Title: PROCESS FOR PREPARING INTERMEDIATES FOR THE SYNTHESIS OF ANTIFUNGAL AGENTS

Abstract

Disclosed is a process for preparing chiral compounds of formula (I) wherein: X₁ and X₂ are independently F or Cl; and E is -SO₂Ar, wherein R² is C₁-C₆ alkyl, -C₆H₄CH₃ or -C₆F₅; its enantiomer and racemates thereof, useful in the synthesis of tetrahydrofuran azole antifungals. Novel compounds of formula (II) or (III) wherein: X₁ and X₂ are independently F or Cl; B represents -C(O)O⁻⁺⁺ or -CH₂OR⁺⁺; Q⁺⁺ represents a chiral auxiliary group; R⁻ represents a hydroxy protecting group; and A represents Cl, Br, I, triazolyl or imidazolyl; are also disclosed.
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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

\[
\begin{align*}
\text{CH}_2\text{-}O\text{-}N\text{-}\text{Z} \\
\text{CH}_2\text{-}N\text{a} \\
\text{CH}_2\text{-}N\text{b}
\end{align*}
\]

wherein: \(a\) is \(N\) or \(\text{CH}\); \(X = F\) or \(\text{Cl}\); \(Z=\text{loweralkyl, (C}_2\text{-C}_8\text{) 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

\[
\begin{align*}
\text{CH}_2\text{-}O\text{Y}
\end{align*}
\]

wherein: \(X\) is both \(F\) or both \(\text{Cl}\) or one \(X\) is \(F\) and the other is \(\text{Cl}\); and \(Y\) is a group of the formula.
wherein:

\[ R' = (C_1-C_{10})\text{alkyl}, (C_2-C_{10})\text{alkenyl}, (C_2-C_{10})\text{alkynyl}, (C_3-C_8)\text{cycloalkyl}, \text{or CH}_2R^2; \ R^2 = (C_1-C_3) \text{perhaloalkyl}, \text{CO}_2R^3; \]

*\[ \text{Cl(OR')CH}_2OR^4 \text{ or CH}_2N(R^5)_2; \ R^3 = \text{lower alkyl or H}; \ R^4 = R^3 \text{ or (CH}_2)_2OR^3; \ R^5 = \text{lower alkyl}; \ Z = \text{H or (C}_1-C_5) \text{ alkanoyl}; \]

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.

5 SUMMARY OF THE INVENTION

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

![Chemical structure](image)

wherein: a is CH or N; X¹ and X² are independently F or Cl; and E is -SO₂R⁶, wherein R⁶ is C₁-C₆ alkyl, aryl, substituted aryl or -CF₃; comprising the steps:

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

![Chemical structure](image)

wherein X¹ and X² are as defined above, and R is a hydroxy protecting group selected from -CH₂-C₆H₅, tetrahydropyran-2-yl or -C(O)R¹, wherein R¹ is C₁-C₆ alkyl, aryl or -(CH₂)ₙCO₂H 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)

![Chemical structure](image)
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 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).

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

\[
\begin{align*}
X^1 & \quad X^2 \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

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)

\[
\begin{align*}
X^1 & \quad X^2 \\
\text{H} & \quad \text{R}^1
\end{align*}
\]

wherein $X^1$, $X^2$ are as defined above and $R^1$ is C$_1$-C$_6$ alkyl, aryl or -(CH$_2$)$_n$CO$_2$H 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 X¹, X² and R¹ are as defined above; and

5 (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 X¹, X² and R¹ are as defined above.

10 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 X¹ and X² 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 haloeno, $-\text{OSO}_2\text{CF}_3$ and $-\text{OSO}_2\text{R}^6$, 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)

$$\text{(VIII)}$$

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 $-\text{CH}_2\text{-C}_6\text{H}_5$, for use in preparing compounds of the formula (I), comprising the steps:

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

$$\text{(IX)}$$

wherein $X^1$ and $X^2$ are as defined above and $Q^*$ is a chiral auxiliary group, with a compound of the formula $\text{C}_6\text{H}_5\text{CH}_2\text{-O}\text{-CH}_2\text{L}$, 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)
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$_2$C$_6$H$_5$.

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

is prepared by a process comprising the steps:

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

wherein $X^1$ and $X^2$ are as defined above, with an effective amount of an orthoester of the formula CH$_3$C(OR)$^2$$_3$, wherein R$^2$ is C$_1$-C$_6$ alkyl, and a catalytic amount of R$^2$CO$_2$H, 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)
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 $M^+ \cdot Q^*$, 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

\[
\begin{align*}
\text{R} - \text{O} - \\
\text{CH}_3 - \text{P} - (\text{C}_6\text{H}_5)_3 - \text{Br}
\end{align*}
\]

which is treated with $\text{CH}_3\cdot \text{P} - (\text{C}_6\text{H}_5)_3\cdot \text{Br}$ 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)

\[
\begin{align*}
\text{R} - \text{O} - \\
\text{CH}_3 - \text{P} - (\text{C}_6\text{H}_5)_3 - \text{Br}
\end{align*}
\]

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)
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 \( R = H \).

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 auxiliary 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)

$$
\text{(XVI)}
$$

wherein $X^1$ and $X^2$ are as defined above and $R^a$ is a hydroxy protecting group. Preferably $R^a$ is $-\text{Cl}, \text{C}_6\text{H}_5\text{I}_6$, tetrahydropran-2-yl or $-\text{C}(\text{O})R^1$, 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 $-\text{C}(\text{O})R^1$, and $R^1$ is $\text{C}_1$-$\text{C}_6$ alkyl, is prepared by a process comprising the steps:

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

$$
\text{(II)}
$$

wherein $X^1$ and $X^2$ are as defined above, and $R$ is $-\text{CH}_2\text{C}_6\text{H}_5$, by treating with an effective amount of an acylating agent to form a chiral compound of the formula (XIX)

$$
\text{(XIX)}
$$
wherein \( X^1, X^2 \) are as defined above, \( R \) is -\( CH_2CH_5H_5 \), 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)

\[
\begin{align*}
\text{(III)}
\end{align*}
\]

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)

\[
\begin{align*}
\text{(XVII)} & \quad \text{or} \quad \text{(XVIII)}
\end{align*}
\]

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 -\( CH_2CH_5H_5 \), or -\( C(O)R^1 \), wherein \( R^1 \) is \( C_1-C_6 \) alkyl, -\( CH_2CH_5H_5 \) or aryl; and \( Q^* \) represents a chiral auxiliary group selected from chiral oxazolidinones of the formula

\[
\begin{align*}
\text{or}
\end{align*}
\]
wherein R⁵ is isopropyl or benzyl, and chiral sultams of the formula

\[
\text{\textbf{or}}
\]

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 auxiliary group, or alternatively an enzyme, to stereoselectively produce chiral compounds from achiral starting materials. The stereochemical designations represented by - - and - - 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 auxiliary is used to form a single enantiomer of a compound, the opposite enantiomer can be prepared by utilizing the opposite enantiomer of the chiral auxiliary 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_{4}OH, Na_{2}CO_{3}, K_{2}CO_{3};
NaHCO_{3} or KHCO_{3};
"nonaqueous base" means a non-nucleophilic reagent capable of generating a carbon cation, 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_{3}N 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_{3}CN;
"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_{2}R^{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 -OSO₂R⁶, wherein R⁶ is C₁₋C₆ alkyl, aryl, substituted aryl or -CF₃;

"Lewis acid" means a reagent capable of catalyzing a Friedel-Crafts acylation reaction, including reagents such as AlCl₃, BF₃, SnCl₄, BCl₃ or ZnCl₂;

"acylating agent" means a reagent of the formula R¹-C(O)-Z, wherein R¹ is C₁₋C₆ 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 R¹-C(O)-OR³, wherein R³ is trifluoroethyl, C₁₋C₆ alkyl or C₂₋C₆ 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 auxiliary "Q" is a chiral oxazolidinone of the formula

wherein R 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 used herein the following reagents and solvents are identified by the abbreviations indicated: methanol (MeOH); tetrahydrofuran (THF); diethyl ether (Et2O); lithium di-isopropylamide (LDA); triethylamine (Et3N); 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.
In Reaction Scheme 1, Step (a), the compound II is reacted with a halogen, such as Cl₂, Br₂ or I₂, preferably Br₂ or I₂, in the presence of a base, such as pyridine or NaHCO₃, in a suitable solvent, such as CH₃CN, THF, EtOAc or CH₂Cl₂, at -20° to 30°C, preferably about 0° to 25°C, to form the halide III, wherein X³ is Cl, Br or I.

In Step (b) the halide III 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°C to 100°C, preferably about 80°C, for 10 to 24 h, preferably about 15 h; and

(2) deprotected by:

(i) where R is \(-\text{C(O)R}^1\), treating with a base, preferably \(\text{K}_2\text{CO}_3\), \(\text{Na}_2\text{CO}_3\) or \(\text{NH}_4\text{OH}\), in a suitable solvent, such as MeOH/water, at 0°C to 25°C, preferably about 0°C to 5°C; or

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

(iii) where R is \(-\text{CH}_2\text{C}_6\text{H}_5\), hydrogenating under H₂ atmosphere in a suitable solvent, such as EtOH, in the presence of a suitable catalyst, such as Pd on carbon, preferably 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 \(-\text{SO}_2\text{C}_6\text{H}_4\text{CH}_3\) or \(-\text{SO}_2\text{C}_6\text{H}_4\text{Cl}\), 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 \(-\text{C(O)R}^1\), treating with a base, preferably \(\text{K}_2\text{CO}_3\), \(\text{Na}_2\text{CO}_3\) or \(\text{NH}_4\text{OH}\), in a suitable solvent, such as MeOH/water, at 0°C to 25°C, preferably about 0°C to 5°C; or

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

(iii) where R is \(-\text{CH}_2\text{C}_6\text{H}_5\), hydrogenating under H₂ atmosphere in a suitable solvent, such as EtOH, in the presence of a suitable catalyst, such as Pd on carbon, preferably 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 -SO₂C₆H₄CH₃ or -SO₂C₆H₄Cl, 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)R¹ and R¹ 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

In Reaction Scheme A, the prochiral diol IV is treated with a mild acylating agent, preferably an ester of the formula R¹-C(O)-OR³, wherein R¹ is as defined above and R³ is trifluoroethyl, C₁-C₆ alkyl or C₂-C₆ alkenyl, most preferably vinyl acetate, in the presence of an
enzyme, most preferably Novo SP435, in a suitable solvent, such as toluene or CH$_3$CN, 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

\[ \text{acylating agent} \rightarrow V \]

Step (b)

\[ V \xrightarrow{\text{enzymatic hydrolysis}} \text{IIa} \]
```

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)

\[
\begin{align*}
\text{VI} & \xrightarrow{\text{brominating agent or sulfonating agent}} \text{VII} \\
\end{align*}
\]

Step (A2)

\[
\begin{align*}
\text{VII} & \xrightarrow{\text{M}^+ \cdot \text{CO}_2R^2} \text{VIII} \\
\end{align*}
\]

Step (A3)

\[
\begin{align*}
\text{VIII} & \xrightarrow{\text{hydride reducing agent}} \text{IV} \\
\end{align*}
\]

In Reaction Scheme AAA, Step (A1), the allylic alcohol VI is treated with a brominating agent, preferably PBBr₃, in a suitable solvent, such as CH₂Cl₂, 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 L¹ 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 Et₃N, and DMAP, in a suitable solvent,
such as CH₂Cl₂, at -10° to 35°C, preferably 0° to 25°C, to form the
sulfonylated product, i.e., a compound of the formula VII wherein L¹ is
-OSO₂R⁶ and R⁶ is as defined above.

In Step (A2), the compound of formula VII is treated with
an alkali metal salt of the anion derived from dl(C₁₋C₆ alkyl)malonate,
preferably NaCH(CO₂C₂H₅)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 LiAlH₄, in a suitable solvent, such as THF or
Et₂O, 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
NaBH₄, 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 1½ 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 -CH₂C₆H₅. The chiral benzyl ether of formula
(IIb) is prepared by the process shown in Reaction Scheme B.

**Reaction Scheme B**

**Step (B1)**

![Reaction Scheme B Diagram]
In Reaction Scheme B, Step (B1), a compound of the formula $IX$ is treated with $\text{TiCl}_4$ and a compound of the formula $C_6\text{H}_5\text{CH}_2\text{OCH}_2\text{L}$, wherein $L$ is a leaving group, preferably a halide, in the presence of a tertiary amine base, such as $\text{Et}_3\text{N}$, at $-10^\circ$ to $10^\circ$C, preferably about $0^\circ$C, to form a chiral compound of the formula $X$.

In Step (B2), the chiral compound of formula $X$ is treated with $\text{LiAlH}_4$ in a suitable solvent, such as THF or $\text{Et}_2\text{O}$, at $0^\circ$ to $35^\circ$C, preferably about $25^\circ$C, to form the chiral benzyl ether $\text{IIb}$.

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.
Step (B4)

In Reaction Scheme BB, Step (B3), the allylic alcohol VI is treated with CH₃C(O)(C₂H₅)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 SOCl₂ 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.
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 Br₂ or I₂, and a base, preferably pyridine, in a suitable solvent, such as CH₃CN, THF, EtOAc or CH₂Cl₂, 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 X³ is Br or I.
In Step (C3), the chiral halide XIII is treated with a hydride reducing agent, such as LiBH₄, in a suitable solvent, such as THF or Et₂O, 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)R¹, wherein R¹ is C₁-C₆ alkyl, aryl or -(CH₂)ₙC₂OH 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 -CH₂C₆H₄, 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 $-20^\circ$ to $30^\circ$C, preferably about $0^\circ$ to $25^\circ$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.

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.
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 CH₂Cl₂, 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 Na₂SO₄ 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 Et₂O, 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 CH₂Cl₂, then co-evaporate the CH₂Cl₂ 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**

\[
\text{PBr}_3 
\]

Dissolve the allylic alcohol (5.37 g, 31.58 mmol) in 50 mL of CH₂Cl₂ and cool the resulting solution to 0° to 5°C. Add PBr₃ (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 MgSO₄. Concentrate in vacuo to give 6.45 g of the bromide product. MS = 233 M⁺

**PREPARATION 4**

\[
\text{tosyl chloride} \quad \text{Et}_3\text{N}
\]

25 **Step (a):**
Dissolve the allylic alcohol (8.51 g, 50 mmol) in 200 mL of CH₂Cl₂, add Et₃N (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 MgSO₄, then concentrate *in vacuo* to give 13.1 g of the tosylate product. (Ts = -SO₂C₆H₄CH₃).

**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 Et₂O and 100 mL of water, stir for 10 min, separate the layers and wash the organic layer with 50 mL of brine. Dry over MgSO₄, 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 LiAlH₄ 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 CH₂Cl₂ and dry over MgSO₄. 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 NaBH₄ (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 MgSO₄, 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, 63-90 (1989) to give the chiral oxazolidinone product, [α]D = -44.4° (c = 1.67, CHCl₃). 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 Et₃N, 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 Na₂CO₃, then dry over MgSO₄. 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 AlCl₃ (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 MgSO₄ and
concentrate in vacuo to a residue. Crystallize the residue from EtOH, or a mixture of CH$_2$Cl$_2$ and hexane, to give 16.6 g of the keto acid product. **Step (b):**

Combine 876 mg of CH$_3$P(C$_6$H$_5$)$_3$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$_2$SO$_4$, and concentrate to a residue. Purify the residue by chromatography (silica gel, 5% MeOH/CH$_2$Cl$_2$) to give 142 mg of the title compound, (for use in Preparations 2 and 6).

**EXAMPLE 1**

![Chemical Structure]

**Step (a):**

Combine the product of Preparation 2 (2.8 g, 8.66 mmol) and 12 mL of CH$_2$Cl$_2$ 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 Et₃N (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 NH₄Cl, extract with CH₂Cl₂, dry the extract over Na₂SO₄, 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):**

![Chemical structure](image)

Reduce the product of Step (a) by treating with LiAlH₄ 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, [α]D = -28.4° (c = 1.18, CHCl₃). MS = 341 (M+Na)⁺

**EXAMPLE 2**

![Chemical structure](image)
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, \([\alpha]_D = +6.2^\circ\) (c = 1.11, CHCl₃).

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 CH₃CN, add pyridine (45 µL, 0.56 mmol) and I₂ (0.188 g, 0.74 mmol) and stir the mixture at 0° to 5° for 6 h. Add 50 mL Et₂O and 25 mL of water, then add a saturated solution of Na₂S₂O₃ (dropwise) until the mixture is colorless. Stir for 10 min, separate the layers, dry the organic layer over Na₂SO₄, 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 K₂CO₃ (0.148 g, 1.07 mmol) and stir the mixture at 0° to 5°C for 1 h. Add CH₂Cl₂, wash with water, then dry over Na₂SO₄. 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, \([\alpha]_D = +9.5^\circ \ (c = 1.1, CHCl_3)\), 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, \([\alpha]_D = +37.0^\circ \ (c = 1.19, CHCl_3)\).

**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 I₂ (a base is not used) according to the procedure of Example 2, Step (b) to form the chiral iodide product.

**EXAMPLE 3**

![Chemical structure diagram]

**Step (a):**

Dissolve the product of Example 1 (1.7 g, 5.34 mmol) in 12 mL of CH₃CN, cool the solution to 0° to 5°C and add I₂ (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 Na₂S₂O₃ (aqueous) and Et₂O and stir until the mixture is colorless. Extract with Et₂O, wash the extract with 0.01 N HCl, then with saturated NaHCO₃, and dry over Na₂SO₄. 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, [α]D = +3.7° (c = 1.17, CHCl₃). 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 Na₂SO₄. 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, [α]D = - 42.1° (c = 1.17, CHCl₃). MS = 386 (M+H)⁺

R-trans triazole, 0.24 g, [α]D = + 10.6° (c = 1.12, CHCl₃). MS = 386
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 NaHCO₃. Dry the EtOAc solution over Na₂SO₄, 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, [α]D = -43.9° (c = 1.16, CHCl₃).

**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 CH₃CN, 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 R² is CH₃); and the absolute configuration and e.e. of chiral hydroxy acetate (IIa). The results are summarized in Table 1 below.

**TABLE 1**

<table>
<thead>
<tr>
<th>Source &amp; Enzyme</th>
<th># mgs</th>
<th>Time (hr.)</th>
<th>Product composition (%)</th>
<th>* % e.e</th>
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<tbody>
<tr>
<td>Amano Acylase</td>
<td>53.8</td>
<td>22</td>
<td>41.12</td>
<td>55.76</td>
</tr>
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<td>Sigma Protease Type XIII Aspergillus saitoi</td>
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<td>86.60</td>
<td>12.88</td>
</tr>
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<td>Enzyme Type</td>
<td>Conc.</td>
<td>Kcat</td>
<td>Km</td>
<td>kcat/Km</td>
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<td>---------</td>
</tr>
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<td>85.72</td>
<td>12.11</td>
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<td>94</td>
<td>86.31</td>
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<td>45</td>
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<td>Wako Lipase B Pseudomonas fragil</td>
<td>1.0</td>
<td>45</td>
<td>0.00</td>
<td>64.72</td>
</tr>
</tbody>
</table>

* 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.
<table>
<thead>
<tr>
<th>diol</th>
<th>lipase</th>
<th>time (min)</th>
<th>% mono acetate</th>
<th>e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.9 g</td>
<td>0.54 g</td>
<td>85</td>
<td>87.2</td>
<td>90 %</td>
</tr>
<tr>
<td>6.1 g</td>
<td>0.50 g</td>
<td>190</td>
<td>87.6</td>
<td>89 %</td>
</tr>
<tr>
<td>11.4 g*</td>
<td>0.51 g</td>
<td>210</td>
<td>75.6</td>
<td>94 %</td>
</tr>
<tr>
<td>10.7 g**</td>
<td>1.0 g</td>
<td>80</td>
<td>71.1</td>
<td>96 %</td>
</tr>
</tbody>
</table>

* 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.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>vinyl acetate</th>
<th>diol/ enzyme</th>
<th>Temp.</th>
<th>product composition (%)</th>
<th>e.e</th>
</tr>
</thead>
<tbody>
<tr>
<td># equiv</td>
<td>ratio g/g</td>
<td>°C</td>
<td>I V</td>
<td>IIa</td>
<td>V</td>
</tr>
<tr>
<td>iPr₂O</td>
<td>10.0</td>
<td>4.0</td>
<td>0</td>
<td>5.76</td>
<td>83.85</td>
</tr>
<tr>
<td>THF</td>
<td>10.0</td>
<td>4.0</td>
<td>0</td>
<td>2.41</td>
<td>80.65</td>
</tr>
<tr>
<td>Dioxane</td>
<td>10.0</td>
<td>4.0</td>
<td>20-23</td>
<td>1.01</td>
<td>74.71</td>
</tr>
<tr>
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<td>4.0</td>
<td>0</td>
<td>0</td>
<td>77.06</td>
</tr>
<tr>
<td>Acetone</td>
<td>10.0</td>
<td>4.0</td>
<td>0</td>
<td>1.19</td>
<td>83.07</td>
</tr>
<tr>
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<td>10.0</td>
<td>4.0</td>
<td>0</td>
<td>0.86</td>
<td>89.21</td>
</tr>
<tr>
<td>tAmyl</td>
<td>10.0</td>
<td>4.0</td>
<td>0</td>
<td>35.04</td>
<td>57.56</td>
</tr>
<tr>
<td>Alcohol</td>
<td>5.0</td>
<td>4.0</td>
<td>0</td>
<td>35.04</td>
<td>57.56</td>
</tr>
</tbody>
</table>

Preferably the reaction is run using a 0.9 M solution of the prochiral diol and 1.5 equivalents of vinyl acetate in CH₃CN at 0° to 5°C.

**EXAMPLE 4B**

[Diagram of chemical structures]
The reaction was run using the commercially available enzyme Amano CE (Humicola 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.

<table>
<thead>
<tr>
<th>diol</th>
<th>lipase</th>
<th>time (min)</th>
<th>% mono acetate</th>
<th>e.e.</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0.05 g</td>
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<td>1.0 g**</td>
<td>170</td>
<td>91.3</td>
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** The enzyme used in these experiments was recovered from a previous run and re-used.

**EXAMPLE 5**

Combine the diol product of Preparation 4 or 5 (0.5 g, 2.19 mmol) and 10 mL of CH₂Cl₂, cool to 0° to 5°C, then add Br₂ (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 CH₂Cl₂, wash successively with 10 mL of 10% Na₂SO₃, 10 mL of 1N HCl, and 10 mL of NaHCO₃, then dry over MgSO₄. 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 CH₃CN and 2.0 mL (25.0 mmol) of pyridine, cool the mixture to 0° to 5°C, then add I₂ (8.45 g, 33.3 mmol) and stir at 0° to 5°C for 1 h. Add 500 mL of Et₂O and 100 mL of 10% Na₂SO₃, stir for 5 min, then separate the layers. Wash the organic layer with 50 mL of 1N HCl, 50 mL of 5% NaHCO₃, and 50 mL of brine, then dry over MgSO₄. 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 CH₂Cl₂, 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 CH₂Cl₂, wash with 50 mL of 5% Na₂CO₃ and 50 mL of water, then dry over MgSO₄. 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 MgSO₄, 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 CH₂Cl₂ and 50 mL of water, then add 10% Na₂CO₃ (dropwise) to adjust the aqueous layer to pH = 8. Separate the layers, wash the organic layer with 50 mL of brine, dry over MgSO₄, 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 CH₂Cl₂, wash with 50 mL of water, 50 mL of 5% NaHCO₃, and 50 mL of brine, then dry over MgSO₄. 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).

![Chemical Structure](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 CH₂Cl₂ at 0°C, add 6.5 mL of 1M TiCl₄ in CH₂Cl₂. Stir for 5 min, then add 1.12 mL of Hüning 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 CH₂Cl₂, then add another 6.5 mL of 1 M TiCl₄ in CH₂Cl₂ and stir at 0° to 3°C for 2.5 h. Add 10 mL of saturated NH₄Cl and stir for 5 min, then separate the layers and extract the aqueous phase with 20 mL CH₂Cl₂. Combine the organic phase and the extract, wash with brine, dry over MgSO₄, 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, [α]D = - 62.9° (c = 1.7, CHCl₃). 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 CH₃CN, cool to 0°C, then add 1.78 g of I₂. Stir the mixture at room temperature for 20 h, then quench the reaction with dilute aqueous Na₂S₂O₄. Extract with Et₂O (2 X 20 mL), combine the extracts and dry over MgSO₄. 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 LiBH4 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 NH4Cl. Stir for 0.5 h, concentrate in vacuo to a residue, partition the residue between CH2Cl2 and water, separate the layers and dry the organic layer over MgSO4. 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 CH2Cl2 (2 X 40 mL). Combine the extracts, wash with brine, dry over MgSO4, 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 Na₂CO₃, then brine, and dry over MgSO₄. 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 aqueous NaOH 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)

   \[
   \begin{align*}
   &H \quad \text{OE} \\
   &X_1 \quad X_2 \\
   \end{align*}
   \]

   \( \text{I} \)

   wherein: a is CH or N; \( X_1 \) and \( X_2 \) are independently F or Cl; and E is \(-\text{SO}_2\text{R}^6\), wherein \( \text{R}^6 \) is \( \text{C}_1-\text{C}_6 \) alkyl, aryl, substituted aryl or \(-\text{CF}_3\); comprising the steps:

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

   \[
   \begin{align*}
   &\quad X_1 \quad H \quad \text{OH} \\
   &X_2 \\
   \end{align*}
   \]

   \( \text{II} \)

   wherein \( X_1 \) and \( X_2 \) are as defined above, and R is a hydroxy protecting group selected from \(-\text{CH}_2-\text{C}_6\text{H}_5\), tetrahydropyran-2-yl or \(-\text{C(O)}\text{R}^1\), wherein \( \text{R}^1 \) is \( \text{C}_1-\text{C}_6 \) alkyl, aryl or \(-\text{(CH}_2)_n\text{CO}_2\text{H} \) 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)

   \[
   \begin{align*}
   &\quad \text{Q} \\
   &X_1 \quad X_2 \quad X_3 \\
   \end{align*}
   \]

   \( \text{III} \)

   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 imidazoyl 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

(b) 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 X₃ 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)R¹, and the starting compound of formula (II) of Step (a) is prepared by selectively esterifying a prochiral diol of the formula (IV)

![Chemical Structure](image)

(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)

![Chemical Structure](image)

(IIa)

wherein X¹ and X² are as defined above, and R¹ is C₁-C₆ alkyl, aryl or -(CH₂)ₙCO₂H, wherein n is 1, 2, 3 or 4.

3. A process according to claim 1 wherein R is -C(O)R¹, 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)
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)

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)

wherein $X^1$ and $X^2$ are as defined above, to a compound of the formula (VII)
wherein X¹ and X² are as defined above and L¹ is a leaving group selected from halogeno, -OSO₂CF₃ and -OSO₂R⁶, wherein R⁶ 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(C₁₋C₆ alkyl)malonate effective to form a diester of the formula (VIII)

\[ \text{Formula VIII} \]

wherein X¹ and X² are as defined above, and R² is C₁₋C₆ 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 -CH₂-C₆H₅, is prepared by a process comprising the steps:

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

\[ \text{Formula IX} \]

wherein X¹ and X² are as defined above and Q⁺ is a chiral auxiliary group, with a compound of the formula C₆H₅CH₂-O-CH₂L, wherein L is a leaving group selected from Cl, Br and I, in the presence of TiCl₄ and a tertiary amine base, in amounts effective to form a chiral compound of the formula (X)
wherein X¹, X² and Q⁺ are as defined above; and

(B2) treating the product of formula (X) of Step (B1) with an amount of LiAlH₄ effective to form a chiral compound of the formula (II) wherein R is -CH₂C₆H₅.

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 X¹ and X² are as defined above and Q⁺ is a chiral auxiliary group, with effective amounts of trioxane, TiCl₄ and a tertiary amine base to form a chiral compound of the formula (XII)

(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)
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)

\[\text{(IX)}\]

is prepared by a process comprising the steps:

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

\[\text{(VI)}\]

wherein $X^1$ and $X^2$ are as defined above, with effective amounts of an orthoester of the formula $\text{CH}_3\text{C(OR}_2)_3$, wherein $R^2$ is $C_1$-$C_6$ alkyl, and a catalytic amount of $R^2\text{CO}_2\text{H}$, 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)
wherein X¹ and X² 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-(X¹)-3-(X²)-benzene, wherein X¹ and X² are as defined above, with succinic anhydride in the presence of a Lewis acid to form a keto acid of the formula

![Diagram of keto acid]

and treating the keto acid with CH₃·P(C₆H₅)₃·Br and a nonaqueous 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)R¹, and R¹ is C₁-C₆ alkyl, is prepared by a process comprising the steps:

(D1) esterifying a chiral alcohol of the formula (II)
wherein \( X^1 \) and \( X^2 \) are as defined above, and \( R \) is \(-\text{CH}_2\text{-C}_6\text{H}_5\), by treating with an effective amount of an acylating agent to form a chiral compound of the formula (XIX)

\[
\text{(XIX)}
\]

wherein \( X^1, X^2 \) are as defined above, \( R \) is \(-\text{CH}_2\text{C}_6\text{H}_5\), and \( R^1 \) is \( \text{C}_1\text{-C}_6 \) 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)

\[
\text{(III)}
\]

wherein \( X^1, X^2 \) are as defined above, \( R \) is \(-\text{C(O)R}^1\), \( R^1 \) is \( \text{C}_1\text{-C}_6 \) alkyl, and \( X^3 \) is Cl, Br or I.

10. A process according to claim 1 wherein:

15 (a) in Step (a): the halogen is Br or I; the base is pyridine or NaHCO₃; and the cyclization is carried out in the presence of a solvent selected from CH₃CN, tetrahydrofuran, ethyl acetate and CH₂Cl₂; 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:
(i) where R is -C(OR)R', and R' is C\textsubscript{1}-C\textsubscript{6} alkyl, aryl or -(CH\textsubscript{2})\textsubscript{n}CO\textsubscript{2}H wherein n is 1, 2, 3 or 4, treating with a base selected from K\textsubscript{2}CO\textsubscript{3}, Na\textsubscript{2}CO\textsubscript{3} and NH\textsubscript{4}OH, 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\textsubscript{2}C\textsubscript{6}H\textsubscript{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\textsuperscript{3} is triazolyl; or

(b1) in Step (b):

(1) the protecting group R is removed by:

(i) where R is -C(OR)R', and R' is C\textsubscript{1}-C\textsubscript{6} alkyl, aryl or -(CH\textsubscript{2})\textsubscript{n}CO\textsubscript{2}H wherein n is 1, 2, 3 or 4, treating with a base selected from K\textsubscript{2}CO\textsubscript{3}, Na\textsubscript{2}CO\textsubscript{3} and NH\textsubscript{4}OH, 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\textsubscript{2}C\textsubscript{6}H\textsubscript{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\textsuperscript{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 (Humicola lanugiosa), Amano AY-30, Biocatalysts H. lanugiosa, Biocatalysts M. meii, Biocatalysts Ps. fluorescens, Meito MY, Meito PL, Novo Lipozyme IM-20, and Novo SP435 (Candida antarctica).

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. meiheli*, 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 LiAlH₄ or LiBH₄.

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

![Diagram](image)

wherein R⁵ 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 SOCl₂, M⁺ is Li⁺, and "Q" is

![Diagram](image)

wherein R⁵ is isopropyl.

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

![Diagram](image)
wherein $R^5$ is $\text{-CH}_2\text{C}_6\text{H}_5$; in Step (C2) the halogen is $\text{Br}_2$ or $\text{I}_2$, and the base is pyridine; and in Step (C3) the hydride reducing agent is $\text{LiBH}_4$.

17. A process according to claim 9 wherein: in Step (D1), the acetylated agent is acetic anhydride; and in Step (D2), the halogen is $\text{I}_2$.

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

(XVII) $X^1$ and $X^2$ are independently $\text{F}$ or $\text{Cl}$;
A represents $\text{Cl}$, $\text{Br}$, $\text{I}$, triazolyl or imidazolyl
B represents $\text{-C(O)Q}^*$ or $\text{-CH}_2\text{OR}^*$;
$\text{R}^*$ represents a hydroxy protecting group selected from
$\text{-CH}_2\text{C}_6\text{H}_5$, or $\text{-C(O)R}^1$, wherein $R^1$ is $\text{C}_1$-$\text{C}_6$ alkyl, aryl or $\text{-CH}_2\text{H}_n\text{CO}_2\text{H}$ wherein $n$ is 1, 2, 3 or 4; and
$Q^*$ represents a chiral auxiliary group selected from

(XVIII)

wherein $R^5$ is isopropyl or benzyl.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D405/06 C07D307/12 C07D413/06 C07D417/06 C12P7/62

According to International Patent Classification (IPC) or to both national classification and IPC.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO,A,89 04829 (SCHERING CORPORATION) 1 June 1989 cited in the application see claims</td>
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<td>A</td>
<td>US,A,5 039 676 (A.K. SAKSENA ET AL.) 13 August 1991 cited in the application see claims</td>
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"A" document member of the same patent family

Date of the actual completion of the international search

18 August 1994

Date of mailing of the international search report

26.08.94

Name and mailing address of the ISA

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Fax (+ 31-70) 340-3016

Authorized officer

Chouly, J
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<td>WO,A,93 09114 (SCHERING CORPORATION) 13 May 1993 cited in the application see page 8 - page 17; claims</td>
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