxy-naphth-2-yloxy)-3"-hydroxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of tri(6-tert-butyl-dimethylsilyloxynaphth-2-yl)bismuthine (252 mg., 0.257 mmol., 2 eq.) in methylene chloride (4 mL.) was added peracetic acid (.054 mL., 0.257 mmol., 2 eq., 32% solution in dilute acetic acid). To this stirred solution was added 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (100 mg., 0.126 mmol., 1 eq.), THF (0.5 mL.), and copper (II) acetate (7 mg., 0.038 mmol., 0.3 eq.). The mixture was allowed to stir for 7 days. The reaction was quenched with saturated aqueous NaCl plus 2 drops 2N HCl and extracted 4x with methylene chloride. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The products were separated by preparative TLC on silica gel (2:1 hexanes/acetone) affording 39.8 mg. of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(4'''-tert-butyldimethylsilyloxy-

phenyloxy)-3''-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and 41.6 mg. of 17-ethyl-1,14-dihydroxy-12-[2'-(3''-(4'''-tert-butyldimethylsilyloxyphenyloxy)-4''-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone. (^{1}H NMR and mass spectral analysis were consistent with the desired structures).

EXAMPLE 18

17-Ethyl-1,14-dihydroxy-12-[2'-(4''-(6'''-hydroxy-naphth-2-yloxy)-3''-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4''-(6'''-tert-butyldimethylsilyloxy-naphth-2-yloxy)-3''-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (39.8 mg) in CH_2Cl_2 (1.5 mL.) at 0°C was added a solution of p-toluenesulfonic acid in methanol (1.5 mL. of a 10% w/v solution). The mixture was stirred 1.25h at 0°C and then 1.75h at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted 4x with CH_2Cl_2. The organic extracts were combined and dried over anhydrous Na_2SO_4. The mixture was filtered and

concentrated in vacuo. The product was isolated by preparative TLC on silica gel (eluted 2x with 2:1 hexanes/acetone) affording 17 mg of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(6'''-hydroxynaphth-2-yloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone. (^{1}H NMR and mass spectral analysis were consistent with the desired structure).

EXAMPLE 19

17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(6'''-hydroxy-naphth-2-yloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(6'''-tert-butyldimethylsilyloxy-naphth-2-yloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (41.6 mg) in CH_2Cl_2 (1.5 mL.) at 0°C was added a solution of p-toluenesulfonic acid in methanol (1.5 mL. of a 10% w/v solution). The mixture was stirred 1.25h at 0°C and then 1.75h at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted 4x with CH_2Cl_2. The organic extracts were combined and dried over anhydrous Na_2SO_4. The mixture was filtered and concentrated in vacuo. The product was isolated by

preparative TLC on silica gel (eluted 2x with 2:1 hexanes/acetone) affording 20.8 mg of 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(6'''-hydroxynaphth-2-yloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone. (^{1}H NMR and mass spectral analysis were consistent with the desired structure).

EXAMPLE 20

17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(1''',4'''-benzo-dioxane-6-yl)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of tris(1,4-benzo-dioxan-6-yl)bismuthine (90 mg, 0.146 mmol) in CH_2Cl_2 (1 mL) is added peracetic acid (0.030 mL, 0.13 mmol, 32 wt% in dilute acetic acid). After 20 minutes the mixture is treated with 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (100 mg, 0.126 mmol) followed by $Cu(OAc)_2$ (15 mg, 0.08 mmol) and stirred for several days. The reaction mixture is quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extracts are combined, dried with Na_2SO_4, filtered and concentrated in vacuo. The

product is purified by preparative TLC on silica gel to give 17-ethyl-1,14-dihydroxy-12-[2'-(3"-(1''',4'''-benzodioxane-6-yl)-4"-hydroxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone.

EXAMPLE 21

A. 17-Ethyl-1-hydroxy-12-[2'-(4"-phenoxy-3"-hydroxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,18,16-tetraone

and

B. 17-Ethyl-1-hydroxy-12-[2'-(4"-hydroxy-3"-phenoxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,-27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone

Acetic acid (0.136 ml) was added to a solution of triphenylbismuth carbonate in dichloromethane (4.6 ml) at room temperature under a nitrogen atmosphere and the resulting solution stirred for 20 minutes. This was added to a solution of 17-ethyl-1-hydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclco[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone (296 mg) in dichloromethane (5.5 ml) containing cupric acetate (13 mg) and stirred at room temperature for 6 hours. The reaction mixture was washed with saturated sodium bicarbonate solution and the aqueous layer re-extracted with ether (2 x 25 ml).

The combined organics were dried ($MgSO_4$) and concentrated to give the crude phenylated isomer mixture. These were separated by column chromatography on silica gel eluting with 70% hexane:30% ethyl acetate to give title compounds (4"-ether:93 mg, 28%) and (3"-ether:102 mg, 31%) each as white solids. (^1H NMR analysis were consistent with the desired structures).

EXAMPLE 22

17-Ethyl-1-hydroxy-12-[2'-(3"-azido-4"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone

17-Ethyl-1-hydroxy-12-[2'-(4"-phenoxy-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone (63 mg) was treated with diisopropylethylamine (0.079 ml) followed by 4-dimethylaminopyridine (37 mg) in dichloromethane solution at 0°C. Trifluoromethanesulphonic anhydride (0.051 ml) was then added slowly immediately forming a deep purple solution which was stirred at 0°C for 45 minutes. The reaction mixture was then filtered through a pad of silica gel, rinsing with ethyl acetate, and concentrated. The residue was diluted with dry dimethylformamide (1.5 ml), treated with sodium azide (15 mg) and heated at 60°C for 1 hour. The reaction mixture was diluted with dichloromethane, washed with brine, dried ($MgSO_4$)

and concentrated. Purified by column chromatography on silica gel eluting with 60% hexane:40% ethyl acetate to give the title compound as a white solid (24 mg, 37%). (^{1}H NMR analysis was consistent with the desired structure).

EXAMPLE 23

17-Ethyl-1-hydroxy-12-[2'-(4"-azido-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[23.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone

17-Ethyl-1-hydroxy-12-[2'-(4"-hydroxy-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone (84 mg) was treated with diisopropylethylamine (0.104 ml) followed by 4-dimethylaminopyridine (49 mg) in dichloromethane solution at 0°C. Trifluoromethanesulphonic anhydride (0.067 ml) was then added slowly immediately forming a deep purple solution which was stirred at 0°C for 45 minutes. The reaction mixture was then filtered through a pad of silica gel, rinsing with ethyl acetate, and concentrated. The residue was diluted with dry dimethylformamide (2 ml), treated with sodium azide (20 mg) and heated at 60°C for 1 hour. The reaction mixture was diluted with dichloromethane, washed with brine, dried ($MgSO_4$) and concentrated. Purified by column chromatography on silica gel eluting with 60% hexane:40% ethyl acetate to give the title compound as a white solid (43 mg, 50%). (^{1}H NMR analysis was consistent with the desired structure).

EXAMPLE 24

17-Ethyl-1-hydroxy-12-[2'-(3"-amino-4"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone

17-Ethyl-1-hydroxy-12-[2'-(3"-azido-4"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone (24 mg) in THF (1 ml) containing 1 drop of water was treated with triphenylphosphine (9 mg) and the mixture stirred at room temperature for 72 hours. The reaction mixture was purified directly by preparative thin layer chromatography eluting eith 90% dichloromethane:10% methanol to give the title compound (5 mg, 20%) as a white solid. (^{1}H NMR analysis was consistent with the desired structure).

EXAMPLE 25

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone

17-Ethyl-1-hydroxy-12-[2'-(4"-azido-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-

[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone (64 mg) in THF (1.5 mml) containing 1 drop of water was treated with triphenylphosphine (24 mg) and the mixture stirred at room temperature for 72 hours. The reaction mixture was purified directly by preparative thin layer chromatography eluting with 90% dichloromethane:10% methanol to give the title compound (43 mg, 68%) as a white solid. (^{1}H NMR analysis was consistent with the desired structure).

EXAMPLE 26

17-Ethyl-1-hydroxy-12-[2'-(4"-acetylamino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.31.$0^{4,9}$]octacos-18-ene-2,3,20,26-tetraone

To a solution of 17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (30 mg) in dry methylene chloride (0.2 ml) is added triethylamine (10 µl) followed by a solution of acetic anhydride in methylene chloride (10 mg in 1 ml) at r.t. Reaction is stirred for 30 minutes and the solvent removed under nitrogen flow. The crude product is purified by preparative tlc on silica gel to give of the title compound.

EXAMPLE 27

17-Ethyl-1-hydroxy-12-[2'-(4"-N-(2-propenyl)-amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

The compound 17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (31 mg) is placed in a dry flask equipped with stir bar and condenser. Dry toluene (1 ml) is added followed by diisopropyl-ethylamine (13 mg) and freshly distilled allyl bromide (41 mg) at 0°C with stirring. Reaction temperature is raised to 70°C gradually and stirred for 2 hr. The reaction mixture is cooled, and the solvent is removed under nitrogen flow. The residue is purified by preparative tlc on silica gel to give the title compound.

EXAMPLE 28

17-Ethyl-1-hydroxy-12-[2'-[4"-(N'-t-butoxy-carbonyl-D-phenylalanine)amido-3"-phenoxycyclohexyl]- 1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (46 mg) in dry methylene chloride (2 ml) is added 102 mg of freshly prepared BOC-D-phenylalanine

anhydride (prepared as described in Solid Peptide Sythesis, p. 32, J.M. Steward and J.D. Young, Pierce Chemical Company) under nitrogen. Reaction is stirred at room temperature and the process is followed by tlc analysis. After 2.5 hr, the reaction mixture is subjected to work-up and preparative tlc on silica gel to give the title compound.

EXAMPLE 29

17-Ethyl-1-hydroxy-12-[2'-[4"-(N'-t-butoxy-carbonyl-L-phenylalanine)amido-3"-phenoxycyclohexyl]-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

The title compound is prepared by the method of Example 28 utilizing BOC-L-phenylalanine anhydride.

EXAMPLE 30

17-Ethyl-1-hydroxy-12-[2'-(4"-acetoxyacetylamino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

A solution of 17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (42 mg) in dry methylene chloride (0.4 ml) is cooled to 0°C. To this solution is added a solution of acetoxyacetyl chloride (9 mg) in methylene chloride (0.5 ml). The reaction mixture is

stirred at 0°C for 30 minutes, and quenched with a drop of methanol. Purification by preparative tlc on silica gel gives the title compound.

EXAMPLE 31

17-Ethyl-1-hydroxy-12-[2'-(4"-1"'-adamantane-carboxamido-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

A solution of 17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (37 mg) in dry methylene chloride (0.4 ml) is cooled to 0°C. To this solution is added triethylamine (10 µl) followed by a solution of 1-adamantane carbonyl chloride (10 mg) in methylene chloride (0.1 ml). The reaction mixture is stirred at 0°C for 20 minutes. The reaction is purified by preparative tlc on silica gel to give the title compound.

EXAMPLE 32

17-Ethyl-1-hydroxy-12-[2'-(4"-cyclopropanecarboxamido-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

A solution of 34 mg of 17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-

dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene- 2,3,-10,16-tetraone in dry methylene chloride (0.4 ml) is cooled to 0°C. To this solution is added triethylamine (10 µl) followed by a solution of cyclopropane carbonyl chloride (5 mg) in methylene chloride (0.1 ml). The reaction mixture is stirred at 0°C for 30 min. The reaction mixture is purified by preparative tlc on silica gel to give the title compound.

EXAMPLE 33

17-Ethyl-1-hydroxy-12-[2-(4"-formamido-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy- 13,19,-21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

The compound 17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (30 mg) is mixed with methyl formate (0.5 ml) and is stirred at 0°C for 1 hr. The reaction mixture is allowed to warm to room temperature and then is stirred overnight. The excess methylformate is removed with nitrogen flow and the crude mixture is purified by preparative tlc on silica gel to give the title compound.

EXAMPLE 34

17-Ethyl-1-hydroxy-12-{2'-[4"',5"'-dicarboethoxy-1"',-2"',3"'-triazole)-3"-phenoxycyclohexyl]-1'-methyl-vinyl}-23,23-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

A mixture of 17-ethyl-1-hydroxy-12-[2'- (4"-azido-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (20 mg) in neat diethylacetylene dicarboxylate (0.1 ml) is stirred at room temperature overnight. The cycloaddition product is isolated by preparative tlc on silica gel to give the title compound.

EXAMPLE 35

17-Ethyl-1-hydroxy-12-[2'-(3"-phenoxy-4"-oxocyclo-hexyl)-1'-methylvinyl]-14-triisopropylsilyloxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a cooled solution (-78°C) of oxalyl chloride is added dimethyl sulfoxide dropwise, followed by a solution of 17-ethyl-1-hydroxy-12-[2'-(4"-hydroxy-3"-phenoxycyclohexyl)-1'-methylvinyl]-14-triisopropylsiloxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone in dry methylene chloride. The reaction mixture is stirred for 30 min. at -78°C and then triethylamine is added. The reaction temperature is raised to room temperature,

reaction was poured into water, and extracted with ethyl acetate (three times). Combined organic layers are washed (water, sat'd $NaHCO_3$), dried (anhydrous Na_2SO_4), and filtered. Removal of solvent followed by purification (silica gel column chromatography) gives the title compound.

EXAMPLE 36

17-Ethyl-1,14-dihydroxy-12-[2'-(3"-phenoxy-4"-oxo-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of 17-ethyl-1-hydroxy-12-[2'-(3"-phenoxy-4"-oxocyclohexyl)-1'-methylvinyl]-14-triisopropylsilyloxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone in acetonitrile was added hydrofluoric acid at room temperature. The reaction progress is monitored by tlc analysis and then the reaction mixture is quenched with sat'd aqueous sodium bicarbonate. The organic layer is separated and the aqueous layer is extracted with ethyl acetate three times. Combined organic layers are washed (sat'd $NaHCO_3$, sat'd NaCl), dried (anhydrous Na_2SO_4), and filtered. Removal of solvent followed by purification (silica gel column chromatography. 50% ethyl acetate/hexane) gives the title compound.

EXAMPLE 37

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-benzylamino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(3"-phenoxy-4"-oxocyclohexyl]-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone in dry isopropyl alcohol (3 ml) is added benzyl amine (87 mg). The mixture is stirred at r.t. for 30 minutes, and cooled to -78°C. To this solution is added a solution of sodium cyanoborohydride (6.7 mg) in isopropyl alcohol (0.5 ml). The reaction is stirred at -78°C and poured into ice water. Extraction with ethyl acetate, followed by purification gives the title compound as a mixture of epimers at C-4".

EXAMPLE 38

17-Ethyl-1-hydroxy-12-[2'-(4"-trimethylamino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone Iodide

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone is dissolved in absolute ethanol in a heavy walled glass tube. Methyl iodide (large excess) and $NaHCO_3$ are

added, the tube is sealed, and then the tube is heated. Progress of the reaction is followed by watching disappearance of the starting amine on thin layer chromatography and the appearance of a more polar new spot. Upon completion of reaction, the quarternary iodide is obtained by evaporation of excess methyl iodide and solvent.

EXAMPLE 39

17-Ethyl-1,2-dihydroxy-12-[2'-(4"-acetylamino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,1927-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-3,10,16-trione

To a suspension of samarium iodide (63 mg) in dry THF (1 ml) is added a solution of diiodoethane (56 mg in 1 ml THF) at r.t., and stirred for 1 hr. The dark blue solution is cooled to -78°C, and to this mixture is added a solution of 17-ethyl-1-hydroxy-12-[2'-(4"-acetylamino-3"-phenoxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (170 mg) in 50% THF/MeOH (3 ml). The reaction is stirred for -78°C for 10 minutes., allowed to warm to room temperature over a period of 10 min., and then quenched with saturated potassium carbonate solution. The organic layer is extracted with ether/ethyl acetate, washed (sat'd NaCl), and dried (anhydrous Na_2SO_4). Removal of solvent followed by chromatography on silica gel gives the title compound.

EXAMPLE 40

17-Ethyl-1-hydroxy-12-{2'-[4"-(N'-phenylamino-carbonyl)amino-3"-phenoxycyclohexy]-1'-methylvinyl}-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (40 mg) in methylene chloride (2 ml) is added phenyl isocyanate (12 mg) at 0°C with stirring. The reaction mixture is warmed to room temperature and the reaction progress is followed by tlc analysis. The reaction mixture is concentrated under a stream of nitrogen and purified by preparative tlc on silica to give the title compound.

EXAMPLE 41

17-Ethyl-1-hydroxy-12-{2'-[4"-(ethoxycarbonyl)-amino-3"-phenoxycyclohexyl]-1'-methylvinyl}-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (40 mg) in methylene chloride (2 ml) is added triethylamine (10 µl), followed by ethyl chloroformate (15 µl) at 0°C with stirring. The

reaction mixture is warmed to room temperature and the reaction progress is followed by tlc analysis. The solution is quenched with a drop of methanol and purified by preparative tlc on silica to give the title compound.

EXAMPLE 42

17-Ethyl-1-hydroxy-12-[2'-(4"-(2"'R-hydroxypropyl)-amino-3"-phenyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,-16-tetraone

To a solution of 17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone (19mg) in methanol (1ml) at ambient temperature was added R-(+)-propylene oxide (85ml) and the mixture stirred for 46hrs. The reaction was quenched by the addition of saturated sodium bicarbonate solution and extracted into ether. The crude mixture was purified by column chromatography on silica gel eluting with 97% methylene chloride : 3% methanol to give the title compound (11mg) as a white solid.

MS(FAB) 895(M^+)

partial ^1H NMR d : 7.25 (m, 2H): 6.90 (m, 2H); 4.52 (d, J = 6Hz, 1H): 3.85 (d, J = 9, 2Hz, 1H).

EXAMPLE 43

17-Ethyl-1-hydroxy-12-[2'-(4"-(2"'S-hydroxypropyl)-amino-3"-phenyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,-16-tetraone

Prepared essentially as described in the above example using S-(-)-propylene oxide as the amine alkylating agent.

MS(FAB) 895(M^+)

partial ^1H NMR d : 7.25 (m, 2H); 6.90 (m, 2H); 4.52 (d, J = 6Hz, 1H); 3.85(d, 9Hz).

EXAMPLE 44

17-Ethyl-1-hydroxy-12-[2'-(4"-(2""R-hydroxypropyl)-amino-3"-(4"'-methyl)phenyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

Prepared essentially as described in the above example using R-(-)-propylene oxide as the amine alkylating agent.

MS(FAB) 910(M^++1)

partial ^1H NMR d : 7.15 (d, J = 9Hz, 2H); 6.78 (d, J = 9Hz, 2H); 4.52 (d, J = 6Hz, 1H); 2.24 (s, 3H).

EXAMPLE 45

17-Ethyl-1-hydroxy-12-[2'-(4"-(2""S-hydroxypropyl)-amino-3"-(4"'-methyl)phenyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

Prepared essentially as described in the above example using S-(-)-propylene oxide as the amine alkylating agent.

MS(FAB) 910(M^++1)

partial ^1H NMR d : 7.05 (d, J = 9Hz, 2H); 6.79 (d, J = 9Hz, 2H); 4.52 (d, J = 6Hz, 1H); 2.24 (s, 3H).

EXAMPLE 46

17-Ethyl-1-hydroxy-12-[2'-(4"-(2""R-hydroxypropyl)-amino-3"-(4"'-methoxy)phenyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

Prepared essentially as described in the above example using R-(-)-propylene oxide as the amine alkylating agent.

MS(FAB) 925(M^+)

partial ^1H NMR d : 6.80 (m, 4H); 3.96 (d, J = 6Hz, 1H); 3.72 (s, 3H).

EXAMPLE 47

17-Ethyl-1-hydroxy-12-[2'-(4"-(2'''S-hydroxypropyl)-amino-3"-(4"'-methoxy)phenyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

Prepared essentially as described in the above example using S-(-)-propylene oxide as the amine alkylating agent.

MS(FAB) 925(M^+)

partial ^1H NMR d : 6.82 (m, 4H); 3.83 (d, J = 7Hz, 1H); 3.72 (s, 3H).

EXAMPLE 48

17-Ethyl-1-hydroxy-12-[2'-(4"-(2'''R-hydroxypropyl)-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

Prepared essentially as described in the above example using R-(-)-propylene oxide as the amine alkylating agent.

MS(FAB) 860(M^++1)

partial ^1H NMR d : 5.85 (m, 1H); 4.52 (d, J = 6Hz, 1H); 3.97 (d, J = 6Hz, 1H).

EXAMPLE 49

17-Ethyl-1-hydroxy-12-[2'-(4"-(2"'S-hydroxypropyl)-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

Prepared essentially as described in the above example using S-(-)-propylene oxide as the amine alkylating agent.

MS(FAB) 860(M^++1)

partial ^{1}H NMR d : 5.89 (ddd, J = 22,10,6Hz, 1H); 4.53 (d, J = 6Hz, 1H); 3.99 (d, J = 6Hz, 1H).

EXAMPLE 50

17-Ethyl-1-hydroxy-12-[2'-(4"-dimethylamino-3"-(3"'-methoxy)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3"'-methoxy)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone (25mg) in tetrahydrofuran was added aqueous formaldehyde solution (36%)(66ml) and the reaction stirred until t.l.c. indicated disappearance of starting material. At this point 2 drops of acetic acid were added followed by 66ml of sodium cyanoborohydride solution in methanol (7mg/ml). When complete the reaction was quenched by

the addition of saturated sodium bicarbonate solution and extracted into ethyl acetate and dichloromethane. The organic extracts were dried, concentrated and purified by preparative chromatography eluting with 95% dichloromethane : 5% methanol + 1% ammonium hydroxide to give the product (5mg) as a white solid.

MS(FAB) 895(M^++ 1)

partial ^1H NMR d : 7.11 (m, 2H); 6.42 (m, 2H); 3.73 (s, 6H).

EXAMPLE 51

17-Ethyl-1-hydroxy-12-[2'-(4"-(4"'-dimethylamino)-phenyloxy-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone (A) and 17-Ethyl-1-hydroxy-12-[2'-(4"-hydroxy-3"-(4"'-di-methylamino)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16 -tetraone (B)

Peracetic acid (850ml) was added to a solution of tri(4-dimethylaminophenyl)bismuthine (1.27g) in 30ml tetrahydrofuran. After 10 minutes 17-ethyl-1-hydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone (100mg) was added followed by copper acetate (280mg) and the mixture heated to 60oC for 48 hours. The mixture was then cooled and quenched by pouring into saturated sodium bicarbonate, extracting with ether (3x25ml). The

combined organic washes were dried with magnesium sulphate and concentrated. The crude residue was purified by column chromatography on silica gel eluting with70% hexane : 30% ethyl acetate to give the title compounds A (93mg) and B (102mg) each as white solids.

EXAMPLE 52

17-Ethyl-1-hydroxy-12-[2'-(4"-azido-3"-(4"'-dimethylamino)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

17-Ethyl-1-hydroxy-12-[2'-(4"-hydroxy-3"-(4"'-dimethylamino)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone (84 mg) was treated with diisopropylethylamine (0.104 ml) followed by 4-dimethylaminopyridine (49 mg) in dichloromethane solution at 0oC. Trifluoromethanesulphonic anhydride (0.067 ml) was then added slowly immediately forming a deep purple solution which was stirred at 0oC for 45 minutes. The reaction mixture was then filtered through a pad of silica gel, rinsing with ethyl acetate, and concentrated. The residue was diluted with dry dimethylformamide (2 ml), treated with sodium azide (20 mg) and heated at 60oC for 1 hour. The reaction mixture was diluted with dichloromethane, washed with brine, dried (MgSO4) and concentrated. Purified by column chromatagraphy on silica gel eluting with 60% hexane : 40% ethyl acetate to give the title compound as a white solid (43 mg).

EXAMPLE 53

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-dimethylamino)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

17-Ethyl-1-hydroxy-12-[2'-(4"-azido-3"-(4"'-dimethylamino)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone (64 mg) in benzene (4 ml) containing 500ml of water was treated with triphenylphosphine (125mg) and the mixture heated to 60oC for 17 hours. The mixture was cooled, concentrated and purified by column chromatography on silica gel eluting with 98% dichloromethane : 2% methanol to give the title compound (43 mg) as a white solid.

MS(FAB) 880(M+)

partial 1H NMR d : 7.82 (d, J = 8Hz, 2H); 7.66 (d, J = 8Hz, 2H); 5.17 (m, 1H), 2.82 (s, 3H), 2.81 (s, 3H).

EXAMPLE 54

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-methyl)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11.28-dioxa-4-azatricyclo [22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

Prepared essentially as described in the above examples using tri(4-methylphenyl)bismuthine as the arylating agent.

MS(FAB) 851(M+)

partial 1H NMR d : 7.04 (d, J = 7Hz, 2H); 6.77 (d, J = 7Hz); 5.16 (m, 1H); 2.23 (s,3H).

EXAMPLE 55

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxymethyl)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

Prepared essentially as described in the above examples using tri(4-hydroxymethylphenyl)-bismuthine as the arylating agent.

MS(FAB) 867(M^++1)

partial 1H NMR d : 7.25 (m, 2H); 6.88 (m, 2H); 5.21d(minor) and 5.17d(major) (J = 6.5Hz, 1H); 4.59 (d, J = 2Hz, 2H).

EXAMPLE 56

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-methoxy)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

Prepared essentially as described in the above examples using tri(4-methoxyphenyl)bismuthine as the arylating agent.

MS(FAB) 867(M+)

partial 1H NMR d : 6.81 (m, 4H); 5.20 (m,major and minor, 1H); 3.72 (s,major) and 3.71 (s, minor)(3H).

EXAMPLE 57

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3"'-methoxy)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

Prepared essentially as described in the above examples using tri(3-methoxyphenyl)bismuthine as the arylating agent.

MS(FAB) 868(M^++1)

partial 1H NMR d : 7.15 (m,2H); 6.50 (m, 3H); 3.74 (s, 3H).

EXAMPLE 58

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxy)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

Prepared essentially as described in the above examples using tri(4-hydroxyphenyl)bismuthine as the arylating agent.

MS(FAB) 853(M+)

partial 1H NMR d : 6.72 (m, 4H); 5.27d(minor) and 5.18d(major) (9Hz, 1H); 4.85 (m, 1H).

EXAMPLE 59

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-formyl)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone

Prepared essentially as described in the above examples using tri(4-formylphenyl)bismuthine as the arylating agent.

partial 1H NMR d : 9.86 (s, 1H); 7.80 (d, J = 9Hz, 2H); 6.98 (d, J = 9Hz, 2H).

EXAMPLE 60

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-allyloxy-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-allyloxy-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (100 mg in 1.5 ml 33% methylene chloride in cyclohexane) allyl trichloroacetimidate (53 µl neat) was added and the reagents allowed to mix for 5 minutes. Trifluoromethanesulfonic acid (2 µl neat) was added slowly via syringe and the mixture stirred at room temperature. After 3 hours the reaction was quenched by the addition of saturated sodium bicarbonate and extracted with ethyl acetate (3 x 5 ml). The combined organics were washed with brine and dried over magnesium sulfate. Purification of the concentrate by flash chromatography on silica gel (ethyl acetate : hexane (1:1) + 1% methanol) gave the title compounds (21 mg 4"-ether; 17 mg 3"-ether).

A. (4"-ether):

Partial ^{1}H NMR δ: 5.9

B. (3"-ether):

Partial ^{1}H NMR δ: 5.93 (m, 1H); 4.83m, 4.23M (brs, 1H); 4.59 (brd J = 4.0Hz, 1H); 4.41 (brd J = 14Hz, 1H); 2.63 (brs, 1H).

EXAMPLE 61

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-sec-butenyloxy-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-sec-butenyloxy-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (150 mg in 3 ml 33% methylene chloride in cyclohexane) sec-butenyl trichloroacetimidate (62 µl neat) was added and the reagents allowed to mix for 5 minutes. Trifluoromethanesulfonic acid (2 µl neat) was added slowly via syringe and the mixture stirred at room temperature. After 15 minutes the reaction was quenched by the addition of saturated sodium bicarbonate and extracted with ethyl acetate (3 x 8 ml). The combined organics were washed with brine and dried over magnesium sulfate. Purification of the concentrate by preparative TLC on silica gel (ethyl acetate : hexane (1:1) + 1% methanol) gave the title compounds (11 mg 4"-ether: 13 mg 3"-ether).

A. (4"-ether):

MASS: (FAB) 831 (M+Na)

Partial ^{1}H NMR δ: 5.65 (m, 1H); 5.32 (brd J = 3.0Hz, 1H); 4.87m, 4.1 8M (brs, 1H); 4.58 (brd J = 4.0Hz, 1H); 4.41 (brd J = 14Hz, 1H).

B. (3"-ether):
MASS: (FAB) 831 (M+Na)
Partial ^{1}H NMR δ: 5.65 (m, 1H); 5.31 (brs, 1H); 4.82m, 4.22M (brs, 1H); 4.58 (brd J = 4.0Hz, 1H); 4.41 (brd J = 14Hz, 1H).

EXAMPLE 62

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(trans-2-butenyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone
and
B. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(trans-2-butenyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (115 mg in 3 ml 33% methylene chloride in cyclohexane) trans-2-butenyl trichloroacetimidate (48 µl neat) was added and the reagents allowed to mix for 5 minutes. Trifluoromethanesulfonic acid (2 µl neat) was added slowly via syringe and the mixture stirred at room temperature. After 35 minutes the reaction was quenchedby the addition of saturated sodium bicarbonate and extracted with ethyl acetate (3 x 8 ml). The combined organics were washed with

brine and dried over magnesium sulfate. Purification of the concentrate by preparative TLC on silica gel (ethyl acetate : hexane (1:1) + 1% methanol) gave the title compounds (14 mg 4"-ether; 12 mg 3"-ether).

A. (4"-ether):

MASS: (FAB) 831 (M+Na)

Partial ^{1}H NMR δ: 5.65(m, 1H); 5.31 (brd J = 3.0Hz, 1H); 4.86m, 4.19M (brs, 1H); 4.59 (brd J = 4.0Hz, 1H); 4.41 (brd J =14Hz, 1H); 2.68 (brs, 1H).

B. (3"-ether):

MASS: (FAB) 831 (M+Na)

Partial ^{1}H NMR δ: 5.65 (m,1H); 5.30 (brs, 1H); 4.81m, 4.22M (brs, 1H); 4.59 (brd J = 4.0Hz, 1H); 4.41 (brd J = 14Hz, 1H); 2.64 (brs, 1H).

EXAMPLE 63

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-hydroxy-4"-(3-methyl-2-butenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-hydroxy-3"-(3-methyl-2-butenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (100 mg in 2 ml methylene chloride) 3-methyl-2-

butenyl trichloroacetimidate (39 µl neat) was added and the reagents allowed to mix for 5 minutes. Camphorsulfonic acid (5 mg) was added and the mixture stirred at room temperature. After 21 hours the reaction was quenched by the addition of saturated sodium bicarbonate and extracted with ethyl acetate (3 x 8 ml). The combined organics were washed with brine and dried over magnesium sulfate. Purification of the concentrate by preparative TLC on silica gel (ethyl acetate : hexane (1:1) + 1% methanol) gave the title compounds (24 mg 4"-ether; 21 mg 3"-ether).

A. (4"-ether):

MASS: (FAB) 845 (M+Na)

Partial ^{1}H NMR δ: 4.87m, 4.19M (brs, 1H); 4.58 (brd J = 4.0Hz, 1H); 4.41 (brd J = 14Hz, 1H); 2.70 (brs, 1H); 1.75 (s, 3H); 1.67(s, 3H).

B. (3"-ether):

MASS: (FAB) 845 (M+Na)

Partial ^{1}H NMR δ: 4.82m, 4.23M (brs, 1H);4.58 (brd J = 4.0Hz, 1H); 4.41 (brd J = 14Hz, 1H); 2.67 (brs, 1H); 1.75 (s,3H); 1.67 (s, 3H).

EXAMPLE 64

A. 17-Ethyl-1,14-dihydroxy-12-[2'-(3"-hydroxy-4"-(2-methylpropenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

and

B. 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-hydroxy-3"-(2-methylpropenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (200 mg in 3 ml 33% methylene chloride in cyclohexane), 2-methylpropenyl trichloroacetimidate (84 µl neat) was added and the reagents allowed to mix for 5 minutes. Trifluoromethanesulfonic acid (2 µl neat) was added slowly via syringe and the mixture stirred at room temperature. After 1 hour the reaction was quenched by the addition of saturated sodium bicarbonate and extracted with ethyl acetate (3 x 8 ml). The combined organics were washed with brine and dried over magnesium sulfate. Purification of the concentrate by preparative TLC on silica gel (ethyl acetate : hexane (1:1) + 1% methanol) gave the title compounds (34 mg 4"-ether; 24 mg 3"-ether).

A. (4"-ether):

MASS: (FAB) 831 (M+Na)

Partial ^{1}H NMR δ: 5.32 (brs, 1H); 4.87 (brs, 1H); 4.59 (brs, 1H); 4.41 (brd J = 14Hz, 1H); 4.19M (brs, 1H); 2.60 (brs, 1H); 1.74(s, 3H).

B. (3"-ether):

MASS: (FAB) 831 (M+Na)

Partial ^{1}H NMR δ: 5.32 (brs, 1H); 4.87 (brs, 1H); 4.81m, 4.23M (brs, 1H); 2.63 (brs, 1H); 1.74 (s, 3H).

EXAMPLE 65

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-cinnamyloxy-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (100 mg in 3 ml 33% methylene chloride in cyclohexane), cinnamyl trichloroacetimidate (52 µl neat) was added and the reagents allowed to mix for 5 minutes. Trifluoromethanesulfonic acid (2 µl neat) was added slowly via syringe and the mixture stirred at room temperature. After 15 minutes the reaction was quenched by the addition of saturated sodium bicarbonate and extracted with ethyl acetate (3 x 8 ml). The combined organics were washed with brine and dried over magnesium sulfate. Purification of the concentrate by preparative TLC on silica gel (ethyl acetate : hexane (1:1) + 1% methanol) gave the title compound (17 mg).

MASS: (FAB) 893 (M+Na)

Partial ^{1}H NMR δ: 6.61 (d J = 15Hz, 1H); 6.28 (dt J = 15, 6.0Hz, 1H); 5.32m, 5.19M (brd J = 3.0Hz, 1H); 4.82m, 4.22M (brs,1H); 4.52 (brd J = 4.0Hz, 1H); 4.41 (brd J = 14Hz, 1H); 2.66 (brs, 1H).

EXAMPLE 66

17-Ethyl-1,14-dihydroxy-12-[2'-(3"-hydroxy-4"-phenpropyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-cinnamyloxy-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (37 mg in 2 ml ethanol) is added 4 mg of 5% rhodium on carbon catalyst. The reaction flask is fitted with a hydrogen balloon, evacuated and recharged with hydrogen (3 times) and stirred at room temperature. After 1.5 hours, the mixture is filtered over diatomaceous earth, concentrated and purified by preparative TLC on silica gel

EXAMPLE 67

A. 17-Ethyl-1-hydroxy-12-[2'-(4"-sec-butenyloxy-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

and

B. 17-Ethyl-1-hydroxy-12-[2'-(3"-sec-butenyloxy-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-

tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (150 mg in 3 ml 33% methylene chloride in cyclohexane), sec-butenyl trichloroacetimidate (62 µl neat) is added and the reagents allowed to mix for 5 minutes. Trifluoromethanesulfonic acid (2 µl neat) is then added slowly via syringe and the mixture stirred at room temperature. After 15 minutes the reaction is quenched by the addition of saturated sodiumbicarbonate and extracted with ethyl acetate (3 x 8 ml). The combined organics are washed with brine and dried over magnesium sulfate. Purification of the concentrate by preparative TLC on silica gel the title compounds.

EXAMPLE 68

17-Ethyl-1,14-dihydroxy-12-[2'-(3"-(2-butynyloxy)-4"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone and
17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(2-butynyloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4",3"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (50 mg in 1.5 ml 33% methylene chloride in cyclohexane) is added 2-butynyl trichloroacetimidate (20 µl neat) and the reagents are allowed to mix for 5 minutes. Trifluoromethanesulfonic acid (2 µl neat)

is added slowly via syringe and the mixture stirred at room temperature. After 16 hours the reaction is quenched by the addition of saturated sodium bicarbonate and extracted with ethyl acetate (3 x 5 ml). The combined organics are washed with brine and dried over magnesium sulfate. Purification of the concentrate by preparative TLC on silica gel gives the title compound.

EXAMPLE 69

17-Ethyl-1-hydroxy-12-[2'-(3"-hydroxy-4"-phenpropyl-oxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-12-[2'-(4"-cinnamyloxy-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (16 mg in 2 ml ethanol) is added 2 mg of 5% rhodium on carbon catalyst. The reaction flask is fitted with a hydrogen balloon, evacuated and recharged with hydrogen (3 times) and stirred at room temperature. After 30 minutes, the mixture is filtered over diatomaceuis earth, concentrated and purified by preparative TLC on silica gel to give the title compound.

EXAMPLE 70

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-azido-3"-allyloxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

Step A: 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(tert-butyldimethylsiloxy)-3"-hydroxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (1.75 g) in dry methylene chloride (25 ml) was added an excess of imidazole (462 mg) followed by tert-butyldimethylsilyl chloride (375 mg). After 22 hours of stirring at room temperature, the mixture was quenched by the addition of half-saturated sodium bicarbonate and extracted with ethyl acetate. The combined organics were washed with brine, dried over magnesium sulfate and purified by flash chromatography (ethyl acetae:hexane (1:2) + 1% methanol) to give the title compound (680 mg).

4"-ether:

Partial ^{1}H NMR δ: 5.32M, 5.29m (brd J = 3.0Hz, 1H); 4.86m, 4.29M (brs, 1H); 4.59 (brd J = 4.0Hz, 1H); 4.41 (brd J = 14Hz, 1H); 3.03 (d J = 4Hz,1H); 2.41 (brs, 1H); 0.88 (s, 9H); 0.10 (s, 3H); 0.09 (s, 3H).

Step B: 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-(tert-butyldimethylsiloxy)-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.-1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(tert-butyldimethylsiloxy)-3"-hydroxycyclohexyl)1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$] octacos-18-ene-2,3,10,16-tetraone (90 mg in 3 ml 33% methylene chloride in cyclohexane) allyl trichloroacetimidate (27 µl neat) was added and the reagents allowed to mix for 5 minutes. Trifluoromethanesulfonic acid (2 µl neat) was added slowly via syringe and the mixture stirred at room temperature. After 17 hours the reaction was quenched by the addition of saturated sodium bicarbonate and extracted with ethyl acetate (3 x 5 ml). The combined organics were washed with brine and dried over magnesium sulfate. Purification of the concentrate by preparative TLC on silica gel (ethyl acetate : hexane (1:2) + 1% methanol) gave the title compound (20 mg).

Partial ^{1}H NMR δ: 5.91 (m, 1H); 4.83m, 4.21M (brs, 1H); 4.59 (brd J = 4.0Hz, 1H); 4.41 (brd J = 14Hz, 1H); 4.10 (m, 2H); 3.09 (d J = 4Hz. 1H).

Step C: 17-Ethyl-1-hydroxy-14-(tert-butyldimethyl-siloxy)-12-[2'-(4"-(tert-butyldimethyl-siloxy)-3"-allyloxycyclohexyl)-1'-methyl-

vinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-(tert-butyldimethylsiloxy)-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (165 mg) in dry methylene chloride (4 ml) was added an excess of 2,6-lutidine (41 µl) and the mixture was stirred at room temperature. After 10 minutes, tert-butyldimethylsilyl trifluoromethanesulfonate (49 µl) was added via syringe. After 1 hour the reaction mixture was diluted with ethyl acetate, extracted from saturated sodium bicarbonate, washed with brine and the organic phase dried over magnesium sulfate. Removal of the solvent in vacuo and flash chromatography on silica gel (ethyl acetate: hexane (1:4) + 1% methanol) gave the title compound (130 mg). Partial ^{1}H NMR δ: 5.90 (m, 1H); 5.47m, 4.18M (brs, 1H); 4.81 (brd J = 11Hz, 1H); 3.79(dd J = 9, 2Hz, 1H); 2.76 (dd J = 14, 7Hz, 1H).

Step D: 17-Ethyl-1-hydroxy-14-(tert-butyldimethylsiloxy)-12-[2'-(4"-hydroxy-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-14-(tert-butyldimethylsiloxy)-12-[2'-(4"-(tert-butyldimethylsiloxy)-3"-allyloxycyclohexyl)-1'-methylvinyl]-

23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (130 mg) in acetonitrile (4 ml) was added a solution of 2% HF in aqueous acetonitrile (200 µl), and the mixture stirred at room temperature. After 4 hours, the solution was diluted with ethyl acetate, extracted with saturated sodium bicarbonate solution and the organic phase dried over magnesium sulfate. Purification of the concentrate by flash chromatography on silica gel (ethyl acetate: hexane (1:2) + 1% methanol) gave the title compound (65mg). Partial ^{1}H NMR δ: 5.91 (m, 1H); 5.44m, 4.20M (brs, 1H); 5.02 (brd J = 11Hz, 1H); 4.81 (brd J = 11Hz, 1H); 3.80 (brd J = 9Hz, 1H); 2.64 (s, 1H).

Step E: 17-Ethyl-1-hydroxy-14-(tert-butyldimethyl-siloxy)-12-[2'-(4"-(o-nitrobenzenesulfonyloxy)-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-14-(tert-butyldimethylsiloxy)-12-[2'-(4"-hydroxy-3"-allyloxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone (65 mg) in dry methylene chloride (1 ml) was added an excess of diisopropylethyl amine (29 µl) and o-nitrobenzene-sulfonyl chloride (31 mg) followed by addition of 4-dimethylaminopyridine (20 mg). The mixture was stirred at room temperature for 4 hours at which time

it was diluted with ethyl acetate, extracted from saturated sodium bicarbonate solution and washed with brine. The combined organics were dried over magnesium sulfate and the concentrate purified by flash chromatography on silica gel (ethyl acetate: hexane (1:2) + 1% methanol to give the title compound (68 mg).

Partial ^{1}H NMR δ: 5.57 (m, 1H); 5.44m, 4.20M (brs, 1H); 4.79 (brd J = 11Hz, 1H); 4.44(m, 1H); 2.87 (dd J = 14, 7Hz, 1H).

Step F: 17-Ethyl-1-hydroxy-14-(tert-butyldimethyl-siloxy)-12-[2'-(4"-azido-3"-allyloxycyclo-hexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[2 2.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-14-(tert-butyldimethylsiloxy)-12-[2'-(4"-(o-nitrophenyl-sulfonyloxy)-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (68 mg) in N,N-dimethyl formamide (1 ml) was added an excess of sodium azide (20 mg) and the mixture heated to 70°C. After 4 hours the reaction was cooled to room temperature, diluted with ethyl acetate, extracted from half-saturated ammonium chloride, and washed with brine. The combined organics were dried over sodium sulfate and purified by flash chromatography on silica gel (ethyl acetate: hexane (1:2) + 1% methanol) to give the title compound (17.5 mg).

Partial ^{1}H NMR δ: 5.91 (m, 1H); 5.54m, 4.18M (brs, 1H); 4.81 (brd J = 11Hz, 1H); 3.78(dd J = 9, 2Hz, 1H); 2.78(dd J = 14, 7Hz, 1H).

Step G: 17-Ethyl-1,14-dihydroxy-12-[2'-(4"-azido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-14-(tert-butyldimethylsiloxy)-12-[2'-(4"-azido-3"-allyloxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (17.5 mg) in acetonitrile (1 ml) was added a solution of 2% HF in aqueous acetonitrile (100 µl), and the mixture stirred at room temperature. After 4 hours, the solution was diluted with ethyl acetate, extracted with saturated sodium bicarbonate solution and the organic phase dried over magnesium sulfate. Purification of the concentrate by flash chromatography on silica gel (ethyl acetate: hexane (1:2) + 1% methanol) gave the title compound (10 mg).

Partial ^{1}H NMR δ: 5.91 (m, 1H); 4.81m, 4.19M (brs, 1H): 4.59 (brd J = 4.0Hz, 1H); 4.41 (brd J = 14Hz, 1H); 3.12 (d J = 4Hz, 1H).

EXAMPLE 71

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-allyloxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-azido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$] octacos-18-ene-2,3,10,16-tetraone (10 mg) in 10% aqueous benzene (400 µl) was added triphenylphosphine (3.4 mg) and the mixture heated to 70°C with stirring. After 25 hours, the stir bar was removed and the reaction cooled to room temperature. The mixture was concentrated to 10% volume in vacuo and applied directly to a column of silica gel for purification by flash chromatography (ethyl acetate : hexane (1:1) + 1% methanol then 2% ammonium hydroxide, 5% methanol in methylene chloride) to give the title compound (6.0 mg).

MASS: (FAB) 817 (M+H)

Partial ^{1}H NMR δ : 5.91 (m, 1H); 4.59(brd J = 4.0Hz, 1H); 4.41(brd J = 14Hz, 1H); 4.09(brd J = 6Hz, 2H); 3.65 (brd J = 12Hz, 1H).

EXAMPLE 72

17-Ethyl-1-hydroxy-12-[2'-(4"-azido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28- dioxa-4-azatricyclo[22.3.1.$0^{4,9}$] octacos-18-ene-2,3,10,16-tetraone

Step A: 17-Ethyl-1-hydroxy-12-[2'-(4"-(tert-butyldimethylsiloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-12-[2'-(3",4"-dihydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (1.04 g) in dry methylene chloride (25 ml) was added an excess of imidazole (280 mg) followed by tert-butyldimethylsilyl chloride (228 mg). After 21 hours of stirring at room temperature, the mixture was quenched by the addition of half-saturated sodium bicarbonate and extracted with ethyl acetate. The combined organics were washed with brine, dried over magnesium sulfate and purified by flash chromatography (ethyl acetate:hexane (1:2) + 1% methanol) to give the title compound (370 mg). Partial ^{1}H NMR δ: 4.58 (brd J = 4Hz, 1H); 4.42m, 4.31M (brs, 1H); 4.41 (brd J = 14Hz, 1H); 2.43(s, 1H); 0.88(s, 9H); 0.09(s, 3H); 0.07 (s, 3H).

Step B: 17-Ethyl-1-hydroxy-12-[2'-(4"-(tert-butyldimethylsiloxy)-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-12-[2'-(4"(tert-butyldimethylsiloxy)-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone (186 mg in 6 ml 33% methylene chloride in cyclohexane) allyltrichloro-acetimidate (62 µl neat) was added and the reagents

allowed to mix for 5 minutes. Trifluoromethanesulfonic acid (5 µl neat) was added slowly via syringe and the mixture stirred at room temperature. After 24 hours the reaction was quenched by the addition of saturated sodium bicarbonate and extracted with ethyl acetate (3 x 5 ml). The combined organics were washed with brine and dried over magnesium sulfate. Purification of the concentrate by flash chromatography on silica gel (ethyl acetate: hexane (1:4) + 1% methanol) gave the title compound (80 mg).

Partial ^{1}H NMR δ: 5.90 (m, 1H); 4.57(brd J = 4Hz, 1H); 4.42m, 4.33M (brs, 1H); 4.41(brd, J = 14Hz, 1H); 4.09(m, 2H).

Step C: 17-Ethyl-1-hydroxy-12-[2'-(4"-hydroxy-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-12-[2'-(4"-(tert-butyldimethylsiloxy)-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone (80 mg) in acetonitrile (5 ml) was added a solution of 2% HF in aqueous acetonitrile (100 µl). and the mixture stirred at room temperature. After 24 hours, the solution was diluted with ethyl acetate, extracted with saturated sodium bicarbonate solution and the organic phase dried over magnesium sulfate. Purification of the concentrate by flash

chromatography on silica gel (ethyl acetate:hexane (1:1) + 1% methanol) gave the title compound (66 mg).

Partial ^{1}H NMR δ: 5.90 (m, 1H); 4.87 (d J = 11Hz, 1H); 4.57 (brd J = 4Hz, 1H); 4.45m, 4.33M (brs, 1H); 4.41 (brd, J = 14Hz, 1H); 2.65 (s, 1H).

Step D: 17-Ethyl-1-hydroxy-12-[2'-(4"-(o-nitrobenzenesulfonyloxy)-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.-1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-12-[2'-(4"-hydroxy-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (66 mg) in dry methylene chloride (1.4 ml) was added an excess of diisopropylethyl amine (34 µl) and o-nitrobenzenesulfonyl chloride (36 mg) followed by addition of 4-dimethylaminopyridine (24 mg). The mixture was stirred at room temperature for 18 hours at which time it was diluted with ethyl acetate, extracted from saturated sodium bicarbonate solution and washed with brine. The combined organics were dried over magnesium sulfate and the concentrate purified by flash chromatography on silica gel (ethyl acetate: hexane (1:1) + 1% methanol to give the title compound (66 mg).

Partial ^{1}H NMR δ: 8.15 (m, 1H); 7.73 (m, 3H); 5.55 (m, 1H); 4.87 (d J = 11Hz, 1H); 4.58 (brd J = 4Hz, 1H); 4.57 (m, 1H); 4.42m, 4.31M (brs, 1H).

Step E: 17-Ethyl-1-hydroxy-12-[2'-(4"-azido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$] octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-12-[2'-(4"-(o-nitrophenylsulfonyloxy)-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$] octacos-18-ene-2,3,10,16-tetraone (66 mg) in N,N-dimethyl formamide (1 ml) was added an excess of sodium azide (22 mg) and the mixture heated to 70°C. After 2.5 hours the reaction was cooled to room temperature, diluted with ethyl acetate, extracted from half-saturated ammonium chloride, and washed with brine. The combined organics were dried over sodium sulfate and purified by flash chromatography on silica gel (ethyl acetate: hexane (1:2) + 1% methanol) to give the title compound (25 mg). Partial ^{1}H NMR δ: 5.91 (m, 1H); 4.59 (brd J = 4Hz, 1H); 4.45m, 4.31M (brs, 1H); 4.41(brd J = 14Hz, 1H).

EXAMPLE 73

17-Ethyl-1-hydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1-hydroxy-12-[2'-(4"-azido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-

4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone (25 mg) in 10% aqueous benzene (850 µl) was added triphenylphosphine (12 mg) and the mixture heated to 70°C with stirring. After 15 hours, the stir bar was removed and the reaction cooled to room temperature. The mixture was concentrated to 10% volume in vacuo and applied directly to a column of silica gel for purification by flash chromatography (ethyl acetate : hexane (1:1) + 1% methanol then 2% ammonium hydroxide, 5% methanol in methylene chloride) to give the title compound (15.8 mg).

MASS: (FAB) 800 (M+Na)

Partial ^{1}H NMR δ: 5.91 (m, 1H); 4.58 (brd J = 4Hz, 1H); 4.41 (brd J = 14Hz, 1H); 4.01 (dd J = 7, 2Hz, 2H).

EXAMPLE 74

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-acetylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.31.$0^{4,9}$]octacos-18-ene-2,3,20,26-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (30 mg) in dry methylene chloride (0.3 ml) is added triethylamine (10 µl) followed by a solution of acetic anhydride in methylene chloride (10 mg in 1 ml) at r.t. Reaction is stirred for 30 minutes and the solvent is removed under nitrogen flow. The crude product is purified by preparative tlc on silica gel to give the title compound.

EXAMPLE 75

17-Ethyl-1-hydroxy-12-[2'-(4"-N-(2-propenyl)-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

The compound 17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (30 mg) is placed in a dry flask equipped with stir bar and condenser. Dry toluene (1 ml) is added followed by diisopropylethylamine (13 mg) and freshly distilled allyl bromide (40.5 mg) at 0°C with stirring. Reaction temperature is raised to 70°C gradually and stirred for 2 hr. The reaction mixture is cooled, and the solvent is removed under nitrogen flow. The residue is purified by preparative tlc on silica gel to give the title compound.

EXAMPLE 76

17-Ethyl-1,14-dihydroxy-12-[2'-[4"-(D-phenylalanine)-amido-3"-allyloxycyclohexyl]-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (44.7 mg) in dry methylene chloride (2 ml)

is added 102 mg of freshly prepared BOC-D-phenylalanine anhydride (prepared as described in Solid Peptide Sythesis, p. 32, J.M. Steward and J.D. Young, Pierce Chemical Company) under nitrogen. Reaction is stirred at room temperature and the process is followed by tlc analysis. After 2.5 hr, the reaction mixture is subjected to work-up and preparative tlc on silica gel to give the protected compound. A cold solution (-15°C) of this compound in trifluoroacetic acid is stirred for 30 minutes and then freeze-dried to give the crude product. Purification by preparative TLC on silica gel gives the title compound.

EXAMPLE 77

17-Ethyl-1,14-dihydroxy-12-[2'-[4"-(L-phenylalanine)-amido-3"-allyloxycyclohexyl]-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

The title compound is prepared by the method of Example 76 utilizing BOC-L-phenylalanine anhydride.

EXAMPLE 78

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-acetoxyacetylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

A solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-

azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (40 mg) in dry methylene chloride (0.4 ml) is cooled to 0°C. To this solution is added a solution of acetoxyacetyl chloride (9 mg) in methylene chloride (0.5 ml). The reaction mixture is stirred at 0°C for 30 minutes, and quenched with a drop of methanol. Purification by preparative tlc on silica gel gives the title compound.

EXAMPLE 79

17-Ethyl-1-hydroxy-12-[2'-(4"-cyclopropanecarboxamido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

A solution of 17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone in dry methylene chloride (0.4 ml) is cooled to 0°C. To this solution is added triethylamine (10 µl) followed by a solution of cyclopropane carbonyl chloride (5 mg) in methylene chloride (0.1 ml). The reaction mixture is stirred at 0°C for 30 min. The reaction mixture is purified by preparative tlc on silica gel to give the title compound.

EXAMPLE 80

17-Ethyl-1-hydroxy-12-[2-(4"-formamido-3"-allyloxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

The compound 17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (30 mg) is mixed with methyl formate (0.5 ml) and is stirred at 0°C for 1 hr. The reaction mixture is allowed to warm to room temperature and then is stirred overnight. The excess methylformate is removed with nitrogen flow and the crude mixture is purified by preparative tlc on silica gel to give the title compound.

EXAMPLE 81

17-Ethyl-1,14-dihydroxy-12-{2'-[-4"-(4"',5"'-dicarboethoxy-1"',2"',3"'-triazole)-3"-allyloxycyclohexyl]-1'-methyl-vinyl}-23,23-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

A mixture of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-azido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (20 mg) in neat diethylacetylene dicarboxylate (0.1 ml) is stirred at room temperature overnight. The cycloaddition product is isolated by preparative tlc on silica gel to give the title compound.

EXAMPLE 82

17-Ethyl-1-hydroxy-12-[2'-(3"-allyloxy-4"-oxocyclohexyl)-1'-methylvinyl]-14-triisopropylsilyloxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a cooled solution (-78°C) of oxalyl chloride added dimethyl sulfoxide dropwise, followed by a solution of 17-ethyl-1-hydroxy-12-[2'-(4"-hydroxy-3"-allyloxycyclohexyl)-1'-methylvinyl]-14-triisopropylsiloxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone in dry methylene chloride. The reaction mixture is stirred for 30 min. at -78°C and then triethylamine is added. The reaction mixture is allowed to rise to room temperature, poured into water, and extracted with ethyl acetate (three times). Combined organic layers are washed (water, sat'd $NaHCO_3$), dried (anhydrous Na_2SO_4), and filtered. Removal of solvent followed by purification (silica gel column chromatography), gives the title compound.

EXAMPLE 83

17-Ethyl-1,14-dihydroxy-12-[2'-(3"-allyloxy-4"-oxocyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone

To a stirred solution of 17-ethyl-1-hydroxy-12-[2'-(3"-allyloxy-4"-oxocyclohexyl)-1'-methylvinyl]-14-triisopropylsilyloxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone in acetonitrile was added hydrofluoric acid at room temperature. The reaction progress is monitored by tlc analysis. The reaction mixture is quenched with sat'd aqueous sodium bicarbonate. The organic layer is separated

and the aqueous layer is extracted with ethyl acetate three times. Combined organic layers are washed (sat'd $NaHCO_3$, sat'd NaCl), dried (anhydrous Na_2SO_4), and filtered. Removal of solvent followed by purification (silica gel column chromatography), gives the title compound.

EXAMPLE 84

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-benzylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(3"-allyloxy-4"-oxocyclohexyl]-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone in dry isopropyl alcohol (3 ml) is added benzyl amine (86.5 mg). The mixture is stirred at r.t. for 30 minutes, and then cooled to -78°C. To this solution is added a solution of sodium cyanoborohydride (6.7 mg) in isopropyl alcohol (0.5 ml). The reaction is stirred at -78°C and poured into ice water. Extraction with ethyl acetate, followed by purification gives the title compound as a mixture of epimers at C-4".

EXAMPLE 85

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-trimethylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone Iodide

17-Ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone is dissolved in absolute ethanol in a heavy walled glass tube. Methyl iodide (large excess) and $NaHCO_3$ is added. The tube is sealed and then heated. Progress of the reaction is followed by watching disappearance of the starting amine on thin layer chromatography and the appearance of a more polar new spot. Upon completion of reaction, the quarternary iodide is obtained by evaporation of excess methyl iodide and solvent.

EXAMPLE 86

17-Ethyl-1,2,14-trihydroxy-12-[2'-(4"-acetylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,1927-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-3,10,16-trione

To a suspension of samarium (63 mg) in dry THF (1 ml) is added a solution of diiodoethane (56 mg in 1 ml THF) at r.t., and the reaction mixture is stirred for 1 hr. The dark blue solution is cooled to -78°C, and to this mixture is added a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-acetylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (166 mg) in 50% THF/MeOH (3 ml). The reaction is stirred for -78°C for 10 minutes., allowed to warm to room temperature over a period of 10 min., and then

quenched with saturated potassium carbonate solution. The organic layer is extracted with ether/ethyl acetate, washed (sat'd NaCl), and dried (anhydrous Na_2SO_4). Removal of solvent followed by chromatography on silica gel gives the title compound.

EXAMPLE 87

17-Ethyl-1,14-dihydroxy-12-{2'-[4"-(N'-phenylamino-carbonyl)amino-3"-allyloxycyclohexyl]-1'-methylvinyl}-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (40 mg) in methylene chloride (2 ml) is added phenyl isocyanate (12 mg) at 0°C with stirring. The reaction mixture is warmed to room temperature and the reaction progress is followed by tlc analysis. The reaction mixture is concentrated under a stream of nitrogen and purified by preparative tlc on silica to give the title compound.

EXAMPLE 88

17-Ethyl-1,14-dihydroxy-12-{2'-[4"-(ethoxycarbonyl)-amino-3"-allyloxycyclohexyl]-1'-methylvinyl}-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]otacos-18-ene-2,3,10,16-tetraone

To a solution of 17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (40 mg) in methylene chloride (2 ml) is added triethylamine (10 µl), followed by ethyl chloroformate (15 µl) at 0°C with stirring. The

reaction mixture is warmed to room temperature and the reaction progress is followed by tlc analysis. The solution is quenched with a drop of methanol and purified by preparative tlc on silica to give the title compound.

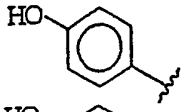
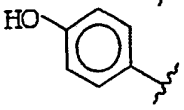
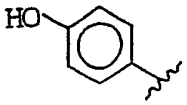
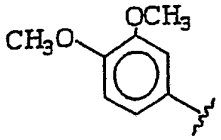
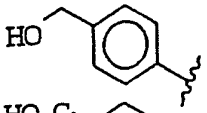
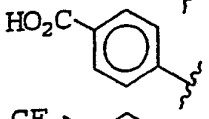
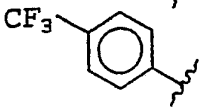
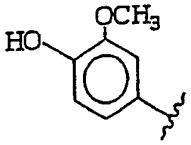
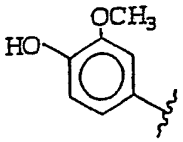
EXAMPLE 89

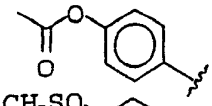
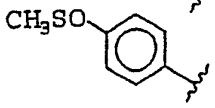
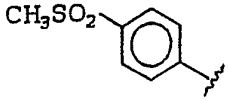
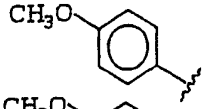
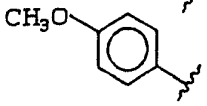
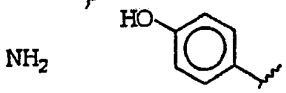
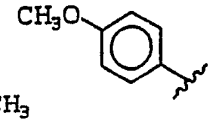
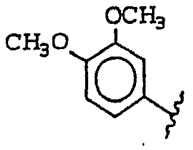
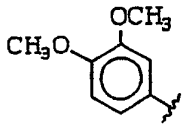
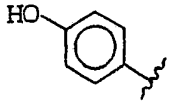
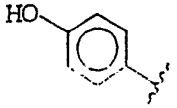
17-Ethyl-1-hydroxy-12-[2'-(4''-acetylamino-3''-allyloxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone

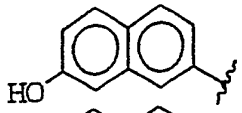
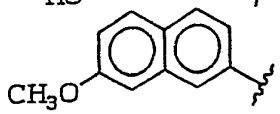
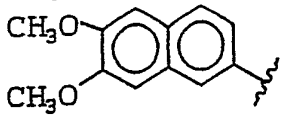
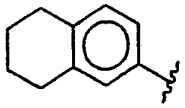
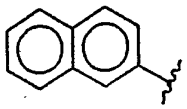
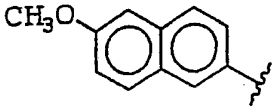
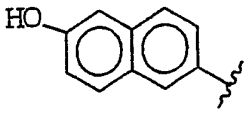
To a solution of 17-ethyl-1-hydroxy-12-[2'-(4''-amino3''-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone (60 mg) in dry CH_2Cl_2 (0.5 ml) is added Et_3N (20 µl) followed by a solution of acetic anhydride (20 mg in 1 ml). Work-up and purification on silica gel affords the title compound.

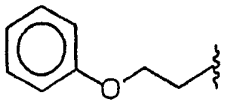
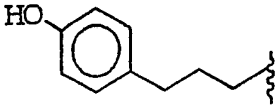
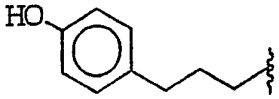
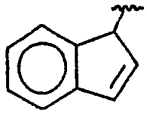
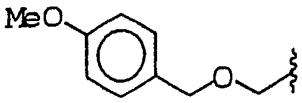
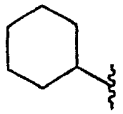
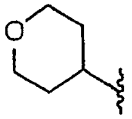
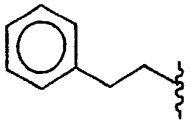
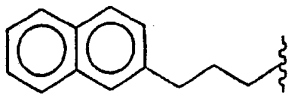
EXAMPLES 90-153

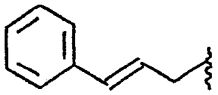
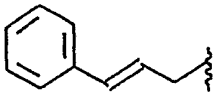
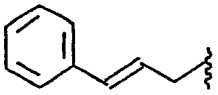
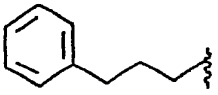
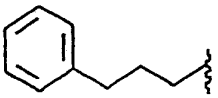
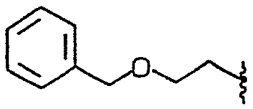
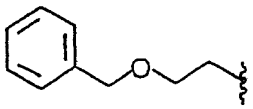
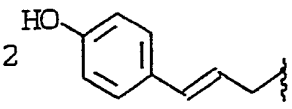
Utilizing the general procedures described in Examples 1 to 89, the following compounds of Formula I (wherein R^4 is hydrogen, and n is 2) are prepared from the appropriately substituted starting materials and reagents.

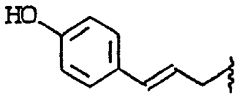
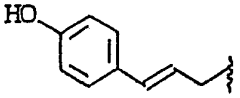
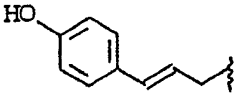
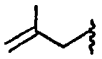
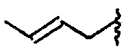
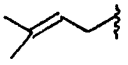
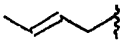
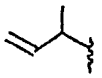
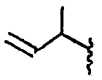
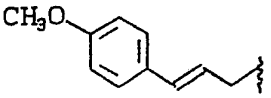
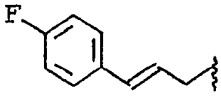
EXAMPLE NO.	R^2	R^1	R^3	R^5
90		NH_2	H	CH_3CH_2
91		NH_2	OH	CH_3CH_2
92		NH_2	H	$CH_2=CHCH_2-$
93		NH_2	OH	$CH_3CH_2CH_2$
94		NH_2	OH	CH_3CH_2
95		NH_2	H	CH_3CH_2
96		NH_2	OH	$CH_3CH_2CH_2$
97		NH_2	H	$CH_2=CHCH_2-$
98		$(CH_3)_2N$	OH	CH_3CH_2

EXAMPLE NO.	R^2	R^1	R^3	R^5
99		NH_2	H	CH_2CH_3
100		NH_2	OH	CH_3CH_2
101		$(CH_3)_2N$	OH	CH_2CH_3
102		NH_2	OH	CH_2CH_3
103		NH_2	H	CH_3CH_2
104		NH_2	H	CH_3CH_2
105		NH_2	H	CH_3CH_2
106		NH_2	OH	CH_3CH_2
107		NH_2	OH	CH_3CH_2
108		$(CH_3)_2N$	OH	CH_3CH_2
109		$(CH_3)_3N^+$	OH	CH_2CH_3

EXAMPLE NO.	R^2	R^1	R^3	R^5
110		NH_2	OH	$CH_3CH_2CH_2$
111		NH_2	H	CH_3CH_2
112		NH_2	H	$CH_2=CHCH_2-$
113		NH_2	OH	CH_3CH_2
114	NH_2 		H	CH_3CH_2
115	NH_2 CH_3O 		H	CH_3CH_2
116	NH_2 HO 		H	CH_3CH_2

EXAMPLE NO.	R^2	R^1	R^3	R^5
117		NH_2	OH	CH_3CH_2
118		NH_2	OH	CH_3CH_2
		NH_2	H	CH_3CH_2
119		NH_2	H	CH_3CH_2
120		NH_2	OH	CH_3CH_2
121		NH_2	OH	CH_3CH_2
122		NH_2	OH	CH_3CH_2
123		NH_2	H	CH_3CH_2
124		NH_2	H	CH_3CH_2

EXAMPLE NO.	R^2	R^1	R^3	R^5
125		NH_2	OH	CH_3CH_2
126		NH_2	H	CH_3CH_2
127		NH_2	OH	$CH_2=CHCH_2$
128		NH_2	OH	CH_3CH_2
129		NH_2	H	CH_3CH_2
130		NH_2	OH	CH_3CH_2
131		NH_2	H	CH_3CH_2
132		NH_2	OH	CH_3CH_2

EXAMPLE NO.	R^2	R^1	R^3	R^5
133		NH_2	H	CH_3CH_2
134		NH_2	OH	$CH_2=CHCH_2$
135		NH_2	H	$CH_2=CHCH_2$
136		NH_2	H	CH_3CH_2
137		NH_2	H	$CH_3CH_2CH_2$
138		NH_2	H	CH_3CH_2
139		NH_2	H	CH_3CH_2
140		NH_2	H	CH_3CH_2
141		NH_2	H	CH_3
142		NH_2	H	CH_2CH_3
143		NH_2	H	CH_2CH_3
144	$CH_3C\equiv C-CH_2-$	NH_2	H	$CH_2CH_2CH_3$

EXAMPLE NO.	R^2	R^1	R^3	R^5
145	$H_2NCH_2CH_2$	NH_2	OH	CH_3CH_2
146	$H_2NCH_2CH_2$	NH_2	H	CH_3CH_2
147	$(CH_3)_2NCH_2CH_2$	NH_2	OH	CH_3CH_2
148	$(CH_3)_2NCH_2CH_2$	NH_2	H	CH_3CH_2
149	$CH_3NHCH_2CH_2$	NH_2	OH	CH_3CH_2
150	$CH_3NHCH_2CH_2$	NH_2	H	CH_3CH_2
151	$H_2NCH_2CH_2$	$(CH_3)_2N$	OH	CH_3CH_2
152	$(CH_3)_2NCH_2CH_2$	$(CH_3)_2N$	OH	CH_3CH_2
153	$CH_3NHCH_2CH_2$	CH_3NH	OH	CH_3CH_2

EXAMPLE 154

T-Cell Proliferation Assay

1. Sample Prpearation

The compounds to be assayed were dissolved in absolute ethanol at 1 mg/ml.

2. Assay

Spleens from C57B1/6 mice were taken under sterile conditions and gently dissociated in ice-cold RPMI 1640 culture medium (GIBC), Grand Island, N. Y.) supplemented with 10% heat-inactivated fetal calf serum (GIBO)). Cells were pelleted by centrifugation at 1500 rpm for 8 minutes. Contaminating red cells were removed by treating the pellet with ammonium chloride lysing buffer (GIBO)) for 2 minutes at 4°C. Cold medium was added and cells were again centrifuged at 1500 rpm for 8 minutes. T lymphocytes were then isolated by separation of the cell suspension on nylon wool columns as follows: Nylon wool columns were prepared by packing approximately 4 grams of washed and dried nylon wool into 20 ml plastic syringes. The columns were sterilized by autoclaving at 25°F for 30 minutes. Nylon wool columns were wetted with warm (37°C) culture medium and rinsed with the same medium. Washed spleen cells resuspended in warm medium were slowly applied to the nylon wool. The columns were then incubated in an upright position at 37°C for 1 hour. Non-adherent T lymphocytes were eluted from the columns with warm culture medium and the cell suspensions were spun as above.

Purified T lymphocytes were resuspended at 2.5×10^5 cells/ml in complete culture medium composed of RPMI 1640 medium with 10% heat-inactivated fetal calf serum, 100 mM glutamine, 1 mM sodium pyruvate, 2×10^{-5} M 2-mercaptoethanol and 50 µg/ml gentamycin. Ionomycin was added at 250 ng/ml and PMA at 10 ng/ml. The cell suspension was immediately distributed into 96 well flat-bottom microculture plates (Costar) at 200 µl/well. The various dilutions of the compound to be tested were then added in triplicate wells at 20 µl/well. The compound 17-allyl-1,14-dihydroxy-12-[2'-(4''-hydroxy-3''-methoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone was used as a standard. The culture plates were then incubated at 37°C in a humidified atmosphere of 5% CO_2-95% air for 44 hours. The proliferation of T lymphocytes was assessed by measurement of tritiated thymidine incorporation. After 44 hours of culturing, the cells were pulse-labelled with 2 µCi/well of tritiated thymidine (NEN, Cambridge, MA). After another 4 hours of incubation, cultures were harvested on glass fiber filters using a multiple sample harvester. Radioactivity of filter discs corresponding to individual wells was measured by standard liquid scintillation counting methods (Betacounter). Mean counts per minute of replicate wells were calculated and the results expressed as concentration of compound required to inhibit tritiated thymidine uptake of T-cells by 50%.

A selection of compounds were tested according to the previous procedure. The title compounds of the following Examples had activity in inhibiting the proliferation of T-cells in the aforementioned assay:

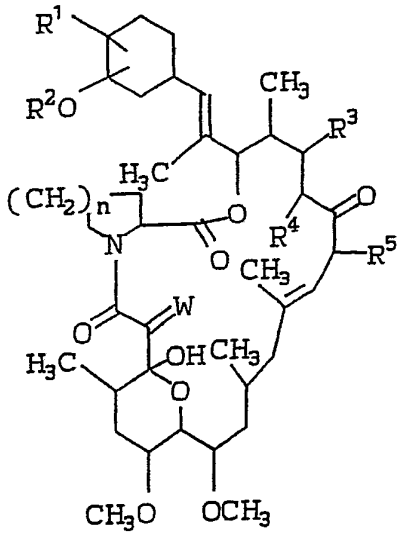
24, 25, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 71, and 73.

The results of this assay are representative of the intrinsic immunosuppressive activity of the compounds of the present invention.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the casual variations, adaptations, modifications, deletions, or additions of procedures and protocols described herein, as come within the scope of the following claims and its equivalents.

WHAT IS CLAIMED IS:

1. A compound of formula I:



I

or a pharmaceutically acceptable salt thereof,
wherein:
R^1 is selected from:

1) $-N_3$;
2) $-NHCN$;
3) $-NR^6R^7$, wherein R^6 and R^7 independently, are,
   a) hydrogen,
   b) C_1-C_{12} alkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are independently selected from the group consisting of:
      i) hydrogen,
      ii) -OH,

iii) C_1-C_6alkoxy,
iv) -O-CO-C_1-C_6alkyl,
v) $-NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently, hydrogen, or C_1-C_6alkyl, unsubstituted or substituted with phenyl
vi) $-CONR^{10}R^{11}$,
vii) $-CO_2H$,
viii) -CO-O-C_1-C_6alkyl,
ix) -S-C_1-C_6alkyl,
x) -SO-C_1-C_6alkyl,
xi) $-SO_2$-C_1-C_6alkyl,
xii) halo, such as Cl, Br, F or I,
xiii) -C_3-C_7-cycloalkyl,
xiv) phenyl, unsubstituted or substituted with X, Y and Z,
xv) naphthyl, unsubstituted or substituted with X, Y and Z,
xvi) $-CF_3$,

c) C_3-C_{12} alkenyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above,

d) C_3-C_7 cycloalkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above,

e) phenyl, unsubstituted or substituted with X, Y and Z,

f) naphthyl, unsubstituted or substituted with X, Y and Z,

g) $-SO_2$-phenyl, wherein phenyl is unsubstituted or substituted with with X, Y and Z,

h) $-SO_2-C_1-C_6$alkyl,

i) or where R^6 and R^7 and the N to which they are attached may form a 3- to 7-membered heterocyclic ring selected from the group consisting of: morpholine, thiomorpholine, piperidine, piperizine, and where the substituent(s), attached to the carbon atom(s) in the heterocyclic ring is/are independently selected from the group consisting of:

i) hydrogen,

ii) -OH,

iii) C_1-C_6 alkoxy,

iv) $-O-CO-C_1-C_6$ alkyl,

v) $-NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently, hydrogen, or C_1-C_6alkyl, unsubstituted or substituted with phenyl,

vi) $-CONR^{10}R^{11}$,

vii) $-CO_2H$,

viii) $-CO-O-C_1-C_6$ alkyl,

ix) -SH,

x) halo, such as Cl, Br, F or I,

xi) phenyl, unsubstituted or substituted with X, Y and Z,

xii) naphthyl, unsubstituted or substituted with X, Y and Z,

xiii) $-CF_3$;

4) $-N(R^6)CO-O-R^{12}$, wherein R^6 is as defined above and R^{12} is

C_1-C_{12} alkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above;

5) $-N(R^6)CO-R^{13}$, wherein R^6 is as defined above and R^{13} is

a) hydrogen,

b) C_1-C_{12} alkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above,

c) C_3-C_{12} cycloalkyl, unsubstituted or substituted with R^8 and R^9, wherein R^8 and R^9 are as defined above,

d) phenyl, unsubstituted or substituted with X, Y and Z,

e) naphthyl, unsubstituted or substituted with X, Y and Z, or

f) where R^6 and R^{13} and the -NCO to which they are attached may form an unsubstituted or substituted 5- to 7-membered heterocyclic ring selected from the group consisting of: pyrrolidone, and piperidinone;

6) $-N(R^{14})COCH(R^{22})NR^6R^7$ wherein R^6 and R^7 are as defined above, R^{14} is selected from the definitions of R^6, and R^{22} is

a) hydrogen,

b) C_1-C_4alkyl, unsubstituted or substituted with R^{23} wherein R^{23} is selected from the group consisting of:

i) -OH,

ii) C_1-C_6alkoxy,

iii) -O-CO-C_1-C_6alkyl,

iv) -SH,

v) -S-C_1-C_6alkyl,

vi) $-NR^{10}R^{11}$, wherein R^{10} and R^{11} are as defined above,

vii) $-CO_2H$,

viii) $-CONH_2$,

ix) imidazolyl,

x) indolyl,

xi) phenyl, and

xii) p-hydroxyphenyl, or,

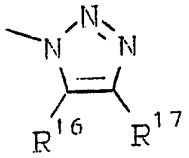
c) phenyl;

7) $-N(R^{14})CO(CH_2)_mNR^6R^7$, wherein m is 0 or 2-6, R^6 and R^7 are as defined above, and R^{14} is selected from the definitions of R^6, or where R^{14} and R^6 and the $-NCO(CH_2)_mN-$ to which they are attached may form an unsubstituted or substituted 5- to 7-membered heterocyclic ring, selected from: 2-imidazolidone;

8) $-N=C(R^{14})-NR^6R^7$, wherein R^6 and R^7 are as defined above, and R^{14} is selected from the definitions of R^6, and wherein if either R^6 or R^7 are hydrogen, the tautomeric structure $-NHC(R^{14})=NR^{6or7}$ is also possible;

9) $-N(R^{15})_3^+ A^-$, wherein R^{15} is C_1-C_6 alkyl, unsubstituted or substituted with phenyl or naphthyl, and wherein A^- is a counterion; selected from the group consisting of: acetate, adipate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, ethanesulfonate, fumarate, hemisulfate, hemitartrate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, methanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalene-sulfonate, nitrate oxalate, pamoate, perchlorate, persulfate, picrate, pivalate, propionate, succinate, tartrate, tosylate, and undecanoate;

10)



wherein R^{16} and R^{17} are independently,

a) hydrogen,
b) phenyl, unsubstituted or substituted with X, Y and Z,
c) naphthyl, unsubstituted or substituted with X, Y and Z,
d) -CN,
e) $-CF_3$,
f) $-CO-C_1-C_6$alkyl, or
g) $-CO-O-C_1-C_6$alkyl;

R^2 is selected from:

1) phenyl;
2) substituted phenyl in which the substituents are X, Y and Z;
3) 1- or 2- naphthyl;
4) substituted 1-or 2- naphthyl in which the substituents are X, Y and Z;
5) biphenyl;
6) substituted biphenyl in which the substituents are X, Y and Z;
7) substituted C_{1-10} alkyl in which one or more substituent(s) is(are) selected from
   a) hydroxy,
   b) C_{1-6} alkoxy,
   c) phenyl C_{1-3} alkoxy,
   d) substituted phenyl C_{1-3} alkoxy, in which the substituents on phenyl are X, Y and Z,
   e) $-OCOC_{1-6}$ alkyl,

f) $-NR^{10}R^{11}$, wherein R^{10} and R^{11} are independently hydrogen, or C_{1-6} alkyl unsubstituted or substituted with phenyl, which may be substituted with X, Y and Z,

g) $-NR^6COC_{1-6}$ alkyl, wherein R^6 is as defined above,

h) $-COOR^6$, wherein R^6 is as defined above,

i) -CHO,

j) phenyl,

k) substituted phenyl in which the substituents are X, Y and Z,

l) phenyloxy,

m) substituted phenyloxy in which the substituents are X, Y and Z,

n) 1- or 2- naphthyl,

o) substituted 1- or 2- naphthyl in which the substituents are X, Y and Z,

p) biphenyl, and

q) substituted biphenyl in which the substituents are X, Y and Z;

8) C_{3-10} alkenyl;

9) substituted C_{3-10} alkenyl in which one or more substituent(s) is(are) selected from

a) hydroxy,

b) C_{1-6} alkoxy,

c) $-OCO-C_{1-6}$ alkyl.

d) C_{2-8} alkenyl,

e) phenyl,

f) substituted phenyl in which the substituents are X, Y and Z,

g) 1- or 2- naphthyl,

h) substituted 1- or 2- naphthyl in which the substituents are X, Y and Z,
i) biphenyl, and
j) substituted biphenyl in which the substituents are X, Y and Z;

10) C_{3-10} alkynyl; and
11) substituted C_{3-10} alkynyl in which one or more substituent(s) is(are) selected from
a) hydroxy,
b) C_{1-6} alkoxy,
c) $-OCO-C_{1-6}$ alkyl,
d) phenyl,
e) substituted phenyl in which the substituents are X, Y and Z,
f) 1- or 2- naphthyl,
g) substituted 1- or 2- naphthyl in which the substituents are X, Y and Z,
h) biphenyl, and
i) substituted biphenyl in which the substituents are X, Y and Z;

R^3 is hydrogen, hydroxy, or C_1-C_6 alkoxy;
R^4 is hydrogen, or R^3 and R^4 taken together form a double bond;
R^5 is methyl, ethyl, propyl or allyl;

W is O or (H, OH):
X, Y and Z independently are selected from:
a) hydrogen,
b) C_{1-7} alkyl,
c) C_{2-6} alkenyl,
d) halo,

e) $-(CH_2)_p-NR^{10}R^{11}$, wherein R^{10} and R^{11} are as defined above, and p is 0 to 2,

f) -CN,

g) -CHO,

h) $-CF_3$,

i) $-SR^{18}$, wherein R^{18} is hydrogen, C_{1-6}alkyl, or phenyl,

j) $-SOR^{18}$, wherein R^{18} is as defined above,

k) $-SO_2R^{18}$, wherein R^{18} is as defined above,

l) $-CONR^{10}R^{11}$, wherein R^{10} and R^{11} are as defined above,

m) $R^{19}O(CH_2)_p-$ wherein R^{19} is hydrogen, C_{1-3} alkyl, hydroxy-C_{2-3}alkyl, phenyl or naphthyl and p is as defined above;

n) $-CH(OR^{20})(OR^{21})$, wherein R^{20} and R^{21} are C_{1-3}alkyl or taken together form an ethyl or propyl bridge,

o) $R^{19}\overset{O}{\overset{\|}{C}}O(CH_2)_p-$ wherein R^{19} and p are as defined above, and

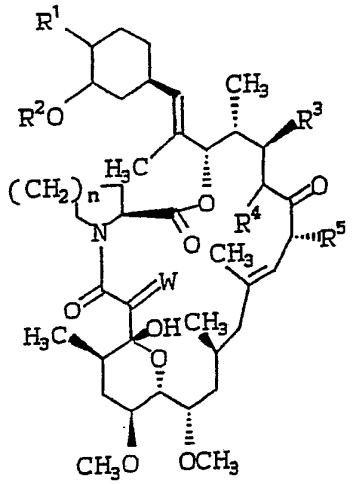
p) $R^{19}O\overset{O}{\overset{\|}{C}}(CH_2)_p-$ wherein R^{19} and p are as defined above;

or any two of X, Y and Z may be joined to form a saturated ring having 5, 6 or 7 ring atoms, said ring atoms comprising 0, 1 or 2 oxygen atoms,

the remaining ring atoms being carbon selected from the group consisting of: dihydropyranyl, dihydrofuranyl, dioxolanyl and dioxanyl; and

n is 1 or 2.

2. The compound according to Claim 1 wherein the steric configuration of formula I is as defined in formula III:



III

3. A compound which is selected from:

17-allyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-phenoxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-allyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-phenoxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-phenoxy-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-phenoxy-3"-amino-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-dimethylamino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4'''-methoxyphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4'''-hydroxyphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-acetylamino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo [22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4'''-fluorophenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(4'''-carboxyphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4'''-trifluoromethylphenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3''',4'''-dimethoxyphenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-allyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(4'''-methoxyphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4'''-methylphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(4'''-methylphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3'''-methoxyphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3'''-hydroxyphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-N-(2-propenyl)amino-3"-phenoxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone; and

17-ethyl-1-hydroxy-12-[2'-(4"-(acetylamino-3"-(4'''-methoxyphenoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2"'R-hydroxypropyl)-amino-3"-phenyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,-16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2"'S-hydroxypropyl)-amino-3"-phenyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,-16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2""R-hydroxypropyl)-amino-3"-(4"'-methyl)phenyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2""S-hydroxypropyl)-amino-3"-(4"'-methyl)phenyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2""R-hydroxypropyl)-amino-3"-(4"'-methoxy)phenyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2""S-hydroxypropyl)-amino-3"-(4"'-methoxy)phenyloxycyclohexyl)-1'-methyl-vinyl]-23,25-dimethoxy-13,19,21,27-tetra-methyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2"'R-hydroxypropyl)-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(2"'S-hydroxypropyl)-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,-25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-dimethylamino-3"-(3"'-methoxy)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-(4"'-dimethylamino)-phenyloxy-3"-hydroxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-hydroxy-3"-(4"'-dimethylamino)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16 -tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-azido-3"-(4"'-dimethylamino)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-dimethylamino)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-methyl)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxy-methyl)phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-methoxy)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3"'-methoxy)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxy)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-formyl)-phenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.04,9]-octacos-18-ene-2,3,10,16-tetraone;

and pharmaceutically acceptable salts thereof.

4. A compound which is selected from:

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-allyloxy-3"-aminocyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$] octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-cinnamyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-cinnamyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-allyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-cinnamyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(3"'-phenylpropyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3"'-phenyl-propyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(2"'-benzyloxyethoxy)-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(2"'-benzyloxy-ethoxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxycinnamyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxy-cinnamyloxy)cyclohexyl)-1'-methylvinyl]-23,25-di-methoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatri-cyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-allyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxycinnamyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-allyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-hydroxy-cinnamyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-acetylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-acetylamino-3"-allyl-oxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-N-(2-propenyl)amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-(L-phenylalanine)-amido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatri cyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-(D-phenylalanine)-amido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatri cyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-cyclopropanecarboxamido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-formamido-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-(4"',5"'-dicarboethoxy-1"',2"',3"'-triazole)-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]-octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-benzylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-dimethylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-trimethylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,2,14-trihydroxy-12-[2'-(4"-acetylamino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-3,10,16-trione;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-(N-phenylaminocarbonyl)amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-(ethoxycarbonyl)-amino-3"-allyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-sec-butenyloxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-sec-butenyl-oxycyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(3-methyl-2-butenyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(3-methyl-2-butenyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1,14-dihydroxy-12-[2'-(4"-amino-3"-(2-methyl-propenyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(2-methyl-propenyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"(-4"'-methoxy-cinnamyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(4"'-fluoro-cinnamyloxy)cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone; and

17-ethyl-1-hydroxy-12-[2'-(4"-amino-3"-(2-butynyloxy)-cyclohexyl)-1'-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone;

and pharmaceutically acceptable salts thereof.

5. A use of the compound of Claim 1 as a pharmaceutical.

6. A pharmaceutical composition comprising a compound of Claim 1 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

7. A method for the treatment or prevention of: resistance to transplantation; graft-versus-host diseases by medulla ossium; autoimmune diseases, or infectious diseases comprising the administration to a mammalian species in need of such treatment of an effective amount of the compound of Claim 1.

8. A method for the prevention or treatment of: inflammatory and hyperproliferative skin diseases and or cutaneous manifestations of immunologically-mediated illnesses; reversible obstructive airways disease; male or female pattern alopecia, alopecia senilis or alopecia areata; inflammation of mucosa or blood vessels; LTB_4-mediated diseases, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel disease, inflammatory bowel disease, necrotizing enterocolitis, or intestinal lesions associated with thermal burns; resistance to chemotherapeutic agents; idiopathic thrombocytopenic purpura and Basedow's disease; or cytomegalovirus infection, comprising the administration to a mammalian species in need of such treatment of an effective amount of the compound of Claim 1.

9. A use of the compound of Claim 1 in the manufacture of a medicament for treating or preventing: resistance to transplantation; graft-versus-host diseases by medulla ossium; autoimmune diseases; infectious diseases; inflammatory and hyperproliferative skin diseases and or cutaneous manifestations of immunologically-mediated illnesses; reversible obstructive airways disease; male or female pattern alopecia, alopecia senilis or alopecia areata; inflammation of mucosa or blood vessels; LTB_4-mediated diseases, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel disease, inflammatory bowel disease, necrotizing enterocolitis, or intestinal lesions associated with thermal burns; resistance to chemotherapeutic agents; idiopathic thrombocytopenic purpura and Basedow's disease; or cytomegalovirus infection.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/03918

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 498/18 A 61 K 31/445 //(C 07 D 498/18
C 07 D 311:00 C 07 D 273:00 C 07 D 221:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

	Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
1	P,A	EP,A,0428365 (MERCK) 22 May 1991, see claims 1,8-10 (cited in the application) ---	1,9
1	P,A	EP,A,0427680 (SANDOZ) 15 May 1991, see claims 1,7 (cited in the application) ---	1,6
2	P,A	WO,A,9113889 (FISONS) 19 September 1991, see claims 1,10 -----	1,9

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
02-09-1992	07. 10. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Marielle Wellborg

Form PCT/ISA/210 (second sheet) (January 1985)

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 7 and 8 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9203918 SA 60568

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 28/09/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0428365	22-05-91	CA-A- 2029860	14-05-91
		JP-A- 3209386	12-09-91
EP-A- 0427680	15-05-91	AU-A- 6584390	23-05-91
		CA-A- 2029694	10-05-91
		JP-A- 3223291	02-10-91
WO-A- 9113889	19-09-91	None	