PRINS REACTION AND INTERMEDIATES 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 discloses 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 Wang et 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; 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.

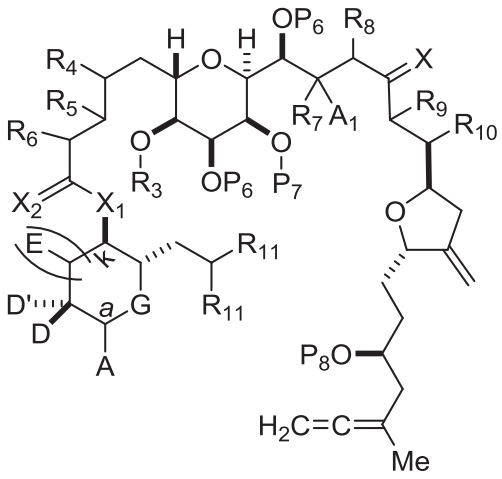
Summary

In general, the present disclosure provides methods for the preparation of macrocyclic intermediates in the synthesis of a halichondrin macrolide or an analog thereof. In particular, the methods disclosed herein may be useful in the preparation of a halichondrin macrolide or an analog thereof by forming a C.26-C.27 bond through an allene-Prins reaction performed on an intermediate. The disclosure also provides intermediates that can be employed in the reactions described herein.

In one aspect, the disclosure provides a method of preparing a macrocyclic intermediate in the synthesis of a halichondrin macrolide or an analog thereof, the method comprising reacting an intermediate of formula (IA) with $R_{12}OH$ and a Lewis acid, the reaction producing the macrocyclic intermediate by forming a bond in the structure of the halichondrin macrolide or an analog thereof,

where R_{12} is optionally substituted acyl;

where the compound of formula (IA) is:

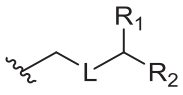


(IA),

or a salt or a tautomer thereof,

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, or a hydroxyl protecting group; and A is a group of formula (1) or 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, the group of formula (1) having the structure:



(1),

where

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

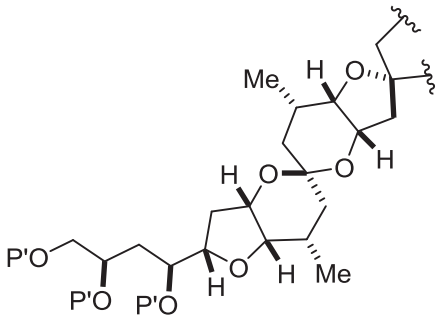
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, where P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 is $–(CH_2)_nNP_3P_4$, where P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 is $–(CH_2)_nOP_5$, where 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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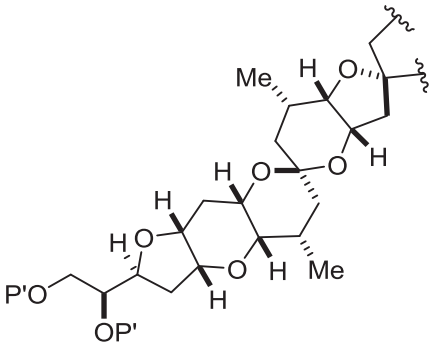
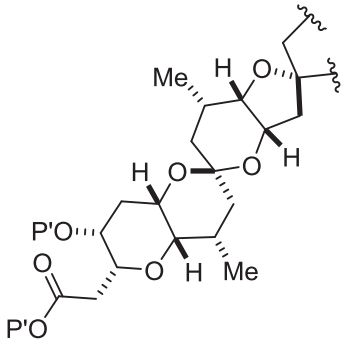


, and



, where 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, where 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 $O(CO)NR_BR_A$, where 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(Y)–, $–CH_2–$, or –O–,

X_2 is =O or X_2, together with the carbon atom to which it is attached, is $–(C(R_X)_2)–$; where each R_X is independently H, $–OR_{X1}$, or $–SR_{X1}$, provided that at least one R_X, when present, is $–OR_{X1}$ or $–SR_{X1}$; where each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene, provided that, when X_1 is –O–, X_2 is =O;

Y is SO_2R_C or $COOR_C$, where, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

A_1 and R_7 combine to form oxo, P_7 is H or a hydroxyl protecting group, and R_8 is H;

or

A_1 is H or OP", and:

(a) P_7 is H or a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

or

(b) P_7 and R_7 combine to form a bond, and R_8 is H or OP";

(i) each P_6 is independently H or a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal; X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP$_9$))–, where P_9 is H or a hydroxyl protecting group; and each R_{11} is –OP$_{10}$, or both R_{11} combine to form oxo, where P_{10} is alkyl or a hydroxyl protecting group;

(ii) both P_6 and X, together with the atoms to which each is attached, combine to form ketal, P_7 and R_7 combine to form a bond, and R_8 is H or OP"; and each R_{11} is –OP$_{10}$, or both R_{11} combine to form oxo, where P_{10} is alkyl or a hydroxyl protecting group; or

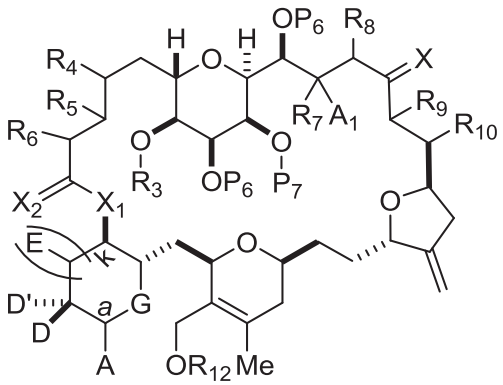
(iii) both P_6 and both R_{11}, together with the atoms to which they are attached, combine to form acetal; and X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP$_9$))–, where P_9 is H or a hydroxyl protecting group;

R_9 is H, OP", or Y, and R_{10} is H; or R_9 and R_{10}, together with the atoms to which each is attached, combine to form a double bond;

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

P_8 is H or silyl; and

where the macrocyclic intermediate in the synthesis of a halichondrin macrolide or an analog thereof is a compound of formula (IB):

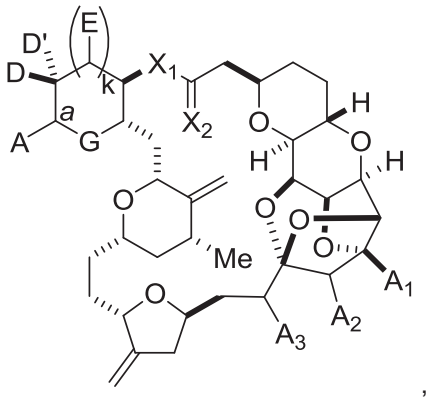


(IB)

or a salt or a tautomer thereof.

In some examples, the Lewis acid is an oxophilic Lewis acid (e.g., boron trifluoride or a solvate thereof).

In another aspect, the disclosure provides a method of preparing a halichondrin macrolide or an analog thereof:

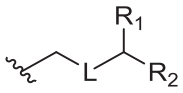


,

or a salt thereof,

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, or a hydroxyl protecting group; and A is a group of formula (1) or 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, the group of formula (1) having the structure:



(1),

where

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

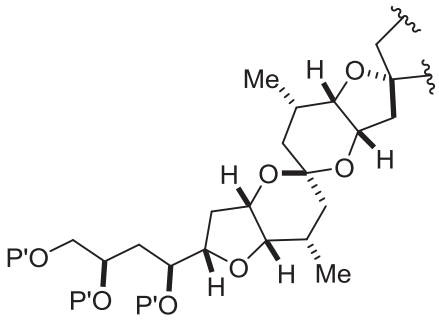
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, where P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 is $–(CH_2)_nNP_3P_4$, where 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_2 is $–(CH_2)_nOP_5$, where 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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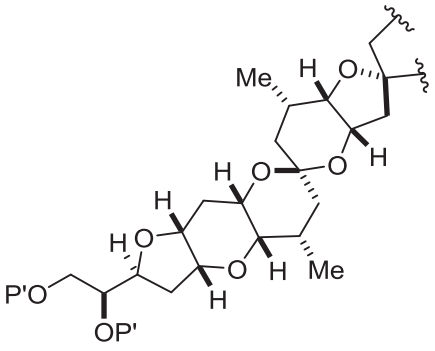

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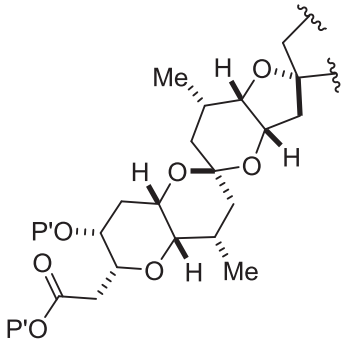


, where each P' is independently H or a hydroxyl protecting group;

each of A_1, A_2, and A_3 is independently H or OP", where 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, where 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 $O(CO)NR_BR_A$, where 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;

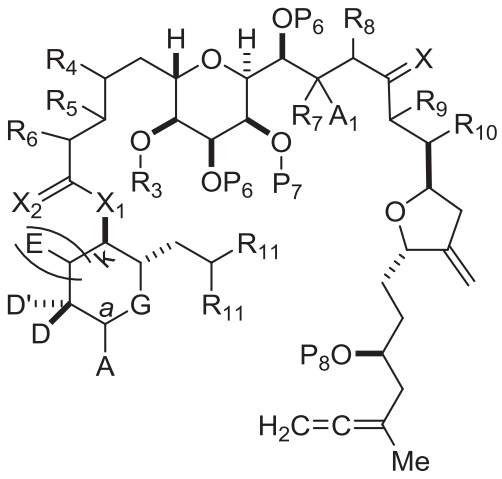
k is 0 or 1;

X_1 is $–CH_2–$ or –O–, and

X_2 is =O;

by

(A) producing a compound of formula (IB) from a compound of formula (IA) and $R_{12}OH$, where R_{12} is optionally substituted acyl, and the compound of formula (IA) is of the following structure:

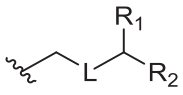


(IA)

or a salt or a tautomer thereof,

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, or a hydroxyl protecting group; and A is a group of formula (1) or 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, the group of formula (1) having the structure:



(1),

where

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

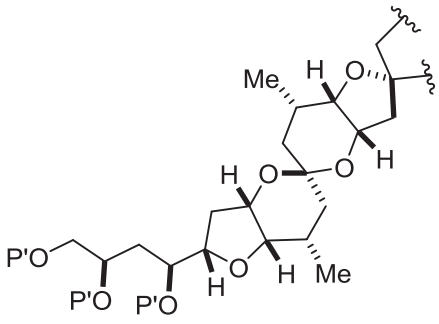
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, where P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 is $–(CH_2)_nNP_3P_4$, where P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 is $–(CH_2)_nOP_5$, where 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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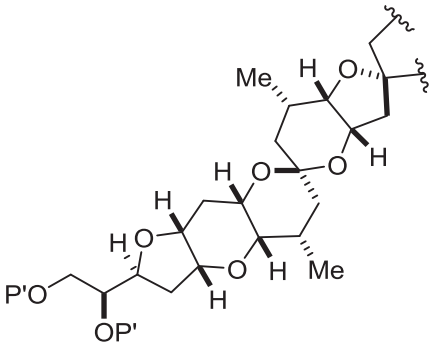
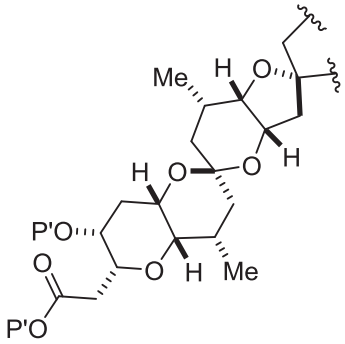


, and


, where 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, where 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 $O(CO)NR_BR_A$, where 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(Y)–, $–CH_2–$, or –O–,

X_2 is =O or X_2, together with the carbon atom to which it is attached, is $–(C(R_X)_2)–$; where each R_X is independently H, $–OR_{X1}$, or $–SR_{X1}$, provided that at least one R_X, when present, is $–OR_{X1}$ or $–SR_{X1}$; where each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene, provided that, when X_1 is –O–, X_2 is =O;

Y is SO_2R_C or $COOR_C$, where, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

A_1 and R_7 combine to form oxo, P_7 is H or a hydroxyl protecting group, and R_8 is H;

or

A_1 is H or OP", and:

(a) P_7 is H or a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

or

(b) P_7 and R_7 combine to form a bond, and R_8 is H or OP";

(i) each P_6 is independently H or a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal; X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP$_9$))–, where P_9 is H or a hydroxyl protecting group; and each R_{11} is –OP$_{10}$, or both R_{11} combine to form oxo, where P_{10} is alkyl or a hydroxyl protecting group;

(ii) both P_6 and X, together with the atoms to which each is attached, combine to form ketal, P_7 and R_7 combine to form a bond, and R_8 is H or OP"; and each R_{11} is –OP$_{10}$, or both R_{11} combine to form oxo, where P_{10} is alkyl or a hydroxyl protecting group; or

(iii) both P_6 and both R_{11}, together with the atoms to which they are attached, combine to form acetal; and X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP$_9$))–, where P_9 is H or a hydroxyl protecting group;

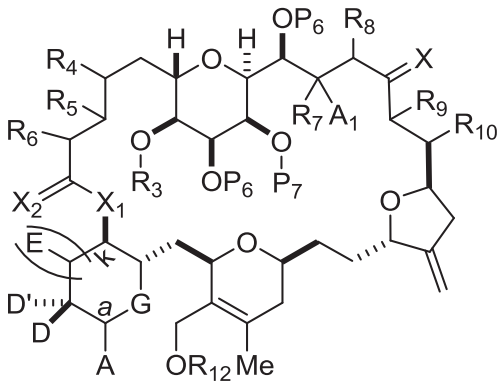
R_9 is H, OP", SO_2R_c or $COOR_c$, , and R_{10} is H; or R_9 and R_{10}, together with the atoms to which each is attached, combine to form a double bond;

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

P_8 is H or silyl;

and

the compound of formula (IB) is of the following structure:



(IB)

or a salt or a tautomer thereof;

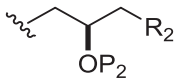
where

R_{12} is optionally substituted acyl; and

(B) producing the halichondrin macrolide or the analog thereof from compound (IB).

In certain examples, producing the compound of formula (IB) includes reacting the compound of formula (IA) with R_{12}OH and a Lewis acid (e.g., an oxophilic Lewis acid (e.g., boron trifluoride or a solvate thereof). In particular examples, producing the halichondrin macrolide or the analog thereof includes reacting the compound of formula (IB) with an allylic reducing agent. In further examples, R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H. In some examples, R_5 and R_6, together with the

atom to which each is attached, combine to form a double bond, R_4 is H, and R_3 is a hydroxyl protecting group. In other examples, each P_6 is a hydroxyl protecting group, and X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP_9))–. In yet other examples, R_7 and P_7 combine to form a bond, and R_8 is H. In still other examples, P_7 is a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond. In some examples, R_9 is H or SO_2R_C, and R_{10} is H. In other examples, P_8 is silyl. In particular examples, each R_{11} is $–OP_{10}$, where P_{10} is alkyl. In certain examples, G is O. In further examples, D is H. In yet further examples, D' is OP_1, where P_1 is alkyl. In other examples, the stereogenic center designated by *a* is (*R*), and A is of the following structure:



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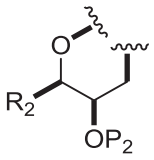
In yet other examples, k is 0 and X_1 is $–CH_2–$. In still other examples, R_2 is $–(CH_2)_nNP_3P_4$ or $–(CH_2)_nOP_5$, wherein n is 0. In further examples, A and D combine to form the following structure:



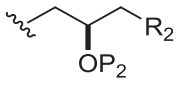
,

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

where R_2 is $–(CH_2)_nNP_3P_4$ or $–(CH_2)_nOP_5$, where n is 2.

In some examples, k is 1, and E is optionally substituted alkyl. In particular examples, X_1 is –O–.

The methods of the disclosure may be used in the preparation of eribulin or its salt (e.g., eribulin mesylate). Compounds of formula (IA), (IB), (IC), (IE), (IJ), or (IN), where k is 0, X_1 is –CH(Y)– or $–CH_2–$, D is H, D' is OP_1, G is O, and A is of the following structure:



,

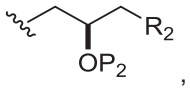
where

(i) R_2 is $–(CH_2)_nNP_3P_4$, where n is 0, P_3 is H or an N-protecting group, and P_2 and P_4 combine to form an alkylidene or P_2 is H, an optionally substituted alkyl or a hydroxyl protecting group and P_4 is an N-protecting group; or

(ii) R_2 is $–(CH_2)_nOP_5$, where n is 0, P_2 is 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;

can be used for the synthesis of eribulin or its salt (e.g., eribulin mesylate).

In certain examples of formula (IA), (IB), (IC), (IE), (IJ), or (IN), k is 0, X_1 is –CH(Y)– or $–CH_2–$, D is H, D' is OP_1, G is O, and A is of the following structure:



where

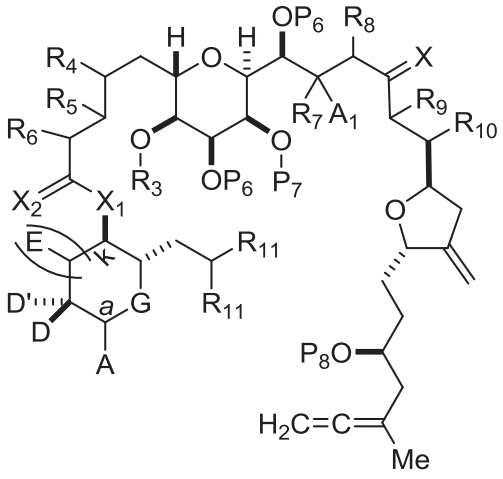
(i) R_2 is $–(CH_2)_nNP_3P_4$, where n is 0, P_3 is an N-protecting group, and P_2 and P_4 combine to form an alkylidene; or

(ii) R_2 is $–(CH_2)_nOP_5$, where n is 0, P_2 is 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;

can be used for the synthesis of eribulin or its salt (e.g., eribulin mesylate).

In another aspect, the disclosure provides the compounds of formula (IA), (IB), (IC), (ID), (IDa), (IDb), (IDc), (IDd), (IE), (IF), (IH), (IHa), (IHb), (IJ), or (IN).

The structure of the compound of formula (IA) is as follows:

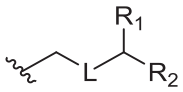


(IA),

or a salt or a tautomer thereof,

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, or a hydroxyl protecting group; and A is a group of formula (1) or 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, the group of formula (1) having the structure:



(1),

where

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

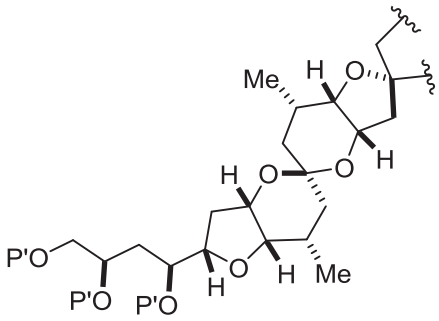
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, where P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

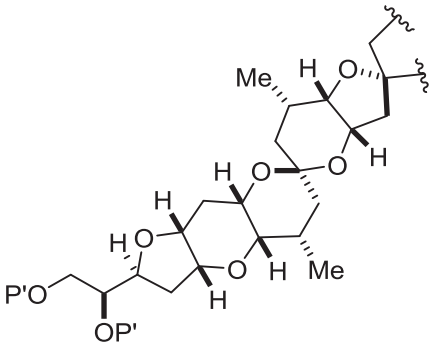
(ii) R_2 is $–(CH_2)_nNP_3P_4$, where P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 is $–(CH_2)_nOP_5$, where 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

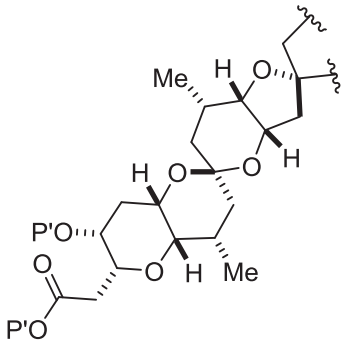
(iv) R_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, where 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, where 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 $O(CO)NR_BR_A$, where 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(Y)–, $–CH_2–$, or –O–;

X_2 is =O or X_2, together with the carbon atom to which it is attached, is $–(C(R_X)_2)–$; where each R_X is independently H, $–OR_{X1}$, or $–SR_{X1}$, provided that at least one R_X, when present, is $–OR_{X1}$ or $–SR_{X1}$;

where each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene, provided that, when X_1 is –O–, X_2 is =O;

Y is SO_2R_C or $COOR_C$, where, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

A_1 and R_7 combine to form oxo, P_7 is H or a hydroxyl protecting group, and R_8 is H;

or

A_1 is H or OP", and:

(i) P_7 is H or a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

or

(ii) P_7 and R_7 combine to form a bond, and R_8 is H or OP";

(i) each P_6 is independently H or a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal; X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP$_9$))–, where P_9 is H or a hydroxyl protecting group; and each R_{11} is $–OP_{10}$, or both R_{11} combine to form oxo, where P_{10} is alkyl or a hydroxyl protecting group;

(ii) both P_6 and X, together with the atoms to which each is attached, combine to form ketal, P_7 and R_7 combine to form a bond, and R_8 is H or OP"; and each R_{11} is $–OP_{10}$, or both R_{11} combine to form oxo, where P_{10} is alkyl or a hydroxyl protecting group; or

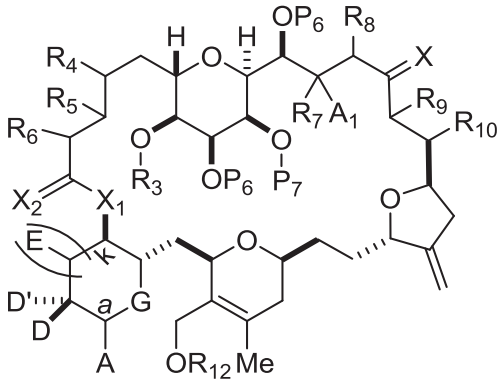
(iii) both P_6 and both R_{11}, together with the atoms to which they are attached, combine to form acetal; and X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP$_9$))–, where P_9 is H or a hydroxyl protecting group;

R_9 is H, OP", or Y, and R_{10} is H; or R_9 and R_{10}, together with the atoms to which each is attached, combine to form a double bond;

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

P_8 is H or silyl.

The structure of the compound of formula (IB) is as follows:

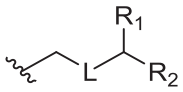


(IB)

or a salt or a tautomer 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 group of formula (1) or 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, the group of formula (1) having the structure:



(1),

wherein

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

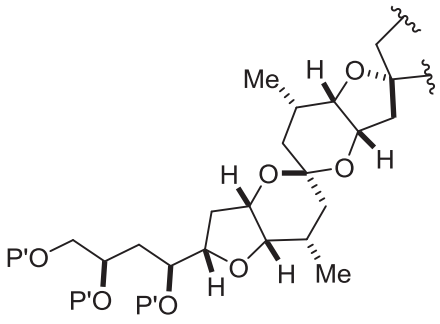
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 is $–(CH_2)_nNP_3P_4$, wherein P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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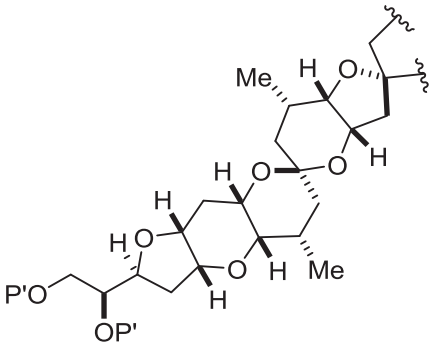
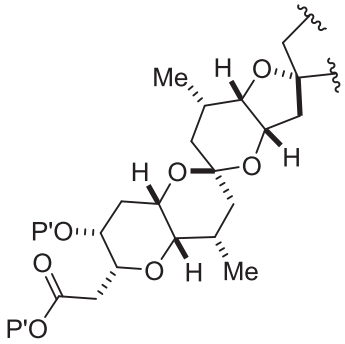


, and



, 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(Y)–, $–CH_2–$, or –O–;

X_2 is =O or X_2, together with the carbon atom to which it is attached, is $–(C(R_X)_2)–$; wherein each R_X is independently H, $–OR_{X1}$, or $–SR_{X1}$, provided that at least one R_X, when present, is $–OR_{X1}$ or $–SR_{X1}$; wherein each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene, provided that, when X_1 is –O–, X_2 is =O;

Y is SO_2R_C or $COOR_C$, where, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

A_1 and R_7 combine to form oxo, P_7 is H or a hydroxyl protecting group, and R_8 is H;

or

A_1 is H or OP", and:

(a) P_7 is H or a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

or

(b) P_7 and R_7 combine to form a bond, and R_8 is H or OP";

(i) each P_6 is independently H or a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal; X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP$_9$))–, wherein P_9 is H or a hydroxyl protecting group; or

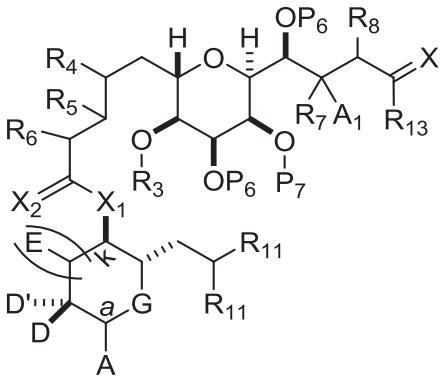
(ii) both P_6 and X, together with the atoms to which each is attached, combine to form ketal, P_7 and R_7 combine to form a bond, and R_8 is H or OP";

R_9 is H, OP", or Y, and R_{10} is H; or R_9 and R_{10}, together with the atoms to which each is attached, combine to form a double bond;

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

R_{12} is optionally substituted acyl.

The structure of the compound of formula (IC) is as follows:

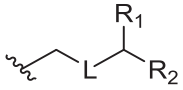


(IC),

or a salt or tautomer thereof,

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, or a hydroxyl protecting group; and A is a group of formula (1) or 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, and Q_1, the group of formula (1) having the structure:



(1),

where

L is –(CH(OP$_2$))– or –C(O)–;

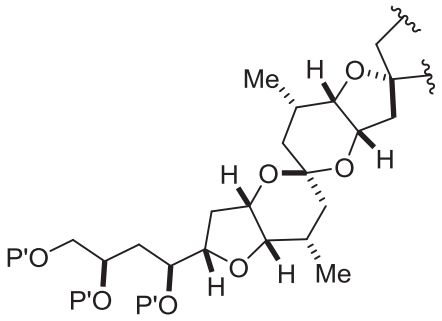
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, where P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 is $–(CH_2)_nNP_3P_4$, where P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 is $–(CH_2)_nOP_5$, where P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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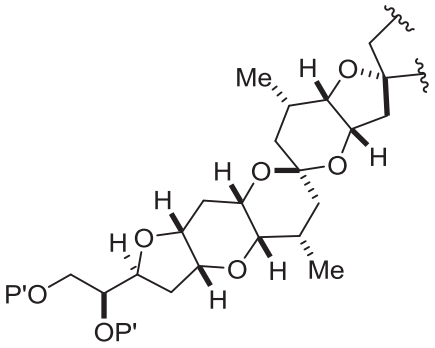
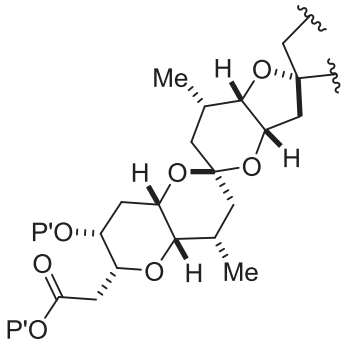


, and



, where each P' is independently a hydroxyl protecting group;

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

G is O, S, CH_2, or NR_N, where 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 $O(CO)NR_BR_A$, where each of R_A and R_B is independently 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(Y)– or $–CH_2–$;

X_2 is =O or X_2, together with the carbon atom to which it is attached, is $-(C(R_X)_2)–$; where each R_X is independently H, $–OR_{X1}$, or $–SR_{X1}$, provided that at least one R_X, when present, is $–OR_{X1}$ or $-SR_{X1}$; where each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene;

Y is SO_2R_C or $COOR_C$, where, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

(a) each P_6 is independently a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal;

each R_{11} is independently $–OP_{10}$, or

both R_{11} combine to form oxo, where P_{10} is alkyl or a hydroxyl protecting group;

or

(b) both P_6 and both R_{11}, together with the atoms to which they are attached, combine to form an acetal;

R_{13} is H or $–CH_2P(O)(OR_E)_2$, where each R_E, when present, is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

X is =O or X combines with the carbon atom, to which it is attached, to form $–(CH(OP_9))–$, where P_9 is H or a hydroxyl protecting group;

A_1 and R_7 combine to form oxo, P_7 is H or a hydroxyl protecting group, and R_8 is H;

or

A_1 is H or OP", and:

(i) P_7 is H or a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

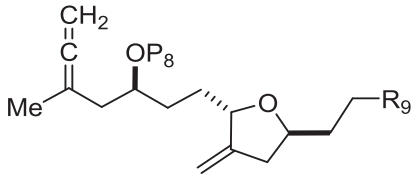
or

(ii) P_7 and R_7 combine to form a bond, and R_8 is H or OP";

and

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

The structure of the compound of formula (ID) is as follows:



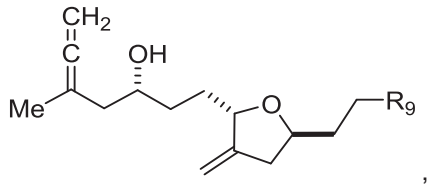
(ID),

where

P_8 is H or a hydroxyl protecting group; and

R_9 is SO_2R_C or $COOR_C$, when R_9 is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when R_9 is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl.

The structure of the compound of formula (IDa) is as follows:

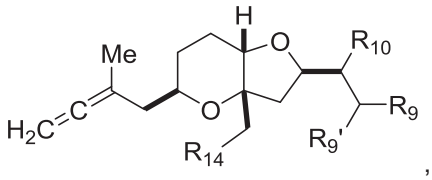


,

(IDa)

where R_9 is SO_2R_C or $COOR_C$, when R_9 is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when R_9 is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl.

The structure of the compound of formula (IDb) is as follows:

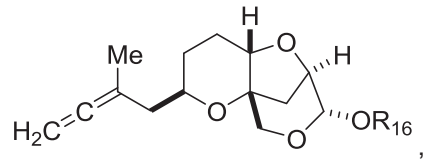


,

(IDb)

where R_9' and R_{10} are both H, or R_9' and R_{10} combine to form a double bond; R_{14} is hydroxyl, a halogen (e.g., iodide), or a pseudohalogen (e.g., triflate); and R_9 is SO_2R_C or $COOR_C$, when R_9 is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when R_9 is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl.

The structure of the compound of formula (IDc) is as follows:

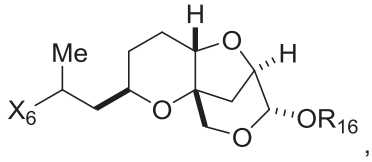


,

(IDc)

where R_{16} is H, a hydroxyl protecting group, or an optionally substituted alkyl.

The structure of the compound of formula (IDd) is as follows:

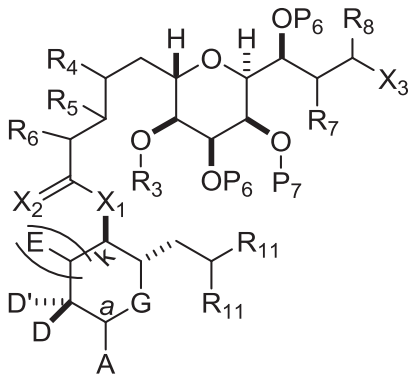


,

(IDd)

where X_6 is $–C(R_{17})=CH_2$, or –C(O)–Me, where R_{17} is a pseudohalogen (e.g., triflate) or halogen; and R_{16} is H, a hydroxyl protecting group, or an optionally substituted alkyl.

The structure of the compound of formula (IE) is as follows:

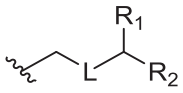


(IE),

or a salt or tautomer thereof,

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, or a hydroxyl protecting group; and A is a group of formula (1) or 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, and Q_1, the group of formula (1) having the structure:



(1),

where

L is $–(CH(OP_2))–$ or $–C(O)–$;

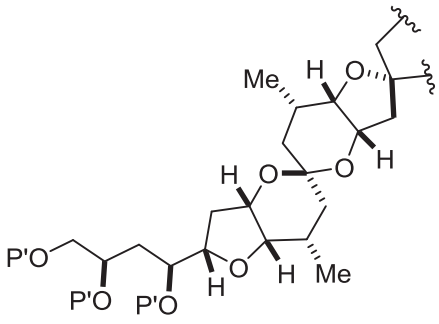
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, where P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 is $–(CH_2)_nNP_3P_4$, where P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 is $–(CH_2)_nOP_5$, where P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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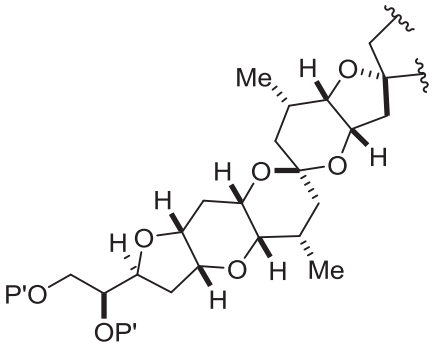
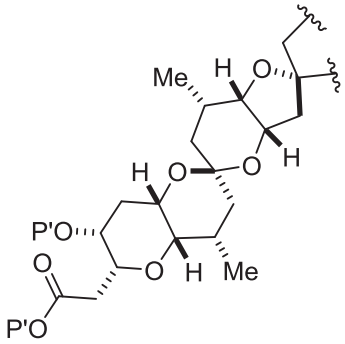


, and



, where each P' is independently a hydroxyl protecting group;

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

G is O, S, CH_2, or NR_N, where 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 $O(CO)NR_BR_A$, where each of R_A and R_B is independently 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(Y)– or $–CH_2–$;

X_2 is =O or X_2, together with the carbon atom to which it is attached, is $–(C(R_X)_2)–$; where each R_X is independently H, $–OR_{X1}$, or $–SR_{X1}$, provided that at least one R_X, when present, is $–OR_{X1}$ or $–SR_{X1}$; where each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene;

Y is SO_2R_C or $COOR_C$, where, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

R_7 and P_7 combine to form a bond, and R_8 is H; or P_7 is a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

(i) each P_6 is independently a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal;

each R_{11} is independently $–OP_{10}$, or

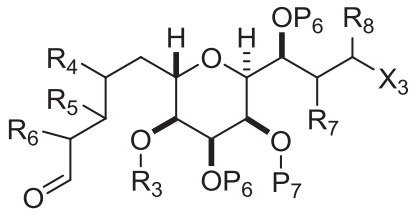
both R_{11} combine to form oxo, where P_{10} is alkyl or a hydroxyl protecting group;

or

(ii) both P_6 and both R_{11}, together with the atoms to which they are attached, combine to form an acetal; and

X_3 is $–CH_2OP_A$, $–CH=CH_2$, or $–CH(OP_A)CH_2OP_A$, where each R_E is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl, and where each P_A is independently H or a hydroxyl protecting group, or both P_A combine to form a cyclic protected diol.

In a further aspect, the present disclosure refers to a compound of formula (IF):



(IF),

wherein

X_3 is $–CHO$, $–CH_2OP_A$, $–CH=CH_2$, or $–CH(OP_A)CH_2OP_A$;

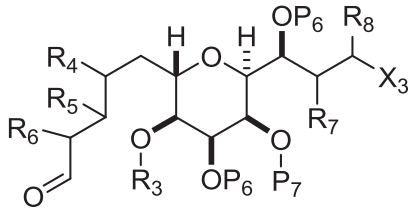
R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

R_7 and P_7 combine to form a bond, and R_8 is H; or P_7 is a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond; and

each P_6 is independently a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal; and

each P_A is independently H or a hydroxyl protecting group, or both P_A combine to form a cyclic protected diol.

In one example, the structure of the compound of formula (IF) is as follows:



(IF),

where

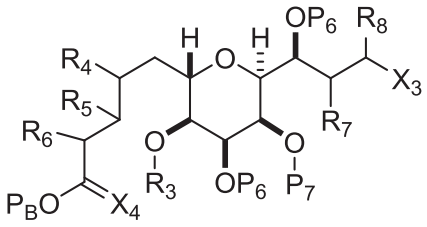
X_3 is $–CHO$, $–CH_2OP_A$, $–CH=CH_2$, or $–CH(OP_A)CH_2OP_A$;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

R_7 and P_7 combine to form a bond, and R_8 is H; or P_7 is a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond; and

each P_6 is independently a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal.

The structure of the compound of formula (IH) is as follows:



(IH),

or a salt thereof,

where

X_3 is $–CHO$, $–CH_2OP_A$, $–CH=CH_2$, or $–CH(OP_A)CH_2OP_A$;

X_4 is =O or X_4, together with the carbon atom to which it is attached, combine to form $–CH_2–$;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

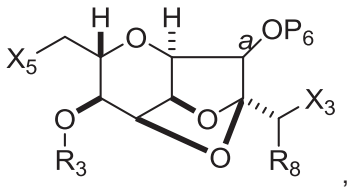
R_7 and P_7 combine to form a bond, and R_8 is H; or P_7 is a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

each P_6 is independently a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal;

each P_A is independently H or a hydroxyl protecting group, or both P_A combine to form a cyclic protected diol; and

P_B is H, a hydroxyl protecting group, or optionally substituted alkyl.

In a further aspect, the present disclosure refers to a compound of formula (IHa):



(IHa)

wherein

a identifies the carbon-oxygen bond as or ,

X_3 is $–CHO$, $–CH_2OP_A$, $–CH=CH_2$, or $–CH(OP_A)CH_2OP_A$;

X_5 is $–CH=CH_2$ or $–CH(R_4)–CH(R_5)–CH(R_6)–C(X_4)OP_B$;

X_4 is =O or X_4, together with the carbon atom to which it is attached, combine to form $–CH_2–$;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

P_6 is a hydroxyl protecting group;

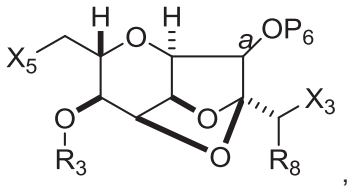
each P_A is independently H or a hydroxyl protecting group, or both P_A combine to form a

cyclic protected diol;

P_B is H, a hydroxyl protecting group, or optionally substituted alkyl; and

R_8 is H.

In one example, the structure of the compound of formula (IHa) is as follows:



(IHa)

where

a identifies the carbon-oxygen bond as | or ⋮,

X_3 is –CHO, $–CH_2OP_A$, $–CH=CH_2$, or $–CH(OP_A)CH_2OP_A$;

X_5 is $–CH=CH_2$ or $–CH(R_4)–CH(R_5)–CH(R_6)–C(X_4)OP_B$;

X_4 is =O or X_4, together with the carbon atom to which it is attached, combine to form $–CH_2–$;

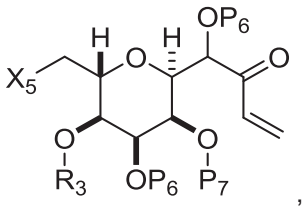
R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

P_6 is a hydroxyl protecting group, or both P_6;

each P_A is independently H or a hydroxyl protecting group, or both P_A combine to form a cyclic protected diol; and

P_B is H, a hydroxyl protecting group, or optionally substituted alkyl.

In a further aspect, the present disclosure refers to a compound of formula (IHb):



(IHb)

wherein

X_5 is $–CH=CH_2$ or $–CH(R_4)–CH(R_5)–CH(R_6)–C(X_4)OP_B$;

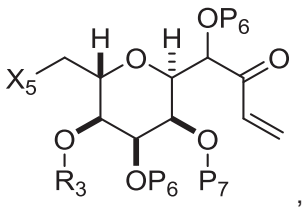
X_4 is =O or X_4, together with the carbon atom to which it is attached, combine to form $–CH_2–$;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

each of P_6 and P_7 is independently a hydroxyl protecting group, or one P_6 and P_7, together with the atoms to which each is attached, combine to form a ketal, and the remaining P_6 is a hydroxyl protecting group; or both P_6, together with the atoms to which each is attached, combine to form a ketal, and P_7 is a hydroxyl protecting group; and

P_B is H, a hydroxyl protecting group, or optionally substituted alkyl.

In one example, the structure of the compound of formula (IHb) is as follows:



(IHb)

where

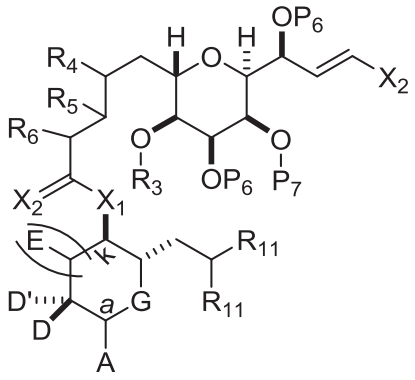
X_5 is $–CH=CH_2$ or $–CH(R_4)–CH(R_5)–CH(R_6)–C(X_4)OP_B$;

X_4 is =O or X_4, together with the carbon atom to which it is attached, combine to form $–CH_2–$;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H; and

each of P_6 and P_7 is independently a hydroxyl protecting group, or one P_6 and P_7, together with the atoms to which each is attached, combine to form a ketal (e.g., one P_6 and P_7 combine to form cyclohexylidene), and the remaining P_6 is a hydroxyl protecting group; or both P_6, together with the atoms to which each is attached, combine to form a ketal, and P_7 is a hydroxyl protecting group.

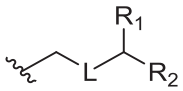
The structure of the compound of formula (IJ) is as follows:



(IJ),

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, or a hydroxyl protecting group; and A is a group of formula (1) or 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, and Q_1, the group of formula (1) having the structure:



(1),

where

L is $–(CH(OP_2))–$ or $–C(O)–$;

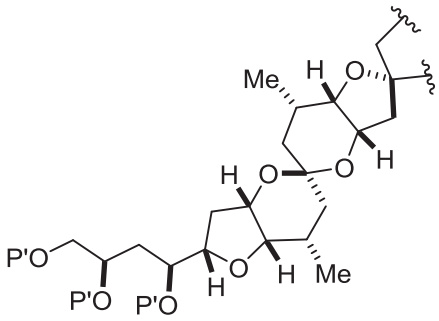
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, where P_2 absent, is H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 is $–(CH_2)_nNP_3P_4$, where P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 is $–(CH_2)_nOP_5$, where P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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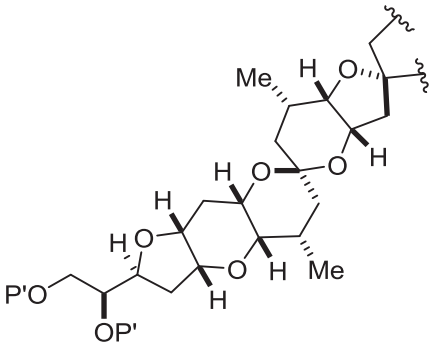
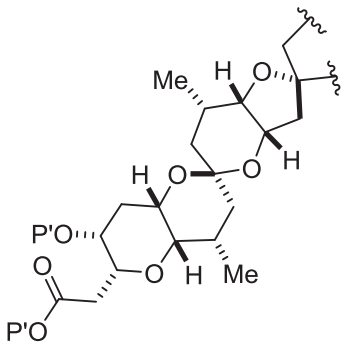


, and



, where each P' is independently a hydroxyl protecting group;

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

G is O, S, CH_2, or NR_N, where 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 $O(CO)NR_BR_A$, where each of R_A and R_B is independently 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(Y)–, $–CH_2–$, or –O–;

X_2 is =O or X_2, together with the carbon atom to which it is attached, is $–(C(R_X)_2)–$; where each R_X is independently H, $–OR_{X1}$, or $–SR_{X1}$, provided that at least one R_X, when present, is $–OR_{X1}$ or $–SR_{X1}$;

where each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene, provided that, when X_1 is –O–, X_2 is =O;

Y is SO_2R_C or $COOR_C$, where, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

(i) each P_6 is independently a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal;

each R_{11} is independently $–OP_{10}$, or

both R_{11} combine to form oxo, where P_{10} is alkyl or a hydroxyl protecting group;

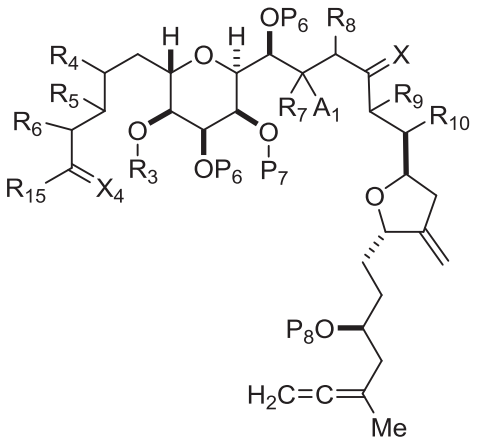
or

(ii) both P_6 and both R_{11}, together with the atoms to which they are attached, combine to form an acetal;

P_7 is a hydroxyl protecting group; and

X_2 is a halogen or pseudohalogen.

The structure of the compound of formula (IN) is as follows:



(IN),

or a salt or tautomer thereof,

where

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

A_1 and R_7 combine to form oxo, P_7 is H or a hydroxyl protecting group, and R_8 is H;

or

A_1 is H or OP", and:

(i) P_7 is H or a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

or

(ii) P_7 and R_7 combine to form a bond, and R_8 is H or OP";

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

each P_6 is independently H or a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal, and X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP_9))–, where P_9 is H or a hydroxyl protecting group; or both P_6 and X, together with the atoms to which each is attached, combine to form ketal; where, when both P_6 and X, together with the atoms to which each is attached, combine to form ketal, P_7 and R_7 combine to form a bond, and R_8 is H or OP";

R_9 is H, SO_2R_C, or $COOR_C$, and R_{10} is H, wherein, when R_9 is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when R_9 is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl; or R_9 and R_{10}, together with the atoms to which each is attached, combine to form a double bond;

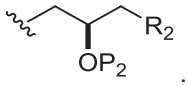
R_{15} is H or $–OP_{11}$, where P_{11} is H, a hydroxyl protecting group, or optionally substituted alkyl;

X_4 is =O or, together with the carbon atom to which it is attached, is $–CH_2–$, provided that when R_{15} is H, X_4 is =O; and

P_8 is H or silyl.

In some examples, each P_A is H, or both P_A combine to form a cyclic protected diol. In other examples, A_1 is H. In yet other examples, each R_{11} is $–OP_{10}$, where P_{10} is alkyl. In still other examples, R_9 is H or SO_2R_C, and R_{10} is H. In certain examples, R_9 is SO_2R_C.In further examples, P_8 is silyl. In particular examples, P_6 is a hydroxyl protecting group, and X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP_9))–. In certain examples, R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H. In further examples, R_5 and R_6, together with the atom to which each is attached, combine to form a double bond, R_4 is H, and R_3 is a hydroxyl protecting group. In yet further examples, R_7 and P_7 combine to form a bond, and R_8 is H. In still further examples, P_7 is a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond. In certain examples, A_3 is H. In particular examples, A_2 is H.

In further examples, the stereogenic center designated by *a* is (*R*), and A is of the following structure:



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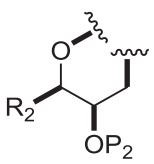
In yet further examples, k is 0 and X_1 is $–CH_2–$. In still further examples, R_2 is $–(CH_2)_nNP_3P_4$ or $–(CH_2)_nOP_5$, wherein n is 0.

In other examples, A and D combine to form the following structure:

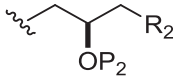


,

where, the bond to oxygen atom originates at the carbon atom, to which D is attached in formula (IA), and where R_2 is $–(CH_2)_nNP_3P_4$ or $–(CH_2)_nOP_5$, wherein n is 2.

In yet other examples, k is 1, and E is optionally substituted alkyl. In still other examples, X_1 is –O–.

In certain examples of the compound of formula (IA), (IB), (IC), (IE), (IJ), or (IN), k is 0, D is H, D' is OP_1, and A is of the following structure:

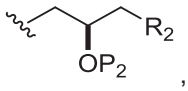


where

(i) R_2 is $–(CH_2)_nNP_3P_4$, where n is 0, P_3 is H or an N-protecting group, and P_2 and P_4 combine to form an alkylidene; or

(ii) R_2 is $–(CH_2)_nOP_5$, where n is 0, P_2 is 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.

In particular examples of the compound of formula (IA), (IB), (IC), (IE), (IJ), or (IN), k is 0, D is H, D' is OP_1, and A is of the following structure:



,

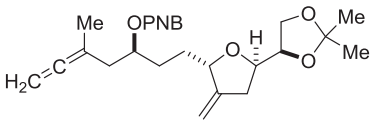
where

(i) R_2 is $–(CH_2)_nNP_3P_4$, where n is 0, P_3 is an N-protecting group, and P_2 and P_4 combine to form an alkylidene; or

(ii) R_2 is $–(CH_2)_nOP_5$, where n is 0, each of P_2 and P_5 is independently 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.

In yet another example, the disclosure provides compounds **1**, **2**, **3**, **5**, **7**, **7a**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, **16**, **17**, **18**, **21**, **23**, **24**, **25**, **27**, **28**, **29**, **31**, **32**, **33**, **34**, **35**, **36**, **36b**, **36c**, **37**, **38**, **39**, **40**, **41**, **43**, **44**, **44a**, **45**, **47**, **47a**, **47b**, **47c**, **48**, **49**, **50**, **50a**, **51**, **52**, **53**, **54**, **55**, **56**, **57**, **58**, **59**, **61**, **62**, **63**, **66**, **67**, **68**, **69**, **70**, **71**, **72**, **73**, **77**, **78**, **79**, **80**, **81**, **82**, **83**, **84**, **85**, **86**, and **87**.

In another aspect, the present disclosure refers to a compound selected from the group consisting of:



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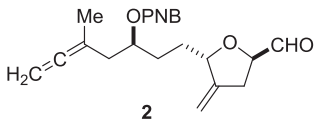

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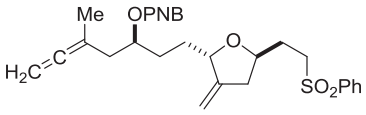

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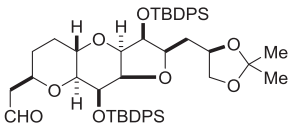

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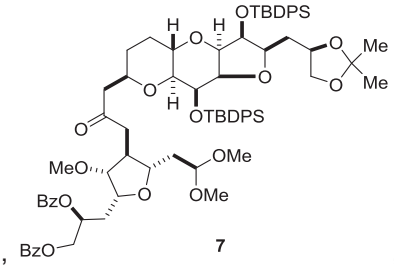

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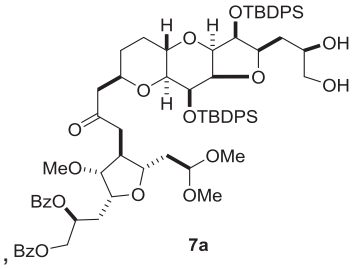

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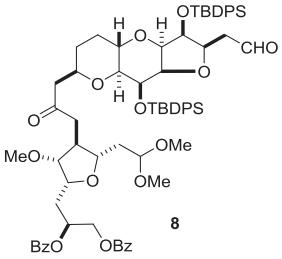

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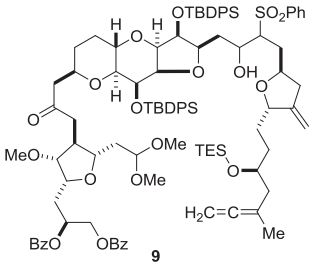

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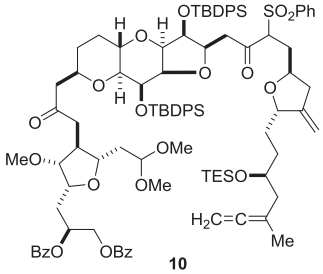

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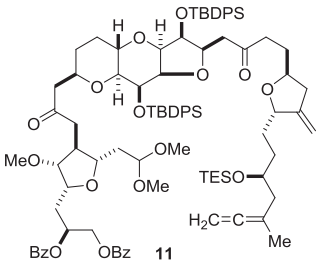

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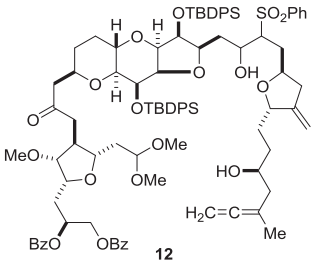

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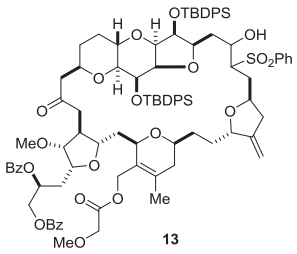

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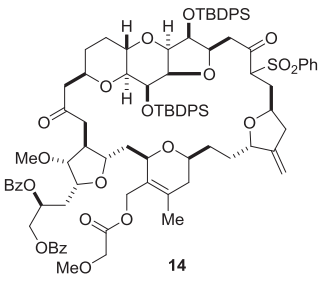

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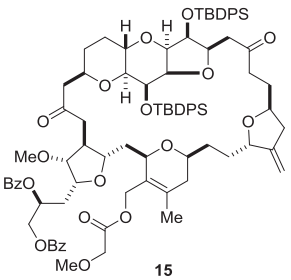

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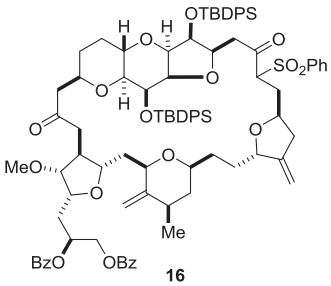

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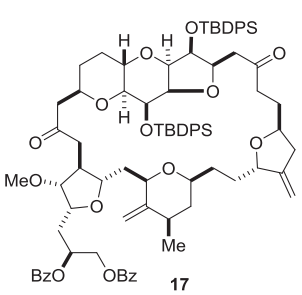
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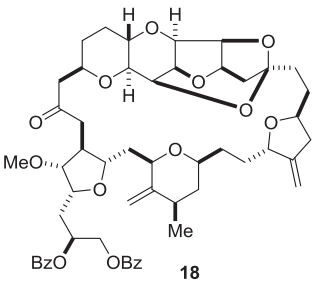
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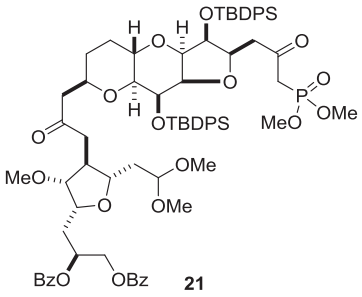
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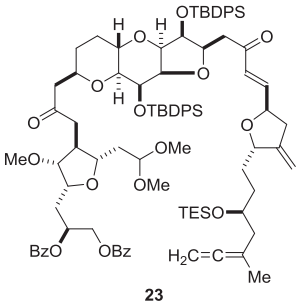
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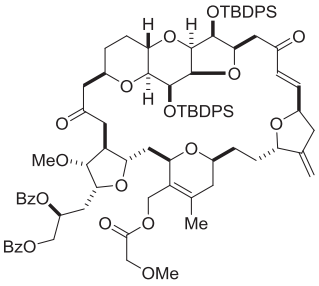
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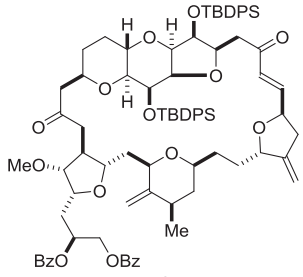
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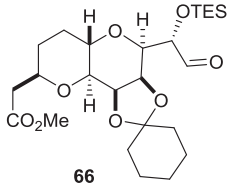
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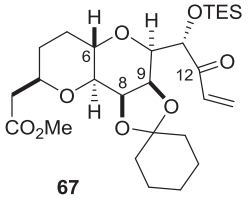
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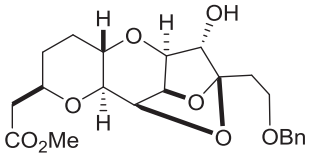
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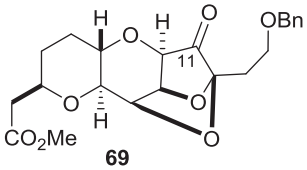
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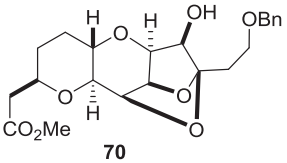
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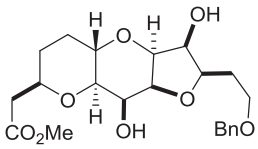
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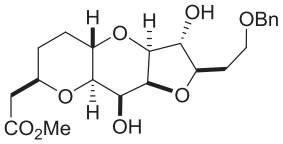
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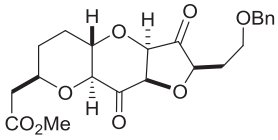
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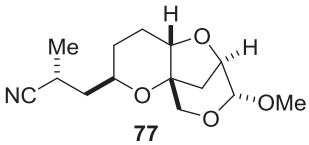
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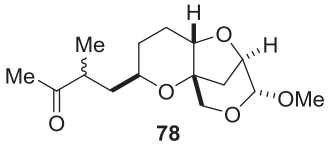
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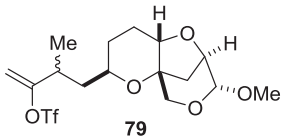
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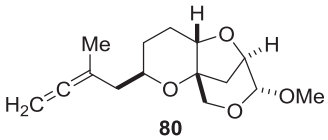
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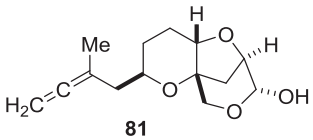
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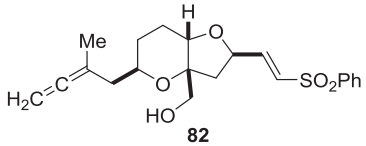
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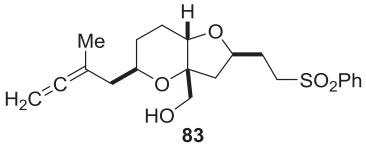
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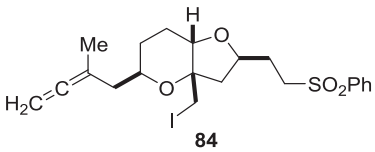
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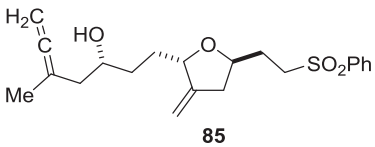
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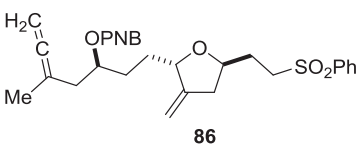
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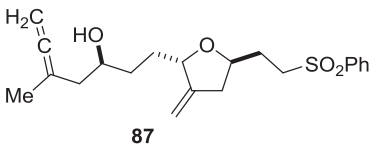
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Definitions

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.

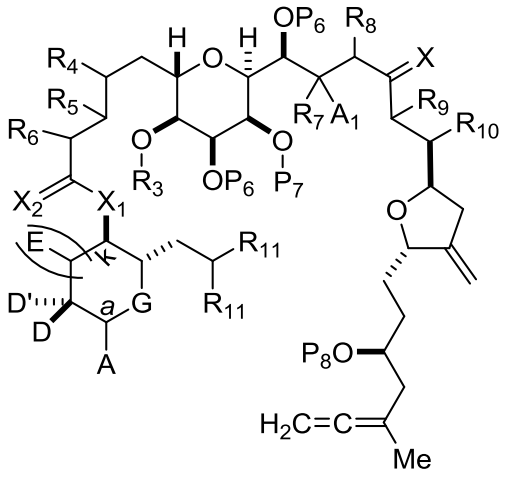
For any of the following chemical definitions, a number following an atomic symbol indicates that total number of atoms of that element that are present in a particular chemical moiety. As will be understood, other atoms, such as hydrogen atoms, or substituent groups, as described herein, may be present, 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.

Claims

1. A method of preparing a macrocyclic intermediate in the synthesis of a halichondrin macrolide or an analog thereof, the method comprising reacting an intermediate of formula (IA) with $R_{12}OH$ and a Lewis acid, the reaction producing the macrocyclic intermediate by forming a bond in the structure of the halichondrin macrolide or an analog thereof,

wherein R_{12} is optionally substituted acyl;

wherein the compound of formula (IA) is:

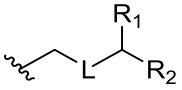


(IA),

or a salt or a tautomer 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 group of formula (1) or a $C_{1\text{-}6}$ saturated or $C_{2\text{-}6}$ 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, the group of formula (1) having the structure:



(1),

wherein

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

R_1 is H, or R_1 and P_1 combine to form a bond;

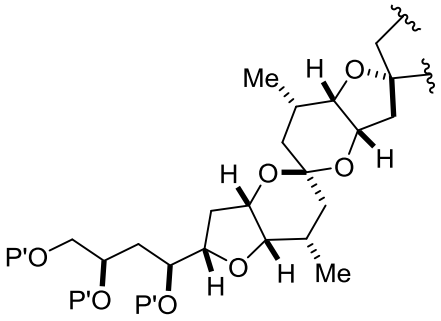
(i) R_2 is H, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 is $–(CH_2)_nNP_3P_4$, wherein P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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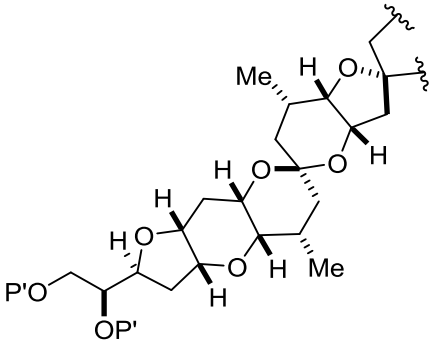

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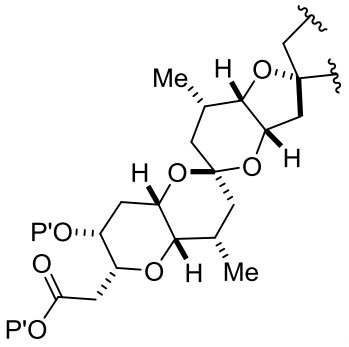


, wherein each P' is independently H or a hydroxyl protecting group;

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;

X_1 is –CH(Y)–, $–CH_2–$, or –O–;

X_2 is =O or X_2, together with the carbon atom to which it is attached, is $–(C(R_X)_2)–$; wherein each R_X is independently H, $–OR_{X1}$, or $–SR_{X1}$, provided that at least one R_X, when present, is $–OR_{X1}$ or $–SR_{X1}$; wherein each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene, provided that, when X_1 is –O–, X_2 is =O;

Y is SO_2R_C or $COOR_C$, where, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

A_1 and R_7 combine to form oxo, P_7 is H or a hydroxyl protecting group, and R_8 is H;

or

A_1 is H or OP", and:

(a) P_7 is H or a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

or

(b) P_7 and R_7 combine to form a bond, and R_8 is H or OP";

(i) each P_6 is independently H or a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal; X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP_9))–, wherein P_9 is H or a hydroxyl protecting group; and each R_{11} is –OP_{10}, or both R_{11} combine to form oxo, wherein P_{10} is alkyl or a hydroxyl protecting group;

(ii) both P_6 and X, together with the atoms to which each is attached, combine to form ketal, P_7 and R_7 combine to form a bond, and R_8 is H or OP"; and each R_{11} is –OP_{10}, or both R_{11} combine to form oxo, wherein P_{10} is alkyl or a hydroxyl protecting group; or

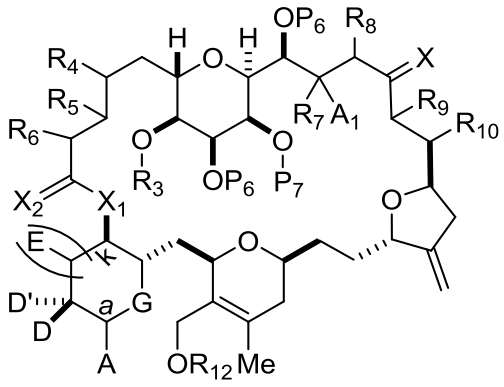
(iii) both P_6 and both R_{11}, together with the atoms to which they are attached, combine to form acetal; and X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP_9))–, wherein P_9 is H or a hydroxyl protecting group;

R_9 is H, OP", or Y, and R_{10} is H; or R_9 and R_{10}, together with the atoms to which each is attached, combine to form a double bond;

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

P_8 is H or silyl; and

wherein the macrocyclic intermediate in the synthesis of a halichondrin macrolide or an analog thereof is a compound of formula (IB):



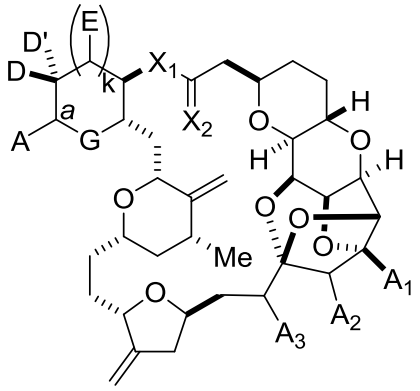
(IB)

or a salt or a tautomer thereof.

2. The method of claim 1, wherein the Lewis acid is an oxophilic Lewis acid.

3. The method of claim 2, wherein the oxophilic Lewis acid is boron trifluoride or a solvate thereof.

4. A method of preparing

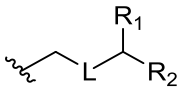


a halichondrin macrolide or an analog thereof,

or a salt 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 group of formula (1) or 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, the group of formula (1) having the structure:



(1),

wherein

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

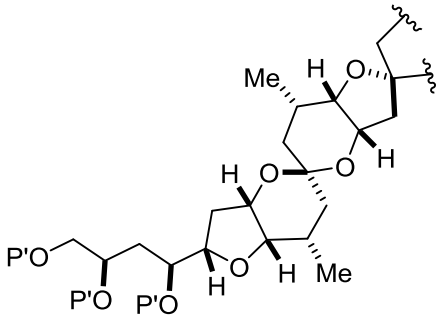
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 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 an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene, or (c) each of P_2 and P_4 is H;

(iii) R_2 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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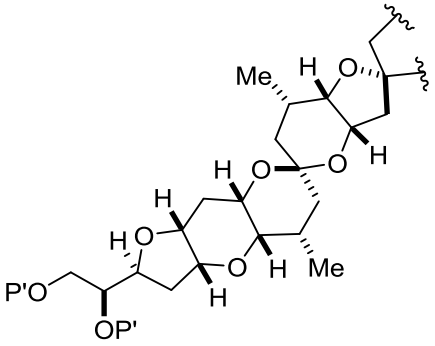

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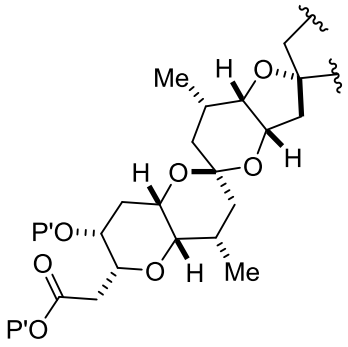


, wherein each P' is independently H or a hydroxyl protecting group;

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;

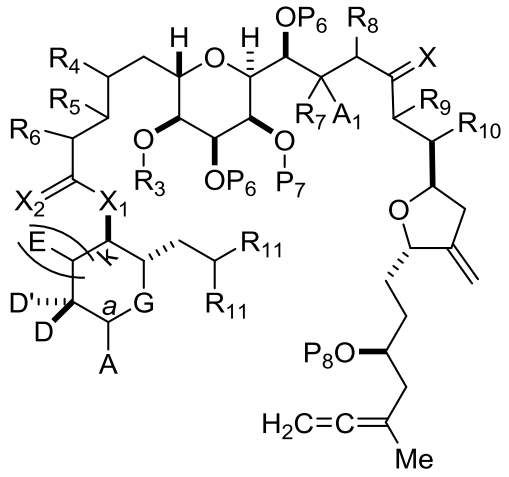
n, when present, is 0, 1, or 2;

k is 0 or 1; and

X_1 is $–CH_2–$ or –O–, and X_2 is =O;

the method comprising:

(A) producing a compound of formula (IB) from a compound of formula (IA) and $R_{12}OH$, wherein R_{12} is optionally substituted acyl, and the compound of formula (IA) is of the following structure:

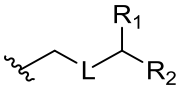


(IA)

or a salt or a tautomer 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 group of formula (1) or 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, the group of formula (1) having the structure:



(1),

wherein

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

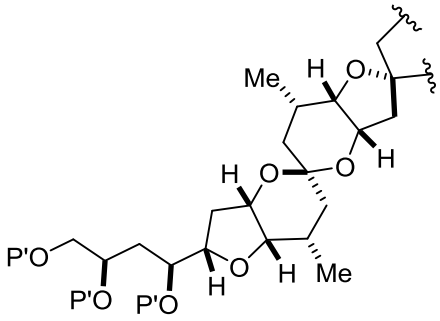
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 is $–(CH_2)_nNP_3P_4$, wherein P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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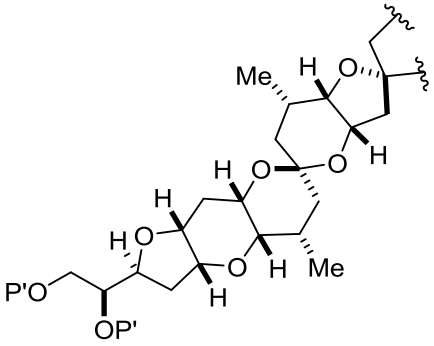
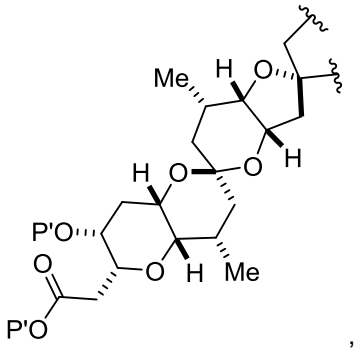


, and


, 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(Y)–, $–CH_2–$, or –O–, and X_2 is =O or X_2, together with the carbon atom to which it is attached, is $–(C(R_X)_2)–$; wherein each R_X is independently H, $–OR_{X1}$, or $–SR_{X1}$, provided that at least one R_X, when present, is $–OR_{X1}$ or $–SR_{X1}$; wherein each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene, provided that, when X_1 is –O–, X_2 is =O; and wherein Y is SO_2R_C or $COOR_C$, where, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

A_1 and R_7 combine to form oxo, P_7 is H or a hydroxyl protecting group, and R_8 is H;

or

A_1 is H or OP", and:

(i) P_7 is H or a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

or

(ii) P_7 and R_7 combine to form a bond, and R_8 is H or OP";

(i) each P_6 is independently H or a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal; X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP_9))–, wherein P_9 is H or a hydroxyl protecting group; and each R_{11} is –OP_{10}, or both R_{11} combine to form oxo, wherein P_{10} is alkyl or a hydroxyl protecting group;

(ii) both P_6 and X, together with the atoms to which each is attached, combine to form ketal, P_7 and R_7 combine to form a bond, and R_8 is H or OP"; and each R_{11} is –OP_{10}, or both R_{11} combine to form oxo, wherein P_{10} is alkyl or a hydroxyl protecting group; or

(iii) both P_6 and both R_{11}, together with the atoms to which they are attached, combine to form acetal; and X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP_9))–, wherein P_9 is H or a hydroxyl protecting group;

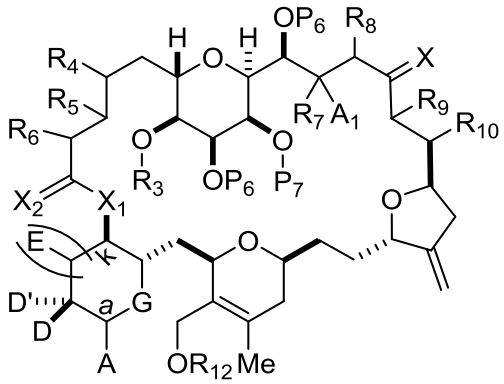
R_9 is H, OP", SO_2R_C, or $COOR_C$, and R_{10} is H; or R_9 and R_{10}, together with the atoms to which each is attached, combine to form a double bond;

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

P_8 is H or silyl;

and

the compound of formula (IB) is of the following structure:



(IB)

or a salt or a tautomer thereof;

wherein

R_{12} is optionally substituted acyl;

(B) producing the halichondrin macrolide or the analog thereof from compound (IB).

5. The method of claim 4, wherein the producing the compound of formula (IB) comprises reacting the compound of formula (IA) with R_{12}OH and a Lewis acid.

6. The method of claim 5, wherein the Lewis acid is an oxophilic Lewis acid.

7. The method of any one of claims 4 to 6, wherein the producing the halichondrin macrolide or the analog thereof comprises reacting the compound of formula (IB) with an allylic reducing agent.

8. The method of any one of claims 1 to 7, wherein R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H.

9. The method of any one of claims 1 to 7, wherein R_5 and R_6, together with the atom to which each is attached, combine to form a double bond, R_4 is H, and R_3 is a hydroxyl protecting group.

10. The method of any one of claims 1 to 9, wherein P_6 is a hydroxyl protecting group, and X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP_9))–.

11. The method of any one of claims 1 to 10, wherein R_7 and P_7 combine to form a bond, and R_8 is H.

12. The method of any one of claims 1 to 10, wherein P_7 is a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond.

13. The method of any one of claims 1 to 12, wherein R_9 is H or SO_2R_C, and R_{10} is H.

14. The method of any one of claims 1 to 13, wherein P_8 is silyl.

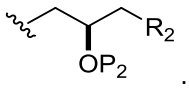
15. The method of any one of claims 1 to 14, wherein each R_{11} is $–OP_{10}$, wherein P_{10} is alkyl.

16. The method of any one of claims 1 to 15, wherein G is O.

17. The method of any one of claims 1 to 16, wherein D is H.

18. The method of any one of claims 1 to 17, wherein D' is OP_1, wherein P_1 is alkyl.

19. The method of any one of claims 1 to 18, wherein the stereogenic center designated by *a* is (*R*), and A is of the following structure:



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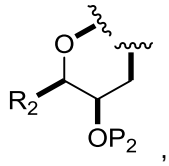
20. The method of any one of claims 1 to 19, wherein k is 0 and X_1 is $–CH_2–$.

21. The method of any one of claims 1 to 20, wherein R_2 is $–(CH_2)_nNP_3P_4$ or $–(CH_2)_nOP_5$, wherein n is 0.

22. The method of any one of claims 1 to 17, wherein A and D combine to form the following structure:



,

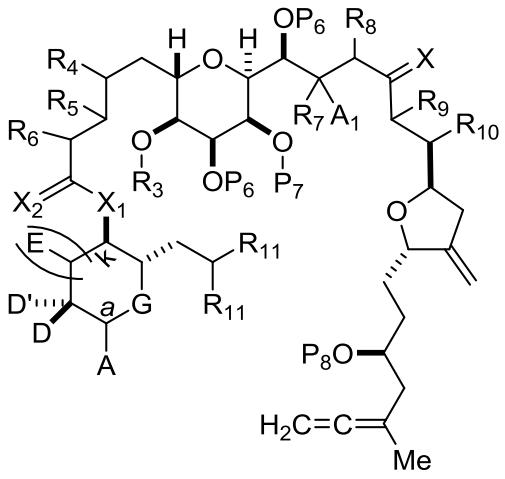
wherein, the bond to oxygen atom originates at the carbon atom, to which D is attached in formula (IA), and

wherein R_2 is $–(CH_2)_nNP_3P_4$ or $–(CH_2)_nOP_5$, wherein n is 2.

23. The method of claim 22, wherein k is 1, and E is optionally substituted alkyl.

24. The method of claim 22 or 23, wherein X_1 is –O–.

25. A compound of formula (IA):

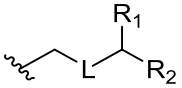


(IA),

or a salt or a tautomer 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 group of formula (1) or 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, the group of formula (1) having the structure:



(1),

wherein

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

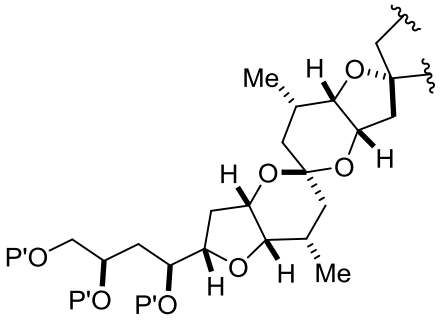
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 is $–(CH_2)_nNP_3P_4$, wherein P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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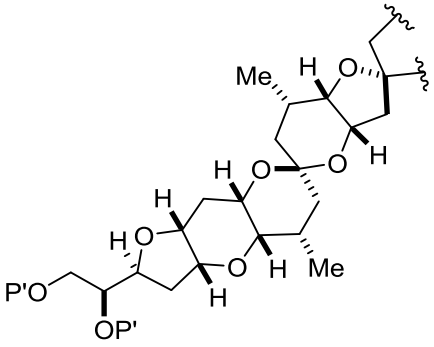

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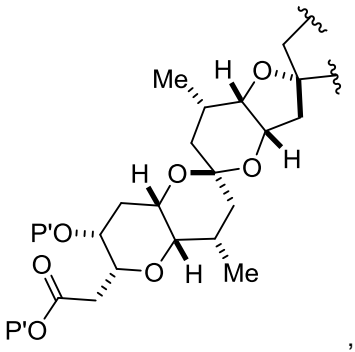


, wherein each P' is independently H or a hydroxyl protecting group;

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;

X_1 is –CH(Y)–, –CH_2–, or –O–;

X_2 is =O or X_2, together with the carbon atom to which it is attached, is –($C(R_X)_2$)–; wherein each R_X is independently H, –OR_{X1}, or –SR_{X1}, provided that at least one R_X, when present, is –OR_{X1} or –SR_{X1}; wherein each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene, provided that, when X_1 is –O–, X_2 is =O;

Y is SO_2R_C or $COOR_C$, where, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

A_1 and R_7 combine to form oxo, P_7 is H or a hydroxyl protecting group, and R_8 is H;

or

A_1 is H or OP", and:

(i) P_7 is H or a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

or

(ii) P_7 and R_7 combine to form a bond, and R_8 is H or OP";

(i) each P_6 is independently H or a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal; X is =O or X combines with the carbon atom, to which it is attached, to form –($CH(OP_9)$)–, wherein P_9 is H or a hydroxyl protecting group; and each R_{11} is –OP_{10}, or both R_{11} combine to form oxo, wherein P_{10} is alkyl or a hydroxyl protecting group;

(ii) both P_6 and X, together with the atoms to which each is attached, combine to form ketal, P_7 and R_7 combine to form a bond, and R_8 is H or OP"; and each R_{11} is –OP_{10}, or both R_{11} combine to form oxo, wherein P_{10} is alkyl or a hydroxyl protecting group; or

(iii) both P_6 and both R_{11}, together with the atoms to which they are attached, combine to form acetal; and X is =O or X combines with the carbon atom, to which it is attached, to form –($CH(OP_9)$)–, wherein P_9 is H or a hydroxyl protecting group;

R_9 is H, OP", or Y, and R_{10} is H; or R_9 and R_{10}, together with the atoms to which each is attached, combine to form a double bond;

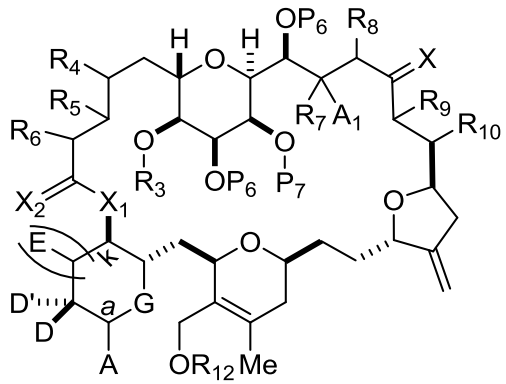
each P", when present, is independently H or a hydroxyl protecting group; and

P_8 is H or silyl.

26. The compound of claim 25, wherein P_8 is silyl.

27. The compound of claim 25 or 26, wherein each R_{11} is –OP_{10}, wherein P_{10} is alkyl.

28. A compound of formula (IB):

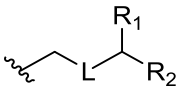


(IB)

or a salt or a tautomer 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 group of formula (1) or 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, the group of formula (1) having the structure:



(1),

wherein

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

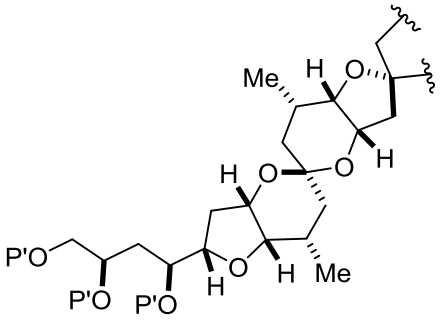
R_1 is H, or R_1 and P_1 combine to form a bond;

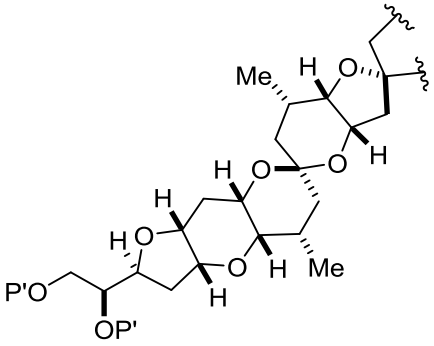
(i) R_2 is H, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

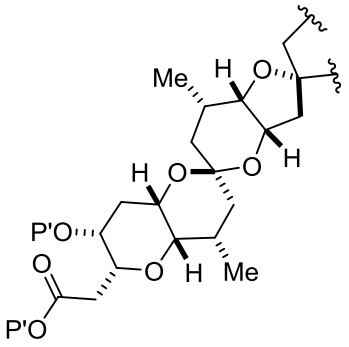
(ii) R_2 is $–(CH_2)_nNP_3P_4$, wherein P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 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_2 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(Y)–, $–CH_2–$, or –O–;

X_2 is =O or X_2, together with the carbon atom to which it is attached, is $–(C(R_X)_2)–$; wherein each R_X is independently H, $–OR_{X1}$, or $–SR_{X1}$, provided that at least one R_X, when present, is $–OR_{X1}$ or $–SR_{X1}$; wherein each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene, provided that, when X_1 is –O–, X_2 is =O;

Y is SO_2R_C or $COOR_C$, where, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

A_1 and R_7 combine to form oxo, P_7 is H or a hydroxyl protecting group, and R_8 is H;

or

A_1 is H or OP", and:

(a) P_7 is H or a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

or

(b) P_7 and R_7 combine to form a bond, and R_8 is H or OP";

(i) each P_6 is independently H or a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal; X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP$_9$))–, wherein P_9 is H or a hydroxyl protecting group; or

(ii) both P_6 and X, together with the atoms to which each is attached, combine to form ketal, P_7 and R_7 combine to form a bond, and R_8 is H or OP";

R_9 is H, OP", or Y, and R_{10} is H; or R_9 and R_{10}, together with the atoms to which each is attached, combine to form a double bond;

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

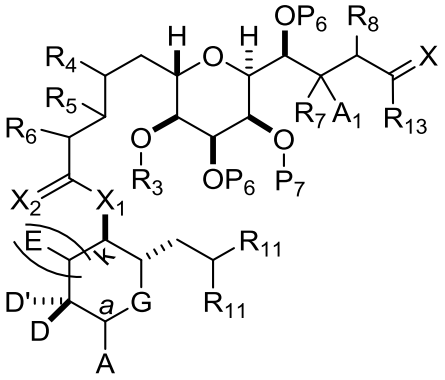
R_{12} is optionally substituted acyl.

29. The compound of any one of claims 25 to 28, wherein R_9 is H or SO_2R_C, and R_{10} is H.

30. The compound of any one of claims 25 to 29, wherein P_6 is a hydroxyl protecting group, and X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP$_9$))–.

31. The compound of any one of claims 25 to 30, wherein A_1 is H.

32. A compound of formula (IC)

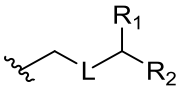


(IC),

or a salt or tautomer 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 group of formula (1) or 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, and Q_1, the group of formula (1) having the structure:



(1),

wherein

L is –(CH(OP$_2$))– or –C(O)–;

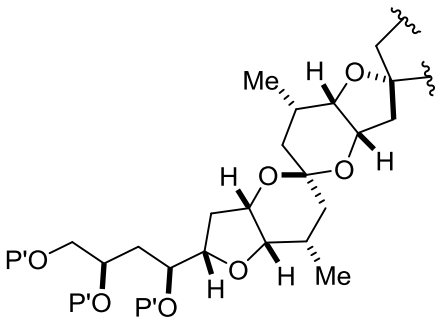
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 is –$(CH_2)_nNP_3P_4$, wherein P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 is –$(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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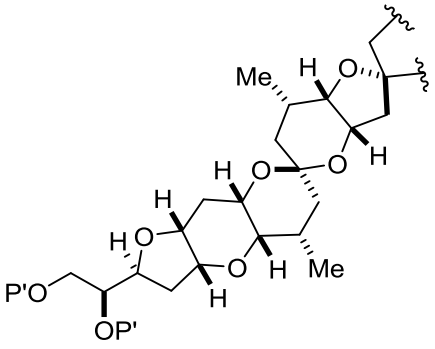
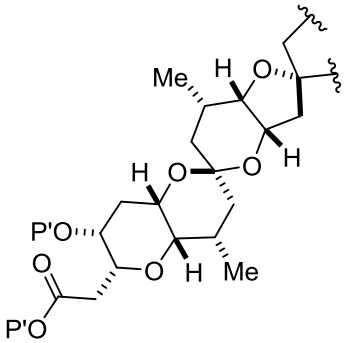


, and



, wherein each P' is independently 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 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(Y)– or –CH_2–;

X_2 is =O or X_2, together with the carbon atom to which it is attached, is -($C(R_X)_2$)–; wherein each R_X is independently H, –OR_{X1}, or –SR_{X1}, provided that at least one R_X, when present, is –OR_{X1} or -SR_{X1}; wherein each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene;

Y is SO_2R_C or $COOR_C$, wherein, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

(i) each P_6 is independently a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal;

each R_{11} is independently –OP_{10}, or

both R_{11} combine to form oxo, wherein P_{10} is alkyl or a hydroxyl protecting group;

or

(ii) both P_6 and both R_{11}, together with the atoms to which they are attached, combine to form an acetal;

R_{13} is H or –$CH_2P(O)(OR_E)_2$, wherein each R_E, when present, is independently optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

X is =O or X combines with the carbon atom, to which it is attached, to form –(CH(OP_9))–, wherein P_9 is H or a hydroxyl protecting group;

A_1 and R_7 combine to form oxo, P_7 is H or a hydroxyl protecting group, and R_8 is H;

or

A_1 is H or OP", and:

(i) P_7 is H or a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

or

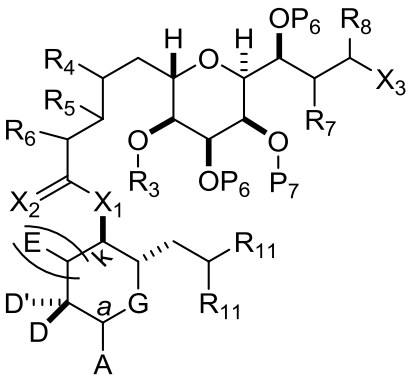
(ii) P_7 and R_7 combine to form a bond, and R_8 is H or OP";

and

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

33. The compound of any one of claims 25 to 32, wherein A_1 is H.

34. A compound of formula (IE):

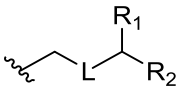


(IE),

or a salt or tautomer 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 group of formula (1) or 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, and Q_1, the group of formula (1) having the structure:



(1),

wherein

L is $–(CH(OP_2))–$ or $–C(O)–$;

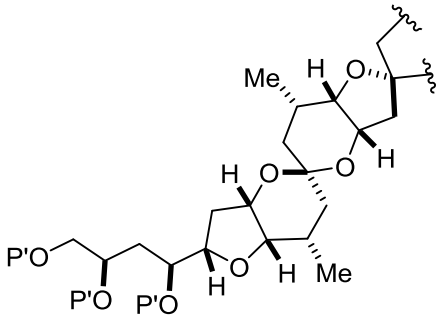
R_1 is H, or R_1 and P_1 combine to form a bond;

(i) R_2 is H, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group;

(ii) R_2 is $–(CH_2)_nNP_3P_4$, wherein P_3 is an N-protecting group, and (a) P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_4 is an N-protecting group, or (b) P_2 and P_4 combine to form an alkylidene;

(iii) R_2 is $–(CH_2)_nOP_5$, wherein P_2 is absent, H, optionally substituted alkyl, or a hydroxyl protecting group, and P_5 is 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_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



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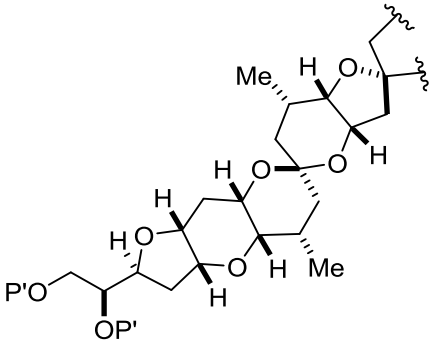
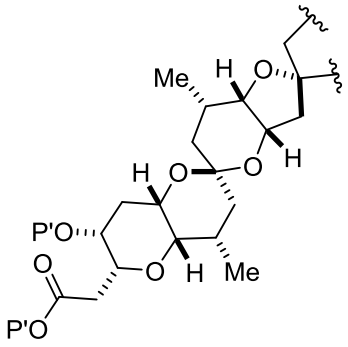


, and


, wherein each P' is independently 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 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(Y)– or $–CH_2–$,

X_2 is =O or X_2, together with the carbon atom to which it is attached, is $–(C(R_X)_2)–$; wherein each R_X is independently H, $–OR_{X1}$, or $–SR_{X1}$, provided that at least one R_X, when present, is $–OR_{X1}$ or $–SR_{X1}$; wherein each R_{X1} is independently optionally substituted alkyl, or both R_{X1} combine to form optionally substituted alkylene;

Y is SO_2R_C or $COOR_C$, wherein, when Y is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when Y is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

R_7 and P_7 combine to form a bond, and R_8 is H; or P_7 is a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

(i) each P_6 is independently a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal;

each R_{11} is independently $–OP_{10}$, or

both R_{11} combine to form oxo, wherein P_{10} is alkyl or a hydroxyl protecting group;

or

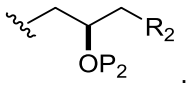
(ii) both P_6 and both R_{11}, together with the atoms to which they are attached, combine to form an acetal;

X_3 is $–CH_2OP_A$, $–CH=CH_2$, or $–CH(OP_A)CH_2OP_A$, wherein each R_E is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl, and wherein each P_A is independently H or a hydroxyl protecting group, or both P_A combine to form a cyclic protected diol.

35. The compound of claim 34, wherein each P_A is H, or both P_A combine to form a cyclic protected diol.

36. The compound of any one of claims 32 to 35, wherein each R_{11} is $–OP_{10}$, wherein P_{10} is alkyl.

37. The compound of any one of claims 25 to 36, wherein the stereogenic center designated by *a* is (*R*), and A is of the following structure:



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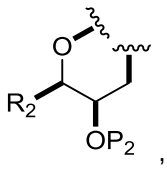
38. The compound of any one of claims 25 to 37, wherein k is 0 and X_1 is $–CH_2–$.

39. The compound of any one of claims 25 to 38, wherein R_2 is $–(CH_2)_nNP_3P_4$ or $–(CH_2)_nOP_5$, wherein n is 0.

40. The compound of any one of claims 25 to 36, wherein A and D combine to form the following structure:



,

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

wherein R_2 is $–(CH_2)_nNP_3P_4$ or $–(CH_2)_nOP_5$, wherein n is 2.

41. The compound of claim 40, wherein k is 1, and E is optionally substituted alkyl.

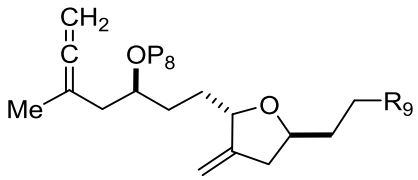
42. The compound of claim 40 or 41, wherein X_1 is –O–.

43. The compound of any one of claims 25 to 42, wherein R_5 and R_6, together with the atom to which each is attached, combine to form a double bond, R_4 is H, and R_3 is a hydroxyl protecting group.

44. The compound of any one of claims 25 to 43, wherein R_7 and P_7 combine to form a bond, and R_8 is H.

45. The compound of any one of claims 25 to 43, wherein P_7 is a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond.

46. A compound of formula (ID):



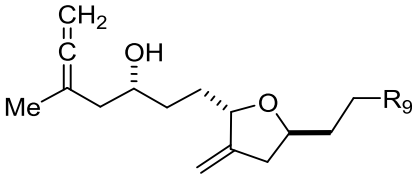
(ID),

wherein

P_8 is H or a hydroxyl protecting group; and

R_9 is SO_2R_C or $COOR_C$, when R_9 is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when R_9 is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl.

47. A compound of formula (IDa):



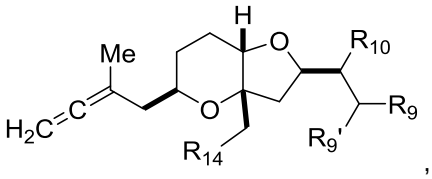
,

(IDa)

wherein

R_9 is SO_2R_C or $COOR_C$, when R_9 is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when R_9 is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl.

48. A compound of formula (IDb):



(IDb)

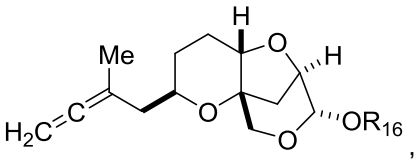
wherein

R_9' and R_{10} are both H, or R_9' and R_{10} combine to form a double bond; R_{14} is hydroxyl, a halogen, or a pseudohalogen; and

R_9 is SO_2R_C or $COOR_C$, when R_9 is SO_2R_C, R_C is optionally substituted aryl or optionally substituted non-enolizable alkyl, and when R_9 is $COOR_C$, R_C is optionally substituted alkyl, optionally substituted aryl, or optionally substituted arylalkyl.

49. The compound of any one of claims 46 to 48, wherein R_9 is SO_2R_C.

50. A compound of formula (IDc):

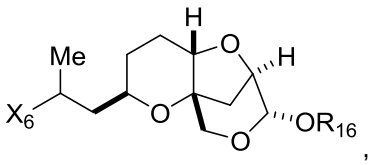


(IDc)

wherein

R_{16} is H, a hydroxyl protecting group, or an optionally substituted alkyl.

51. A compound of formula (IDd):



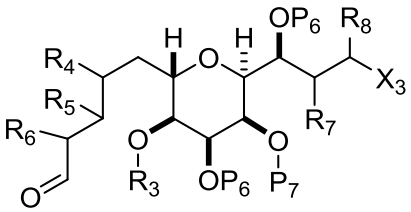
(IDd)

wherein

X_6 is $–C(R_{17})=CH_2$ or –C(O)–Me, wherein R_{17} is a pseudohalogen or halogen; and

R_{16} is H, a hydroxyl protecting group, or an optionally substituted alkyl.

52. A compound of formula (IF):



(IF),

wherein

X_3 is –CHO, $–CH_2OP_A$, $–CH=CH_2$, or $–CH(OP_A)CH_2OP_A$;

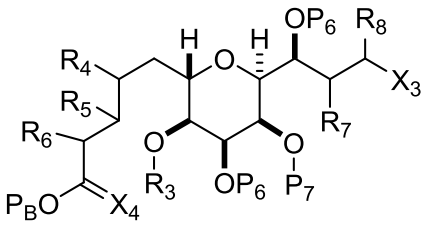
R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

R_7 and P_7 combine to form a bond, and R_8 is H; or P_7 is a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond; ~~and~~

each P_6 is independently a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal; and

each P_A is independently H or a hydroxyl protecting group, or both P_A combine to form a cyclic protected diol.

53. A compound of formula (IH):



(IH),

or a salt thereof,

where

X_3 is –CHO, $–CH_2OP_A$, $–CH=CH_2$, or $–CH(OP_A)CH_2OP_A$;

X_4 is =O or X_4, together with the carbon atom to which it is attached, combine to form $–CH_2–$;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

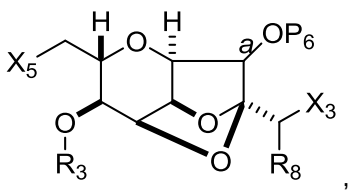
R_7 and P_7 combine to form a bond, and R_8 is H; or P_7 is a hydroxyl protecting group, and R_7 and R_8, together with the atoms to which each is attached, combine to form a double bond;

each P_6 is independently a hydroxyl protecting group, or both P_6, together with the atoms to which each is attached, combine to form a ketal or acetal;

each P_A is independently H or a hydroxyl protecting group, or both P_A combine to form a cyclic protected diol; and

P_B is H, a hydroxyl protecting group, or optionally substituted alkyl.

54. A compound of formula (IHa):



(IHa)

wherein

a identifies the carbon-oxygen bond as  or ,

X_3 is –CHO, $–CH_2OP_A$, $–CH=CH_2$, or $–CH(OP_A)CH_2OP_A$;

X_5 is $–CH=CH_2$ or $–CH(R_4)–CH(R_5)–CH(R_6)–C(X_4)OP_B$;

X_4 is =O or X_4, together with the carbon atom to which it is attached, combine to form $–CH_2–$;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

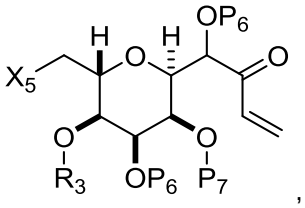
P_6 is a hydroxyl protecting group;

each P_A is independently H or a hydroxyl protecting group, or both P_A combine to form a cyclic protected diol;

P_B is H, a hydroxyl protecting group, or optionally substituted alkyl; and

R_8 is H.

55. A compound of formula (IHb):



(IHb)

wherein

X_5 is $–CH=CH_2$ or $–CH(R_4)–CH(R_5)–CH(R_6)–C(X_4)OP_B$;

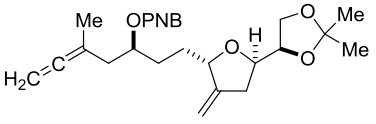
X_4 is =O or X_4, together with the carbon atom to which it is attached, combine to form $–CH_2–$;

R_3 and R_5 combine to form a bond, and each of R_4 and R_6 is H; or R_3 is H or a hydroxyl protecting group, R_5 and one of R_4 and R_6, together with the atoms to which each is attached, combine to form a double bond, and the remaining R_4 or R_6 is H;

each of P_6 and P_7 is independently a hydroxyl protecting group, or one P_6 and P_7, together with the atoms to which each is attached, combine to form a ketal, and the remaining P_6 is a hydroxyl protecting group; or both P_6, together with the atoms to which each is attached, combine to form a ketal, and P_7 is a hydroxyl protecting group; and

P_B is H, a hydroxyl protecting group, or optionally substituted alkyl.

56. A compound selected from the group consisting of:



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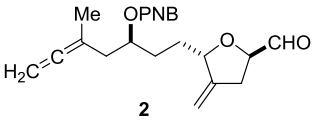

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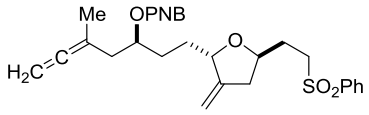

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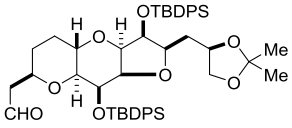

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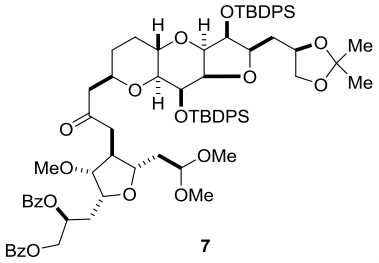

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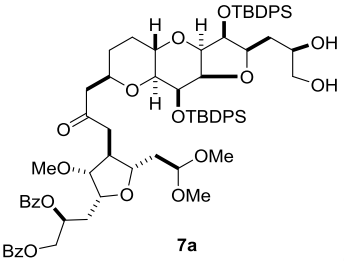

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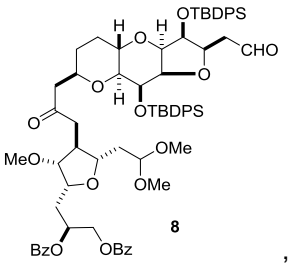

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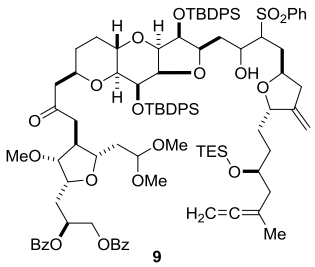

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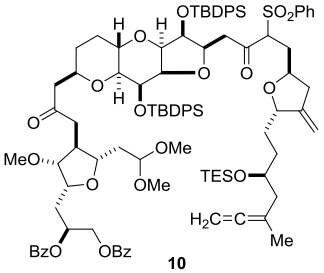

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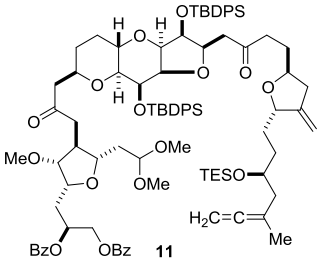

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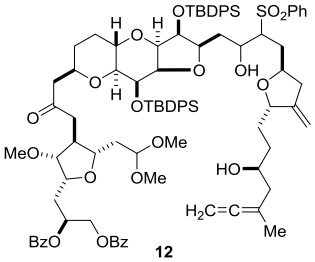

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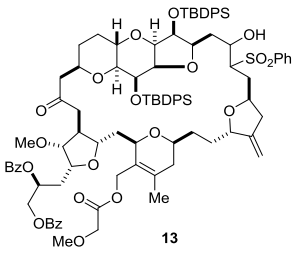

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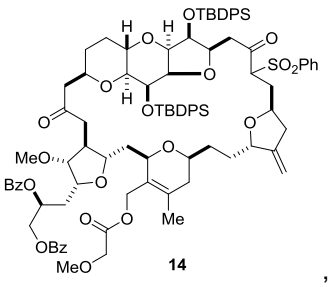

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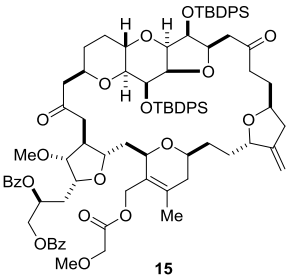

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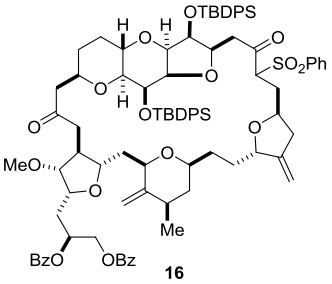

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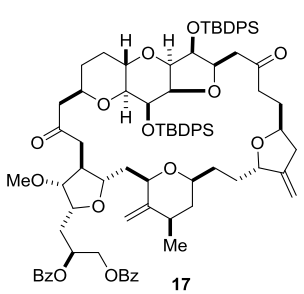
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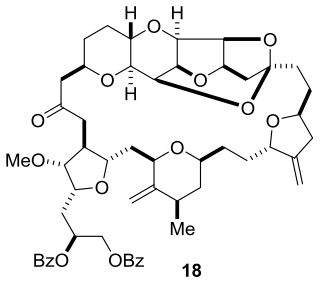
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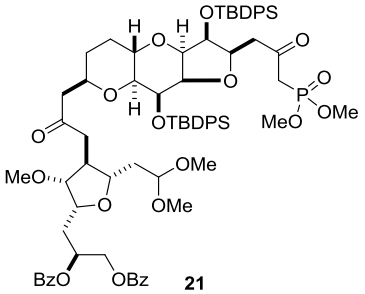
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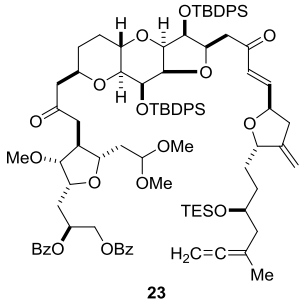
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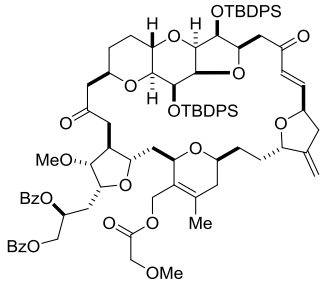
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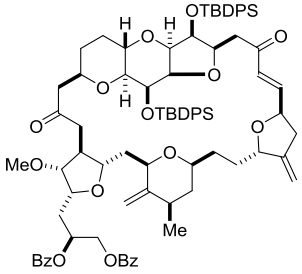
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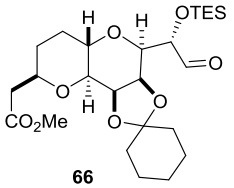
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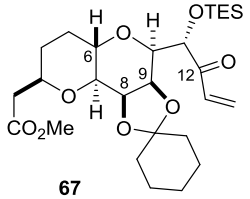
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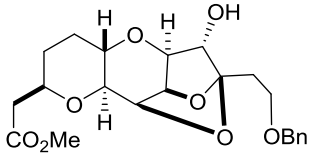
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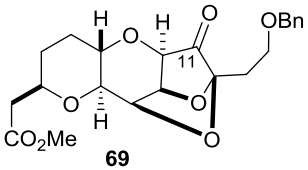
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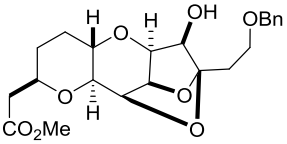
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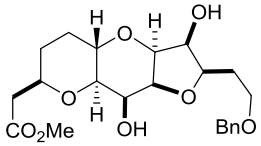
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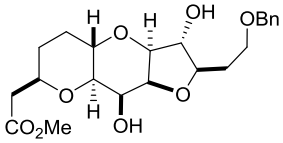
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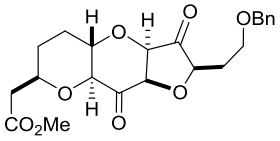
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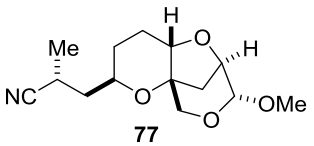
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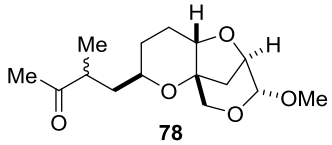
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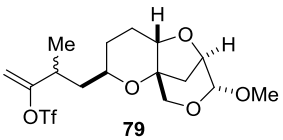
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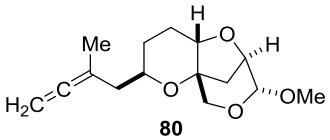
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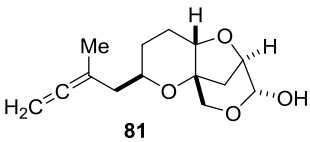
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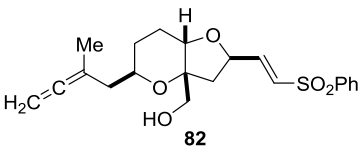
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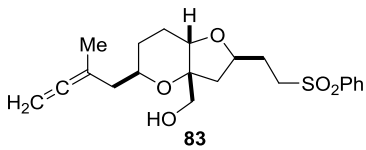
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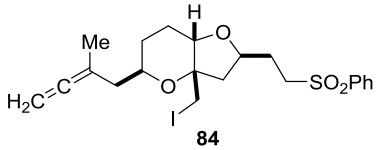
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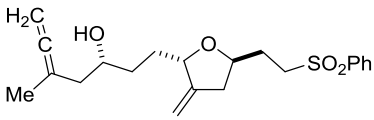
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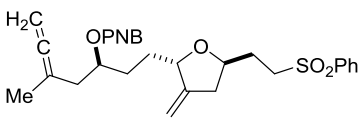
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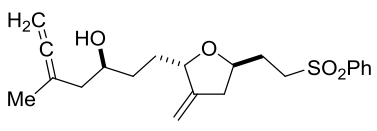
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