(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 September 2009 (17.09.2009)

PCT

(10) International Publication Number
WO 2009/114080 A2

(51) International Patent Classification:
A61K 31/496 (2006.01)

(21) International Application Number:
PCT/US2009/001315

(22) International Filing Date:
2 March 2009 (02.03.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/033,266 3 March 2008 (03.03.2008) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: PROCESSES FOR PREPARING ENANTIOMERICALLY PURE DIOL AND DIOXOLANE COMPOUNDS

(57) Abstract: The present invention relates to novel processes for preparing enantiomerically pure diol and dioxolane compounds from racemic starting materials and the use of these compounds for preparing therapeutically active agents.

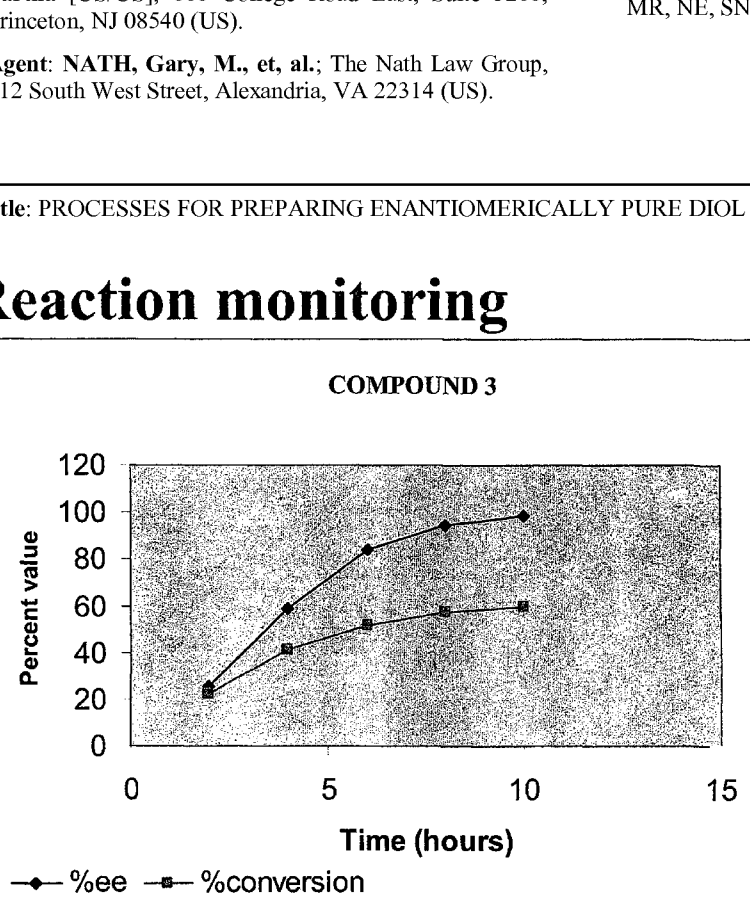


FIG. 1

WO 2009/114080 A2

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

Title: Processes for Preparing Enantiomerically Pure Diol and Dioxolane Compounds

Field of the Invention

[0001] The present invention relates to novel processes for preparing enantiomerically pure diol and dioxolane compounds from racemic starting materials and the use of these compounds for preparing therapeutically active agents.

Background of the Invention

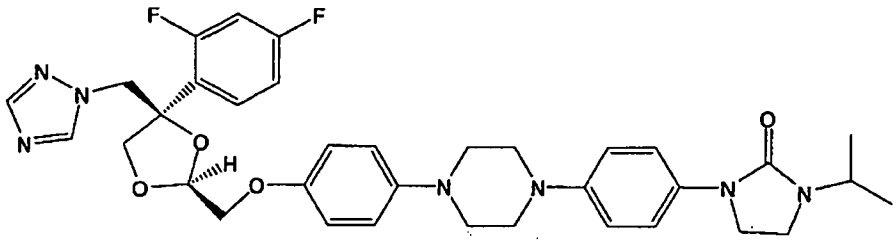
[0002] The increasing global incidence of systemic fungal and Gram-positive bacterial infections may largely be attributed to advances in medical technology and organ transplantation, an increase in the prevalence of cytotoxic chemotherapeutic interventions, the widespread use of broad spectrum antimicrobials and indwelling catheters, and an increasing number of immunocompromised patients.

[0003] The most common causes of the fungal infections are due to *Candida* spp., of which *C. albicans* accounts for approximately 50%, and filamentous fungi such as *Aspergillus* spp. [Kremery and Barnes, 2002]. Mortality associated with invasive *Candida* ranges from around 40% [Edmond *et al.*, 1999], while mortality associated with invasive *Aspergillus* approaches 100% in solid organ transplant recipients [Minari *et al.*, 2002].

[0004] Gram-positive infections due to *Staphylococcus* spp. predominate. When bacteremia is caused by resistant isolates, mortality rates are high [Elsayed and Laupland, 2004].

[0005] Given the lack of readily available fungal vaccines, the only clinical resource available to combat fungal infections is antifungal therapeutics (antimycotics). The antimycotics currently in clinical use are limited either by their general ineffectiveness and inadequate pharmacological profile, including undesired drug-drug interactions and narrow activity spectrum, or by their high overall cytotoxicity [White *et al.*, 1998]. Accordingly, there is a critical need for new antifungal compounds that could overcome these disadvantages.

[0006] Pramiconazole (1-[4-[4-[[(2S,4R)-4-(2,4-difluorophenyl)-4-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-imidazolidinone) is a potent oral broad-spectrum antifungal agent for the short course treatment

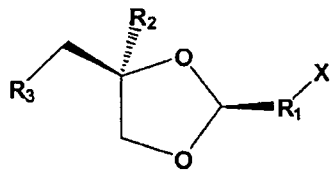


of acute skin and mucosal fungal infections, as well as a treatment for chronic fungal infections. U.S. Patent No. 6,387,906, which is herein incorporated by reference in its entirety, describes the antifungal activity and preparation of azole compounds that include pramiconazole. In 2005, Phase 2A clinical trials were conducted with pramiconazole for the treatment of tinea pedis (athlete's foot), tinea corpis (ring worm), tinea cruris (jock itch), tinea versicolor and seborrheic dermatitis. A phase 2A clinical trial with pramiconazole is currently underway for the treatment of toenail onychomycosis.

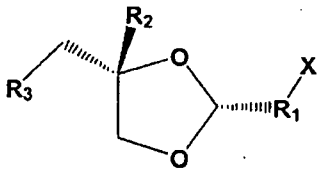
[0007] Given the above-indicated potential importance of pramiconazole in the treatment of a number of fungal infections, efficient syntheses of pramiconazole and pramiconazole-like compounds are desired. The present invention relates to the discovery of new methods for the preparation of the chiral dioxolane portion of the pramiconazole molecule in enantiomerically pure form. The present invention also relates to the use of this technology for the preparation of other therapeutically active compounds that contain this particular dioxolane moiety or other chiral dioxolane moieties described herein.

Summary of the Invention

[0008] An aspect of the invention is a process for preparing an enantiomerically pure compound of Formula (1) and Formula (2), or a salt thereof,

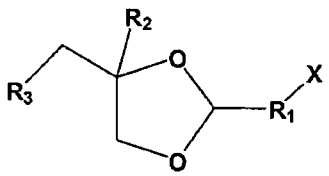


Formula (1)



Formula (2)

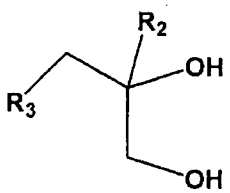
comprising treating the racemic dioxolane of Formula (3)



Formula (3)

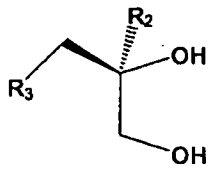
with a suitable enzyme, wherein R_1 is -(C_{1-6} alkylene); R_2 and R_3 are independently aryl or heteroaryl; and X is -OH or a leaving group.

[0009] Another aspect of the invention is a process for preparing an enantiomerically pure compound of Formula (1) and Formula (2), or a salt thereof, comprising treating the racemic diol of Formula (4)

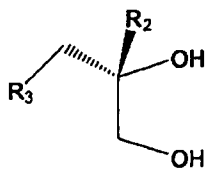


Formula (4)

wherein R_2 and R_3 are independently aryl or heteroaryl, with a suitable enzyme to provide an enantiomerically pure compound of Formula (5) and Formula (6)

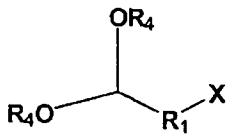


Formula (5)



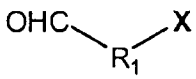
Formula (6),

followed by treatment with an acetal of Formula (7)



Formula (7),

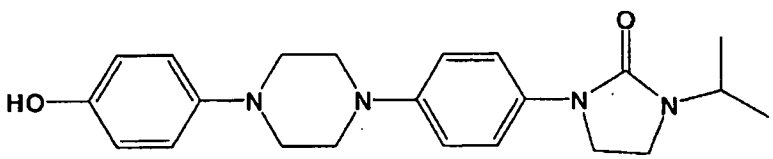
or an aldehyde of Formula (8)



Formula (8)

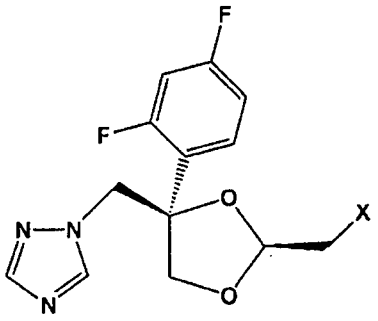
wherein for Formula (7), R_1 is -(C_{1-6} alkylene); each R_4 is independently C_{1-6}alkyl or aryl; and X is -OH or a leaving group; and for Formula (8), R_1 is -(C_{1-6} alkylene) and X is -OH or a leaving group.

[0010] Another aspect of the invention is a process for preparing enantiomerically pure pramiconazole, comprising combining the dioxolane of Formula (1), wherein the dioxolane of Formula (1) is prepared by the enzyme-facilitated methods as herein described, with the piperazine derivative of Formula (9)



Formula (9),

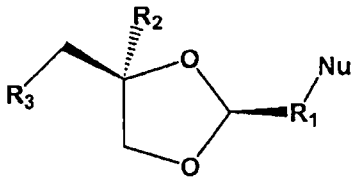
wherein for the dioxolane of Formula (1), R_1 is $-CH_2-$; R_2 is 2,4-difluorophenyl; and R_3 is 1,2,4-triazole (*i.e.*, the compounds of Formula (10) as shown below):



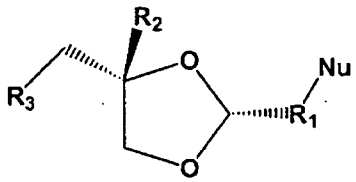
Formula (10).

[0011] In an exemplary embodiment, the variable "X" in Formula (10) is Br or O-mesyl.

[0012] Another aspect of the invention is a method for preparing a therapeutically active compound, or a pharmaceutically acceptable salt thereof, comprising combining an enantiomerically pure dioxolane of Formula (1) or Formula (2) with a carbon, oxygen or nitrogen nucleophile ("Nu") under reaction conditions sufficient for the nucleophile to displace the variable X of Formula (1) or Formula (2) to provide the products of Formula (11) and Formula (12) as shown below:



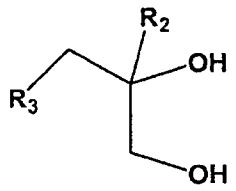
Formula (11)



Formula (12)

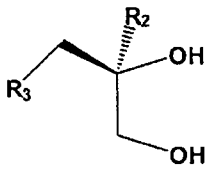
In an exemplary embodiment, the therapeutic compound exhibits antimicrobial or an antifungal properties. In an exemplary embodiment, the nucleophile is the compound of Formula (9) or a similar compound where the phenolic oxygen is the moiety that displaces the variable X of Formula (1) or Formula (2).

[0013] Another aspect of the invention is a method for preparing a therapeutically active compound, or a pharmaceutically acceptable salt thereof, comprising a step of treating the racemic diol of Formula (4)

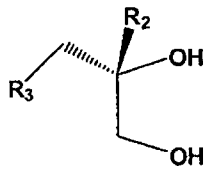


Formula (4)

wherein R_2 and R_3 are independently aryl or heteroaryl, with a suitable enzyme to provide the enantiomerically pure diol of Formula (5) and Formula (6)

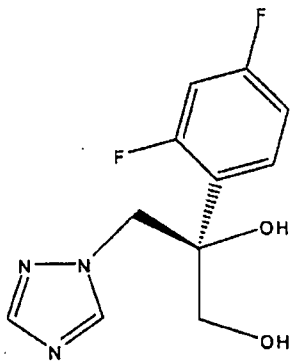


Formula (5)



Formula (6)

wherein R_2 and R_3 are independently aryl or heteroaryl. In an exemplary embodiment, the compound of Formula (5) is a compound of Formula (13)



Formula (13)

and the therapeutically active compound prepared by this method is posaconazole. In another exemplary embodiment, the therapeutically active compound prepared by this method is ZD-0870.

Brief Description of the Drawings

[0014] Each of the following figures illustrates an exemplary embodiment of the invention. Accordingly, the figures are not intended to restrict the scope of the invention as described herein.

[0015] **Figure 1** shows that the production of compound 3 (as identified in Scheme 1) from treatment of the corresponding racemate with CAL-B proceeded steadily over a 10-hour period, during which the enantiomeric excess approached 100% and the percent conversion approached 60%.

Detailed Description of the Invention

Definitions

[0016] Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0017] As defined herein, "effective amount" or "an amount effective to" or a "therapeutically effective amount" or any grammatically equivalent term refers to the amount that, when administered to an animal for treating a disease or condition, is sufficient to effect treatment for that disease or condition. Alternatively, an "effective amount" may be viewed as the amount of a compound or composition that is sufficient to induce an antifungal effect.

[0018] As defined herein, "enantiomerically pure" refers to enantiomeric forms of the compounds as mentioned herein that are substantially free of other enantiomeric forms of the same basic molecular structure of said compounds. In particular, the term "enantiomerically pure" refers to compounds having an enantiomeric excess (e.e.) of at least about 80% (*i.e.*, a minimum of about 90% of one enantiomer and a maximum of about 10% of the other possible

enantiomer) up to an enantiomeric excess of 100% (*i.e.*, 100% of one enantiomer and none of the other enantiomer), such as, for example, compounds having an enantiomeric excess of about 90% up to 100%, such as, for example, compounds having an enantiomeric excess of about 95% up to 100%, such as, for example, compounds having an enantiomeric excess of about 97% up to 100%. In exemplary embodiments of the invention, the enantiomeric excess of the dioxolane of Formula (1) or Formula (2) is at least about 95% or at least about 96% or at least about 97% or at least about 98% or at least about 99% or at least about 99.2% or at least about 99.4% or at least about 99.6% or at least about 99.8%.

[0019] As defined herein, the variable "X" may include any conventional leaving group known to those of skill in the art. In exemplary embodiments, the leaving group "X" includes, but is not limited to, halo (F, Cl, Br, I), mesylate (OMs), tosylate (OTs), nosylate (ONs), brosylate (OBs), triflate (OTf) or acetate (OAc).

[0020] As defined herein, a nucleophile is a molecule or ion that donates a pair of electrons to form a new covalent bond. Nucleophiles are typically Lewis bases and include the anion conjugate base of a protic acid. Specific nucleophiles include oxygen atoms (*e.g.* alcohols, alkoxides or phenoxides), nitrogen atoms (*e.g.* amines or amides) and carbon atoms (*e.g.*, Grignards (*i.e.*, compounds containing a carbon-magnesium bond) or compounds containing a carbon-lithium bond, carbon-sodium bond, and other carbon-metal bond).

[0021] As defined herein, the enzyme employed to resolve the racemic compounds represented by Formula (3) and Formula (4) may be, but is not limited to being a lipase. Exemplary embodiments of the enzyme used in the present invention include, but are not limited to, *Candida antarctica* lipase B (CAL-B), *Aspergillus niger, Pseudomonas sp., Candida rugosa, Candida cylindracea, Humicola lanuginesa, Rhizopus delemar, Penicilliium camemberti, Geotrichum candidum, Hog pancrease, Candida lipolytica, Mucor javanicus, Rhizopus niveus, Pig liver esterase, Porcine pancrease lipase, Pseudomonas cepacia (formerly called Pseudomonas fluorescens)* and *Penicillium roqueforti*. Other possibilities for the enzyme include a dioxygenase, dihydrogenase, enone reductase, acetohydroxyacid synthase, N-acylamino racemase, Baker's yeast and artificial enzymes.

[0022] The absolute configuration of each asymmetric carbon center in the herein described chiral compounds may be indicated by the stereochemical descriptors "R" and "S". The R and S notation corresponds to the rules described in, for example, Pure Appl. Chem. (1976), 45, 11-30. The terms "cis" and "trans" are used herein in accordance with Chemical Abstracts nomenclature (J. Org. Chem. (1970), 35(9), 2849-2867), and refer to the position of the substituents on a ring moiety, such as on the dioxolane ring in the compounds of Formula (1) or Formula (2). For instance, when establishing the cis or trans configuration of the dioxolane ring, the substituent with the highest priority on the carbon atom in the 2 position of the dioxolane ring, and the substituent with the highest priority on the carbon atom in the 4 position of the dioxolane ring are considered (the priority of a substituent being determined according to the Cahn-Ingold-Prelog sequence rules). When said two substituents with highest priority are at the same side of the ring then the configuration is designated cis, if not, the configuration is designated trans.

[0023] Pure enantiomeric forms of the compounds of this invention may be purified by the application of procedures that are well-known to those of skill in the art. For example, enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids or by chromatographic techniques using chiral stationary phases.

[0024] As defined herein, an "antimicrobial" is an agent that inhibits the growth of fungal and/or bacterial microorganisms or kills them outright. More specifically, an "antifungal" is an agent that inhibits the growth of fungi (*i.e.*, a fungistat) or kills them outright (*i.e.*, a fungicide) and an "antibacterial" or "antibiotic" is a substance that kills or slows the growth of bacteria.

[0025] As defined herein, the term "alkyl" refers to an optionally substituted straight chain, branched chain or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C_{1-6} means one to six carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl

group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. Substituents for the alkyl radical are generally selected from the group of substituents described below.

[0026] As defined herein, the term "alkylene" refers to, unless otherwise stated, divalent carbon radicals. In exemplary embodiments, an alkylene group is an eight carbon chain (*i.e.*, C_{1-8}) or a six carbon chain (*i.e.*, C_{1-6}) or a three carbon chain (*i.e.*, C_{1-3}). The alkylene chains may be further substituted. Specific embodiments include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)-$, $-CH(OCH_3)-$, $-CH_2CH(CH_2OCH_3)CH_2CH_2-$ and $-CH_2CH(Ph)CH_2-$.

[0027] As defined herein, the terms "halo" or "halogen" refer to, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0028] As defined herein, the term "aryl" refers to, unless otherwise stated, an optionally substituted polyunsaturated, aromatic, substituent that can be a single ring or multiple rings (preferably from 1 to 3 rings), which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, tetrazolyl, benzo[b]furanyl, benzo[b]thienyl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, benzo[1,3]dioxol-5-yl and 6-quinolyl. Substituents for each of

the above noted aryl and heteroaryl ring systems are generally selected from the group of substituents described below.

[0029] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, alkylaryl) includes both aryl and heteroaryl rings as defined above. Thus, as defined herein, the term "alkylaryl" refers to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxymethyl, 3-(1-naphthyloxy)propyl, and the like).

[0030] Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl" and "heteroaryl") is meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

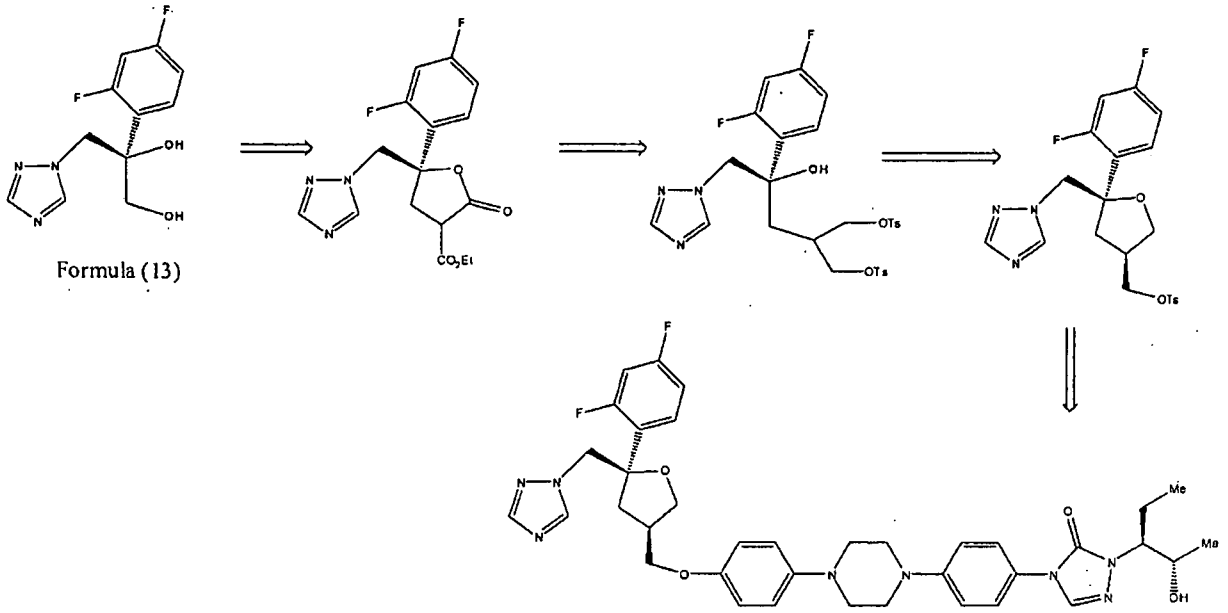
[0031] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) are generically referred to as "alkyl group substituents" and they can be one or more of a variety of groups selected from, but not limited to: -C_{1-10}alkyl, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2 in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R", R"' and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"' and R"" groups when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl.

[0032] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are generically referred to as "aryl group substituents." The substituents are

selected from, for example: -C_{1-10}alkyl, halogen, -OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"C$(O)_2$R', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -SR', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2, -R', -N_3, -$CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R"' and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"' and R"" groups when more than one of these groups is present.

[0033] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are independently -NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -Y-$(CH_2)_r$-Z-, wherein Y and Z are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X-$(CR"R"')_d$-, where s and d are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. In exemplary embodiments, the substituents R, R', R" and R"' are independently selected from hydrogen or substituted and unsubstituted (C_1-$_6$)alkyl.

[0034] U.S. Patent No. 5,714,490, which is incorporated by reference in its entirety, describes a synthesis of posaconazole that proceeds through the diol of Formula (13) as shown below:

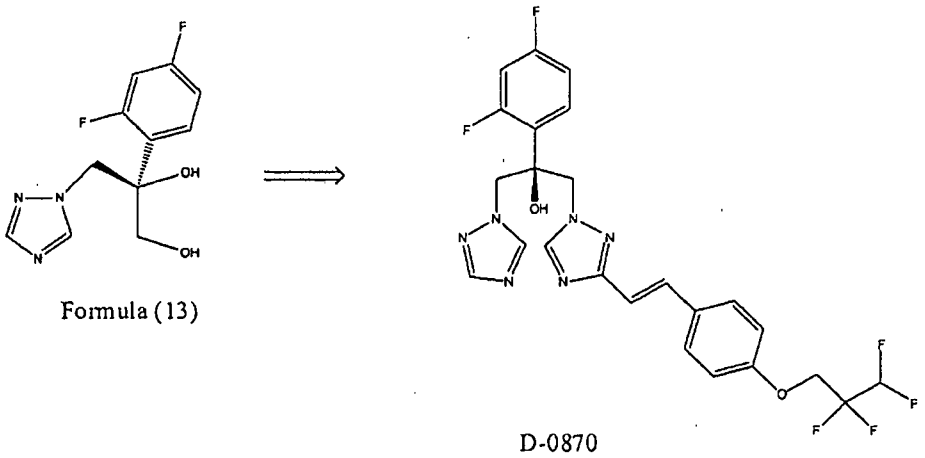


Formula (13)

Posaconazole

The present invention provides for a facile synthesis of the enantiomerically pure compound of Formula (13), which in turn may be used, in an exemplary embodiment, to provide a novel synthesis of the antifungal posaconazole.

[0035] U.S. Patent No. 4,925,863, which is incorporated by reference in its entirety, describes a synthesis of the antifungal ZD-0870 that also proceeds through the diol of Formula (13) as shown below:

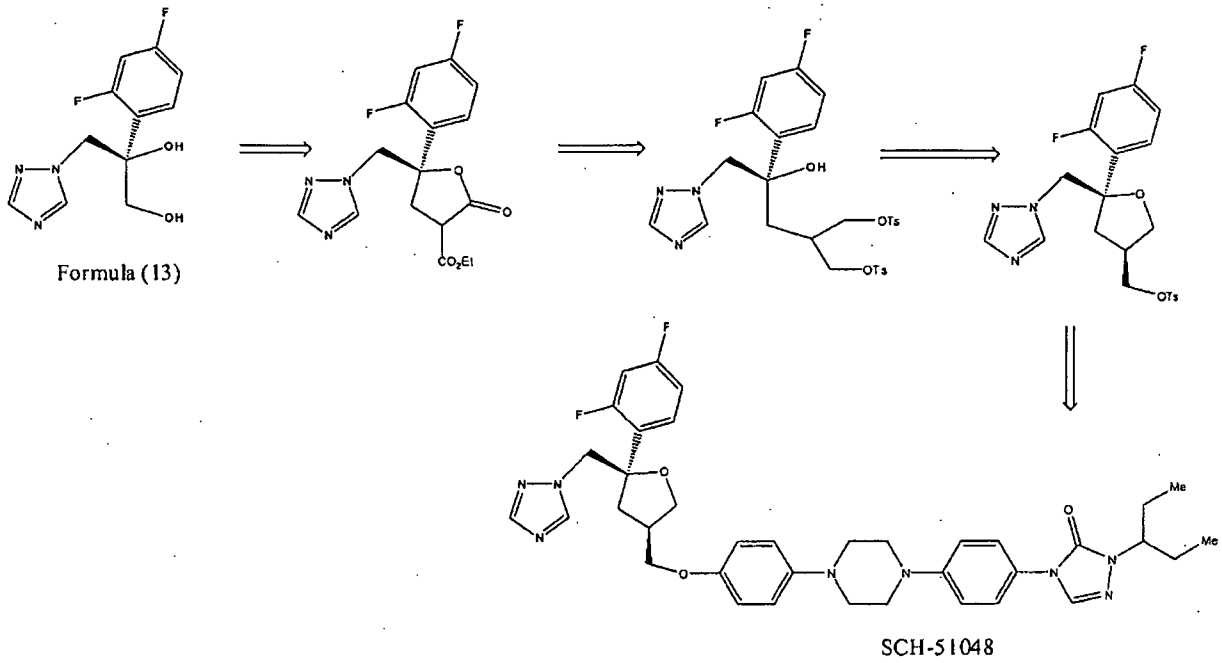


Formula (13)

D-0870

The present invention provides for a facile synthesis of the enantiomerically pure compound of Formula (13), which in turn may be used, in an exemplary embodiment, to provide a novel synthesis of the antifungal D-0870.

[0036] WO 93/09114 and U.S. Patent No. 5,625,064, both of which are incorporated by reference in their entireties, describe syntheses of antifungal compounds such as SCH-51048 that also proceed through the diol of Formula (13) as shown below:



Formula (13)

SCH-51048

The present invention provides for a facile synthesis of the enantiomerically pure compound of Formula (13), which in turn may be used, in an exemplary embodiment, to provide a novel synthesis of the antifungal SCH-51048.

[0037] Other antifungal compounds that may possibly be prepared by the methodology of the present invention for preparing enantiomerically pure compounds of, for example, Formulae (1), (2), (5) and (6) include, but are not limited to, ketoconazole, itraconazole, isoconazole, miconazole, econazole, sulconazole, fluconazole, fenticonazole, sertaconazole, tioconazole, fluconazole, voriconazole and ravuconazole.

[0038] The enantiomerically pure compounds of Formula (1) and Formula (2) may exist as pharmaceutically acceptable salts, either alone or as part of a larger molecule. Suitable pharmaceutical acceptable salts are those of organic or inorganic acids, including, but not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, trifluoroacetic acid, phosphoric acid, acetic acid, succinic acid, oxalic acid, malic acid, fumaric acid and the like.

[0039] Given that the therapeutic activity of compounds, such as pramiconazole, that contain the moiety represented by Formula (3) may be significantly enhanced if the Formula (1) moiety was in enantiomerically pure form, the present invention allows facile resolution of the compounds of Formula (3) and ultimately Formula (4) to the enantiomerically pure compounds of Formula (1) and Formula (2) on a economically beneficial scale.

[0040] Pramiconazole exhibits antifungal properties against, for example, *Candida* spp., *Pityrosporum* spp., *Malassezia* spp. and *Trichophyton* spp. For the most part, *Candida* spp. are ubiquitous fungi found throughout the world as normal body flora. Candidiasis is a common mycotic infection, especially in immunocompromised hosts, that contributes to a variety of diseases, such as, but not limited to, vaginal candidiasis (*e.g.*, vaginitis, vulvovaginitis and vulvar rash), oral thrush, conjunctivitis, oropharyngeal candidiasis, endophthalmitis, diaper rash, nail infections, infections of skin folds, systemic candidiasis, oral candidiasis, gastrointestinal candidiasis and red macerated intertriginous areas. Exemplary species of *Candida* include, but are not limited to, *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsiliosis*, *Candida guilliermondi*, *Candida lusitaniae* and *Candida krusei*. Exemplary embodiments of *Trichophyton* include, but are not limited to, *Trichophyton mentagrophytes* and *Trichophyton rubrum*. Exemplary embodiments of *Pityrosporum* include, but are not limited to, *Pityrosporum orbiculare*, *Pityrosporum ovale*, *Pityrosporum canis* and *Pityrosporum pachydermatis*. Exemplary embodiments of *Malassezia* include, but are not limited to, *Malassezia sympodialis*, *Malassezia globosa*, *Malassezia restricta*, *Malassezia slooffiae*, *Malassezia furfur*, *Malassezia obtusa* and *Malassezia pachydermatis*. Specific disorders that may be treated by administration of pramiconazole include, but are not limited to, tinea capitis (*e.g.*, seborrheic dermatitis, psoriasis, folliculitis and impetigo), tinea corporis (ring worm), tinea

cruris (jock itch), tinea versicolor, tinea pedis (athlete's foot) and onychomycosis (nail fungus, such as toenail onychomycosis).

[0041] Generalized and specific formulations of pramiconazole are described in U.S. Patent No. 6,387,906, which is herein incorporated by reference in its entirety.

[0042] Pharmaceutical compositions containing therapeutically active compounds that structurally incorporate the enantiomerically pure moieties of Formula (1) or Formula (2) may also optionally include other carriers, stabilizers, preservatives or adjuvants. For typical examples of these classes of compounds and for the compounds themselves, see Remington: The Science and Practice of Pharmacy, Lippincott, Williams & Wilkins (2005), which is herein incorporated by reference in its entirety.

[0043] Additional therapeutic agents that may be used in combination with the compounds of the invention include, but are not limited to, antimicrobial agents (*e.g.*, amphotericin B, clotrimazole, econazole nitrate, fluconazole, flucytosine, haloprogin, itraconazole, ketoconazole, miconazole, AN-1677, AN2690, bifonazole, luliconazole, neticonazole, sertaconazole, tioconazole, voraconazole, posaconazole and nystatin), anti-allergic agents (*e.g.*, astemizole, betamethasone, carbinoxamine maleate, chlorpheniramine maleate, clemastine fumarate, dexbrompheniramine maleate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenylpyraline hydrochloride and trimeprazine tartrate), anti-inflammatory agents (*e.g.*, ibuprofen, fenoprofen, ketoprofen, naproxen, diclofenac, etodolac, meclofenamate sodium phenylbutazone, indomethacin, piroxicam, sulindac and tolmetin), anti-proliferating agents (*e.g.*, mycophenolate mofetil and evodiamine), anti-acne agents (*e.g.*, tretinoin, isotretinoin, salicylic acid, benzoyl peroxide and azelaic acid), anti-pruritic agents (*e.g.*, azelastine, cetirizine permethrin and lindane), anti-aging agents and combinations thereof.

[0044] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the invention and practice the claimed methods. The following working examples

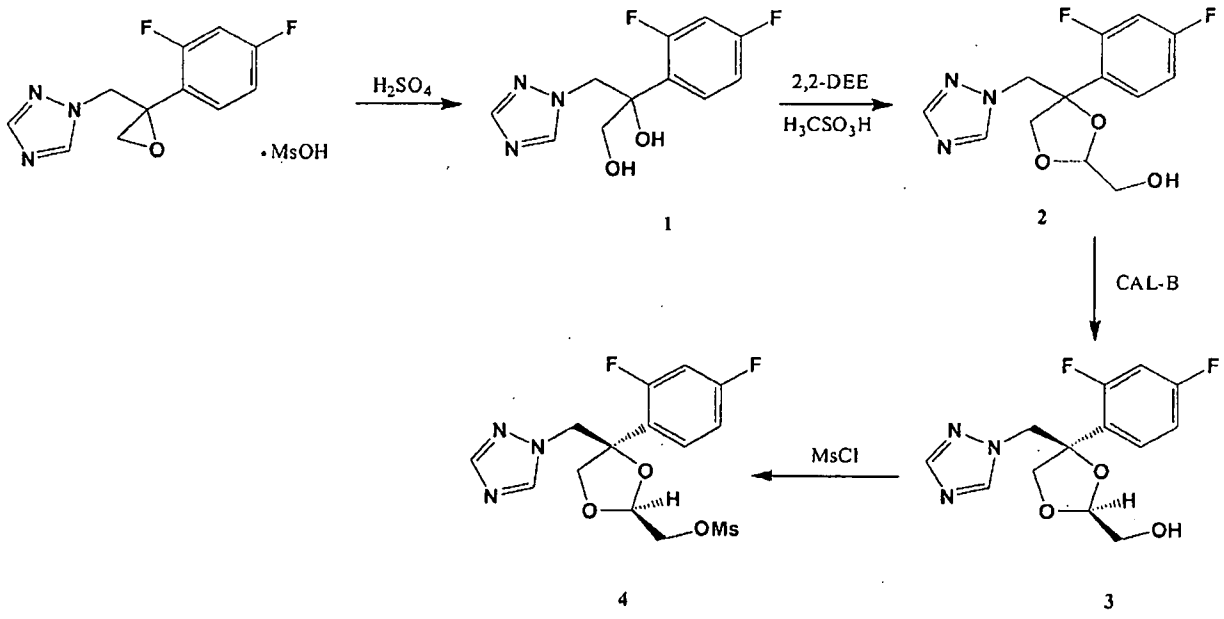
describe embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

Experimental

[0045] In the following schemes and examples, the treatment of racemic compounds 2 or 7 with a suitable resolving enzyme, results in the production of a pair of enantiomers. For simplicity, the undesired enantiomer is not shown or noted.

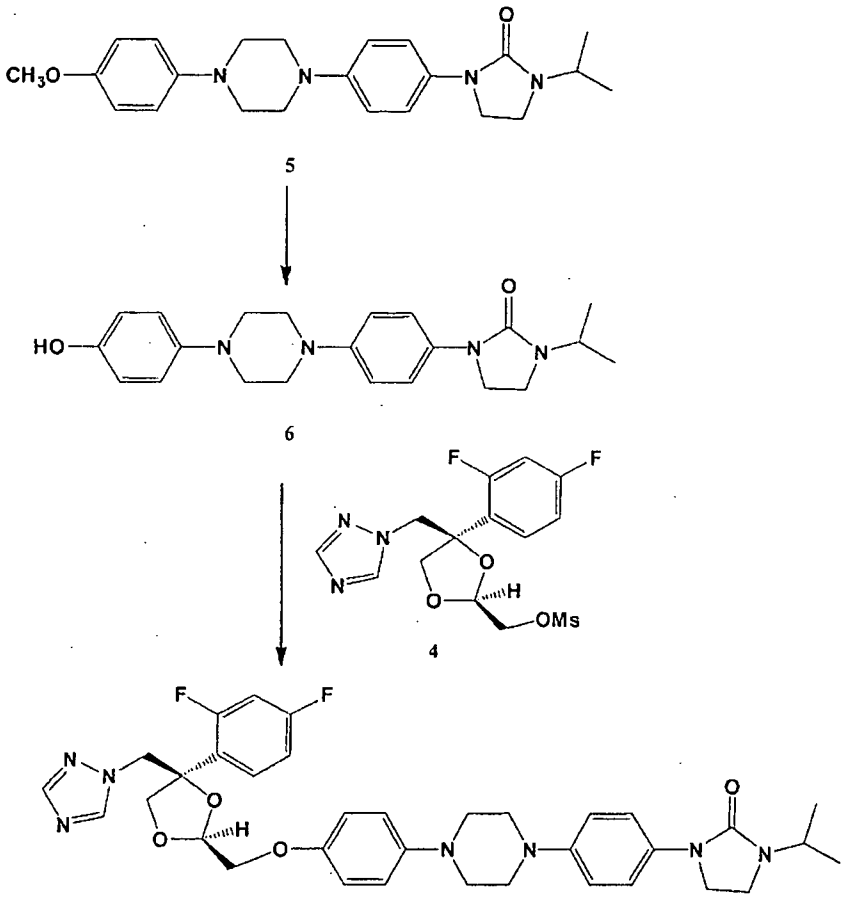
[0046] Scheme 1 below shows an exemplary embodiment of the invention in which enantiomerically pure pramiconazole is ultimately prepared. A commercially available racemic epoxide is converted to the corresponding diol (1), which is then transformed to the corresponding hydroxy-ketal (2). Hydroxy-ketal (2) is then resolved into its 2S,4R and 2R,4S enantiomeric components, with the component that is compound (3) (*i.e.*, 2S,4R) being treated with mesyl chloride to provide compound (4), which is a representative compound of Formula (1) (*i.e.*, R_1 is $-CH_2-$, X is mesylate, R_2 is 2,4-difluorophenyl and R_3 is a 1,2,4-triazole).

Scheme 1:



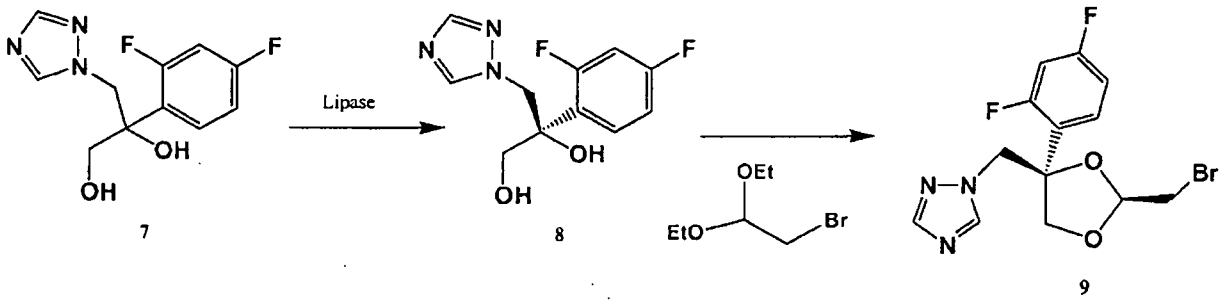
[0047] Scheme 2 below shows an exemplary embodiment of the invention in which enantiomerically pure compound (4) is combined with the known hydroxyphenyl piperazine compound (6) (derived from the methoxyphenyl piperazine compound (5)) to provide enantiomerically pure pramiconazole.

Scheme 2:



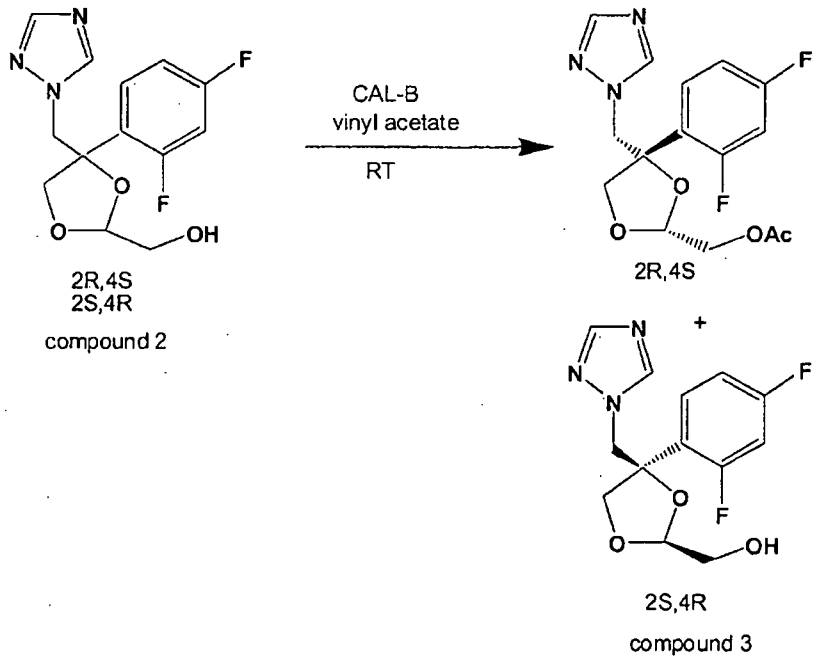
[0048] Scheme 3 below shows an exemplary embodiment of an alternative method of preparing enantiomerically pure compounds like compound (4). In the depicted case, compound (9), which differs from compound 4 in the identity of the "X" variable (*i.e.*, Br versus OMs), is prepared through lipase resolution of racemic compound 7.

Scheme 3:



[0049] Just like with compound (4), compound (9) can be combined with the hydroxyphenyl piperazine compound (6) to provide enantiomerically pure pramiconazole.

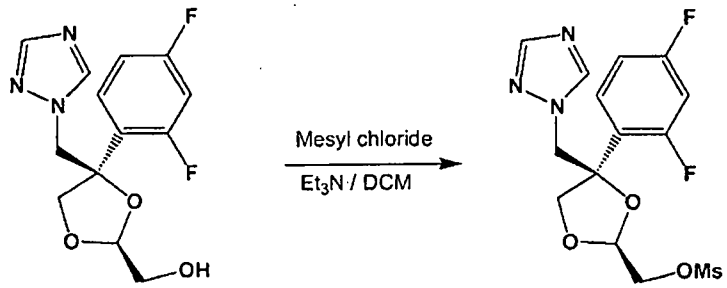
[0050] Example 1 from Scheme 1:



Approximately 4,000 mL of vinyl acetate was added to a round-bottomed flask. The initial moisture content of the vinyl acetate was then measured and adjusted to 0.8 to 1.0% by adding water. Approximately 100 g of compound 2 was added to the vinyl acetate at 30 to 35°C and stirred for 5 to 10 minutes before the addition of 3.6 g of 2,6-lutidine, also at 30 to 35°C for 5 to 10 minutes. Approximately 5 g of CAL-B enzyme was then added to the round-bottomed flask and the reaction was maintained for 10 hours at 30 to 35°C. After 10 hours, the reaction was

monitored periodically by HPLC to assess the progress of the resolution reaction. When the enantiomeric excess of compound 3 was greater than 98, the enzyme was filtered from the reaction mixture and the vinyl acetate was evaporated at a temperature below 45°C until approximately 500 mL of the reaction mixture remained. Approximately 1,500 mL of demineralized water was added and the remaining vinyl acetate was removed under vacuum at 50 to 55°C. The resulting solids were cooled to 5 to 10°C and then stirred for 1 hour before being filtered and washed with approximately 300 mL of water chilled to 5 to 10°C. The solid filter cake was set aside. The pooled mother liquor was mixed with approximately 1,000 mL of methyl isobutyl ketone (MIBK) and stirred for 15 to 30 minutes at 30 to 35°C before the layers were separated. The aqueous layer was washed with successive portions of MIBK and the combined organic layers were evaporated under vacuum at 50 to 55°C until the volume was less than 200 mL. Approximately 1,000 mL of hexane were added and the mixture was stirred for 10 to 15 minutes before being cooled to 0 to 5°C and stirred for 1 to 2 hours. The resulting solid was filtered and washed with hexane. The solid filter cake that was set aside in an earlier step was combined with this most recently collected solid and then mixed with 180 mL of MIBK in a round-bottomed flask and stirred for 30 to 60 minutes at 30 to 35°C. Approximately 1,000 mL of hexane were added over 30 minutes at 30 to 35°C and the mixture was stirred an additional 30 to 60 minutes at 30 to 35°C before being cooled to 0 to 5°C and stirred for 1 hour. The mixture was then filtered and washed with chilled (0 to 5°C) hexane before being dried under vacuum.

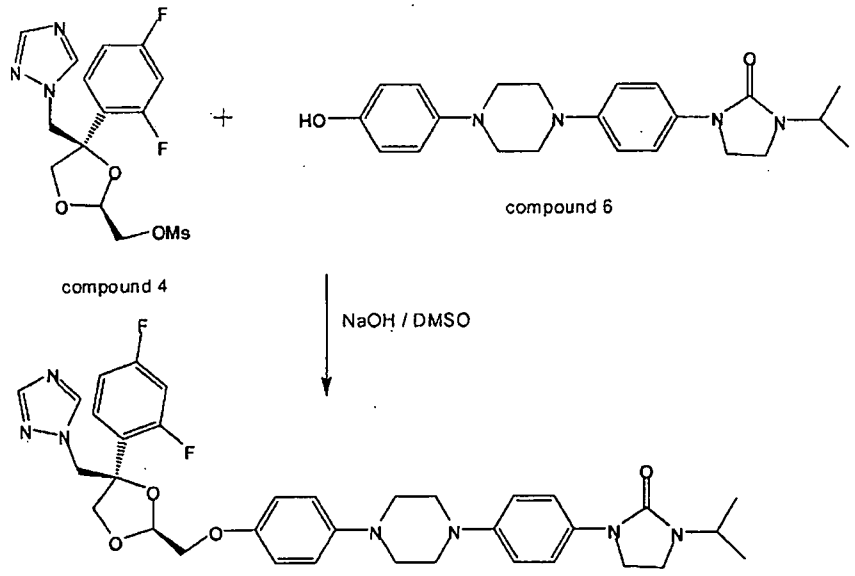
[0051] Example 2 from Scheme 1:



compound 3 compound 4

Approximately 50 g of compound 3 and 500 mL of dichloromethane were combined in a round-bottomed flask at 25 to 35°C. Approximately 34 g of triethylamine were added at 25 to 35°C and the reaction mixture was cooled to 0 to 10°C before the dropwise addition of 29 mL of methanesulfonyl chloride at 0 to 10°C. After being allowed to stir for 2 to 3 hours at 0 to 10°C, the reaction mixture was diluted with 150 mL of demineralized water and stirred for 5 to 10 minutes. The layers were separated and the aqueous layer was extracted successively with two 150 mL portions of dichloromethane. The organic layers were combined and washed successively with three 150 mL portions of water. The organic layer was then concentrated to a minimum volume, charged with 500 mL isopropylamine and concentrated under vacuum. The resulting mass was cooled to 25 to 35°C and maintained for 2 to 3 hours before being cooled to 8 to 12°C and maintained for an additional 2 to 3 hours. The mass was then filtered and the solid washed with 100 mL of isopropylamine cooled to 8 to 12°C. Yield of compound 4: 75 to 85%. Chemical purity: not less than 98%. Chiral purity: not less than 98%.

[0052] Example 1 from Scheme 2:



Approximately 200 mL of DMSO and 20 g of compound 6 were combined in a round-bottomed flask. The mixture was maintained at a temperature of 25 to 35°C while 20 g of compound 4 was added. The mixture was heated at 61 to 64°C while 2.5 g of sodium hydroxide in 5 mL of

demineralized water was added dropwise over 15 to 20 minutes. The mixture was then heated at 63 to 67°C for 5 to 6 hours or until the reaction appeared complete by TLC. The reaction mixture was then cooled to 25 to 35°C, afterwhich 400 mL of demineralized water at 25 to 35°C was added. Addition of water was exothermic and resulted in elevation of the reaction mixture to 45°C. The reaction mixture was stirred for 1 hour at 25 to 35°C before being filtered. The resulting solid cake was washed with successive 40 mL amounts of methanol and dried under vacuum for 5 to 7 hours at 80 to 85°C. Yield: 80%.

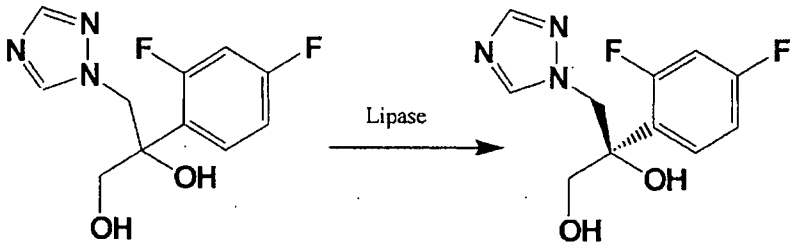
[0053] Table 1 confirms the reproducibility of the enzymatic resolution step involving treatment of compound 2 with CAL-B (as depicted in Scheme 1) by showing that for three separate 100-g samples, the enantiomeric purity of compound 3 was between 99.1 to 99.6, while the chemical purity ranged from 98.25 to 98.94. As depicted in Table 1, "% of conversion" refers to the percent of the racemic mixture that is represented by compound 2 that is converted to the individual enantiomers and "yield (%)" refers to the isolated yield of the enantiomerically pure compound 3.

[0054] Table 1: Data for Resolution of Compound 2 using CAL-B

Batch No.	Batch Size (g)	% of conversion	Chiral purity	Chemical Purity	Yield (%)
1	100	60.6	99.6	98.25	30
2	100	62.5	99.5	98.75	29
3	100	60.5	99.1	98.94	29.3

[0055] Figure 1 shows that the resolution of compound 2 into its enantiomeric components (as shown in Scheme 1) proceeded steadily over a 10-hour period, during which the enantiomeric excess approached 100% and the percent conversion approached 60%.

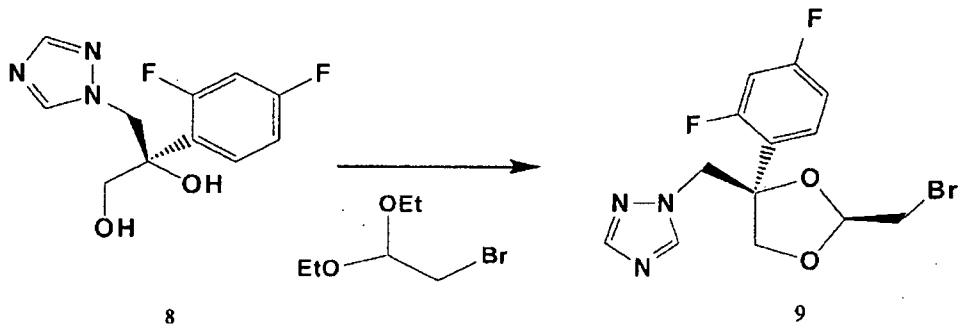
[0056] Example 1 from Scheme 3:



7 8

[0057] Approximately 4.5 kg of lipase, 75 kg of compound 7, 271 kg of ethyl acetate (EtOAc), 281 kg of vinyl acetate and 0.8 kg of water were combined in a reactor. The temperature of the mixture was raised to 40±5°C and the reaction was continued for 12 hours. During this time, the reaction mixture is analyzed by HPLC to confirm that the optical purity of compound 8 is not less than 90 % e.e., which is a condition to finish the reaction. If the e.e. of compound 8 does not meet this requirement, the reaction is continued and analyzed every 3 hours. After the reaction is complete, it is cooled to less than 30°C. The reaction mixture is then filtered through Hyflo super-cel and the residual cake is washed with approximately 150 kg of EtOAc. The combined filtrate is concentrated under vacuum to remove the solvent. Approximately 225 kg of acetonitrile was added and the reaction mixture was concentrated under vacuum at a temperature of no higher than 50°C. Approximately 225 kg of acetonitrile was added and the reaction mixture was cooled to 20±5°C and stirred for not less than two hours. The reaction mixture was then cooled to -5±5°C and stirred for not less than two hours. The resulting crystals were filtered and washed with 165 kg of acetonitrile at a temperature of-5±5°C before being dried under vacuum at a temperature of no higher than 50°C. Yield: 30-45%.

[0058] Example 2 from Scheme 3:



8 9

[0059] Approximately 38.0 kg of enantiomerically pure compound 8 and 209 kg of methanesulphonic acid were combined in a reactor. Approximately 31.1 kg of bromoacetaldehyde diethyl acetal (BADE) was added dropwise at 25±10°C with stirring. The reaction was complete when the content of compound 8 in the reaction mixture was no more than 5.0 % and R-cis (compound 9)/R-trans product ratio is not less than 1.60. If these requirements are not met, the reaction mixture is analyzed by every 2 hours. After the reaction is completed, it is quenched with aqueous sodium hydrogen carbonate and MTBE. The pH value of the aqueous layer is ascertained - if the pH is less than 6, an aqueous solution of sodium hydrogen carbonate is added. After separation, the organic layer is concentrated under vacuum and purified by silica gel column (mobile phase: MTBE-EtOAc). The fractions corresponding to compound 9 were collected and concentrated under vacuum. Methyl tert-butyl ether (MTBE) was added to the concentrated material, followed by dropwise addition of methanesulphonic acid. (Note: the methansulfonic acid may be diluted by MTBE or EtOAc before the dropwise addition). The amount of methanesulfonic acid was based on the recovered amount of compound 9. The resulting crystals were filtered, rinsed and dried under vacuum. Yield: 30-75%.

[0060] Unless defined otherwise, all technical and scientific terms herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials, similar or equivalent to those described herein, can be used in the practice or testing of the present invention, the preferred methods and materials are described herein. All publications and patent applications cited herein are incorporated herein by reference for the purpose of disclosing and describing specific aspects of the invention for which the publication is cited.

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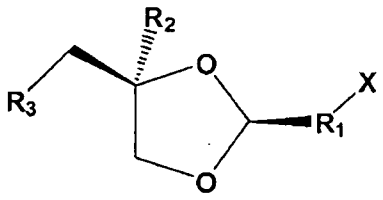
[0063] Elsayed, S.; Laupland, K.B., "Emerging gram-positive bacterial infections," Clin. Lab. Med., **2004**, 24, 587-603.

[0064] Minari, A.; Husni, R.; Avery, R.K.; Longworth, D.L.; DeCamp, M.; Bertin, M.; Schilz, R.; Smedira, N.; Haug, M.T.; Mehta, A.; Gordon, S.M., Transpl. Infect. Dis., **2002**, 4, 195.

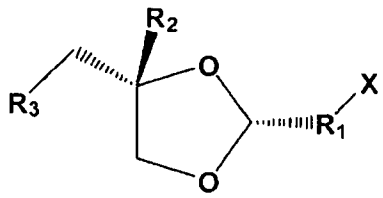
[0065] White, T.C.; Marr, K.A.; Bowden, R.A., "Clinical, Cellular, and Molecular Factors That Contribute to Antifungal Drug Resistance," Clin. Microbiol. Rev. **1998**, 11, 382-402.

We claim:

1. A process for preparing an enantiomerically pure compound of Formula (1) or Formula (2), or a salt thereof,

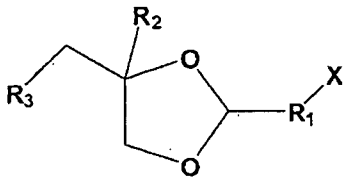


Formula (I)



Formula (2)

comprising treating the racemic dioxolane of Formula (3)



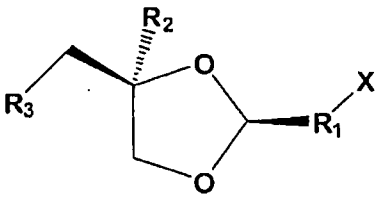
wherein

R_1 is -(C_{1-6} alkylene);

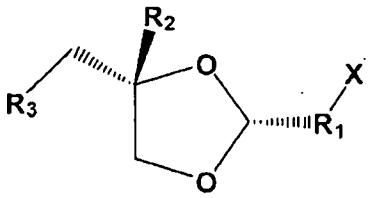
R_2 and R_3 are independently aryl or heteroaryl; and

X is -OH or a leaving group.

2. A process for preparing an enantiomerically pure compound of Formula (1) or Formula (2), or a salt thereof,

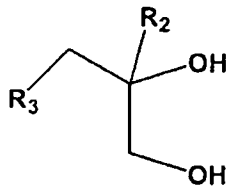


Formula (I)



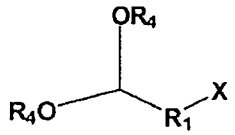
Formula (2)

comprising treating the racemic diol of Formula (4)



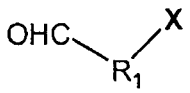
Formula (4)

with an enzyme, followed by treatment with an acetal of Formula (5)



Formula (5),

or an aldehyde of Formula (6)



Formula (6)

wherein for Formula (5),

R_1 is -(C_{1-6} alkylene);

each R_4 is independently C_{1-6}alkyl or aryl;

and X is -OH or a leaving group;

and for Formula (6),

R_1 is -(C_{1-6} alkylene) and

X is -OH or a leaving group.

3. The process according to claim 1 or claim 2, wherein

R_1 is -CH_2-;

R_2 is phenyl, where the phenyl is optionally substituted; and

R_3 is a heteroaryl ring.

4. The process according to claim 1 or claim 2, wherein

R_1 is $-CH_2-$;

R_2 is difluorophenyl; and

R_3 is a triazole ring.

5. The process according to claim 2, wherein each R_4 is C_{1-6} alkyl.

6. The process according to claim 2, wherein each R_4 is methyl or ethyl.

7. The process of claim 1 or claim 2, wherein the compounds of Formula (1) and Formula (2) have an enantiomeric excess of at least about 80%.

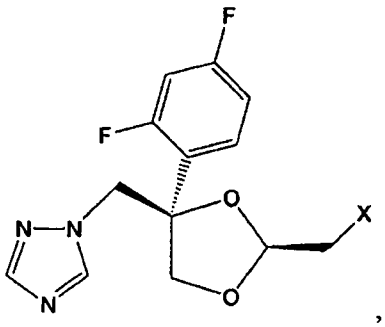
8. The process of claim 1 or claim 2, wherein the compounds of Formula (1) and Formula (2) have an enantiomeric excess of at least about 90%.

9. The process of claim 1 or claim 2, wherein the compounds of Formula (1) and Formula (2) have an enantiomeric excess of at least about 95%.

10. The process of claim 1 or claim 2, wherein the compounds of Formula (1) and Formula (2) have an enantiomeric excess of at least about 97%.

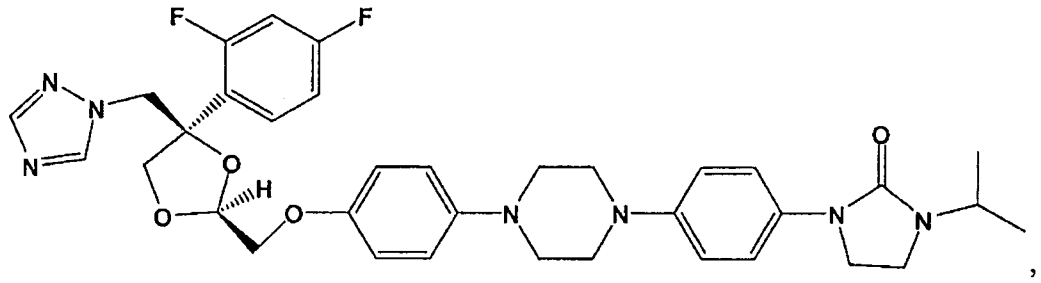
11. The process of claim 1 or claim 2, wherein the compounds of Formula (1) and Formula (2) have an enantiomeric excess of at least about 99%.

12. The process according to claim 1, wherein the compound of Formula (I) is the compound of Formula (8)

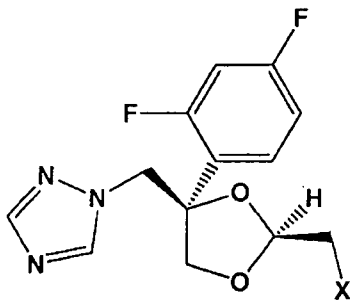


or a salt thereof.

13. A process for preparing enantiomerically pure pramiconazole, or a pharmaceutically acceptable salt thereof,

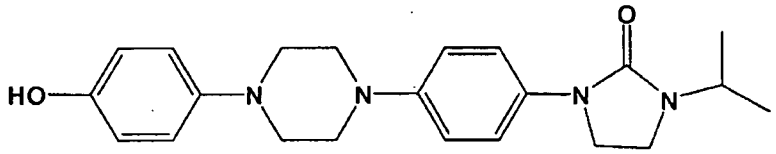


comprising combining a dioxolane of Formula (8)



Formula (8)

with the piperazine of Formula (7)



Formula (7)

wherein X is selected from the group consisting of Cl, Br, I, OMs, OTs, ONs, OBs, OTf and OAc, and

wherein the compound of Formula (8) is prepared according to the process of claim 1.

14. The process of claim 13, wherein R is selected from the group consisting of OMs and Br.

15. The process of claim 13, wherein the pramiconazole has an enantiomeric excess of at least about 80%.

16. The process of claim 13, wherein the pramiconazole has an enantiomeric excess of at least about 90%.

17. The process of claim 13, wherein the pramiconazole has an enantiomeric excess of at least about 95%.

18. The process of claim 13, wherein the pramiconazole has an enantiomeric excess of at least about 97%.

19. The process of claim 13, wherein the pramiconazole has an enantiomeric excess of at least about 99%.

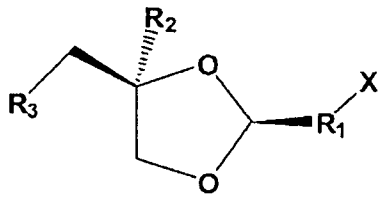
20. The process of any one of claims 1, 2 and 13, wherein the enzyme is selected from the group consisting of *Candida antarctica* lipase B (CAL-B), *Aspergillus niger, Pseudomonas sp., Candida rugosa, Candida cylindracea, Humicola lanuginesa, Rhizopus delemar, Penicilliium camemberti, Geotrichum candidum, Hog pancrease, Candida lipolytica, Mucor javanicus,*

Rhizopus niveus, Pig liver esterase, Porcine pancrease lipase, Pseudomonas cepacia (formerly called Pseudomonas fluorescens) and *Penicillium roqueforti.*

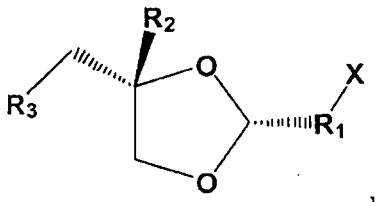
21. The process according to claim 20, wherein the enzyme is *Candida antarctica* lipase B (CAL-B).

22. A process for preparing a therapeutically active molecule, or a pharmaceutically acceptable salt thereof, comprising

combining an enantiomerically pure dioxolane of Formula (1) or Formula (2)

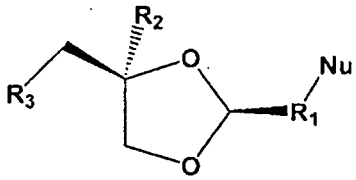


Formula (I)

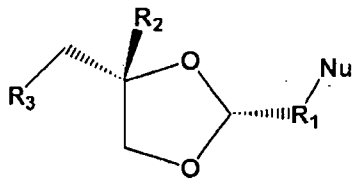


Formula (2)

with a carbon, oxygen or nitrogen nucleophile (Nu) under reaction conditions sufficient for the nucleophile to displace the variable X of Formula (I) or Formula (2) to provide a compound of Formula (9) or Formula (10)



Formula (9)



Formula (10).

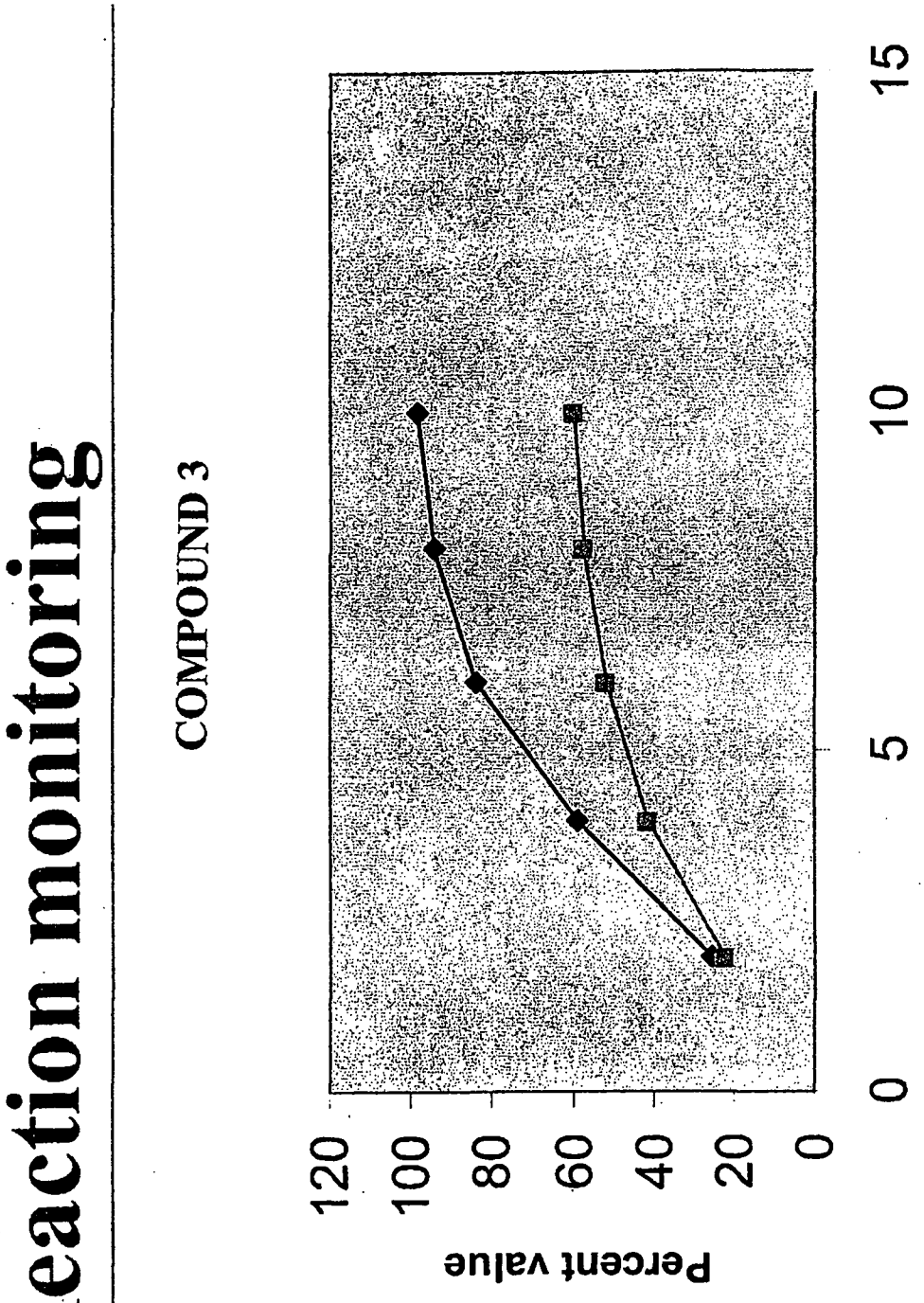

Reaction monitoring
COMPOUND 3
Percent value
120
100
80
60
40
20
0
0
5
10
15
Time (hours)
%ee
%conversion

FIG. 1