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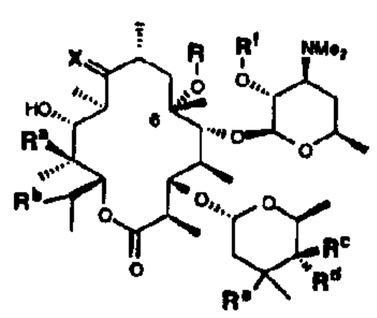
(54) Titre : ERYTHROMYCINES 6-O SUBSTITUEES ET LEUR PROCEDE DE PREPARATION
(54) Title: 6-O-SUBSTITUTED ERYTHROMYCINS AND METHOD FOR MAKING THEM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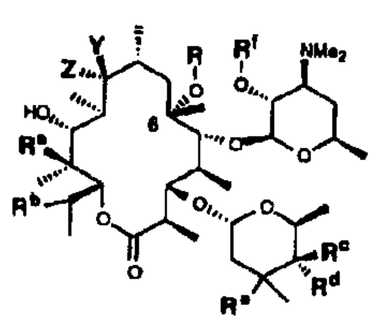
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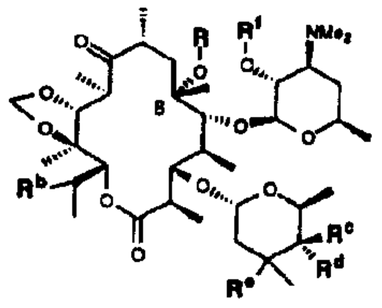
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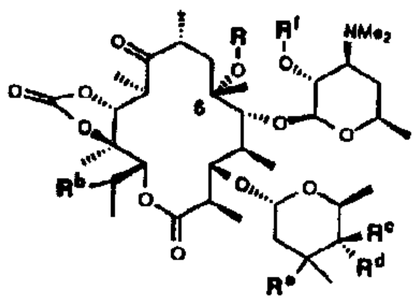
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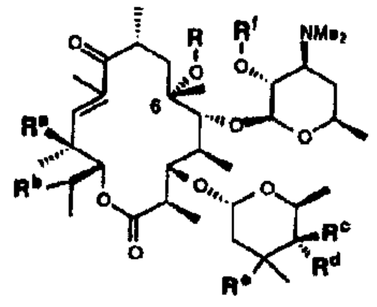
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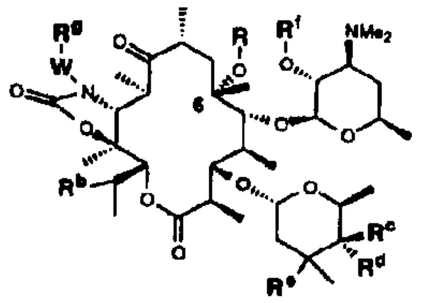
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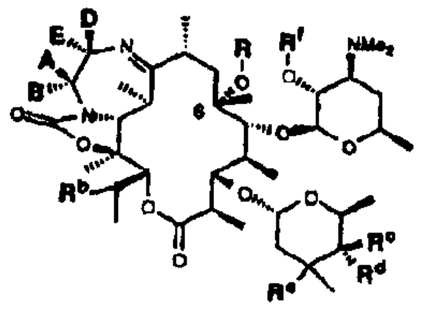
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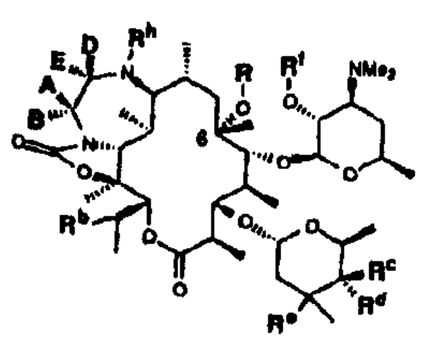
(IX)

(57) Abrégé/Abstract:
Antimicrobial compounds having formula (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) as well as the pharmaceutically acceptable salts, esters and prodrugs thereof; pharmaceutical compositions comprising such compounds; methods of treating bacterial infections by the administration of such compounds; and processes for the preparation of the compounds.

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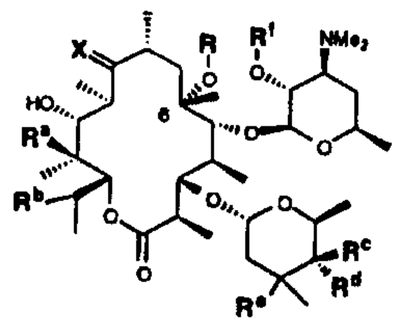
(54) Title: 6-O-SUBSTITUTED ERYTHROMYCINS AND METHOD FOR MAKING THEM

(57) Abstract

Antimicrobial compounds having formula (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) as well as the pharmaceutically acceptable salts, esters and prodrugs thereof; pharmaceutical compositions comprising such compounds; methods of treating bacterial infections by the administration of such compounds; and processes for the preparation of the compounds.



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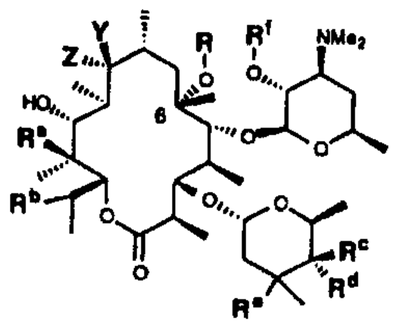

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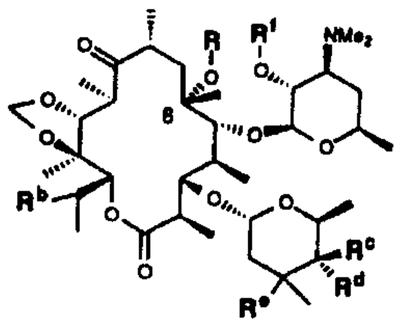

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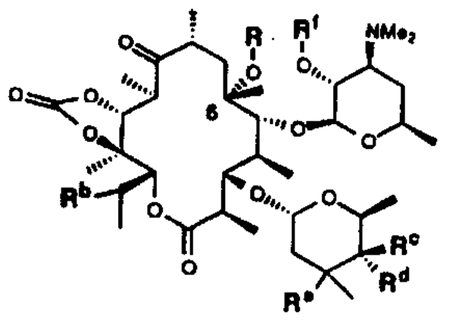

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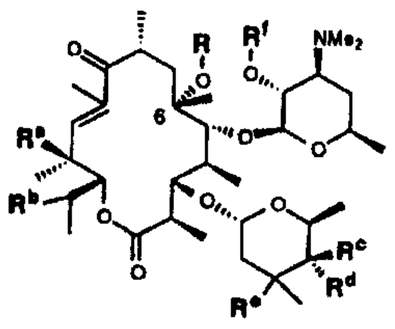

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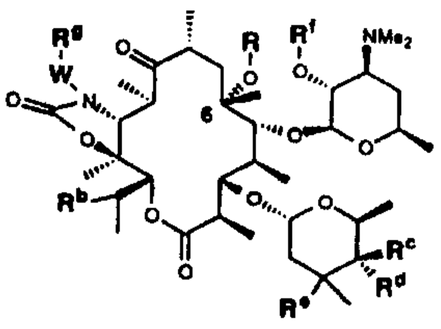

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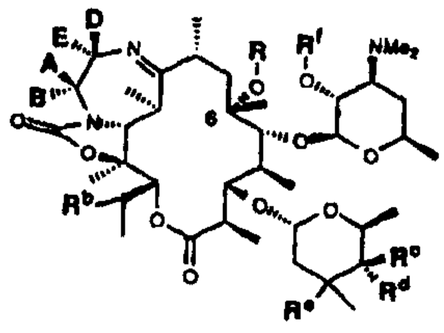

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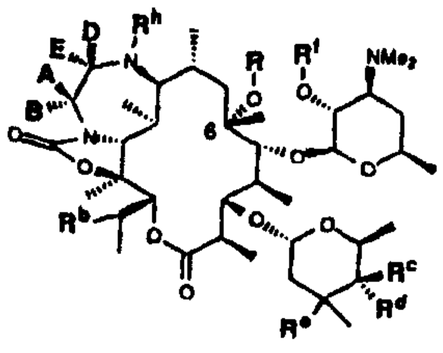


(IX)

WO 97/42204 PCT/US97/04622

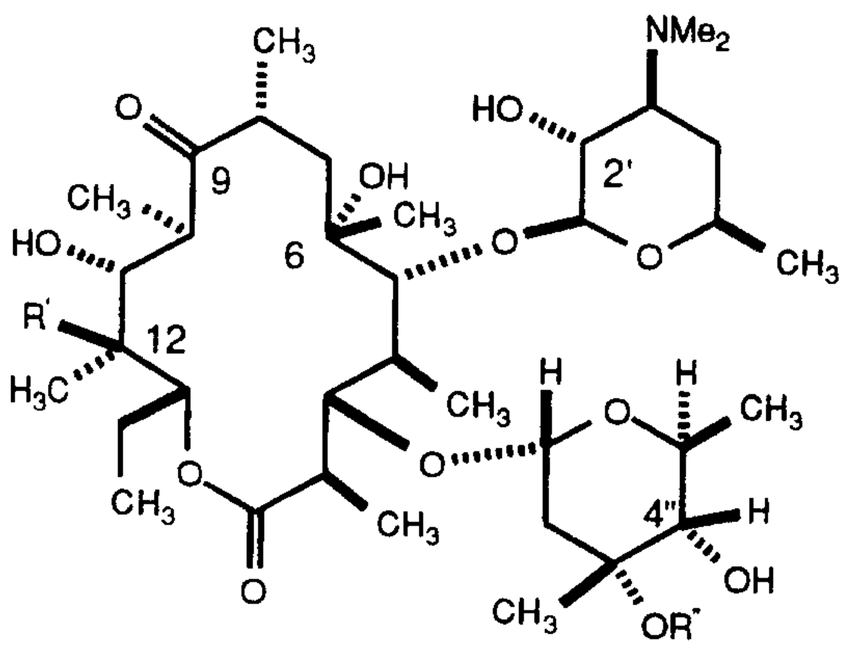
6-O-SUBSTITUTED ERYTHROMYCINS AND METHOD FOR MAKING THEM

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-O-substituted 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 (I),



Erythromycin	R'	R"
A	-OH	$-CH_3$
B	-H	$-CH_3$
C	-OH	-H
D	-H	-H

(I)

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.

Morimoto, *et al.* described the preparation of 6-O-methyl erythromycin A in J. Antibiotics 37:187 (1984). Morimoto, *et al.* further disclosed a series of O-alkyl erythromycin A derivatives in J. Antibiotics 43: 286 (1990). In their experience, "O-alkylation, other than methylation, took place at the C-11 hydroxyl group exclusively." However, in European

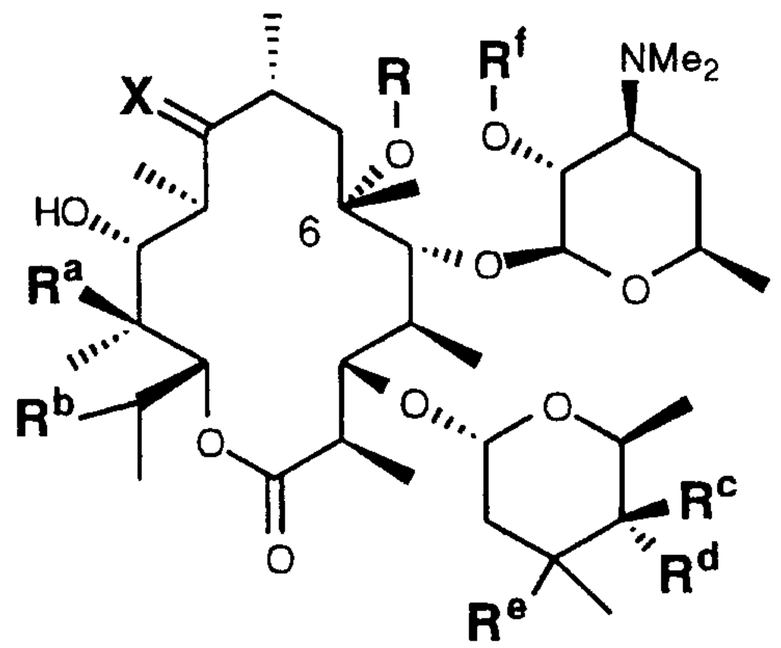
Patent Application 272,110, published June 22, 1988, Morimoto, *et al.* disclose 6-O-C_1-C_3-alkyl erythromycin A compounds.

In European Patent Application 215,355, published March 28, 1987, Omura and Itoh disclose 6-O-loweralkyl erythromycins as stimulants of gastrointestinal contractile motion.

Summary Of The Invention

The present invention provides a novel class of 6-O-substituted erythromycin compounds which possess antibacterial activity.

In one aspect of the present invention is disclosed a novel 6-O-substituted erythromycin compound selected from the formulae:



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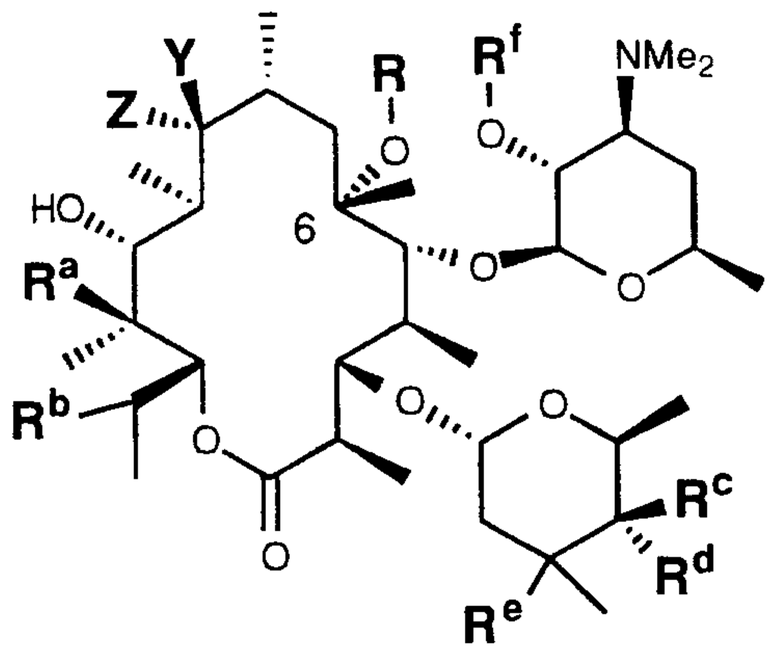

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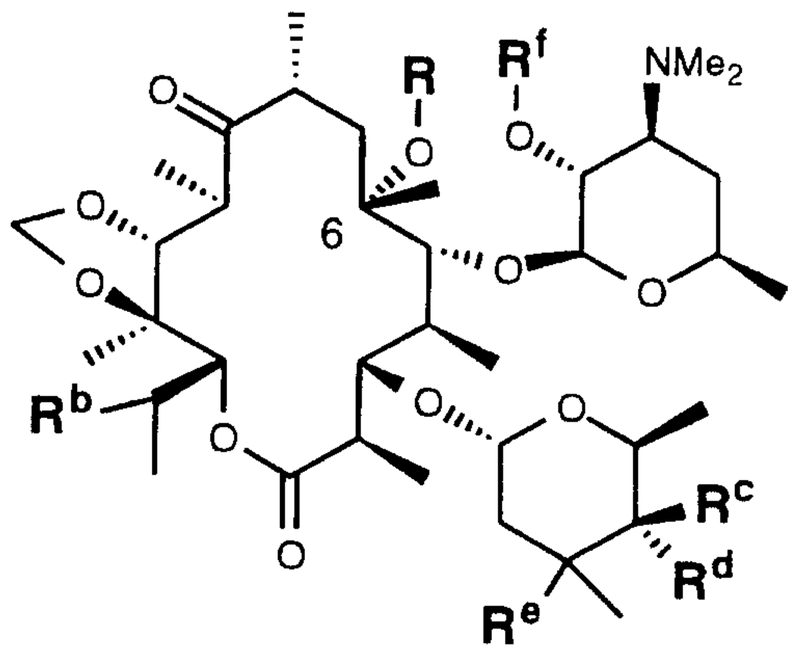

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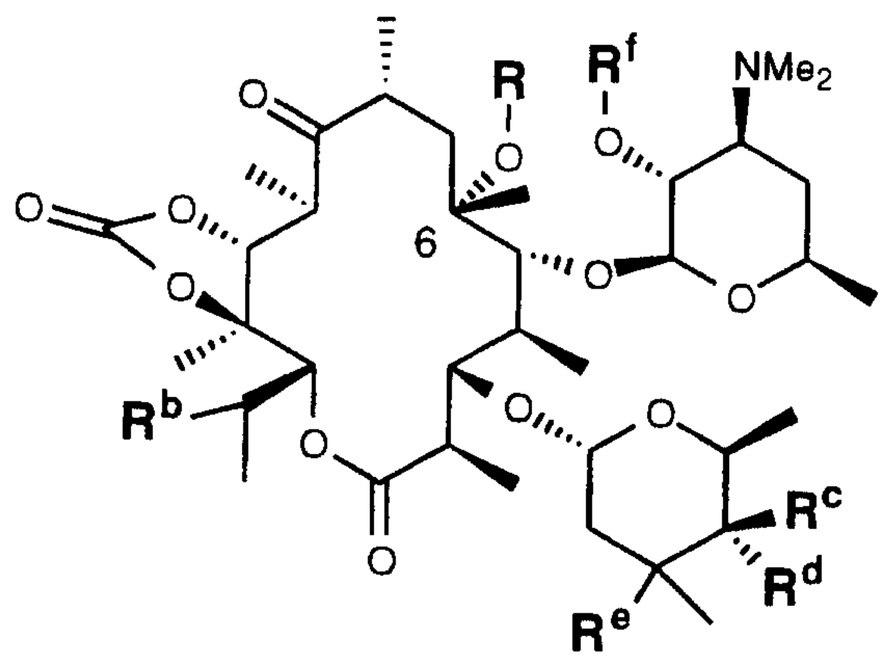

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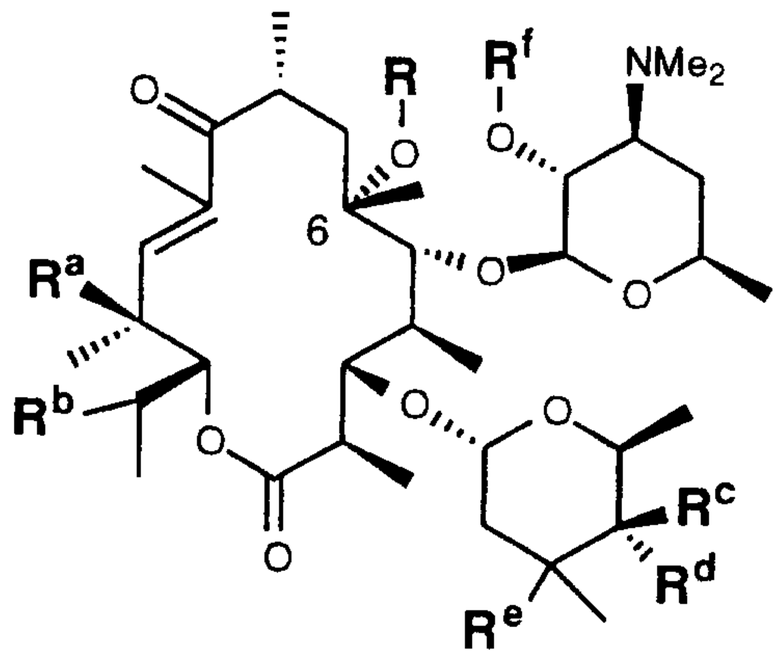

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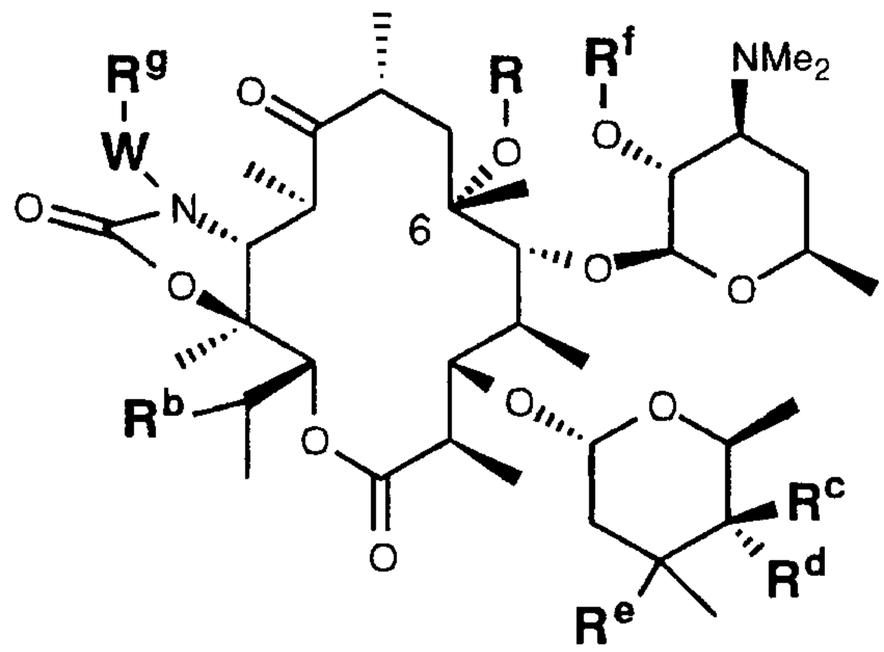

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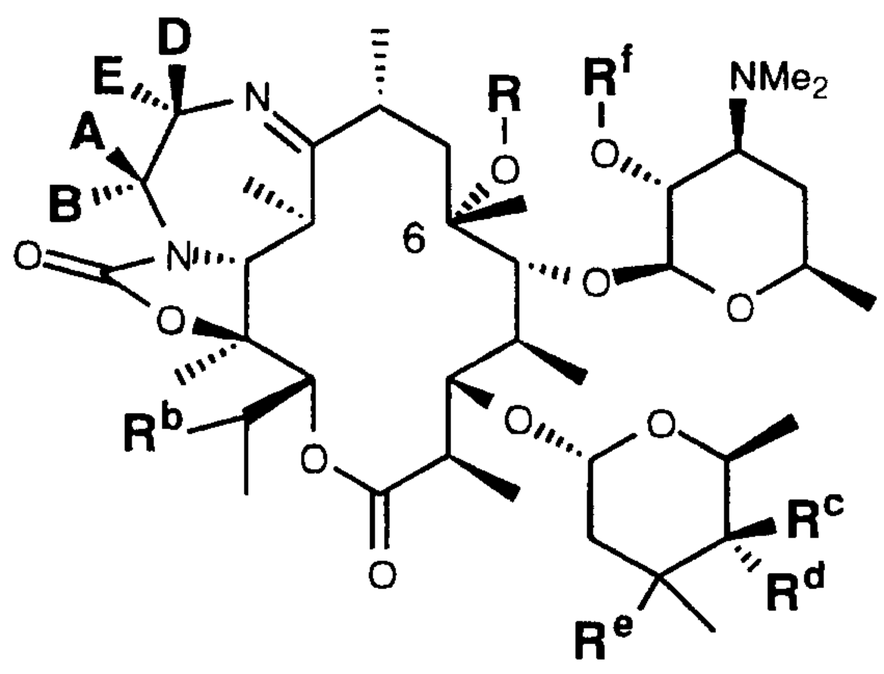
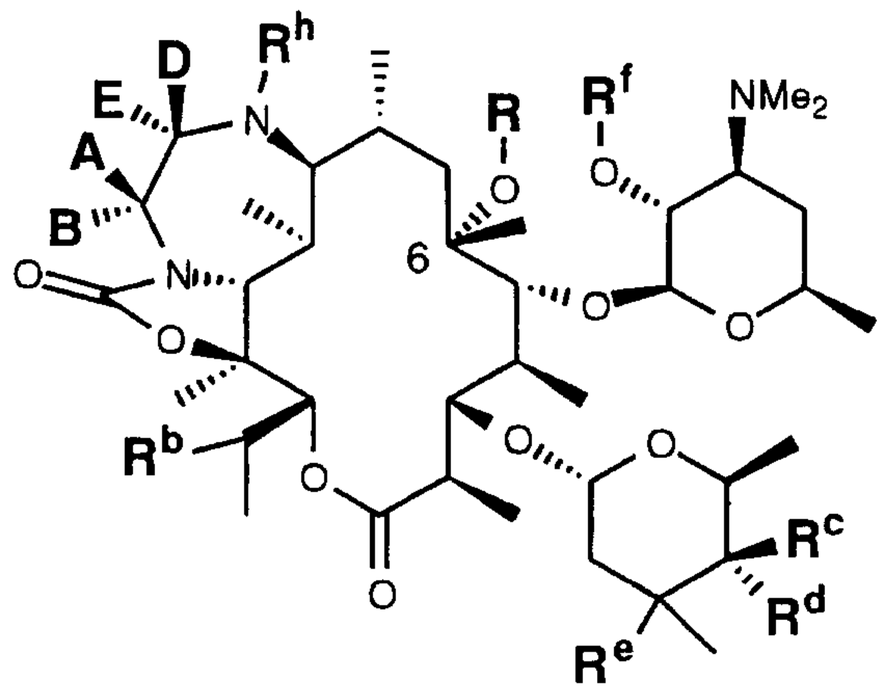


(VIII); and



(IX);

as well as the pharmaceutically acceptable salts, esters and prodrugs thereof. In formulae (II) - (IX) above,

X is:

(1) =O,

(2) =N-OH,

(3) =N-O-R^1 where R^1 is

(a) unsubstituted C_1-C_{12}-alkyl,

(b) C_1-C_{12}-alkyl substituted with aryl,

(c) C_1-C_{12}-alkyl substituted with substituted aryl,

(d) C_3-C_{12}-cycloalkyl,

(e) -Si-(R^{11})(R^{12})(R^{13}) wherein R^{11}, R^{12} and R^{13} are each independently selected from C_1-C_{12}-alkyl,

(f) -Si-(Aryl)$_3$, or

(4) =N-O-C(R^9)(R^{10})-O-R^1 where R^1 is as defined above and R^9 and R^{10} are each independently selected from the group consisting of:

(a) hydrogen,

(b) unsubstituted C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl, and

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

or R^9 and R^{10} taken together with the carbon to which they are attached form a C_3-C_{12}-cycloalkyl ring;

R^a is hydrogen or hydroxy;

R^b is hydrogen or hydroxy;

one of R^c and R^d is hydrogen and the other of R^c and R^d is:

(1) hydroxy,

(2) protected hydroxy,

(3) halogen, or

(4) NR^3R^4 where R^3 and R^4 are independently selected from

(a) hydrogen,

(b) C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl,

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

(e) C_1-C_{12}-alkyl substituted with heteroaryl, and

(d) C_1-C_{12}-alkyl substituted with substituted heteroaryl, or

(5) -SO_2-(substituted C_1-C_6-alkyl, or

R^3 and R^4 taken together with the carbon to which they are attached form a 3-7 membered hetereocyclicalkyl ring,

or

R^c and **R^d** taken together is:

(1) =O,

(2) =N-OH, or

(3) =N-OR[1] wherein R[1] is as defined above;

R[e] is methoxy, fluorine or hydroxy;

R[f] is hydrogen or an hydroxy protecting group;

R[g] is selected from a group consisting of:

(1) unsubstituted C_1-C_6-alkyl,

(2) C_1-C_6-alkyl substituted with one or more substituents selected from the group consisting of:

(a) aryl,

(b) substituted aryl,

(c) heteroaryl,

(d) substituted heteroaryl,

(e) heteroarylalkyl,

(f) hydroxy,

(g) C_1-C_6-alkoxy,

(h) NR^3R^4 wherein R^3 and R^4 are as defined above, and

(i) $-CH_2-M-R^5$ where M is selected from a group consisting of:

(i) -O-,

(ii) -NH-,

(iii) -NMe-,

(iv) $-S(O)_n-$ where n is 0, 1 or 2,

(v) -NHC(=O)-, and

(vi) -C(=O)-NH-,

and

R^5 is selected from a group consisting of:

(i) $-(CH_2)_n$-aryl where n is 0, 1 or 2,

(ii) $-(CH_2)_n$-substituted aryl where n is 0, 1 or 2,

(iii) $-(CH_2)_n$-heteroaryl where n=0, 1 or 2,

(iv) $-(CH_2)_n$-substituted heteroaryl where n is 0, 1 or 2, and

(v) $-(CH_2)_n$-heteroarylalkyl where n is 0, 1 or 2,

(3) C_3-C_{12}-cycloalkyl,

(4) aryl,

(5) substituted aryl,

(6) heteroaryl, and

(7) substituted heteroaryl;

R[h] is selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl,

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

(e) C_1-C_{12}-alkyl substituted with heteroaryl, and

(d) C_1-C_{12}-alkyl substituted with substituted heteroaryl;

R is selected from the group consisting of:

(1) C_1-alkyl substituted with a substituent selected from the group consisting of:

(a) F,

(b) $S(O)_nR^6$ where n is 0, 1 or 2 and C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(c) $NHC(O)R^6$ where R^6 is as defined above, and

(d) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are independently selected from hydrogen and C_1-C_3-alkyl,

(2) C_2-C_{10}-alkyl;

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N-O-R^6$ where R^6 is as previously defined,

(j) $-C\equiv N$,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) =N-NHC(O)R^6 where R^6 is as previously defined, and

(v) =N-NHC(O)NR^3R^4 wherein R^3 and R^4 are as previously defined;

(4) C_2-C_{10}-alkenyl;

(5) C_2-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) -CO_2R^6 where R^6 is as defined above,

(g) -C(O)NR^3R^4 wherein R^3 and R^4 are as previously defined,

(h) -NR^3R^4 wherein R^3 and R^4 are as previously defined,

(i) =N-O-R^6 where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) NHC(O)R^6 where R^6 is as previously defined,

(s) NHC(O)NR^3R^4 wherein R^3 and R^4 are as previously defined,

(t) =N-NR^3R^4 wherein R^3 and R^4 are as previously defined,

(u) =N-NHC(O)R^6 where R^6 is as previously defined, and

(v) =N-NHC(O)NR^3R^4 wherein R^3 and R^4 are as previously defined;

(6) C_2-C_{10}-alkynyl; and

(7) C_2-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of:

(a) trialkylsilyl,

(b) aryl,

(c) substituted aryl,

(d) heteroaryl, and

(e) substituted heteroaryl;

one of **Y** and **Z** is hydrogen and the other is selected from a group consisting of:

(1) hydrogen,

(2) hydroxy,

(3) protected hydroxy, and

(4) NR^3R^4 wherein R^3 and R^4 are as defined above;

W is:

(1) -O-,

(2) -NH-,

(3) -NMe-, or

(4) absent;

A, B, D and **E** are, at each occurrence, independently selected from the group consisting of:

(1) hydrogen,

(2) unsubstituted C_1-C_6-alkyl, and

(3) C_1-C_6-alkyl substituted with one or more substituents selected from the group consisting of:

(a) aryl,

(b) substituted aryl,

(c) heteroaryl,

(d) substituted heteroaryl,

(e) heteroarylalkyl,

(f) hydroxy,

(g) C_1-C_6-alkoxy,

(h) NR^3R^4, where R^3 and R^4 are as defined above, and

(i) $-CH_2-M-R^5$ where M is selected from a group consisting of:

(i) -O-,

(ii) -NH-,

(iii) -NMe-,

(iv) $-S(O)_n-$ where n is 0, 1 or 2,

(v) -NHC(=O)-, and

(vi) -C(=O)-NH-,

and

R^5 is selected from a group consisting of:

(i) $-(CH_2)_n$-aryl where n is 0, 1 or 2,

(ii) $-(CH_2)_n$-substituted aryl where n is 0, 1 or 2,

(iii) $-(CH_2)_n$-heteroaryl where n=0, 1 or 2,

(iv) $-(CH_2)_n$-substituted heteroaryl where n is 0, 1 or 2, and

(v) $-(CH_2)_n$-heteroarylalkyl where n is 0, 1 or 2,

or any pair of substituents, consisting of AB, AD, AE, BD, BE or DE, is taken together with the atom or atoms to which they are attached to form a 3- to 7-membered ring optionally containing a hetero function selected from:

(1) -O-,

(2) $-S(O)_n-$, where n is 0, 1 or 2,

(3) -NH-,

(4) $-N(CH_3)-$, and

(5) $-N(R^5)-$ wherein R^5 is as previously defined.

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

In a further aspect of the present invention are provided processes for the preparation of 6-O-substituted macrolide derivatives of Formula (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) above.

Detailed Description Of The Invention

One embodiment of the present invention comprises a compound of formula (II) above, wherein X, R, R^a, R^b, R^c, R^d, R^e and R^f are as defined above.

Another embodiment of the present invention comprises a compound of formula (III) above, wherein Y, Z, R, R^a, R^b, R^c, R^d, R^e and R^f are as defined above.

Another embodiment of the present invention comprises a compound of formula (IV) above, wherein R, R^b, R^c, R^d, R^e and R^f are as defined above.

Another embodiment of the present invention comprises a compound of formula (V) above, wherein R, R^b, R^c, R^d, R^e and R^f are as defined above.

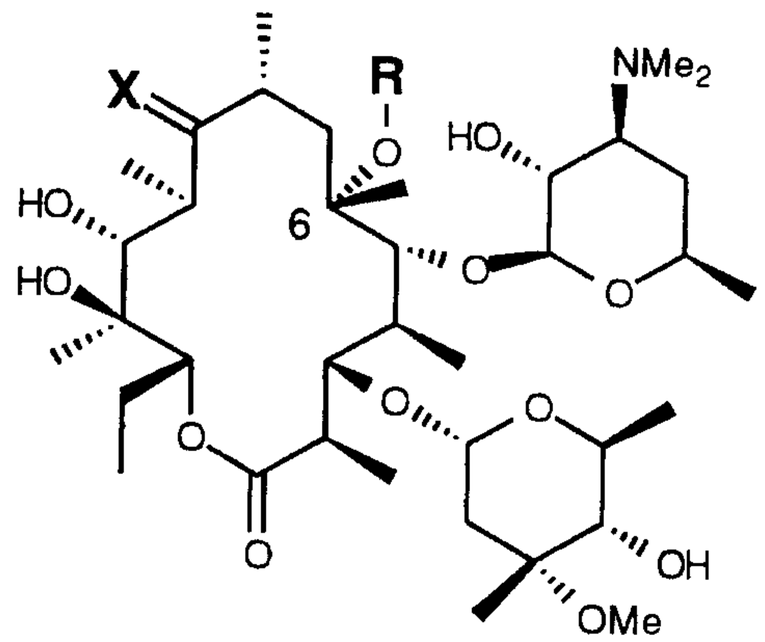
Another embodiment of the present invention comprises a compound of formula (VI) above, wherein R, R^a, R^b, R^c, R^d, R^e and R^f are as defined above.

Another embodiment of the present invention comprises a compound of formula (VII) above, wherein W, R, R^b, R^c, R^d, R^e, R^f and R^g are as defined above.

Another embodiment of the present invention comprises a compound of formula (VIII) above, wherein A, B, D, E, R, R^b, R^c, R^d, R^e and R^f are as defined above.

Another embodiment of the present invention comprises a compound of formula (IX) above, wherein A, B, D, E, R, R^b, R^c, R^d, R^e, R^f and R^h are as defined above.

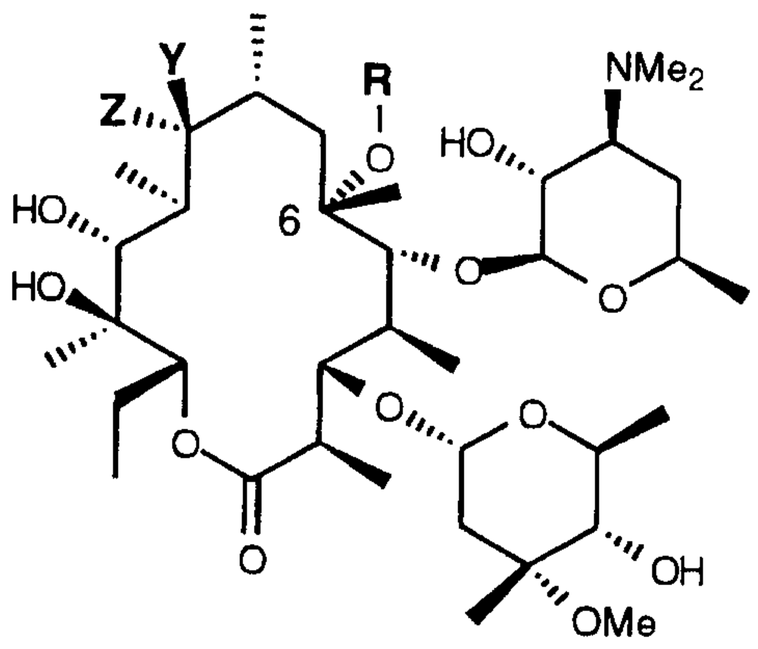
A preferred embodiment of the present invention is the compound of formula (X):



(X)

where X and R are as defined above.

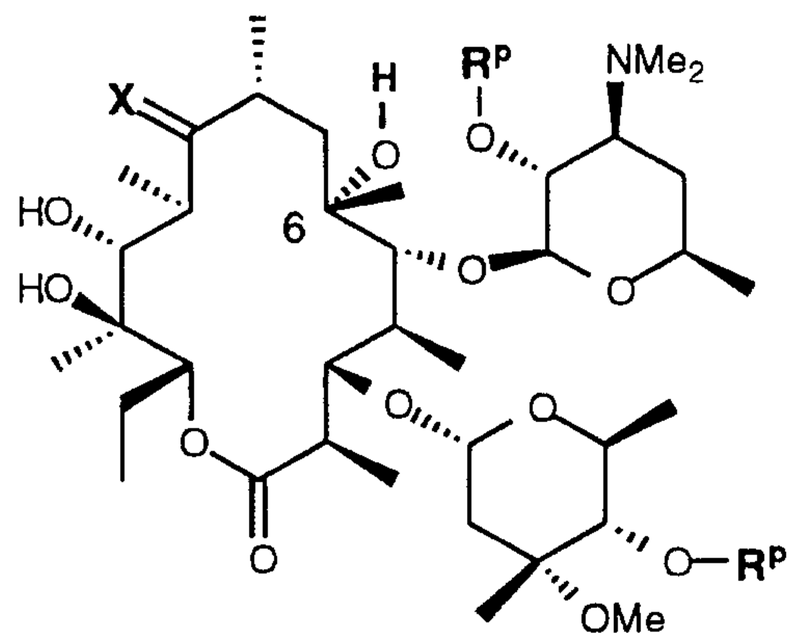
Another preferred embodiment of the present invention is the compound of formula (XI):



(XI)

where Y, Z and R are as defined above.

A preferred intermediate in the preparation of the compound of formula (X) is the compound of formula (XII):



(XII)

where X is as defined above and R^P is an hydroxy protecting group.

Representative of the compounds of the invention include:

Compound of Formula (X): X is =N-O-(1-isopropoxycyclohexyl), R is allyl;

Compound of Formula (X): X is =O, R is allyl;

Compound of Formula (X): X is =O, R is propyl;

Compound of Formula (X): X is =O, R is 2,3-dihydroxypropyl;

Compound of Formula (X): X is =O, R is 2,3-epoxypropyl;

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(imidazol-1-yl)propyl;

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(morpholin-4-yl)propyl;

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(benzylamino)propyl;

Compound of Formula (X): X is =O, R is $-CH_2-CHO$;

Compound of Formula (X): X is =O, R is $-CH_2-C(O)-CH_3$;

Compound of Formula (X): X is =O, R is $-CH_2-C\equiv CH$;

Compound of Formula (X): X is =O, R is $-CH_2-CHOH-CH_2-N_3$;

Compound of Formula (X): X is =O, R is $-CH_2-CH=N-OH$;

Compound of Formula (X): X is =O, R is $-CH_2-CH_2OH$;

Compound of Formula (X): X is =O, R is $-CH_2-CH_2NH_2$;

Compound of Formula (X): X is =O, R is $-CH_2-CN$;

Compound of Formula (X): X is =O, R is $-CH_2$-Phenyl;

Compound of Formula (X): X is =O, R is $-CH_2-CH=CH$(Phenyl);

Compound of Formula (X): X is =O, R is $-CH_2-CH=N-O-CH_3$;

Compound of Formula (X): X is =O, R is $-CH_2-CH=N-O-CH_2$-Phenyl;

Compound of Formula (X): X is =O, R is $-CH_2-CH=N-N(CH_3)_2$;

Compound of Formula (X): X is =O, R is $-CH_2-CH=N-NH(CH_3)$;

Compound of Formula (X): X is =O, R is $-CH_2-CH=N-$(4-Morpholinyl);

Compound of Formula (X): X is =O, R is $-CH_2-CH=N-NH$(Phenyl);

Compound of Formula (X): X is =O, R is -CH_2-CH=N-N(Phenyl)$_2$;
Compound of Formula (X): X is =O, R is -$CH_2CH_2CH_2OH$;
Compound of Formula (X): X is =O, R is -CH_2-CO_2H;
Compound of Formula (X): X is =O, R is -$CH_2CH_2NH(CH_3)$;
Compound of Formula (X): X is =O, R is -$CH_2CH_2NHCH_2CH_3$;
Compound of Formula (X): X is =O, R is -$CH_2CH_2NHCH_2CH_2$-Phenyl;
Compound of Formula (X): X is =O, R is -$CH_2CH_2N(CH_3)_2$;
Compound of Formula (X): X is =O, R is -CH_2CH_2-(4-morpholinyl);
Compound of Formula (X): X is =O, R is -$CH_2C(O)NH_2$;
Compound of Formula (X): X is =O, R is -$CH_2NHC(O)NH_2$;
Compound of Formula (X): X is =O, R is -$CH_2NHC(O)CH_3$;
Compound of Formula (X): X is =O, R is -CH_2F;
Compound of Formula (X): X is =O, R is -$CH_2CH_2OCH_3$;
Compound of Formula (X): X is =O, R is -CH_2CH_3;
Compound of Formula (X): X is =O, R is -$CH_2CH=C(CH_3)_{23}$;
Compound of Formula (X): X is =O, R is -CH_2CH=CHPh;
Compound of Formula (X): X is =O, R is -$(CH_2)_3$-Ph;
Compound of Formula (X): X is =O, R is -$(CH_2)_2$-$CH(CH_3)_2$;
Compound of Formula (X): X is =O, R is -$(CH_2)_2$-O-$(CH_2)_2$-O-CH_3;
Compound of Formula (X): X is =O, R is -CH_2-Ph;
Compound of Formula (X): X is =N-OH, R is -CH_2-C≡CH;
Compound of Formula (X): X is =N-O-CH_3, R is -CH_2-C≡CH;
Compound of Formula (X): X is =N-O-Benzyl, R is -CH_2-C≡CH;
Compound of Formula (X): X is =N-O-CH_2-O-CH_3, R is -CH_2-C≡CH;
Compound of Formula (X): X is =N-O-CH_2-O-CH_2-CH_2-O-CH_3, R is -CH_2-C≡CH;
Compound of Formula (X): X is =N-OH, R is -CH_2-CH=CH_2;
Compound of Formula (X): X is =N-O-CH_3, R is -CH_2-CH=CH_2;
Compound of Formula (X): X is =N-O-Benzyl, R is -CH_2-CH=CH_2;
Compound of Formula (X): X is =N-O-CH_2-O-CH_3, -CH_2-CH=CH_2;
Compound of Formula (X): X is =N-O-CH_2-O-CH_2-CH_2-O-CH_3, R is -CH_2-CH=CH_2;
Compound of Formula (XI): Y is NH_2, Z is H, R is -CH_2-C≡CH;
Compound of Formula (XI): Y is NH-$CH_2CH_2CH_3$, Z is H, R is -CH_2-C≡CH;
Compound of Formula (XI): Y is NH-$(CH_2)_9$-CH_3, Z is H, R is -CH_2-C≡CH;
Compound of Formula (XI): Y is NH-$CH(CH_3)_2$, Z is H, R is -CH_2-C≡CH;
Compound of Formula (XI): Y is 1-piperidinyl, Z is H, R is -CH_2-C≡CH;
Compound of Formula (XI): Y is H, Z is 1-piperidinyl, R is -CH_2-C≡CH;

Compound of Formula (XI): Y is H, Z is NH_2, R is $-CH_2-C\equiv CH$;

Compound of Formula (XI): Y is H, Z is $NH-CH_2CH_2CH_3$, R is $-CH_2-C\equiv CH$;

Compound of Formula (XI): Y is H, Z is $NH-(CH_2)_9-CH_3$, R is $-CH_2-C\equiv CH$;

Compound of Formula (XI): Y is H, Z is $NH-CH(CH_3)_2$, R is $-CH_2-C\equiv CH$;

Compound of Formula (XI): Y is OH, Z is H, R is $-CH_2-C\equiv CH$;

Compound of Formula (XI): Y is H, Z is OH, R is $-CH_2-C\equiv CH$;

Compound of Formula (IV): R is $-CH_2CH=CH_2$, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (IV): R is $-CH_2-C\equiv CH$, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (IV): R is $-CH_2-C\equiv N$, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (V): R is $-CH_2CH=CH_2$, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (V): R is $-CH_2-C\equiv CH$, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (V): R is $-CH_2-C\equiv N$, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (VI): R is $-CH_2CH=CH_2$, R^a is OH, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (VI): R is $-CH_2-C\equiv CH$, R^a is OH, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (VI): R is $-CH_2-C\equiv N$, R^a is OH, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (VII): R is $-CH_2CH=CH_2$ and W, R^b, R^c, R^d, R^e, R^f and R^g are as previously defined;

Compound of Formula (VII): R is $-CH_2-C\equiv CH$ and W, R^b, R^c, R^d, R^e, R^f and R^g are as previously defined;

Compound of Formula (VII): R is $-CH_2-C\equiv N$ and W, R^b, R^c, R^d, R^e, R^f and R^g are as previously defined;

Compound of Formula (VIII): R is $-CH_2CH=CH_2$ and A, B, D, E, R^b, R^c, R^d, R^e and R^f are as previously defined;

Compound of Formula (VIII): R is $-CH_2-C\equiv CH$ and A, B, D, E, R^b, R^c, R^d, R^e and R^f are as previously defined;

Compound of Formula (VIII): R is $-CH_2-C\equiv N$ and A, B, D, E, R^b, R^c, R^d, R^e and R^f are as previously defined;

Compound of Formula (IX): R is $-CH_2CH=CH_2$, and A, B, D, E, R^b, R^c, R^d, R^e, R^f and R^h are as previously defined;

Compound of Formula (IX): R is $-CH_2-C\equiv CH$, and A, B, D, E, R^b, R^c, R^d, R^e, R^f and R^h are as previously defined;

Compound of Formula (IX): R is $-CH_2-C\equiv N$, and A, B, D, E, R^b, R^c, R^d, R^e, R^f and R^h are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2CH=CH_2$, R^c and R^d taken together are =O, and R^a, R^b, R^e and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2-C\equiv CH$, R^c and R^d taken together are =O, and R^a, R^b, R^e and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2-C\equiv N$, R^c and R^d taken together are =O, and R^a, R^b, R^e and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2CH=CH_2$, R^c is -OH, R^d is -H, R^e is $-OCH_3$; and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2-C\equiv CH$, R^c is -OH, R^d is -H, R^e is $-OCH_3$; and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2-C\equiv N$, R^c is -OH, R^d is -H, R^e is $-OCH_3$; and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2CH=CH_2$, R^c is $-N(CH_3)_2$, R^d is -H, R^e is $-OCH_3$ and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2-C\equiv CH$, R^c is $-N(CH_3)_2$, R^d is -H, R^e is $-OCH_3$ and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2-C\equiv N$, R^c is $-N(CH_3)_2$, R^d is -H, R^e is $-OCH_3$ and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2CH=CH_2$, R^c is -H, R^d is $-N(CH_3)_2$, R^e is $-OCH_3$ and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2-C\equiv CH$, R^c is -H, R^d is $-N(CH_3)_2$, R^e is $-OCH_3$ and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2-C\equiv N$, R^c is -H, R^d is $-N(CH_3)_2$, R^e is $-OCH_3$ and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2CH=CH_2$, R^c is -H, R^d is $-OCH_3$, R^e is -F and R^a, R^b and R^f are as previously defined;

Compound of Formula (II): X is =O, R is $-CH_2-C\equiv CH$, R^c is -H, R^d is $-OCH_3$, R^e is -F and R^a, R^b and R^f are as previously defined; and

Compound of Formula (II): X is =O, R is $-CH_2-C\equiv N$, R^c is -H, R^d is $-OCH_3$, R^e is -F and R^a, R^b and R^f are as previously defined;

as well as the pharmaceutically acceptable salts, esters and prodrugs thereof.

Preferred compounds are selected from the group consisting of:

Compound of Formula (X): X is =N-O-(1-isopropoxycyclohexyl), R is allyl;

Compound of Formula (X): X is =O, R is allyl;

Compound of Formula (X): X is =O, R is propyl;

Compound of Formula (X): X is =O, R is 2,3-dihydroxypropyl;

Compound of Formula (X): X is =O, R is 2,3-epoxypropyl;

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(imidazol-1-yl)propyl;

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(morpholin-4-yl)propyl;

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(benzylamino)propyl;

Compound of Formula (X): X is =O, R is 2-oxoethyl;

Compound of Formula (X): X is =O, R is 2-oxopropyl;

Compound of Formula (X): X is =O, R is -CH_2-C≡CH;

Compound of Formula (X): X is =O, R is -CH_2-CHOH-CH_2-N_3;

Compound of Formula (X): X is =O, R is -CH_2-CH=N-OH;

Compound of Formula (X): X is =O, R is -CH_2-CH_2OH;

Compound of Formula (X): X is =O, R is -CH_2-CH_2NH_2;

Compound of Formula (X): X is =O, R is -CH_2-CN;

Compound of Formula (X): X is =O, R is -CH_2-Phenyl;

Compound of Formula (X): X is =O, R is -CH_2-CH=CH(Phenyl);

Compound of Formula (X): X is =O, R is -CH_2-CH=N-O-CH_3;

Compound of Formula (X): X is =O, R is -CH_2-CH=N-O-CH_2-Phenyl;

Compound of Formula (X): X is =O, R is -CH_2-CH=N-N$(CH_3)_2$;

Compound of Formula (X): X is =O, R is -CH_2-CH=N-NH(CH_3);

Compound of Formula (X): X is =O, R is -CH_2-CH=N-(4-Morpholinyl);

Compound of Formula (X): X is =O, R is -CH_2-CH=N-NH(Phenyl); and

Compound of Formula (X): X is =O, R is -CH_2-CH=N-N$(Phenyl)_2$; as well as the pharmaceutically acceptable salts, esters and prodrugs thereof.

More preferred compounds are selected from the group consisting of:

Compound of Formula (X): X is =O, R is allyl;

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(benzylamino)propyl;

Compound of Formula (X): X is =O, R is 2-oxopropyl;

Compound of Formula (X): X is =O, R is -CH_2-C≡CH;

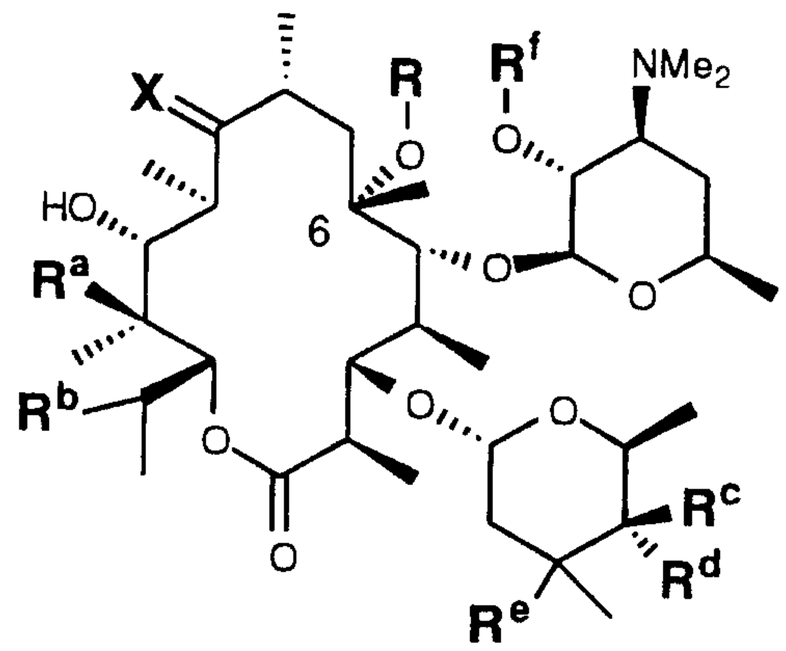
Compound of Formula (X): X is =O, R is -CH_2-CH=N-OH;

Compound of Formula (X): X is =O, R is -CH_2-CH_2OH;

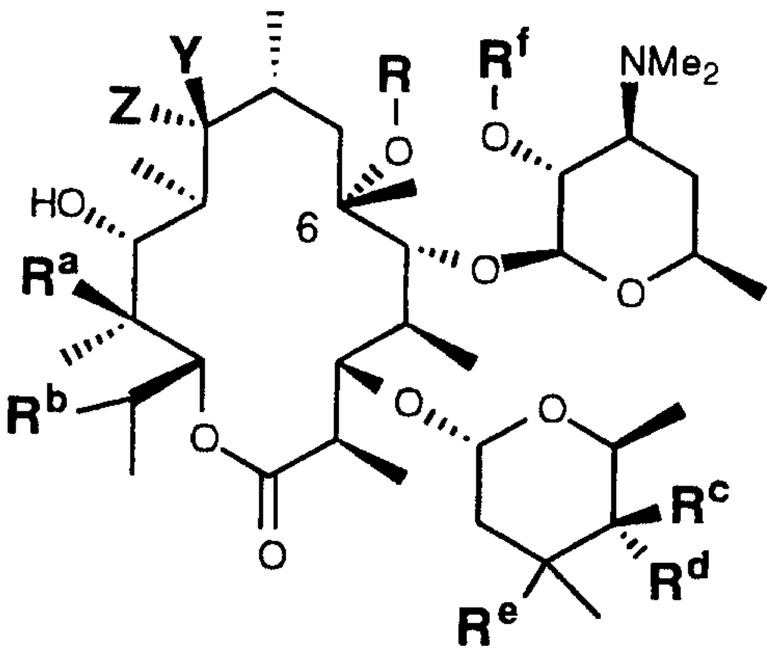
Compound of Formula (X): X is =O, R is -CH_2-CH_2NH_2; and

Compound of Formula (X): X is =O, R is -CH_2-CN; as well as the pharmaceutically acceptable salts, esters and prodrugs thereof.

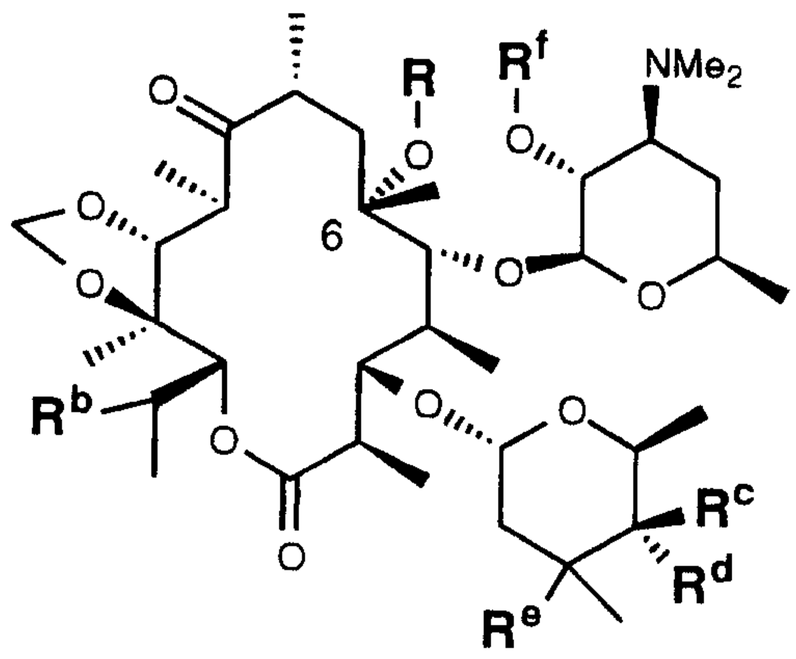
A process for the preparation of 6-O-substituted macrolide derivatives having the Formulae:



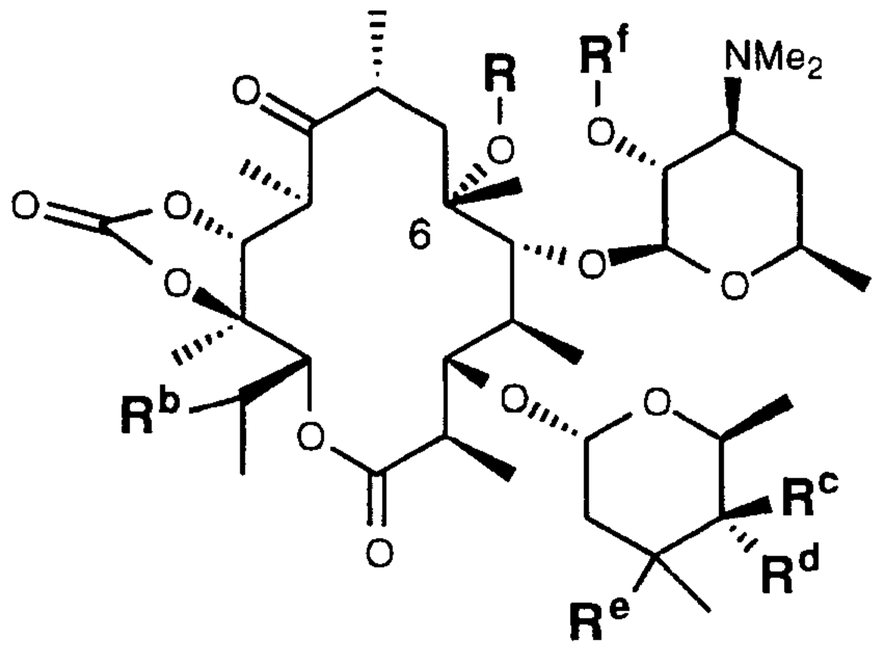
(II);



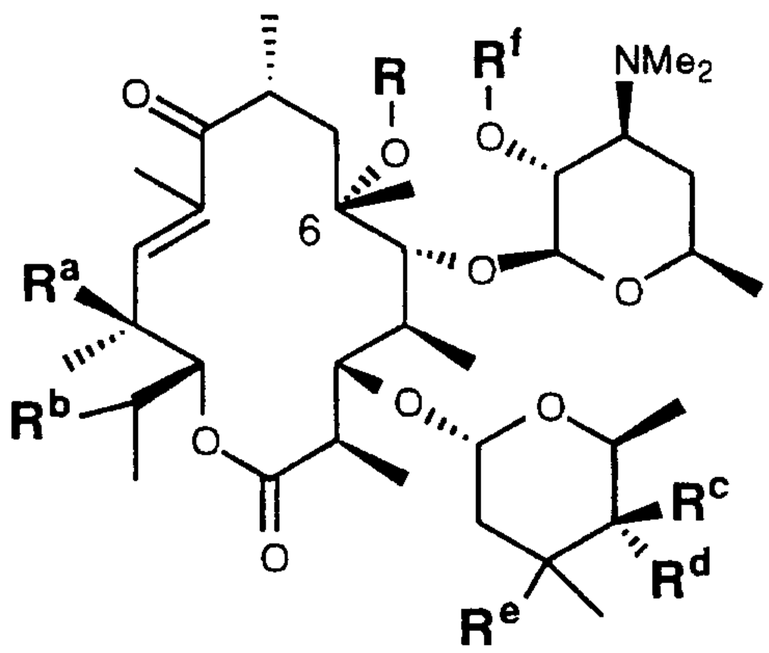
(III);



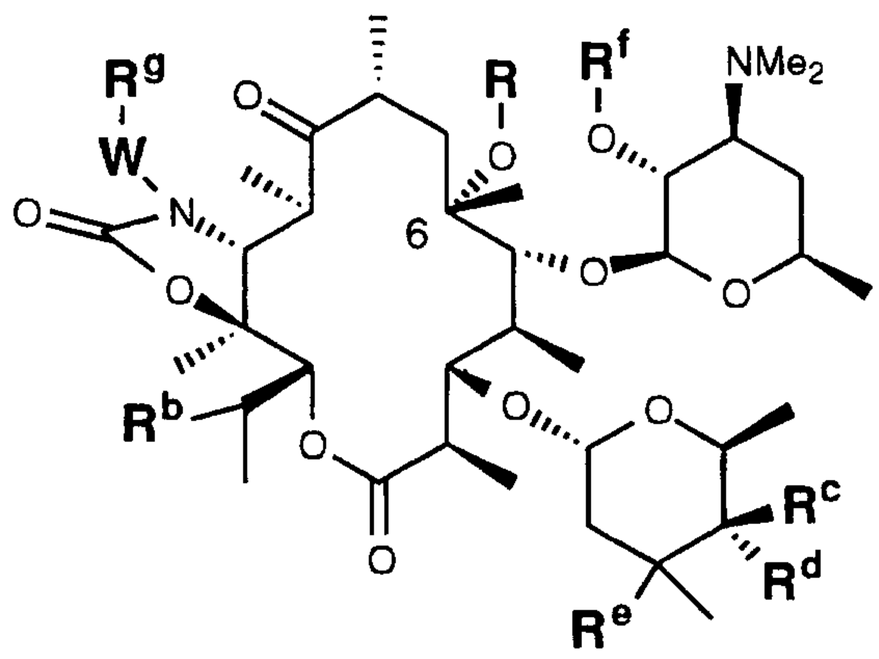
(IV);



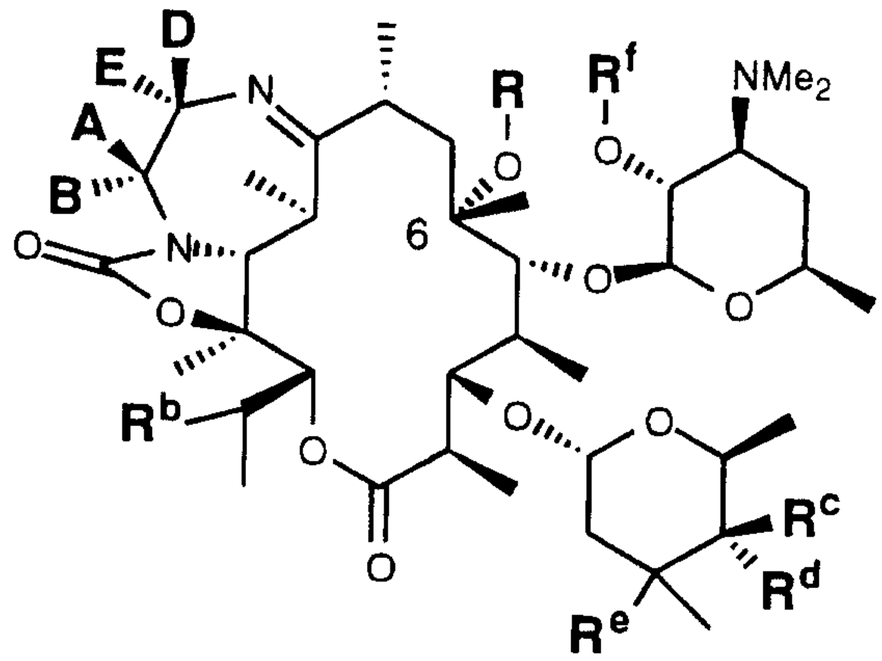
(V);



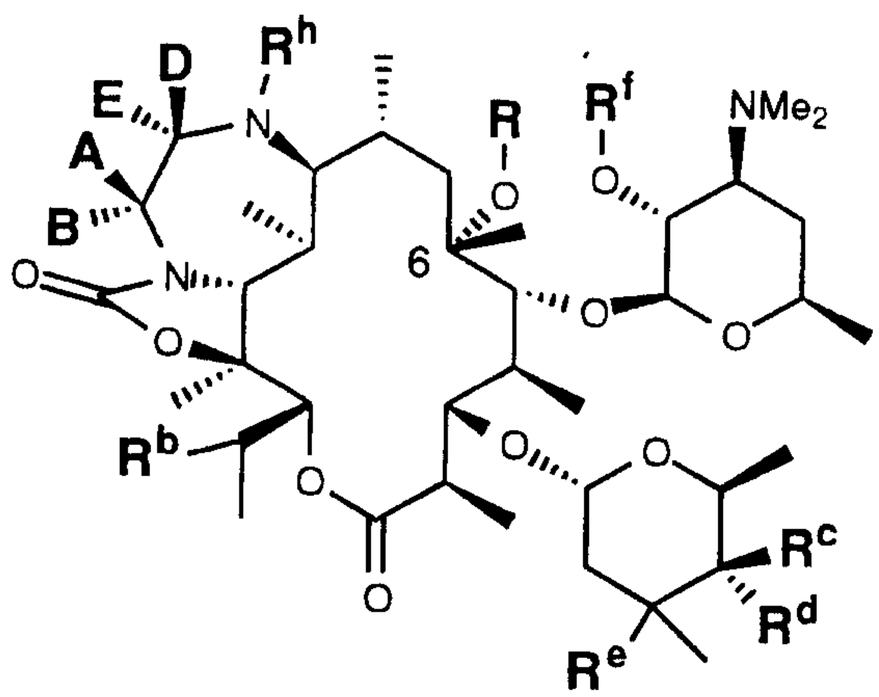
(VI);



(VII);



(VIII); or



(IX);

wherein X is:

(1) =O,

(2) =N-OH,

(3) =N-O-R^1 where R^1 is

(a) unsubstituted C_1-C_{12}-alkyl,

(b) C_1-C_{12}-alkyl substituted with aryl,

(c) C_1-C_{12}-alkyl substituted with substituted aryl,

(d) C_3-C_{12}-cycloalkyl,

(e) -Si-(R^{11})(R^{12})(R^{13}) wherein R^{11}, R^{12} and R^{13} are each independently selected from C_1-C_{12}-alkyl,

(f) -Si-(Aryl)$_3$, or

(4) =N-O-C(R^9)(R^{10})-O-R^1 where R^1 is as defined above and R^9 and R^{10} are each independently selected from the group consisting of:

(a) hydrogen,

(b) unsubstituted C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl, and

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

or R^9 and R^{10} taken together with the carbon to which they are attached form a C_3-C_{12}-cycloalkyl ring;

R^a is hydrogen or hydroxy;

R^b is hydrogen or hydroxy;

one of R^c and R^d is hydrogen and the other of R^c and R^d is:

(1) hydroxy,

(2) protected hydroxy,

(3) halogen, or

(4) NR^3R^4 where R^3 and R^4 are independently selected from:

(a) hydrogen,

(b) C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl, and

(d) C_1-C_{12}-alkyl substituted with substituted aryl, or

R^3 and R^4 taken together with the carbon to which they are attached form a 3-7 membered hetereocyclicalkyl ring,

or

R^c and R^d taken together is:

(1) =O,

(2) =N-OH, or

(3) =N-OR^1 wherein R^1 is as defined above;

R^e is methoxy, fluorine or hydroxy;

R^f is hydrogen or an hydroxy protecting group;

R^g is selected from a group consisting of:

(1) unsubstituted C_1-C_6-alkyl,

(2) C_1-C_6-alkyl substituted with one or more substituents selected from the group consisting of:

(a) aryl,

(b) substituted aryl,

(c) heteroaryl,

(d) substituted heteroaryl,

(e) heteroarylalkyl,

(f) hydroxy,

(g) C_1-C_6-alkoxy,

(h) NR^3R^4 wherein R^3 and R^4 are as defined above, and

(i) $-CH_2-M-R^5$ where M is selected from a group consisting of:

(i) -O-,

(ii) -NH-,

(iii) -NMe-,

(iv) $-S(O)_n-$ where n is 0, 1 or 2,

(v) -NHC(=O)-, and

(vi) -C(=O)-NH-,

and

R^5 is selected from a group consisting of:

(i) $-(CH_2)_n$-aryl where n is 0, 1 or 2,

(ii) $-(CH_2)_n$-substituted aryl where n is 0, 1 or 2,

(iii) $-(CH_2)_n$-heteroaryl where n=0, 1 or 2,

(iv) $-(CH_2)_n$-substituted heteroaryl where n is 0, 1 or 2, and

(v) $-(CH_2)_n$-heteroarylalkyl where n is 0, 1 or 2,

(3) C_3-C_{12}-cycloalkyl,

(4) aryl,

(5) substituted aryl,

(6) heteroaryl, and

(7) substituted heteroaryl;

R is selected from the group consisting of:

(1) C_1-alkyl substituted with a substituent selected from the group consisting of:

(a) F,

(b) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(c) $NHC(O)R^6$ where R^6 is as defined above, and

(d) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(2) C_2-C_{10}-alkyl;

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N-O-R^6$ where R^6 is as previously defined,

(j) $-C\equiv N$,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N-NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N-NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(4) C_2-C_{10}-alkenyl;

(5) C_2-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N-O-R^6$ where R^6 is as previously defined,

(j) $-C\equiv N$,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N\text{-}NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N\text{-}NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N\text{-}NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(6) C_2-C_{10}-alkynyl; and

(7) C_2-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of:

(a) trialkylsilyl,

(b) aryl,

(c) substituted aryl,

(d) heteroaryl, and

(e) substituted heteroaryl;

one of Y and Z is hydrogen and the other is selected from a group consisting of:

(1) hydrogen,

(2) hydroxy,

(3) protected hydroxy, and

(4) NR^3R^4 wherein R^3 and R^4 are as previously defined;

W is:

(1) -O-,

(2) -NH-,

(3) -NMe-, or

(4) absent;

A, B, D and E are, at each occurrence, independently selected from the group consisting of:

(1) hydrogen,

(2) unsubstituted C_1-C_6-alkyl,

(3) C_1-C_6-alkyl substituted with one or more substituents selected from the group consisting of:

(a) aryl,

(b) substituted aryl,

(c) heteroaryl,

(d) substituted heteroaryl,

(e) heteroarylalkyl,

(f) hydroxy,

(g) C_1-C_6-alkoxy,

(h) NR^3R^4, where R^3 and R^4 are as defined above, and

(i) $-CH_2-M-R^5$ where M is selected from a group consisting of:

(i) -O-,

(ii) -NH-,

(iii) -NMe-,

(iv) $-S(O)_n-$ where n is 0, 1 or 2,

(v) -NHC(=O)-, and

(vi) -C(=O)-NH-,

and

R^5 is selected from a group consisting of:

(i) $-(CH_2)_n$-aryl where n is 0, 1 or 2,

(ii) $-(CH_2)_n$-substituted aryl where n is 0, 1 or 2,

(iii) $-(CH_2)_n$-heteroaryl where n=0, 1 or 2,

(iv) $-(CH_2)_n$-substituted heteroaryl where n is 0, 1 or 2, and

(v) $-(CH_2)_n$-heteroarylalkyl where n is 0, 1 or 2,

or any pair of substituents, consisting of AB, AD, AE, BD, BE or DE, is taken together with the atom or atoms to which they are attached to form a 3- to 7-membered ring optionally containing a hetero function selected from:

(1) -O-,

(2) $-S(O)_n-$, where n is 0, 1 or 2,

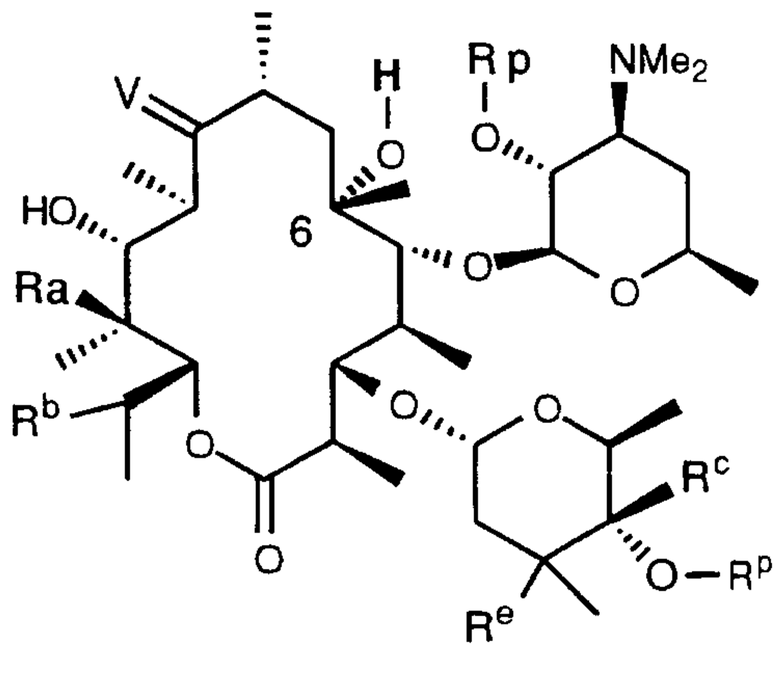
(3) -NH-,

(4) $-N(CH_3)-$, and

(5) $-N(R^5)-$ wherein R^5 is as previously defined;

is a method comprising:

(a) treating a compound having the formulae:



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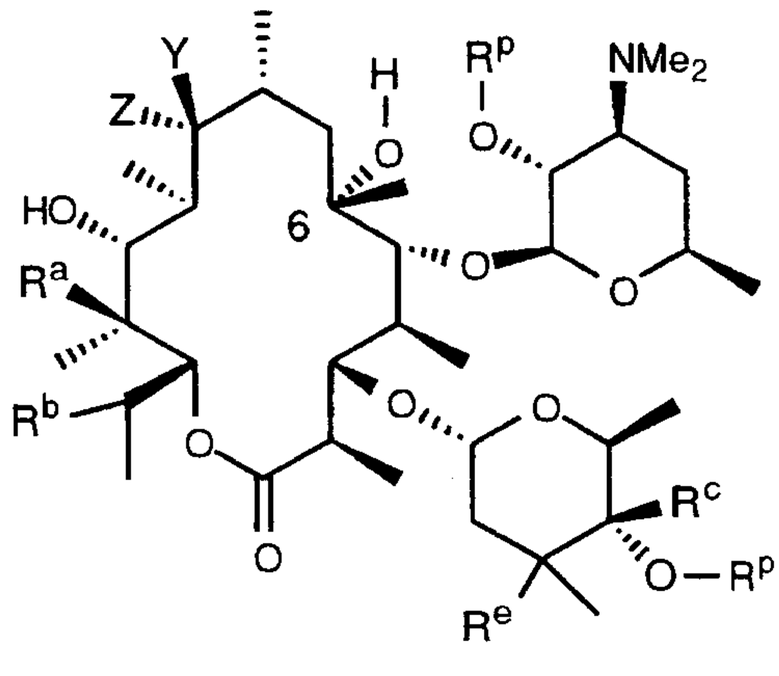

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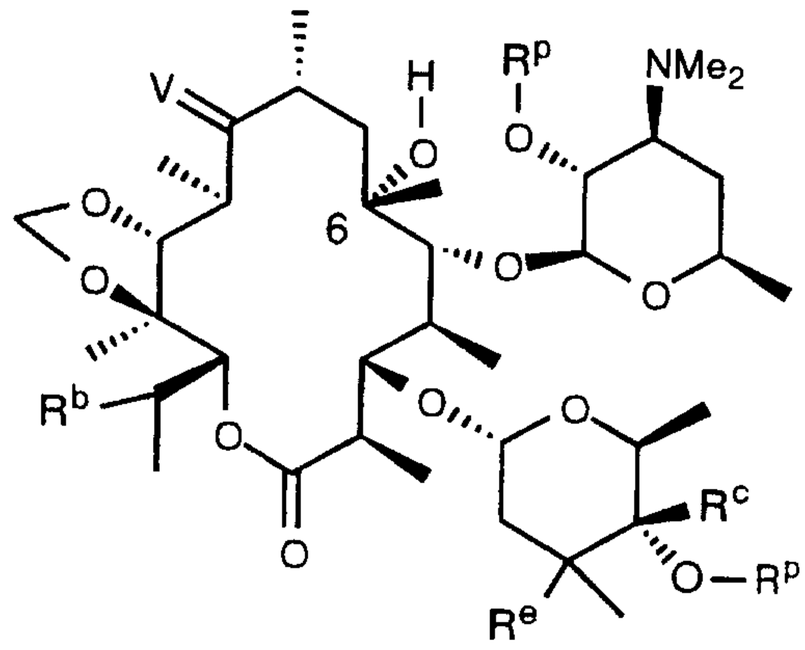

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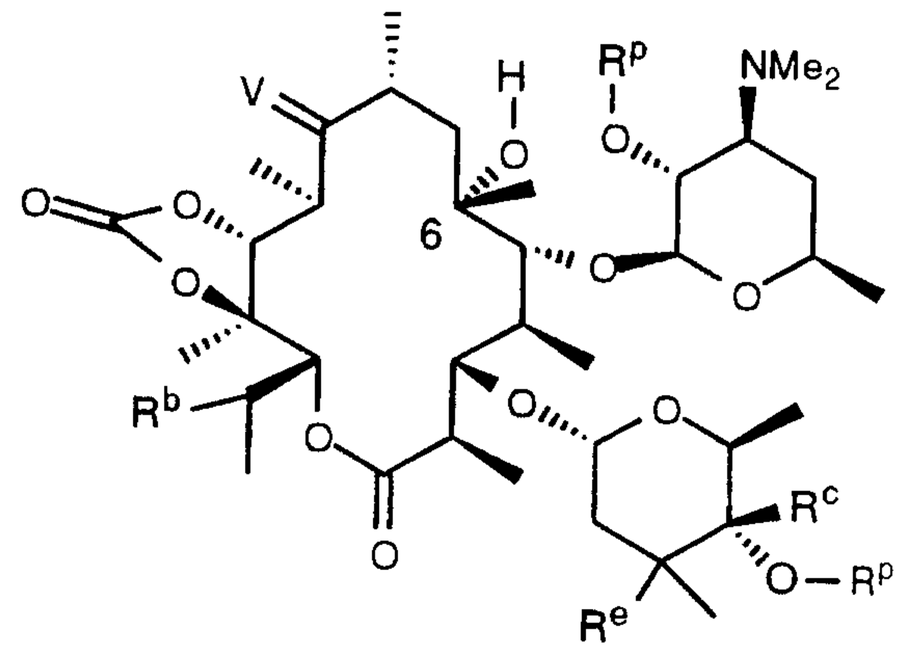

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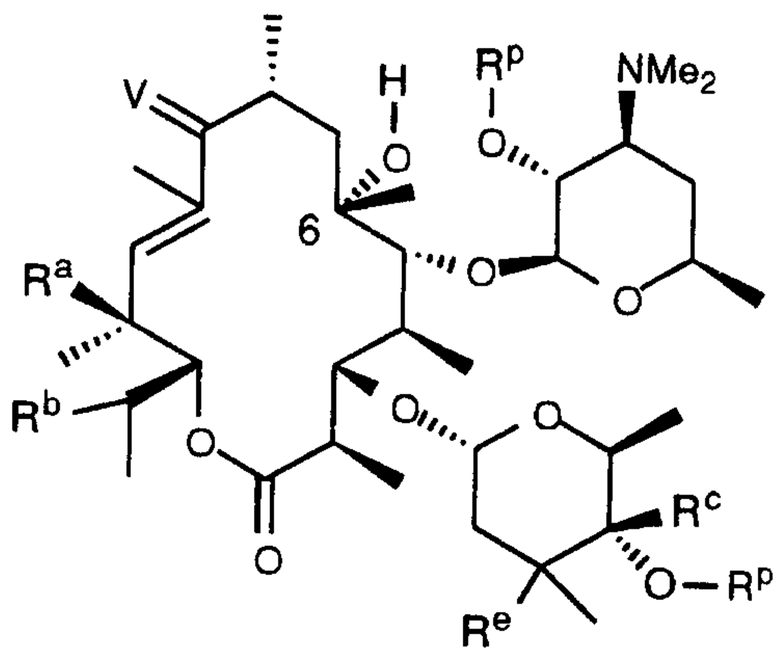

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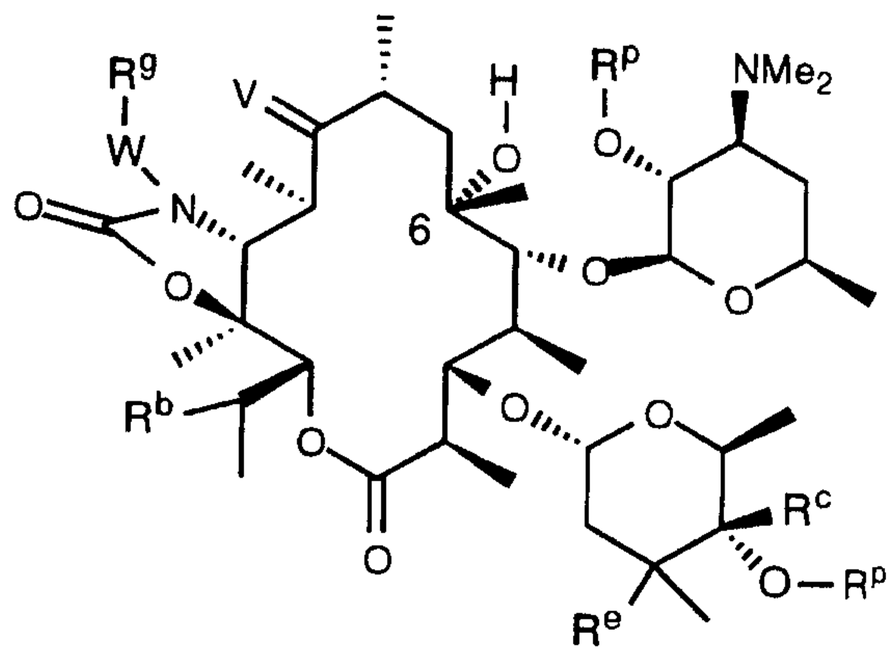

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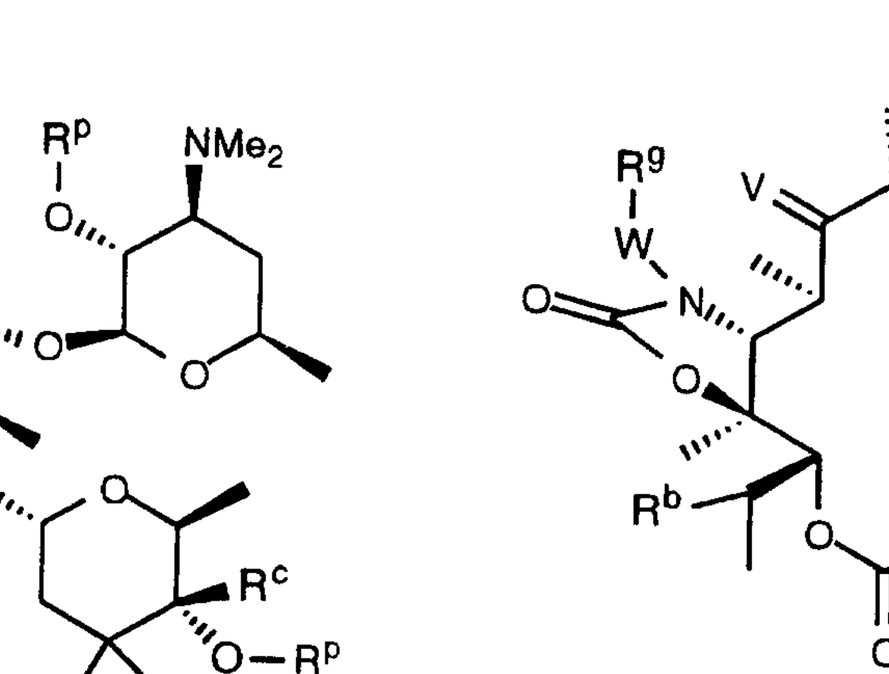

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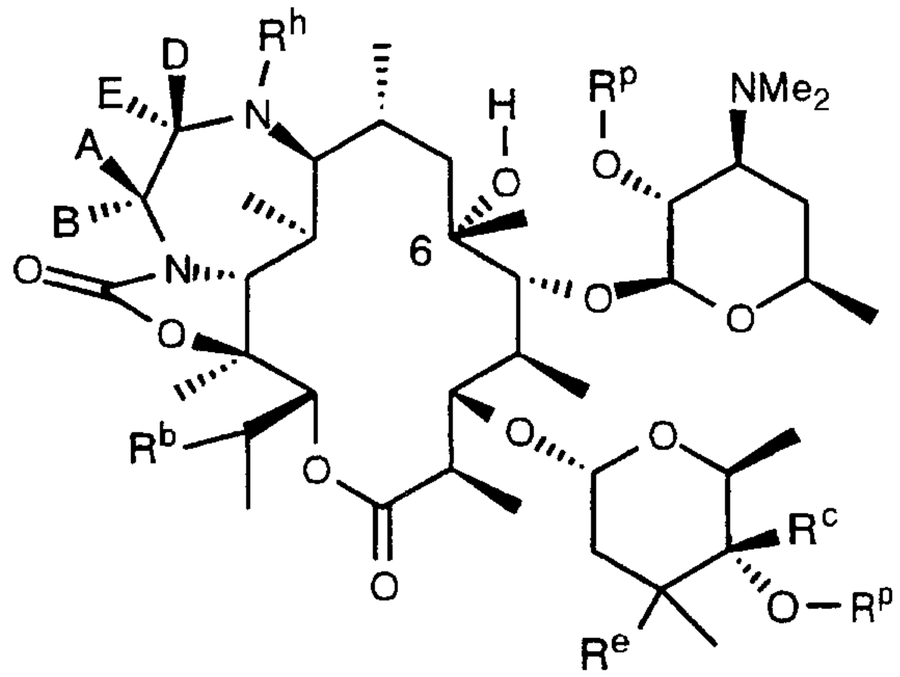
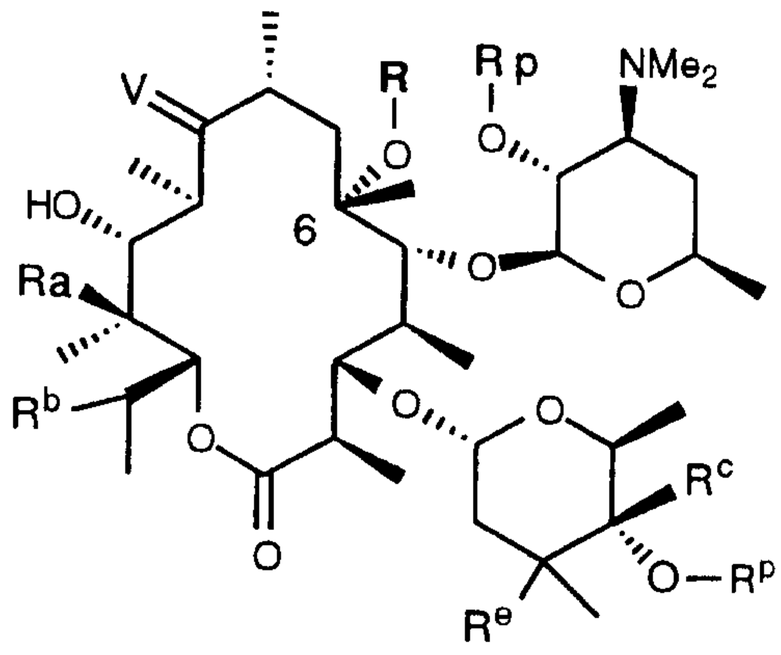
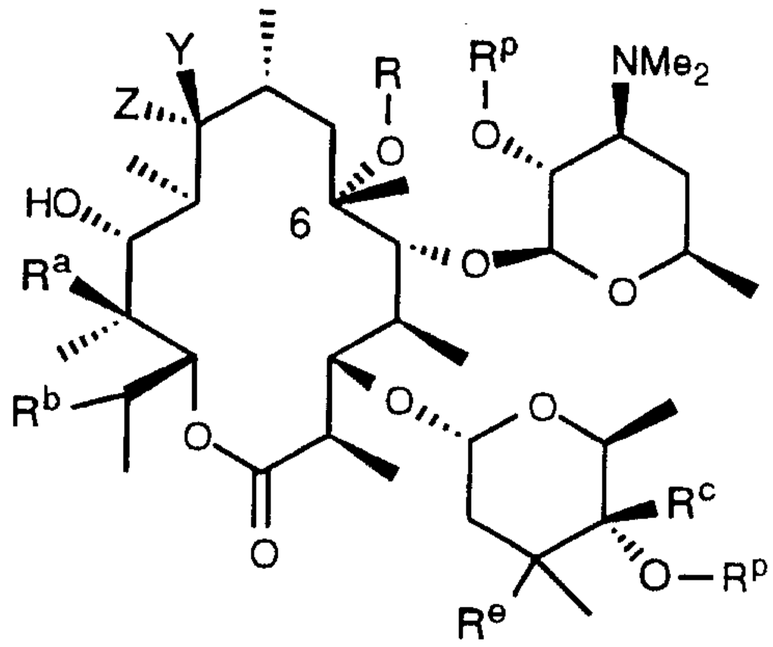


wherein R^p is an hydroxy protecting group and V is =N-O-R^1 or =N-O-C(R^9)(R^{10})-O-R^1 wherein R^1, R^9 and R^{10} are as defined above, with a base, such as potassium hydroxide, cesium hydroxide, tetraalkylammonium hydroxide, sodium hydride, potassium hydride, potassium isopropoxide, potassium tert-butoxide, potassium isobutoxide, in an aprotic solvent, as defined below, which does not adversely affect the reaction, preferably dimethylsulfoxide, diethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, a mixture thereof or a mixture of one of these solvents with ether, tetrahydrofuran, 1,2-dimethoxyethane, acetonitrile, ethyl acetate, acetone, with cooling or heating, depending on the conditions used, at a temperature from about -15 °C to about 50 °C, for a period from 0.5 hours to 10 days, preferably 1-5 days, with an alkylating agent such as allyl bromide, propargyl bromide, benzyl bromide, 2-fluoroethyl bromide, 4-nitrobenzyl bromide, 4-chlorobenzyl bromide, 4-methoxybenzyl bromide, α-bromo-p-tolunitrile, cinnamyl bromide, methyl 4-bromocrotonate, crotyl bromide, 1-bromo-2-pentene, 3-bromo-1-propenyl phenyl sulfone, 3-bromo-1-trimethylsilyl-1-propyne, 3-bromo-2-octyne, 1-bromo-2-butyne, 2-picolyl chloride, 3-picolyl chloride, 4-picolyl chloride, 4-bromomethyl quinoline, bromoacetonitrile, epichlorohydrin, bromofluoromethane, bromonitromethane, methyl bromoacetate, methoxymethyl chloride, bromoacetamide, 2-bromoacetophenone, 1-bromo-2-butanone, bromo chloromethane, bromomethyl phenyl sulfone, 1,3-dibromo-1-propene, allyl O-tosylate, 3-phenylpropyl-O-trifluoromethane sulfonate, or n-butyl-O-methanesulfonate;

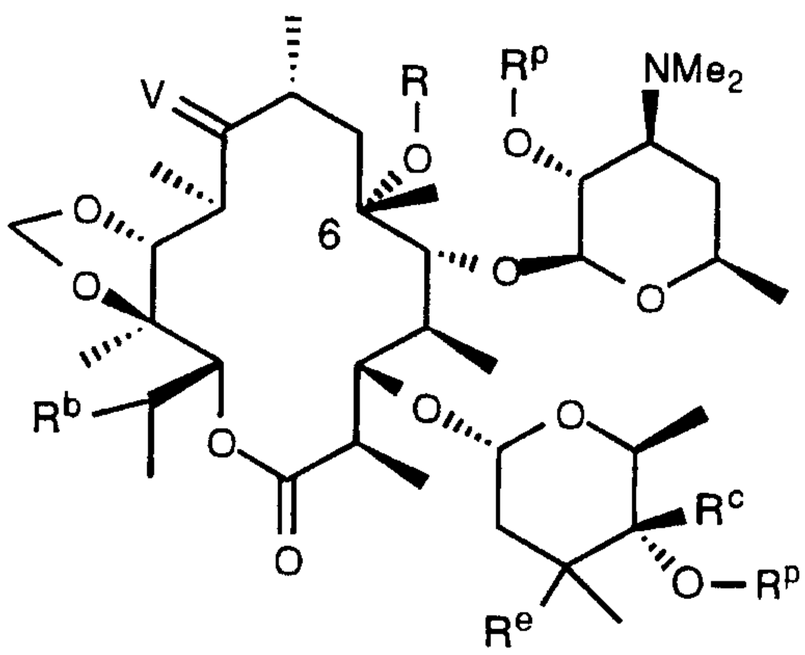
to give a compound having the formula:


V
R
Rp
NMe2
HO
6
Ra
Rb
O
Rc
O—Rp
Re

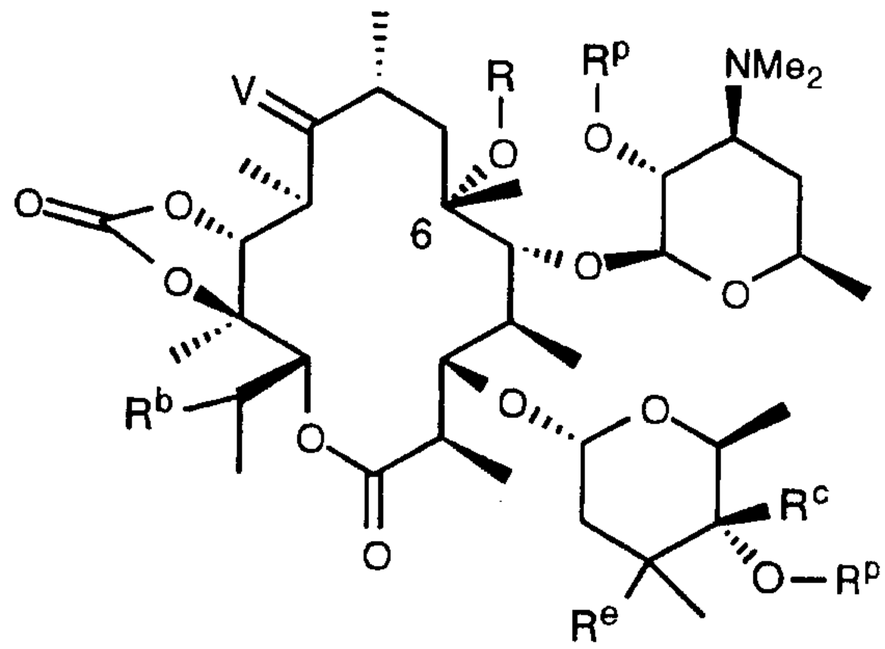
,


Y
Z
R
Rp
NMe2
HO
6
Ra
Rb
O
Rc
O—Rp
Re

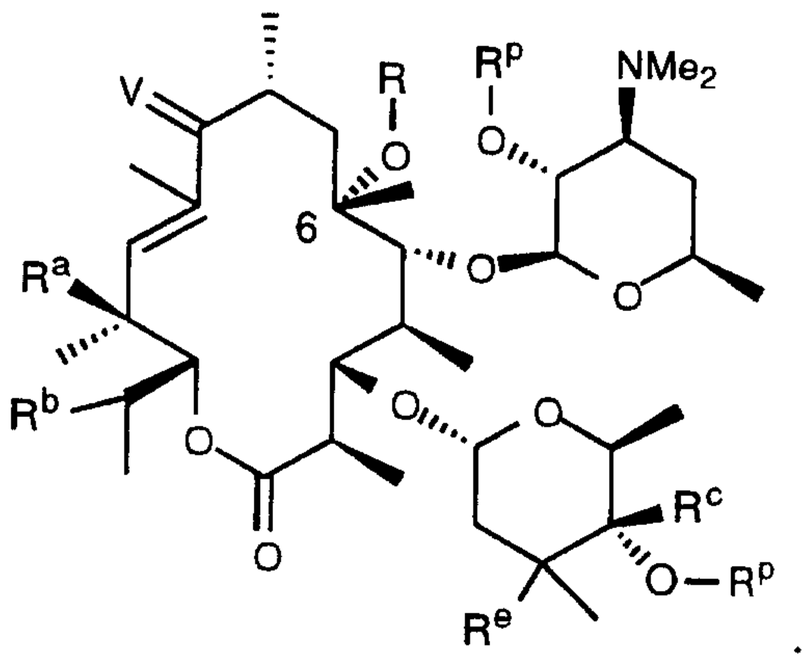
;


V
R
Rp
NMe2
6
Rb
O
Rc
O—Rp
Re

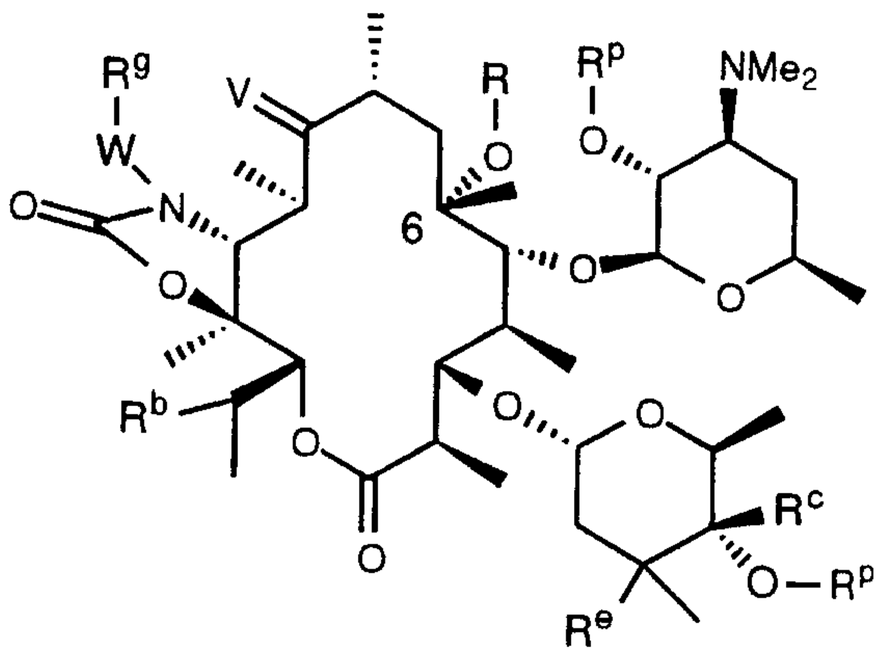
;


V
R
Rp
NMe2
6
Rb
O
Rc
O—Rp
Re

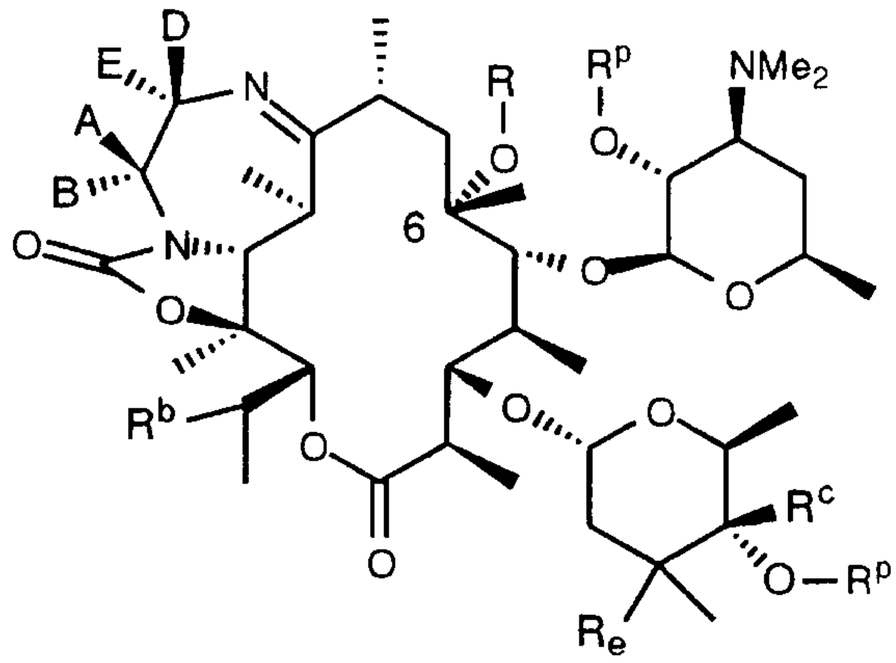
;


V
R
Rp
NMe2
6
Ra
Rb
O
Rc
O—Rp
Re

;


Rg
W
N
V
R
Rp
NMe2
6
Rb
O
Rc
O—Rp
Re

;



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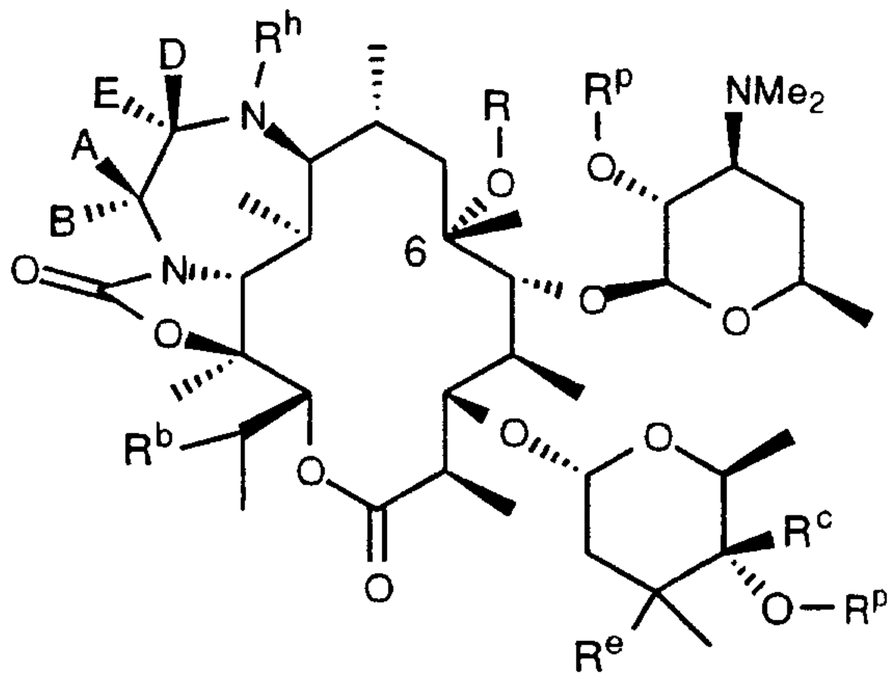
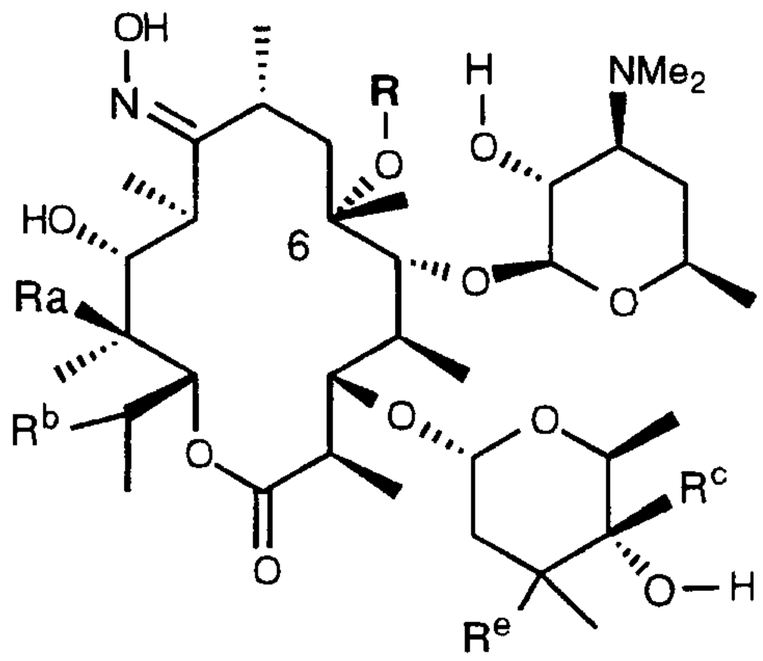


;

wherein A, B, D, E, W, X, Y, Z, R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h are as defined above, V is =N-O-R^1 or =N-O-C(R^9)(R^{10})-O-R^1 wherein R^1, R^9 and R^{10} are as defined above, and R is the "alkyl group" derived from the corresponding alkylating agent;

(b) deprotecting of the 2'- and 4'-hydroxyl groups, for example, using acetic acid in water and acetonitrile to give a compound of the formula:



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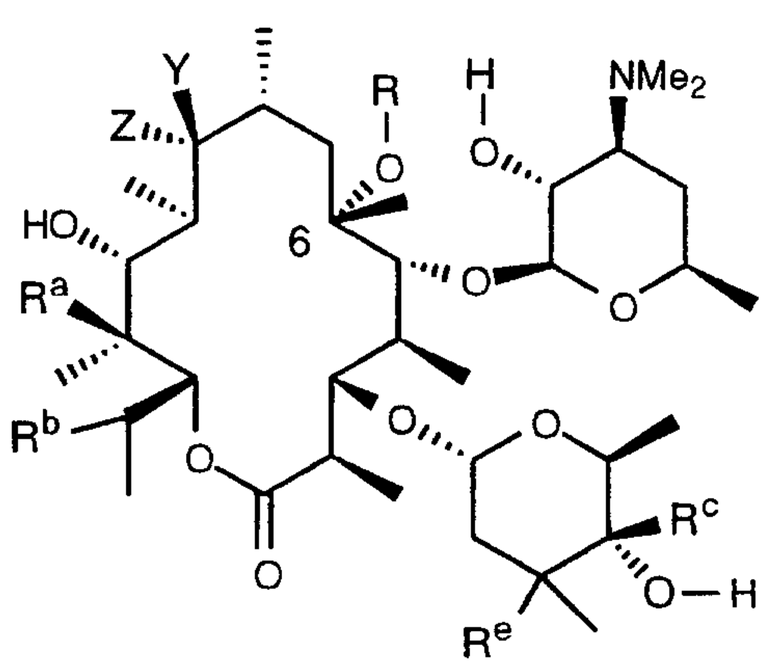

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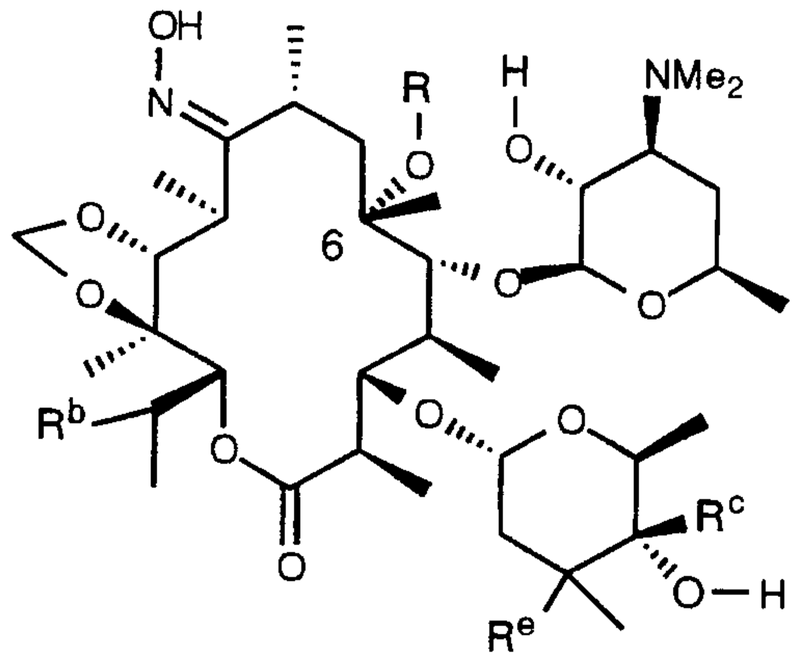

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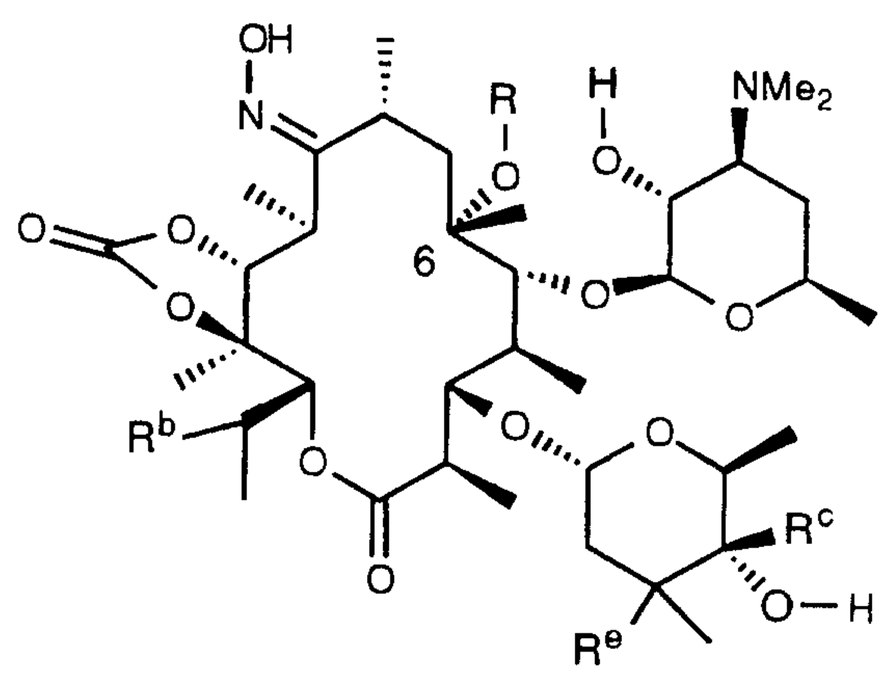

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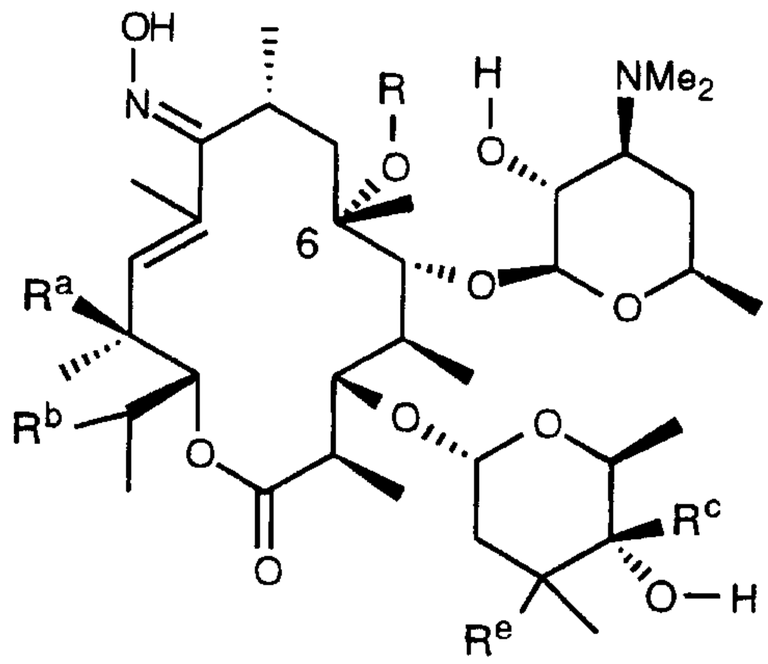

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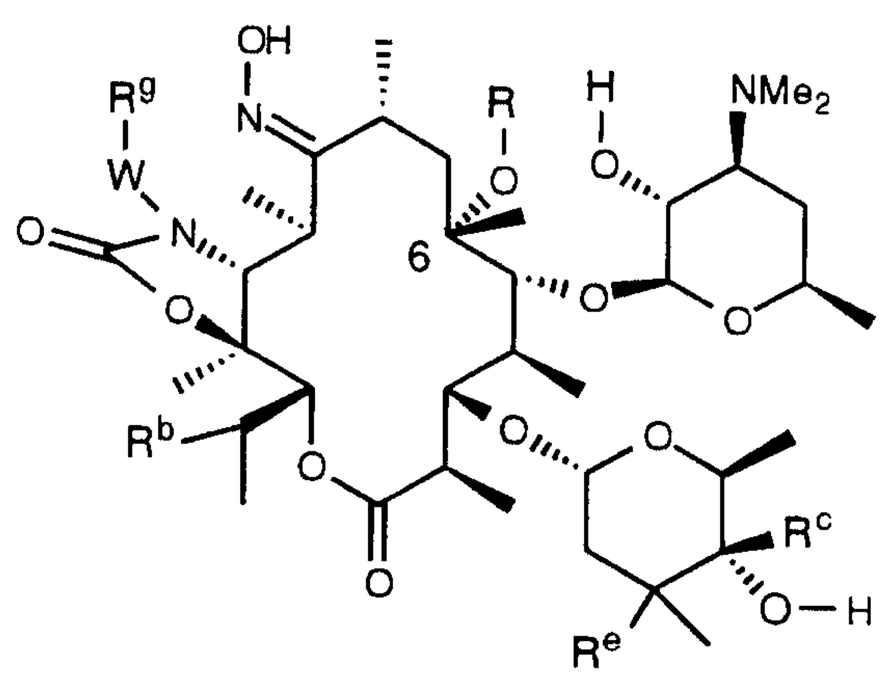

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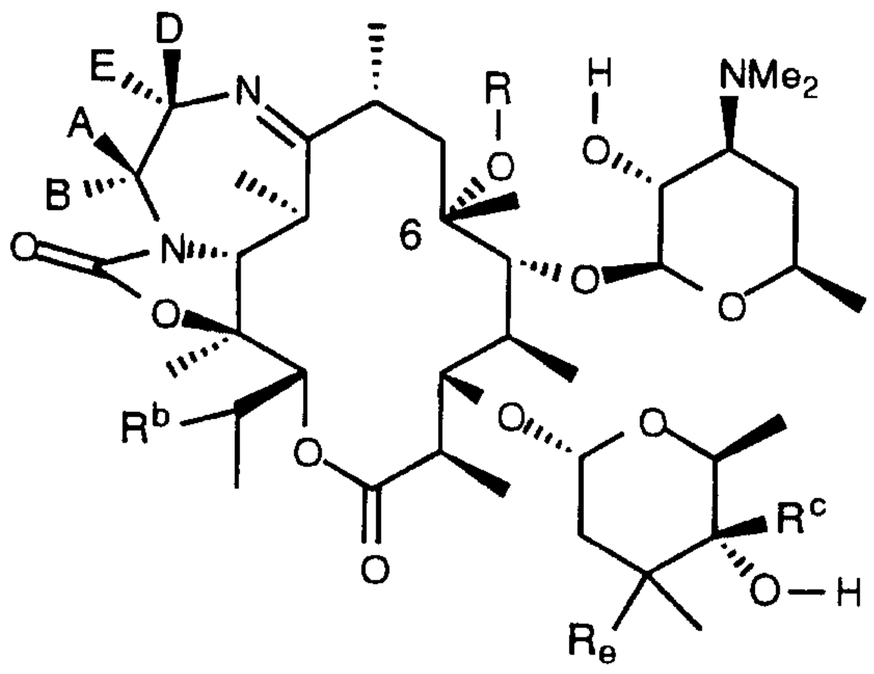

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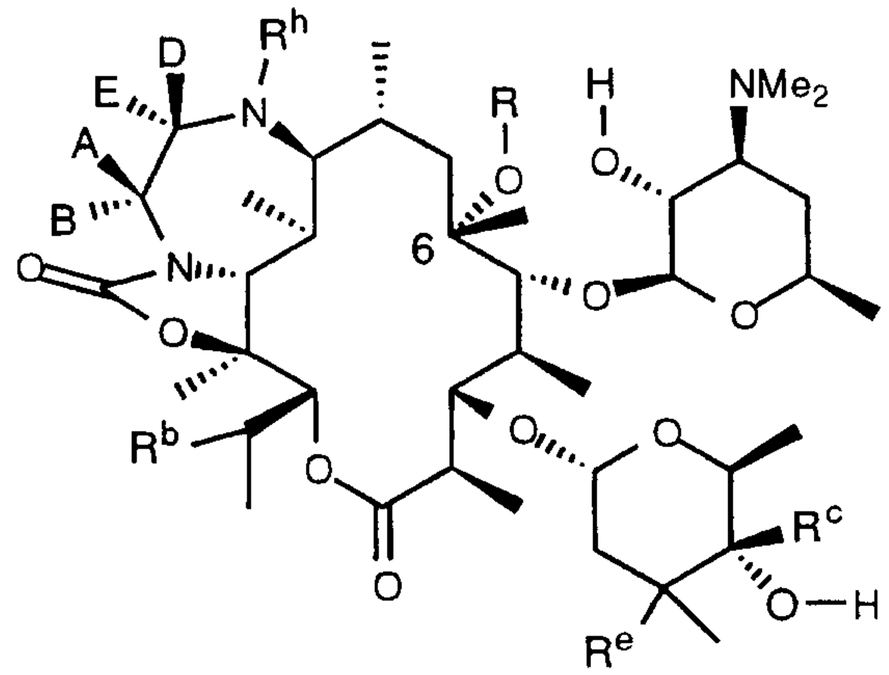
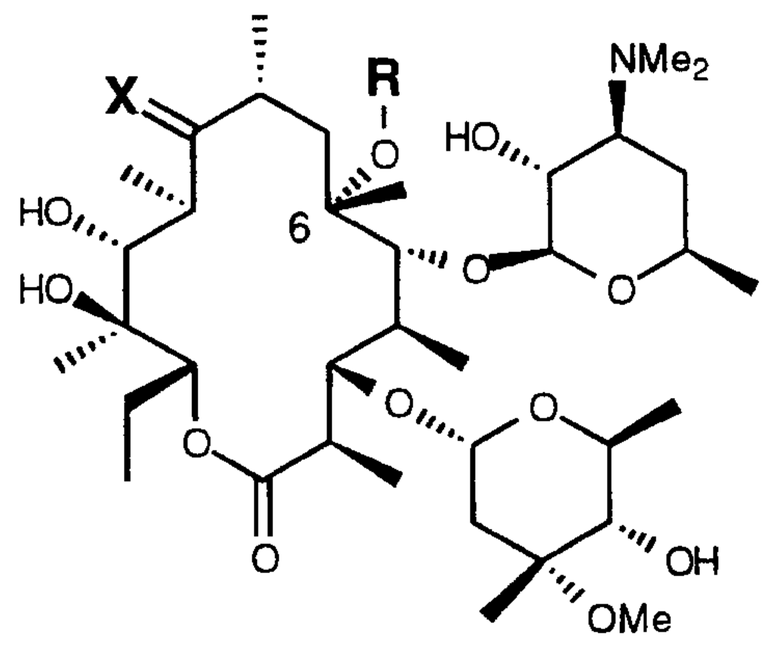


wherein A, B, D, E, W, X, Y, Z, R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h are as defined above and R is the "alkyl group" derived from the corresponding alkylating agent;
and

(c) deoximation, for example, using inorganic sulfur oxide compounds such as sodium hydrogen sulfite, sodium pyrosulfate, sodium thiosulfate, sodium sulfate, sodium sulfite, sodium hydrosulfite, sodium metabisulfite, sodium dithionate, potassium thiosulfate, or potassium metabisulfite in a solvent such as water, methanol, ethanol, propanol, isopropanol, trimethylsilanol or a mixture of one or more of the mentioned solvents to give the desired products.

A preferred process for the preparation of 6-O-substituted macrolide compounds having the formula:



wherein X is:

(1) =O,

(2) =N-OH,

(3) =N-O-R^1 where R^1 is:

(a) unsubstituted C_1-C_{12}-alkyl,

(b) C_1-C_{12}-alkyl substituted with aryl,

(c) C_1-C_{12}-alkyl substituted with substituted aryl,

(d) C_3-C_{12}-cycloalkyl,

(e) -Si-(R^{11})(R^{12})(R^{13}) wherein R^{11}, R^{12} and R^{13} are each independently selected from C_1-C_{12}-alkyl,

(f) -Si-(Aryl)$_3$, or

(4) =N-O-C(R^9)(R^{10})-O-R^1 where R^1 is as defined above and R^9 and R^{10} are each independently selected from the group consisting of:

(a) hydrogen,

(b) unsubstituted C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl, and

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

or R^9 and R^{10} taken together with the carbon to which they are attached form a C_3-C_{12}-cycloalkyl ring; and

R is selected from the group consisting of:

(1) C_1-alkyl substituted with a substituent selected from the group consisting of:

(a) F,

(b) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(c) $NHC(O)R^6$ where R^6 is as defined above, and

(d) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are independently selected from hydrogen and C_1-C_3-alkyl,

(2) C_2-C_{10}-alkyl;

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N-O-R^6$ where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N\text{-}NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N\text{-}NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N\text{-}NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(4) C_2-C_{10}-alkenyl;

(5) C_2-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N\text{-}O\text{-}R^6$ where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N-NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N-NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(6) C_2-C_{10}-alkynyl; and

(7) C_2-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of:

(a) trialkylsilyl,

(b) aryl,

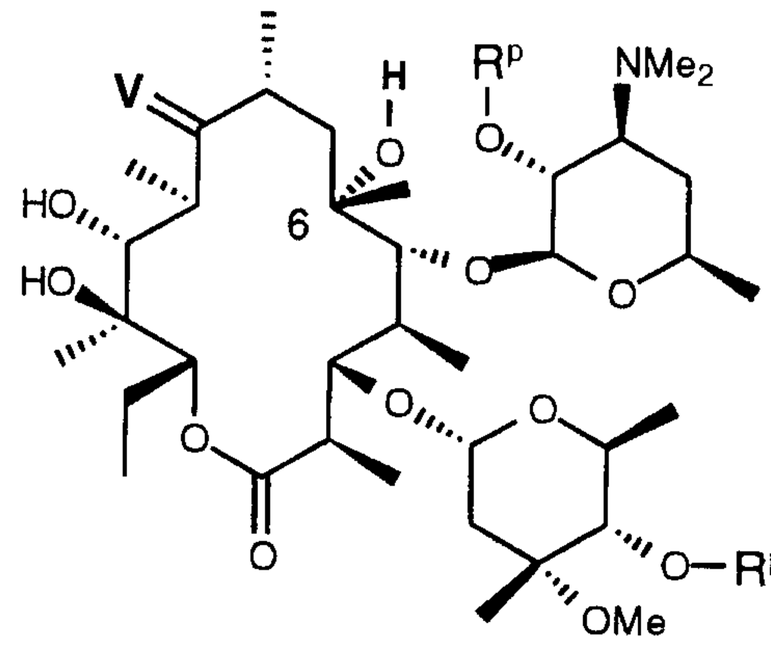
(c) substituted aryl,

(d) heteroaryl, and

(e) substituted heteroaryl;

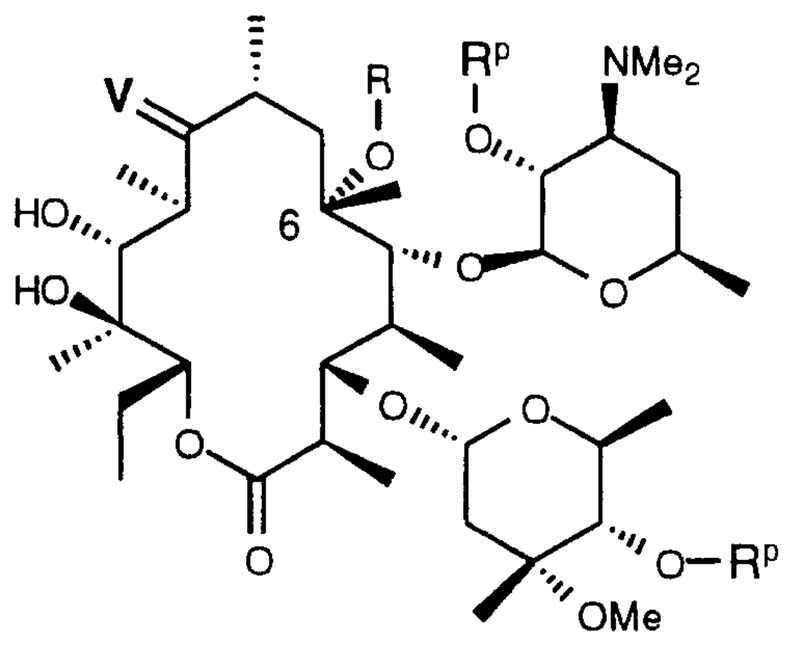
is a method comprising:

(a) treating a compound having the formulae:



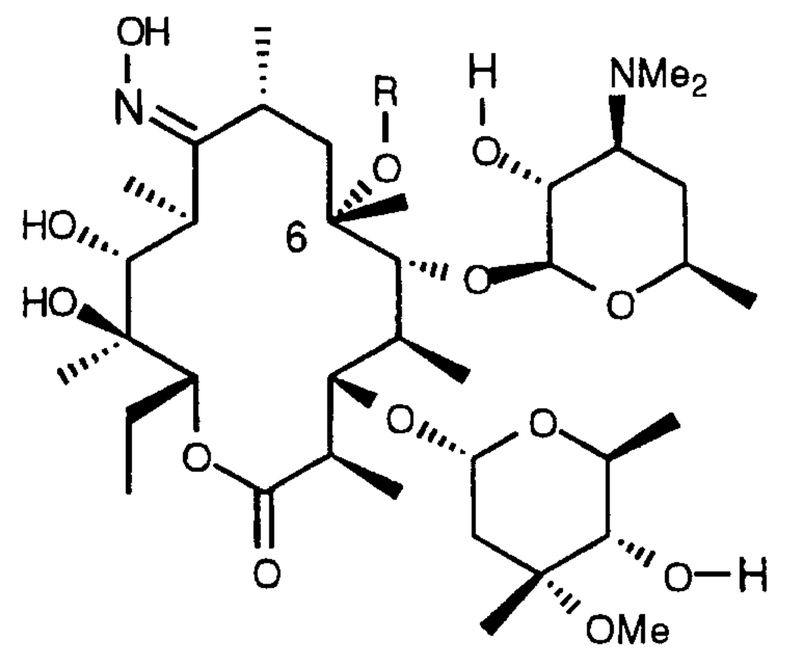
wherein R^p is an hydroxy protecting group and V is $=N-O-R^1$ or $=N-O-C(R^9)(R^{10})-O-R^1$ wherein R^1, R^9 and R^{10} are as defined above, with a base, such as potassium hydroxide, cesium hydroxide, tetraalkylammonium hydroxide, sodium hydride, potassium hydride, potassium isopropoxide, potassium tert-butoxide, potassium isobutoxide, in an aprotic solvent, as defined below, which does not adversely affect the reaction, preferably dimethylsulfoxide, diethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, a mixture thereof or a mixture of one of these solvents with ether, tetrahydrofuran, 1,2-dimethoxyethane, acetonitrile, ethyl acetate, acetone, with cooling or heating, depending on the conditions used, at a temperature from about -15 °C to about 50 °C, for a period from 0.5 hours to 10 days, preferably 1-5 days, with an alkylating agent such as allyl bromide, propargyl bromide, benzyl bromide, 2-fluoroethyl bromide, 4-nitrobenzyl bromide, 4-chlorobenzyl bromide, 4-methoxybenzyl bromide, α-bromo-p-tolunitrile, cinnamyl bromide, methyl 4-bromocrotonate, crotyl bromide,

1-bromo-2-pentene, 3-bromo-1-propenyl phenyl sulfone, 3-bromo-1-trimethylsilyl-1-propyne, 3-bromo-2-octyne, 1-bromo-2-butyne, 2-picolyl chloride, 3-picolyl chloride, 4-picolyl chloride, 4-bromomethyl quinoline, bromoacetonitrile, epichlorohydrin, bromofluoromethane, bromonitromethane, methyl bromoacetate, methoxymethyl chloride, bromoacetamide, 2-bromoacetophenone, 1-bromo-2-butanone, bromo chloromethane, bromomethyl phenyl sulfone, 1,3-dibromo-1-propene, allyl O-tosylate, 3-phenylpropyl-O-trifluoromethane sulfonate, or n-butyl-O-methanesulfonate; to give a compound having the formula:



wherein V and RP are as defined above and R is the "alkyl group" derived from the corresponding alkylating agent;

(b) deprotecting of the 2'- and 4'-hydroxyl groups, for example, using acetic acid in water and acetonitrile to give a compound having the formula:



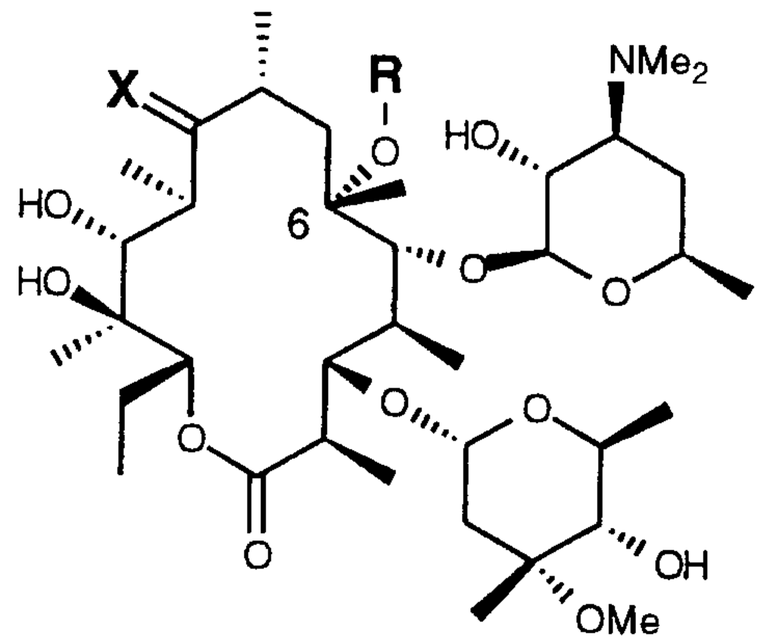
;

and

(c) deoximation, for example, using inorganic sulfur oxide compounds such as sodium hydrogen sulfite, sodium pyrosulfate, sodium thiosulfate, sodium sulfate, sodium sulfite, sodium hydrosulfite, sodium metabisulfite, sodium dithionate, potassium thiosulfate,

or potassium metabisulfite in a solvent such as water, methanol, ethanol, propanol, isopropanol, trimethylsilanol or a mixture of one or more of the mentioned solvents.

A more preferred process for the preparation of 6-O-substituted macrolide compounds having the formula:



wherein X is:

(1) =O,

(2) =N-OH,

(3) =N-O-R^1 where R^1 is

(a) unsubstituted C_1-C_{12}-alkyl,

(b) C_1-C_{12}-alkyl substituted with aryl,

(c) C_1-C_{12}-alkyl substituted with substituted aryl,

(d) C_3-C_{12}-cycloalkyl,

(e) -Si-(R^{11})(R^{12})(R^{13}) wherein R^{11}, R^{12} and R^{13} are each independently selected from C_1-C_{12}-alkyl,

(f) -Si-(Aryl)$_3$, or

(4) =N-O-C(R^9)(R^{10})-O-R^1 where R^1 is as defined above and R^9 and R^{10} are each independently selected from the group consisting of:

(a) hydrogen,

(b) unsubstituted C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl, and

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

or R^9 and R^{10} taken together with the carbon to which they are attached form a C_3-C_{12}-cycloalkyl ring; and

R is selected from the group consisting of:

(1) C_1-alkyl substituted with a substituent selected from the group consisting of:

(a) F,

(b) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(c) $NHC(O)R^6$ where R^6 is as defined above, and

(d) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are independently selected from hydrogen and C_1-C_3-alkyl,

(2) C_2-C_{10}-alkyl;

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N-O-R^6$ where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N-NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N-NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(4) C_2-C_{10}-alkenyl;

(5) C_2-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N-O-R^6$ where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N-NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N-NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(6) C_2-C_{10}-alkynyl; and

(7) C_2-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of:

(a) trialkylsilyl,

(b) aryl,

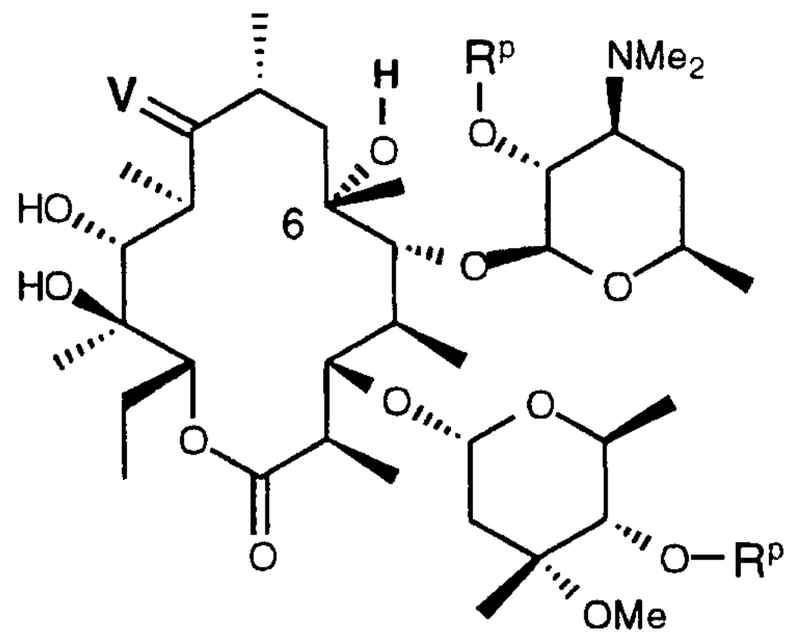
(c) substituted aryl,

(d) heteroaryl, and

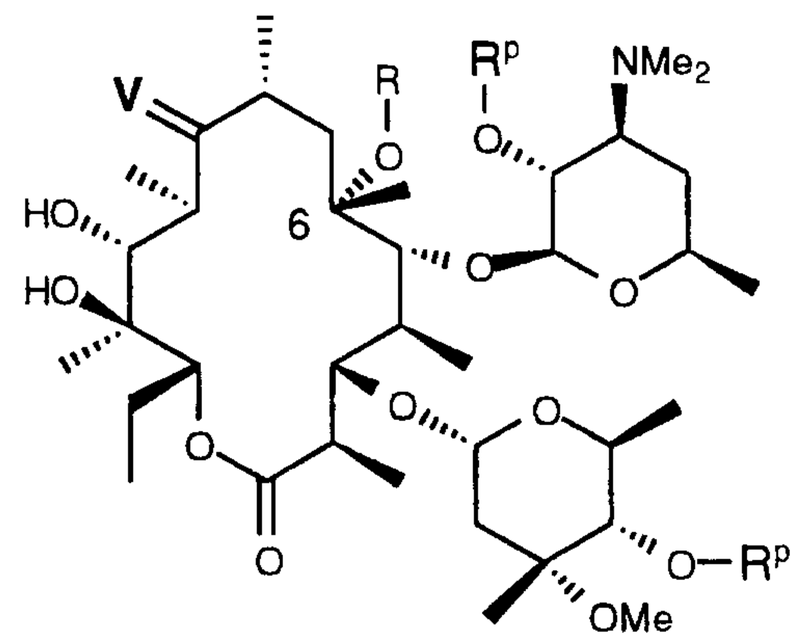
(e) substituted heteroaryl;

is a method comprising:

(a) treating a compound having the formula:

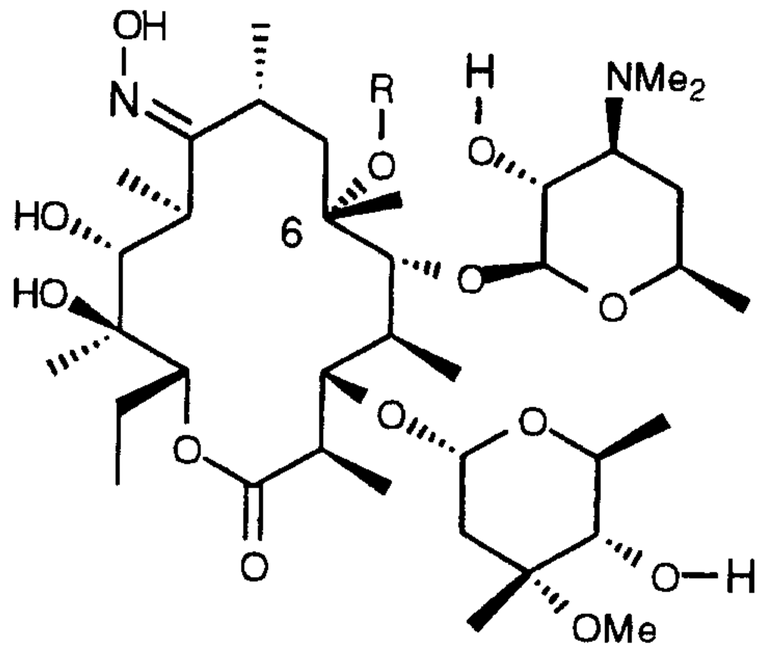


wherein R^p is trimethylsilyl and V is O-(1-isopropoxycyclohexyl) oxime with potassium hydroxide in a mixture of THF and DMSO with an alkylating agent such as allyl bromide, propargyl bromide, benzyl bromide, 2-fluoroethyl bromide, 4-nitrobenzyl bromide, 4-chlorobenzyl bromide, 4-methoxybenzyl bromide, α-bromo-p-tolunitrile, cinnamyl bromide, methyl 4-bromocrotonate, crotyl bromide, 1-bromo-2-pentene, 3-bromo-1-propenyl phenyl sulfone, 3-bromo-1-trimethylsilyl-1-propyne, 3-bromo-2-octyne, 1-bromo-2-butyne, 2-picolyl chloride, 3-picolyl chloride, 4-picolyl chloride, 4-bromomethyl quinoline, bromoacetonitrile, epichlorohydrin, bromofluoromethane, bromonitromethane, methyl bromoacetate, methoxymethyl chloride, bromoacetamide, 2-bromoacetophenone, 1-bromo-2-butanone, bromo chloromethane, bromomethyl phenyl sulfone, 1,3-dibromo-1-propene, allyl O-tosylate, 3-phenylpropyl-O-trifluoromethane sulfonate, or n-butyl-O-methanesulfonate; to give a compound having the formula:



wherein V and R^p are as defined above and R is the "alkyl group" derived from the corresponding alkylating agent;

(b) deprotecting of the 2'- and 4'-hydroxyl groups using acetic acid in water and acetonitrile to give a compound having the formula:



; and

(c) deoximinating the 9-oxime using $NaHSO_3$ and formic acid in ethanol-water to give the desired product.

Definitions

The terms "C_1-C_{12}-alkyl" as used herein refer to saturated, straight- or branched-chain hydrocarbon radicals containing between one and twelve carbon atoms. Examples of C_1-C_3 alkyl radicals include methyl, ethyl, propyl and isopropyl, and examples of C_1-C_6-alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl, neopentyl and n-hexyl.

The term "C_1-C_6-alkoxy" as used herein refers to an C_1-C_6-alkyl group, as previously defined, attached to the parent molecular moiety through an oxygen atom. Examples of C_1-C_6-alkoxy, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, *n*-butoxy, *tert*-butoxy, neopentoxy and n-hexoxy.

The term "alkenyl" as used herein refers to a branched or straight hydrocarbon chain comprising two to ten carbon atoms which also comprises one or more carbon-carbon double bonds. Representative alkenyl groups include 2-propenyl (*i.e.*, allyl), 3-methyl-2-butenyl, 3,7-dimethyl-2,6-octadienyl, 4,8-dimethyl-3,7-nonadienyl, 3,7,11-trimethyl-2,6,10-dodecatrienyl and the like.

The term "alkynyl" as used herein refers to a branched or straight hydrocarbon chain comprising two to ten carbon atoms which also comprises one or more carbon-carbon triple bonds. Representative alkynyl groups include ethynyl, 2-propynyl (propargyl), 1-propynyl and the like.

The term "C_1-C_3-alkyl-amino" as used herein refers to one or two C_1-C_3-alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. Examples of C_1-C_3-alkyl-amino include, but are not limited to methylamino, dimethylamino, ethylamino, diethylamino, and propylamino.

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, chlorofom, and the like, heteroaryl 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 "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, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "C_3-C_{12}-cycloalkyl" as used herein refers to carbocyclic groups of 3 to 12 carbons, respectively, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

The term "C_1-C_3-alkyl-C_3-C_5-cycloalkyl", as used herein refers to a C_3-C_5-cycloalkyl radical, as defined above, attached to a C_1-C_3-alkyl radical by replacement of a hydrogen atom on the latter.

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

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 "heteroarylalkyl" as used herein, refers to a non-aromatic 5-, 6- or 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 heteroaryl 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.

"Hydroxy-protecting group", as used herein, refers to an easily removable group which is known in the art to protect a hydroxyl group against undesirable reaction during 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, 2nd edition, John Wiley & Sons, New York (1991). Examples of hydroxy-protecting groups include, but are not limited to, methylthiomethyl, *tert*-dimethylsilyl, *tert*-butyldiphenylsilyl, acyl substituted with an aromatic group and the like.

The term "ketone protecting group", as used herein, refers to an easily removable group which is known in the art to protect a ketone group against undesirable reactions during synthetic procedures and to be selectively removable. The use of ketone-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, 2nd edition, John Wiley & Sons, New York (1991). Examples of ketone-protecting groups include, but are not limited to, ketals, oximes, O-substituted oximes for example O-benzyl oxime, O-phenylthiomethyl oxime, 1-isopropoxycyclohexyl oxime, and the like.

A 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.

The term "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.

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 Cl, Br, F, I, OH, C_1-C_3-alkyl, C_1-C_6-alkoxy, methoxymethoxy, amino, or C_1-C_3-alkyl-amino.

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 Cl, Br, F, I, OH, C_1-C_3-alkyl, C_1-C_6-alkoxy, methoxymethoxy, amino, or C_1-C_3-alkyl-amino.

The term "substituted heterocycloalkyl" as used herein, refers to a heterocycloalkyl group, as defined above, substituted by independent replacement of one, two or three of the hydrogen atoms thereon with Cl, Br, F, I, OH, C_1-C_3-alkyl, C_1-C_6-alkoxy, methoxymethoxy, amino, or C_1-C_3-alkyl-amino.

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).

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 alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters includes formates, acetates, propionates, butyates, acrylates and ethylsuccinates.

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 with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the 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 discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987.

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 a propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as

magnesium hydroxide and aluminun 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, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants 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), bucally, or as an oral or nasal spray. Liquid dosage forms for oral administration include pharmaceutically acceptable 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 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 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 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.

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 microencapsule 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.

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 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 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 polethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more 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 normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a 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, 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 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, 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 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 lower mammal by administering to 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 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 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 other mammal 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 from about 10 mg to about 1000 mg of the compound(s) of this invention per day in single or multiple doses.

Abbreviations

Abbreviations which have been used in the descriptions of the scheme and the examples that follow are: AIBN for azobisisobutyronitrile; Bu_3SnH for tributyltin hydride; CDI for carbonyldiimidazole; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; DEAD for diethylazodicarboxylate; DMF for dimethylformamide; DMSO for dimethylsulfoxide; DPPA for diphenylphosphoryl azide; Et_3N for triethylamine; EtOAc for ethyl acetate; Et_2O for diethyl ether; EtOH for ethanol; HOAc for acetic acid; MeOH for methanol; $NaN(TMS)_2$ for sodium bis(trimethylsilyl)amide; NMMO for N-methylmorpholine N-oxide; TEA for triethylamine; THF for tetrahydrofuran; and TPP for triphenylphosphine.

Synthetic Methods

The compounds and processes of the present invention will be better understood in connection with the following synthetic schemes which illustrate the methods by which the compounds of the invention may be prepared. The groups A, B, D, E, W, X, Y, Z, R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h are as defined above unless otherwise noted below.

Scheme I illustrates the preparation of the starting material derived from erythromycin A, a compound of formula (XII). The preparation of protected erythromycin A is described in the following United States patents, US 4,990,602; US 4,331,803, US 4,680,368, and US 4,670,549. Reference may also be made to European Patent Application EP 260,938. In general, the 9-ketone of compound 1 is protected, for example as an oxime (V is =N-O-OR^1 or =N-O-C(R^9)(R^{10})-O-R^1 where R^1, R^9 and R^{10} are as defined above), and then either as a separate step or in the same pot, the 2'- and 4"-hydroxyls are protected.

The 9-ketone of compound (1) is protected to give compound (2) where V is =N-O-R^1 where R^1 is as defined above or =N-O-C(R^9)(R^{10})-O-R^1 where R^1, R^9 and R^{10} are as defined above. In a preferred embodiment of the process, V is O-(1-isopropoxycyclohexyl) oxime.

The 2'- and 4"-hydroxy groups of erythromycin A (2) are protected by reaction with a suitable hydroxy protecting reagent, such as those described by T. W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Son, Inc., 1991, for example, acetic anhydride, benzoic anhydride, benzyl chloroformate or a trialkylsilyl chloride in an aprotic solvent. Examples of aprotic solvents are dichloromethane, chloroform, DMF, tetrahydrofuran (THF), N-methyl pyrrolidinone, dimethylsulfoxide, diethylsulfoxide, N,N-dimethylformamide, NN-dimethylacetamide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, a mixture thereof or a mixture of one of these solvents with ether, tetrahydrofuran, 1,2-dimethoxyethane, acetonitrile, ethyl acetate, acetone and the like. Aprotic solvents do not adversely affect the reaction, and are preferably dichloromethane, chloroform, DMF, tetrahydrofuran (THF), N-methyl pyrrolidinone or a mixture thereof. Protection of 2'- and 4"-hydroxy groups of erythromycin A thus affords compound (3) where RP is a hydroxy protecting group. In a preferred embodiment of the process, RP is trimethylsilyl.

Scheme II illustrates the general preparation of the compounds of the invention derived from erythromycin A. The alkylation of the 6-hydroxy group of compound 3 can be carried out with an alkylating agent in a solvent in the presence of a base at a temperature from about -15 °C to about 50 °C to give compound 4. Alkylating agents include alkyl chlorides, bromides, iodides or alkyl sulfonates. Specific examples of alkylating agents include allyl bromide, propargyl bromide, benzyl bromide, 2-fluoroethyl bromide, 4-nitrobenzyl bromide, 4-chlorobenzyl bromide, 4-methoxybenzyl bromide, α-bromo-p-tolunitrile, cinnamyl bromide, methyl 4-bromocrotonate, crotyl bromide, 1-bromo-2-pentene, 3-bromo-1-propenyl phenyl sulfone, 3-bromo-1-trimethylsilyl-1-propyne, 3-bromo-2-octyne, 1-bromo-2-butyne, 2-picolyl chloride, 3-picolyl chloride, 4-picolyl chloride, 4-bromomethyl quinoline, bromoacetonitrile, epichlorohydrin, bromofluoromethane, bromonitromethane, methyl bromoacetate, methoxymethyl chloride, bromoacetamide, 2-bromoacetophenone, 1-bromo-2-butanone,

bromo chloromethane, bromomethyl phenyl sulfone, 1,3-dibromo-1-propene, and the like. Examples of alkyl sulfonates are: allyl O-tosylate, 3-phenylpropyl-O-trifluoromethane sulfonate, n-butyl -O-methanesulfonate and the like. It is sufficient to use 1 to 4 mole equivalents of alkylating agents relative to compound 3. Examples of the solvents used are aprotic solvents such as dimethylsulfoxide, diethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, a mixture thereof or a mixture of one of these solvents with ether, tetrahydrofuran, 1,2-dimethoxyethane, acetonitrile, ethyl acetate, acetone and the like. Examples of the base which can be used include potassium hydroxide, cesium hydroxide, tetraalkylammonium hydroxide, sodium hydride, potassium hydride, potassium isopropoxide, potassium tert-butoxide, potassium isobutoxide and the like. The amount of base used is usually 1 to 4 equivalents relative to compound 3.

The deprotection of the 2'- and 4'-hydroxyl groups is carried out according to methods described in literature, for example, by T. W. Greene and P.G.M. Wuts in Protective Groups in Organic Synthesis, 2nd ed., John Wiley & Son, Inc., 1991.

The conditions used for the deprotection of the 2'- and 4'-hydroxyl groups usually results in the conversion of X to =N-OH. (For example, using acetic acid in acetonitrile and water results in the deprotection of the 2'- and 4'-hydroxyl groups and the conversion of X from =N-O-OR^1 or =N-O-C(R^9)(R^{10})-O-R^1 where R^1, R^9 and R^{10} are as defined above to =N-OH). If this is not the case, the conversion is carried out in a separate step.

The deoximation reaction can be carried out according to the methods described in the literature, for example by Greene op. cit. and others. Examples of the deoximating agent are inorganic sulfur oxide compounds such as sodium hydrogen sulfite, sodium pyrosulfate, sodium thiosulfate, sodium sulfate, sodium sulfite, sodium hydrosulfite, sodium metabisulfite, sodium dithionate, potassium thiosulfate, potassium metabisulfite and the like. Examples of the solvents used are protic solvents such as water, methanol, ethanol, propanol, isopropanol, trimethylsilanol or a mixture of one or more of the mentioned solvents and the like. The deoximation reaction is more conveniently carried out in the presence of an organic acid such as formic acid, acetic acid and trifluoroacetic acid. The amount of acid used is from about 1 to about 10 equivalents of the amount of compound 5 used. In a preferred embodiment, the deoximination is carried out using an organic acid such as formic acid in ethanol and water to give the desired product (6).

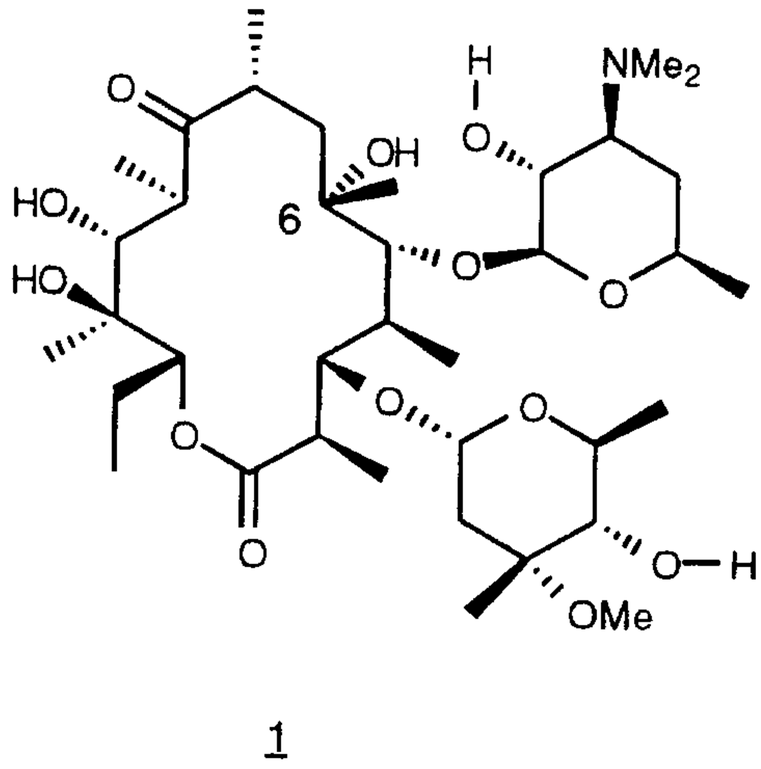
The desired 6-O-"alkylated" compound may be prepared directly as described above or obtained from chemical modification of an initially prepared 6-O-"alkylated" compound. Representative examples of further elaboration of the 6-position are shown in Scheme III. For example, compound 6 where R is 6-O-$CH_2CH=CH_2$ and M represents the macrolide ring system can be further derivatized. The double bond of the allyl compound can be (a) reduced

to give the 6-O-propyl compound (7), (b) treated with osmium tetroxide to give the 2,3-dihydroxypropyl compound (8), (c) oxidized with m-chloroperoxybenzoic acid to give the epoxy methyl compound (9), (d) oxidized under Wacker conditions to give the 6-O-CH_2-C(O)-CH_3 compound (11); (e) the epoxy compound can be opened with nucleophilic compounds, for example, amines or N-containing heteroaryl compounds, to give compounds with N-containing side chains (10), and (f) the 2,3-dihydroxypropyl compound can be oxidized with sodium periodate to give the 6-O-CH_2-CHO compound (12).

It is understood that the foregoing chemistry is merely illustrative and is not to be taken as a limitation upon the scope of the invention. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art, and may be made without departing from the spirit and scope thereof.

While the foregoing chemistry is directed to the preparation of compounds of formula II, the analogous compounds of formulae III, IV, V, VI, VII, VIII and IX can be prepared in like manner. Compounds of formula III wherein R is hydrogen, are described in United States Patents 5,075,289 and 5,217,960. Chemistry relating to these macrolides is also described by Kirst, et al. in J. Med. Chem., 33: 3086 (1990). Compounds of formula IV wherein R is hydrogen are described by Hunt, et al. in J. Antibiotics, 41: 1644 (1989). Compounds of formula V, VI and VII wherein R is hydrogen are described by Baker, et al. in J. Org. Chem., 53: 2340 (1988). Compounds of formula VIII and IX wherein R is hydrogen are described in European Patent Application 559,896.

Scheme I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HO
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O
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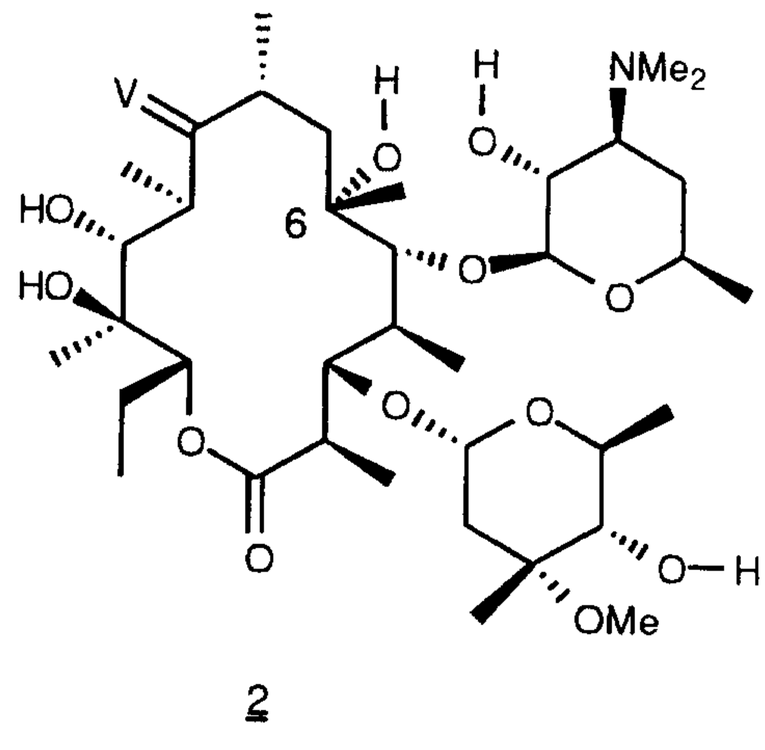
O
O—H
OMe

1


V
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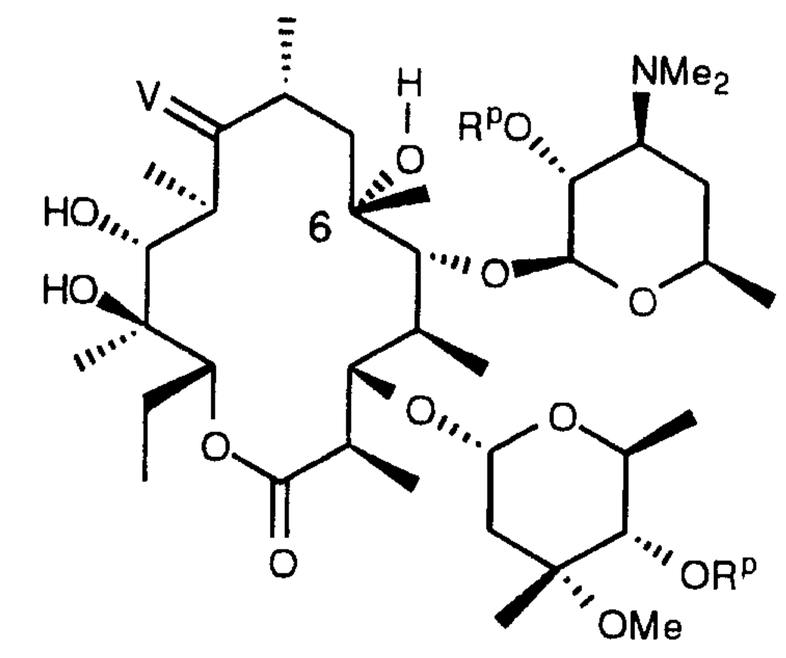
H
O
NMe2
HO
HO
6
O
O
O
O
O
O—H
OMe

2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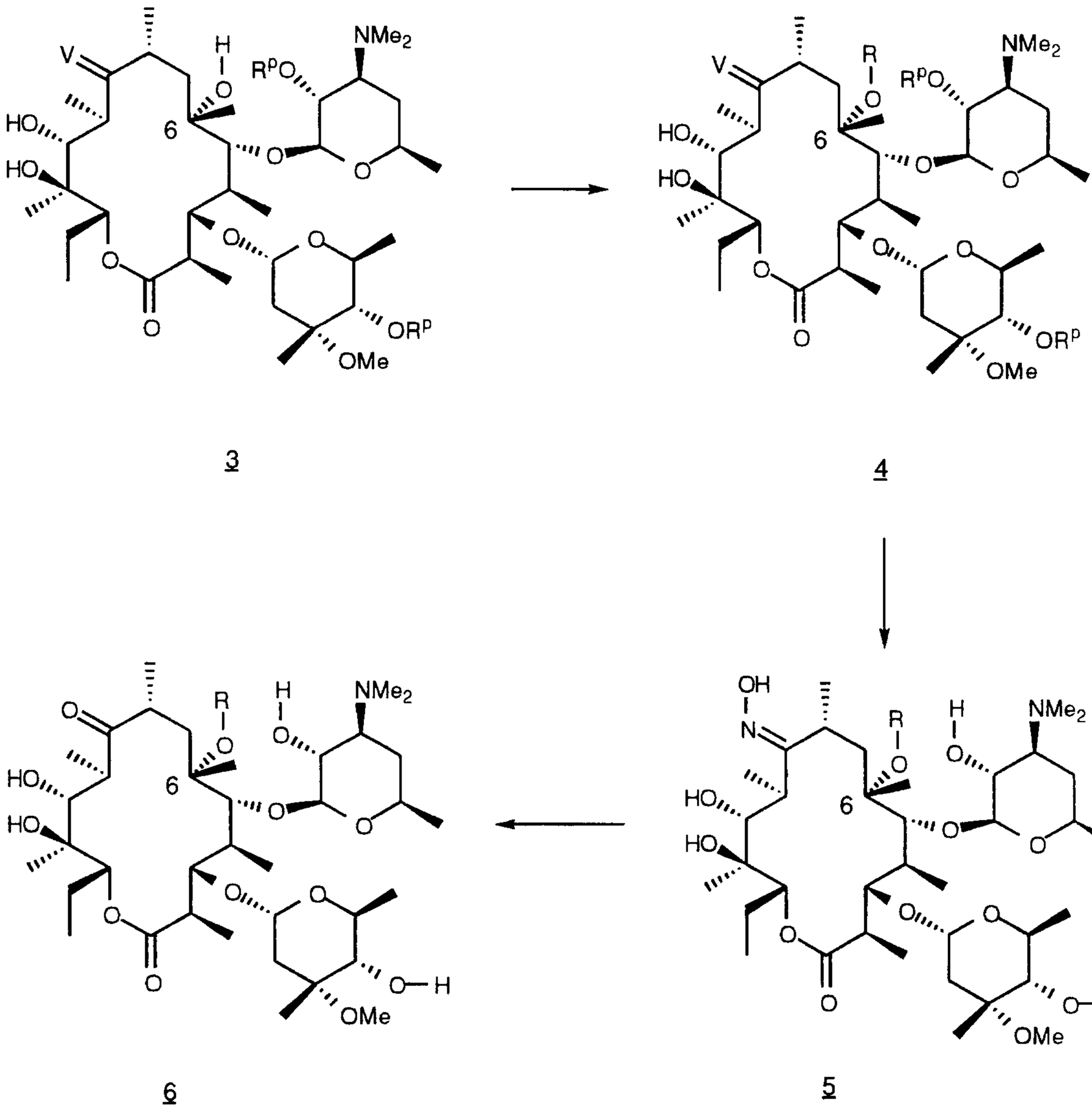
HO
HO
6
O
O
O
O
O
ORp
OMe

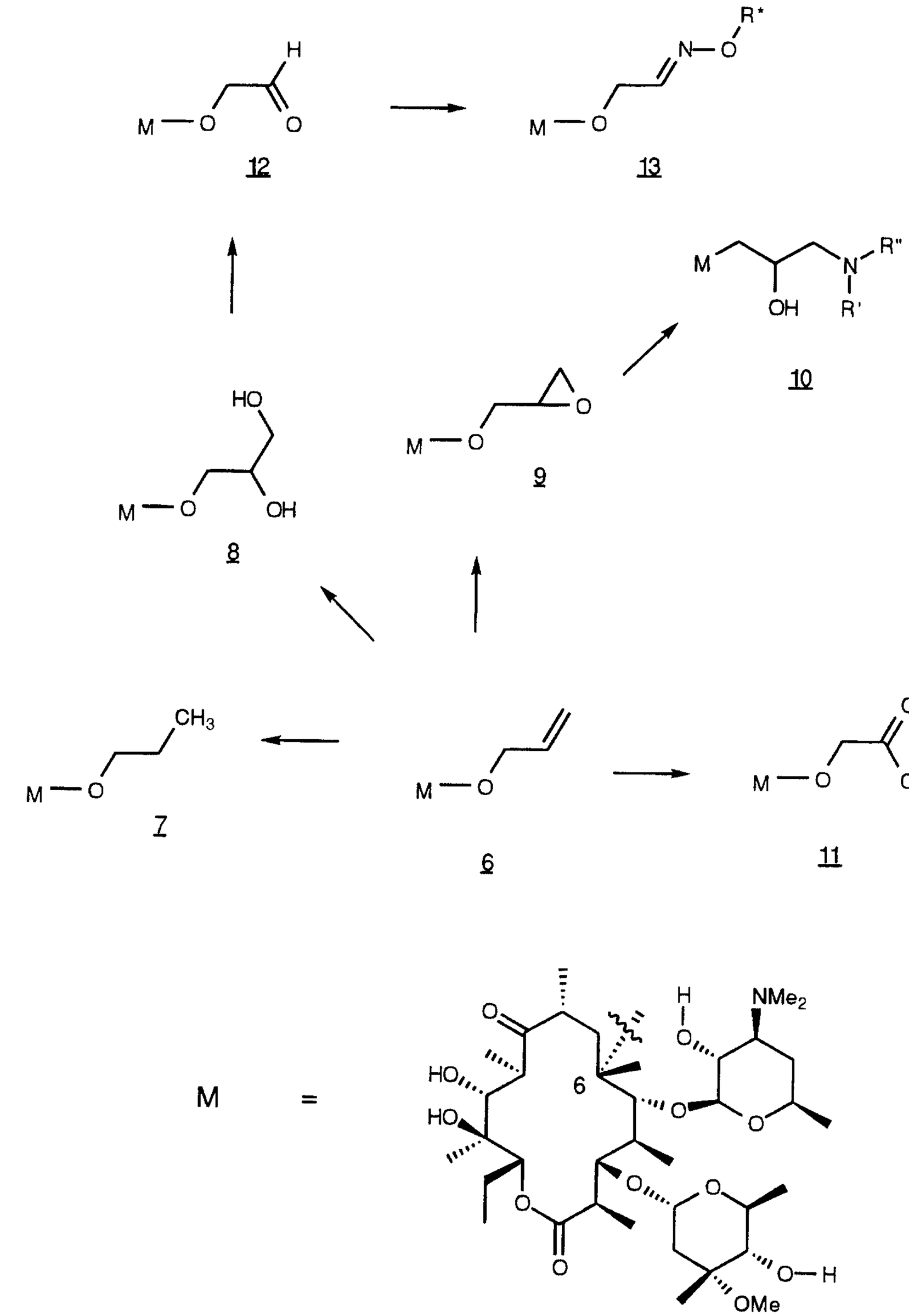
3

Scheme II



3 4 5 6

Scheme III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H
O
12
R*
N — O
M — O
13
M — O
R"
N
R'
OH
10
O
M — O
9
HO
M — O
OH
8
CH3
M — O
7
M — O
6
M — O
CH3
11
M =
O
HO
HO
6
H
O
NMe2
O
O
O
O
O
O
O
O — H
OMe

The compounds and processes of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

Example 1

Compound of Formula (X): X is =O, R is allyl

Example 1A

Compound of Formula (XII): X is =N-O-(1-isopropoxycyclohexyl), R is allyl, R^p is Trimethylsilyl

To a 0 °C solution of 5 g of the compound of Formula XII where X is =N-O-(1-isopropoxycyclohexyl) and R^p is trimethylsilyl in 15 mL of DMSO and 20 mL of THF was added 1.23 mL of freshly distilled allyl bromide. After approximately 10 minutes, a solution prepared by warming and stirring 556 mg, 2.05 equivalents) of powdered KOH in 25 mL of 1:1 THF-DMSO at 50 °C for 20-30 minutes was added dropwise over 5 minutes. After about 1 hour, the chilled reaction mixture was treated with 200 mL of EtOAc followed by 762 µL of allyl amine followed by 60 mL of water. The organic layer was washed with water followed by brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 5.3 g of crude title compound. Purification by silica gel chromatography eluting with 5% acetone in hexanes containing 0.25% triethylamine afforded 2.35 g (45%) of the title compound.

Example 1B

Compound of Formula (X): X is =N-OH, R is allyl

To a solution of the compound resulting from Example 1A (1.7 g) in 17 mL of acetonitrile and 8.5 mL of water was added 9 mL of HOAc at ambient temperature. After several hours at ambient temperature, the reaction mixture was diluted with 200 mL of toluene and concentrated *in vacuo*. The residue obtained was found to contain unreacted starting material, so additional acetonitrile (15 mL), water (70 mL) and HOAc (2 mL) was added. After 2 hours, an additional 1 mL aliquot of HOAc was added. After approximately three more hours, the reaction mixture was placed in the freezer overnight. The reaction mixture was allowed to warm to ambient temperature, diluted with 200 mL of toluene and concentrated *in vacuo*. The residue was chased two time with toluene and dried to constant weight (1.524 g).

Example 1C

Compound of Formula (X): X is =O, R is allyl

The compound resulting from Example 1B (1.225 g) in 16 mL of 1:1 EtOH-water was treated with $NaHSO_3$ (700 mg) and formic acid (141 µL) and warmed at 86 °C for 2.5 hours. After approximately three hours, the reaction mixture was allowed to cool to ambient temperature, diluted with 5-6 mL of water, basified with 1 N NaOH to pH 9-10 and extracted with EtOAc. The combined organic extracts were washed with brine (2x), dried over MgSO4, filtered and concentrated *in vacuo*. The crude material was purified by column chromatography eluting with 1% MeOH in methylene chloride containing 1% ammonium hydroxide to give 686 mg (57%) of the title compound. ^{13}C NMR ($CDCl_3$) δ 219.3 (C-9), 174.8 (C-1), 135.5 (C-17), 116.3 (C-18), 101.9 (C-1'), 95.9 (C-1"), 79.7 (C-5), 78.8 (C-6), 78.5 (C-3), 74.1 (C-12), 72.4 (C-3"), 70.6 (C-11), 68.1 (C-5'), 65.5 (C-16), 65.1 (C2'), 49.0 (C-3" O-CH_3), 45.0 (C-2), 44.1 (C-8), 39.7 (NMe_2), 37.9 (C-4), 37.1 (C-10), 34.6 (C-2"), 28.4 (C-4'), 21.0, 20.6 (C-3" CH3, C-6' CH_3), 20.8 (C-14), 18.3 (C-6"), 18.1 (C-8 CH_3), 15.7, 15.6 (C-2 CH_3, C-6 CH_3), 11.9 (C-10 CH_3), 10.1 (C-15), 8.9 (C-4 CH_3). MS (FAB)+ m/e 774 $(M+H)^+$, 812 (M+K)+.

Example 2

Compound of Formula (X): X is =O, R is propyl

The compound resulting from Example 1 (100 mg) was catalytically hydrogenated in MeOH (10 mL) using a palladium on carbon catalyst and hydrogen. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The crude product (93 mg) was purified by column chromatography on silica gel eluting with 1% MeOH in methylene chloride containing 1% ammonium hydroxide to afford 38 mg (38%) of the title compound. ^{13}C NMR ($CDCl_3$) δ 220.5 (C-9), 175.1 (C-1), 102.2 (C-1'), 96.4 (C-1"), 79.8 (C-5),79.0 (C-3), 78.7 (C-6), 77.8 (C-4"), 77.2, 77.0, 76.7, 76.4 (C-13), 74.4 (C-12), 72.8 (C-3"), 71.1 (C-11), 68.8, 68.5, 49.4 (C-3" -OMe), 45.3 (C-2), 44.5, 40.2 (-NMe_2), 38.4 (C-7), 38.2 (C-4), 37.4 (C-10), 35.1, 28.6, 21.8 (C-17), 21.5 (C-14), 21.3, 21.0 (C-3" Me, 6 Me), (18.7, 18.6 (C-6" Me, 8 Me)), (16.2, 16.1 (C-2 Me, 6 Me)), 12.3 (C-10 Me), 10.5 (C-15), 10.1 (C-18), 9.4 (C-4 Me). MS (DCI/NH_3) m/z 776 $(M+H)^+$.

Example 3

Compound of Formula (X): X is =O, R is 2,3-dihydroxypropyl

To an ambient temperature solution of the compound resulting from Example 1 (100 mg) in 6 mL of THF was added N-methylmorpholine N-oxide (98 mg) followed by 32 µL of 4% by weight osmium tetroxide in water. The reaction mixture was stirred overnight and then quenched by the addition of 3 equivalents of $NaHSO_3$. After stirring at ambient temperature

for 10 minutes, the reaction mixture was filtered through a silica gel plug eluting with 5% MeOH in methylene chloride containing 1% ammonium hydroxide to afford, after concentration at reduced pressure, the title compound (81 mg, 77%). ^{13}C NMR ($CDCl_3$) δ 222.6, 221.6 (C-9), 176.9, 176.0 (C-1), 102.2 (C-1'), 102.1, 96.5 (C-1"), 96.4, 80.0, 79.9, 79.8, 78.8, 78.7, 77.6, 77.5, 77.2, 77.0, 76.7, 74.8, 74.7 (C-12), 72.8 (C-3"), 72.8, 71.0, 71.0, 70.9 (C-11), 70.9, 68.9, 68.9, 68.5, 66.5, 66.3, 66.2, 65.8, 65.6, 63.3, 63.0 (C-18), 55.3, 49.3 (-OCH_3), 46.3, 45.6, 45.4 (C-2), 44.7 (C-8), 40.2 (-NMe_2), 38.4, 38.2, 38.2, 37.9, 37.6, 35.1 (C-2"), 35.0, 30.8, 28.5, 28.5 (C-4'), 21.7, 21.5, 21.5, 21.4, 21.0, 20.9, 18.8, 18.6, 18.5, 16.2, 16.2, 16.0, 11.9 (C-10 CH_3), 10.4 (C-15), 10.4, 9.4 (C-4 CH_3), 9.3. MS m/z 808 $(M+H)^+$.

Example 4

Compound of Formula (X): X is =O, R is 2,3-epoxypropyl

To an ambient temperature solution of the compound resulting from Example 1 (100 mg) in 1.5 mL of methylene chloride was added ~170 mg of m-chloroperoxybenzoic acid. The reaction mixture was stirred at ambient temperature overnight and concentrated *in vacuo*. The residue obtained was taken up in EtOAc and washed with saturated sodium bicarbonate solution (2x) followed by brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford 93 mg of crude product. The crude product was redissolved in EtOAc and washed with 1 M $NaHSO_3$ followed by $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue obtained was chromatographed on silica gel eluting with 5% MeOH in methylene chloride containing 1% NH_4OH to afford the title compound. ^{13}C NMR ($CDCl_3$) δ 219.8, 219.0 (C-9), 175.5, 175.2 (C-1), 102.2, 102.2 (C-1'), 96.3, 96.2 (C-1"), (80.2, 79.9, 79.6, 79.0, 78.8, 77.8, 77.7, 77.2, 77.0, 76.7, 76.6 (C-6,5,3,4",13)), 74.6 (C-12), 72.7 (C-3"), 71.0 (C-11), 68.8, 68.8 (C-17), 68.5 (C-5'), (66.2, 66.1 (C-16)), (66.0, 65.6 (C-5",3')), 50.3, 49.8, 49.3 (3" OMe), (46.6, 45.5 (C-18)), (45.3, 45.2 (C-2)), 44.6, 44.6 (C-8), 40.2 (-NMe_2), 38.4 (C-7), 38.2, 38.2, (37.6, 37.5 (C-10)), 35.1 (C-2"), 35.0, 28.8 (C-4'), (21.4, 21.2, 21.1, 20.9 (C-3" Me, 6' Me, C-14), (18.7, 18.6, 18.5 (C-6" Me, 8 Me)), (16.1, 16.0, 15.9 (C-2 Me, 6 Me)), 12.2 (C-10 Me), 12.2, 10.5 (C-15), 9.3 (C-4 Me), 9.2. MS (FAB) m/e 790 $(M+H)^+$, 812 $(M+Na)^+$, 828 $(M+K)^+$. High Resolution Mass Spec m/z Calcd for $C_{40}H_{71}NO_{14}K$: 828.4512. Found: 828.4516.

Example 5

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(imidazol-1-yl)propyl

To an ambient temperature solution of the compound resulting from Example 4 (100 mg) in ~1 mL of chloroform was added 17 mg of imidazole. The reaction vessel was sealed and stirring was continued at ambient temperature for 1 hour. Two additional equivalents of imidazole were added, and stirring was continued for several days. The solvent was removed under reduced pressure, and the crude material obtained was purified by column chromatography eluting with 5% MeOH in methylene chloride containing 1% NH_4OH to afford 44 mg (41%) of the title compound. ^{13}C NMR ($CDCl_3$) mixture of epimers δ 223.3, 221.2 (C-9), 176.4, 175.9 (C-1), 137.9 (C-19), 128.7 (C-20), 120.1 (C-21), 119.9, 102.2, 102.1 (C-1'), 96.5 (C-1"), 80.3, 79.7, 79.2, 78.9, 77.6, 77.6, 77.4, 77.2, 77.0, 77.0, 76.7, 74.7, 74.6, 72.7, 72.7, 71.0, 69.7, 69.4, 69.0, 69.0, 68.5, 68.5, 66.8 (C-16), 66.0, 65.5, 65.4, 50.2 (C-18), 49.3 (C-18), 49.3 (C-3" -OMe), 45.5 (C-2), 45.2 (C-2), 44.7 (C-8), 44.7 (C-8), 40.1 ($-NMe_2$), 38.2 (C-7), 38.1 (C-7), 37.8, 37.5, 34.9 (C-2"), 28.4 (C-4'), 21.6, 21.4, 21.3, 21.3, 21.2, 20.9, 20.8, 18.9, 18.8, 18.7, 18.6, 16.2, 16.1 (C-2 Me, C-6 Me), 16.0, 11.9 (C-10 Me), 11.9, 10.4 (C-15), 10.4, 9.3 (C-4 Me). MS m/z 858 $(M+H)^+$. High Resolution Mass Spec m/z Calcd for $C_{43}H_{76}N_3O_{14}$: 858.5327. Found: 858.5320.

Example 6

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(morpholin-4-yl)propyl

To an ambient temperature solution of the compound resulting from Example 4 (100 mg) in 1 mL of chloroform was added 22 μL of morpholine. The reaction vessel was sealed and stirring was continued at ambient temperature for 1 hour. Two additional equivalents of morpholine was added and stirring was continued for several days. The solvent was removed under reduced pressure, and the crude material obtained was chromatographed on silica gel eluting with 3% MeOH in methylene chloride containing 1% NH_4OH to give 35 mg (33%) of the title compound. ^{13}C NMR ($CDCl_3$) mixture of epimers δ 220.3, 219.1 (C-9), 176.1, 175.5 (C-1), 102.1, 102.1 (C-1'), 96.2, 96.1 (C-1"), 80.0, 79.8, 79.7, 79.1, 78.6, 78.6, 77.8, 77.7, 77.3, 77.1, 77.0, 76.7, 76.6, 75.0, 75.0, 72.8, 71.0, 68.5, 68.2, 67.8, 67.0, 66.9 (C-21,22), 66.4, 66.0, 65.9, 65.5, 65.5, 61.4 (C-18), 60.8 (C-18), 60.3, 53.9, 53.8, 51.9, 49.3, 49.3 (-OMe), 46.4, 45.5, 45.4 (C-2), 44.8, 44.7 (C-8), 40.2 ($-NMe_2$), 38.3 (C-10,4), 38.2, 38.1, 37.9 (C-7), 37.7, 35.0, 29.6, 28.5 (C-4'), 21.7, 21.5, 21.4, 21.4, 21.3, 21.3 (C-14, 3"-Me, 6'-Me), 21.1, 20.9, 19.0, 18.7 (C-8 Me, C-6" Me), 18.6, 16.3, 16.2, 16.0 (C-2 Me, 6 Me), 16.0, 14.1, 12.1 (C-10 Me), 10.6, 10.5 (C-15), 9.3 (C-4 Me). MS (FAB) m/e 877 $(M+H)^+$, 915 $(M+K)^+$.

Example 7

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(benzylamino)propyl

To an ambient temperature solution of the compound resulting from Example 4 (140 mg) in 1.5 mL of chloroform was added 3 equivalents (58 μL) of benzylamine. The reaction mixture was stirred overnight at ambient temperature and then warmed at 62 °C for approximately 3 hours and then stirred overnight at ambient temperature. The reaction mixture was then heated at 70 °C for 2 hours and then concentrated *in vacuo*. The residue was chased two times with toluene to afford 170 mg of crude title compound. Crude product was purified by silica gel chromatography eluting with 2% MeOH in methylene chloride containing 1% NH_4OH to give the title compound as a mixture of epoxide epimers. ^{13}C NMR ($CDCl_3$) δ 221.7, 220.1 (C-9), 176.4 (C-1), 175.7, 140.7 (C-20), 140.5, 128.5, 128.2, 128.1, 128.1, 127.0, 126.7, 126.6, 126.5, 102.2 (C-11), 96.2 (C-1"), 79.9, 79.6, 79.3, 78.8, 78.7, 77.6, 77.6, 76.8, 76.7, 74.9, 72.7, 72.7, 71.0, 69.7, 69.1, 68.7, 68.5, 67.9, 67.8 (C-16), 66.0, 65.6, 53.8, 53.6, 51.6, 51.3, 49.3 (-OCH_3), 45.5 (C-2), 45.4, 44.7, 44.6 (C-8), 40.2 (-NMe_2), 38.2, 38.2 (C-7), 38.0 (C-10, 4), 37.9, 35.0, 34.8 (C-2"), 28.5 (C-4'), 21.7, 21.4, 21.4, 21.1, 21.1, 18.9, 18.6, 18.6, 16.2, 16.2, 16.0, 15.9, 12.1, 12.0 (C-10 CH_3), 10.5 (C-15), 9.3 (C-4 CH_3), 9.3. MS m/z 897 $(M+H)^+$.

Example 8

Compound of Formula (X): X is =O, R is 2-oxoethyl

To a solution of the compound resulting from Example 3 (275 mg) in 6.5 mL of a 20% aqueous THF was added 87 mg of $NaIO_4$. The reaction was stirred at ambient temperature for 2 hours and then 0.5 equivalents of NaIO4 was added. After 2 additional hours, another 0.5 equivalent of $NaIO_4$ was added. After two more hours, the reaction mixture was filtered through a silica gel plug eluting with 4% MeOH in methylene chloride containing 1% NH_4OH to afford 195 mg (65%) of the title compound. ^{13}C NMR ($CDCl_3$) δ 221.0 (C-9), 203.2 (CHO), 175.5 (C-1), 102.4 (C-1'), 101.9, 96.7, 96.3 (C-1"), 96.0, 80.5, 79.8, 78.5,77.7, 76.7, 74.5 (C-12), 72.7 (C-3"), 71.1, 70.3, 68.9, 68.7, 68.0, 66.4, 66.1, 65.6, 49.4 (C-3" OMe), 45.8, 44.9, 44.7, 41.0, 40.2 (-NMe_2), 38.4 (C-4), 38.2 (C-7), 37.9, 37.4 (C-10), 35.1, 34.9 (C-2"), 28.5 (C-4'), 21.7, (21.5, 21.4, 21.1 (C-3" Me, 6 Me)), 21.0 (C-17), (18.8, 18.6, 18.5 (C-8 Me, 6" me)), 16.3, 16.0 (C-2 Me), 12.2 (C-10 Me), 12.1, 10.4 (C-15), 9.3, 9.2 (C-4 Me). Mass Spec m/z 776 $(M+H)^+$.

Example 9

Compound of Formula (X): X is =O, R is 2-oxopropyl

A mixture of 1.5 mL of 7:1 DMF-H_2O, 5 mg $PdCl_2$ and 21 mg of CuCl was stirred under an oxygen atmosphere for ~1.33 hours. To this mixture was added a solution of the compound resulting from Example 1 (150 mg) in 1.5 mL of 7:1 DMF-H_2O dropwise over 10 minutes. The reaction mixture was warmed to 50 °C and maintained at that temperature for approximately 1 hour and at ambient temperature overnight. Additional aliquots of $PdCl_2$ (5 mg) and CuCl (21 mg) were added. The reaction mixture was warmed to 54 °C and maintained at that temperature for about 3 hours. The reaction mixture was allowed to cool to ambient temperature and then O_2 was bubbled through the reaction mixture which was stirred overnight at ambient temperature. Additional $PdCl_2$ (10 mg) and CuCl (42 mg) were added, and the O_2 was continued. The reaction mixture was warmed to 40 °C for about 3 hours and then stirred over the weekend at ambient temperature. The reaction mixture was diluted with EtOAc and washed two times with 30% aqueous ammonium hydroxide solution and two times with brine, dried over MgSO4 and concentrated *in vacuo* to afford 85 mg of crude title compound. Purification by eluting through a silica gel plug with 1% MeOH in methylene chloride containing 1% ammonium hydroxide afforded 47 mg of the title compound. ^{13}C NMR ($CDCl_3$) δ 217.9, 205.3, 175.0, 102.9, 102.4, 101.8, 96.5, 95.9, 94.7, 80.6, 79.0, 78.9, 78.2, 77.7, 77.5, 77.3, 77.0, 76.8, 76.7, 75.1, 72.7, 71.2, 71.0, 70.8, 70.5, 69.6, 68.8, 68.7, 68.3, 66.1, 65.9, 65.6, 49.5, 49.4, 45.1, 44.8, 43.3, 42.7, 40.3, 40.2, 38.4, 37.6, 35.0, 34.7, 30.4, 28.7, 28.5, 26.5, 26.2, 25.9, 21.5, 21.4, 21.3, 21.3, 21.1, 19.2, 18.7, 18.3, 16.2, 15.9, 14.8, 13.6, 12.2, 11.9, 10.9, 10.6, 9.3, 8.7. High Resolution Mass Spec (FAB) Calcd for m/z $(M+H)^+$ $C_{40}H_{72}NO_{12}$: 790.4953. Found: m/z 790.4932.

Example 10

Compound of Formula (X): X is =O, R is $-CH_2-C\equiv CH$

Example 10A

Compound of Formula (X): X is =N-O-(1-isopropoxycyclohexyl), R is $-CH_2-C\equiv CH$

A solution of 1.14 g of powdered KOH in 30 mL of anhydrous DMSO and 30 mL of anhydrous freshly distilled THF was added via addition funnel to a 0 °C solution of the compound of Formula XII where X is =N-O-(1-isopropoxycyclohexyl) and RP is trimethylsilyl (10 g) in 60 mL of 1:1 DMSO-THF. This was followed by a solution containing 2.38 mL of propargyl bromide (80%) in toluene added over 10-15 minutes. The reaction mixture was stirred at 0 °C for about one hour and then 2 additional equivalents of propargyl bromide was added at 0 °C. After 2 hours, 2 equivalents of powdered KOH (~1 g) was added at 0 °C, and the reaction mixture was placed in the refrigerator overnight. The next day an

additional 4 mL of propargyl bromide was added at 0 °C. When tlc indicated that the reaction was complete, the reaction was quenched with 10 equivalents of allylamine at 0 °C and stirred for 5 minutes. Dilute the mixture was H2O and EtOAc and wash the organic layer with water followed 2 times with brine. The organic layer was dried over MgSO4 and concentrated under reduced pressure to afford 11.5 g of crude title compound. Filtration through a silica gel plug eluting with 10% acetone in hexane containing 0.25% Et_3N afforded 9.3 of purified title compound.

Example 10B

Compound of Formula (X): R is $-CH_2-C\equiv CH$, X is =N-O-H

To the compound resulting from Example 10A (9.3 g) in 50 mL of acetonitrile and 35 mL of water was added 50 mL of HOAc. The reaction mixture was stirred in the dark at ambient temperature for 2 hours and placed in the refrigerator overnight. The reaction mixture was allowed to warm to ambient temperature, diluted with toluene and concentrated *in vacuo*. The residue obtained was used without further purification.

Example 10C

Compound of Formula (X): X is =O, R is $-CH_2-C\equiv CH$

The compound resulting from Example 10B (8.16 g) in 1:1 EtOH-H_2O (140 ml) was treated with 4 equivalents of $NaHSO_3$ and formic acid (960 µL, 2.4 equivalents) and warmed to ~82 °C. After approximately 2.5 hours, the reaction mixture was allowed to cool to ambient temperature, basified to pH 10 with 1 N NaOH solution and extracted with EtOAc. The combined organic extracts were washed, dried and concentrated *in vacuo*. The crude product obtained was chromatographed on silica gel eluting with 1% MeOH in methylene chloride containing 1% ammonium hydroxide to afford 2.9 g (40%) of the title compound which was recrystallized from acetonitrile. ^{13}C NMR ($CDCl_3$) δ 219.7 (C-9), 175.2 (C-1), 151.7, 104.4, 103.0, 102.6 (C-1'), 101.5, 96.2 (C-1"), 95.9, 94.6, 92.0, 85.6, 81.2, 81.1, 80.7 (C-5), 80.3 (C-6), 80.1, 78.8 (C-3), 78.2, 78.1, 77.9 (C-4"), 77.3, 77.3, 77.0, 77.0, 76.8, 76.7, 76.6, 76.3, 75.3, 74.5 (C-17), 73.9 (C-12), 72.7, 71.0 (C-11), 70.8, 70.0, 69.3, 68.8, 68.7 (C-5'), 65.9, 65.8, 65.6, 65.5, 65.0, 51.8 (C-16), 49.5, 49.4 (C-3' OMe), 45.2 (C-2), 44.8 (C-8), 44.7, 43.3, 42.6, 40.3, 40.2 (NMe_2), 39.3, 38.6 (C-7), 38.5 (C-4), 37.5 (C-10), 35.0 (C-2"), 34.6, 30.5, 29.4, 28.7, 28.6 (C-4'), 26.2, 25.8, 23.9, 21.6, 21.5 (C-3" Me, 6' Me), 21.3, 21.2 (C-14), 21.0 (C-3" Me, 6' Me), (18.7, 18.4 (C-2 Me, 6 Me)), 18.3, 18.2, 17.6, 16.1, 16.0, 15.0, 14.8, 13.7, 13.4, 13.1, 12.3 (C-10 Me), 11.9, 11.2, 10.9, 10.6 (C-15), 9.2 (C-4 Me), 8.7. MS (FAB) m/e 772 $(M+H)^+$, 810 $(M+K)^+$.

Example 11

Compound of Formula (X): X is =O, R is -CH_2-CHOH-CH_2-N_3

To an ambient temperature solution of the compound resulting from Example 4 (100 mg) in 0.75 mL of DMF was added 12 mg of NaN_3. The reaction mixture was stirred at ambient temperature approximately 5.5 hours and then an additional 8 mg of NaN_3 was added. The reaction mixture was stirred at ambient temperature overnight, heated at 70 °C-90 °C for 3 hours and then treated with an additional 14 mg of NaN_3. The reaction mixture was heated at 60 °C overnight. Four drops of water were added, and the reaction mixture was heated at 80 °C for 4 hours. One equivalent of ammonium chloride was added and heating was continued at 80 °C for 2 hours. The reaction mixture was allowed to cool to ambient temperature, diluted with ethyl acetate and washed with 0.5 N NaOH solution and brine, dried and concentrated *in vacuo*. The residue obtained was filtered through a silica gel plug eluting with 4% MeOH in methylene chloride containing 1% ammonium hydroxide to give 47 mg (50%) of the title compound containing trace amounts of DMF. The DMF was removed by dissolving the compound in 1:1 EtOAc-Et_2O, washing with water followed by brine, drying over magnesium sulfate and concentrating *in vacuo* to give 45 mg of title compound which was further purified by filtering through silica gel eluting with 4% MeOH in methylene chloride containing 1% ammonium hydroxide to give the title compound. ^{13}C NMR ($CDCl_3$) mixture of epimers δ 222.8, 221.2 (C-9), 176.6, 175.8 (C-1), (102.2, 102.1 (C-1')), (96.4, 96.3 (C-1")), 94.4, 80.2, 80.1, 79.4, 78.9, 78.7, 77.6, 77.5, 77.4, 77.0, 76.6, 74.8, 74.7, 72.8, 71.0 (C-11), 70.0, 69.7, 68.9, 68.6, 67.3, 66.8, 66.2, 65.8, 65.6, 53.8, 53.2 (C-18), 49.3 (C-3" OMe), 45.6 (C-2), 45.4, 44.7 (C-8), 42.0, 40.2 (-NMe_2), 38.4, 38.2, 37.9, 37.6, (35.1, 35.0 (C-2")), 29.6, 28.5 (C-4'), 23.0, 21.8, 21.5, 21.2, (21.1, 21.0 (C-14)), 20.9, 18.8, 18.2, 16.1, 12.0 (C-10 Me), 12.0, 11.0, 10.4 (C-15), 10.1, 9.3, 9.3 (C-4 Me), 8.6. MS (FAB) m/e 833 $(M+H)^+$, 871 $(M+K)^+$. High Resolution Mass Spec m/z (M+H)+ Calcd for $C_{40}H_{73}N_4O_{14}$: 833.5123. Found: 833.5137.

Example 12

Compound of Formula (X): X is =O, R is -CH_2-CH=N-OH

To a solution of the compound resulting from Example 8 (600 mg) in 5 mL of MeOH was added a solution of 80 mg of hydroxylamine hydrochloride and 255 μL of N-methylmorpholine in 2 mL of MeOH. The reaction mixture was stirred at ambient temperature for 5 hours and then concentrated *in vacuo*. The residue obtained was purified by eluting from silica gel using 4% MeOH in methylene chloride containing 1% ammonium hydroxide to give the title compound as a 1:1 mixture of oxime isomers. ^{13}C NMR ($CDCl_3$) δ 220.8, 219.9 (C-9), 175.4, 175.3 (C-1), 151.7 (CH=N), 149.2 (CH=N), 102.4, 102.3 (C-1'), 96.3 (C-1"), 92.0, 86.6, 80.0, 80.0, 79.9, 79.8, 78.8, 78.8, 77.7, 77.3, 77.0, 76.7, 76.5, 76.4, 74.5,

74.4 (C-12), 72.7 (C-3"), 72.7, 71.1, 68.8, 68.7, 68.5, 68.5, 66.6, 66.0, 65.9, 65.6, 65.4, 65.0, 61.4, 58.6, 55.2, 49.4, 49.3 (3" -OCH_3), 46.2, 45.9, 45.2, 45.2, 44.6, 40.3, 40.2 (-NMe_2), 39.2, (38.4, 38.3 (C-4)), 38.2 (C-7), 37.4, 37.2 (C-10), 35.0 (C-2"), 28.6 (C-4'), 24.8, 23.0, 21.6, 21.4, 21.4, 21.2, 21.1, 21.0, 20.9, 20.5, 18.7, 18.6, (18.4, 18.4 (C-8 Me, 6" Me)), 18.2, 17.7, 16.1, 16.0, 16.0 (C-2 Me), 15.9, 12.2 (C-10 Me), 10.4 (C-15), 9.2 (C-4 Me). MS m/z 791 $(M+H)^+$.

Example 13

Compound of Formula (X): X is =O, R is -CH_2-CH_2OH

To a -78 °C solution of the compound resulting from Example 8 (75 mg) in 1 mL of anhydrous THF was added 1.1 equivalents of L-Selectride dropwise over 2 minutes. The reaction mixture was stirred at -78 °C for approximately one hour and then quenched at -78 °C with an aqueous solution of tris-hydroxymethylaminomethane followed by EtOAc. The organic phase was washed twice with brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude material (76 mg) was chromatographed on silica gel eluting with 3% MeOH in methylene chloride containing 1% ammonium hydroxide to afford 20 mg of the desired title compound. ^{13}C NMR ($CDCl_3$) δ 222.1 (C-9), 215.7, 203.2, 176.7, 175.9 (C-1), 175.5, 102.7, 102.4, 102.1, 96.6, 96.3, 83.8, 80.4, 80.2, 80.0, 79.8, 79.6, 79.4, 79.2, 78.8, 77.7, 77.4, 77.0, 76.6, 74.8, 74.5, 72.8, 72.7, 71.1, 70.3, 68.8, 68.5, 66.1, 66.0, 65.6, 65.4, 62.3, 62.0, 49.4, 45.6, 45.4, 44.7, 42.0, 41.1, 40.2 (NMe_2), 39.4, 38.6, 38.1, 37.8, 37.4, 35.1 (C-2"), 28.8, 28.5 (C-4'), 25.9, 23.5, 21.8, 21.6, 21.5, 21.0, 18.7, 18.6, 18.5, 16.2, 15.4, 15.1, 14.4, 13.3, 12.1, 11.8, 10.5, 9.4. MS m/e 778 $(M+H)^+$.

Example 14

Compound of Formula (X): X is =O, R is -CH_2-CH_2NH_2

The compound resulting from Example 12 (160 mg) was subjected to catalytic hydrogenation using a Raney nickel catalyst under 4 atmospheres of hydrogen over 20 hours. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to afford 159 mg of crude title compound. Purification by column chromatography on silica gel eluting with 7% MeOH in methylene chloride containing 1% ammonium hydroxide afforded 87 mg (55%) of the title compound. ^{13}C NMR ($CDCl_3$) δ 219.9 (C-9), 175.5 (C-1), 101.6 (C-1'), 96.1 (C-1"), 79.3 (C-5), 78.9 (C-3), 78.4 (C-6), 77.3 (C-4"), 77.0, 76.7, 76.3 (C-13), 74.8 (C-12), 72.5 (C-3"), 71.1 (C-11), (68.0, 67.7, 65.6, 64.4, 64.2 (C-2',3',5",5',16)), 48.8 (C-3" OMe), 48.7, 48.5, 48.4, 48.2, 48.0, 47.9, 47.7, 45.0 (C-2), 44.4, 40.6, 39.6 (NMe_2), (37.9, 37.8 (C-4, 10)), 37.5 (C-7), 34.8 (C-2"), 29.0 (C-4'), 21.0, 20.9, 20.8 (C-17), 20.7, (18.4, 18.1 (C-8 Me, 6" Me), (15.9, 15.4 (C-2 Me, 6 Me), 11.4 (C-10 Me), 10.0 (C-15), 9.0 (C-4 Me). MS m/z 777 $(M+H)^+$.

Example 15

Compound of Formula (X): X is =O, R is -CH_2-CN

To a solution of the compound resulting from Example 12 (165 mg) in 5 mL of freshly distilled THF was added 2 equivalents of diisopropylcarbodiimide (65 µL) followed by a catalytic amount of CuCl. After stirring approximately 2 hours at ambient temperature, two additional aliquots of diisopropylcarbodiimide (65 µL) were added plus additional CuCl. After 3 more hours, the reaction was complete and the solvent was removed *in vacuo* to afford the title compound. Mass Spec m/z 773 $(M+H)^+$.

Example 16

Compound of Formula (X): X is =O, R is -CH_2-Phenyl

Example 16A

Compound of Formula (XII): X is =N-O-(1-isopropoxycyclohexyl), R is -CH_2-Phenyl, R^p is Trimethylsilyl

To a 0 °C solution of 30 mL of a 1:1 solution of THF and DMSO containing 5 g of the compound of Formula (X) wherein X is =N-O-(1-isopropoxycyclohexyl) and R is hydrogen was added 1.2 mL of benzyl bromide. A second solution of 30 mL of 1:1 DMSO and THF containing 560 mg of powdered KOH was added in portions over 45 minutes at 0 °C with good stirring. Upon completion of the addition, stir at 0 °C under nitrogen for 1 hour and then allylamine (700 µL) and ethyl acetate were added. The solution was washed with water and brine (2x), dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford 6 g of the title compound.

Example 16B

Compound of Formula (XII): X is =N-O-(1-isopropoxycyclohexyl), R is -CH_2-Phenyl, R^p is H

To a room temperature solution of 6 g of the compound resulting from Example 16A in 65 mL of anhydrous THF was added 14.5 mL of 1 M tetrabutylammonium fluoride. After several hours, the solvent was removed under reduced pressure and the residue was dried to constant weight. Purification by column chromatography eluting with 4% methanol in methylene chloride containing 1% ammonium hydroxide afforded 2.8 g of the title compound.

Example 16C

Compound of Formula (XII): X is =N-OH, R is -CH_2-Phenyl, R^p is H

To the compound resulting from Example 16B (2.8 g) in 26 mL of acetonitrile was added 14 mL of water followed by 14 mL of acetic acid. The reaction mixture was stirred for

~4 hours at ambient temperature and then placed in the freezer overnight. The volatiles were removed *in vacuo*, and the residue was chased twice with toluene and dried to constant weight to afford 2.73 g of the title compound.

Example 16D

Compound of Formula (X): X is =O, R is -CH_2-Phenyl

To the compound resulting from Example 16C (2.7 g) in 23 mL of EtOH and water (23 mL) was added 1.4 g of $NaHSO_3$. This was followed by 292 µL of formic acid, and the reaction mixture was warmed to 80 °C. After approximately 90 minutes, the reaction mixture was allowed to cool to ambient temperature, basified to pH ~10-11 with 2 N NaOH solution and extracted with ethyl acetate. The combined organic extracts were washed with water followed by brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude material (1.95 g) was chromatographed on silica gel eluting with 1% methanol in methylene chloride containing 1% ammonium hydroxide followed by 2% methanol in methylene chloride containing 1% ammonium hydroxide to afford 715 mg of the title compound. Further purification was effected by chromatography on silica gel eluting with 2% ammonium hydroxide in methylene chloride followed by 2% methanol in methylene chloride containing 1% ammonium hydroxide to afford 435 mg of the title compound. ^{13}C NMR ($CDCl_3$) δ 219.28, 174.69, 139.20, 128.51, 127.95, 127.12, 102.20, 96.42, 80.14, 79.80, 78.96, 77.79, 77.42, 77.00, 76.56, 74.77, 72.84, 71.11, 68.75, 68.56, 66.39, 66.21, 65.61, 49.41, 45.15, 44.62, 40.27, 38.02, 37.91, 35.19, 28.54, 21.95, 21.56, 21.53, 21.28, 19.2, 18.82, 16.25, 16.09, 12.24, 10.61, 9.56. MS (FAB) m/e 824 $(M+H)^+$.

Example 17

Compound of Formula (X): X is =O, R is -CH_2-CH=CH(Phenyl)

The title compound was prepared by the procedures described in Example 16 substituting 3-phenyl allyl bromide for benzyl bromide. For conversion of the oxime to the ketone, the reaction mixture was heated about 3 hours and then placed in the freezer overnight. Chromatography on silica gel eluting with 1% methanol in methylene chloride containing 1% ammonium hydroxide afforded ~700 mg (17% yield for three steps) of the title compound.

Example 18

Compound of Formula (X): X is =O, R is -CH_2-CH=N-O-CH_3

To a room temperature solution of 150 mg of the compound resulting from Example 8 in 1 mL of methanol was added a solution of 14 mg of methoxylamine hydrochloride in 0.5 mL methanol containing 64 µL of N-methyl morpholine in one portion. The reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for about 6 hours and then

treated with 0.75 equivalents (12 mg) of methoxylamine hydrochloride. The reaction mixture was stirred at ambient temperature for 1 hour and then placed in the refrigerator overnight. The volatiles were removed under reduced pressure to afford 215 mg of crude title compound. Purification by column chromatography on silica gel eluting with 1% methanol in methylene chloride containing 1% ammonium hydroxide afforded 120 mg (78%) of the title compound as a 1:1 syn:anti mixture. ^{13}C NMR ($CDCl_3$) δ 219.3, 218.4, 173.8, 173.7, 157.9, 157.9, 149.5, 146.8, 100.8, 100.7, 94.7, 94.5, 93.0, 78.4, 78.2, 77.3, 77.1, 76.2, 75.9, 75.4, 75.0, 74.9, 74.8, 72.9, 72.7, 71.2, 71.1, 69.4, 67.2, 67.1, 67.0, 65.3, 64.5, 64.4, 64.0, 59.9, 57.3, 47.8, 47.8, 44.8, 43.7, 43.6, 43.0, 38.6, 36.8, 36.7, 36.7, 35.7, 33.4, 26.9, 19.9, 19.8, 19.4, 18.9, 17.1, 16.9, 16.8, 14.4, 14.4, 10.6, 8.9, 8.8, 7.6, 7.5. MS (FAB) m/e 805 $(M+H)^+$.

Example 19

Compound of Formula (X): X is =O, R is $-CH_2-CH=N-O-CH_2-Phenyl$

The title compound was prepared as a 1:1 syn:anti mixture by the procedures described in Example 18 substituting O-benzyl hydroxylamine hydrochloride for methoxylamine hydrochloride to afford 118 mg (70%). ^{13}C NMR ($CDCl_3$) δ 219.3, 218.5, 173.8, 173.7, 157.8, 149.8, 147.6, 136.6, 126.5, 126.5, 126.2, 125.8, 125.8, 100.8, 100.8, 94.7, 94.5, 93.0, 78.5, 78.4, 78.2, 77.2, 76.2, 76.2, 75.8, 75.4, 75.0, 74.9, 74.2, 74.0, 72.8, 72.7, 71.2, 71.1, 69.4, 67.2, 67.1, 67.0, 65.3, 64.4, 64.4, 60.1, 57.5, 53.8, 47.8, 47.8, 44.8, 43.6, 43.0, 38.6, 36.8, 36.8, 36.7, 36.7, 35.6, 33.4, 33.4, 26.9, 19.9, 19.8, 19.8, 19.5, 19.4, 19.0, 17.1, 17.0, 16.8, 16.8, 14.4, 14.4, 10.6, 10.6, 8.9, 7.6. MS (FAB) m/e 881 $(M+H)^+$.

Example 20

Compound of Formula (X): X is =O, R is $-CH_2-CH=N-N(CH_3)_2$

The title compound was prepared by the procedures described in Example 18 substituting N,N-dimethyl hydrazine for methoxylamine hydrochloride. Purification by column chromatography eluting with 2% methanol in methylene chloride containing 1% ammonium hydroxide afforded 115 mg (73%) of the title compound as a single (syn or anti) isomer. ^{13}C NMR ($CDCl_3$) δ 217.8, 173.5, 157.6, 132.4, 100.5, 94.5, 92.7, 78.1, 77.4, 76.0, 75.6, 75.2, 74.7, 74.6, 72.6, 70.9, 69.2, 66.7, 64.1, 63.7, 63.0, 47.5, 43.4, 42.7, 41.0, 38.4, 36.6, 36.5, 35.4, 33.1, 26.7, 19.6, 19.6, 19.4, 19.2, 16.8, 16.6, 14.3, 14.0, 10.4, 8.8, 7.4. MS (FAB) m/e 818 $(M+H)^+$.

Example 21

Compound of Formula (X): X is =O, R is -CH_2-CH=N-NH(CH_3)

The title compound was prepared by the procedures described in Example 18 substituting N-methyl hydrazine for methoxylamine hydrochloride. Purification by column chromatography eluting with 2% methanol in methylene chloride containing 1% ammonium hydroxide afforded 89 mg (58%) of the title compound as a single pure isomer of unknown stereochemistry. ^{13}C NMR ($CDCl_3$) δ 219.7, 175.5, 136.2, 102.5, 96.5, 80.1, 79.4, 79.1, 77.9, 77.2, 77.0, 76.7, 76.5, 74.5, 72.8, 71.1, 68.7, 66.1, 65.7, 64.4, 49.4, 45.3, 44.6, 40.3, 38.6, 38.5, 37.4, 35.1, 34.8, 28.6, 21.5, 21.5, 21.3, 21.0, 18.8, 18.5, 16.2, 15.9, 12.3, 10.7, 9.2. MS (FAB) m/e 804 $(M+H)^+$.

Example 22

Compound of Formula (X): X is =O, R is -CH_2-CH=N-(4-Morpholinyl)

The title compound was prepared by the procedures described in Example 18 substituting N-amino morpholine for methoxylamine hydrochloride. Purification by column chromatography eluting with 5% methanol in methylene chloride containing 1% ammonium hydroxide followed by re-chromatography eluting with 2% methanol in methylene chloride containing 1% ammonium hydroxide afforded 125 mg (75%) of the title compound as a single pure isomer of unknown stereochemistry. Diagnostic peaks ^1H NMR ($CDCl_3$, 500 MHz) δ 0.84 (t, 3H), 2.29 (s, 6H), 3.12 (m, 4H), 3.34 (s, 3H), 3.85 (t, 4H), 4.50 (d, 1H), 4.92 (d, 1H), 5.06 (d of d, 1H). MS (FAB) m/e 860 $(M+H)^+$.

Example 23

Compound of Formula (X): X is =O, R is -CH_2-CH=N-NH(Phenyl)

The title compound was prepared by the procedures described in Example 18 substituting N-phenyl hydrazine for methoxylamine hydrochloride. Purification by column chromatography eluting with 1% methanol in methylene chloride containing 1% ammonium hydroxide afforded 50 mg of the title compound as a single pure isomer of unknown stereochemistry. ^{1}MS (FAB) m/e 866 $(M+H)^+$.

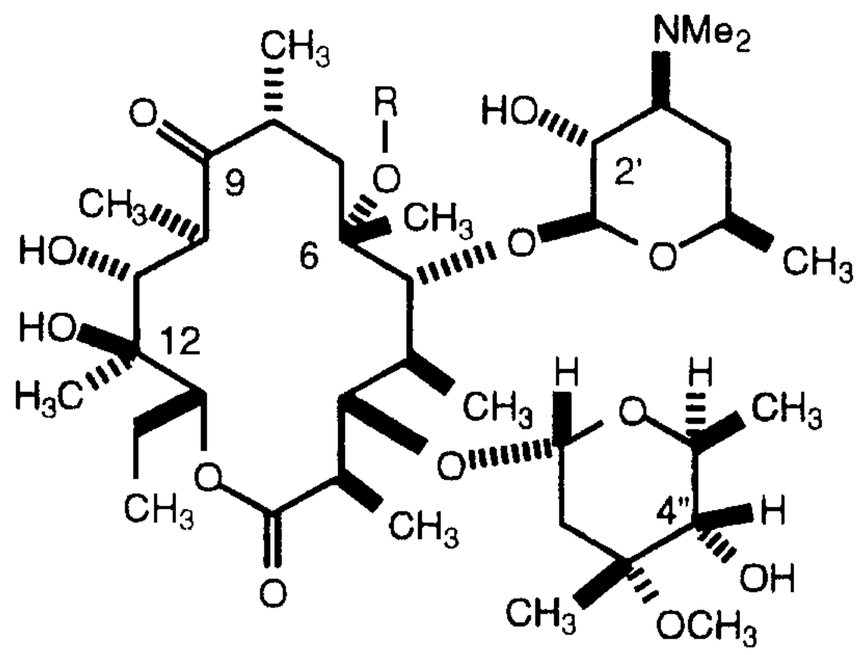
Example 24

Compound of Formula (X): X is =O, R is -CH_2-CH=N-N(Phenyl)$_2$

The title compound was prepared by the procedures described in Example 18 substituting N,N-diphenyl hydrazine for methoxylamine hydrochloride. Purification by column chromatography eluting with 2% methanol in methylene chloride containing 1% ammonium hydroxide afforded 156 mg of the title compound as a single pure isomer of unknown stereochemistry. Diagnostic peaks ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07-7.39 (m, 10H), (m, 6.46 (t, 1H). MS (FAB) m/e 942 $(M+H)^+$.

Examples 25-75

Using the procedures described in the preceding examples and schemes and methods known in the synthetic organic chemistry art, the following compounds can be prepared.



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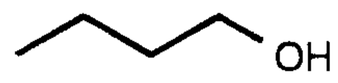
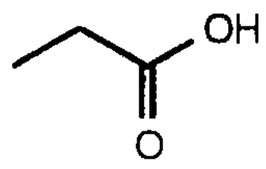
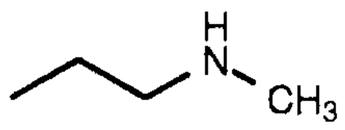
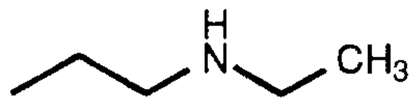
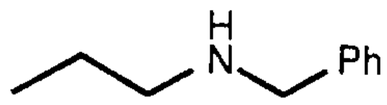
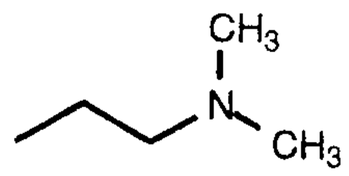
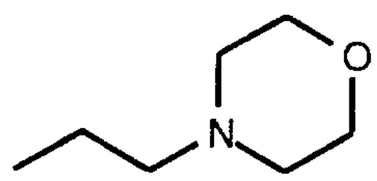
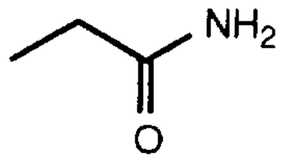
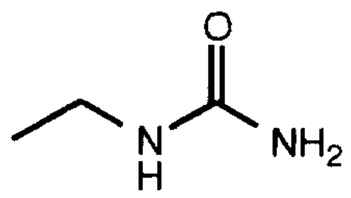
25	
26	
27	
28	

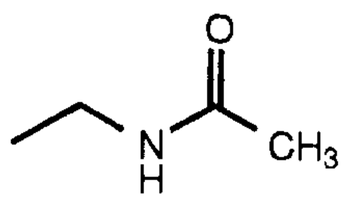
29 

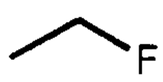
30 

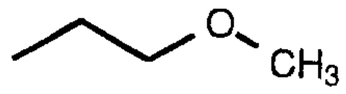
31 

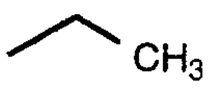
32 

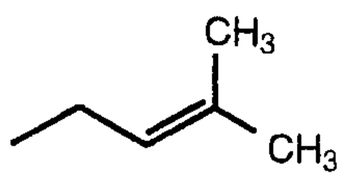
33 

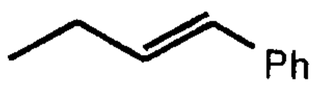
34 

35 

36 

37 

38 

39 

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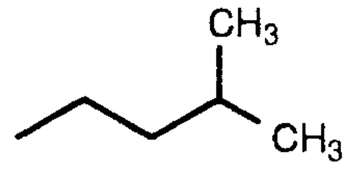
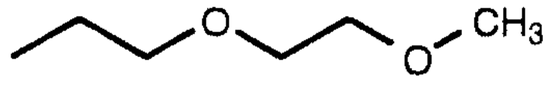
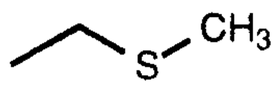
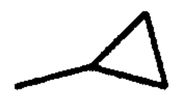
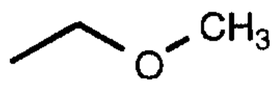
41 

42 

43 

44 

45 

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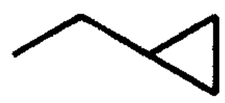
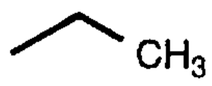
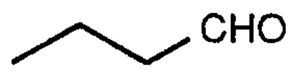
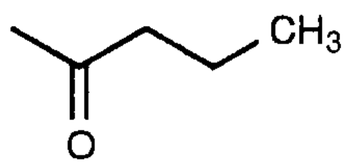
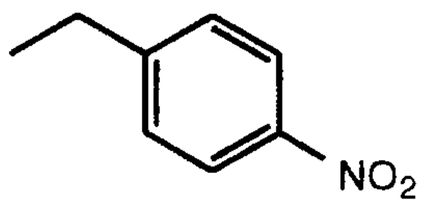
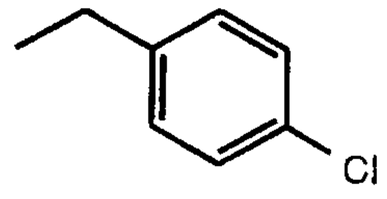
47 

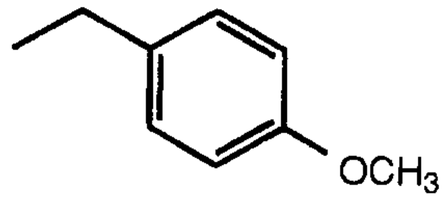
48 

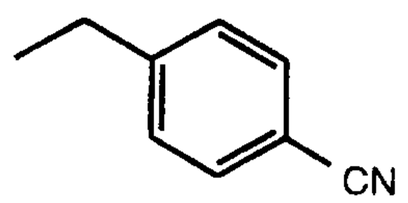
49 

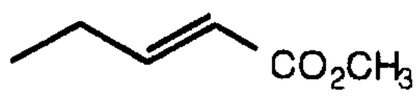
50 

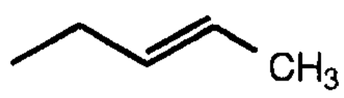
51 

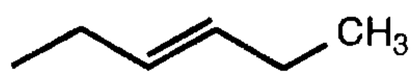
52 

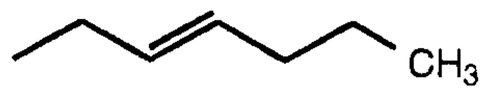
53 

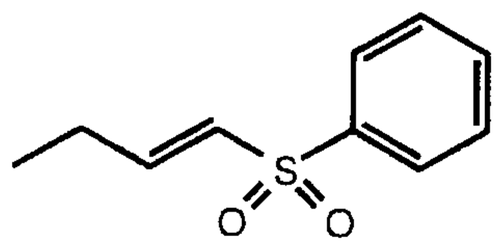
54 

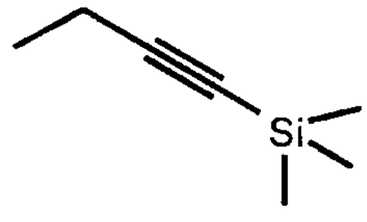
55 

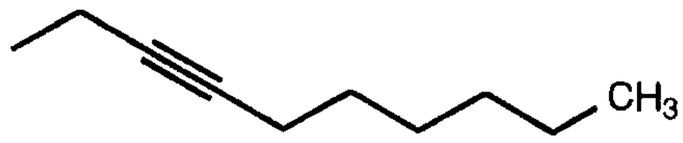
56 

57 

58 

59 

60 

61 

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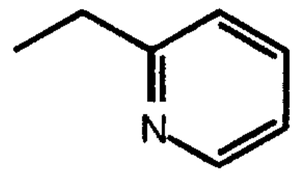
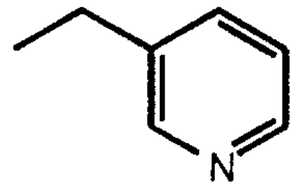
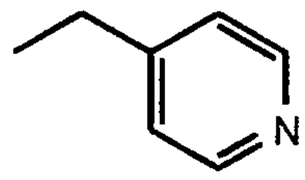
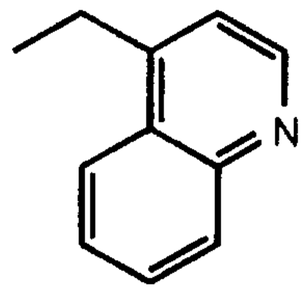
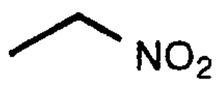
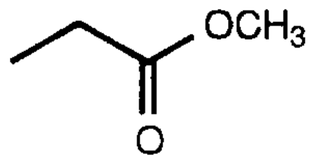
63 

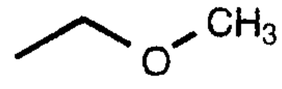
64 

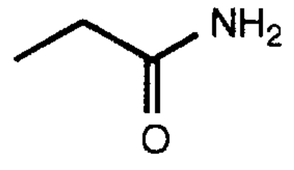
65 

66 

67 

68 

69 

70 

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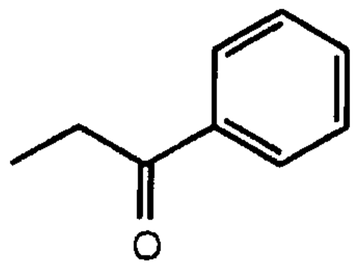

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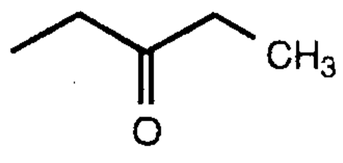

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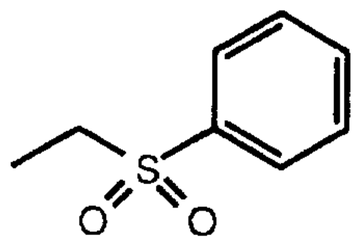

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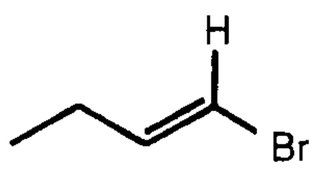
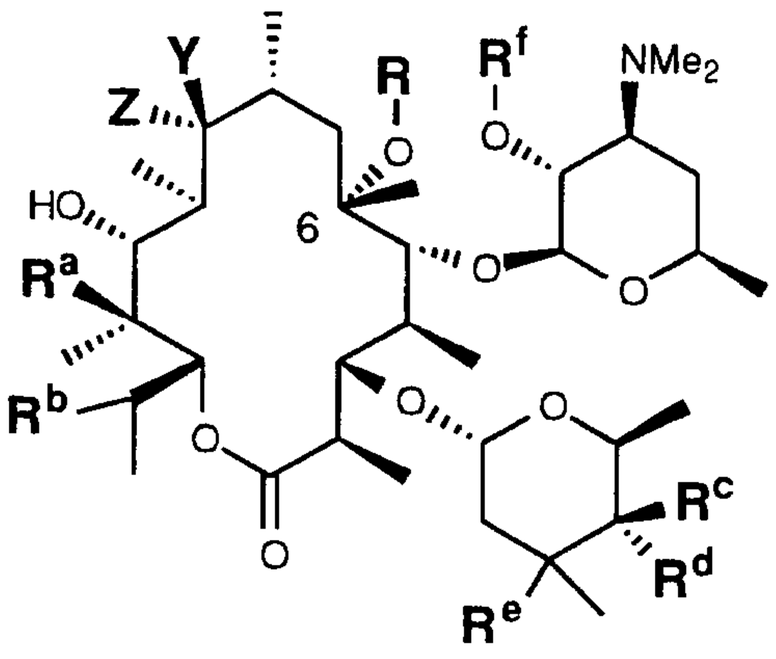


Examples 76-107

Using the procedures described in the preceding examples and schemes and methods known in the synthetic organic chemistry art, the following compounds can be prepared. The macrolide ring systems are selected from the group consisting of:



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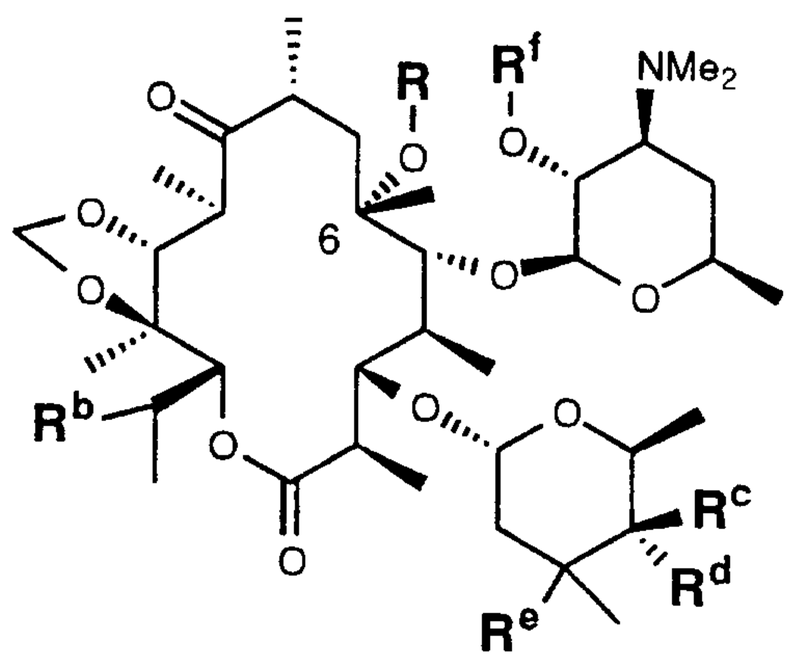

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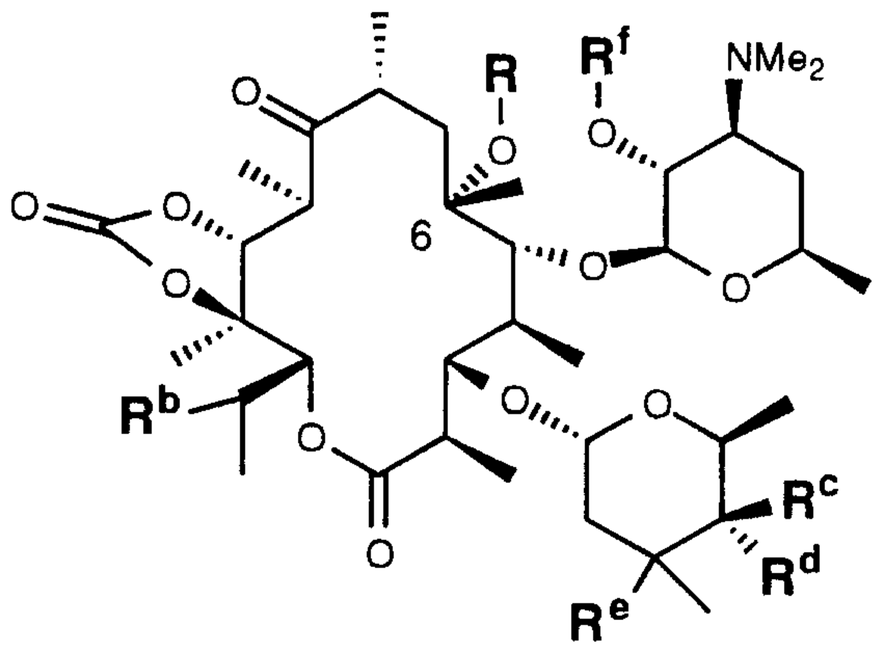

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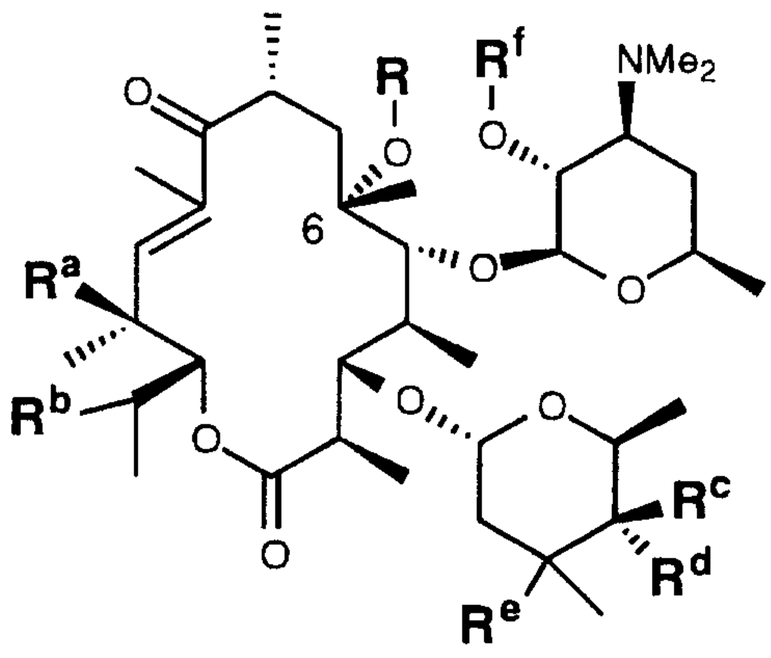

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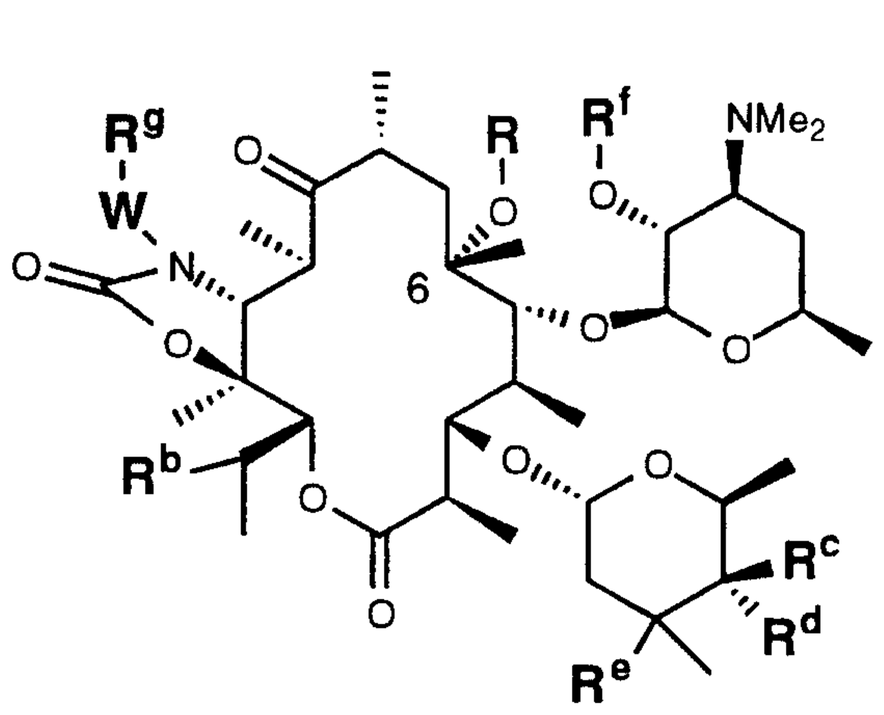

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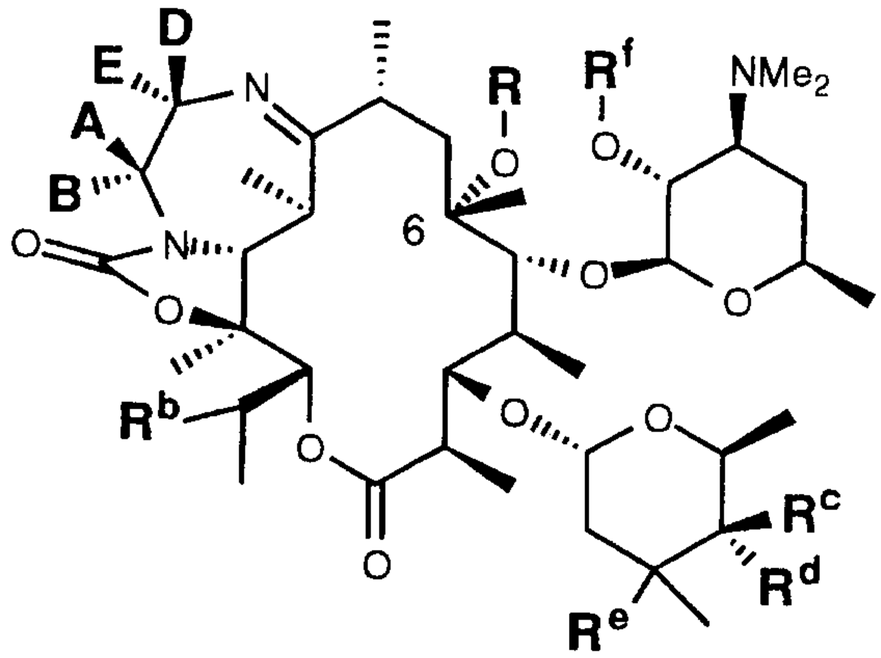
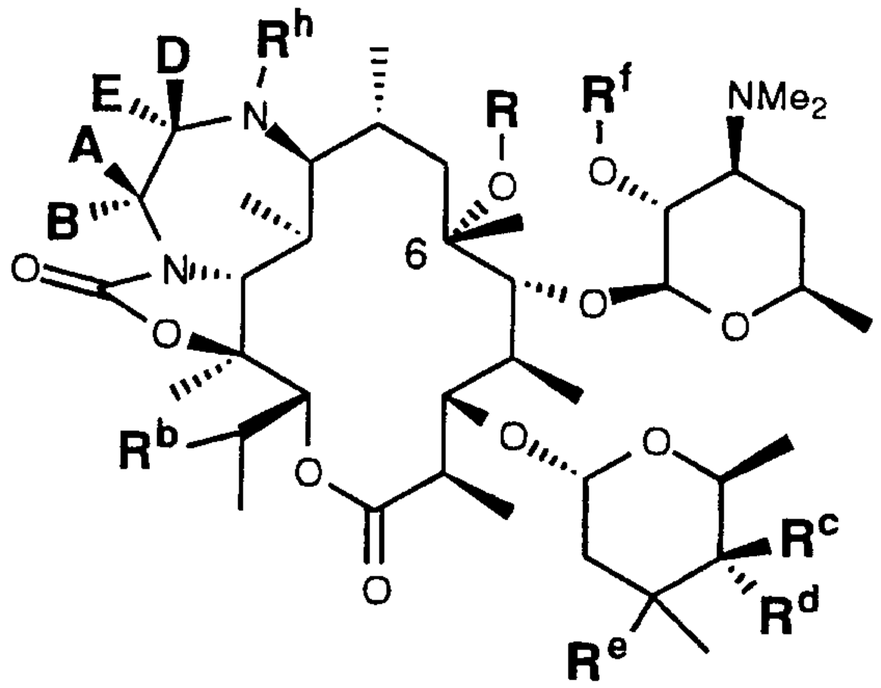
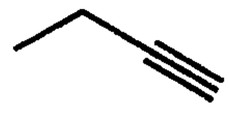
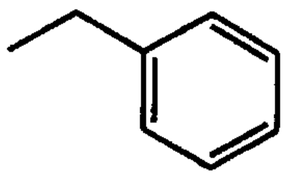


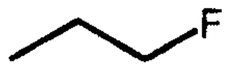
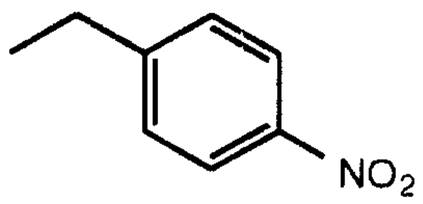
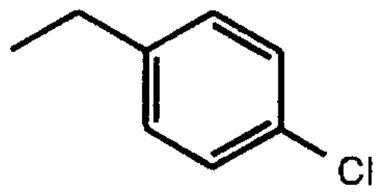
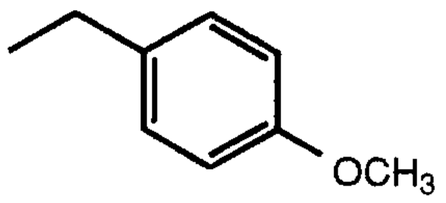
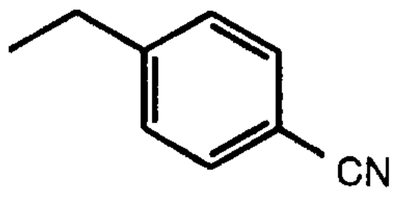
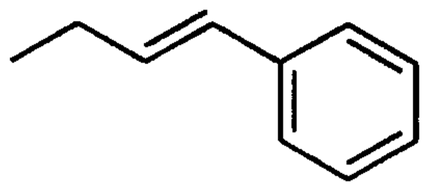
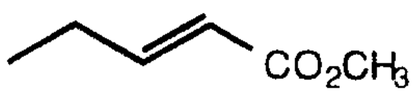
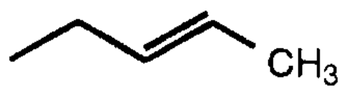
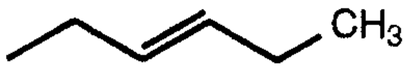
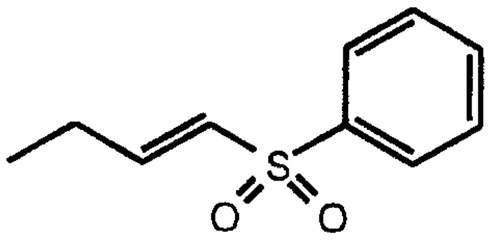
;

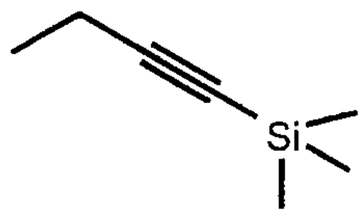
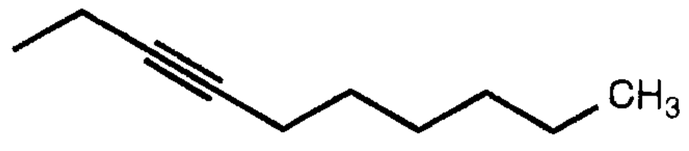
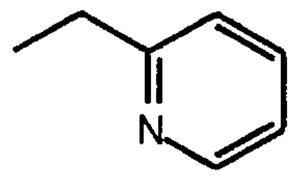
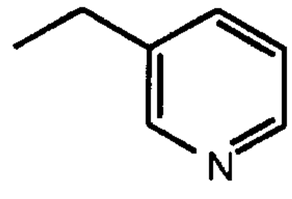
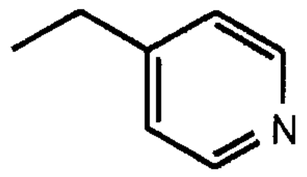
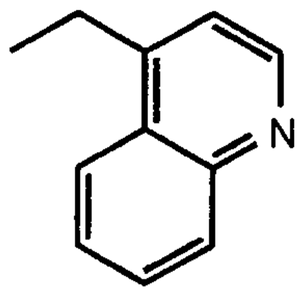
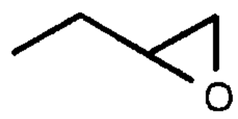
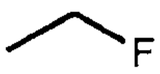
and

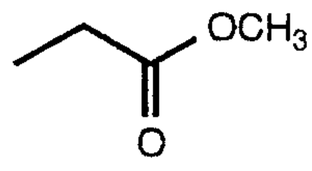
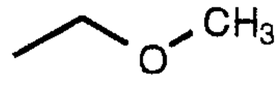
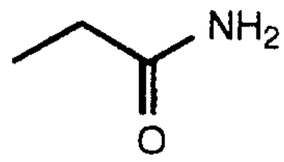
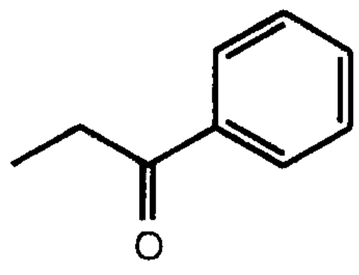
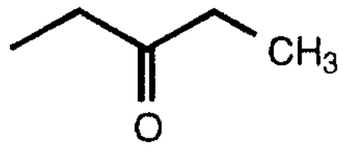
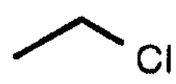
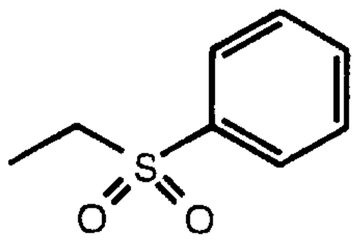
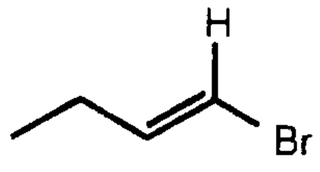


wherein A, B, D, E, W, X, Y, Z, R, R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h are as previously defined.

Ex. No.	Precursor of R	Structure of R
76	Allyl bromide	
77	Propargyl bromide	
78	Benzyl bromide	

79	2-Fluoroethyl bromide	
80	4-Nitrobenzyl bromide	
81	4-Chlorobenzyl bromide	
82	4-Methoxybenzyl bromide	
83	α-Bromo-p-tolunitrile	
84	Cinnamyl bromide	
85	Methyl 4-bromocrotonate	
86	Crotyl bromide	
87	1-Bromo-2-pentene	
88	3-Bromo-1-propenyl phenyl sulfone	

89	3-Bromo-1-trimethylsilyl-1-propyne	
90	3-Bromo-2-octyne	
91	1-Bromo-2-butyne	
92	2-Picolyl chloride	
93	3-Picolyl chloride	
94	4-Picolyl chloride	
95	4-Bromomethyl quinoline	
96	Bromoacetonitrile	
97	Epichlorohydrin	
98	Bromofluoromethane	

99	Bromonitromethane	
100	Methyl bromoacetate	
101	Methoxymethyl chloride	
102	Bromoacetamide	
103	2-Bromoacetophenone	
104	1-Bromo-2-butanone	
105	Bromo chloromethane	
106	Bromomethyl phenyl sulfone	
107	1,3-Dibromo-1-propene	

Example 62

In Vitro Assay of Antibacterial Activity

Representative compounds of the present invention were assayed *in vitro* for antibacterial activity as follows: Twelve petri dishes containing successive aqueous dilutions

of the test compound mixed with 10 mL of sterilized Brain Heart Infusion (BHI) agar (Difco 0418-01-5) were prepared. Each plate was inoculated with 1:100 (or 1:10 for slow-growing strains, such as *Micrococcus* and *Streptococcus*) dilutions of up to 32 different microorganisms, using a Steers replicator block. The inoculated plates were incubated at 35-37 °C for 20 to 24 hours. In addition, a control plate, using BHI agar containing no test compound, was prepared and incubated at the beginning and end of each test.

An additional plate containing a compound having known susceptibility patterns for the organisms being tested and belonging to the same antibiotic class as the test compound was also prepared and incubated as a further control, as well as to provide test-to-test comparability. Erythromycin A was used for this purpose.

After incubation, each plate was visually inspected. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of drug yielding no growth, a slight haze, or sparsely isolated colonies on the inoculum spot as compared to the growth control. The results of this assay, shown below in Table 2 demonstrate the antibacterial activity of the compounds of the invention.

Table 2

Antibacterial Activity (MIC's) of Selected Compounds

Microorganism	Ery. A	Example 1B	Example 1C
Staphylococcus aureus ATCC 6538P	0.2	0.78	0.78
Staphylococcus aureus A5177	3.1	12.5	12.5
Staphylococcus aureus A-5278	>100	>100	>100
Staphylococcus aureus CMX 642A	0.39	1.56	1.56
Staphylococcus aureus NCTC10649M	0.39	3.1	0.78
Staphylococcus aureus CMX 553	0.39	1.56	0.78
Staphylococcus aureus 1775	>100	>100	>100
Staphylococcus epidermidis 3519	0.39	0.39	0.39
Enterococcus faecium ATCC 8043	0.05	0.2	0.2
Streptococcus bovis A-5169	0.02	0.02	0.01
Streptococcus agalactiae CMX 508	0.05	0.1	0.01
Streptococcus pyogenes EES61	-	-	-
Streptococcus pyogenes 930	>100	>100	>100
Streptococcus pyogenes PIU 2548	3.1	6.2	3.1
Micrococcus luteus ATCC 9341	0.05	0.2	0.1
Micrococcus luteus ATCC 4698	0.2	3.1	1.56

Table 2

Antibacterial Activity (MIC's) of Selected Compounds (Continued)

Escherichia coli JUHL	>100	>100	100
Escherichia coli SS	0.78	3.1	0.78
Escherichia coli DC-2	>100	>100	>100
Escherichia coli H560	50	100	100
Escherichia coli KNK 437	100	>100	>100
Enterobacter aerogenes ATCC 13048	>100	>100	>100
Klebsiella pneumoniae ATCC 8045	>100	>100	>100
Providencia struartii CMX 640	>100	>100	>100
Pseudomonas aeruginosa BMH10	>100	>100	>100
Pseudomonas aeruginosa 5007	>100	>100	>100
Pseudomonas aeruginosa K799/WT	100	>100	>100
Pseudomonas aeruginosa K799/61	1.56	6.2	6.2
Pseudomonas capacia 296I	>100	>100	>100
Actinetobacter calcoaceticus CMX 669	12.5	50	50
Pseudomonas aeruginosa DPHD-5263	>100	>100	>100
Pseudomonas aeruginosa DPHD-2862	>100	>100	>100
Candida albicans CCH 442	>100	>100	>100
Mycobacterium smegmatis ATCC 114	3.1	-	0.2

Table 2

Antibacterial Activity (MIC's) of Selected Compounds (Continued)

Microorganism	Ery. A	Example 2	Example 3
Staphylococcus aureus ATCC 6538P	0.2	3.1	1.56
Staphylococcus aureus A5177	3.1	25	50
Staphylococcus aureus A-5278	>100	>100	>100
Staphylococcus aureus CMX 642A	0.39	12.5	1.56
Staphylococcus aureus NCTC10649M	0.39	6.2	1.56
Staphylococcus aureus CMX 553	0.39	3.1	3.1
Staphylococcus aureus 1775	>100	>100	>100
Staphylococcus epidermidis 3519	0.39	1.56	0.78
Enterococcus faecium ATCC 8043	0.05	3.1	0.39
Streptococcus bovis A-5169	0.02	0.05	0.2

Table 2

Antibacterial Activity (MIC's) of Selected Compounds (Continued)

Streptococcus agalactiae CMX 508	0.05	0.2	0.39
Streptococcus pyogenes EES61	-	0.05	0.2
Streptococcus pyogenes 930	>100	>100	>100
Streptococcus pyogenes PIU 2548	3.1	6.2	12.5
Micrococcus luteus ATCC 9341	0.05	0.2	0.1
Micrococcus luteus ATCC 4698	0.2	3.1	1.56
Escherichia coli JUHL	>100	>100	50
Escherichia coli SS	0.78	1.56	1.56
Escherichia coli DC-2	>100	>100	50
Escherichia coli H560	50	>100	25
Escherichia coli KNK 437	100	>100	100
Enterobacter aerogenes ATCC 13048	>100	>100	>100
Klebsiella pneumoniae ATCC 8045	>100	>100	>100
Providencia struartii CMX 640	>100	>100	>100
Pseudomonas aeruginosa BMH10	>100	>100	>100
Pseudomonas aeruginosa 5007	>100	>100	>100
Pseudomonas aeruginosa K799/WT	100	6.2	>100
Pseudomonas aeruginosa K799/61	1.56	>100	1.56
Pseudomonas capacia 296I	>100	50	>100
Actinetobacter calcoaceticus CMX 669	12.5	>100	12.5
Pseudomonas aeruginosa DPHD-5263	>100	>100	>100
Pseudomonas aeruginosa DPHD-2862	>100	>100	>100
Candida albicans CCH 442	>100	0.1	>100
Mycobacterium smegmatis ATCC 114	3.1	-	0.78

Table 2

Antibacterial Activity (MIC's) of Selected Compounds (Continued)

Microorganism		Ery. A	Example 5	Example 6
Staphylococcus aureus	ATCC 6538P	0.2	0.78	0.78
Staphylococcus aureus	A5177	3.1	12.5	25
Staphylococcus aureus	A-5278	>100	>100	>100
Staphylococcus aureus	CMX 642A	0.39	0.78	1.56
Staphylococcus aureus	NCTC10649M	0.39	0.78	0.78

Table 2

Antibacterial Activity (MIC's) of Selected Compounds (Continued)

Staphylococcus aureus CMX 553	0.39	0.78	0.78
Staphylococcus aureus 1775	>100	>100	>100
Staphylococcus epidermidis 3519	0.39	1.56	0.78
Enterococcus faecium ATCC 8043	0.05	0.39	0.39
Streptococcus bovis A-5169	0.02	0.05	-
Streptococcus agalactiae CMX 508	0.05	0.1	0.1
Streptococcus pyogenes EES61	-	0.05	0.05
Streptococcus pyogenes 930	>100	>100	>100
Streptococcus pyogenes PIU 2548	3.1	-	6.2
Micrococcus luteus ATCC 9341	0.05	0.1	0.1
Micrococcus luteus ATCC 4698	0.2	3.1	1.56
Escherichia coli JUHL	>100	25	>100
Escherichia coli SS	0.78	0.78	0.78
Escherichia coli DC-2	>100	50	>100
Escherichia coli H560	50	50	100
Escherichia coli KNK 437	100	50	>100
Enterobacter aerogenes ATCC 13048	>100	100	>100
Klebsiella pneumoniae ATCC 8045	>100	100	>100
Providencia struartii CMX 640	>100	>100	>100
Pseudomonas aeruginosa BMH10	>100	100	>100
Pseudomonas aeruginosa 5007	>100	>100	>100
Pseudomonas aeruginosa K799/WT	100	>100	>100
Pseudomonas aeruginosa K799/61	1.56	1.56	12.5
Pseudomonas capacia 296I	>100	>100	>100
Actinetobacter calcoaceticus CMX 669	12.5	12.5	25
Pseudomonas aeruginosa DPHD-5263	>100	>100	>100
Pseudomonas aeruginosa DPHD-2862	>100	>100	>100
Candida albicans CCH 442	>100	>100	>100
Mycobacterium smegmatis ATCC 114	3.1	1.56	0.2

Table 2

Antibacterial Activity (MIC's) of Selected Compounds (Continued)

Microorganisms	Ery. A	Example 7	Example 8
Staphylococcus aureus ATCC 6538P	0.2	0.39	0.78
Staphylococcus aureus A5177	3.1	3.1	12.5
Staphylococcus aureus A-5278	>100	>100	>100
Staphylococcus aureus CMX 642A	0.39	0.39	0.78
Staphylococcus aureus NCTC10649M	0.39	0.39	0.78
Staphylococcus aureus CMX 553	0.39	0.39	0.78
Staphylococcus aureus 1775	>100	>100	>100
Staphylococcus epidermidis 3519	0.39	0.39	0.78
Enterococcus faecium ATCC 8043	0.05	0.39	0.39
Streptococcus bovis A-5169	0.02	0.01	0.2
Streptococcus agalactiae CMX 508	0.05	0.01	0.39
Streptococcus pyogenes EES61	-	0.01	0.1
Streptococcus pyogenes 930	>100	>100	>100
Streptococcus pyogenes PIU 2548	3.1	-	25
Micrococcus luteus ATCC 9341	0.05	0.02	0.1
Micrococcus luteus ATCC 4698	0.2	0.78	1.56
Escherichia coli JUHL	>100	12.5	100
Escherichia coli SS	0.78	0.2	1.56
Escherichia coli DC-2	>100	6.2	>100
Escherichia coli H560	50	1.56	50
Escherichia coli KNK 437	100	12.5	>100
Enterobacter aerogenes ATCC 13048	>100	50	>100
Klebsiella pneumoniae ATCC 8045	>100	25	>100
Providencia struartii CMX 640	>100	>100	>100
Pseudomonas aeruginosa BMH10	>100	25	>100
Pseudomonas aeruginosa 5007	>100	>100	>100
Pseudomonas aeruginosa K799/WT	100	100	>100
Pseudomonas aeruginosa K799/61	1.56	0.39	3.1
Pseudomonas capacia 296I	>100	>100	>100
Actinetobacter calcoaceticus CMX 669	12.5	12.5	50
Pseudomonas aeruginosa DPHD-5263	>100	>100	>100
Pseudomonas aeruginosa DPHD-2862	>100	>100	>100
Candida albicans CCH 442	>100	>100	>100

Table 2

Antibacterial Activity (MIC's) of Selected Compounds (Continued)

Mycobacterium smegmatis ATCC 114	3.1	0.2	6.2
			0.39

Table 2

Antibacterial Activity (MIC's) of Selected Compounds (Continued)

Microorganism	Ery. A	Example 9	Example 10
Staphylococcus aureus ATCC 6538P	0.2	3.1	0.2
Staphylococcus aureus A5177	3.1	-	6.2
Staphylococcus aureus A-5278	>100	>100	>100
Staphylococcus aureus CMX 642A	0.39	3.1	0.39
Staphylococcus aureus NCTC10649M	0.39	3.1	0.39
Staphylococcus aureus CMX 553	0.39	-	0.39
Staphylococcus aureus 1775	>100	>100	>100
Staphylococcus epidermidis 3519	0.39	3.1	0.2
Enterococcus faecium ATCC 8043	0.05	3.1	0.1
Streptococcus bovis A-5169	0.02	3.1	0.01
Streptococcus agalactiae CMX 508	0.05	3.1	0.05
Streptococcus pyogenes EES61	-	-	0.01
Streptococcus pyogenes 930	>100	>100	>100
Streptococcus pyogenes PIU 2548	3.1	12.5	-
Micrococcus luteus ATCC 9341	0.05	3.1	0.05
Micrococcus luteus ATCC 4698	0.2	-	0.78
Escherichia coli JUHL	>100	>100	50
Escherichia coli SS	0.78	-	0.78
Escherichia coli DC-2	>100	-	100
Escherichia coli H560	50	>100	25
Escherichia coli KNK 437	100	>100	>100
Enterobacter aerogenes ATCC 13048	>100	>100	>100
Klebsiella pneumoniae ATCC 8045	>100	>100	>100
Providencia struartii CMX 640	>100	>100	>100
Pseudomonas aeruginosa BMH10	>100	>100	100
Pseudomonas aeruginosa 5007	>100	>100	>100
Pseudomonas aeruginosa K799/WT	100	>100	>100

Pseudomonas aeruginosa K799/61	1.56	12.5	3.1
Pseudomonas capacia 296I	>100	>100	>100
Actinetobacter calcoaceticus CMX 669	12.5	50	12.5
Pseudomonas aeruginosa DPHD-5263	>100	>100	>100
Pseudomonas aeruginosa DPHD-2862	>100	>100	>100
Candida albicans CCH 442	>100	>100	>100
Mycobacterium smegmatis ATCC 114	3.1	3.1	0.39
Nocarrdia asteroides ATCC 9970			

Table 2

Antibacterial Activity (MIC's) of Selected Compounds (Continued)

Microorganism	Ery. A	Example 11	Example 12
Staphylococcus aureus ATCC 6538P	0.2	0.78	0.39
Staphylococcus aureus A5177	3.1	6.2	-
Staphylococcus aureus A-5278	>100	>100	>100
Staphylococcus aureus CMX 642A	0.39	1.56	0.39
Staphylococcus aureus NCTC10649M	0.39	0.78	0.39
Staphylococcus aureus CMX 553	0.39	0.78	0.39
Staphylococcus aureus 1775	>100	>100	>100
Staphylococcus epidermidis 3519	0.39	0.78	0.39
Enterococcus faecium ATCC 8043	0.05	0.39	0.1
Streptococcus bovis A-5169	0.02	0.2	0.05
Streptococcus agalactiae CMX 508	0.05	0.05	0.05
Streptococcus pyogenes EES61	-	0.05	0.05
Streptococcus pyogenes 930	>100	>100	>100
Streptococcus pyogenes PIU 2548	3.1	25	12.5
Micrococcus luteus ATCC 9341	0.05	0.05	0.05
Micrococcus luteus ATCC 4698	0.2	-	0.78
Escherichia coli JUHL	>100	100	50
Escherichia coli SS	0.78	1.56	0.78
Escherichia coli DC-2	>100	>100	>100
Escherichia coli H560	50	50	25
Escherichia coli KNK 437	100	>100	100
Enterobacter aerogenes ATCC 13048	>100	>100	>100
Klebsiella pneumoniae ATCC 8045	>100	>100	-

Table 2

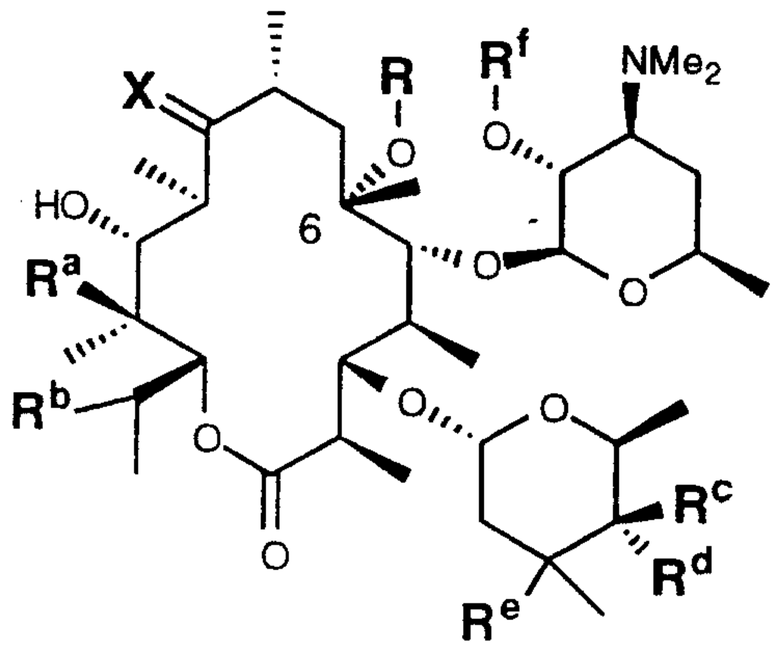
Antibacterial Activity (MIC's) of Selected Compounds (Continued)

Providencia struartii CMX 640	>100	>100	>100
Pseudomonas aeruginosa BMH10	>100	>100	>100
Pseudomonas aeruginosa 5007	>100	>100	>100
Pseudomonas aeruginosa K799/WT	100	>100	>100
Pseudomonas aeruginosa K799/61	1.56	-	1.56
Pseudomonas capacia 296I	>100	>100	>100
Actinetobacter calcoaceticus CMX 669	12.5	25	12.5
Pseudomonas aeruginosa DPHD-5263	>100	>100	>100
Pseudomonas aeruginosa DPHD-2862	>100	>100	>100
Candida albicans CCH 442	>100	>100	>100
Mycobacterium smegmatis ATCC 114	3.1	0.39	0.78
Nocarrdia asteroides ATCC 9970		0.1	

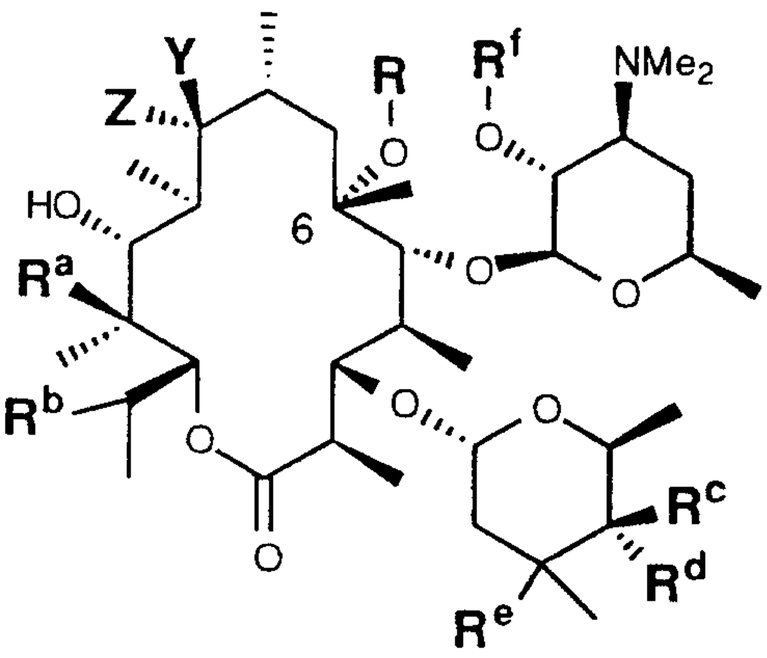
It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art, and may be made without departing from the spirit and scope thereof.

WHAT IS CLAIMED IS:

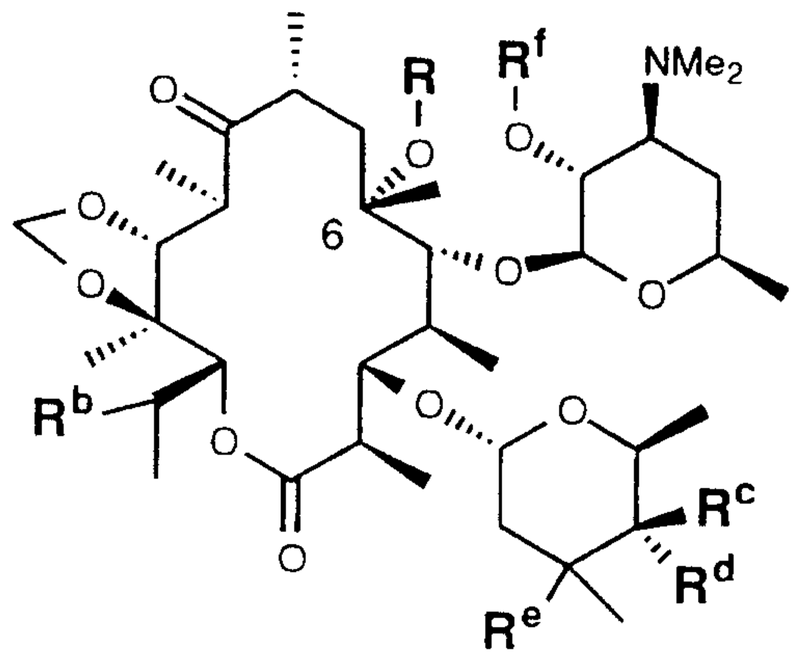
1. A compound having the formula:



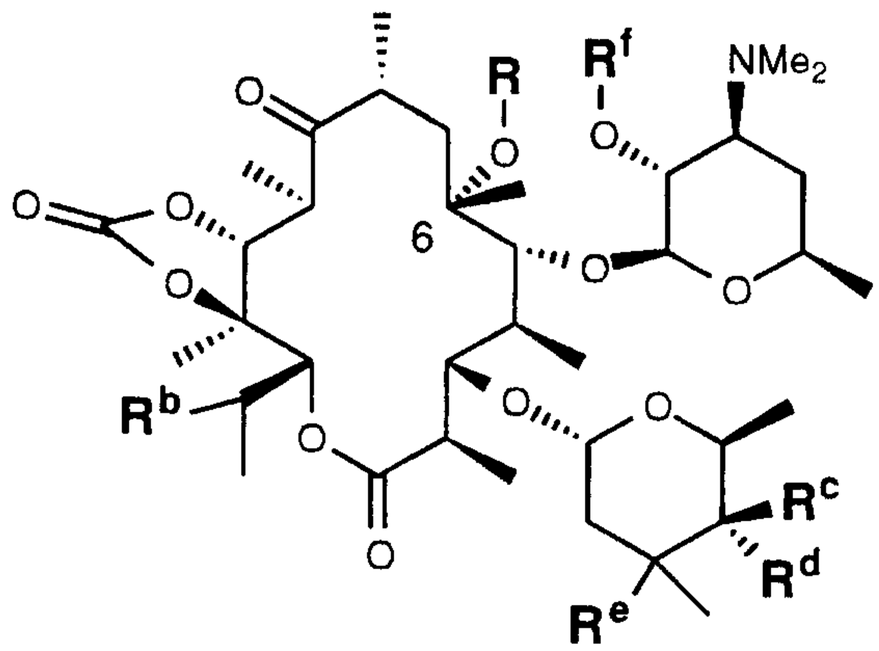
(II);



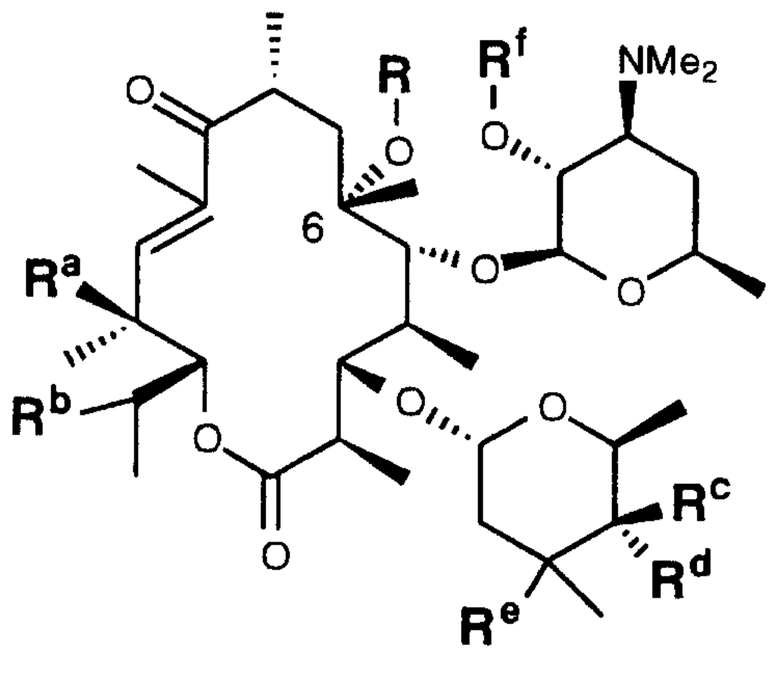
(III);



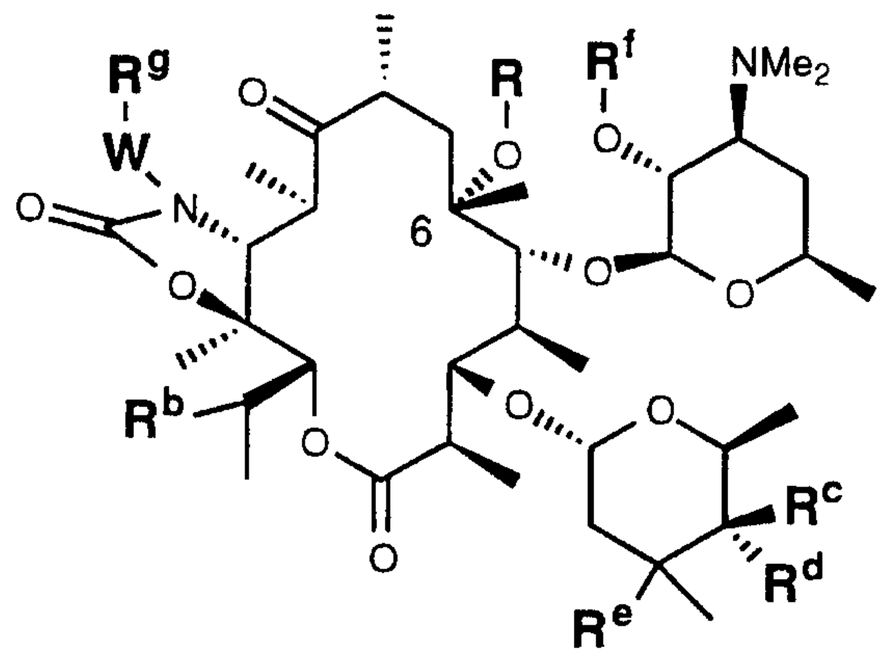
(IV);



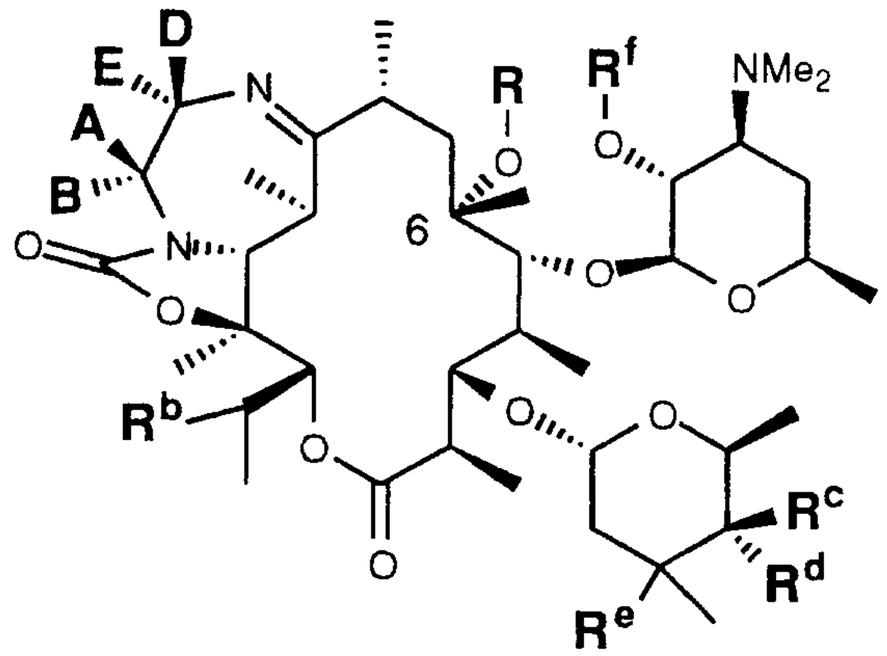
(V);



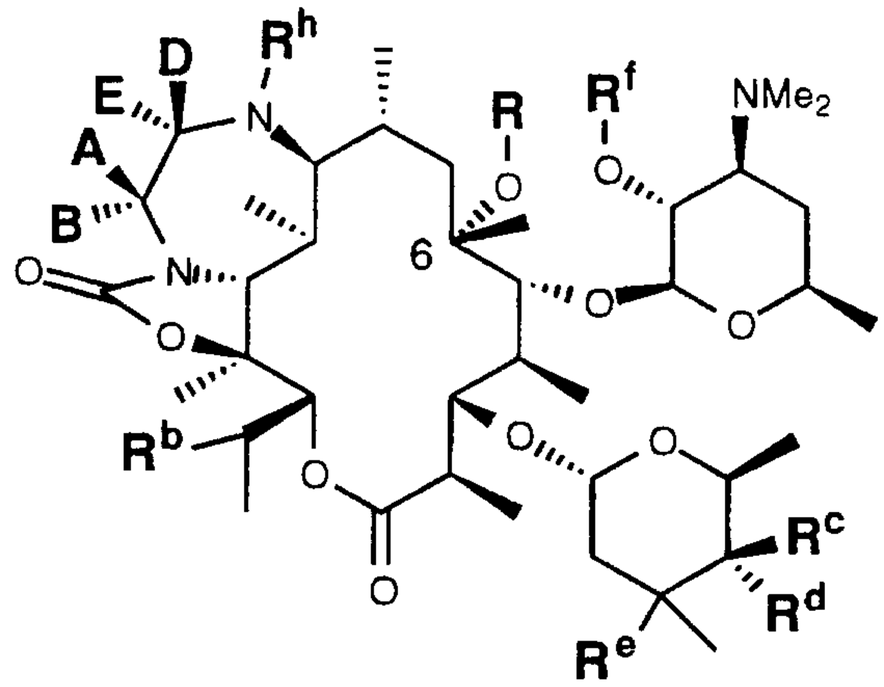
(VI);



(VII);



(VIII); or



(IX);

as well as the pharmaceutically acceptable salts, esters and prodrugs thereof:

wherein X is:

(1) =O,

(2) =N-OH,

(3) =N-O-R^1 where R^1 is

(a) unsubstituted C_1-C_{12}-alkyl,

(b) C_1-C_{12}-alkyl substituted with aryl,

(c) C_1-C_{12}-alkyl substituted with substituted aryl,

(d) C_3-C_{12}-cycloalkyl,

(e) -Si-(R^{11})(R^{12})(R^{13}) wherein R^{11}, R^{12} and R^{13} are each independently selected from C_1-C_{12}-alkyl,

(f) -Si-(Aryl)$_3$, or

(4) =N-O-C(R^9)(R^{10})-O-R^1 where R^1 is as defined above and R^9 and R^{10} are each independently selected from the group consisting of:

(a) hydrogen,

(b) unsubstituted C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl, and

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

or R^9 and R^{10} taken together with the carbon to which they are attached form a C_3-C_{12}-cycloalkyl ring;

R^a is hydrogen or hydroxy;

R^b is hydrogen or hydroxy;

one of R^c and R^d is hydrogen and the other of R^c and R^d is:

(1) hydroxy,

(2) protected hydroxy,

(3) halogen, or

(4) NR^3R^4 where R^3 and R^4 are independently selected from

(a) hydrogen,

(b) C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl,

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

(e) C_1-C_{12}-alkyl substituted with heteroaryl, and

(d) C_1-C_{12}-alkyl substituted with substituted heteroaryl, or

(5) -SO_2-(substituted C_1-C_6-alkyl, or

R^3 and R^4 taken together with the carbon to which they are attached form a 3-7 membered hetereocyclicalkyl ring,

or

R^c and R^d taken together is:

(1) =O,

(2) =N-OH, or

(3) =N-OR^1 wherein R^1 is as defined above;

R^e is methoxy, fluorine or hydroxy;

R^f is hydrogen or an hydroxy protecting group;

R^g is selected from a group consisting of:

(1) unsubstituted C_1-C_6-alkyl,

(2) C_1-C_6-alkyl substituted with one or more substituents selected from the group consisting of:

(a) aryl,

(b) substituted aryl,

(c) heteroaryl,

(d) substituted heteroaryl,

(e) heteroarylalkyl,

(f) hydroxy,

(g) C_1-C_6-alkoxy,

(h) NR^3R^4 wherein R^3 and R^4 are as defined above, and

(i) $-CH_2-M-R^5$ where M is selected from a group consisting of:

(i) -O-,

(ii) -NH-,

(iii) -NMe-,

(iv) $-S(O)_n-$ where n is 0, 1 or 2,

(v) -NHC(=O)-, and

(vi) -C(=O)-NH-,

and

R^5 is selected from a group consisting of:

(i) $-(CH_2)_n$-aryl where n is 0, 1 or 2,

(ii) $-(CH_2)_n$-substituted aryl where n is 0, 1 or 2,

(iii) $-(CH_2)_n$-heteroaryl where n=0, 1 or 2,

(iv) $-(CH_2)_n$-substituted heteroaryl where n is 0, 1 or 2, and

(v) $-(CH_2)_n$-heteroarylalkyl where n is 0, 1 or 2,

(3) C_3-C_{12}-cycloalkyl,

(4) aryl,

(5) substituted aryl,

(6) heteroaryl, and

(7) substituted heteroaryl;

R^h is selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl,

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

(e) C_1-C_{12}-alkyl substituted with heteroaryl, and

(d) C_1-C_{12}-alkyl substituted with substituted heteroaryl;

R is selected from the group consisting of:

(1) C_1-alkyl substituted with a substituent selected from the group consisting of:

(a) F,

(b) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(c) $NHC(O)R^6$ where R^6 is as defined above, and

(d) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are independently selected from hydrogen and C_1-C_3-alkyl,

(2) C_2-C_{10}-alkyl;

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N-O-R^6$ where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N-NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N-NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(4) C_2-C_{10}-alkenyl;

(5) C_2-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N-O-R^6$ where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N-NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N-NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(6) C_2-C_{10}-alkynyl; and

(7) C_2-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of:

(a) trialkylsilyl,

(b) aryl,

(c) substituted aryl,

(d) heteroaryl, and

(e) substituted heteroaryl;

one of Y and Z is hydrogen and the other is selected from a group consisting of:

(1) hydrogen,

(2) hydroxy,

(3) protected hydroxy, and

(4) NR^3R^4 wherein R^3 and R^4 are as previously defined;

W is:

(1) -O-,

(2) -NH-,

(3) -NMe-, or

(4) absent;

A, B, D and E are, at each occurrence, independently selected from the group consisting of:

(1) hydrogen,

(2) unsubstituted C_1-C_6-alkyl, and

(3) C_1-C_6-alkyl substituted with one or more substituents selected from the group consisting of:

(a) aryl,

(b) substituted aryl,

(c) heteroaryl,

(d) substituted heteroaryl,

(e) heteroarylalkyl,

(f) hydroxy,

(g) C_1-C_6-alkoxy,

(h) NR^3R^4, where R^3 and R^4 are as defined above, and

(i) $-CH_2-M-R^5$ where M is selected from a group consisting of:

(i) -O-,

(ii) -NH-,

(iii) -NMe-,

(iv) $-S(O)_n-$ where n is 0, 1 or 2,

(v) -NHC(=O)-, and

(vi) -C(=O)-NH-,

and

R^5 is selected from a group consisting of:

(i) $-(CH_2)_n$-aryl where n is 0, 1 or 2,

(ii) $-(CH_2)_n$-substituted aryl where n is 0, 1 or 2,

(iii) $-(CH_2)_n$-heteroaryl where n=0, 1 or 2,

(iv) $-(CH_2)_n$-substituted heteroaryl where n is 0, 1 or 2, and

(v) $-(CH_2)_n$-heteroarylalkyl where n is 0, 1 or 2,

or any pair of substituents, consisting of AB, AD, AE, BD, BE or DE, is taken together with the atom or atoms to which they are attached to form a 3- to 7-membered ring optionally containing a hetero function selected from:

(1) -O-,

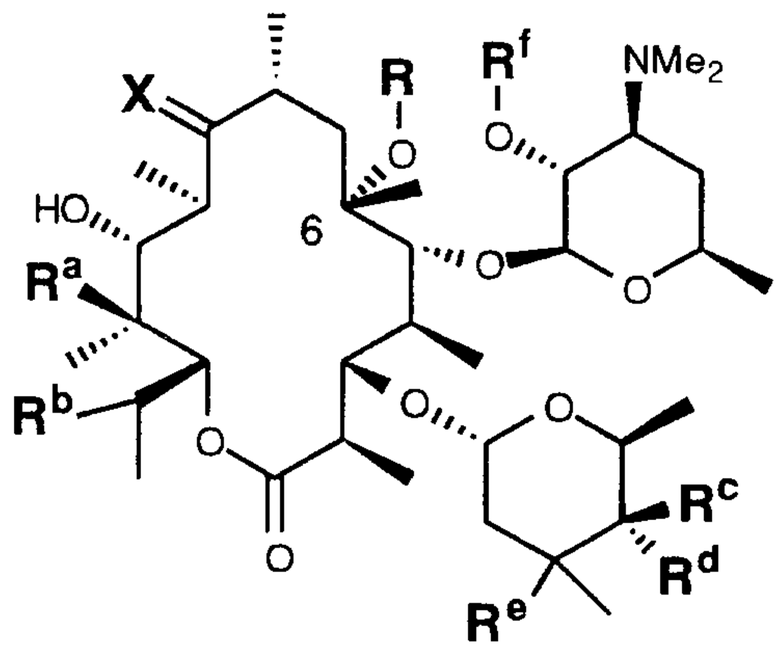
(2) $-S(O)_n-$, where n is 0, 1 or 2,

(3) -NH-,

(4) $-N(CH_3)-$, and

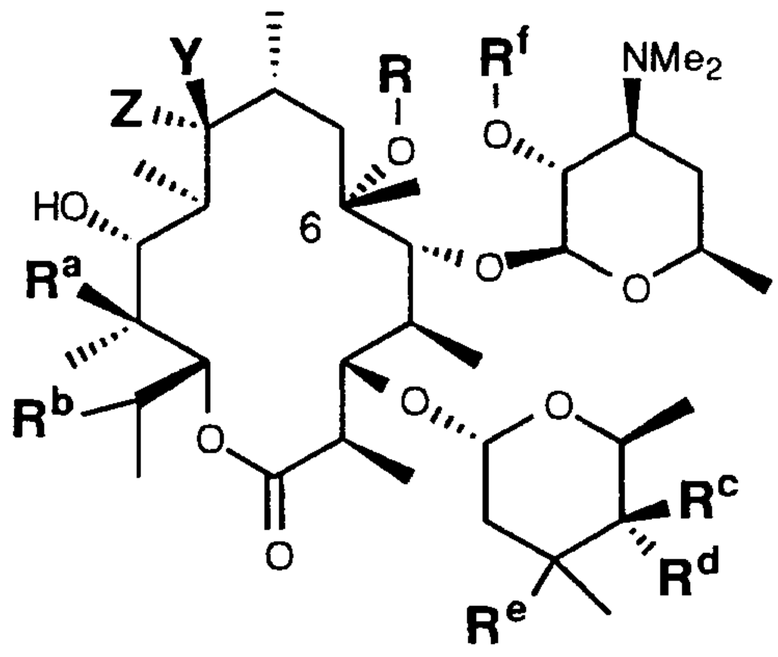
(5) $-N(R^5)-$ wherein R^5 is as previously defined.

2. A compound according to Claim 1 having the formula:



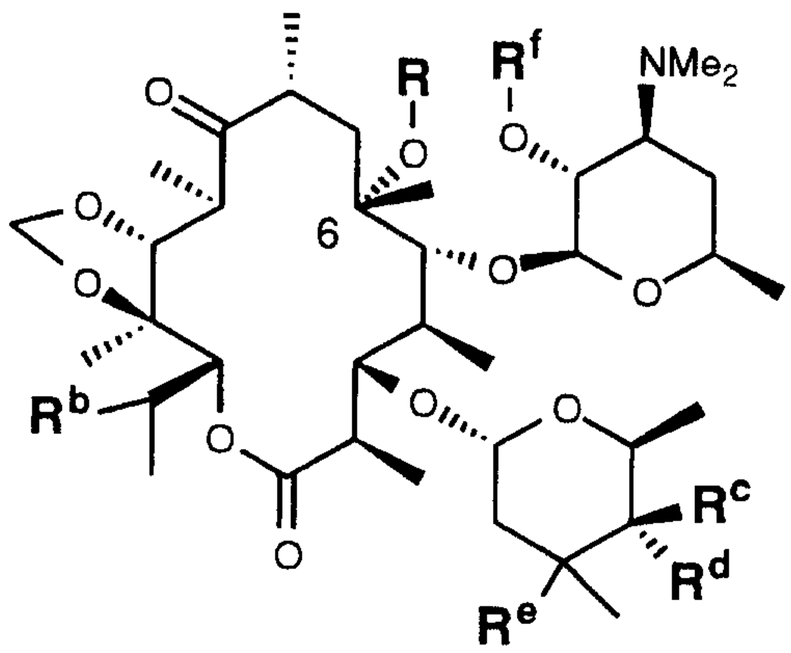
wherein X, R, R^a, R^b, R^c, R^d, R^e and R^f are as defined therein.

3. A compound according to Claim 1 having the formula:



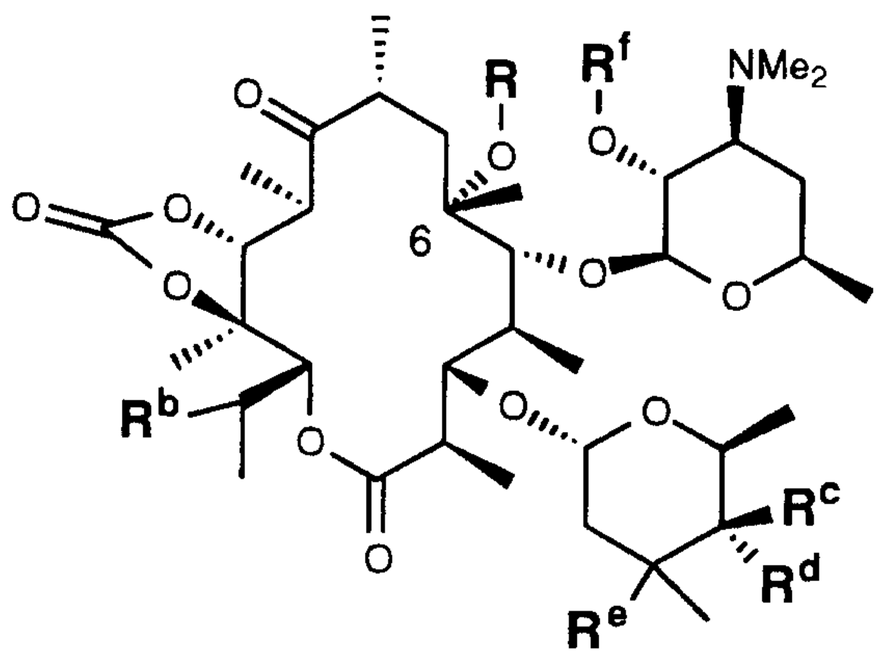
wherein Y, Z, R, R^a, R^b, R^c, R^d, R^e and R^f are as defined therein.

4. A compound according to Claim 1 having the formula:



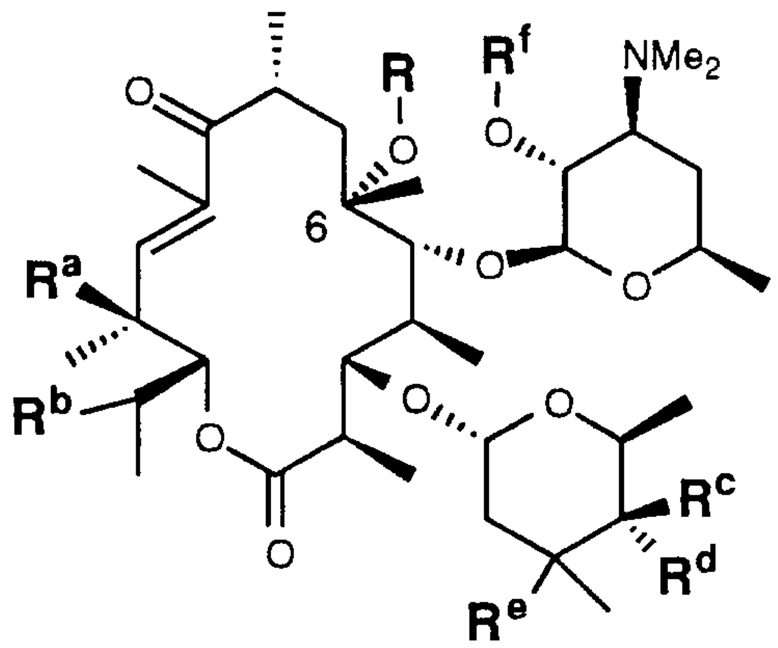
wherein R, R^b, R^c, R^d, R^e and R^f are as defined therein.

5. A compound according to Claim 1 having the formula:



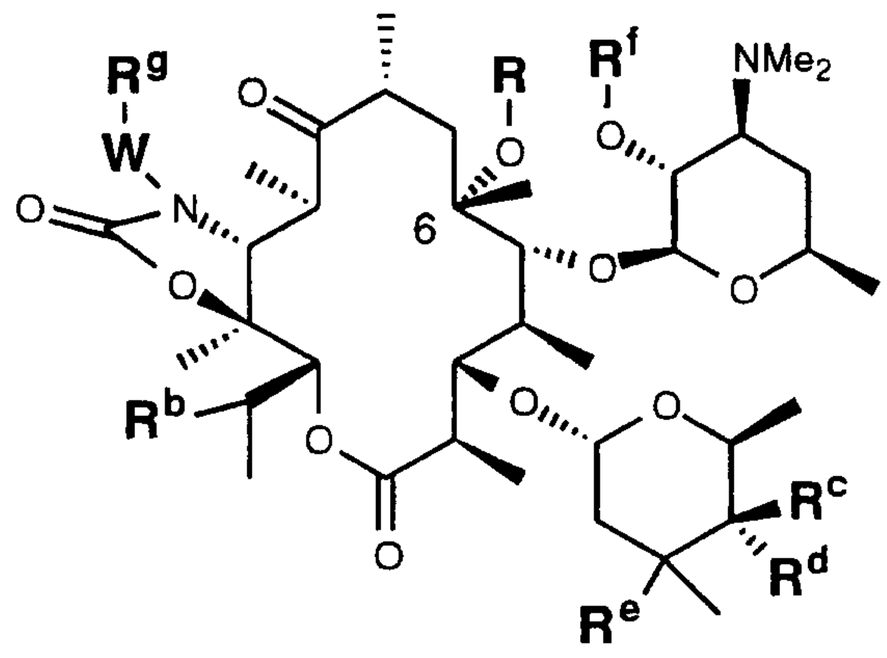
wherein R, R^b, R^c, R^d, R^e and R^f are as defined therein.

6. A compound according to Claim 1 having the formula:



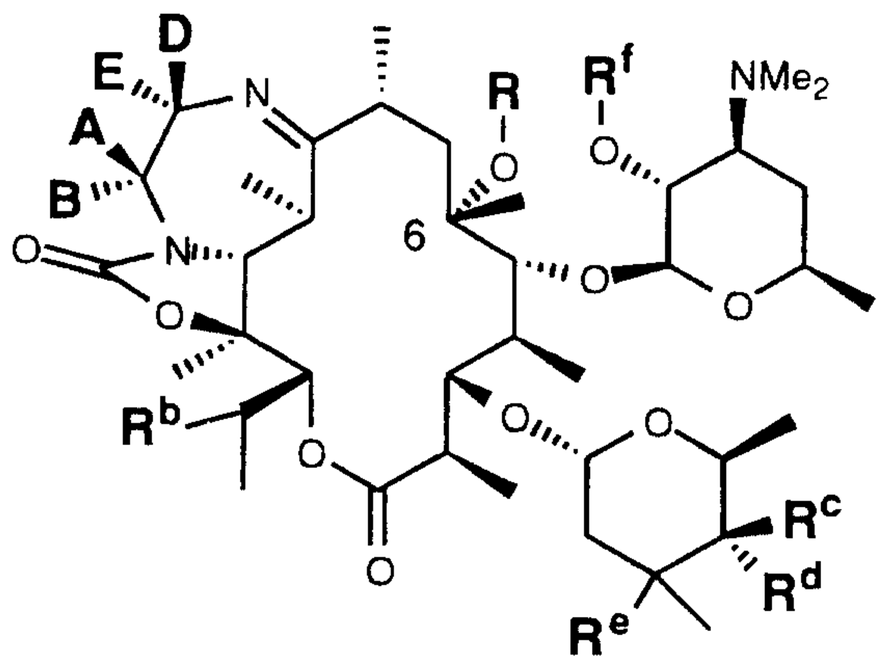
wherein R, R^a, R^b, R^c, R^d, R^e and R^f are as defined therein.

7. A compound according to Claim 1 having the formula:



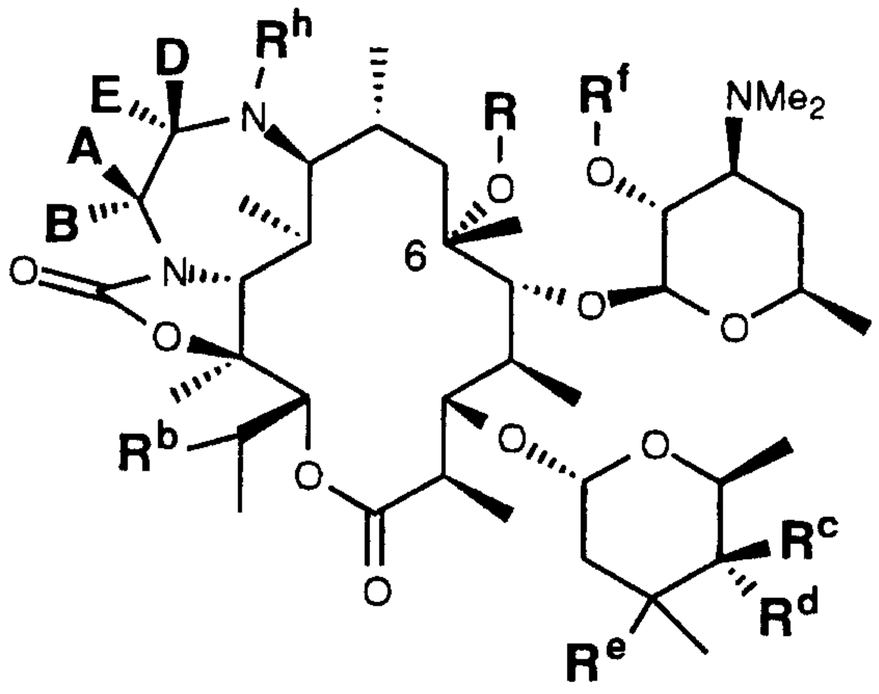
wherein W, R, R^b, R^c, R^d, R^e, R^f and R^g are as defined therein.

8. A compound according to Claim 1 having the formula:



wherein A, B, D, E, R, R^b, R^c, R^d, R^e and R^f are as defined therein.

9. A compound according to Claim 1 having the formula:



wherein A, B, D, E, R, R^b, R^c, R^d, R^e, R^f and R^h are as defined therein.

10. A compound according to Claim 2 wherein R^a is hydroxy, R^b is hydrogen, R^c is hydrogen, R^d is hydroxy, R^e is methoxy, and R^f is hydrogen.

11. A compound according to Claim 3 wherein R^a is hydroxy, R^b is hydrogen, R^c is hydrogen, R^d is hydroxy, R^e is methoxy, and R^f is hydrogen.

12. A compound according to Claim 1 which is selected from the group consisting of:

Compound of Formula (X): X is =N-O-(1-isopropoxycyclohexyl), R is allyl;

Compound of Formula (X): X is =O, R is allyl;
Compound of Formula (X): X is =O, R is propyl;
Compound of Formula (X): X is =O, R is 2,3-dihydroxypropyl;
Compound of Formula (X): X is =O, R is 2,3-epoxypropyl;
Compound of Formula (X): X is =O, R is 2-hydroxy-3-(imidazol-1-yl)propyl;
Compound of Formula (X): X is =O, R is 2-hydroxy-3-(morpholin-4-yl)propyl;
Compound of Formula (X): X is =O, R is 2-hydroxy-3-(benzylamino)propyl;
Compound of Formula (X): X is =O, R is 2-oxoethyl;
Compound of Formula (X): X is =O, R is 2-oxopropyl;
Compound of Formula (X): X is =O, R is $-CH_2-C\equiv CH$;
Compound of Formula (X): X is =O, R is $-CH_2-CHOH-CH_2-N_3$;
Compound of Formula (X): X is =O, R is $-CH_2-CH=N-OH$;
Compound of Formula (X): X is =O, R is $-CH_2-CH_2OH$;
Compound of Formula (X): X is =O, R is $-CH_2-CH_2NH_2$;
Compound of Formula (X): X is =O, R is $-CH_2-CN$;
Compound of Formula (X): X is =O, R is $-CH_2$-Phenyl;
Compound of Formula (X): X is =O, R is $-CH_2-CH=CH$(Phenyl);
Compound of Formula (X): X is =O, R is $-CH_2-CH=N-O-CH_3$;
Compound of Formula (X): X is =O, R is $-CH_2-CH=N-O-CH_2$-Phenyl;
Compound of Formula (X): X is =O, R is $-CH_2-CH=N-N(CH_3)_2$;
Compound of Formula (X): X is =O, R is $-CH_2-CH=N-NH(CH_3)$;
Compound of Formula (X): X is =O, R is $-CH_2-CH=N-$(4-Morpholinyl);
Compound of Formula (X): X is =O, R is $-CH_2-CH=N-NH$(Phenyl);
Compound of Formula (X): X is =O, R is $-CH_2-CH=N-N(\text{Phenyl})_2$;
Compound of Formula (X): X is =O, R is $-CH_2CH_2CH_2OH$;
Compound of Formula (X): X is =O, R is $-CH_2-CO_2H$;
Compound of Formula (X): X is =O, R is $-CH_2CH_2NH(CH_3)$;
Compound of Formula (X): X is =O, R is $-CH_2CH_2NHCH_2CH_3$;
Compound of Formula (X): X is =O, R is $-CH_2CH_2NHCH_2CH_2$-Phenyl;
Compound of Formula (X): X is =O, R is $-CH_2CH_2N(CH_3)_2$;
Compound of Formula (X): X is =O, R is $-CH_2CH_2-$(4-morpholinyl);
Compound of Formula (X): X is =O, R is $-CH_2C(O)NH_2$;
Compound of Formula (X): X is =O, R is $-CH_2NHC(O)NH_2$;
Compound of Formula (X): X is =O, R is $-CH_2NHC(O)CH_3$;
Compound of Formula (X): X is =O, R is $-CH_2F$;
Compound of Formula (X): X is =O, R is $-CH_2CH_2OCH_3$;
Compound of Formula (X): X is =O, R is $-CH_2CH_3$;

Compound of Formula (X): X is =O, R is -$CH_2CH=C(CH_3)_{23}$;

Compound of Formula (X): X is =O, R is -$CH_2CH=CHPh$;

Compound of Formula (X): X is =O, R is -$(CH_2)_3$-Ph;

Compound of Formula (X): X is =O, R is -$(CH_2)_2$-$CH(CH_3)_2$;

Compound of Formula (X): X is =O, R is -$(CH_2)_2$-O-$(CH_2)_2$-O-CH_3;

Compound of Formula (X): X is =O, R is -CH_2-Ph;

Compound of Formula (X): X is =N-OH, R is -CH_2-C≡CH;

Compound of Formula (X): X is =N-O-CH_3, R is -CH_2-C≡CH;

Compound of Formula (X): X is =N-O-Benzyl, R is -CH_2-C≡CH;

Compound of Formula (X): X is =N-O-CH_2-O-CH_3, R is -CH_2-C≡CH;

Compound of Formula (X): X is =N-O-CH_2-O-CH_2-CH_2-O-CH_3, R is -CH_2-C≡CH;

Compound of Formula (X): X is =N-OH, R is -CH_2-$CH=CH_2$;

Compound of Formula (X): X is =N-O-CH_3, R is -CH_2-$CH=CH_2$;

Compound of Formula (X): X is =N-O-Benzyl, R is -CH_2-$CH=CH_2$;

Compound of Formula (X): X is =N-O-CH_2-O-CH_3, -CH_2-$CH=CH_2$;

Compound of Formula (X): X is =N-O-CH_2-O-CH_2-CH_2-O-CH_3, R is -CH_2-$CH=CH_2$;

Compound of Formula (XI): Y is NH_2, Z is H, R is -CH_2-C≡CH;

Compound of Formula (XI): Y is NH-$CH_2CH_2CH_3$, Z is H, R is -CH_2-C≡CH;

Compound of Formula (XI): Y is NH-$(CH_2)_9$-CH_3, Z is H, R is -CH_2-C≡CH;

Compound of Formula (XI): Y is NH-$CH(CH_3)_2$, Z is H, R is -CH_2-C≡CH;

Compound of Formula (XI): Y is 1-piperidinyl, Z is H, R is -CH_2-C≡CH;

Compound of Formula (XI): Y is H, Z is 1-piperidinyl, R is -CH_2-C≡CH;

Compound of Formula (XI): Y is H, Z is NH_2, R is -CH_2-C≡CH;

Compound of Formula (XI): Y is H, Z is NH-$CH_2CH_2CH_3$, R is -CH_2-C≡CH;

Compound of Formula (XI): Y is H, Z is NH-$(CH_2)_9$-CH_3, R is -CH_2-C≡CH;

Compound of Formula (XI): Y is H, Z is NH-$CH(CH_3)_2$, R is -CH_2-C≡CH;

Compound of Formula (XI): Y is OH, Z is H, R is -CH_2-C≡CH;

Compound of Formula (XI): Y is H, Z is OH, R is -CH_2-C≡CH;

Compound of Formula (IV): R is -$CH_2CH=CH_2$, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (IV): R is -CH_2-C≡CH, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (IV): R is -CH_2-C≡N, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (V): R is -$CH_2CH=CH_2$, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (V): R is -CH_2-C≡CH, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (V): R is -CH_2-C≡N, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (VI): R is -$CH_2CH=CH_2$, R^a is OH, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (VI): R is -CH_2-C≡CH, R^a is OH, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (VI): R is -CH_2-C≡N, R^a is OH, R^b is H, R^c is H, R^d is OH, R^e is OCH_3, R^f is hydrogen;

Compound of Formula (VII): R is -$CH_2CH=CH_2$ and W, R^b, R^c, R^d, R^e, R^f and R^g are as previously defined;

Compound of Formula (VII): R is -CH_2-C≡CH and W, R^b, R^c, R^d, R^e, R^f and R^g are as previously defined;

Compound of Formula (VII): R is -CH_2-C≡N and W, R^b, R^c, R^d, R^e, R^f and R^g are as previously defined;

Compound of Formula (VIII): R is -$CH_2CH=CH_2$ and A, B, D, E, R^b, R^c, R^d, R^e and R^f are as previously defined;

Compound of Formula (VIII): R is -CH_2-C≡CH and A, B, D, E, R^b, R^c, R^d, R^e and R^f are as previously defined;

Compound of Formula (VIII): R is -CH_2-C≡N and A, B, D, E, R^b, R^c, R^d, R^e and R^f are as previously defined;

Compound of Formula (IX): R is -$CH_2CH=CH_2$, and A, B, D, E, R^b, R^c, R^d, R^e, R^f and R^h are as previously defined;

Compound of Formula (IX): R is -CH_2-C≡CH, and A, B, D, E, R^b, R^c, R^d, R^e, R^f and R^h are as previously defined;

Compound of Formula (IX): R is -CH_2-C≡N, and A, B, D, E, R^b, R^c, R^d, R^e, R^f and R^h are as previously defined;

Compound of Formula (II): X is =O, R is -$CH_2CH=CH_2$, R^c and R^d taken together are =O, and R^a, R^b, R^e and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -CH_2-C≡CH, R^c and R^d taken together are =O, and R^a, R^b, R^e and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -CH_2-C≡N, R^c and R^d taken together are =O, and R^a, R^b, R^e and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -$CH_2CH=CH_2$, R^c is -OH, R^d is -H, R^e is -OCH_3;, and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -CH_2-C≡CH, R^c is -OH, R^d is -H, R^e is -OCH_3; and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -CH_2-C≡N, R^c is -OH, R^d is -H, R^e is -OCH_3; and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -$CH_2CH=CH_2$, R^c is -$N(CH_3)_2$, R^d is -H, R^e is -OCH_3 and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -CH_2-C≡CH, R^c is -$N(CH_3)_2$, R^d is -H, R^e is -OCH_3 and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -CH_2-C≡N, R^c is -$N(CH_3)_2$, R^d is -H, R^e is -OCH_3 and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -$CH_2CH=CH_2$, R^c is -H, R^d is -$N(CH_3)_2$, R^e is -OCH_3 and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -CH_2-C≡CH, R^c is -H, R^d is -$N(CH_3)_2$, R^e is -OCH_3 and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -CH_2-C≡N, R^c is -H, R^d is -$N(CH_3)_2$, R^e is -OCH_3 and R^a, R^b, and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -$CH_2CH=CH_2$, R^c is -H, R^d is -OCH_3, R^e is -F and R^a, R^b and R^f are as previously defined;

Compound of Formula (II): X is =O, R is -CH_2-C≡CH, R^c is -H, R^d is -OCH_3, R^e is -F and R^a, R^b and R^f are as previously defined; and

Compound of Formula (II): X is =O, R is -CH_2-C≡N, R^c is -H, R^d is -OCH_3, R^e is -F and R^a, R^b and R^f are as previously defined; as well as the pharmaceutically acceptable salts, esters and prodrugs thereof.

13. A compound according to Claim 2 which is selected from the group consisting of:

Compound of Formula (X): X is =N-O-(1-isopropoxycyclohexyl), R is allyl;

Compound of Formula (X): X is =O, R is allyl;

Compound of Formula (X): X is =O, R is propyl;

Compound of Formula (X): X is =O, R is 2,3-dihydroxypropyl;

Compound of Formula (X): X is =O, R is 2,3-epoxypropyl;

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(imidazol-1-yl)propyl;

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(morpholin-4-yl)propyl;

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(benzylamino)propyl;

Compound of Formula (X): X is =O, R is 2-oxoethyl;

Compound of Formula (X): X is =O, R is 2-oxopropyl;

Compound of Formula (X): X is =O, R is -CH_2-C≡CH;

Compound of Formula (X): X is =O, R is -CH_2-CHOH-CH_2-N_3;

Compound of Formula (X): X is =O, R is -CH_2-CH=N-OH;

Compound of Formula (X): X is =O, R is -CH_2-CH_2OH;

Compound of Formula (X): X is =O, R is -CH_2-CH_2NH_2;

Compound of Formula (X): X is =O, R is -CH_2-CN;

Compound of Formula (X): X is =O, R is -CH_2-Phenyl;

Compound of Formula (X): X is =O, R is -CH_2-CH=CH(Phenyl);

Compound of Formula (X): X is =O, R is -CH_2-CH=N-O-CH_3;

Compound of Formula (X): X is =O, R is -CH_2-CH=N-O-CH_2-Phenyl;

Compound of Formula (X): X is =O, R is -CH_2-CH=N-$N(CH_3)_2$;

Compound of Formula (X): X is =O, R is -CH_2-CH=N-$NH(CH_3)$;

Compound of Formula (X): X is =O, R is -CH_2-CH=N-(4-Morpholinyl);

Compound of Formula (X): X is =O, R is -CH_2-CH=N-NH(Phenyl); and

Compound of Formula (X): X is =O, R is -CH_2-CH=N-$N(Phenyl)_2$; as well as the pharmaceutically acceptable salts, esters and prodrugs thereof.

14. A compound according to Claim 2 which is selected from the group consisting of:

Compound of Formula (X): X is =O, R is allyl, R^b is CH_3;

Compound of Formula (X): X is =O, R is 2-hydroxy-3-(benzylamino)propyl, R^b is CH_3;

Compound of Formula (X): X is =O, R is 2-oxopropyl, R^b is CH_3;

Compound of Formula (X): X is =O, R is -CH_2-C≡CH, R^b is CH_3;

Compound of Formula (X): X is =O, R is -CH_2-CH=N-OH, R^b is CH_3;

Compound of Formula (X): X is =O, R is -CH_2-CH_2OH, R^b is CH_3;

Compound of Formula (X): X is =O, R is -CH_2-CH_2NH_2; and

Compound of Formula (X): X is =O, R is -CH_2-CN; as well as the pharmaceutically acceptable salts, esters and prodrugs thereof.

15. A pharmaceutical composition comprising a compound of any one of Claims 1 to 14, or a pharmaceutically acceptable salt , ester or prodrug thereof, in combination with a pharmaceutically acceptable carrier.

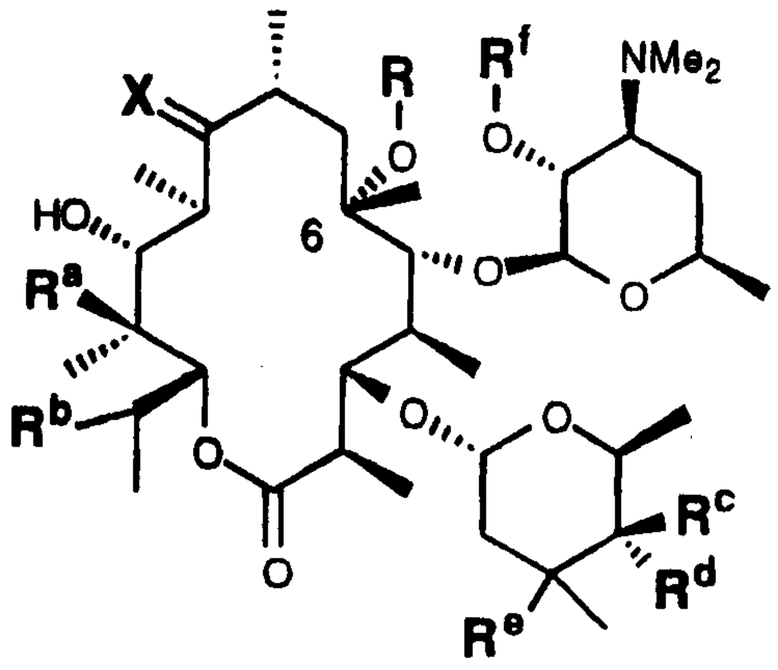
16. Use of a compound of any one of Claims 1 to 14, or a pharmaceutically acceptable salt , ester or prodrug thereof, in the manufacture of a medicament for controlling a bacterial infection in a mammal.

17. A pharmaceutical composition for controlling a bacterial infection in a mammal comprising a compound of any one of Claims 1 to 14, or a pharmaceutically acceptable salt , ester or prodrug thereof, in combination with a pharmaceutically acceptable carrier.

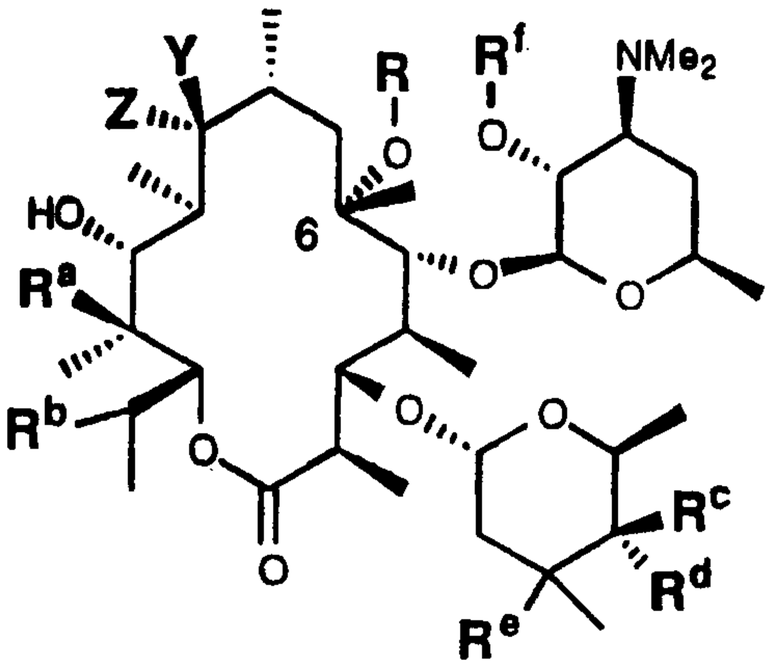
18. A compound of any one of Claims 1 to 14, or a pharmaceutically acceptable salt , ester or prodrug thereof, for use in controlling a bacterial infection in a mammal.

19. An antibacterial pharmaceutical composition comprising an antibacterially effective amount of a compound of any one of Claims 1 to 14, or a pharmaceutically acceptable salt , ester or prodrug thereof, in combination with a pharmaceutically acceptable carrier.

20. A process for the preparation of 6-O-substituted macrolide compounds having the formula



(II);



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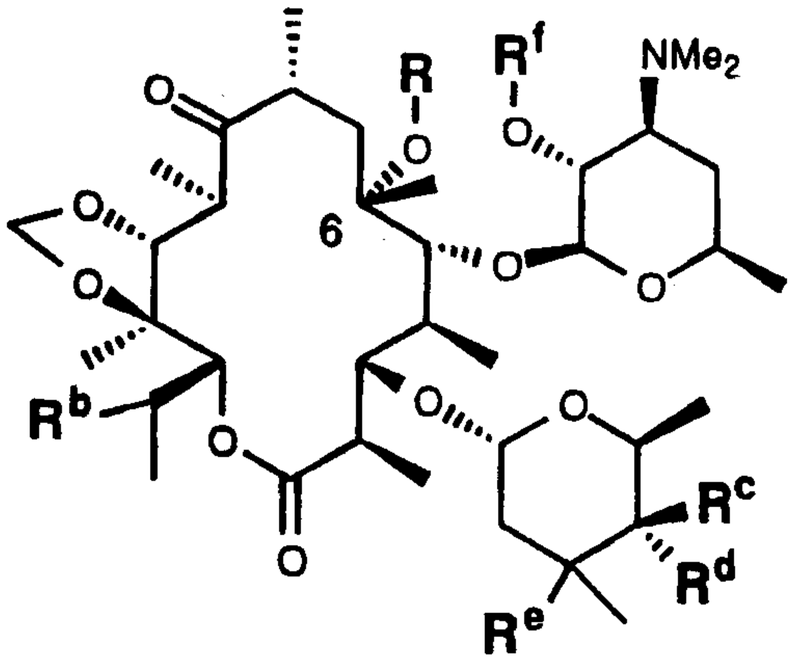
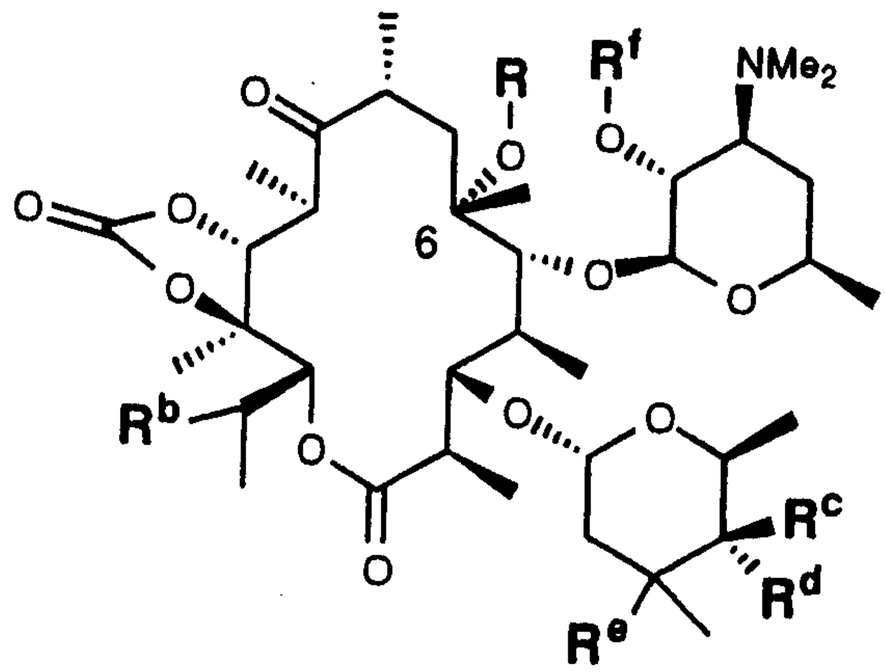
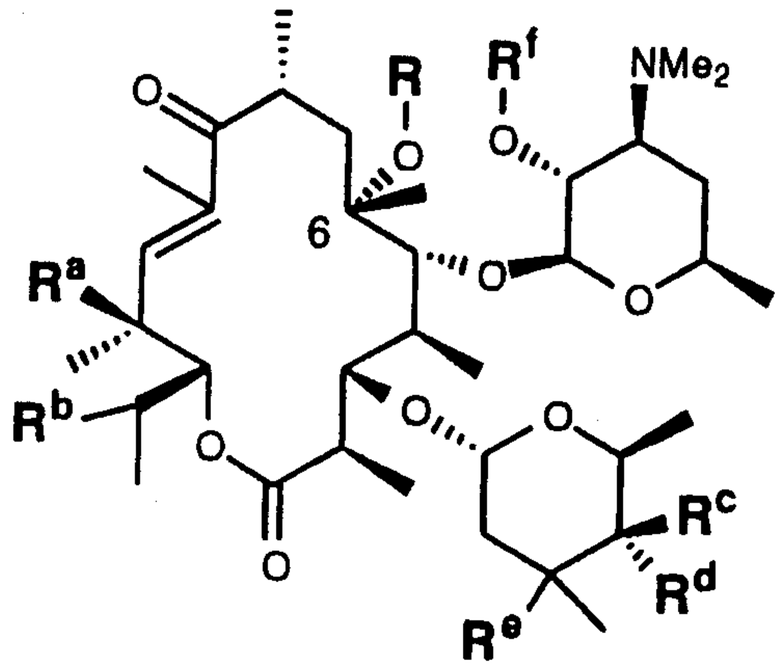


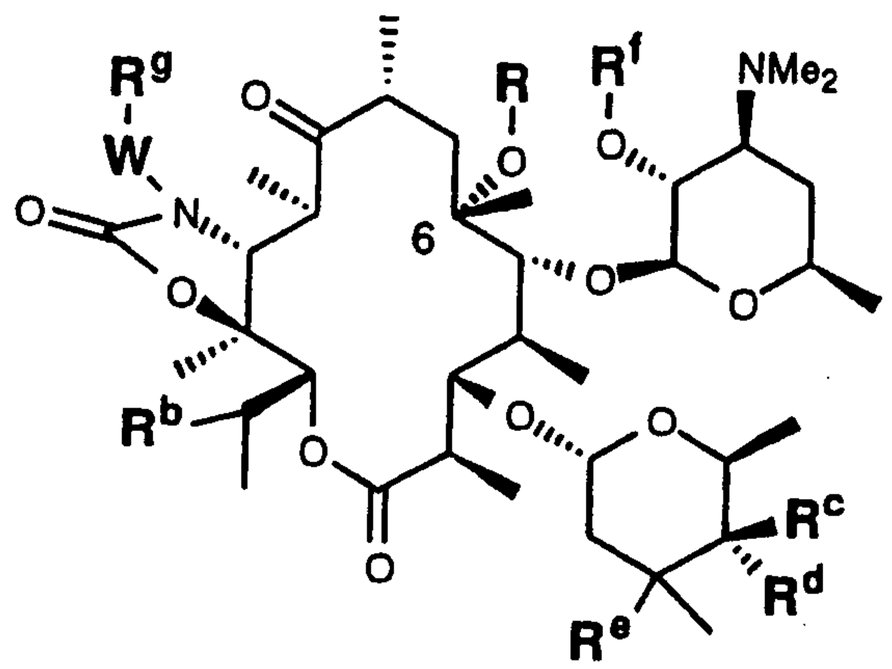
(IV);



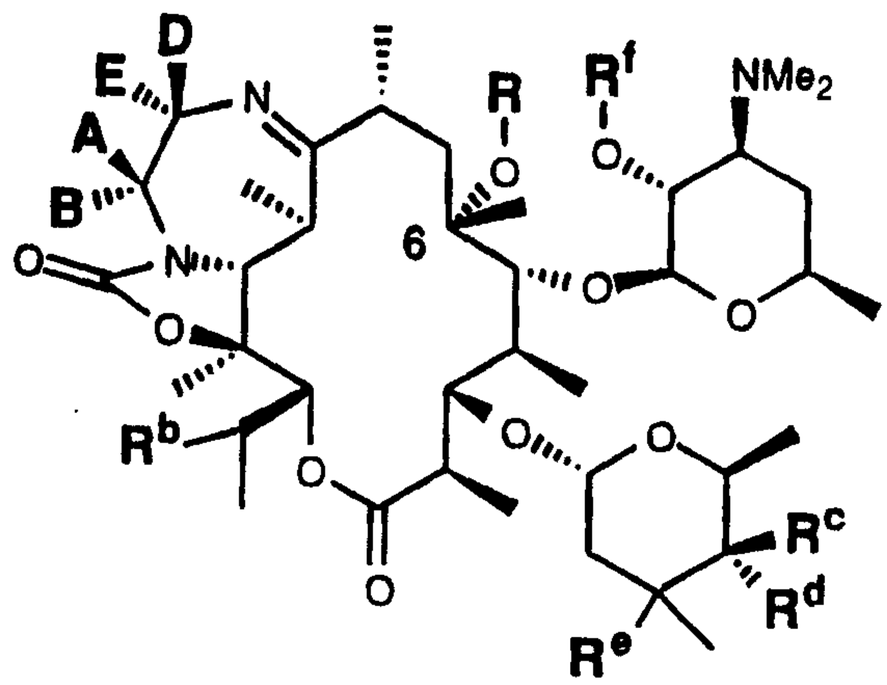
(V);



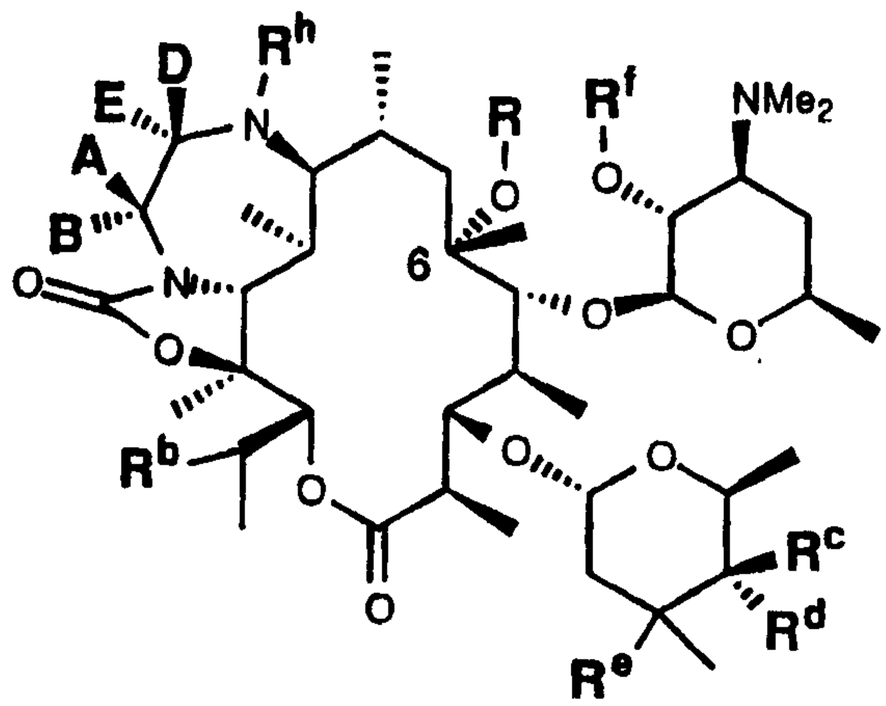
(VI);



(VII);



(VIII); or



(IX);

wherein X is:

(1) =O,

(2) =N-OH,

(3) =N-O-R^1 where R^1 is

(a) unsubstituted C_1-C_{12}-alkyl,

(b) C_1-C_{12}-alkyl substituted with aryl,

(c) C_1-C_{12}-alkyl substituted with substituted aryl,

(d) C_3-C_{12}-cycloalkyl,

(e) -Si-(R^{11})(R^{12})(R^{13}) wherein R^{11}, R^{12} and R^{13} are each independently selected from C_1-C_{12}-alkyl,

(f) -Si-(Aryl)$_3$, or

(4) =N-O-C(R^9)(R^{10})-O-R^1 where R^1 is as defined above and R^9 and R^{10} are each independently selected from the group consisting of:

(a) hydrogen,

(b) unsubstituted C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl, and

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

or R^9 and R^{10} taken together with the carbon to which they are attached form a C_3-C_{12}-cycloalkyl ring;

R^a is hydrogen or hydroxy;

R^b is hydrogen or hydroxy;

one of R^c and R^d is hydrogen and the other of R^c and R^d is:

(1) hydroxy,

(2) protected hydroxy,

(3) halogen, or

(4) NR^3R^4 where R^3 and R^4 are independently selected from

(a) hydrogen,

(b) C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl,

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

(e) C_1-C_{12}-alkyl substituted with heteroaryl, and

(d) C_1-C_{12}-alkyl substituted with substituted heteroaryl, or

(5) -SO_2-(substituted C_1-C_6-alkyl, or

R^3 and R^4 taken together with the carbon to which they are attached form a 3-7 membered hetereocyclicalkyl ring,

or

R^c and R^d taken together is:

(1) =O,

(2) =N-OH, or

(3) =N-OR^1 wherein R^1 is as defined above;

R^e is methoxy, fluorine or hydroxy;

R^f is hydrogen or an hydroxy protecting group;

R^g is selected from a group consisting of:

(1) unsubstituted C_1-C_6-alkyl,

(2) C_1-C_6-alkyl substituted with one or more substituents selected from the group consisting of:

(a) aryl,

(b) substituted aryl,

(c) heteroaryl,

(d) substituted heteroaryl,

(e) heteroarylalkyl,

(f) hydroxy,

(g) C_1-C_6-alkoxy,

(h) NR^3R^4 wherein R^3 and R^4 are as previously defined, and

(i) $-CH_2-M-R^5$ where M is selected from a group consisting of:

(i) -O-,

(ii) -NH-,

(iii) -NMe-,

(iv) $-S(O)_n-$ where n is 0, 1 or 2,

(v) -NHC(=O)-, and

(vi) -C(=O)-NH-,

and

R^5 is selected from a group consisting of:

(i) $-(CH_2)_n$-aryl where n is 0, 1 or 2,

(ii) $-(CH_2)_n$-substituted aryl where n is 0, 1 or 2,

(iii) $-(CH_2)_n$-heteroaryl where n=0, 1 or 2,

(iv) $-(CH_2)_n$-substituted heteroaryl where n is 0, 1 or 2, and

(v) $-(CH_2)_n$-heteroarylalkyl where n is 0, 1 or 2,

(3) C_3-C_{12}-cycloalkyl,

(4) aryl,

(5) substituted aryl,

(6) heteroaryl, and

(7) substituted heteroaryl;

R^h is selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl,

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

(e) C_1-C_{12}-alkyl substituted with heteroaryl, and

(d) C_1-C_{12}-alkyl substituted with substituted heteroaryl;

R is selected from the group consisting of:

(1) C_1-alkyl substituted with a substituent selected from the group consisting of:

(a) F,

(b) $S(O)_nR^6$ where n is 0, 1 or 2 and C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(c) $NHC(O)R^6$ where R^6 is as defined above, and

(d) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are independently selected from hydrogen and C_1-C_3-alkyl,

(2) C_2-C_{10}-alkyl;

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N-O-R^6$ where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N-NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N-NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(4) C_2-C_{10}-alkenyl;

(5) C_2-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N-O-R^6$ where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined.

(t) $=N-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N-NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N-NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(6) C_2-C_{10}-alkynyl; and

(7) C_2-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of:

(a) trialkylsilyl,

(b) aryl,

(c) substituted aryl,

(d) heteroaryl, and

(e) substituted heteroaryl;

one of Y and Z is hydrogen and the other is selected from a group consisting of:

(1) hydrogen,

(2) hydroxy,

(3) protected hydroxy, and

(4) NR^3R^4 wherein R^3 and R^4 are as previously defined;

W is:

(1) -O-,

(2) -NH-,

(3) -NMe-, or

(4) absent;

A, B, D and E are, at each occurrence, independently selected from the group consisting of:

(1) hydrogen,

(2) unsubstituted C_1-C_6-alkyl,

(3) C_1-C_6-alkyl substituted with one or more substituents selected from the group consisting of:

(a) aryl,

(b) substituted aryl,

(c) heteroaryl,

(d) substituted heteroaryl,

(e) heteroarylalkyl,

(f) hydroxy,

(g) C_1-C_6-alkoxy,

(h) NR^3R^4, where R^3 and R^4 are as defined above, and

(i) $-CH_2-M-R^5$ where M is selected from a group consisting of:

(i) -O-,

(ii) -NH-,

(iii) -NMe-,

(iv) $-S(O)_n-$ where n is 0, 1 or 2,

(v) -NHC(=O)-, and

(vi) -C(=O)-NH-,

and

R^5 is selected from a group consisting of:

(i) $-(CH_2)_n$-aryl where n is 0, 1 or 2,

(ii) $-(CH_2)_n$-substituted aryl where n is 0, 1 or 2,

(iii) $-(CH_2)_n$-heteroaryl where n=0, 1 or 2,

(iv) $-(CH_2)_n$-substituted heteroaryl where n is 0, 1 or 2, and

(v) $-(CH_2)_n$-heteroarylalkyl where n is 0, 1 or 2,

or any pair of substituents, consisting of AB, AD, AE, BD, BE or DE, is taken together with the atom or atoms to which they are attached to form a 3- to 7-membered ring optionally containing a hetero function selected from:

(1) -O-,

(2) $-S(O)_n-$, where n is 0, 1 or 2,

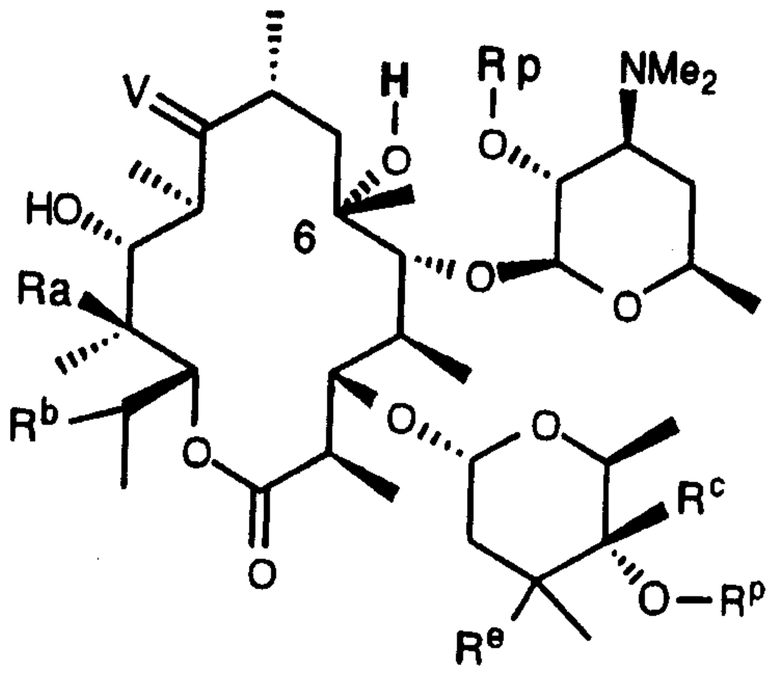
(3) -NH-,

(4) $-N(CH_3)-$, and

(5) $-N(R^5)-$ wherein R^5 is as previously defined;

is a method comprising:

(a) treating a compound having the formulae:



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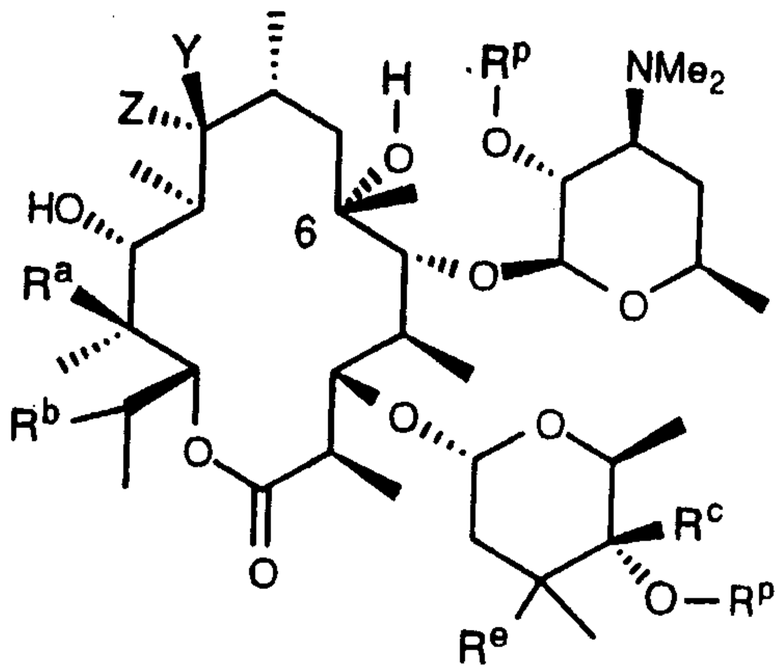

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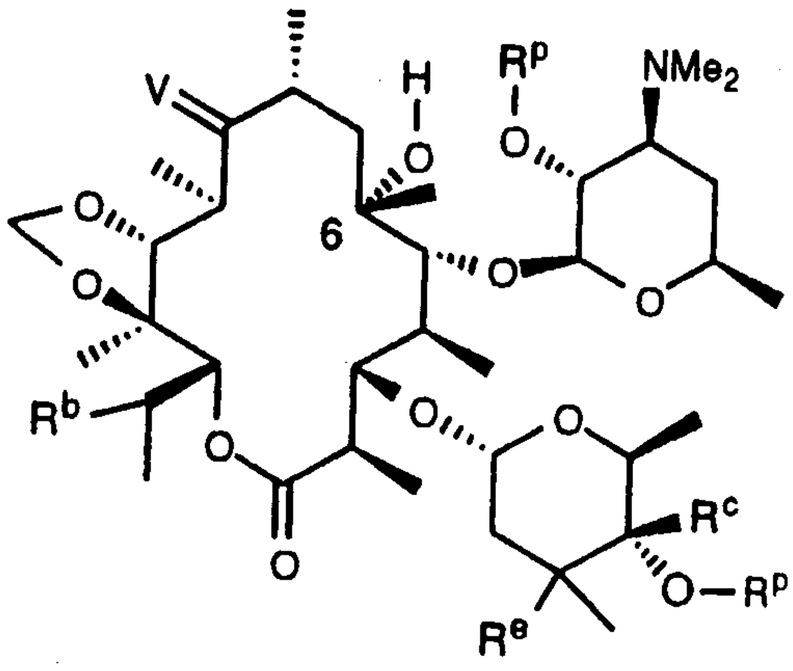

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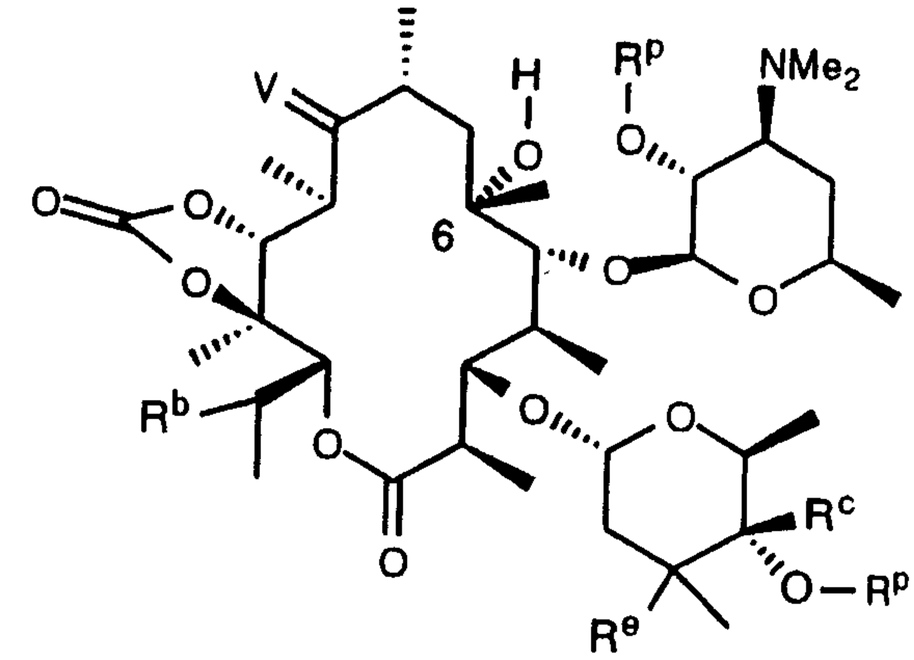

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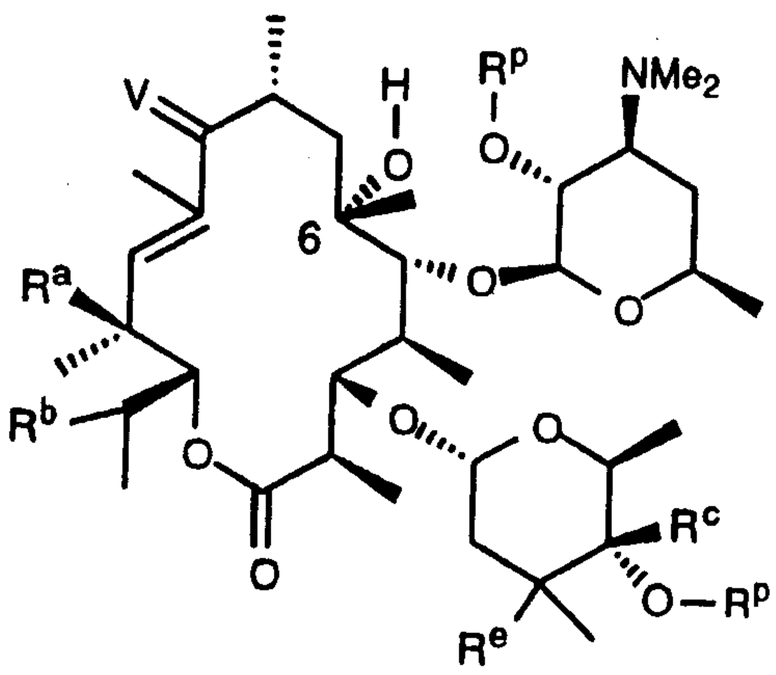

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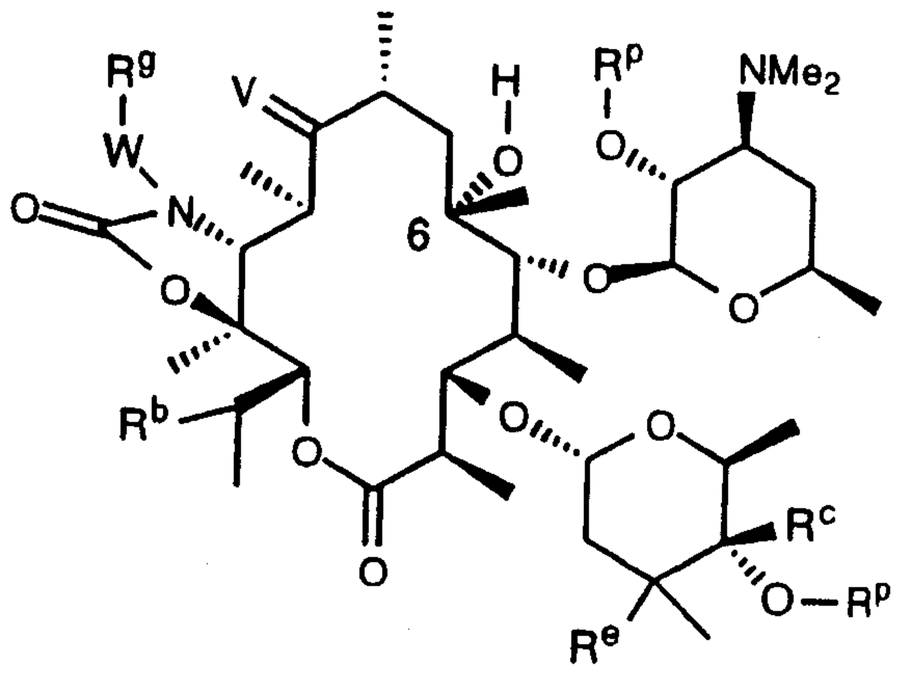

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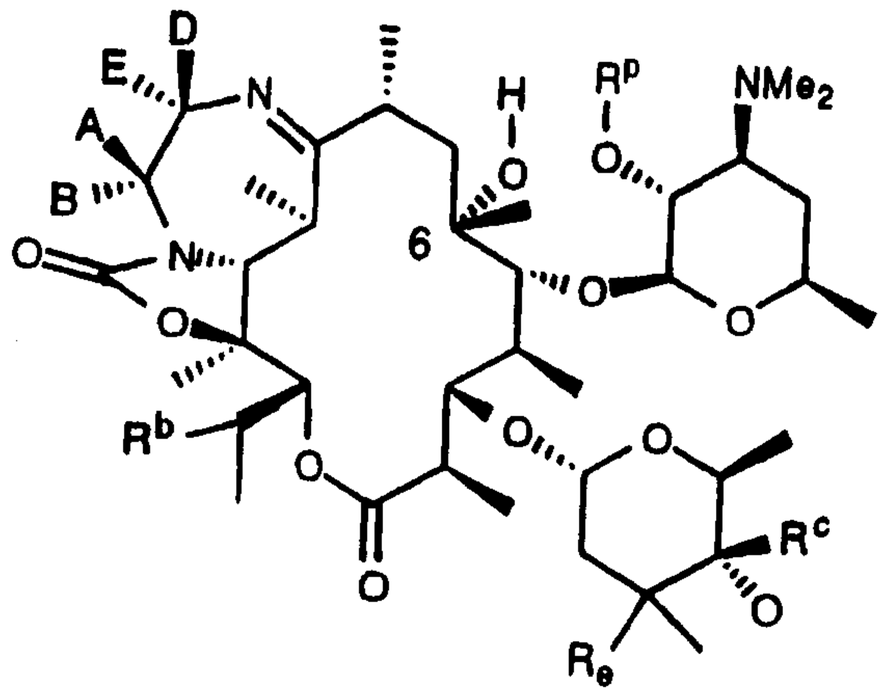
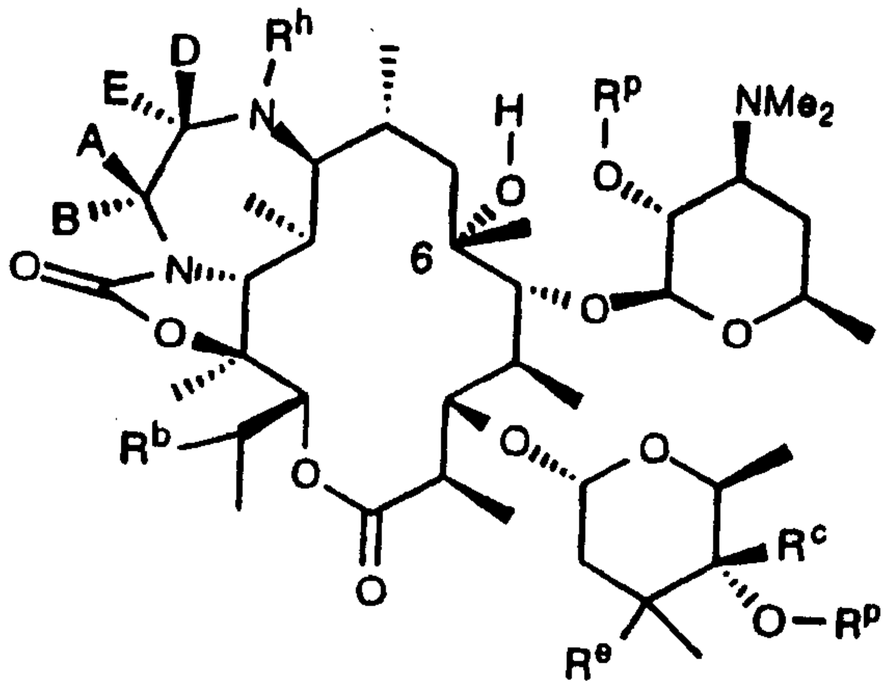
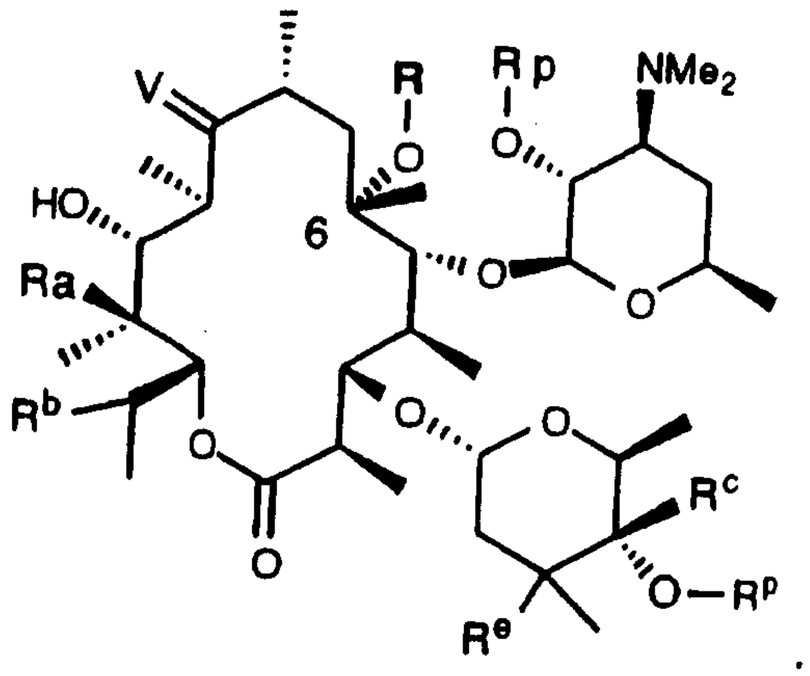


; or

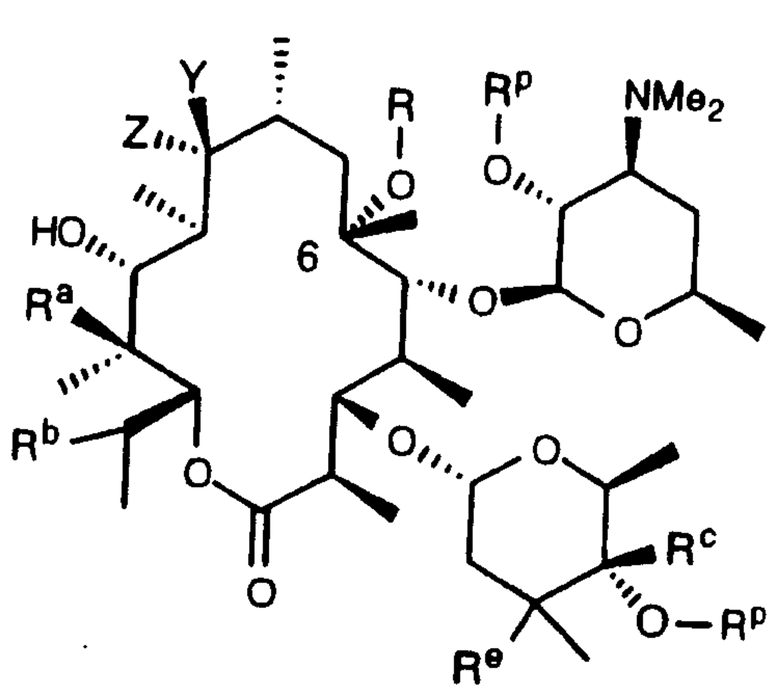


;

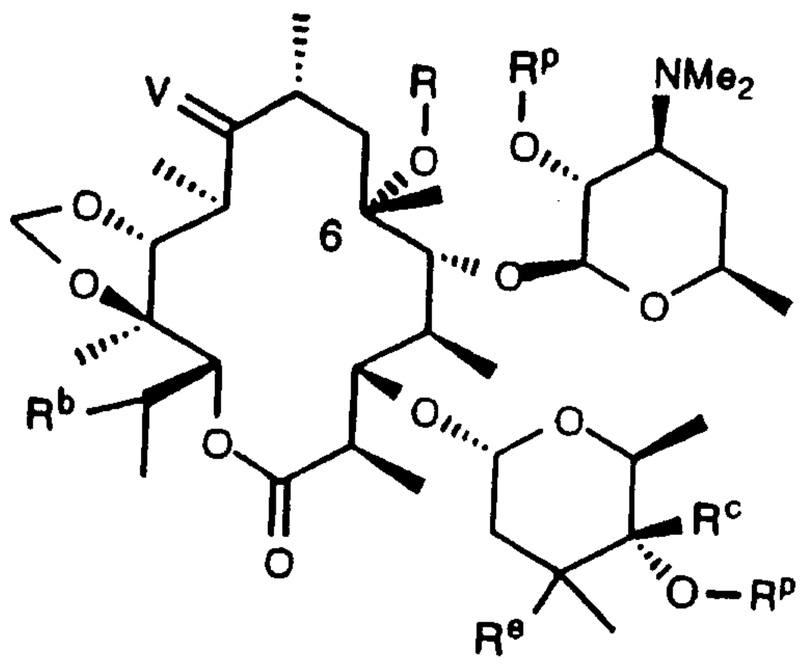
wherein R^p is an hydroxy protecting group and V is =N-O-R^1 or =N-O-C(R^9)(R^{10})-O-R^1 wherein R^1, R^9 and R^{10} are as defined above, with a base, in an aprotic solvent, which does not adversely affect the reaction, with cooling or heating, depending on the conditions used, at a temperature from about -15°C to about 50°C, for a period from 0.5 hours to 10 days, with an alkylating agent to give a compound having the formula:


V
R
Rp
NMe2
HO
6
Ra
Rb
O
Rc
O—Rp
Re

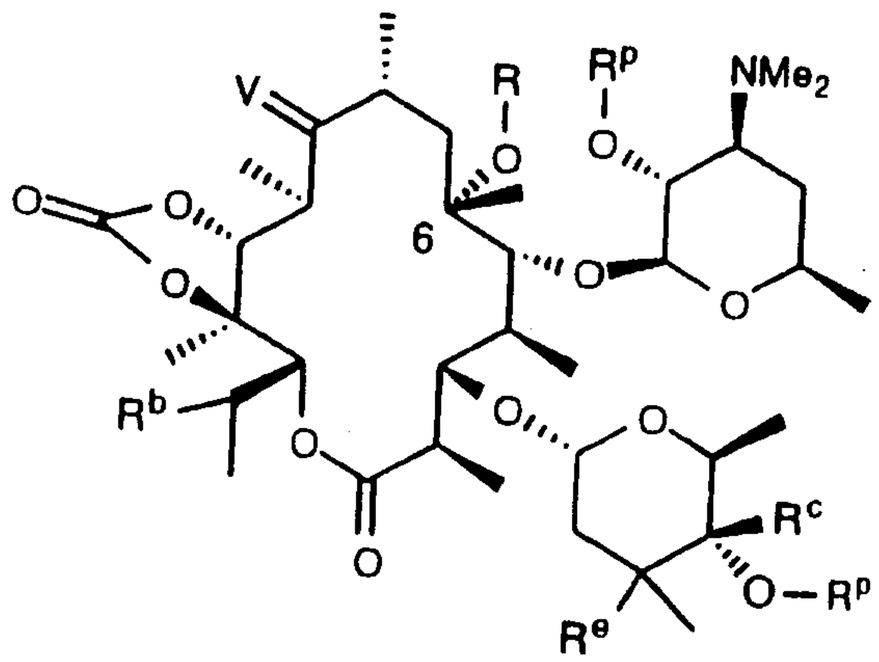
;


Y
Z
R
Rp
NMe2
HO
6
Ra
Rb
O
Rc
O—Rp
Re

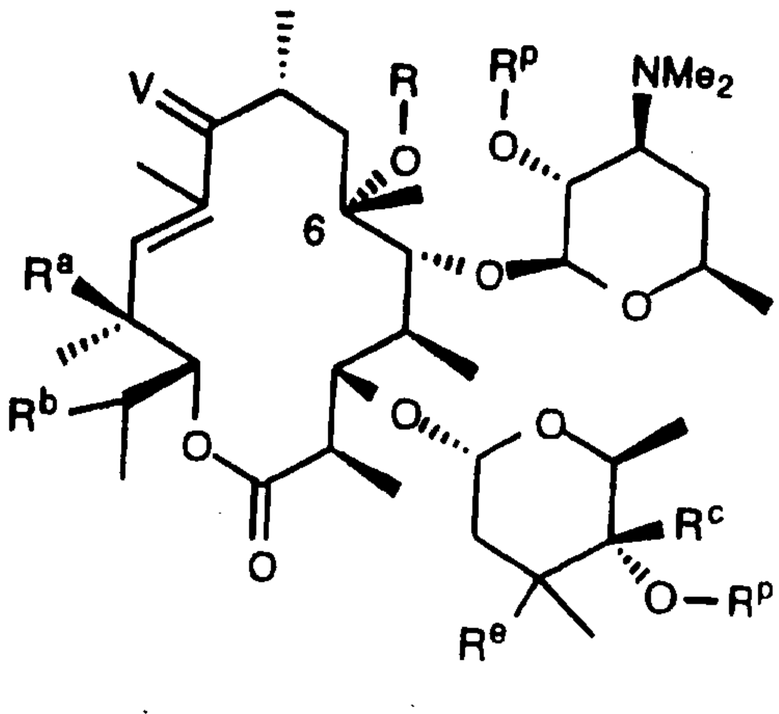
;


V
R
Rp
NMe2
O
6
Rb
Rc
O—Rp
Re

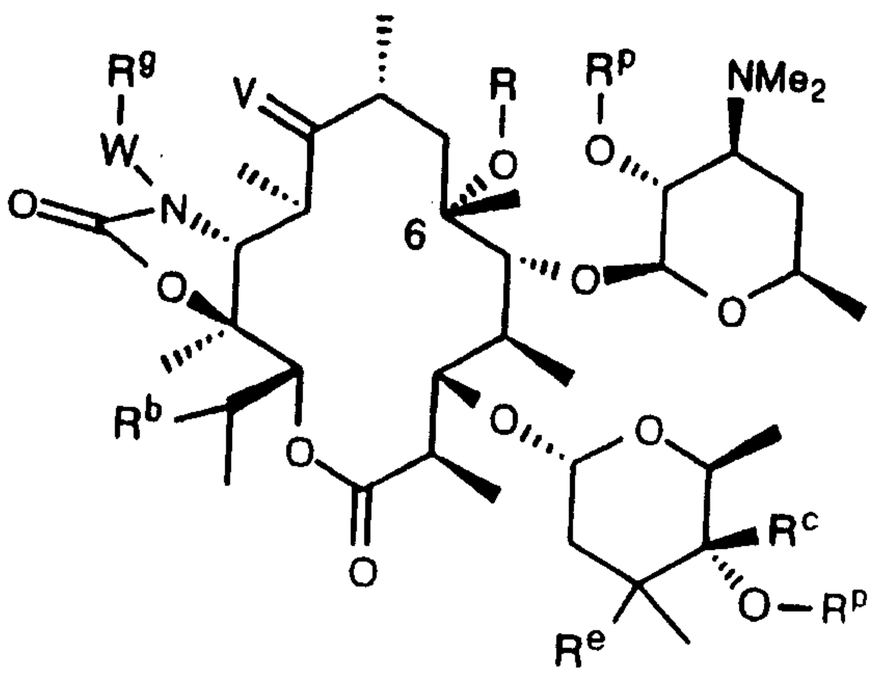
;


V
R
Rp
NMe2
O
6
Rb
Rc
O—Rp
Re

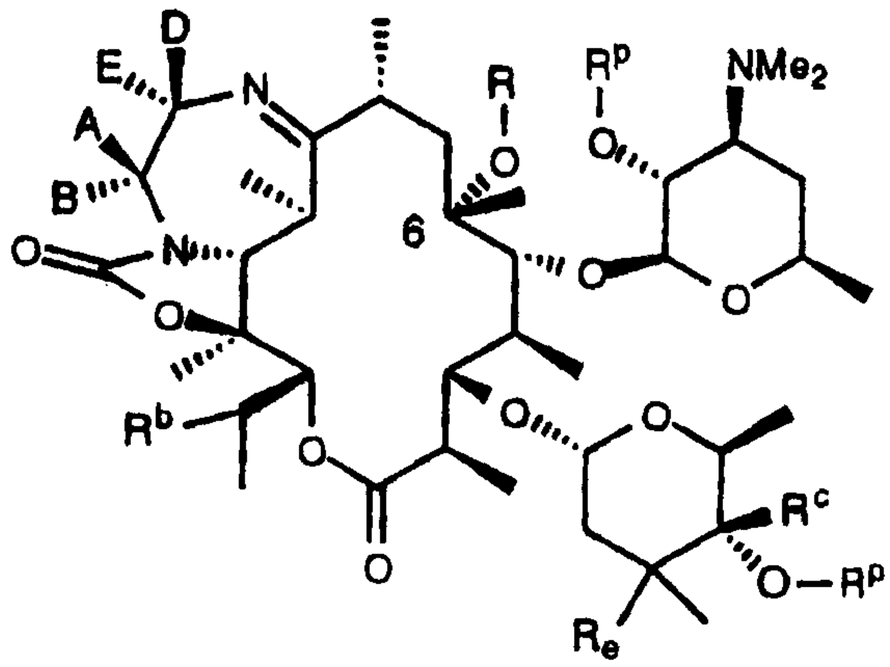
;


V
R
Rp
NMe2
6
Ra
Rb
O
Rc
O—Rp
Re

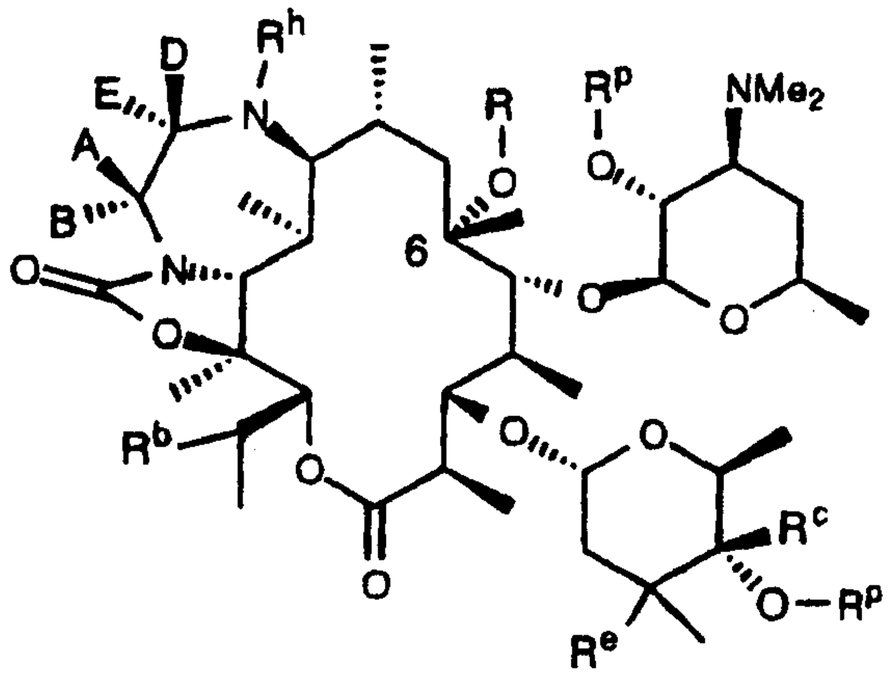
;


Rg
W
N
V
R
Rp
NMe2
O
6
Rb
Rc
O—Rp
Re

;



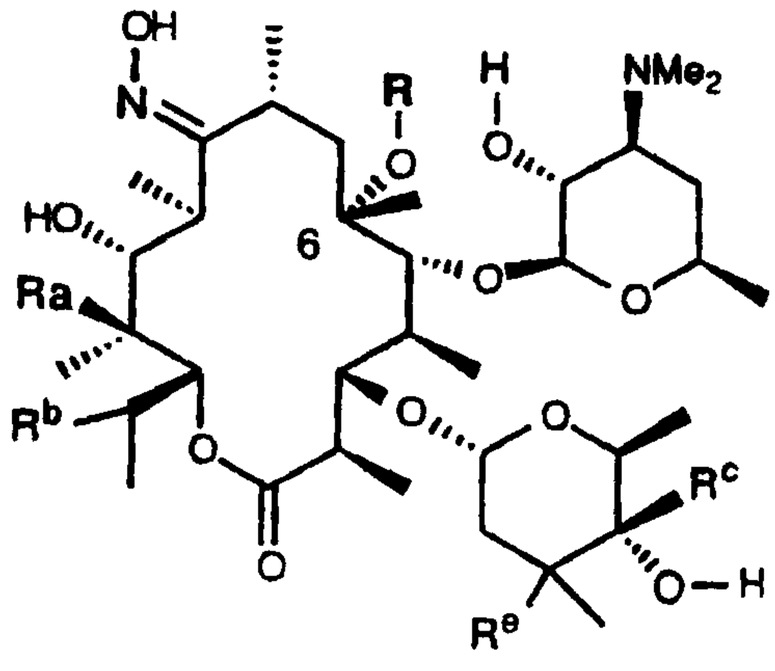
; or



;

wherein A, B, D, E, W, X, Y, Z, R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h are as defined above, V is =N-O-R^1 or =N-O-C(R^9)(R^{10})-O-R^1 wherein R^1, R^9 and R^{10} are as defined above, and R is the "alkyl group" derived from the corresponding alkylating agent;

(b) deprotecting of the 2'- and 4'-hydroxyl groups, to give a compound of the formula:



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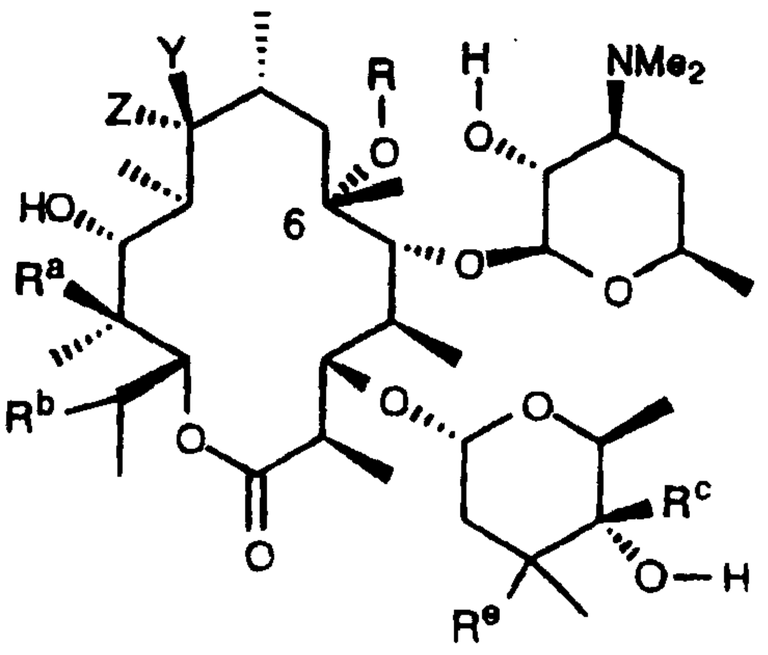

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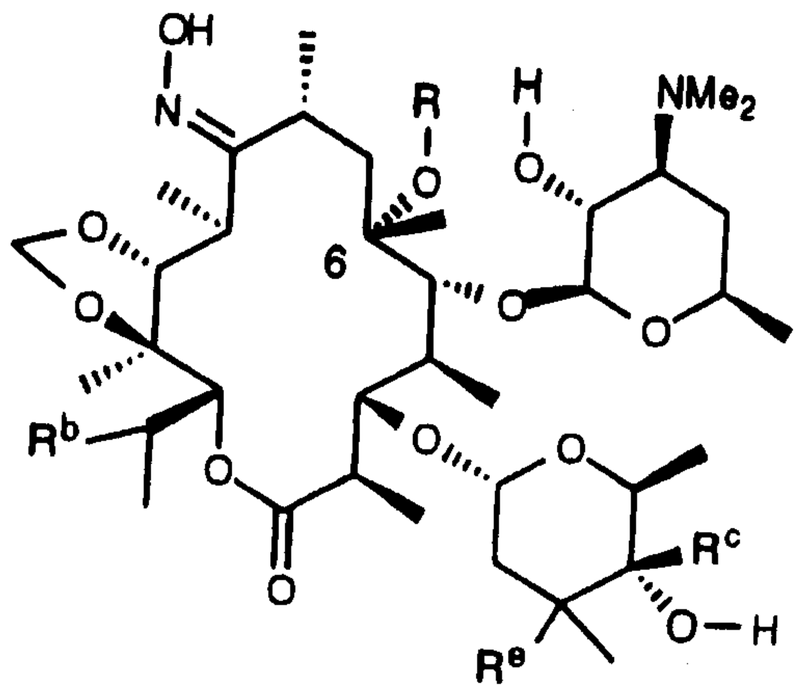
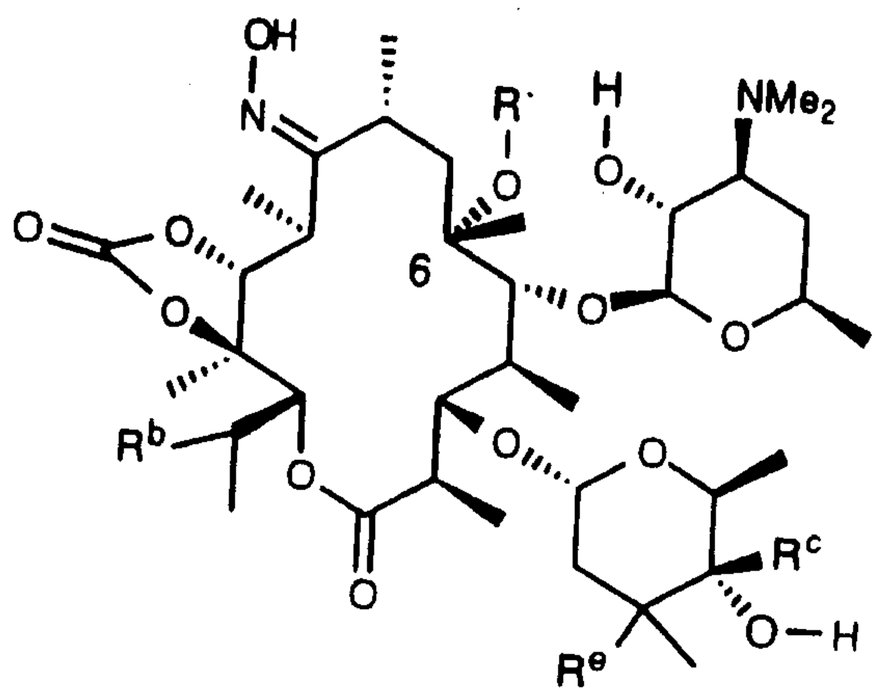
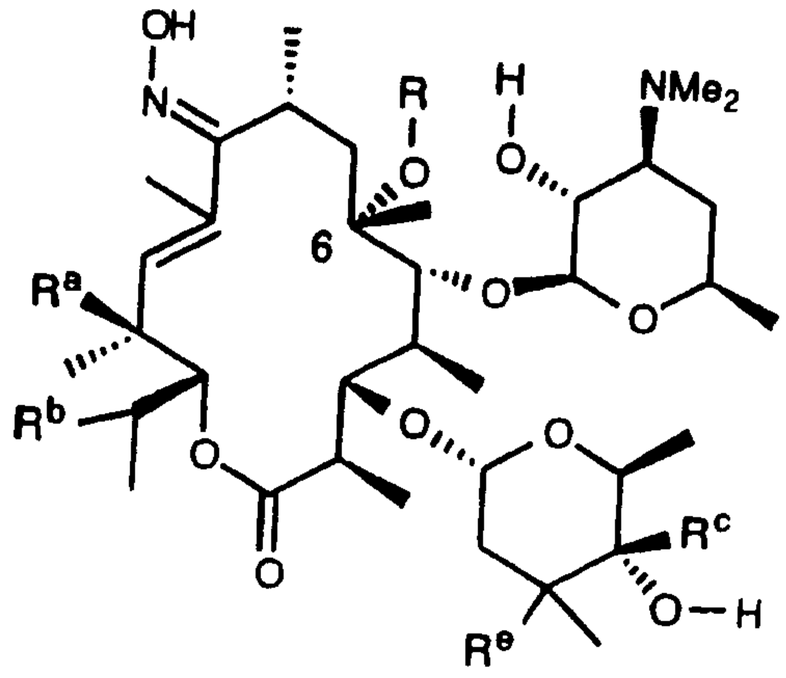
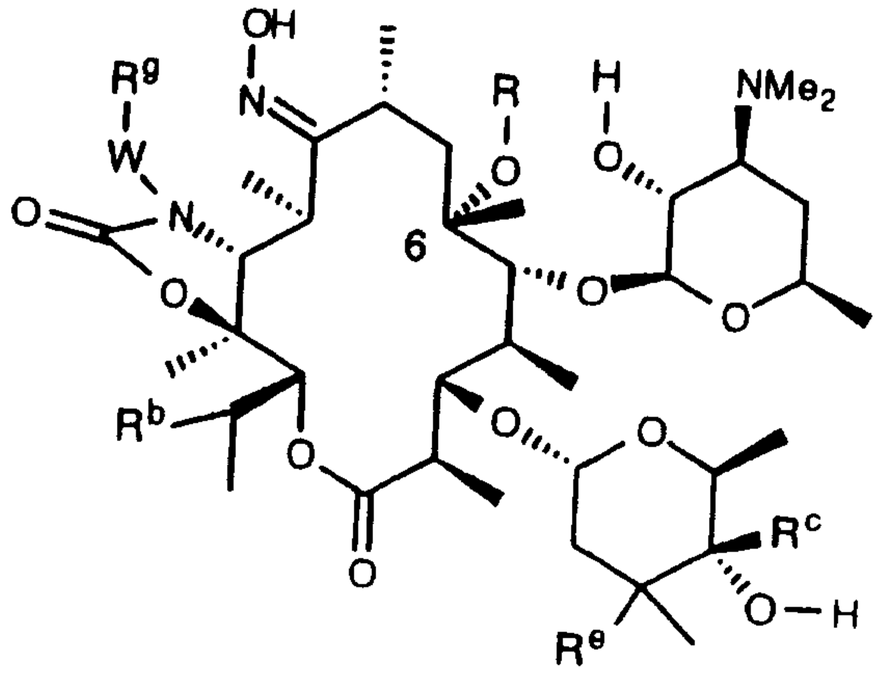
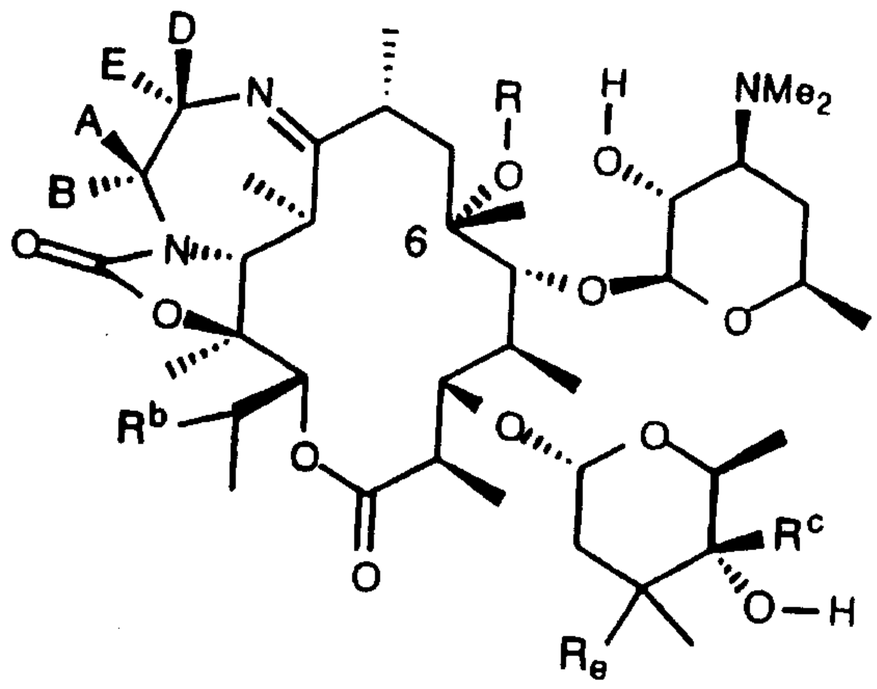


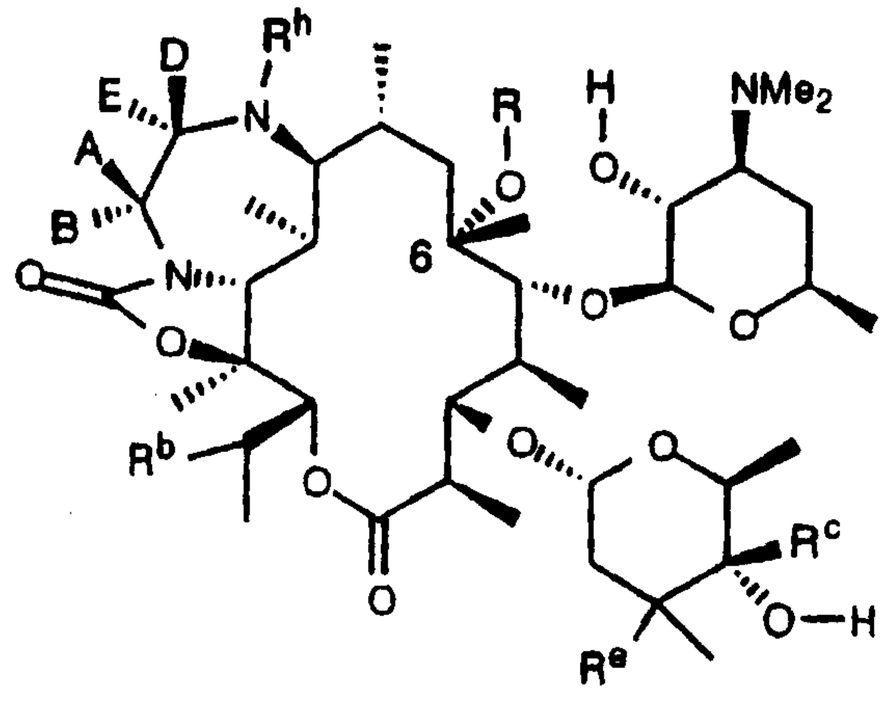








; or



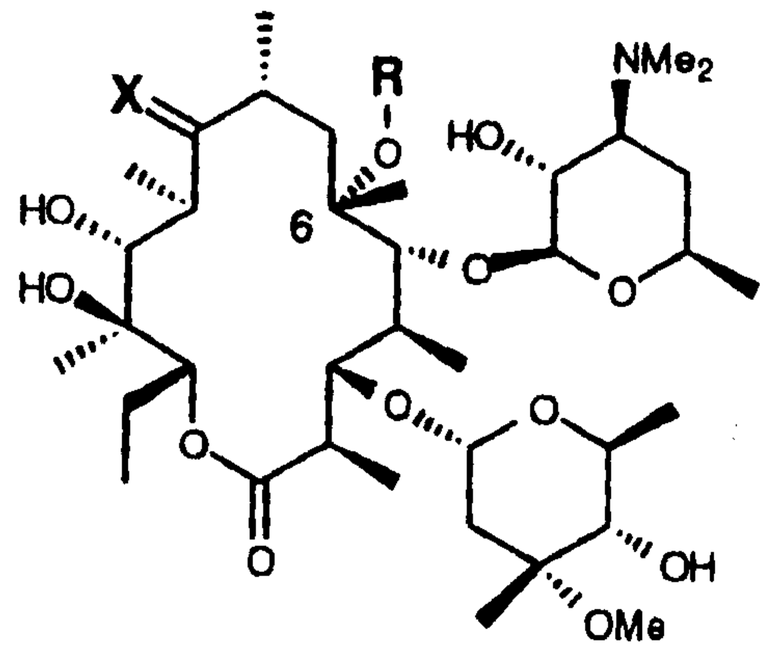
;

wherein A, B, D, E, W, X, Y, Z, R^a, R^b, R^c, R^d, R^e, R^f, R^g and R^h are as defined above and R is the "alkyl group" derived from the corresponding alkylating agent;

and

(c) deoximation, with an inorganic sulphur oxide compound in a solvent to give the desired products.

21. The process according to Claim 20 for the preparation of 6-O-substituted macrolide compounds having the formula:



wherein X is:

(1) =O,

(2) =N-OH,

(3) =N-O-R^1 where R^1 is

(a) unsubstituted C_1-C_{12}-alkyl,

(b) C_1-C_{12}-alkyl substituted with aryl,

(c) C_1-C_{12}-alkyl substituted with substituted aryl,

(d) C_3-C_{12}-cycloalkyl,

(e) -Si-(R^{11})(R^{12})(R^{13}) wherein R^{11}, R^{12} and R^{13} are each independently selected from C_1-C_{12}-alkyl,

(f) -Si-(Aryl)$_3$, or

(4) =N-O-C(R^9)(R^{10})-O-R^1 where R^1 is as defined above and R^9 and R^{10} are each independently selected from the group consisting of:

(a) hydrogen,

(b) unsubstituted C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl, and

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

or R^9 and R^{10} taken together with the carbon to which they are attached form a C_3-C_{12}-cycloalkyl ring; and

R is selected from the group consisting of:

(1) C_1-alkyl substituted with a substituent selected from the group consisting of:

(a) F,

(b) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(c) $NHC(O)R^6$ where R^6 is as defined above, and

(d) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are independently selected from hydrogen and C_1-C_3-alkyl,

(2) C_2-C_{10}-alkyl;

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) =N-O-R^6 where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N\text{-}NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N\text{-}NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N\text{-}NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(4) C_2-C_{10}-alkenyl;

(5) C_2-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N\text{-}O\text{-}R^6$ where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) =N-NR^{3}R^4 wherein R^3 and R^4 are as previously defined,

(u) =N-NHC(O)R^6 where R^6 is as previously defined, and

(v) =N-NHC(O)NR^{3}R^4 wherein R^3 and R^4 are as previously defined;

(6) C_2-C_{10}-alkynyl; and

(7) C_2-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of:

(a) trialkylsilyl,

(b) aryl,

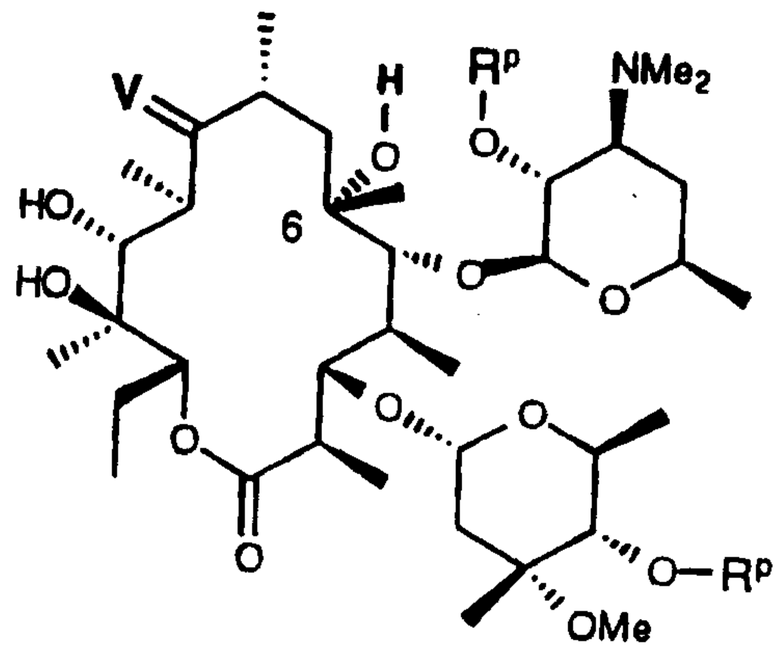
(c) substituted aryl,

(d) heteroaryl, and

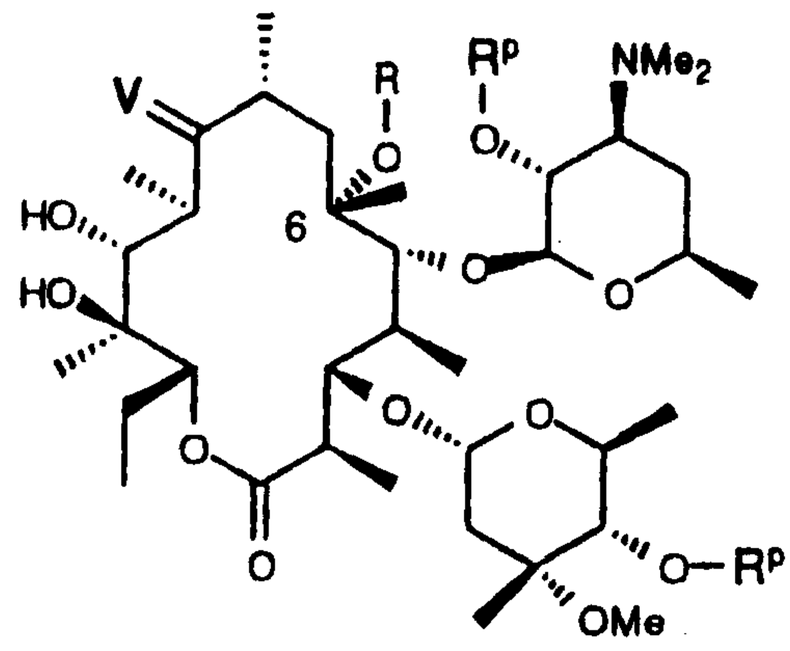
(e) substituted heteroaryl;

in a method comprising:

(a) treating a compound having the formula:

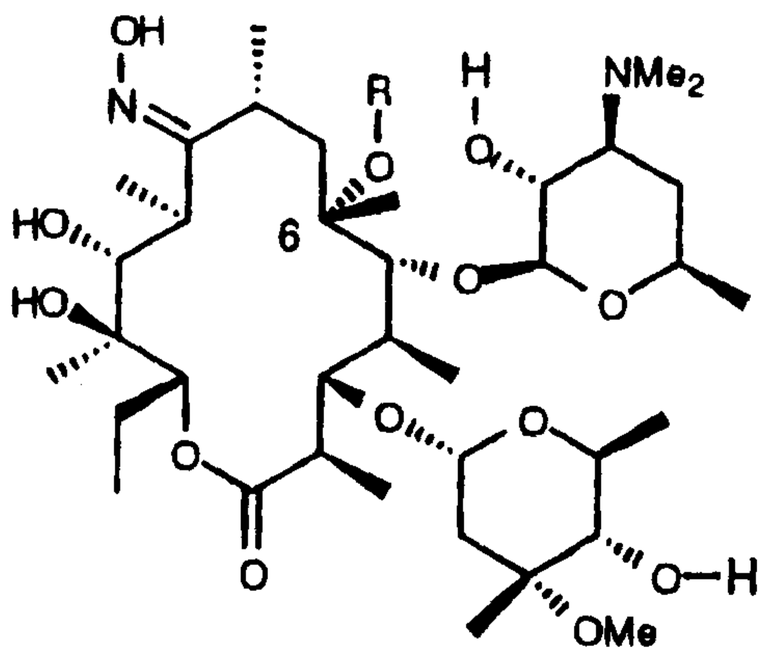


wherein R^p is an hydroxyl protecting group and V is a ketone protecting group with a base, in an aprotic solvent, which does not adversely affect the reaction, with cooling or heating, depending on the conditions used, at a temperature from about -15°C to about 50°C, for a period from 0.5 hours to 10 days, to give a compound having the formula:



wherein V and RP are as defined above and R is the "alkyl group" derived the corresponding **alkylating agent;**

(b) deprotecting of the 2'- and 4'- hydroxyl groups, to give a compound having the formula:



and

(c) deoximation, using an inorganic sulphur oxide compound in a solvent.

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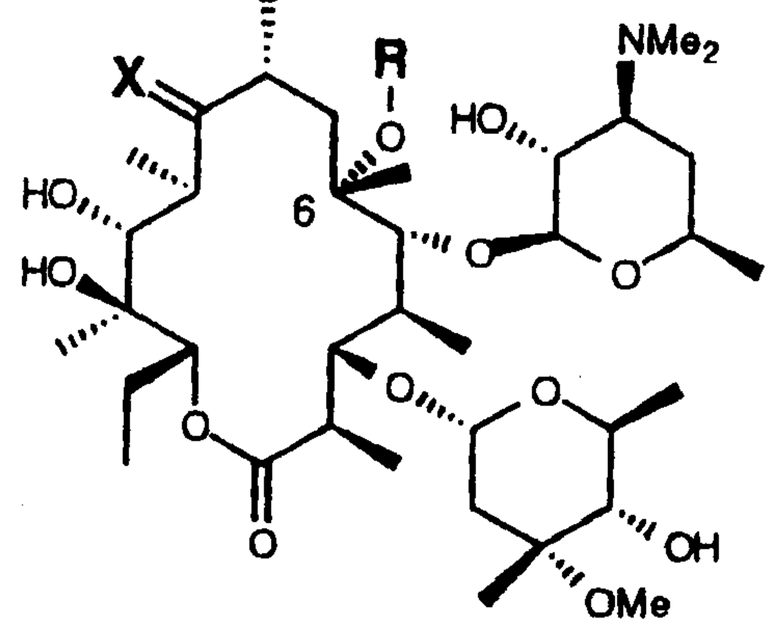
22. The process according to Claim 21 for the preparation of 6-O-substituted macrolide compounds having the formula:



wherein X is:

(1) =O,

(2) =N-OH,

(3) =N-O-R^1 where R^1 is:

(a) unsubstituted C_1-C_{12}-alkyl,

(b) C_1-C_{12}-alkyl substituted with aryl,

(c) C_1-C_{12}-alkyl substituted with substituted aryl,

(d) C_3-C_{12}-cycloalkyl,

(e) -Si-(R^{11})(R^{12})(R^{13}) wherein R^{11}, R^{12} and R^{13} are each independently selected from C_1-C_{12}-alkyl,

(f) -Si-(Aryl)$_3$, or

(4) =N-O-C(R^9)(R^{10})-O-R^1 where R^1 is as defined above and R^9 and R^{10} are each independently selected from the group consisting of:

(a) hydrogen,

(b) unsubstituted C_1-C_{12}-alkyl,

(c) C_1-C_{12}-alkyl substituted with aryl, and

(d) C_1-C_{12}-alkyl substituted with substituted aryl,

or R^9 and R^{10} taken together with the carbon to which they are attached form a C_3-C_{12}-cycloalkyl ring; and

R is selected from the group consisting of:

(1) C_1-alkyl substituted with a substituent selected from the group consisting of:

(a) F,

(b) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(c) $NHC(O)R^6$ where R^6 is as defined above, and

(d) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are independently selected from hydrogen and C_1-C_3-alkyl,

(2) C_2-C_{10}-alkyl;

(3) C_2-C_{10}-alkyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N-O-R^6$ where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N-NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N-NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(4) C_2-C_{10}-alkenyl;

(5) C_2-C_{10}-alkenyl substituted with one or more substituents selected from the group consisting of:

(a) halogen,

(b) hydroxy,

(c) C_1-C_3-alkoxy,

(d) oxo (C=O),

(e) -CHO,

(f) $-CO_2R^6$ where R^6 is as defined above,

(g) $-C(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(h) $-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(i) $=N-O-R^6$ where R^6 is as previously defined,

(j) -C≡N,

(k) $S(O)_nR^6$ where n is 0, 1 or 2 and R^6 is C_1-C_3-alkyl or aryl substituted C_1-C_3-alkyl,

(l) aryl,

(m) substituted aryl,

(n) heteroaryl,

(o) substituted heteroaryl,

(p) C_3-C_7-cycloalkyl,

(q) (heteroaryl)alkyl,

(r) $NHC(O)R^6$ where R^6 is as previously defined,

(s) $NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(t) $=N-NR^3R^4$ wherein R^3 and R^4 are as previously defined,

(u) $=N-NHC(O)R^6$ where R^6 is as previously defined, and

(v) $=N-NHC(O)NR^3R^4$ wherein R^3 and R^4 are as previously defined;

(6) C_2-C_{10}-alkynyl; and

(7) C_2-C_{10}-alkynyl substituted with one or more substituents selected from the group consisting of:

(a) trialkylsilyl,

(b) aryl,

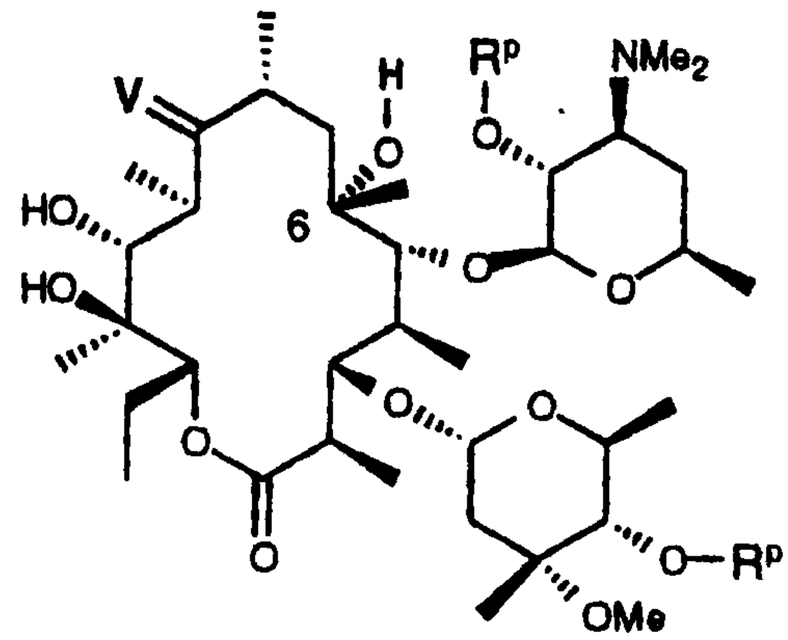
(c) substituted aryl,

(d) heteroaryl, and

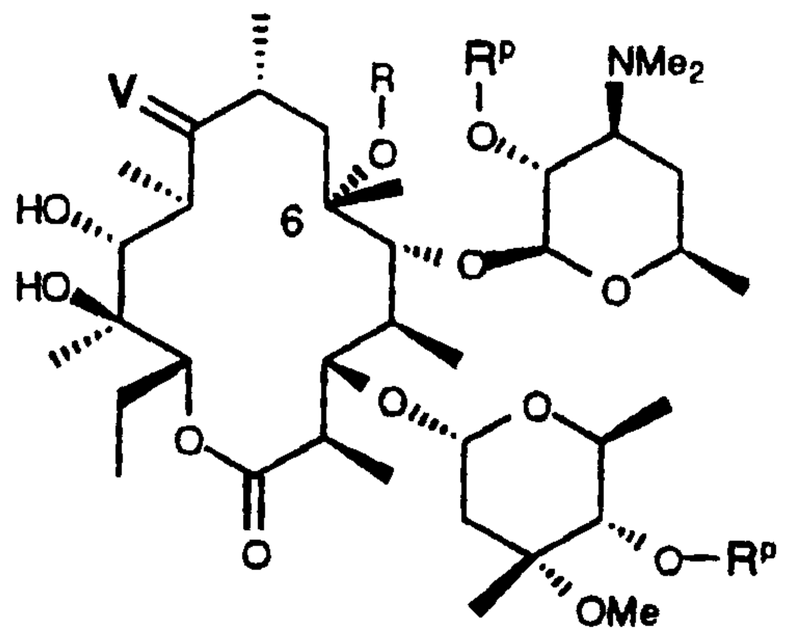
(e) substituted heteroaryl;

in a method comprising:

(a) treating a compound having the formula:

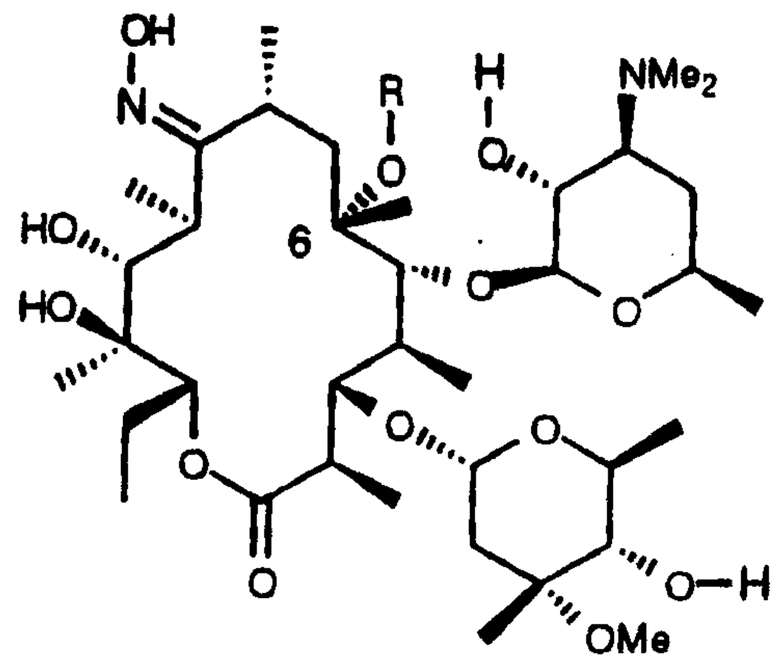


wherein RP is trimethylsilyl and V is O-(1-isopropoxycyclohexyl) oxime with potassium hydroxide in a mixture of THF and DMSO with an alkylating agent to give a compound having the fomula:



wherein V and RP are as defined above and R is the "alkyl group" derived from the corresponding alkylating agent;

(b) deprotecting of the 2'- and 4'-hydroxyl groups using acetic acid in water and acetonitrile to give a compound having the formula:



; and

(c) deoximinating the 9-oxime using $NaHSO_3$ and formic acid in ethanol-water to give the desired product.

23. A process according to claim 20 or 21, wherein in step a) said base is potassium hydroxide, cesium hydroxide, tetraalkylammonium hydroxide, sodium hydride, potassium hydride, potassium isopropoxide, potassium tert-butoxide or potassium isobutoxide.

24. A process as claimed in claim 20, 21 or 23, wherein in step a) said aprotic solvent is dimethylsulfoxide, diethylsulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, a mixture thereof or a mixture of one of these solvents with ether, tetrahydrofuran, 1,2-dimethoxyethane, acetonitrile, ethyl acetate or acetone.

25. A process as claimed in any one of claims 20, 21, 23 or 24, wherein in step a) said alkylating agent is allyl bromide, propargyl bromide, benzyl bromide, 2-fluoroethyl bromide, 4-nitrobenzyl bromide, 4-chlorobenzyl bromide, 4-methoxybenzyl bromide, α-bromo-p-tolunitrile, cinnamyl bromide, methyl 4-bromocrotonate, crotyl bromide, 1-bromo-2-pentene, 3-bromo- 1-propenyl phenyl sulfone, 3-bromo- 1-trimethylsilyl-1-propyne, 3-bromo-2-octyne, 1-bromo-2-butyne, 2-picolyl chloride, 3-picolyl chloride, 4-picolyl chloride, 4-bromomethyl quinoline, bromoacetonitrile, epichlorohydrin, bromofluoromethane, bromonitromethane, methyl bromoacetate, methoxymethyl chloride, bromoacetamide, 2-bromoacetophenone, 1-bromo-2-butanone, bromochloromethane, bromomethyl phenylsulfone, 1,3-dibromo-1-propene, allyl O-tosylate, 3-phenylpropyl-O-trifluoromethane sulfonate or n-butyl-O-methanesulfonate.

26. A process as claimed in any one of claims 20, 21, 23, 24 or 25, wherein said deprotecting in step b) is with acetic acid in water and acetronitrile.

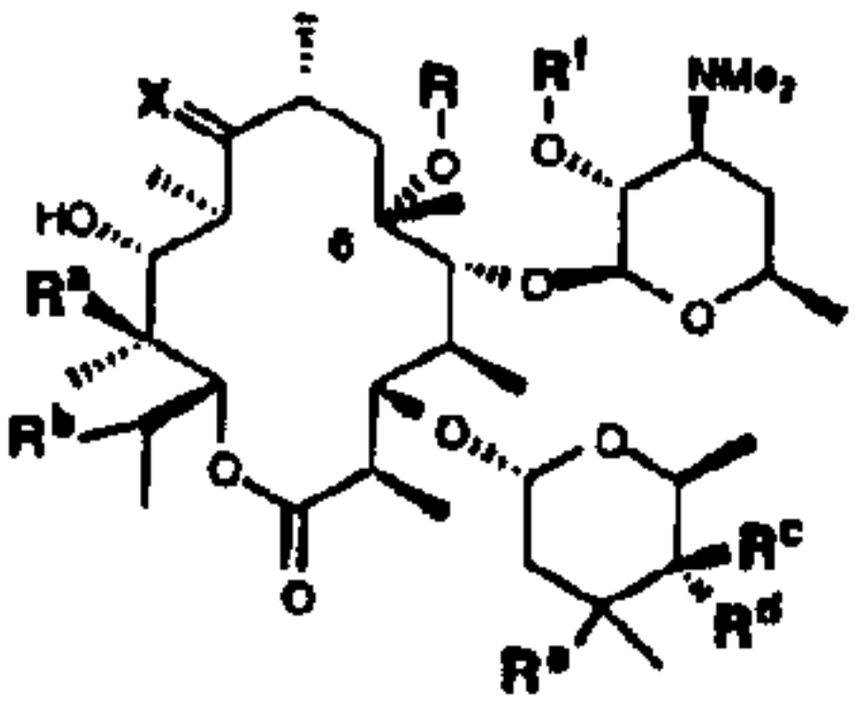
27. A process as claimed in any one of claims 20 or 21 or 23 to 26, wherein said inorganic sulphur oxide compound in step c) is sodium hydrogen sulfite, sodium pyrosulfate, sodium thiosulfate, sodium sulfate, sodium sulfite, sodium hydrosulfite,

sodium metabisulfite, sodium dithionate, potassium thiosulfate or potassium metabisulfite.

28. A process as claimed in claim 20 or any one of claims 23 to 27, wherein said solvent in step c) is water, methanol, ethanol, propanol, isopropanol, trimethylsilanol or a mixture of one or more thereof.

29. A process as claimed in any one of claims 20 or 21 or 23 to 28, wherein said period in step a) is 1-5 days.

30. A process as in claim 22, wherein in step a) said alkylating agent is allyl bromide, propargyl bromide, benzyl bromide, 2-fluoroethyl bromide, 4-nitrobenzyl bromide, 4-chlorobenzyl bromide, 4-methoxybenzyl bromide, α-bromo-p-tolunitrile, cinnamyl bromide, methyl 4-bromocrotonate, crotyl bromide, 1-bromo-2-pentene, 3-bromo- 1-propenyl phenyl sulfone, 3-bromo- 1-trimethylsilyl-1-propyne, 3-bromo-2-octyne, 1-bromo-2-butyne, 2-picolyl chloride, 3-picolyl chloride, 4-picolyl chloride, 4-bromomethyl quinoline, bromoacetonitrile, epichlorohydrin, bromofluoromethane, bromonitromethane, methyl bromoacetate, methoxymethyl chloride, bromoacetamide, 2-bromoacetophenone, 1-bromo-2-butanone, bromochloromethane, bromomethyl phenylsulfone, 1,3-dibromo-1-propene, allyl O-tosylate, 3-phenylpropyl-O-trifluoromethane sulfonate or n-butyl-O-methanesulfonate.



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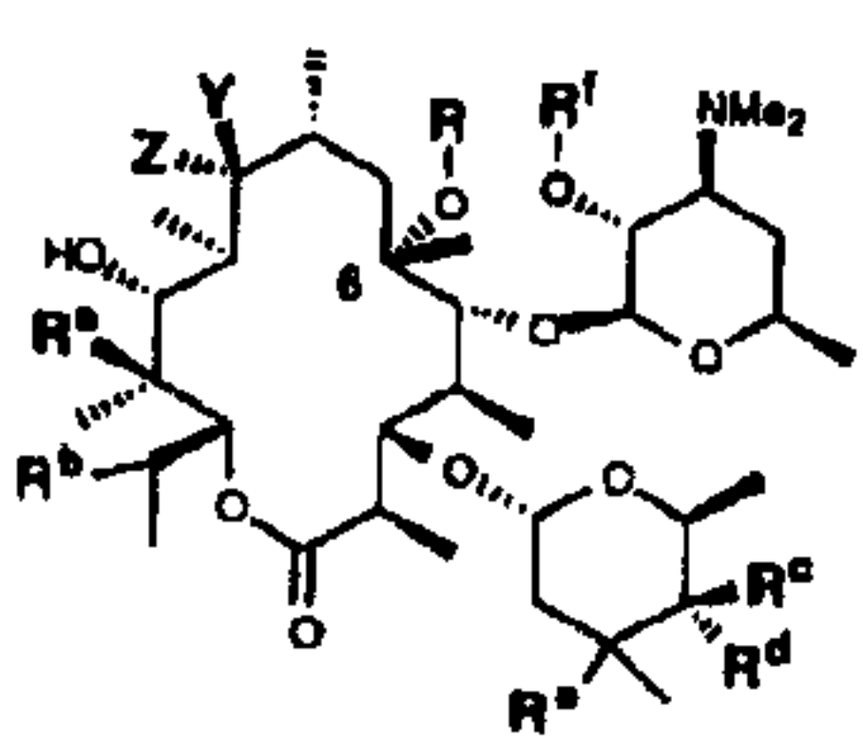

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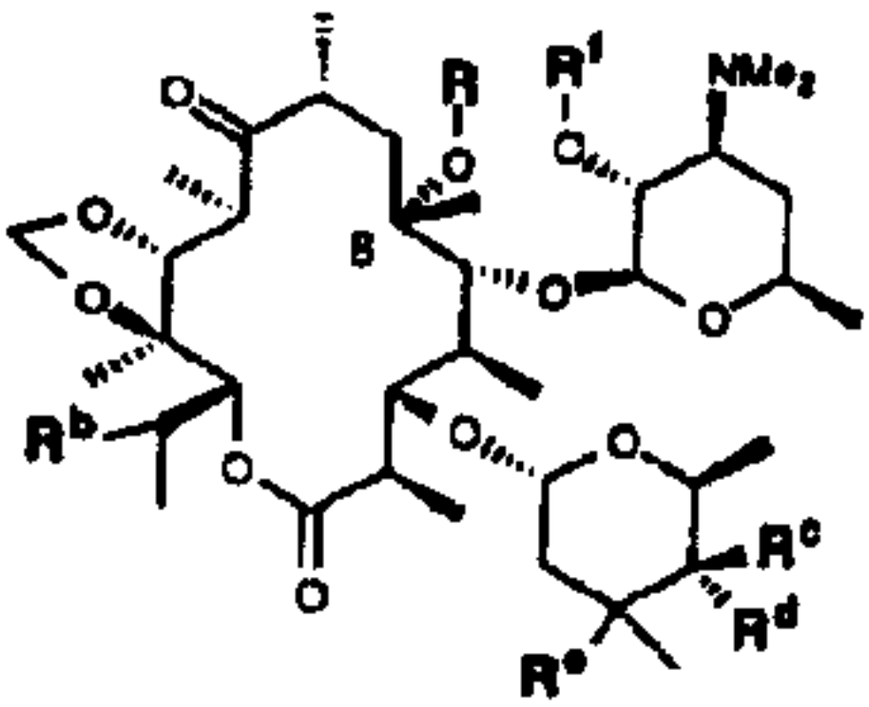

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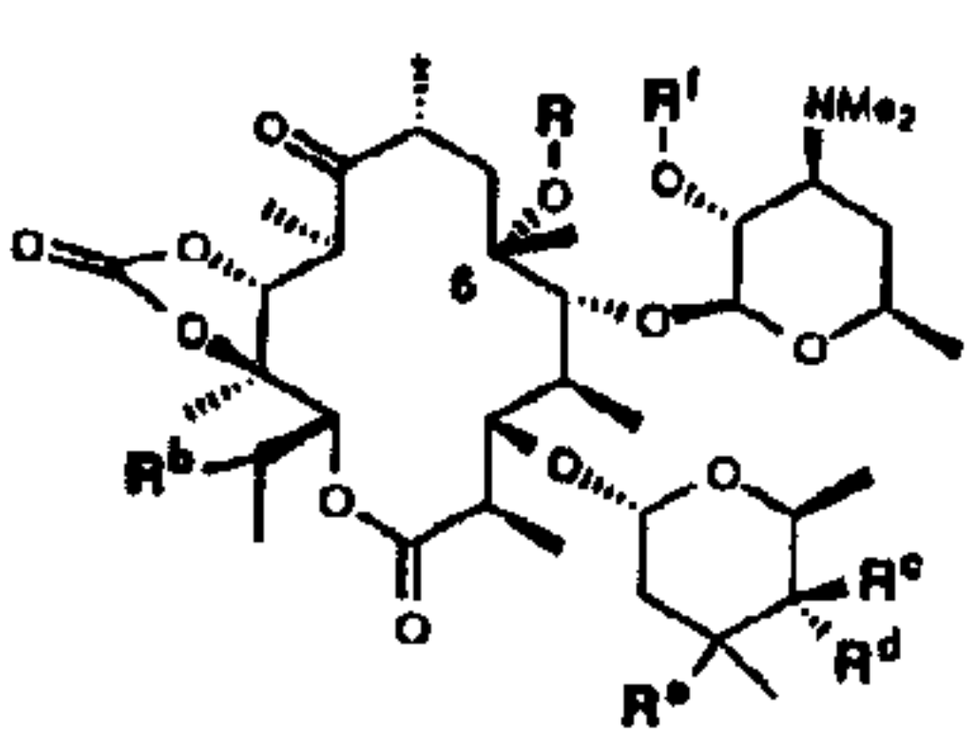

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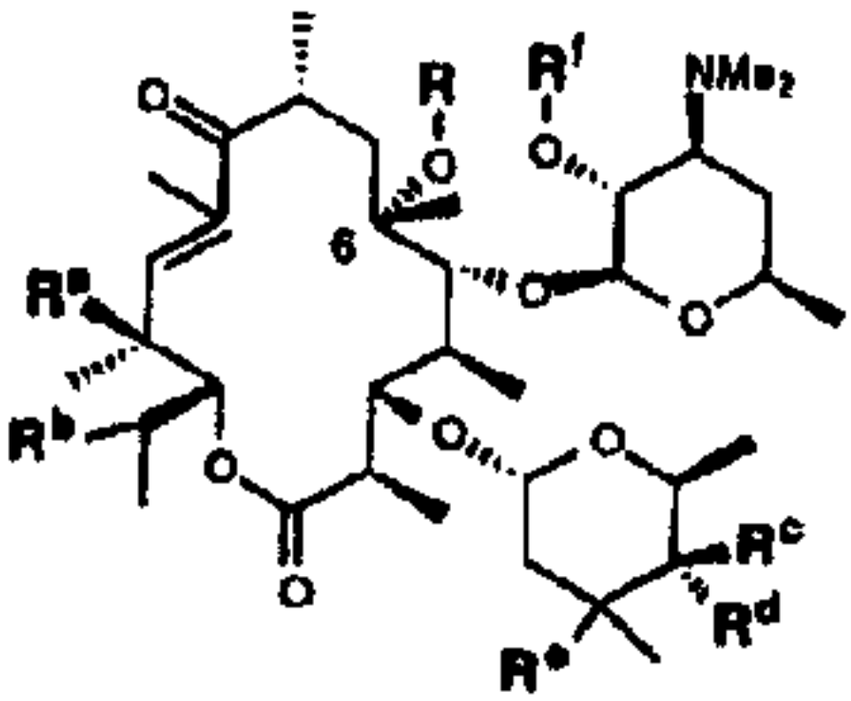

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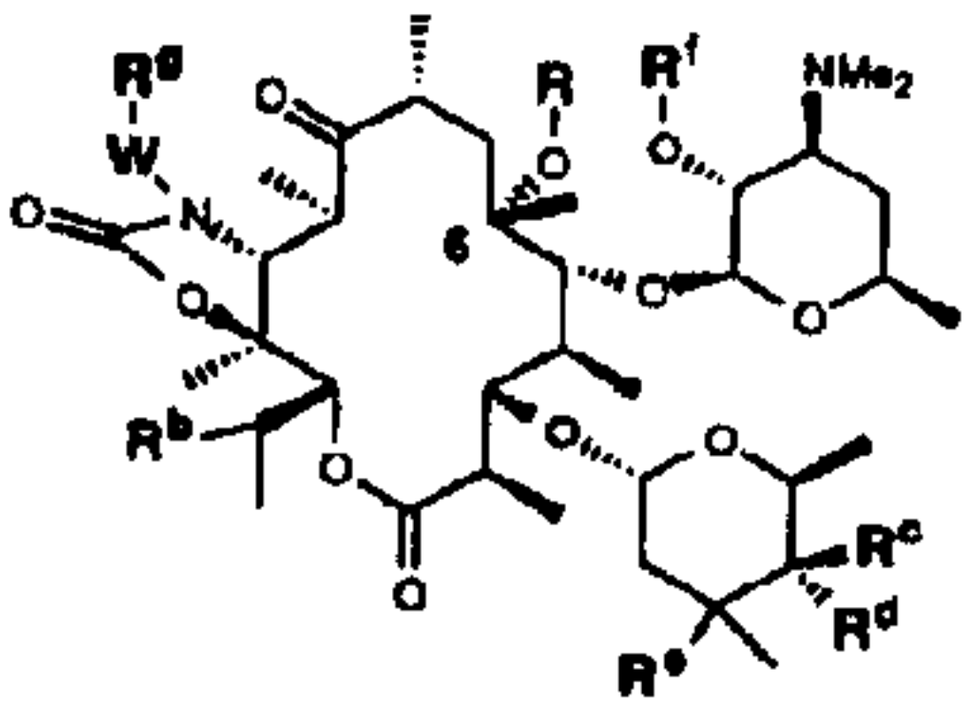

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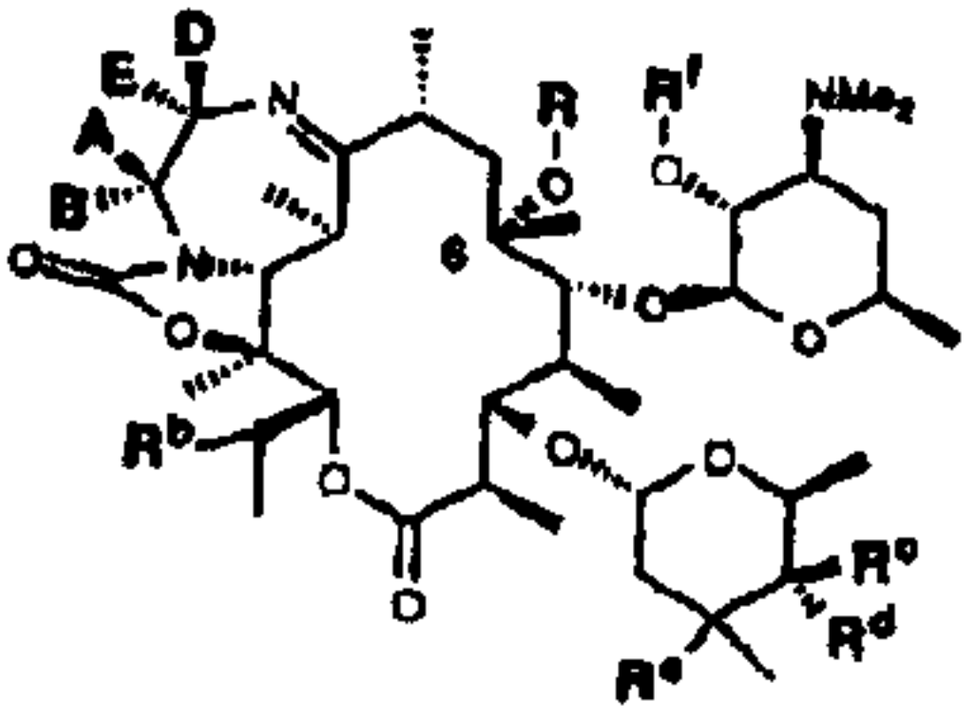

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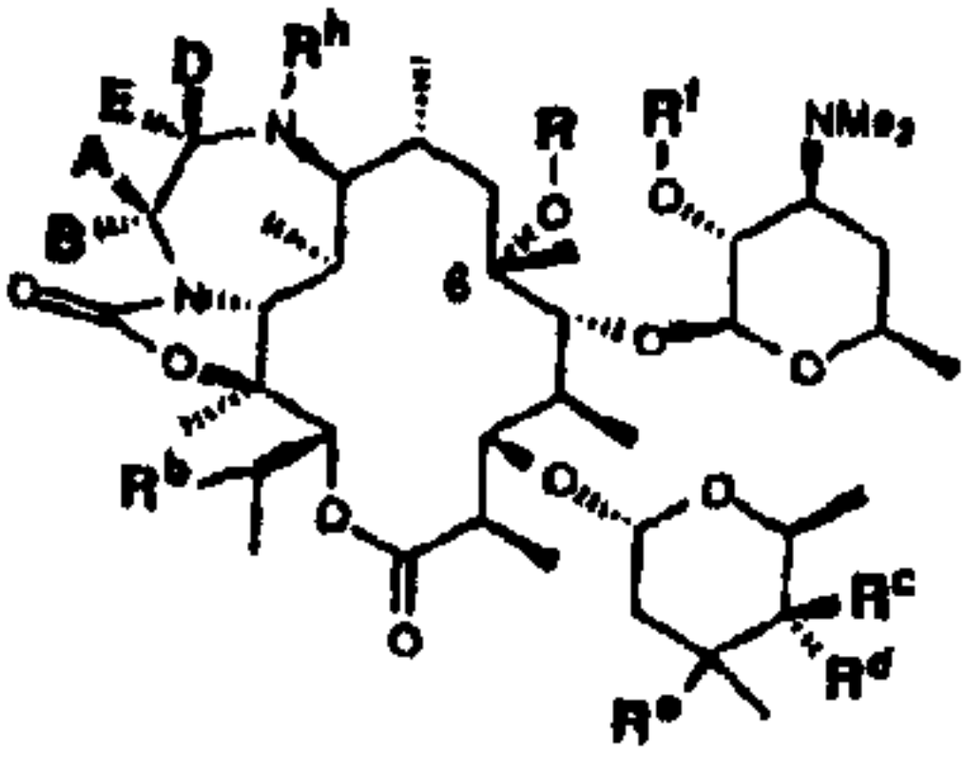

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