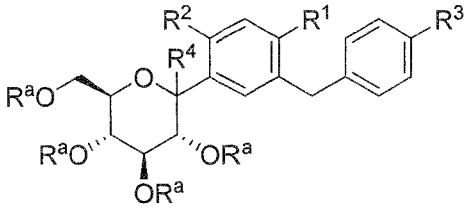
[0004] The compounds prepared according to the present invention have been prepared previously according to the methods described in WO2001/027128, US2004/0230045, US2005/0124555, US2006/0122126, US2007/0238866, US2007/0275907, US2008/0242596, US2008/0132563, US2008/0318874, WO2008/034859, US2009/0030006, US2009/0030198, US2009/0118201, US2009/0156516, US2010/0056618, US2010/0063141 and WO2010/147430. The aim of the present invention is to provide improved methods for the preparation of such compounds.

SUMMARY

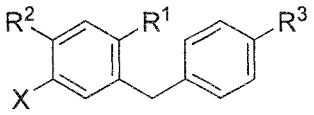
[0004a] In one aspect of the present disclosure, there is provided a method of preparing a compound of Formula Ia:



Ia

the method comprising:

(a) forming a first reaction mixture comprising a compound of formula IIa:



IIa,

an alkyl-magnesium complex selected from the group consisting of

C_1-C_4 alkylmagnesium chloride, C_1-C_4 alkylmagnesium bromide,

di(C_1-C_4 alkyl)magnesium, C_3-C_7 cycloalkylmagnesium chloride,

C_3-C_7 cycloalkylmagnesium bromide, and

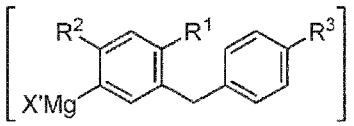
di(C_3-C_7 cycloalkyl)magnesium, and

a first organic solvent,

wherein the ratio of the alkyl-magnesium complex to the compound of Formula IIa is from 0.9 to 0.97 (mol/mol),

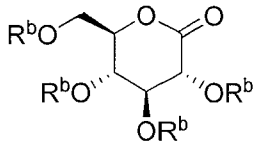
wherein the first reaction mixture is at a temperature of less than or equal to -50 °C,

to afford an intermediate compound having the formula



wherein X' is selected from the group consisting of C_1-C_4 alkyl, C_3-C_7 cycloalkyl and halo; and

(b) forming a second reaction mixture comprising the intermediate, a second organic solvent, and a compound of Formula IIIa:



IIIa

to afford the compound of Formula Ia, wherein R^4 is OH and each R^a is R^b;

(c) forming a third reaction mixture comprising a C_1-C_3 alkylhydroxy, a strong acid and the compound of Formula Ia, wherein R^4 is OH and each R^a is R^b, thereby forming the compound of Formula Ia wherein R^4 is C_1-C_3 alkoxy, and each R^a is independently selected from the group consisting of H and R^b; and

(d) forming a fourth reaction mixture comprising a reducing agent and a compound of Formula Ia, wherein R^4 is C_1-C_3 alkoxy, and wherein the reaction mixture contains below 0.1 equivalents of magnesium compared to the amount of the compound of Formula Ia, thereby preparing the compound of Formula Ia, where R^4 is H,

wherein

X is iodo,

R^1 is chloro,

R^2 is H,

R^3 is (C_3-C_6 cycloalkoxy)C_1-C_3 alkoxy,

R^4 is selected from the group consisting of H, OH, and C_{1-3}alkoxy,

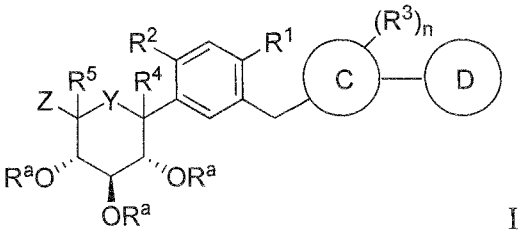
each R^a is independently selected from the group consisting of H, C_1-C_3 alkyl and R^b,

R^b is a protecting group,

wherein the alkyl, alkoxy, and cycloalkyl groups or portions thereof may optionally be partially or completely fluorinated, and

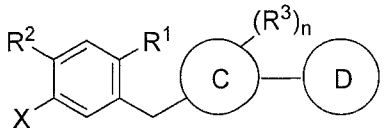
one or more hydrogen atoms optionally may be replaced with deuterium.

[0005] In one embodiment, the present disclosure provides a method of preparing a compound of formula I:



I .

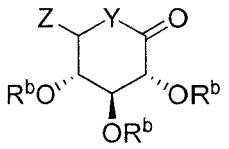
[0006] The method of preparing the compound of formula I includes forming a first reaction mixture of a compound of formula II:



II

The first reaction mixture also includes an alkyl-magnesium complex such as C_1-C_4 alkylmagnesium chloride, C_1-C_4 alkylmagnesium bromide, di(C_1-C_4 alkyl)magnesium, C_3-C_7 cycloalkylmagnesium chloride, C_3-C_7 cycloalkylmagnesium bromide, or di(C_3-C_7 cycloalkyl)magnesium, and a first organic solvent, wherein the ratio of the alkyl-magnesium complex to the compound of Formula II is less than or equal to 1.0 (mol/mol), and wherein the first reaction mixture is at a temperature of less than about -50 °C, to afford an intermediate compound.

[0007] The method also includes forming a second reaction mixture of the intermediate compound, a second organic solvent, and a compound of formula III:

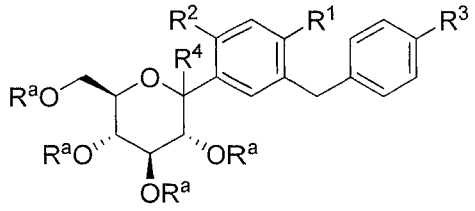


III .

CLAIMS

WHAT IS CLAIMED IS:

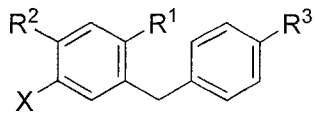
1. A method of preparing a compound of Formula Ia:



Ia

the method comprising:

(a) forming a first reaction mixture comprising a compound of formula IIa:



IIa,

an alkyl-magnesium complex selected from the group consisting of

C_1-C_4 alkylmagnesium chloride, C_1-C_4 alkylmagnesium bromide,

di(C_1-C_4 alkyl)magnesium, C_3-C_7 cycloalkylmagnesium chloride,

C_3-C_7 cycloalkylmagnesium bromide, and

di(C_3-C_7 cycloalkyl)magnesium, and

a first organic solvent,

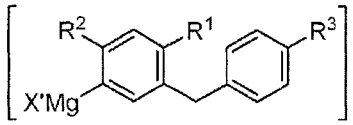
wherein the ratio of the alkyl-magnesium complex to the compound of

Formula IIa is from 0.9 to 0.97 (mol/mol),

wherein the first reaction mixture is at a temperature of less than or equal to

-50 °C,

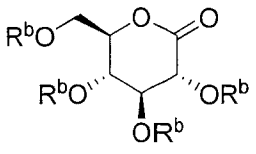
to afford an intermediate compound having the formula



wherein X' is selected from the group consisting of C_1-C_4 alkyl, C_3-C_7

cycloalkyl and halo; and

(b) forming a second reaction mixture comprising the intermediate, a second organic solvent, and a compound of Formula IIIa:



IIIa

to afford the compound of Formula Ia, wherein R^4 is OH and each R^a is R^b;

(c) forming a third reaction mixture comprising a C_1-C_3 alkylhydroxy, a strong acid and the compound of Formula Ia, wherein R^4 is OH and each R^a is R^b, thereby forming the compound of Formula Ia wherein R^4 is C_1-C_3 alkoxy, and each R^a is independently selected from the group consisting of H and R^b; and

(d) forming a fourth reaction mixture comprising a reducing agent and a compound of Formula Ia, wherein R^4 is C_1-C_3 alkoxy, and wherein the reaction mixture contains below 0.1 equivalents of magnesium compared to the amount of the compound of Formula Ia, thereby preparing the compound of Formula Ia, where R^4 is H,

wherein

X is iodo,

R^1 is chloro,

R^2 is H,

R^3 is (C_3-C_6 cycloalkoxy)C_1-C_3 alkoxy,

R^4 is selected from the group consisting of H, OH, and C_{1-3}alkoxy,

each R^a is independently selected from the group consisting of H, C_1-C_3 alkyl and R^b,

R^b is a protecting group,

wherein the alkyl, alkoxy, and cycloalkyl groups or portions thereof may optionally be partially or completely fluorinated, and

one or more hydrogen atoms optionally may be replaced with deuterium.

2. The method of claim 1, wherein R^3 is 2-cyclopropoxyethoxy.

3. The method of any one of claims 1-2, wherein the ratio of the alkyl-magnesium complex in step (a) to the compound of Formula IIa is from 0.94 to 0.97 (mol/mol).

4. The method of any one of claims 1-3, wherein the first reaction mixture further comprises an accelerating agent selected from the group consisting of LiCl, $ZnCl_2$, diisobutylaluminum hydride, sodium bis(2-methoxyethoxy)aluminum hydride, tri-methylsilyl chloride, and 2,2'-oxybis(N,N-dimethylethanamine).

5. The method of claim 4, wherein the first reaction mixture further comprises LiCl.

6. The method of any one of claims 4-5, wherein the ratio of the accelerating agent to the alkyl-magnesium complex is 1.0 (mol/mol).

7. The method of any one of claims 1-6, wherein the first reaction mixture is at a temperature of from -60 to -50 °C.

8. The method of any one of claims 1-7, wherein the second reaction mixture further comprises additional alkyl-magnesium complex.

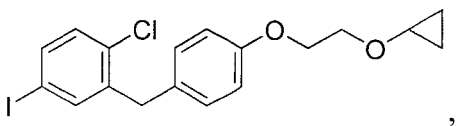
9. The method of claim 8, wherein the ratio of additional alkyl magnesium complex in the second reaction mixture to the compound of Formula IIa is from 0.01 to 0.1 (mol/mol).

10. The method of any one of claims 1-9, wherein the second reaction mixture is at a temperature of from -60 to 25 °C.

11. The method of any one of claims 1-10, wherein the second reaction mixture is at a temperature of from -60 to -10 °C.

12. The method of any one of claims 1-11, wherein steps (a)-(d) comprise

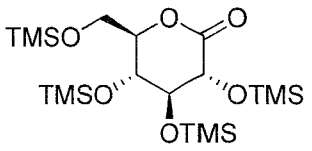
(a) forming the first reaction mixture comprising the compound of Formula IIa having the structure:



,

isopropylmagnesium chloride, lithium chloride, tetrahydrofuran and heptane, wherein the ratio of the isopropylmagnesium chloride to the compound of Formula IIa is from 0.94 to 0.97 (mol/mol), the ratio of the isopropylmagnesium chloride to the LiCl is 1.0 (mol/mol), wherein the first reaction mixture is at a temperature of less than or equal to -50 °C, to afford the intermediate; and

(b) forming the second reaction mixture comprising the intermediate, the second organic solvent, and the compound of Formula III having the structure:



,

to afford the compound of Formula Ia wherein

R^1 is chloro,

R^2 is H,

R^3 is 2-cyclopropoxyethoxy,

R^4 is OH, and

R^a is TMS;

(c) forming a third reaction mixture comprising a C_1-C_3 alkylhydroxy, a strong acid and the compound of Formula Ia, wherein R^4 is OH and each R^a is TMS, thereby forming the compound of Formula Ia wherein R^4 is C_1-C_3 alkoxy, and each R^a is H; and

(d) forming a fourth reaction mixture comprising a reducing agent and a compound of Formula Ia, wherein R^4 is C_1-C_3 alkoxy, and wherein the reaction mixture contains below 0.1 equivalents of magnesium compared to the amount of the compound of Formula Ia, thereby preparing the compound of Formula Ia, where R^4 is H.

13. The method of claim 12, wherein the second reaction mixture further comprises additional isopropylmagnesium chloride and lithium chloride, where the ratio of the additional isopropylmagnesium chloride to the compound of Formula IIa is from 0.01 to 0.1 (mol/mol), and the ratio of the additional isopropylmagnesium chloride to the additional LiCl is 1.0 (mol/mol).

14. The method of any one of claims 1-13, wherein the first and second reaction mixtures are formed in the same reaction vessel.

15. The method of any one of claims 1-11, wherein each R^b of the compound of Formula Ia is an acid-labile protecting group, thereby removing the acid-labile protecting groups and forming the compound of Formula Ia such that each R^a is H.

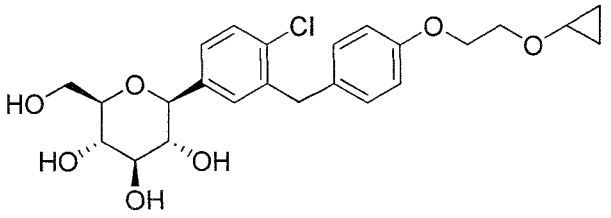
16. The method of any one of claims 1-15, wherein the third reaction mixture is at a temperature of from -10 to 25 °C.

17. The method of claim 16, wherein the third reaction mixture is at a temperature of 0 °C.

18. The method of any one of claims 1-17, wherein the fourth reaction mixture is at a temperature from -40 to -10 °C.

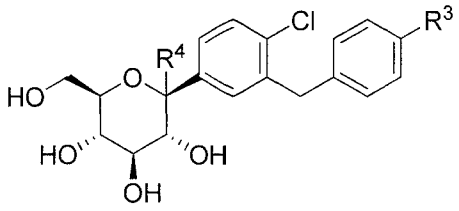
19. The method of claim 18, wherein the fourth reaction mixture is at a temperature from -25 to -22 °C.

20. The method of any one of claims 1-19, wherein the compound of Formula Ia has the structure:

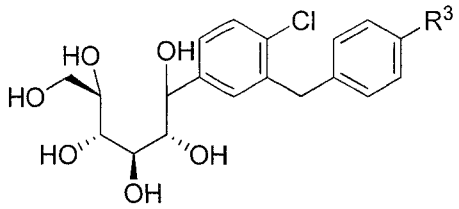


21. The method of claim 1, wherein performing steps (a)-(d) produces a product mixture comprising

at least 95% of the compound of formula Ia having the structure:

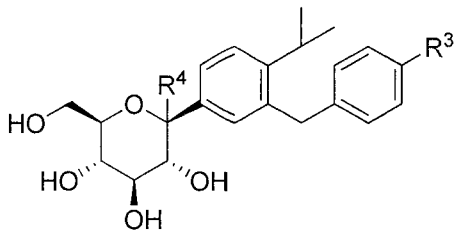


a side-product A having the structure:



in an amount of less than 1% of the product mixture, and

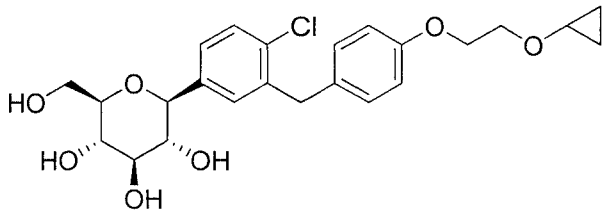
a side-product B having the structure:



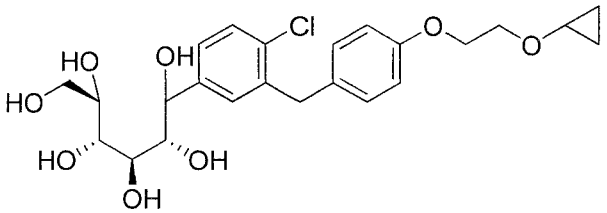
in an amount of less than 3% of the product mixture.

22. The method of claim 12, wherein performing steps (a)-(d) produces a product mixture comprising

at least 95% of the compound of formula Ia having the structure:

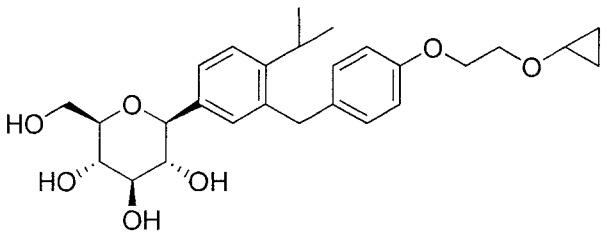


a side-product A having the structure:



in an amount of less than 1% of the product mixture, and

side-product B having the structure:



in an amount of less than 3% of the product mixture.