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(71) Applicant: **ENANTA PHARMACEUTICALS, INC.**
[US/US]; 500 Arsenal Street, Watertown, MA 02472 (US).

(72) Inventors: **OR, Yat, Sun**; 169 Fayette Street, Watertown,
MA 02472 (US). **WANG, Guogiang**; 63 Creeley Road,
Belmont, MA 02478 (US). **NIU, Deqiang**; 30 Grapevine
Avenue, Lexington, MA 02421 (US). **PHAN, Ly, Tam**; 66
Devir Street, Apt. 211, Malden, MA 02148 (US).

(74) Agent: **FERRONE, Jason, D.**; Enanta Pharmaceuticals,
Inc., Attn.: Patent Dept., 500 Arsenal Street, Watertown,
MA 02472 (US).

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(54) Title: 6, 11-4-CARBON BRIDGED ERYTHROMYCIN DERIVATIVES

(57) Abstract: Novel 6,11-4-carbon bridged erythromycin derivatives and pharmaceutically-acceptable compositions comprising a therapeutically effective amount of a compound of the invention in combination with a pharmaceutically-acceptable carrier are described. Also described are methods for treating bacterial infections by administering to an animal a pharmaceutical composition containing a therapeutically effective amount of a compound of the invention and processes for the preparation of such compounds.

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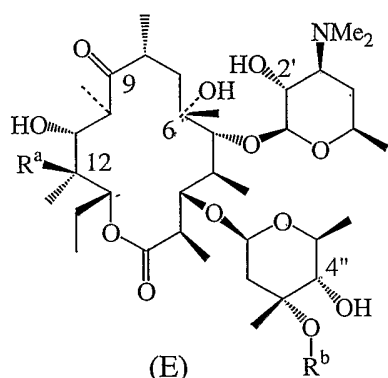
6, 11-4-Carbon Bridged Erythromycin Derivatives

TECHNICAL FIELD

The present invention relates to novel semisynthetic macrolides having antibacterial activity and useful in the treatment and prevention of bacterial infections. More particularly, the invention relates to 6, 11-4-carbon bridged erythromycin derivatives, compositions containing such compounds and methods for using the same, as well as processes for making such compounds.

BACKGROUND OF THE INVENTION

Erythromycins A through D, represented by formula (E) as illustrated below,



Erythromycin	R ^a	R ^b
A	-OH	-CH ₃
B	-H	-CH ₃
C	-OH	-H
D	-H	-H

are well-known and potent antibacterial agents, used widely to treat and prevent bacterial infection. As with other antibacterials, however, bacterial strains having resistance or insufficient susceptibility to erythromycin have been identified. Also, erythromycin A has only weak activity against Gram-negative bacteria. Therefore, there is a continuing need to identify new erythromycin derivative compounds which possess improved antibacterial activity, which have less potential for developing resistance, which possess the desired Gram-negative activity, or which possess unexpected selectivity against target microorganisms. Consequently, numerous investigators have prepared chemical derivatives of erythromycin in an attempt to obtain analogs having modified or improved profiles of antibiotic activity.

Kashimura *et al.* have disclosed 6-O-methylethromycin derivatives having a tricyclic basic nuclear structure in European Application 559896, published November 11, 1991. Also, Asaka *et al.* have disclosed 5-O-desoaminylerthronolide derivatives

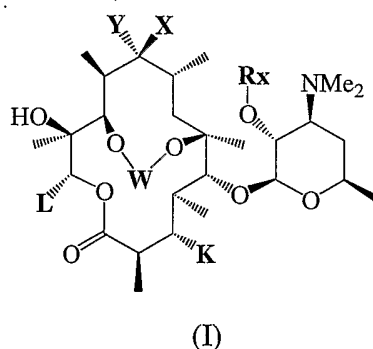
containing a tricyclic carbamate structure in PCT Application WO 93/21200, published April 22, 1992.

Recently erythromycin derivatives containing a variety of substituents at the 6-O position have been disclosed in U.S. Patent Nos. 5,866,549 and 6,075,011 as well as PCT Application WO00/78773. Furthermore, Ma, Or *et. al.* have described erythromycin derivatives with aryl groups tethered to the C-6 position in *J. Med Chem.*, 44, pp 4137-4156 (2001). United States Patent 6,046,171 and PCT application WO 99/21864, published May 6, 1999, disclose certain 6,11-bridged erythromycin derivatives.

10 SUMMARY OF THE INVENTION

The present invention provides a novel class of C6-C11 bridged macrolide compounds that possess antibacterial activity.

In one embodiment, the compounds of the present invention are represented by formula I, as illustrated below or their pharmaceutically acceptable salts, esters and
15 prodrugs:



wherein

20 W is selected from the group consisting of:

(a) $-\text{CH}_2-\text{C}(\text{A})=\text{C}(\text{B})-\text{CH}_2-$;

wherein,

A and B are independently selected from the group consisting of:

- (i) hydrogen;
 - (ii) deuterium;
 - (iii) halogen;
 - (iv) R_1 , wherein R_1 is selected from the group consisting of:
- 25

- 5
- a. C₁-C₆ alkyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- b. C₂-C₆ alkenyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and
- 10 c. C₂-C₆ alkynyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- (v) R₂, wherein R₂ is selected from the group consisting of:
- a. aryl;
- b. heteroaryl;
- c. substituted aryl; and
- 15 d. substituted heteroaryl;
- (vi) -(C₁-C₃-alkyl)-M-(C₁-C₃-alkyl)-R₂, wherein M = -O-, -NH-, -N(CH₃)-, -NHC(O)-, -S(O)_n-, wherein n = 0, 1 or 2, and R₂ is as previously defined;
- (vii) -(C₁-C₃-alkyl)-M-R₂, wherein M and R₂ are as previously defined;
- 20 (viii) -C(O)-J-R₃, wherein J is absent, O or S, and R₃ is H, R₁ or R₂, where R₁ and R₂ are as previously defined; and
- (ix) -C(O)-NR₁₁R₁₂, wherein R₁₁ and R₁₂ are each independently selected from the group consisting of:
- a. hydrogen;
- 25 b. C₁-C₆-alkyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- c. C₂-C₆-alkenyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- 30 d. C₂-C₆-alkynyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

e. R_{11} and R_{12} taken together with the nitrogen atom to which they are connected form a 3- to 7-membered ring which may optionally contain one or more heterofunctions selected from the group consisting of: -O-, -NH-, -N(C_1 - C_6 -alkyl)-, -N(R_2)-, -S(O) $_n$ -, wherein n and R_2 are as previously defined;

(b) $-\text{CH}_2-\text{CH}(\text{A})-\text{C}(\text{B})=\text{CH}-$, wherein A and B are as previously defined;

(c) $-\text{CH}_2-\text{CH}(\text{E})-\text{CH}(\text{G})-\text{CH}_2-$;

wherein E and G are independently selected from the group consisting of:

(i) A, wherein A is as previously defined;

(ii) -OH;

(iii) $-\text{OR}^{\text{P}}$, wherein R^{P} is a hydroxy protecting group;

(iv) $-\text{O}-\text{R}_9$, wherein R_9 is R_1 or R_2 , and wherein R_1 and R_2 are as previously defined;

(v) $-\text{S}(\text{O})_n\text{R}_9$, wherein n and R_9 are as previously defined;

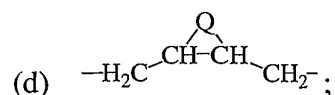
(vi) $-\text{NHC}(\text{O})\text{R}_3$, wherein R_3 is as previously defined;

(vii) $-\text{NHC}(\text{O})\text{NR}_{11}\text{R}_3$, wherein R_{11} and R_3 are as previously defined;

(viii) $-\text{NHS}(\text{O})_2\text{R}_9$, wherein R_9 is as previously defined;

(ix) $-\text{NHR}_{13}$, wherein R_{13} is an amino protecting group; and

(x) $-\text{NR}_{11}\text{R}_{12}$, wherein R_{11} and R_{12} are as previously defined;



wherein:

(i) -Q- is selected from the group consisting of: -O-; $-\text{O}-\text{C}(\text{O})-\text{CH}(\text{R}_7)-$; $-\text{N}(\text{R}_7)-$; $-\text{O}-\text{C}(\text{O})-\text{N}(\text{R}_7)-$; $-\text{O}-\text{C}(\text{O})-\text{O}-$; $-\text{N}(\text{R}_7)-\text{N}=\text{N}-$; $-\text{C}(\text{R}_7)=\text{N}-$; $-\text{O}-$; and $-\text{CH}(\text{R}_7)-\text{N}(\text{R}_8)-\text{O}-$; wherein R_7 and R_8 are independently selected from R_3 , wherein R_3 is as previously defined; or

(ii) -Q- taken together with the two carbon atoms it is attached to is selected from the group consisting of:

a. cycloalkylene;

b. cycloalkenylene; and

c. heterocycloalkylene; and

(e) $-\text{CH}_2-\text{C}(\text{R}_4)(\text{R}_5)-\text{CH}_2-\text{CH}_2-$;

wherein R_4 and R_5 taken together with the carbon atom to which they are attached are selected from the group consisting of:

- (i) $C=O$;
- (ii) $C(OR_1)_2$, wherein R_1 is as previously defined;
- 5 (iii) $C(SR_1)_2$, wherein R_1 is as previously defined;
- (iv) $C[-O(CH_2)_m]_2$, wherein m is 2 or 3;
- (v) $C[-S(CH_2)_m]_2$, wherein m is as previously defined,
- (vi) $C=CHR_3$, wherein R_3 is as previously defined;
- (vii) $C=N-O-R_3$, wherein R_3 is as previously defined;
- 10 (viii) $C=NNHR_3$, wherein R_3 is as previously defined;
- (ix) $C=NNHC(O)R_3$, wherein R_3 is as previously defined;
- (x) $C=NNHC(O)NR_{11}R_3$, wherein R_{11} and R_3 are as previously defined;
- (xi) $C=NNHS(O)_2R_9$, wherein R_9 is as previously defined;
- 15 (xii) $C=NNHR_{13}$, wherein R_{13} is as previously defined; and
- (xiii) $C=NR_9$, wherein R_9 is as previously defined;

X and Y are:

- (a) independently selected from the group consisting of:
 - (i) hydrogen;
 - 20 (ii) deuterium;
 - (iii) $-OH$;
 - (iv) $-OR^P$, wherein R^P is as previously defined; and
 - (v) $-NR_{14}R_{15}$, wherein R_{14} and R_{15} are each independently selected from the group consisting of:
 - 25 a. hydrogen;
 - b. C_1 - C_{12} alkyl, optionally substituted with one or more substituents selected from the group consisting of halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl; and
 - 30 c. R_{14} and R_{15} , taken together with the nitrogen atom to which they are attached form a 3 to 10 membered heterocycloalkyl ring optionally substituted with one or more hetero atoms selected from the group consisting of O, S and N; or

(b) taken together with the carbon atom to which they are attached are selected from the group consisting of:

- (i) $C=O$;
- (ii) $C=NR_3$, wherein R_3 is as previously defined;
- (iii) $C=NC(O)R_3$, wherein R_3 is as previously defined;
- (iv) $C=N-OR_6$, wherein R_6 is selected from the group consisting of:
 - a. hydrogen;
 - b. $-CH_2O(CH_2)_2OCH_3$;
 - c. $-CH_2O(CH_2O)_nCH_3$, wherein n is as previously defined;
 - d. C_1 - C_{12} alkyl, optionally substituted with one or more substituents selected from the group consisting of halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl;
 - e. C_3 - C_{12} cycloalkyl;
 - f. $C(O)$ - C_1 - C_{12} alkyl;
 - g. $C(O)$ -(C_3 - C_{12} cycloalkyl);
 - h. $C(O)$ - R_2 , wherein R_2 is as previously defined; and
 - i. $-Si(R_a)(R_b)(R_c)$, wherein R_a , R_b and R_c are each independently selected from the group consisting of C_1 - C_{12} alkyl, aryl and substituted aryl; and
- (v) $C=N-O-C(R_{16})(R_{17})-O-R_{18}$, wherein R_{16} and R_{17} taken together with the carbon atom to which they are attached form a C_3 to C_{12} cycloalkyl group or each independently is selected from the group consisting of: hydrogen, and C_1 - C_{12} alkyl; and R_{18} is selected from the group consisting of:
 - a. hydrogen;
 - b. $-CH_2O(CH_2)_2OCH_3$;
 - c. $-CH_2O(CH_2O)_nCH_3$, wherein n is as previously defined;
 - d. C_1 - C_{12} alkyl, optionally substituted with one or more substituents selected from the group consisting of halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl;
 - e. C_3 - C_{12} cycloalkyl; and
 - f. $-Si(R_a)(R_b)(R_c)$, wherein R_a , R_b and R_c are as previously defined;

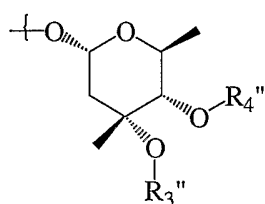
L is selected from the group consisting of:

- (a) $-\text{CH}(\text{OH})\text{CH}_3$;
- (b) $\text{C}_1\text{-C}_6$ alkyl, optionally substituted with one or more substituents selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- 5 (c) $\text{C}_2\text{-C}_6$ alkenyl, optionally substituted with one or more substituents selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and
- (d) $\text{C}_2\text{-C}_6$ alkynyl, optionally substituted with one or more substituents selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- 10

K is selected from the group consisting of:

- (a) R_{10} , wherein R_{10} is selected from the group consisting of:
- (i) hydrogen;
- (ii) $-\text{OR}^{\text{P}}$, wherein R^{P} is as previously defined;
- 15 (iii) $-\text{OR}_3$, wherein R_3 is as previously defined;
- (iv) $-\text{OC}(\text{O})\text{R}_3$, wherein R_3 is as previously defined;
- (v) $-\text{OC}(\text{O})\text{NR}_{11}\text{R}_3$, wherein R_{11} and R_3 are as previously defined;
- and
- (vi) $-\text{S}(\text{O})_n\text{R}_9$, wherein n and R_9 are as previously defined; and
- 20

(b)



wherein R_3'' is hydrogen or methyl; R_4'' is hydrogen or R^{P} , wherein R^{P} is as previously defined; and

R_x is hydrogen or R^{P} , wherein R^{P} is as previously defined.

25

In another aspect of the present invention, pharmaceutical compositions are disclosed that comprise a therapeutically effective amount of a compound of the invention in combination with a pharmaceutically acceptable carrier. The invention also includes a method of treatment of antibacterial infections with such compositions. Suitable carriers and methods of formulation are also disclosed. The compounds and compositions of the

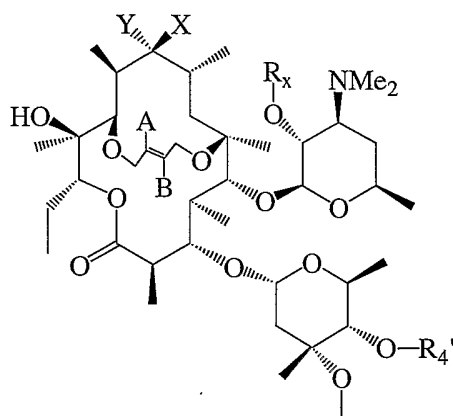
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present invention have antibacterial activity. In a further aspect of the present invention, processes for the preparation of 6,11-4 carbon bridged macrolides of formula I are provided.

5 DETAILED DESCRIPTION OF THE INVENTION

A first embodiment of the invention is a compound represented by formula I as illustrated above, or a pharmaceutically acceptable salt, ester or prodrug thereof.

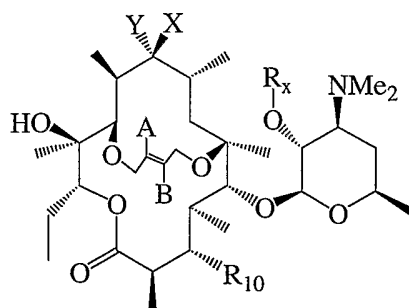
A preferred group of compounds according to the present invention is represented by formula II as illustrated below, or a pharmaceutically acceptable salt, ester or prodrug thereof:



(II)

wherein A, B, X, Y, R_x and R₄' are as previously defined.

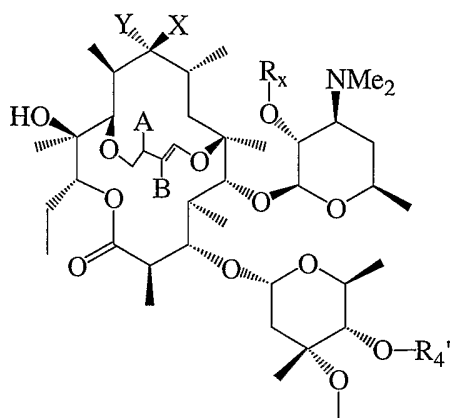
Another preferred group of compounds according to the present invention is represented by formula III as illustrated below, or a pharmaceutically acceptable salt, ester or prodrug thereof:



(III)

wherein A, B, X, Y, R₁₀ and R_x are as previously defined.

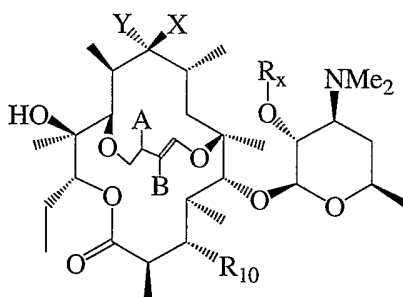
Yet another preferred group of compounds according to the present invention is represented by formula IV as illustrated below, or a pharmaceutically acceptable salt, ester or prodrug thereof:



5 (IV)

wherein A, B, X, Y, R_x and R₄'' are as previously defined.

Another preferred group of compounds according to the present invention is represented by formula V as illustrated below, or a pharmaceutically acceptable salt, ester or prodrug thereof:

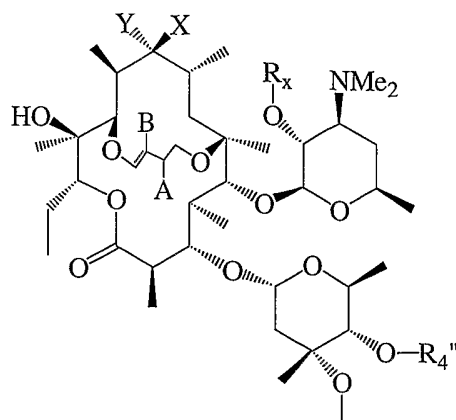


10 (V)

wherein A, B, X, Y, R₁₀ and R_x are as previously defined.

Yet another preferred group of compounds according to the present invention is represented by formula VI as illustrated below, or a pharmaceutically acceptable salt, ester or prodrug thereof:

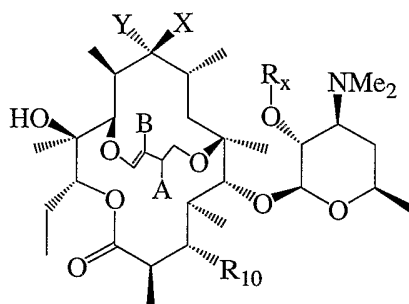
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(VI)

wherein A, B, X, Y, R_x and R_4'' are as previously defined.

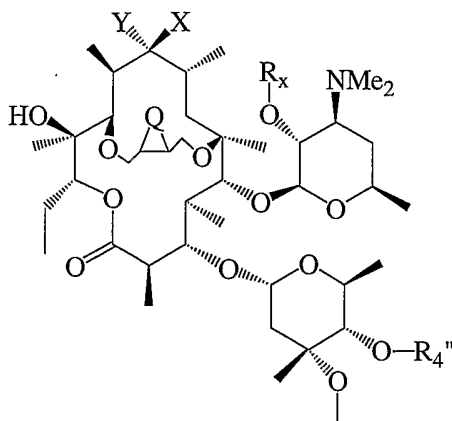
Another preferred group of compounds according to the present invention is
 5 represented by formula VII as illustrated below, or a pharmaceutically acceptable salt, ester
 or prodrug thereof:



(VII)

wherein A, B, X, Y, R_{10} and R_x are as previously defined.

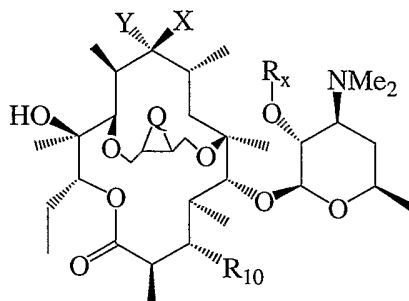
10 Yet another preferred group of compounds according to the present invention is
 represented by formula VIII as illustrated below, or a pharmaceutically acceptable salt,
 ester or prodrug thereof:



(VIII)

wherein Q, X, Y, R_x and R₄" are as previously defined.

Another preferred group of compounds according to the present invention is represented by formula IX as illustrated below, or a pharmaceutically acceptable salt, ester or prodrug thereof:



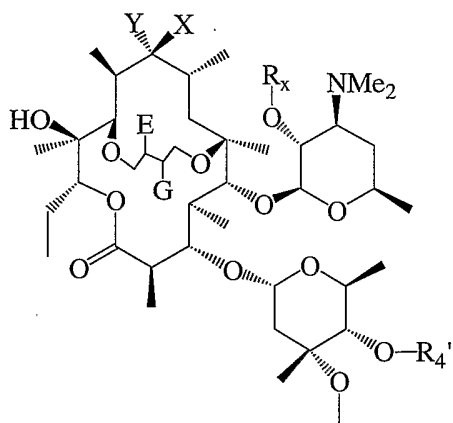
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(IX)

wherein Q, X, Y, R₁₀ and R_x are as previously defined.

Yet another preferred group of compounds according to the present invention is represented by formula X as illustrated below, or a pharmaceutically acceptable salt, ester or prodrug thereof:

10

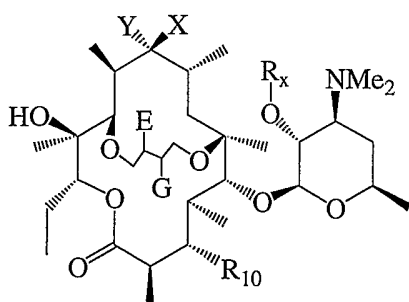


(X)

wherein E, G, X, Y, R_x and R₄" are as previously defined.

Another preferred group of compounds according to the present invention is represented by formula XI as illustrated below, or a pharmaceutically acceptable salt, ester or prodrug thereof:

15

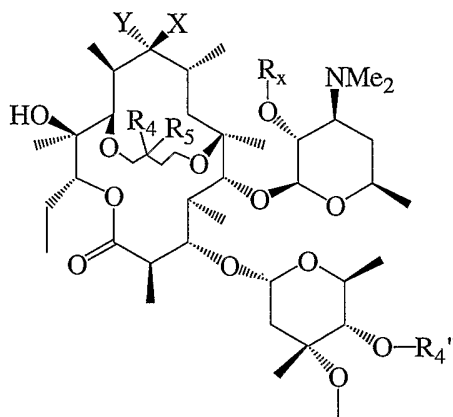


(XI)

wherein E, G, X, Y, R₁₀ and R_x are as previously defined.

Yet another preferred group of compounds according to the present invention is represented by formula XII as illustrated below, or a pharmaceutically acceptable salt, ester

5 or prodrug thereof:

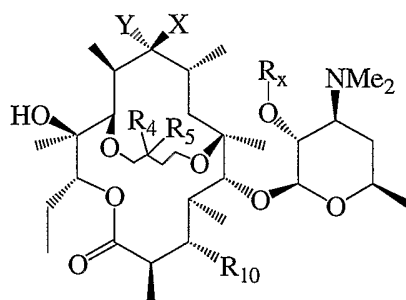


(XII)

wherein X, Y, R₄, R₅, R_x and R₄^{''} are as previously defined.

Another preferred group of compounds according to the present invention is represented by formula XIII as illustrated below, or a pharmaceutically acceptable salt, ester or prodrug thereof:

10

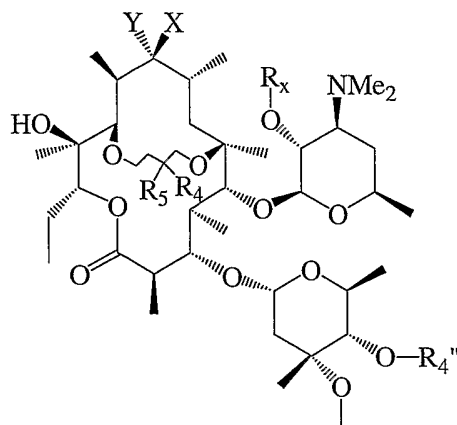


(XIII)

wherein X, Y, R₄, R₅, R₁₀ and R_x are as previously defined.

15

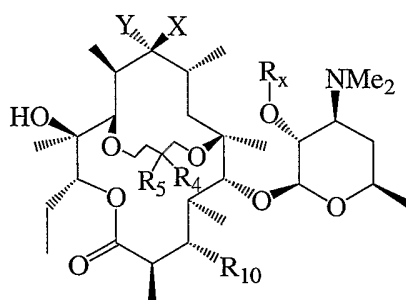
Yet another preferred group of compounds according to the present invention is represented by formula XIV as illustrated below, or a pharmaceutically acceptable salt, ester or prodrug thereof:



(XIV)

wherein X, Y, R₄, R₅, R_x and R₄^{''} are as previously defined.

Another preferred group of compounds according to the present invention is
 5 represented by formula XV as illustrated below, or a pharmaceutically acceptable salt, ester
 or prodrug thereof:



(XV)

wherein X, Y, R₄, R₅, R₁₀ and R_x are as previously defined.

10 Another preferred embodiment of the invention are compounds represented by any
 of the above formulas I through XV wherein: X and Y taken together with the carbon atom
 to which they are attached are selected from the group consisting of: C=O, C=NR₃, C=N-
 O-R₆, C=N-C(O)R₃ and C=N-O-C(R₁₆)(R₁₇)-O-R₁₈ and R_x is hydrogen, where R₃, R₆, R₁₆,
 R₁₇ and R₁₈ are as previously defined.

15 Yet another preferred embodiment of the invention are compounds represented by
 any of the above formulas I through XV wherein: X and Y taken together with the carbon
 atom to which they are attached are selected from the group consisting of: C=NC(O)R₃ and
 C=N-O-C(R₁₆)(R₁₇)-O-R₁₈; and R_x is hydrogen, where R₃ is methyl, R₁₈ is methyl and R₁₆
 and R₁₇ are each hydrogen.

20 Still yet another preferred embodiment of the invention are compounds represented
 by formula I wherein L is -CH₂CH₃-.

Another preferred embodiment of the invention are compounds represented by any of the above formulas III, V, VII, IX, XI, XIII and XV wherein $R_{10} = OH$.

Representative compounds according to the invention include those selected from the group consisting of:

- 5 Compound of Formula (II): $A = B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-OH$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
Compound of Formula (IV): $A = 3\text{-quinolyl}$; $B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-OH$; $R_x = H$ and $R_4'' = C(O)CH_3$;
Compound of Formula (II): $A = C(O)OCH_3$; $B = H$; X and Y taken together with
10 the carbon atom they are attached to $= C=N-OH$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
Compound of Formula (II): $A = B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
Compound of Formula (VIII): $Q = -C(C_6H_5)=N-O-$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
15 Compound of Formula (VIII): $Q = -O-C(O)-O-$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
Compound of Formula (VIII): $Q = -O-$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
Compound of Formula (VIII): $Q = -O-$; X and Y taken together with the carbon
20 atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = H$;
Compound of Formula (II): $A = B = H$; X and Y taken together with the carbon atom they are attached to $= C=NC(O)CH_2OCH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
Compound of Formula (II): $A = B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)-CH_2OCH_3$; $R_x = H$ and $R_4'' = H$;
25 Compound of Formula (IV): $A = 3\text{-quinolyl}$; $B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
Compound of Formula (IV): $A = 3\text{-quinolyl}$; $B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = H$;
Compound of Formula (II): $A = C(CH=CH-C_6H_5)$; $B = H$; X and Y taken together
30 with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
Compound of Formula (II): $A = C(CH=CH-C_6H_5)$; $B = H$; X and Y taken together with the carbon atom they are attached to $= C=NC(O)CH_3$; $R_x = H$ and $R_4'' = H$;

Compound of Formula (II): A = C(CH=CH-C₆H₅); B = H; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; R_x = H and R₄" = C(O)C₆H₅;

5 Compound of Formula (II): A = C(CH=CH-C₆H₅); B = H; X and Y taken together with the carbon atom they are attached to = C=NC(O)CH₃; R_x = H and R₄" = H;

Compound of Formula (II): A = H; B = H; X and Y taken together with the carbon atom they are attached to = C=N-Ac; R_x = H and R₄" = H;

Compound of Formula (II): A = C(O)-OH; B = H; X and Y taken together with the carbon atom they are attached to = C=N-OH; R_x = H and R₄" = H; and

10 Compound of Formula (II): A = B = H, X and Y taken together with the carbon atom they are attached to = C=O, R_x = H and R₄" = C(O)CH₃.

Definitions

The terms "C₁-C₃ alkyl," "C₁-C₆ alkyl" or "C₁-C₁₂ alkyl," as used herein, refer to
 15 saturated, straight- or branched-chain hydrocarbon radicals containing between one and three, one and twelve, or one and six carbon atoms, respectively. Examples of C₁-C₃ alkyl radicals include methyl, ethyl, propyl and isopropyl radicals; examples of C₁-C₆ alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl and *n*-hexyl radicals; and examples of C₁-C₁₂ alkyl radicals include, but are not
 20 limited to, ethyl, propyl, isopropyl, *n*-hexyl, octyl, decyl, dodecyl radicals.

The term "substituted alkyl" or "alkyl substituent" refers to an alkyl group substituted by, for example, one to four substituents, such as, halo, phenyl, substituted phenyl, heterocyclo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, cycloalkoxy, heterocylooxy, oxo, alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino,
 25 aralkylamino, cycloalkylamino, heterocycloamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl, alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl,
 30 sulfonamido (e.g. SO₂NH₂), substituted sulfonamido, nitro, cyano, carbamyl (e.g. CONH₂), substituted carbamyl (e.g. CONH alkyl, CONH aryl, CONH aralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl), alkoxycarbonyl, aryl, substituted aryl, guanidine and heterocyclos, such as, indolyl, imidazolyl, furyl,

thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl, and the like. Where, if noted above, the substituent is further substituted, it will be with halogen, alkyl, alkoxy, aryl or aralkyl.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

5 The term "alkylene" denotes a divalent group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, for example, methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, and the like.

10 The terms " C_2-C_{12} alkenyl" or " C_2-C_6 alkenyl," as used herein, denote a monovalent group derived from a hydrocarbon moiety containing from two to twelve or two to six carbon atoms having at least one carbon-carbon double bond by the removal of a single hydrogen atom. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, and the like.

15 The term "alkenylene" denotes a divalent group derived from an alkenyl group as defined previously by the removal a second hydrogen atom, containing from two to twelve carbon atoms and having at least one carbon-carbon double bond, for example, 1,2-ethenyl, 1,2-propylene, 1,4- butenyl, 1-methyl-but-1-en-1,4-yl, and the like.

20 The terms " C_2-C_{12} alkynyl" or " C_2-C_6 alkynyl," as used herein, denote a monovalent group derived from a hydrocarbon moiety containing from two to twelve or two to six carbon atoms having at least one carbon-carbon triple bond by the removal of two hydrogen atoms. Representative alkynyl groups include, but are not limited to, for example, ethynyl, 1-propynyl, 1-butyne, and the like.

The terms "halo" and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

25 The term "haloalkyl" denotes an alkyl group, as defined above, having one, two or three halogen atoms attached thereto and is exemplified by such groups as chloromethyl, bromoethyl, trifluoromethyl, and the like.

30 The term "aryl," as used herein, refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, substituted loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, acylamino, cyano, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylene" denotes a divalent group derived from an aryl moiety as defined previously by the removal of a second hydrogen atom. Arylene groups include, for example, 1, 2-phenyl, 1, 3-phenyl, 1, 4-phenyl, 1, 2-naphthyl, 1, 4-naphthyl, 1, 6-naphthyl, and the like.

5 The term "substituted aryl," as used herein, refers to an aryl group, as defined herein, substituted by independent replacement of one, two or three of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO₂, CN, C(O)-C₁-C₆-alkyl, C(O)-aryl, C(O)-heteroaryl, CO₂-alkyl, CO₂-aryl, CO₂-heteroaryl, CONH₂, CONH-C₁-C₆-alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-C₁-C₆-alkyl, OC(O)-aryl, OC(O)-heteroaryl, OCO₂-alkyl, OCO₂-aryl, 10 OCO₂-heteroaryl, OCONH₂, OCONH-C₁-C₆-alkyl, OCONH-aryl, OCONH-heteroaryl, NHC(O)-C₁-C₆-alkyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHCO₂-alkyl, NHCO₂-aryl, NHCO₂-heteroaryl, NHCONH₂, NHCONH-C₁-C₆-alkyl, NHCONH-aryl, NHCONH-heteroaryl, SO₂-C₁-C₆-alkyl, SO₂-aryl, SO₂-heteroaryl, SO₂NH₂, SO₂NH-C₁-C₆-alkyl, SO₂NH-aryl, SO₂NH-heteroaryl, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, CF₃, CH₂CF₃, CHCl₂, 15 CH₂OH, CH₂CH₂OH, CH₂NH₂, CH₂SO₂CH₃, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C₁-C₆-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C₁-C₃-alkylamino, thio, aryl-thio, heteroarylthio, benzyl-thio, C₁-C₆-alkyl-thio, or methylthiomethyl.

20 The term "substituted arylene" as used herein refers to an arylene group as defined herein substituted by independent replacement of one, two or three of the hydrogen atoms thereon with halo, hydroxyl, cyano, C₁-C₃-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkoxy substituted with aryl, haloalkyl, thioalkoxy, amino, alkylamino, dialkylamino, acylamino, mercapto, nitro, carboxaldehyde, carboxyl, alkoxycarbonyl and carboxamide. In addition, any one substituent may be an aryl, heteroaryl, or heterocycloalkyl group. Also, substituted aryl 25 groups include tetrafluorophenyl and pentafluorophenyl.

30 The term "heteroaryl," as used herein, refers to a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from S, O and N; zero, one or two ring atoms are additional heteroatoms independently selected from S, O and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms, such as, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and the like.

The term "heteroarylene" denotes a divalent group derived from a heteroaryl moiety as defined previously by the removal a second hydrogen atom. Heteroarylene groups include, for example, 2,3-pyridyl, 2,4-pyridyl, 2,6-pyridyl, 2,3-quinolyl, 2,4-quinolyl, 2,6-quinolyl, 1,4-isoquinolyl, 1,6-isoquinolyl, and the like.

5 The term "substituted heteroaryl," as used herein, refers to a heteroaryl group as defined herein, substituted by independent replacement of one, two or three of the hydrogen atoms thereon with F, Cl, Br, I, OH, NO₂, CN, C(O)-C₁-C₆-alkyl, C(O)-aryl, C(O)-heteroaryl, CO₂-alkyl, CO₂-aryl, CO₂-heteroaryl, CONH₂, CONH-C₁-C₆-alkyl, CONH-aryl, CONH-heteroaryl, OC(O)-C₁-C₆-alkyl, OC(O)-aryl, OC(O)-heteroaryl, OCO₂-alkyl,
 10 OCO₂-aryl, OCO₂-heteroaryl, OCONH₂, OCONH-C₁-C₆-alkyl, OCONH-aryl, OCONH-heteroaryl, NHC(O)-C₁-C₆-alkyl, NHC(O)-aryl, NHC(O)-heteroaryl, NHCO₂-alkyl, NHCO₂-aryl, NHCO₂-heteroaryl, NHCONH₂, NHCONH-C₁-C₆-alkyl, NHCONH-aryl, NHCONH-heteroaryl, SO₂-C₁-C₆-alkyl, SO₂-aryl, SO₂-heteroaryl, SO₂NH₂, SO₂NH-C₁-C₆-alkyl, SO₂NH-aryl, SO₂NH-heteroaryl, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, CF₃, CH₂CF₃,
 15 CHCl₂, CH₂OH, CH₂CH₂OH, CH₂NH₂, CH₂SO₂CH₃, aryl, heteroaryl, benzyl, benzyloxy, aryloxy, heteroaryloxy, C₁-C₆-alkoxy, methoxymethoxy, methoxyethoxy, amino, benzylamino, arylamino, heteroarylamino, C₁-C₃-alkyl-amino, thio, aryl-thio, heteroarylthio, benzyl-thio, C₁-C₆-alkyl-thio, or methylthiomethyl.

 The term "substituted heteroarylene," as used herein, refers to a heteroarylene group
 20 as defined herein substituted by independent replacement of one, two or three, of the hydrogen atoms thereon with Cl, Br, F, I, OH, CN, C₁-C₃-alkyl, C₁-C₆-alkoxy, C₁-C₆-alkoxy substituted with aryl, haloalkyl, thioalkoxy, amino, alkylamino, dialkylamino, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl, and the like. In addition, any one substituent may be an aryl, heteroaryl, or heterocycloalkyl group.

25 The term "C₃-C₁₂-cycloalkyl" or "cycloalkyl," as used herein, refers to a monovalent group derived from a monocyclic or bicyclic saturated carbocyclic ring compound by the removal of a single hydrogen atom. Examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl.

30 The term "heterocycloalkyl," as used herein, refers to a non-aromatic 3- to 7-membered ring or a bi- or tri-cyclic group comprising fused six-membered rings having between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, wherein (i) each 5-membered ring has 0 to 1 double bonds and each 6-membered

ring has 0 to 2 double bonds, (ii) the nitrogen and sulfur heteroatoms may optionally be oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to a benzene ring. Representative heterocycles include, but are not limited to, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

The term "cycloalkylene" refers to a divalent cycloalkyl moiety with two hydrogen atoms removed--one each from two adjacent carbon atoms--derived by the removal of the two hydrogen atoms from a cycloalkyl group as previously defined that is optionally substituted, or from saturated cyclic hydrocarbon ring systems, preferably containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused to an unsaturated C3-C7 carbocyclic ring. Exemplary cycloalkyl groups from which the cycloalkylene groups can be derived include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, and adamantly. Exemplary substituents include one or more alkyl, aryl, heteroaryl groups as described above, or one or more groups described above as alkyl substituents.

The term "cycloalkenylene" refers to a divalent cycloalkenyl moiety with two hydrogen atoms removed--one each from two adjacent carbon atoms--derived by the removal of the two hydrogen atoms from a cycloalkenyl group that contains one or more unsaturated double bonds optionally substituted, or from unsaturated cyclic ring systems, preferably containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C3-C7 carbocyclic ring. Exemplary cycloalkenyl groups from which the cycloalkenylene groups can be derived include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and the like. Exemplary substituents include one or more alkyl, aryl, heteroaryl groups as described above, or one or more groups described above as alkyl substituents.

The term "heterocycloalkylene" refers to a divalent heterocyclic moiety with two hydrogen atoms removed--one each from two adjacent carbon atoms--derived by the removal of the two hydrogen atoms from a heterocycloalkyl group previously defined that is optionally substituted, or from a fully saturated or unsaturated, nonaromatic cyclic group which may be further fused with or substituted with an aromatic ring, for example, which is a 3 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3

heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom. Exemplary monocyclic heterocyclic groups from which the heterocycloalkylene groups can be derived include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolidinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl, pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranlyl, tetrahydrothiopyranlyl, tetrahydrothiopyranlyl sulfone, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1, 1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiranyl, triazinyl, and triazolyl, and the like. Exemplary bicyclic heterocyclic groups from which the heterocycloalkylene groups can be derived include benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranlyl, indoliziny, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxaliny, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl, (such as 3,4-dihydro-4-oxo-quinazolinyl), benzisothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, benzothiopyranlyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranlyl, dihydrobenzothiopyranlyl sulfone, dihydrobenzopyranlyl, indolinyl, isochromanlyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl, purinyl, pyridopyridyl, quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl, and the like. Exemplary substituents include one or more alkyl, aryl or heteroaryl groups as described above or one or more groups described above as alkyl substituents. Also included are smaller heterocyclics, such as epoxides and aziridines.

The term "heteroatoms" includes, but is not limited to, oxygen, sulfur and nitrogen.

The term "C₁-C₆ alkoxy," as used herein, refers to a C₁-C₆ alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom. Examples of C₁-C₆-alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *tert*-butoxy, neopentoxy and *n*-hexoxy.

The term "C₁-C₃-alkyl-amino," as used herein, refers to one or two C₁-C₃-alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. Examples of C₁-C₃-alkyl-amino include, but are not limited to methylamino, dimethylamino, ethylamino, diethylamino, and propylamino.

5 The term "alkylamino" refers to a group having the structure -NH (C₁-C₁₂ alkyl) where C₁-C₁₂ alkyl is as previously defined.

 The term "dialkylamino" refers to a group having the structure -N (C₁-C₁₂ alkyl) (C₁-C₁₂ alkyl), where C₁-C₁₂ alkyl is as previously defined. Examples of dialkylamino include, but are not limited to, dimethylamino, diethylamino,
10 methylethylamino, piperidino, and the like.

 The term "alkoxycarbonyl" represents an ester group, i.e. an alkoxy group, attached to the parent molecular moiety through a carbonyl group such as methoxycarbonyl, ethoxycarbonyl, and the like.

 The term "carboxaldehyde," as used herein, refers to a group of formula -CHO.

15 The term "carboxy," as used herein, refers to a group of formula -COOH.

 The term "carboxamide," as used herein, refers to a group of formula -C(O)NH(C₁-C₁₂ alkyl) or -C(O)N(C₁-C₁₂ alkyl) (C₁-C₁₂ alkyl).

 "Hydroxy protecting group," as used herein, refers to an easily removable group such as is known in the art to protect a hydroxy group against undesirable reaction during
20 synthetic procedures and to be selectively removable. The use of hydroxy-protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, *cf.* for example, T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of hydroxy protecting groups include, but are not
25 limited to, methylthiomethyl, *tert*-dimethylsilyl, *tert*-butyldiphenylsilyl, acyl substituted with an aromatic group and the like.

 The term "protected hydroxy" refers to a hydroxy group protected with a hydroxy protecting group, as defined above, including benzoyl, acetyl, trimethylsilyl, triethylsilyl, methoxymethyl groups, for example.

30 "Amino protecting group," as used herein, refers to an easily removable group such as is known in the art to protect an amino group against undesirable reaction during synthetic procedures and to be selectively removable. The use of amino-protecting groups is well known in the art for protecting groups against undesirable reactions during a

synthetic procedure and many such protecting groups are known, *cf.* for example, T.H. Greene and P.G. M. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, New York (1999). Examples of amino protecting groups include, but are not limited to, 9-fluorenylmethyl carbamate, benzylcarbonate, tert-butylcarbonate, benzyl, p-toluene sulfonyl, acyl and the like.

The term "aprotic solvent," as used herein, refers to a solvent that is relatively inert to proton activity, i.e., not acting as a proton-donor. Examples include, but are not limited to, hydrocarbons, such as hexane and toluene, for example, halogenated hydrocarbons, such as, for example, methylene chloride, ethylene chloride, chloroform, and the like, heterocyclic compounds, such as, for example, tetrahydrofuran and N-methylpyrrolidinone, and ethers such as diethyl ether, bis-methoxymethyl ether. Such compounds are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of aprotic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

The term "protic solvent" or "protogenic organic solvent," as used herein, refers to a solvent that tends to provide protons, such as an alcohol, for example, methanol, ethanol, propanol, isopropanol, butanol, t-butanol, and the like. Such solvents are well known to those skilled in the art, and it will be obvious to those skilled in the art that individual solvents or mixtures thereof may be preferred for specific compounds and reaction conditions, depending upon such factors as the solubility of reagents, reactivity of reagents and preferred temperature ranges, for example. Further discussions of protogenic solvents may be found in organic chemistry textbooks or in specialized monographs, for example: Organic Solvents Physical Properties and Methods of Purification, 4th ed., edited by John A. Riddick *et al.*, Vol. II, in the Techniques of Chemistry Series, John Wiley & Sons, NY, 1986.

Numerous asymmetric centers may exist in the compounds of the present invention. Except where otherwise noted, the present invention contemplates the various stereoisomers and mixtures thereof. Accordingly, whenever a bond is represented by a

wavy line, it is intended that a mixture of stereo-orientations or an individual isomer of assigned or unassigned orientation may be present.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977), incorporated herein by reference. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety

advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

5 In addition, zwitterions ("inner salts") may be formed from the compounds of the present invention.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a
10 reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present invention. The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussions is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems, Vol. 14 of the ACS
15 Symposium Series, and in Edward B. Roche, ed., "Bioreversible Carriers in Drug Design", American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- 20 a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985) and *Methods in Enzymology*, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);
- b) *A Textbook of Drug Design and Development*, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H.
25 Bundgaard, p. 113-191 (1991);
- c) H. Bundgaard, et al., *Advanced Drug Delivery Reviews*, 8, 1-38 (1992);
- d) H. Bundgaard, et al., *Journal of Pharmaceutical Sciences*, 77, 285 (1998);
- and
- e) N. Kakeya, et al., *Chem Phar Bull*, 32, 692 (1984).

30 It should further be understood that solvates (e.g., hydrates) of the compounds of the present invention are also within the scope of the present invention. Methods of solvation are generally known in the art.

Antibacterial Activity

Susceptibility tests can be used to quantitatively measure the *in vitro* activity of an antimicrobial agent against a given bacterial isolate. Compounds were tested for *in vitro* antibacterial activity by a micro-dilution method. Minimal Inhibitory Concentration (MIC) was determined in 96 well microtiter plates utilizing the appropriate Mueller Hinton Broth medium (CAMHB) for the observed bacterial isolates. Antimicrobial agents were serially diluted (2-fold) in DMSO to produce a concentration range from about 64 µg/ml to about 0.03 µg/ml. The diluted compounds (2 µl/well) were then transferred into sterile, uninoculated CAMHB (0.2 mL) by use of a 96 fixed tip-pipetting station. The inoculum for each bacterial strain was standardized to 5×10^5 CFU/mL by optical comparison to a 0.5 McFarland turbidity standard. The plates were inoculated with 10 µl/well of adjusted bacterial inoculum. The 96 well plates were covered and incubated at $35 \pm 2^\circ\text{C}$ for 24 hours in ambient air environment. Following incubation, plate wells were visually examined by Optical Density measurement for the presence of growth (turbidity). The lowest concentration of an antimicrobial agent at which no visible growth occurs was defined as the MIC. The compounds of the invention generally demonstrated an MIC in the range from about 64 µg/ml to about 0.03 µg/ml.

All *in vitro* testing follows the guidelines described in the Approved Standards M7-A4 protocol, published by the National Committee for Clinical Laboratory Standards (NCCLS).

Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum

hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate. Coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants
5 can also be present in the composition, according to the judgment of the formulator. The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

Liquid dosage forms for oral administration include pharmaceutically acceptable
10 emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in
15 particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous
20 suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable
25 vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

30 The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microcapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known

in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and
5 waxes.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more
10 excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is
15 normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract,
20 optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a
25 pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones,
30 bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and

polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the
5 compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

According to the methods of treatment of the present invention, bacterial infections are treated or prevented in a patient such as a human or other animals by administering to
10 the patient a therapeutically effective amount of a compound of the invention, in such amounts and for such time as is necessary to achieve the desired result. By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to treat bacterial infections, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily
15 usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body
20 weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or
25 other animal in single or in divided doses can be in amounts, for example, from 0.01 to 50 mg/kg body weight or more usually from 0.1 to 25 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof to make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment of from about 10 mg to about 1000 mg of the
30 compound(s) of this invention per day in single or multiple doses.

The pharmaceutical compositions of this invention can be administered to fish by blending them in the fish feed to be administered orally or may be dissolved in water in which sick fish are placed to swim around (a method using a so-called "medicated bath"). The dosage for the treatment of fish differs depending upon the purpose of administration

(prevention or cure of disease) and type, size and extent of infection of the fish to be treated. Generally, a dosage of 5 – 1000 mg, preferably 20 – 100 mg, per kg of body weight of fish may be administered per day, either at one time or divided into several times. It will be recognized that the above-specified dosage is only a general range which may be
5 reduced or increased depending upon the age, body weight, condition of disease, etc. of the fish.

Abbreviations

Abbreviations which have been used in the description of the schemes and the
10 examples are as follows: AIBN for azobisisobutyronitrile; Boc for tert-Butoxycarbonyl; BSA for bis(trimethylsilyl)acetamide; Bu₃SnH for tributyltin hydride; CDI for carbonyldiimidazole; dba for dibenzylideneacetone; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP for 4- N,N- dimethylamino-pyridine; DCC for 1,3-dicyclohexylcarbodiimide; DEAD for diethylazodicarboxylate; DMF for dimethyl
15 formamide; DMSO for dimethylsulfoxide; DPPA for diphenylphosphoryl azide; dppb for 1,4-bis(diphenylphosphino)butane; dppe for 1,2-bis(diphenylphosphino)ethane; EDC for 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; EtOAc for ethyl acetate; HMDS for 1,1,1,3,3,3-Hexamethyldisilazane; KHMDS for potassium bis(trimethylsilyl)amide; m-CPBA for meta-chloroperbenzoic acid; MeOH for methanol; MOMCl for
20 methoxymethylchloride; NaHMDS for sodium bis(trimethylsilyl)amide; NaN(TMS)₂ for sodium bis(trimethylsilyl)amide; NCS for N-Chlorosuccinimide; NMO for N-methylmorpholine N-oxide; PCC for pyridinium chlorochromate; PDC for pyridinium dichromate; Ph for phenyl; TBS for tert-butyl dimethyl silyl; TEA for triethylamine; THF for tetrahydrofuran; TPP for triphenylphosphine; TBAF for tetra-*n*-butyl ammonium
25 fluoride; TFA for trifluoroacetic acid; TMS for trimethyl silyl; TPAP for tetrapropylammonium perruthenate; Ac for acetyl and Bz for benzoyl.

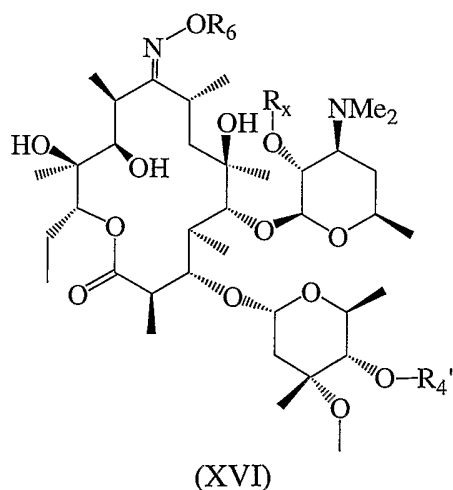
Synthetic Methods

The compounds and processes of the present invention will be better understood in
30 connection with the following synthetic schemes (schemes 1 – 12) that illustrate the methods by which the compounds of the invention may be prepared. The groups A, B, R_x, R₃, R₆, R^p, X and Y are as defined previously herein, unless otherwise noted below. As used in the schemes and examples, the group “V” taken together with the carbon atom it is

attached to is selected from the group: C=O, C=NR₃, C=N-O-R₆, C=NC(O)R₃ and C=N-O-C(R₁₆)(R₁₇)-O-R₁₈, where R₃, R₆, R₁₆, R₁₇ and R₁₈ are as previously defined herein.

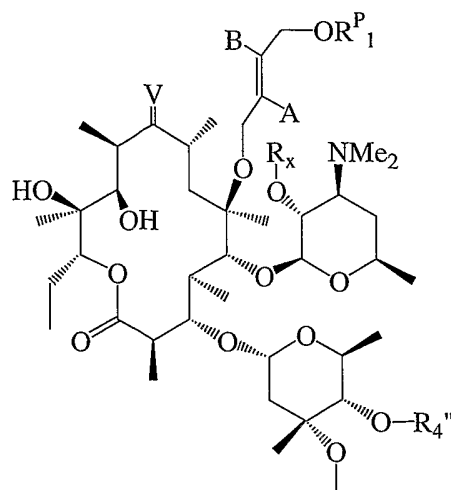
Compounds of formula (1-2) or (1-4), which are useful as the starting materials for the preparation of compounds of the present invention, may be synthesized as detailed in schemes 1 and 3 below. An erythromycin derivative (1-1) is prepared from erythromycin using the procedures described in U.S. Patents 4,990,602; 4,331,803; 4,680,386; and 4,670,549 which are incorporated herein by reference. Also incorporated by reference is European Patent Application EP 260,938. The procedures for preparing the 6,11-bridged compounds of the present invention are described in U.S. Patent Application Serial Nos. 10/144,396 and 10/144,558, filed on May 13, 2002, which are herein incorporated by reference in their entirety. The C-9 position (X, Y) can be further derivatized with suitable procedures that are well-known in the art and those mentioned in PCT publications: WO 00/62783 and WO 98/38199 as well as publications: "Synthetic Modifications of the Erythromycin A Macrolactone: Effects on Biological Activity," Lartey, P. A. and Perun, T. J., Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry*, Vol. 13, 1993, and "Recent developments in 14- and 15-membered macrolides," Chu, Daniel T. W., Section Review: Anti-infectives, *Exp. Opin. Invest. Drugs* 1995, 4(2), page 65-94, which are herein incorporated by reference in their entirety.

A preferred intermediate for the preparation of compounds represented by formula I is a compound represented by formula XVI as illustrated below:



wherein R₆ and R_x are as previously defined and R₄" is a hydroxy protecting group.

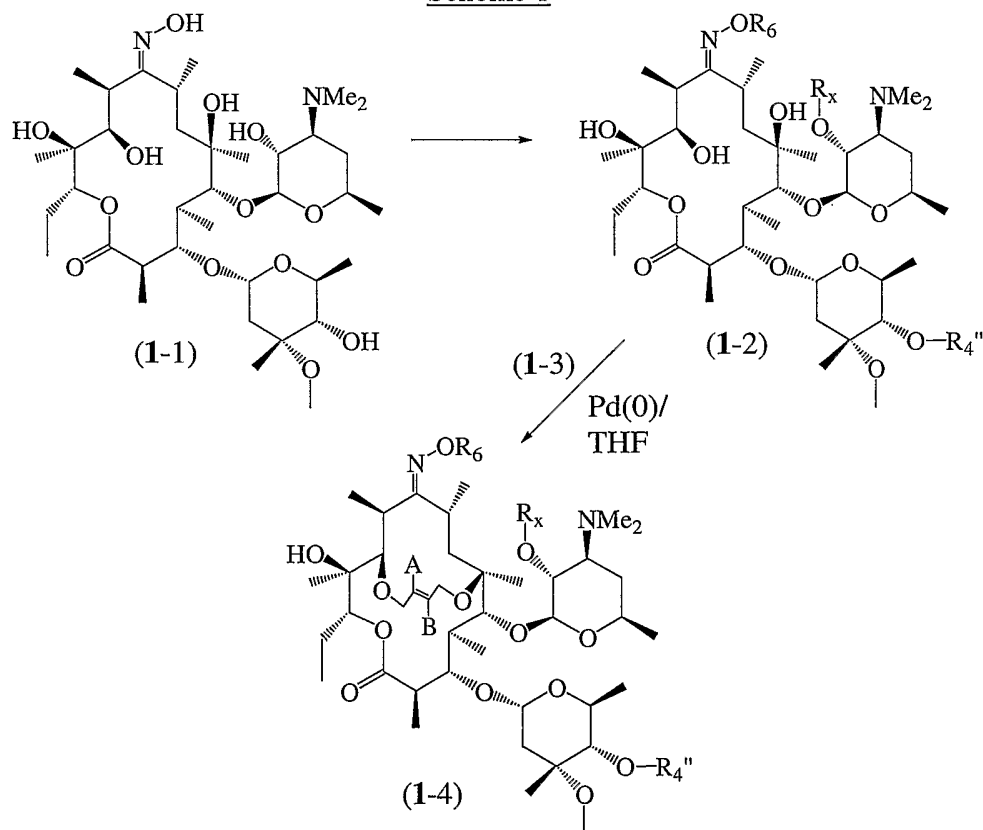
A second preferred intermediate for the preparation of compounds represented by
25 formula I is a compound represented by formula XVII as illustrated below:



(XVII)

- wherein A, B, R_x and R₄" are as previously defined; V taken together with the carbon atom it is attached to is selected from the groups: C=O, C=NR₃, C=N-O-R₆, C=NC(O)R₃ and
- 5 C=N-O-C(R₁₆)(R₁₇)-O-R₁₈, where R₃, R₆, R₁₆, R₁₇ and R₁₈ are as previously defined; and R^P₁ is H or R^P, where R^P is as previously defined.

Scheme 1



A synthetic method of the present invention, as illustrated in scheme 1, involves preparing a compound of formula (1-4) by reacting a compound of formula (1-2) with a suitable alkylating agent.

In accordance with scheme 1, the 9-keto group of the erythromycin backbone can be initially converted into an oxime by methods described in U.S. Patent No. 4,990,602, followed by the protection of the 2'- and 4''-hydroxy groups with R_x and R₄'' respectively, and if desired, the resulting oxime group can be further derivatized with R₆ to obtain the compounds of formula (1-2).

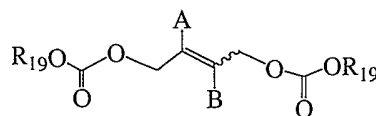
The 2'- and 4''-hydroxy groups are protected by reaction with suitable hydroxy protecting agents in an aprotic solvent. Typical hydroxy protecting reagents include, but are not limited to, acetylating agents, silylating agents, acid anhydrides, and the like. Examples of hydroxy protecting reagents are, for example, acetyl chloride, acetic anhydride, benzoyl chloride, benzoic anhydride, benzyl chloroformate, hexamethyldisilazane, and trialkylsilyl chlorides.

Examples of aprotic solvents are dichloromethane, chloroform, tetrahydrofuran, N-methylpyrrolidinone, dimethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, hexamethylphosphoric triamide, a mixture thereof or a mixture of one of these solvents with ether, tetrahydrofuran, 1,2-dimethoxyethane, 1,2-dichloroethane, acetonitrile, ethyl acetate, acetone and the like. Aprotic solvents do not adversely affect the reaction. Preferably, the solvent is selected from dichloromethane, chloroform, N, N-dimethylformamide, tetrahydrofuran, N-methylpyrrolidinone or mixtures thereof. A more thorough discussion of solvents and conditions for protecting the hydroxy group can be found in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis" 3rd ed., John Wiley & Son, Inc, 1999, which is incorporated by reference herein.

Protection of the 2'- and 4''-hydroxy groups may be accomplished sequentially or simultaneously to provide compound (1-2) where R_x and/or R₄'' can be, for example, but not limited to, acetyl, benzoyl, trimethylsilyl, and the like. Preferred protecting groups include acetyl, benzoyl, and trimethylsilyl. A particularly preferred group for protecting the hydroxy and oxime groups is the acetyl protecting group, wherein R_x = R₄'' = R₆ = Ac.

Acetylation of the hydroxy group is typically accomplished by treating the compound (1-1) with an acetylating reagent, for example, acetic anhydride or acetyl chloride.

The erythromycin derivative of formula (1-2) is then reacted with an alkylating agent of the formula:



(1-3)

where R₁₉ is C₁-C₁₂-alkyl.

The reaction is carried out in an aprotic solvent with a palladium catalyst [Pd(0) or Pd(II)] with a phosphorus ligand such as, for example, dppb, dppe, and the like, in aprotic solvents to provide compound (1-4) from about room temperature to about 100°C, preferably at elevated temperature, for example, at or above 50°C (*see* (a) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* 1989, 28, 1179; (b) Heck, *Palladium Reagents in Organic Synthesis*, Academic Press: New York, 1985, Chapter 1; (c) Tsuji, *Tetrahedron Lett.* 1992, 33, 2987; (d) Beller et al. *Angew. Chem. Int. Ed. Engl.*, 1995, 34 (17), 1848, etc.). Suitable aprotic solvents include, but are not limited to, tetrahydrofuran, N, N-dimethylformamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, 1,2-dimethoxyethane, methyl-*tert*-butyl ether, heptane, acetonitrile, isopropyl acetate and ethyl acetate. The most preferred solvents are tetrahydrofuran or toluene.

The palladium catalyst suitable in the present invention can be selected from, but not limited to, the group consisting of palladium (II) acetate, tetrakis (triphenylphosphine) palladium (0), tris(dibenzylideneacetone) dipalladium, tetradi(benzylideneacetone)dipalladium and the like. Palladium on carbon and palladium (II) halide catalysts are less preferred than other palladium catalysts for this process.

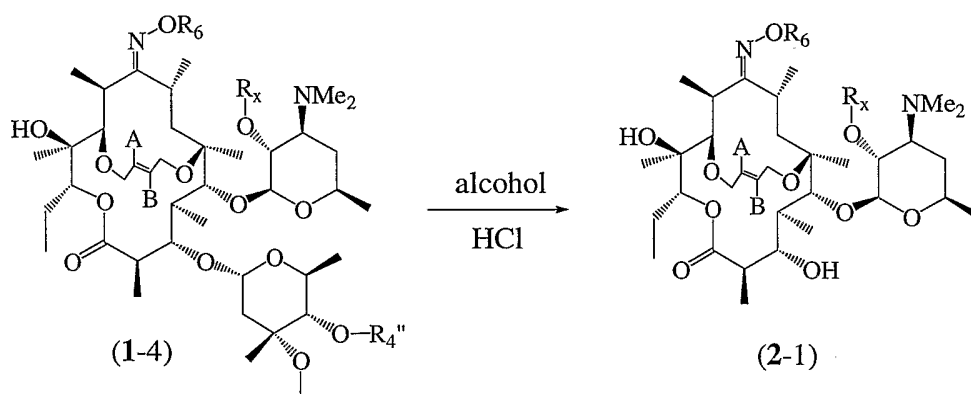
Phosphorus ligands useful in the present invention include, but are not limited to, triphenylphosphine, bis(diphenylphosphino)methane, bis(diphenylphosphino)ethane, bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, bis(diphenylphosphino)pentane, and tri(o-tolyl)phosphine, and the like.

The alkylating agents useful in the present invention are di-carbonates having the formula (1-3), as previously described. The preferred alkylating agents are those wherein R₁₉ is a *tert*-butyl, isopropyl or isobutyl group. The alkylating reagents are prepared by reaction of a di-ol with a wide variety of compounds for incorporating the di-carbonate moiety. The compounds include, but are not limited to, *tert*-butyl chloroformate, di-*tert*-butyl dicarbonate, 1-(*tert*-butoxycarbonyl) imidazole etc. The reaction is carried out in the presence of an organic or an inorganic base such as, for example, but not limited to, sodium hydride, potassium hydride, potassium *tert*-butoxide, potassium hydroxide, ammonium hydroxide, sodium carbonate, potassium carbonate, ammonium carbonate, KHMDS, DMAP, pyridine, triethylamine, and the like, in an aprotic solvent such as THF, DMSO,

DMF, dioxane, and the like, or mixtures thereof. The temperature for the reaction ranges from about -20°C to about 60°C, preferably from about -30°C to about 30°C.

The conversion of the di-ol into the di-carbonate can also be done by treating the di-ol with phosgene or triphosgene to prepare the chloroformate derivative of the di-ol. The di-chloroformate derivative is then converted into the di-carbonate by the methods described in Cotarca, L., Delogu, P., Nardelli, A., Sunijic, V, *Synthesis*, 1996, 553, incorporated by reference herein in its entirety. The reaction can be carried out in a variety of organic solvents such as dichloromethane, toluene, diethyl ether, ethyl acetate, chloroform, and the like, in the presence of a base as previously described herein. The temperature conditions can vary from about -30°C to about 60°C. The reaction takes from about 1 hour to about 12 hours, preferably from about 2 to about 6 hours, to run to completion.

Scheme 2

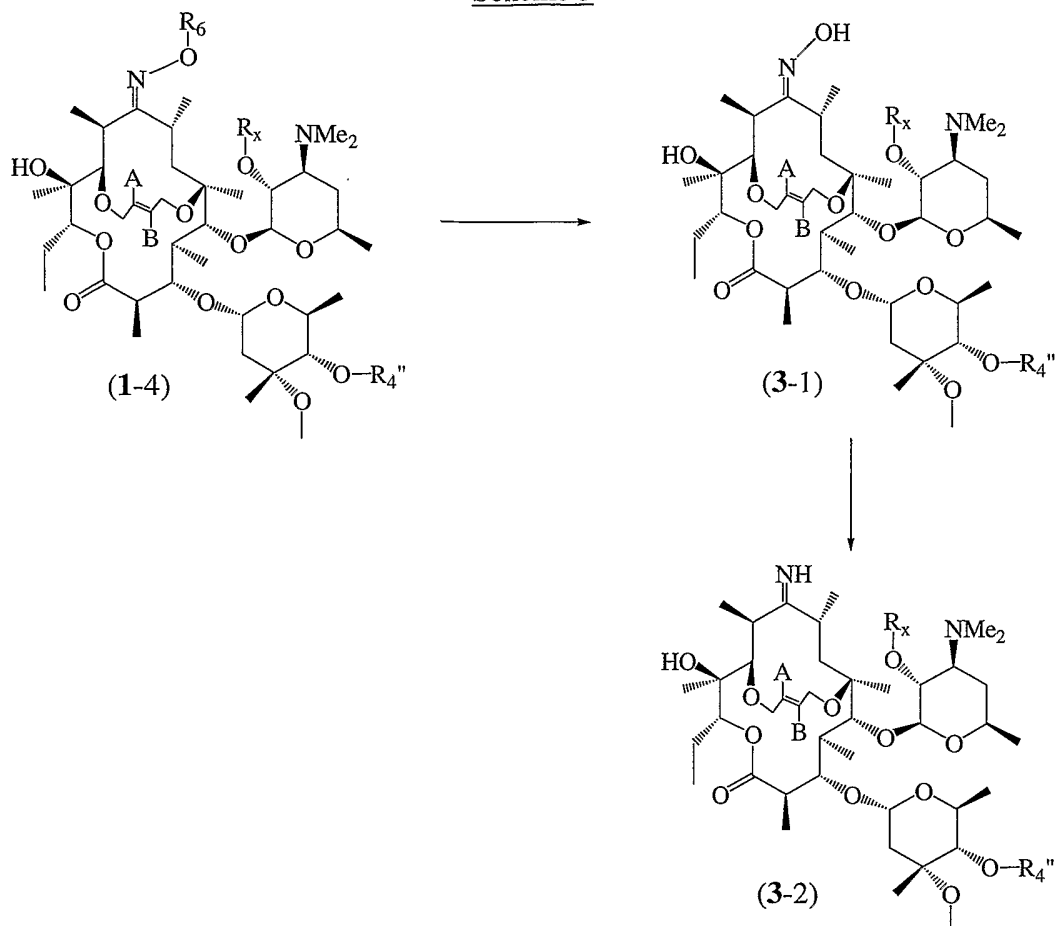


The cladinoso moiety of macrolide (1-4) is removed by mild acid hydrolysis to give compounds of formula (2-1). Representative acids include, but are not limited to, hydrochloric acid, sulfuric acid, perchloric acid, chloroacetic acid, dichloroacetic acid, trifluoroacetic acid, and the like. Suitable solvents for the reaction include, but are not limited to, methanol, ethanol, isopropanol, butanol and the like. Reaction times range from about 0.5 hours to about 24 hours. The reaction temperature is preferably from about -10°C to about 80°C. Simultaneous deprotection, of both the oxime and the 2' hydroxy group, can be accomplished similarly.

Conditions for deprotection include, but are not limited to, treating with an alcoholic solvent from room temperature to reflux, or treatment with an amine, preferably a primary amine, for example, propylamine, butylamine, and the like. Alcoholic solvents preferred for the deprotection are methanol and ethanol. A more thorough discussion of the

procedures, reagents and conditions for removing protecting groups is described in the literature, for example, by T.W. Greene and P.G.M. Wuts in "Protective Groups in Organic Synthesis" 3rd ed., John Wiley & Son, Inc, 1999, which is incorporated by reference herein.

Scheme 3



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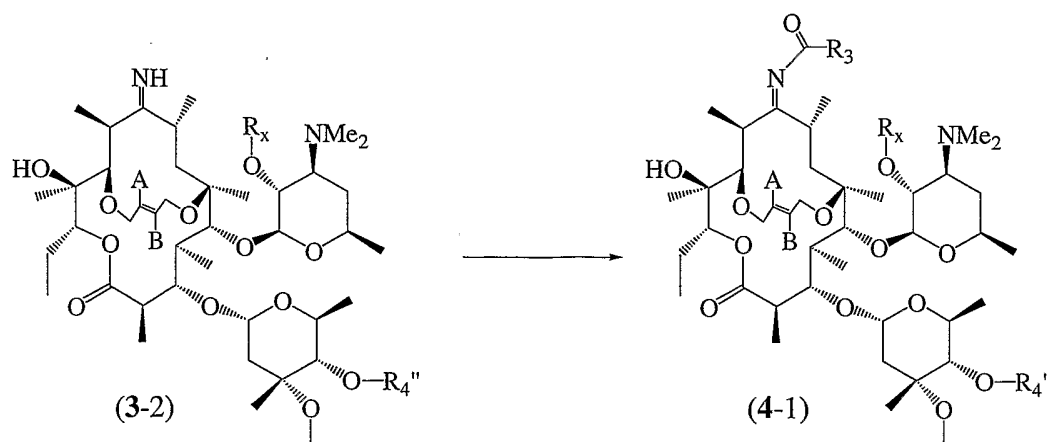
Compounds of formula (1-4) where R₆ is an acetyl group can be converted into the corresponding imine as outlined in Scheme 3. Selective deprotection of the oxime is typically accomplished via alkaline hydrolysis in protic solvents. Representative bases include lithium hydroxide, sodium hydroxide, potassium hydroxide, and the like. Solvents which are suitable include, but are not limited to, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, isopropanol, ethanol, butanol, water and mixtures thereof. The reaction temperature is preferably 0° to 35° C, and reaction time is preferably 0.5 to 24 hours.

Deoxygenation of compounds of formula (1-4) where R₆ is H can be done under reducing conditions to give the macrocyclic imine of formula (3-2). Many reducing agents can be used to effect this transformation including, but not limited to, lithium aluminum hydride, titanium trichloride, sodium cyanoborohydride, borane, sodium nitrite, sulfur oxides such as, for example, sodium pyrosulfate, sodium thiosulfate, sodium sulfate,

sodium sulfite, sodium hydrogensulfite, sodium metabisulfite, sodium dithionate, potassium thiosulfate, potassium metabisulfite, and the like (*also see*, (a) Greene (*op. cit.*); (b) J. March, *Advanced Organic Chemistry*, 4th ed., Wiley & Son, Inc., 1992, 9-51, and references therein). For example, when appropriate the reaction is carried out under acidic
5 conditions in protic solvents. Representative acids include, but are not limited to, acetic acid, citric acid, oxalic acid, tartaric acid, formic acid, dilute hydrochloric acid, dilute phosphoric acid, dilute sulfuric acid, and the like. Suitable protic solvents include, but are not limited to, mixtures of water and methanol, ethanol, isopropanol, butanol etc. The reaction is carried out at a temperature from about room temperature to about 110 °C, for
10 about 1 to about 24 hours.

An example of a method for the reduction of oximes to the corresponding imine uses a sulfite reducing agent such as sodium hydrogensulfite or titanium trichloride, under acidic conditions in protic solvents. Representative acids that may be used include, but are not limited to, acetic acid, formic acid, dilute hydrochloric acid, dilute phosphoric acid,
15 dilute sulfuric acid, and the like. Suitable protic solvents include, but are not limited to, mixtures of water and methanol, ethanol, isopropanol, or butanol. The reaction is typically carried out from about 25 °C to about 110 °C, preferably for about 1 to about 10 hours.

Scheme 4



5 Another method of the present invention, as illustrated in Scheme 4, involves a procedure for the acylation of imines of the formula (3-2). The imine in the 9 position of compounds of formula (3-2) can be acylated with an acylating agent such as, for example, R₃C(O)T, where T is a halide or -OH, or (R₃C(O))₂O, where R₃ is as previously defined using standard acylating conditions to give compounds of formula (4-1). For example,

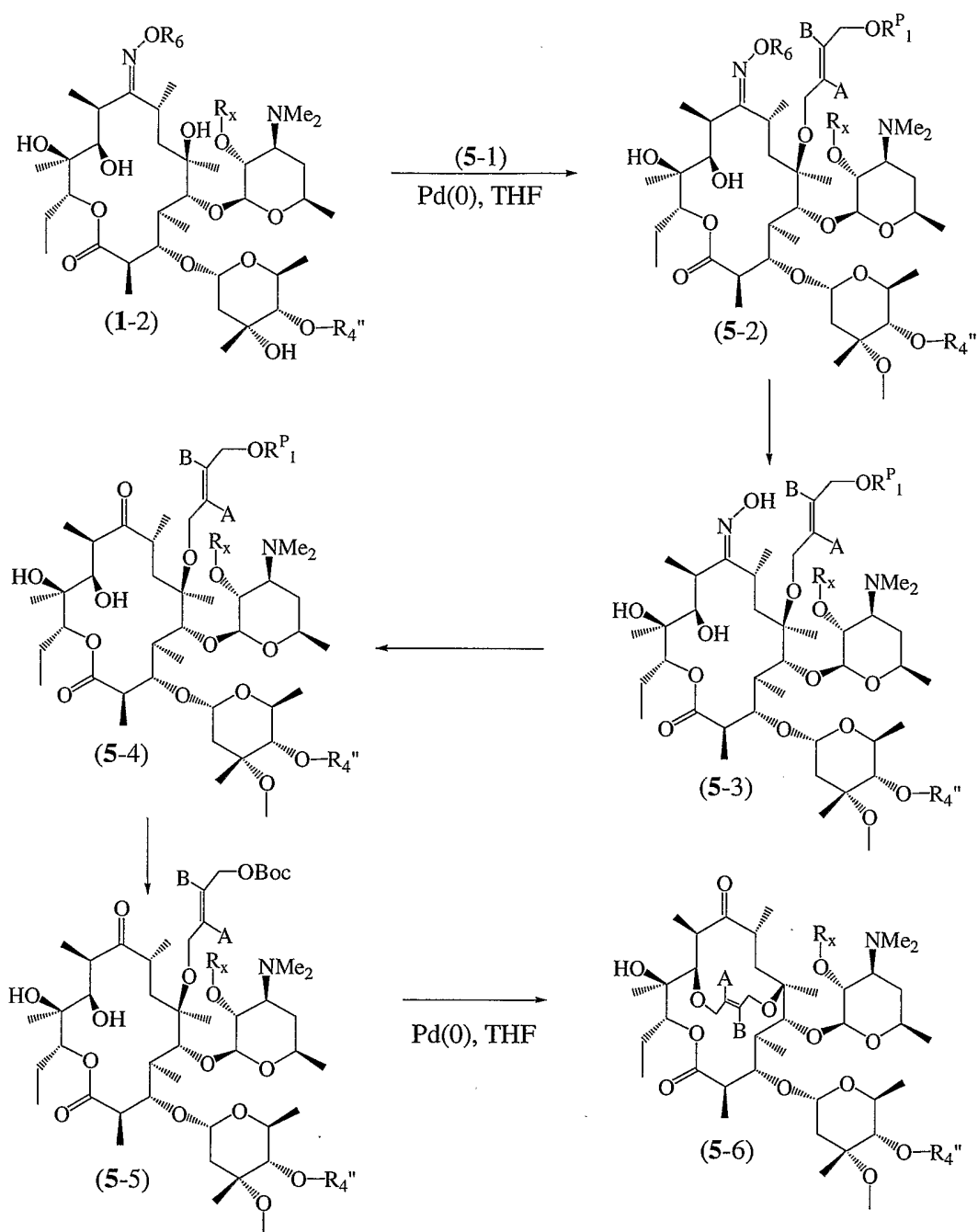
10 imines of formula (3-2) can be acylated under basic conditions using a suitable acylating agent in an aprotic solvent, with or without an activation agent. Typical acylating agents include, but are not limited to, acetyl chloride, acetic anhydride, benzoyl chloride, benzoic anhydride, benzyl chloroformate, and the like. Examples of activation agents for acids include, but are not limited to, DCC, EDC, 1-(3-dimethylaminopropyl)-3-

15 ethylcarbodiimide hydrochloride, etc.

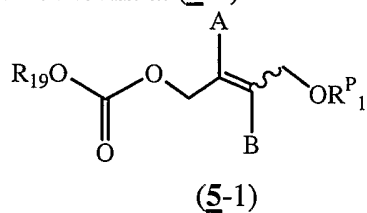
Typical bases useful in acylation reactions include, but are not limited to, pyridine, DMAP, triethylamine, diisopropyl ethylamine, N-methyl morpholine, N-methyl pyrrolidine, 2,6-lutidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, and the like (*see*, T.W. Greene and P.G.M. Wuts in "Protective Groups in Organic Synthesis" 3rd ed., John Wiley & Son, Inc, 1999, and references therein). Compounds of formula (2-3) can be further

20 deprotected as described in scheme 1 to obtain the 2' free hydroxy group and the 9-position oxime.

Scheme 5



Stepwise formation of the 6,11-4-carbon bridged macrolides is also possible as outlined in scheme 5. In a similar manner as previously described, the procedure involves reacting a compound of formula (1-2) with a suitable alkylating agent. As before, the erythromycin derivative of formula (1-2) is reacted with an alkylating agent of the formula:



where R₁₉ is C₁-C₁₂-alkyl and A and B are as previously defined and R^P₁ is H or R^P where R^P is as previously defined.

As discussed previously in scheme 1, compounds of formula (1-2) may be converted to compounds of formula (5-2) using a palladium catalyst with a phosphorous ligand in an aprotic solvent, preferably at elevated temperature, more preferably at or above 50 °C. The preferred solvents are tetrahydrofuran and toluene.

The alkylating agents useful in the process of the invention are mixed silyl ether carbonates. Generally, the alkylating agents have the formula (5-1), as previously described. The preferred alkylating agents are those wherein R₁₉ is *tert*-butyl, isopropyl or isobutyl and R^P is *tert*-butyl dimethyl silyl, triisopropyl silyl, *tert*-butyl diphenyl silyl or the like.

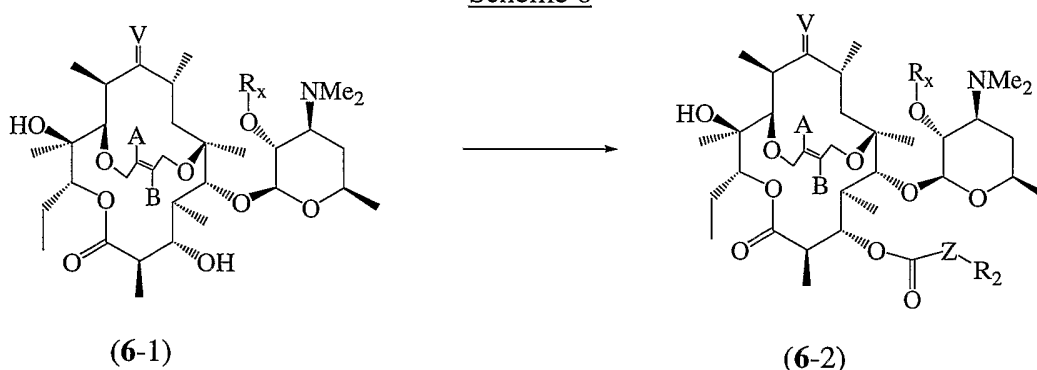
The alkylating reagents of formula (5-1) are prepared by reaction of a diol sequentially with a wide variety of compounds for incorporating the carbonate moiety, followed by a wide variety of compounds for incorporating the silyl moiety. Alkylating reagents include, but are not limited to, *tert*-butyl chloroformate, di-*tert*-butyl dicarbonate, and 1-(*tert*-butoxycarbonyl)imidazole; where as silylating reagents include, but are not limited to *tert*-butyl dimethyl silyl chloride, *tert*-butyl dimethyl silyl triflate, *tert*-butyl dimethyl silyl cyanide, and *tert*-butyl dimethyl silyl imidazole. Both reactions are carried out in the presence of an organic or an inorganic base as previously described in scheme 1. The temperature of the reactions varies from about -30°C to about 60°C. Preferably, the alkylating reagent is di-*tert*-butyl dicarbonate and the silylating reagent is *tert*-butyl dimethyl silyl chloride.

The free oxime (5-3) is prepared using essentially the same procedure as for the deprotection of oxime (1-4) to (3-1) where R₆ is acetyl in scheme 1.

Reduction of oximes of formula (5-3) to the corresponding ketone compounds of formula (5-4) may be done by, for example, but not limited to, using a sulfite reducing agent, such as sodium hydrogensulfite, under acidic conditions, typically in protic solvents, as previously described for the reduction of oximes of formula (3-1) to compounds of formula (3-2). Representative acids include, but are not limited to, acetic acid, formic acid, dilute hydrochloric acid, dilute phosphoric acid, dilute sulfuric acid, and the like. Suitable protic solvents include, but are not limited to, mixtures of water and methanol, ethanol, isopropanol, or butanol. The reaction is typically carried out at a temperature from about 50 °C to about 110 °C, preferably for about 1 to about 10 hours.

When the R^P_1 group is R^P (i.e., a hydroxy protecting group) in a compound of formula (5-4) then the hydroxy protecting group is removed using appropriate conditions. For example, when the protecting group is a silyl group, TBAF, hydrofluoric acid or trifluoroacetic acid may be used (*see*, T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis* 3rd ed., John Wiley & Son, Inc, 1999). The resulting primary hydroxy group (where $R^P_1 = H$) is converted to the corresponding *tert*-butyl carbonate by standard methods known in the art, followed by alkylation of the 11-hydroxy group using a palladium (0) catalyst as previously described in scheme 1, to form compounds of formula (5-6).

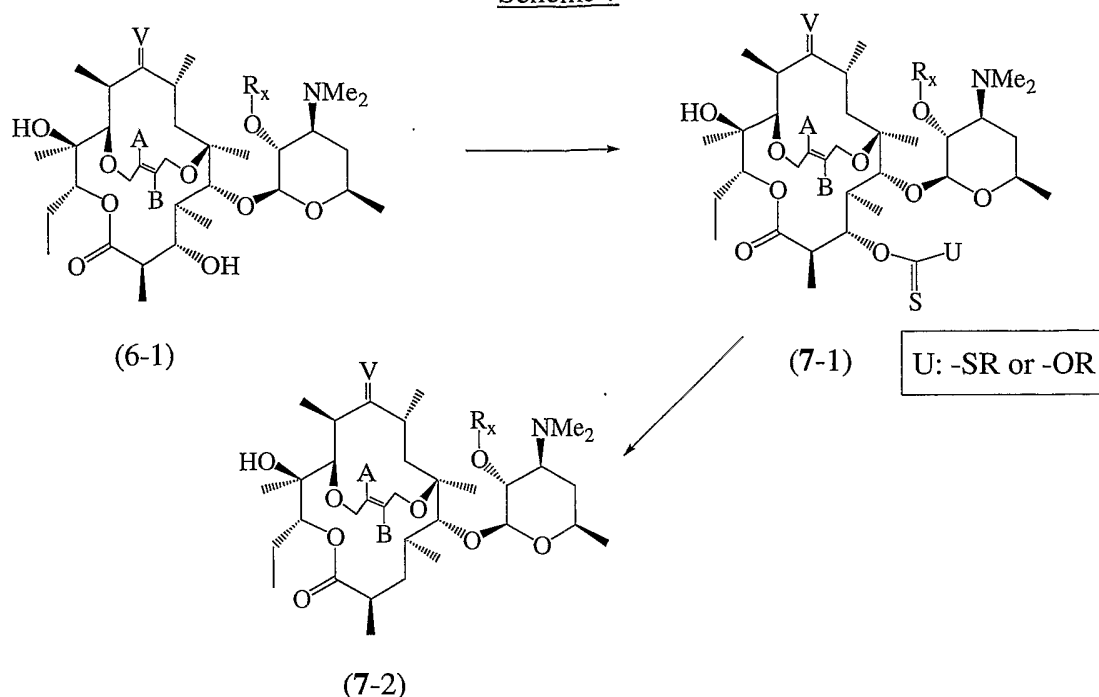
Scheme 6



Scheme 6 illustrates a procedure for the acylation of the C-3 hydroxy group of compounds of formula (6-1). The C-3 hydroxy group is acylated under basic conditions using a suitable acylating agent to introduce the acyl group of the formula -C(O)-Z-R₂, where Z is O, N, S or -(CH₂)_t, where t = 0 to 4 and R₂ is as previously described, in an aprotic solvent as previously described for acylating compounds of formula (3-2). Typical acylating agents include, but are not limited to, acid halides, acid anhydrides, free acids and chloroformates. Typical bases include, but are not limited to, pyridine, DMAP, triethylamine, diisopropyl ethylamine, N-methyl morpholine, N-methyl pyrrolidine, 2, 6-lutidine, 1, 8-diazabicyclo[5.4.0]undec-7-ene. (*See*, T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis* 3rd ed., John Wiley & Son, Inc, 1999, and references therein).

Alternately, in compounds of formula (6-1) the C-3 hydroxy group may be further derivatized to form, for example, ethers, esters, sulfonates, and the like, using methods well known in the art (*see*, for example, J. March, *Advanced Organic Chemistry* 4th ed., Wiley & Son, Inc., 1992; and the references therein).

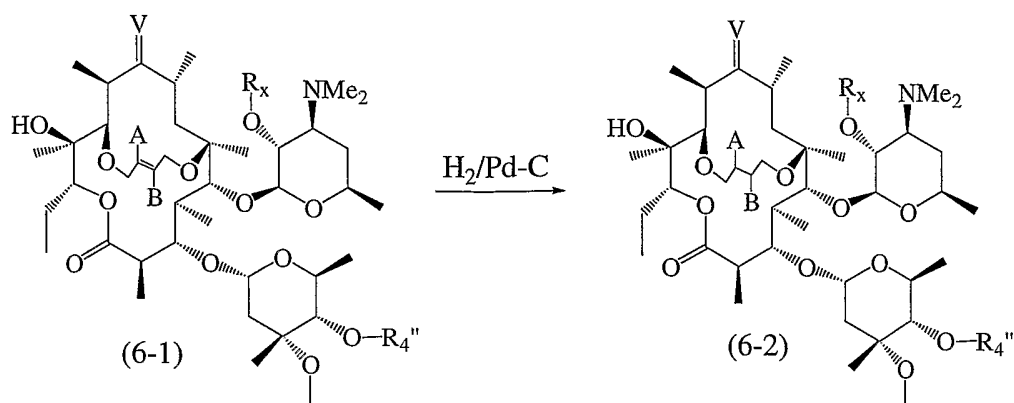
Scheme 7



Another method of the present invention, as illustrated in Scheme 7, involves synthesis of the C-3 deoxygenated macrolide (7-2) which can be accomplished via the two step procedure shown above. In the first step, the xanthate or thiocarbonate of formula (7-1) is formed by the reaction of alcohol of formula (6-1) with the appropriate thiocarbonyl compound. These reactions are typically run in a polar aprotic solvent, preferably tetrahydrofuran, acetonitrile, N,N-dimethylformamide, and the like. Formation of the xanthate can be accomplished, for example, by reaction of the alcohol (6-1) with, for example, but not limited to, carbondisulfide followed by methyl iodide, or a dithiocarbonyl imidazole etc. The thiocarbonate can be prepared by the reaction of the alcohol with for example, but not limited to, thiocarbonyldimidazole followed by methanol, ethanol or the like, or a thiochloroformate etc. One skilled in the art will appreciate that other reagents and conditions exist to perform these transformations and that the examples above are for illustrative purposes only and do not limit the scope of this invention.

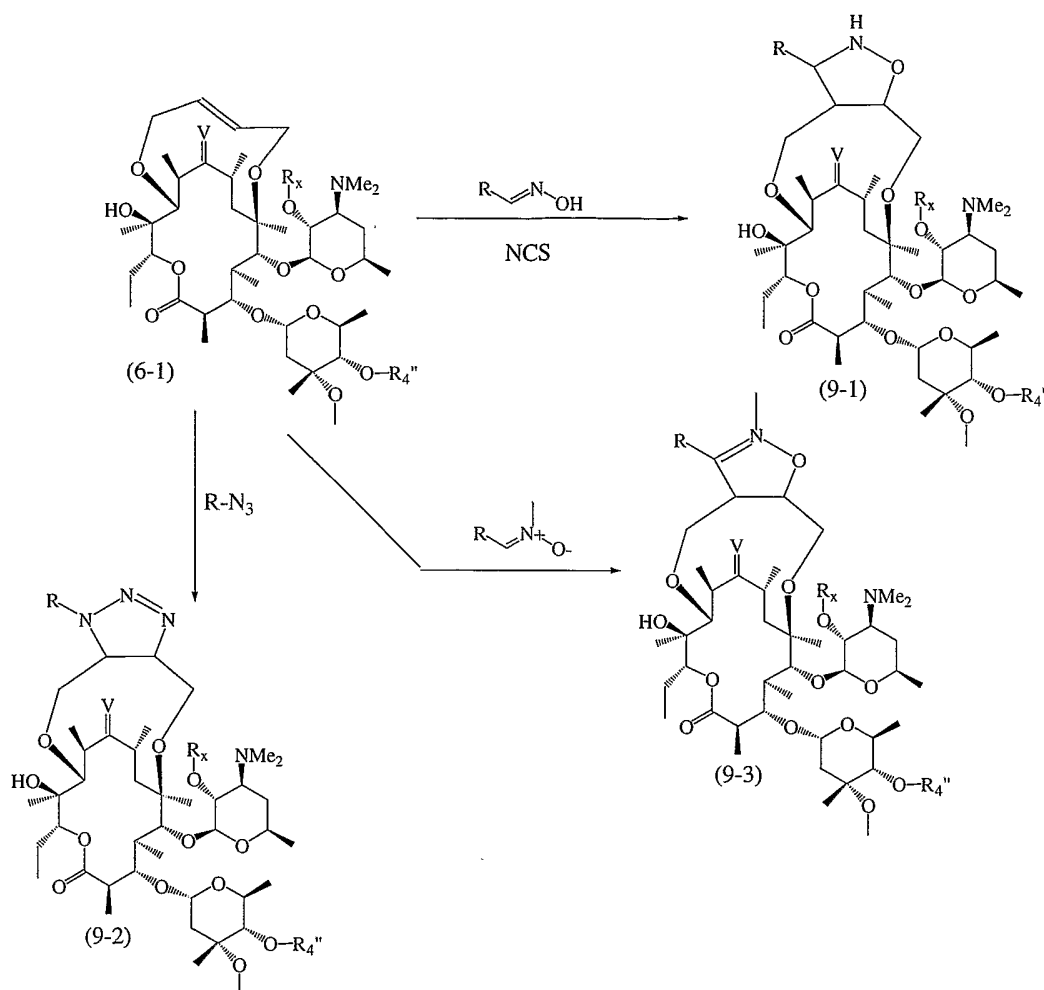
In the second step, the thiocarbonate or xanthate of formula (7-1) is converted to compound (7-2). Most typically this is done under radical conditions using, for example, a silyl hydride such as SiH(TMS)₃, SiH₂Ph₂ or the like, a tin hydride such as Bu₃SnH, Ph₃SnH or the like, and a radical initiator such as AIBN or *t*-butyl peroxide. The preferred solvent is toluene.

Scheme 8



Compounds according to the formula (6-2) may be prepared from compounds of formula (6-1) by selective hydrogenation methods known in the art, for example, but not limited to, metal hydrides, such as, borane, or hydrogen in the presence of a catalyst, such as, palladium-on-charcoal, platinum metal or oxide, Wilkinson's catalyst and the like (*see*, Rylander, *Hydrogenation Methods*; Academic Press: New York, 1985; J. March, *Advanced Organic Chemistry* 4th ed., Wiley & Son, Inc., 1992; and the references therein).

Scheme 9

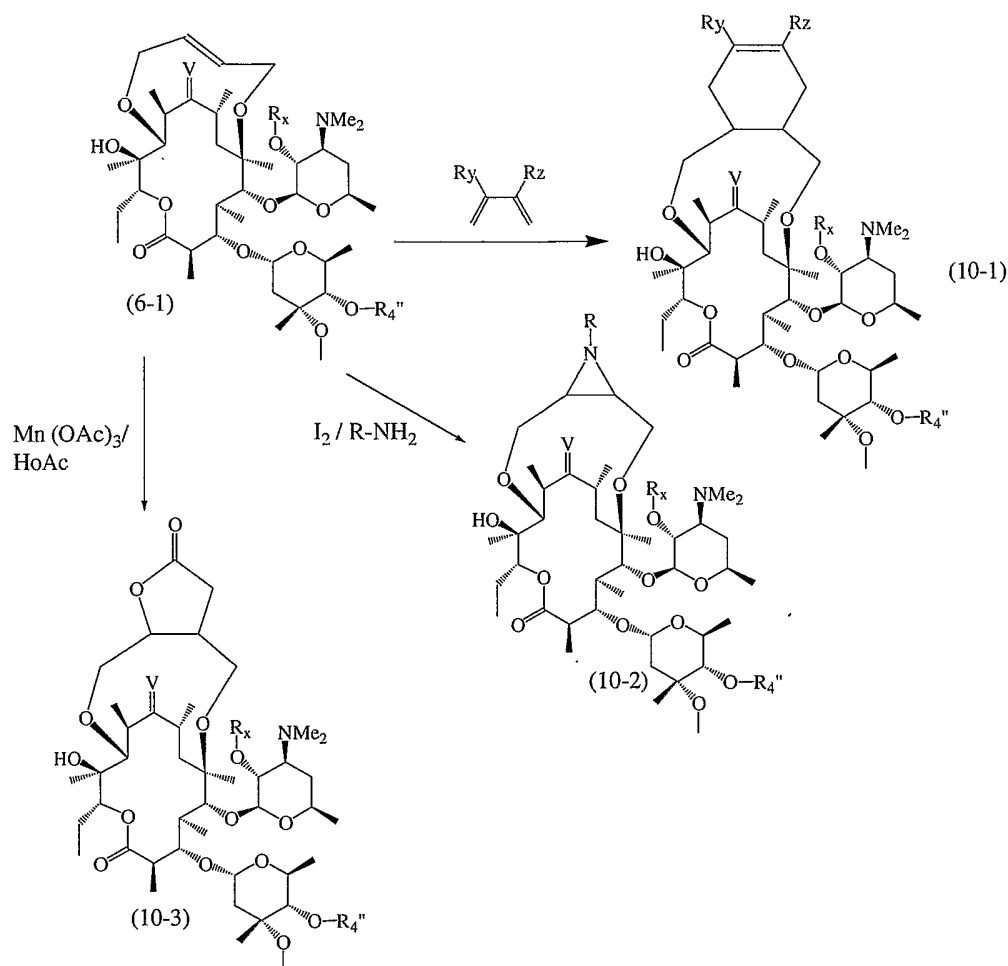


Compounds **9-1**, **9-2** and **9-3**, where R is R₃ as previously defined herein) can be prepared by the well-established 1, 3-dipolar cycloaddition reactions, such as, but not limited to, reaction of compound **6-1** and an oxime in the presence of NCS in an aprotic solvent such as ethyl acetate, methylene chloride, THF, or the like, to form compound **9-1** (see (a) Tufariello, Joseph J. *Nitrones in 1,3 [One,Three]-Dipolar Cycloaddit. Chem.* (1984), 2, 83-168. (b) Huisgen, Rolf. *1,3-Dipolar cycloaddition - introduction, survey, mechanism in 1,3 [One,Three]-Dipolar Cycloaddit. Chem.* (1984), 1, 1-176, and the references therein). Compounds **9-2** and **9-3** can be prepared similarly by reacting compound **9-1** with an azide or a nitron respectively.

Other 1,3-Dipolar cycloaddition reactants useful in forming cycloaddition products with compounds of the present invention such as compound **6-1** include, but are not limited to, diazoalkane, nitrous oxide, nitrile imine, nitrile ylide, nitrile oxide, etc. (see, Padwa *1,3-Dipolar Cycloaddition Chemistry*, 2 vols.; Wiley: New York, 1984, and J.

March, *Advanced Organic Chemistry*, 4th edition; Wiley: New York, 1992, and the references therein).

Scheme 10



5

Compound (10-1) is prepared by Diels-Alder reactions, where R_y and R_z are for example, but not limited to, CHO, COOH, COOR, COR, COAr, CN, NO₂, Ar, CH₂OH, CH₂Cl, CH₂NH₂, CH₂CN, CH₂COOH, halogen, -C=C-, R and the like, R being R₃ as previously defined herein (see (a) Danishefsky, Samuel. *Cycloaddition and cyclocondensation reactions of highly functionalized dienes: applications to organic synthesis* in *Chemtracts: Org. Chem.* (1989), 2 (5), 273-97, (b) Larock *Comprehensive Organic Transformation*; VCH: New York, 1989, 263-272, and the references therein).

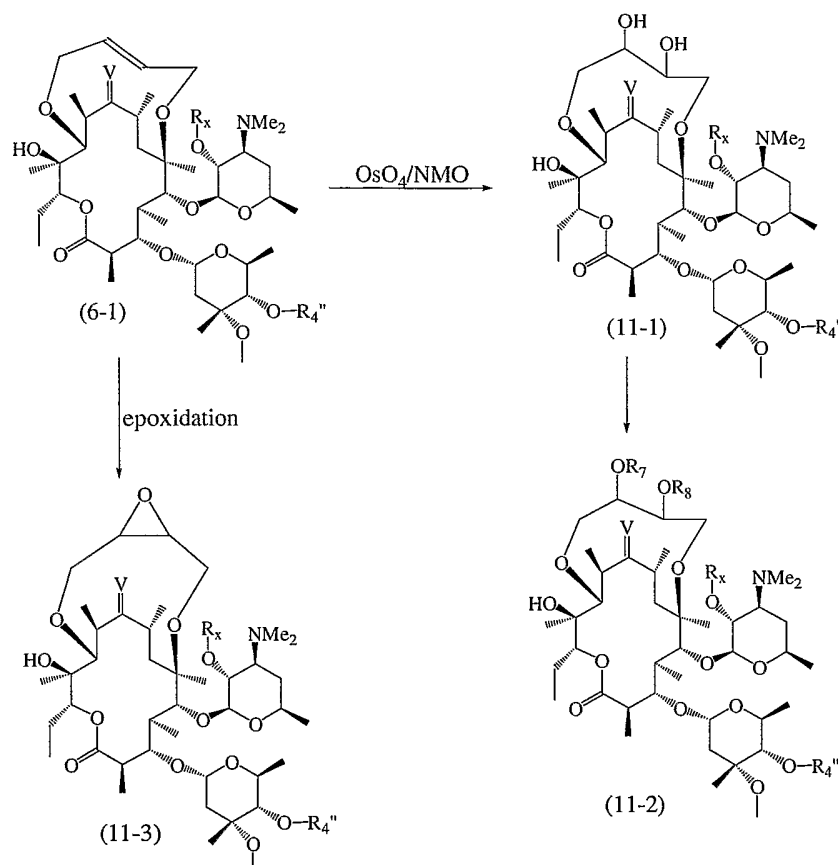
10

Aziridines such as compound (10-2) can be obtained from, for example, but not limited to, the reaction of compound (6-1) with iodine in the presence of a primary amine in an aprotic solvent such as methylene chloride, THF, and the like.

15

Lactones such as compound (10-3) can be obtained by a variety of reactions such as but not limited to, reaction with: manganese (III) acetate in the presence of acetic acid, lead tetraacetate, α -bromocarboxylic acids in the presence of benzoyl peroxide etc. (*see*, Larock *Comprehensive Organic Transformation*; VCH: New York, 1989; J. March, *Advanced Organic Chemistry*, 4th edition; Wiley: New York, 1992, and the references therein).

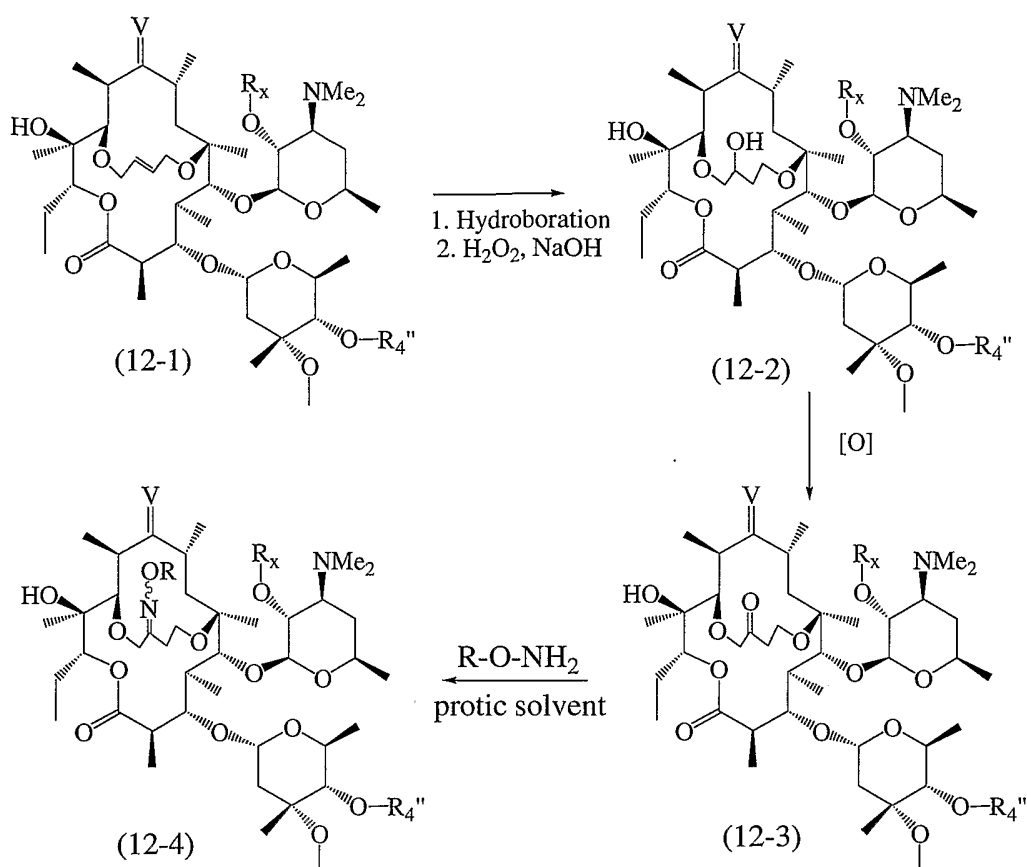
Scheme 11



Compound (11-1) is prepared by osmium tetroxide (OsO₄) catalyzed dihydroxylation of the double bond. In a typical procedure, compound (6-1) is treated with about 1 to about 3 equivalents of NMO in a solvent like t-butanol or acetone, with or without water, in the presence of about 1 to about 10% of OsO₄. Compound (11-2) can then be obtained from compound (11-3) through standard acylation or alkylation of the diol, where R₇ and R₈ are independently selected from R₃ and where R₃ is as previously defined herein.

Compound (11-3) is prepared by epoxidation of the double bond with reagents such as, but not limited to, peracids, e.g. m-CPBA, hydrogen peroxide, t-BuOOH etc. (*see* (a) *Chem. Rev.* 1989, 89, 431; (b) *Chem. Rev.* 1992, 92, 873, and references therein).

Scheme 12



Compounds of formula (12-1) can be converted to compounds of formula (12-2) by, for example, but not limited to, hydroboration with a borane reagent, for example, B₂H₆ - THF, 9-BBN (9-borabicyclo[3.3.1]nonane), and the like, (optionally complexed with THF, dimethylsulfide, phosphines, tertiary amines and the like) and followed by treatment with hydrogen peroxide and NaOH.

Compounds of formula (12-2) may be oxidized to compounds of formula (12-3) with a suitable oxidizing agent. Compounds of formula (12-3) can be reacted with appropriate substituted hydroxylamines of the general formula R₃ONH₂ where R is preferably R₃, where R₃ is as previously defined, in a protic solvent under acidic or basic conditions to give compounds of the formula (12-4). Representative acids include, but are not limited to, hydrochloric acid, phosphoric acid, sulfuric acid, p-toluenesulfonic acid, etc. Representative bases include, for example, triethylamine, pyridine, diisopropylethyl amine, 1,5-lutidine, and the like. Appropriate solvents include, but are not limited to, methanol, ethanol, water, tetrahydrofuran, 1,2-dimethoxyethane and ethyl acetate.

Also, compounds of the formula (12-3), where the ketone is on the 6,11-4-carbon bridge, may be further derivatized, for example, but not limited to, conversion to the

corresponding amines by reductive amination, reaction with hydrazines to form the corresponding hydrazones, conversion to substituted alkenes by Wittig reaction, alkylation with Grignard reagent etc., by standard methods known in the art and from references incorporated herein.

5

EXAMPLES

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration only and not limiting of the scope of the invention. Various changes and modifications to the disclosed
 10 embodiments will be apparent to those skilled in the art, and such changes and modifications including, without limitation, those relating to the chemical structures, substituents, derivatives, formulations and/or methods of the invention may be made without departing from the spirit of the invention and the scope of the appended claims.

15

Example 1

Compound of Formula (II): A = B = H; X and Y taken together with the carbon atom which they are attached to = C=N-OH; R_x = H and R₄' = C(O)C₆H₅.

Step 1a: Compound of Formula (XVI): R₆ = C(O)C₆H₅, R_x = C(O)C₆H₅ and R₄' = C(O)C₆H₅;

20

A solution of erythromycin A oxime (27.5 g, 36.7 mmol), benzoic anhydride (34.9 g, 154 mmol) in 200 ml THF was added to triethylamine (22.5 ml, 161.6 mmol) and DMAP (4.49 g, 36.7 mmol) at room temperature and stirred for 24 hrs. The reaction mixture was condensed to ~100 ml. Then 300 ml of ethyl acetate was added and washed with sat. NaHCO₃ (300 ml X 3) and brine (300 ml X 1). The organic phase was dried on
 25 anhydrous sodium sulfate and the solvent was removed *in vacuo*. To this second residue was added hexane (100 ml) and the solvent was removed *in vacuo*. This procedure (addition of hexane and concentration *in vacuo*) was repeated 3 times. The resulting white foam residue was dried *in vacuo* to afford the title compound (~90 g).

MS (ESI) m/z = 1061 (M+H)⁺.

30

Step 1b: Compound of Formula (II): A = B = H, X and Y taken together with the carbon atom they are attached to = C=N-O-C(O)C₆H₅, R_x = C(O)C₆H₅ and R₄' = C(O)C₆H₅.

A mixture of the compound from step 1a (21.9 g, 25 mmol), 2-methylene-1,3-propane-[bis-(tert-butyl)carbonate] (18.02 g, 62.25 mmol) and 1,4-bis(diphenylphosphino)-butane (640 mg, 1.5 mmol) was dissolved in freshly distilled THF (250 ml). To the

solution was added $\text{Pd}_2(\text{dba})_3$ (687 mg, 0.75 mmol). The reaction mixture was heated to reflux slowly. After refluxing for 14 hours, the reaction was cooled to room temperature, diluted with 400 ml ethyl acetate, and washed with saturated NaHCO_3 (400 ml) and brine (400 ml). The organic phase was dried over Na_2SO_4 , the solvent was removed *in vacuo* and the solid residue was purified by silica gel chromatography (acetone: hexane/1:2) to give the title compound (22g).

MS (ESI) $m/z = 1113$ ($\text{M}+\text{H}$)⁺.

Step 1c: Compound of Formula (II): A = B = H; X and Y taken together with the carbon atom they are attached to = C=N-OH; $R_x = \text{H}$ and $R_4'' = \text{C}(\text{O})\text{C}_6\text{H}_5$.

10 A solution of the compound from Step 1b (22g) in 400 ml methanol was refluxed for 48 hours. The solvent was removed *in vacuo* and the compound was purified by column chromatography (CH_2Cl_2 : 2M ammonia in MeOH/95:5) to give the title compound (18.5 g).

MS (ESI) $m/z = 905$ ($\text{M}+\text{H}$)⁺.

15

Example 2

Compound of Formula (IV): A = 3-quinolyl; B = H; X and Y taken together with the carbon atom they are attached to = C=N-OH; $R_x = \text{H}$ and $R_4'' = \text{C}(\text{O})\text{CH}_3$.

Step 2a: Compound of Formula (XVI): $R_6 = \text{C}(\text{O})\text{CH}_3$, $R_x = \text{C}(\text{O})\text{CH}_3$ and $R_4'' = \text{C}(\text{O})\text{CH}_3$.

20 Erythromycin A oxime was treated with acetic anhydride following the same procedure described in step 1a to give the title compound.

Step 2b: Compound of Formula (II): A = B = H, X and Y taken together with the carbon atom they are attached to = C(O)CH₃, $R_x = \text{C}(\text{O})\text{CH}_3$ and $R_4'' = \text{C}(\text{O})\text{CH}_3$.

25 The compound from step 1a (0.54 g, 0.60 mmol) in 20 mL anhydrous THF with $\text{Pd}_2(\text{dba})_3$ (46 mg, 0.05 mmol) and dppb (46 mg, 0.05 mmol) was degassed at -78°C . Then 2-methylene-1,3-propane-[bis-(tert-butyl)carbonate] (0.50 g, 1.8 mmol) was introduced quickly under nitrogen. The reaction solution was heated to reflux slowly and kept refluxing for 12 hours. The reaction was cooled and solvent was removed under vacuum. The residue was purified by chromatography on a silica gel column (eluting with acetone:hexanes/1:1) to provide the title compound (0.4 g, 70 %).

30

MS (ESI) $m/z = 927$ ($\text{M}+\text{H}$)⁺.

Step 2c: Compound of Formula (IV): A = 3-quinolyl, B = H, X and Y taken together with the carbon atom they are attached to = C(O)CH₃, $R_x = \text{C}(\text{O})\text{CH}_3$ and $R_4'' = \text{C}(\text{O})\text{CH}_3$.

The compound from step 2b (0.46 g, 0.50 mmol), 3-bromoquinoline (0.21 g, 1.0 mmol), Pd(OAc)₂ (15 mg, 0.07 mmol), (o-Tolyl)₃P (50 mg, 0.16 mmol) and triethyl amine (0.5 mL, 4.0 mmol) were dissolved in 10 mL CH₃CN and the solution was degassed at – 40°C. The reaction mixture was warmed up to room temperature and sealed under
 5 nitrogen, then was heated at 50°C for 1.5 hours, then left at 78°C for 12 hours. Then the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous NaHCO₃, and dried over anhydrous Na₂SO₄. The solvent was evaporated and the residue was purified by chromatography on a silica gel column (eluting with acetone : hexanes/2:3) to provide the title compound (0.17 g, 33 %).

10 MS (ESI) m/z = 1054 (M+H)⁺.

Step 2d: Compound of Formula (IV): A = 3-quinolylyl; B = H; X and Y taken together with the carbon atom they are attached to = C=N-OH; R_x = H and R₄' = C(O)CH₃.

A solution of the compound from Step 2c in methanol (10 mL) was heated at 65°C for 48 hours. The solvent was evaporated under vacuum. Purification on silica gel column
 15 (eluting with CH₂Cl₂ containing 5% 2M ammonia solution in methanol) gave the title compound (0.14 g, 90 %) as a white solid.

MS (ESI) m/z = 970 (M+H)⁺.

Selected ¹³C-NMR (100 MHz, CDCl₃): δ 170.8, 164.6, 152.2, 151.0, 146.8, 135.8, 134.0, 128.7, 128.3, 128.2, 127.5, 126.4, 112.8, 102.7, 97.5, 82.1, 81.0, 79.6, 79.1, 78.9, 77.8,
 20 77.5, 75.9, 73.2, 71.2, 68.5, 65.5, 63.3, 60.6, 53.6, 49.9, 45.9, 44.5, 41.7, 40.4.

Example 3

Compound of Formula (II): A = C(O)OCH₃; B = H; X and Y taken together with the carbon atom they are attached to = C=N-OH; R_x = H and R₄' = C(O)C₆H₅.

25 Step 3a: Compound of Formula (II): A = C(O)OCH₃, B = H, X and Y taken together with the carbon atom they are attached to = C=N-O-C(O)C₆H₅, R_x = C(O)C₆H₅ and R₄' = C(O)C₆H₅.

A mixture of the compound from step 1a (1.3 mmole), tBuOC(O)OCH₂C(CO₂Me)=CHCH₂OC(O)OtBu and 1,4-bis(diphenylphosphino)-butane
 30 (0.04 mmole) are dissolved in freshly distilled THF. To the solution is added Pd₂(dba)₃ (0.02 mmole). The reaction mixture is heated to reflux slowly. After refluxing for 14 hours, the reaction is cooled to room temperature, diluted with ethyl acetate, and washed with saturated NaHCO₃ and brine. The organic phase is dried over Na₂SO₄, the solvent is

removed *in vacuo* and the solid residue is purified by silica gel chromatography (acetone : hexane/1:2) to give the title compound.

Step 3b: Compound of Formula (II): A = C(O)OCH₃; B = H; X and Y taken together with the carbon atom they are attached to = C=N-OH; R_x = H and R₄' = C(O)C₆H₅.

- 5 The compound from Step 3a is refluxed in methanol for 12 hours. The solvent is evaporated and the residue is purified by silica gel chromatography (5-10% 2M NH₃ in methanol in CH₂Cl₂) to give the title compound.

Example 4

- 10 Compound of Formula (II): A = C(O)-OH; B = H; X and Y taken together with the carbon atom they are attached to = C=N-OH; R_x = H and R₄' = H.

- To a solution of the compound from Example 3 (10 mg, 0.01 mmol) in THF (1 mL) and distilled water (1 mL) is added 1N LiOH (0.1 mL, 0.10 mmol). The mixture is stirred for 5-10 hours at 50°C. Then water (10 mL) is added and the mixture extracted with ethyl acetate. The combined organic layer is dried over anhydrous Na₂SO₄. The solvent is concentrated under vacuum and the residue is purified on a silica gel column to provide the title compound.
- 15

Example 5

- 20 Compound of Compound of Formula (II): A = B = H, X and Y taken together with the carbon atom they are attached to = C=O, R_x = H and R₄' = C(O)CH₃.

Step 5a: Compound: HO-CH₂-CH=CH-CH₂-OSi(CH₃)₂(C(CH₃)₃).

- A suspension of NaH (1.26 g, 50 mmol) in 40 ml of THF was added to a solution of diol (4.4 g, 50 mmol) in 30 ml of THF. The mixture was stirred at room temperature for 45 minutes and was added with a solution of tert-butyldimethylsilyl chloride (7.54 g, 50 mmol) in 30 ml of THF. The mixture was stirred at room temperature for 1 hour and quenched with saturated NaHCO₃ (200 ml), then extracted with ether (150 ml X2), and the combined organic layers were dried over MgSO₄. The solvent was removed and the resulting oil was purified on silica chromatography (Hexane : ethyl acetate/10:1) to give the title compound (8.4g).
- 25
- 30

Step 5b: Compound: (CH₃)₃C-O-C(O)-O-CH₂-CH=CH-CH₂-OSi(CH₃)₂(C(CH₃)₃).

A solution of compound from Step 5a (8.1 g, 40 mmol) in 100 ml of methylenechloride was added to Boc₂O (13.1 g, 60 mmol), tetrabutylammoniumhydrogensulfate (1.2 g, 3.5 mmol) and 30 ml of 6N NaOH. The reaction mixture was stirred at room temperature for 16 hours, then diluted with 100 ml of methylene chloride and washed with saturated NaHCO₃ (200 ml X 3). The organic layer was dried over Na₂SO₄. The solvent was removed and the residue was purified on silica gel chromatography (Hexane : ethylacetate/ 96:4) to give the title compound (6.8 g).

Step 5c: Compound of Formula (XVII): A = B = H, V taken together with the carbon atom it is attached to = C=N-O-C(O)CH₃, R_x = C(O)CH₃, R^P₁ = -Si(CH₃)₂(C(CH₃)₃) and R₄' = C(O)CH₃.

The compound from Step 5b, *tert*-Butyl-OC(O)-OCH₂CH=CHCH₂-O-*tert*-butyldimethylsilyl (0.9 g, 3 mmol), 1,4-bis(diphenylphosphino)butane (170 mg, 0.4 mmol) and Pd₂(dba)₃ (183 mg, 0.2 mmol) were added into a solution of ery-9-oxime triacetate (1.75 g, 2 mmol) in tetrahydrofuran (10 ml) at room temperature. The reaction mixture was refluxed under nitrogen overnight, cooled to room temperature and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (acetone:hexanes/1:3) to give the title compound (1.5 g). MS (ESI) m/z = 1059 (M+H).

Step 5d: Compound of Formula (XVII): A = B = H, V taken together with the carbon atom it is attached to = C=N-OH, R_x = H, R^P₁ = -Si(CH₃)₂(C(CH₃)₃) and R₄' = C(O)CH₃.

A solution of the compound from Step 5c (3.18 g, 3 mmol) in methanol (80 ml) was refluxed for 8 hours. The reaction was cooled to room temperature, the solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (2M ammonia in methanol: dichloromethane/3:97) to give the title compound (2.6 g).

MS (ESI) m/z = 975 (M+H).

Step 5e: Compound of Formula (XVII): A = B = H, V taken together with the carbon atom it is attached to = C=O, R_x = R^P₁ = H and R₄' = C(O)CH₃.

Formic acid (0.38 ml, 10 mmol) and Na₂S₂O₄ (1.39, 8 mmol) was added into an emulsion of the compound from Step 5d (2.44 g, 2.5 mmol) in isopropanol (25 ml) and water (30 ml). The mixture was heated to 90°C and stirred at that temperature for 8 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (60 ml), washed with saturated sodium bicarbonate (3x60 ml), and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (2M ammonia in methanol:dichloromethane/3:97) to give the title compound (1.7 g).

MS (ESI) $m/z = 846$ (M+H).

Step 5f: Compound of Formula (XVII): A = B = H, V taken together with the carbon atom it is attached to = C=O, $R_x = C(O)CH_3$, $R^p_1 = H$ and $R_4'' = C(O)CH_3$.

Acetic anhydride (94 μ l, 1 mmol) was added into a solution of the compound from Step 5e (338.4 mg, 0.4 mmol) in dichloromethane (5 ml). The mixture was stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (acetone:hexane/4:6) to give the title compound (330 mg). MS (ESI) $m/z = 888$ (M+H).

Step 5g: Compound of Formula (XVII): A = B = H, V taken together with the carbon atom it is attached to = C=O, $R_x = C(O)CH_3$, $R^p_1 = C(O)-O-C(CH_3)_3$ and $R_4'' = C(O)CH_3$.

Di-*tert*-butyl-dicarbonate (69 μ l, 0.3 mmol) was added to a solution of the compound of Step 5f (178 mg, 0.2 mmol) and triethylamine (56 μ l, 0.4 mmol) in dichloromethane (8 ml) at room temperature. After 10 minutes, N,N-dimethylamino pyridine (12.2 mg, 0.1 mmol) was added. The resulting solution was stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (acetone:hexane/1:3) to give the title compound (180 mg). MS (ESI) $m/z = 988$ (M+H).

Step 5h: Compound of Formula (II): A = B = H, X and Y taken together with the carbon atom they are attached to = C=O, $R_x = C(O)CH_3$ and $R_4'' = C(O)CH_3$.

1,4-Bis(diphenylphosphino)butane (8.5 mg, 0.02 mmol) and $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol) is added to a solution of the compound of Step 5g (98.8 mg, 0.1 mmol) in 2 ml anhydrous THF at room temperature. The resulting mixture is refluxed for 30 minutes. The solvent is removed *in vacuo* and the residue is used for next step reaction without purification.

Step 5i: Compound of Formula (II): A = B = H, X and Y taken together with the carbon atom they are attached to = C=O, $R_x = H$ and $R_4'' = C(O)CH_3$.

The compound from Step 5h is stirred in methanol for 24 hours. Removal of the solvent gives the title compound.

Example 6

Compound of Formula (II): A = B = H; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; $R_x = H$ and $R_4'' = C(O)C_6H_5$.

Step 6a: Compound of Formula (II): A = B = H, X and Y taken together with the carbon atom they are attached to = C=NH, $R_x = H$ and $R_4'' = C(O)C_6H_5$.

The compound from Step 1c in methanol is treated with titanium trichloride (20% in 3% hydrochloric acid) following the procedure described in Step 1d, except the reaction is quenched with aqueous sodium bicarbonate after 2-3 hours. The aqueous solution is extracted with methylene chloride 4 times and the organic phase is combined and dried over sodium sulfate. The solvent is then removed under vacuum and the crude residue is purified by chromatography on a silica gel column to provide the title compound.

Step 6b: Compound of Formula (II): A = B = H, X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃, $R_x = C(O)CH_3$ and $R_4'' = C(O)C_6H_5$.

The compound from Step 6a is treated with 2.5 equivalents of acetic anhydride and triethylamine in dichloromethane. The reaction mixture is stirred at room temperature for 3 hours, then diluted with dichloromethane and washed with saturated sodium bicarbonate and brine. The organic phase is dried over sodium sulfate and the solvent is removed *in vacuo*. The residue is purified by silica gel chromatography (hexanes:acetone/1:1) to give the title compound.

Step 6c: Compound of Formula (II): A = B = H; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; $R_x = H$ and $R_4'' = C(O)C_6H_5$.

The compound from Step 6b is stirred in methanol for 24 hours. Removal of the solvent gives the title compound.

Example 7

Compound of Formula (VIII): Q = -C(C₆H₅)=N-O-; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; $R_x = H$ and $R_4'' = C(O)C_6H_5$.

Step 7a: Compound of Formula (VIII): Q = -C(C₆H₅)=N-O-, X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃, $R_x = C(O)CH_3$ and $R_4'' = C(O)C_6H_5$.

To a solution of benzaldoxime (1.2 mmol) in 5 mL ethyl acetate is added NCS (0.17g, 1.2 mmol) and NaHCO₃ (0.25g, 2.5 mmol) and 1 drop of water. The compound from Step 6b (1.0 mmol) is added to the reaction mixture and stirred at room temperature for 12 hours. Then the reaction mixture is diluted with ethyl acetate, washed with saturated aqueous NaHCO₃, and dried over anhydrous Na₂SO₄. The solvent is evaporated and the residue is purified on silica gel column to give the title compound.

Step 7b Compound of Formula (VIII): Q = -C(C₆H₅)=N-O-; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; $R_x = H$ and $R_4'' = C(O)C_6H_5$.

The compound from Step 7a is stirred in methanol for 24 hours. Removal of the solvent gives the title compound.

Example 8

5 Compound of Formula (VIII): Q = -O-C(O)-O-; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; R_x = H and R₄' = C(O)C₆H₅.

Step 8a: Compound of Formula (X): E = G = -OH, X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃, R_x = C(O)CH₃ and R₄' = C(O)C₆H₅.

To a solution of the compound from Step 6b (1.0 mmol) and NMO (1.2 mmol) in 5
10 mL t-butanol is added 4% OsO₄ (catalytic amount). The reaction mixture is stirred for 3 hours at room temperature. The solvent is then removed under vacuum and the crude residue is purified by chromatography on a silica gel column to provide the title compound.

Step 8b: Compound of Formula (VIII): Q = -O-C(O)-O-, X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃, R_x = C(O)CH₃ and R₄' = C(O)C₆H₅.

15 The compound from Step 8a (1.0 mmol), CDI (1.2 mmol) and 0.2 mL triethylamine are dissolved in 15 mL methylene chloride. The reaction mixture is stirred for 12 hours at room temperature. The reaction is quenched with NaHCO₃ aqueous solution and extracted with methylene chloride. The combined organic layers are dried over anhydrous Na₂SO₄. The solvent is evaporated and the residue is purified by chromatography on a silica gel
20 column to provide the title compound.

Step 8c: Compound of Formula (VIII): Q = -O-C(O)-O-; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; R_x = H and R₄' = C(O)C₆H₅.

The compound from Step 8b is stirred in methanol for 24 hours. Removal of the solvent gives the title compound.

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Example 9

Compound of Formula (VIII): Q = -O-; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; R_x = H and R₄' = C(O)C₆H₅.

Step 9a: Compound of Formula (VIII): Q = -O-; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; R_x = C(O)CH₃ and R₄' = C(O)C₆H₅.

To a solution of the compound from Step 6b (1.0 mmol) in CH₂Cl₂ is added m-CPBA (1.2 mmol). The reaction mixture is stirred for 3 hours at room temperature. The solvent is then removed under vacuum and the crude residue is purified by chromatography on a silica gel column to provide the title compound.

Step 9b: Compound of Formula (VIII): Q = -O-; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; R_x = H and R₄' = C(O)C₆H₅.

The compound from Step 9a is stirred in methanol for 24 hours. Removal of the solvent gives the title compound.

5

Example 10

Compound of Formula (VIII): Q = -O-; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; R_x = H and R₄' = H.

To a solution of the compound from Example 9 (10 mg, 0.01 mmol) in THF (1 mL) and distilled water (1 mL) is added 1N LiOH (0.1 mL, 0.10 mmol). The mixture is stirred for 5-10 hours at 50°C. Then water (10 mL) is added and extracted with ethyl acetate. The combined organic layer is dried over anhydrous Na₂SO₄. The solvent is concentrated under vacuum and the residue is purified on a silica gel column to provide the title compound.

15

Example 11

Compound of Formula (II): A = B = H; X and Y taken together with the carbon atom they are attached to = C=NC(O)CH₂OCH₃; R_x = H and R₄' = C(O)C₆H₅.

Step 11a: Compound of Formula (II): A = B = H, X and Y taken together with the carbon atom they are attached to = C=NC(O)CH₂OCH₃, R_x = C(O)CH₂OCH₃ and R₄' = C(O)C₆H₅.

To a solution of methoxyacetic acid (2.5 mmol) in CH₂Cl₂ is added DCC (2.5 mmol) at 0°C. The mixture is stirred for 10 minutes. The compound from Step 6a (1.0 mmol) in CH₂Cl₂ is added and the solution is stirred for 12 hours. The solvent is removed under vacuum and the residue is purified on a silica gel column to provide the title compound.

25

Step 11b: Compound of Formula (II): A = B = H; X and Y taken together with the carbon atom they are attached to = C=NC(O)CH₂OCH₃; R_x = H and R₄' = C(O)C₆H₅.

The compound from Step 11a is stirred in methanol for 24 hours. Removal of the solvent gives the title compound.

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Example 12

Compound of Formula (II): A = B = H; X and Y taken together with the carbon atom they are attached to = C=N-C(O)-CH₂OCH₃; R_x = H and R₄' = H.

To a solution of the compound from Example 11 (10 mg, 0.01 mmol) in THF (1 mL) and distilled water (1 mL) is added 1N LiOH (0.1 mL, 0.10 mmol). The mixture is stirred for 5-10 hours at 50°C. Then water (10 mL) is added and extracted with ethyl acetate. The combined organic layer is dried over anhydrous Na₂SO₄. The solvent is concentrated under vacuum and the residue is purified on a silica gel column to provide the title compound.

Example 13

Compound of Formula (IV): A = 3-quinolyl; B = H; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; R_x = H and R₄' = C(O)C₆H₅.

Step 13a: Compound of Formula (IV): A = 3-quinolyl, B = H, X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃, R_x = C(O)CH₃ and R₄' = C(O)C₆H₅;

The compound from Step 6b (0.50 mmol), 3-bromoquinoline (0.21 g, 1.0 mmol), Pd(OAc)₂ (15 mg, 0.07 mmol), (o-Tolyl)₃P (50 mg, 0.16 mmol) and triethyl amine (0.5 mL, 4.0 mmol) are dissolved in 10 mL CH₃CN and the solution is degassed at -40°C. The reaction mixture is warmed up to room temperature and sealed under nitrogen, then is heated at 50°C for 1.5 hours, then left at 78°C for 12 hours. Then the reaction mixture is diluted with ethyl acetate, washed with saturated aqueous NaHCO₃, and dried over anhydrous Na₂SO₄. The solvent is evaporated and the residue is purified by chromatography on a silica gel column to provide the title compound.

Step 13b: Compound of Formula (IV): A = 3-quinolyl; B = H; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; R_x = H and R₄' = C(O)C₆H₅.

The compound from Step 13a is stirred in methanol for 24 hours. Removal of the solvent gives the title compound.

Example 14

Compound of Formula (IV): A = 3-quinolyl; B = H; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; R_x = H and R₄' = H.

To a solution of the compound from Example 13 (10 mg, 0.01 mmol) in THF (1 mL) and distilled water (1 mL) is added 1N LiOH (0.1 mL, 0.10 mmol). The mixture is stirred for 5-10 hours at 50°C. Then water (10 mL) is added and extracted with ethyl acetate. The combined organic layer is dried over anhydrous Na₂SO₄. The solvent is concentrated under vacuum and the residue is purified on a silica gel column to provide the title compound.

Example 15

Compound of Formula (II): A = C(CH=CH-C₆H₅); B = H; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; R_x = H and R₄'' = C(O)C₆H₅.

- 5 Step 15a: Compound of Formula (II): A = C(CH=CH-C₆H₅), B = H, X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃, R_x = C(O)CH₃ and R₄'' = C(O)C₆H₅.

The compound from Step 6b (1.0 equiv.) is dissolved in anhydrous DMF. β-bromostyrene (3.0 equiv.) and K₂CO₃ (4 equiv.) are added at room temperature. The mixture is degassed briefly and a catalytic amount of dihydrogen dichlorobis(di-tert-butylphosphinito-κP)palladate(2-) (POPd from Combiphos catalysts, Inc.) is added. The reaction mixture is heated to 100°C in a sealed tube for 48 hours. Ethyl acetate is added and the solution is washed 3 times with NaHCO₃ aqueous solution. The organic layer is dried over anhydrous Na₂SO₄. The solvent is evaporated under vacuum and the residue is purified by chromatography on a silica gel column to provide the title compound.

Step 15b: Compound of Formula (II): A = C(CH=CH-C₆H₅); B = H; X and Y taken together with the carbon atom they are attached to = C=N-C(O)CH₃; R_x = H and R₄'' = C(O)C₆H₅.

The compound from Step 15a is stirred in methanol for 24 hours. Removal of the solvent gives the title compound.

Example 16

Compound of Formula (II): A = C(CH=CH-C₆H₅); B = H; X and Y taken together with the carbon atom they are attached to = C=NC(O)CH₃; R_x = H and R₄'' = H.

- 25 To a solution of the compound from eExample 15 (10 mg, 0.01 mmol) in THF (1 mL) and distilled water (1 mL) is added 1N LiOH (0.1 mL, 0.10 mmol). The mixture is stirred for 5-10 hours at 50°C. Then water (10 mL) is added and extracted with ethyl acetate. The combined organic layer is dried over anhydrous Na₂SO₄. The solvent is concentrated under vacuum and the residue is purified on a silica gel column to provide the title compound.
- 30

Example 17

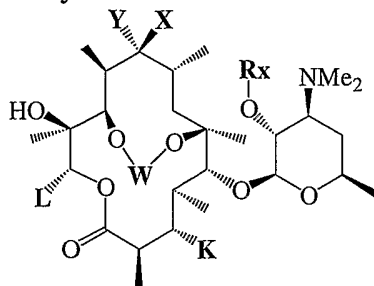
Compound of Formula (II): A = H; B = H; X and Y taken together with the carbon atom they are attached to = C=NC(O)CH₃; R_x = H and R₄' = H.

5 To a solution of the compound from Step 6c (10 mg, 0.01 mmol) in THF (1 mL) and distilled water (1 mL) is added 1N LiOH (0.1 mL, 0.10 mmol). The mixture is stirred for 5-10 hours at 50°C. Then water (10 mL) is added and extracted with ethyl acetate. The combined organic layer is dried over anhydrous Na₂SO₄. The solvent is concentrated under vacuum and the residue is purified on a silica gel column to provide the title compound.

10 Although the invention has been described in detail with respect to various preferred embodiments it is not intended to be limited thereto, but rather those skilled in the art will recognize that variations and modifications may be made therein which are within the spirit of the invention and the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound represented by the formula:



(I)

or a pharmaceutically acceptable salt, ester or prodrug thereof wherein

W is selected from the group consisting of:

- (a) $-\text{CH}_2-\text{C}(\text{A})=\text{C}(\text{B})-\text{CH}_2-$;

wherein,

A and B are independently selected from the group consisting of:

- (i) hydrogen;
- (ii) deuterium;
- (iii) halogen;

- (iv) R_1 , wherein R_1 is selected from the group consisting of:

- a. C_1-C_6 alkyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- b. C_2-C_6 alkenyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and
- c. C_2-C_6 alkynyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

- (v) R_2 , wherein R_2 is selected from the group consisting of:

- a. aryl;
- b. heteroaryl;
- c. substituted aryl; and

d. substituted heteroaryl;

(vi) $-(C_1-C_3\text{-alkyl})-M-(C_1-C_3\text{-alkyl})-R_2$, wherein $M = -O-$, $-NH-$, $-N(CH_3)-$, $-NHC(O)-$ or $-S(O)_n-$, wherein $n = 0, 1$ or 2 , and R_2 is as previously defined;

(vii) $-(C_1-C_3\text{-alkyl})-M-R_2$, wherein M and R_2 are as previously defined;

(viii) $-C(O)-J-R_3$, wherein J is absent, O or S , and R_3 is H , R_1 or R_2 ;

where R_1 and R_2 are as previously defined; and

(ix) $-C(O)-NR_{11}R_{12}$, wherein R_{11} and R_{12} are each independently selected from the group consisting of:

a. hydrogen;

b. C_1-C_6 -alkyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

c. C_2-C_6 -alkenyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

d. C_2-C_6 -alkynyl, optionally substituted with one or more substituents selected from the group consisting of: halogen, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and

e. R_{11} and R_{12} taken together with the nitrogen atom to which they are connected form a 3- to 7-membered ring which may optionally contain one or more heterofunctions selected from the group consisting of: $-O-$, $-NH-$, $-N(C_1-C_6\text{-alkyl})-$, $-N(R_2)-$, $-S(O)_n-$, wherein n and R_2 are as previously defined;

(b) $-CH_2-CH(A)-C(B)=CH-$, wherein A and B are as previously defined;

(c) $-CH_2-CH(E)-CH(G)-CH_2-$;

wherein E and G are independently selected from the group consisting of:

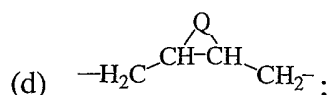
(i) A , wherein A is as previously defined;

(ii) $-OH$;

(iii) $-OR^p$, wherein R^p is a hydroxy protecting group;

(iv) $-O-R_9$, wherein R_9 is R_1 or R_2 , and wherein R_1 and R_2 are as previously defined;

- (v) $-\text{S}(\text{O})_n\text{R}_9$, wherein n and R_9 are as previously defined;
- (vi) $-\text{NHC}(\text{O})\text{R}_3$, wherein R_3 is as previously defined;
- (vii) $-\text{NHC}(\text{O})\text{NR}_{11}\text{R}_3$, wherein R_{11} and R_3 are as previously defined;
- (viii) $-\text{NHS}(\text{O})_2\text{R}_9$, wherein R_9 is as previously defined;
- (ix) $-\text{NHR}_{13}$, wherein R_{13} is an amino protecting group; and
- (x) $-\text{NR}_{11}\text{R}_{12}$, wherein R_{11} and R_{12} are as previously defined;



wherein:

- (i) $-\text{Q}-$ is selected from the group consisting of: $-\text{O}-$; $-\text{O}-\text{C}(\text{O})-\text{CH}(\text{R}_7)-$; $-\text{N}(\text{R}_7)-$; $-\text{O}-\text{C}(\text{O})-\text{N}(\text{R}_7)-$; $-\text{O}-\text{C}(\text{O})-\text{O}-$; $-\text{N}(\text{R}_7)-\text{N}=\text{N}-$; $-\text{C}(\text{R}_7)=\text{N}-\text{O}-$; and $-\text{CH}(\text{R}_7)-\text{N}(\text{R}_8)-\text{O}-$; wherein R_7 and R_8 are independently selected from R_3 , wherein R_3 is as previously defined; or
 - (ii) $-\text{Q}-$ taken together with the two carbon atoms it is attached to is selected from the group consisting of:
 - a. cycloalkylene;
 - b. cycloalkenylene; and
 - c. heterocycloalkylene; and
 - (e) $-\text{CH}_2-\text{C}(\text{R}_4)(\text{R}_5)-\text{CH}_2-\text{CH}_2^-$;
- wherein R_4 and R_5 taken together with the carbon atom to which they are attached are selected from the group consisting of:
- (i) $\text{C}=\text{O}$;
 - (ii) $\text{C}(\text{OR}_1)_2$, wherein R_1 is as previously defined;
 - (iii) $\text{C}(\text{SR}_1)_2$, wherein R_1 is as previously defined;
 - (iv) $\text{C}[-\text{O}(\text{CH}_2)_m]_2$, wherein m is 2 or 3;
 - (v) $\text{C}[-\text{S}(\text{CH}_2)_m]_2$, wherein m is as previously defined;
 - (vi) $\text{C}=\text{CHR}_3$, wherein R_3 is as previously defined;
 - (vii) $\text{C}=\text{N}-\text{O}-\text{R}_3$, wherein R_3 is as previously defined;
 - (viii) $\text{C}=\text{NNHR}_3$, wherein R_3 is as previously defined;
 - (ix) $\text{C}=\text{NNHC}(\text{O})\text{R}_3$, wherein R_3 is as previously defined;
 - (x) $\text{C}=\text{NNHC}(\text{O})\text{NR}_{11}\text{R}_3$, wherein R_{11} and R_3 are as previously defined;
 - (xi) $\text{C}=\text{NNHS}(\text{O})_2\text{R}_9$, wherein R_9 is as previously defined;

(xii) $C=NNHR_{13}$, wherein R_{13} is as previously defined; and

(xiii) $C=NR_9$, wherein R_9 is as previously defined;

X and Y are:

(a) independently selected from the group consisting of:

(i) hydrogen;

(ii) deuterium;

(iii) $-OH$;

(iv) $-OR^P$, wherein R^P is as previously defined; and

(v) $-NR_{14}R_{15}$, wherein R_{14} and R_{15} are each independently selected

from the group consisting of:

a. hydrogen;

b. C_1 - C_{12} alkyl, optionally substituted with one or more substituents selected from the group consisting of halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl; and

c. R_{14} and R_{15} , taken together with the nitrogen atom to which they are attached form a 3 to 10 membered heterocycloalkyl ring optionally substituted with one or more hetero atoms selected from the group consisting of O, S and N; or

(b) taken together with the carbon atom to which they are attached are selected from the group consisting of:

(i) $C=O$;

(ii) $C=NR_3$, wherein R_3 is as previously defined;

(iii) $C=NC(O)R_3$, wherein R_3 is as previously defined;

(iv) $C=N-OR_6$, wherein R_6 is selected from the group consisting of:

a. hydrogen;

b. $-CH_2O(CH_2)_2OCH_3$;

c. $-CH_2O(CH_2O)_nCH_3$, wherein n is as previously defined;

d. C_1 - C_{12} alkyl, optionally substituted with one or more substituents selected from the group consisting of halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl;

e. C_3 - C_{12} cycloalkyl;

f. $C(O)$ - C_1 - C_{12} alkyl;

- g. $C(O)-(C_3-C_{12} \text{ cycloalkyl})$;
- h. $C(O)-R_2$, wherein R_2 is as previously defined; and
- i. $-Si(R_a)(R_b)(R_c)$, wherein R_a , R_b and R_c are each independently selected from the group consisting of C_1-C_{12} alkyl, aryl and substituted aryl; and

(v) $C=N-O-C(R_{16})(R_{17})-O-R_{18}$, wherein R_{16} and R_{17} taken together with the carbon atom to which they are attached form a C_3 to C_{12} cycloalkyl group or each independently is selected from the group consisting of: hydrogen, and C_1-C_{12} alkyl; and R_{18} is selected from the group consisting of:

- a. hydrogen;
- b. $-CH_2O(CH_2)_2OCH_3$;
- c. $-CH_2O(CH_2O)_nCH_3$, wherein n is as previously defined;
- d. C_1-C_{12} alkyl, optionally substituted with one or more substituents selected from the group consisting of halogen, aryl, substituted aryl, heteroaryl and substituted heteroaryl;
- e. C_3-C_{12} cycloalkyl; and
- f. $-Si(R_a)(R_b)(R_c)$, wherein R_a , R_b and R_c are as previously defined;

L is selected from the group consisting of:

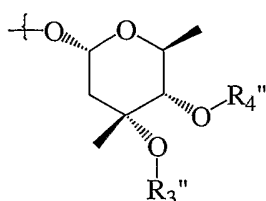
- (a) $-CH(OH)CH_3$;
- (b) C_1-C_6 alkyl, optionally substituted with one or more substituents selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- (c) C_2-C_6 alkenyl, optionally substituted with one or more substituents selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl; and
- (d) C_2-C_6 alkynyl, optionally substituted with one or more substituents selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

K is selected from the group consisting of:

- (a) R_{10} , wherein R_{10} is selected from the group consisting of:
 - (i) hydrogen;
 - (ii) $-OR^p$, wherein R^p is as previously defined;

- (iii) $-\text{OR}_3$, wherein R_3 is as previously defined;
- (iv) $-\text{OC}(\text{O})\text{R}_3$, wherein R_3 is as previously defined;
- (v) $-\text{OC}(\text{O})\text{NR}_{11}\text{R}_3$, wherein R_{11} and R_3 are as previously defined;
- and
- (vi) $-\text{S}(\text{O})_n\text{R}_9$, wherein n and R_9 are as previously defined; and

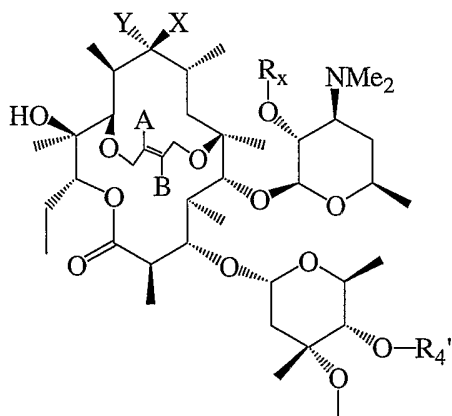
(b)



wherein R_3'' is hydrogen or methyl; R_4'' is hydrogen or R^p , wherein R^p is as previously defined; and

R_x is hydrogen or R^p , wherein R^p is as previously defined.

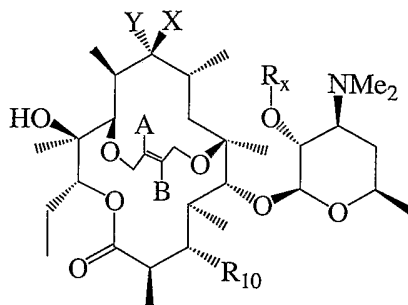
2. A compound according to Claim 1 wherein X and Y taken together with the carbon atom to which they are attached are selected from the group consisting of: $\text{C}=\text{O}$, $\text{C}=\text{NR}_3$, $\text{C}=\text{N}-\text{O}-\text{R}_6$, $\text{C}=\text{N}-\text{C}(\text{O})\text{R}_3$ and $\text{C}=\text{N}-\text{O}-\text{C}(\text{R}_{16})(\text{R}_{17})-\text{O}-\text{R}_{18}$, wherein R_3 , R_6 , R_{16} , R_{17} and R_{18} are as defined in Claim 1.
3. A compound according to Claim 2 wherein X and Y taken together with the carbon atom to which they are attached are selected from the group consisting of: $\text{C}=\text{NC}(\text{O})\text{CH}_3$ and $\text{C}=\text{N}-\text{O}-\text{CH}_2-\text{O}-\text{CH}_3$.
4. A compound according to Claim 1 represented by the formula:



wherein A, B, X, Y, R_x and R_4'' are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

5. A compound according to Claim 4 wherein X and Y taken together with the carbon atom to which they are attached are selected from the group consisting of: C=O, C=NR₃, C=N-O-R₆, C=N-C(O)R₃ and C=N-O-C(R₁₆)(R₁₇)-O-R₁₈, wherein R₃, R₆, R₁₆, R₁₇ and R₁₈ are as defined in Claim 1.

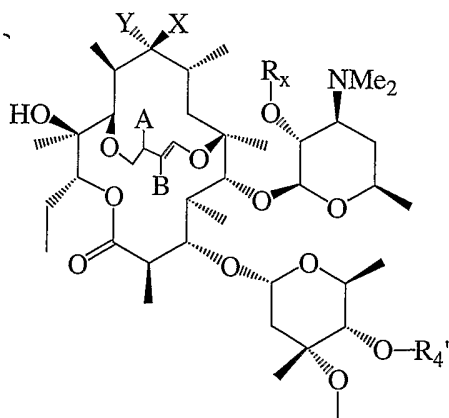
6. A compound according to Claim 1 represented by the formula:



wherein A, B, X, Y, R₁₀ and R_x are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

7. A compound according to Claim 6 wherein X and Y taken together with the carbon atom to which they are attached are selected from the group consisting of: C=O, C=NR₃, C=N-O-R₆, C=N-C(O)R₃ and C=N-O-C(R₁₆)(R₁₇)-O-R₁₈, wherein R₃, R₆, R₁₀, R₁₆, R₁₇ and R₁₈ are as defined in Claim 1.

8. A compound according to Claim 1 represented by the formula:

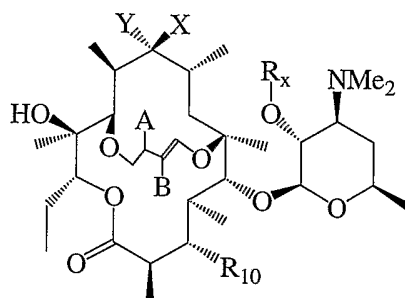


wherein A, B, X, Y, R_x and R₄'' are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof

9. A compound according to Claim 8 wherein X and Y taken together with the carbon atom to which they are attached are selected from the group consisting of: C=O, C=NR₃, C=N-O-R₆, C=N-C(O)R₃ and C=N-O-C(R₁₆)(R₁₇)-O-R₁₈, wherein R₃, R₆, R₁₆, R₁₇ and R₁₈ are as defined in Claim 1.

5

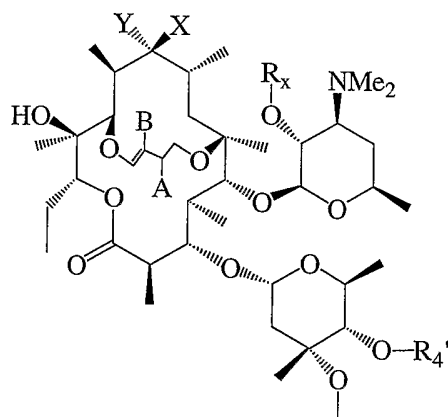
10. A compound according to Claim 1 represented by the formula:



wherein A, B, X, Y, R₁₀ and R_x are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

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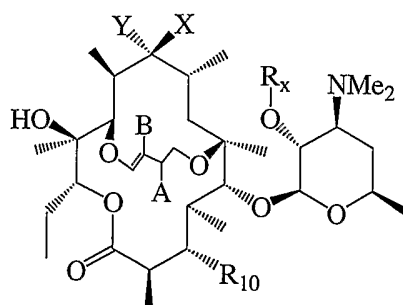
11. A compound according to Claim 1 represented by the formula:



wherein A, B, X, Y, R_x and R₄" are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

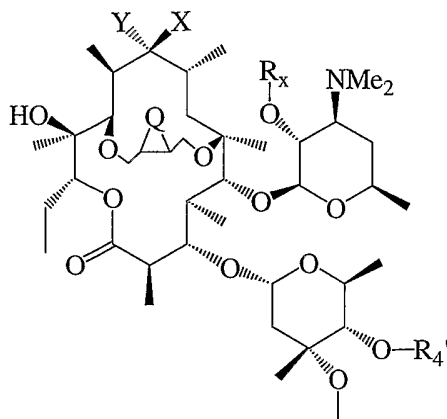
15

12. A compound according to Claim 1 represented by the formula:



wherein A, B, X, Y, R₁₀ and R_x are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

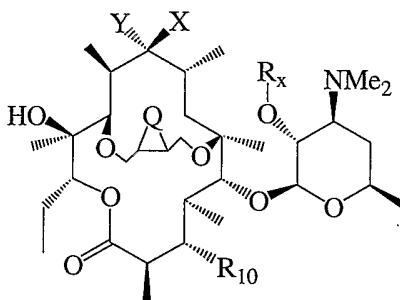
13. A compound according to Claim 1 represented by the formula:



5

wherein Q, X, Y, R_x and R₄" are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

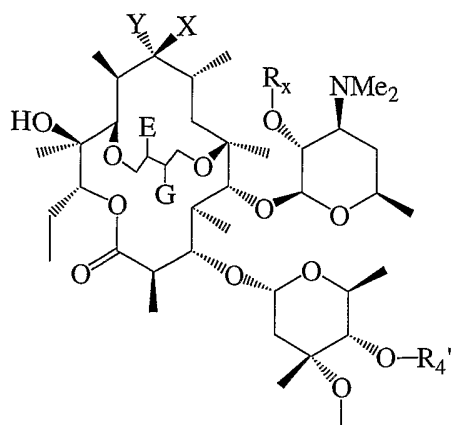
14. A compound according to Claim 1 represented by the formula:



10

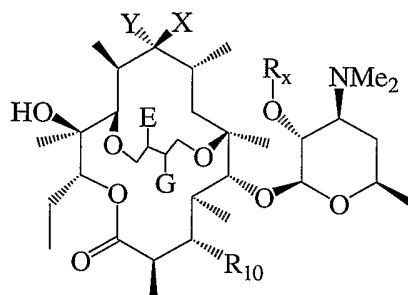
wherein Q, X, Y, R₁₀ and R_x are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

15. A compound according to Claim 1 represented by the formula:



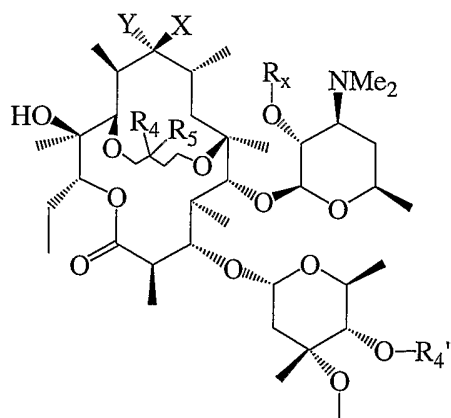
wherein E, G, X, Y, R_x and R₄" are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

- 5 16. A compound according to Claim 1 represented by the formula:



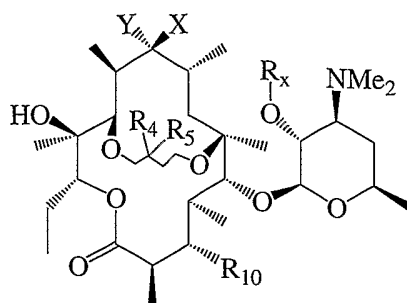
wherein E, G, X, Y, R₁₀ and R_x are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

- 10 17. A compound according to Claim 1 represented by the formula:



wherein X, Y, R₄, R₅, R_x and R₄" are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

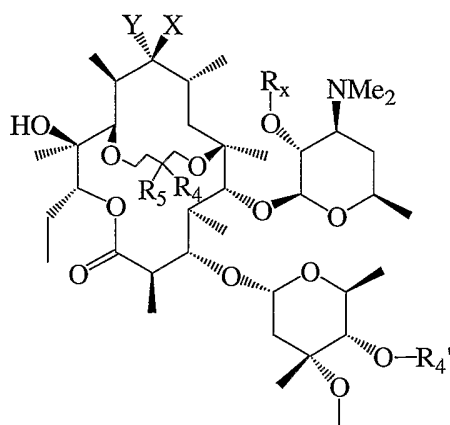
18. A compound according to Claim 1 represented by the formula:



wherein X, Y, R₄, R₅, R₁₀ and R_x are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

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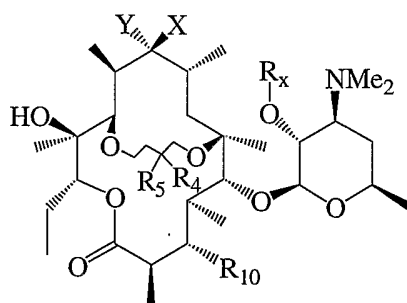
19. A compound according to Claim 1 represented by the formula:



wherein X, Y, R₄, R₅, R_x and R₄^{''} are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

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20. A compound according to Claim 1 represented by the formula:



wherein X, Y, R₄, R₅, R₁₀ and R_x are as defined in Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof.

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21. A compound according to Claim 1 selected from the group consisting of:
- Compound of Formula (II): $A = B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-OH$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
- Compound of Formula (IV): $A = 3\text{-quinolyl}$; $B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-OH$; $R_x = H$ and $R_4'' = C(O)CH_3$;
- Compound of Formula (II): $A = C(O)OCH_3$; $B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-OH$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
- Compound of Formula (II): $A = B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
- Compound of Formula (VIII): $Q = -C(C_6H_5)=N-O-$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
- Compound of Formula (VIII): $Q = -O-C(O)-O-$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
- Compound of Formula (VIII): $Q = -O-$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
- Compound of Formula (VIII): $Q = -O-$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = H$;
- Compound of Formula (II): $A = B = H$; X and Y taken together with the carbon atom they are attached to $= C=NC(O)CH_2OCH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
- Compound of Formula (II): $A = B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)-CH_2OCH_3$; $R_x = H$ and $R_4'' = H$;
- Compound of Formula (IV): $A = 3\text{-quinolyl}$; $B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
- Compound of Formula (IV): $A = 3\text{-quinolyl}$; $B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = H$;
- Compound of Formula (II): $A = C(CH=CH-C_6H_5)$; $B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;
- Compound of Formula (II): $A = C(CH=CH-C_6H_5)$; $B = H$; X and Y taken together with the carbon atom they are attached to $= C=NC(O)CH_3$; $R_x = H$ and $R_4'' = H$;
- Compound of Formula (II): $A = C(CH=CH-C_6H_5)$; $B = H$; X and Y taken together with the carbon atom they are attached to $= C=N-C(O)CH_3$; $R_x = H$ and $R_4'' = C(O)C_6H_5$;

Compound of Formula (II): A = C(CH=CH-C₆H₅); B = H; X and Y taken together with the carbon atom they are attached to = C=NC(O)CH₃; R_x = H and R₄" = H;

Compound of Formula (II): A = H; B = H; X and Y taken together with the carbon atom they are attached to = C=N-Ac; R_x = H and R₄' = H;

5 Compound of Formula (II): A = C(O)-OH; B = H; X and Y taken together with the carbon atom they are attached to = C=N-OH; R_x = H and R₄' = H; and

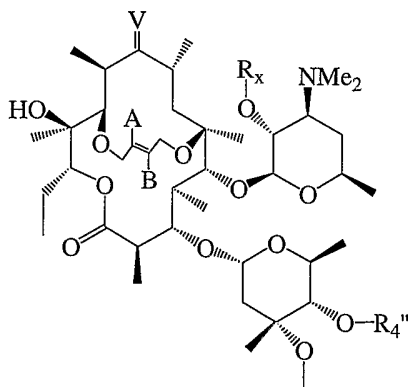
Compound of Compound of Formula (II): A = B = H, X and Y taken together with the carbon atom they are attached to = C=O, R_x = H and R₄' = C(O)CH₃.

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22. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt, ester or prodrug thereof, in combination with a pharmaceutically acceptable carrier.

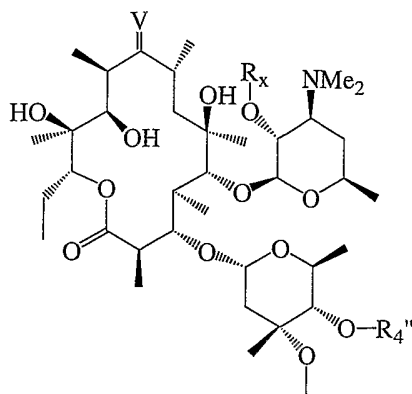
15 23. A method for controlling a bacterial infection in an animal comprising
administering to an animal a therapeutically effective amount of a pharmaceutical
composition according to Claim 22.

24. A process for preparing a compound of formula:

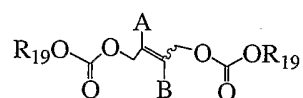


wherein A, B, and R_x are as defined in Claim 1, V taken together with the carbon atom it is attached to is selected from the group consisting of: C=O, C=NR₃, C=N-O-R₆, C=N-C(O)R₃ and C=N-O-C(R₁₆)(R₁₇)-O-R₁₈, where R₃, R₆, R₁₆, R₁₇ and R₁₈ are as defined in Claim 1, and R₄” is a hydroxy protecting group;

25 comprising the step of reacting a compound of the formula:

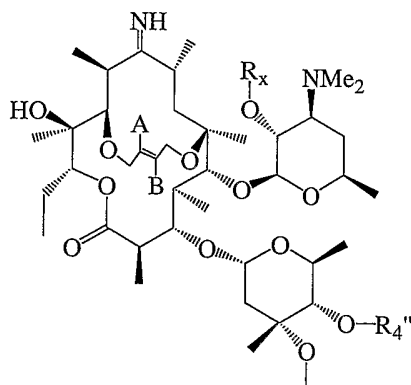


wherein R₄'', R_x and V are as defined previously,
with an alkylating agent of the formula:



- 5 wherein R₁₉ is C₁-C₆ alkyl and A and B are as defined in Claim 1,
in an aprotic solvent in the presence of a palladium catalyst at a temperature
between room temperature and 80°C to produce the claimed compound.

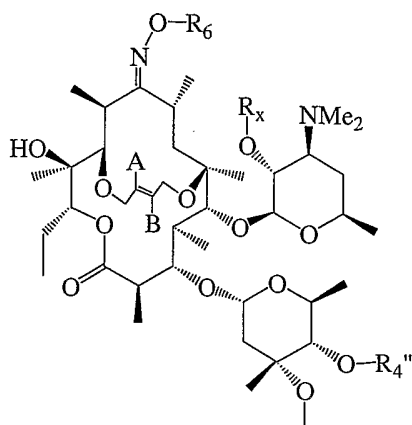
25. A process for preparing a compound of formula:



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wherein R₄'', R_x and V are as defined previously,
with an alkylating agent of the formula:

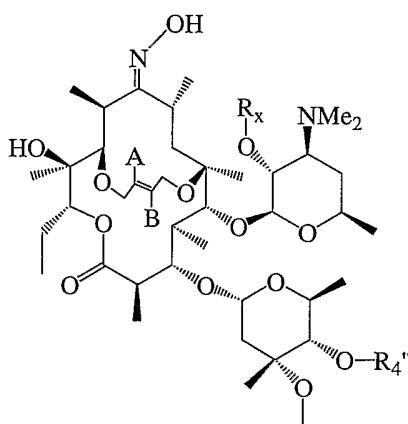
- (a) hydrolyzing a compound of formula:



wherein R_4'' is a hydroxy protecting group and A, B, R_6 and R_x are as defined in Claim 1,

in a protic solvent optionally with aqueous acid or base to obtain the compound of formula:

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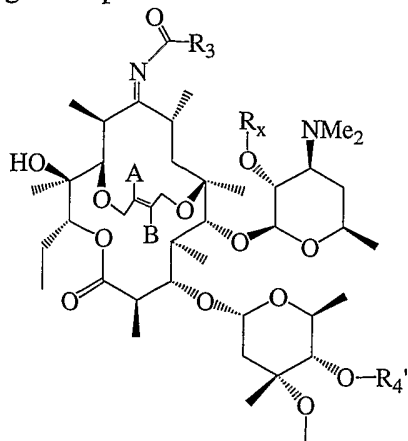


wherein R_4'' , A, B and R_x are as defined previously; and

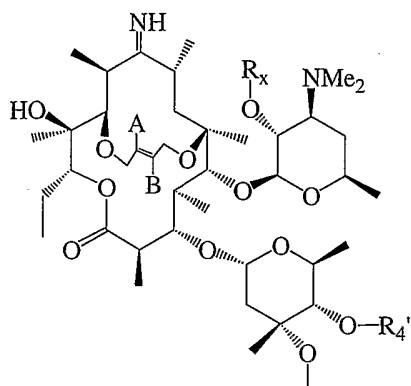
(b) reducing the product of step (a) with a reducing agent to obtain the claimed compound.

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26. A process for preparing a compound of formula:



wherein A, B, R_3 , R_x and R_4'' are as defined in Claim 1;
the process comprising the step of acylating a compound of formula:

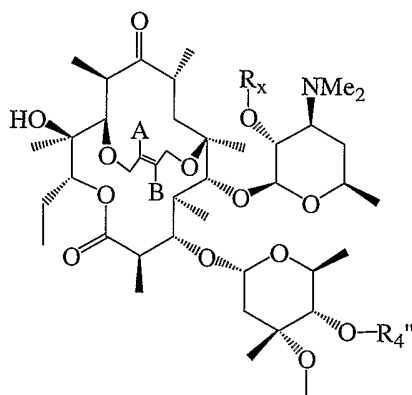


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wherein A, B, R_x and R_4'' are as previously defined,
with $R_3C(O)T$ or $(R_3C(O))_2O$, where R_3 is as defined in Claim 1 and T is a hydroxy
group or halogen, under basic conditions using an acylating agent in an aprotic
solvent, optionally using an activation agent.

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27. A process for preparing a compound of formula:

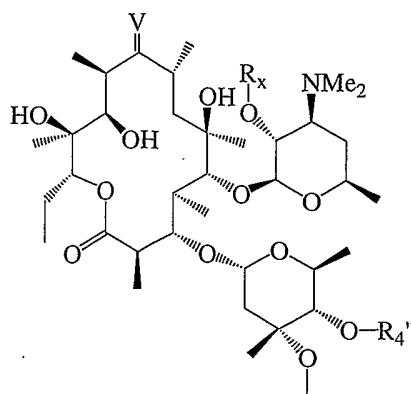


wherein R_4'' is a hydroxy protecting group, and A, B and R_x are as defined in
Claim 1;

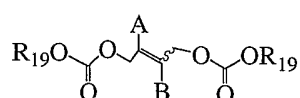
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the process comprising the steps:

(a) reacting a compound of the formula:

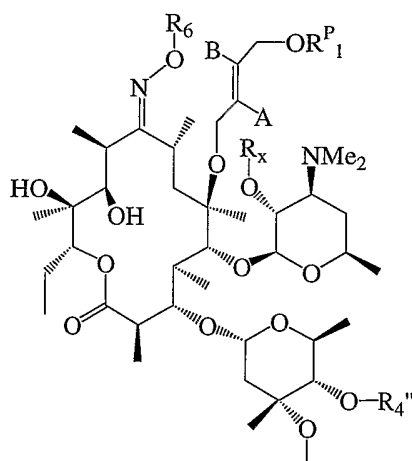


wherein R_4'' and V are as defined in Claim 1 and R_x is as previously defined, with an alkylating agent of the formula:



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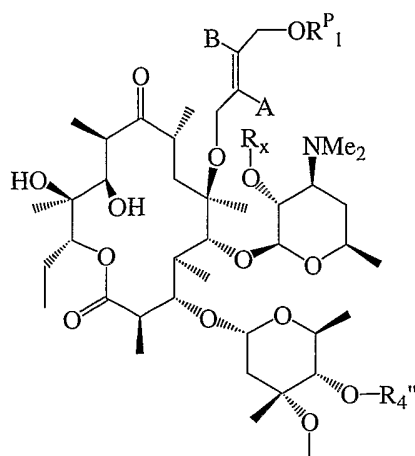
wherein R_{19} is C_1 - C_6 alkyl and A and B are as previously defined, in an aprotic solvent in the presence of a palladium catalyst at a temperature between room temperature and 80°C to produce the compound of formula:



wherein R_6 is as defined in Claim 1, R^P_1 is H or R^P where R^P is as defined in Claim 1, and R_4'' , A, B and R_x are as defined previously;

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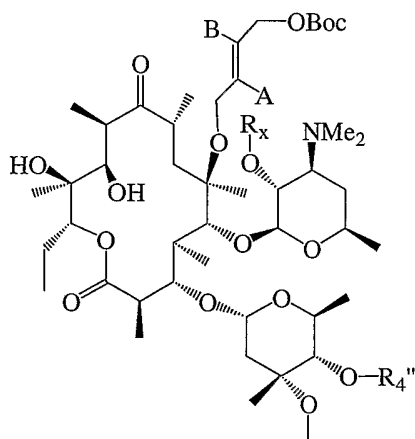
- (b) reacting the compound from step (a) with a protic solvent optionally with aqueous base followed by reduction with a reducing agent to produce a compound of formula:



wherein R_4'' , A, B, R_1^P and R_x are as previously defined;

- (c) removing the R_1^P protecting group from the compound of step (b) and acylating the resulting hydroxy group with di-tert-butoxycarbonate to produce compound of formula:

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wherein Boc is a tert-butoxycarbonyl group and wherein R_4'' , A, B and R_x are as previously defined; and

- (d) reacting the compound from step (b) with a palladium catalyst and a phosphorous ligand to obtain the claimed compound.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 03/20860

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/70 C07H17/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 21864 A (ABBOTT LAB) 6 May 1999 (1999-05-06) cited in the application ----	
A	MA, ZHENKUN ET AL: "Regioselective Synthesis of Bifunctional Macrolides for Probing Ribosomal Binding" ORGANIC LETTERS (2002), 4(6), 987-990 , 2002, XP002259390 -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- *&* document member of the same patent family

Date of the actual completion of the international search

28 October 2003

Date of mailing of the international search report

10/11/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bardili, W

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT, No. 03/20860

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