PRINS REACTION AND COMPOUNDS USEFUL IN THE SYNTHESIS OF HALICHONDRIN MACROLIDES AND ANALOGS THEREOF

Background

The invention relates to intermediates useful in the synthesis of pharmaceutically active macrolide compounds and methods of synthesizing macrolide compounds. Halichondrin B is a potent anticancer agent originally isolated from the marine sponge *Halichondria okadai*, and subsequently found in *Axinella* sp., *Phakellia carteri*, and *Lissodendoryx* sp. A total synthesis of halichondrin B was published in 1992 (Aicher, T. D. et al., J. Am. Chem. Soc. 114:3162-3164). Further synthetic and structure-activity relationship studies have been disclosed in U.S. Patent Nos. 5,338,865 and 5,436,238 and in Towle et al., *Annual Meeting of the American Association for Cancer Research*, April 6-10, 2002, 5721 and Wanget al., *Bioorg. Med. Chem. Lett.*, 10:1029-1032, 2000. Eribulin mesylate (also called Halaven®, E7389, and the mesylate salt of B1939), a nontaxane microtubule dynamics inhibitor, is a structurally simplified, synthetic analog of halichondrin B. Methods and intermediates for the synthesis of certain halichondrin B analogs and intermediates are described in International Publication Nos. WO 2005/118565, WO 2009/046308, WO 2009/064029, and WO 2009/124237, WO 2015/066729, and WO 2016/179607; U.S. Patent No. 6,214,865; Austad et al., Synlett 24(3):333-337, 2013; Austad et al., Synlett. 24(3):327-332, 2013; and Chase et al., Synlett 24(3):323-326, 2013. New methods for the synthesis of halichondrin and its analogs (e.g., macrolide analogs) are desirable.

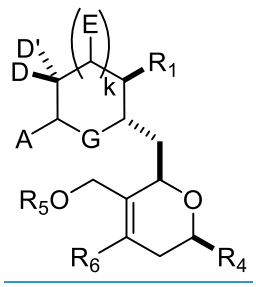
Summary

In general, the present disclosure provides methods and compounds useful for the preparation of macrocyclic intermediates in the synthesis of a halichondrin macrolide or analog thereof. In particular, the methods disclosed herein may be useful in the preparation of a halichondrin macrolide or analog thereof through a synthesis including a C.23-C.24 bond-forming Prins reaction. Prins reaction precursors may be prepared using a Sakurai reaction, as described herein.

In one aspect, the present disclosure provides a method of preparing a compound of formula (A), the method comprising producing the compound of formula (A) from a compound of formula (B), a compound of formula (C), and R_5OH:

wherein R_5 is optionally substituted acyl;

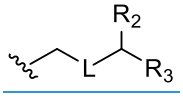
wherein the compound of formula (A) is:



(A),

wherein

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



(1),

wherein

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

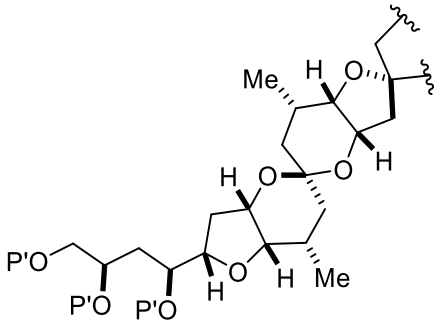
R$_2$ is H, or R$_2$ and P$_1$ combine to form a bond;

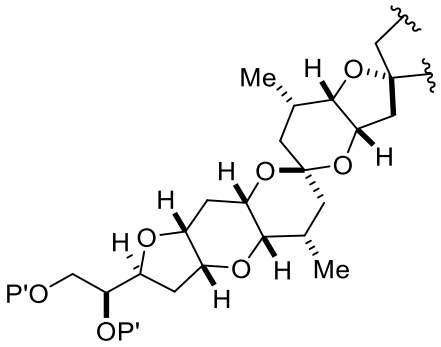
(i) R$_3$ is H, and P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

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

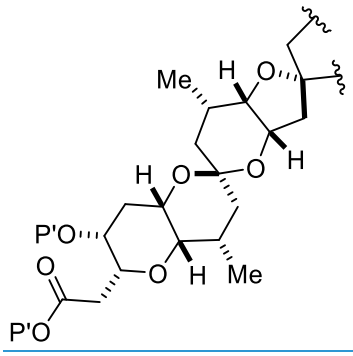
(iii) R$_3$ is –(CH$_2$)$_n$OP$_5$, wherein P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P$_5$ is H, optionally substituted alkyl, or a hydroxyl protecting group; or P$_2$ and P$_5$, together with the atoms to which each is attached, combine to form a ketal, a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

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





, and



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

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

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

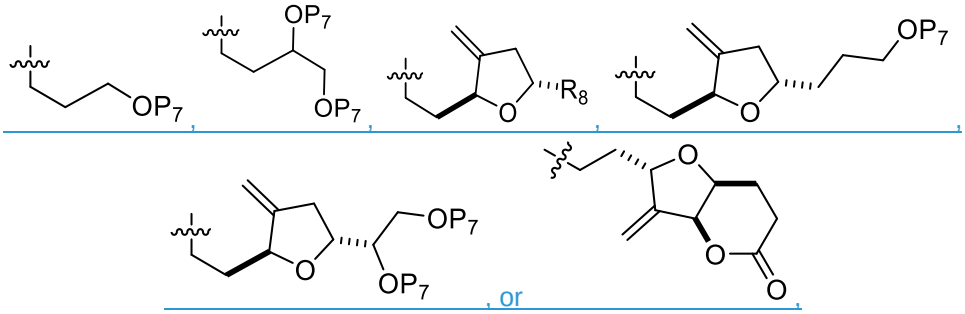
each Q$_1$ is independently OR$_A$, SR$_A$, SO$_2$R$_A$, OSO$_2$R$_A$, NR$_B$R$_A$, NR$_B$(CO)R$_A$, NR$_B$(CO)(CO)R$_A$, NR$_B$(CO)NR$_B$R$_A$, NR$_B$(CO)OR$_A$, (CO)OR$_A$, O(CO)R$_A$, (CO)NR$_B$R$_A$, or O(CO)NR$_B$R$_A$, wherein each of R$_A$ and R$_B$ is independently H, alkyl, haloalkyl, hydroxyalkyl,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

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

k is 0 or 1;

R$_1$ is –OP$_6$, –CH(Y)$_2$, or –CH$_2$(Y), wherein P$_6$ is H or a hydroxyl protecting group;

R$_4$ is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl,



wherein

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

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

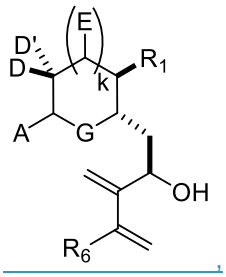
R_6 is H, optionally substituted alkyl, or optionally substituted arylalkyl;

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

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

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

wherein the compound of formula (B) is:



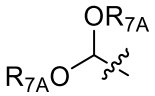
(B)

and

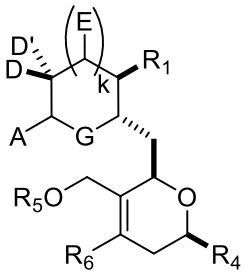
wherein the compound of formula (C) is:

R_4-R_7,

(C)

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

In one ~~aspect~~example, the ~~invention~~ disclosure provides a method of preparing a compound of formula (A):



(A),

where

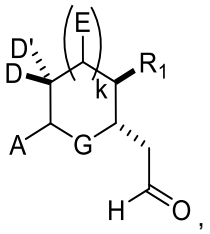
each of D and D’ is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D’ is OP_1, where P_1 is H, alkyl, a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10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

A is a group of formula (1)

In some examples, the producing the compound of formula (A) includes reacting the compound of formula (B), the compound of formula (C), R_5OH, and a Lewis acid (e.g., an oxophilic Lewis acid (e.g., boron trifluoride or a solvate thereof)).

In certain examples, the method further includes producing the compound of formula (B) including reacting a compound of formula (D), a compound of formula (E), and a second Lewis acid.

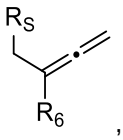
The compound of formula (D) is:



(D)

where all variables are as described for the compound of formula (B).

The compound of formula (E) is:



(E)

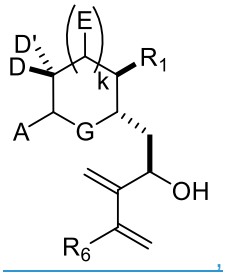
where R_S is silyl, and R_6 is as described for the compound of formula (B).

In some examples, the second Lewis acid is an oxophilic second Lewis acid (e.g., boron trifluoride or a solvate thereof). In particular examples, the Lewis acid and the second Lewis acid are same. In further examples, the Lewis acid and the second Lewis acid are different.

In certain examples, the preparing the compound of formula (B) and the preparing the compound of formula (A) are performed as a single-pot transformation. In other examples, the method further includes epimerizing the product of reacting the compound of formula (D), the compound of formula (E), and the second Lewis acid.

In another aspect, the present disclosure refers to a method of preparing a compound of formula (B), the method comprising producing the compound of formula (B) from a compound of formula (D) and a compound of formula (E);

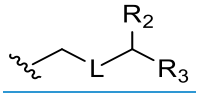
wherein the compound of formula (B) is:



(B)

wherein

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



(1),

wherein

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

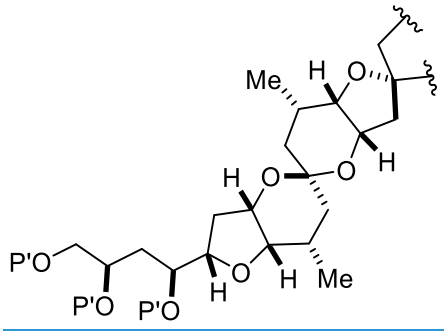
R_2 is H, or R_2 and P_1 combine to form a bond;

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

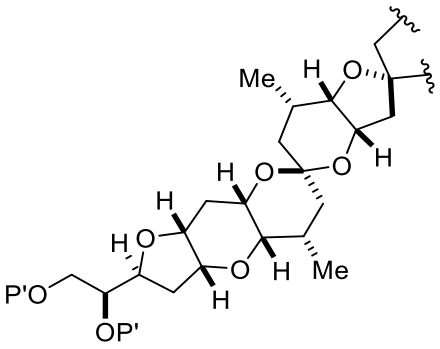
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

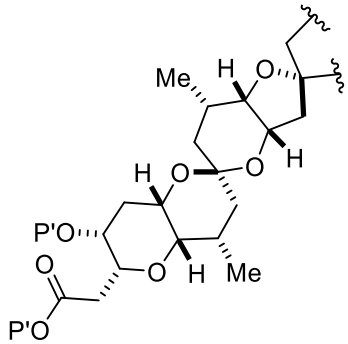
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

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

k is 0 or 1;

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

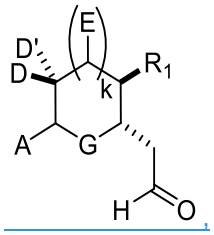
R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and

Y is independently –$COOR_C$ or –SO_2R_D;

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

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

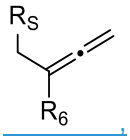
wherein the compound of formula (D) is:



(D)

and

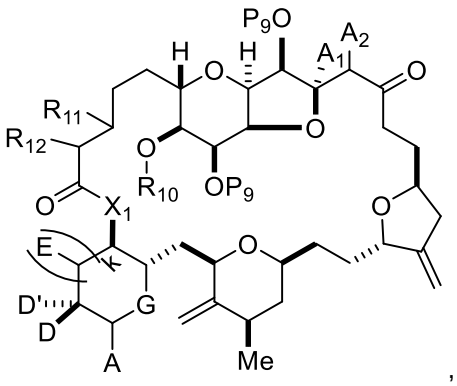
wherein the compound of formula (E) is:



(E)

wherein R_S is silyl.

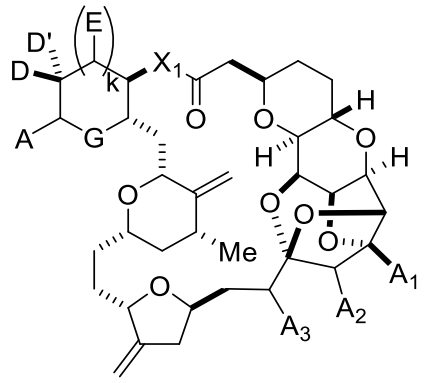
In another ~~aspect~~example, the disclosure provides a method of preparing a compound of formula (B). The compound of formula (B) can be used as a reactant in the Prins reaction described herein. The method includes producing the compound of formula (B) from a compound of formula (D) and a compound of formula (E)



(IVD)

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

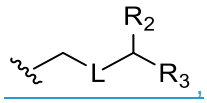
In another aspect, the present disclosure refers to a method of preparing



a 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, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1)

wherein

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

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

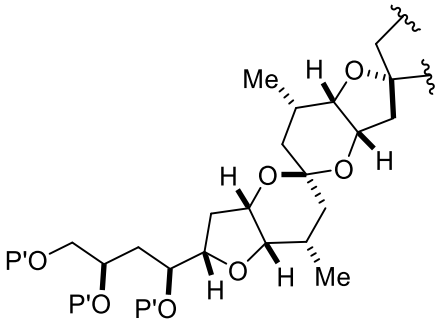
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

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

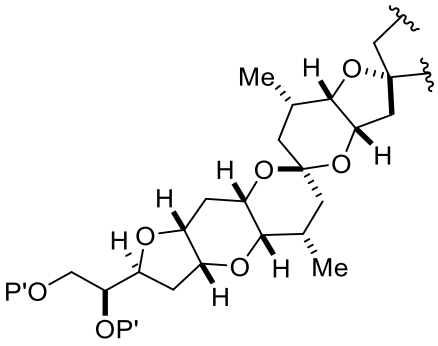
(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting

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

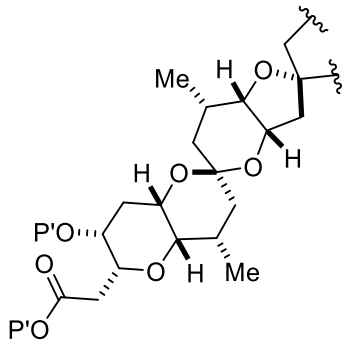
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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;

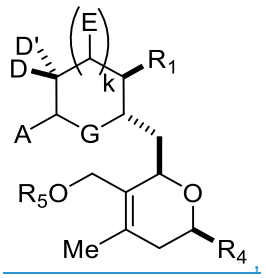
k is 0 or 1; and

X_1 is $–CH_2–$ or –O–;

the method comprising:

(1)

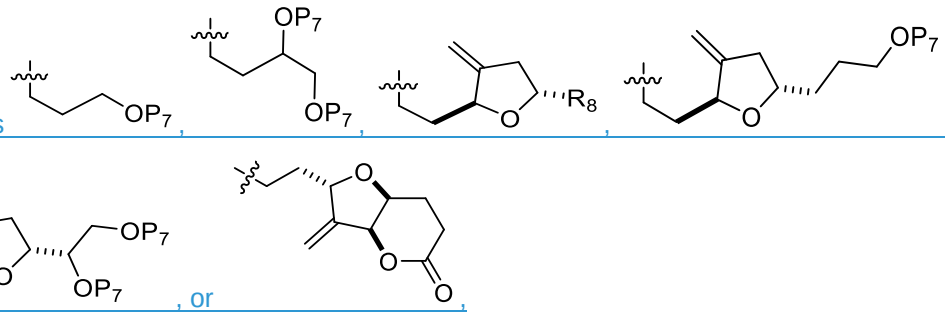
(A) producing a compound of formula (IA) from a compound of formula (IIC), a compound of formula (III), and R_5OH, wherein the compound of formula (IA) is:



(IA)

wherein

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

R_4 is 

wherein

each P_7 is independently H or a hydroxyl protecting group;

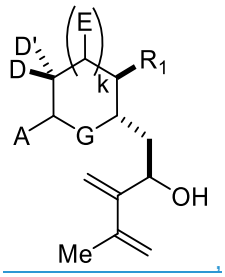
R_8 is $–CH_2CH_2–COOR_C$, $–CH=CH–COOR_C$, $–CH_2CH_2–SO_2R_D$, or $–CH=CH–SO_2R_D$;

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

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

R_5 is optionally substituted acyl;

wherein the compound of formula (IIC) is:



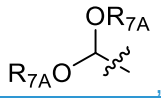
(IIC)

and

wherein the compound of formula (III) is:

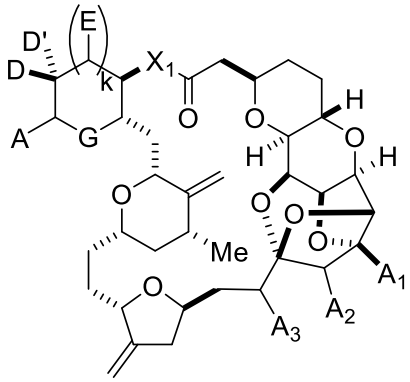
R_4-R_7,

(III)

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

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

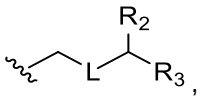
In another ~~aspect~~example, the present disclosure refers to a method of preparing



a halichondrin macrolide or analog thereof,

wherein

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



(1)

wherein

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

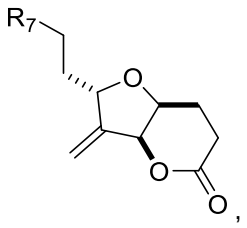
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

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

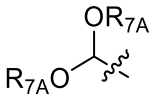
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

(1)



(Z)

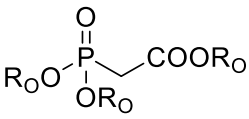
wherein R_7 is –CHO or  , and

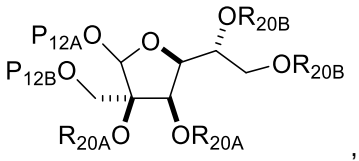
each R_{7A} is independently alkyl or a hydroxyl protecting group; or

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

 ,

(Z1)

wherein

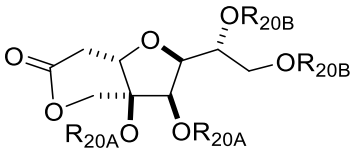
each R_{20A} is independently a hydroxyl protecting group, or both R_{20A}, together with the atoms to which each is attached, combine to form an acetal, ketal, cyclic carbonate, dicarbonyl-dioxo, or silylene-dioxo;

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;

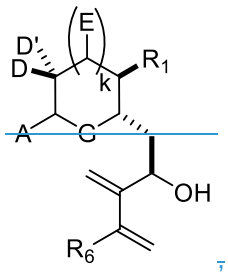
and the compound of formula (Z2) is:

 ;

(Z2)

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.

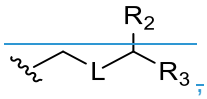
In yet another aspect, the disclosure refers to a compound of (1) formula (II):



(II)

wherein

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



(1)

wherein

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

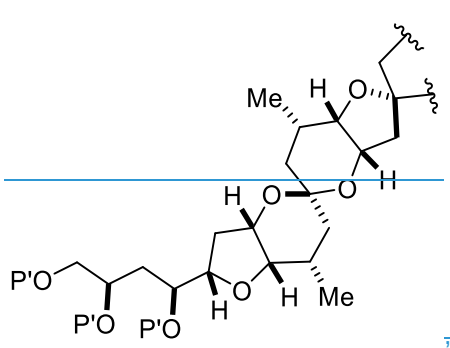
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

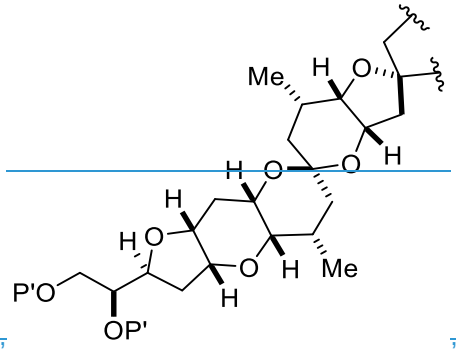
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

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

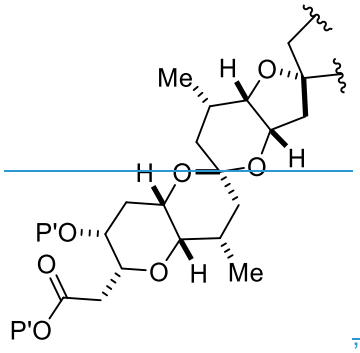
(iii) R_3 is $-(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate,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

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





, ~~and~~



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

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

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

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

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

~~k is 0 or 1;~~

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

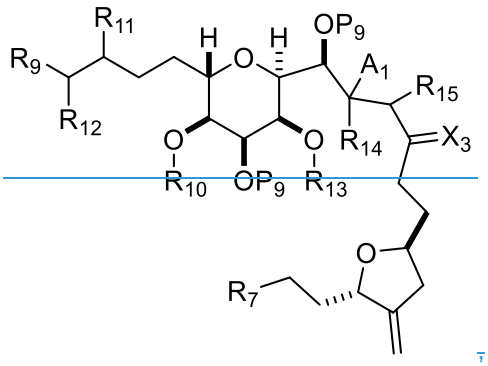
~~R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and~~

~~Y is independently $-COOR_C$ or $-SO_2R_D$;~~

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

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

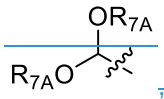
(2) formula (VIIAa):



(VIIAa)

where

R_7 is $-CH_2OP_A$, –CHO, or



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

R_9 is $-CH_2-OP''$, –CHO, or –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 –OP", and:

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

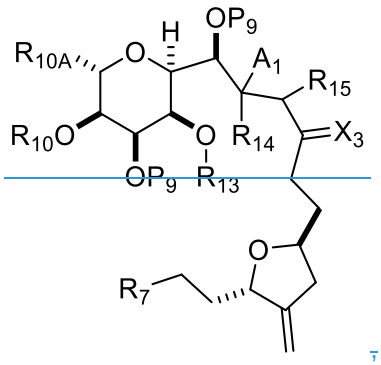
or

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

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 $-(CH(OP_{11}))-$, 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;

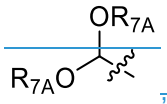
(3) formula (VIAa):



(VIAa)

where

R_7 is –CHO or



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

R_{10A} is $–CH_2–CH=CH_2$, $–(CH_2)_2–CH=CH_2$, or $–(CH_2)_3–OP_{10}$;

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 –OP", and:

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

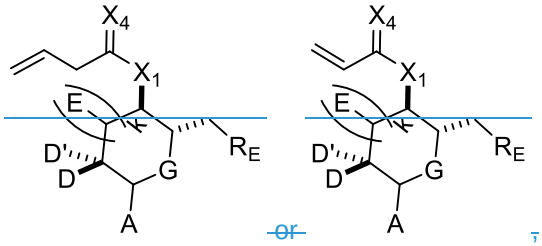
or

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

and

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 ketal;

(4) formula (IID) or (IIF):



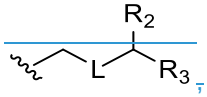
or

(IID) (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):



,

(1)

wherein

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

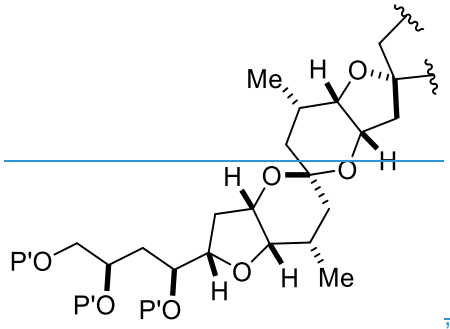
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

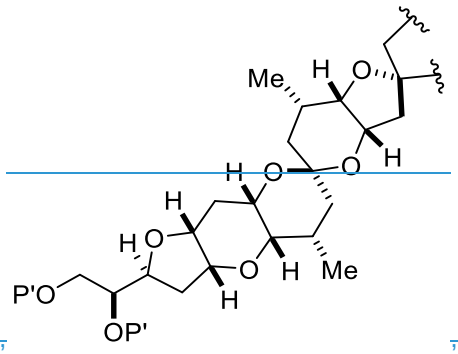
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

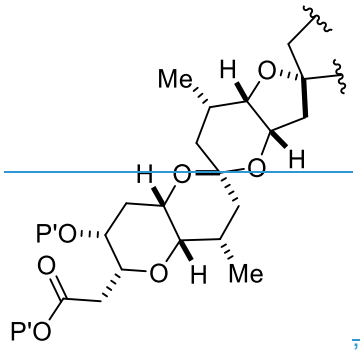
(ii) R_3 is $-(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(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:



, 

, and 

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

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

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

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

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

k is 0 or 1;

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

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,

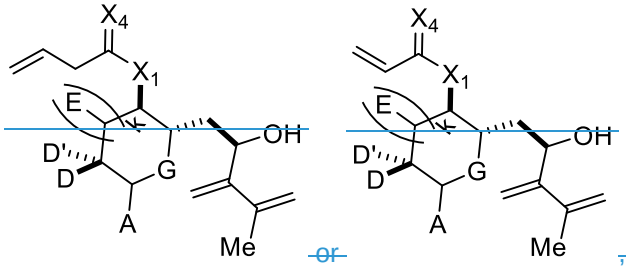
or

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;

(5) formula (IIE) or (IIG):

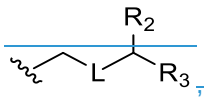


or ,

(IIE) (IIG)

wherein

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



,

(1)

wherein

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

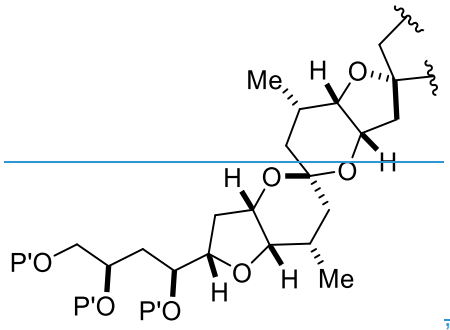
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

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

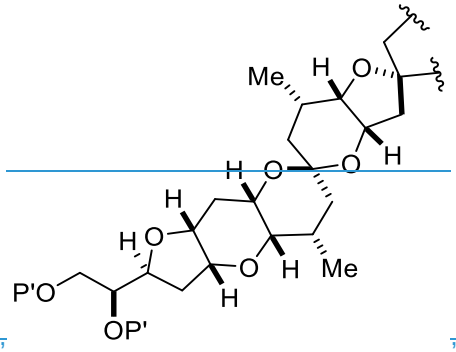
(ii) R_3 is $-(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

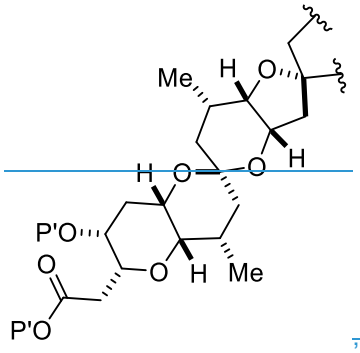
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

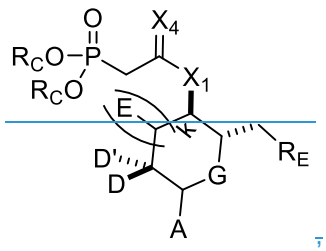
n, when present, is 0, 1, or 2;

k is 0 or 1;

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

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

(6) formula (IIH):



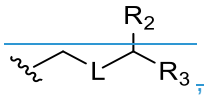
,

(IIH)

wherein

each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6}

unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1)

wherein

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

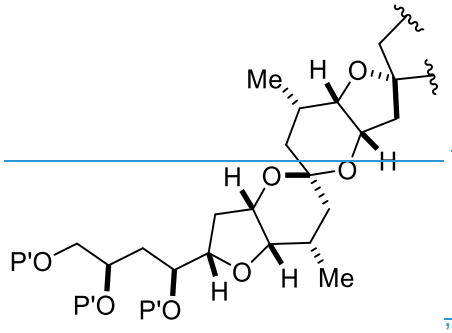
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

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

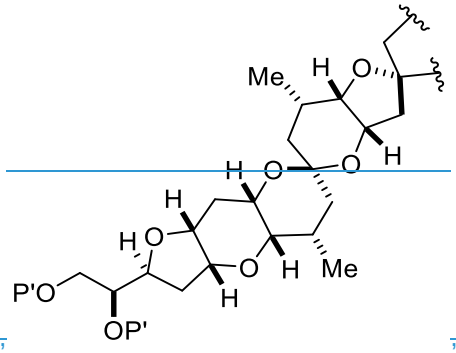
(ii) R_3 is $-(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

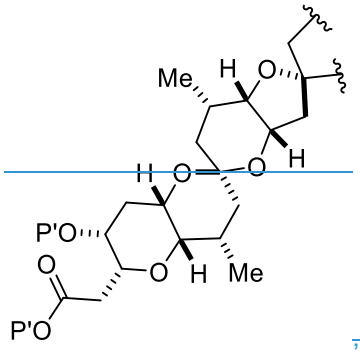
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

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

k is 0 or 1;

each R_C is 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,

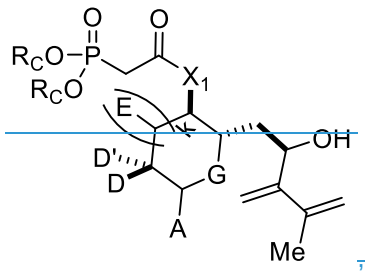
or

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;

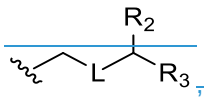
(7) formula (IIi):



(IIi)

wherein

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



(1)

wherein

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

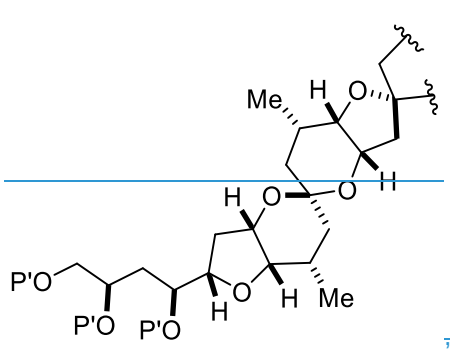
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

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

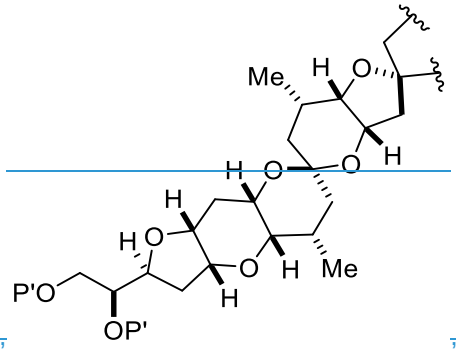
(ii) R_3 is $-(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

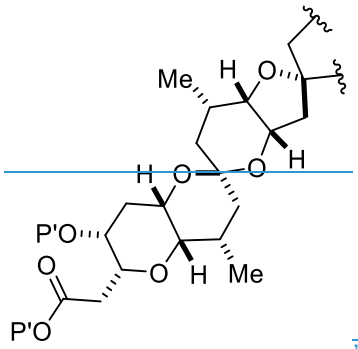
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

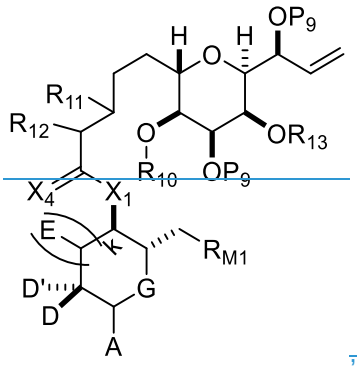
n, when present, is 0, 1, or 2;

k is 0 or 1;

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

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

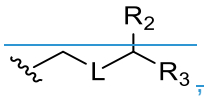
(8) formula (VIIID):



(VIIID)

wherein

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



(1)

wherein

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

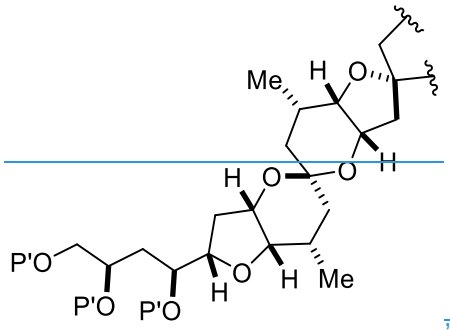
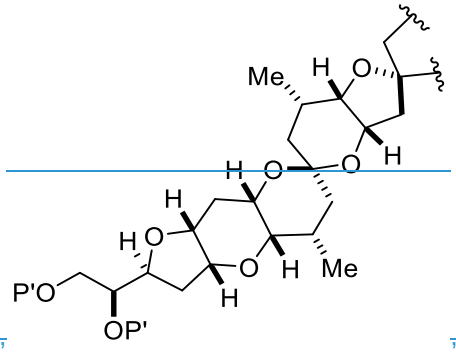
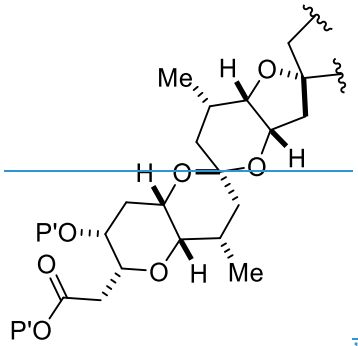
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

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

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

(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;

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

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

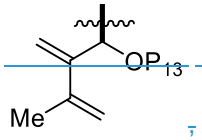
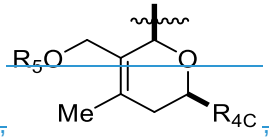
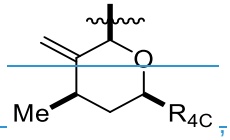
each P_9 and R_{13} is independently a hydroxyl protecting group;

(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_{M1} is

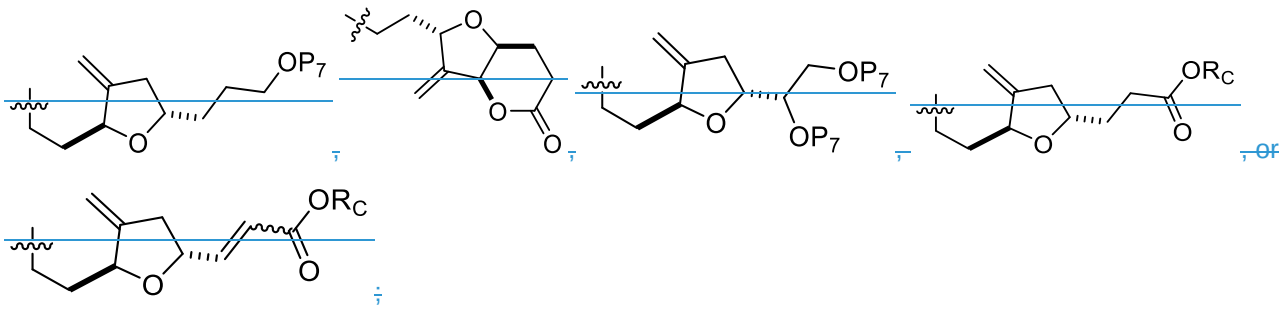




wherein

R_5 is optionally substituted acyl;

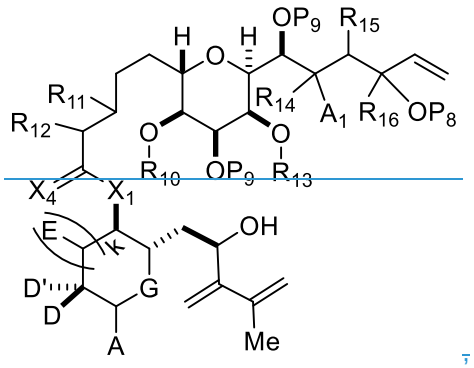
P_{13} is H or a hydroxyl protecting group; and

R_{4C} is



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

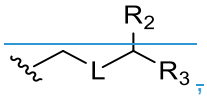
(9) formula (IVAb):



(IVAb)

wherein

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



(1)

wherein

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

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

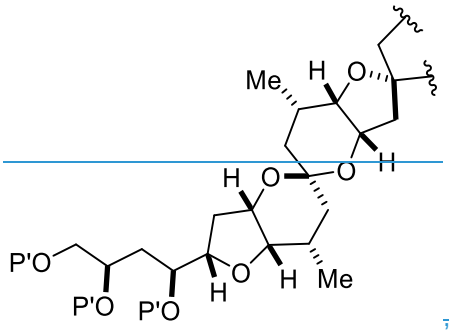
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

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

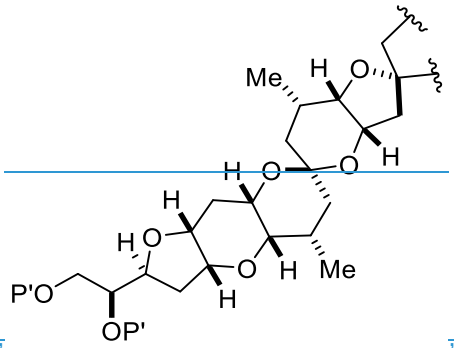
(iii) R_3 is $-(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting

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

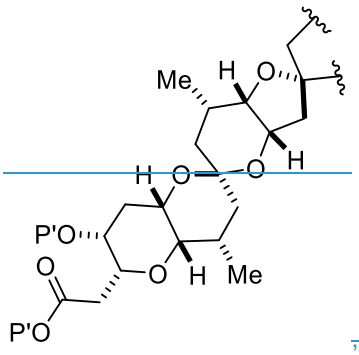
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

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

k is 0 or 1;

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

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

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

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

each P_9 is independently a hydroxyl protecting group;

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

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

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

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

or

(b2) A_1 is H or –OP", and:

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

or

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

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

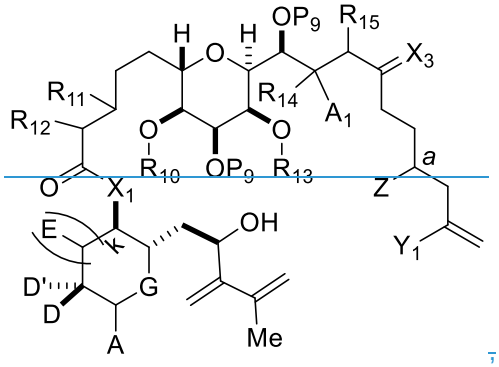
or

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

and

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

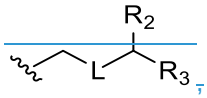
(10) formula (VAb):



(VAb)

wherein

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



(1)

wherein

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

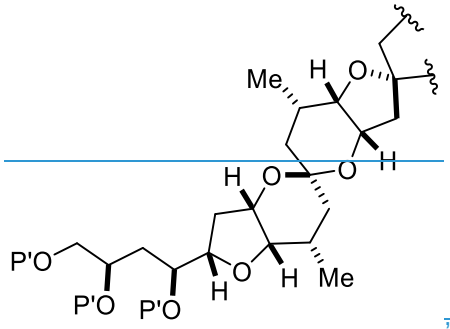
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

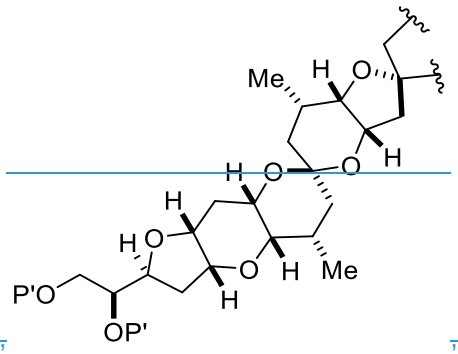
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

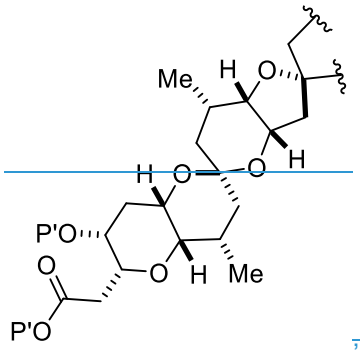
(ii) R_3 is $-(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

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



, 

, and 

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

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

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

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

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

k is 0 or 1;

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

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

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

Y_1 is iodide, bromide, or trifluoromethanesulfonate;

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

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

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

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

or

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

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

or

(b2) A_1 is H or –OP", and:

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

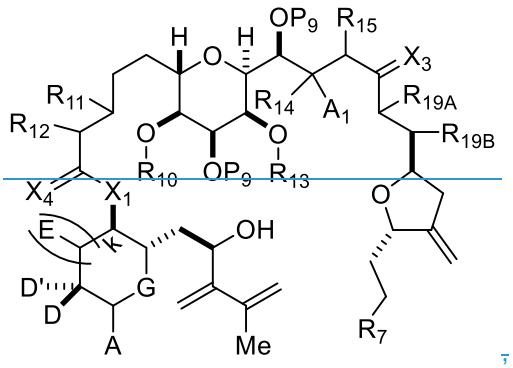
or

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

and

each P" is independently a hydroxyl protecting group;

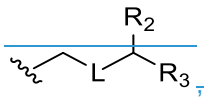
(11) formula (IXD):



(IXD)

wherein

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



(1)

wherein

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

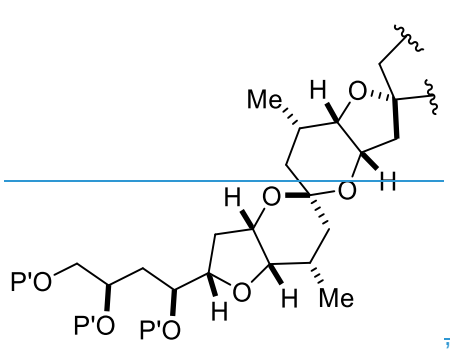
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

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

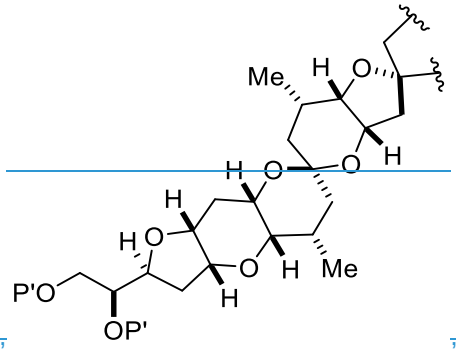
(ii) R_3 is $-(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

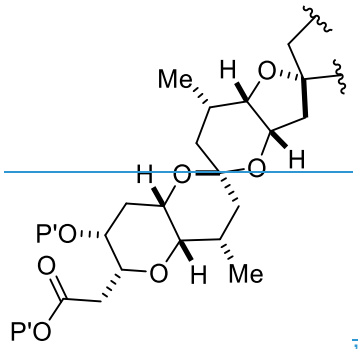
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

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

k is 0 or 1;

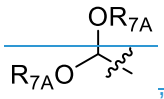
X_1 is $-CH_2-$, $-CH(Y)-$, $-C(Y)_2-$, or $-O-$, each Y is independently $-COOR_C$ or $-SO_2R_D$;

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

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

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

R_7 is –CHO, $-CH_2OP_A$ or



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

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

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

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

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

or

A_1 is H or -OP", and

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

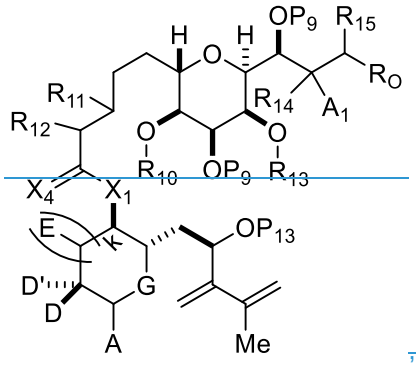
or

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

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

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

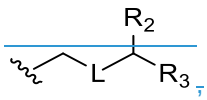
(12) formula (IXF):



, (IXF)

wherein

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



(1)

wherein

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

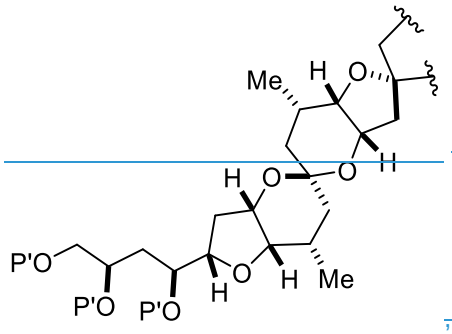
R$_2$ is H and P$_1$ is absent, H, alkyl, or a hydroxyl protecting group, or R$_2$ and P$_1$ combine to form a bond;

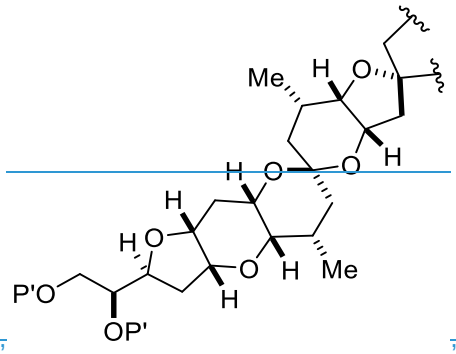
(i) R$_3$ is H, and P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

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

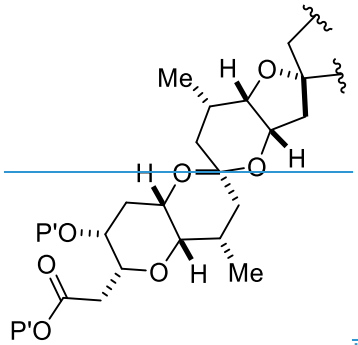
(iii) R$_3$ is –(CH$_2$)$_n$OP$_5$, wherein P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P$_5$ is H, optionally substituted alkyl, or a hydroxyl protecting group; or P$_2$ and P$_5$, together with the atoms to which each is attached, combine to form a ketal, a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

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





, and



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

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

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

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

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

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

k is 0 or 1;

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

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

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

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

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

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

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

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

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

or

A_1 is H or -OP'', and

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

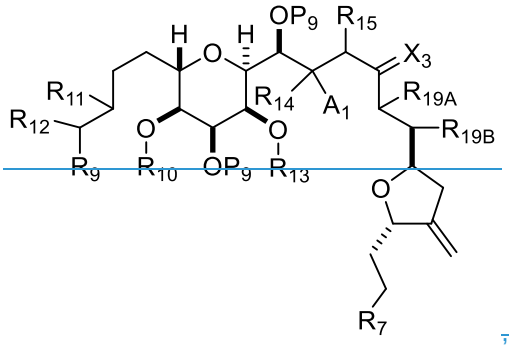
or

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

and

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

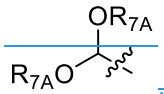
(13) formula (IXG):



(IXG)

wherein

R_7 is $-CHO$, $-CH_2OP_A$, or



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

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

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

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

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

or

A_1 is H or -OP", and

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

or

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

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

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

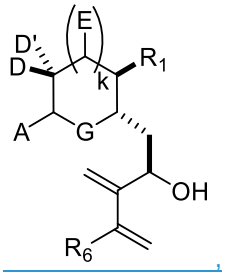
(14) formula (Z), (Z1), (Z2), (Z3), (Z4), (Z5), (Z5A), (Z5B), or (Z6).

In a yet further example, the disclosure provides a compound of formula (Z), (Z1), (Z2), (Z3), (Z4), (Z5), (Z5A), (Z5B), or (Z6), as described herein.

In the halichondrin macrolide and halichondrin macrolide analog structures herein, when P_1 is absent, each of D and D' is independently H or optionally substituted alkyl, and, when P_2 is absent, L is -C(O)-.

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.

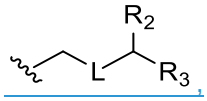
In another aspect, the present disclosure refers to a compound of (1) formula (II):



(II)

wherein

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



(1)

wherein

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

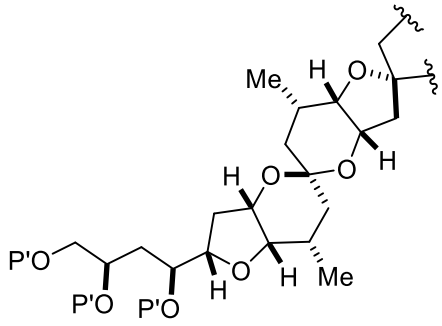
R_2 is H, or R_2 and P_1 combine to form a bond;

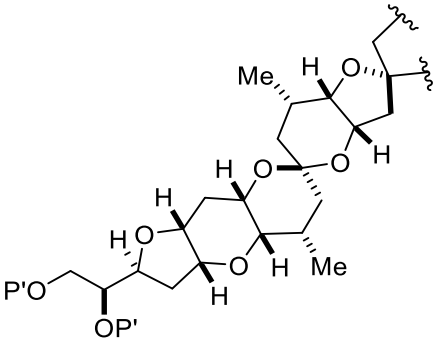
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

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

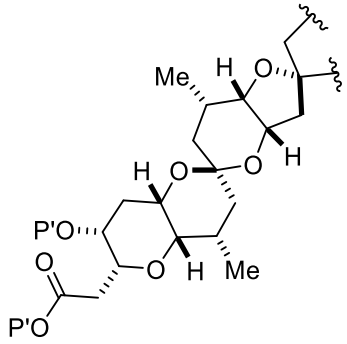
(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate,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

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





, and



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

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

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

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

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

k is 0 or 1;

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

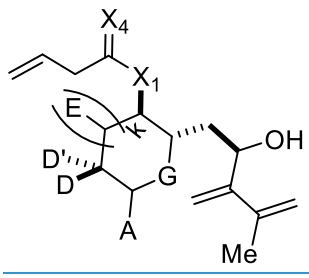
R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and

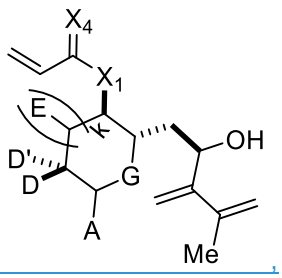
Y is independently $–COOR_C$ or $–SO_2R_D$;

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

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

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



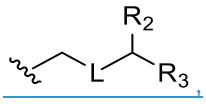
or


,

(IIE) (IIG)

wherein

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



(1)

wherein

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

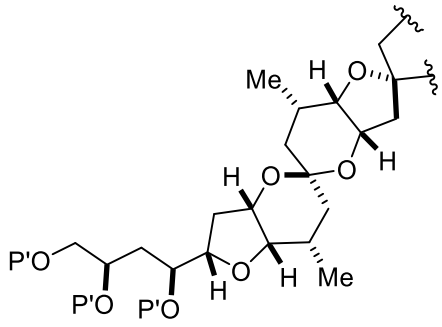
R_2 is H, or R_2 and P_1 combine to form a bond;

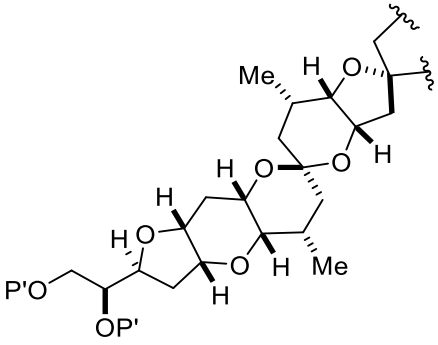
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

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

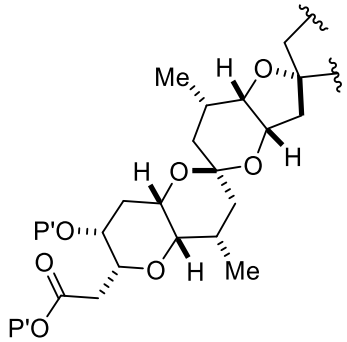
(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate,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

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





, and



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

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

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

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

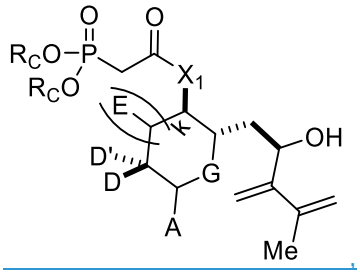
n, when present, is 0, 1, or 2;

k is 0 or 1;

X_1 is $–CH_2–$ or –O–; and

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

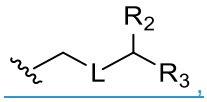
(3) formula (IIi):



(IIi)

wherein

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



(1)

wherein

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

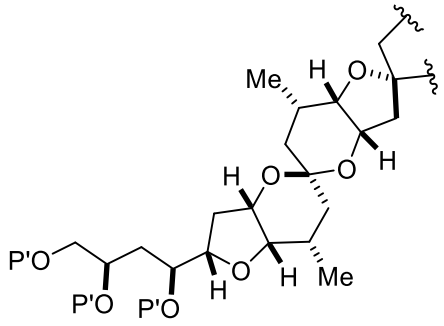
R_2 is H, or R_2 and P_1 combine to form a bond;

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

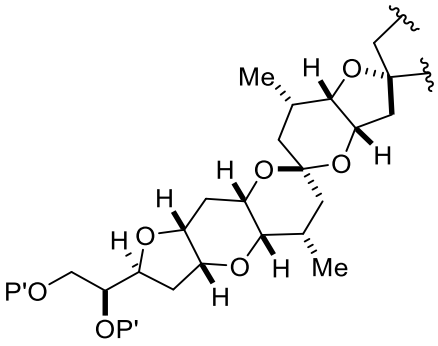
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

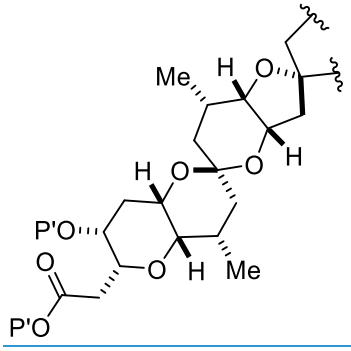
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

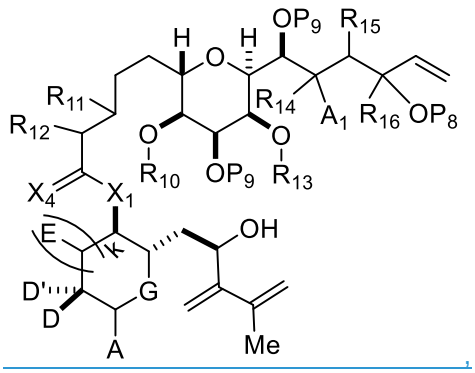
n, when present, is 0, 1, or 2;

k is 0 or 1;

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

X_1 is $–CH_2–$ or $–O–$;

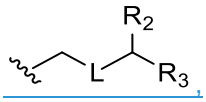
(4) formula (IVAb):



(IVAb)

wherein

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



(1)

wherein

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

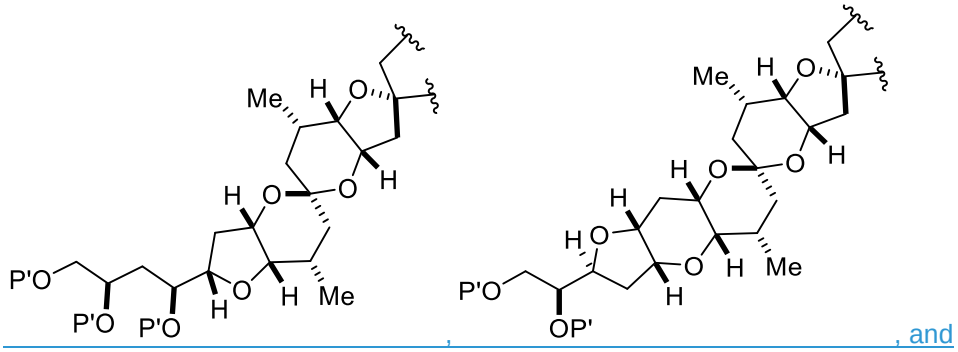
R_2 is H, or R_2 and P_1 combine to form a bond;

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

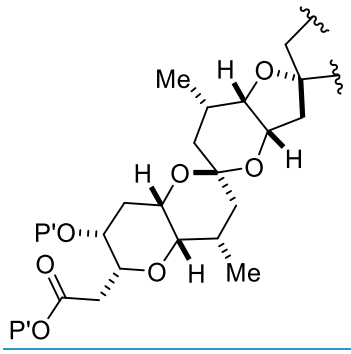
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

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



, and



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

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

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

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

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

k is 0 or 1;

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

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

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

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

each P_9 is independently a hydroxyl protecting group;

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

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

or

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

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

or

(b2) A_1 is H or –OP", and:

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

or

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

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

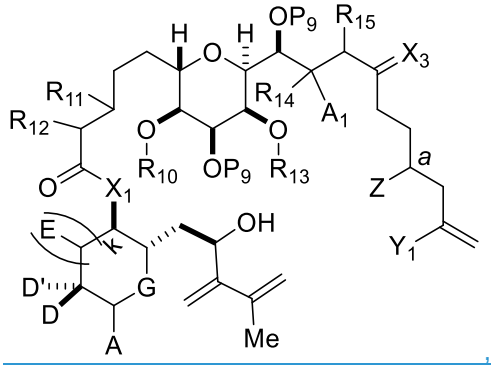
or

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

and

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

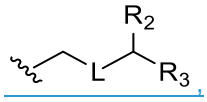
(5) formula (VAb):



(VAb)

wherein

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



(1)

wherein

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

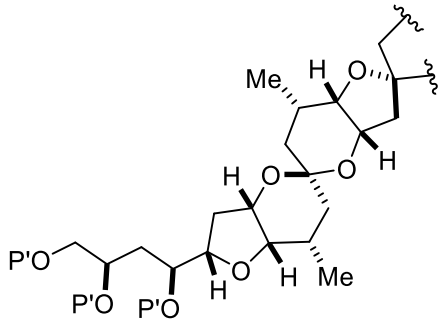
R_2 is H, or R_2 and P_1 combine to form a bond;

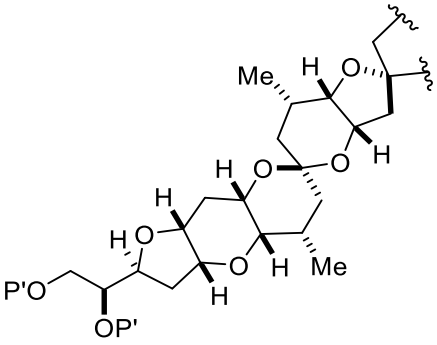
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

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

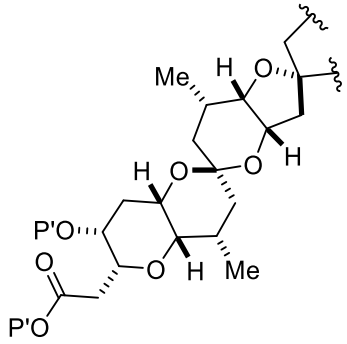
(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate,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

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





, and



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

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

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

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

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

k is 0 or 1;

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

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

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

Y_1 is iodide, bromide, or trifluoromethanesulfonate;

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

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

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

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

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

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

or

(b2) A_1 is H or –OP", and:

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

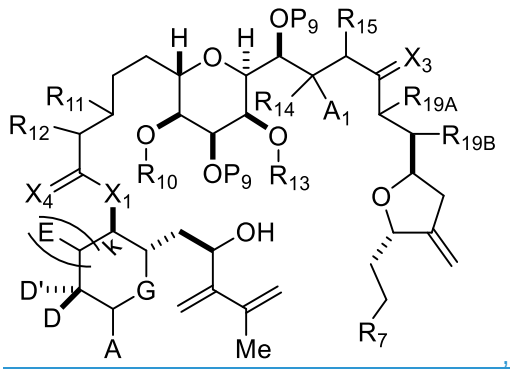
or

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

and

each P" is independently a hydroxyl protecting group;

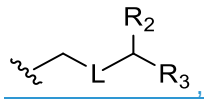
(6) formula (IXD):



(IXD)

wherein

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



(1)

wherein

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

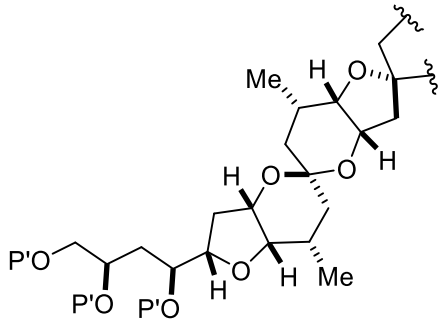
R_2 is H, or R_2 and P_1 combine to form a bond;

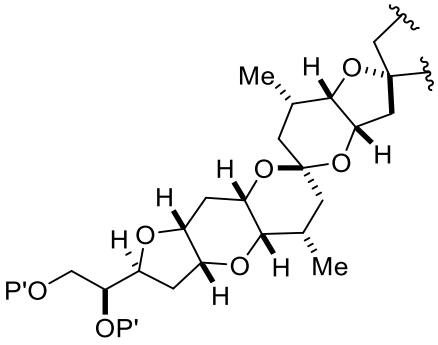
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

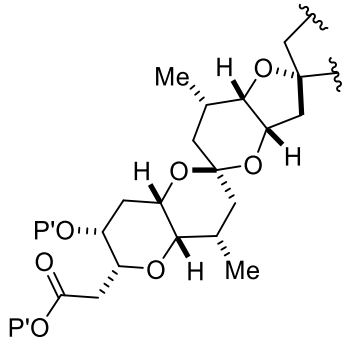
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

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



,


, and


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

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

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

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

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

k is 0 or 1;

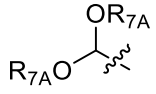
X_1 is $–CH_2–$, $–CH(Y)–$, $–C(Y)_2–$, or –O–, each Y is independently $–COOR_C$ or $–SO_2R_D$;

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

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

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

R_7 is $–CHO$, $–CH_2OP_A$ or



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

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

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

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

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

or

A_1 is H or -OP", and

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

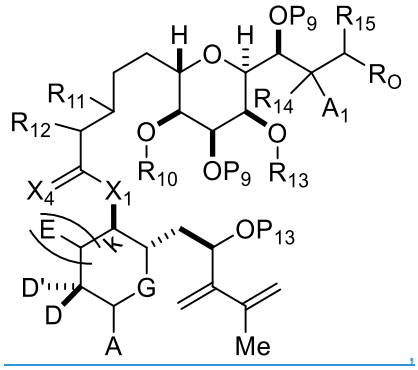
or

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

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

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

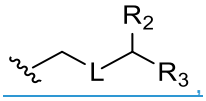
(7) formula (IXF):



(IXF)

wherein

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



(1)

wherein

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

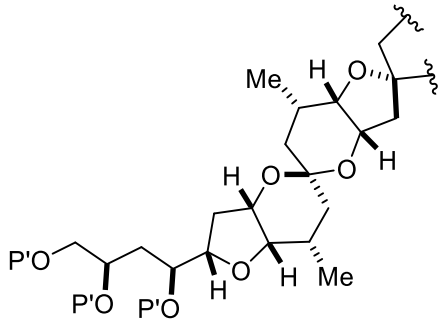
R_2 is H, or R_2 and P_1 combine to form a bond;

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

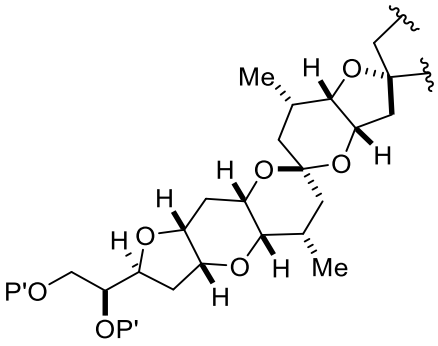
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

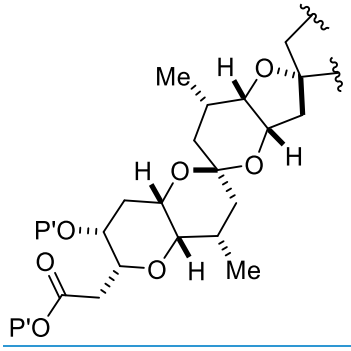
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

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

k is 0 or 1;

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

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

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

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

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

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

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

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

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

or

A_1 is H or -OP", and

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

or

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

and

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

In a yet further example, the disclosure provides a compound of formula (Z), (Z1), (Z2), (Z3), (Z4), (Z5), (Z5A), (Z5B), or (Z6), as described herein.

In the halichondrin macrolide and halichondrin macrolide analog structures herein, when P_1 is absent, each of D and D' is independently H or optionally substituted alkyl, and, when P_2 is absent, L is -C(O)-.

Definitions

Compounds useful in the invention may be isotopically labeled compounds. Useful isotopes include hydrogen, carbon, nitrogen, and oxygen (e.g., ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, and ^{17}O). Isotopically-labeled compounds can be prepared by synthesizing a compound using a readily available isotopically-labeled reagent in place of a non-isotopically-labeled reagent.

For any of the following chemical definitions, a number following an atomic symbol indicates that total number of atoms of that element that are present in a particular chemical moiety. As will be understood, other atoms, such as hydrogen atoms, or substituent groups, as described herein, may be present, as necessary, to satisfy the valences of the atoms. For example, an unsubstituted C_2 alkyl group has the formula $–CH_2CH_3$. When used with the groups defined herein, a reference to the number of carbon atoms includes the divalent carbon in acetal and ketal groups but does not include the carbonyl carbon in acyl, ester, carbonate, or carbamate groups. A reference to the number of oxygen, nitrogen, or sulfur atoms in a heteroaryl group only includes those atoms that form a part of a heterocyclic ring.

By “acetal” is meant –O–(CHR)–O–, where R is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, or optionally substituted arylalkyl, or R group is a bond to an enumerated carbon atom, as shown in Chart 1, within the intermediate or within the halichondrin macrolide or analog thereof.

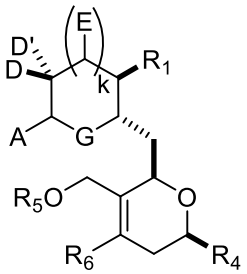
By “acetyl” is meant an acyl, in which R is $–CX_nH_{3-n}$, where n is 0, 1, 2, or 3, and each X is independently alkoxy or halogen, provided that, when n is 3, each X is independently halogen, and, when n is 2, either both of the X groups are independently halogen or both of the X groups are independently alkoxy. An acetyl group may be substituted (i.e., n is 1, 2, or 3) or unsubstituted (i.e., n is 0).

By “acyl” is meant –C(O)R, where R is H, alkyl, alkenyl, aryl, or arylalkyl. In exemplary acyl groups, R is H, C_{1-12} alkyl (e.g., C_{1-8}, C_{1-6}, C_{1-4}, C_{2-7}, C_{3-12}, or C_{3-6} alkyl), C_{2-12} alkenyl (e.g., C_{2-8}, C_{2-6}, C_{2-4}, C_{3-12}, or C_{3-6} alkenyl), C_{6-20} aryl (e.g., C_{6-14}, C_{6-10}, C_{8-20}, or C_{8-14} aryl), monocyclic C_{1-6} heteroaryl (e.g., monocyclic C_{1-4} or C_{2-6} heteroaryl), C_{4-19} heteroaryl (e.g., C_{4-10} heteroaryl), (C_{6-14})aryl(C_{1-6})alkyl, (C_{1-6})heteroaryl(C_{1-6})alkyl, or (C_{4-9})heteroaryl(C_{1-6})alkyl. As defined herein, any heteroaryl group present in an acyl group has from 1 to 4 heteroatoms selected independently from O, N, and S. An acyl group can be unsubstituted or substituted (e.g., optionally substituted acyl). In the optionally substituted acyl group, the substituent R is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, or optionally substituted arylalkyl. In some embodiments, acyl is C_{2-10} acyl.

What is claimed is:

Claims

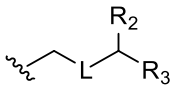
1. A method of preparing a compound of formula (A), the method comprising producing the compound of formula (A) from a compound of formula (B), a compound of formula (C), and R_5OH:
wherein R_5 is optionally substituted acyl;
wherein the compound of formula (A) is:



(A),

wherein

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



(1),

wherein

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

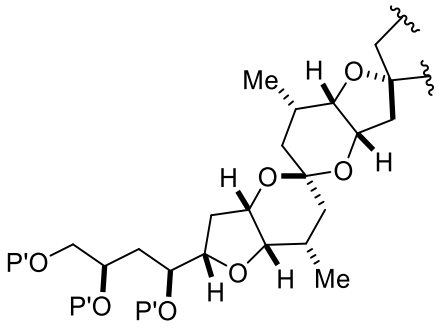
R_2 is H ~~and P_1 is absent, H, alkyl, or a hydroxyl protecting group~~, or R_2 and P_1 combine to form a bond;

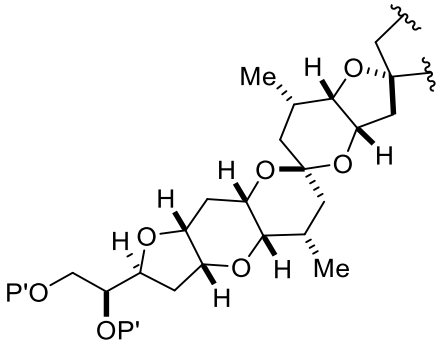
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

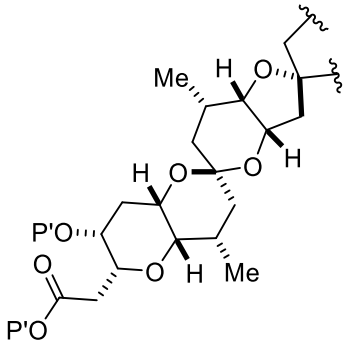
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(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:



,


, and


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

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

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

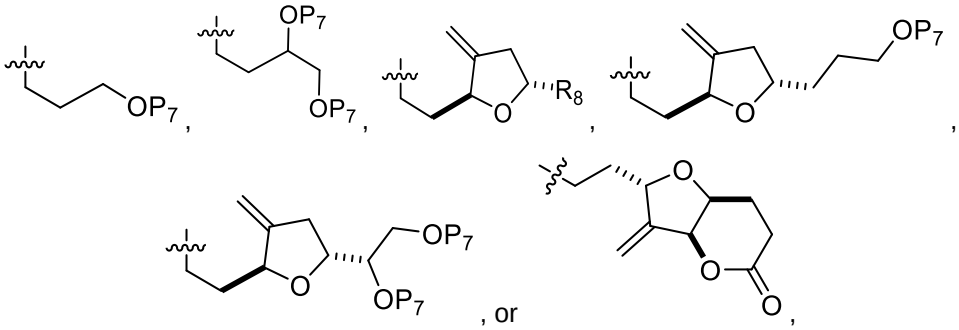
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_B(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl,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

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

k is 0 or 1;

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

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



, or ,

wherein

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

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

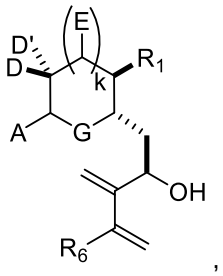
R_6 is H, optionally substituted alkyl, or optionally substituted arylalkyl;

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

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

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

wherein the compound of formula (B) is:



,

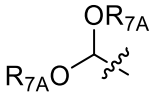
(B)

and

wherein the compound of formula (C) is:

R_4-R_7,

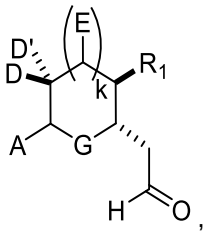
(C)

wherein R_7 is –CHO or 

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

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

wherein the compound of formula (D) is:

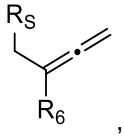


,

(D)

and

where the compound of formula (E) is:



,

(E)

where R_S is silyl.

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

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

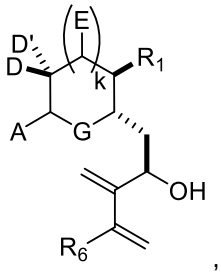
5. The method of claim 2, wherein:

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

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

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

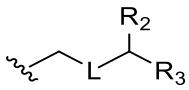
6. A method of preparing a compound of formula (B), the method comprising producing the compound of formula (B) from a compound of formula (D) and a compound of formula (E);
wherein the compound of formula (B) is:



(B)

wherein

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



(1),

wherein

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

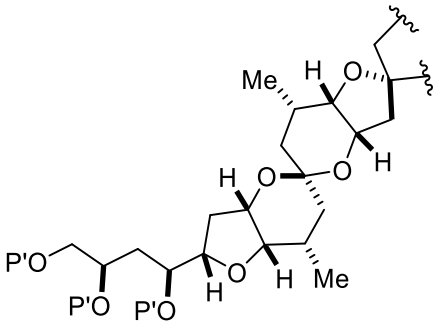
R_2 is H ~~and P_1 is absent, H, alkyl, or a hydroxyl protecting group~~, or R_2 and P_1 combine to form a bond;

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

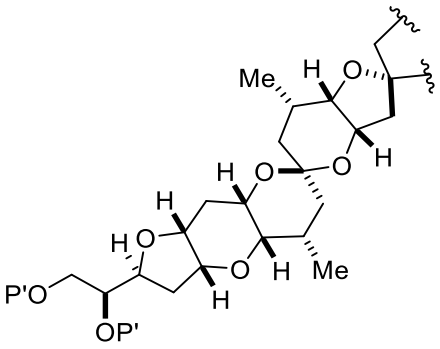
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(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

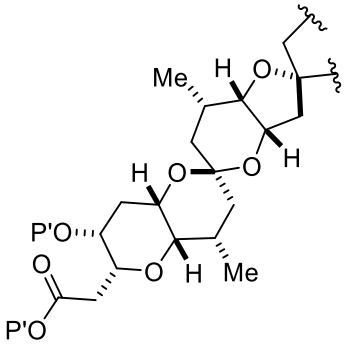
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

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

k is 0 or 1;

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

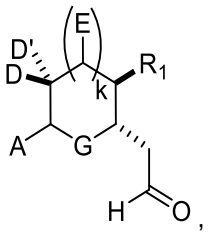
R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and

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

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

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

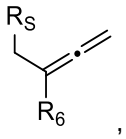
wherein the compound of formula (D) is:



(D)

and

wherein the compound of formula (E) is:



(E)

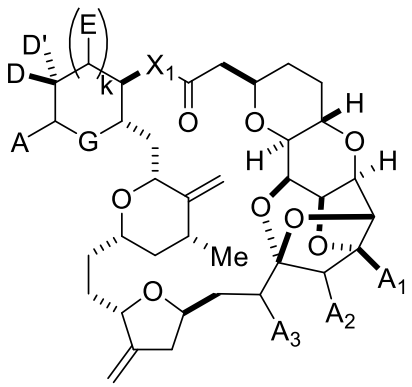
wherein R_S is silyl.

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

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

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

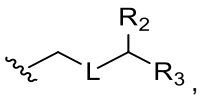
10. A method of preparing



a 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, or a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, or A is a group of formula (1):



(1)

wherein

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

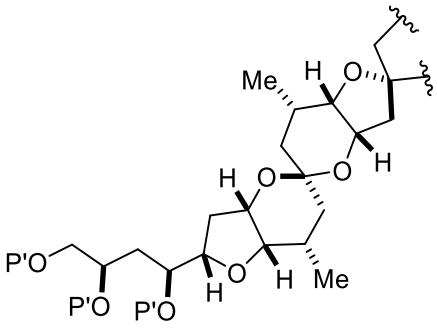
R$_2$ is H ~~and P$_1$ is absent, H, alkyl, or a hydroxyl protecting group~~, or R$_2$ and P$_1$ combine to form a bond;

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

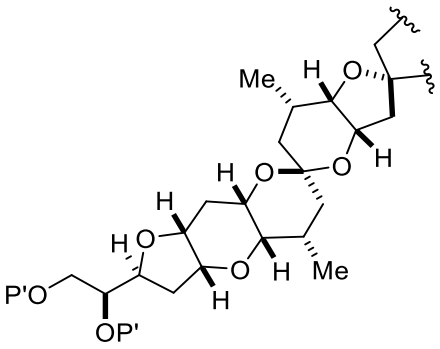
(ii) R$_3$ is –(CH$_2$)$_n$NP$_3$P$_4$, wherein P$_3$ is H or an N-protecting group, and (a) P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P$_4$ is H or an N-protecting group, (b) P$_2$ and P$_4$ combine to form an alkylidene, or (c) each of P$_2$ and P$_4$ is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

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

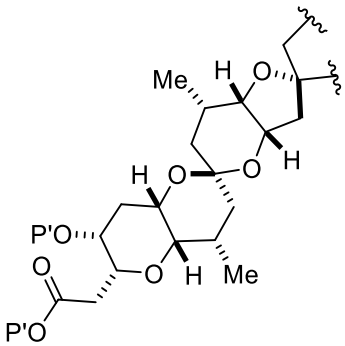
(iv) R$_3$ and P$_2$ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

each Q$_1$ is independently OR$_A$, SR$_A$, SO$_2$R$_A$, OSO$_2$R$_A$, NR$_B$R$_A$, NR$_B$(CO)R$_A$, NR$_B$(CO)(CO)R$_A$, NR$_B$(CO)NR$_B$R$_A$, NR$_B$(CO)OR$_A$, (CO)OR$_A$, O(CO)R$_A$, (CO)NR$_B$R$_A$, or O(CO)NR$_B$R$_A$, wherein each of R$_A$ and

R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl, alkoxyaryl, arylalkyl, alkylaryl, haloarylalkyl, alkylhaloaryl, (alkoxyaryl)alkyl, heterocyclic radical, or heterocyclic radical-alkyl;

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

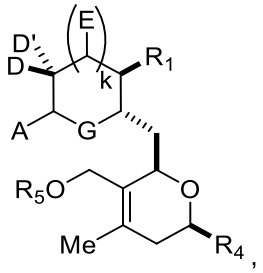
k is 0 or 1; and

X_1 is $–CH_2–$ or –O–;

the method comprising:

(1)

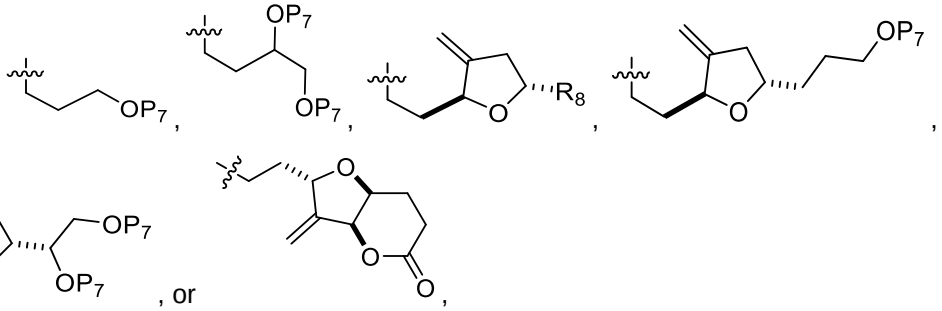
(A) producing a compound of formula (IA) from a compound of formula (IIC), a compound of formula (III), and R_5OH, wherein the compound of formula (IA) is:



(IA)

wherein

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

R_4 is 

, or

wherein

each P_7 is independently H or a hydroxyl protecting group;

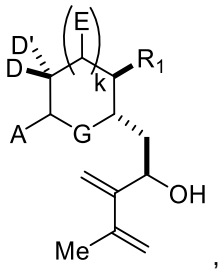
R_8 is $–CH_2CH_2–COOR_C$, $–CH=CH–COOR_C$, $–CH_2CH_2–SO_2R_D$, or $–CH=CH–SO_2R_D$;

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

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

R_5 is optionally substituted acyl;

wherein the compound of formula (IIC) is:



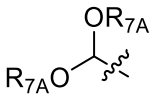
(IIC)

and

wherein the compound of formula (III) is:

R_4-R_7,

(III)

wherein R_7 is –CHO or 

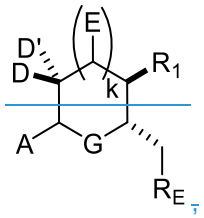
, wherein each R_{7A} is independently an optionally substituted alkyl; and

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

~~(2)~~

~~(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:~~



~~(IIA)~~

~~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,~~

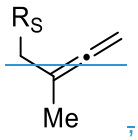
~~or~~

~~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:



(IIB)

wherein R_S is silyl;

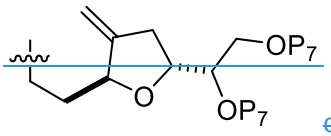
wherein the compound of formula (IIIA) is:

R_{4A}-R_7,

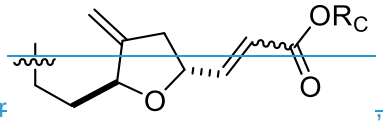
(IIIA)

wherein

R_{4A} is

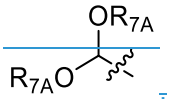


or



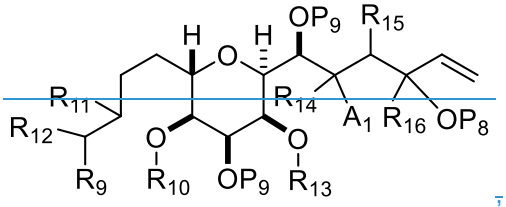
wherein R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl, and each P_7 is independently H or a hydroxyl protecting group;

R_7 is –CHO or



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

wherein the compound of formula (IVA) is:



(IVA)

wherein

each P_9 is independently a hydroxyl protecting group;

R_9 is –CHO or –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 –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;

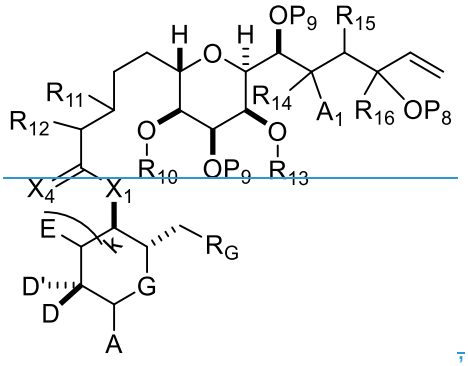
or

(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;

wherein the compound of formula (IVB) is:



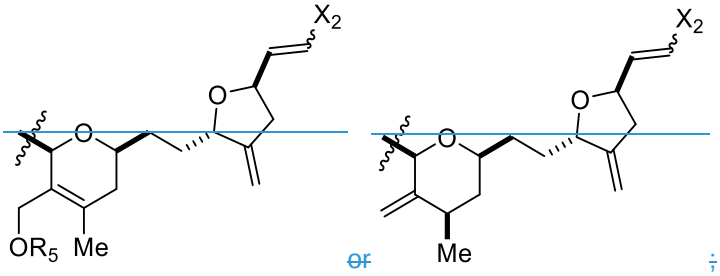
(IVB)

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



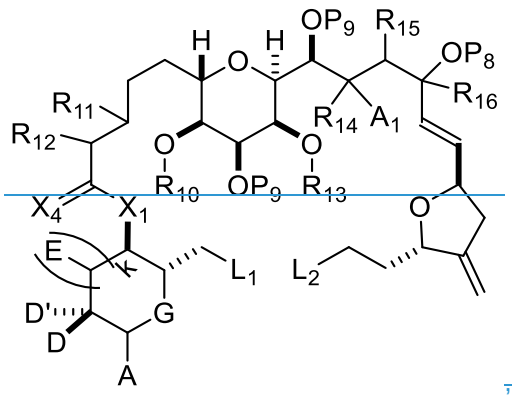
or

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

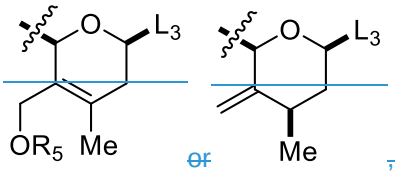
(B) producing a compound of formula (IVC) from the compound of formula (IVB), wherein the compound of formula (IVC) is:



(IVC)

wherein

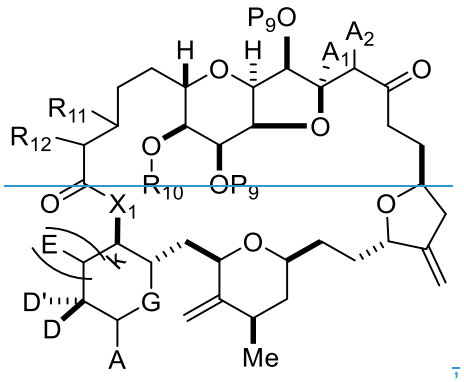
L_1 is



or

wherein L_2 and L_3 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:



(IVD)

wherein each of A_1 and A_2 is independently H or –OP";

and

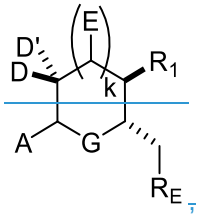
(D) producing the halichondrin macrolide or analog thereof from the compound of formula (IVD); or

(3)

(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:



(IIA)

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,

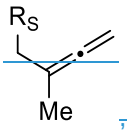
or

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:



(IIB)

wherein R_S is silyl;

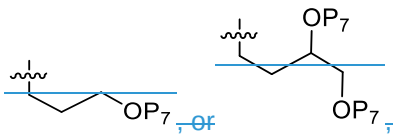
wherein the compound of formula (IIIB) is:

R_{4B}-R_7,

(IIIB)

wherein

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

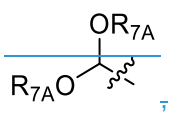


, or

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

and

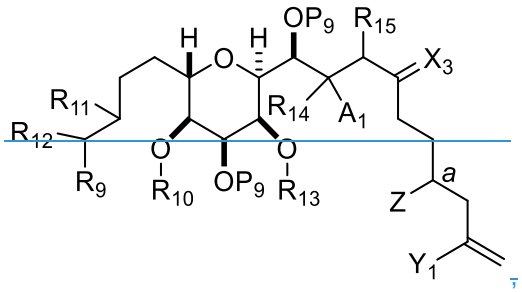
R_7 is $-CHO$ or



,

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 OR_{16}, wherein R_{16} is a hydroxyl protecting group;

(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";

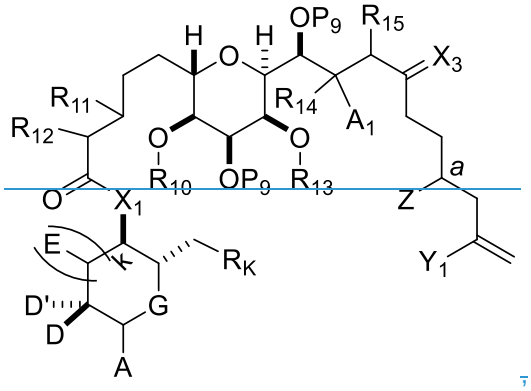
Y_1 is iodide, bromide, or trifluoromethanesulfonate;

R_9 is –CHO or –COOH;

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 a ketal; and

each P" is independently a hydroxyl protecting group; and

wherein the compound of formula (VB) is:



(VB)

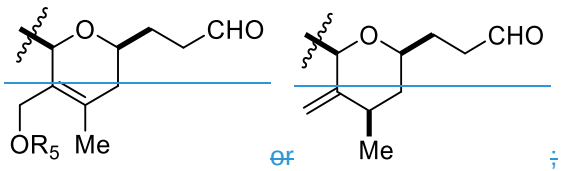
wherein

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

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

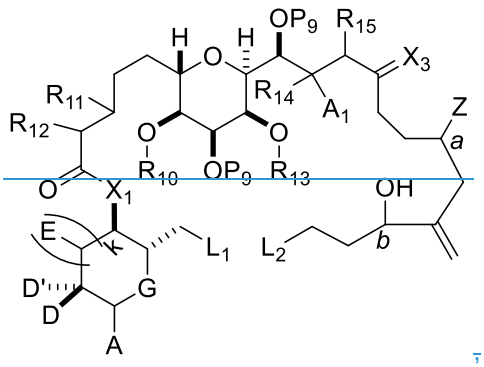
each R_D, when present, is independently optionally substituted aryl or optionally substituted non-enolizable alkyl; and

R_K is



or ;

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

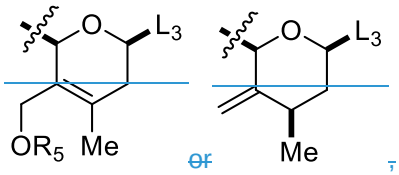


;

(VC)

wherein

L_1 is



or ;

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

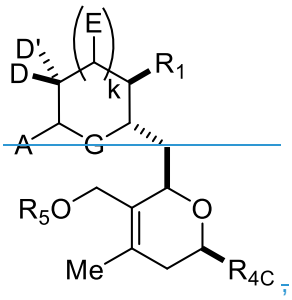
(C) producing the halichondrin macrolide or analog thereof from the compound of formula (VC); or

(4)

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

wherein R_5 is optionally substituted acyl;

wherein the compound of formula (IF) is:



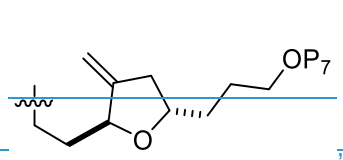
(IF)

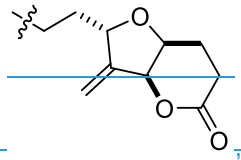
wherein

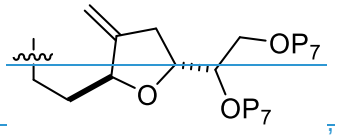
R_1 is $-OP_6$, $-CH(Y)_2$, or $-CH_2(Y)$, wherein P_6 is H or a hydroxyl protecting group, and each Y is independently $-COOR_C$ or $-SO_2R_D$;

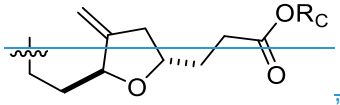
each R_C, when present, is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

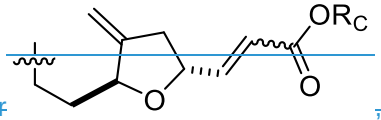
each R_D, when present, is independently optionally substituted aryl or optionally substituted non-enolizable alkyl;

R_{4C} is 

, 

, 

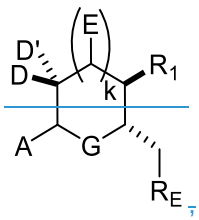
, 

, 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:



(IIA)

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,

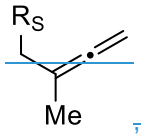
or

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:



,

(IIB)

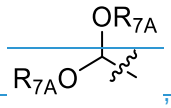
wherein R_S is silyl;

and

wherein the compound of formula (IIIC) is:

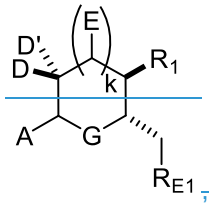
R_{4C}-R_7,

(IIIC)

wherein R_7 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:

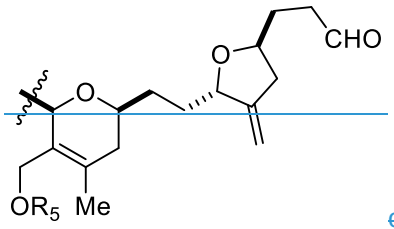


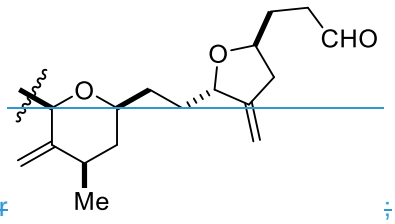
,

(IG)

wherein

R_{E1} is



or 

;

and

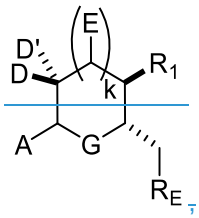
(C) producing the halichondrin macrolide or analog thereof from the compound of formula (IG) and one or more intermediates; or

(5)

(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:



(IIA)

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,

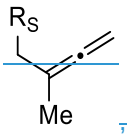
or

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:



(IIB)

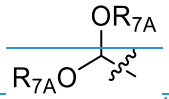
wherein R_S is silyl;

wherein the compound of formula (IIIC) is:

R_{4C}-R_7,

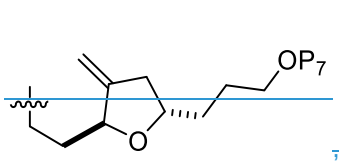
(IIIC)

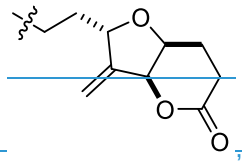
wherein

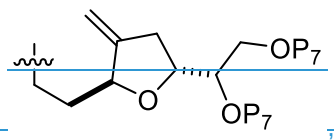
R_7 is $-CHO$ or 

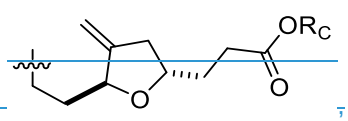
, wherein each R_{7A} is independently an optionally substituted alkyl;

R_{4C} is



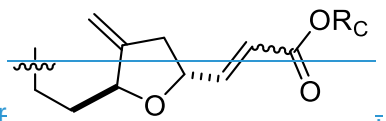
,


,


,


,

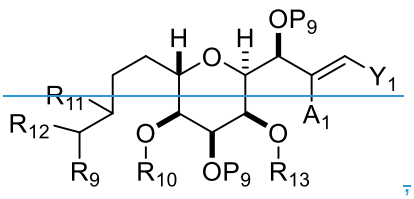
or



,

wherein each P_7, when present, is independently H or a hydroxyl protecting group;

wherein the compound of formula (VIIA) is:



(VIIA)

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;

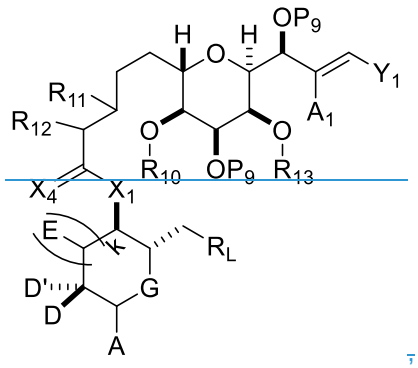
R_9 is –CHO or –COOH;

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

A_1 is H or –OP", wherein P" is H or a hydroxyl protecting group; and

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

wherein the compound of formula (VIID) is:



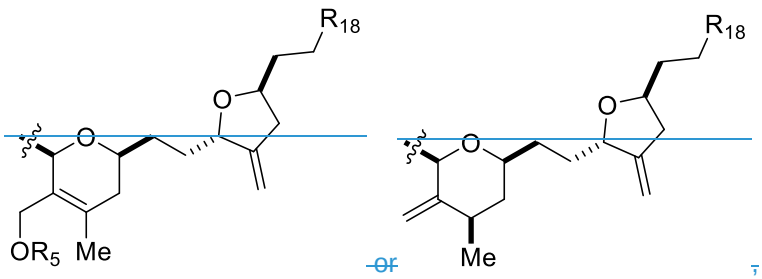
(VIID)

wherein

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

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

R_L is



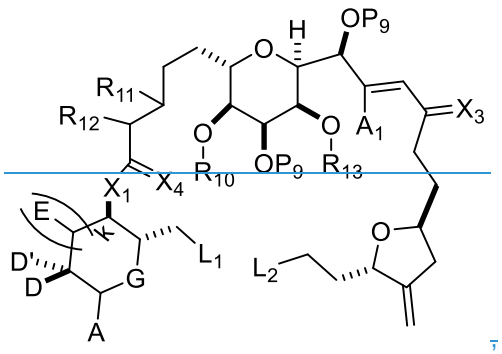
or

wherein

R_{18} is –CHO or $-CH_2OP_7$;

R_5 is optionally substituted acyl;

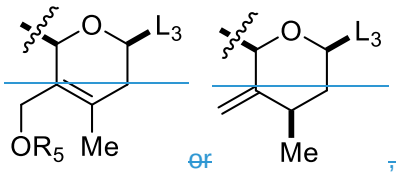
(B) producing a compound of formula (VIIE) from the compound of formula (VIID), wherein the compound of formula (VIIE) is:



(VIIE)

wherein

L_1 is



or

wherein L_2 and L_3 combine to form a bond;

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;

and

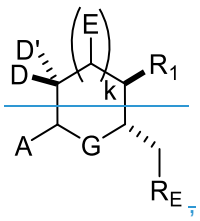
(C) producing the halichondrin macrolide or analog thereof from the compound of formula (VIIC)

(6)

(A) producing a compound of formula (VIIIB) from a compound of formula (VIIIA), a compound of formula (IIA), a compound of formula (IIB), and a compound of formula (IIIC), and R_5OH,

wherein R_5 is optionally substituted acyl;

wherein the compound of formula (IIA) is:



(IIA)

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,

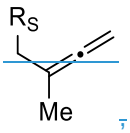
or

m is 0

(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:



(IIB)

wherein R_S is silyl;

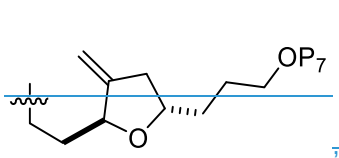
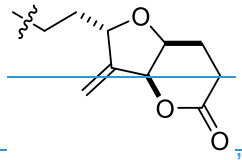
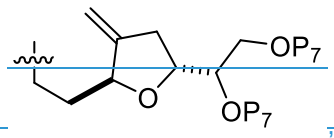
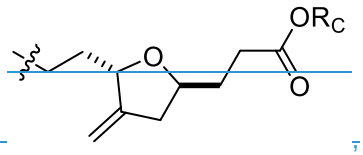
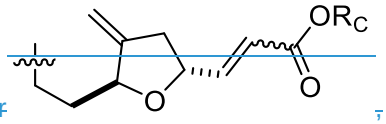
wherein the compound of formula (IIIC) is:

R_{4C}-R_7,

(IIIC)

wherein

R_{4C} is

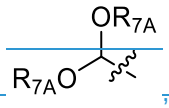






or

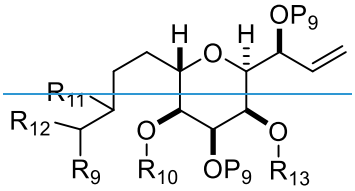
wherein

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

each P_7, when present, is independently H or a hydroxyl protecting group;

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

wherein the compound of formula (VIIIA) is:



(VIIIA),

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

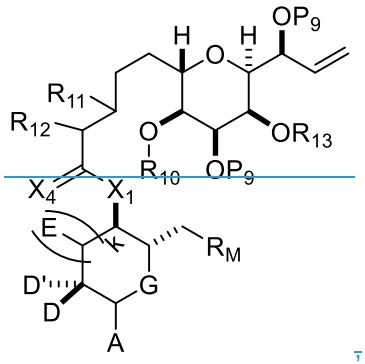
(iii) R_{10} and R_{11} combine to form a bond, and R_{12} is H;

R_9 is –CHO or –COOH;

and

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

wherein the compound of formula (VIIIB) is:

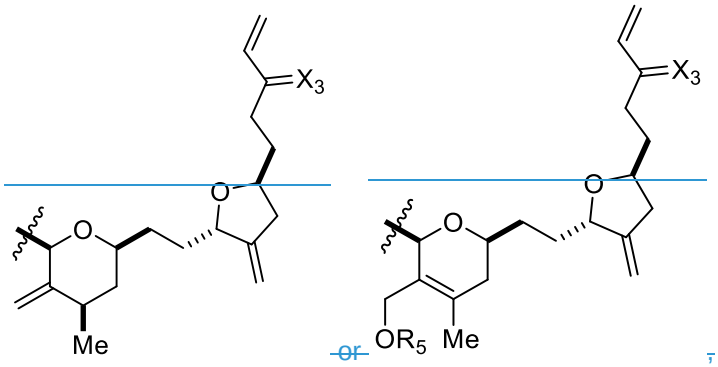


(VIIIB)

wherein

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

R_M is



or

wherein

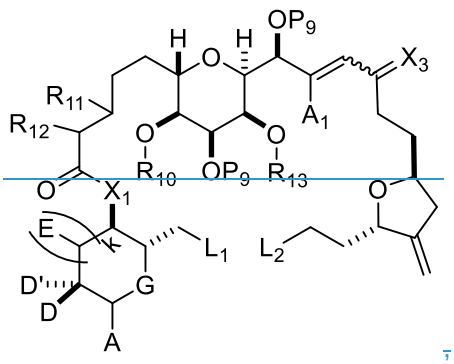
R_5 is optionally substituted acyl; and

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

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 $-(CH(OP_{12}))-$, where P_{12} is H or a hydroxyl protecting group;

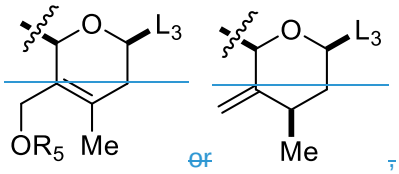
(B) producing a compound of formula (VIIIC) from the compound of formula (VIIIB), wherein the compound of formula (VIIIC) is:



(VIIIC)

wherein

L_1 is



or

, wherein L_2 and L_3 combine to form a bond;

A_1 is H or –OP", wherein P" is H or a hydroxyl protecting group;

and

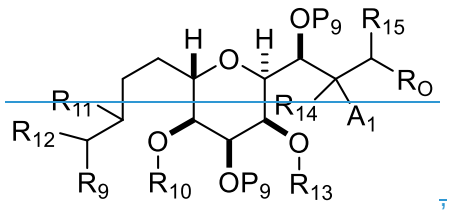
(C) producing the halichondrin macrolide or analog thereof from the compound of formula (VIIIC); or

(7)

(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 R_5OH,

wherein R_5 is optionally substituted acyl;

wherein the compound of formula (IXA) is:



,

(IXA)

wherein

R_9 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";

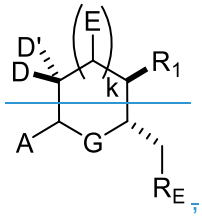
R_O is –CHO, $–CH_2OP"$, $–CH=CH_2$, $–CH(OP")CH_2OP"$, $–C(O)–CH_2P(O)(OR_C)_2$, or halogen;

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:



(IIA)

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

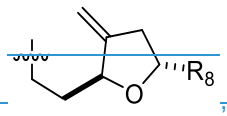
(ii) both R_F combine to form an alkylene;

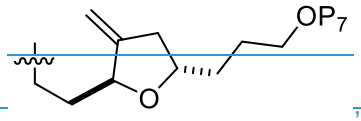
wherein the compound of formula (IIIE) is:

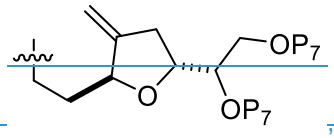
R_{4E}-R_7,

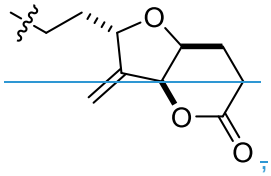
(IIIE)

wherein

R_{4E} is 

, 

, 

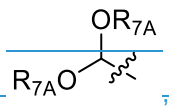
, or 

,

wherein

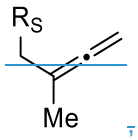
each P_7 is independently H or a hydroxyl protecting group; and

R_8 is $-CH_2CH_2-COOR_C$, $-CH=CH-COOR_C$, $-CH_2CH_2-SO_2R_D$, or $-CH=CH-SO_2R_D$; and

R_7 is $-CHO$ or 

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

wherein the compound of formula (IIB) is:

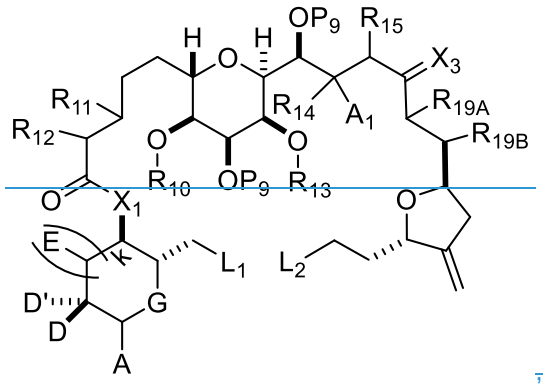


(IIB)

wherein R_S is silyl;

and

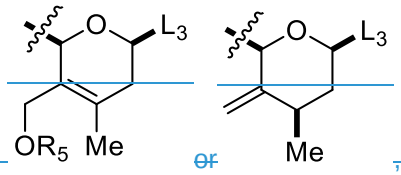
wherein the compound of formula (IXB) is:



(IXB)

wherein

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

A_1 is H or -OP", and:

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

or

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

each P_9 is independently H or a hydroxyl protecting group, and X_3 is oxo, or X_3, together with the atom to which it is attached, combines to form $-(CH(OP_{11}))-$, wherein 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

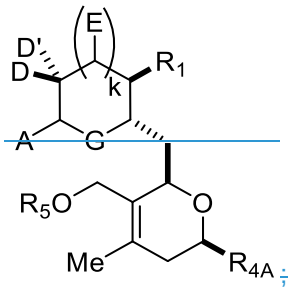
R_{19A} is H, -OP", or Y, and R_{19B} is H; or R_{19A} and R_{19B}, together with the atoms to which each is attached, combine to form a double bond;

and

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

11. The method of claim 10, wherein, for (2), step (A) comprises:

(E) producing a compound of formula (IA) from the compound of formula (IIA), the compound of formula (IIIA), and R_5OH, wherein the compound of formula (IA) is:



(IA)

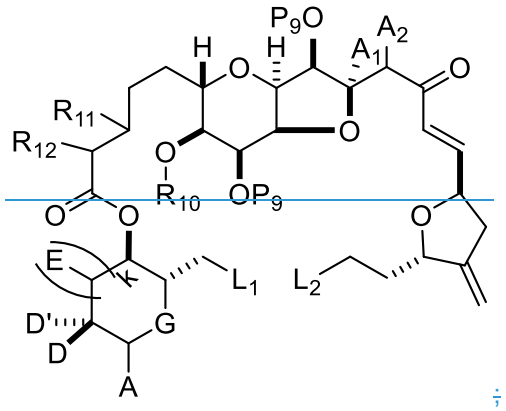
and

(F) producing the compound of formula (IVB) from the compound of formula (IF) and the compound of formula (IVA); and/or

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 or 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; and/or

step (B) comprises reacting the compound of formula (IVB) with an olefin metathesis catalyst; and/or P_9 is H, R_{16} is H, and step (C) comprises:

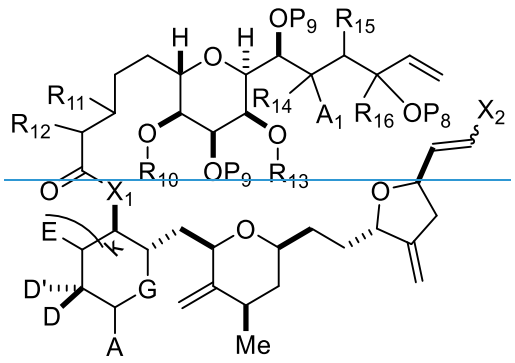
oxidizing the compound of formula (IVC) to produce a compound of formula (IVCa):



(IVCa)

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

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:

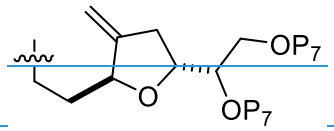


(IVBa); and/or

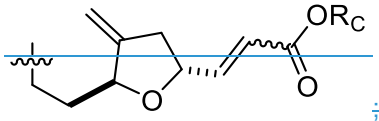
the producing the halichondrin macrolide or analog thereof comprises reacting the compound of formula (IVD) with a hydroxyl protecting group removing agent.

12. The method of claim 11, wherein:

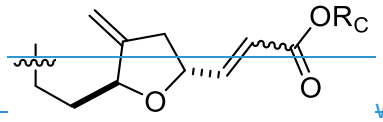
step (E) comprises reacting the compound of formula (IIA), the compound of formula (IIIA), R_5OH, and a Lewis acid; and/or



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



; and/or



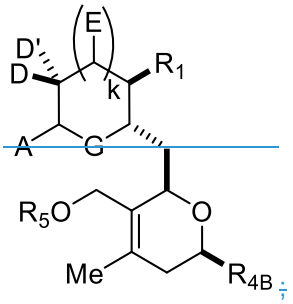
step (F) comprises reacting R_{4A} that is with a 1,2-reducing agent and further reacting with an allyl halide or allyl pseudohalide.

13. The method of claim 12, wherein the Lewis acid is an oxophilic Lewis acid.

14. The method of claim 13, wherein the oxophilic Lewis acid is boron trifluoride or a solvate thereof.

15. The method of claim 10, wherein, for (3), 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 (IIIB), and R_5OH, wherein the compound of formula (ID) is:



;

(ID)

and

(E) producing the compound of formula (VB) from the compound of formula (ID) and the compound of formula (VA); and/or

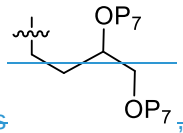
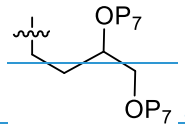
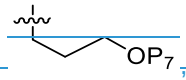
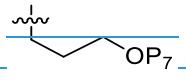
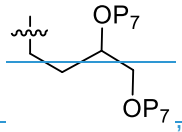
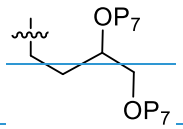
X_1 is $-CH_2-$, $-CH(Y)-$, or $-C(Y)_2-$, and step (A) comprises reacting R_9, wherein R_9 is $-CHO$, with R_1 that is $-CH(Y)_2$ or $-CH_2(Y)$ treated with a Brønsted base, to produce $-CO-X_1-$ or X_1 is $-O-$, and step (A) comprises esterifying R_9 that is $-COOH$ with R_1 that is $-OP_6$, where P_6 is H, to produce $-CO-X_1-$; and/or

step (B) comprises reacting the compound of formula (VB) with a Cr(II) salt and a Ni(II) salt; and/or

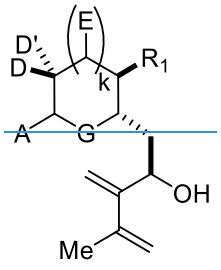
step (C) comprises a step of nucleophilic ring-closing of the compound of formula (VC); and/or

both P_9 groups and X_3, together with the atoms to which each is attached, combine to form a ketal; and/or

R_{10} and R_{11} combine to form a bond, and R_{12} is H; and/or

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; or R_{4B} is  , and step (A) comprises reacting the  with an oxidizing agent capable of converting an alcohol into a carbonyl group; or R_{4B} is  , and step (A) comprises cleaving the  through a reaction with a glycol cleaving agent.

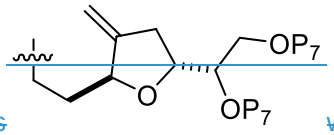
16. The method of claim 15, wherein the producing the compound of formula (ID) comprises reacting the compound of formula (IIC), the compound of formula (IIIB), R_5OH, and a Lewis acid; and/or step (D) comprises a Sakurai reaction between the compound of formula (IIA) and the compound of formula (IIB) to produce a compound of formula (IIC), and a Prins reaction between the compound of formula (IIC), the compound of formula (IIIB), and R_5OH, wherein the compound of formula (IIC) is:

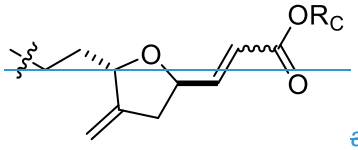
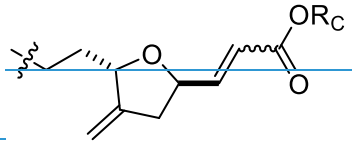


(IIC).

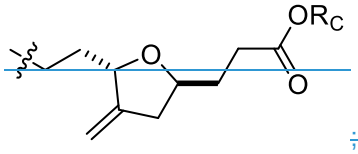
17. The method of claim 16, wherein the Lewis acid is boron trifluoride or a solvate thereof.

18. The method of claim 10, wherein for (4):

(i) step (B) comprises reacting R_{4C} that is  with a glycol cleaving agent to produce an aldehyde, reacting the aldehyde with $(R_CO)_2P(O)\text{-}CH_2\text{-}COOR_C$ to produce R_{4C} that is

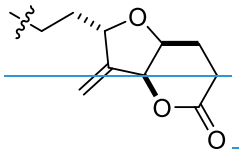
 and/or step (B) comprises reducing R_{4C} that is 

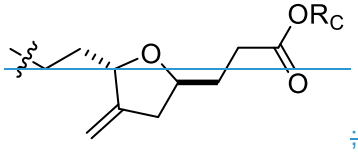
with a 1,4-reducing agent to produce R_{4C} that is



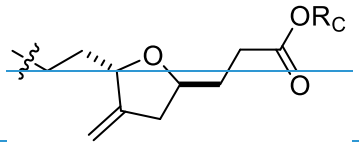
; or

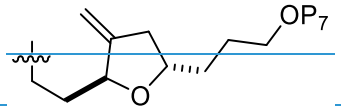
(ii) step (B) comprises reducing R_{4C} that is

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

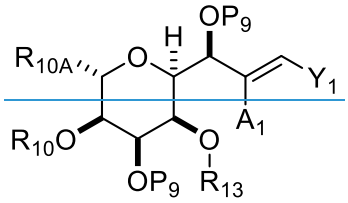


; or

(iii) step (B) comprises reducing R_{4C} that is  with a 1,2-reducing agent to produce a carbonyl group in R_{E1}; or

(iv) step (B) comprises reacting R_{4C} that is  with an oxidizing agent capable of converting an alcohol to a carbonyl group in R_{E1}; and/or

(v) the one or more intermediates is a compound of formula (VIA):



(VIA),

wherein

R_{10A} is $-CH_2-CH=CH_2$, $-(CH_2)_2-CH=CH_2$, or $-(CH_2)_3-OP_{10}$;

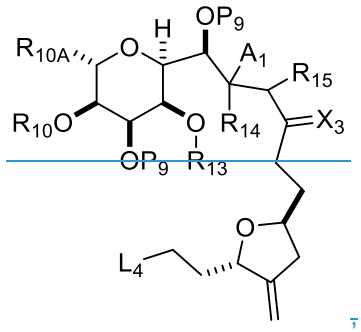
each R_{10}, R_{13}, P_9 and P_{10} is independently a hydroxyl protecting group;

A_1 is H or –OP"; and

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

and step (C) comprises:

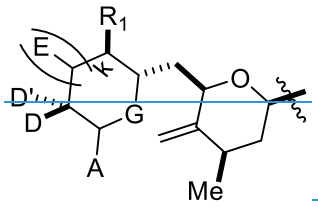
(D) producing a compound of formula (VIB) from the compound of formula (IG) and the compound of formula (VIA), wherein the compound of formula (VIB) is:



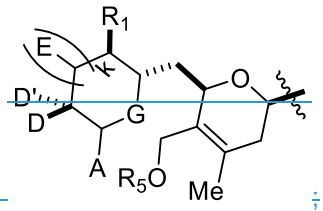
(VIB)

wherein

L_4 is



or



;

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

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 $-OP''$, and:

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

or

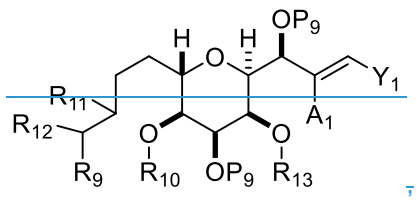
(ii) R_{13} and R_{14} combine to form a bond, and R_{15} is H or $-OP''$;

and

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; or

(vi) step (C) comprises:

(N) producing a compound of formula (VIIB) from the compound of formula (IG) and a compound of formula (VIIA):



(VIIA)

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";

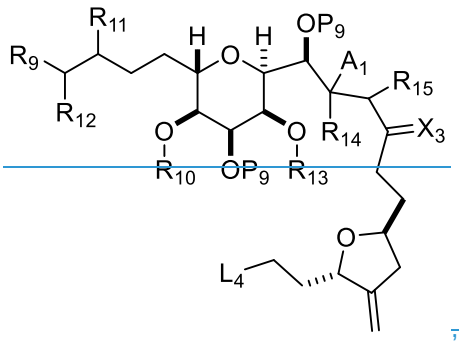
R_{13} and each P_9 is independently a hydroxyl protecting group;

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;

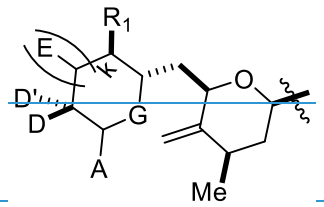
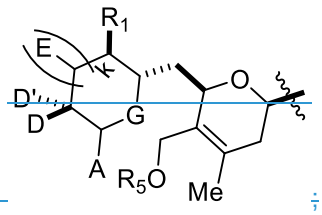
wherein the compound of formula (VIIB) is:



;

(VIIB)

wherein

L_4 is  or  ;

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

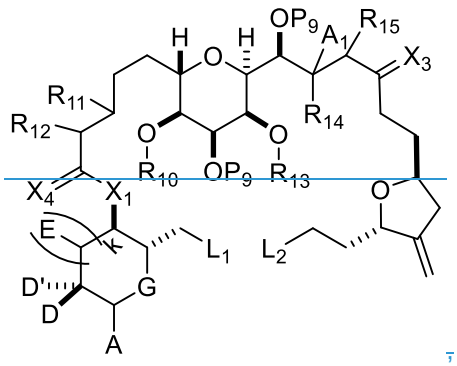
(ii) R_{13} and R_{14} combine to form a bond, and R_{15} is H or –OP";

R_9 is –CHO or –COOP";

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;

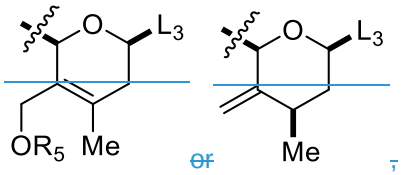
(O) producing a compound of formula (VIIC) from the compound of formula (VIIB), wherein the compound of formula (VIIC) is:



(VIIC)

wherein

L_1 is



or

wherein L_2 and L_3 combine to form a bond;

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

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

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

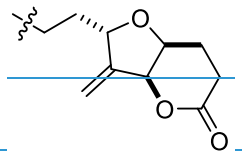
X_4 is oxo, or X_4, together with the atom to which it is attached, is $-(CH(OP_{12}))-$, where P_{12} is H or a hydroxyl protecting group;

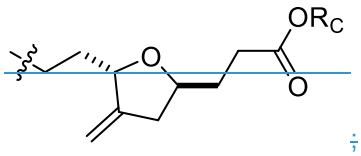
and

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

19. The method of claim 18, wherein:

for (ii):

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

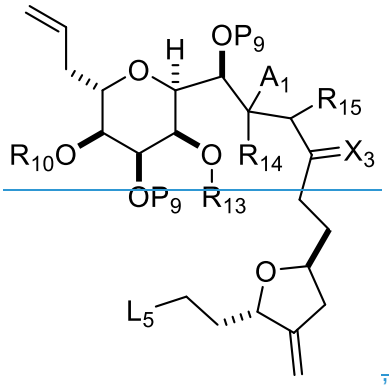


for (v):

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; and/or

R_{10A} is $-CH_2-CH=CH_2$, and step (C) comprises:

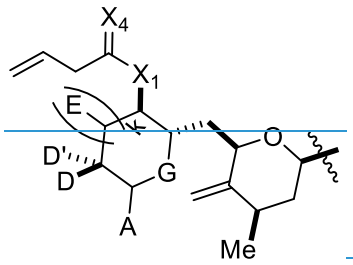
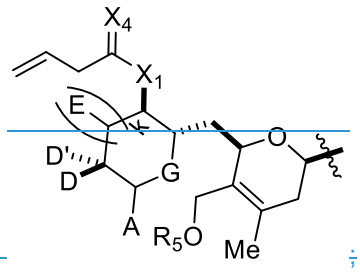
(E) producing a compound of formula (VIC) from the compound of formula (VIB) and R_{17}–$CH_2CH{=}CH_2$, wherein R_{17} is –COOH or a metallic or metalloid moiety, and the compound of formula (VIC) is:



(VIC)

wherein

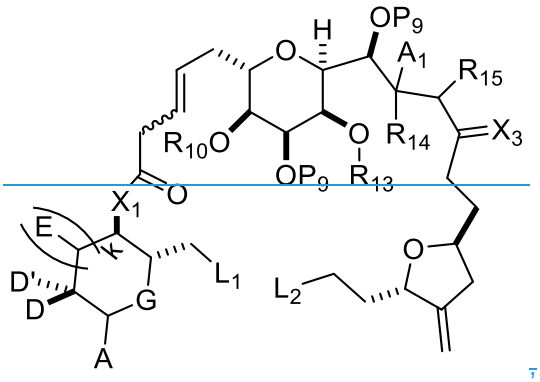
L_5 is


or

;

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

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

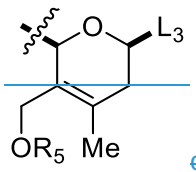
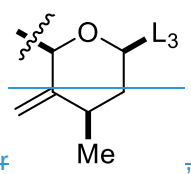
(F) producing a compound of formula (VID) from the compound of formula (VIC), wherein the compound of formula (VID) is:



(VID)

wherein

L_1 is

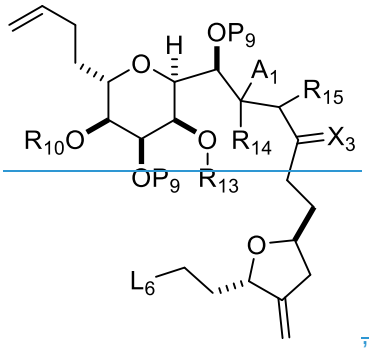

or

, wherein L_2 and L_3 combine to form a bond;

and

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

R_{10A} is $-CH_2-CH_2-CH=CH_2$, R_1 is $-OP_6$ or $-CH_2(Y)$, wherein P_6 is H or a hydroxyl protecting group, and Y is $-COOR_C$, and step (C) comprises:

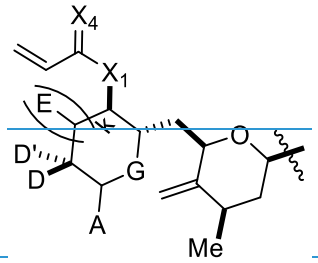
(H) producing a compound of formula (VIE) from the compound of formula (VIB) and $R_{17}-CH=CH_2$, wherein R_{17} is –COOH or a metallic or metalloid moiety, wherein the compound of formula (VIE) is:



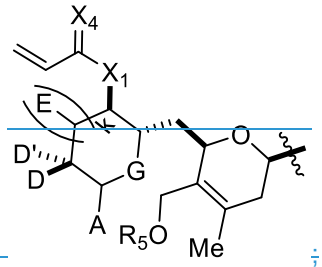
,

(VIE)

wherein



L_6 is or

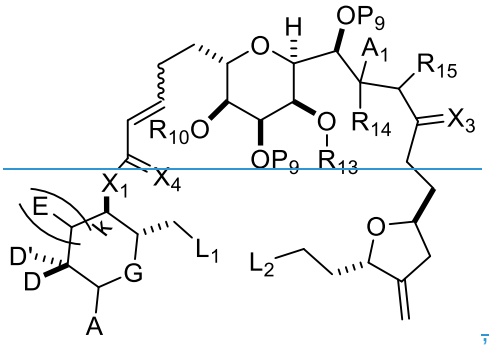


;

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

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

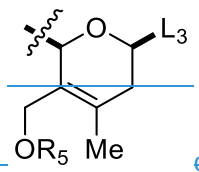
(I) producing a compound of formula (VIF) from the compound of formula (VIE), wherein the compound of formula (VIF) is:



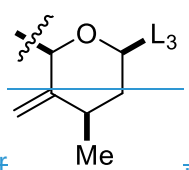
,

(VIF)

wherein



L_1 is or



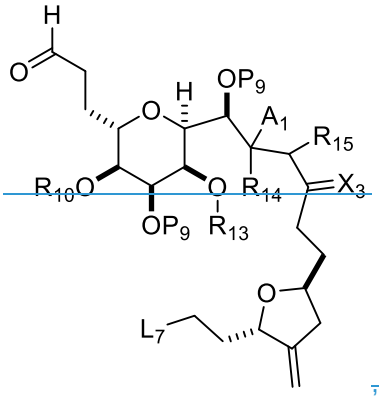
, wherein L_2 and L_3 combine to form a bond;

and

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

R_{10A} is $-(CH_2)_3-OP_{10}$, and step (C) comprises:

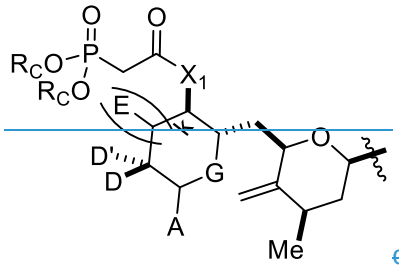
(K) producing a compound of formula (VIG) from the compound of formula (VIB) and $(R_CO)_2P(O)-CH_2-R_P$, wherein each R_C is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl, and R_P is H or –COOH, and wherein the compound of formula (VIG) is:



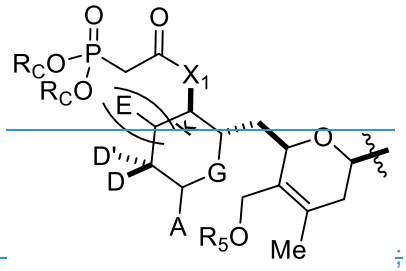
(VIG)

wherein

L_7 is



or

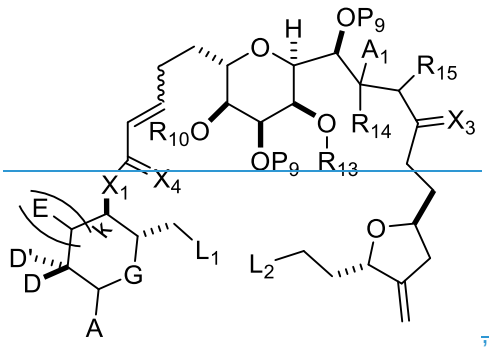


;

and

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

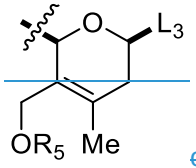
(L) producing a compound of formula (VIF) from the compound of formula (VIG), wherein the compound of formula (VIF) is:



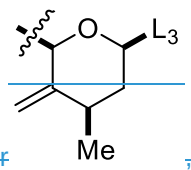
(VIF)

wherein

L_1 is



or



, wherein L_2 and L_3 combine to form a bond; and

~~X_4 is oxo; and~~

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

~~and~~

~~for (vi):~~

~~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; and/or~~

~~step (O) comprises an esterification reaction between R_1 that is $-OP_6$, wherein P_6 is H, and R_9 that is $-COOH$ or a reaction between R_1 that is $-CH(Y)_2$ or $-CH_2(Y)$, and R_9 that is $-CHO$; and/or~~

~~step (P) comprises reacting the compound of formula (VIIC) with a hydroxyl protecting group removing agent.~~

~~20. The method of claim 19, wherein:~~

~~R_1 is $-CH_2(Y)$, X_1 is $-CH_2-$, X_4 is oxo or $-(CH(OP_{12}))-$, and step (E) comprises reacting the compound of formula (VIB) with $R_{17}-CH_2CH=CH_2$, wherein R_{17} is a metallic or metalloid moiety or R_1 is $-OP_6$, P_6 is H, X_1 is $-O-$, X_4 is oxo, and step (E) comprises esterifying the compound of formula (VIB) with $R_{17}-CH_2CH=CH_2$, wherein R_{17} is $-COOH$;~~

~~step (F) comprises reacting the compound of formula (VIC) with an olefin metathesis catalyst; and/or~~

~~step (G) comprises reacting the compound of formula (VID) with a hydroxyl protecting group removing agent;~~

~~step (I) comprises reacting the compound of formula (VIE) with an olefin metathesis catalyst; and/or~~

~~step (J) comprises reacting the compound of formula (VIF) with a hydroxyl protecting group removing agent;~~

~~step (K) comprises:~~

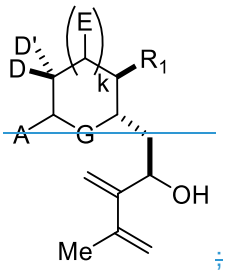
~~reacting the compound of formula (VIB) with $(R_CO)_2P(O)-CH_2-R_P$ under Claisen reaction conditions, wherein R_P is H and R_1 is $-CH_2(Y)$, or~~

~~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; and/or~~

~~step (M) comprises reacting the compound of formula (VIF) with a hydroxyl protecting group removing agent.~~

~~21. The method of claim 10, wherein, for (5), step (A) comprises:~~

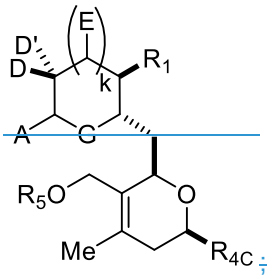
~~(D) producing a compound of formula (IIC) from the compound of formula (IIA) and the compound of formula (IIB), wherein the compound of formula (IIC) is:~~



;

~~(IIC)~~

(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:

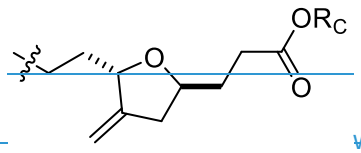


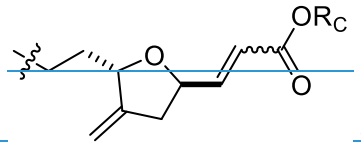
(IF)

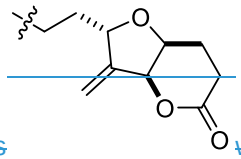
and

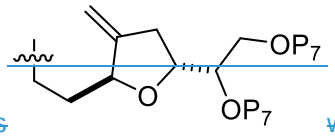
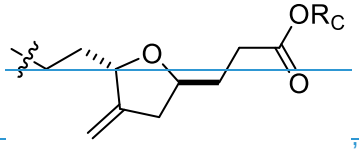
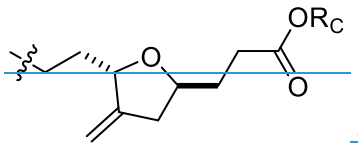
(F) producing the compound of formula (VIIB) from the compound of formula (VIIA) and the compound of formula (IF); and/or

step (A) comprises:

(i) reducing R_{4C} that is  with a 1,2-reducing agent;

(ii) 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;

(iii) 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; or

(iv) cleaving R_{4C} that is  with a glycol cleaving agent to produce an aldehyde, reacting the aldehyde $(R_CO)_2P(O)\text{-}CH_2\text{-}COOR_C$ 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;

and/or

step (B) comprises reacting the compound of formulas (VIID) with a Cr(II) salt and a Ni(II) salt; and/or

step (A) comprises an esterification reaction between R_1 that is $-OP_6$, where P_6 is H, and R_9 that is –COOH or a reaction between R_1 that is $-CH(Y)_2$ or $-CH_2(Y)$, and R_9 that is –CHO; and/or

step (C) comprises reacting the compound of formula (VIIE) with a hydroxyl protecting group removing agent.

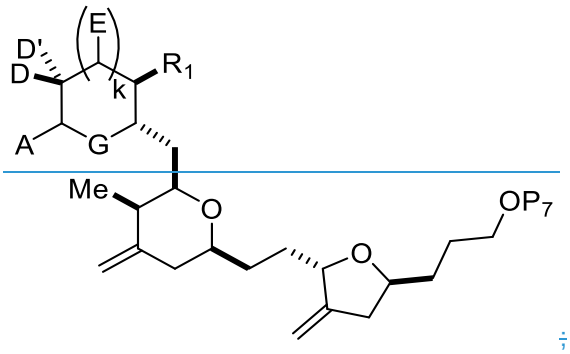
22. The method of claim 21, wherein the producing the compound of formula (IF) comprises reacting the compound of formula (IIC), the compound of formula (IIIC), R_5OH, and a Lewis acid.

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

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

25. The method of any one of claims 21 to 24, wherein step (F) comprises:

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



;

(IH)

and

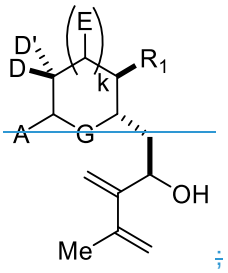
(H) producing the compound of formula (VIID) from the compound of formula (IH) and the compound of formula (VIIA).

26. The method of claim 25, wherein the producing step (G) comprises reacting the compound of formula (IF) with an allylic reducing agent.

27. The method of claim 10, wherein, for (6), step (A) comprises:

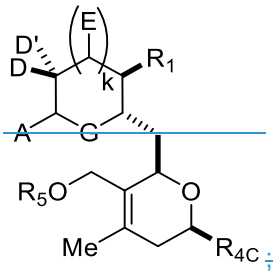
(i)

(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:



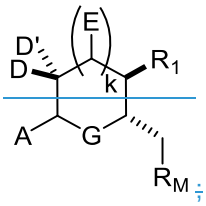
(IIC)

(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:



(IF)

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



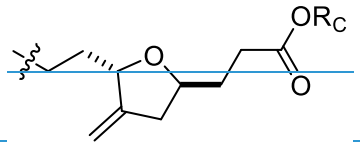
(IJ)

and

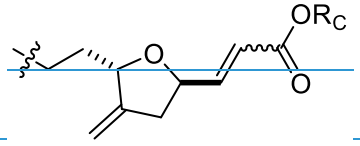
(G) producing the compound of formula (VIIIB) from the compound of formula (VIIIA) and the compound of formula (IJ);

and/or

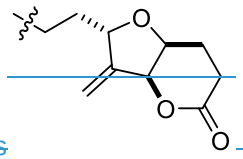
(ii)

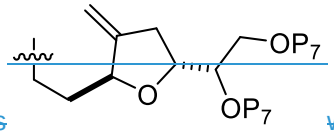
reacting R_{4C} that is 

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

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; or

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; or

cleaving R_{4C} that is  with a glycol cleaving agent to produce an aldehyde, reacting the aldehyde with $(R_CO)_2P(O)\text{-}CH_2\text{-}COOR_C$ 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 product a reduced product, and reacting the reduced product with a vinyl nucleophile;

and/or

(iii)

step (A) comprises an esterification reaction between R_1 that is $-OP_6$, where P_6 is H, and R_9 that is –COOH or a reaction between R_1 that is $-CH(Y)_2$ or $-CH_2(Y)$, and R_9, wherein R_9 is –CHO;

and/or

(iv)

step (B) comprises reacting the compound of formula (VIIIB) with an olefin metathesis catalyst;

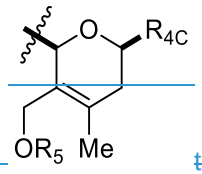
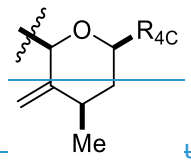
and/or

(v)

step (C) comprises reacting the compound of formula (VIIIC) with a hydroxyl protecting group removing agent.

28. The method of claim 27, wherein step (D) comprises reacting the compound of formula (IIB), the compound of formula (IIA), and a Lewis acid; and/or

step (E) comprises reacting the compound of formula (IIC), the compound of formula (IIIC), R_5OH and a Lewis acid; and/or

step (F) comprises converting  to  using an allylic reducing agent.

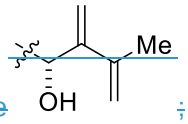
29. The method of claim 28, wherein the Lewis acid in step (D) and the Lewis acid in step (E) are different; and/or each of the Lewis acid in step (D) and/or the Lewis acid in step (E) is an oxophilic Lewis acid.

30. The method of claim 28 or 29, wherein the Lewis acid is an oxophilic Lewis acid.

31. The method of claim 30, wherein the oxophilic Lewis acid is boron trifluoride or a solvate thereof.

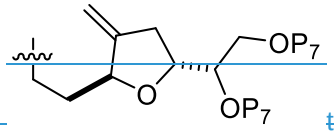
32. The method of claim 10, wherein step (A), for (7), comprises:

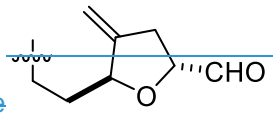
(i)

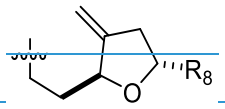
reacting R_E that is –CHO with the compound of formula (IIB) and a first Lewis acid to produce a group of the structure 

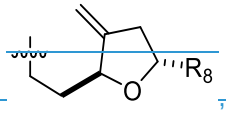
;

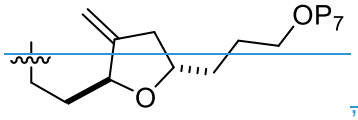
and/or

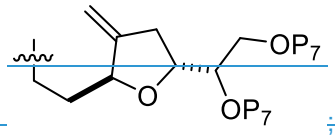
(ii) converting R_{4E} that is 

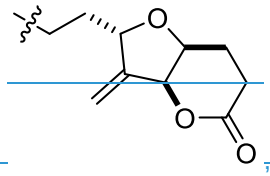
to a group of the structure 

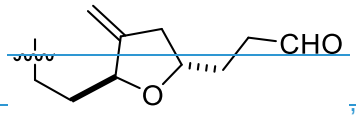
, and reacting this group with R_O that is –C(O)–CH_2P(O)(OR_C)$_2$ under Horner-Wadsworth-Emmons reaction conditions; or reacting R_{4E} that is 

with R_O that is –CHO under Claisen reaction conditions, wherein R_8 is –CH_2CH_2–$COOR_C$ or –CH_2CH_2–SO_2R_D; or converting R_{4E} that is 

, 

, 

; or 

, to a group of the structure 

, and reacting this group with R_O that is a halogen under Nozaki-Hiyama-Kishi reaction conditions, wherein R_8, when present, is –CH_2CH_2–$COOR_C$ or –CH=CH–$COOR_C$, and R_{14} and R_{15} combine to form a double bond;

and/or

(iii)

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–;

and/or

(iv)

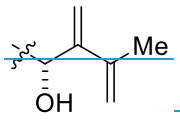
reacting R_1 that is –$CH(Y)_2$ or –CH_2(Y) with R_9 under Claisen reaction conditions to produce a group of the structure –X_1–C(O)–, wherein R_9 is –CHO, and X_1 is –$C(Y)_2$– or –CH(Y)–, respectively;

and/or

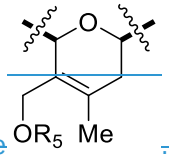
(v)

step (B) comprises reacting the compound of formula (IXB) with a hydroxyl protecting group removing agent.

~~33. The method of claim 32, wherein, for (i), step (A) comprises reacting the group of the structure~~



~~with R_7, R_5OH, and a second Lewis acid to produce a group of the structure~~



~~.~~

~~34. The method of claim 33, wherein the first Lewis acid and/or second Lewis acid is an oxophilic Lewis acid; and/or the first Lewis acid is same as the second Lewis acid.~~

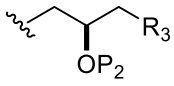
~~35.~~11. The method of any one of claims ~~1-34~~1-10, wherein:

(i)

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

D is H; and/or

wherein A is of the following structure:



; and/or

k is 0; and/or

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

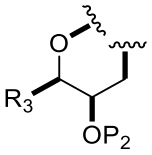
G is O;

or

(ii)

D' is H; and/or

A and D combine to form the following structure:



,

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

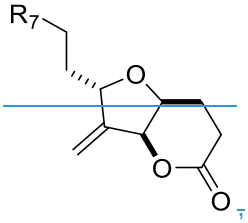
wherein R_3 is $–(CH_2)_nNP_3P_4$ or $–(CH_2)_nOP_5$, wherein n is 2; and/or

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

G is O.

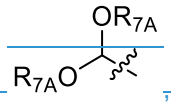
~~36. A method of preparing:~~

~~(1)~~



~~,~~

~~(Z)~~

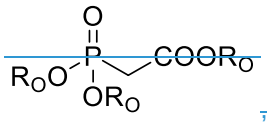
wherein R_7 is –CHO or  , and

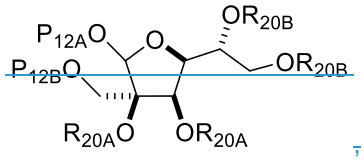
each R_{7A} is independently alkyl or a hydroxyl protecting group; or

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

 ,

(Z1)

wherein

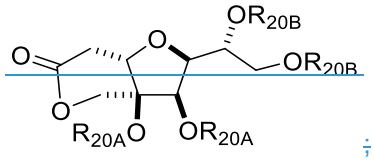
each R_{20A} is independently a hydroxyl protecting group, or both R_{20A}, together with the atoms to which each is attached, combine to form an acetal, ketal, cyclic carbonate, dicarbonyl-dioxo, or silylene-dioxo;

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;

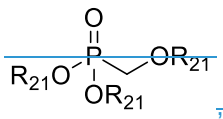
P_{12B} is H or a hydroxyl protecting group;

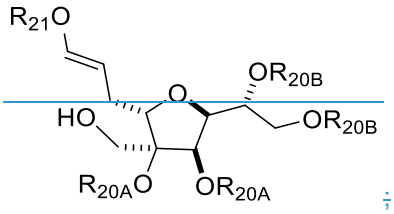
and the compound of formula (Z2) is:

 ;

(Z2)

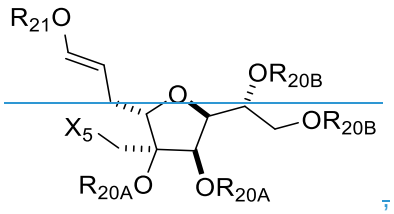
(B) producing a compound of formula (Z3) from the compound of formula (Z2) and

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

 ;

(Z3)

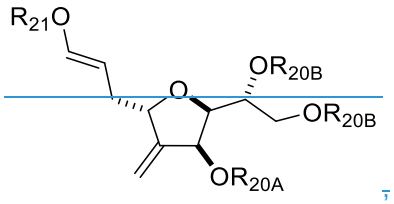
(C) producing a compound of formula (Z4) from the compound of formula (Z3), wherein the compound of formula (Z4) is:



(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:



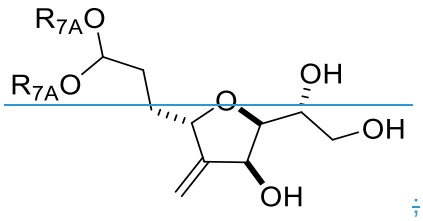
(Z5)

wherein

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

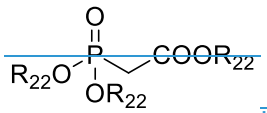
each R_{20B} is independently H or a hydroxyl protecting group, or both R_{20B}, together with the atoms to which each is attached, combine to form an acetal, ketal, cyclic carbonate, dicarbonyl-dioxo, or silylene-dioxo;

(E) producing a compound of formula (Z6) from the compound of formula (Z5) and $R_{7A}OH$

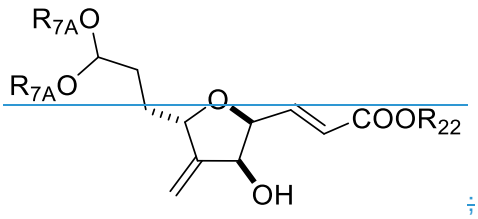


(Z6)

(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:

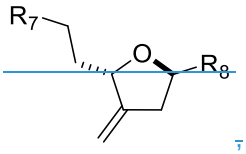


(Z7)

and

(G) producing the compound of formula (Z) from the compound of formula (Z7); or

(2)

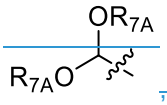


,

(Z8)

wherein

R_7 is –CHO or



, and

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

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

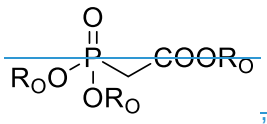
R_8 is $–CH_2CH_2–COOR_C$, $–CH=CH–COOR_C$, $–CH_2CH_2–SO_2R_D$, or $–CH=CH–SO_2R_D$;

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

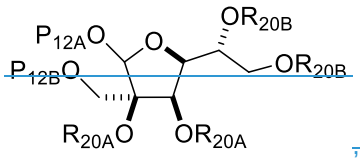
R_D, when present, is independently optionally substituted aryl or optionally substituted non-enolizable alkyl;

the method comprising:

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



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



,

(Z1)

wherein

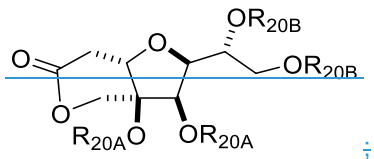
each R_{20A} is independently a hydroxyl protecting group, or both R_{20A}, together with the atoms to which each is attached, combine to form an acetal, ketal, cyclic carbonate, dicarbonyl-dioxo, or silylene-dioxo;

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;

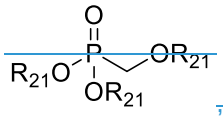
and the compound of formula (Z2) is:



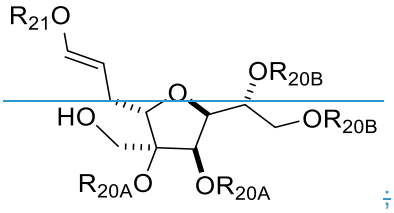
;

(Z2)

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



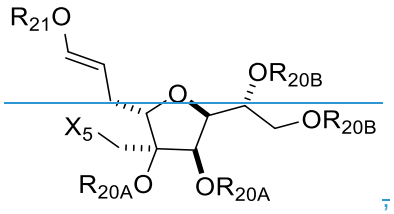
, wherein each R_{21} is independently optionally substituted alkyl, wherein the compound of formula (Z3) is:



;

(Z3)

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

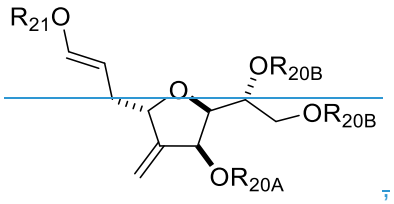


;

(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:



;

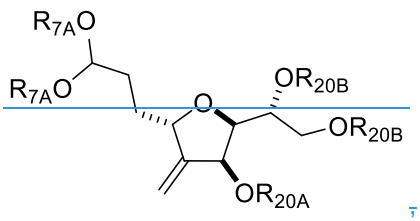
(Z5)

wherein

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 (Z5A) from the compound of formula (Z5) and $R_{7A}OH$, wherein the compound of formula (Z5A) is:



;

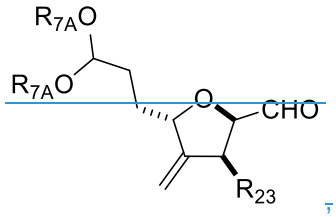
(Z5A)

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:

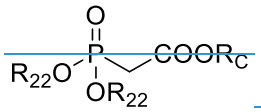
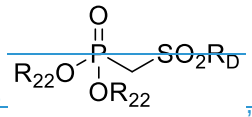


(Z5B)

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

and

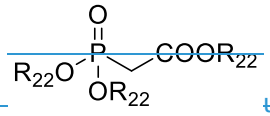
(G) producing the compound of formula (Z8) from the compound of formula (Z5B) and

 or , in which each R_{22} is independently optionally substituted alkyl.

37. The method of claim 36, wherein:

for (1):

step (E) comprises reacting the compound of formula (Z5) with $R_{7A}OH$ and a Brønsted acid; and/or

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; and/or

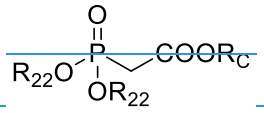
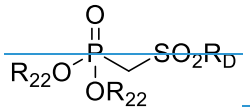
step (G) comprises reacting the compound of formula (Z6) with a 1,4-reducing agent; and

for (2):

step (E) comprises reacting the compound of formula (Z5) with $R_{7A}OH$ and a Brønsted acid; and/or

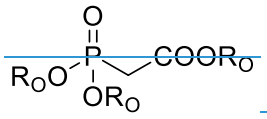
step (F) comprises reacting the compound of formula (Z5A), in which both R_{20B} are H, with a glycol cleaving agent; and/or

step (E) or step (F) further comprises reacting $-OR_{20A}$, wherein R_{20A} is optionally substituted acyl with an allylic reducing agent; and/or

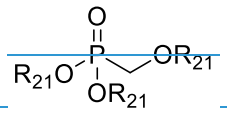
step (G) comprises reacting the compound of formula (Z5B) with  or  under Horner-Wadsworth-Emmons reaction conditions to produce the compound of formula (Z8), in which R_8 is $-CH=CH-COOR_C$ or $-CH=CH-SO_2R_D$, respectively; and/or

~~for (1) or (2):~~

~~the producing the compound of formula (Z2) comprises reacting the compound of formula (Z1) with~~



~~under Horner-Wadsworth-Emmons reaction conditions; and/or~~

~~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; and/or~~

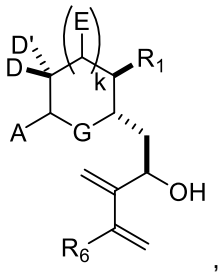
~~step (C) comprises substituting free hydroxyl group in the compound of formula (Z3) with a halogen; and/or~~

~~step (D) comprises subjecting the compound of formula (Z4) to reductive metal conditions.~~

~~38. The method of claim 37, 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.~~

~~39.~~12. A compound of

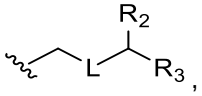
(1) formula (II):



(II)

wherein

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



(1)

wherein

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

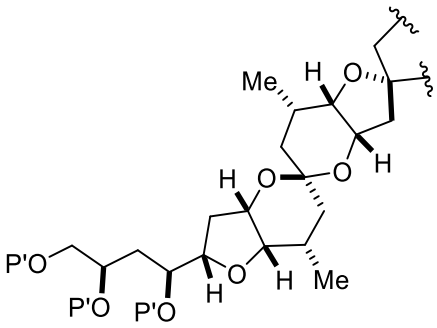
R_2 is H ~~and P_1 is absent, H, alkyl, or a hydroxyl protecting group~~, or R_2 and P_1 combine to form a bond;

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

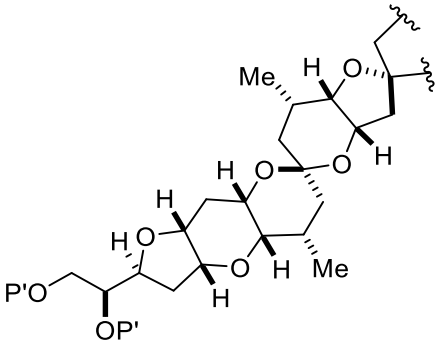
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(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

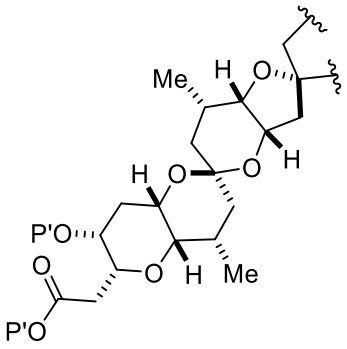
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

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

k is 0 or 1;

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

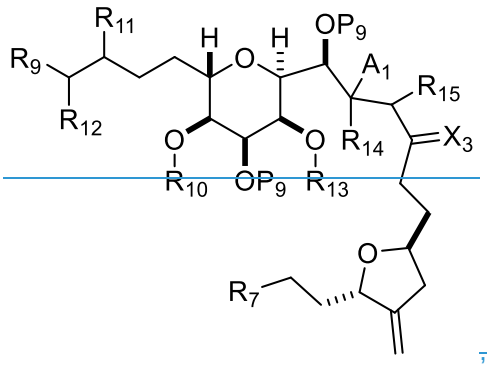
R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and

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

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

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

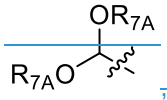
~~(2) formula (VIIAa):~~



~~(VIIAa)~~

~~where~~

~~R_7 is $-CH_2OP_A$, $-CHO$, or~~



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

~~R_9 is $-CH_2-OP"$, $-CHO$, or $-COOP"$;~~

~~(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 $-OP"$, and:~~

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

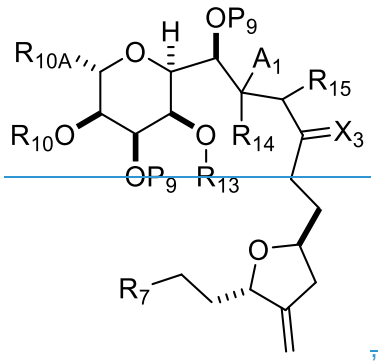
~~or~~

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

~~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 $-(CH(OP_{11}))-$, 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;~~

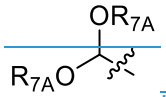
(3) formula (VIAa):



(VIAa)

where

R_7 is –CHO or



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

R_{10A} is $–CH_2–CH=CH_2$, $–(CH_2)_2–CH=CH_2$, or $–(CH_2)_3–OP_{10}$;

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 –OP", and:

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

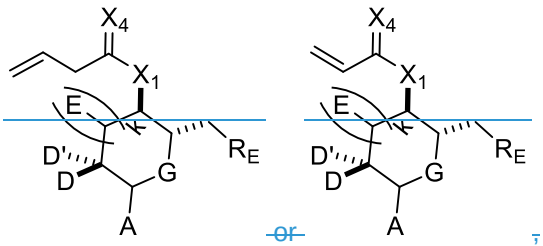
or

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

and

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 ketal;

(4) formula (IID) or (IIF):

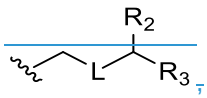


(IID) or (IIF)

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):



(1)

wherein

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

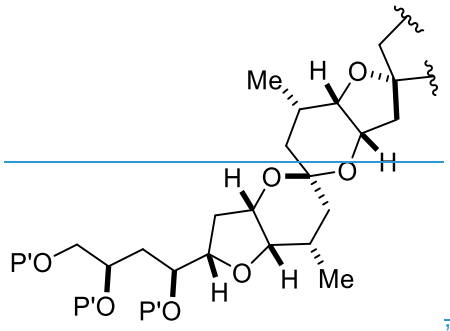
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

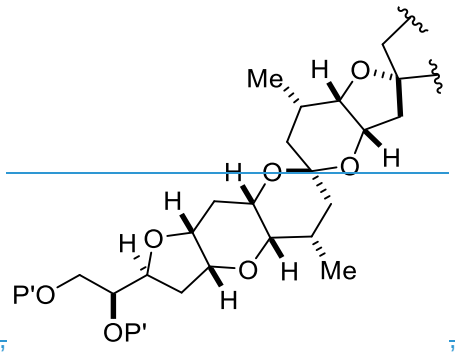
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(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;

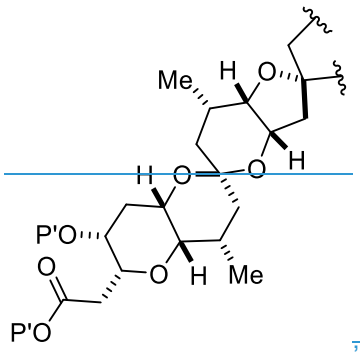
(iii) R_3 is $-(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate,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





, and



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

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

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

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

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

~~k is 0 or 1;~~

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

~~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,~~

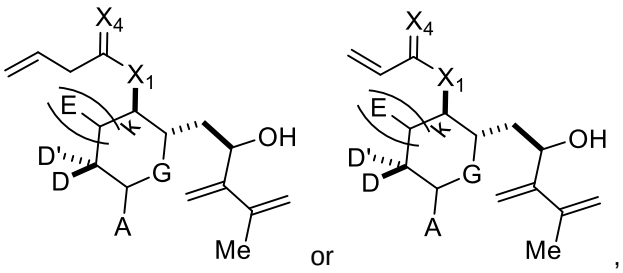
~~or~~

~~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;~~

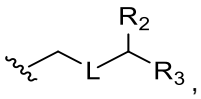
~~(5)~~(2) formula (IIE) or (IIG):



(IIE) (IIG)

wherein

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



(1)

wherein

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

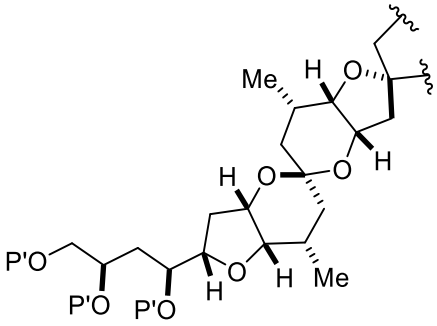
R_2 is H ~~and P_1 is absent, H, alkyl, or a hydroxyl protecting group~~, or R_2 and P_1 combine to form a bond;

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

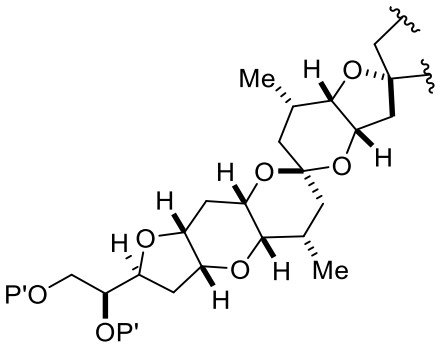
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(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

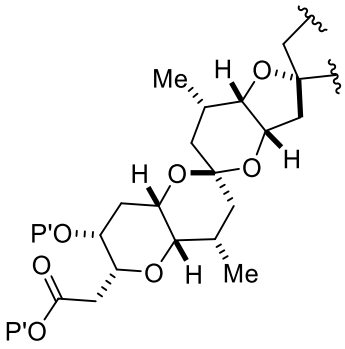
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

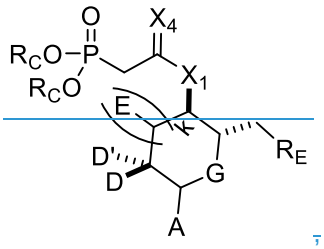
n, when present, is 0, 1, or 2;

k is 0 or 1;

X_1 is $–CH_2–$ or –O–; and

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

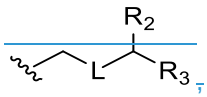
(6) formula (IIH):



(IIH)

wherein

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



(1)

wherein

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

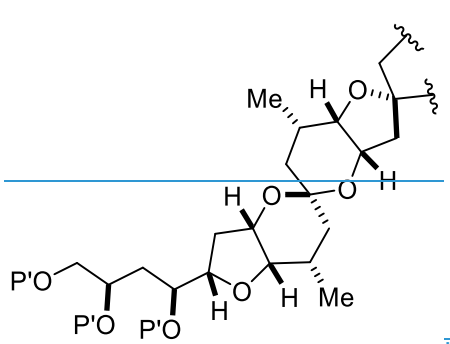
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

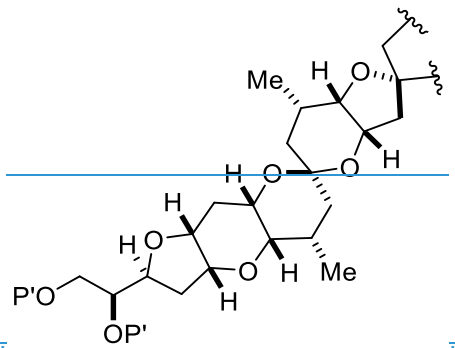
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

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

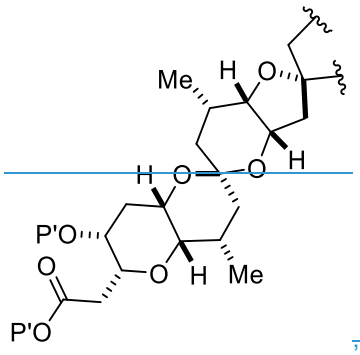
(iii) R_3 is $-(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate,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

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





, and



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

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

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

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

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

k is 0 or 1;

each R_C is 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,

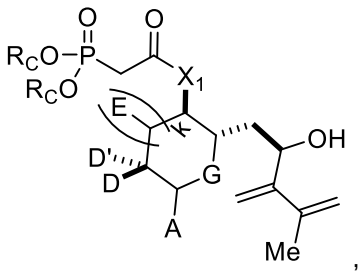
or

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;

(7)(3) formula (IIi):

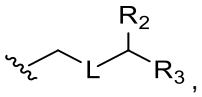


,

(IIi)

wherein

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



(1)

wherein

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

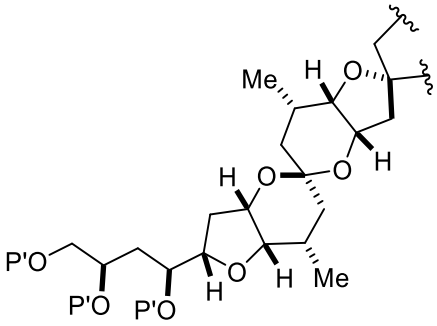
R_2 is H ~~and P_1 is absent, H, alkyl, or a hydroxyl protecting group~~, or R_2 and P_1 combine to form a bond;

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

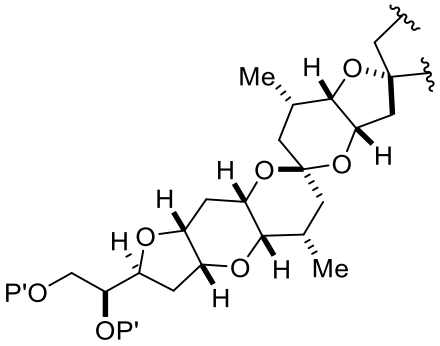
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(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

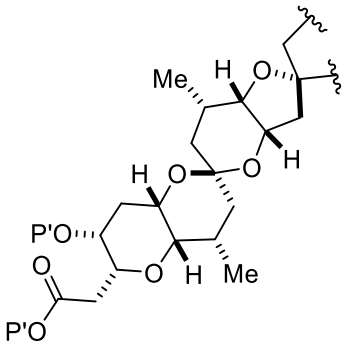
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

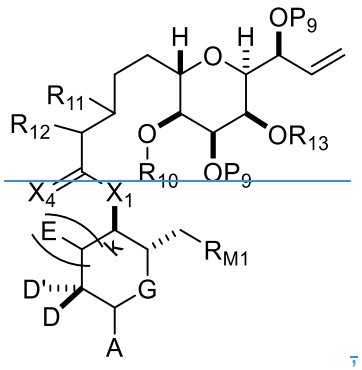
n, when present, is 0, 1, or 2;

k is 0 or 1;

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

X_1 is $–CH_2–$ or –O–;

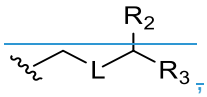
~~(8) formula (VIIID):~~



~~(VIIID)~~

~~wherein~~

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



~~(1)~~

~~wherein~~

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

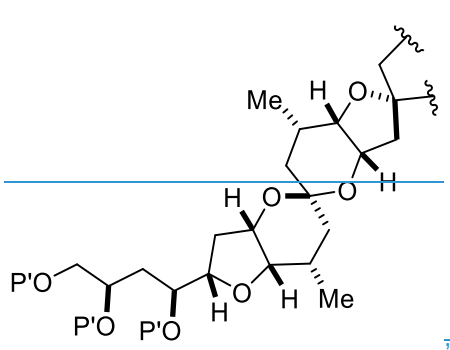
~~R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;~~

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

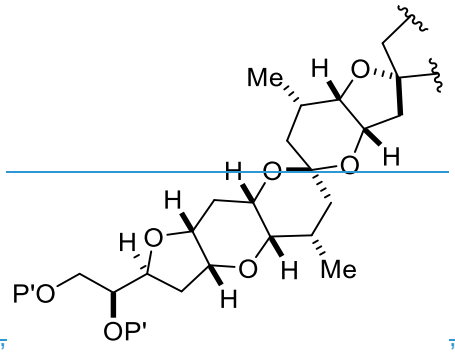
~~(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;~~

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

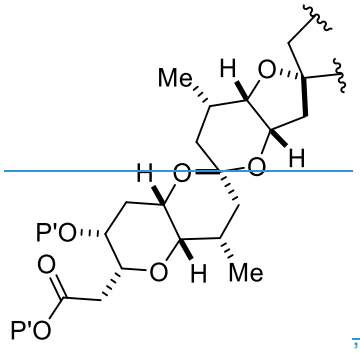
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

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

k is 0 or 1;

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

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;

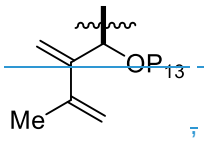
each P_9 and R_{13} is independently a hydroxyl protecting group;

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

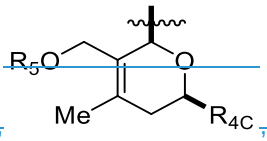
(ii) R_{10} is a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond; or

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

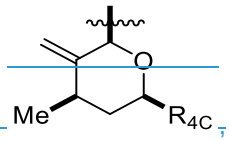
R_{M1} is



,



, or



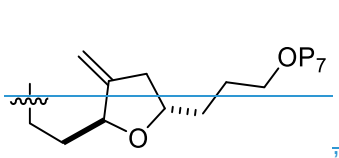
,

wherein

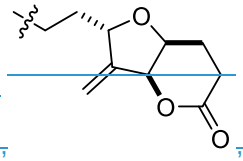
R_5 is optionally substituted acyl;

P_{13} is H or a hydroxyl protecting group; and

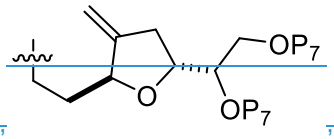
R_{4C} is



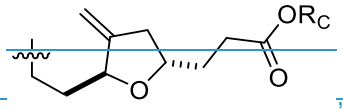
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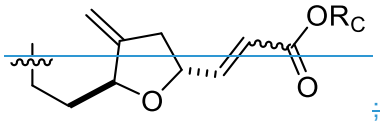
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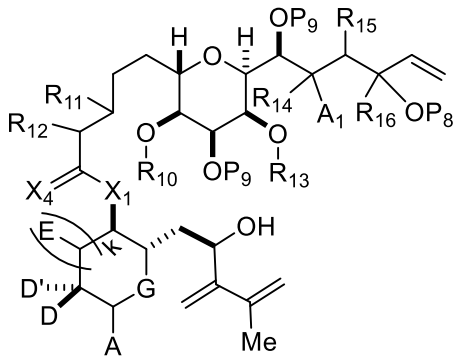
, or



;

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

(9) (4) formula (IVAb):

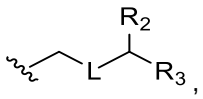


,

(IVAb)

wherein

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



,

(1)

wherein

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

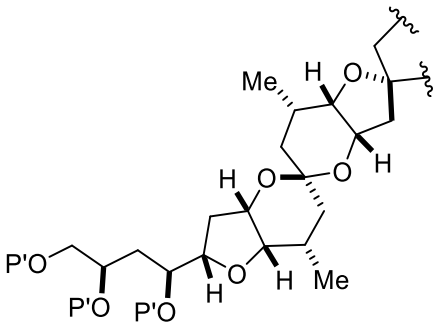
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

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

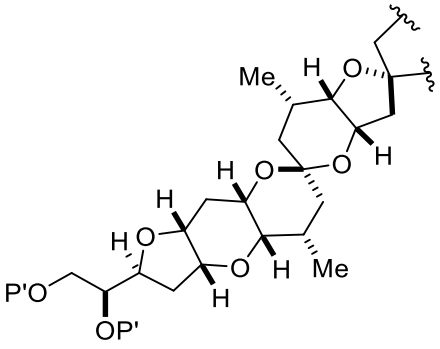
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(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

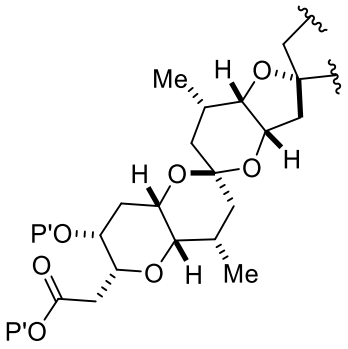
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

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

k is 0 or 1;

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

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

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

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

each P_9 is independently a hydroxyl protecting group;

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

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

or

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

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

or

(b2) A_1 is H or –OP", and:

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

or

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

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

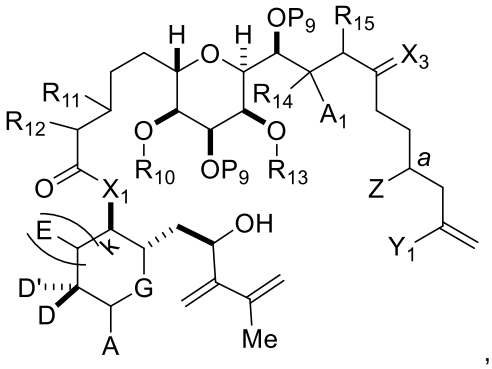
or

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

and

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

~~(10)~~ (5) formula (VAb):

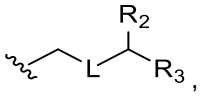


,

(VAb)

wherein

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



,

(1)

wherein

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

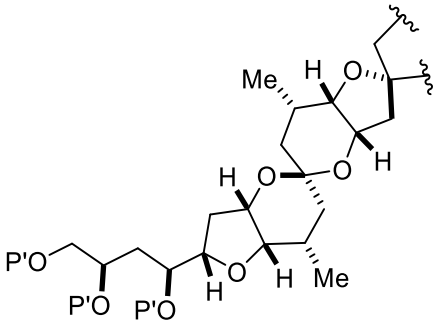
R$_2$ is H ~~and P$_1$ is absent, H, alkyl, or a hydroxyl protecting group~~, or R$_2$ and P$_1$ combine to form a bond;

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

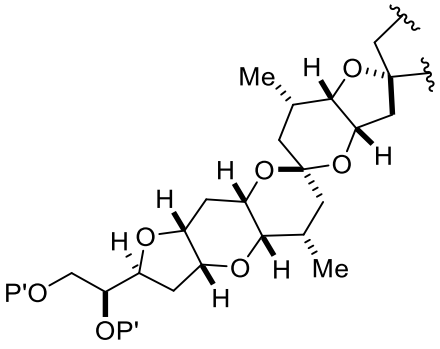
(ii) R$_3$ is –(CH$_2$)$_n$NP$_3$P$_4$, wherein P$_3$ is H or an N-protecting group, and (a) P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P$_4$ is H or an N-protecting group, (b) P$_2$ and P$_4$ combine to form an alkylidene, or (c) each of P$_2$ and P$_4$ is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

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

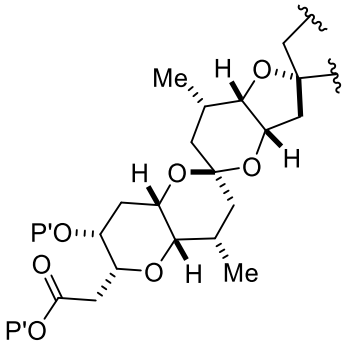
(iv) R$_3$ and P$_2$ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

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

k is 0 or 1;

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;

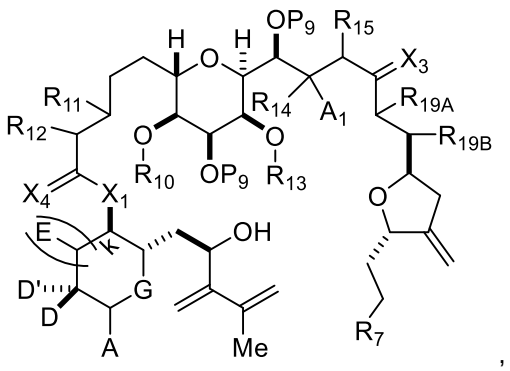
or

(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;

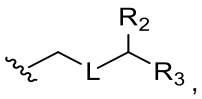
~~(11)~~ (6) formula (IXD):



(IXD)

wherein

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



(1)

wherein

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

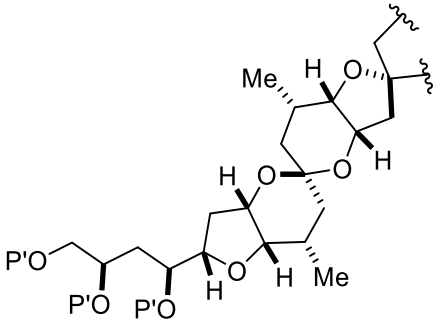
R$_2$ is H ~~and P$_1$ is absent, H, alkyl, or a hydroxyl protecting group~~, or R$_2$ and P$_1$ combine to form a bond;

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

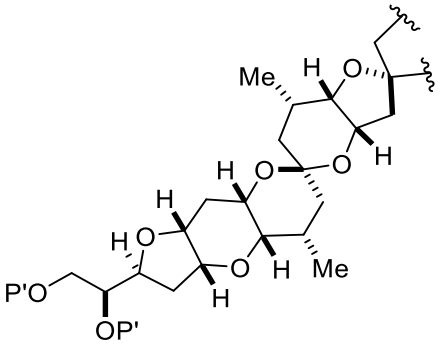
(ii) R$_3$ is –(CH$_2$)$_n$NP$_3$P$_4$, wherein P$_3$ is H or an N-protecting group, and (a) P$_2$ is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P$_4$ is H or an N-protecting group, (b) P$_2$ and P$_4$ combine to form an alkylidene, or (c) each of P$_2$ and P$_4$ is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

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

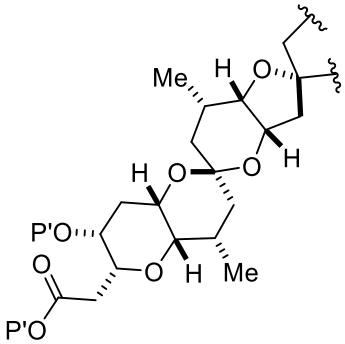
(iv) R$_3$ and P$_2$ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

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

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

k is 0 or 1;

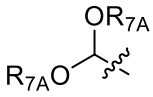
X_1 is $–CH_2–$, $–CH(Y)–$, $–C(Y)_2–$, or –O–, each Y is independently $–COOR_C$ or $–SO_2R_D$;

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

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

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

R_7 is $–CHO$, $–CH_2OP_A$ or



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

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

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

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

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

or

A_1 is H or -OP", and

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

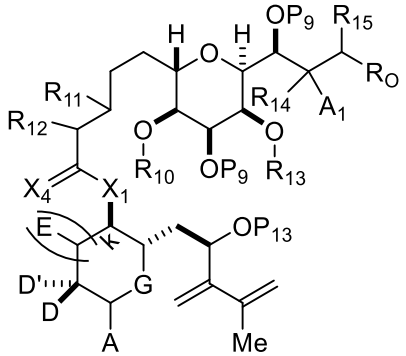
or

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

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

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

~~(12)~~(7) formula (IXF):

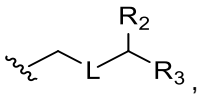


,

(IXF)

wherein

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



(1)

wherein

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

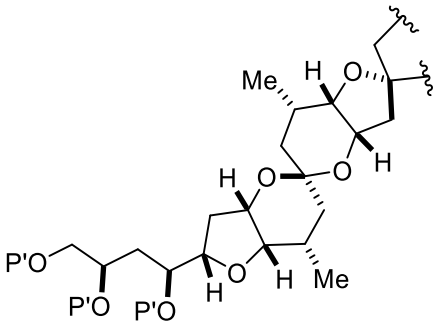
R_2 is H ~~and P_1 is absent, H, alkyl, or a hydroxyl protecting group~~, or R_2 and P_1 combine to form a bond;

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

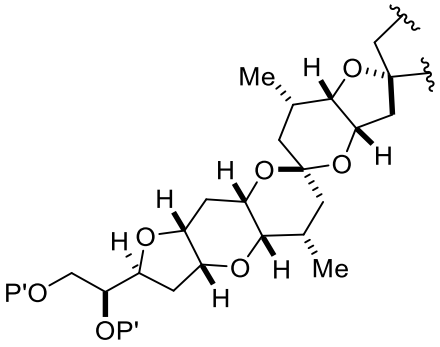
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(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

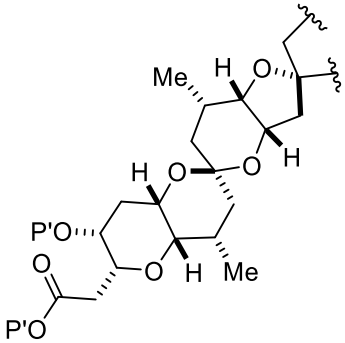
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

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

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

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

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

k is 0 or 1;

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

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

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

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

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

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

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

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

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

or

A_1 is H or -OP”, and

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

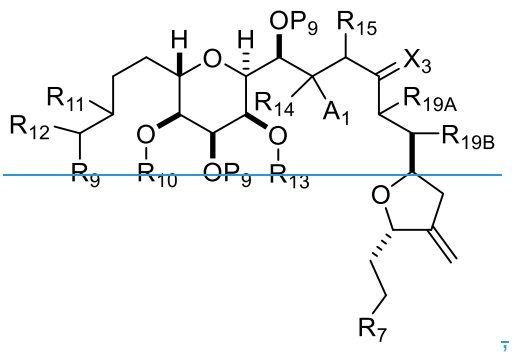
or

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

and

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

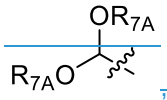
~~(13) formula (IXG):~~



~~(IXG)~~

wherein

R_7 is $-CHO$, $-CH_2OP_A$, or



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

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

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

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

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

or

A_1 is H or -OP", and

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

or

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

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

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

(14) formula (Z), (Z1), (Z2), (Z3), (Z4), (Z5), (Z5A), (Z5B), or (Z6).