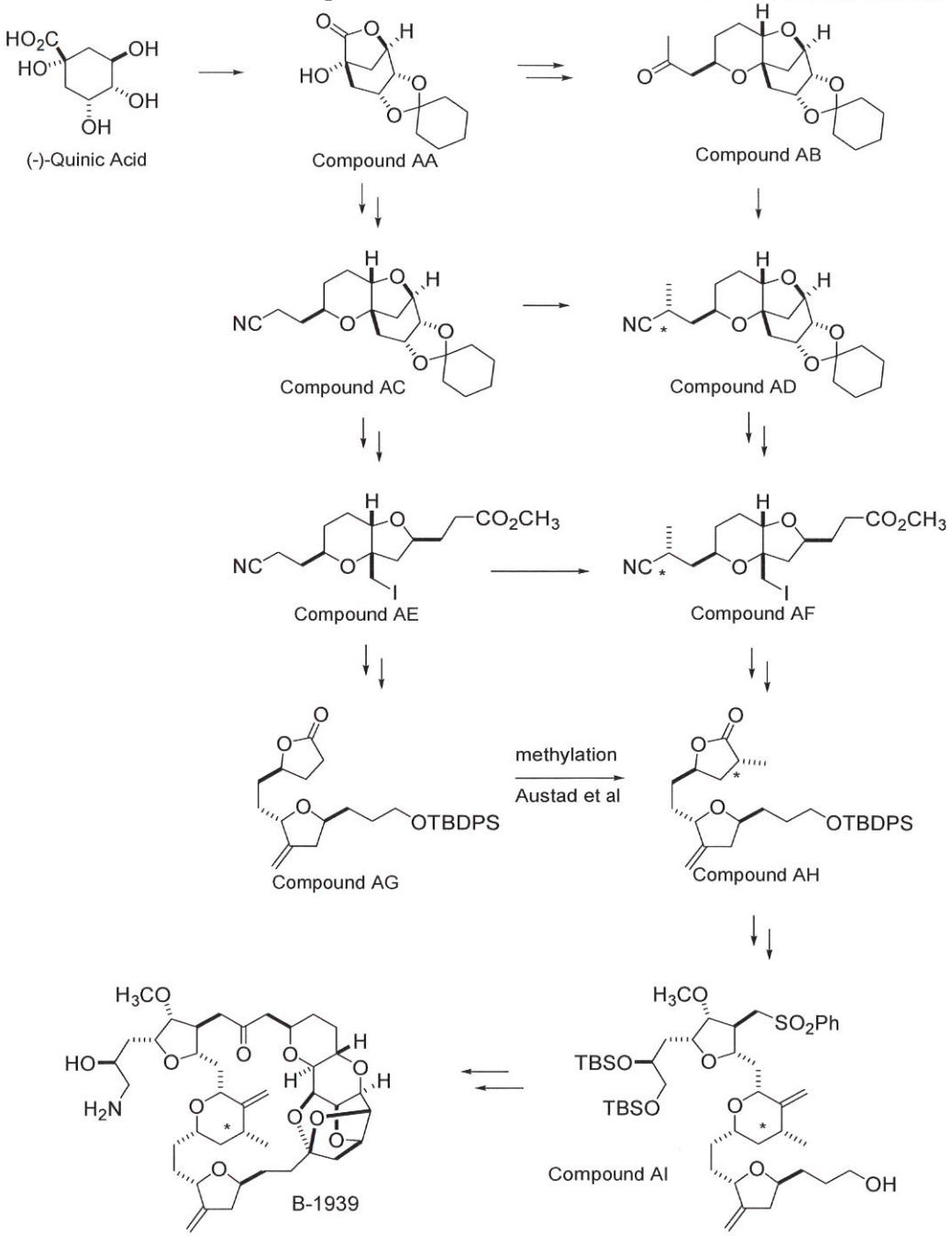
Summary

The current disclosure relates to a method for the synthesis of Halichondrin B analogs, such as B-1939, from (-)-quinic acid according to the process illustrated in Scheme 1, below. The method introduces a number of new and crystalline intermediates which greatly improve the stereochemical quality of the compounds synthesized and reduces the need for chromatographic steps. Unlike the previously described methods, the presently claimed method is substantially more appropriate for pharmaceutical manufacturing.

The disclosure also pertains to the novel intermediates disclosed herein.



Scheme 1

WO 2005/118565 disclosed a method for making Halichondrin B analogs, such as B-1939, that included synthetic routes for (1) producing the compound of formula Ia from (-)-quinic acid, and for (2) producing the B-1939 from Compound AG. Both synthetic routes are suitable for use in the method of the present invention, and are incorporated by reference herein.

The method of the present disclosure differs from the method disclosed in WO 2005/118565 in the process of synthesizing Compound AH from Compound AA. In particular, the present disclosure discloses highly efficient methods for generating the C25 chiral center, marked with an asterisk(*) in the relevant compounds in Scheme 1, by a process of equilibrating and selectively crystallizing the desired C25 isomer *via* an alpha-methylated nitrile. In the method described in WO 2005/118565, Compound AH is synthesized by adding a methyl group to Compound AG, as shown above. This reaction generates the C25 chiral center.. The product of that reaction is a mixture of diastereomers with each possible configuration around that chiral center. Chromatography can be used to partially isolate Compound AH from the mixture of diastereomers, as disclosed in WO2005/118565; however, the remaining diastereomers of Compound AH result in undesired impurities in subsequent reaction steps, impurities which can only be removed through additional purification procedures.

Unlike the methods of syntheses of halichondrin B analogs previously described, the method of the present disclosure involves the formation of the C25 chiral center at an earlier stage in the synthesis of Compound AH. Several of the methylated intermediates, including Compound AD and Compound AF are crystallizable. By crystallizing one or more of the methylated intermediates in accordance with the methods of the present disclosure, one can produce a composition of comprising Compound AH that is substantially diastereomerically pure. For example, Compound AC can be methylated to produce Compound AD. When Compound AD is produced, a the C25 chiral center is produced, the same chiral center discussed with respect to Compound AH. When this reaction occurs, a diastereomeric mixture is produced with each possible stereomeric configuration around that chiral center. Although the methylation itself occurs with low stereoselectivity, surprisingly, the desired diastereomer of Compound AD stereoselectively crystallizes. Moreover, the undesired C25 stereoisomer can be epimerized under conditions from which the desired C25 stereoisomer crystallizes. Thus, the yield and quality of the C25 stereoisomer can be enhanced by crystallization induced dynamic resolution (CIDR).

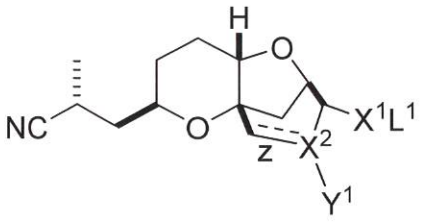
Several other intermediates produced in the synthetic route from Compound AD to Compound AH can also be crystallized from reaction mixtures, resulting in an even higher purity composition of Compound AH than could be produced by previously

disclosed methods. In particular, Compound AF is a crystalline compound, while the corresponding non-methylated Compound AE requires chromatography for purification. Compound AF may be synthesized from Compound AD or it can be synthesized by methylating Compound AE.

Removal of chromatography steps from the processes used to synthesize halichondrin B analogs dramatically increases the product yield and reproducibility, while decreasing cost and production time. The present method also enables one to resolve difficult to resolve chiral centers at a considerably earlier points in the process, even as early as the production of Compound AH and Compound AI. B-1939 is suitably synthesized from Compound AI using methods such as those described in WO/2005/118565.

In an aspect, there is provided a method of obtaining a substantially diastereomerically pure composition of a compound of formula (I), comprising:

crystallizing said compound of formula (I) from a mixture of diastereomers under appropriate crystallization conditions, wherein said compound of formula (I) is:



(I)

wherein:

z is a single or double bond, provided that when z is a double bond, X^2 is C and Y^1 is hydrogen; and provided that when z is a single bond, X^2 is CH or O;

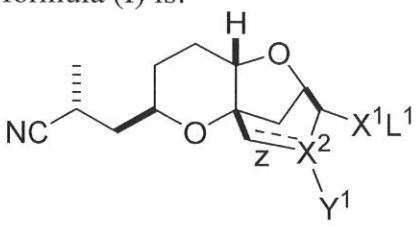
X^1 is O, S, or CN, provided that when X^1 is CN or S, X^2 is O;

Y^1 is a halide, hydrogen or O-L^2, or absent when X^2 is O;

L^1 and L^2 are independently selected from hydrogen and a protecting group, or L^1 and L^2 together are a protecting group, provided that when X^1 is CN, L^1 is absent; or a salt thereof,

wherein the protecting group of L^1 and L^2 is silyl, C_1-C_{12} alkylcarbonyl, C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, carbonate, C_1-C_6 alkoxy-(C_1-C_6) alkyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, benzoyl, or C_1-C_6 ester, or L^1 and L^2 together are a protecting group selected from benzylidene, cyclic C_1-C_6 acetal, cyclic C_3-C_6 ketal, cyclic carbonate, and a C_4-C_7 alkyl ring with one member of the ring covalently linked to both the O of Y^1 and to X^1; or when X^1 and X^2 are O, L^1 and L^2 together are cyclic C_3-C_7 ketal.

In one embodiment, the disclosure pertains, at least in part, to a method of obtaining a substantially diastereomerically pure composition comprising a compound of formula (I). The method includes crystallizing the compound of formula (I) from a mixture of diastereomers under appropriate crystallization conditions, such that a substantially diastereomerically pure composition comprising a compound of formula (I) is formed. The compound of formula (I) is:



(I)

wherein:

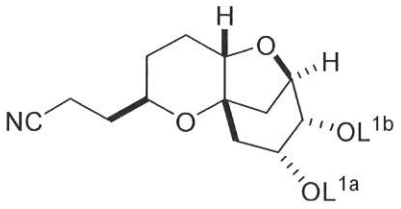
z is a single or double bond, provided that when z is a double bond, X^2 is C and Y^1 is hydrogen; and provided that when z is single bond, X^2 is CH or O;

X^1 is O, S, or CN, provided that when X^1 is CN or S, X^2 is O;

Y^1 is a halide, hydrogen or O-L^2, or absent when X^2 is O; and

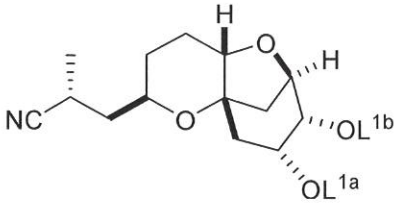
L^1 and L^2 are independently selected from hydrogen and a protecting group, or L^1 and L^2 together are a protecting group, provided that when X^1 is CN, L^1 is absent; and salts thereof. The disclosure also pertains to compositions of compounds of formula (I) that are substantially free of diastereomers, as well as compounds of formula (I).

In another embodiment, the disclosure also pertains to a method of making a diastereomerically pure composition of a compound of formula (Ib) from a compound of formula (Ia), wherein the compound of formula (Ia) is:



(Ia)

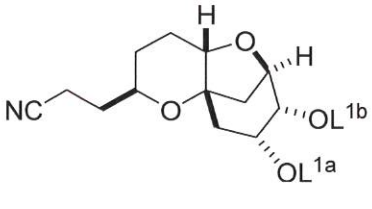
and the compound of formula (Ib) is:



(Ib)

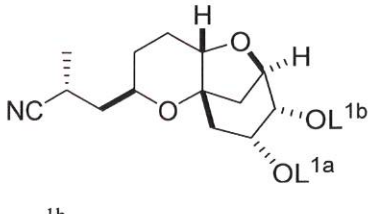
wherein L^{1a} and L^{1b} are independently selected from hydrogen and a protecting group, or L^{1a} and L^{1b} together are a divalent protecting group, provided that L^{1a} of formulae (Ia) and (Ib) are the same and L^{1b} of formulae (Ia) and (Ib) are the same. When L^{1a} or L^{1b} is a protecting group, it is preferably selected from the group consisting of C_1-C_6 alkyl ethers, aryl (C_1-C_6) alkyl ethers, silyl (C_1-C_{10}) ethers, C_1-C_6 alkyl esters, cyclic C_1-C_6 acetals, cyclic C_2-C_7 ketals, and cyclic carbonates. The method includes reacting the compound of formula (Ia) under alkylating conditions to form a mixture comprising the compound of formula (Ib) and diastereomers thereof; and crystallizing the compound of formula (Ib) from the mixture, under appropriate crystallization conditions.

In another aspect, there is provided a method of making a substantially diastereomerically pure composition of a compound of formula (Ib) from a compound of formula (Ia), wherein the compound of formula (Ia) is:



(Ia)

and the compound of formula (Ib) is:



(Ib)

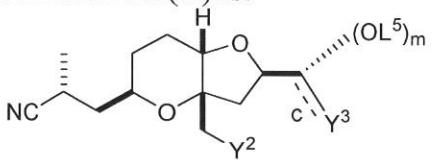
wherein L^{1a} and L^{1b} are independently selected from hydrogen and a protecting group selected from C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, silyl (C_1-C_{10}), and C_1-C_6 alkyl ester,

or L^{1a} and L^{1b} together are a divalent protecting group selected from cyclic C_1-C_6 acetal, cyclic C_3-C_7 ketal, and cyclic carbonate, provided that L^{1a} of formulae (Ia) and (Ib) are the same and L^{1b} of formulae (Ia) and (Ib) are the same, said method comprising:

reacting the compound of formula (Ia) under alkylating conditions to form a mixture comprising the compound of formula (Ib) and diastereomers thereof; and

crystallizing the compound of formula (Ib) from the mixture, under appropriate crystallization conditions.

In another embodiment, the disclosure pertains, at least in part, to a method of obtaining a substantially diastereomerically pure composition comprising a compound of formula (II). The method includes crystallizing the compound of formula (II) from a mixture of diastereomers under second appropriate crystallization conditions, such that a substantially diastereomerically pure composition comprising a compound of formula (II) is formed. The compound of formula (II) is:



(II)

wherein:

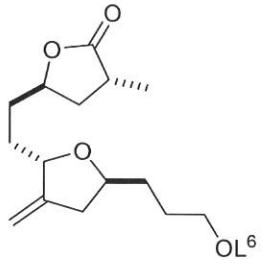
c is a single or double bond, provided that when c is a double bond m is 0 and Y^3 is O or $CHCO_2$-L^3, and provided that when c is a single bond m is 0 or 1 and Y^3 is CH_2O-L^3, CH_2CO_2-L^3 or CH_2CH_2O-L^3;

Y^2 is C_1-C_7 sulfonate, O-L^4 or a halide;

L^4 is hydrogen or a protecting group; and

L^3 and L^5 are each independently hydrogen or a protecting group, or L^3 and L^5 together are a protecting group, or a salt thereof. The disclosure also pertains to compositions of compounds of formula (II) that are substantially free of diastereomers, as well as compounds of formula (II).

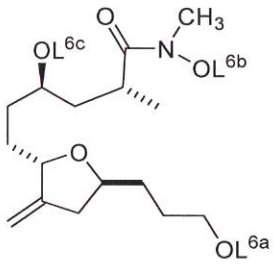
In yet another embodiment, the disclosure also pertains to compounds of formula (III):



(III)

wherein: L^6 is hydrogen or a protecting group; and salts thereof.

In yet another embodiment, the disclosure also pertains to a composition comprising a compound of formula (IIIa):

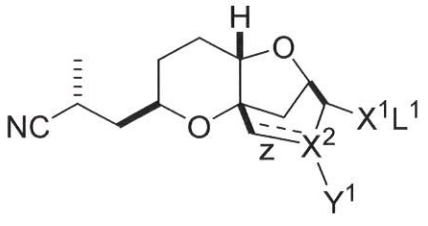


(IIIa)

L^{6a}, L^{6b}, and L^{6c} are each protecting groups, or a salt thereof, and wherein the composition is substantially free of diastereomers.

Furthermore, the disclosure also pertains to a composition comprising a compound selected from the group consisting of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (II), (IIa), (IIb), (III) and (IIIa). The disclosure also pertains to each of the compounds described in herein.

In another aspect, there is provided a compound of formula (I):



(I)

wherein:

z is a single or double bond, provided that when z is a double bond, X^2 is C and Y^1 is hydrogen; and provided that when z is single bond, X^2 is CH or O;

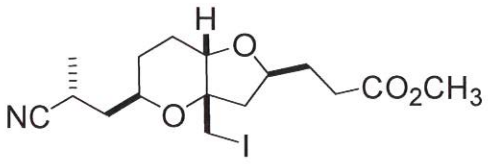
X^1 is O, S, or CN, provided that when X^1 is CN or S, X^2 is O;

Y^1 is a halide, hydrogen or O-L^2, or absent when X^2 is O; and

L^1 and L^2 are independently selected from hydrogen and a protecting group, or L^1 and L^2 together are a protecting group, provided that when X^1 is CN, L^1 is absent; or a salt thereof,

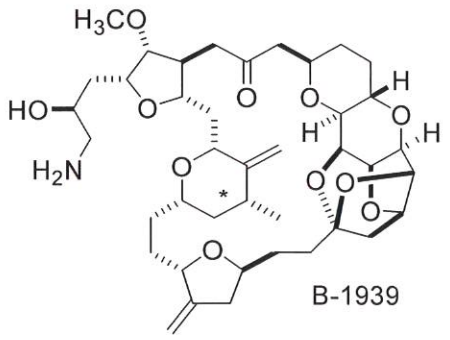
wherein the protecting group of L^1 and L^2 is silyl, C_1-C_{12} alkylcarbonyl, C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, carbonate, C_1-C_6 alkoxy-(C_1-C_6) alkyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, benzoyl, or C_1-C_6 ester, or L^1 and L^2 together are a protecting group selected from benzylidene, cyclic C_1-C_6 acetal, cyclic C_3-C_6 ketal, cyclic carbonate, and a C_4-C_7 alkyl ring with one member of the ring covalently linked to both the O of Y^1 and to X^1; or when X^1 and X^2 are O, L^1 and L^2 together are cyclic C_3-C_7 ketal.

In another aspect, there is provided a compound, wherein said compound is:



Compound AF.

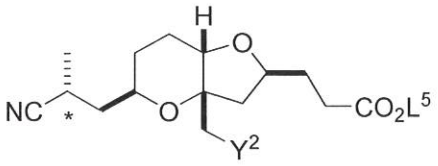
In another aspect, there is provided a method for producing compound B-1939



B-1939

which method comprises:

(i) reducing a compound of formula 8-20:



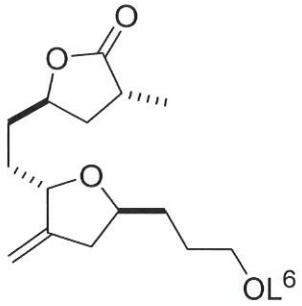
8-20

wherein:

Y^2 is a halide; and

L^5 is C_1-C_{10} alkyl, C_4-C_{10} aryl-C_1-C_6 alkyl, or C_4-C_{10} aryl

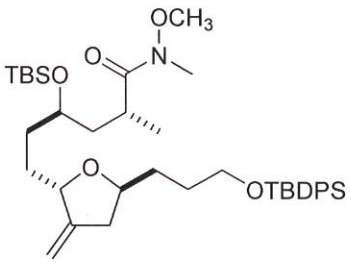
and converting the product to a compound of formula (III):



(III)

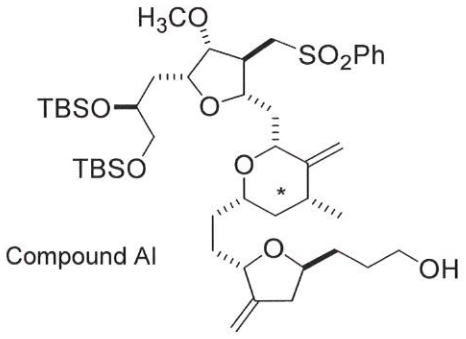
wherein: L^6 is hydrogen or silyl C_1-C_{10}; or a salt thereof;

(ii) converting the compound of formula (III) or salt thereof to produce compound AV



Compound AV

and converting compound AV into compound AI

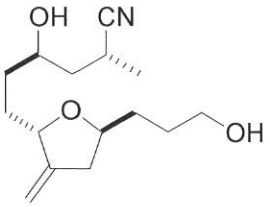


Compound AI

; and

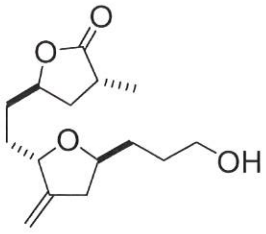
(iii) converting compound AI into compound B-1939.

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



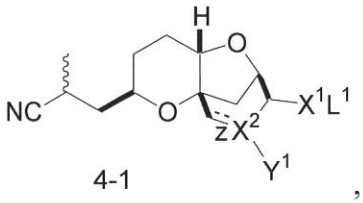
Compound AU.

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



Compound AR.

In another aspect, there is provided a composition comprising a compound having the formula:



4-1 ,

wherein:

z is a single or double bond, provided that when z is a double bond, X^2 is C and Y^1 is hydrogen; and provided that when z is a single bond, X^2 is CH or O;

X^1 is O, S, or CN, provided that when X^1 is CN or S, X^2 is O;

Y^1 is a halide, hydrogen or O-L^2, or absent when X^2 is O;

L^1 and L^2 are independently selected from hydrogen and a protecting group, or L^1 and L^2 together are a protecting group, provided that when X^1 is CN, L^1 is absent; or a salt thereof,

wherein the protecting group of L^1 and L^2 is silyl, C_1-C_{12} alkylcarbonyl, C_1-C_6 alkyl, aryl (C_1-C_6) alkyl, carbonate, C_1-C_6 alkoxy-(C_1-C_6) alkyl, 3,4-dimethoxybenzyl, p-methoxybenzyl, benzoyl, or C_1-C_6 ester, or L^1 and L^2 together are a protecting group selected from benzylidene, cyclic C_1-C_6 acetal, cyclic C_3-C_6 ketal, cyclic carbonate, and a C_4-C_7 alkyl ring with one member of the ring covalently linked to both the O of Y^1 and to X^1; or when X^1 and X^2 are O, L^1 and L^2 together are cyclic C_3-C_7 ketal.

Detailed Description

The current invention pertains, at least in part, to methods and intermediates for the preparation and crystallization of intermediates and other compounds useful in the synthesis of halichondrin B and its analogs.

A. Definitions

In order that the present invention may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.