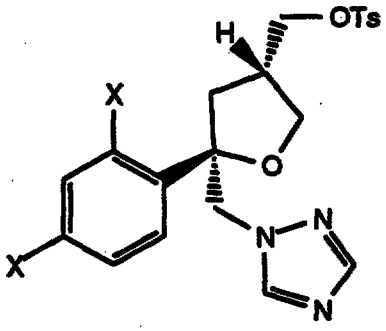
PROCESS FOR THE PREPARATION OF CHIRAL INTERMEDIATES USEFUL FOR THE SYNTHESIS OF ANTIFUNGAL AGENTS

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.

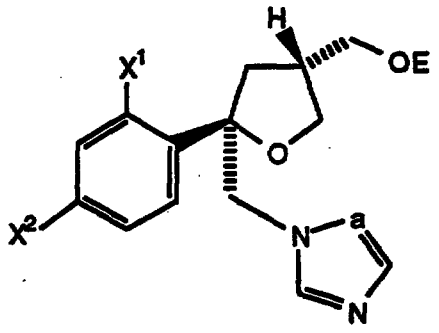
PCT International Publication No. WO 89/04829, U.S. Patent No. 5,039,676, and PCT International Publication No. WO 93/09114 disclose substituted tetrahydrofuran azole and imidazole compounds having utility as antifungal agents. A number of processes for the synthesis of these compounds are known.

PCT International Application No. PCT/US92/08981 discloses a process for the synthesis of tri-substituted tetrahydrofuran azole antifungals via a tosylate intermediate of the formula



wherein X is both F or both Cl or one X is F and the other is Cl.

PCT International Application No. PCT/US94/04355 describes a process for preparing chiral intermediates of the formula (I)

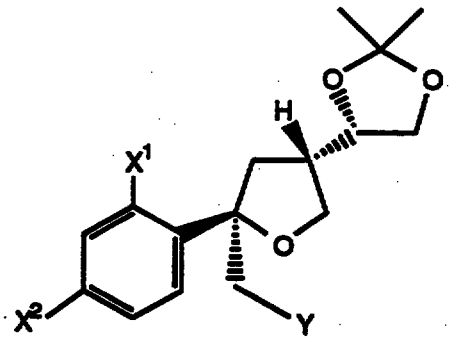


(I)

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 $-CF_3$. Compounds of the formula (I) are useful as intermediates in the preparation of tetrahydrofuran azole or imidazole antifungal agents.

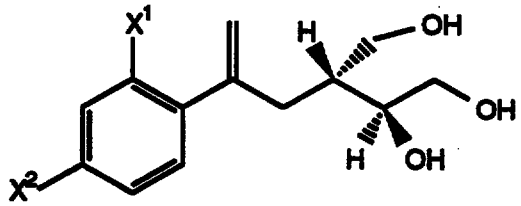
SUMMARY OF THE INVENTION

The present invention provides a process for preparing chiral compounds of the formula (II)



(II)

wherein X^1 and X^2 are independently F or Cl, and Y is Cl, Br or I. The process of the present invention comprises reacting a triol of the formula

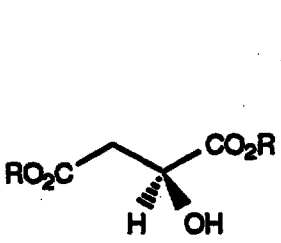
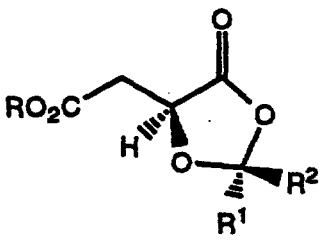


wherein X^1 and X^2 are as defined above, with acetone in the presence of a catalyst, then with a halogen selected from Cl_2, Br_2 or I_2, or with NBS or NIS, to form a compound of formula (II).

Preferably the catalyst is I_2.

The present invention also provides a process for preparing a compound of the formula (II) comprising the steps:

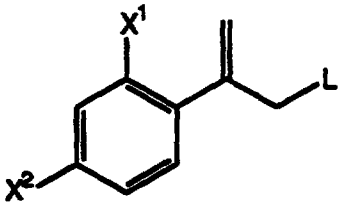
(a) using a nonaqueous base to deprotonate a chiral compound of the formula

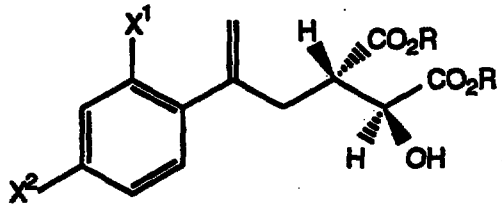
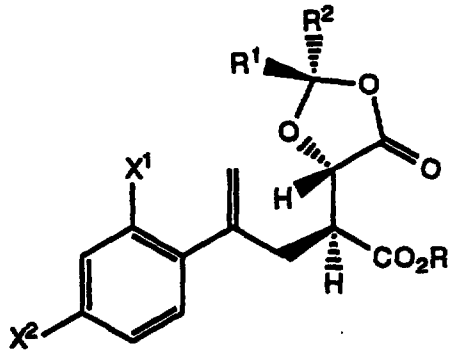
or

wherein: R is C_1-C_6 alkyl;

one of R^1 or R^2 is H and the other is $-C(CH_3)_3$ or $-CCl_3$, or R^1 and R^2 are both C_1-C_6 alkyl, or R^1 and R^2 together with the carbon to which they are attached comprise a 6-membered carbocyclic ring, then treating with a compound of the formula



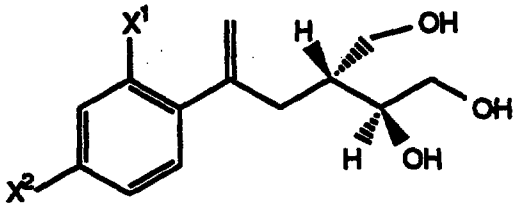
wherein X^1 and X^2 are as defined above and L is a leaving group, to form a chiral compound of the formula

or

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

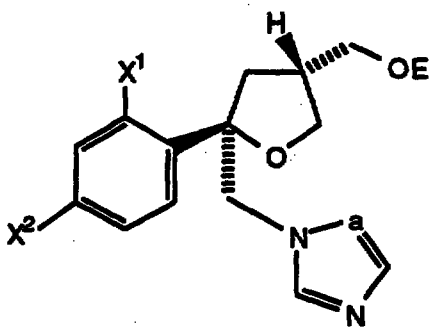
(b) reducing the product of step (a) with a hydride reducing agent to form a chiral triol of the formula



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

(c) reacting the triol of step (b) with acetone in the presence of a catalyst, then with a halogen selected from Cl_2, Br_2 or I_2, or with NBS or NIS, to form a chiral compound of formula (II).

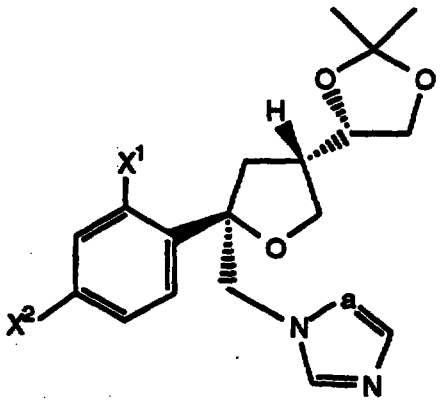
The present invention further provides a process for converting a compound of the formula (II) to a compound of the formula (I)



(I)

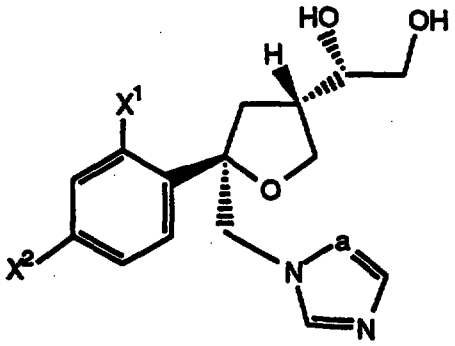
wherein: a is CH or N; X^1 and X^2 are independently F or Cl; and E is $-SO_2R^6$, wherein R^6 is C_1-C_6 alkyl, aryl, substituted aryl or $-CF_3$, comprising the steps:

(d) treating a compound of formula (II) with an alkali metal triazole or imidazole to form a chiral compound of the formula

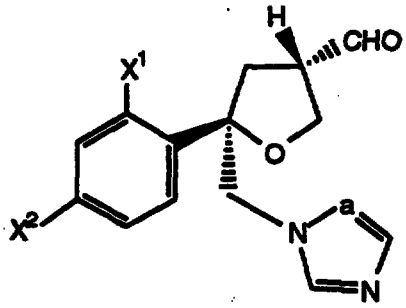


wherein a, X^1 and X^2 are as defined above;

(e) hydrolyzing the product of step(d) with an aqueous acid to form a diol intermediate of the formula

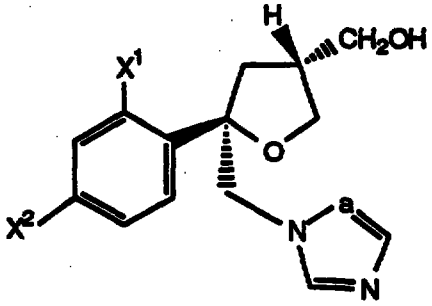


followed by oxidatively cleaving the diol using H_5IO_6, $NaIO_4$ or $Pb(OAc)_4$ to form an aldehyde of the formula



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

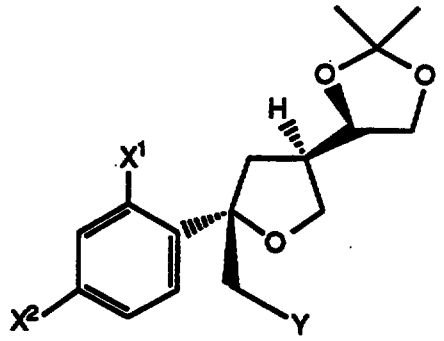
(f) reducing the aldehyde of step (e) with a hydride reducing agent to form an alcohol of the formula



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

(g) treating the alcohol of step (f) with a compound of the formula E-X, wherein X is Cl or Br, and E is as defined above, to form a compound of formula (I).

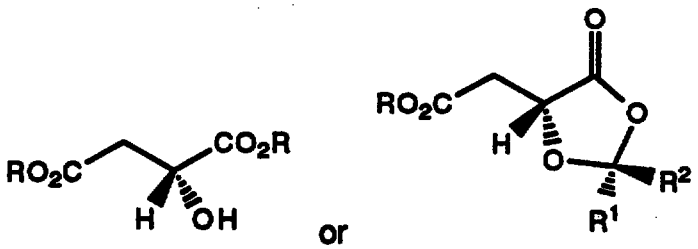
In an alternative embodiment, the present invention provides a process for preparing a compound of the formula (III)



(III)

Compounds of the formula (III) are enantiomers of compounds of the formula (II). In this embodiment the process of the present invention comprises the steps:

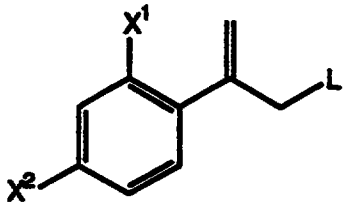
(ai) using a nonaqueous base to deprotonate a chiral compound of the formula



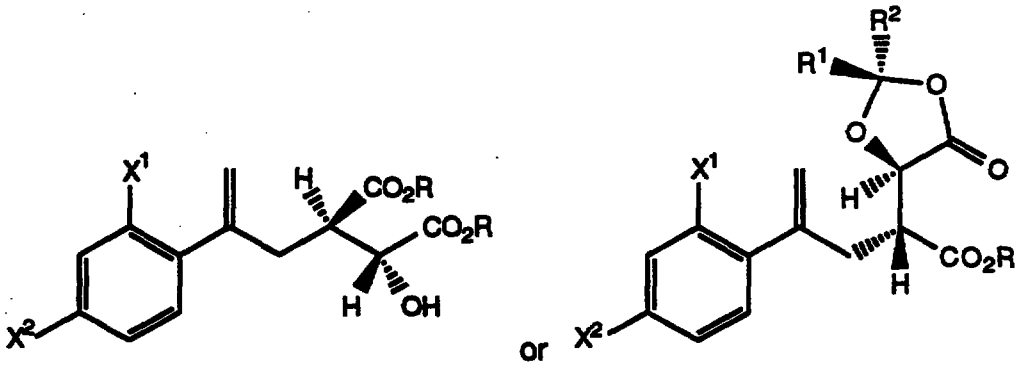
or

wherein: R is C_1-C_6 alkyl;

one of R^1 or R^2 is H and the other is $-C(CH_3)_3$ or $-CCl_3$, or R^1 and R^2 are both C_1-C_6 alkyl, or R^1 and R^2 together with the carbon to which they are attached comprise a 6-membered carbocyclic ring, then treating with a compound of the formula

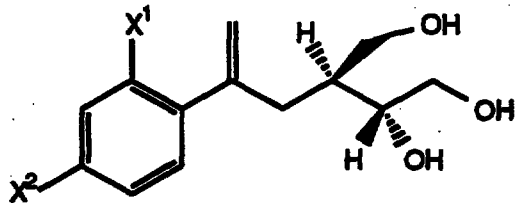


wherein X^1 and X^2 are as defined above and L is a leaving group, to form a chiral compound of the formula



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

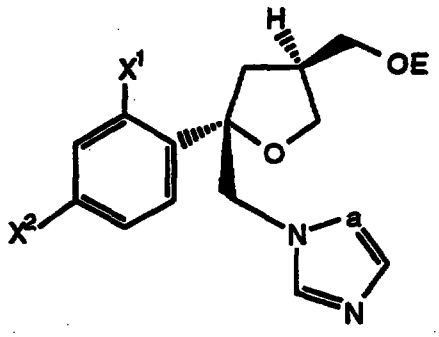
(bi) reducing the product of step (ai) with a reducing agent to form a chiral triol of the formula



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

(ci) reacting the triol of step (bi) with acetone in the presence of a catalyst, then with a halogen selected from Cl_2, Br_2 or I_2, or with NBS or NIS, to form a chiral compound of formula (III).

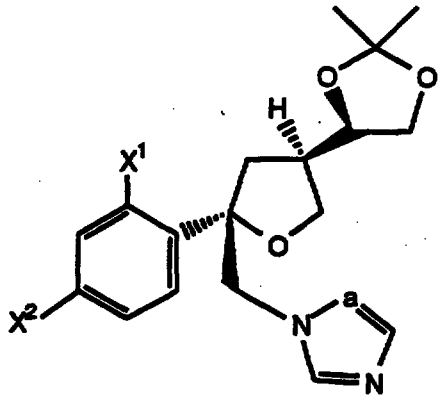
In this embodiment, the present invention further comprises a process for converting a compound of the formula (III) to an enantiomer of a compound of formula (I), i.e., a compound of the formula (IV)



(IV)

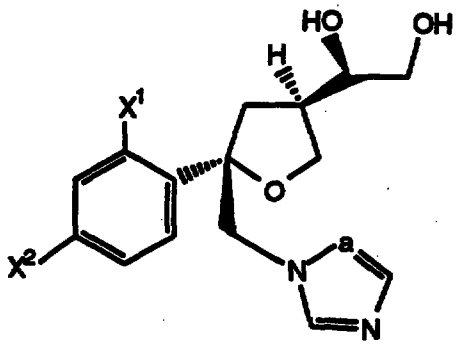
wherein: a is CH or N; X^1 and X^2 are independently F or Cl; and E is $-SO_2R^6$, wherein R^6 is C_1-C_6 alkyl, aryl, substituted aryl or $-CF_3$, comprising the steps:

(di) treating a compound of formula (III) with an alkali metal triazole or imidazole to form a chiral compound of the formula

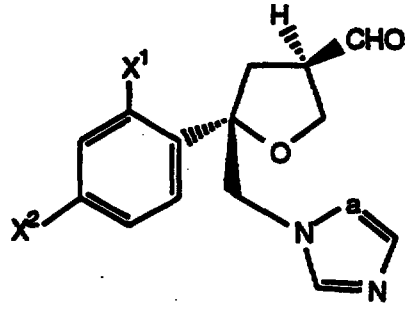


wherein a, X^1 and X^2 are as defined above;

(ei) hydrolyzing the product of step(di) with an aqueous acid to form a diol intermediate of the formula

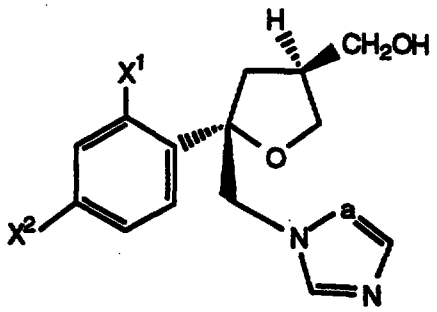


followed by oxidatively cleaving the diol using H_5IO_6, $NaIO_4$ or $Pb(OAc)_4$ to form an aldehyde of the formula



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

(fi) reducing the aldehyde of step (ei) with a hydride reducing agent to form an alcohol of the formula



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

(gi) treating the alcohol of step (fi) with a compound of the formula E-X, wherein X is Cl or Br, and E is as defined above, to form a compound of formula (IV).

DETAILED DESCRIPTION

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;

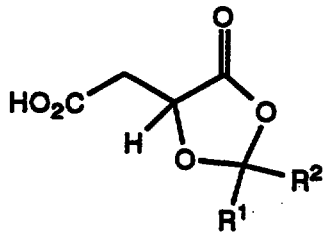
"halogeno" means Cl, Br or I;

"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 $-CF_3$;

"hydride reducing agent" means $LiAlH_4$, $NaBH_4$, $LiBH_4$, $NaBH_3CN$, or a combination of $NaBH_4$ and LiCl;

"catalyst" means a reagent capable of catalyzing the reaction of acetone with the chiral triols of steps (b) and (bi) to form a cyclic ketal group, and is preferably iodine;

"acid catalyst" means a Lewis acid, such as $BF_3 \cdot OEt_2$, or protic acid, such as p-TSA or H_2SO_4, capable of catalyzing the reaction between a ketone or aldehyde and malic acid to form compound of the general formula



as described herein;

"aqueous acid" means an aqueous solution of an acid, such as HCl;

"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;

"base" means a basic compound capable of deprotonating a carboxylic acid and catalyzing an esterification reaction, including moderate bases, hydroxide bases, tertiary amine bases, Bu_4NOH and Bu_4NF.

"moderate base" means Na_2CO_3, Li_2CO_3 or K_2CO_3;

"hydroxide base" means an alkali metal hydroxide, such as NaOH, KOH, LiOH;

"tertiary amine base" means bases such as pyridine, DMAP, Et_3N and Hünigs base;

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

"organic water miscible solvent" means an organic solvent which is soluble in water, and which is suitable for use with hydride reducing agents, such solvents including THF or C_1-C_6 alkanols, such as MeOH, EtOH and iPrOH.

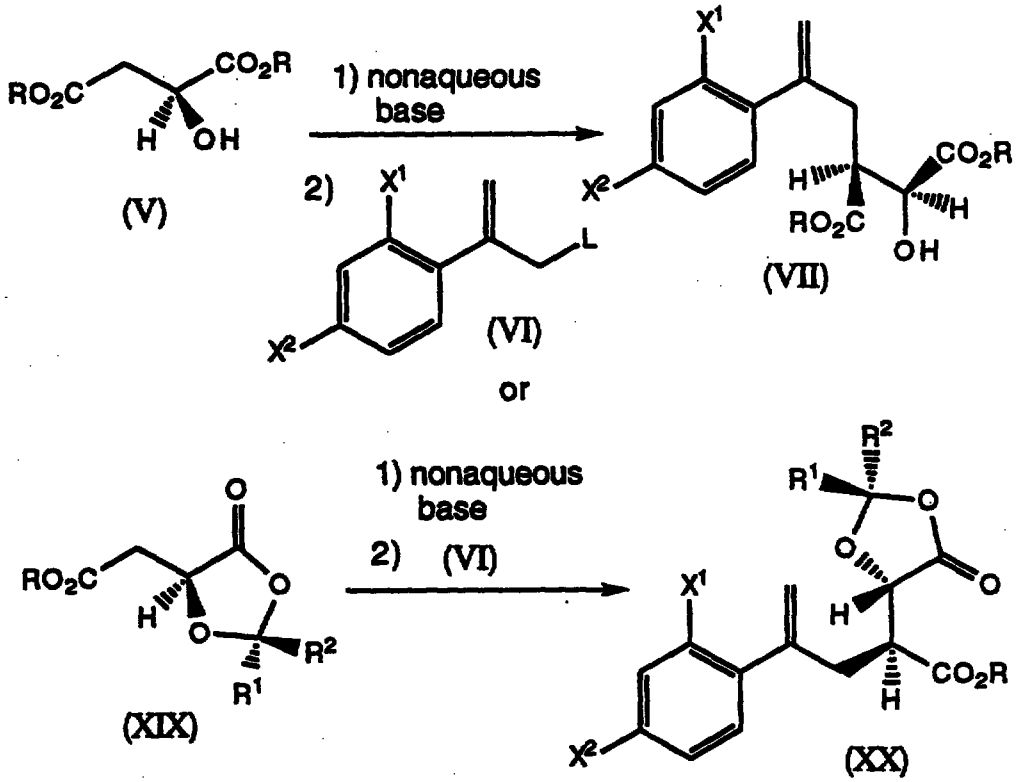
As used herein the following reagents and solvents are identified by the abbreviations indicated: methanol (MeOH); tetrahydrofuran (THF); diethyl ether (Et_2O); t-butyl methyl ether (TBME); lithium di-isopropylamide (LDA); triethylamine (Et_3N); di-isopropylethylamine (Hünigs base); ethyl acetate (EtOAc); ethanol

(EtOH); N,N-dimethylformamide (DMF); lithium hexamethyldisilazide (LiHMDS); 4-dimethylaminopyridine (DMAP); p-toluenesulfonyl chloride (tosyl chloride or TsCl); methanesulfonyl chloride (mesyl chloride or MsCl); p-toluenesulfonic acid (p-TSA); tetrabutylammonium hydroxide (Bu_4NOH); tetrabutylammonium fluoride (Bu_4NF); trimethylsilyltriflate (TMSOTf); (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((R)-MTPACl); lead tetraacetate ($Pb(OAc)_4$); N-bromosuccinimide (NBS); N-iodosuccinimide (NIS).

The present invention comprises a process for preparing a compound of the formula (II) and for converting the compound of formula (II) into a compound of the formula (I), as shown in Reaction Scheme 1.

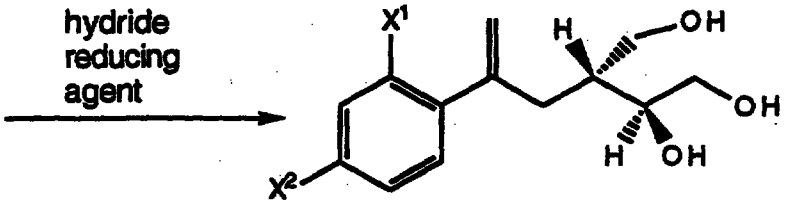
Reaction Scheme 1

Step (a)



Step (b)

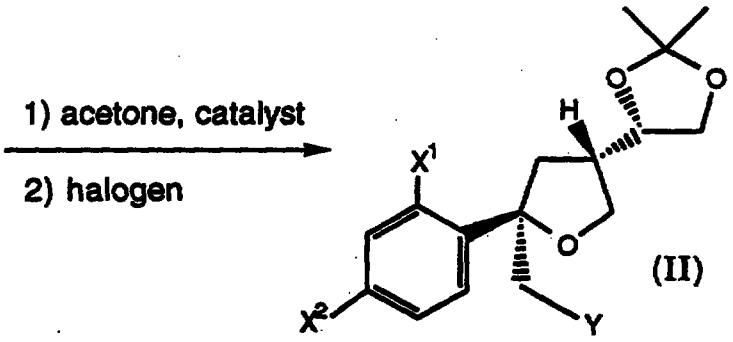
(VII)
or
(XX)



(VIII)

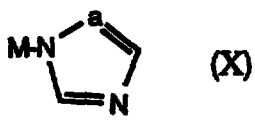
Step (c)

(VIII)



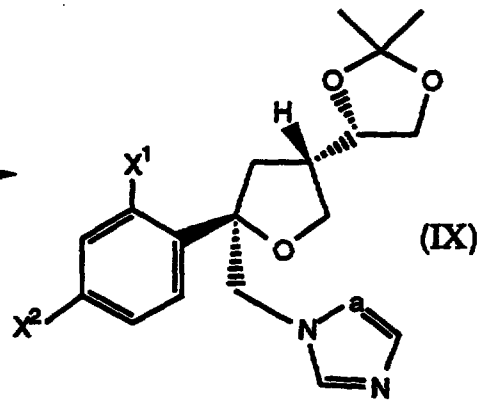
(II)

Step (d)



(X)

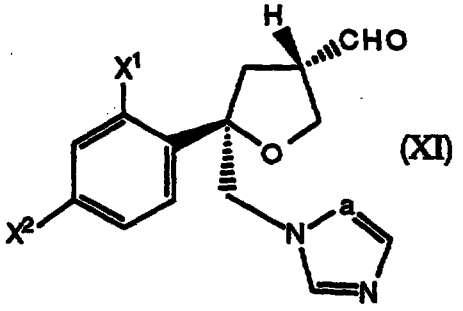
(II)



(IX)

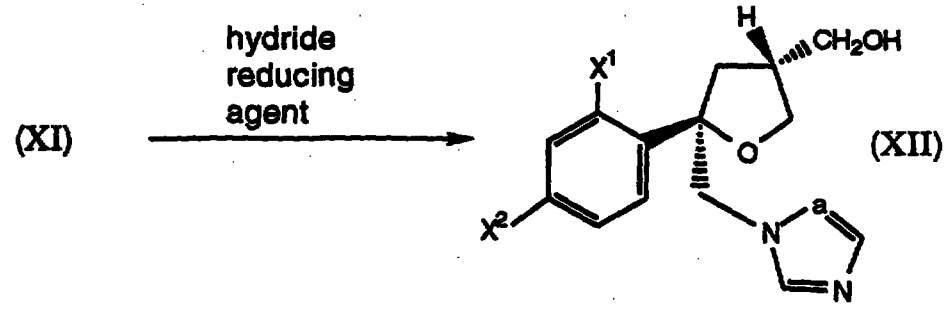
Step (e)

(IX)

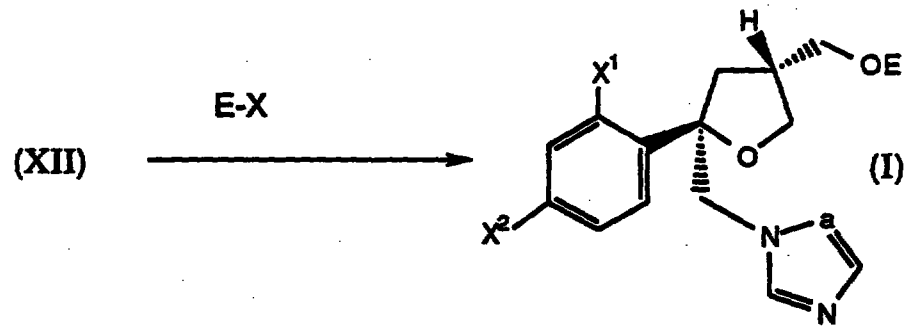


(XI)

Step (f)



Step (g)



In Step (a) of Reaction Scheme 1, a diester of L-malic acid (V) wherein R is C_1-C_6 alkyl, or a L-malic acid derivative of the formula (XIX) wherein R, R^1 and R^2 are as defined above, is deprotonated by treating with a nonaqueous base, such as LiHMDS, in a suitable solvent, such as THF, at -100° to 0°C, preferably at -80°C to -20°C, and the resulting anion reacted with a compound of the formula (VI), wherein X^1, X^2 and L are as defined above, at -100° to 0°C, preferably at -80°C to -10°C, then quenched with KH_2PO_4 (aqueous) and extracted with an organic solvent, such as EtOAc, to give the product (VII) or (XX), respectively.

In Step (b), compound (VII) or (XX) is treated with a hydride reducing agent, such as $LiBH_4$ or a mixture of $NaBH_4$ and LiCl, in a suitable solvent, such as an organic water miscible solvent, preferably THF, MeOH, EtOH or iPrOH, and optionally in the presence of water, at -30° to 50°C, preferably at -10° to 30°C, and most preferably at 0° to 25°C, to give the triol product (VIII). When using a more reactive

hydride reducing agent, such as $LiAlH_4$, the reaction is carried out under anhydrous conditions in an organic solvent such as THF or Et_2O.

In Step (c), the triol (VIII) is reacted with acetone and a catalyst, such as a catalytic amount of I_2, at 0° to 50°C, preferably at 10° to 30°C, and most preferably at about 25°C. The reaction mixture is treated with a halogen, preferably I_2, and a moderate base, such as Na_2CO_3, or alternatively with NBS or NIS, at -50° to 25°C, preferably about -30° to 0°C, then quenched with a mixture of $Na_2S_2O_3$, water and a moderate base, such as K_2CO_3, and extracted with an organic solvent, such as EtOAc to give a compound of the formula (II).

In Step (d), a compound of formula (II) is treated with an alkali metal triazole or imidazole of formula (X), wherein M is an alkali metal selected from Li, Na or K, and a is as defined above, at 50° to 150°C, preferably at 80°-120°C, and most preferably at 100°-110°C, in a suitable solvent, such as DMSO or DMF, to give the product (IX).

In Step (e), a compound (IX) is hydrolyzed by treating with an aqueous acid, such as aqueous HCl, and a suitable solvent, such as THF at 0° to 50°C, preferably at 20° to 30°C, then treated with H_5IO_6, $NaIO_4$ or $Pb(OAc)_4$, at 0° to 50°C, preferably at 20° to 30°C, then quenched with a mixture of $Na_2S_2O_3$, water and a moderate base, such as K_2CO_3, and extracted with an organic solvent, such as EtOAc, to give the aldehyde (XI).

In Step (f), the aldehyde (XI) is treated with a hydride reducing agent, such as $NaBH_4$, in a suitable solvent, such as an organic water miscible solvent, preferably THF, MeOH, EtOH or iPrOH, preferably MeOH or iPrOH, at -30° to 50°C, preferably at -10° to 30°C, and most preferably at 0° to 25°C, to give an alcohol of the formula (XII). When using a more reactive hydride reducing agent, such as $LiAlH_4$, the reaction is carried out under anhydrous conditions in an organic solvent such as THF or Et_2O.

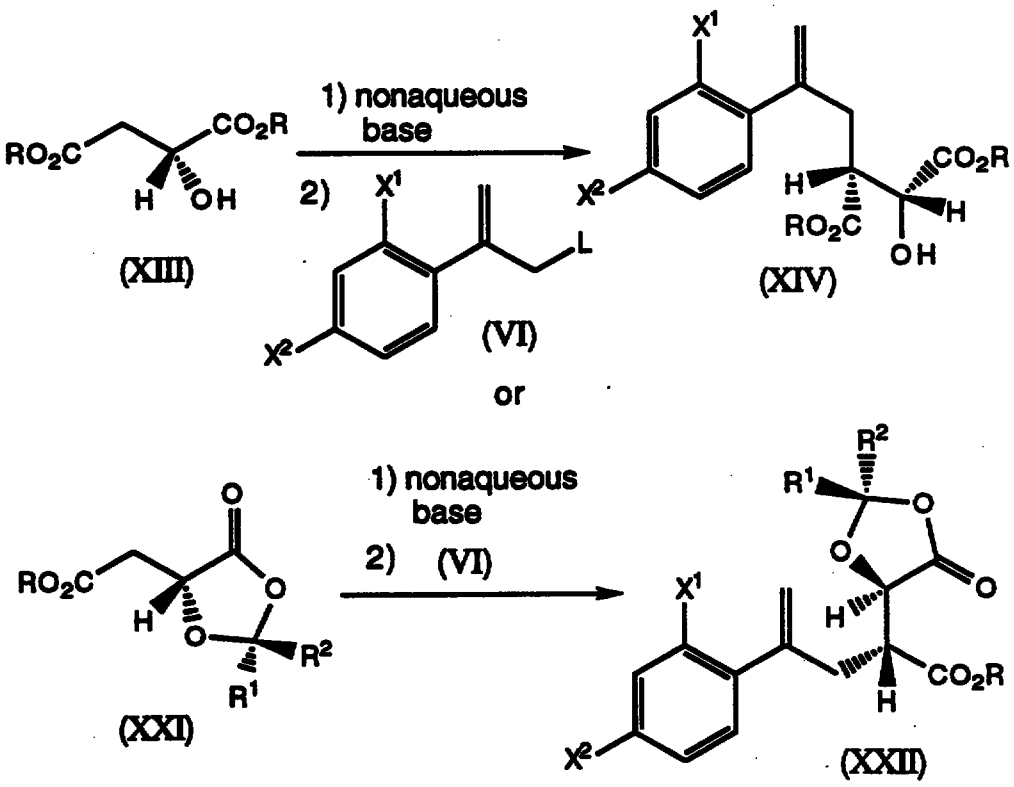
In Step (g), the alcohol (XII) is treated with a compound of the formula E-X, wherein X is Cl or Br, preferably Cl, and E is as defined above, preferably $-SO_2C_6H_4CH_3$ or $-SO_2C_6H_4Cl$, in the presence of a base and a suitable solvent to form a compound of the formula (I). Where the base is a hydroxide base, such as NaOH, the solvent is

preferably THF, and where the base is a tertiary amine base, such as pyridine, the solvent is preferably CH_2Cl_2,

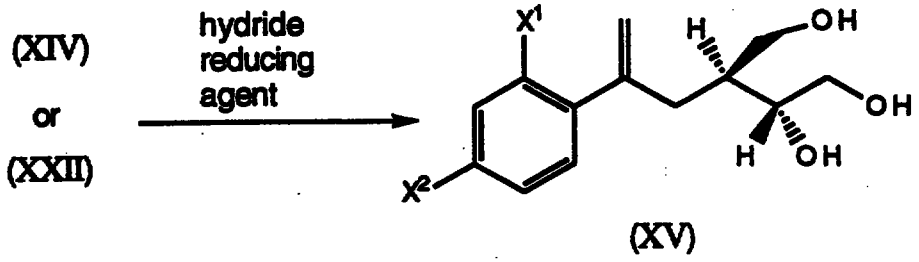
In an alternative embodiment the present invention comprises a process for preparing an enantiomer of a compound (II), e.g. a compound of the formula (III), and for converting compound (III) to an enantiomer of compound (I), e.g. a compound of the formula (IV), as shown in Reaction Scheme 2.

Reaction Scheme 2

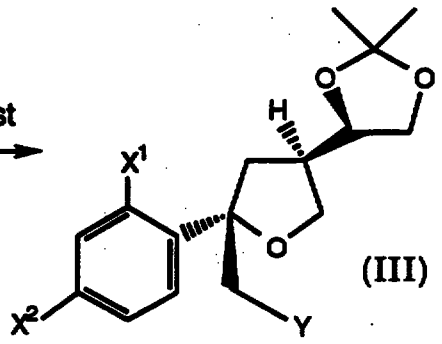
Step (ai)



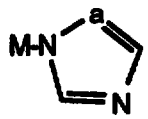
Step (bi)

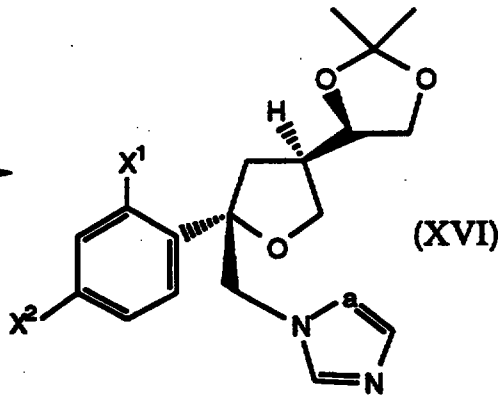


Step (ci)

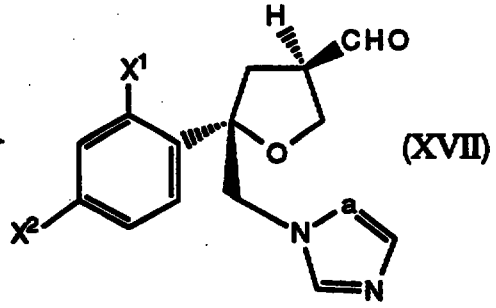
(XV) —1) acetone, catalyst; 2) halogen→  (III)

Step (di)

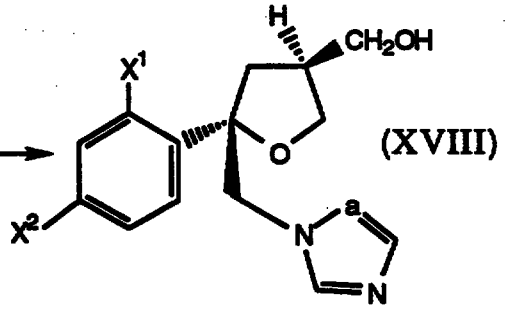
 (X)

(III) →  (XVI)

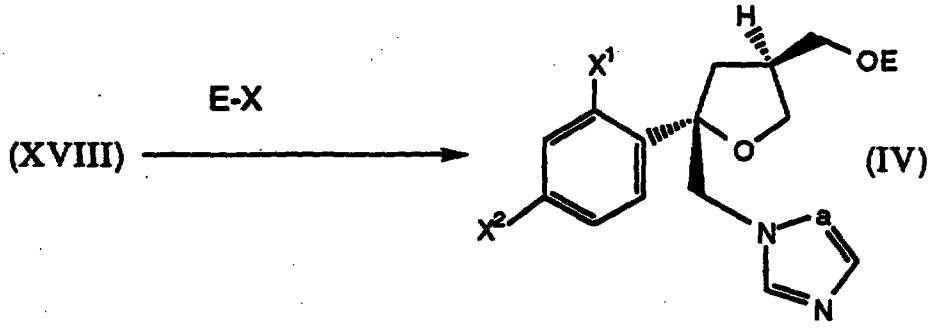
Step (ei)

(XVI) —1) aqueous acid; 2) H_5IO_6→  (XVII)

Step (fi)

(XVII) —hydride reducing agent→  (XVIII)

Step (gi)

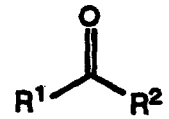


In Step (ai) of Reaction Scheme 2, a diester of D-malic acid (XIII) wherein R is C_1-C_6 alkyl, or a D-malic acid derivative of the formula (XXI) wherein R, R^1 and R^2 are as defined above, is converted to the product (XIV) or (XXII), respectively, via essentially the same procedure as described for Step (a) of Reaction Scheme 1.

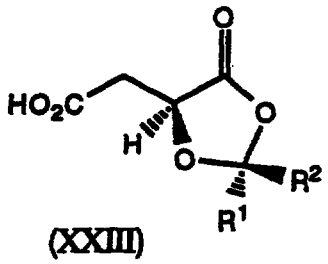
Steps (bi) through (gi) are carried out via essentially the same procedures as described for Steps (b) through (g) of Reaction Scheme 1 to give compounds of formulae (III) and (IV).

Compounds of the formula (V) and (XIII) are known and can be prepared via esterification of L- or D-malic acid, respectively, using standard methods.

Compounds of the formula (XIX) and (XXI) can be prepared from L- or D-malic acid, respectively, using standard methods. For example, by reacting L- or D-malic acid with a compound of the formula

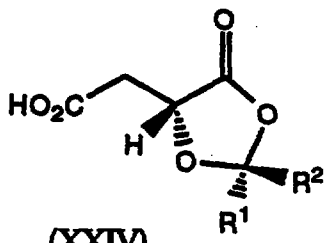


wherein R^1 and R^2 are as defined above, in the presence of an acid catalyst, such as BF_3•OEt_2, p-TSA, or H_2SO_4, in a suitable solvent, such as CH_2Cl_2, pentane, THF or toluene, to form a compound of the formula



(XXIII)

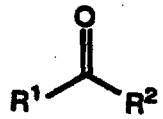
or



(XXIV)

respectively. The compound (XXIII) or (XXIV) is then esterified using standard methods, such as treating with diazomethane in an ether solvent, such as Et_2O or THF, or treating with a compound of the formula R-L, wherein R and L are as defined above, in the presence of a base to form the desired compound (XIX) or (XXI), respectively.

Compounds of the formula (XIX) or (XXI) can also be prepared from a compound of the formula (V) or (XIII), respectively, by treating (V) or (XIII) with a compound of the formula



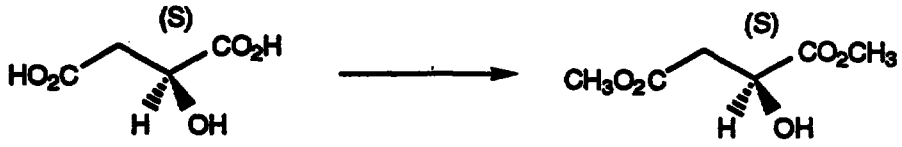
wherein R^1 and R^2 are as defined above, in the presence of an acid catalyst, such as $BF_3 \cdot OEt_2$, p-TSA, or H_2SO_4, in a suitable solvent, such as CH_2Cl_2, pentane, THF or toluene.

Compounds of the formula (XIX) or (XXI), wherein one of R^1 or R^2 is H and the other is $-C(CH_3)_3$, can also be prepared by reacting L- or D-malic acid, respectively, with $[(CH_3)_3Si]_2NH$ and $(CH_3)_3SiCl$, followed by treatment with $(CH_3)_3CCHO$ in the presence of TMSOTf in a suitable solvent, such as CH_2Cl_2, at -40° to 10°C, preferably at -25° to 0°C.

Compounds of the formula (VI) and (X) are known and can be readily prepared via established methods.

The following preparations and examples are illustrative of the process of the present invention.

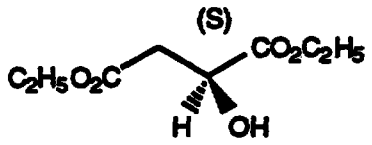
PREPARATION 1



P-1A

Combine 6.7 g (50 mmol) of (-)-L-malic acid and 100 mL of MeOH, then add 0.95 g (50 mmol) of p-TSOH. Heat the mixture at reflux for 12 h., then cool to room temperature and concentrate *in vacuo* to a residue. Dissolve the residue in 30 mL of CH_2Cl_2 and wash with 30 mL of saturated $NaHCO_3$ (aqueous). Extract the aqueous layer with CH_2Cl_2 (3 X 10 mL), combine the organic phases and dry over anhydrous $MgSO_4$. Concentrate *in vacuo* to give 6.35 g (78% yield) of the product P-1A. MS m/z 163.2 (M+1).

Using essentially the same procedure compounds P-1B and P-1C were prepared by substituting EtOH, or iPrOH, respectively, for MeOH:

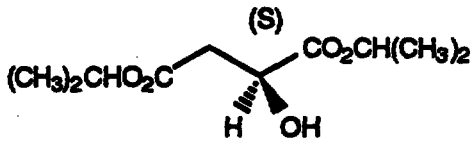


P-1B

MS m/z 191.25 (M+1)

$[\alpha]_D^{27} = -12.2°$

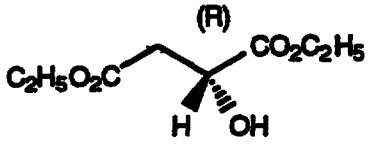
(c = 1.0, MeOH)



P-1C

MS m/z 219.25 (M+1)

The (R)-isomer of compound P-1B, (e.g. compound P-1D) was also prepared from (R)-(+)-L-malic acid via essentially the same procedure:



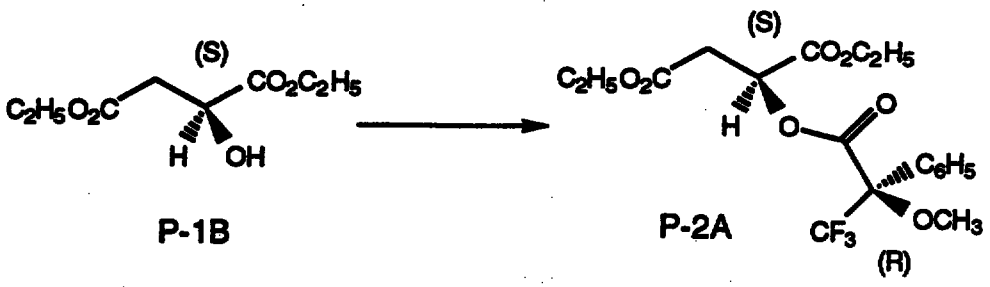
P-1D

MS m/z 191.25 (M+1)

$[\alpha]_D^{27} = +12.0°$

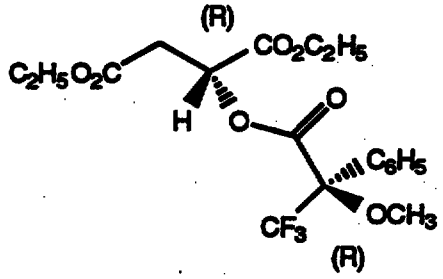
(c = 1.0, MeOH)

PREPARATION 2



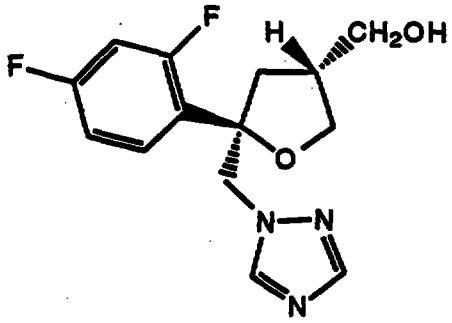
P-1B P-2A

The Enantiomeric purity of compound P-1B was determined by treating a solution of 57 mg (0.3 mmol) of compound P-1B in 0.5 mL of CH_2Cl_2 with 0.3 mL of pyridine and 101 mg (0.4 mmol) of (R)-MTPACl at 0°-10°C. Stir the mixture for 1 h. at room temperature, then add 0.5 mL of 5% HCl (aqueous). Extract the aqueous phase with CH_2Cl_2, combine the organic phases and dry over $MgSO_4$. Concentrate *in vacuo* to give 180 mg of the product. Analyze the product by ^1H NMR ($CDCl_3$, 300 MHz) to determine the ratio of diastereomers: 98% (S),(R)-isomer (compound P-2A) at 3.62 ppm (doublet, J = 1.16 Hz) and 2% (R),(R)-isomer (compound P-2B) 3.54 ppm, (doublet, J = 1.10 Hz).

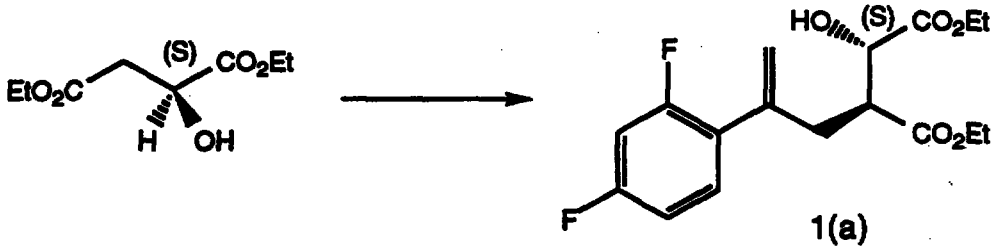


P-2B

EXAMPLE 1



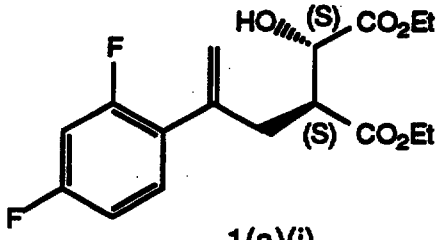
Step (a):



1(a)

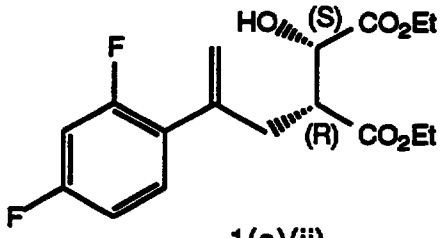
Combine 36.1 g (0.19 mole) of compound P-1B and 95 mL of THF under nitrogen atmosphere. Stir the mixture at -78°C and slowly add (dropwise) 380 mL (0.38 mole) of a 1.0 M solution of LiHMDS in THF. Stir at -78°C for 30 min., gradually warm to -20°C, then cool to -78°C. Slowly add (dropwise) a solution of 26.6 g (95 mmol) of 2-(2',3'-difluorophenyl)-3-iodo-1-propene in 95 mL of THF. Stir at -78°C for 30 min., then at -20°C overnight. Warm to 0°C, then quench with 100 mL of 5% KH_2PO_4 (aqueous) and extract with 200 mL of EtOAc. Extract the aqueous phase with EtOAc 3 X 100 mL, combine the organic extracts and wash successively with 5% HCl (aqueous) and 100 mL of brine, then dry over $MgSO_4$. Concentrate *in vacuo* to give 37.6 g of a residue. Combine the residue with 5 mL of a 1 M solution of $(nBu)_4NF$ in THF and 10 mL of hexane, and stir for 30 min. at room temperature. Concentrate *in vacuo* to a residue and chromatograph (silica gel, 20% acetone in hexane) to give 27.63 g (85% yield) of the product 1(a). $[\alpha]_D^{22.8} = +18.2°$ (c = 1.0, MeOH). High Resolution MS: M^+ 343.1349, theoretical 343.1357.

^1H NMR ($CDCl_3$, 300 MHz) shows product 1(a) is a mixture of 93% of the 2S,3S-isomer 1(a)(i) and 7% 2S,3R-isomer 1(a)(ii):



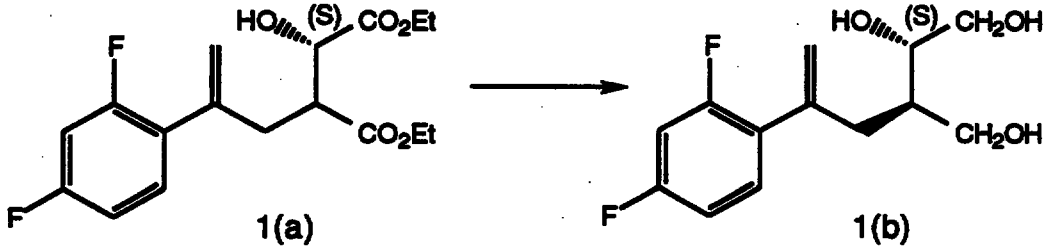
1(a)(i)

;



1(a)(ii)

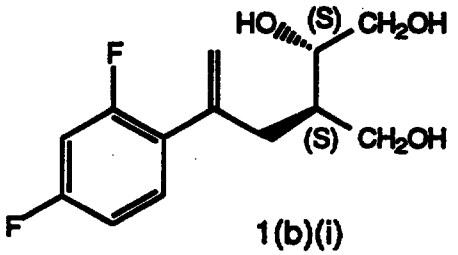
Step (b):



1(a) 1(b)

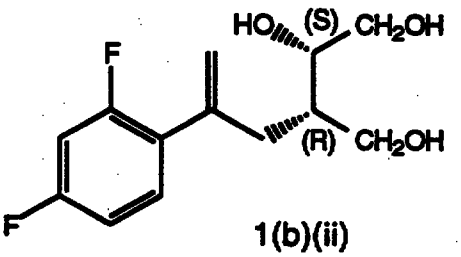
Combine 0.73 g (19.2 mmol) of $NaBH_4$, 0.80 g (19.2 mmol) of LiCl and 16 mL of 1:1 THF/water. Stir the mixture at 0°C and add a solution of 2.75 g (8.0 mmol) of the product 1(a) from Step (a) in 2 mL of THF. Stir the mixture at room temperature for 24 h., then add 4 mL of 1 N NaOH (aqueous) and stir for 16 h. Add 2 N HCl (aqueous) to acidify the mixture to pH = 3-4, then extract with EtOAc (5 X 5 mL). Combine the organic extracts, wash with saturated K_2CO_3 (aqueous) and dry over $MgSO_4$. Concentrate *in vacuo* to give 1.60 g (77% yield) of the product. $[\alpha]_D^{25}$ = -4.1° (c = 1.0, MeOH). MS m/z 259.2 (M+1).

^1H NMR ($CDCl_3$, 300 MHz) shows product 1(b) is a mixture of 94% of the 2S,3S-isomer 1(b)(i) and 6% 2S,3R-isomer 1(b)(ii):



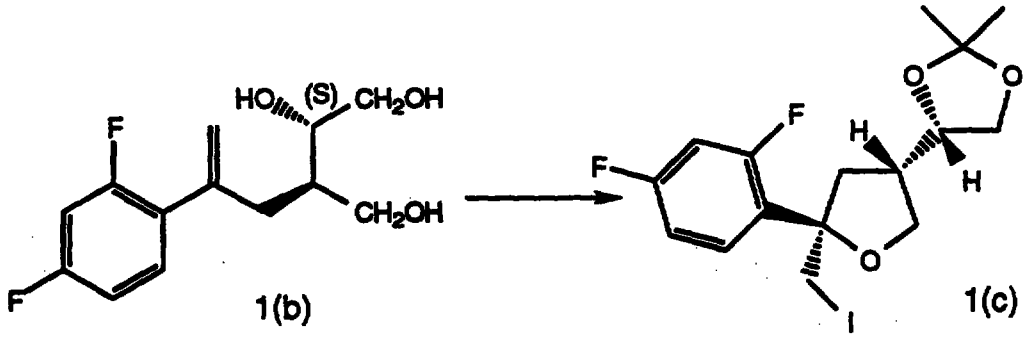
1(b)(i)

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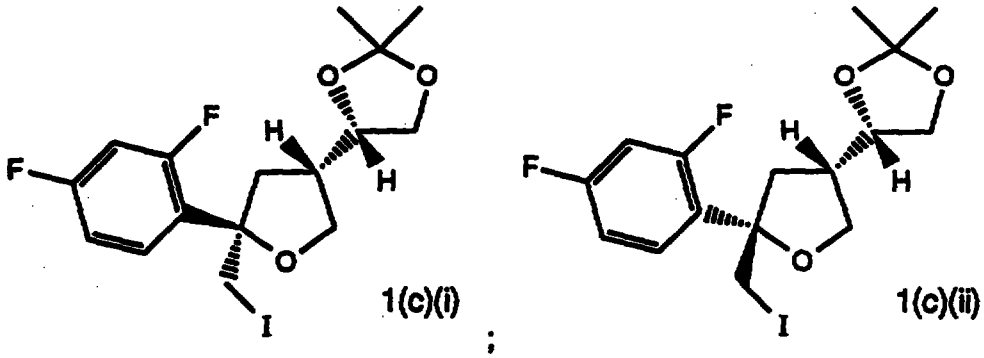


1(b)(ii)

Step (c):



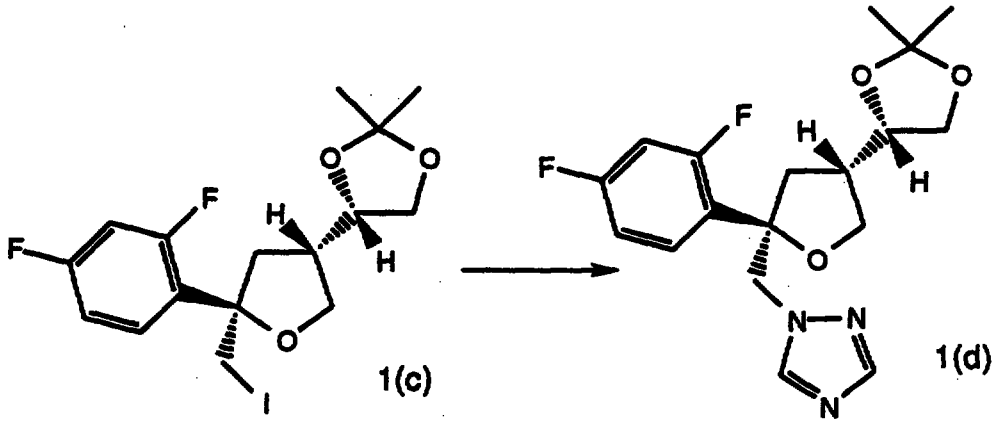
Combine 2.31 g (9.0 mmol) of compound 1(b) from Step (b), 18 mL of acetone, stir at room temperature and add 0.69 g (0.27 mmol) of I_2. Stir at room temperature for 4 h., then cool to -25° to -30°C and add 3.82 g (36 mmol) of Na_2CO_3 (anhydrous). Slowly add (in eight portions) 5.67 g (22.5 mmol) of I_2 and stir at -25°C for 24 h. Slowly warm to 0°C, stir for 30 min., then add 18 mL of a 20% solution of $Na_2S_2O_3$ in saturated K_2CO_3 (aqueous). Extract with EtOAc (5 X 10 mL), combine the extracts and was with a 20% solution of $Na_2S_2O_3$ in saturated K_2CO_3 (aqueous). Dry over $MgSO_4$ and concentrate *in vacuo* to give a 100% yield of the product 1(c), which can be used directly in Step (d). Analysis by ^1H NMR shows the product 1(c) is 97% pure and is a 91:9 mixture of compounds 1(c)(i) and 1(c)(ii):



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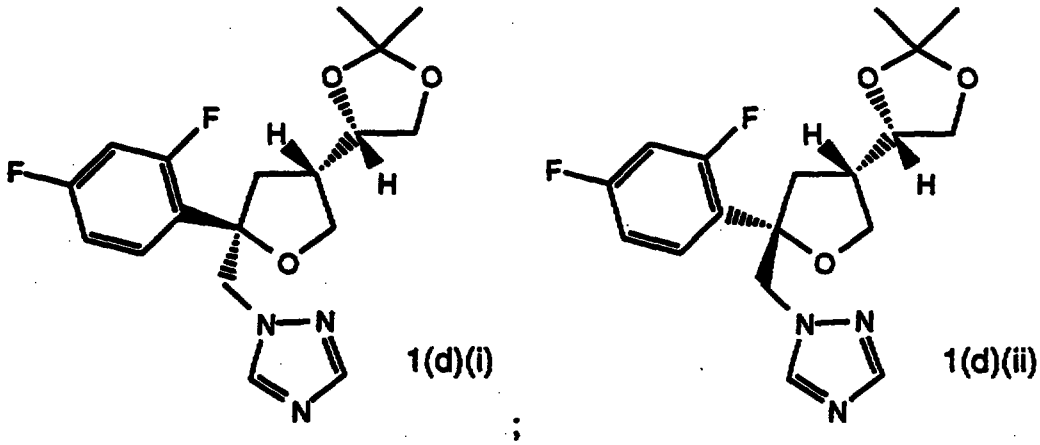
The product 1(c) is purified by chromatography (silica gel, 82:10:7:1 CH_2Cl_2/hexane/MeOH/NH_4OH) to give 3.17 g (84% yield) of compound 1(c)(i). MS m/z 425.0 (M+1).

Step (d):



1(c) 1(d)

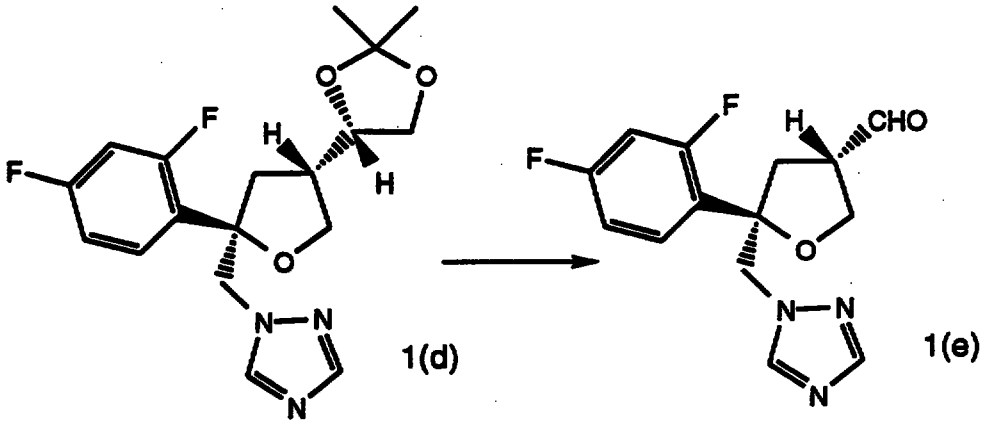
Combine 2.54 g (6.0 mmol) of the product 1(c) of Step (c), 6 mL of DMSO and 1.64 g (18 mmol) of sodium 1,3,4-triazole. Stir the mixture at 100°-105°C for 24 h., then cool to room temperature. Partition between 24 mL of water and 6 mL of EtOAc. Extract the aqueous layer with EtOAc (5 X 3 mL), combine the organic phases, wash with brine and dry over $MgSO_4$. Concentrate *in vacuo* to a residue and purify by chromatography (silica gel, 82:10:7:1 CH_2Cl_2/hexane/MeOH/NH_4OH) to give 1.56 g (69% yield) of the product 1(d). MS m/z 366.4 (M+1). The product 1(d) is a 90:10 mixture of the compounds 1(d)(i) and 1(d)(ii):



1(d)(i) 1(d)(ii)

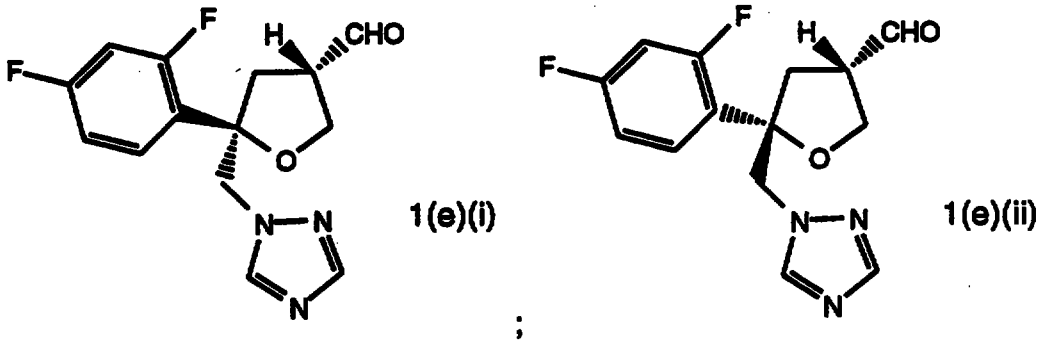
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Step (e):



1(d) 1(e)

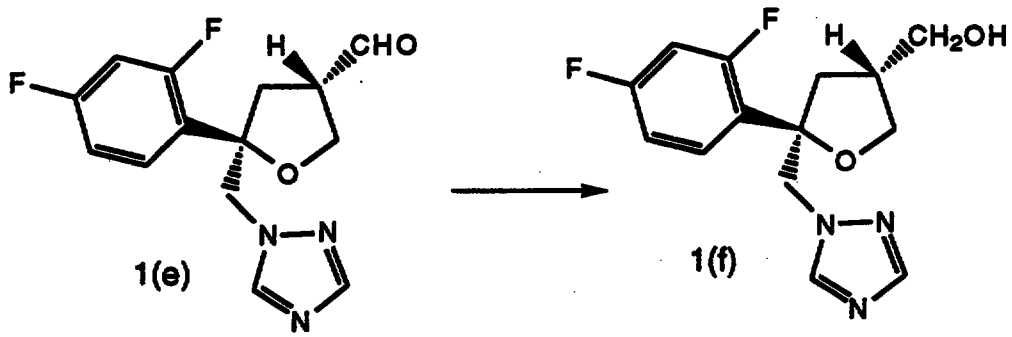
Combine 0.78 g (2.13 mmol) of the product 1(d) from Step (d), 2.1 mL of THF and 2.1 mL of 1 N HCl (aqueous), and stir at room temperature for 3 h. Add 0.73 g (3.2 mmol) of H_5IO_6 and stir for 24 h. Add 8 mL of a 20% solution of $Na_2S_2O_3$ in saturated K_2CO_3 (aqueous), then dilute with 4 mL of water. Extract with EtOAc (5 X 10 mL), combine the extracts and wash with a 20% solution of $Na_2S_2O_3$ in saturated K_2CO_3 (aqueous). Dry over $MgSO_4$, then concentrate *in vacuo* to a residue. Purify the residue by chromatography (silica gel, 5% MeOH in CH_2Cl_2) to give 0.49 g (79% yield) of the product 1(e). MS m/z 294.1 (M+1). The product 1(e) is a 90:10 mixture of the compounds 1(e)(i) and 1(e)(ii):



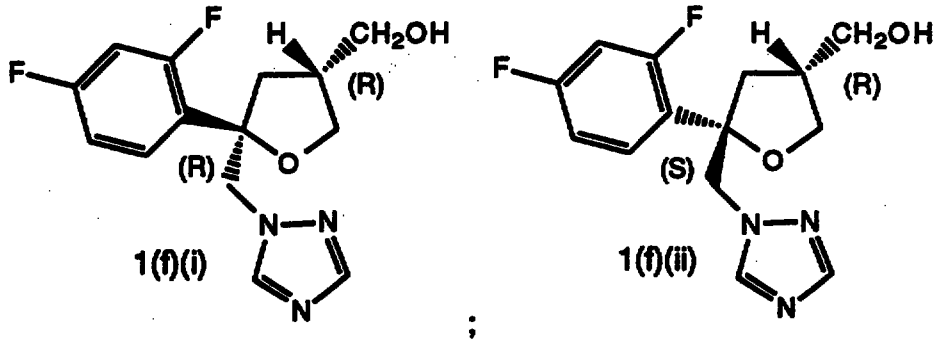
1(e)(i) 1(e)(ii)

;

Step (f):

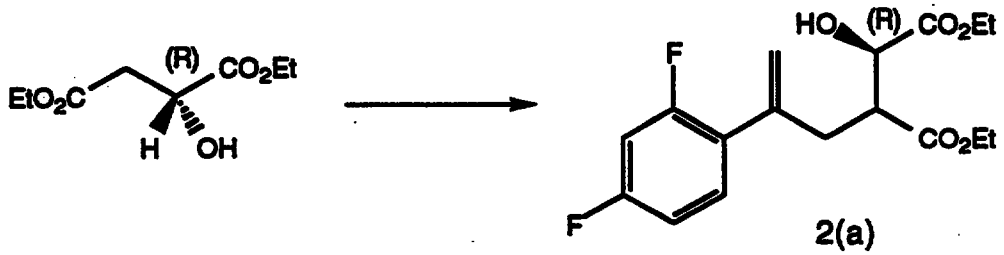


Combine 0.40 g (1.36 mmol) of the product 1(e) from Step (e) and 2.7 mL of MeOH, then cool to 10°C and add 0.052 g (1.36 mmol) of $NaBH_4$. Stir the mixture for 1 h., then add 1 mL of 1 N NaOH (aqueous) and stir for 15 min. Extract with EtOAc (5 X 2 mL), combine the extracts, wash with saturated K_2CO_3 (aqueous) and dry over $MgSO_4$. Concentrate *in vacuo* to give 0.40 g (100% yield) of the product 1(f). MS m/z 296.1 (M+1). $[\alpha]_D^{27}$ = -48.8° (c = 0.85, $CHCl_3$). ^1H NMR analysis ($CDCl_3$, 300 MHz) shows that product 1(f) is 94% of the R,R-isomer 1(f(i) and 6% of the R,S-isomer 1(f)(ii):



;

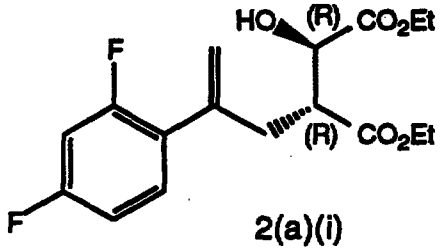
EXAMPLE 2



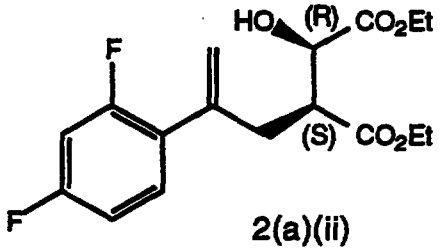
Following essentially the same procedure as described in Example 1, Step (a), and using 2.85 g (15 mole) of compound P-1D, and

corresponding amounts of the other reagents, 1.93 g (75% yield) of the product 2(a) was prepared. $[\alpha]_D^{25}$ = -14.54° (c = 1.0, MeOH). MS (m/z) = 343.2 (M+1).

^{1}H NMR ($CDCl_3$, 300 MHz) shows that the product 2(a) is a mixture of 94% of the 2R,3R-isomer 2(a)(i) and 6% 2R,3S-isomer 2(a)(ii):

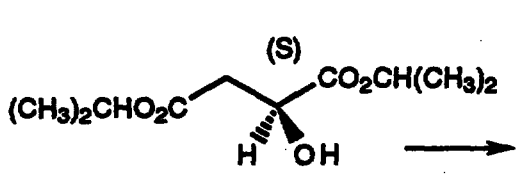


2(a)(i)

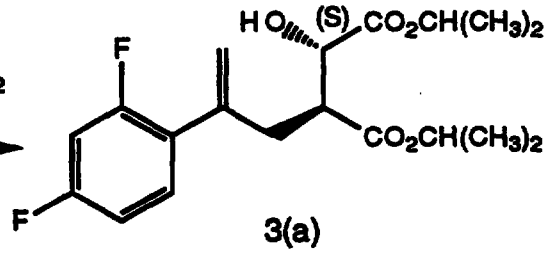


2(a)(ii)

EXAMPLE 3



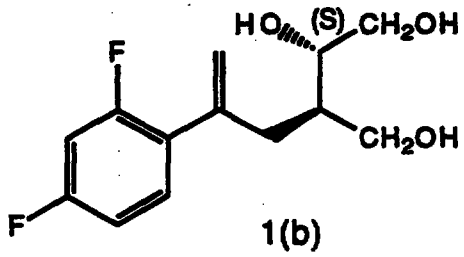
P-1C



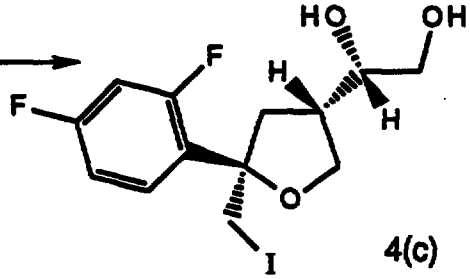
3(a)

The product P-1C prepared according to Preparation 1 (65 mg, 0.3 mmol) is treated with 84 mg of 2-(2',3'-difluorophenyl)-3-iodo-1-propene and 0.93 mmol of LiHMDS by essentially the same procedure as described in Example 1, Step (a) to give 67 mg (60% yield) of the product 3(a). MS m/z 371.4 (M+1).

EXAMPLE 4



1(b)

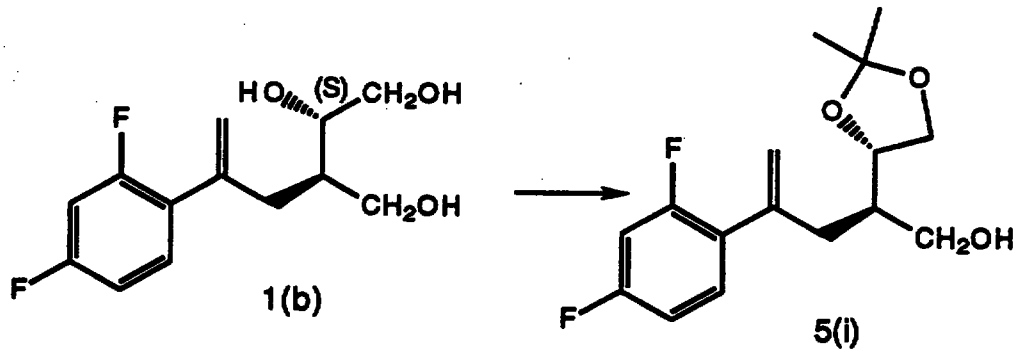


4(c)

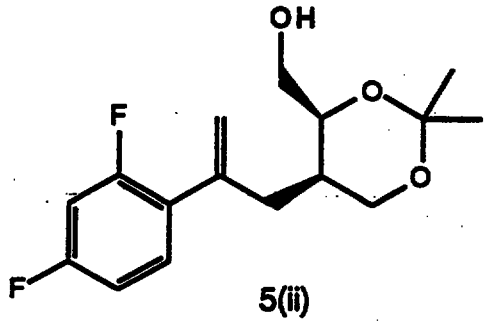
Combine 28 mg (0.1 mmol) of the product 1(b) from Example 1, Step (b) and 0.2 mL of CH_3CN, stir the mixture, then add 42

mg (0.4 mmol) of Na_2CO_3. Cool the mixture to -25° to -20°C, add 63 mg (0.25 mmol) of Iodine and stir at -25°C for 3h. Slowly warm the mixture to 0°C and stir for 6 h., then quench with 0.5 mL of 20% $Na_2S_2O_3$ in saturated K_2CO_3 (aqueous). Extract with EtOAc (5 X 2 mL) and wash the combined extracts with 20% $Na_2S_2O_3$ in saturated K_2CO_3 (aqueous). Dry the combined extracts over $MgSO_4$ and concentrate *in vacuo* to give 40 mg (96% yield) of the diol product 4(c). MS m/z 385.1 (M+1), 367.1 (M+1-H_2O), 349.1 (M+1-2H_2O). (The product is an 85:15 mixture of cis to trans isomers by ^1H NMR.)

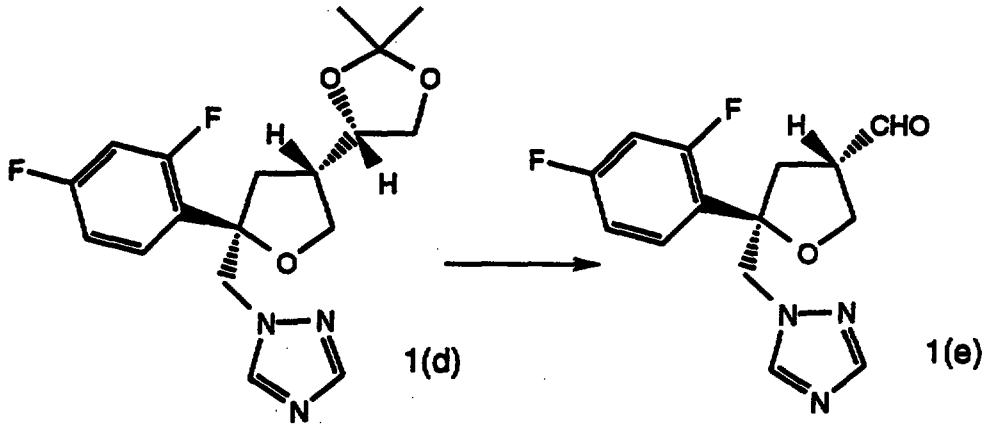
EXAMPLE 5



Combine 0.102 g (0.4 mmol) of the product 1(b) from Example 1, Step (b) and 0.5 mL of acetone. Cool the mixture at -30° to -25°C, add 2.1 mg (0.008 mmol) of I_2, then stir at -25°C for 4 h. Add $Na_2S_2O_3$ (about 0.05 g) stir for 30 min., then warm to room temperature and filter through celite®. Concentrate the filtrate to give 78 mg of the ketal product 5(i). MS m/z 385.1 (M+1). The product is a 87:13 mixture of 5(i) and its regioisomer 5(ii) by ^1H NMR

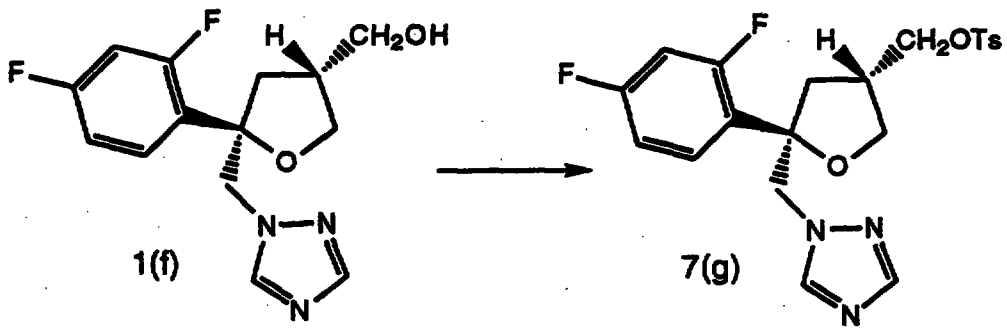


EXAMPLE 6



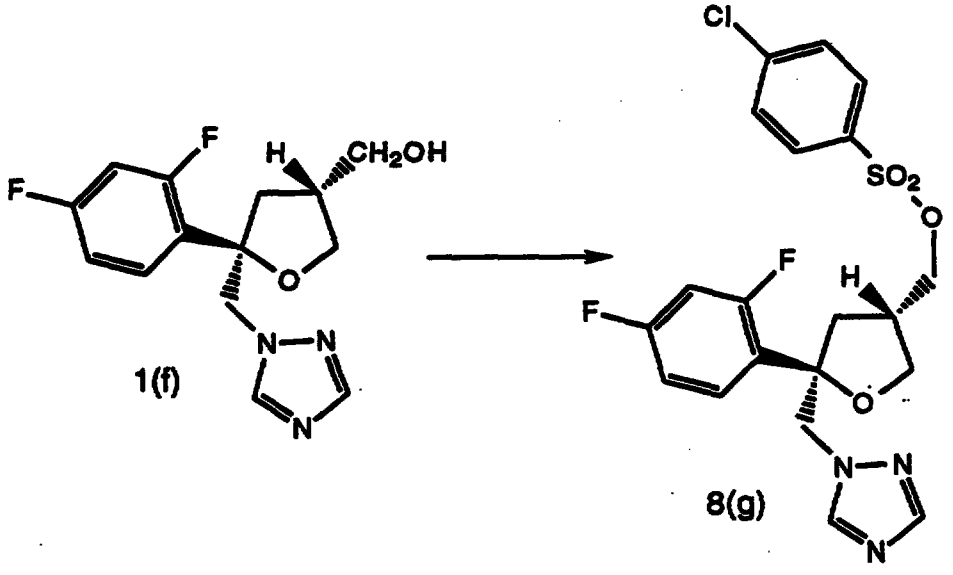
Combine 50 mg (0.13 mmol) of the product 1(d) from Step (d), 0.4 mL of 1:1 MeOH/water and 45 mg (0.2 mmol) of H_5IO_6. Stir the mixture at room temperature for 4 h., then quench with 2 mL of saturated K_2CO_3 (aqueous). Extract with EtOAc (5 X 2 mL), combine the extracts and wash with a 20 % solution of $Na_2S_2O_3$ in saturated K_2CO_3 (aqueous). Dry over MgSO, then concentrate *in vacuo* to give 33 mg (82% yield) of the aldehyde product 1(e). MS m/z 294.3 (M+1).

EXAMPLE 7



Combine 0.182 g (0.61 mmol) of the product 1(f) of Example 1, Step (f), and 0.6 mL of THF. Add 0.3 mL of 25% NaOH (aqueous) and 0.174 g (0.92 mmol) of TsCl. Stir the resulting biphasic mixture at room temperature for 4 h., then add 0.85 g of TsCl and stir for 18 h. Separate the layers and extract the aqueous layer with TBME (4 X 5 mL). Combine the organic layer and the extracts and wash with saturated Na_2CO_3 (aqueous). Dry over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, TBME) to give 0.08 g (76% yield) of the tosylate product 7(g). MS m/z 450.0 (M+1).

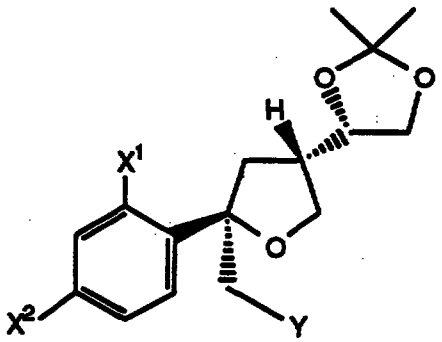
EXAMPLE 8



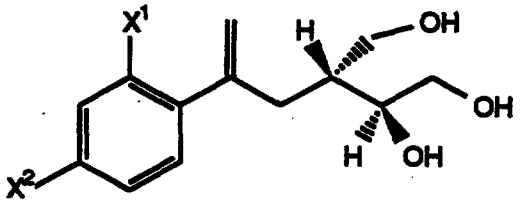
Combine 0.32 g (1.1 mmol) of the product 1(f) of Example 1, Step (f), and 2.2 mL of CH_2Cl_2. Add 0.32 mL (2.3 mmol) of Et_3N and 0.33 g (1.54 mmol) of 4-chlorobenzenesulfonyl chloride and stir the mixture at room temperature for 18 h. Add 5 mL of 25% NaOH (aqueous) and stir for 1 h. Chill to 0° to 5°C and slowly add 4 M H_2SO_4 (aqueous) to bring the mixture to pH 6-8. Separate the layers and extract the aqueous layer with CH_2Cl_2 (4 X 5 mL). Combine the organic phases and wash with saturated Na_2CO_3 (aqueous). Dry over $MgSO_4$ and concentrate *in vacuo* to a residue. Chromatograph the residue (silica gel, EtOAc) to give 0.38 g (76% yield) of the product 8(g). MS m/z 470.0 (M+1).

We Claim:

1. A process for preparing chiral compounds of the formula



wherein X^1 and X^2 are independently F or Cl, and Y is Cl, Br or I, comprising reacting a triol of the formula



wherein X^1 and X^2 are as defined above, with acetone in the presence of a catalyst, then with a halogen selected from Cl_2, Br_2 or I_2, or N-bromosuccinimide or N-iodosuccinimide.

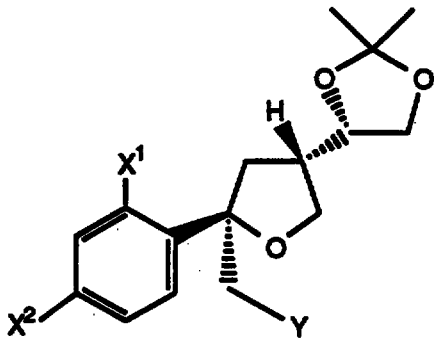
2. The process of claim 1 wherein X^1 and X^2 are both F, Y is I, and the halogen is I_2.

3. The process of claim 2 wherein the catalyst is I_2.

4. The process of claim 3 wherein the treatment with halogen is carried out in the presence of a moderate base at a temperature of -50° to 25°C.

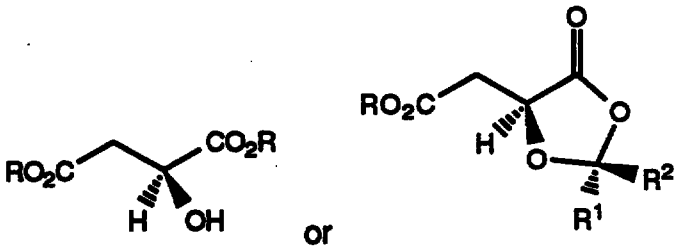
5. The process of claim 4 wherein the moderate base is Na_2CO_3 or K_2CO_3 and the temperature is -30° to 0°C.

6. A process for preparing chiral compounds of the formula



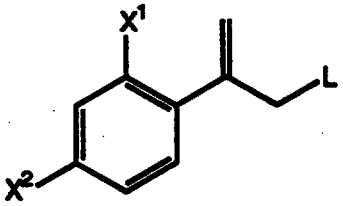
wherein X^1 and X^2 are independently F or Cl, and Y is Cl, Br or I, comprising the steps:

(a) using a nonaqueous base to deprotonate a chiral compound of the formula

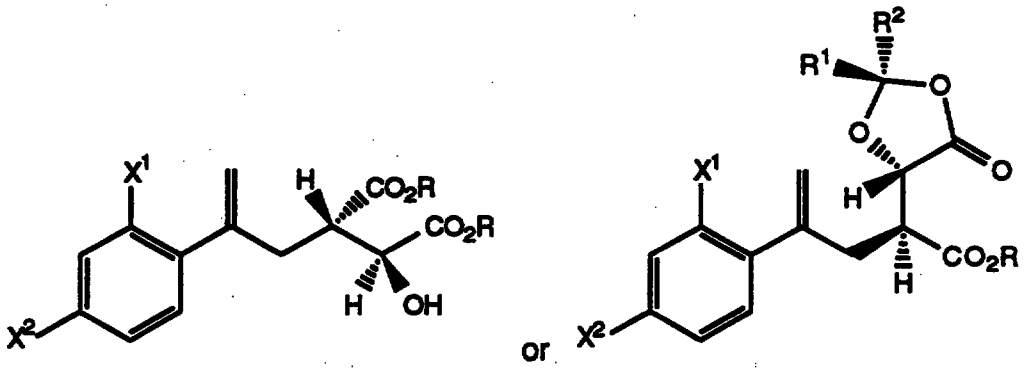


wherein: R is C_1-C_6 alkyl;

one of R^1 or R^2 is H and the other is $-C(CH_3)_3$ or $-CCl_3$, or R^1 and R^2 are both C_1-C_6 alkyl, or R^1 and R^2 together with the carbon to which they are attached comprise a 6-membered carbocyclic ring, then treating with a compound of the formula

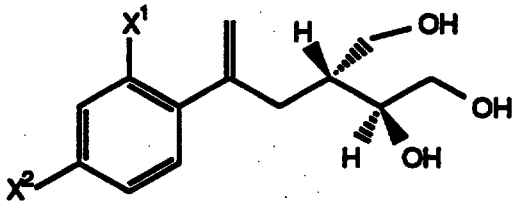


wherein X^1 and X^2 are as defined above and L is a leaving group, to form a chiral compound of the formula



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

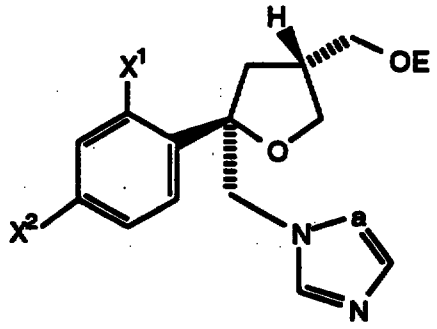
(b) reducing the product of step (a) with a hydride reducing agent to form a chiral triol of the formula



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

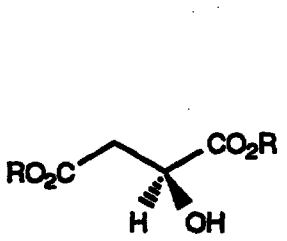
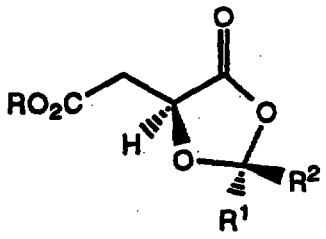
(c) reacting the triol of step (b) with acetone in the presence of a catalyst, then with a halogen selected from Cl_2, Br_2 or I_2, or N-bromosuccinimide or N-iodosuccinimide.

7. A process for preparing a compound of the formula



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:

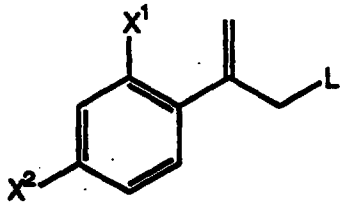
(a) using a nonaqueous base to deprotonate a chiral compound of the formula

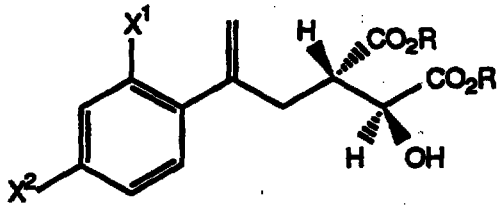
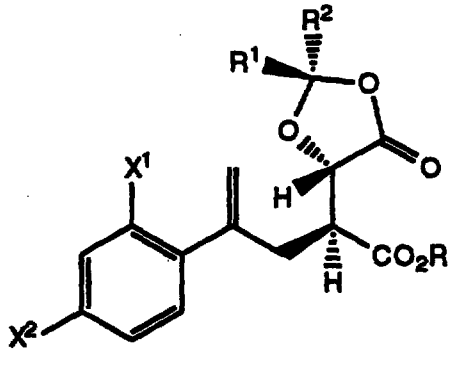
wherein: R is C_1-C_6 alkyl;

one of R^1 or R^2 is H and the other is $-C(CH_3)_3$ or $-CCl_3$, or R^1 and R^2 are both C_1-C_6 alkyl, or R^1 and R^2 together with the carbon to which they are attached comprise a 6-membered carbocyclic ring,

then treating with a compound of the formula

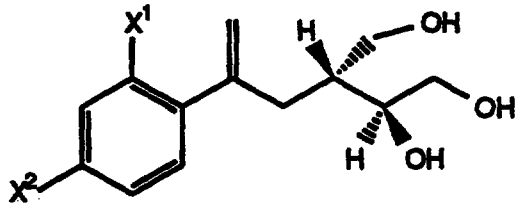


wherein X^1 and X^2 are as defined above and L is a leaving group, to form a chiral compound of the formula

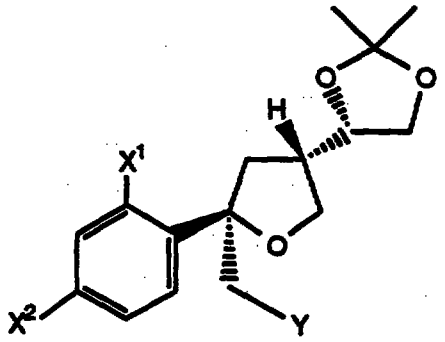
respectively, wherein X^1, X^2, R, R^1 and R^2 are as defined above;

(b) reducing the product of step (a) with a hydride reducing agent to form a chiral triol of the formula



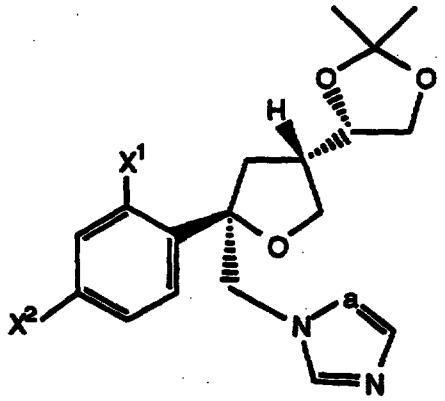
wherein X^1 and X^2 are as defined above;

(c) reacting the triol of step (b) with acetone in the presence of a catalyst, then with a halogen selected from Cl_2, Br_2 or I_2, or N-bromosuccinimide or N-iodosuccinimide, to form a chiral tetrahydrofuran of formula



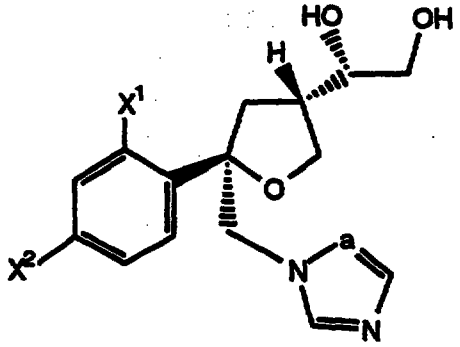
wherein X^1 and X^2 are as defined above and Y is Cl, Br or I;

(d) treating the tetrahydrofuran of step (c) with an alkali metal triazole or imidazole to form a chiral triazole or imidazole derivative of the formula

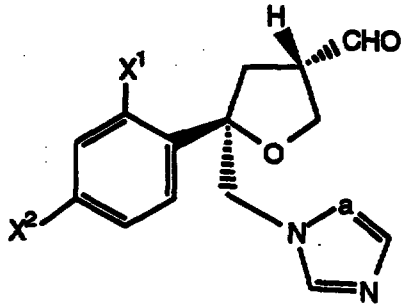


wherein a, X^1 and X^2 are as defined above;

(e) hydrolyzing the triazole or imidazole product of step(d) with an aqueous acid to form a diol intermediate of the formula

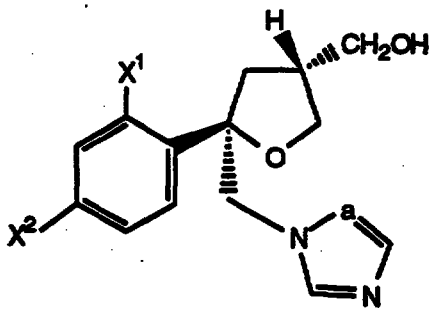


followed by oxidatively cleaving the diol using H_5IO_6, $NaIO_4$ or $Pb(OAc)_4$ to form an aldehyde of the formula



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

(f) reducing the aldehyde of step (e) with a hydride reducing agent to form an alcohol of the formula

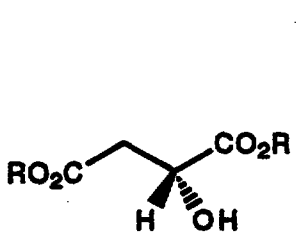


wherein a, X^1 and X^2 are as defined above; and

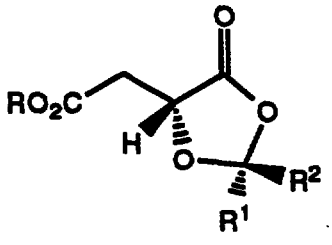
(g) treating the alcohol of step (f) with a compound of the formula E-X, wherein X is Cl or Br, and E is as defined above.

8. A process for preparing an enantiomer of a compound of claim 6 comprising

(ai) using a nonaqueous base to deprotonate a chiral compound of the formula

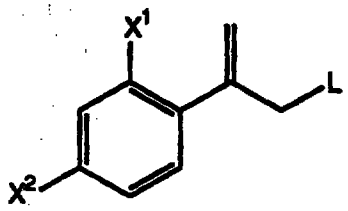


or

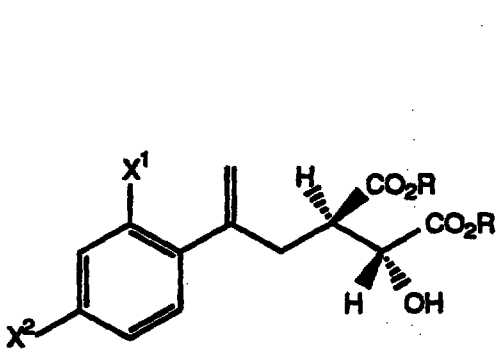


wherein: R is C_1-C_6 alkyl;

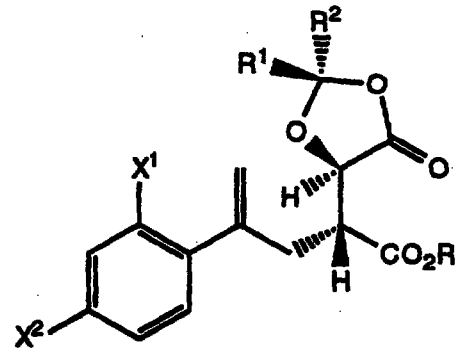
one of R^1 or R^2 is H and the other is $-C(CH_3)_3$ or $-CCl_3$, or R^1 and R^2 are both C_1-C_6 alkyl, or R^1 and R^2 together with the carbon to which they are attached comprise a 6-membered carbocyclic ring, then treating with a compound of the formula



wherein X^1 and X^2 are as defined above and L is a leaving group, to form a chiral compound of the formula

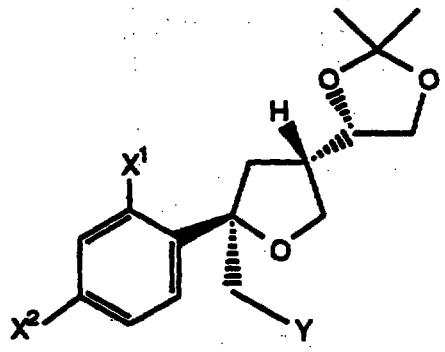


or



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

(bi) sequentially treating the product of step (ai) as described in steps (b) and (c) of claim 6 to give the enantiomer having the formula



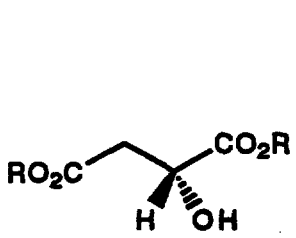
wherein X^1, X^2 and Y are as defined in claim 6.

9. The process of claims 6 or 8 wherein: X^1 and X^2 are both F; L is I; R is methyl, ethyl or i-propyl; the nonaqueous base is

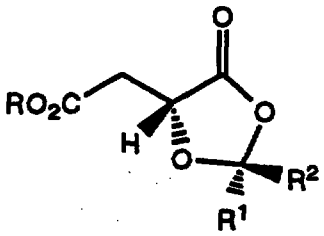
$LiN[Si(CH_3)_3]_2$; the hydride reducing agent is $LiBH_4$ or a mixture of $NaBH_4$ and LiCl; the catalyst in step (c) is I_2; and the halogen is I_2.

10. A process for preparing an enantiomer of a compound of claim 7 comprising:

(ai) using a nonaqueous base to deprotonate a chiral compound of the formula

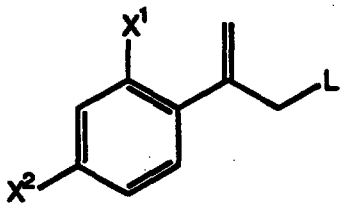


or

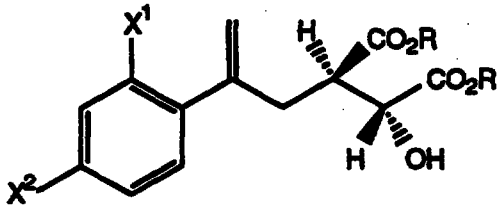


wherein: R is C_1-C_6 alkyl;

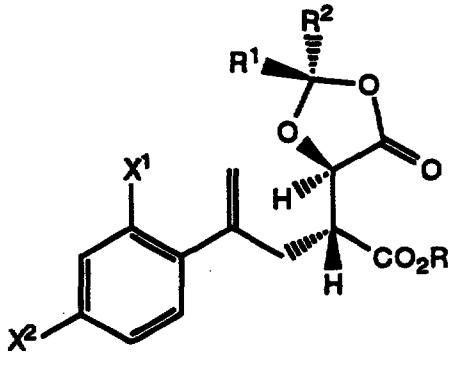
one of R^1 or R^2 is H and the other is $-C(CH_3)_3$ or $-CCl_3$, or R^1 and R^2 are both C_1-C_6 alkyl, or R^1 and R^2 together with the carbon to which they are attached comprise a 6-membered carbocyclic ring, then treating with a compound of the formula



wherein X^1 and X^2 are as defined above and L is a leaving group, to form a chiral compound of the formula

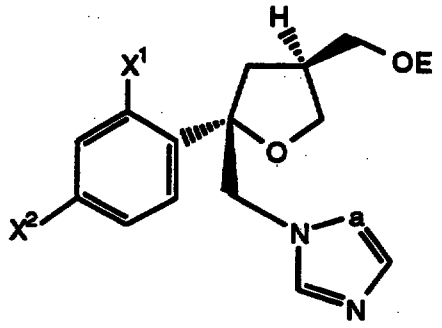


or



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

(bi) sequentially treating the product of step (ai) as described in steps (b), (c), (d), (e), (f) and (g) of claim 8 to form an enantiomer of the formula



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 $-CF_3$.

11. The process of claims 7 or 10 wherein: a is N; X^1 and X^2 are both F; L is I; R is methyl, ethyl or i-propyl; in step (a) the nonaqueous base is $LiN[Si(CH_3)_3]_2$; in step (b) the hydride reducing agent is $LiBH_4$ or a mixture of $NaBH_4$ and LiCl; n step (c) the catalyst is I_2, and the halogen is I_2, and Y is I; in step (d) the alkali metal triazole is sodium triazole; in step (e) the aqueous acid is aqueous HCl; in step (f) the hydride reducing agent is $NaBH_4$; and in step (g) E is $CH_3C_6H_4SO_2$- or $ClC_6H_4SO_2$- and X is Cl.

12. The process of claim 11 wherein: step (a) is carried out in tetrahydrofuran at a temperature of -100° to 0°C; step (b) is carried out in an organic water miscible solvent in the presence of water; in step (c) the treatment with halogen is carried out in the presence of a moderate base at a temperature of -50° to 25°C; step (d) is carried out at 50° to 150°C in N,N-dimethylformamide or dimethylsulfoxide; step (e) is carried out in tetrahydrofuran at 0° to 50°C; step (f) is carried out in an organic water miscible solvent at -30° to 50°C; and step (g) is carried out in the presence of a base and a solvent selected tetrahydrofuran or CH_2Cl_2.

13. The process of claim 12 wherein: in step (b) the water miscible solvent is tetrahydrofuran; in step (c) the moderate base is

Na_2CO_3; in step (f) the water miscible solvent is MeOH; and in step (g) the base is pyridine or NaOH.

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(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).

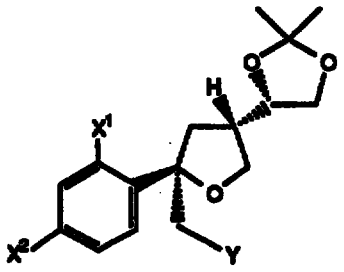
(72) Inventors: LEONG, William; 705 Carleton Road, Westfield, NJ 07090 (US). SMITH, Lyman, H.; 1857 Olive Street, Piscataway, NJ 08854 (US).

(74) Agents: THOMPSON, Paul, A. et al.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

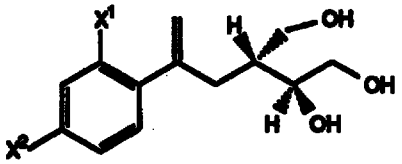
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(II)



(VIII)

(57) Abstract

Described is a process for preparing chiral compounds of formula (II), wherein X^1 and X^2 are independently F or Cl, and Y is Cl, Br or I, comprising reacting a triol of formula (VIII), wherein X^1 and X^2 are as defined above, with acetone in the presence of a catalyst, then with a halogen selected from Cl_2, Br_2 or I_2, or N-bromosuccinimide or N-iodosuccinimide.