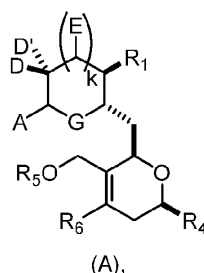


What is claimed is:

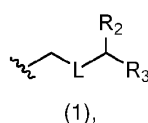
Claims

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:



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):



wherein

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

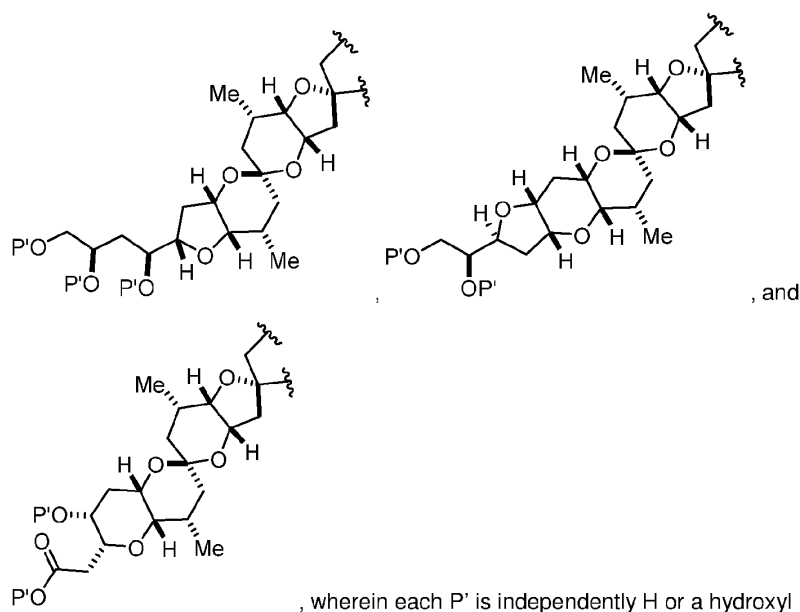
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

(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;

(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:



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

G is O, S, CH₂, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

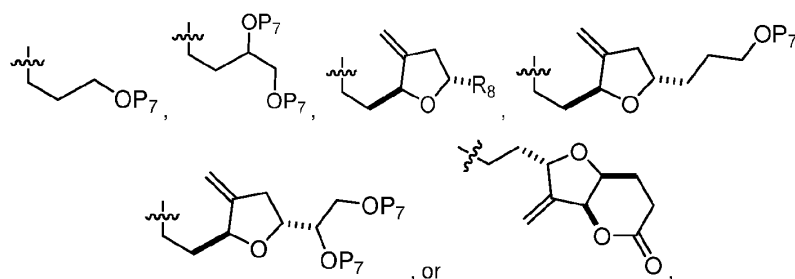
each Q₁ is independently OR_A, SR_A, SO₂R_A, OSO₂R_A, NR_BR_A, NR_B(CO)R_A, NR_B(CO)(CO)R_A, NR_B(CO)NR_BR_A, NR_B(CO)OR_A, (CO)OR_A, O(CO)R_A, (CO)NR_BR_A, or O(CO)NR_BR_A, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl, alkoxyaryl, 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;

R₁ is -OP₆, -CH(Y)₂, or -CH₂(Y), wherein P₆ is H or a hydroxyl protecting group;

R₄ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl,



wherein

each P₇ is independently H or a hydroxyl protecting group; and

R₈ is -CH₂CH₂-COOR_C, -CH=CH-COOR_C, -CH₂CH₂-SO₂R_D, or -CH=CH-SO₂R_D;

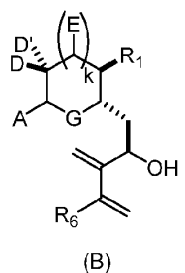
R₆ is H, optionally substituted alkyl, or optionally substituted arylalkyl;

each Y is independently -COOR_C or -SO₂R_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:



and

wherein the compound of formula (C) is:



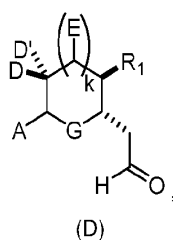
wherein R_7 is $-\text{CHO}$ or $R_{7A}\text{O}-\text{C}(\text{OR}_{7A})_2$, wherein each R_{7A} is independently an optionally substituted alkyl.

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), $R_5\text{OH}$, and a Lewis acid.

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

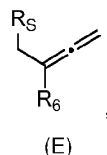
4. The method of claim 3, wherein the oxophilic Lewis acid is boron trifluoride or a solvate thereof.

5. The method of any one of claims 1 to 3, further comprising producing the compound of formula (B) comprising reacting a compound of formula (D), a compound of formula (E), and a second Lewis acid, wherein the compound of formula (D) is:



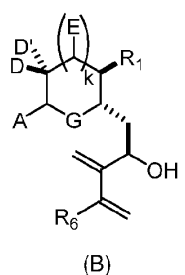
and

where the compound of formula (E) is:



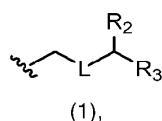
where R₅ is silyl.

6. The method of claim 5, wherein the second Lewis acid is an oxophilic second Lewis acid.
7. The method of claim 6, wherein the oxophilic second Lewis acid is boron trifluoride or a solvate thereof.
8. The method of any one of claims 5 to 7, wherein the Lewis acid and the second Lewis acid are same.
9. The method of any one of claims 5 to 8, wherein the preparing the compound of formula (B) and the preparing the compound of formula (A) are performed as a single-pot transformation.
10. The method of any one of claims 5 to 9, further comprising epimerizing the product of reacting the compound of formula (D), the compound of formula (E), and the second Lewis acid.
11. The method of any one of claims 5 to 10, wherein the preparing the compound of formula (B) and the preparing the compound of formula (A) are performed as a single-pot transformation.
12. 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:



wherein

each of D and D' is independently H, optionally substituted alkyl, or OP₁, provided that only one of D and D' is OP₁, wherein P₁ is H, alkyl, a hydroxyl protecting group, and A is a C₁₋₆ saturated or C₂₋₆ 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 Q₁, or A is a group of formula (1):



wherein

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

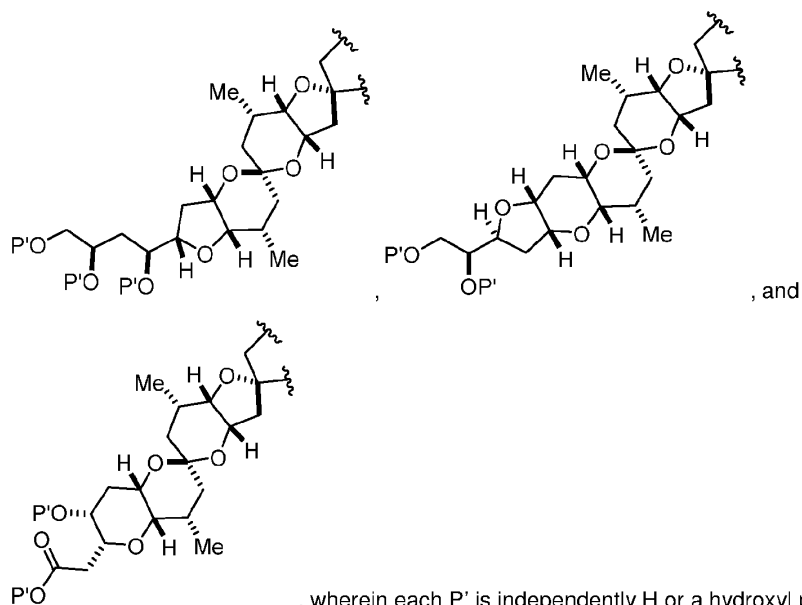
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

(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;

(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:



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 $-\text{OP}_6$, $-\text{CH}(\text{Y})_2$, or $-\text{CH}_2(\text{Y})$, wherein P_6 is H or a hydroxyl protecting group;

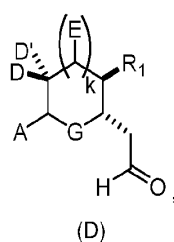
R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and

Y is independently $-\text{COOR}_C$ or $-\text{SO}_2\text{R}_D$;

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

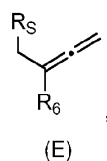
R_D , when present, is optionally substituted aryl or optionally substituted non-enolizable alkyl;

wherein the compound of formula (D) is:



and

wherein the compound of formula (E) is:



wherein R_5 is silyl.

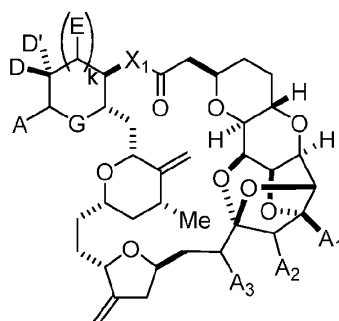
13. The method of claim 12, wherein the producing the compound of formula (B) comprises reacting the compound of formula (D), the compound of formula (E), and a Lewis acid.

14. The method of claim 13, wherein the Lewis acid is an oxophilic Lewis acid.

15. The method of claim 14, wherein the oxophilic Lewis acid is boron trifluoride or a solvate thereof.

17. The method of any one of claims 13 to 15, further comprising epimerizing the product of reacting the compound of formula (D), the compound of formula (E), and the Lewis acid.

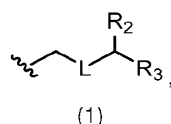
18. A method of preparing



a halichondrin macrolide or analog thereof,

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP₁, provided that only one of D and D' is OP₁, wherein P₁ is H, alkyl, a hydroxyl protecting group, and A is a C₁₋₆ saturated or C₂₋₆ 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 Q₁, or A is a group of formula (1):



wherein

L is $-(\text{CH}(\text{OP}_2))-$, $-(\text{C}(\text{OH})(\text{OP}_2))-$, or $-\text{C}(\text{O})-$;

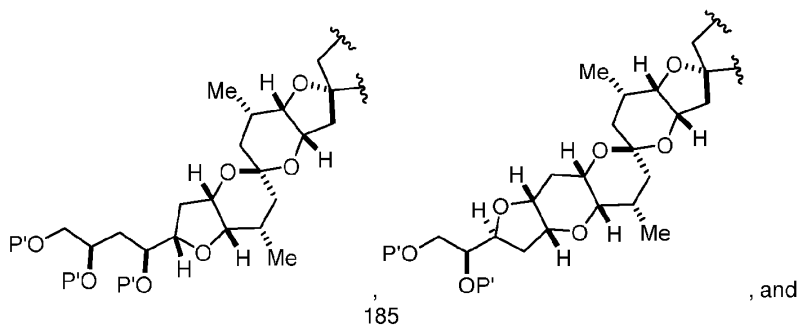
R₂ is H and P₁ is absent, H, alkyl, or a hydroxyl protecting group, or R₂ and P₁ combine to form a bond;

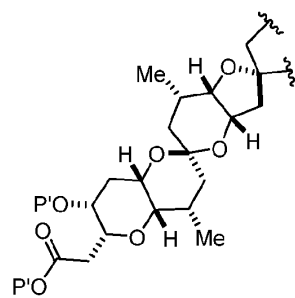
(i) R₃ is H, and P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R₃ is $-(CH_2)_nNP_3P_4$, wherein P₃ is H or an N-protecting group, and (a) P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₄ is H or an N-protecting group, (b) P₂ and P₄ combine to form an alkylidene, or (c) each of P₂ and P₄ is H;

(iii) R₃ is $-(CH_2)_nOP_5$, wherein P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₅ is H, optionally substituted alkyl, or a hydroxyl protecting group; or P₂ and P₅, 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) R₃ and P₂ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:





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

each of A₁, A₂, and A₃ 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, CH₂, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q₁ is independently OR_A, SR_A, SO₂R_A, OSO₂R_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;

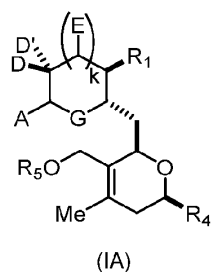
n, when present, is 0, 1, or 2;

k is 0 or 1; and

X₁ is —CH₂— or —O—;

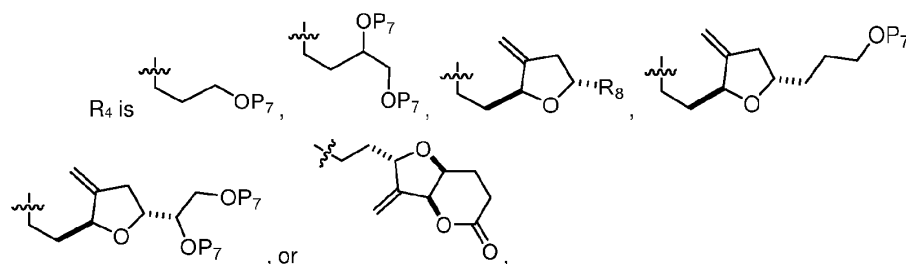
the method comprising:

(A) producing a compound of formula (IA) from a compound of formula (IIC), a compound of formula (III), and R₅OH, wherein the compound of formula (IA) is:



wherein

R₁ is —OP₆, —CH(Y)₂, or —CH₂(Y), where P₆ is H or a hydroxyl protecting group, and each Y is independently —COOR_C or —SO₂R_D;



wherein

each P_7 is independently H or a hydroxyl protecting group;

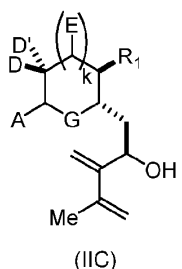
R_8 is $-\text{CH}_2\text{CH}_2-\text{COOR}_C$, $-\text{CH}=\text{CH}-\text{COOR}_C$, $-\text{CH}_2\text{CH}_2-\text{SO}_2\text{R}_D$, or $-\text{CH}=\text{CH}-\text{SO}_2\text{R}_D$;

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:



and

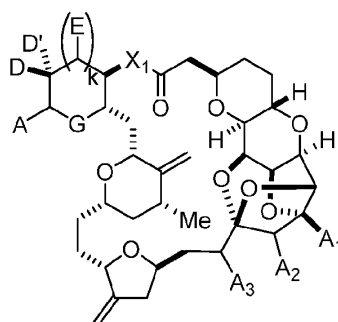
wherein the compound of formula (III) is:



wherein R_7 is $-\text{CHO}$ or $\text{R}_{7A}\text{O}-\text{C}(\text{OR}_{7A})_2$, wherein each R_{7A} is independently an optionally substituted alkyl; and

(B) producing the halichondrin macrolide or analog thereof from the compound of formula (IA).

19. A method of preparing:

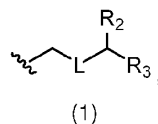


a halichondrin macrolide or analog thereof,

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 Q₁, or A is a group of formula (1):



wherein

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

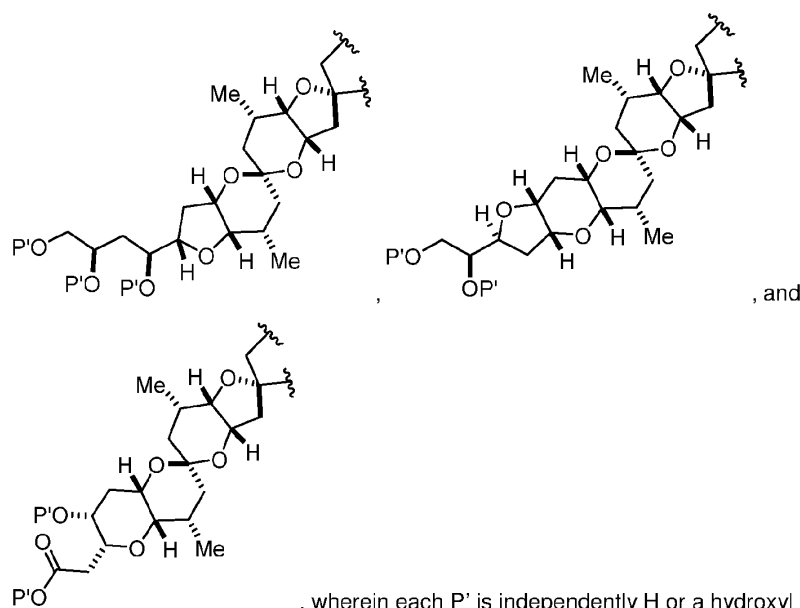
R₂ is H and P₁ is absent, H, alkyl, or a hydroxyl protecting group, or R₂ and P₁ combine to form a bond;

(i) R₃ is H, and P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R₃ is $-(CH_2)_nNP_3P_4$, wherein P₃ is H or an N-protecting group, and (a) P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₄ is H or an N-protecting group, (b) P₂ and P₄ combine to form an alkylidene, or (c) each of P₂ and P₄ is H;

(iii) R₃ is $-(CH_2)_nOP_5$, wherein P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₅ is H, optionally substituted alkyl, or a hydroxyl protecting group; or P₂ and P₅, 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) R₃ and P₂ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



each of A₁, A₂, and A₃ 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, CH₂, 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;

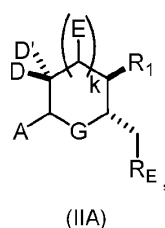
k is 0 or 1; and

X_1 is $-CH_2-$ or $-O-$;

the method comprising:

(A) producing a compound of formula (IVB) from a compound of formula (IIA), a compound of formula (IIB), a compound of formula (IIIA), a compound of formula (IVA), and R_5OH ,

wherein the compound of formula (IIA) is:



wherein

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

R_E is $-CHO$ or $-CH_{(1+m)}(OR_F)_{(2-m)}$,

wherein

m is 1, and R_F is a hydroxyl protecting group,

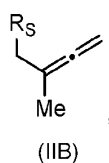
or

m is 0, and

(i) each R_F is independently an alkyl or hydroxyl protecting group, or

(ii) both R_F combine to form an alkylene;

wherein the compound of formula (IIB) is:

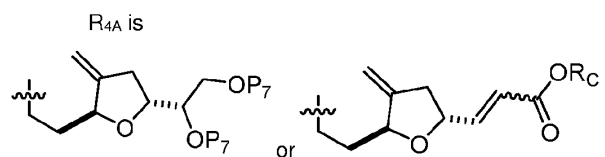


wherein R_S is silyl;

wherein the compound of formula (IIIA) is:

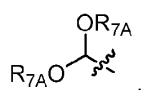


wherein



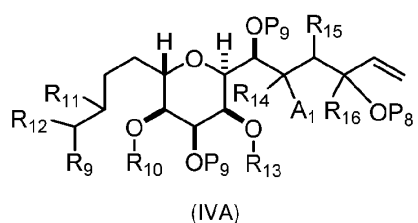
wherein R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl, and each P_7 is independently H or a hydroxyl protecting group;

R_7 is $-\text{CHO}$ or



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

wherein the compound of formula (IVA) is:



wherein

each P_9 is independently a hydroxyl protecting group;

R_9 is $-\text{CHO}$ or $-\text{COOH}$;

(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 $-\text{OP}''$, 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 $-\text{OP}''$; and

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

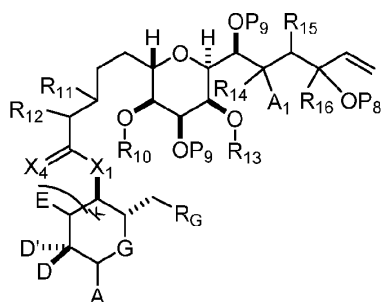
or

(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;

wherein the compound of formula (IVB) is:



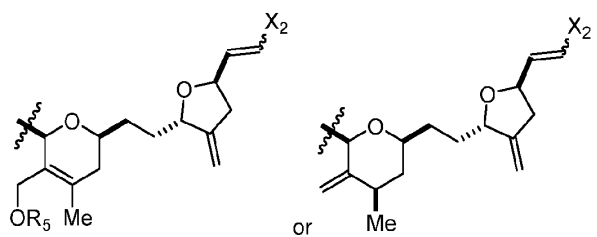
(IVB)

wherein

X_1 is $-O-$, $-C(Y)_2-$, $-CH(Y)-$, or $-CH_2-$;

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; and

R_G is

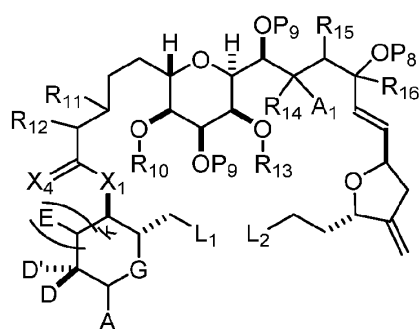


wherein

R_5 is an optionally substituted acyl; and

X_2 is H or $-CH_2-X_{2A}-CH_2-CH=CH_2$, wherein X_{2A} is $-O-$, $-C(R_H)_2-$, or $-NR_I-$, wherein each R_H is independently H or $-COOR_J$, R_I is an *N*-protecting group, and R_J is C_{1-6} alkyl; and

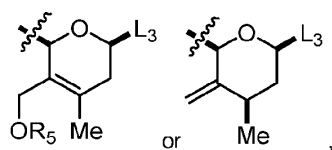
(B) producing a compound of formula (IVC) from the compound of formula (IVB), wherein the compound of formula (IVC) is:



(IVC)

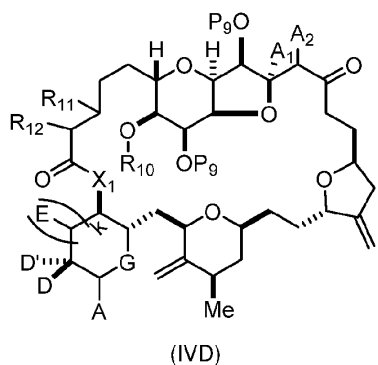
wherein

L_1 is



wherein L₂ and L₃ combine to form a bond;

(C) producing a compound of formula (IVD) from the compound of formula (IVC), wherein the compound of formula (IVD) is:



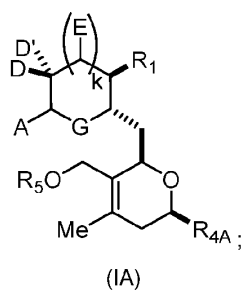
wherein each of A₁ and A₂ is independently H or -OP⁺;

and

(D) producing the halichondrin macrolide or analog thereof from the compound of formula (IVD).

20. The method of claim 19, wherein step (A) comprises:

(E) producing a compound of formula (IA) from the compound of formula (IIA), the compound of formula (IIIA), and R₅OH, wherein the compound of formula (IA) is:



and

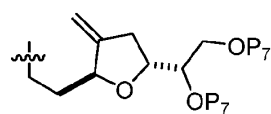
(F) producing the compound of formula (IVB) from the compound of formula (IF) and the compound of formula (IVA).

21. The method of claim 20, wherein step (E) comprises reacting the compound of formula (IIA), the compound of formula (IIIA), R₅OH, and a Lewis acid.

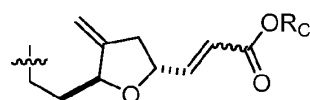
22. The method of claim 21, wherein the Lewis acid is an oxophilic Lewis acid.

23. The method of claim 22, wherein the oxophilic Lewis acid is boron trifluoride or a solvate thereof.

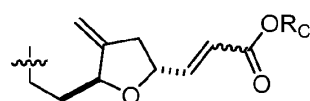
24. The method of any one of claims 20 to 23, wherein step (F) comprises reacting R_{4A} that is



with a glycol cleaving agent, and a Horner-Wadsworth-Emmons reaction with $(R_CO)_2P(O)-CH_2-COOR_C$ to produce R_{4A} that is



25. The method of any one of claims 20 to 24, wherein step (F) comprises reacting R_{4A} that is



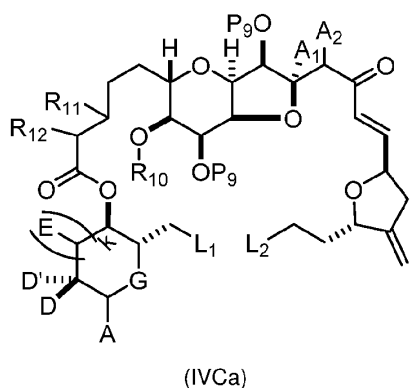
with a 1,2-reducing agent and further reacting with an allyl halide or allyl pseudohalide.

26. The method of any one of claims 19 to 25, wherein R_9 is $-CHO$, X_1 is $-C(Y)_2-$, $-CH(Y)-$, or $-CH_2-$, and step (A) comprises reacting R_9 with R_1 that is $-CH(Y)_2$ or $-CH_2(Y)$ treated with a Brønsted base.

27. The method of any one of claims 19 to 25, wherein X_1 is $-O-$, and step (A) comprises esterifying R_1 that is $-OP_6$, where P_6 is H, with R_9 that is $-COOH$.

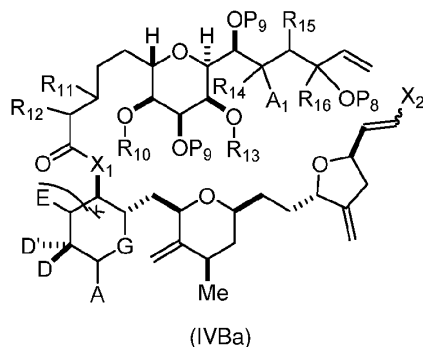
28. The method of any one of claims 19 to 27, wherein step (B) comprises reacting the compound of formula (IVB) with an olefin metathesis catalyst

29. The method of any one of claims 19 to 28, wherein P_9 is H, R_{16} is H, and step (C) comprises: oxidizing the compound of formula (IVC) to produce a compound of formula (IVCa):



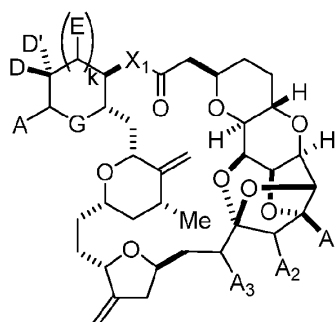
and reacting the compound of formula (IVCa) with a 1,4-reducing agent to produce the compound of formula (IVD).

30. The method of any one of claims 19 to 29, wherein the compound of formula (IVB) is, or is converted to, a compound of formula (IVBa) prior to producing the compound of formula (IVC), wherein the compound of formula (IVBa) is:



31. The method of any one of claims 19 to 30, wherein the producing the halichondrin macrolide or analog thereof comprises reacting the compound of formula (IVD) with a hydroxyl protecting group removing agent.

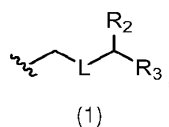
32. A method of preparing:



a halichondrin macrolide or analog thereof,

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP₁, provided that only one of D and D' is OP₁, wherein P₁ is H, alkyl, a hydroxyl protecting group, and A is a C₁₋₆ saturated or C₂₋₆ 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 Q₁, or A is a group of formula (1):



wherein

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

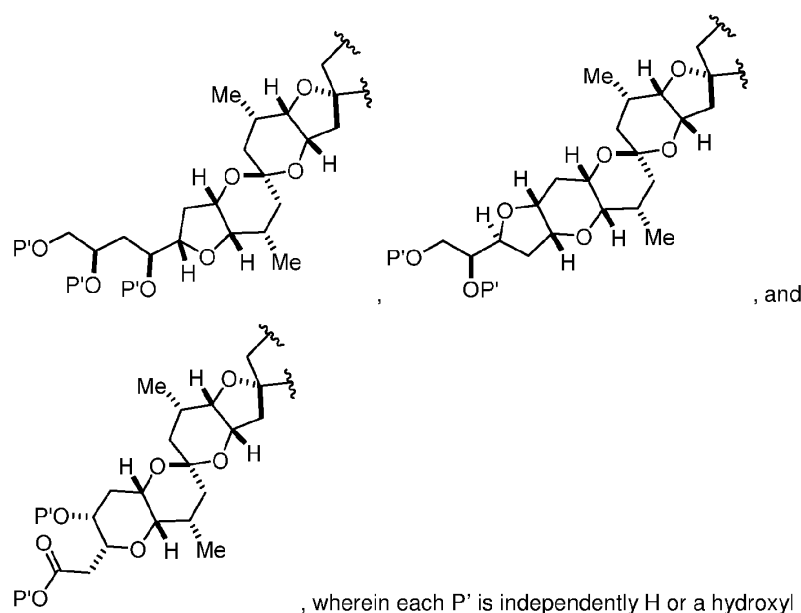
R₂ is H and P₁ is absent, H, alkyl, or a hydroxyl protecting group, or R₂ and P₁ combine to form a bond;

(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:



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_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; and

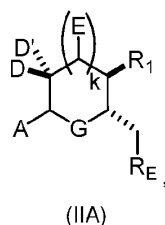
X_1 is $-CH_2-$ or $-O-$;

the method comprising:

(A) producing a compound of formula (VB) from a compound of formula (IIA), a compound of formula (IIB), a compound of formula (IIIB), a compound of formula (VA), and R_5OH ,

wherein R_5 is optionally substituted acyl;

wherein the compound of formula (IIA) is:



wherein

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

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

R_E is $-CHO$ or $-CH_{(1+m)}(OR_F)_{(2-m)}$,

wherein

m is 1, and R_F is a hydroxyl protecting group,

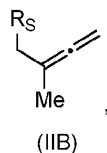
or

m is 0, and

(i) each R_F is independently an alkyl or hydroxyl protecting group, or

(ii) both R_F combine to form an alkylene;

wherein the compound of formula (IIB) is:



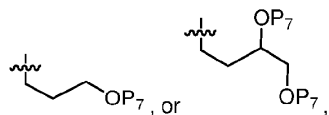
wherein R_S is silyl;

wherein the compound of formula (IIIB) is:



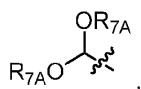
wherein

R_{4B} is but-3-en-1-yl,



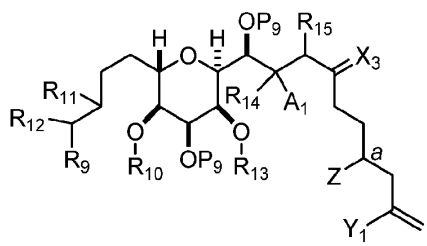
and

R₇ is -CHO or



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

wherein the compound of formula (VA) is:



(VA)

wherein

a designates (*R*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide; or *a* designates (*S*)-stereogenic center, and Z is OR₁₆, wherein R₁₆ is a hydroxyl protecting group;

- (a1) R₁₀ is a hydroxyl protecting group, R₁₁ is alkyl ether, and R₁₂ is H;
- (a2) R₁₀ is a hydroxyl protecting group, and R₁₁ and R₁₂ combine to form a double bond;
- or
- (a3) R₁₀ and R₁₁ combine to form a bond, and R₁₂ is H;
- (b1) A₁ and R₁₄ combine to form oxo, R₁₃ is a hydroxyl protecting group, and R₁₅ is H;
- or
- (b2) A₁ is H or -OP'', and:
 - (i) R₁₃ is a hydroxyl protecting group, and R₁₄ and R₁₅ combine to form a double bond;
 - or
 - (ii) R₁₃ and R₁₄ combine to form a bond, and R₁₅ is H or -OP'';

Y₁ is iodide, bromide, or trifluoromethanesulfonate;

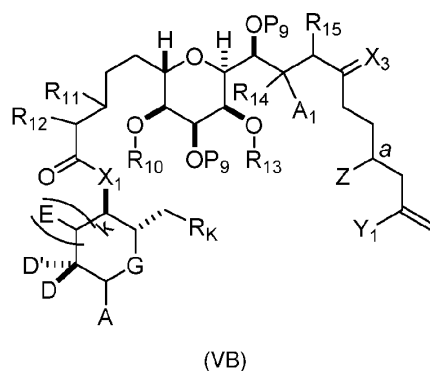
R₉ is -CHO or -COOH;

each P₉ is independently a hydroxyl protecting group, and X₃ is oxo; or both P₉ groups and

X₃, together with the atoms to which each is attached, combine to form a ketal; and

each P'' is independently a hydroxyl protecting group; and

wherein the compound of formula (VB) is:



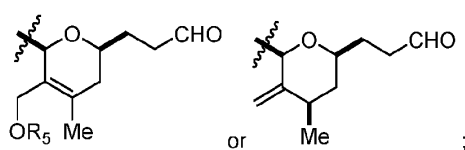
wherein

X_1 is $-\text{CH}_2-$, $-\text{CH}(\text{Y})-$, $-\text{C}(\text{Y})_2-$, or $-\text{O}-$, wherein each Y is independently $-\text{COOR}_C$ or $-\text{SO}_2\text{R}_D$;

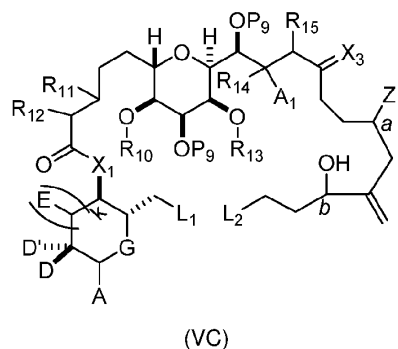
each R_C , when present, is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

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

R_K is

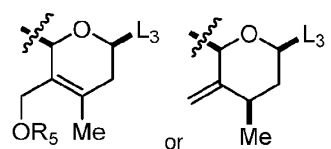


(B) producing a compound of formula (VC) from the compound of formula (VB), wherein the compound of formula (VC) is:



wherein

L_1 is



wherein L_2 and L_3 combine to form a bond;

b designates (*S*)-stereogenic center, if a designates (*R*)-stereogenic center;

and

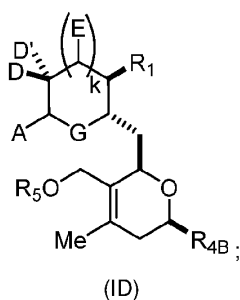
b designates (*R*)-stereogenic center, if *a* designates (*S*)-stereogenic center;

and

(C) producing the halichondrin macrolide or analog thereof from the compound of formula (VC).

33. The method of claim 32, wherein step (A) comprises:

(D) producing a compound of formula (ID) from the compound of formula (IIA), the compound of formula (IIB), the compound of formula (IIB), and R_5OH , wherein the compound of formula (ID) is:



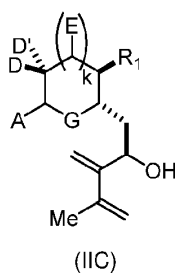
and

(E) producing the compound of formula (VB) from the compound of formula (ID) and the compound of formula (VA).

34. The method of claim 33, wherein the producing the compound of formula (ID) comprises reacting the compound of formula (IIC), the compound of formula (IIB), R_5OH , and a Lewis acid.

35. The method of claim 34, wherein the Lewis acid is boron trifluoride or a solvate thereof.

36. The method of any one of claims 33 to 35, wherein step (D) comprises a Sakurai reaction between the compound of formula (IIA) and the compound of formula (IIB) to produce a compound of formula (IIC), and a Prins reaction between the compound of formula (IIC), the compound of formula (IIB), and R_5OH , wherein the compound of formula (IIC) is:



37. The method of any one of claims 32 to 36, wherein X_1 is $-CH_2-$, $-CH(Y)-$, or $-C(Y)_2-$, and step (A) comprises reacting R_9 , wherein R_9 is $-CHO$, with R_1 that is $-CH(Y)_2$ or $-CH_2(Y)$ treated with a Brønsted base, to produce $-CO-X_1-$.

38. The method of any one of claims 32 to 36, wherein X_1 is $-O-$, and step (A) comprises esterifying R_9 that is $-COOH$ with R_1 that is $-OP_6$, where P_6 is H, to produce $-CO-X_1-$.

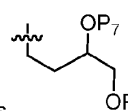
39. The method of any one of claims 32 to 38, wherein step (B) comprises reacting the compound of formula (VB) with a Cr(II) salt and a Ni(II) salt.

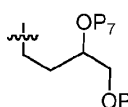
40. The method of any one of claims 32 to 39, wherein step (C) comprises a step of nucleophilic ring-closing of the compound of formula (VC).

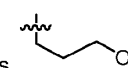
41. The method of any one of claims 32 to 40, wherein both P_9 groups and X_3 , together with the atoms to which each is attached, combine to form a ketal.

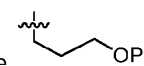
42. The method of any one of claims 32 to 41, wherein R_{10} and R_{11} combine to form a bond, and R_{12} is H.

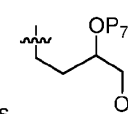
43. The method of any one of claims 32 to 42, wherein R_{4B} is but-3-en-1-yl, and step (A) comprises

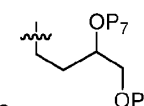
reacting the but-3-en-1-yl group with a dihydroxylating agent to produce R_{4B} that is , and

cleaving the  through a reaction with a glycol cleaving agent.

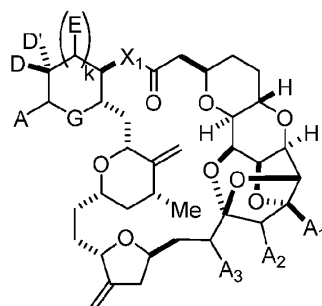
44. The method of any one of claims 32 to 42, wherein R_{4B} is , and step (A)

comprises reacting the  with an oxidizing agent capable of converting an alcohol into a carbonyl group.

45. The method of any one of claims 32 to 42, wherein R_{4B} is , and step (A)

comprises cleaving the  through a reaction with a glycol cleaving agent.

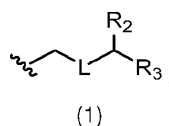
46. A method of preparing:



a halichondrin macrolide or analog thereof,

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP₁, provided that only one of D and D' is OP₁, wherein P₁ is H, alkyl, a hydroxyl protecting group, and A is a C₁₋₆ saturated or C₂₋₆ 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 Q₁, or A is a group of formula (1):



wherein

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

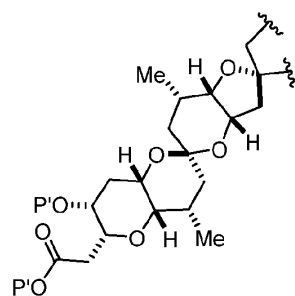
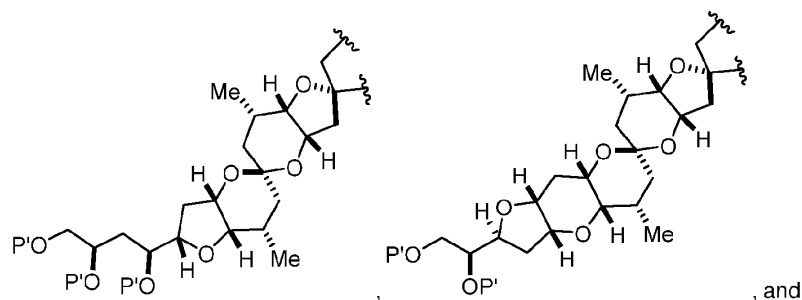
R₂ is H and P₁ is absent, H, alkyl, or a hydroxyl protecting group, or R₂ and P₁ combine to form a bond;

(i) R₃ is H, and P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R₃ is $-(CH_2)_nNP_3P_4$, wherein P₃ is H or an N-protecting group, and (a) P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₄ is H or an N-protecting group, (b) P₂ and P₄ combine to form an alkylidene, or (c) each of P₂ and P₄ is H;

(iii) R₃ is $-(CH_2)_nOP_5$, wherein P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₅ is H, optionally substituted alkyl, or a hydroxyl protecting group; or P₂ and P₅, 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) R₃ and P₂ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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

each of A₁, A₂, and A₃ 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, CH₂, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q₁ is independently OR_A, SR_A, SO₂R_A, OSO₂R_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; and

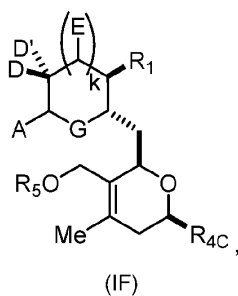
X₁ is —CH₂— or —O—;

the method comprising:

(A) producing a compound of formula (IF) from a compound of formula (IIA), a compound of formula (IIB), a compound of formula (IIIC), and R₅OH,

wherein R₅ is optionally substituted acyl;

wherein the compound of formula (IF) is:

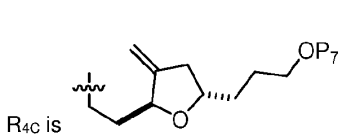
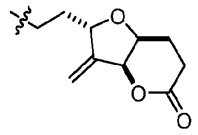
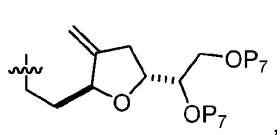
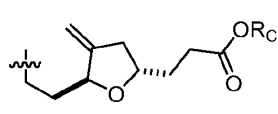
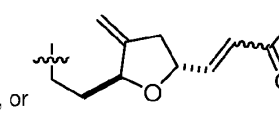


wherein

R_1 is $-\text{OP}_6$, $-\text{CH}(\text{Y})_2$, or $-\text{CH}_2(\text{Y})$, wherein P_6 is H or a hydroxyl protecting group, and each Y is independently $-\text{COOR}_C$ or $-\text{SO}_2\text{R}_D$;

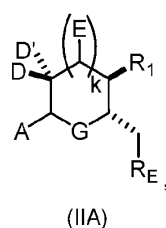
each R_C , when present, is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

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

R_{4C} is , , , , or , wherein R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl, and each P_7 is independently H or a hydroxyl protecting group; and

R_5 is optionally substituted acyl;

wherein the compound of formula (IIA) is:



wherein

R_1 is $-\text{OP}_6$, $-\text{CH}(\text{Y})_2$, or $-\text{CH}_2(\text{Y})$, wherein P_6 is H or a hydroxyl protecting group, and each Y is independently $-\text{COOR}_C$ or $-\text{SO}_2\text{R}_D$;

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

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

R_E is $-\text{CHO}$ or $-\text{CH}_{(1+m)}(\text{OR}_F)_{(2-m)}$,

wherein

m is 1, and R_F is a hydroxyl protecting group,

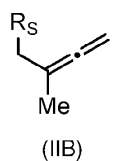
or

m is 0, and

(i) each R_F is independently an alkyl or hydroxyl protecting group, or

(ii) both R_F combine to form an alkylene;

wherein the compound of formula (IIB) is:



wherein R_S is silyl;

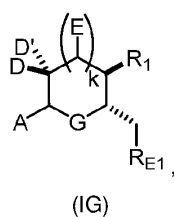
and

wherein the compound of formula (IIIC) is:



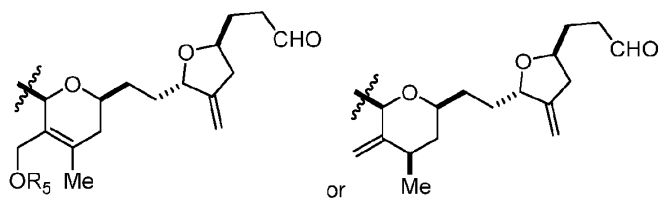
wherein R₇ is -CHO or , wherein each R_{7A} is independently an optionally substituted alkyl;

(B) producing a compound of formula (IG) from the compound of formula (IF), wherein the compound of formula (IG) is:



wherein

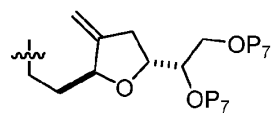
R_{E1} is



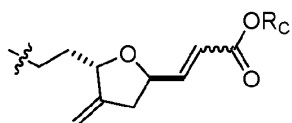
and

(C) producing the halichondrin macrolide or analog thereof from the compound of formula (IG) and one or more intermediates.

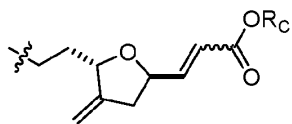
47. The method of claim 46, wherein step (B) comprises reacting R_{4C} that is



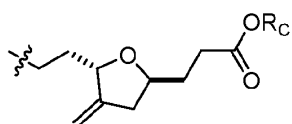
with a glycol cleaving agent to produce an aldehyde, reacting the aldehyde with (R_CO)₂P(O)-CH₂-COOR_C to produce R_{4C} that is



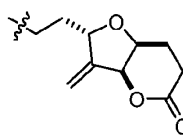
48. The method of claim 46 or 47, wherein step (B) comprises reducing R_{4C} that is



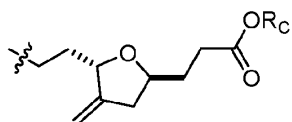
with a 1,4-reducing agent to produce R_{4C} that is



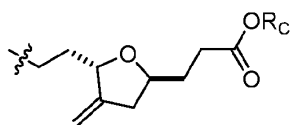
49. The method of claim 46, wherein step (B) comprises reducing R_{4C} that is



with an allylic reducing agent to produce R_{4C} that is

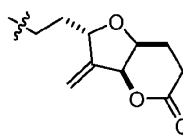


50. The method of claim 46, 48, or 49, wherein step (B) comprises reducing R_{4C} that is

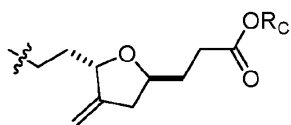


with a 1,2-reducing agent to produce a carbonyl group in R_{E1} .

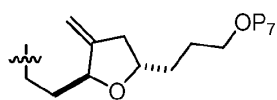
51. The method of claim 49, wherein the reducing R_{4C} that is



comprises an esterification reaction producing R_{4C} that is



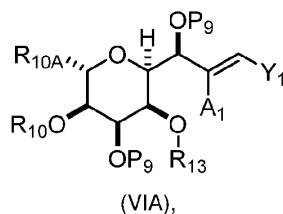
52. The method of claim 46, wherein step (B) comprises reacting R_{4C} that is



with an oxidizing agent capable of converting an alcohol to a carbonyl group in

R_{E1} .

53. The method of any one of claims 46 to 52, wherein the one or more intermediates is a compound of formula (VIA):



wherein

R_{10A} is $-\text{CH}_2-\text{CH}=\text{CH}_2$, $-(\text{CH}_2)_2-\text{CH}=\text{CH}_2$, or $-(\text{CH}_2)_3-\text{OP}_{10}$;

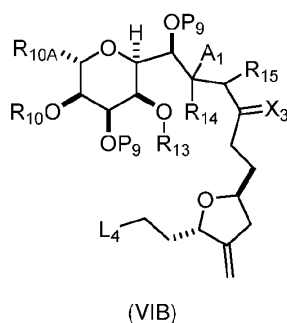
each R_{10} , R_{13} , P_9 and P_{10} is independently a hydroxyl protecting group;

A_1 is H or $-\text{OP}''$; and

Y_1 is chloro, bromo, iodo, trifluoromethanesulfonate, or trialkylsilane;

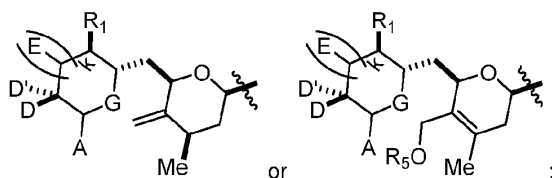
and step (C) comprises:

(D) producing a compound of formula (VIB) from the compound of formula (IG) and the compound of formula (VIA), wherein the compound of formula (VIB) is:



wherein

L_4 is



R_1 is $-\text{OP}_6$ or $-\text{CH}(Y)$, wherein P_6 is H or a hydroxyl protecting group, and Y is $-\text{COOR}_C$ or $-\text{CHO}$;

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 $-\text{OP}''$, 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 $-\text{OP}''$;

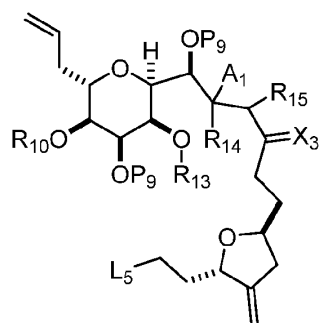
and

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

54. The method of claim 53, wherein step (D) comprises reacting the compound of formula (VIA) and the compound of formula (IG) with a Cr(II) salt and a Ni(II) salt.

55. The method of claim 53 or 54, wherein R_{10A} is $-\text{CH}_2-\text{CH}=\text{CH}_2$, and step (C) comprises:

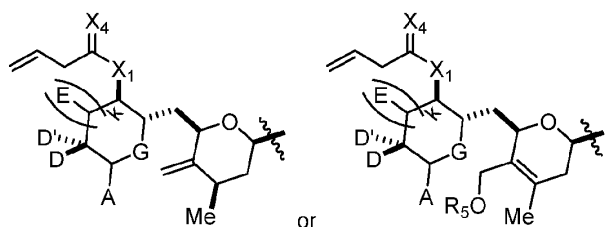
(E) producing a compound of formula (VIC) from the compound of formula (VIB) and $R_{17}-\text{CH}_2\text{CH}=\text{CH}_2$, wherein R_{17} is $-\text{COOH}$ or a metallic or metalloid moiety, and the compound of formula (VIC) is:



(VIC)

wherein

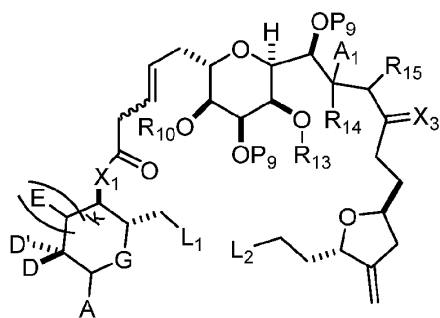
L_5 is



X_1 is $-\text{CH}_2-$ or $-\text{O}-$;

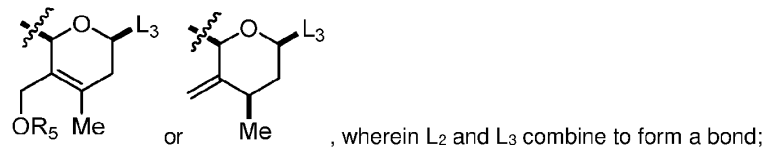
X_4 is oxo, or X_4 , together with the atom to which it is attached, is $-(CH(OP_{12}))-$, wherein P_{12} is H or a hydroxyl protecting group;

(F) producing a compound of formula (VID) from the compound of formula (VIC), wherein the compound of formula (VID) is:



(VID)

wherein

L₁ is

and

(G) producing the halichondrin macrolide or analog thereof from the compound of formula (VID).

56. The method of claim 55, wherein R₁ is -CH₂(Y), X₁ is -CH₂-, X₄ is oxo or -(CH(OP₁₂))-, and step (E) comprises reacting the compound of formula (VIB) with R₁₇-CH₂CH=CH₂, wherein R₁₇ is a metallic or metalloid moiety.

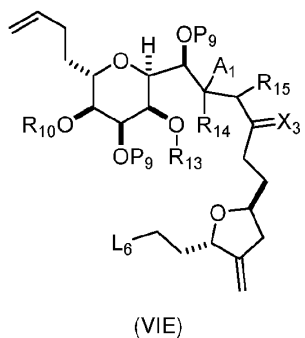
57. The method of claim 55, wherein R₁ is -OP₆, P₆ is H, X₁ is -O-, X₄ is oxo, and step (E) comprises esterifying the compound of formula (VIB) with R₁₇-CH₂CH=CH₂, wherein R₁₇ is -COOH.

58. The method of any one of claims 55 to 57, wherein the producing step (F) comprises reacting the compound of formula (VIC) with an olefin metathesis catalyst.

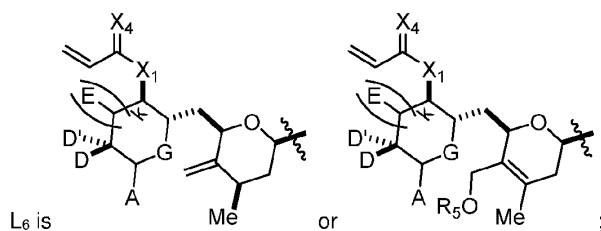
59. The method of any one of claims 55 to 58, wherein step (G) comprises reacting the compound of formula (VID) with a hydroxyl protecting group removing agent.

60. The method of claim 53 or 54, wherein R_{10A} is -CH₂-CH₂-CH=CH₂, R₁ is -OP₆ or -CH₂(Y), wherein P₆ is H or a hydroxyl protecting group, and Y is -COOR_C, and step (C) comprises:

(H) producing a compound of formula (VIE) from the compound of formula (VIB) and R₁₇-CH=CH₂, wherein R₁₇ is -COOH or a metallic or metalloid moiety, wherein the compound of formula (VIE) is:



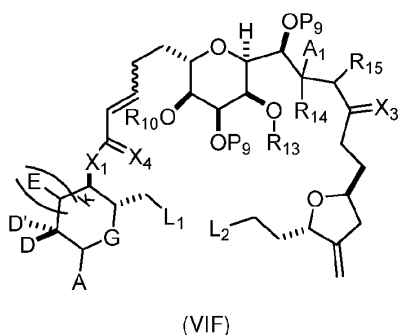
wherein



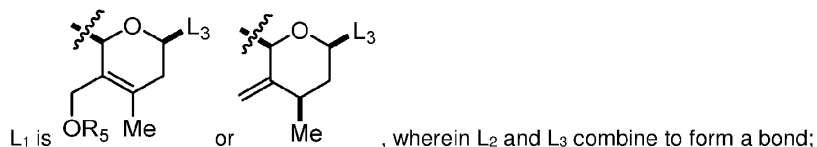
X₁ is $-\text{CH}_2-$ or $-\text{O}-$; and

X₄ is oxo, or X₄, together with the atom to which it is attached, is $-(\text{CH}(\text{OP}_{12}))-$, wherein P₁₂ is H or a hydroxyl protecting group;

(I) producing a compound of formula (VIF) from the compound of formula (VIE), wherein the compound of formula (VIF) is:



wherein



and

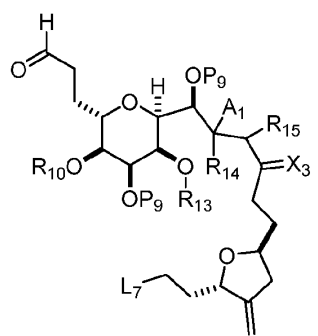
(J) producing the halichondrin macrolide or analog thereof from the compound of formula (VIF).

61. The method of claim 60, wherein step (I) comprises reacting the compound of formula (VIE) with an olefin metathesis catalyst.

62. The method of claim 60 or 61, wherein step (J) comprises reacting the compound of formula (VIF) with a hydroxyl protecting group removing agent.

63. The method of claim 53 or 54, wherein R_{10A} is $-(\text{CH}_2)_3-\text{OP}_{10}$, and step (C) comprises:

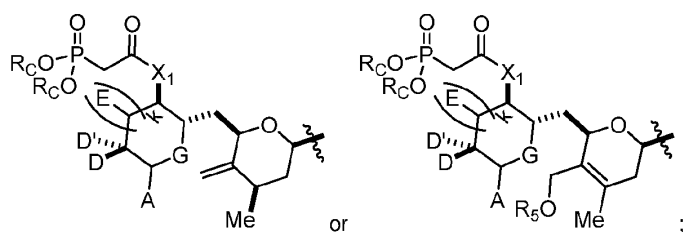
(K) producing a compound of formula (VIG) from the compound of formula (VIB) and $(\text{R}_\text{C}\text{O})_2\text{P}(\text{O})-\text{CH}_2-\text{R}_\text{P}$, wherein each R_C is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl, and R_P is H or $-\text{COOH}$, and wherein the compound of formula (VIG) is:



(VIG)

wherein

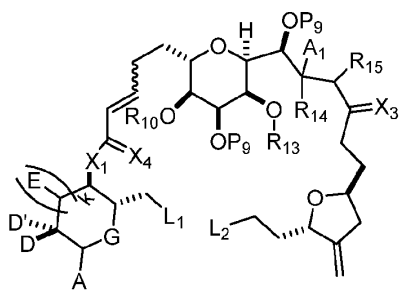
L₇ is



and

X₁ is -CH₂- or -O-;

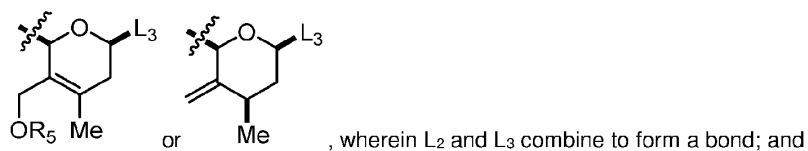
(L) producing a compound of formula (VIF) from the compound of formula (VIG), wherein the compound of formula (VIF) is:



(VIF)

wherein

L₁ is



, wherein L₂ and L₃ combine to form a bond; and

X₄ is oxo;

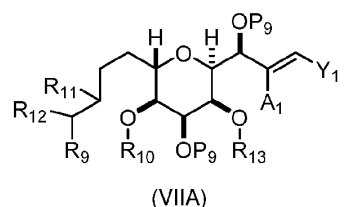
and

(M) producing the halichondrin macrolide or analog thereof from the compound of formula (VIF).

64. The method of claim 63, wherein the producing step (K) comprises:
 reacting the compound of formula (VIB) with $(R_cO)_2P(O)-CH_2-R_P$ under Claisen reaction conditions,
 wherein R_P is H and R_1 is $-CH_2(Y)$, or
 esterifying the compound of formula (VIB) with $(R_cO)_2P(O)-CH_2-R_P$, wherein R_P is $-COOH$ and R_1
 is $-OP_6$, wherein P_6 is H.

65. The method of claim 63 or 64, wherein step (M) comprises reacting the compound of formula
 (VIF) with a hydroxyl protecting group removing agent.

66. The method of any one of claims 46 to 52, wherein step (C) comprises:
 (N) producing a compound of formula (VIIB) from the compound of formula (IG) and a compound of
 formula (VIA):



wherein

- (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;

R_9 is $-CH_2-OP''$ or $-COOP''$;

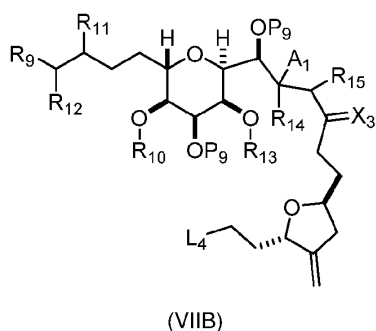
R_{13} and each P_9 is independently a hydroxyl protecting group;

A_1 is H or $-OP''$;

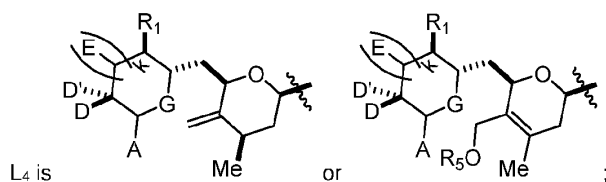
each P'' is independently H or a hydroxyl protecting group; and

Y_1 is chloro, bromo, iodo, trifluoromethanesulfonate, or trialkylsilane;

wherein the compound of formula (VIIB) is:



wherein



R₁ is $-\text{OP}_6$, $-\text{CH}_2(\text{Y})$, or $-\text{CH}(\text{Y})_2$, wherein P₆ is H or a hydroxyl protecting group, and Y is $-\text{COOR}_C$ or $-\text{CHO}$;

A₁ and R₁₄ combine to form oxo, R₁₃ is H or a hydroxyl protecting group, and R₁₅ is H;

or

A₁ is H or $-\text{OP}''$, and:

(i) R₁₃ is H or a hydroxyl protecting group, and R₁₄ and R₁₅ combine to form a double bond;

or

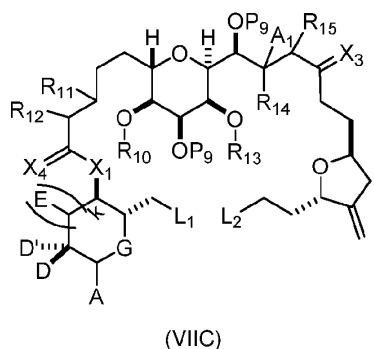
(ii) R₁₃ and R₁₄ combine to form a bond, and R₁₅ is H or $-\text{OP}''$;

R₉ is $-\text{CHO}$ or $-\text{COOP}''$;

and

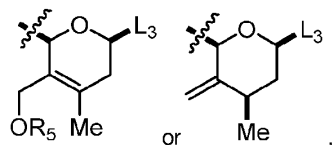
each P₉ is independently a hydroxyl protecting group, and X₃ is oxo or X₃, together with the carbon atom to which it is attached, is $-(\text{CH}(\text{OP}_{11}))$ -, wherein P₁₁ is H or a hydroxyl protecting group; or both P₉ groups and X₃, together with the atoms to which each is attached, combine to form a ketal;

(O) producing a compound of formula (VIIC) from the compound of formula (VIIB), wherein the compound of formula (VIIC) is:



wherein

L₁ is



wherein L₂ and L₃ combine to form a bond;

X₁ is $-\text{CH}_2-$, $-\text{CH}(\text{Y})-$, $-\text{C}(\text{Y})_2-$, or $-\text{O}-$, wherein each Y is independently $-\text{COOR}_C$ or $-\text{SO}_2\text{R}_D$;

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

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;

and

(P) producing the halichondrin macrolide or analog thereof from the compound of formula (VIIC).

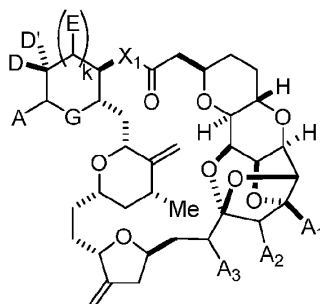
67. The method of claim 66, wherein step (N) comprises reacting the compound of formula (VIIA) and the compound of formula (IH) with a Cr(II) salt and a Ni(II) salt.

68. The method of claim 66 or 67, wherein step (O) comprises an esterification reaction between R_1 that is $-OP_6$, wherein P_6 is H, and R_9 that is $-COOH$.

69. The method of claim 66 or 67, wherein step (O) comprises a reaction between R_1 that is $-CH(Y)_2$ or $-CH_2(Y)$, and R_9 that is $-CHO$.

70. The method of any one of claims 66 to 69, wherein step (P) comprises reacting the compound of formula (VIIC) with a hydroxyl protecting group removing agent.

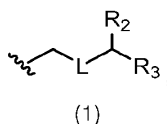
71. A method of preparing:



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):



wherein

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

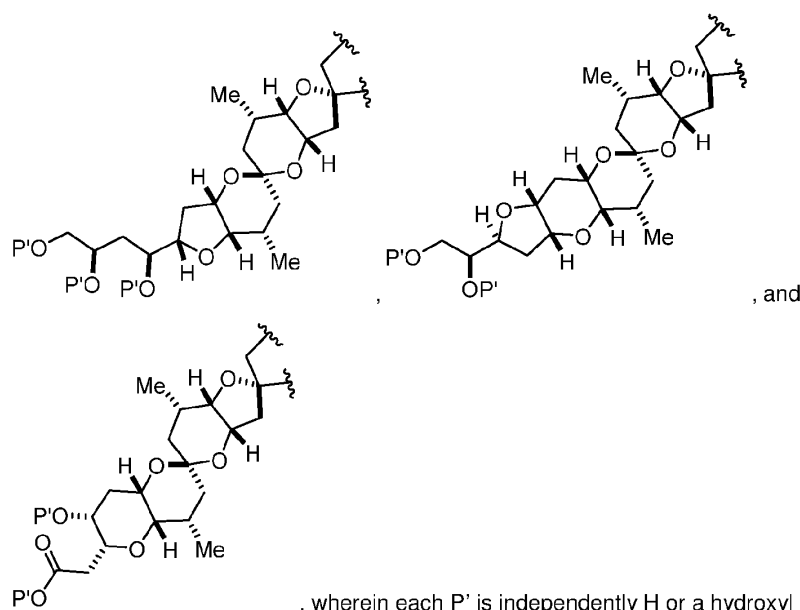
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

(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;

(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:



, 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_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; and

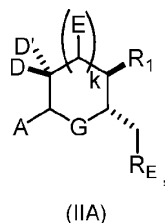
X_1 is $-CH_2-$ or $-O-$;

the method comprising:

(A) producing a compound of formula (VIID) from a compound of formula (IIA), a compound of formula (IIB), a compound of formula (IIIC), a compound of formula (VIIA), and R_5OH ,

wherein R_5 is optionally substituted acyl;

wherein the compound of formula (IIA) is:



wherein

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

R_E is $-CHO$ or $-CH_{(1+m)}(OR_F)_{(2-m)}$,

wherein

m is 1, and R_F is a hydroxyl protecting group,

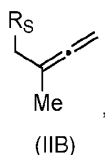
or

m is 0, and

(i) each R_F is independently an alkyl or hydroxyl protecting group, or

(ii) both R_F combine to form an alkylene;

wherein the compound of formula (IIB) is:



wherein R_S is silyl;

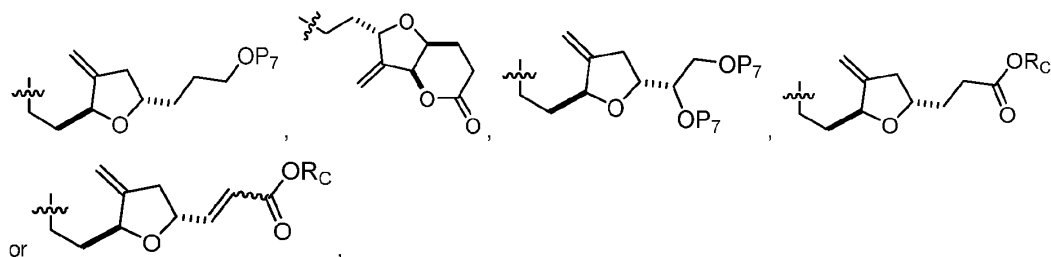
wherein the compound of formula (IIIC) is:



wherein

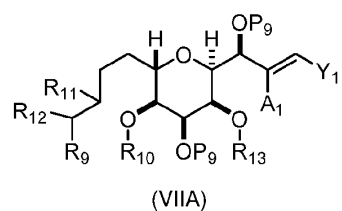
R_7 is $-CHO$ or $R_{7A}O$, wherein each R_{7A} is independently an optionally substituted alkyl;

R_{4C} is



wherein each P₇, when present, is independently H or a hydroxyl protecting group;

wherein the compound of formula (VIIA) is:



wherein

- (i) R₁₀ is a hydroxyl protecting group, R₁₁ is alkyl ether, and R₁₂ is H;
- (ii) R₁₀ is a hydroxyl protecting group, and R₁₁ and R₁₂ combine to form a double bond;
- or
- (iii) R₁₀ and R₁₁ combine to form a bond, and R₁₂ is H;

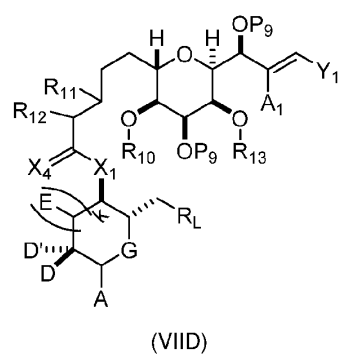
R₉ is -CHO or -COOH;

R₁₃ and each P₉ is independently a hydroxyl protecting group;

A₁ is H or -OP'', wherein P'' is H or a hydroxyl protecting group; and

Y₁ is chloro, bromo, iodo, trifluoromethanesulfonate, or trialkylsilane;

wherein the compound of formula (VIID) is:

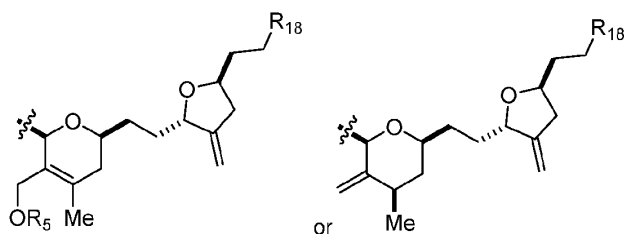


wherein

X₁ is -CH₂-, -CH(Y)-, -C(Y)₂-, or -O-, wherein each Y is independently -COOR_C or -SO₂R_D;

X₄ is oxo, or X₄, together with the atom to which it is attached, is -(CH(OP₁₂))- , where P₁₂ is H or a hydroxyl protecting group;

R_L is

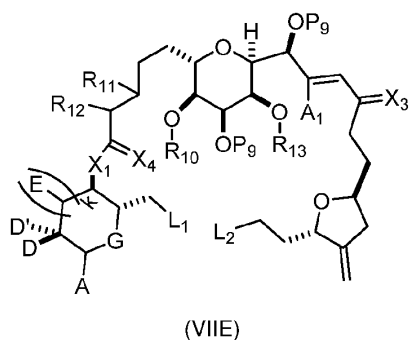


wherein

R₁₈ is $-\text{CHO}$ or $-\text{CH}_2\text{OP}_7$;

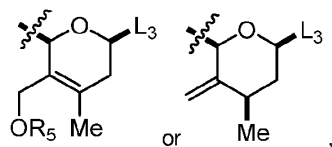
R₅ is optionally substituted acyl;

(B) producing a compound of formula (VIIIE) from the compound of formula (VIID), wherein the compound of formula (VIIIE) is:



wherein

L₁ is



wherein L₂ and L₃ combine to form a bond;

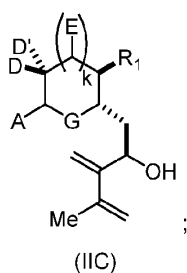
each P₉ is independently a hydroxyl protecting group, and X₃ is oxo or X₃, together with the carbon atom to which it is attached, is $-(\text{CH}(\text{OP}_{11}))-$, wherein P₁₁ is H or a hydroxyl protecting group;

and

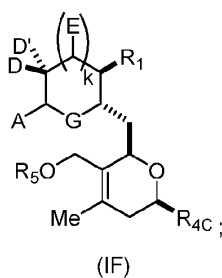
(C) producing the halichondrin macrolide or analog thereof from the compound of formula (VIIC).

72. The method of claim 71, wherein step (A) comprises:

(D) producing a compound of formula (IIC) from the compound of formula (IIA) and the compound of formula (IIB), wherein the compound of formula (IIC) is:



(E) producing a compound of formula (IF) from the compound of formula (IIC), the compound of formula (IIIC), and R_5OH , wherein the compound of formula (IF) is:



and

(F) producing the compound of formula (VIIB) from the compound of formula (VIIA) and the compound of formula (IF).

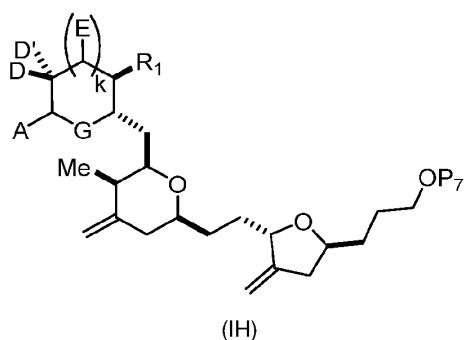
73. The method of claim 72, wherein the producing the compound of formula (IF) comprises reacting the compound of formula (IIC), the compound of formula (IIIC), R_5OH , and a Lewis acid.

74. The method of claim 73, wherein the Lewis acid is an oxophilic Lewis acid.

75. The method of claim 74, wherein the oxophilic Lewis acid is boron trifluoride or a solvate thereof.

76. The method of any one of claims 71 to 75, wherein step (F) comprises:

(G) producing a compound of formula (IH) from the compound of formula (IF), wherein the compound of formula (IH) is:

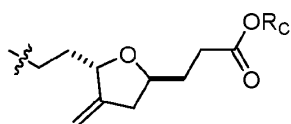


and

(H) producing the compound of formula (VIID) from the compound of formula (IH) and the compound of formula (VIIA).

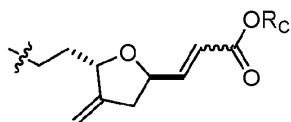
77. The method of claim 76, wherein the producing step (G) comprises reacting the compound of formula (IF) with an allylic reducing agent.

78. The method of any one of claims 71 to 77, wherein step (A) comprises reducing R_{4C} that is



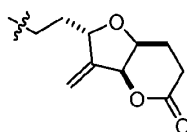
with a 1,2-reducing agent.

79. The method of any one of claims 71 to 77, wherein step (A) comprises reducing R_{4C} that is



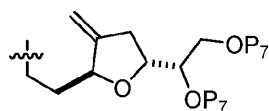
with a 1,4-reducing agent to produce a reduction product, and reducing the reduction product with a 1,2-reducing agent.

80. The method of any one of claims 71 to 77, wherein step (A) comprises reducing R_{4C} that is

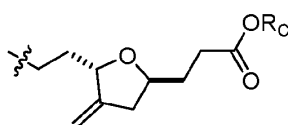
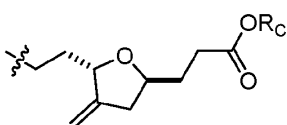


with an allylic reducing agent to produce an acid product, and reducing the acid product with a 1,2-reducing agent capable of converting the carboxylic acid to an aldehyde.

81. The method of any one of claims 71 to 77, wherein step (A) comprises cleaving R_{4C} that is



with a glycol cleaving agent to produce an aldehyde, reacting the aldehyde $(R_{4C})_2P(O)-CH_2-COOR_C$ to produce an enoate, reacting the enoate with a 1,4-reducing agent to produce

R_{4C} that is , and reacting R_{4C} that is  with a 1,2-reducing agent capable of converting the carboxylic acid to an aldehyde.

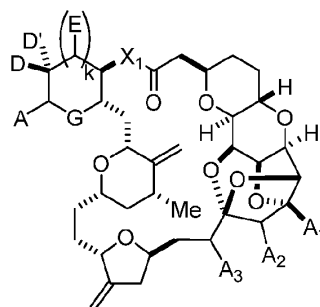
82. The method of any one of claims 71 to 81, wherein step (A) comprises an esterification reaction between R_1 that is $-OP_6$, where P_6 is H, and R_9 that is $-COOH$.

83. The method of any one of claims 71 to 81, wherein step (A) comprises a reaction between R_1 that is $-CH(Y)_2$ or $-CH_2(Y)$, and R_9 that is $-CHO$.

84. The method of any one of claims 71 to 78, wherein step (B) comprises reacting the compound of formulas (VIID) with a Cr(II) salt and a Ni(II) salt.

85. The method of any one of claims 71 to 84, wherein step (C) comprises reacting the compound of formula (VIIIE) with a hydroxyl protecting group removing agent.

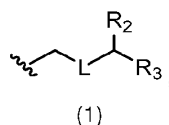
86. A method of preparing:



a halichondrin macrolide or analog thereof,

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP₁, provided that only one of D and D' is OP₁, wherein P₁ is H, alkyl, a hydroxyl protecting group, and A is a C₁₋₆ saturated or C₂₋₆ 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 Q₁, or A is a group of formula (1):



wherein

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

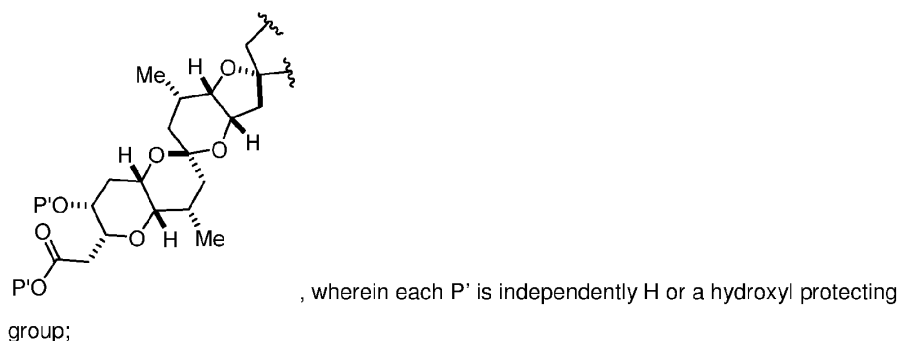
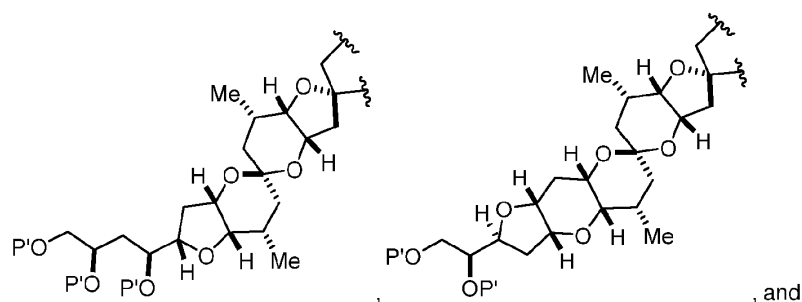
R₂ is H and P₁ is absent, H, alkyl, or a hydroxyl protecting group, or R₂ and P₁ combine to form a bond;

(i) R₃ is H, and P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R₃ is $-(CH_2)_nNP_3P_4$, wherein P₃ is H or an N-protecting group, and (a) P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₄ is H or an N-protecting group, (b) P₂ and P₄ combine to form an alkylidene, or (c) each of P₂ and P₄ is H;

(iii) R₃ is $-(CH_2)_nOP_5$, wherein P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₅ is H, optionally substituted alkyl, or a hydroxyl protecting group; or P₂ and P₅, 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) R₃ and P₂ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



each of A₁, A₂, and A₃ 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, CH₂, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q₁ is independently OR_A, SR_A, SO₂R_A, OSO₂R_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; and

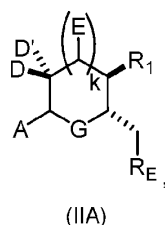
X₁ is —CH₂— or —O—;

the method comprising:

(A) producing a compound of formula (VIII B) from a compound of formula (VIII A), a compound of formula (IIA), a compound of formula (IIB), and a compound of formula (IIIC), and R₅OH,

wherein R₅ is optionally substituted acyl;

wherein the compound of formula (IIA) is:



wherein

R₁ is -OP₆, -CH(Y)₂, or -CH₂(Y), wherein P₆ is H or a hydroxyl protecting group, and each Y is independently -COOR_C or -SO₂R_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;

$$R_E \text{ is } -\text{CHO} \text{ or } -\text{CH}_{(1+m)}(\text{OR}_F)_{(2-m)},$$

wherein

m is 1, and R_F is a hydroxyl protecting group,

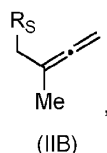
or

m is 0

(i) each R_F is independently an alkyl or hydroxyl protecting group, or

(ii) both R_F combine to form an alkylene;

wherein the compound of formula (IIB) is:



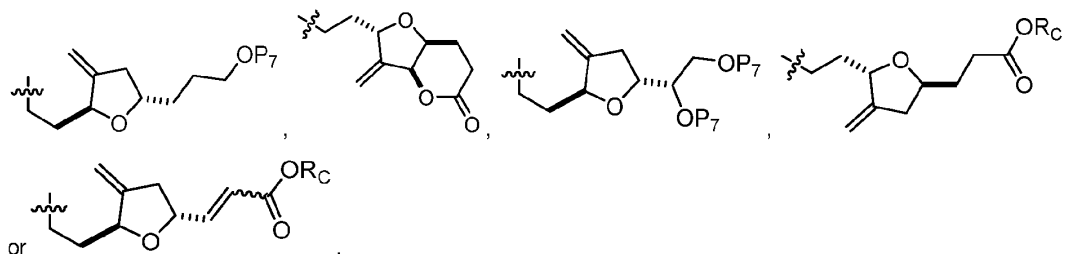
wherein R_S is silyl;

wherein the compound of formula (IIIC) is:



wherein

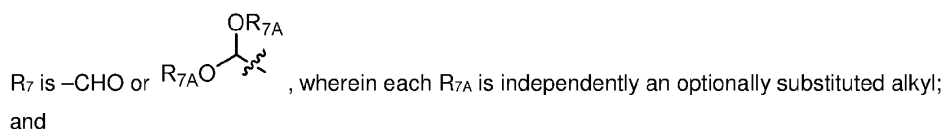
R₄C is



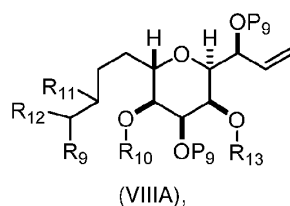
wherein

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

each P₇, when present, is independently H or a hydroxyl protecting group;;



wherein the compound of formula (VIIIa) is:



wherein

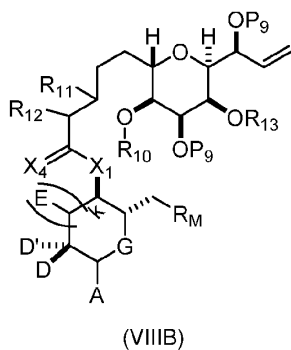
- (i) R_{10} is a hydroxyl protecting group, R_{11} is alkyl ether, and R_{12} is H;
- (ii) R_{10} is a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;
- or
- (iii) R_{10} and R_{11} combine to form a bond, and R_{12} is H;

R_9 is $-\text{CHO}$ or $-\text{COOH}$;

and

each P_9 and R_{13} is independently a hydroxyl protecting group;

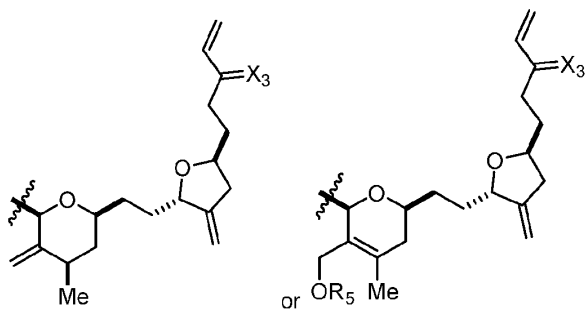
wherein the compound of formula (VIII B) is:



wherein

X_1 is $-\text{CH}_2-$, $-\text{CH}(\text{Y})-$, $-\text{C}(\text{Y})_2-$, or $-\text{O}-$, wherein each Y is independently $-\text{COOR}_C$ or $-\text{SO}_2\text{R}_D$;

R_M is



wherein

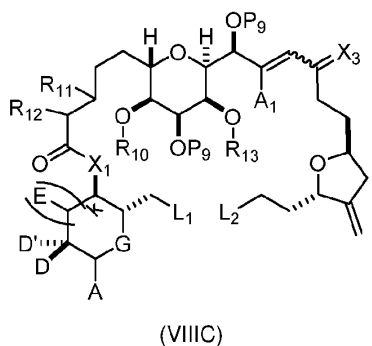
R_5 is optionally substituted acyl; and

X_3 is oxo or X_3 , together with the carbon atom to which it is attached, is $-(\text{CH}(\text{OP}_{11}))-$,

wherein P_{11} is H or a hydroxyl protecting group; and

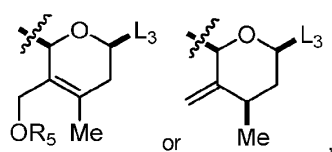
X_4 is oxo, or X_4 , together with the atom to which it is attached, is $-(\text{CH}(\text{OP}_{12}))-$, where P_{12} is H or a hydroxyl protecting group;

(B) producing a compound of formula (VIII C) from the compound of formula (VIII B), wherein the compound of formula (VIII C) is:



wherein

L₁ is



wherein L₂ and L₃ combine to form a bond;

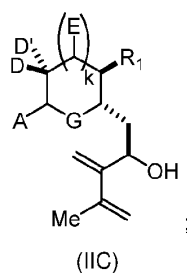
A₁ is H or -OP'', wherein P'' is H or a hydroxyl protecting group;

and

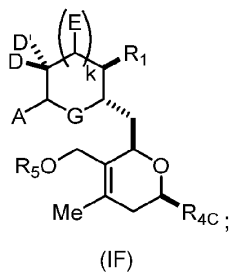
(C) producing the halichondrin macrolide or analog thereof from the compound of formula (VIII C).

87. The method of claim 86, wherein step (A) comprises:

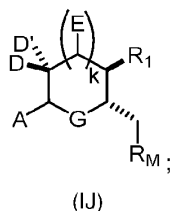
(D) producing a compound of formula (IIC) from the compound of formula (IIA) and the compound of formula (IIB), wherein the compound of formula (IIC) is:



(E) producing a compound of formula (IF) from the compound of formula (IIC), the compound of formula (IIIC), and R₅OH, wherein the compound of formula (IF) is:



(F) producing a compound of formula (IJ) from the compound of formula (IF), wherein the compound of formula (IJ) is:



and

(G) producing the compound of formula (VIIB) from the compound of formula (VIIIA) and the compound of formula (IJ).

88. The method of claim 87, wherein step (D) comprises reacting the compound of formula (IIB), the compound of formula (IIA), and a Lewis acid.

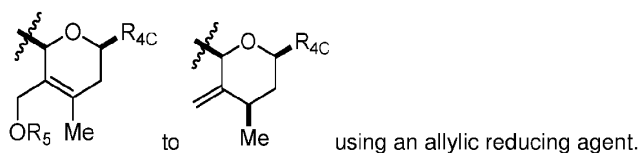
89. The method of claim 87 or 88, wherein step (E) comprises reacting the compound of formula (IIC), the compound of formula (IIIC), R_5OH and a Lewis acid.

90. The method of claim 88 or 89, wherein the Lewis acid in step (D) and the Lewis acid in step (E) are different.

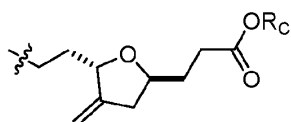
91. The method of any one of claims 88 to 90, wherein the Lewis acid is an oxophilic Lewis acid.

92. The method of claim 91, wherein the oxophilic Lewis acid is boron trifluoride or a solvate thereof.

93. The method of any one of claims 87 to 92, wherein step (F) comprises converting

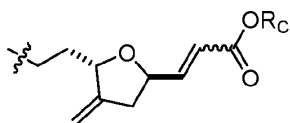


94. The method of claim any one of claims 86 to 92, wherein step (A) comprises reacting R_{4C} that is



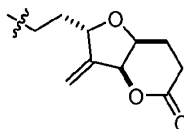
with a 1,2-reducing agent to produce a product, and reacting the product with a vinyl nucleophile.

95. The method of any one of claims 86 to 92, wherein step (A) comprises reacting R_{4C} that is



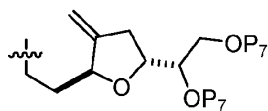
with a 1,4-reducing agent to produce a product, reducing the product with a 1,2-reducing agent to produce a reduced product, and reacting the reduced product with a vinyl nucleophile.

96. The method of any one of claims 86 to 92, wherein step (A) comprises reacting R_{4C} that is



with an allylic reducing agent to produce an acid, reducing the acid with a 1,2-reducing agent to produce a reduced product, and reacting the reduced product with a vinyl nucleophile.

97. The method of any one of claims 86 to 92, wherein step (A) comprises cleaving R_{4C} that is



with a glycol cleaving agent to produce an aldehyde, reacting the aldehyde with $(R_{cO})_2P(O)-CH_2-COOR_c$ to produce an enoate, reacting the enoate with a 1,4-reducing agent to produce a product, reducing the product with a 1,2-reducing agent to produce a reduced product, and reacting the reduced product with a vinyl nucleophile.

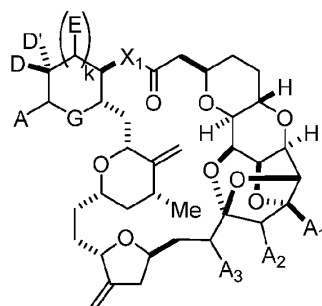
98. The method of any one of claims 86 to 97, wherein step (A) comprises an esterification reaction between R_1 that is $-OP_6$, where P_6 is H, and R_9 that is $-COOH$.

99. The method of any one of claims 86 to 97, wherein step (A) comprises a reaction between R_1 that is $-CH(Y)_2$ or $-CH_2(Y)$, and R_9 , wherein R_9 is $-CHO$.

100. The method of any one of claims 86 to 99, wherein step (B) comprises reacting the compound of formula (VIII B) with an olefin metathesis catalyst.

101. The method of any one of claims 86 to 100, wherein step (C) comprises reacting the compound of formula (VIII C) with a hydroxyl protecting group removing agent.

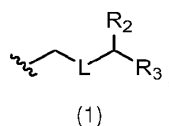
102. A method of preparing:



a halichondrin macrolide or analog thereof,

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP₁, provided that only one of D and D' is OP₁, wherein P₁ is H, alkyl, a hydroxyl protecting group, and A is a C₁₋₆ saturated or C₂₋₆ 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 Q₁, or A is a group of formula (1):



wherein

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

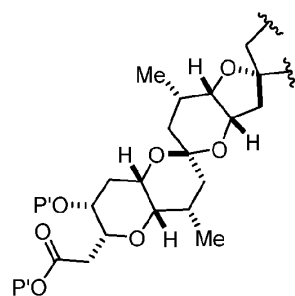
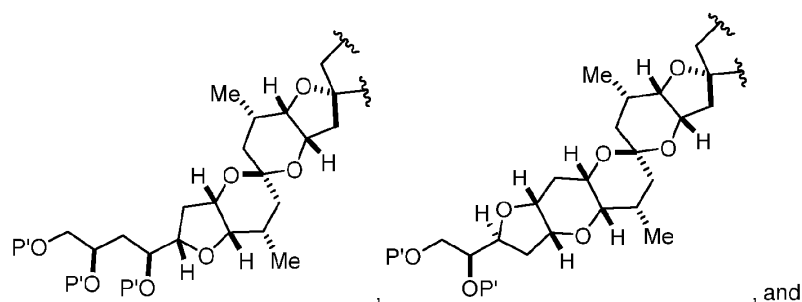
R₂ is H and P₁ is absent, H, alkyl, or a hydroxyl protecting group, or R₂ and P₁ combine to form a bond;

(i) R₃ is H, and P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R₃ is $-(CH_2)_nNP_3P_4$, wherein P₃ is H or an N-protecting group, and (a) P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₄ is H or an N-protecting group, (b) P₂ and P₄ combine to form an alkylidene, or (c) each of P₂ and P₄ is H;

(iii) R₃ is $-(CH_2)_nOP_5$, wherein P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₅ is H, optionally substituted alkyl, or a hydroxyl protecting group; or P₂ and P₅, 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) R₃ and P₂ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



each of A₁, A₂, and A₃ 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, CH₂, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q₁ is independently OR_A, SR_A, SO₂R_A, OSO₂R_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; and

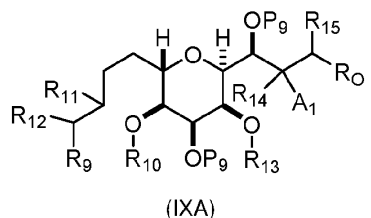
X₁ is —CH₂— or —O—;

the method comprising:

(A) producing a compound of formula (IXB) from a compound of formula (IXA), a compound of formula (IIB), a compound of formula (IIA), a compound of formula (IIIE), and R₅OH,

wherein R₅ is optionally substituted acyl;

wherein the compound of formula (IXA) is:



wherein

R₉ is —CHO or —COOP'';

(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;

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} combine to form a double bond;

or

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

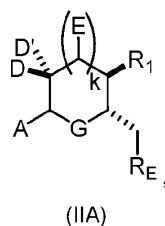
R_O is $-CHO$, $-CH_2OP''$, $-CH=CH_2$, $-CH(OP'')CH_2OP''$, $-C(O)-CH_2P(O)(OR_C)_2$, or halogen;

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

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

each P_9 is independently a hydroxyl protecting group;

wherein the compound of formula (IIA) is:



wherein

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

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

R_E is $-CHO$ or $-CH_{(1+m)}(OR_F)_{(2-m)}$,

wherein

m is 1, and R_F is a hydroxyl protecting group,

or

m is 0, and

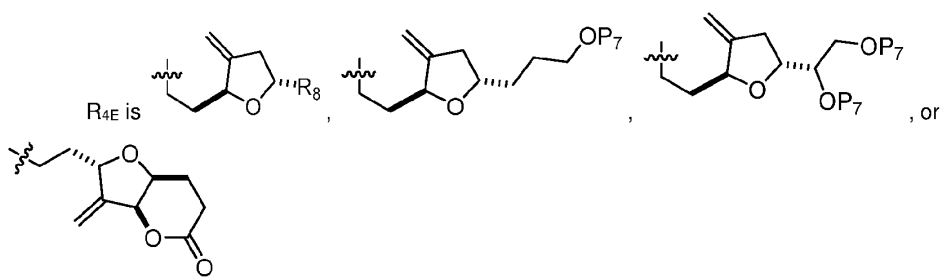
(i) each R_F is independently an alkyl or hydroxyl protecting group, or

(ii) both R_F combine to form an alkylene;

wherein the compound of formula (IIIE) is:



wherein



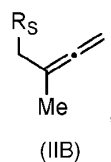
wherein

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

R_8 is $-\text{CH}_2\text{CH}_2-\text{COOR}_C$, $-\text{CH}=\text{CH}-\text{COOR}_C$, $-\text{CH}_2\text{CH}_2-\text{SO}_2\text{R}_D$, or $-\text{CH}=\text{CH}-\text{SO}_2\text{R}_D$;

and

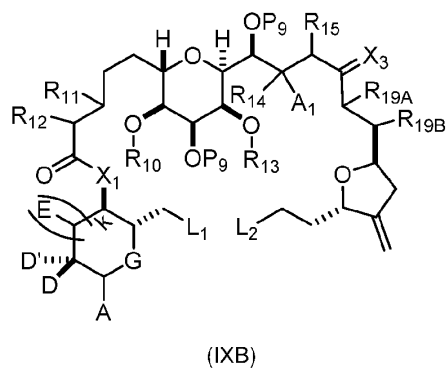
R_7 is $-\text{CHO}$ or , wherein each R_{7A} is independently an optionally substituted alkyl; wherein the compound of formula (IIB) is:



wherein R_S is silyl;

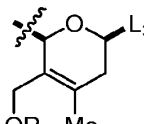
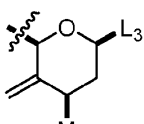
and

wherein the compound of formula (IXB) is:



wherein

X_1 is $-\text{CH}_2-$, $-\text{CH}(\text{Y})-$, $-\text{C}(\text{Y})_2-$, or $-\text{O}-$;

L_1 is  or , wherein L_2 and L_3 combine to form a bond;

R_5 is optionally substituted acyl;

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

or

A₁ is H or -OPⁿ, and:

- (i) R₁₃ is H or a hydroxyl protecting group, and R₁₄ and R₁₅, together with the atoms to which each is attached, combine to form a double bond;

or

- (ii) R₁₃ and R₁₄ combine to form a bond, and R₁₅ is H or -OPⁿ;

each P₉ is independently H or a hydroxyl protecting group, and X₃ is oxo, or X₃, together with the atom to which it is attached, combines to form -(CH(OP₁₁))- , wherein P₁₁ is H or a hydroxyl protecting group;

or

both P₉ and X₃, together with the atoms to which each is attached, combine to form a ketal;

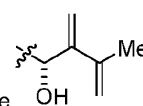
and

R_{19A} is H, -OPⁿ, 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;

and

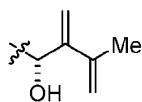
(B) producing the halichondrin macrolide or analog thereof from the compound of formula (IXB).

103. The method of claim 102, wherein step (A) comprises reacting R_E that is -CHO with the

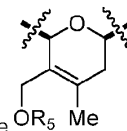


compound of formula (IIB) and a first Lewis acid to produce a group of the structure

104. The method of claim 103, wherein step (A) comprises reacting the group of the structure



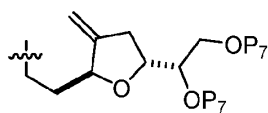
with R₇, R₅OH, and a second Lewis acid to produce a group of the structure



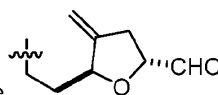
105. The method of claim 104, wherein the first Lewis acid and/or second Lewis acid is an oxophilic Lewis acid.

106. The method of claim 104 or 105, wherein the first Lewis acid is same as the second Lewis acid.

107. The method of any one of claims 102 to 106, wherein step (A) comprises converting R_{4E} that is



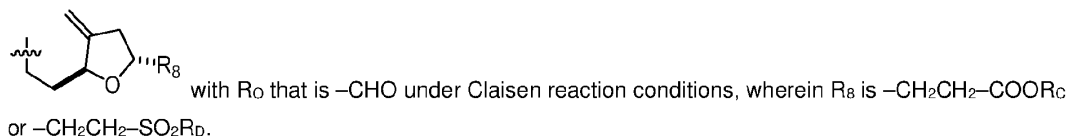
to a group of the structure



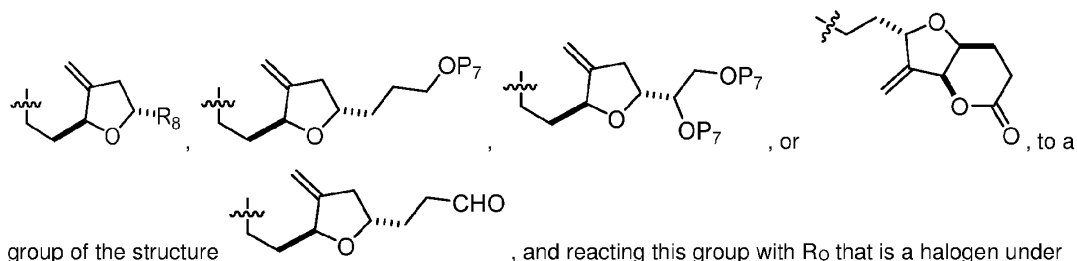
, and reacting this group with R₀

that is -C(O)-CH₂P(O)(OR_C)₂ under Horner-Wadsworth-Emmons reaction conditions.

108. The method of any one of claims 102 to 106, wherein step (A) comprises reacting R_{4E} that is



109. The method of any one of claims 102 to 106, wherein step (A) comprises converting R_{4E} that is



110. The method of any one of claims 102 to 109, wherein step (A) comprises reacting R_1 that is $-OP_6$ and R_9 under esterification reaction conditions to produce a group of the structure $-X_1-C(O)-$, wherein P_6 is H, R_9 is $-COOH$, and X_1 is $-O-$.

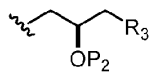
111. The method of any one of claims 102 to 110, wherein step (A) comprises reacting R_1 that is $-CH(Y)_2$ or $-CH_2(Y)$ with R_9 under Claisen reaction conditions to produce a group of the structure $-X_1-C(O)-$, wherein R_9 is $-CHO$, and X_1 is $-C(Y)_2-$ or $-CH(Y)-$, respectively.

112. The method of any one of claims 102 to 111, wherein step (B) comprises reacting the compound of formula (IXB) with a hydroxyl protecting group removing agent.

113. The method of any one of claims 1 to 112, wherein D' is OP_1 , wherein P_1 is alkyl.

114. The method of any one of claims 1 to 113, wherein D is H.

115. The method of any one of claims 1 to 114, wherein A is of the following structure:

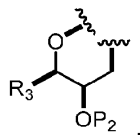


116. The method of any one of claims 1 to 115, wherein k is 0.

117. The method of any one of claims 1 to 116, wherein R_3 is $-(CH_2)_nNP_3P_4$ or $-(CH_2)_nOP_5$, wherein n is 0.

118. The method of any one of claims 1 to 112, wherein D' is H.

119. The method of any one of claims 1 to 112 and 118, wherein A and D combine to form the following structure:



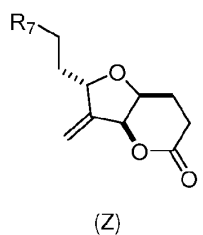
wherein, the bond to oxygen atom originates at the carbon atom, to which D is attached in formula (IA), and

wherein R₃ is $-(CH_2)_nNP_3P_4$ or $-(CH_2)_nOP_5$, wherein n is 2.

120. The method of any one of claims 1 to 112, 118, and 119, wherein k is 1, and E is optionally substituted alkyl.

121. The method of any one of claims 1 to 120, wherein G is O.

122. A method of preparing:



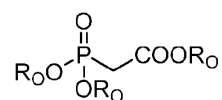
wherein R₇ is $-CHO$ or $R_{7A}O-CH(OR_{7A})-$, and

each R_{7A} is independently alkyl or a hydroxyl protecting group; or

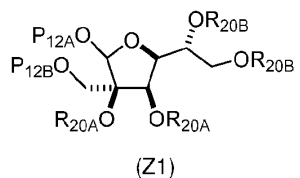
both R_{7A} combine to form an optionally substituted alkylene;

the method comprising:

(A) producing a compound of formula (Z2) from a compound of formula (Z1) and



, wherein each R₀ is independently optionally substituted alkyl, wherein the compound of formula (Z1) is:



wherein

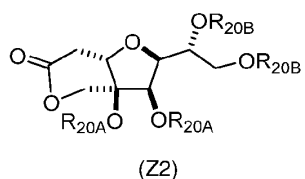
each R_{20A} is independently a hydroxyl protecting group, or both R_{20A} , together with the atoms to which each is attached, combine to form an acetal, ketal, cyclic carbonate, dicarbonyl-dioxo, or silylene-dioxo;

each R_{20B} is independently a hydroxyl protecting group, or both R_{20B} , together with the atoms to which each is attached, combine to form an acetal, ketal, cyclic carbonate, dicarbonyl-dioxo, or silylene-dioxo;

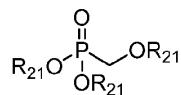
P_{12A} is H;

P_{12B} is H or a hydroxyl protecting group;

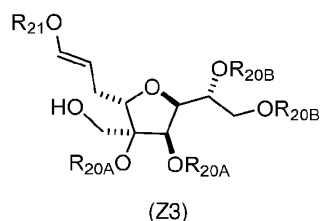
and the compound of formula (Z2) is:



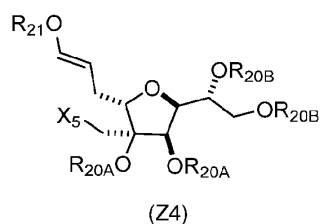
(B) producing a compound of formula (Z3) from the compound of formula (Z2) and



, wherein each R_{21} is independently optionally substituted alkyl, wherein the compound of formula (Z3) is:

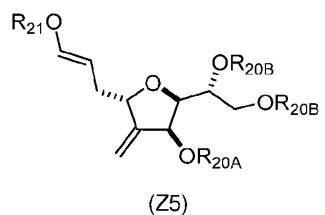


(C) producing a compound of formula (Z4) from the compound of formula (Z3), wherein the compound of formula (Z4) is:



wherein X_5 is a halogen;

(D) producing a compound of formula (Z5) from the compound of formula (Z4), wherein the compound of formula (Z5) is:

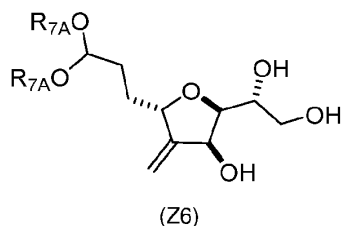


wherein

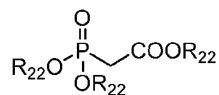
R_{20A} is H or a hydroxyl protecting group; and

each R_{20B} is independently H or a hydroxyl protecting group, or both R_{20B} , together with the atoms to which each is attached, combine to form an acetal, ketal, cyclic carbonate, dicarbonyl-dioxo, or silylene-dioxo;

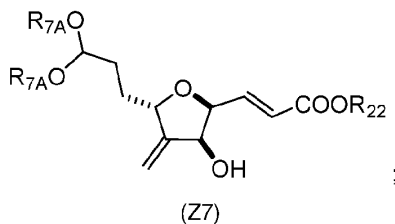
(E) producing a compound of formula (Z6) from the compound of formula (Z5) and R_7A OH



(F) producing a compound of formula (Z7) from the compound of formula (Z6) and



, wherein each R_{22} is independently optionally substituted alkyl, and the compound of formula (Z7) is:

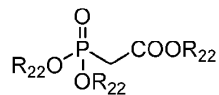


and

(G) producing the compound of formula (Z) from the compound of formula (Z7).

123. The method of claim 122, wherein step (E) comprises reacting the compound of formula (Z5) with R_7A OH and a Brønsted acid.

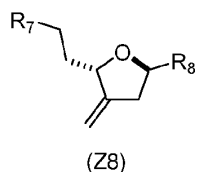
124. The method of claim 122 or 123, wherein step (F) comprises reacting the compound of formula (Z6) with a glycol cleaving agent to produce an aldehyde product, and reacting the aldehyde product with



under Horner-Wadsworth-Emmons reaction conditions.

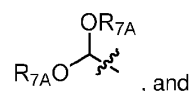
125. The method of any one of claims 122 to 124, wherein step (G) comprises reacting the compound of formula (Z6) with a 1,4-reducing agent.

126. A method of preparing:



wherein

R₇ is -CHO or



each R_{7A} is independently alkyl or a hydroxyl protecting group; or

both R_{7A} combine to form an optionally substituted alkylene;

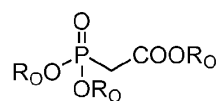
R₈ is -CH₂CH₂-COOR_C, -CH=CH-COOR_C, -CH₂CH₂-SO₂R_D, or -CH=CH-SO₂R_D;

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

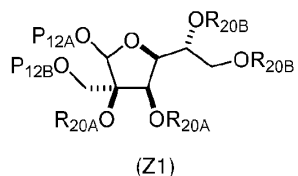
R_D, when present, is independently optionally substituted aryl or optionally substituted non-enolizable alkyl;

the method comprising:

(A) producing a compound of formula (Z2) from a compound of formula (Z1) and



of formula (Z1) is:



wherein

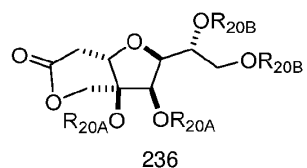
each R_{20A} is independently a hydroxyl protecting group, or both R_{20A}, together with the atoms to which each is attached, combine to form an acetal, ketal, cyclic carbonate, dicarbonyl-dioxo, or silylene-dioxo;

each R_{20B} is independently a hydroxyl protecting group, or both R_{20B}, together with the atoms to which each is attached, combine to form an acetal, ketal, cyclic carbonate, dicarbonyl-dioxo, or silylene-dioxo;

P_{12A} is H;

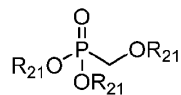
P_{12B} is H or a hydroxyl protecting group;

and the compound of formula (Z2) is:

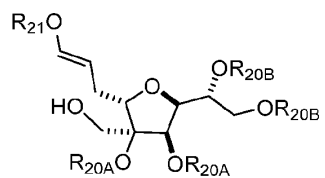


(Z2)

(B) producing a compound of formula (Z3) from the compound of formula (Z2) and

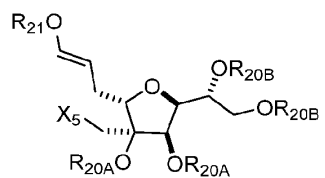


, wherein each R_{21} is independently optionally substituted alkyl, wherein the compound of formula (Z3) is:



(Z3)

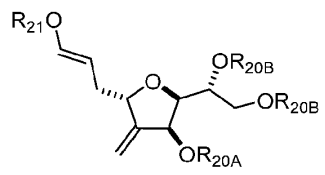
(C) producing a compound of formula (Z4) from the compound of formula (Z3), wherein the compound of formula (Z4) is:



(Z4)

wherein X_5 is a halogen;

(D) producing a compound of formula (Z5) from the compound of formula (Z4), wherein the compound of formula (Z5) is:



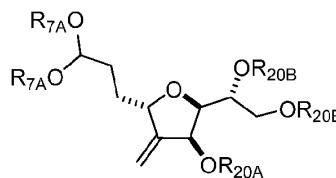
(Z5)

wherein

$\text{R}_{20\text{A}}$ is H or a hydroxyl protecting group; and

each $\text{R}_{20\text{B}}$ is independently H or a hydroxyl protecting group, or both $\text{R}_{20\text{B}}$, together with the atoms to which each is attached, combine to form an acetal, ketal, cyclic carbonate, dicarbonyl-dioxo, or silylene-dioxo;

(E) producing a compound of formula (Z5A) from the compound of formula (Z5) and $\text{R}_7\text{A}\text{OH}$, wherein the compound of formula (Z5A) is:



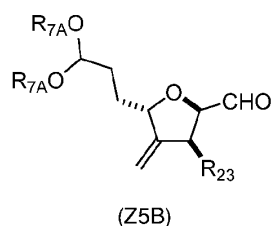
(Z5A)

wherein

R_{20A} is H or a hydroxyl protecting group; and

each R_{20B} is independently H or a hydroxyl protecting group, or both R_{20B} , together with the atoms to which each is attached, combine to form an acetal, ketal, cyclic carbonate, dicarbonyl-dioxo, or silylene-dioxo;

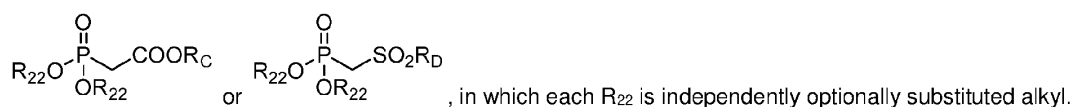
(F) producing a compound of formula (Z5B) from the compound of formula (Z5A), wherein the compound of formula (Z5B) is:



wherein R_{23} is H or $-OR_{20A}$;

and

(G) producing the compound of formula (Z8) from the compound of formula (Z5B) and



127. The method of claim 126, wherein step (E) comprises reacting the compound of formula (Z5) with $R_{7A}OH$ and a Brønsted acid.

128. The method of claim 126 or 127, wherein step (F) comprises reacting the compound of formula (Z5A), in which both R_{20B} are H, with a glycol cleaving agent.

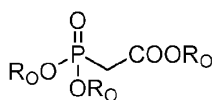
129. The method of any one of claims 126 to 128, wherein step (E) or step (F) further comprises reacting $-OR_{20A}$, wherein R_{20A} is optionally substituted acyl with an allylic reducing agent.

130. The method of any one of claims 126 to 129, wherein step (G) comprises reacting the

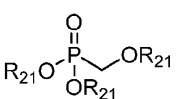
compound of formula (Z5B) with $R_{22}O-P(=O)(OR_{22})-CH_2-COOR_C$ or $R_{22}O-P(=O)(OR_{22})-CH_2-SO_2R_D$ under Horner-Wadsworth-Emmons reaction conditions to produce the compound of formula (Z8), in which R_8 is $-CH=CH-COOR_C$ or $-CH=CH-SO_2R_D$, respectively.

131. The method of claim 130, wherein step (G) further comprises reacting the compound of formula (Z8), in which R_8 is $-CH=CH-COOR_C$ or $-CH=CH-SO_2R_D$, with a 1,4-reducing agent to produce the compound of formula (Z8), in which R_8 is $-CH_2CH_2-COOR_C$ or $-CH_2CH_2-SO_2R_D$, respectively.

132. The method of any one of claims 122 to 131, wherein the producing the compound of formula

(Z2) comprises reacting the compound of formula (Z1) with  under Horner-Wadsworth-Emmons reaction conditions.

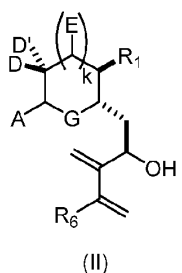
133. The method of any one of claims 122 to 132, wherein step (B) comprises reacting the compound of formula (Z2) with a 1,2-reducing agent to produce a reduction product, and reacting the

reduction product with  under Horner-Wadsworth-Emmons reaction conditions.

134. The method of any one of claims 122 to 133, wherein step (C) comprises substituting free hydroxyl group in the compound of formula (Z3) with a halogen.

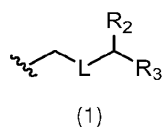
135. The method of any one of claims 122 to 134, wherein step (D) comprises subjecting the compound of formula (Z4) to reductive metal conditions.

136. A compound of formula (II):



wherein

each of D and D' is independently H, optionally substituted alkyl, or OP₁, provided that only one of D and D' is OP₁, wherein P₁ is H, alkyl, a hydroxyl protecting group, and A is a C₁₋₆ saturated or C₂₋₆ 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 Q₁, or A is a group of formula (1):



wherein

L is -(CH(OP₂))- , -(C(OH)(OP₂))- , or -C(O)-;

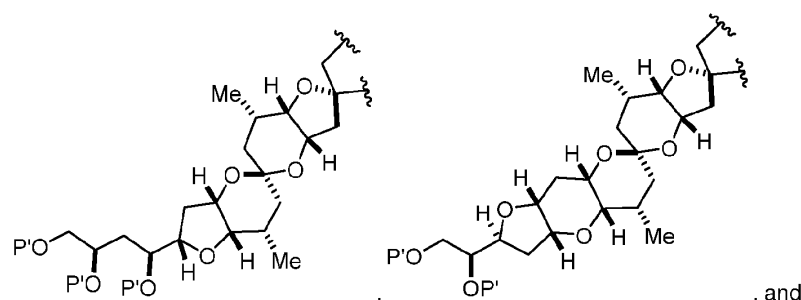
R₂ is H and P₁ is absent, H, alkyl, or a hydroxyl protecting group, or R₂ and P₁ combine to form a bond;

(i) R₃ is H, and P₂ 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:



, 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;

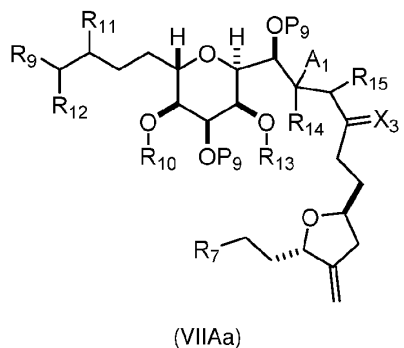
R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and

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

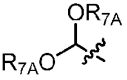
R_D , when present, is optionally substituted aryl or optionally substituted non-enolizable alkyl.

137. A compound of formula (VIIAa):



where

R_7 is $-\text{CH}_2\text{OP}^*$, $-\text{CHO}$, or

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

R_9 is $-\text{CH}_2\text{OP}^*$, $-\text{CHO}$, or $-\text{COOP}^*$;

(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 $-\text{OP}^*$, and:

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

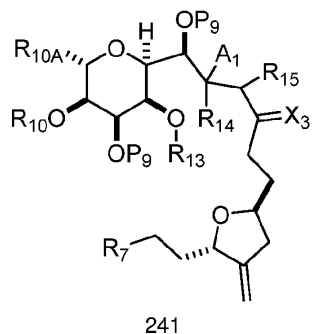
or

(ii) R_{13} and R_{14} combine to form a bond, and R_{15} is H or $-\text{OP}^*$;

each P^* is independently H or a hydroxyl protecting group; and

each P_9 is independently a hydroxyl protecting group, and X_3 is oxo or X_3 , together with the carbon atom to which it is attached, is $-(\text{CH}(\text{OP}_{11}))$, where P_{11} is H or a hydroxyl protecting group; or both P_9 groups and X_3 , together with the atoms to which each is attached, combine to form a ketal.

138. A compound of formula (VIAa):



(VIAa)

where

 R_7 is $-\text{CHO}$ or R_{10A} is $-\text{CH}_2-\text{CH}=\text{CH}_2$, $-(\text{CH}_2)_2-\text{CH}=\text{CH}_2$, or $-(\text{CH}_2)_3-\text{OP}_{10}$;each of R_{10} and P_{10} is independently a hydroxyl protecting group; 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 $-\text{OP}''$, and:(i) R_{13} is H or a hydroxyl protecting group, and R_{14} and R_{15} combine to form a double bond;

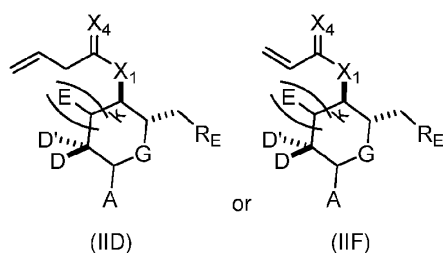
or

(ii) R_{13} and R_{14} combine to form a bond, and R_{15} is H or $-\text{OP}''$;

and

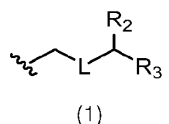
each P_9 is independently a hydroxyl protecting group, and X_3 is oxo or X_3 , together with the carbon atom to which it is attached, is $-(\text{CH}(\text{OP}_{11}))$ -, wherein P_{11} is H or a hydroxyl protecting group; or both P_9 groups and X_3 , together with the atoms to which each is attached, combine to form ketal.

139. A compound of formula (IID) or (IIF):



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):



wherein

 L is $-(\text{CH}(\text{OP}_2))$ -, $-(\text{C}(\text{OH})(\text{OP}_2))$ -, or $-\text{C}(\text{O})$ -;

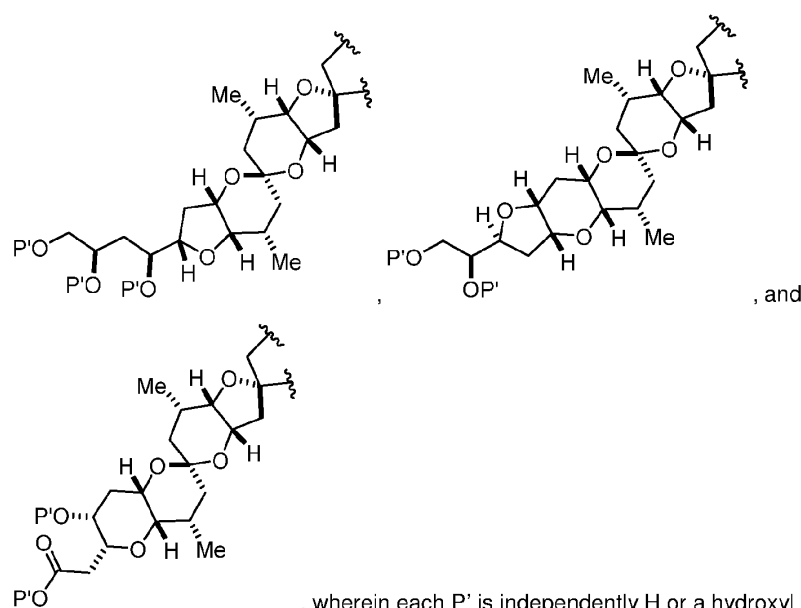
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

(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;

(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:



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 $-O-$;

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; and

R_E is $-CHO$ or $-CH_{(1+m)}(OR_F)_{(2-m)}$, wherein

m is 1, and R_F is a hydroxyl protecting group,

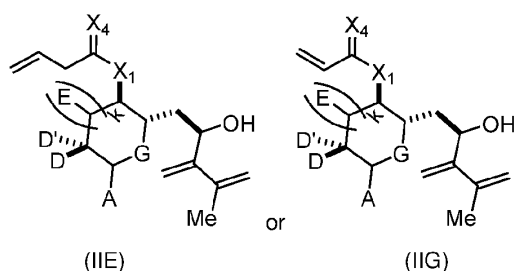
or

m is 0, and

(i) each R_F is independently an alkyl or hydroxyl protecting group, or

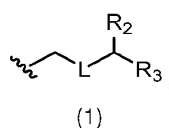
(ii) both R_F combine to form an alkylene.

140. A compound of formula (IIE) or (IIG):



wherein

each of D and D' is independently H, optionally substituted alkyl, or OP₁, provided that only one of D and D' is OP₁, wherein P₁ is H, alkyl, a hydroxyl protecting group, and A is a C₁₋₆ saturated or C₂₋₆ 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 Q₁, or A is a group of formula (1):



wherein

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

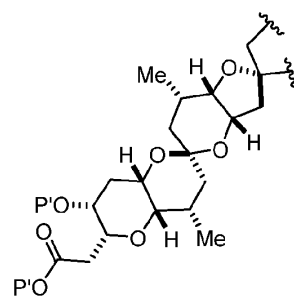
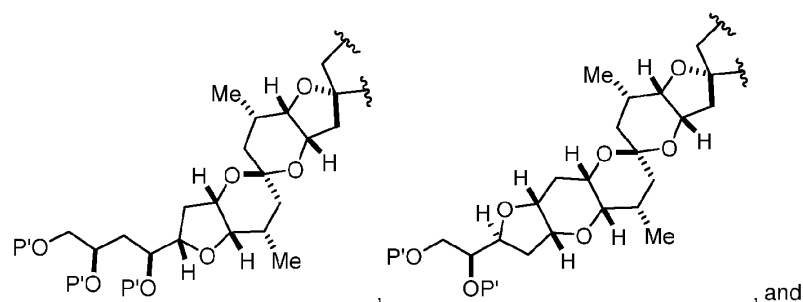
R₂ is H and P₁ is absent, H, alkyl, or a hydroxyl protecting group, or R₂ and P₁ combine to form a bond;

(i) R₃ is H, and P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R₃ is $-(CH_2)_nNP_3P_4$, wherein P₃ is H or an N-protecting group, and (a) P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₄ is H or an N-protecting group, (b) P₂ and P₄ combine to form an alkylidene, or (c) each of P₂ and P₄ is H;

(iii) R₃ is $-(CH_2)_nOP_5$, wherein P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₅ is H, optionally substituted alkyl, or a hydroxyl protecting group; or P₂ and P₅, 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) R₃ and P₂ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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

G is O, S, CH₂, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q₁ is independently OR_A, SR_A, SO₂R_A, OSO₂R_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;

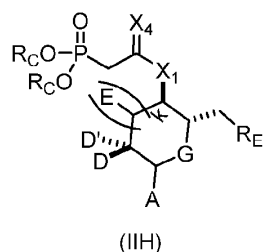
n, when present, is 0, 1, or 2;

k is 0 or 1;

X₁ is -CH₂- or -O-; and

X₄ is oxo, or X₄, together with the atom to which it is attached, is -(CH(OP₁₂))- , where P₁₂ is H or a hydroxyl protecting group.

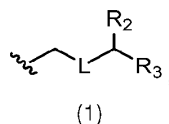
141. A compound of formula (IIH):



wherein

each of D and D' is independently H, optionally substituted alkyl, or OP₁, provided that only one of D and D' is OP₁, wherein P₁ is H, alkyl, a hydroxyl protecting group, and A is a C₁₋₆ saturated or C₂₋₆

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 Q₁, or A is a group of formula (1):



wherein

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

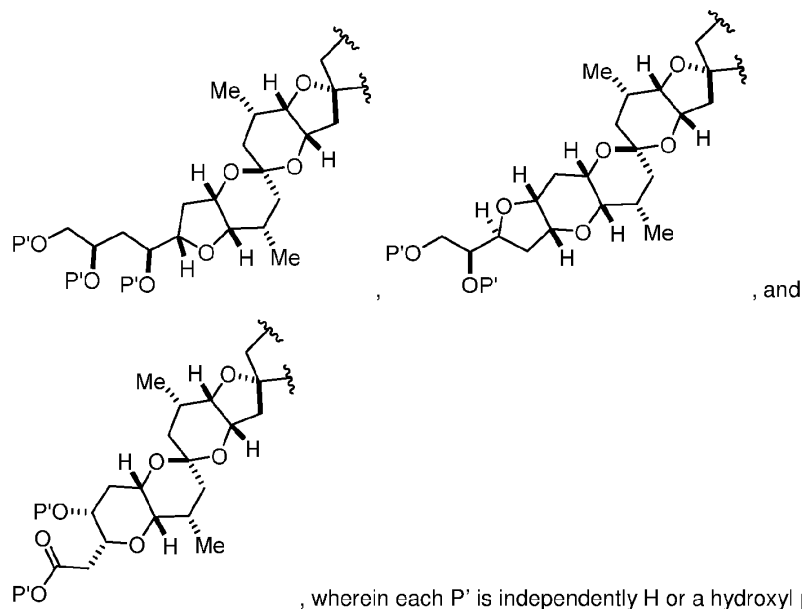
R₂ is H and P₁ is absent, H, alkyl, or a hydroxyl protecting group, or R₂ and P₁ combine to form a bond;

(i) R₃ is H, and P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R₃ is $-(CH_2)_nNP_3P_4$, wherein P₃ is H or an N-protecting group, and (a) P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₄ is H or an N-protecting group, (b) P₂ and P₄ combine to form an alkylidene, or (c) each of P₂ and P₄ is H;

(iii) R₃ is $-(CH_2)_nOP_5$, wherein P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₅ is H, optionally substituted alkyl, or a hydroxyl protecting group; or P₂ and P₅, 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) R₃ and P₂ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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

G is O, S, CH₂, 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 independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

X_1 is $-CH_2-$ or $-O-$;

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; and

R_E is $-CHO$ or $-CH_{(1+m)}(OR_F)_{(2-m)}$, wherein

m is 1, and R_F is a hydroxyl protecting group,

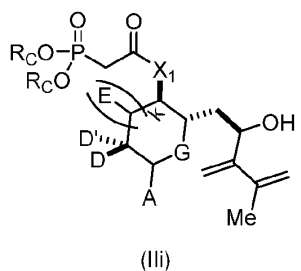
or

m is 0, and

(i) each R_F is independently an alkyl or hydroxyl protecting group, or

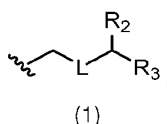
(ii) both R_F combine to form an alkylene.

142. A compound of formula (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, 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):



wherein

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

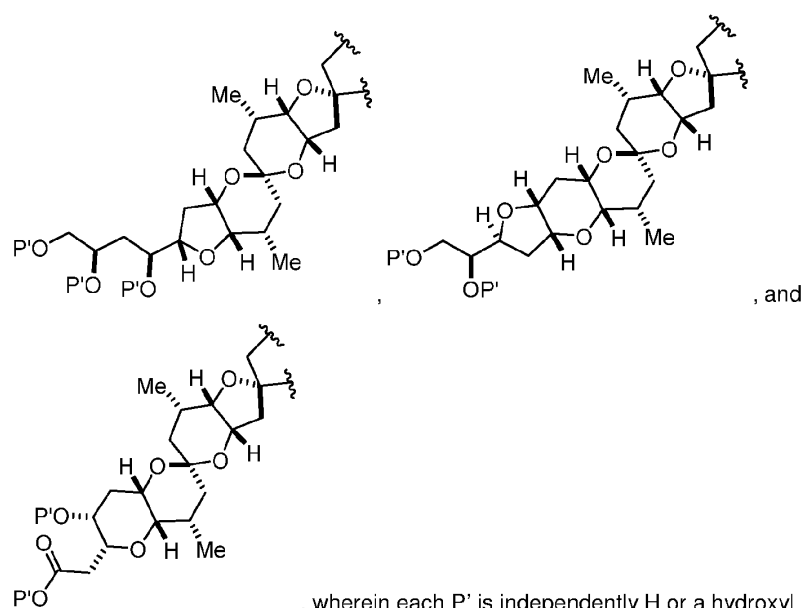
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

(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;

(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:



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;

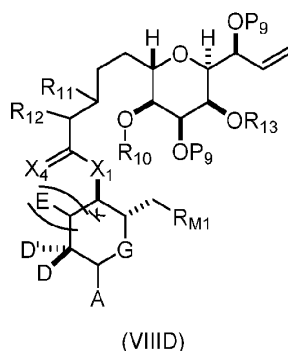
n , when present, is 0, 1, or 2;

k is 0 or 1;

each R_c is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl; and

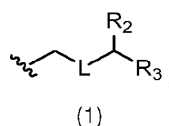
X_1 is $-CH_2-$ or $-O-$.

143. A compound of formula (VIII D):



wherein

each of D and D' is independently H, optionally substituted alkyl, or OP₁, provided that only one of D and D' is OP₁, wherein P₁ is H, alkyl, a hydroxyl protecting group, and A is a C₁₋₆ saturated or C₂₋₆ 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 Q₁, or A is a group of formula (1):



wherein

L is $\text{---}(\text{CH}(\text{OP}_2))\text{---}$, $\text{---}(\text{C}(\text{OH})(\text{OP}_2))\text{---}$, or $\text{---}\text{C}(\text{O})\text{---}$;

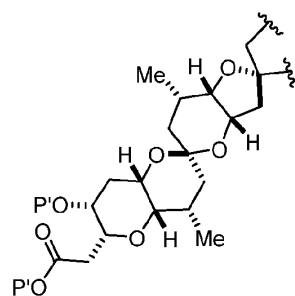
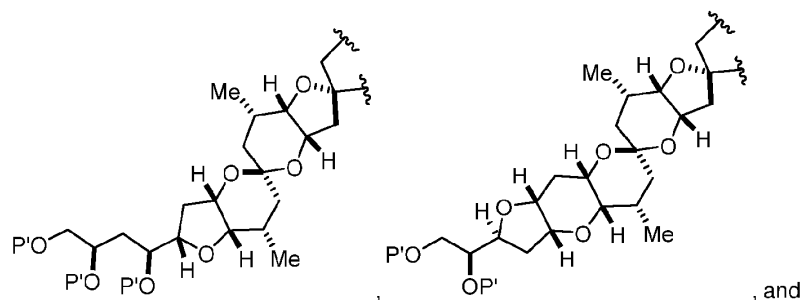
R₂ is H and P₁ is absent, H, alkyl, or a hydroxyl protecting group, or R₂ and P₁ combine to form a bond;

(i) R₃ is H, and P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R₃ is $\text{---}(\text{CH}_2)_n\text{NP}_3\text{P}_4$, wherein P₃ is H or an N-protecting group, and (a) P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₄ is H or an N-protecting group, (b) P₂ and P₄ combine to form an alkylidene, or (c) each of P₂ and P₄ is H;

(iii) R₃ is $\text{---}(\text{CH}_2)_n\text{OP}_5$, wherein P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₅ is H, optionally substituted alkyl, or a hydroxyl protecting group; or P₂ and P₅, 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) R₃ and P₂ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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

G is O, S, CH₂, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q₁ is independently OR_A, SR_A, SO₂R_A, OSO₂R_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;

X₁ is -CH₂-, -CH(Y)-, -C(Y)₂-, or -O-, wherein each Y is independently -COOR_C or -SO₂R_D;

X₄ is oxo, or X₄, together with the atom to which it is attached, is -(CH(OP₁₂))- , wherein P₁₂ is H or a hydroxyl protecting group;

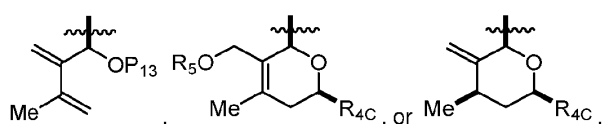
each P₉ and R₁₃ is independently a hydroxyl protecting group;

(i) R₁₀ is a hydroxyl protecting group, R₁₁ is alkyl ether, and R₁₂ is H;

(ii) R₁₀ is a hydroxyl protecting group, and R₄ and R₅ combine to form a double bond; or

(iii) R₁₀ and R₁₁ combine to form a bond, and R₁₂ is H;

R_{M1} is

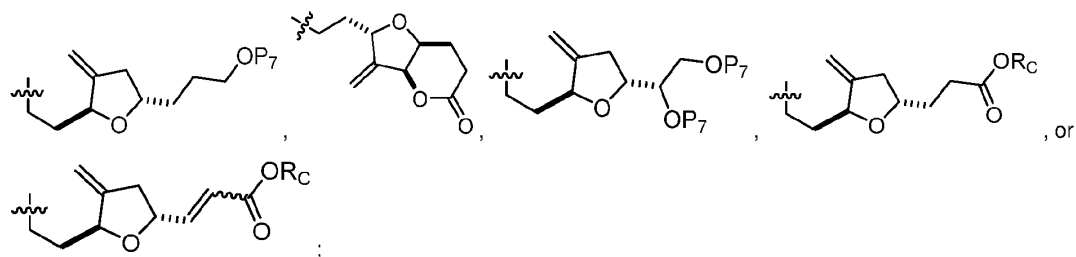


wherein

R₅ is optionally substituted acyl;

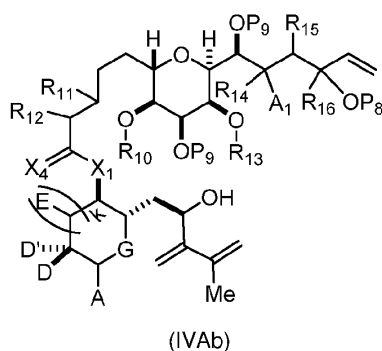
P₁₃ is H or a hydroxyl protecting group; and

R_{4C} is



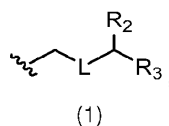
wherein R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl; and P₇, when present, is independently H or a hydroxyl protecting group.

144. A compound of formula (IVAb):



wherein

each of D and D' is independently H, optionally substituted alkyl, or OP₁, provided that only one of D and D' is OP₁, wherein P₁ is H, alkyl, a hydroxyl protecting group, and A is a C₁₋₆ saturated or C₂₋₆ 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 Q₁, or A is a group of formula (1):



wherein

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

R₂ is H and P₁ is absent, H, alkyl, or a hydroxyl protecting group, or R₂ and P₁ combine to form a bond;

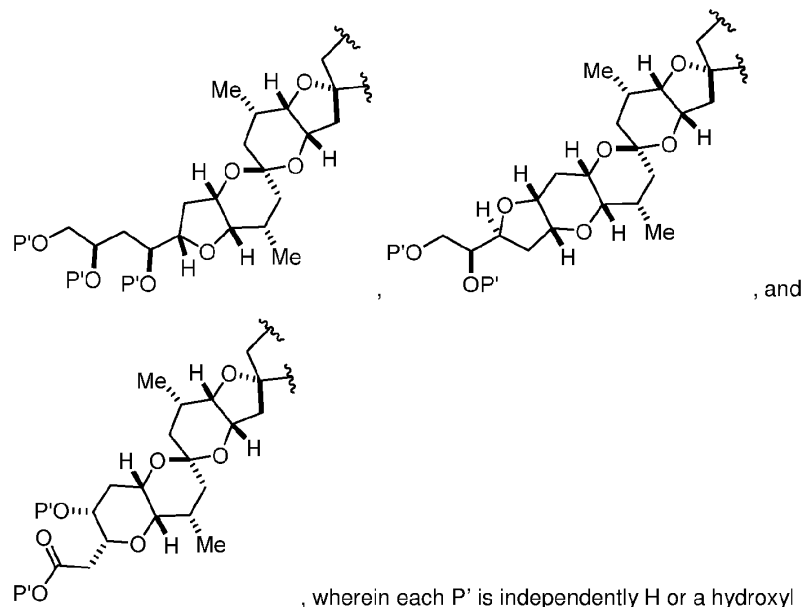
(i) R₃ is H, and P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R₃ is $-(CH_2)_nNP_3P_4$, wherein P₃ is H or an N-protecting group, and (a) P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₄ is H or an N-protecting group, (b) P₂ and P₄ combine to form an alkylidene, or (c) each of P₂ and P₄ is H;

(iii) R₃ is $-(CH_2)_nOP_5$, wherein P₂ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P₅ is H, optionally substituted alkyl, or a hydroxyl protecting group

group; or P₂ and P₅, 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) R₃ and P₂ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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

G is O, S, CH₂, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q₁ is independently OR_A, SR_A, SO₂R_A, OSO₂R_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;

X₁ is —CH₂—, —CH(Y)—, —C(Y)₂—, or —O—, wherein each Y is independently —COOR_C or —SO₂R_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;

X₄ is oxo, or X₄, together with the atom to which it is attached, is —(CH(OP₁₂))—, where P₁₂ is H or a hydroxyl protecting group;

each P₉ is independently a hydroxyl protecting group;

(a1) R₁₀ is H or a hydroxyl protecting group, R₁₁ is alkyl ether, and R₁₂ is H;

(a2) R₁₀ is H or a hydroxyl protecting group, and R₁₁ and R₁₂ combine to form a double bond;

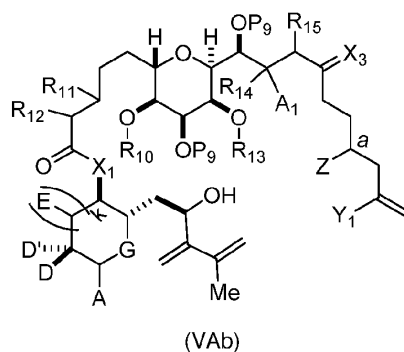
or

- (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

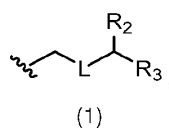
each P'' , when present, is independently H or a hydroxyl protecting group.

145. A compound of formula (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, 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):



wherein

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

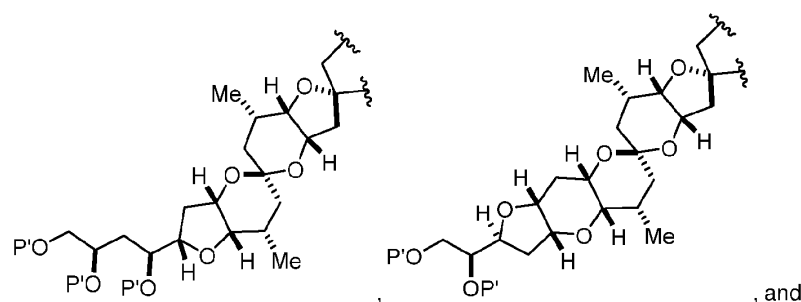
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

(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;

(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:



, 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;

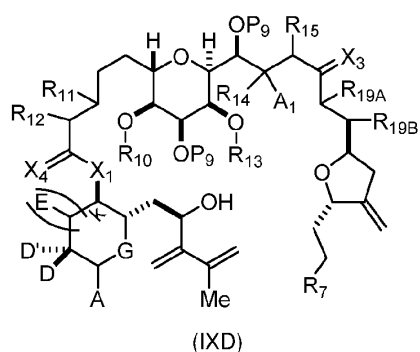
or

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

and

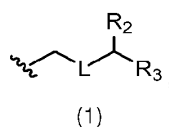
each P'' is independently a hydroxyl protecting group.

146. A compound of formula (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, 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):



wherein

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

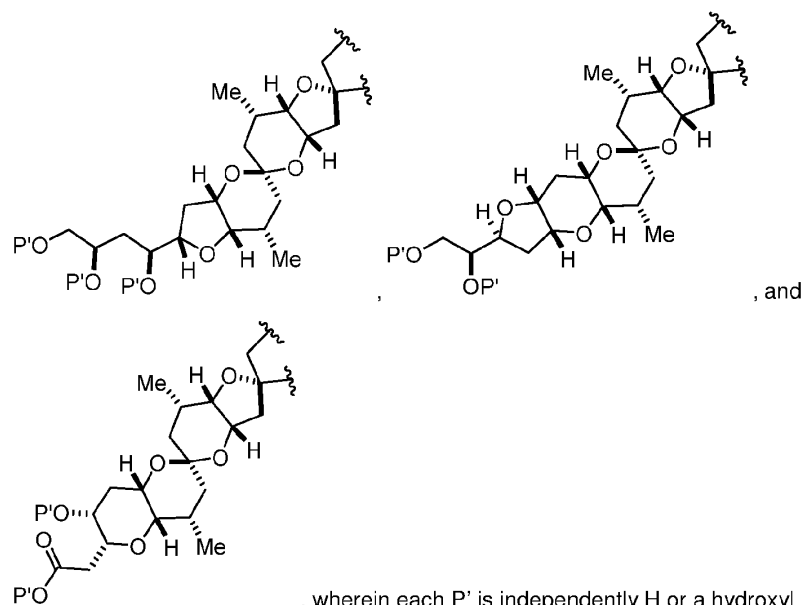
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

(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;

(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:



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



(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;

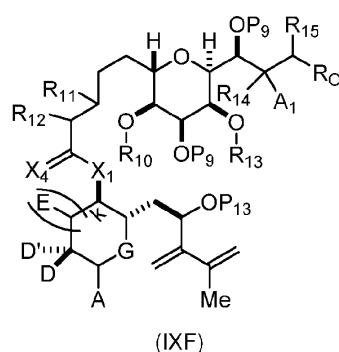
or

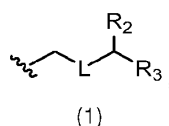
(ii) R_{13} and R_{14} combine to form a bond, and R_{15} is H or $-OP''$; each P_9 is independently H or a hydroxyl protecting group,

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.

147. A compound of formula (IXF):





wherein

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

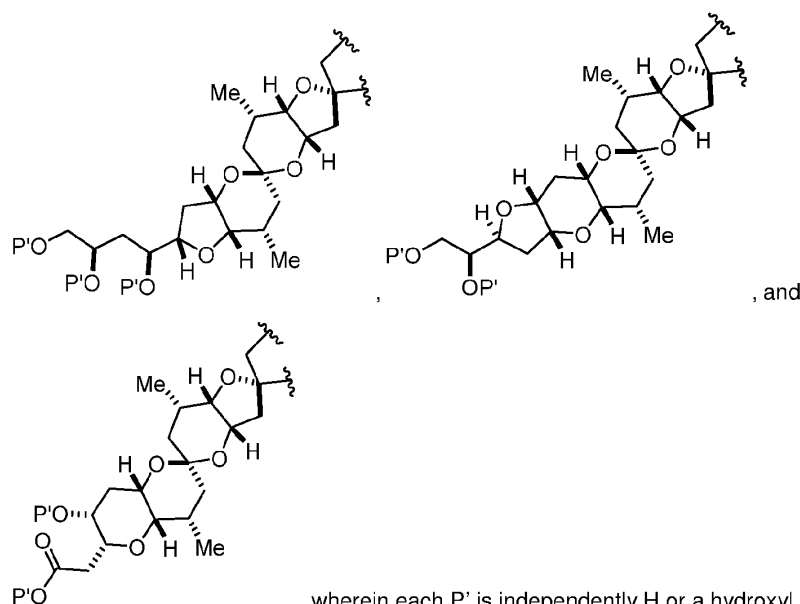
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

(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;

(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:



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;

X₁ is $-\text{CH}_2-$, $-\text{CH}(\text{Y})-$, $-\text{C}(\text{Y})_2-$, or $-\text{O}-$, wherein each Y is independently $-\text{COOR}_\text{C}$ or $-\text{SO}_2\text{R}_\text{D}$;

X₄ is oxo, or X₄, together with the atom to which it is attached, is $-(\text{CH}(\text{OP}_{12}))-$, where P₁₂ 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 $-\text{CHO}$, $-\text{CH}_2\text{OP}''$, $-\text{CH}=\text{CH}_2$, $-\text{CH}(\text{OP}'')\text{CH}_2\text{OP}''$, $-\text{C}(\text{O})-\text{CH}_2\text{P}(\text{O})(\text{OR}_\text{C})_2$, or halogen;

(i) R₁₀ is a hydroxyl protecting group, R₁₁ is alkyl ether, and R₁₂ is H;

(ii) R₁₀ is a hydroxyl protecting group, and R₁₁ and R₁₂ combine to form a double bond; or

(iii) R₁₀ and R₁₁ combine to form a bond, and R₁₂ is H;

A₁ and R₁₄ combine to form oxo, R₁₃ is H or a hydroxyl protecting group, and R₁₅ is H;

or

A₁ is H or $-\text{OP}''$, and

(i) R₁₃ is H or a hydroxyl protecting group, and R₁₄ and R₁₅, together with the atoms to which each is attached, combine to form a double bond;

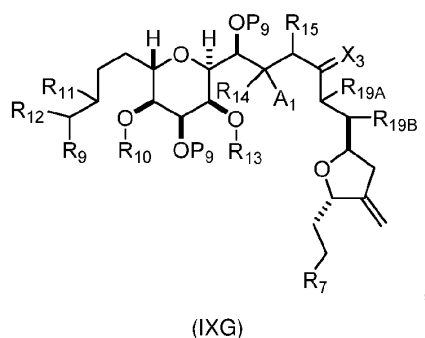
or

(ii) R₁₃ and R₁₄ combine to form a bond, and R₁₅ is H or $-\text{OP}''$; each P₉ is independently H or a hydroxyl protecting group;

and

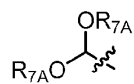
each of P'', P₉, and P₁₃ is independently H or a hydroxyl protecting group.

148. A compound of formula (IXG):



wherein

R₇ is $-\text{CHO}$, $-\text{CH}_2\text{OP}_\text{A}$, or



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

(i) R₁₀ is a hydroxyl protecting group, R₁₁ is alkyl ether, and R₁₂ is H;

(ii) R₁₀ is a hydroxyl protecting group, and R₁₁ and R₁₂ combine to form a double bond; or

(iii) R₁₀ and R₁₁ combine to form a bond, and R₁₂ is H;

A₁ and R₁₄ combine to form oxo, R₁₃ is H or a hydroxyl protecting group, and R₁₅ is H;

or

A₁ is H or -OP", and

(i) R₁₃ is H or a hydroxyl protecting group, and R₁₄ and R₁₅, together with the atoms to which each is attached, combine to form a double bond;

or

(ii) R₁₃ and R₁₄ combine to form a bond, and R₁₅ is H or -OP"; each P₉ is independently H or a hydroxyl protecting group,

each P₉ is independently a hydroxyl protecting group, and X₃ is oxo, or X₃, together with the atom to which it is attached, combines to form -(CH(OP₁₁))- , where P₁₁ is H or a hydroxyl protecting group; or both P₉ and X₃, 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.

149. A compound of formula (Z), (Z1), (Z2), (Z3), (Z4), (Z5), (Z5A), (Z5B), or (Z6).