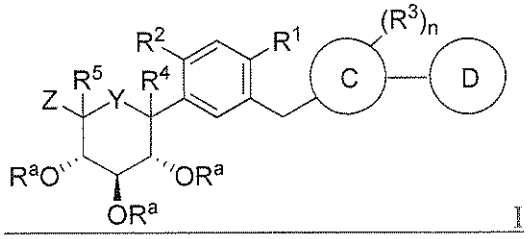
[0004] The compounds prepared according to the present invention have been prepared previously according to the methods described in WO2001/027128, US2004/0230045, US2005/0124555, US2006/0122126, US2007/0238866, US2007/0275907, US2008/0242596, US2008/0132563, US2008/0318874, WO2008/034859, US2009/0030006, 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.

~~BRIEF~~ SUMMARY ~~OF THE INVENTION~~

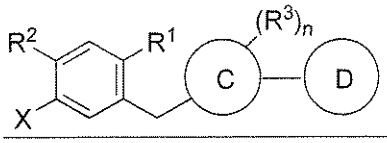
[0004a] In a first aspect of the present disclosure, there is provided a method of preparing a compound of Formula I:



I

the method comprising:

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



II ,

an alkyl-magnesium complex selected from the group consisting of

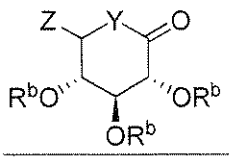
C_1-C_4 alkylmagnesium chloride, C_1-C_4 alkylmagnesium bromide, di(C_1-C_4 alkyl)magnesium, C_3-C_7 cycloalkylmagnesium chloride, C_3-C_7 cycloalkylmagnesium bromide, and di(C_3-C_7 cycloalkyl)magnesium, and

a first organic solvent,

wherein the ratio of the alkyl-magnesium complex to the compound of Formula 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; and

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



III

thereby preparing the compound of Formula I,

wherein

X is bromo or iodo,

Y is selected from the group consisting of CHR^c, C(=O), O and S,

Z is selected from the group consisting of CH_2OR^a, OR^a, SR^a and $S(O)_m$-R^a,

R^1 is chloro,

each R^2 and R^3 is independently selected from the group consisting of hydrogen, halo, hydroxy, C_1-C_3 alkyl, -CH_2OR^a, C_2-C_4 alkenyl, C_1-C_3 alkoxy, C_3-C_6 cycloalkyl, (C_1-C_3 alkoxy)C_1-C_3 alkyl, (C_1-C_3 haloalkoxy)C_1-C_3 alkyl, (C_2-C_4 alkenyloxy)C_1-C_3 alkyl, (C_2-C_4 alkynyloxy)C_1-C_3 alkyl, (C_3-C_6 cycloalkoxy)C_1-C_3 alkyl, C_1-C_3 hydroxyalkoxy, C_3-C_6 cycloalkoxy, C_3-C_6 heterocycloalkoxy, (C_1-C_3 alkoxy)C_1-C_3 alkoxy, (C_1-C_3 haloalkoxy)C_1-C_3 alkoxy, (C_2-C_4 alkenyloxy)C_1-C_3 alkoxy, (C_2-C_4 alkynyloxy)C_1-C_3 alkoxy, (C_3-C_6 cycloalkoxy)C_1-C_3 alkoxy, (C_3-C_6 heterocycloalkoxy)C_1-C_3 alkoxy, (C_3-C_6 cycloalkyl)C_1-C_3 alkoxy, (C_3-C_6 cycloalkyl)C_2-C_4 alkenyloxy and (C_3-C_6 cycloalkyl)C_2-C_4 alkynyloxy,

wherein at least one of R^2 and R^3 is selected from the group consisting of hydrogen, halo, hydroxy, C_1-C_3 alkyl, C_1-C_3 alkoxy, and C_3-C_6 cycloalkyl,

wherein at least one of R^2 and R^3 is selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxy, C_3-C_6 cycloalkyl, (C_1-C_3 alkoxy)C_1-C_3 alkyl, (C_1-C_3 haloalkoxy)C_1-C_3 alkyl, (C_2-C_4 alkenyloxy)C_1-C_3 alkyl, (C_2-C_4 alkynyloxy)C_1-C_3 alkyl, (C_3-C_6 cycloalkoxy)C_1-C_3 alkyl, C_1-C_3 hydroxyalkoxy, C_3-C_6 cycloalkoxy, C_3-C_6 heterocycloalkoxy, (C_1-C_3 alkoxy)C_1-C_3 alkoxy, (C_1-C_3 haloalkoxy)C_1-C_3 alkoxy, (C_2-C_4 alkenyloxy)C_1-C_3 alkoxy, (C_2-C_4 alkynyloxy)C_1-C_3 alkoxy, (C_3-C_6 cycloalkoxy)C_1-C_3 alkoxy, (C_3-C_6 heterocycloalkoxy)C_1-C_3 alkoxy, (C_3-C_6 cycloalkyl)C_1-C_3 alkoxy, (C_3-C_6 cycloalkyl)C_2-C_4 alkenyloxy and (C_3-C_6 cycloalkyl)C_2-C_4 alkynyloxy,

R^4 is selected from the group consisting of H and OR^{4a}, wherein R^{4a} is selected from the group consisting of H and C_1-C_3 alkyl,

alternatively, R^2 and R^4 are combined with the atoms to which each is attached to form a 5 to 6 membered cycloalkyl or heterocycloalkyl,

R^5 is selected from the group consisting of H and $-CH_2OR^a$,

alternatively, R^4 and R^5 are combined with the atoms to which each is attached to form a 5 to 6 membered heterocycloalkyl,

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,

R^c is selected from the group consisting of H, OH and C_1-C_3 alkoxy,

alternatively, R^c is combined with either R^4 or R^5 to form a bond,

ring C is an aryl or heteroaryl,

ring D is absent or a heteroaryl,

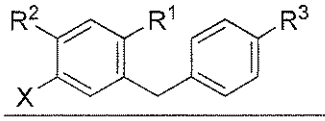
subscript m is an integer from 1 to 2,

subscript n is an integer from 1 to 4,

wherein the alkyl, alkoxy, cycloalkyl, alkenyloxy, alkynyloxy, cycloalkoxy, hydroxyalkoxy, and heterocycloalkoxy groups or portions thereof may optionally be partially or completely fluorinated, and

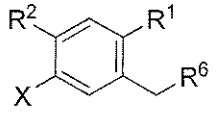
one or more hydrogen atoms optionally may be replaced with deuterium.

[0004b] In a second aspect of the present disclosure, there is provided a method of preparing a compound of Formula IIa:



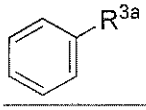
IIa

the method comprising forming a first reaction mixture comprising a compound of Formula IV:



IV

and a compound of Formula V:



V

under conditions suitable to prepare the compound of Formula IIa,

wherein

R^1 is selected from the group consisting of hydrogen, halo, hydroxy, C_1-C_3 alkyl and C_1-C_3 alkoxy,

R^2 and R^3 are each independently selected from the group consisting of hydrogen, halo, hydroxy, C_1-C_3 alkyl, C_1-C_3 alkoxy, C_3-C_6 cycloalkyl, (C_1-C_3 alkoxy)C_1-C_3 alkyl, (C_1-C_3 haloalkoxy)C_1-C_3 alkyl, (C_2-C_4 alkenyloxy)C_1-C_3 alkyl, (C_2-C_4 alkynyloxy)C_1-C_3 alkyl, (C_3-C_6 cycloalkoxy)C_1-C_3 alkyl, C_1-C_3 hydroxyalkoxy, C_3-C_6 cycloalkoxy, C_3-C_6 heterocycloalkoxy, (C_1-C_3 alkoxy)C_1-C_3 alkoxy, (C_1-C_3 haloalkoxy)C_1-C_3 alkoxy, (C_2-C_4 alkenyloxy)C_1-C_3 alkoxy, (C_2-C_4 alkynyloxy)C_1-C_3 alkoxy, (C_3-C_6 cycloalkoxy)C_1-C_3 alkoxy, (C_3-C_6 heterocycloalkoxy)C_1-C_3 alkoxy, (C_3-C_6 cycloalkyl)C_1-C_3 alkoxy, (C_3-C_6 cycloalkyl)C_2-C_4 alkenyloxy and (C_3-C_6 cycloalkyl)C_2-C_4 alkynyloxy,

R^{3a} is OH,

R^6 is selected from the group consisting of OH and Br,

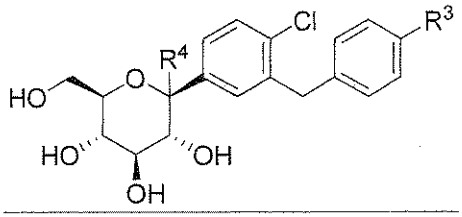
X is bromo or iodo,

wherein the alkyl, alkoxy, cycloalkyl, alkenyloxy, alkynyloxy, cycloalkoxy, hydroxyalkoxy, and heterocycloalkoxy groups or portions thereof may optionally be partially or completely fluorinated, and

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

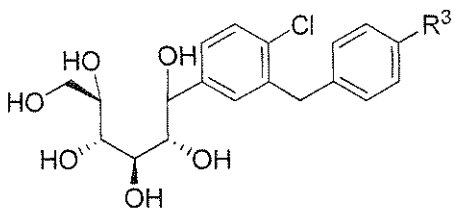
[0004c] In a third aspect of the present disclosure, there is provided a composition comprising

a compound of formula Ia having the structure:



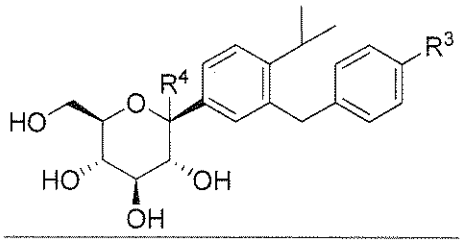
in an amount of at least 95% of the composition,

side-product A having the structure:



in an amount of less than about 1% of the composition, and

side-product B having the structure:



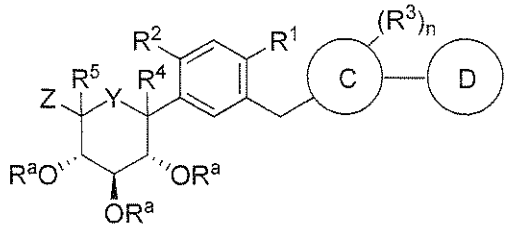
in an amount of less than about 3% of the composition,

wherein the composition is prepared by the method of the first aspect, and wherein

R^3 is selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 alkoxy, C_3-C_6 cycloalkyl, (C_1-C_3 alkoxy)C_1-C_3 alkyl, (C_1-C_3 haloalkoxy)C_1-C_3 alkyl, (C_2-C_4 alkenyloxy)C_1-C_3 alkyl, (C_2-C_4 alkynyloxy)C_1-C_3 alkyl, (C_3-C_6 cycloalkoxy)C_1-C_3 alkyl, C_1-C_3 hydroxyalkoxy, C_3-C_6 cycloalkoxy, C_3-C_6 heterocycloalkoxy, (C_1-C_3 alkoxy)C_1-C_3 alkoxy, (C_1-C_3 haloalkoxy)C_1-C_3 alkoxy, (C_2-C_4 alkenyloxy)C_1-C_3 alkoxy, (C_2-C_4 alkynyloxy)C_1-C_3 alkoxy, (C_3-C_6 cycloalkoxy)C_1-C_3 alkoxy, (C_3-C_6 heterocycloalkoxy)C_1-C_3 alkoxy, (C_3-C_6 cycloalkyl)C_1-C_3 alkoxy, (C_3-C_6 cycloalkyl)C_2-C_4 alkenyloxy and (C_3-C_6 cycloalkyl)C_2-C_4 alkynyloxy, and

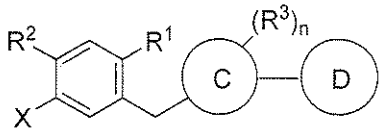
R^4 is selected from the group consisting of H and OR^{4a}, wherein R^{4a} is selected from the group consisting of H and C_1-C_3 alkyl.

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



I .

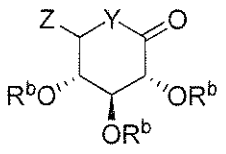
[0006] The method of preparing the compound of formula I includes forming a first reaction mixture of a compound of formula II:



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:



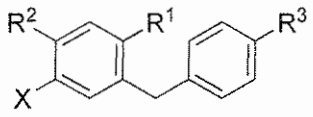
III .

[0015] Ring C of formula I can be an aryl or heteroaryl. Ring D of formula I can be absent or a heteroaryl.

[0016] Subscript m of formula I can be an integer from 1 to 2. Subscript n of formula I can be an integer from 1 to 4.

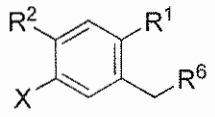
[0017] The alkyl, alkoxy, cycloalkyl, alkenyloxy, alkynyloxy, cycloalkoxy, hydroxyalkoxy, and heterocycloalkoxy groups or portions thereof can optionally be partially or completely fluorinated. And one or more hydrogen atoms of the compounds of formula I optionally can be replaced with deuterium.

[0018] In a second embodiment, the present ~~invention~~ disclosure provides a method of preparing a compound of formula IIa:



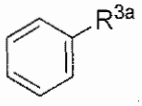
IIa .

[0019] The method of preparing the compound of formula IIa includes forming a first reaction mixture having a compound of Formula IV:



IV

The first reaction mixture also includes a compound of Formula V:



V

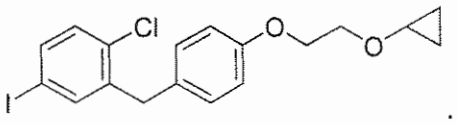
The method of preparing the compound of formula IIa is performed under conditions suitable to prepare the compound of Formula IIa.

[0020] R^1 of formula IIa can be hydrogen, halo, hydroxy, C_1-C_3 alkyl or C_1-C_3 alkoxy. R^2 and R^3 of formula IIa can each independently be hydrogen, halo, hydroxy, C_1-C_3 alkyl, C_1-C_3 alkoxy, C_3-C_6 cycloalkyl, (C_1-C_3 alkoxy)C_1-C_3 alkyl, (C_1-C_3 haloalkoxy)C_1-C_3 alkyl, (C_2-C_4 alkenyloxy)C_1-C_3 alkyl, (C_2-C_4 alkynyloxy)C_1-C_3 alkyl, (C_3-C_6 cycloalkoxy)C_1-C_3 alkyl, C_1-C_3 hydroxyalkoxy, C_3-C_6 cycloalkoxy, C_3-C_6 heterocycloalkoxy, (C_1-C_3 alkoxy)C_1-C_3 alkoxy, (C_1-C_3 haloalkoxy)C_1-C_3 alkoxy, (C_2-C_4 alkenyloxy)C_1-C_3 alkoxy, (C_2-C_4 alkynyloxy)C_1-C_3 alkoxy, (C_3-C_6 cycloalkoxy)C_1-C_3 alkoxy, (C_3-C_6 heterocycloalkoxy)C_1-C_3 alkoxy, (C_3-C_6 cycloalkyl)C_1-C_3 alkoxy, (C_3-C_6 cycloalkyl)C_2-C_4 alkenyloxy or (C_3-C_6 cycloalkyl)C_2-C_4 alkynyloxy.

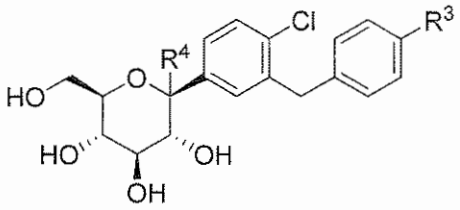
[0021] R^{3a} of formula IIa can be OH. R^6 of formula IIa can be OH or Br. X of formula IIa can be bromo or iodo.

[0022] The alkyl, alkoxy, cycloalkyl, alkenyloxy, alkynyloxy, cycloalkoxy, hydroxyalkoxy, and heterocycloalkoxy groups or portions of formula IIa can optionally be partially or completely fluorinated. And one or more hydrogen atoms of formula IIa can optionally be substituted with deuterium.

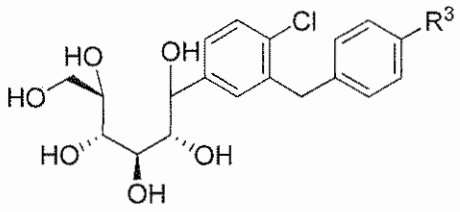
[0023] In a third embodiment, the present ~~invention~~ disclosure provides a compound having the structure:



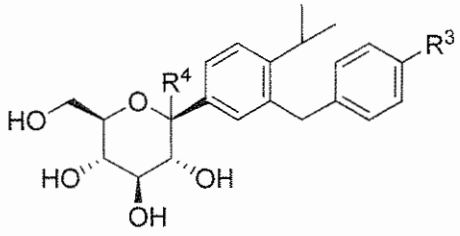
[0024] In another embodiment, the present ~~invention~~ disclosure provides a composition having a compound of formula Ia having the structure:



in an amount of at least 95% of the composition. The composition can also include side-product A having the structure:



in an amount of less than about 1% of the composition. The composition can also include side-product B having the structure:



in an amount of less than about 3% of the composition. The composition can be prepared by the methods of the present ~~invention~~disclosure. The compounds of the composition are those wherein R^3 can be hydrogen, halo, hydroxy, C_1-C_3 alkyl, C_1-C_3 alkoxy, or C_3-C_6 cycloalkyl. And at