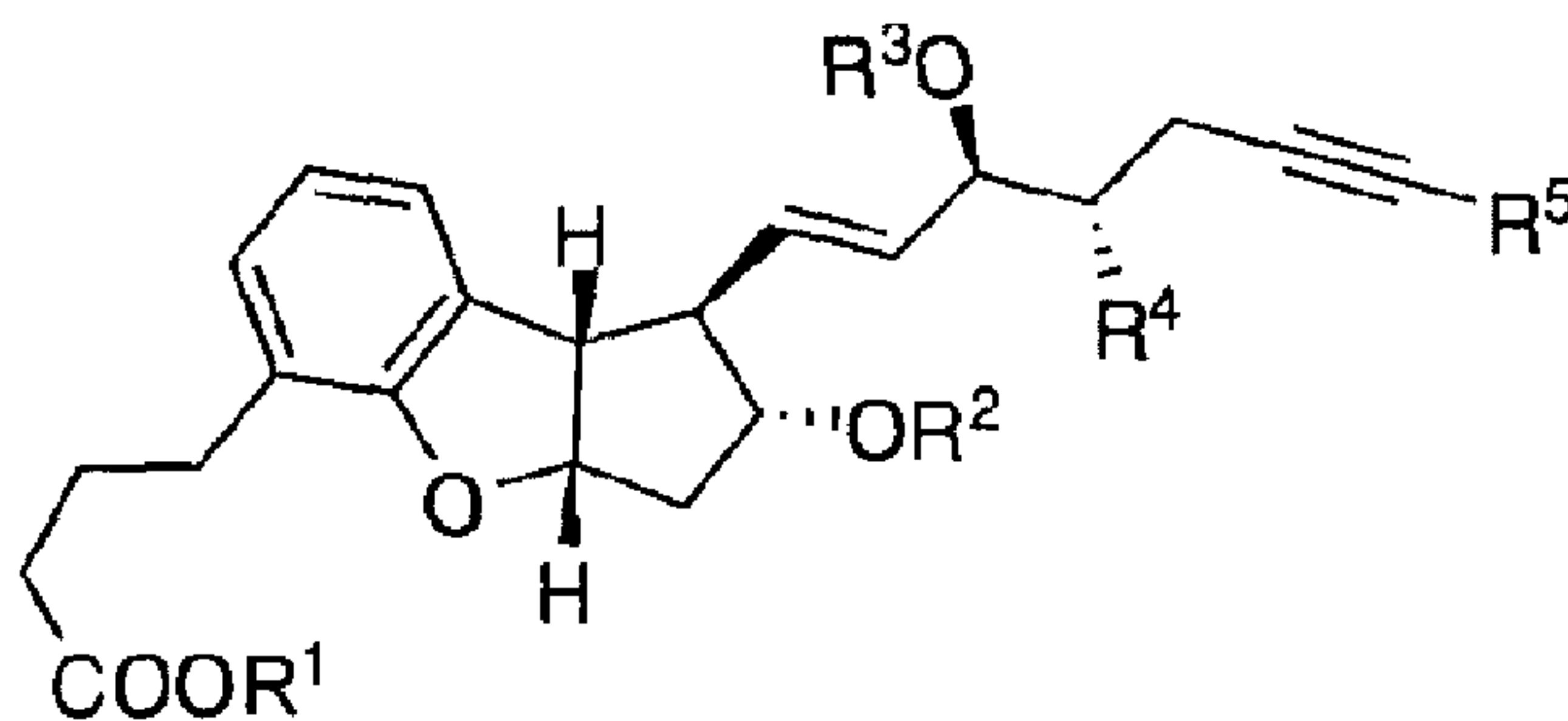




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(54) Titre : PROCEDE DE PREPARATION DE BERAPROST
(54) Title: PROCESS FOR MAKING BERAPROST



(57) **Abrégé/Abstract:**

A method is described for making single isomers of synthetic beraprost diol, a key intermediate for making 314-d isomer of beraprost. The method requires fewer steps than the known methods for making these compounds and can be used to scale up the reaction more easily to produce commercial quantities.

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(54) Title: PROCESS FOR MAKING BERAPROST

(57) Abstract: A method is described for making single isomers of synthetic beraprost diol, a key intermediate for making 314-d isomer of beraprost. The method requires fewer steps than the known methods for making these compounds and can be used to scale up the reaction more easily to produce commercial quantities.

WO 2017/027706 A1

PROCESS FOR MAKING BERAPROST

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from US provisional application no. 62/204,145 filed August 12, 2015.

FIELD OF THE INVENTION

The present application relates to a process for selectively producing single-isomer benzoprostacyclin derivatives, including beraprost and its derivatives.

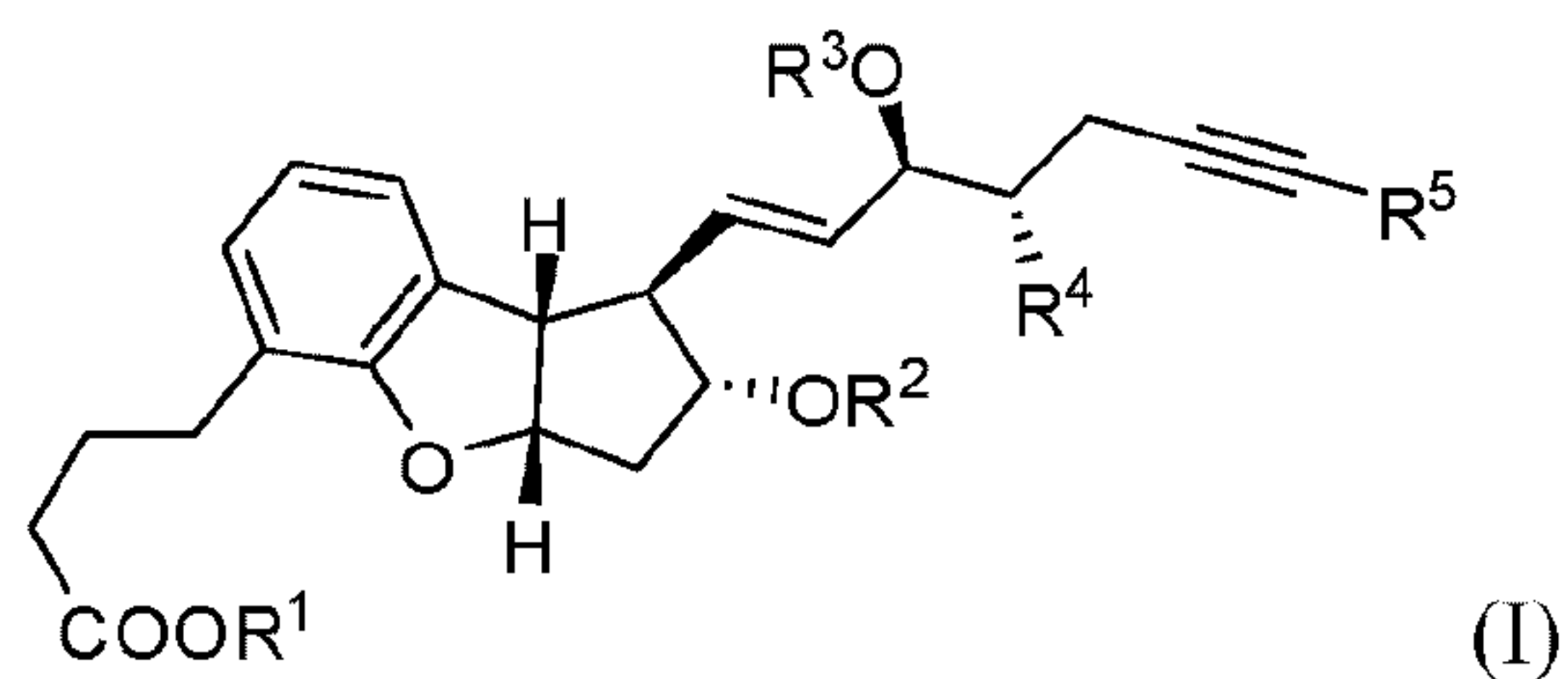
BACKGROUND OF THE INVENTION

Prostacyclin derivatives are useful pharmaceutical compounds and possess activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, and bronchodilation. Beraprost is a synthetic benzoprostacyclin analogue of natural prostacyclin that is currently under clinical trials for the treatment of pulmonary hypertension and vascular disease (excluding renal disease) in North America and Europe. Beraprost and related benzoprostacyclin analogues of the formula (I), as defined below, are disclosed, for example, in U.S. Patent No. 5,202,447 and Tetrahedron Lett. 31, 4493 (1990). Furthermore, as described in U.S. Patent No. 7,345,181, several synthetic methods are known to produce benzoprostacyclin analogues. Known synthetic methods generally require one or more resolutions of intermediates to obtain a pharmacologically active isomer of beraprost, such as beraprost 314-d, or a related benzoprostacyclin analogue. Also, current pharmaceutical formulations of beraprost or a related benzoprostacyclin analogue may consist of several isomers of the pharmaceutical compound, and only one of which is primarily responsible for the pharmacologic activity of the drug. Isolation of isomers of beraprost compounds from current synthetic methods requires multiple preparative HPLC or chromatographic purification procedures or multiple recrystallizations, which are not preferable or feasible on a commercially applicable scale. Therefore, it is desired to achieve an efficient,

commercially applicable synthetic route to the isomers of beraprost or a related benzoprostacyclin analogue.

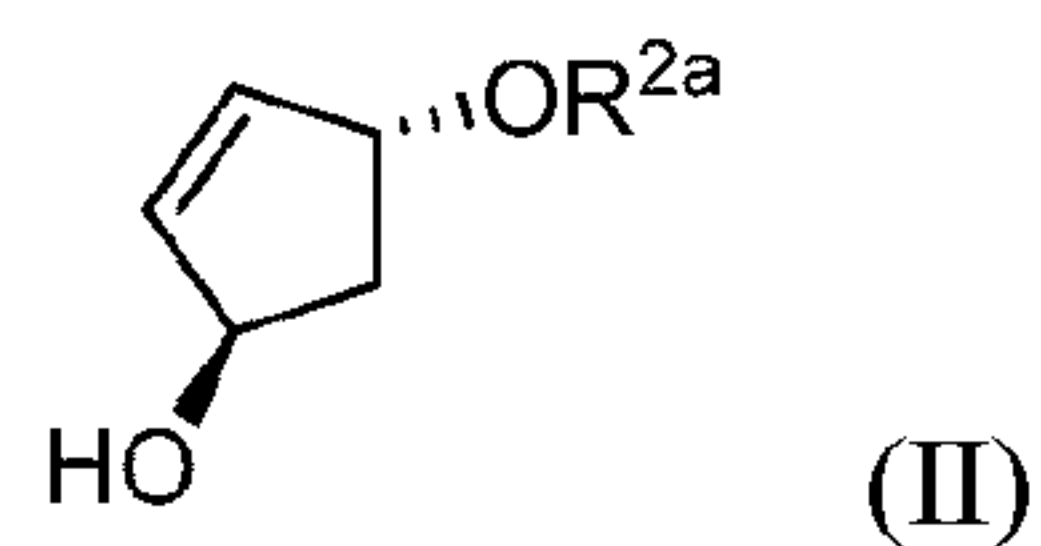
SUMMARY OF THE INVENTION

In some embodiments, the present invention provides a process for preparing a compound of the following formula:

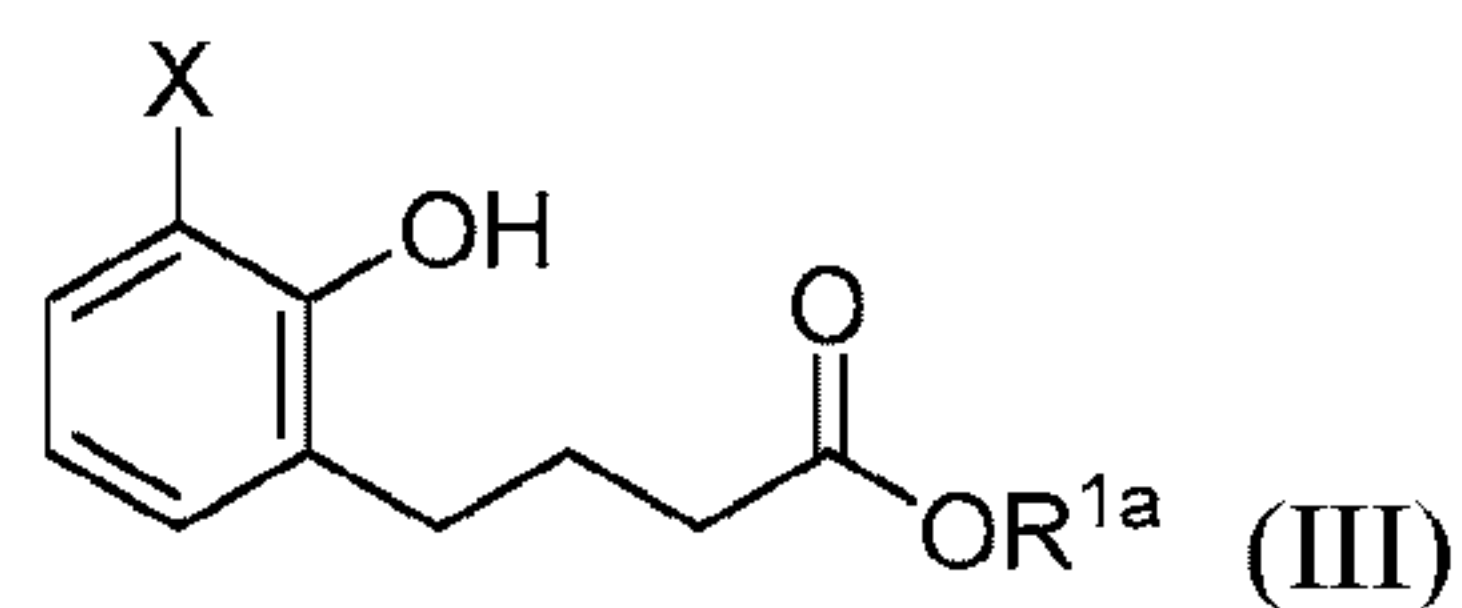


wherein R^1 represents a cation, H, or C_{1-12} alkyl,
 R^2 and R^3 each represent H or a hydroxy protective group
 R^4 represents H or C_{1-3} alkyl, and
 R^5 represents H or C_{1-6} alkyl, comprising:

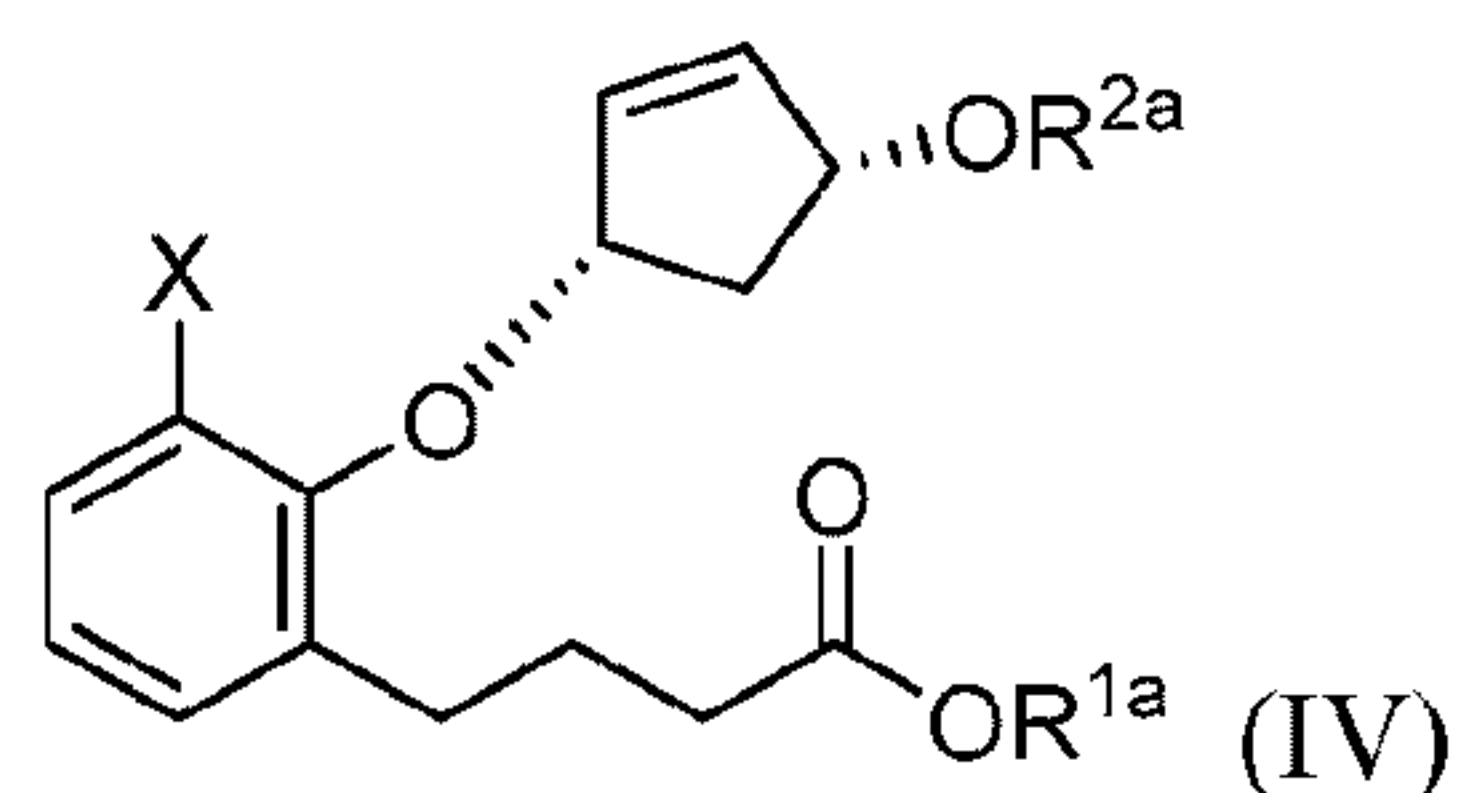
(1) reacting a compound of the following formula:



, wherein R^{2a} is H or an hydroxy protective group
 with a compound of the following formula:

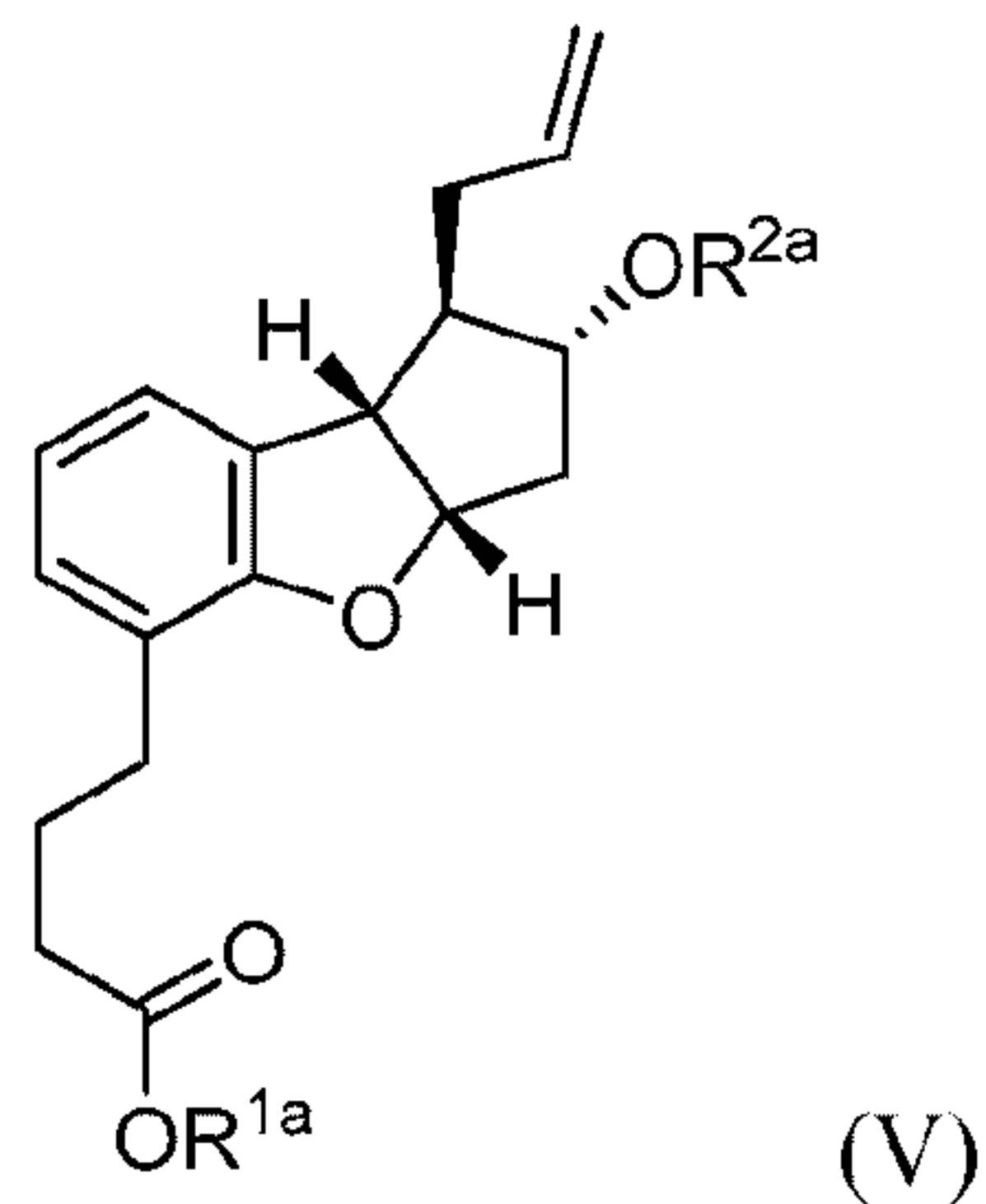


, wherein R^{1a} is a cation, H, or C_{1-12} alkyl, X is halogen
 to form a compound of the following formula:



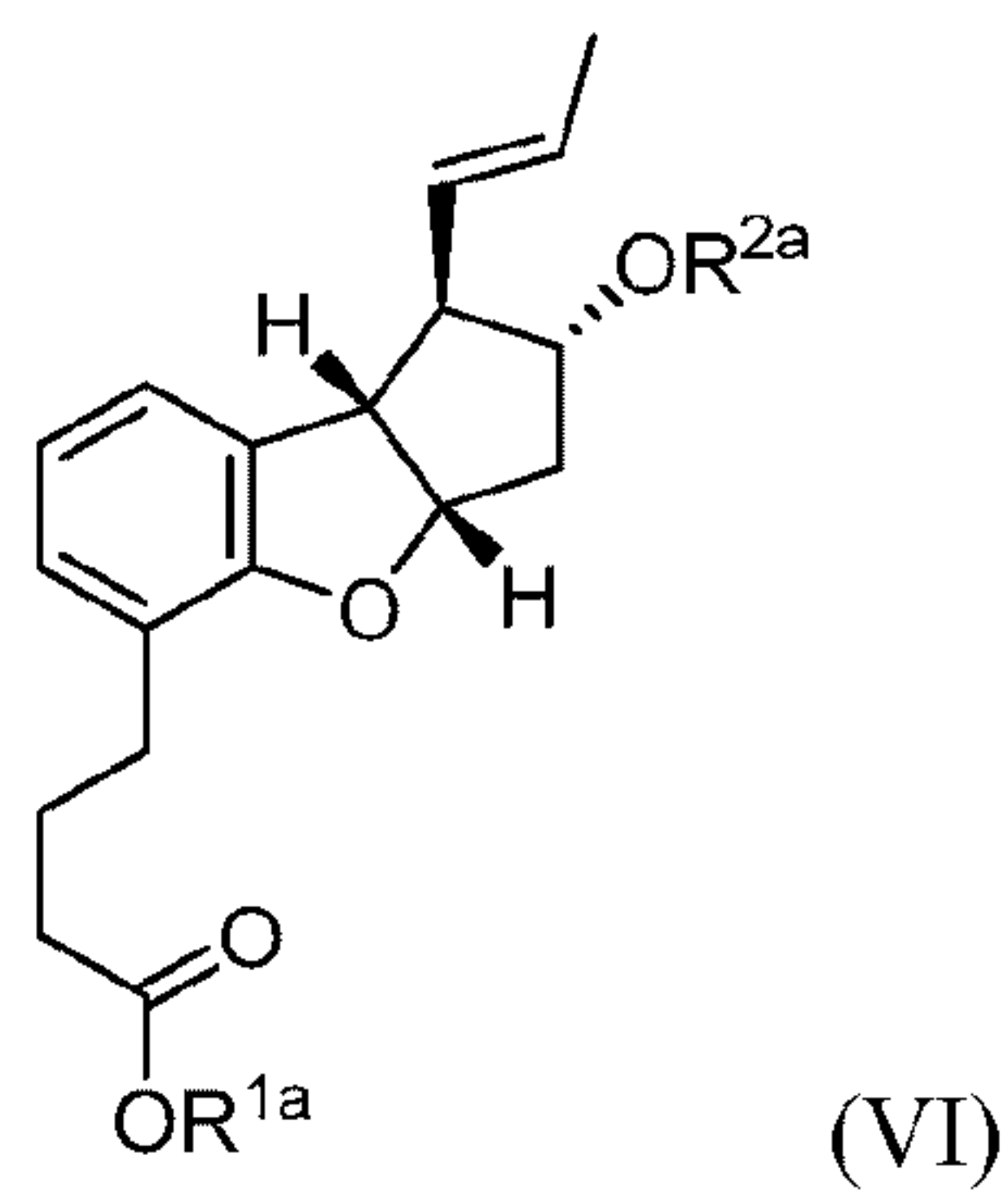
, wherein R^{1a} , R^{2a} and X are each defined above;

(2) cyclizing a compound of formula (IV) to form a compound of the following formula:



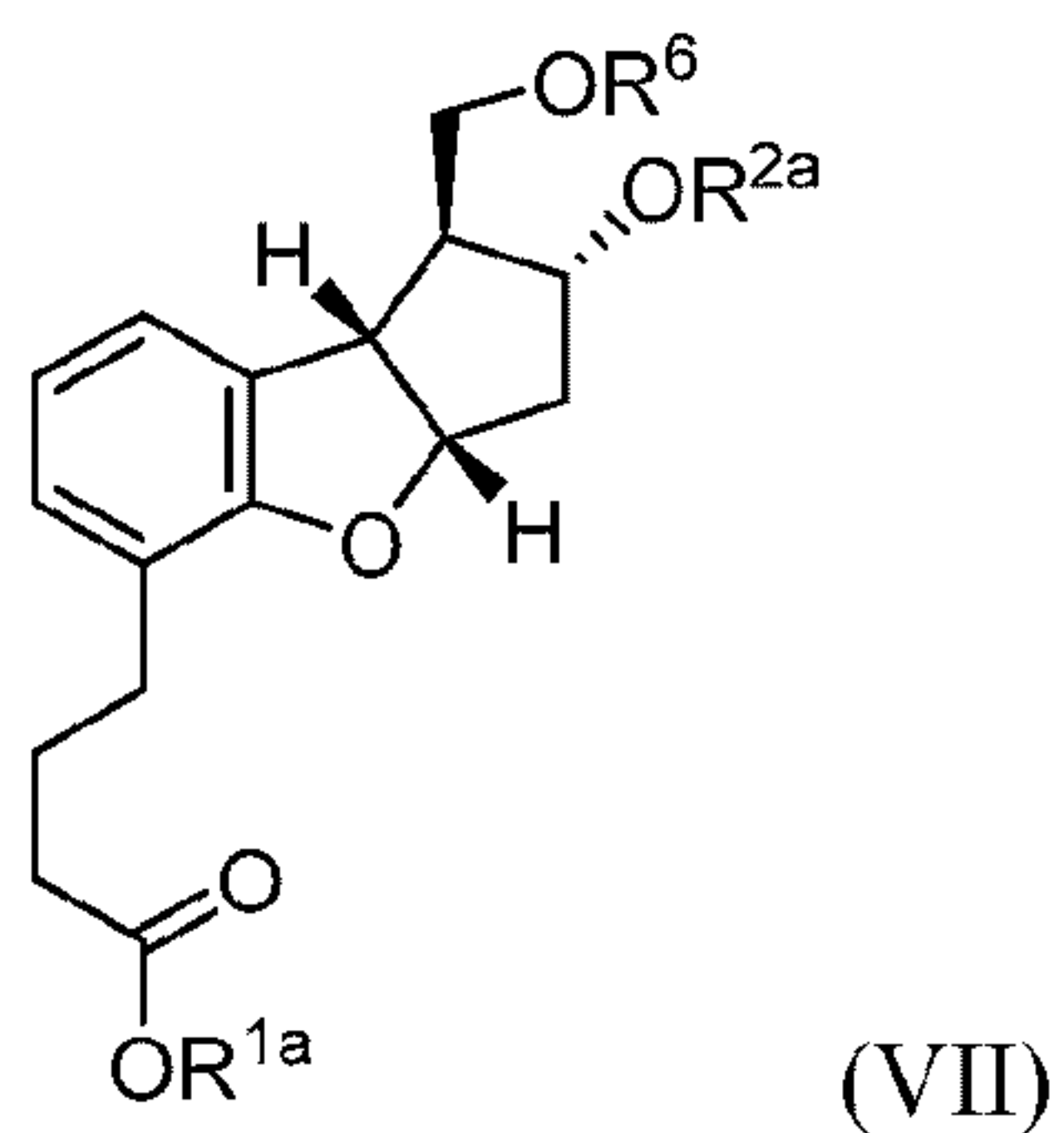
, wherein R^{1a} and R^{2a} are each defined above;

(3) isomerizing an allyl of the compound of formula (V) to form a propenyl resulting in a compound of the following formula:



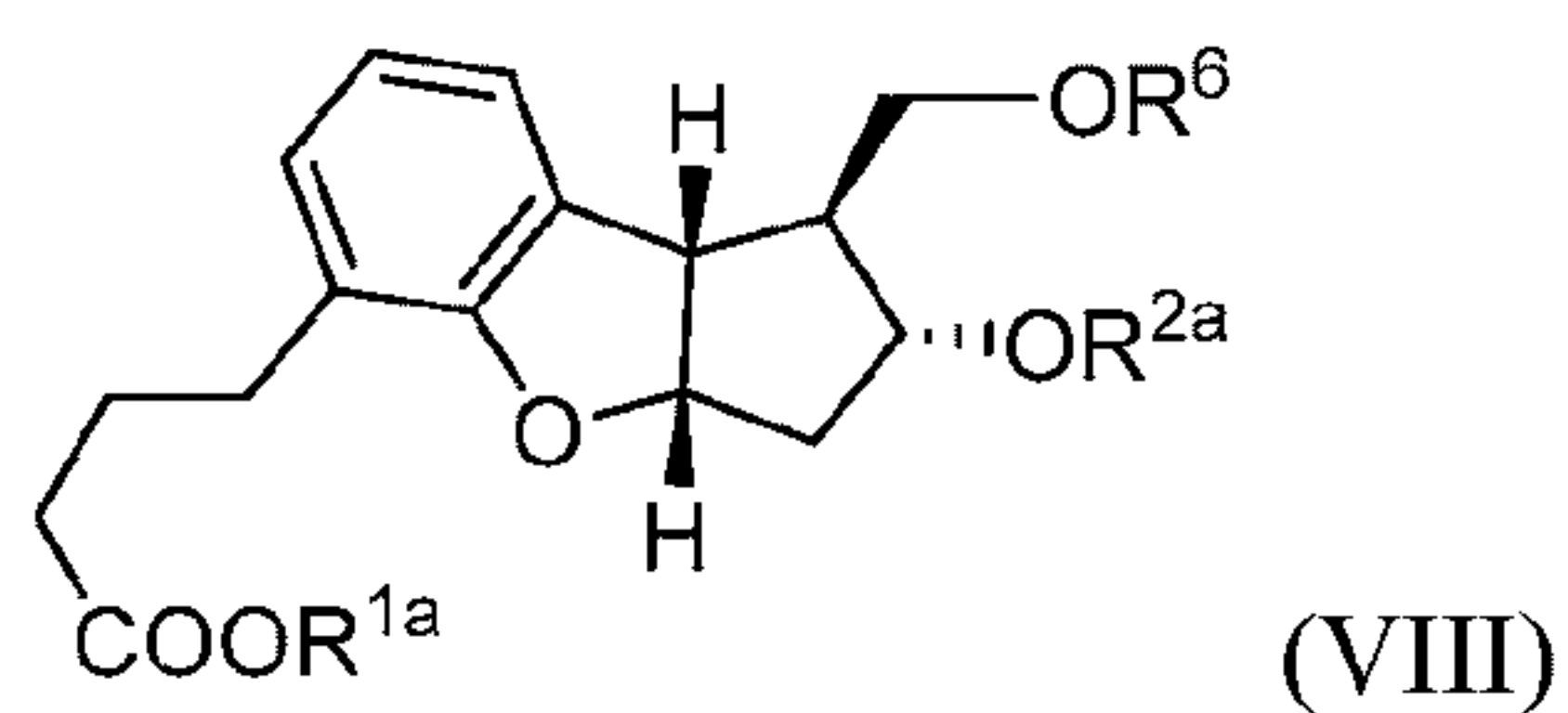
, wherein R^{1a} and R^{2a} are each defined above;

(4) ozonolysis and *in situ* reduction to convert the propenyl of the compound of formula (VI) to an alcohol resulting in a compound of the following formula:



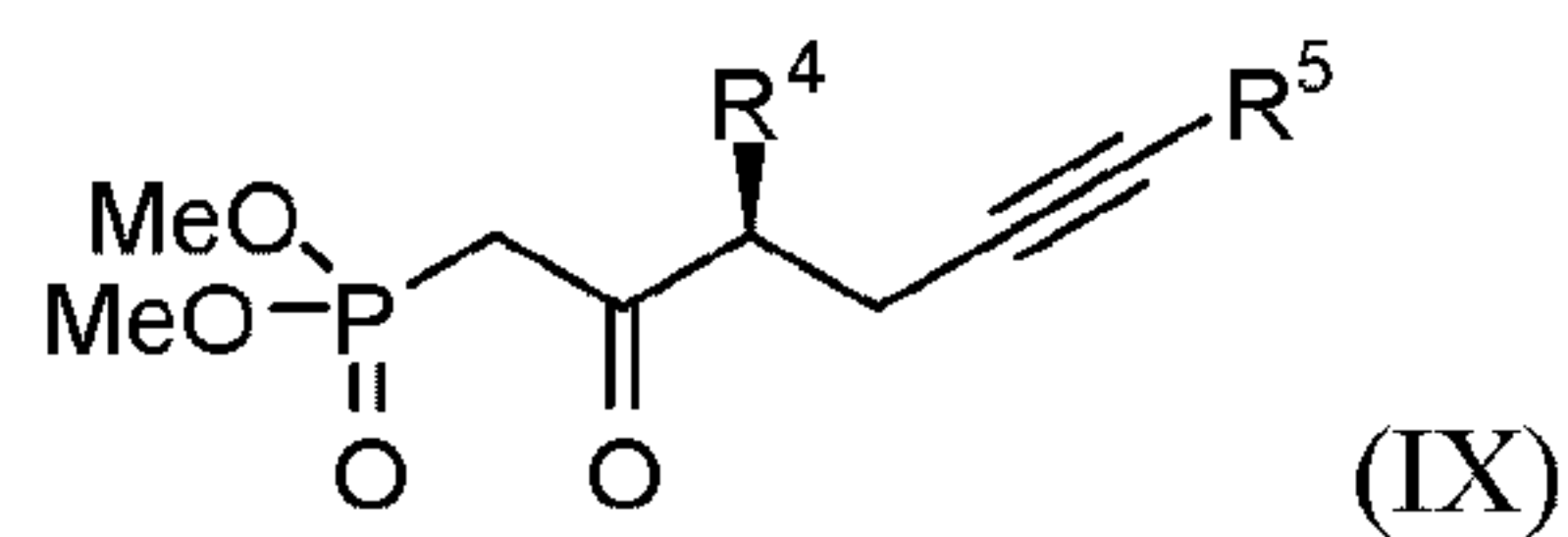
, wherein R^{1a} and R^{2a} are each defined above, R^6 is H or a hydroxy protective group;

(5) deprotecting an acetate of the compound of formula (VII) to form a compound of the following formula:

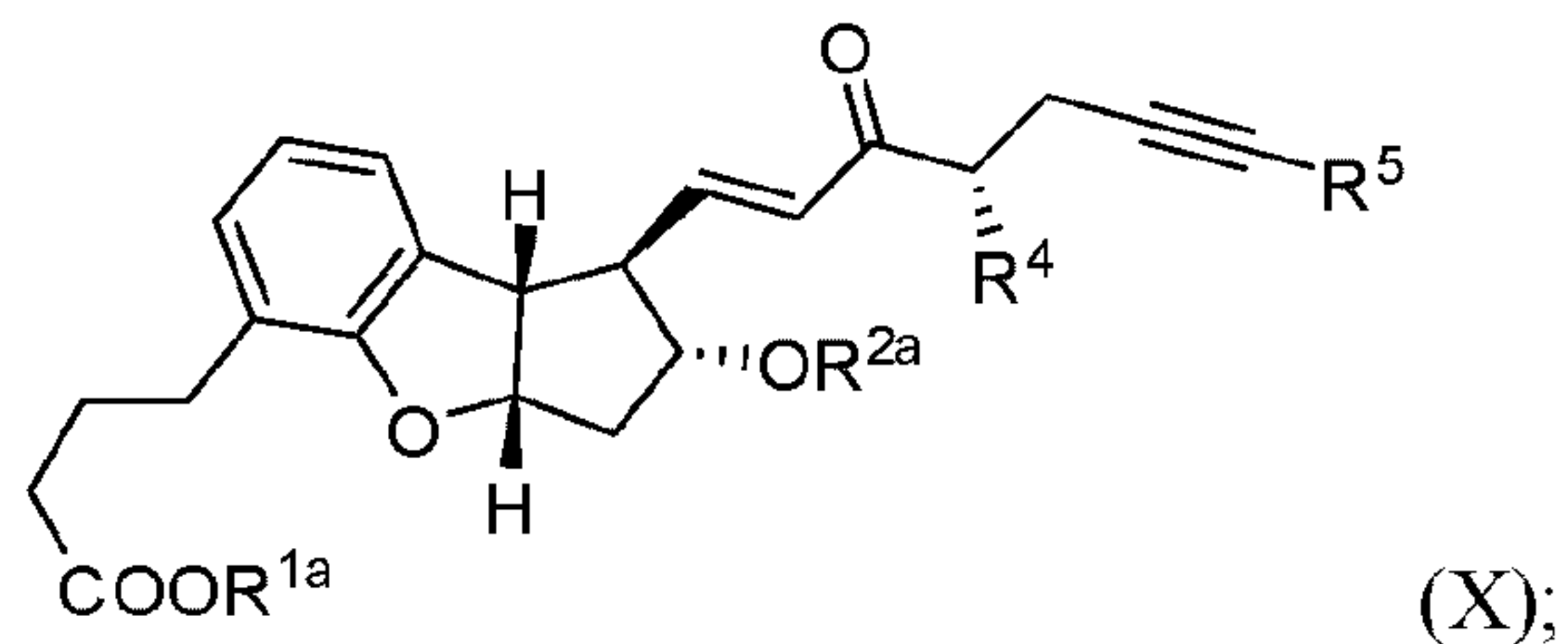


, wherein R^{1a} , R^{2a} and R^6 are each defined above;

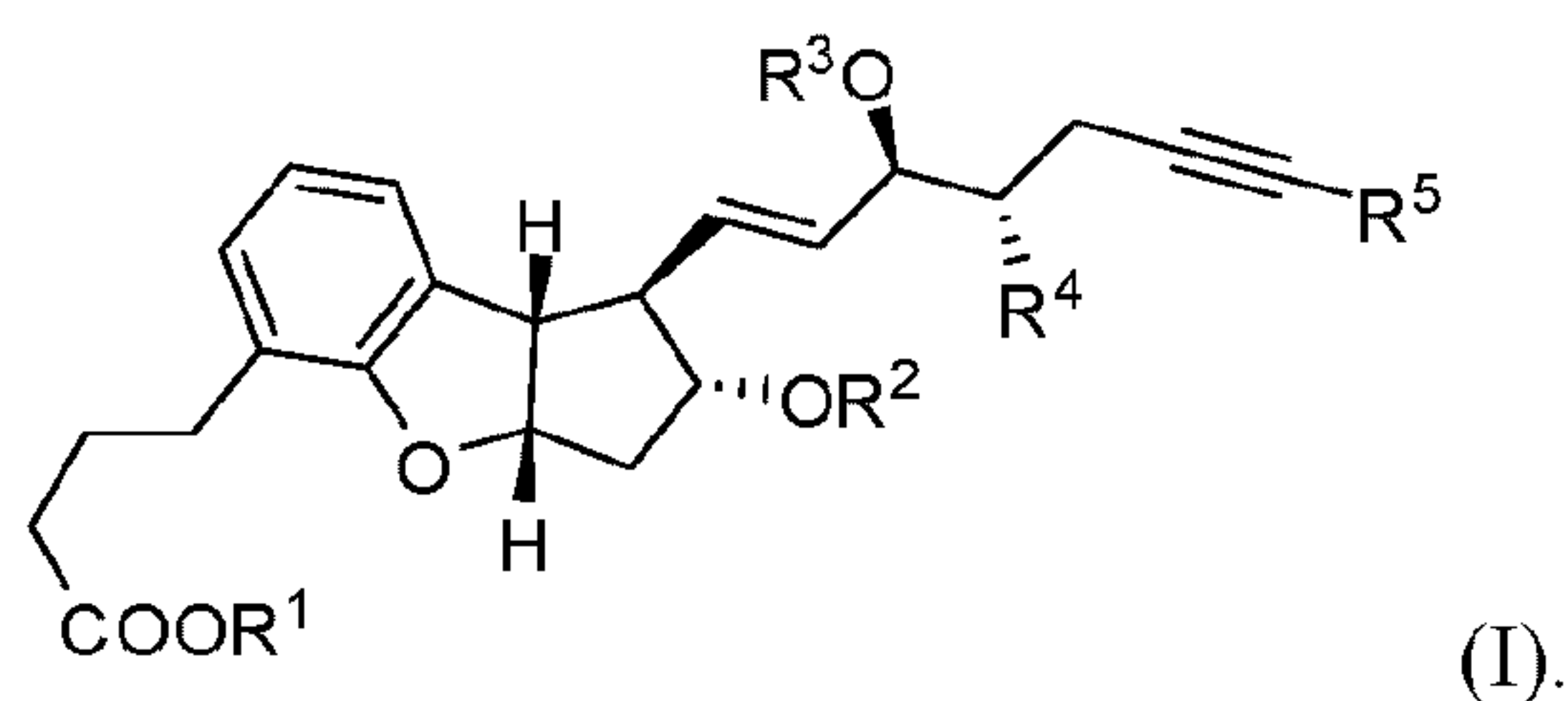
(6) selectively deprotecting the primary hydroxy protective group, followed by oxidation of the primary hydroxy group to form an aldehyde, followed by coupling with a side-chain of the formula:



, wherein R^4 and R^5 are each defined above, to form a compound of the following formula:



(7) reduction of the ketone, deprotection of any remaining hydroxy protective group and optionally converting the R^{1a} into a cation or H to form a compound of the following formula:



In some embodiments, the present invention provides a method that produces the compound of formula (I) as a substantially pure single isomer.

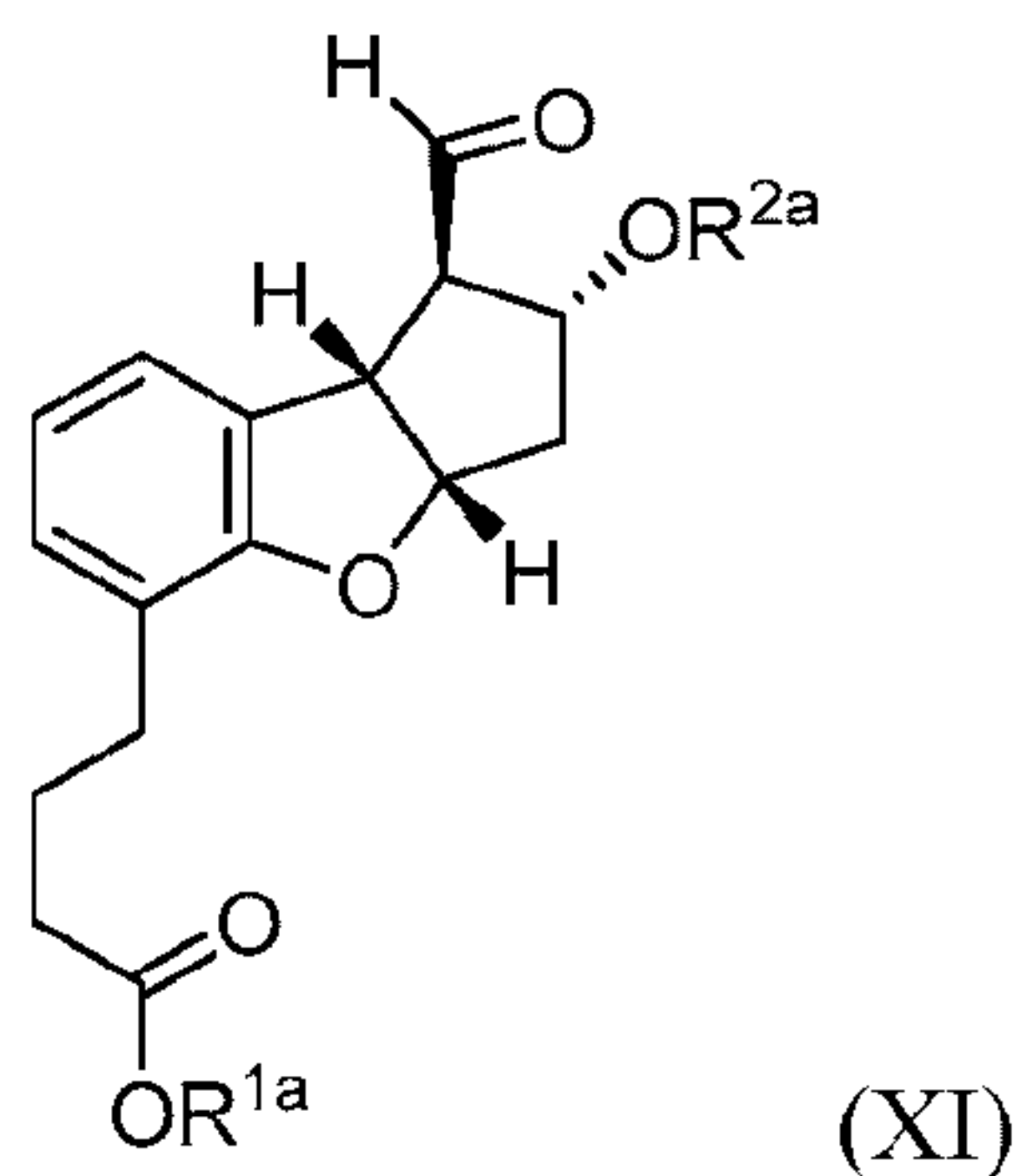
In some embodiments, R^2 , R^3 , R^{2a} and R^6 each independently represent an acetate, a silyl ester (for example trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, phenyldimethylsilyl, tetrahydropyranyl), benzoate ester, benzyl or substituted benzyl.

In some embodiments, R^{1a} is CH_3 and R^{2a} and R^6 are both H. In some embodiments, X is bromo, iodo, or chloro.

In some embodiments, azobisisobutyronitrile is used as a radical initiator in step (2).

In some embodiments, a catalytic amount of carbonylchlorohydridotris(triphenylphosphine) ruthenium (II) is used in step (3).

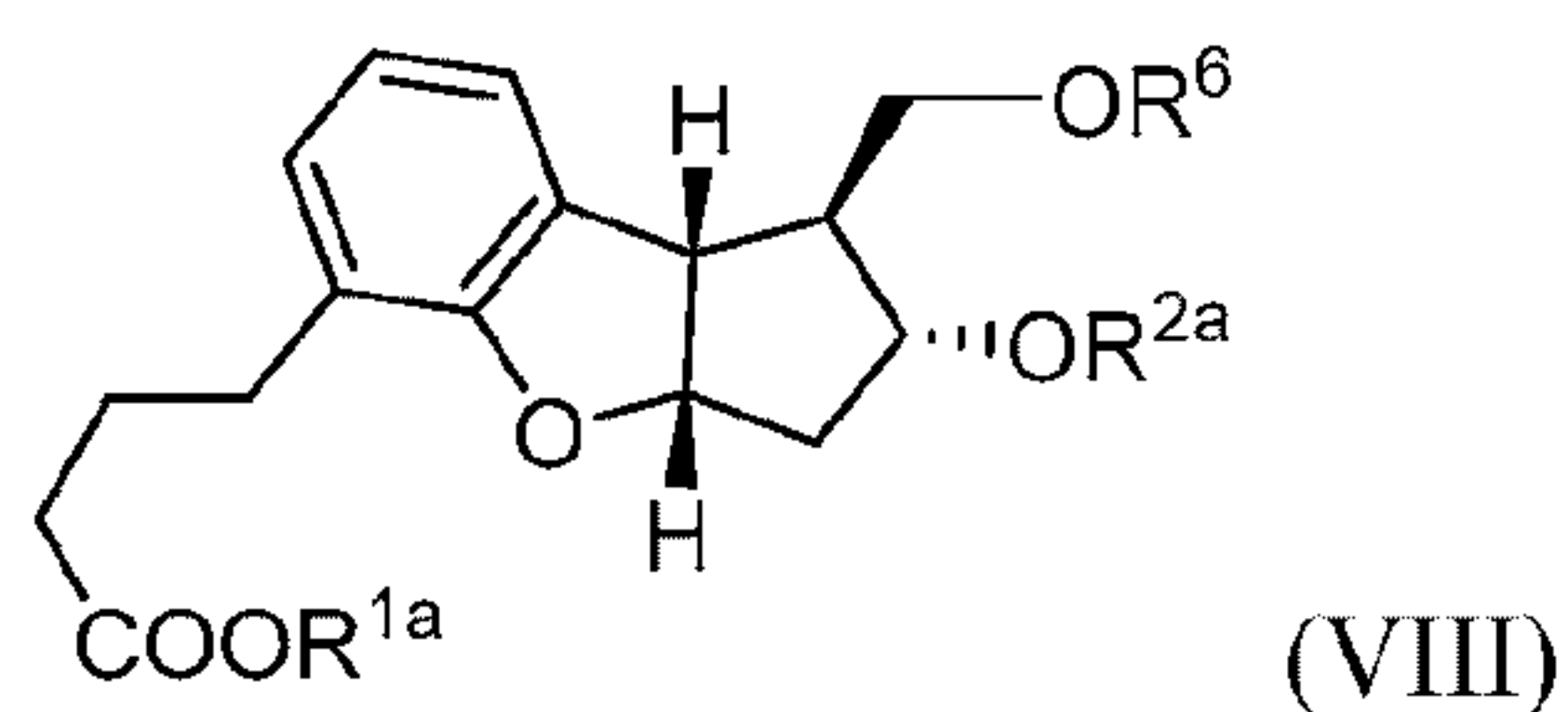
In some embodiments, step (4) produces an *in situ* trapped aldehyde intermediate represented by the compound of formula (XI)



wherein R^{1a} and R^{2a} is each defined above.

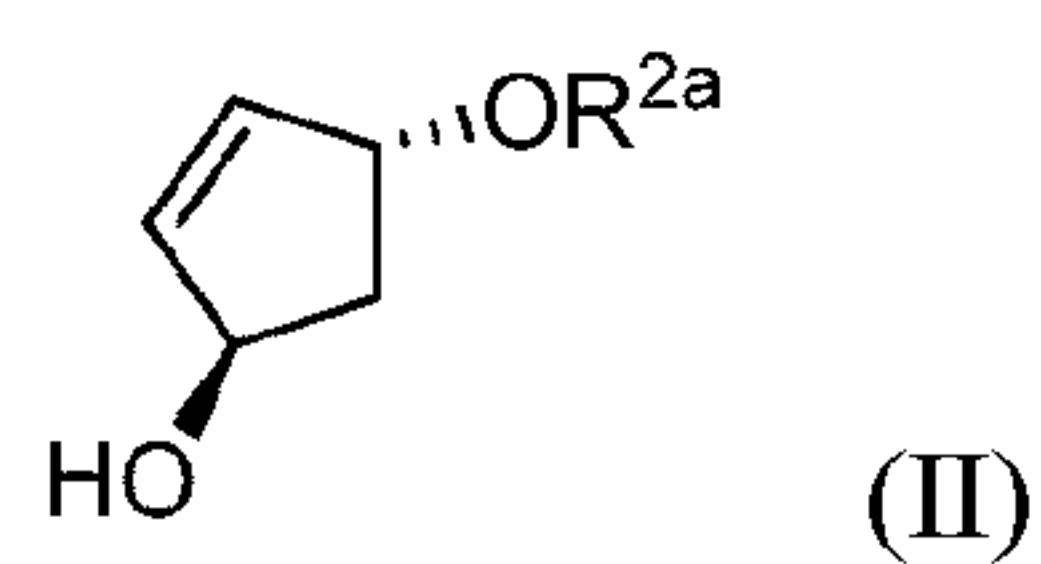
In some embodiments, sulfuric acid is used in step (5).

In another aspect, the present invention also provides a process for preparing a compound of the following formula:



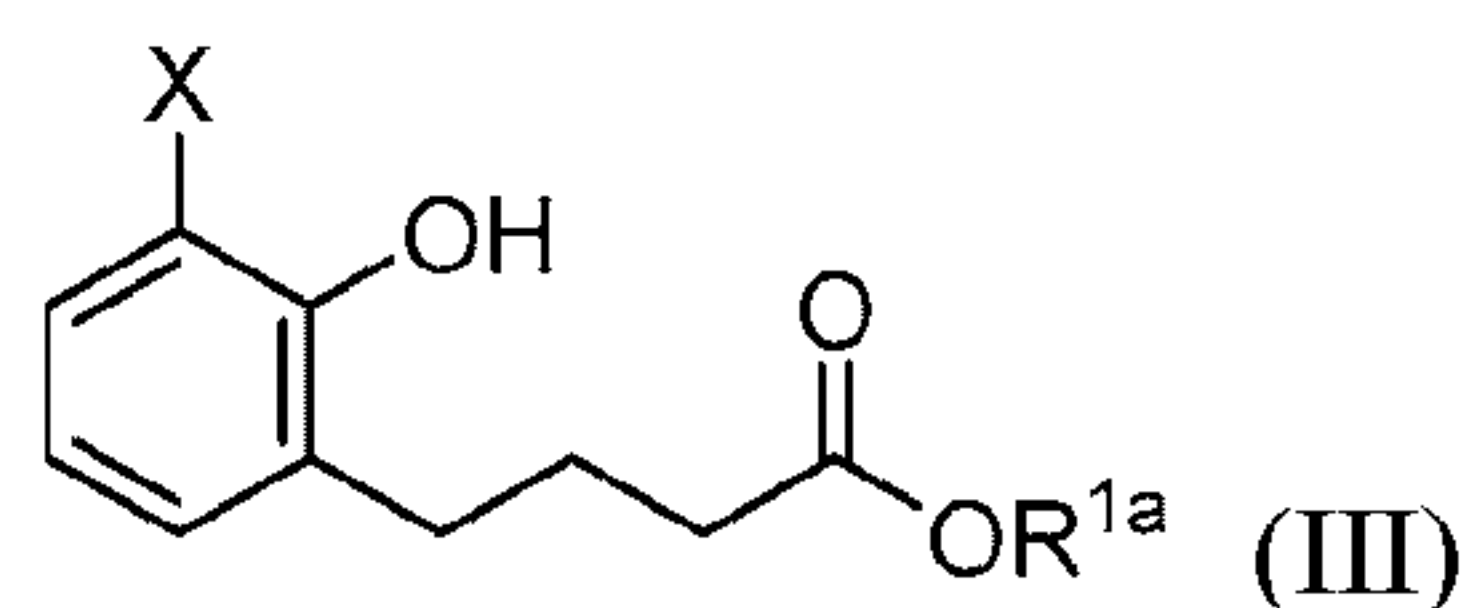
wherein R^{1a} represents a cation, H, or C_{1-12} alkyl and R^{2a} and R^6 each represent H, a hydroxyl protective group, an acetate protective group, a silyl ether, benzoate ester, benzyl, or substituted benzyl comprising:

(1) performing a Mitsunobu reaction on the compound of the following formula:



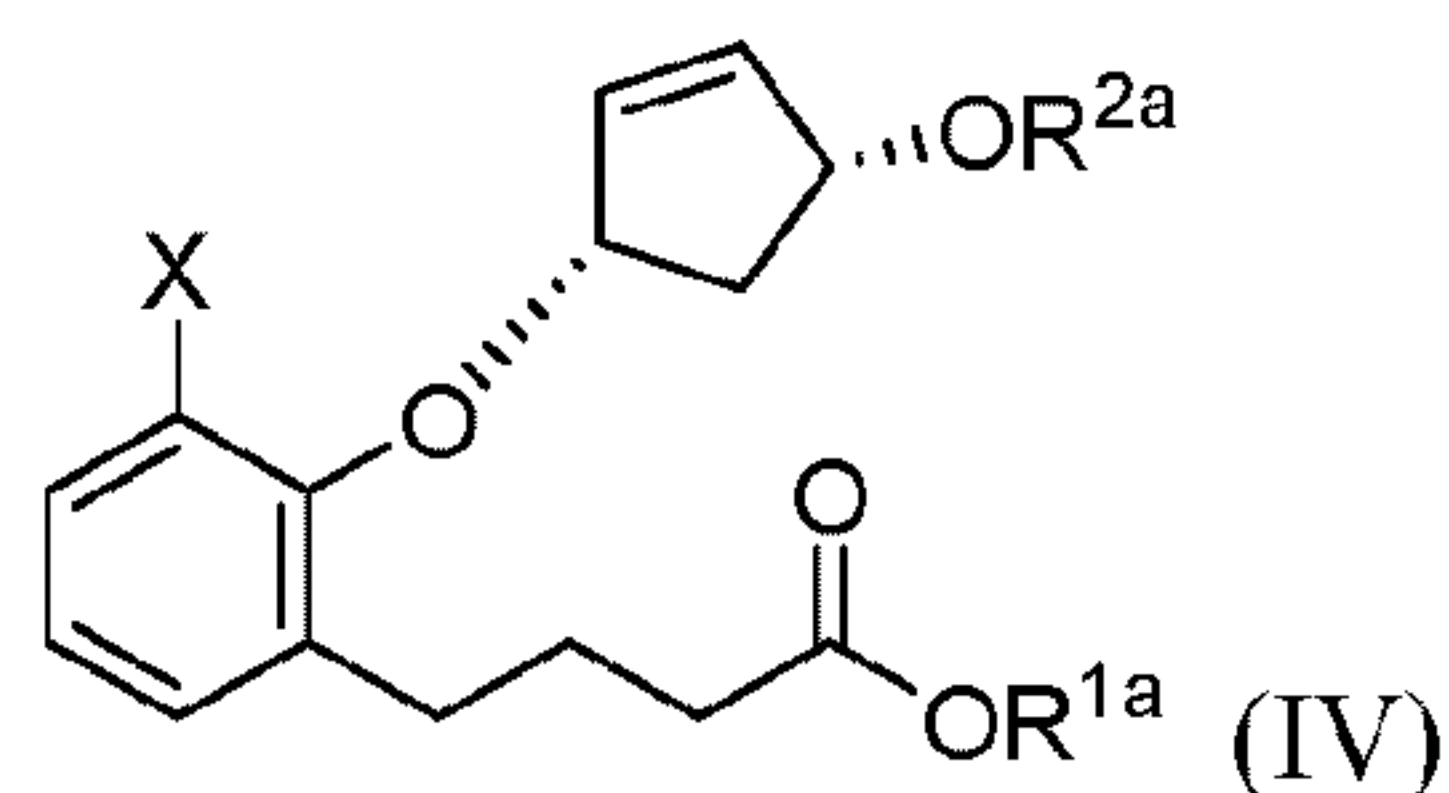
, wherein R^{2a} is defined above,

with a compound of the following formula:



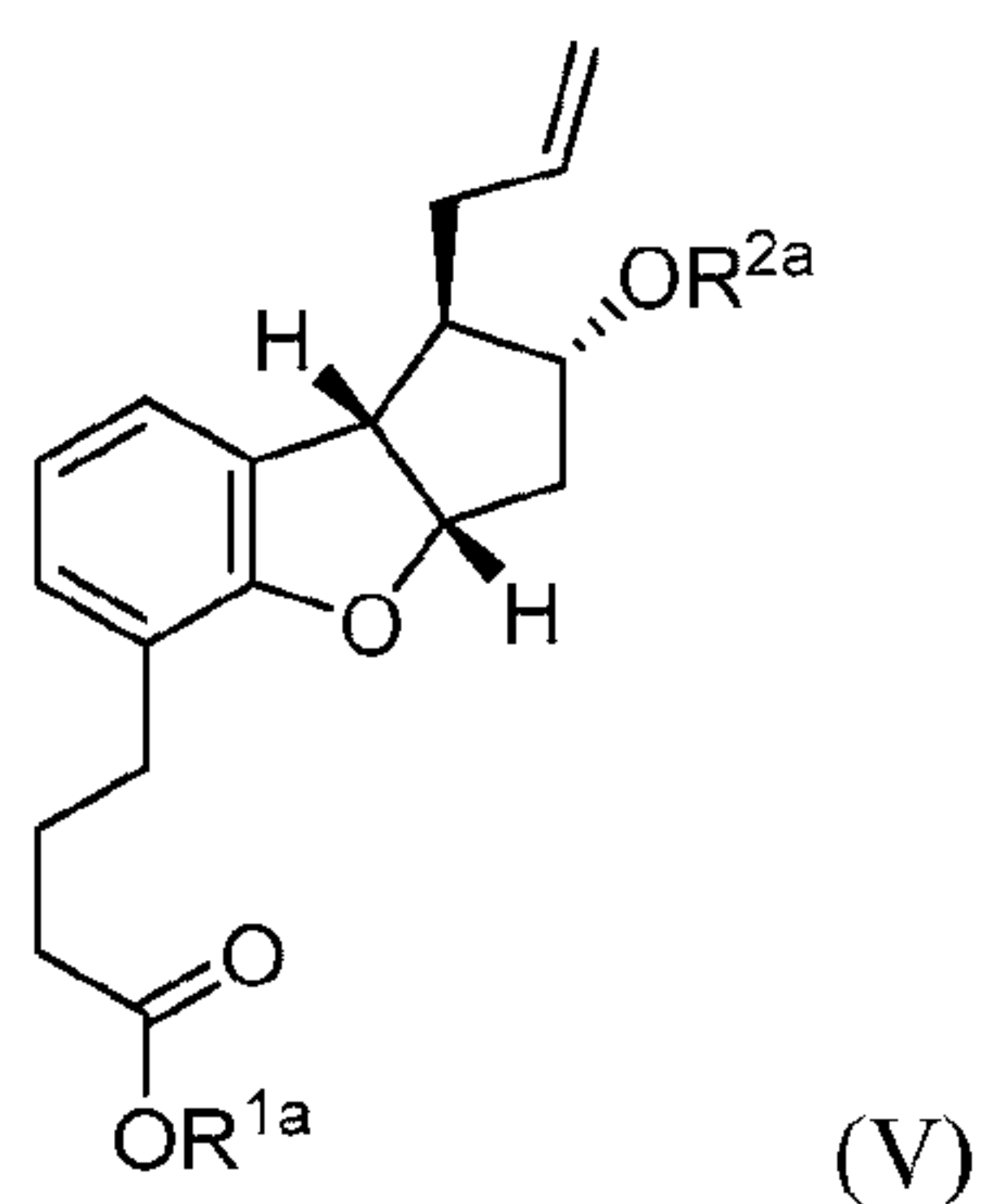
, wherein R^{1a} is defined above, X is halogen

to form a compound of the following formula:



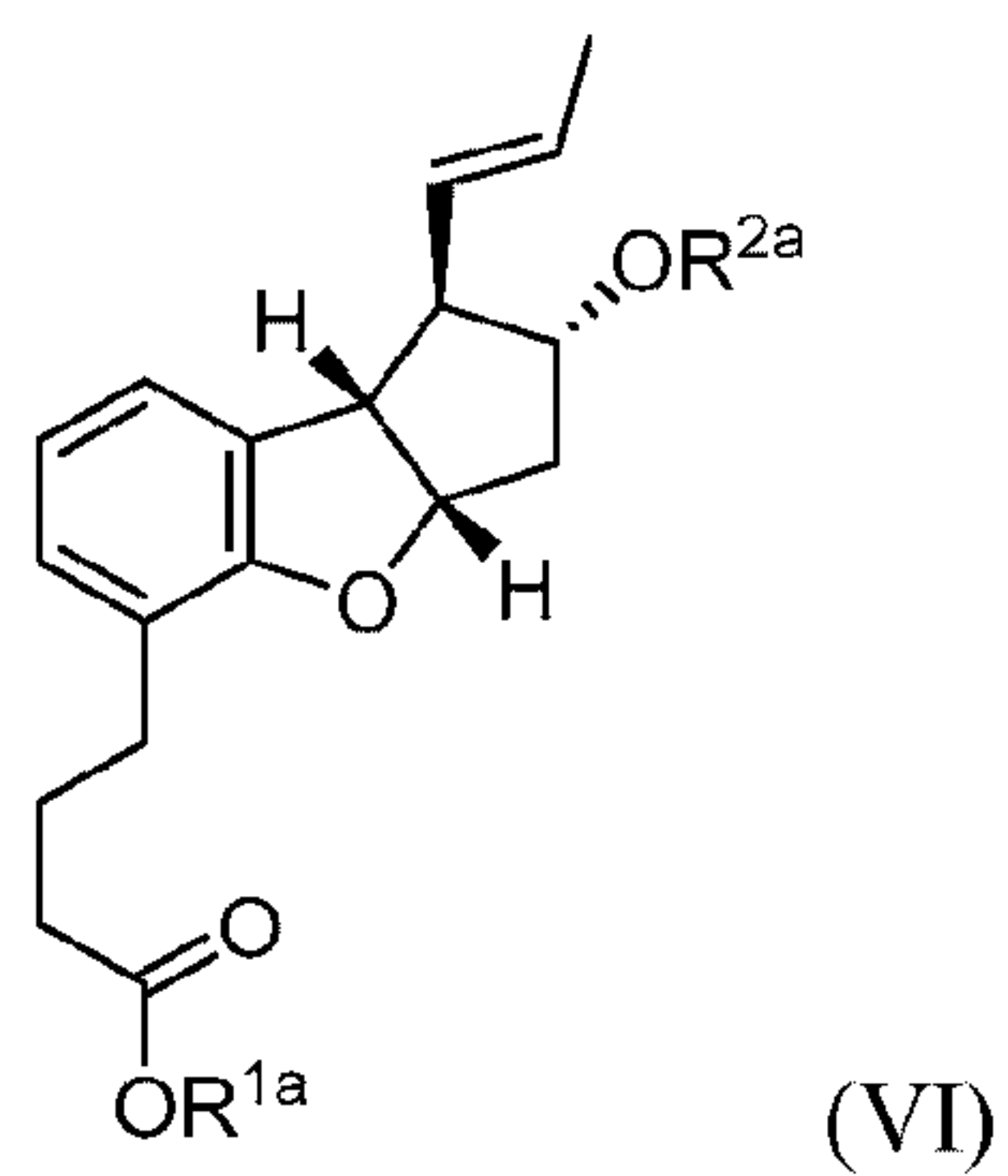
, wherein R^{1a} , R^{2a} and X is each defined above;

(2) radical cyclization of formula (IV) to form a compound of the following formula:



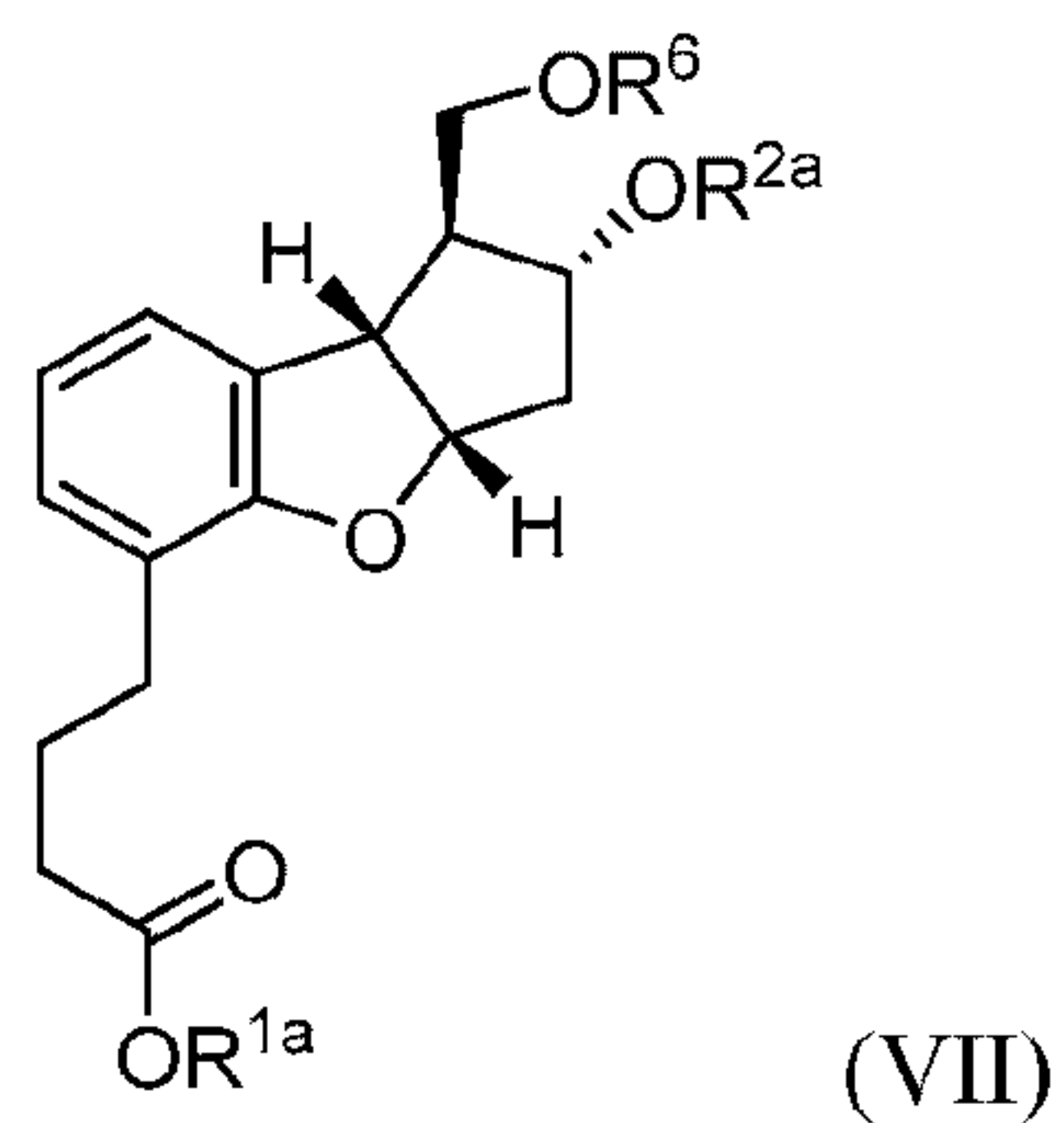
,wherein R^{1a} and R^{2a} is each defined above;

(3) isomerizing the allyl of the compound of formula (V) to form a propenyl resulting in a compound of the following formula:



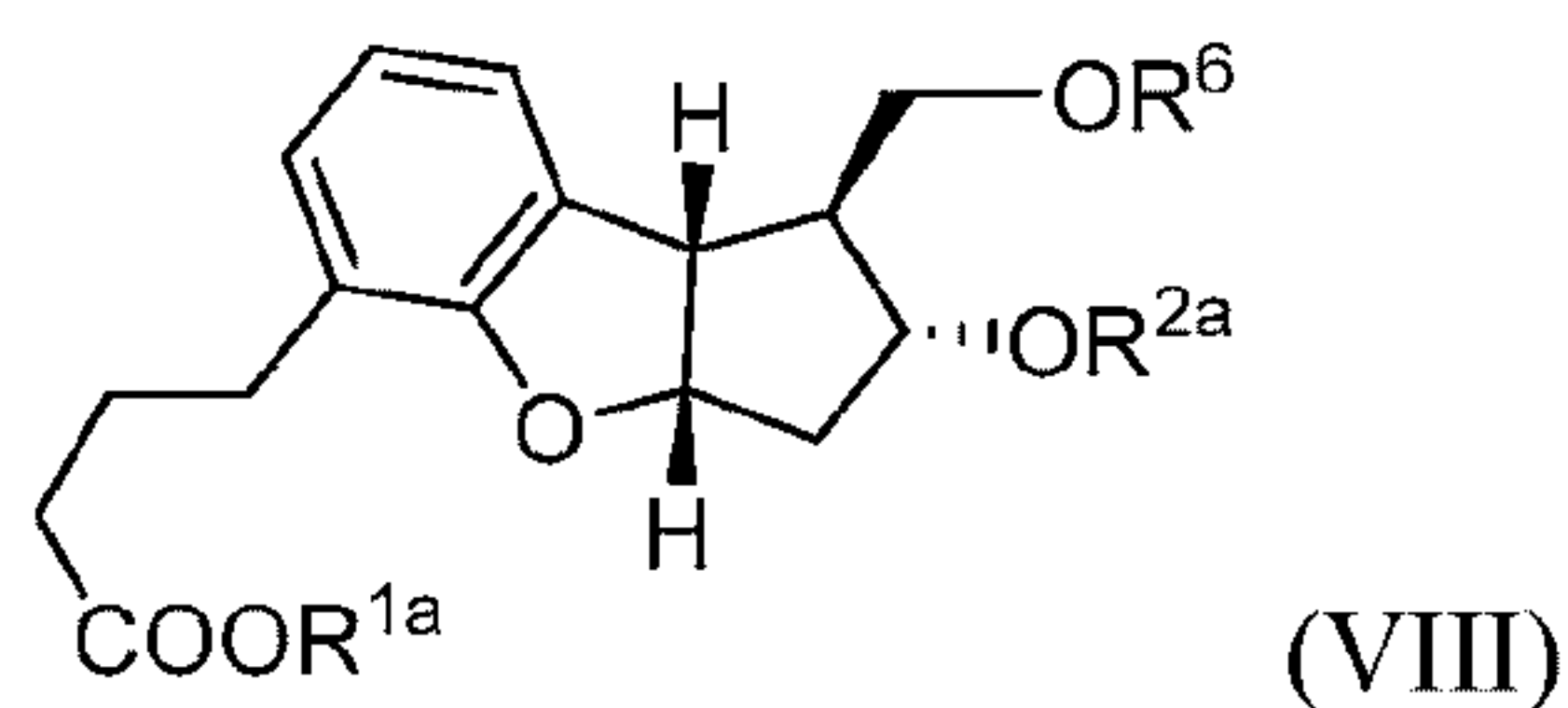
,wherein R^{1a} and R^{2a} is each defined above;

(4) ozonolysis and *in situ* reduction to convert the propenyl of the compound of formula (VI) to form an alcohol resulting in a compound of the following formula:



,wherein R^{1a} , R^{2a} and R^6 are each defined above;

(5) deprotection of the acetate of the compound of formula (VII) to form a compound of the following formula:



,wherein R^{1a}, R^{2a} and R⁶ is each defined above.

In some embodiments, the compound of formula (VIII) is produced as a substantially pure single isomer.

In some embodiments, R^{2a} and R⁶ each independently represent an acetate, a silyl ester (for example, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, phenyldimethylsilyl, tetrahydropyranyl), benzoate ester, benzyl or substituted benzyl.

In some embodiments, R^{1a} is CH₃, and R^{2a} and R⁶ are both H. In some embodiment, X is chloro, bromo or iodo.

In some embodiments, azobisisobutyronitrile is used in step (2) as a radical initiator.

In some embodiments, a catalytic amount of carbonylchlorohydridotris(triphenylphosphine) ruthenium (II) is used in step (3).

In some embodiments, sulfuric acid is used in step (5).

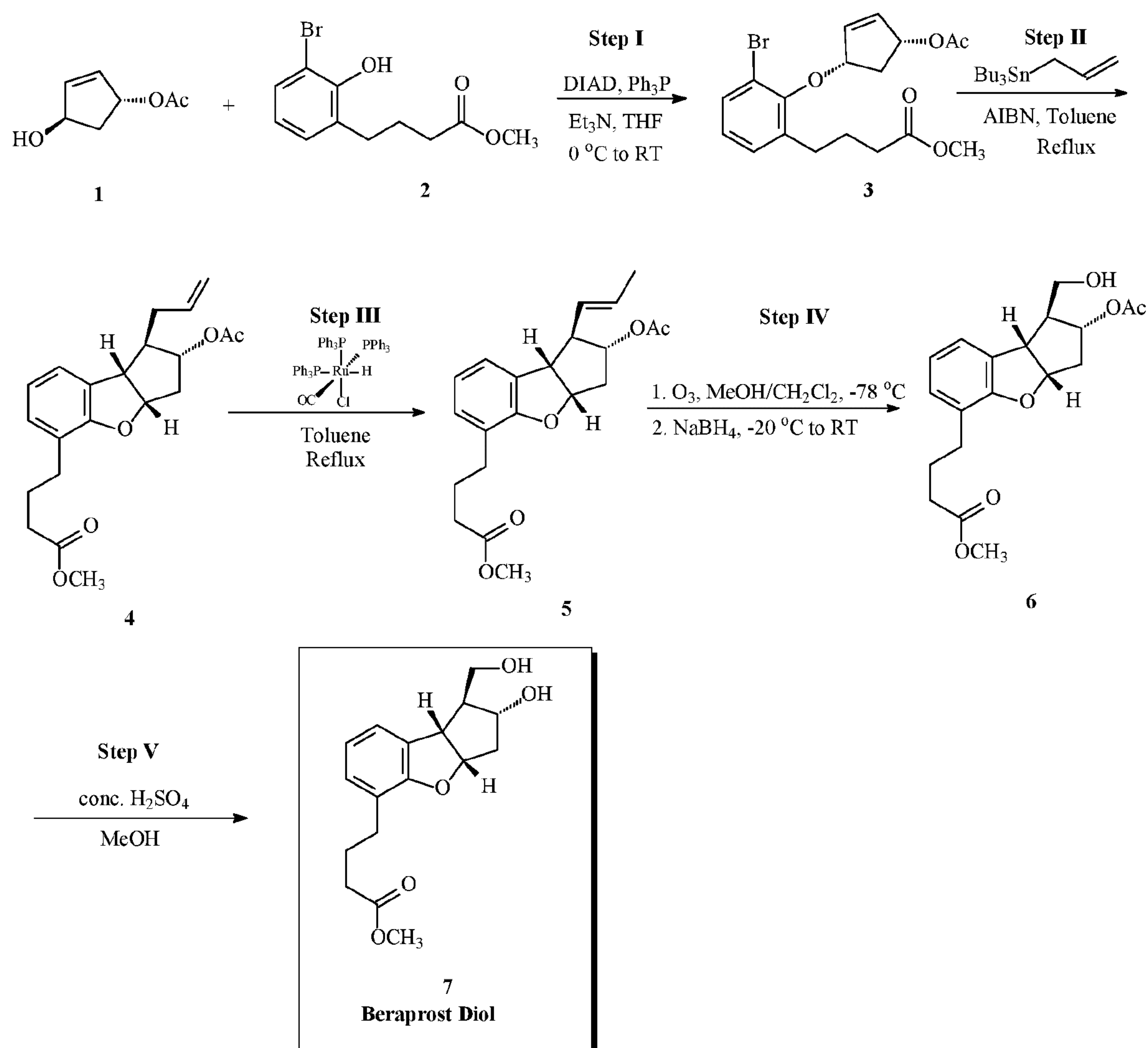
In some embodiments, the present invention provides a method that can produce a compound of formula (I), as defined below, in a substantially isomerically pure form. In some embodiments, the present invention provides a method for preparing a compound of formula (I) in fewer steps than the prior art. In a preferred embodiment, the present invention provides a method for preparing a compound of formula (I) in commercially useful quantities. In another preferred embodiment, the present invention provides a method that can produce the beraprost diol intermediates represented by formula (VIII), as defined below, in a substantially isomerically pure form, which can be used for the production of pharmaceutical compounds represented by the general formula (I) or other similar compounds. In yet another preferred embodiment, the present invention provides a method comprising a key radical cyclization step for the synthesis of tricyclic beraprost and its derivatives on a larger scale, preferably more than about 2 grams, more preferably more than about 10 grams. In other embodiments, the invention relates to any of the compounds in the reaction schemes

depicted herein in a more pure form compared to those obtained by presently known methods, including an isomerically more pure form.

In some embodiments, the synthesis of beraprost diol (7) is carried out in five steps. The first step of the synthesis comprises the coupling of (1*R*,4*R*)-4-hydroxycyclopent-2-en-1-yl acetate and 2-bromophenol-6-carbomethoxypropane using a Mitsunobu reaction to obtain bromophenyl acetoxycyclopentenyl ether (3) with a yield of about 89.5%. The second step comprises radical cyclization and *in situ* radical trapping by reacting with allyltributyltin using azobisisobutyronitrile as a radical initiator. This step permits the formation of a tricyclic core in a stereochemical fashion. The stereochemistry is governed by the stereochemistry of the coupled compound bromophenyl acetoxycyclopentenyl ether (3) at the ether linkage and acetate group, as shown by the chiral purity of beraprost diol (99.9% by HPLC). In some embodiments, the isolated yield for this step is 65.5%. The fourth step comprises isomerizing the allyl group of allyl acetoxycyclopentabenzofuran (4) to propenyl group by using catalytic amount of carbonylchlorohydridotris(triphenylphosphine)ruthenium (II) to obtain alkenyl acetoxycyclopentabenzofuran (5) in 92.6% yield. The propenyl group of alkenyl acetoxycyclopentabenzofuran (5) is converted into alcohol functionality by the process of ozonolysis and *in situ* reduction using sodium borohydride, which provides hydroxy acetoxycyclopentabenzofuran (6) in 85.5% yield (over two steps). The last step involves deprotecting the acetate group using concentrated sulfuric acid to obtain beraprost diol (7), which is crystallized from MTBE in 80% yield. In some embodiments, the yield may be greater than 80%, greater than 85%, greater than 90%, or greater than 95%. In a preferred embodiment, the overall yield of this process over 5 steps is 37%, or greater than 37% with a chiral purity of 99.9% or more by HPLC. In some embodiments, the overall yield is greater than 40%, greater than 45%, or greater than 50%.

In some embodiments, a method of producing beraprost diol comprises the steps shown below.

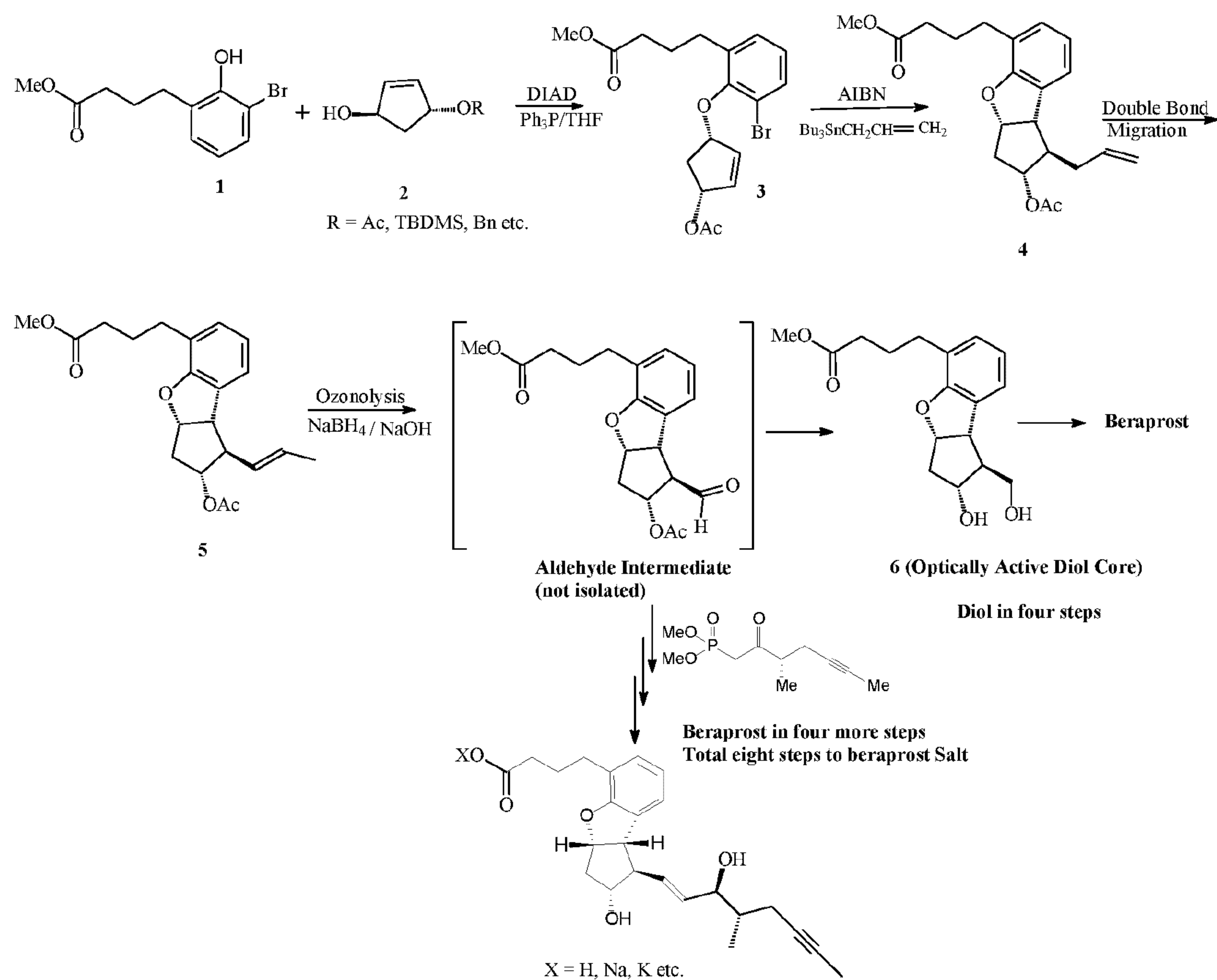
Scheme 1: Synthesis of Chiral Beraprost Diol by Radical Cyclization



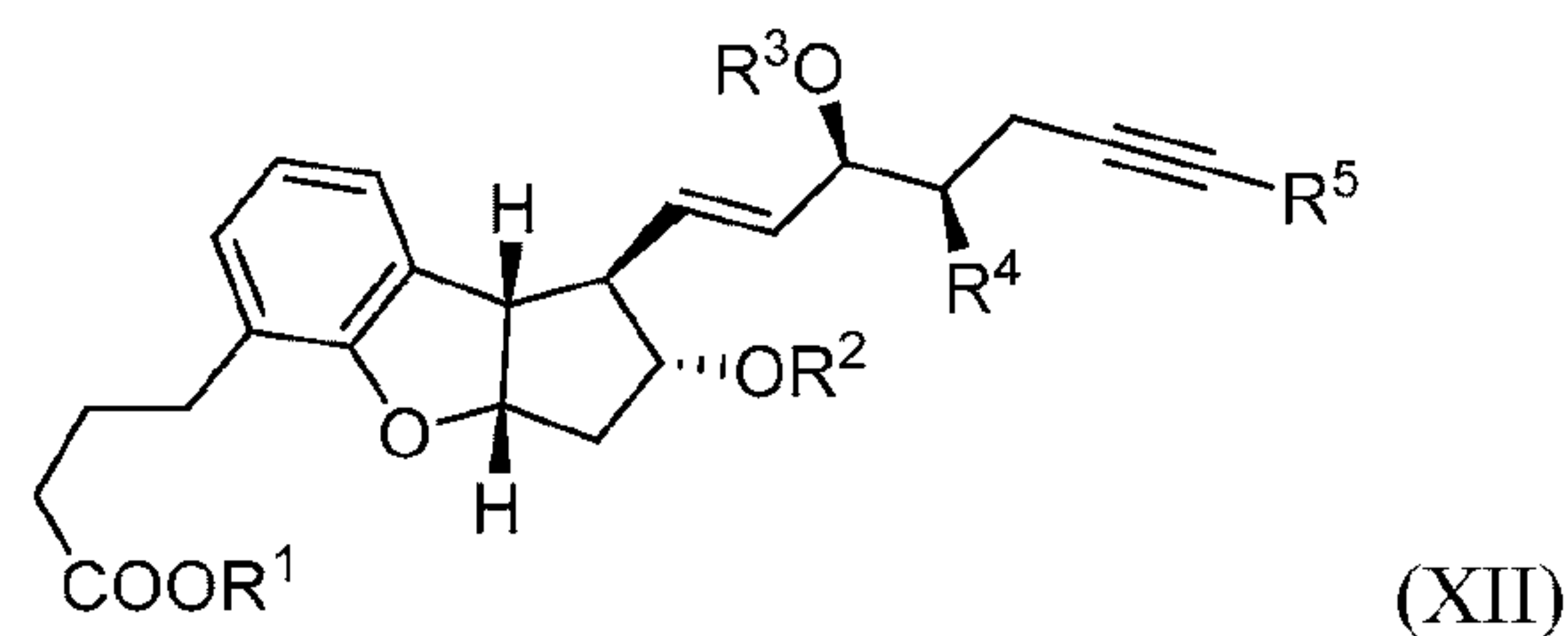
In some embodiments, the methods described herein are advantageous over the previous methods for making beraprost or its derivatives as it directly produces the optically active diol, and thus does not require separating the desired isomer from a racemic mixture. In addition, in some embodiments, the methods described herein can be used to synthesize beraprost in only seven or eight steps, which is the shortest chiral route to obtain the beraprost 314d isomer as well as its derivatives.

In some embodiments, the synthesis of beraprost is carried out according to the following scheme.

Scheme 2: Synthesis of Beraprost

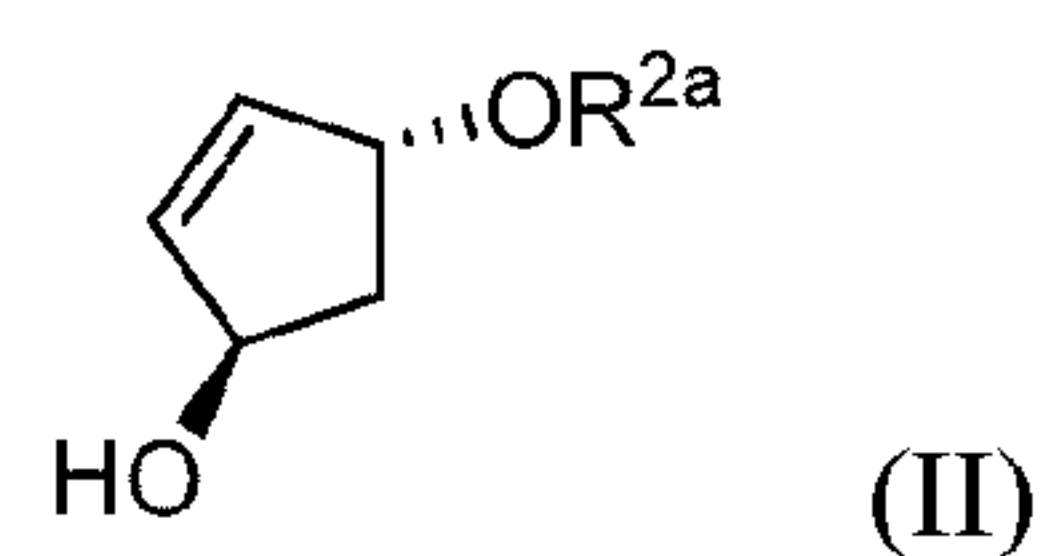


In some embodiments, the present invention provides a process for preparing a compound of the following formula:

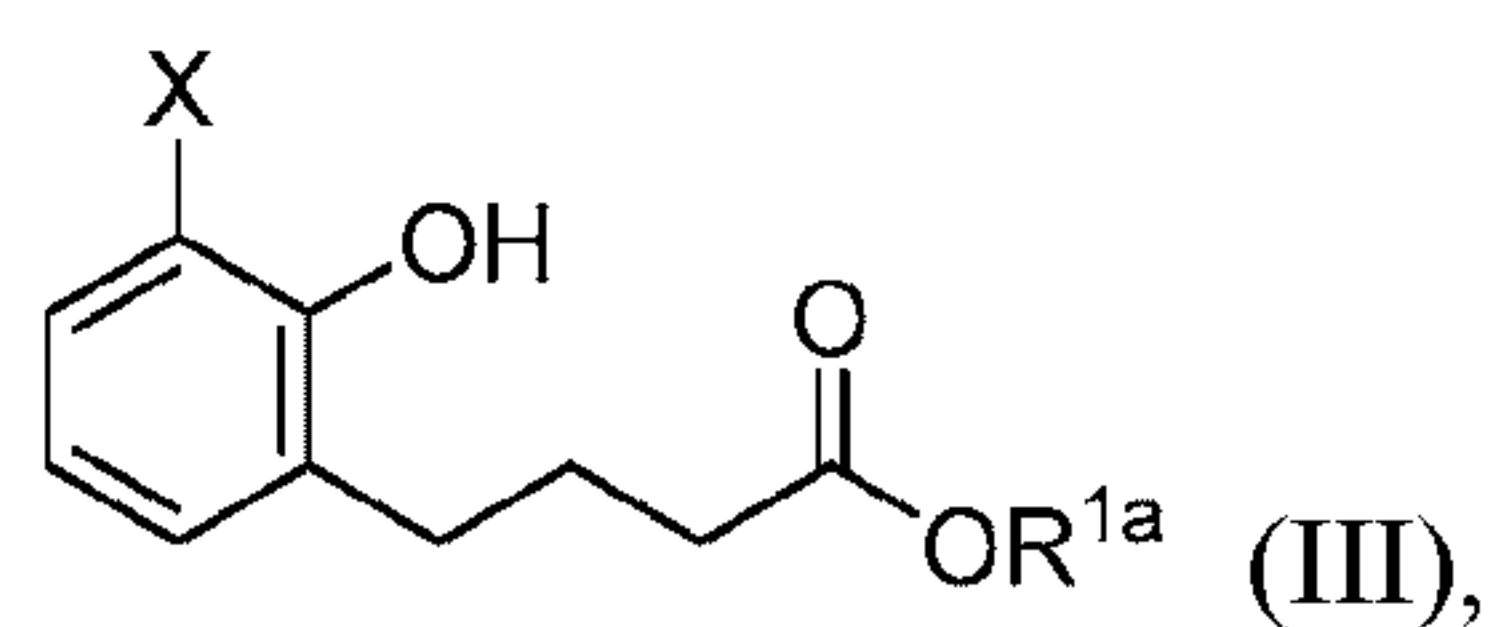


wherein R^1 represents a cation, H, or C_{1-12} alkyl,
 R^2 and R^3 each represent H or a hydroxy protective group,
 R^4 represents H or C_{1-3} alkyl, and
 R^5 represents H or C_{1-6} alkyl, comprising:

(1) reacting a compound of the following formula:

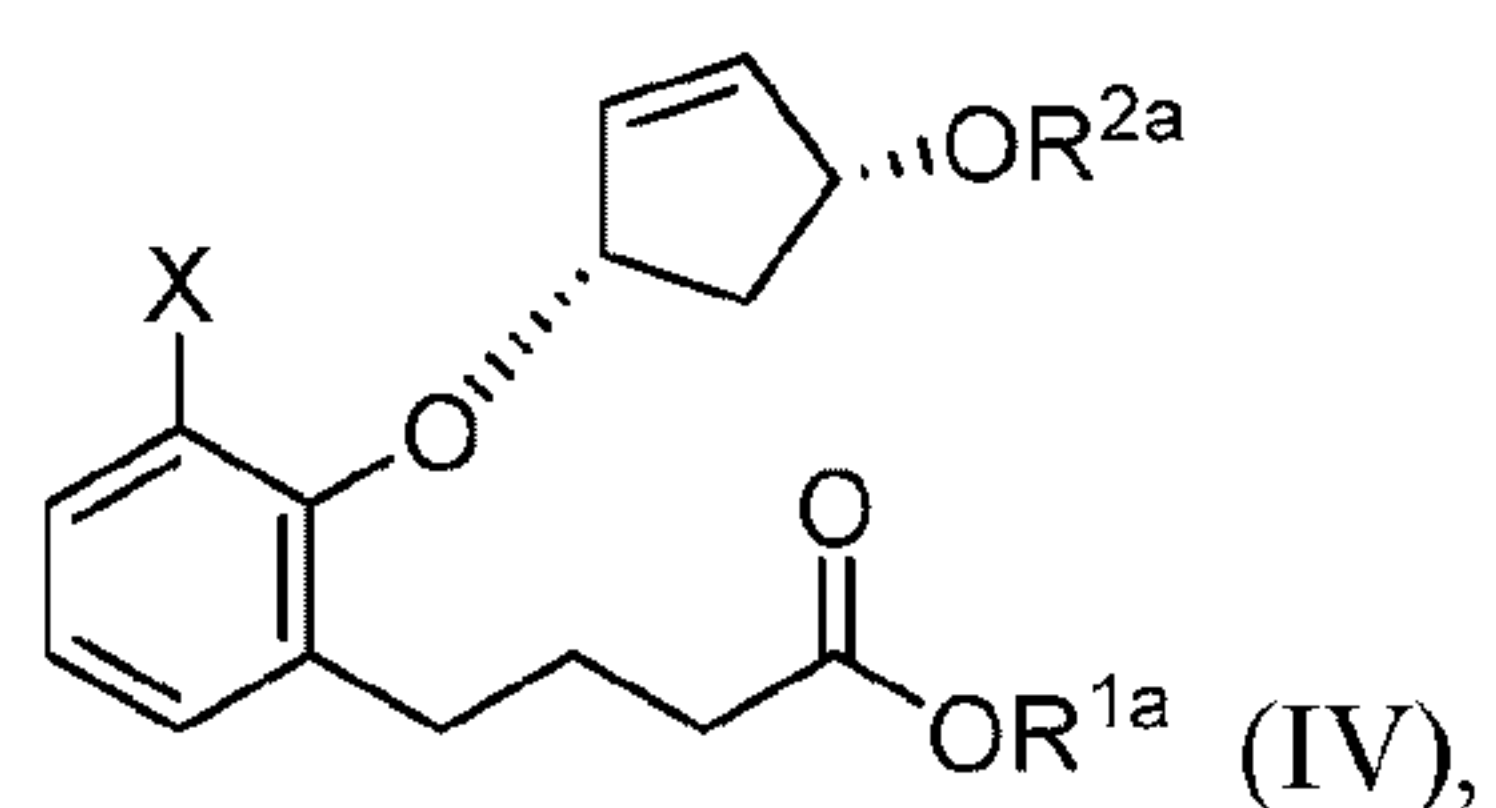


, wherein R^{2a} is H or an hydroxy protective group,
with a compound of the following formula:



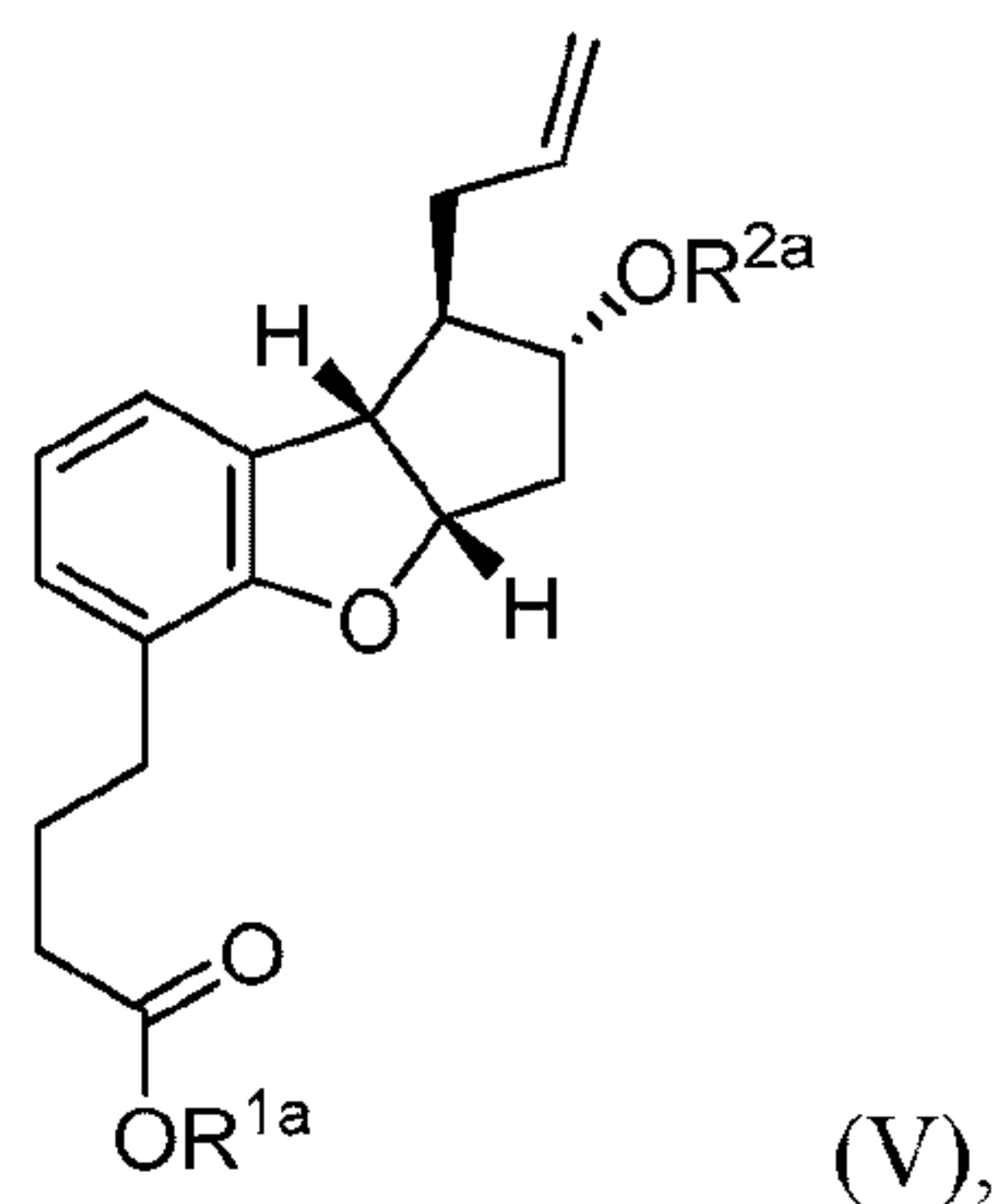
wherein R^{1a} is a cation, H, or C_{1-12} alkyl, X is a halogen selected from chloro, bromo and iodo,

to form a compound of the following formula:



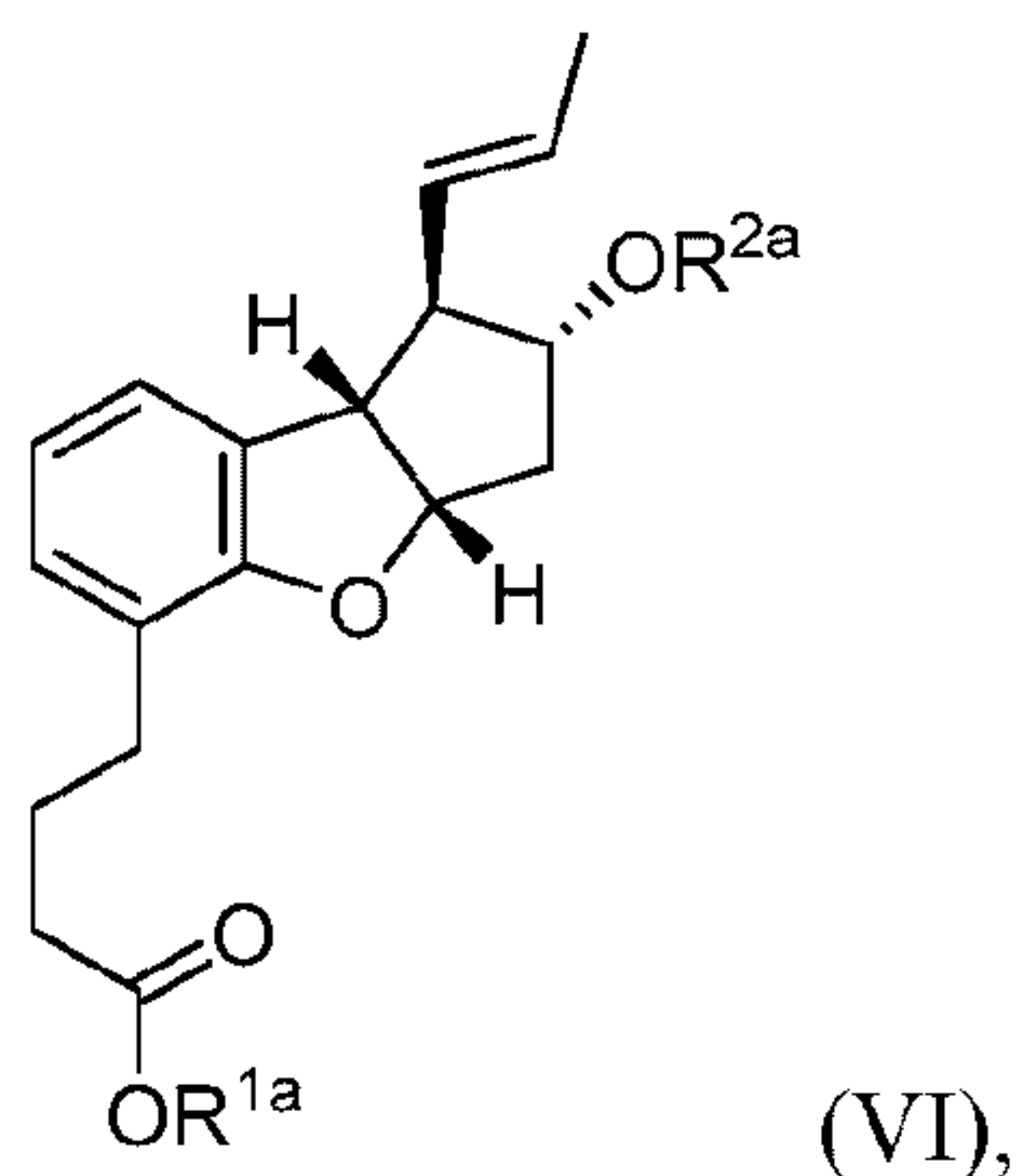
wherein R^{1a} , R^{2a} and X are each defined above;

(2) cyclizing a compound of formula (IV) to form a compound of the following formula:



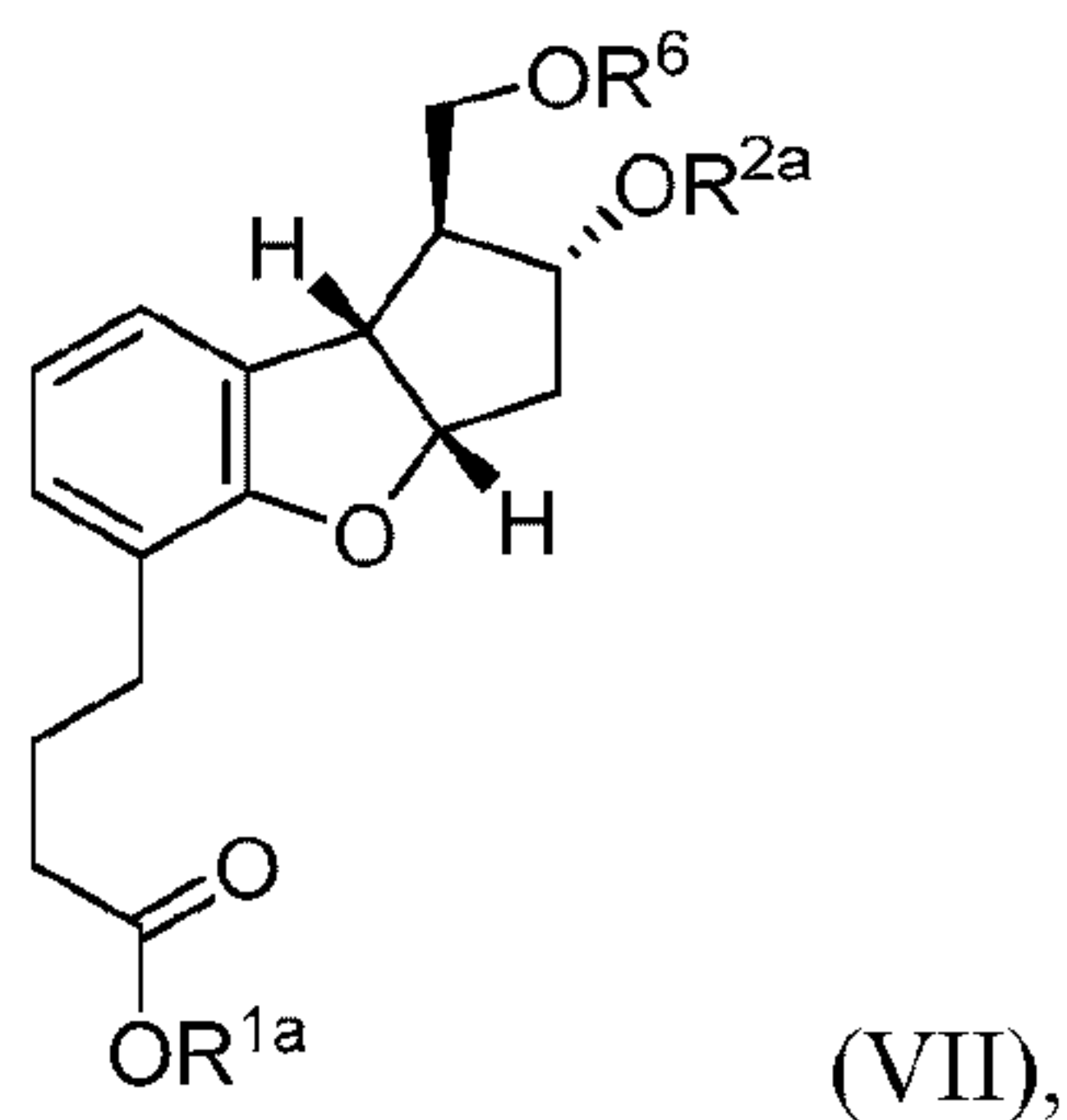
wherein R^{1a} and R^{2a} are each defined above;

(3) isomerizing an allyl of the compound of formula (V) to form a propenyl resulting in a compound of the following formula:



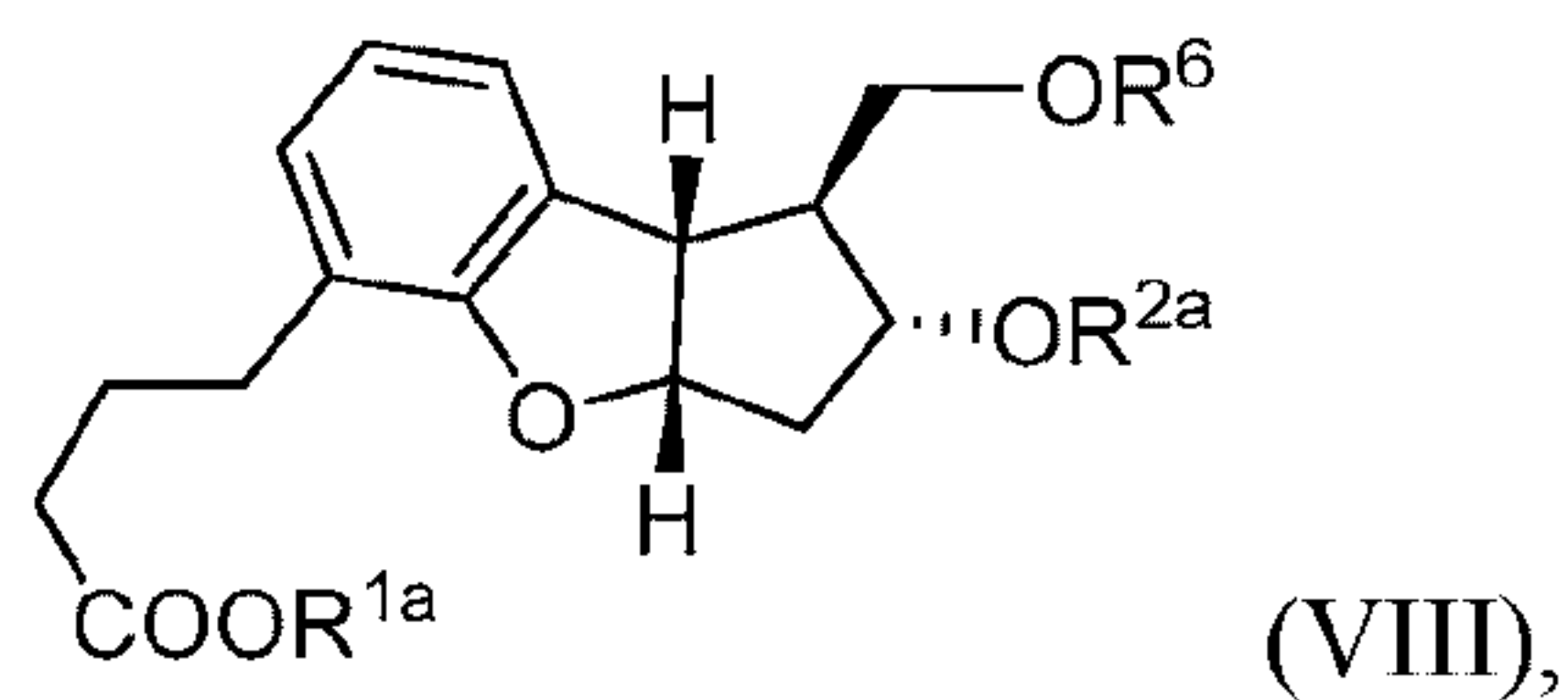
wherein R^{1a} and R^{2a} are each defined above;

(4) ozonolysis and *in situ* reduction to convert the propenyl of the compound of formula (VI) to form an alcohol resulting in a compound of the following formula:



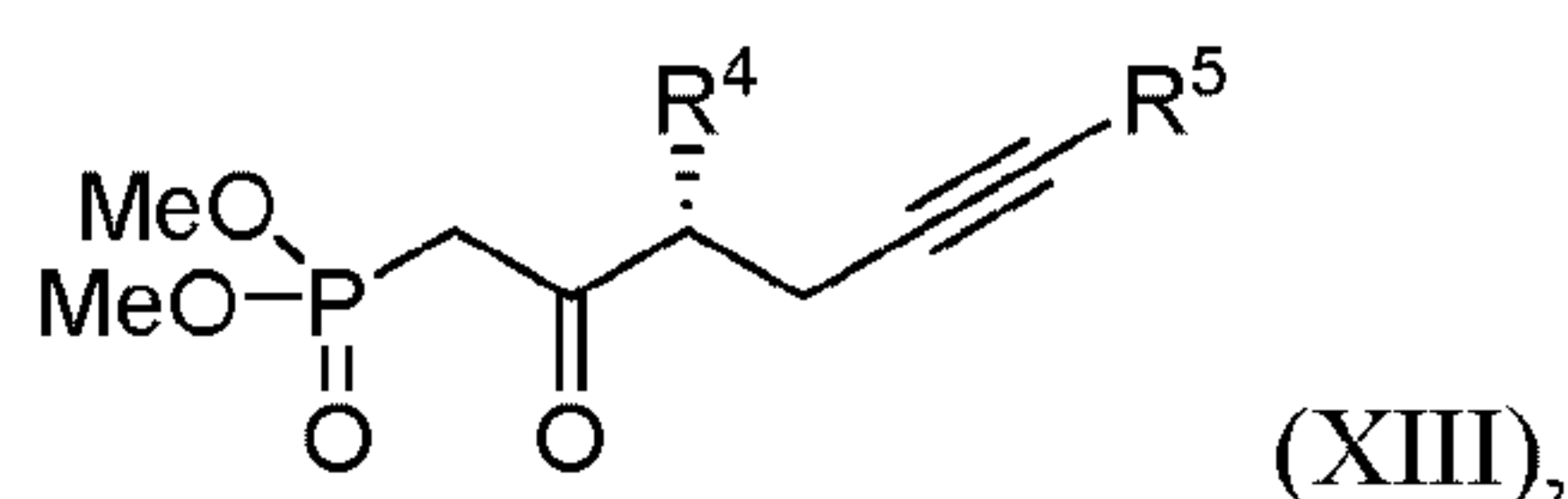
wherein R^{1a} and R^{2a} are each defined above, R⁶ is H or a hydroxy protective group;

(5) deprotecting an acetate of the compound of formula (VII) to form a compound of the following formula:

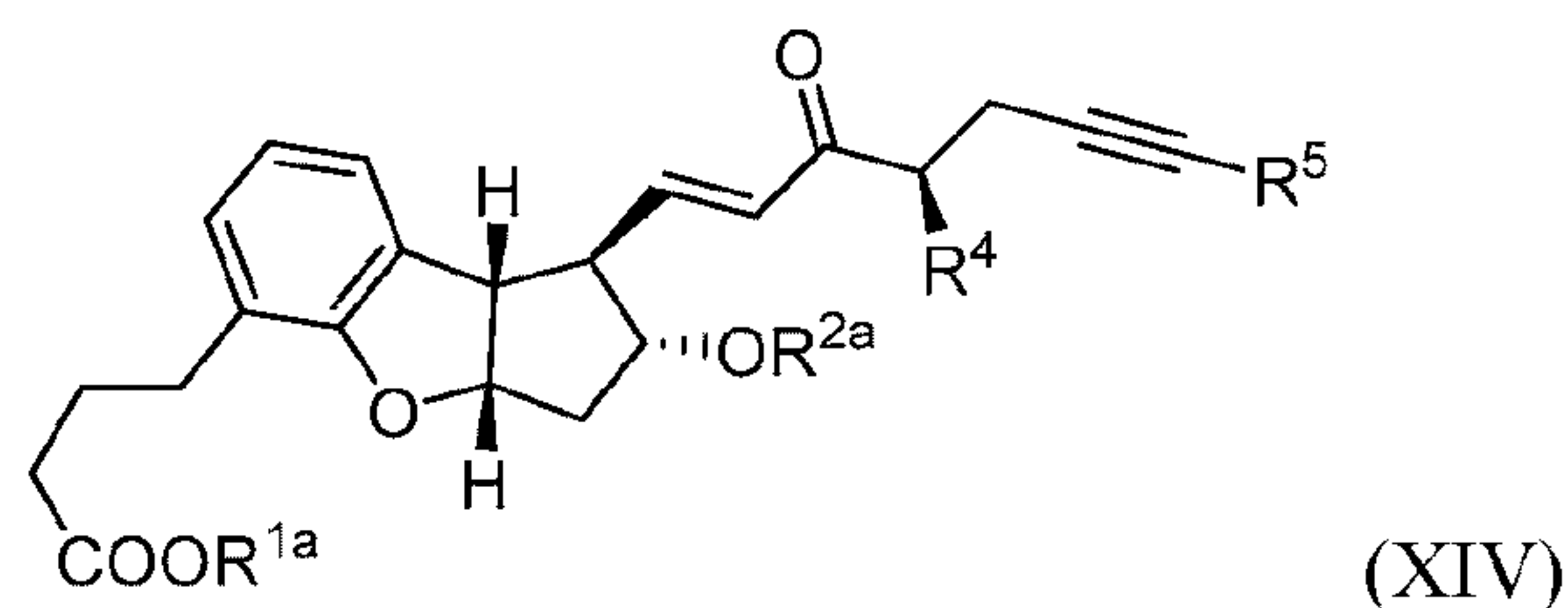


wherein R^{1a}, R^{2a} and R⁶ are each defined above;

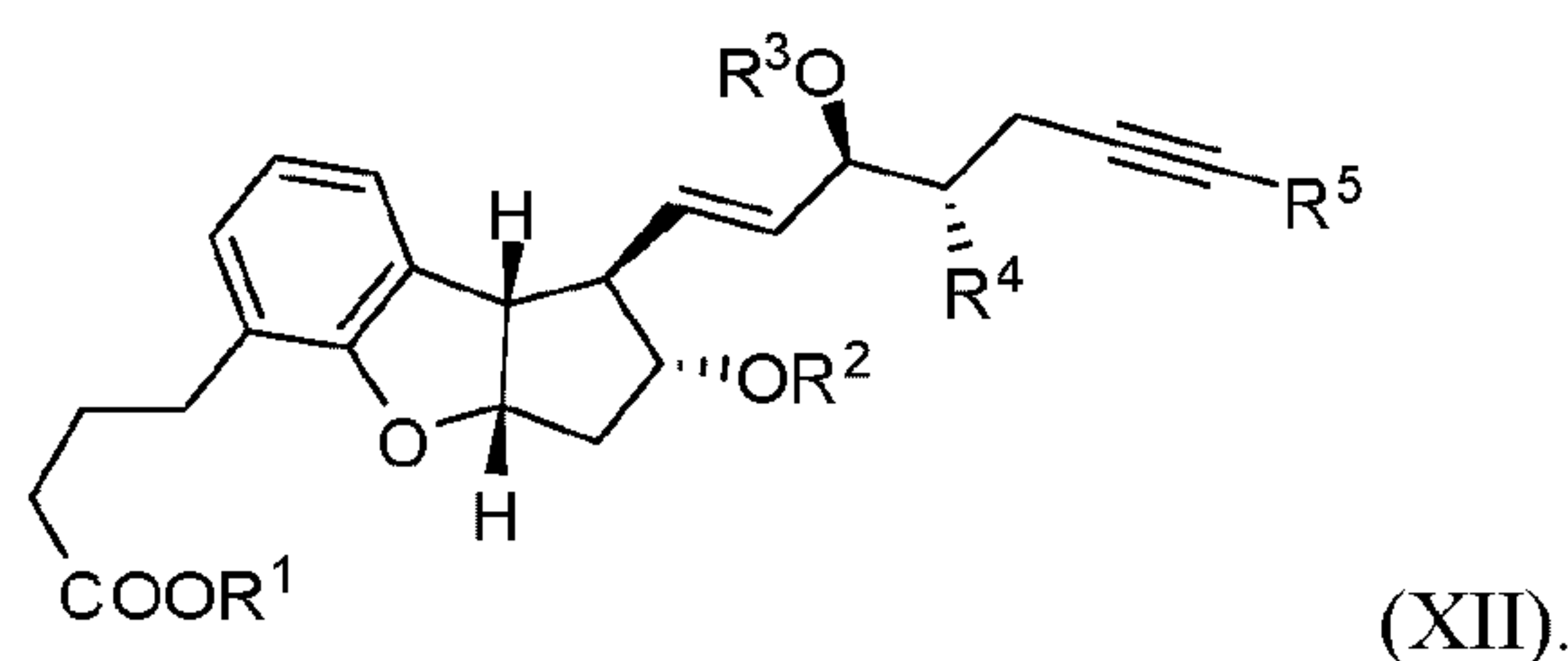
(6) selectively deprotecting the primary hydroxy protective group, followed by oxidation of the primary hydroxy group to form an aldehyde, followed by coupling with a side-chain of the formula:



wherein R^4 and R^5 are each defined above to form a compound of the following formula:



(7) reduction of the ketone, deprotection of any remaining hydroxy protective group and optionally converting the R^{1a} into a cation or H to form a compound of the following formula:



In some embodiments, the present invention provides a method that produces the compound of formula (XII) as a substantially pure single isomer.

In some embodiments, R^2 , R^3 , R^{2a} and R^6 each independently represent acetate, trimethylsilyl, triethylsilyl, t-butyl dimethylsilyl, t-butyl diphenylsilyl, phenyl dimethylsilyl, tetrahydropyranyl, benzoate ester, benzyl, or substituted benzyl.

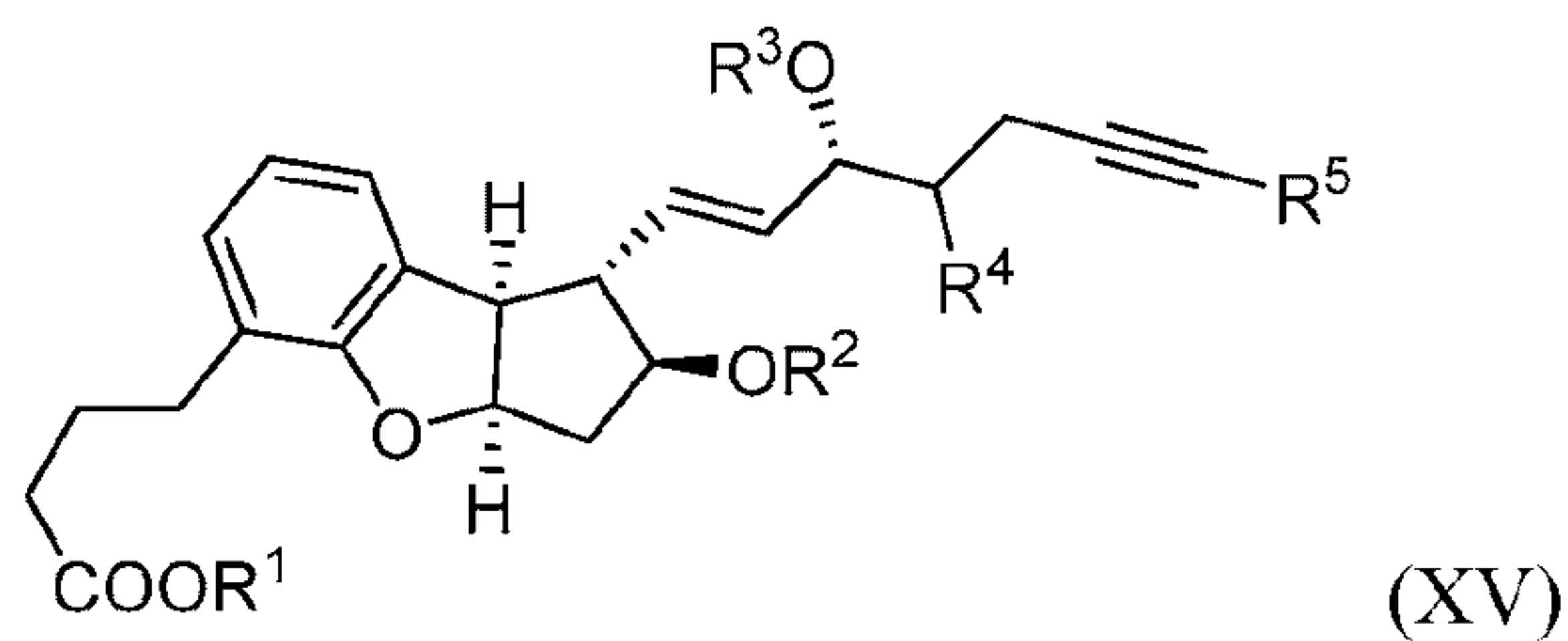
In some embodiments, R^{1a} is CH_3 and R^{2a} and R^6 are both H.

In some embodiments, azobisisobutyronitrile is used as a radical initiator in step (2).

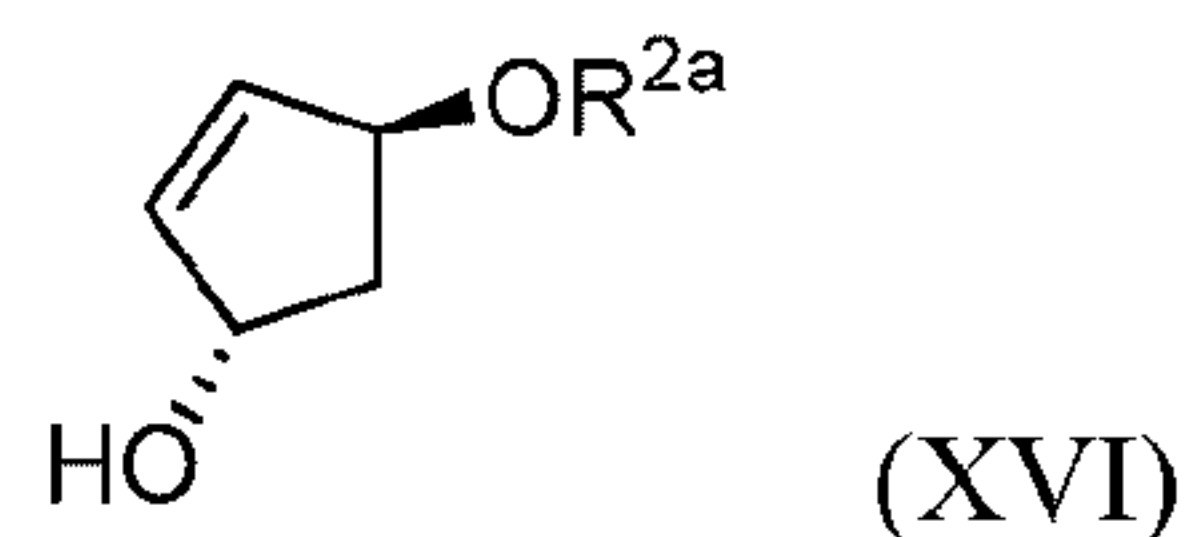
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In some embodiments, sulfuric acid is used in step (5).

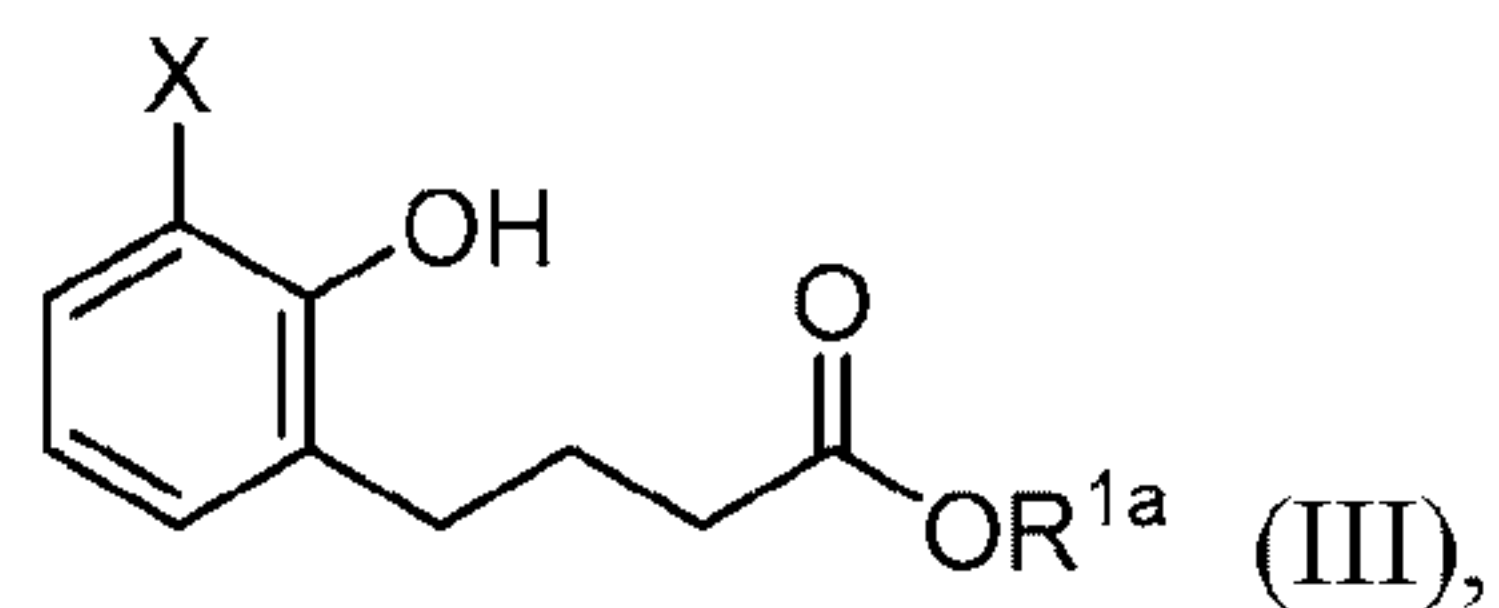
In some embodiments, the present invention provides a process for preparing a compound of the following formula:



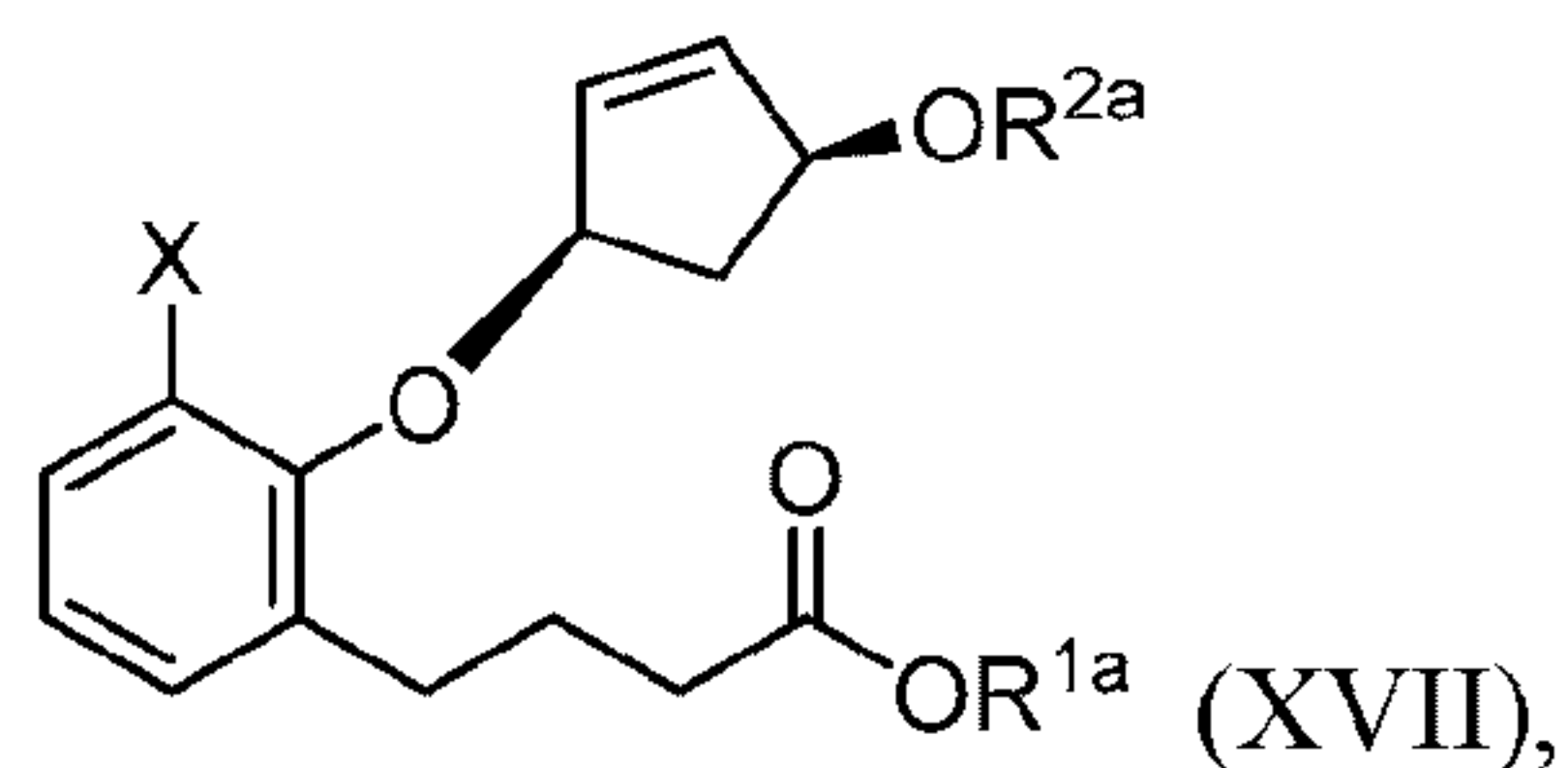
wherein R^1 represents a cation, H, or C_{1-12} alkyl,
 R^2 and R^3 each represent H or a hydroxy protective group,
 R^4 represents H or C_{1-3} alkyl, and
 R^5 represents H or C_{1-6} alkyl, comprising:
 (1) reacting a compound of the following formula:



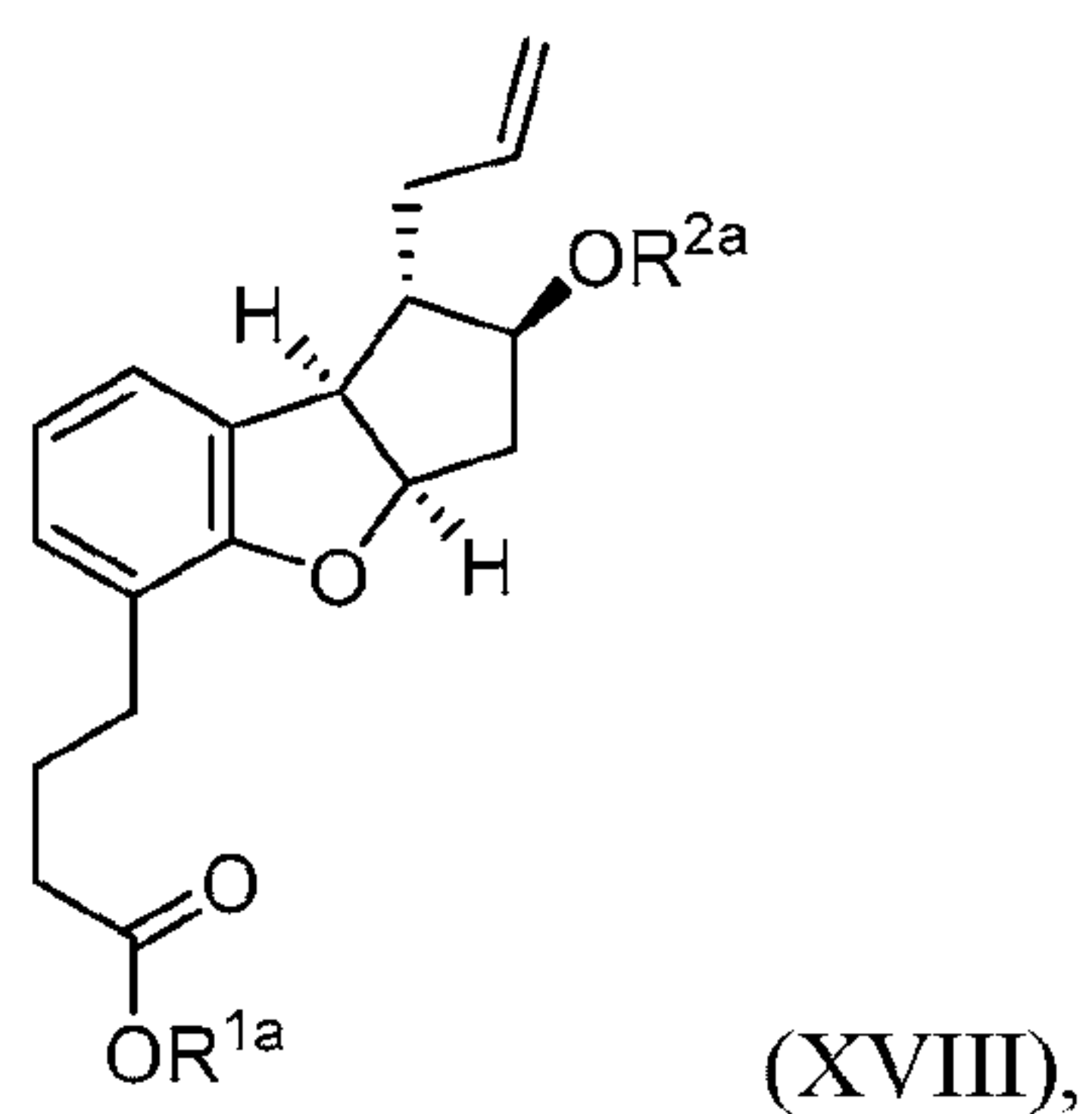
, wherein R^{2a} is H or an hydroxy protective group,
 with a compound of the following formula:



wherein R^{1a} is a cation, H, or C_{1-12} alkyl, X is a halogen selected from chloro, bromo and iodo,
 to form a compound of the following formula:

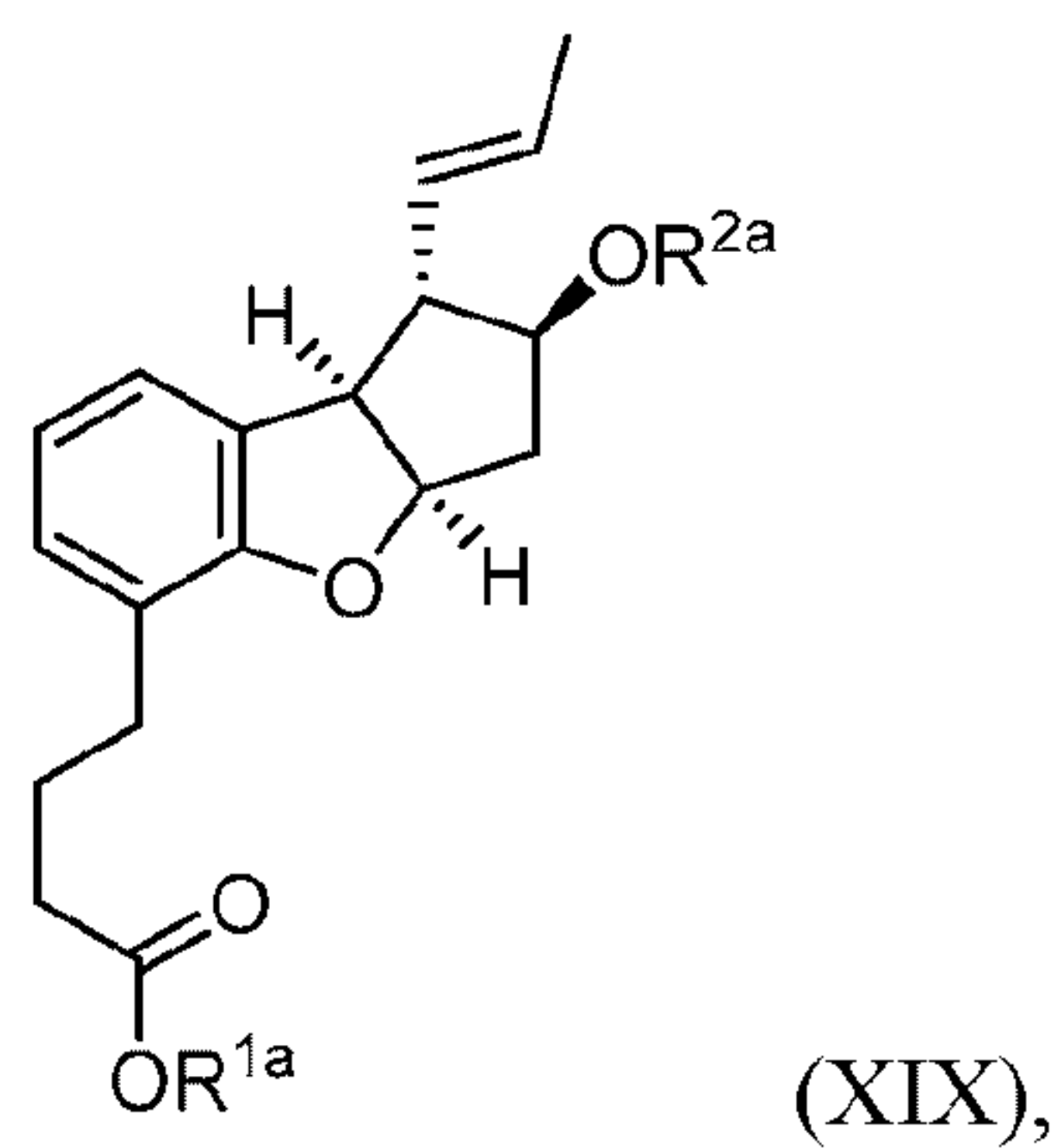


wherein R^{1a} , R^{2a} and X are each defined above;
 (2) cyclizing a compound of formula (XVII) to form a compound of the following formula:



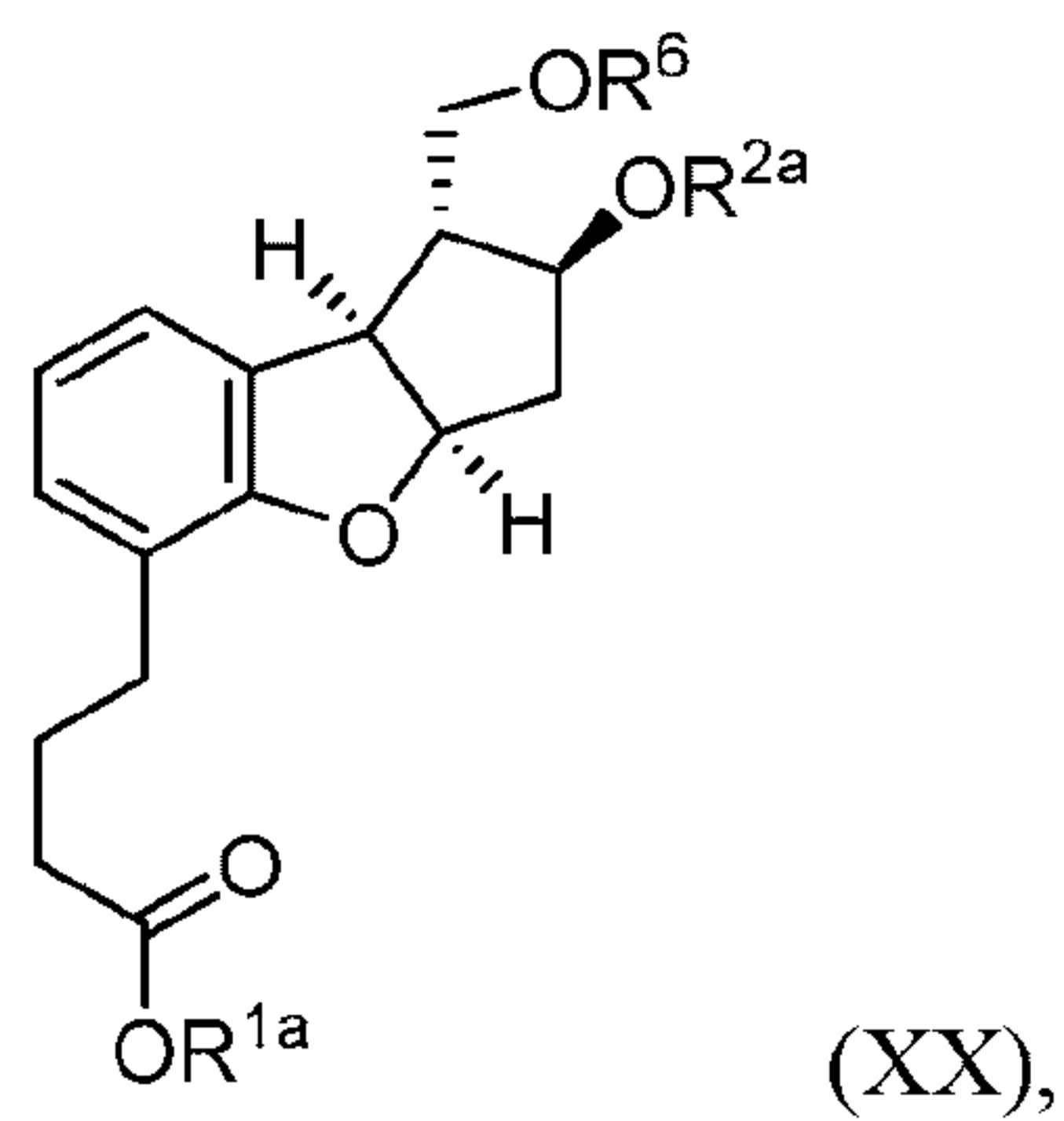
wherein R^{1a} and R^{2a} are each defined above;

(3) isomerizing an allyl of the compound of formula (XVIII) to form a propenyl resulting in a compound of the following formula:



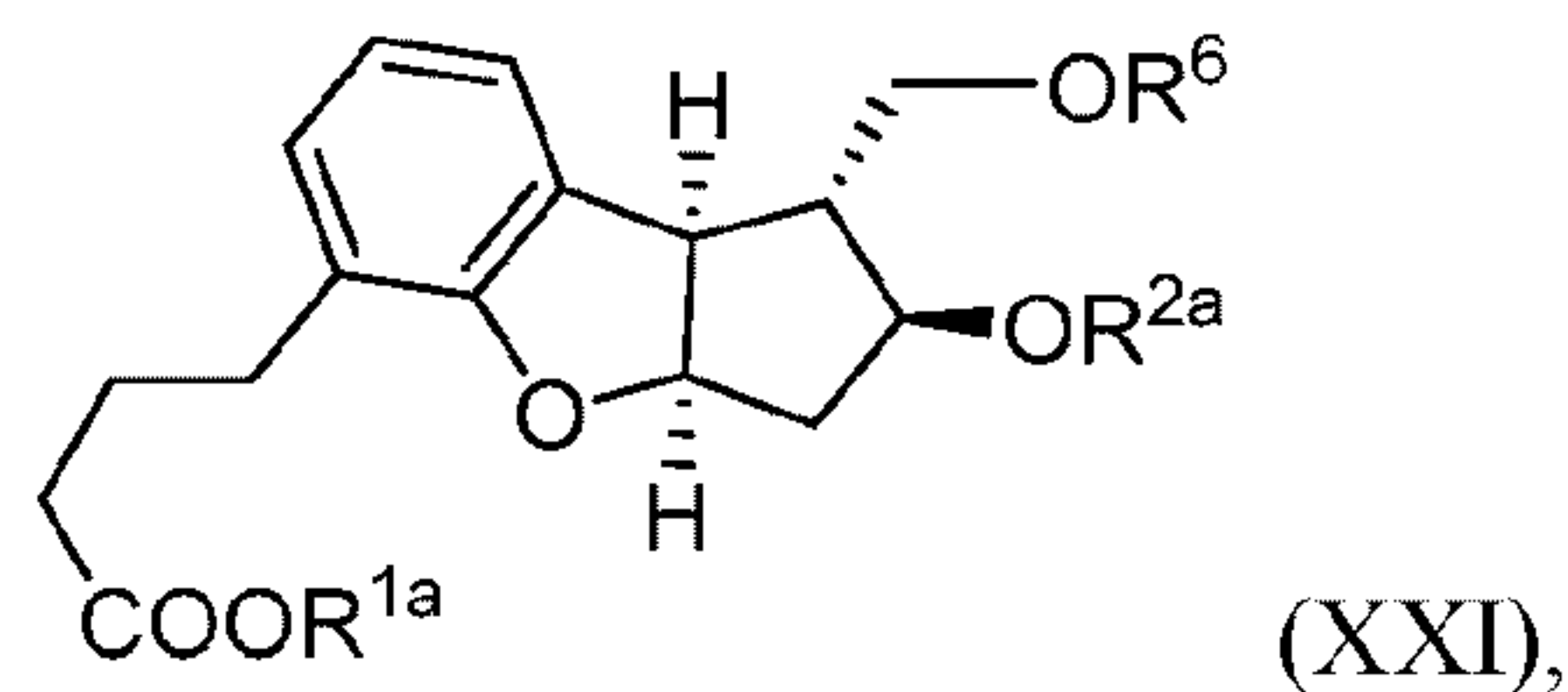
wherein R^{1a} and R^{2a} are each defined above;

(4) ozonolysis and *in situ* reduction to convert the propenyl of the compound of formula (XIX) to form an alcohol resulting in a compound of the following formula:



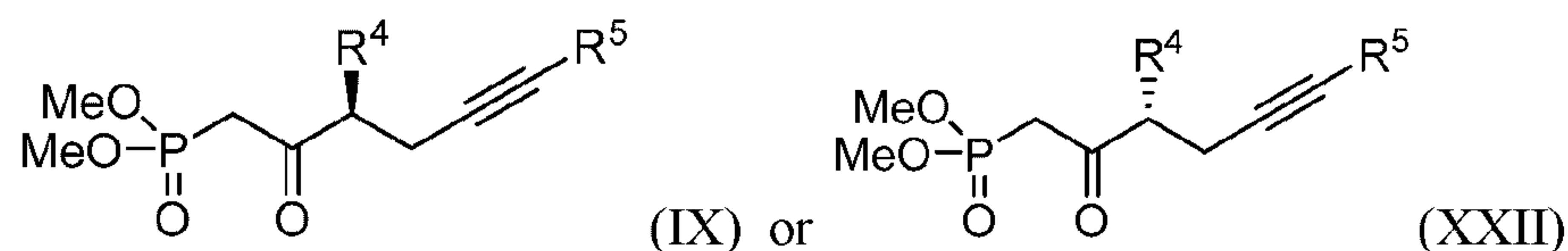
wherein R^{1a} and R^{2a} are each defined above, R^6 is H or a hydroxy protective group;

(5) deprotecting an acetate of the compound of formula (XX) to form a compound of the following formula:

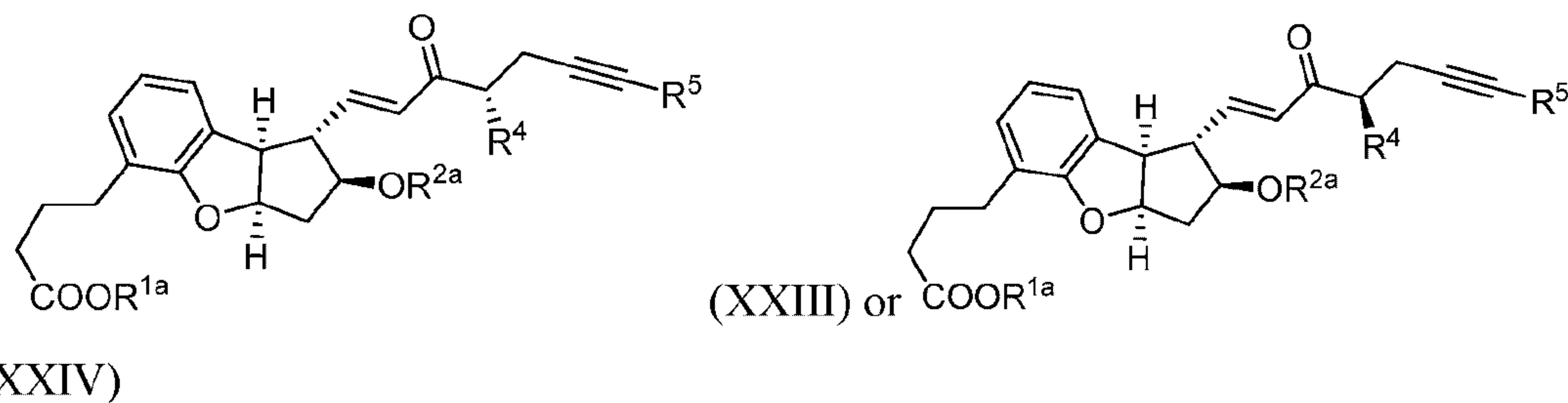


wherein R^{1a} , R^{2a} and R^6 are each defined above;

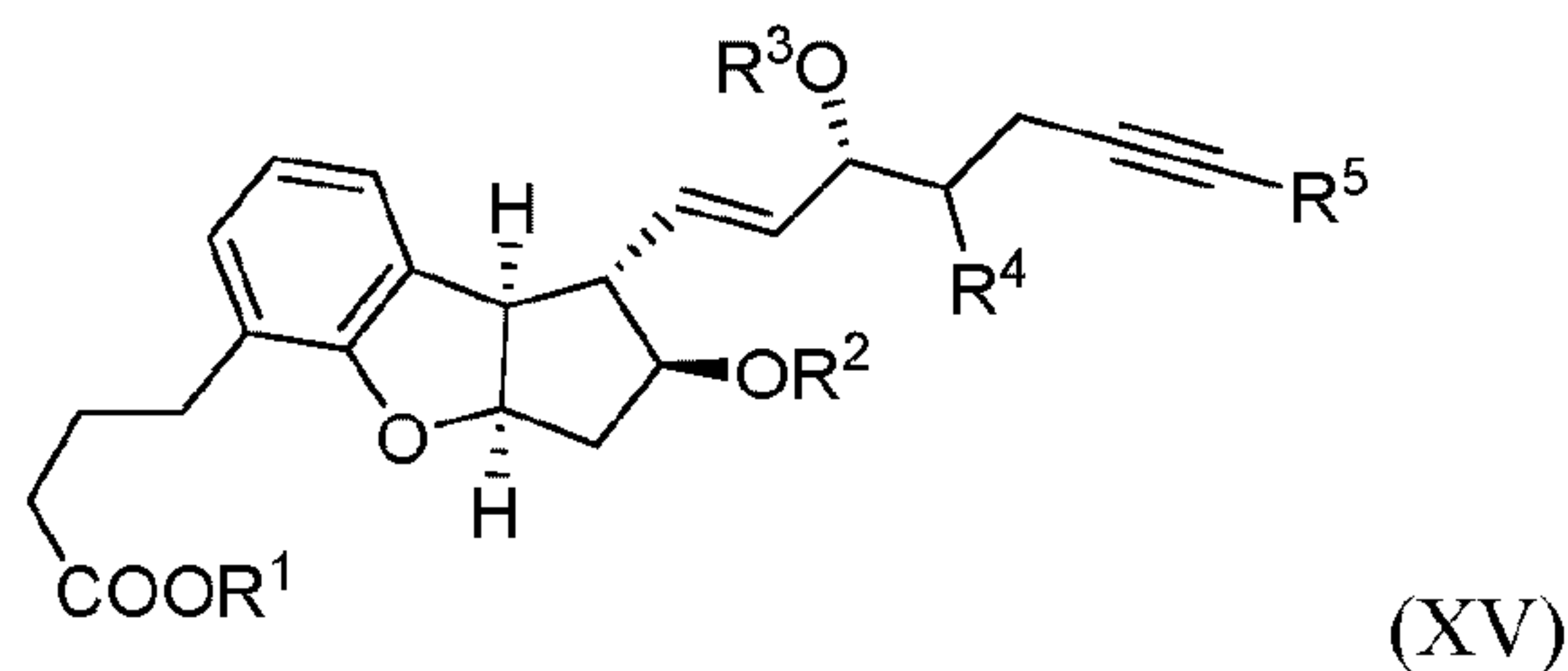
(6) selectively deprotecting the primary hydroxy protective group, followed by oxidation of the primary hydroxy group to form an aldehyde, followed by coupling with a side-chain of the formula:



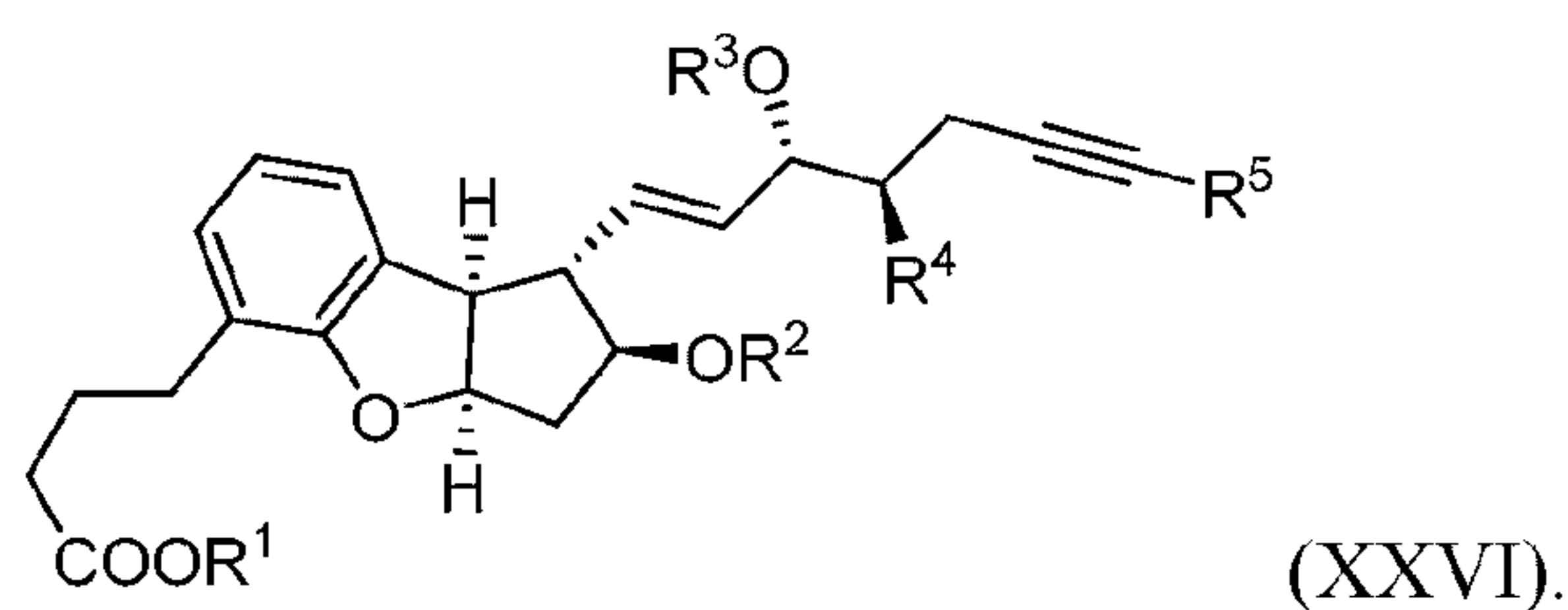
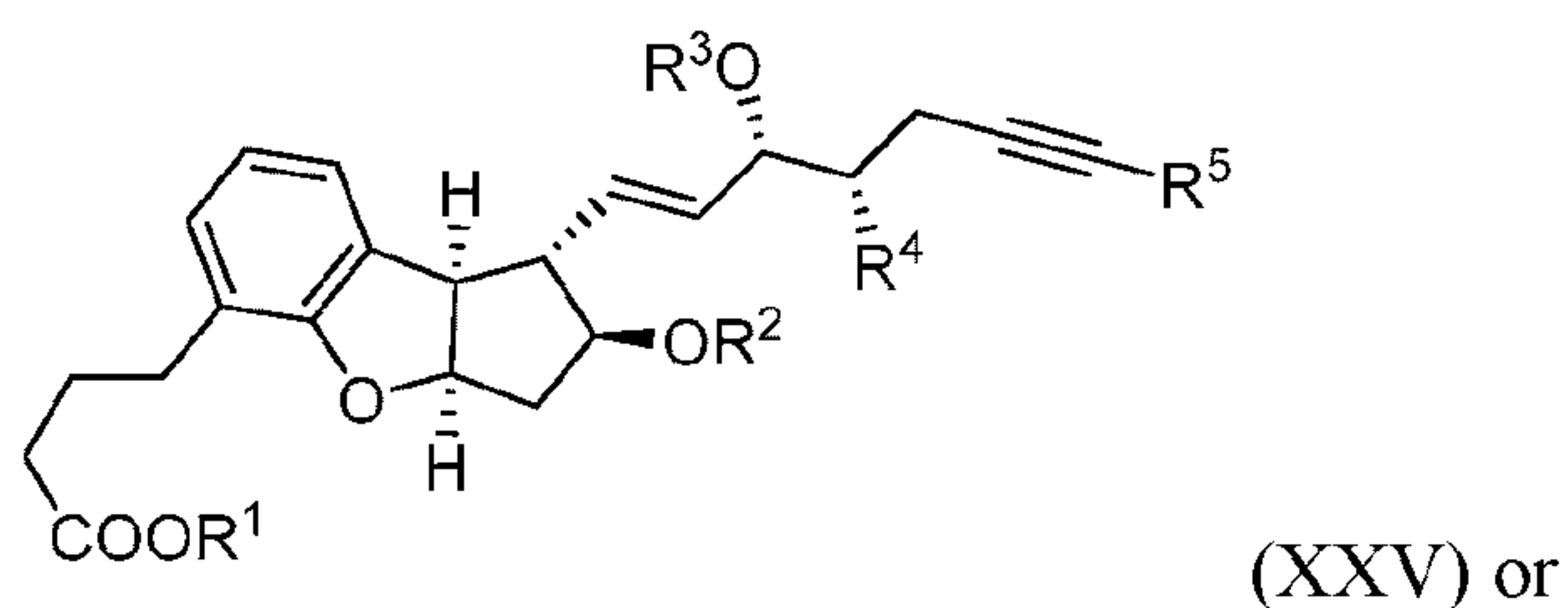
wherein R^4 and R^5 are each defined above to form a compound of the following formula:



(7) reduction of the ketone, deprotection of any remaining hydroxy protective group and optionally converting the R^{1a} into a cation or H to form a compound of the following formula:



In some embodiments, the present invention provides a method that produces the compound of formula (XV) as a substantially pure single isomer of the formula



In some embodiments, R^2 , R^3 , R^{2a} and R^6 each independently represent acetate, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, phenyldimethylsilyl, tetrahydropyranyl, benzoate ester, benzyl, or substituted benzyl.

In some embodiments, R^{1a} is CH_3 and R^{2a} and R^6 are both H.

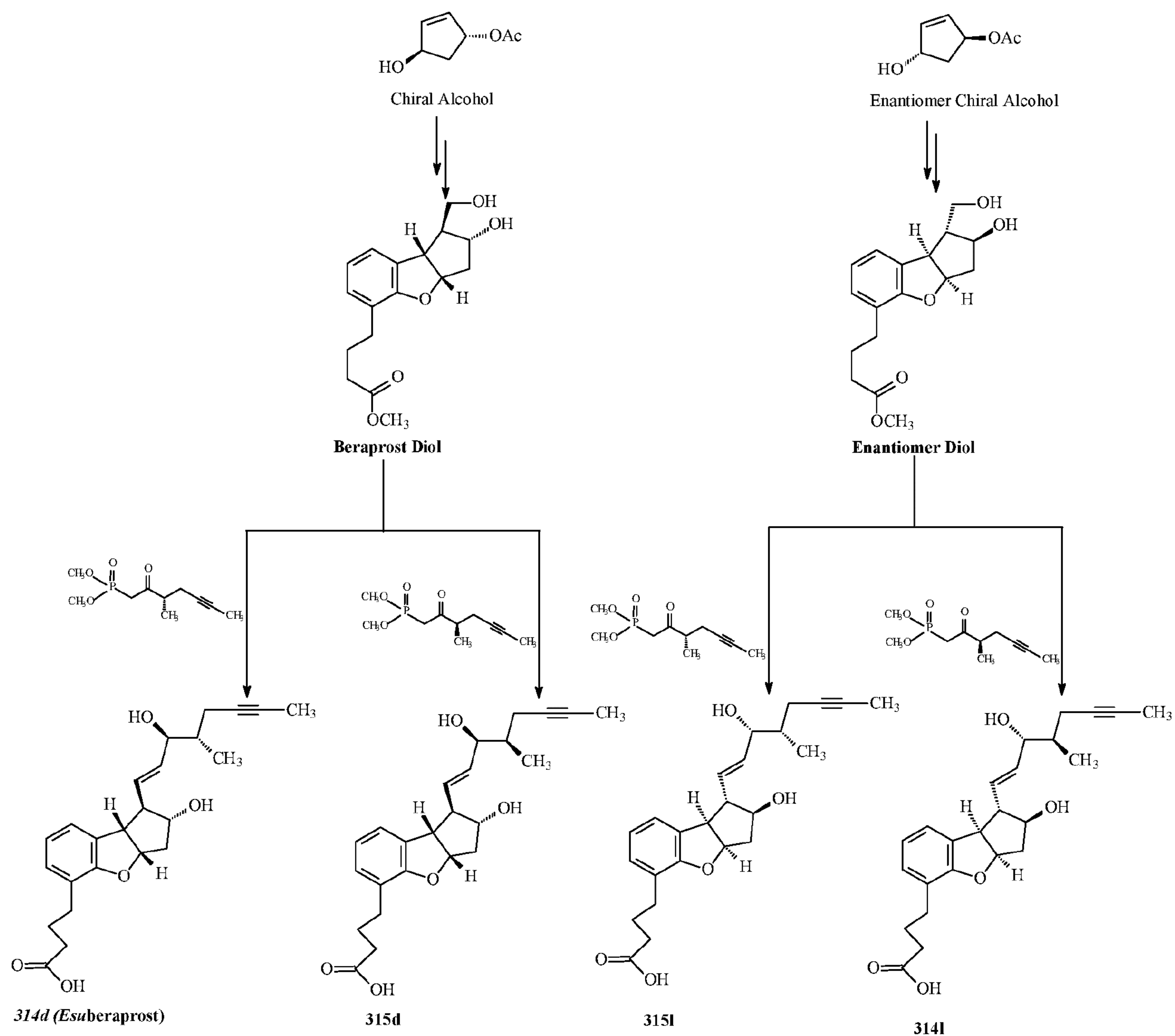
In some embodiments, azobisisobutyronitrile is used as a radical initiator in step (2).

In some embodiments, a catalytic amount of carbonylchlorohydridotris(triphenylphosphine) ruthenium (II) is used in step (3).

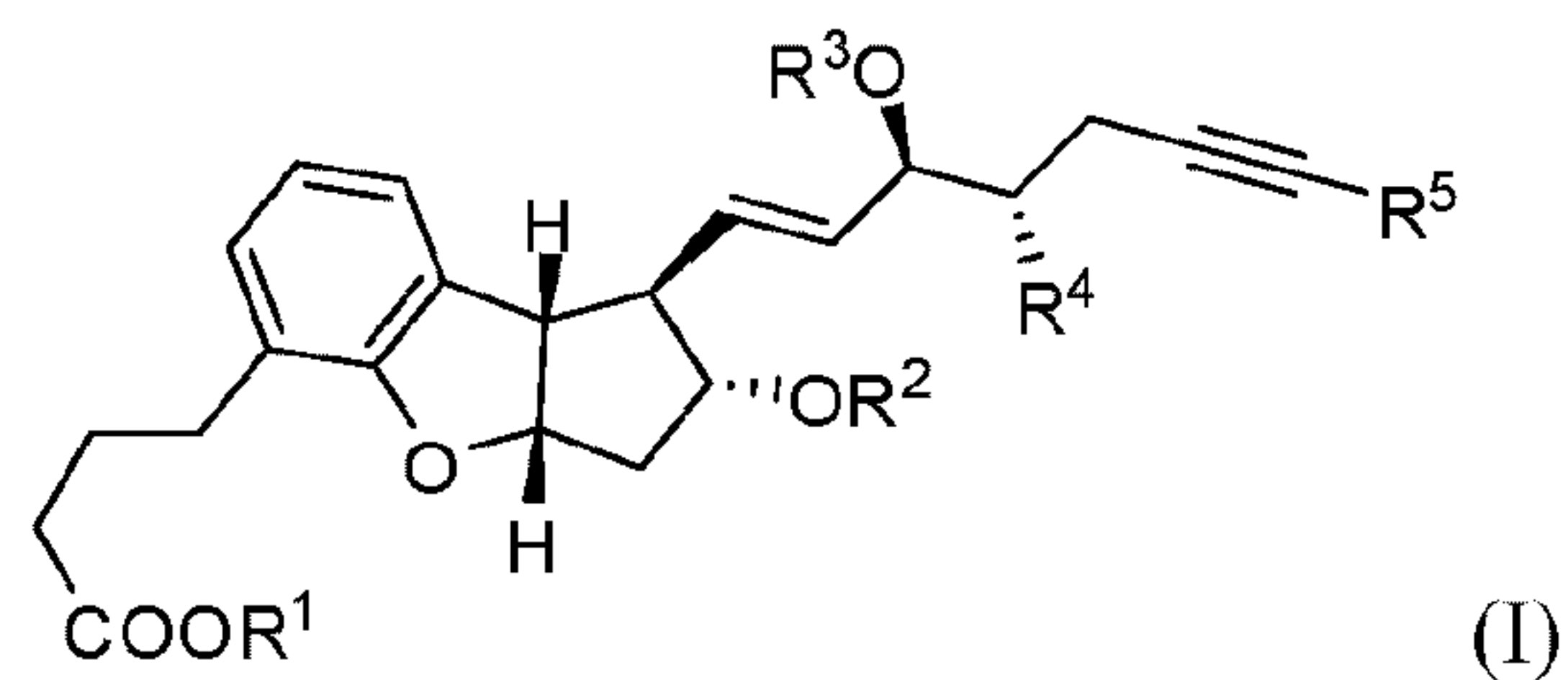
In some embodiments, sulfuric acid is used in step (5).

In some embodiments, the present invention provides a process for preparing four single isomers of the formula (I), (XII), (XXV) and (XXVI). In some embodiment, a method of producing the four isomers comprises the steps shown below.

Scheme 3. Synthesis of Four Isomers of Esuberaprost



In some embodiments, the present invention provides a process for preparing a compound of the following formula:

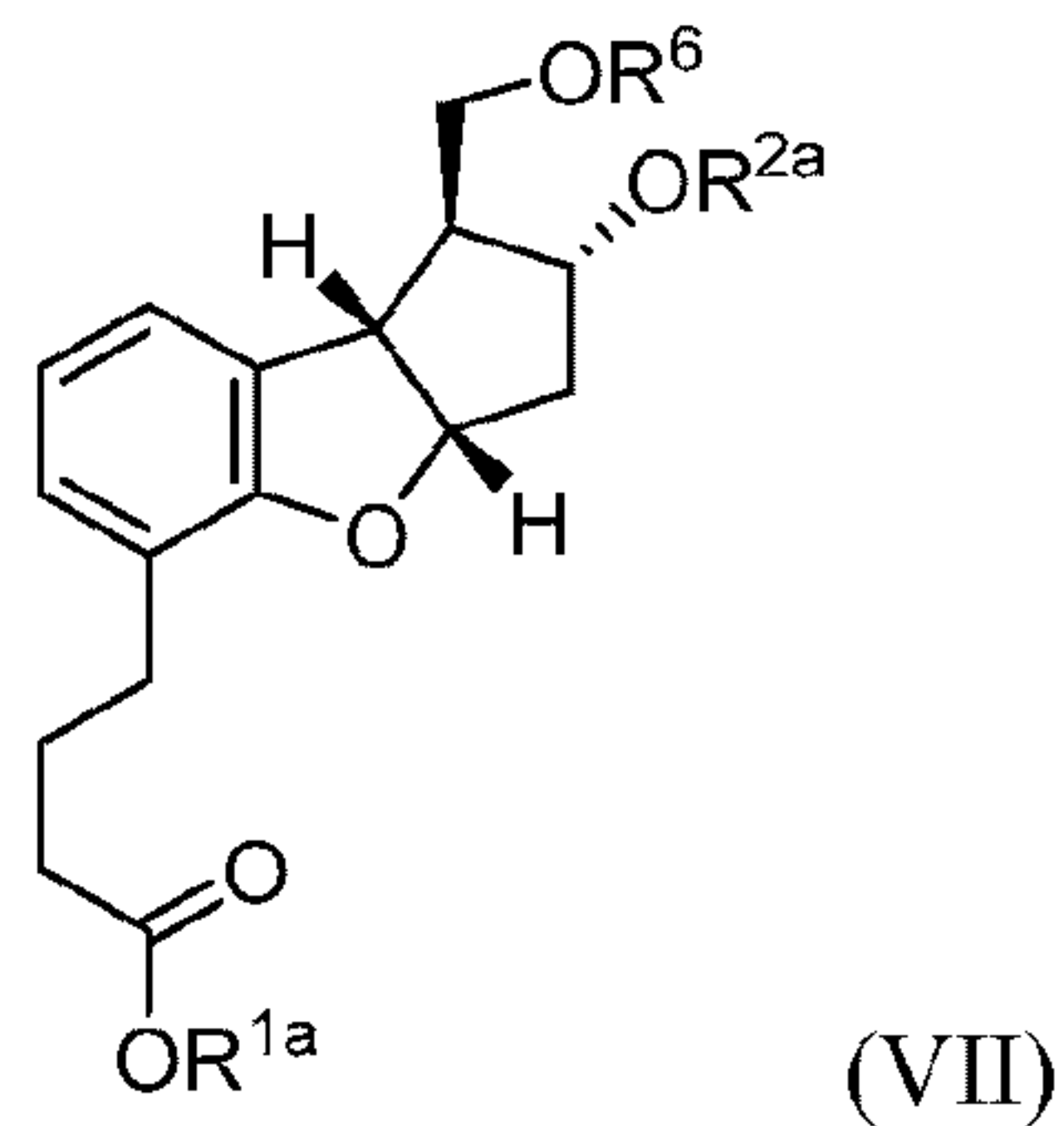


wherein R¹ represents a cation, H, or C₁₋₁₂ alkyl,
R² and R³ each represent H or a hydroxy protective group,

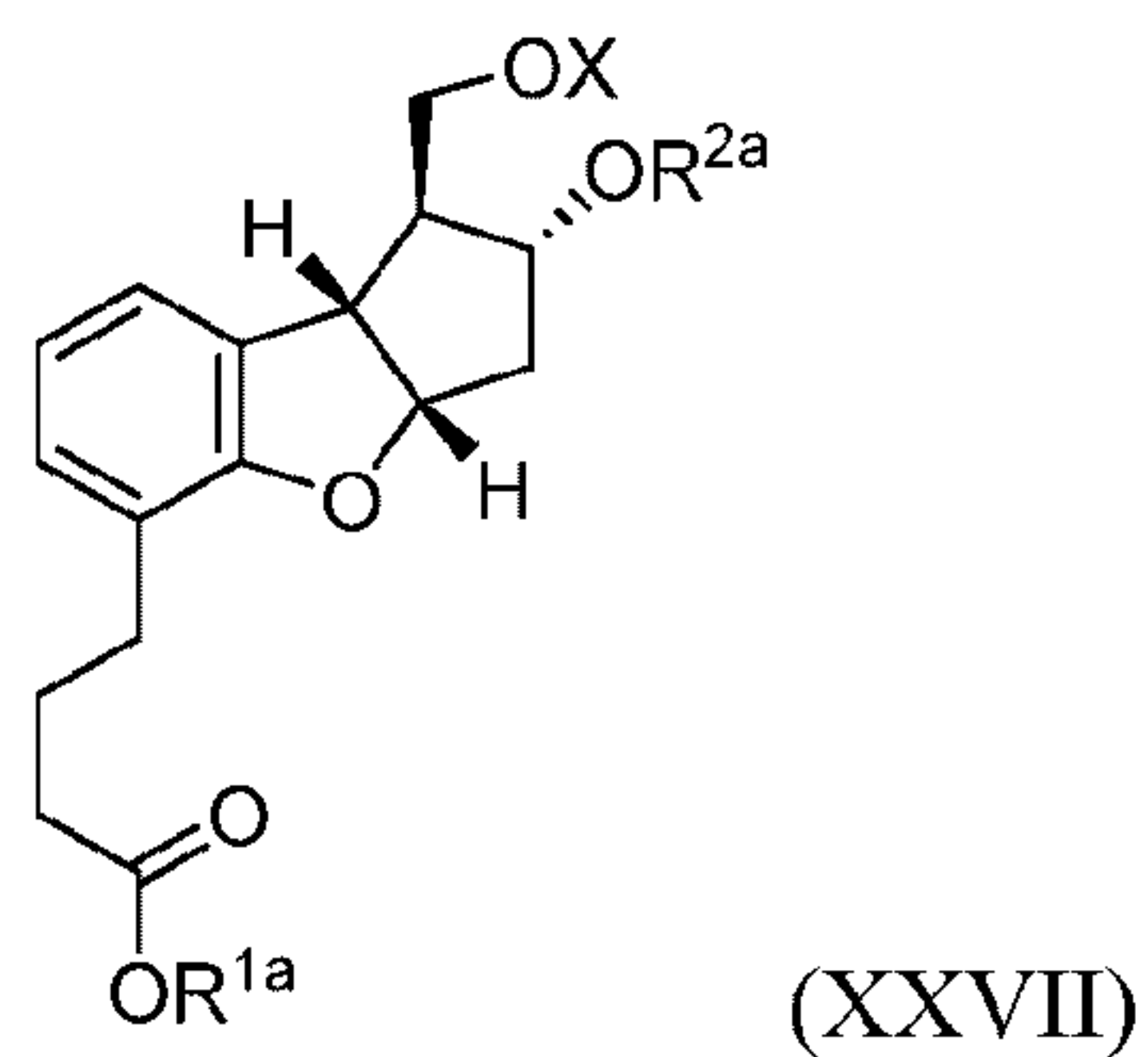
R^4 represents H or C_{1-3} alkyl, and

R^5 represents H or C_{1-6} alkyl, comprising:

(1) protecting a hydroxyl group of a compound of the following formula:

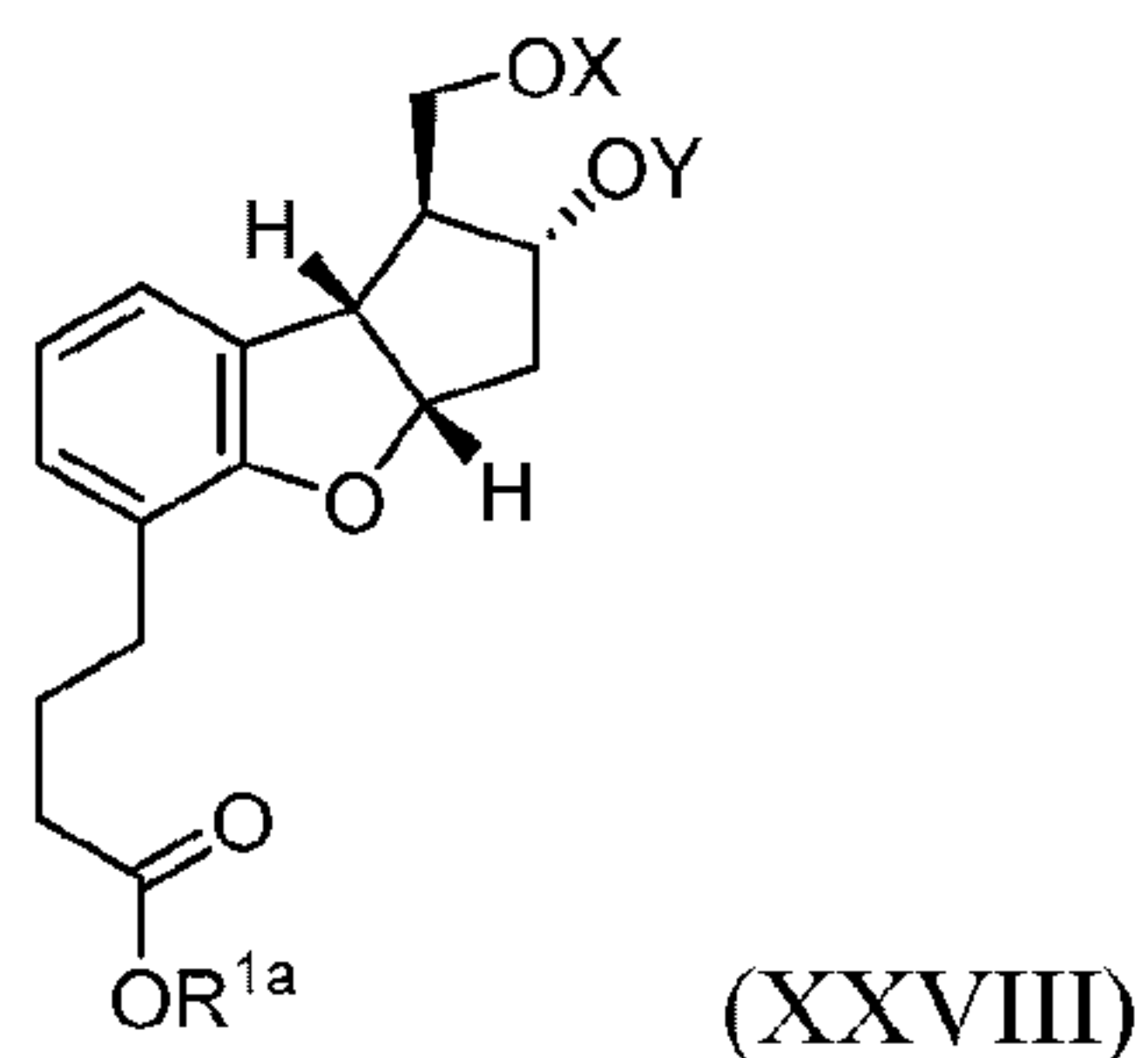


wherein R^{1a} is a cation, H, or C_{1-12} alkyl; R^{2a} and R^6 are each H or a hydroxy protective group, to produce a compound of the following formula:



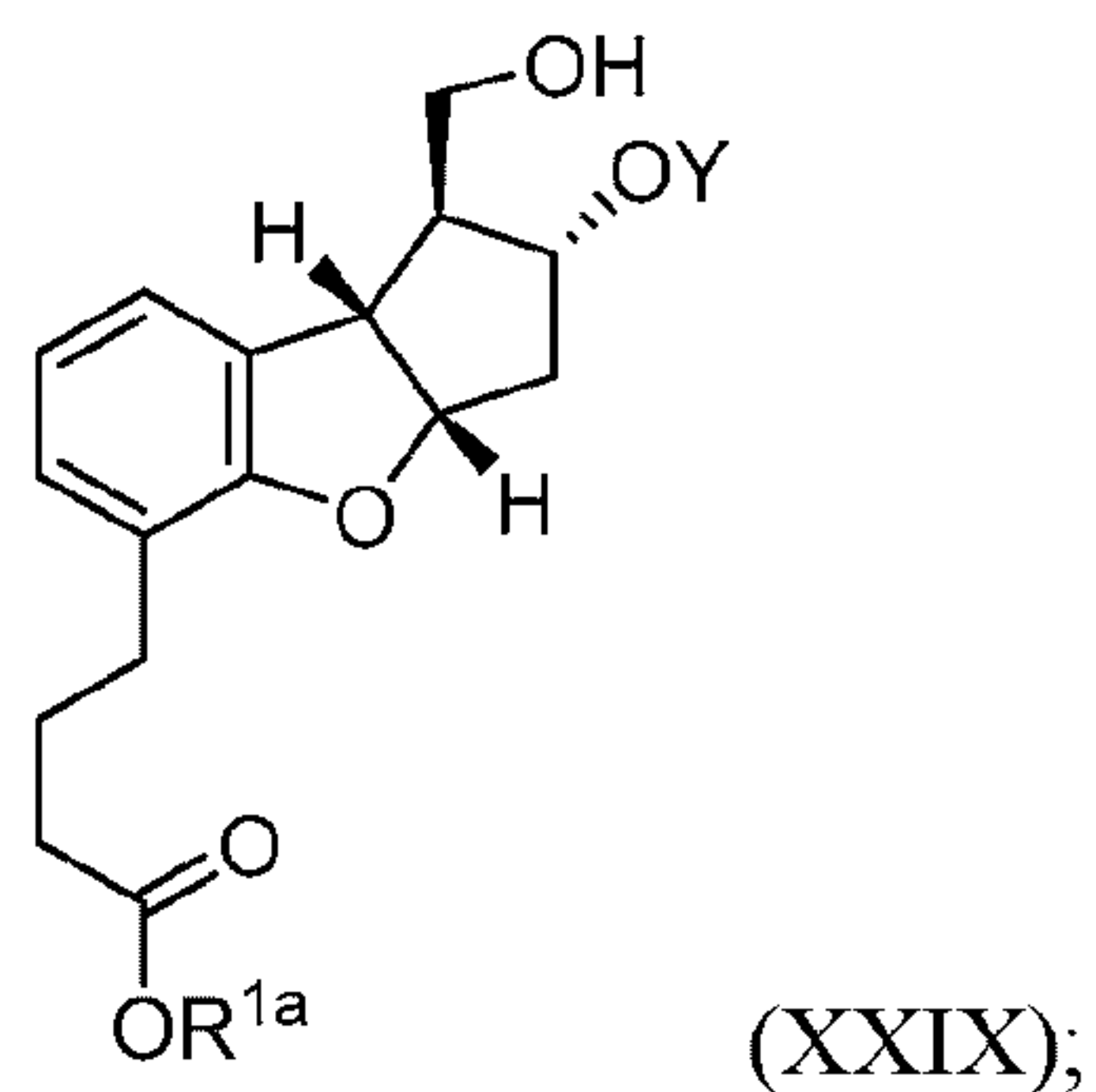
wherein X is a trityl protecting group, tertiary butyldimethyl silyl (TBDMS), triethyl silyl (TES), methoxy methane (MOM), tertiary butyldiphenyl silyl (TBDPS), acetate, benzoate, or benzyl;

(2) protecting a hydroxyl group of the compound of (XXVII) to form a compound of the following formula:

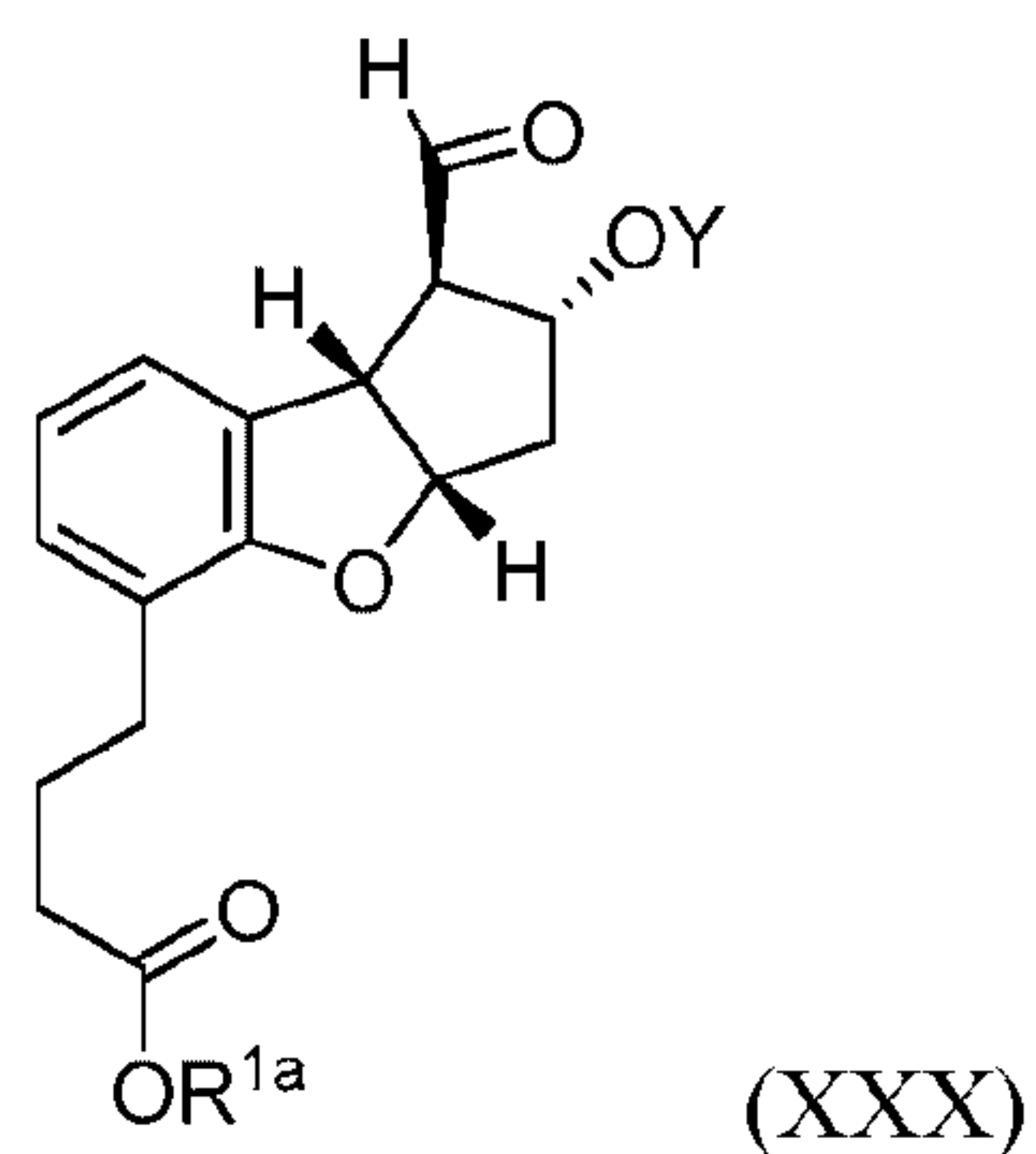


wherein Y is tertiary butyldimethyl silyl (TBDMS) group, triethyl silyl (TES), methoxy methane (MOM), tertiary butyldiphenyl silyl (TBDPS), acetate, benzoate, or benzyl;

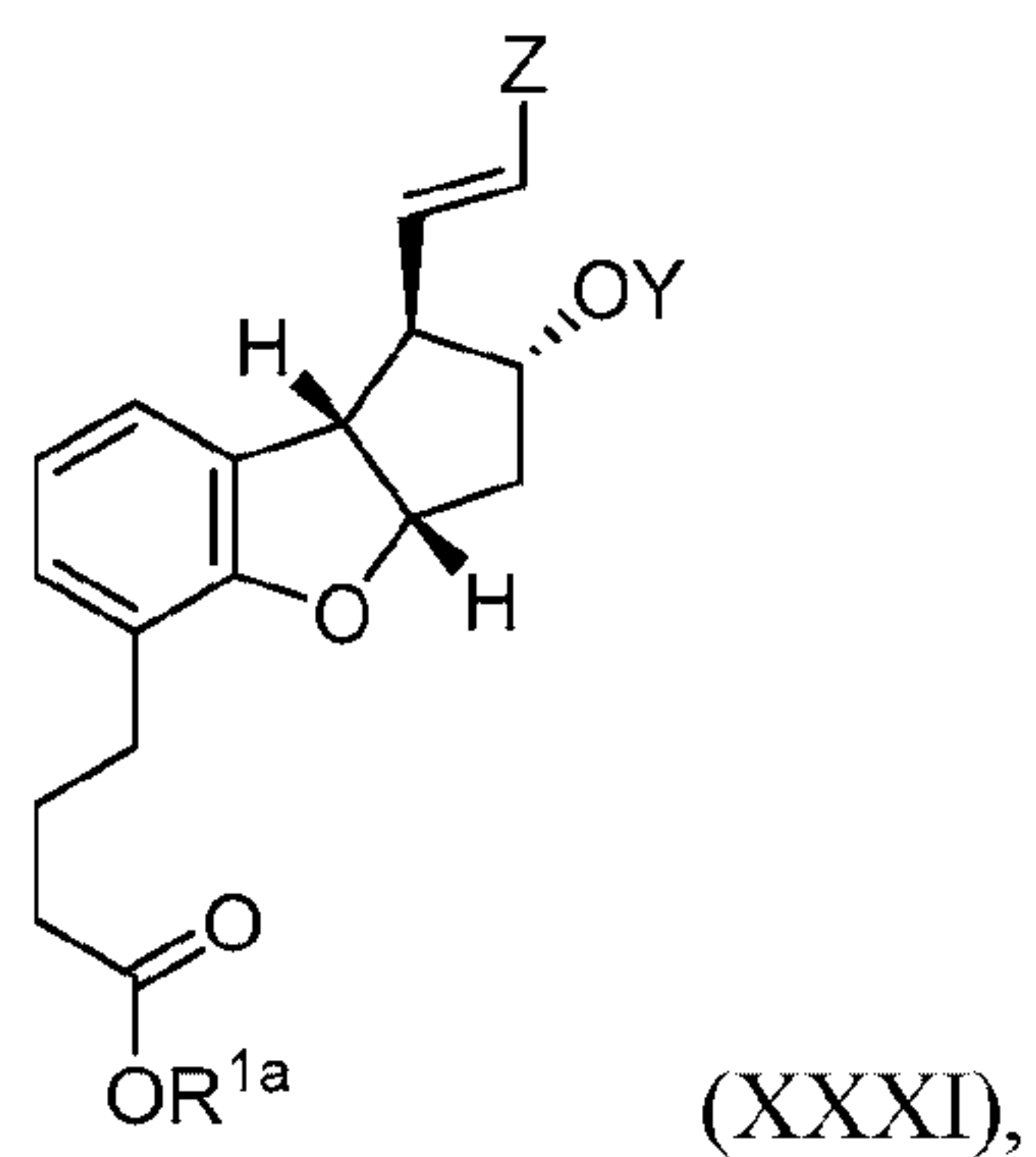
(3) deprotection one of the hydroxyl protective groups to form a compound of the following formula:



(4) oxidation of a hydroxyl group of the compound to form a compound of the following formula:

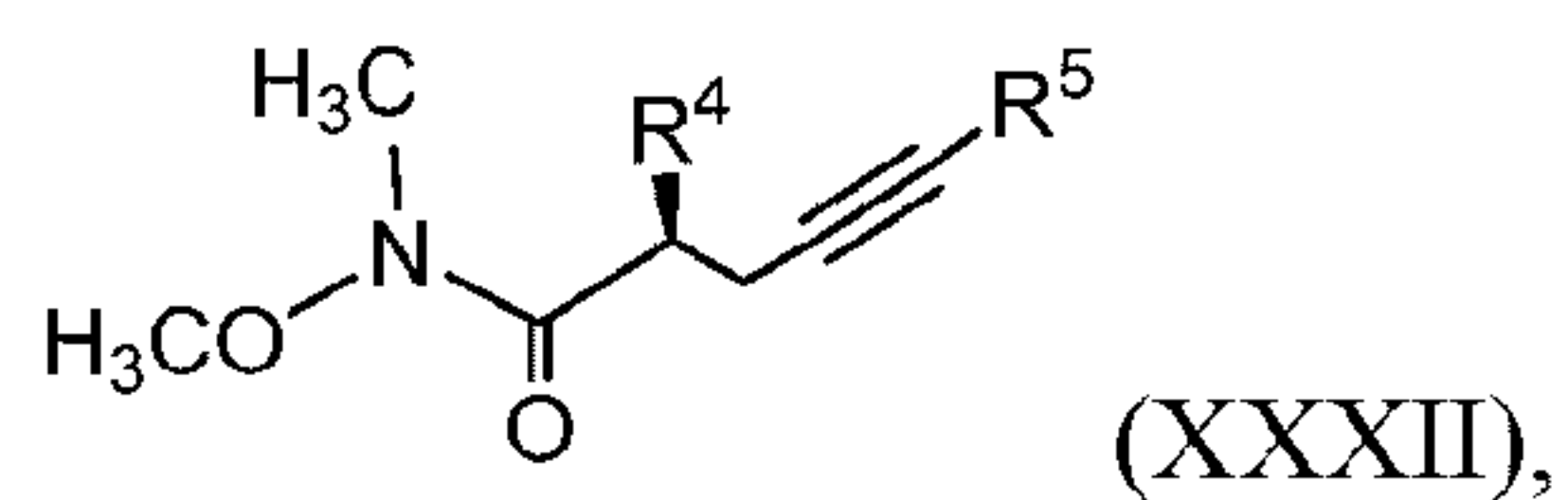


(5) Reacting with stannanes to form a compound of the following formula:

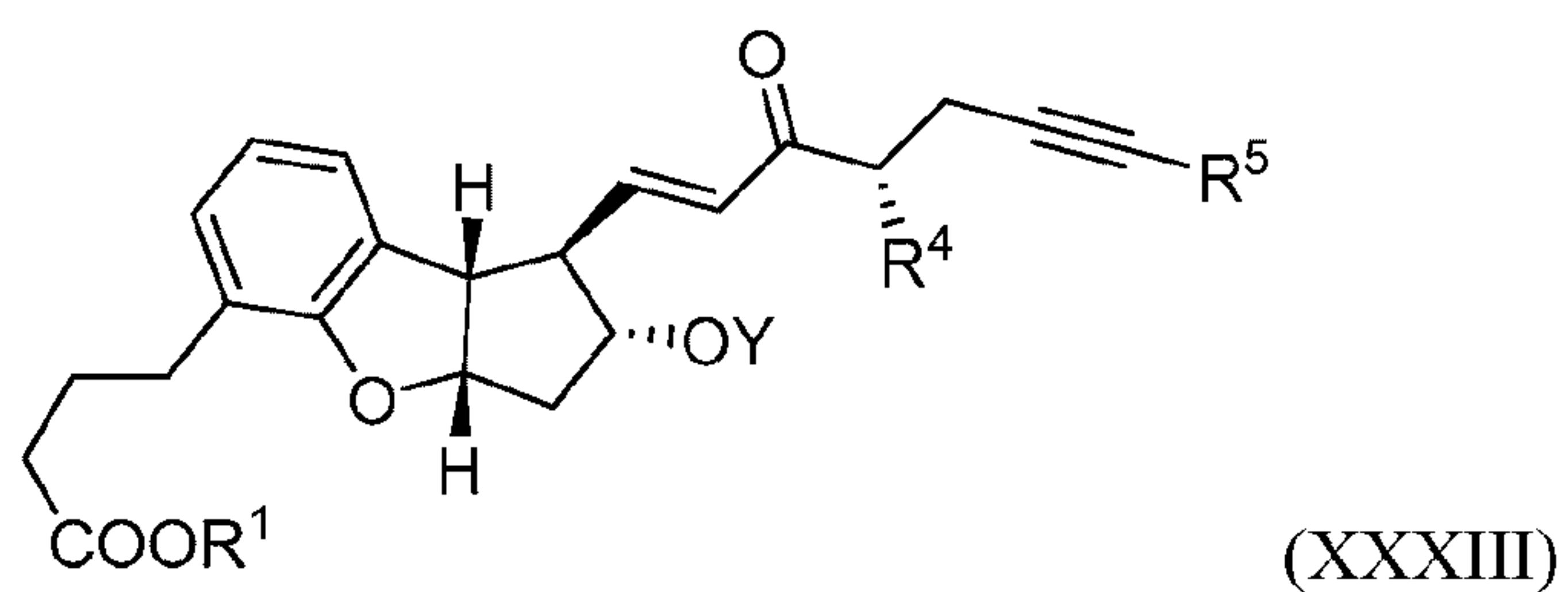


wherein Z is tributyl tin (SnBu_3);

(6) coupling with a compound of the following formula:

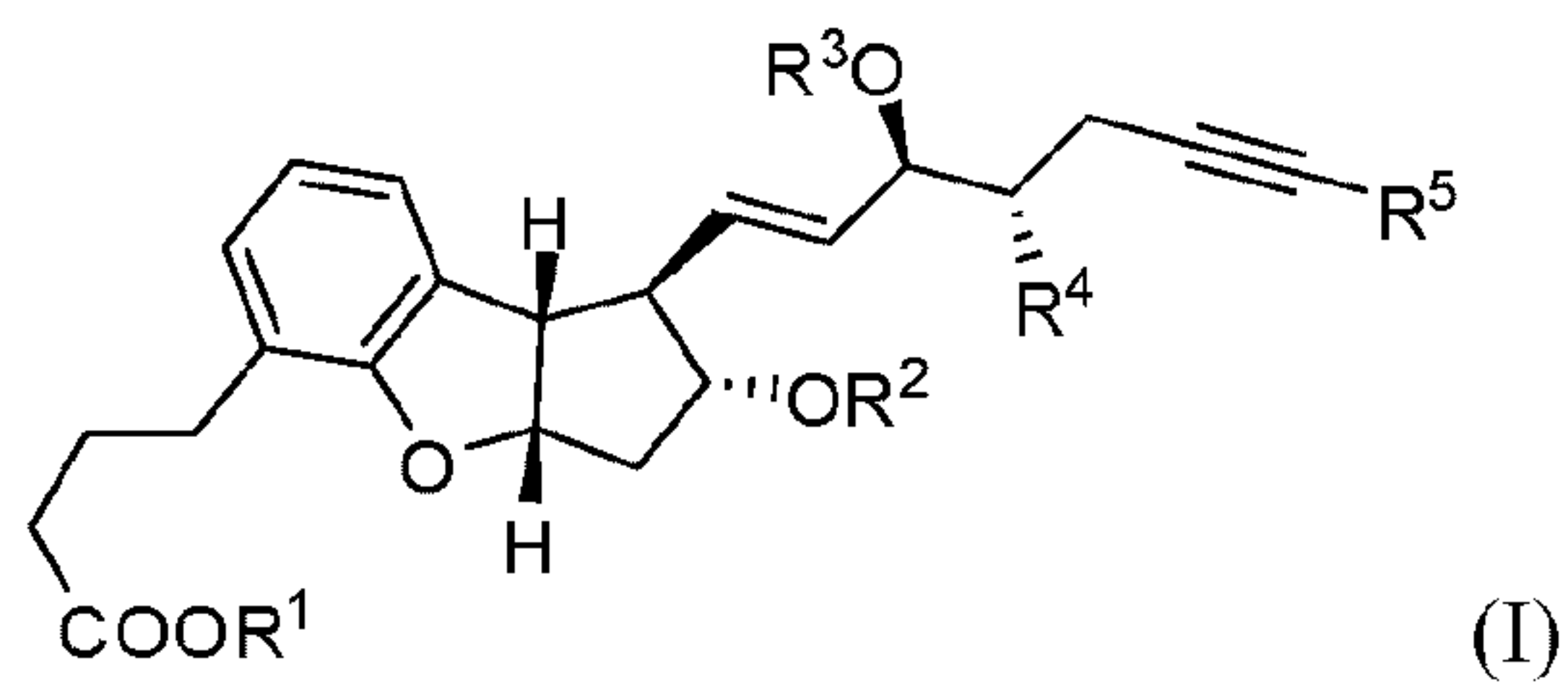


to form a compound of the following formula:



wherein R^1 , R^2 , R^4 and R^5 are each defined above,

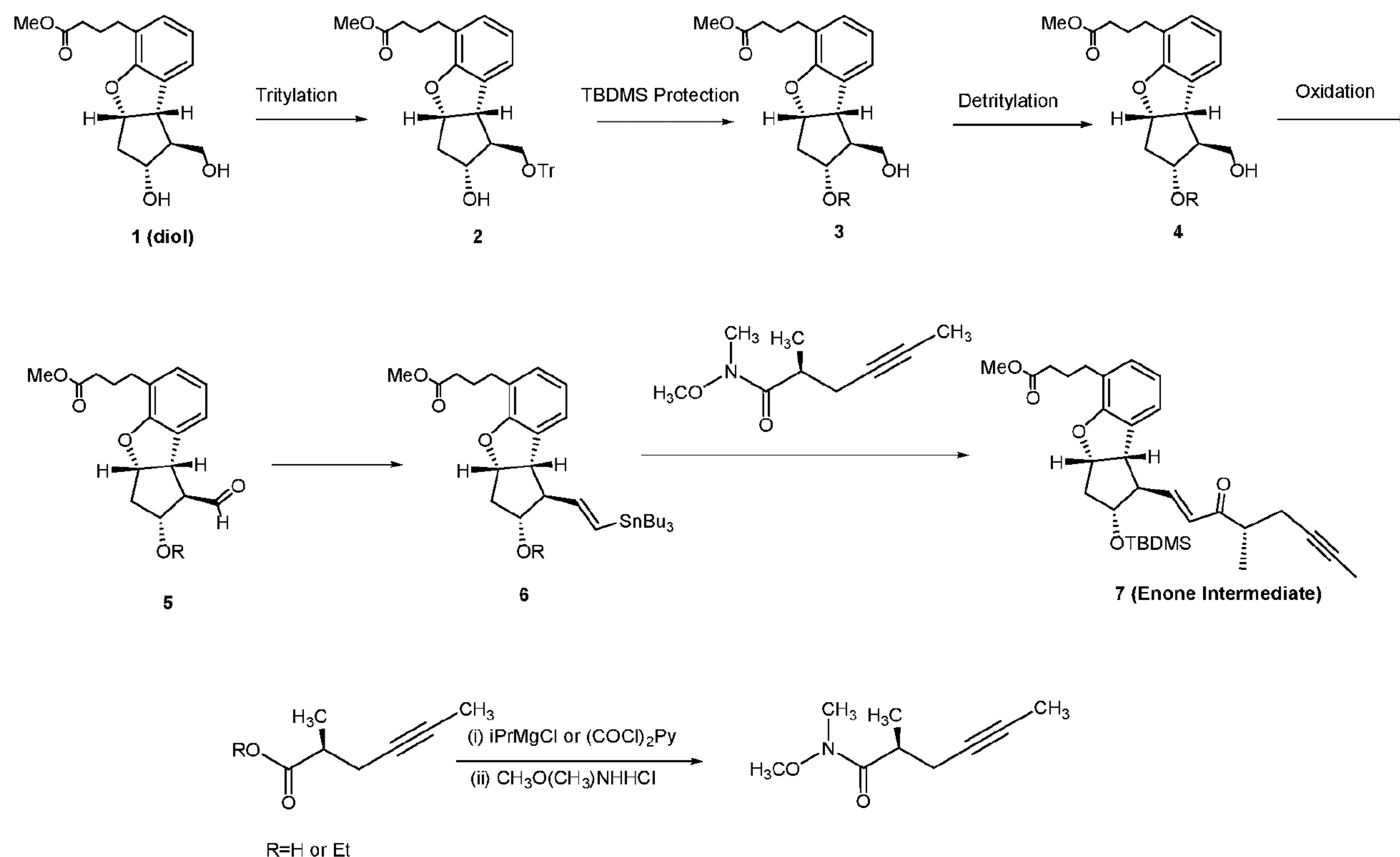
(7) deprotecting the protective group Y and reducing the ketone of the compound of the formula (XXXIII) to form a compound of the following formula:



In some embodiments, the methods described herein produce the compound of formula (I) as a substantially pure single isomer.

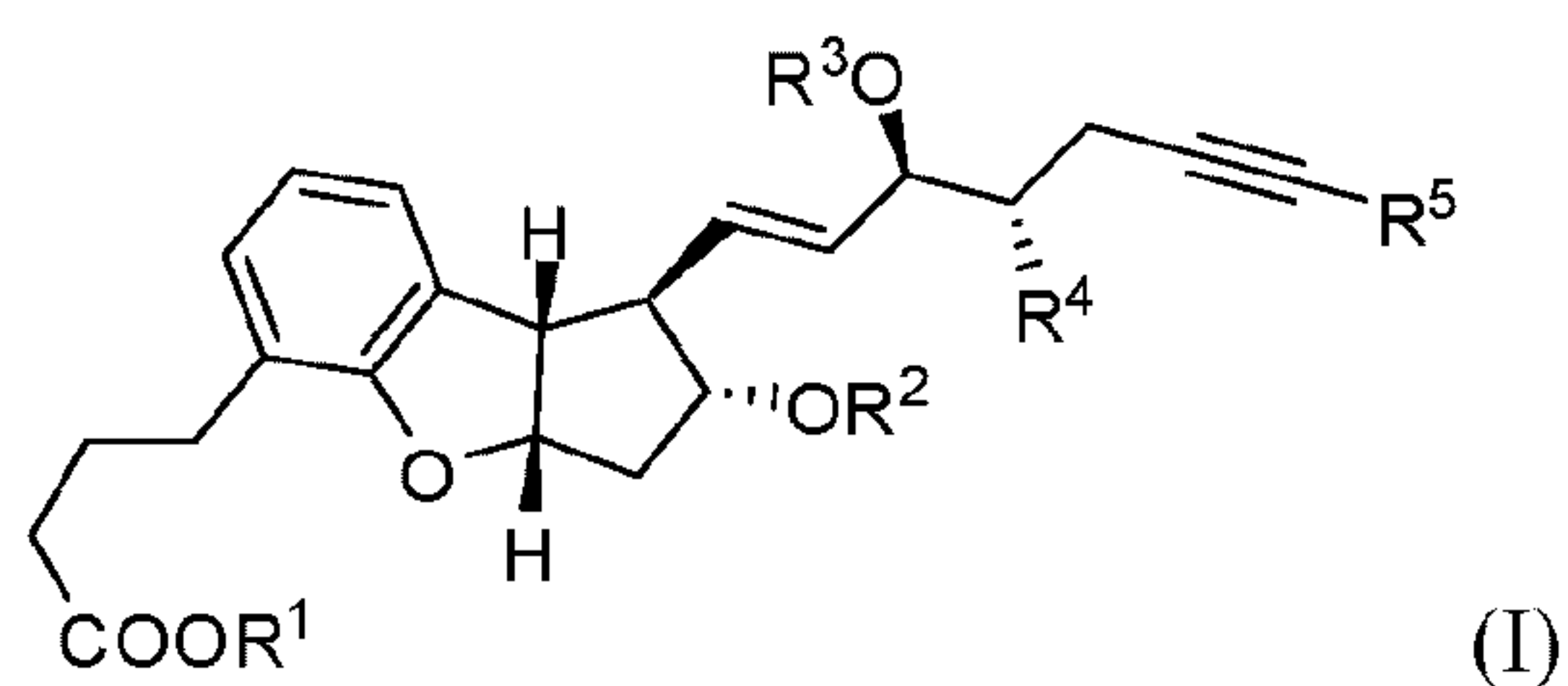
In some embodiments, a method of producing a compound of formula (I) comprises the steps shown below.

Scheme 4. Synthesis of Beraprost



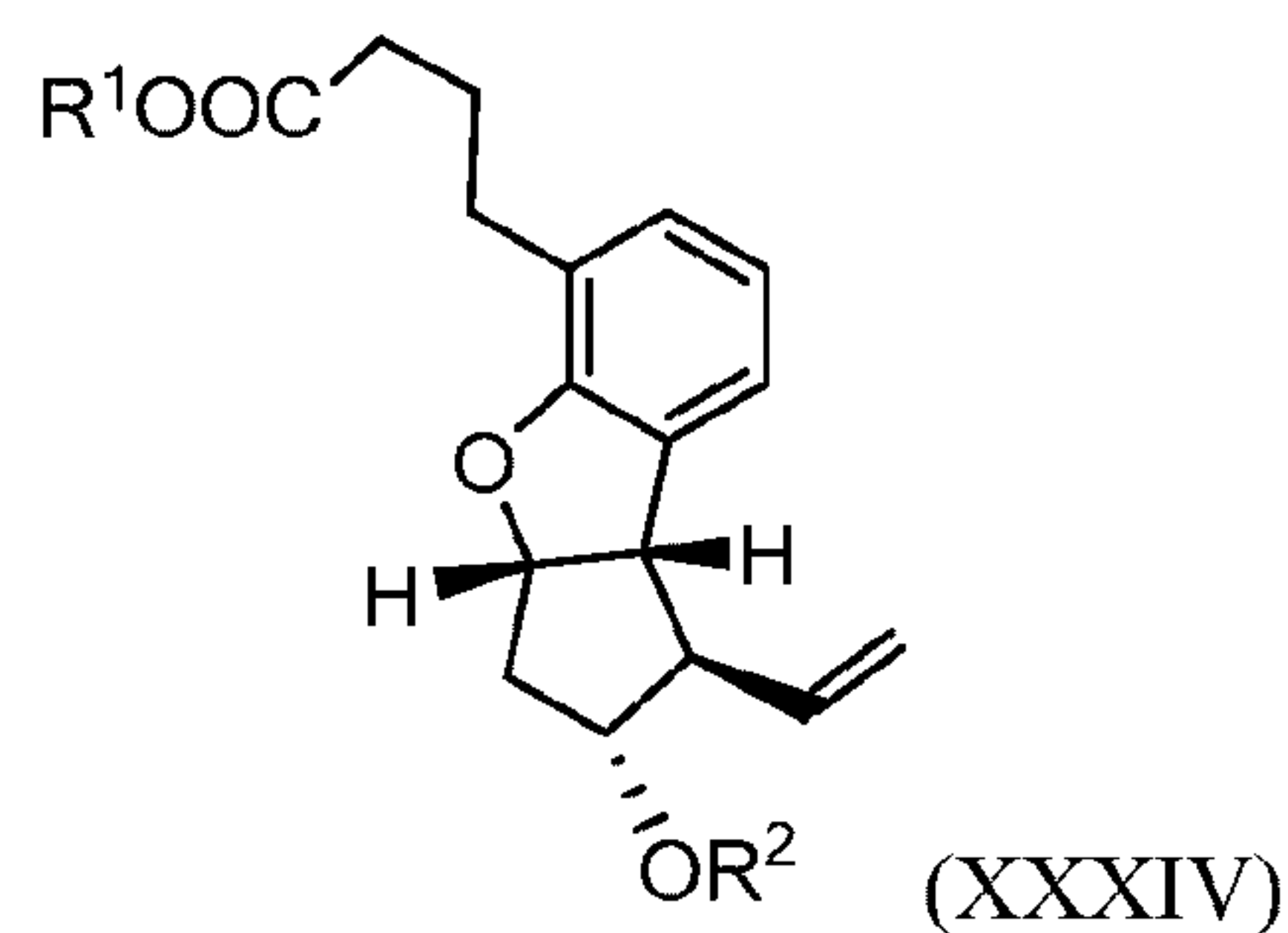
In some embodiment, the methods described herein can be used to prepare a compound of formula (I) without the formation of keto-phosphonate side chain from Weinreb amide, and thus avoids the use of butyl lithium which is a strong base. Under strong basic conditions, the methyl group on the keto-phosphate side chain can racemize and hence lose the optical purity (chiral purity). In contrast, the methods described herein use Weinreb amide, which not only reduces the step of conversion to phosphate but also avoids the problem of racemization and reduces impurities in the subsequent steps. Therefore, in some embodiments, the methods described herein provide the advantage of easily obtaining a desired single isomer of esuberaprost with high chiral impurity.

In some embodiments, the a process for preparing a compound of the following formula:

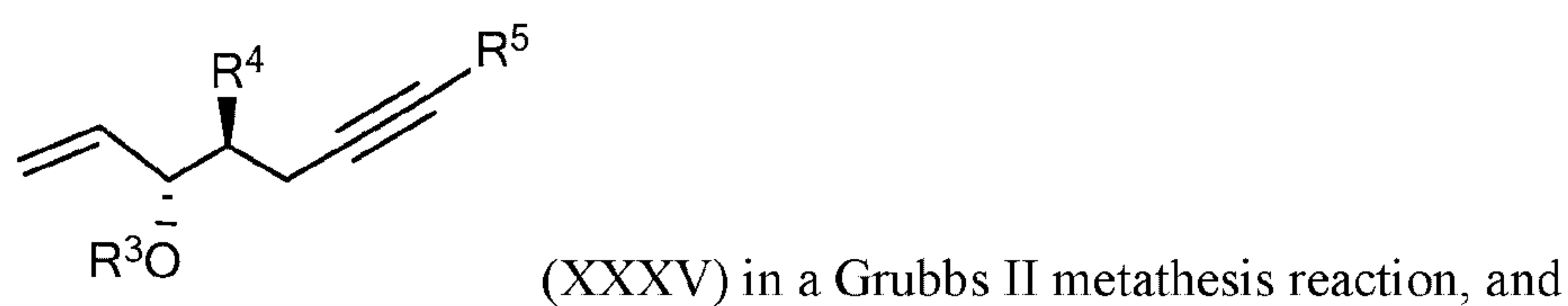


wherein R^1 represents a cation, H, or C_{1-12} alkyl,
 R^2 and R^3 each represent H or a hydroxy protective group,
 R^4 represents H or C_{1-3} alkyl, and
 R^5 represents H or C_{1-6} alkyl, comprises:

(1) reacting a compound of the following formula:



with a compound of the following formula:

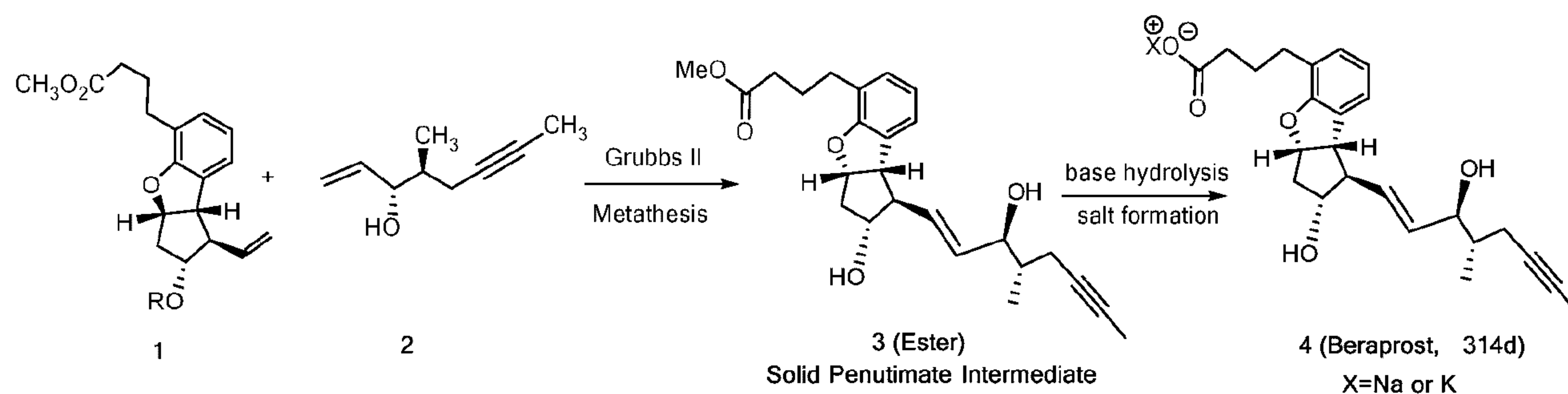


(2) base hydrolysis to produce the compound of formula (I).

In some embodiments, the present invention provides a method that produces the compound of formula (I) as a substantially pure single isomer.

In some embodiments, a method of producing a compound of formula (I) comprises the steps shown below.

Scheme 5. Synthesis of Beraprost



BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows ^1H NMR spectrum of compound (3).

Figure 2 shows ^1H NMR spectrum of compound (4).

Figure 3 shows HPLC profile of compound (4).

Figure 4 shows ^1H NMR spectrum of compound (4).

Figure 5 shows HPLC profile of compound (4).

Figure 6 shows ^1H NMR spectrum of compound (5).

Figure 7a and 7b show HPLC profile of compound (5).

Figure 8 shows ^1H NMR spectrum of compound (6).

Figure 9a and 9b show HPLC profile of compound (6).

Figure 10 shows ^1H NMR spectrum of compound (7).

Figure 11 shows HPLC profile of crude sample of compound (7).

Figure 12 shows HPLC profile of compound (7).

Figure 13 shows HPLC profile of compound (7) spiked with reference.

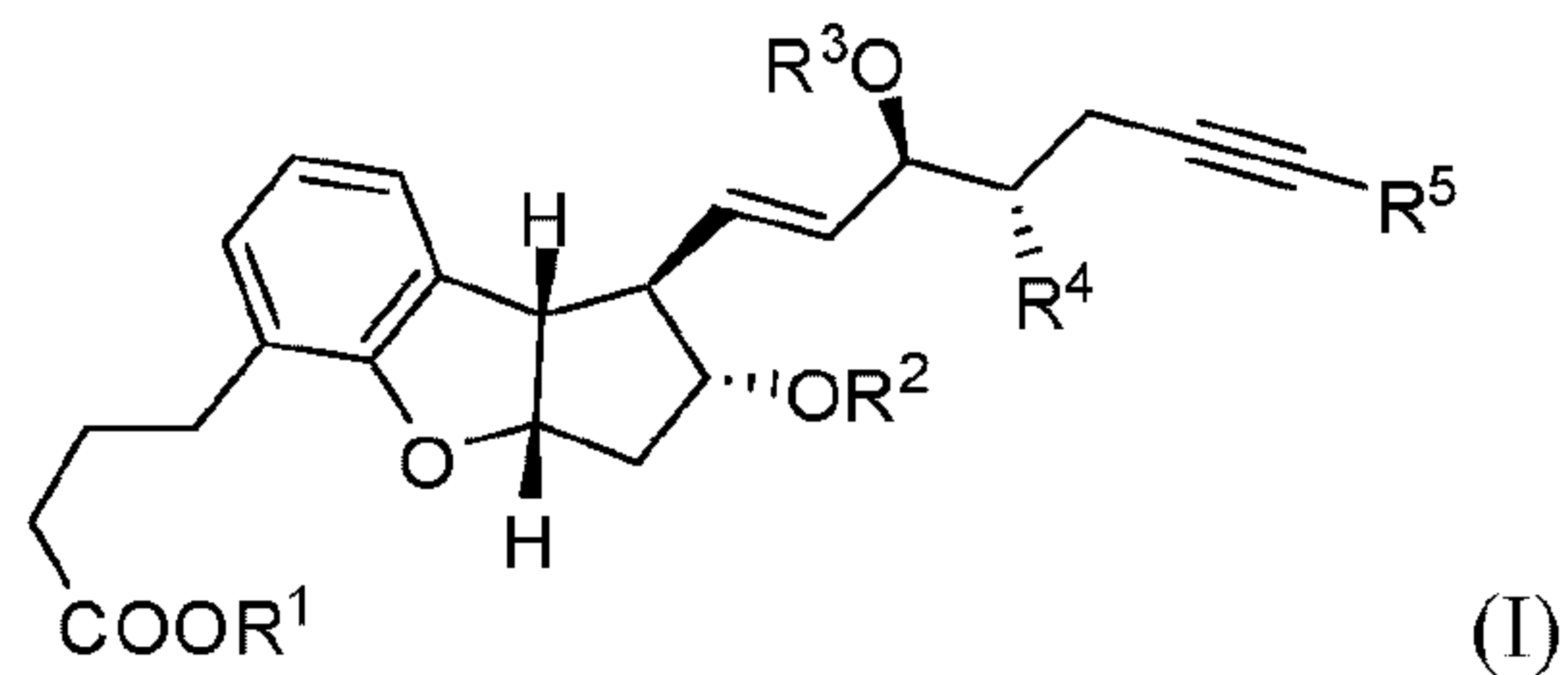
Figure 14 shows HPLC profile of compound (7) spiked with racemic diol.

Figure 15 shows ^{13}C NMR spectrum of compound (7).

Figure 16 shows mass spectrum of compound (7).

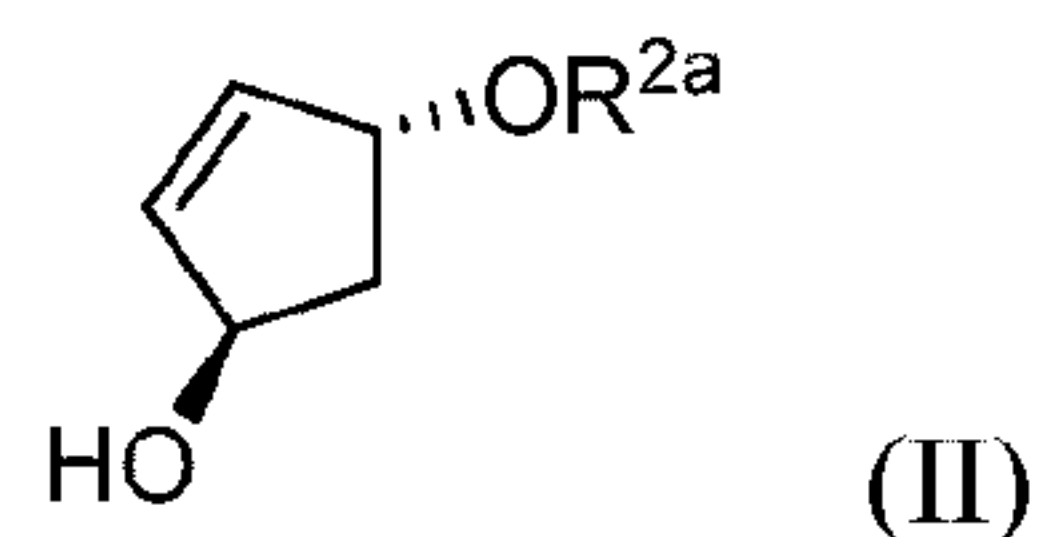
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Unless otherwise specified, “a” or “an” means “one or more.” In one embodiment, a method for making a substantially pure isomer of beraprost or its related derivatives of following formula:

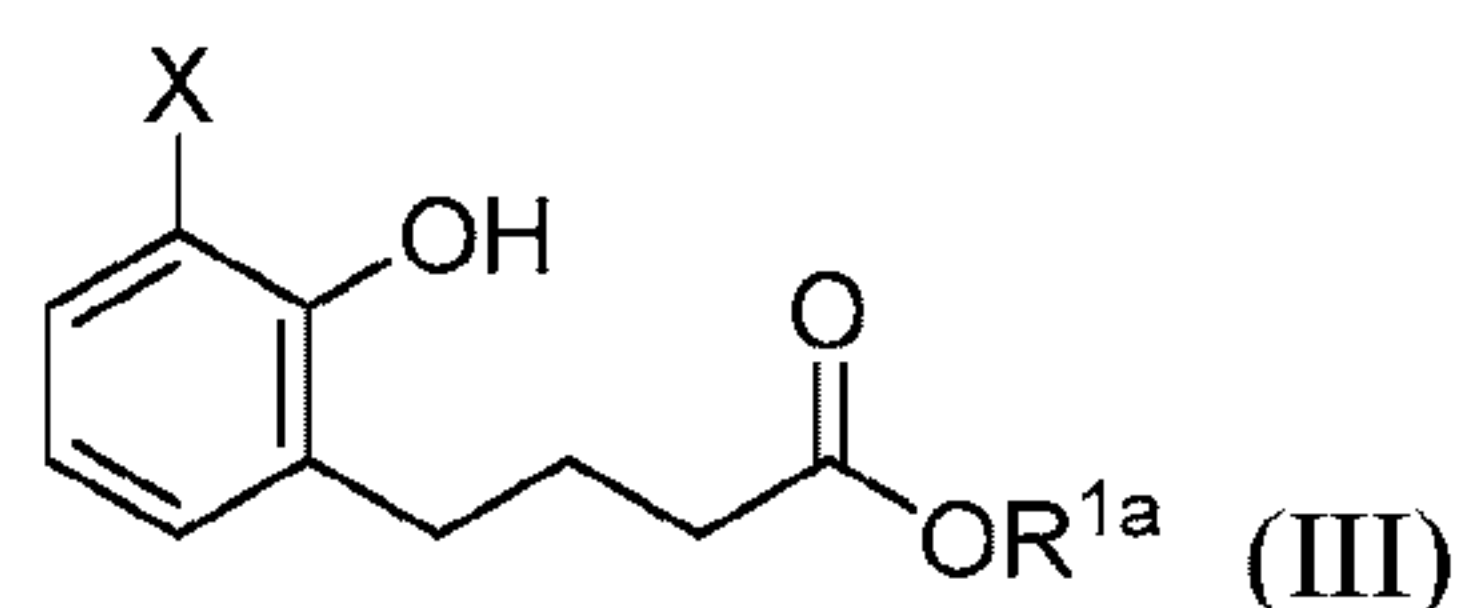


wherein R¹ represents a cation, H, or C₁₋₁₂ alkyl,
 R² and R³ each represent H or a hydroxy protective group,
 R⁴ represents H or C₁₋₃ alkyl, and
 R⁵ represents H or C₁₋₆ alkyl, comprises:

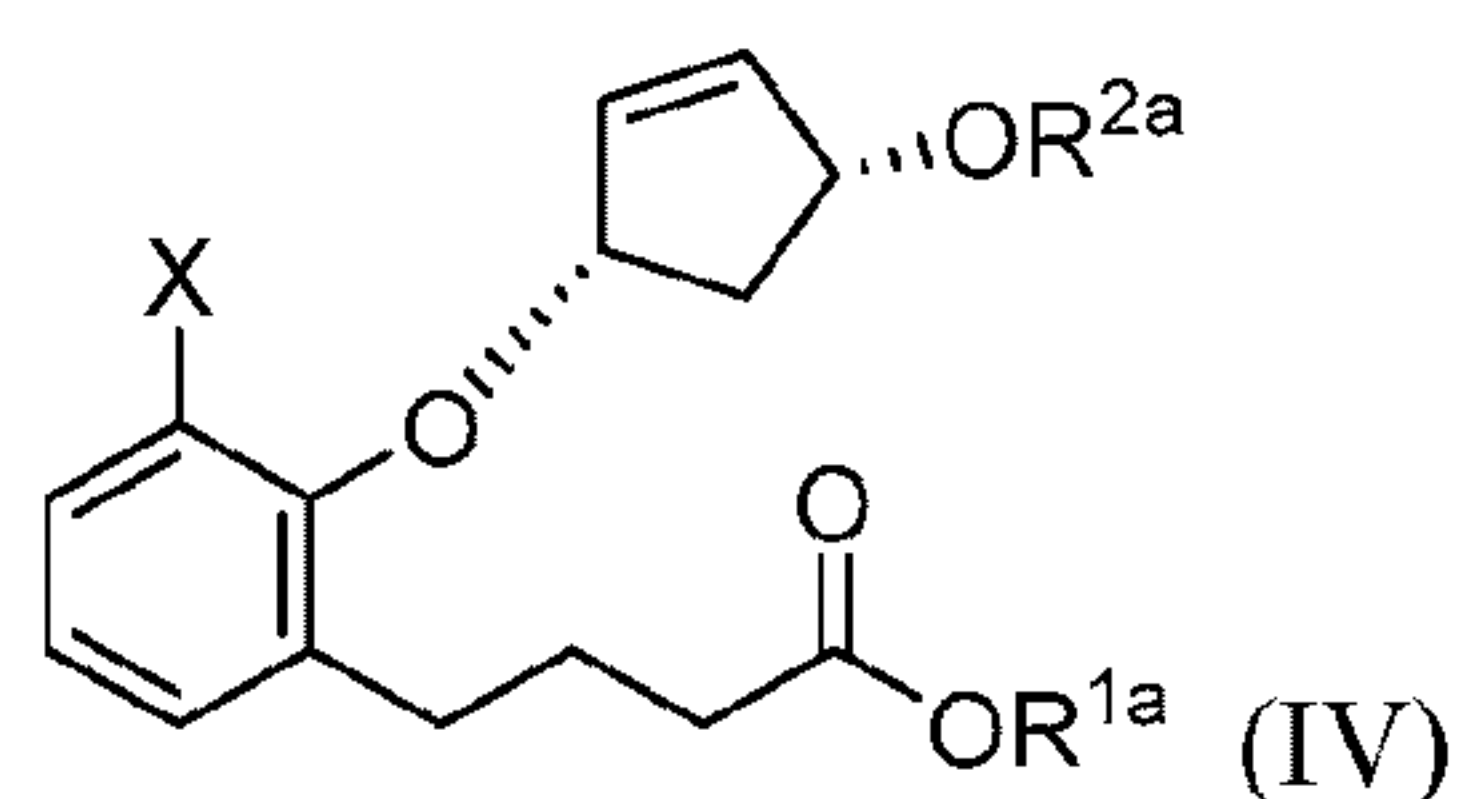
(1) performing a Mitsunobu reaction on a compound of the following formula:



, wherein R^{2a} is H or an hydroxy protective group,
 with a compound of the following formula:

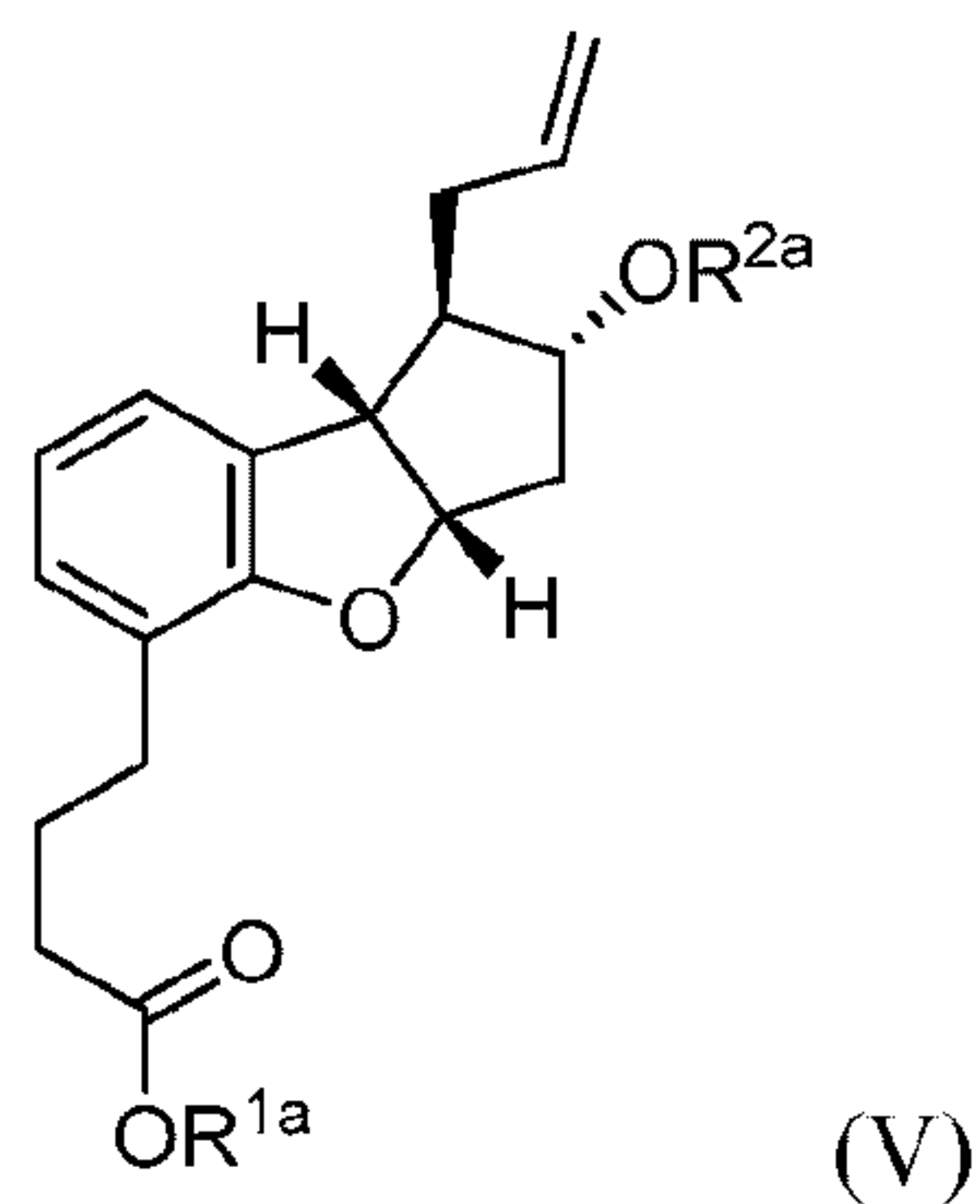


, wherein R^{1a} is a cation, H, or C₁₋₁₂ alkyl, X is halogen
 to form a compound of the following formula:



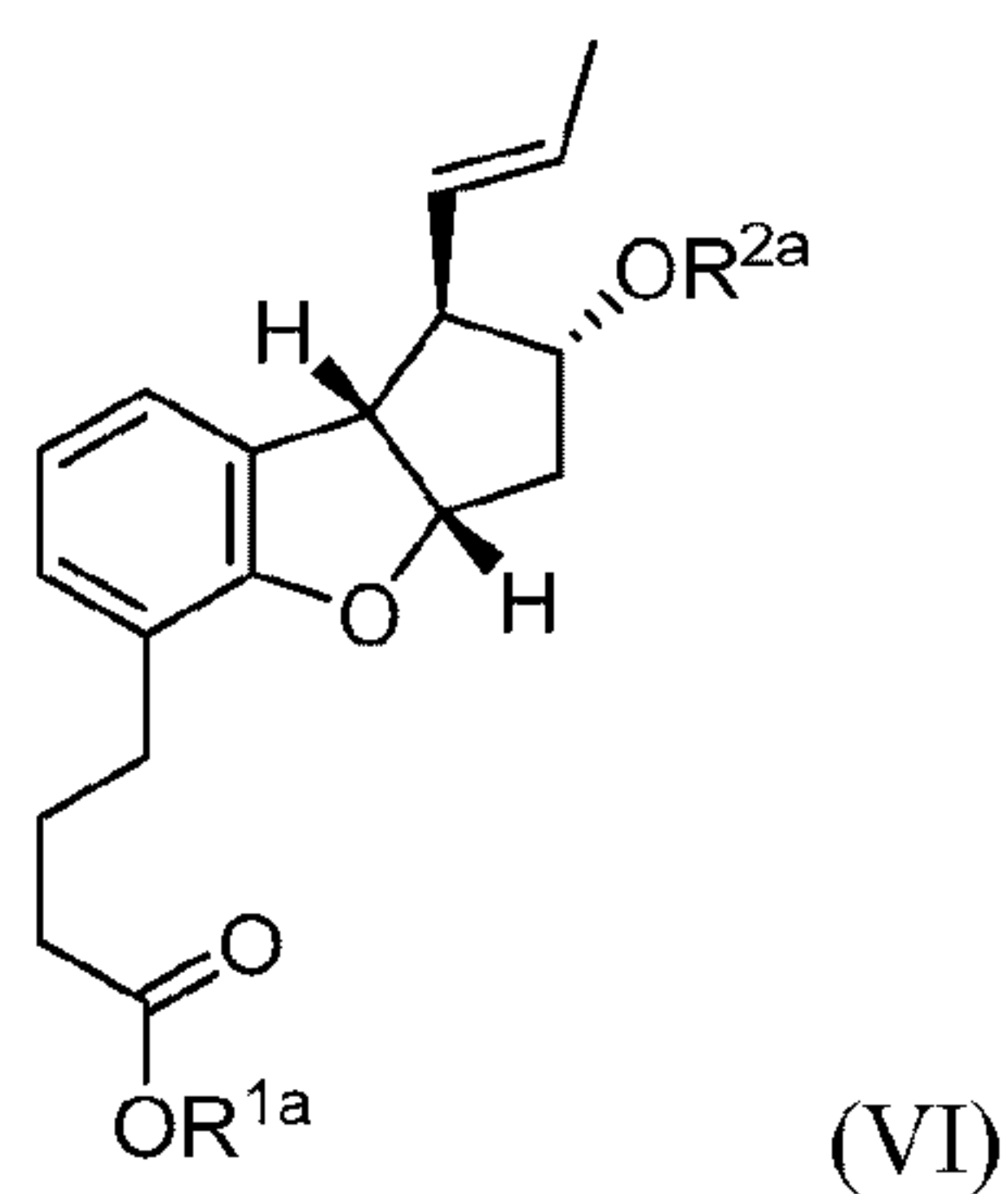
, wherein R^{1a}, R^{2a} and X are each defined above;

(2) radical cyclization of formula (IV) to form a compound of the following formula:



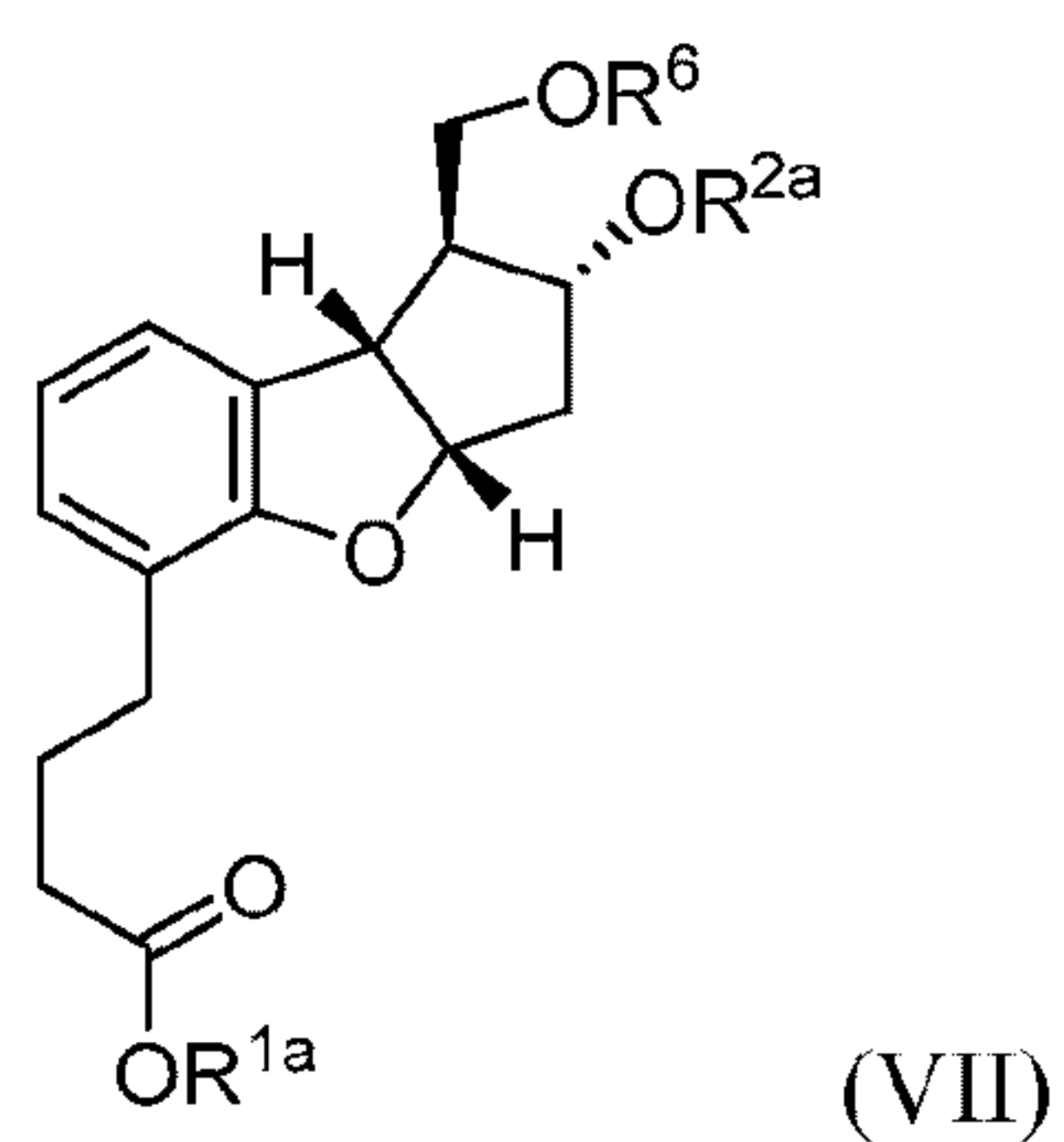
,wherein R^{1a} and R^{2a} are each defined above;

(3) isomerizing the allyl of the compound of formula (V) to form a propenyl resulting in a compound of the following formula:



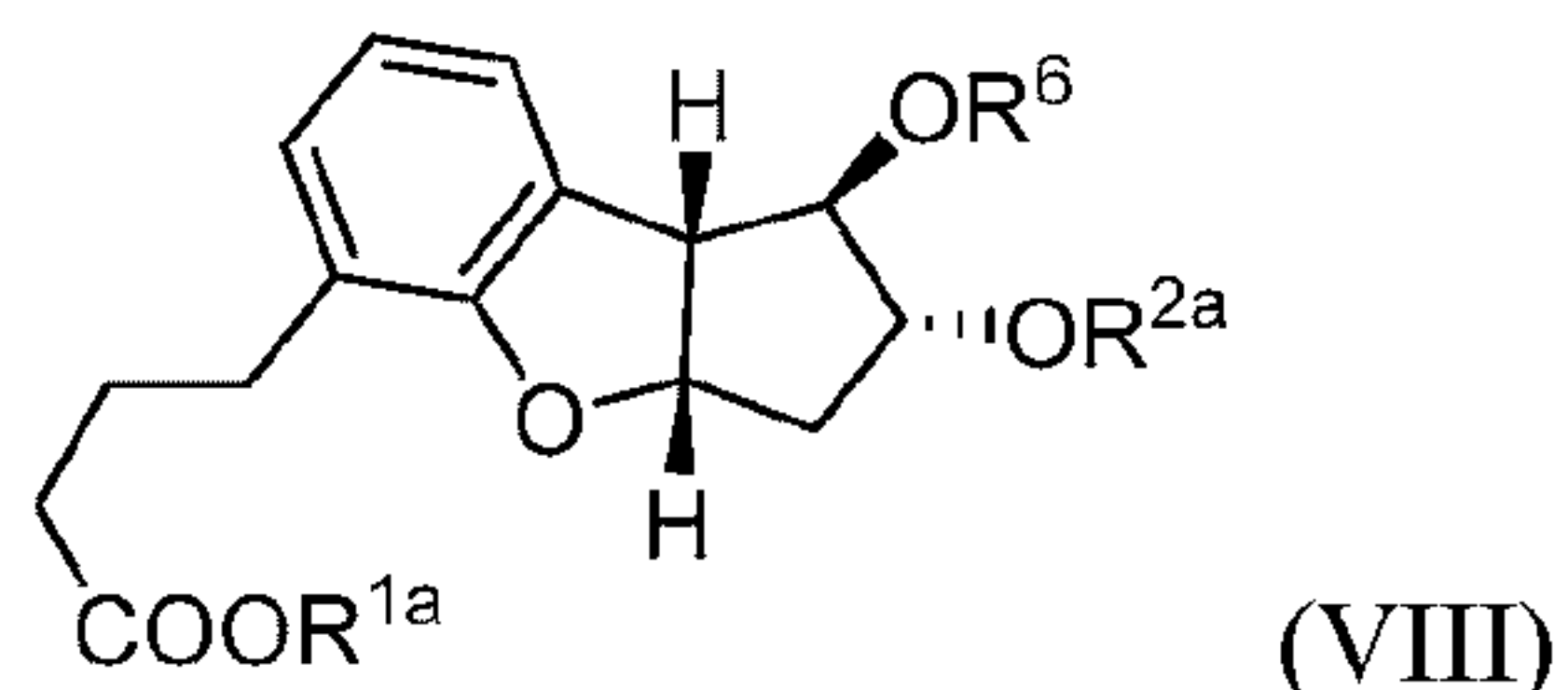
,wherein R^{1a} and R^{2a} are each defined above;

(4) ozonolysis and *in situ* reduction to convert the propenyl of the compound of formula (VI) to form an alcohol resulting in a compound of the following formula:



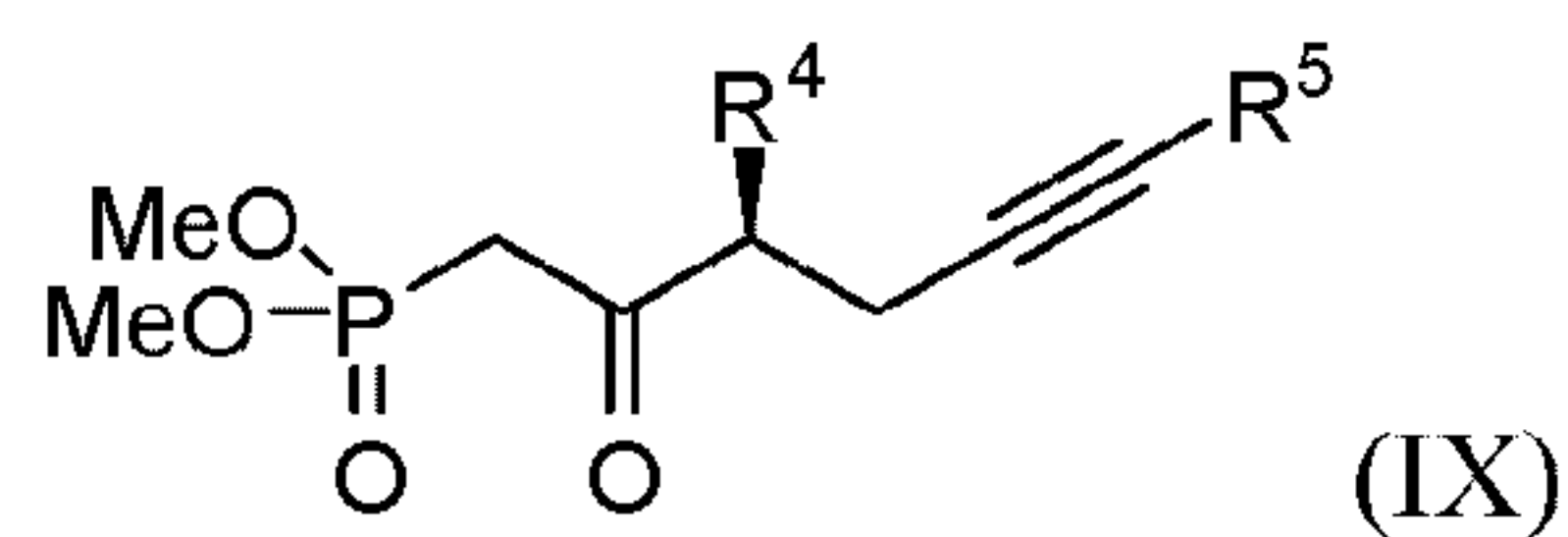
, wherein R^{1a} and R^{2a} are each defined above, R^6 is H or a hydroxy protective group;

(5) deprotection of the acetate of the compound of formula (VII) to form a compound of the following formula:

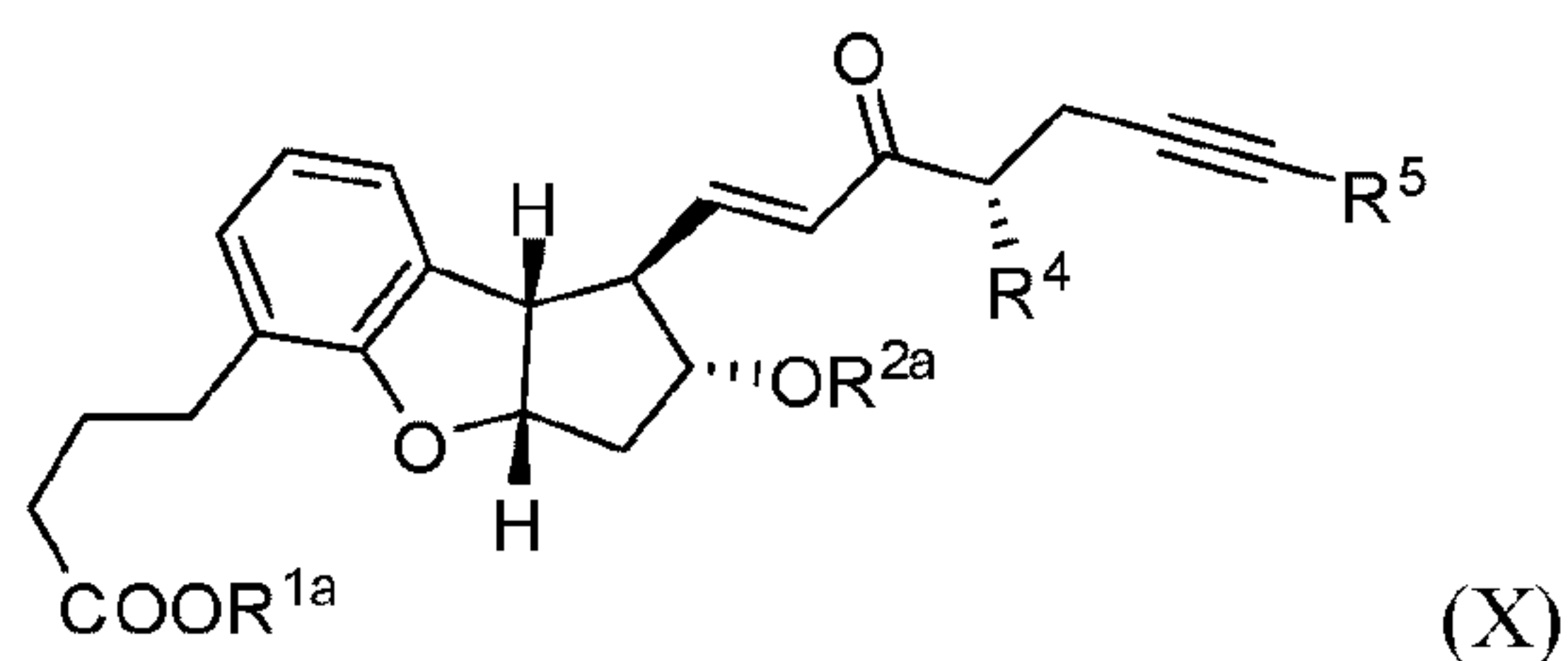


, wherein R^{1a} , R^{2a} , and R^6 are each defined above.;

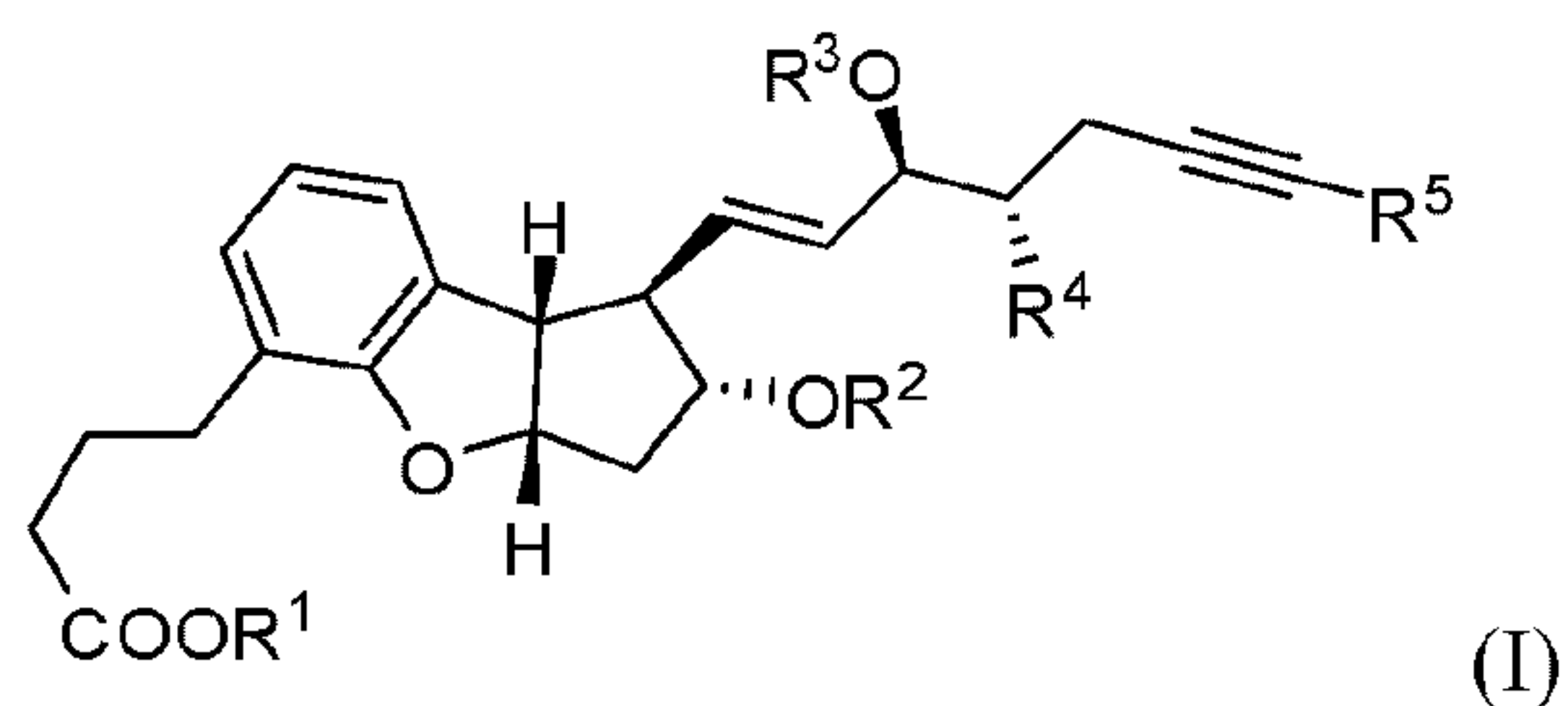
(6) selectively deprotecting the primary hydroxy protective group, followed by oxidation of the primary hydroxy group to the corresponding aldehyde, followed by coupling with a side-chain of the formula:



, wherein R^4 and R^5 are each defined above to form a compound of the following formula:



(7) reduction of the ketone, deprotection of any remaining hydroxy protective group, and optionally converting the R^{1a} into a cation or H to form a compound of the following formula.:



Beraprost 314-d is known as the pharmacologically active isomer of beraprost, which exists as a racemic mixture of four isomers and beraprost 314-d can exist as a pharmaceutically acceptable salt. This compound is represented by the compound of formula (I) wherein R^1 is a cation or H, R^2 and R^3 are H, and R^4 and R^5 are CH_3 .

In a preferred embodiment, the compound of formula (I) is produced as a substantially pure single isomer without need for separating the desired isomer from other isomers.

“Substantially pure” can mean greater than 90% of the desired isomer, greater than 95% of the desired isomer, or greater than 98% of the desired isomer. In some embodiments, R^2 and R^3 , R^{2a} , and R^6 of the compound of formula (I) each independently represent acetate, trimethylsilyl, triethylsilyl, t-butyl dimethylsilyl, t-butyl diphenylsilyl, phenyl dimethylsilyl, tetrahydropyranyl, benzoate ester, benzyl, or substituted benzyl. In a preferred embodiment, R^{1a} is CH_3 , R^{2a} and R^6 are both H.

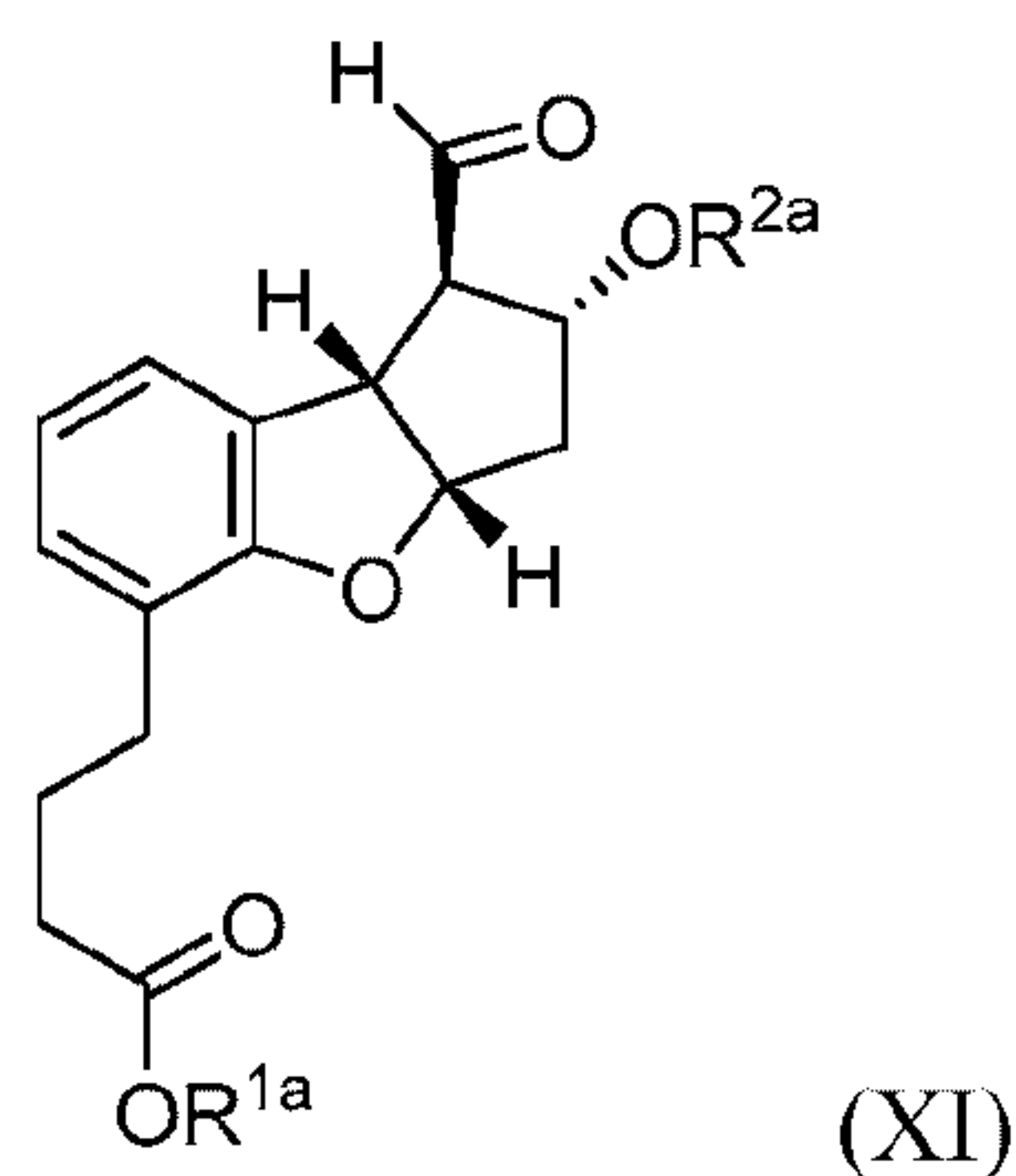
In some embodiments, the radical cyclization of step (2) uses azobisisobutyronitrile as a radical initiator however, it is not limited to only azobisisobutyronitrile there are various other reagents that can be used as radical initiators including but not limited to 4,4'-Azobis(4-cyanovaleric acid), 4,4'-Azobis(4-cyanovaleric acid), 1,1'-Azobis(cyclohexanecarbonitrile), 2,2'-Azobis(2-methylpropionitrile) and 2,2'-Azobis(2-methylpropionamide) dihydrochloride .

In some embodiments, the isomerization of step (3) uses a catalytic amount of carbonylchlorohydridotris(triphenylphosphine) ruthenium (II). The isomerization can also be performed by using various other catalysts, including metal catalysts, such as ruthenium metal complexes, such as ruthenium hydride complex and Grubbs catalyst, rhodium metal, such as rhodium chloride ($RhCl_3 \cdot xH_2O$), and palladium metal, such as palladium chloride ($PdCl_2$).

In some embodiments, the deprotection of step (5) uses sulfuric acid. However, various other inorganic acids such as HCl and HNO_3 can also be used.

In some embodiments, R^{2a} can be a protecting group known to a person of ordinary skill in the art, for example, an alkyl, benzyl (Bn), trimethylsilyl (TMS), tert-butyl dimethylsilyl (TBDMS), tert-butyl diphenylsilyl (TBDPS), or an acetate (Ac) group.

In some embodiments, step (4) of the claimed method produces an *in situ* trapped aldehyde intermediate represented by the compound of formula (XI).

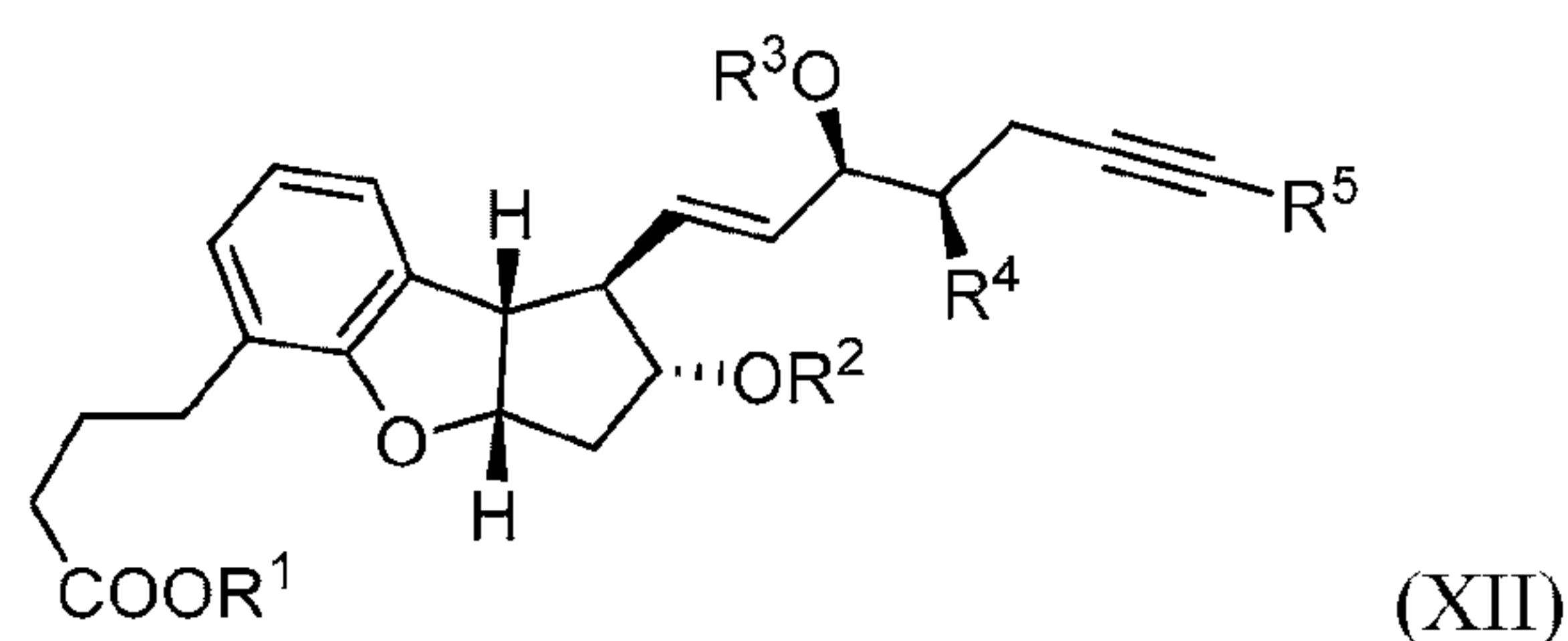


In some embodiments, the reduction of the ketone of formula X may be achieved using a non-selective reducing agent, such as for example sodium borohydride with cerium trichloride heptahydrate, and the subsequent diastereomers separated, or alternatively a chiral reducing agent capable of selectively reducing the ketone may be used to obtain substantially one isomer of the resulting alcohol. Selective reducing agents are known in the art and include, for example, (R)-(+)-2-Butyl-CBS-oxazaborolidine and catecholborane, (R)-(+)-2-Methyl-CBS-oxazaborolidine and catecholborane, (+) DIP-chloride, NaBH₄ and 2-(3-Nitrophenyl)-1,3,2-dioxaborolane-4S,5S-dicarboxylic acid (D-TarB-NO₂), modified DIBAL reagents, and modified LAH agents.

In one embodiment, the compound of formula (I) is produced as a single isomer represented by formula (I) and in substantially isomerically pure form. In one embodiment, the product represented by formula (I) comprises 90% of the resulting isomeric mixture, or preferably 95% of the resulting isomeric mixture, or more preferably 98% of the resulting isomeric mixture, or even more preferably 99% of the resulting isomeric mixture, and most preferably greater than 99% of the resulting isomeric mixture.

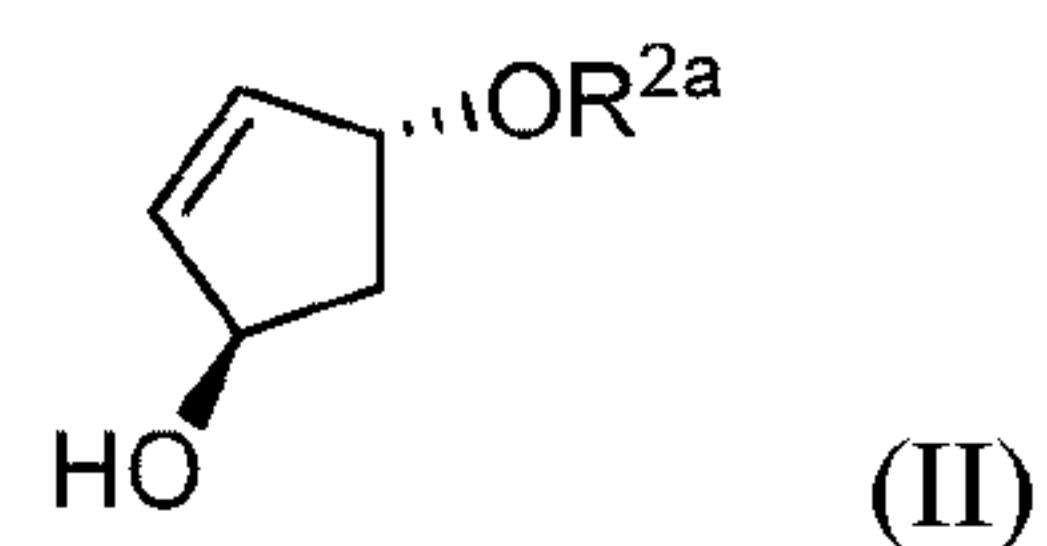
In some embodiments, the beraprost diol of formula (I) is crystallized from MTBE in about 80% yield. In some embodiments, the method produces the compound of formula (I) with a yield of at least 37%. In some embodiments, the method produces the compound of formula (I) with a chiral purity of 99.9% by HPLC.

In some embodiments, a process for preparing a compound of the following formula:

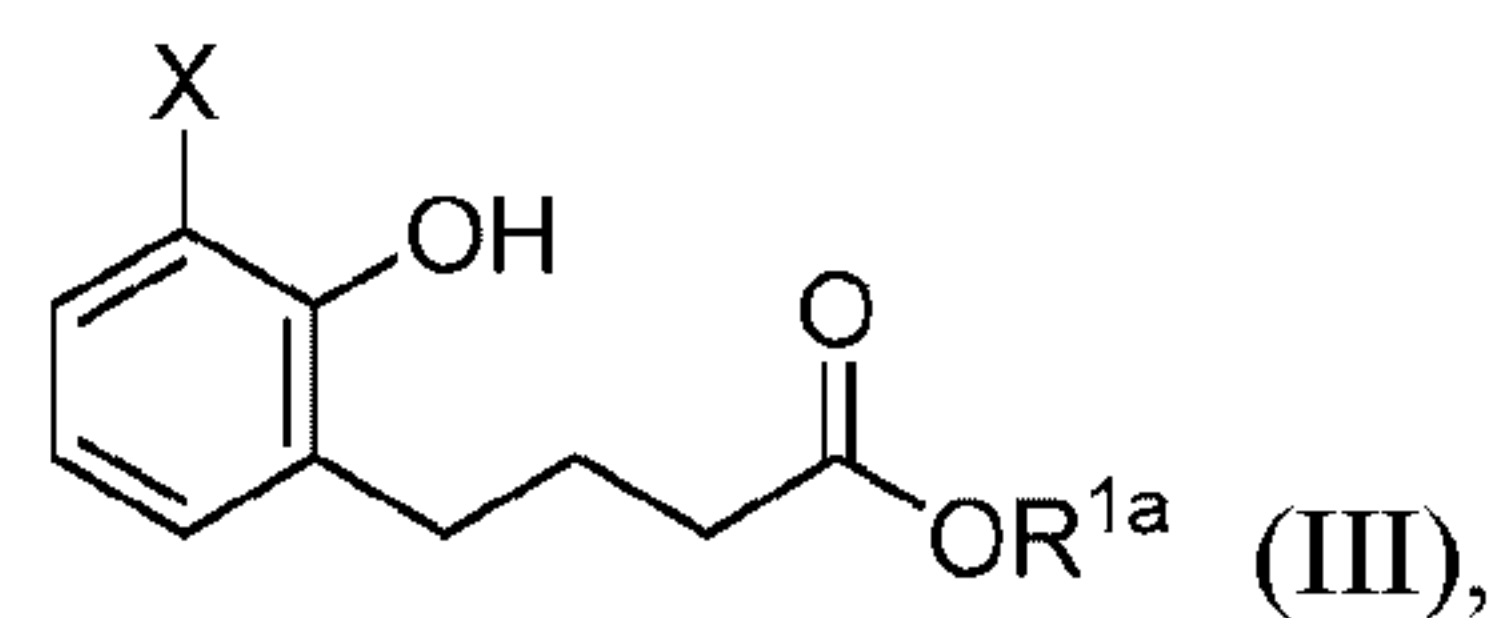


wherein R^1 represents a cation, H, or C_{1-12} alkyl,
 R^2 and R^3 each represent H or a hydroxy protective group,
 R^4 represents H or C_{1-3} alkyl, and
 R^5 represents H or C_{1-6} alkyl, comprises:

(1) reacting a compound of the following formula:

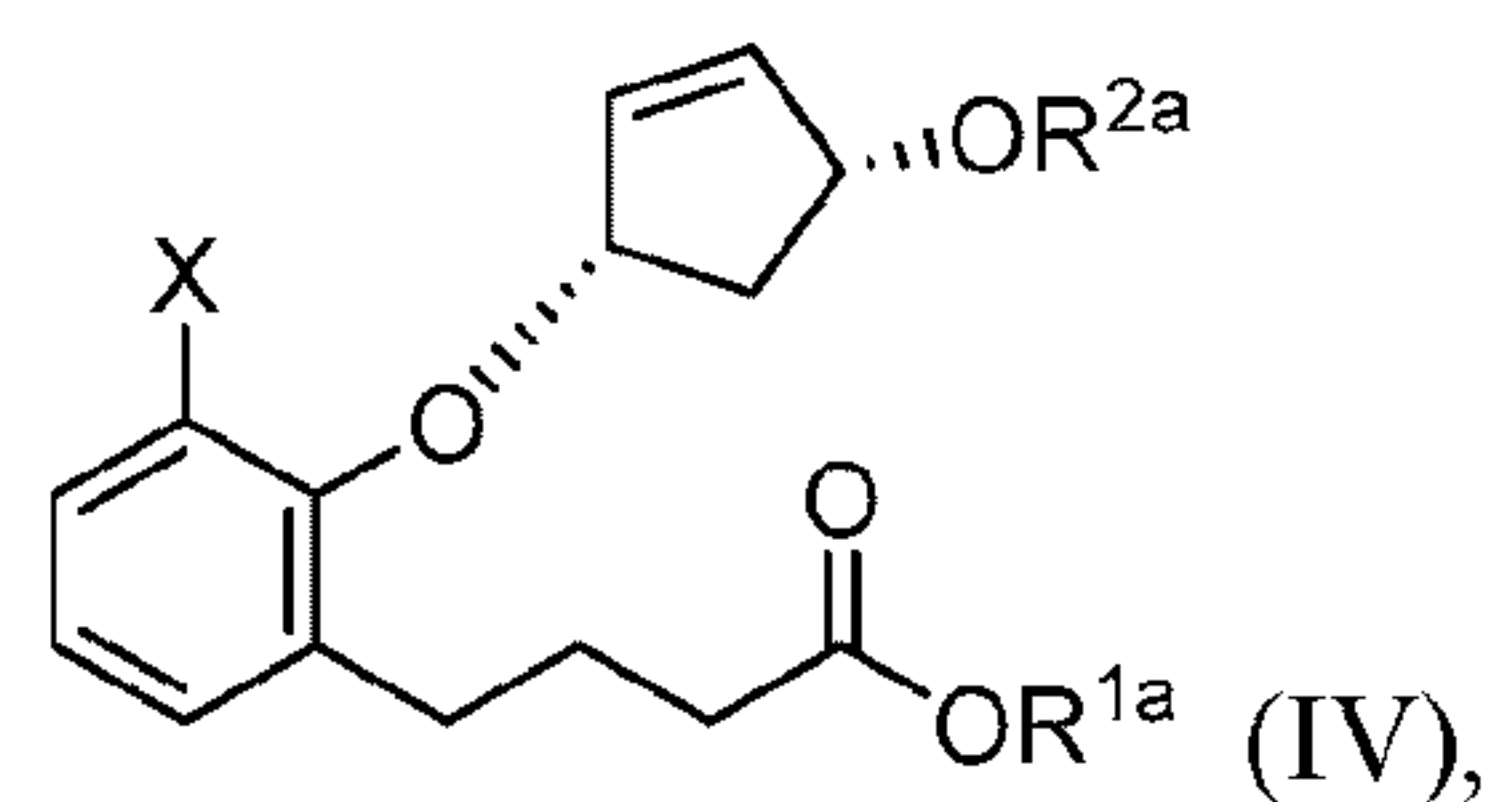


, wherein R^{2a} is H or an hydroxy protective group,
 with a compound of the following formula:



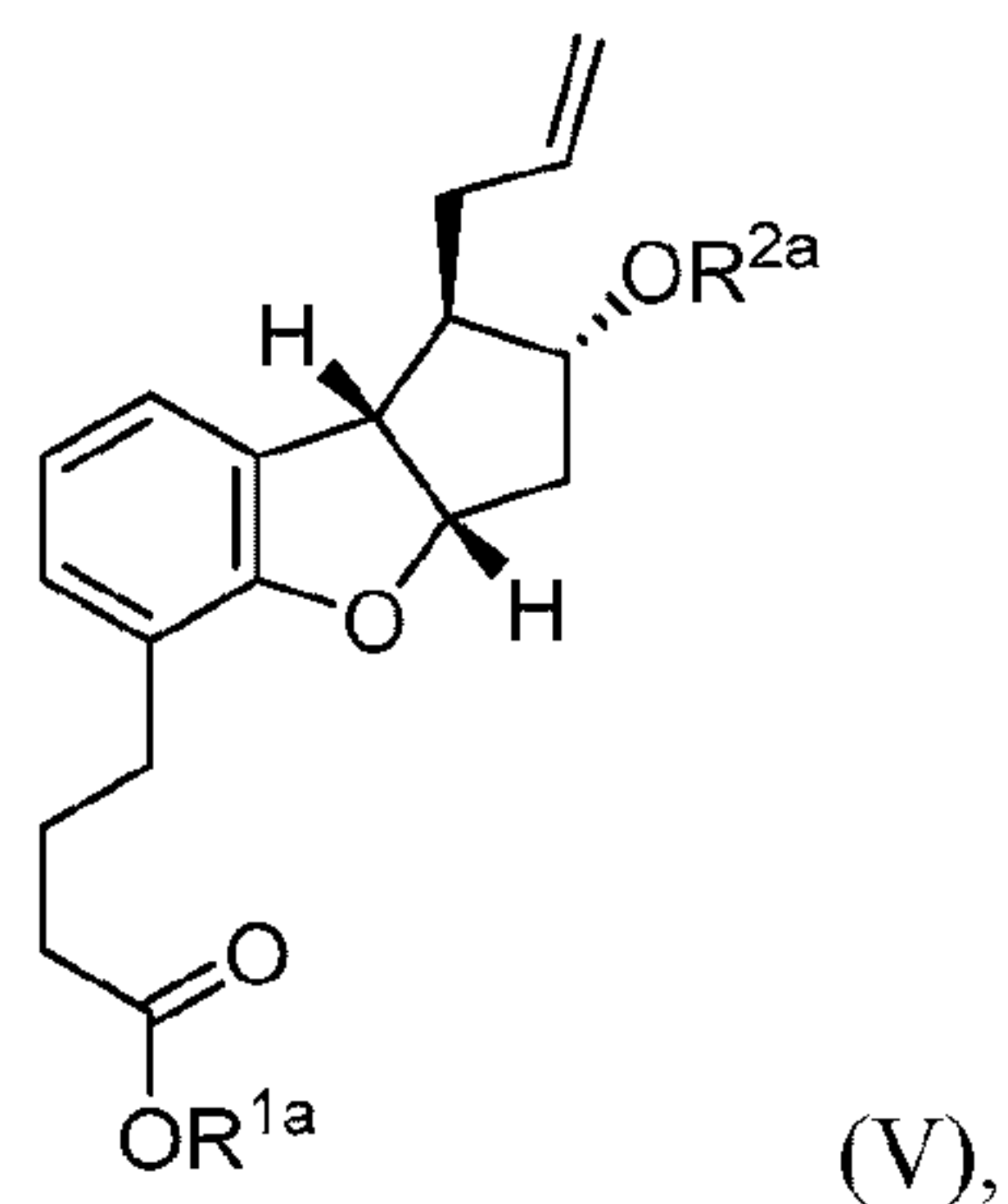
wherein R^{1a} is a cation, H, or C_{1-12} alkyl, X is a halogen selected from chloro, bromo and iodo,

to form a compound of the following formula:



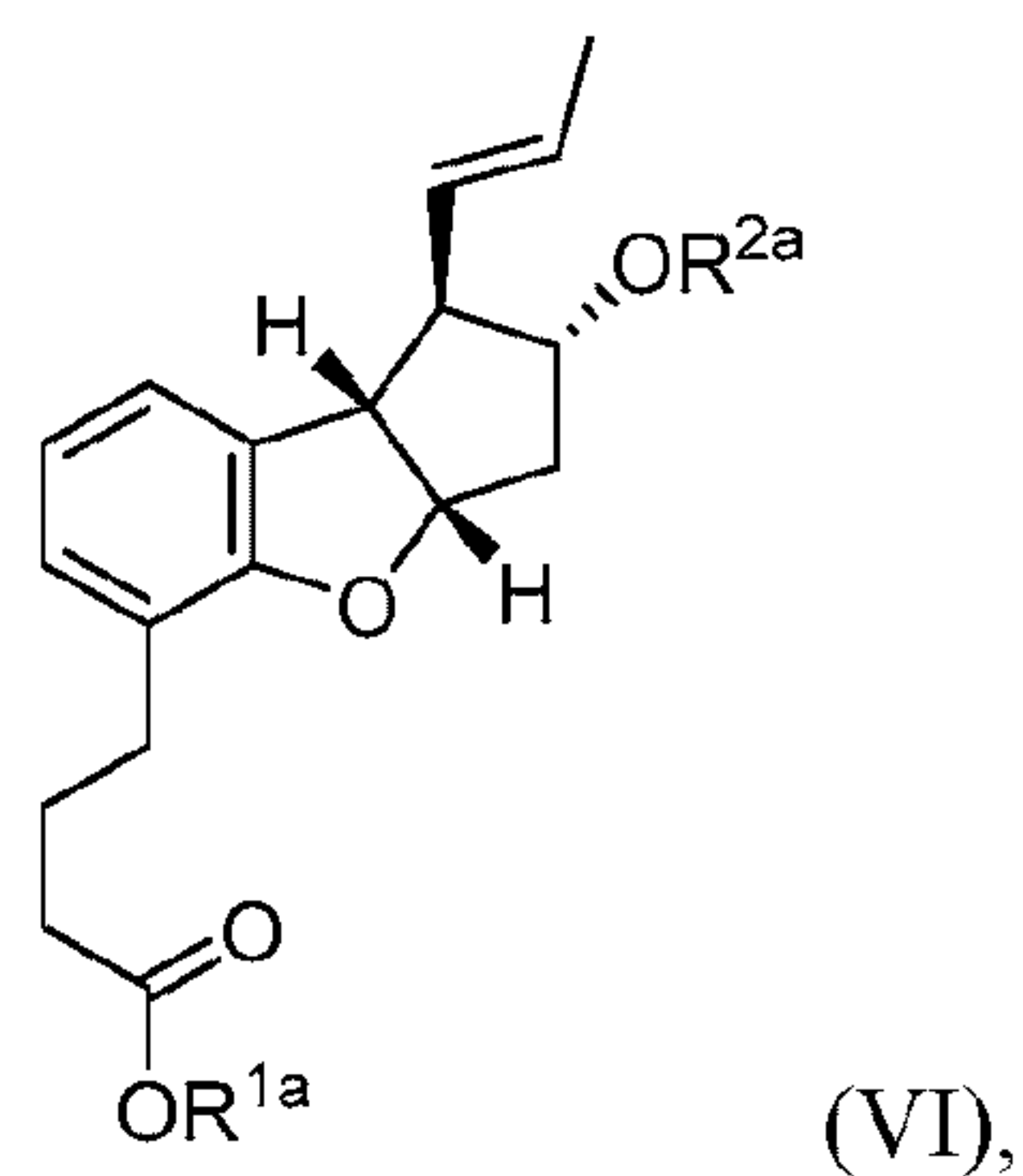
wherein R^{1a} , R^{2a} and X are each defined above;

(2) cyclizing a compound of formula (IV) to form a compound of the following formula:



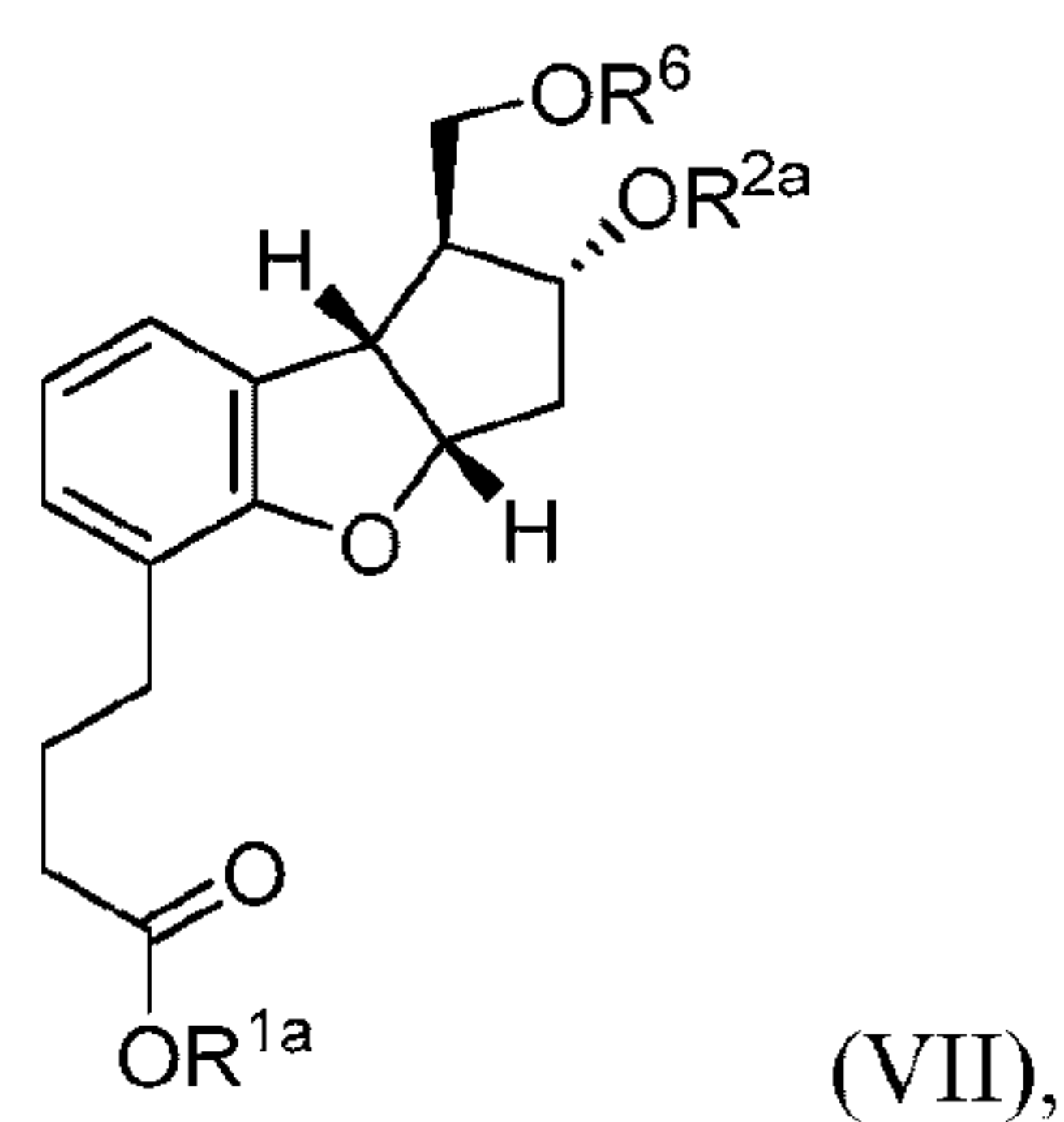
wherein R^{1a} and R^{2a} are each defined above;

(3) isomerizing an allyl of the compound of formula (V) to form a propenyl resulting in a compound of the following formula:



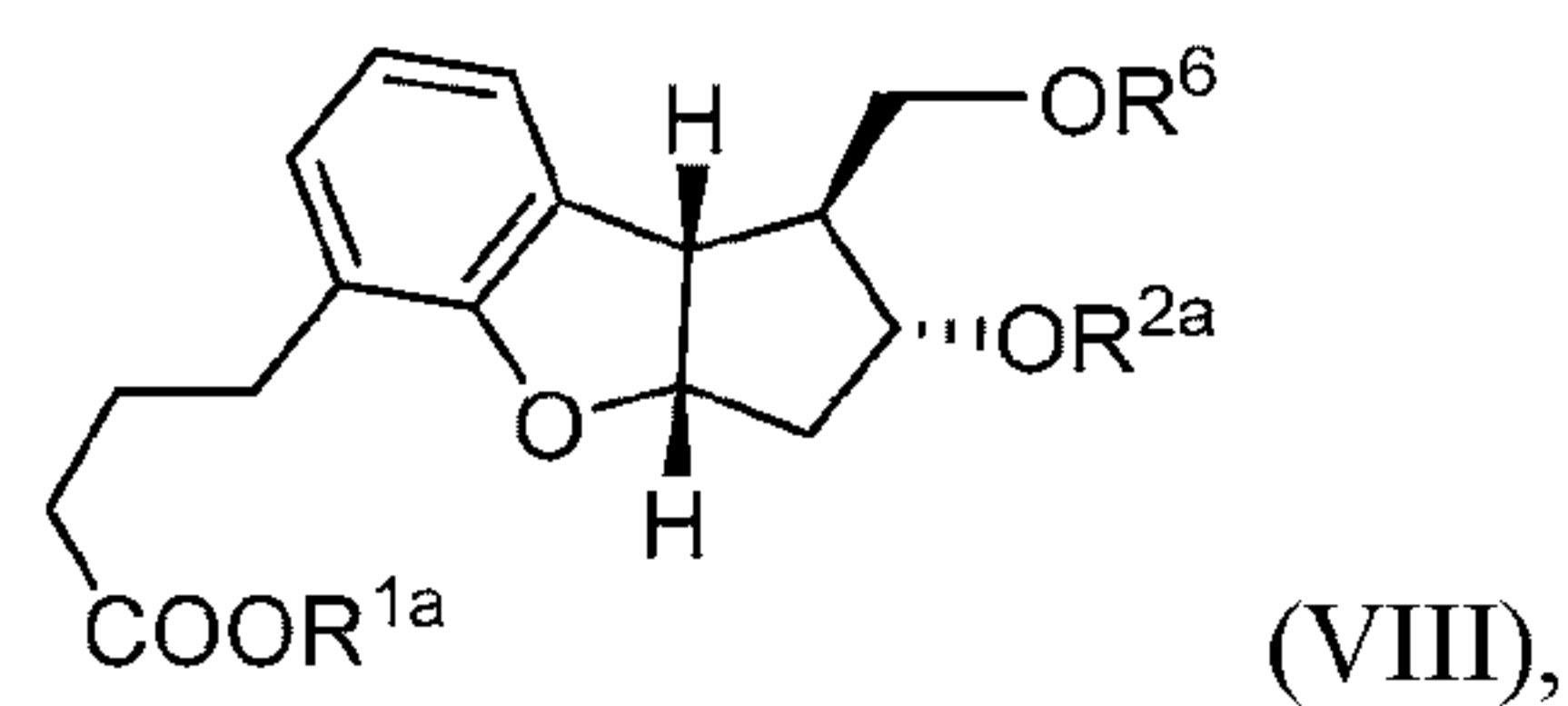
wherein R^{1a} and R^{2a} are each defined above;

(4) ozonolysis and *in situ* reduction to convert the propenyl of the compound of formula (VI) to form an alcohol resulting in a compound of the following formula:



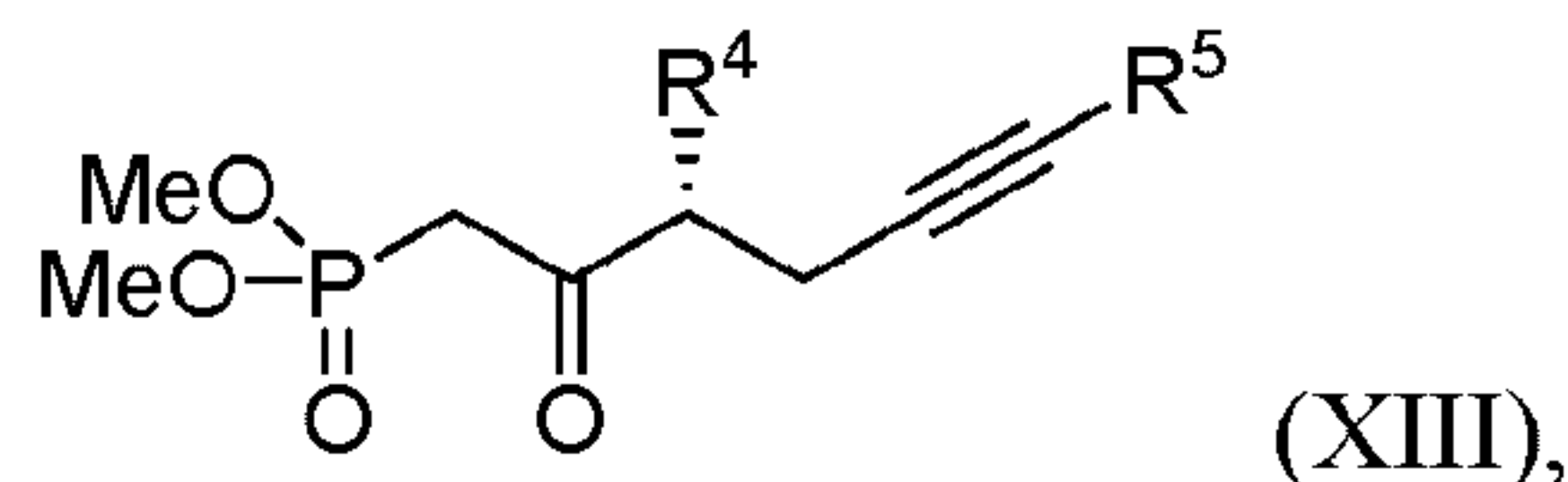
wherein R^{1a} and R^{2a} are each defined above, R^6 is H or a hydroxy protective group;

(5) deprotecting an acetate of the compound of formula (VII) to form a compound of the following formula:

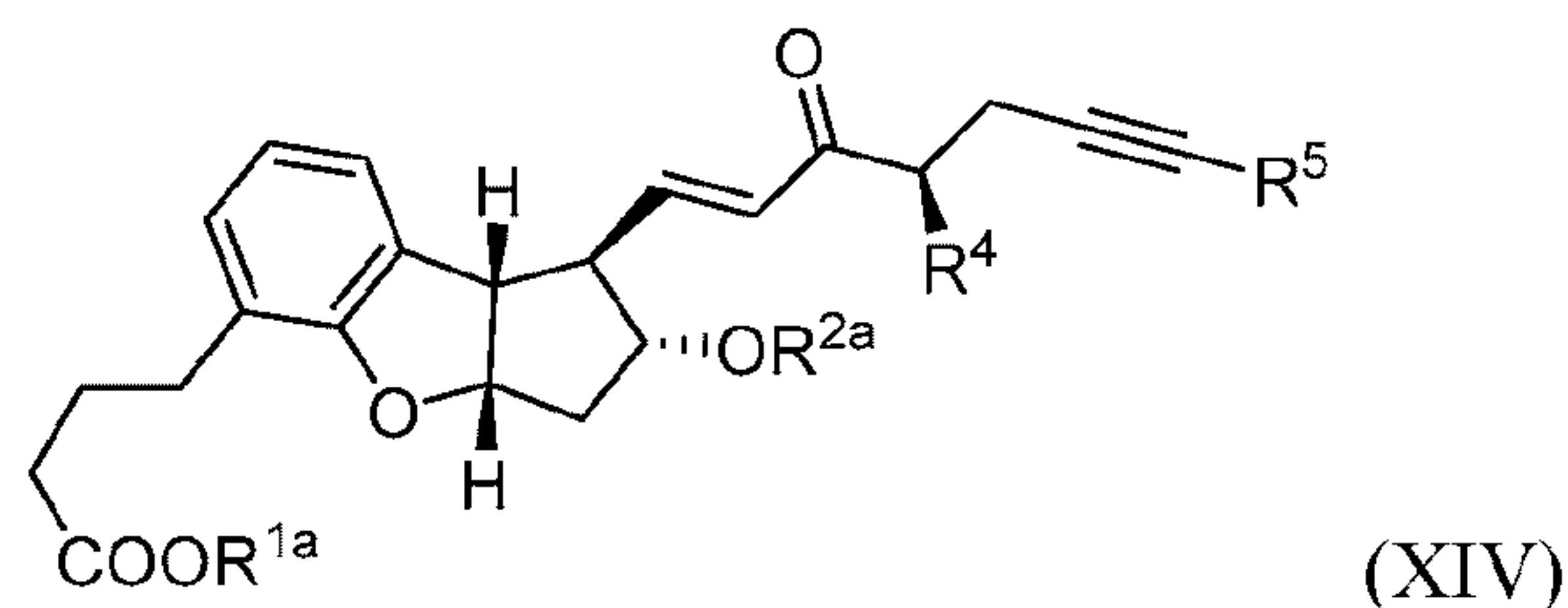


wherein R^{1a} , R^{2a} and R^6 are each defined above;

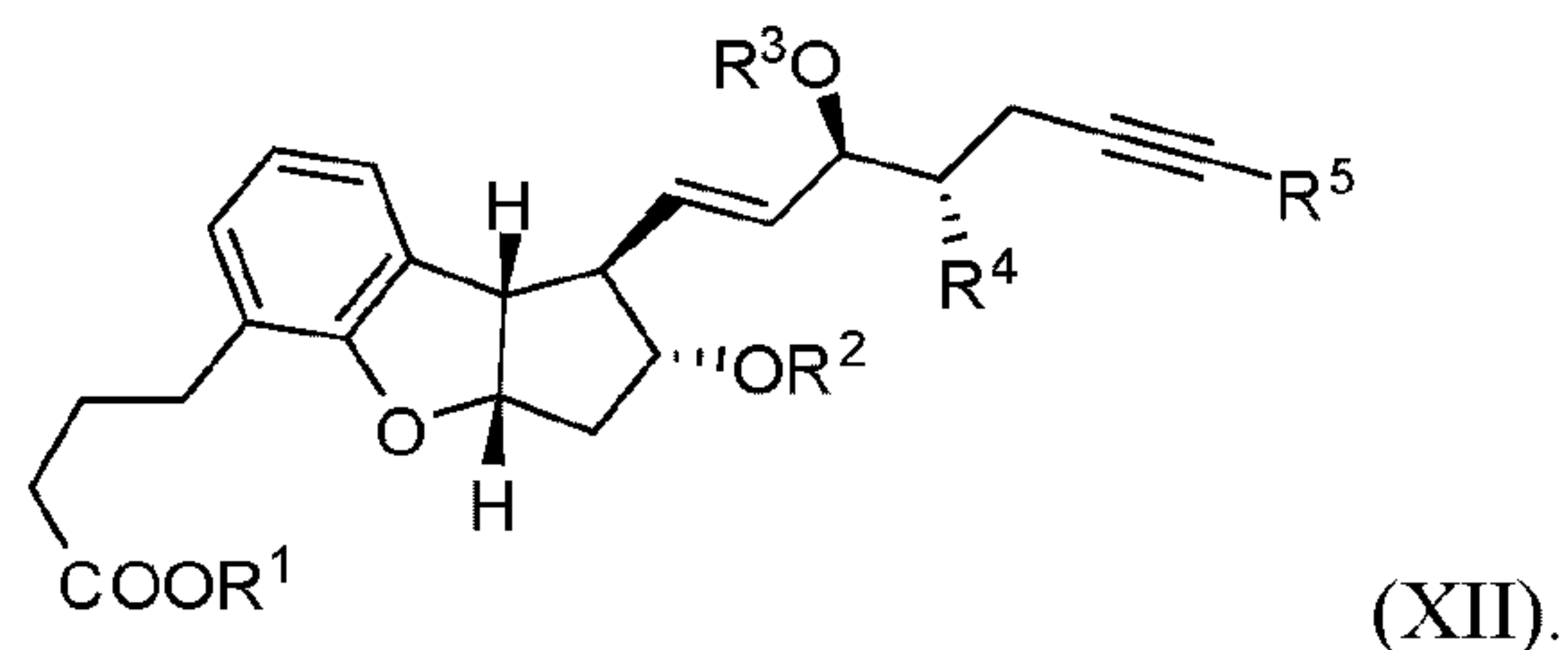
(6) selectively deprotecting the primary hydroxy protective group, followed by oxidation of the primary hydroxy group to form an aldehyde, followed by coupling with a side-chain of the formula:



wherein R^4 and R^5 are each defined above to form a compound of the following formula:



(7) reduction of the ketone, deprotection of any remaining hydroxy protective group and optionally converting the R^{1a} into a cation or H to form a compound of the following formula:



In some embodiments, the present invention provides a method that produces the compound of formula (XII) as a substantially pure single isomer.

In some embodiments, R^2 , R^3 , R^{2a} and R^6 each independently represent acetate, trimethylsilyl, triethylsilyl, t-butyl dimethylsilyl, t-butyl diphenylsilyl, phenyl dimethylsilyl, tetrahydropyranyl, benzoate ester, benzyl, or substituted benzyl.

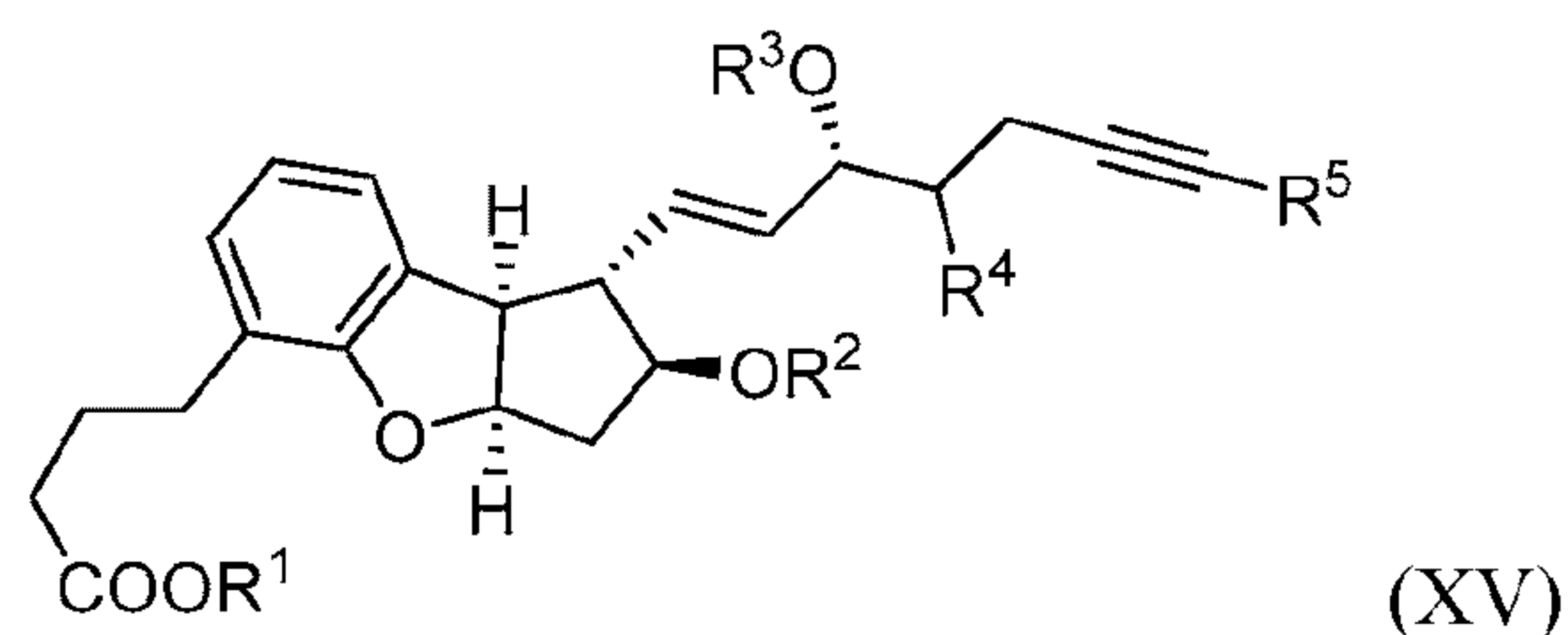
In some embodiments, R^{1a} is CH_3 and R^{2a} and R^6 are both H.

In some embodiments, azobisisobutyronitrile is used as a radical initiator in step (2).

In some embodiments, a catalytic amount of carbonylchlorohydridotris(triphenylphosphine) ruthenium (II) is used in step (3).

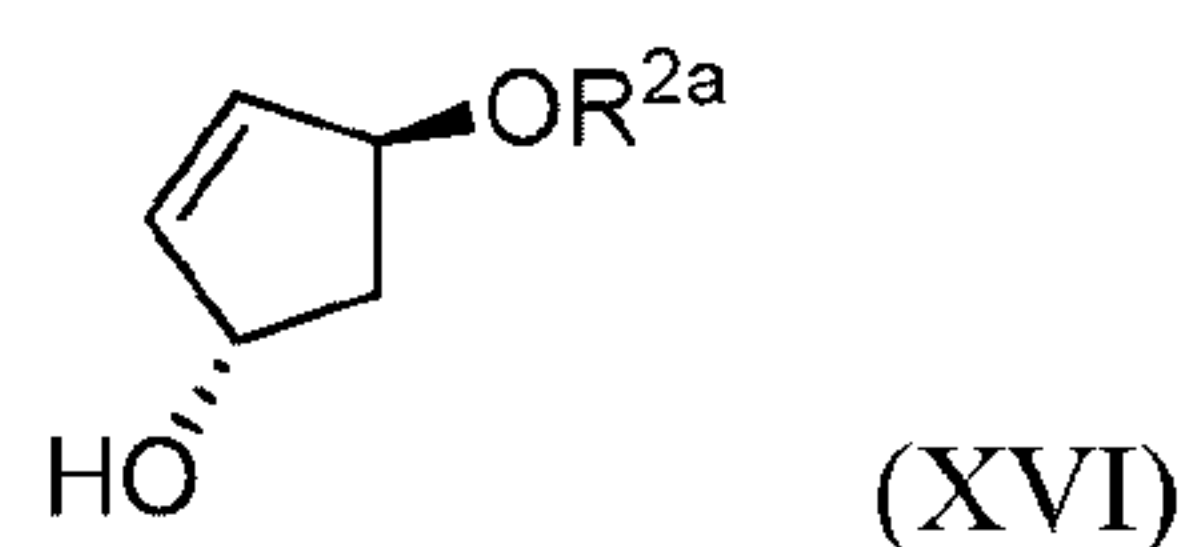
In some embodiments, sulfuric acid is used in step (5).

In some embodiments, the present invention provides a process for preparing a compound of the following formula:

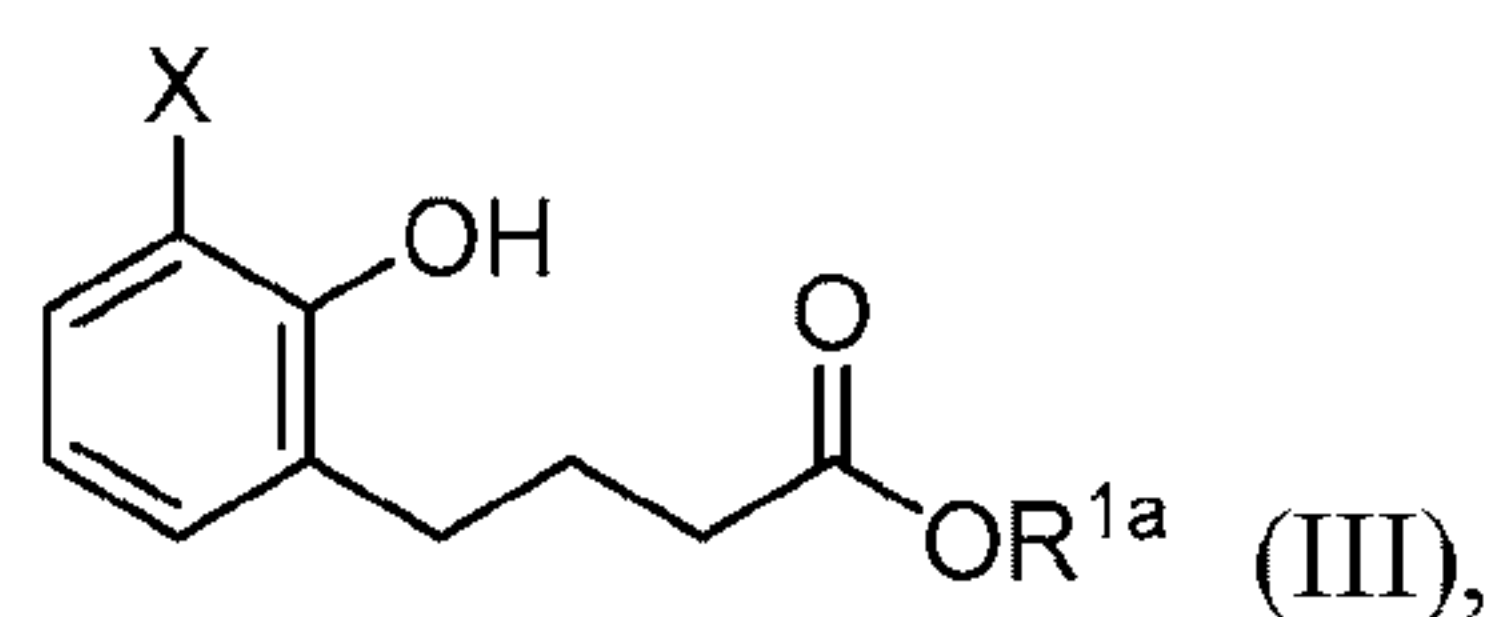


wherein R^1 represents a cation, H, or C_{1-12} alkyl,
 R^2 and R^3 each represent H or a hydroxy protective group,
 R^4 represents H or C_{1-3} alkyl, and
 R^5 represents H or C_{1-6} alkyl, comprising:

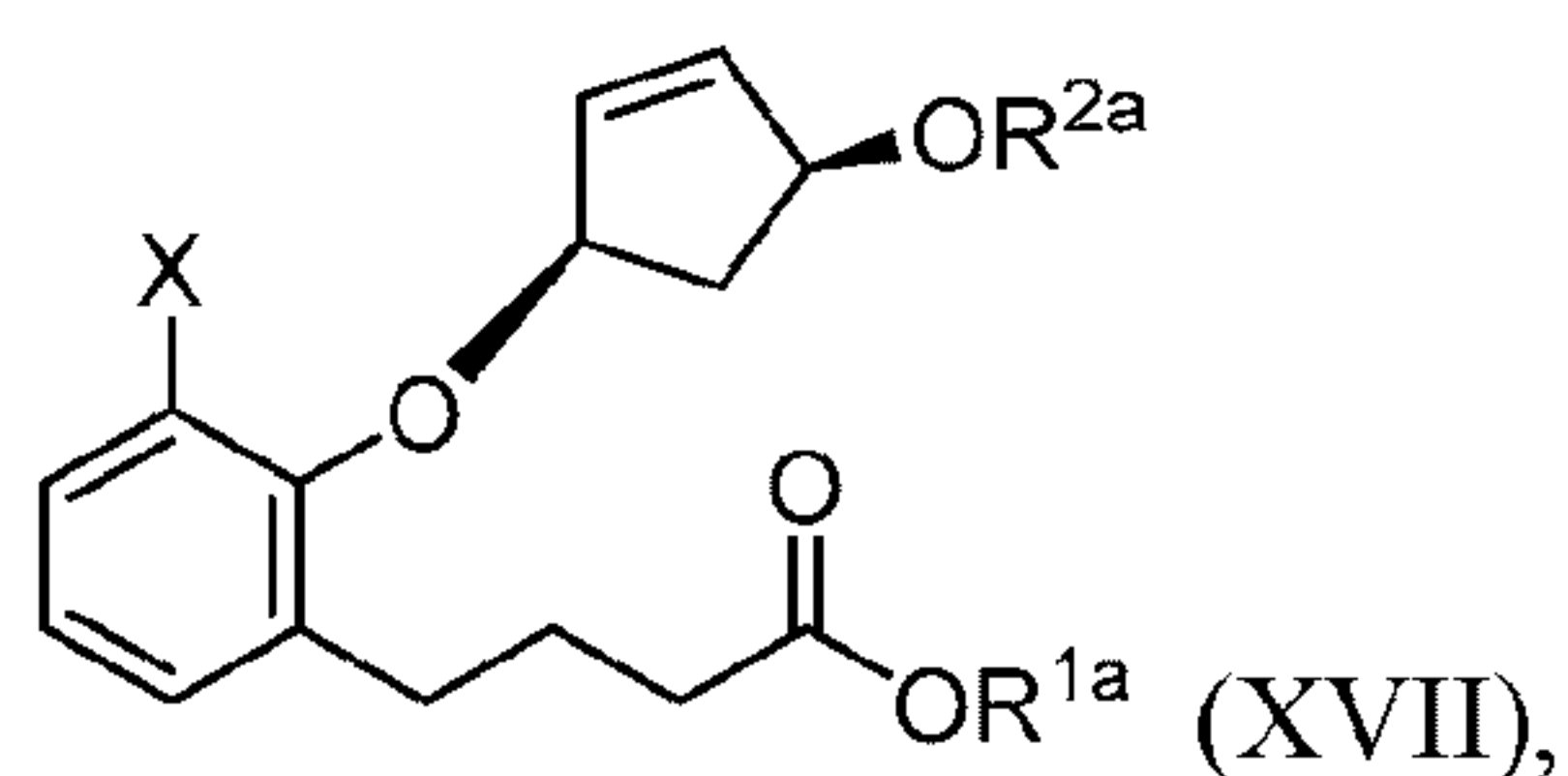
(1) reacting a compound of the following formula:



, wherein R^{2a} is H or an hydroxy protective group,
 with a compound of the following formula:

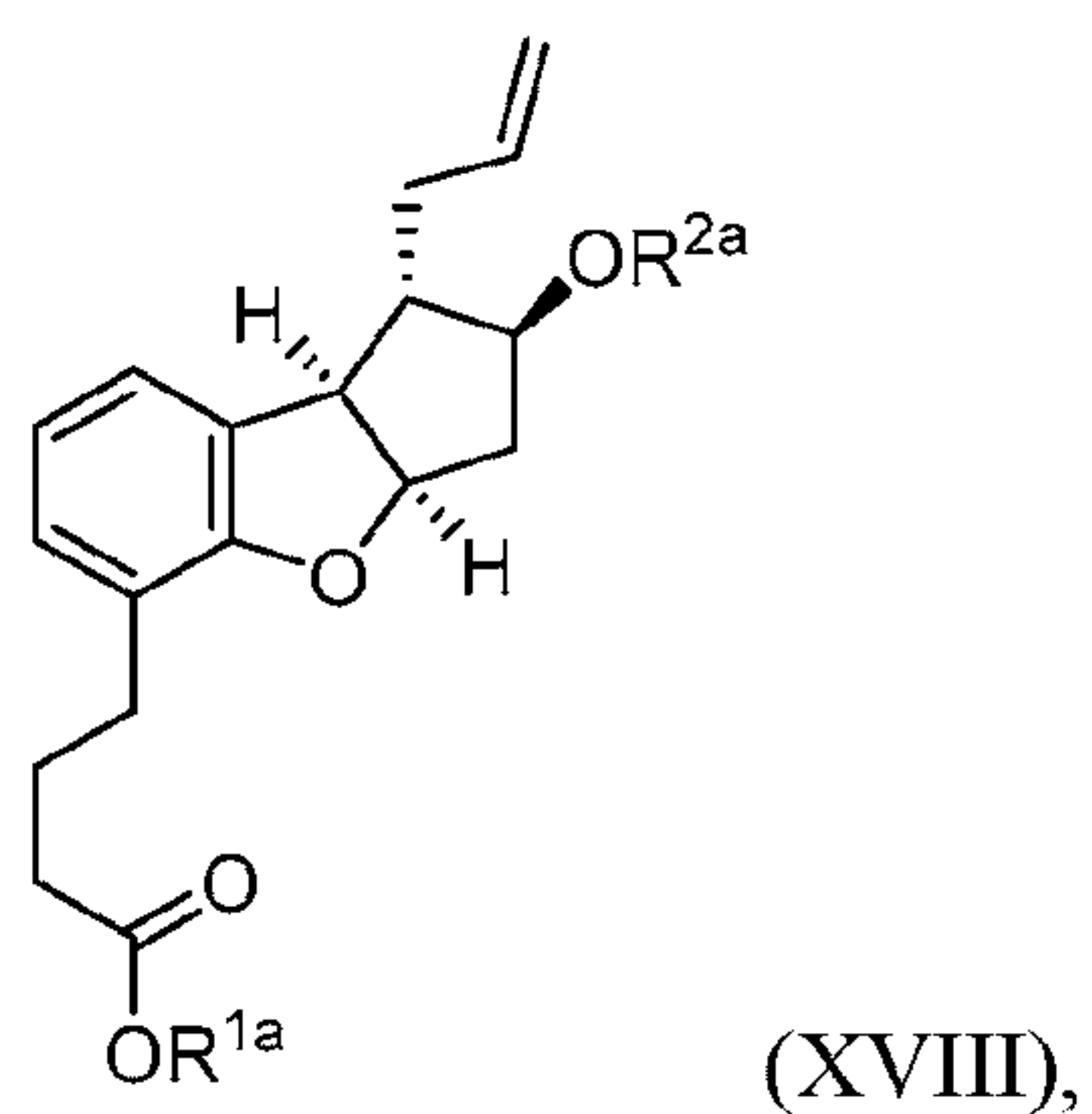


wherein R^{1a} is a cation, H, or C_{1-12} alkyl, X is a halogen selected from chloro, bromo and iodo,
 to form a compound of the following formula:



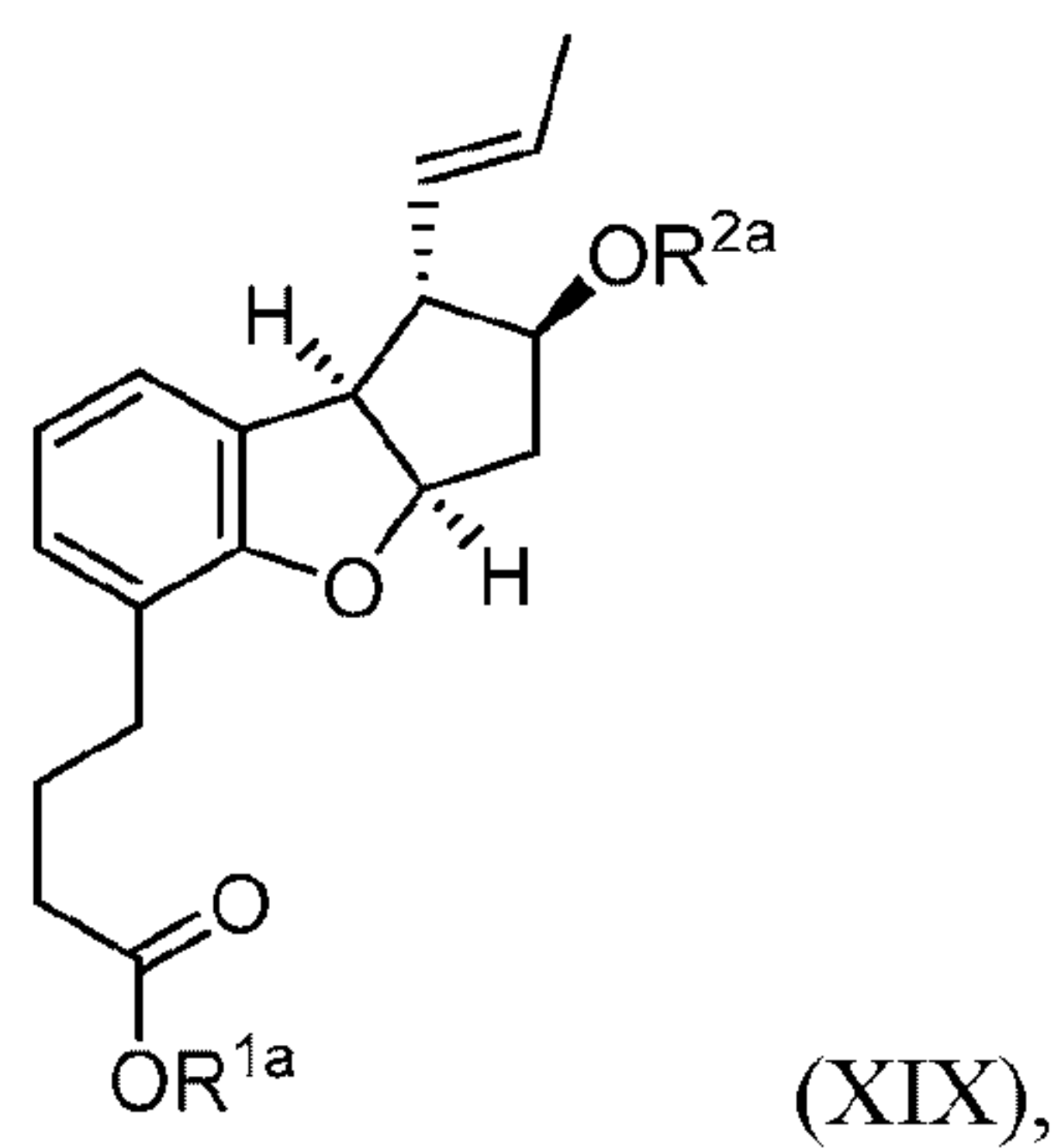
wherein R^{1a} , R^{2a} and X are each defined above;

(2) cyclizing a compound of formula (XVII) to form a compound of the following formula:



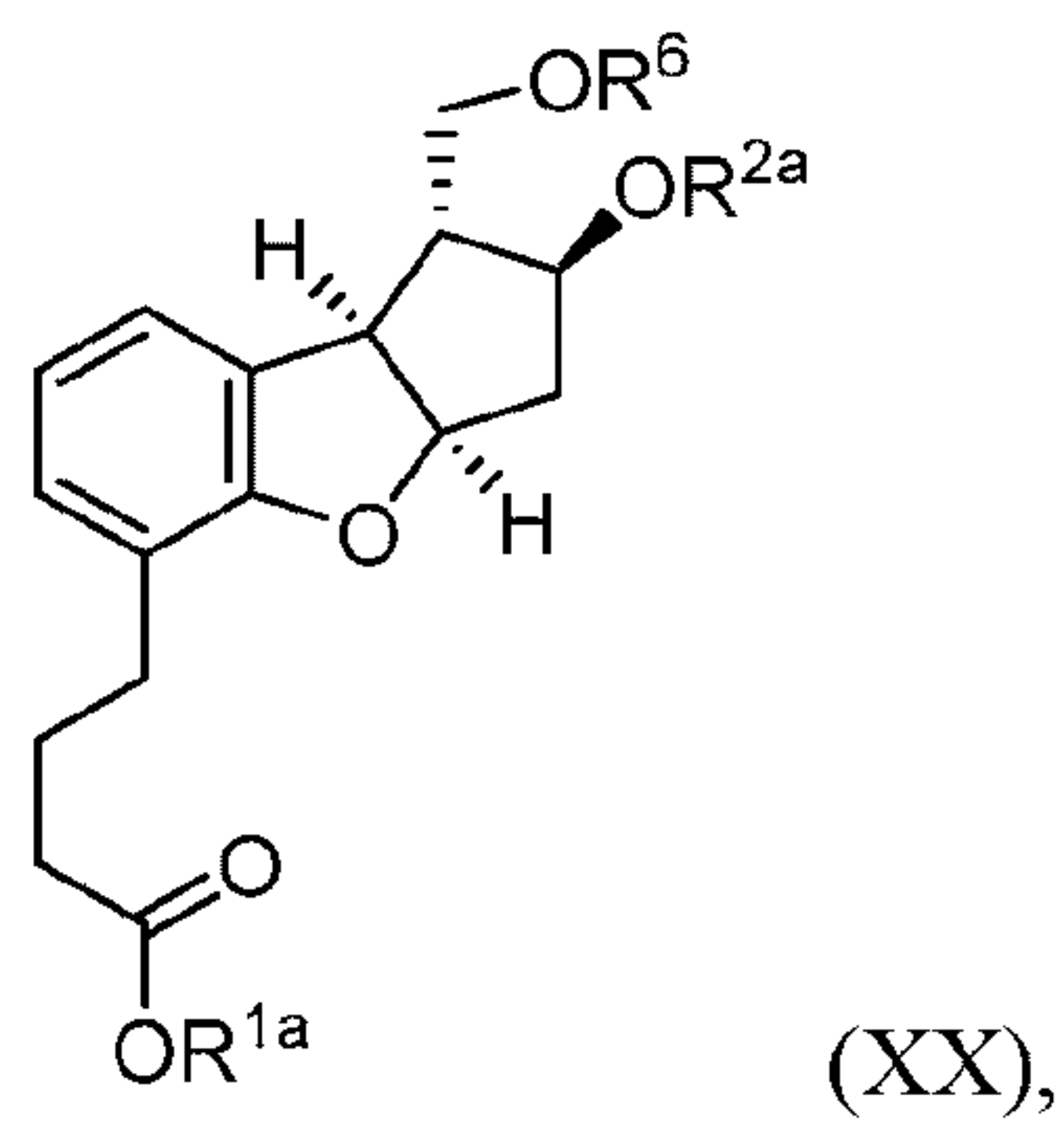
wherein R^{1a} and R^{2a} are each defined above;

(3) isomerizing an allyl of the compound of formula (XVIII) to form a propenyl resulting in a compound of the following formula:



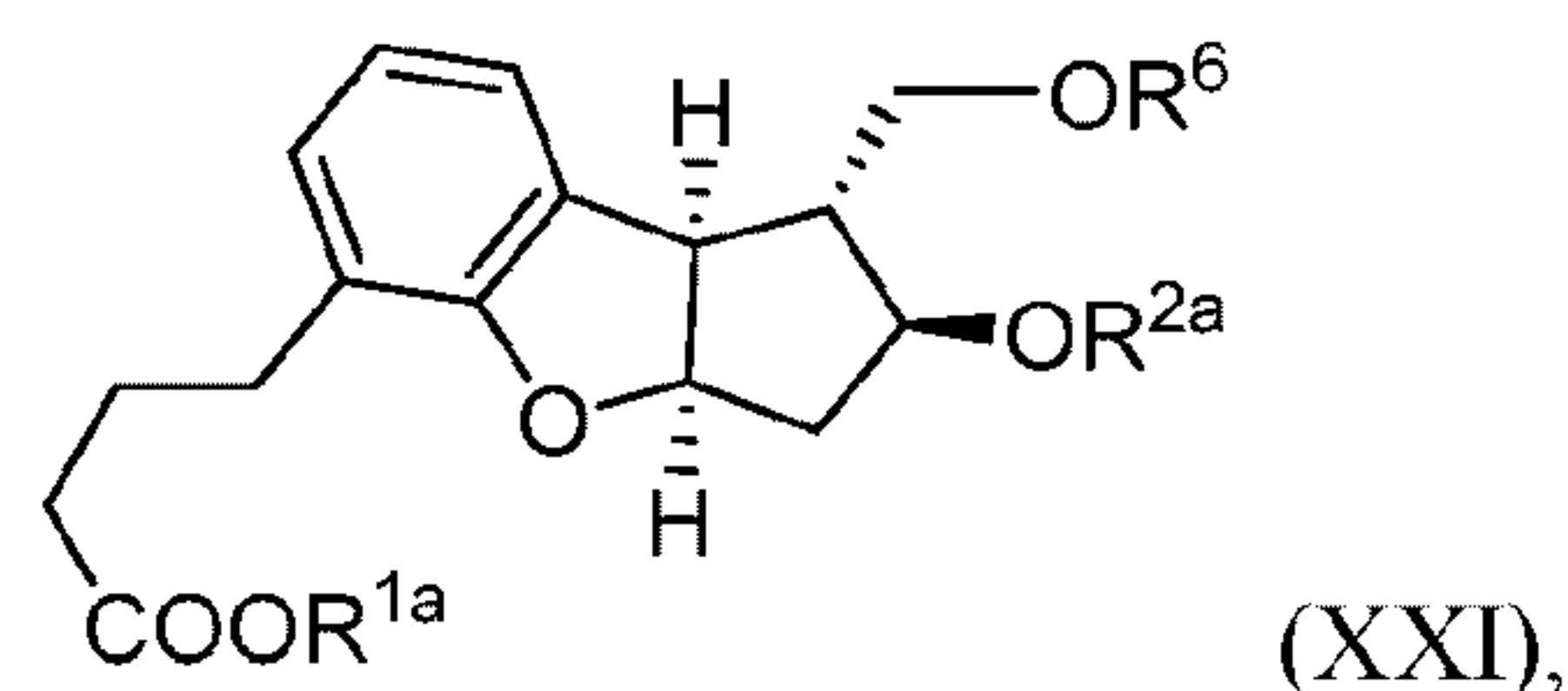
wherein R^{1a} and R^{2a} are each defined above;

(4) ozonolysis and *in situ* reduction to convert the propenyl of the compound of formula (XIX) to form an alcohol resulting in a compound of the following formula:



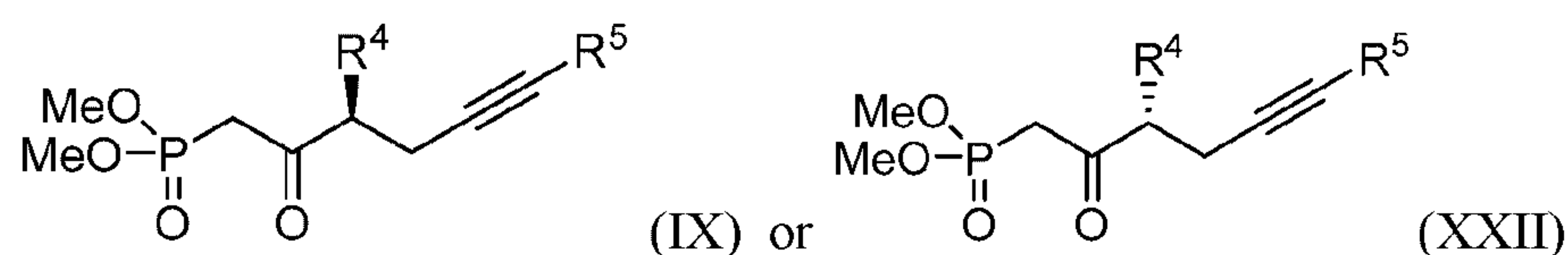
wherein R^{1a} and R^{2a} are each defined above, R^6 is H or a hydroxy protective group;

(5) deprotecting an acetate of the compound of formula (XX) to form a compound of the following formula:

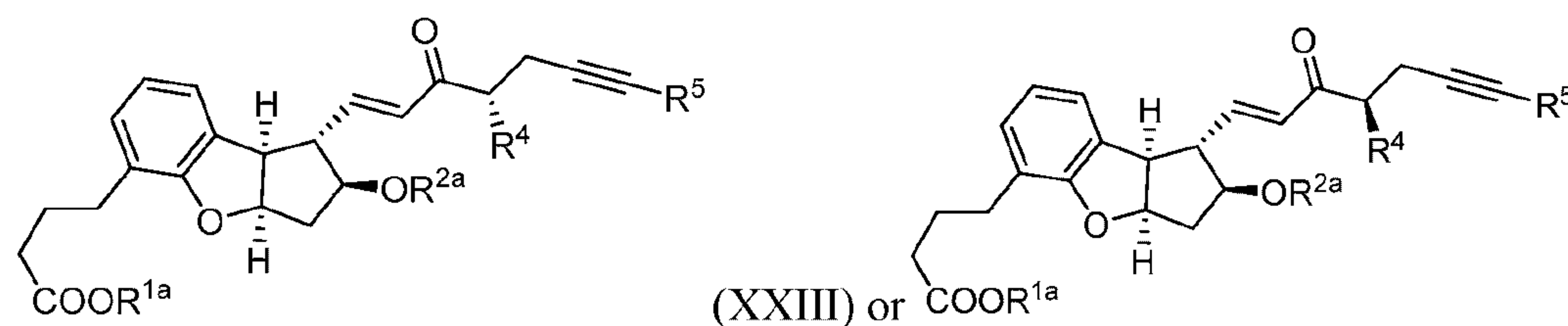


wherein R^{1a}, R^{2a} and R⁶ are each defined above;

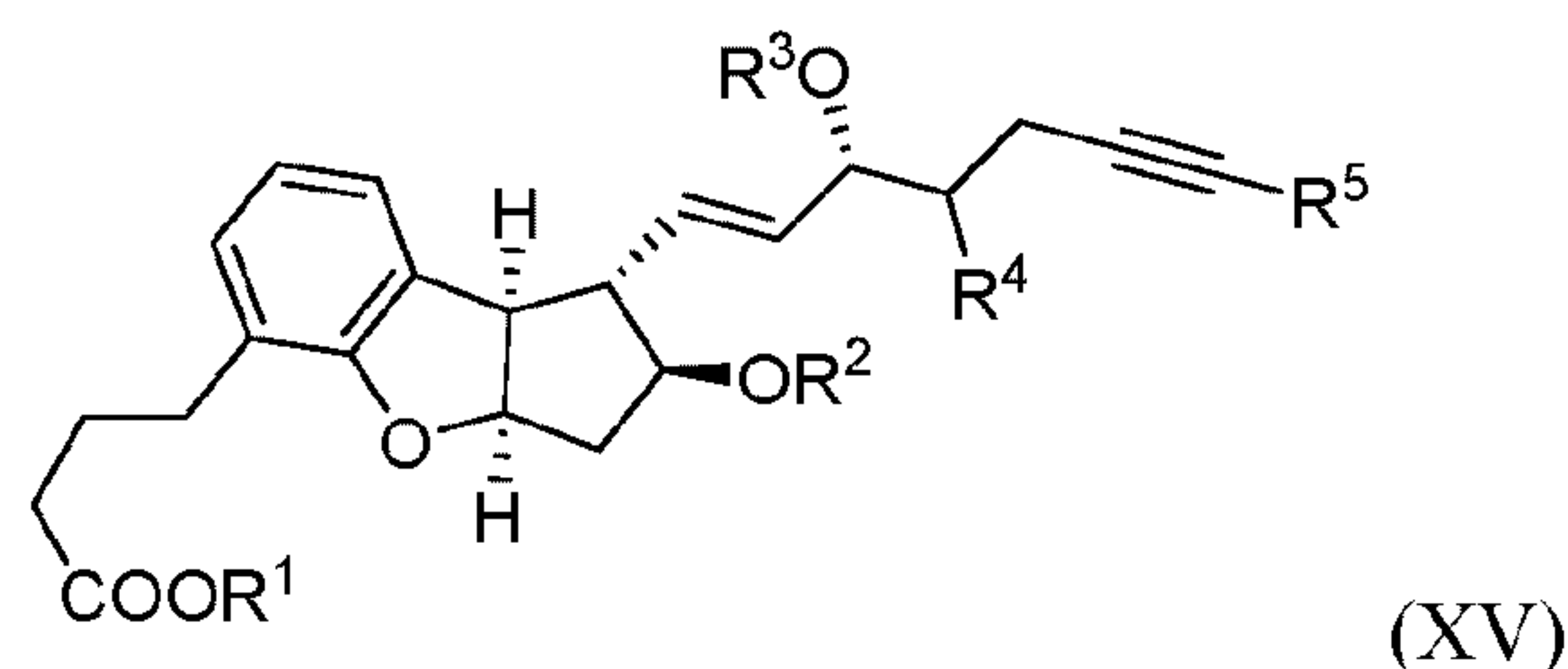
(6) selectively deprotecting the primary hydroxy protective group, followed by oxidation of the primary hydroxy group to form an aldehyde, followed by coupling with a side-chain of the formula:



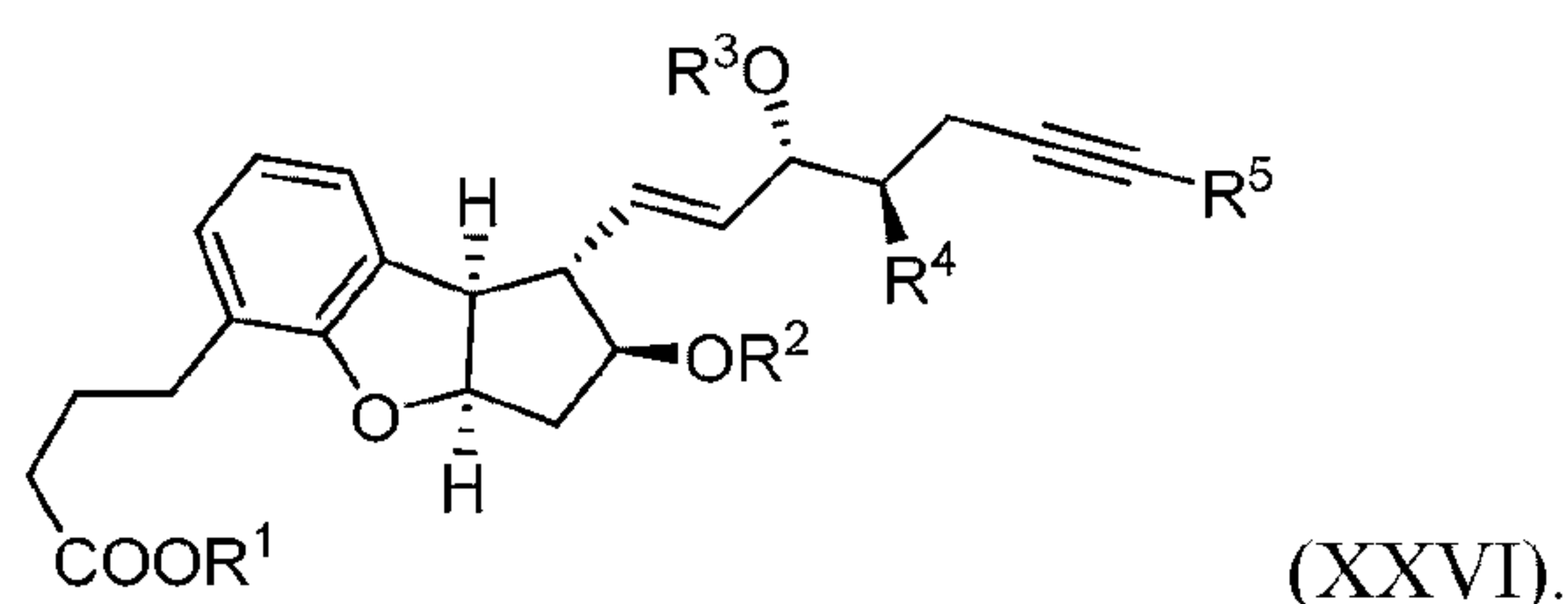
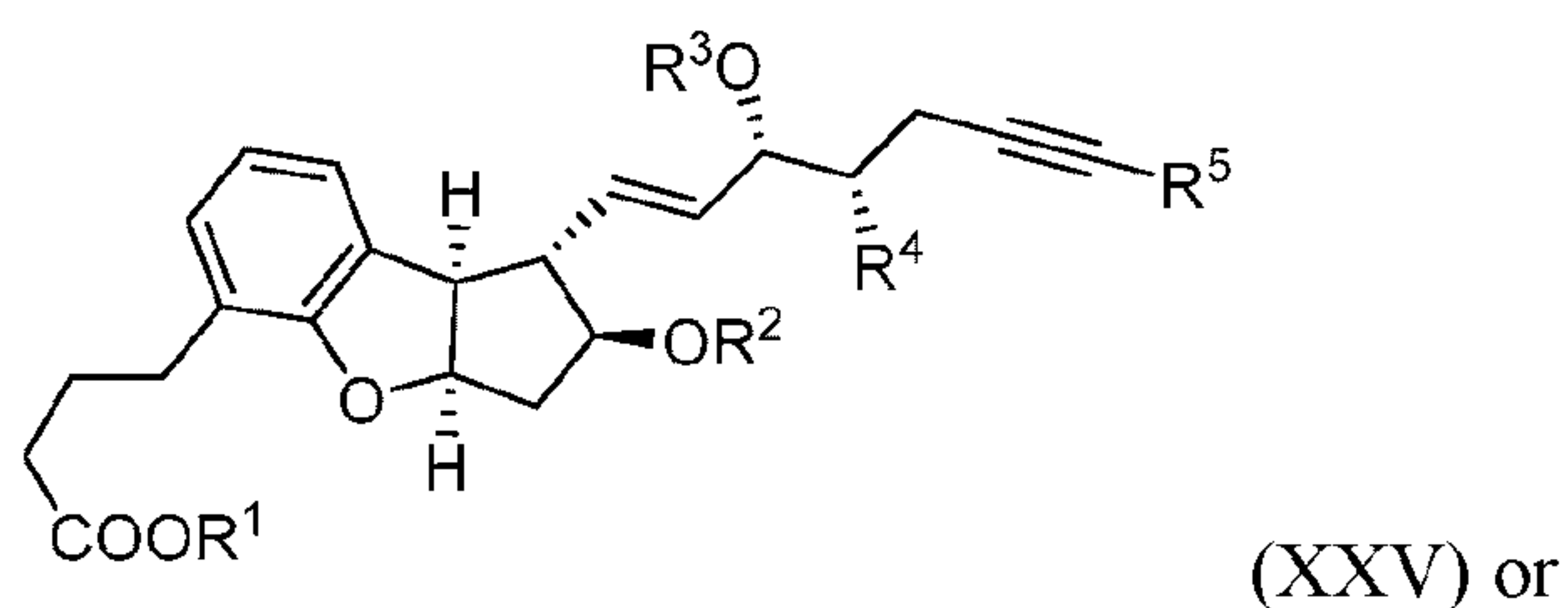
wherein R⁴ and R⁵ are each defined above to form a compound of the following formula:



(7) reduction of the ketone, deprotection of any remaining hydroxy protective group and optionally converting the R^{1a} into a cation or H to form a compound of the following formula:



In some embodiments, the methods described herein produce the compound of formula (XV) as a substantially pure single isomer of the formula



In some embodiments, R^2 , R^3 , R^{2a} and R^6 each independently represent acetate, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, phenyldimethylsilyl, tetrahydropyranyl, benzoate ester, benzyl, or substituted benzyl.

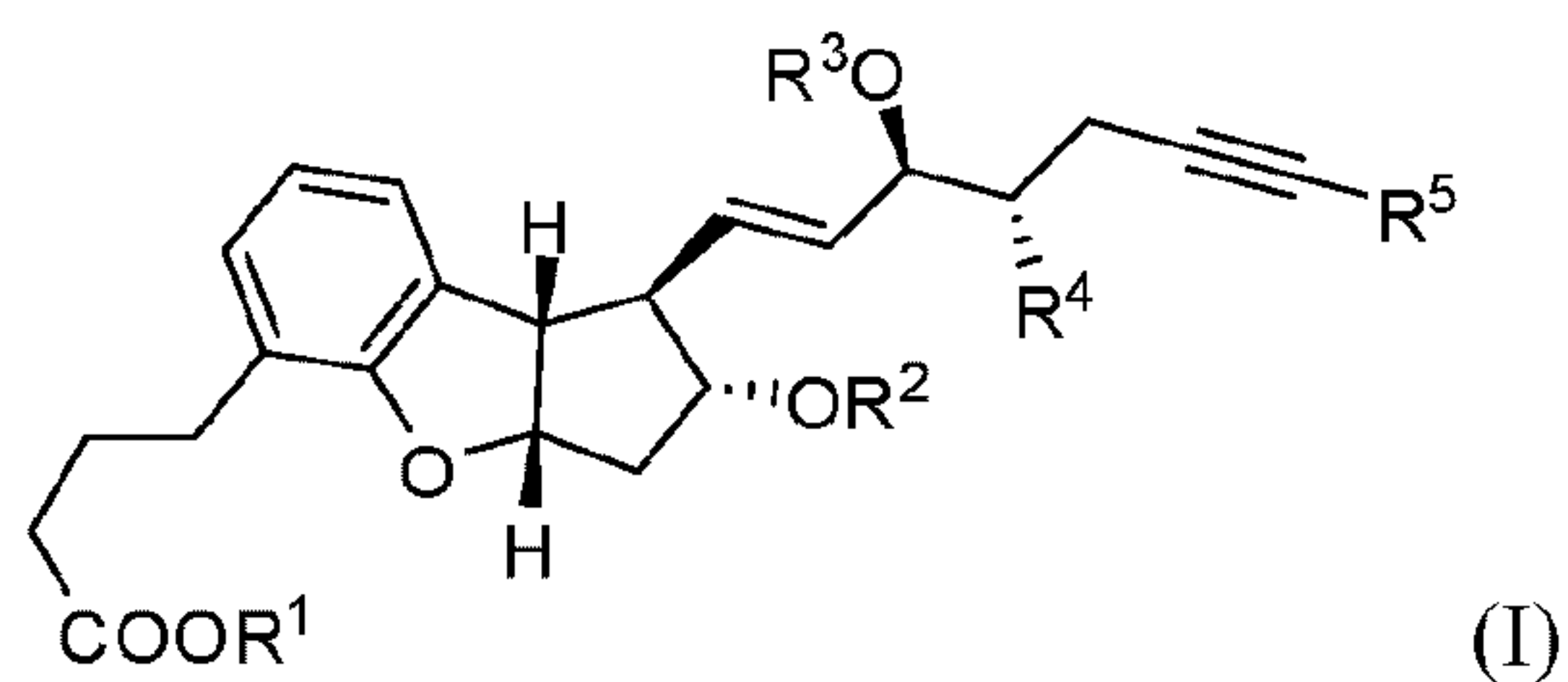
In some embodiments, R^{1a} is CH_3 and R^{2a} and R^6 are both H.

In some embodiments, azobisisobutyronitrile is used as a radical initiator in step (2).

In some embodiments, a catalytic amount of carbonylchlorohydridotris(triphenylphosphine) ruthenium (II) is used in step (3).

In some embodiments, sulfuric acid is used in step (5).

In some embodiments, the present invention provides a process for preparing a compound of the following formula:



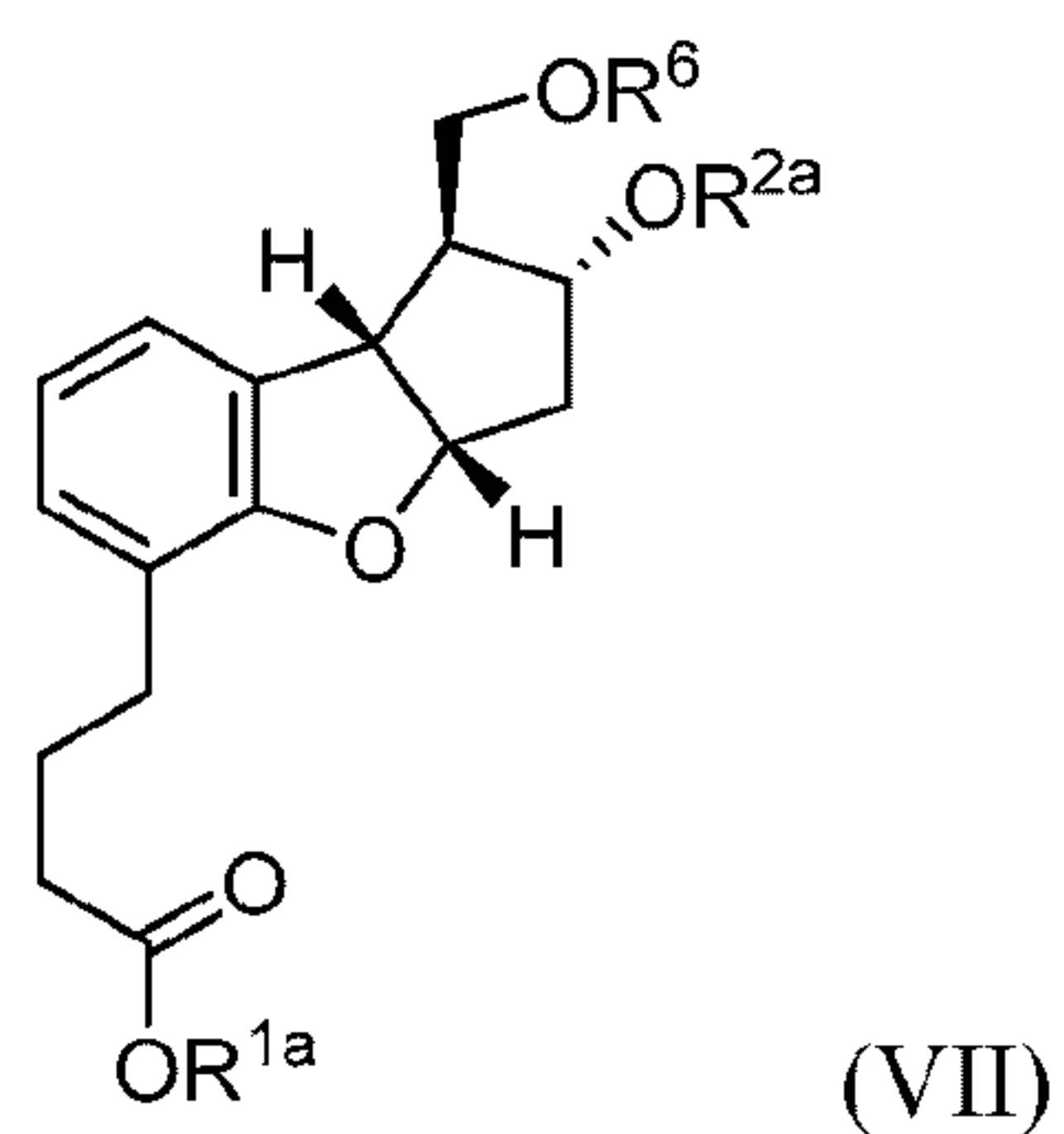
wherein R^1 represents a cation, H, or C_{1-12} alkyl,

R^2 and R^3 each represent H or a hydroxy protective group,

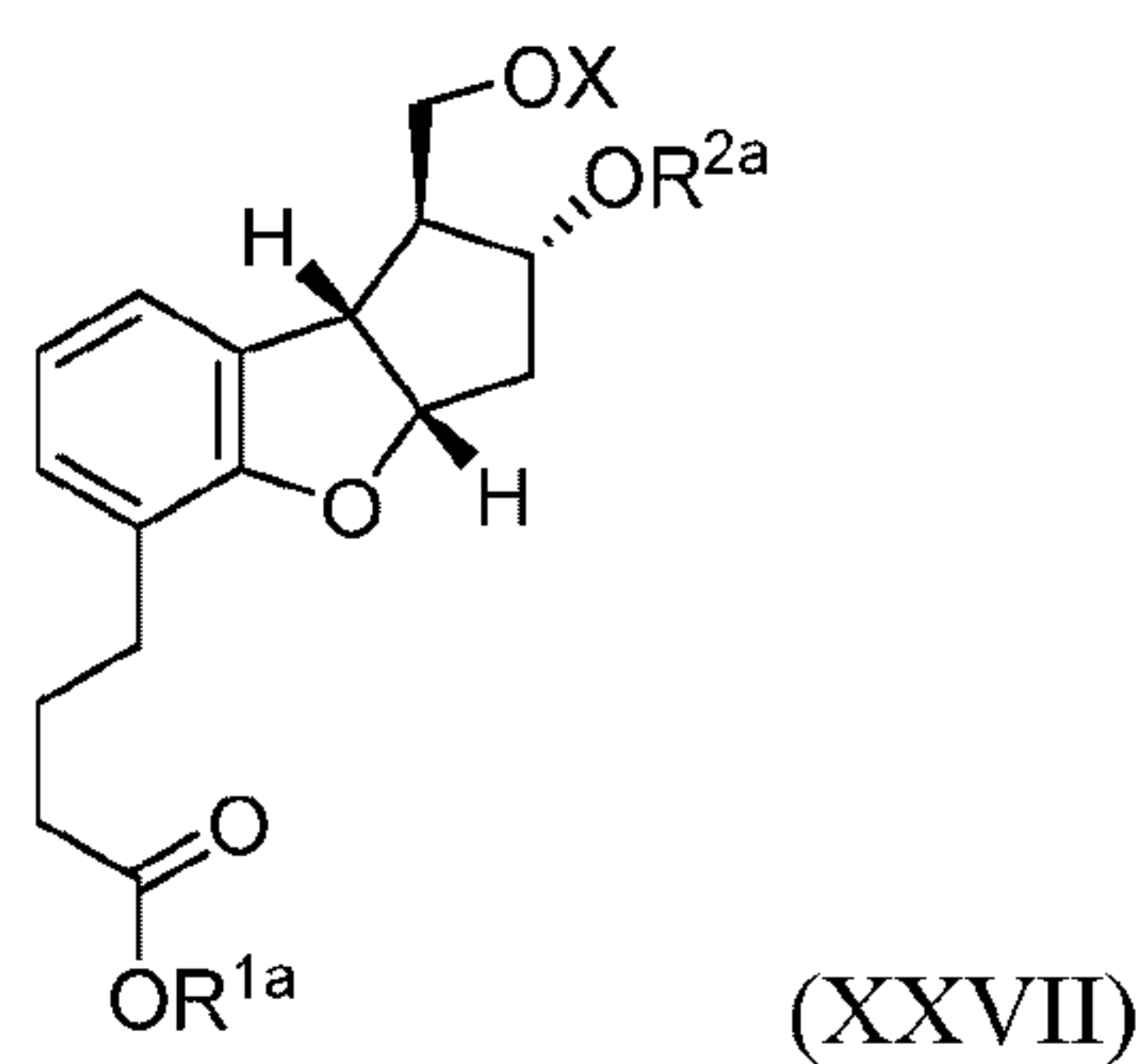
R^4 represents H or C_{1-3} alkyl, and

R^5 represents H or C_{1-6} alkyl, comprising:

(1) protecting a hydroxyl group of a compound of the following formula:

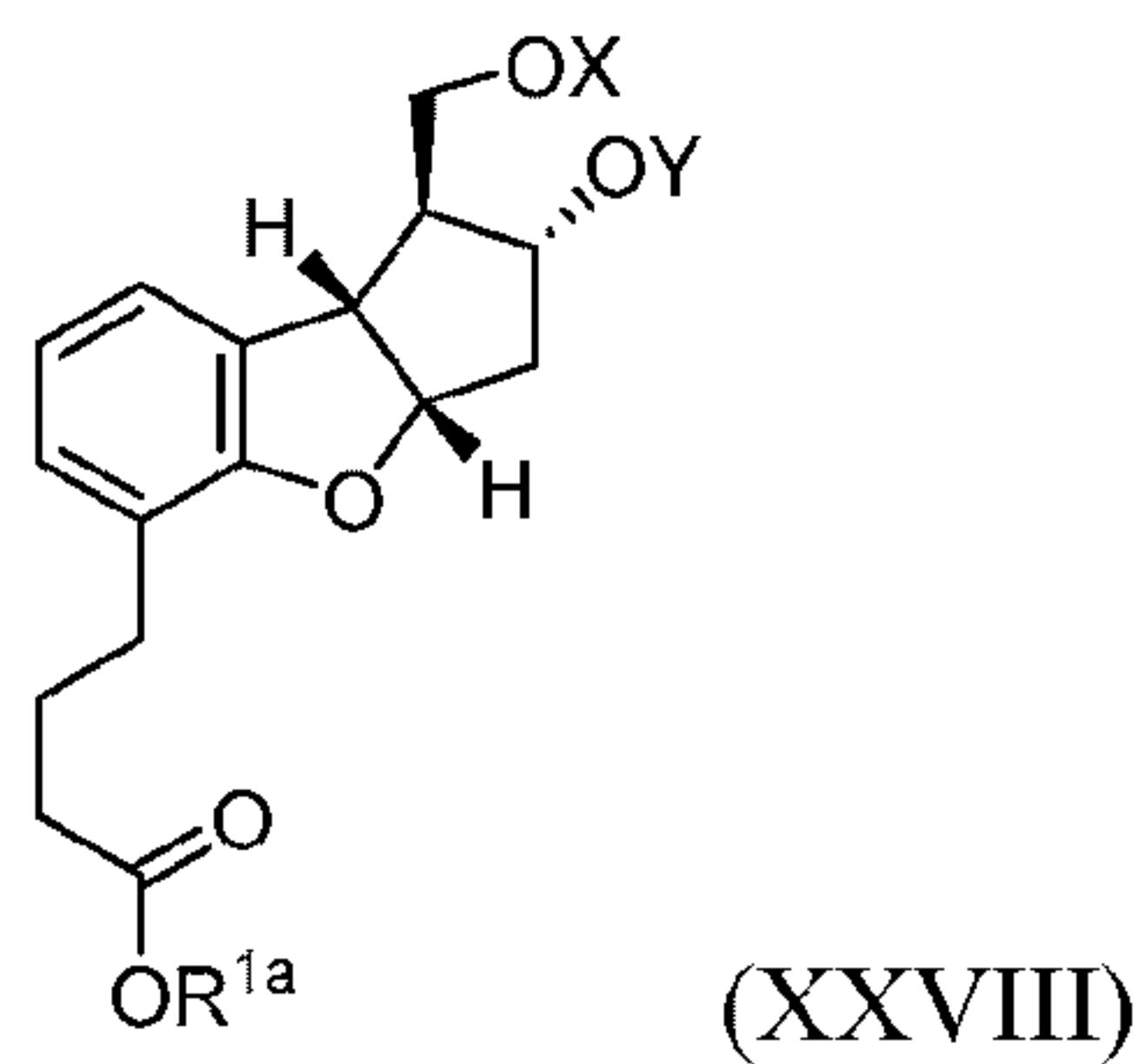


wherein R^{1a} is a cation, H, or C_{1-12} alkyl; R^{2a} and R^6 are each H or a hydroxy protective group, to produce a compound of the following formula:



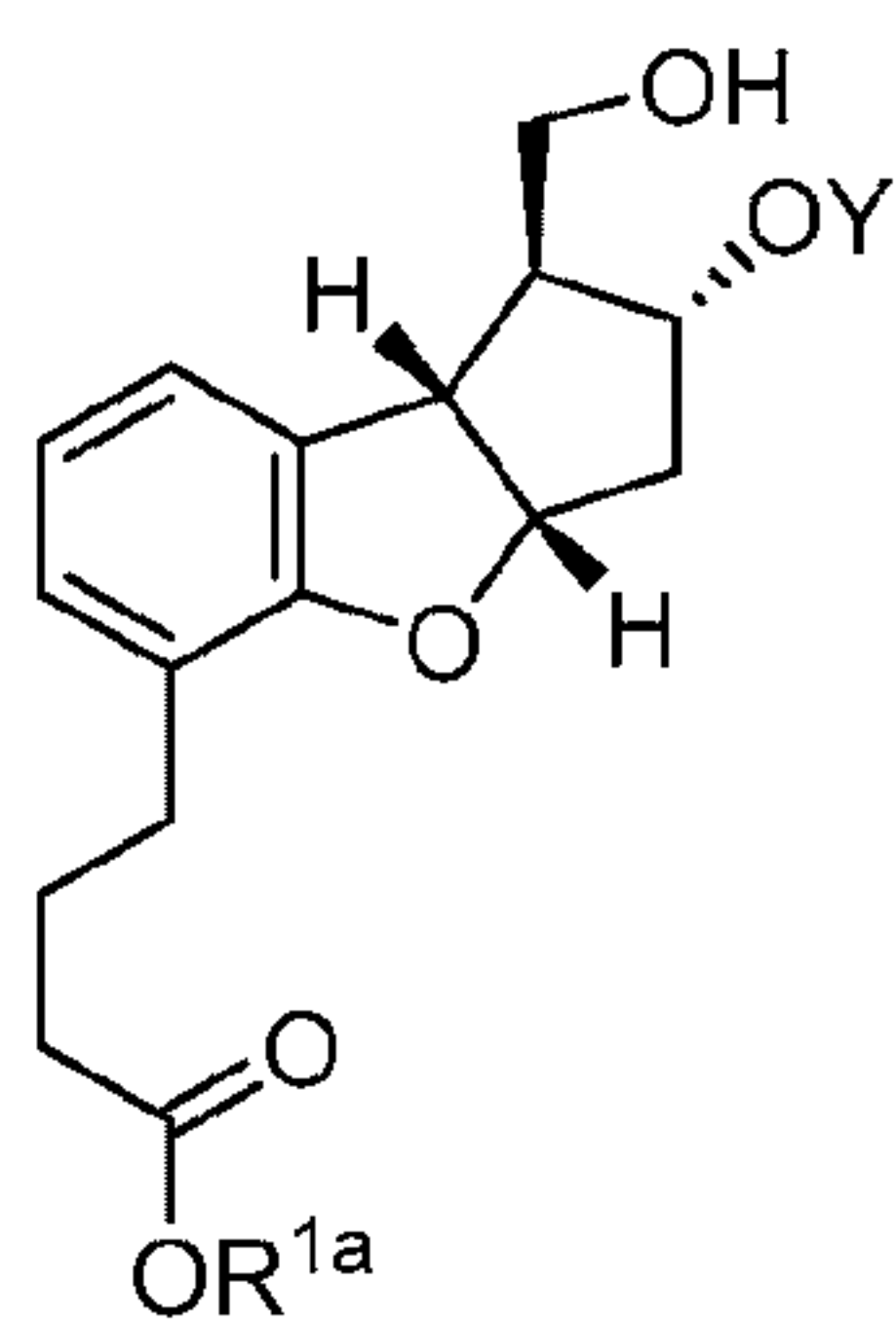
wherein X is a trityl protecting group;

(2) protecting a hydroxyl group of the compound of (XXVII) to form a compound of the following formula:



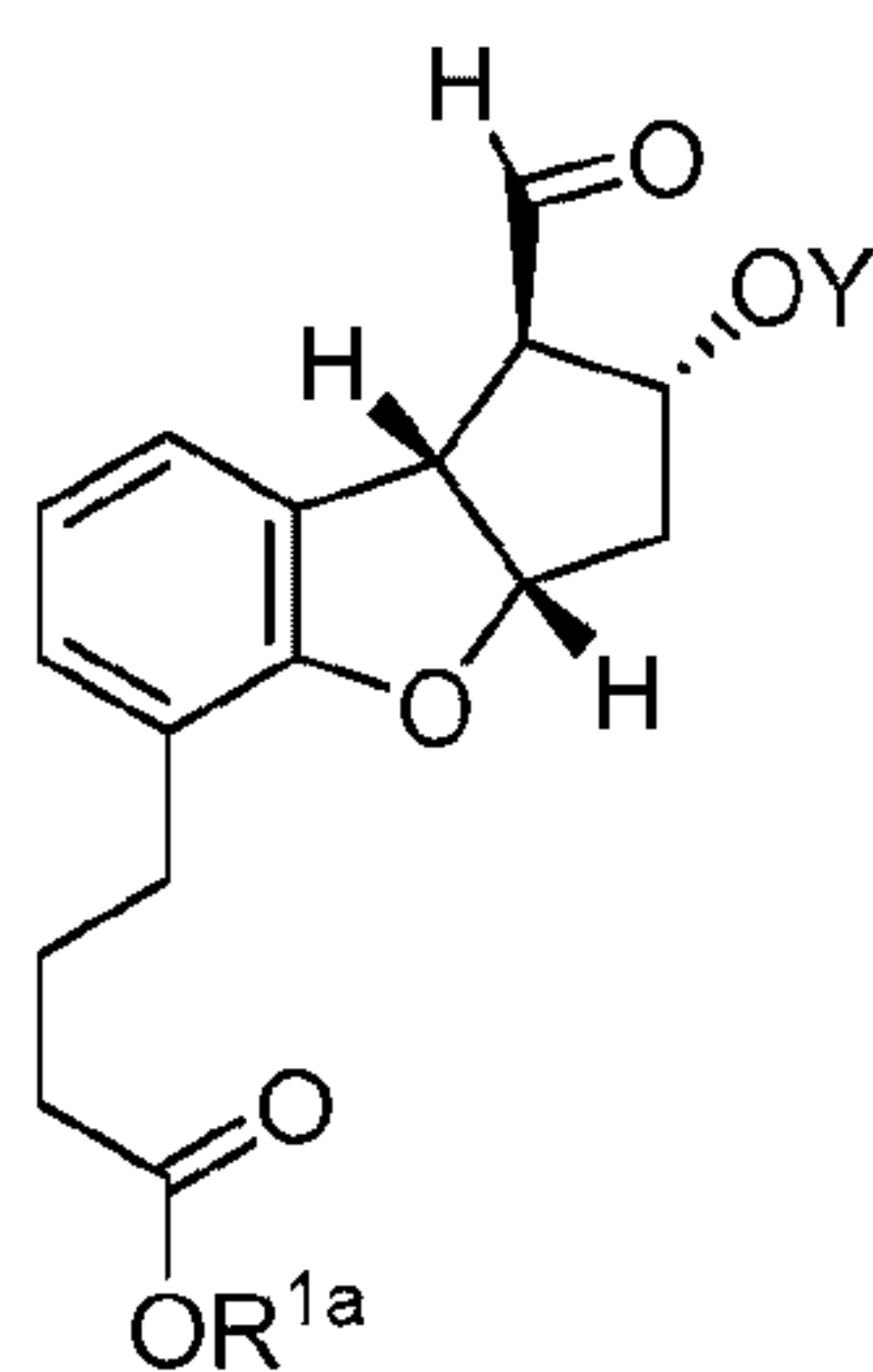
wherein Y is TBDMS group;

(3) deprotection one of the hydroxyl protective groups to form a compound of the following formula:



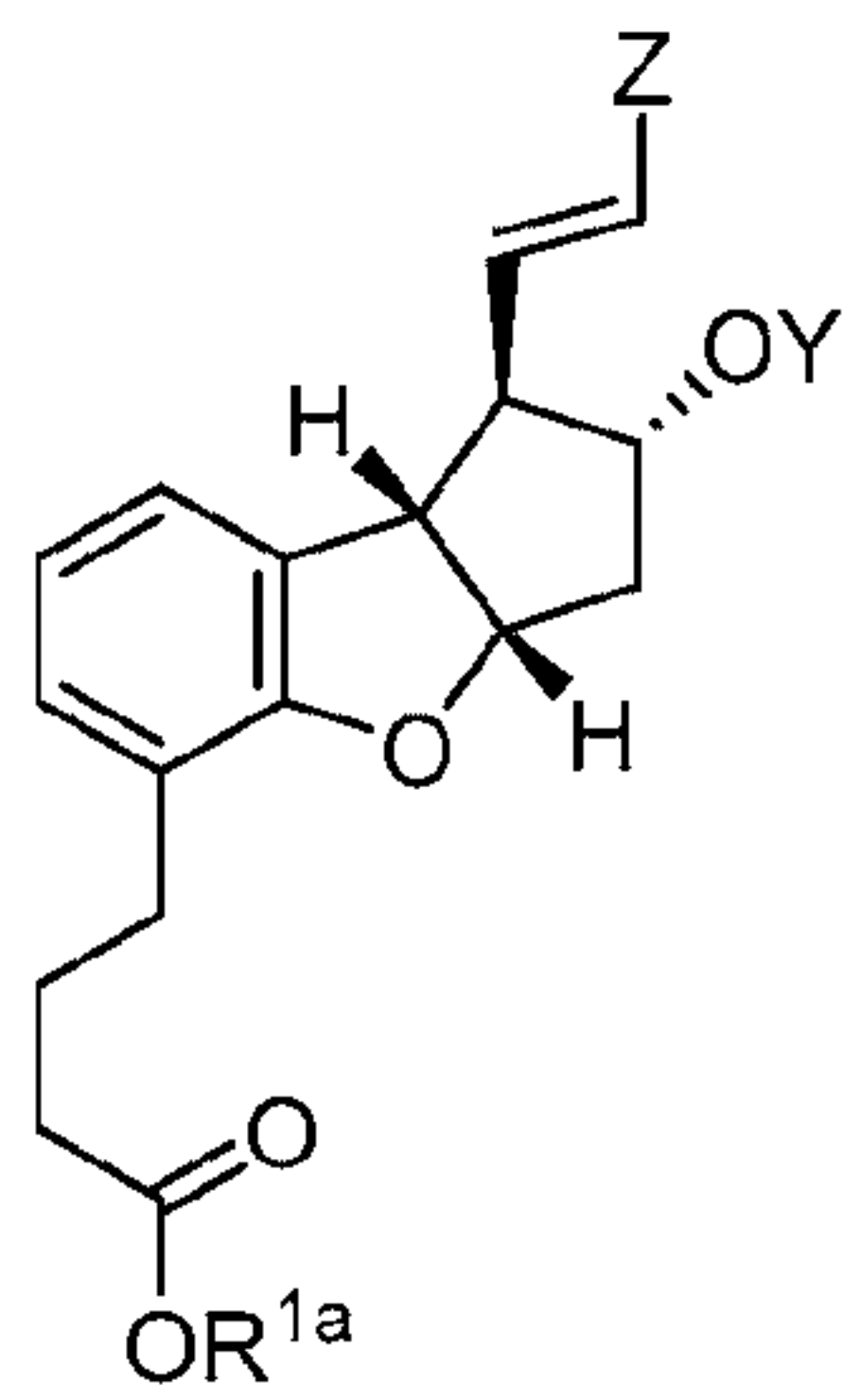
(XXIX);

(4) oxidation of a hydroxyl group of the compound to form a compound of the following formula:



(XXX)

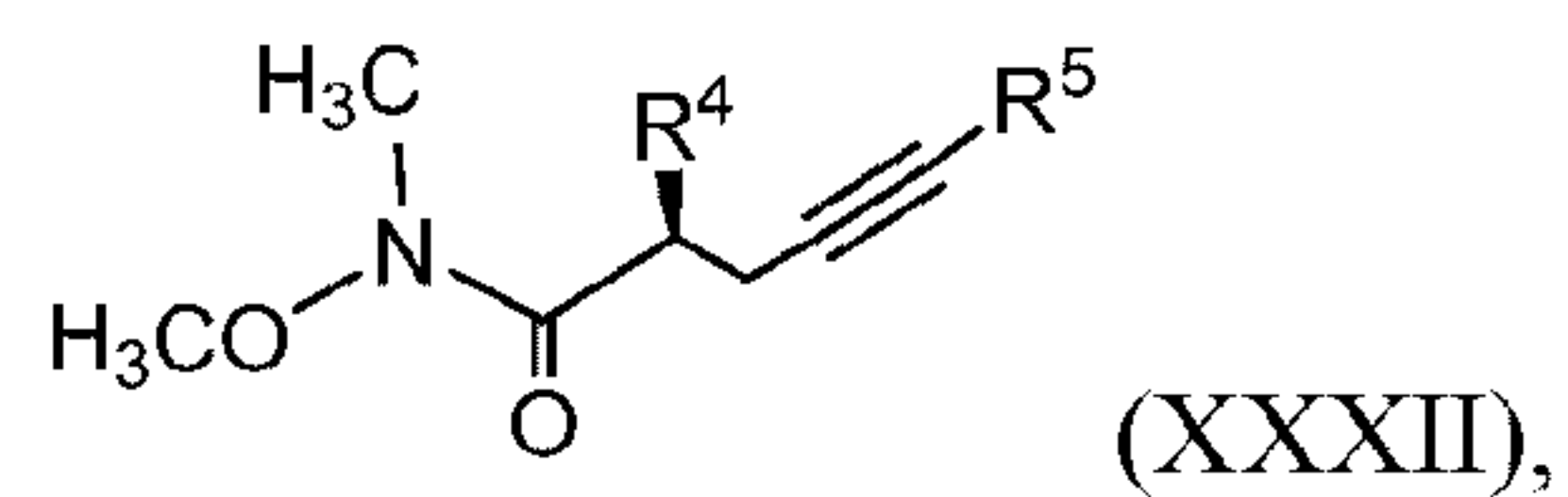
(5) Reacting with stannanes to form a compound of the following formula:



(XXXI),

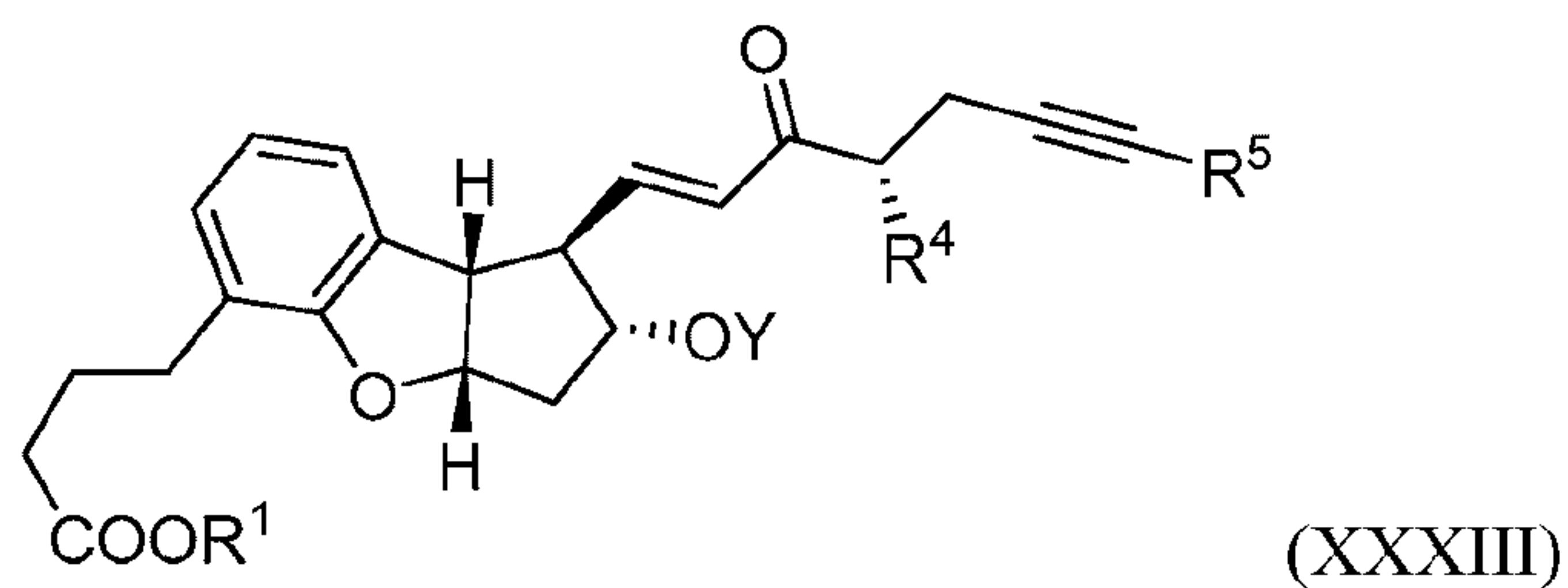
where in Z is SnBu₃

(6) coupling with a compound of the following formula:



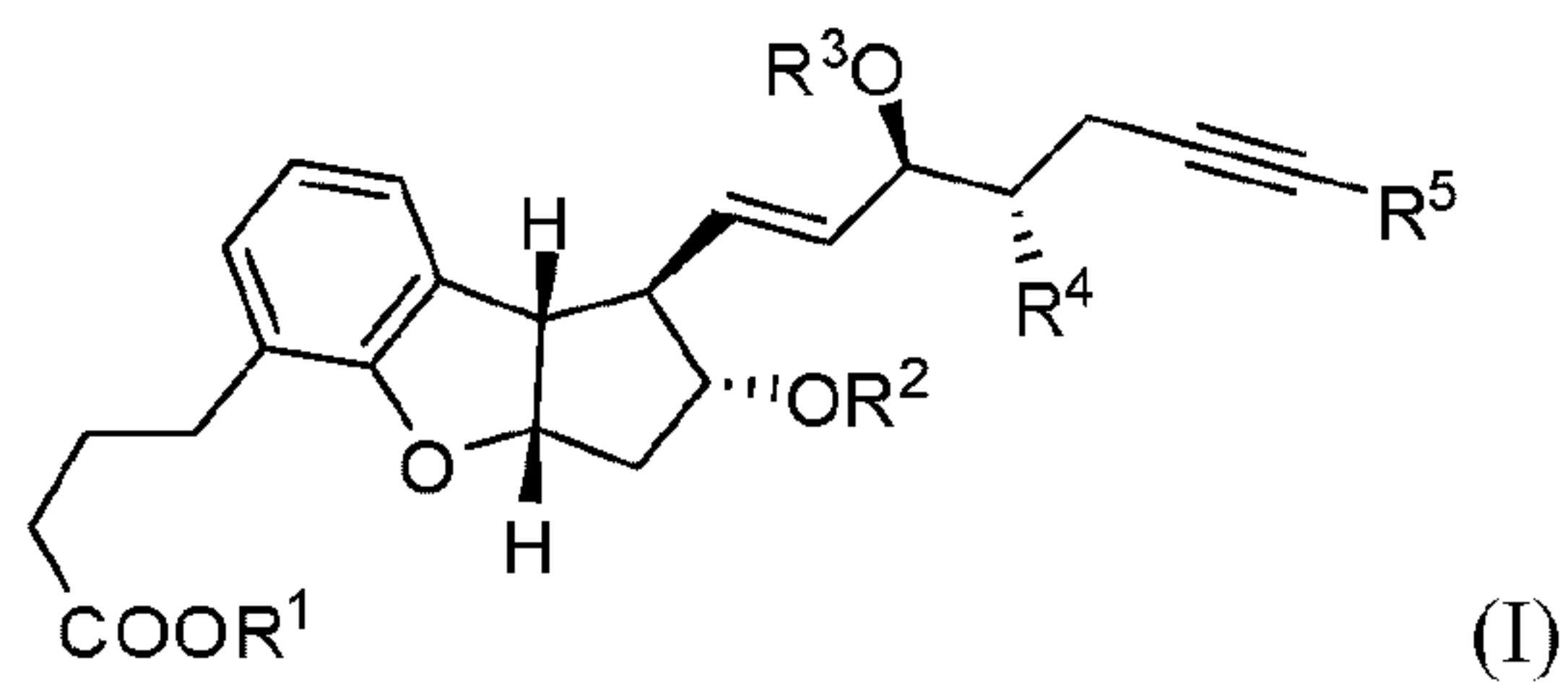
(XXXII),

to form a compound of the following formula:



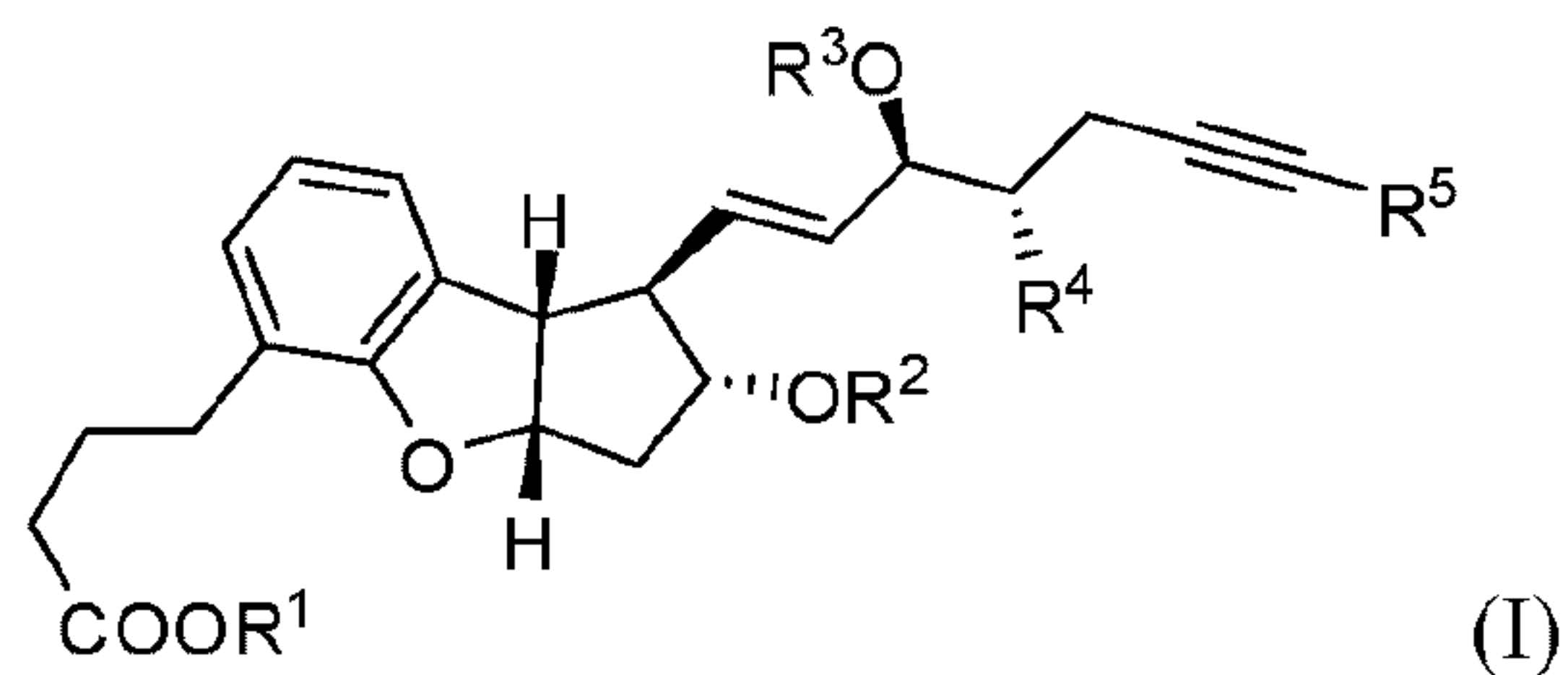
wherein R^1 , R^2 , R^4 and R^5 are each defined above,

(7) deprotecting the protective group Y and reducing the ketone of the compound of the formula (XXXIII) to form a compound of the following formula:



In some embodiments, the present invention provides a method that produces the compound of formula (I) as a substantially pure single isomer.

In some embodiments, the present invention provides a process for preparing a compound of the following formula:



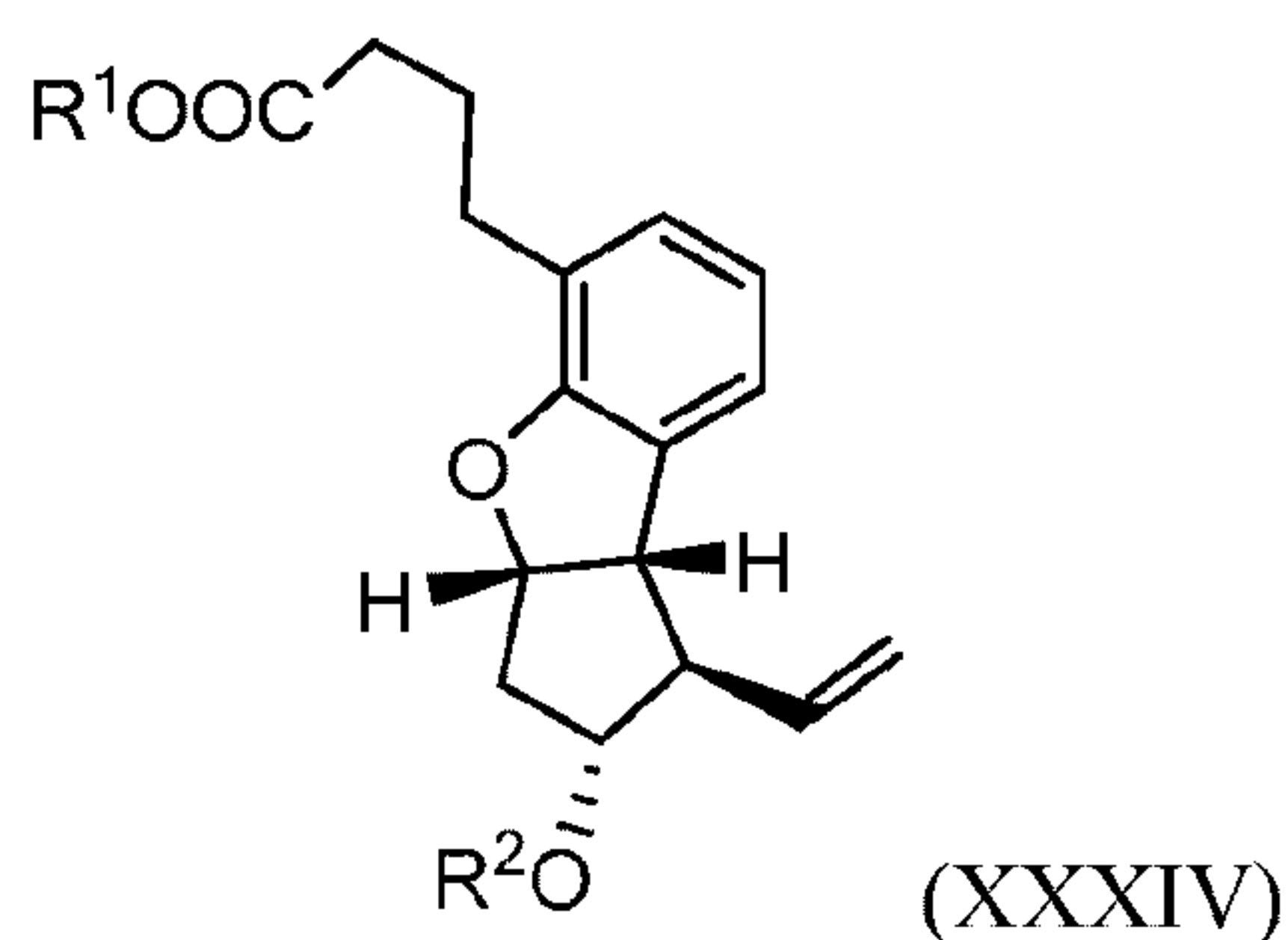
wherein R^1 represents a cation, H, or C_{1-12} alkyl,

R^2 and R^3 each represent H or a hydroxy protective group,

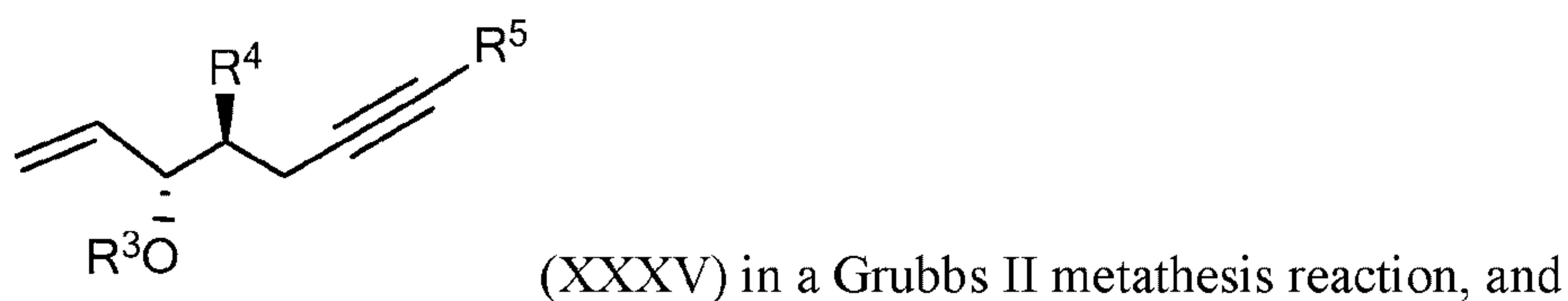
R^4 represents H or C_{1-3} alkyl, and

R^5 represents H or C_{1-6} alkyl, comprising:

(1) reacting a compound of the following formula:



with a compound of the following formula:



(2) base hydrolysis to produce the compound of formula (I).

In some embodiments, the methods described herein produce the compound of formula (I) as a substantially pure single isomer.

The present invention is further illustrated by, though in no way limited to, the following examples.

Example 1: Synthesis of Bromophenyl Acetoxycyclopentenyl Ether (**3**)

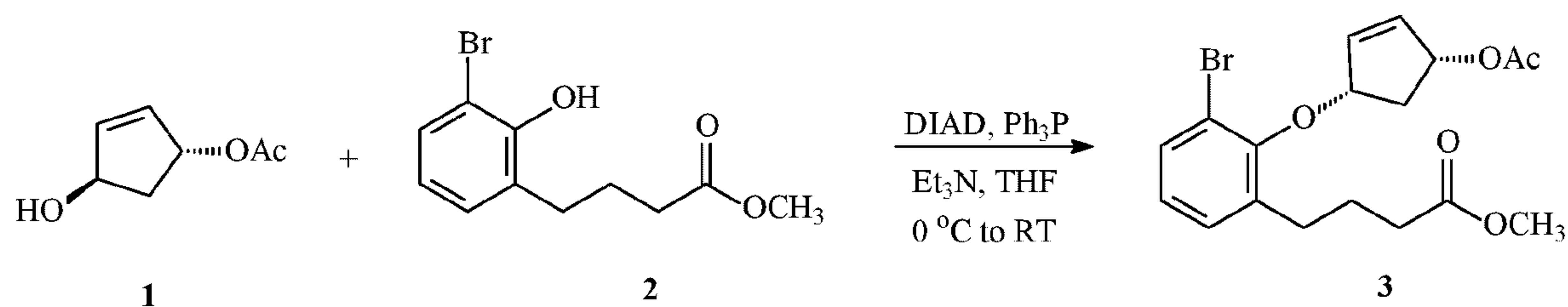
A 500 mL, three necked, round bottom flask fitted with a dropping funnel, argon inlet and a rubber septum was charged with a solution of (1*R*,4*R*)-4-hydroxycyclopent-2-en-1-yl acetate (**1**) (10.0 g, 70.34 mmol), 2-bromophenol-6-carbomethoxypropane (**2**) (21.1 g, 77.37 mmol), triphenylphosphine (20.29 g, 77.37 mmol) and triethylamine (7.8 g, 77.37 mmol) in anhydrous tetrahydrofuran (100 mL). To this, diisopropyl azodicarboxylate (15.6 g, 77.37 mmol) was added drop wise at 0 °C over a period of 45 mins. After complete addition, reaction mixture was allowed to attain room temperature slowly. The progress of the reaction was monitored by a TLC with dimensions of 2.5 X 7.5 cm was used to elute reaction mixture in 20% ethyl acetate and hexanes to confirm complete consumption of starting material. At this stage, the reaction was complete and quenched with a saturated solution of ammonium chloride (150 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 X 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and evaporated *in vacuo* to obtain crude product (78 g). This was combined

with Lot # RD-UT-1137-169 (1 g scale) and purified by chromatography to obtain pure bromophenyl acetoxycyclopentenyl ether (**3**) (27.5 g, 89.5%). Specifically, a filter-type column of diameter 11.5 cm and 18 cm in length packed with silica gel (551.7 g) was used for purification using ethyl acetate and hexanes. The polarity of the solvent was increased from 0 to 13 %. This compound was characterized by ^1H NMR.

Table 1. Materials used in Example 1

Name	MW	Lot No.	Amount	mmol	Eq.
(1 <i>R</i> ,4 <i>R</i>)-4-hydroxycyclopent-2-en-1-yl acetate (1)	142.16	SSL-0080-148-30	10.0 g	70.34	1.0
2-Bromopenol-6-carbomethoxypropane (2)	273.12	20141104	21.1 g	77.37	1.1
Diisopropyl azodicarboxylate (DIAD)	202.21	T-09-0210	15.6 g	77.37	1.1
Triphenylphosphine	262.29	MK BK2887V	20.29 g	77.37	1.1
Triethylamine	101.19	T-11-0541	7.8 g	77.37	1.1
Tetrahydrofuran (anhydrous)	NA	SHBD8022V	100 mL	NA	NA
Silica gel (230-400 mesh)	NA	80107	551.7 g	NA	NA

The reaction in Example 1 is described in the scheme below:



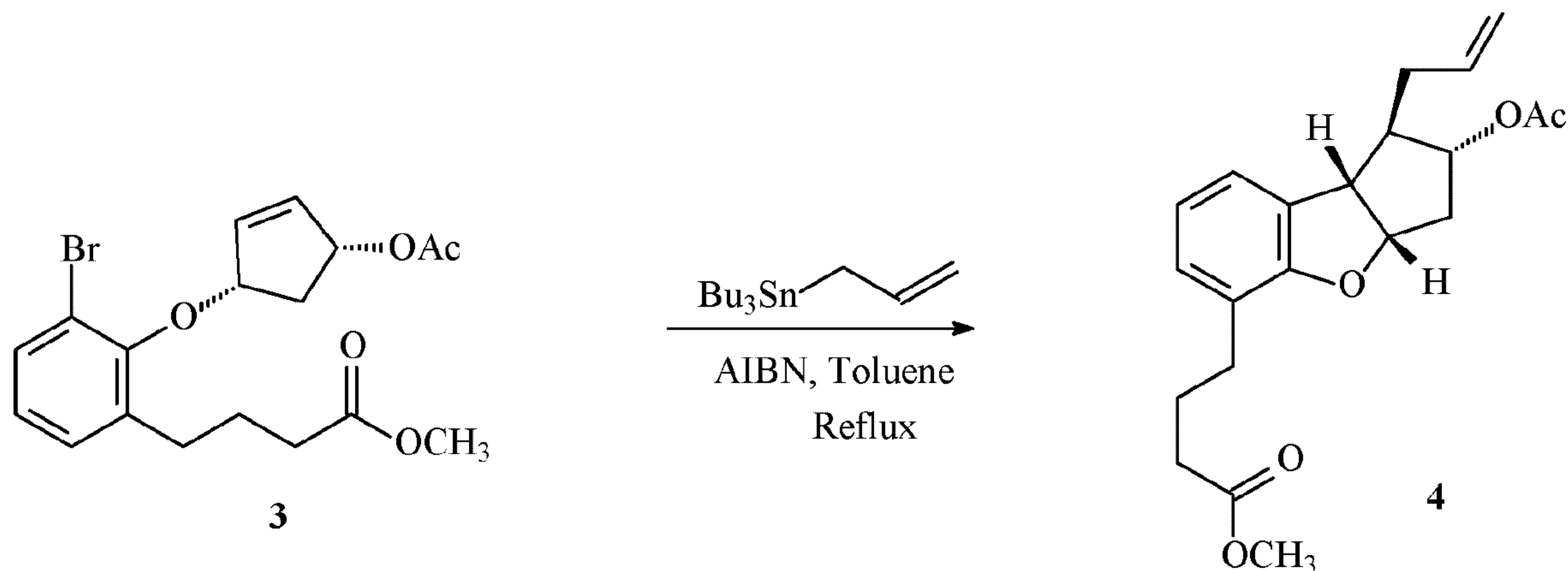
Example 2: Synthesis of Allyl Acetoxycyclopentabenzofuran (**4**)

A 1000 mL, three necked, round bottom flask fitted with a condenser, a dropping funnel and a rubber septum was charged with a solution of bromophenyl acetoxycyclopentenyl ether (**3**)

(27.0 g, 68.00 mmol) and allyltributylstannane (135.1 g, 408.00 mmol) in anhydrous toluene (50 mL) and heated to 110 °C under argon. The reaction system was evacuated to remove atmospheric air and replaced with argon. To this solution a suspension of AIBN (5.6 g, 34.00 mmol) in toluene (100 mL) was added in one portion and heating was continued at reflux temperature for 10 minutes. The progress of the reaction was monitored by a TLC with dimensions of 2.5 X 7.5 cm was used to elute reaction mixture in 25% ethyl acetate and hexanes to confirm complete consumption of starting material. A longer TLC helped in resolving the spot closer to the R_f value of starting material. At this stage, the reaction was complete and the reaction mixture was cooled to ambient temperature. This reaction mixture was concentrated *in vacuo* to remove toluene to half the original volume and then loaded directly onto the silica gel packed column for purification. Specifically, a filter-type column of diameter 11.5 cm and 18 cm length was packed with silica gel (579.7 g) was used for purification using ethyl acetate and hexanes. The polarity of the solvent was increased from 0 to 9 %. A smaller filter type column of diameter 9.5 cm and 15 cm length packed with silica gel (396.2 g) was used for purifying impure fractions using the above solvents and polarity. The pure fractions yielded 8.9 g (Lot # RD-UT-1137-175-I) with 95.5% purity (by UPLC) and impure fractions were purified again by a second column chromatography to yield 7.03 g (Lot # RD-UT-1137-175-II) with 96.26% purity (by UPLC). The total isolated yield of allyl acetoxycyclopentabenzofuran (**4**) was 15.9 g (65.5%). The compound was characterized by ¹H NMR.

Table 2. Material used in Example 2					
Name	MW	Lot No.	Amount	mmol	Eq.
Bromophenyl acetoxycyclopentenyl ether (3)	397.27	RD-UT- 1137-172	27.0 g	68.00	1.0
Allyltributylstannane	331.12	05013BJV	135.1 g	408.00	6.0
Azobisisobutyronitrile (AIBN)	164.21	MKBJ4237V	5.6 g	34.00	0.5
Toluene (anhydrous)	NA	SHBD4769V	150 mL	NA	NA
Silica gel (230-400 mesh)	NA	80107	975.9 g	NA	NA

The reaction in Example 2 is described in the scheme below:



Example 3: Synthesis of Alkenyl Acetoxycyclopentabenzofuran (**5**)

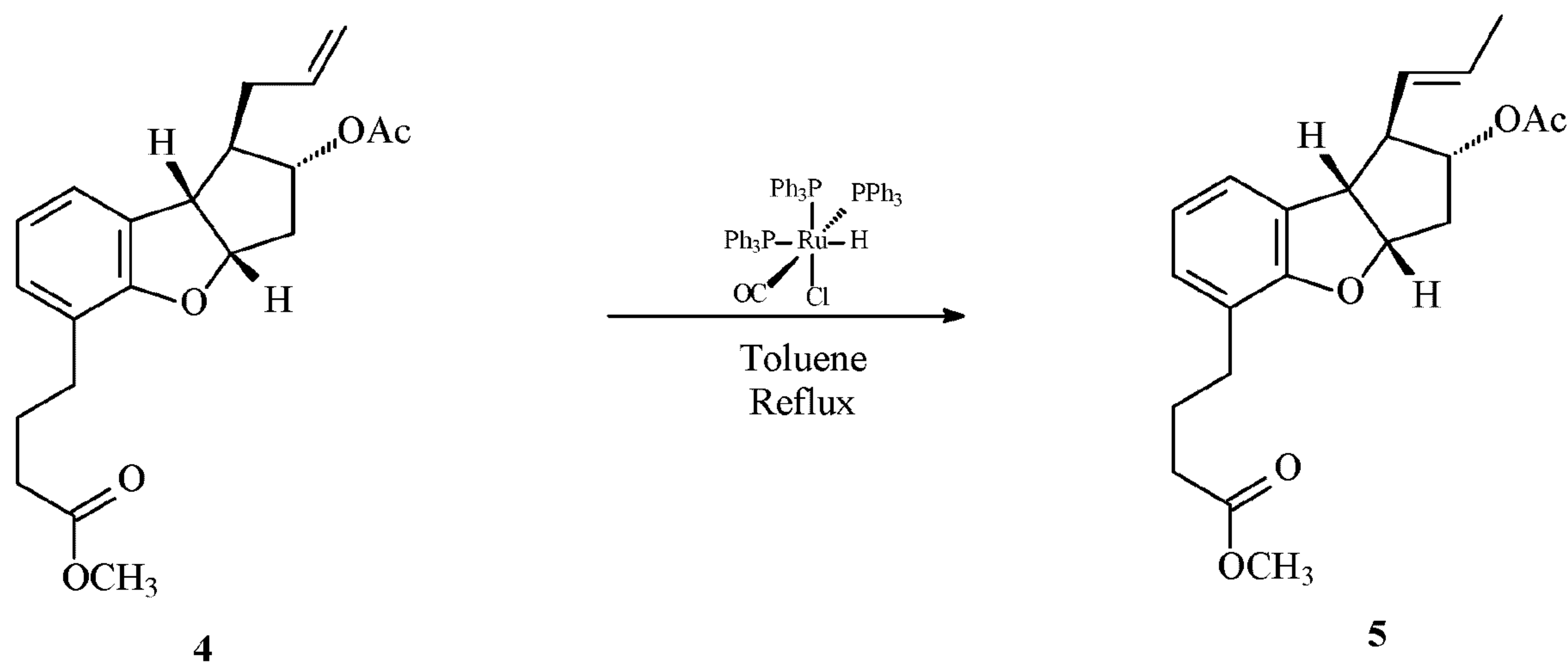
A 1000 mL, single necked, round bottom flask fitted with a condenser was charged with a solution of allyl acetoxycyclopentabenzofuran (**4**) (15.6 g, 43.52 mmol) in anhydrous toluene (500 mL). To this, carbonylchlorohydridotris(triphenylphosphine)ruthenium (II) (2.07 g, 2.17 mmol) was added and then the system was evacuated three times and replaced with argon. This was heated to reflux at 110 °C under argon. The progress of the reaction was monitored by UPLC every 20 mins for 1 hour, which showed 96% conversion and no progress beyond that point. After 1 h, the reaction was concentrated *in vacuo* to reduce the amount of toluene and then loaded directly onto the silica gel packed column for purification to yield alkenyl acetoxycyclopentabenzofuran (**5**) (14.5 g, 92.6%) (Lot# RD-UT-1137-178). Specifically, a filter-type column of diameter 11.5 cm and 18 cm in length packed with silica gel (580 g) was used for purification using ethyl acetate and hexanes. The polarity of the solvent was increased from 0 to 8%. The compound was characterized by ¹H NMR and UPLC (ratio of product: starting material, 98.5: 1.5).

Table 3. Material used in Example 3

Name	MW	Lot No.	Amount	mmol	Eq.
Allyl acetoxycyclopentabenzofuran (4)	358.42	RD-UT- 1137-175-I	15.6 g	43.52	1.0

Carbonylchlorohydridotris(tri phenylphosphine)ruthenium(II)	952.40	RD-UT-1137-175-II	2.07 g	2.17	0.05
Toluene (anhydrous)	NA	MKBP7702V	500 mL	NA	NA
Silica gel (230-400 mesh)	NA	SHBD6439V	580 g	NA	NA

The reaction in Example 3 is described in the scheme below:



Example 4: Synthesis of Hydroxy Acetoxycyclopentabenzofuran (**6**)

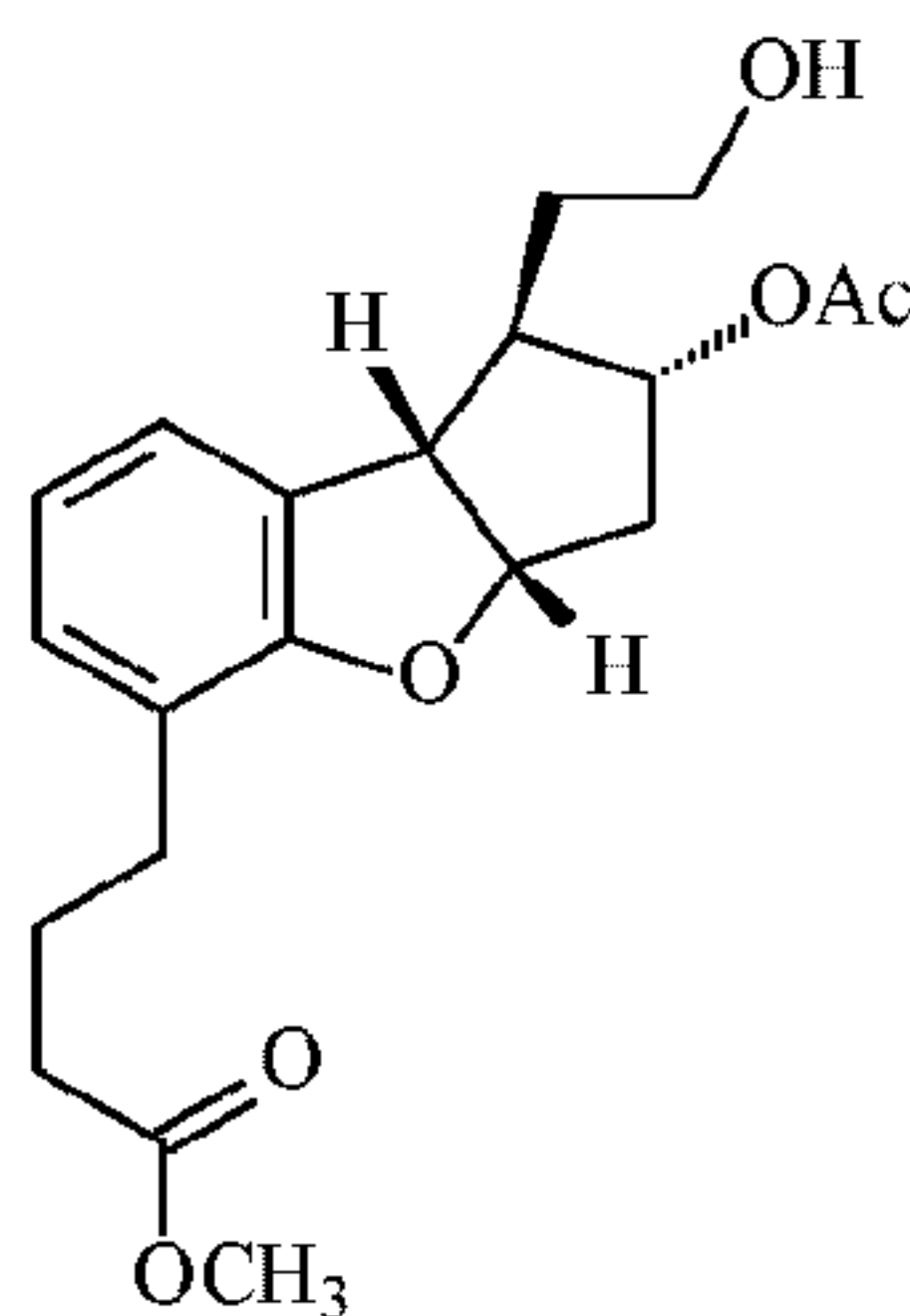
A 500 mL, three necked, round bottom flask fitted with an ozone bubbler, rubber septa was charged with a solution of alkenyl acetoxycyclopentabenzofuran (**5**) (14.2 g, 39.61 mmol) in anhydrous methanol (150 mL) and anhydrous dichloromethane (50 mL), and this was cooled to -78 °C. Then ozone gas was bubbled through the solution for 2h. Specifically, a Wedeco GSO 10 series ozone generator was used as a source for ozone. The oxygen pressure was maintained at 0.5 psi with instrument running at power level of 81W. Utmost care should be taken while bubbling the ozone through the reaction mixture. Excess ozone may generate side products in the reaction mixture. Progress of the reaction mixture should be monitored every 25 minutes. Time required for conversion may be higher of lager amounts.

The progress of the reaction was monitored by TLC, which indicated complete conversion of starting material. A small aliquot was quenched with dimethyl sulfide to convert ozonide to aldehyde for in process analysis using 60% ethyl acetate:hexane as mobile phase for TLC. At

this stage, the temperature of the reaction mixture was increased to -20 °C and flushed with argon gas for 5 minutes.

To this solution (ozonide intermediate), sodium borohydride (2.99 g, 79.23 mmol) was added at -20 °C and stirred under argon for 0.5 h while allowing the reaction mixture to attain ambient temperature. The progress of the reaction was monitored by TLC. Specifically, a 80% ethyl acetate:hexane mobile phase was used for elution. After completion of the reaction, it was quenched with a saturated solution of ammonium chloride (30 mL) and organic volatiles were evaporated *in vacuo*. The residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 X 150 mL). The combined organic layers were washed with brine (150 mL), dried over sodium sulfate and evaporated *in vacuo* to obtain crude product. This was loaded on to the silica gel packed column for purification to obtain hydroxy acetoxycyclopentabenzofuran (**6**) (11.8 g, 85.5 %) (Lot # RD-UT-1137-180). Specifically, a filter-type column of diameter 11.5 cm and 18 cm in length packed with silica gel (622 g) was used for purification using ethyl acetate and hexanes. The polarity of the solvent was increased from 0 to 50%.

The compound was characterized by ¹H NMR and HPLC to determine the amount of homolog impurity formed due to carried over starting material from the previous olefin isomerization step (Step III) (ratio of product: homolog, 99.3: 0.7). The structure of homolog impurity is given below.



Acetate Homolog Impurity

The reaction in Example 4 is described in the scheme below:

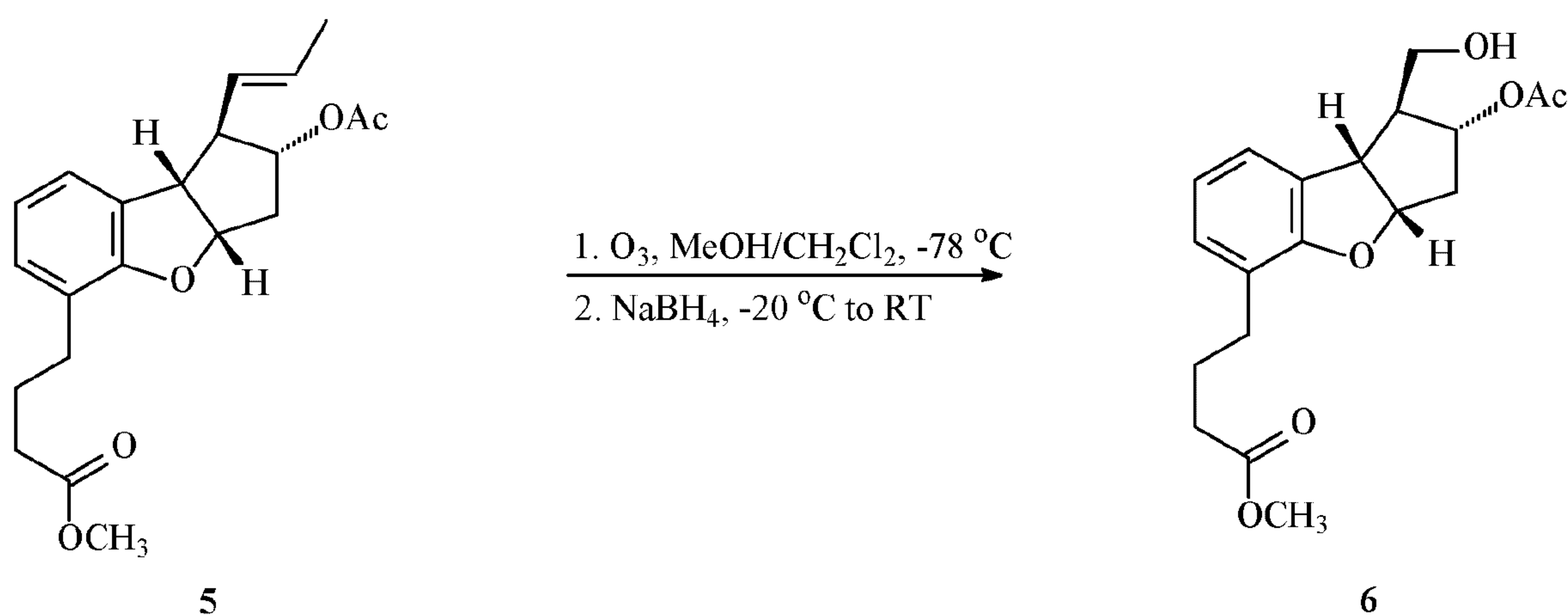


Table 4. Material used in Example 4

Name	MW	Lot No.	Amount	mmol	Eq.
Alkenyl acetoxycyclopentabenzofuran (5)	358.42	RD-UT-1137-178	14.2 g	39.61	1.0
Methanol (anhydrous)	NA	T-08-0195	150 mL	NA	NA
Dichloromethane (anhydrous)	NA	SHBF0333V	50 mL	NA	NA
Sodium borohydride	37.83	0000023281	2.99 g	79.23	2.0
Silica gel (230-400 mesh)	NA	80107	622 g	NA	NA

Example 5: Synthesis of Beraprost Diol (7)

A 500 mL, single necked, round bottom flask was charged with a solution of hydroxy acetoxycyclopentabenzofuran (6) (10.7 g, 30.71 mmol) in anhydrous methanol (150 mL). Then a solution of conc. H_2SO_4 (0.1 mL) in 50 mL methanol was added and stirred overnight (14 h). Reaction rate was found to be slow based on TLC. A 5% methanol:DCM mobile phase was used for TLC elution. At this stage additional amount of conc. H_2SO_4 (0.27 mL in 10 mL methanol solution) was charged four times at different intervals (14 h, 21 h, 38 h, 62 h) until completion of the reaction. Reaction was found to be complete after 68 h (total conc. H_2SO_4 used is 1.18 mL). At this point, the reaction mixture was cooled to 0 °C and a solution

of saturated sodium bicarbonate (25 mL) was added over a period of 5 minutes until pH reached 8. This mixture was evaporated *in vacuo* to remove organic volatiles and the residue was partitioned between ethyl acetate (150 mL) and water (150 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 X 100 mL). The combined organic layers were washed with brine, dried over sodium sulfate and evaporated *in vacuo* to obtain crude product (9.3 g). Crude product was crystallized from MTBE to obtain beraprost diol (7) (7.5 g, 80 % isolated yield) (Lot# RD-UT-1137-182-CI). Specifically, crude product was dissolved in 45 mL (5 volumes) MTBE by heating to reflux temperature and slowly cooled to RT. At approx. 30 °C, 90 mg of pure seed (beraprost diol, Lot# 13-13206-01) was added and stirred at room temperature for 2 h, which yielded thick off-white solid. This was cooled to 10 °C and stirred for 15 minutes and filtered through filter paper (No.4) while using 5% MTBE:Hexane (50 mL) for washing. The off-white solid material was air dried until constant weight was obtained. This was characterized by ¹H NMR, ¹³C NMR, MS, optical rotation, chiral HPLC and melting point. See summary of analytical data table for values. The reaction in Example 5 is described in the scheme below:

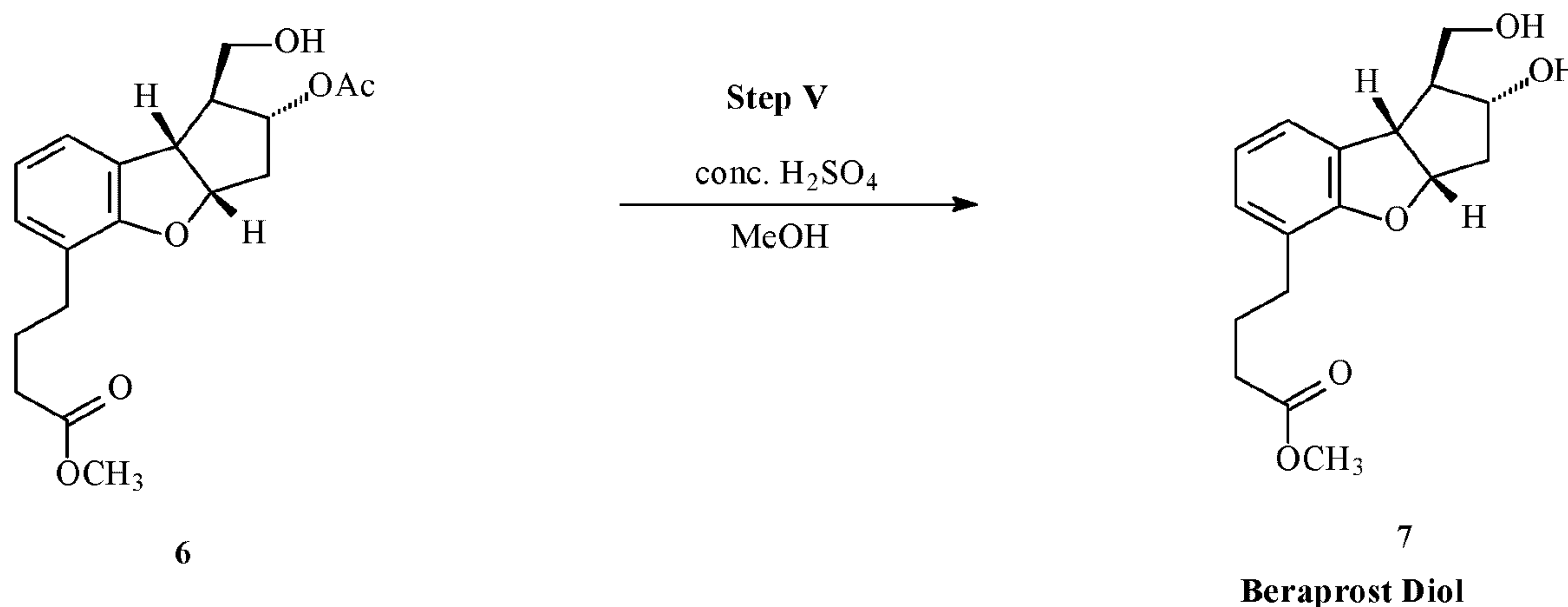
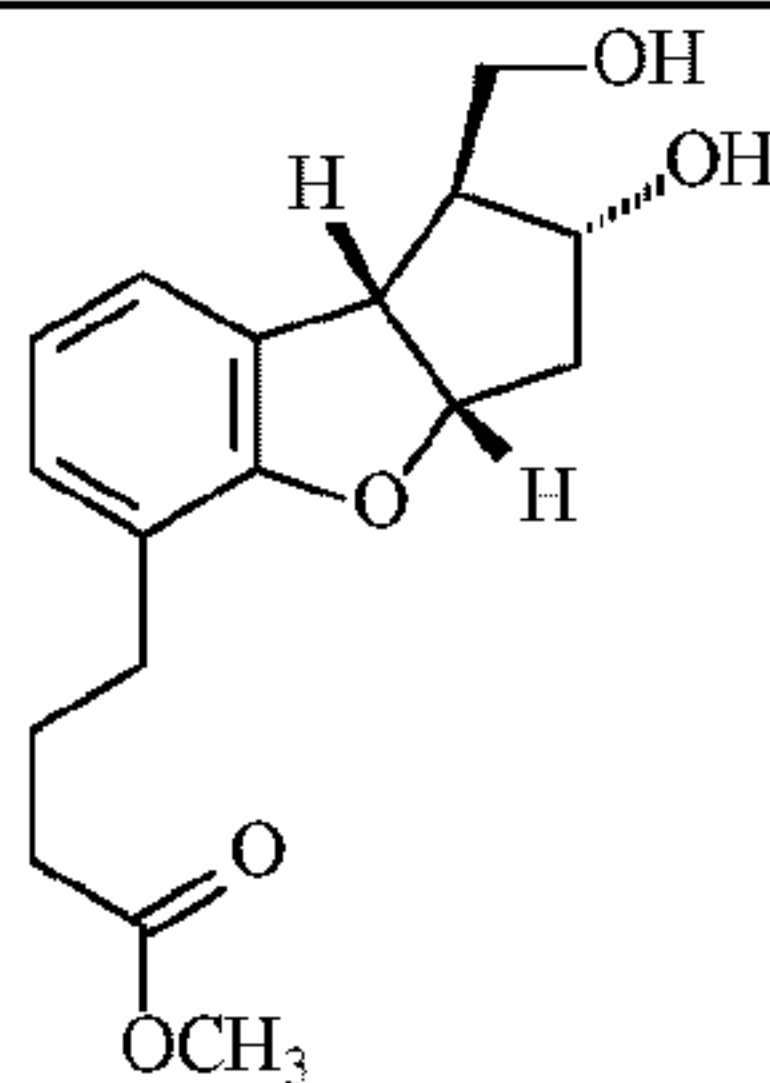


Table 5. Material used in Example 5

Name	MW	Lot No.	Amount	mmol	Eq.
Hydroxyacetoxycyclopentabenzofuran (6)	348.40	RD-UT-1137-180	10.7 g	30.71	1.0
Concentrated sulfuric acid	NA	T-07-0373	1.18 mL	NA	NA

Methanol (anhydrous)	NA	T-08-0195	240 mL	NA	NA
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A summary of Analytical Data on single isomer of Beraprost Diol is shown in the table below.

Table 6. Summary of Analytical Data on Single Isomer of Beraprost Diol		
S. No.	Description	Results
1.	Structure	
2.	Chemical Name	methyl 4-((1<i>S</i>,2<i>R</i>,3<i>aS</i>,8<i>bS</i>)-2-hydroxy-1-(hydroxymethyl)-2,3,3<i>a</i>,8<i>b</i>-tetrahydro-1<i>H</i>-cyclopenta[<i>b</i>]benzofuran-5-yl)butanoate (or) 1<i>H</i>-Cyclopenta[<i>b</i>]benzofuran-5-butanoic acid, 2,3,3<i>a</i>,8<i>b</i>-tetrahydro-2-hydroxy-1-(hydroxymethyl)-, methyl ester, (1<i>S</i>,2<i>R</i>,3<i>aS</i>,8<i>bS</i>)-
3.	CAS Number	132203-90-8
4.	Lot Number	RD-UT-1137-182-CI
5.	Molecular Formula	C ₁₇ H ₂₂ O ₅
6.	Molecular Weight	306.35
7.	MS	Practical Value: [M+Na]⁺ = 329.51 Calculated Value: [M+Na]⁺ = 329.35
8.	Melting Point	64.5 to 66.3 °C
9.	Optical Rotation	[α]_D = +25.6 at 25 °C (c 1.000, EtOH) Ref: [α]_D = +25.6 at 24.9 °C (c 1.000, EtOH)

10.	¹ H NMR	Conforms to the structure
11.	¹³ C NMR	Conforms to the structure
12.	Purity by Chiral HPLC	99.90%

Example 6: Synthesis of Beraprost based on Scheme 4.

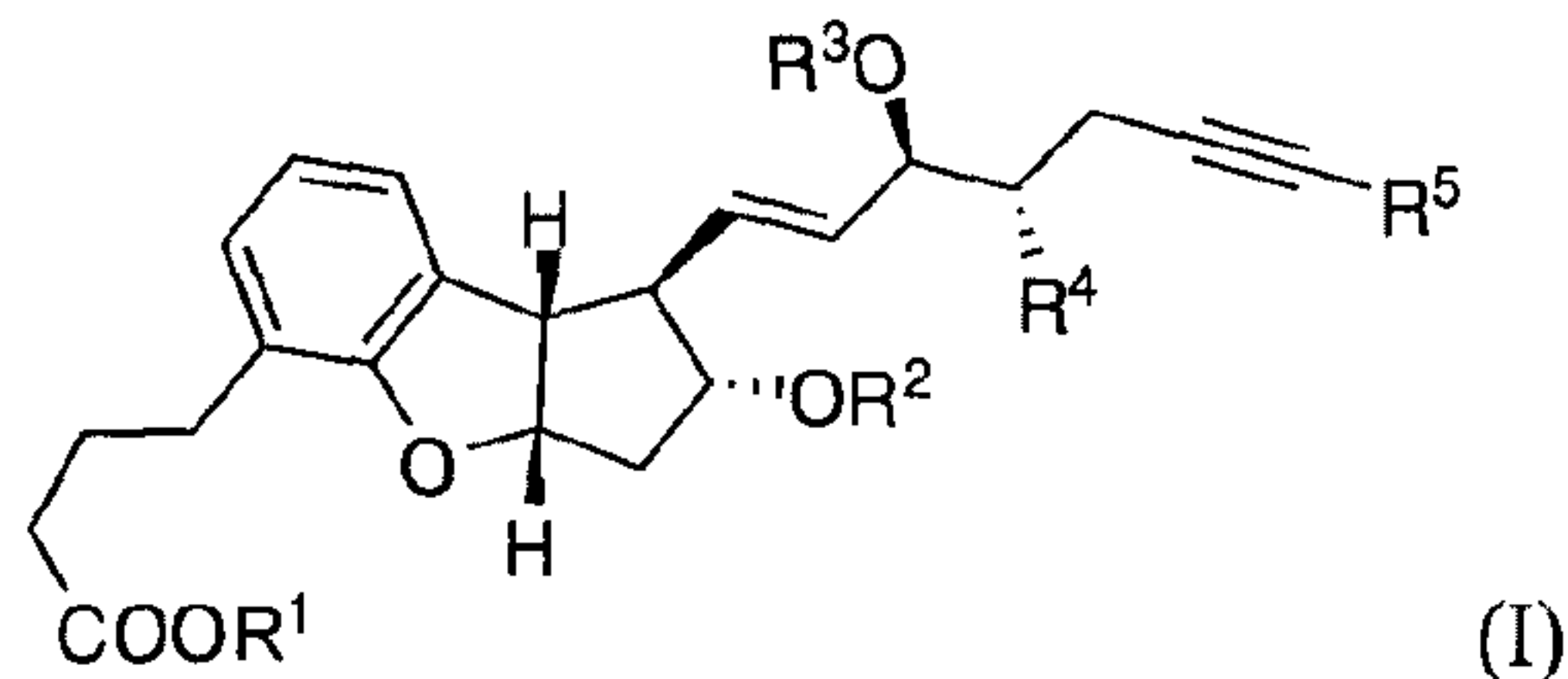
Beraprost is synthesized according to the method shown in Scheme 4. In particular, the synthesis has the following steps: 1) tritylation of compound **1** having a tricyclic core and side chain for coupling to form compound **2**; 2) TBDMS protection to form compound **3**; 3) detritylation to form compound **4**; 4) oxidation to form compound **5**; 5) coupling with tributyl tin to form compound **6**; 6) reaction with Weinreb amide to form compound **7**; 7) reduction and deprotection to form Beraprost. The reaction conditions for each step is well known in the art, such as described in Das et al., *Chem. Rev.* (2007), 107:3286-3337.

Example 7: Synthesis of Beraprost based on Scheme 5.

Beraprost is synthesized according to the method shown in Scheme 4, including a Grubbs II metathesis step and base hydrolysis step. In particular, ruthenium metal catalyst is used for Grubb's metathesis reaction. It involves the use of Grubb's II (the second generation ruthenium catalyst) in solvents, e.g. dichloromethane, methyl tertiary butyl methylether, pentane, hexane, methanol, isopropyl alcohol, tetrahydrofuran, and acetone. The reaction conditions for each step is well known in the art, such as described in Das et al., *Chem. Rev.* (2007), 107:3286-3337.

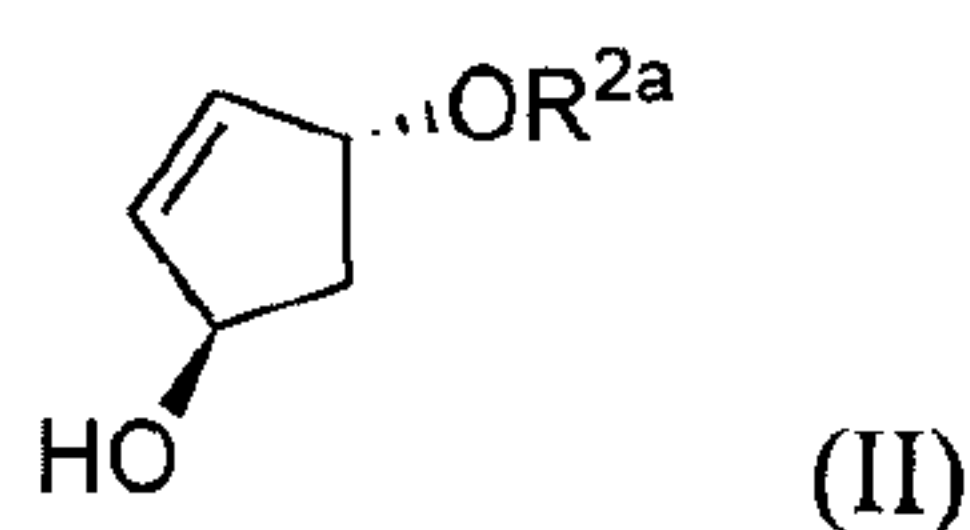
WHAT IS CLAIMED IS:

1. A process for preparing a compound of formula:

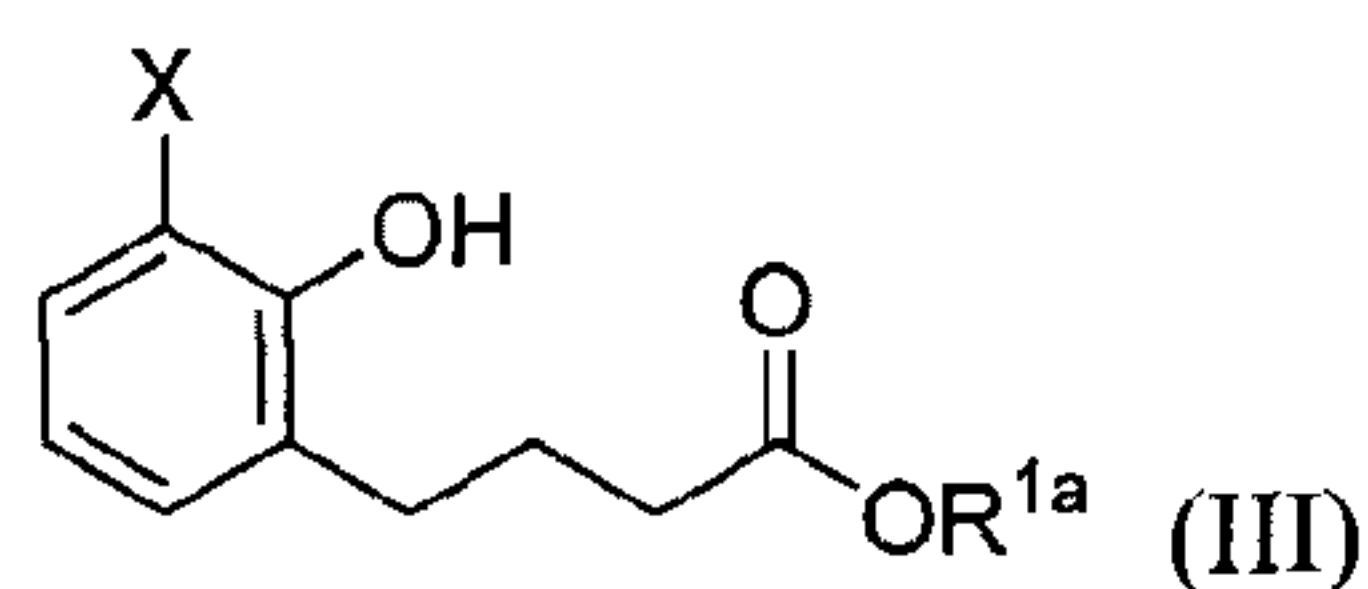


wherein R^1 represents a cation, H, or C_{1-12} alkyl,
 R^2 and R^3 each represent H or a hydroxy protective group,
 R^4 represents H or C_{1-3} alkyl, and
 R^5 represents H or C_{1-6} alkyl, comprising:

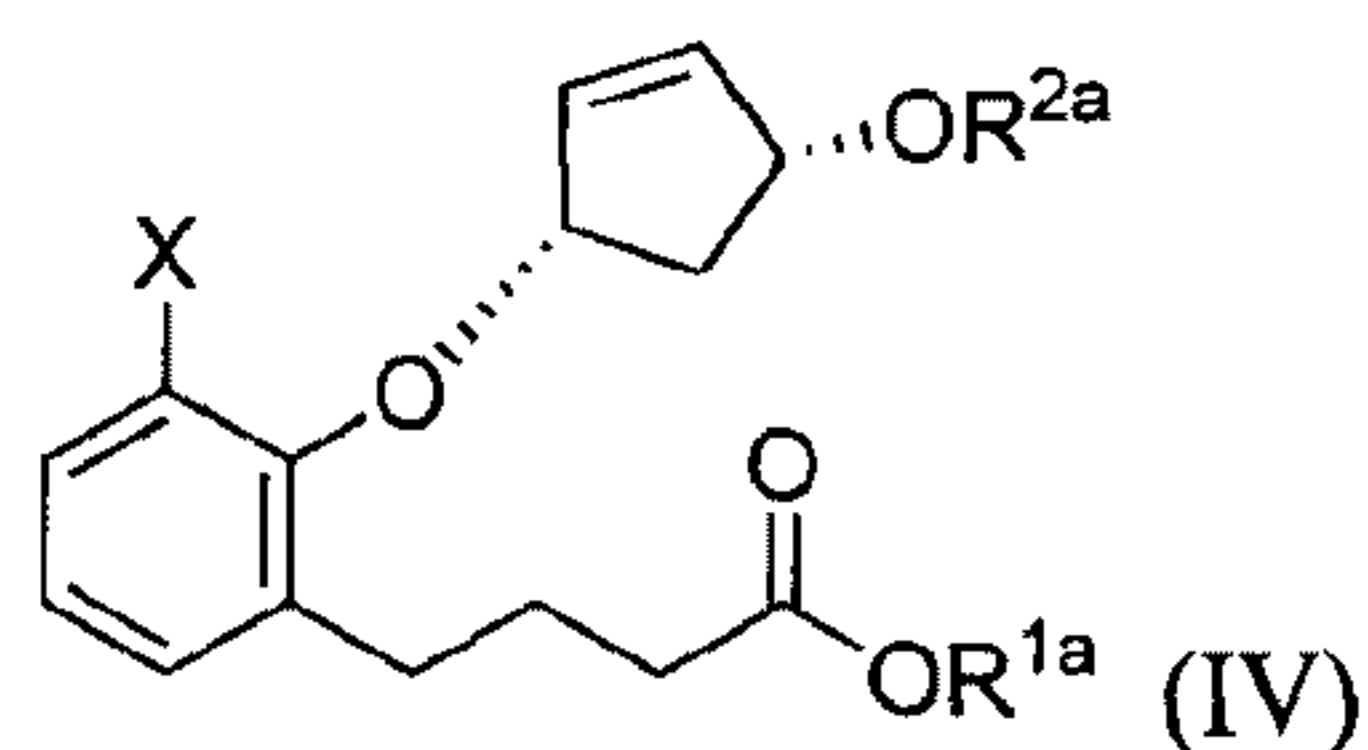
- (1) reacting a compound of formula:



, wherein R^{2a} is H or an hydroxy protective group,
 with a compound of formula:

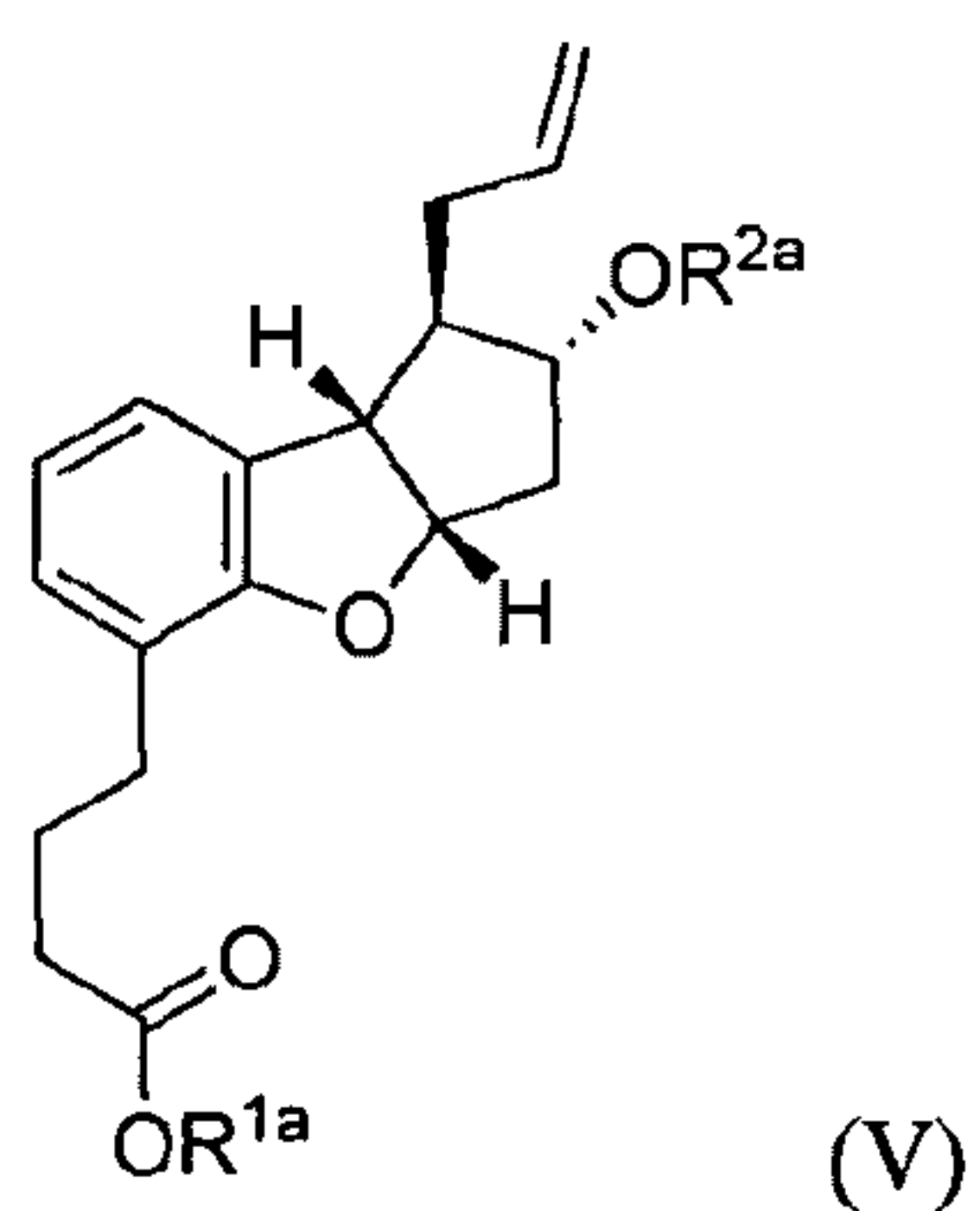


, wherein R^{1a} is a cation, H, or C_{1-12} alkyl, X is a halogen selected from chloro, bromo and iodo,
 to form a compound of formula:



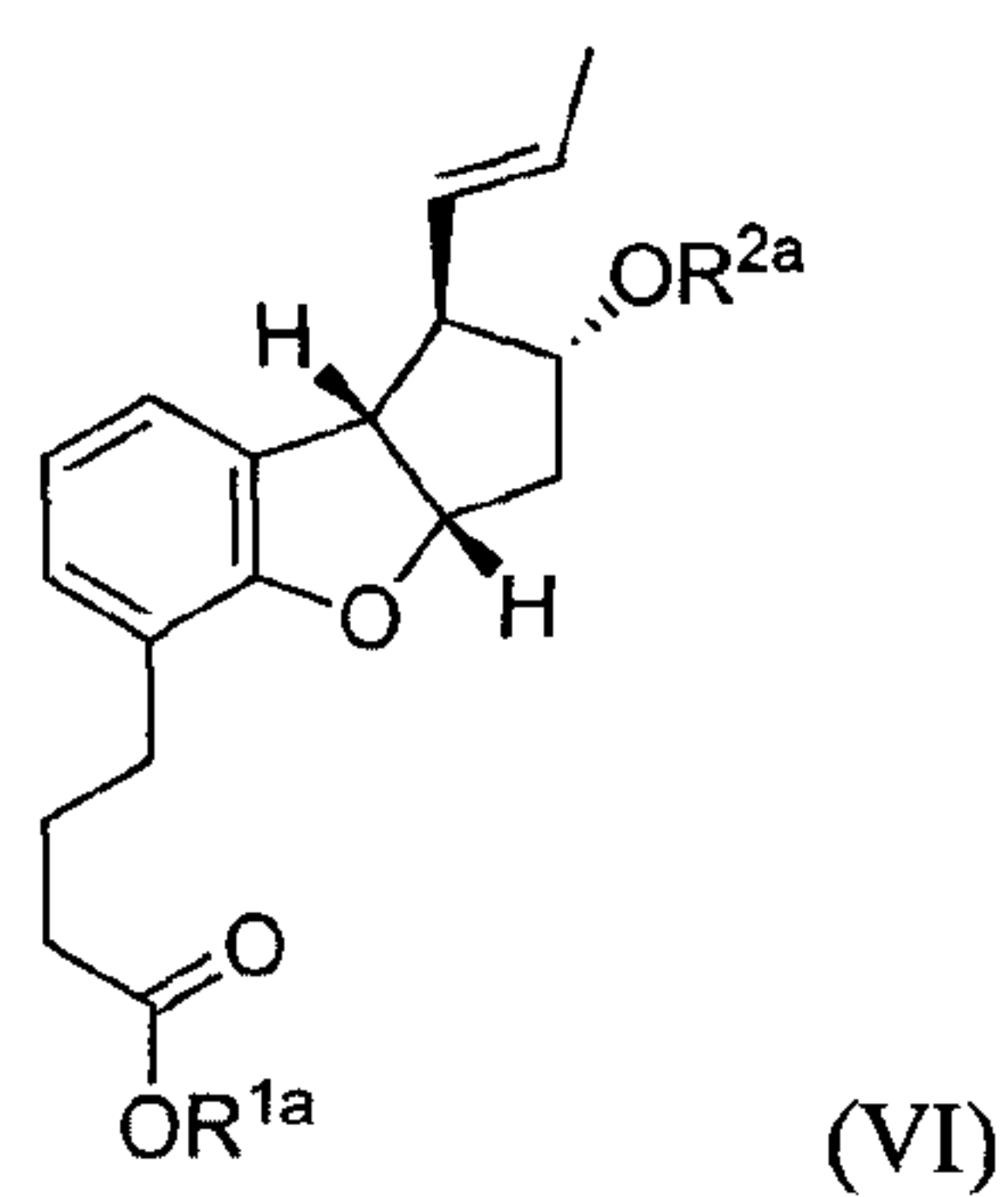
, wherein R^{1a} , R^{2a} and X are each defined above;

- (2) radical cyclizing and in situ radical trapping by reacting the compound of formula (IV) with allyltributyltin using a radical initiator to form a compound of formula:



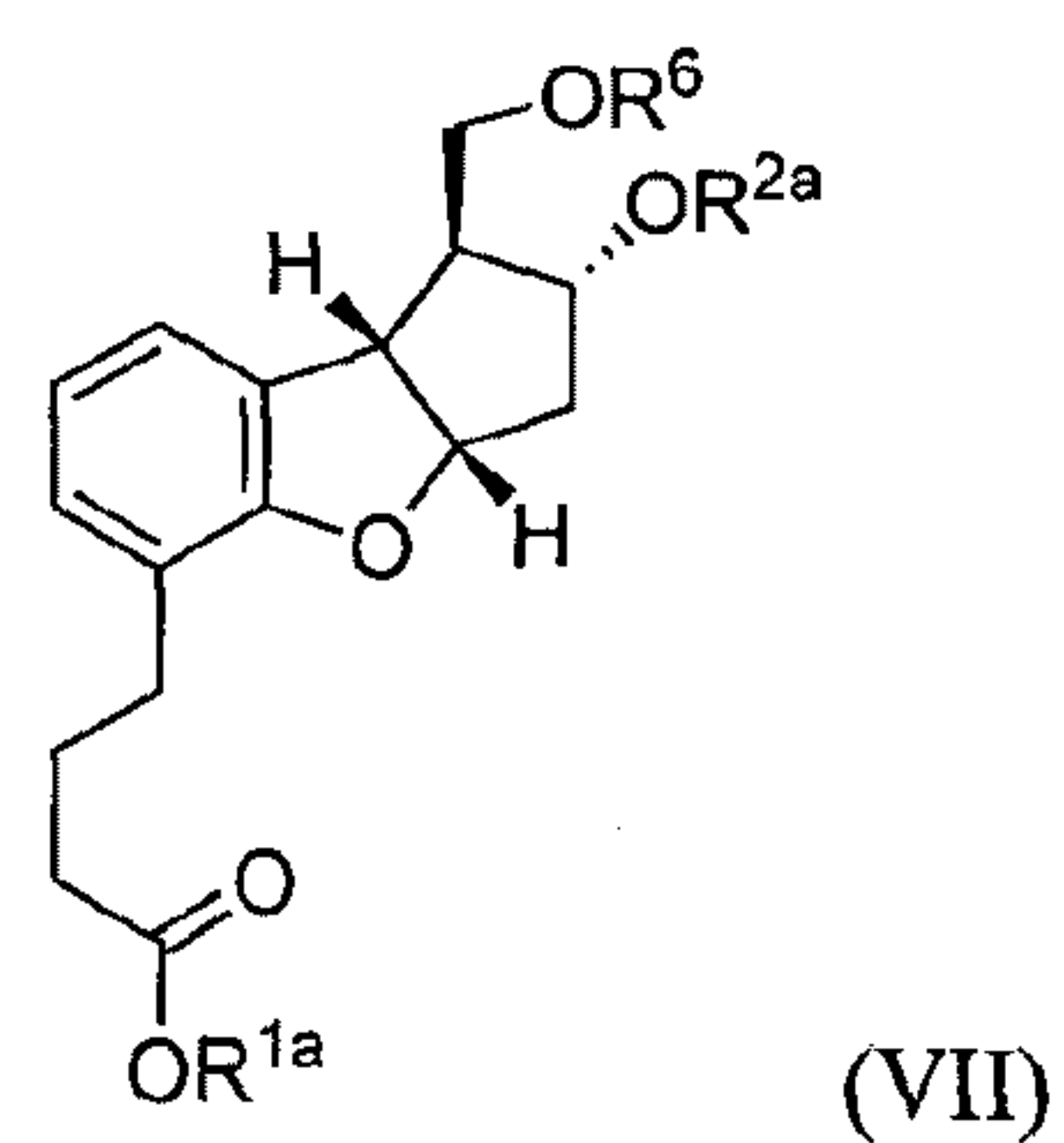
, wherein R^{1a} and R^{2a} are each defined above;

(3) isomerizing an allyl of the compound of formula (V) to form a propenyl resulting in a compound of formula:



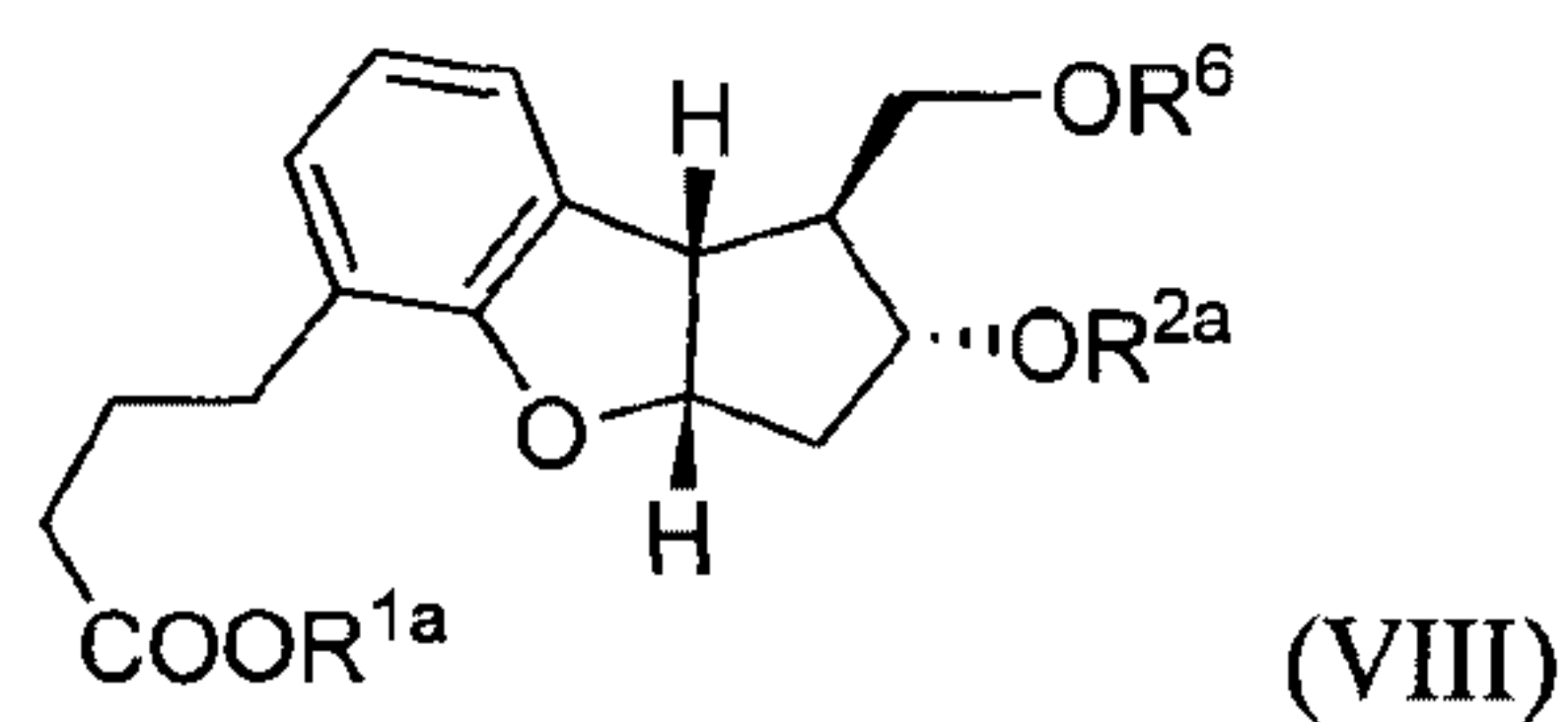
, wherein R^{1a} and R^{2a} are each defined above;

(4) ozonolysis and *in situ* reduction to convert the propenyl of the compound of formula (VI) to form an alcohol resulting in a compound of formula:



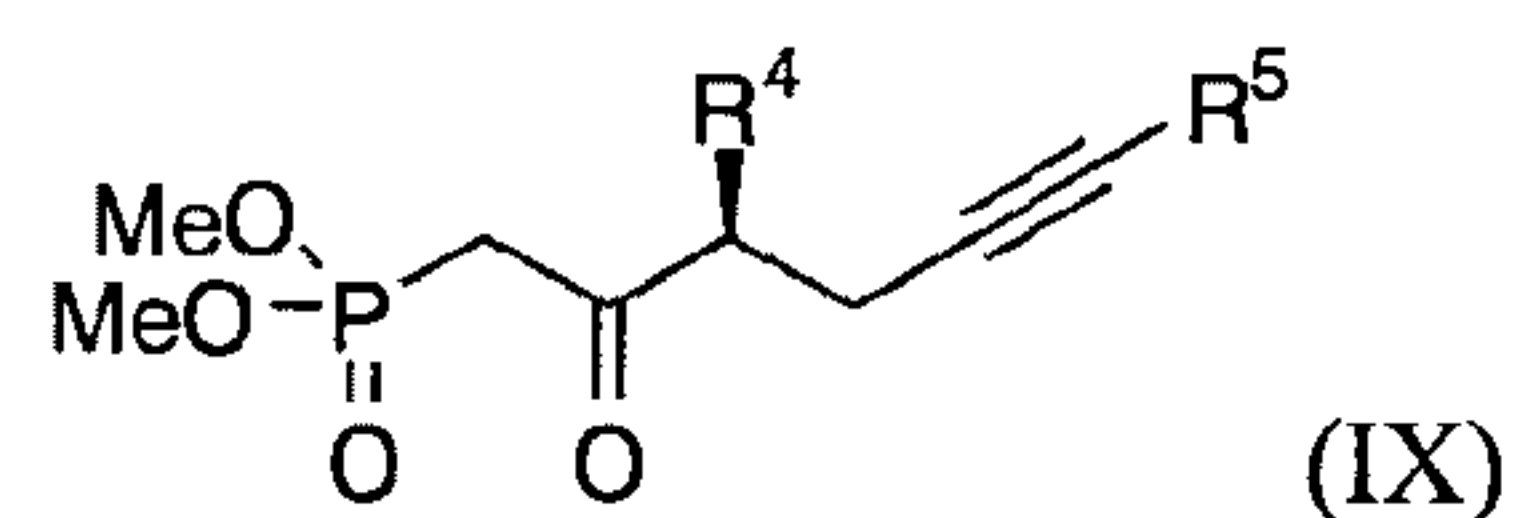
, wherein R^{1a} and R^{2a} are each defined above, R⁶ is H or a hydroxy protective group;

(5) deprotecting the compound of formula (VII) to form a compound of formula:

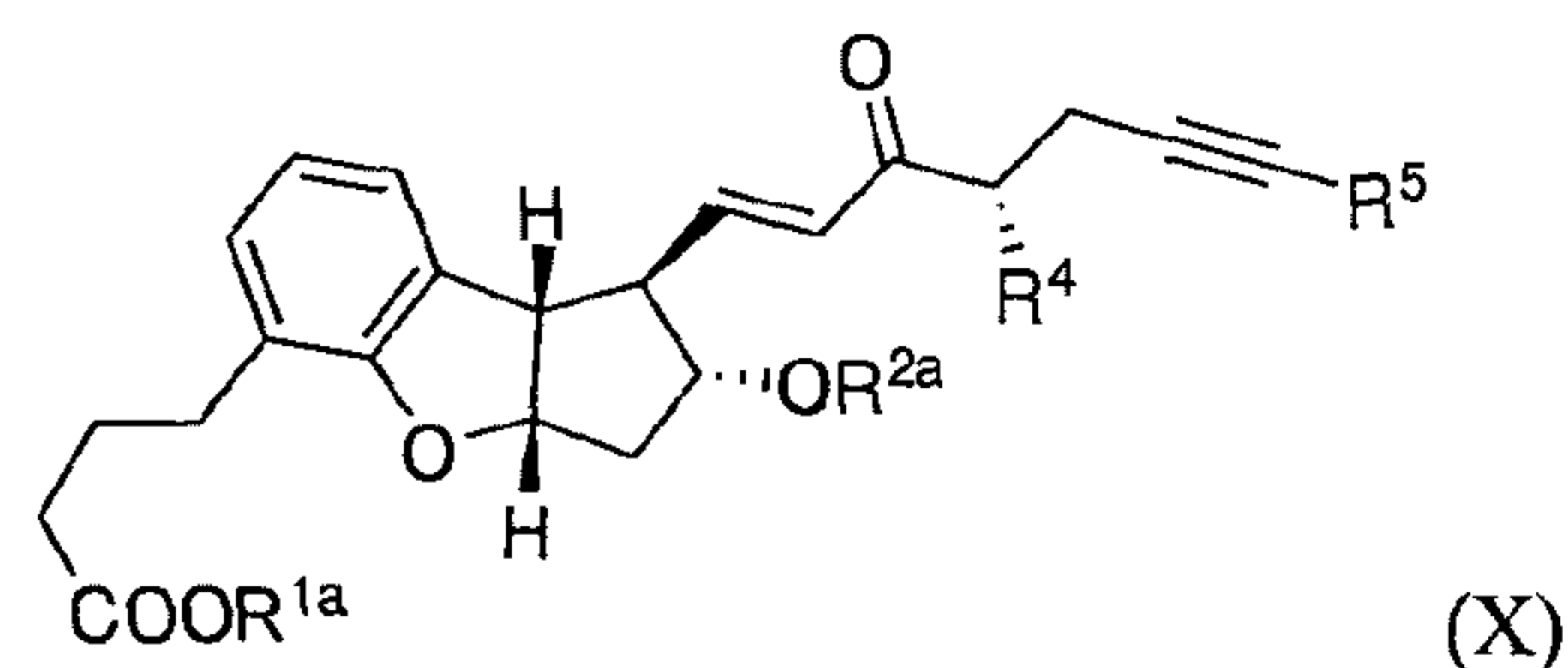


, wherein R^{1a} and R⁶ are each defined above, R^{2a} is H ;

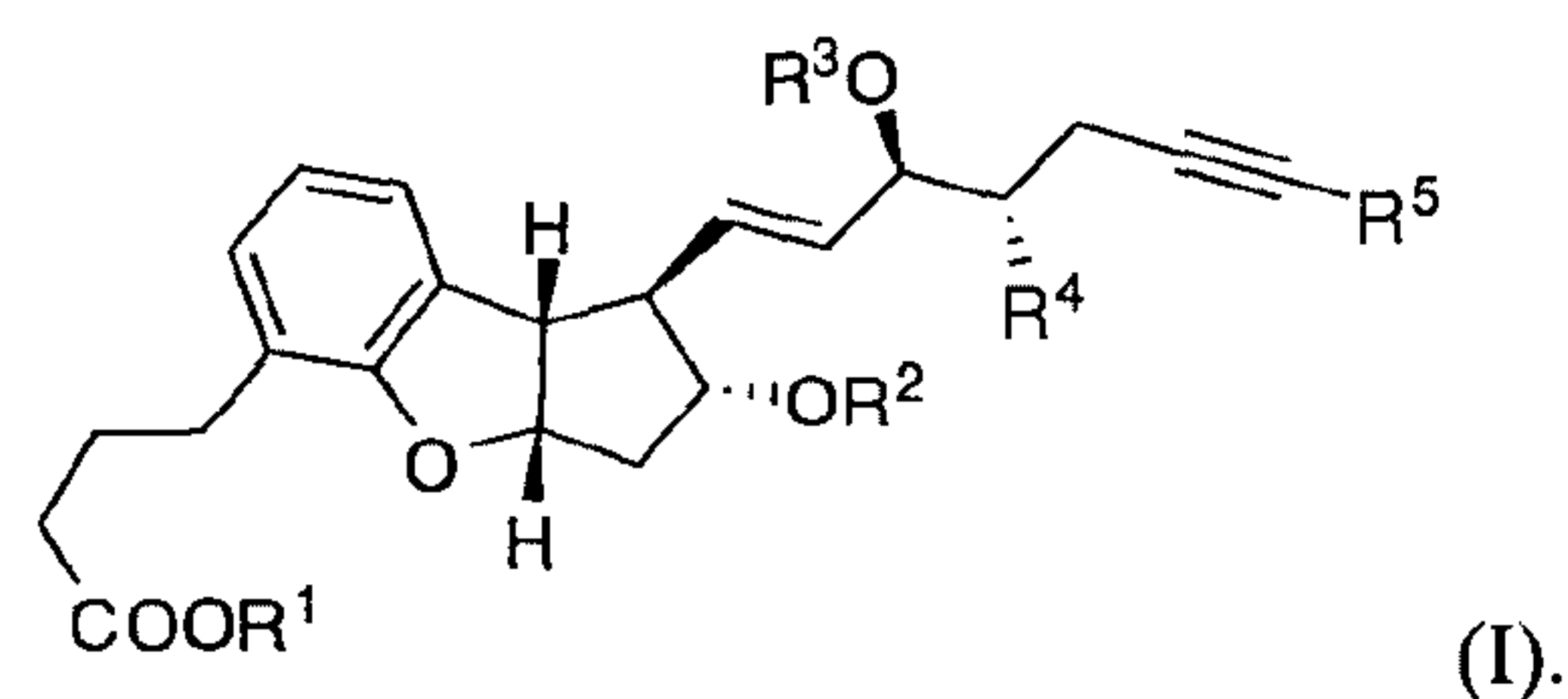
(6) selectively deprotecting the primary hydroxy protective group, followed by oxidation of the primary hydroxy group to form an aldehyde, followed by coupling with a side-chain of the formula:



, wherein R⁴ and R⁵ are each defined above to form a compound of formula:



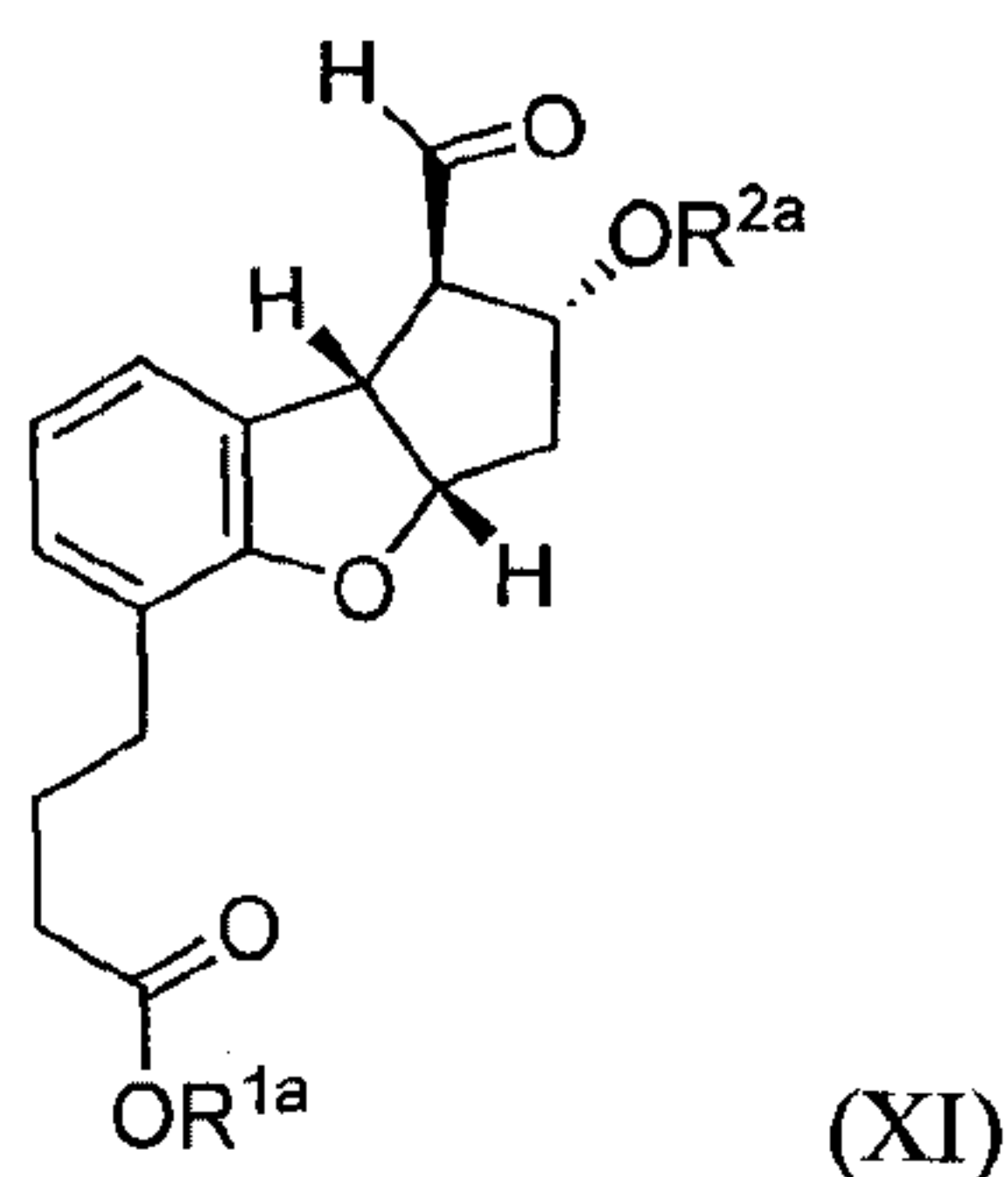
(7) reduction of the ketone, deprotection of any remaining hydroxy protective group and optionally converting the R^{1a} into a cation or H to form a compound of formula:



2. The process of claim 1, wherein the produced compound of formula (I) has an isomeric purity of greater than 90%.

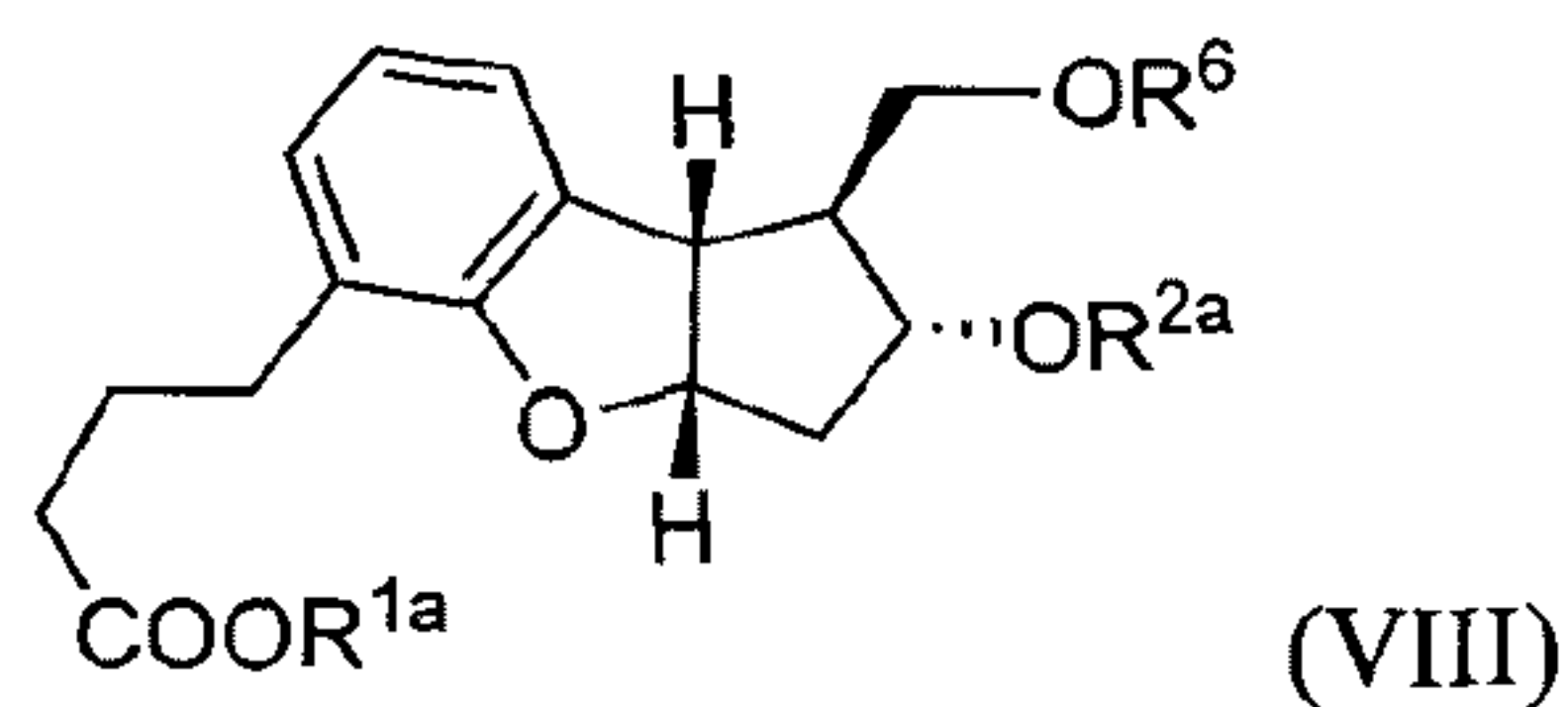
3. The process of claim 1, wherein R², R³, R^{2a} and R⁶ each independently represent acetate, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, phenyldimethylsilyl, tetrahydropyranyl, benzoate ester, benzyl, or substituted benzyl.

4. The process of claim 1, wherein R^{1a} is CH_3 and R^{2a} and R^6 are both H.
5. The process of claim 1, wherein the radical initiator is azobisisobutyronitrile.
6. The process of claim 1, wherein a catalytic amount of carbonylchlorohydridotris(triphenylphosphine) ruthenium (II) is used in step (3).
7. The process of claim 1, wherein step (4) produces an *in situ* trapped aldehyde intermediate represented by the compound of formula (XI)



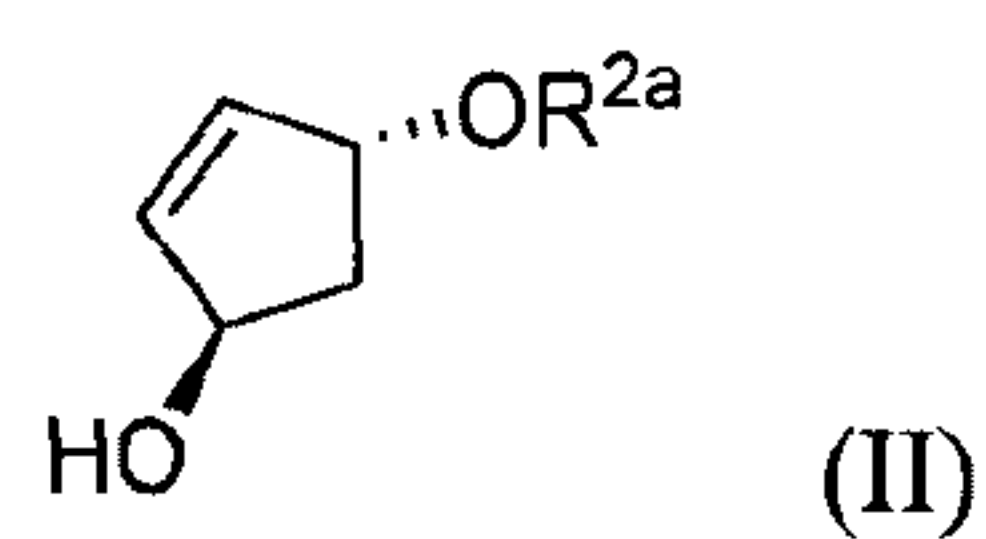
wherein R^{1a} and R^{2a} is each defined above.

8. The process of claim 1, wherein sulfuric acid is used in step (5).
9. A process for preparing a compound of formula:

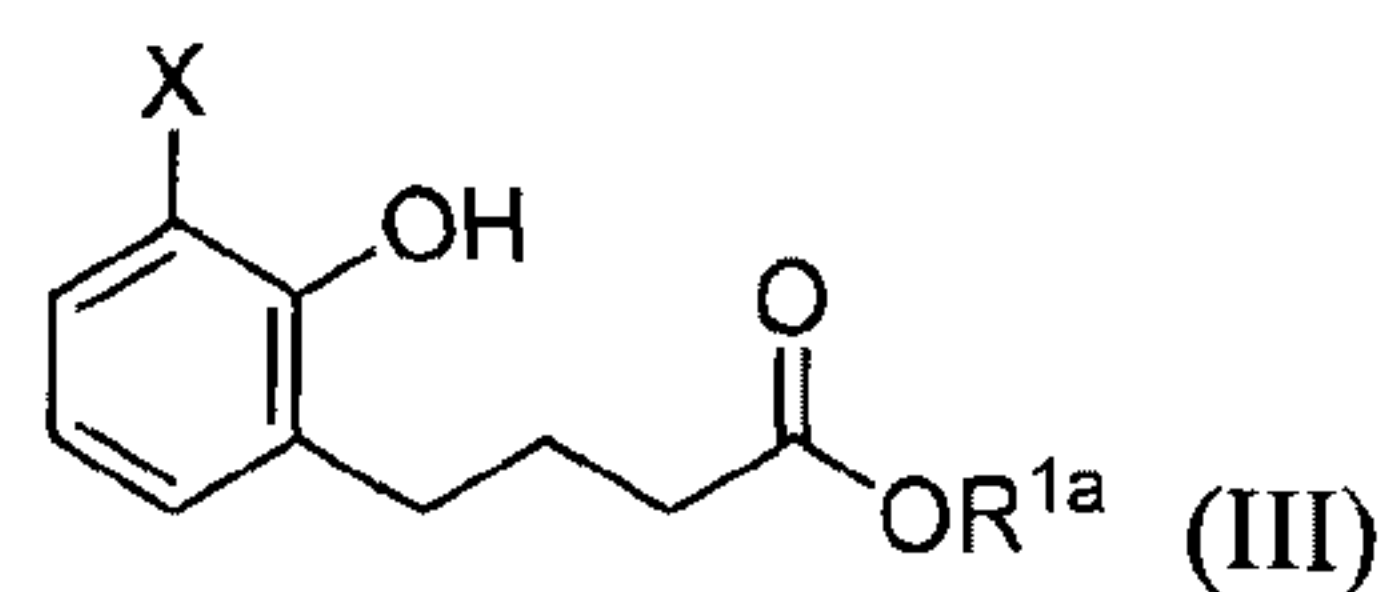


wherein R^{1a} represents a cation, H, or C_{1-12} alkyl and R^{2a} and R^6 each represent H, an acetate or a hydroxy protective group, comprising:

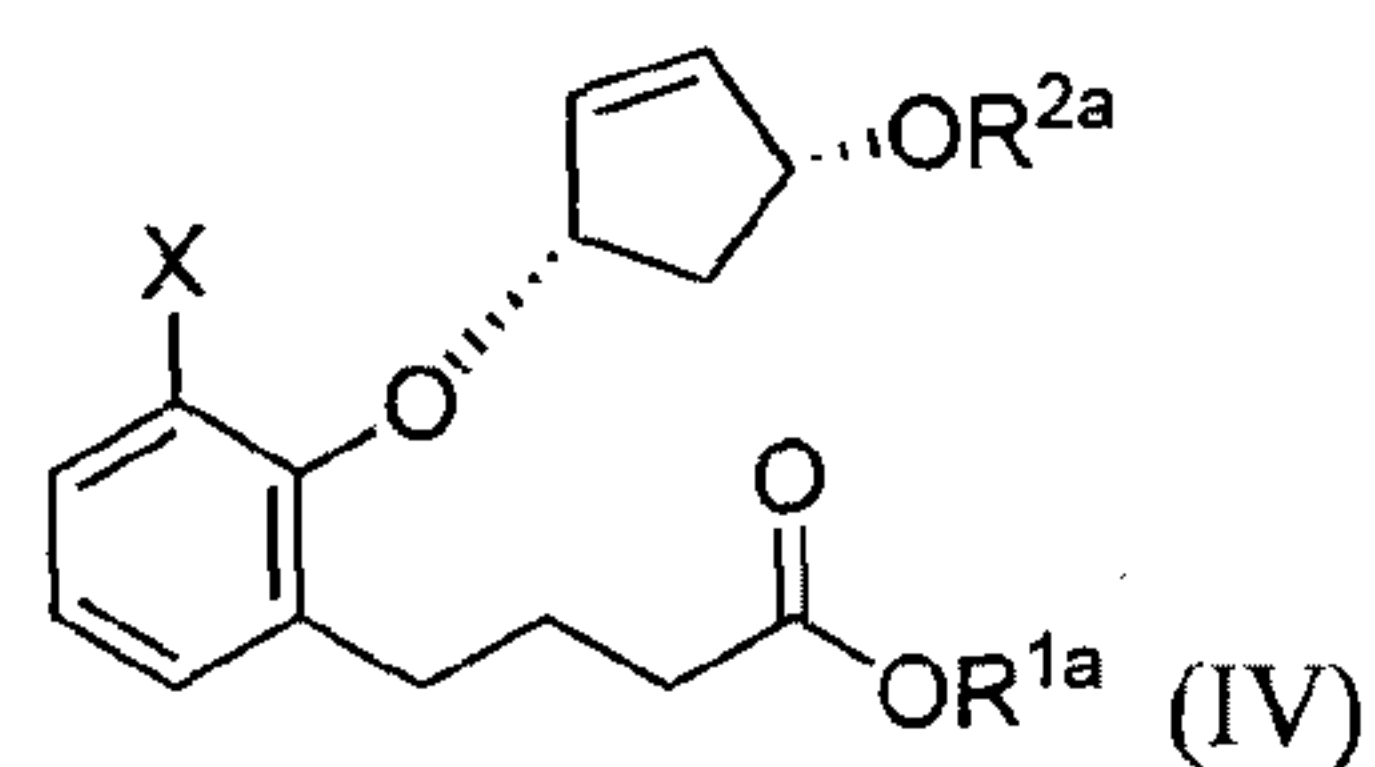
- (1) performing a Mitsunobu reaction on the compound of formula:



, wherein R^{2a} is defined above,
with a compound of formula:

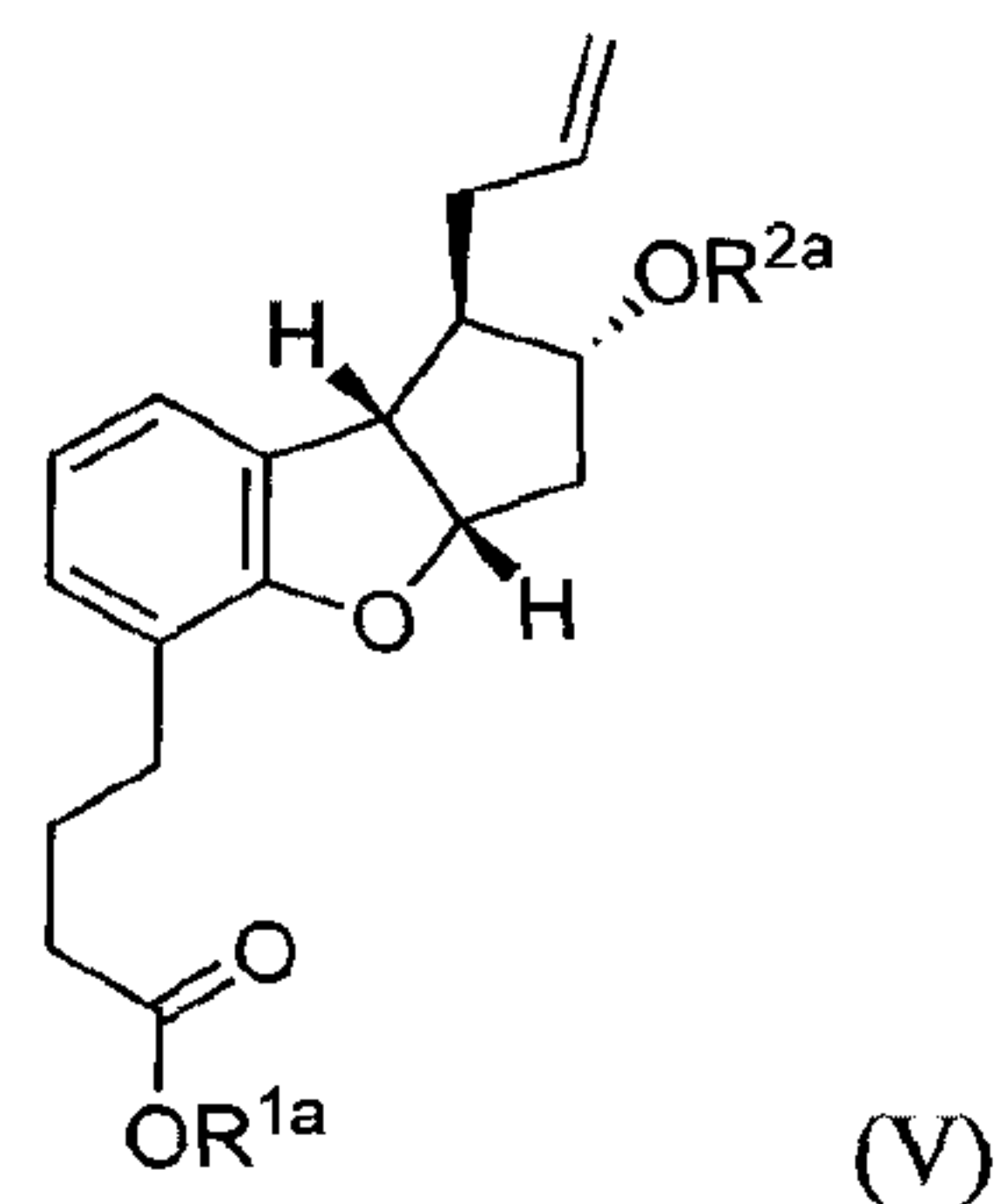


, wherein R^{1a} is defined above, X is a halogen selected from chloro, bromo and iodo,
to form a compound of formula:



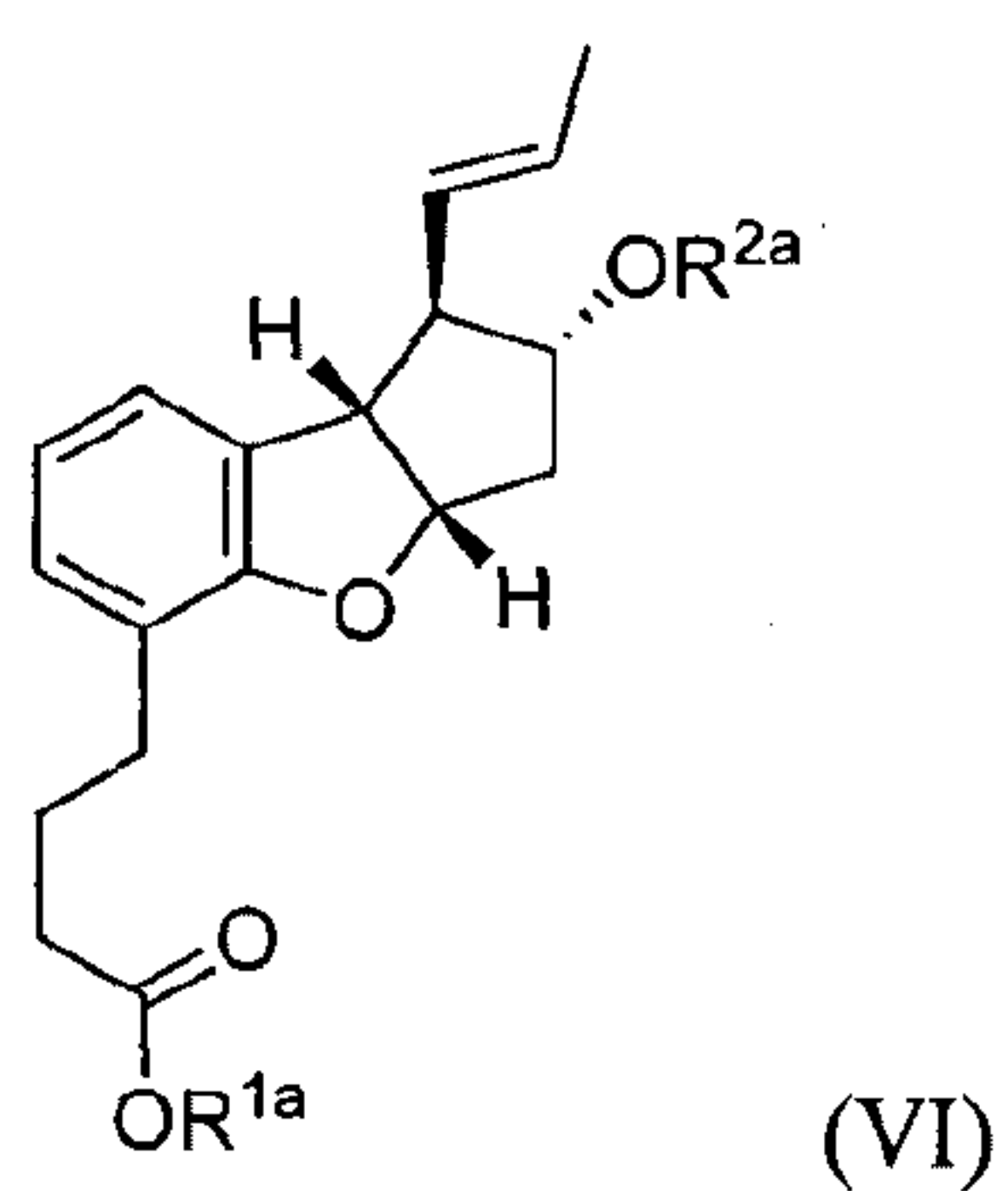
, wherein R^{1a}, R^{2a} and X is each defined above;

(2) radical cyclization and *in situ* radical trapping by reacting the compound of formula (IV) with allyltributyltin using a radical initiator to form a compound of formula:



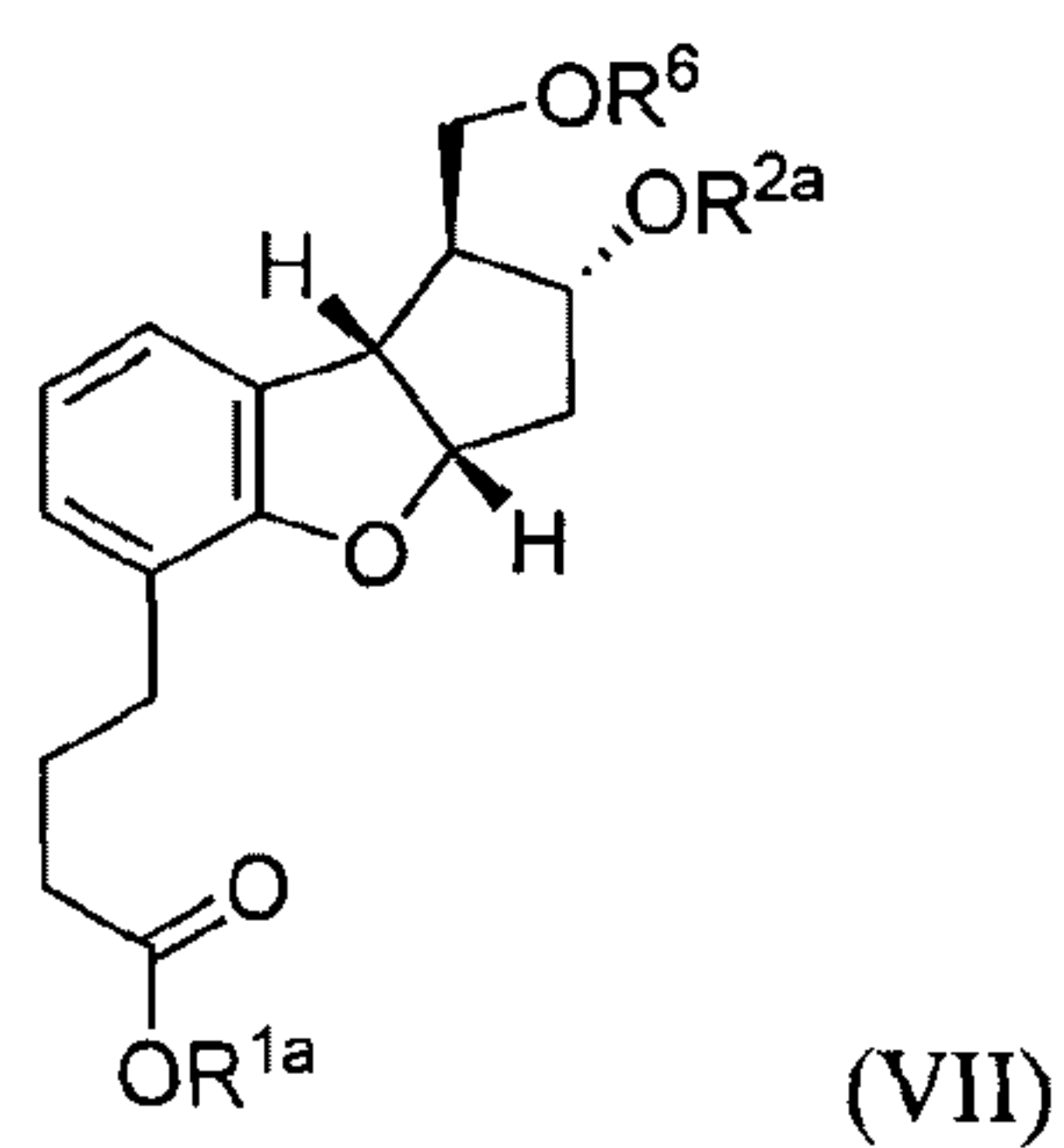
, wherein R^{1a} and R^{2a} is each defined above;

(3) isomerizing the allyl of the compound of formula (V) to form a propenyl resulting in a compound of formula:



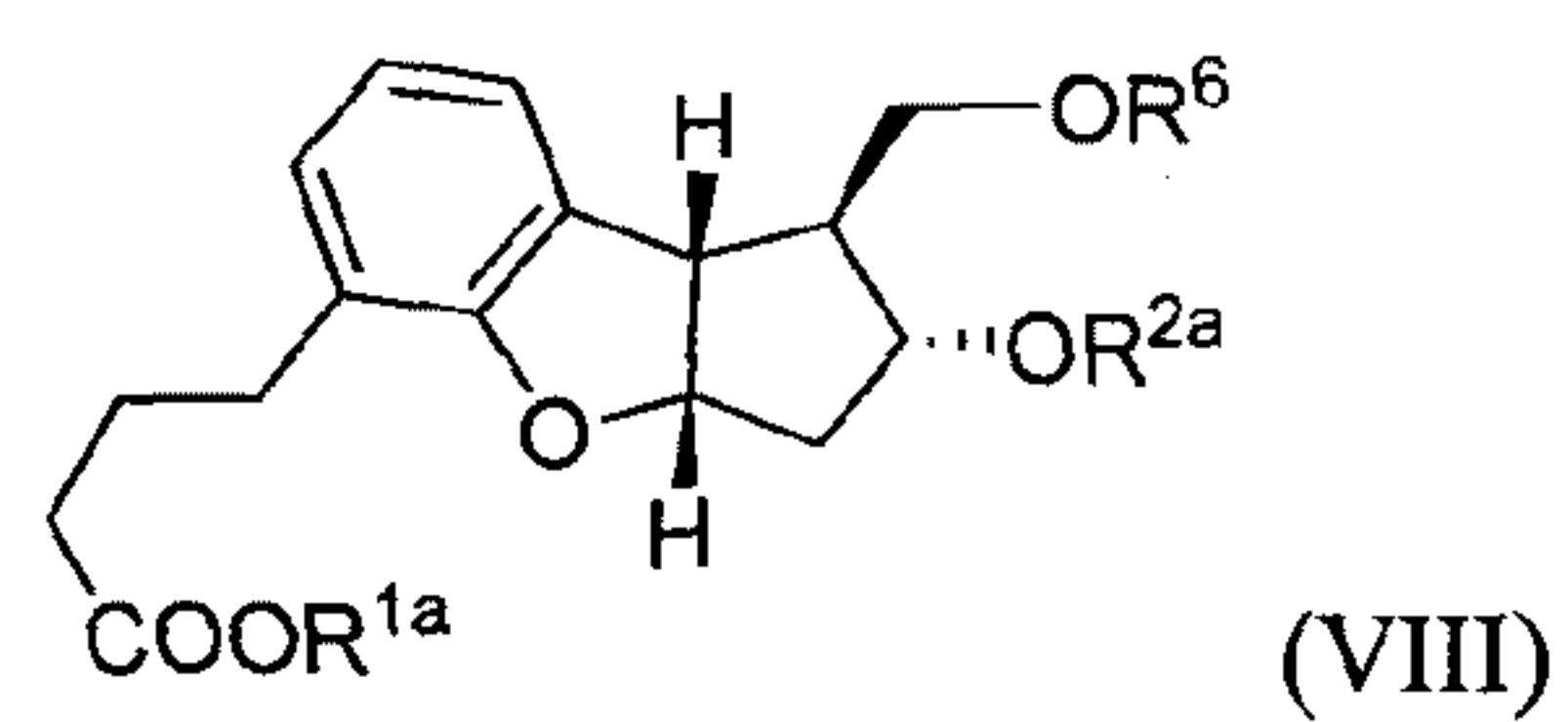
, wherein R^{1a} and R^{2a} is each defined above;

(4) ozonolysis and *in situ* reduction to convert the propenyl of the compound of formula (VI) to form an alcohol resulting in a compound of formula:



, wherein R^{1a}, R^{2a} and R⁶ are each defined above;

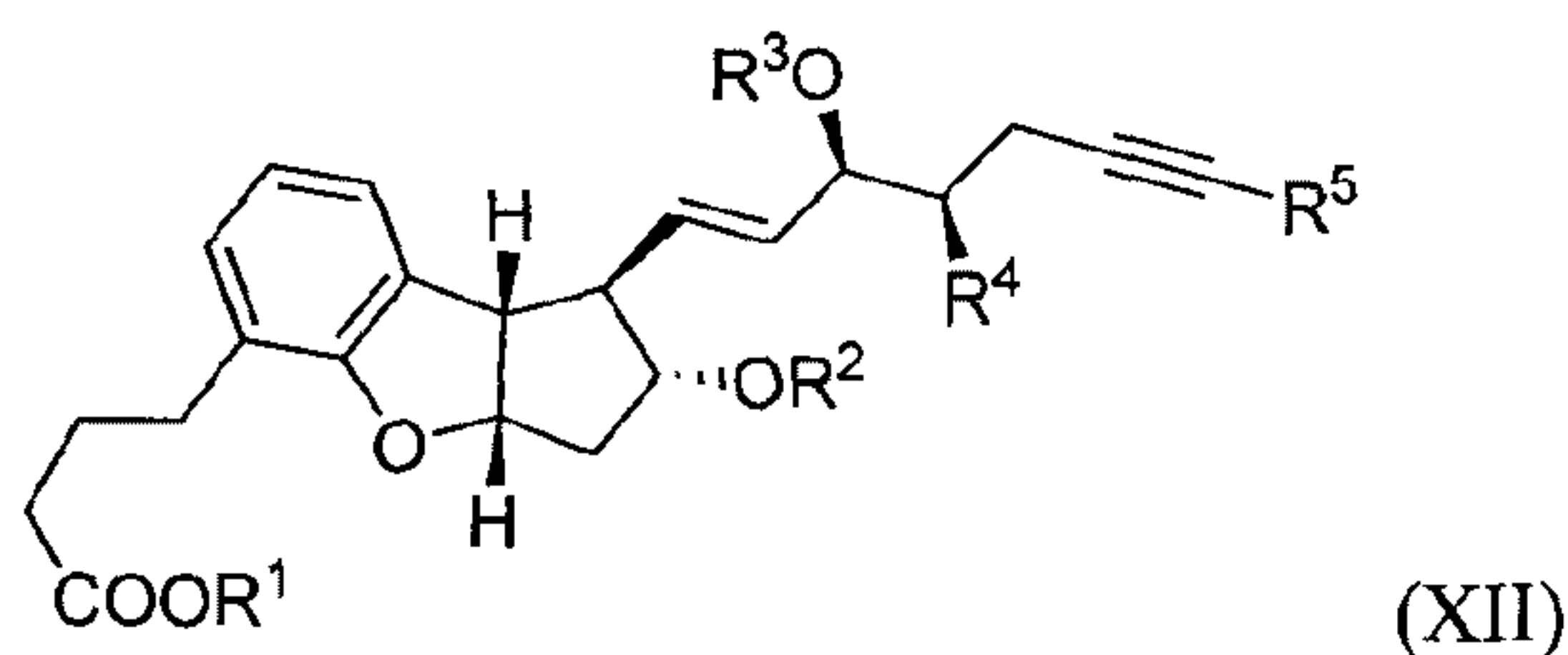
(5) deprotection of the compound of formula (VII) to form a compound of formula:



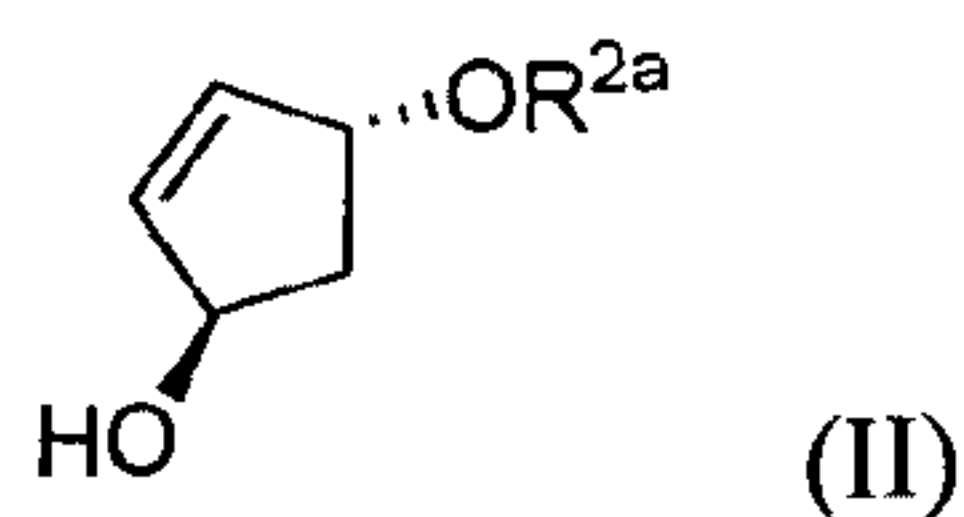
, wherein R^{1a} and R⁶ is each defined above; R^{2a} is H.

10. The process of claim 9, wherein the produced compound of formula (VIII) has an isomeric purity of greater than 90%.

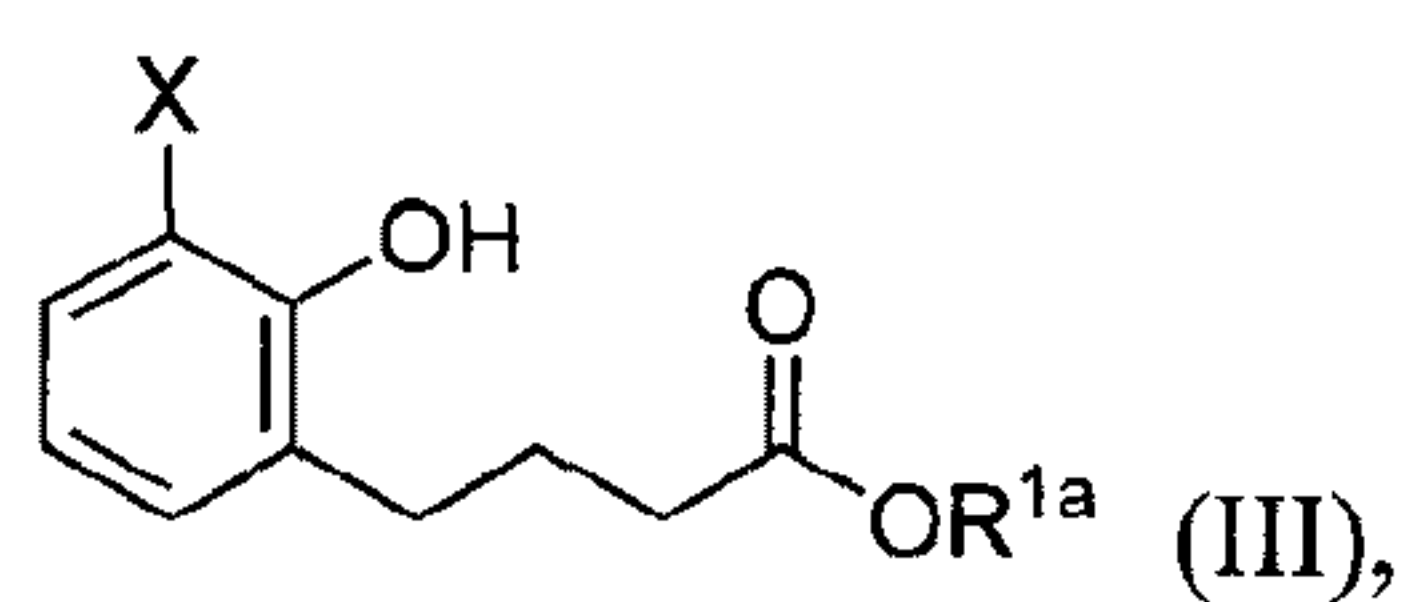
11. The process of claim 9, wherein R^{2a} and R^6 each independently represent acetate, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, phenyldimethylsilyl, tetrahydropyranyl, benzoate ester, benzyl, or substituted benzyl.
12. The process of claim 9, wherein R^{1a} is CH_3 , and R^{2a} and R^6 are both H.
13. The process of claim 9, wherein the radical initiator is azobisisobutyronitrile.
14. The process of claim 9, wherein a catalytic amount of carbonylchlorohydridotris(triphenylphosphine) ruthenium (II) is used in step (3).
15. The process of claim 9, wherein sulfuric acid is used in step (5).
16. A process for preparing a compound of formula:



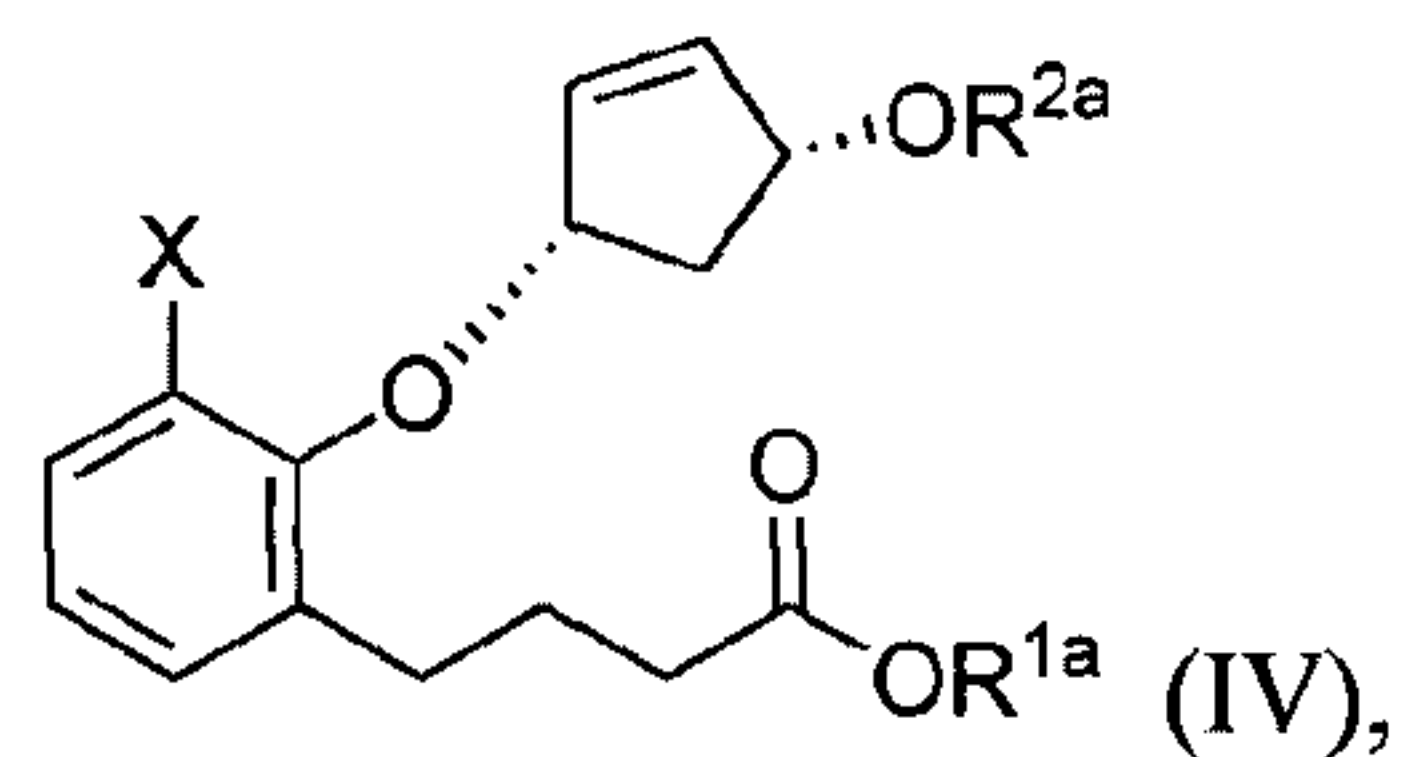
wherein R^1 represents a cation, H, or C_{1-12} alkyl,
 R^2 and R^3 each represent H or a hydroxy protective group,
 R^4 represents H or C_{1-3} alkyl, and
 R^5 represents H or C_{1-6} alkyl, comprising:
 (1) reacting a compound of formula:



, wherein R^{2a} is H or an hydroxy protective group,
 with a compound of formula:

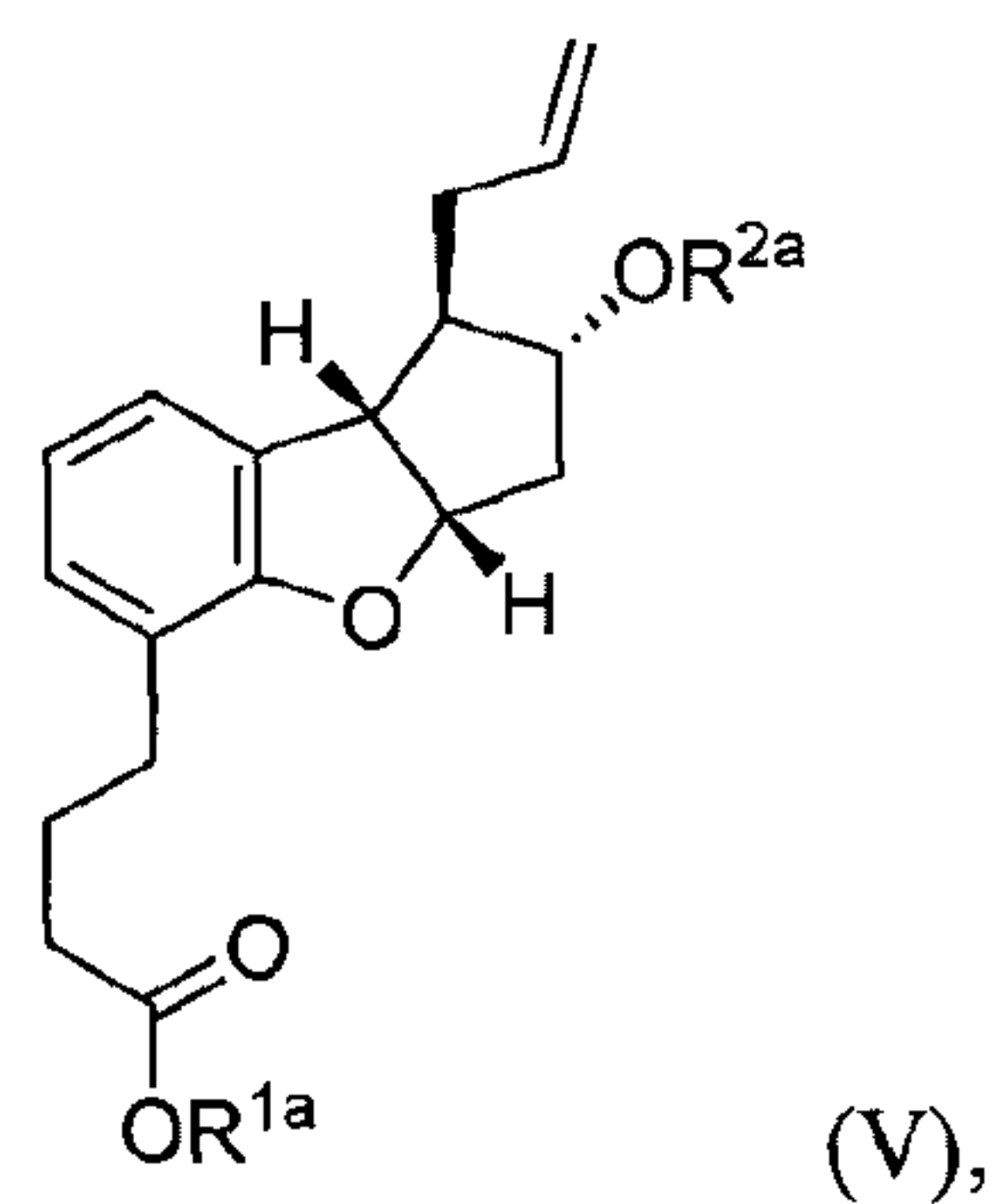


wherein R^{1a} is a cation, H, or C₁₋₁₂ alkyl, X is a halogen selected from chloro, bromo and iodo, to form a compound of formula:



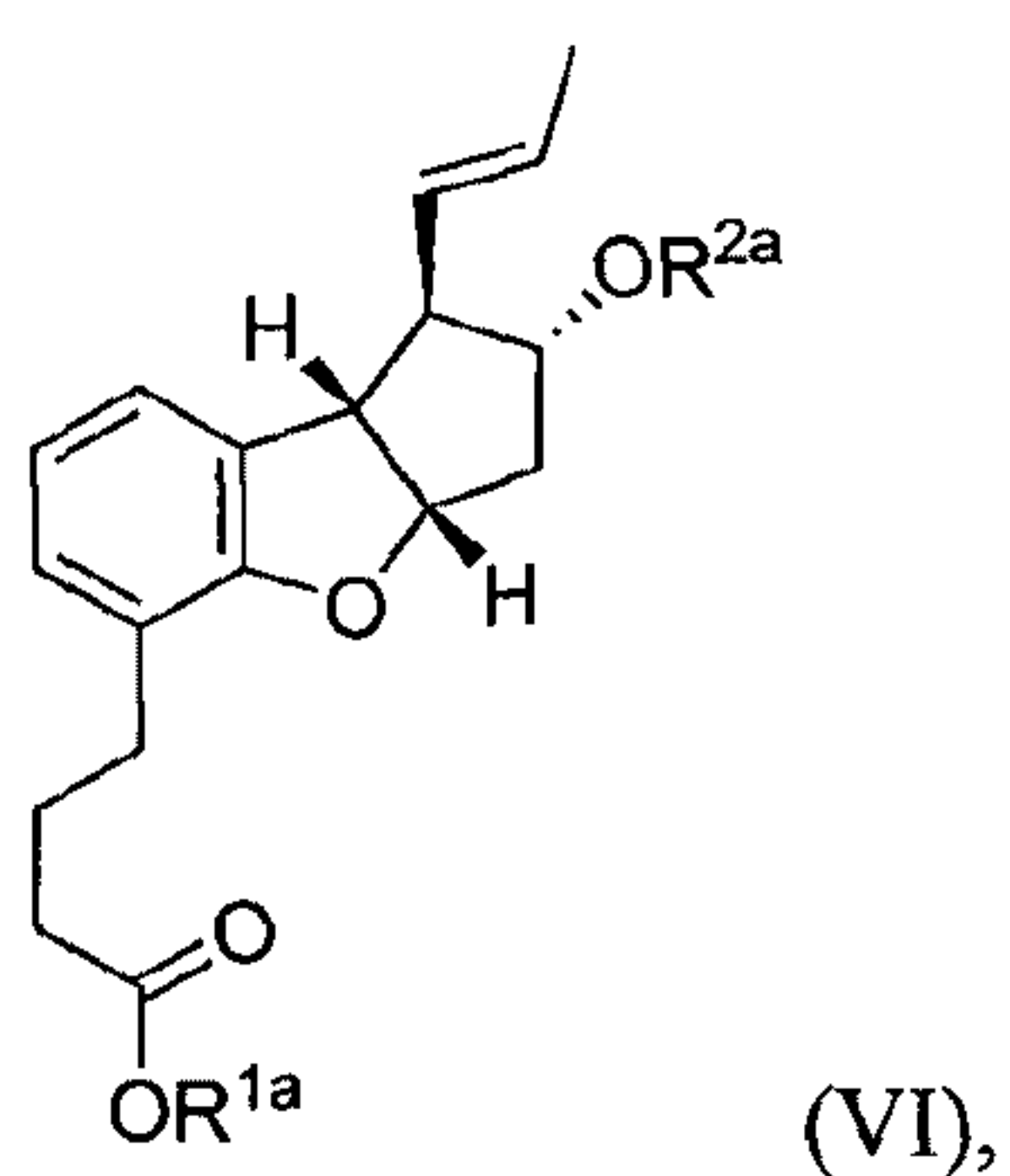
wherein R^{1a}, R^{2a} and X are each defined above;

(2) radical cyclizing and *in situ* trapping by reacting the compound of formula (IV) with allyltributyltin using a radical initiator to form a compound of formula:



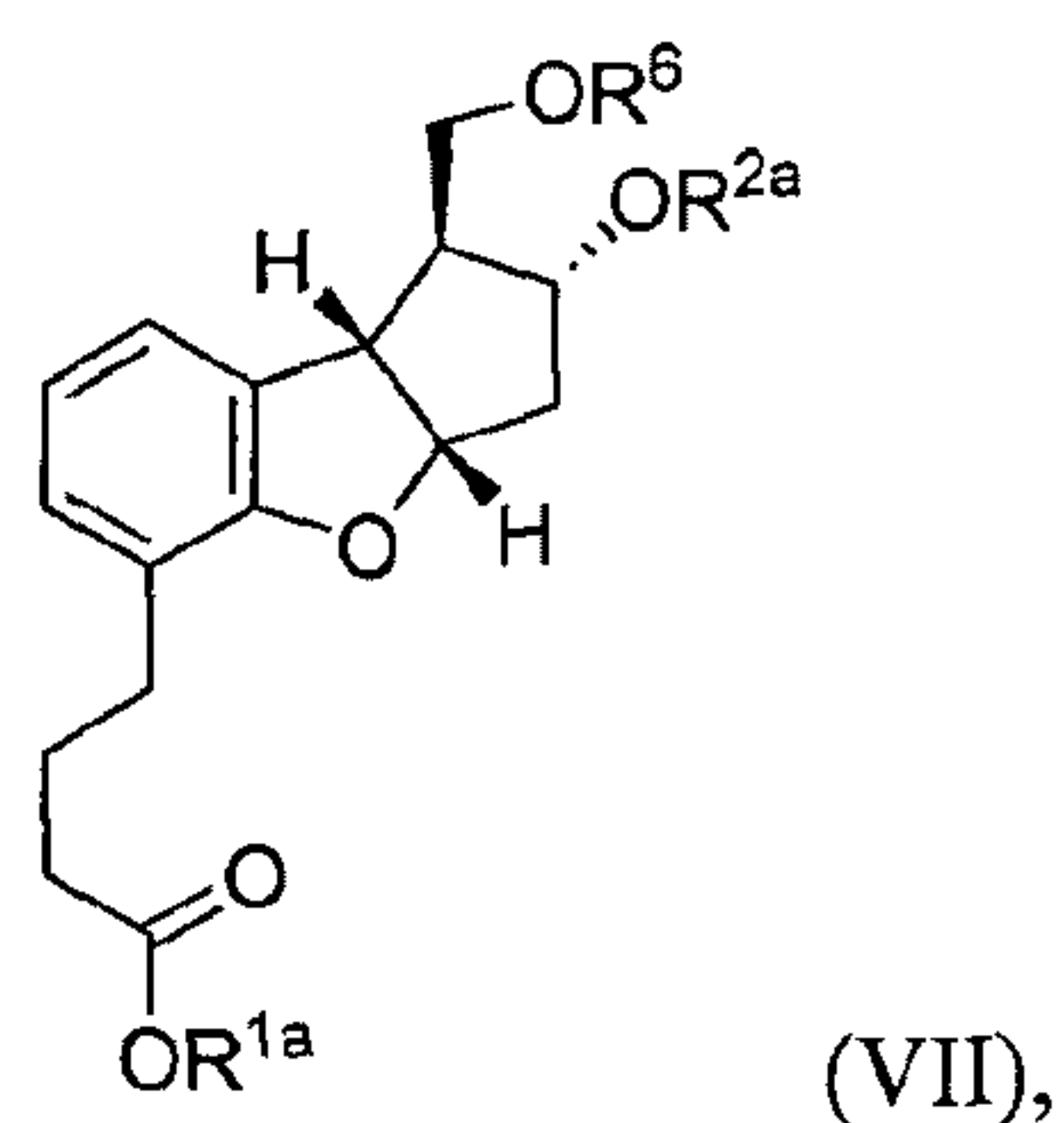
wherein R^{1a} and R^{2a} are each defined above;

(3) isomerizing an allyl of the compound of formula (V) to form a propenyl resulting in a compound of formula:



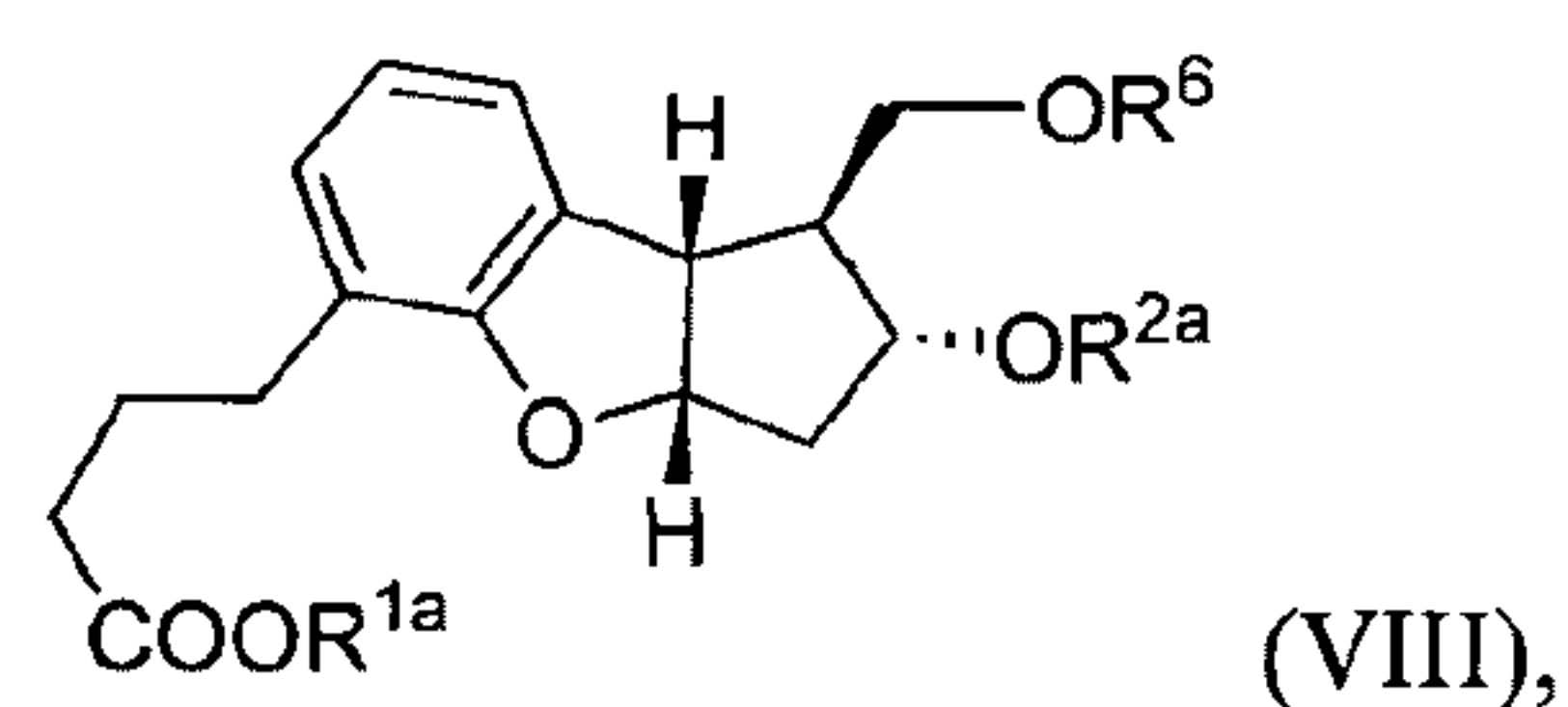
wherein R^{1a} and R^{2a} are each defined above;

(4) ozonolysis and *in situ* reduction to convert the propenyl of the compound of formula (VI) to form an alcohol resulting in a compound of formula:



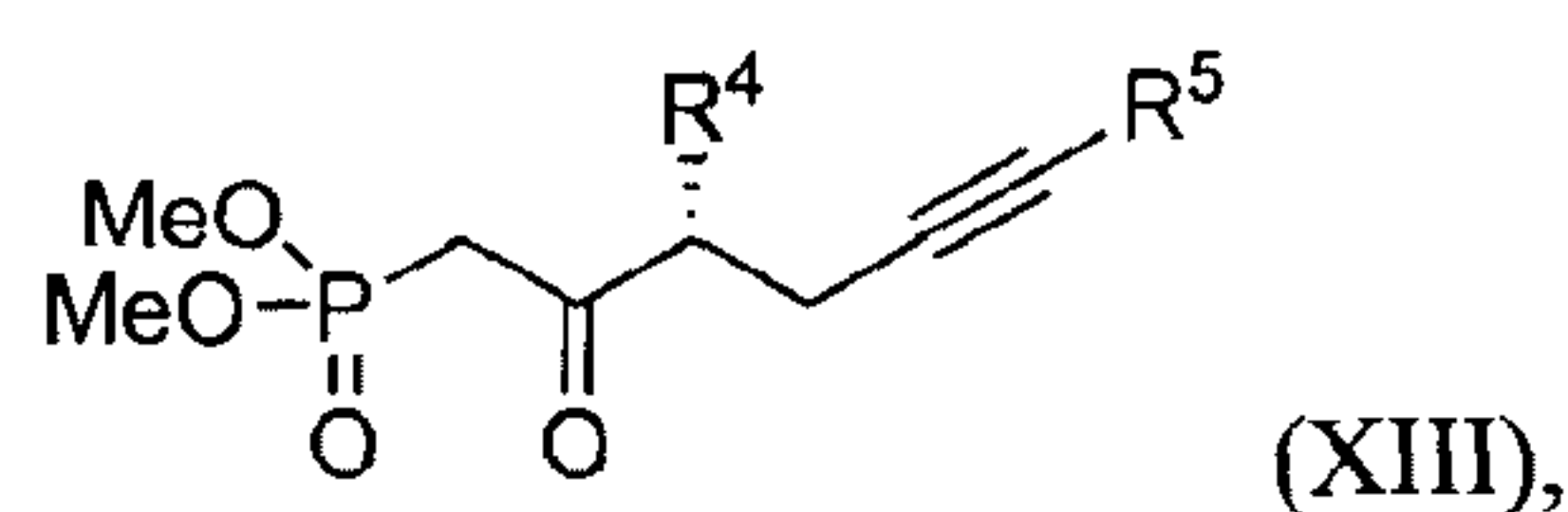
wherein R^{1a} and R^{2a} are each defined above, R⁶ is H or a hydroxy protective group;

(5) deprotecting the compound of formula (VII) to form a compound of formula:

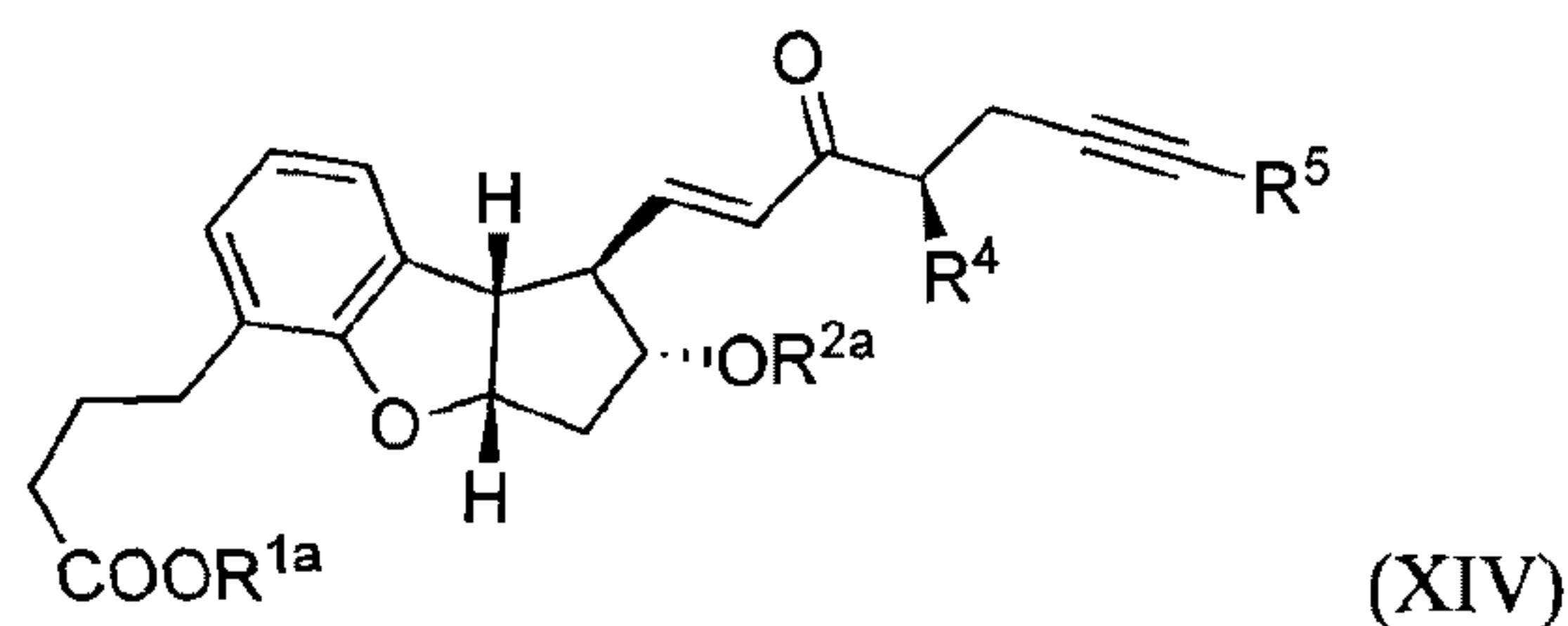


wherein R^{1a} and R⁶ are each defined above, R^{2a} is H ;

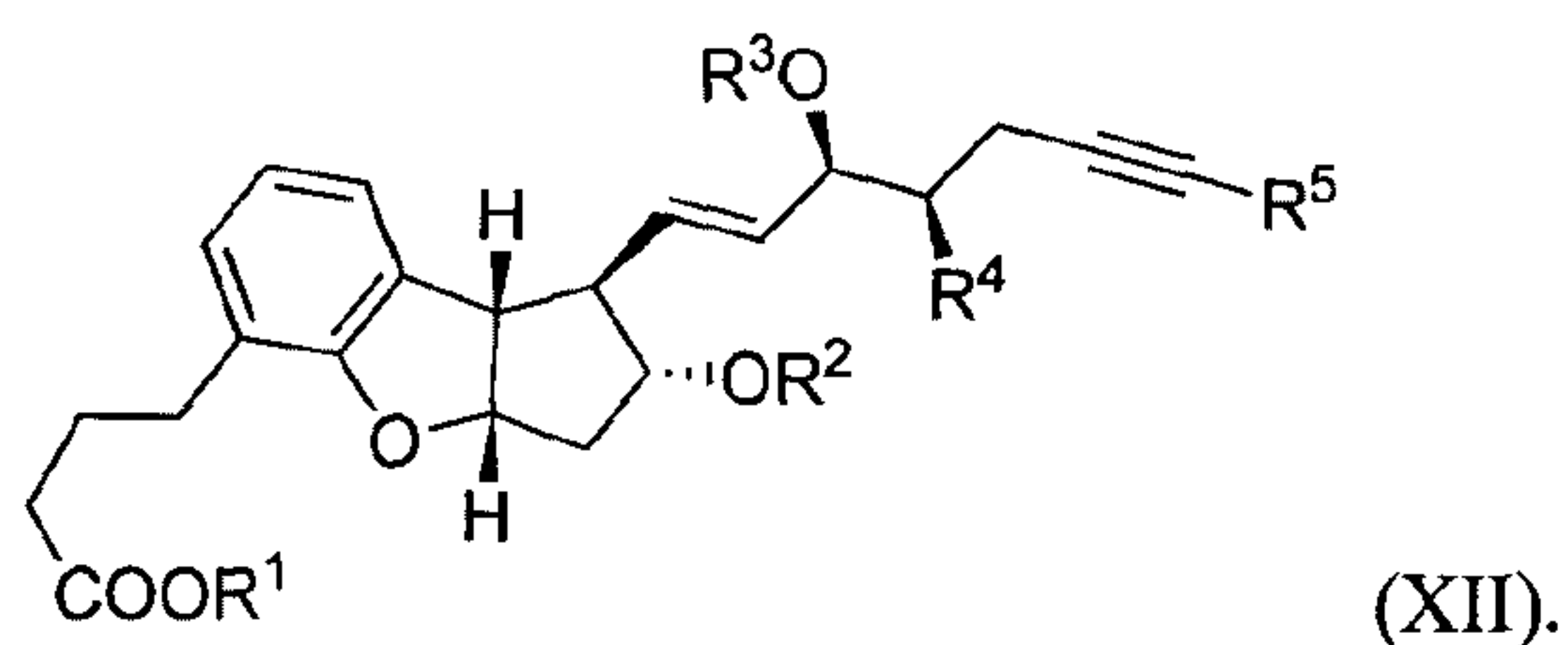
(6) selectively deprotecting the primary hydroxy protective group, followed by oxidation of the primary hydroxy group to form an aldehyde, followed by coupling with a side-chain of the formula:



wherein R^4 and R^5 are each defined above to form a compound of formula:



(7) reduction of the ketone, deprotection of any remaining hydroxy protective group and optionally converting the R^{1a} into a cation or H to form a compound of formula:



17. The process of claim 16, wherein the produced compound of formula (XII) has an isomeric purity of greater than 90%.

18. The process of claim 16, wherein R^2 , R^3 , R^{2a} and R^6 each independently represent acetate, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, phenyldimethylsilyl, tetrahydropyranyl, benzoate ester, benzyl, or substituted benzyl.

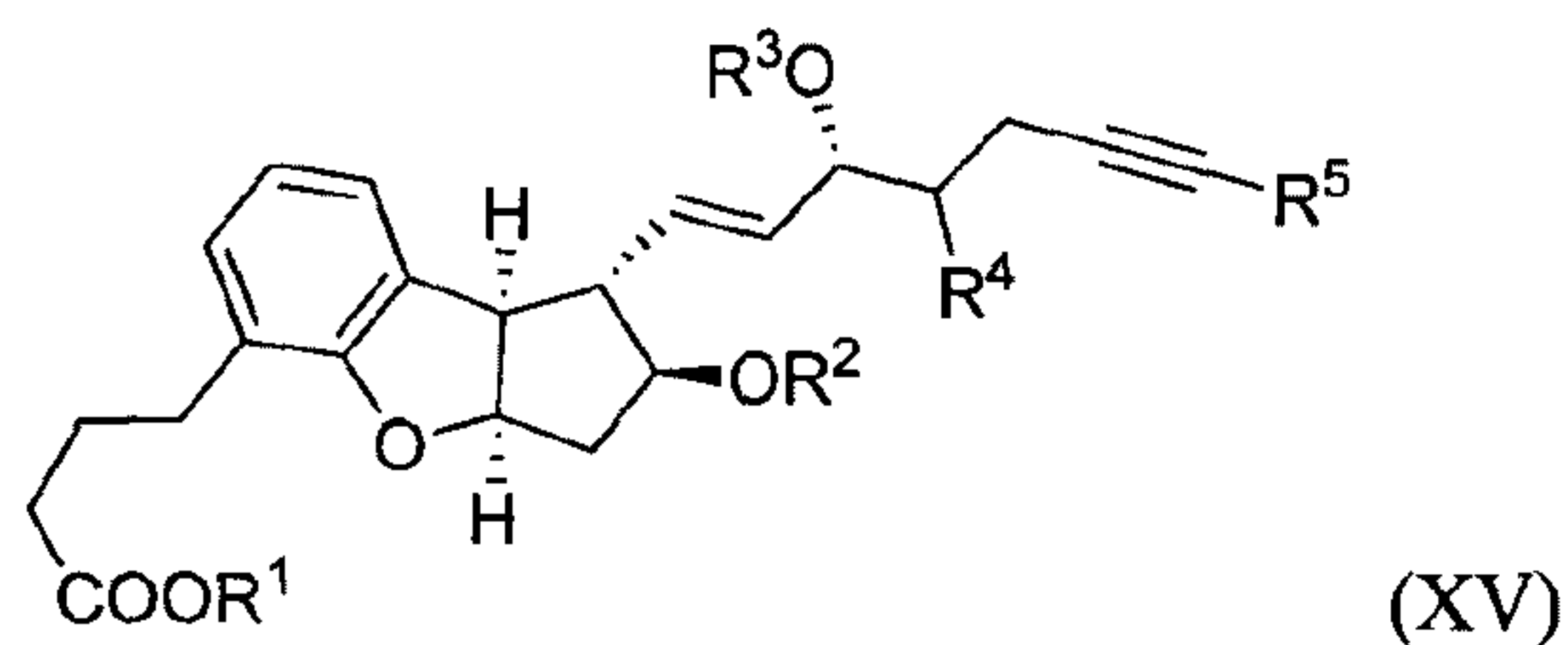
19. The process of claim 16, wherein R^{1a} is CH_3 and R^{2a} and R^6 are both H.

20. The process of claim 16, wherein the radical initiator is azobisisobutyronitrile.

21. The process of claim 16, wherein a catalytic amount of carbonylchlorohydridotris(triphenylphosphine) ruthenium (II) is used in step (3).

22. The process of claim 16, wherein sulfuric acid is used in step (5).

23. A process for preparing a compound of formula:



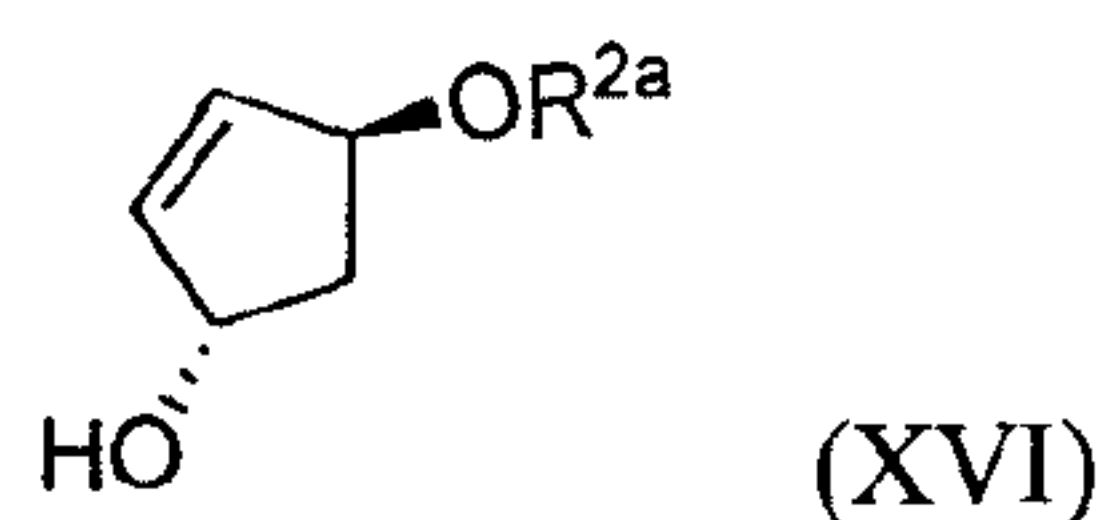
wherein R^1 represents a cation, H, or C_{1-12} alkyl,

R^2 and R^3 each represent H or a hydroxy protective group,

R^4 represents H or C_{1-3} alkyl, and

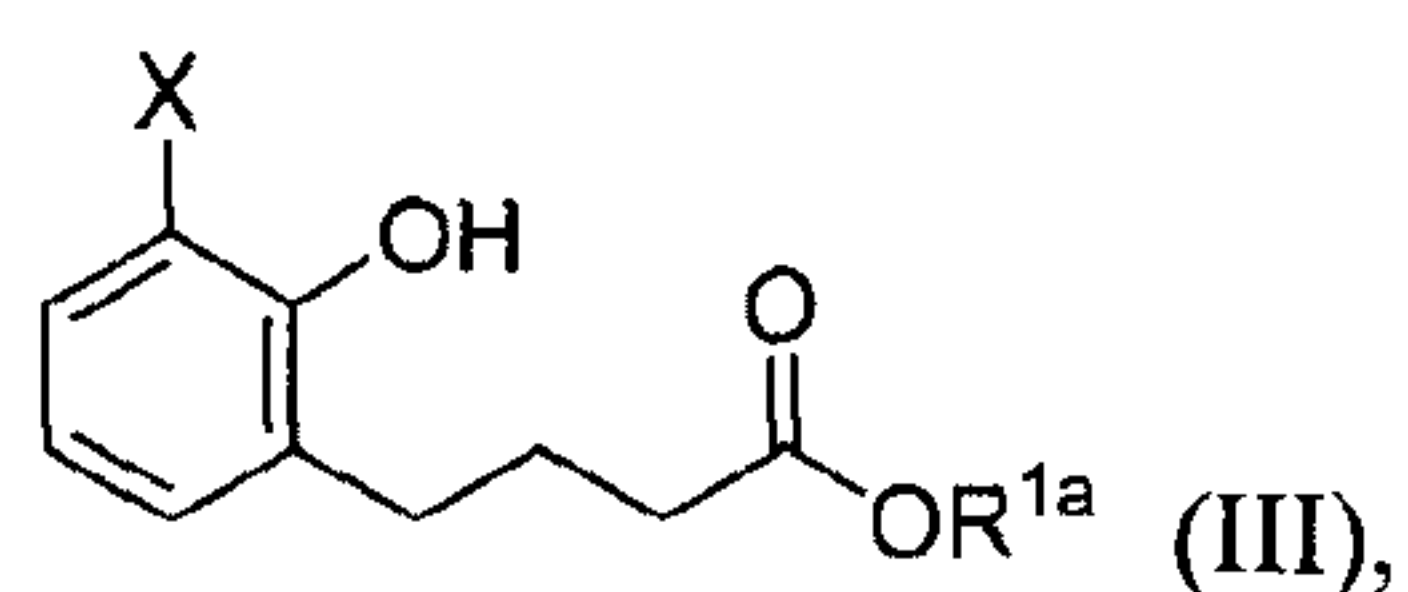
R^5 represents H or C_{1-6} alkyl, comprising:

(1) reacting a compound of formula:



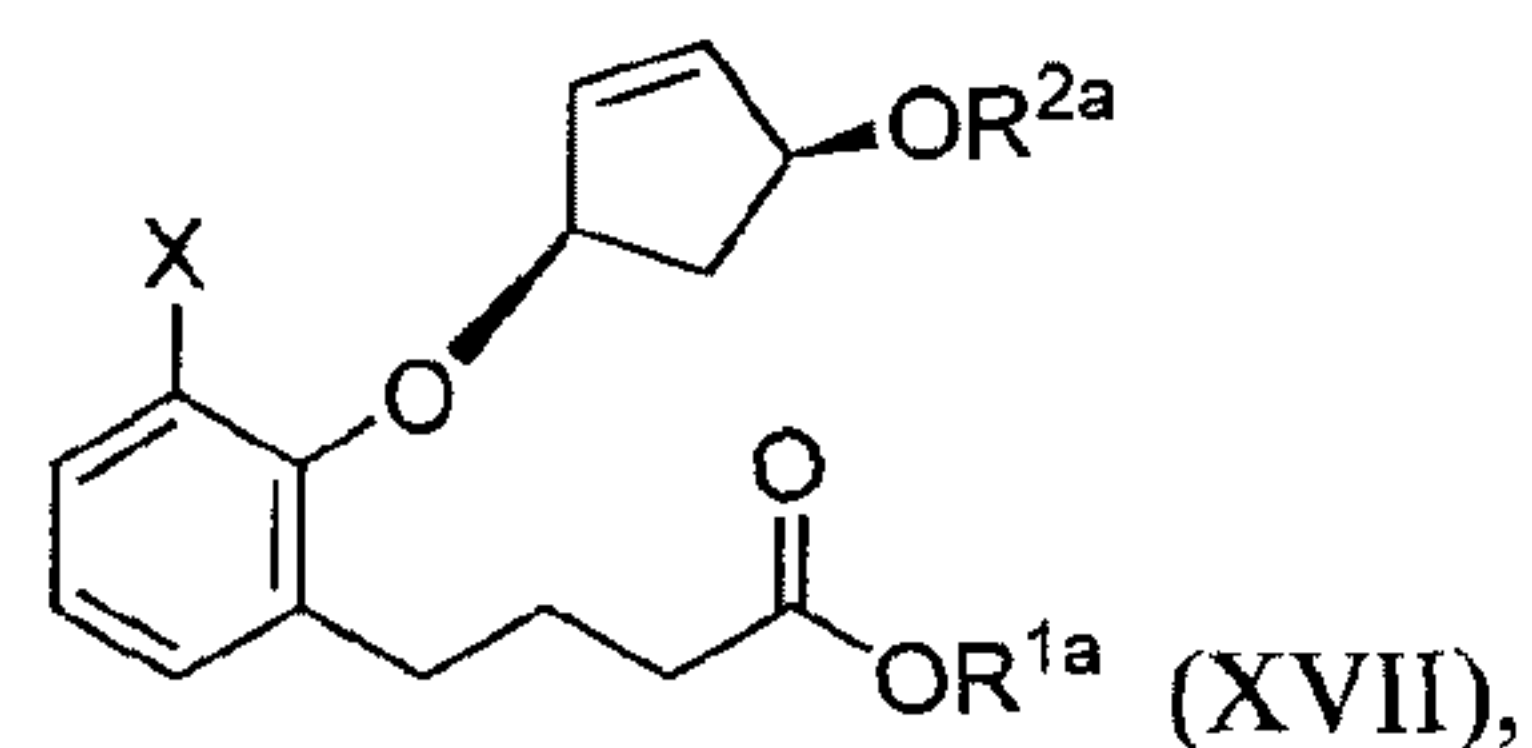
, wherein R^{2a} is H or an hydroxy protective group,

with a compound of formula:



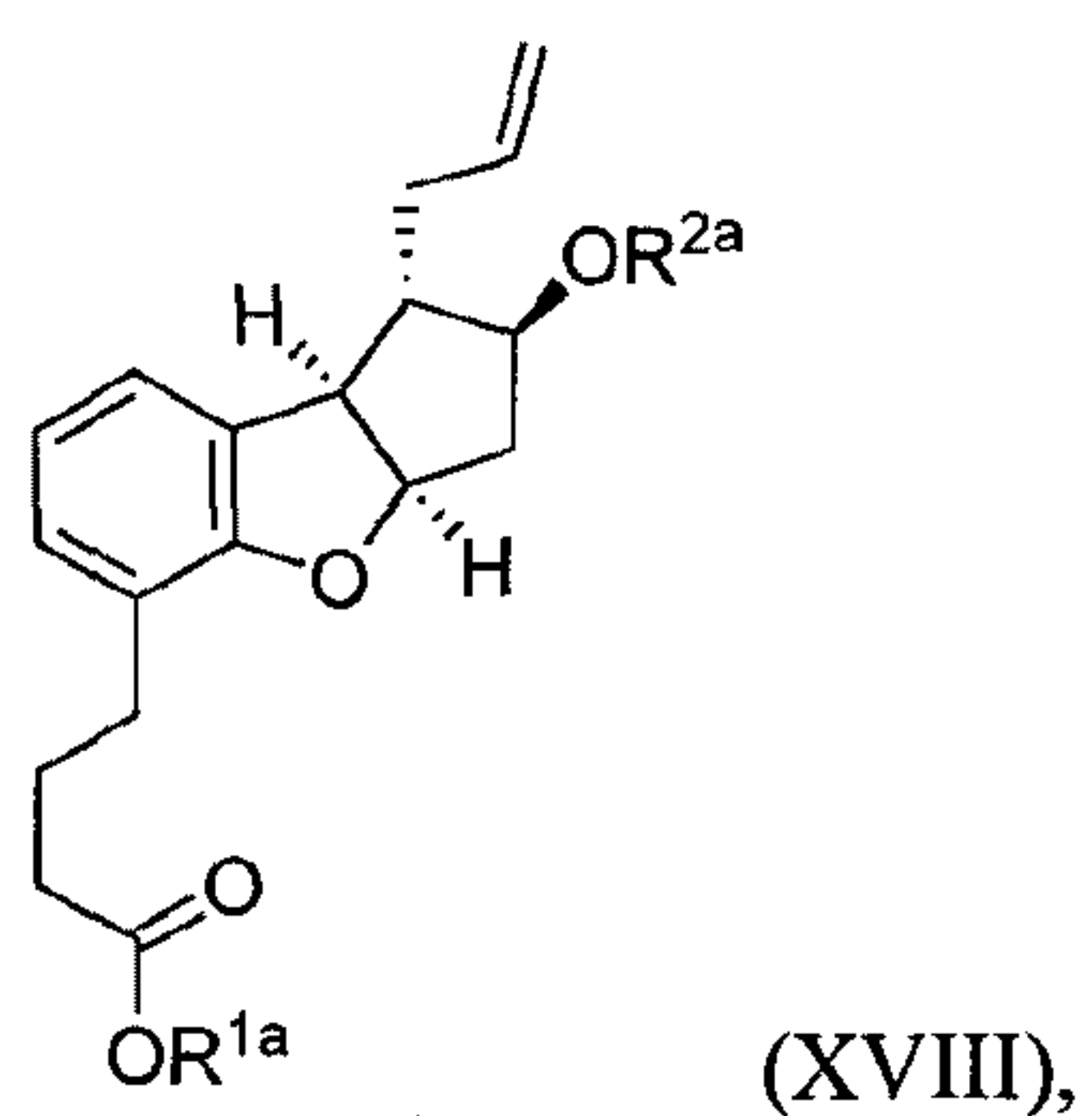
wherein R^{1a} is a cation, H, or C_{1-12} alkyl, X is a halogen selected from chloro, bromo and iodo,

to form a compound of formula:



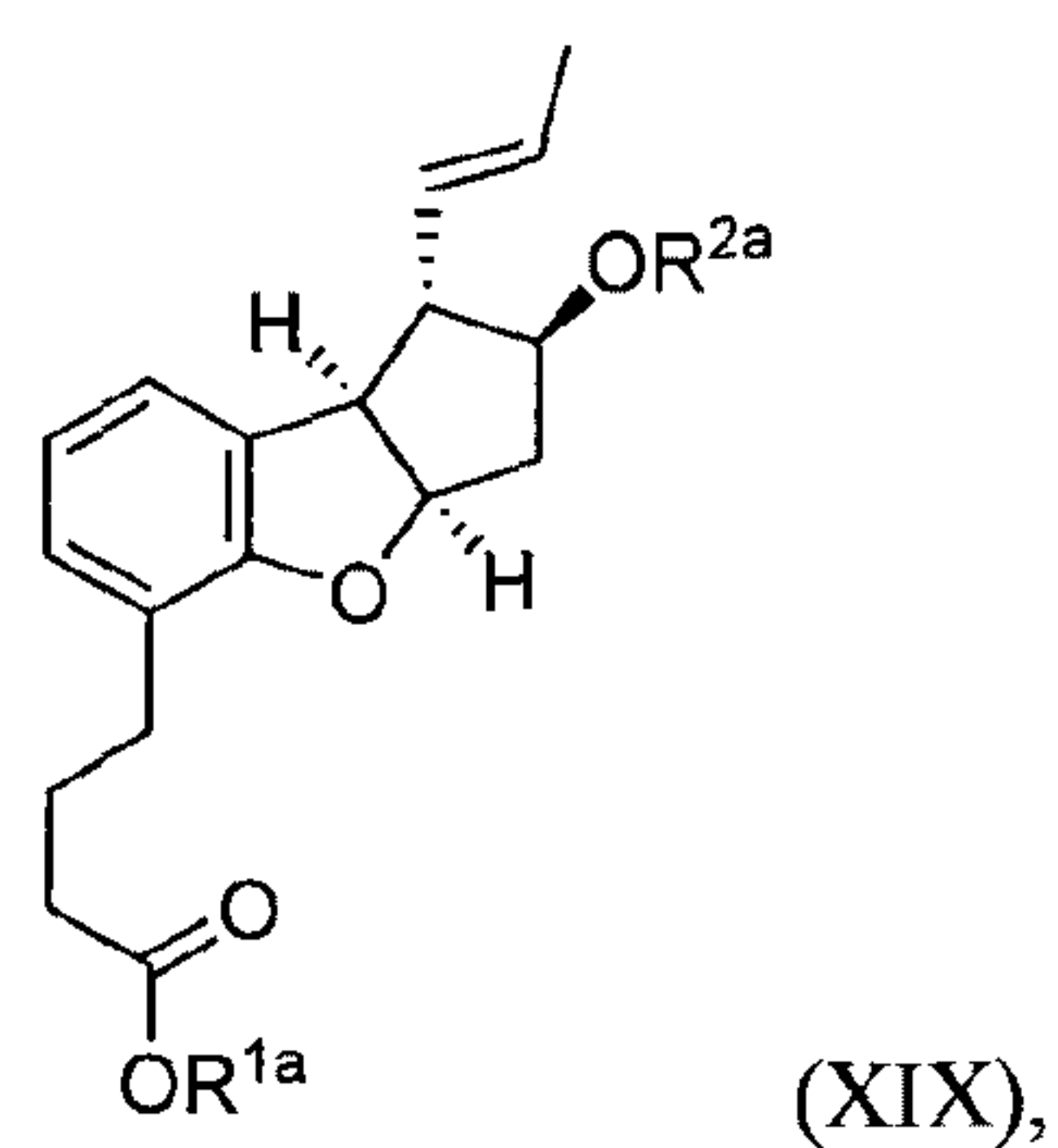
wherein R^{1a} , R^{2a} and X are each defined above;

(2) radical cyclizing and *in situ* trapping by reacting the compound of formula (XVII) with allyltributyltin using a radical initiator to form a compound of formula:



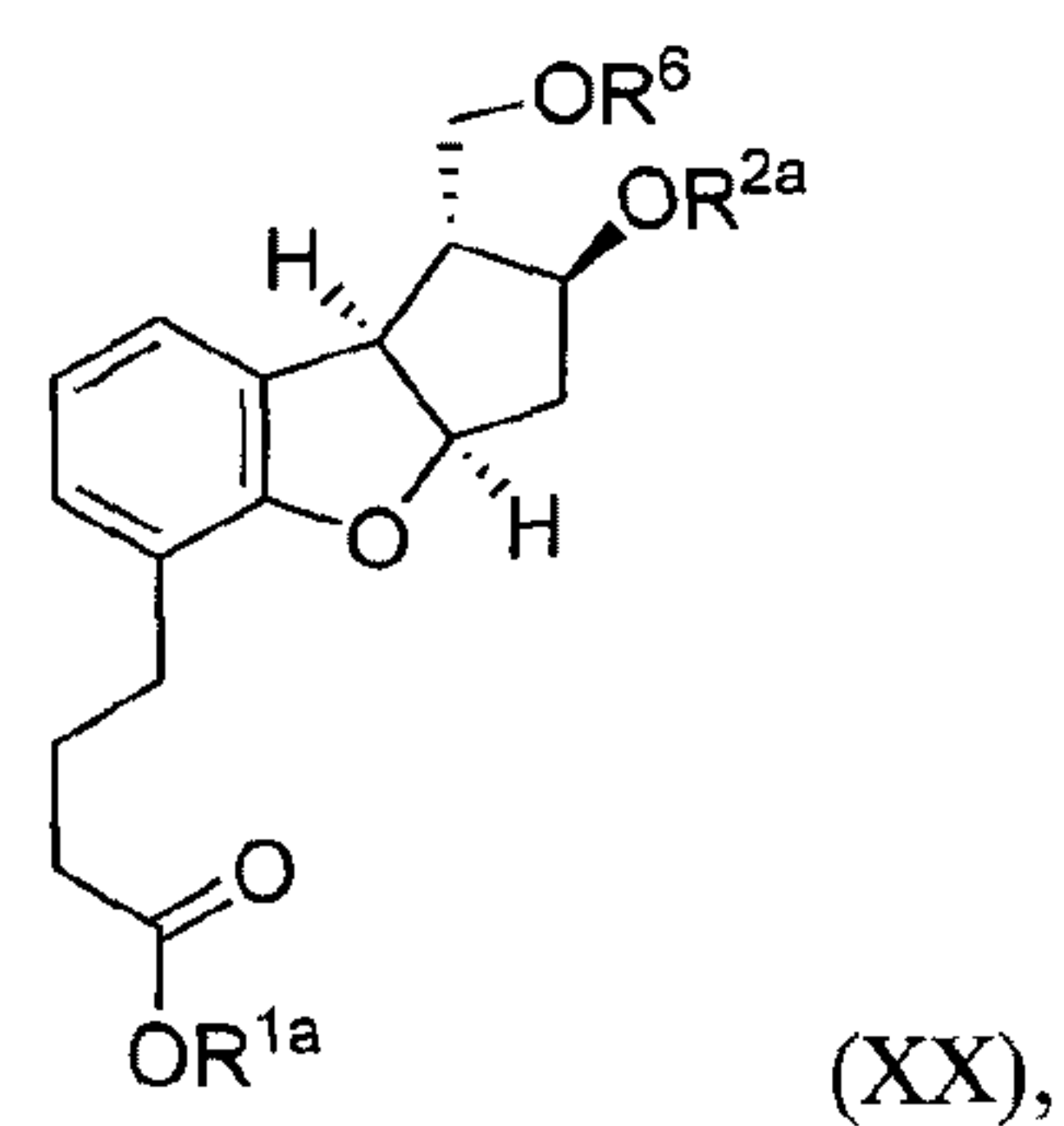
wherein R^{1a} and R^{2a} are each defined above;

(3) isomerizing an allyl of the compound of formula (XVIII) to form a propenyl resulting in a compound of formula:



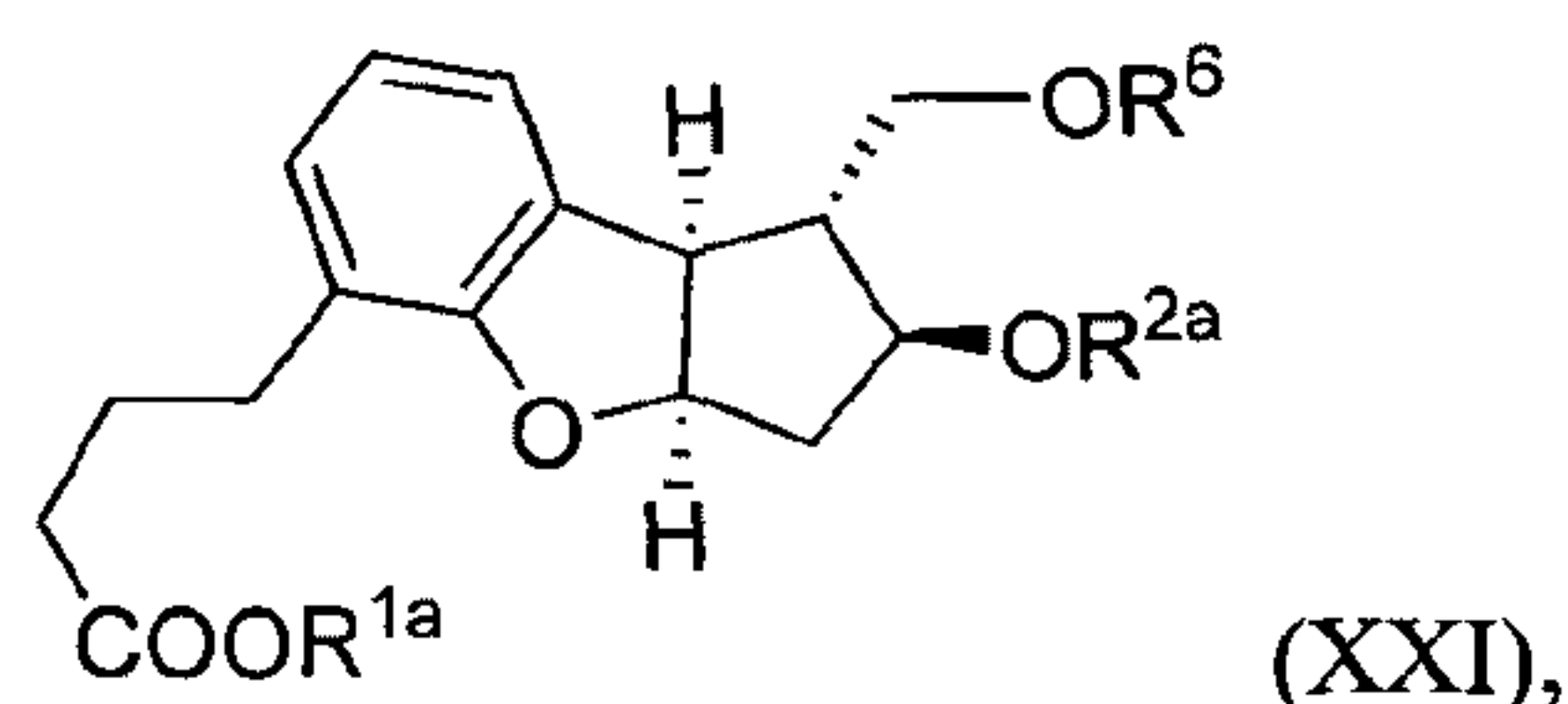
wherein R^{1a} and R^{2a} are each defined above;

(4) ozonolysis and *in situ* reduction to convert the propenyl of the compound of formula (XIX) to form an alcohol resulting in a compound of formula:



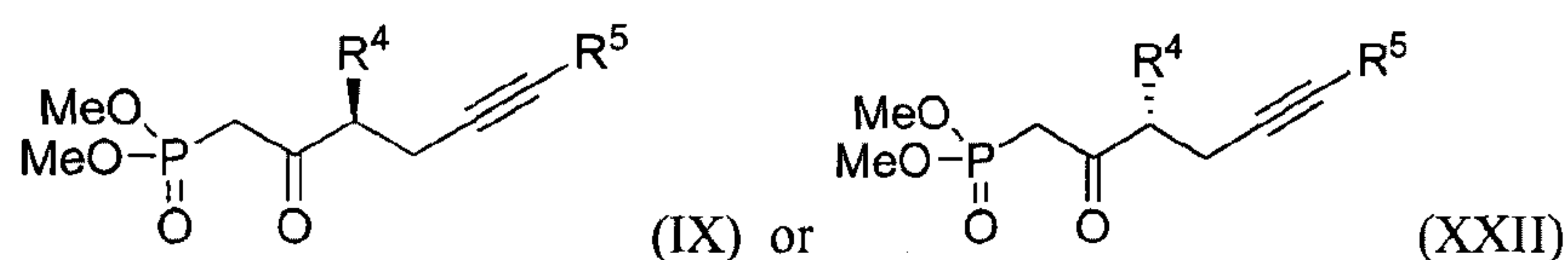
wherein R^{1a} and R^{2a} are each defined above, R^6 is H or a hydroxy protective group;

(5) deprotecting the compound of formula (XX) to form a compound of formula:

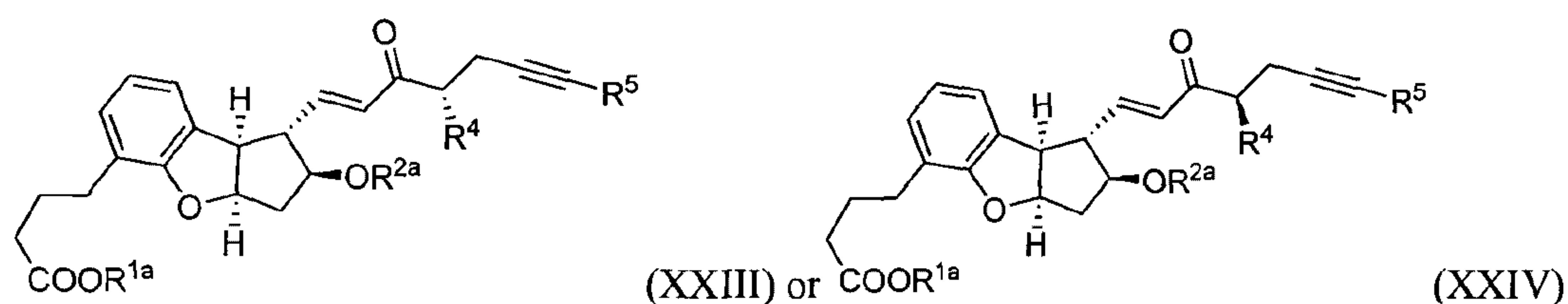


wherein R^{1a} and R^6 are each defined above, R^{2a} is H;

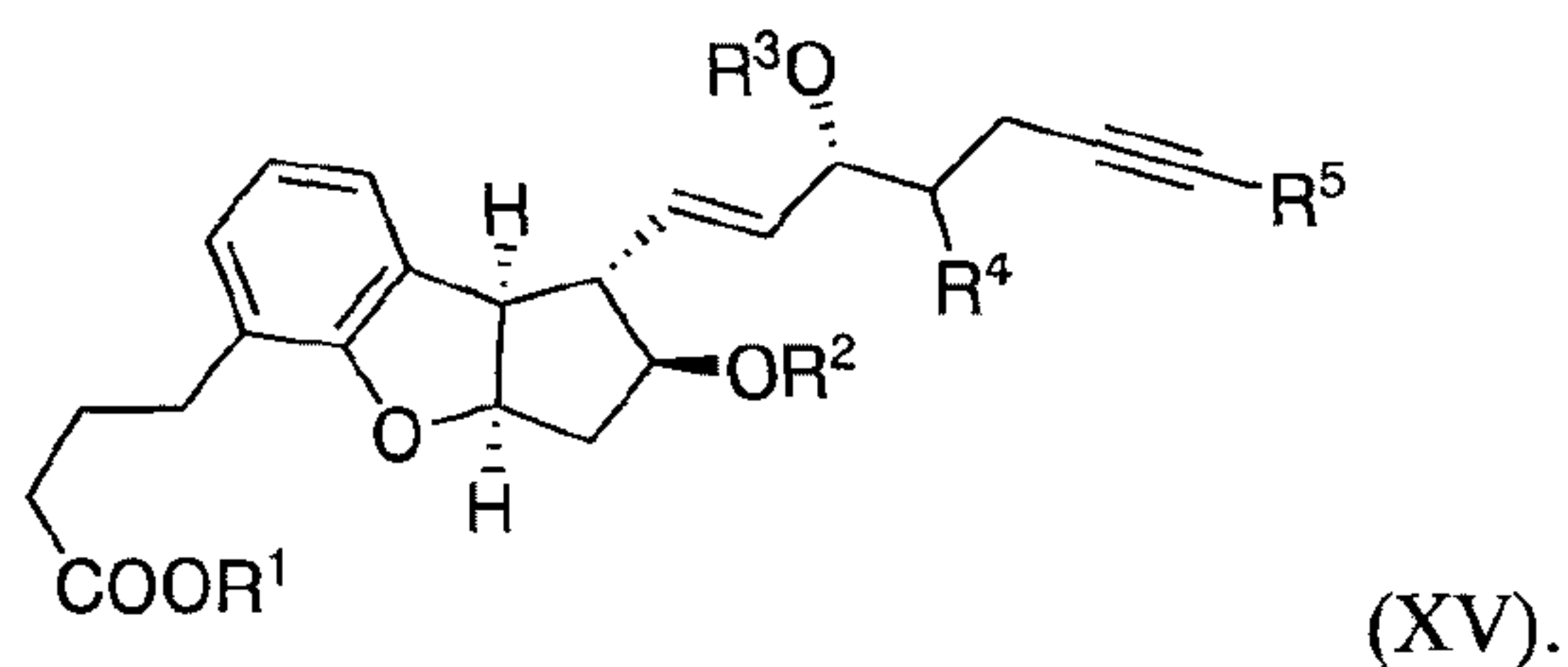
(6) selectively deprotecting the primary hydroxy protective group, followed by oxidation of the primary hydroxy group to form an aldehyde, followed by coupling with a side-chain of the formula:



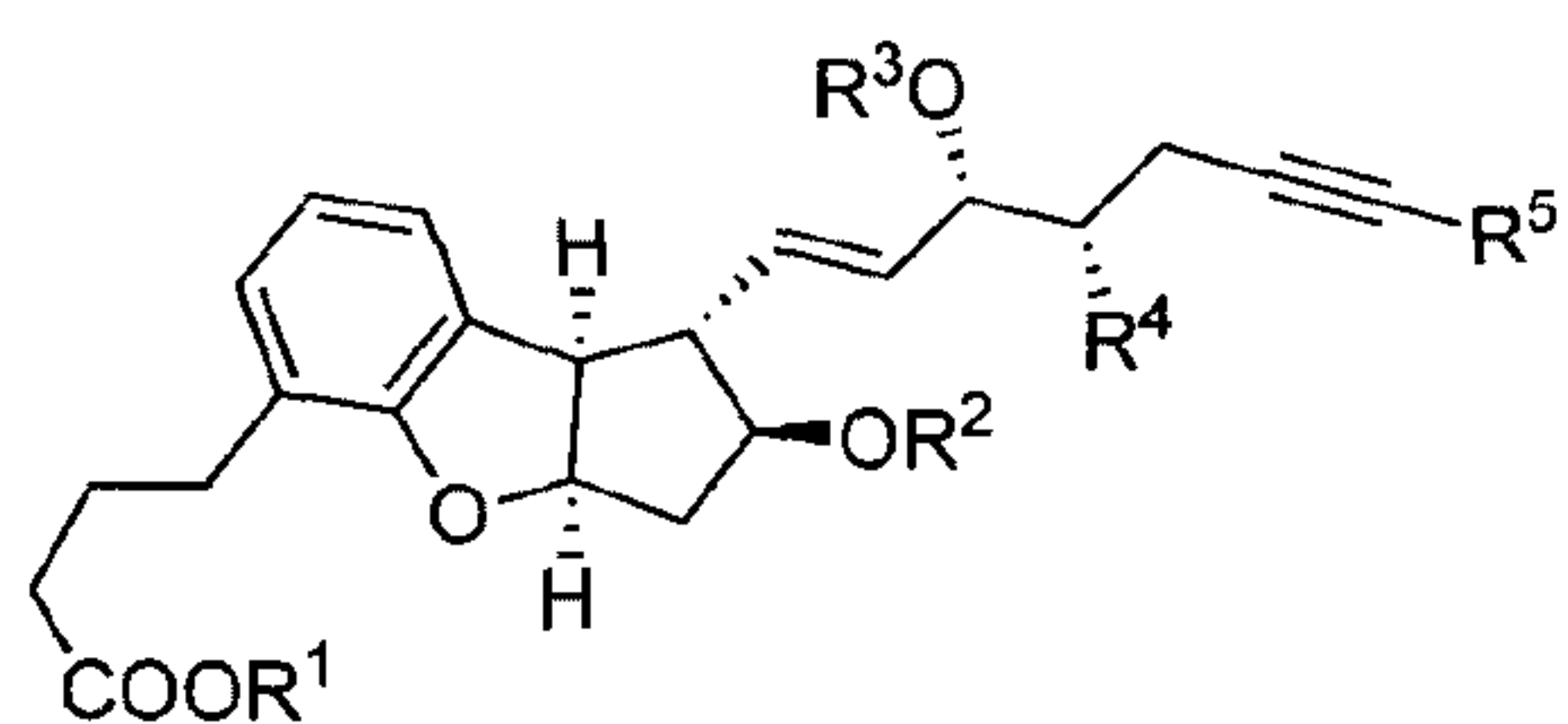
wherein R^4 and R^5 are each defined above to form a compound of formula:



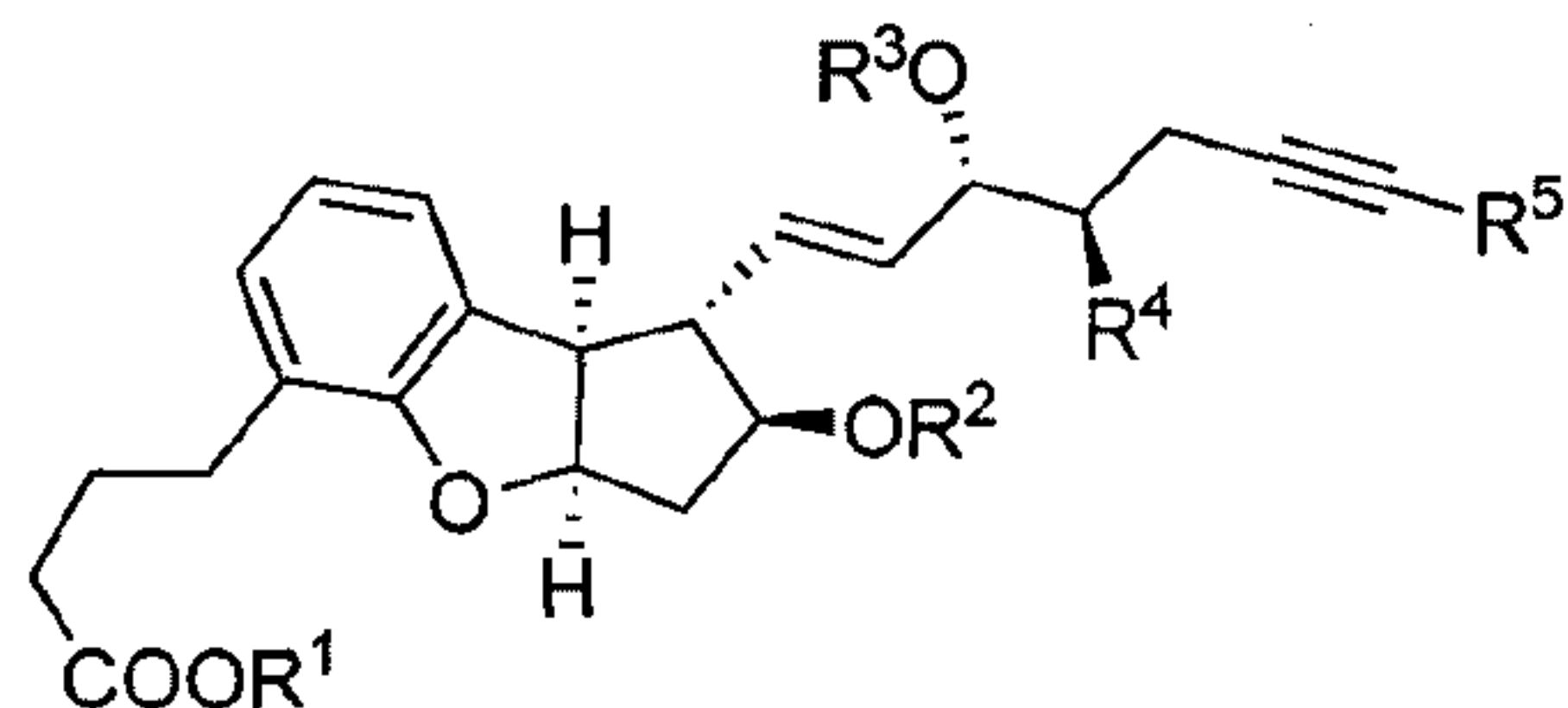
(7) reduction of the ketone, deprotection of any remaining hydroxy protective group and optionally converting the R^{1a} into a cation or H to form a compound of formula:



24. The process of claim 23, wherein the compound of formula (XV) is produced as an isomer of formula:



(XXV) or



(XXVI) having an isomeric purity of greater than 90%.

25. The process of claim 16, wherein R^2 , R^3 , R^{2a} and R^6 each independently represent acetate, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, phenyldimethylsilyl, tetrahydropyranyl, benzoate ester, benzyl, or substituted benzyl.
26. The process of claim 23, wherein R^{1a} is CH_3 and R^{2a} and R^6 are both H.
27. The process of claim 23, wherein the radical initiator is azobisisobutyronitrile.
28. The process of claim 23, wherein a catalytic amount of carbonylchlorohydridotris(triphenylphosphine) ruthenium (II) is used in step (3).
29. The process of claim 23, wherein sulfuric acid is used in step (5).

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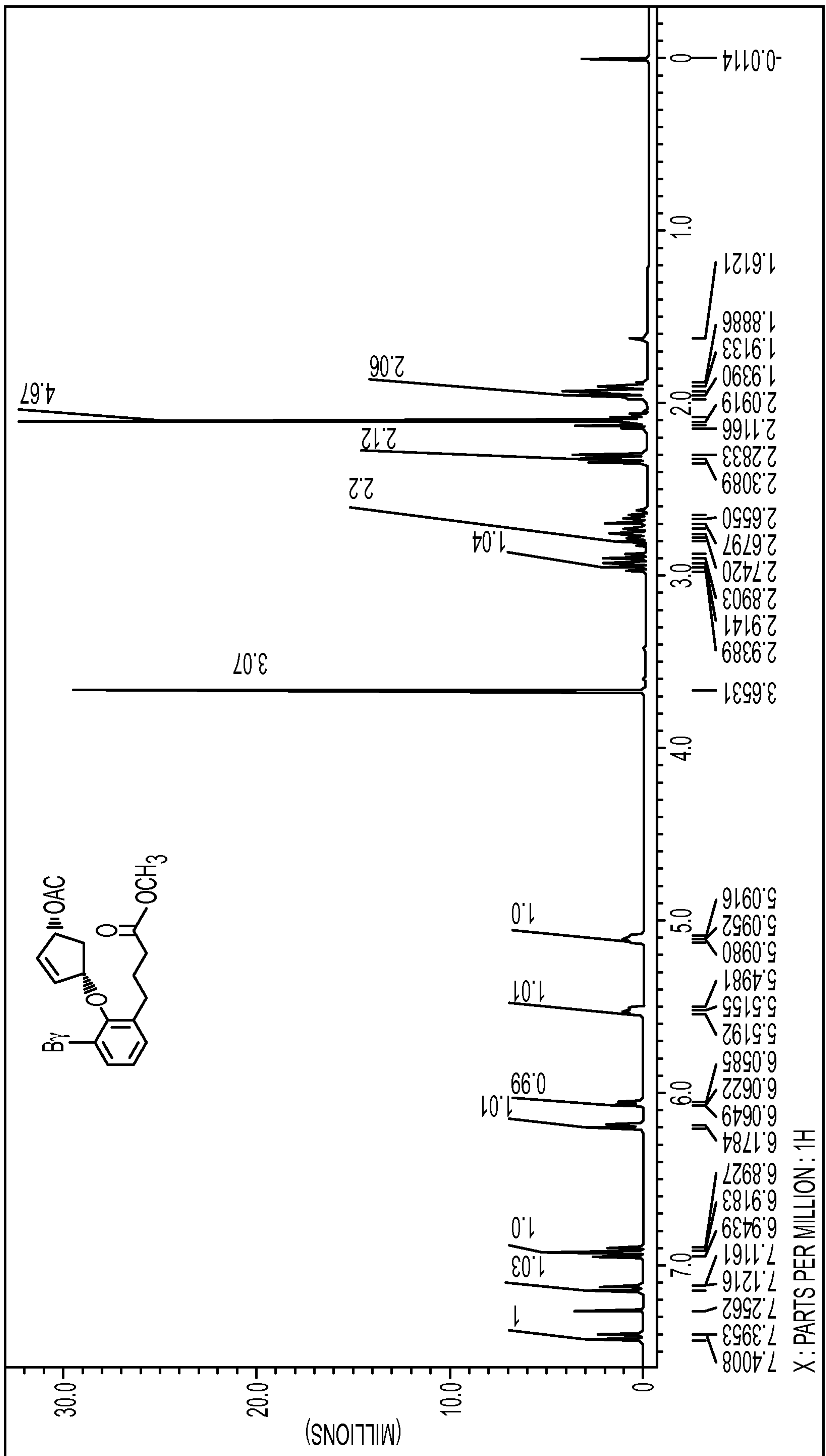


FIGURE 1

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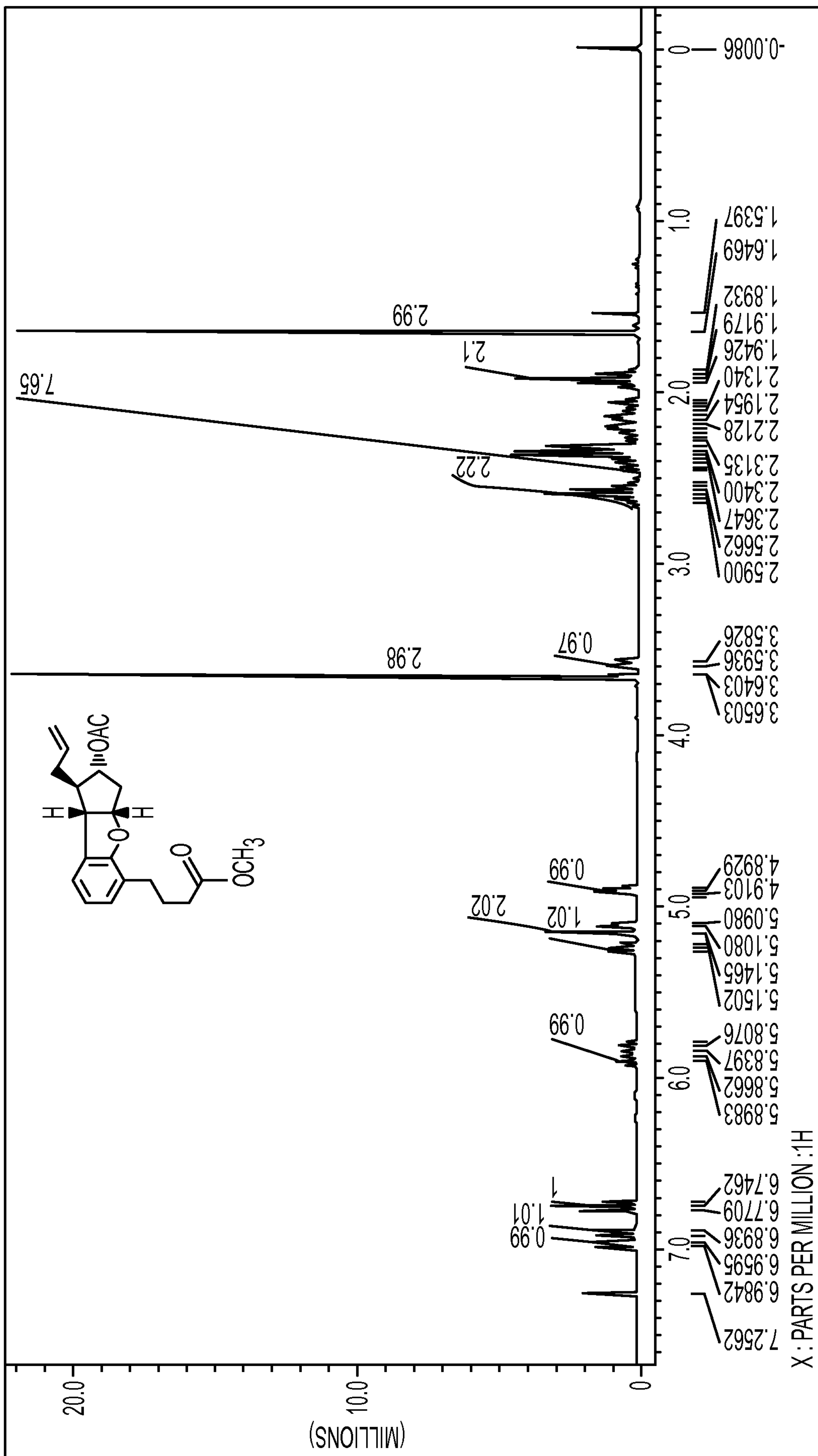
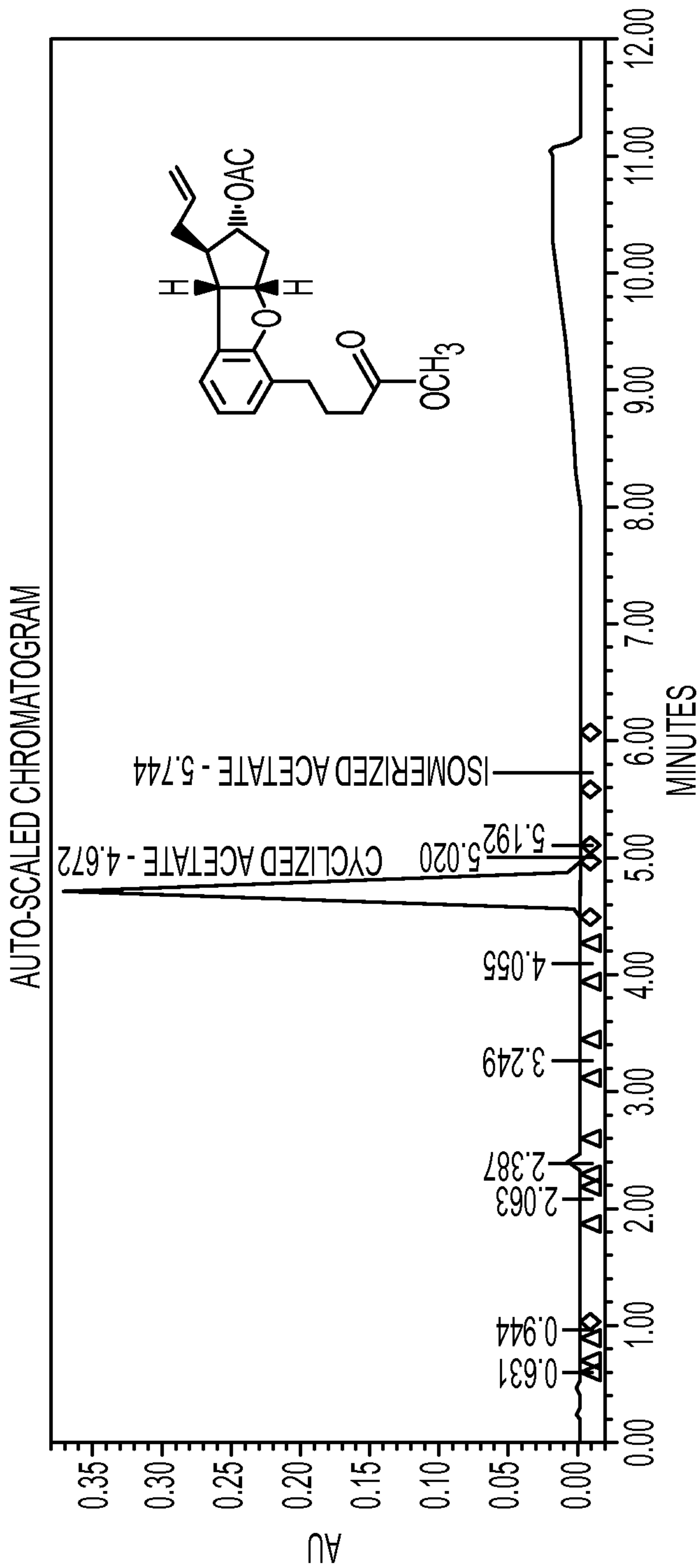


FIGURE 2



PEAK RESULTS

	NAME	RT	RT RATIO	AREA	% AREA
1		0.631		1750	0.05
2		0.944		494	0.02
3		2.063		5328	0.16
4		2.387		53621	1.64
5		3.249		4018	0.12
6		4.055		12670	0.39
7	CYCLIZED ACETATE	4.672		3116438	95.52
8		5.020		15031	0.46
9		5.192		41032	1.26
10	ISOMERIZED ACETATE	5.744		12125	0.37

FIGURE 3

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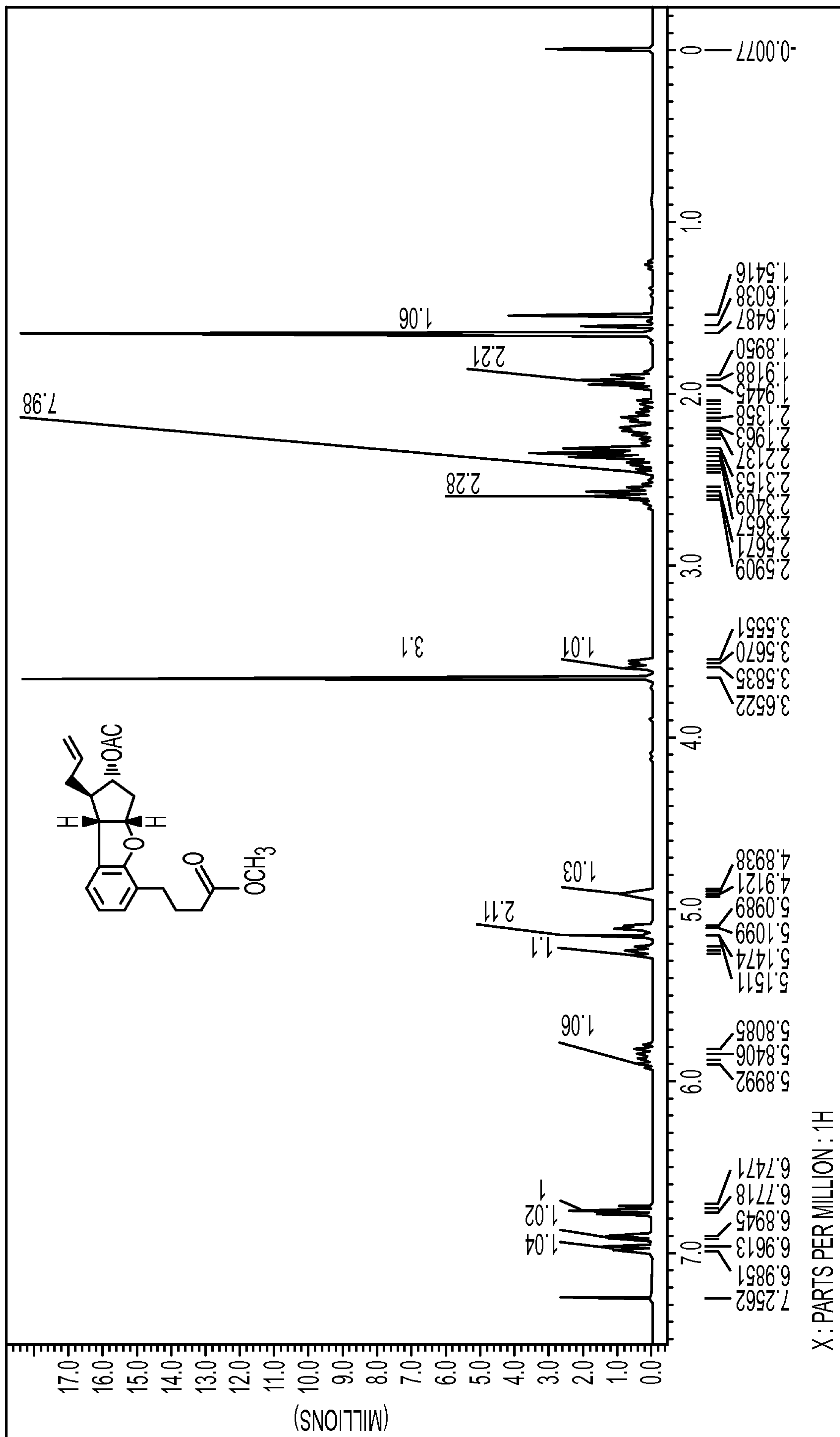


FIGURE 4

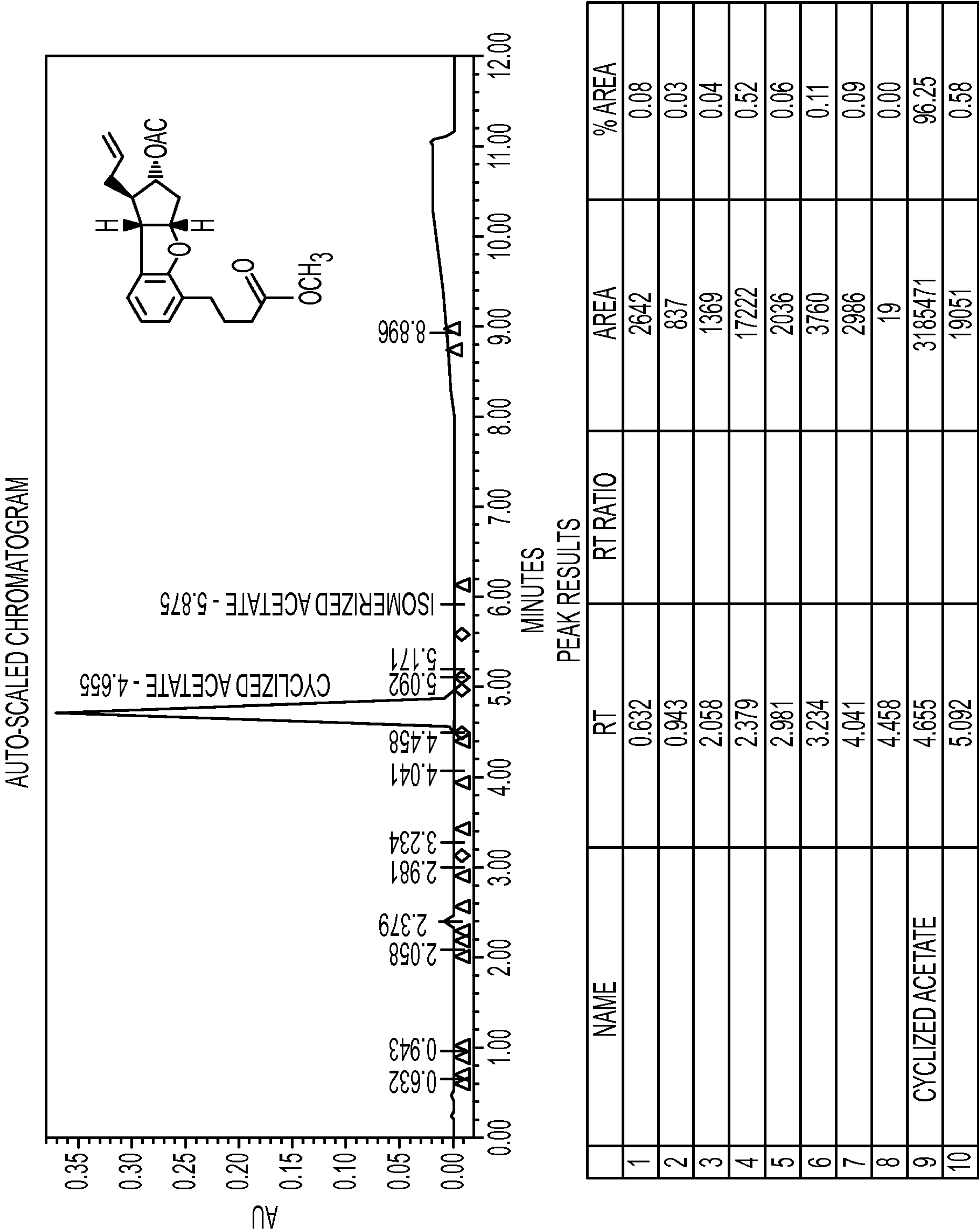


FIGURE 5

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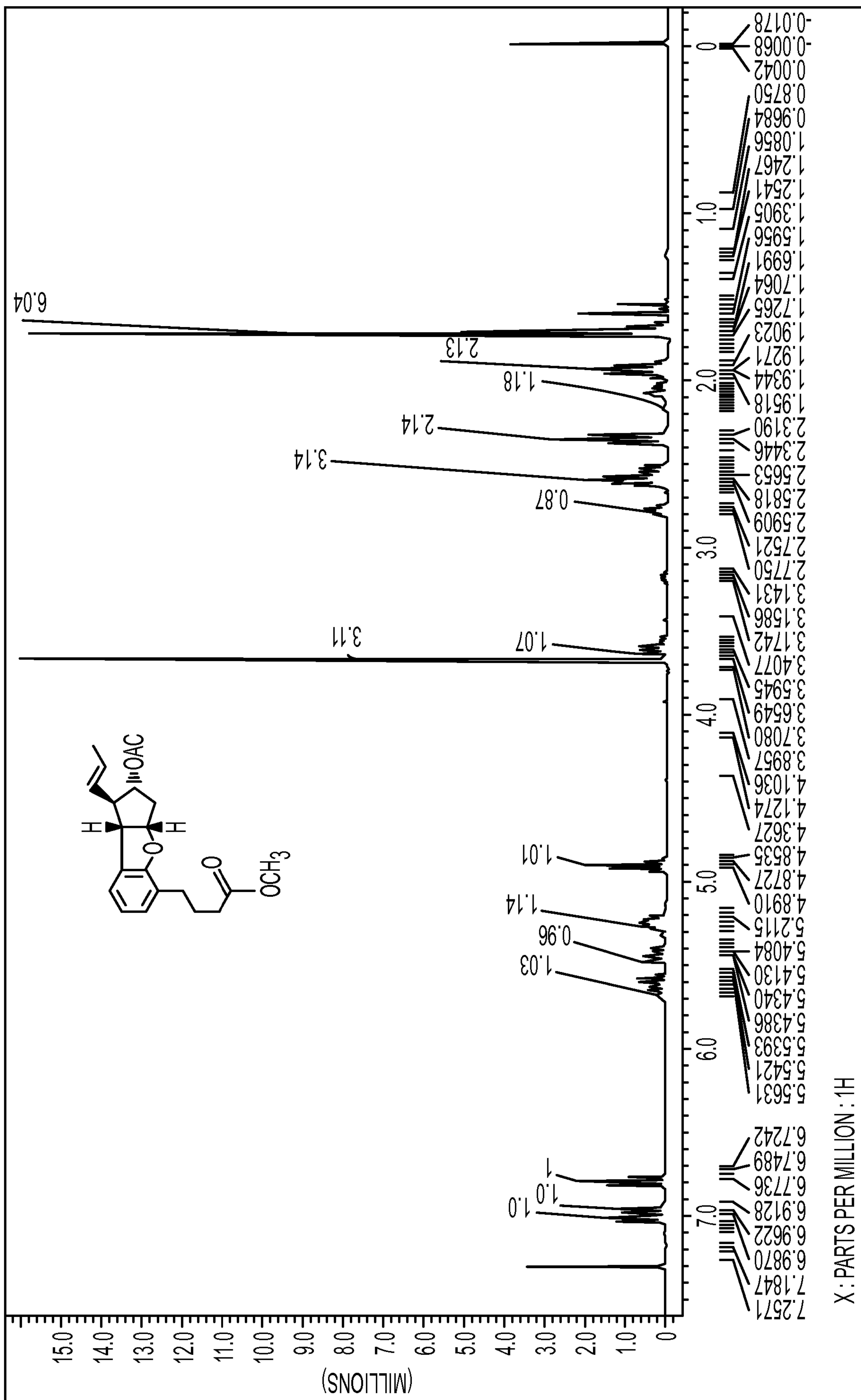


FIGURE 9

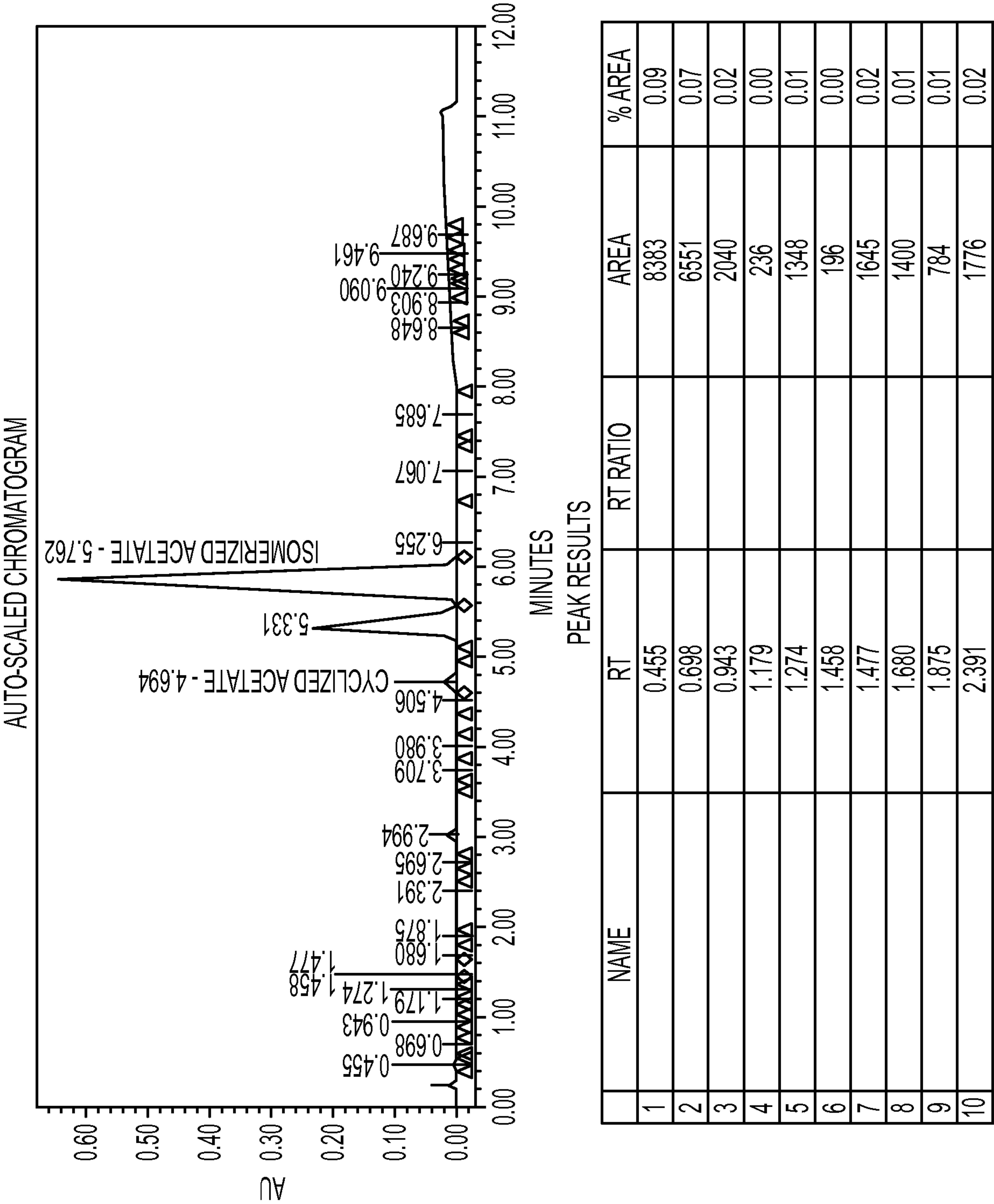


FIGURE 7(a)

PEAK RESULTS

	NAME	RT	RT RATIO	AREA	% AREA
11		2.695		481	0.00
12		2.994		104376	1.07
13		3.709		1753	0.02
14		3.980		7424	0.08
15		4.506		21390	0.22
16	CYCLIZED ACETATE	4.694		145685	1.49
17	E/Z ISOMER	5.331		2011715	20.53
18	E/Z ISOMER ISOMERIZED ACETATE	5.762		7285735	74.34
19		6.255		70069	0.71
20		7.067		22444	0.23
21		7.685		58191	0.59
22		8.648		2315	0.02
23		8.903		23640	0.24
24		9.090		7751	0.08
25		9.240		3040	0.03
26		9.461		2566	0.03
27		9.687		7102	0.07

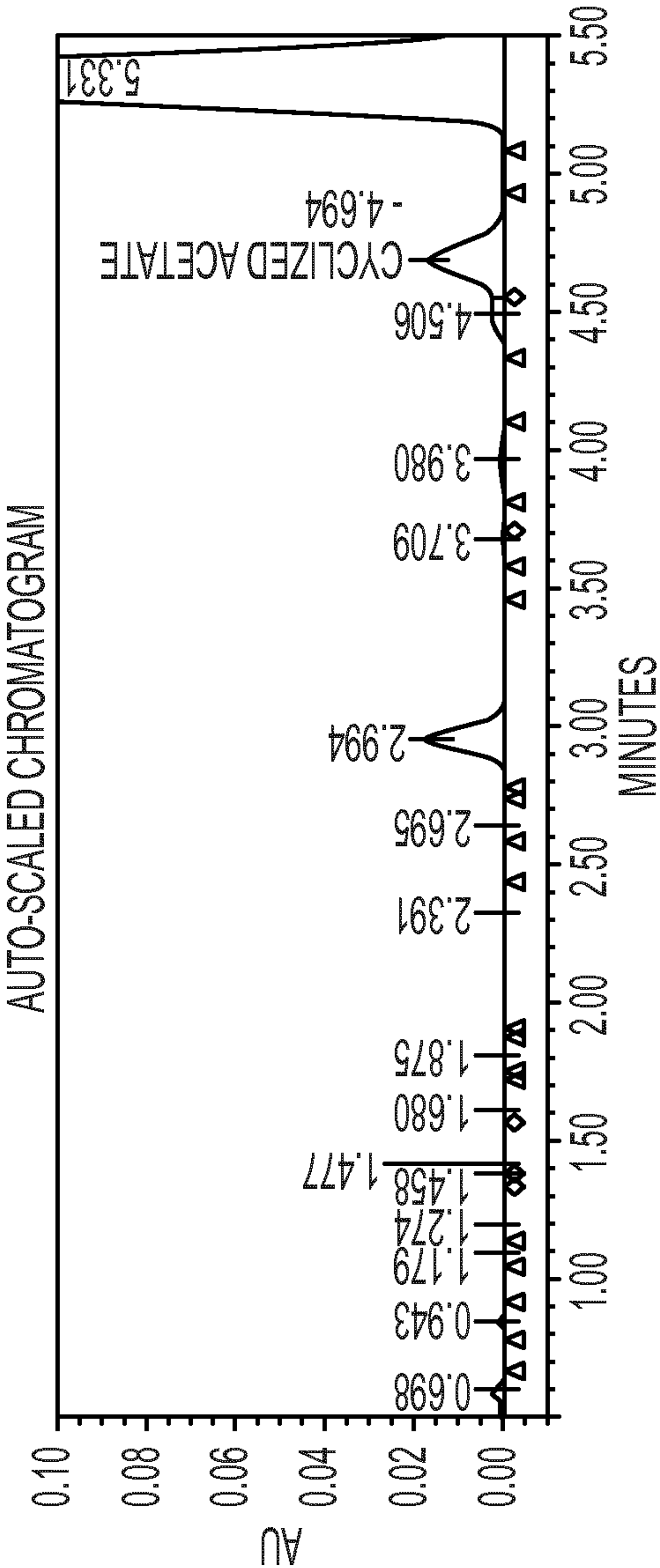


FIGURE 7(b)

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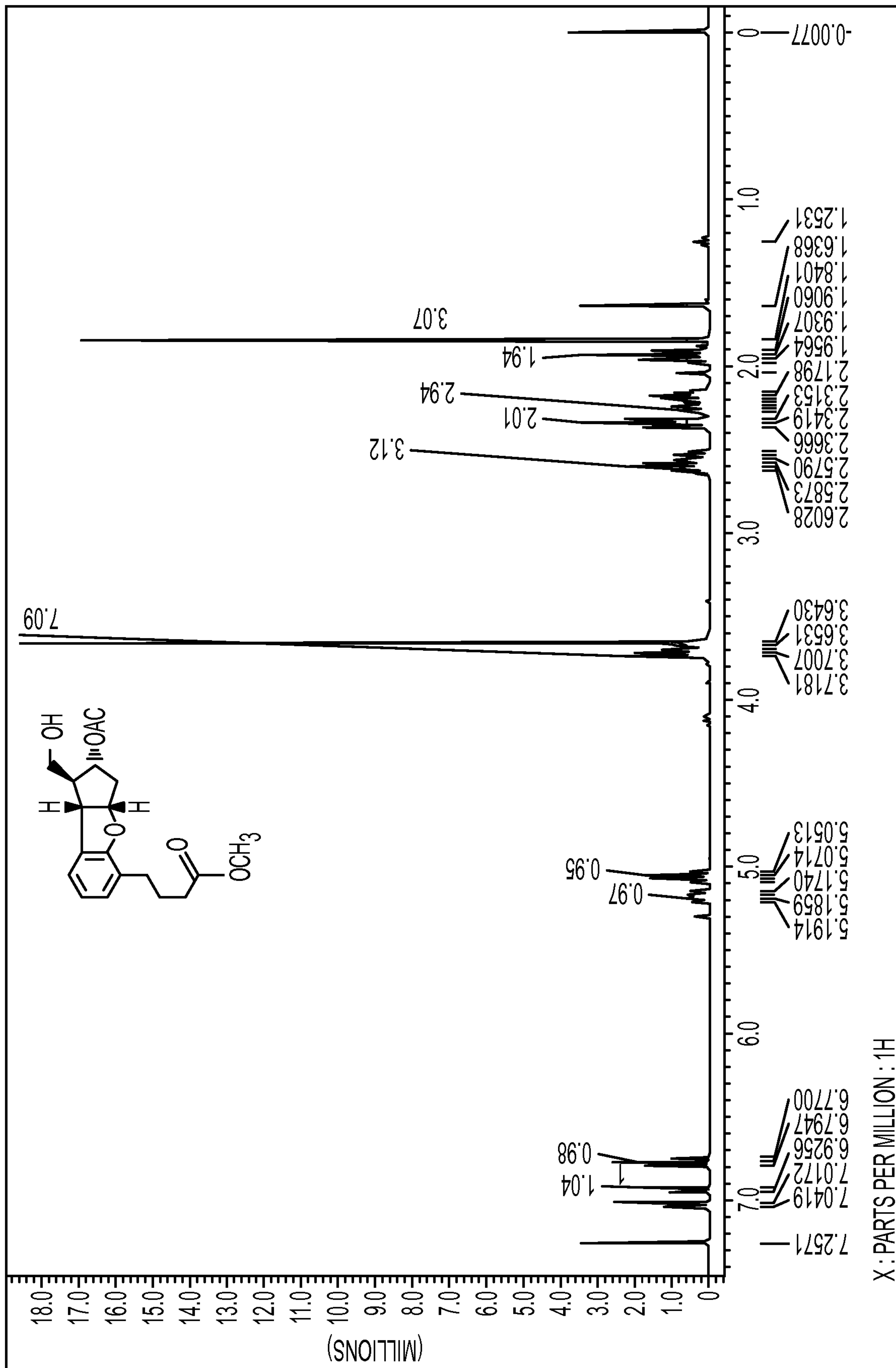
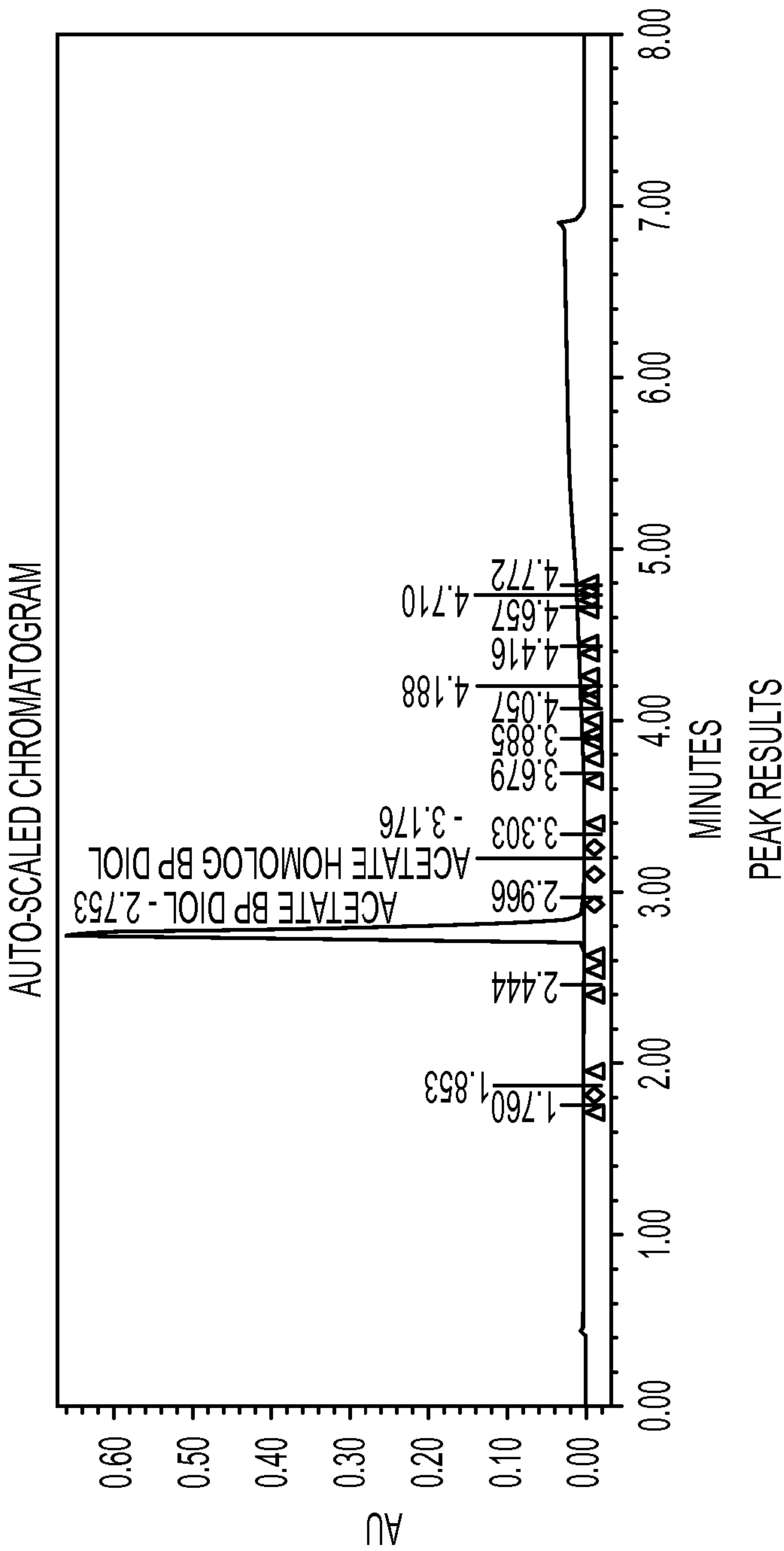


FIGURE 8

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PEAK RESULTS

	NAME	RT	RT RATIO	AREA	% AREA
1		1.760		4002	0.12
2		1.853		2273	0.07
3		2.444		1780	0.05
4	ACETATE BPdiol	2.753		3336514	97.74
5		2.966		22669	0.66
6	ACETATE HOMOLOG EPdiol	3.176		23936	0.70
7		3.303		5640	0.17
8		3.679		3447	0.10
9		3.865		542	0.02
10		4.057		5259	0.15

FIGURE 9(a)

PEAK RESULTS				
	NAME	RT	RT RATIO	% AREA
11		4.188		0.05
12		4.416		0.01
13		4.657		0.01
14		4.710		0.02
15		4.772		0.12

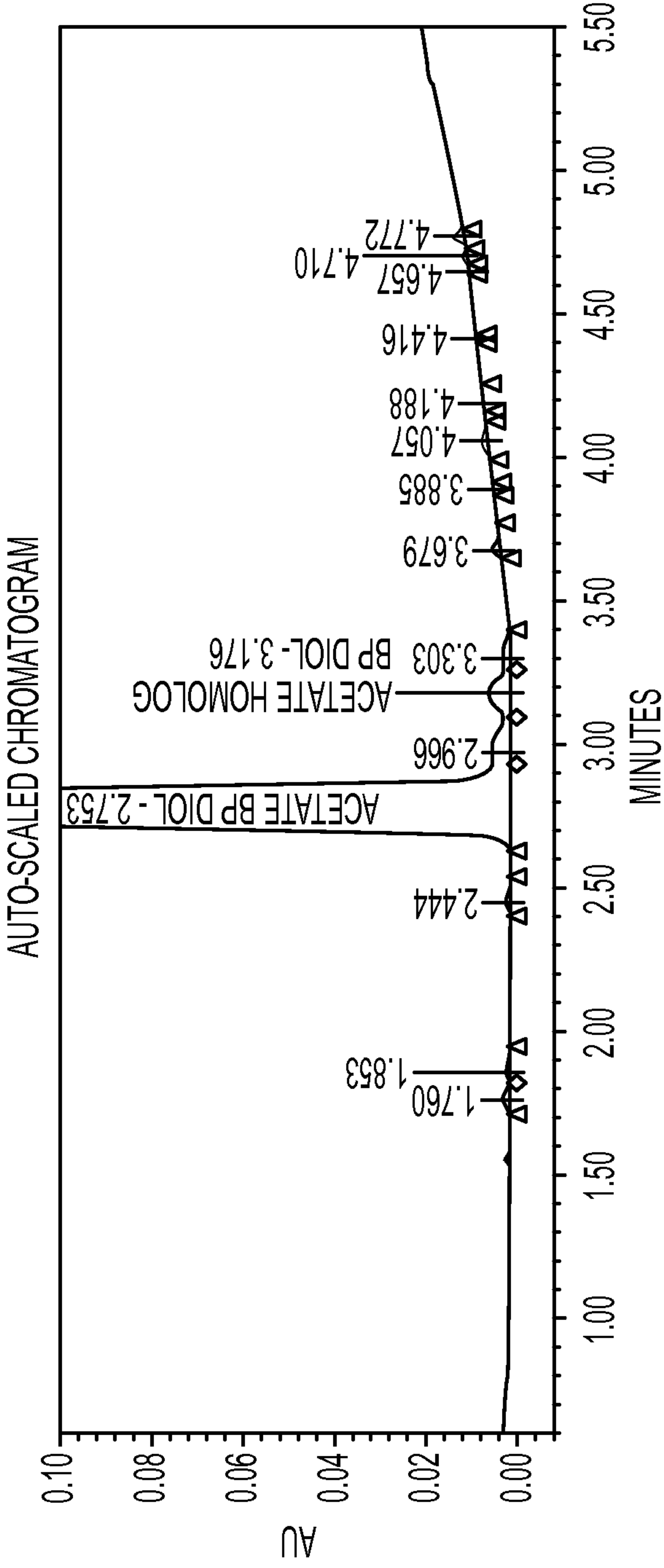


FIGURE 9(b)

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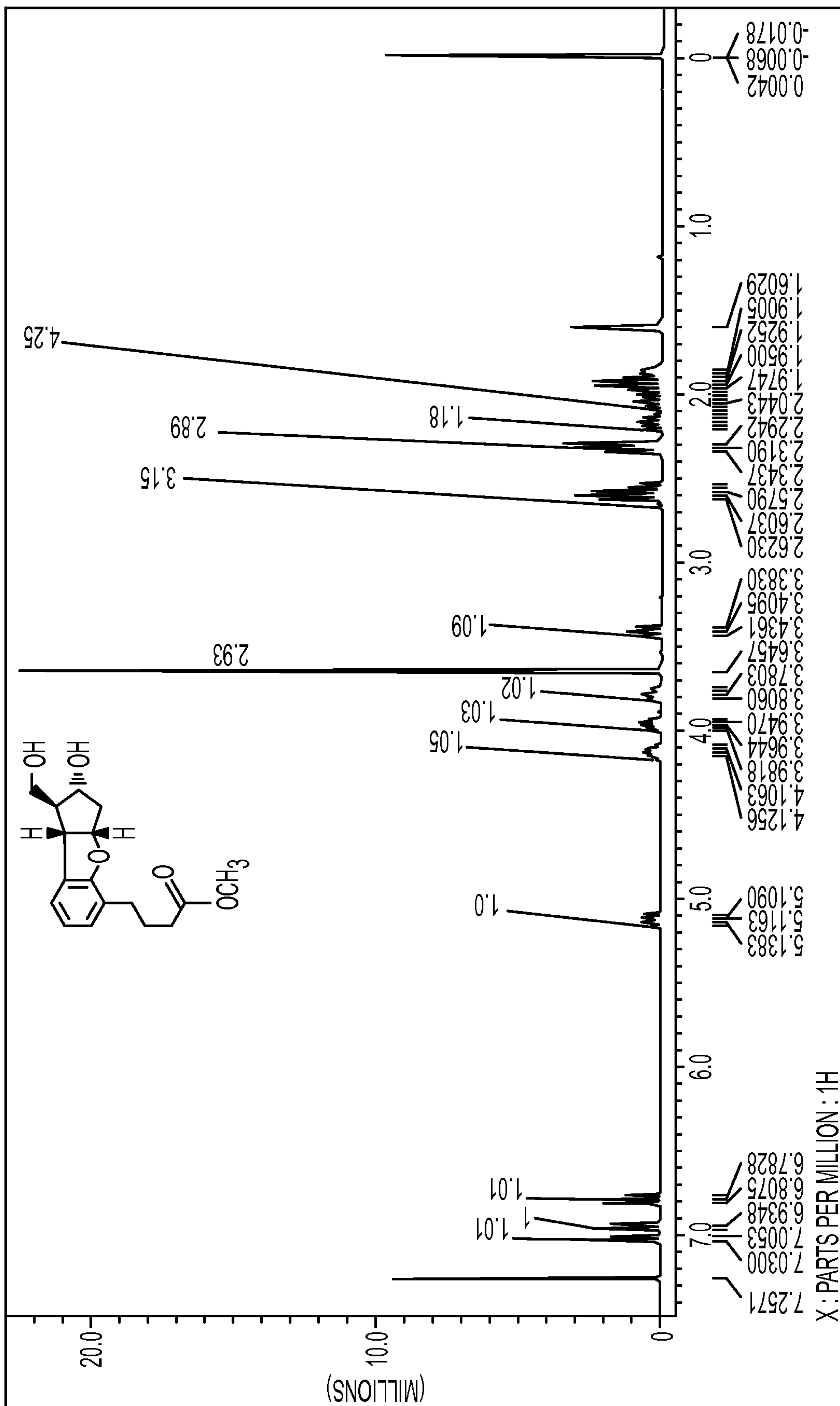
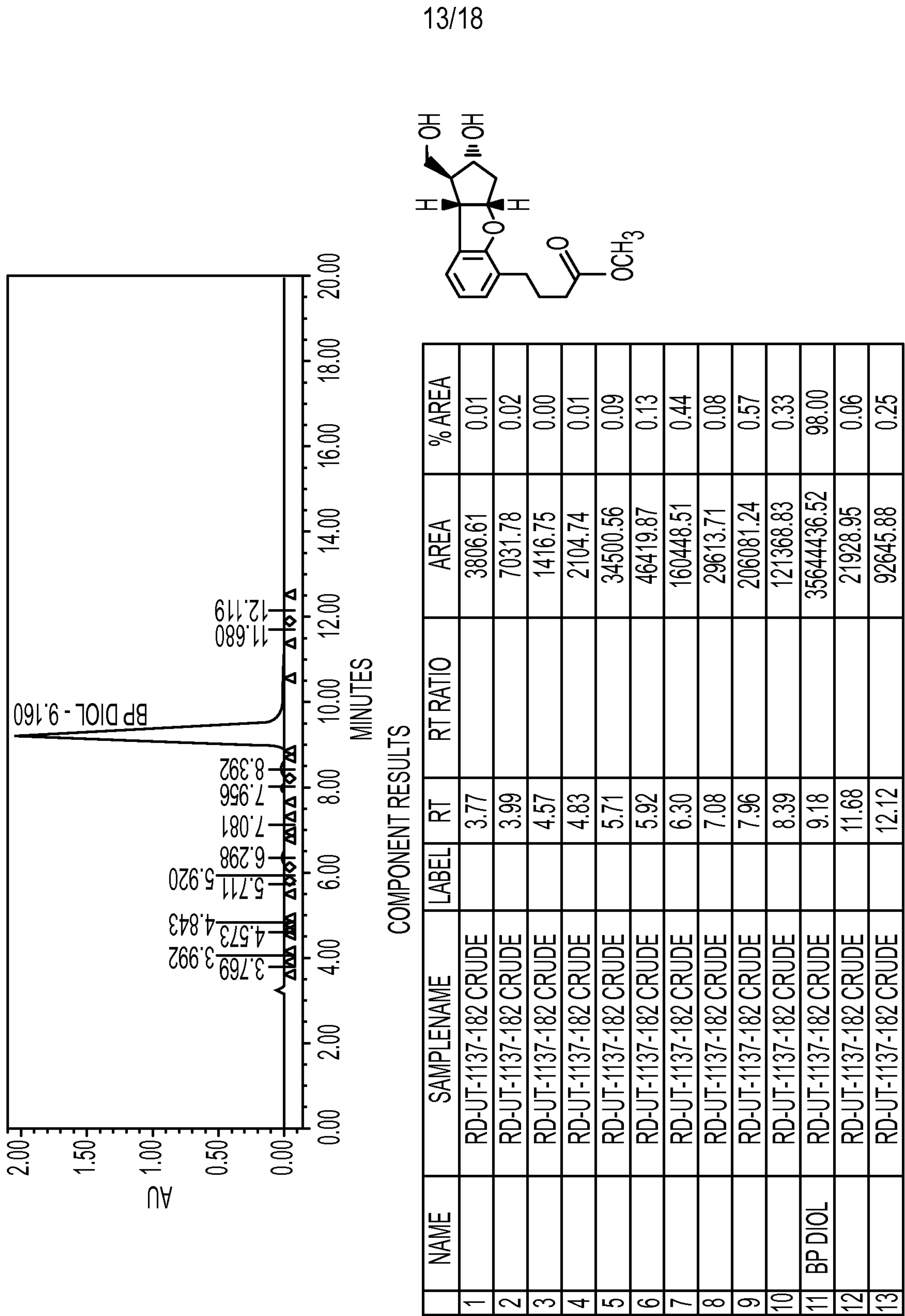
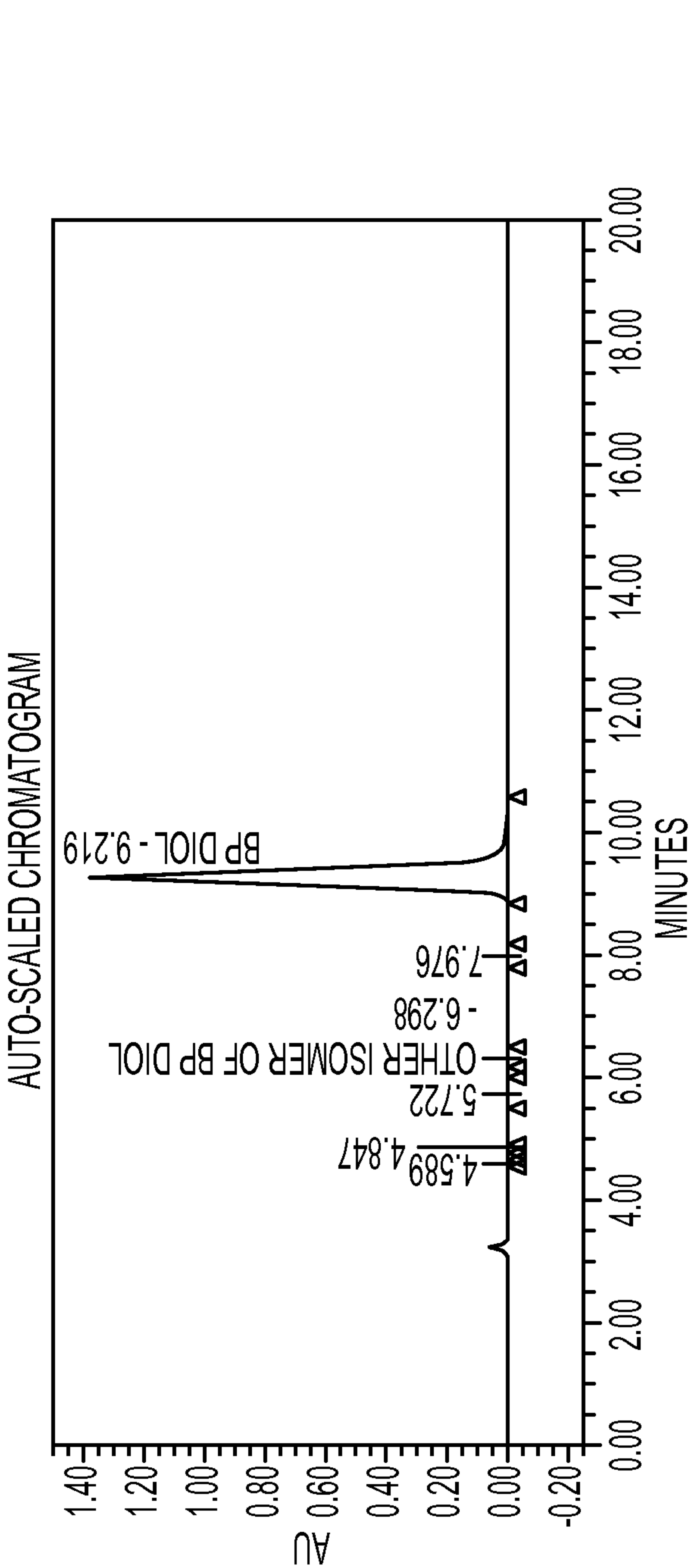


FIGURE 10





COMPONENT RESULTS

	NAME	SAMPLENAME	LABEL	RT	RT RATIO	AREA	% AREA
1		RD-UT-1137-182 CI		4.59		1435.40	0.01
2		RD-UT-1137-182 CI		4.85		1650.44	0.01
3		RD-UT-1137-182 CI		5.72		9118.61	0.04
4	OTHER ISOMER OF BP DIOL	RD-UT-1137-182 CI		6.30		5627.81	0.02
5		RD-UT-1137-182 CI		7.98		5667.95	0.02
6	BP DIOL	RD-UT-1137-182 CI		9.22		23337516.92	99.90

CO/C=C/C/Cc1ccc(O[C@H]2[C@@H](O)[C@H](O)C[C@H]2O)c1

FIGURE 12

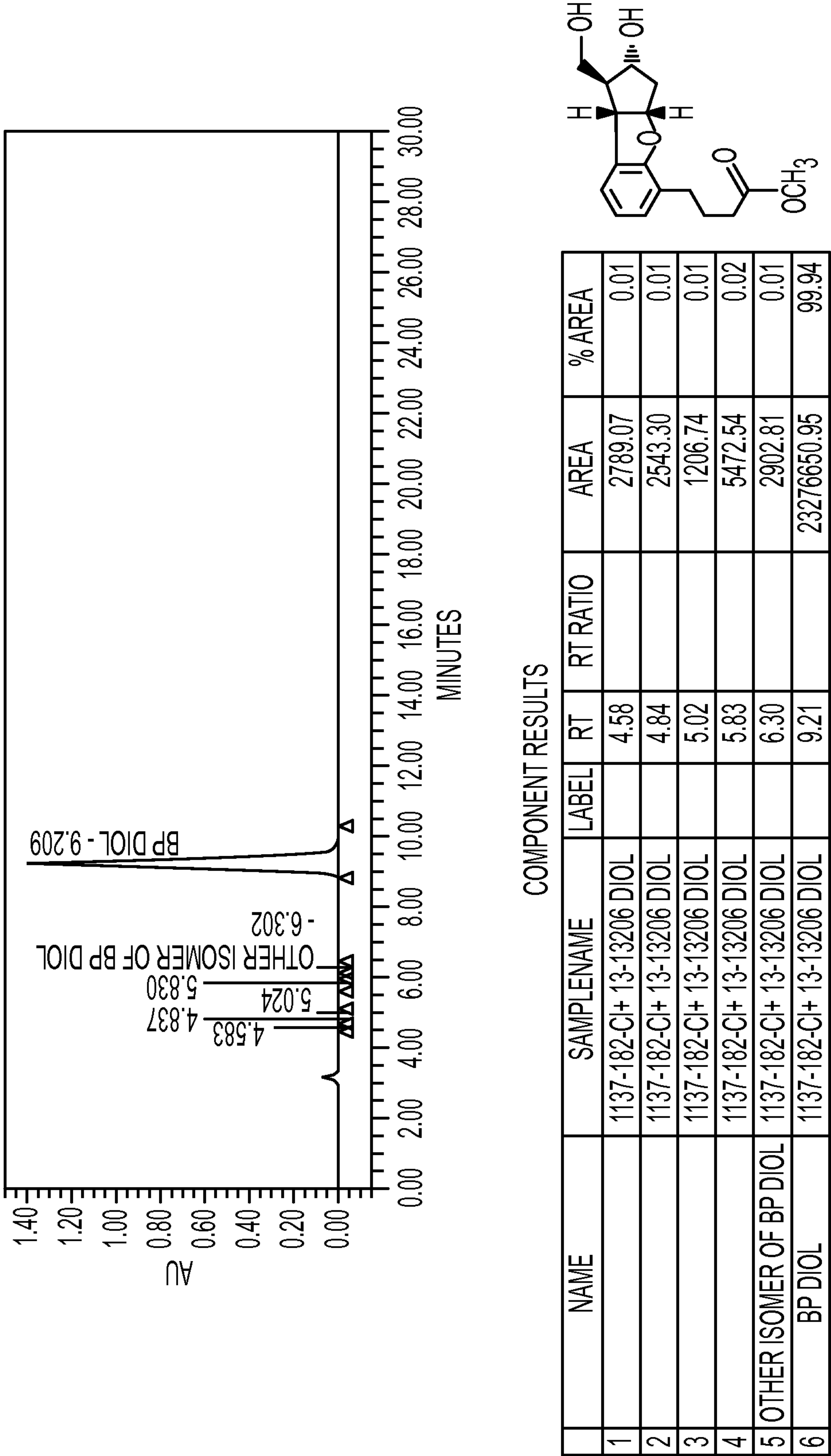
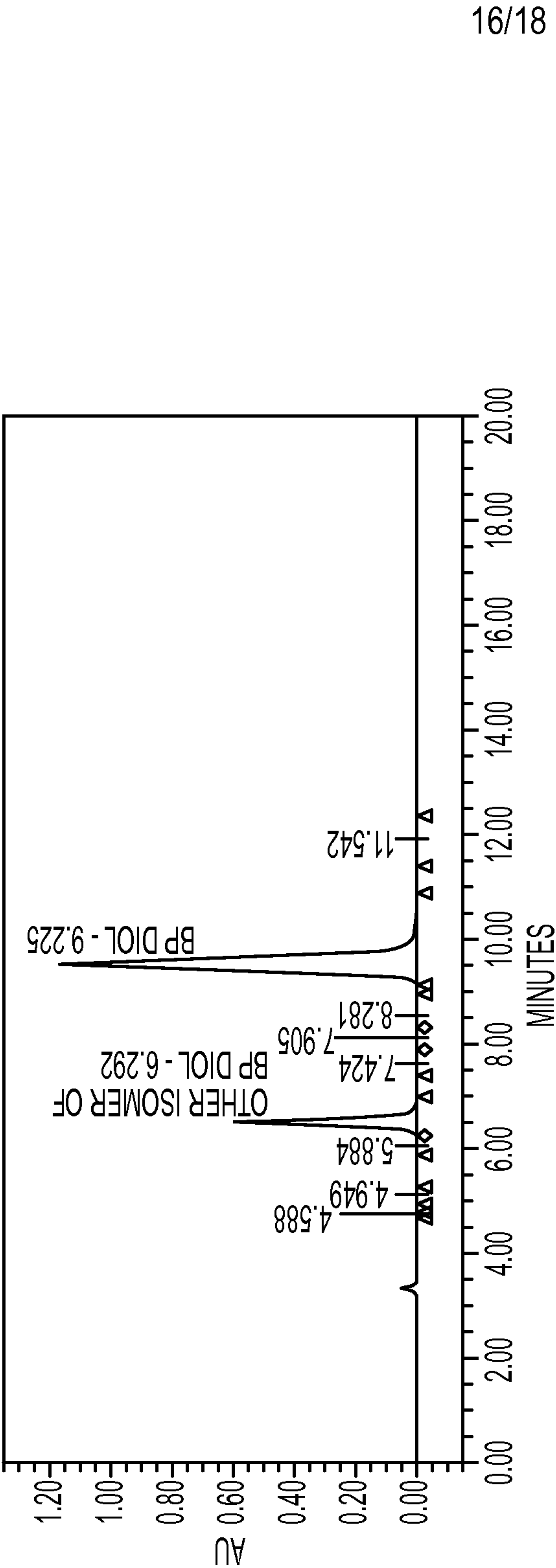


FIGURE 13



COMPONENT RESULTS

	NAME	SAMPLENAME	LABEL	RT	RT RATIO	AREA	% AREA
1		1137-182-CI+ RECEMIC 128		4.59		1854.88	0.01
2		1137-182-CI+ RECEMIC 128		4.95		15052.67	0.06
3		1137-182-CI+ RECEMIC 128		5.88		22937.42	0.09
4	OTHER ISOMER OF BP DIOL	1137-182-CI+ RECEMIC 128		6.29		5410981.83	22.24
5		1137-182-CI+ RECEMIC 128		7.42		17756.16	0.07
6		1137-182-CI+ RECEMIC 128		7.91		64606.30	0.27
7		1137-182-CI+ RECEMIC 128		8.28		78166.97	0.32
8	BP DIOL	1137-182-CI+ RECEMIC 128		9.22		18683280.24	76.78
9		1137-182-CI+ RECEMIC 128		11.54		39768.45	0.16

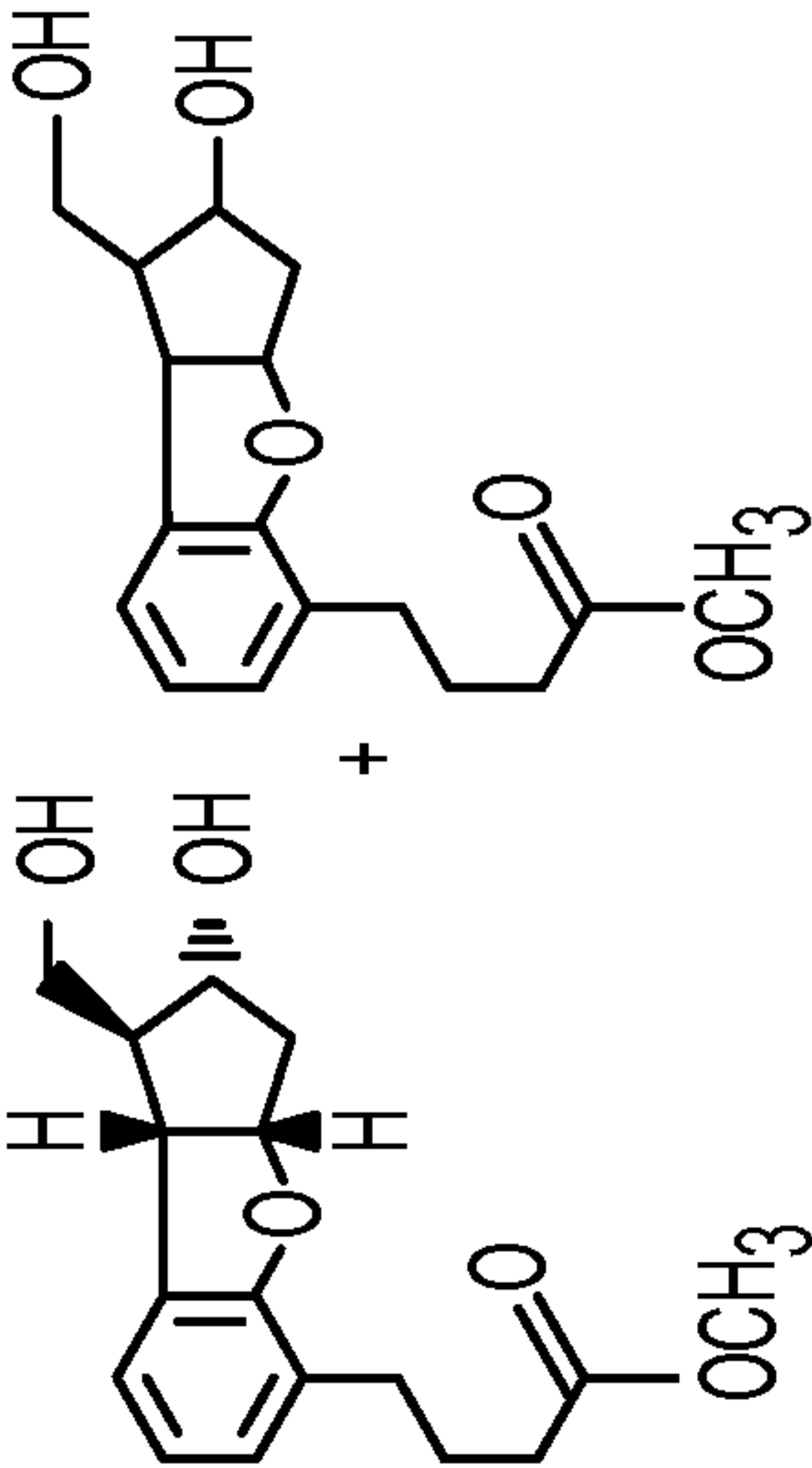


FIGURE 14

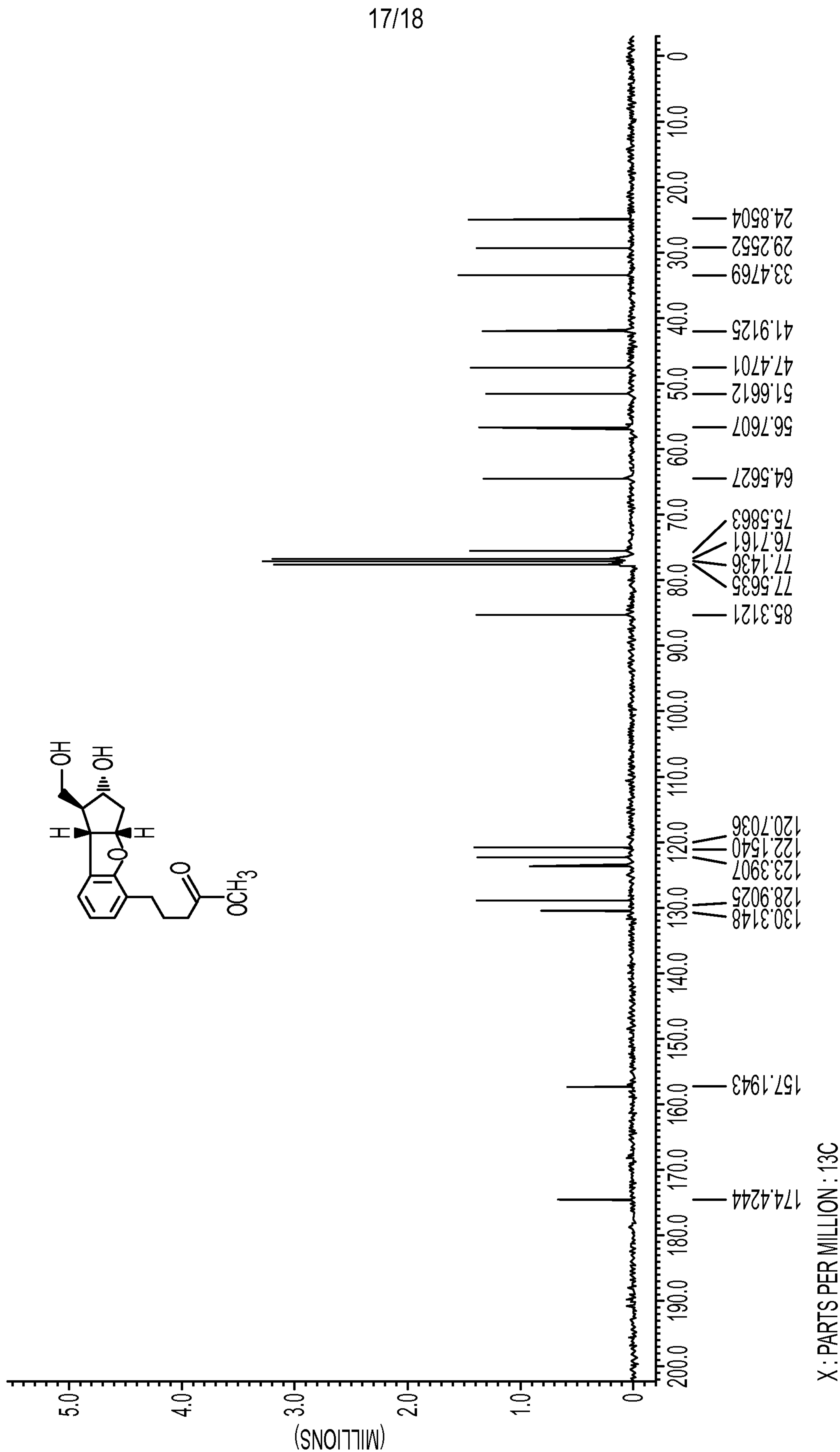


FIGURE 15

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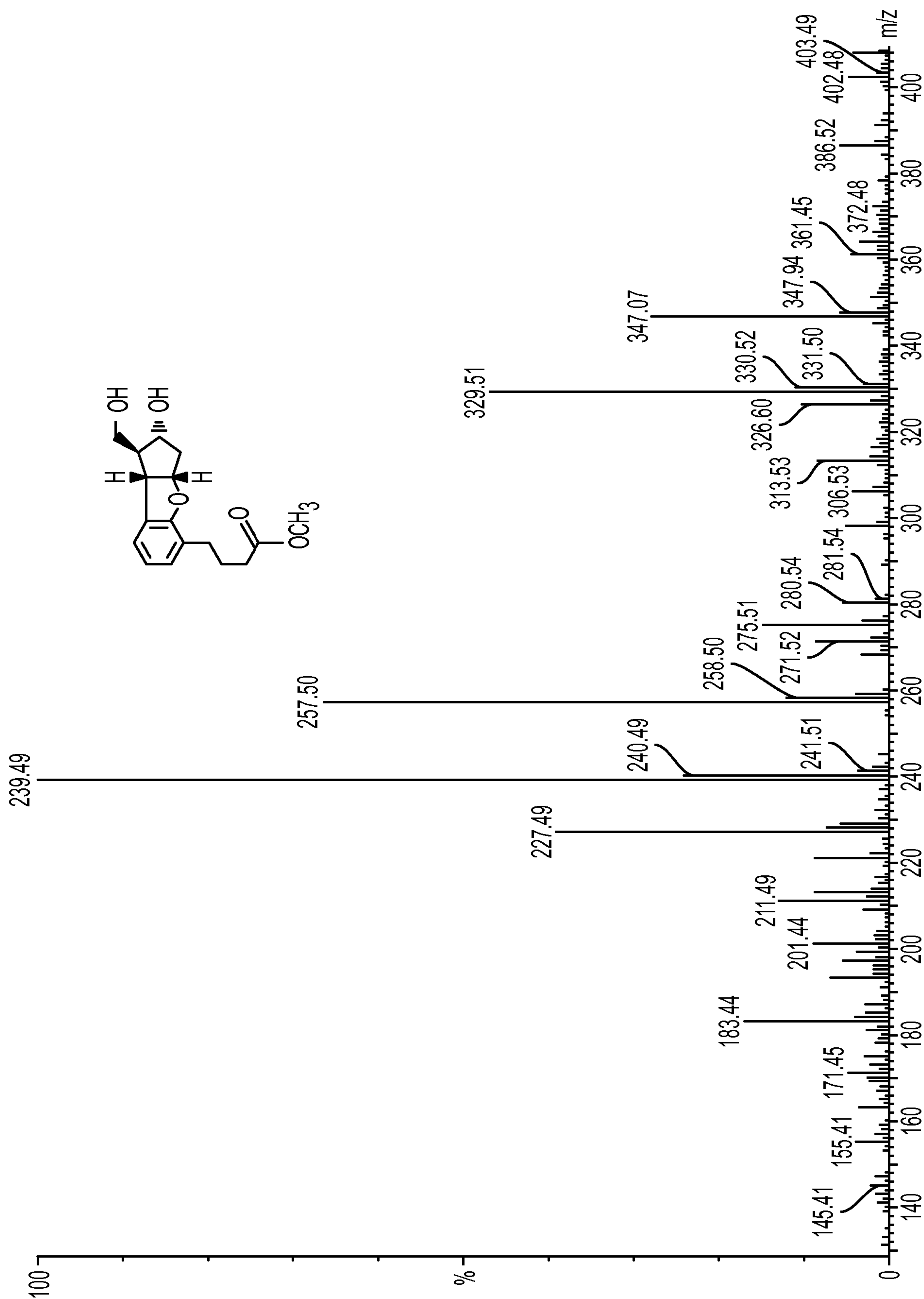


FIGURE 16

