# Process for the Stereoselective Preparation of (-)-Halofenate and Intermediates Thereof

## CROSS-REFERENCES TO RELATED APPLICATIONS

**[0001]** This application claims the benefit of U.S. Patent Application No. 60/720,300, filed September 23, 2005; and the benefit of U.S. Patent Application Serial No.: yet to be assigned, filed September 20, 2006 and entitled PROCESS FOR THE STEREOSELECTIVE PREPARATION OF (-)-HALOFENATE AND DERIVATIVES THEREOF (attorney docket no. 016325-020510US), the content of which are incorporated herein by reference.

## FIELD OF THE INVENTION

**[0002]** The present invention relates to a stereoselective process for the preparation of (-)-halofenate (4-Chloro-α-(3-trifluoromethylphenoxy)phenylacetic acid) and intermediates thereof.

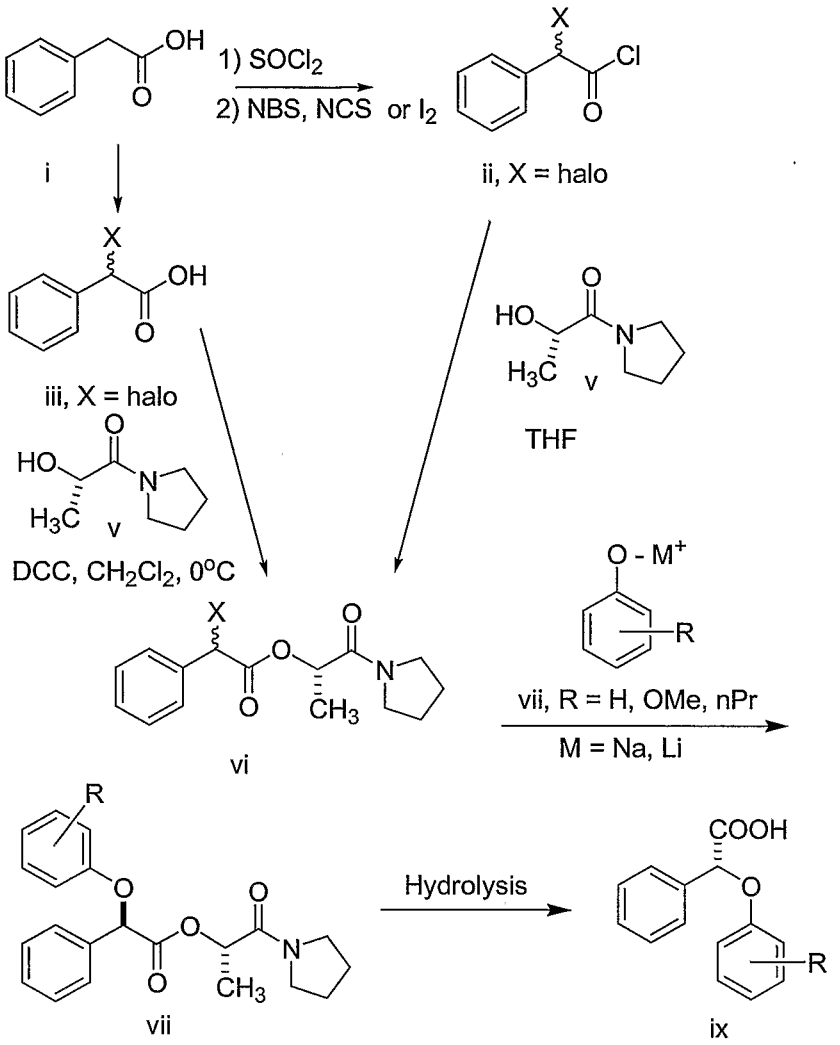
## BACKGROUND OF THE INVENTION

**[0003]** Esters and amides derivatives of (-)-4-Chloro-α-(3-trifluoromethylphenoxy)phenylacetic acid (halofenic acid) are chiral compounds and are useful in ameliorating a variety of physiological conditions, including conditions associated with blood lipid deposition, Type II diabetes and hyperlipidema (*see, e.g.*, U.S. Patent Application No. 10/656,567 and U.S. Patent No. 6,262,118 which are incorporated herein by reference in their entirety). Halofenic acid contains a single chiral center at an asymmetrically substituted carbon atom alpha to the carbonyl carbon atom, and therefore exist in two enantiomeric forms. It has been found that the (-)-enantiomer of halofenic acid is about twenty-fold less active in its ability to inhibit cytochrome P450 2C9 compared to the (+)-enantiomer. *Id.* Administration of a racemic halofenic acid or its derivatives can lead to a variety of drug interaction problems with other drugs, including anticoagulants, anti-inflammatory agents and other drugs, that are metabolized by this enzyme. *Id.* It is desirable to administer the (-)-enantiomer of halofenic acid or its derivatives which is substantially free of the (+)-enantiomer to reduce the possibility of drug interactions. Thus, enantiomerially

enriched forms of α-(phenoxy)phenylacetic acids or its derivatives are valuable chemical intermediates for the preparation of pharmaceutical compounds.

**[0004]** As shown below, various synthetic routes for making α-(phenoxy)phenylacetic acid derivatives have been reported in literature. Unfortunately, these molecules are often difficult to be produced with high enantiomeric purity and in high yields by known synthetic methods.

**Scheme 1. Synthesis of α-(phenoxy)phenylacetic acids.**

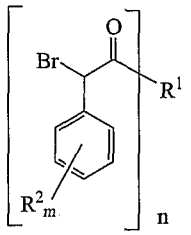



**[0005]** As illustrated in Scheme 1, Devine *et al.* were able to make α-(phenoxy)phenylacetic acids stereoselectively using a pyrrolidine derived lactamide as a chiral auxiliary (*see,* U.S. Patent Nos. 5,708,186 and 5,856,519, the teachings of which are incorporated herein by reference). However this method also has several drawbacks including a) multiple isolation steps and b) low isolated yields. Therefore, there is a need for a more efficient process for producing α-(phenoxy)phenylacetic acid stereoselectively as well as derivatives thereof, e.g., (-)-halofenate. Quite surprisingly, the present invention fulfills this and other needs.

## SUMMARY OF THE INVENTION

**[0006]** The present invention provides methods that can be used to reliably convert substituted phenylacetic acids to corresponding α-(substituted)phenylacetic acid derivatives in high yields and in high enantiomeric purity.

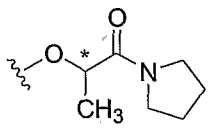
**[0007]** As such, in one embodiment, the present invention provides a method for producing a compound of formula (I):



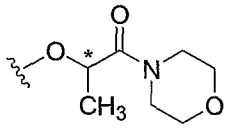
(I)

wherein

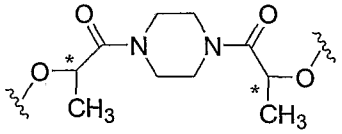
$R^1$ is a member selected from the group consisting of:



(a)

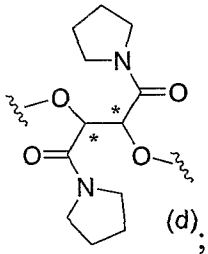


(b)



(c)

and



(d);

each $R^2$ is a member independently selected from the group consisting of ($C_1$-$C_4$)alkyl, halo, ($C_1$-$C_4$)haloalkyl, amino, ($C_1$-$C_4$)aminoalkyl, amido, ($C_1$-$C_4$)amidoalkyl, ($C_1$-$C_4$)sulfonylalkyl, ($C_1$-$C_4$)sulfamylalkyl, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)heteroalkyl, carboxy and nitro;

the subscript n is 1 when $R^1$ has the formula (a) or (b) and 2 when $R^1$ has the formula (c) or (d);

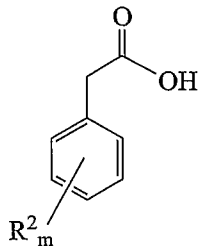
the subscript m is an integer of from 0 to 3;

* indicates a carbon which is enriched in one stereoisomeric configuration; and

the wavy line indicates the point of attachment of $R^1$;

the method comprising:

(a) contacting a compound of formula (II):

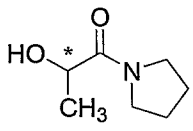
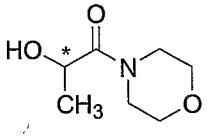
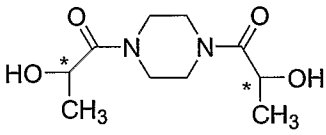
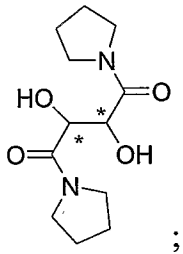


(II)

with a carboxylic acid activating reagent selected from the group consisting of a thionyl halide, an anhydride and a thioester generating reagent; in a compatible solvent;

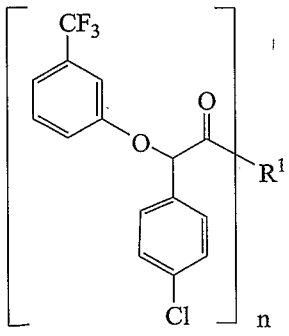
(b) brominating the product of step (a) with bromine in a compatible solvent;

(c) esterifying the product of step (b) with a chiral alcohol selected from the group consisting of:


,

,

and

;

in a compatible solvent.

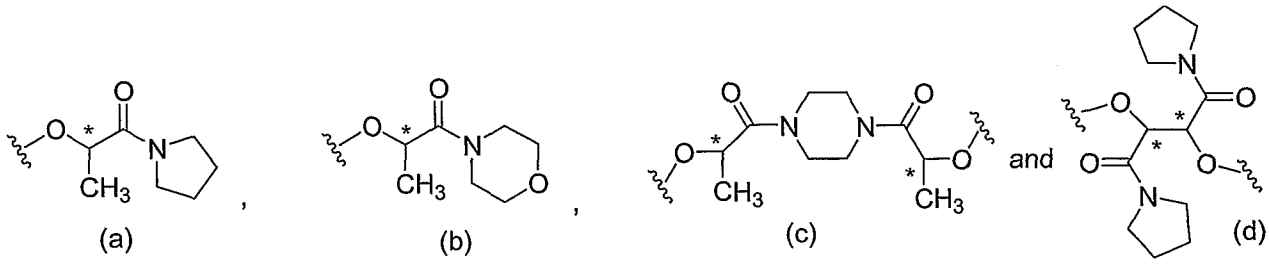
**[0008]** In another embodiment, the present invention provides α-(substituted)phenylacetic acid compounds of the formula (IV):



(IV)

wherein

$R^1$ is a member selected from the group consisting of:




;

the subscript n is 1 when $R^1$ has the formula (a) or (b) and 2 when $R^1$ has the formula (c) or (d);

* indicates a carbon which is enriched in one stereoisomeric configuration; and

the wavy line indicates the point of attachment of $R^1$.

**[0009]** Other features, objects and advantages of the invention and its preferred embodiments will become apparent from the detailed description which follows.

## DETAILED DESCRIPTION

I. Definitions

**[0010]** "Alkyl" refers to straight or branched aliphatic hydrocarbons chain groups of one to ten carbon atoms, preferably one to six carbon atoms, and more preferably one to four carbon atoms. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, *n*-propyl, 2-propyl, *tert*-butyl, pentyl, and the like.

**[0011]** "Aryl" refers to a monovalent monocyclic or bicyclic aromatic hydrocarbon moiety of 6 to 10 carbon ring atoms. Unless stated or indicated otherwise, an aryl group can be substituted with one or more substituents, preferably one, two, or three substituents, and more preferably one or two substituents selected from alkyl, haloalkyl, nitro, and halo. More specifically the term aryl includes, but is not limited to, phenyl, 1-naphthyl, and 2-naphthyl, and the like, each of which is optionally substituted with one or more substituent(s) discussed above.

**[0012]** "Chiral" or "chiral center" refers to a carbon atom having four different substituents. However, the ultimate criterion of chirality is non-superimposability of mirror images.

**[0013]** The terms "CPTA" and "halofenic acid" are used interchangeably herein and refer to (4-chlorophenyl)(3-trifluoromethylphenoxy)acetic acid.

**[0014]** "Enantiomeric mixture" means a chiral compound having a mixture of enantiomers, including a racemic mixture. Preferably, enantiomeric mixture refers to a chiral compound having a substantially equal amounts of each enantiomers. More preferably, enantiomeric mixture refers to a racemic mixture where each enantiomer is present in an equal amount.

**[0015]** "Enantiomerically enriched" refers to a composition where one enantiomer is present in a higher amount than prior to being subjected to a separation process.

**[0016]** "Enantiomeric excess" or "%ee" refers to the amount of difference between the first enantiomer and the second enantiomer. Enantiomeric excess is defined by the equation: %ee = (% of the first enantiomer) - (% of the second enantiomer). Thus, if a composition comprises 98% of the first enantiomer and 2% of the second enantiomer, the enantiomeric excess of the first enantiomer is 98%-2% or 96%.

**[0017]** The terms "halide" and "halo" are used interchangeably herein and refer to halogen, which includes F, Cl, Br, and I, as well as pseudohalides, such as –CN and –SCN.

**[0018]** "Haloalkyl" refers to alkyl group as defined herein in which one or more hydrogen atoms have been replaced with halogens, including perhaloalkyls, such as trifluoromethyl.

**[0019]** "Halofenate" refers to 2-acetamidoethyl 4-chlorophenyl-(3-trifluoromethyl-phenoxy)acetate (i.e., 4-chloro-α-(3-(trifluoromethyl)phenoxy)benzeneacetic acid, 2-(acetylamino)ethyl ester or (4-chlorophenyl)(3-trifluoromethylphenoxy)acetic acid), 2-(acetylamino)ethyl ester).

**[0020]** "Heteroalkyl" means a branched or unbranched acyclic saturated alkyl moiety containing one or more heteroatoms or one or more heteroatom-containing substituents, where the heteroatom is O, N, or S. Exemplary heteroatom-containing substituents include =O, $-OR^a$, $-C(=O)R^a$, $-NR^aR^b$, $-N(R^a)C(=O)R^b$, $-C(=O)NR^aR^b$ and $-S(O)_nR^a$ (where n is an integer from 0 to 2 ). Each of $R^a$ and $R^b$ is independently hydrogen, alkyl, haloalkyl, aryl, or aralkyl. Representative examples of heteroalkyl include, for example, N-acetyl 2-aminoethyl (i.e., $-CH_2CH_2NHC(=O)CH_3$).

**[0021]** The term "metal" includes Group I, II, and transition metals as well as main group metals, such as B and Si.

**[0022]** "Optical purity" refers to the amount of a particular enantiomer present in the composition. For example, if a composition comprises 98% of the first enantiomer and 2% of the second enantiomer, the optical purity of the first enantiomer is 98%.

**[0023]** Unless otherwise stated, the term "phenyl" refers to an optionally substituted phenyl group. Suitable phenyl substituents are same as those described in the definition of "aryl." Similarly, the term "phenoxy" refers to a moiety of the formula $-OAr^a$, wherein $Ar^a$ is phenyl as defined herein. Thus, the term "α-(phenoxy)phenylacetic acid" refers to acetic acid that is substituted on the 2-position with an optionally substituted phenyl and optionally substituted phenoxy moieties.

**[0024]** "Protecting group" refers to a moiety that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, New York, 1999, and Harrison and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8 (John Wiley and Sons, 1971-1996), which are incorporated herein by reference in their entirety. Representative hydroxy protecting groups include acyl groups, benzyl and trityl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers. Representative amino protecting groups include, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), *tert*-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (FMOC), nitro-veratryloxycarbonyl (NVOC), and the like.

**[0025]** The term "rate" when referring to a formation of a reaction product refers to kinetic and/or thermodynamic rates.

**[0026]** As used herein, the term "treating", "contacting" or "reacting" refers to adding or mixing two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product.

**[0027]** As used herein, the terms "those defined above" and "those defined herein" when referring to a variable incorporates by reference the broad definition of the variable as well as preferred, more preferred and most preferred definitions, if any.

**[0028]** Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes "d" and "1" or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or (1) meaning that the compound is "levorotatory" and with (+) or (d) is meaning that the compound is "dextrorotatory". There is no correlation between nomenclature for the absolute stereochemistry and for the rotation of an enantiomer. For a given chemical structure, these compounds, called "stereoisomers," are identical except that they are mirror images of one another. A specific stereoisomer can also be referred to as an "enantiomer," and a mixture of such isomers is often called an "enantiomeric" or "racemic" mixture. See, e.g., Streitwiesser, A. & Heathcock, C. H., INTRODUCTION TO ORGANIC CHEMISTRY, 2nd Edition, Chapter 7 (MacMillan Publishing Co., U.S.A. 1981).

**[0029]** The terms "substantially free of its (+)-stereoisomer," "substantially free of its (+)-enantiomer," are used interchangeably herein and mean that the compositions contain a substantially greater proportion of the (-)-isomer in relation to the (+)-isomer. In a preferred embodiment, the term "substantially free of its (+) stereoisomer" means that the composition is at least 90% by weight of the (-)-isomer and 10% by weight or less of the (+)-isomer. In a more preferred embodiment, the term "substantially free of its (+)-stereoisomer" means that the composition contains at least 99% by weight of the (-)-isomer and 1% by weight or less of the (+)-isomer. In the most preferred embodiment, the term "substantially free of its (+)-stereoisomer" means that the composition contains greater than 99% by weight of the (-)-isomer. These percentages are based upon the total amount of isomers in the composition.

## II. Introduction

**[0030]** Although enantiomers of a chiral compound have exact same chemical bonds, the spatial orientation of atoms in enantiomers is different. Thus, one enantiomer of a chiral drug often exerts desired activity with a significantly less side-effect(s) than the other enantiomer. While resolution of racemates is often used in industrial processes for preparation of optically active, i.e., chiral, compounds; chiral synthesis has made an extensive progress in recent years.

**[0031]** The present invention provides a method for synthesizing a α-(halo)phenylacetic acid chiral ester derivative. The chiral ester on the α-(halo)phenylacetic acid directs the alkylation of 3-trifluoromethylphenol to stereoselectively produce α-(phenoxy)phenylacetic acid derivatives. Thus, compounds produced using methods of the present invention are useful in producing α-(phenoxy)phenylacetic acid derivatives such as those disclosed in U.S. Patent Application No. 10/656,567 and U.S. Patent No. 6,262,118 in high yields. In particular, compounds and methods of the present invention are useful in producing (-)-halofenate.

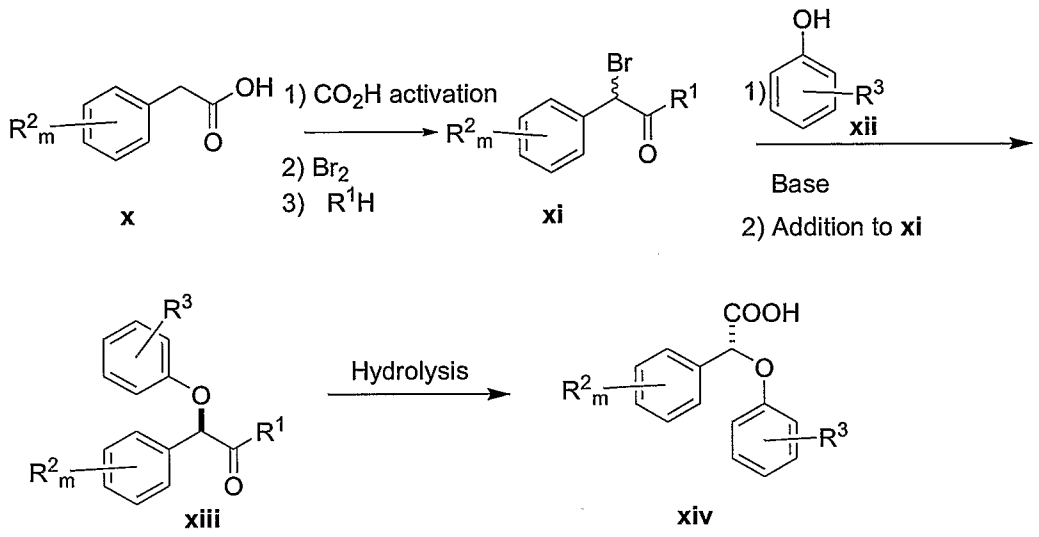
III. Stereoselective Synthesis

**[0032]** As noted above, previous stereoselective processes to produce (-)-halofenate require multiple steps and result in a composition in low yield or is of insufficient optical purity to be commercially viable. However, present inventors have found that under certain conditions disclosed herein, α-(phenoxy)phenylacetic acid compound of a sufficient optical purity can be produced in high yield and high optical purity with few isolation steps. These high yields are unusual since bromination of similar compounds with bromine do not result in high yields (*see* Harpp *et al. J. Org. Chem.* 40(23): 3420 (1975). Thus, in one aspect, methods of the present invention are based on the surprising and unexpected discovery by the present inventors that substitutedphenylacetic acids can be activated, brominated with bromine and esterified to result in a chiral α-halophenyl acetic ester intermediate in high yield.

**[0033]** This intermediate can then be used to stereoselectively produce α-(phenoxy)phenylacetic acid derivatives. In particular, methods of the present invention provide a desired enantiomer of a α-(phenoxy)phenylacetic acid derivative in yields of at least about 40%, preferably at least about 50%, more preferably at least about 60%, and most preferably at least about 70%. In particular, methods of the present invention provide a desired enantiomer of the α-(phenoxy)phenylacetic acid compound in optical purity of at least about 90%, preferably at least about 95%, more preferably at least about 97%, and most preferably at least about 98%.

**[0034]** One method of stereoselectively producing a α-(phenoxy)phenylacetic acid derivatives, such as **xiv**, is shown generally in Scheme 2 below.

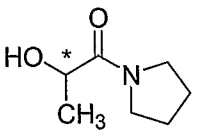
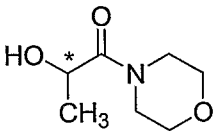
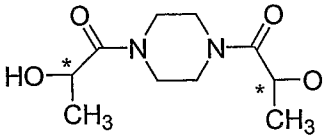
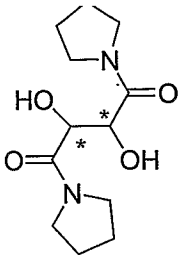
**Scheme 2:** General Route



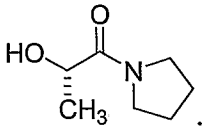

**[0035]** Thus, phenylacetic acid **x** can be converted to an activated carboxylic acid derivative and subsequently halogenated with molecular bromine to give α-bromophenylacetyl halide **xi** in two steps. The phenyl acetic acid is preferably a halophenylacetic acid, more preferably 4-halo-phenylacetic acid and more preferably 4-chloro-phenylacetic acid.

**[0036]** Examples of carboxylic activating agents suitable for use in the present invention, include, but are not limited to thionyl halides such as thionyl chloride ($SOCl_2$); anhydrides, such as trifluoroacetic anhydride (TFAA), and thioester generating reagents. The carboxylic acid activating agent is preferably a thionyl halide and more preferably thionyl chloride. It is commercially available as a clear liquid and may be used neat or in a compatible solvent.

**[0037]** The acid halide is then converted to chiral ester **xiii**, where $R^1$ is a chiral alcohol auxiliary. A wide variety of chiral auxiliaries can be used, including those disclosed in the Examples section below. Preferably, the chiral auxiliary used results in making only one diasteromer of α-(phenoxy)phenylacetic acid. It should be recognized that the chiral alcohol auxiliary compound itself should be of a sufficient enantiomeric purity in order to yield a highly enantiomerically enriched α-(phenoxy)phenylacetic acid derivative. In this manner, one enantiomer at the α-position is readily made, for example, by removing the chiral auxiliary. In one particular embodiment, the chiral auxiliary is an chiral alcohol compound of the formula:




and


Preferably the chiral alcohol has the formula:

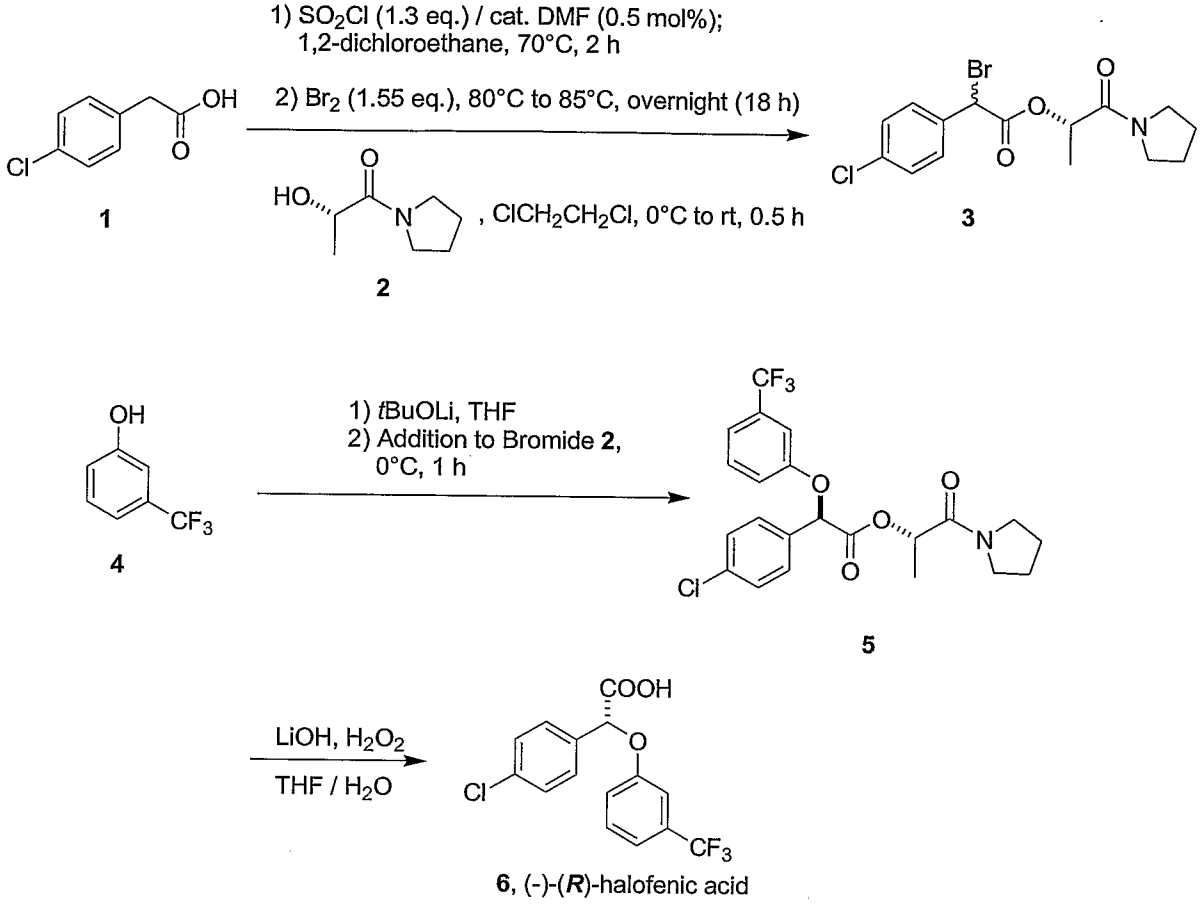


**[0038]** The displacement reaction of ester **xi** with an appropriately substituted phenol compound **xii** in the presence of a base, such as a hydroxide gives α-(phenoxy)phenylacetic acid ester **xiii.** Examples of bases that may be used in the displacement reaction include, but are not limited to hydroxide, such as lithium hydroxide, potassium hydroxide, sodium hydroxide and the like; alkoxide, such as lithium alkoxide, potassium alkoxide, sodium hydroxide and the like; and the like; hydride, such as lithium hydride, potassium hydride, sodium hydride and the like; and the like.

**[0039]** Hydrolysis of the α-(phenoxy)phenylacetic acid ester **xiii** affords α-(phenoxy)phenylacetic acid **xiv.** Examples of hydrolyzing agents that may be used include, but are not limited to hydroxide, such as lithium hydroxide, potassium hydroxide, sodium hydroxide and the like; hydroperoxide, such as lithium hydroperoxide, potassium hydroperoxide, sodium hydroperoxoide and the like; and the like.

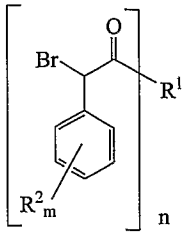
**[0040]** This synthetic route is shown more specifically in Scheme 3 below:

**Scheme 3:** Stereoselective synthesis of halofenic acid




For example, 4-chlorophenylacetic acid **1**, can be treated with thionyl chloride to activate the carboxylic acid. This can then be treated with bromine to form 4-chlorophenylacetyl chloride. The esterification is conveniently carried out with (S)-N,N-tetramethylenelactamide **2**. This reaction sequence is particularly advantageous as the reactions are conveniently carried out in one reaction vessel with only one isolation step. The displacement reaction of ester **3** with 3-trifluoromethylphenol **4** in the presence of potassium hydroxide gives α-(phenoxy)phenylacetic acid ester **5**. Hydrolysis of the α-(phenoxy)phenylacetic acid ester **5** with lithium hydroxide afforded α-(phenoxy)phenylacetic acid **6**. In this manner, (4-chlorophenyl)-(3-trifluoromethylphenoxy)-acetic acid, i.e., CPTA, can be prepared in five steps in about 73% yield following crystallization from heptane.

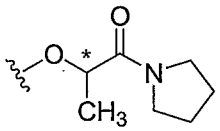
**[0041]** Thus in one embodiment, the present invention provides a method of producing a compound of formula (I):



(I)

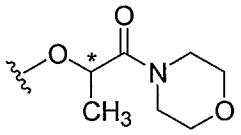
wherein

$R^1$ is a member selected from the group consisting of:



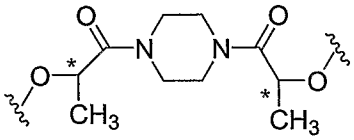
(a)

,



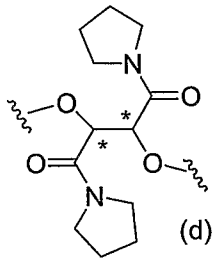
(b)

,



(c)

and



(d)

;

each $R^2$ is a member independently selected from the group consisting of ($C_1$-$C_4$)alkyl, halo, ($C_1$-$C_4$)haloalkyl, amino, ($C_1$-$C_4$)aminoalkyl, amido, ($C_1$-$C_4$)amidoalkyl, ($C_1$-$C_4$)sulfonylalkyl, ($C_1$-$C_4$)sulfamylalkyl, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)heteroalkyl, carboxy and nitro;

the subscript n is 1 when $R^1$ has the formula (a) or (b) and 2 when $R^1$ has the formula (c) or (d);

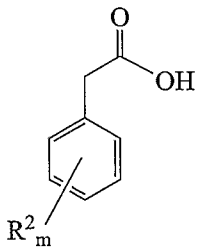
the subscript m is an integer of from 0 to 3;

* indicates a carbon which is enriched in one stereoisomeric configuration; and

the wavy line indicates the point of attachment of $R^1$.

The method generally involves:

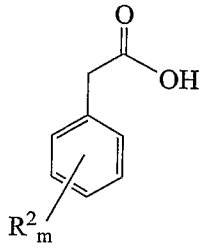
(a) activation the carboxylic acid of a compound of formula (II):



(II)

with a carboxylic activating agent in a compatible solvent;

(a) contacting a compound of formula (II):

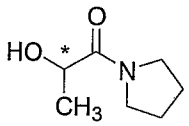
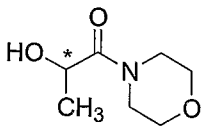
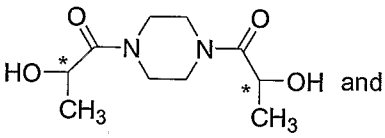
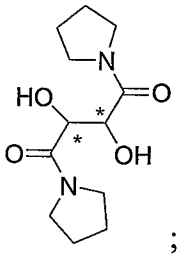


(II)

with a carboxylic acid activating reagent selected from the group consisting of a thionyl halide, an anhydride and a thioester generating reagent; in a compatible solvent;

(b) brominating the product of step (a) with bromine in a compatible solvent;

(c) esterifying the product of step (b) with a chiral alcohol selected from the group consisting of:


,

,

and

;

in a compatible solvent.

**[0042]** The present inventors have found that the brominating agent used in the preparation of the α-(phenoxy)phenylacetic acid has a significant effect on ease of isolation and overall yield of the process. For example, when bromine is used in the process of making the α-(phenoxy)phenylacetic acid compound, higher overall yields are obtained than by using other halogenating agents. The amount of halogenating agent used is not particularly important. The amount used is typically more than 1.00 molar equivalent, preferably about 1.5 molar equivalent or more, more preferably about 1.55 molar equivalent.

**[0043]** The reactions are typically conducted in an compatible solvent. A compatible solvent is one which is inert to the reaction condtions and can readily dissolve the reactants. Suitable solvents for the above reactions are known by those of skill in the art. For example, suitable solvents for the carboxylic acid activation, bromination, and esterification reactions include, but are not limited to, aprotic solvents, such as halogenated alkanes, tetrahydrofuran,

aromatic hydrocarbons, dialkylethers, and mixtures thereof. A particularly preferred solvent is a halogenated alkane, more preferably 1, 2-dichloroethane.

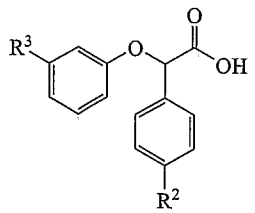
**[0044]** In one embodiment, the bromination process involves heating the reaction mixture to a temperature in the range of from about 70 °C to the boiling point of the solution, preferably from about 80 °C to about 85 °C. Heating is carried out until the reaction is complete, which typically ranges from about 1 to about 24 hours, preferably from about 2 to about 18 hours. At lower temperatures, longer reaction times may be needed. It will be readily apparent to those of skill in the art that the progress of this and other reactions in the method of the present invention can be monitored by, for example, HPLC, and the reaction deemed complete when the amount of unreacted starting reagents is less than about 1%.

**[0045]** The bromine can be removed prior to addition of the chiral alcohol auxiliary. This can be done by connecting the reaction vessel to a vacuum pump and removing the bromine under reduced pressure. The pressure, rate and degree of removal is not particularly important.

**[0046]** The solution can be cooled prior to and/or after the chiral alcohol auxiliary is added. This allows for the exothermic nature of the esterification reaction. The rate and amount of cooling of the reaction solution is not particularly important. In one embodiment, the esterification reaction involves cooling the reaction mixture to a temperature in the range of from about 0 °C to room temperature. The reaction is carried out until complete, which typically ranges from about 5 to about 60 minutes, typically about 30 minutes.

**[0047]** In one embodiment, this method can be done in one reaction vessel. In another embodiment, only the final product, the compound of formula (I), is isolated.

**[0048]** In particular, methods of the present invention are directed to intermediates in the synthesis of α-(phenoxy)phenylacetic acids of formula (V):

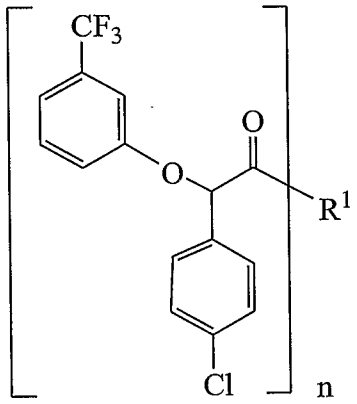



(V)

wherein $R^3$ is haloalkyl and $R^2$ is halide. In one particular embodiment, methods of the present invention are directed to the synthesis of α-(phenoxy)phenylacetic acid of Formula I

or, preferably of Formula V, where $R^2$ is chloro. In another embodiment, methods of the present invention are directed to the resolution of α-(phenoxy)phenylacetic acid of Formula I or, preferably, Formula V, where $R^3$ is preferably trifluoromethyl. In yet another embodiment of the present invention, the methods are directed to the stereoselective synthesis of compounds of Formula V wherein $R^2$ is Cl and $R^3$ is $CF_3$ e.g. halofenic acid.

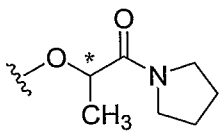
**[0049]** In one particular embodiment, α-(substituted)phenylacetic acid compounds of the formula (IV):



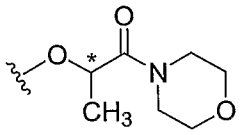
(IV)

wherein

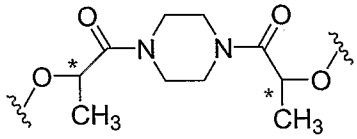
$R^1$ is a member selected from the group consisting of:



(a)

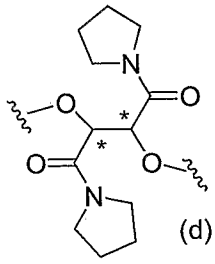


(b)



(c)

and



(d)

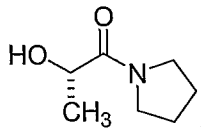
;

the subscript n is 1 when $R^1$ has the formula (a) or (b) and 2 when $R^1$ has the formula (c) or (d);

* indicates a carbon which is enriched in one stereoisomeric configuration;

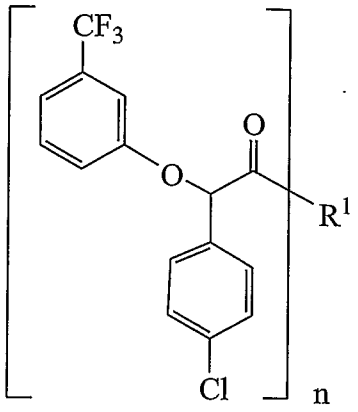
and

the wavy line indicates the point of attachment of $R^1$ are synthesized using the chiral auxiliary. A particularly preferred compound of Formula I and IV above is wherein $R^1$ is



.

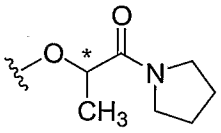
**[0050]** Unexpectedly, α-(substituted)phenylacetic acid compounds of the formula (IV):



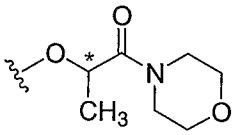
(IV)

wherein

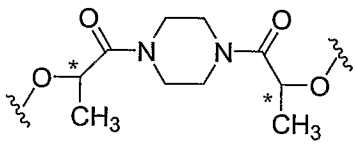
$R^1$ is a member selected from the group consisting of:



(a)

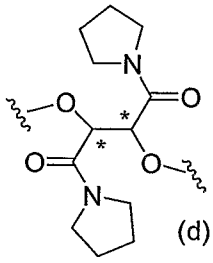


(b)



(c)

and



(d)

;

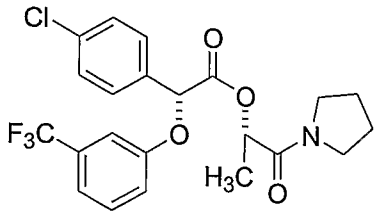
the subscript n is 1 when $R^1$ has the formula (a) or (b) and 2 when $R^1$ has the formula (c) or (d);

* indicates a carbon which is enriched in one stereoisomeric configuration; and

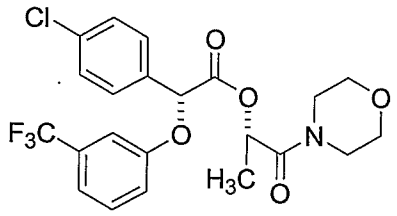
the wavy line indicates the point of attachment of $R^1$;

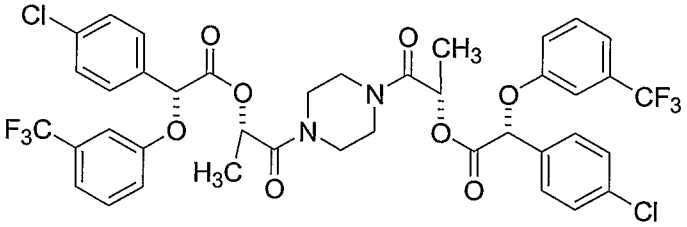
are produced in high stereoselectivity and in high yield. In order to be economically desirable, methods of the present invention provide at least about 50% yield of the desired enantiomer, preferably at least about 60%, more preferably at least about 70%, and most preferably at least about 75%.

**[0051]** In one embodiment the compound is selected from the group consisting of:

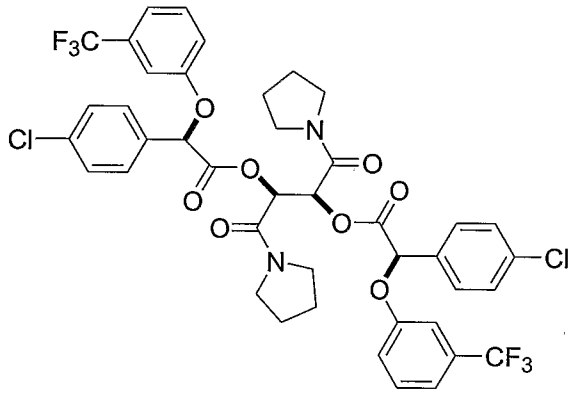


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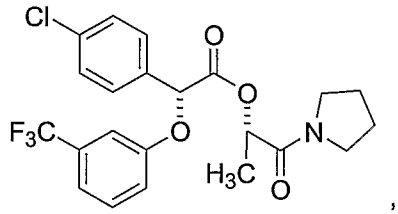




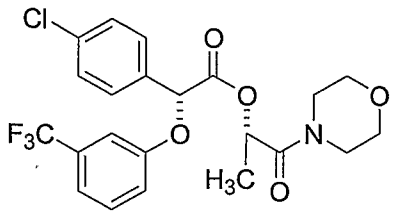
and

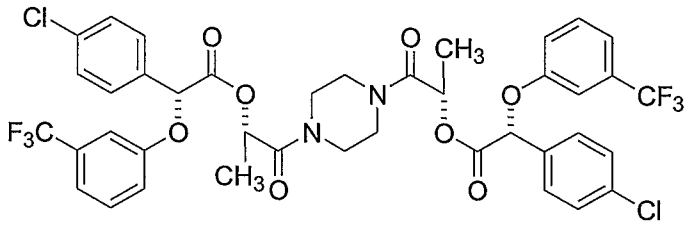


wherein the dashed and bold lines indicate the relative stereochemistry of the compound. In another embodiment the compound is selected from the group consisting of:

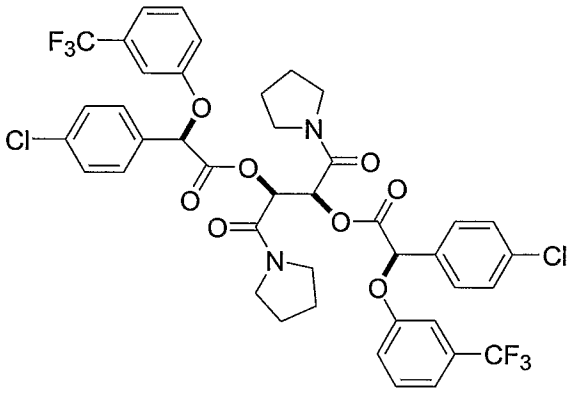


,





and



wherein the dashed and bold lines indicate the absolute stereochemistry of the compound.

**[0052]** It should be noted that while methods of the present invention are discussed in reference to the enrichment of the (-)-enantiomer of halofenic acid, methods of the present invention are also applicable for enriching the (+)-enantiomer. The method of the present invention essentially provides a compound enriched in the (-)-enantiomer based on the enantiomeric enrichment of the chiral auxiliary and the stereoselectivity of the reaction. Use of the (+)-enantiomer can be readily accomplished by use of the opposite enantiomer of the chiral alcohol auxiliary. For example, the (+)-enantiomer can be made using (R)-N,N-tetramethylenelactamide.

**[0053]** The chiral auxiliary can be recovered from the above described conversion step and reused/recycled. Thus, the process of the present invention lends itself readily to a recycling-type of procedure.

IV. Synthesis of chiral alcohol auxiliaries

**[0054]** One method of producing a chiral alcohol auxiliary **2** is shown in Scheme 4 below.

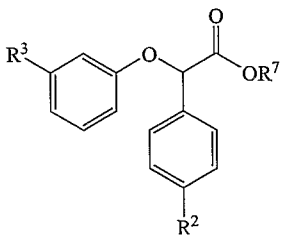
**Scheme 4:** Synthesis of Chiral Auxiliary




**[0055]** Reaction of lactic ester **7** with an excess of the appropriate cyclic amine gives the chiral auxiliary **2**. By using an excess of cyclic amine per equivalent of ester the conversion is high and the amount of racemization is minimized. For example, pyrrolidine **8** (i.e., where $R^6$ is combined to form a five membered ring) is particularly advantageous as pyrrolidine is a good solvent for the lactic ester and the reaction is conveniently carried out neat. In this manner, (S)-N,N-tetramethylenelactamide can be prepared in one step in about 95% yield.

V. Utility of enantiomerically enriched α-(phenoxy)phenylacetic acid

**[0056]** Enantiomerically pure α-(phenoxy)phenylacetic acid compounds are useful intermediates in preparing a variety of pharmaceutically active compounds, including α-(phenoxy)phenylacetic acid compounds disclosed in U.S. Patent Application No. 10/656,567 and U.S. Patent No. 6,262,118. Thus, another aspect of the present invention provides a method for enantioselectively producing a α-(phenoxy)phenylacetate compound of the formula:




VI

from a α-(phenoxy)phenylacetic acid compound Formula V, wherein $R^3$ is alkyl or haloalkyl, $R^2$ is halo and $R^7$ is heteroalkyl, preferably N-acetyl 2-aminoethyl (i.e., a moiety of the formula $-CH_2CH_2NHC(=O)CH_3$). The method involves stereoselectively synthesizing a α-(phenoxy)phenylacetic acid compound of Formula V as described above and reacting the

enantiomerically enriched α-(phenoxy)phenylacetic acid with a carboxylic acid activating reagent. Suitable carboxylic acid activating reagents include thionyl halides (e.g., thionyl chloride), anhydrides (e.g. TFAA), thioester generating reagents, and other carboxylic acid activating reagents known to one skilled in the art.

**[0057]** The activated α-(phenoxy)phenylacetic acid is than reacted with a compound of the formula $(R^7–O)_wM$, e.g., N-acetyl ethanolamine derivative, to produce enantiomerically enriched α-(phenoxy)phenylacetate compound of Formula VI, where $R^7$ is as defined above, M is hydrogen or a metal, e.g., Na, K, Li, Ca, Mg, Cs, etc. and the superscript w is the oxidation state of M. The present inventors have discovered that the reaction between the activated acid and the compound of formula $(R^7–O)_wM$ can be carried out without any significant racemization.

**[0058]** Additional objects, advantages, and novel features of this invention will become apparent to those skilled in the art upon examination of the following examples thereof, which are not intended to be limiting.

## EXAMPLES

Reagents and Experimental Setup

**[0059]** Unless otherwise stated, reagents and solvents were purchased from Aldrich Chemical or Fisher Scientific. Operations were conducted under a positive nitrogen atmosphere. A Camile process control computer attached to a recirculating heating and cooling system was used to regulate jacket temperatures in the jacketed straight-walled bottom-drain glass reactors. Unless otherwise indicated, solvents were removed using a Buchi rotary evaporator at 15 to 25 torr with a bath temperature of up to 40 °C. Solid samples were dried in a vacuum oven at 40 °C, 15 to 25 torr. A Cenco HYVAC vacuum pump was used to supply vacuum of less than 1 torr for vacuum distillations. Water levels were determined by Karl Fisher analysis using a Metrohm 756 KF Coulometer and HYDRANAL Coulomat AG reagent. Melting points were determined using a Mettler Toledo FP62 melting point apparatus. pH was measured using a calibrated Orion Model 290A pH meter. Proton and $^{13}C$ NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer.

**[0060]** Chiral HPLC analysis was carried out at λ=240 nm by injecting 10 μL of sample dissolved in mobile phase onto a (R,R)WHELK-O 1.5 μm 250 x 4.6 mm column (Regis Technologies) and eluting with a 1.0 mL/min flow of 95/5/0.4 (v/v/v) hexanes/2-propanol/acetic acid.

**[0061]** Achiral HPLC analysis was carried out at λ=220 nm by injecting 5 μL of sample dissolved in mobile phase onto a Phenomenex LUNA 5 μm C18(2) 250 x 4.6 mm column at 25 °C. A 1.5 mL/min flow of the gradient starting at 66 vol% water/34 vol% acetonitrile/0.1 vol% trifluoroacetic acid and increasing linearly to 26 vol% water/74 vol% acetonitrile/0.1 vol% trifluoroacetic acid at 20 minutes was used.

**[0062]** For analysis of acidic solutions of esters, such as halofenate, acetonitrile was used as the injection solvent. When determined, product concentrations for halofenate were evaluated by HPLC assay using the external standard method and the achiral analysis procedure at sample concentrations of less than 2.5 mg/mL.

Example 1: Synthesis of a chiral alcohol auxiliary.

*(S)-N,N-Tetramethylenelactamide* **(2)**

**[0063]** Pyrrolidine (120 g, 1.69 mol; 2 eq.) was added dropwise to 100g (0.847 mol) of ethyl (S)-(-)-lactate at 0°C and stirred at room temperature for 3 days. After removal of excess pyrrolidine and resulting ethanol *in vacuo*, the oil residue was purified with distillation (104 °C, 2 mmHg) to give 113 g (93%) of (S)-N,N-tetramethylenelactamide (**2**) as a pale-yellow oil. $^1$H NMR ($CDCl_3$): δ 4.30 (1H, q, $J$ = 6.63 Hz), 3.74 (1H, br, OH), 3.31-3.61 (4H, m), 1.85-2.03 (4H, m), 1.34 (1H, d, $J$ = 6.24 Hz) ppm.

Example 2: Preparation of (-)-halofenate (**6**)

*Preparation of compound* **(3)**

**[0064]** To a 2-L 3-neck flask under air, immersed in an oil bath and fitted with an addition funnel and a condenser was added 500 mL of anhydrous 1,2-dichloroethane, 4-chlorophenylacetic acid (174.04 g 98%, 1.0 mol (Acros)) of in one-portion, DMF (0.40 mL, ca. 0.5 mol%) in one-portion and thionyl chloride (95 mL, 1.3 mol, 1.3 eq.) over ~ 1 minute.

The resulting mixture was heated to 70 °C (oil-bath temperature) over 15 minutes. Vigorous gas evolution began approximately 5 minutes after heating (at ~40-45 °C). The vigorous gas evolution slowed to a steady stream and then the gas evolution stopped. After stirring at 70 °C for 2 hours, bromine (80 mL, ca. 249 g, 1.55 mol; 1.55 eq.) was added to the resulting pale yellow solution (at 65 °C) over ~ 1 minute to give a brown solution. The reaction was stirred at 80 °C to 85 °C (oil-bath temperature) overnight (ca. 18 hours) and then cooled to room temperature. This α-bromo acid chloride solution was stored at room temperature and used in the next ester formation step without further purification.

**[0065]** The solution of crude acid chloride (138 g, ~ 0.138 mol) in 1,2-dichloroethane prepared above was diluted with 100 mL of 1,2-dichloroethane. Excess bromine was removed by distillation *in vacuo* until ca. 100 mL of solution remained. The acid chloride solution was then added dropwise to a solution of (S)-N,N-tetramethylenelactamide (20.1g, 0.140 mol) and triethylamine (14.78 g, 0.147 mol) in 100 mL of 1,2-dichloroethane at 0 °C. The resulting brown mixture was warmed up to room temperature over 1 h. The reaction mixture was quenched with water (100 mL), and the organic layer was separated and washed with 100 mL of 10% $Na_2S_2O_3$ and then with saturated $NaHCO_3$ (100 mL). The organic layer was dried over $Na_2SO_4$ and then concentrated *in vacuo* to give 45.8 g of crude product as a brown oil which was used in the next step without further purification.

*Preparation of compound* **(6)**

**[0066]** To a solution of α,α,α-trifluoro-m-cresol (3.3 g; 0.0204 mol) in anhydrous THF (20 mL) at room temperature was added dropwise lithium tert-butoxide (20 mL of a 1.0 M solution in THF; 0.02 mol). The resulting lithium phenoxide solution was added dropwise to a solution of bromide **3** (crude, 7.5 g; 0.02 mol) in 40 mL of THF at -5 °C. After stirring at -5 °C for 1 hour, a pre-mixed solution of hydrogen peroxide (Fisher 30%; 105 mL, 0.4 mol) and $LiOH•H_2O$ (21g, 0.05 mol) in water (50 mL) was added at room temperature over 20 min. The reaction was stirred at 0-4 °C for 1 hour, quenched with saturated aqueous sodium bisulfite (150 mL), then 1N HCl was added to adjust the pH of the solution to about 2. THF was removed by distillation *in vacuo*, and then the reaction mixture was diluted with EtOAc (100 mL). The organic layer was washed with water and brine, dried over $Na_2SO_4$ and evaporated to give 7g of crude acid. The crude acid was crystallized from heptane to give 4.6g of a white solid. Chiral HPLC analysis 96.5:3.5 enantiomers.

**[0067]** Preparation of halofenic acid can be carried out using similar conditions with other chiral auxiliaries listed above.

Example 3: Alternative Preparation of halofenate **(6)**

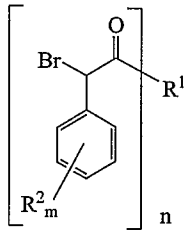
**[0068]** To a solution of α,α,α-trifluoro-m-cresol (6.71g; 0.041 mol) in anhydrous THF (20 mL) and toluene (30 mL) at room temperature was added lithium hydroxide hydrate (1.68 g, 40 mmol). The solvent was removed after 1 hr and the residue was dissolved in 30 mL anhydrous THF (30 mL). The resulting lithium phenoxide solution was added dropwise to a solution of bromide **3** (crude, 14.9 g; 0.04 mol) and NaI (0.3g) in 100 mL of THF with stirring at room temperature for 1 h at -5 °C and for an additional 3 hr. at -5 °C to 0°C. $^1$H NMR showed the disappearance of bromide **3**.

**[0069]** Hydrogen peroxide (Fisher 30%; 209 mL, 0.8 mol) was added to a solution of lithium hydroxide (4.2 g, 0.09 mol) in water (100 mL), and the mixture was stirred at room temperature for 20 min. This solution was then slowly added to a cold solution of lactamide **4** in THF at 0 °C. The reaction was stirred at 0-4 °C for 1 hour, quenched with 1N HCl and adjusted pH to 2. THF was removed by distillation *in vacuo* and then the reaction mixture was diluted with EtOAc (150 mL). The organic layer was washed with water, saturated $Na_2S_2O_3$ and brine, dried over $Na_2SO_4$ and evaporated to give crude acid. The crude acid was crystallized from heptane to give 8.4g of a white solid. (99:1 enantiomers, determined by chrial HPLC).

**[0070]** It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

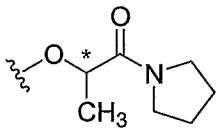
1. A method for preparing a compound of formula (I):



(I)

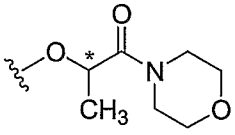
wherein

$R^1$ is a member selected from the group consisting of:



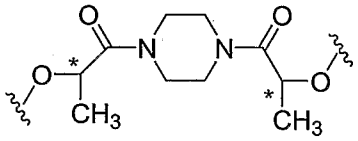
(a)

,



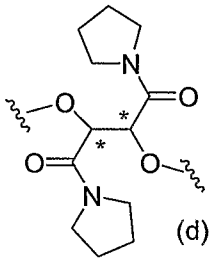
(b)

,



(c)

and



(d)

;

each $R^2$ is a member independently selected from the group consisting of ($C_1$-$C_4$)alkyl, halo, ($C_1$-$C_4$)haloalkyl, amino, ($C_1$-$C_4$)aminoalkyl, amido, ($C_1$-$C_4$)amidoalkyl, ($C_1$-$C_4$)sulfonylalkyl, ($C_1$-$C_4$)sulfamylalkyl, ($C_1$-$C_4$)alkoxy, ($C_1$-$C_4$)heteroalkyl, carboxy and nitro;

the subscript n is 1 when $R^1$ has the formula (a) or (b) and 2 when $R^1$ has the formula (c) or (d);

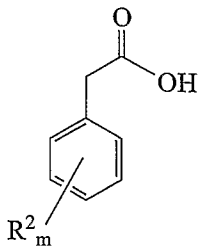
the subscript m is an integer of from 0 to 3;

* indicates a carbon which is enriched in one stereoisomeric configuration; and

the wavy line indicates the point of attachment of $R^1$;

the method comprising:

(a) contacting a compound of formula (II):

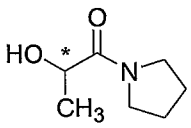
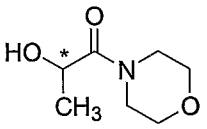
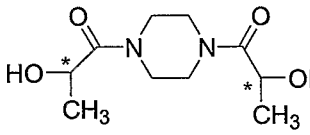
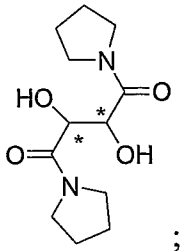


(II)

with a carboxylic acid activating reagent selected from the group consisting of thionyl halides, anhydrides and thioester generating reagents; in a compatible solvent;

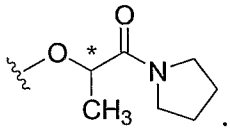
(b) brominating the product of step (a) with bromine in a compatible solvent;

(c) esterifying the product of step (b) with a chiral alcohol selected from the group consisting of:


,

,

and

;

in a compatible solvent to stereoselectively produce a compound of formula (I).

2. The method of claim 1, wherein $R^1$ is


.

3. The method of any of the preceding claims, wherein the compound of formula (II) is 4-chlorophenylacetic acid.

4. The method of any of the preceding claims, wherein the carbonyl activation agent is thionyl halide.

5. The method of any of the preceding claims, wherein the carbonyl activation agent is thionyl chloride.

6. The method of any of the preceding claims, wherein bromine is present in a concentration of about at least about molar equivalent the amount of the compound of formula (II).

7. The method of any of the preceding claims, wherein the solvent is a halogenated alkane solvent.

8. The method of any of the preceding claims, wherein the solvent is 1,2-dichloroethane.

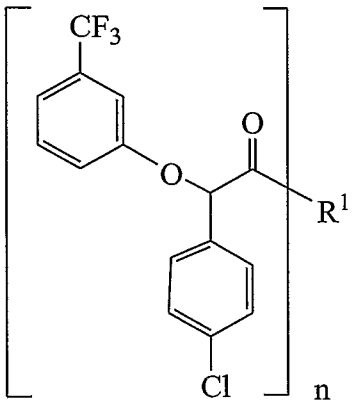
9. The method of any of the preceding claims, wherein said conditions comprise carrying out the bromination at a temperature of at least about 70 °C.

10. The method of any of the preceding claims, further comprising removing excess bromine under reduced pressure before said step (c).

11. The method of any of the preceding claims, wherein the method is conducted in one reaction vessel.

12. The method of any of the preceding claims, wherein only the compound of Formula (I) is isolated.

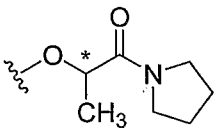
13. A compound of the formula (IV):



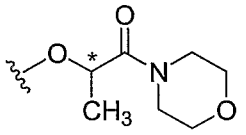
(IV)

wherein

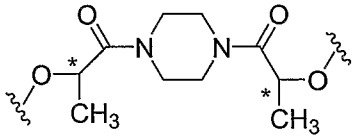
$R^1$ is a member selected from the group consisting of:



(a)

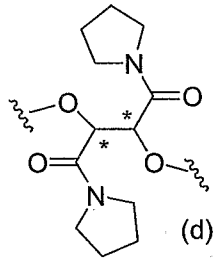


(b)



(c)

and



(d)

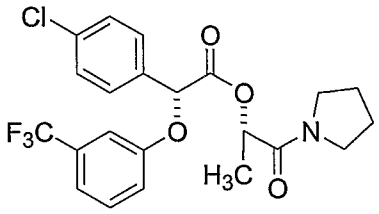
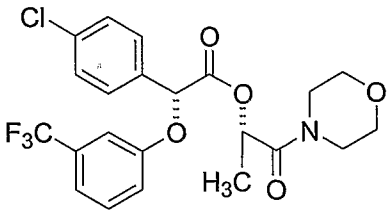
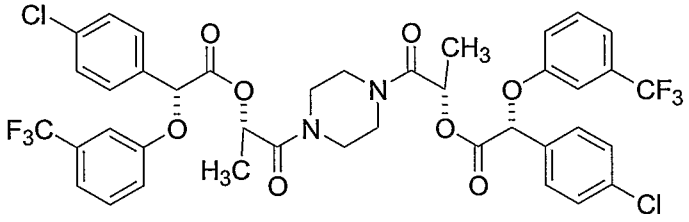
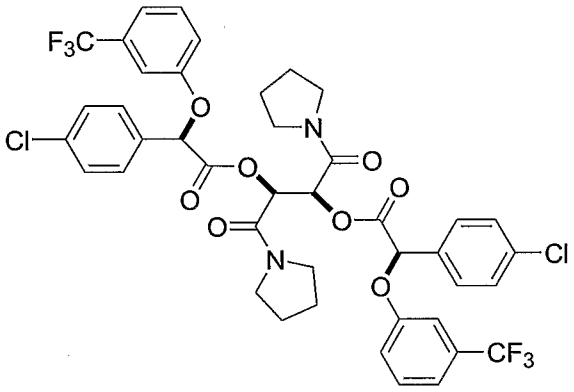
;

the subscript n is 1 when $R^1$ has the formula (a) or (b) and 2 when $R^1$ has the formula (c) or (d);

* indicates a carbon which is enriched in one stereoisomeric configuration; and

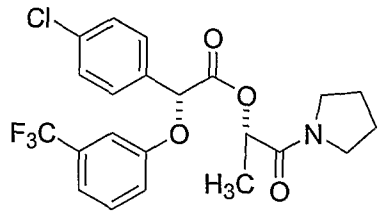
the wavy line indicates the point of attachment of $R^1$.

14. A compound selected from the group having the formula:

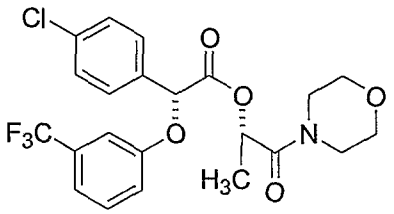



and


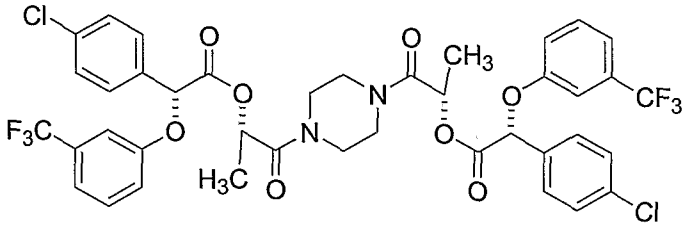
wherein the dashed and bold lines indicate the relative stereochemistry of the compound.

15. A compound selected from the group having the formula:

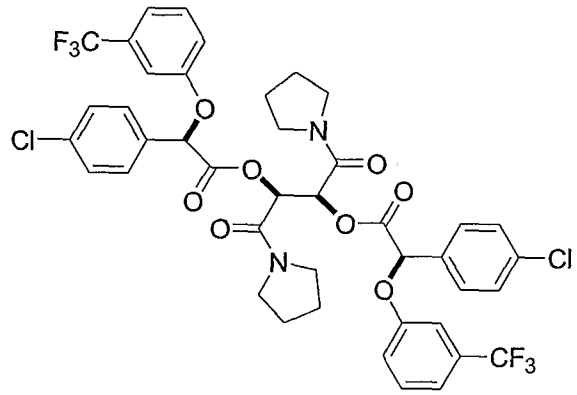



,




and




wherein the dashed and bold lines indicate the absolute stereochemistry of the compound.

16. A composition comprising a compound of claims 14 or 15 in an enantiomeric excess of at least about 95%.