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

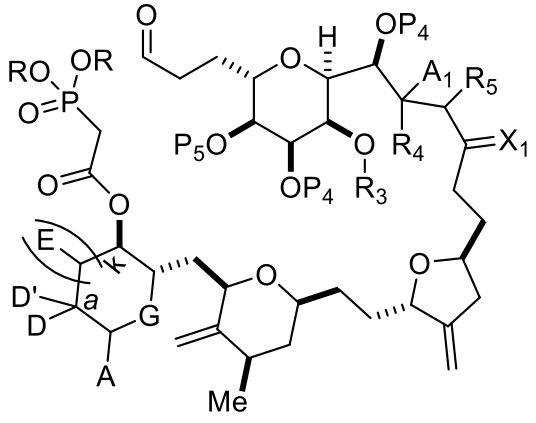
Background

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, wherein (1) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.2-C.3 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with an organic base and a Lewis acid, wherein said non-macrocyclic intermediate is (1) a compound of formula (IA):



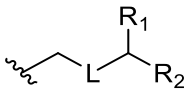
(IA)

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:



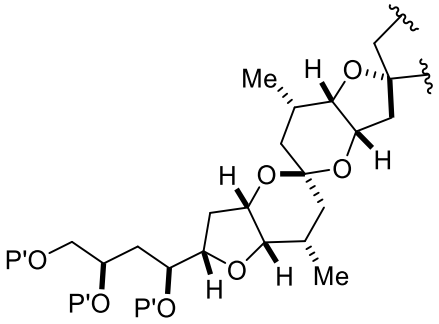
(1),

wherein

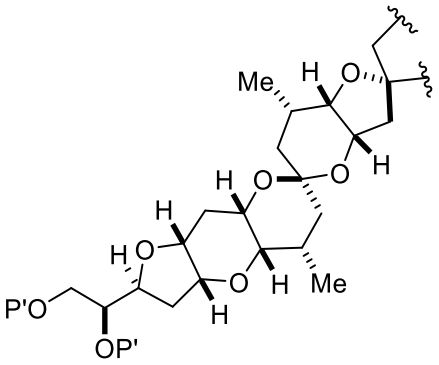
L is –(CH(OP$_2$))–, –(C(OH)(OP$_2$))–, or –C(O)–;

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

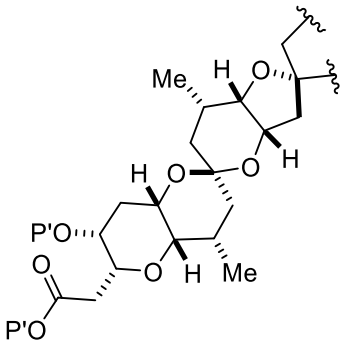
R_2 is H or -(CH$_2$)$_n$OP$_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, 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$_2$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$_A$, 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;

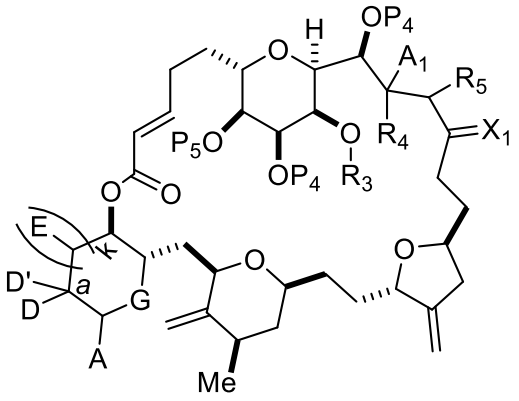
or

(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

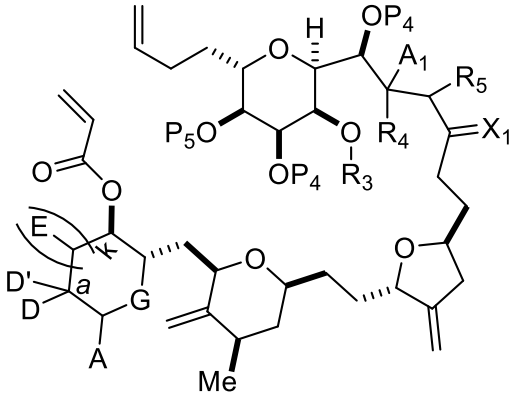
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IB):



(IB)

or a salt or a tautomer thereof;

(2) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.2-C.3 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with an olefin metathesis catalyst, wherein said non-macrocyclic intermediate is a compound of formula (IIA):

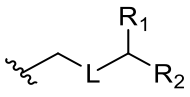


(IIA)

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:



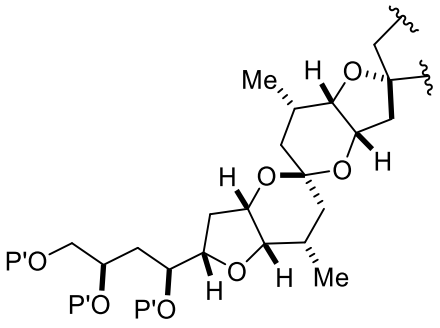
(1),

wherein

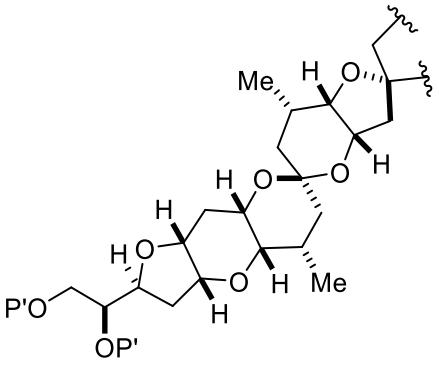
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

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

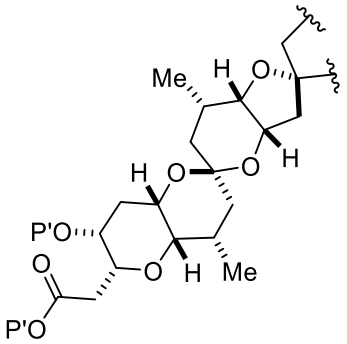
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

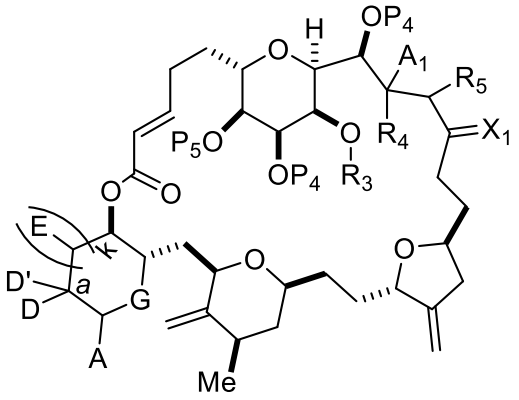
or

(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

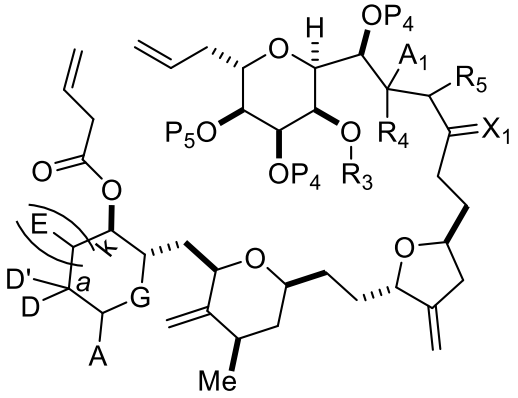
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IB):



(IB)

or a salt or a tautomer thereof;

(3) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.3-C.4 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with an olefin metathesis catalyst, wherein said non macrocyclic intermediate is a compound of formula (IIIA):

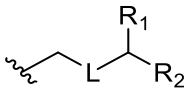


(IIIA)

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),

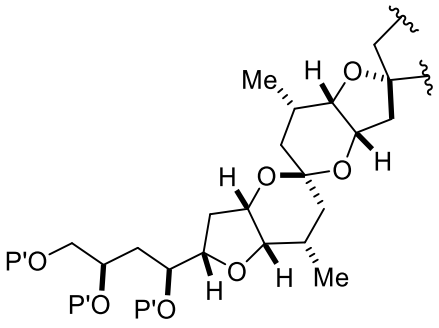
wherein

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

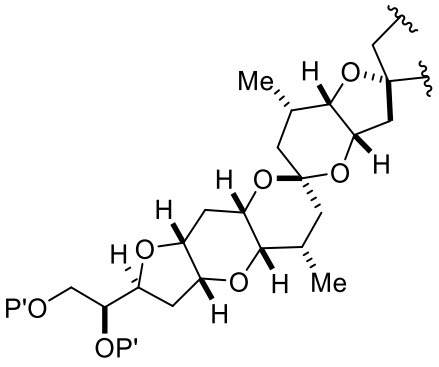
R_1 is H, or R_1 and P_1 combine to form a bond;

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;

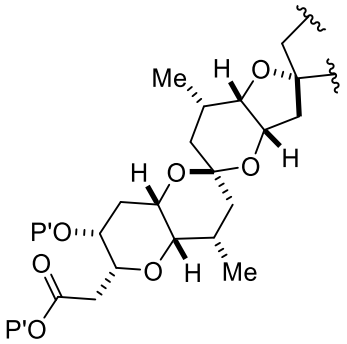
or R_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, 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;

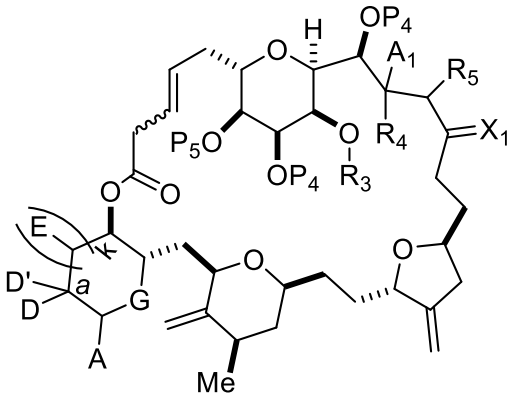
or

(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

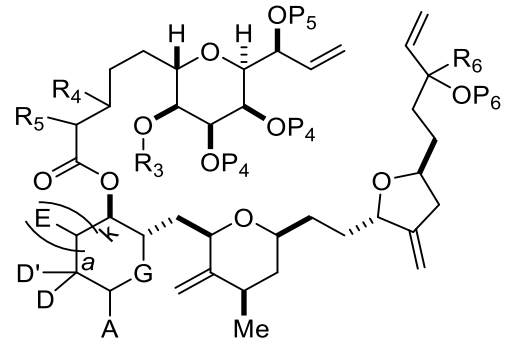
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IIIB):



(IIIB)

or a salt or a tautomer thereof;

(4) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.12-C.13 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with an olefin metathesis catalyst, wherein said non-macrocyclic intermediate is a compound of formula (IVA):

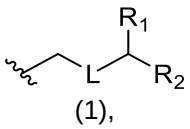


(IVA)

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:



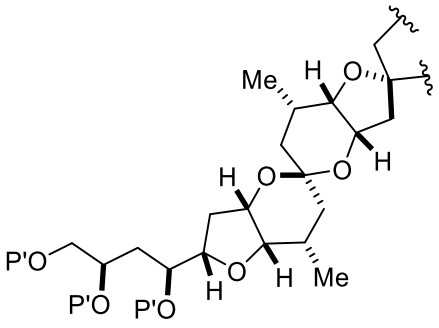
(1),

wherein

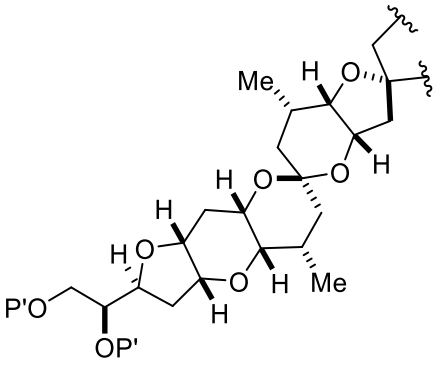
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or $–C(O)–$;

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

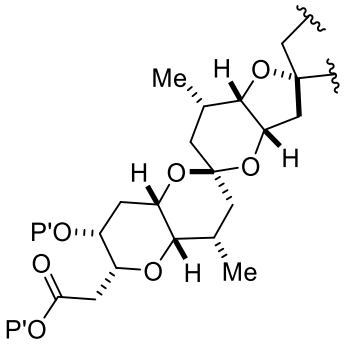
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

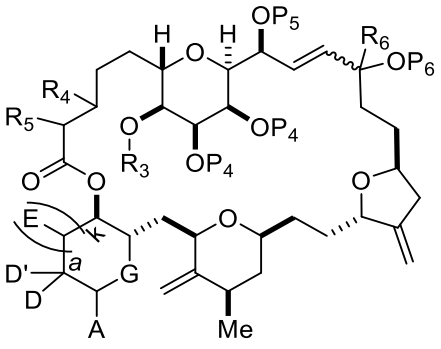
or

(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

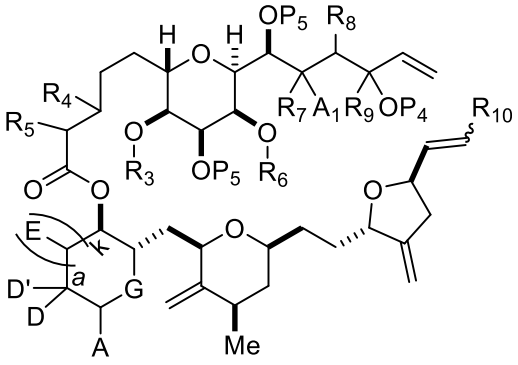
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IVB):



(IVB)

or a salt thereof;

(5) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.15-C.16 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with an olefin metathesis catalyst, wherein said non-macrocyclic intermediate is a compound of formula (VA):

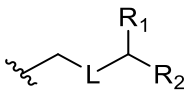


(VA)

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:



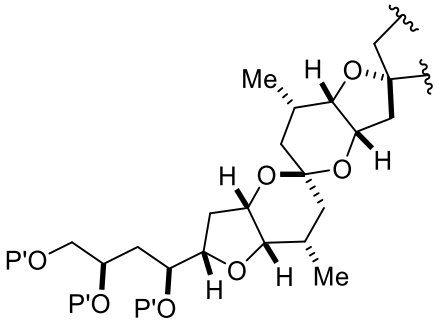
(1),

wherein

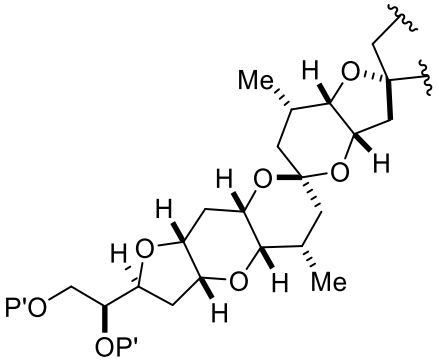
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or $–C(O)–$;

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

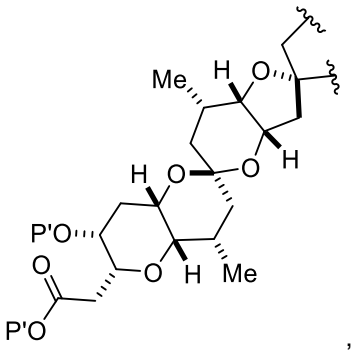
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

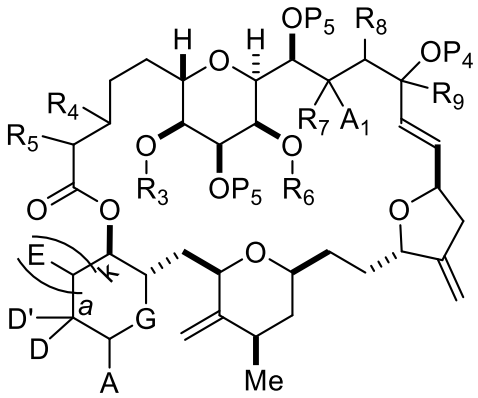
or

(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

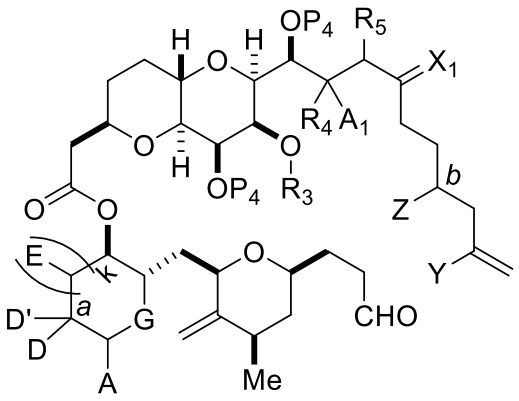
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (VB):



(VB)

or a salt or a tautomer thereof;

(6) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.19-C.20 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with a Cr(II) salt and a Ni(II) salt, wherein said non-macrocyclic intermediate is a compound of formula (VIA):



(VIA)

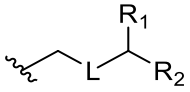
or a salt or a tautomer thereof,

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:



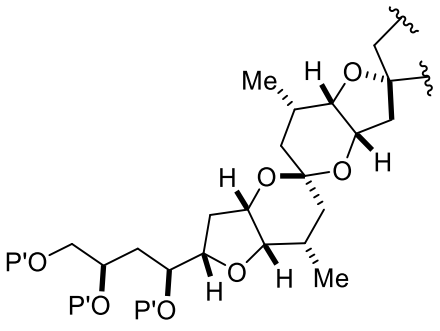
(1),

wherein

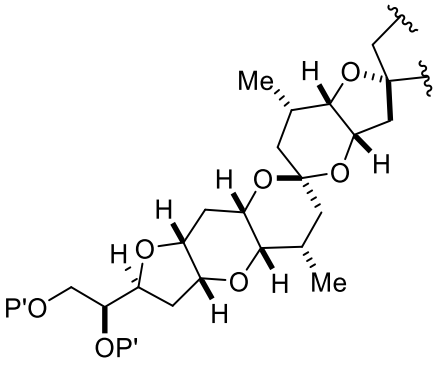
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

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

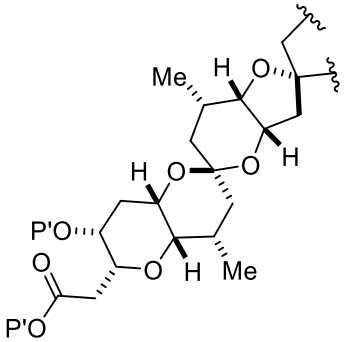
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

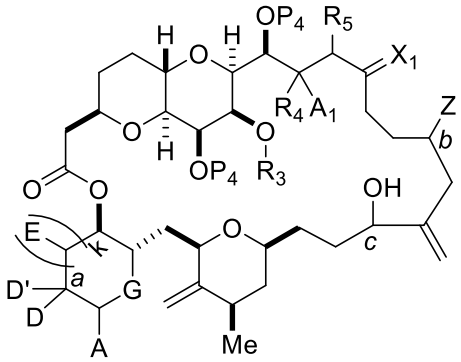
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

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,

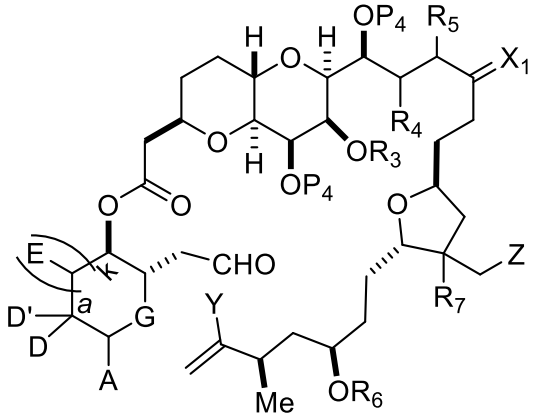
wherein

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; or

(7) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.26-C.27 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with a Cr(II) salt and a Ni(II) salt, wherein said non-macrocyclic intermediate is a compound of formula (VIIA):



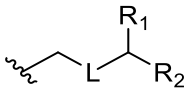
(VIIA)

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:



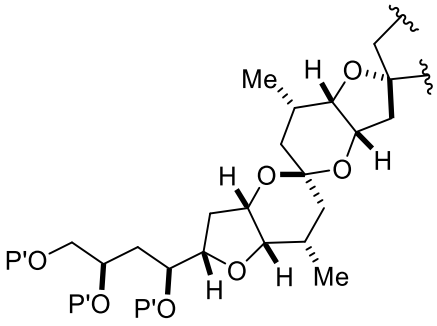
(1),

wherein

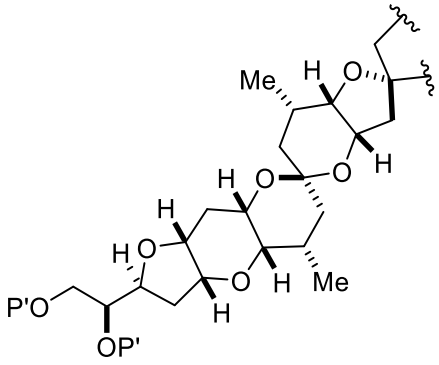
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or $–C(O)–$;

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

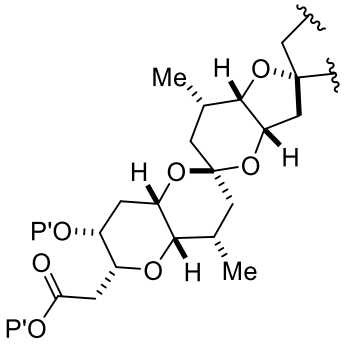
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

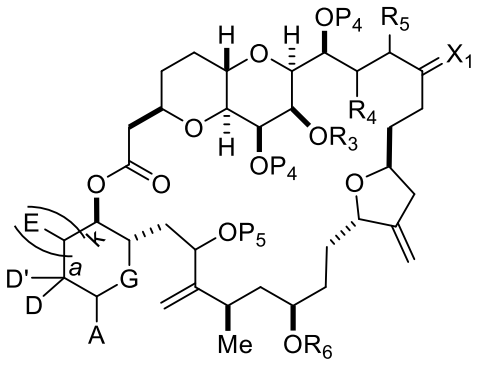
or

(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

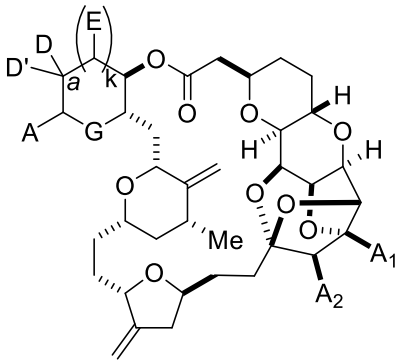
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (VIIB):



(VIIB)

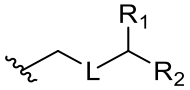
or a salt thereof,
wherein each of P_5 and R_6 is independently H or a hydroxyl protecting group.

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



halichondrin macrolide

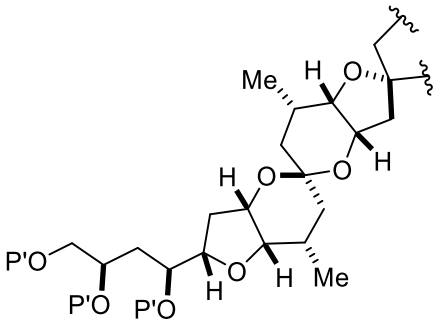
or a salt thereof,
wherein
each of A_1 and A_2 is independently H or OP", where each P" is independently H or a hydroxyl protecting group;
each of D and D' is independently H, optionally substituted alkyl, or OP_1, provided that only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group; A is a group of formula (1) or a $C_{1\text{-}6}$ saturated or $C_{2\text{-}6}$ unsaturated hydrocarbon skeleton, the skeleton being unsubstituted or having from 1 to 10 substituents independently selected from the group consisting of cyano, halo, azido, oxo, and Q_1, the group of formula (1) having the structure:



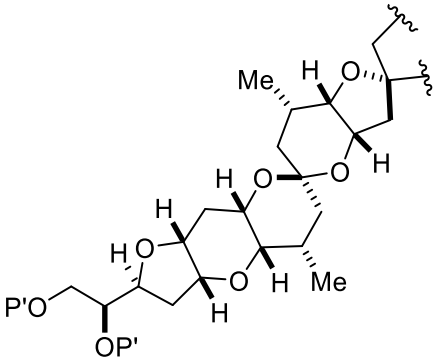
(1),

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

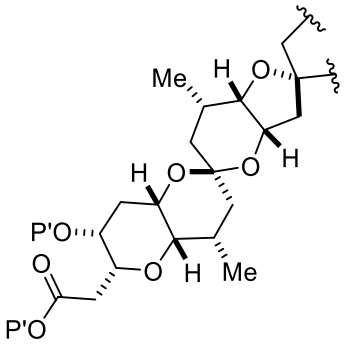
R_1 is H, or R_1 and P_1 combine to form a bond;
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, 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:



,



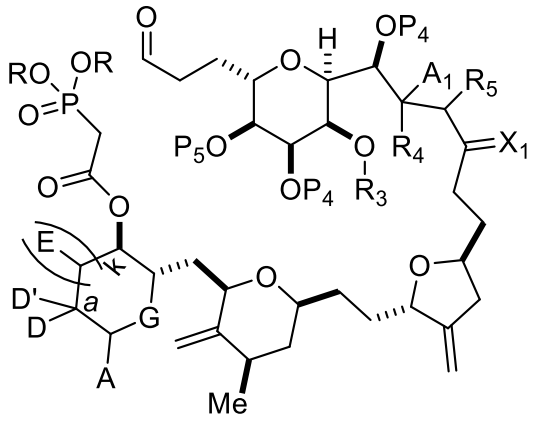
, and



, 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) or a salt or a tautomer thereof from a compound of formula (IA) or a salt or a tautomer thereof, the compound of formula (IA) having the following structure:



(IA),

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;

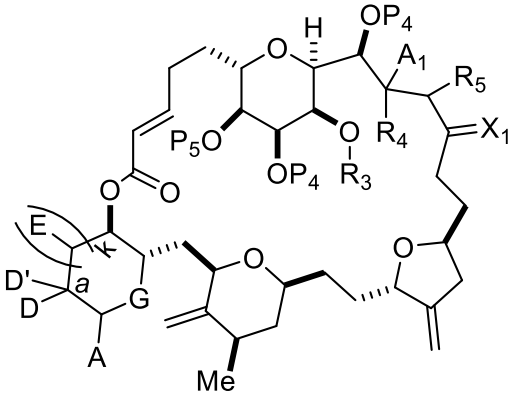
or

(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:



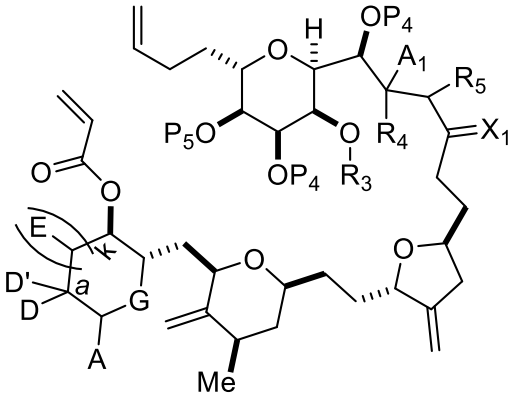
(IB);

and

(B) producing the halichondrin macrolide or the salt thereof from compound (IB) or the salt or the tautomer thereof;

(2) said method comprising:

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



(IIA),

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;

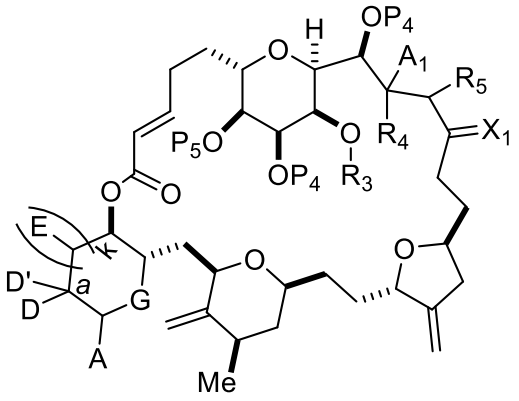
or

(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:



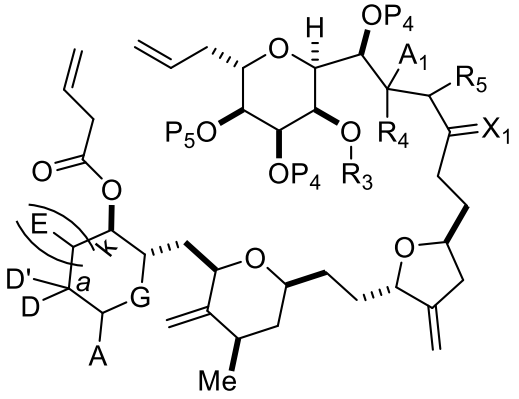
(IB);

and

(B) producing the halichondrin macrolide or the salt thereof from compound (IB) or the salt or the tautomer thereof;

(3) said method comprising:

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



(IIIA),

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;

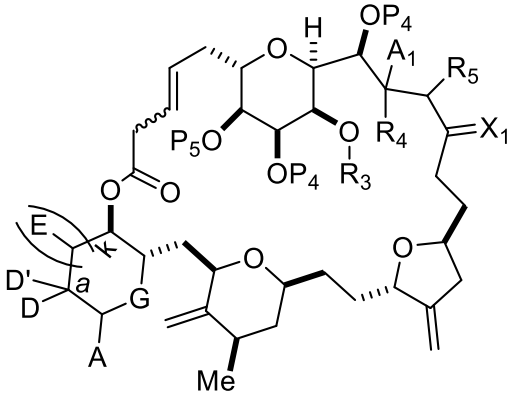
or

(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:



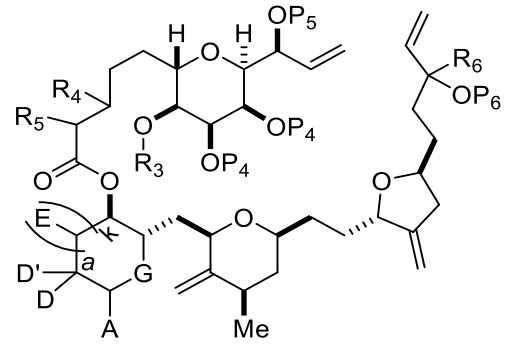
(IIIB);

and

(B) producing the halichondrin macrolide or the salt thereof from the compound of formula (IIIB) or the salt or the tautomer thereof;

(4) said method comprising:

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



(IVA),

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;

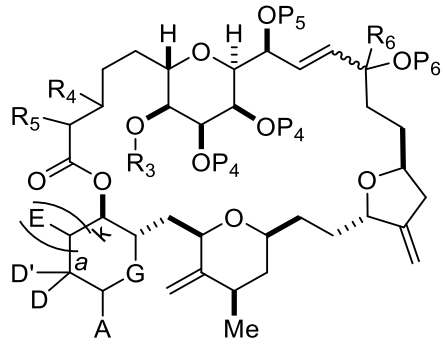
or

(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:



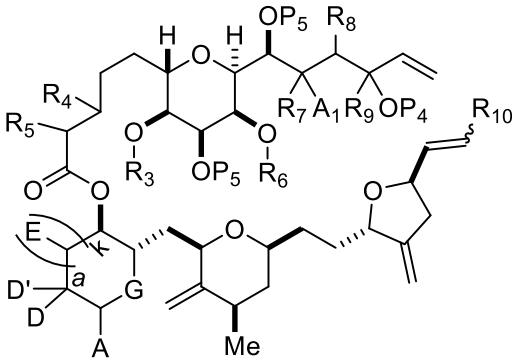
(IVB);

and

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

(5) said method comprising:

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



(VA),

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;

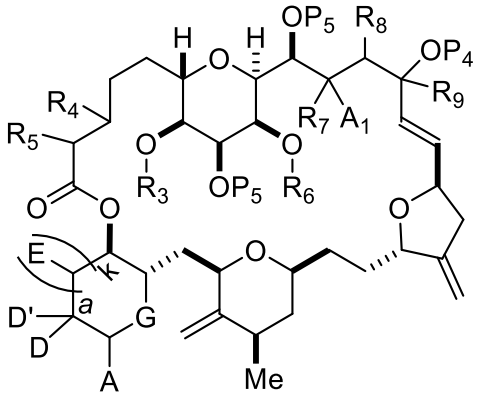
or

(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

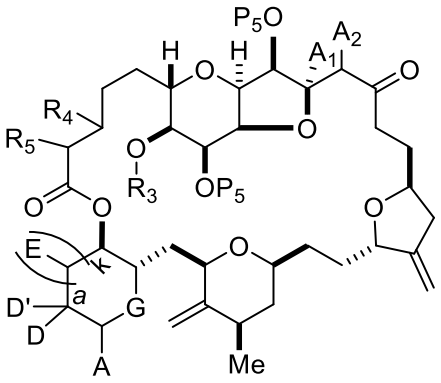
the compound of formula (VB) having the following structure:



(VB)

;

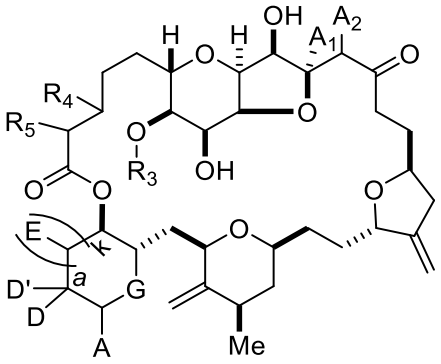
(B) producing a compound of formula (VC) or a salt thereof from the compound of formula (VB) or the salt or the tautomer thereof, the compound of formula (VC) having the following structure:



(VC),

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

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



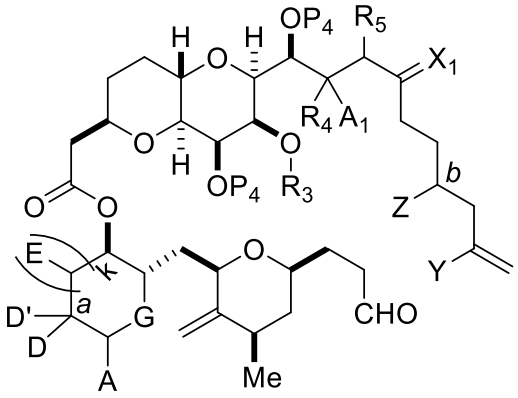
(IVC),

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

(D) producing the halichondrin macrolide or a salt thereof from the compound of formula (IVC) or a salt thereof;

(6) said method comprising:

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



(VIA),

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:

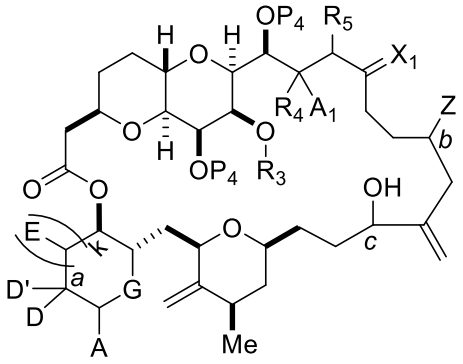
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

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),

wherein

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

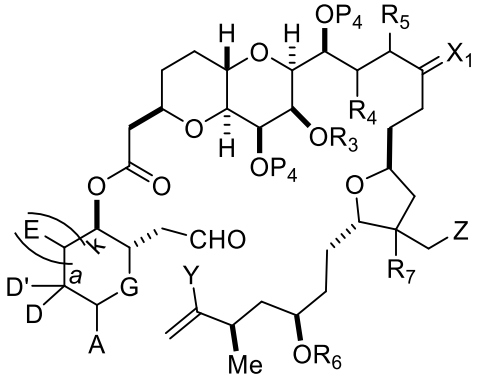
or

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 or the salt thereof from the compound of formula (VIB) or the salt or the tautomer thereof; or

(7) said method comprising:

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



(VIIA),

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

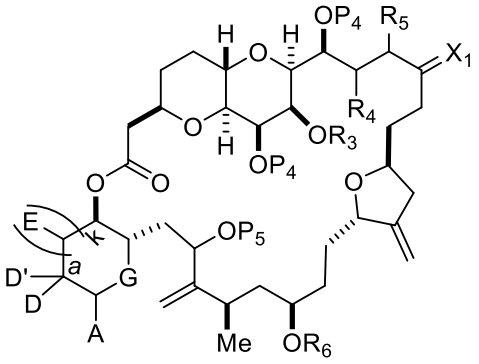
(a2) R_3 and R_4 combine to form a bond, R_5 is H, and

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

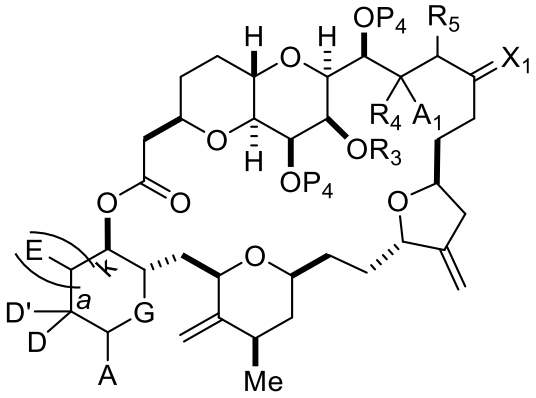
both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

(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:



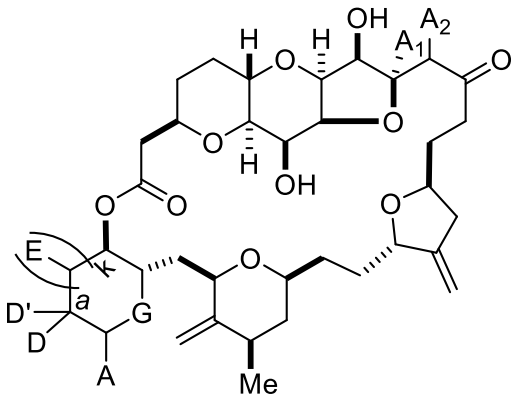
(VIIB),

wherein each of P_5 and R_6 is H or a hydroxyl protecting group;
(B) producing a compound of formula (VIIC) or a salt or a tautomer thereof from the compound of formula (VIIB) or the salt thereof, the compound of formula (VIIC) having the following structure:



(VIIC),

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) or a salt thereof from the compound of formula (VIIC) or the salt or the tautomer thereof, the compound of formula (VIID) having the following structure:



(VIID),

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

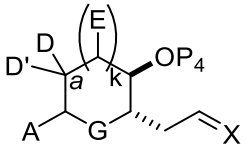
and

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

In another aspect, the disclosure provides a 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) or a salt thereof with a compound of formula (VIIIB) and R_4OH,

wherein R_4 is an optionally substituted acyl;

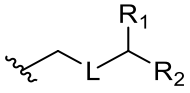
wherein the compound of formula (VIIIA) has the following structure:



(VIIIA),

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:



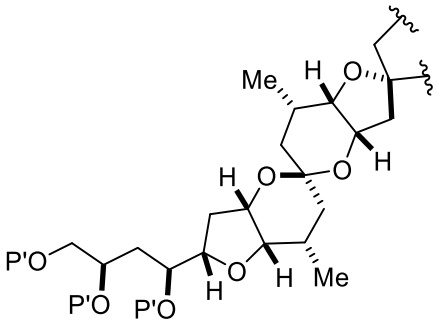
(1),

wherein

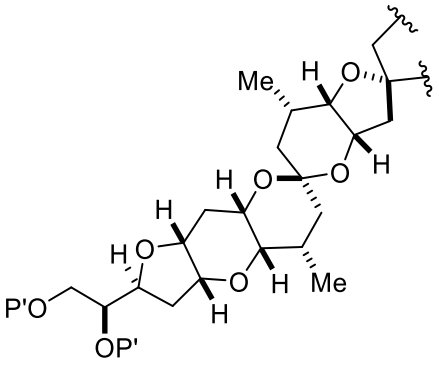
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

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

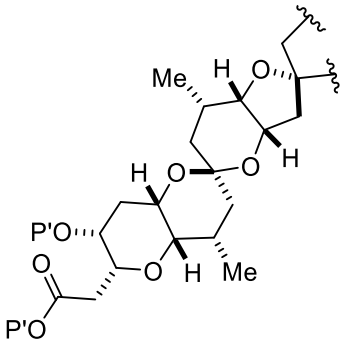
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

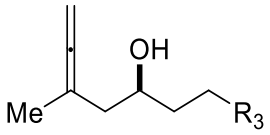
k is 0 or 1;

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;

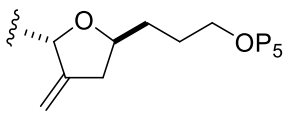
wherein the compound of formula (VIIIB) has the following structure:



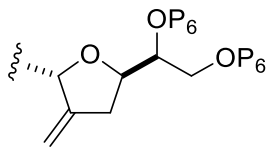
(VIIIB),

wherein

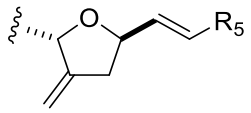
R_3 is $–CH_2–OP_5$, $–CH=CH_2$,



,



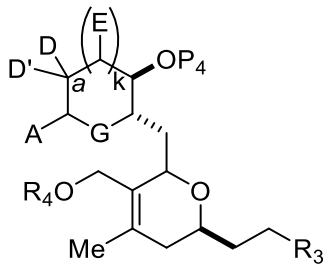
, or



,

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):

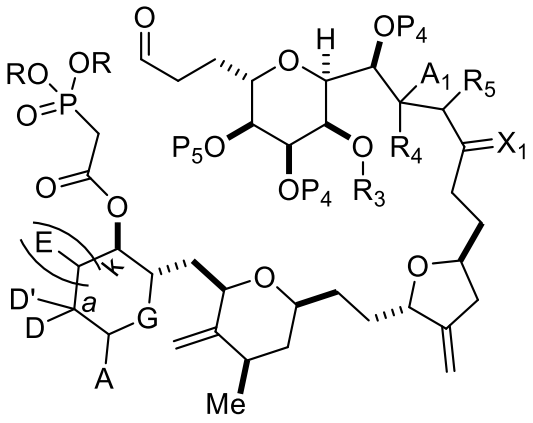


(VIIIC)

or a salt thereof.

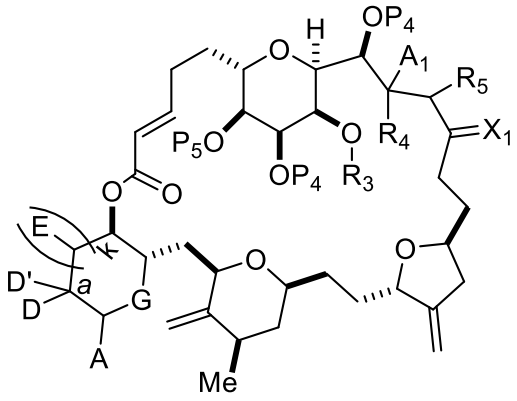
In yet another aspect, the disclosure provides a compound of

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



(IA)

or

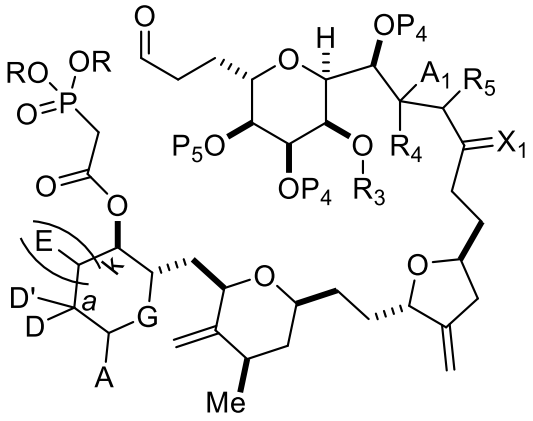


(IB)

or a salt or a tautomer thereof,

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, wherein (1) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.2-C.3 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with an organic base and a Lewis acid, wherein said non-macrocyclic intermediate is (1) a compound of formula (IA):



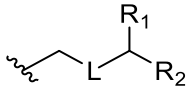
(IA)

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),

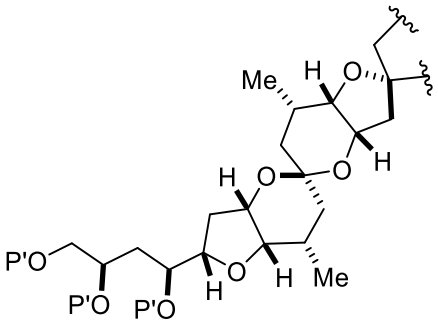
wherein

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

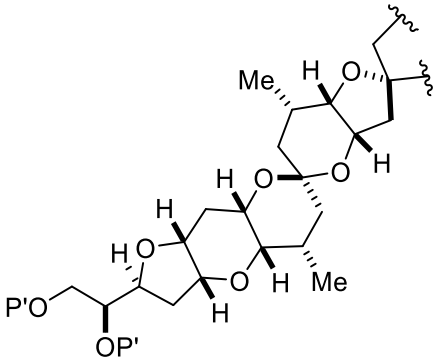
R_1 is H, or R_1 and P_1 combine to form a bond;

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-

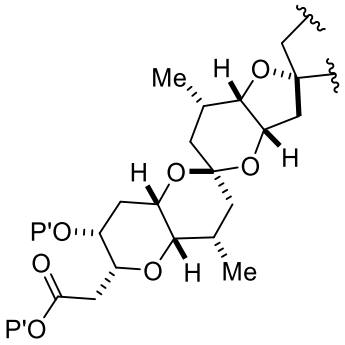
dioxo; or R_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, 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;

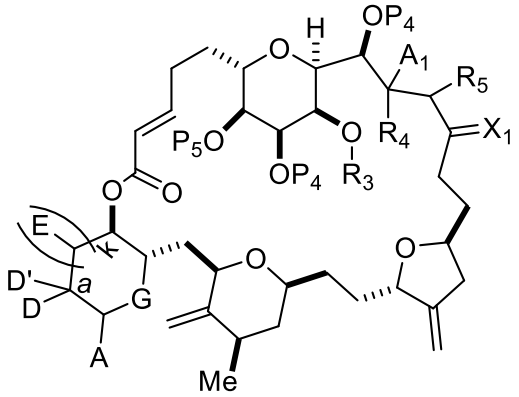
or

(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

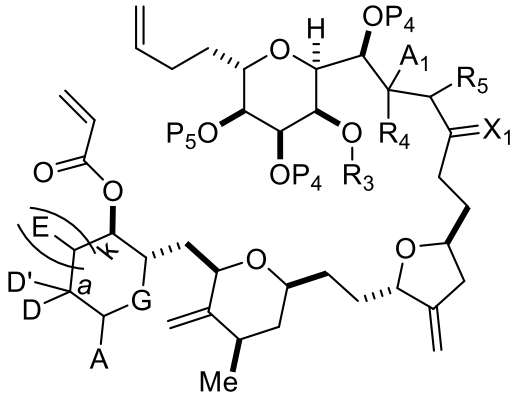
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IB):



(IB)

or a salt or a tautomer thereof;

(2) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.2-C.3 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with an olefin metathesis catalyst, wherein said non-macrocyclic intermediate is a compound of formula (IIA):



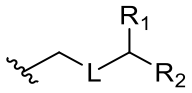
(IIA)

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:



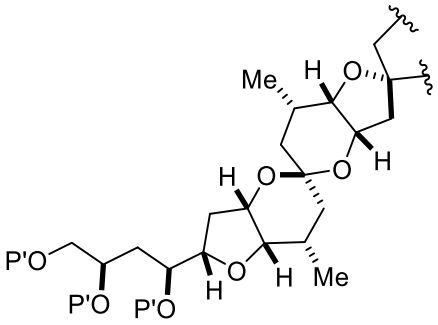
(1),

wherein

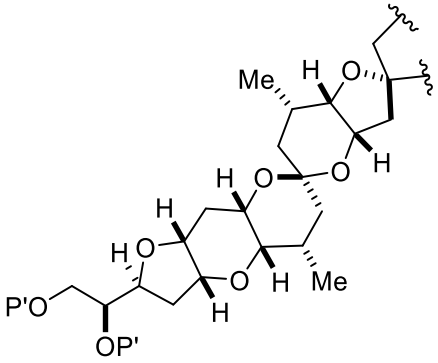
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or $–C(O)–$;

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

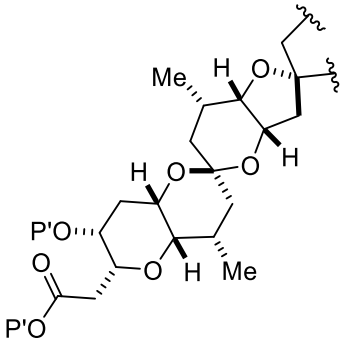
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

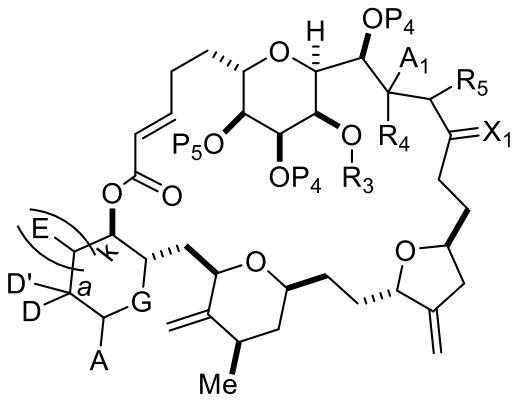
or

(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

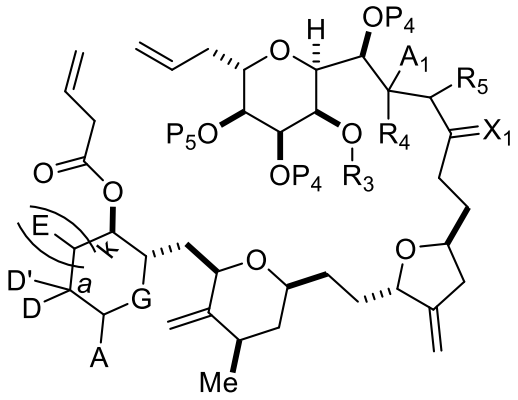
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IB):



(IB)

or a salt or a tautomer thereof;

(3) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.3-C.4 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with an olefin metathesis catalyst, wherein said non macrocyclic intermediate is a compound of formula (IIIA):

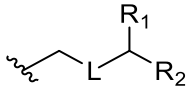


(IIIA)

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:



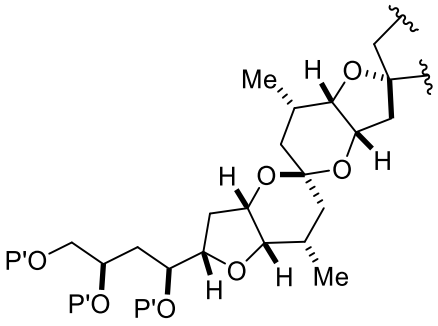
(1),

wherein

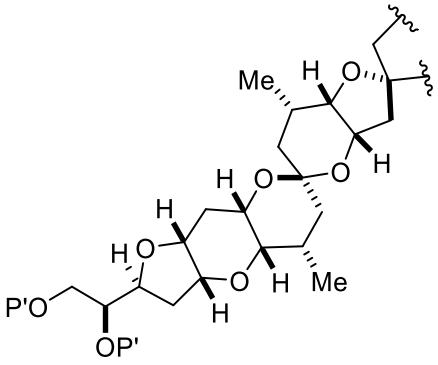
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

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

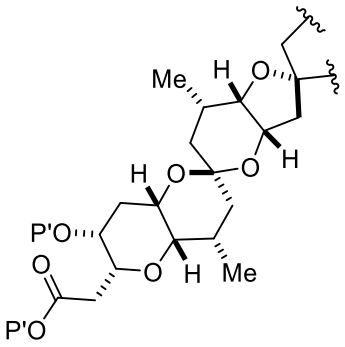
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

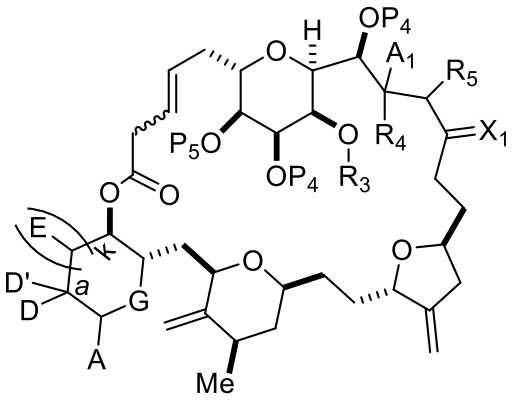
or

(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

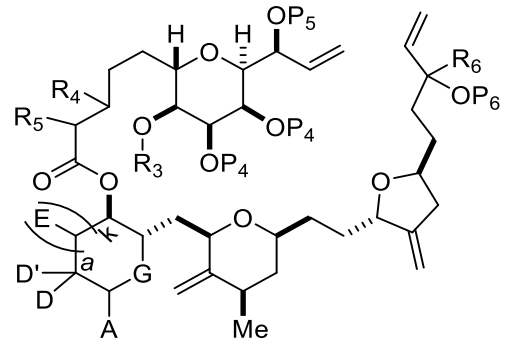
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IIIB):



(IIIB)

or a salt or a tautomer thereof;

(4) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.12-C.13 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with an olefin metathesis catalyst, wherein said non-macrocyclic intermediate is a compound of formula (IVA):

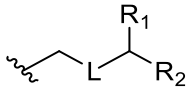


(IVA)

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:



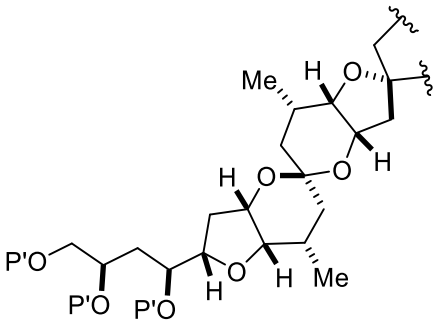
(1),

wherein

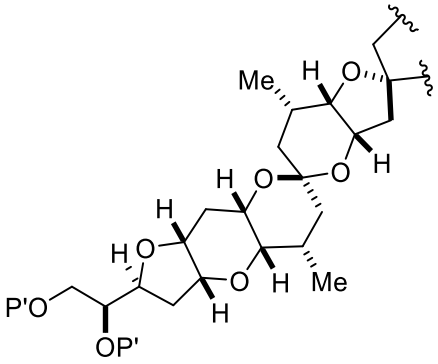
L is –(CH(OP$_2$))–, –(C(OH)(OP$_2$))–, or –C(O)–;

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

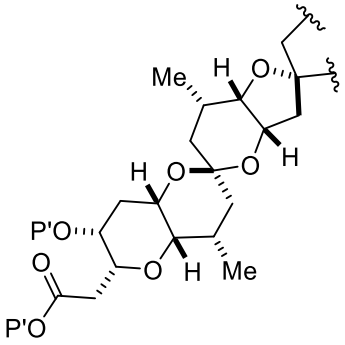
R$_2$ is H or -(CH$_2$)$_n$OP$_3$, and each of P$_2$ and P$_3$ is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P$_2$ and P$_3$, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R$_2$ and P$_2$ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, 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$_2$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$_A$, 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;

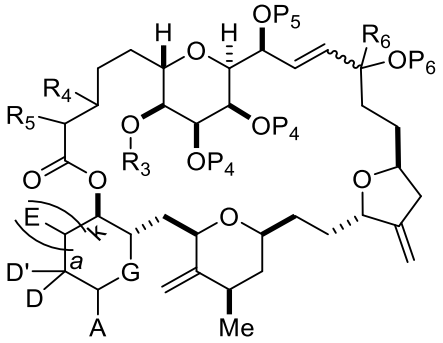
or

(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

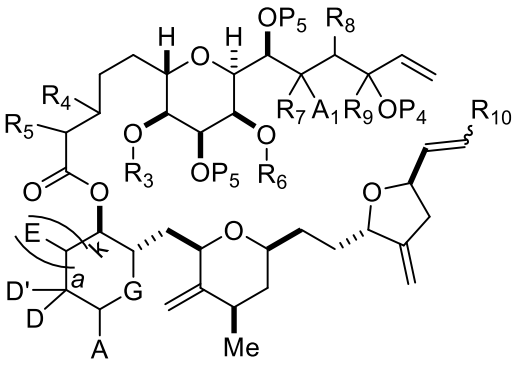
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (IVB):



(IVB)

or a salt thereof;

(5) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.15-C.16 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with an olefin metathesis catalyst, wherein said non-macrocyclic intermediate is a compound of formula (VA):

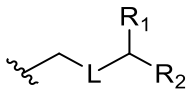


(VA)

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:



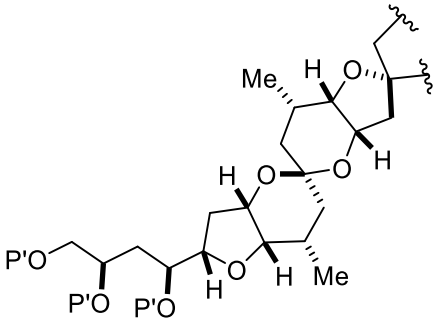
(1),

wherein

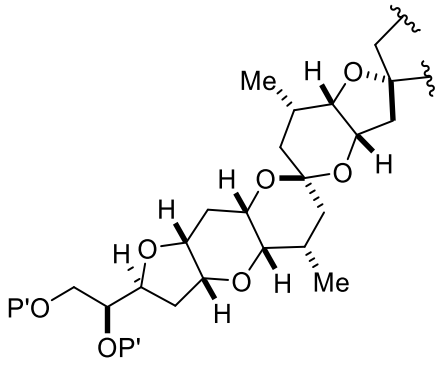
L is –(CH(OP$_2$))–, –(C(OH)(OP$_2$))–, or –C(O)–;

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

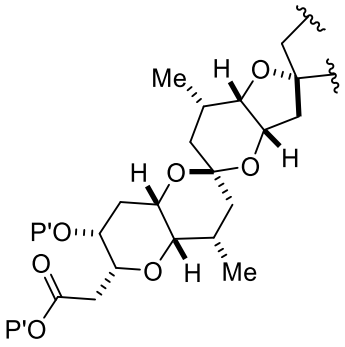
R_2 is H or -(CH$_2$)$_n$OP$_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, 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;

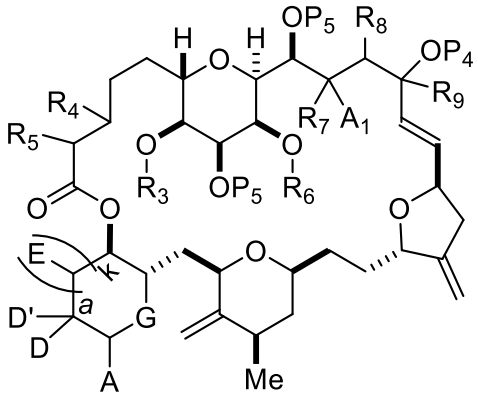
or

(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

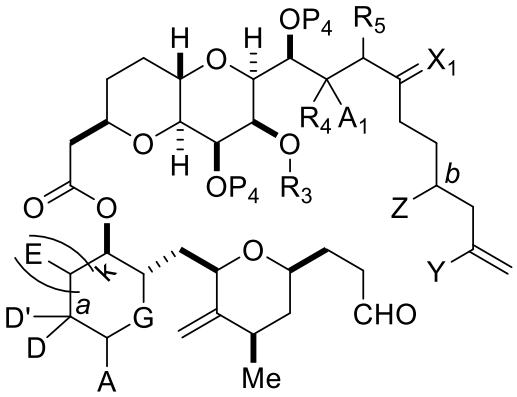
wherein said macrocyclic intermediate in the synthesis of a halichondrin macrolide is a compound of formula (VB):



(VB)

or a salt or a tautomer thereof;

(6) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.19-C.20 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with a Cr(II) salt and a Ni(II) salt, wherein said non-macrocyclic intermediate is a compound of formula (VIA):



(VIA)

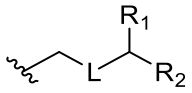
or a salt or a tautomer thereof,

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:



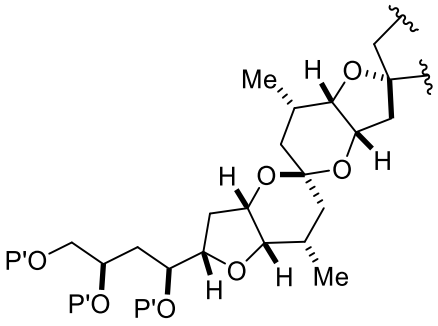
(1),

wherein

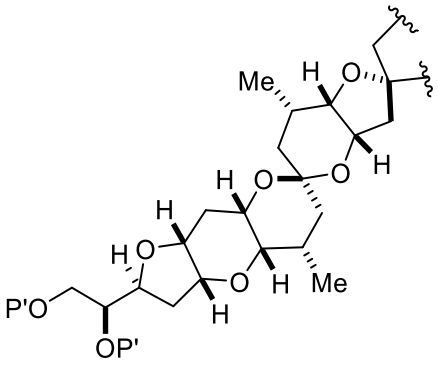
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

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

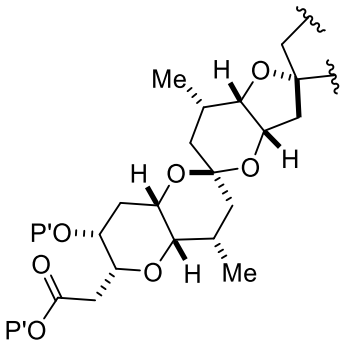
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

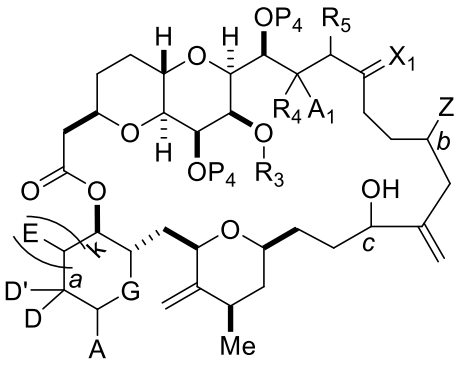
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

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,

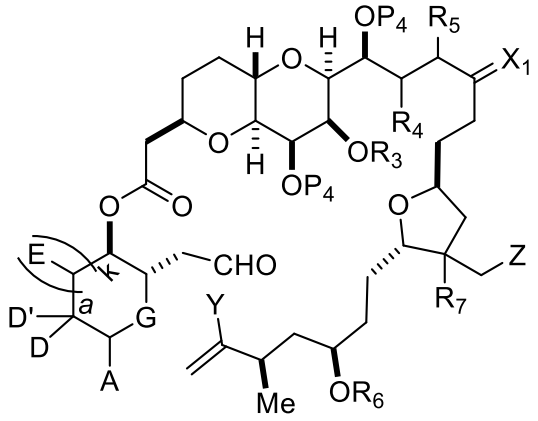
wherein

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; or

(7) said macrocyclization reaction produces said macrocyclic intermediate by forming a C.26-C.27 bond in the structure of the halichondrin macrolide, said performing said macrocyclization reaction comprising contacting said non-macrocyclic intermediate with a Cr(II) salt and a Ni(II) salt, wherein said non-macrocyclic intermediate is a compound of formula (VIIA):



(VIIA)

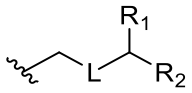
or a salt thereof,

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:



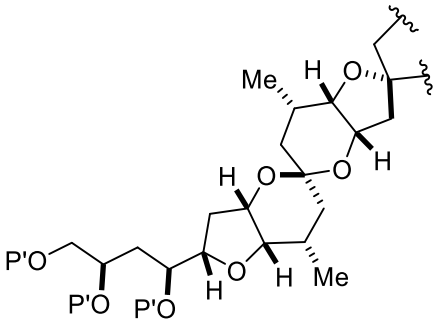
(1),

wherein

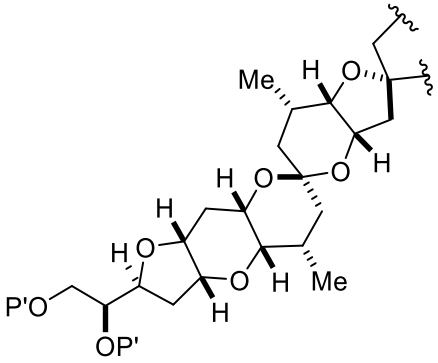
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or $–C(O)–$;

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

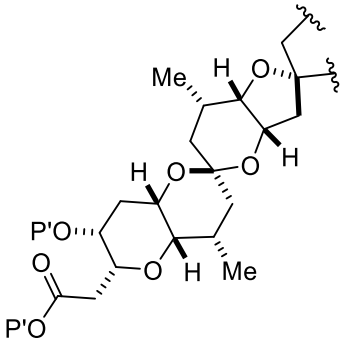
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

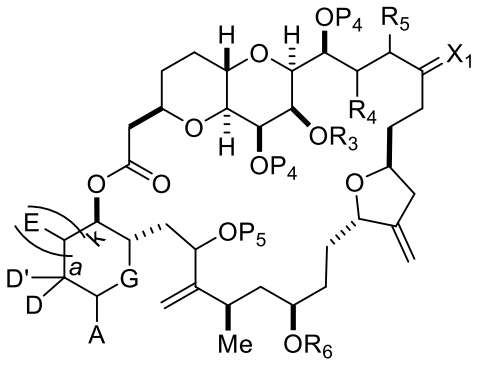
(b1) Z is chloride, bromide, or iodide, and R_6 and R_7 combine to form a bond;

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.

2. The method of claim 1, 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.

3. The method of claim 1, 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.

4. The method of claim 1, wherein for (4), at least one of P_4 and P_5 is H.

5. The method of claim 1, 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.

6. The method of claim 1, wherein for (2), (3), (4), or (5), said olefin metathesis catalyst is a ruthenium-carbene complex.

7. The method of claim 1, 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.

8. The method of claim 1, wherein for (7),

(a) Z is iodide;

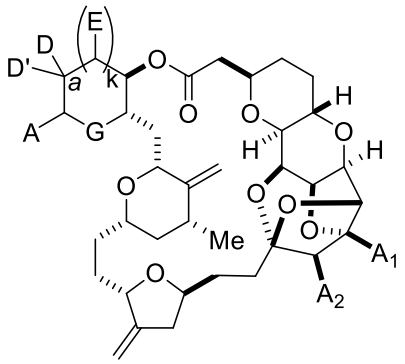
(b) Y is trifluoromethanesulfonate;

(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.

9. A method of preparing:



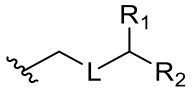
halichondrin macrolide

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:



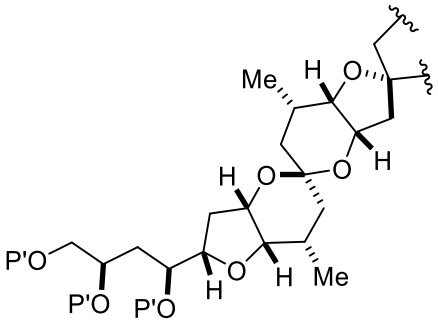
(1),

wherein

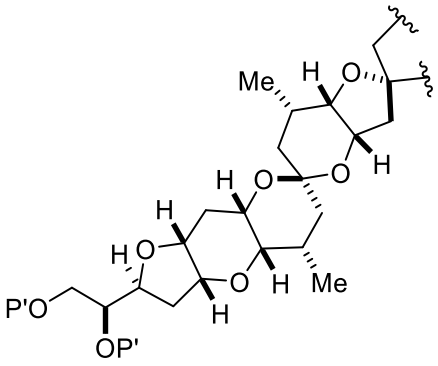
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

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

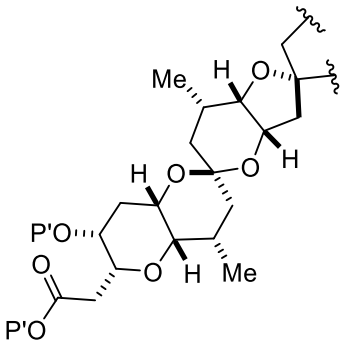
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

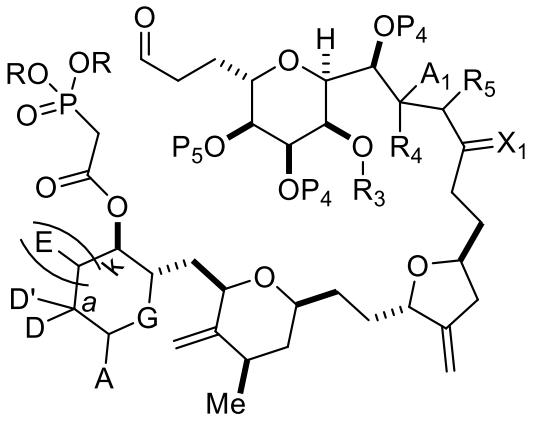
each Q_1 is independently OR_A, SR_A, SO_2R_A, OSO_2R_A, NR_BR_A, $NR_B(CO)R_A$, $NR_B(CO)(CO)R_A$, $NR_A(CO)NR_BR_A$, $NR_B(CO)OR_A$, $(CO)OR_A$, $O(CO)R_A$, $(CO)NR_BR_A$, or $O(CO)NR_BR_A$, wherein each of R_A and R_B is independently H, alkyl, haloalkyl, hydroxyalkyl, aminoalkyl, aryl, haloaryl, 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) or a salt or a tautomer thereof from a compound of formula (IA) or a salt or a tautomer thereof, the compound of formula (IA) having the following structure:



(IA),

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;

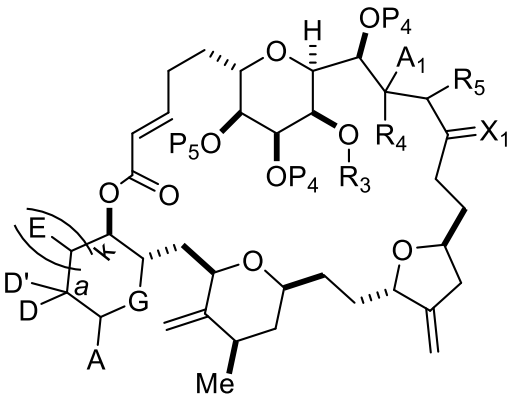
or

(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:



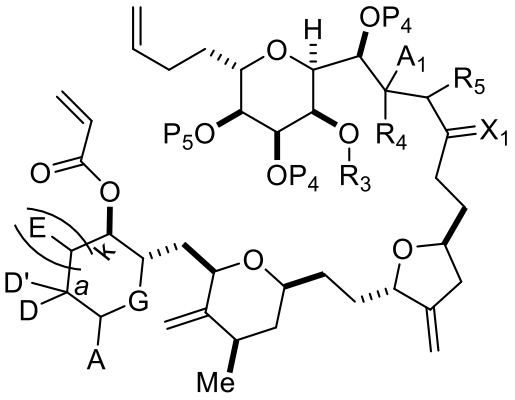
(IB);

and

(B) producing the halichondrin macrolide or the salt thereof from compound (IB) or the salt or the tautomer thereof;

(2) said method comprising:

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



(IIA),

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;

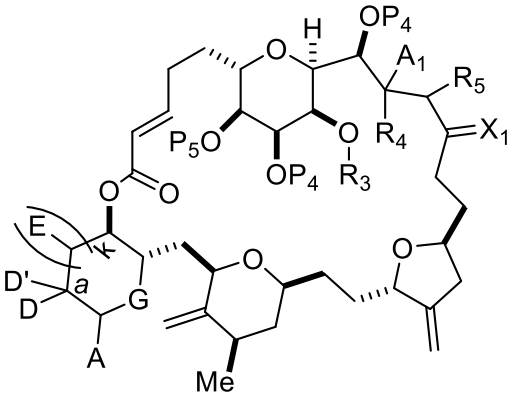
or

(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:



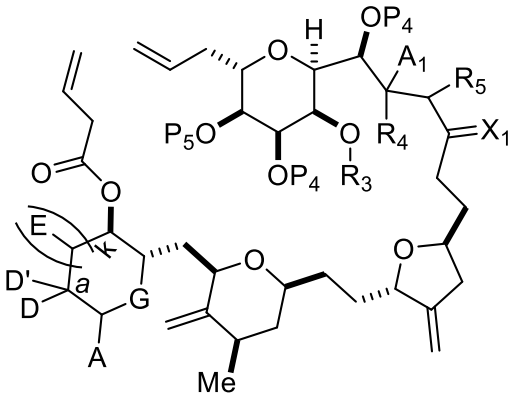
(IB);

and

(B) producing the halichondrin macrolide or the salt thereof from compound (IB) or the salt or the tautomer thereof;

(3) said method comprising:

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



(IIIA),

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;

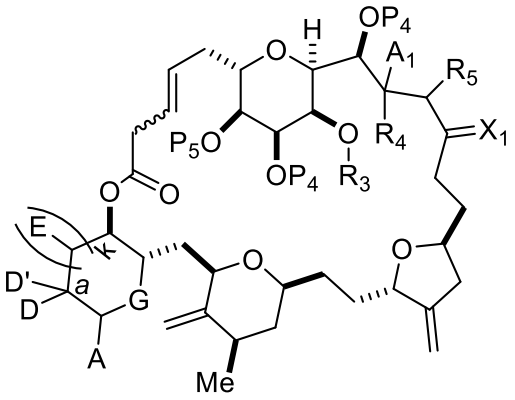
or

(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:



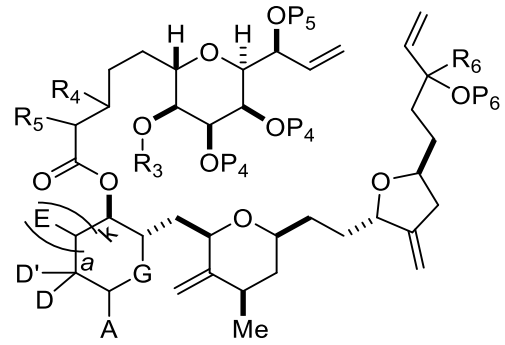
(IIIB);

and

(B) producing the halichondrin macrolide or the salt thereof from the compound of formula (IIIB) or the salt or the tautomer thereof;

(4) said method comprising:

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



(IVA),

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

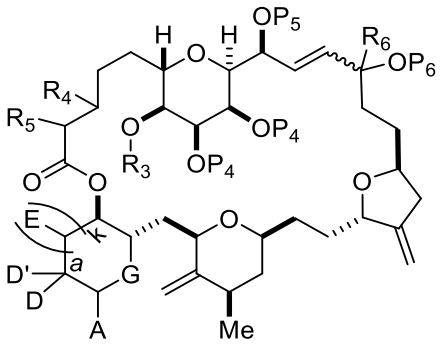
(iii) R_3 and R_4 combine to form a bond, and R_5 is H;

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:



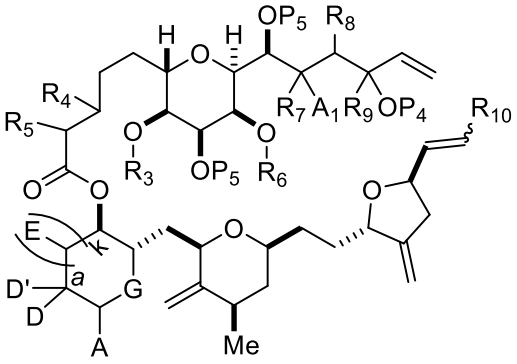
(IVB);

and

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

(5) said method comprising:

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



(VA),

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;

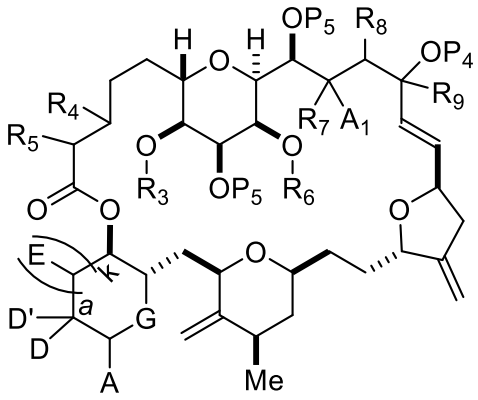
or

(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;

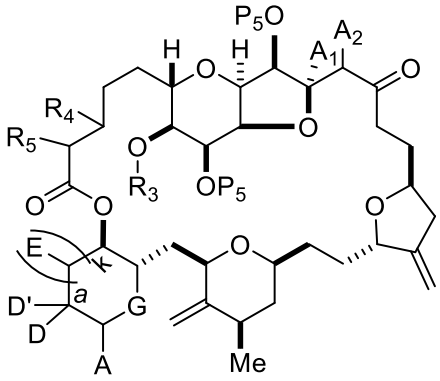
each P_5 is independently H or a hydroxyl protecting group; and

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



(VB);

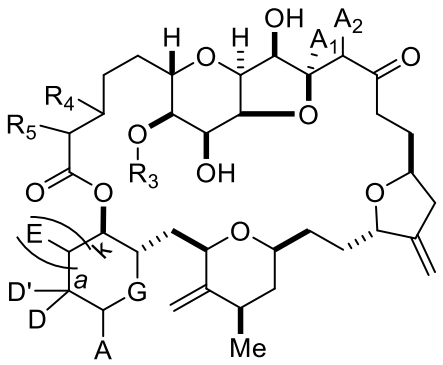
(B) producing a compound of formula (VC) or a salt thereof from the compound of formula (VB) or the salt or the tautomer thereof, the compound of formula (VC) having the following structure:



(VC),

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

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



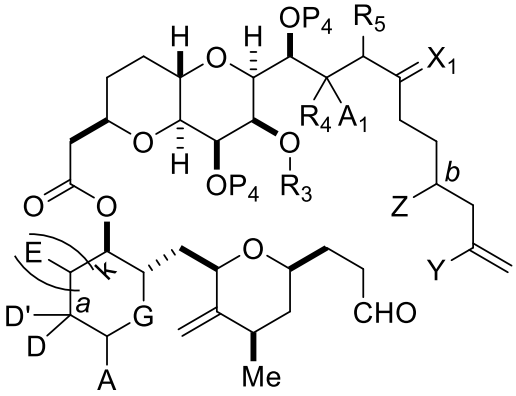
(IVC),

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

(D) producing the halichondrin macrolide or a salt thereof from the compound of formula (IVC) or a salt thereof;

(6) said method comprising:

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



(VIA),

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:

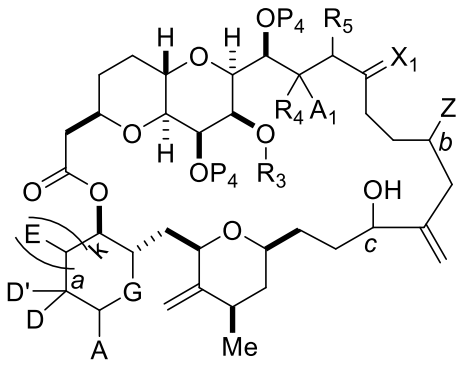
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

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),

wherein

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

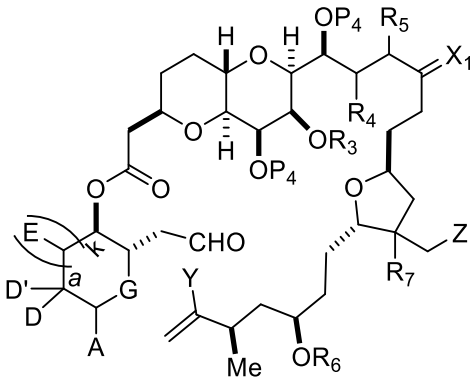
or

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 or the salt thereof from the compound of formula (VIB) or the salt or the tautomer thereof; or

(7) said method comprising:

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



(VIIA),

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;

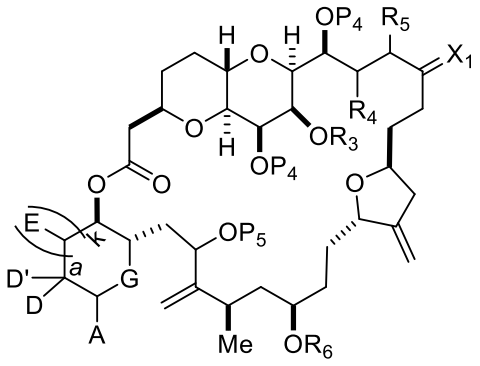
or

(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

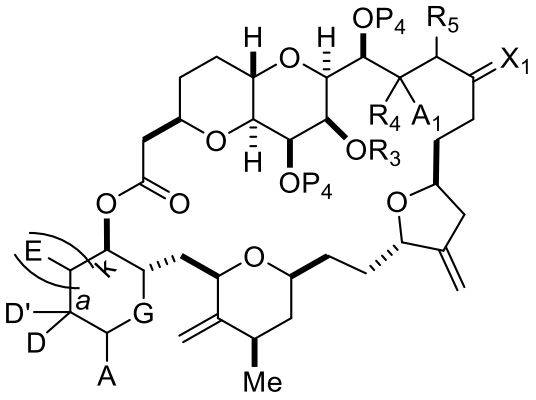
the compound of formula (VIIB) having the following structure:



(VIIB),

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

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



(VIIC),

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

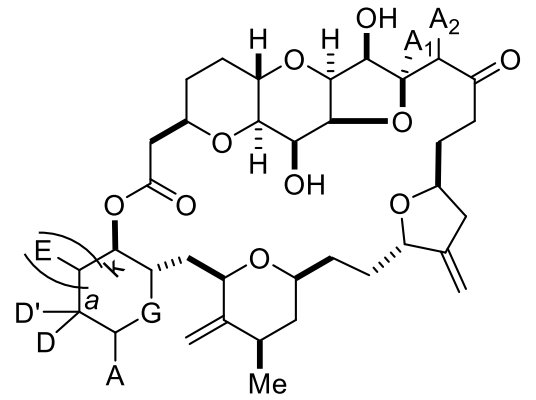
A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(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) or a salt thereof from the compound of formula (VIIC) or the salt or the tautomer thereof, the compound of formula (VIID) having the following structure:



(VIID),

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

and

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

10. The method of claim 9, wherein for (1),

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

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

(c) each R is optionally substituted alkyl.

11. The method of claim 9, wherein for (2)

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

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

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

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

(b) said producing the halichondrin macrolide or the salt thereof comprises reacting the compound of formula (IIIB) or the salt or the tautomer thereof 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.

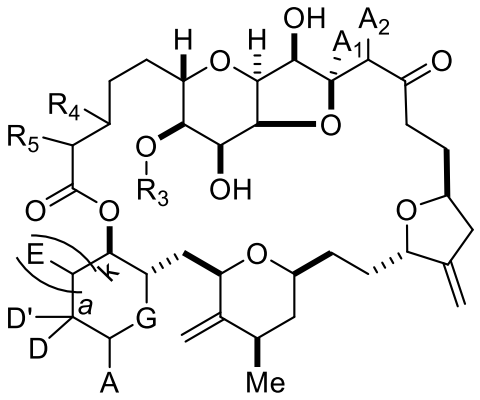
13. The method of claim 9, wherein for (4)

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

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

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

14. The method of claim 9, wherein said producing the halichondrin macrolide or the salt thereof comprises producing the compound of formula (IVC) or the salt thereof, the compound of formula (IVC) having the following structure:



(IVC),

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 or the salt thereof from the compound of formula (IVC).

15. The method of claim 14, wherein

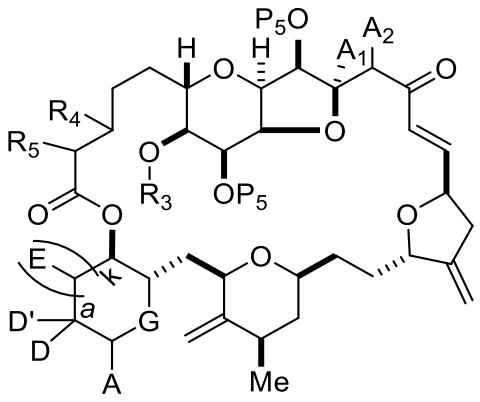
(a) said producing the compound of formula (IVC) or the salt thereof comprises reacting the compound of formula (IVB) or the salt thereof with a hydroxyl protecting group removing agent; and/or

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

16. The method of claim 9, wherein for (5),

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

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



(VBa)

or a salt thereof;

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

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

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

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

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

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

(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.

18. The method of claim 9, wherein for (7),

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

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

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

(d) said producing the halichondrin macrolide comprises reacting the compound of formula (VIID) or the salt thereof 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.

19. The method of claim 1, 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 $–(CH_2)_nOP_3$;

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

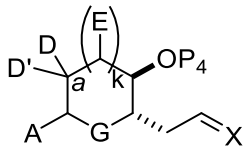
(k) A_1 is H.

20. The method of claim 19, wherein one and only one of D and D' is OP_1, wherein P_1 is H, alkyl, or a hydroxyl protecting group.

21. 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) or a salt thereof 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:

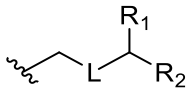


(VIIIA),

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:



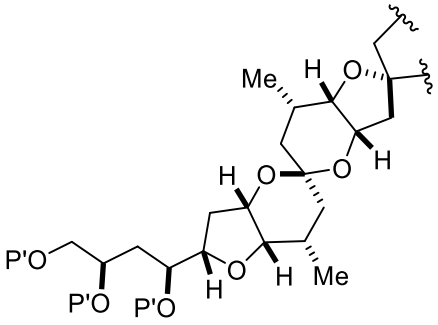
(1),

wherein

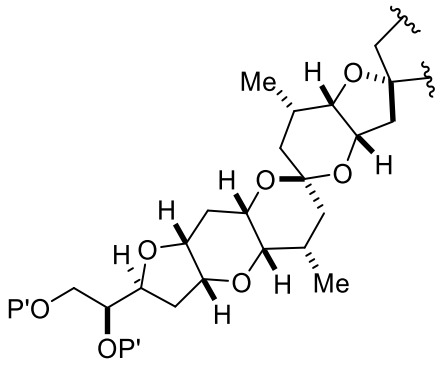
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or $–C(O)–$;

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

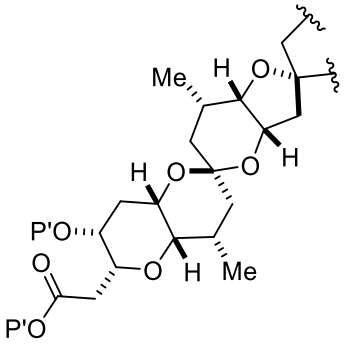
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

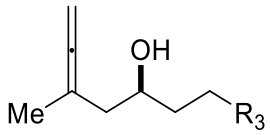
k is 0 or 1;

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

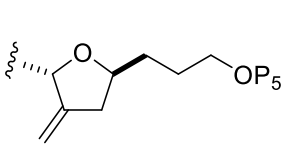
P_4 is H or a hydroxyl protecting group;

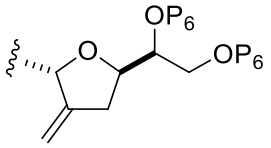
wherein the compound of formula (VIIIB) has the following structure:

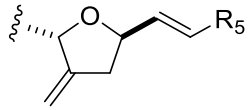


(VIIIB),

wherein

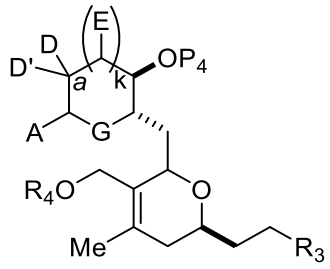
R_3 is $–CH_2–OP_5$, $–CH=CH_2$, 

, 

, 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):



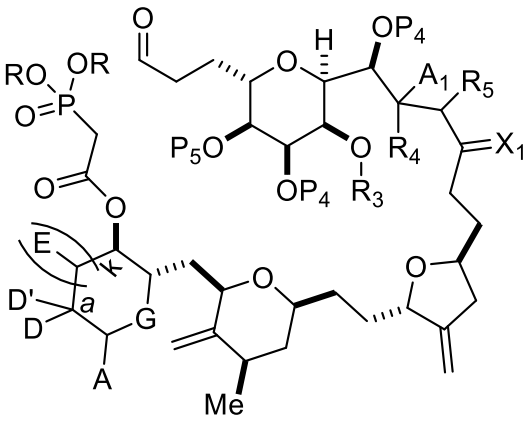
(VIIIC)

or a salt thereof.

22. The method of claim 21, wherein said performing a Prins reaction comprises reacting the compound of formula (VIIIA) or a salt thereof with a Lewis acid; and/or k is 1.

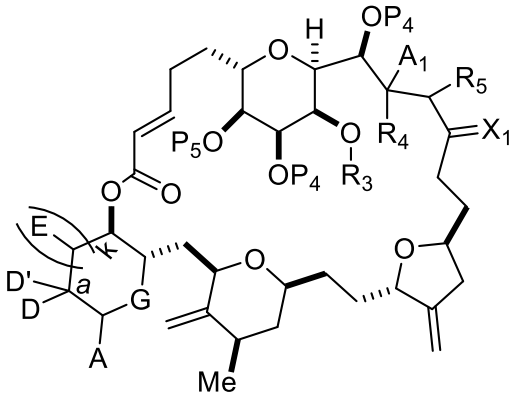
23. A compound of

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



(IA)

or



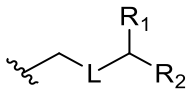
(IB)

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:



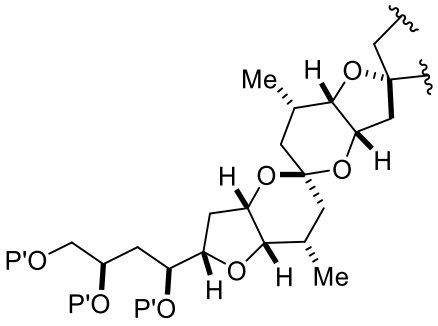
(1),

wherein

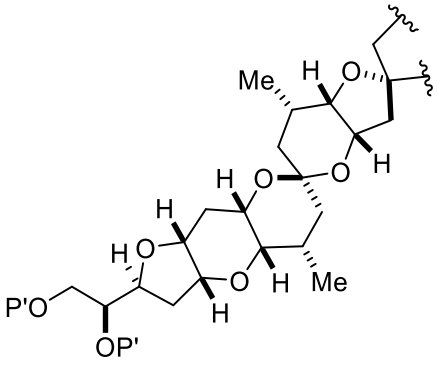
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

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

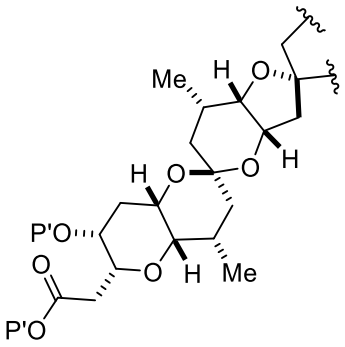
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

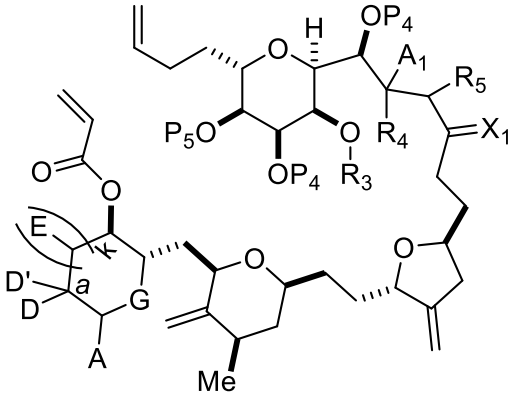
or

(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

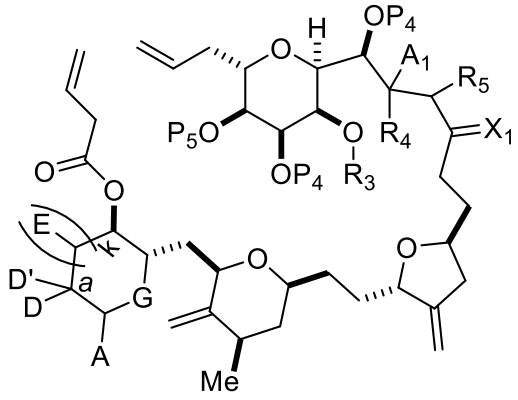
P_5 is H or a hydroxyl protecting group;

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



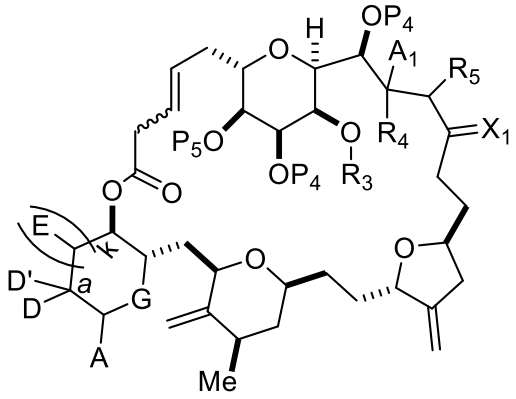
(IIA)

,



(IIIA)

, or



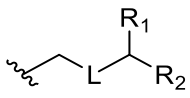
(IIIB)

,

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),

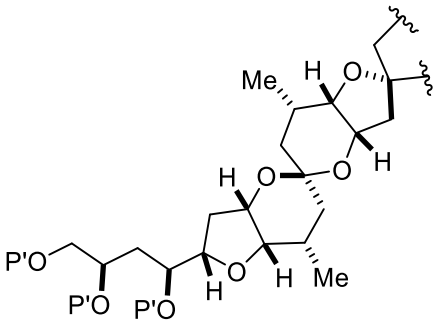
wherein

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

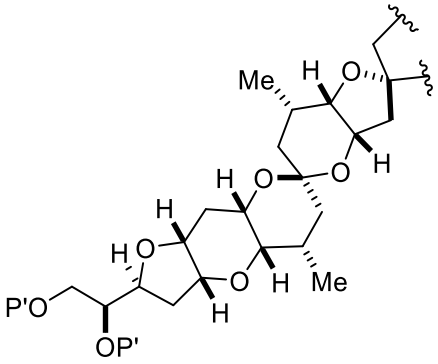
R_1 is H, or R_1 and P_1 combine to form a bond;

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

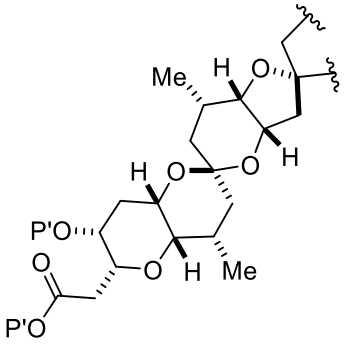
is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2 combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, 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;

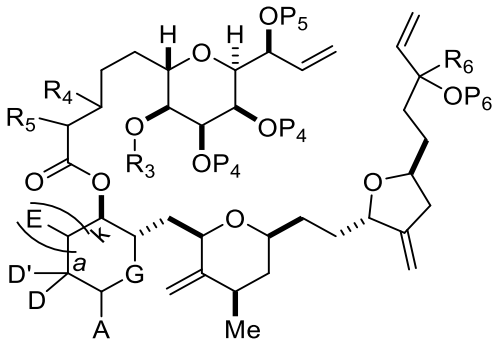
or

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

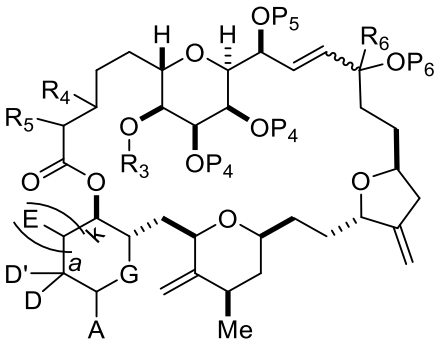
each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is –(CH(OP$_Y$))–, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form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

P_5 is H or a hydroxyl protecting group;

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

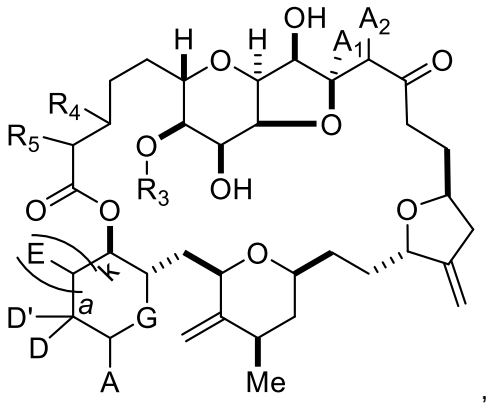


,



, or

(IVA) (IVB)



,

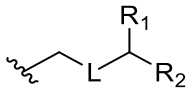
(IVC)

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:



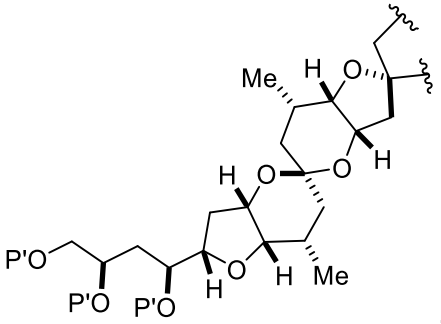
(1),

wherein

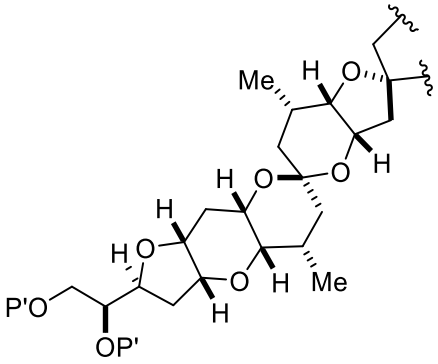
L is –(CH(OP$_2$))–, –(C(OH)(OP$_2$))–, or –C(O)–;

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

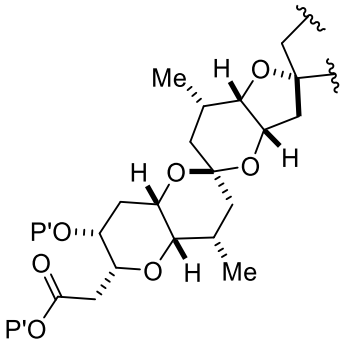
R$_2$ is H or -(CH$_2$)$_n$OP$_3$, and each of P$_2$ and P$_3$ is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P$_2$ and P$_3$, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R$_2$ and P$_2$ combine to form an optionally substituted ethylene or a structure selected from the group consisting of:



,



, and



, 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$_2$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$_A$, 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;

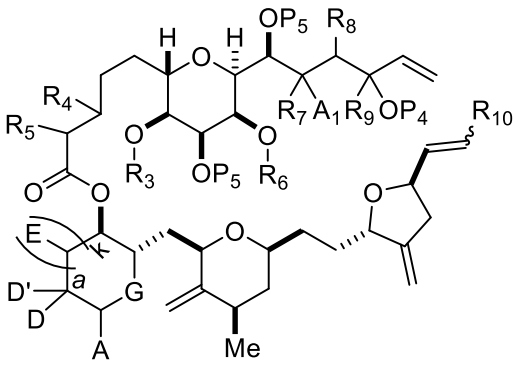
or

(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

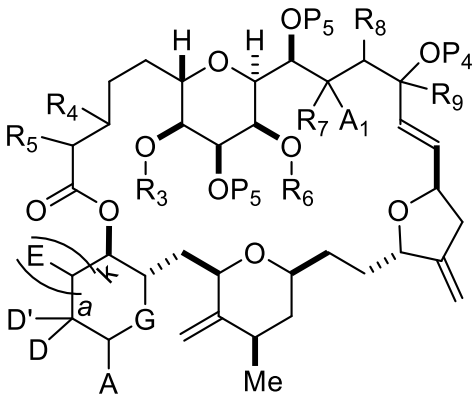
R_6 is H, and P_6 is H or a hydroxyl protecting group; or R_6 and P_6 combine to form a double bond;

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



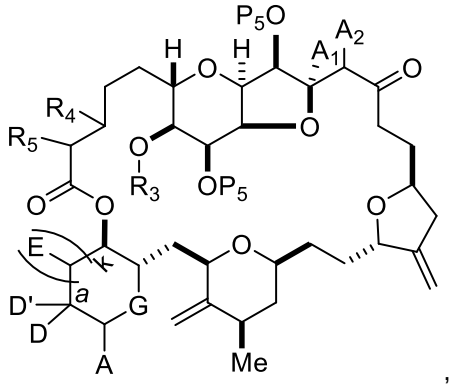
(VA)

,



(VB)

, or



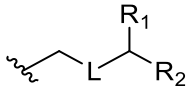
(VC)

,

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:



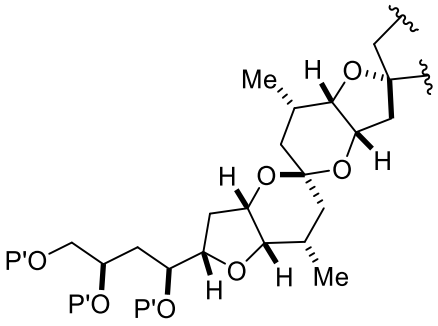
(1),

wherein

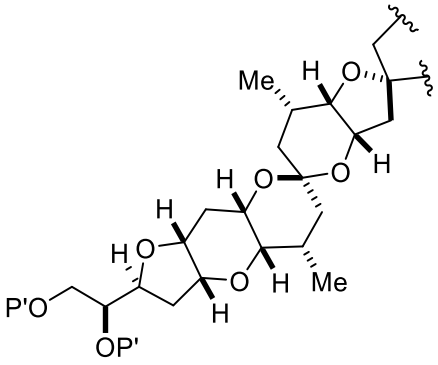
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or $–C(O)–$;

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

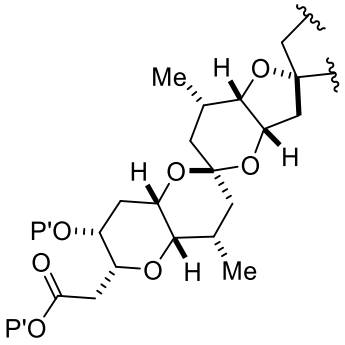
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

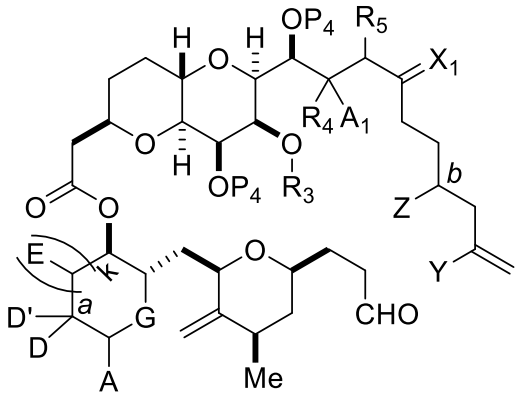
or

(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):

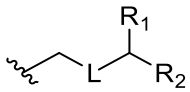


(VIA)

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:



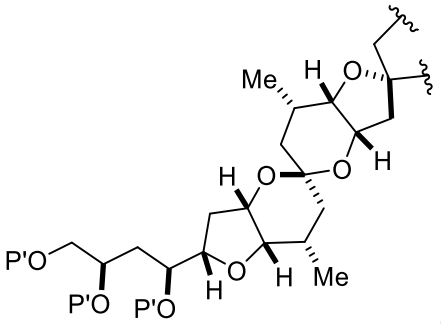
(1),

wherein

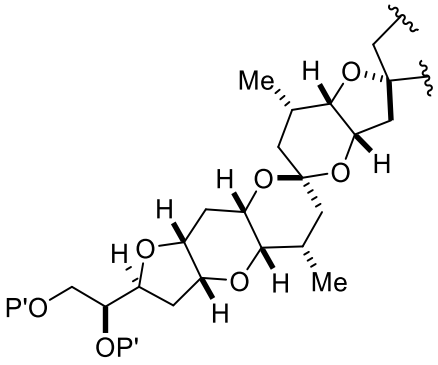
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or $–C(O)–$;

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

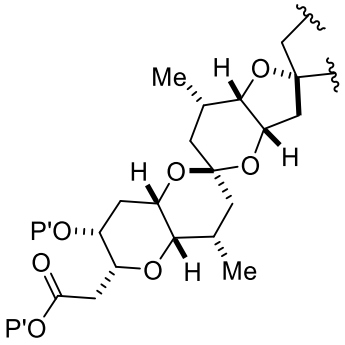
R_2 is H or -$(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

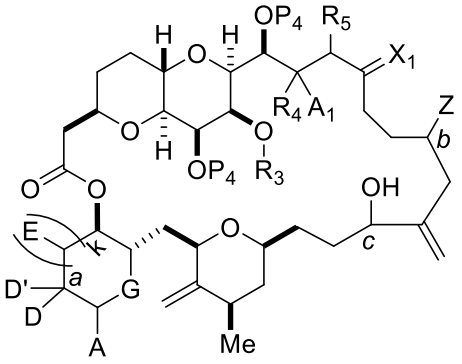
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

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,

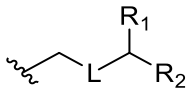
wherein

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:



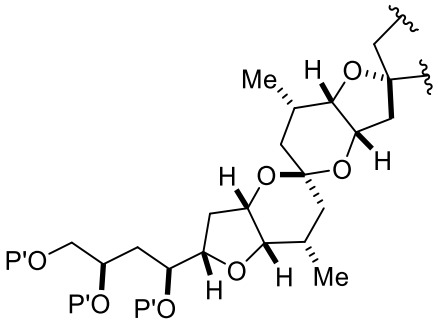
(1),

wherein

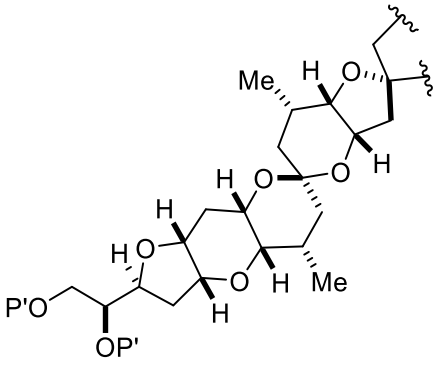
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

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

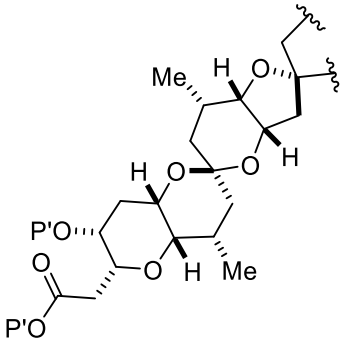
R_2 is H or -$(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

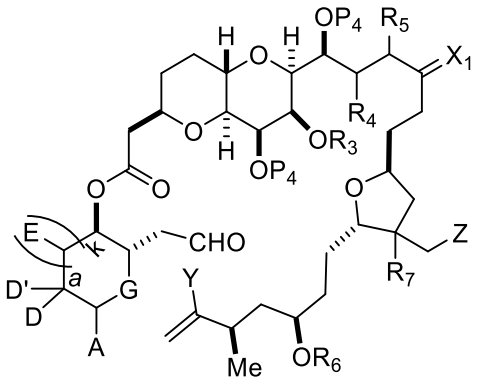
(i) R_3 is H or a hydroxyl protecting group, and R_4 and R_5 combine to form a double bond;

or

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

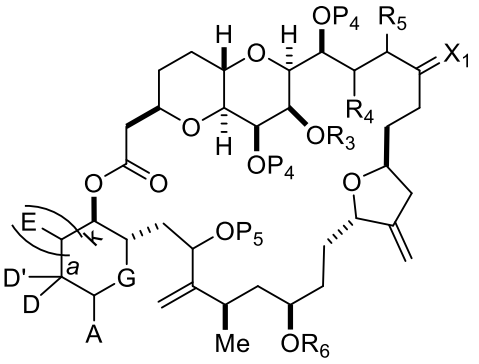
each P_4 is independently H or a hydroxyl protecting group, and X_1 is oxo or X_1, together with the carbon atom to which it is attached, is –(CH(OP_Y))–, wherein P_Y is H or a hydroxyl protecting group; or both P_4 groups and X_1, together with the atoms to which each is attached, combine to form ketal;

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



(VIIA)

or



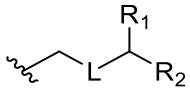
(VIIB)

,

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:



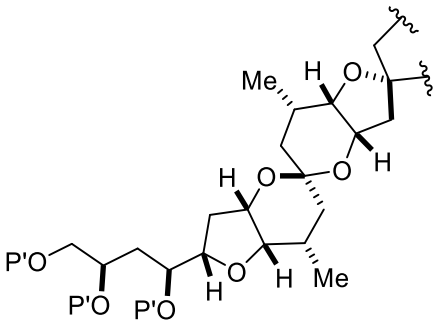
(1),

wherein

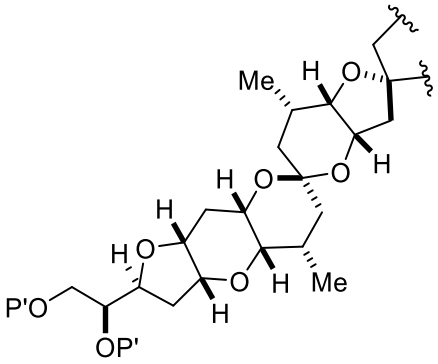
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

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

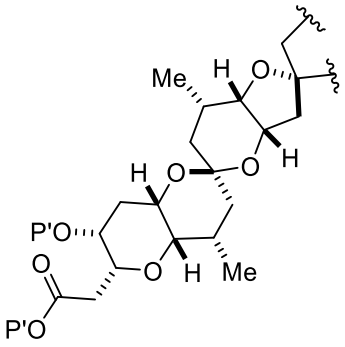
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

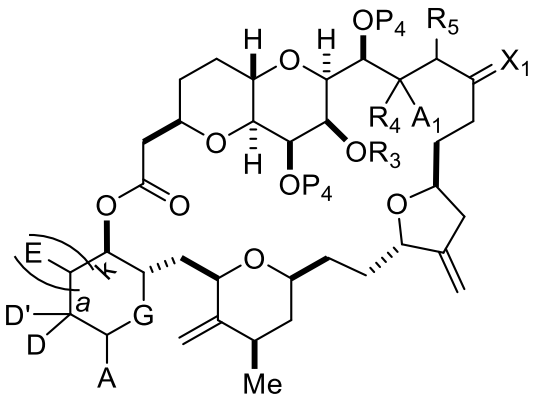
or

(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):

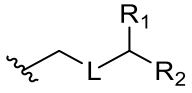


(VIIC)

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:



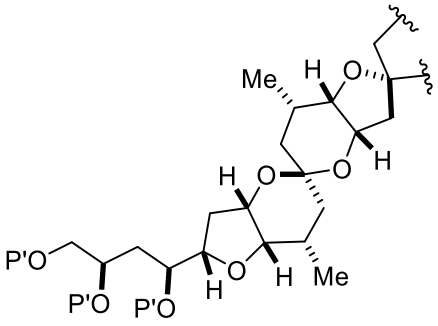
(1),

wherein

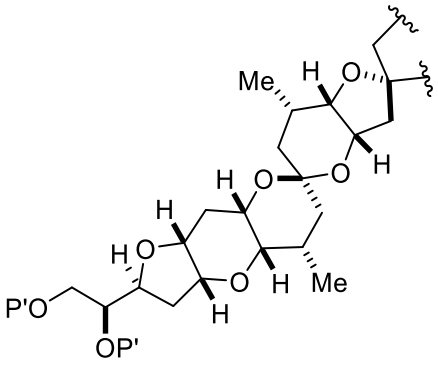
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

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

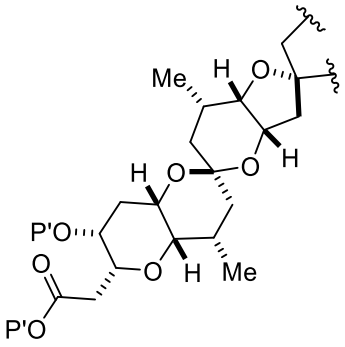
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

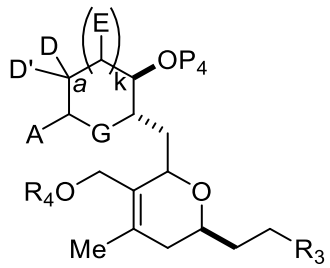
A_1 is H or OP", where P" is H or a hydroxyl protecting group, and:

(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".

24. A compound of formula (VIIC):

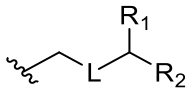


(VIIIC)

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:



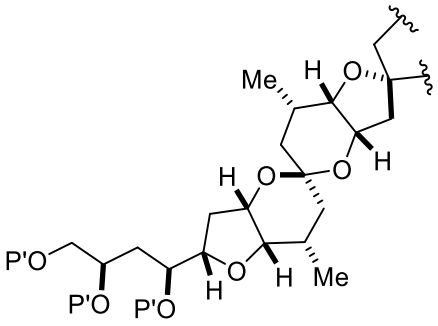
(1),

wherein

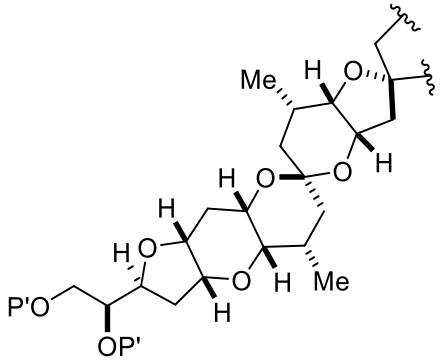
L is $–(CH(OP_2))–$, $–(C(OH)(OP_2))–$, or –C(O)–;

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

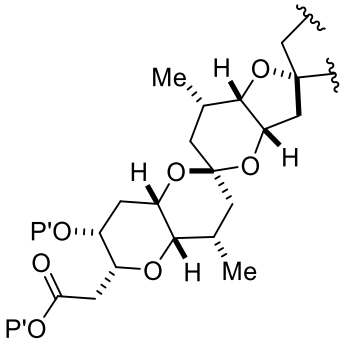
R_2 is H or $-(CH_2)_nOP_3$, and each of P_2 and P_3 is independently H, optionally substituted alkyl, or a hydroxyl protecting group, or P_2 and P_3, together with the atoms to which each is attached, combine to form a ketal, a cyclic carbonate, a dicarbonyl-dioxo, or silylene-dioxo; or R_2 and P_2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

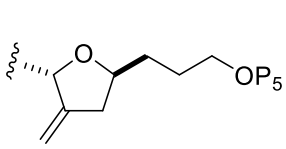
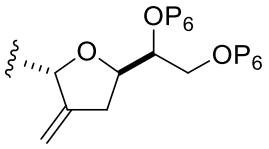
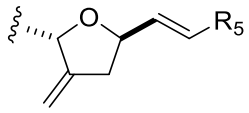
G is O, S, CH_2, or NR_N, wherein R_N is H, an N-protecting group, or optionally substituted alkyl;

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.