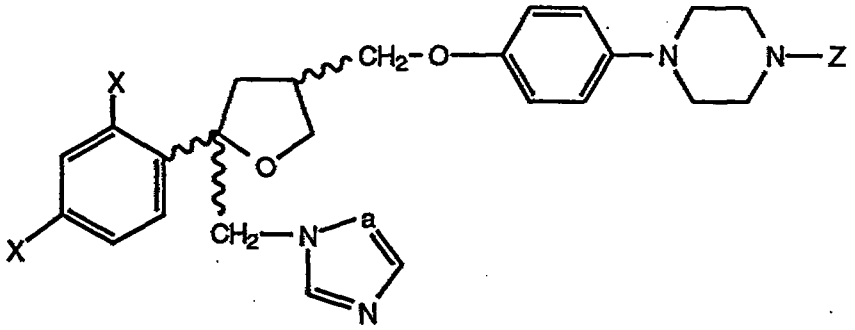
PROCESS FOR PREPARING INTERMEDIATES FOR THE SYNTHESIS OF ANTIFUNGAL AGENTS

BACKGROUND OF THE INVENTION

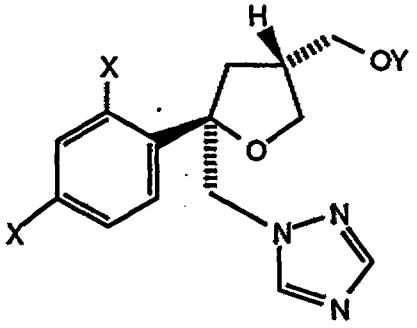
The present invention comprises a process for preparing chiral intermediates useful in the preparation of tri-substituted tetrahydrofuran triazole or imidazole antifungals.

WIPO Publication No. WO 89/04829 and USP 5,039,676 disclose (±) cis and (±) trans antifungal compounds of the formula

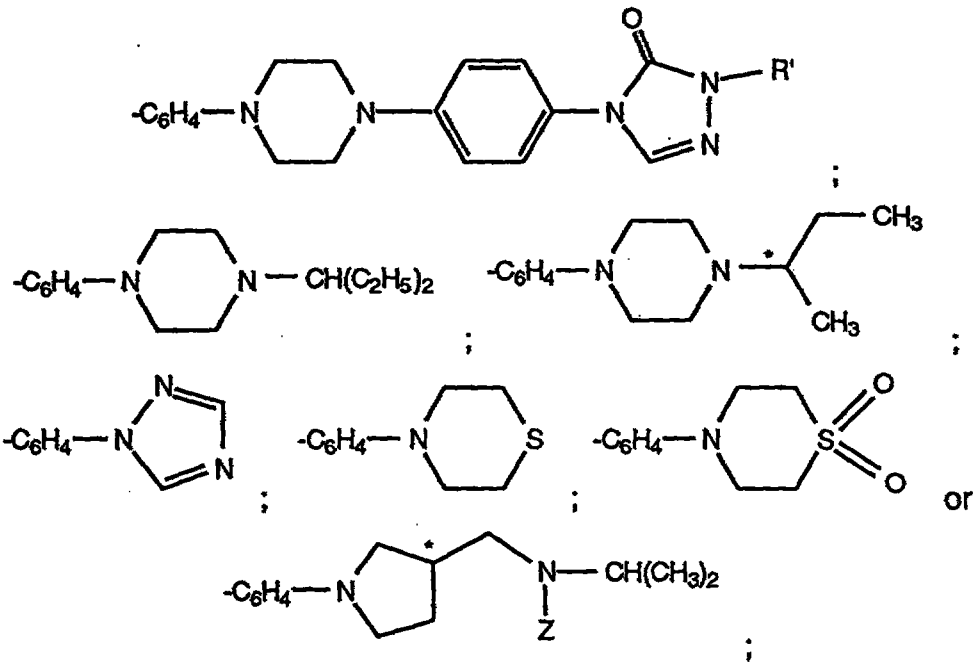


wherein: a is N or CH; X= F or Cl; Z=loweralkyl, (C_2-C_8) alkanoyl or phenyl substituted by 2-loweralkyl-3-oxo-1,2,4-triazol-4-yl, e.g., (±)-cis and (±)-trans-1-[4-[[2-(2,4-difluorophenyl)-2-[(1H-1,2,4-triazol-1-yl)methyl]tetrahydro-4-furanyl]methoxy]phenyl]-4-(1-methylethyl)piperazine.

In addition, PCT International Application No. PCT/US92/08981 relates to antifungal compounds of the formula



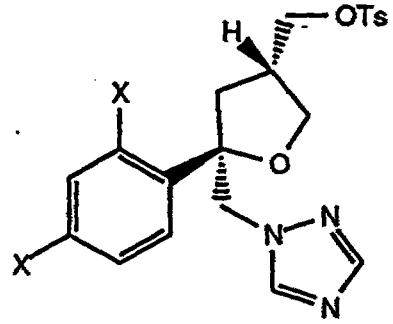
wherein: X is both F or both Cl or one X is F and the other is Cl; and Y is a group of the formula



wherein:

R' = $(C_1\text{-}C_{10})$alkyl, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $(C_3\text{-}C_8)$cycloalkyl, or CH_2R^2; R^2 = $(C_1\text{-}C_3)$ perhaloalkyl, CO_2R^3, *$CH(OR^4)CH_2OR^4$ or $CH_2N(R^5)_2$; R^3 = lower alkyl or H; R^4 = R^3 or $(CH_2)_2OR^3$; R^5 = lower alkyl; Z = H or $(C_1\text{-}C_5)$ alkanoyl; and the carbons with the asterisk (*) have the R or S absolute configuration; or a pharmaceutically acceptable salt thereof.

PCT/US92/08981 further discloses processes for the synthesis of tri-substituted tetrahydrofuran azole antifungals via a tosylate intermediate of the formula



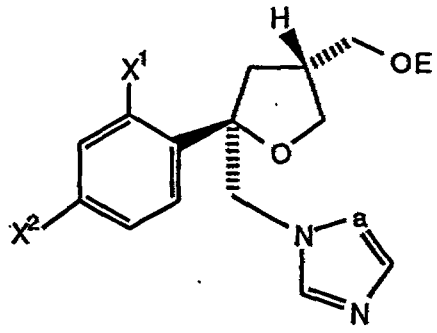
wherein X is as defined above.

The prior art process for preparing the tosylate intermediate is inefficient and requires a costly chiral epoxidation to

introduce the proper stereochemistry in the molecule. It was therefore desirable to develop a chiral synthesis of this key intermediate which does not suffer the shortcomings of the prior art process

SUMMARY OF THE INVENTION

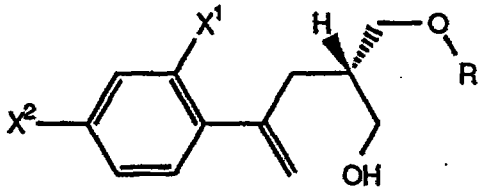
The present invention comprises a process for preparing compounds of the formula (I)



(I)

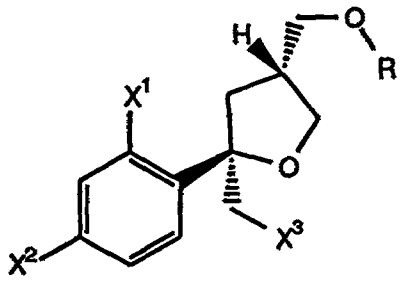
wherein: a is CH or N; X^1 and X^2 are independently F or Cl; and E is $-SO_2R^6$, wherein R^6 is C_1-C_6 alkyl, aryl, substituted aryl or $-CF_3$; comprising the steps:

(a) cyclizing a chiral alcohol of the formula (II)



(II)

wherein X^1 and X^2 are as defined above, and R is a hydroxy protecting group selected from $-CH_2$-C_6H_5, tetrahydropyran-2-yl or $-C(O)R^1$, wherein R^1 is C_1-C_6 alkyl, aryl or $-(CH_2)_nCO_2H$ wherein n is 1, 2, 3 or 4, by treating with a halogen and a base to form a chiral halide of the formula (III)



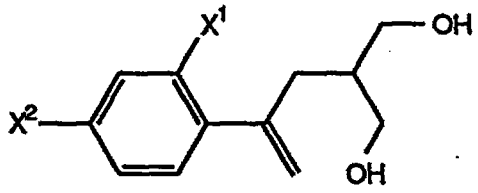
(III)

wherein X^1, X^2 and R are as defined above, and X^3 is Cl, Br or I; and

(b) treating the halide of formula (III) of step (a) with an alkali metal triazole or imidazole to form a chiral compound of the formula (III), wherein X^3 is imidazolyl or triazolyl; removing the protecting group R to form an alcohol of the formula (III), wherein X^3 is triazolyl or imidazolyl, and R is H; and treating the alcohol with a compound of the formula E-X, wherein X is Cl or Br, and E is as defined above, to form the compound of formula (I); or

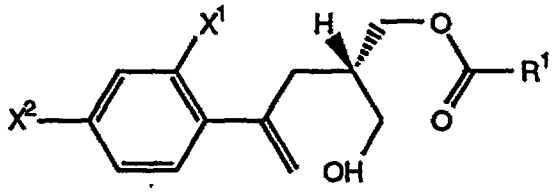
(bi) removing the protecting group R from the halide of formula (III) of Step (a) to form an alcohol, wherein R is H; treating the alcohol with an alkali metal triazole or imidzole to form a chiral compound of the formula (III), wherein X^3 is triazolyl or imidazolyl, and R is H; and treating the alcohol with a compound of the formula E-X, wherein X is Cl or Br, and E is as defined above, to form the compound of formula (I).

The present invention further comprises a process, designated Process A, wherein R is $-C(O)R^1$, and the starting compound of formula (II) of Step (a) is prepared by selectively esterifying a prochiral diol of the formula (IV)



(IV)

with an effective amount of a mild acylating agent in the presence of an enzyme to form a chiral hydroxy ester of the formula (IIa)

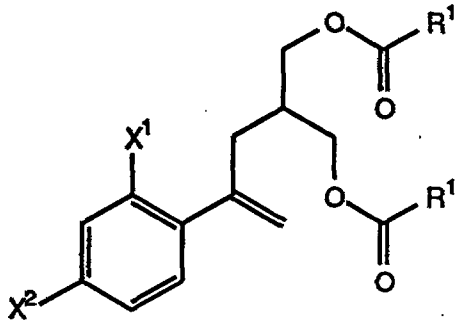


(IIa)

wherein X^1, X^2 are as defined above and R^1 is C_1-C_6 alkyl, aryl or $-(CH_2)_nCO_2H$ wherein n is 1, 2, 3 or 4.

Alternatively, the selective esterification of the prochiral diol of formula (IV) is achieved via a process comprising the steps:

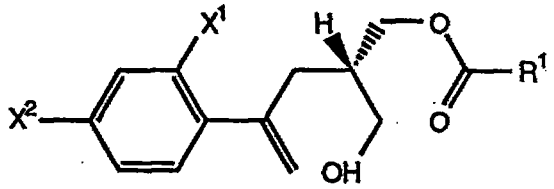
(i) esterifying the prochiral diol of formula (IV) with an amount of an acylating agent effective to form a diester of formula (V)



(V)

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

(ii) stereoselectively hydrolyzing the diester of formula (V) of step (i) in the presence of an enzyme to form a chiral hydroxy ester of the formula (IIa)

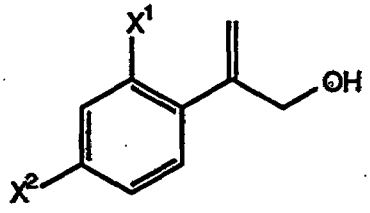


(IIa)

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

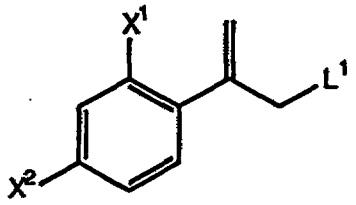
The present invention also further comprises a process according to Process A wherein the prochiral diol of formula (IV) is prepared via a process comprising the steps:

(A1) converting an allylic alcohol of the formula (VI)



(VI)

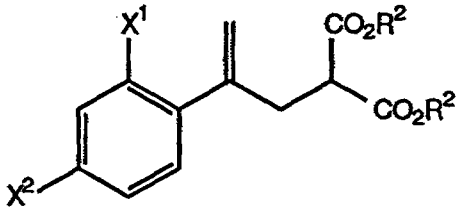
wherein X^1 and X^2 are as defined above, to a compound of the formula (VII)



(VII)

wherein X^1 and X^2 are as defined above and L^1 is a leaving group selected from halogeno, $-OSO_2CF_3$ and $-OSO_2R^6$, wherein R^6 is as defined above;

(A2) reacting the compound of formula (VII) of Step (A1) with an amount of an alkali metal salt of the anion derived from a di(C_1-C_6 alkyl)malonate effective to form a diester of the formula (VIII)



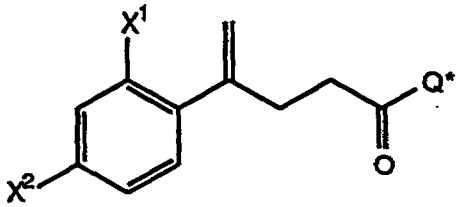
(VIII)

wherein X^1 and X^2 are as defined above, and R^2 is C_1-C_6 alkyl;

(A3) treating the diester of formula (VIII) of Step (A2) with an amount of a hydride reducing agent effective to form the prochiral diol of formula (IV).

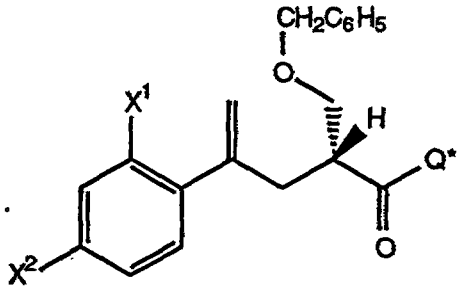
In an alternative embodiment, designated Process B, the present invention comprises a process for preparing chiral compounds of formula (II), wherein R is $-CH_2-C_6H_5$, for use in preparing compounds of the formula (I), comprising the steps:

(B1) reacting a compound of the formula (IX)



(IX)

wherein X^1 and X^2 are as defined above and Q* is a chiral auxilary group, with a compound of the formula $C_6H_5CH_2$-O-CH_2L, wherein L is a leaving group selected from Cl, Br and I, in the presence of $TiCl_4$ and a tertiary amine base, in amounts effective to form a chiral compound of the formula (X)

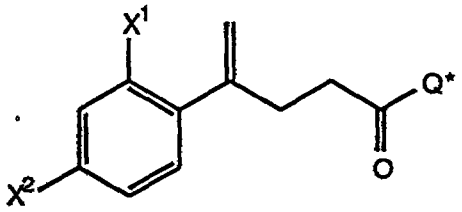


(X)

wherein X^1, X^2 and Q* are as defined above; and

(B2) treating the product of formula (X) of Step (B1) with an amount of $LiAlH_4$ effective to form a chiral compound of the formula (II), wherein R is $-CH_2C_6H_5$.

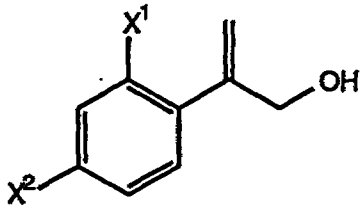
The present invention further comprises a process according to Process B wherein the starting compound of formula (IX)



(IX)

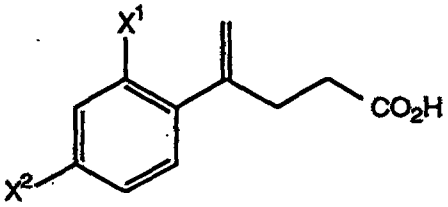
is prepared by a process comprising the steps:

(B3) heating an allylic alcohol of the formula (VI)



(VI)

wherein X^1 and X^2 are as defined above, with an effective amount of an orthoester of the formula $CH_3C(OR^2)_3$, wherein R^2 is C_1-C_6 alkyl, and a catalytic amount of R^2CO_2H, wherein R^2 is as defined above, followed by treatment with an amount of a hydroxide base effective to form an acid of the formula (XI)

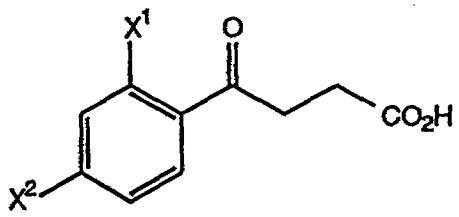


(XI)

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

(B4) treating the acid of formula (XI) of step (B3) with an effective amount of an activating agent, then with an alkali metal salt of the formula $M^+ {}^-Q^*$, wherein M^+ is an alkali metal cation and $^-Q^*$ is the anion derived from a compound of the formula HQ^*, wherein Q^* is as defined above, to form a compound of the formula (IX).

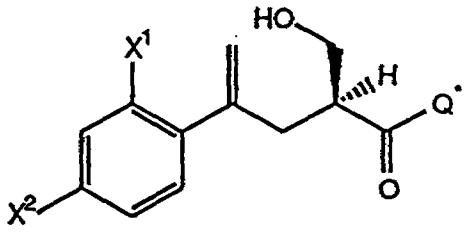
Alternatively, the acid (XI) of step (B3) is prepared by reacting 1-(X^1)-3-(X^2)-benzene, wherein X^1 and X^2 are as defined above, with succinic anhydride in the presence of a Lewis acid to form a keto acid of the formula



which is treated with $CH_3{\bullet}P(C_6H_5)_3{\bullet}Br$ and a nonaqueous base to form the acid (XI) for use in step (B4).

In a second alternative embodiment, designated Process C, the present invention comprises a process for preparing compounds of the formula (I) wherein the chiral halide of formula (III) of Step (a), wherein R is H, is prepared by a process comprising the steps:

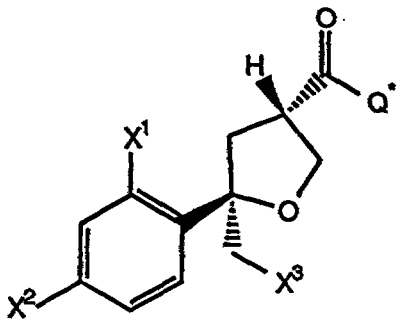
(C1) treating a compound of the formula (IX), as defined above, with effective amounts of S-trioxane, $TiCl_4$ and a tertiary amine base to form a chiral compound of the formula (XII)



(XII)

wherein X^1, X^2 and Q^* are as defined above;

(C2) cyclizing a compound of the formula (XII) of Step (C1) by treating with effective amounts of a halogen and a base to form a chiral halide of the formula (XIII)

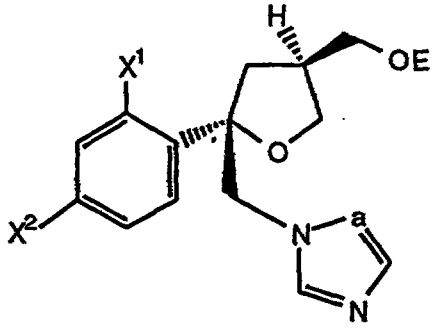


(XIII)

wherein X^3 is Cl, Br or I, and X^1, X^2 and Q^* are as defined above;

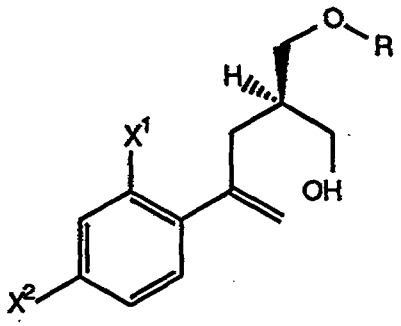
(C3) treating the chiral halide of formula (XIII) of Step (C3) with an amount of a hydride reducing agent effective to form a chiral halide of the formula (III), wherein R is H.

The process of the present invention can also be used to prepare compounds of the formula (XIV)



(XIV)

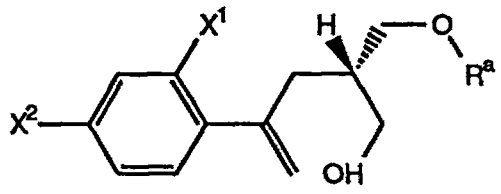
wherein a, X^1, X^2 and E are as defined above, i.e., enantiomers of compounds of the formula (I), by utilizing a chiral auxilary of the opposite configuration, or by the choice of an enzyme which selectively produces the R-enantiomer of a compound of the formula (II), e.g. a compound of the formula (XV)



(XV)

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

The present invention further comprises a process for converting compounds of the formula (XV) to compounds of the formula (II) by protection of the free hydroxy group using a suitable protecting group R^a, and selective hydrolysis of the -OR group to form a compound of the formula (XVI)

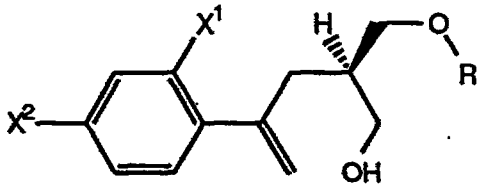


(XVI)

wherein X^1 and X^2 are as defined above and R^a is a hydroxy protecting group. Preferably R^a is $-CH_2C_6H_5$, tetrahydropyran-2-yl or $-C(O)R^1$, wherein R^1 is as defined above, provided that $R \neq R^a$, in which case compounds of formula (XVI) are compounds of the formula (II).

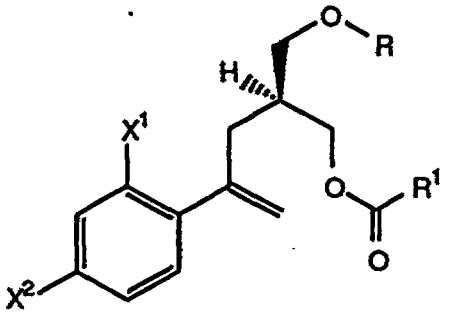
In an alternative embodiment, the process of the present invention further comprises a process designated Process D for preparing a compound of the formula (I) wherein the chiral halide of Step (a), being a compound of the formula (III) wherein R is $-C(O)R^1$, and R^1 is C_1-C_6 alkyl, is prepared by a process comprising the steps:

(D1) esterifying a chiral alcohol of the formula (II)



(II)

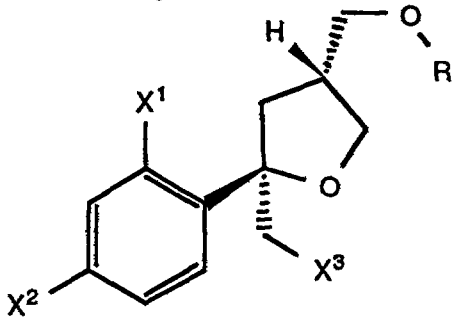
wherein X^1 and X^2 are as defined above, and R is $-CH_2$-C_6H_5, by treating with an effective amount of an acylating agent to form a chiral compound of the formula (XIX)



(XIX)

wherein X^1, X^2 are as defined above, R is $-CH_2C_6H_5$, and R^1 is C_1-C_6 alkyl; and

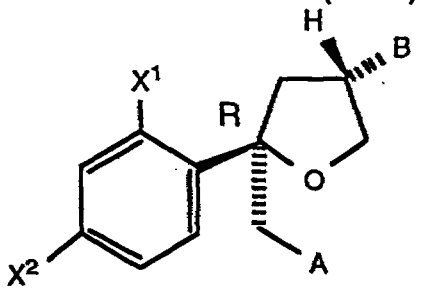
(D2) cyclizing the chiral product of formula (XIX) of Step (D1) by treating with a halogen to form a chiral halide of formula (III)



(III)

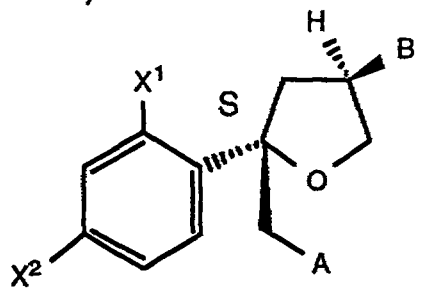
wherein X^1, X^2 are as defined above, R is $-C(O)R^1$, R^1 is C_1-C_6 alkyl, and X^3 is Cl, Br or I.

The present invention also further comprises chiral compounds of the formula (XVII) or (XVIII)



(XVII)

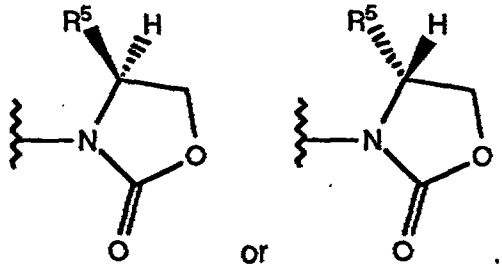
or



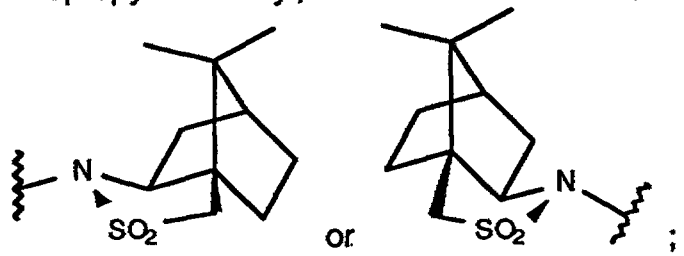
(XVIII)

wherein:

X^1 and X^2 are independently F or Cl; A represents Cl, Br, I, triazolyl or imidazolyl; B represents $-C(O)Q^*$ or $-CH_2OR^*$; wherein R^* represents a hydroxy protecting group selected from $-CH_2C_6H_5$, or $-C(O)R^1$, wherein R^1 is C_1-C_6 alkyl, $-CH_2C_6H_5$ or aryl; and Q^* represents a chiral auxilary group selected from chiral oxazolidinones of the formula



wherein R^5 is isopropyl or benzyl, and chiral sultams of the formula



;

useful as intermediates for preparing antifungal agents.

The process of the present invention is chemically efficient and produces chiral compounds of the formula I in high optical purity. Therefore, the instantly claimed process does not suffer the shortcomings of the prior art process.

The process of the present invention can also be used to prepare compounds of the formula I in racemic form by utilizing the achiral diol IV in place of a chiral compound of the formula II for the cyclization of Step (a) forming a racemic iodide of formula III wherein R is H. No deprotection is necessary in Step (b) where an iodide III, wherein R is H, is used.

DETAILED DESCRIPTION

The process of the present invention utilizes a chiral auxilary group, or alternatively an enzyme, to stereoselectively produce chiral compounds from achiral starting materials. The stereochemical designations represented by ▬ and ····ıı bonds denote both absolute stereochemistry and, where more than one chiral center is present, relative stereochemistry. The optical purity of compounds is generally given in terms of the enantiomeric excess (e.e.) of the indicated stereoisomer.

In the process of the present invention, where a chiral auxillary is used to form a single enantiomer of a compound, the opposite enantiomer can be prepared by utilizing the opposite enantiomer of the chiral auxillary employed. Similarly, where an enzyme is used to prepare a chiral compound from a prochiral starting

material, the specific enantiomer obtained is controlled by selection of the proper enzyme.

As used herein the term "alkyl" means a straight or branched alkyl chains of 1 to 6 carbon atoms;

"aryl" means a C_6-C_{10} carbocyclic aromatic group, such as phenyl or naphthyl; and "substituted aryl" means an aryl group having 1 to 3 substituents selected from halogeno, C_1-C_6 alkyl, NO_2 or CF_3;

"hydroxide base" means LiOH, KOH, NaOH, $Ca(OH)_2$;

"base" means pyridine, NH_4OH, Na_2CO_3, K_2CO_3, $NaHCO_3$ or $KHCO_3$;

"nonaqueous base" means a non-nucleophilic reagent capable of generating a carbanion, such as $NaN[Si(CH_3)_3]_2$, $KN[Si(CH_3)_3]_2$ and $LiN[CH(CH_3)_2]_2$;

"tertiary amine base" means Et_3N or Hünigs base;

"alkali metal triazole or imidazole" means an alkali metal salt of the anion derived from triazole or imidazole, respectively, e.g., sodium triazole, potassium triazole, lithium triazole, sodium imidazole, potassium imidazole or lithium imidazole;

"hydride reducing agent" means $LiAlH_4$, $NaBH_4$, $LiBH_4$, $NaBH_3CN$;

"halogen" means Cl_2, Br_2 or I_2; "halogeno" means a chloro, bromo or iodo group; and "halide" means a chloride, bromide or iodide anion or substituent;

"brominating agent" means a reagent capable of converting an alcohol to a bromide, preferably PBr_3;

"activating agent" means a reagent capable of converting a carboxylic acid into a reactive derivative, such as an acid halide, anhydride or a mixed anhydride, preferably reagents such as $SOCl_2$, oxalyl chloride, carbonylditriazole or oxalylditriazole;

"alkali metal salt" means a salt comprising a cation derived from Li, Na or K, and an anion;

"sulfonylating agent" means a reagent capable of converting an -OH group into a sulfonyl group of the formula $-OSO_2R^6$, wherein R^6 is C_1-C_6 alkyl, aryl, substituted aryl or $-CF_3$, preferably a reagent such as tosyl chloride or mesyl chloride

"leaving group" means a substituent which is readily displaced by a nucleophile, such as Cl, Br, I or $-OSO_2R^6$, wherein R^6 is C_1-C_6 alkyl, aryl, substituted aryl or $-CF_3$;

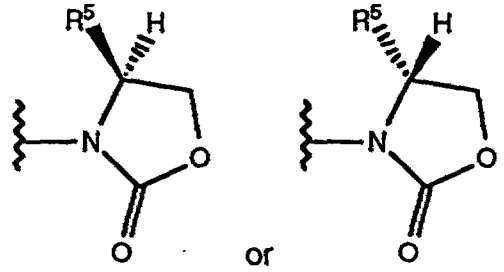
"Lewis acid" means a reagent capable of catalyzing a Friedel-Crafts acylation reaction, including reagents such as $AlCl_3$, BF_3, $SnCl_4$, BCl_3 or $ZnCl_2$;

"acylating agent" means a reagent of the formula R^1-C(O)-Z, wherein R^1 is C_1-C_6 alkyl, and Z is a suitable leaving group, such that said acylating agent is capable of reacting with the hydroxy group of an alcohol to form an ester; preferred are acylating agents selected from acid chlorides, acid anhydrides or mixed anhydrides, and most preferably a reagent such as butyric anhydride, acetyl chloride or acetic anhydride;

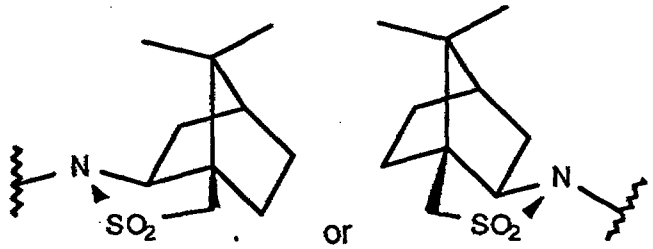
"mild acylating agent" means a reagent that is used in combination with an enzyme to transfer an acyl group to a substrate bearing a hydroxy group; such reagents include: succinic anhydride; esters of the formula R^1-C(O)-OR^3, wherein R^3 is trifluoroethyl, C_1-C_6 alkyl or C_2-C_6 alkenyl, and preferably the ester is vinyl butyrate, vinyl acetate, vinyl benzoate, isopropenyl acetate, methyl acetate, ethyl acetate, isopropyl acetate, trifluoroethyl acetate, trifluoroethyl butyrate, trifluoroethyl isobutyrate or trifluoroethyl 2-methylbutyrate, with vinyl acetate being most preferred; and acetic anhydride.

Enzymes for use in the present invention are selected from enzymes capable of stereoselectively hydrolyzing a symmetrical prochiral diester, or alternatively catalyzing the esterification of a symmetrical prochiral diol, such that a single chiral hydroxy ester is formed in high e.e. Enzymes for use in the process of the present invention include the commercially available enzyme preparations identified in Table 1 of Example 4 below. The preferred enzymes are porcine pancreatic lipase, Amano CE (*Humicloa lanugiosa*), Amano AY-30, Biocatalysts *H. lanugiosa*, Biocatalysts *M. meihei*, Biocatalysts *Ps. fluorescens*, Meito MY, Meito PL, Novo Lipozyme IM-20, Novo SP435 (*Candida antartica*) (Novozyme 435). Most preferred are Amano CE and Novo SP435 (Novozyme 435).

The chiral auxilary "Q*" is a chiral oxazolidinone of the formula



wherein R^5 is isopropyl or benzyl, as disclosed by Evans et al, in J. Amer. Chem. Soc., 103, 2127-2129 (1981) and Tetrahedron, 44, 5525-5540 (1988); or a chiral sultam of the formula



as disclosed by Oppolzer et al, J. Amer. Chem. Soc., 112, 2767-2772 (1990).

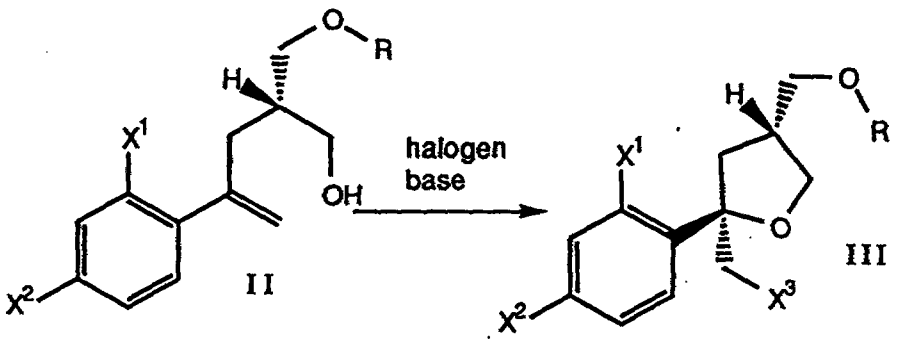
As used herein the following reagents and solvents are identified by the abbreviations indicated: methanol (MeOH); tetrahydrofuran (THF); diethyl ether (Et_2O); lithium di-isopropylamide (LDA); triethylamine (Et_3N); di-isopropylethylamine (Hünigs base); ethyl acetate (EtOAc); ethanol (EtOH); N,N-dimethylformamide (DMF); N,N'-dimethylpropyleneurea (DMPU); 4-dimethylaminopyridine (DMAP); p-toluenesulfonyl chloride (tosyl chloride or TsCl); methanesulfonyl chloride (mesyl chloride or MsCl); p-toluenesulfonic acid (p-TSA)

The following abbreviations are used to identify substituent groups in the structural formulae: tetrahydropyran-2-yl radical (THP); p-toluenesulfonyl radical (Ts); and acetyl radical (Ac).

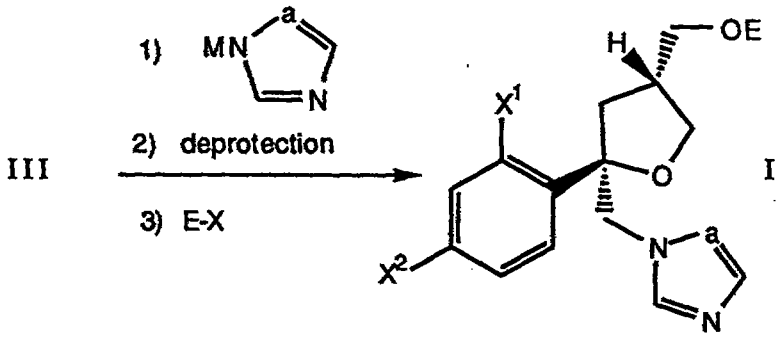
The present invention comprises a process for preparing a compound of the formula I as shown in Reaction Scheme 1.

Reaction Scheme 1

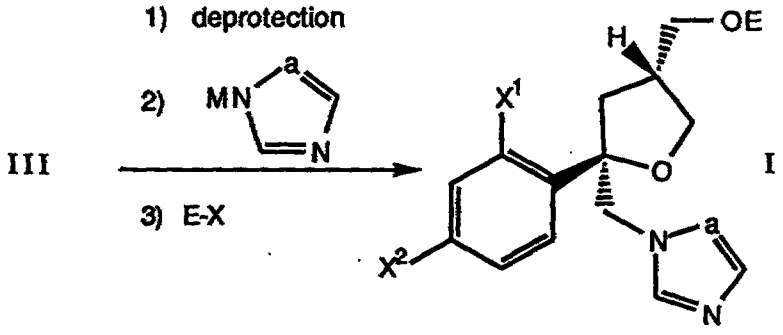
Step (a)



Step (b)



Step (b1)



In Reaction Scheme 1, Step (a), the compound II is reacted with a halogen, such as Cl_2, Br_2 or I_2, preferably Br_2 or I_2, in the presence of a base, such as pryidine or $NaHCO_3$, in a suitable solvent, such as CH_3CN, THF, EtOAc or CH_2Cl_2, at -20° to 30°C, preferably about 0° to 25°C, to form the halide III, wherein X^3 is Cl, Br or I.

In Step (b) the halide III is:

(1) heated with an alkali metal triazole or imidazole (M represents an alkali metal), such as Na-triazole or Na-imidazole, in a suitable solvent, such as DMF, in the presence of DMPU, at 70° to 100°C, preferably about 80°C, for 10 to 24 h, preferably about 15 h; and

(2) deprotected by:

(i) where R is -C(O)R^1, treating with a base, preferably K_2CO_3, Na_2CO_3 or NH_4OH, in a suitable solvent, such as MeOH/water, at 0° to 25°C, preferably about 0° to 5°C; or

(ii) where R is tetrahydropyran-2-yl, treating with HCl, preferably a soultion of 10% HCl (aqueous), at 15° to 35°C, preferably about 25°C, for 1 to 6 h, preferably about 3 h; or

(iii) where R is -$CH_2C_6H_5$, hydrogenating under H_2 atmosphere in a suitable solvent, such as EtOH, in the presence of a suitable catalyst, such as Pd on carbon, preferebly 10% Pd on carbon, and an acid, preferably HCl;

to form an alcohol wherein R is H; and

(3) treated with a compound of the formula E-X, wherein X is a halide, preferably chloride, and E is as defined above, preferably -$SO_2C_6H_4CH_3$ or -$SO_2C_6H_4Cl$, in the presence of a base, such as pyridine, to form a compound of the formula I.

In the alternative Step (b1), the halide III is:

(1) deprotected by:

(i) where R is -C(O)R^1, treating with a base, preferably K_2CO_3, Na_2CO_3 or NH_4OH, in a suitable solvent, such as MeOH/water, at 0° to 25°C, preferably about 0° to 5°C; or

(ii) where R is tetrahydropyran-2-yl, treating with HCl, preferably a solution of 10% HCl (aqueous), at 15° to 35°C, preferably about 25°C, for 1 to 6 h, preferably about 3 h; or

(iii) where R is -$CH_2C_6H_5$; hydrogenating under H_2 atmosphere in a suitable solvent, such as EtOH, in the presence of a suitable catalyst, such as Pd on carbon, preferebly 10% Pd on carbon, and an acid, preferably HCl, according to the procedure disclosed by Freifelder, in "Catalytic Hydrogenation in Organic Synthesis, Procedures and Comments", p. 120, J. Wiley & Sons (1978);

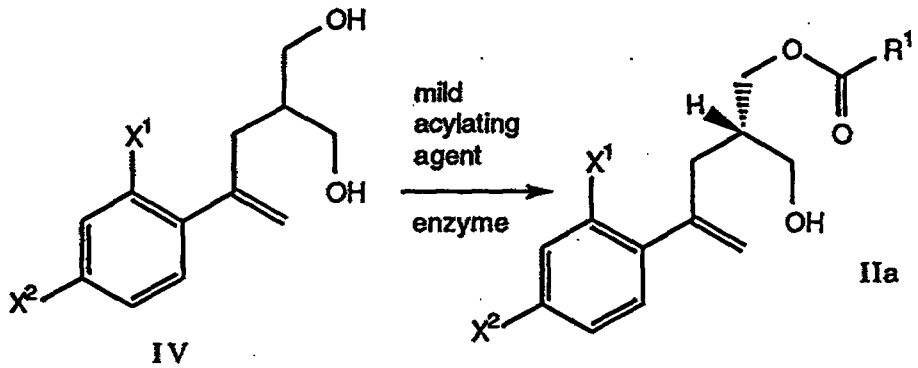
to form an alcohol wherein R is H; and

(2) the alcohol is heated with an alkali metal triazole or imidazole (M represents an alkali metal), such as Na-triazole or Na-imidazole, in a suitable solvent, such as DMF, in the presence of DMPU, at 70° to 100°C, preferably about 80°C, for 10 to 24 h, preferably about 15 h; and

(3) treated with a compound of the formula E-X, wherein X is a halide, preferably chloride, and E is as defined above, preferably $-SO_2C_6H_4CH_3$ or $-SO_2C_6H_4Cl$, in the presence of a base, such as pyridine, to form a compound of the formula I.

In the embodiment of Process A, the present invention further comprises a process wherein the chiral compound of formula (II) is a chiral hydroxy ester of the formula (IIa), i.e., a compound of the formula (II) wherein R is $-C(O)R^1$ and R^1 is as defined above. The chiral hydroxy ester of formula (IIa) is prepared from a prochiral diol of the formula (IV) by using an enzyme to selectively esterify the prochiral diol (IV), thus forming the chiral compound of formula (IIa). The selective esterification is accomplished according to the process shown in Reaction Scheme A.

Reaction Scheme A



IV IIa

In Reaction Scheme A, the prochiral diol IV is treated with a mild acylating agent, preferably an ester of the formula R^1-C(O)-OR^3, wherein R^1 is as defined above and R^3 is trifluoroethyl, C_1-C_6 alkyl or C_2-C_6 alkenyl, most preferably vinyl acetate, in the presence of an

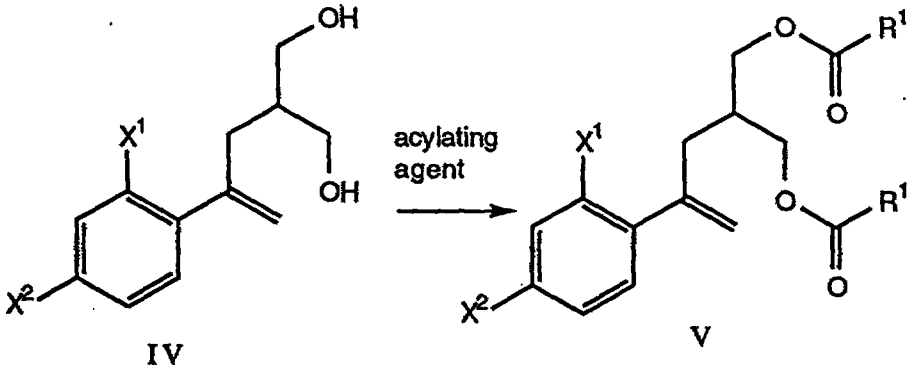
enzyme, most preferably Novo SP435, in a suitable solvent, such as toluene or CH_3CN, at 0° to 35°C, preferably about 25°C, to form the chiral hydroxy ester of the formula IIa.

By utilizing other lipase enzymes, such as Amano CE, in the process of Reaction Scheme A, the R-enantiomer, i.e., a compound of the formula XV, as defined above, can be prepared.

The chiral hydroxy ester IIa is alternatively prepared by the process of Reaction Scheme AA.

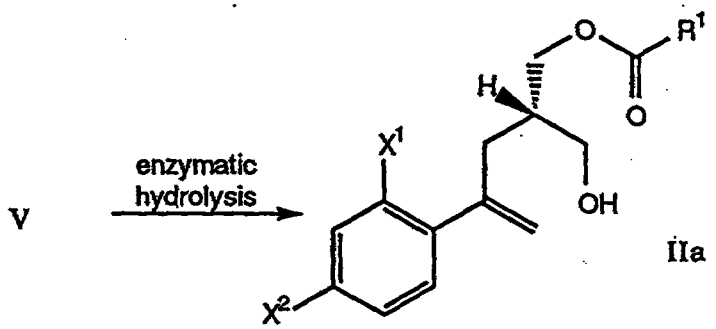
Reaction Scheme AA

Step (a)



IV V

Step (b)



IIa

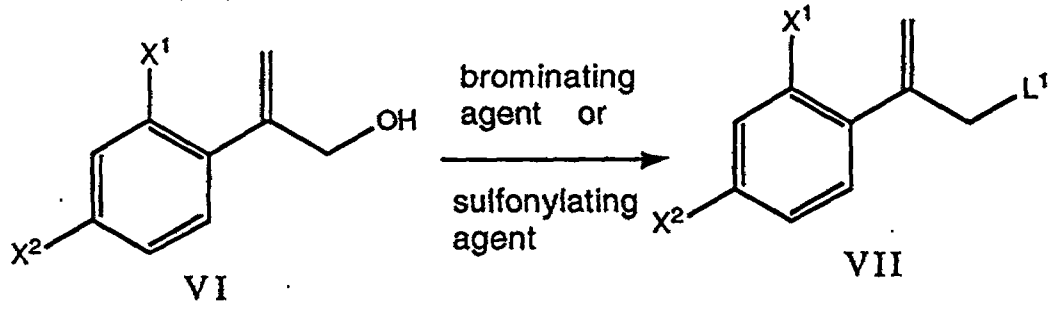
In Reaction Scheme AA, Step (a), the prochiral diol IV is treated with an acylating agent, preferably an acid halide, acid anhydride or mixed anhydride, most preferably butyric anhydride, acetyl chloride or acetic anhydride, in a suitable solvent, such as THF, at 0°C to 40°C, preferably about 25°C, to form the diester V.

In Step (b), the diester V is treated with an enzyme, preferably a lipase, most preferably Amano CE, in a suitable solvent, such as THF/water, at 15° to 35°C, preferably about 25°C, to form the chiral hydroxy ester IIa.

The present invention further comprises a process according to Process A wherein the prochiral diol IV is prepared by the process described in Reaction Scheme AAA.

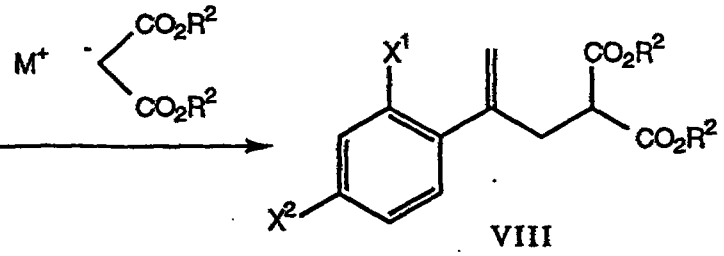
Reaction Scheme AAA

Step (A1)



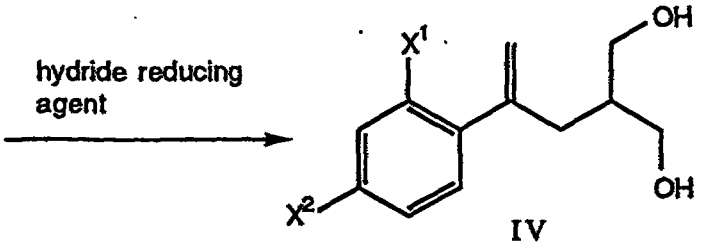
VI VII

Step (A2)



VII VIII

Step (A3)



VIII IV

In Reaction Scheme AAA, Step (A1), the allylic alcohol VI is treated with a brominating agent, preferably PBr_3, in a suitable solvent, such as CH_2Cl_2, at -10° to 35°C, preferably at 0° to 25°C, for 30

to 90 min, preferably about 1 h, to form an allylic bromide, i.e., a compound of formula VII, wherein L^1 is Br.

Alternatively, in Step (A1), the allylic alcohol VI is treated with a sulfonylating agent, such as mesyl chloride or tosyl chloride, a tertiary amine base, such as Et_3N, and DMAP, in a suitable solvent, such as CH_2Cl_2, at -10° to 35°C, preferably 0° to 25°C, to form the sulfonylated product, i.e., a compound of the formula VII wherein L^1 is $-OSO_2R^6$ and R^6 is as defined above.

In Step (A2), the compound of formula VII is treated with an alkali metal salt of the anion derived from di(C_1-C_6 alkyl)malonate, preferably $NaCH(CO_2C_2H_5)_2$, in a suitable solvent, such as THF, at 15° to 35°C, preferably about 25°C, for 1 to 3 h, preferably about 1.5 h, to form the diester VIII.

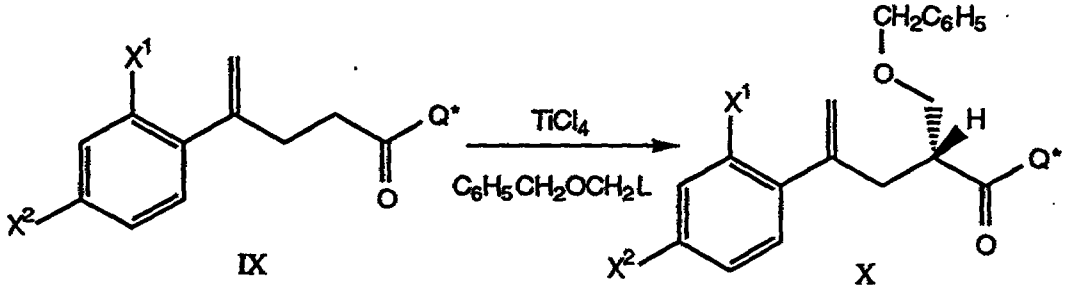
In Step (A3), the diester VIII is treated with a hydride reducing agent, preferably $LiAlH_4$, in a suitable solvent, such as THF or Et_2O, at 0° to 35°C, preferably about 25°C, for 1 to 4 h, preferably about 2 h, to form the prochiral diol IV.

Alternatively in Step (A3), the diester VIII is treated with $NaBH_4$, in the presence of LiCl, in a suitable solvent, such as EtOH, at 0° to 35°C, preferably 0° to 25°C, for 1 to 4 h, preferably about $1^1/_2$ h, to form the prochiral diol IV.

In the alternative embodiment of Process B, the present invention comprises a process wherein the chiral compound of formula (II) is a chiral benzyl ether of the formula (IIb), i.e., a compound of the formula (II) wherein R is $-CH_2C_6H_5$. The chiral benzyl ether of formula (IIb) is prepared by the process shown in Reaction Scheme B.

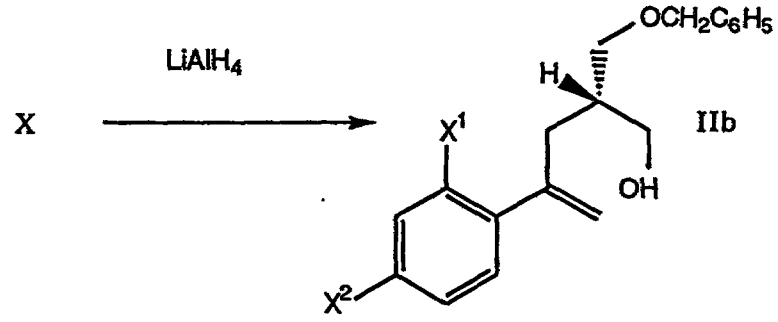
Reaction Scheme B

Step (B1)



IX X

Step (B2)



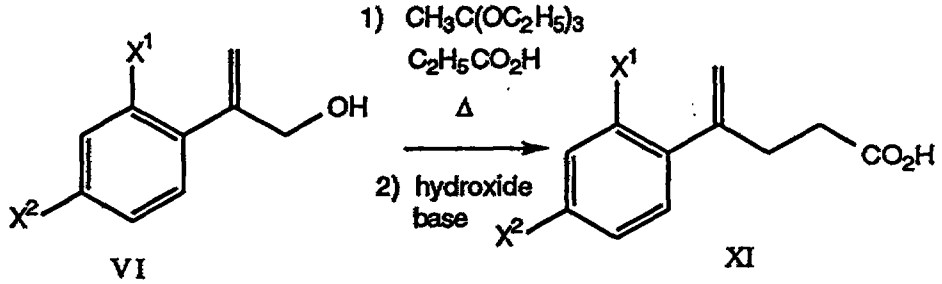
In Reaction Scheme B, Step (B1), a compound of the formula IX is treated with $TiCl_4$ and a compound of the formula $C_6H_5CH_2OCH_2L$, wherein L is a leaving group, preferably a halide, in the presence of a tertiary amine base, such as Et_3N, at -10° to 10°C, preferably about 0°C, to form a chiral compound of the formula X.

In Step (B2), the chiral compound of formula X is treated with $LiAlH_4$ in a suitable solvent, such as THF or Et_2O, at 0° to 35°C, preferably about 25°C, to form the chiral benzyl ether IIb.

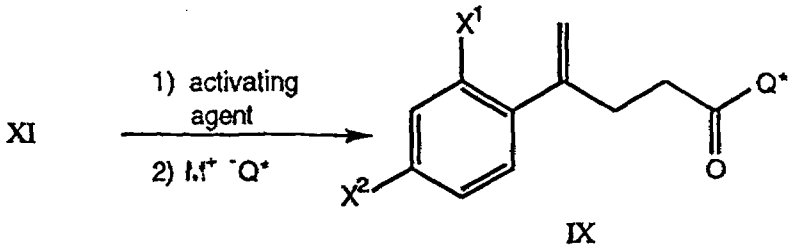
The present invention further comprises a process according to Process B wherein the compound of the formula IX is prepared by the process described in Reaction Scheme BB.

Reaction Scheme BB

Step (B3)



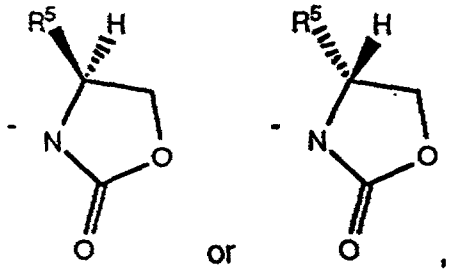
Step (B4)



IX

In Reaction Scheme BB, Step (B3), the allylic alcohol VI is treated with $CH_3C(OC_2H_5)_3$ and a catalytic amount of propionic acid at 90° to 130°C, preferably about 120°C, then treated with a hydroxide base, preferably KOH or NaOH, in a suitable solvent, such as MeOH, preferably MeOH/water, at 15° to 35°C, preferably about 25°C, to form the acid XI.

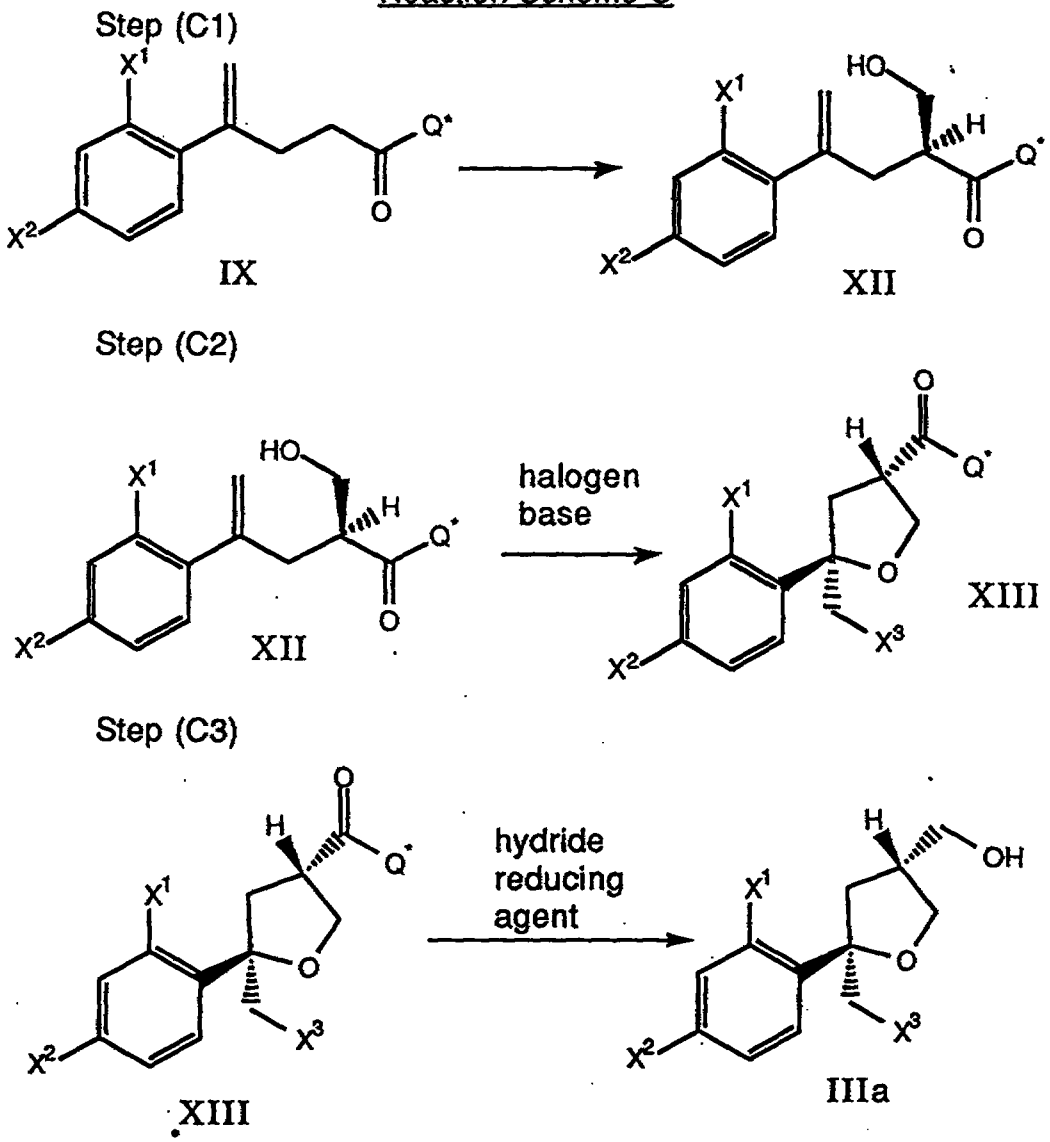
In Step (B4), the acid XI is treated with an activating agent, preferably $SOCl_2$ or oxalyl chloride, at 15° to 35°C, preferably about 25°C, to form a reactive derivative, such as an acid chloride. The reactive derivative is treated with an alkali metal salt of the formula $M^+ {}^-Q^*$, preferably the Li^+ salt, wherein $^-Q^*$ is preferably an anion derived from a chiral oxazolidinone of the formula



at -70° to 25°C, preferably -70° to 0°C, to form the compound of formula IX.

In the second alternative embodiment of Process C, the present invention comprises a process wherein the chiral halide of formula (III) is a chiral alcohol of the formula (IIIa), i.e., a compound of the formula (III) wherein R is H The alcohol of formula (IIIa) is prepared by the process shown in Reaction Scheme C.

Reaction Scheme C



In Reaction Scheme C, Step (C1), the compound of the formula IX is converted to the chiral compound of the formula XII via the general procedure described by Evans et al, J. Amer. Chem. Soc., 112, 8215-8216 (1990).

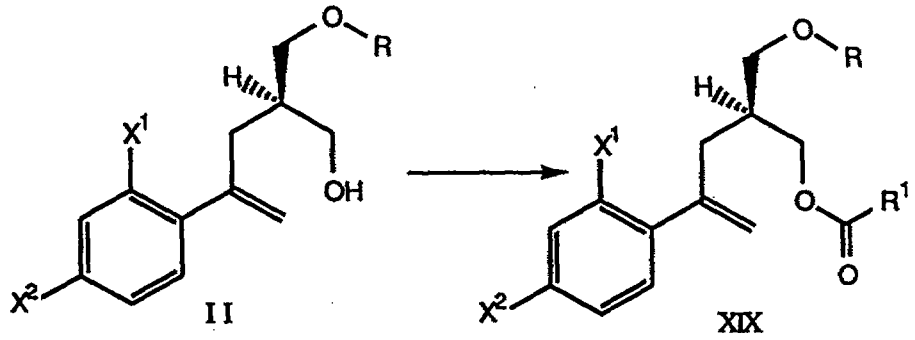
In Step (C2), the chiral compound of formula XII is treated with a halogen, preferably Br_2 or I_2, and a base, preferably pyridine, in a suitable solvent, such as CH_3CN, THF, EtOAc or CH_2Cl_2, at -20°C to 30°C, preferably about 0°C to 25°C, for 10 to 20 h, preferably about 20 h, to form the chiral halide XIII, wherein X^3 is Br or I.

In Step (C3), the chiral halide XIII is treated with a hydride reducing agent, such as $LiBH_4$, in a suitable solvent, such as THF or Et_2O, at -100° to 30°C, preferably starting at -78°C and continuing at 25°C, for 1 to 6 h, preferably about 3 h, to form the chiral hydride IIIa.

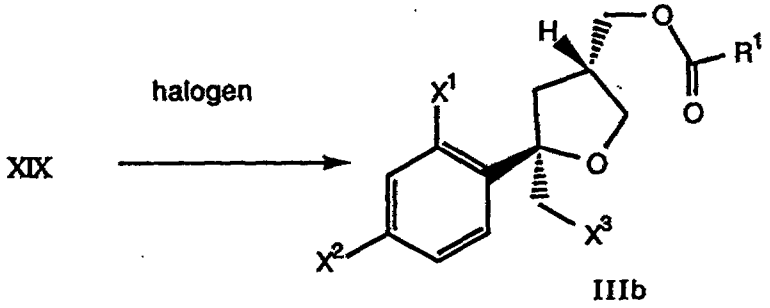
In the third alternative embodiment of Process D, the present invention comprises a process for preparing a compound of the formula I, wherein the chiral halide of formula (III) is a compound of the formula (IIIb), i.e., the a compound of the formula (III) wherein R is $-C(O)R^1$, wherein R^1 is C_1-C_6 alkyl, aryl or $-(CH_2)_nC_2OH$ wherein n is 1, 2, 3 or 4. The halide of formula (IIIb) is prepared by the process shown in Reaction Scheme D.

Reaction Scheme D

Step (D1)



Step (D2)

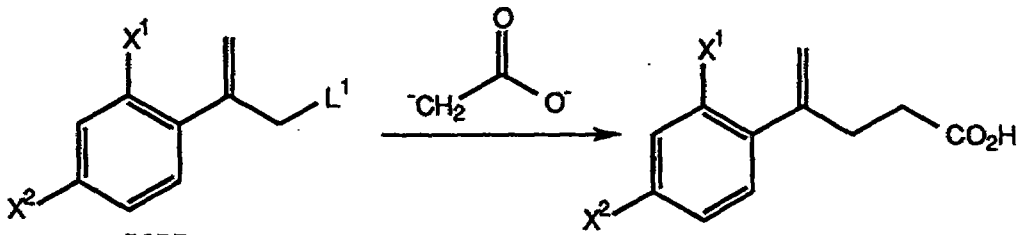


In Reaction Scheme D, Step (D1), the chiral alcohol of formula II, wherein R is $-CH_2C_6H_5$, i.e., a chiral alcohol of the formula IIb, is treated with an acylating agent, preferably acetyl chloride or

acetic anhydride, in the presence of a base, such as pyridine, to form a chiral ester of the formula XIX, wherein X^1, X^2, R and R^1 are as defined above.

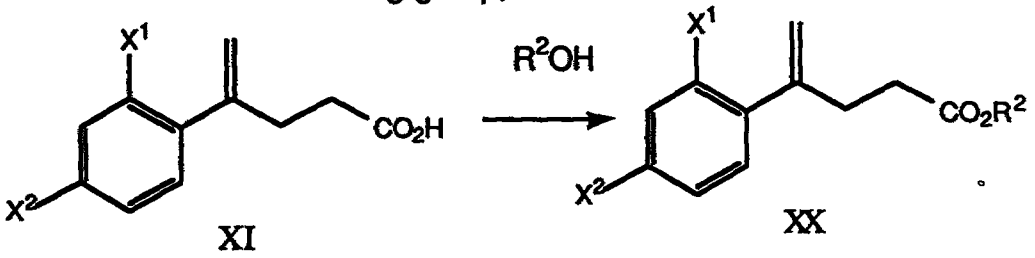
In Step (D2), the ester of the formula XIX is treated with a halogen, such as Cl_2, Br_2 or I_2, preferably Br or I_2, in a suitable solvent, such as CH_3CN, THF, EtOAc or CH_2Cl_2, at -20° to 30°C, preferably about 0° to 25°C, to form the halide IIIb, wherein X^3 is Cl, Br or I, and X^1, X^2 and R^1 are as defined above.

Compounds of the formula XI can also be prepared from a compound of the formula VII by reacting with the dianion derived from acetic acid as shown below.

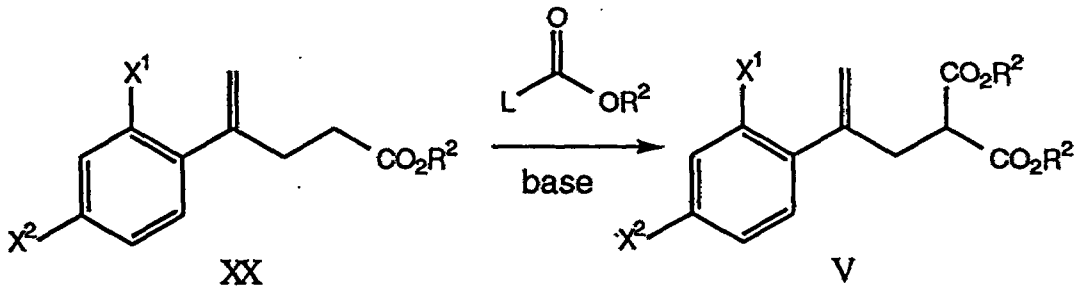


VII XI

Diesters of the formula V can also be prepared from a compound of the formula XI by esterification with an alcohol of the formula R^2OH, wherein R^2 is as defined above, using known methods. The resulting ester XX is deprotonated by treating with base and the resulting anion reacted with a compound of the formula $R^2OC(O)$-L, wherein L is a halide leaving group, as defined above.



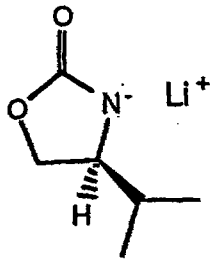
XI XX



Starting compounds of the formula VI can be prepared via known methods.

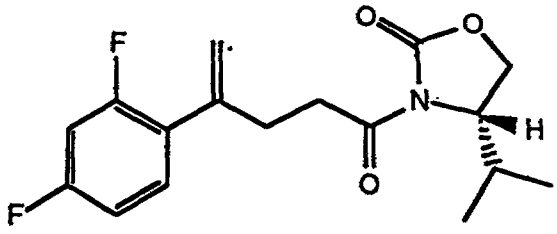
The following preparations and examples illustrate the process of this invention:

PREPARATION 1

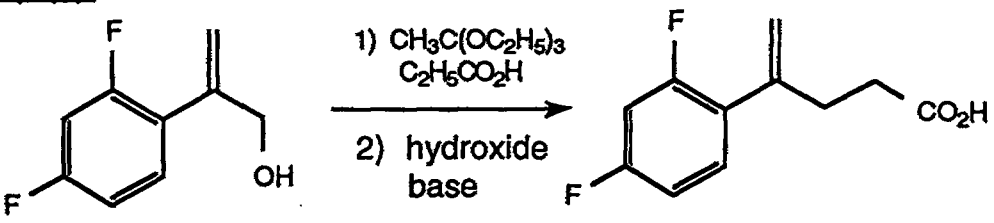


Dissolve (4S)-(-)-4-isopropyl-2-oxazolidinone (400 mg, 3.1 mmol) in 4 mL of THF and cool to -78°C. Add 2 mL (3.2 mmol) of a 1.6 M solution of n-butyllithium in hexane and stir the mixture for 10 min at -78°C to give a solution of the title oxazolidinone salt.

PREPARATION 2

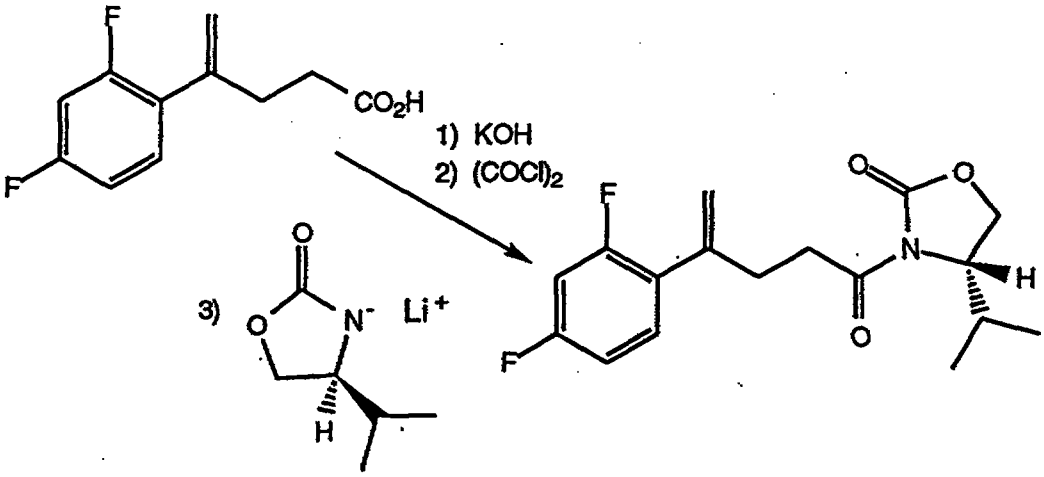


Step (a):



Combine the allylic alcohol (6.25 g, 31.53 mmol), triethyl orthoacetate (20.46 g, 126.12 mmol) and 5 drops of propionic acid, and heat the mixture at 120°C, collecting 4 mL of EtOH by distillation. Continue heating, distilling off the excess triethyl orthoacetate (14 mL) to give a residue. Combine the residue with KOH (3.5 g, 63 mmol), 16 mL of MeOH and 4 mL of water, and stir overnight (@ 18 h) at room temperature. Dilute the mixture with water and wash with cold CH_2Cl_2, then acidify the aqueous layer to pH = 3 by adding 0.1 M HCl. Extract with 3 portions of EtOAc, combine the EtOAc extracts, dry over Na_2SO_4 and concentrate to give 6.75 g of the acid product. MS = 213 $(M+H)^+$

Step (b):

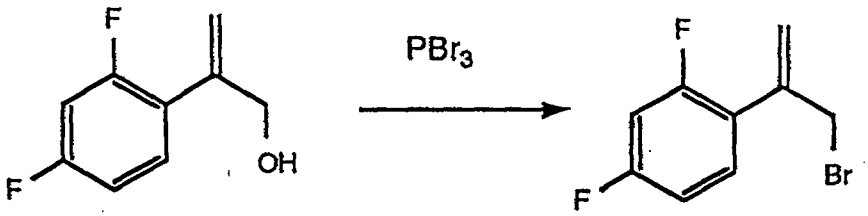


Combine the acid product of Step (a) (0.5 g, 2.36 mmol), KOH (0.13 g, 2.36 mmol) and 5 mL of EtOH, and stir for 2 h at room temperature. Evaporate the solvent to a residue, dissolve the residue in toluene and evaporate to dryness. Add 5 mL of anhydrous Et_2O, cool to 0°C and add 3 mL of oxalyl chloride and 4 drops of DMF. Stir the mixture at 0°C for 2 h, then filter and concentrate the filtrate *in vacuo* to a

residue. Add CH_2Cl_2, then co-evaporate the CH_2Cl_2 and any residual oxalyl chloride to give the acid chloride.

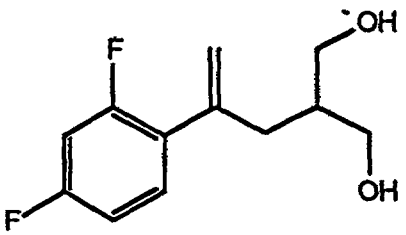
Dissolve the acid chloride (2.36 mmol) in 4 mL of THF and add the resulting solution to the -78°C solution of oxazolidinone salt from Preparation 1. Stir the mixture for 1 h, then remove the solvent *in vacuo* to give a residue. Chromatograph the residue (silica gel, 15%-20% EtOAc/hexane) to give 0.26 g of the title compound. MS = 324 $(M+H)^+$.

PREPARATION 3

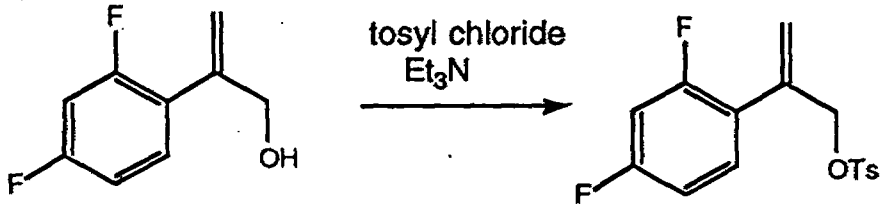


Dissolve the allylic alcohol (5.37 g, 31.58 mmol) in 50 mL of CH_2Cl_2 and cool the resulting solution to 0° to 5°C. Add PBr_3 (1.0 mL, 10.53 mmol), warm to room temperature and stir for 1 h, while monitoring the reaction by TLC (silica gel, 25% EtOAc/hexane). Add 50 mL of ice water, stir for 5 min, separate the layers, and dry the organic layer over $MgSO_4$. Concentrate *in vacuo* to give 6.45 g of the bromide product. MS = 233 M^+

PREPARATION 4

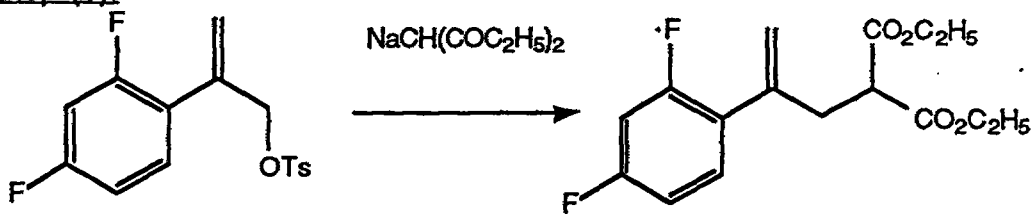


Step (a):



Dissolve the allylic alcohol (8.51 g, 50 mmol) in 200 mL of CH_2Cl_2, add Et_3N (8.36 mL, 60 mmol) and 100 mg of DMAP, then cool the mixture to 0° to 5°C. Add tosyl chloride (10.49 g, 55 mmol), then warm slowly to room temperature. Add 1 mL of MeOH, stir for 20 min, and wash with 100 mL of water, then 100 mL of brine. Dry the organic layer over $MgSO_4$, then concentrate *in vacuo* to give 13.1 g of the tosylate product. (Ts = $-SO_2C_6H_4CH_3$).

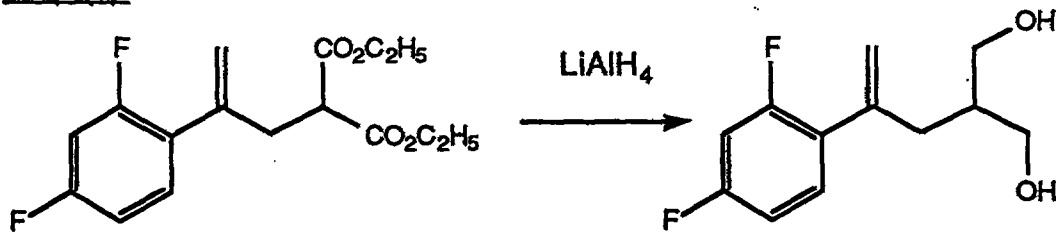
Step (b):



Combine diethyl malonate (1.85 g, 11.6 mmol) and 25 mL of THF, cool to 0° to 5°c, then add 0.339 g (8.48 mmol) of 60% NaH (oil dispersion) and stir the mixture at room temperature for 30 min. Add the tosylate of Step (a) (2.50 g, 7.71 mmol) and stir at room temperature for 90 min. Add 250 mL of Et_2O and 100 mL of water, stir for 10 min, separate the layers and wash the organic layer with 50 mL of brine. Dry over $MgSO_4$, then concentrate *in vacuo* to give 3.2 g of the di-ester product. MS = 313 M^+

Following substantially the same procedure, the allylic bromide of Preparation 3 is converted to the same di-ester product.

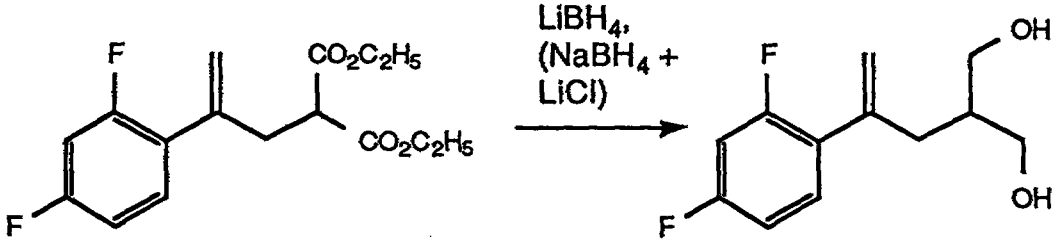
Step (c):



Combine the di-ester of Step (b) (1.68 g, 5.38 mmol), and 15 mL of THF and cool the mixture to 0° to 5°C. Add 7.0 mL (6.99 mmol) of a 1.0 M solution of $LiAlH_4$ in THF dropwise over 5 min, then stir the mixture at room temperature for 2 h. Cool the mixture to 0° to 5°C, add 0.3 mL of water dropwise, then add 0.3 mL of 15% NaOH, followed by

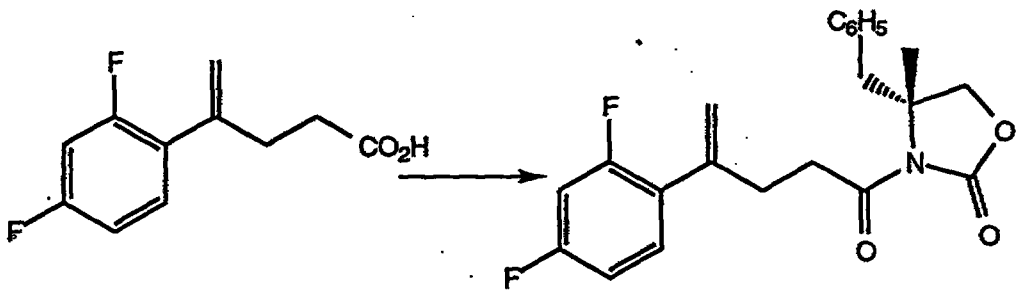
an additional 0.9 mL of water, and stir at room temperature for 1 h. Filter, concentrate the filtrate *in vacuo* to a residue, dissolve the residue in 50 mL of CH_2Cl_2 and dry over $MgSO_4$. Concentrate *in vacuo* to give 1.10 g of the title compound. MS = 229 M^+

PREPARATION 5



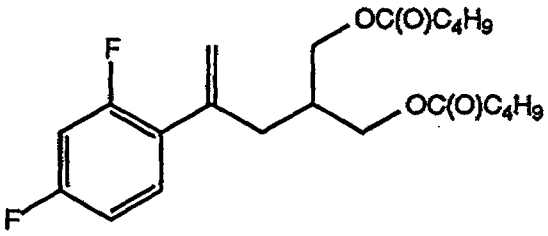
Combine the diester product of Preparation 3, Step (b) (6.77 g, 21.7 mmol), LiCl (2.76 g, 65.1 mmol) and 100 mL of EtOH, cool to 0° to 5°C, then add $NaBH_4$ (2.46 g, 65.1 mmol), then slowly warm the mixture to room temperature and stir overnight. Add 100 mL of MeOH and 100 mL of water, stir for 90 min, then concentrate *in vacuo* to a residue. Partition the residue between 500 mL of EtOAc and 100 mL of water, wash the organic layer with 100 mL of brine, dry over $MgSO_4$, and concentrate *in vacuo* to give 4.94 g of the diol product.

PREPARATION 6



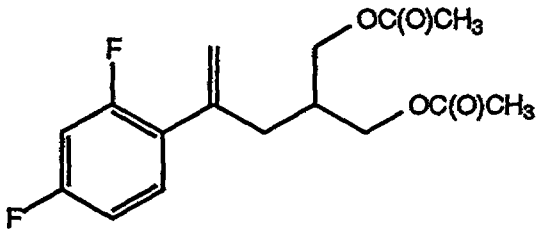
The acid of Preparation 2, Step (a) is reacted according to the general procedure taught by Evans et al, Tetrahedron, 44, 5525-5540 (1988) and Gage et al, Org. Syn., 68, 83-90 (1989) to give the chiral oxazolidinone product, $[\alpha]_D$ = - 44.4° (c = 1.67, $CHCl_3$). MS = 371 $(M+H)^+$

PREPARATION 7



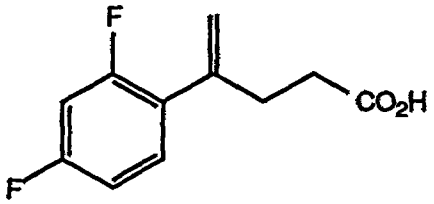
Combine 8.5 g of the diol (IV) of Preparation 4 or 5 and 50 mL THF, add 14 mL of butyric anhydride (1.15 equiv.), 15 mL Et_3N, and 0.22 g of DMAP, and stir the mixture at 20° to 23°C for 16 h. Concentrate *in vacuo* to a residue, dissolve the residue in EtOAc, wash with saturated aqueous Na_2CO_3, then dry over $MgSO_4$. Concentrate *in vacuo* to give the dibutyrate product in near quantitative yield.

Using acetic anhydride and substantially the same procedure the following compound can also be prepared in near quantitative yield:



Preparation 7A

PREPARATION 8



Step (a):

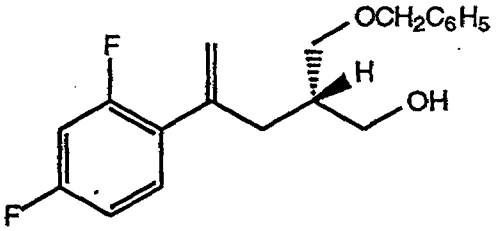
Combine 8.5 g of succinic anhydride and 30 g of 1,3-difluorobenzene, add 29.2 g of $AlCl_3$ (anhydrous) and stir while heating at reflux for 1 h. Cool to room temperature and stir for 2 h, then add 25 mL of water. Extract with EtOAc, dry the extract over $MgSO_4$ and

concentrate *in vacuo* to a residue. Crystallize the residue from EtOH, or a mixture of CH_2Cl_2 and hexane, to give 16.6 g of the keto acid product.

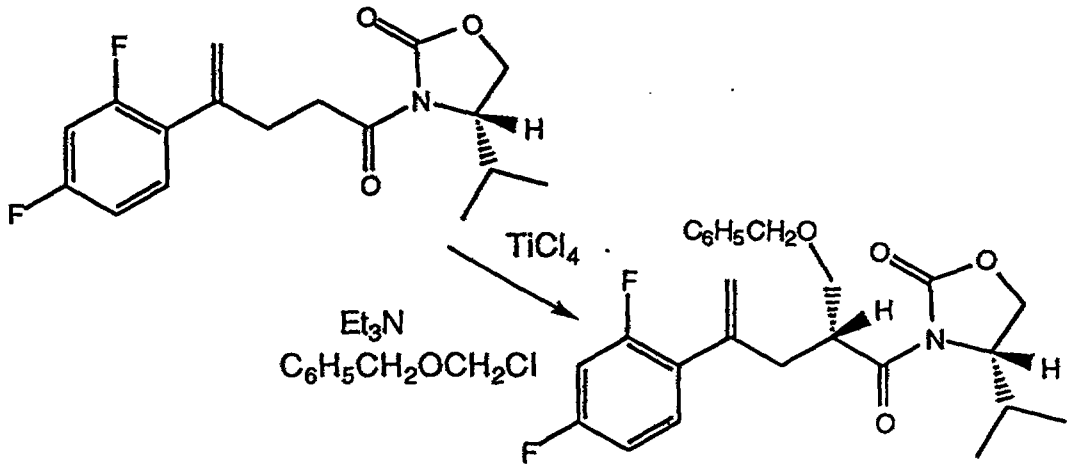
Step (b):

Combine 876 mg of $CH_3{\bullet}P(C_6H_5)_3{\bullet}Br$ and 5 mL of THF, then add 2.6 mL of 1 M $NaN[Si(CH_3)_3]_3$ in THF and stir at room temperature for 30 min. Cool the mixture to -78°C and slowly add (dropwise) a solution of 250 mg of the product of Step (a) in 5 mL of THF. Stir the mixture for 12-18 h, then add an aqueous solution of citric acid while cooling to 0°C. Extract with EtOAc, dry the extract over Na_2SO_4, and concentrate to a residue. Purify the residue by chromatography (silica gel, 5% $MeOH/CH_2Cl_2$) to give 142 mg of the title compound, (for use in Preparations 2 and 6).

EXAMPLE 1



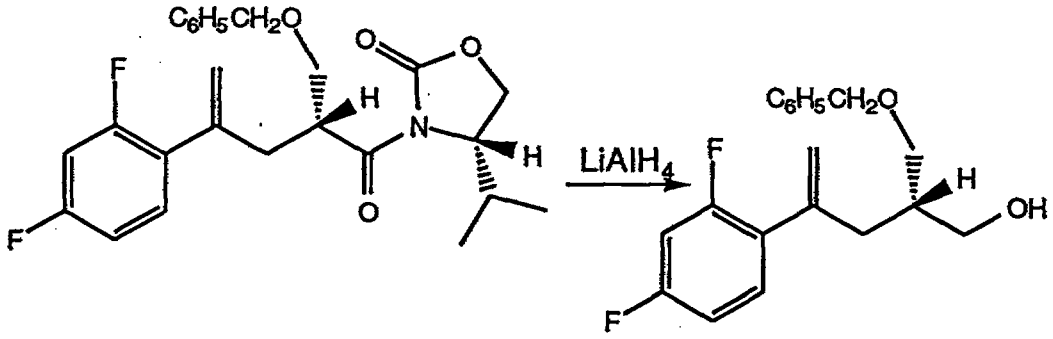
Step (a):



Combine the product of Preparation 2 (2.8 g, 8.66 mmol) and 12 mL of CH_2Cl_2 and cool the mixture to 0°C, stir the mixture, and add 9.1 mL (9.1 mmol) of a 1.0 M solution of $TiCl_4$ dropwise. Stir for 5

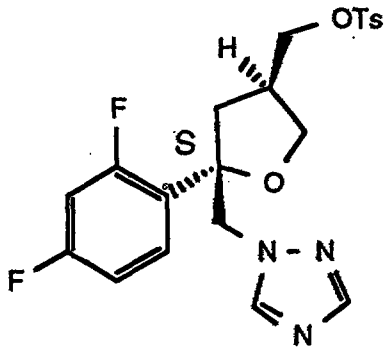
min more. then add Et_3N (1.27 mL, 9.1 mmol) dropwise and stir for 1 h at 0°C. Slowly add benzyl chloromethyl ether (3.15 g, 18.2 mmol) and stir the mixture at 0°C for 3 h. Quench with 15 mL of saturated NH_4Cl, extract with CH_2Cl_2, dry the extract over Na_2SO_4, then concentrate *in vacuo* to a residue. Purify the residue by column chromatography (silica gel, 10% EtOAc/hexane) to give 3.21 g of the product. MS = 444 $(M+H)^+$

Step (b):

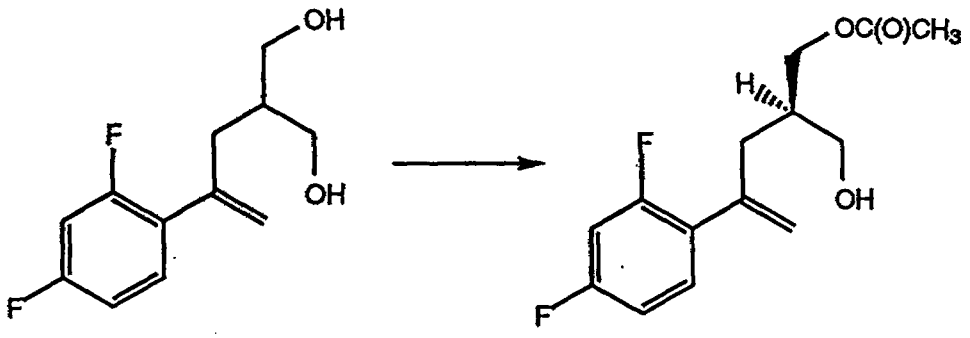


Reduce the product of Step (a) by treating with $LiAlH_4$ according to the procedure described by Evans et al., J. Amer. Chem. Soc., 104, 1737-1739 (1982) to give the S-isomer of the chiral product, $[\alpha]_D$ = -28.4° (c = 1.18, $CHCl_3$). MS = 341 $(M+Na)^+$

EXAMPLE 2

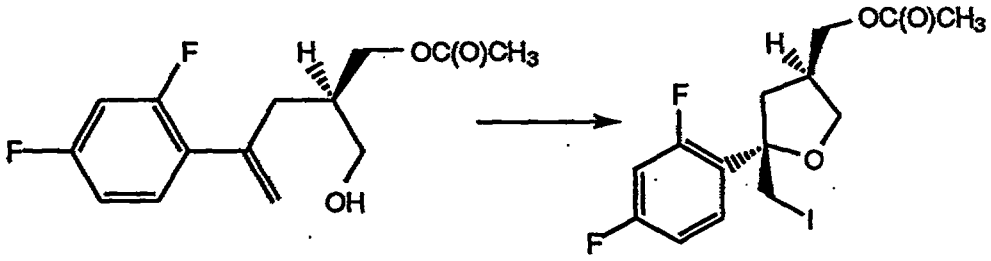


Step (a):



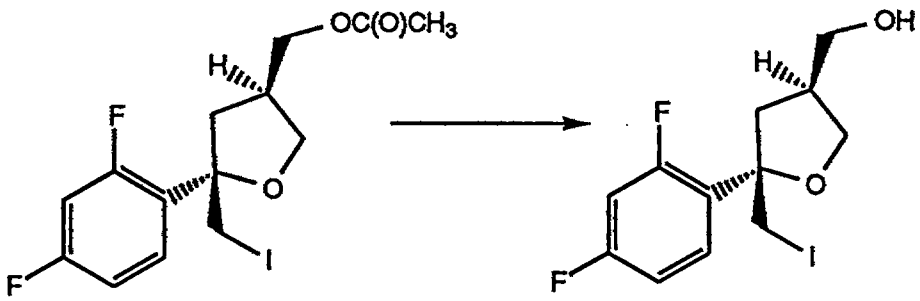
Combine the diol product of Preparation 4 or 5 (0.60 g) and 12 mL of EtOAc, add 1.8 g of porcine pancreas lipase (EC3.1.1.3), de-gas the mixture, and stir at room temperature for 48 h under nitrogen. Filter the mixture, wash the solids with EtOAc, then concentrate the combined filtrate and washings *in vacuo* to a residue. Purify the residue by chromatography (silica gel, 10% to 20% EtOAc/hexane) to give 0.628 g of the R-isomer of the chiral product, $[\alpha]_D = +6.2°$ (c = 1.11, $CHCl_3$). MS = 271 M^+. 20% to 30% e.e. as determined by ^1H NMR using a chiral shift reagent.

Step (b):



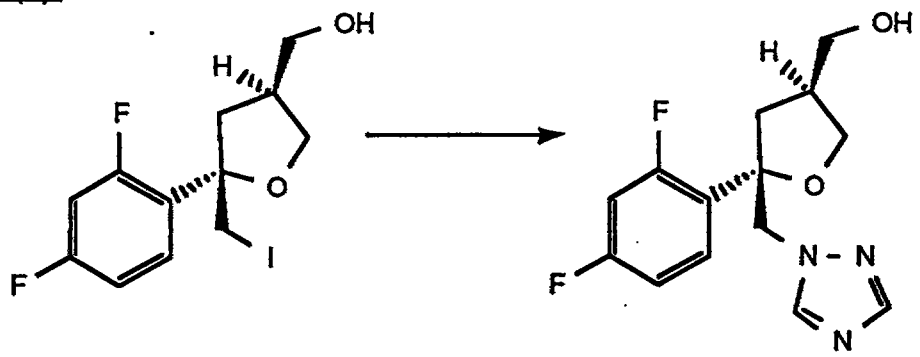
Combine the product of Step (a) (0.1 g, 0.37 mmol) and 3 mL of CH_3CN, add pyridine (45 µL, 0.56 mmol) and I_2 (0.188 g, 0.74 mmol) and stir the mixture at 0° to 5° for 6 h. Add 50 mL Et_2O and 25 mL of water, then add a saturated solution of $Na_2S_2O_3$ (dropwise) until the mixture is colorless. Stir for 10 min, separate the layers, dry the organic layer over Na_2SO_4, then concentrate *in vacuo* to a residue. Purify by chromatography (silica gel, 10%-50% EtOAc/hexane) to give 0.132 mg of the chiral iodide. The product is a 90:10 mixture of cis and trans isomers by ^1H NMR.

Step (c):



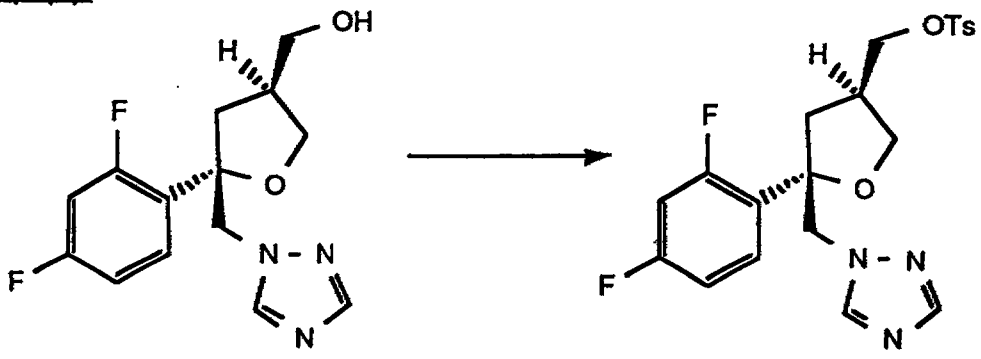
Combine the iodide product of Step (b) (0.387 g, 0.908 mmol) and 9 mL of MeOH, add water until the mixture becomes slightly cloudy, then add K_2CO_3 (0.148 g, 1.07 mmol) and stir the mixture at 0° to 5°C for 1 h. Add CH_2Cl_2, wash with water, then dry over Na_2SO_4. Concentrate *in vacuo* to a residue then purify the residue by preparative TLC (silica gel, 50% EtOAc/heaxane) to give 0.348 g of the chiral alcohol product (90:10 cis/trans ratio).

Step (d):



Treat the chiral alcohol product of Step (c) with sodium triazole according to the procedure of Example 3, Step (b) to give the chiral triazole product.

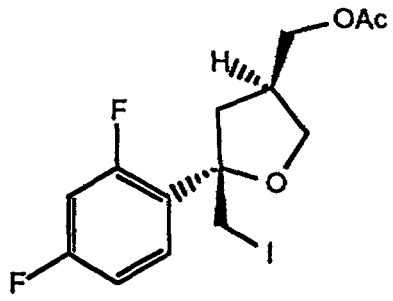
Step (e):



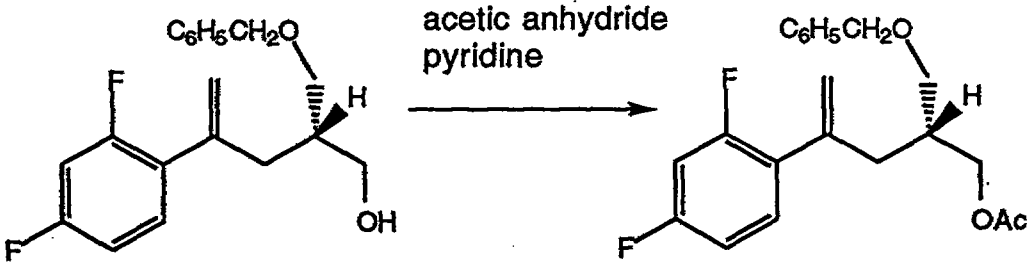
Treat the alcohol product of Step (d) with tosyl chloride and pyridine as described in Example 6, Step (d) (second paragraph) to form the S-cis isomer of the title compound, $[\alpha]_D = +9.5°$ (c = 1.1, $CHCl_3$), in 25% e.e.

Where the chiral iodide of Example 2A is used in Step (c) and carried through Steps (d) and (e), title compound of high optical purity is formed, $[\alpha]_D = +37.0°$ (c = 1.19, $CHCl_3$).

EXAMPLE 2A

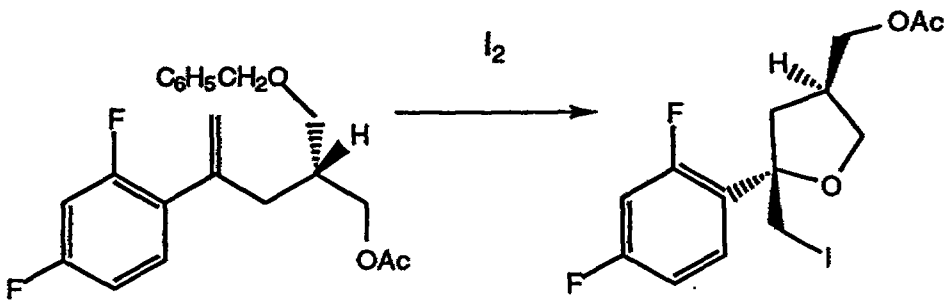


Step (a):



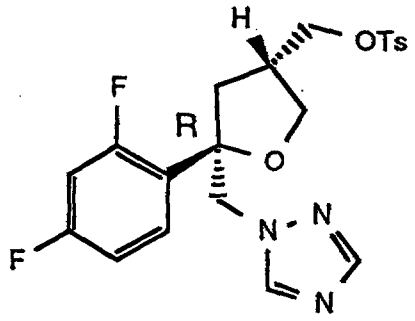
Combine the chiral product of Example 1 and acetic anhydride in CH_2Cl_2, add pyridine and stir at room temperature to form the chiral acetylated product.

Step (b):

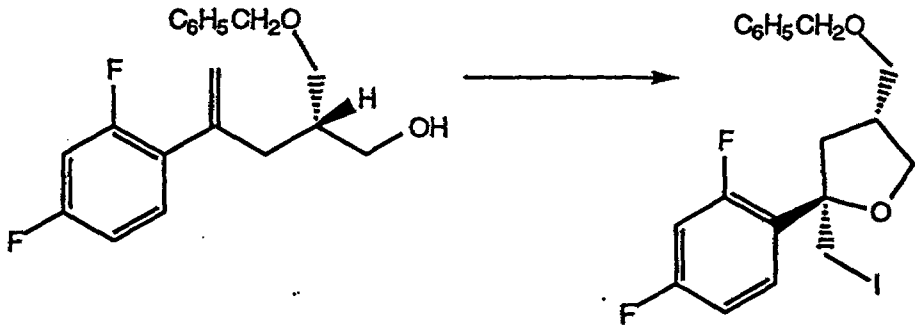


Treat the acylated product of Step (a) with I_2 (a base is not used) according to the procedure of Example 2, Step (b) to form the chiral iodide product.

EXAMPLE 3

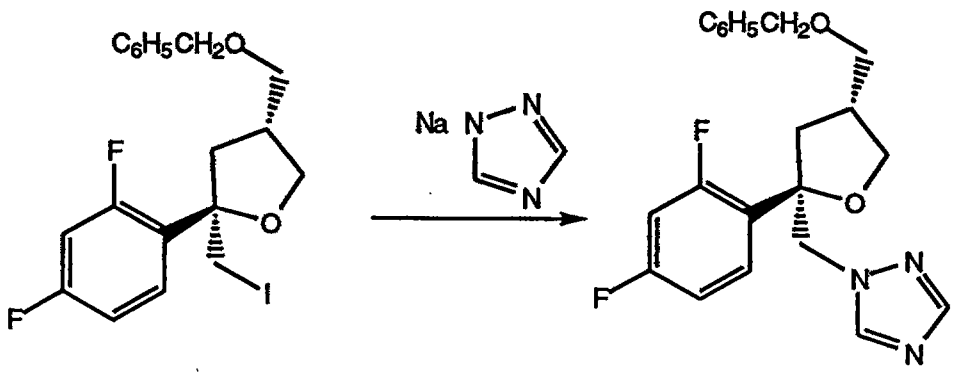


Step (a):

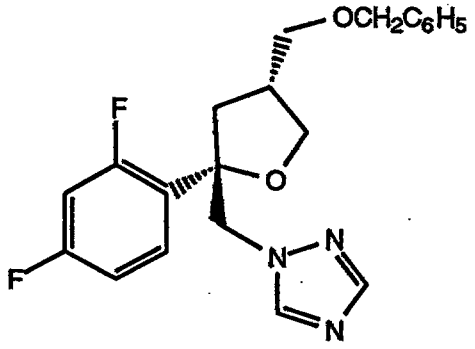


Dissolve the product of Example 1 (1.7 g, 5.34 mmol) in 12 mL of CH_3CN, cool the solution to 0° to 5°C and add I_2 (2.8 g, 11.0 mmol) and pyridine (1.0 mL, 12.4 mmol). Stir the resulting mixture at 0° to 5,C for 6 h, then add saturated $Na_2S_2O_3$ (aqueous) and Et_2O and stir until the mixture is colorless. Extract with Et_2O, wash the extract with 0.01 N HCl, then with saturated $NaHCO_3$, and dry over Na_2SO_4. Concentrate *in vacuo* to a residue and purify the residue by column chromatography (silica gel, 0% to 5% EtOAc/hexane) to give 2.3 g of the cyclized iodide, $[\alpha]_D = +3.7°$ (c = 1.17, $CHCl_3$). MS = 444 $(M+H)^+$

Step (b):

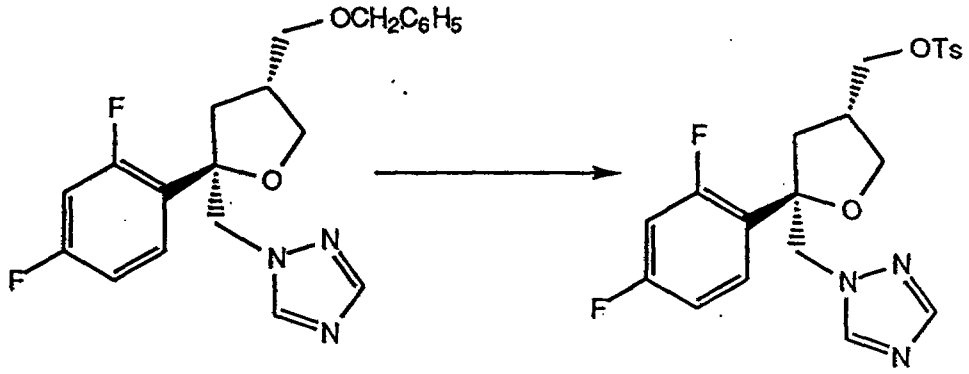


Dissolve the iodide product of Step (a) (1.18 g, 4.01 mmol) in 8 mL of DMF, then add sodium triazole (0.73 g, 8.02 mmol) and 5 drops of DMPU and heat the mixture at 100°C for 30 h. Concentrate *In vacuo* to a residue, then partition the residue with 100 mL water and 100 mL EtOAc. Extract the aqueous layer with EtOAc, combine the organic layers and dry over Na_2SO_4. Concentrate *in vacuo* to a residue and chromatograph the residue (silica gel, 20% to 30% EtOAc/hexane) to give the R-cis triazole product, along with the R-trans isomer, i.e.,



R-cis triazole, 1.0 g, $[\alpha]_D$ = - 42.1° (c = 1.17, $CHCl_3$). MS = 386 $(M+H)^+$
R-trans triazole, 0.24 g, $[\alpha]_D$ = + 10.6° (c = 1.12, $CHCl_3$). MS = 386 $(M+H)^+$

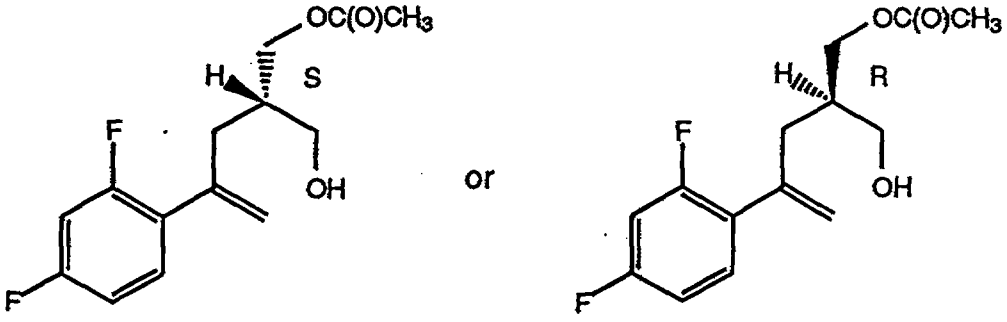
Step (c):



Combine the R-cis triazole product of Step (b) (0.83 g, 2.16 mmol), 0.22 g of 10% Pd on carbon, 20 mL of EtOH and 1.2 mL of 1N HCl, and agitate the mixture under 60 p.s.i. of hydrogen for 3 h. Filter, concentrate the filtrate to a residue, dissolve the residue in EtOAc and wash with aqueous $NaHCO_3$. Dry the EtOAc solution over Na_2SO_4, concentrate *in vacuo* to give the R-cis alcohol product.

Treat the alcohol with tosyl chloride and pyridine as described in Example 6, Step (d) (2nd paragraph) to give the R-cis isomer of the title compound, m.p. = 101°-102°C, $[\alpha]_D$ = -43.9° (c = 1.16, $CHCl_3$).

EXAMPLE 4



Screening of enzymes for the acetylation of the diol (IV) from Preparation 4 or 5 is carried out using a number of commercially available enzymes via the following general procedure. Combine 0.050-0.10 g of diol (IV) and 1.0 ml of toluene or CH_3CN, containing 2-10 equivalents of vinyl acetate. Add 0.001 to 0.30 g of the commercial enzyme preparation and stir the mixture at 20° to 23°C. Analyze the reaction mixture by chiral HPLC to determine: the amounts of remaining

diol (IV), hydroxy acetate (IIa), and diacetate (of formula V wherein R^2 is CH_3); and the absolute configuration and e.e. of chiral hydroxy acetate (IIa). The results are summarized in Table 1 below.

TABLE 1

Source & Enzyme	# mgs	Time (hr.)	Product composition (%) IV	IIa	V	*	% e e
Amano Acylase	53.8	22	41.12	55.76	3.12	R	29
Amano AK	45.2	3.75	0.29	93.04	6.66	R	79
Amano AP-12	47.6	22	83.48	15.96	0.56	R	55
Amano AY-30	50.3	3.75	0.18	58.02	41.80	R	94
Amano CE	47.7	3.75	0.36	92.02	7.62	R	93
Amano CE	50.0	1.66	-	100	-	R	97
Amano CES	46.7	3.75	5.07	93.81	1.12	R	71
Amano D	50.8	22	91.96	7.51	0.53	R	37
Amano FAP-15	53.6	22	92.12	7.29	0.58	R	30
Amano G	77.4	22	2.10	86.98	10.92	R	66
Amano GC-4	47.3	22	69.41	29.85	0.74	S	7
Amano Lilipase A-10	56.5	94	84.85	15.15	-	R	42
Amano MAP-10	48.1	22	49.04	49.55	1.41	R	69
Amano N	55.6	22	94.30	5.20	0.50	R	44
Amano PGE	63.1	22	85.09	14.06	0.85	R	7
Amano PS-30	51.5	3.75	0.28	92.02	7.70	R	77
Amano R	43.9	22	68.66	29.92	1.41	R	44
Amano Peptidase A	89.0	28.5	70.29	29.5	0.21	R	71
Amano Aminoacylase	91.7	28.5	3.82	80.95	15.24	R	34
Amano Lipoprotein Lipase-80	20.7	28.5	8.93	90.31	0.76	R	59.
Amano Lipoprotein Lipase-200S	16.1	28.5	36.07	63.69	0.23	R	63
Amano Newlase A	77.3	28.5	78.67	19.52	1.81	S	22
Amano Protease 2A	91.3	28.5	89.92	10.02	0.05	R	51
Amano Protease B	105.1	28.5	68.16	31.00	0.84	S	4
Amano Protease M	92.3	28.5	12.59	85.26	2.15	R	59
Biocatalyst Alcaligenes sp.	66.7	1.33	-	34.85	65.15	R	45

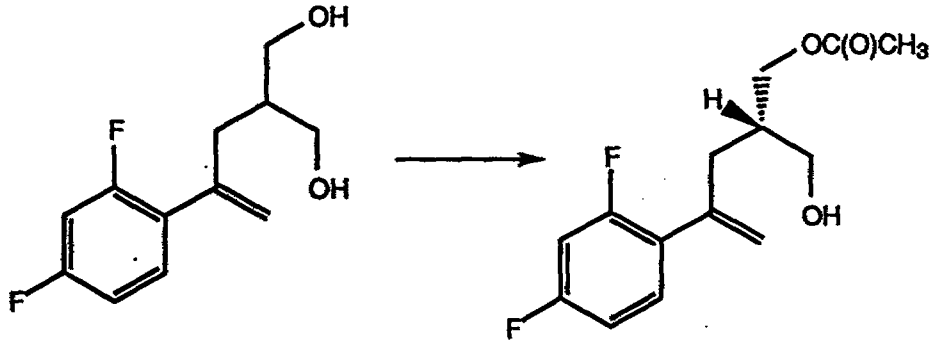
Biocatalyst Asp. niger	76.2	42.25	83.81	15.79	0.40	R	51
Biocatalyst C. cylindracea	67.4	1.33	2.28	74.07	23.65	R	55
Biocatalyst Chr. viscosum	55.6	42.25	67.47	32.31	0.22	R	45
Biocatalyst H. lanugiosa	81.2	1.33	-	98.75	1.25	R	97
Biocatalyst M. javanicus	64.3	42.25	5.03	88.59	6.38	R	62
Biocatalyst M. meihei	70.7	18	-	73.98	26.02	R	87
Biocatalyst P. cyclopium	63.5	18	-	58.51	41.49	R	51
Biocatalyst Ps.fluorescens	65.8	1.33	-	100	-	R	99
Biocatalyst Rh. delemar	84.1	18	-	82.30	17.70	R	69
Biocatalyst Rh. japonicus	96.3	42.25	84.95	15.03	0.02	R	66
Biocatalyst Rh. javanicus	135.2	42.25	88.95	11.05	-	R	36
Biocatalyst Rh. niveus	61.7	3.00	88.78	11.22	-	R	46
EDC Protease 160	131.1	28.5	76.40	23.40	0.20	R	48
EDC Protease 180	159.3	28.5	90.40	9.53	0.07	R	36
EDC Protease Bacterial	102.3	28.5	62.99	35.34	1.66	R	17
EDC Protease S761	146.2	28.5	80.04	19.69	0.27	R	12
Genencor Acyltransferase Cells C.O. 1128	21.1	28.5	88.27	10.93	0.80	S	27
Genzyme C. cylindracea	23.0	94	12.10	65.62	22.28	R	5
Gist Brocades Piccantase A	225.4	28.5	12.45	85.77	1.78	R	76
Gist Brocades Calf lipase	96.3	94	58.68	37.12	4.19	S	8
Gist Brocades Kid lipase	135.2	94	67.55	26.59	5.86	S	1
IBT Peptidase	45.0	22	94.97	4.43	0.60	S	25
Interspex Bacterial Protease BP1 Grade C Immobilized 6/92	254.4	45	27.36	65.53	7.10	S	38
Interspex Bacterial Protease BP2 Grade C Immobilized 6/92	271.4	45	15.45	76.49	8.06	S	58
Interspex Fungal Protease FP1 Grade C 6/92	128.6	45	33.57	61.56	4.87	R	39

ISC BE1	66.7	94	79.91	19.49	0.59	R	2
ISC BP1	55.6	94	76.83	22.96	0.21	R	5
ISC BP1 immob	70.0	94	9.21	77.76	13.03	R	45
ISC BP2	81.2	94	78.16	21.63	0.20	R	5
ISC BP2 immob	63.5	94	46.88	47.41	5.71	S	50
ISC BP3	64.3	45.75	75.79	23.94	0.27	R	4
ISC BP4	76.2	94	96.89	3.11	-	S	34
ISC BPG1	65.8	94	81.62	18.18	0.20	R	8
ISC FP1	65.8	94	71.40	28.25	0.35	R	40
Meito MY	48.3	3.75	0.15	65.27	34.58	R	95
Meito OF	47.1	3.75	3.00	86.63	10.37	S	8
Meito PL	47.0	3.75	-	11.79	88.21	R	55
Nagase Denapsin 10-P	117.8	28.5	80.93	15.69	3.37	R	24
Nagase Denazyme AP	119.4	28.5	86.41	13.99	0.20	R	17
Nagase XP-415 *Rhizopus*	87.1	28.5	81.55	17.86	0.59	?	3
Novo IM20	61.7	3.00	-	81.53	18.47	R	95
Novo SP 522	100	24	98	2	-	-	-
Novo SP 523	100	24	62.93	30.91	5.98	R	67.3
Novo SP 524	100	24	8.49	83.73	5.32	R	91.5
Novo SP 525	100	24	14.21	57.57	26.60	S	26
Novo SP 526	100	24	67.39	27.10	2.52	S	52.5
Novo SP435	84.1	3.00	-	-	100	-	-
Quest Kid PGE IX	86.9	28.5	78.71	19.05	2.24	?	6
Quest Lamb PGE IX	122.6	28.5	91.97	5.531	2.49	?	23
Quest Protease acid	95.0	28.5	77.22	18.94	3.84	S	3
Quest Protease fungal	112.1	28.5	97.04	2.92	0.04	R	50
Scientific Protein Labs PEC High Lipase	175.4	45	0.00	55.33	44.67	R	24
Seikagaki Lipase *Rhizopus delemar*	30.0	45	73.27	26.32	0.41	?	4
Sigma Acylase I *Aspergillus melease*	88.2	45	4.20	76.12	19.68	R	32
Sigma Acylase I Porcine Kidney	19.8	45	80.95	16.81	2.24	S	19
Sigma Protease Type IV *Streptomyces caespitosus*	147.6	45	69.46	30.36	0.18	S	23
Sigma Protease Type XIII *Aspergillus saitoi*	205.3	45	86.60	12.88	0.52	?	9

Sigma Protease Type XXIV bacterial	23.1	45	85.72	12.11	2.16	S	33
Sigma Protease Type XXVII (Nagarse)	50.9	45	66.97	25.80	7.22	R	21
Sigma Protease Type XXXI *Bacillus licheniformis*	238.9	45	86.29	13.02	0.68	S	44
Sigma PPL	102.5	5.50	-	93.97	6.03	R	41
Sigma Wheatgerm	23	94	86.31	13.51	0.18	R	5
Solvay AFP 2000	116.5	45	9.08	83.74	7.18	R	40
Solvay PPL	80.4	20	9.69	90.31	-	R	29
Toyobo LPL	9.7	3.75	2.96	53.66	43.37	R	29
Toyobo NEP-160	51.8	94	68.96	30.71	0.33	S	41
Wako Achromopeptidase TBL-1	17.3	45	44.30	39.10	16.60	?	4
Wako Lipase PN *Phycomyces nitens*	32.3	45	56.11	43.39	0.49	R	77
Wako Lipase B *Pseudomonas fragi*	1.0	45	0.00	64.72	35.28	R	50

* Denotes absolute configuration at the chiral center in (IIa).

EXAMPLE 4A



Prepare a 0.2 M solution of the prochiral diol in toluene. Add the diol solution to a mixture of vinyl acetate (5 equivalents) and the commercially available enzyme Novo SP435 (*Candida antarctica*) (Novozyme 435) and agitate the mixture at 20° to 23°C. Analyze the S hydroxy ester product as described in Example 4. The results of several such experiments, using the quantities of reagents indicated, are presented in the following table.

diol	lipase	time (min)	% mono acetate	e.e.
4.9 g	0.54 g	85	87.2	90 %
6.1 g	0.50 g	190	87.6	89 %
11.4 g*	0.51 g	210	75.6	94 %
10.7 g**	1.0 g	80	71.1	96 %

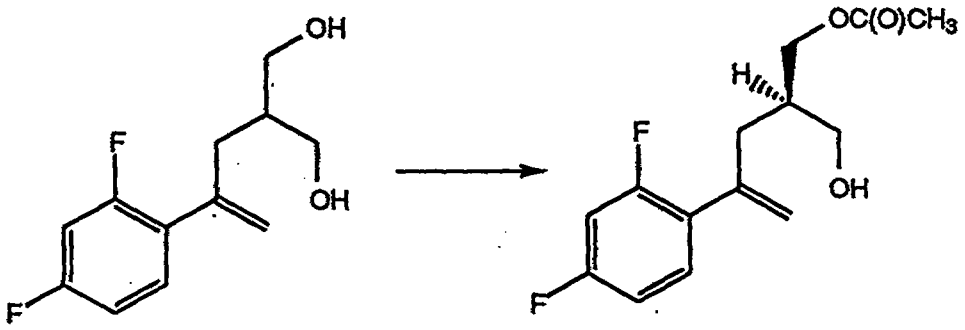
* This reaction was run using a 0.4 M diol solution in toluene
** This reaction was run using molecular seives to dry the diol toluene solution.

The reaction is also run in a variety of solvents, at a temperature of 0° to 35°C, via substantially the same procedure as described above to give the following results.

Solvent	vinyl acetate # equiv	diol/ enzyme ratio g/g	Temp. °C	product composition (%) I V	IIa	V	% e.e
iPr_2O	10.0	4.0	0	5.76	83.85	10.39	91
THF	10.0	4.0	0	2.41	80.65	16.93	87
Dioxane	10.0	4.0	20-23	1.01	74.71	24.26	93
CH_3CN	10.0	4.0	0	0	77.06	22.94	98
Acetone	10.0	4.0	0	1.19	83.07	15.74	94
Toluene	10.0	4.0	0	0.86	89.21	9.93	93
tAmyl Alcohol	5.0	4.0	0	35.04	57.56	7.40	91

Preferably the reaction is run using a 0.9 M solution of the prochiral diol and 1.5 equivalents of vinyl acetate in CH_3CN at 0° to 5°C.

EXAMPLE 4B

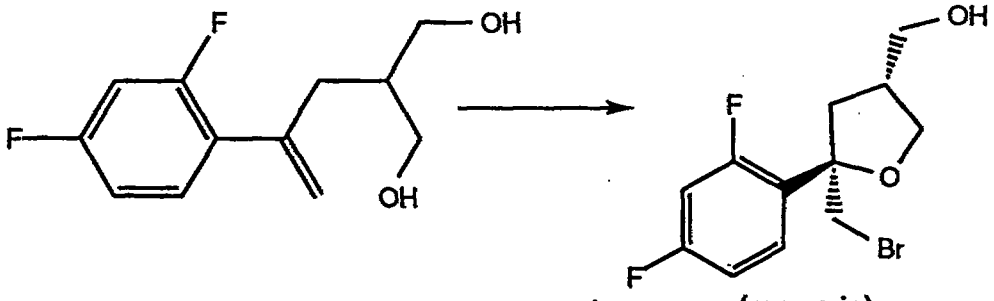


The reaction was run using the commercially available enzyme Amano CE (*Humicloa lanugiosa*) according to the procedure of Example 4A to form the R hydroxy ester. The results of several such experiments are presented in the following table.

diol	lipase	time (min)	% mono acetate	e.e.
0.05 g	0.05 g	95	97	99 %
5.3 g	5.0 g	95	97.3	96%
1.0 g	0.1 g**	930	92.8	91 %
5.0 g	5.0 g	170	97.6	97 %
7.7 g	1.0 g**	170	91.3	95 %

** The enzyme used in these experiments was recovered from a previous run and re-used.

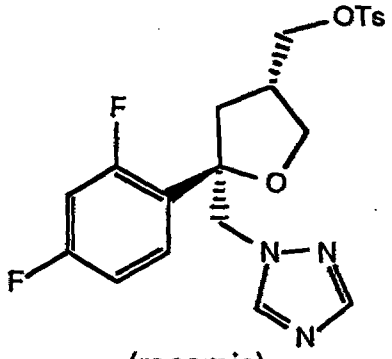
EXAMPLE 5



(racemic)

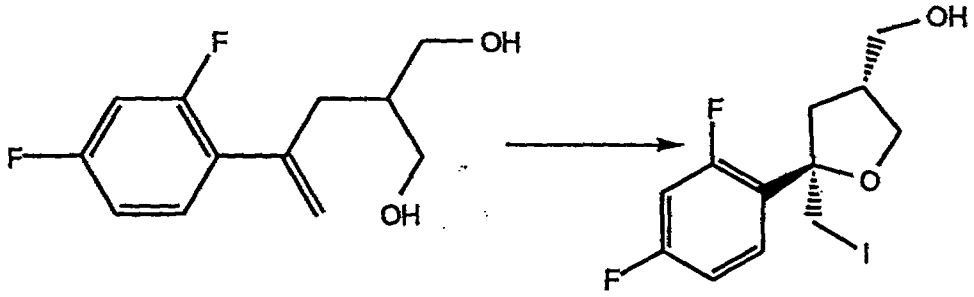
Combine the diol product of Preparation 4 or 5 (0.5 g, 2.19 mmol) and 10 mL of CH_2Cl_2, cool to 0° to 5°C, then add Br_2 (0.112 mL, 2.19 mmol) and pyridine (0.117 mL, 2.19 mmol) and stir the mixture at 0° to 5°C for 18 h. Add 25 mL of CH_2Cl_2, wash successively with 10 mL of 10% Na_2SO_3, 10 mL of 1N HCl, and 10 mL of $NaHCO_3$, then dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph the residue (silica gel, 10% EtOAc/hexane) to give 0.59 g of the bromide product. MS = 307 M^+

EXAMPLE 6



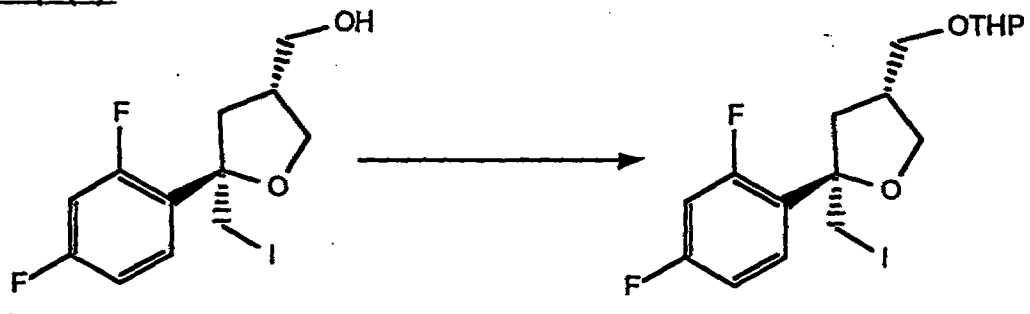
(racemic)

Step (a):



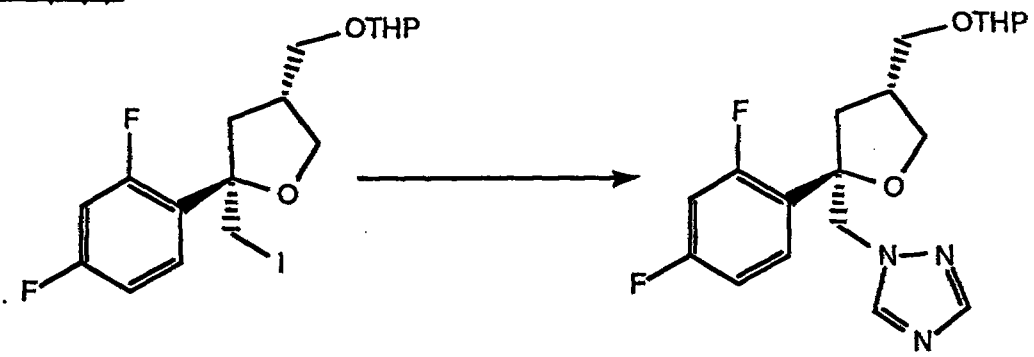
Combine the diol product of Preparation 4 or 5 (3.80 g, 16.6 mmol), 50 mL of CH_3CN and 2.0 mL (25.0 mmol) of pyridine, cool the mixture to 0° to 5°C, then add I_2 (8.45 g, 33.3 mmol) and stir at 0° to 5°C for 1 h. Add 500 mL of Et_2O and 100 mL of 10% Na_2SO_3, stir for 5 min, then separate the layers. Wash the organic layer with 50 mL of 1N HCl, 50 mL of 5% $NaHCO_3$, and 50 mL of brine, then dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph the residue (silica gel, 10% EtOAc/hexane) to give 5.10 g of the racemic iodide product. MS = 354 M^+. ^1H NMR indicates the product is a 84%/16% mixture of trans and cis isomers.

Step (b):



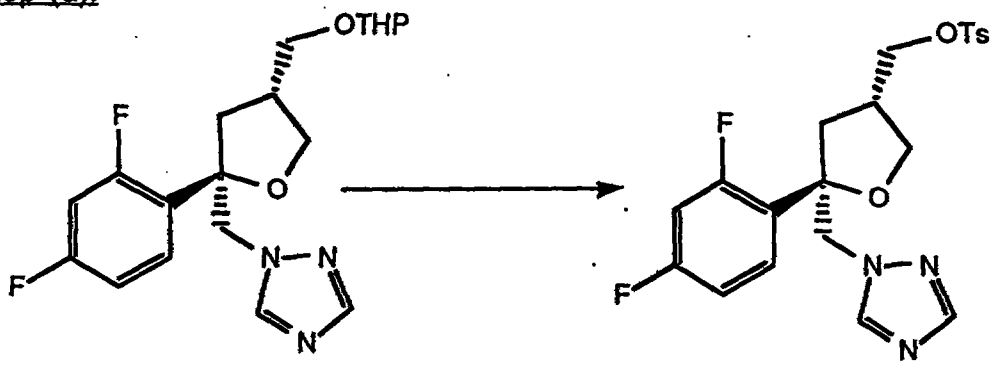
Combine the iodide product of Step (a) (5.00 g, 14.1 mmol) and 50 mL of CH_2Cl_2, add 3,4-dihydro-2H-pyran (1.93 mL, 21.2 mmol) and 0.1 g of p-TSA monohydrate, then stir the mixture at room temperature for 2 h. Add 100 mL of CH_2Cl_2, wash with 50 mL of 5% Na_2CO_3 and 50 mL of water, then dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 2.5% EtOAc/hexane) to give 5.61 g of the racemic THP ether product. MS = 439 M^+

Step (c):



Combine the THP ether product of Step (b) (5.54 g, 12.6 mmol) and 60 mL of DMF, add 90% sodium 1,2,4-triazole (2.30 g, 25.2 mmol) and 5 drops of DMPU, then heat the mixture at 90° to 100°C for 48 h. Cool the mixture to room temperature, concentrate *in vacuo* to a residue, and partition the residue in 100 mL of water and 100 mL of EtOAc. Extract the water layer with 100 mL of EtOAc, dry the combined EtOAc layers over $MgSO_4$, concentrate *in vacuo* to a residue, then chromatograph the residue (silica gel, EtOAc) to give 4.17 g of the racemic triazole product. MS = 380 M^+

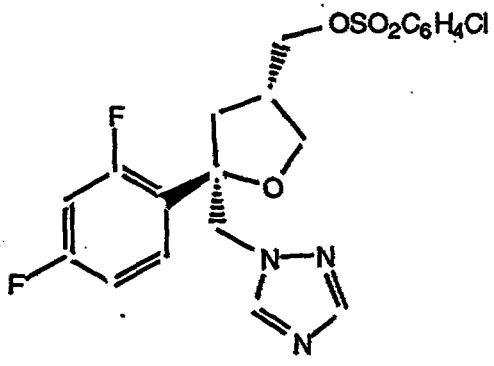
Step (d):



Combine the triazole product of step (c) (4.10 g, 12.2 mmol) and 50 mL of 10% HCl and stir at room temperature for 18 h. Concentrate *in vacuo* to a residue, dissolve the residue in 150 mL CH_2Cl_2 and 50 mL of water, then add 10% Na_2CO_3 (dropwise) to adjust the aqueous layer to pH = 8. Separate the layers, wash the organic layer with 50 mL of brine, dry over $MgSO_4$, then concentrate *in vacuo* to give 3.02 g of the alcohol.

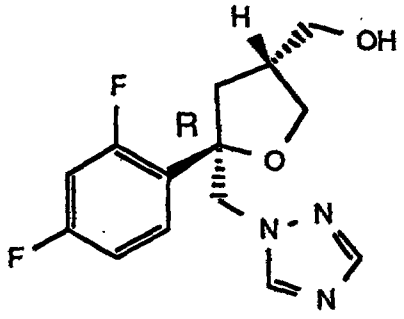
Combine the alcohol and 30 mL of pyridine, cool the mixture to 0° to 5°C, and add tosyl chloride (2.13 g, 11.1 mmol). Stir the mixture at 0° to 5°C for 18 h, then at room temperature for 18 h. Concentrate *in vacuo* to a residue, dissolve the residue in 100 mL of CH_2Cl_2, wash with 50 mL of water, 50 mL of 5% $NaHCO_3$, and 50 mL of brine, then dry over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, EtOAc) to give 3.13 g of the racemic title compound. MS = 450 M^+

Substituting p-chlorobenzenesulfonyl chloride for tosyl chloride in Step (d) and following substantially the same procedure as described above gives the p-chlorobenzenesulfonyl analog (6A).

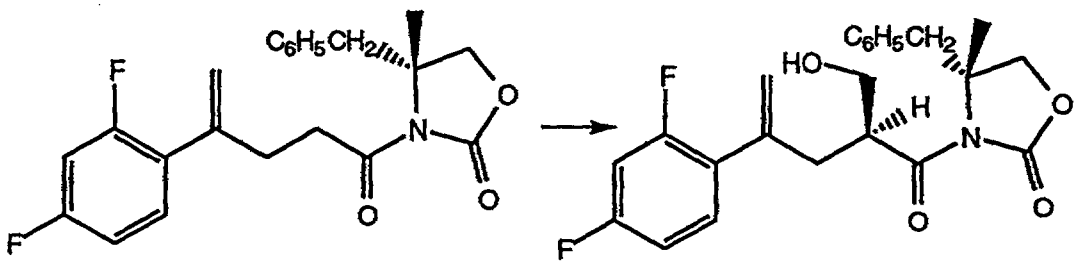


6A

EXAMPLE 7

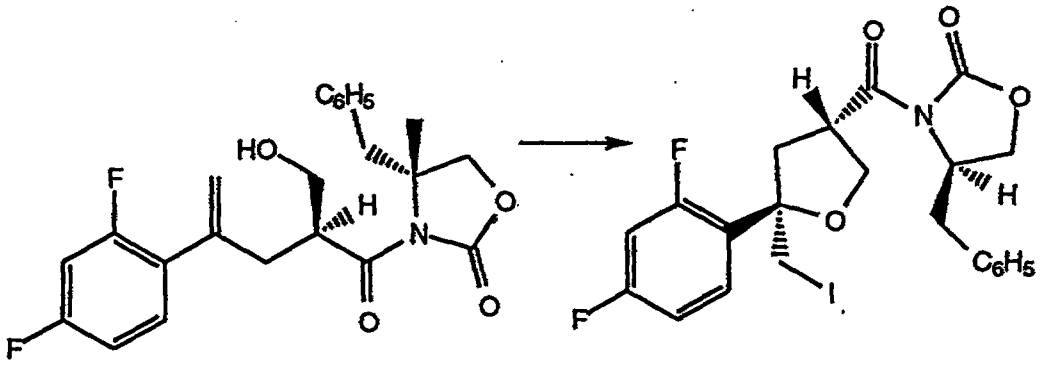


Step (a):



Essentially following the procedure described by Evans et al, J. Amer. Chem. Soc., 112, 8215-8216 (1990), combine the oxazolidinone product of Preparation 6 (2.18 g, 5.88 mmol) and 24 mL of CH_2Cl_2 at 0°C, add 6.5 mL of 1M $TiCl_4$ in CH_2Cl_2. Stir for 5 min, then add 1.12 mL of Hünigs base and stir at 0°C for 30 min. Add a solution of 1,3,5-trioxane (0.67 g, 7.44 mmol) in 5 mL of CH_2Cl_2, then add another 6.5 mL of 1 M $TiCl_4$ in CH_2Cl_2 and stir at 0° to 3°C for 2.5 h. Add 10 mL of saturated NH_4Cl and stir for 5 min, then separate the layers and extract the aqueous phase with 20 mL CH_2Cl_2. Combine the organic phase and the extract, wash with brine, dry over $MgSO_4$, then concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, 15% to 25% EtOAc/hexane) to give 1.33 g of the chiral product, $[\alpha]_D$ = - 62.9° (c = 1.7, $CHCl_3$). MS = 402 $(M+H)^+$

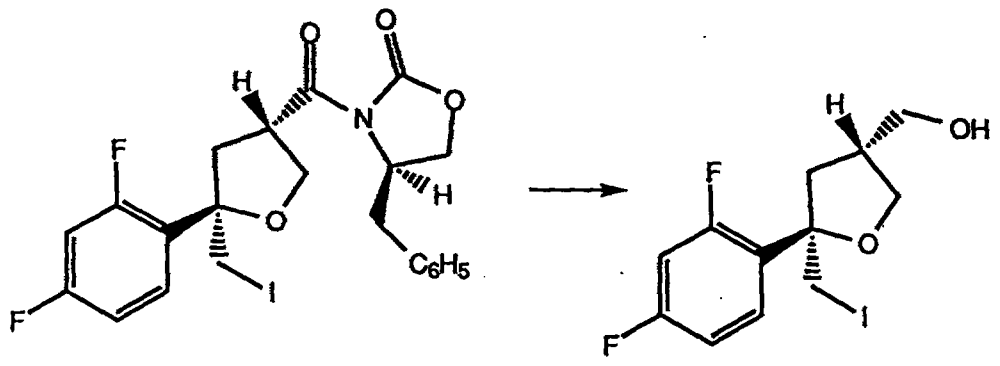
Step (b):



Combine the product of Step (a) (1 g, 2.5 mmol), 0.45 mL of pyridine and 20 mL of CH_3CN, cool to 0°C, then add 1.78 g of I_2. Stir the mixture at room temperature for 20 h, then quench the reaction with dilute aqueous $Na_2S_2O_4$. Extract with Et_2O (2 X 20 mL), combine the extracts and dry over $MgSO_4$. Concentrate *in vacuo* to a residue then

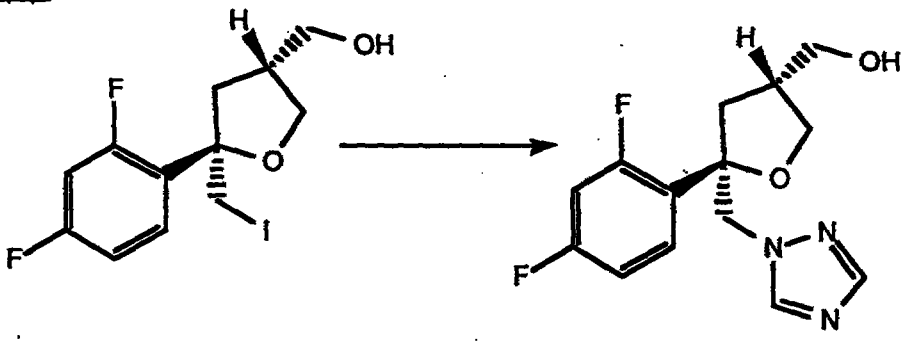
chromatograph (silica gel, 15% to 25% EtOAc/ hexane) to give 1.18 g of the chiral iodide product (89.8% yield). MS = 528 $(M+H)^+$

Step (c):



Combine the iodide product of Step (b) (0.9 g, 1.71 mmol) and 35 mL of THF and cool to -78°C, then add 0.85 mL of 2M $LiBH_4$ in THF and stir the mixture for 1 h while warming to room temperature. Stir for 2 h at room temperature, then cool to -10°C and quench by adding saturated aqueous NH_4Cl. Stir for 0.5 h, concentrate *in vacuo* to a residue, partition the residue between CH_2Cl_2 and water, separate the layers and dry the organic layer over $MgSO_4$. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 15% to 30% EtOAc) to give 0.43 g of the chiral product. MS = 355 $(M+H)^+$

Step (d):

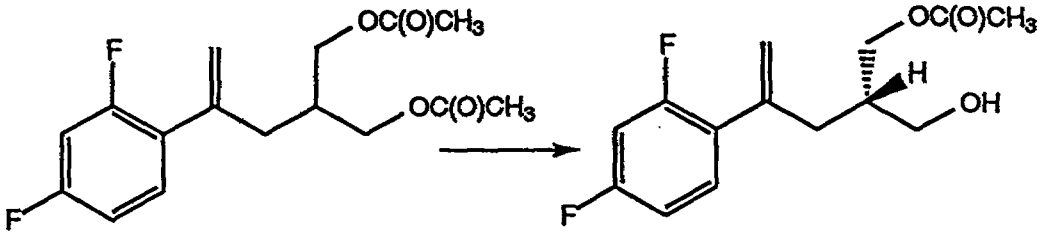


Combine the product of Step (c) (0.3 g, 0.85 mmol), sodium triazole (0.86 g, 8.5 mmol) and 5 mL of DMF and heat at 80°C under nitrogen for 24 h. Cool the mixture, dilute with 50 mL of water and extract with CH_2Cl_2 (2 X 40 mL). Combine the extracts, wash with brine, dry over $MgSO_4$, then concentrate *in vacuo* to a residue.

Chromatograph the residue (silica gel, 50% to 75% EtOAc) to give 0.101 g of the title compound. MS = 296 $(M+H)^+$

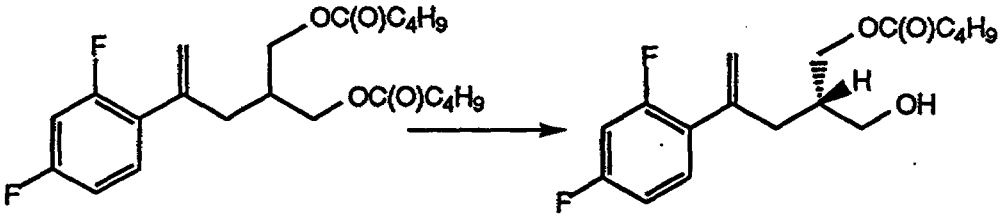
Unreacted starting material (0.138 g) was also recovered.

EXAMPLE 8



Prepare a 50 mM solution of KCl in 20% THF/water. Using this solution, prepare 5 mL of a 0.2 M solution of the diacetate product of Preparation 7A. (The pH of the resulting solution is maintained at 7.5 by titration with aqueous NaOH, as needed, throughout the course of the reaction. Add 0.12 g of Amano CE and stir at room temperature for 18 h. Filter the mixture, wash the filtrate with water, aqueous Na_2CO_3, then brine, and dry over $MgSO_4$. Concentrate *in vacuo* to give the chiral product in 98% e.e., as determined by chiral HPLC.

EXAMPLE 9

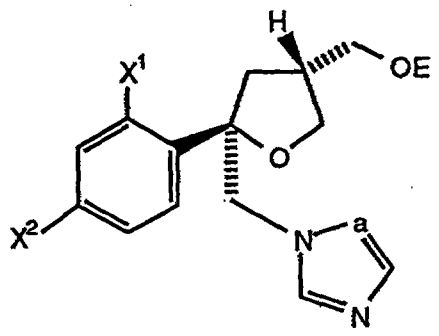


Prepare a solution of 7.0 g of the dibutyrate of Preparation 7 in 63 mL of a 50 mM solution of KCl in 20% THF/water. Add 5.0 g of Amano CE and stir the mixture at 22°C, while maintaining the pH at 7.5 by titration with aqueousNaOH using a pH stat, for 6.5 h. Extract the mixture to give an 81.5% yield of the S product in 99% e.e.

The reaction can also be run in water (excluding THF) by substantially the same procedure as described above.

We Claim:

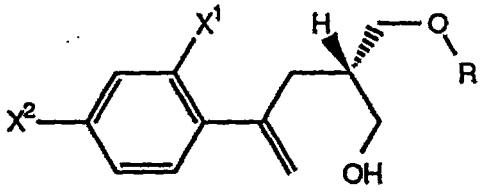
1. A process for preparing compounds of the formula (I)



(I)

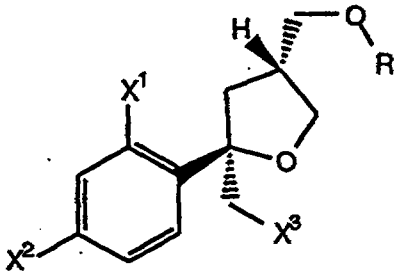
wherein: a is CH or N; X^1 and X^2 are independently F or Cl; and E is $-SO_2R^6$, wherein R^6 is C_1-C_6 alkyl, aryl, substituted aryl or $-CF_3$; comprising the steps:

(a) cyclizing a chiral alcohol of the formula (II)



(II)

wherein X^1 and X^2 are as defined above, and R is a hydroxy protecting group selected from $-CH_2-C_6H_5$, tetrahydropyran-2-yl or $-C(O)R^1$, wherein R^1 is C_1-C_6 alkyl, aryl or $-(CH_2)_nCO_2H$ wherein n is 1, 2, 3 or 4, by treating with a halogen and a base to form a chiral halide of the formula (III)



(III)

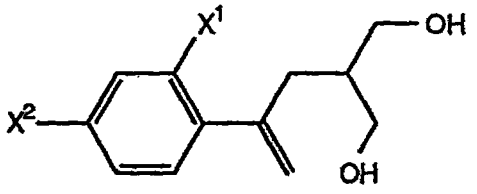
wherein X^1, X^2 and R are as defined above, and X^3 is Cl, Br or I; and

(b) treating the halide of formula (III) of step (a) with an alkali metal triazole or imidazole to form a chiral compound of the formula (III), wherein X^3 is imidazolyl or triazolyl; removing the

protecting group R to form an alcohol of the formula (III), wherein R is H; and treating the alcohol with a compound of the formula E-X, wherein X is Cl or Br, and E is as defined above, to form the compound of formula (I); or

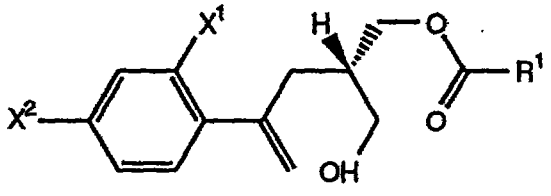
(bi) removing the protecting group R from the halide of formula (III) of Step (a) to form an alcohol of the formula (III), wherein R is H; treating the alcohol with an alkali metal triazole or imidazole to form a chiral compound of the formula (III), wherein X^3 is triazolyl or imidazolyl, and R is H; and treating the alcohol with a compound of the formula E-X, wherein X is Cl or Br, and E is as defined above, to form the compound of formula (I).

2. A process according to claim 1 wherein R is $-C(O)R^1$, and the starting compound of formula (II) of Step (a) is prepared by selectively esterifying a prochiral diol of the formula (IV)



(IV)

with an effective amount of a mild acylating agent in the presence of an enzyme to form the chiral hydroxy ester of formula (IIa)

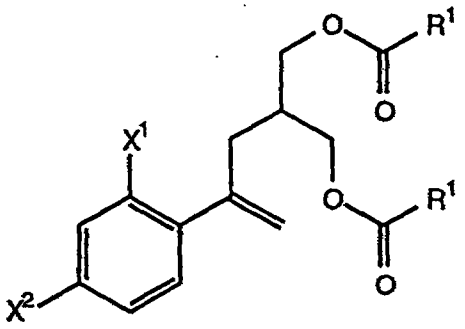


(IIa)

wherein X^1 and X^2 are as defined above, and R^1 is C_1-C_6 alkyl, aryl or $-(CH_2)_nCO_2H$, wherein n is 1, 2, 3 or 4.

3. A process according to claim 1 wherein R is $-C(O)R^1$, and the chiral hydroxy ester of formula (II) of Step (a) is prepared by a process comprising the steps:

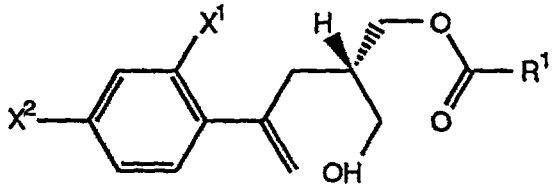
(i) esterifying the prochiral diol of formula (IV) with an amount of an acylating agent effective to form a diester of the formula (V)



(V)

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

(ii) stereoselectively hydrolyzing the diester of formula (V) of step (i) in the presence of an enzyme to form a chiral hydroxy ester of the formula (IIa)

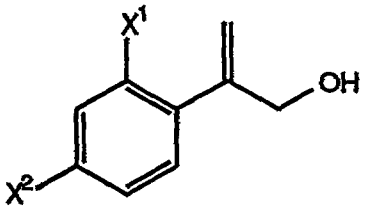


(IIa)

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

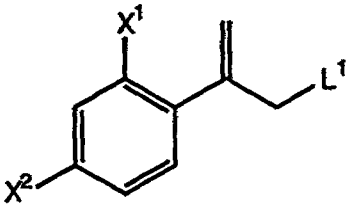
4. A process according to claims 2 or 3 wherein the prochiral diol of the formula (IV) is prepared via a process comprising the steps:

(A1) converting an allylic alcohol of the formula (VI)



(VI)

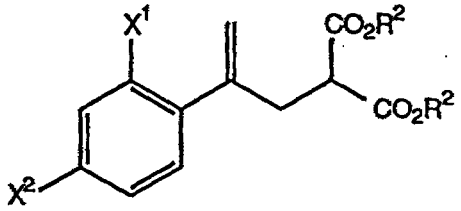
wherein X^1 and X^2 are as defined above, to a compound of the formula (VII)



(VII)

wherein X^1 and X^2 are as defined above and L^1 is a leaving group selected from halogeno, $-OSO_2CF_3$ and $-OSO_2R^6$, wherein R^6 is as defined above;

(A2) reacting the product of Step (A1) with an amount of an alkali metal salt of the anion derived from a di(C_1-C_6 alkyl)malonate effective to form a diester of the formula (VIII)



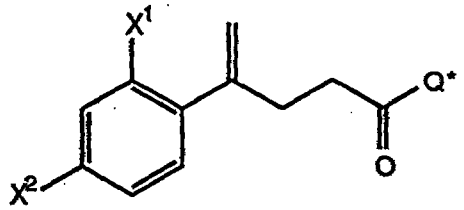
(VIII)

wherein X^1 and X^2 are as defined above, and R^2 is C_1-C_6 alkyl;

(A3) treating the diester of the formula (VIII) of Step (A2) with an amount of a hydride reducing agent effective to form the prochiral diol of the formula (IV).

5. A process according to claim 1 wherein the chiral alcohol of formula (II) of Step (a), wherein R is $-CH_2-C_6H_5$, is prepared by a process comprising the steps:

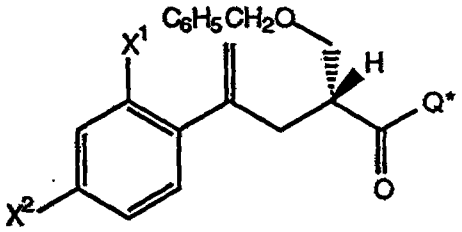
(B1) reacting a compound of the formula (IX)



(IX)

wherein X^1 and X^2 are as defined above and Q* is a chiral auxilary group, with a compound of the formula $C_6H_5CH_2$-O-CH_2L, wherein L is a leaving group selected from Cl, Br and I, in the presence of $TiCl_4$ and a tertiary amine base, in amounts effective to form a chiral compound of the formula (X)

* C L M S *



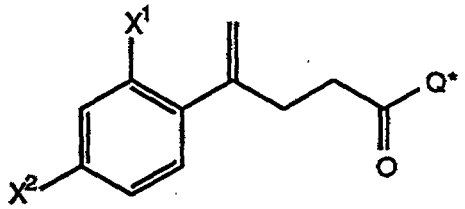
(X)

wherein X^1, X^2 and Q* are as defined above; and

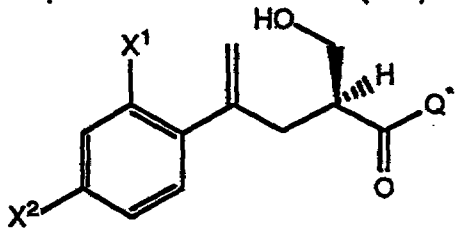
(B2) treating the product of formula (X) of Step (B1) with an amount of $LiAlH_4$ effective to form a chiral compound of the formula (II) wherein R is $-CH_2C_6H_5$.

6. A process according to claim 1 wherein the chiral halide of formula (III) of Step (a), wherein R is H, is prepared by a process comprising the steps:

(C1) treating a compound of the formula (IX)



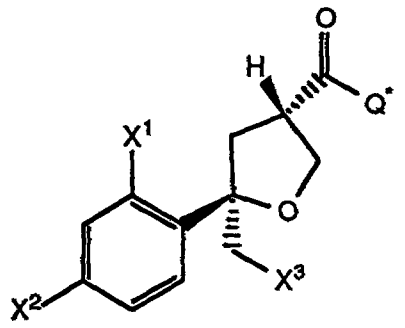
wherein X^1 and X^2 are as defined above and Q* is a chiral auxilary group,with effective amounts of trioxane, $TiCl_4$ and a tertiary amine base to form a chiral compound of the formula (XII)



(XII)

wherein X^1, X^2 and Q* are as defined above;

(C2) cyclizing a compound of the formula (XII) of Step (C1) by treating with effective amounts of a halogen and a base to form a chiral halide of the formula (XIII)

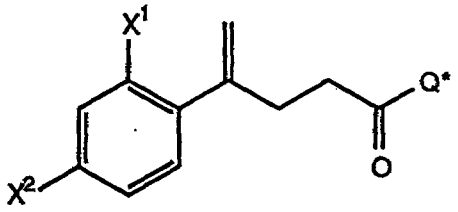


(XIII)

wherein X^3 is Cl, Br or I, and X^1, X^2 and Q^* are as defined above;

(C3) treating the chiral halide of formula (XIII) of Step (C3) with an amount of a hydride reducing agent effective to form a chiral halide of the formula (III), wherein R is H.

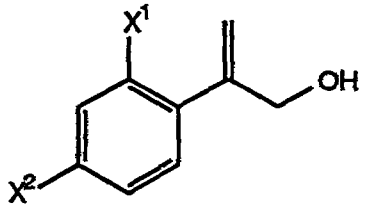
7. A process according to claims 5 or 6 wherein the starting compound of the formula (IX)



(IX)

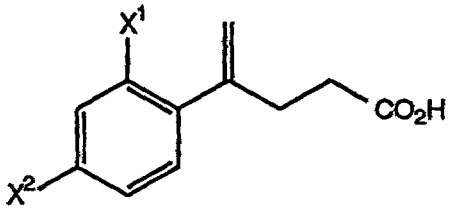
is prepared by a process comprising the steps:

(B3) heating an allylic alcohol of the formula (VI)



(VI)

wherein X^1 and X^2 are as defined above, with effective amounts of an orthoester of the formula $CH_3C(OR^2)_3$, wherein R^2 is C_1-C_6 alkyl, and a catalytic amount of R^2CO_2H, wherein R^2 is as defined above, followed by treatment with an amount of a hydroxide base effective to form an acid of the formula (XI)

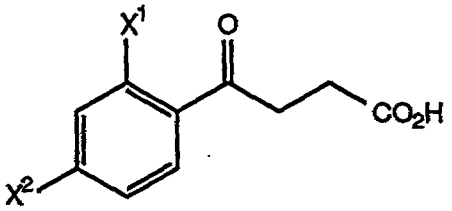


(XI)

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

(B4) treating the acid of formula (XI) of step (B3) with an effective amount of an activating agent, then with an alkali metal salt of the formula $M^+ {}^-Q^*$, wherein M^+ is an alkali metal cation and $^-Q^*$ is the anion derived from a compound of the formula HQ^*, wherein Q^* is as defined above, to form a compound of the formula (IX).

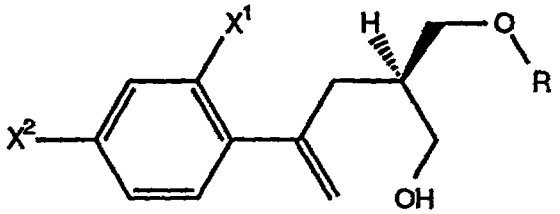
8. A process according to claim 7 wherein the acid (XI) of step (B3) is prepared by reacting 1-(X^1)-3-(X^2)-benzene, wherein X^1 and X^2 are as defined above, with succinic anhydride in the presence of a Lewis acid to form a keto acid of the formula



and treating the keto acid with $CH_3{\bullet}P(C_6H_5)_3{\bullet}Br$ and a nonaqeuous base to form the acid (XI).

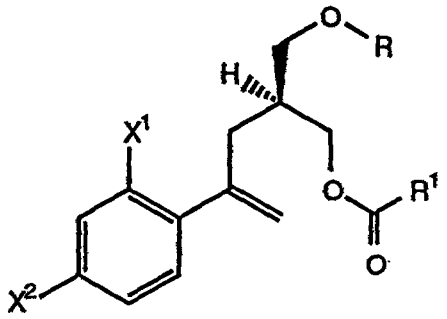
9. A process according to claim 1 wherein the chiral iodide of the formula (III) of Step (a), wherein R is $-C(O)R^1$, and R^1 is C_1-C_6 alkyl, is prepared by a process comprising the steps:

(D1) esterifying a chiral alcohol of the formula (II)



(II)

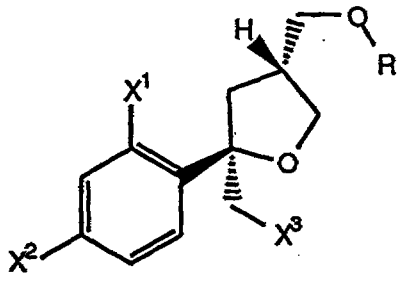
wherein X^1 and X^2 are as defined above, and R is $-CH_2-C_6H_5$, by treating with an effective amount of an acylating agent to form a chiral compound of the formula (XIX)



(XIX)

wherein X^1, X^2 are as defined above, R is $-CH_2C_6H_5$, and R^1 is C_1-C_6 alkyl; and

(D2) cyclizing the chiral product of formula (XIX) of Step (D1) by treating with a halogen to form a chiral halide of the formula (III)



(III)

wherein X^1, X^2 are as defined above, R is $-C(O)R^1$, R^1 is C_1-C_6 alkyl, and X^3 is Cl, Br or I.

10. A process according to claim 1 wherein:

(a) in Step (a): the halogen is Br_2 or I_2; the base is pyridine or $NaHCO_3$; and the cyclization is carried out in the presence of a solvent selected from CH_3CN, tetrahydrofuran, ethyl acetate and CH_2Cl_2; and

(b) in Step (b):

(1) the alkali metal triazole is sodium triazole, and the triazole treatment is carried out in the presence of DMPU and N,N-dimethylformamide at 70° to 100°C; and

(2) the protecting group R is removed from the triazole compound by:

* C L M S *

(i) where R is -C(O)R^1, and R_1 is C_1-C_6 alkyl, aryl or -$(CH_2)_nCO_2H$ wherein n is 1, 2, 3 or 4, treating with a base selected from K_2CO_3, Na_2CO_3 and NH_4OH, in the presence of methanol and water at 0° to 25°C; or

(ii) where R is tetrahydropyran-2-yl, treating with HCl and water at 15° to 35°C; or

(iii) where R is -$CH_2C_6H_5$, hydrogenating in the presence of a Pd on carbon catalyst, an acid, and ethanol;

to form the alcohol wherein R is H and X^3 is triazolyl; or

(b1) in Step (bi):

(1) the protecting group R is removed by:

(i) where R is -C(O)R^1, and R_1 is C_1-C_6 alkyl, aryl or -$(CH_2)_nCO_2H$ wherein n is 1, 2, 3 or 4, treating with a base selected from K_2CO_3, Na_2CO_3 and NH_4OH, in the presence of methanol and water at 0° to 25°C; or

(ii) where R is tetrahydropyran-2-yl, treating with HCl and water at 15° to 35°C; or

(iii) where R is -$CH_2C_6H_5$, hydrogenating in the presence of a Pd on carbon catalyst, an acid, and ethanol; and

(2) the alkali metal triazole is sodium triazole, and the triazole treatment is carried out in the presence of DMPU and N,N-dimethylformamide at 70° to 100°C;

to form the alcohol wherein R is H and X^3 is triazolyl; and

(3) the treatment with E-X is carried out in the presence of pyridine, and X is Cl.

11. A process according to claim 2 wherein: the mild acylating agent is selected from vinyl acetate, isopropenyl acetate, methyl acetate and ethyl acetate; and the enzyme is selected from Amano CE (*Humicloa lanugiosa*), Amano AY-30, Biocatalysts *H. lanugiosa*, Biocatalysts *M. meihei*, Biocatalysts *Ps. fluorescens*, Meito MY, Meito PL, Novo Lipozyme IM-20, and Novo SP435 (*Candida antartica*).

12. A process according to claim 3 wherein: the acylating agent is selected from butyric anhydride, acetic anhydride or acetyl

chloride; and the enzyme is selected from Amano CE (*Humicloa lanugiosa*), Amano AY-30, Biocatalysts *H. lanugiosa*, Biocatalysts *M. meihei*, Biocatalysts *Ps. fluorescens*, Meito MY, Meito PL, Novo Lipozyme IM-20, and Novo SP435 (*Candida antartica*).

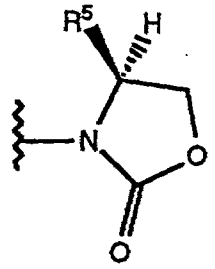
13. A process according to claim 4 wherein:

in Step (A1), the converting is effected by treating with a brominating agent or a sulfonylating agent;

in Step (A2), the alkali metal salt is a sodium salt and the dialkylmalonate is diethylmalonate; and

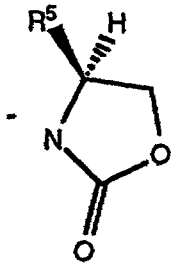
in Step (A3), the hydride reducing agent is $LiAlH_4$ or $LiBH_4$.

14. A process according to claim 5 wherein in Step (B1), L is Cl, the tertiary amine base is triethylamine, and the chiral auxilary Q^* is an oxazolidinone of the formula



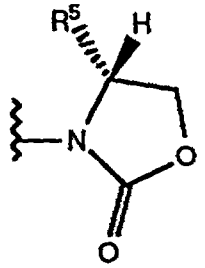
wherein R^5 is isopropyl.

15. A process according to claim 7 wherein: in Step (B3), the hydroxide base is KOH or NaOH; and in step (B4), the activating agent is oxalyl chloride or $SOCl_2$, M^+ is Li^+, and $^-Q^*$ is



wherein R^5 is isopropyl.

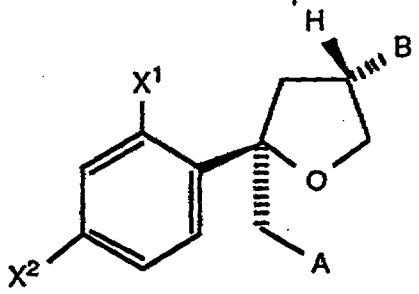
16. A process according to claim 6 wherein: Q^* is an oxazolidinone of the formula



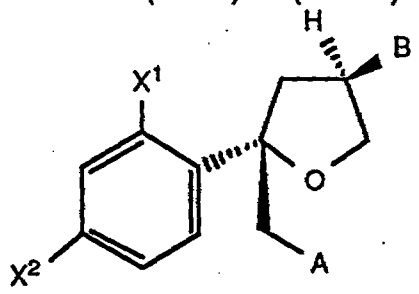
wherein R^5 is $-CH_2C_6H_5$; in Step (C2) the halogen is Br_2 or I_2, and the base is pyridine; and in Step (C3) the hydride reducing agent is $LiBH_4$.

17. A process according to claim 9 wherein: in Step (D1), the acetylating agent is acetic anhydride; and in Step (D2), the halogen is I_2.

18. A chiral compound of the formula (XVII) or (XVIII)



(XVII)



(XVIII)

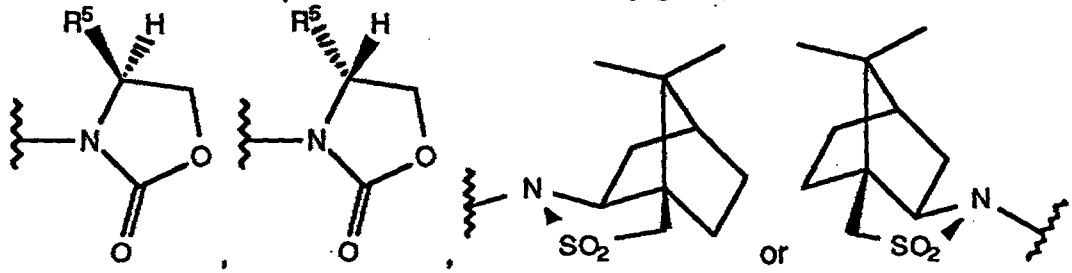
wherein: X^1 and X^2 are independently F or Cl;

A represents Cl, Br, I, triazolyl or imidazolyl

B represents $-C(O)Q^*$ or $-CH_2OR''$;

R'' represents a hydroxy protecting group selected from $-CH_2C_6H_5$, or $-C(O)R^1$, wherein R^1 is C_1-C_6 alkyl, aryl or $-(CH_2)_nCO_2H$ wherein n is 1, 2, 3 or 4; and

Q^* represents a chiral auxilary group selected from

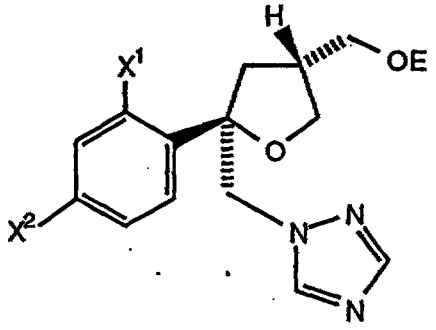


wherein R^5 is isopropyl or benzyl.

PROCESS FOR PREPARING INTERMEDIATES FOR THE SYNTHESIS OF ANTIFUNGAL AGENTS

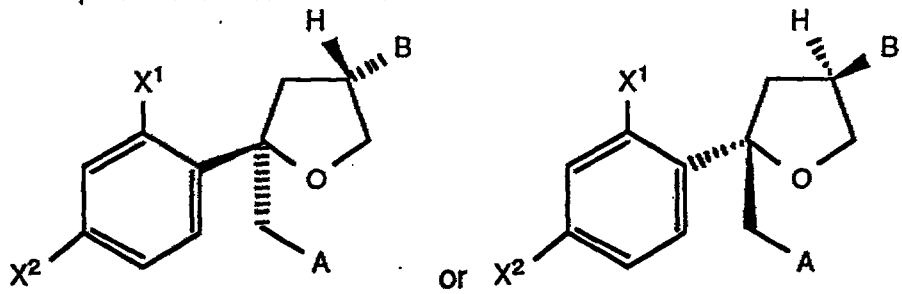
ABSTRACT

Disclosed is a process for preparing chiral compounds of the formula (I)



(I)

wherein: X^1 and X^2 are independently F or Cl; and E is $-SO_2R^2$, wherein R^2 is C_1-C_6 alkyl, $-C_6H_4CH_3$ or $-CF_3$; its enantiomer and racemates thereof, useful in the synthesis of tetrahydrofuran azole antifungals. Novel compounds of the formula



wherein: X^1 and X^2 are independently F or Cl; B represents $-C(O)Q^*$ or $-CH_2OR^"$; Q^* represents a chiral auxillary group; $R^"$ represents a hydroxy protecting group; and A represents Cl, Br, I, triazolyl or imidazolyl; are also disclosed.