FURO [3 , 2-B] PYRANE DERIVATIVES USEFUL IN THE SYNTHESIS OF HALICHONDRIN B ANALOGS

BACKGROUND OF THE INVENTION

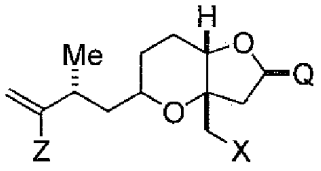
The invention relates to compounds useful in the synthesis of analogs of halichondrin B.

Eribulin mesylate, a nontaxane microtubule dynamics inhibitor, is a structurally simplified, synthetic analog of the marine natural product halichondrin B. Methods for the synthesis of eribulin and other halichondrin B analogs are described in International Publication No. WO 2005/118565 and U.S. Patent No. 6,214,865. New intermediates for the synthesis of halichondrin B analogs, in particular eribulin, are desirable.

SUMMARY

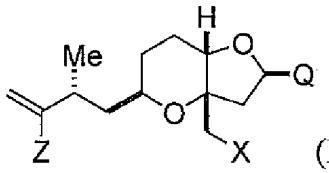
In general, the disclosure features compounds useful for the synthesis of analogs of halichondrin B, such as eribulin, including pharmaceutically acceptable salts thereof, e.g., eribulin mesylate.

Disclosed is a compound having the formula (I):



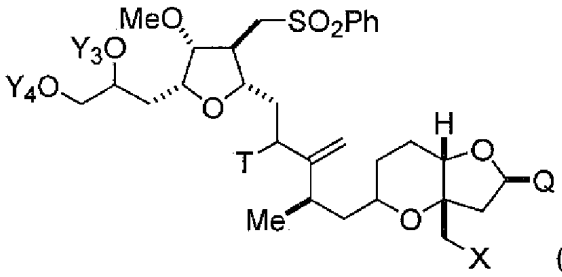
(I),

wherein X is halogen or oxo; Z is a leaving group; Q is -C(O)H, -CH=CHC(O)OY_1, -C(R)H$(CH_2)_n OY_1$, or -C(R)HCH_2C(O)OY_1; R is H or -OY_2; Y_1 and Y_2 are each independently H or a hydroxyl protecting group; and n is 1 or 2. Exemplary compounds have the formula (Ia):



(Ia).

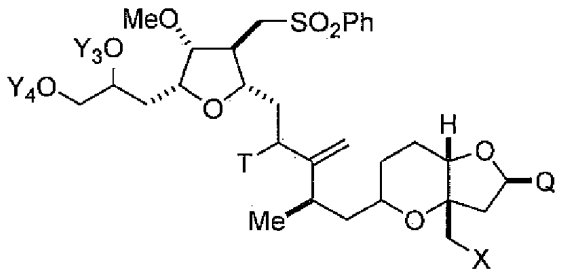
Disclosed are compounds having the formula (II):



(II),

wherein X is halogen or oxo; Q is -C(O)H, -CH=CHC(O)OY_1, -C(R)H$(CH_2)_n OY_1$, or -C(R)HCH_2C(O)OY_1; R is H or -OY_2; n is 1 or 2; Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group; T is oxo or -OY_5; and Y_5 is H or a hydroxyl protecting group, or Y_5, together with the oxygen atom to which it is bound, is a leaving group.

In one aspect, there is provided a compound having the formula:



(II),

wherein X is halogen or oxo;

Q is –C(O)H, –CH=CHC(O)OY_1, –C(R)H$(CH_2)_n OY_1$, or –C(R)HCH_2C(O)OY_1;

R is H or –OY_2;

n is 1 or 2;

Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group;

T is oxo or –OY_5; and

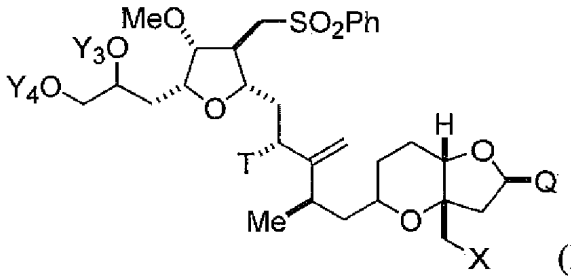
Y_5 is H or a hydroxyl protecting group, or Y_5, together with the oxygen atom to which it is bound, is a leaving group,

wherein the hydroxyl protecting groups of Y_1, Y_2, Y_3, Y_4, and Y_5 are each, independently and together with the oxygen atom to which it is bound, an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group, or

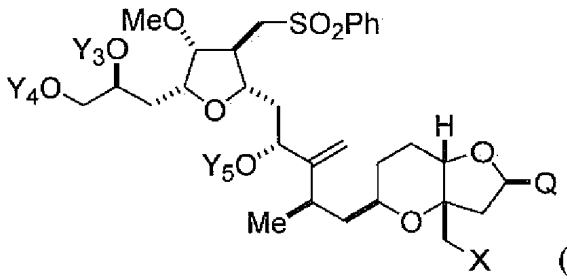
Y_3 and Y_4, together with the oxygen atoms to which they are bound, are a cyclic carbonate, cyclic boronate, or cyclic silylene hydroxyl protecting group, or Y_3 and Y_4 together are acetal, ketal, or 1,1,3,3-tetraisopropylsiloxanediyl; and

the leaving group of Y_5, together with the oxygen atom to which it is bound, is (C1-C12)alkoxy, (C1-C12)alkylsulfonate, (C2-C12)alkenylsulfonate, carbocyclic(C6-C20)arylsulfonate, (C4-C19)heteroarylsulfonate, monocyclic(C1-C6)heteroarylsulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, (C4-C19)heteroaryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate.

Exemplary compounds have the formula:



(IIa) or

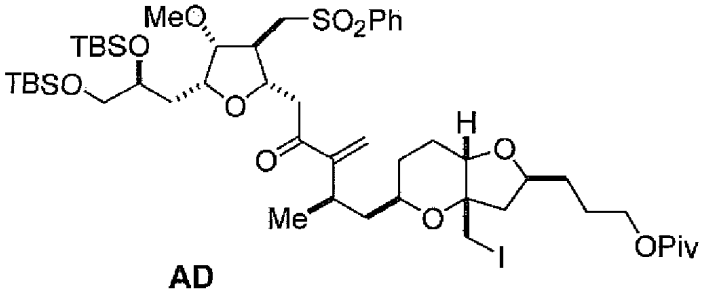


(IIb).

In particular embodiments, Q is $-(CH_2)_3OY_1$. In these embodiments, Y_1, together with the oxygen atom to which it is bound, can be an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group; Y_3 and Y_4 can each, independently and together with the oxygen atom to which it is bound, be an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group, or Y_3 and Y_4 together with the oxygen atoms to which they are bound can be a cyclic carbonate, cyclic boronate, acetal, ketal, or cyclic silylene hydroxyl protecting group or 1,1,3,3-tetraisopropylsiloxanediyl; T can be $-OY_5$; and/or Y_5, together

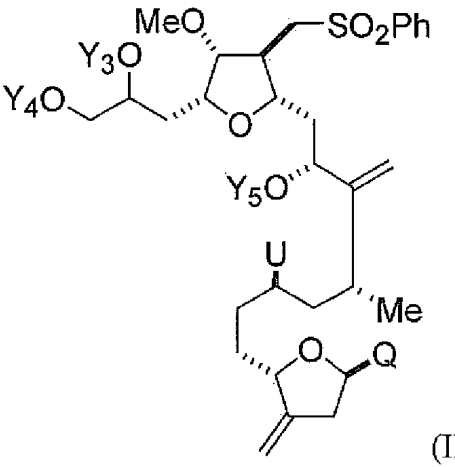
1-naphthoyl	1-naphthoyl
p-methoxybenzoyl	H
p-methoxybenzoyl	p-methoxybenzoyl
o-phthaloyl or salt thereof	H

A specific compound is



AD

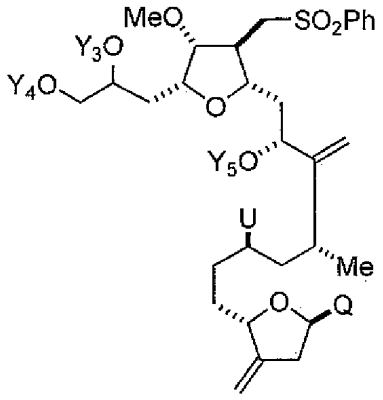
In another embodiment, the disclosure features a compound having the formula (III):



(III),

wherein Q is -C(O)H, -CH=CHC(O)OY_1, -C(R)H$(CH_2)_nOY_1$, or -C(R)HCH_2C(O)OY_1; R is H or -OY_2; n is 1 or 2; Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group; U is halogen or -OY_6; Y_5 is H or a hydroxyl protecting group or Y_5, together with the oxygen atom to which it is bound, is a leaving group; and Y_6 is H or a hydroxyl protecting group or Y_6, together with the oxygen atom to which it is bound, is a leaving group, provided that when Q is –$(CH_2)_3OY_1$, U is -OY_6, wherein -OY_6 is a leaving group, and Y_1, Y_3, and Y_4 are protecting groups, Y_5 is not H.

In one aspect, there is provided a compound having the formula:



(III),

wherein Q is –C(O)H, –CH=CHC(O)OY_1, –C(R)H$(CH_2)_nOY_1$, or –C(R)HCH_2C(O)OY_1;

R is H or –OY_2;

n is 1 or 2;

Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group;

U is –OY_6;

Y_5 is H or a hydroxyl protecting group or Y_5, together with the oxygen atom to which it is bound, is a leaving group; and

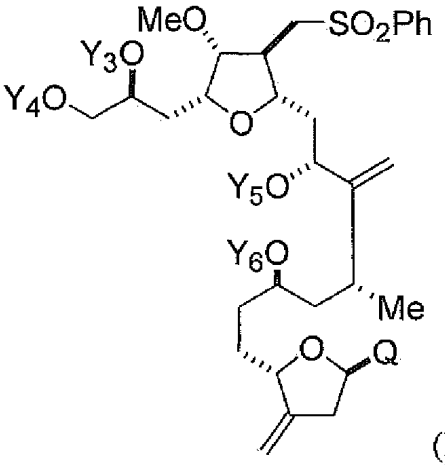
Y_6 is H or a hydroxyl protecting group, or Y_6, together with the oxygen atom to which it is bound, is a leaving group, provided that when Q is –$(CH_2)_3OY_1$, –OY_6 is a leaving group, Y_1, Y_3, and Y_4 are protecting groups, and Y_5 is not H,

wherein the hydroxyl protecting groups of Y_1, Y_2, Y_3, Y_4, Y_5, and Y_6 are each, independently and together with the oxygen atom to which it is bound, an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group, or

Y_3 and Y_4, together with the oxygen atoms to which they are bound, are a cyclic carbonate, cyclic boronate, or cyclic silylene hydroxyl protecting group, or Y_3 and Y_4 together are acetal, ketal, or 1,1,3,3-tetraisopropylsiloxanediyl; and

the leaving groups of Y_5 and Y_6 are each, independently and together with the oxygen atom to which it is bound, (C1-C12)alkoxy, (C1-C12)alkylsulfonate, (C2-C12)alkenylsulfonate, carbocyclic(C6-C20)arylsulfonate, (C4-C19)heteroarylsulfonate, monocyclic(C1-C6)heteroarylsulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, (C4-C19)heteroaryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate.

Exemplary compounds have the formula (IIIa):



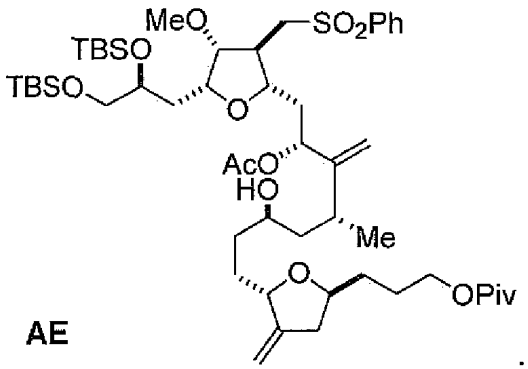
(IIIa).

In particular embodiments, Q is $-(CH_2)_3OY_1$. In these embodiments, Y_1, together with the oxygen atom to which it is bound, is, for example, an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group; each of Y_3 and Y_4 is, for example, independently and together with the oxygen atom to which it is bound, an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group, or Y_3 and Y_4 together with the oxygen atoms to which they are bound are, for example, a cyclic carbonate, cyclic boronate, acetal, ketal, or cyclic silylene hydroxyl protecting group or 1,1,3,3-tetraisopropylsiloxanediyl; and/or Y_5, together with the oxygen atom to which it is bound, is, for example, an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group. In specific examples, Y_1 is pivaloyl, acetyl, benzoyl, p-bromobenzoyl, p-methoxybenzoyl, 1-naphthoyl, 2-naphthoyl, o-phthaloyl, benzyl, p-methoxybenzyl, triphenylmethyl, tri(C1-C6 alkyl)silyl, tri(C6-C10 aryl or C1-C6 heteroaryl)silyl, di(C6-C10 aryl or C1-C6 heteroaryl)(C1-C6 alkyl)silyl, or

(C6-C10 aryl or C1-C6 heteroaryl)di(C1-C6 alkyl)silyl; Y_3 and Y_4 are each independently tri(C1-C6 alkyl)silyl, tri(C6-C10 aryl or C1-C6 heteroaryl)silyl, di(C6-C10 aryl or C1-C6 heteroaryl)(C1-C6 alkyl)silyl, or (C6-C10 aryl or C1-C6 heteroaryl)di(C1-C6 alkyl)silyl, or Y_3 and Y_4 are together di(C1-C6)alkylsilylene; and/or Y_5 is acetyl, benzoyl, p-bromobenzoyl, p-methoxybenzoyl, 1-naphthoyl, 2-naphthoyl, or o-phthaloyl.

In other embodiments, Y_5 is H or a hydroxyl protecting group; Y_6 is H; or $-OY_6$ is a leaving group, such as (C1-C6)alkylsulfonate, (C6-C10 aryl or C1-C6 heteroaryl)sulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate. Specific leaving groups include mesylate, toluenesulfonate, isopropylsulfonate, phenylsulfonate, or benzylsulfonate.

A specific example has the formula:



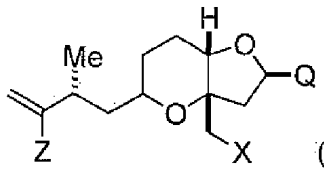
AE

Additional compounds of the disclosure are described herein.

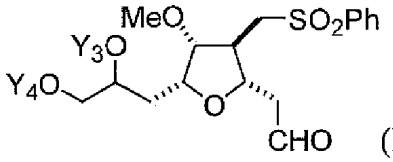
The disclosure further features use of the compounds of the disclosure, e.g., Compounds E-AM, in the manufacture of ER-804028 and analogs of halichondrin B, such as eribulin, or a pharmaceutically acceptable salt thereof, e.g., eribulin mesylate.

Disclosed is a method of synthesizing ER-804028 by

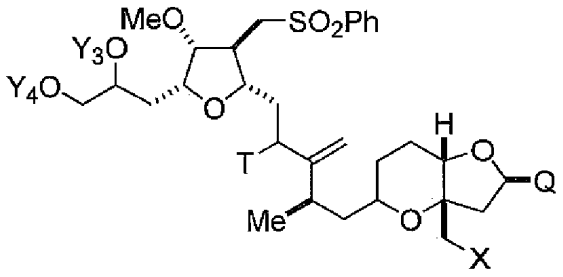
(i) reacting a compound having the formula (I):



(I) with a compound having the formula (IV):

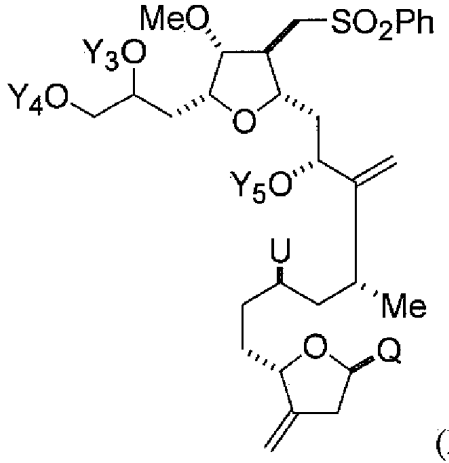


(IV), wherein Y_3, and Y_4, are each independently H or a hydroxyl protecting group, under Nozaki-Hiyama-Kishi (NHK) coupling conditions to produce a compound of formula (II):



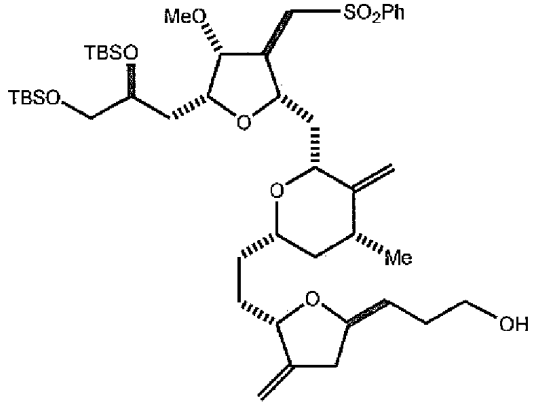
(II);

(ii) reacting the product of step (i) under Vasella fragmentation conditions to produce a compound of formula (III):



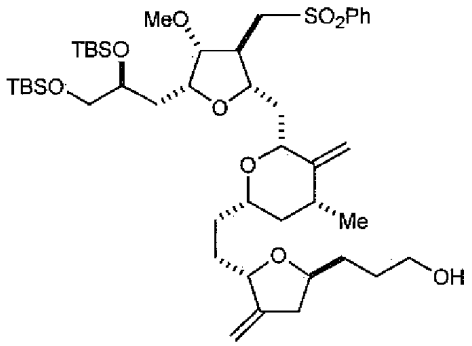
(III); and

(iii) reacting the product of step (ii) under conditions for intramolecular Williamson etherification to produce ER-804028:



(ER-804028).

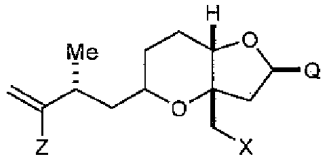
In one aspect, there is provided a method of synthesizing ER-804028:



(ER-804028),

said method comprising the steps of:

(i) reacting a compound having the formula (I):



(I),

wherein X is halogen or oxo;

Z is a leaving group;

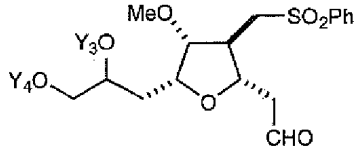
Q is $-C(O)H$, $-CH=CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

Y_1 and Y_2 are each independently H or a hydroxyl protecting group; and

n is 1 or 2,

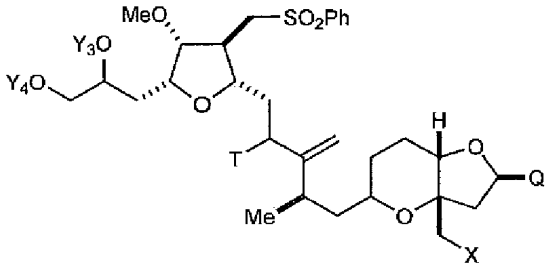
with a compound having the formula (IV):



(IV),

wherein Y_3, and Y_4 are each independently H or a hydroxyl protecting group,

under NHK coupling conditions to produce a compound having the formula:



(II),

wherein X is halogen or oxo;

Q is $-C(O)H$, $-CH=CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

n is 1 or 2;

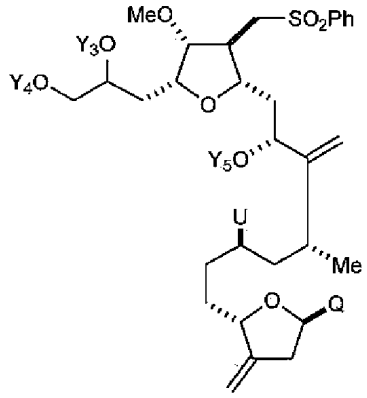
Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting

group;

T is oxo or $-OY_5$; and

Y_5 is H or a hydroxyl protecting group, or Y_5, together with the oxygen atom to which it is bound, is a leaving group,

(ii) reacting the product of step (i) under Vasella fragmentation conditions to produce a compound having the formula:



(III),

wherein Q is $-C(O)H$, $-CH=CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

n is 1 or 2;

Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group;

U is $-OY_6$;

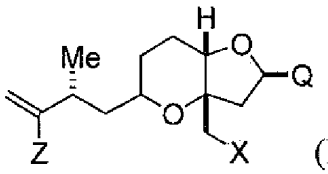
Y_5 is H or a hydroxyl protecting group or Y_5, together with the oxygen atom to which it is bound, is a leaving group; and

Y_6 is H or a hydroxyl protecting group or Y_6, together with the oxygen atom to which it is bound, is a leaving group, provided that when Q is $-(CH_2)_3OY_1$, $-OY_6$ is a leaving group, Y_1, Y_3, and Y_4 are protecting groups, and Y_5 is not H; and

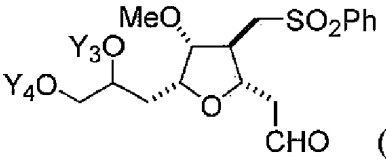
(iii) reacting the product of step (ii) under conditions for intramolecular Williamson etherification to produce ER-804028.

Disclosed is a method of synthesizing eribulin, or a pharmaceutically acceptable salt thereof, by

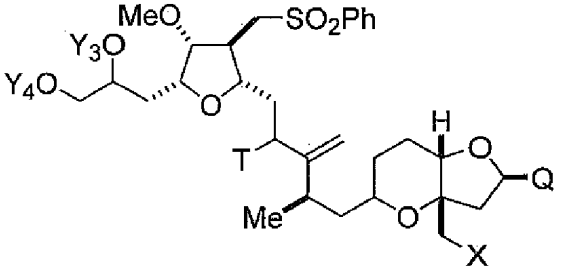
(i) reacting a compound having the formula (I):



(I) with a compound having the formula (IV):

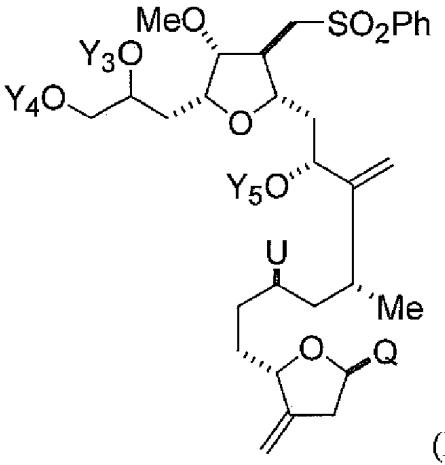


(IV), wherein Y_3, and Y_4, are each independently H or a hydroxyl protecting group, under NHK coupling conditions to produce a compound of formula (II)



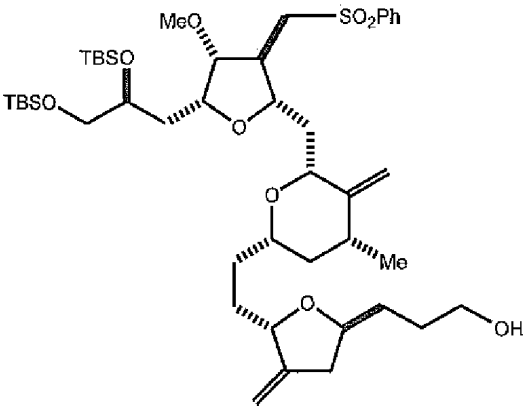
(II);

(ii) reacting the product of step (i) under Vasella fragmentation conditions to produce a compound of formula (III):



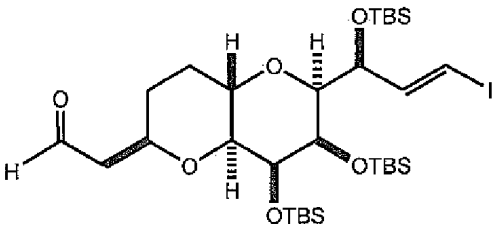
(III);

(iii) reacting the product of step (ii) under conditions for intramolecular Williamson etherification to produce ER-804028:



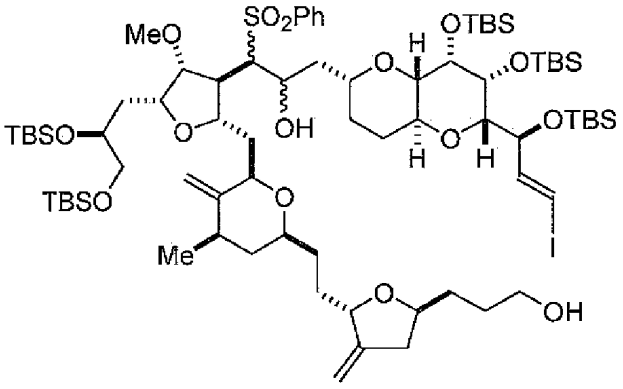
(ER-804028);

(iv) reacting ER-804028 with ER-803896:



(ER-803896)

under conditions to produce ER-804029:

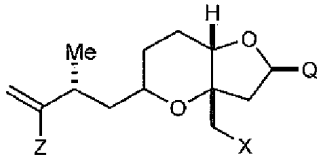


(ER-804029); and

(v) reacting ER-804029 under conditions to produce eribulin, or the pharmaceutically acceptable salt thereof. The method may include salifying eribulin to produce the pharmaceutically acceptable salt thereof, e.g., eribulin mesylate. Additional intermediates and reaction conditions are described herein.

In one aspect, there is provided a method for producing eribulin or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

(i) reacting a compound having the formula (I):



(I),

wherein X is halogen or oxo;

Z is a leaving group;

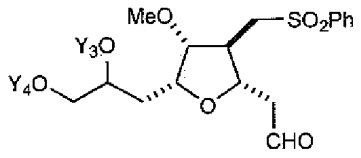
Q is $-C(O)H$, $-CH{=}CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

Y_1 and Y_2 are each independently H or a hydroxyl protecting group; and

n is 1 or 2,

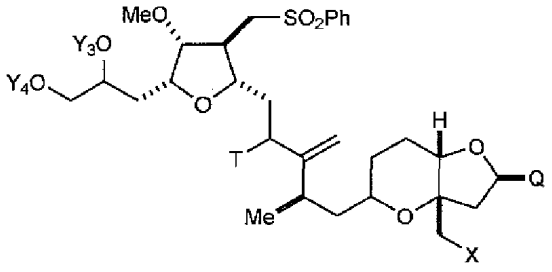
with a compound having the formula (IV):



(IV),

wherein Y_3, and Y_4 are each independently H or a hydroxyl protecting group,

under NHK coupling conditions to produce a compound having the formula:



(II),

wherein X is halogen or oxo;

Q is $-C(O)H$, $-CH{=}CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

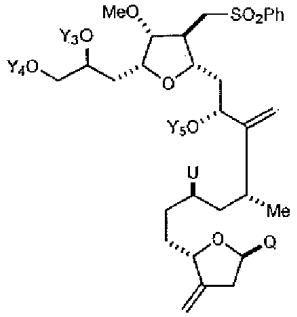
n is 1 or 2;

Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group;

T is oxo or $-OY_5$; and

Y_5 is H or a hydroxyl protecting group, or Y_5, together with the oxygen atom to which it is bound, is a leaving group,

(ii) reacting the product of step (i) under Vasella fragmentation conditions to produce a compound having the formula:



(III),

wherein Q is $-C(O)H$, $-CH=CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

n is 1 or 2;

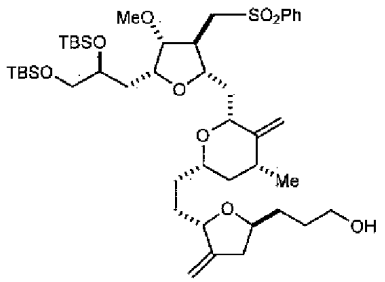
Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group;

U is $-OY_6$;

Y_5 is H or a hydroxyl protecting group or Y_5, together with the oxygen atom to which it is bound, is a leaving group; and

Y_6 is H or a hydroxyl protecting group or Y_6, together with the oxygen atom to which it is bound, is a leaving group, provided that when Q is $-(CH_2)_3OY_1$, $-OY_6$ is a leaving group, and Y_1, Y_3, and Y_4 are protecting groups, Y_5 is not H; and

(iii) reacting the product of step (ii) under conditions for intramolecular Williamson etherification to produce ER-804028:



(ER-804028); and

(iv) converting ER-804028 into eribulin or a pharmaceutically acceptable salt thereof.

Asymmetric or chiral centers exist in the compounds of the disclosure. The present disclosure includes the various stereoisomers of the compounds and mixtures thereof, unless otherwise specified. Individual stereoisomers of the compounds of the present disclosure are prepared synthetically from commercially available starting materials that contain asymmetric or chiral centers or by preparation of mixtures of compounds followed by resolution as

is well known in the art. These methods of resolution are exemplified by direct separation of the mixture of diastereomers on chiral chromatographic columns or by chiral HPLC methods. Methods of chiral separation have been described previously (G.B. Cox (ed.) in *Preparative Enantioselective Chromatography*, 2005, Blackwell Publishing). Alternatively, chiral compounds can be prepared by an asymmetric synthesis that favors the preparation of one diastereomer over another. Geometric isomers may also exist in the compounds of the present disclosure. The present disclosure includes the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond, such as isomers of the Z or E configuration. It is also recognized that for structures in which tautomeric forms are possible, the description of one tautomeric form is equivalent to the description of both, unless otherwise specified. In certain embodiments, a diastereomer of a compound of the disclosure is present in a mixture at a ratio of 10:1, 20:1, 30:1, 50:1, or greater as compared to other diastereomers.

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

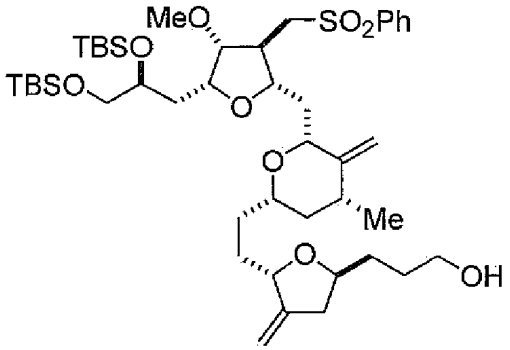
For any of the following chemical definitions, a number following an atomic symbol indicates that total number of atoms of that element that are present in a particular chemical moiety. As will be understood, other atoms, such as hydrogen atoms, or substituent groups, as described herein, may be present, as necessary, to satisfy the valences of the atoms. For example, an unsubstituted C2 alkyl group has the formula $-CH_2CH_3$. When used with the groups defined herein, a reference to the number of carbon atoms includes the divalent carbon in acetal and ketal groups but does not include the carbonyl carbon in acyl, ester, carbonate, or carbamate groups. A reference to the number of oxygen, nitrogen, or sulfur atoms in a heteroaryl group only includes those atoms that form a part of a heterocyclic ring.

thiocyanate, toluenesulfonate, undecanoate, valerate salts and the like. A preferred salt is the mesylate salt.

Other features and advantages of the disclosure will be apparent from the following description and the claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds and methods of their use in the synthesis of halichondrin B analogs. In particular, the compounds are useful for the synthesis of the C14-C35 portion of halichondrin B analogs. ER-804028 is a C14-C35 fragment that has been employed in the synthesis of eribulin:

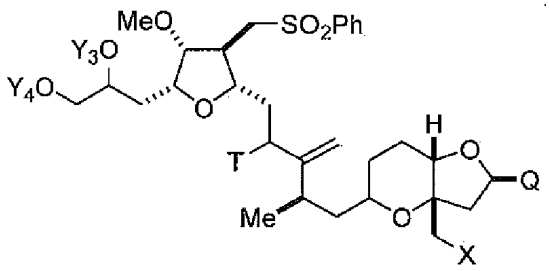


ER-804028.

Halichondrin B analogs, e.g., eribulin or pharmaceutically acceptable salts thereof, can be synthesized from the C14-C35 fragment as described in U.S. Patent No. 6,214,865 and International Publication No. WO 2005/118565. In one example described in these references, the C14-C35 portion, e.g., ER-804028, of the molecule is coupled to the C1-C13 portion, e.g., ER-803896, to produce ER-804029, and additional reactions are carried out to produce eribulin (Scheme 1):

Claims

1. A compound having the formula:



(II),

wherein X is halogen or oxo;

Q is $-C(O)H$, $-CH=CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

n is 1 or 2;

Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group;

T is oxo or $-OY_5$; and

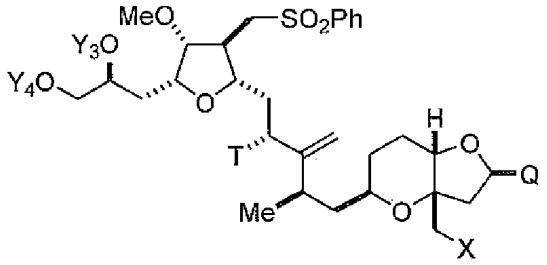
Y_5 is H or a hydroxyl protecting group, or Y_5, together with the oxygen atom to which it is bound, is a leaving group,

wherein the hydroxyl protecting groups of Y_1, Y_2, Y_3, Y_4, and Y_5 are each, independently and together with the oxygen atom to which it is bound, an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group, or

Y_3 and Y_4, together with the oxygen atoms to which they are bound, are a cyclic carbonate, cyclic boronate, or cyclic silylene hydroxyl protecting group, or Y_3 and Y_4 together are acetal, ketal, or 1,1,3,3-tetraisopropylsiloxanediyl; and

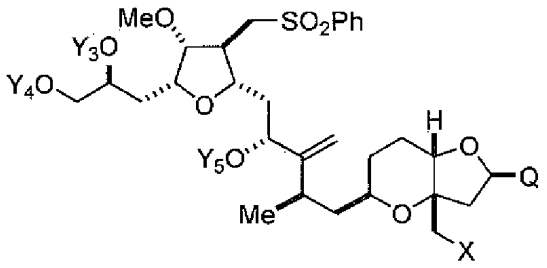
the leaving group of Y_5, together with the oxygen atom to which it is bound, is (C1-C12)alkoxy, (C1-C12)alkylsulfonate, (C2-C12)alkenylsulfonate, carbocyclic(C6-C20)arylsulfonate, (C4-C19)heteroarylsulfonate, monocyclic(C1-C6)heteroarylsulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, (C4-C19)heteroaryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate.

2. The compound of claim 1 having the formula:



(IIa).

3. The compound of claim 1 having the formula:



(IIb).

4. The compound of claim 1, wherein Q is $-(CH_2)_3OY_1$.

5. The compound of claim 4, wherein Y_1, together with the oxygen atom to which it is bound, is an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group;

T is $-OY_5$; and

Y_5, together with the oxygen atom to which it is bound, is an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group.

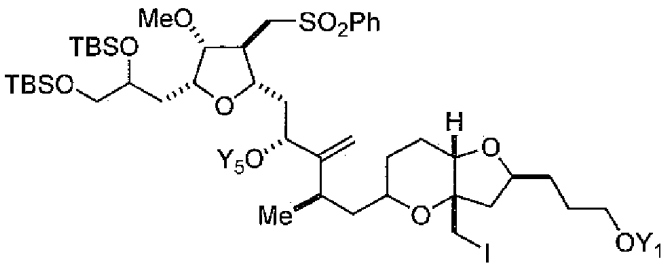
6. The compound of claim 1, wherein Y_1 is pivaloyl, acetyl, benzoyl, p-bromobenzoyl, p-methoxybenzoyl, 1-naphthoyl, 2-naphthoyl, o-phthaloyl, benzyl, p-methoxybenzyl, triphenylmethyl, tri(C1-C6 alkyl)silyl, tri(C6-C10 aryl or C1-C6 heteroaryl)silyl, di(C6-C10 aryl or C1-C6 heteroaryl)(C1-C6 alkyl)silyl, or (C6-C10 aryl or C1-C6 heteroaryl)di(C1-C6 alkyl)silyl.

7. The compound of claim 1, wherein Y_3 and Y_4 are each independently tri(C1-C6 alkyl)silyl, tri(C6-C10 aryl or C1-C6 heteroaryl)silyl, di(C6-C10 aryl or C1-C6 heteroaryl)(C1-C6 alkyl)silyl, or (C6-C10 aryl or C1-C6 heteroaryl)di(C1-C6 alkyl)silyl, or Y_3 and Y_4 are together di(C1-C6alkyl)silylene.

8. The compound of claim 1, wherein Y_5 is acetyl, benzoyl, p-bromobenzoyl, p-methoxybenzoyl, 1-naphthoyl, 2-naphthoyl, or o-phthaloyl.

9. The compound of claim 1, wherein X is halogen.

10. The compound of claim 1 having the formula:

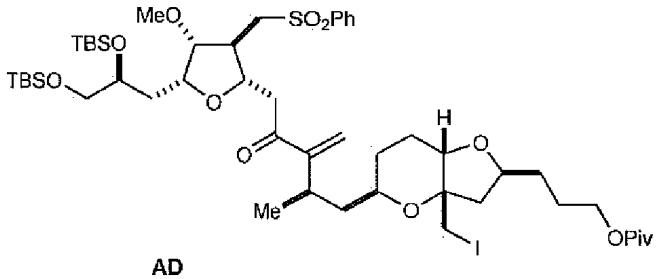


(IIc),

wherein Y_1 and Y_5 are as follows:

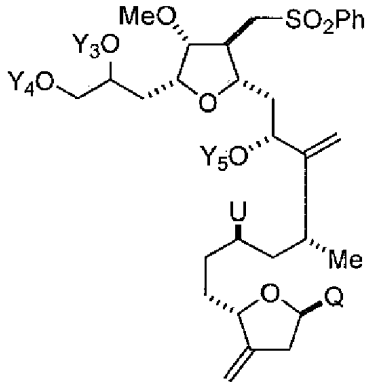
Compound	Y_1	Y_5
(i)	H	H
(ii)	benzoyl	benzoyl
(iii)	p-bromobenzoyl	p-bromobenzoyl
(iv)	pivaloyl	H
(v)	pivaloyl	acetyl
(vi)	pivaloyl	benzoyl
(vii)	2-naphthoyl	H
(viii)	2-naphthoyl	2-naphthoyl
(ix)	1-naphthoyl	H
(x)	1-naphthoyl	1-naphthoyl
(xi)	p-methoxybenzoyl	H
(xii)	p-methoxybenzoyl	p-methoxybenzoyl
(xiii)	o-phthaloyl or salt thereof	H

11. The compound of claim 1 having the formula:



AD

12. A compound having the formula:



(III),

wherein Q is –C(O)H, –CH=CHC(O)OY_1, –C(R)H$(CH_2)_nOY_1$, or –C(R)HCH_2C(O)OY_1;

R is H or –OY_2;

n is 1 or 2;

Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group;

U is –OY_6;

Y_5 is H or a hydroxyl protecting group or Y_5, together with the oxygen atom to which it is bound, is a leaving group; and

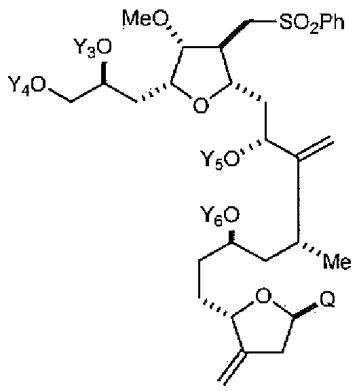
Y_6 is H or a hydroxyl protecting group, or Y_6, together with the oxygen atom to which it is bound, is a leaving group, provided that when Q is –$(CH_2)_3OY_1$, –OY_6 is a leaving group, Y_1, Y_3, and Y_4 are protecting groups, and Y_5 is not H,

wherein the hydroxyl protecting groups of Y_1, Y_2, Y_3, Y_4, Y_5, and Y_6 are each, independently and together with the oxygen atom to which it is bound, an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group, or

Y_3 and Y_4, together with the oxygen atoms to which they are bound, are a cyclic carbonate, cyclic boronate, or cyclic silylene hydroxyl protecting group, or Y_3 and Y_4 together are acetal, ketal, or 1,1,3,3-tetraisopropylsiloxanediyl; and

the leaving groups of Y_5 and Y_6 are each, independently and together with the oxygen atom to which it is bound, (C1-C12)alkoxy, (C1-C12)alkylsulfonate, (C2-C12)alkenylsulfonate, carbocyclic(C6-C20)arylsulfonate, (C4-C19)heteroarylsulfonate, monocyclic(C1-C6)heteroarylsulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, (C4-C19)heteroaryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate.

13. The compound of claim 12 having the formula (IIIa):



(IIIa).

14. The compound of claim 12, wherein Q is $-(CH_2)_3OY_1$.

15. The compound of claim 14, wherein Y_1, together with the oxygen atom to which it is bound, is ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group;

Y_3 and Y_4 are each, independently and together with the oxygen atom to which it is bound, an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group, or Y_3 and Y_4, together with the oxygen atoms to which they are bound, are a cyclic carbonate, cyclic boronate, or cyclic silylene hydroxyl protecting group, or Y_3 and Y_4 together are acetal, ketal, or 1,1,3,3-tetraisopropylsiloxanediyl; and

Y_5, together with the oxygen atom to which it is bound, is an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group.

16. The compound of claim 12, wherein Y_1 is pivaloyl, acetyl, benzoyl, p-bromobenzoyl, p-methoxybenzoyl, 1-naphthoyl, 2-naphthoyl, o-phthaloyl, benzyl, p-methoxybenzyl, triphenylmethyl, tri(C1-C6 alkyl)silyl, tri(C6-C10 aryl or C1-C6 heteroaryl)silyl, di(C6-C10 aryl or C1-C6 heteroaryl)(C1-C6 alkyl)silyl, or (C6-C10 aryl or C1-C6 heteroaryl)di(C1-C6 alkyl)silyl.

17. The compound of claim 12, wherein Y_3 and Y_4 are each independently tri(C1-C6 alkyl)silyl, tri(C6-C10 aryl or C1-C6 heteroaryl)silyl, di(C6-C10 aryl or C1-C6 heteroaryl)(C1-C6 alkyl)silyl, or (C6-C10 aryl or C1-C6 heteroaryl)di(C1-C6 alkyl)silyl, or Y_3 and Y_4 are together di(C1-C6)alkylsilylene.

18. The compound of claim 12, wherein Y_5 is acetyl, benzoyl, p-bromobenzoyl, p-methoxybenzoyl, 1-naphthoyl, 2-naphthoyl, or o-phthaloyl.

19. The compound of claim 12, wherein Y_5 is H or a hydroxyl protecting group.

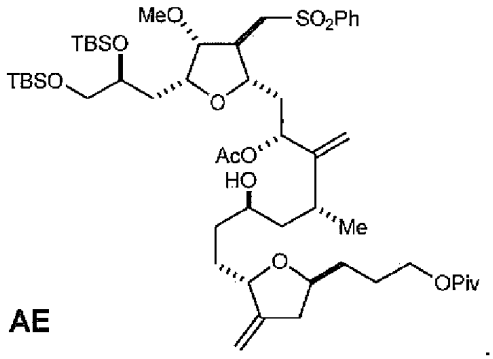
20. The compound of claim 12, wherein Y_6 is H.

21. The compound of claim 12, wherein $-OY_6$ is a leaving group.

22. The compound of claim 21, wherein $-OY_6$ is (C1-C6)alkylsulfonate, (C6-C10 aryl or C1-C6 heteroaryl)sulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate.

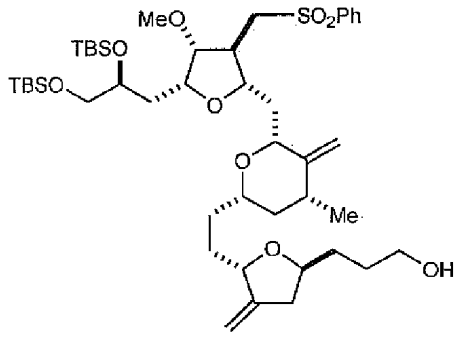
23. The compound of claim 21, wherein $-OY_6$ is mesylate, toluenesulfonate, isopropylsulfonate, phenylsulfonate, or benzylsulfonate.

24. The compound of claim 12 having the formula:



AE

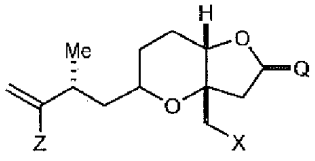
25. A method of synthesizing ER-804028:



(ER-804028),

said method comprising the steps of:

(i) reacting a compound having the formula (I):



(I),

wherein X is halogen or oxo;

Z is a leaving group;

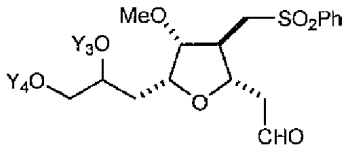
Q is $-C(O)H$, $-CH=CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

Y_1 and Y_2 are each independently H or a hydroxyl protecting group; and

n is 1 or 2,

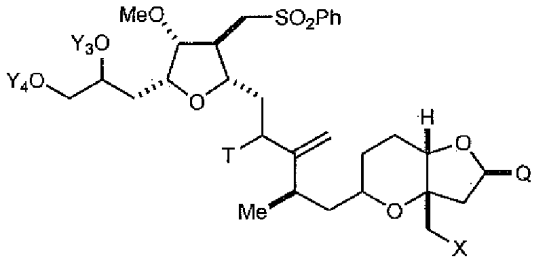
with a compound having the formula (IV):



(IV),

wherein Y_3, and Y_4 are each independently H or a hydroxyl protecting group,

under NHK coupling conditions to produce a compound having the formula:



(II),

wherein X is halogen or oxo;

Q is $-C(O)H$, $-CH=CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

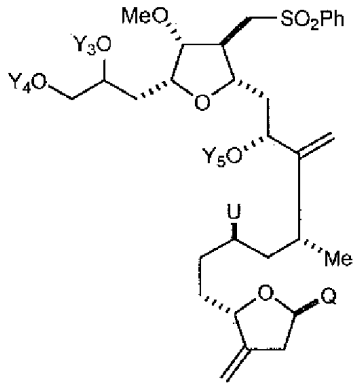
n is 1 or 2;

Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group;

T is oxo or $-OY_5$; and

Y_5 is H or a hydroxyl protecting group, or Y_5, together with the oxygen atom to which it is bound, is a leaving group,

(ii) reacting the product of step (i) under Vasella fragmentation conditions to produce a compound having the formula:



(III),

wherein Q is $-C(O)H$, $-CH=CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

n is 1 or 2;

Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group;

U is $-OY_6$;

Y_5 is H or a hydroxyl protecting group or Y_5, together with the oxygen atom to which it is bound, is a leaving group; and

Y_6 is H or a hydroxyl protecting group or Y_6, together with the oxygen atom to which it is bound, is a leaving group, provided that when Q is $-(CH_2)_3OY_1$, $-OY_6$ is a leaving group, Y_1, Y_3, and Y_4 are protecting groups, and Y_5 is not H; and

(iii) reacting the product of step (ii) under conditions for intramolecular Williamson etherification to produce ER-804028.

26. The method of claim 25, wherein, in formula (IV), the hydroxyl protecting groups of Y_3 and Y_4 are each independently, together with the oxygen atom to which it is bound, ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group; Y_3 and Y_4, together with the oxygen atoms to which they are bound, are cyclic carbonate, cyclic boronate, or cyclic silylene hydroxyl protecting group; or Y_3 and Y_4 together are acetal, ketal, or 1,1,3,3-tetraisopropylsiloxanediyl.

27. The method of claim 25, wherein, in formula (II), the hydroxyl protecting groups of Y_1, Y_2, Y_3, Y_4, and Y_5 are each, independently and together with the oxygen atom to which it is bound, an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group, or

Y_3 and Y_4, together with the oxygen atoms to which they are bound, are a cyclic carbonate, cyclic boronate, or cyclic silylene hydroxyl protecting group, or Y_3 and Y_4 together are acetal, ketal, or 1,1,3,3-tetraisopropylsiloxanediyl; and

the leaving group of Y_5, together with the oxygen atom to which it is bound, is (C1-C12)alkoxy, (C1-C12)alkylsulfonate, (C2-C12)alkenylsulfonate, carbocyclic(C6-C20)arylsulfonate, (C4-C19)heteroarylsulfonate, monocyclic(C1-C6)heteroarylsulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, (C4-C19)heteroaryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate.

28. The method of claim 25, wherein, in formula (III), the hydroxyl protecting groups of Y_1, Y_2, Y_3, Y_4, Y_5, and Y_6 are each, independently and together with the oxygen atom to which it is bound, an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group, or

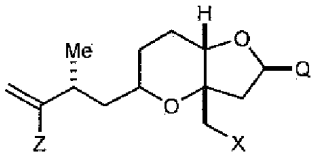
Y_3 and Y_4, together with the oxygen atoms to which they are bound, are a cyclic carbonate, cyclic boronate, or cyclic silylene hydroxyl protecting group, or Y_3 and Y_4 together are acetal, ketal, or 1,1,3,3-tetraisopropylsiloxanediyl; and

the leaving groups of Y_5 and Y_6 are each independently, together with the oxygen atom to which it is bound, (C1-C12)alkoxy, (C1-C12)alkylsulfonate, (C2-C12)alkenylsulfonate, carbocyclic(C6-

C20)arylsulfonate, (C4-C19)heteroarylsulfonate, monocyclic(C1-C6)heteroarylsulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, (C4-C19)heteroaryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate.

29. A method for producing eribulin or a pharmaceutically acceptable salt thereof, said method comprising the steps of:

(i) reacting a compound having the formula (I):



(I),

wherein X is halogen or oxo;

Z is a leaving group;

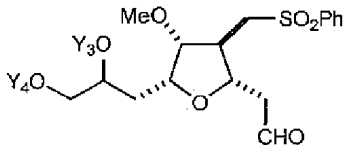
Q is $-C(O)H$, $-CH=CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

Y_1 and Y_2 are each independently H or a hydroxyl protecting group; and

n is 1 or 2,

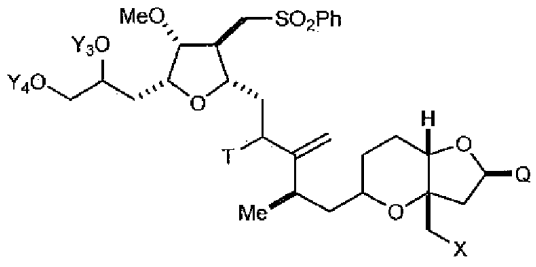
with a compound having the formula (IV):



(IV),

wherein Y_3, and Y_4 are each independently H or a hydroxyl protecting group,

under NHK coupling conditions to produce a compound having the formula:



(II),

wherein X is halogen or oxo;

Q is $-C(O)H$, $-CH=CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

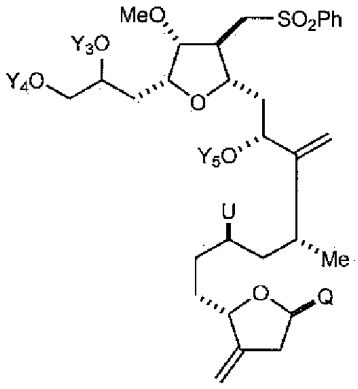
n is 1 or 2;

Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group;

T is oxo or $-OY_5$; and

Y_5 is H or a hydroxyl protecting group, or Y_5, together with the oxygen atom to which it is bound, is a leaving group,

(ii) reacting the product of step (i) under Vasella fragmentation conditions to produce a compound having the formula:



(III),

wherein Q is $-C(O)H$, $-CH=CHC(O)OY_1$, $-C(R)H(CH_2)_nOY_1$, or $-C(R)HCH_2C(O)OY_1$;

R is H or $-OY_2$;

n is 1 or 2;

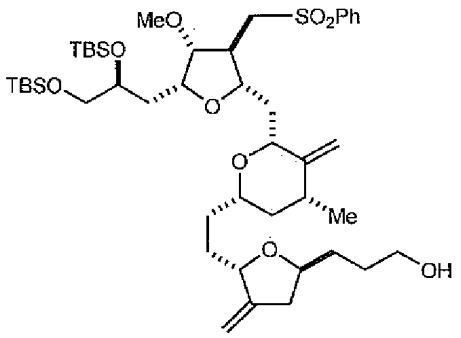
Y_1, Y_2, Y_3, and Y_4 are each independently H or a hydroxyl protecting group;

U is $-OY_6$;

Y_5 is H or a hydroxyl protecting group or Y_5, together with the oxygen atom to which it is bound, is a leaving group; and

Y_6 is H or a hydroxyl protecting group or Y_6, together with the oxygen atom to which it is bound, is a leaving group, provided that when Q is $-(CH_2)_3OY_1$, $-OY_6$ is a leaving group, and Y_1, Y_3, and Y_4 are protecting groups, Y_5 is not H; and

(iii) reacting the product of step (ii) under conditions for intramolecular Williamson etherification to produce ER-804028:



(ER-804028); and

(iv) converting ER-804028 into eribulin or a pharmaceutically acceptable salt thereof.

30. The method of claim 29, wherein, in formula (IV), the hydroxyl protecting groups of Y_3 and Y_4 are each independently, together with the oxygen atom to which it is bound, ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group; Y_3 and Y_4, together with the oxygen atoms to which they are

bound, are cyclic carbonate, cyclic boronate, or cyclic silylene hydroxyl protecting group; or Y_3 and Y_4 together are acetal, ketal, or 1,1,3,3-tetraisopropylsiloxanediyl.

31. The method of claim 29, wherein, in formula (II), the hydroxyl protecting groups of Y_1, Y_2, Y_3, Y_4, and Y_5 are each, independently and together with the oxygen atom to which it is bound, an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group, or

Y_3 and Y_4, together with the oxygen atoms to which they are bound, are a cyclic carbonate, cyclic boronate, or cyclic silylene hydroxyl protecting group, or Y_3 and Y_4 together are acetal, ketal, or 1,1,3,3-tetraisopropylsiloxanediyl; and

the leaving group of Y_5, together with the oxygen atom to which it is bound, is (C1-C12)alkoxy, (C1-C12)alkylsulfonate, (C2-C12)alkenylsulfonate, carbocyclic(C6-C20)arylsulfonate, (C4-C19)heteroarylsulfonate, monocyclic(C1-C6)heteroarylsulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, (C4-C19)heteroaryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate.

32. The method of claim 29, wherein, in formula (III), the hydroxyl protecting groups of Y_1, Y_2, Y_3, Y_4, Y_5, and Y_6 are each, independently and together with the oxygen atom to which it is bound, an ester, carbonate, carbamate, sulfonate, or ether hydroxyl protecting group, or

Y_3 and Y_4, together with the oxygen atoms to which they are bound, are a cyclic carbonate, cyclic boronate, or cyclic silylene hydroxyl protecting group, or Y_3 and Y_4 together are acetal, ketal, or 1,1,3,3-tetraisopropylsiloxanediyl; and

the leaving groups of Y_5 and Y_6 are each independently, together with the oxygen atom to which it is bound, (C1-C12)alkoxy, (C1-C12)alkylsulfonate, (C2-C12)alkenylsulfonate, carbocyclic(C6-C20)arylsulfonate, (C4-C19)heteroarylsulfonate, monocyclic(C1-C6)heteroarylsulfonate, (C6-C15)aryl(C1-C6)alkylsulfonate, (C4-C19)heteroaryl(C1-C6)alkylsulfonate, or (C1-C6)heteroaryl(C1-C6)alkylsulfonate.