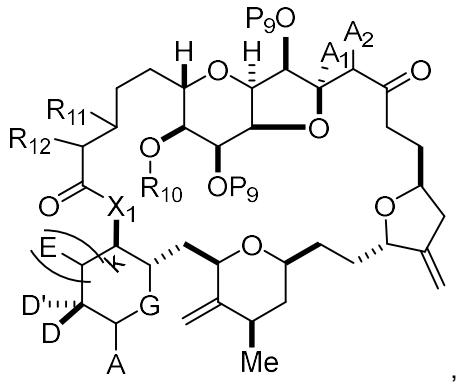
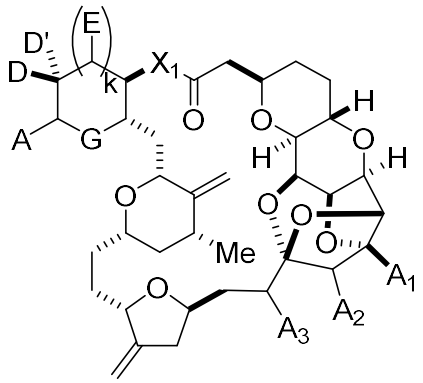


(IVD)

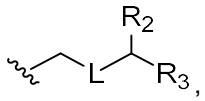
where each of A_1 and A_2 is independently H or –OP", and the remaining variables are as described for the compound of formula (IVC).

In another aspect, the present disclosure refers to a method of preparing a compound of the following formula:



wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1)

wherein

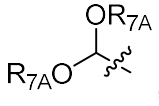
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

R_2 is H, or R_2 and P_1 combine to form a bond;

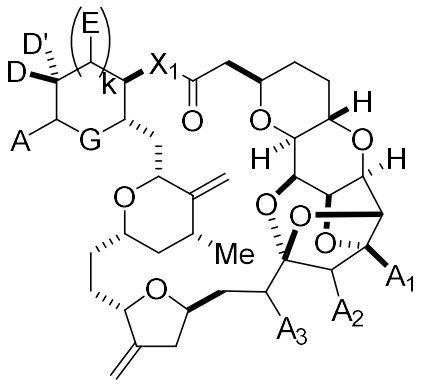
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting

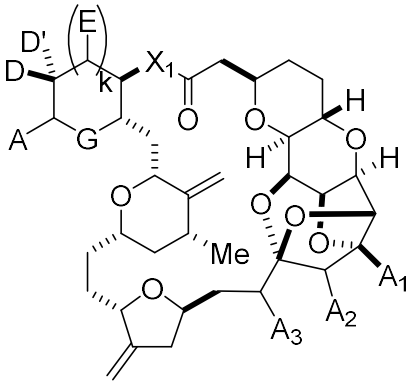
wherein R_7 is –CHO or , wherein each R_{7A} is independently an optionally substituted alkyl; and

(B) producing the compound having the formula



from the compound of formula (IA).

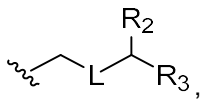
In another example, the present disclosure refers to a method of preparing



a halichondrin macrolide or analog thereof,

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1)

wherein

L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

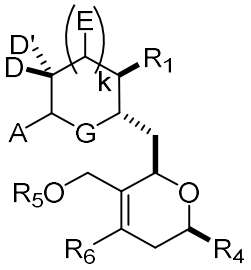
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

What is claimed is:

Claims

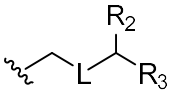
1. A method of preparing a compound of formula (A), the method comprising producing the compound of formula (A) from a compound of formula (B), a compound of formula (C), and R_5OH:
wherein R_5 is optionally substituted acyl;
wherein the compound of formula (A) is:



(A),

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1),

wherein

L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or $–C(O)–$;

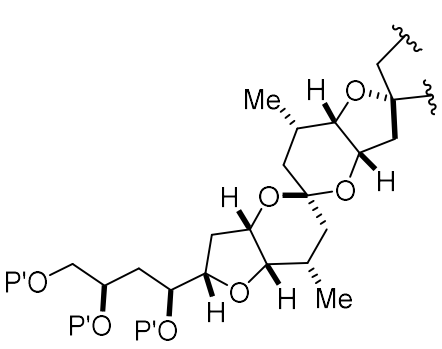
R_2 is H, or R_2 and P_1 combine to form a bond;

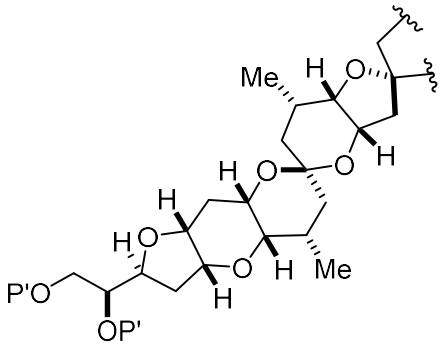
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

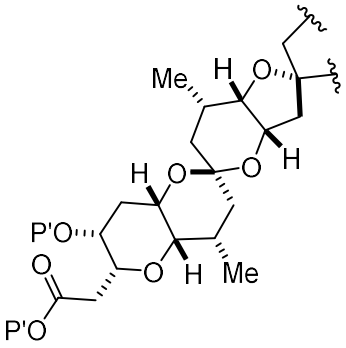
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or

(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,


, and


, wherein each P' is independently H or a hydroxyl protecting group;

E is H, optionally substituted alkyl, or optionally substituted alkoxy;

G is O, S, CH_2, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

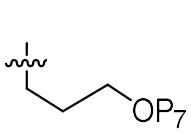
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_B(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl, alkoxyaryl, arylalkyl, alkylaryl, haloarylalkyl, alkylhaloaryl, (alkoxyaryl)alkyl, heterocyclic radical, or heterocyclic radical-alkyl;

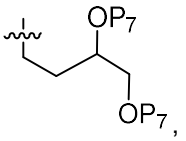
n, when present, is 0, 1, or 2;

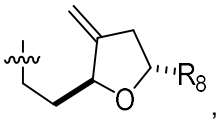
k is 0 or 1;

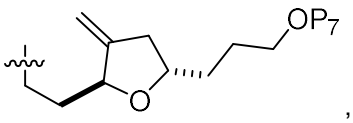
R_1 is $–OP_6$, $–CH(Y)_2$, or $–CH_2(Y)$, wherein P_6 is H or a hydroxyl protecting group;

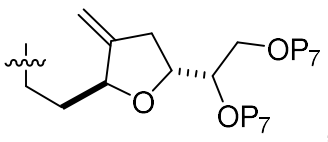
R_4 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl,

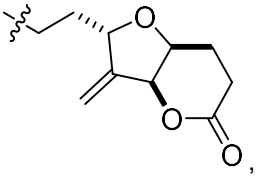


,


,


,


,


, or


,

wherein

each P_7 is independently H or a hydroxyl protecting group; and

R_8 is $–CH_2CH_2–COOR_C$, $–CH=CH–COOR_C$, $–CH_2CH_2–SO_2R_D$, or $–CH=CH–SO_2R_D$;

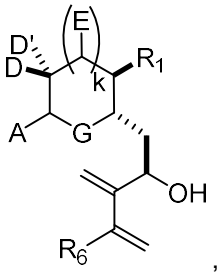
R_6 is H, optionally substituted alkyl, or optionally substituted arylalkyl;

each Y is independently $–COOR_C$ or $–SO_2R_D$;

each R_C, when present, is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl; and

each R_D, when present, is independently optionally substituted aryl or optionally substituted non-enolizable alkyl;

wherein the compound of formula (B) is:



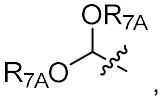
(B)

and

wherein the compound of formula (C) is:

R_4-R_7,

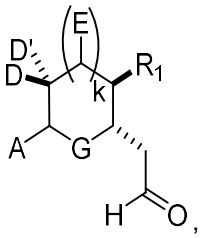
(C)

wherein R_7 is –CHO or 

, wherein each R_{7A} is independently an optionally substituted alkyl.

2. The method of claim 1, wherein the producing the compound of formula (A) comprises reacting the compound of formula (B), the compound of formula (C), R_5OH, and a Lewis acid; and/or wherein the compound of formula (B) is produced by reacting a compound of formula (D), a compound of formula (E), and a second Lewis acid,

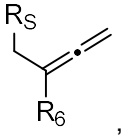
wherein the compound of formula (D) is:



(D)

and

where the compound of formula (E) is:



(E)

where R_S is silyl.

3. The method of claim 2, wherein the Lewis acid or second Lewis acid is an oxophilic Lewis acid.

4. The method of claim 3, wherein the oxophilic Lewis acid is boron trifluoride or a solvate thereof.

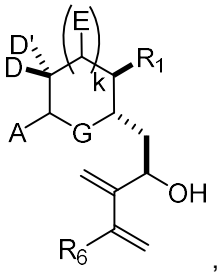
5. The method of claim 2, wherein:

the Lewis acid and the second Lewis acid are the same; and/or

the preparing the compound of formula (B) and the preparing the compound of formula (A) are performed as a single-pot transformation; and/or

the product of reacting the compound of formula (D), the compound of formula (E), and the second Lewis acid is epimerized.

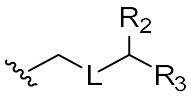
6. A method of preparing a compound of formula (B), the method comprising producing the compound of formula (B) from a compound of formula (D) and a compound of formula (E);
wherein the compound of formula (B) is:



(B)

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1),

wherein

L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or $–C(O)–$;

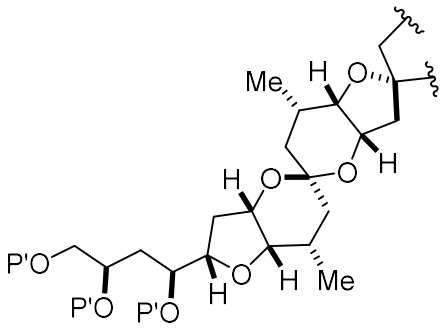
R_2 is H, or R_2 and P_1 combine to form a bond;

(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

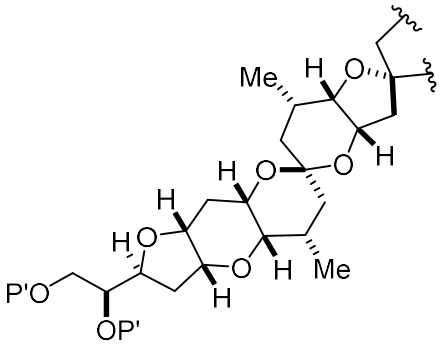
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or

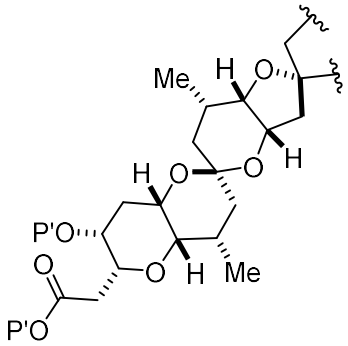
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, wherein each P' is independently H or a hydroxyl protecting group;

E is H, optionally substituted alkyl, or optionally substituted alkoxy;

G is O, S, CH_2, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_B(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl, alkoxyaryl, arylalkyl, alkylaryl, haloarylalkyl, alkylhaloaryl, (alkoxyaryl)alkyl, heterocyclic radical, or heterocyclic radical-alkyl;

n, when present, is 0, 1, or 2;

k is 0 or 1;

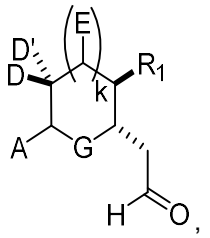
R_1 is $–OP_6$, $–CH(Y)_2$, or $–CH_2(Y)$, wherein P_6 is H or a hydroxyl protecting group;

R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and

Y is independently $–COOR_C$ or $–SO_2R_D$;

R_C, when present, is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl; and

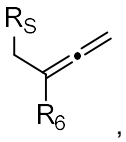
R_D, when present, is optionally substituted aryl or optionally substituted non-enolizable alkyl; wherein the compound of formula (D) is:



(D)

and

wherein the compound of formula (E) is:



(E)

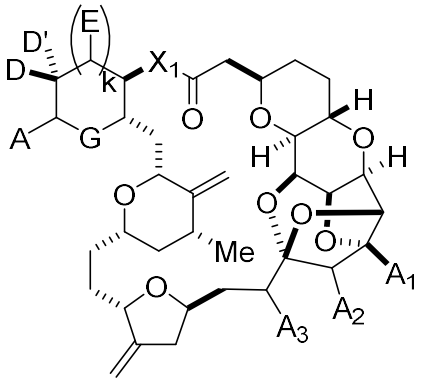
wherein R_S is silyl.

7. The method of claim 6, wherein the producing the compound of formula (B) comprises reacting the compound of formula (D), the compound of formula (E), and a Lewis acid.

8. The method of claim 7, wherein the Lewis acid is an oxophilic Lewis acid; and/or the method further comprises epimerizing the product of reacting the compound of formula (D), the compound of formula (E), and the Lewis acid.

9. The method of claim 8, wherein the oxophilic Lewis acid is boron trifluoride or a solvate thereof.

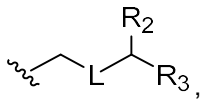
10. A method of preparing a compound of the following formula:



,

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1)

wherein

L is –(CH(OP$_2$))–, –(C(OH)(OP$_2$))–, or –C(O)–;

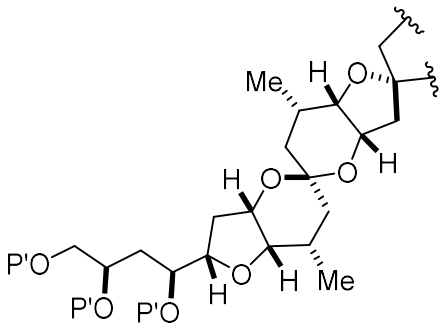
R$_2$ is H, or R$_2$ and P$_1$ combine to form a bond;

(i) R$_3$ is H, and P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

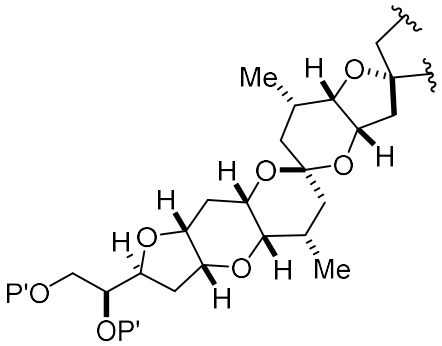
(ii) R$_3$ is –(CH$_2$)$_n$NP$_3$P$_4$, wherein P$_3$ is H or an N-protecting group, and (a) P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P$_4$ is H or an N-protecting group, (b) P$_2$ and P$_4$ combine to form an alkylidene, or (c) each of P$_2$ and P$_4$ is H;

(iii) R$_3$ is –(CH$_2$)$_n$OP$_5$, wherein P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P$_5$ is H, optionally substituted alkyl, or a hydroxyl protecting group; or P$_2$ and P$_5$, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or

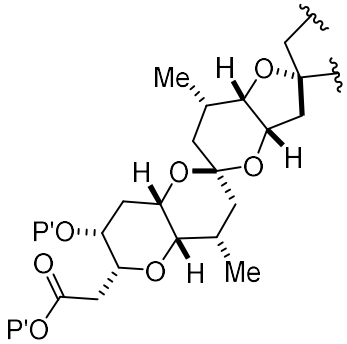
(iv) R$_3$ and P$_2$ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, wherein each P' is independently H or a hydroxyl protecting group;

each of A$_1$, A$_2$, and A$_3$ is independently H or OP", wherein each P" is independently H or a hydroxyl protecting group;

E is H, optionally substituted alkyl, or optionally substituted alkoxy;

G is O, S, CH$_2$, or NR$_N$, wherein R$_N$ is H, an N-protecting group, or optionally substituted alkyl;

each Q$_1$ is independently OR$_A$, SR$_A$, SO$_2$R$_A$, OSO$_2$R$_A$, NR$_B$R$_A$, NR$_B$(CO)R$_A$, NR$_B$(CO)(CO)R$_A$, NR$_B$(CO)NR$_B$R$_A$, NR$_B$(CO)OR$_A$, (CO)OR$_A$, O(CO)R$_A$, (CO)NR$_B$R$_A$, or O(CO)NR$_B$R$_A$, wherein each of R$_A$ and R$_B$ is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl, alkoxyaryl,

arylalkyl, alkylaryl, haloarylalkyl, alkylhaloaryl, (alkoxyaryl)alkyl, heterocyclic radical, or heterocyclic radical-alkyl;

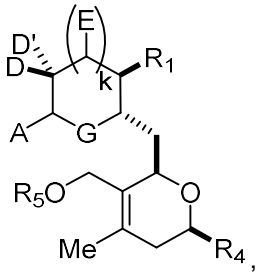
n, when present, is 0, 1, or 2;

k is 0 or 1; and

X_1 is $–CH_2–$ or –O–;

the method comprising:

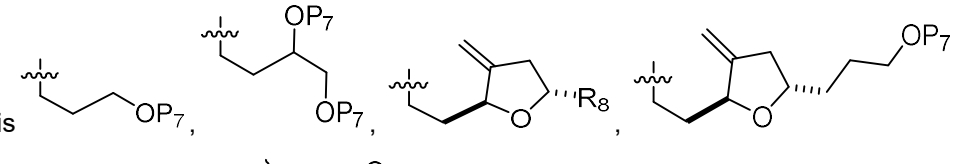
(A) producing a compound of formula (IA) from a compound of formula (IIC), a compound of formula (III), and R_5OH, wherein the compound of formula (IA) is:



(IA)

wherein

R_1 is $–OP_6$, $–CH(Y)_2$, or $–CH_2(Y)$, where P_6 is H or a hydroxyl protecting group, and each Y is independently $–COOR_C$ or $–SO_2R_D$;

R_4 is 

wherein

each P_7 is independently H or a hydroxyl protecting group;

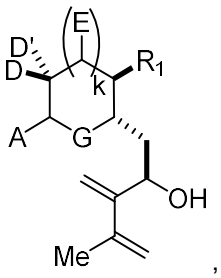
R_8 is $–CH_2CH_2–COOR_C$, $–CH=CH–COOR_C$, $–CH_2CH_2–SO_2R_D$, or $–CH=CH–SO_2R_D$;

each R_C, when present, is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl; and

each R_D, when present, is independently optionally substituted aryl or optionally substituted non-enolizable alkyl; and

R_5 is optionally substituted acyl;

wherein the compound of formula (IIC) is:



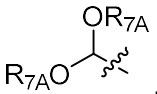
(IIC)

and

wherein the compound of formula (III) is:

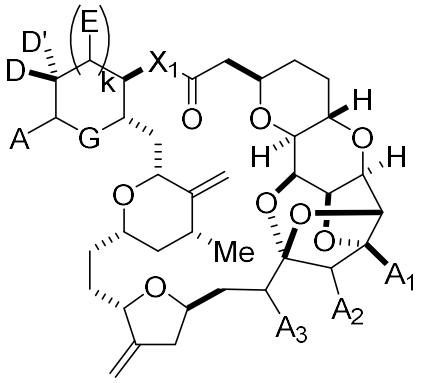
R_4-R_7,

(III)

wherein R_7 is –CHO or 

, wherein each R_{7A} is independently an optionally substituted alkyl; and

(B) producing the compound having the formula:



, from the compound of formula (IA).

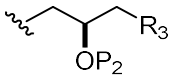
11. The method of any one of claims 1-10, wherein:

(i)

D' is OP_1, wherein P_1 is alkyl; and/or

D is H; and/or

wherein A is of the following structure:



; and/or

k is 0; and/or

R_3 is $–(CH_2)_nNP_3P_4$ or $–(CH_2)_nOP_5$, wherein n is 0; and/or

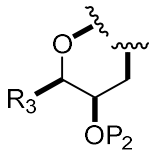
G is O;

or

(ii)

D' is H; and/or

A and D combine to form the following structure:



,

wherein, the bond to oxygen atom originates at the carbon atom, to which D is attached in formula (IA), and

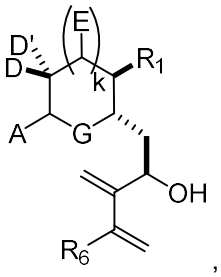
wherein R_3 is $–(CH_2)_nNP_3P_4$ or $–(CH_2)_nOP_5$, wherein n is 2; and/or

k is 1, and E is optionally substituted alkyl; and/or

G is O.

12. A compound of

(1) formula (II):

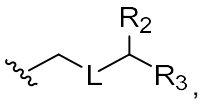


,

(II)

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



,

(1)

wherein

L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

R_2 is H, or R_2 and P_1 combine to form a bond;

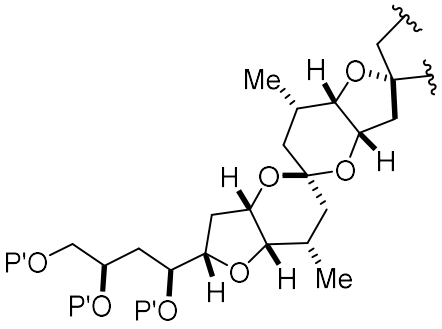
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

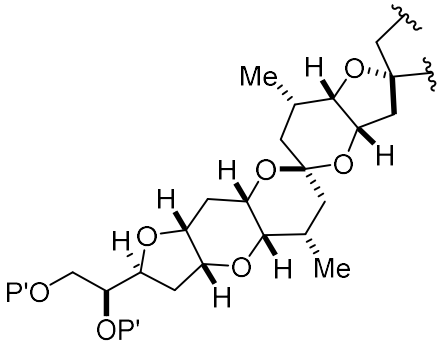
(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting

group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or

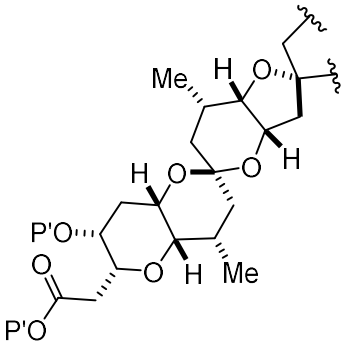
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, wherein each P' is independently H or a hydroxyl protecting group;

E is H, optionally substituted alkyl, or optionally substituted alkoxy;

G is O, S, CH_2, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_B(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl, alkoxyaryl, arylalkyl, alkylaryl, haloarylalkyl, alkylhaloaryl, (alkoxyaryl)alkyl, heterocyclic radical, or heterocyclic radical-alkyl;

n, when present, is 0, 1, or 2;

k is 0 or 1;

R_1 is $–OP_6$, $–CH(Y)_2$, or $–CH_2(Y)$, wherein P_6 is H or a hydroxyl protecting group;

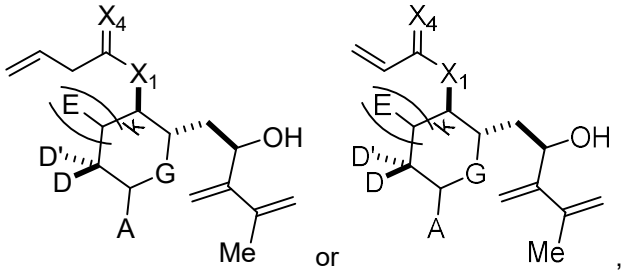
R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and

Y is independently $–COOR_C$ or $–SO_2R_D$;

R_C, when present, is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl; and

R_D, when present, is optionally substituted aryl or optionally substituted non-enolizable alkyl;

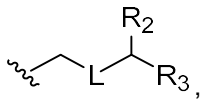
(2) formula (IIE) or (IIG):



(IIE) (IIG)

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1)

wherein

L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

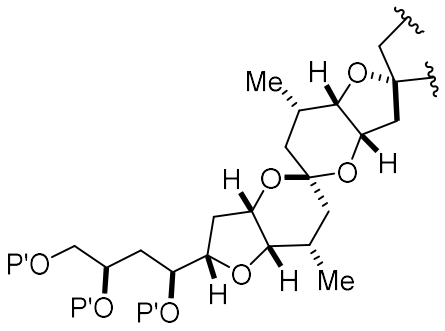
R_2 is H, or R_2 and P_1 combine to form a bond;

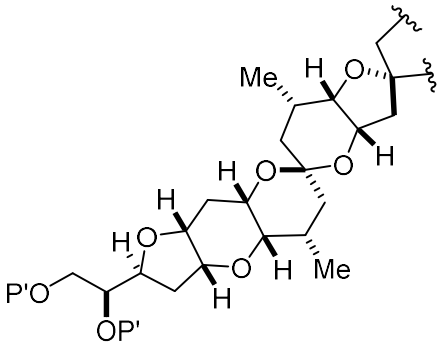
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

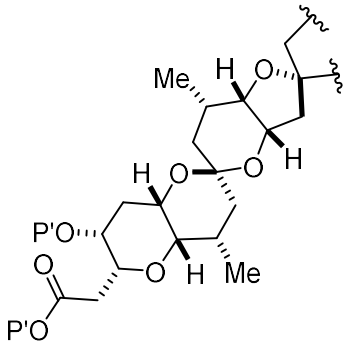
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or

(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,


, and


, wherein each P' is independently H or a hydroxyl protecting group;

E is H, optionally substituted alkyl, or optionally substituted alkoxy;

G is O, S, CH_2, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_B(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl, alkoxyaryl, arylalkyl, alkylaryl, haloarylalkyl, alkylhaloaryl, (alkoxyaryl)alkyl, heterocyclic radical, or heterocyclic radical-alkyl;

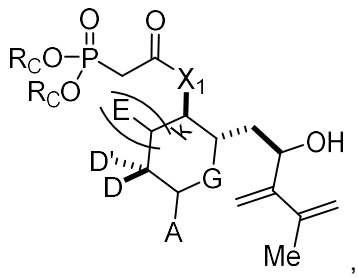
n, when present, is 0, 1, or 2;

k is 0 or 1;

X_1 is $–CH_2–$ or –O–; and

X_4 is oxo, or X_4, together with the atom to which it is attached, is $–(CH(OP_{12}))–$, where P_{12} is H or a hydroxyl protecting group;

(3) formula (IIi):

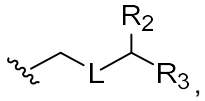


,

(IIi)

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1)

wherein

L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

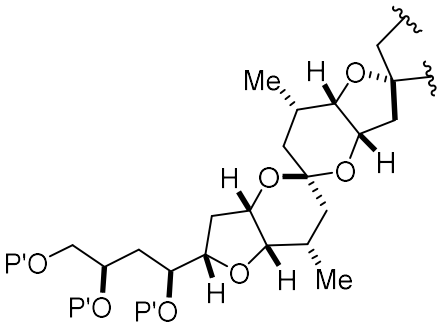
R_2 is H, or R_2 and P_1 combine to form a bond;

(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

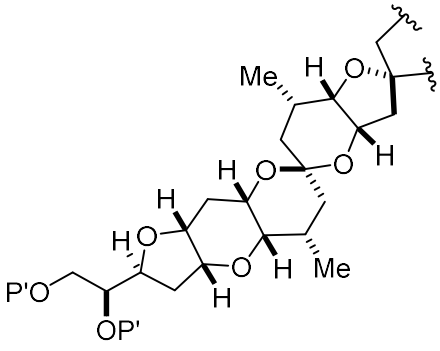
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or

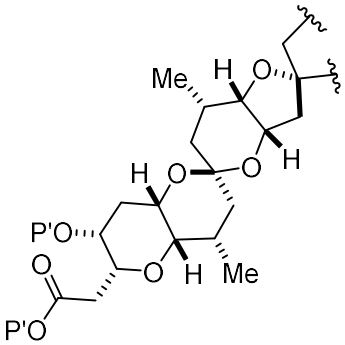
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, wherein each P' is independently H or a hydroxyl protecting group;

E is H, optionally substituted alkyl, or optionally substituted alkoxy;

G is O, S, CH_2, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_B(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl, alkoxyaryl, arylalkyl, alkylaryl, haloarylalkyl, alkylhaloaryl, (alkoxyaryl)alkyl, heterocyclic radical, or heterocyclic radical-alkyl;

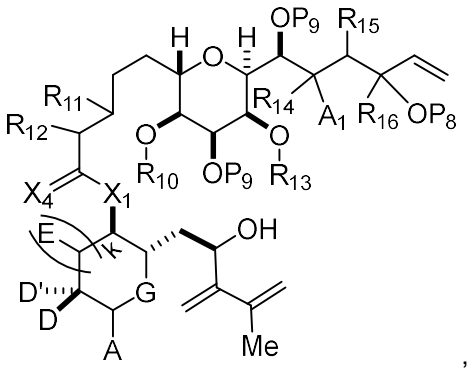
n, when present, is 0, 1, or 2;

k is 0 or 1;

each R_C is indepenedently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl; and

X_1 is $–CH_2–$ or –O–;

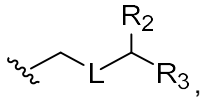
(4) formula (IVAb):



(IVAb)

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1)

wherein

L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

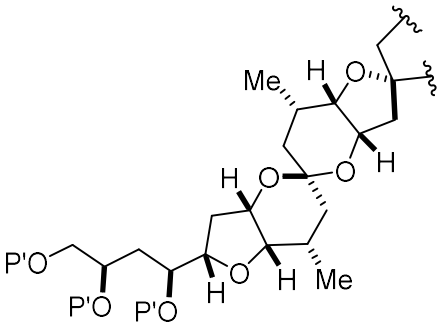
R_2 is H, or R_2 and P_1 combine to form a bond;

(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

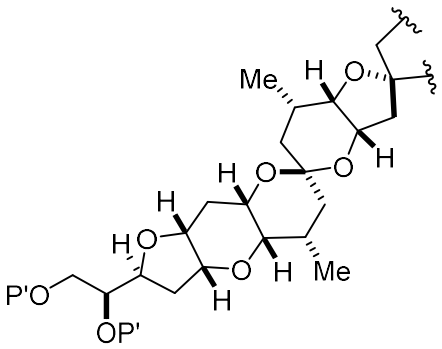
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or

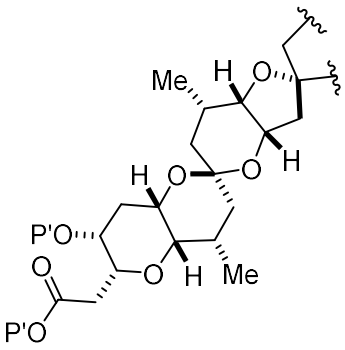
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, wherein each P' is independently H or a hydroxyl protecting group;

E is H, optionally substituted alkyl, or optionally substituted alkoxy;

G is O, S, CH_2, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_B(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl, alkoxyaryl, arylalkyl, alkylaryl, haloarylalkyl, alkylhaloaryl, (alkoxyaryl)alkyl, heterocyclic radical, or heterocyclic radical-alkyl;

n, when present, is 0, 1, or 2;

k is 0 or 1;

X_1 is $–CH_2–$, $–CH(Y)–$, $–C(Y)_2–$, or –O–, wherein each Y is independently $–COOR_C$ or $–SO_2R_D$;;

each R_C, when present, is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

each R_D, when present, is independently optionally substituted aryl or optionally substituted non-enolizable alkyl;

X_4 is oxo, or X_4, together with the atom to which it is attached, is $–(CH(OP_{12}))–$, where P_{12} is H or a hydroxyl protecting group;

each P_9 is independently a hydroxyl protecting group;

(a1) R_{10} is H or a hydroxyl protecting group, R_{11} is alkyl ether, and R_{12} is H;

(a2) R_{10} is H or a hydroxyl protecting group, and R_{11} and R_{12} combine to form a double bond;

or

(a3) R_{10} and R_{11} combine to form a bond, and R_{12} is H;

(b1) A_1 and R_{14} combine to form oxo, R_{13} is H or a hydroxyl protecting group, and R_{15} is H;

or

(b2) A_1 is H or –OP", and:

(i) R_{13} is H or a hydroxyl protecting group, and R_{14} and R_{15} combine to form a double bond;

or

(ii) R_{13} and R_{14} combine to form a bond, and R_{15} is H or –OP"; and

(c1) R_{16} is H, and P_8 is H or a hydroxyl protecting group;

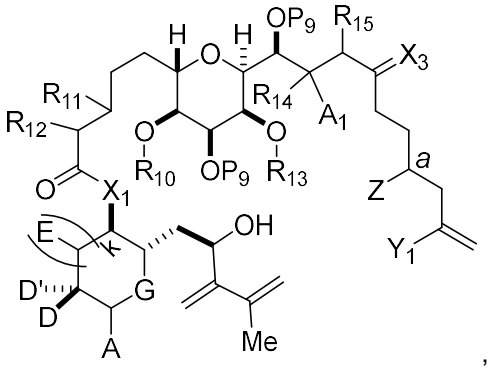
or

(c2) R_{16} and P_8 combine to form a double bond;

and

each P", when present, is independently H or a hydroxyl protecting group;

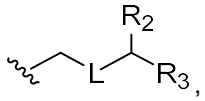
(5) formula (VAb):



(VAb)

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1)

wherein

L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

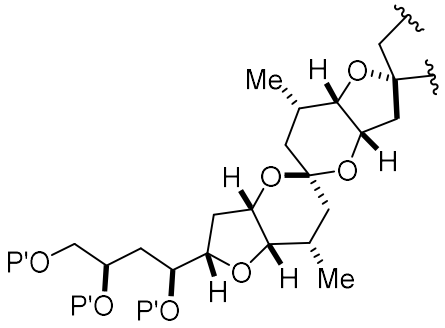
R_2 is H, or R_2 and P_1 combine to form a bond;

(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

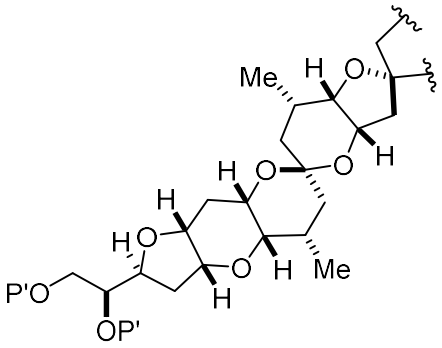
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or

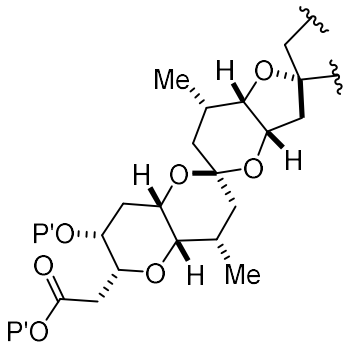
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, wherein each P' is independently H or a hydroxyl protecting group;

E is H, optionally substituted alkyl, or optionally substituted alkoxy;

G is O, S, CH_2, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_B(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl, alkoxyaryl, arylalkyl, alkylaryl, haloarylalkyl, alkylhaloaryl, (alkoxyaryl)alkyl, heterocyclic radical, or heterocyclic radical-alkyl;

n, when present, is 0, 1, or 2;

k is 0 or 1;

a designates (*R*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide; or *a* designates (*S*)-stereogenic center, and Z is OR_{16}, where R_{16} is a hydroxyl protecting group;

X_1 is $–CH_2–$, $–CH(Y)–$, $–C(Y)_2–$, or $–O–$, where each Y is independently $–COOR_C$ or $–SO_2R_D$;

each P_9 is independently a hydroxyl protecting group, and X_3 is oxo; or both P_9 groups and X_3, together with the atoms to which each is attached, combine to form ketal;

Y_1 is iodide, bromide, or trifluoromethanesulfonate;

each R_C, when present, is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl; and

each R_D, when present, is independently optionally substituted aryl or optionally substituted non-enolizable alkyl;

(a1) R_{10} is a hydroxyl protecting group, R_{11} is alkyl ether, and R_{12} is H;

(a2) R_{10} is a hydroxyl protecting group, and R_{11} and R_{12} combine to form a double bond;

or

(a3) R_{10} and R_{11} combine to form a bond, and R_{12} is H;

(b1) A_1 and R_{14} combine to form oxo, R_{13} is a hydroxyl protecting group, and R_{15} is H;

or

(b2) A_1 is H or –OP", and:

(i) R_{13} is a hydroxyl protecting group, and R_{14} and R_{15} combine to form a double bond;

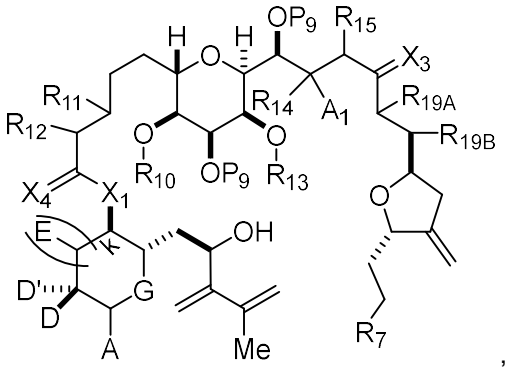
or

(ii) R_{13} and R_{14} combine to form a bond, and R_{15} is H or –OP";

and

each P" is independently a hydroxyl protecting group;

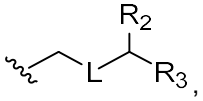
(6) formula (IXD):



(IXD)

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1)

wherein

L is –(CH(OP_2))–, –(C(OH)(OP_2))–, or –C(O)–;

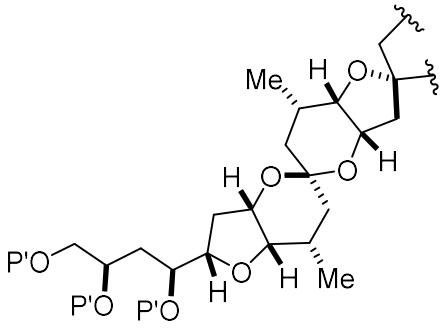
R_2 is H, or R_2 and P_1 combine to form a bond;

(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

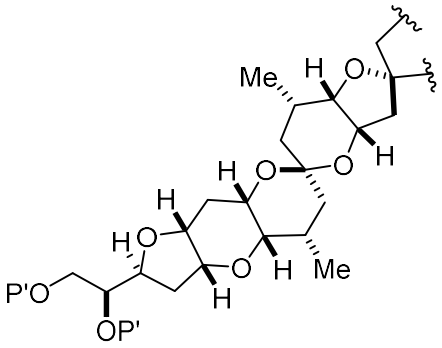
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or

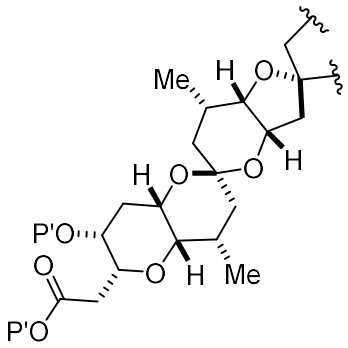
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, wherein each P' is independently H or a hydroxyl protecting group;

E is H, optionally substituted alkyl, or optionally substituted alkoxy;

G is O, S, CH_2, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_B(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl, alkoxyaryl, arylalkyl, alkylaryl, haloarylalkyl, alkylhaloaryl, (alkoxyaryl)alkyl, heterocyclic radical, or heterocyclic radical-alkyl;

n, when present, is 0, 1, or 2;

k is 0 or 1;

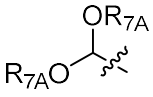
X_1 is $–CH_2–$, $–CH(Y)–$, $–C(Y)_2–$, or –O–, each Y is independently $–COOR_C$ or $–SO_2R_D$;

each R_C, when present, is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

each R_D, when present, is independently optionally substituted aryl or optionally substituted non-enolizable alkyl;

X_4 is oxo, or X_4, together with the atom to which it is attached, is –(CH(OP_{12}))–, where P_{12} is H or a hydroxyl protecting group;

R_7 is –CHO, –CH_2OP_A or



, wherein each R_{7A} is independently an optionally substituted alkyl;

(i) R_{10} is a hydroxyl protecting group, R_{11} is alkyl ether, and R_{12} is H;

(ii) R_{10} is a hydroxyl protecting group, and R_{11} and R_{12} combine to form a double bond; or

(iii) R_{10} and R_{11} combine to form a bond, and R_{12} is H;

A_1 and R_{14} combine to form oxo, R_{13} is H or a hydroxyl protecting group, and R_{15} is H;

or

A_1 is H or -OP", and

(i) R_{13} is H or a hydroxyl protecting group, and R_{14} and R_{15}, together with the atoms to which each is attached, combine to form a double bond;

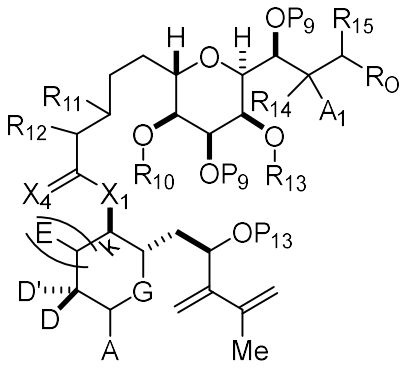
or

(ii) R_{13} and R_{14} combine to form a bond, and R_{15} is H or -OP"; each P_9 is independently H or a hydroxyl protecting group,

each P_9 is independently a hydroxyl protecting group, and X_3 is oxo, or X_3, together with the atom to which it is attached, combines to form –(CH(OP_{11}))–, where P_{11} is H or a hydroxyl protecting group; or both P_9 and X_3, together with the atoms to which each is attached, combine to form a ketal; and

R_{19A} is H, -OP", or Y, and R_{19B} is H; or R_{19A} and R_{19B}, together with the atoms to which each is attached, combine to form a double bond; or

(7) formula (IXF):

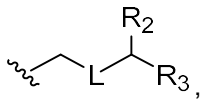


,

(IXF)

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1)

wherein

L is –(CH(OP$_2$))–, –(C(OH)(OP$_2$))–, or –C(O)–;

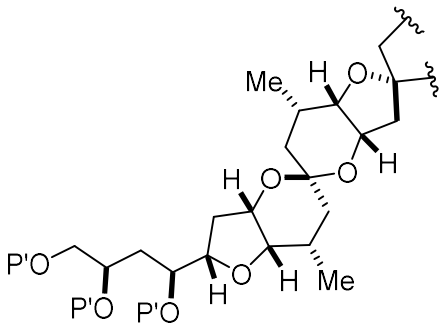
R$_2$ is H, or R$_2$ and P$_1$ combine to form a bond;

(i) R$_3$ is H, and P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

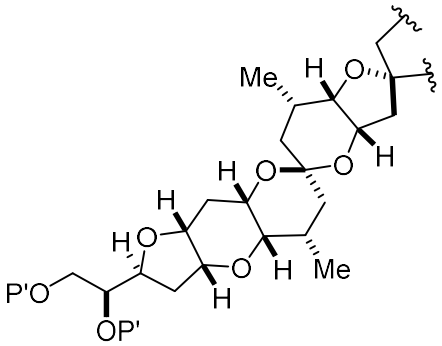
(ii) R$_3$ is –(CH$_2$)$_n$NP$_3$P$_4$, wherein P$_3$ is H or an N-protecting group, and (a) P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P$_4$ is H or an N-protecting group, (b) P$_2$ and P$_4$ combine to form an alkylidene, or (c) each of P$_2$ and P$_4$ is H;

(iii) R$_3$ is –(CH$_2$)$_n$OP$_5$, wherein P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P$_5$ is H, optionally substituted alkyl, or a hydroxyl protecting group; or P$_2$ and P$_5$, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or

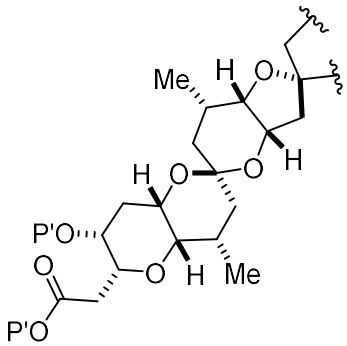
(iv) R$_3$ and P$_2$ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, wherein each P' is independently H or a hydroxyl protecting group;

E is H, optionally substituted alkyl, or optionally substituted alkoxy;

G is O, S, CH$_2$, or NR$_N$, wherein R$_N$ is H, an N-protecting group, or optionally substituted alkyl;

each Q$_1$ is independently OR$_A$, SR$_A$, SO$_2$R$_A$, OSO$_2$R$_A$, NR$_B$R$_A$, NR$_B$(CO)R$_A$, NR$_B$(CO)(CO)R$_A$, NR$_B$(CO)NR$_B$R$_A$, NR$_B$(CO)OR$_A$, (CO)OR$_A$, O(CO)R$_A$, (CO)NR$_B$R$_A$, or O(CO)NR$_B$R$_A$, wherein each of R$_A$ and R$_B$ is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl,

alkoxyaryl, arylalkyl, alkylaryl, haloarylalkyl, alkylhaloaryl, (alkoxyaryl)alkyl, heterocyclic radical, or heterocyclic radical-alkyl;

n, when present, is 0, 1, or 2;

k is 0 or 1;

X_1 is $–CH_2–$, $–CH(Y)–$, $–C(Y)_2–$, or –O–, wherein each Y is independently $–COOR_C$ or $–SO_2R_D$;

X_4 is oxo, or X_4, together with the atom to which it is attached, is $–(CH(OP_{12}))–$, where P_{12} is H or a hydroxyl protecting group;

each R_C, when present, is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

each R_D, when present, is independently optionally substituted aryl or optionally substituted non-enolizable alkyl;

R_O is $–CHO$, $–CH_2OP”$, $–CH=CH_2$, $–CH(OP”)CH_2OP”$, $–C(O)–CH_2P(O)(OR_C)_2$, or halogen;

(i) R_{10} is a hydroxyl protecting group, R_{11} is alkyl ether, and R_{12} is H;

(ii) R_{10} is a hydroxyl protecting group, and R_{11} and R_{12} combine to form a double bond; or

(iii) R_{10} and R_{11} combine to form a bond, and R_{12} is H;

A_1 and R_{14} combine to form oxo, R_{13} is H or a hydroxyl protecting group, and R_{15} is H;

or

A_1 is H or -OP”, and

(i) R_{13} is H or a hydroxyl protecting group, and R_{14} and R_{15}, together with the atoms to which each is attached, combine to form a double bond;

or

(ii) R_{13} and R_{14} combine to form a bond, and R_{15} is H or -OP”; each P_9 is independently H or a hydroxyl protecting group;

and

each of P”, P_9, and P_{13} is independently H or a hydroxyl protecting group.