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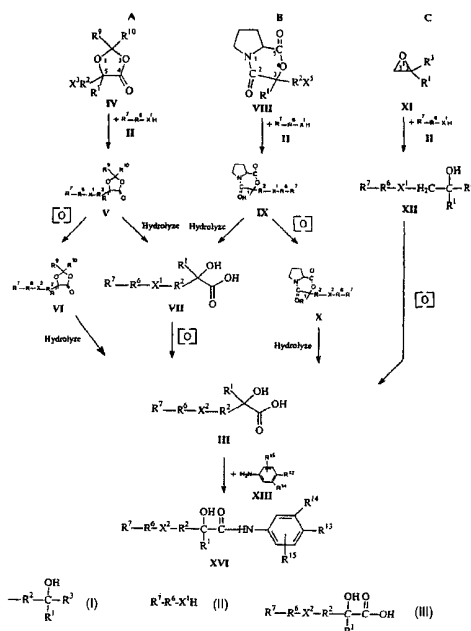
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(54) Title: METHODS OF ASYMMETRICALLY SYNTHESIZING ENANTIOMERS OF CASODEX, ITS DERIVATIVES AND INTERMEDIATES THEREOF



(57) Abstract: A method of synthesizing pure enantiomers of acylalanalides such as Casodex<sup>®</sup> (bicalutamide) and its derivatives includes contacting a compound having a ring structure that, when opened, provides a substituent having the structure of Formula (I), with a compound having a structure of the Formula (II): R<sup>7</sup>-R<sup>6</sup>-X<sup>1</sup>H, under conditions sufficient to provide a compound having the structure of Formula (III) wherein X<sup>2</sup> is oxygen, sulfur, sulphonyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-), oxidized imino alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms, or oxidized alkylimino. The method further includes treating the compound of Formula (III) under conditions sufficient to provide a pure enantiomer of acylalanalides such as Casodex<sup>®</sup> (bicalutamide) and/or derivatives thereof. In preferred embodiments, R<sup>1</sup> is methyl, R<sup>2</sup> is methylene, R<sup>6</sup> is a direct link, R<sup>7</sup> is 4-fluorophenyl, X<sup>1</sup> is sulfur, the compound of Formula (II) is 4-fluorobenzenethiol, and X<sup>2</sup> is sulphonyl. Methods of synthesizing acylalanalides such as Casodex<sup>®</sup> (bicalutamide) and/or derivatives thereof from a starting material of citramalic acid are also provided.

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**METHODS OF ASYMMETRICALLY SYNTHESIZING  
ENANTIOMERS OF CASODEX, ITS DERIVATIVES AND  
INTERMEDIATES THEREOF**

**Field Of The Invention**

The present invention relates to methods of synthesizing organic compounds, and more particularly to methods of asymmetrically synthesizing optically active pharmaceutical compounds and their intermediates.

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**Related Applications**

This application claims priority from N. Ekwuribe, United States Provisional Application 60/160,412, filed October 19, 1999, the disclosure of which is incorporated by reference herein in its entirety.

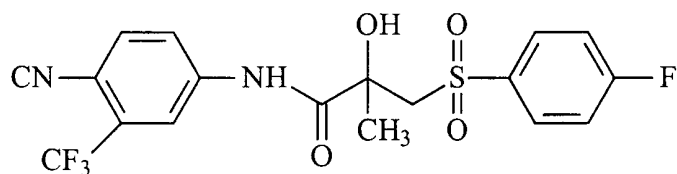
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**Background Of The Invention**

Androgen deprivation is a common treatment for persons with prostate cancer. Various non-steroidal antiandrogens are known for use in the treatment of prostate cancer. For example, bicalutamide, which may be among the most commonly used non-steroidal antiandrogens in the world, is typically used in the treatment of prostate cancer. Bicalutamide is commercially available as Casodex<sup>®</sup> (bicalutamide) from Zeneca Pharmaceuticals.

15

The chemical name of bicalutamide is N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-propanamide,(+/-). The structural formula of bicalutamide is:



20

The  $\beta$ -carbon atom in the propanamide is a chiral carbon. As a result, bicalutamide is an optically active compound.

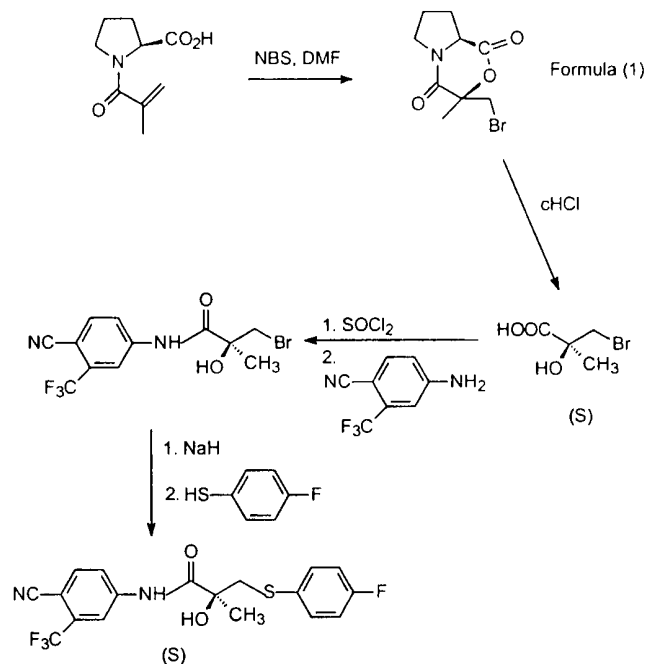
Optically active compounds have the ability to rotate the plane of polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are used to denote the optical rotation of the compound (*i.e.*, the direction in which a plane of polarized light is rotated by the optically active compound). The l or (-) prefix indicates that the compound is levorotatory (*i.e.*, rotates the plane of polarized light to the left or counterclockwise) while the d or (+) prefix means that the compound is dextrarotatory (*i.e.*, rotates the plane of polarized light to the right or clockwise). The sign of optical rotation, (-) and (+), is not related to the absolute configuration of the molecule, R and S.

Optically active compounds, such as bicalutamide, exist as a pair of stereoisomers that are identical with the notable exception that they are non-superimposable mirror images of one another. A specific stereoisomer, such as the R isomer, may be referred to as an enantiomer. A mixture of R and S enantiomers may be referred to as a racemic mixture.

Bicalutamide, is presently commercially available as a racemic mixture. The racemic mixture of bicalutamide may be synthesized by various methods including, for example, the methods described in U.S. Patent No. 4,636,505 to Tucker. Tucker further describes various derivatives and analogs of bicalutamide having antiandrogenic properties. Tucker, however, does not disclose or suggest methods for asymmetrically synthesizing enantiomers of Casodex<sup>®</sup> (bicalutamide) and/or its intermediates.

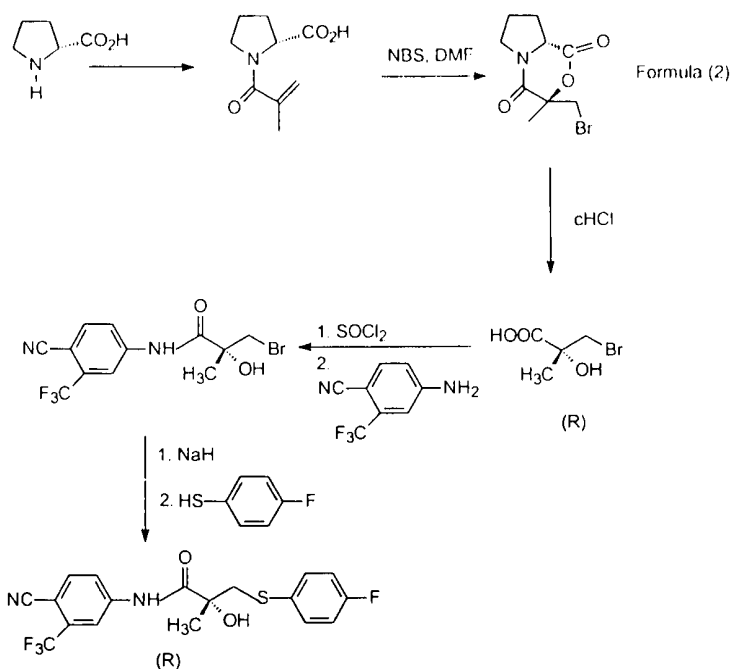
U.S. Patent No. 5,985,868 to Gray proposes synthesizing racemic mixtures of Casodex<sup>®</sup> (bicalutamide) using methods as described in U.S. Patent No. 4,636,505 to Tucker, and obtaining the (-) isomer of Casodex<sup>®</sup> (bicalutamide) by resolution of the enantiomers of Casodex<sup>®</sup> (bicalutamide) or of intermediates thereto using fractional crystallization or chromatography of diastereomeric esters of chiral acids. Gray notes that other standard methods of resolution such as simple crystallization and chromatographic resolution can also be used. Gray does not disclose or suggest methods of asymmetrically synthesizing enantiomers of Casodex<sup>®</sup> (bicalutamide) and/or its derivatives and/or intermediates.

In Howard Tucker et al., *Resolution of the Nonsteroidal Antiandrogen 4'-Cyano-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-3'-(trifluoromethyl)-propioanilide and the Determination of the Absolute Configuration of the Active Enantiomer*, 31 J. MED. CHEM. 885-887 (1988), the authors propose an asymmetric synthesis of (S)-Casodex<sup>®</sup> (bicalutamide) using the N-methacrylamide of (S)-proline as a starting material. The proposed reaction scheme is as follows:



The authors state that this approach is not suitable for the general synthesis of the active enantiomers of analogous anti-androgens, which would require the inaccessible and expensive (R)-proline as a starting material.

U.S. Patent No. 6,019,957 to Miller et al. proposes an asymmetric synthesis of (R)-Casodex<sup>®</sup> (bicalutamide) using (R)-proline as a starting material. The proposed reaction scheme is as follows:

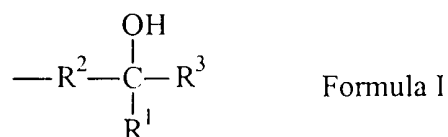


- As noted above, (R)-proline is an inaccessible and expensive starting material. It would be desirable to provide more cost effective methods for asymmetrically synthesizing enantiomers of Casodex<sup>®</sup> (bicalutamide) and/or its derivatives and/or intermediates that do not rely on (R)-proline as a starting material.

### Summary Of The Invention

- Embodiments of the present invention provide methods for asymmetrically synthesizing enantiomers of Casodex<sup>®</sup> (bicalutamide) and/or its intermediates.
- 10 Asymmetric synthesis methods according to embodiments of the present invention are more cost effective than conventional methods. For example, asymmetric synthesis methods according to embodiments of the present invention react 4-fluorobenzenethiol with the bromolactone of Formula 1 or 2 above. By reacting the 4-fluorobenzenethiol with the bromolactone prior to hydrolyzing the bromolactone
- 15 instead of hydrolyzing the bromolactone and then reacting the 4-fluorobenzenethiol with the resulting acid as proposed above, improved separation of the reaction products and thus higher yields may be provided. Furthermore, asymmetric synthesis methods according to embodiments of the present invention produce (R)- Casodex<sup>®</sup> (bicalutamide) and/or its intermediates using (S)-citramalic acid (2-hydroxy-2-
- 20 methylbutanedioic acid) as a starting material, which may be more cost effective than the conventional scheme, which uses the inaccessible and expensive (R)-proline as a starting material.

According to embodiments of the present invention, methods of asymmetrically synthesizing an enantiomer of an acylalanide such as Casodex<sup>®</sup> (bicalutamide) or its derivatives are provided. The methods include contacting a compound having a ring structure that, when opened, provides a substituent having the structure of Formula I:



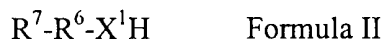
wherein

R<sup>1</sup> is alkyl or haloalkyl having up to 4 carbons;

R<sup>2</sup> is alkyl having up to 6 carbon atoms; and

R<sup>3</sup> is CH<sub>2</sub>OR<sup>4</sup> where R<sup>4</sup> is hydrogen or benzyl, C(O)CH<sub>3</sub>, or C(O)OR<sup>5</sup> where R<sup>5</sup> is hydrogen or alkyl;

with a compound having a structure of Formula II:

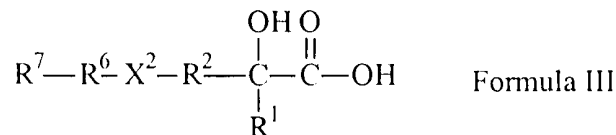


wherein

R<sup>6</sup> is a direct link or alkyl having up to 6 carbon atoms;

R<sup>7</sup> is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbons; or R<sup>7</sup> is phenyl which bears one, two or three substituents independently selected from hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxy carbonyl and N-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R<sup>7</sup> is naphthyl; or R<sup>7</sup> is a 5- or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulfur, which heterocyclic may be a single ring or may be fused to a benzo-ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents; and

$X^1$  is oxygen, sulfur, sulphanyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-) or alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms; under conditions sufficient to provide a compound having the structure of Formula III:



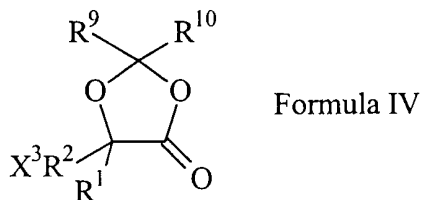
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wherein  $X^2$  is oxygen, sulfur, sulphanyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-), oxidized imino alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms, or oxidized alkylimino. The method further includes treating the compound of Formula III under conditions sufficient to provide a pure enantiomer of Casodex<sup>®</sup> (bicalutamide) or a pure enantiomer of a Casodex<sup>®</sup> (bicalutamide) derivative. In preferred embodiments, R<sup>1</sup> is methyl, R<sup>2</sup> is methylene, R<sup>6</sup> is a direct link, R<sup>7</sup> is 4-fluorophenyl, X<sup>1</sup> is sulfur, the compound of Formula II is 4-fluorobenzenethiol, and X<sup>2</sup> is sulphonyl.

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In other embodiments according to the present invention, the compound having a ring structure is a compound of Formula IV:

15



wherein

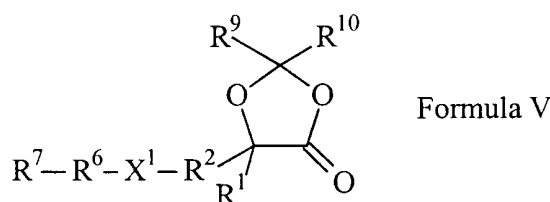
R<sup>9</sup> is hydrogen, or straight, branched or cyclic alkyl;

R<sup>10</sup> is straight or branched alkyl, aryl, or R<sup>11</sup>X<sub>3</sub><sup>4</sup>, where R<sup>11</sup> is alkyl and X<sup>4</sup> is alkyl, halogen or aryl; and

20

X<sup>3</sup> is a leaving group.

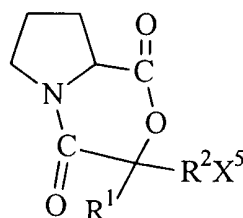
The compound of Formula IV is contacted with the compound of Formula II under conditions sufficient to provide a compound having the structure of Formula V:





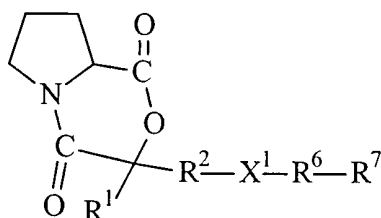
In preferred embodiments, R<sup>1</sup> is methyl and R<sup>2</sup> is methylene. In particularly preferred embodiments, citramalic acid is used as a starting material to provide a compound having the structure of Formula IV. The citramalic acid may be either the (R) or the (S) enantiomer; however, it is preferable to use the (S)-enantiomer of citramalic acid because it may be more readily available and thus, unlike (R)-proline, may be a relatively inexpensive starting material in the synthesis of arylanilides such as Casodex<sup>®</sup> (bicalutamide) and/or its derivatives. Furthermore, the more active form of Casodex<sup>®</sup> (bicalutamide) ((R)-Casodex<sup>®</sup> (bicalutamide)) can be synthesized according to methods of the present invention using (S)-citramalic acid.

10 In still other embodiments according to the present invention, the compound having a ring structure is a compound of Formula VIII:



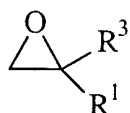
Formula VIII

wherein X<sup>5</sup> is a leaving group. The compound of Formula VIII is contacted with the compound of Formula II under conditions sufficient to provide a compound having the structure of Formula IX:



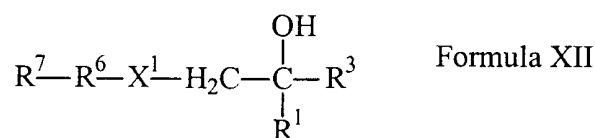
Formula IX

In yet other embodiments of the present invention, the compound having a ring structure is a compound of Formula XI:



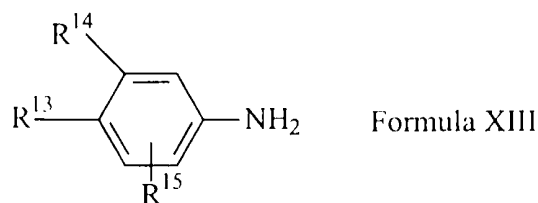
Formula XI

20 The compound of Formula XI is contacted with the compound of Formula II under conditions sufficient to provide a compound having the structure of Formula XII:



Formula XII

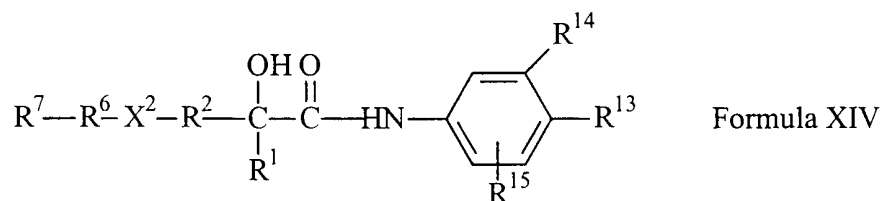
In preferred embodiments, the compound of Formula III is treated with a compound having the structure of Formula XIII:



wherein

- 5             $R^{13}$  is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo, or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each having up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
- 10            $R^{14}$  is cyano, cabamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of having up to 4 carbon atoms; or phenylthio, phenylsulphinyl or phenylsulphonyl; and
- 15            $R^{15}$  is hydrogen or halogen;

under conditions sufficient to provide a compound of Formula XIV:



- wherein  $X^2$  is oxygen, sulfur, sulphinyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-), oxidized imino alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms, or
- 20           oxidized alkylimino. In preferred embodiments, the compound of Formula XIII is 4-amino-2-trifluoromethylbenzonitrile, and the compound of Formula XIV is Casodex<sup>®</sup> (bicalutamide).

- Asymmetric synthesis methods according to the present invention may provide pure enantiomers of Casodex<sup>®</sup> (bicalutamide) and/or its intermediates in a
- 25           more cost effective manner than conventional methods. For example, as noted above, conventional methods that attempt to provide the more active (R)-enantiomer of Casodex<sup>®</sup> (bicalutamide) do so either by synthesizing ester derivatives of the racemic

mixture and then separating the (R) enantiomer from the (S) enantiomer to produce a Casodex<sup>®</sup> (bicalutamide) mixture having a higher concentration of (R) enantiomer than (S) enantiomer or by asymmetrically synthesizing the (R)-enantiomer using the inaccessible and expensive (R)-proline as a starting material. By asymmetrically  
5 synthesizing the (R) enantiomer of Casodex<sup>®</sup> (bicalutamide) rather than synthesizing and then separating a racemic mixture, methods according to embodiments of the present invention eliminate the economic waste associated with discarding the (S) enantiomer. Furthermore, according to embodiments of the present invention, (R)-Casodex<sup>®</sup> (bicalutamide) is asymmetrically synthesized using the readily available  
10 (S)-citramalic acid as a starting material rather than the inaccessible and expensive (R)-proline.

### **Brief Description of the Drawings**

**Figure 1** illustrates a reaction scheme for synthesizing acylanilides such as  
15 Casodex<sup>®</sup> (bicalutamide) that includes attaching the compound of Formula II to compounds having ring structures according to the present invention.

**Figure 2** illustrates three routes for synthesizing acylanilides such as  
Casodex<sup>®</sup> (bicalutamide) using citramalic acid as a starting material and attaching the  
20 compound of Formula II to the heterocyclic ring structure prior to hydrolyzing the heterocycle according to the present invention.

**Figure 3** illustrates three routes for synthesizing acylanilides such as  
Casodex<sup>®</sup> (bicalutamide) using citramalic acid as a starting material and hydrolyzing  
the heterocycle before reacting the citramalic acid derivative with the compound of  
Formula II according to the present invention.

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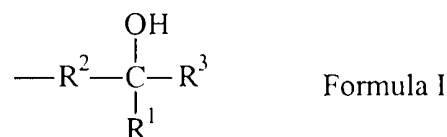
### **Detailed Description Of Preferred Embodiments**

The invention will now be described with respect to preferred embodiments described herein. It should be appreciated however that these embodiments are for the purpose of illustrating the invention, and are not to be construed as limiting the  
30 scope of the invention as defined by the claims. As the substituents R<sup>1</sup>-R<sup>15</sup>, X<sup>1</sup>-X<sup>5</sup> have been defined above, they will not be further defined herein other than to describe preferred substituents for the preferred embodiments.

Embodiments of the present invention provide methods of asymmetrically synthesizing an enantiomer of an acylanilide. Particularly preferred methods provide

synthesis routes for Casodex<sup>®</sup> (bicalutamide) and its derivatives that are more cost effective than conventional preparation techniques.

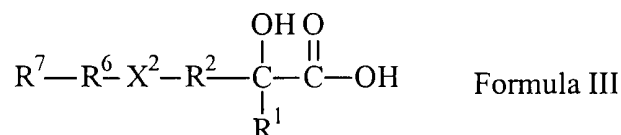
In a first embodiment, methods of asymmetrically synthesizing an enantiomer of acylanilide comprises contacting a compound having a ring structure that, when  
 5 opened, provides a substituent having the structure of Formula I:



with a compound having a structure of Formula II:



under conditions sufficient to provide a compound having the structure of Formula  
 10 III:

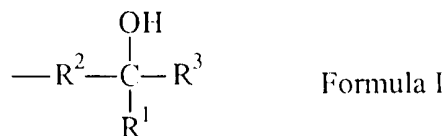


and, synthesizing the compound of Formula III under conditions sufficient to provide a pure enantiomer of an acylanilide. The pure enantiomer of the acylanilide is preferably a pure enantiomer of Casodex<sup>®</sup> (bicalutamide) or a derivative thereof.

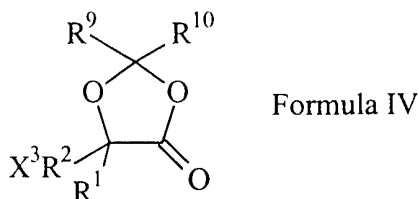
15 More preferably, the pure enantiomer of the acylanilide is (R)-Casodex<sup>®</sup> (bicalutamide) or a derivative thereof.

Preferably, R<sup>1</sup> and R<sup>2</sup> are each lower alkyl having up to 6 carbons. More preferably, R<sup>1</sup> is methyl and R<sup>2</sup> is methylene. R<sup>3</sup> is preferably CH<sub>2</sub>OH or C(O)OH. Preferably R<sup>6</sup> is a direct link (*i.e.*, one or more bonds between X<sup>1</sup> and R<sup>7</sup>). R<sup>7</sup> is  
 20 preferably phenyl which bears one, two or three substituents independently selected from hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and N-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio,  
 25 phenylsulphinyl and phenylsulphonyl. More preferably, R<sup>7</sup> is phenyl which bears one, two or three substituents independently selected from hydrogen and halogen. Most preferably, R<sup>7</sup> is 4-fluorophenyl. Preferably, X<sup>1</sup> is sulfur, sulphinyl, sulphonyl or imino. X<sup>1</sup> is more preferably sulfur, sulphinyl, or sulphonyl and is most preferably sulfur. X<sup>2</sup> is preferably sulphonyl.

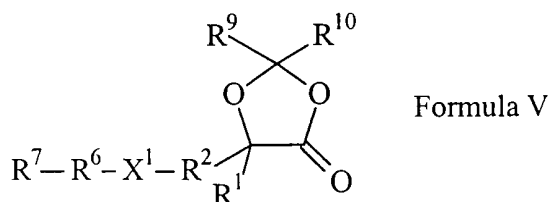
Referring to **Figure 1**, embodiments of preferred compounds having ring structures that, when opened, provide substituents having the structure of Formula I:



will now be described. Referring first to **Scheme A**, the compound having a ring structure is a compound of Formula IV:



The compound of Formula IV contacts the compound of Formula II under conditions sufficient to provide a compound having the structure of Formula V:



10 As illustrated in **Figure 1, Scheme A**, the compound of Formula V may follow one of two separate synthesis routes to provide the compound of Formula III. The compound of Formula V may be oxidized to convert  $X^1$  to  $X^2$  providing the compound of Formula VI, which may then be hydrolyzed to open the lactone (heterocyclic ring) of Formula VI, providing the compound of Formula III.

15 Alternatively, the compound of Formula V may be hydrolyzed to deprotect the hydroxy acid and provide the compound of Formula VII, which may then be oxidized to convert  $X^1$  to  $X^2$ , providing the compound of Formula III. While the synthesis routes shown in **Figure 1, Scheme A** show an oxidation step, it is to be understood that an oxidation step may not be required. For example, an oxidation step may not  
 20 be required when  $X^1$  is sulphonyl, when the oxidation step occurs later in the process (*e.g.*, after the amidation step), or when the acylanilide derivative is not fully oxidized. As will be understood by those skilled in the art, various means may be used to hydrolyze the lactone, including, but not limited to, contacting the lactone of Formula V with an aqueous acid or aqueous base solution. The lactone of Formula V  
 25 is preferably hydrolyzed using HCl. Those in the art will also understand that a

variety of methods and agents may be used to oxidize the compound of Formula V to obtain the compound of Formula III.

Preferably,  $R^9$  and  $R^{10}$  are selected to allow for hydrolysis of the lactone of Formula IV.  $R^9$  is preferably hydrogen, or straight, branched or cyclic lower alkyl. More preferably,  $R^9$  is hydrogen.  $R^{10}$  is preferably aryl or  $R^{11}X^4$  where  $R^{11}$  is lower alkyl and  $X^4$  is lower alkyl, halogen, or aryl. More preferably,  $R^{10}$  is benzyl or  $R^{11}X^4$  where  $R^{11}$  is methyl and  $X^4$  is methyl, Cl, Br, or phenyl.  $X^3$  is a leaving group, as will be understood by those skilled in the art.  $X^3$  is preferably halogen, and is more preferably bromine.

10 In a most preferred embodiment, the compound of Formula IV is synthesized from citramalic acid, as illustrated in **Figures 2** and **3**, which will now be described. The following synthesis routes may be employed using (R)-citramalic acid, (S)-citramalic acid, or a racemic mixture thereof as the starting material. Citramalic acid is commercially available from Fluka, a business unit of Sigma-Aldrich Corporation  
15 of St. Louis, Missouri. For the synthesis of the acylalanide Casodex<sup>®</sup> (bicalutamide) and its derivatives, it is preferable to use (S)-citramalic acid as the starting material. (S)-citramalic acid may be used as a starting material in methods of the present invention to provide (R)-Casodex<sup>®</sup> (bicalutamide). (R)-Casodex<sup>®</sup> (bicalutamide) is believed to be the most active Casodex<sup>®</sup> (bicalutamide) enantiomer for the treatment  
20 of prostate cancer, as well as other androgen related diseases. In sharp contrast to the (R)-proline starting material, which is inaccessible and expensive, (S)-citramalic acid is readily available. Thus, the synthesis methods of the present invention that utilize (S)-citramalic acid as a starting material may be more cost effective than conventional methods that rely on (R)-proline.

25 The various synthesis routes illustrated in **Figures 2** and **3** are denoted by the designations next to the reaction arrows. The primary designator (the initial small roman numeral) designates the step number, while the secondary designator(s) (the capital letter, the arabic numeral, and the second small roman numeral) designate the particular route. Synthesis routes having steps that have all of the secondary  
30 designators of an earlier step in common have that step in common. For example, in **Figure 2**, the steps (vi)(A)(1)(i) and (v)(A)(1)(ii) have all of the secondary designators of step (iv)(A)(1) in common; therefore, step (iv)(A)(1) is a step in both the (A)(1)(i) synthesis route as well as the (A)(1)(ii) synthesis route.

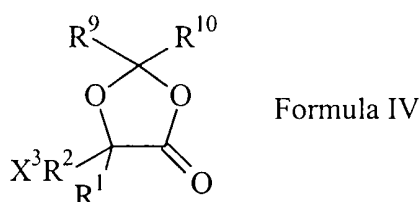
Turning first to **Figure 2**, in step (i) a protecting group is added to the citramalic acid to provide the compound of Formula XV. The protecting group is used to protect the hydroxy acid from the decarboxylation step (ii) by forming the dioxolanone of Formula XV. The protecting group may also add molecular weight to the citramalic acid molecule. This larger citramalic acid derivative may be more easily separated after formation of the sulfide as compared to derivatives from which the protecting group is removed prior to formation of the sulfide (*e.g.*, **Figure 3**, steps (iii)(B) and (iv)(B)(1)). The protecting group is preferably added by aldol condensation reaction, and more preferably is added by the aldol condensation reaction of bromal and citramalic acid in the presence of sulfuric acid.

In step (ii), the compound of Formula XV undergoes decarboxylative halogenation to provide the compound of Formula XVI. To avoid the heavy metals associated with the Hunsdiecker reaction, it is preferable to use the decarboxylative bromination method proposed by Barton et al. in 24 TETRAHEDRON LETT. 4979-4982 (1983), which is incorporated herein by reference in its entirety. An example of this bromination method is provided in Example 2, described hereinbelow. While **Figures 2** and **3** show a step (ii) that is a decarboxylative halogenation step, it will be understood by those skilled in the art that various decarboxylation steps may be used, such as other decarboxylation steps that replace the carboxylic acid group with a non-halogen leaving group.

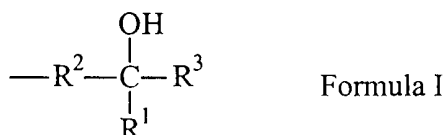
In step (iii)(A), the compound of Formula II is added to the compound of Formula XVI to provide the compound of Formula XVII. The compound of Formula II is preferably added by a substitution reaction, as will be understood by those skilled in the art. An example of this substitution reaction is provide in Example 3, described hereinbelow.

Referring now to synthesis route (A)(2), the compound of Formula XVII is oxidized in step (iv)(A)(2) to provide the compound of Formula XXII. The protecting group is then removed from the compound of Formula XXII in step (v)(A)(2), preferably by hydrolysis, to provide the compound of Formula XXI. In step (vi)(A)(2), the compound of Formula XIII is then added to the compound of Formula XXI to provide the acylanilide of Formula XX. The amidation may be performed by various methods as will be understood by those skilled in the art. The amidation is preferably accomplished via *in situ* generation of the acid chloride. Thionyl chloride is the preferred for this procedure.

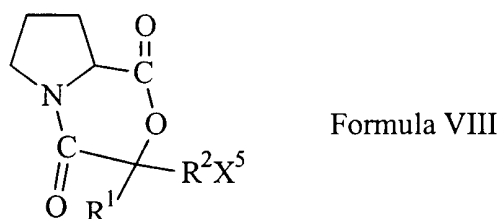
Synthesis routes (A)(1)(i) and (A)(1)(ii) utilize processes similar to those described for synthesis route (A)(2), and will not be further described. Referring to **Figure 3**, the synthesis routes (B)(1)(i) and (B)(2) utilize processes similar to those described for synthesis route (A)(2), and will not be further described. Synthesis route (B)(1)(ii) utilizes processes similar to those employed in the other synthesis routes of **Figures 2** and **3**. Synthesis route (B)(1)(ii) is described in some detail in Examples 1-5 hereinbelow. Thus, citramalic acid may be used as a starting material to form the compound of Formula IV:



which has a ring structure that, when opened, provides a substituent having the structure of Formula I:



Returning to **Figure 1**, **Scheme B** illustrates other methods according to embodiments of the present invention where the compound having a ring structure that, when opened, provides a substituent having the structure of Formula I is a compound having the structure of Formula VIII:

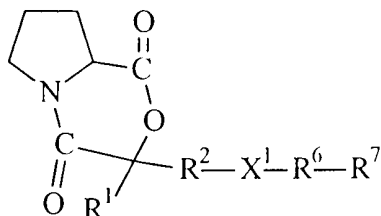


The compound of Formula VIII may be made, for example, according to the synthesis routes described, for example, in U.S. Patent No. 6,019,957 to Miller et al. and Howard Tucker et al., *Resolution of the Nonsteroidal Antiandrogen 4'-Cyano-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-3'-(trifluoromethyl)-propioanilide and the Determination of the Absolute Configuration of the Active Enantiomer*, 31 J. MED. CHEM. 885-887 (1988), the disclosures of which are incorporated herein by reference



in their entirety. As noted above,  $X^5$  is a leaving group.  $X^5$  is preferably halogen and is more preferably bromine.

The compound of Formula VIII contacts the compound of Formula II under conditions sufficient to provide a compound having the structure of Formula IX:



5

The compound of Formula II is preferably added to the compound of Formula VIII via a substitution reaction, as will be understood by those skilled in the art. For example, a substitution reaction similar to the one described below in Example 3 may be used.

10 As illustrated in **Figure 1, Scheme B**, the compound of Formula IX may follow one of two separate synthesis routes to provide the compound of Formula III. The compound of Formula IX may be hydrolyzed to deprotect the hydroxy acid and provide the compound of Formula VII, which may then be oxidized to convert  $X^1$  to  $X^2$ , providing the compound of Formula III. Alternatively, the compound of Formula

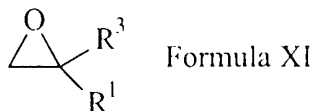
15 IX may be oxidized to convert  $X^1$  to  $X^2$  providing the compound of Formula X, which may then be hydrolyzed to open the 6-membered heterocyclic ring of Formula X, providing the compound of Formula III. While the synthesis routes shown in **Figure 1, Scheme B** show an oxidation step, it is to be understood that an oxidation step may not be required and/or desired. For example, an oxidation step may not be required

20 and/or desired when  $X^1$  is sulphonyl, when the oxidation step occurs later in the process (*e.g.*, after the amidation step), or when the acylanilide derivative is not fully oxidized. As will be understood by those skilled in the art, various means may be used to hydrolyze the 6-membered heterocyclic ring, including, but not limited to, contacting the heterocyclic ring of Formula IX with an aqueous acid or aqueous base

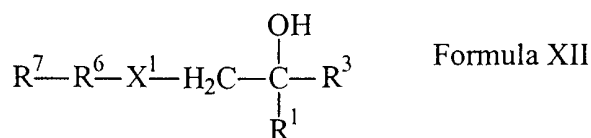
25 solution. Preferably, the compound of Formula IX is hydrolyzed using HCl. Those in the art will also understand that a variety of methods and agents may be used to oxidize the compound of Formula IX to obtain the compound of Formula III.

Referring now to **Figure 1, Scheme C**, embodiments of methods according to the present invention wherein the compound having a ring structure that, when

opened, provides a substituent having the structure of Formula I is a compound of Formula XI:

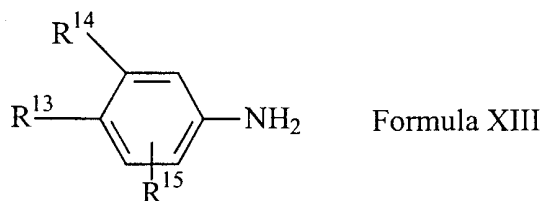


will now be described. The compounds of Formula IX may be made, for example, by chiral epoxidation of alkenes such as alkenols, as will be understood by those skilled in the art. The preferred compound of Formula XI is 2-methyl-1,2-epoxypropanol (R<sup>1</sup> is -CH<sub>3</sub> and R<sup>3</sup> is -CH<sub>2</sub>OH), which is commercially available from Acros Organics USA of Fair Lawn, New Jersey. The compound of Formula XI contacts the compound of Formula II under conditions sufficient to provide a compound having the structure of Formula XII:

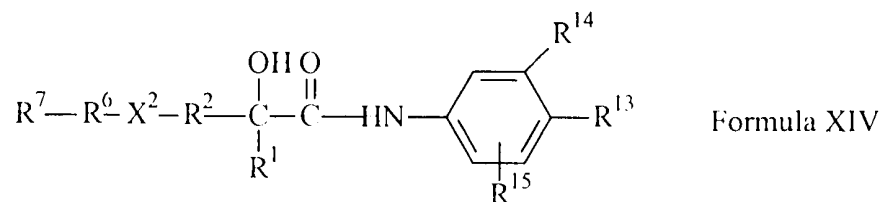


The compound of Formula II is preferably added to the compound of Formula XI via a substitution reaction, as will be understood by those skilled in the art. For example, a substitution reaction similar to the one described below in Example 3 may be used. The compound of Formula XII is then oxidized, as will be understood by those skilled in the art, to convert X<sup>1</sup> to X<sup>2</sup> and, if necessary, convert R<sup>3</sup> to the carboxylic acid to provide the compound of Formula III. While the synthesis routes shown in **Figure 1**, **Scheme C** show an oxidation step, it is to be understood that an oxidation step may not be required and/or desired. For example, an oxidation step may not be required and/or desired when X<sup>1</sup> is sulphonyl and/or R<sup>3</sup> is C(O)OH.

As illustrated in **Figure 1**, the compound of Formula III may be converted to the acylanilide by treating the compound of Formula III with a compound having the structure of Formula XIII:



under conditions sufficient to provide a compound of Formula XIV:



The amidation may be performed by various methods as will be understood by those skilled in the art. The amidation is preferably accomplished via *in situ* generation of the acid chloride using thionyl chloride as described above.

5           R<sup>13</sup> is preferably cyano, fluoro, chloro, bromo, iodo, or hydrogen. More preferably, R<sup>13</sup> is cyano, fluoro, chloro, bromo, iodo, and, most preferably, R<sup>13</sup> is cyano. R<sup>14</sup> is preferably perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of having up to 4 carbon atoms. More preferably, R<sup>14</sup> is perfluoroalkyl, and, most preferably, R<sup>14</sup> is perfluoromethyl. Most preferably, R<sup>15</sup> is  
 10 hydrogen. X<sup>2</sup> is preferably sulphonyl.

As described above, pure enantiomers of Casodex<sup>®</sup> (bicalutamide) and/or its derivatives may be asymmetrically synthesized by methods according to embodiments of the present invention. These enantiomers may be used to treat various diseases. For example, it is preferable to use the (R)-enantiomer of Casodex<sup>®</sup>  
 15 (bicalutamide) synthesized by methods of the present invention to treat androgen-dependent diseases, such as prostate cancer. Casodex<sup>®</sup> (bicalutamide) and/or derivatives thereof synthesized by methods of the present invention may be used in various methods of treatment and pharmaceutical compositions such as, for example, those methods of treatment and pharmaceutical compositions described in U.S. Patent  
 20 No. 5,985,868 to Gray, the disclosure of which is incorporated herein by reference in its entirety.

The present invention will now be described with reference to the following examples. It should be appreciated that these examples are for the purposes of illustrating aspects of the present invention, and do not limit the scope of the  
 25 invention as defined by the claims.

### Example 1

#### Synthesizing 4-Methyl-5-oxo-2-trihromomethyl-[1,3,1-dioxolan-4y1]-acetic acid

30

Bromal (89.1 mmol) and (S)-citramalic acid (74.2 mmol) were cooled to 0°C in a 125 mL flask under inert atmosphere. Sulfuric acid (25 mL) was added dropwise with stirring. After 2 hrs. the contents were a yellow solution with a white precipitate. The ice bath was removed and the reaction was stirred overnight at room temperature.

5 The dark solution was diluted with ice and extracted 4 times with ethyl acetate. The organic layer was back extracted with water and then was dried with MgSO<sub>4</sub>. After filtration, the filtrate was concentrated to an oil. The product was obtained as a white solid after crystallization from toluene/hexanes. Yield 60%; mp 151°C (sublimes); MS (FAB<sup>+</sup>) 433 (M+Na); <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 5.77 (s, 1H), 3.06 (d, J=1.79, 2H), 1.74

10 (s, 3H); <sup>13</sup>C NMR: δ 174.05, 105.55, 79.63, 43.68, 42.73, 25.38; IR: 3158, 2939, 1825, 1792, 1732; UV: λ<sub>max</sub> 208, λ<sub>1/2 max</sub> 237. Anal. Calculated for C<sub>7</sub>H<sub>7</sub>Br<sub>3</sub>O<sub>5</sub>: C, 20.46; H, 1.72. Found: C, 20.89; H, 1.74.

### Example 2

15

#### **Synthesizing 5-Bromomethyl-5-methyl-2-tribromomethyl-[1,3]dioxolan-4-one**

The dioxolanone prepared in Example 1 and 2-mercaptopyridine N-oxide were suspended in CBrCl<sub>3</sub>. The reaction was heated to reflux and a solution of DCC

20 (dicyclohexylcarbodiimide) in CBrCl<sub>3</sub> was added slowly over the course of 30 minutes. The reaction was stirred for an additional hour. The product was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub> / hexanes (1/2)) and was obtained as white needles from the same solvents. Yield 65%; mp 110-113°C; MS (FAB<sup>+</sup>) no parent ion; <sup>1</sup>H NMR δ 5.93 (s, 1H), 3.65 (d, J=1.4, 1H), 1.79 (s, 3H); <sup>13</sup>C NMR δ 170.58, 105.39,

25 83.00, 43.51, 35.97, 23.38. IR: 2926, 1825, 1176. UV: λ<sub>max</sub> 210, λ<sub>1/2 max</sub> 242. Anal. Calculated for C<sub>6</sub>H<sub>6</sub>Br<sub>4</sub>O<sub>3</sub>: C, 16.17; H, 1.36. Found: C, 16.38; H, 1.29.

### Example 3

#### **Synthesizing 3-(4-Fluoro-phenylsulfanyl)-2-hydroxy-2-methyl-propionic acid**

The protected hydroxyacid prepared in Example 2 was dissolved in a 1:1 mixture of isopropanol: 1M NaOH. After 3 hrs, the reaction mixture was a solution and no starting material was detectable by TLC (thin-layer chromatography). 4-

Fluorobenzenethiol was then added and the reaction was stirred overnight. The reaction was then adjusted to pH 8 with HCl and was extracted 2 times with CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was then adjusted to pH 1 and was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was concentrated to an oil, which crystallized on standing. The

5 hydroxyacid was either used in the next reaction without further purification or was recrystallized from chloroform/petroleum ether. Yield 80%; mp 73-75°C; MS (FAB<sup>+</sup>) 230; <sup>1</sup>H NMR: δ 7.43 (dd, J=9.0, J=5.1, 2H), 6.96 (dd, J=9.0, J=9.0, 2H), 3.40 (dd, J=13.8, J=0.9, 1H), 3.15 (dd, J=13.8, J=0.9, 1H), 1.53 (s, 3H); <sup>13</sup>CNMR: δ 180.06, 162.37 (d, J=327.8), 133.93 (d, J=10.6), 130.30, 116.31 (J=29.2), 74.95, 46.22, 25.83;

10 <sup>19</sup>F NMR: 6-114.21. IR: 3065, 1719. UV: λ<sub>max</sub> 251.

**Example 4****Synthesizing N-(4-Cyano-3-trifluoromethyl-phenyl)-3-(4-fluoro-phenylsulfanyl)-2-hydroxy-2-methyl-propionamide**

5

The hydroxyacid prepared in Example 3 (8.5 mmol) and 4-amino-2-trifluoromethylbenzonitrile (11 mmol) were dissolved in dry DMA (dimethylacetamide) (15 mL) under inert atmosphere. After the solution had been cooled to -10°C, thionyl chloride (10 mmol) was added slowly. The reaction was stirred for 15 min at -10°C, and then the ice bath was removed. After stirring overnight at room temperature, the reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> and was extracted one time with saturated NaHCO<sub>3</sub>. The organic layer was dried with MgSO<sub>4</sub> and concentrated. The product was purified by silica gel chromatography (6% ethyl acetate in CH<sub>2</sub>Cl<sub>2</sub>). Yield 45%; MS (FAB<sup>+</sup>) 399 (M+1); <sup>1</sup>H NMR: δ 8.98 (s, 1H), 7.91 (s, 1H), 7.74 (m, 2H), 7.39 (m, 2H), 6.88 (m, 2H), 3.75 (d, J=14.1, 1H), 3.10 (d, J=14.1, 1H), 1.53 (s, 3H); <sup>13</sup>C NMR: δ 173.10, 160.87, 141.38, 135.90, 133.97, 128.64, 121.84, 117.34, 116.57, 115.68, 104.83, 75.60, 46.07, 26.61; <sup>19</sup>F NMR: δ-62.74, -113.22. IR: 3357, 3095, 2981, 2232, 1685.

20

**Example 5****Synthesizing N-(4-cyano-3-trifluoromethyl-phenyl)-3-(4-fluoro-phenylsulfonyl)-2-hydroxy-2-methyl-propionamide**

To a solution of the sulfide prepared in Example 4 (3.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (43 mL) was added mCPBA (meta-chloroperbenzoic acid) (9.57 mmol). After stirring overnight at room temperature, the reaction was diluted with ethyl acetate and extracted two times with Na<sub>2</sub>SO<sub>3</sub> and NaHCO<sub>3</sub>. The organic layer was dried with MgSO<sub>4</sub> and concentrated. After purification by silica gel chromatography, the product was obtained as white crystals from benzene/petroleum ether. Yield 94%; mp 178°C; MS (FAB<sup>+</sup>) 431 (M+1); <sup>1</sup>H NMR: 5.916 (s, 1H), 8.00 (d, J=1.5, 1H), 7.88-7.93 (m, 2H), 7.79-7.80 (m, 2H), 7.14-7.20 (m, 2H), 5.02 (s, 1H), 4.00 (d, J=14.5, 1H), 3.51 (d, J=14.5, 1H), 1.61 (s, 3H); <sup>13</sup>C NMR: δ 171.40, 166.03 (J<sub>FC</sub>=256.7), 141.01, 135.65, 135.01, 133.88 (J<sub>FC</sub>=32.4), 130.78 (J<sub>FC</sub>=9.7), 121.92 (J<sub>FC</sub>=272.0), 121.79, 117.23, 116.75 (J<sub>FC</sub>=22.7), 115.26, 104.82, 74.44, 61.83, 27.80; <sup>19</sup>F NMR: δ-

35

62.71, -101.63. IR: 3449, 3333, 3104, 2984, 2933, 2231, 1697, 1587, 1517. UV:  $\lambda_{\text{max}}$  214, 271. Anal. Calculated for  $\text{C}_{18}\text{H}_{14}\text{F}_4\text{N}_2\text{O}_4\text{S}$ : C, 50.23; H, 3.28; N, 6.51. Found: C, 50.01; H, 3.26; N, 6.23.

5

**Example 6**

**Biological Data Comparing Pure Enantiomers of  
Casodex<sup>®</sup> (bicalutamide) Synthesized by Methods of the Present Invention  
with Racemic Mixtures of Casodex<sup>®</sup> (bicalutamide)**

The data for dihydrotestosterone are EC50 values. The rest of the data are  
10 IC50 values, since the assay is measuring the amount of compound it takes to reduce  
the testosterone response 50%.

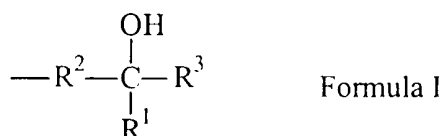
Compound	Experiment 1	Experiment 2
DHT (Standard)	0.18 nM	0.18 nM
OH Flut. (Standard)	19 nM	41 nM
Racemate	900 nM	1000 nM
(R)	374 nM	359 nM
(S)	7700 nM	11000 nM

15 In the drawings and specification, there have been disclosed typical preferred  
embodiments of the invention and, although specific terms are employed, they are  
used in a generic and descriptive sense only and not for purposes of limitation, the  
scope of the invention being set forth in the following claims.

**What Is Claimed Is:**

1. A method of asymmetrically synthesizing an enantiomer of an acylanilide or a derivative thereof comprising:

(a) contacting a compound having a ring structure that, when opened, provides a substituent having the structure of Formula I:



5

wherein

R<sup>1</sup> is alkyl or haloalkyl having up to 4 carbons;

R<sup>2</sup> is alkyl having up to 6 carbon atoms; and

R<sup>3</sup> is CH<sub>2</sub>OR<sup>4</sup> where R<sup>4</sup> is hydrogen or benzyl, C(O)CH<sub>3</sub>, or C(O)OR<sup>5</sup> where R<sup>5</sup> is

10 hydrogen or alkyl;

with a compound having a structure of Formula II:



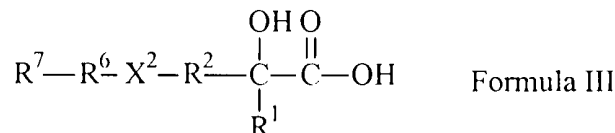
wherein

R<sup>6</sup> is a direct link or alkyl having up to 6 carbon atoms;

15 R<sup>7</sup> is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbons; or R<sup>7</sup> is phenyl which bears one, two or three substituents independently selected from hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxy carbonyl and N-alkylcarbamoyl each of up to 4 carbon atoms, and  
20 phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R<sup>7</sup> is naphthyl; or R<sup>7</sup> is a 5- or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulfur, which heterocyclic may be a single ring or may be fused to a benzo-  
25 ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents; and



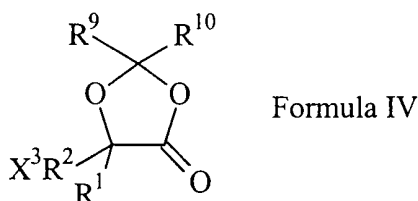
30  $X^1$  is oxygen, sulfur, sulphinyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-) or alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms; under conditions sufficient to provide a compound having the structure of Formula III:



35 wherein  $X^2$  is oxygen, sulfur, sulphinyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-), oxidized imino alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms, or oxidized alkylimino; and

(b) treating the compound of Formula III under conditions sufficient to provide a pure enantiomer of an acylanilide or a derivative thereof.

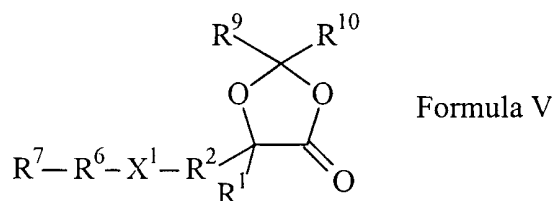
2. The method according to Claim 1, wherein the compound having a ring structure is a compound of Formula IV:



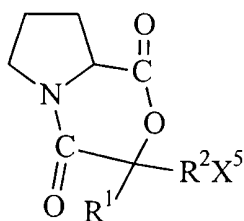
wherein

- 5  $R^9$  is hydrogen, or straight, branched or cyclic alkyl;  
 $R^{10}$  is straight or branched alkyl, aryl, or  $R^{11}X_3^4$ , where  $R^{11}$  is alkyl and  $X^4$  is alkyl, halogen or aryl; and  
 $X^3$  is a leaving group; and

10 wherein step (a) comprises contacting the compound of Formula IV with the compound of Formula II under conditions sufficient to provide a compound having the structure of Formula V:



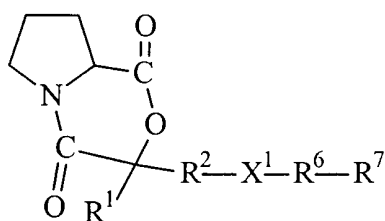
3. The method according to Claim 2, wherein R<sup>1</sup> is methyl and R<sup>2</sup> is methylene.
4. The method according to Claim 2, further comprising treating a starting compound of citramalic acid under conditions sufficient to provide a compound having the structure of Formula IV.
5. The method according to Claim 4, wherein the citramalic acid is (S)-citramalic acid, and wherein the pure enantiomer of an acylanilide is (R)-Casodex<sup>(R)</sup> (bicalutamide) or a derivative there.
6. The method according to Claim 1, wherein the compound having a ring structure is a compound of Formula VIII:



Formula VIII

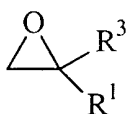
wherein X<sup>5</sup> is a leaving group; and

- 5 wherein step (a) comprises contacting the compound of Formula VIII with the compound of Formula II under conditions sufficient to provide a compound having the structure of Formula IX:



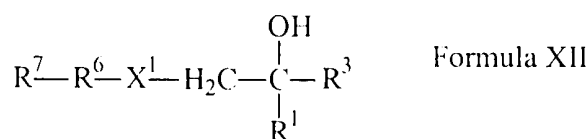
Formula IX

7. The method according to Claim 1, wherein the compound having a ring structure is a compound of Formula XI:



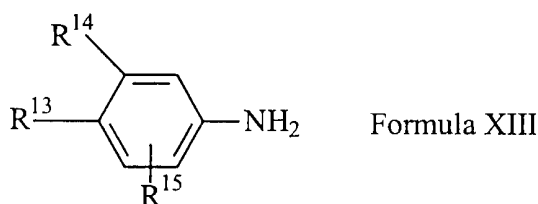
Formula XI

wherein step (a) comprises contacting the compound of Formula XI with the  
 5 compound of Formula II under conditions sufficient to provide a compound having  
 the structure of Formula XII:

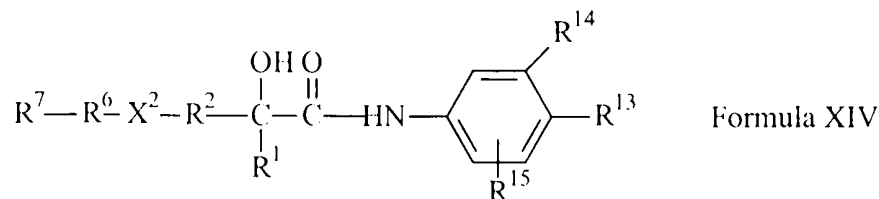


8. The method according to Claim 1, wherein  $X^1$  is sulfur,  $R^6$  is a direct link, and  $R^7$  is 4-fluorophenyl, and the compound of Formula II is 4-fluorobenzenethiol.

9. The method according to Claim 1, wherein step (b) comprises:  
 treating the compound of Formula III with a compound having the structure of  
 Formula XIII:

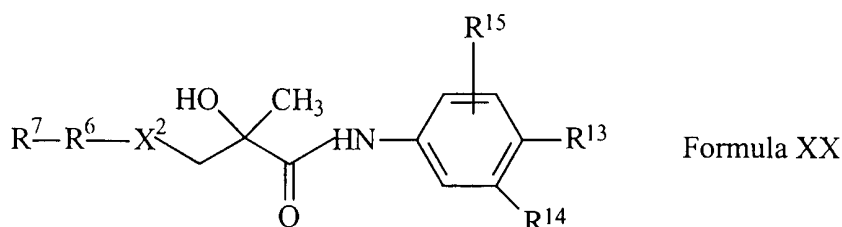


5 wherein  
 $R^{13}$  is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo, or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each having up to 4 carbon atoms, or phenylthio, phenylsulphinyl or  
 10 phenylsulphonyl;  
 $R^{14}$  is cyano, cabamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of having up to 4 carbon atoms; or phenylthio, phenylsulphinyl or phenylsulphonyl; and  
 15  $R^{15}$  is hydrogen or halogen;  
 under conditions sufficient to provide a compound of Formula XIV:



wherein X<sup>2</sup> is oxygen, sulfur, sulphinyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-), oxidized imino alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms, or oxidized alkylimino.

10. A method of asymmetrically synthesizing a pure enantiomer of an acylanilide or a derivative thereof comprising treating citramalic acid under conditions sufficient to provide a compound having the structure of Formula XX:



5 wherein

R<sup>6</sup> is a direct link or alkyl having up to 6 carbon atoms;

R<sup>7</sup> is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbons; or R<sup>7</sup> is phenyl which bears one, two or three substituents independently selected from hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxy carbonyl and N-alkyl carbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R<sup>7</sup> is naphthyl; or R<sup>7</sup> is a 5- or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulfur, which heterocyclic may be a single ring or may be fused to a benzene ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents;

$X^2$  is oxygen, sulfur, sulphinyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-), oxidized imino alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms, or oxidized alkylimino;

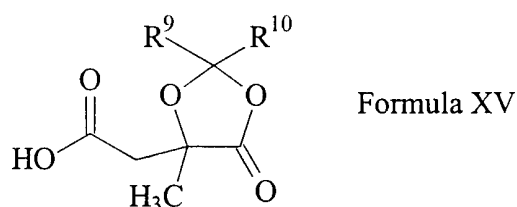
25 R<sup>13</sup> is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo, or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each having up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

30 R<sup>14</sup> is cyano, cabamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of having up to 4 carbon atoms; or phenylthio, phenylsulphinyl or phenylsulphonyl; and

R<sup>15</sup> is hydrogen or halogen.

11. The method according to Claim 10, wherein the step of treating citramalic acid under conditions sufficient to provide a compound having the structure of Formula XX comprises:

5 aldol condensation reacting citramalic acid with a compound capable of undergoing an aldol condensation reaction under conditions sufficient to provide a compound having the structure of Formula XV:

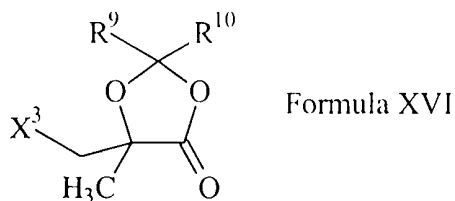


wherein

10 R<sup>9</sup> is hydrogen, or straight, branched or cyclic alkyl; and R<sup>10</sup> is straight or branched alkyl, aryl, or R<sup>11</sup>X<sub>3</sub><sup>4</sup>, where R<sup>11</sup> is alkyl and X<sup>4</sup> is alkyl, halogen or aryl.

12. The method according to Claim XV, wherein the aldol condensation reacting step comprises contacting the citramalic acid with bromal in the presence of sulfuric acid.

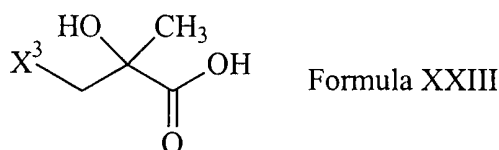
13. The method according to Claim 11, further comprising:  
 decarboxylating the compound of Formula XV under conditions sufficient to  
 provide a compound having the structure of Formula XVI:



5 wherein X<sup>3</sup> is a leaving group.

14. The method according to Claim 13, wherein the decarboxylating step  
 comprises decarboxylatively brominating the compound of Formula XV with 2-  
 mercaptopyridine N-oxide, dicyclohexylcarbodiimide, and CBrCl<sub>3</sub>.

15. The method according to Claim 13, further comprising:  
 hydrolyzing the compound of Formula XVI under conditions sufficient to  
 provide a compound having the structure of Formula XXIII:



16. The method according to Claim 15, wherein the hydrolyzing step  
 comprises contacting the compound of Formula XVI with HCl.

17. The method according to Claim 15, further comprising:  
 treating the compound of Formula XXIII with a compound having the  
 structure of Formula II:



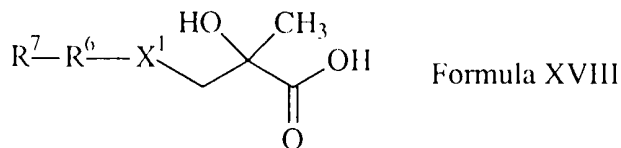
5 wherein

X<sup>1</sup> is oxygen, sulfur, sulphinyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-) or  
 alkylimino

(-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms;

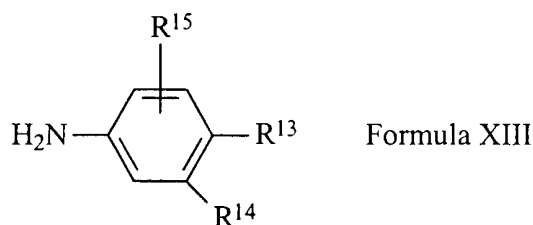
under conditions sufficient to provide a compound having the structure of Formula

10 XVIII:

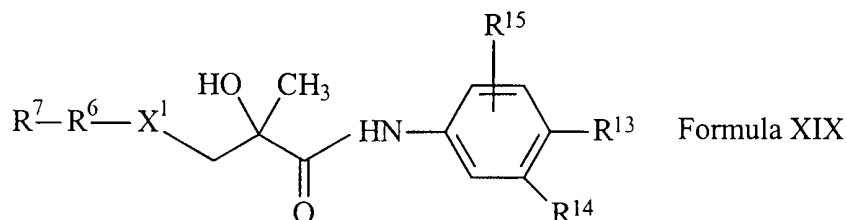


18. The method according to Claim 17, wherein the compound of Formula II is 4-fluorobenzenethiol.

19. The method according to Claim 17, further comprising:  
treating the compound of Formula XVIII with a compound having the structure of Formula XIII:



5 under conditions sufficient to provide a compound having the structure of Formula XIX:



20. The method according to Claim 19, wherein the step of treating the compound of Formula XVIII with a compound of Formula XIII comprises:

contacting the compound of Formula XVIII with thionyl chloride to provide an acid chloride; and

5 contacting the acid chloride with 4-amino-2-trifluoromethylbenzonitrile.

21. The method according to Claim 19, wherein X<sup>1</sup> is capable of being oxidized, the method further comprising:

oxidizing the compound of Formula XIX under conditions sufficient to provide the compound of Formula XX.

22. The method according to Claim 21, wherein the oxidizing step comprises contacting the compound of Formula XIX with meta-chloroperbenzoic acid.

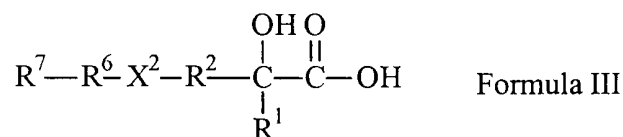
23. The method according to Claim 10, wherein the citramalic acid is (S)-citramalic acid and the pure enantiomer of the acylanalide is (R)-Casodex<sup>®</sup> (bicalutamide).

24. The method according to Claim 10, wherein the citramalic acid is (R)-citramalic acid and the pure enantiomer of the acylanalide is (S)-Casodex<sup>®</sup> (bicalutamide).

25. A method of treating prostate cancer comprising administering a therapeutically effective amount of a pure enantiomer prepared by the method of Claim 10.

26. The method according to Claim 25, wherein the pure enantiomer of the acylanalide is (R)-Casodex<sup>®</sup> (bicalutamide).

27. A method of forming an optically active compound having the structure of Formula III:



wherein

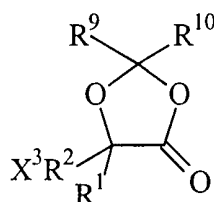
- 5      R<sup>1</sup> is alkyl or haloalkyl having up to 4 carbons;  
        R<sup>2</sup> is alkyl having up to 6 carbon atoms;  
        R<sup>6</sup> is a direct link or alkyl having up to 6 carbon atoms;  
        R<sup>7</sup> is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbons; or R<sup>7</sup> is  
 10      phenyl which bears one, two or three substituents independently selected from  
        hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy,  
        alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl,



perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxy carbonyl and N-alkyl carbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R<sup>7</sup> is naphthyl; or R<sup>7</sup> is a 5- or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulfur, which heterocyclic may be a single ring or may be fused to a benzene ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents; and X<sup>2</sup> is oxygen, sulfur, sulphinyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-), oxidized imino alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms, or oxidized alkylimino;

25 said method comprising:

(a) treating a compound having the structure of Formula IV:



Formula IV

wherein

R<sup>9</sup> is hydrogen, or straight, branched or cyclic alkyl; and  
 30 R<sup>10</sup> is straight or branched alkyl, aryl, or R<sup>11</sup>X<sub>3</sub><sup>4</sup>, where R<sup>11</sup> is alkyl and X<sup>4</sup> is alkyl, halogen or aryl; and  
 X<sup>3</sup> is a leaving group;

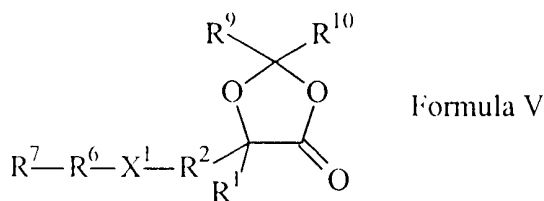
with a compound having the structure of Formula II:



35 wherein

X<sup>1</sup> is oxygen, sulfur, sulphinyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-) or alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms;

under conditions sufficient to provide a compound having the structure of Formula V:



40

;and

(b) treating the compound of Formula V under conditions sufficient to provide a compound having the structure of Formula III.

28. The method according to Claim 27, wherein the compound of Formula II is 4-fluorobenzenethiol.

29. The method according to Claim 27, wherein step (b) comprises contacting the compound of Formula IV with a hydrolyzing agent to open the heterocyclic ring of Formula IV.

30. The method according to Claim 27, wherein  $X^1$  is sulfur or sulphanyl and  $X^2$  is sulphonyl.

31. The method according to Claim 30, wherein step (b) comprises the steps of:

contacting the compound of Formula V with an oxidizing agent to convert  $X^1$  to  $X^2$ ; and then

5 contacting the oxidized compound with a hydrolyzing agent to open the heterocyclic ring of Formula V and provide the compound of Formula III.

32. The method according to Claim 30, wherein step (b) comprises the steps of:

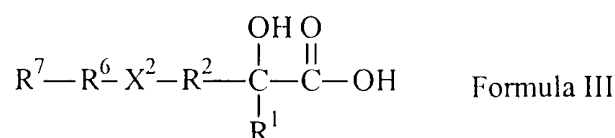
contacting the compound of Formula V with a hydrolyzing agent to open the heterocyclic ring of Formula V; and then

5 contacting the hydrolyzed compound with an oxidizing agent to convert  $X^1$  to  $X^2$  and provide the compound of Formula III.

33. The method according to Claim 27, further comprising the step of:

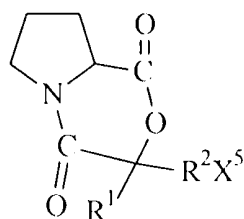
treating a starting compound of citramalic acid under conditions sufficient to provide a compound having the structure of Formula IV wherein R<sup>1</sup> is methyl and R<sup>2</sup> is methylene.

34. A method of forming an optically active compound having the structure of Formula III:



wherein

- 5        R<sup>1</sup> is alkyl or haloalkyl having up to 4 carbons;  
           R<sup>2</sup> is alkyl having up to 6 carbon atoms;  
           R<sup>6</sup> is a direct link or alkyl having up to 6 carbon atoms;  
           R<sup>7</sup> is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbons; or R<sup>7</sup> is  
 10        phenyl which bears one, two or three substituents independently selected from  
           hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy,  
           alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl,  
           perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl,  
           alkoxy carbonyl and N-alkyl carbamoyl each of up to 4 carbon atoms, and  
           phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R<sup>7</sup> is naphthyl;  
 15        or R<sup>7</sup> is a 5- or 6-membered saturated or unsaturated heterocyclic which  
           contains one, two or three heteroatoms selected from oxygen, nitrogen and  
           sulfur, which heterocyclic may be a single ring or may be fused to a benzo-  
           ring, and which heterocyclic is unsubstituted or bears one or two halogen,  
           cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl  
 20        each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if  
           sufficiently saturated may bear one or two oxo substituents; and  
           X<sup>2</sup> is oxygen, sulfur, sulphinyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-), oxidized  
           imino alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms, or  
           oxidized alkylimino;  
 25        said method comprising:  
           (a) treating a starting compound having the structure of Formula VIII:



Formula VIII

wherein

- $R^1$  is alkyl having up to 6 carbon atoms;  
 30  $R^2$  is alkyl or haloalkyl having up to 4 carbons; and  
 $X^5$  is a leaving group;

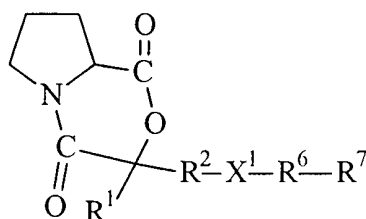
with a compound having the structure of Formula II:



wherein

- 35  $X^1$  is oxygen, sulfur, sulphinyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-) or  
 alkylimino  
 (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms;

under conditions sufficient to provide a compound having the structure of Formula IX:



Formula IX

40

; and

(b) treating the compound of Formula IX under conditions sufficient to provide a compound having the structure of Formula III.

35. The method according to Claim 34, wherein the compound of Formula II is 4-fluorobenzenethiol.

36. The method according to Claim 34, wherein step (b) comprises contacting the compound of Formula IX with a hydrolyzing agent to open the 6-membered heterocyclic ring of Formula IX.

37. The method according to Claim 34, wherein X<sup>1</sup> is sulfur or sulphinyl and X<sup>2</sup> is sulphonyl.

38. The method according to Claim 37, further comprising the steps of: contacting the compound of Formula IX with an oxidizing agent to convert X<sup>1</sup> to X<sup>2</sup>; and then

5 contacting the oxidized compound with a hydrolyzing agent to open the 6-membered heterocyclic ring of Formula IX to provide a compound having the structure of Formula III.

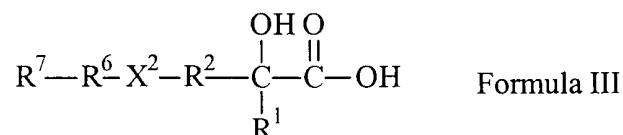
39. The method according to Claim 37, further comprising the steps of: contacting the compound of Formula IX with a hydrolyzing agent to open the 6-membered heterocyclic ring of Formula IX and form an acid; and then

5 contacting the hydrolyzed compound with an oxidizing agent to convert X<sup>1</sup> to X<sup>2</sup> to provide a compound having the structure of Formula III.

40. The method according to Claim 34, wherein the chiral carbon at the 3 position of the 6-membered heterocyclic ring of Formula IX has an R configuration.

41. The method according to Claim 34, wherein the chiral carbon at the 3 position of the 6-membered heterocyclic ring of Formula IX has an S configuration.

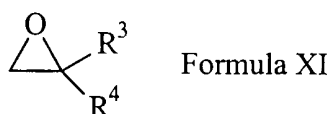
42. A method of forming an optically active compound having the structure of Formula III:



wherein

- 5 R<sup>1</sup> is alkyl or haloalkyl having up to 4 carbons;  
 R<sup>2</sup> is alkyl having up to 6 carbon atoms;  
 R<sup>6</sup> is a direct link or alkyl having up to 6 carbon atoms;  
 R<sup>7</sup> is alkyl, alkenyl, hydroxyalkyl or cycloalkyl each of up to 6 carbons; or R<sup>7</sup> is phenyl which bears one, two or three substituents independently selected from

- 10 hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxy carbonyl and N-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or R<sup>7</sup> is naphthyl;
- 15 or R<sup>7</sup> is a 5- or 6-membered saturated or unsaturated heterocyclic which contains one, two or three heteroatoms selected from oxygen, nitrogen and sulfur, which heterocyclic may be a single ring or may be fused to a benzene ring, and which heterocyclic is unsubstituted or bears one or two halogen, cyano or amino, or alkyl, alkoxy, alkylthio, alkylsulphinyl or alkylsulphonyl
- 20 each of up to 4 carbon atoms, or oxy or hydroxy substituents, or which if sufficiently saturated may bear one or two oxo substituents; and X<sup>2</sup> is oxygen, sulfur, sulphinyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-), oxidized imino alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms, or oxidized alkylimino;
- 25 said method comprising treating a starting compound having the structure of Formula XI:



wherein

- R<sup>3</sup> is CH<sub>2</sub>OR<sup>4</sup> where R<sup>4</sup> is hydrogen or benzyl, C(O)CH<sub>3</sub>, or C(O)OR<sup>5</sup> where R<sup>5</sup> is hydrogen or alkyl;
- 30

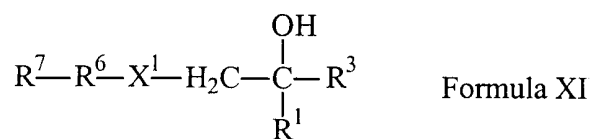
with a compound having the structure of Formula II:



wherein

- X<sup>1</sup> is oxygen, sulfur, sulphinyl (-SO-), sulphonyl (-SO<sub>2</sub>-), imino (-NH-) or
- 35 alkylimino (-NR<sup>8</sup>-) where R<sup>8</sup> is alkyl having up to 6 carbon atoms;

under conditions sufficient to provide a compound having the structure of Formula XII:



40 ; and

(b) treating the compound of Formula XII under conditions sufficient to provide the compound of Formula III.

43. The method according to Claim 42, wherein the compound of Formula II is 4-fluorobenzenethiol.

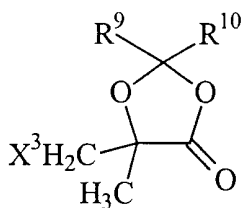
44. The method according to Claim 42, wherein  $X^1$  is sulfur or sulphonyl and  $X^2$  is sulphonyl.

45. The method according to Claim 42, wherein step (b) comprises contacting the compound of Formula XI with an oxidizing agent to convert  $X^1$  to  $X^2$ .

46. The method according to Claim 42, wherein the chiral carbon at the 2 position of the heterocyclic ring of Formula XI has an R configuration.

47. The method according to Claim 42, wherein the chiral carbon at the 2 position of the heterocyclic ring of Formula XI has an S configuration.

48. A method of synthesizing an optically active compound having the structure of Formula XVI:



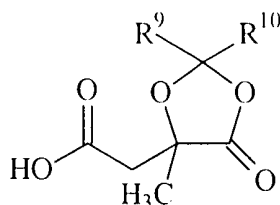
Formula XVI

wherein

- 5  $R^9$  is hydrogen, or straight, branched or cyclic alkyl;  
 $R^{10}$  is straight or branched alkyl, aryl, or  $R^{11}X_3^4$ , where  $R^{11}$  is alkyl and  $X^4$  is  
 alkyl, halogen or aryl; and  
 $X^3$  is a leaving group;

10 said method comprising treating citramalic acid under conditions sufficient to provide the compound having the structure of Formula XVI.

49. The method according to Claim 48, wherein the treating step comprises the step of aldol condensation reacting citramalic acid with a compound capable of undergoing an aldol condensation reaction to provide a compound having the structure of Formula XV:



Formula XV

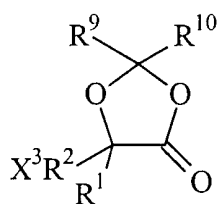
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50. The method according to Claim 49, wherein  $R^9$  is hydrogen,  $R^{10}$  is  $CBR_3$  and the compound is tribromoacetaldehyde.

51. The method according to Claim 49, wherein the treating step further comprises the step of decarboxylation reacting the compound of Formula XV to provide a compound having the structure of Formula XVI.

52. The method according to Claim 51, wherein the decarboxylation reacting step comprises decarboxylatively brominating the compound of Formula XV with 2-mercaptopyridine N-oxide and dicyclohexylcarbodiimide in the presence of  $CBRCl_3$  to provide a compound having the structure of Formula XVI.

53. A compound having a chemical structure of Formula IV:



Formula IV

wherein

- $R^1$  is alkyl or haloalkyl having up to 4 carbons;
- $R^2$  is alkyl having up to 6 carbon atoms;
- $R^9$  is hydrogen, or straight, branched or cyclic alkyl;
- $R^{10}$  is straight or branched alkyl, aryl, or  $R^{11}X_3^4$ , where  $R^{11}$  is alkyl and  $X^4$  is alkyl, halogen or aryl; and
- $X^3$  is a leaving group.



54. The compound according to Claim 52, wherein R<sup>1</sup> is methyl, R<sup>2</sup> is methylene, R<sup>9</sup> is hydrogen, R<sup>10</sup> is benzyl or CX<sub>3</sub><sup>4</sup> where X<sup>5</sup> is CH<sub>3</sub>, Cl, Br, or phenyl, and X<sup>3</sup> is Br.

55. The compound according to Claim 52, wherein the compound is 5-bromomethyl-5-methyl-2-tribromomethyl-[1,3]dioxolan-4-one.

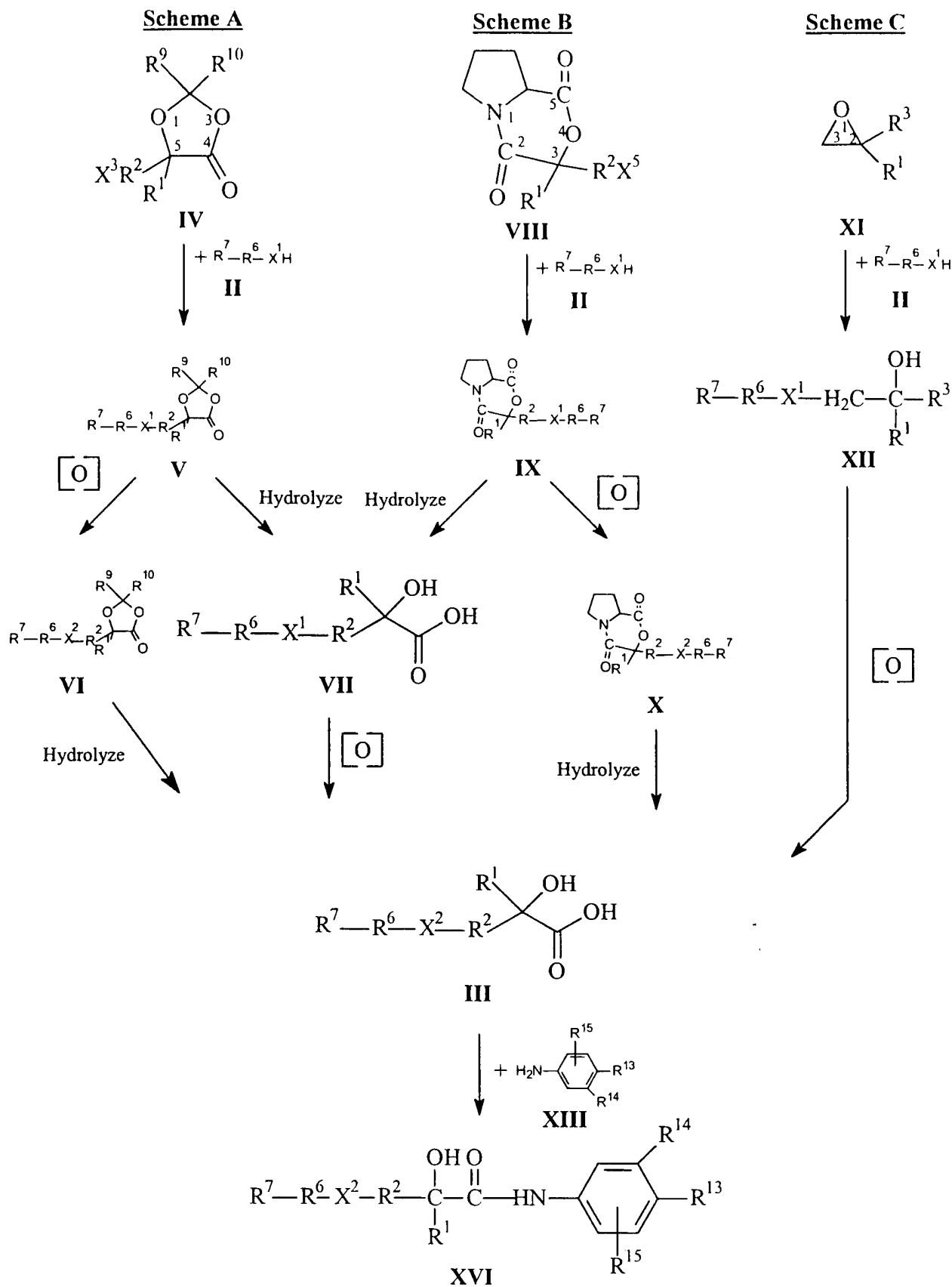


FIG. 1

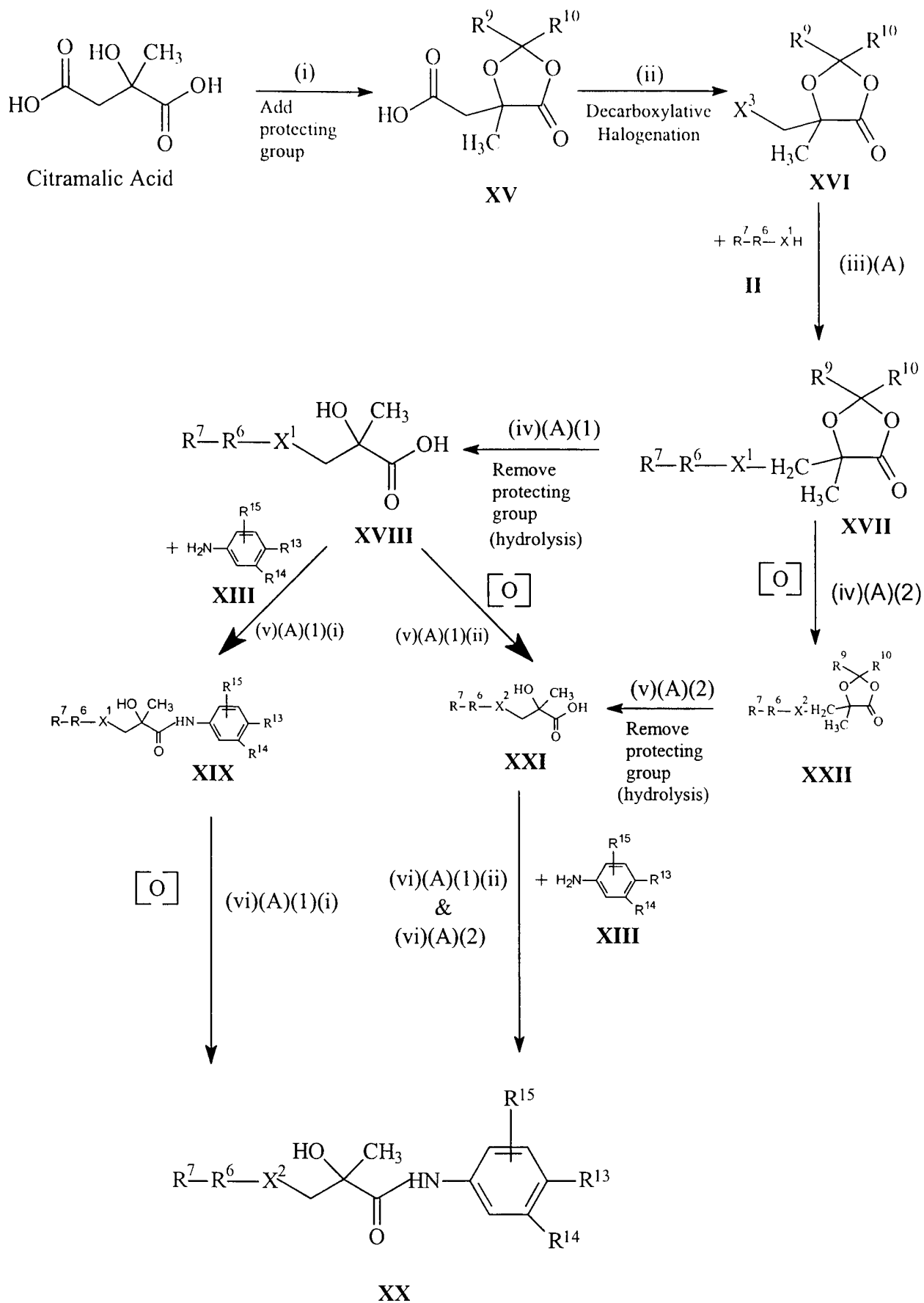
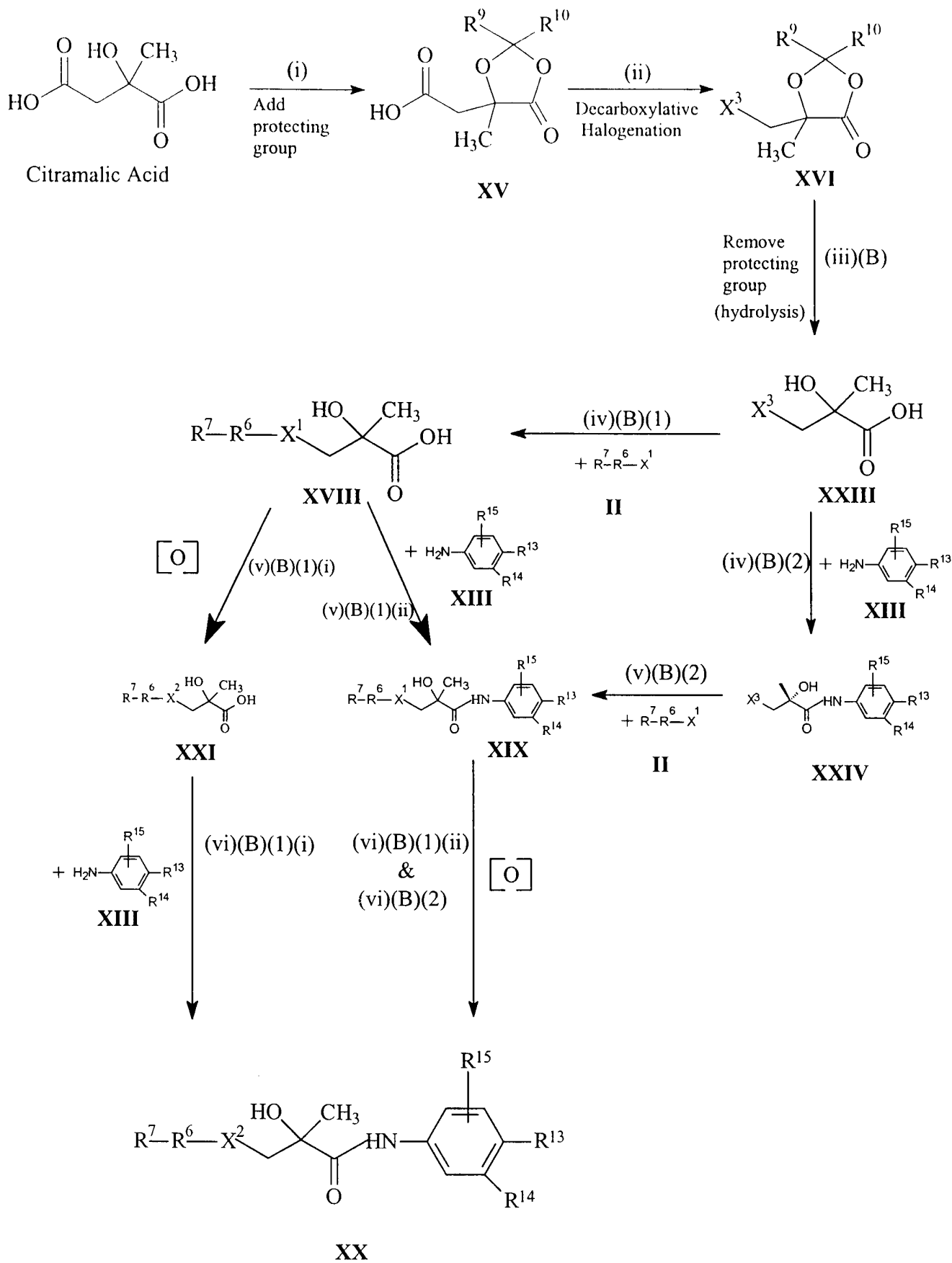


FIG. 2



**FIG. 3**