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

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). Eribulin mesylate (also called Halaven®, E7389, and the mesylate salt of B1939), a nontaxane microtubule dynamics inhibitor, is a structurally simplified, synthetic analogue of halichondrin B. Methods and intermediates for the synthesis of eribulin mesylate and other halichondrin B analogues 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; each of which is hereby incorporated by reference in its entirety. New methods for the synthesis of halichondrin B analogs, in particular eribulin, are desirable.

Summary of the Invention

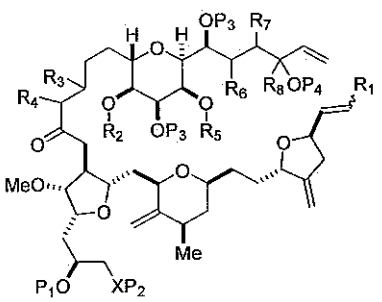
In one aspect, there is provided a method of preparing an intermediate in the synthesis of eribulin as stated in claim 1. In another aspect, there is provided a method of preparing as stated in claim 7.

Summary

In general, the present invention provides methods for macrocyclization of intermediates in the synthesis of eribulin or a pharmaceutically acceptable salt thereof (e.g., eribulin mesylate). The invention also provides intermediates that can be employed in the macrocyclization reactions described herein.

In a first aspect, the invention provides a method of preparing an intermediate in the synthesis of eribulin, the method including performing a macrocyclization reaction on a non-macrocyclic intermediate, the macrocyclization reaction producing the intermediate in the synthesis of eribulin by forming a C.15-C.16, C.2-C.3, C.3-C.4, C.19-C.20, C.0-C.1, or C.26-C.27 bond in the structure of eribulin.

In some embodiments of the first aspect, performing the macrocyclization reaction can involve contacting the non-macrocyclic intermediate (e.g., a compound of formula (IA)) with an olefin metathesis catalyst (e.g., a ruthenium-carbene complex). The non-macrocyclic intermediate can be a compound of formula (IA) or a salt thereof:

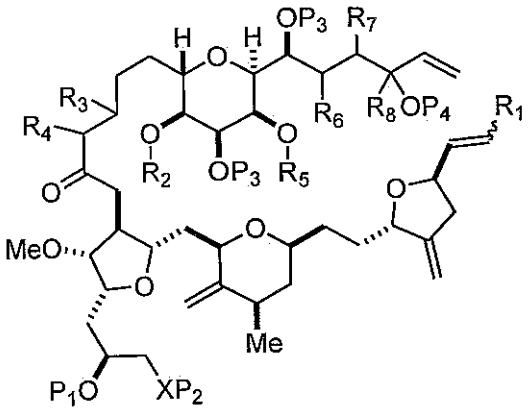


(IA),

Claims

1. A method of preparing an intermediate in the synthesis of eribulin, said method comprising performing a macrocyclization reaction on a non-macrocyclic intermediate, said macrocyclization reaction producing said intermediate in the synthesis of eribulin by forming a C.15-C.16 or C.3-C.4, bond in the structure of eribulin, wherein said non-macrocyclic intermediate is

(1) a compound of formula (IA) or a salt thereof:



(IA),

wherein

R_1 is H or $-CH_2X_1CH_2CH=CH_2$, wherein X_1 is O, $-C(R_9)_2-$, or NP_5, and wherein each R_9 is independently H or $-COOR_{10}$, P_5 is an *N*-protecting group, and R_{10} is C_{1-6} alkyl;

(a1) R_2 is H or a hydroxyl protecting group, R_3 is C_{1-6} alkyl ether, and R_4 is H;

(a2) R_2 is H or a hydroxyl protecting group, and R_3 and R_4 combine to form a double bond;

or

(a3) R_2 and R_3 combine to form a bond, and R_4 is H;

(b1) R_5 is H or a hydroxyl protecting group, and R_6 and R_7 combine to form a double bond;

or

(b2) R_5 and R_6 combine to form a bond, and R_7 is H;

(c1) R_8 is H, and P_4 is H or a hydroxyl protecting group;

or

(c2) R_8 and P_4 combine to form a double bond;

each P_3 is independently H or a hydroxyl protecting group; and

X is O, and

each of P_1 and P_2 is independently H or a hydroxyl protecting group,

or

P_1 and P_2, together with the atoms to which each is attached, combine to form a cyclic protected diol;

or

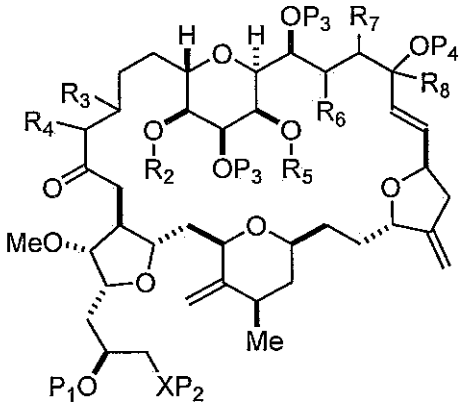
X is N, and

P_1 is H or a hydroxyl protecting group, and X and P_2 combine to form optionally masked amino;

or

P_1 and P_2, together with the atoms to which each is attached, combine to form an aminal or 1,3-oxazolidin-2-one-5-yl; and

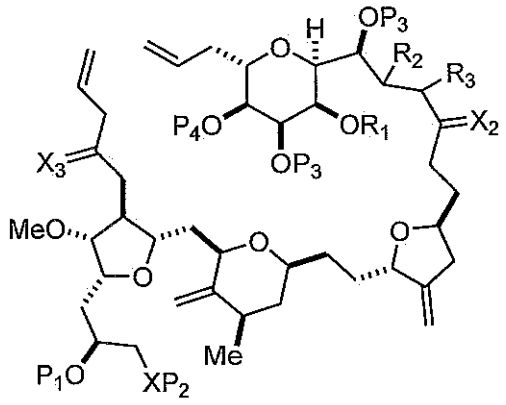
wherein said intermediate in the synthesis of eribulin is a compound of formula (IB) or a salt thereof:



(IB);

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

(2) a compound of formula (IIIA) or a salt thereof:



(IIIA),

wherein

(i) R_1 is H or a hydroxyl protecting group, and R_2 and R_3 combine to form a double bond; or

(ii) R_1 and R_2 combine to form a bond, and R_3 is H;

X_3 is oxo, or X_3 combines with the carbon atom to which it is attached to form a ketal, a thioketal, or $-(CH(OP_5))-$, wherein P_5 is H or a hydroxyl protecting group;

each P_3 is independently H or a hydroxyl protecting group, and X_2 is oxo; or both P_3 groups and X_2, together with the atoms to which each is attached, combine to form ketal;

P_4 is H or a hydroxyl protecting group; and

X is O, and

each of P_1 and P_2 is independently H or a hydroxyl protecting group,

or

P_1 and P_2, together with the atoms to which each is attached, combine to form a cyclic protected diol;

or

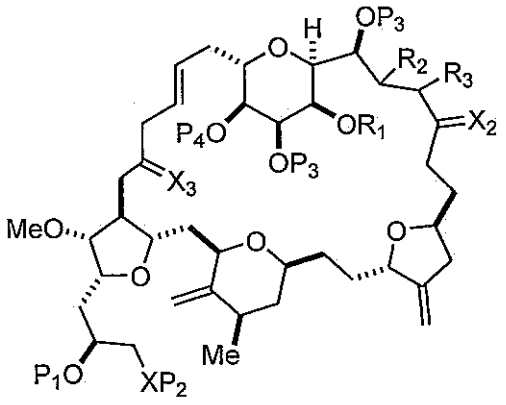
X is N, and

P_1 is H or a hydroxyl protecting group, and X and P_2 combine to form optionally masked amino;

or

P_1 and P_2, together with the atoms to which each is attached, combine to form an aminal or 1,3-oxazolidin-2-one-5-yl; and

wherein said intermediate in the synthesis of eribulin is a compound of formula (IIIB) or a salt thereof:



(IIIB);

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

2. The method of claim 1, wherein said non-macrocyclic intermediate is the compound of formula (IA) or a salt thereof.

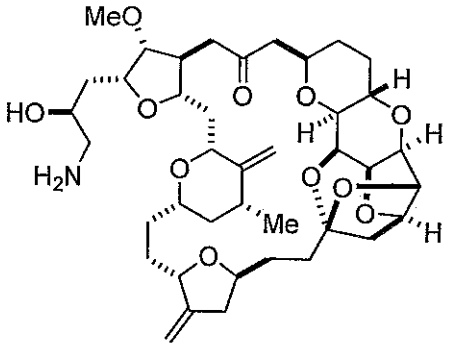
3. The method of claim 2, wherein each P_3 and P_4 is independently a hydroxyl protecting group.

4. The method of claim 1, wherein X is O.

5. The method of claim 1, wherein X is N.

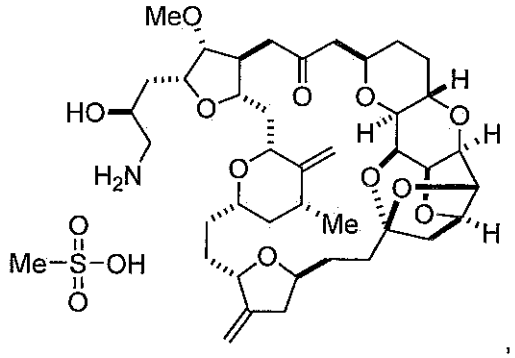
6. The method of claim 5, wherein X and P_2 combine to form optionally masked amino.

7. A method of preparing:



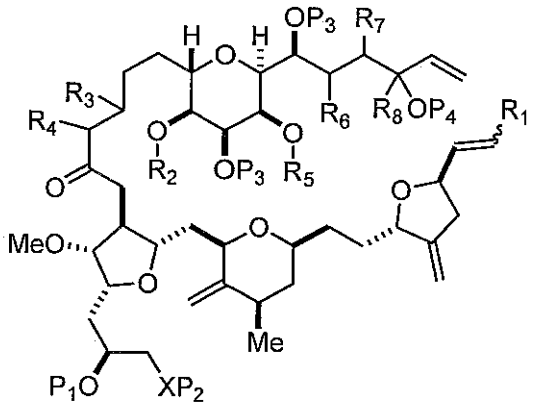
eribulin

or



eribulin mesylate

(1) said method comprising: (A) producing a compound of formula (IB) or salt thereof from a compound of formula (IA) or salt thereof by reacting the compound of formula (IA) or salt thereof with an olefin metathesis catalyst, the compound of formula (IA) having the following structure:



(IA),

wherein

R_1 is H or $-CH_2X_1CH_2CH=CH_2$, wherein X_1 is O, $-C(R_9)_2-$, or NP_5, and wherein each R_9 is independently H or $-COOR_{10}$, P_5 is an *N*-protecting group, and R_{10} is C_{1-6} alkyl;

(a1) R_2 is H or a hydroxyl protecting group, R_3 is C_{1-6} alkyl ether, and R_4 is H;

(a2) R_2 is H or a hydroxyl protecting group, and R_3 and R_4 combine to form a double bond;

or

(a3) R_2 and R_3 combine to form a bond, and R_4 is H;

(b1) R_5 is H or a hydroxyl protecting group, and R_6 and R_7 combine to form a double bond;

or

(b2) R_5 and R_6 combine to form a bond, and R_7 is H;

(c1) R_8 is H, and P_4 is H or a hydroxyl protecting group;

or

(c2) R_8 and P_4 combine to form a double bond;

each P_3 is independently H or a hydroxyl protecting group; and

X is O, and

each of P_1 and P_2 is independently H or a hydroxyl protecting group,

or

P_1 and P_2, together with the atoms to which each is attached, combine to form a cyclic protected diol;

or

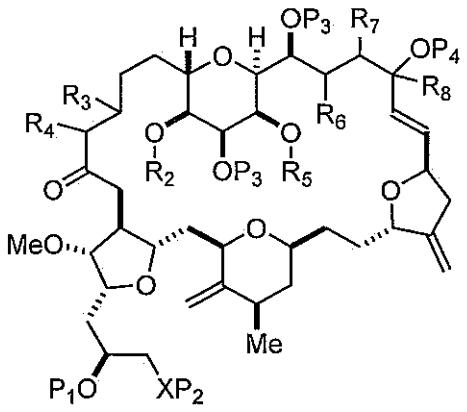
X is N, and

P_1 is H or a hydroxyl protecting group, and X and P_2 combine to form optionally masked amino;

or

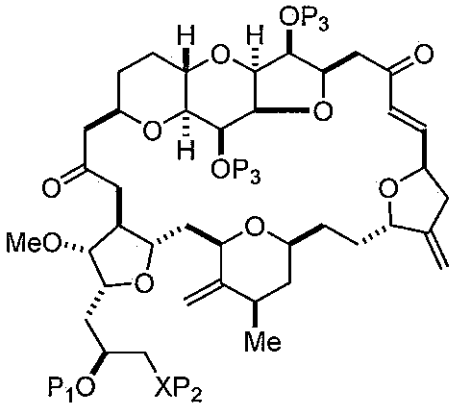
P_1 and P_2, together with the atoms to which each is attached, combine to form an aminal or 1,3-oxazolidin-2-one-5-yl;

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



(IB);

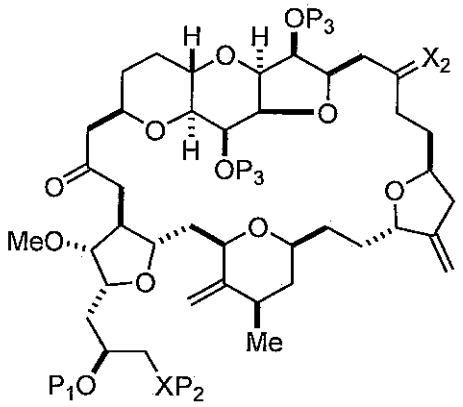
(B) producing a compound of formula (IC) or salt thereof from the compound of formula (IB) or salt thereof, the compound of formula (IC) having the following structure:



(IC) or

proceeding to step (C) if the compound of formula (IB) or salt thereof is the compound of formula (IC) or salt thereof;

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



(ID),

wherein

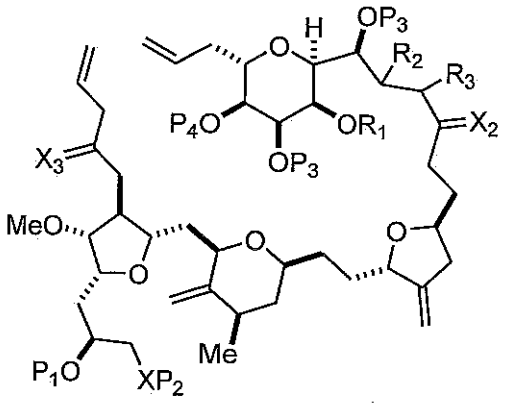
each P_3 is independently H or a hydroxyl protecting group, and X_2 is oxo; or both P_3 groups and X_2, together with the atoms to which each is attached, combine to form ketal;

and

(D) producing eribulin, if the compound of (ID) is not eribulin, or eribulin mesylate from the compound of formula (ID) or salt thereof; or

(2) said method comprising:

(A) producing a compound of formula (IIIB) or salt thereof from the compound of formula (IIIA) or salt thereof by reacting the compound of formula (IIIA) or salt thereof with an olefin metathesis catalyst, the compound of formula (IIIA) having the following structure:



(IIIA),

wherein

(i) R_1 is H or a hydroxyl protecting group, and R_2 and R_3 combine to form a double bond; or

(ii) R_1 and R_2 combine to form a bond, and R_3 is H;

X_3 is oxo, or X_3 combines with the carbon atom to which it is attached to form a ketal, a thioketal, or $-(CH(OP_5))-$, wherein P_5 is H or a hydroxyl protecting group; each P_3 is independently H or a hydroxyl protecting group, and X_2 is oxo; or both P_3 groups and X_2, together with the atoms to which each is attached, combine to form ketal;

P_4 is H or a hydroxyl protecting group; and

X is O, and

each of P_1 and P_2 is independently H or a hydroxyl protecting group,

or

P_1 and P_2, together with the atoms to which each is attached, combine to form a cyclic protected diol;

or

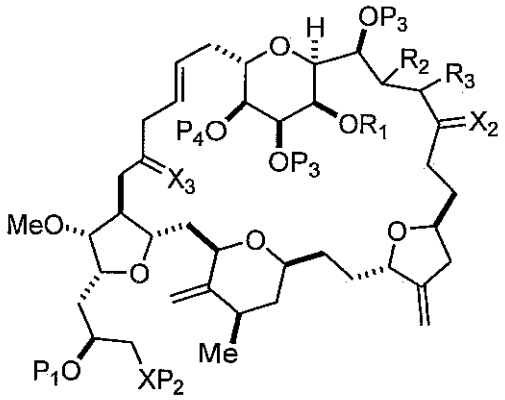
X is N, and

P_1 is H or a hydroxyl protecting group, and X and P_2 combine to form optionally masked amino;

or

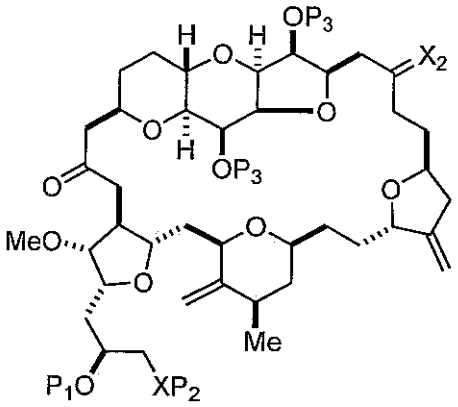
P_1 and P_2, together with the atoms to which each is attached, combine to form an aminal or 1,3-oxazolidin-2-one-5-yl;

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



(IIIB);

(B) producing a compound of formula (ID) or salt thereof from the compound of formula (IIIB) or salt thereof, the compound of formula (ID) having the following structure:



(ID);

and

(C) producing eribulin, if the compound of (ID) is not eribulin, or eribulin mesylate from the compound of formula (ID) or salt thereof.

8. The method of claim 7, wherein, in the compound of formula (ID) or salt thereof, both P_3 groups and X_2, together with the atoms to which each is attached, combine to form ketal.

9. The method of claim 7, wherein, in the compound of formula (ID) or salt thereof, P_1 is H.

10. The method of claim 7, wherein, in the compound of formula (ID) or salt thereof, X is O, and P_2 is H.

11. The method of claim 10, wherein said producing eribulin or eribulin mesylate from the compound of formula (ID) or salt thereof comprises aminating the compound of formula (ID) or salt thereof.

12. The method of claim 7, wherein, in the compound of formula (ID) or salt thereof, X and P_2 combine to form a masked amino.

13. The method of claim 12, wherein said producing eribulin or eribulin mesylate from the compound of formula (ID) or salt thereof comprises reacting the compound of formula (ID) or salt thereof with an amino unmasking agent.

14. The method of claim 7, wherein eribulin mesylate is produced by salifying eribulin with methanesulfonic acid.

15. The method of claim 2, wherein at least one of P_1 and P_2 is a hydroxyl protecting group.

16. The method of claim 2, wherein R_2 and R_3 combine to form a bond, and R_4 is H.

17. The method of claim 2, wherein R_5 and R_6 combine to form a bond, and R_7 is H.

18. The method of claim 1, wherein the non-macrocyclic intermediate is the compound of formula (IIIA) or a salt thereof.

19. The method of claim 18, wherein P_4 is a hydroxyl protecting group.

20. The method of claim 18, wherein both P_3 groups and X_2, together with the atoms to which each is attached, combine to form ketal.

21. The method of claim 18, wherein at least one of P_1 and P_2 is a hydroxyl protecting group.

22. The method of claim 18, wherein X_3 combines with the carbon atom to which it is attached to form $-(CH(OP_5))-$.

23. The method of claim 18, wherein R_1 and R_2 combine to form a bond, and R_3 is H.

24. The method of claim 18, wherein said olefin metathesis catalyst is a ruthenium-carbene complex.

25. The method of claim 7, wherein said method comprises producing the compound of formula (IB) or salt thereof from the compound of formula (IA) of salt thereof.

26. The method of claim 25, wherein said producing said compound of formula (IC) or salt thereof comprises oxidizing the compound of formula (IB) or salt thereof, wherein, in the compound of formula (IB) or salt thereof, R_8 is H, and P_4 is H.

27. The method of claim 25, wherein said producing the compound of formula (ID) or salt thereof comprises reacting the compound of formula (IC) or salt thereof with a 1,4-reducing agent.

28. The method of claim 27, wherein said producing the compound of formula (ID) or salt thereof further comprises reacting with a hydroxyl protecting group removing agent after said reacting the compound of formula (IC) or salt thereof with said 1,4-reducing agent.

29. The method of claim 28, wherein, in the compound of formula (ID) or salt thereof, X is O, and P_2 is H.

30. The method of claim 7, wherein said method comprises producing the compound of formula (IIIB) or salt thereof from the compound of formula (IIIA) of salt thereof.

31. The method of claim 30, wherein said producing said compound of formula (ID) or salt thereof, comprises oxidizing the compound of formula (IIIB) or salt thereof, wherein, in the compound of formula (IIIB) or salt thereof, X_3, together with the carbon to which it is attached, forms $-(CH(OP_5))-$, wherein P_5 is H.

32. The method of claim 30, wherein said producing said compound of formula (ID) or salt thereof, comprises reacting the compound of formula (IIIB) or salt thereof with a hydroxyl protecting group removing agent, wherein, in the compound of formula (IIIB) or salt thereof, P_4 is a hydroxyl protecting group, and X_3 is O.