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

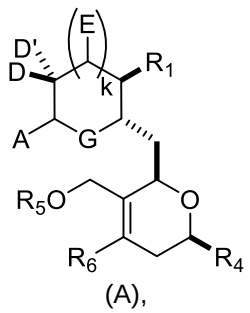
Background

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.

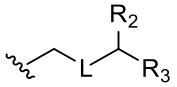
In one aspect, the present disclosure provides a method of preparing a compound of formula (A), the method comprising producing the compound of formula (A) from a compound of formula (B), a compound of formula (C), and R_5OH:
wherein R_5 is optionally substituted acyl;
wherein the compound of formula (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)–;

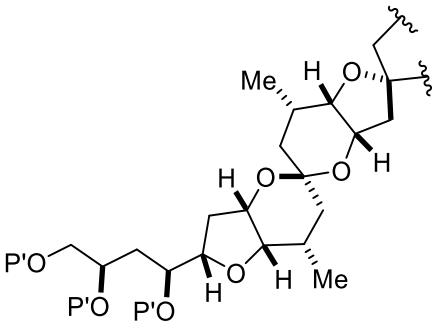
R$_2$ is H, or R$_2$ and P$_1$ combine to form a bond;

(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:



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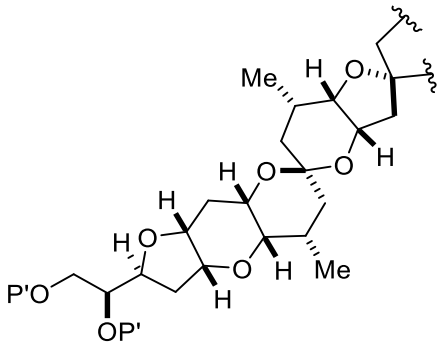
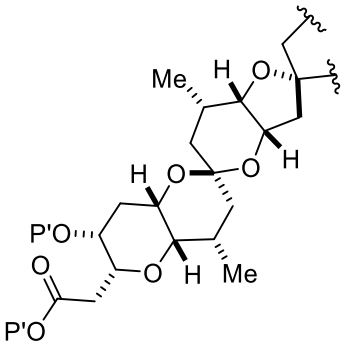


, and



, 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;

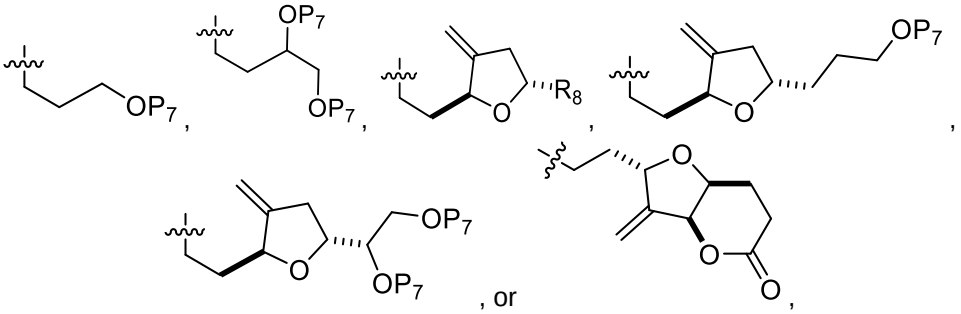
each Q$_1$ is independently OR$_A$, SR$_A$, SO$_2$R$_A$, OSO$_2$R$_A$, NR$_B$R$_A$, NR$_B$(CO)R$_A$, NR$_B$(CO)(CO)R$_A$, NR$_B$(CO)NR$_B$R$_A$, NR$_B$(CO)OR$_A$, (CO)OR$_A$, O(CO)R$_A$, (CO)NR$_B$R$_A$, or O(CO)NR$_B$R$_A$, wherein each of R$_A$ and R$_B$ is independently H, alkyl, haloalkyl, hydroxyalkyl,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



, 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 $–CH=CH–SO_2R_D$;

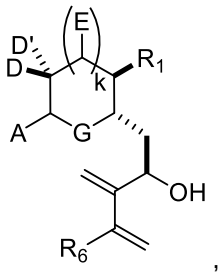
R_6 is H, optionally substituted alkyl, or optionally substituted arylalkyl;

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:



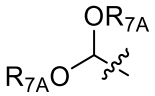
(B)

and

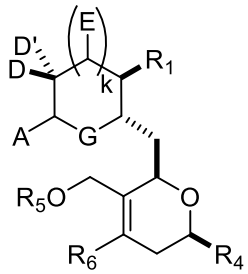
wherein the compound of formula (C) is:

R_4-R_7,

(C)

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

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



(A),

where

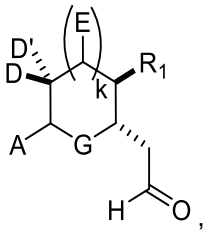
each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, where P_1 is H, alkyl, a hydroxyl protecting group, and A is a C_{1-6} saturated or C_{2-6} unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 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.

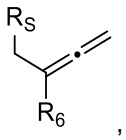
The compound of formula (D) is:



(D)

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

The compound of formula (E) is:

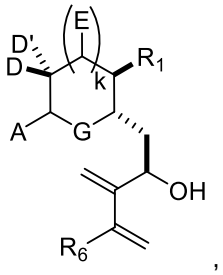


(E)

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.

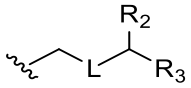
In another aspect, the present disclosure refers to a method of preparing a compound of formula (B), the method comprising producing the compound of formula (B) from a compound of formula (D) and a compound of formula (E);
wherein the compound of formula (B) is:



(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 $–C(O)–$;

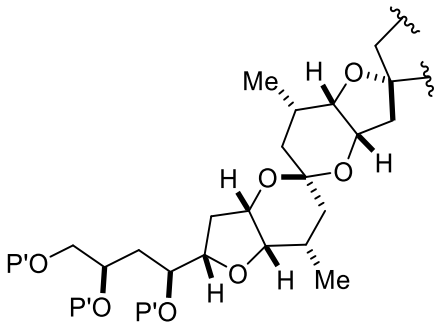
R_2 is H, or R_2 and P_1 combine to form a bond;

(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:



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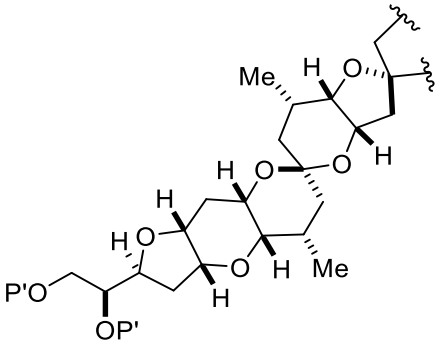

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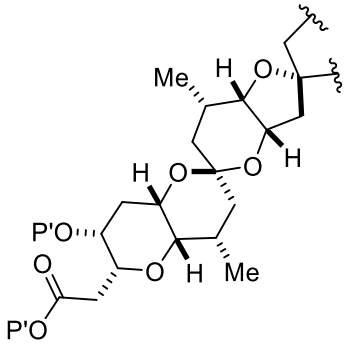


, wherein each P' is independently H or a hydroxyl protecting group;

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;

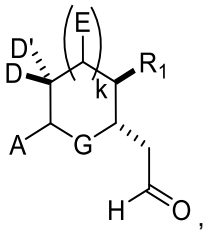
R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and

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;

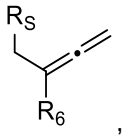
wherein the compound of formula (D) is:



(D)

and

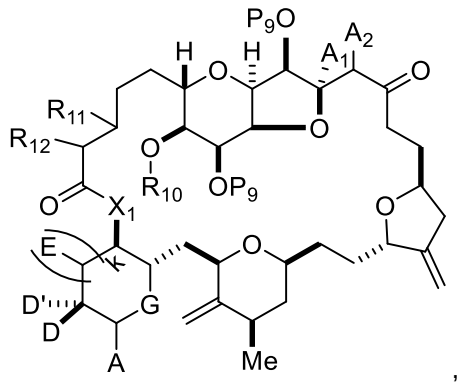
wherein the compound of formula (E) is:



(E)

wherein R_S is silyl.

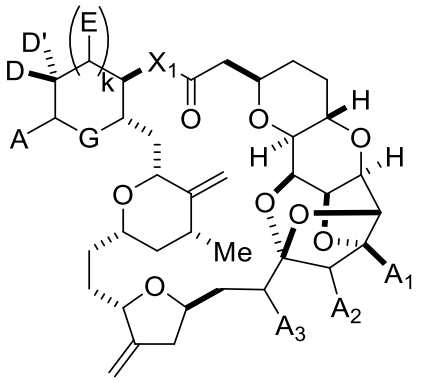
In another example, the disclosure provides a method of preparing a compound of formula (B). The compound of formula (B) can be used as a reactant in the Prins reaction described herein. The method includes producing the compound of formula (B) from a compound of formula (D) and a compound of formula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

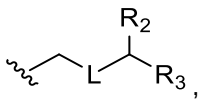
In another aspect, the present disclosure refers to a method of preparing



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;

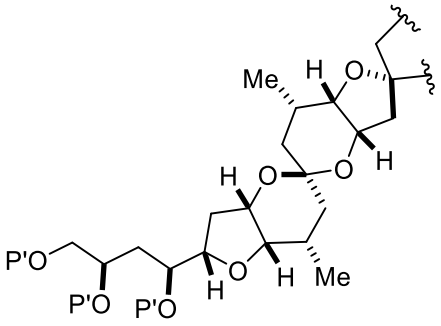
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(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:



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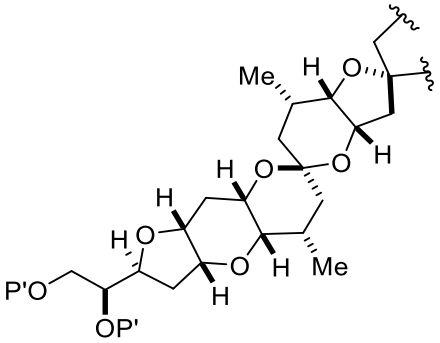

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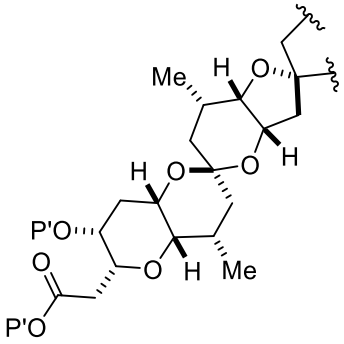


, wherein each P' is independently H or a hydroxyl protecting group;

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;

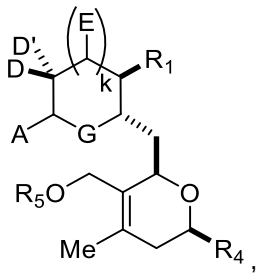
k is 0 or 1; and

X_1 is $–CH_2–$ or –O–;

the method comprising:

(1)

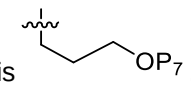
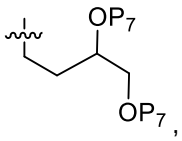
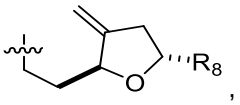
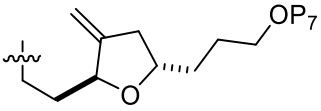
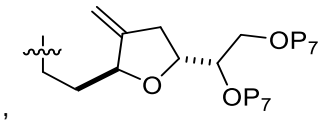
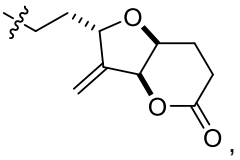
(A) producing a compound of formula (IA) from a compound of formula (IIC), a compound of formula (III), and R_5OH, wherein the compound of formula (IA) is:



(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;

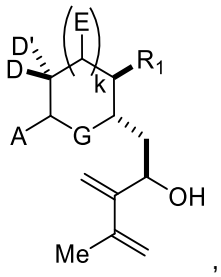
R_8 is $–CH_2CH_2–COOR_C$, $–CH=CH–COOR_C$, $–CH_2CH_2–SO_2R_D$, or $–CH=CH–SO_2R_D$;

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:



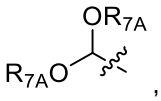
(IIC)

and

wherein the compound of formula (III) is:

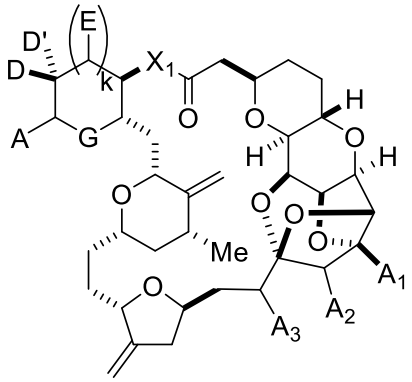
R_4-R_7,

(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).

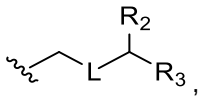
In another example, the present disclosure refers to a method of preparing



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)–;

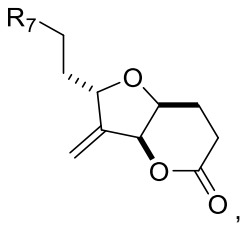
R_2 is H and P_1 is absent, H, alkyl, or a hydroxyl protecting group, or R_2 and P_1 combine to form a bond;

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

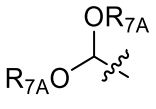
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

(1)



(Z)

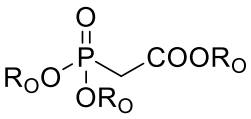
wherein R_7 is –CHO or  , and

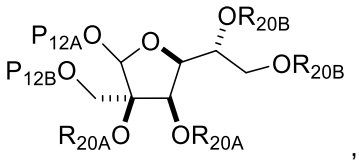
each R_{7A} is independently alkyl or a hydroxyl protecting group; or

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

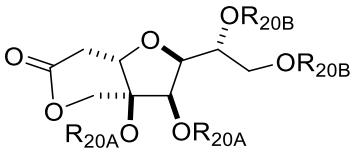
each R_{20A} is independently a hydroxyl protecting group, or both R_{20A}, together with the atoms to which each is attached, combine to form an acetal, ketal, cyclic carbonate, dicarbonyl-dioxo, or silylene-dioxo;

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:

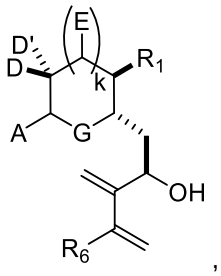
 ;

(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 another aspect, the present disclosure refers to a compound of

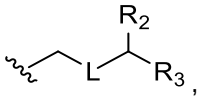
(1) formula (II):



(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)–;

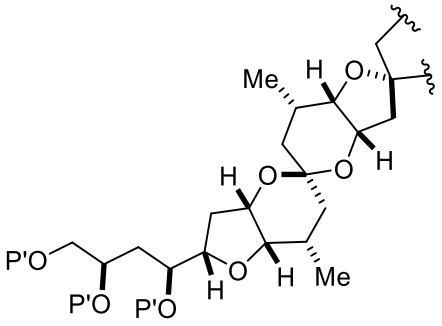
R_2 is H, or R_2 and P_1 combine to form a bond;

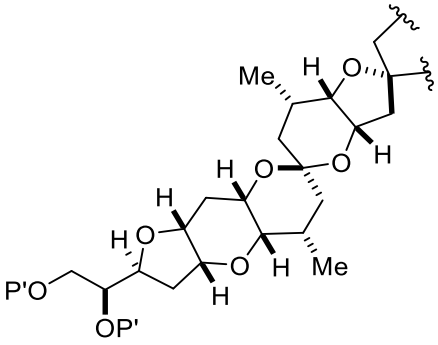
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

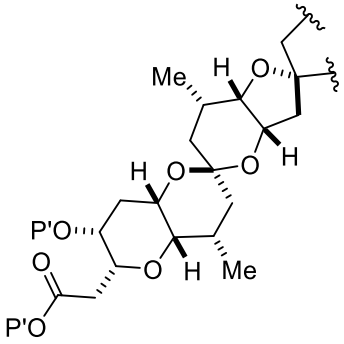
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(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;

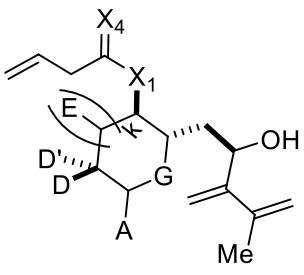
R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and

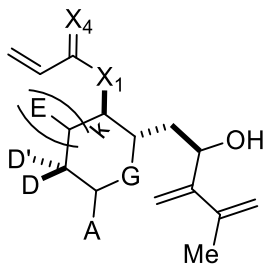
Y is independently $–COOR_C$ or $–SO_2R_D$;

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):



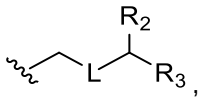
or


,

(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)–;

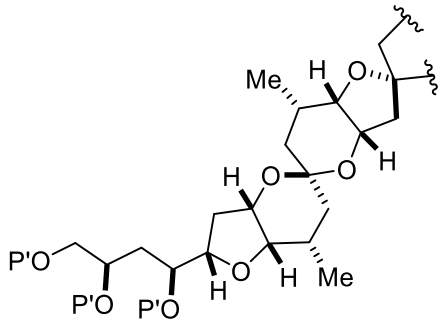
R_2 is H, or R_2 and P_1 combine to form a bond;

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

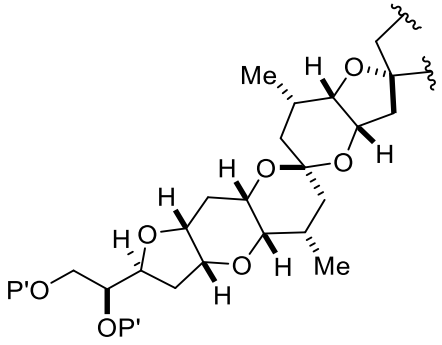
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(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

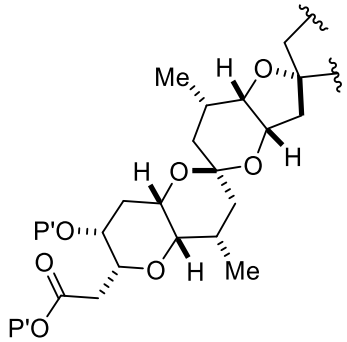
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, 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;

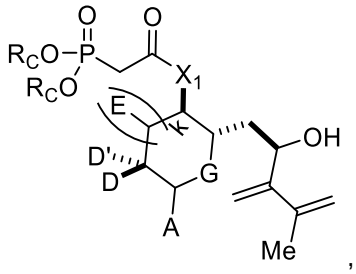
n, when present, is 0, 1, or 2;

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;

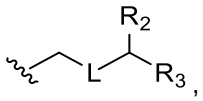
(3) formula (IIi):



(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)–;

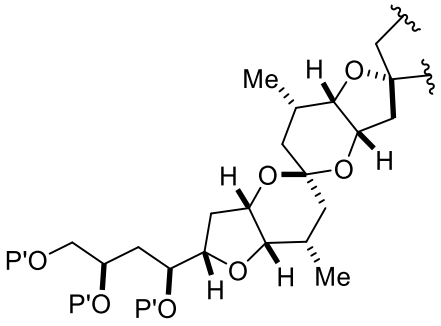
R_2 is H, or R_2 and P_1 combine to form a bond;

(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:



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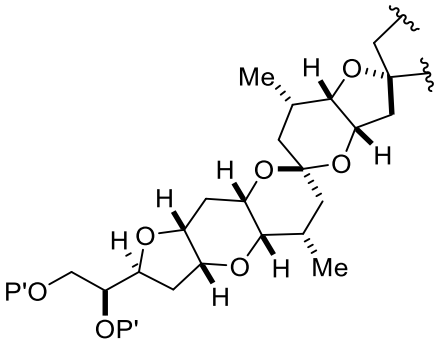
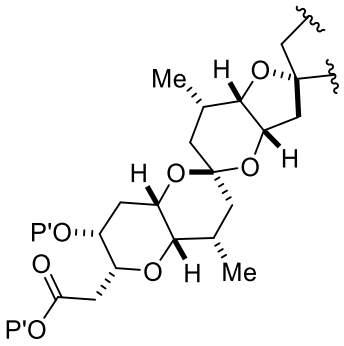


, and



, 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;

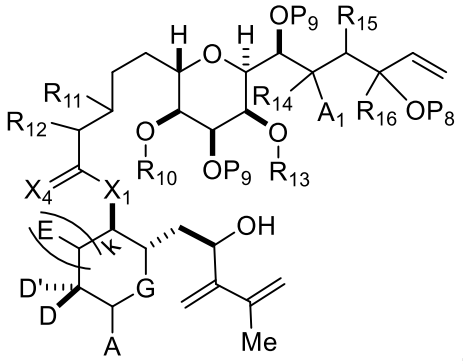
n, when present, is 0, 1, or 2;

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–;

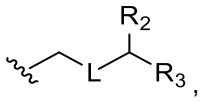
(4) formula (IVAb):



(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)–;

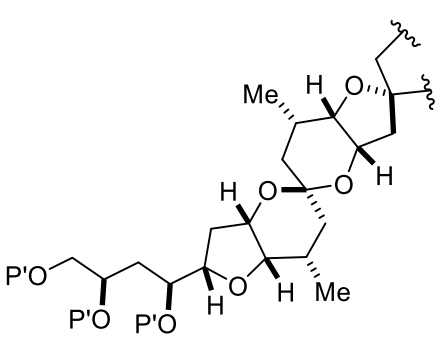
R_2 is H, or R_2 and P_1 combine to form a bond;

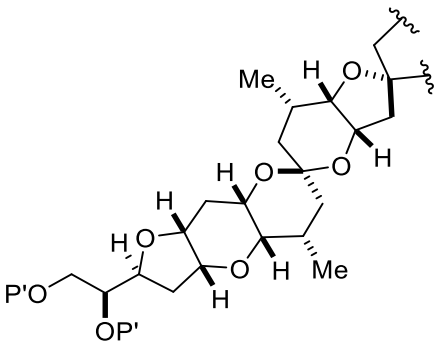
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(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;

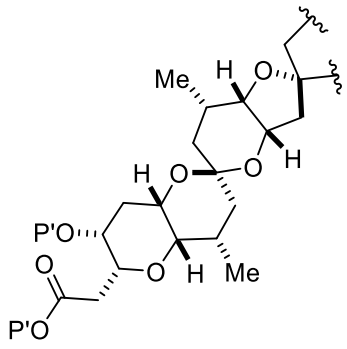
(iii) R_3 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is H, optionally substituted alkyl, or a hydroxyl protecting group; or P_2 and P_5, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate,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

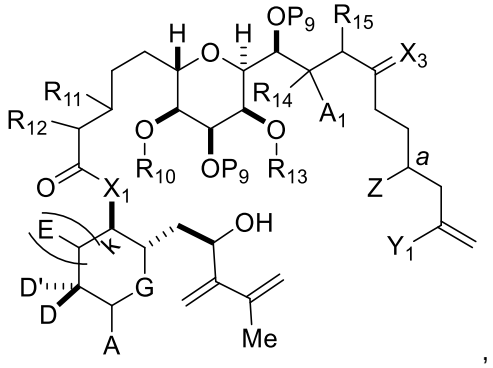
or

(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;

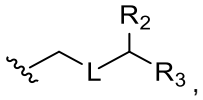
(5) formula (VAb):



(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)–;

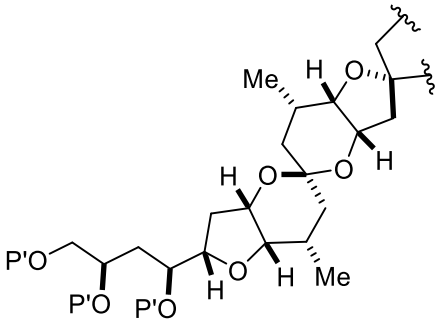
R_2 is H, or R_2 and P_1 combine to form a bond;

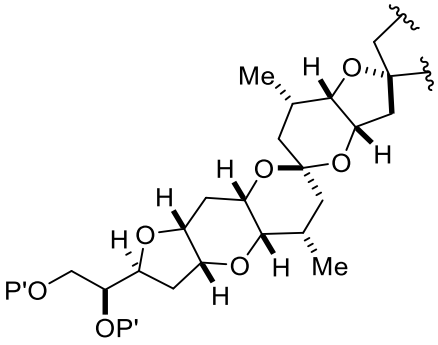
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

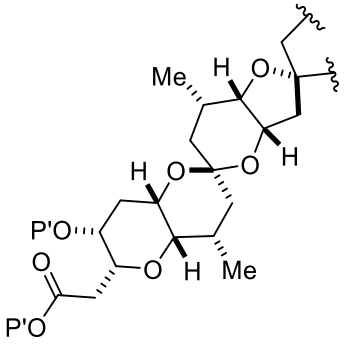
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(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;

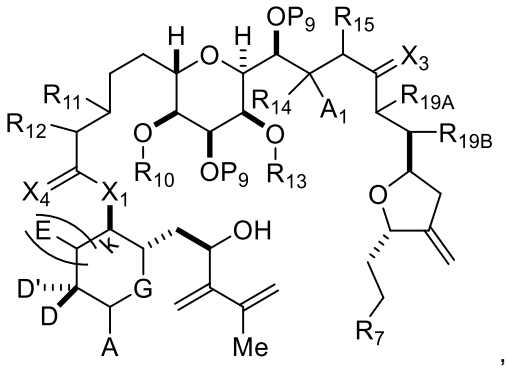
or

(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):

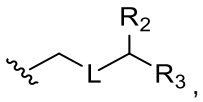


,

(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)–;

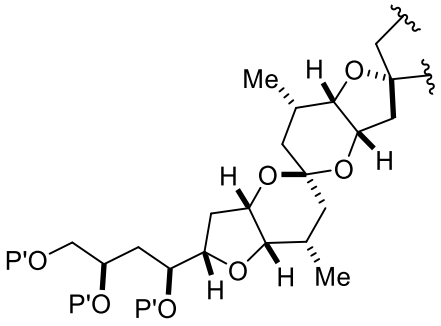
R_2 is H, or R_2 and P_1 combine to form a bond;

(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:



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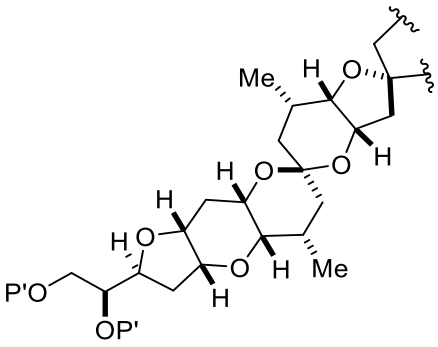
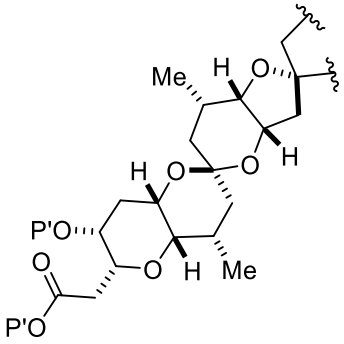


, and


, 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;

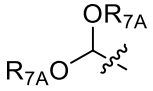
X_1 is $–CH_2–$, $–CH(Y)–$, $–C(Y)_2–$, or –O–, each Y is independently $–COOR_C$ or $–SO_2R_D$;

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;

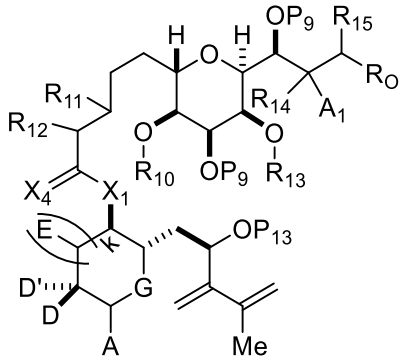
or

(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):

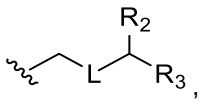


,

(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)–;

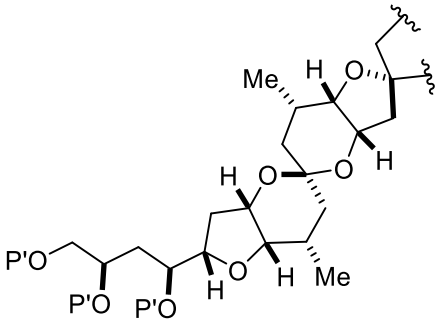
R_2 is H, or R_2 and P_1 combine to form a bond;

(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:



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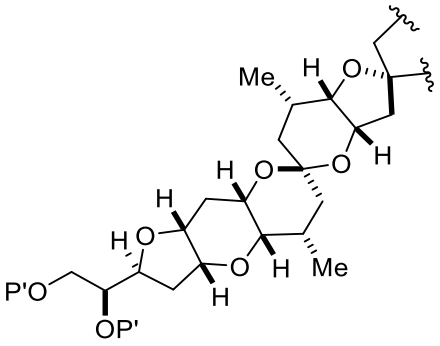
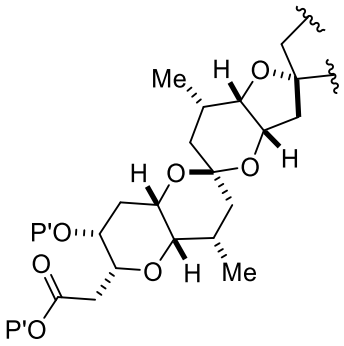


, and



, 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.

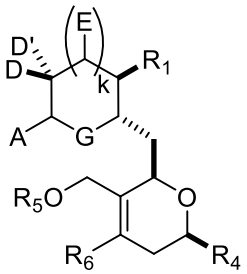
By “acetyl” is meant an acyl, in which R is $–CX_nH_{3-n}$, where n is 0, 1, 2, or 3, and each X is independently alkoxy or halogen, provided that, when n is 3, each X is independently halogen, and, when n is 2, either both of the X groups are independently halogen or both of the X groups are independently 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

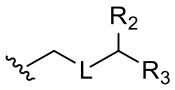
1. A method of preparing a compound of formula (A), the method comprising producing the compound of formula (A) from a compound of formula (B), a compound of formula (C), and R_5OH:
wherein R_5 is optionally substituted acyl;
wherein the compound of formula (A) is:



(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 $–C(O)–$;

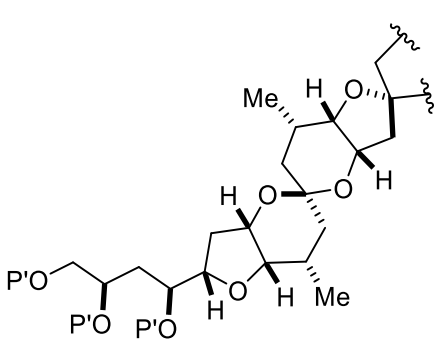
R_2 is H, or R_2 and P_1 combine to form a bond;

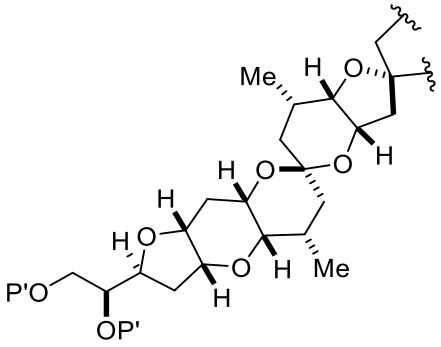
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

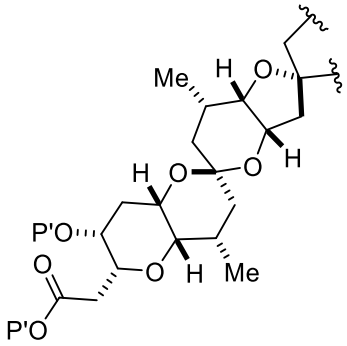
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

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



,


, and


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

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

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

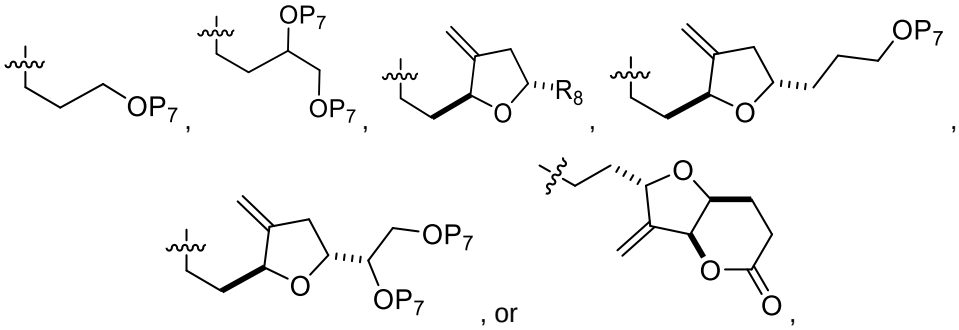
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_B(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl,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

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

k is 0 or 1;

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

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



, or ,

wherein

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

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

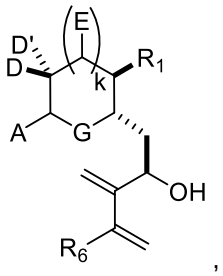
R_6 is H, optionally substituted alkyl, or optionally substituted arylalkyl;

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

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

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

wherein the compound of formula (B) is:



,

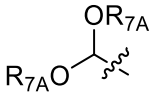
(B)

and

wherein the compound of formula (C) is:

R_4-R_7,

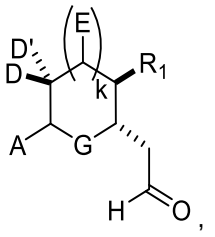
(C)

wherein R_7 is –CHO or 

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

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

wherein the compound of formula (D) is:

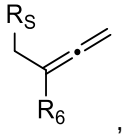


,

(D)

and

where the compound of formula (E) is:



,

(E)

where R_S is silyl.

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

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

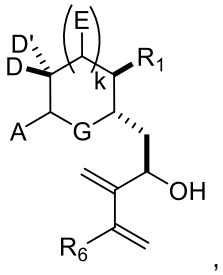
5. The method of claim 2, wherein:

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

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

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

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

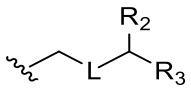


,

(B)

wherein

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



(1),

wherein

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

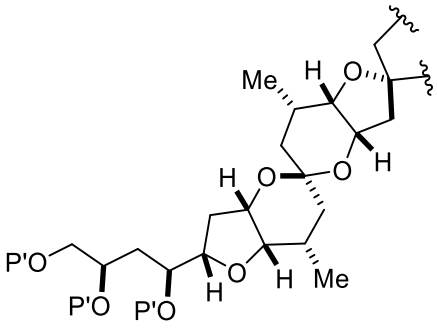
R_2 is H, or R_2 and P_1 combine to form a bond;

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

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

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

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



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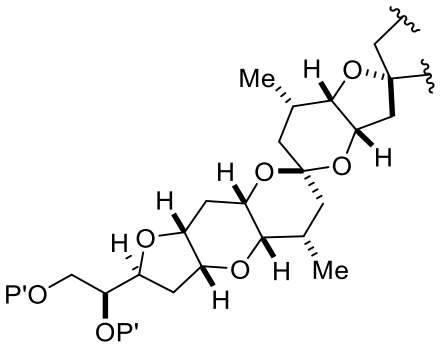
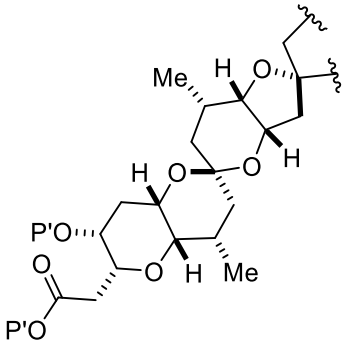


, and



, 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;

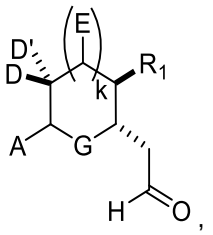
R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and

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;

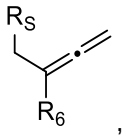
wherein the compound of formula (D) is:



(D)

and

wherein the compound of formula (E) is:



(E)

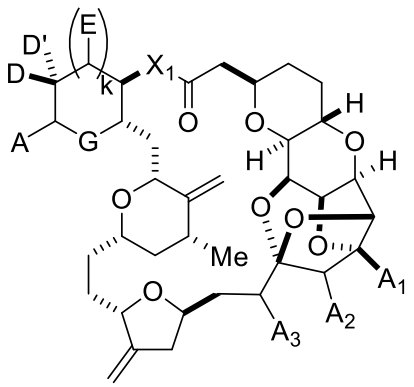
wherein R_S is silyl.

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.

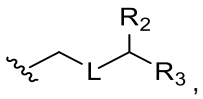
10. A method of preparing



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)–;

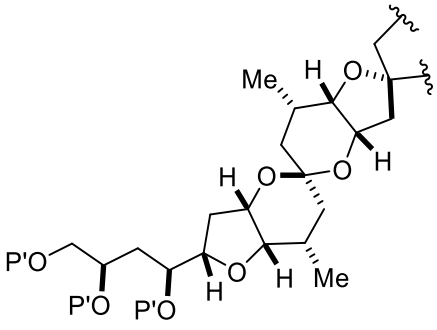
R$_2$ is H, or R$_2$ and P$_1$ combine to form a bond;

(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:



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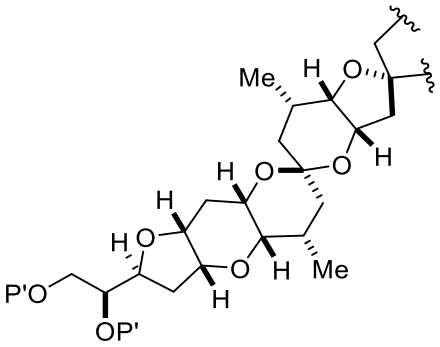
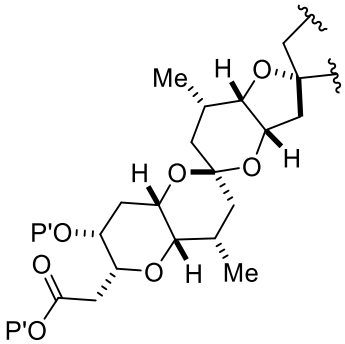


, and



, 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;

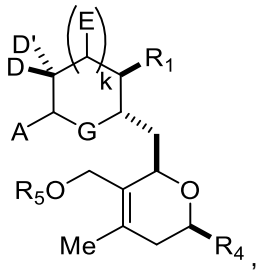
k is 0 or 1; and

X_1 is $–CH_2–$ or –O–;

the method comprising:

(1)

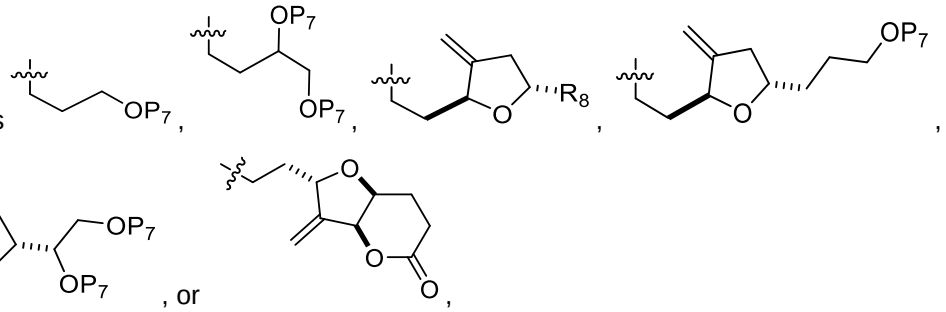
(A) producing a compound of formula (IA) from a compound of formula (IIC), a compound of formula (III), and R_5OH, wherein the compound of formula (IA) is:



(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 

wherein

each P_7 is independently H or a hydroxyl protecting group;

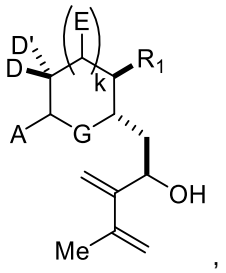
R_8 is $–CH_2CH_2–COOR_C$, $–CH=CH–COOR_C$, $–CH_2CH_2–SO_2R_D$, or $–CH=CH–SO_2R_D$;

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:



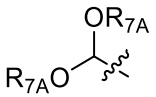
(IIC)

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).

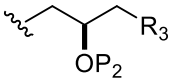
11. The method of any one of claims 1-10, wherein:

(i)

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

D is H; and/or

wherein A is of the following structure:



; and/or

k is 0; and/or

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

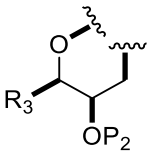
G is O;

or

(ii)

D' is H; and/or

A and D combine to form the following structure:



,

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

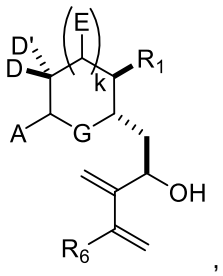
wherein R_3 is $–(CH_2)_nNP_3P_4$ or $–(CH_2)_nOP_5$, wherein n is 2; and/or

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

G is O.

12. A compound of

(1) formula (II):

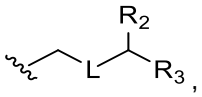


,

(II)

wherein

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



,

(1)

wherein

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

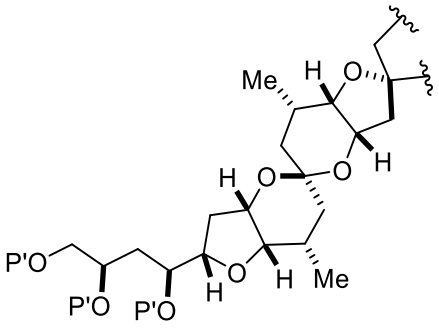
R_2 is H, or R_2 and P_1 combine to form a bond;

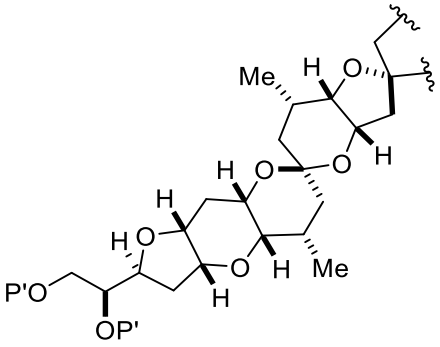
(i) R_3 is H, and P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

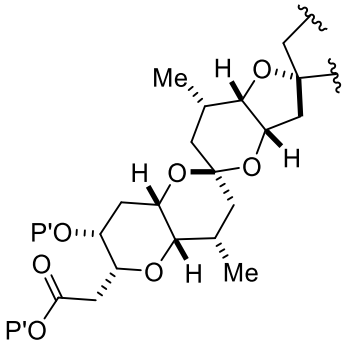
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

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

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



,


, and


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

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

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

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

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

k is 0 or 1;

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

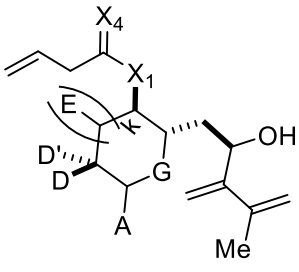
R_6 is H, optionally substituted alkyl, or optionally substituted aryl; and

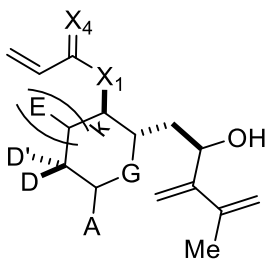
Y is independently $–COOR_C$ or $–SO_2R_D$;

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

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

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



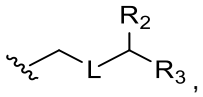
or


,

(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)–;

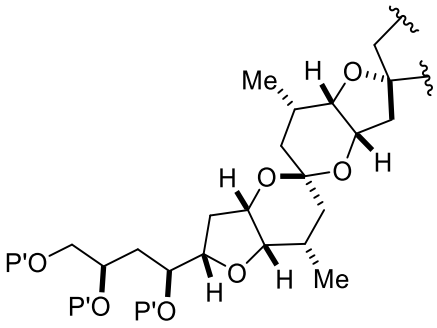
R_2 is H, or R_2 and P_1 combine to form a bond;

(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:



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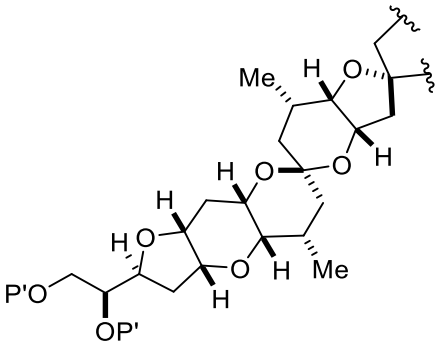
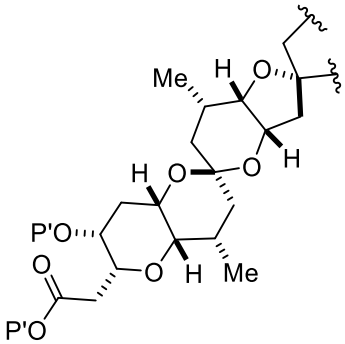


, and



, 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;

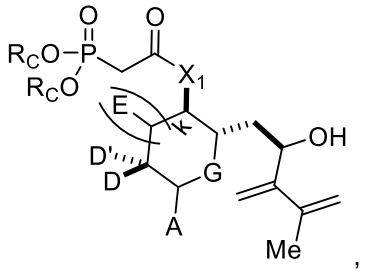
n, when present, is 0, 1, or 2;

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;

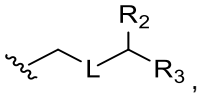
(3) formula (IIi):



(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)–;

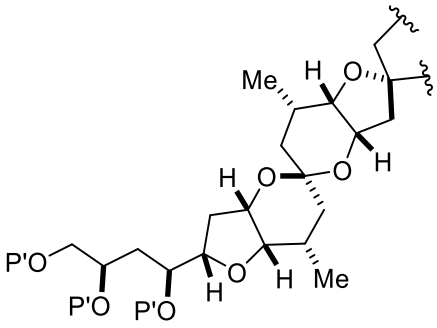
R_2 is H, or R_2 and P_1 combine to form a bond;

(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:



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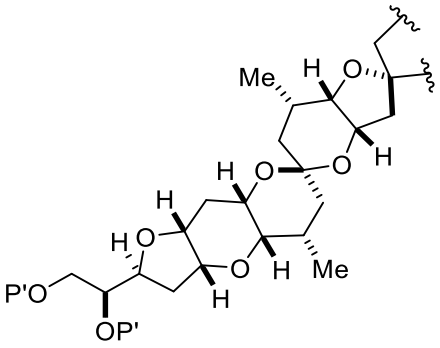
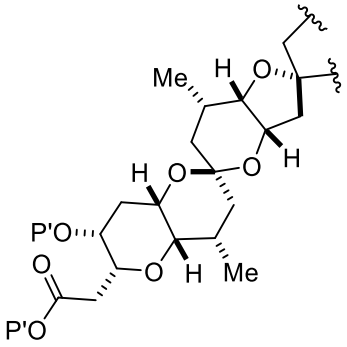


, and



, 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;

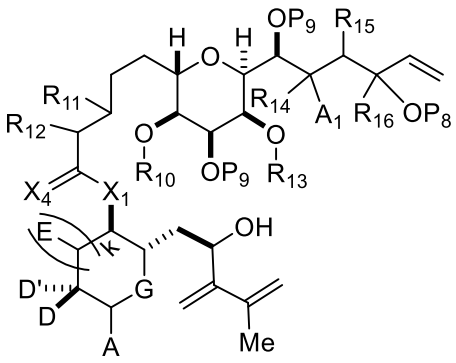
n, when present, is 0, 1, or 2;

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–;

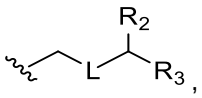
(4) formula (IVAb):



(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)–;

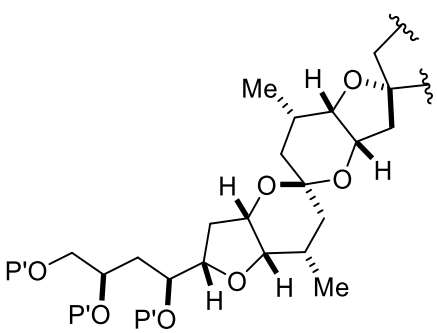
R_2 is H, or R_2 and P_1 combine to form a bond;

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

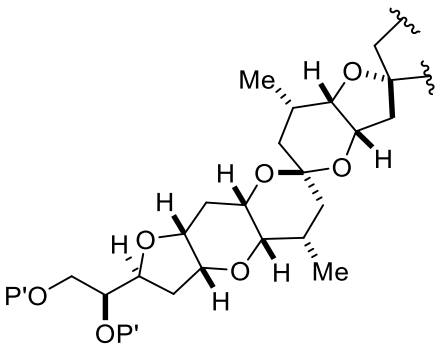
(ii) R_3 is $–(CH_2)_nNP_3P_4$, wherein P_3 is H or an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is H or an N-protecting group, (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(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

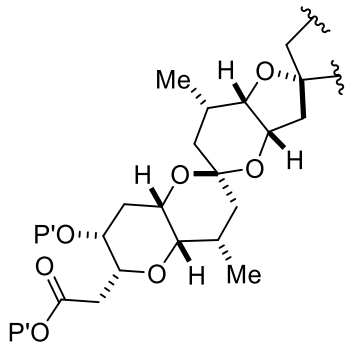
(iv) R_3 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, 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;

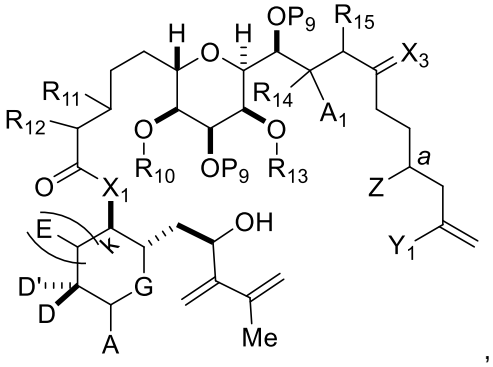
or

(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;

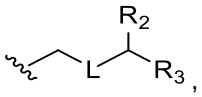
(5) formula (VAb):



(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)–;

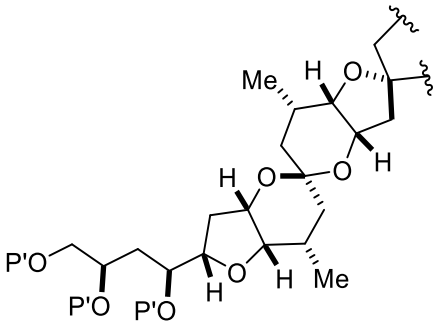
R_2 is H, or R_2 and P_1 combine to form a bond;

(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:



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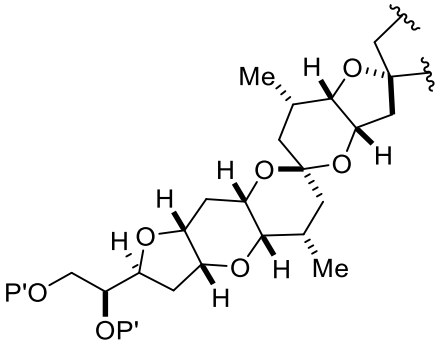
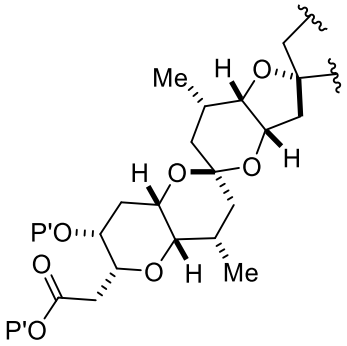


, and


, 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;

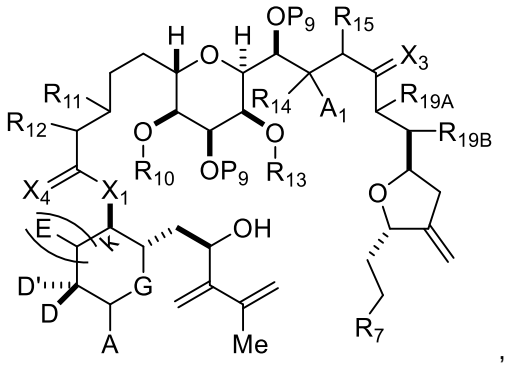
or

(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):

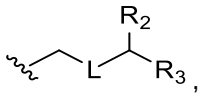


,

(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)–;

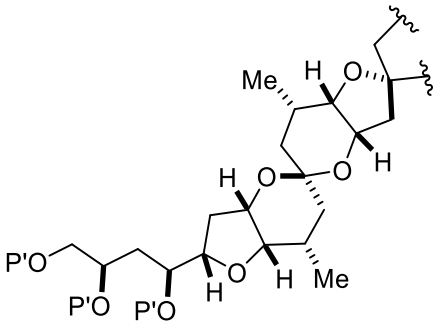
R_2 is H, or R_2 and P_1 combine to form a bond;

(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:



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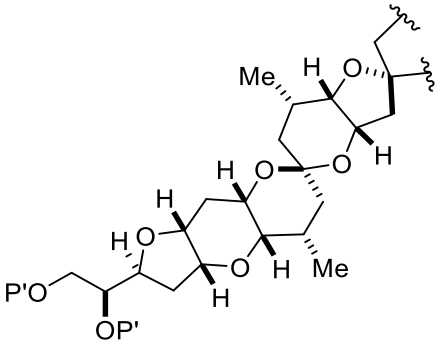
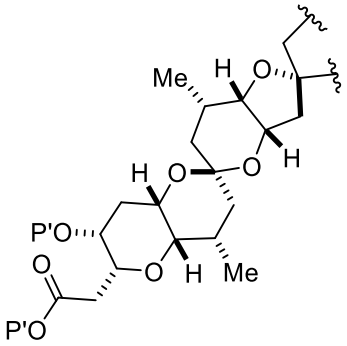


, and


, 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;

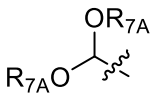
X_1 is $–CH_2–$, $–CH(Y)–$, $–C(Y)_2–$, or –O–, each Y is independently $–COOR_C$ or $–SO_2R_D$;

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;

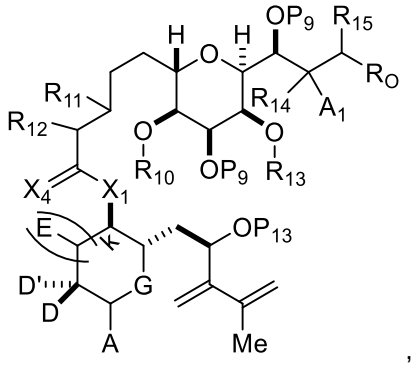
or

(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

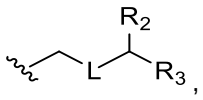
(7) formula (IXF):



(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)–;

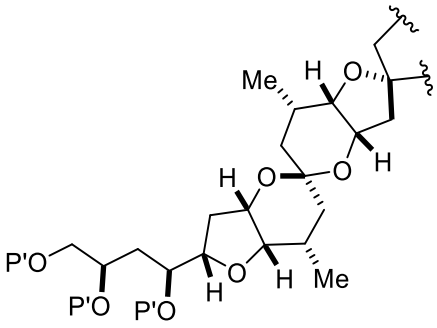
R_2 is H, or R_2 and P_1 combine to form a bond;

(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:



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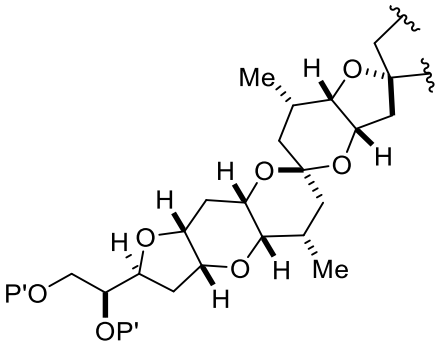
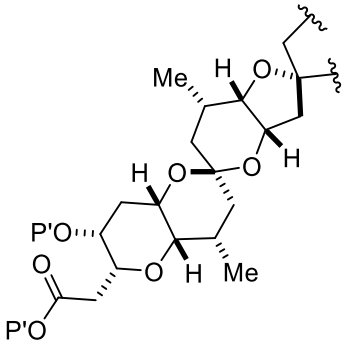


, and



, 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.