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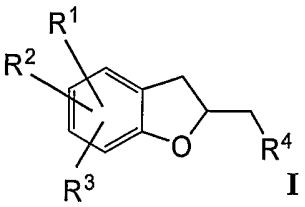
(54) Title: ASYMMETRIC SYNTHESIS OF DIHYDROBENZOFURAN DERIVATIVES



I

(57) Abstract: This invention concerns a process for the preparation of benzofuran derivatives. In some aspects, these compounds are of formula I: wherein each of R', R^2, R^3, and R^4 is as defined herein.

ASYMMETRIC SYNTHESIS OF DIHYDROBENZOFURAN DERIVATIVES

FIELD OF THE INVENTION

[0001] The present invention concerns processes for the asymmetric synthesis of dihydrobenzofuran derivatives.

BACKGROUND OF THE INVENTION

[0002] Schizophrenia affects approximately 5 million people. The most prevalent treatments for schizophrenia are currently the 'atypical' antipsychotics, which combine dopamine (D_2) and serotonin (5-HT_{2A}) receptor antagonism. Despite the reported improvements in efficacy and side-effect liability of atypical antipsychotics relative to typical antipsychotics, these compounds do not appear to adequately treat all the symptoms of schizophrenia and are accompanied by problematic side effects, such as weight gain (Allison, D. B., et. al., Am. J. Psychiatry, 156: 1686-1696, 1999; Masand, P. S., Exp. Opin. Pharmacother. I: 377-389, 2000; Whitaker, R., Spectrum Life Sciences. Decision Resources. 2:1-9, 2000).

[0003] Atypical antipsychotics also bind with high affinity to 5-HT_{2C} receptors and function as 5-HT_{2C} receptor antagonists or inverse agonists. Weight gain is a problematic side effect associated with atypical antipsychotics such as clozapine and olanzapine, and it has been suggested that 5-HT_{2C} antagonism is responsible for the increased weight gain. Conversely, stimulation of the 5-HT_{2C} receptor is known to result in decreased food intake and body weight (Walsh et. al., Psychopharmacology 124: 57-73, 1996; Cowen, P. J., et. al., Human Psychopharmacology 10: 385-391, 1995; Rosenzweig-Lipson, S., et. al., ASPET abstract, 2000).

[0004] Several lines of evidence support a role for 5-HT_{2C} receptor agonism or partial agonism as a treatment for schizophrenia. Studies suggest that 5-HT_{2C} antagonists increase

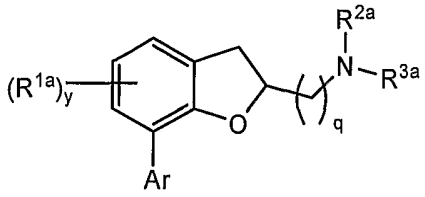
synaptic levels of dopamine and may be effective in animal models of Parkinson's disease (Di Matteo, V., et. al., Neuropharmacology 37: 265-272, 1998; Fox, S. H., et. al., Experimental Neurology 151: 35-49, 1998). Since the positive symptoms of schizophrenia are associated with increased levels of dopamine, compounds with actions opposite to those of 5-HT_{2C} antagonists, such as 5-HT_{2C} agonists and partial agonists, should reduce levels of synaptic dopamine. Recent studies have demonstrated that 5-HT_{2C} agonists decrease levels of dopamine in the prefrontal cortex and nucleus accumbens (Millan, M. J., et. al., Neuropharmacology 37: 953-955, 1998; Di Matteo, V., et. al., Neuropharmacology 38: 1195-1205, 1999; Di Giovanni, G., et. al., Synapse 35: 53-61, 2000), brain regions that are thought to mediate critical antipsychotic effects of drugs like clozapine. However, 5-HT_{2C} agonists do not decrease dopamine levels in the striatum, the brain region most closely associated with extrapyramidal side effects. In addition, a recent study demonstrates that 5-HT_{2C} agonists decrease firing in the ventral tegmental area (VTA), but not in the substantia nigra. The differential effects of 5-HT_{2C} agonists in the mesolimbic pathway relative to the nigrostriatal pathway suggest that 5-HT_{2C} agonists have limbic selectivity, and will be less likely to produce extrapyramidal side effects associated with typical antipsychotics.

[0005] Certain dihydrobenzofurans are believed to possess affinity for the $5HT_{2C}$ receptor. Preferably, such dihydrobenzofurans act as agonists or partial agonists at the $5HT_{2C}$ receptor and therefore are believed to be useful in a variety of medicinal applications, for example, as discussed above. The present invention provides stereoselective methods for synthesizing dihydrobenzofurans.

SUMMARY OF THE INVENTION

[0006] As described herein, the present invention provides methods for preparing compounds having activity as $5HT_{2C}$ agonists or partial agonists. These compounds are useful for treating disorders including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, substance-induced psychotic disorder, L-DOPA-induced psychosis, psychosis associated with Alzheimer's dementia, psychosis associated with Parkinson's disease, psychosis associated with Lewy body disease, dementia, memory deficit, intellectual deficit associated with Alzheimer's disease, bipolar disorders, depressive disorders, mood episodes, anxiety disorders, adjustment disorders,

eating disorders, epilepsy, sleep disorders, migraines, sexual dysfunction, gastrointestinal disorders, obesity, or a central nervous system deficiency associated with trauma, stroke, or spinal cord injury. Such compounds include those of formula **II**:



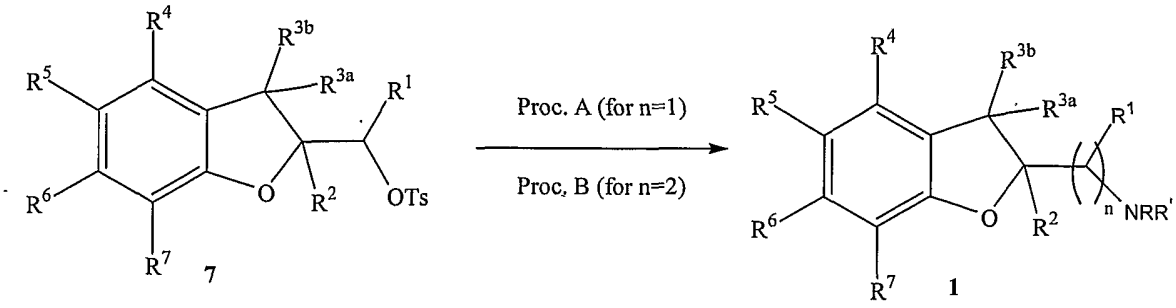
II

or a pharmaceutically acceptable salt thereof, wherein each of R^{1a}, R^{2a}, R^{3a}, Ar, q, and y is as defined herein.

[0007] The present invention also provides synthetic intermediates useful for preparing such compounds.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0008] The methods and intermediates of the present invention are useful for preparing compounds as described in, e.g. U.S. patent application entitled "Dihydrobenzofuranyl Alkanamine Derivatives and Methods for Using Same," filed in the name of Jonathan Gross, et al., having serial number 11/113,170, filed April 22, 2005, and claiming benefit to US application 10/970,014, filed October 21, 2004, and US provisional application 60/514,454, filed on October 24, 2003, each of which is hereby incorporated herein by reference in its entirety for all purposes. US application 10/970,014, filed October 21, 2004 is published as US 2005/0143452 A1. It teaches that conversion of the tosylate (7) to the amine (1) can be accomplished, for example, by treatment with sodium azide in a solvent such as dimethylsulfoxide followed by reduction of the azide or direct treatment with an appropriately substituted amine to provide the compounds of Formula 1. Additionally, longer alkyl chains (i.e. 2-aminoethyl) may be prepared, for example, via treatment of (7) with sodium cyanide in a solvent such as dimethylsulfoxide followed by reduction of the nitrile.

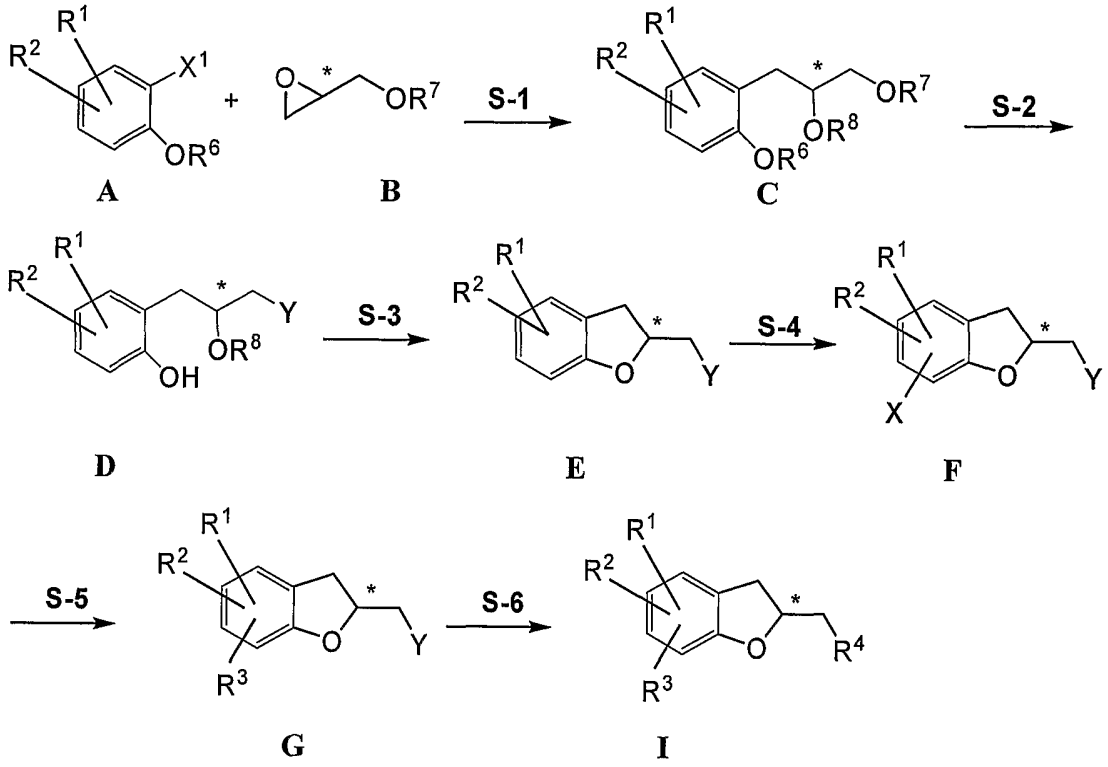


Proc. A: 1. a) NaN3, DMSO and b) reduction, or 2. NHRR'/DMSO

Proc. B: 1. a) NaCN/DMSO and b) H_2/5% Rh on Al_2O_3, NH_4OH

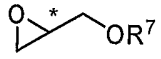
In certain embodiments, the present compounds are generally prepared according to Scheme I set forth below:

Scheme I



[0009] In Scheme I above, each of R^1, R^2, R^3, R^4, R^6, R^8, Y, X, and X^1 is as defined below and in classes and subclasses as described herein.

[0010] At step **S-1**, the conversion of a compound of formula **A** to compound of formula **C**, wherein R^8 is hydrogen, is performed *via* a metal-halogen exchange reaction, followed by formation of an organocuprate. First, the compound of formula **A** is treated with a suitable Grignard reagent or an alkyl lithium then a chiral non-racemic epoxide of formula **B**:



B

wherein R^7 is a suitable hydroxyl protecting group. n other embodiments, said reagent is of formula $RMgX^2$, wherein X^2 is halogen and R is an alkyl group. In some embodiments, the organocuprate is formed utilizing $CuBrSMe_2$ or CuCN. In other embodiments the chiral non-racemic glycidyl ether is a glycidyl benzyl ether. One of ordinary skill in the art would recognize that the compound of formula **C** wherein R^8 is hydrogen may be protected such that R^8 is a hydroxyl protecting group.

[0011] At step **S-2**, the hydroxyl protecting group R^6 of formula **C** is removed by suitable deprotection conditions. Deprotection conditions for removing hydroxyl protecting groups are known to one of ordinary skill in the art and include those described in detail in T. W. Greene and P. G. M. Wuts, "Protecting Groups in Organic Synthesis" (1991). A wide variety of techniques and reagents are available for the removal of hydroxyl protecting groups. Such techniques and agents are known to one skilled in the art. Hydroxyl protecting group can be removed, for example, by base hydrolysis, acid hydrolysis, or hydrogenation. In some embodiments, the removal of an hydroxyl protecting group is accomplished by acid hydrolysis. In some embodiments, the acid hydrolysis is performed in the presence of BBr_3 or a mixture of BBr_3 and BCl_3. In other embodiments, the removal of the protecting group is accomplished under basic conditions.

[0012] One of ordinary skill in the art would recognize that in certain embodiments, the R^6 protecting group is removed under HBr/HOAc conditions, the R^8 protecting group and Y group may be incorporated into the compound of formula **D** as acetyl and bromo, respectively.

[0013] The cyclization of a compound of formula **D** to a compound of formula **E**, as depicted at step **S-3**, is achieved by a variety of conditions. For example, when R^8 is a base-labile hydroxyl protecting group, then the treatment of a compound of formula **D** can effect both deprotection of the R^8 group and cyclization. Alternatively, the R^8 protecting group may be removed prior to cyclization by conditions suitable for removing that group. Such conditions include reduction, treatment with acid, and the like as described in Greene. When the R^8 protecting group is removed prior to cyclization such that a diol compound is formed, the cyclization of that compound to afford a compound of formula **E** may be achieved by dehydration. Such dehydration reactions are known to one of ordinary skill in the art and include Mitsunobu reactions.

[0014] As defined herein, the X group of formula **F** is halogen or triflate. The conversion of a compound of formula **E** to a compound of formula **F** wherein X is halogen is accomplished by halogenation reaction. One of ordinary skill in the art would recognize that a variety of halogenating agents are suitable for preparing a compound of formula **F** from a compound of formula **E**. In certain embodiments, X is bromo and the halogenating agent used at step **S-4** is bromine. In other embodiments, X is bromo and the halogenating agent used at step **S-4** is a compound containing an N–Br group (e.g., N-bromosuccinimide). Other brominating agents are known to those skilled in the art.

[0015] For preparing compounds of formula **F** wherein the X group is triflate, the compound of formula **E** is first formylated then the formyl group is converted to a hydroxyl group *via* Baeyer-Villiger procedure. The resulting hydroxyl group is then converted to a triflate group by ordinary methods.

[0016] At step **S-5**, the X group of formula **F** is coupled to the aryl or heteroaryl ring of R^3 *via* Suzuki coupling reaction. Catalyst and reaction conditions for the Suzuki reaction of step **S-5** above are well known in the art. See, for example, Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. In certain embodiments, the Suzuki coupling at step **S-5** is performed in the presence of a palladium containing compound. In other embodiments, the palladium containing compound is $Pd(PPh_3)_4$.

[0017] As defined herein, the Y group of formulae **D**, **E**, **F**, and **G** is a suitable leaving group. At step **S-6**, the Y group of formula **G** is displaced with a suitably protected amino group to form a compound of formula **I** wherein R^4 is a protected amino group or an amino group of formula $HN(R^5)(R^{5a})$. Alternatively, a compound of formula **F** is treated with an alkali metal azide to produce a compound of formula **G** wherein R^4 is N_3.

[0018] Unless otherwise indicated, the following terms have the following meanings:

[0019] The term "alkyl," as used herein, refers to a hydrocarbon group having 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms, and more preferably 1 to 4 carbon atoms. The term "alkyl" includes, but is not limited to, straight and branched groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, and isohexyl. The term "lower alkyl" refers to an alkyl group having 1 to 4 carbon atoms.

[0020] The term "alkenyl," as used herein refers to a straight or branched hydrocarbon group having 2 to 8 carbon atoms and that contains 1 to 3 double bonds. Examples of alkenyl groups include vinyl, prop-1-enyl, allyl, methallyl, but-1-enyl, but-2-enyl, but-3-enyl, or 3,3-dimethylbut-1-enyl. The term "lower alkenyl" refers to a straight or branched alkenyl group having 1 to 4 carbon atoms.

[0021] The term "cycloaliphatic," as used herein, refers to a saturated or partially unsaturated hydrocarbon monocyclic or bicyclic ring having 3 to 10 carbon atoms and more preferably 5 to 7 carbon atoms. In certain embodiments, the cyclic cycloaliphatic group is bridged. As used herein, the term "bridged" refers to a cycloaliphatic group that contains at least one carbon-carbon bond between two non-adjacent carbon atoms of the cycloalkyl ring. As used herein, the term "partially unsaturated" refers to a nonaromatic

cycloaliphatic group containing at least one double bond and, in certain embodiments, only one double bond. In certain embodiments, the cycloaliphatic group is saturated. The cycloaliphatic group may be unsubstituted or substituted as described hereinafter.

[0022] The term "alkylcycloaliphatic," as used herein, refers to the group $-(CH_2)_r$cycloaliphatic, where cycloaliphatic is as defined above and r is 1 to 6, preferably 1 to 4, and more preferably 1 to 3.

[0023] The term "heterocycloalkyl," as used herein, refers to a 3 to 10 membered monocyclic or bicyclic ring having 1-3 heteroatoms independently selected from oxygen, nitrogen, or sulfur. In certain embodiments, heterocycloalkyl refers to a 5 to 7 membered ring having 1-2 heteroatoms independently selected from oxygen, nitrogen, or sulfur. The heterocycloalkyl group may be saturated or partially unsaturated, and may be monocyclic or bicyclic (such as bridged). Preferably, the heterocycloalkyl is monocyclic. The heterocycloalkyl group may be unsubstituted or substituted as described hereinafter.

[0024] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic and tricyclic ring systems having a total of six to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryloxy," as used herein, refers to the group -OAr, where Ar is a 6-10 membered aryl group. The term "aralkoxy", as used herein, refers to a group of the formula $-O(CH_2)_r$Ar, wherein r is 1-6. The term "aryloxyalkyl", as used herein, refers to a group of the formula $-(CH_2)_r$OAr, wherein r is 1-6.

[0025] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic". In certain embodiments, such heteroaryl ring systems include furanyl, thienyl, pyrazolyl, imidazolyl, isoxazolyl, oxadiazolyl, oxazolyl, pyrrolyl, pyridyl, pyrimidyl, pyridazinyl, triazinyl, thiazolyl, triazolyl, tetrazolyl, quinolinyl, isoquinolinyl, quinazolinyl, indolinyl, indazolyl, benzothienyl, benzofuranyl, benzisoxazolyl, benzimidazolyl, benzothiazolyl,

benzoxazolyl, isoindolyl, and acridinyl, to name but a few. Any aryl, heteroaryl, cycloaliphatic or heterocycloalkyl may optionally be substituted with 1 to 5 substituents independently selected from halogen, hydroxyl, cyano, alkyl of 1 to 6 carbon atoms, perfluoroalkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, or perfluoroalkoxy of 1 to 6 carbon atoms.

[0026] Any aryl, heteroaryl, cycloaliphatic, or heterocycloaliphatic group may optionally be substituted with 1 to 5 substituents independently selected from halogen, hydroxyl, C_{1-6} alkyl, C_{1-6} haloalkyl, $O(C_{1-6}$ alkyl), or $O(C_{1-6}$ haloalkyl).

[0027] The term "heteroaralkyl", as used herein, refers to a group of the formula $-(CH_2)_rHet$, wherein Het is a heteroaryl group as defined above and r is 1-6. The term "heteroarylalkoxy", as used herein, refers to a group of the formula $-O(CH_2)_rHet$ wherein Het is a heteroaryl group as defined above and r is 1-6.

[0028] The term "perfluoroalkyl," as used herein, refers to an alkyl group as defined herein in which all hydrogen atoms are replaced with fluorine.

[0029] The term "lower haloalkyl", as used herein, refers to a C_{1-4} alkyl group as defined herein in which one or more hydrogen atoms are replaced with a halogen atom.

[0030] The term "alkanesulfonamido," as used herein, refers to the group $R-S(O)_2-NH-$ where R is an alkyl group of 1 to 6 carbon atoms.

[0031] The term "alkoxy," as used herein, refers to the group R-O- where R is an alkyl group of 1 to 6 carbon atoms.

[0032] The term "perfluoroalkoxy," as used herein, refers to the group R-O where R is a perfluoroalkyl group of 1 to 6 carbon atoms.

[0033] The terms "monoalkylamino" and "dialkylamino," as used herein, respectively refer to -NHR and $-NR^aR^b$, where R, R^a and R^b are each an independently selected C_{1-6} alkyl group.

[0034] The terms "halogen" or "halo," as used herein, refer to chlorine, bromine, fluorine or iodine.

[0035] The term "protecting group" such as "hydroxyl protecting group" and "amine protecting group" are well understood by one skilled in the art. In particular one skilled in the art is aware of various protecting groups for use to protect hydroxyl and primary and secondary amine groups. Protecting groups, including include those described for example, in T. W. Greene and P. G. M. Wuts, "Protecting Groups in Organic Synthesis" (1991) provided that they are suitable for use in the chemistries described herein.

Particular examples of hydroxyl protecting groups include methyl, benzyl, benzyloxymethyl, or allyl.

[0036] Amino protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Suitable amino protecting groups, taken with the -NH- moiety to which it is attached, include, but are not limited to, aralkylamines, carbamates, allyl amines, amides, and the like. Examples of such groups include t-butyloxycarbonyl (BOC), ethyloxycarbonyl, methyloxycarbonyl, trichloroethyloxycarbonyl, allyloxycarbonyl (Alloc), benzyloxocarbonyl (CBZ), allyl, benzyl (Bn), fluorenylmethylcarbonyl (Fmoc), acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, trifluoroacetyl, benzoyl, and the like. In other embodiments, an amino protecting group is acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, or trifluoroacetyl. In still other embodiments, an amino protecting group is phthalimide or azide.

[0037] Suitable leaving groups are well known in the art, e.g., see, "Advanced Organic Chemistry," Jerry March, 5th Ed., pp. 445–448, John Wiley and Sons, N.Y. Such leaving groups include, but are not limited to, halogen, alkoxy, sulphonyloxy, optionally substituted alkylsulphonyloxy, optionally substituted alkenylsulfonyloxy, optionally substituted arylsulfonyloxy. Examples of suitable leaving groups include chloro, iodo, bromo, fluoro, methanesulfonyl (mesyl), tosyl, triflate, nitrophenylsulfonyl (nosyl), bromophenylsulfonyl (brosyl), and the like.

[0038] Halogenating agents are those agents known in the art of organic synthesis to be capable of donating a halogen to an aromatic system. Examples of halogenating agents include, but are not limited to halophosphorous (such as phosphorous triiodide, phosphorous tribromide or phosphorous pentachloride), N-halosuccinimide, and thionyl halide (such as thionyl chloride).

[0039] The Baeyer-Villiger reaction or procedure is well known to those skilled in the art. This reaction is commonly used to covert aryl aldehydes for ketones to phenols via hydrolysis of the intermediate esters. See, for example, Jerry March, Advanced Organic Chemistry, 1992, 4th Ed., p. 1098. The oxidation utilizes a peracid reagent.

[0040] The Suzuki coupling reaction is well known to those skilled in the art. In this reaction, a boronic acid and an aryl halide or triflate are coupled via a catalyzed process. Typical catalysts include palladium catalysts.

[0041] The compounds of the present invention may contain an asymmetric atom, and some of the compounds may contain one or more asymmetric atoms or centers, which may thus give rise to optical isomers (enantiomers) and diastereomers. In certain embodiments, the asymmetric atom is indicated with a "*". When shown without respect to the stereochemistry, the present invention includes all optical isomers (enantiomers) and diastereomers (geometric isomers); as well as the racemic and resolved, enantiomerically pure *R* and *S* stereoisomers; as well as other mixtures of the *R* and *S* stereoisomers and pharmaceutically acceptable salts thereof. Optical isomers may be obtained in pure form by standard procedures known to those skilled in the art, and include, but are not limited to, diastereomeric salt formation, kinetic resolution, and asymmetric synthesis. It is also understood that this invention encompasses all possible isomers, and mixtures thereof, which may be obtained in pure form by standard separation procedures known to those skilled in the art, and include, but are not limited to, column chromatography, thin-layer chromatography, and high-performance liquid chromatography. Thus, the compounds of this invention include racemates, enantiomers, or geometric isomers of the compounds shown herein.

[0042] It is recognized that atropisomers of the present compounds may exit. The present invention thus encompasses atropisomeric forms of compounds of formula **I** and **II**, as defined above, and in classes and subclasses described above and herein. For definitions and an extensive discourse on atropisomers, see: Eliel, E.L. Stereochemistry of Organic Compounds (John Wiley & Sons, 1994, p 1142), which is incorporated herein by reference in its entirety.

[0043] The term "pharmaceutically acceptable salts" or "pharmaceutically acceptable salt" refers to salts derived from treating a compound of formula **I** with an organic or inorganic acid such as, for example, acetic, lactic, citric, cinnamic, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, oxalic, propionic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, glycolic, pyruvic, methanesulfonic, ethanesulfonic, toluenesulfonic, salicylic, benzoic, or similarly known acceptable acids. In certain embodiments, the present invention provides the hydrochloride salt of a compound of formula **I**.

[0044] In some embodiments, certain reactions of the present invention are stereoselective. In other embodiments, certain reactions of the present invention are stereospecific.

[0045] The term "stereospecific" as used herein, is meant a reaction where starting materials differing only in their spacial configuration are converted to stereoisomerically distinct products. For example, in a stereospecific reaction, if the starting material is enantiopure (100% enantiomer excess "ee"), the final product will also be enantiopure. Similarly if the starting material has an enantiomer excess of about 50%, the final product will also have about a 50% enantiomer excess.

[0046] By "stereoselective" as used herein, it is meant a reaction where one stereoisomer is preferentially formed over another. Preferably, the process of the present invention will produce a dihydrobenzofuran having an enantiomer excess of at least about 30%, more preferably at least about 40%, and most preferably at least about 50%, where enantiomer excess is the mole percent excess of a single enantiomer over the racemate.

[0047] "Enantiomer excess" or "% ee" as used herein refers to the mole percent excess of a single enantiomer over the racemate.

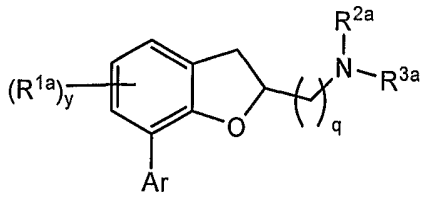
[0048] As used herein, the term "chiral non-racemic" is used interchangeably with "enantiomerically enriched" and signifies that one enantiomer makes up more than 50% of the preparation. In certain embodiments, the term enantiomerically enriched signifies that at least 60% of the preparation is one of the enantiomers. In other embodiments, the term signifies that at least 75% of the preparation is one of the enantiomers. In other embodiments, the term signifies that at least 95% of the preparation is one of the enantiomers. is meant a nonracemic mixture of chiral molecules. In some embodiments, the chiral non-racemic compounds have more than about 30% ee. In other embodiments, the compounds have more than about 50% ee, or more than about 80% ee, or more than about 90% ee, or more than 95% ee, or more than 99% ee.

[0049] The process of the present invention preferably produces dihydrobenzofuran derivatives having an enantiomer excess of at least about 30%, more preferably at least about 50%, and most preferably at least about 95%.

[0050] "Organic impurities" as used herein, refers to any organic by-product or residual material present in the desired dihydrobenzofuran product, and do not include residual solvents or water. "Total organic impurities" refer to the total amount of organic impurities present in the desired dihydrobenzofuran product. Percent organic impurities such as total organic impurities and single largest impurity, unless otherwise stated are expressed herein as HPLC area percent relative to the total area of the HPLC

chromatogram. The HPLC area percent is reported at a wavelength where the desired product and maximum number of organic impurities absorb.

[0051] According to one aspect, the present invention provides a method for preparing an enantiomerically enriched compound of formula **II**:



II

or a pharmaceutically acceptable salt thereof, wherein:

q is one or two;

each of R^{2a} and R^{3a} is independently hydrogen, methyl, ethyl, 2-fluoroethyl, 2,2-difluoroethyl or cyclopropyl;

each R^{1a} is independently hydrogen, halogen, OH, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, or CN;

Ar is thienyl, furyl, pyridyl, or phenyl, wherein Ar is optionally substituted with one or more R^x subsituents;

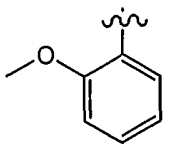
each R^x is independently selected from halogen, OH, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, or CN; and

y is 0, 1, 2, or 3.

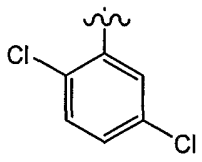
[0052] As defined generally above, the Ar group of formula **II** is thienyl, furyl, pyridyl, or phenyl, wherein Ar is optionally substituted with one or more subsituents independently selected from halogen, OH, lower alkyl, lower alkoxy, haloalkyl, haloalkoxy, or CN. In certain embodiments, the Ar group of formula **II** is unsubstituted phenyl. In other embodiments, the Ar group of formula **II** is phenyl with at least one substituent in the ortho position. In other embodiments, the Ar group of formula **II** is phenyl with at least one substituent in the ortho position selected from halogen, lower alkyl, lower alkoxy, or trifluoromethyl. According to another aspect the present invention provides a compound of formula **II** wherein Ar is phenyl di-substituted in the ortho and meta positions with independently selected halogen, lower alkyl, or lower alkoxy. Yet another aspect of the present invention provides a compound of formula **II** wherein Ar is phenyl di-subsituted in the ortho and para positions with independently selected halogen, lower alkyl, or lower alkoxy. In other embodiment, the present invention provides a

compound of formula **II** wherein Ar is phenyl di-subsituted in the two ortho positions with independently selected halogen, lower alkyl, or lower alkoxy. Exemplary substituents on the phenyl moiety of the Ar group of formula **II** include OMe, fluoro, chloro, methyl, and trifluoromethyl.

[0053] In certain embodiments, the Ar group of formula **II** is selected from the following:



i



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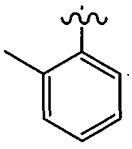

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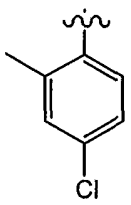

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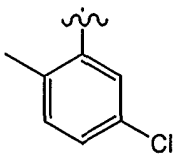
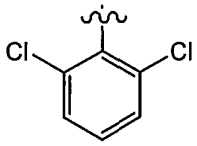


v



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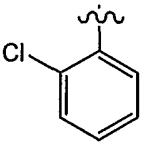

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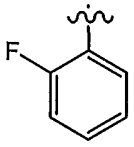

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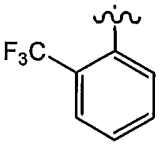

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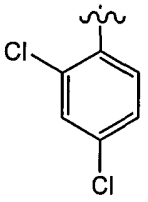
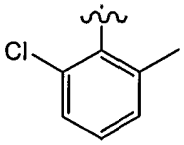
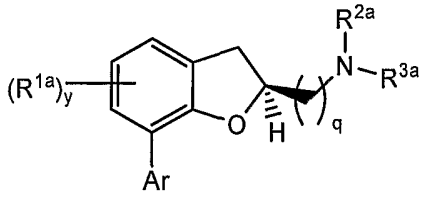


x, or

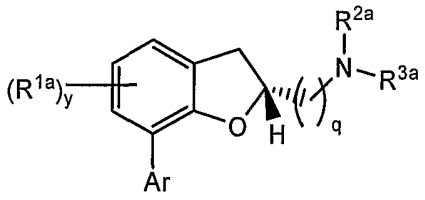


xi.

[0054] In certain embodiments, the present invention provides methods for preparing a compound of formula **IIIa** or **IIIb**:



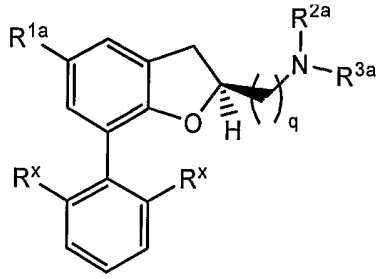
IIIa



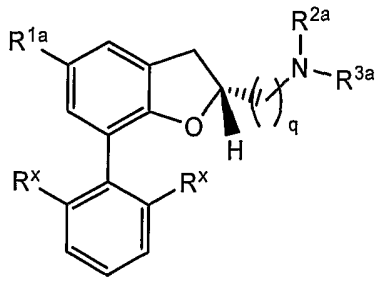
IIIb

or a pharmaceutically acceptable salt thereof, wherein each R^{1a}, R^{2a}, R^{3a}, R^{x}, y, and q are as defined above for compounds of formula **II** and in classes and subclasses as described above and herein.

[0055] According to another embodiment, the present invention provides methods for preparing a compound of formula **IIIc** or **IIId**:



IIIc

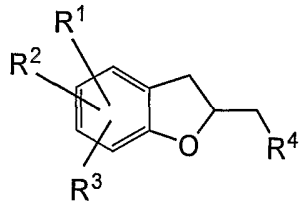


IIId

or a pharmaceutically acceptable salt thereof, wherein each of R^{1a}, R^{2a}, R^{3a}, R^x, y, and q is as defined above for compounds of formula **II** and in classes and subclasses as described above and herein.

[0056] The invention also concerns intermediates of the processes of the present invention.

[0057] In certain embodiments, the present invention provides a method for preparing a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl

having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

R^3 is hydrogen, 6-10 membered aryl, or 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein R^3 is optionally substituted with one or more R^x groups;

each R^x is independently selected from halogen, OH, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, or CN;

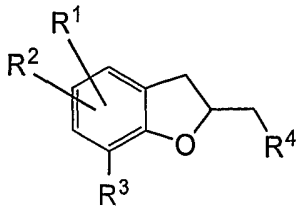
R^4 is CN, N_3, or $N(R^5)(R^{5a})$; and

R^5 and R^{5a} are each independently hydrogen, an amine protecting group, C_{1-6} alkyl, lower haloalkyl, 3-6 membered cycloaliphatic, or alkylcycloaliphatic, or R^5 and R^{5a} are taken together with the nitrogen to which they are attached to form a cyclic amine protecting group or a 3-6 membered saturated or partially unsaturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

wherein said method comprises one or more of the steps depicted in Scheme I above. In certain embodiments, said method comprises all of the steps depicted in Scheme I above.

[0058] In certain embodiments, at least one of the R^1, R^2, and R^3 groups of formula **I** is 6-10 membered aryl, or 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur. In certain other embodiments, R^1 and R^2 are adjacent to each other and may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group.

[0059] According to another embodiment, the present invention provides a method for preparing a compound of formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

R^3 is hydrogen, 6-10 membered aryl, or 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein R^3 is optionally substituted with one or more R^x groups;

each R^x is independently selected from halogen, OH, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, or CN;

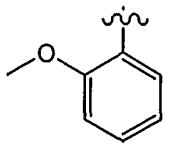
R^4 is CN, N_3, or $N(R^5)(R^{5a})$; and

R^5 and R^{5a} are each independently hydrogen, an amine protecting group, C_{1-6} alkyl, lower haloalkyl, 3-6 membered cycloaliphatic, or alkylcycloaliphatic, or R^5 and R^{5a} are taken together with the nitrogen to which they are attached to form a cyclic amine protecting

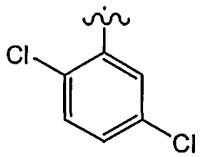
group or a 3-6 membered saturated or partially unsaturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

wherein said method comprises one or more of the steps depicted in Scheme I above. In certain embodiments, said method comprises all of the steps depicted in Scheme I above.

[0060] According to another embodiment, the R^3 group of formula **I-a** is selected from the following:



i



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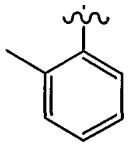
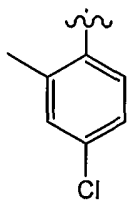


iii



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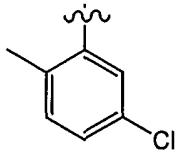
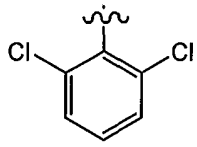


v



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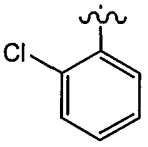
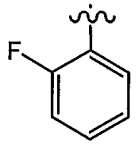
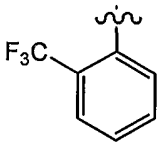


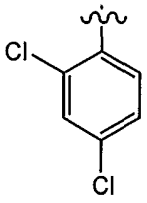
vii



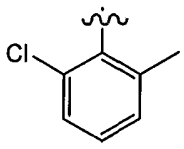
viii



ix

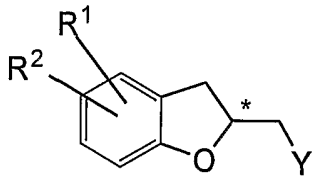


x, or



xi.

[0061] In certain embodiments, the present invention provides a method for preparing a compound of formula **E**:



E

wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and

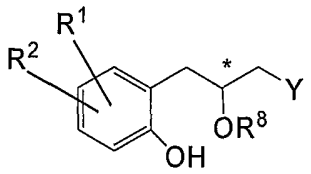
R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

and

Y is Br, Cl, or I,

comprising the steps of:

(a) providing a chiral non-racemic compound of formula **D**:



D

wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each

independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

Y is Br, Cl, or I; and

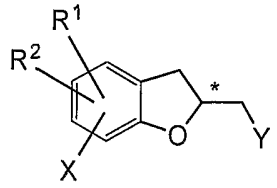
R^8 is hydrogen or a suitable hydroxyl protecting group,

and

(b) cyclizing said compound of formula **D** to form a compound of formula **E**.

[0062] In some embodiments, the cyclization reaction is accomplished using a stereospecific dehydration reaction such as a dehydration reaction with Mitsunobu reaction conditions.

[0063] In certain embodiments, the process further comprises converting the compound of formula **E** to a compound of formula **F**:

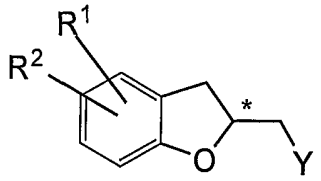


F

wherein R^1, R^2, and Y are as defined above and X is halogen or triflate.

[0064] In some aspects, the invention concerns the preparation of the compound of formula **F**, wherein X is halogen, by a process which comprises:

contacting a compound of formula **E**:



E

wherein R^1, R^2 and Y are as defined above,

with a halogenating agent.

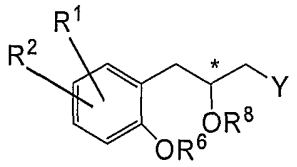
[0065] In other aspects, the present invention provides a method for preparing a compound of formula **F**, wherein X is triflate, said method comprising the steps of:

(a)formylating the compound of formula **E** to provide a formyl group,

(b) converting the formyl group to a hydroxyl group *via* Baeyer-Villiger conditions, and (c) triflating the resulting hydroxyl group.

[0066] In certain embodiments, step (c) is performed with trifluoromethanesulfonic anhydride in the presence of a tertiary amine.

[0067] In some embodiments, the compound of formula **D** is produced by providing a compound of formula **C'**

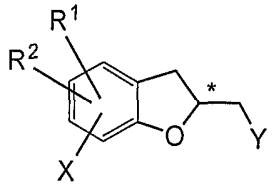


C'

wherein R^1, R^2, R^8 and Y are as defined above and R^6 is a suitable hydroxyl protecting group,

and removing the R^6 protecting group from the compound of formula **C'**.

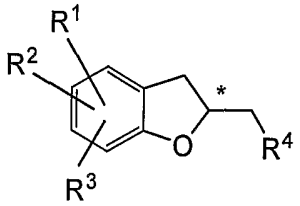
[0068] In certain aspects, the invention further comprises converting the compound of formula **F**:



F

wherein R^1, R^2, X, and Y are as defined above,

to a compound of formula **I**:



I

wherein R^1 and R^2 are as defined above;

R^3 is 6-10 membered aryl, or 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein R^3 is optionally substituted with one or more R^x groups;

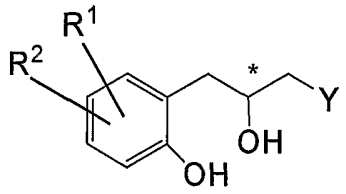
each R^x is independently selected from halogen, OH, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, or CN;

R^4 is CN, N_3, or $N(R^5)(R^{5a})$; and

R^5 and R^{5a} are each independently hydrogen, an amine protecting group, C_{1-6} alkyl, lower haloalkyl, 3-6 membered cycloaliphatic, or alkylcycloaliphatic, or R^5 and R^{5a} are taken together with the nitrogen to which they are attached to form a cyclic amine protecting group or a 3-6 membered saturated or partially unsaturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0069] In some embodiments of the invention, the conversion of the compound of formula **D** to the compound of formula **E** comprises the steps of:

(a) removing the R^8 hydroxyl protecting group from the compound of formula **D** to produce a compound of the formula **D-1**:

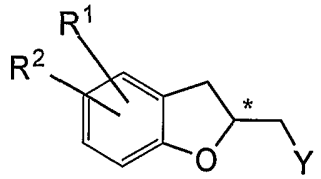


D-1

wherein R^1, R^2, R^8 and Y are as defined above,

and

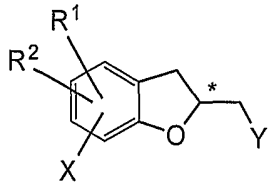
(b) stereospecifically cyclizing the compound of formula **D-1** to produce a compound of formula **E**:



E

wherein R^1, R^1 and Y are as defined above.

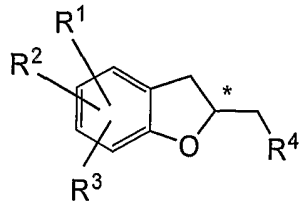
[0070] In some aspects, the present invention provides a method for converting a compound of formula **F**:



F

wherein R^1, R^2, X, and Y are as defined above,

to a compound of formula **I**:

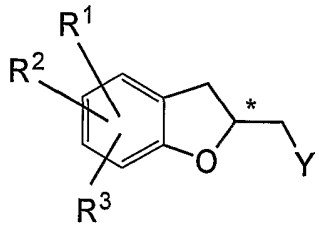


I

wherein R^1, R^2, R^3, and R^4 are as defined above;

wherein said method comprises the steps of:

(a) converting the compound of formula **F** to a compound of formula **G**:



G

wherein R^1, R^2, R^3, and Y are as defined above;

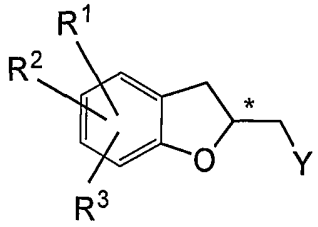
and

(b) reacting the compound of formula **G** with an amine or protected amine to produce a compound of formula **I**.

[0071] In yet other aspects, the compound of formula **F** is converted to a compound of formula **G** *via* a Suzuki coupling reaction.

[0072] In some aspects, the invention concerns processes where the compound of formula **F** is converted to a compound of formula **I** by a process which comprises the steps of:

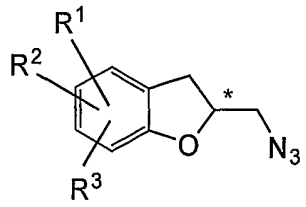
(a) converting the compound of formula **F** to a compound of formula **G**:



G

wherein R^1, R^2, R^3, and Y are as defined above;

(b) reacting the compound of formula **G** with an alkali metal azide such as sodium azide to produce a compound of formula **G-1**:



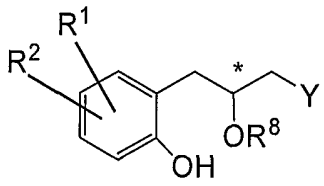
G-1

wherein R^1, R^2, and R^3 are as defined above;

and

(c) reducing the compound of formula **G-1** to produce a compound of formula **I** where R^4 is NH_2.

[0073] In certain aspects, the present invention provides a method for preparing a compound of formula **D**:

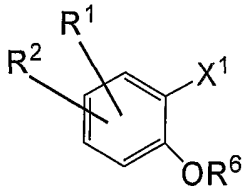


D

wherein each of R^1, R^2, R^8, and Y is as defined above;

comprising the steps of:

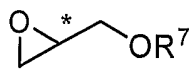
(a) providing a compound of formula **A**:



A

wherein each of R^1, R^2, R^6, and X^1 is as defined above;

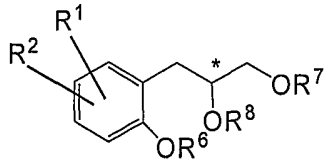
(b) treating the compound of formula **A** with an chiral non-racemic compound of formula **B**:



B

wherein R^7 is a suitable hydroxyl protecting group;

to form a compound of formula **C**:



C

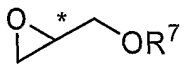
wherein R^1, R^2, R^6, and R^8 are as defined above and R^7 is an acid-labile hydroxyl protecting group;

and

(c) reacting the compound of formula **C** with a hydrogen halide to produce a compound of formula **D-1**.

[0074] In some embodiments, the conversion of the compound of formula **A** to the compound of formula **D** comprises the steps of:

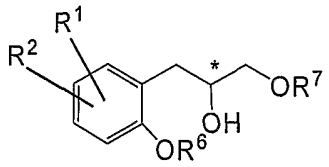
(a) treating a compound of the formula **A** with an chiral non-racemic compound of formula **B**:



B

wherein R^7 is a suitable hydroxyl protecting group;

to form a compound of formula **C-1**:



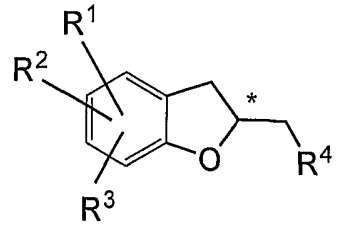
C-1

wherein R^1, R^2, and R^6 are as defined above and R^7 is a hydroxyl protecting group; and

(b) converting the compound **C-1** to a compound of formula **D**.

[0075] In certain embodiments, the conversion of compound **A** to compound **C-1** comprises a metal-halogen exchange reaction, followed by formation of an organocuprate. The organocuprate is preferably reacted with an chiral non-racemic glycidyl ether to form **C-1**. In certain embodiments, the metal-halogen exchange reaction utilizes at least one of n-butyl lithium and iso-propyl magnesium chloride. In some embodiments, the organocuprate is formed utilizing $CuBrSMe_2$ or CuCN. In other embodiments the chiral non-racemic glycidyl ether is a glycidyl benzyl ether.

[0076] According to another embodiment, the present invention provides a method for preparing a compound of formula **I**:

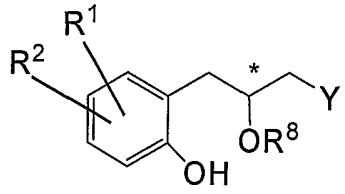


I

wherein each of R^1, R^2, R^3, and R^4 are as defined above;

comprising the steps of:

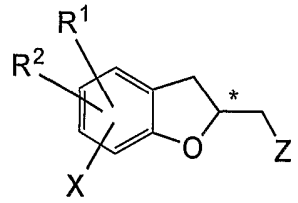
(a) providing a compound of formula **D**:



D

wherein R^1 and R^2 are as defined above, Y is Br and R^8 is hydrogen or a base-labile hydroxyl protecting group;

(b) converting the compound of formula **D** to a compound of the formula **F-1**:



F-1

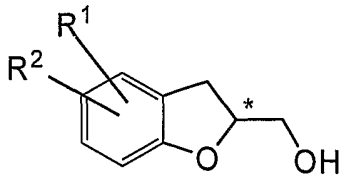
wherein R^1, R^2 and X are as defined above and Z is a suitable leaving group; and

(c) converting the compound of formula **F-1** to a compound of formula **I**.

[0077] In certain embodiments, the Z group of formula **F-1** is an arylsulfonyl, alkylsulfonyl or halogen.

[0078] In certain embodiments, the conversion of the compound of formula **D** to the compound of formula **F-1** comprises the steps of:

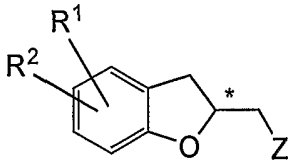
(a) cyclizing the compound of formula **D** (where R^8 is H or a base-labile hydroxyl protecting group) by reacting with base to produce a compound of the formula:



E-1

wherein R^1 and R^2 are as defined above;

(b) converting the hydroxyl group of the compound of formula **E-1** to a leaving group to provide a compound of the formula **E-2**:



E-2

wherein R^1 and R^2 are as defined above and Z is a suitable leaving group;

and

(c) converting the compound of formula **E-2** to a compound of formula **F-1**.

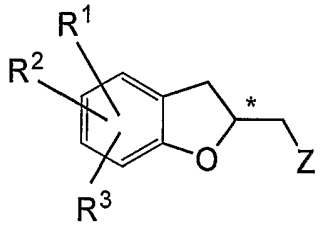
[0079] In some aspects of the invention, the conversion of the compound of formula **E-2** to a compound of formula **F-1** comprises either of the steps of:

(a) formylating the compound of formula **E-2** to provide a formyl group, converting the formyl group to a hydroxyl group *via* a Baeyer-Villiger procedure, and triflating the resulting hydroxyl group with trifluoromethanesulfonic anhydride in the presence of a tertiary amine to form a compound of formula **F-1** wherein X is triflate, or

(b) contacting a compound of formula **E-2** with a halogenating agent to form a compound of formula **F-1** wherein X is halogen.

[0080] In certain embodiments, the conversion of the compound of formula **F-1** to the compound of formula **I** comprises the steps of:

(a) converting the compound of formula **F-1** to a compound of formula **G-1**:



G-1

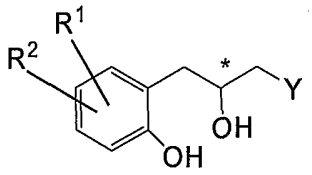
wherein R^1, R^2, R^3, and Z are as defined above;

and

(b) converting the compound of formula **G-1** to a compound of formula **I**.

[0081] In certain embodiments, the compound of formula **F-1** is converted to a compound of formula **G-1** by a Suzuki coupling reaction. In certain aspects, the conversion of the compound of formula **G-1** to a compound of formula **I** comprises contacting the compound of formula **G-1** with an amine or with sodium azide followed by reduction.

[0082] In some embodiments, the present invention provides a method for preparing a compound of formula **D-1**:

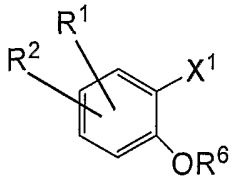


D-1

wherein R^1, R^2, R^8 and Y are as defined above,

comprising the steps of:

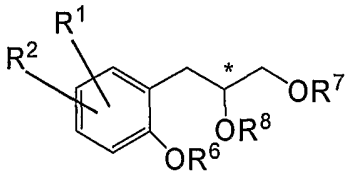
(a) providing a compound of formula **A**:



A

wherein R^1, R^2, R^6 and X^1 are as defined above,

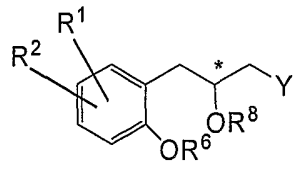
(b) converting a compound of formula **A** to a compound of formula **C**:



C

wherein R^1, R^2, R^6, R^7, and R^8 are as defined above,

(c) reacting the compound of formula **C** with a hydrogen bromide to produce a compound of formula **C'**:



C'

wherein R^1, R^2, R^8, and R^6 are as defined above and Y is Br,

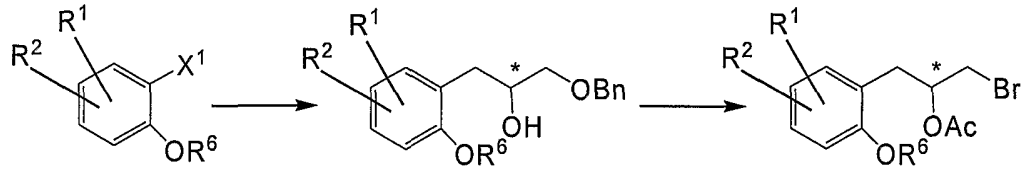
and

(d) if R^6 group of formula **C'** is a hydroxyl protecting group, then further comprising the step of removing the protecting group to produce a compound of formula **D** where Y is Br.

[0083] In other aspects, the invention concerns products of the processes of the invention.

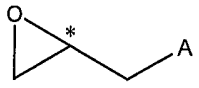
General Synthetic Schemes

Scheme 2



A **IV** **2**

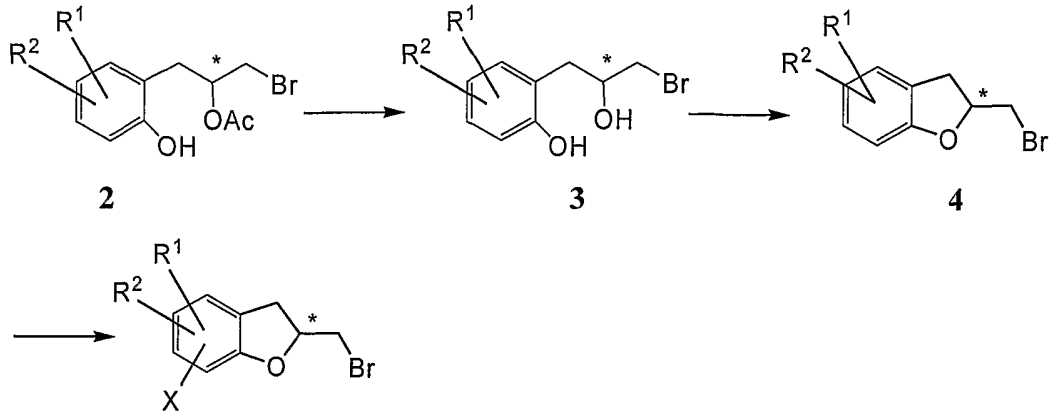
[0084] In Scheme 2 above, incorporation of the R^6 protecting group of intermediate **A** may be accomplished using any hydroxyl protecting reagent known to those skilled in the art. Such reagents include, but are not limited to, iodomethane or benzyl bromide. In one embodiment, R^6 is a methyl group. As defined generally herein, X^1 is a halogen atom. In some embodiments, X^1 is bromine or iodine. The X^1 is then converted into a chiral non-racemic derivative of formula **IV**. This conversion includes the step of metal-halogen exchange, using, for example, n-butyl lithium or isopropylmagnisium chloride, followed by forming an organocuprate, using, for example, $CuBrSMe_2$ or CuCN. The organocuprate intermediate is then reacted with an chiral non-racemic glycidyl ether of the formula



where A is a protected hydroxyl group and/or a leaving group to form **IV**. Preferred chiral non-racemic glycidyl ethers include chiral non-racemic glycidylbenzyl ether. In other embodiments, the glycidylbenzyl ether is the (+)-S-enantiomer. The chiral non-racemic compound of formula **IV** may then be further reacted to produce the bromine derivative **2**.

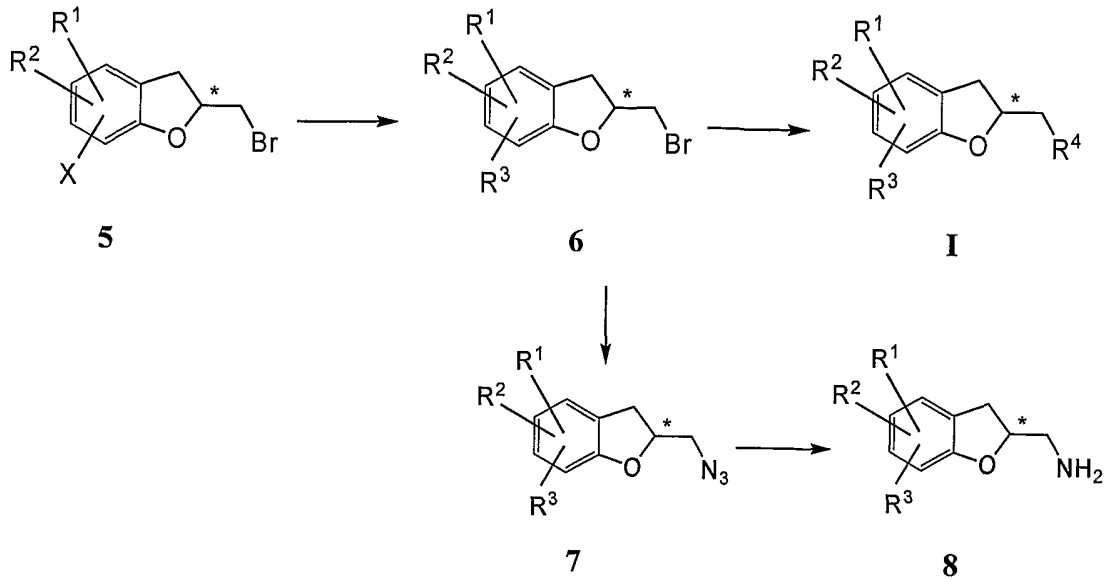
This reaction may be accomplished, for example, with a solution of 30% hydrogen bromide in acetic acid to provide intermediate **2**.

Scheme 3



[0085] There are various ways to carry out the stereospecific cyclization reaction starting with intermediate **2**. According to one embodiment, the cyclization is carried out using a stereospecific dehydration reaction, such as under Mitsunobu reaction conditions in the presence of triphenylphosphine and diethylazodicarboxylate. As shown in Scheme 3 above, acetoxy group of intermediate **2** can be deprotected according to conventional techniques to form compound **3**. In some embodiments, this deprotection is accomplished under acidic condition. The cyclization reaction, Mitsunobu reaction in some embodiments, will stereospecifically convert **3** to intermediate **4**. A halogen or trifluoromethanesulfonyloxy group (X) is then introduced to intermediate **4** by any suitable method known to those skilled in the art, such as bromination or iodination to form a compound **5** where X is Br or I. Alternatively, compound **4** is formylated followed by oxidation, hydrolysis and treatment with trifluoromethanesulfonic anhydride to generate triflate, to form intermediate **5** where X is triflate.

Scheme 4

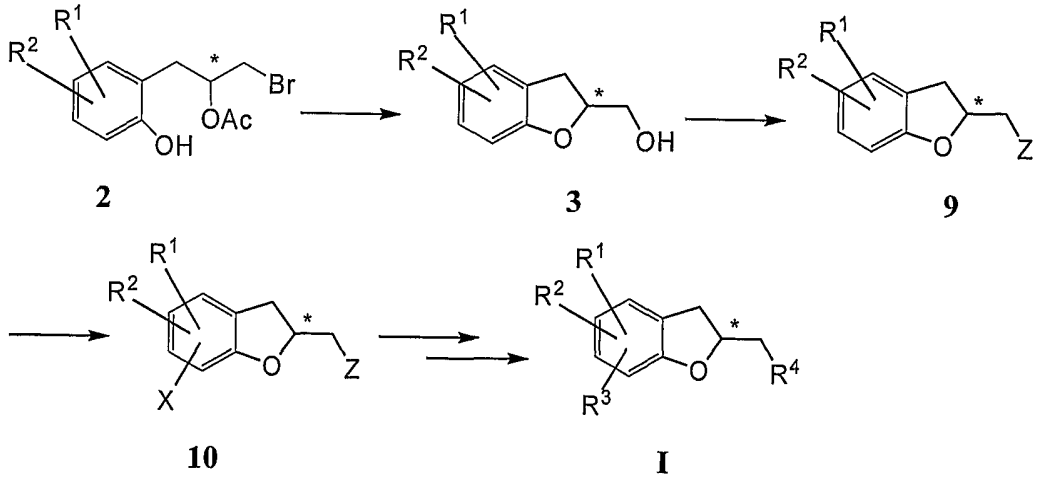


5 6 I

7 8

[0086] In Scheme 4 above, an aryl or heteroaryl R^3 may be introduced to form a compound **6**. This introduction is accomplished by the Suzuki coupling reaction. The bromine moiety of intermediate **6** may be displaced by different amines using conventional techniques to generate corresponding dihydrobenzofuran derivatives of formula **I**. The bromine in intermediate **6** may also be displaced by sodium azide using conventional techniques to form intermediate **7**. Reduction of the azide is accomplished by any suitable method known to those skilled in the art forms the corresponding primary amine **8**.

Scheme 5

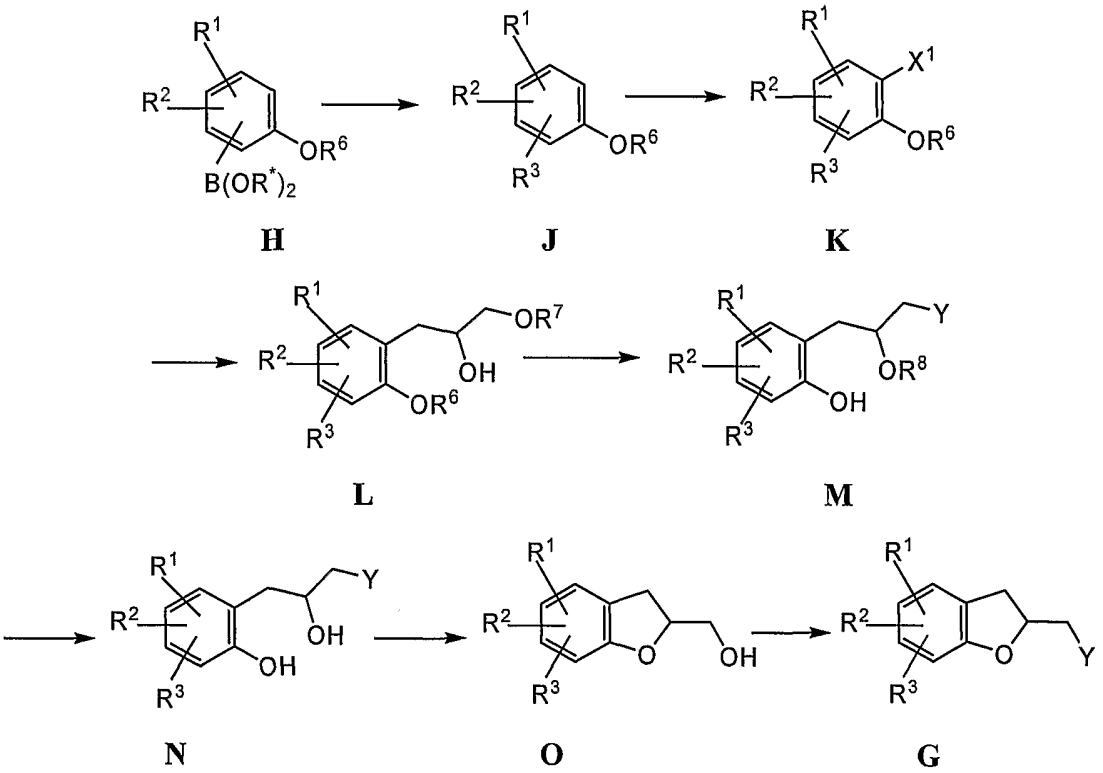


2 3 9

10 I

[0087] Cyclization of the bromide intermediate **2** to give **3** may be carried out in the presence of a suitable base that is, in some embodiments, an inorganic base such as an alkali metal or alkaline earth metal hydroxide or carbonate, such as potassium or sodium hydroxide or potassium carbonate. The reaction may be conducted in any suitable solvent. In some embodiments, the suitable solvent is a polar solvent, such as an alcoholic solvent (methanol or ethanol). In one embodiment, the cyclization reaction is carried out with aqueous sodium hydroxide in methanol to generate compound **3**. The hydroxyl group of the compound of formula **3** may be converted to a leaving group such as arylsulfonyl, alkylsulfonyl or halogen. For example, compound **3** is treated with any arylsulfonyl chloride to form intermediate **9**. A compound of formula **I** is then prepared according to Scheme 4 above.

Scheme 6



[0088] Scheme 6 above depicts an alternate method for preparing compounds of formula **I** or **II** in accordance with the present invention. As depicted in Scheme 6, the R^3 moiety is incorporated to form a compound of formula **J** *via* Suzuki coupling. Specifically, a compound of formula **H**, wherein R^* is hydrogen or a C_{1-6} alkyl group, is treated with a compound of formula R^3-OTf or R^3Br in the presence of a palladium

catalyst. The resulting compound of formula **J** is halogenated by methods known to one of ordinary skill in the art to form a compound of formula **K** wherein X^1 is halogen.

[0089] The conversion of a compound of formula **K** to a compound of formula **G** is performed in a manner substantially similar to that described herein for the conversion of a compound of formula **A** to a compound of formula **G**. Each of these steps is described in detail herein. One of ordinary skill in the art would recognize that the compound of formula **G**, prepared in accordance with Scheme 6, is readily transformed to a compound of formula **I** by the methods described herein.

EXAMPLES

Example 1

(S)-1-Benzyloxy-3-(5-fluoro-2-methoxy-phenyl)propan-2-ol

[0090] To a solution of compound 4-fluoro-2-bromanisole (12.6 ml, 0.1 mol) in anhydrous tetrahydrofuran was added n-BuLi (2.5M in hexane, 39 ml, 0.1 mol)) at –78 °C. The resulting mixture was stirred at –78 °C for a few hours until no more starting material was present. $CuBrSMe_2$ (10.0 g, 0.05 mol) was added to above mixture at –78 °C, and the reaction temperature was slowly increased from –78 °C to –40 °C in 2 hours. Optical active glycidyl benzyl ether (3.71 ml, 0.025 mol) was introduced at –60 °C, followed by BF_3OEt_2 (0.15 ml, 1.2 mmol). The reaction mixture was stirred at –60 °C to 10 °C in the overnight period. The solvent was removed under vacuum. Chromatography with 30% ethyl acetate in hexane afforded desired product 5.0 g (70%) as a clear oil. HRMS ESI m/e 308.1666 $[M+NH4]^+$, Calc'd m/e 308.1662 $[M+NH4]^+$; $[\alpha] = +8.1^\circ$ (0.89%, MeOH).

Example 2

(S)-1-Benzyloxy-3-(5-chloro-2-methoxy-phenyl)propan-2-ol

[0091] To a solution of 4-chloro-2-bromanisole (21.5 g, 0.1 mol) in anhydrous tetrahydrofuran was added n-BuLi (2.5M in hexane, 38.8 ml, 0.1 mol)) at –78 °C. The resulting mixture was stirred at –78 °C for a few hours until no more starting material present. $CuBrSMe_2$ (10.0 g, 0.05 mol) was added to above mixture at –78 °C once, the reaction temperature was slowly increased from –78 °C to –40 °C in 2 hours. Optical active glycidyl benzoether (3.71 ml, 0.025 mol) was introduced at –60 °C, followed by BF_3OEt_2 (0.15 ml, 1.2 mmol). The reaction mixture was stirred at –60 °C to 10 °C in the overnight period. The solvent was removed under vacuum. Chromatography with 30%

ethyl acetate in hexane afforded desired product 5.1 g (%) as a clear oil. HRMS ESI m/e 307.1096 $[M+H]^+$, Calc'd 307.1101; $[\alpha] = +6.6^\circ$ (1%, MeOH).

Example 3

(S)-1-Benzyloxy-3-(2-methoxy-5-methyl-phenyl)propan-2-ol

[0092] Starting from 2-bromo-4-methylanisole (14.05 ml, 0.1 mol) and following the procedure described for Example 1 gave the desired product 6.74 g (96%) as a clear oil. HRMS EI m/e 286.1565 (M)+, Calc'd. 286.1569; $[\alpha] = 15.67^\circ$ (6.7 mg/0.7 ml, MeOH).

Example 4

(S)-1-Benzyloxy-3-(2-methoxy-phenyl)propan-2-ol

[0093] Starting from 2-bromoanisole (12.1 ml, 0.1 mol) and following the procedure described for Example 1 gave the desired product 5.4 g (82%) as a clear oil. HRMS EI m/e 272.1413 (M)+, Calc'd. 272.1412 $[\alpha] = +18.07^\circ$ (c 5.5mg/0.7 ml, MeOH).

Example 5

(S)-1-Benzyloxy-3-(2', 6'-dichloro-5-fluoro-2-methoxybiphenyl-3-yl)propan-2-ol

[0094] To a solution of 3-bromo-2',6'-dichloro-5-fluoro-2-methoxy-biphenyl (2.2 g, 6.3 mmol) in anhydrous tetrahydrofuran was added i-PrMgCl (2.0 M in hexane, 3.45 ml, 6.9 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for hours until no more starting material present. A slurry of CuCN (0.28 g, 3.1 mmol) in THF was added to above mixture at –30 °C once, the mixture was stirred at –30 °C for 1 hour. Then (+)-(2S)-glycidyl benzylether (0.48 ml, 3.1 mmol) was introduced at –30 °C. The reaction mixture was stirred at –30 °C to 10 °C in overnight period. The solvent was removed under vacuum. Chromatography with 30% ethyl acetate in hexane afforded desired product 1.28 g (94%) as a clear oil. HRMS ESI m/e 435.0946 [M - H]-, Calc'd 435.0930; $[\alpha] = -+2.8^\circ$ (c 5.7 mg/0.7 ml, DMSO).

Example 6

(S)-1-Benzyloxy-3-(6'-chloro-5,2'-difluoro-2-methoxybiphenyl-3-yl)propan-2-ol

[0095] Starting from 6'-chloro-5,2'-difluoro-2-methoxy-biphenyl (9.8 g, 29.3 mmol) and following the procedure described for Example 5 gave the desired product 7.4 g (60%) as a clear oil. MS ESI m/e 419.1 $[M + H]^+$.

Example 7

(S)-Acetic acid 1-bromomethyl-2-(5-fluoro-2-hydroxy-phenyl)-ethyl ester

[0096] 1-Benzyloxy-3-(5-fluoro-2-methoxy-phenyl)propan-2-ol (5.17g, 17.8 mmol) was dissolved in 30% hydrogen bromide in acetic acid (40 ml). The reaction mixture was heated at 70 °C overnight. The solvent was removed under vacuum. The residue was dissolved in methylene chloride and washed with ammonium hydroxide. The organic solvent was removed under vacuum. Chromatography with 30% ethyl acetate in hexane afforded product 3.60 g (70%) as a light brown oil.

Elemental Analysis for: $C_{11}H_{12}BrFO_3$

Theory: C, 45.38 H, 4.15

Found: C, 45.24 H, 4.09

Example 8

(S)-Acetic acid 1-bromomethyl-2-(5-chloro-2-hydroxy-phenyl)-ethyl ester

[0097] Starting from 1-benzyloxy-3-(5-chloro-2-methoxy-phenyl)propan-2-ol (5.4 g, 17.6 mmol) and following the procedure described for Example 7 gave the desired product 3.8g (70%) as a light brown oil. HRMS EI m/e 305.9647 (M)+.

Example 9

(S)-Acetic acid 1-bromomethyl-2-(2-hydroxy-5-methyl-phenyl)-ethyl ester

[0098] Starting from 1-benzyloxy-3-(2-methoxy-5-methyl-phenyl)propan-2-ol (6.7 g, 23.3mmol) and following the procedure described for Example 7 gave the desired product 6.24g (93%) as a yellow oil. MS EI m/e 286 (M)+; $[\alpha] = -2.41°$ (c 5.8 mg/0.7 ml, MeOH)

Example 10

(S)-Acetic acid 1-bromomethyl-2-(2-hydroxy-phenyl)-ethyl ester

[0099] Starting from 1-benzyloxy-3-(2-methoxy-phenyl)propan-2-ol (5.40 g, 19.8 mmol) and following the procedure described for Example 7 gave the desired product 3.42 g (63%) as a yellow oil. [α] = - 12.2° (c 1%, MeOH)

Elemental Analysis for: $C_{16}H_{15}BrO_3$

Theory: C, 48.37 H, 4.80

Found: C, 48.48 H, 4.78

Example 11

(S)-Acetic acid 3-(2-acetoxy-3-bromo-propyl)-2',6'-dichloro-5-fluoro-biphenyl-2-yl ester

[00100] Starting from 1-benzyloxy-3-(2', 6'-dichlor-5-fluoro-2-methoxybiphenyl-3-yl)propan-2-ol (1.28 g, 2.9 mmol) and following the procedure described for Example 7 gave the desired product (1.12 g (80%)) as a light yellow oil. HRMS ESI m/e 476.9686 [M+H]+, Calc'd. 476.9671; [α] = + 13.2° (c 1%, MeOH)

Example 12

(S)-Acetic acid 1-bromomethyl-2-(6'-chloro-5, 2'-difluoro-2-hydroxy-biphenyl-3-yl)-ethyl ester

[00101] Starting from (S)-1-benzyloxy-3-(6'-chloro-5,2'-difluoro-2-methoxybiphenyl-3-yl)propan-2-ol (7.4 g, 17.7 mmol) and following the procedure described for Example 7 gave the desired product 2.72 g (37%) as a light yellow oil. MS EI m/e 418 M^+; [α] = - 7.4° (c 1%, MeOH)

Example 13

(S)-2-(3-Bromo-2-hydroxy-propyl)-4-fluoro-phenol

[00102] To a solution of acetic acid 1-bromomethyl-2-(5-fluoro-2-hydroxy-phenyl)-ether ester (3.57 g, 12.2 mmol) in methanol was added hydrogen chloride in ether (1.0 M, 49 ml, 48.8 mmol) at room temperature. The mixture was stirred at room temperature overnight. The solvent was removed under vacuum. Chromatography with 30% ethyl

acetate afforded product 2.95 g (97%) as a clear oil. HRMS ESI m/e 246.9761 [M-H]+; Calc'd 246.9755. [α] = +8.2° (c 0.71%, MeOH)

Example 14

(S)-2-(3-Bromo-2-hydroxy-propyl)-4-chloro-phenol

[00103] Starting from acetic acid 1-bromomethyl-2-(5-chloro-2-hydroxy-phenyl)-ether ester (2.47 g, 3.2 mmol) and following the procedure described for Example 13 gave the desired product 1.68 g (79%) as a yellow oil. [α] = +9.8° (c 1%, MeOH), HRMS EI m/e 263.956 (M)+.

Example 15

(S)-2-(3-Bromo-2-hydroxy-propyl)-4-metyl-phenol

[00104] Starting from acetic acid 1-bromomethyl-2-(2-hydroxy-5-methyl-phenyl)-ether ester (6.24 g, 22 mmol) and following the procedure described for Example 13 gave the desired product 5.0 g (94%) as a clear oil. [α] = + 13.8° (c 1%, MeOH), HRMS ESI m/e 243.0020 [M-H]-, Calc'd. 243.0021

Example 16

(S)-2-(3-Bromo-2-hydroxy-propyl)-phenol

[00105] Starting from acetic acid 1-bromomethyl-2-(2-hydroxy-phenyl)-ether ester (3.42 g, 12.5 mmol) and following the procedure described for Example 13 gave the desired product 2.71 g (93 %) as a light yellow oil. MS ES m/e 229.0 [M-H]-; [α] = +16.46° (c 5.7mg/0.7 ml, MeOH)

Example 17

(S)-3-(3-Bromo-2-hydroxy-propyl)-2',6',-dichloro-5-fluoro-biphenyl-2-ol

[00106] Starting from acetic acid 2-(2-acetoxy-2',6'-dichloro-5-fluoro-biphenyl-3-yl)-1-bromomethyl-ethyl ester (1.6 g, 33.4 mmol) and following the procedure described for Example 13 gave the desired product 1.48 g (100 %) as a light yellow oil. HRMS EI m/e 391.9391 (M)+, Calc'd. 391.9391; [α] = - 4.76° (c 5.0mg/0.7 ml, MeOH

Example 18

(S)-3-(3-Bromo-2-hydroxy-propyl)-2'-chloro-5,6'-difluorobiphenyl-2-ol

[00107] Starting from (S)-acetic acid 1-bromomethyl-2-(6'-chloro-5, 2'-difluoro-2-hydroxy-biphenyl-3-yl)-ethyl ester (2.72 g, 6.5 mmol) and following the procedure described for Example 13 gave the desired product 2.2 g (90 %) as a light yellow oil. MS EI m/e 376 (M)+.

Example 19

(R)-2-Bromomethyl-5-fluoro-2,3-dihydro-benzofuran

[00108] To a solution of 2-(3-bromo-2-hydroxy-propyl)-4-fluoro-phenol(1.97 g, 8 mmol) in tetrahydrofuran was added triphenyl phosphine (5.2 g, 20 mmol) and followed by DEAD (3.11 ml, 20 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h. Solvent was removed under vacuum. Chromatography with 5% ethyl acetate afforded product 1.40 g (76%) as a clear oil. HRMS ESI m/e 228.9661 [M-H]-. [α] = -33.0° (c 1%, MeOH)

Example 20

(R)-2-Bromomethyl-5-methyl-2,3-dihydro-benzofuran

[00109] Starting from 2-(3-bromo-2-hydroxy-propyl)-4-metyl-phenol (5.0 g, 20 mmol) and following the procedure described for Example 19 gave the desired product 3.04 g (70 %) as a yellow oil. HRMS EI m/e 225.9998 (M)+; [α] = - 41.13° (c 6.2/0.7ml, MeOH)

Example 21

(R)-2-Bromomethyl-2,3-dihydro-benzofuran

[00110] Starting from 2-(3-bromo-2-hydroxy-propyl)-phenol (2.71 g, 12 mmol) and following the procedure described for Example 19 gave the desired product 1.62g (65 %) as a yellow oil. [α] = –37° (c 1%, MeOH); HRMS EI m/e 211.9840 (M)+, Calc'd. 211.9837

Example 22

(R)-2-Bromomethyl-7-(2,6-dichloro-phenyl)-5-fluoro-2,3-dihydro-benzofuran

[00111] Starting from 3-(3-bromo-2-hydroxy-propyl)-2',6',-dichloro-5-fluoro-biphenyl-2-ol (1.48 g, 3.7 mmol) and following the procedure described for Intermediate 19 gave the desired product 1.16 g (82 %) as a clear oil. HRMS EI m/e 373.9277 (M)+, Calc'd. 373.9277; [α] = - 15.75° (c, 5.6 mg/0.7 ml, MeOH)

Example 23

(R)-2-Bromomethyl-7-(2-chloro-6-fluoro-phenyl)-5-fluoro-2,3-dihydro-benzofuran

[00112] Starting from (S)-3-(3-bromo-2-hydroxy-propyl)-2'-chloro-5,6'-difluorobiphenyl-2-ol (2.2 g, 5.8 mmol) and following the procedure described for Example 19 gave the desired product 2.12 g (100 %) as a clear oil. MS APPI m/e 358 $(M)^+$.

Example 24

(R)-7-Bromo-2-bromomethyl-5-fluoro-2,3-dihydrobenzofuran

[00113] To a solution of 2-bromomethyl-5-fluoro-2,3-dihydro-benzofuran (3.20 g, 14 mmol) in acetic acid was added bromine (2.2 ml, 42 mmol) at room temperature. The mixture was stirred at room temperature for overnight. The solvent was removed under the vacuum and the residue was washed with Na_2SO_3 and extracted with methylene chloride. Chromatography with 5% ethyl acetate in hexanes afforded product 3.16 g (74%) as a light yellow oil. HRMS EI m/e 307.8846 (M)+, Calc'd. 307.8848. [α] = +24.8 (c 1%, MeOH)

Example 25

(R)-2-Bromomethyl-5-fluoro-7-o-toly-2,3-dihydrobenzofuran

[00114] To a solution of 7-bromo-2-bromomethyl-5-fluoro-2,3-dihydrobenzofuran (2.57 g, 8.2 mmol) and o-tolyboronic acid (3.4 g, 24 mmol) in dioxane-water (4/1) was added dichlorobis(tri-o-tolyphosphine)-palladium (0.33 g, 0.41 mmol) and potassium carbonate (2.86 g, 21 mmol) at 90 °C. The mixture was heated at 90 °C for 3 hours. The mixture was filtered through the pad of celite and concentrated under vacuum.

Chromatography with 10-30% ethyl acetate in hexanes afforded product 2.54 g (95%) as a clear oil. HRMS EI m/e 320.0224 (M)+; [α] = +35.00° (c 1%, MeOH)

Example 26

(R)-2-Bromomethyl-7-(2-chloro-phenyl)-5-fluoro-2,3-dihydrobenzofuran

[00115] Starting from 7-bromo-2-bromomethyl-5-fluoro-2,3-dihydrobenzofuran (0.5 g, 1.6 mmol) and 2-chlorobenzene boronic acid (0.76 g, 4.8 mmol) and following the procedure described for Example 25 gave the desired product 0.55 g (99%) as a clear oil. HRMS EI M+ 339.9657; [α] = +29.6° (c 5.7mg/0.7 ml, MeOH)

Example 27

(R)-2-Bromomethyl-7-(2-methyl-5-chloro -phenyl)-5-fluoro-2,3-dihydrobenzofuran

[00116] Starting from 7-bromo-2-bromomethyl-5-fluoro-2,3-dihydrobenzofuran (0.40 g, 1.3 mmol) and 5-chloro-o-toluene boronic acid (0.88 g, 5.2 mmol) and following the procedure described for Intermediate 25 gave the desired product 0.41 g (90%) as a clear oil. HRMS EI M+ 353.9829; [α] = +47.38° (c 6.5 mg/0.7 ml, MeOH).

Example 28

(R)-2-Bromomethyl-7-(2-methyl-4-chloro -phenyl)-5-fluoro-2,3-dihydrobenzofuran

[00117] Starting from 7-bromo-2-bromomethyl-5-fluoro-2,3-dihydrobenzofuran (0.42 g, 1.3 mmol) and 4-chloro-o-toluene boronic acid (0.88 g, 5.2 mmol) and following the procedure described for Example 25 gave the desired product 0.43 g (95%) as a clear oil. HRMS EI M+ 353.9825, Calc'd. 353.9825; [α] = 39.14° (c 4.9 mg/0.7 ml, MeOH)

Example 29

(R)-2-Azidomethyl-7-(4-chloro-2-methyl-phenyl)-5-fluoro-2,3-dihydrobenzofuran

[00118] To a solution of 2-bromomethyl-7-(2-methyl-4-chloro-phenyl)-5-fluoro-2,3-dihydrobenzofuran (0.4 g, 1.1 mmol) in DMF was added sodium azide (0.33 g, 6.6 mmol). The mixture was heated at 90 °C overnight. The reaction was quenched with water. The mixture was extracted with methylene chloride. The organic layer was washed with water and dried over sodium sulfate. The organic solvent was removed under

vacuum. Chromatography with 10% ethyl acetate in hexanes afforded product 0.30 g (85%) as a clear oil. HRMS EI m/e 317.0719 (M)+, Calc'd. 317.0718; [α] = +16.76° (c 6.1 mg/0.7 ml, MeOH)

Example 30

(R)-2-Azidomethyl-7-(5-chloro-2-methyl-phenyl)-5-fluoro-2,3-dihydrobenzofuran

[00119] Starting from 2-bromomethyl-7-(2-methyl-5-chloro-phenyl)-5-fluoro-2,3-dihydrobenzofuran (0.41 g, 1.2 mmol) following the procedure described for Example 29 gave arise the desired product 0.31 g (85%) as a clear oil. HRMS EI m/e 317.0734 (M)+, Calc'd. 317.0733; [α] = +3.12° (c 5.4 mg/0.7 ml, MeOH).

Example 31

(R)-2-Azidomethyl-7-(2-chloro-6-fluoro-phenyl)-5-fluoro-2,3-dihydrobenzofuran

[00120] Starting from (R)-2-bromomethyl-7-(2-chloro-6-fluoro-phenyl)-5-fluoro-2,3-dihydro-benzofuran (2.2 g, 5.8 mmol) following the procedure described for Example 29 gave arise the desired product 1.42 g (75%) as a clear oil. MS EI m/e 321 $(M)^+$; [α] = + 40.0° (1% solution in MeOH).

Example 32

(R)- (5-Fluoro-7-o-toly-2,3-dihydro-benzofuran-2-ylmethyl)methyl-amine

[00121] To a solution of 2-bromomethyl-5-fluoro-7-o-toly-2,3-dihydrobenzofuran (2.54 g, 7.9 mmol) in DMSO was added methyl amine (2.0 M in THF, 79 mmol)). The mixture was stirred at 50 °C for 10 hours. The mixture was extracted with methylene chloride and organic layer was washed with water. The solvent was removed under vacuum. The oil was dissolved in ethyl acetate and made into its hydrochloric salt using excess ethereal hydrochloric acid to give a white solid: mp. 145-147°C. [α] = +16.42° (c 5.2 mg/0.7 ml, MeOH)

Elemental Analysis for: $C_{17}H_{18}FNO \cdot 1HCl$

Theory: C, 66.34 H, 6.22 N, 4.55

Found: C, 66.22 H, 6.20 N, 4.38

Example 33

(R)- [7-(2-Chloro-phenyl)-(5-fluoro-2,3-dihydro-benzofuran-2-ylmethyl)methyl-amine

[00122] Starting from 2-bromomethyl-7-(2-chloro-phenyl)-5-fluoro-2,3-dihydrobenzofuran (0.55 g, 1.6 mmol) following the procedure described for Example 32 gave arise the desired product 0.36 g (77 %) as a clear oil. The oil was dissolved in ethyl acetate and made into its hydrochloric salt using excess ethereal hydrochloric acid to give a white foam. [α] = +11.57° (c 5.2 mg/0.7 ml, MeOH)

Elemental Analysis for: $C_{16}H_{15}ClFNO \cdot 1HCl \cdot 1H_2O$

Theory: C, 55.51 H, 5.24N, 4.05

Found: C, 56.86 H, 5.27 N, 3.91

Example 34

(R)- [7-(2,6-dichloro-phenyl)-5-Fluoro-2,3-dihydro-benzofuran-2-ylmethyl]ethyl-amine

[00123] Starting from 2-bromomethyl-7-(2,6-dichloro-phenyl)-5-fluoro-2,3-dihydrobenzofuran (0.42 g, 1.1 mmol) and ethyl amine (2.0 M in THF, 5.6 ml, 11 mmol) following the procedure described for Example 32 gave the desired product 0.28 g (74 %) as a clear oil. The oil was dissolved in ethyl acetate and made into its hydrochloric salt using excess ethereal hydrochloric acid to give a white foam. MS ES [M+H]+ 340.1; [α] = -7.12° (c 5.5 mg/0.7 ml, MeOH)

Elemental Analysis for: $C_{17}H_{16}Cl_2FNO \cdot 1HCl \cdot 1H_2O$;

Theory: C, 51.73 H, 4.85N, 3.55

Found: C, 51.85 H, 4.88 N, 3.50

Example 35

(R)- [7-(2,6-Dichloro-phenyl)-5-fluoro-2,3-dihydro-benzofuran-2-ylmethyl]-dimethyl-amine

[00124] Starting from 2-bromomethyl-7-(2,6-dichloro-phenyl)-5-fluoro-2,3-dihydrobenzofuran (0.41 g, 1.1 mmol) and N,N-dimethyl amine (2.0 M in THF, 5.4 ml, 11 mmol) following the procedure described for Example 32 gave the desired product 0.29 g

(80%) as a clear oil. The oil was dissolved in ethyl acetate and made into its hydrochloric salt using excess ethereal hydrochloric acid to give a white solid: mp.156-158°C; [α] = -21.04° (c 5.4 mg/0.7 ml)

Elemental Analysis for $C_{17}H_{16}Cl_2FNO \cdot 1HCl$:

Theory: C, 54.21 H, 4.55 N, 3.72

Found: C, 53.98 H, 4.62 N, 3.56

Example 36

(R)-C-[7-(5-Chloro-2-methyl phenyl)-5-fluoro-2,3-dihydro-benzofuran-2-yl]-methylamine

[00125] To a solution of 2-azidomethyl-7-(5-chloro-2-methyl-phenyl)-5-fluoro-2,3-dihydro-benzofuran (0.40 g, 1.2 mmol) in tetrahydrofuran was added polymer-supported triphenylphosphine (~3mmol/g, 3.6 mmol) and water. The mixture was stirred at room temperature for 24 hours, and filtered through the pad of celite. The solvent was removed under vacuum to form a clear oil. The oil was dissolved in ethyl acetate and made into its hydrochloric salt using excess ethereal hydrochloric acid to give a white solid: mp. 148-150°C; [α] = +1.45° (c 5.8 mg/0.7 ml, MeOH)

Elemental Analysis for: $C_{16}H_{15}ClFNO \cdot 1HCl$

Theory: C, 58.55 H, 4.91 N, 4.27

Found: C, 58.55 H, 4.78 N, 3.88

Example 37

(R)-C-[7-(4-Chloro-2-methyl phenyl)-5-fluoro-2,3-dihydro-benzofuran-2-yl]-methylamine

[00126] Starting from 2-azidomethyl-7-(4-chloro-2-methyl-phenyl)-5-fluoro-2,3-dihydrobenzo-furan (0.40 g, 1.2 mmol) following the procedure described for Example 36 gave the desired product 0.29 g (80 %) as a clear oil. The oil was dissolved in ethyl acetate and made into its hydrochloric salt using excess ethereal hydrochloric acid to give a white solid: mp. 183-185°C; [α] = +7.22° (c 6.4 mg/0.7 ml, MeOH)

Elemental Analysis for: $C_{16}H_{15}ClFNO \cdot 1HCl$

Theory: C, 58.55 H, 4.91 N, 4.27

Found: C, 58.55 H, 4.87 N, 4.52

Example 38

(R)-C-[7-(2-Chloro-6-fluoro-phenyl)-5-fluoro-2,3-dihydro-benzofuran-2-yl]-methylamine

[00127] Starting from (R)-2-azidomethyl-7-(2-chloro-6-fluoro-phenyl)-5-fluoro-2,3-dihydrobenzofuran (1.42 g, 4.4 mmol) following the procedure described for Example 36 gave the desired product 1.10 g (90 %) as a clear oil. The oil was dissolved in ethyl acetate and made into its hydrochloric salt using excess ethereal hydrochloric acid to give a white solid: mp. 197-200°C

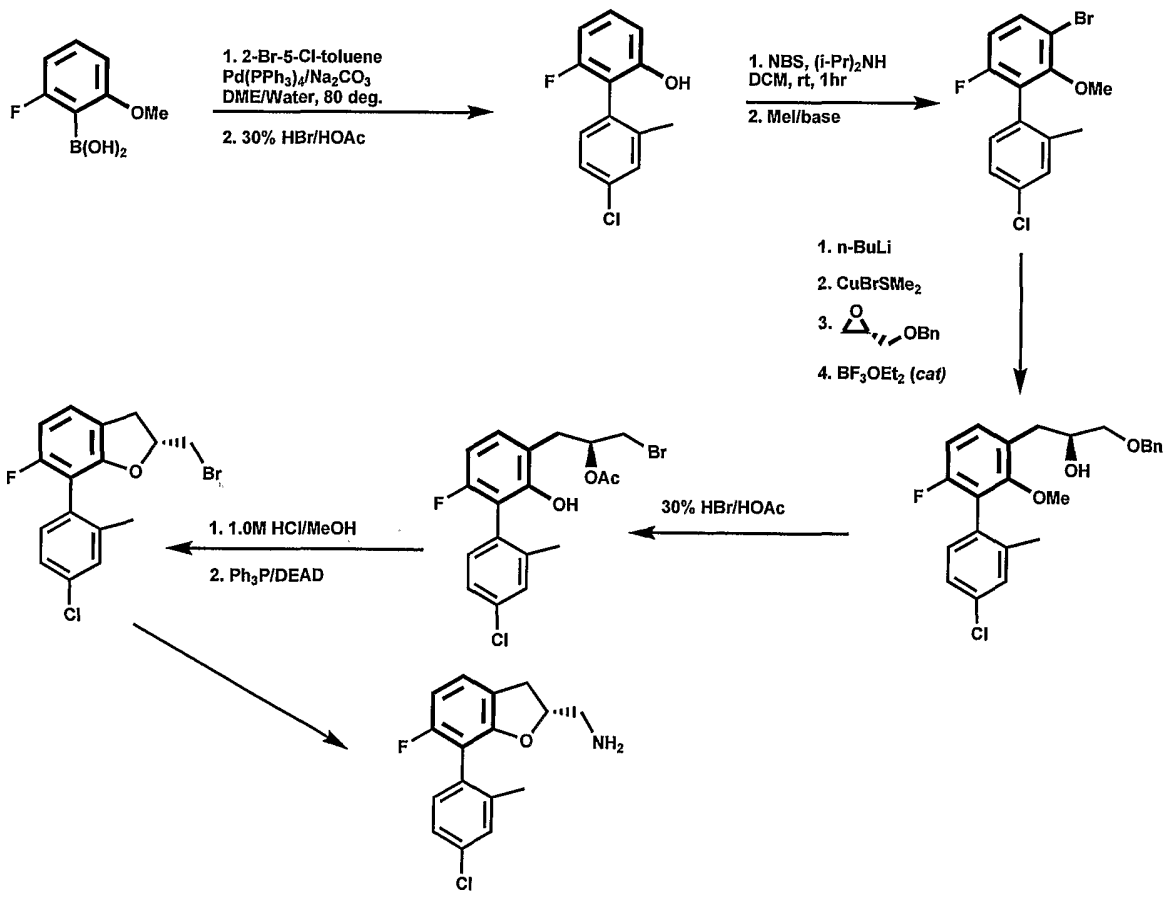
Elemental Analysis for: $C_{15}H_{12}ClF_2NO \cdot 1HCl$

Theory: C, 54.24 H, 3.95 N, 4.22

Found: C, 54.08 H, 3.83 N, 3.78

Example 39

((2R)-7-(4-Chloro-2-methylphenyl)-6-fluoro-2,3-dihydrobenzofuran-2-yl)methanamine:

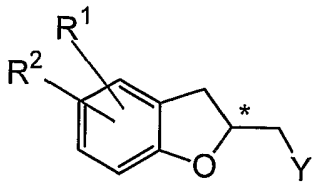


[00128] All patents, publications, and other documents cited herein are hereby incorporated by reference in their entirety.

CLAIMS

We claim:

1. A method for preparing a compound of formula **E**:



E

wherein:

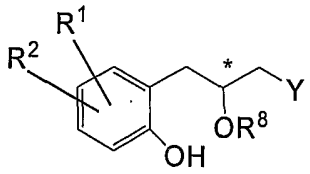
R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

and

Y is Br, Cl, or I,

comprising the steps of:

(a) providing a chiral non-racemic compound of formula **D**:



D

wherein:

Y is Br, Cl, or I; and

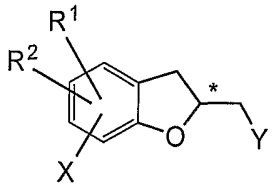
R^8 is hydrogen or a suitable hydroxyl protecting group,

and

(b) cyclizing said compound of formula **D** to form a compound of formula **E**.

2. The method of claim 1 wherein the cyclizing step is accomplished using Mitsunobu reaction conditions.

3. The method of claim 1 further comprising the step of converting the compound of formula **E** to a compound of formula **F**:



F

wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from

nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

Y is Br, Cl, or I; and

X is halogen or triflate.

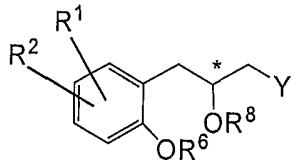
4. The method of claim 3 wherein the step of converting the compound of formula **E** to a compound of formula **F** comprises the steps of:

(a) formylating the compound of formula **E** to provide a formyl group,

(b) converting the formyl group to a hydroxyl group *via* Baeyer-Villiger conditions, and

(c) triflating the resulting hydroxyl group.

5. The method of claim 1 wherein the compound of formula **D** is prepared by providing a compound of formula **C'**:



C'

wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3

heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

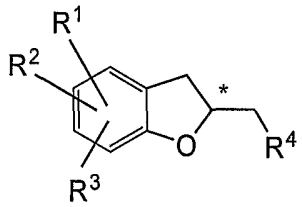
Y is Br, Cl, or I;

R^6 is a suitable hydroxyl protecting group; and

R^8 is hydrogen or a suitable hydroxyl protecting group,

and removing the R^6 protecting group from the compound of formula **C'** to produce a compound of formula **D**.

6. The method of claim 3 further comprising the step of converting the compound of formula **F** to a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl

having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

R^3 is hydrogen, 6-10 membered aryl, or 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein R^3 is optionally substituted with one or more R^x groups;

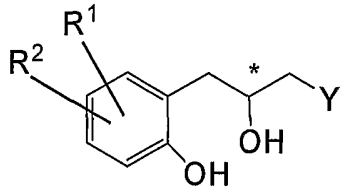
each R^x is independently selected from halogen, OH, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, or CN;

R^4 is CN, N_3, or $N(R^5)(R^{5a})$; and

R^5 and R^{5a} are each independently hydrogen, an amine protecting group, C_{1-6} alkyl, lower haloalkyl, 3-6 membered cycloaliphatic, or alkylcycloaliphatic, or R^5 and R^{5a} are taken together with the nitrogen to which they are attached to form a cyclic amine protecting group or a 3-6 membered saturated or partially unsaturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

7. The method of claim 1 wherein conversion of the compound of formula **D** to the compound of formula **E** comprises the steps of:

(a) removing the R^8 hydroxyl protecting group from the compound of formula **D** to produce a compound of the formula **D-1**:



D-1

wherein:

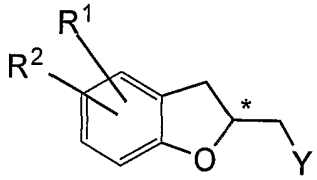
R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3

heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group; and

Y is Br, Cl, or I;

and

(b) cyclizing the compound of formula **D-1** to produce a compound of formula **E**:



E

wherein:

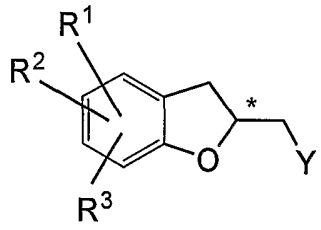
R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10

membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group; and

Y is Br, Cl, or I.

8. The method of claim 6 wherein conversion of the compound of formula **F** to the compound of formula **I** comprises the steps of:

(a) converting the compound of formula **F** to a compound of formula **G**:



G

wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the

monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

R^3 is hydrogen, 6-10 membered aryl, or 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein R^3 is optionally substituted with one or more R^x groups;

each R^x is independently selected from halogen, OH, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, or CN; and

Y is Br, Cl, or I;

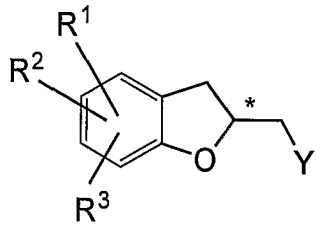
and

(b) reacting the compound of formula **G** with an amine or a protected amine to produce a compound of formula **I**.

9. The method of claim 8 wherein step (a) is achieved *via* a Suzuki reaction.

10. The method of claim 6 wherein conversion of the compound of formula **F** to a compound of formula **I** comprises the steps of:

(a) converting the compound of formula **F** to a compound of formula **G**:



G

wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and

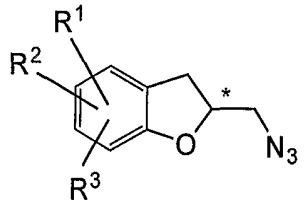
R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

R^3 is hydrogen, 6-10 membered aryl, or 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein R^3 is optionally substituted with one or more R^x groups;

each R^x is independently selected from halogen, OH, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, or CN; and

Y is Br, Cl, or I,

(b) reacting the compound of formula **G** with an alkali metal azide to produce a compound of formula **G-1**:



G-1

wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to

which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group; and

R^3 is hydrogen, 6-10 membered aryl, or 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein R^3 is optionally substituted with one or more R^x groups;

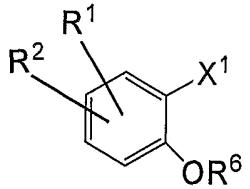
each R^x is independently selected from halogen, OH, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, or CN;

and

(c) reducing the compound of formula **G-1** to produce a compound of formula **I** where R^4 is NH_2.

11. The method of claim 1 wherein the step of providing the compound of formula **D** comprises the steps of:

(a) providing a compound of formula **A**:



A

wherein:

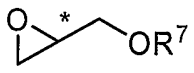
R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl

moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

R^6 is a suitable hydroxyl protecting group; and

X^1 is halogen,

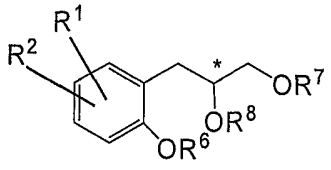
(b) treating the compound of formula **A** with an chiral non-racemic compound of formula **B**:



B

wherein R^7 is a suitable hydroxyl protecting group;

to form a compound of formula **C**:



C

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and

R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

R^6 is a suitable hydroxyl protecting group;

R^7 is an acid-labile hydroxyl protecting group; and

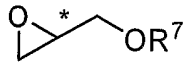
R^8 is hydrogen or a hydroxyl protecting group,

and

(c) reacting the compound of formula **C** with a hydrogen halide to produce a compound of formula **D**.

12. The method of claim 11 wherein the conversion of the compound of formula **A** to the compound of formula **D** comprises the steps of:

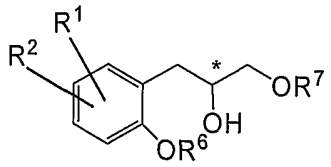
(a) treating a compound of the formula **A** with an chiral non-racemic compound of formula **B**:



B

wherein R^7 is a suitable hydroxyl protecting group;

to form a compound of formula **C-1**:



C-1

wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

R^6 is a suitable hydroxyl protecting group; and

R^7 is a hydroxyl protecting group;

and

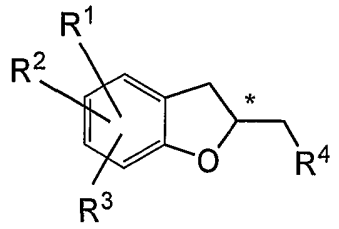
(b) converting the compound **C-1** to a compound of formula **D**.

13. The method of claim 12 wherein conversion of compound **A** to compound **C-1** comprises performing a metal-halogen exchange reaction followed by forming an organocuprate.

14. The method of claim 13 wherein the metal-halogen exchange reaction utilizes at least one of n-butyl lithium or iso-propyl magnesium chloride.

15. The method of claim 14 wherein the organocuprate is formed utilizing $CuBrSMe_2$ or CuCN.

16. A method for preparing a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

R^3 is hydrogen, 6-10 membered aryl, or 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein R^3 is optionally substituted with one or more R^x groups;

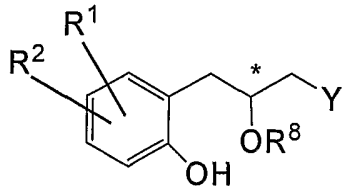
each R^x is independently selected from halogen, OH, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, or CN;

R^4 is CN, N_3, or $N(R^5)(R^{5a})$; and

R^5 and R^{5a} are each independently hydrogen, an amine protecting group, C_{1-6} alkyl, lower haloalkyl, 3-6 membered cycloaliphatic, or alkylcycloaliphatic, or R^5 and R^{5a} are taken together with the nitrogen to which they are attached to form a cyclic amine protecting group or a 3-6 membered saturated or partially unsaturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

comprising the steps of:

(a) providing a compound of formula **D**:



D

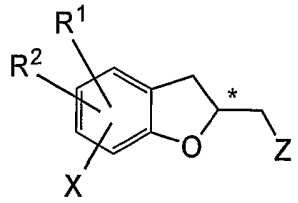
wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

Y is Br, Cl, or I; and

R^8 is hydrogen or a base-labile hydroxyl protecting group,

(b) converting the compound of formula **D** to a compound of the formula **F-1**:



F-1

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

X is halogen or triflate; and

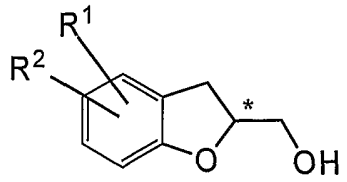
Z is a suitable leaving group,

and

(c) converting the compound of formula **F-1** to a compound of formula **I**.

17. The method of claim 16 wherein conversion of the compound of formula **D** to the compound of formula **F-1** comprises the steps of:

(a) cyclizing the compound of formula **D** by reacting with base to produce a compound of formula **E-1**:

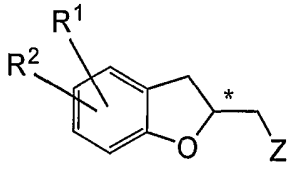


E-1

wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

(b) converting the hydroxyl group of the compound of formula **E-1** to a leaving group to provide a compound of the formula **E-2**:



E-2

wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group; and

Z is a suitable leaving group;

and

(c) converting the compound of formula **E-2** to a compound of formula **F-1**.

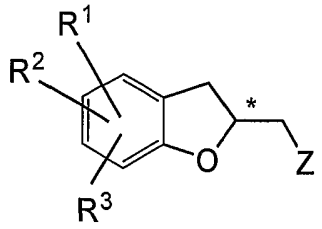
18. The method of claim 17 wherein conversion of the compound of formula **E-2** to a compound of formula **F-1** comprises either of the steps of:

(a) formylating the compound of formula **E-2** to provide a formyl group, converting the formyl group to a hydroxyl group *via* a Baeyer-Villiger procedure, and triflating the resulting hydroxyl group with trifluoromethanesulfonic anhydride in the presence of a tertiary amine to form a compound of formula **F-1** wherein X is triflate, or

(b) contacting a compound of formula **E-2** with a halogenating agent to form a compound of formula **F-1** wherein X is halogen.

19. The method of claim 16 wherein conversion of the compound of formula **F-1** to the compound of formula **I** comprises the steps of:

(a) converting the compound of formula **F-1** to a compound of formula **G-1**:



G-1

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

R^3 is hydrogen, 6-10 membered aryl, or 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein R^3 is optionally substituted with one or more R^x groups;

each R^x is independently selected from halogen, OH, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, or CN; and

Z is a suitable leaving group;

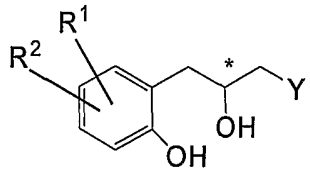
and

(b) converting the compound of formula **G-1** to a compound of formula **I**.

20. The method of claim 19 wherein conversion of the compound of formula **F-1** to a compound of formula **G-1** comprises a Suzuki reaction.

21. The method of claim 19 wherein conversion of the compound of formula **G-1** to a compound of formula **I** comprises contacting the compound of formula **G-1** with an amine or an alkali metal azide, followed by reduction.

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



D-1

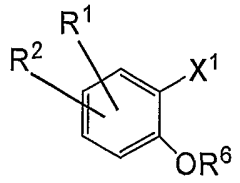
wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group; and

Y is Br, Cl, or I;

comprising the steps of:

(a) providing a compound of formula **A**:



A

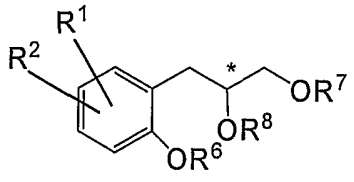
wherein:

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

R^6 is a suitable hydroxyl protecting group; and

X^1 is halogen,

(b) converting a compound of formula **A** to a compound of formula **C**



C

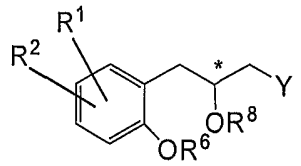
R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3 heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

R^6 is a suitable hydroxyl protecting group;

R^7 is a hydroxyl protecting group; and

R^8 is hydrogen or a hydroxyl protecting group,

(c) reacting the compound of formula **C** with a hydrogen bromide to produce a compound of formula **C'**:



C'

R^1 and R^2 are each independently hydrogen, chlorine, fluorine, CN, -OH, C_{1-8} alkyl, C_{1-6} perfluoroalkyl, C_{1-6} alkoxy, C_{1-6} perfluoroalkoxy, 6-10 membered aryl, 6-10 membered aryloxy, 5-10 membered heteroaryl having 1 to 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, C_{2-8} alkenyl, C_{1-6} alkanesulfonamido, dialkylamino of 1 to 6 carbon atoms per alkyl moiety, C_{3-8} cycloaliphatic, or 3-8 membered heterocycloalkyl having 1 to 3

heteroatoms independently selected from nitrogen, oxygen or sulfur; or R^1 and R^2 when adjacent to each other may be taken together with the carbon atoms to which they are attached to form a cyclic moiety selected from a monocyclic cycloaliphatic of 3 to 8 carbon atoms, a bridged cycloaliphatic of 5 to 10 carbon atoms, a 3 to 8 membered heterocycloaliphatic having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, 6-10 membered aryl, or a 5-10 membered heteroaryl having 1 to 3 heteroatoms each independently selected from nitrogen, oxygen, or sulfur, wherein the monocyclic cycloaliphatic or the heterocycloaliphatic may be optionally substituted at a single carbon atom with a 3-5 membered cycloalkyl ring or a 3-5 membered heterocycloalkyl ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, to form a spirocyclic group;

Y is Br, Cl, or I;

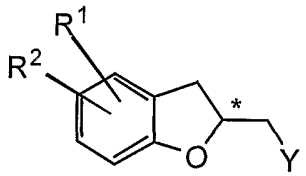
R^6 is a suitable hydroxyl protecting group; and

R^8 is hydrogen or a suitable hydroxyl protecting group,

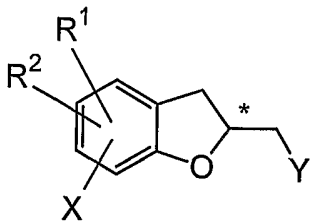
and

(d) if the R^6 group of formula **C'** is a hydroxyl protecting group, then further comprising the step of removing the protecting group to produce a compound of formula **D** where Y is Br.

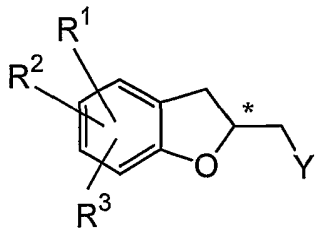
23. A compound having the formula E, F or G



E



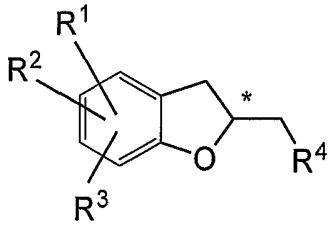
F



G

wherein R^1, $R^2$and Y are as defined in claim 1, X is halogen or triflate and R^3 is as defined in claim 6.

24. A method for preparing a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:
R^1, R^2, R^3 and R^4 are as defined in claim 16, which comprises reacting a compound having formula G as claimed in claim 23 with a compound having the formula HR^4 or a salt thereof and, if desired, treating the resultant product to convert a protected amino group as R^4 into an amino group or reducing the resultant product where R^4 is N_3 to form an amino group.