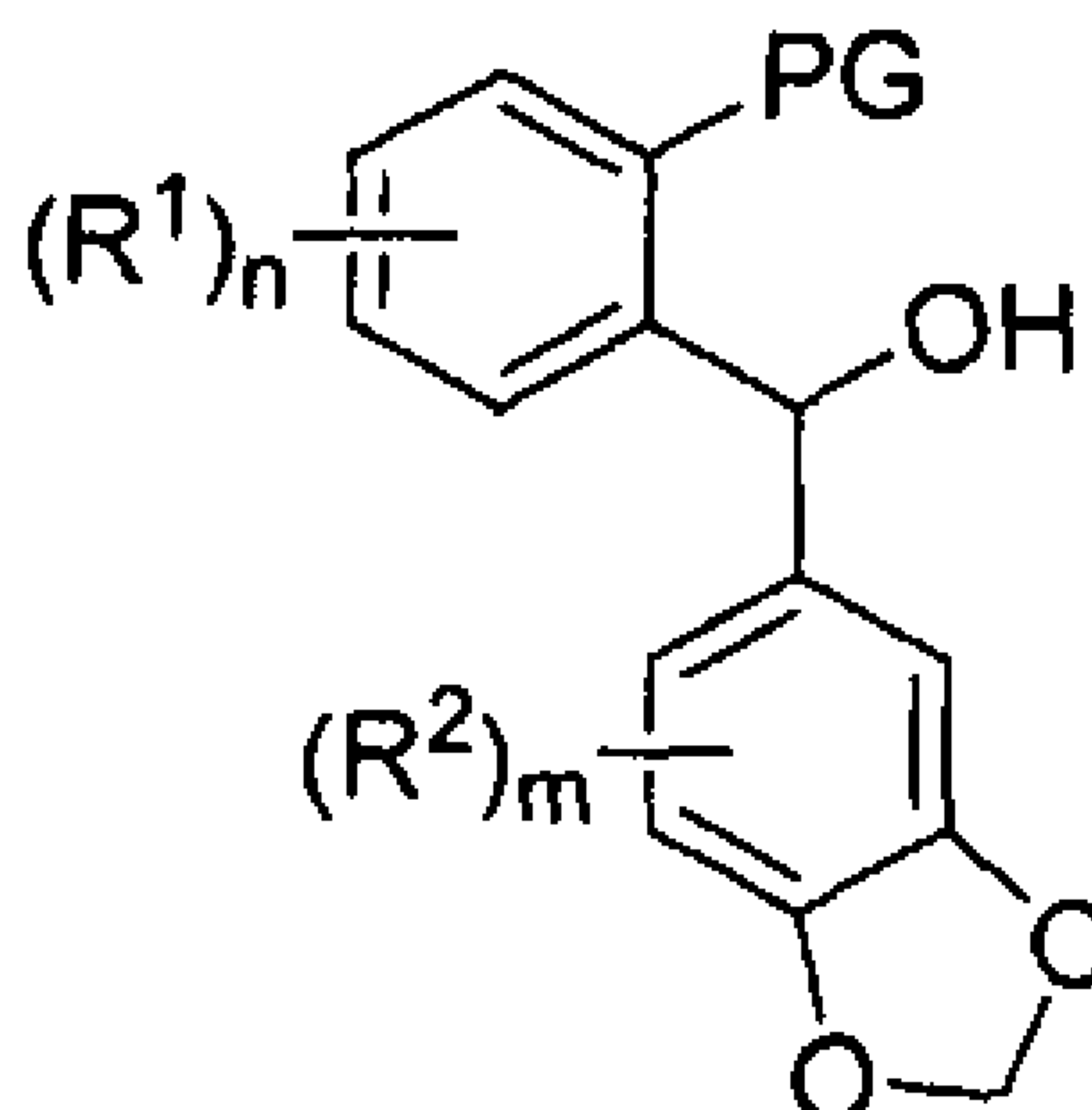




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(54) Title: SYNTHESIS OF CLEISTANTHIN A AND DERIVATIVES THEREOF



D

(57) **Abrégé/Abstract:**

The present invention provides a method for preparing Cleistanthin A, a diphyllin glycoside, derivatives thereof and intermediates thereto. In particular the present invention provides in one of the aspect a method for synthesis of compound of formula D a key intermediate of diphyllin, which can be carried out in a shorter duration and at an ordinary temperature.



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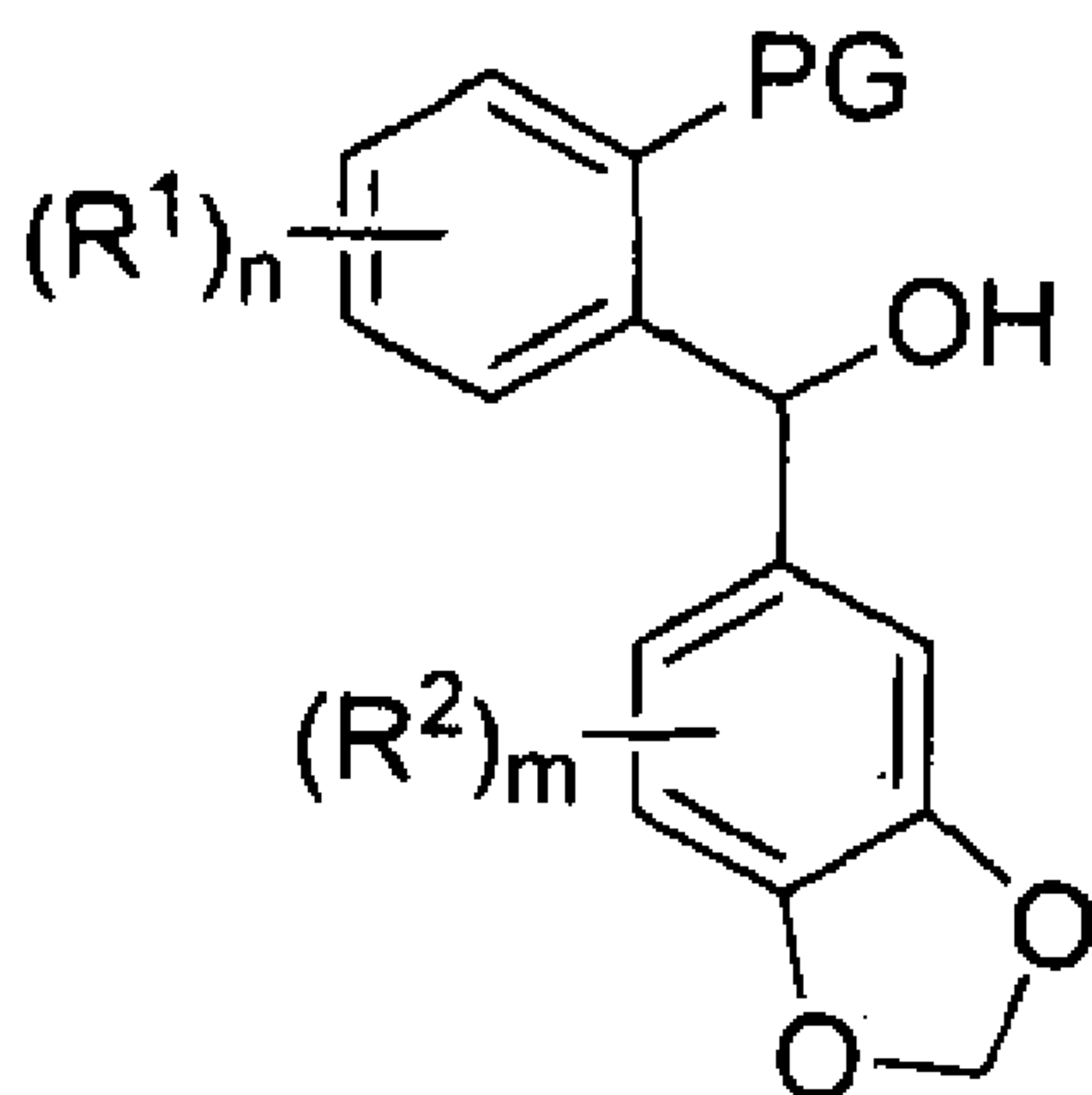
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(54) Title: SYNTHESIS OF CLEISTANTHIN A AN DERIVATIVES THEREOF



D

(57) Abstract: The present invention provides a method for preparing Cleistanthin A, a diphyllin glycoside, derivatives thereof and intermediates thereto. In particular the present invention provides in one of the aspect a method for synthesis of compound of formula D a key intermediate of diphyllin, which can be carried out in a shorter duration and at an ordinary temperature.

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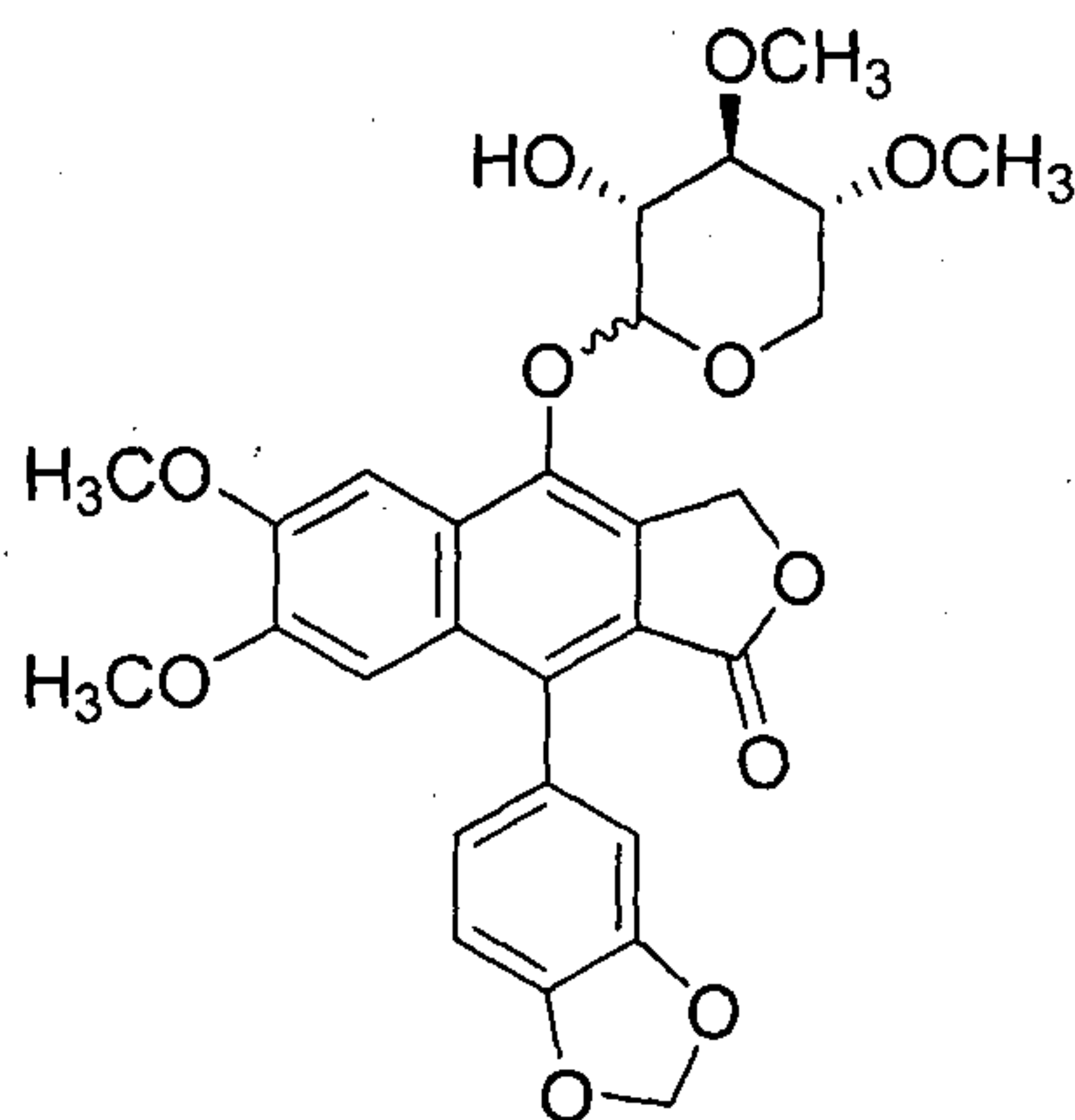
SYNTHESIS OF CLEISTANTHIN A AND DERIVATIVES THEREOF

FIELD OF THE INVENTION

5 The present invention relates to methods for synthesizing cleistanthin A, derivatives thereof, and to intermediates thereto.

BACKGROUND OF THE INVENTION

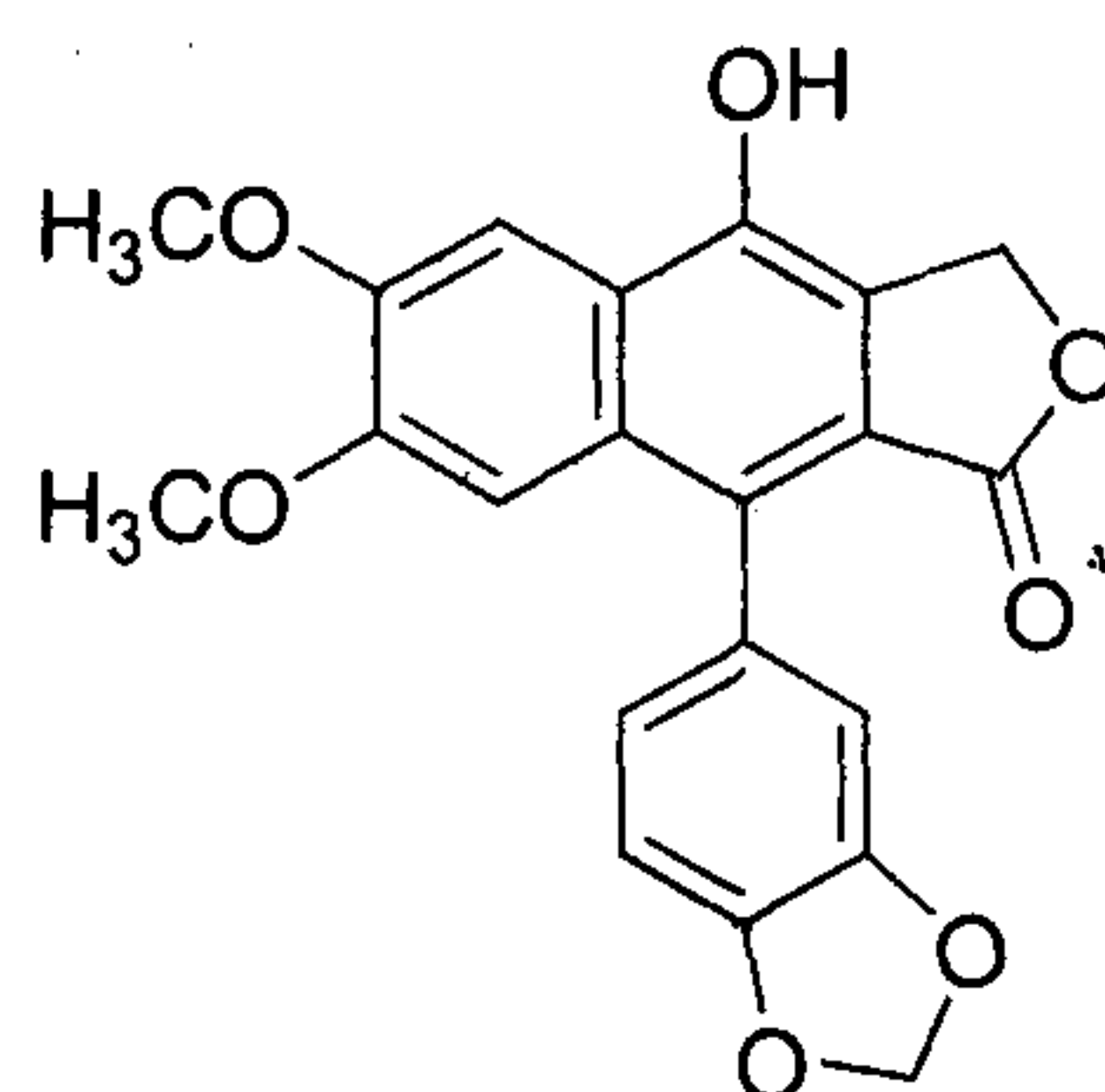
10 Cleistanthin A (I) is a diphyllin glycoside isolated from the tropical plant *Cleistanthus collinus*:



I

15 Cleistanthin A is a diphyllin glycoside having anticancer potential. It is found to arrest growth by inhibiting DNA synthesis and cancer cell division and by driving cancer cells to apoptosis. These properties of cleistanthin A renders it promising agent useful in regimens for treating cancer. The conventional process for the isolation of cleistanthin A comprises the steps of treating the dried leaves of *Cleistanthus collinus* with petroleum ether to obtain a defatted powder, which is subsequently extracted with acetone and treated with benzene and chloroform to afford a black residue. Pure cleistanthin A is then isolated following recrystallization with acetone. Because such a process is lengthy and not sufficient for gram scale quantities, synthetic procedures have been developed which culminate in the glycosylation of diphyllin (II):

20



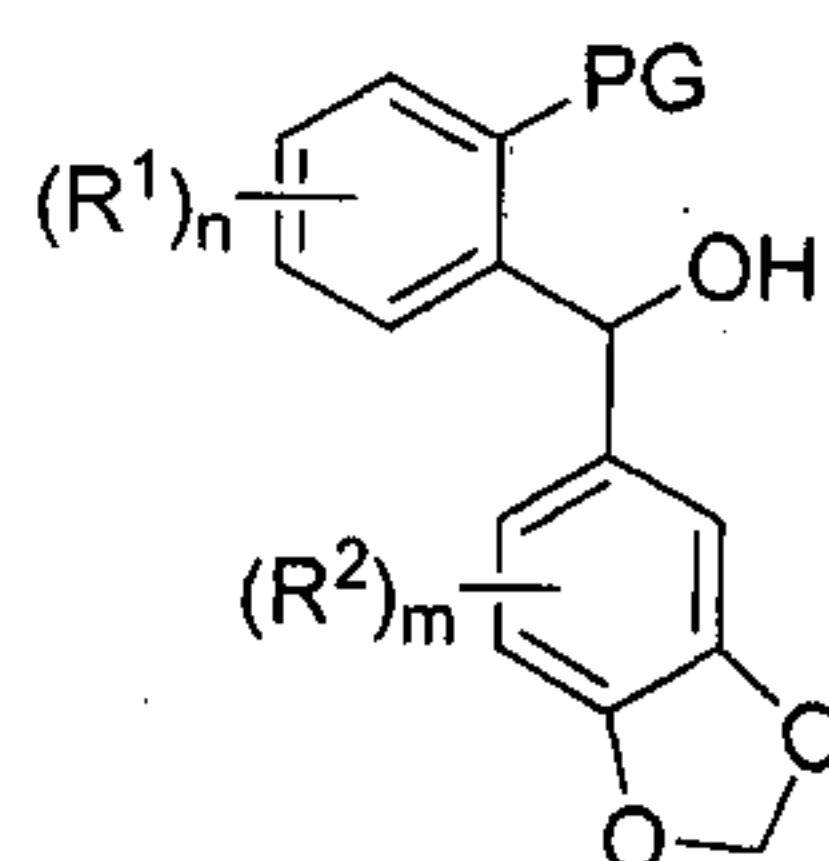
II

Diphyllin (II) is thus a key intermediate in the synthesis of cleistanthin A. The synthesis of diphyllin as well as cleistanthin A is reported in WO 2010/089778, the entirety of which is herein incorporated by reference. This synthesis of diphyllin, while accomplished in only five linear steps from commercially available starting material, includes a metallation step requiring extremely low temperatures. Such temperatures, while may be easy to carry out on small laboratory scale, are exponentially problematic on a commercial scale, requiring the use of hazardous reagents and long reaction times. Further, such conditions limit the scale on which a compound can be manufactured, ultimately increasing the production cost of the active pharmaceutical ingredient (API). Hence, there remains a need for a more robust, of shorter duration and commercially viable synthesis of diphyllin, its analogs and intermediates thereof.

SUMMARY OF THE INVENTION

Accordingly, in one aspect the present invention provides a method for synthesis of an intermediate compound of diphyllin, which can be carried out in a shorter duration and at an ordinary temperature.

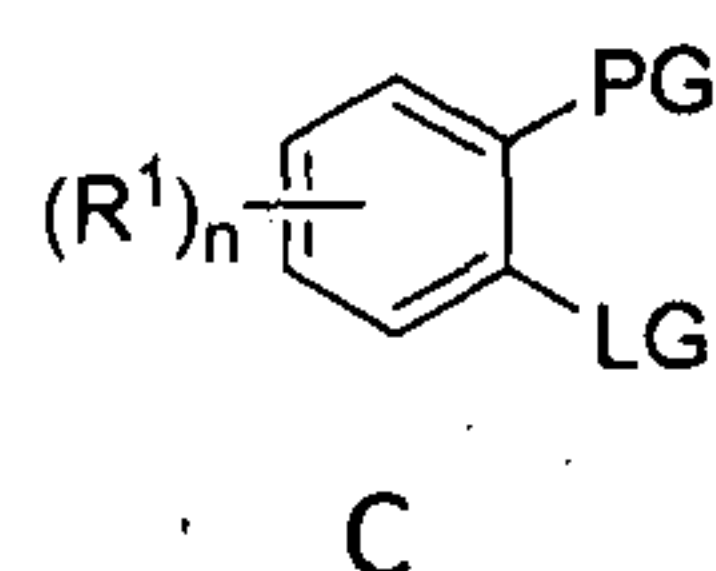
In one embodiment the present invention provides a method for synthesis of compound of formula D:



D

comprising the steps of:

(a) providing a solution of a compound of formula C:

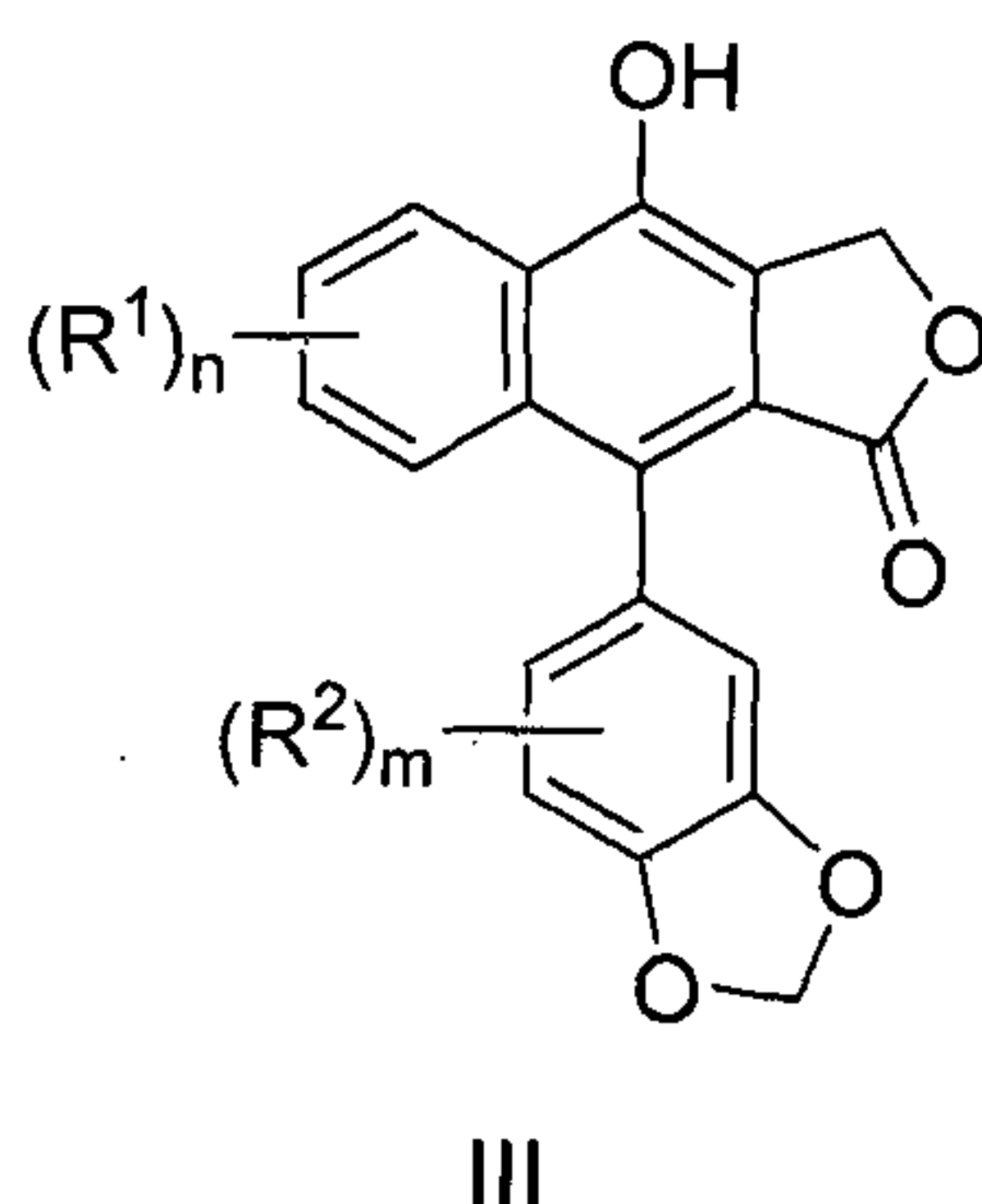


5 (b) sonicating said solution; and

(c) reacting said solution with an aryl aldehyde solution and an alkyl lithium reagent under sonication to form a compound of formula D. The compounds of formula D and C are described in detail herein below.

10 In another aspect, the present invention provides a method for synthesis of a diphyllin (II) or its derivatives, which can be carried out in a shorter duration and at an ordinary temperature.

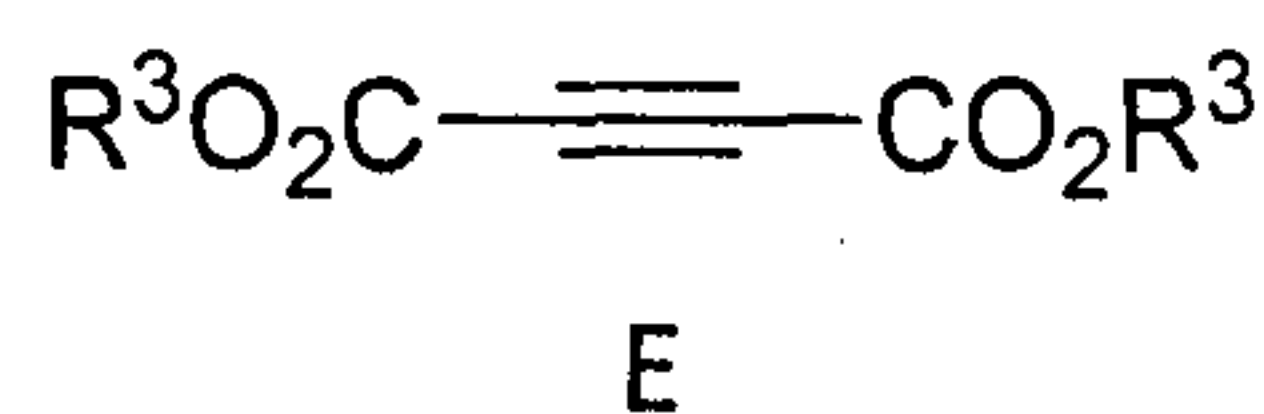
In some embodiments the present invention provides a method for synthesis of compounds of formula III:



15

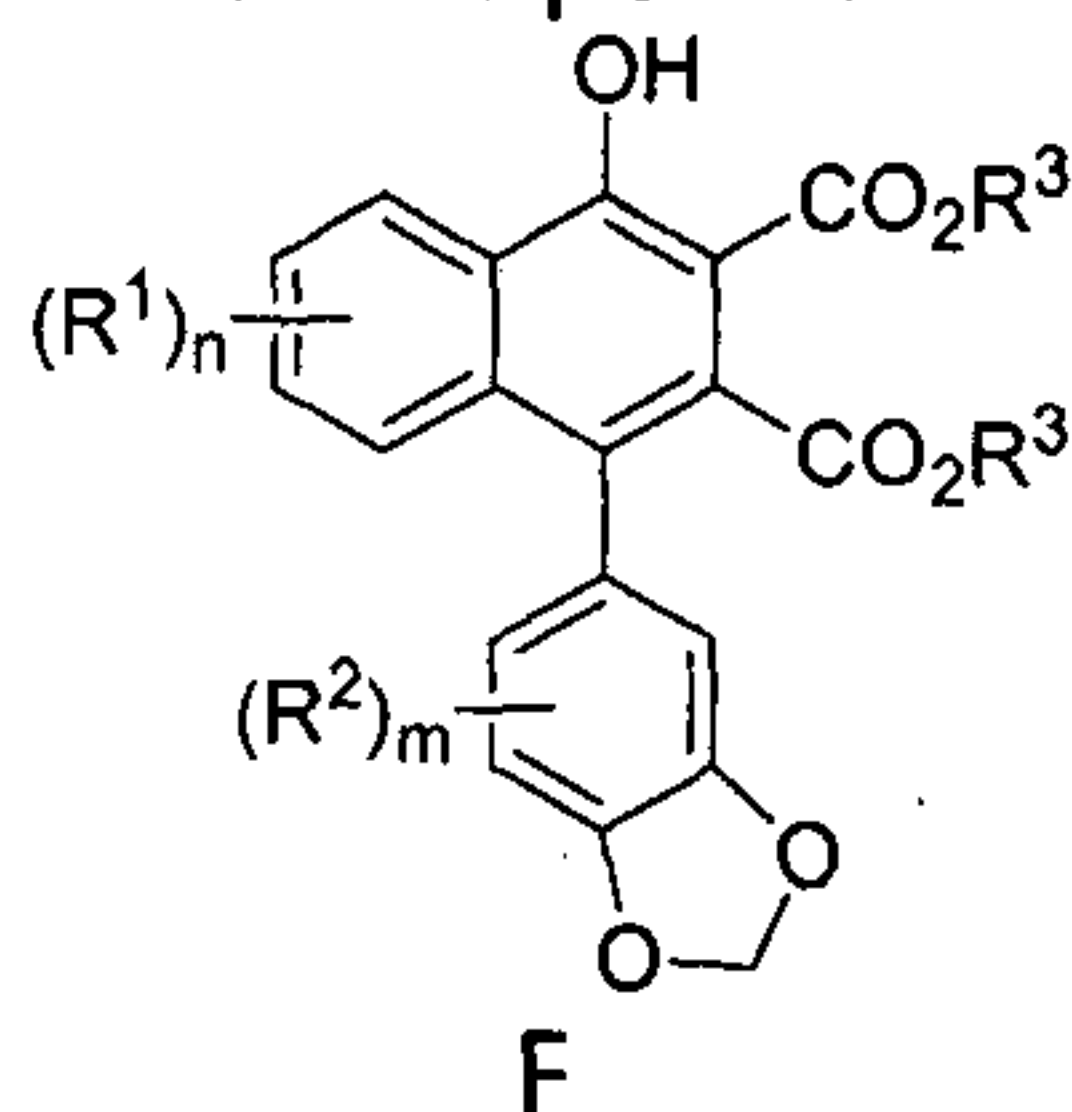
comprising the steps of:

(a) reacting compound of formula D with a compound of formula E:



20

under conditions effective to form a compound of formula F; and



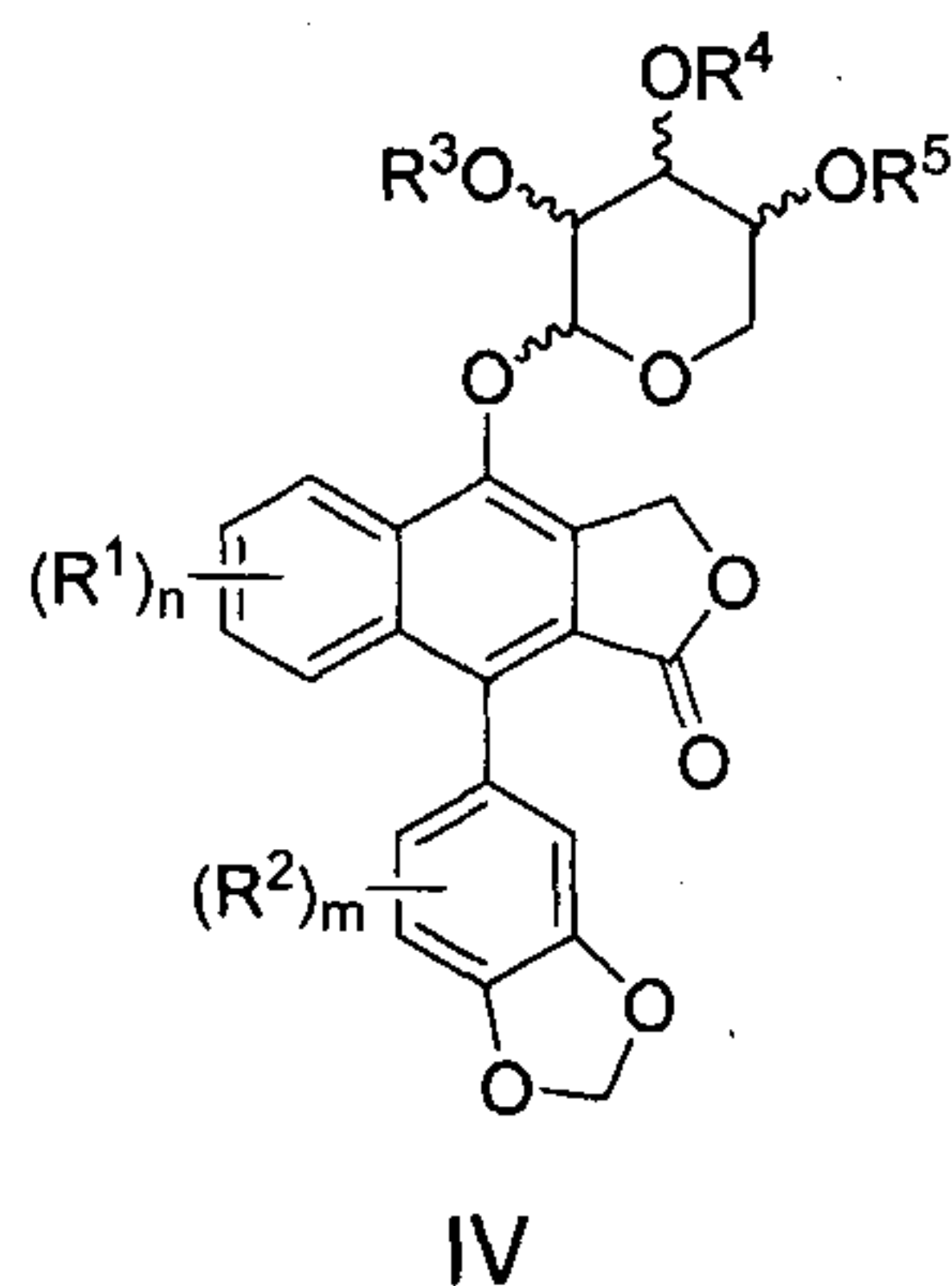
(b) reacting said compound F with a metal hydride to form a compound of formula III

The compounds of formula E, F and III are described in detail herein below.

In one embodiment said intermediate compound F is dimethyl 1-(benzo[d][1,3]dioxol-5-yl)-4-hydroxynaphthalene-2,3-dicarboxylate, the reduction of said dimethyl 1-(benzo[d][1,3]dioxol-5-yl)-4-hydroxynaphthalene-2,3-dicarboxylate with lithium aluminum hydride provides diphyllin (II).

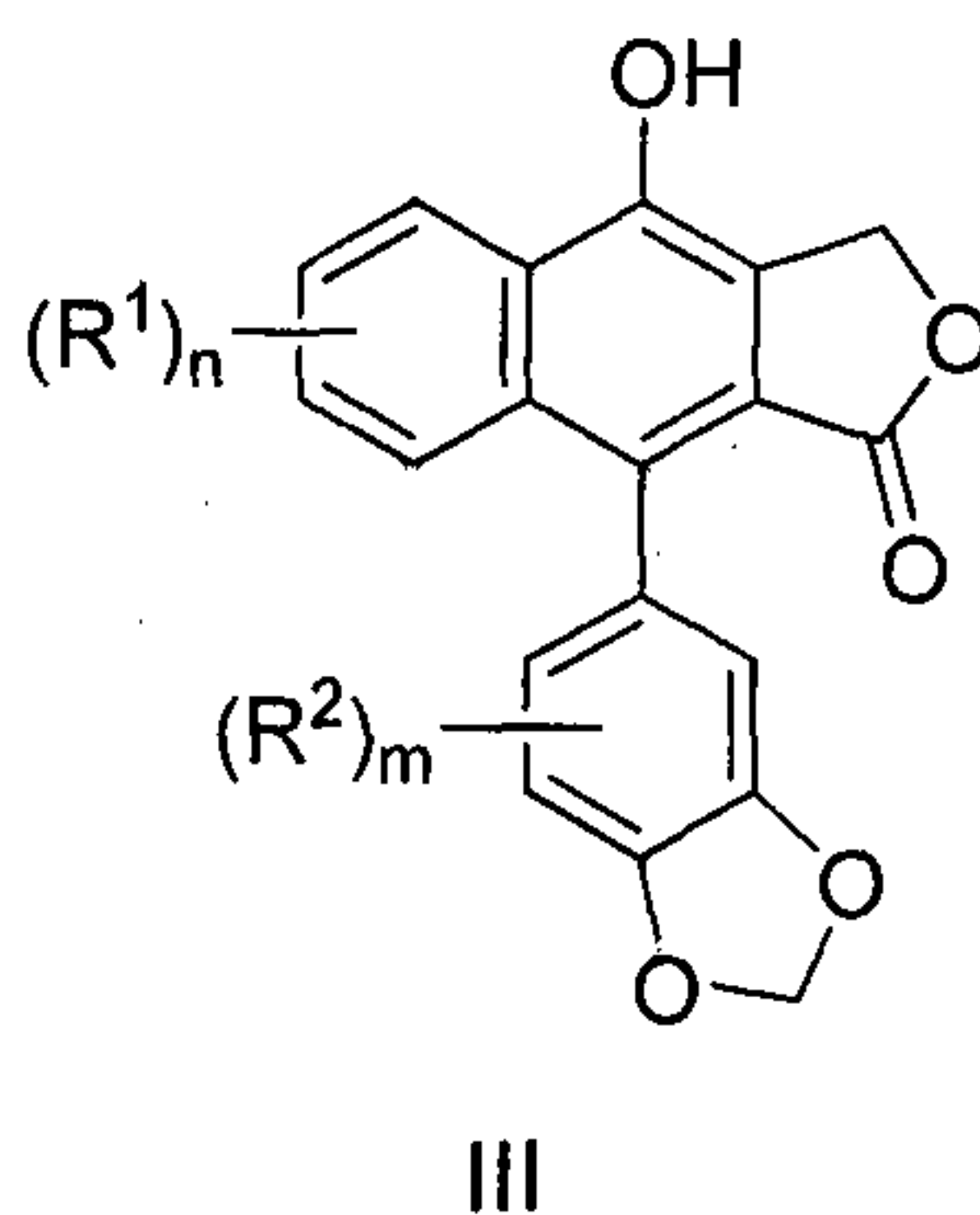
In still another aspect the present invention provides a method for synthesis of an improved method for preparing an acetate derivative of Cleistanthin A.

In an embodiment, the present invention provides a method for preparing a compound of formula IV:



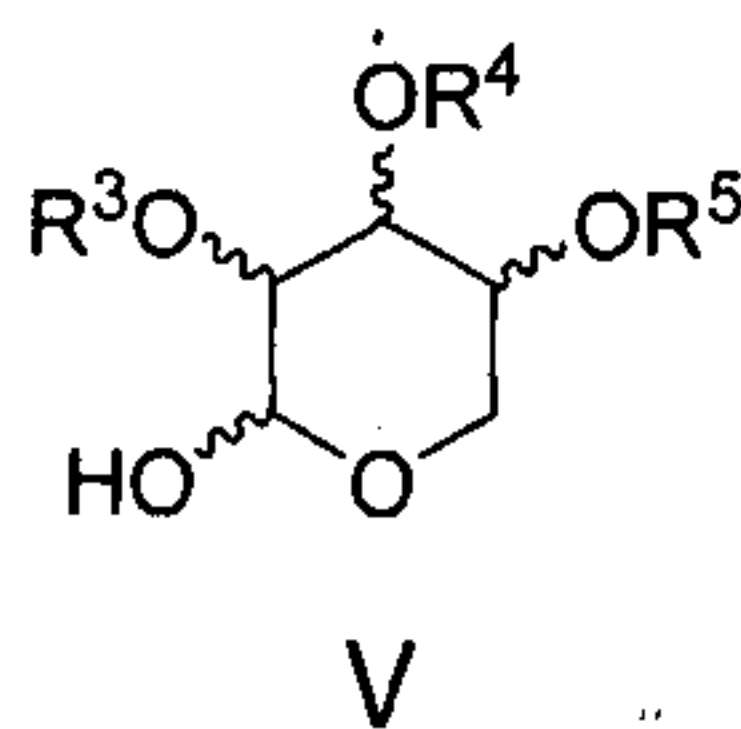
comprising the steps of:

(a) providing a compound of formula III:



and

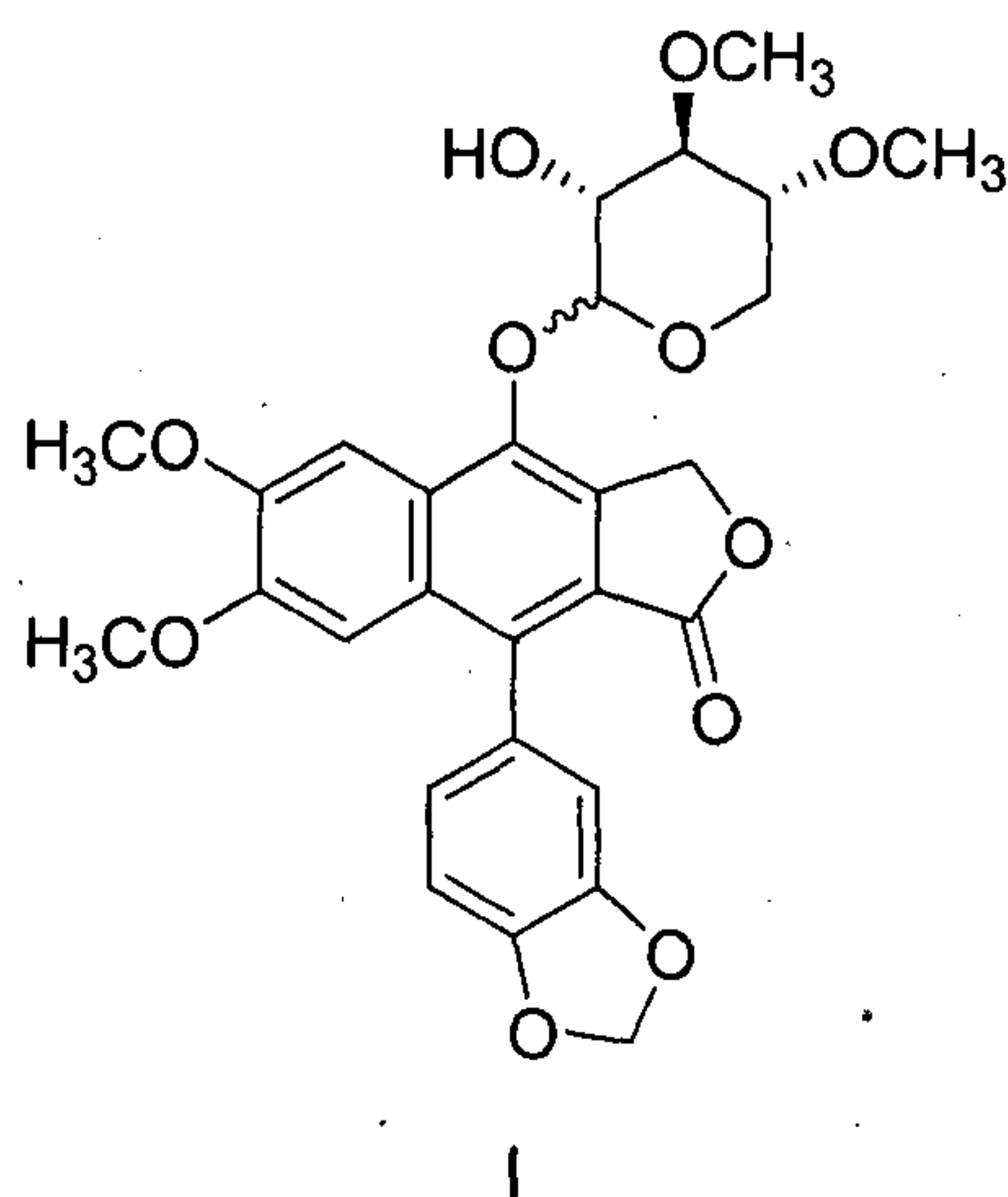
(b) reacting said compound of formula III with a pyranose of formula V:



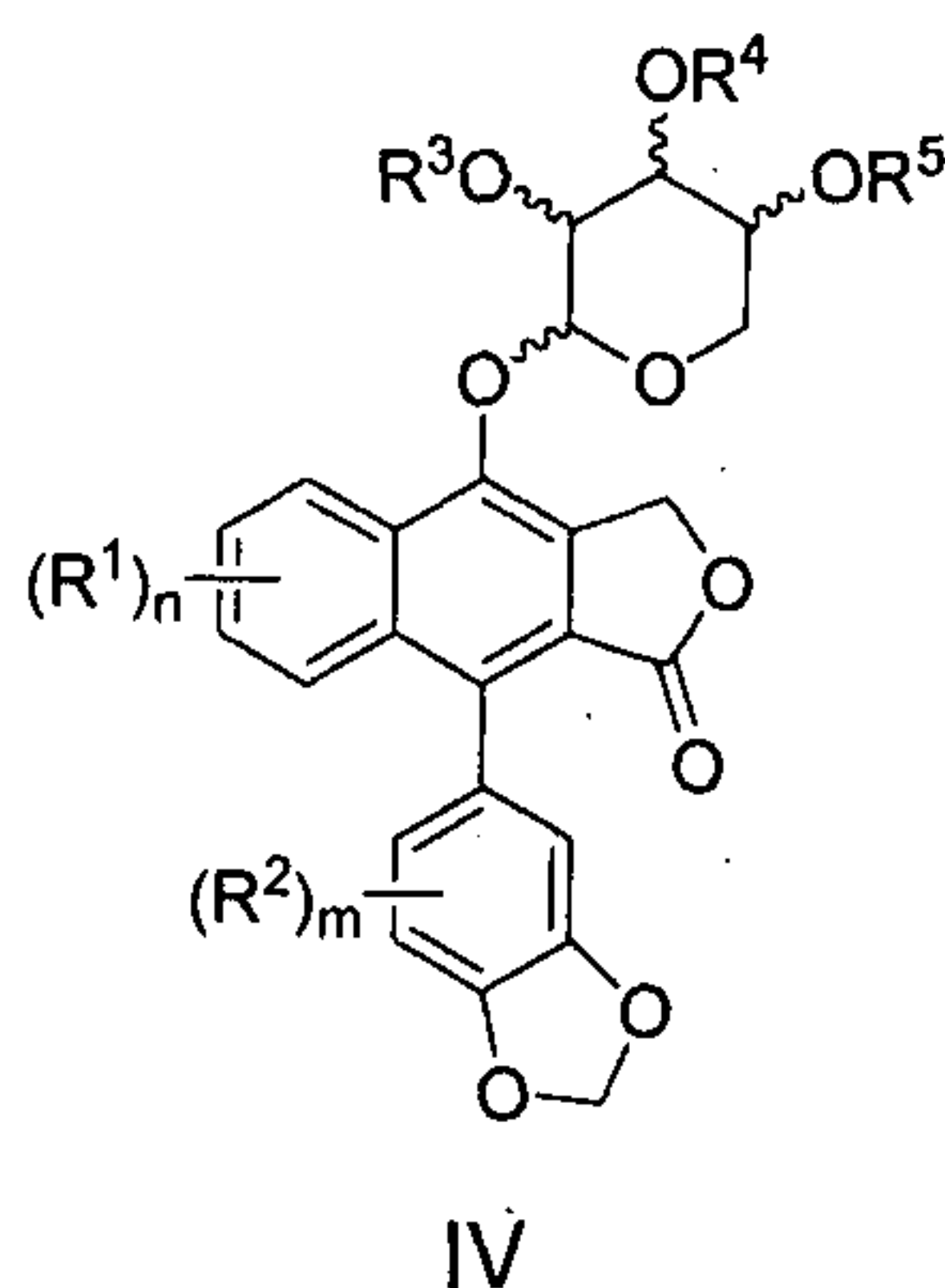
under conditions effective to form a compound of formula IV. The compounds of formula III, IV and V are described in detail herein below.

In yet another aspect the present invention provides an improved method for preparing Cleistanthin A, which can be carried out in a shorter duration and wherein the metallation step is carried out at an ordinary temperature.

In one of the embodiment, the present invention provides a method for preparing Cleistanthin A (I):



comprising a step of reacting compound of formula IV:



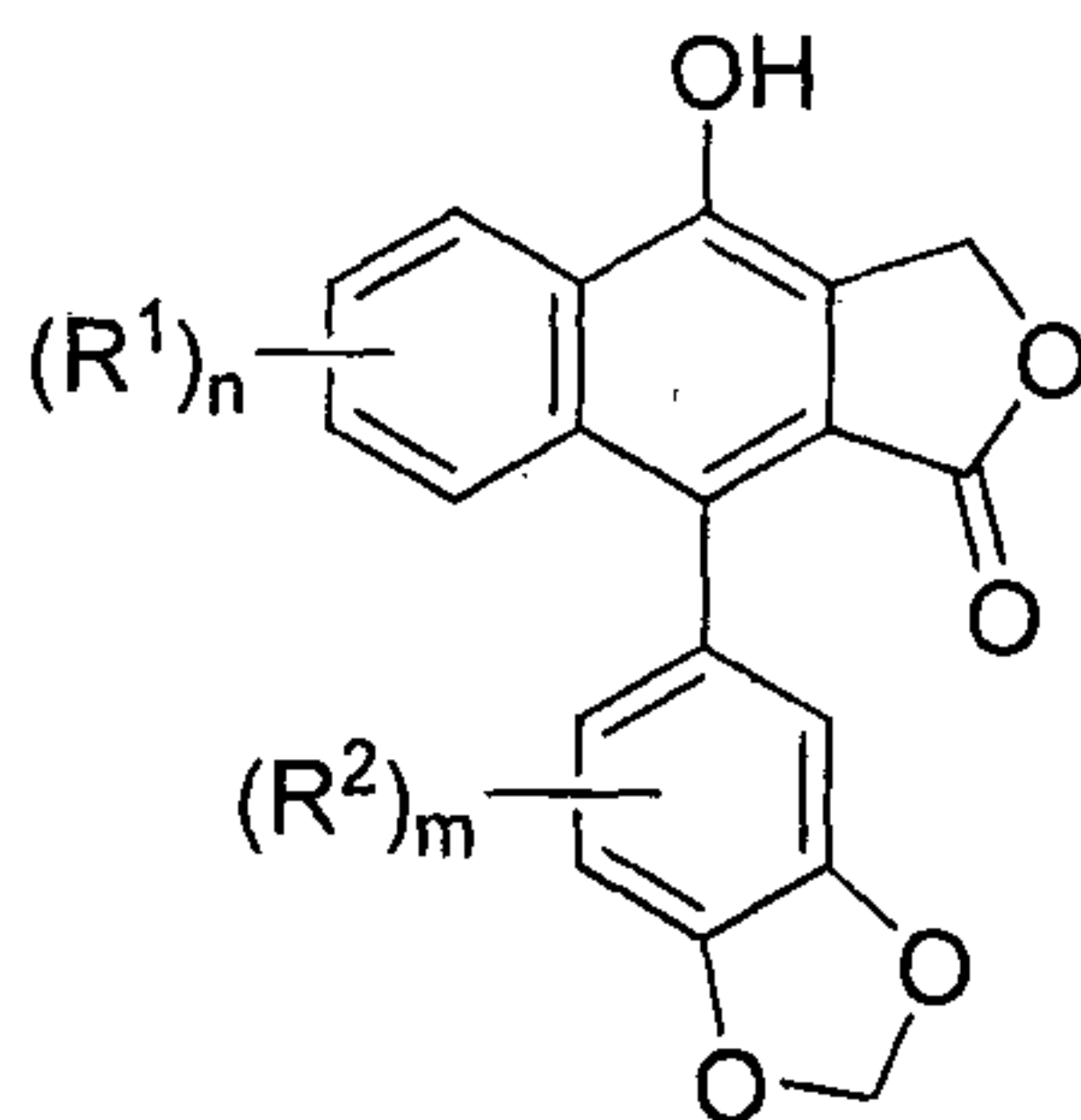
under conditions effective to form cleistanthin A (I). In one specific embodiment, the effective conditions include treating compound of formula IV with an alkali and a solvent to form compound of formula I.

DETAILED DESCRIPTION OF THE INVENTION

In general aspects the present invention provides methods for synthesizing cleistanthin A, derivatives thereof, and intermediates thereof. Cleistanthin A is a

diphyllin glycoside and one of the main step in synthesizing it, is glycosylation of an intermediate diphyllin. One key step in the synthesis of diphyllin is the condensation of an aryl lithium anion, formed from the reaction of an aryl lithium and an aryl aldehyde. Such aryl lithium anions are readily generated *in situ* via a lithium-halogen exchange from the treatment of an aryl halide with a lithium reagent. Lithium reagents are moisture-sensitive and/or pyrophoric, requiring the reactions to be conducted at very low temperatures. Moreover, because the reactivity of lithium reagents is in part due to their high nucleophilicity, they are prone to unwanted side reactions. Such side reactions include the S_NAr addition of the alkyl lithium to the aryl halide, resulting in an alkylated aryl species rather than the desired aryl lithium anion. Alkylated aryl species account for the majority of byproducts associated with lithium-halogen exchange and render the starting material unusable. While the generation of such byproducts may be acceptable at the first step of a synthesis, it is particularly undesirable at later stages of a synthesis when advanced intermediates are converted to unusable materials. Thus, low temperatures are necessary to minimize both the hazards associated with the use of lithium reagents as well as the potential for side reactions. As discussed above, such temperatures, though may appear trivial on small scale, are much more difficult to reach, maintain and/or control at small as well as on a larger, commercial scale, thus rendering such reactions inefficient and costly.

It has now been surprisingly found that such condensations may be performed at higher temperatures. Moreover, such condensations run at higher temperatures result in fewer side reactions. Accordingly, the present invention provides methods of preparing compounds of formula III:



III.

or a pharmaceutically acceptable salt thereof, wherein:

m is 0-3;

n is 0-4;

each of R¹ and R² is independently selected from halogen, -NO₂, -CN, or -L-R;

5 each L is independently a covalent bond or an optionally substituted bivalent C₁₋₆ hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-; and

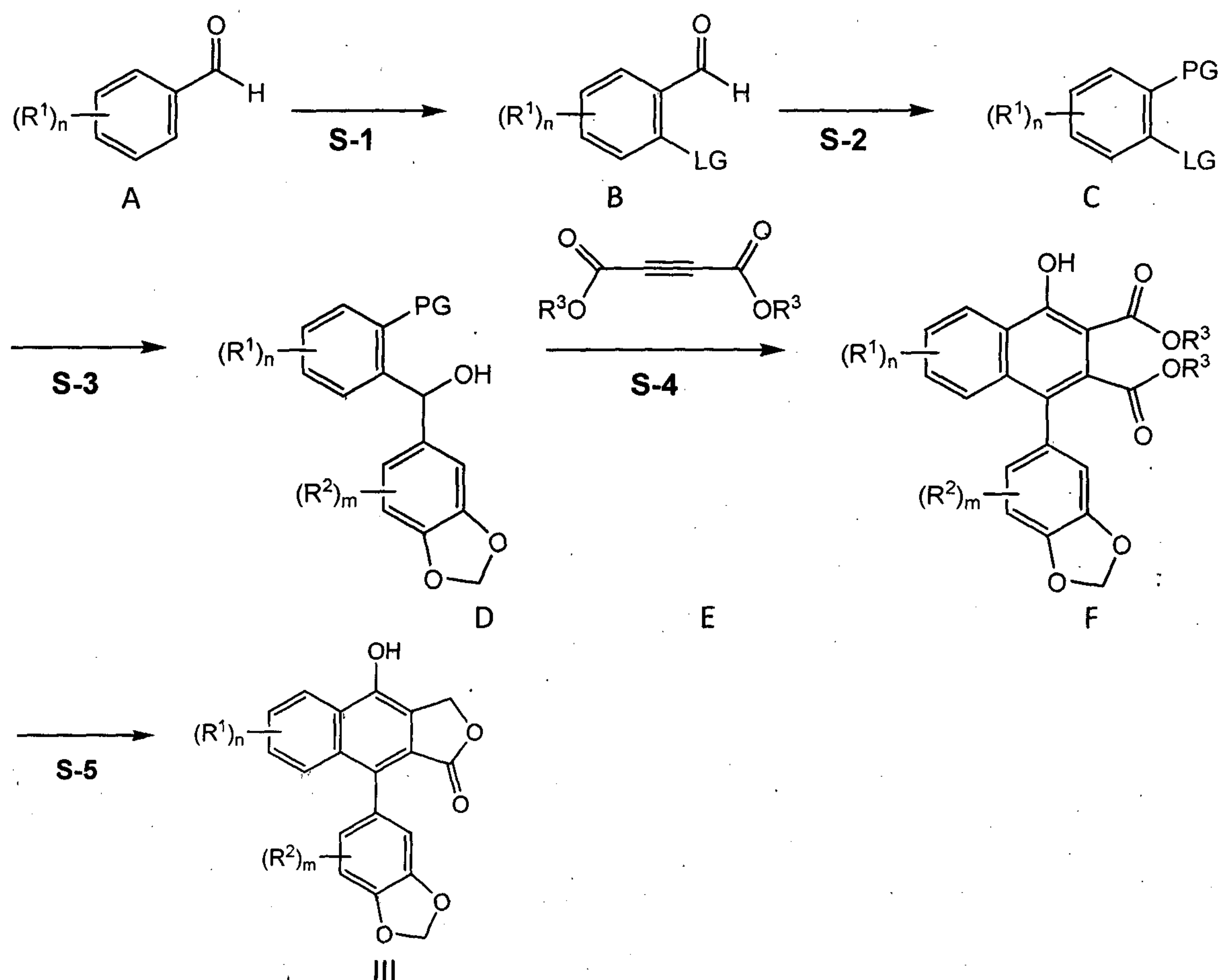
10 each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2
15 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

20 two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

In particular, the present invention provides methods of preparing synthetic
25 intermediates useful for preparing such compounds.

In certain embodiments, the present compounds are generally prepared according to Scheme I set forth below:

Scheme I



wherein each of R^1 , R^2 , R^3 , n , m , PG, and LG are as defined and described in embodiments herein.

In one aspect, the present invention provides methods for preparing benzo[d][1,3]dioxol-5-yl(phenyl)methanol compounds of formula D according to the steps depicted in Scheme I, above. At step S-1, a leaving group, LG, is incorporated into intermediate A to form intermediate B. One of ordinary skill in the art will recognize that a variety of leaving groups are suitable for use in provided methods. As used herein, the term "leaving group" refers to a chemical moiety that is readily displaced by a desired incoming chemical moiety. Suitable leaving groups are well known to a person having ordinary skill in the art and can be selected suitably. Such leaving groups include halogens. In certain embodiments, LG is Bromine. In some embodiments, LG is iodine.

In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

In some embodiments, R^1 is L-R. In some embodiments, R^1 is L-R, wherein L is a covalent bond.

In some embodiments, R^1 is L-R, wherein L is an optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-. In some embodiments, R^1 is L-R, wherein L is an optionally substituted bivalent C_{1-5} hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-. In some embodiments, R^1 is L-R, wherein L is an optionally substituted bivalent C_{1-4} hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-. In some embodiments, R^1 is L-R, wherein L is an optionally substituted bivalent C_{1-3} hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-.

In some embodiments, R^1 is L-R, wherein L is an optionally substituted bivalent C_{1-2} hydrocarbon chain, wherein one or both methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-.

In some embodiments, R^1 is L-R, wherein L is an optionally substituted bivalent C_{1-2} hydrocarbon chain, wherein one methylene unit of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-.

In some embodiments, R^1 is L-R, wherein L is $-O-$.

In some embodiments, R^1 is L-R, wherein R is hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

In some embodiments, R^1 is L-R, wherein R is hydrogen. In some embodiments, R^1 is L-R, wherein L is a covalent bond and R is hydrogen.

In some embodiments, R^1 is L-R, wherein R is an optionally substituted group selected from C_{1-6} aliphatic. In some embodiments, R^1 is L-R, wherein R is an optionally substituted group selected from C_{1-5} aliphatic. In some embodiments, R^1 is L-R, wherein R is an optionally substituted group selected from C_{1-4} aliphatic. In some embodiments, R^1 is L-R, wherein L is a covalent bond and R is *n*-butyl, *sec*-butyl or *tert*-butyl. In some embodiments, R^1 is L-R, wherein L is a covalent bond and R is $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$.

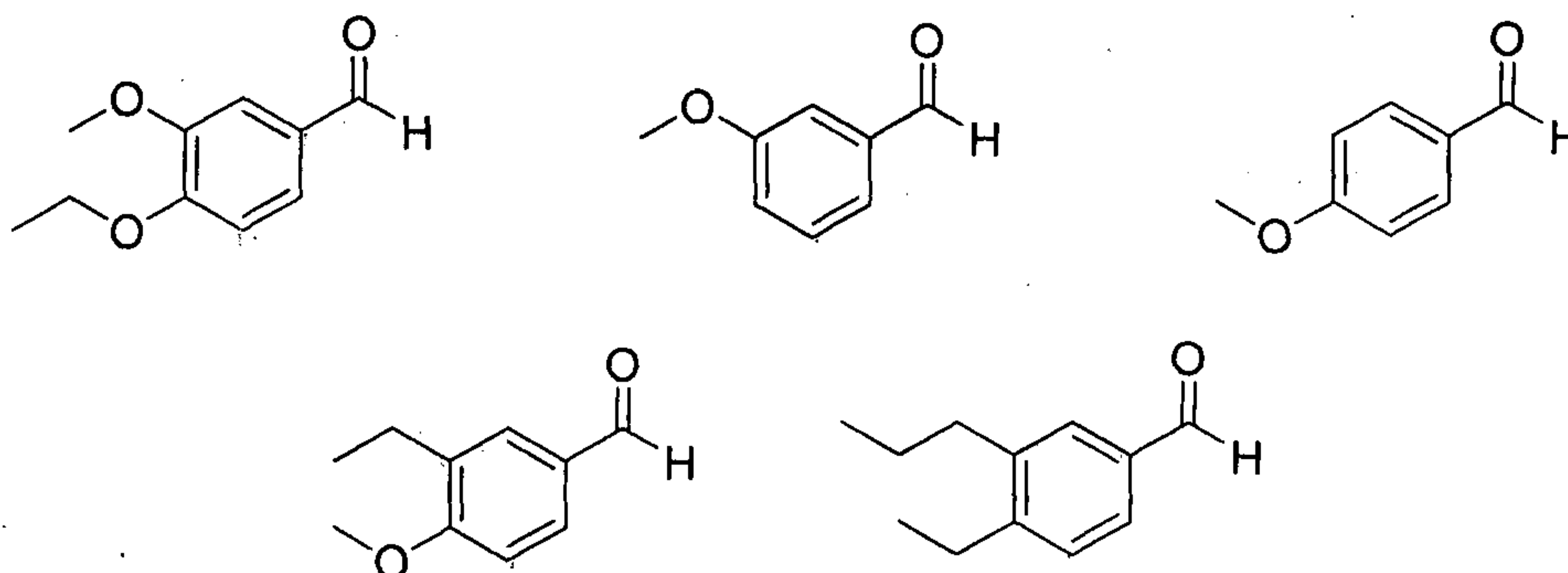
In some embodiments, R^1 is L-R, wherein R is an optionally substituted group selected from C_{1-3} aliphatic. In some embodiments, R^1 is L-R, wherein L is a covalent bond and R is propyl or isopropyl. In some embodiments, R^1 is L-R, wherein L is a covalent bond and R is $-\text{CH}_2\text{CH}_2\text{CH}_3$.

In some embodiments, R^1 is L-R, wherein R is an optionally substituted group selected from C_{1-2} aliphatic. In some embodiments, R^1 is L-R, wherein L is a covalent bond and R is $-\text{CH}_2\text{CH}_3$. In some embodiments, R^1 is L-R, wherein L is $-O-$ and R is $-\text{CH}_2\text{CH}_3$.

In some embodiments, R^1 is L-R, wherein R is an optionally substituted methyl group. In some embodiments, R^1 is L-R, wherein L is a covalent bond and R is $-CH_3$.

5 In some embodiments, R^1 is L-R, wherein L is $-O-$ and R is $-CH_3$.

In some embodiments, intermediate A is selected from:



10 In some embodiments of S-1, such LG may be incorporated via an electrophilic aromatic substitution reaction. In some embodiments of S-1, a halogen LG is incorporated into intermediate A via an electrophilic aromatic substitution reaction. In some such embodiments of S-1, compounds of intermediate B are prepared by reacting intermediate A with X_2 . In some embodiments, X_2 is Cl_2 , Br_2 or I_2 . In some embodiments of S-1, compounds of intermediate B are prepared by reacting intermediate A with X_2 in the presence of an acid. Suitable acids for use
15 in step S-1 include, but are not limited to, mineral acids such as hydrochloric acid, as well as organic acids such as acetic acid. In some embodiments of step S-1, intermediate A is treated with X_2 in the presence of acetic acid. In certain embodiments, the electrophilic aromatic substitution of 3,4-dimethoxybenzaldehyde in the presence of bromine and acetic acid provides 2-bromo-4,5-dimethoxybenzaldehyde.
20

At step S-2, the aryl aldehyde is converted to a protecting group PG. The PG of intermediate C is a suitable carbonyl protecting group. Suitable carbonyl protecting groups are well known to a person having ordinary skill in the art and can be selected suitably by such a person. Suitable carbonyl protecting groups
25 include, but are not limited to, cyclic and dialkyl acetals, monothioacetals or

thioacetals. Cyclic acetals include 1,3-dioxolanes and 1,3-dioxanes. Cyclic thioacetals include 1,3-dithianes and 1,3-dithiolanes. In some embodiments of step S-2, the PG moiety of intermediate C is a 1,3-dioxolanyl moiety. In some embodiments of step S-2, the PG moiety of intermediate C is a 1,3-dioxanyl moiety. In some embodiments of step S-2, the PG moiety of intermediate C is a 1,3-dithiolanyl moiety. In some embodiments of step S-2, the PG moiety of intermediate C is a 1,3-dithianyl moiety. In some embodiments of step S-2, the PG moiety is $-\text{CH}(\text{OCH}_3)_2$. In some embodiments of step S-2, the PG moiety is $-\text{CH}(\text{SCH}_3)_2$. In some embodiments of step S-2, the PG moiety is $-\text{CH}(\text{OC}_2\text{H}_5)_2$. In some embodiments of step S-2, the PG moiety is $-\text{CH}(\text{OC}_3\text{H}_7)_2$. In certain embodiments, the present invention provides a method of preparing intermediate C by treating benzaldehyde B with ethylene glycol, or an equivalent thereof. In some embodiments, the present invention provides a method of preparing intermediate C by treating benzaldehyde B with a catalytic amount of acid and ethylene glycol, or an equivalent thereof. Suitable acids for catalyzing the condensation of ethylene glycol and an aldehyde include both mineral acids, such as hydrochloric acid, and organic acids, such as p-toluenesulfonic acid. In certain embodiments, the condensation of 2-bromo-4,5-dimethoxybenzaldehyde and ethylene glycol in the presence of catalytic p-toluenesulfonic acid provides 2-(2-bromo-4,5-dimethoxyphenyl)-1,3-dioxolane. One of ordinary skill will appreciate that the oxidation state of the aldehyde moiety in intermediate A can be modified so as to permit access to other starting materials of formula A. For example, in some embodiments, an appropriately substituted benzoic acid is subjected to electrophilic aromatic substitution conditions to provide the benzoic acid analog of intermediate B. The benzoic acid moiety is then protected as, for example, an orthoester to enable aryl lithium formation at step S-3. The orthoester PG is then deprotected and/or converted to an aldehyde or aldehydic oxidation state prior to or during step S-4.

At step S-3, the aryl ring of intermediate C is metallated with an alkyl lithium to form an aryl lithium anion *in situ*. Suitable alkyl lithiums for use in the present

invention include *n*-butyllithium, *sec*-butyllithium and *tert*-butyllithium. In some embodiments, the aryl ring of formula C is treated with *n*-butyllithium.

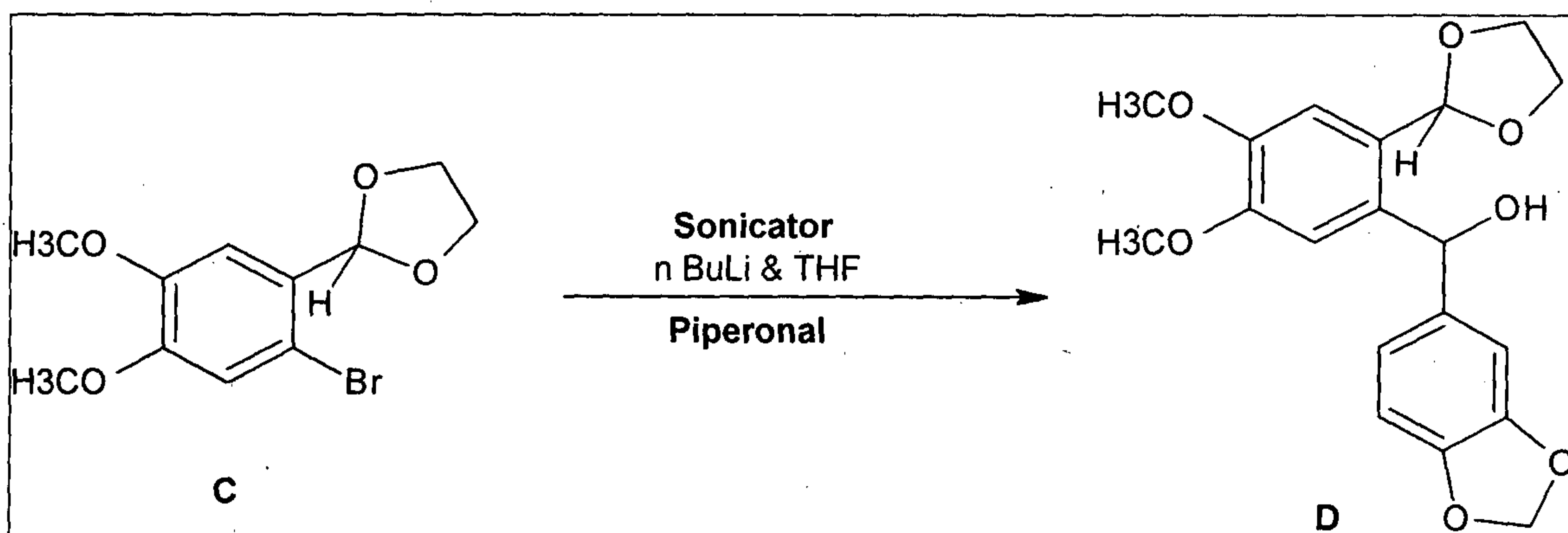
The aryl anion formed from treating intermediate C with an alkyl lithium is thereby reacted with an aryl aldehyde to form intermediate D. In some
5 embodiments, the aryl aldehyde is optionally substituted pipronal. As discussed above, such nucleophilic additions are generally performed at low temperatures, for example, at -70 °C. Typically, reactions run at such low temperatures take 3 or more hours to achieved the desired temperature. Once the reaction has reached the target temperature, such as -70 °C, the reaction temperature must be
10 carefully maintained by slow addition of or to the electrophile.

Temperatures of about -60 °C to about -80 °C are generally achieved through the use of solid carbon dioxide (e.g., dry ice) or liquid nitrogen. Both of these reagents are hazardous on small scale, and the hazards which is only amplified on larger scales. For example, both dry ice and liquid nitrogen rapidly freeze or burn
15 unprotected skin, resulting in frostbite. Further, dry ice readily sublimates at room temperature, releasing carbon dioxide gas into the air and displacing the oxygen in confined locations. Similarly, liquid nitrogen evaporates below room temperature and can also displace the oxygen in the air. Thus, both dry ice and liquid nitrogen can act as asphyxiates when used in poorly ventilated spaces.
20 Further, both carbon dioxide and nitrogen are odorless, colorless and tasteless, and can asphyxiate a subject without any sensation or prior warning.

At temperatures of about -60 °C to about -80 °C, a nucleophilic addition reaction such as step S-3 can require reaction times of at least 8-9 hours or longer, depending on the scale, as larger volumes require longer cooling times. Further,
25 the temperature of larger volumes is more difficult maintain and control. Due to the difficulties in maintaining such a temperature, side reactions are common and result in higher percentages of impurities. Such impurities render the isolation of the product difficult and contribute to overall low yields.

Sonication is the agitation of particles in a sample through the application of sound energy (i.e., ultrasound). It has now been surprisingly found that the use of sonication in the nucleophilic addition of the aryl lithium anion to the aryl aldehyde results in a cleaner reaction profile. Thus, in some embodiments, the present invention provides method of preparing a compound of intermediate D comprising a nucleophilic addition reaction of an aryl lithium anion to an aryl aldehyde, wherein the nucleophilic addition reaction is performed under sonication. It has further been surprisingly found that such a nucleophilic addition reaction can be run at room temperature, thereby decreasing the reaction times and eliminating the hazards associated with the use of dry ice and/or liquid nitrogen. Moreover, the impurities formed during sonication are minimal, thus demonstrating the enhanced selectivity of the reaction. Accordingly, in some embodiments, the present invention provides a method of preparing intermediate D comprising the nucleophilic addition of an aryl anion to an aryl aldehyde, wherein the nucleophilic addition is performed under sonication at room temperature. In certain embodiments, the nucleophilic addition of (2-(1,3-dioxolan-2-yl)4,5-dimethoxyphenyl)lithium anion to piperonal provides (2-(1,3-dioxolan-2-yl)4,5-dimethoxyphenyl)(benzo[d][1,3]dioxol-5-yl)methanol, wherein the nucleophilic addition is performed under sonication and at room temperature as per Scheme II.

Scheme II:



In some embodiments, such a sonication reaction is complete within 1-3 hours.

Further, the use of sonication is environmentally friendly and doesn't generate

waste (such as gaseous emissions and/or solvent waste) related to temperature control.

At step S-4, intermediate D is converted to an isobenzofuran moiety *in situ*, which then undergoes a cycloaddition reaction with dicarboxylacetylene intermediate E to afford intermediate F. See, for example, Charlton *et al.*, "Hindered Rotation in Arylnaphthalene Lignans," *J. Org. Chem.* 1996, 61(10), 3452-3457. In some
5 embodiments of step S-4, the cycloaddition reaction is a Diels-Alder reaction.

One of ordinary skill will recognize that a cycloaddition reaction such as step S-4 requires removal or unmasking of the PG (i.e. the aldehyde) to enable the
10 formation of the isobenzofuran intermediate. Suitable conditions for removing the PG moiety in intermediate D are well known in the art. In some embodiments of step S-4, intermediate D is treated with an acid. Suitable acids for removing PG in step S-4 include organic acids and mineral acids. In some embodiments, intermediate D is treated with an organic acid. In some such embodiments,
15 intermediate D is treated with acetic acid. In some embodiments, intermediate D is treated with a mineral acid. In some such embodiments, intermediate D is treated with hydrochloric acid. Thus, in some embodiments, the cycloaddition of an isobenzofuran and a dicarboxylacetylene moiety E in the presence of acetic acid provides the alkyl 1-(benzo[d][1,3]dioxol-5-yl)-4-hydroxynaphthalene-2,3-
20 dicarboxylate F.

In some embodiments, intermediate D is treated with acid and heated to effect *in situ* generation of an isobenzofuran. One of ordinary skill in the art would recognize that a wide variety of acids are useful for deprotecting acid-sensitive acetal groups. In some such embodiments, intermediate D is treated with a
25 mineral acid and heated. In some embodiments, intermediate D is treated with an organic acid and heated. In some embodiments, the Diels-Alder reaction of step S-4 is heated to a temperature of at least 100°C in the presence of an organic acid. In some embodiments, the Diels-Alder reaction of step S-4 is heated to a temperature of at least 100°C in the presence of acetic acid. In some
30 embodiments, the Diels-Alder reaction of step S-4 is heated to a temperature of

at least 120°C in the presence of acetic acid. In some embodiments, the Diels-Alder reaction of step S-4 is heated to a temperature of at least 140 °C in the presence of acetic acid.

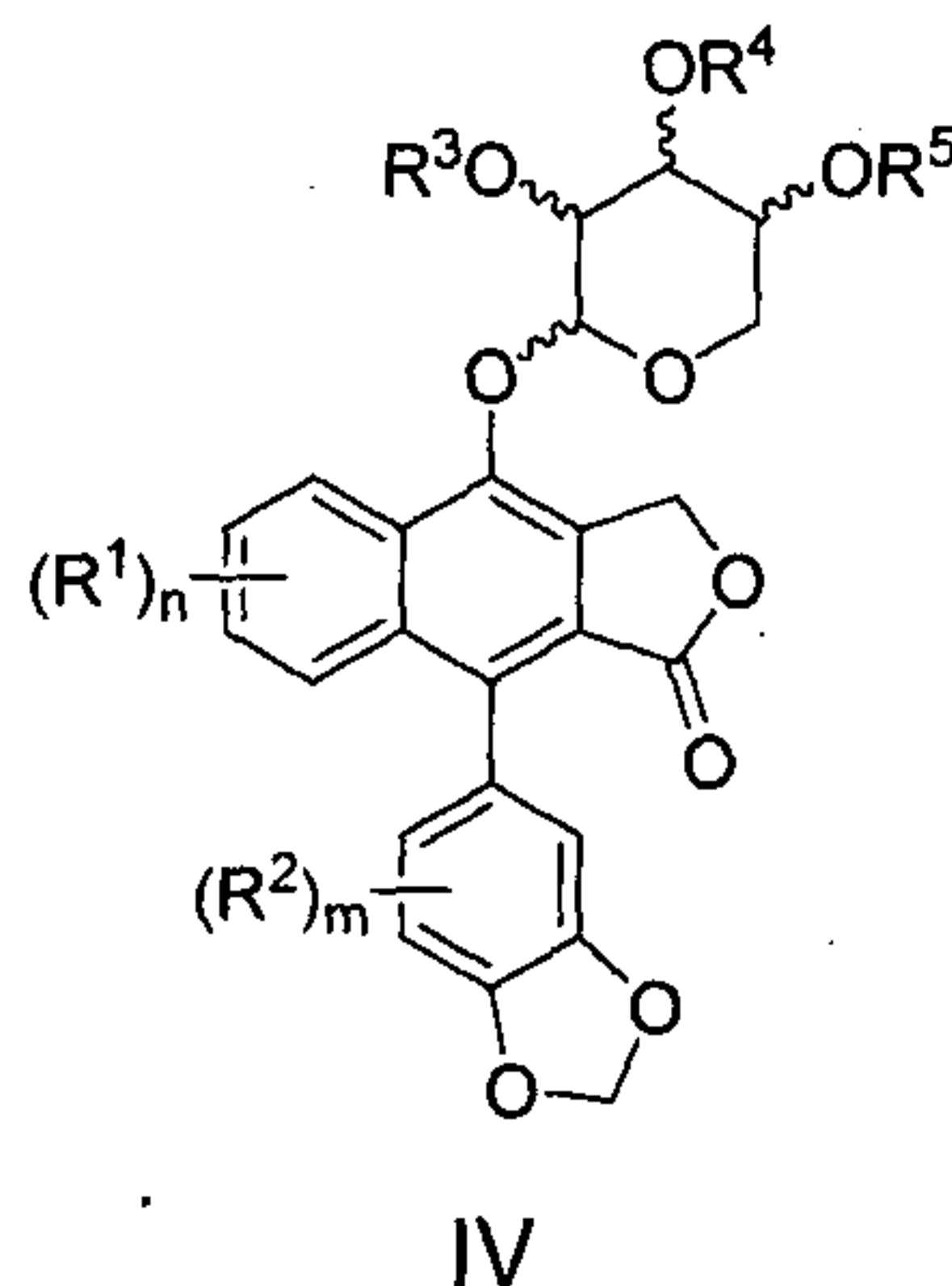
5 In some embodiments, each R^3 of intermediate E is independently an optionally substituted C_{1-6} aliphatic. In some embodiments, each R^3 of intermediate E is independently an optionally substituted C_{1-5} aliphatic. In some embodiments, each R^3 of intermediate E is independently an optionally substituted C_{1-4} aliphatic. In some embodiments, each R^3 of intermediate E is independently an optionally substituted C_{1-3} aliphatic. In some embodiments, each R^3 of intermediate E is an optionally substituted propyl group. In some embodiments, each R^3 of intermediate E is independently an optionally substituted C_{1-2} aliphatic. In some embodiments, each R^3 of intermediate E is an optionally substituted ethyl group. In some embodiments, each R^3 of intermediate E is an optionally substituted methyl group. In some embodiments, each R^3 of intermediate E is $-CH_3$. In some
10
15
embodiments, each R^3 of intermediate E is $-CH_2CH_3$. In some embodiments, each R^3 of intermediate E is $-CH_3$. In some embodiments, each R^3 of intermediate E is $-CH_2CH_2CH_3$.

20 In certain embodiments, the Diels-Alder reaction of 5-(5,6-dimethoxyisobenzofuran-1-yl)benzo[d][1,3]dioxole and diethyl acetylenedicarboxylate in the presence of acetic acid and at 140 °C provides dimethyl 1-(benzo[d][1,3]dioxol-5-yl)-4-hydroxynaphthalene-2,3-dicarboxylate.

At step S-5, the naphthylenedicarboxylate F is treated with a metal hydride to effect the condensation-cyclization of the lactone moiety of intermediate III. One of ordinary skill in the art would recognize that the hydroxyl group of
25
intermediate F controls the selectivity of the reduction through a six-membered coordination of the metal, directing reduction of the proximal carboxylate ester. Suitable metal hydrides useful in the selected reduction of intermediate F include borohydrides, boranes and aluminum hydrides. In some embodiments of step S-5, the metal hydride is selected from lithium aluminum hydride,
30
diisobutylaluminum hydride, sodium borohydride, lithium borohydride, zinc

borohydride and borane. In certain embodiments, the reduction of dimethyl 1-(benzo[d][1,3]dioxol-5-yl)-4-hydroxynaphthalene-2,3-dicarboxylate with lithium aluminum hydride provides diphyllin (II).

According to another aspect, the present invention provides a method for preparing a compound of formula IV:



or a pharmaceutically acceptable salt thereof, wherein:

m is 0-3;

n is 0-4;

each of R^1 and R^2 is independently selected from halogen, $-\text{NO}_2$, $-\text{CN}$, or $-\text{L-R}$;

each L is independently a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by $-\text{O}-$, $-\text{S}-$, $-\text{N(R)}-$, $-\text{C(O)}-$, $-\text{C(S)}-$, $-\text{C(O)N(R)}-$, $-\text{N(R)C(O)N(R)}-$, $-\text{N(R)C(O)}-$, $-\text{N(R)C(O)O}-$, $-\text{OC(O)N(R)}-$, $-\text{S(O)}-$, $-\text{S(O)}_2-$, $-\text{S(O)}_2\text{N(R)}-$, $-\text{N(R)S(O)}_2-$, $-\text{OC(O)}-$ or $-\text{C(O)O}-$;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

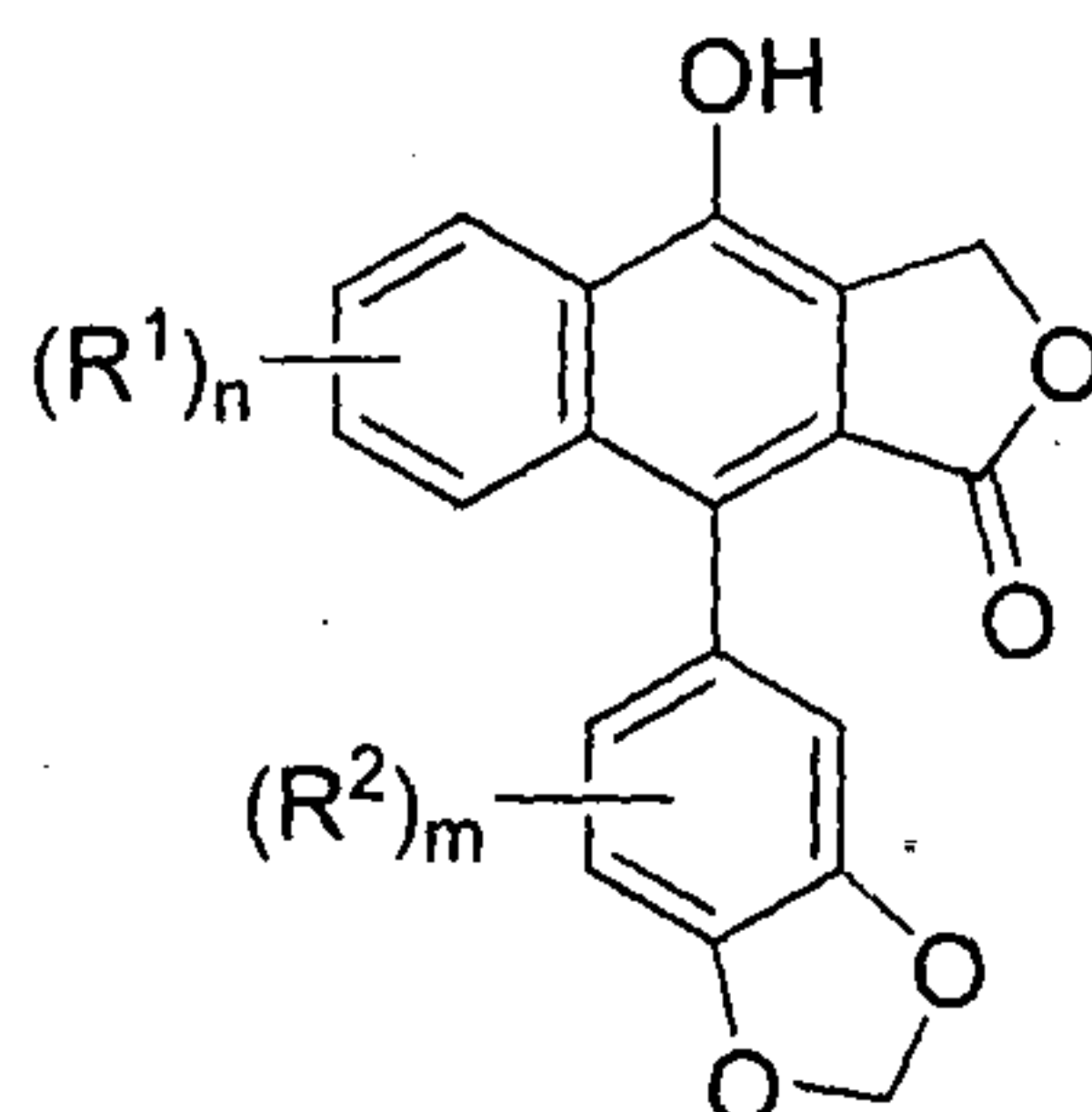
two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

5 each R^3 , R^4 and R^5 is independently hydrogen, R^6 , or $-C(O)R^6$;

each R^6 is independently an optionally substituted C_{1-6} aliphatic group or a suitable hydroxyl protecting group;

comprising the steps of:

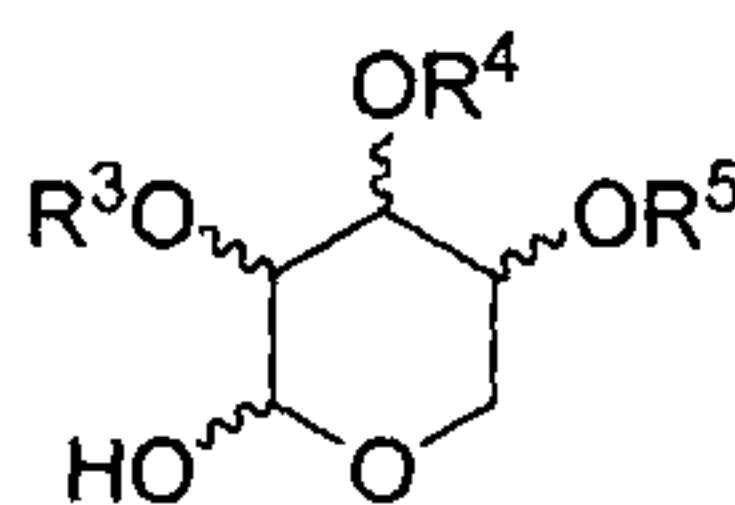
(a) providing a compound of formula III:



III

wherein each of n , m , R^1 , and R^2 is as defined above and described herein, and

(b) reacting said compound of formula III with a pyranose of formula V:



V

wherein each of R^3 , R^4 and R^5 is independently hydrogen, R^6 , or $-C(O)R^6$; and

each R^6 is independently an optionally substituted C_{1-6} aliphatic group or a suitable hydroxyl protecting group;

under conditions effective to form a compound of formula IV.

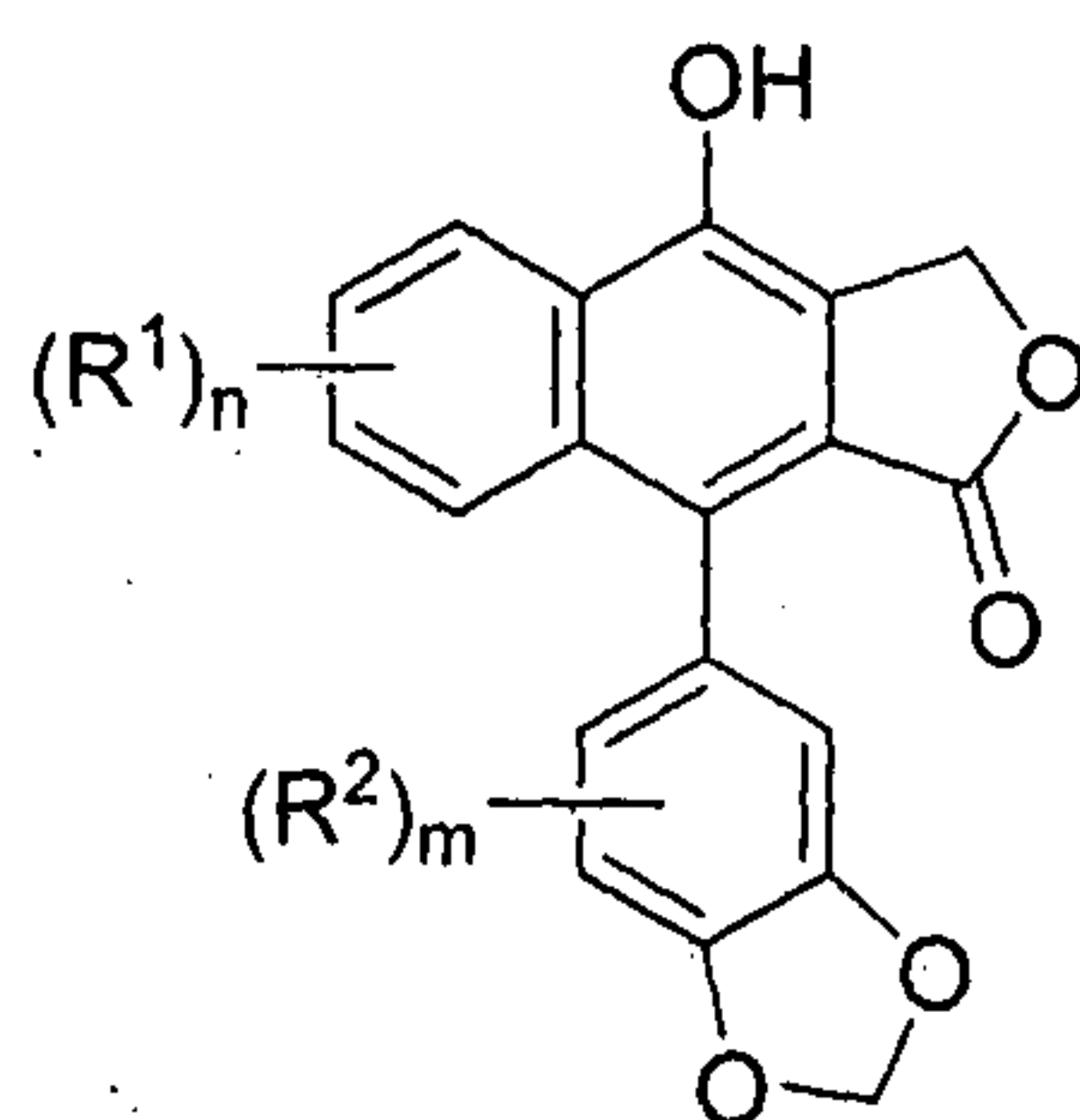
20 The synthesis of compounds of formula V is set forth in WO 2010/089778, the entirety of which is herein incorporated by reference.

According to one embodiment, conditions effective to form a compound of formula III include a base. One of ordinary skill will recognize that a variety of bases are suitable for use in step (b) above. Suitable bases include inorganic or
25 mineral bases, such as hydroxides, and organic bases such as alkyl amines and

alkoxides. In some embodiments, a compound of formula III is reacted with a compound of formula V in the presence of sodium hydroxide. In some such embodiments, the sodium hydroxide is aqueous. In some embodiments, a compound of formula III is reacted with a compound of formula V in the presence of a 2 molar aqueous solution of sodium hydroxide.

One of ordinary skill will recognize that a compound of formula III is not soluble in an aqueous solution of sodium hydroxide. One of ordinary skill in the art will further recognize that the use of aqueous sodium hydroxide in step (b) above requires a phase transfer reagent. Thus, in some embodiments, one or more phase transfer reagents are utilized in step (b) above. Suitable phase transfer reagents include tetraalkylammonium salts such as tetrabutylammonium salts. In some embodiments, a compound of formula III is reacted with a compound of formula V in the presence of aqueous sodium hydroxide and tetrabutylammonium bromide.

In some embodiments, the present invention provides a method for preparing a compound of formula III:



III

wherein:

m is 0-3;

n is 0-4;

each of R^1 and R^2 is independently selected from halogen, $-NO_2$, $-CN$, or $-L-R$;

each L is independently a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein one or two methylene units of L is optionally and

independently replaced by $-O-$, $-S-$, $-N(R)-$, $-C(O)-$, $-C(S)-$, $-C(O)N(R)-$,

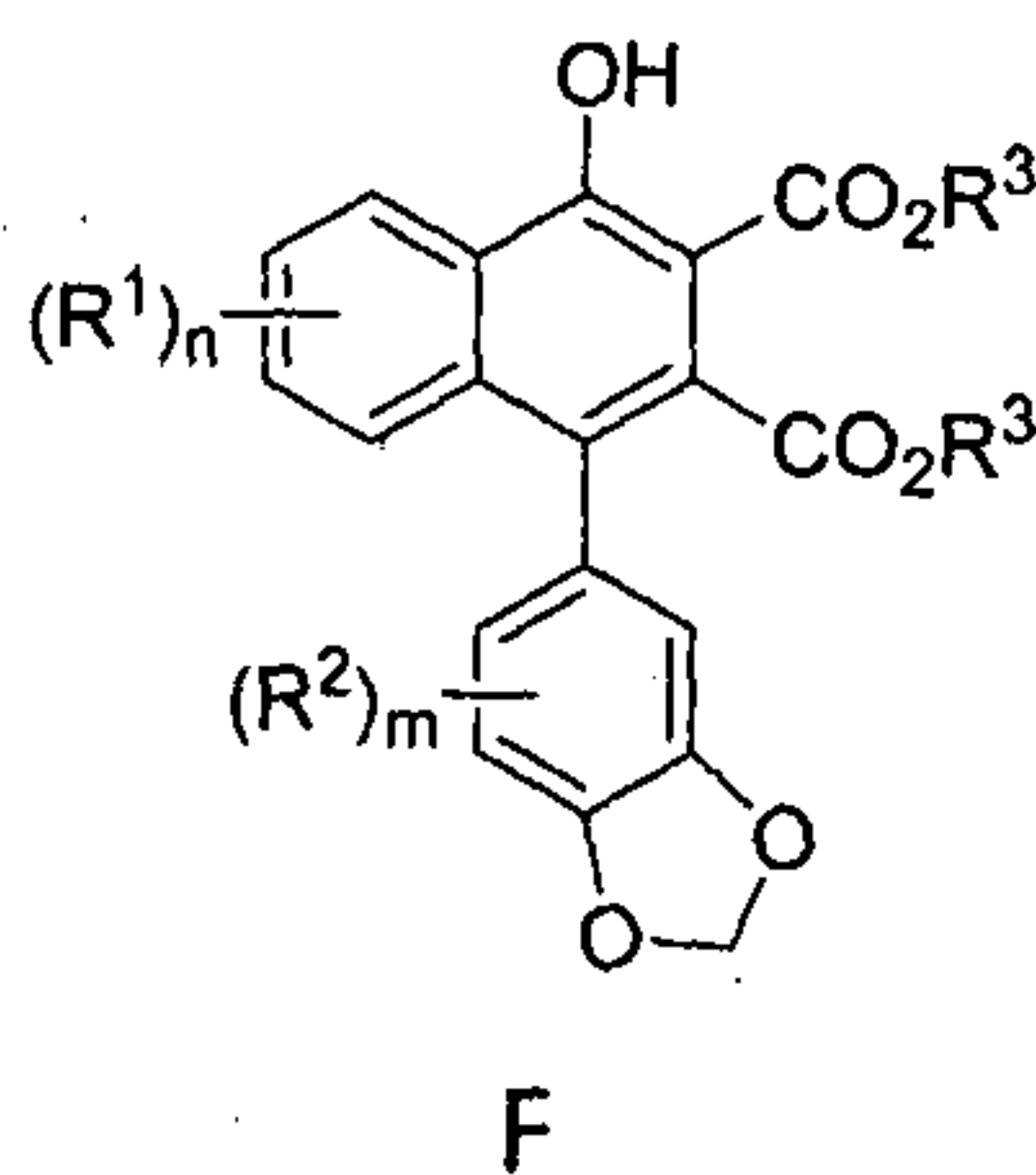
-N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-,
-S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-;

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

comprising the steps of:

(a) providing a compound of formula F:



wherein

m is 0-3;

n is 0-4;

each of R¹ and R² is independently selected from halogen, -NO₂, -CN, or -L-R;

each L is independently a covalent bond or an optionally substituted bivalent C₁₋₆ hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-,

-N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-,
-S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-;

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially
5 unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-
10 10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring
15 having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
each R³ is an optionally substituted aliphatic; and

(b) reacting said compound F with a metal hydride to form a compound of formula III.

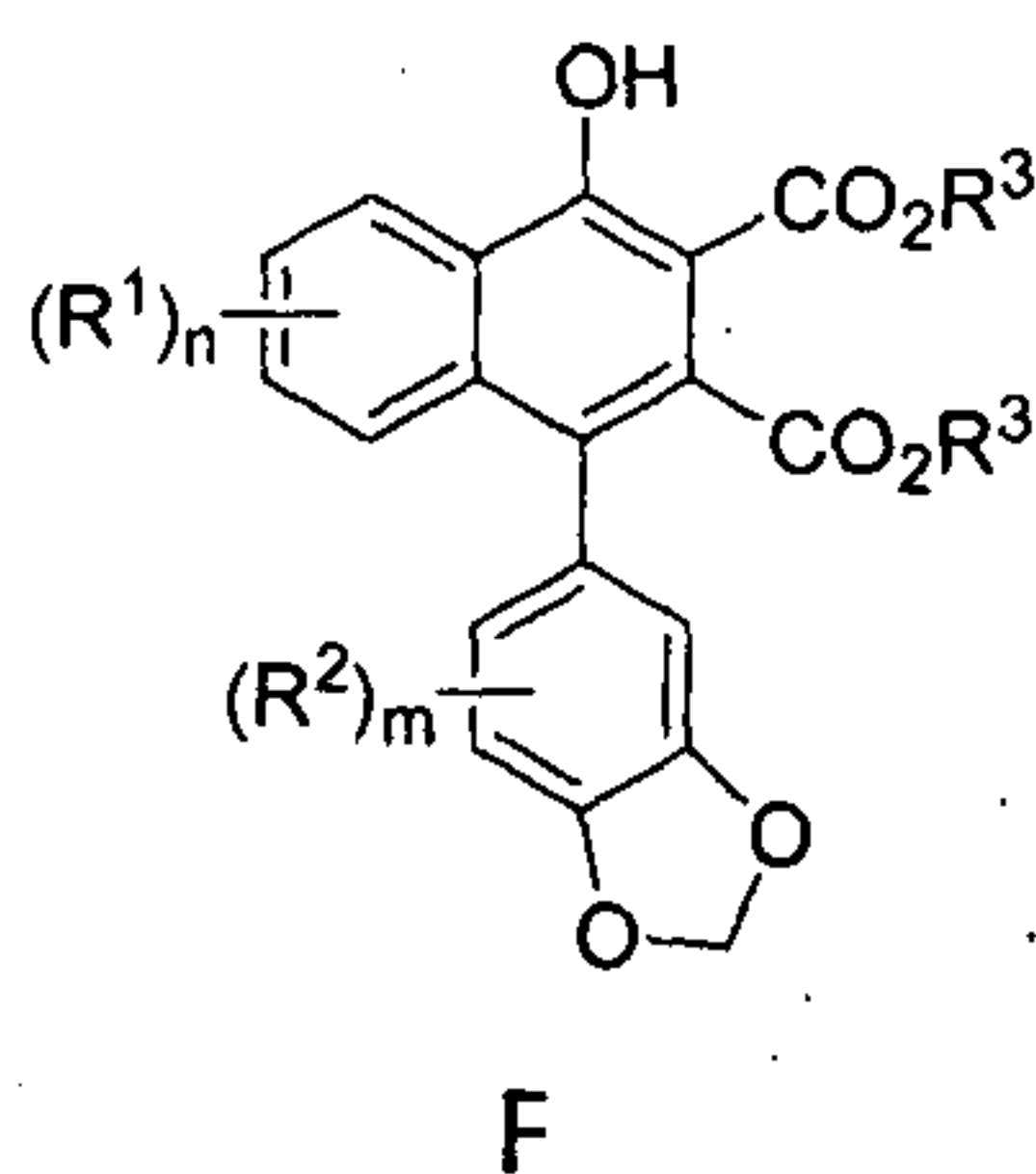
As described above, suitable metal hydrides for use in step (b) above include
20 aluminum hydrides, borohydrides and boranes. In some embodiments, the metal hydride is selected from lithium aluminum hydride, diisobutylaluminum hydride, sodium borohydride, lithium borohydride, zinc borohydride and borane. In some embodiments, the metal hydride for use in step (b) is lithium aluminum hydride. One of ordinary skill will recognize that two molar equivalents of hydride are
25 necessary to effect the reduction of the carboxylate proximal to the hydroxyl group on the naphthalene ring ("the proximal carboxylate"). One of ordinary skill will further recognize that many metal hydride reagents have two or more hydrides which may be transferred to a compound of formula F. Thus, in some embodiments, less than two molar equivalents of a metal hydride reagent is
30 required to completely reduce the proximal carboxylate.

One of ordinary skill in the art will also appreciate that the treatment of a compound of formula F with a base such as a metal hydride will result in the immediate deprotonation of the hydroxyl group. Accordingly, in some embodiments of step (b) above, a compound of formula F is treated with at least two molar equivalents of a metal hydride to provide a compound of formula III. In some embodiments of step (b) above, a compound of formula F is treated with at least two molar equivalents of lithium aluminum hydride, wherein the first equivalent of the metal hydride is consumed by the deprotonation of the hydroxyl group and the second equivalent is effective to reduce the proximal carboxylate.

One of ordinary skill in the art will recognize that reactive reagents such as metal hydrides require the use of a non polar, aprotic solvent. Suitable non polar, aprotic solvents for use in step (b) above include ethers such as diethyl ether, tetrahydrofuran, dioxane and MTBE and hydrocarbon solvents such as hexanes or cyclohexane.

In some embodiments, step S-5 is performed at a temperature range of about -10 °C to about 0 °C. In some embodiments, step S-5 is performed at room temperature.

In some embodiments, the present invention provides a method for preparing a compound of formula F:



wherein:

m is 0-3;

n is 0-4

each of R¹ and R² is independently selected from halogen, -NO₂, -CN, or -L-R;

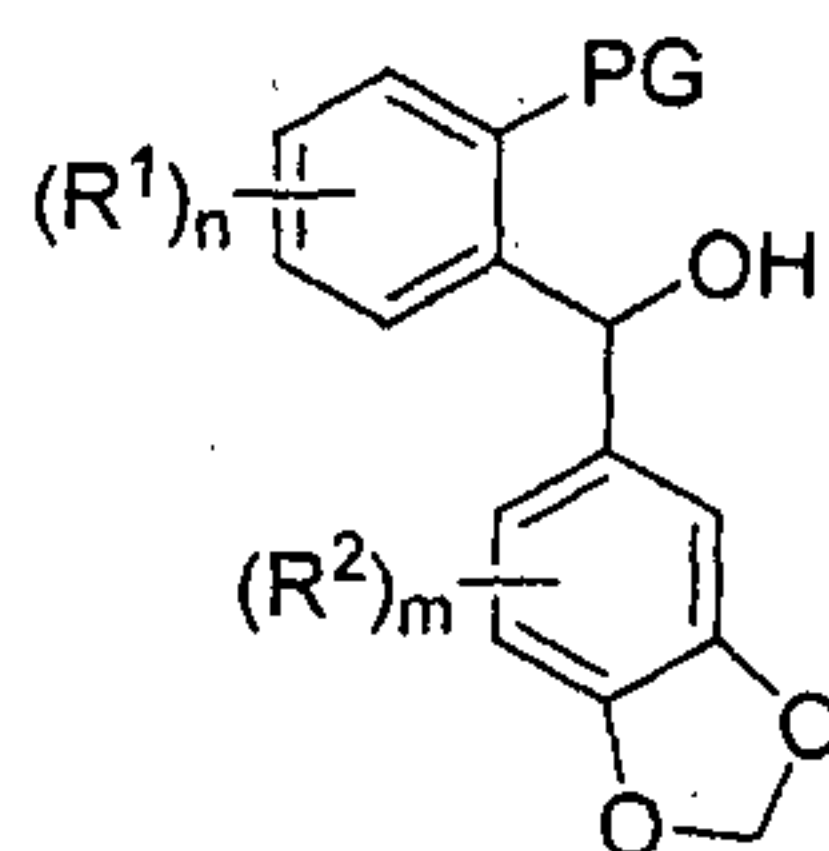
each L is independently a covalent bond or an optionally substituted bivalent C₁₋₆ hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-;

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each R³ is independently an optionally substituted C₁₋₆ aliphatic; comprising the steps of:

(a) providing a compound of formula D:



D

wherein:

m is 0-3;

n is 0-4;

each of R¹ and R² is independently selected from halogen, -NO₂, -CN, or -L-R;

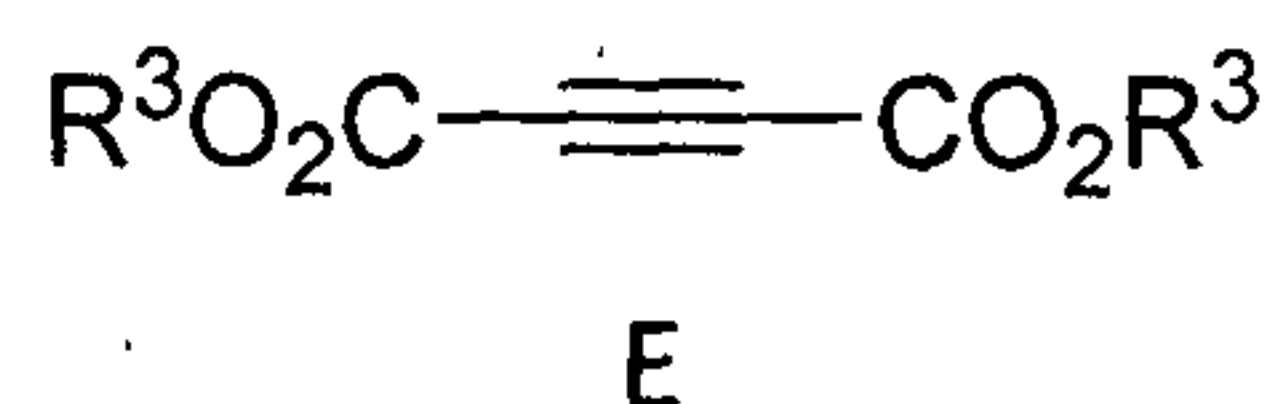
each L is independently a covalent bond or an optionally substituted bivalent C₁₋₆ hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-;

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

PG is -CH(OR³), 2-(1,3-dioxolanyl) or 2-(1,3-dioxanyl);

(b) reacting said compound of formula D with a compound of formula E:



wherein each R³ is an optionally substituted C₁₋₆ aliphatic;

(c) under conditions effective to form a compound of formula F.

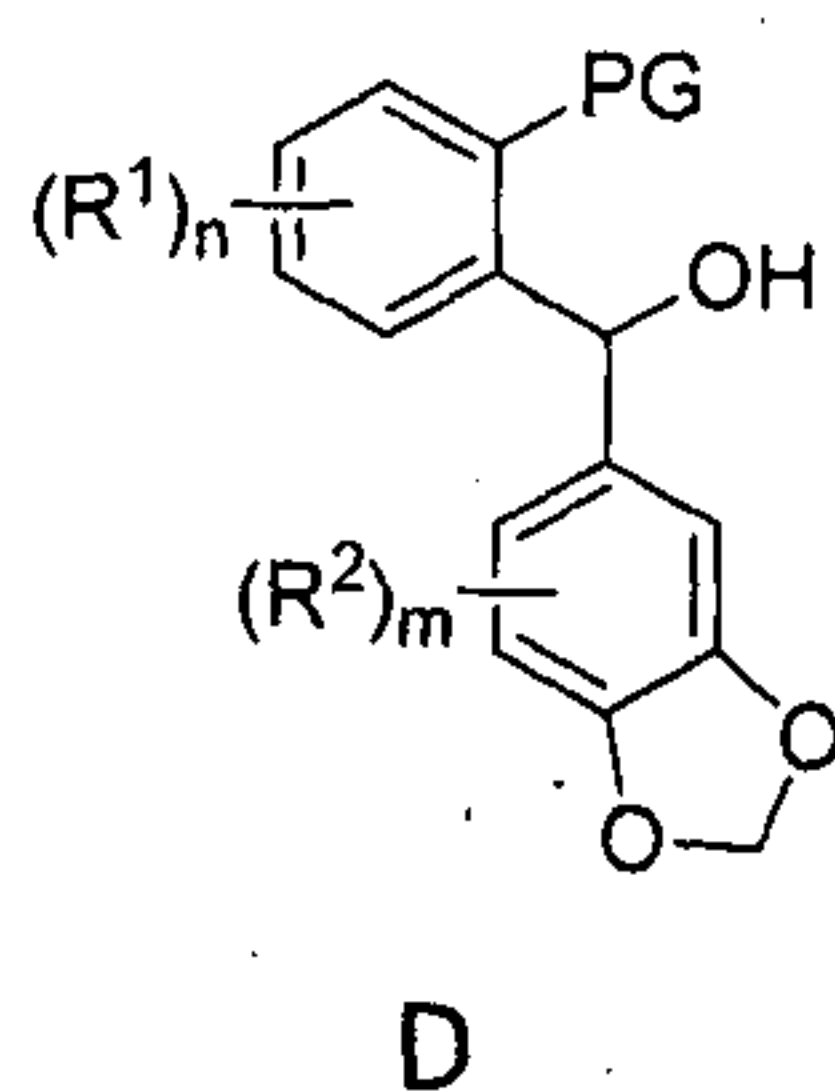
As described above, the reaction of a compound of formula D and a compound of formula E is a cyclization reaction. In particular, such a reaction is a Diels-Alder reaction. As further described above, one of ordinary skill will recognize that the diene component of the Diels-Alder reaction is an isobenzofuran, which is generated *in situ* from a compound of formula D. In some embodiments, conditions effective to generate an isobenzofuran *in situ* from a compound of

formula D include heating a compound of formula D in the presence of an acid. One of ordinary skill in the art will recognize that a variety of acids are useful to promote and/or facilitate such a reaction. Suitable acids include, without limitation, acetic acid, hydrochloric acid, p-toluenesulfonic acid, and the like. In some embodiments, a compound of formula D is treated with acetic acid.

One of ordinary skill in the art will recognize that a reaction such as the Diels-Alder reaction described above is performed at a temperature range of about 100 °C to about 200 °C. In some embodiments, step (c) above is performed using acetic acid at a temperature of about 100 °C. In some embodiments, step (c) above is performed using acetic acid at a temperature of about 120 °C. In some embodiments, step (c) above is performed using acetic acid at a temperature of about 140 °C. In some embodiments, step (c) above is performed using acetic acid at a temperature of at least 140 °C.

One of ordinary skill will appreciate that suitable solvents for use in step (c) above include those which have a boiling point at or greater than 100 °C. Suitable solvents useful in the present invention include polar, protic solvents such acetic acid and high-boiling alcohols, benzene and its derivatives (e.g. toluene, xylenes), dimethylformamide, dimethylacetamide and diglyme. In some embodiments, step (c) above is performed in acetic acid.

In some embodiments, a suitable solvent includes halogenated hydrocarbon solvents such as chloroform or methylene chloride, ethers such as diethyl ether or tetrahydrofuran and hydrocarbon solvents such as hexanes or cyclohexane. In some embodiments, one or more reagents may perform as a suitable solvent. In certain embodiments, the present invention provides a method for preparing a compound of formula D:



wherein:

m is 0-3;

n is 0-4

each of R^1 and R^2 is independently selected from halogen, $-\text{NO}_2$, $-\text{CN}$, or $-\text{L-R}$;

5 each L is independently a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by $-\text{O}-$, $-\text{S}-$, $-\text{N(R)}-$, $-\text{C(O)}-$, $-\text{C(S)}-$, $-\text{C(O)N(R)}-$, $-\text{N(R)C(O)N(R)}-$, $-\text{N(R)C(O)}-$, $-\text{N(R)C(O)O}-$, $-\text{OC(O)N(R)}-$, $-\text{S(O)}-$, $-\text{S(O)}_2-$, $-\text{S(O)}_2\text{N(R)}-$, $-\text{N(R)S(O)}_2-$, $-\text{OC(O)}-$ or $-\text{C(O)O}-$;

10 each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2
15 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

20 two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

PG is selected from $-\text{CH}(\text{OR}^8)_2$, $-\text{CH}(\text{SR}^8)_2$, 2-(1,3-dioxolanyl), 2-(1,3-dioxanyl), 2-(1,3-dithiolanyl) or 2-(1,3-dithianyl); and

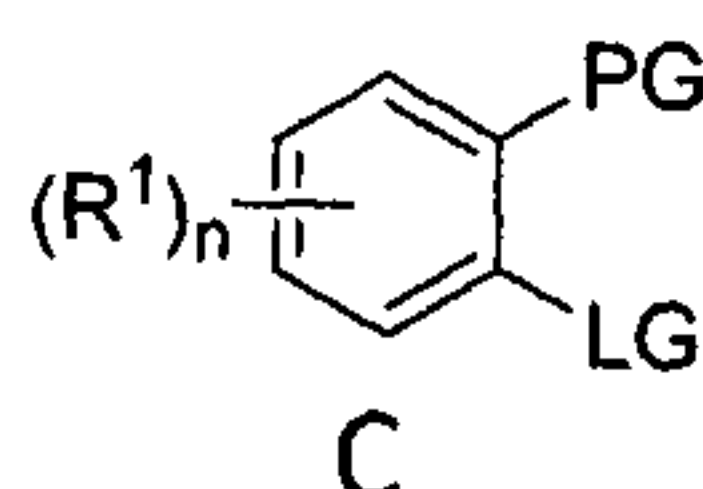
R^8 is an optionally substituted C_{1-6} aliphatic group;

comprising the steps of:

(a) providing a solution of:

a compound of formula C:

30



wherein

n is 0-4;

each R¹ is independently selected from halogen, -NO₂, -CN, or -L-R;

5 each L is independently a covalent bond or an optionally substituted bivalent C₁₋₆ hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-;

10 each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2
15 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

20 two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

PG is selected from -CH(OR⁸)₂, -CH(SR⁸)₂, 2-(1,3-dioxolanyl), 2-(1,3-dioxanyl), 2-(1,3-dithiolanyl) or 2-(1,3-dithianyl); R⁸ is an optionally substituted C₁₋₆ aliphatic
25 group; and

LG is halogen;

(b) sonicating said solution; and

(c) reacting said solution with an aryl aldehyde solution and an alkyl lithium
30 reagent under sonication to form a compound of formula D.

As described above, the reaction of an aryl halide of formula C with an alkyl lithium reagent to form an aryl lithium anion is generally performed at low

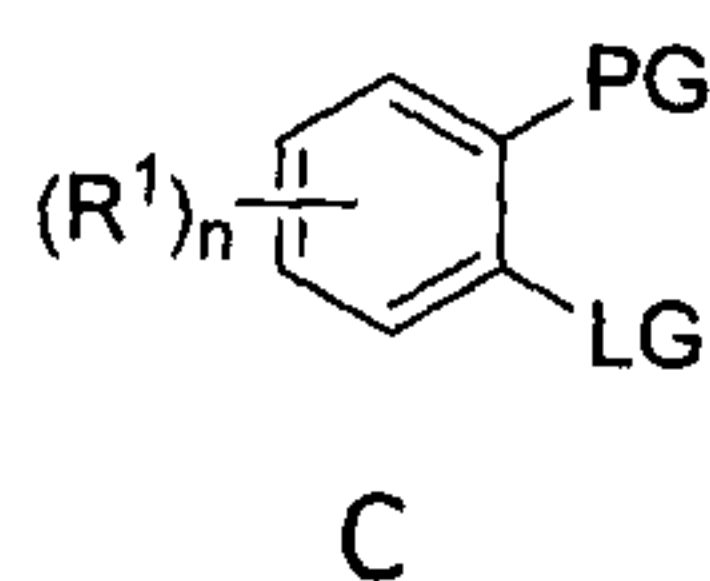
temperatures to avoid unwanted side reactions. Such temperatures are typically -65°C to about -80°C. In some embodiments, step (c) above is performed at temperatures above -65°C. In some embodiments, step (c) above under sonication is performed at temperatures within the range of about 0°C to about 25°C. In some embodiments, step (c) above is performed at room temperature for example about 25°C to about 35°C under sonication.

As described above, suitable alkyl lithium reagents include *n*-butyllithium, *sec*-butyllithium and *tert*-butyllithium. In some embodiments, the alkyl lithium reagent *n*-butyllithium.

In some embodiments, the present invention provides a method of preparing a compound of formula D comprising the steps of (a) providing a solution of a compound of formula C, (b) sonicating said solution, and (c) reacting said solution with an aryl aldehyde solution and an alkyl lithium reagent to form a compound of formula D. In some embodiments, the aryl aldehyde is pipronal.

One of ordinary skill will appreciate that such reactions require the use of non polar, aprotic solvents. Suitable non polar, aprotic solvents include ethers such as diethyl ether, Methyl Tertiary Butyl Ether (MTBE), tetrahydrofuran or dioxane or hydrocarbon solvents such as hexanes or cyclohexane.

In some embodiments, the present invention provides a method for preparing a compound of formula C:



wherein:

each R^1 is independently selected from halogen, $-\text{NO}_2$, $-\text{CN}$, or $-\text{L-R}$;

each L is independently a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})\text{N}(\text{R})-$, $-\text{N}(\text{R})\text{C}(\text{O})\text{N}(\text{R})-$, $-\text{N}(\text{R})\text{C}(\text{O})-$, $-\text{N}(\text{R})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R})-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R})-$, $-\text{N}(\text{R})\text{S}(\text{O})_2-$, $-\text{OC}(\text{O})-$ or $-\text{C}(\text{O})\text{O}-$;

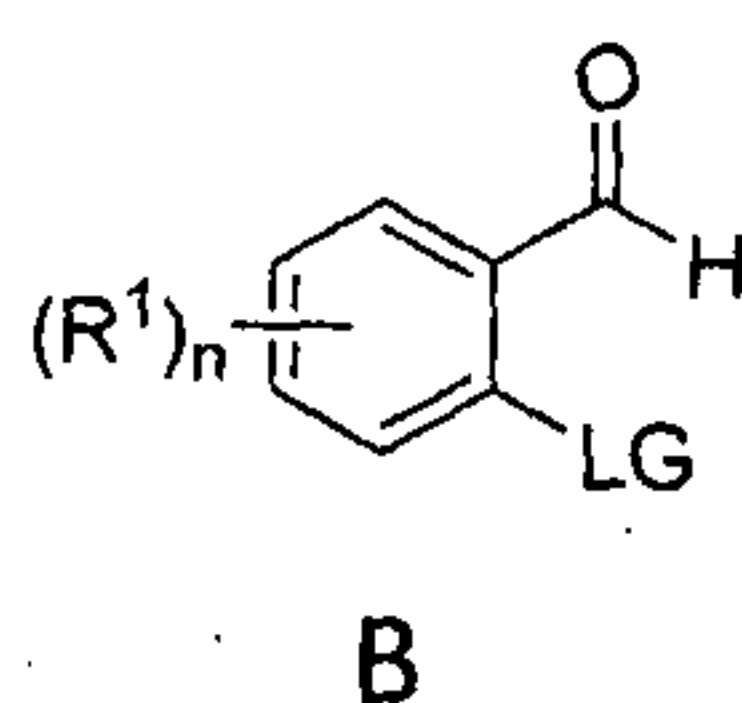
each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

PG is selected from -CH(OR⁸)₂, -CH(SR⁸)₂, 2-(1,3-dioxolanyl), 2-(1,3-dioxanyl), 2-(1,3-dithiolanyl) or 2-(1,3-dithianyl); R⁸ is C₁₋₆ aliphatic; and LG is halogen;

comprising the steps of:

(a) providing a compound of formula B:



wherein:

n is 0-4;

each R¹ is independently selected from halogen, -NO₂, -CN, or -L-R;

each L is independently a covalent bond or an optionally substituted bivalent C₁₋₆ hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-;

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

LG is halogen, and

(b) reacting said compound of formula B with an alcohol to form a compound of formula C, wherein the alcohol is selected from:

HOR⁸, ethylene glycol, HSR⁸, 1,3-propanediol, 1,2-ethanedithiol or 1,3-propanedithiol,

wherein R⁸ is C₁₋₆ aliphatic.

In some embodiments, step (b) above is performed using a catalytic amount of an acid. Suitable catalytic acids include both mineral acids, such as hydrochloric acid, and organic acids, such as p-toluenesulfonic acid. In some embodiments, step (b) is performed using p-toluenesulfonic acid.

In some embodiments, step (b) above is performed using methanol or ethanol. Thus, in some embodiments, a compound of formula B is reacted with methanol or ethanol to provide a compound of formula C wherein PG is -CH(OCH₃)₂ or -CH(OCH₂CH₃)₂, respectively. In some embodiments, a compound of formula B is reacted with ethylene glycol to provide a compound of formula C wherein PG is -2-(1,3-dioxolanyl). In some embodiments, a compound of formula B is reacted with 1,3-propanediol to provide a compound of formula C wherein PG is -2-(1,3-

dioxanyl). In some embodiments, a compound of formula B is reacted with CH_3SH to provide a compound of formula C wherein PG is $-\text{CH}(\text{SCH}_3)_2$. In some embodiments, a compound of formula B is reacted with $\text{CH}_3\text{CH}_2\text{SH}$ to provide a compound of formula C wherein PG is $-\text{CH}(\text{SCH}_2\text{CH}_3)_2$.

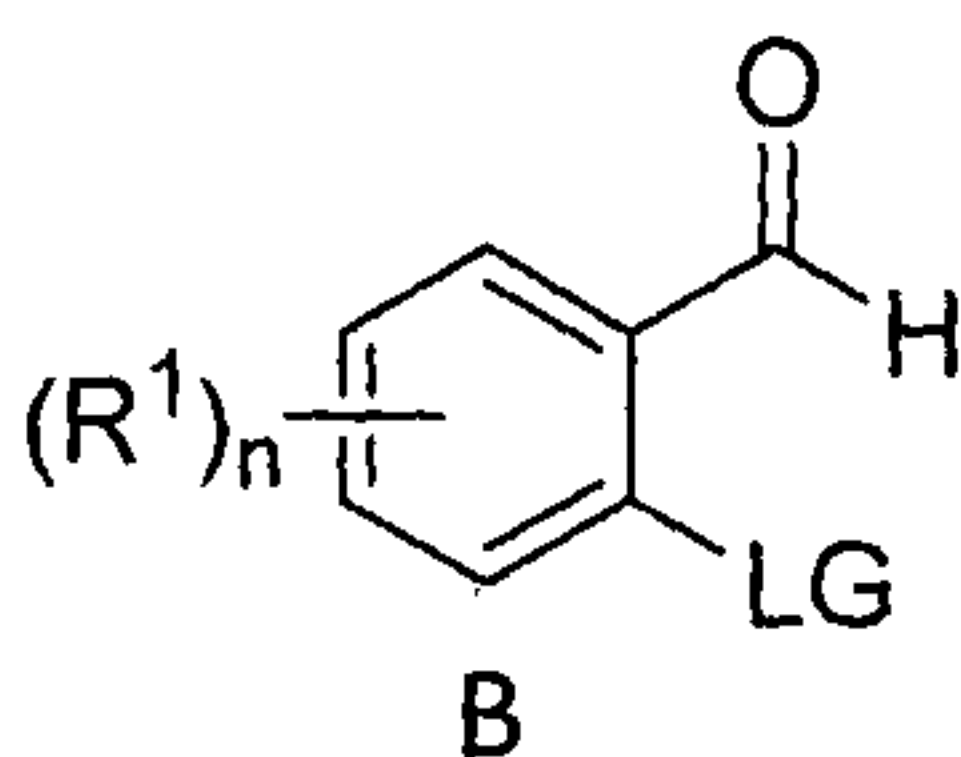
- 5 In some embodiments, a compound of formula B is reacted with 1,2-ethanedithiol to provide a compound of formula C wherein PG is 1,3-dithiolanyl. In some embodiments, a compound of formula B is reacted with 1,3-propanedithiol to provide a compound of formula C wherein PG is 1,3-dithianyl.

10 A suitable solvent or solvent mixture is selected such that the solvent solubilizes the reaction components and/or facilitates the progress of the reaction. Suitable solvents include halogenated hydrocarbon solvents (e.g. chloroform or methylene chloride), benzene and derivatives thereof (e.g., toluene, xylenes), ethers (e.g. MTBE, tetrahydrofuran and dioxane), and the like. In some embodiments, a suitable solvent is a polar, aprotic solvent such as tetrahydrofuran or dioxane.

- 15 According to one embodiment, the alcohol of step (b) above performs as the reaction solvent. When ethylene glycol or 1,3-propanediol is used as a solvent, one of ordinary skill in the art will appreciate that the reaction mixture is poured into a non-miscible organic solvent such as ethyl acetate or methylene chloride. The non-miscible organic layer is then washed with water to remove the excess
20 alcohol.

In some embodiments, the reaction of a compound of formula B with an alcohol in the presence of catalytic acid is heated. In some embodiments, the reaction mixture is refluxed. In some embodiments, step S-2 is heated to about 90°C to about 95°C .

- 25 In some embodiments, the present invention provides a method for preparing a compound of formula B:



wherein

n is 0-4;

each R¹ is independently selected from halogen, -NO₂, -CN, or -L-R;

each L is independently a covalent bond or an optionally substituted bivalent C₁₋₆

5 hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-;

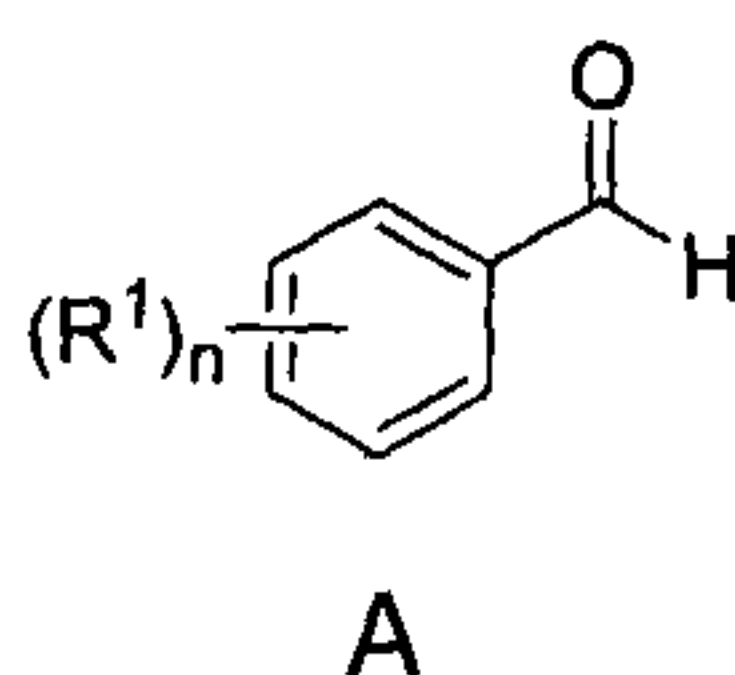
each R is independently hydrogen or an optionally substituted group selected
10 from C₁₋₆ aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2
15 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their
20 intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

LG is halogen,

comprising the steps of:

25 (a) providing a compound of formula A:



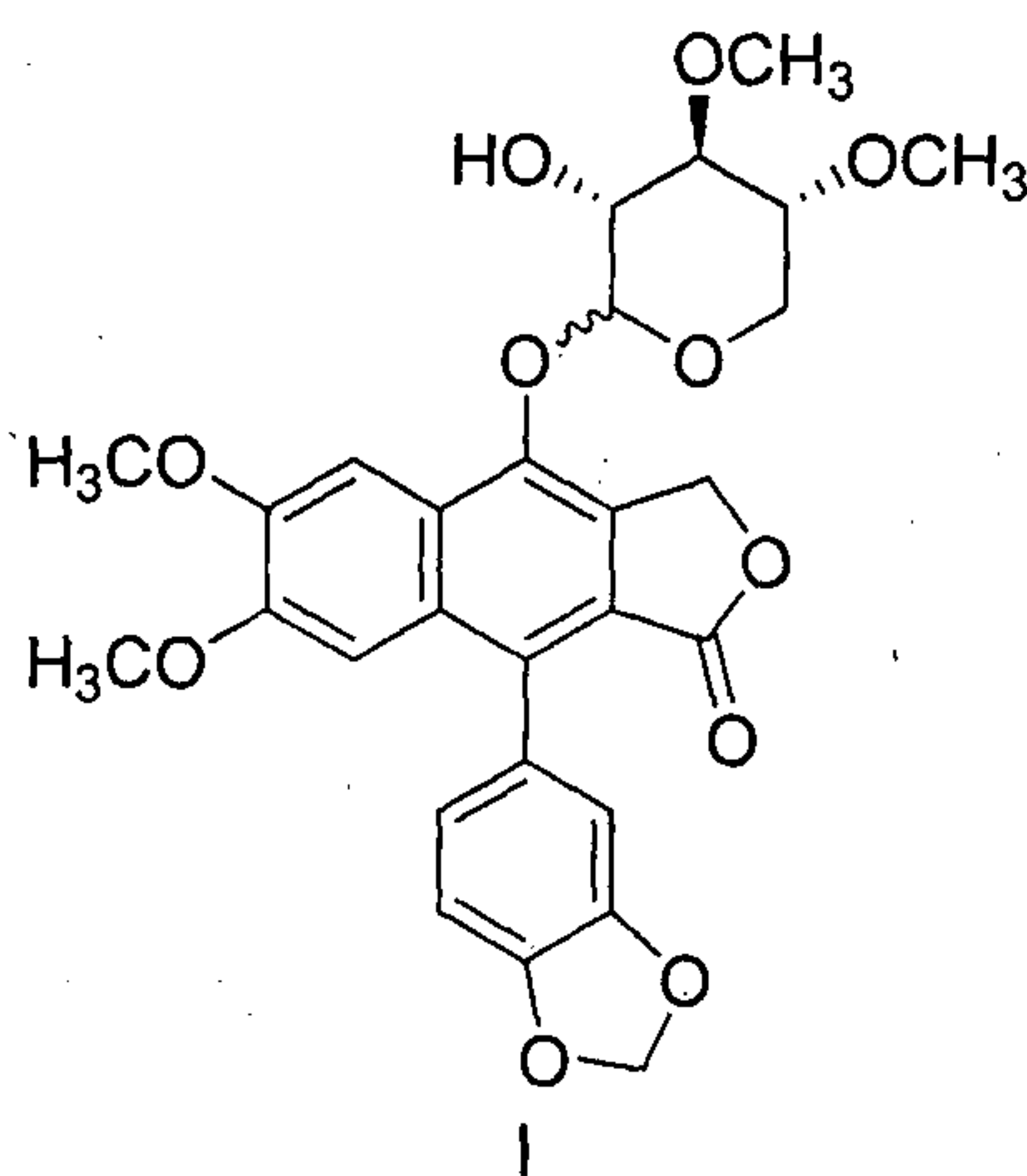
and

(b) reacting said compound of formula A with a dihalogen to form a compound of
30 formula B.

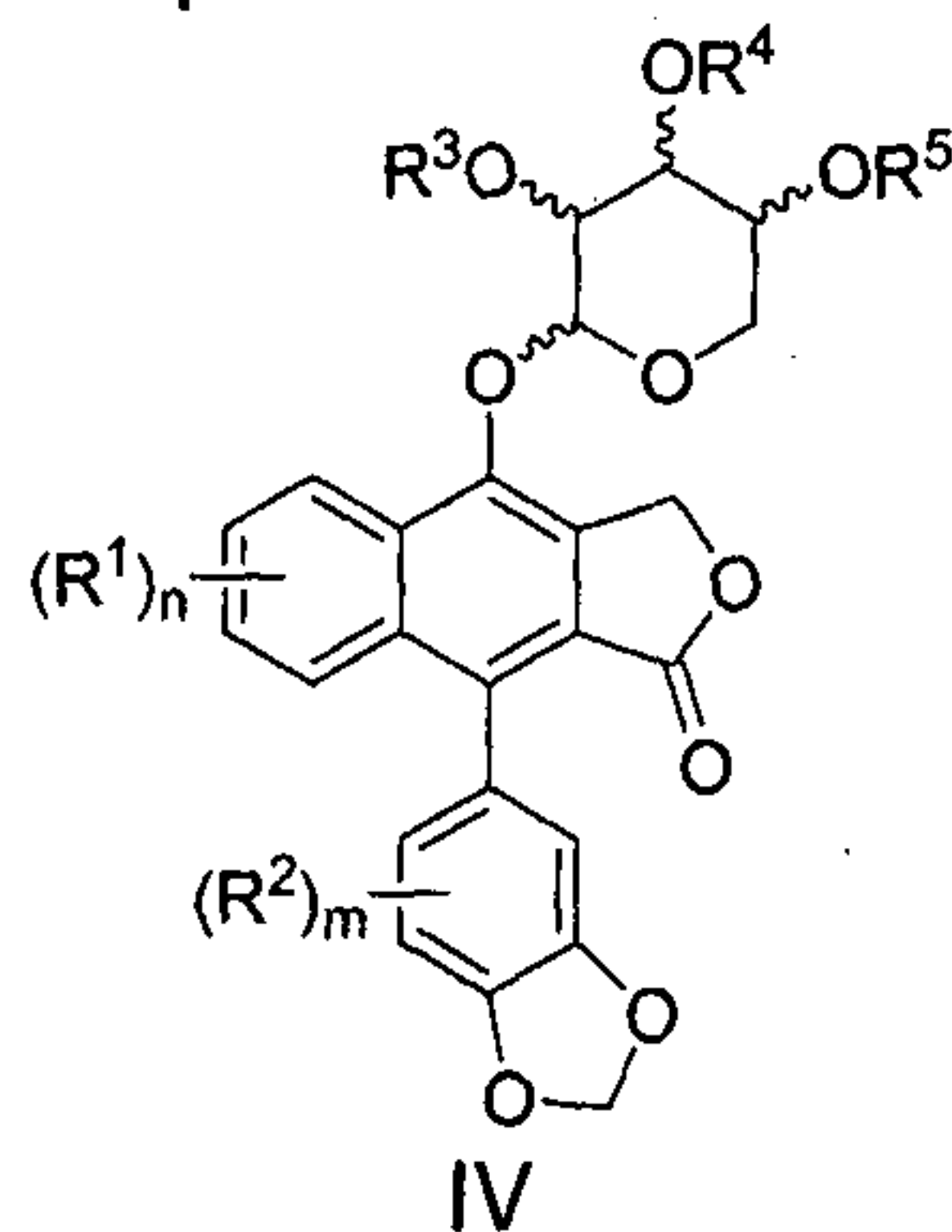
In some embodiments, a compound of formula A is reacted with chlorine gas, bromine or iodine. In some embodiments, a compound of formula A is reacted with bromine. In some embodiments, a compound of formula A is reacted with hydrobromic acid. In some embodiments, a compound of formula A is reacted with N-bromosuccinimide. In some embodiments, step (b) is performed in a polar, protic solvent. Suitable polar, protic solvents include alcohols (e.g. methanol, ethanol, isopropanol), organic acids (acetic acid, formic acid, propionic acid) and water. In some embodiments, a compound of formula A is dissolved in acetic acid and treated with bromine.

One of ordinary skill in the art will recognize that, in some circumstances, electrophilic aromatic substitutions require elevated temperatures. In some embodiments, a compound of formula A is dissolved in acetic acid and treated with bromine at room temperature.

In one of the embodiment, the present invention provides a method for preparing Cleistanthin A (I):



comprising a step of reacting compound of formula IV:



under conditions effective to form Cleistanthin A (I). In one specific embodiment, the effective conditions include treating compound of formula IV with an alkali and a solvent to form compound of formula I. One of ordinary skill will further recognize that many alkalis and solvents can be used in this reaction. In a preferred embodiment alkali is potassium carbonate and solvent is methanol.

The present invention provides an improved method for preparing Cleistanthin A, derivatives thereof and intermediates thereto, which can be carried out in a shorter duration and wherein the metallation step is carried out at an ordinary temperature. The metallation step is carried out in much shorter duration of 1-3 hours, preferably metallation step is carried out in 0.5 – 1 hour, thus shortening the period of the entire synthesis method and rendering it efficient.

The following examples serve to illustrate the invention without liming the scope thereof:

EXAMPLES

15 Synthesis of (2-(1,3-dioxolan-2-yl)4,5-dimethoxyphenyl)(benzo[d][1,3] dioxol-5-yl)methanol - General Procedure:

A clean and dry four necked round bottom flask equipped with a thermometer pocket, water condenser and dropping funnel was placed in a sonicator. The flask was charged with dry tetrahydrofuran and 2-(2-bromo-4,5-dimethoxy)-1,3-dioxolane. The reaction was sonicated at room temperature. Pipronal dissolved in tetrahydrofurna was slowly charged via dropping funnel. n-Butyllithium was simultaneously charged to the reaction. The reaction was maintained at room temperature for 15 minutes and monitored by TLC. Once the reaction was complete, water was added and the reaction mixture was stirred. The organic layer was separated and concentrated under vacuum. Methanol was added to the sticky residue and the flask was scratched to initiate crystallization. The solid was filtered, washed with methanol and dried in a vacuum oven at 50°C. The isolated product was obtained in 36.9% yield.

30

Comparative Example 1A

Synthesis of (2-(1, 3-Dioxolane – 2-yl) – 4, 5 – dimethoxy phenyl) (benzo(d) (1,3) dioxol – 5 – yl) – methanol (carried out as per known method):

To a flame dried four necked round bottom flask (100mL) were added 2-(2-bromo-4, 5-dimethoxyphenyl)-1, 3-dioxolane (formula VII; 1.0 g, 0.9934 mole) and anhydrous tetrahydrofuran (25mL) under nitrogen atmosphere. The flask was cooled to -78°C in dry ice-acetone bath; n- Butyllithium (5.3mL, 0.005 mole) was added drop wise with stirring at -78°C and stirred for 15 minutes. A separate flame dried flask was charged with Piperonal (0.517g, 1.0034 mole) and dry tetrahydrofuran (6mL). The Piperonal solution was cannulated to the reaction mixture during 30 minutes and after the addition, reaction mixture was slowly warmed to room temperature and further stirred for 2.5 hours. After the consumption of all bromine compound, as confirmed by TLC (50:50, EtOAc: Hexane), reaction mixture was quenched by the addition of saturated ammonium chloride solution and extracted with ethyl acetate (3 x 20mL). All the organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated to yield 80% of crude product. The crude product was purified by column chromatography using column of 2 meter length, diameter 2.5 cm and filled with silica gel 60-120 (column chromatographic grade). Finally column eluted with EtOAc: Hexane (50:50), to get pure product (2-(1, 3-Dioxolane – 2-yl) – 4, 5 – dimethoxy phenyl) (benzo(d) (1,3) dioxol – 5 – yl) – methanol with 30% yield. The total time required was about 7 hours.

The NMR details of compound (2-(1, 3-Dioxolane – 2-yl) – 4, 5 – dimethoxy phenyl) (benzo(d) (1,3) dioxol – 5 – yl) – methanol were as follows:

¹HNMR (300 MHz, CDCl₃): δ = 7.14 (s, 1H), 6.90-6.78(m,4H), 6.11(s,1H),5.96(s,2H),5.90(s,1H),4.19(t,2H,J=6.6Hz), 4.16(t,2H,J=6.8Hz),4.02(s,3H),3.81(s,3H),3.17(s, 1H). ¹³CNMR (300 MHz, CDCl₃): δ=149.42, 148.11, 147.57, 146.58, 136.95, 135.43, 126.83, 121.04, 119.69, 111.48, 109.50, 107.92, 107.26, 101.65, 100.93, 71.34, 65.05, 55.94, 55.89.

Example 1

Synthesis of (2-(1, 3-Dioxolane – 2-yl) – 4, 5 – dimethoxy phenyl) (benzo(d) (1,3) dioxol – 5 – yl) – methanol (carried out as per the present invention):

A clean, dry four neck round bottom flask equipped with mechanical stirrer,
 5 thermometer pocket, condenser, guard tube and dropping funnel was arranged
 on sonicator. It was charged with dry tetrahydrofuran (120 mL) and 2-(2-bromo-4,
 5-dimethoxy)-1,3-dioxalane (5 gm, 0.017 mol). Said reaction mass was sonicated
 at temperature 25°C. Pipronal (3g, 0.019 mol) previously dissolved in 10 mL
 tetrahydrofuran, was added by dropping funnel, simultaneously n-Butyllithium
 10 (20 g, 0.3125 mol) was slowly added to the reaction mixture under sonication at
 room temperature within 45 minutes. Following the addition, the reaction was
 monitored by TLC (50:50, EtOAc: Hexane), saturated ammonium chloride solution
 was added and extracted with ethyl acetate (2 X 30mL). After completion of the
 reaction, 20 mL water was added, all organic layers were separated dried over
 15 anhydrous sodium sulphate, filtered and concentrated under vacuum to afford a
 sticky solid. Methanol (10 mL) was added and the flask was scratched to initiate
 crystallization. 2.3 g solid was isolated and dried under vacuum at 50 °C. The
 isolated product was obtained in 37.55% yield. The NMR details of compound (2-
 (1, 3-Dioxolane – 2-yl) – 4, 5 – dimethoxy phenyl) (benzo(d) (1,3) dioxol – 5 – yl) –
 20 methanol were as below:

¹HNMR (300 MHz, CDCl₃): δ = 7.14 (s, 1H), 6.90-6.78(m,4H),
 6.11(s,1H),5.96(s,2H),5.90(s,1H),4.19(t,2H,J=6.6Hz),
 4.16(t,2H,J=6.8Hz),4.02(s,3H),3.81(s,3H),3.17(s, 1H). ¹³CNMR (300 MHz, CDCl₃):
 δ= 149.42, 148.11, 147.57, 146.58, 136.95, 135.43, 126.83, 121.04, 119.69,
 25 111.48, 109.50, 107.92, 107.26, 101.65, 100.93, 71.34, 65.05, 55.94, 55.89.

Example 2

Synthesis of (2-(1, 3-Dioxolane – 2-yl) – 4, 5 – dimethoxy phenyl) (benzo(d) (1,3) dioxol – 5 – yl) – methanol (carried out as per the present invention):

30 A clean, dry four neck round bottom flask equipped with mechanical stirrer,
 thermometer pocket, condenser, guard tube and dropping funnel was arranged
 on sonicator. It was charged with dry tetrahydrofuran (120 mL) and 2-(2-bromo-4,

5-dimethoxy)-1,3-dioxalane (5 gm, 0.0172 mol). Said reaction mass was sonicated at temperature 25°C. Pipronal (2.55 g, 0.0169 mol) previously dissolved in 10 mL tetrahydrofuran, was added by dropping funnel, simultaneously n-Butyllithium (3.96 g, 0.061 mole) was slowly added to the reaction mixture under sonication at room temperature within 60 minutes. Following the addition, the reaction was monitored by TLC (50:50, EtOAc: Hexane), after the consumption of all bromine compound, saturated ammonium chloride solution was added and extracted with ethyl acetate (3 X 30 mL). After completion of the reaction, 20 mL water was added, all organic layers were separated dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to afford a sticky solid. Methanol (30 mL) was added and the flask was scratched to initiate crystallization. 2.3 g solid was isolated and dried under vacuum at 50 °C. The isolated product was obtained in 36.55% yield.

The NMR details of compound (2-(1, 3-Dioxolane – 2-yl) – 4, 5 – dimethoxy phenyl) (benzo(d) (1,3) dioxol – 5 – yl) – methanol were as below:

¹HNMR (300 MHz, CDCl₃): δ = 7.14 (s, 1H), 6.90-6.78(m,4H), 6.11(s,1H),5.96(s,2H),5.90(s,1H),4.19(t,2H,J=6.6Hz), 4.16(t,2H,J=6.8Hz),4.02(s,3H),3.81(s,3H),3.17(s, 1H). ¹³CNMR (300 MHz, CDCl₃): δ= 149.42, 148.11, 147.57, 146.58, 136.95, 135.43, 126.83, 121.04, 119.69, 111.48, 109.50, 107.92, 107.26, 101.65, 100.93, 71.34, 65.05, 55.94, 55.89.

Example 3

Synthesis of (2-(1, 3-Dioxolane – 2-yl) – 4, 5 – dimethoxy phenyl) (benzo(d) (1,3) dioxol – 5 – yl) – methanol (carried out as per the present invention):

A clean, dry four neck round bottom flask equipped with mechanical stirrer, thermometer pocket, condenser, guard tube and dropping funnel was arranged on sonicator. It was charged with dry tetrahydrofuran (120 mL) and 2-(2-bromo-4, 5-dimethoxy)-1,3-dioxalane (5 gm, 0.0172 mol). Said reaction mass was sonicated at temperature 30°C. Pipronal (2.55 g, 0.0169 mol) previously dissolved in 10 mL tetrahydrofuran, was added by dropping funnel, simultaneously n-Butyllithium (3.96 g, 0.061 mole) was slowly added to the reaction mixture under sonication at room temperature within 50 minutes. Following the addition, the reaction was

monitored by TLC (50:50, EtOAc: Hexane), after the consumption of all bromine compound, saturated ammonium chloride solution was added and extracted with ethyl acetate (3 X 30 mL). After completion of the reaction, 20 mL water was added, all organic layers were separated dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to afford a sticky solid. Methanol (30 mL) was added and the flask was scratched to initiate crystallization. 2.3 g solid was isolated and dried under vacuum at 50 °C. The isolated product was obtained in 37% yield.

The NMR details of compound (2-(1, 3-Dioxolane – 2-yl) – 4, 5–dimethoxy phenyl) (benzo(d) (1,3) dioxol – 5 – yl) – methanol were as below:

¹HNMR (300 MHz, CDCl₃): δ = 7.14 (s, 1H), 6.90-6.78(m,4H), 6.11(s,1H),5.96(s,2H),5.90(s,1H),4.19(t,2H,J=6.6Hz), 4.16(t,2H,J=6.8Hz),4.02(s,3H),3.81(s,3H),3.17(s, 1H). ¹³CNMR (300 MHz, CDCl₃): δ= 149.42, 148.11, 147.57, 146.58, 136.95, 135.43, 126.83, 121.04, 119.69, 111.48, 109.50, 107.92, 107.26, 101.65, 100.93, 71.34, 65.05, 55.94, 55.89.

Example 4

Synthesis of Cleistanthin A using (2-(1, 3-Dioxolane – 2-yl) – 4, 5 – dimethoxy phenyl) (benzo(d) (1,3) dioxol – 5 – yl) – methanol (prepared as per the present invention):

Sealed tube was charged with (2-(1, 3-Dioxolane – 2-yl) – 4, 5 – dimethoxy phenyl) (benzo(d) (1,3) dioxol – 5 – yl) – methanol (prepared as per any one of the examples 1-3) (0.30 g, 0.833 mmole), diethyl acetylenedicarboxylate (0.141 g, 0.833 mole), dichloromethane (0.4 mL) and glacial acetic acid (0.242 mL) and mixture was heated at 140 °C for 1 hour. After completion of reaction as judged by TLC (50:50, EtOAc: Hexane), reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), washed with 5 % sodium bicarbonate solution (3 x 10 mL), organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude reaction mass was purified by flash column chromatography over silica gel using EtOAc:hexane (15:85) to afford diethyl 1-(3',4'-methylenedioxyphenyl)-4-hydroxy-6,7-dimethoxynaphthalene-2,3-dicarboxylate as white solid 0.3 g (75 %).

Two necked round bottom flask was charged with lithium aluminium hydride (0.032 g, 0.852 mmol) and anhydrous tetrahydrofuran (4 mL) and the mixture was cooled to 0°C with stirring. To this suspension, a solution of diethyl 1-(3',4'-methylenedioxyphenyl)-4-hydroxy-6,7-dimethoxynaphthalene-2,3-dicarboxylate
5 (0.200 g, 0.426 mmol) in tetrahydrofuran (4 mL) was added drop wise and stirring was continued for 2 hours. After completion of reaction as judged by TLC (1:9, MeOH:DCM), reaction mixture was quenched with saturated sodium sulfate solution and extracted with n-butanol (4 x 20 mL). Organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.
10 The crude residue was purified by flash column chromatography over silica gel to give yellow solid 9-(3',4'-Methylenedioxyphenyl)-4-hydroxy-6,7-dimethoxynaphtho[2,3-c]furan-1(3H)-one 0.07 g (85 %).

To a flame dried three necked round bottom flask (250 mL), 9-(3',4'-methylenedioxyphenyl) - 4-hydroxy - 6,7-dimethoxynaphtho[2, 3-c] furan-1(3H)-
15 one compound (1.2 g 0.0031 mole), and methylene dichloride (100 mL) were added and stirred to dissolve completely. Then 2-O-Acetyl-3,4-dimethoxy- α -D-bromoxylopyranose (1.8 g , 0.0063 mole), tetra butyl ammonium bromide (0.49 g , 0.00151 mole) and 1 N sodium hydroxide solution (4 mL) were added in above solution. Reaction mass was kept for digestion under stirring for 2 hours,
20 conversion was checked by TLC (MeOH:MDC, 0.5:9.5) and the conversion if found unconverted then digestion continued till conversion was complete. After completion of reaction, the reaction mass was washed with 1% sodium bicarbonate solution. After layer separation, methylene dichloride was concentrated to give solid 1.62 gms (yield 55%) of Cleistanthin A acetate.

25 In a clean dry three necked round bottom flask cleistanthin A acetate (1.26g, 0.0027 mole), potassium carbonate catalytic amount (0.1g, 0.00072 mole) and methanol (100 mL) were added & stirred well for 1 Hr at temperature 25°C. Reaction was monitored by TLC and HPLC. After completion of reaction, the reaction mass was quenched by water and extracted with ethyl acetate (2 X 30
30 mL) to get the final product. Ethyl acetate was concentrated to get pure 1.2 gm (yield 97%) of cleistanthin A.

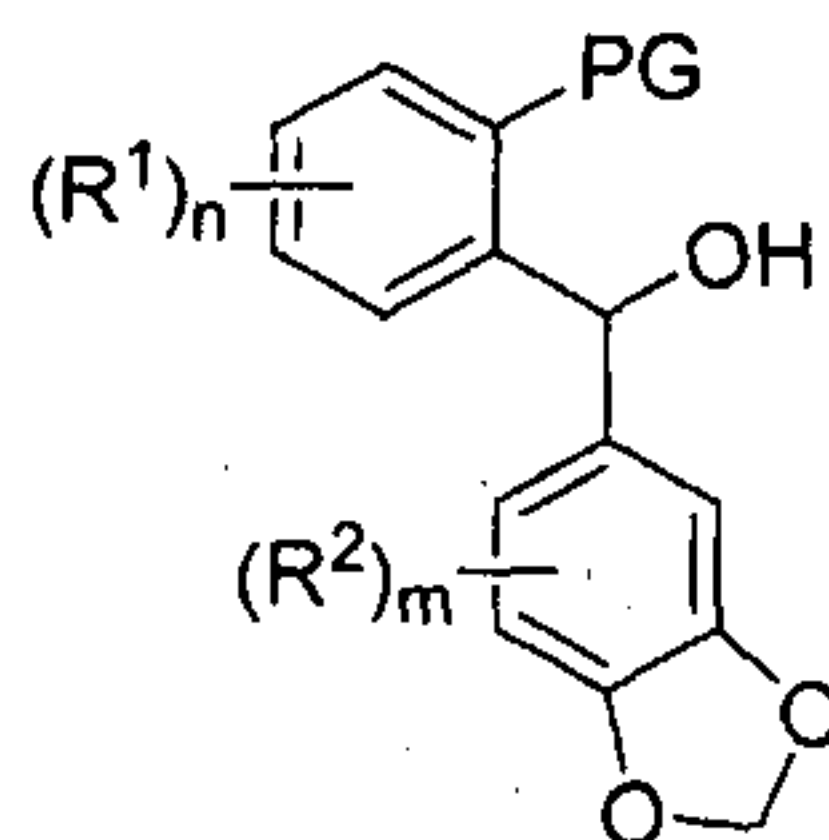
The NMR details cleistanthin A were as follows:

¹HNMR (CDCl₃, 300 MHz): δ = 7.92 (s, 1H), 7.05 (d, 1H, J = 1.5 Hz), 6.94 (dd, 1H, J = 1.2, 7.8 Hz), 6.83-6.78 (m, 2H), 6.07 (d, 1H, J = 14.1 Hz), 6.06 (d, 1H, J = 14.4 Hz), 5.49 (d, 1H, J = 14.7 Hz), 5.42 (d, 1H, J = 14.7 Hz), 5.10 (d, 1H, J = 5.7 Hz), 4.10 (dd, 1H, J = 2.4, 12.0 Hz), 4.04 (s, 3H), 3.95-3.88 (m, 1H), 3.80 (s, 3H), 3.68 (s, 3H), 3.49 (s, 3H), 3.45 (dd, 1H, J = Hz), 3.93-3.30 (m, 3H). ¹³CNMR (300 MHz, CDCl₃): δ = 169.75, 151.77, 150.15, 147.41, 144.09, 135.84, 130.61, 128.90, 128.87, 128.35, 126.79, 123.55, 119.13, 110.68, 108.10, 106.04, 103.45, 101.16, 101.02, 82.10, 78.20, 71.13*, 71.11*, 67.26, 61.13, 60.01, 57.91, 56.15, 55.76.

10

CLAIMS

1. A method for preparing a compound of formula D:



D

wherein:

m is 0-3;

n is 0-4;

each of R^1 and R^2 is independently selected from halogen, $-\text{NO}_2$, $-\text{CN}$, or $-\text{L-R}$;

each L is independently a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})\text{N}(\text{R})-$, $-\text{N}(\text{R})\text{C}(\text{O})\text{N}(\text{R})-$, $-\text{N}(\text{R})\text{C}(\text{O})-$, $-\text{N}(\text{R})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R})-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R})-$, $-\text{N}(\text{R})\text{S}(\text{O})_2-$, $-\text{OC}(\text{O})-$ or $-\text{C}(\text{O})\text{O}-$;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

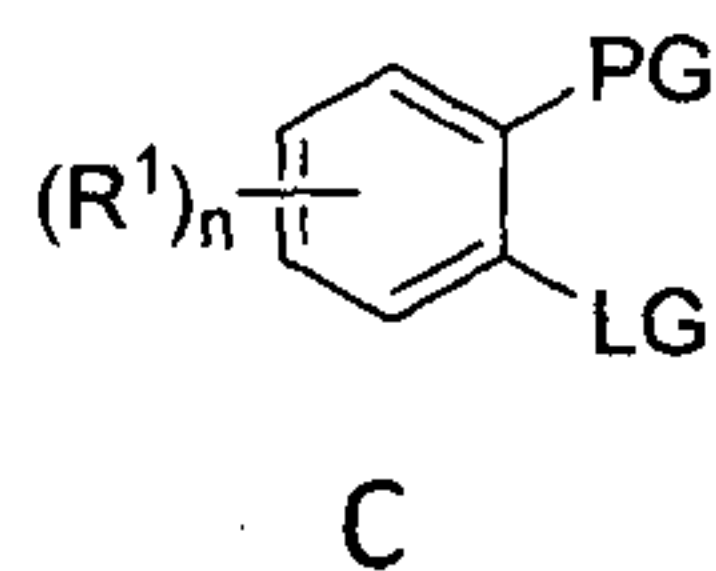
two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

PG is selected from $-\text{CH}(\text{OR}^3)$, 2-(1,3-dioxolanyl) or 2-(1,3-dioxanyl); and

R^3 is an optionally substituted aliphatic group;

comprising the steps of:

(a) providing a solution of a compound of formula C:



wherein

n is 0-4;

each R^1 is independently selected from halogen, $-\text{NO}_2$, $-\text{CN}$, or $-\text{L-R}$;

each L is independently a covalent bond or an optionally substituted bivalent C_{1-6}

hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})\text{N}(\text{R})-$, $-\text{N}(\text{R})\text{C}(\text{O})\text{N}(\text{R})-$, $-\text{N}(\text{R})\text{C}(\text{O})-$, $-\text{N}(\text{R})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R})-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R})-$, $-\text{N}(\text{R})\text{S}(\text{O})_2-$, $-\text{OC}(\text{O})-$ or $-\text{C}(\text{O})\text{O}-$;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

PG is selected from $-\text{CH}(\text{OR}^3)$, 2-(1,3-dioxolanyl) or 2-(1,3-dioxanyl);

R^3 is an optionally substituted aliphatic group; and

LG is halogen;

(b) sonicating said solution; and

(c) reacting said solution with an aryl aldehyde solution and an alkyl lithium reagent under sonication to form a compound of formula D.

2. The method according to claim 1, wherein the reaction is performed at 0-25 degree centigrade or at a room temperature.

3. The method according to claim 1, wherein LG is bromine or iodine.

4. The method according to claim 1, wherein the alkyl lithium reagent is *n*-butyllithium.

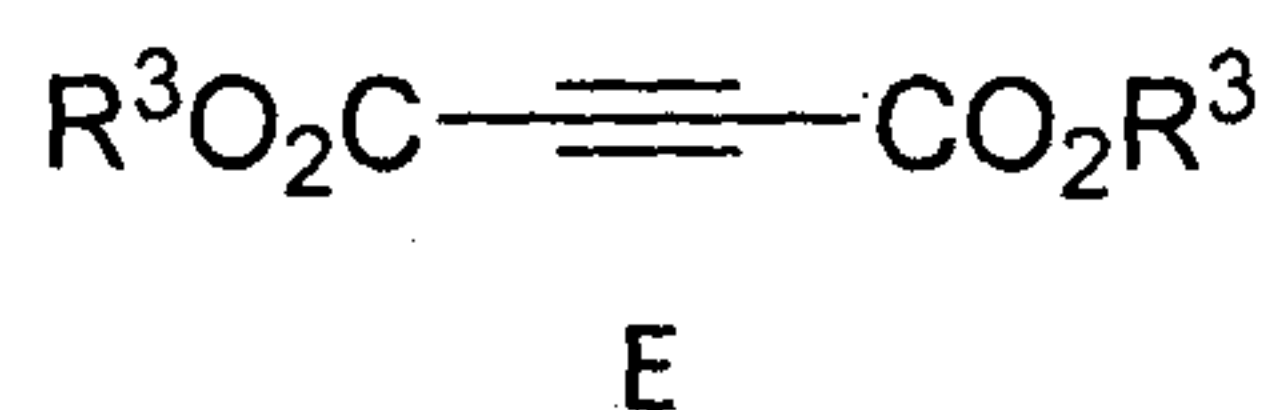
5. The method according to claim 1, wherein the aryl aldehyde is pipronal or optionally substituted pipronal.

6. The method according to claim 1, wherein the solution of compound of formula C and aryl aldehyde is prepared in a non polar, aprotic solvent selected from but not limited to the ether such as diethyl ether, MTBE, tetrahydrofuran or dioxane or hydrocarbon solvent such as hexane or cyclohexane.

7. The method according to claim 1, wherein PG is 2-(1,3-dioxolanyl).

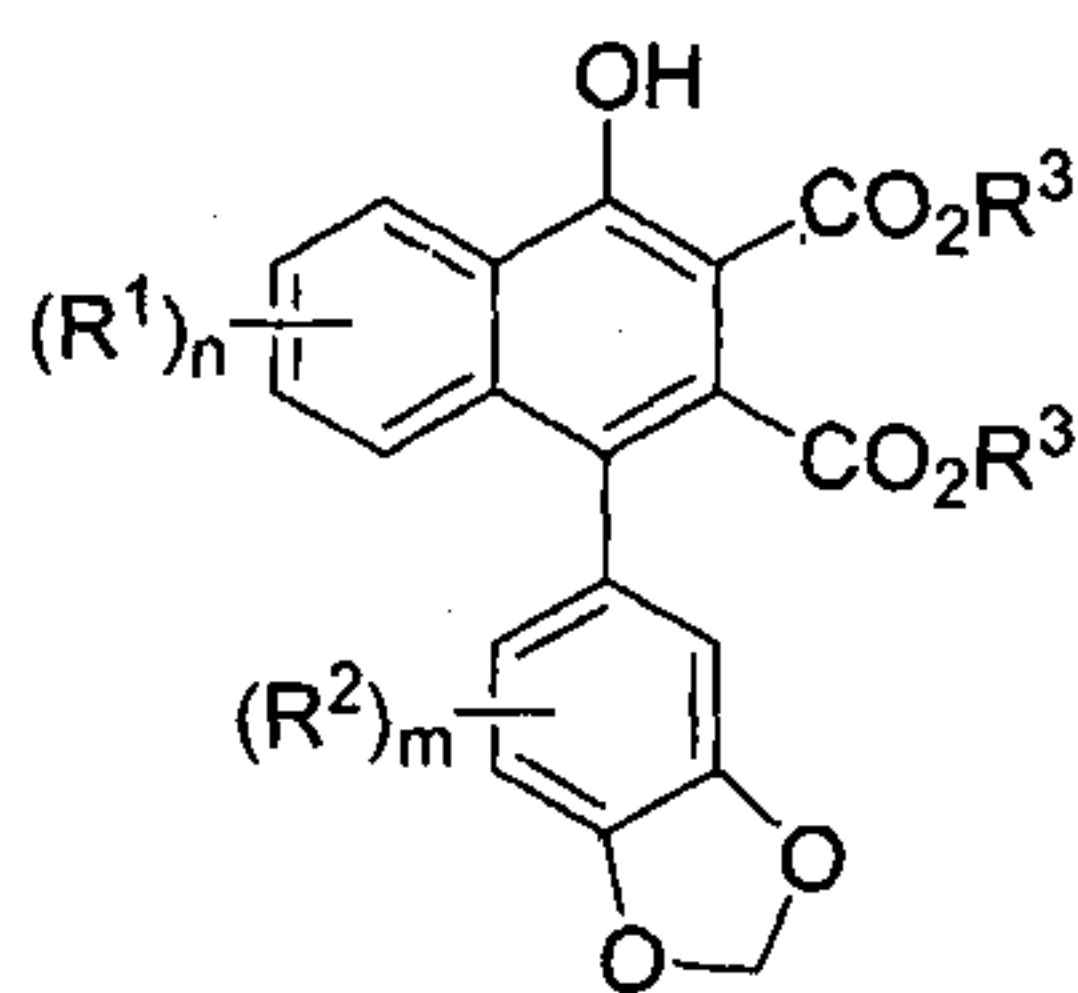
8. The method according to claim 1, further comprising the steps of:

(a) reacting said compound of formula D with a compound of formula E:



wherein each R^3 is an optionally substituted C_{1-6} aliphatic;

under conditions effective to form a compound of formula F:



F

wherein:

m is 0-3;

5 n is 0-4;

each of R^1 and R^2 is independently selected from halogen, $-\text{NO}_2$, $-\text{CN}$, or $-\text{L-R}$;

each L is independently a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{C}(\text{O})\text{N}(\text{R})-$, $-\text{N}(\text{R})\text{C}(\text{O})\text{N}(\text{R})-$, $-\text{N}(\text{R})\text{C}(\text{O})-$, $-\text{N}(\text{R})\text{C}(\text{O})\text{O}-$, $-\text{OC}(\text{O})\text{N}(\text{R})-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})_2\text{N}(\text{R})-$, $-\text{N}(\text{R})\text{S}(\text{O})_2-$, $-\text{OC}(\text{O})-$ or $-\text{C}(\text{O})\text{O}-$;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

each R^3 is independently an optionally substituted C_{1-6} aliphatic.

9. The method according to claim 8, wherein each R^3 is ethyl.

10. The method according to claim 9, wherein PG is 2-(1,3-dioxolanyl).

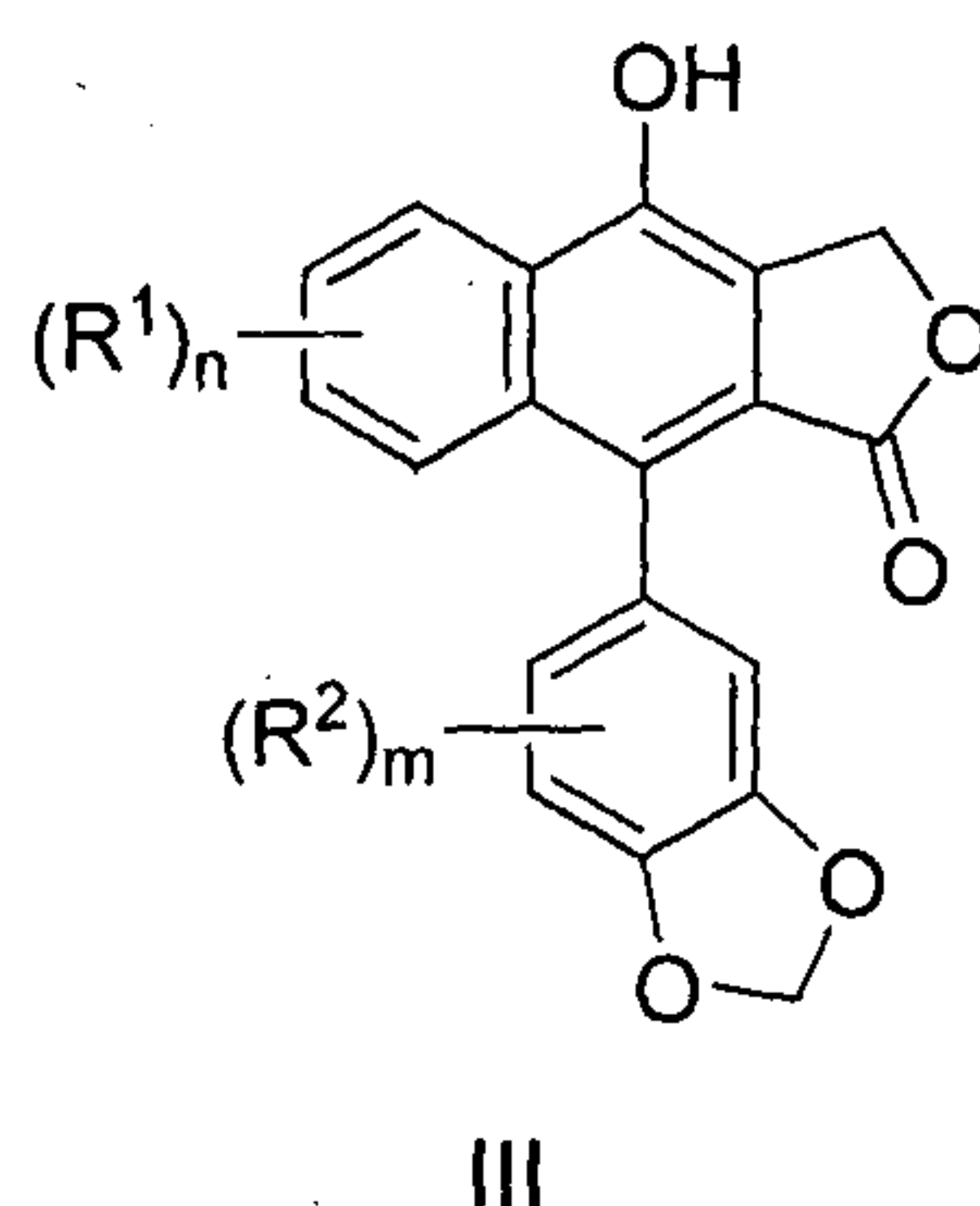
11. The method according to claim 10, wherein the compound of formula D and the compound of formula E are heated in acetic acid.

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12. The method according to claim 11, wherein the compound of formula D and the compound of formula E are heated to about 120 °C to about 140 °C.

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13. The method according to claim 8, further comprising the step of reacting said compound F with a metal hydride to form a compound of formula III:



wherein:

m is 0-3;

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n is 0-4;

each of R¹ and R² is independently selected from halogen, -NO₂, -CN, or -L-R;

each L is independently a covalent bond or an optionally substituted bivalent C₁₋₆ hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-, -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-; and

20

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-

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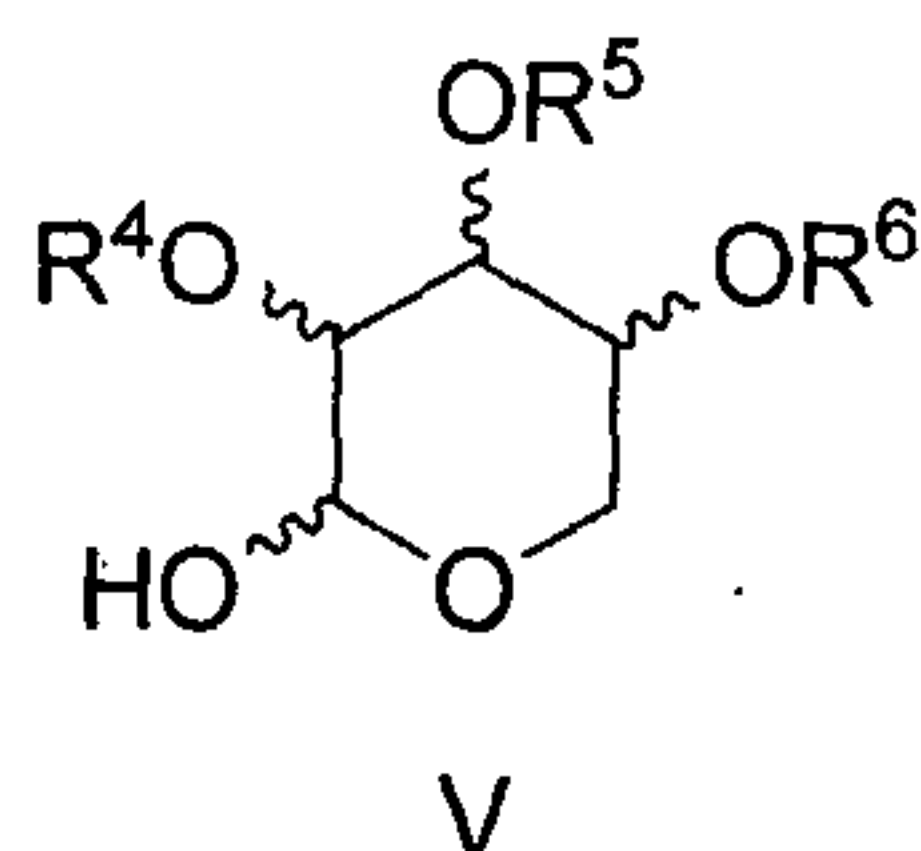
10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

5 two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

14. The method according to claim 13, wherein the metal hydride is lithium aluminum hydride.

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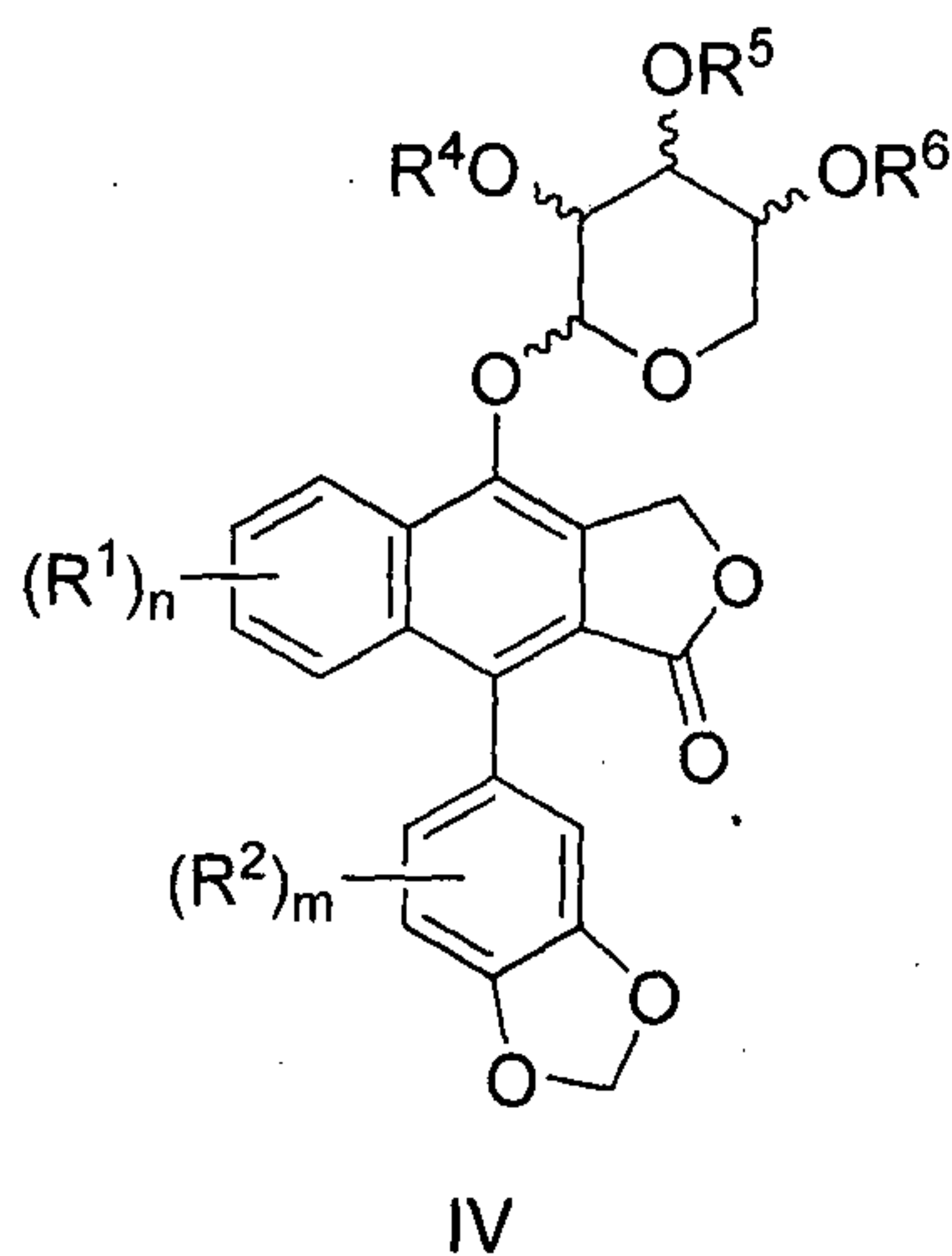
15. The method according to claim 13, further comprising the step of: reacting said compound of formula III with a pyranose of formula V:



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wherein each of R^4 , R^5 and R^6 is independently hydrogen, R^7 , or $-C(O)R^7$; and each R^7 is independently an optionally substituted C_{1-6} aliphatic group or a suitable hydroxyl protecting group;

under conditions effective to form a compound of formula IV:



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or a pharmaceutically acceptable salt thereof, wherein:

m is 0-3;

n is 0-4;

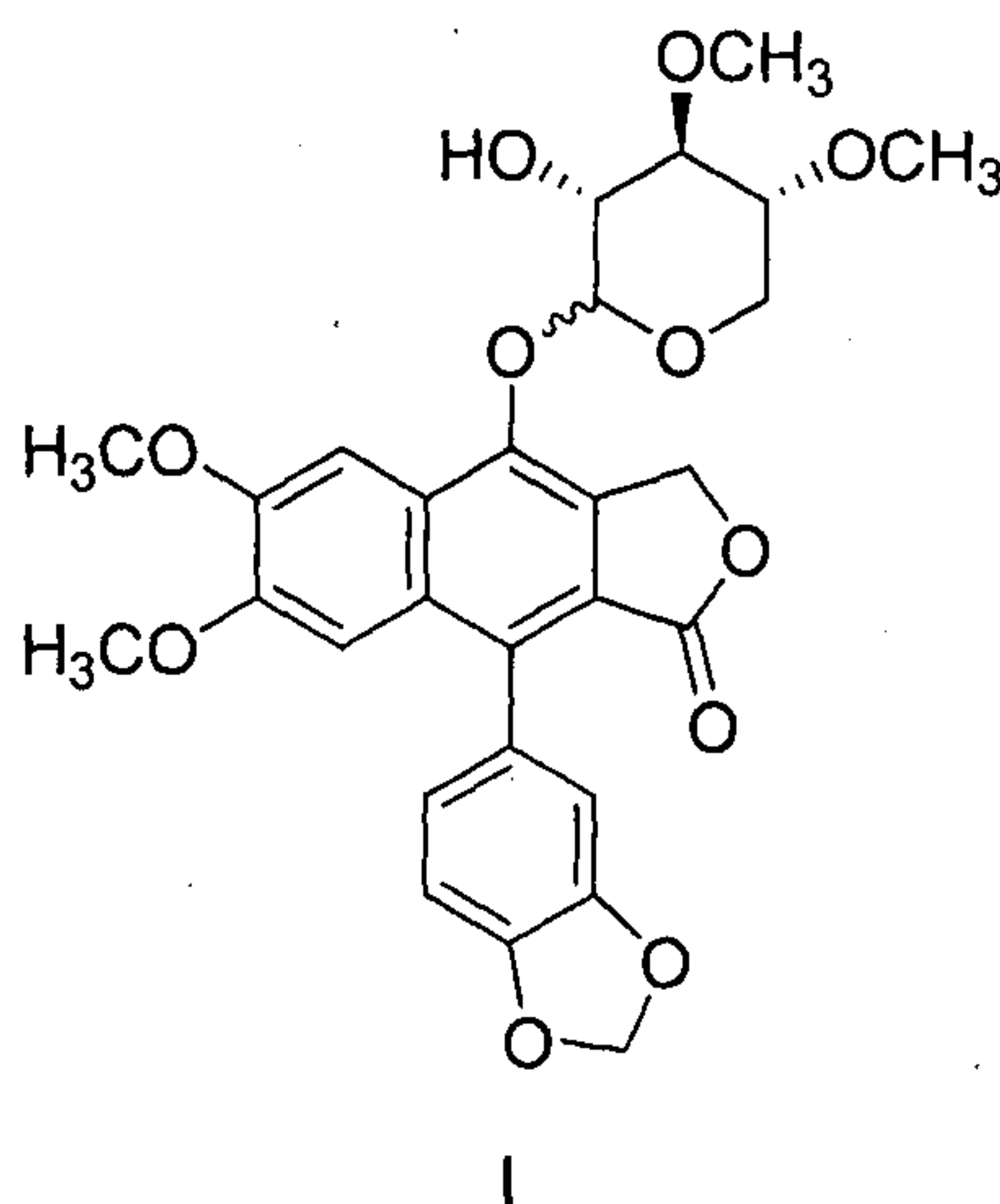
each of R^1 and R^2 is independently selected from halogen, $-NO_2$, $-CN$, or $-L-R$;

each L is independently a covalent bond or an optionally substituted bivalent C₁₋₆ hydrocarbon chain, wherein one or two methylene units of L is optionally and independently replaced by -O-, -S-, -N(R)-, -C(O)-, -C(S)-, -C(O)N(R)-, -N(R)C(O)N(R)-, -N(R)C(O)-, -N(R)C(O)O-, -OC(O)N(R)-, -S(O)-, -S(O)₂-,
 5 -S(O)₂N(R)-, -N(R)S(O)₂-, -OC(O)- or -C(O)O-; and

each R is independently hydrogen or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic carbocyclic ring, a 3-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently
 10 selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic saturated, partially unsaturated, or aromatic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or
 15 sulfur, or:

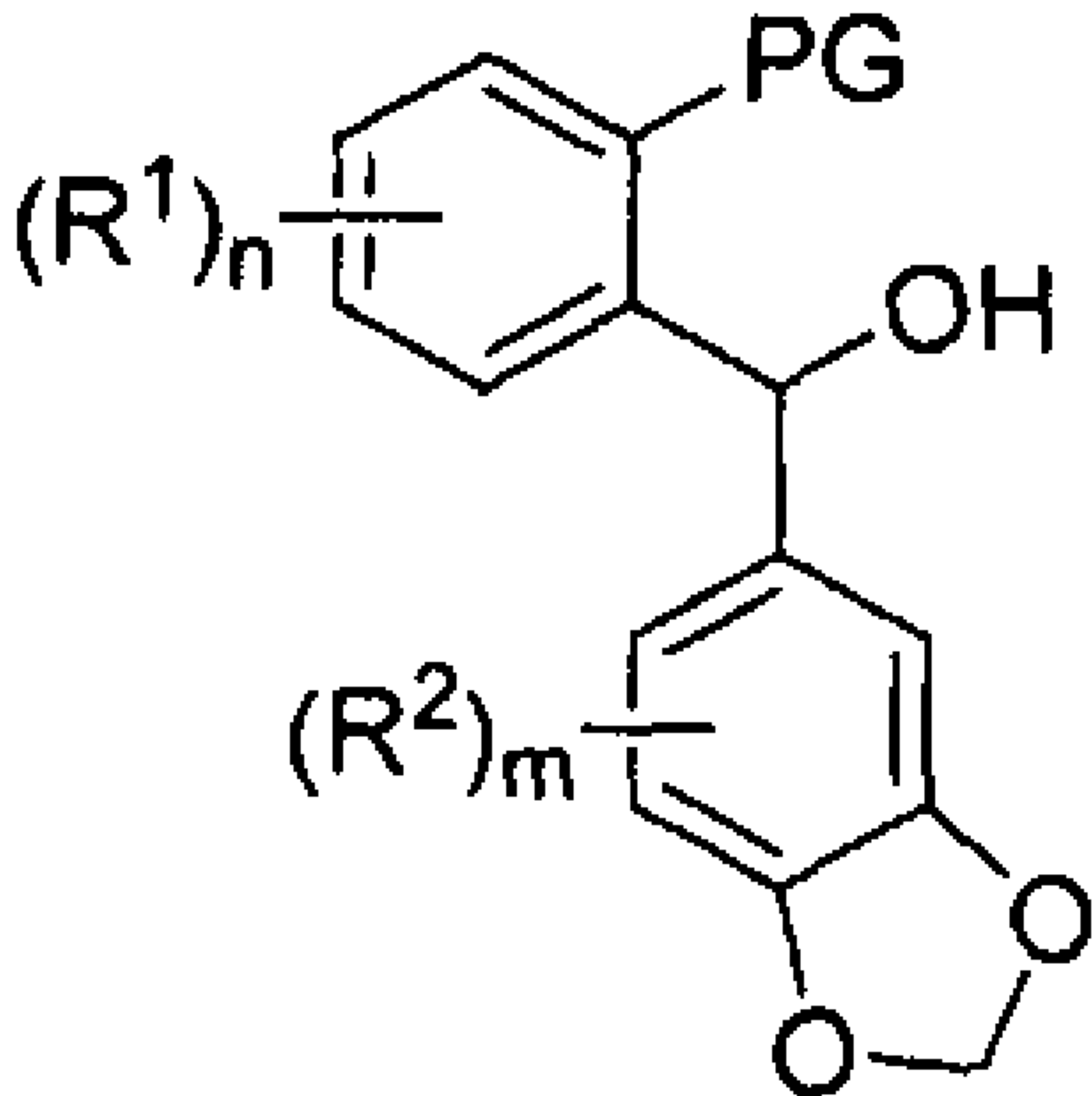
two R groups on the same nitrogen are taken together with their intervening atoms to form a 3-8 membered saturated, partially unsaturated, or aromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

20 16. A method for preparing cleistanthin A (I):



comprising a step of reacting compound of formula IV obtained by method of claim 15 with an alkali and a solvent to form Cleistanthin A (I).

17. The method according to claim 16, wherein the alkali is potassium carbonate and solvent is methanol.



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