MACROCYCLIZATION REACTIONS AND INTERMEDIATES AND OTHER FRAGMENTS USEFUL IN THE SYNTHESIS OF HALICHONDRIN MACROLIDES

Background

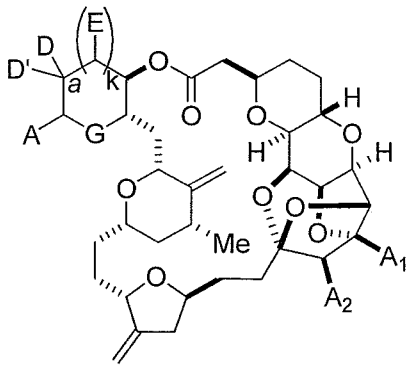
The invention relates to intermediates useful in the synthesis of pharmaceutically active macrolide compounds and methods of synthesizing macrolide compounds. Halichondrin B is a potent anticancer agent originally isolated from the marine sponge *Halichondria okadai*, and subsequently found in *Axinella* 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. 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 B and its analogs (e.g., macrolide analogs) are desirable.

Summary

In general, the present disclosure provides methods for macrocyclization of intermediates in the synthesis of a halichondrin macrolide. The disclosure also provides intermediates that can be employed in the macrocyclization reactions described herein.

In one aspect, the disclosure provides a method of preparing a macrocyclic intermediate in the synthesis of a halichondrin macrolide, said method comprising performing a macrocyclization reaction on a non-macrocyclic intermediate, said macrocyclization reaction producing said macrocyclic intermediate by forming C.2-C.3, C.3-C.4, C.12-C.13, C.15-C.16, C.19-C.20, or C.26-C.27 bond in the structure of the halichondrin macrolide.

In another aspect, the disclosure provides a method of preparing:



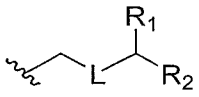
halichondrin macrolide

or a salt thereof,

wherein

each of A_1 and A_2 is independently H or OP", where each P" is independently H or a hydroxyl protecting group;

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; 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:



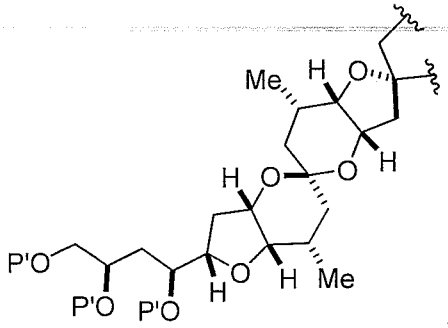
(1),

wherein

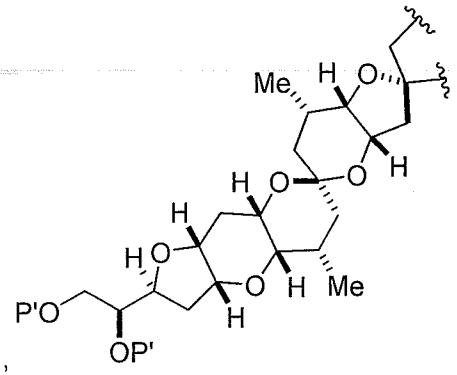
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

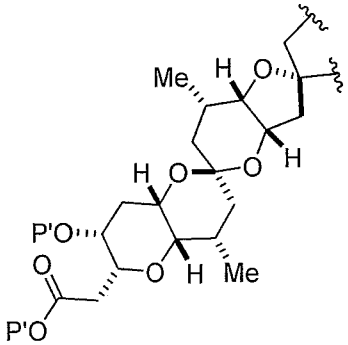
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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;

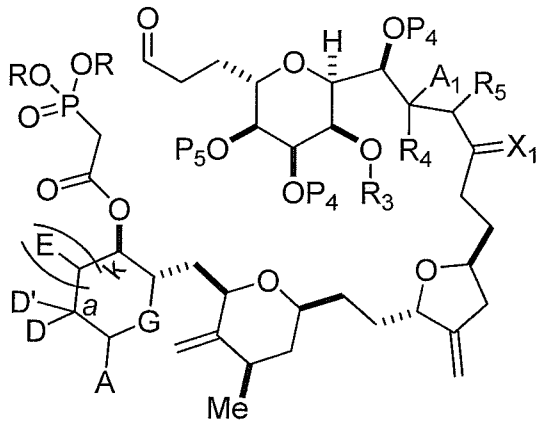
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl,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

k is 0 or 1;

n is 0, 1, or 2;

(1) said method comprising:

(A) producing a compound of formula (IB) from a compound of formula (IA), the compound of formula (IA) having the following structure:



(IA)

or a salt or a tautomer thereof,

wherein

each R is independently optionally substituted alkyl or optionally substituted aryl;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

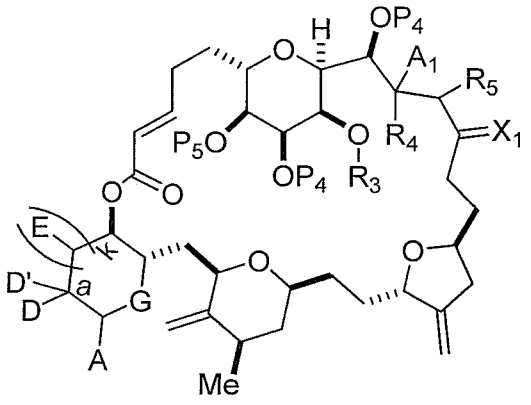
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

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



(IB)

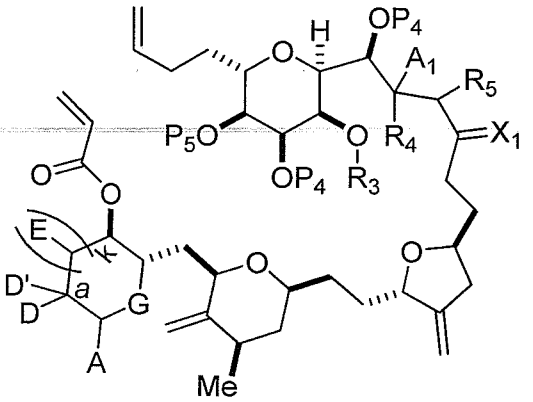
or a salt or a tautomer thereof;

and

(B) producing the halichondrin macrolide from compound (IB);

(2) said method comprising:

(A) producing a compound of formula (IB) from a compound of formula (IIA), the compound of formula (IIA) having the following structure:



(IIA)

or a salt or a tautomer thereof,

wherein

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

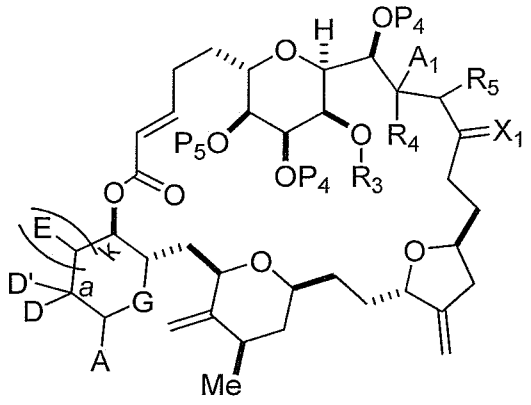
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

The compound of formula (IB) having the following structure:



(IB)

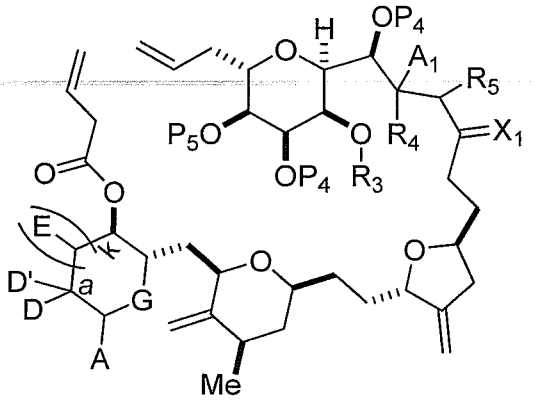
or a salt or a tautomer thereof;

and

(B) producing the halichondrin macrolide from compound (IB);

(3) said method comprising:

(A) producing a compound of formula (IIIB) from a compound of formula (IIIA), the compound of formula (IIIA) having the following structure:



(IIIA)

or a salt or a tautomer thereof,

wherein

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

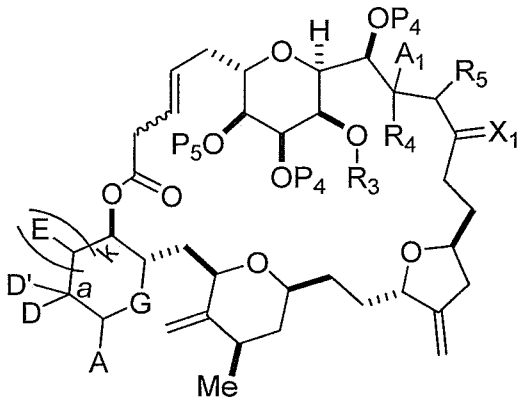
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is –(CH(OP$_Y$))–, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

the compound of formula (IIIB) having the following structure:



(IIIB),

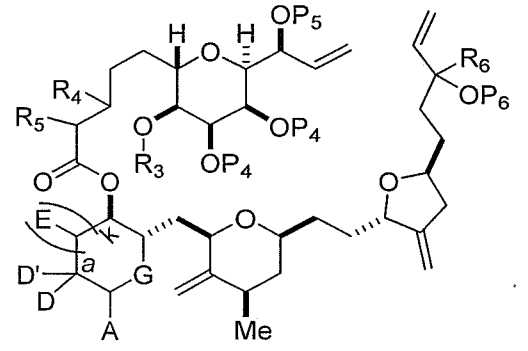
or a salt or a tautomer thereof;

and

(B) producing the halichondrin macrolide from the compound of formula (IIIB);

(4) said method comprising:

(A) producing a compound of formula (IVB) from a compound of formula (IVA), the compound of formula (IVA) having the following structure:



(IVA)

or a salt thereof,

wherein

(i) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(ii) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

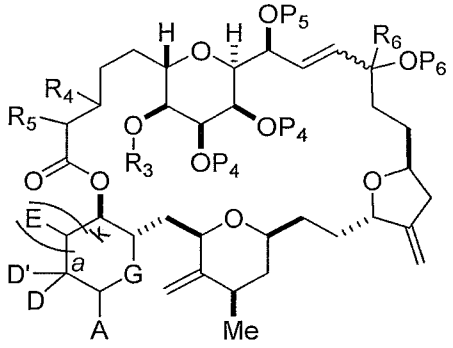
or

(iii) R_3 and R_4 combine to form a bond, and R_5 is H;

each P_4 and P_5 is independently H or a hydroxyl protecting group;

R_6 is H, and P_6 is H or a hydroxyl protecting group; or R_6 and P_6 combine to form a double bond; and

the compound of formula (IVB) having the following structure:



(IVB)

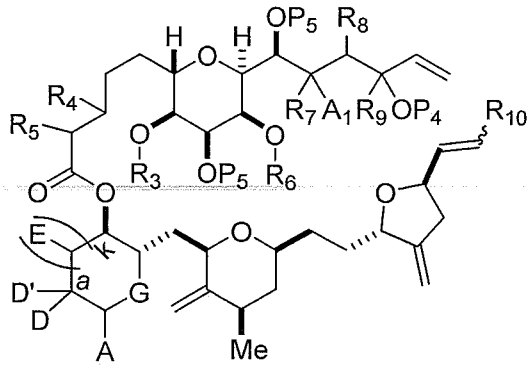
or a salt thereof;

and

(B) producing the halichondrin macrolide from the compound of formula (IVB);

(5) said method comprising:

(A) producing a compound of formula (VB) from a compound of formula (VA), the compound of formula (VA) having the following structure:



(VA)

or a salt or a tautomer thereof,

wherein

(a1) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(a2) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(a3) R_3 and R_4 combine to form a bond, and R_5 is H;

(b1) A_1 and R_7 combine to form oxo, R_6 is H or a hydroxyl protecting group, and R_8 is H;

or

(b2) A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_6 is H or a hydroxyl protecting group, and R_7 and R_8 combine to form a double bond;

or

(ii) R_6 and R_7 combine to form a bond, and R_8 is H or OP";

(c1) R_9 is H, and P_4 is H or a hydroxyl protecting group;

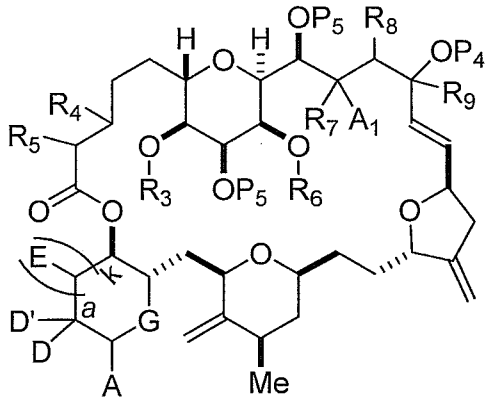
or

(c2) R_9 and P_4 combine to form a double bond;

R_{10} is H or $-CH_2X_1CH_2CH=CH_2$, wherein X_1 is O, $-C(R_{11})_2-$, or NP_6, and wherein each R_{11} is independently H or $-COOR_{12}$, P_6 is an *N*-protecting group, and R_{12} is alkyl;

each P_5 is independently H or a hydroxyl protecting group; and

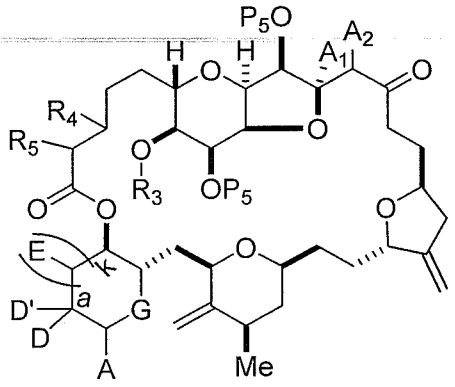
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (VB):



(VB)

or a salt or a tautomer thereof;

(B) producing a compound of formula (VC) from the compound of formula (VB), the compound of formula (VC) having the following structure:

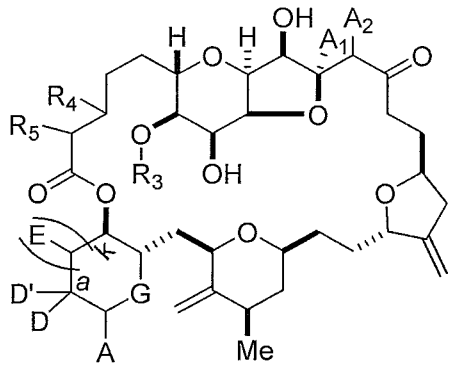


(VC)

or a salt thereof,

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

(C) producing a compound of formula (IVC) from the compound of formula (VC), the compound of formula (IVC) having the following structure:



(IVC)

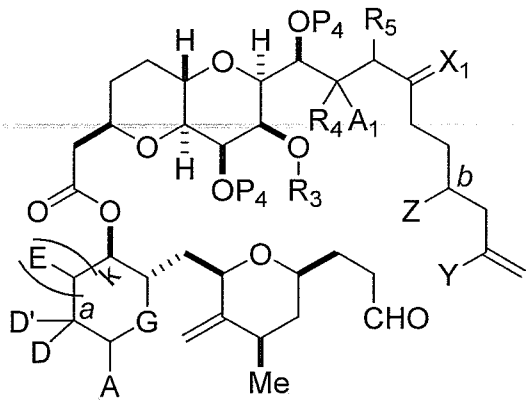
or a salt thereof,

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

(D) producing the halichondrin macrolide from the compound of formula (IVC);

(6) said method comprising:

(A) producing a compound of formula (VIB) from a compound of formula (VIA), the compound of formula (VIA) having the following structure:



(VIA)

or a salt or a tautomer thereof,

wherein

Y is iodide, bromide, or trifluoromethanesulfonate;

b designates (*R*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide; or *b* designates (*S*)-stereogenic center, and Z is OR_6, wherein R_6 is a hydroxyl protecting group;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

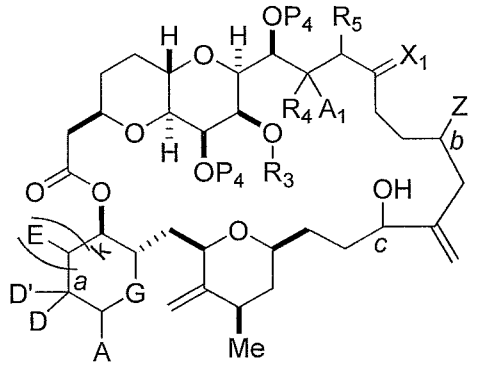
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

and each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

the compound of formula (VIB) having the following structure:



(VIB)

or a salt or a tautomer thereof,

wherein

b designates (*R*)-stereogenic center, *c* designates (*S*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide;

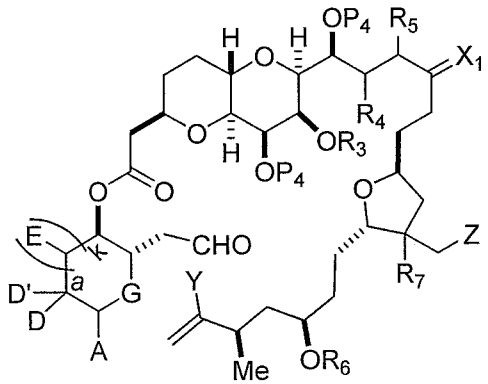
or

b designates (*S*)-stereogenic center, *c* designates (*R*)-stereogenic center, and Z is OR_6, wherein R_6 is a hydroxyl protecting group;

(B) producing the halichondrin macrolide from the compound of formula (VIB); or

(7) said method comprising:

(A) producing a compound of formula (VIIB) from a compound of formula (VIIA), the compound of formula (VIIA) having the following structure:



(VIIA)

or a salt thereof,

wherein

Y is iodide, bromide, or trifluoromethanesulfonate;

(a1) R_3 is H or a hydroxyl protecting group, R_4 and R_5 combine to form a double bond, each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$;

or

(a2) R_3 and R_4 combine to form a bond, R_5 is H, and

each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$;

or

both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(b1) Z is chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond;

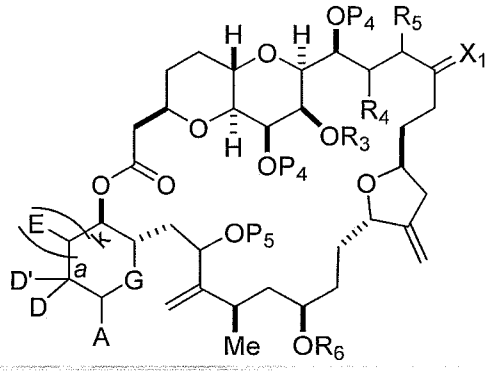
or

(b2) Z and R_7 combine to form a double bond, and R_6 is a hydroxyl protecting group;

and

wherein R_8 is H or a hydroxyl protecting group

the compound of formula (VIIB) having the following structure:

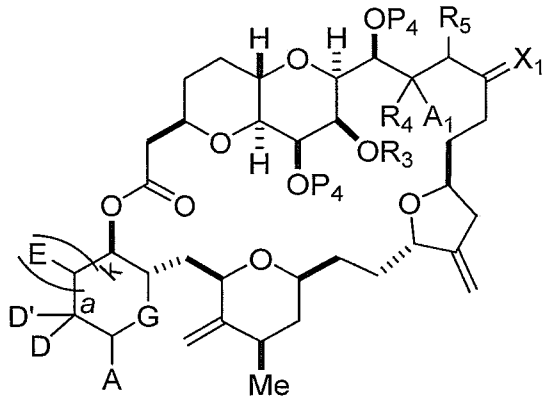


(VIIB)

or a salt thereof,

wherein each of P_5 and R_6 is H or a hydroxyl protecting group;

(B) producing a compound of formula (VIIC) from the compound of formula (VIIB), the compound of formula (VIIC) having the following structure:



(VIIC)

or a salt or a tautomer thereof,

wherein A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

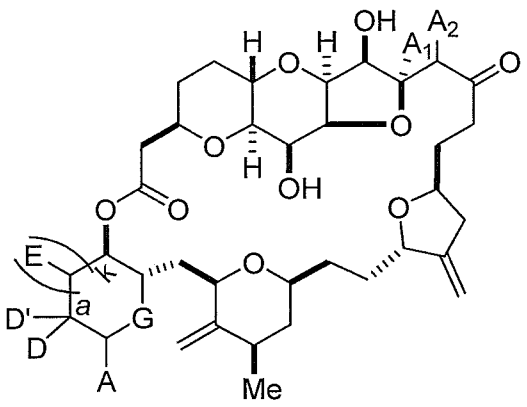
A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

(C) producing a compound of formula (VIID) from the compound of formula (VIIC), the compound of formula (VIID) having the following structure:



(VIID)

or a salt thereof,

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

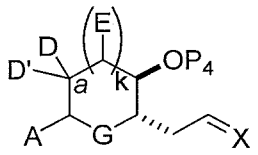
and

(D) producing the halichondrin macrolide from the compound of formula (VIID).

In another aspect, the disclosure provides a method of preparing an intermediate in the synthesis of a halichondrin macrolide, said method comprising performing an allene-Prins reaction by contacting a compound of formula (VIIIA) with a compound of formula (VIIIB) and R_4OH,

wherein R_4 is an optionally substituted acyl;

wherein the compound of formula (VIIIA) has the following structure:

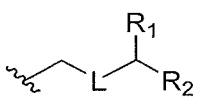


(VIIIA)

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; 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:



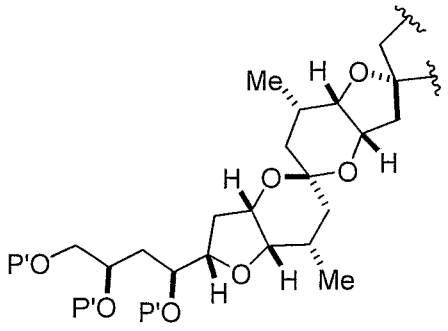
(1),

wherein

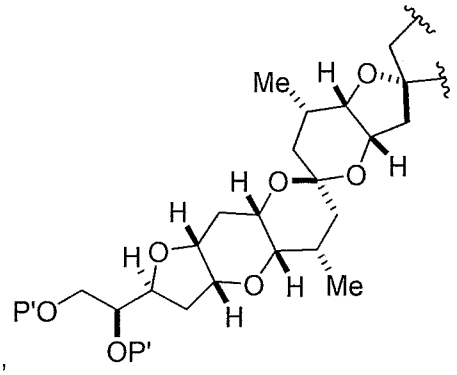
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

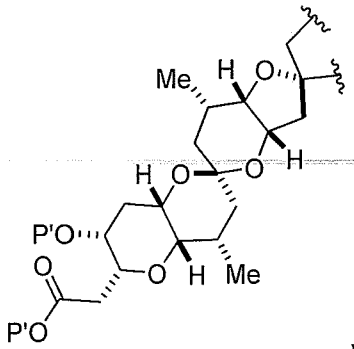
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

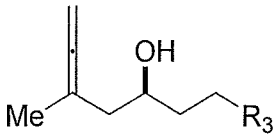
k is 0 or 1;

n is 0, 1, or 2;

X is O, or X, together with the carbon atom to which it is attached, forms $-(C(OP_Z)_2)-$, wherein each P_Z is independently optionally substituted alkyl or optionally substituted aryl, or both P_Z combine to form optionally substituted alkylene or optionally substituted arylene; and

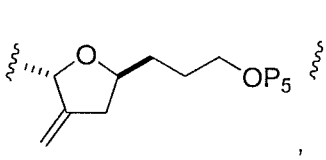
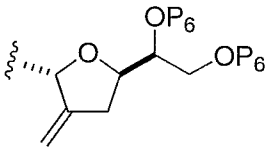
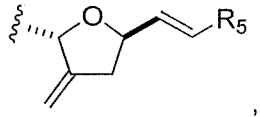
P_4 is H or a hydroxyl protecting group;

wherein the compound of formula (VIIIB) has the following structure:



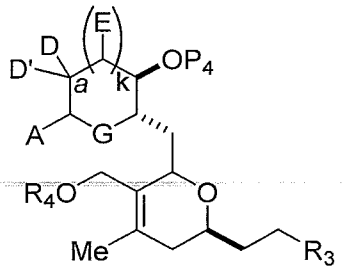
(VIIIB),

wherein

R_3 is $-CH_2-OP_5$, $-CH=CH_2$, , , or ,

wherein P_5 is H or a hydroxyl protecting group; each P_6 is independently a hydroxyl protecting group, or both P_6 groups, together with the atoms to which each is attached, combine to form a cyclic protected diol; and R_5 is is H or -$CH_2X_1CH_2CH=CH_2$, wherein X_1 is O, -CH_2-, or NP_7, wherein P_7 is a sulfonyl;

and wherein said intermediate is a compound of formula (VIIIC):

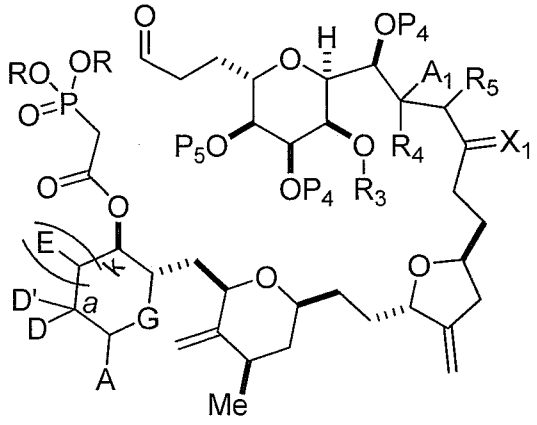


(VIIIC)

or a salt thereof.

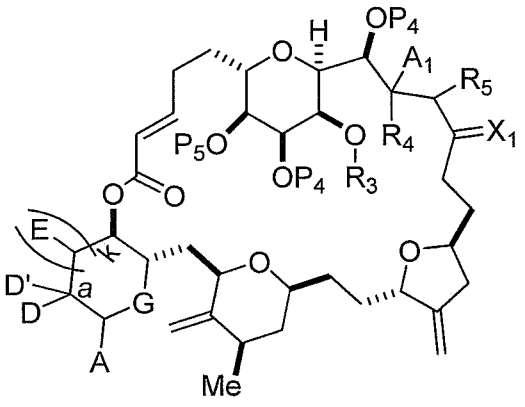
In yet another aspect, the disclosure provides a compound of

(1) formula (IA) or formula (IB),



(IA)

or



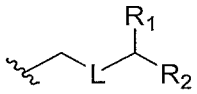
(IB)

or a salt or a tautomer thereof,

wherein

each R is independently optionally substituted alkyl or optionally substituted aryl;

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; 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:



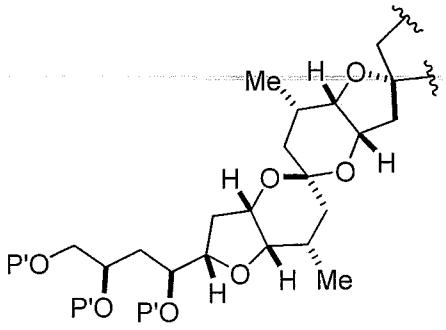
(1),

wherein

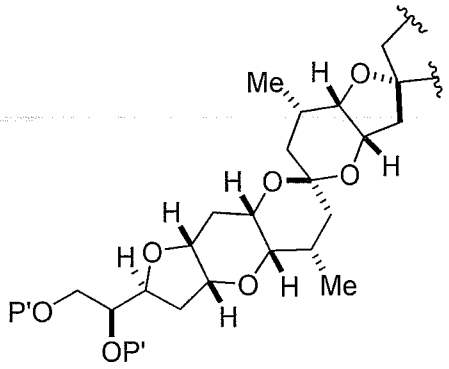
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

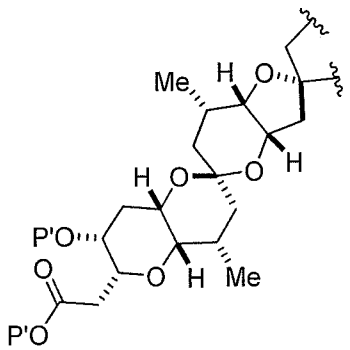
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

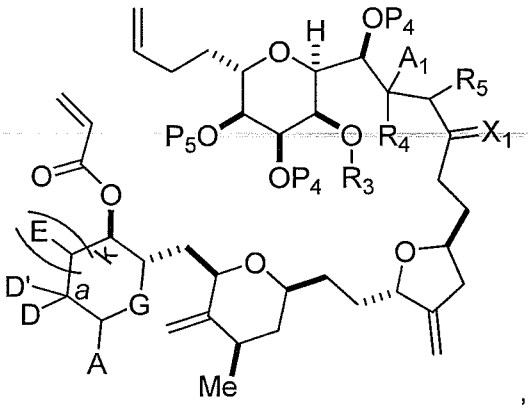
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

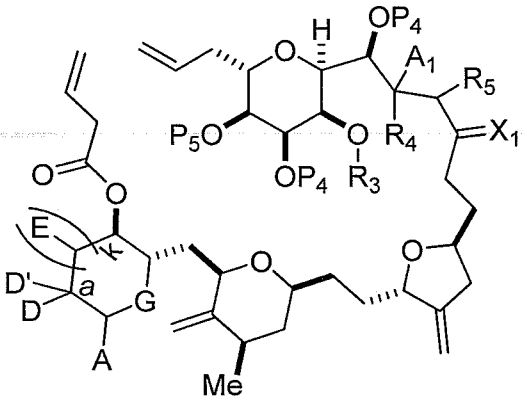
each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group;

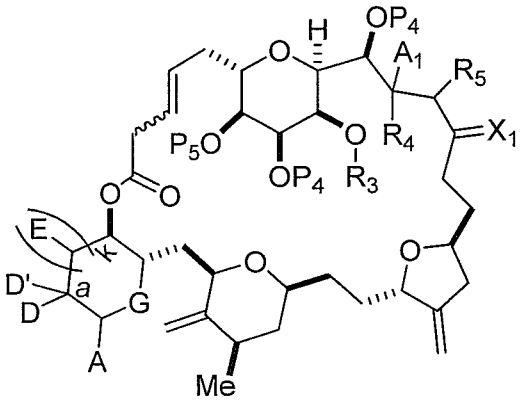
(2) formula (IIA), formula (IIIA), or formula (IIIB):



(IIA)



(IIIA), or

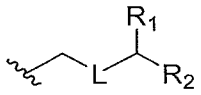


(IIIB)

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; 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:



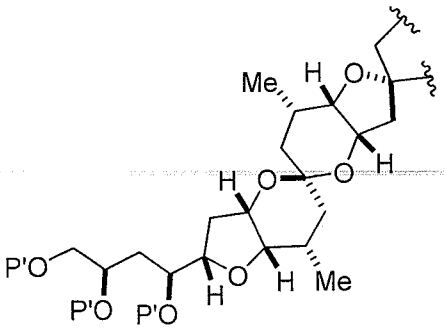
(1),

wherein

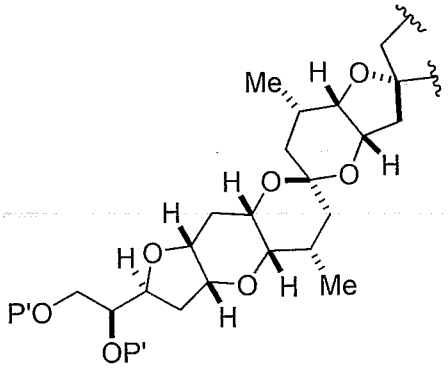
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

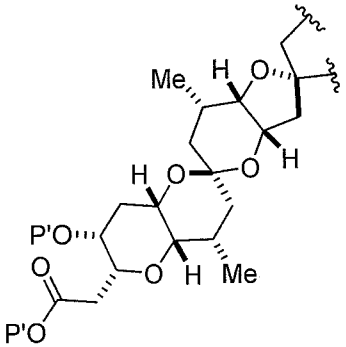
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

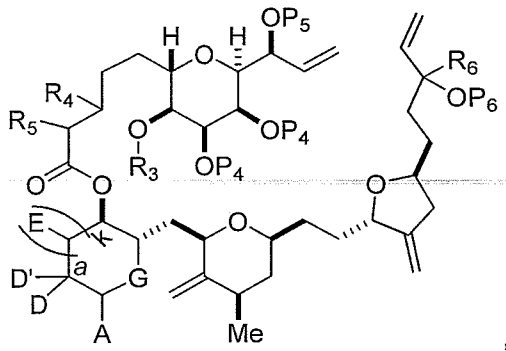
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

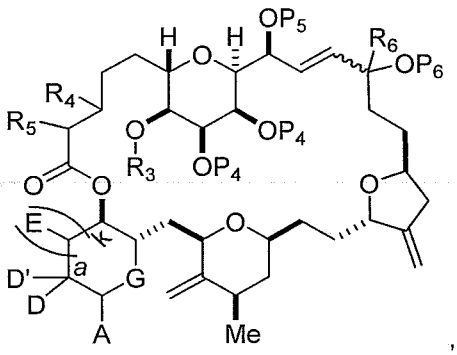
each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group;

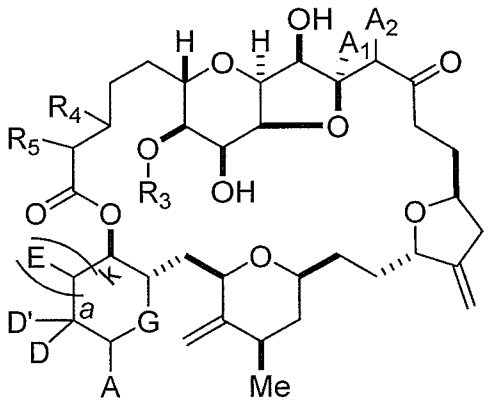
(3) formula (IVA), formula (IVB), or formula (IVC):



(IVA)



(IVB)



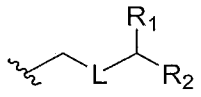
(IVC)

or a salt thereof,

wherein

each of A_1 and A_2 is H or OP", where P" is H or a hydroxyl protecting group;

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; 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:



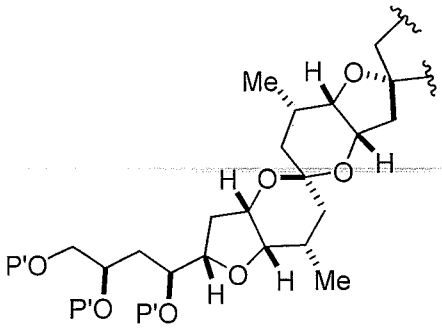
(1),

wherein

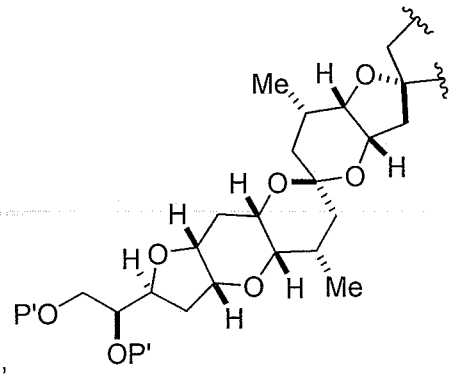
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

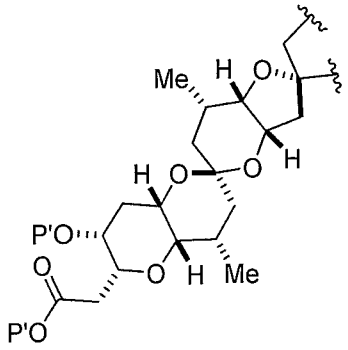
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(i) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(ii) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

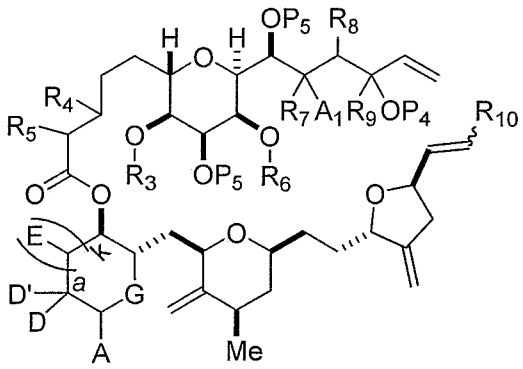
or

(iii) R_3 and R_4 combine to form a bond, and R_5 is H;

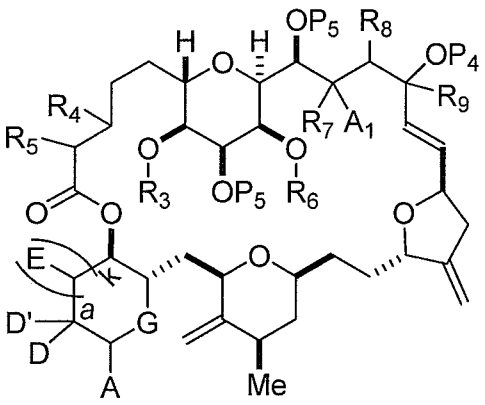
each P_4 and P_5 is independently H or a hydroxyl protecting group; and

R_6 is H, and P_6 is H or a hydroxyl protecting group; or R_6 and P_6 combine to form a double bond;

(4) formula (VA), formula (VB), or formula (VC):

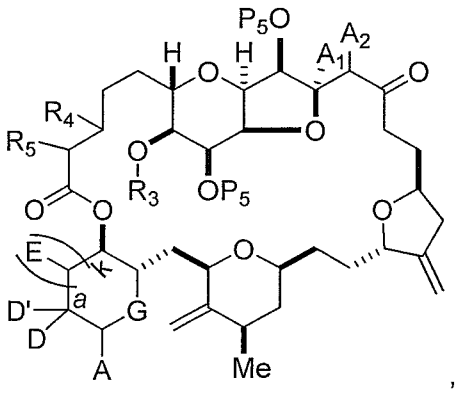


(VA)



(VB)

, or

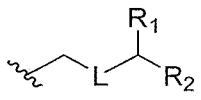


(VC)

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; 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:



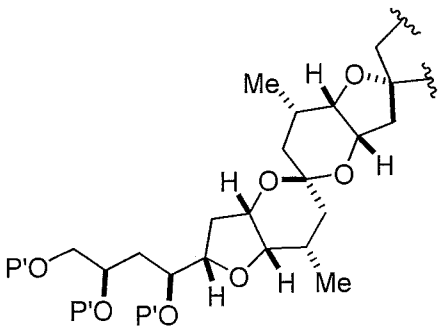
(1),

wherein

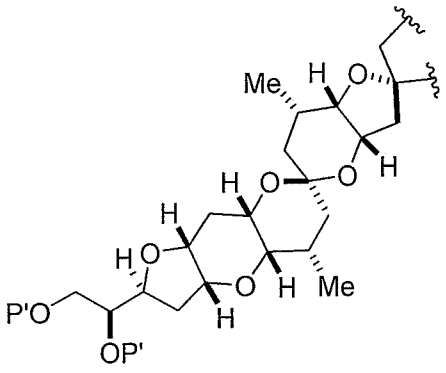
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

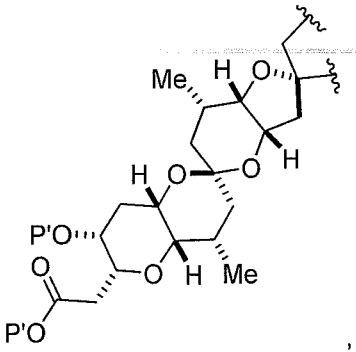
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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;

A_2 is H or OP";

E is 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(a1) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(a2) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(a3) R_3 and R_4 combine to form a bond, and R_5 is H;

(b1) A_1 and R_7 combine to form oxo, R_6 is H or a hydroxyl protecting group, and R_8 is H;

or

(b2) A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_6 is H or a hydroxyl protecting group, and R_7 and R_8 combine to form a double bond;

or

(ii) R_6 and R_7 combine to form a bond, and R_8 is H or OP";

(c1) R_9 is H, and P_4 is H or a hydroxyl protecting group;

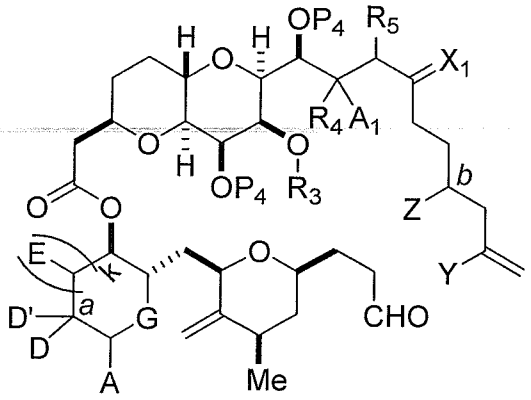
or

(c2) R_9 and P_4 combine to form a double bond;

R_{10} is H or $-CH_2X_1CH_2CH=CH_2$, wherein X_1 is O, $-C(R_{11})_2-$, or NP_6, and wherein each R_{11} is independently H or $-COOR_{12}$, P_6 is an *N*-protecting group, and R_{12} is alkyl;

each P_5 is independently H or a hydroxyl protecting group;

(5) formula (VIA):

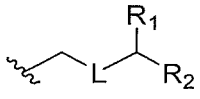


(VIA)

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; 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:



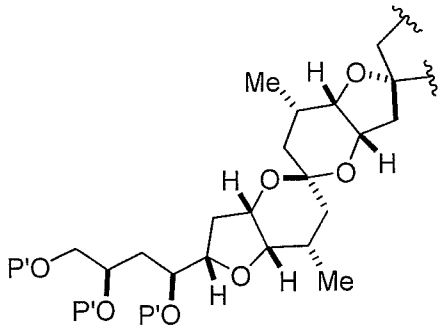
(1),

wherein

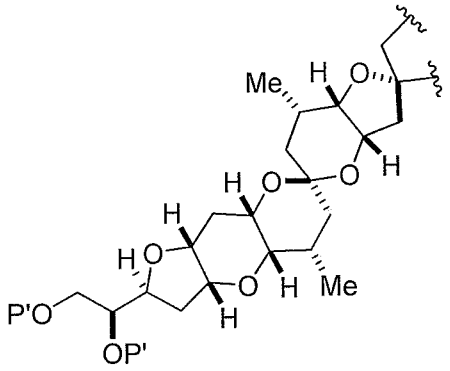
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

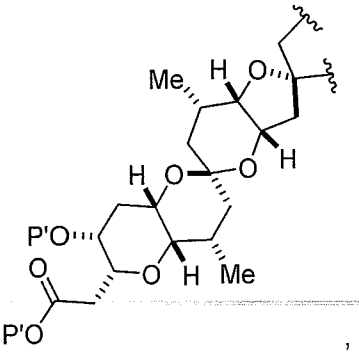
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

Y is iodide, bromide, or trifluoromethanesulfonate;

b designates (*R*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide; or *b* designates (*S*)-stereogenic center, and Z is OR_6, wherein R_6 is a hydroxyl protecting group;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

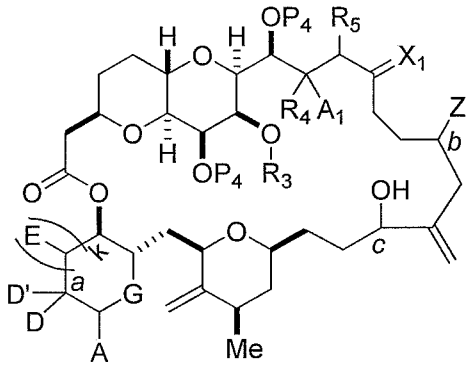
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(6) formula (VIB):



(VIB)

or a salt or a tautomer thereof,

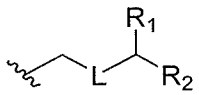
wherein

b designates (*R*)-stereogenic center, *c* designates (*S*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide;

or

b designates (*S*)-stereogenic center, *c* designates (*R*)-stereogenic center, and Z is OR_6, wherein R_6 is a hydroxyl protecting group;

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; 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),

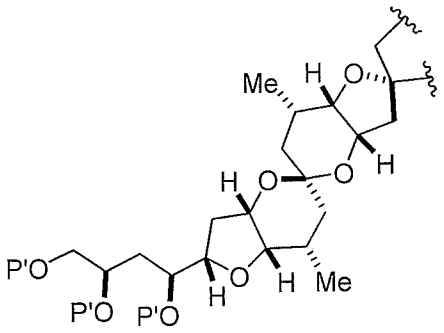
wherein

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

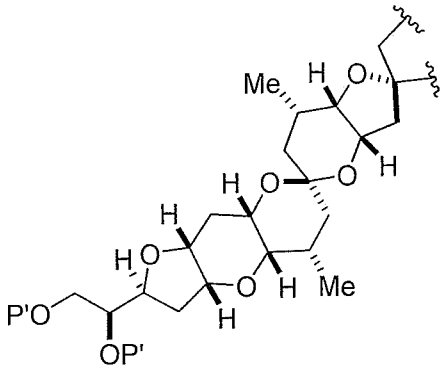
R_1 is H, or R_1 and P_1 combine to form a bond;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo;

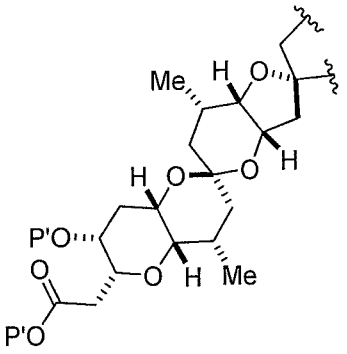
or R_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

E is 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

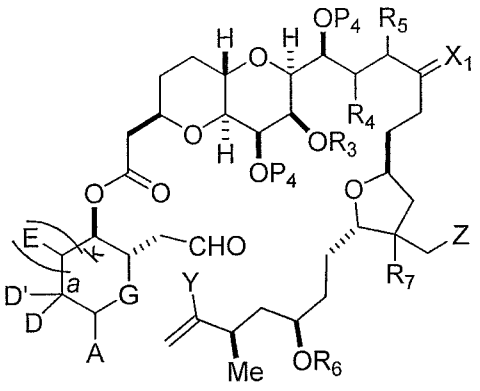
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

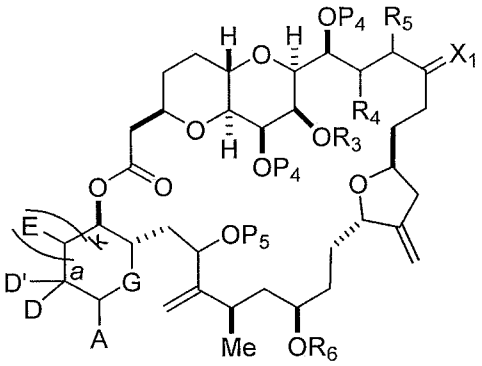
(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(7) formula (VIIA) or formula (VIIB):



or

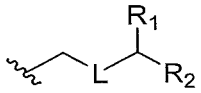


(VIIA) (VIIB)

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; 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:



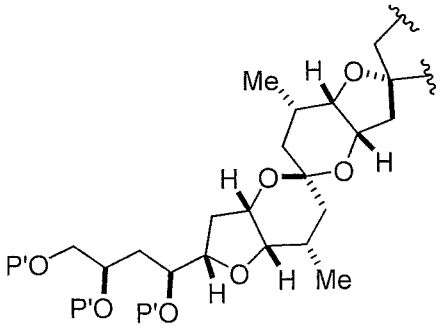
(1),

wherein

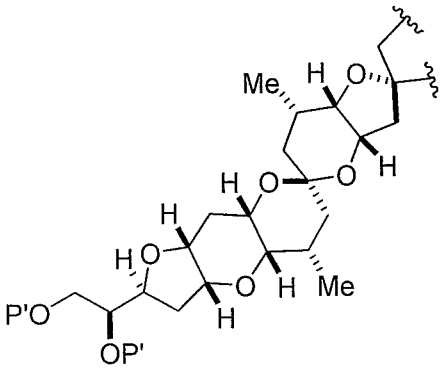
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

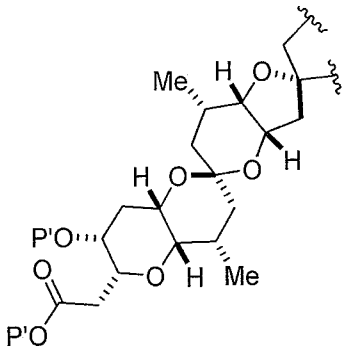
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(a1) R_3 is H or a hydroxyl protecting group, R_4 and R_5 combine to form a double bond, each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$;

or

(a2) R_3 and R_4 combine to form a bond, R_5 is H, and

each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$;

or

both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(b1) Z is chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond;

(b2) Z and R_7 combine to form a double bond, and R_6 is a hydroxyl protecting group;

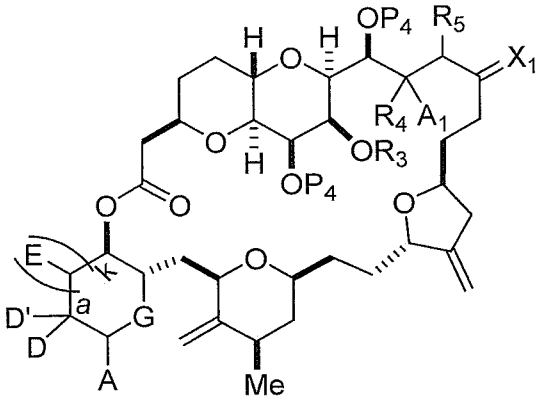
or

(b3) when Z and R_7 are absent, R_6 is H or a hydroxyl protecting group;

P_5 is H or a hydroxyl protecting group;

wherein R_8 is H or a hydroxyl protecting group; or

(8) formula (VIIC):

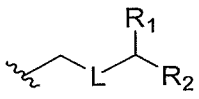


(VIIC)

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; 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:



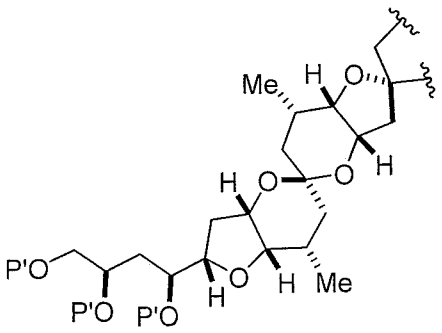
(1),

wherein

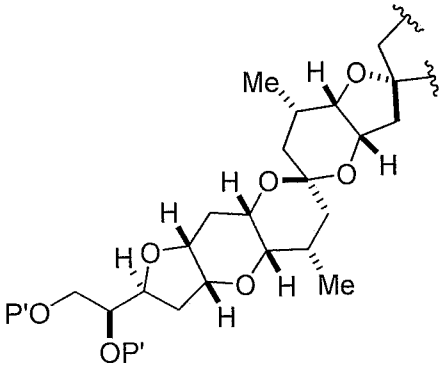
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

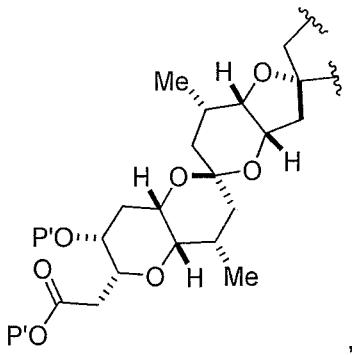
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

each P_4 is H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form a ketal; and

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

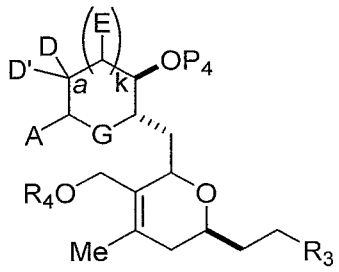
A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP".

In yet another aspect, the disclosure provides a compound of formula (VIIC):

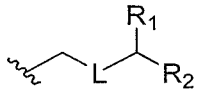


(VIIIC)

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; 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:



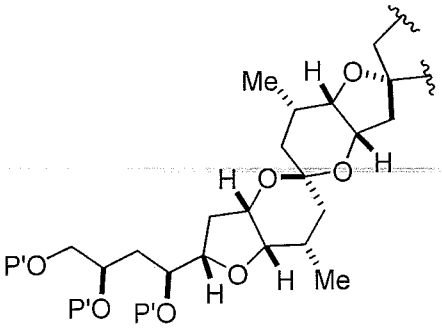
(1),

wherein

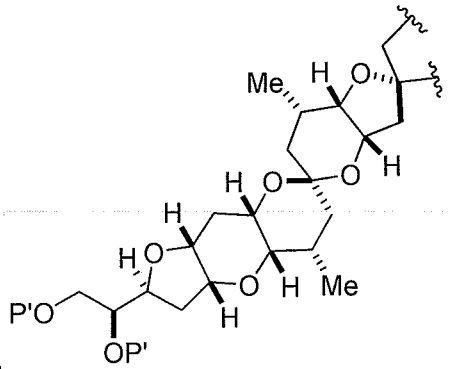
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

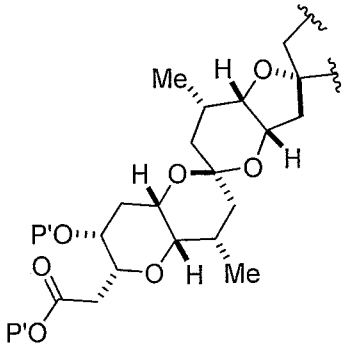
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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;

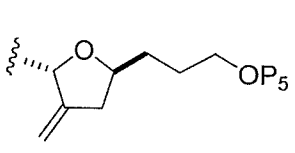
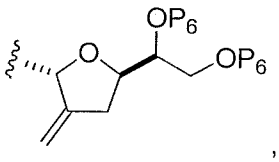
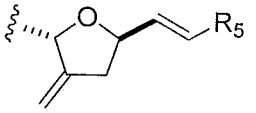
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl, alkoxyaryl,

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

k is 0 or 1;

n is 0, 1, or 2;

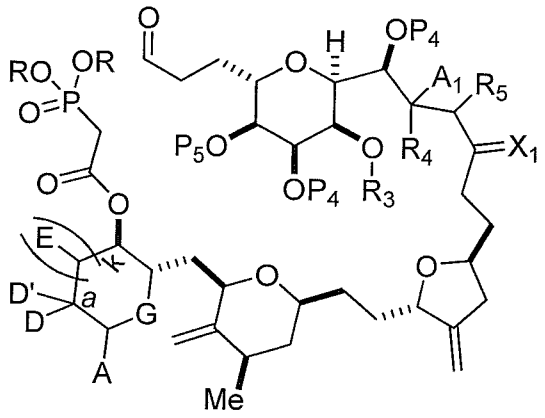
P_4 is H or a hydroxyl protecting group; and

R_3 is $-CH_2-OP_5$, $-CH=CH_2$, , , or ,

wherein P_5 is H or a hydroxyl protecting group; each P_6 is independently a hydroxyl protecting group, or both P_6 groups, together with the atoms to which each is attached, combine to form a cyclic protected diol; and R_5 is is H or $-CH_2X_1CH_2CH=CH_2$, wherein X_1 is O, $-CH_2-$, or NP_7, wherein P_7 is a sulfonyl.

As described herein, the disclosure provides a method of preparing a macrocyclic intermediate in the synthesis of a halichondrin macrolide, the method involving performing a macrocyclization reaction on a non-macrocyclic intermediate, the macrocyclization reaction producing the macrocyclic intermediate by forming C.2-C.3, C.3-C.4, C.12-C.13, C.15-C.16, C.19-C.20, or C.26-C.27 bond in the structure of the halichondrin macrolide.

In some examples, performing the macrocyclization reaction involves contacting the non-macrocyclic intermediate (e.g., a compound of formula (IA)) with an organic base (e.g., DBU or triethylamine) and a Lewis acid (e.g., a salt of Li or Zn). The non-macrocyclic intermediate can be a compound of formula (IA):



(IA)

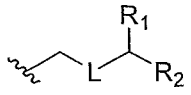
or a salt or a tautomer thereof,

where

each R is independently optionally substituted alkyl or optionally substituted aryl;

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; 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:



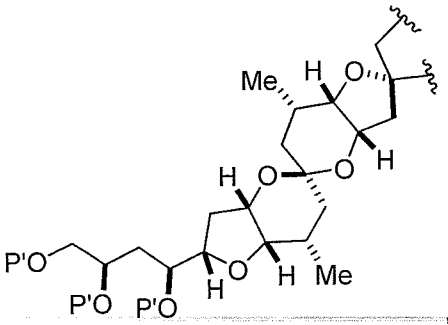
(1),

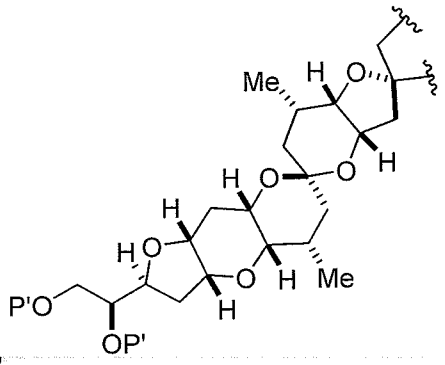
where

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

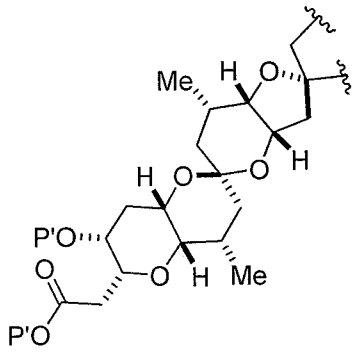
R_1 is H, or R_1 and P_1 combine to form a bond;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

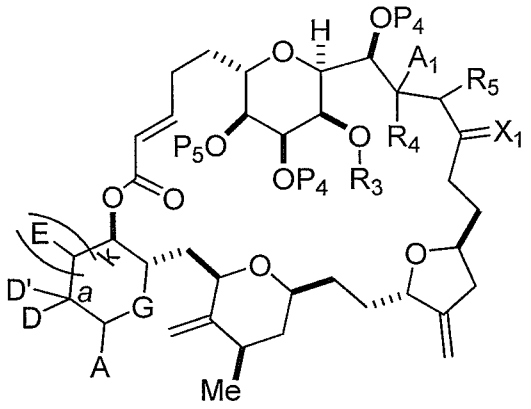
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

the macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IB):



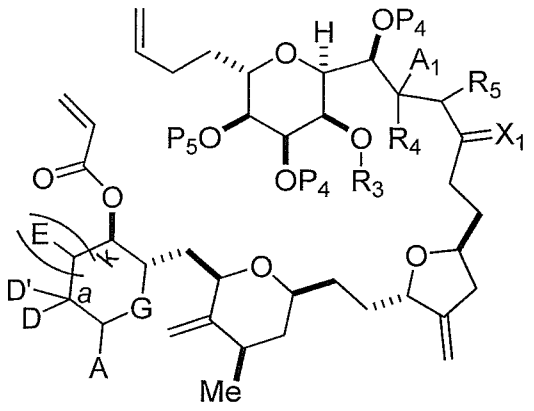
(IB)

or a salt or a tautomer thereof.

In formula (IA) or (IB), each R can be optionally substituted C_{1-6} alkyl. In formula (IA) or (IB), both P_4 groups and X_1, together with the atoms to which each is attached, can combine to form ketal. In formula (IA) or (IB), X_1, together with the carbon atom to which it is attached, can be $-(CH(OP_Y))-$, where P_Y is H or a hydroxyl protecting group. In formula (IA) or (IB), P_5 can be a hydroxyl protecting group. In formula (IA) or (IB), R_3 and R_4 can combine to form a bond, and R_5 can be H.

In particular examples, performing the macrocyclization reaction involves contacting the non-macrocyclic intermediate (e.g., a compound of formula (IIA), formula (IIIA), formula (IVA), or formula (VA)) with an olefin metathesis catalyst (e.g., a ruthenium-carbene complex).

The non-macrocyclic intermediate can be a compound of formula (IIA):

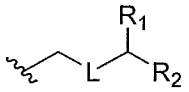


(IIA)

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; 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:



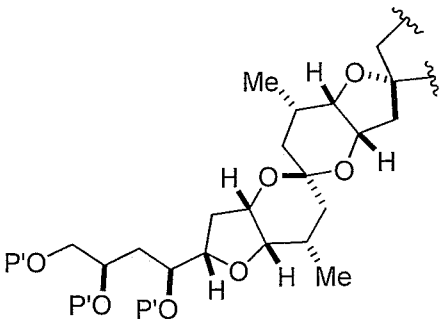
(1),

where

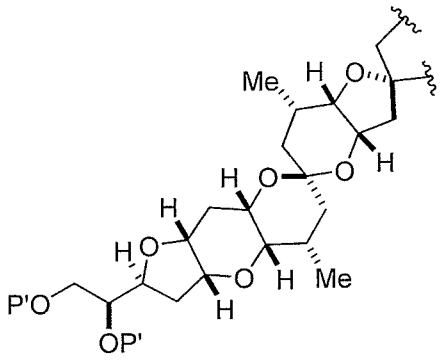
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

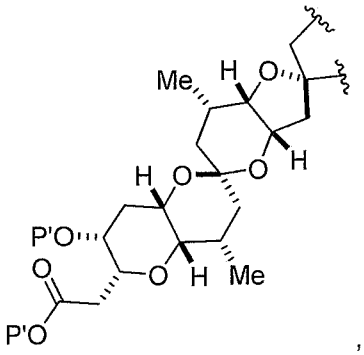
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

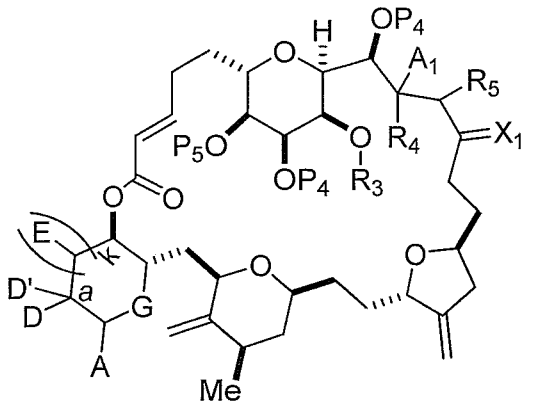
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

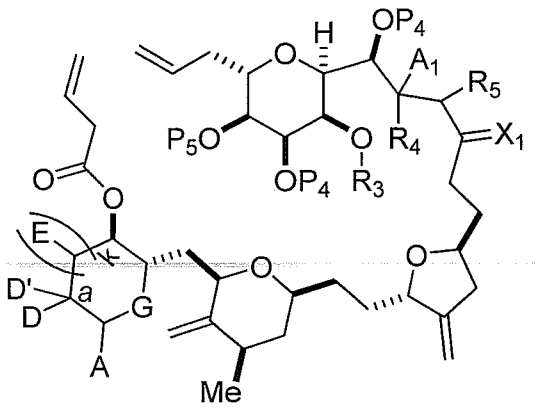
where the macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IB):



(IB)

or a salt or a tautomer thereof.

The non-macrocyclic intermediate can be a compound of formula (IIIA):

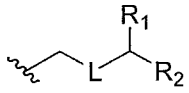


(IIIA)

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; 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),

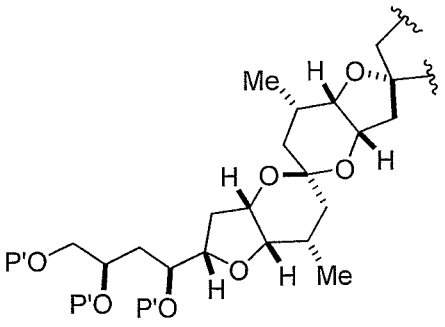
where

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

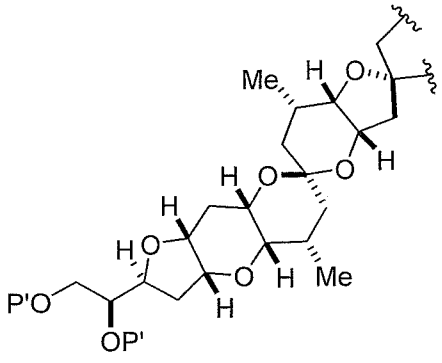
R_1 is H, or R_1 and P_1 combine to form a bond;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is

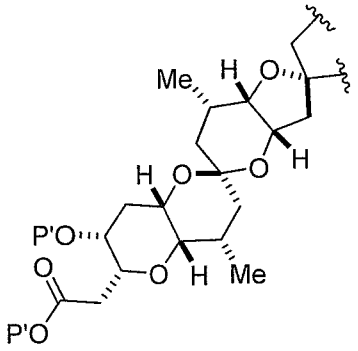
attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

E is 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

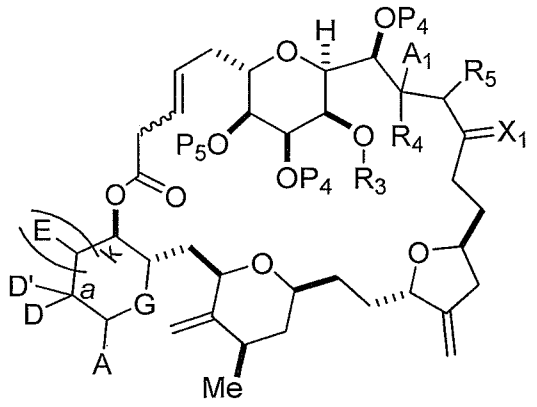
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

where the macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IIIB):

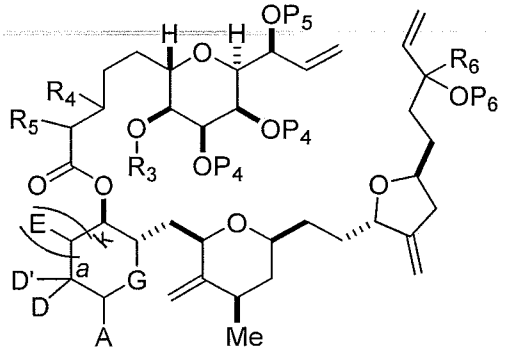


(IIIB)

or a salt or a tautomer thereof.

In formula (IIA), (IIB), (IIIA), or (IIIB), both P_4 groups and X_1, together with the atoms to which each is attached, can combine to form ketal. In formula (IIA), (IIB), (IIIA), or (IIIB), P_5 can be a hydroxyl protecting group. In formula (IIA), (IIB), (IIIA), or (IIIB), X_1, together with the carbon atom to which it is attached, can be $-(CH(OP_Y))-$, where P_Y is H. In formula (IIA), (IIB), (IIIA), or (IIIB), X_1 can be oxo.

the non-macrocyclic intermediate is a compound of formula (IVA):

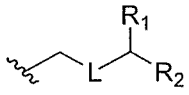


(IVA)

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; 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:



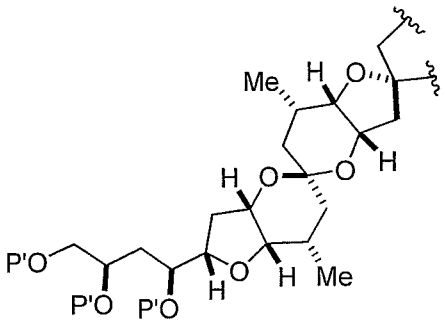
(1),

where

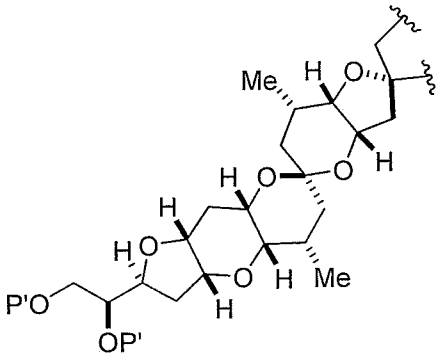
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

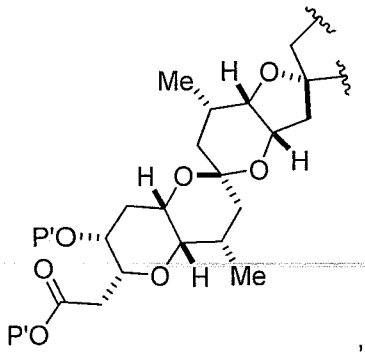
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(i) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(ii) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

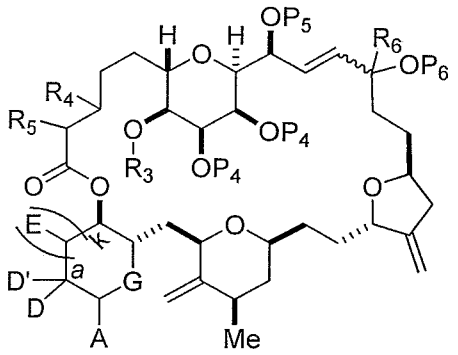
or

(iii) R_3 and R_4 combine to form a bond, and R_5 is H;

each P_4 and P_5 is independently H or a hydroxyl protecting group;

R_6 is H, and P_6 is H or a hydroxyl protecting group; or R_6 and P_6 combine to form a double bond; and

where the macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IVB):

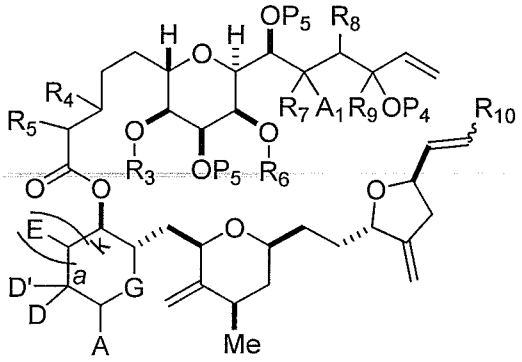


(IVB)

or a salt thereof.

In formula (IVA) or (IVB), at least one of P_4 and P_5 can be H. In formula (IVA) or (IVB), R_6 and P_6 can combine to form a double bond.

The non-macrocyclic intermediate can be a compound of formula (VA):

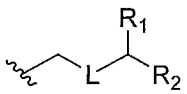


(VA)

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; 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:



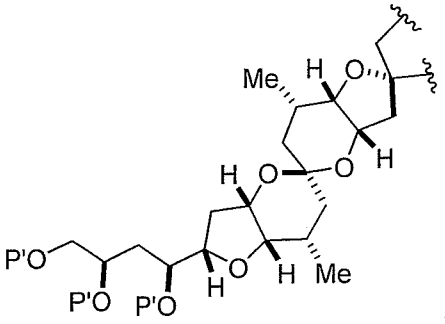
(1),

where

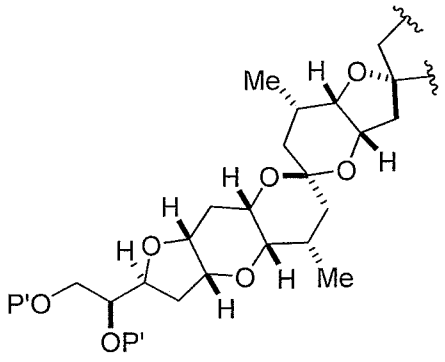
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

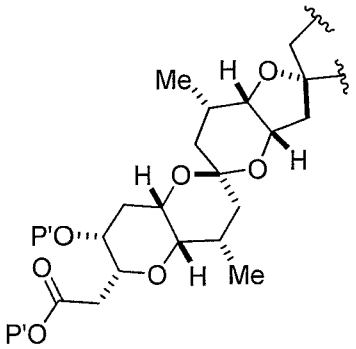
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(a1) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(a2) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(a3) R_3 and R_4 combine to form a bond, and R_5 is H;

(b1) A_1 and R_7 combine to form oxo, R_6 is H or a hydroxyl protecting group, and R_8 is H;

or

(b2) A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_6 is H or a hydroxyl protecting group, and R_7 and R_8 combine to form a double bond;

or

(ii) R_6 and R_7 combine to form a bond, and R_8 is H or OP";

(c1) R_9 is H, and P_4 is H or a hydroxyl protecting group;

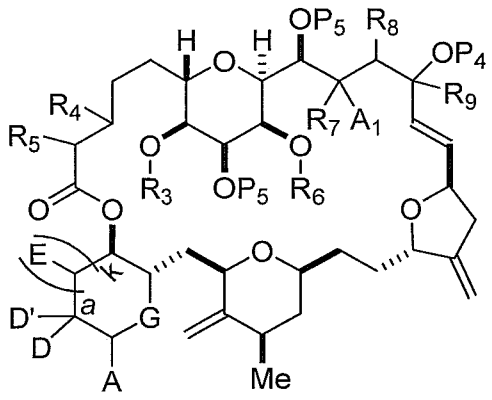
or

(c2) R_9 and P_4 combine to form a double bond;

R_{10} is H or $-CH_2X_1CH_2CH=CH_2$, where X_1 is O, $-C(R_{11})_2-$, or NP_6, and where each R_{11} is independently H or $-COOR_{12}$, P_6 is an *N*-protecting group, and R_{12} is alkyl;

each P_5 is independently H or a hydroxyl protecting group; and

where the macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (VB):



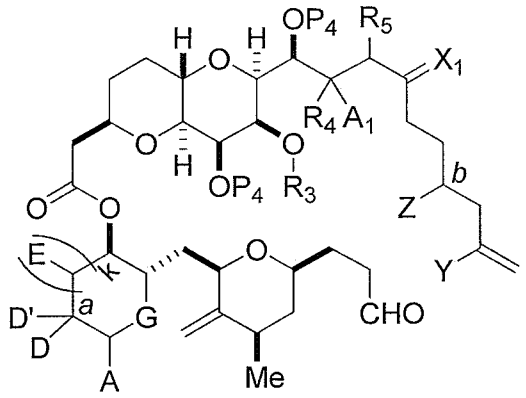
(VB)

or a salt or a tautomer thereof.

In formula (VA) or (VB), R_9 can be H, and P_4 can be H. In formula (VA) or (VB), R_{10} can be $-CH_2X_1CH_2CH=CH_2$, and X_1 can be O. In formula (VA) or (VB), R_6 and R_7 can combine to form a bond, and R_8 can be H. In formula (VA) or (VB), each P_5 can be independently a hydroxyl protecting group. In formula (VA) or (VB), at least one P_5 can be H. In formula (VA) or (VB), R_3 and R_4 can combine to form a bond, and R_5 can be H.

In certain examples, performing the macrocyclization reaction involves contacting the non-macrocyclic intermediate (e.g., a compound of formula (VIA) or (VIIA)) with a Cr(II) salt and a Ni(II) salt.

The non-macrocyclic intermediate can be a compound of formula (VIA):



(VIA)

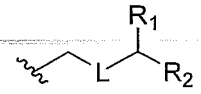
or a salt or a tautomer thereof,

where

Y is iodide, bromide, or trifluoromethanesulfonate;

b designates (*R*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide; or *b* designates (*S*)-stereogenic center, and Z is OR_6, where R_6 is a hydroxyl protecting group;

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; 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:



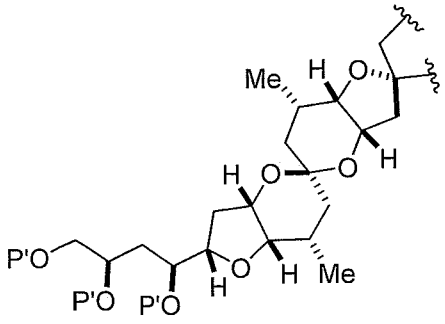
(1),

where

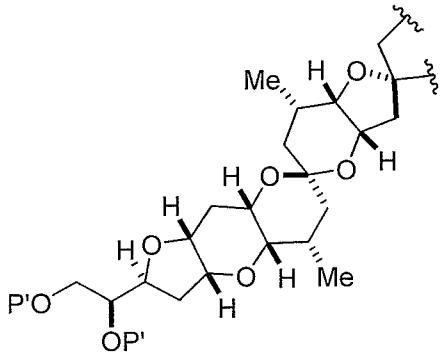
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

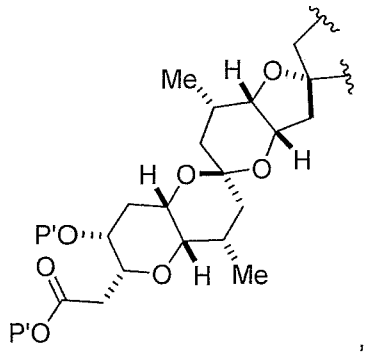
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

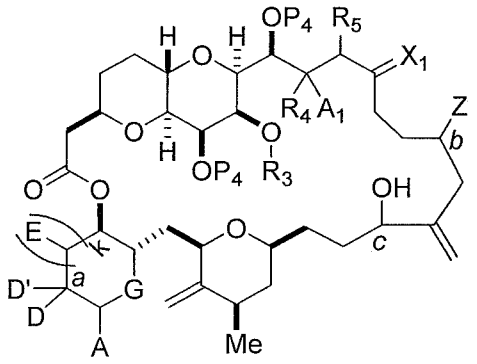
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

where the macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IVB):



(VIB)

or a salt or a tautomer thereof,

where

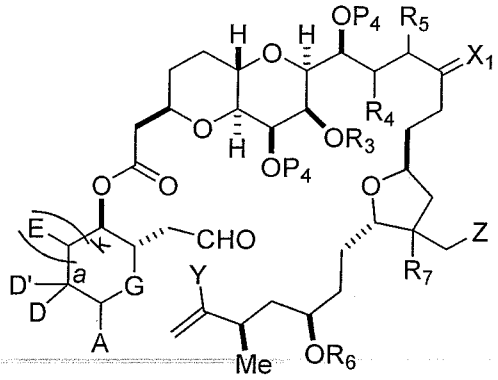
b designates (*R*)-stereogenic center, *c* designates (*S*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide;

or

b designates (*S*)-stereogenic center, *c* designates (*R*)-stereogenic center, and Z is OR_6, where R_6 is a hydroxyl protecting group.

In formula (VIA) or (VIB), Y can be bromide. In formula (VIA) or (VIB), R_3 and R_4 can combine to form a bond, and R_5 can be H. In formula (VIA) or (VIB), both P_4 groups and X_1, together with the atoms to which each is attached, can combine to form ketal. In formula (VIA) or (VIB), Z can be a sulfonate. In formula (VIA) or (VIB), Z can be OR_6, where R_6 is a hydroxyl protecting group. In formula (VIA) or (VIB), Z can be an ester, carbonate, or carbamate.

The non-macrocyclic intermediate can be a compound of formula (VIIA):



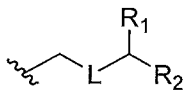
(VIIA)

or a salt thereof,

where

Y is iodide, bromide, or trifluoromethanesulfonate;

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; 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),

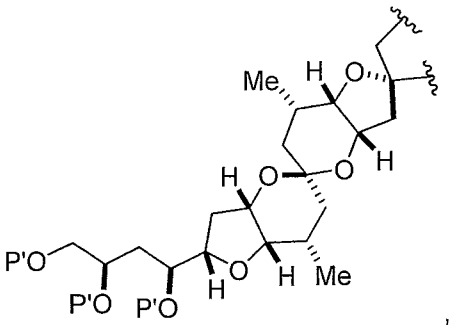
where

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

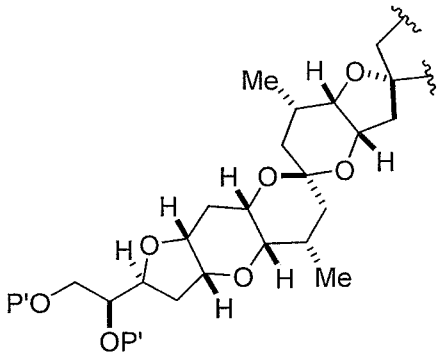
R_1 is H, or R_1 and P_1 combine to form a bond;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo;

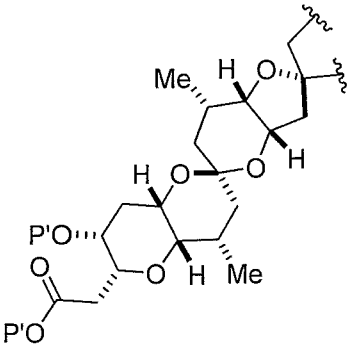
or R_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

E is 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(a1) R_3 is H or a hydroxyl protecting group, R_4 and R_5 combine to form a double bond, each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$, where R_8 is H or a hydroxyl protecting group;

or

(a2) R_3 and R_4 combine to form a bond, R_5 is H, and

each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$;

or

both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

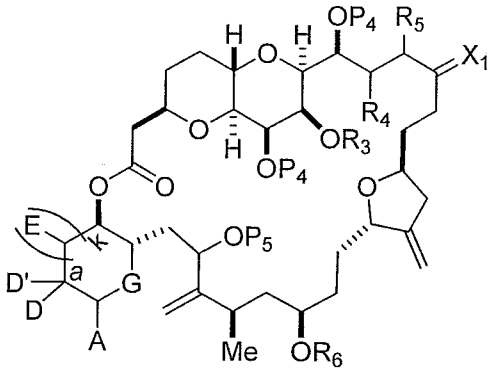
(b1) Z is chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond;

or

(b2) Z and R_7 combine to form a double bond, and R_6 is a hydroxyl protecting group;

and

where the macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (VIIB):



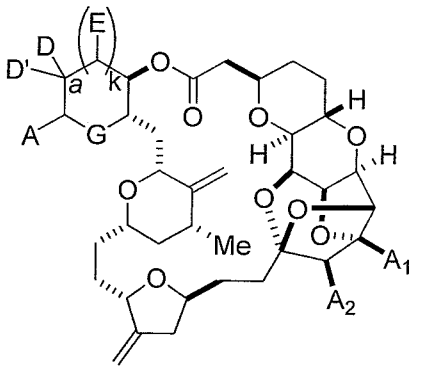
(VIIB)

or a salt thereof,

where each of P_5 and R_6 is independently H or a hydroxyl protecting group.

In formula (VIIA), Z can be iodide. In formula (VIIA) or (VIIB), Y can be trifluoromethanesulfonate. In formula (VIIA) or (VIIB), R_3 can be H or a hydroxyl protecting group, R_4 and R_5 can combine to form a double bond, each P_4 can independently be H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, can form –(CH(OR$_8$))–, where R_8 is H or a hydroxyl protecting group. In formula (VIIA) or (VIIB), at least one of P_3, P_4, and R_6 can be a hydroxyl protecting group. In formula (VIIA), Z can be chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond.

Further described herein is a method of preparing:



halichondrin macrolide

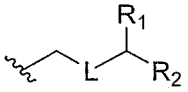
or a salt thereof,

where

each of A_1 and A_2 is independently H or OP", where each P" is independently H or a hydroxyl protecting group;

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; 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:



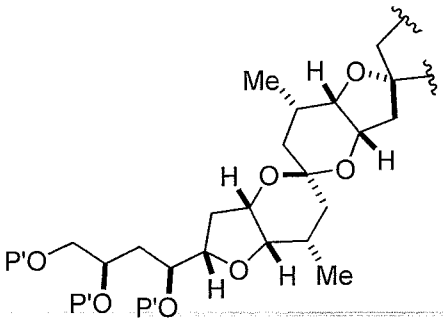
(1),

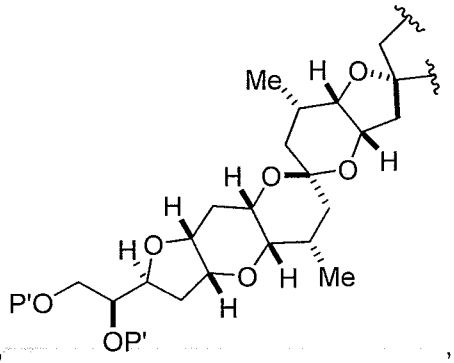
where

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

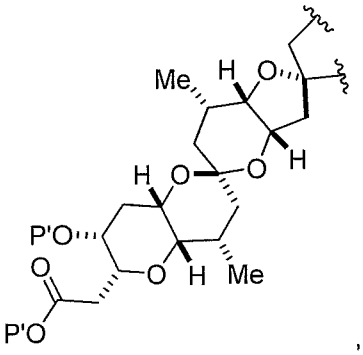
R_1 is H, or R_1 and P_1 combine to form a bond;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or 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 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;

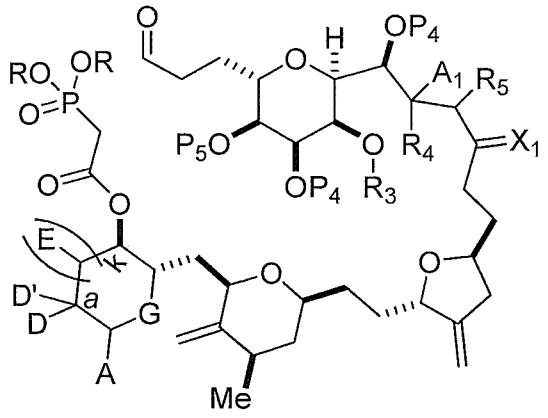
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, where each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl,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

k is 0 or 1;

n is 0, 1, or 2;

the method involving:

(A) producing a compound of formula (IB) from a compound of formula (IA), the compound of formula (IA) having the following structure:



(IA)

or a salt or a tautomer thereof,

wherein

each R is independently optionally substituted alkyl or optionally substituted aryl;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

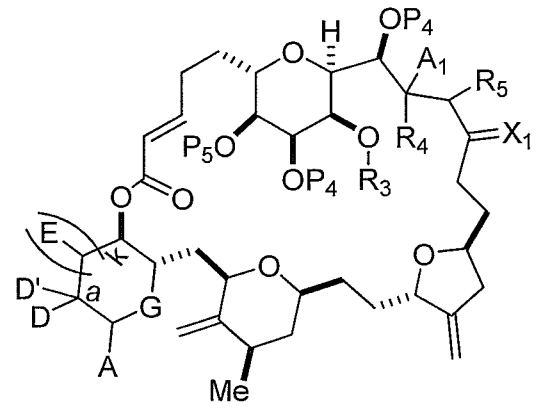
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

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



(IB)

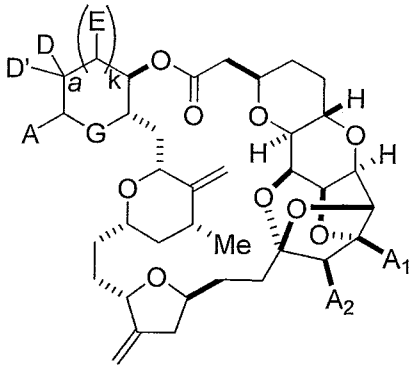
or a salt or a tautomer thereof;

and

(B) producing the halichondrin macrolide from compound (IB).

In some examples, the producing the compound of formula (IB) involves reacting the compound of formula (IA) with with an organic base and a Lewis acid. In certain examples, the producing the halichondrin macrolide inolves reacting the compound of formula (IB) with a hydroxyl protecting group removing agent. In particular examples, each R is optionally substituted alkyl.

Further described herein is a method of preparing:



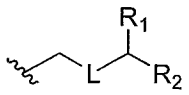
halichondrin macrolide

or a salt thereof,

where

each of A_1 and A_2 is independently H or OP", where each P" is independently H or a hydroxyl protecting group;

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; 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:



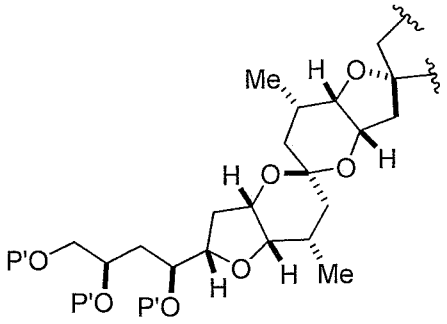
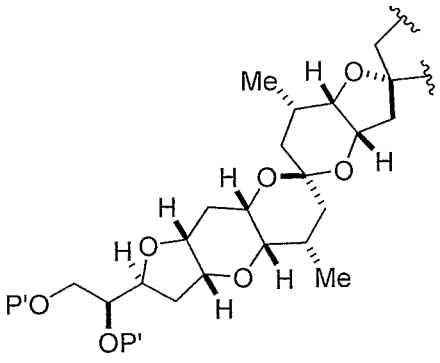
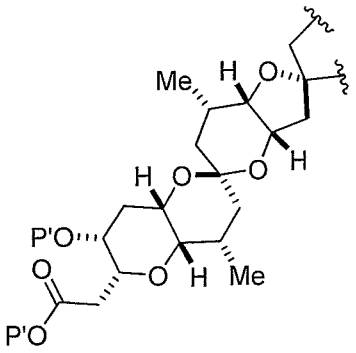
(1),

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;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or 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 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;

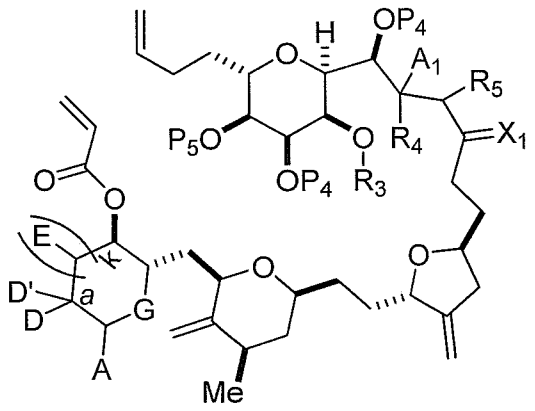
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, where each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl,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

k is 0 or 1;

n is 0, 1, or 2;

the method involving:

(A) producing a compound of formula (IB) from a compound of formula (IIA), the compound of formula (IIA) having the following structure:



(IIA)

or a salt or a tautomer thereof,

wherein

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

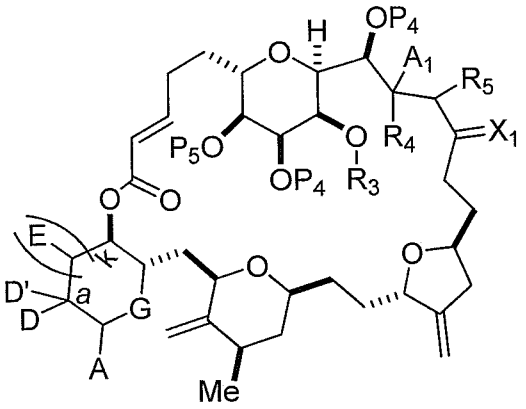
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

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



(IB)

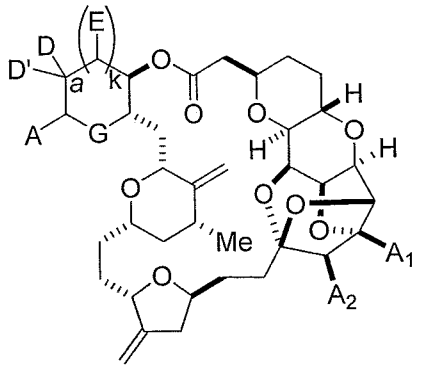
or a salt or a tautomer thereof;

and

(B) producing the halichondrin macrolide from compound (IB).

In some examples, the producing the compound of formula (IB) involves reacting the compound of formula (IIA) with an olefin metathesis catalyst (e.g., a ruthenium-carbene complex). In some examples, the producing the halichondrin macrolide involves reacting the compound of formula (IB) with a hydroxyl protecting group removing agent.

Further described herein is a method of preparing:



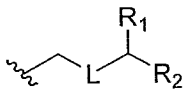
halichondrin macrolide

or a salt thereof,

wherein

each of A_1 and A_2 is independently H or OP", where each P" is independently H or a hydroxyl protecting group;

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; 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:



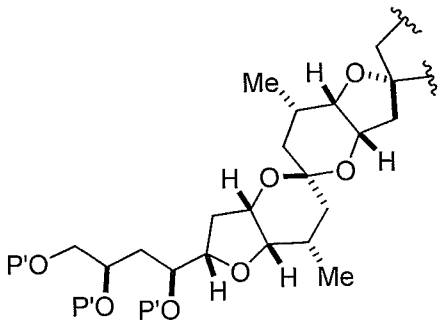
(1),

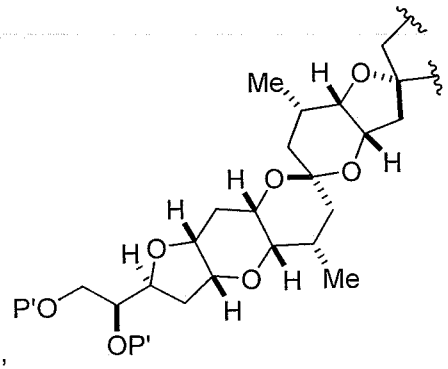
where

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

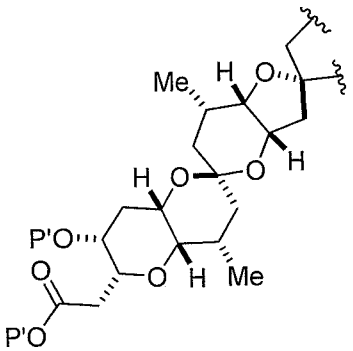
R_1 is H, or R_1 and P_1 combine to form a bond;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or 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 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;

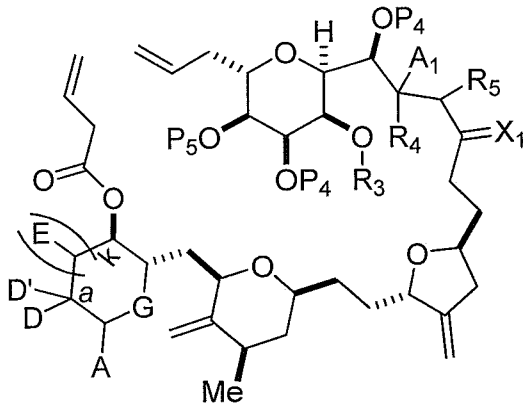
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, where each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl,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

k is 0 or 1;

n is 0, 1, or 2;

the method involving:

(A) producing a compound of formula (IIIB) from a compound of formula (IIIA), the compound of formula (IIIA) having the following structure:



(IIIA)

or a salt or a tautomer thereof,

wherein

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

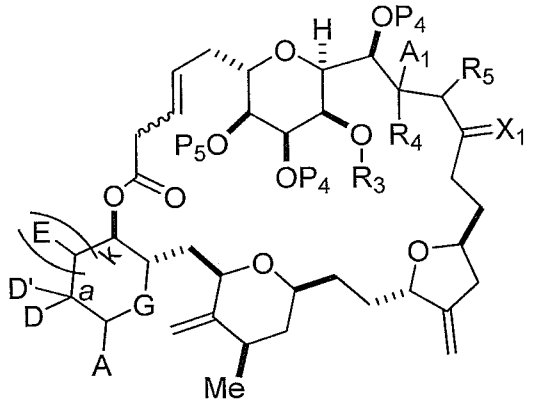
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

the compound of formula (IIIB) having the following structure:



(IIIB),

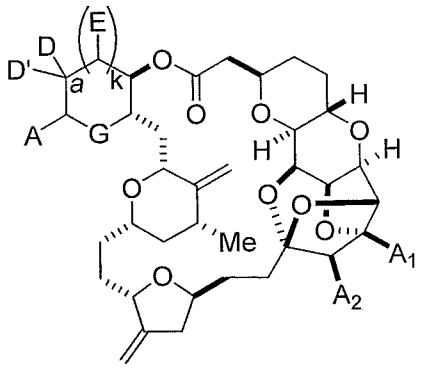
or a salt or a tautomer thereof;

and

(B) producing the halichondrin macrolide from the compound of formula (IIIB).

In some examples, the producing the compound of formula (IIIB) involves reacting the compound of formula (IIIA) with an olefin metathesis catalyst. In certain examples, the producing the halichondrin macrolide involves reacting the compound of formula (IIIB) with a hydroxyl protecting group removing agent. In particular examples, both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal. In further examples, P_5 is a hydroxyl protecting group.

Further described herein is a method of preparing:



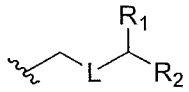
halichondrin macrolide

or a salt thereof,

where

each of A_1 and A_2 is independently H or OP", where each P" is independently H or a hydroxyl protecting group;

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; 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:



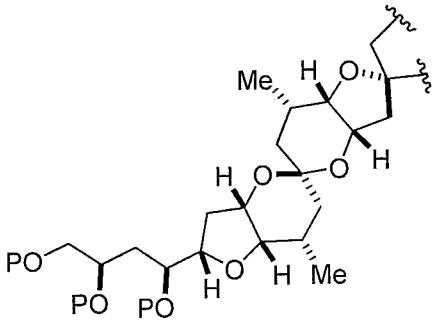
(1),

where

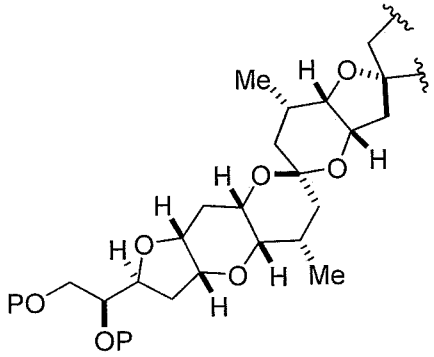
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

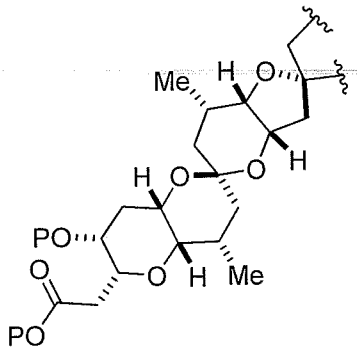
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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;

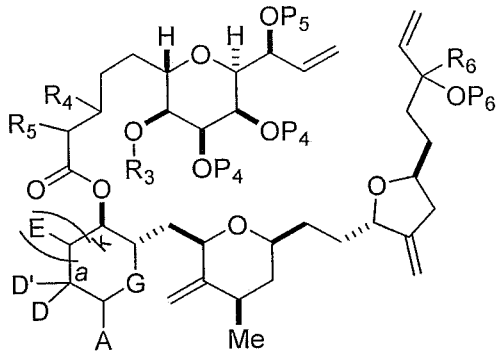
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, where each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl,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

k is 0 or 1;

n is 0, 1, or 2;

the method involving:

(A) producing a compound of formula (IVB) from a compound of formula (IVA), the compound of formula (IVA) having the following structure:



(IVA)

or a salt thereof,

where

(i) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(ii) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

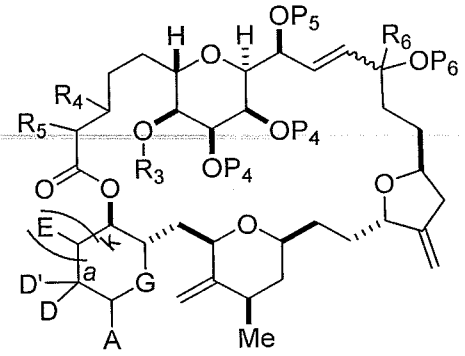
or

(iii) R_3 and R_4 combine to form a bond, and R_5 is H;

each P_4 and P_5 is independently H or a hydroxyl protecting group;

R_6 is H, and P_6 is H or a hydroxyl protecting group; or R_6 and P_6 combine to form a double bond; and

the compound of formula (IVB) having the following structure:



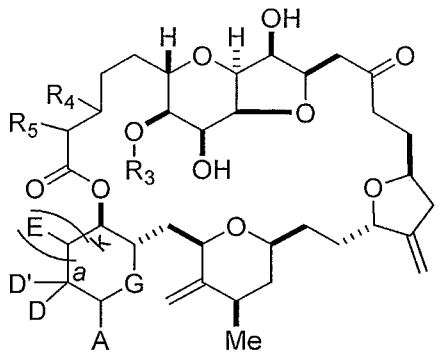
(IVB)

or a salt thereof;

and

(B) producing the halichondrin macrolide from the compound of formula (IVB).

In some examples, the producing the compound of formula (IVB) involves reacting the compound of formula (IVA) with an olefin metathesis catalyst. In certain examples, the producing the halichondrin macrolide from the compound of formula (IVB) involves reacting the compound of formula (IVB) with a Brønsted acid. In other examples, the producing the halichondrin macrolide involves producing the compound of formula (IVC), the compound of formula (IVC) having the following structure:



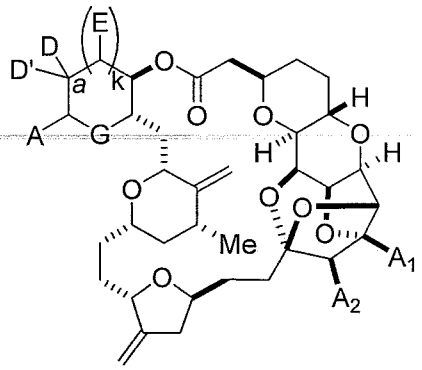
(IVC)

or a salt thereof;

and producing the halichondrin macrolide from the compound of formula (IVC).

In yet other examples, the producing the compound of formula (IVC) involves reacting the compound of formula (IVB) with a hydroxyl protecting group removing agent. In still other examples, the producing the halichondrin macrolide from the compound of formula (IVC) involves reacting the compound of formula (IVC) with a Brønsted acid. In particular examples, at least one of P_4 and P_5 is H.

Further described herein is a method of preparing:



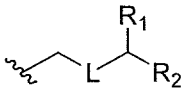
halichondrin macrolide

or a salt thereof,

where

each of A_1 and A_2 is independently H or OP", where each P" is independently H or a hydroxyl protecting group;

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; 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:



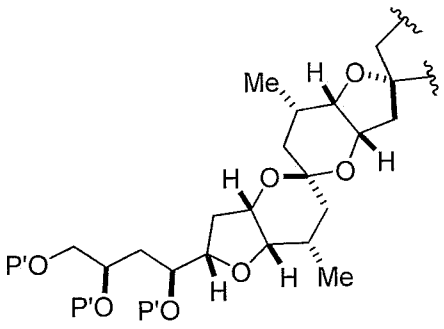
(1),

where

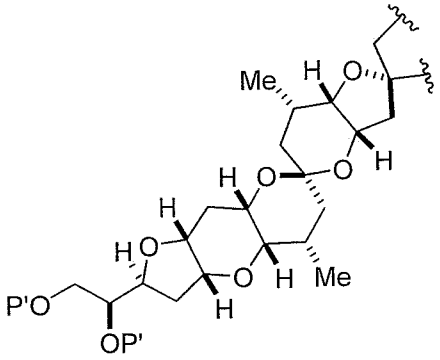
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

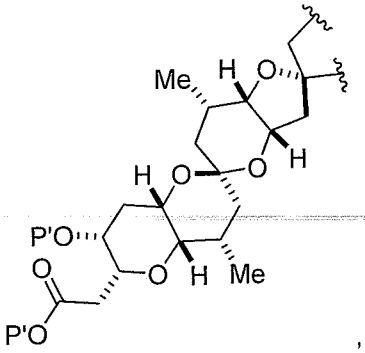
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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;

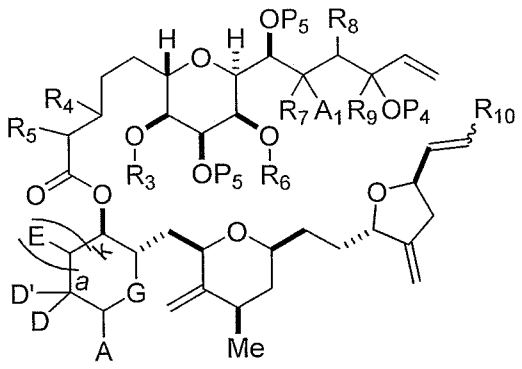
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, where each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl,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

k is 0 or 1;

n is 0, 1, or 2;

the method involving:

(A) producing a compound of formula (VB) from a compound of formula (VA), the compound of formula (VA) having the following structure:



(VA)

or a salt or a tautomer thereof,

where

(a1) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(a2) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(a3) R_3 and R_4 combine to form a bond, and R_5 is H;

(b1) A_1 and R_7 combine to form oxo, R_6 is H or a hydroxyl protecting group, and R_8 is H;

or

(b2) A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_6 is H or a hydroxyl protecting group, and R_7 and R_8 combine to form a double bond;

or

(ii) R_6 and R_7 combine to form a bond, and R_8 is H or OP";

(c1) R_9 is H, and P_4 is H or a hydroxyl protecting group;

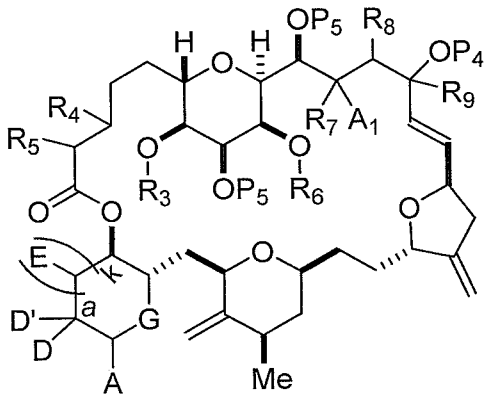
or

(c2) R_9 and P_4 combine to form a double bond;

R_{10} is H or $-CH_2X_1CH_2CH=CH_2$, where X_1 is O, $-C(R_{11})_2-$, or NP_6, and where each R_{11} is independently H or $-COOR_{12}$, P_6 is an *N*-protecting group, and R_{12} is alkyl;

each P_5 is independently H or a hydroxyl protecting group; and

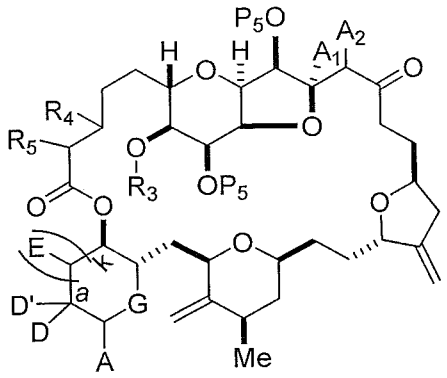
where the macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (VB):



(VB)

or a salt or a tautomer thereof;

(B) producing a compound of formula (VC) from the compound of formula (VB), the compound of formula (VC) having the following structure:

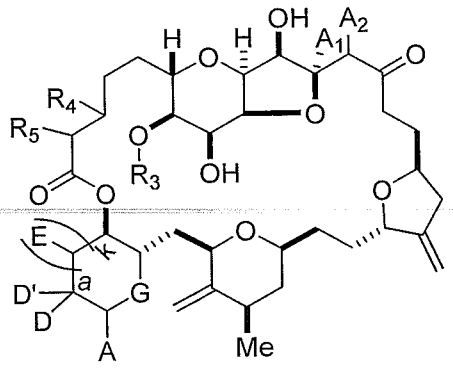


(VC)

or a salt thereof,

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

(C) producing a compound of formula (IVC) from the compound of formula (VC), the compound of formula (IVC) having the following structure:



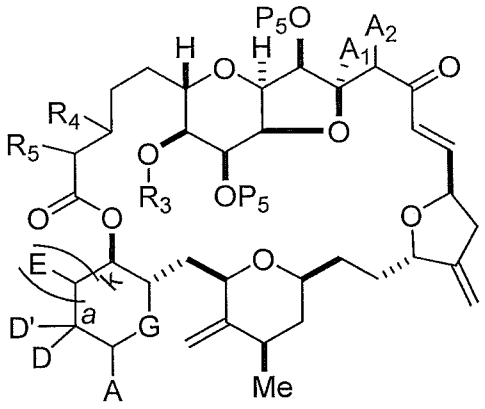
(IVC)

or a salt thereof,

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

(D) producing the halichondrin macrolide from the compound of formula (IVC).

In some examples, the producing the compound of formula (VB) involves contacting the compound of formula (VA) with an olefin metathesis catalyst. In certain examples, P_4 is H, R_9 is H, and the producing the compound of formula (VC) involves oxidizing the compound of formula (VB) to produce a compound of formula (VBa):



(VBa)

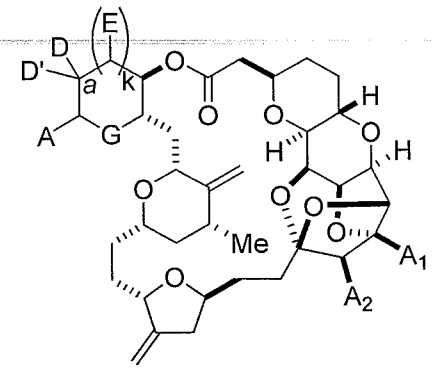
or a salt thereof;

where each of A_1 and A_2 is independently H or OP"

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

In particular examples, the producing the compound of formula (IVC) involves contacting the compound of formula (VC) with a hydroxyl protecting group removing agent. In further examples, the producing the halichondrin macrolide involves contacting the compound of formula (IVC) with a Brønsted acid.

Further described herein is a method of preparing:



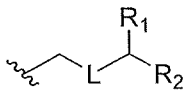
halichondrin macrolide

or a salt thereof,

where

each of A_1 and A_2 is independently H or OP", where each P" is independently H or a hydroxyl protecting group;

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; 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:



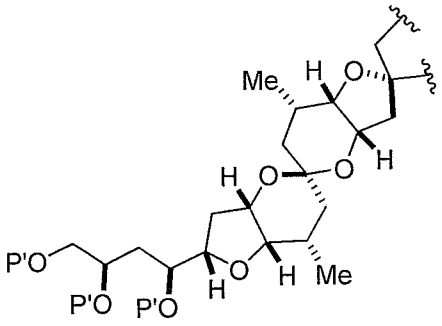
(1),

where

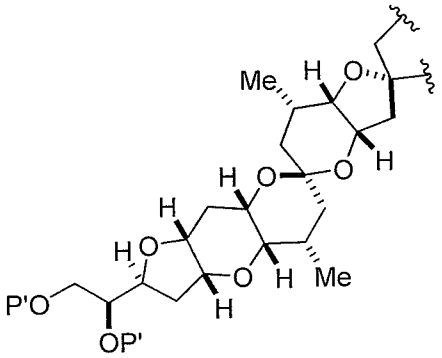
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

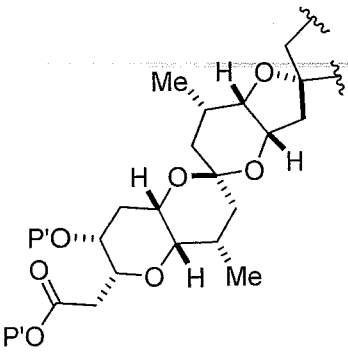
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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;

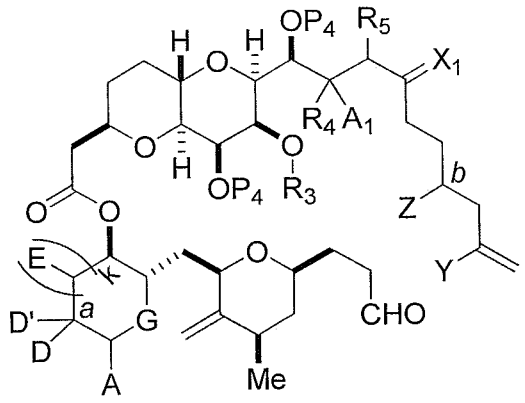
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, where each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl,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

k is 0 or 1;

n is 0, 1, or 2;

the method involving:

(A) producing a compound of formula (VIB) from a compound of formula (VIA), the compound of formula (VIA) having the following structure:



(VIA)

or a salt or a tautomer thereof,

where

Y is iodide, bromide, or trifluoromethanesulfonate;

b designates (*R*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide; or *b* designates (*S*)-stereogenic center, and Z is OR_6, where R_6 is a hydroxyl protecting group;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

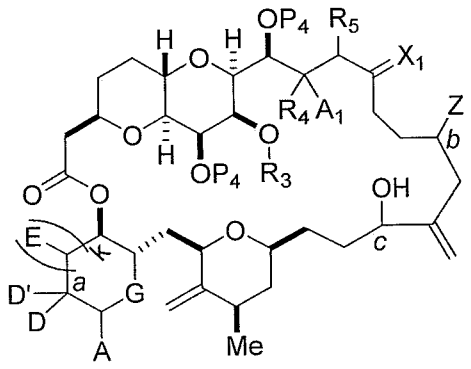
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

the compound of formula (VIB) having the following structure:



(VIB)

or a salt or a tautomer thereof,

where

b designates (*R*)-stereogenic center, *c* designates (*S*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide;

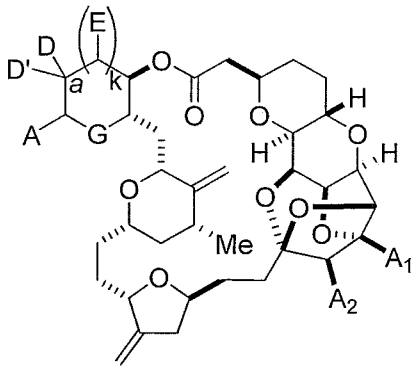
or

b designates (*S*)-stereogenic center, *c* designates (*R*)-stereogenic center, and Z is OR_6, where R_6 is a hydroxyl protecting group;

(B) producing the halichondrin macrolide from the compound of formula (VIB).

In some examples, the producing the compound of formula (VIB) involves reacting the compound of formula (VIA) with a Cr(II) salt and a Ni(II) salt. In particular examples, the producing the halichondrin macrolide involves the step of nucleophilic ring-closing of the compound of formula (VIB). In certain examples, both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal. In further examples, R_3 and R_4 combine to form a bond, and R_5 is H.

Further described herein is a method of preparing:



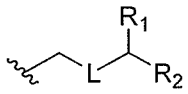
halichondrin macrolide

or a salt thereof,

where

each of A_1 and A_2 is independently H or OP", where each P" is independently H or a hydroxyl protecting group;

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; 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:



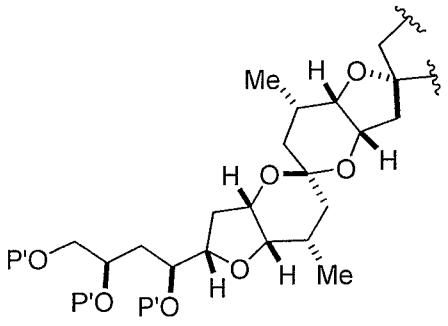
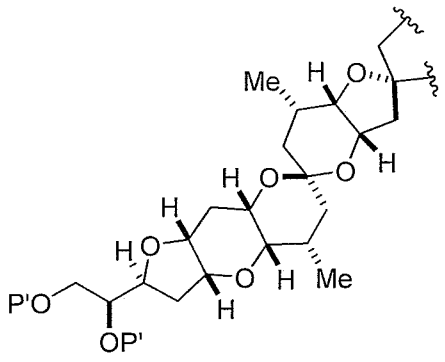
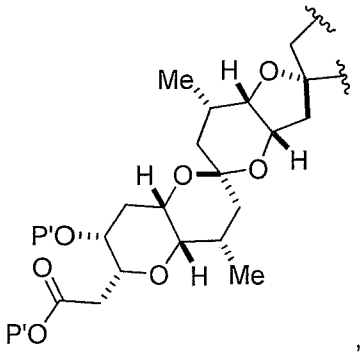
(1),

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;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or 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 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;

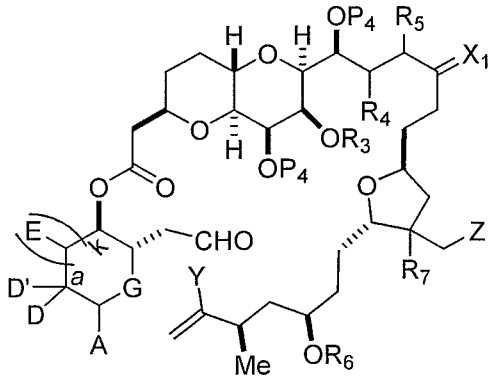
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, where each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, hydroxyaryl,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

k is 0 or 1;

n is 0, 1, or 2;

the method involving:

(A) producing a compound of formula (VIIB) from a compound of formula (VIIA), the compound of formula (VIIA) having the following structure:



(VIIA)

or a salt thereof,

where

Y is iodide, bromide, or trifluoromethanesulfonate;

(a1) R_3 is H or a hydroxyl protecting group, R_4 and R_5 combine to form a double bond, each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or –(CH(OR$_8$))–;

or

(a2) R_3 and R_4 combine to form a bond, R_5 is H, and

each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or –(CH(OR$_8$))–;

or

both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(b1) Z is chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond;

or

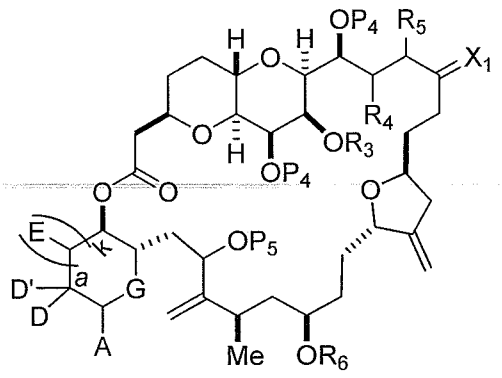
(b2) Z and R_7 combine to form a double bond, and R_6 is a hydroxyl protecting group;

and

where R_8 is H or a hydroxyl protecting group;

and

the compound of formula (VIIB) having the following structure:

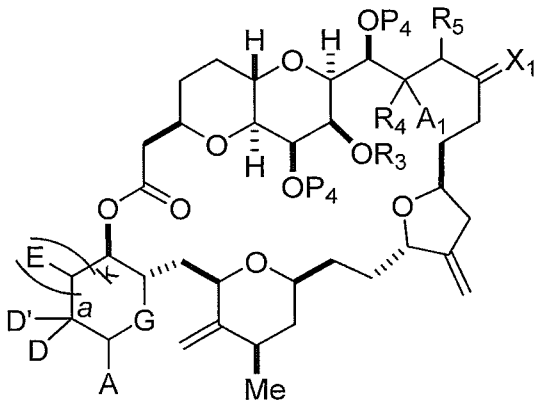


(VIIB)

or a salt thereof,

where each of P_5 and R_6 is independently H or a hydroxyl protecting group;

(B) producing a compound of formula (VIIC) from the compound of formula (VIIB), the compound of formula (VIIC) having the following structure:



(VIIC)

or a salt or a tautomer thereof,

where

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

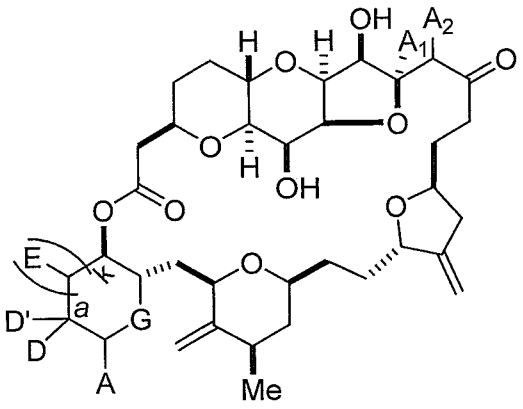
A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

(C) producing a compound of formula (VIID) from the compound of formula (VIIC), the compound of formula (VIID) having the following structure:



(VIID)

or a salt thereof,

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

and

(D) producing the halichondrin macrolide from the compound of formula (VIID).

In some examples, the producing the compound of formula (VIIB) involves reacting the compound of formula (VIIA) with a Cr(II) salt and a Ni(II) salt. In certain examples, the producing the compound of formula (VIIC) involves the step of nucleophilic ring-closing of the compound of formula (VIIB). In particular examples, the producing the compound of formula (VIID) involves reacting the compound of formula (VIIC) with a hydroxyl protecting group removing agent. In further examples, the producing the halichondrin macrolide involves reacting the compound of formula (VIID) with a Brønsted acid. In other examples, Z is iodide. In yet other examples, Y is trifluoromethanesulfonate. In other examples, R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond. In some examples, each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms $-(CH(OR_8))-$, where R_8 is H or a hydroxyl protecting group. In particular examples, P_5 is H. In certain examples, Z is chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond.

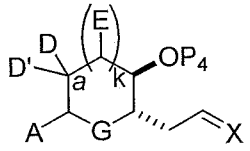
In some examples, *a* designates (*S*)-stereogenic center. In certain examples, one and only one of D and D' is optionally substituted alkyl or OP_1. In particular examples, one and only one of D and D' is OP_1, where P_1

is H, alkyl, or a hydroxyl protecting group. In further examples, A is a group of formula (1). In certain examples, L is $-(CH(OP_2))-$. In other examples, R_1 and P_1 combine to form a bond. In yet other examples, G is O. In still other examples, E is optionally substituted alkyl. In some examples, k is 1. In certain examples, R_2 is $-(CH_2)_nOP_3$. In particular examples, at least one of P_2 and P_3 is a hydroxyl protecting group. In certain examples, A_1 is H. In some examples, A_2 is H.

Further described herein is a method of preparing an intermediate in the synthesis of a halichondrin macrolide. The method involves performing an allene-Prins reaction by contacting a compound of formula (VIIIA) with a compound of formula (VIIIB) and R_4OH,

where R_4 is an optionally substituted acyl;

where the compound of formula (VIIIA) has the following structure:

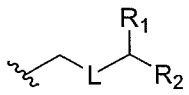


(VIIIA)

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; 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:



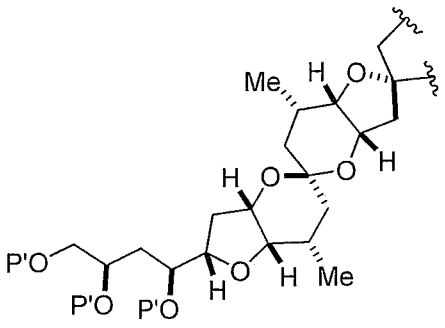
(1),

where

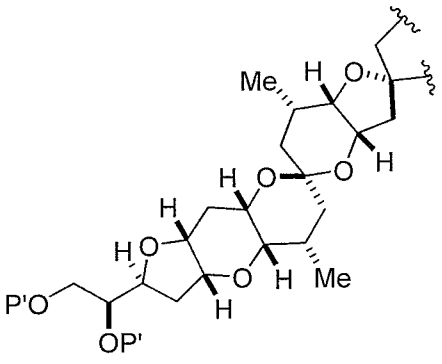
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

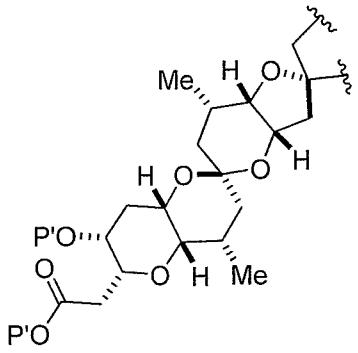
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

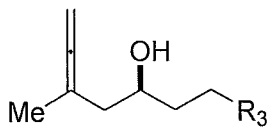
k is 0 or 1;

n is 0, 1, or 2;

X is O, or X, together with the carbon atom to which it is attached, forms $-(C(OP_Z)_2)-$, wherein each P_Z is independently optionally substituted alkyl or optionally substituted aryl, or both P_Z combine to form optionally substituted alkylene or optionally substituted arylene; and

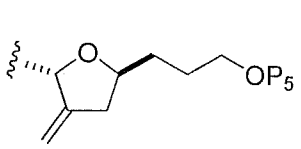
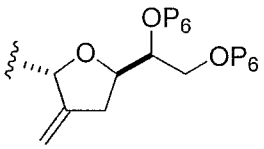
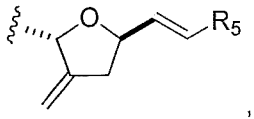
P_4 is H or a hydroxyl protecting group;

where the compound of formula (VIIIB) has the following structure:



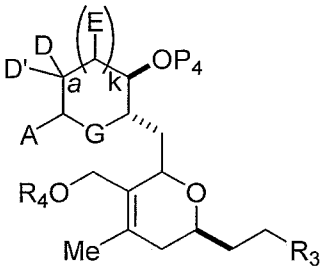
(VIIIB),

where

R_3 is $-CH_2-OP_5$, $-CH=CH_2$, , , or ,

where P_5 is H or a hydroxyl protecting group; each P_6 is independently a hydroxyl protecting group, or both P_6 groups, together with the atoms to which each is attached, combine to form a cyclic protected diol; and R_5 is is H or -$CH_2X_1CH_2CH=CH_2$, where X_1 is O, -CH_2-, or NP_7, where P_7 is a sulfonyl;

and where the intermediate is a compound of formula (VIIIC):



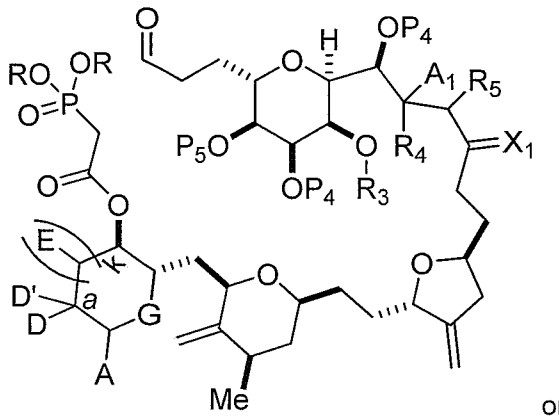
(VIIIC)

or a salt thereof,

where *a* designates (*R*)-stereogenic center or (*S*)-stereogenic center.

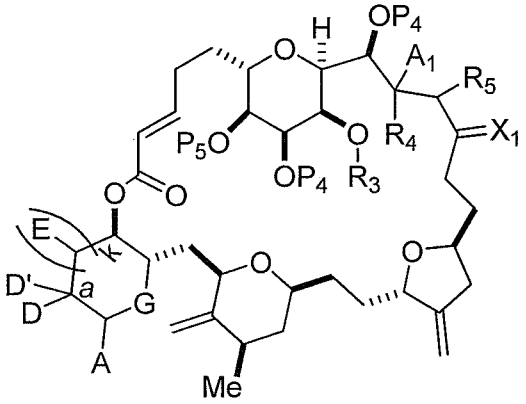
In some examples, the performing a Prins reaction involves reacting the compound of formula (VIIIA) with a Lewis acid. In certain examples, k is 1.

Further described herein is a compound of formula (IA) or formula (IB),



(IA)

or



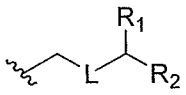
(IB)

or a salt or a tautomer thereof,

where

each R is independently optionally substituted alkyl or optionally substituted aryl;

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; 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:



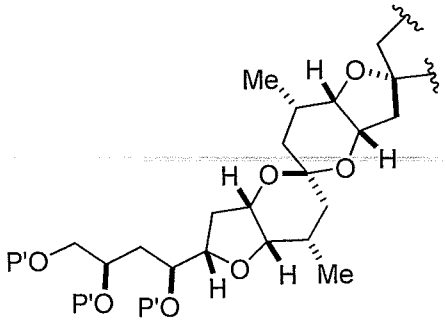
(1),

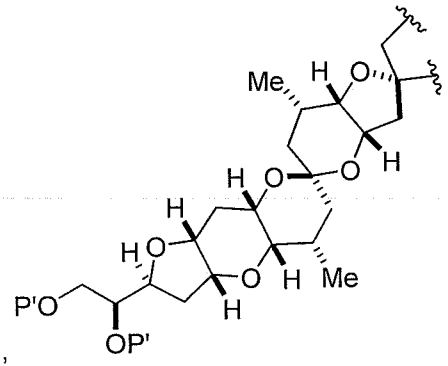
where

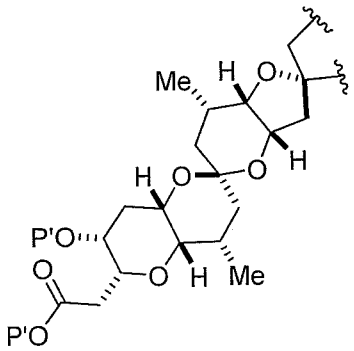
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

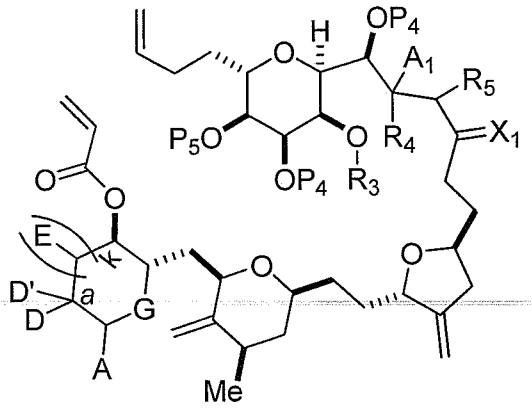
or

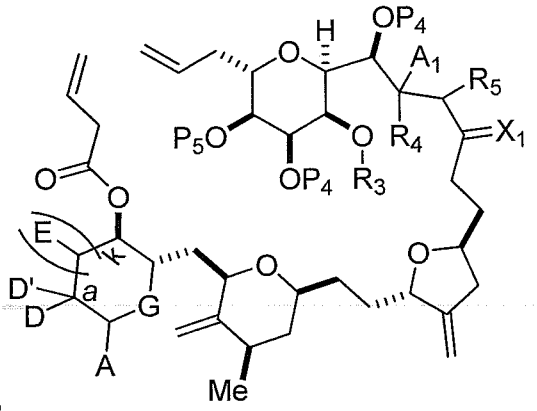
(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group.

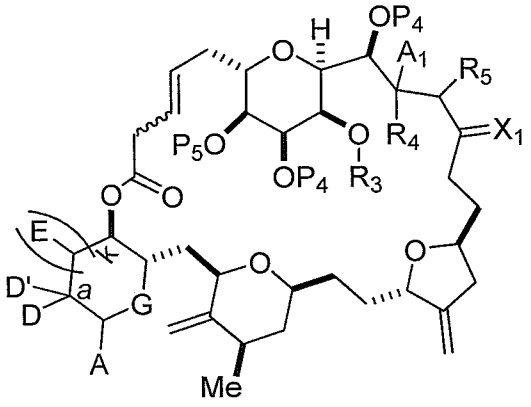
Further described herein is a compound of formula (IIA), formula (IIIA), or formula (IIIB):



, 

, or

(IIA) (IIIA)



,

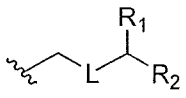
(IIIB)

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; 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:



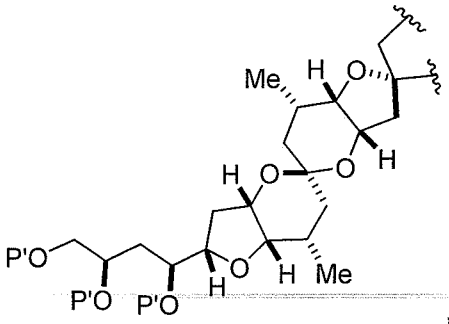
(1),

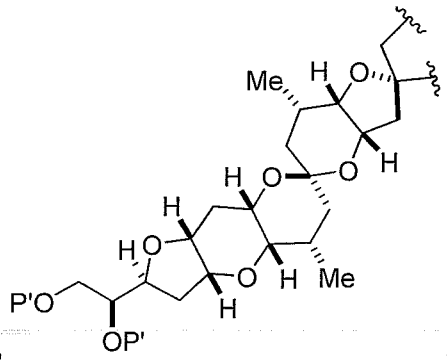
where

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

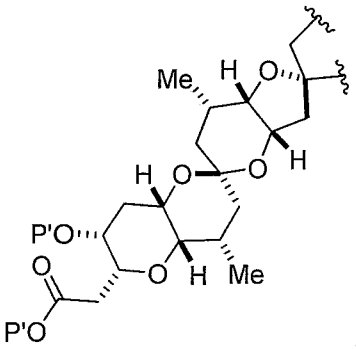
R_1 is H, or R_1 and P_1 combine to form a bond;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

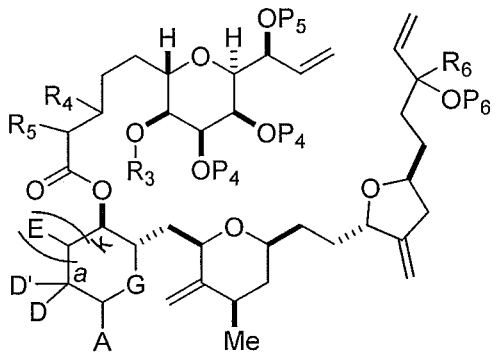
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is –(CH(OP$_Y$))–, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

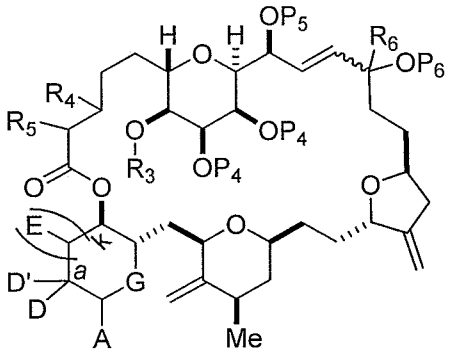
P_5 is H or a hydroxyl protecting group.

Further described herein is a compound of formula (IVA), formula (IVB), or formula (IVC):



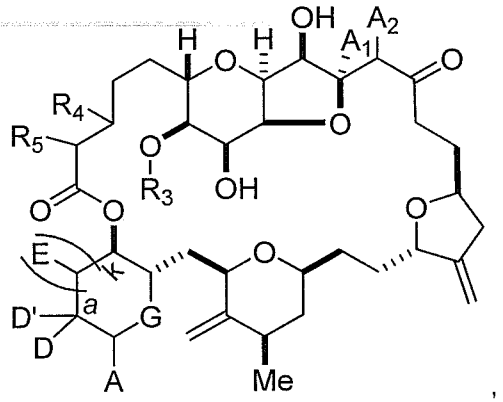
(IVA)

,



(IVB)

, or



(IVC)

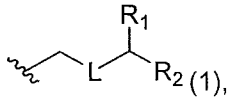
,

or a salt thereof,

where

each of A_1 and A_2 is H or OP", where P" is H or a hydroxyl protecting group;

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; 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:



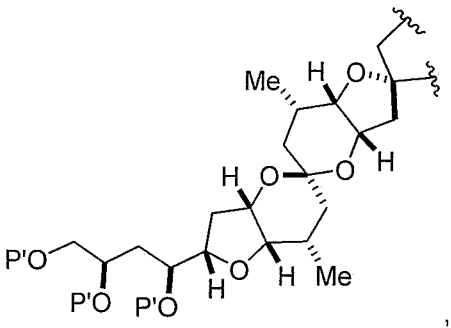
(1),

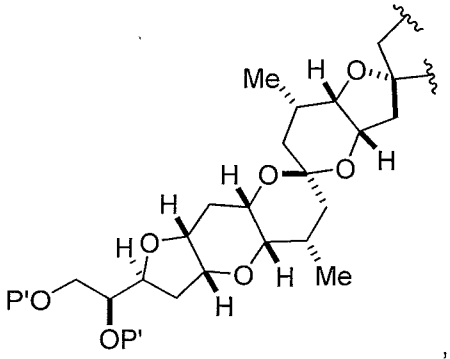
where

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

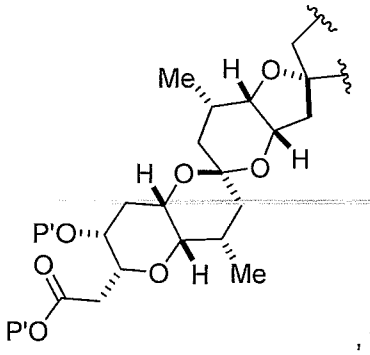
R$_1$ is H, or R$_1$ and P$_1$ combine to form a bond;

R$_2$ is H or -(CH$_2$)$_n$OP$_3$, and each of P$_2$ and P$_3$ is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P$_2$ and P$_3$, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or 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 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$_2$R$_A$, OSO$_2$R$_A$, NR$_B$R$_A$, NR$_B$(CO)R$_A$, NR$_B$(CO)(CO)R$_A$, NR$_A$(CO)NR$_B$R$_A$, NR$_B$(CO)OR$_A$, (CO)OR$_A$, O(CO)R$_A$, (CO)NR$_B$R$_A$, or O(CO)NR$_B$R$_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(i) R$_3$ is H or a hydroxyl protecting group, R$_4$ is alkyl ether, and R$_5$ is H;

(ii) R$_3$ is H or a hydroxyl protecting group, and R$_4$ and R$_5$ combine to form a double bond;

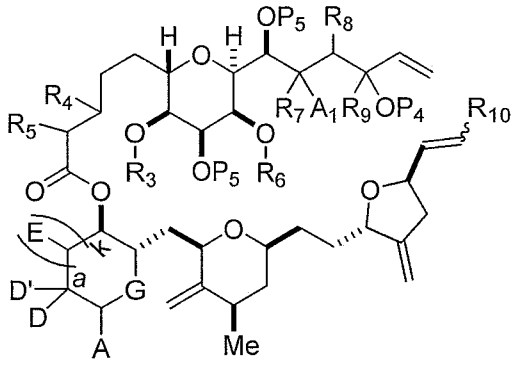
or

(iii) R$_3$ and R$_4$ combine to form a bond, and R$_5$ is H;

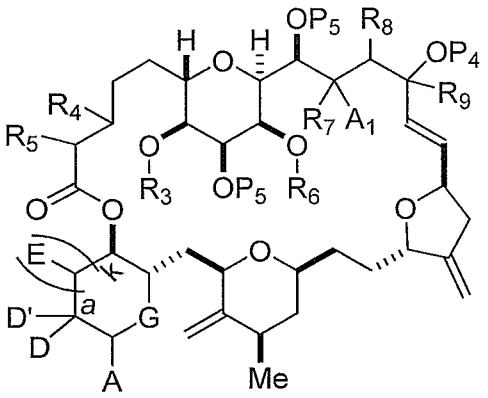
each P$_4$ and P$_5$ is independently H or a hydroxyl protecting group; and

R$_6$ is H, and P$_6$ is H or a hydroxyl protecting group; or R$_6$ and P$_6$ combine to form a double bond.

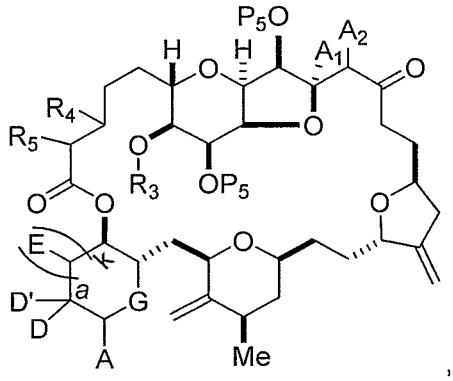
Further described herein is a compound of formula (VA), formula (VB), or formula (VC):



(VA)



(VB)

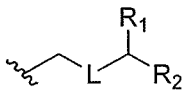


(VC)

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; 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:



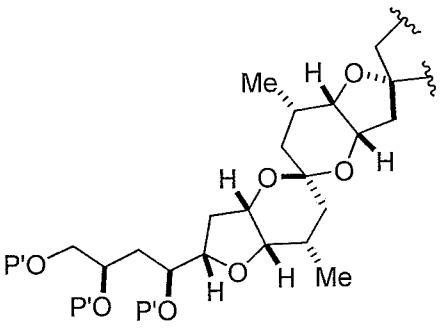
(1),

where

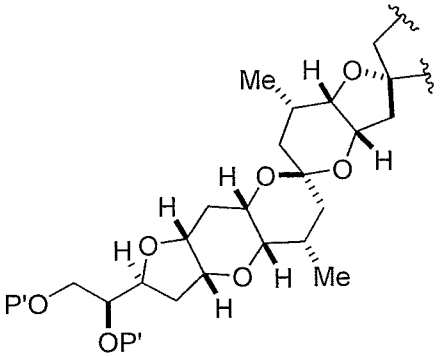
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

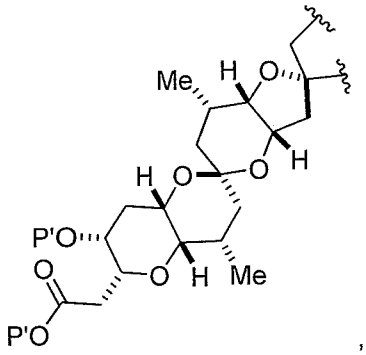
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(a1) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(a2) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(a3) R_3 and R_4 combine to form a bond, and R_5 is H;

(b1) A_1 and R_7 combine to form oxo, R_6 is H or a hydroxyl protecting group, and R_8 is H;

or

(b2) A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_6 is H or a hydroxyl protecting group, and R_7 and R_8 combine to form a double bond;

or

(ii) R_6 and R_7 combine to form a bond, and R_8 is H or OP";

(c1) R_9 is H, and P_4 is H or a hydroxyl protecting group;

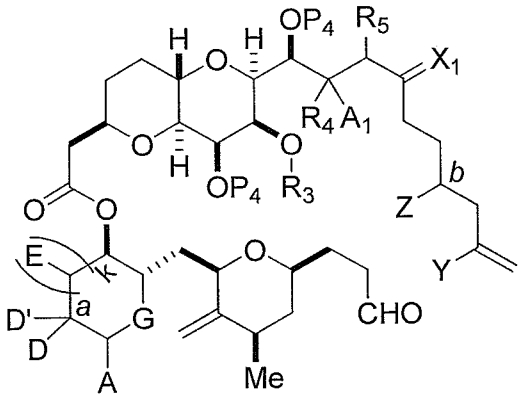
or

(c2) R_9 and P_4 combine to form a double bond;

R_{10} is H or $-CH_2X_1CH_2CH=CH_2$, where X_1 is O, $-C(R_{11})_2-$, or NP_6, and where each R_{11} is independently H or $-COOR_{12}$, P_6 is an *N*-protecting group, and R_{12} is alkyl;

each P_5 is independently H or a hydroxyl protecting group; and

Further described herein is a compound of formula (VIA):

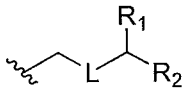


(VIA)

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; 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:



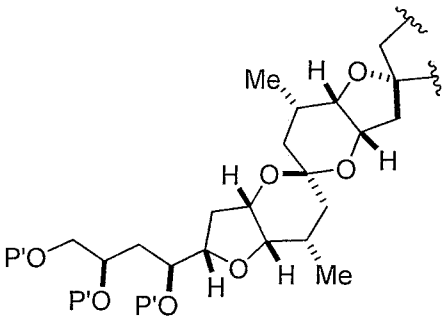
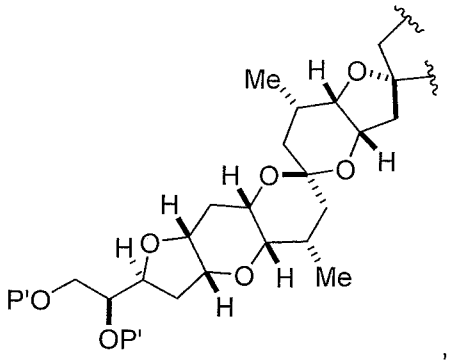
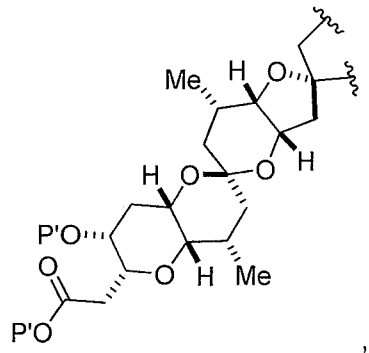
(1),

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;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

Y is iodide, bromide, or trifluoromethanesulfonate;

b designates (*R*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide; or *b* designates (*S*)-stereogenic center, and Z is OR_6, where R_6 is a hydroxyl protecting group;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

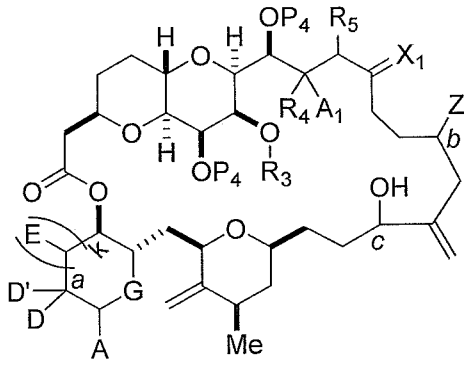
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal.

Further described herein is a compound of formula (VIB):



(VIB)

or a salt or a tautomer thereof,

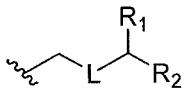
where

b designates (*R*)-stereogenic center, *c* designates (*S*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide;

or

b designates (*S*)-stereogenic center, *c* designates (*R*)-stereogenic center, and Z is OR_6, where R_6 is a hydroxyl protecting group;

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; 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:



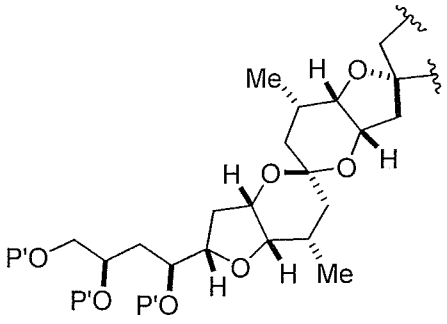
(1),

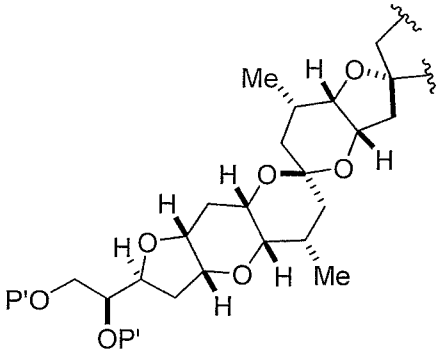
where

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

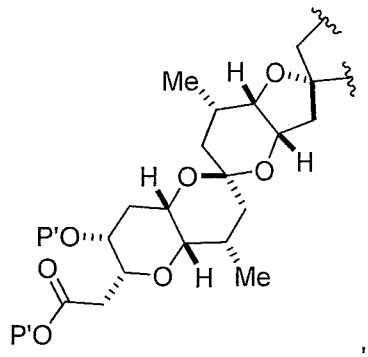
R_1 is H, or R_1 and P_1 combine to form a bond;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or 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 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

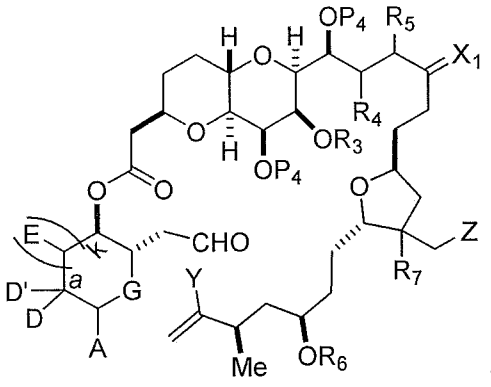
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

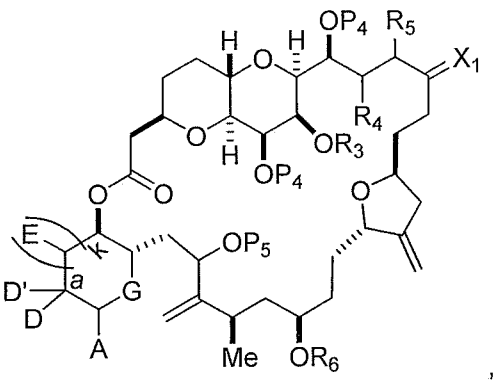
each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal.

Further described herein is a compound of formula (VIIA) or formula (VIIB):



(VIIA)

or

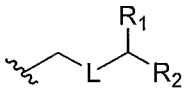


(VIIB)

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; 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:



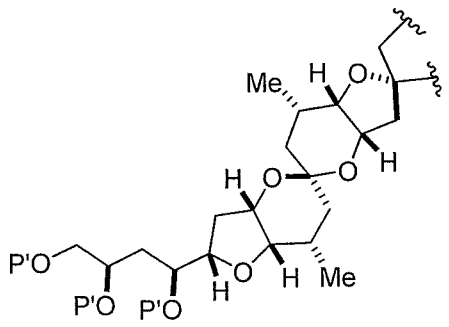
(1),

where

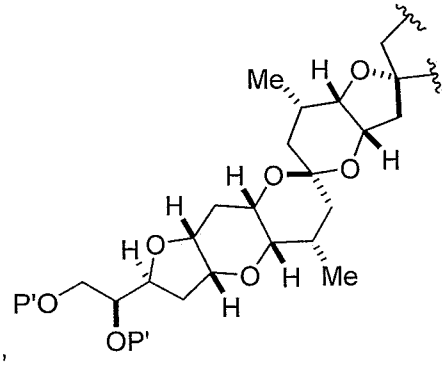
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

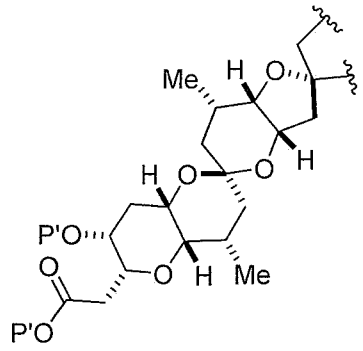
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(a1) R_3 is H or a hydroxyl protecting group, R_4 and R_5 combine to form a double bond, each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$;

or

(a2) R_3 and R_4 combine to form a bond, R_5 is H, and

each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$;

or

both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(b1) Z is chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond;

(b2) Z and R_7 combine to form a double bond, and R_6 is a hydroxyl protecting group;

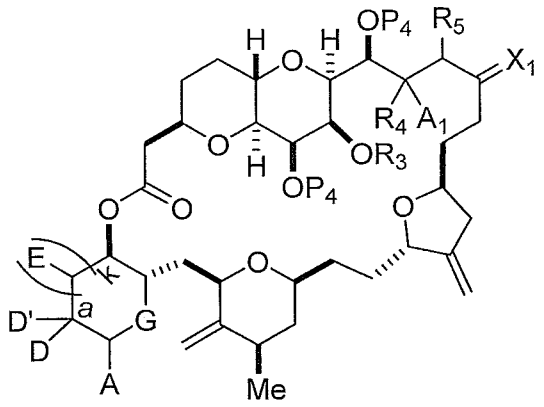
or

(b3) when Z and R_7 are absent, R_6 is H or a hydroxyl protecting group;

P_5 is H or a hydroxyl protecting group;

where R_8 is H or a hydroxyl protecting group.

Further described herein is a compound of formula (VIIC):

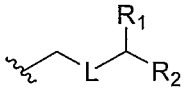


(VIIC)

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; 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:



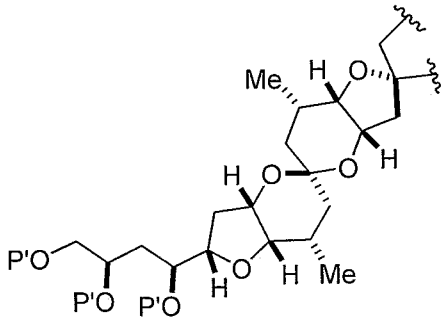
(1),

where

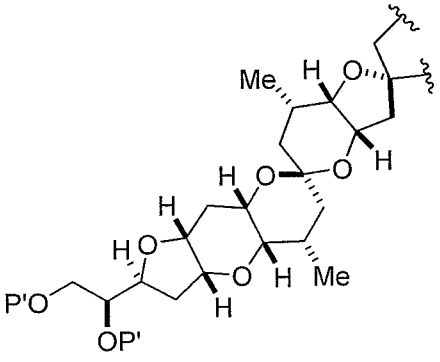
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

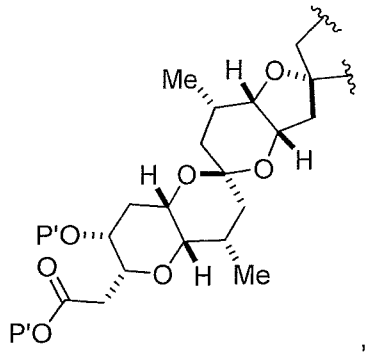
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

each P_4 is H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form a ketal; and

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

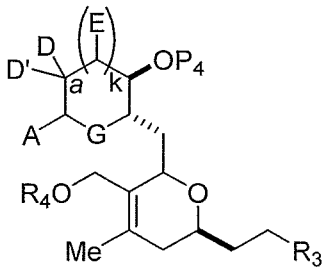
A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP".

Further described herein is a compound of formula (VIIIC):



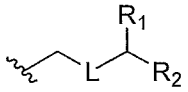
(VIIIC)

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; 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:



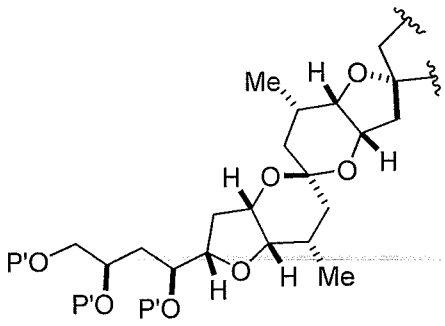
(1),

where

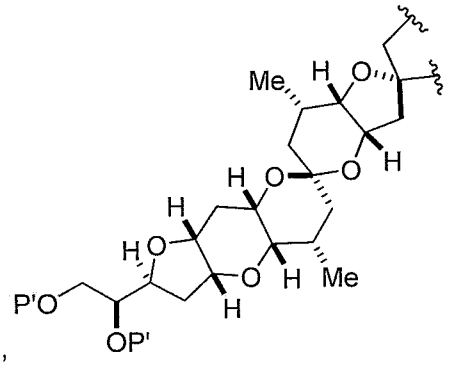
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

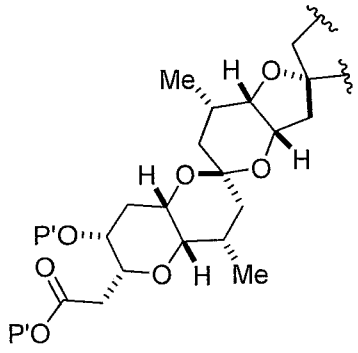
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 optionally substituted alkyl or optionally substituted alkoxy;

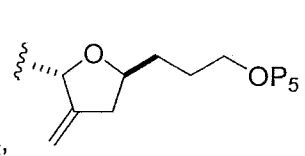
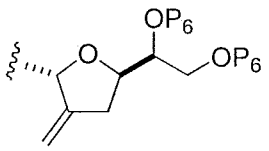
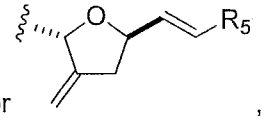
G is O, S, CH_2, or NR_N, where R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

P_4 is H or a hydroxyl protecting group; and

R_3 is $-CH_2-OP_5$, $-CH=CH_2$, , , or ,

where P_5 is H or a hydroxyl protecting group; each P_6 is independently a hydroxyl protecting group, or both P_6 groups, together with the atoms to which each is attached, combine to form a cyclic protected diol; and R_5 is is H or $-CH_2X_1CH_2CH=CH_2$, where X_1 is O, $-CH_2-$, or NP_7, where P_7 is a sulfonyl.

The disclosure also features compounds of formula (IA), (IB), (IC), (IE), (IF), (IIA), (IIB), (IIC), (IICa), (IIIA), (IIIB), (IVA), (IVB), (IVC), (IVD), (IVE), (VA), (VB), (VBa), (VC), (VIA), (VIB), (VIC), (VIIA), (VIIB), (VIIC), (VIID), (VIIE), (VIIF), (VIIG), (VIIIA), (VIIIB), (VIIIC), or (VIIID).

In certain examples of formula (IA), (IB), (IC), (IIA), (IIB), (IIIA), (IIIB), (VIA), (VIB), (VIC), (VIIA), (VIIB), and/or (VIIC) as described above, each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal (e.g., each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo).

In particular examples of formula (VIIIA) as described above, X is O or X, together with the carbon to which it is attached, forms an acetal (e.g., cyclic acetal).

Definitions

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

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

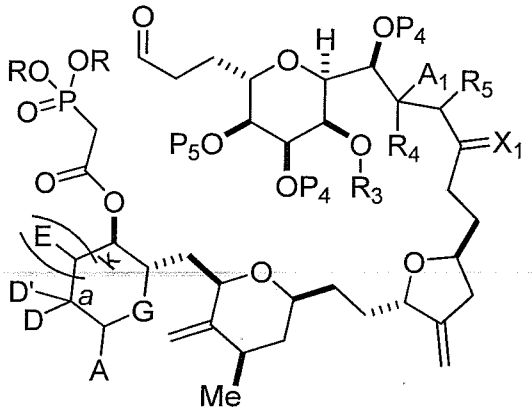
By "acetal" is meant –O–(CHR)–O–, where R is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted arylalkyl, or a bond to the chain of carbon atoms within an intermediate in the synthesis of the halichondrin macrolide.

Claims

1. A method of preparing a macrocyclic intermediate in the synthesis of a halichondrin macrolide, said method comprising performing a macrocyclization reaction on a non-macrocyclic intermediate, said macrocyclization reaction producing said macrocyclic intermediate by forming C.2-C.3, C.3-C.4, C.12-C.13, C.15-C.16, C.19-C.20, or C.26-C.27 bond in the structure of the halichondrin macrolide.

2. The method of claim 1, wherein said performing said macrocyclization reaction comprises contacting said non-macrocyclic intermediate with an organic base and a Lewis acid, contacting said non-macrocyclic intermediate with an olefin metathesis catalyst, or contacting said non-macrocyclic intermediate with a Cr(II) salt and a Ni(II) salt.

3. The method of claim 2, wherein said non-macrocyclic intermediate is (1) a compound of formula (IA):



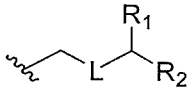
(IA)

or a salt or a tautomer thereof,

wherein

each R is independently optionally substituted alkyl or optionally substituted aryl;

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; 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:



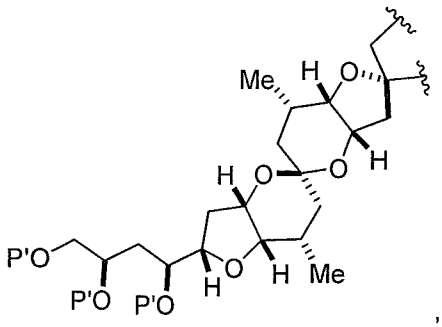
(1),

wherein

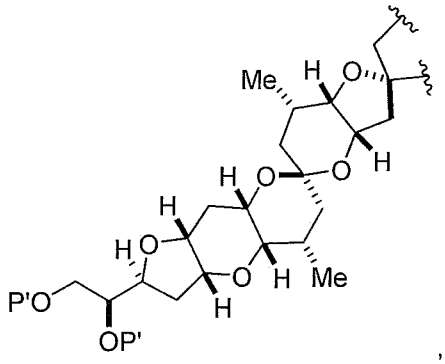
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

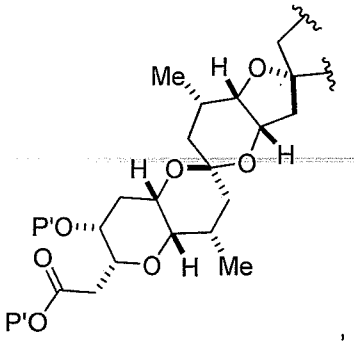
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

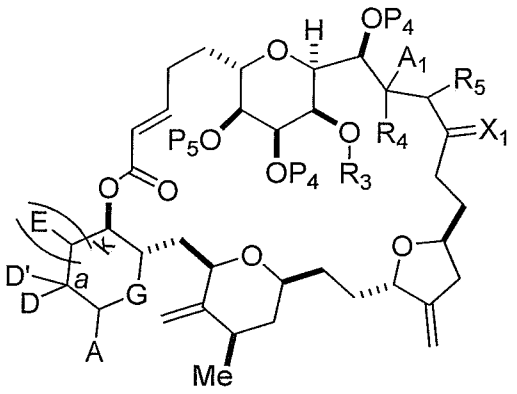
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IB):

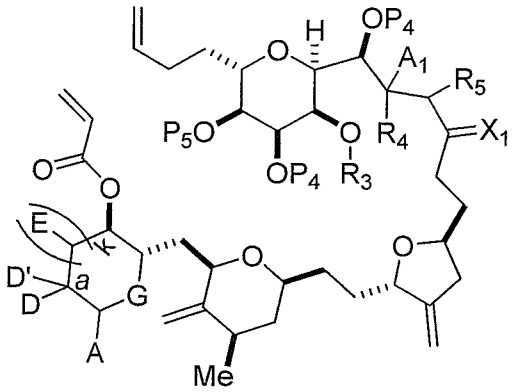


(IB)

or a salt or a tautomer thereof;

and said performing said macrocyclization reaction comprises contacting said compound of formula (IA) or a salt or a tautomer thereof with an organic base and a Lewis acid;

(2) a compound of formula (IIA):

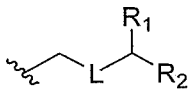


(IIA)

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; 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:



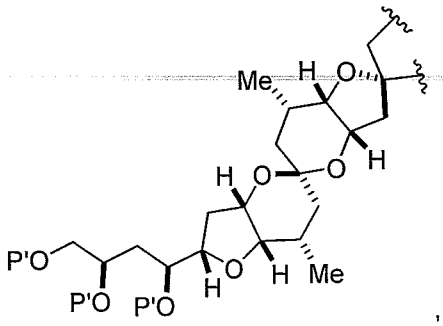
(1),

wherein

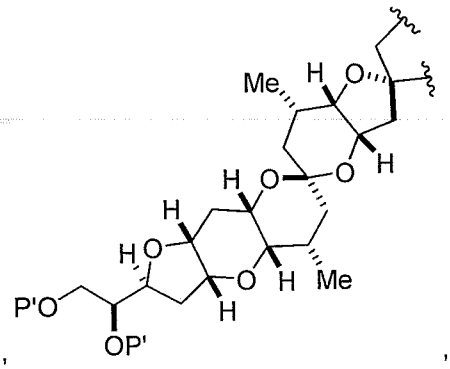
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

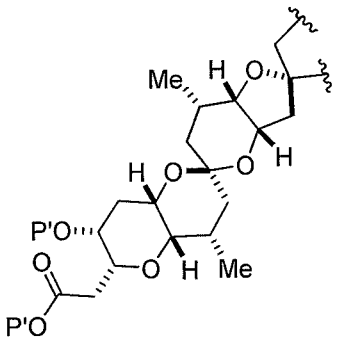
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

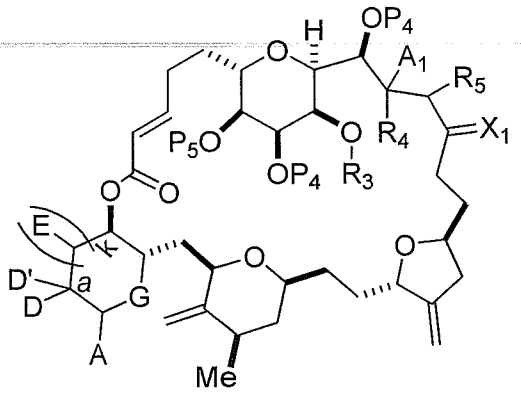
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IB):

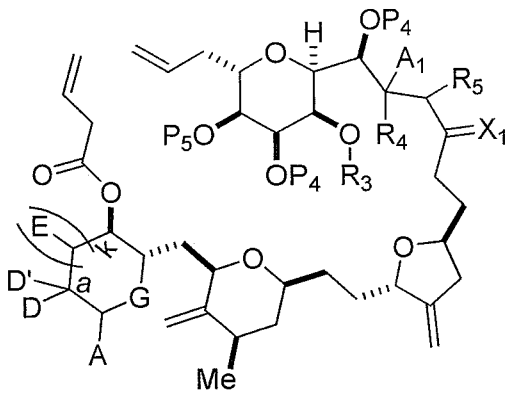


(IB)

or a salt or a tautomer thereof;

and said performing said macrocyclization reaction comprises contacting said compound of formula (IIA) or a salt or a tautomer thereof with an olefin metathesis catalyst;

(3) a compound of formula (IIIA):

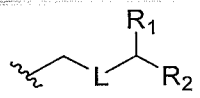


(IIIA)

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; 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:



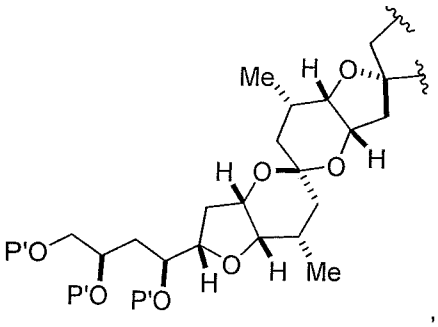
(1),

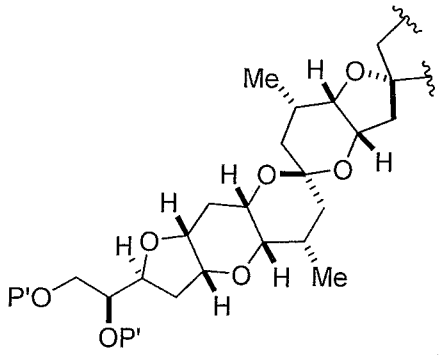
wherein

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

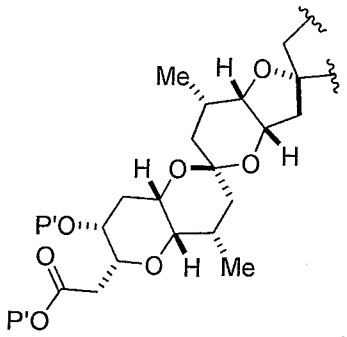
R_1 is H, or R_1 and P_1 combine to form a bond;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

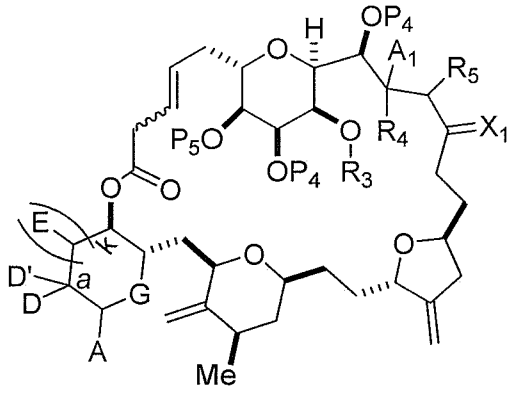
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IIIB):

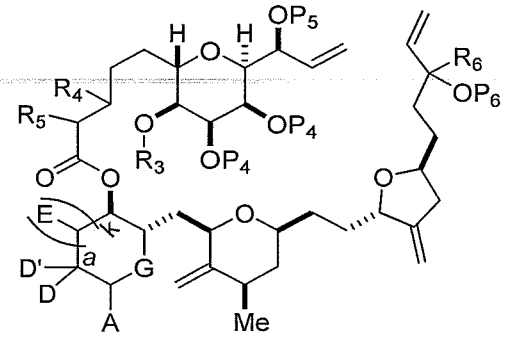


(IIIB)

or a salt or a tautomer thereof;

and said performing said macrocyclization reaction comprises contacting said compound of formula (IIIA) or a salt or a tautomer thereof with an olefin metathesis catalyst;

(4) a compound of formula (IVA):

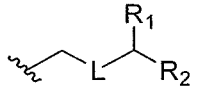


(IVA)

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; 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:



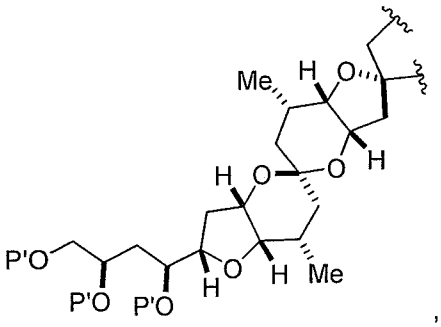
(1),

wherein

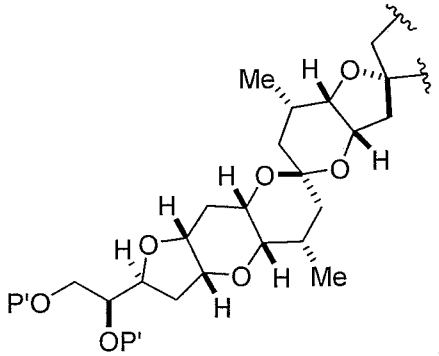
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

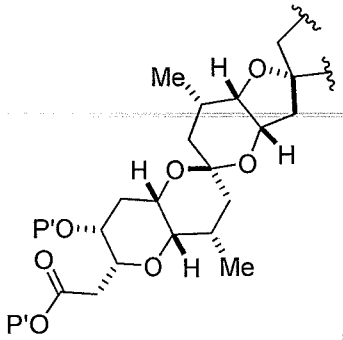
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(i) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(ii) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

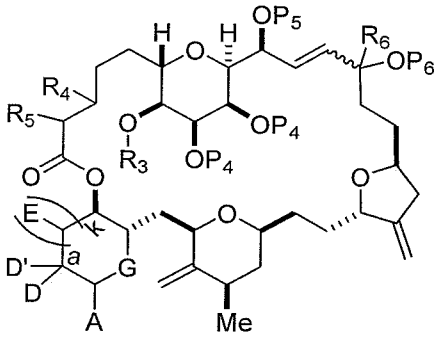
or

(iii) R_3 and R_4 combine to form a bond, and R_5 is H;

each P_4 and P_5 is independently H or a hydroxyl protecting group;

R_6 is H, and P_6 is H or a hydroxyl protecting group; or R_6 and P_6 combine to form a double bond; and

wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IVB):

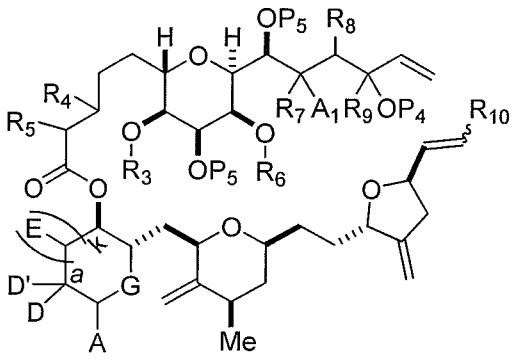


(IVB)

or a salt thereof;

and said performing said macrocyclization reaction comprises contacting said compound of formula (IVA) or a salt thereof with an olefin metathesis catalyst;

(5) a compound of formula (VA):

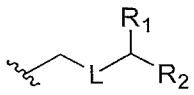


(VA)

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; 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:



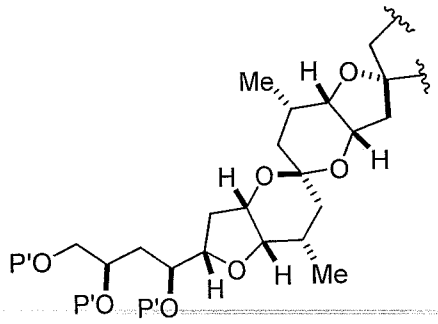
(1),

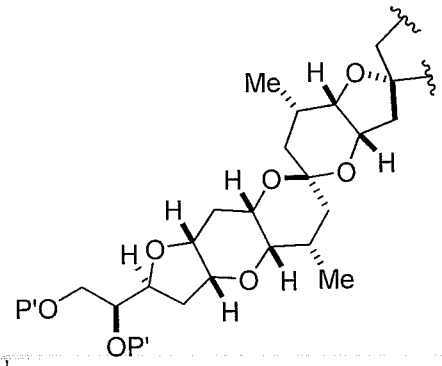
wherein

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

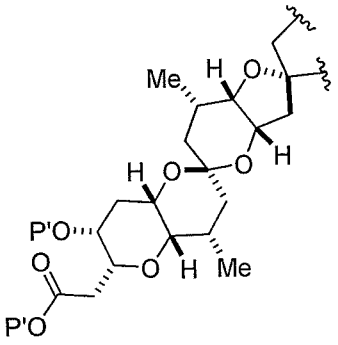
R_1 is H, or R_1 and P_1 combine to form a bond;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(a1) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(a2) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(a3) R_3 and R_4 combine to form a bond, and R_5 is H;

(b1) A_1 and R_7 combine to form oxo, R_6 is H or a hydroxyl protecting group, and R_8 is H;

or

(b2) A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_6 is H or a hydroxyl protecting group, and R_7 and R_8 combine to form a double bond;

or

(ii) R_6 and R_7 combine to form a bond, and R_8 is H or OP";

(c1) R_9 is H, and P_4 is H or a hydroxyl protecting group;

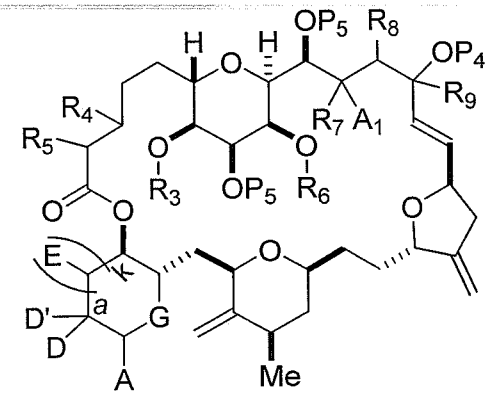
or

(c2) R_9 and P_4 combine to form a double bond;

R_{10} is H or $-CH_2X_1CH_2CH=CH_2$, wherein X_1 is O, $-C(R_{11})_2-$, or NP_6, and wherein each R_{11} is independently H or $-COOR_{12}$, P_6 is an *N*-protecting group, and R_{12} is alkyl;

each P_5 is independently H or a hydroxyl protecting group; and

wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (VB):

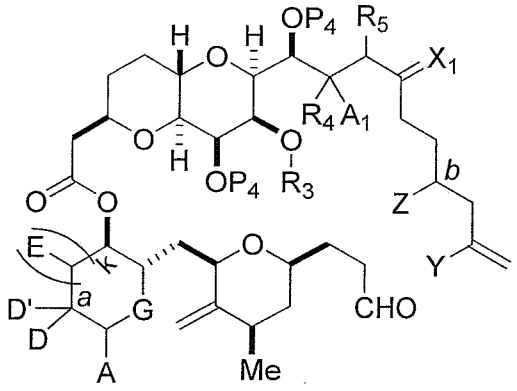


(VB)

or a salt or a tautomer thereof;

and said performing said macrocyclization reaction comprises contacting said compound of formula (VA) or a salt or a tautomer thereof with an olefin metathesis catalyst;

(6) a compound of formula (VIA):



(VIA)

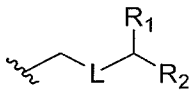
or a salt or a tautomer thereof,

wherein

Y is iodide, bromide, or trifluoromethanesulfonate;

b designates (*R*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide; or *b* designates (*S*)-stereogenic center, and Z is OR_6, wherein R_6 is a hydroxyl protecting group;

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; 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:



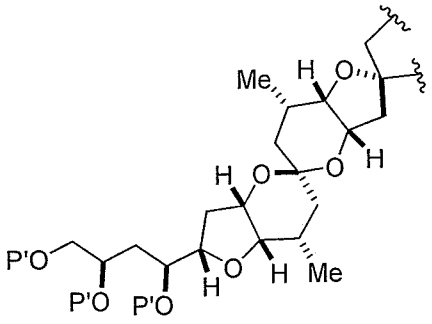
(1),

wherein

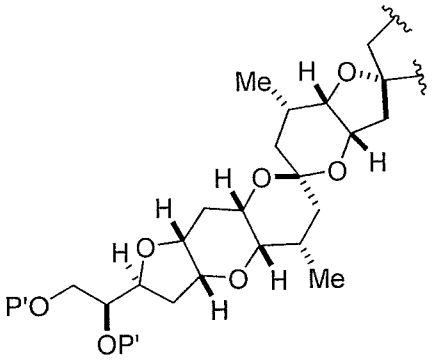
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

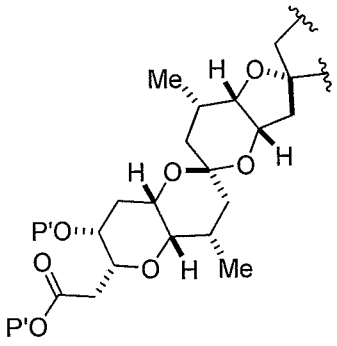
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

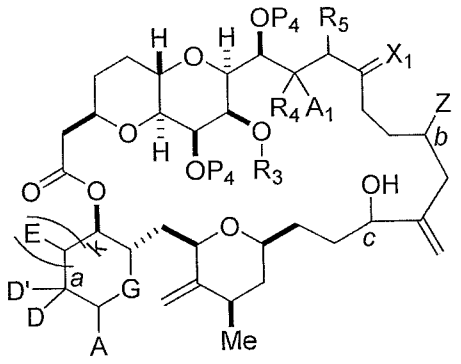
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IVB):



(VIB)

or a salt or a tautomer thereof,

wherein

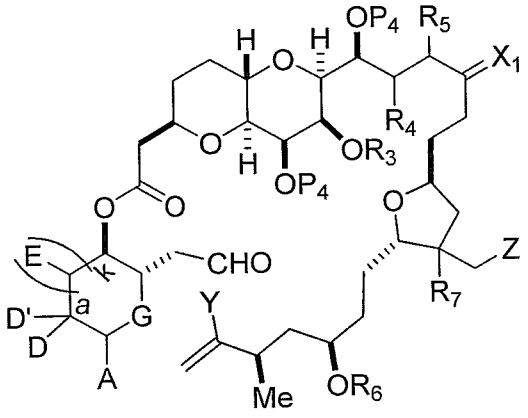
b designates (*R*)-stereogenic center, *c* designates (*S*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide;

or

b designates (*S*)-stereogenic center, *c* designates (*R*)-stereogenic center, and Z is OR_6, wherein R_6 is a hydroxyl protecting group;

and said performing said macrocyclization reaction comprises contacting said compound of formula (VIA) or a salt or a tautomer thereof with a Cr(II) salt and a Ni(II) salt; or

(7) a compound of formula (VIIA):



(VIIA)

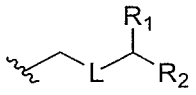
or a salt thereof,

wherein

Y is iodide, bromide, or trifluoromethanesulfonate;

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; 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:



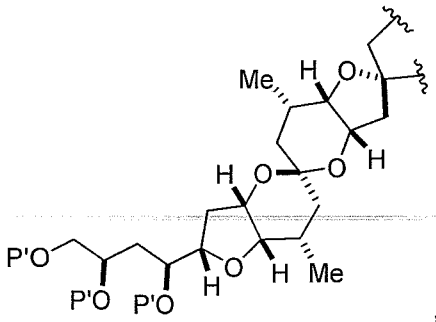
(1),

wherein

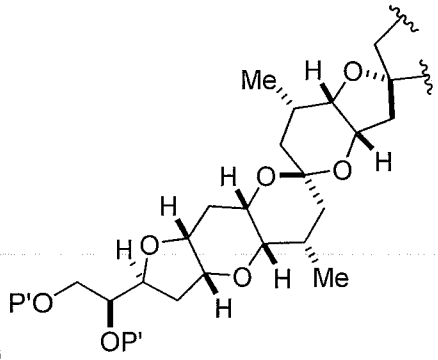
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

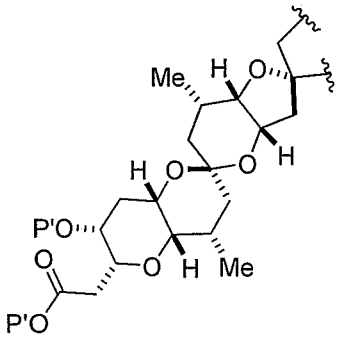
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(a1) R_3 is H or a hydroxyl protecting group, R_4 and R_5 combine to form a double bond, each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$, wherein R_8 is H or a hydroxyl protecting group;

or

(a2) R_3 and R_4 combine to form a bond, R_5 is H, and

each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$;

or

both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

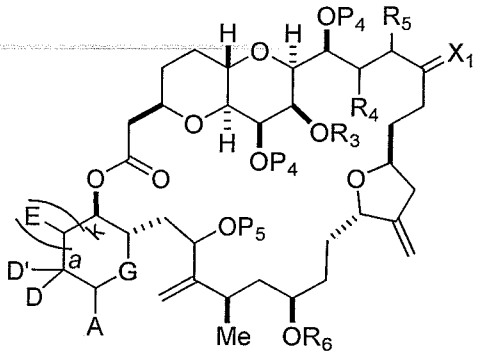
(b1) Z is chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond;

or

(b2) Z and R_7 combine to form a double bond, and R_6 is a hydroxyl protecting group;

and

wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (VIIB):



(VIIB)

or a salt thereof,

wherein each of P_5 and R_6 is independently H or a hydroxyl protecting group;

and said performing said macrocyclization reaction comprises contacting said compound of formula (VIIA) or a salt thereof with a Cr(II) salt and a Ni(II) salt.

4. The method of claim 3, wherein for (1),

(a) each R is optionally substituted alkyl;

(b) both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(c) P_5 is a hydroxyl protecting group;

(d) R_3 and R_4 combine to form a bond, and R_5 is H;

(e) said organic base is DBU or trimethylamine; and/or

(f) said Lewis acid is a salt of Li or Zn.

5. The method of claim 3, wherein for (2) or (3),

(a) both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and/or

(b) P_5 is a hydroxyl protecting group.

6. The method of claim 3, wherein for (4), at least one of P_4 and P_5 is H.

7. The method of claim 3, wherein for (5),

(a) R_9 is H, and P_4 is H;

(b) R_{10} is $-CH_2X_1CH_2CH=CH_2$, and X_1 is O;

(c) R_6 and R_7 combine to form a bond, and R_8 is H;

(d) each P_5 is independently a hydroxyl protecting group

(e) at least one P_5 is H; and/or

(f) R_3 and R_4 combine to form a bond, and R_5 is H.

8. The method of claim 3, wherein for (2), (3), (4), or (5), said olefin metathesis catalyst is a ruthenium-carbene complex.

9. The method of claim 3, wherein for (6),

(a) Y is bromide;

(b) R_3 and R_4 combine to form a bond, and R_5 is H;

(c) both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(d) Z is a sulfonate;

(e) Z is OR_6, wherein R_6 is a hydroxyl protecting group; and/or

(f) Z is an ester, carbonate, or carbamate.

10. The method of claim 3, wherein for (7),

(a) Z is iodide;

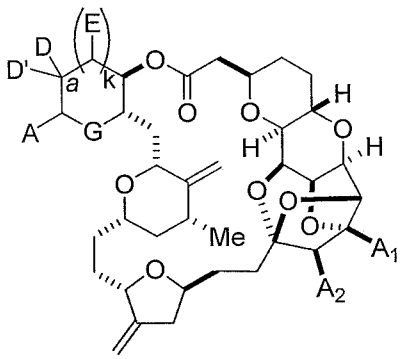
(b) Y is trifluoromethanesulfonate;

(c) R_3 is H or a hydroxyl protecting group, R_4 and R_5 combine to form a double bond, each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms $-(CH(OR_8))-$, wherein R_8 is H or a hydroxyl protecting group;

(d) at least one of P_3, P_4, and R_6 is a hydroxyl protecting group; and/or

(e) Z is chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond.

11. A method of preparing:



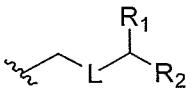
halichondrin macrolide

or a salt thereof,

wherein

each of A_1 and A_2 is independently H or OP", where each P" is independently H or a hydroxyl protecting group;

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; 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:



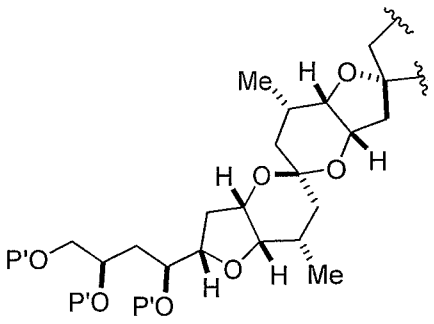
(1),

wherein

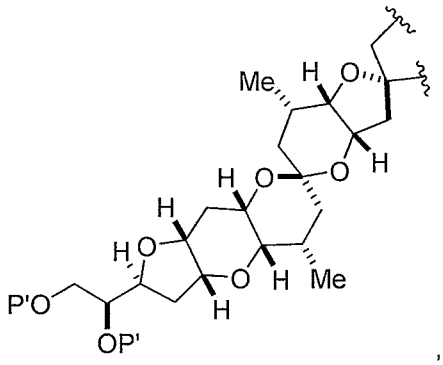
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

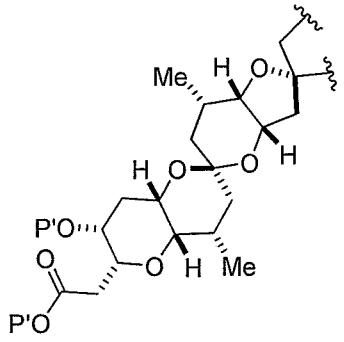
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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;

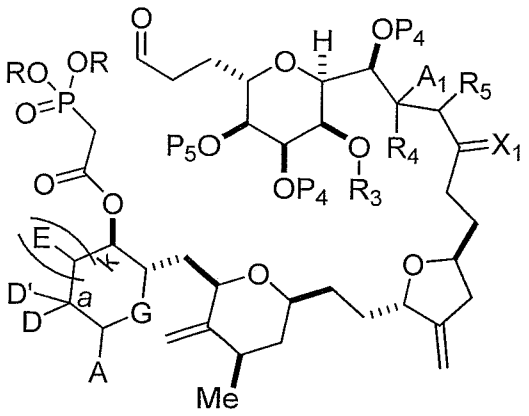
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl,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

k is 0 or 1;

n is 0, 1, or 2;

(1) said method comprising:

(A) producing a compound of formula (IB) from a compound of formula (IA), the compound of formula (IA) having the following structure:



(IA)

or a salt or a tautomer thereof,

wherein

each R is independently optionally substituted alkyl or optionally substituted aryl;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

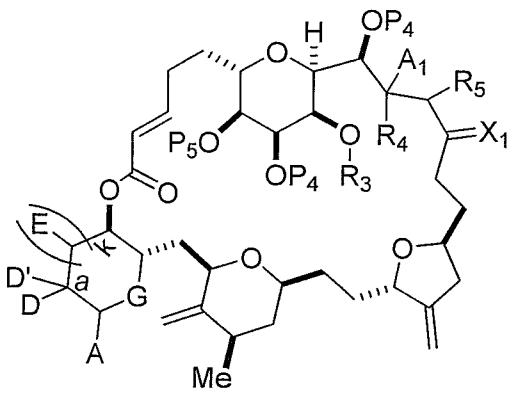
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

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



(IB)

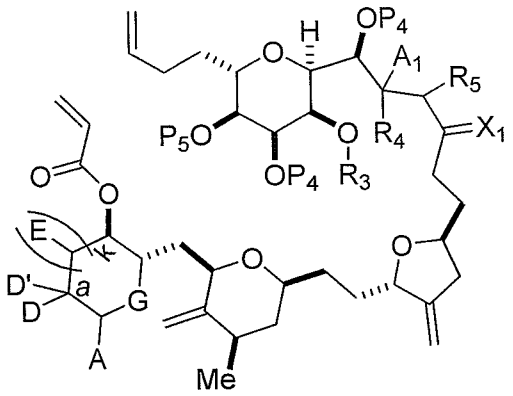
or a salt or a tautomer thereof;

and

(B) producing the halichondrin macrolide from compound (IB);

(2) said method comprising:

(A) producing a compound of formula (IB) from a compound of formula (IIA), the compound of formula (IIA) having the following structure:



(IIA)

or a salt or a tautomer thereof,

wherein

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

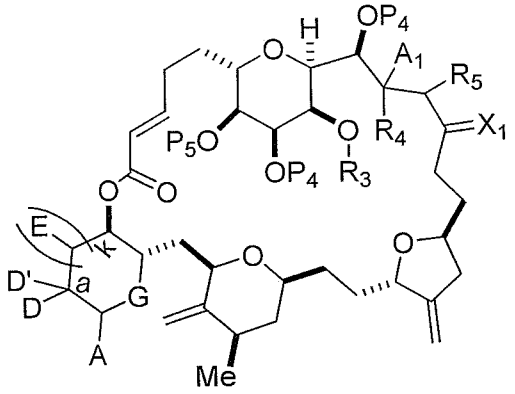
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

The compound of formula (IB) having the following structure:



(IB)

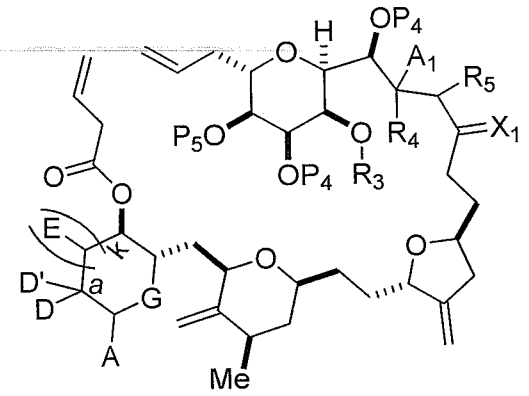
or a salt or a tautomer thereof;

and

(B) producing the halichondrin macrolide from compound (IB);

(3) said method comprising:

(A) producing a compound of formula (IIIB) from a compound of formula (IIIA), the compound of formula (IIIA) having the following structure:



(IIIA)

or a salt or a tautomer thereof,

wherein

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

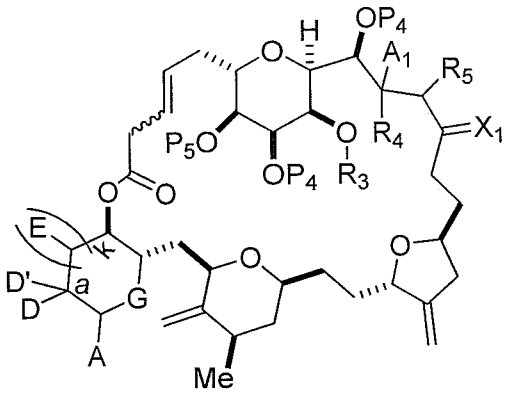
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is –(CH(OP$_Y$))–, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group; and

the compound of formula (IIIB) having the following structure:



(IIIB),

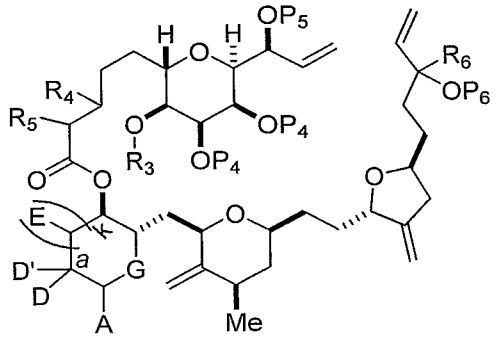
or a salt or a tautomer thereof;

and

(B) producing the halichondrin macrolide from the compound of formula (IIIB);

(4) said method comprising:

(A) producing a compound of formula (IVB) from a compound of formula (IVA), the compound of formula (IVA) having the following structure:



(IVA)

or a salt thereof,

wherein

(i) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(ii) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

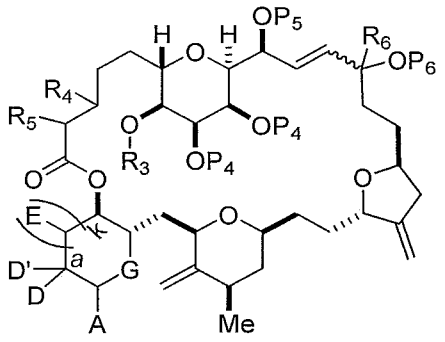
(iii) R_3 and R_4 combine to form a bond, and R_5 is H;

each P_4 and P_5 is independently H or a hydroxyl protecting group;

R_6 is H, and P_6 is H or a hydroxyl protecting group; or R_6 and P_6 combine to form a double bond;

and

the compound of formula (IVB) having the following structure:



(IVB)

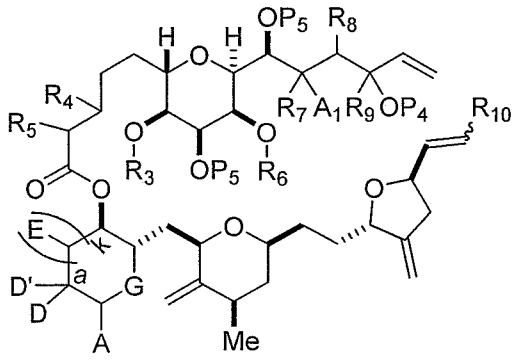
or a salt thereof;

and

(B) producing the halichondrin macrolide from the compound of formula (IVB);

(5) said method comprising:

(A) producing a compound of formula (VB) from a compound of formula (VA), the compound of formula (VA) having the following structure:



(VA)

or a salt or a tautomer thereof,

wherein

(a1) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(a2) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(a3) R_3 and R_4 combine to form a bond, and R_5 is H;

(b1) A_1 and R_7 combine to form oxo, R_6 is H or a hydroxyl protecting group, and R_8 is H;

or

(b2) A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_6 is H or a hydroxyl protecting group, and R_7 and R_8 combine to form a double bond;

or

(ii) R_6 and R_7 combine to form a bond, and R_8 is H or OP";

(c1) R_9 is H, and P_4 is H or a hydroxyl protecting group;

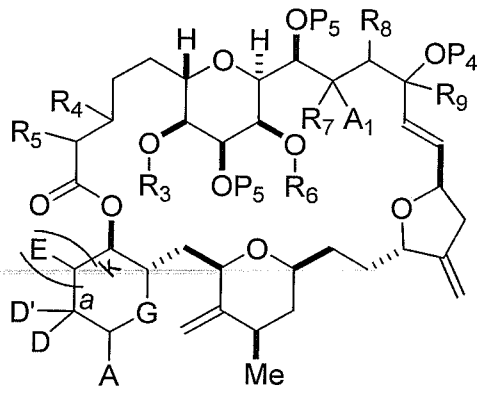
or

(c2) R_9 and P_4 combine to form a double bond;

R_{10} is H or $-CH_2X_1CH_2CH=CH_2$, wherein X_1 is O, $-C(R_{11})_2-$, or NP_6, and wherein each R_{11} is independently H or $-COOR_{12}$, P_6 is an *N*-protecting group, and R_{12} is alkyl;

each P_5 is independently H or a hydroxyl protecting group; and

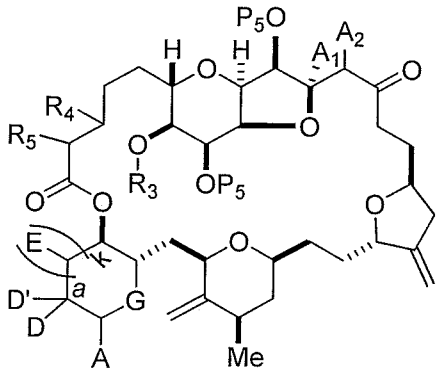
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (VB):



(VB)

or a salt or a tautomer thereof;

(B) producing a compound of formula (VC) from the compound of formula (VB), the compound of formula (VC) having the following structure:

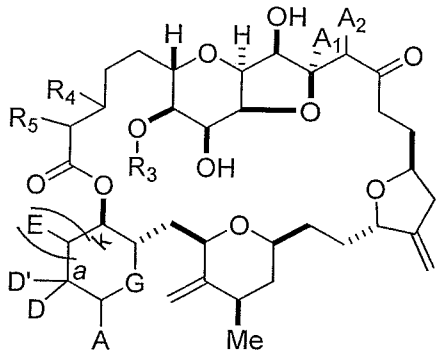


(VC)

or a salt thereof,

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

(C) producing a compound of formula (IVC) from the compound of formula (VC), the compound of formula (IVC) having the following structure:



(IVC)

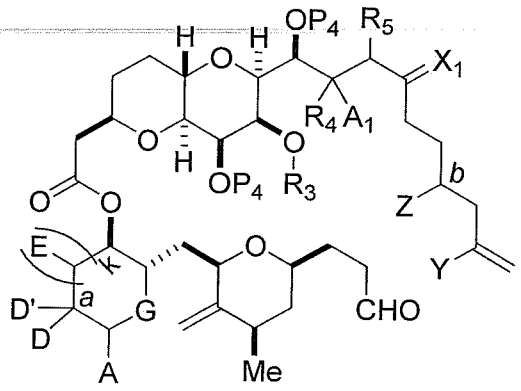
or a salt thereof,

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

(D) producing the halichondrin macrolide from the compound of formula (IVC);

(6) said method comprising:

(A) producing a compound of formula (VIB) from a compound of formula (VIA), the compound of formula (VIA) having the following structure:



(VIA)

or a salt or a tautomer thereof,

wherein

Y is iodide, bromide, or trifluoromethanesulfonate;

b designates (*R*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide; or *b* designates (*S*)-stereogenic center, and Z is OR_6, wherein R_6 is a hydroxyl protecting group;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

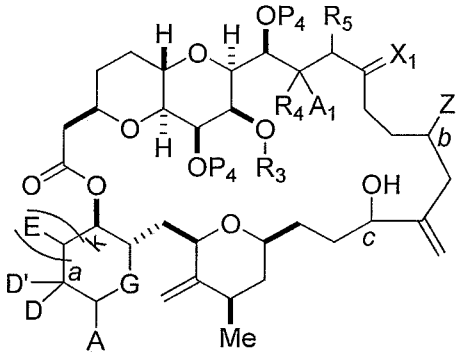
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

and each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

the compound of formula (VIB) having the following structure:



(VIB)

or a salt or a tautomer thereof,

wherein

b designates (*R*)-stereogenic center, *c* designates (*S*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide;

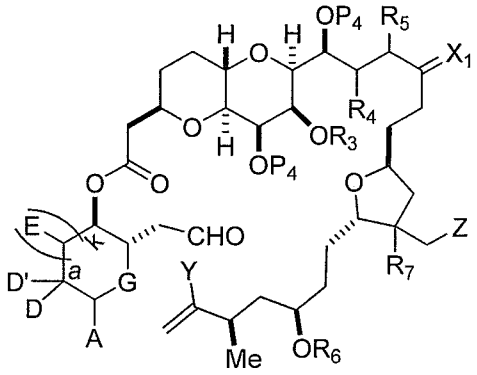
or

b designates (*S*)-stereogenic center, *c* designates (*R*)-stereogenic center, and Z is OR_6, wherein R_6 is a hydroxyl protecting group;

(B) producing the halichondrin macrolide from the compound of formula (VIB); or

(7) said method comprising:

(A) producing a compound of formula (VIIB) from a compound of formula (VIIA), the compound of formula (VIIA) having the following structure:



(VIIA)

or a salt thereof,

wherein

Y is iodide, bromide, or trifluoromethanesulfonate;

(a1) R_3 is H or a hydroxyl protecting group, R_4 and R_5 combine to form a double bond, each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$;

or

(a2) R_3 and R_4 combine to form a bond, R_5 is H, and

each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$;

or

both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(b1) Z is chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond;

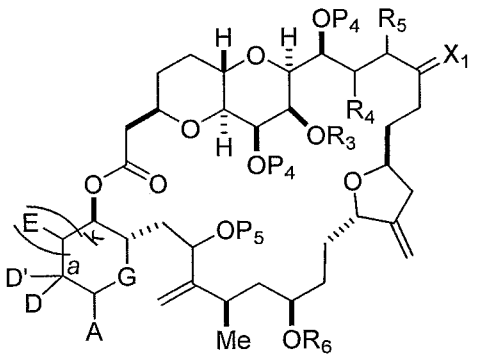
or

(b2) Z and R_7 combine to form a double bond, and R_6 is a hydroxyl protecting group;

and

wherein R_8 is H or a hydroxyl protecting group

the compound of formula (VIIB) having the following structure:

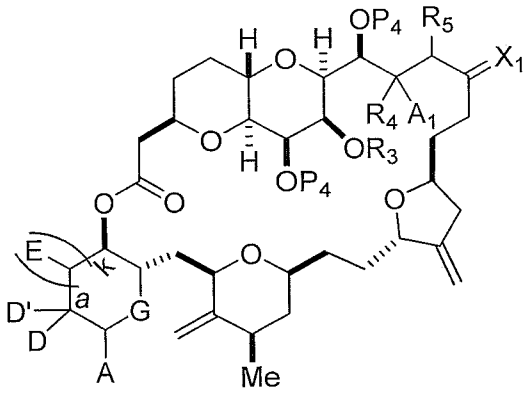


(VIIB)

or a salt thereof,

wherein each of P_5 and R_6 is H or a hydroxyl protecting group;

(B) producing a compound of formula (VIIC) from the compound of formula (VIIB), the compound of formula (VIIC) having the following structure:



(VIIC)

or a salt or a tautomer thereof,

wherein A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

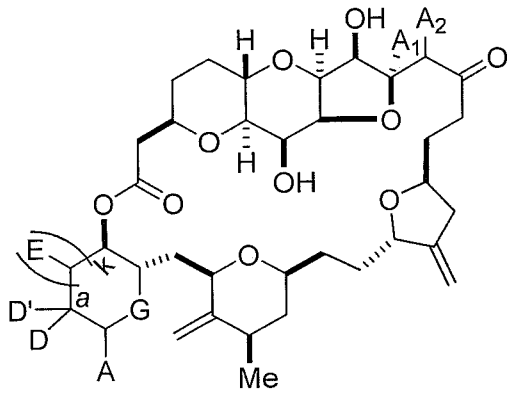
A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

(C) producing a compound of formula (VIID) from the compound of formula (VIIC), the compound of formula (VIID) having the following structure:



(VIID)

or a salt thereof,

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

and

(D) producing the halichondrin macrolide from the compound of formula (VIID).

12. The method of claim 11, wherein for (1),

(a) said producing the compound of formula (IB) comprises reacting the compound of formula (IA) with with an organic base and a Lewis acid;

(b) said producing the halichondrin macrolide comprises reacting the compound of formula (IB) with a hydroxyl protecting group removing agent; and/or

(c) each R is optionally substituted alkyl.

13. The method of claim 11, wherein for (2)

(a) said producing the compound of formula (IB) comprises reacting the compound of formula (IIA) with an olefin metathesis catalyst; and/or

(b) said producing the halichondrin macrolide comprises reacting the compound of formula (IB) with a hydroxyl protecting group removing agent.

14. The method of claim 11, wherein for (3)

(a) said producing the compound of formula (IIIB) comprises reacting the compound of formula (IIIA) with an olefin metathesis catalyst;

(b) said producing the halichondrin macrolide comprises reacting the compound of formula (IIIB) with a hydroxyl protecting group removing agent;

(c) both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and/or

(d) P_5 is a hydroxyl protecting group.

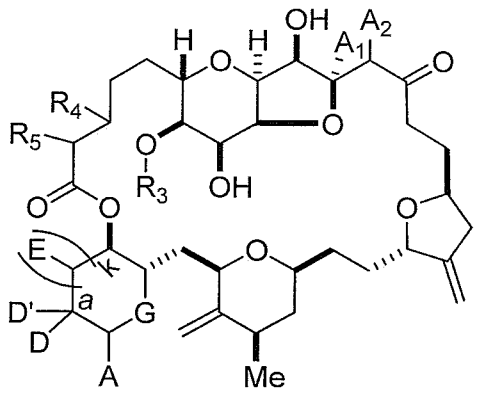
15. The method of claim 11, wherein for (4)

(a) said producing the compound of formula (IVB) comprises reacting the compound of formula (IVA) with an olefin metathesis catalyst;

(b) said producing the halichondrin macrolide from the compound of formula (IVB) comprises reacting the compound of formula (IVB) with a Brønsted acid; and/or

(c) at least one of P_4 and P_5 is H.

16. The method of claim 11, wherein said producing the halichondrin macrolide comprises producing the compound of formula (IVC), the compound of formula (IVC) having the following structure:



(IVC)

or a salt thereof,

wherein each of A_1 and A_2 is H or OP", and wherein P" is H or a hydroxyl protecting group; and producing the halichondrin macrolide from the compound of formula (IVC).

17. The method of claim 16, wherein

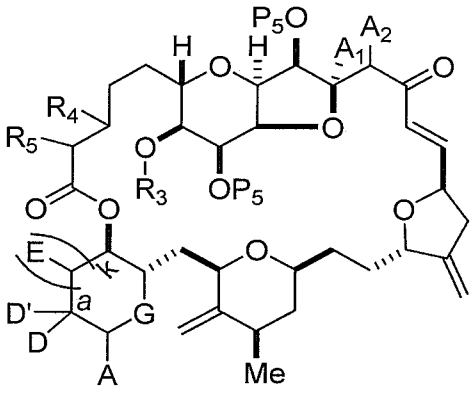
(a) said producing the compound of formula (IVC) comprises reacting the compound of formula (IVB) with a hydroxyl protecting group removing agent; and/or

(b) said producing the halichondrin macrolide from the compound of formula (IVC) comprises reacting the compound of formula (IVC) with a Brønsted acid.

18. The method of claim 11, wherein for (5),

(a) said producing the compound of formula (VB) comprises contacting the compound of formula (VA) with an olefin metathesis catalyst;

(b) P_4 is H, R_9 is H, and said producing the compound of formula (VC) comprises oxidizing the compound of formula (VB) to produce a compound of formula (VBa):



(VBa)

or a salt thereof;

and reacting the compound of formula (VBa) with a 1,4-reducing agent to produce the compound of formula (VC);

(c) said producing the compound of formula (IVC) comprises contacting the compound of formula (VC) with a hydroxyl protecting group removing agent; and/or

(d) said producing the halichondrin macrolide comprises contacting the compound of formula (IVC) with a Brønsted acid.

19. The method of claim 11, wherein for (6),

(a) said producing the compound of formula (VIB) comprises reacting the compound of formula (VIA) with a Cr(II) salt and a Ni(II) salt;

(b) said producing the halichondrin macrolide comprises the step of nucleophilic ring-closing of the compound of formula (VIB);

(c) wherein both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and/or

(d) R_3 and R_4 combine to form a bond, and R_5 is H.

20. The method of claim 11, wherein for (7),

(a) said producing the compound of formula (VIIB) comprises reacting the compound of formula (VIIA) with a Cr(II) salt and a Ni(II) salt;

(b) said producing the compound of formula (VIIC) comprises the step of nucleophilic ring-closing of the compound of formula (VIIB);

(c) said producing the compound of formula (VIID) comprises reacting the compound of formula (VIIC) with a hydroxyl protecting group removing agent;

(d) said producing the halichondrin macrolide comprises reacting the compound of formula (VIID) with a Brønsted acid;

(e) Z is iodide;

(f) Y is trifluoromethanesulfonate;

(g) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

(h) each P_4 is independently H or a hydroxyl protecting group, and

X_1, together with the carbon to which it is attached, forms $-(CH(OR_8))-$, wherein R_8 is H or a hydroxyl protecting group;

(i) P_5 is H; and/or

(j) Z is chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond.

21. The method of claim 3, wherein

(a) *a* designates (*S*)-stereogenic center;

(b) one and only one of D and D' is optionally substituted alkyl or OP_1;

(c) A is a group of formula (1);

(d) L is –(CH(OP$_2$))–;

(e) R_1 and P_1 combine to form a bond;

(f) G is O;

(g) E is optionally substituted alkyl;

(h) k is 1;

(i) R_2 is –(CH$_2$)$_n$OP$_3$;

(j) at least one of P_2 and P_3 is a hydroxyl protecting group; and/or

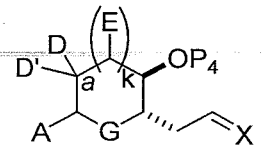
(k) A_1 is H.

22. The method of claim 21, wherein one and only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group.

23. A method of preparing an intermediate in the synthesis of a halichondrin macrolide, said method comprising performing an allene-Prins reaction by contacting a compound of formula (VIIIA) with a compound of formula (VIIIB) and R_4OH,

wherein R_4 is an optionally substituted acyl;

wherein the compound of formula (VIIIA) has the following structure:

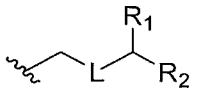


(VIIIA)

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; 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:



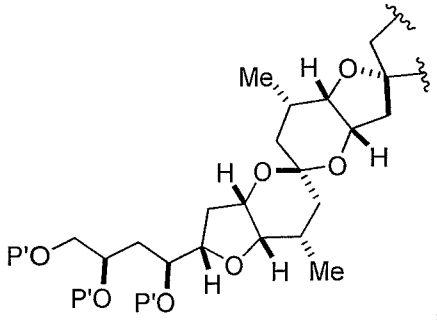
(1),

wherein

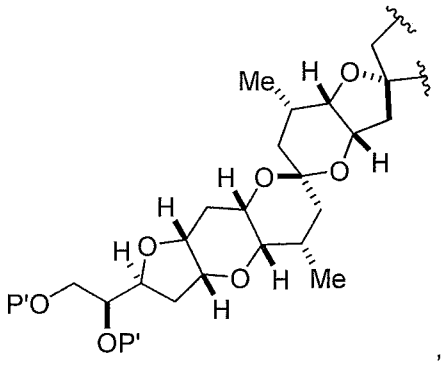
L is –(CH(OP$_2$))–, –(C(OH)(OP$_2$))–, or –C(O)–;

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

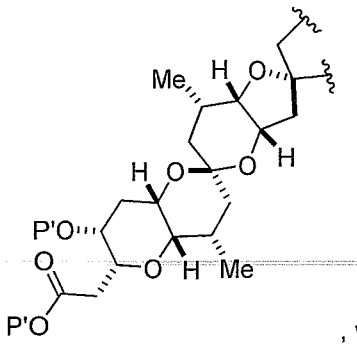
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

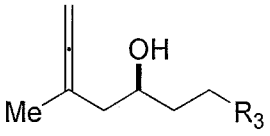
k is 0 or 1;

n is 0, 1, or 2;

X is O, or X, together with the carbon atom to which it is attached, forms $-(C(OP_Z)_2)-$, wherein each P_Z is independently optionally substituted alkyl or optionally substituted aryl, or both P_Z combine to form optionally substituted alkylene or optionally substituted arylene; and

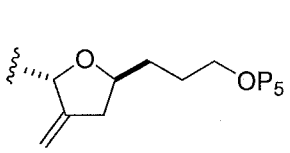
P_4 is H or a hydroxyl protecting group;

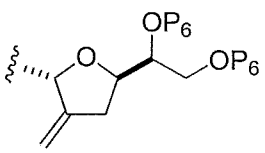
wherein the compound of formula (VIIIB) has the following structure:

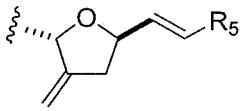


(VIIIB),

wherein

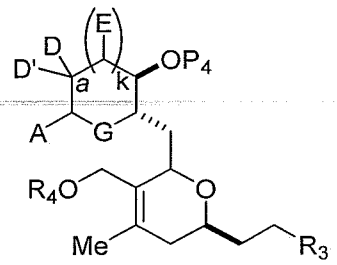
R_3 is $-CH_2-OP_5$, $-CH=CH_2$, 

, 

, or 

,

wherein P_5 is H or a hydroxyl protecting group; each P_6 is independently a hydroxyl protecting group, or both P_6 groups, together with the atoms to which each is attached, combine to form a cyclic protected diol; and R_5 is is H or -$CH_2X_1CH_2CH=CH_2$, wherein X_1 is O, -CH_2-, or NP_7, wherein P_7 is a sulfonyl; and wherein said intermediate is a compound of formula (VIIIC):



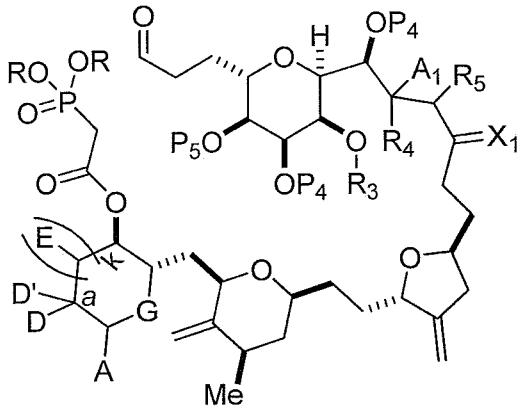
(VIIIC)

or a salt thereof.

24. The method of claim 23, wherein said performing a Prins reaction comprises reacting the compound of formula (VIIIA) with a Lewis acid; and/or k is 1.

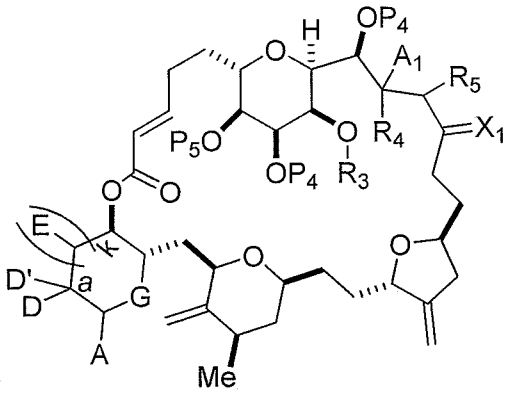
25. A compound of

(1) formula (IA) or formula (IB),



(IA)

or



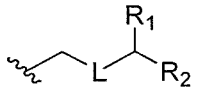
(IB)

or a salt or a tautomer thereof,

wherein

each R is independently optionally substituted alkyl or optionally substituted aryl;

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; 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:



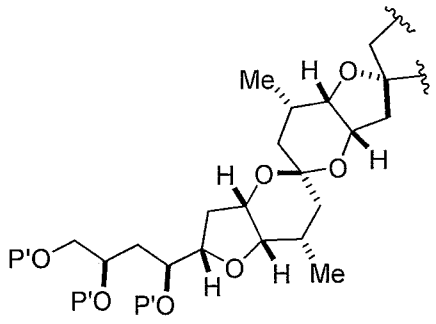
(1),

wherein

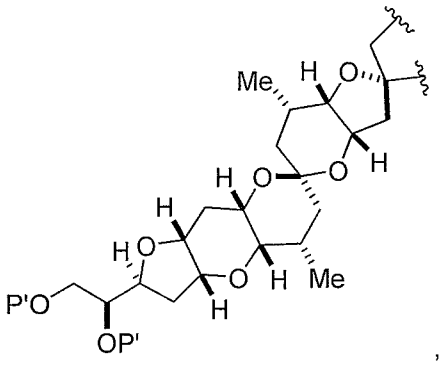
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

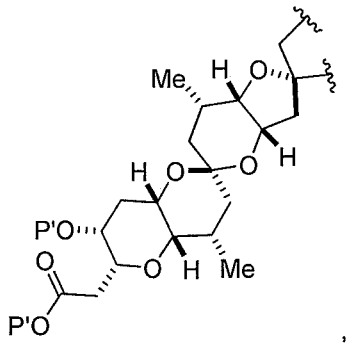
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

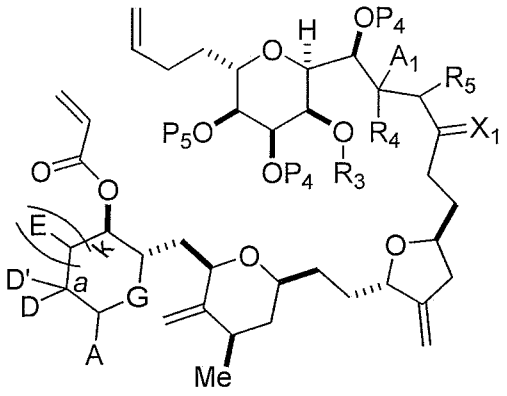
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

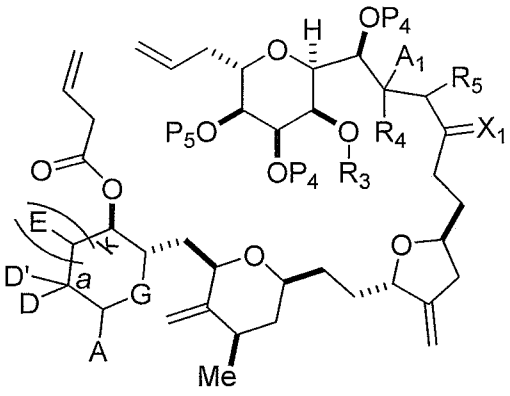
each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

P_5 is H or a hydroxyl protecting group;

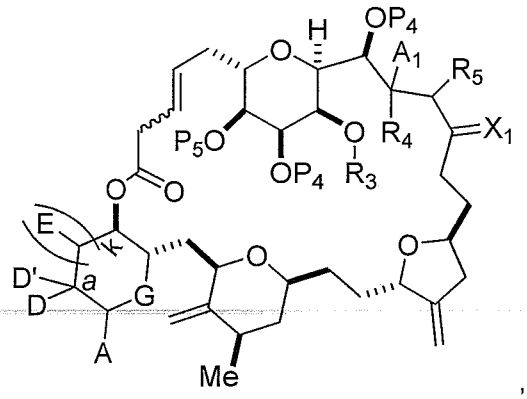
(2) formula (IIA), formula (IIIA), or formula (IIIB):



(IIA)



(IIIA)

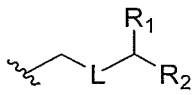


(IIIB)

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; 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),

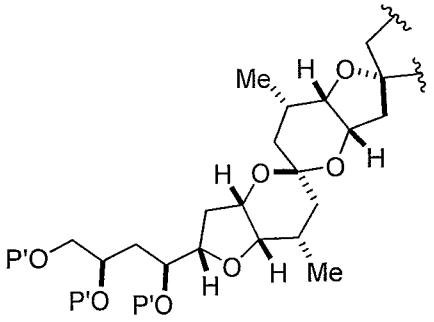
wherein

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

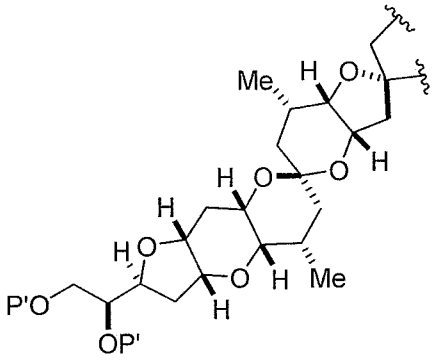
R_1 is H, or R_1 and P_1 combine to form a bond;

R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each

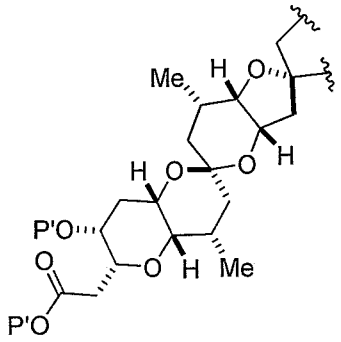
is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



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

E is 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

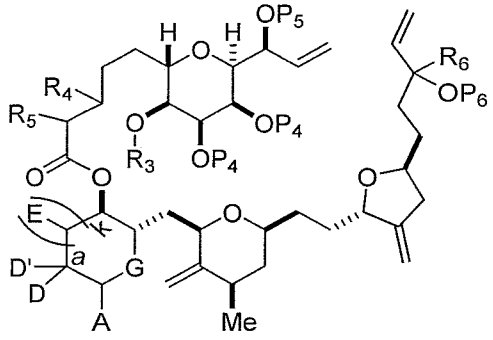
or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is –(CH(OP$_Y$))–, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal; and

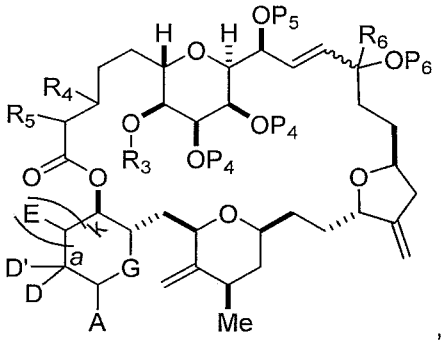
P_5 is H or a hydroxyl protecting group;

(3) formula (IVA), formula (IVB), or formula (IVC):



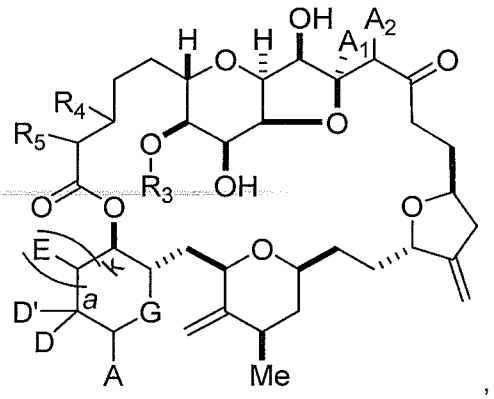
(IVA)

,



(IVB)

, or



(IVC)

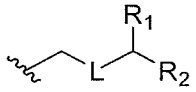
,

or a salt thereof,

wherein

each of A_1 and A_2 is H or OP", where P" is H or a hydroxyl protecting group;

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; 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:



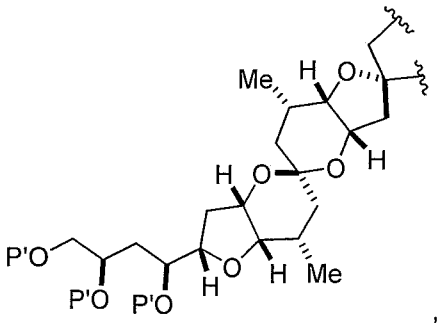
(1),

wherein

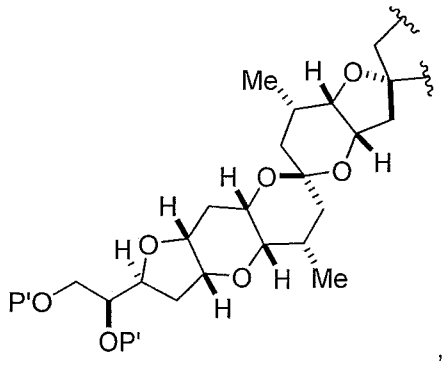
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

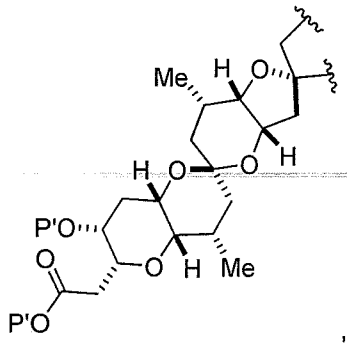
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(i) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(ii) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

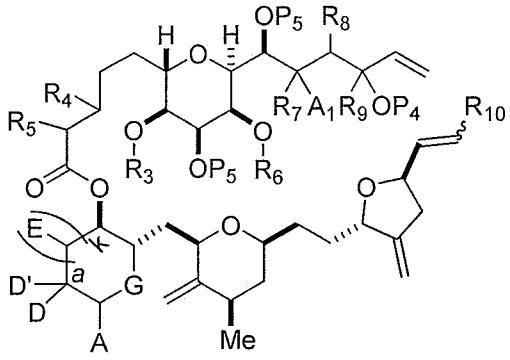
or

(iii) R_3 and R_4 combine to form a bond, and R_5 is H;

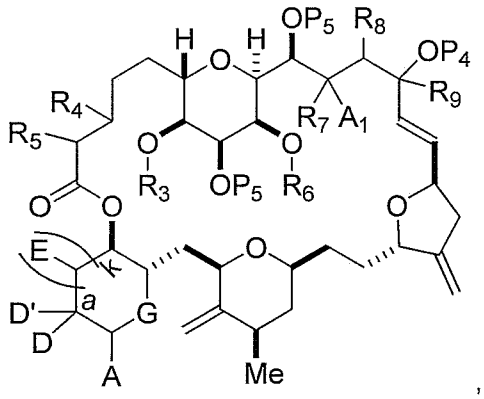
each P_4 and P_5 is independently H or a hydroxyl protecting group; and

R_6 is H, and P_6 is H or a hydroxyl protecting group; or R_6 and P_6 combine to form a double bond;

(4) formula (VA), formula (VB), or formula (VC):

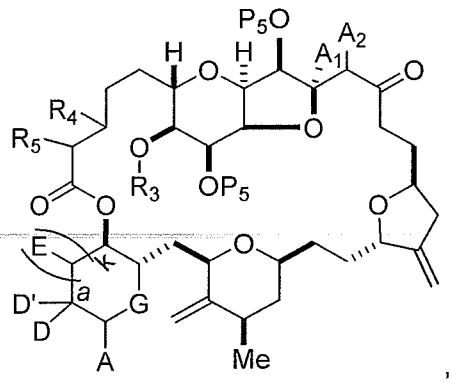


(VA)



(VB)

, or

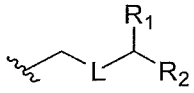


(VC)

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; 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:



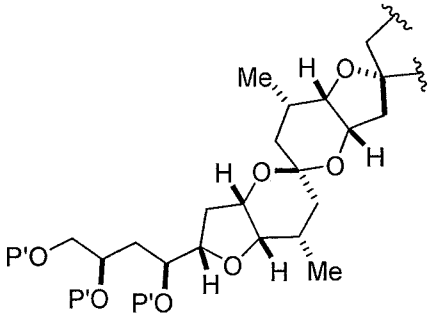
(1),

wherein

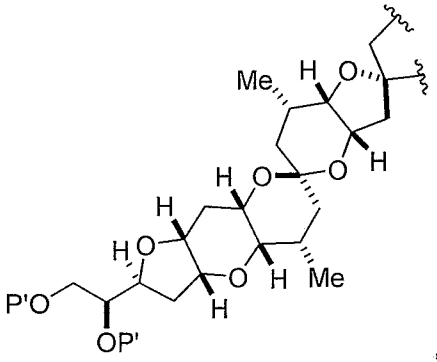
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

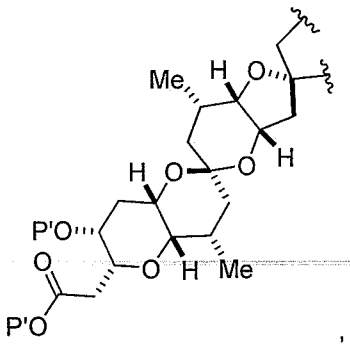
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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;

A_2 is H or OP";

E is 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(a1) R_3 is H or a hydroxyl protecting group, R_4 is alkyl ether, and R_5 is H;

(a2) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(a3) R_3 and R_4 combine to form a bond, and R_5 is H;

(b1) A_1 and R_7 combine to form oxo, R_6 is H or a hydroxyl protecting group, and R_8 is H;

or

(b2) A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_6 is H or a hydroxyl protecting group, and R_7 and R_8 combine to form a double bond;

or

(ii) R_6 and R_7 combine to form a bond, and R_8 is H or OP";

(c1) R_9 is H, and P_4 is H or a hydroxyl protecting group;

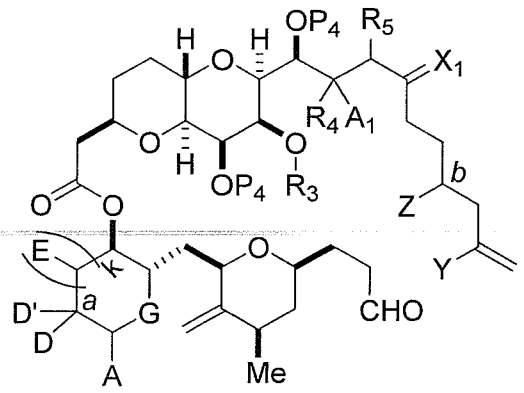
or

(c2) R_9 and P_4 combine to form a double bond;

R_{10} is H or $-CH_2X_1CH_2CH=CH_2$, wherein X_1 is O, $-C(R_{11})_2-$, or NP_6, and wherein each R_{11} is independently H or $-COOR_{12}$, P_6 is an *N*-protecting group, and R_{12} is alkyl;

each P_5 is independently H or a hydroxyl protecting group;

(5) formula (VIA):

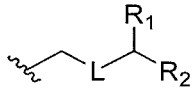


(VIA)

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; 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:



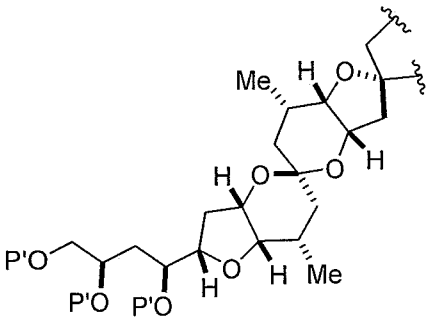
(1),

wherein

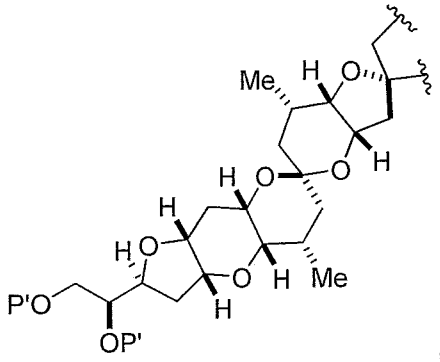
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

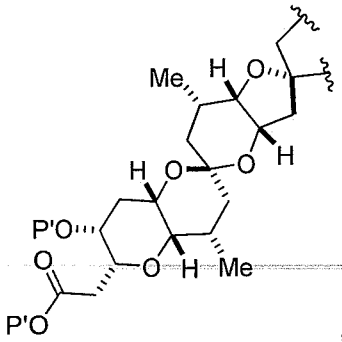
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

Y is iodide, bromide, or trifluoromethanesulfonate;

b designates (*R*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide; or *b* designates (*S*)-stereogenic center, and Z is OR_6, wherein R_6 is a hydroxyl protecting group;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

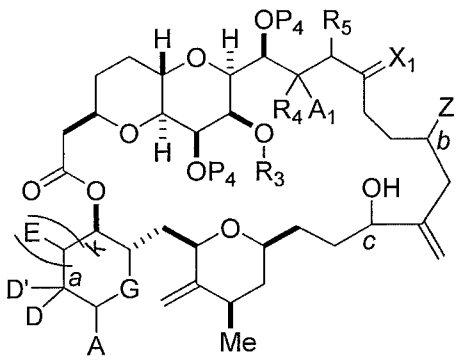
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(6) formula (VIB):



(VIB)

or a salt or a tautomer thereof,

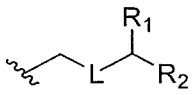
wherein

b designates (*R*)-stereogenic center, *c* designates (*S*)-stereogenic center, and Z is a sulfonate, chloride, bromide, or iodide;

or

b designates (*S*)-stereogenic center, *c* designates (*R*)-stereogenic center, and Z is OR_6, wherein R_6 is a hydroxyl protecting group;

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; 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:



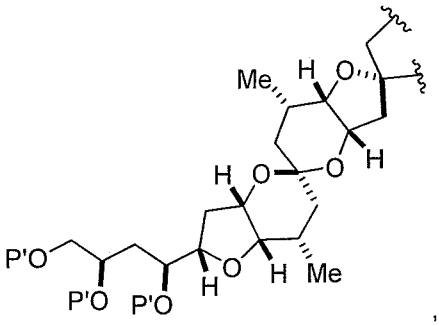
(1),

wherein

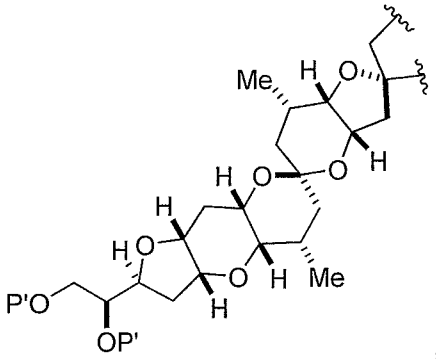
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

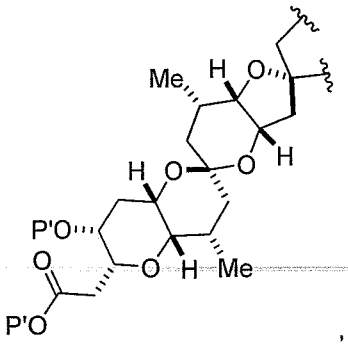
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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;

k is 0 or 1;

n is 0, 1, or 2;

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

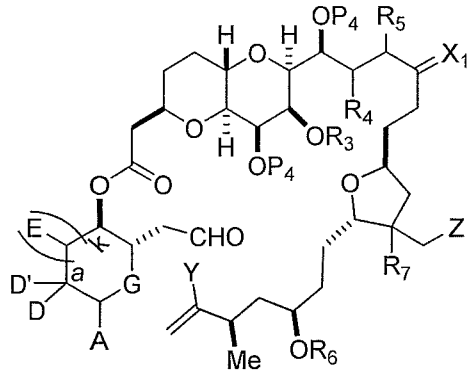
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP";

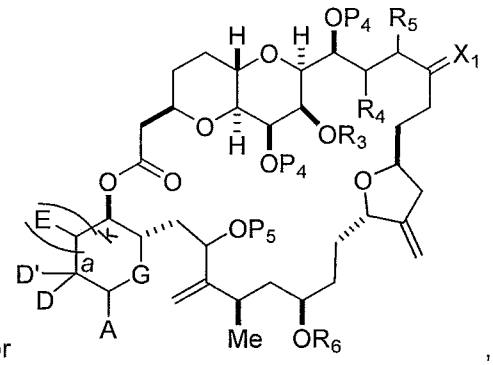
each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(7) formula (VIIA) or formula (VIIB):



(VIIA)

or

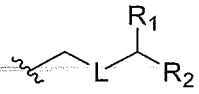


(VIIB)

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; 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:



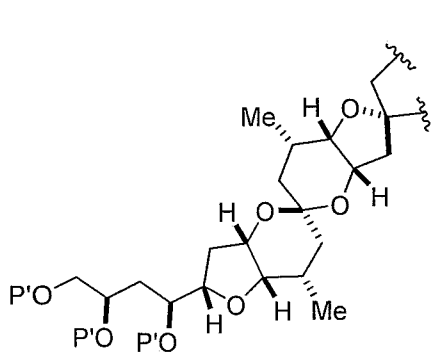
(1),

wherein

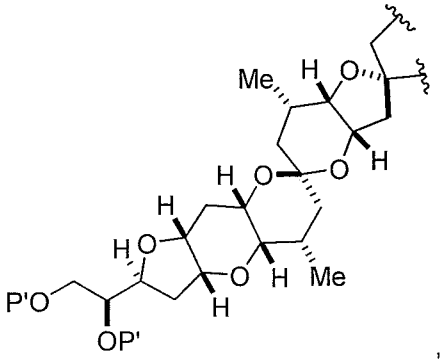
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

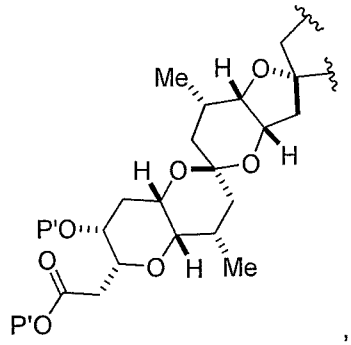
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

(a1) R_3 is H or a hydroxyl protecting group, R_4 and R_5 combine to form a double bond, each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$;

or

(a2) R_3 and R_4 combine to form a bond, R_5 is H, and

each P_4 is independently H or a hydroxyl protecting group, and X_1, together with the carbon to which it is attached, forms a carbonyl or $-(CH(OR_8))-$;

or

both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(b1) Z is chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond;

(b2) Z and R_7 combine to form a double bond, and R_6 is a hydroxyl protecting group;

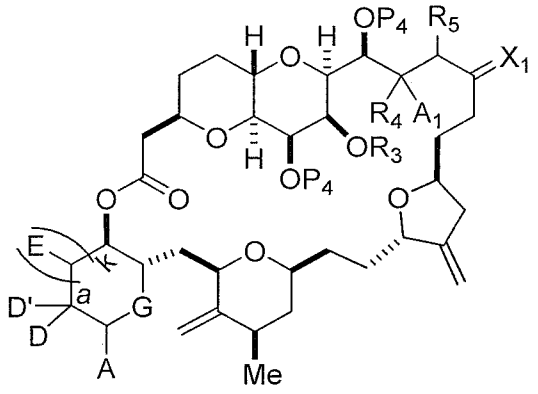
or

(b3) when Z and R_7 are absent, R_6 is H or a hydroxyl protecting group;

P_5 is H or a hydroxyl protecting group;

wherein R_8 is H or a hydroxyl protecting group; or

(8) formula (VIIC):

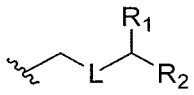


(VIIC)

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; 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:



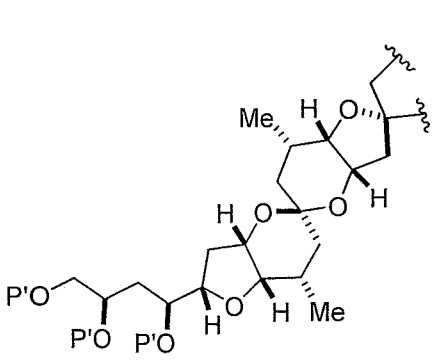
(1),

wherein

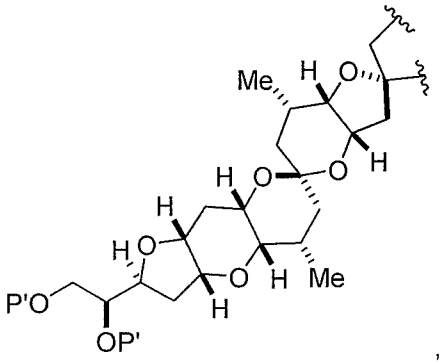
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

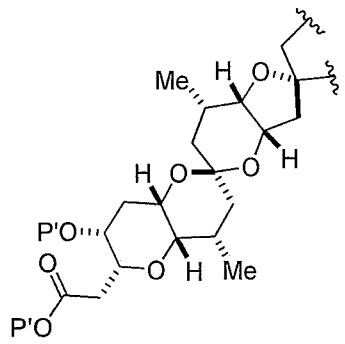
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 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, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

each P_4 is H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is $-(CH(OP_Y))-$, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form a ketal; and

A_1 and R_4 combine to form oxo, R_3 is H or a hydroxyl protecting group, and R_5 is H;

or

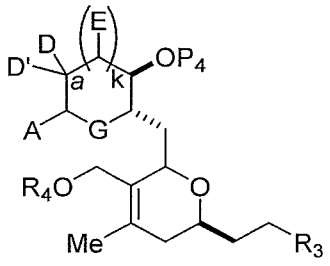
A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

(ii) R_3 and R_4 combine to form a bond, and R_5 is H or OP".

26. A compound of formula (VIIC):

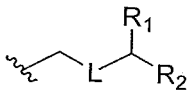


(VIIIC)

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; 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:



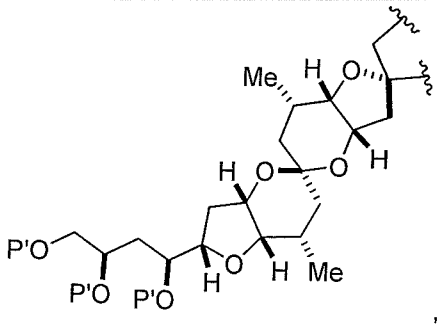
(1),

wherein

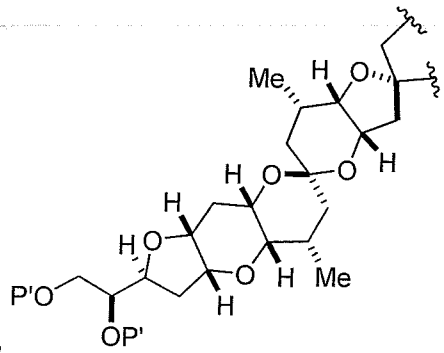
L is $-(CH(OP_2))-$, $-(C(OH)(OP_2))-$, or $-C(O)-$;

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

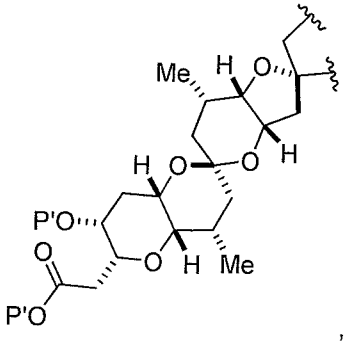
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 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 optionally substituted alkyl or optionally substituted alkoxy;

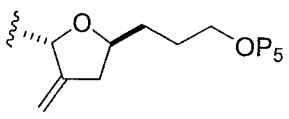
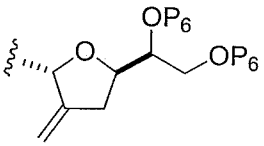
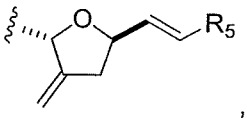
G is O, S, CH_2, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, 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;

k is 0 or 1;

n is 0, 1, or 2;

P_4 is H or a hydroxyl protecting group; and

R_3 is $-CH_2-OP_5$, $-CH=CH_2$, , , or ,

wherein P_5 is H or a hydroxyl protecting group; each P_6 is independently a hydroxyl protecting group, or both P_6 groups, together with the atoms to which each is attached, combine to form a cyclic protected diol; and R_5 is is H or $-CH_2X_1CH_2CH=CH_2$, wherein X_1 is O, $-CH_2-$, or NP_7, wherein P_7 is a sulfonyl.