

(19) World Intellectual Property Organization
International Bureau



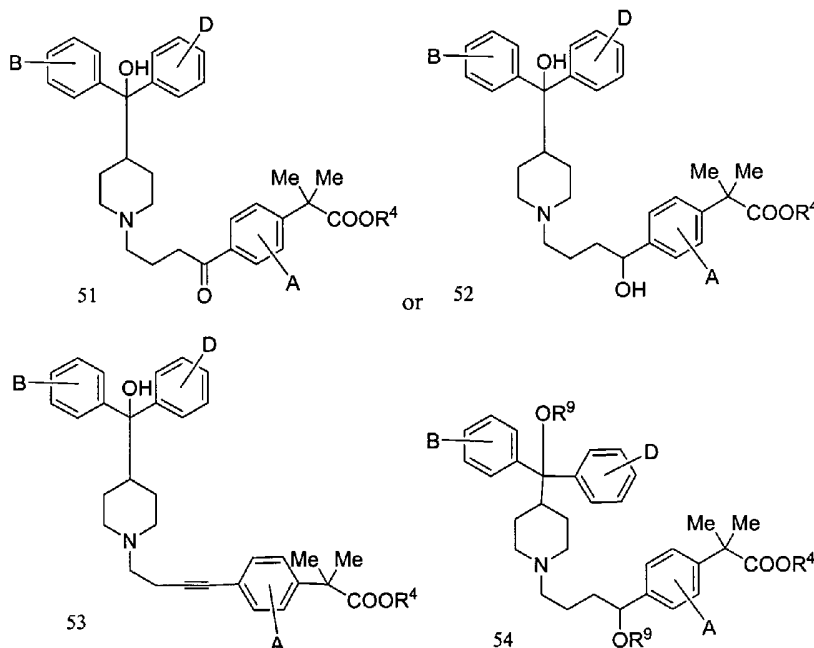
(43) International Publication Date
30 March 2006 (30.03.2006)

PCT

(10) International Publication Number
WO 2006/034092 A2

- (51) International Patent Classification: **Not classified**
- (21) International Application Number: PCT/US2005/033276
- (22) International Filing Date: 19 September 2005 (19.09.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 10/943,276 17 September 2004 (17.09.2004) US
- (71) Applicant (for all designated States except US): **AMR TECHNOLOGY, INC.** [US/US]; 5429 Main Street, Manchester, VT 05255 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **MECKLER, Harold** [US/US]; 45 Preston Road, Delmar, NY 12054 (US). **LITTLER, Benjamin J.** [GB/US]; 175 Beacon Street, Apartment 114, Somerville, Massachusetts 02143 (US). **RAJE, Prasad** [IN/US]; 66 Ivy Wood Drive, Glenmont, NY 12077 (US). **VAN BRUNT, Michael** [US/US]; 16619 SE 261st Street, Covington, WA 98042 (US). **VOGT, Paul F.** [US/US]; 7 Fairway Court, Albany, NY 12208 (US). **REISCH, Helge** [DE/US]; 1805 9th Street, Rensselaer, NY 12144 (US).
- (74) Agent: **HANSEN, Philip E.**; Heslin Rothenberg Farley & Mesiti, P.C., 5 Columbia Circle, Albany, NY 12203 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, 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, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR PRODUCTION OF PIPERIDINE DERIVATIVES



(1)

(57) Abstract: Processes are disclosed for preparing piperidine derivative compounds of Formulae (51, 52, 53 or 54). The processes involve reacting a compound of Formulae (41, 42, 43 or 44) with isobutyrate or an isobutyrate equivalent.

PROCESS FOR PRODUCTION OF PIPERIDINE DERIVATIVES

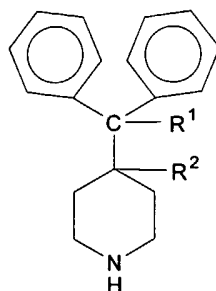
FIELD OF THE INVENTION

[0001] The present invention relates to processes for the production of piperidine derivatives.

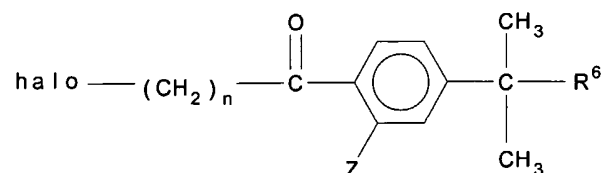
BACKGROUND OF THE INVENTION

[0002] Fexofenadine, 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylphenylacetic acid, formerly known as terfenadine carboxylic acid metabolite, is a potent non-sedating antihistamine sold by Aventis in the United States under the tradename ALLEGRA[®] and elsewhere in the world under the tradename TELFAST[®].

[0003] The importance of commercially viable syntheses of fexofenadine is attested to by the scores of patents to fexofenadine processes. Piperidine derivatives related to fexofenadine are disclosed in the following U.S. patents: 4,254,129; 4,254,130; 4,285,957; and 4,285,958. In these patents, 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]- α,α -dimethylbenzeneacetic acid and related compounds are prepared by alkylation of a substituted piperidine derivative of the formula:

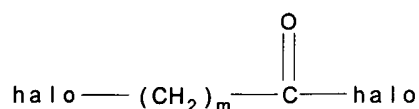


with an ω -haloalkyl substituted phenyl ketone of the formula:



wherein the substituents halo, R^1 , R^2 , n , Z , and R^6 are described in column 6 of U.S. Patent No. 4,254,130.

[0004] U.S. Patent No. 4,254,130 indicates that ω -haloalkyl substituted phenyl ketones, wherein Z is hydrogen, are prepared by reacting an appropriate straight or branched lower alkyl C_{1-6} ester of α - α -dimethylphenylacetic acid with a compound of the following formula:



under the general conditions of a Friedel-Crafts acylation, wherein halo and m are described in column 11 of U.S. Patent No. 4,254,129. The reaction is carried out in carbon disulfide as the preferred solvent.

[0005] A more recent approach via Friedel-Crafts acylation with succinic anhydride, condensation with the piperidine and reduction of the ketone and amide carbonyls has issued as US patent 6,743,941.

[0006] It has been found that the Friedel-Crafts methods have two significant shortcomings: (1) only acyl halides or anhydrides can be used; (2) in the particular case of the fexofenadine intermediate phenyl ketones, a higher regioselectivity of the Friedel-Crafts acylation would be desirable.

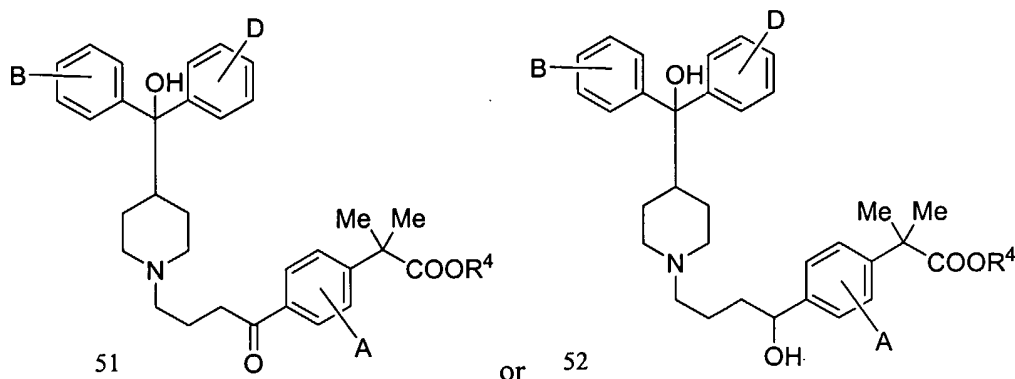
[0007] In another approach, which is the subject of a series of patents to D'Ambra and others (U.S. patents 5,589,487; 6,153,754 and 6,201,124), fexofenadine is synthesized by a regioselective method employing non-Friedel-Crafts acylation. The processes of the D'Ambra patents involve acylation of an aromatic ring at a position already para-substituted with a reactive species. Acylation can be carried out by a variety of techniques, including a butyl derivative acylating agent, a 4-(α,α -disubstituted)-toluic acid derivative acylating agent, or an organometallic coupling reaction. Since such procedures do not involve replacement of hydrogen on an aromatic ring, they are distinguished from electrophilic aromatic substitutions like the Friedel-Crafts acylation reaction.

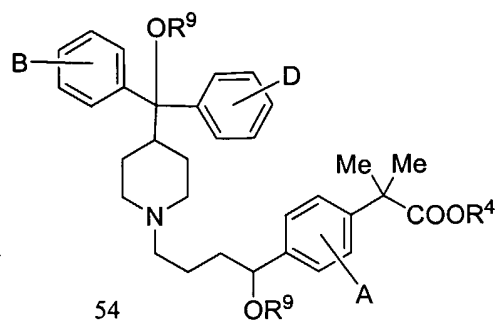
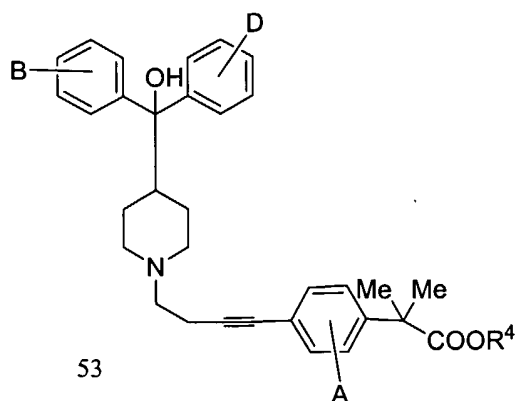
[0008] Other procedures for producing fexofenadine are disclosed in PCT Application Nos. WO95/00482, WO94/03170, and WO95/00480. A more recent approach is outlined in US published application 2003/0166682, in which an intermediate nitrile is hydrolyzed to fexofenadine.

[0009] The present invention is directed toward an improved process for preparation of fexofenadine.

SUMMARY OF THE INVENTION

[0010] The present invention relates to processes for preparing piperidine derivative compounds of the formula 51, 52, 53 or 54:



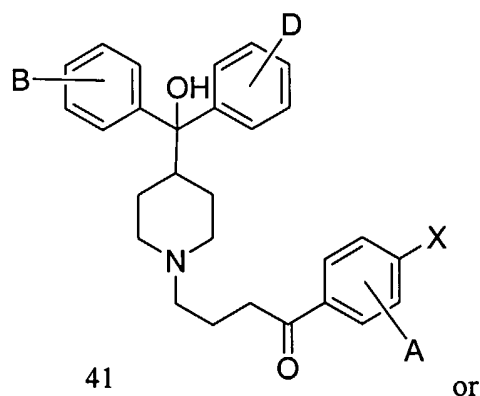


wherein

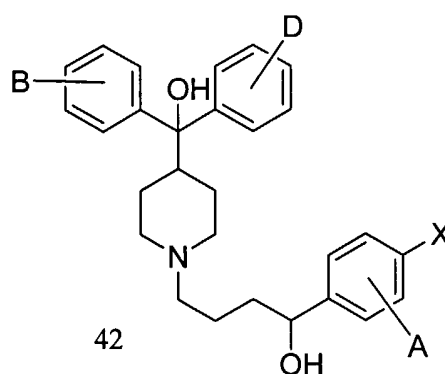
R^4 is H, alkyl, aryl or substituted aryl;

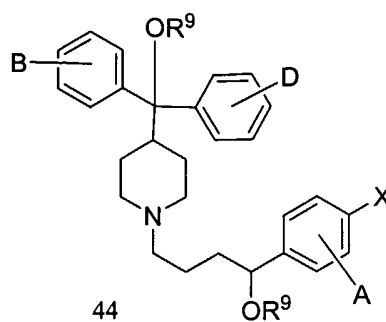
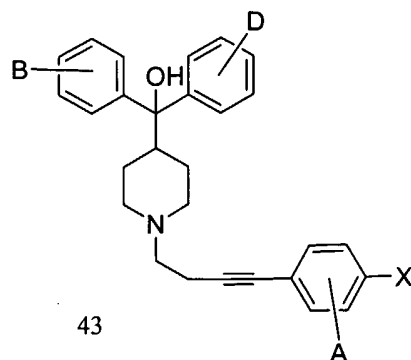
R^9 is a protecting group for an alcohol chosen from a benzyl ether, a silyl ether and an acyl;

A, B, and D are the substituents of their rings, each of which may be different or the same, and are selected from the group consisting of hydrogen, fluorine, chlorine, alkyl, aryl, hydroxyl, alkoxy, and aryloxy. The process comprises providing a compound of formula 41, 42, 43 or 44:



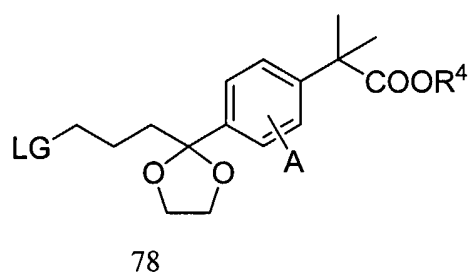
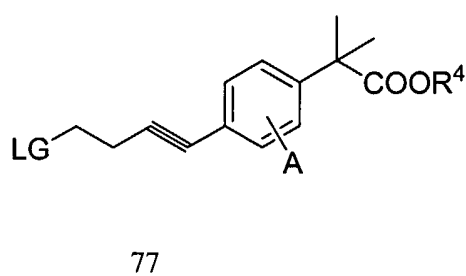
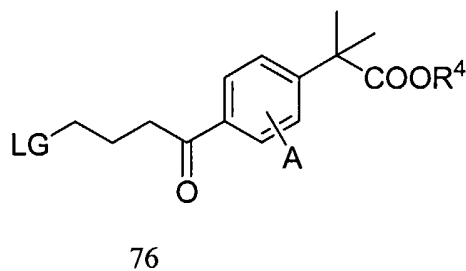
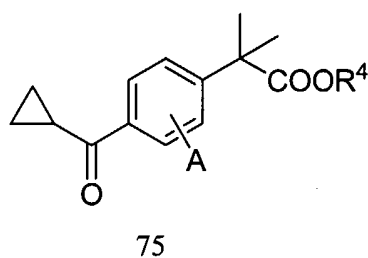
or



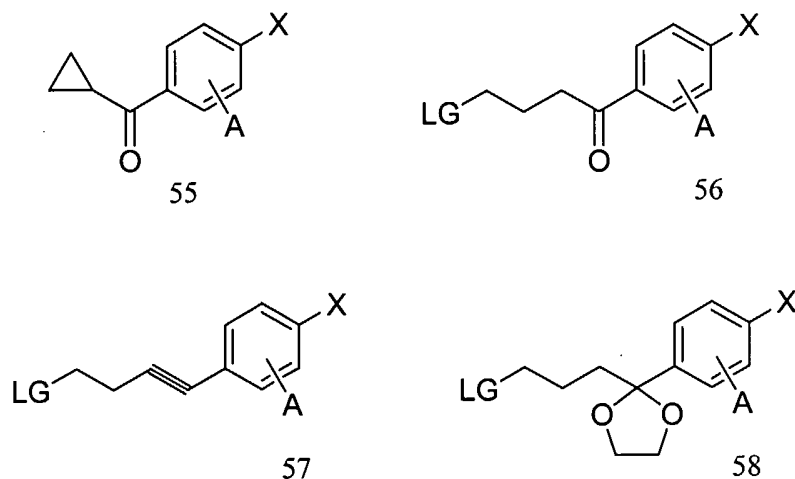


wherein X is any group displaceable via an oxidative metallic addition, and converting the compound of formula 41-44 to 51-54, respectively, by reacting with isobutyrate or an isobutyrate equivalent.

[0011] In another aspect the invention relates to a process for preparing an α,α -dimethylphenylacetate of the formula 75, 76, 77 or 78:

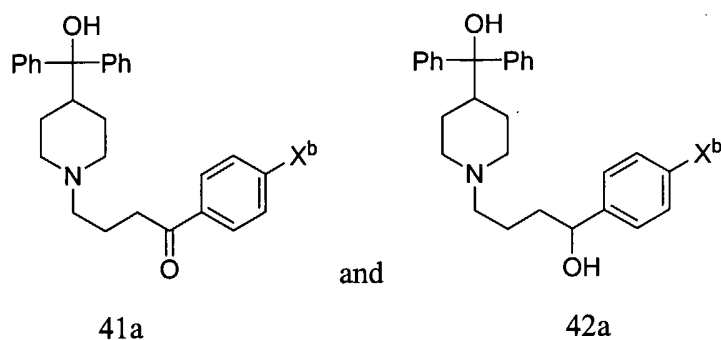


wherein LG is a leaving group displaceable by a secondary amine. The process comprises providing a compound of formula 55, 56, 57 or 58:



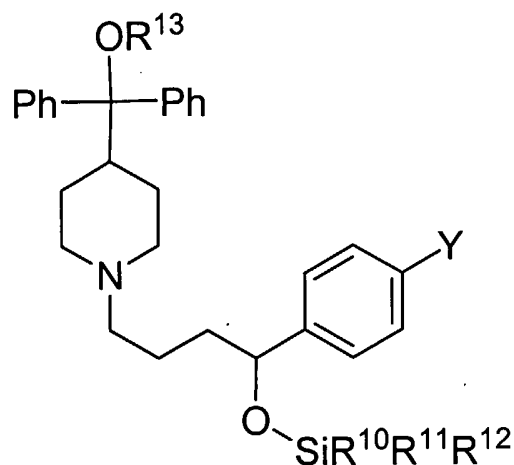
and converting the compound of formula 55-58 to 75-78 respectively by reacting with isobutyrate or an isobutyrate equivalent.

[0012] In another aspect the invention relates to compounds of formula 41a and 42a:



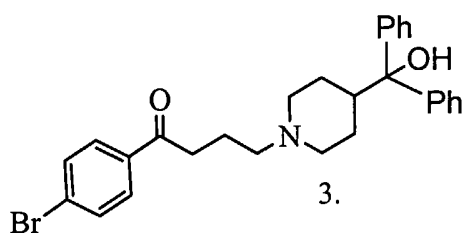
in which X^b is $-\text{OSO}_2\text{R}^5$, $-\text{N}_2^+$, $-\text{OP}(\text{O})\text{OR}^6(\text{OR}^7)$ or $-\text{B}(\text{OR}^6)(\text{OR}^7)$, wherein R^5 is chosen from fluoro, alkyl, fluoroalkyl, aryl, heteroaryl and substituted aryl; and R^6 and R^7 are chosen from H and $\text{C}_1\text{-C}_{20}$ hydrocarbon.

[0013] In another aspect the invention relates to compounds of formula

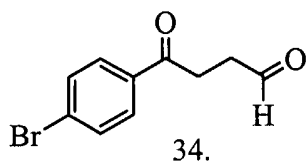


In these compounds Y is Cl, Br, I, $-\text{OSO}_2\text{R}^5$, $-\text{N}_2^+$, $-\text{OH}$, $-\text{B}(\text{OR}^6)(\text{OR}^7)$, $-\text{OP}(\text{O})(\text{OR}^6)(\text{OR}^7)$ or $-\text{C}(\text{CH}_3)_2\text{COOR}^4$; R^{10} , R^{11} and R^{12} are chosen independently from $(\text{C}_1\text{-C}_6)\text{alkyl}$, phenyl and benzyl; and R^{13} is H or $\text{SiR}^{10}\text{R}^{11}\text{R}^{12}$.

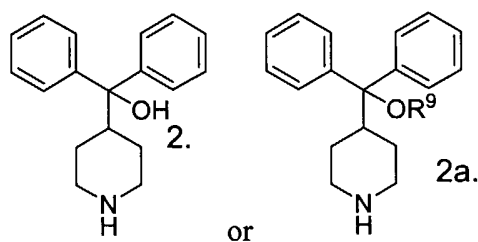
[0014] In another aspect the invention relates to a process for preparing compounds of formula 3



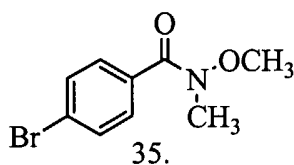
comprising reductively aminating a compound of formula 34



with an amine of formula 2 or 2a

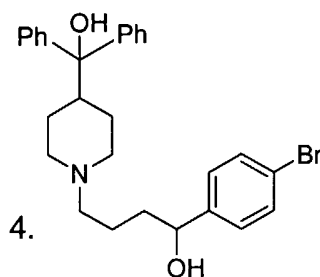


Compound 34 may be provided by reacting a compound of formula 35:



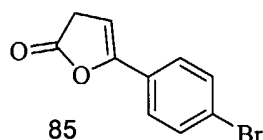
with 2-(2-bromoethyl)-1,3-dioxolane and magnesium followed by hydrolysis of the dioxolane.

[0015] In another aspect the invention relates to a process for preparing compounds of formula 4

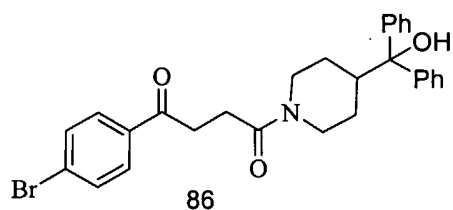


comprising

(a) reacting a compound of formula 85



with an amine of formula 2 to provide a compound of formula 86



(b) converting said compound 86 to compound 4 by reduction.

DETAILED DESCRIPTION OF THE INVENTION

[0016] Throughout this application, various references are referred to. The disclosures of each of these publications in their entireties are hereby incorporated by reference as if written herein.

[0017] In this specification the terms and substituents are defined when introduced and retain their definitions throughout.

[0018] Alkyl is intended to include linear, branched, or cyclic hydrocarbon structures and combinations thereof. Lower alkyl refers to alkyl groups of from 1 to 6 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl and the like. Preferred alkyl groups are those of C₂₀ or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from 3 to 8 carbon atoms. Examples of cycloalkyl groups include c-propyl, c-butyl, c-pentyl, norbornyl and the like.

[0019] C₁ to C₂₀ Hydrocarbon includes alkyl, cycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include phenethyl, cyclohexylmethyl, camphoryl and naphthylethyl.

[0020] Alkoxy or alkoxyl refers to groups of from 1 to 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to four carbons.

[0021] Oxaalkyl refers to alkyl residues in which one or more carbons has been replaced by oxygen. Examples include methoxypropoxy, 3,6,9-trioxadecyl and the like.

[0022] Acyl refers to groups of from 1 to 8 carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through an carbonyl functionality. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, t-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to four carbons.

[0023] Aryl and heteroaryl mean a 5- or 6-membered aromatic or heteroaromatic ring containing 0-3 heteroatoms selected from O, N, or S; a bicyclic 9- or 10-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S; or a tricyclic 13- or 14-membered aromatic or heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S. The aromatic 6- to 14-membered carbocyclic rings include, e.g., benzene, naphthalene, indane, tetralin, and fluorene and the 5- to 10-membered aromatic heterocyclic rings include, e.g., imidazole, pyridine, indole, thiophene, benzopyranone, thiazole, furan, benzimidazole, quinoline, isoquinoline, quinoxaline, pyrimidine, pyrazine, tetrazole and pyrazole.

[0024] Arylalkyl means an alkyl residue attached to an aryl ring. Examples are benzyl, phenethyl and the like.

[0025] Substituted alkyl, aryl, cycloalkyl, etc. refer to alkyl, aryl or cycloalkyl, wherein up to three H atoms in each residue are replaced with halogen, haloalkyl, hydroxy, loweralkoxy, carboxy, carboalkoxy (also referred to as alkoxycarbonyl), carboxamido (also referred to as alkylaminocarbonyl), cyano, carbonyl, nitro, amino, alkylamino, dialkylamino, mercapto, alkylthio, sulfoxide, sulfone, acylamino, amidino, phenyl, benzyl, heteroaryl, phenoxy, benzyloxy, or heteroaryloxy.

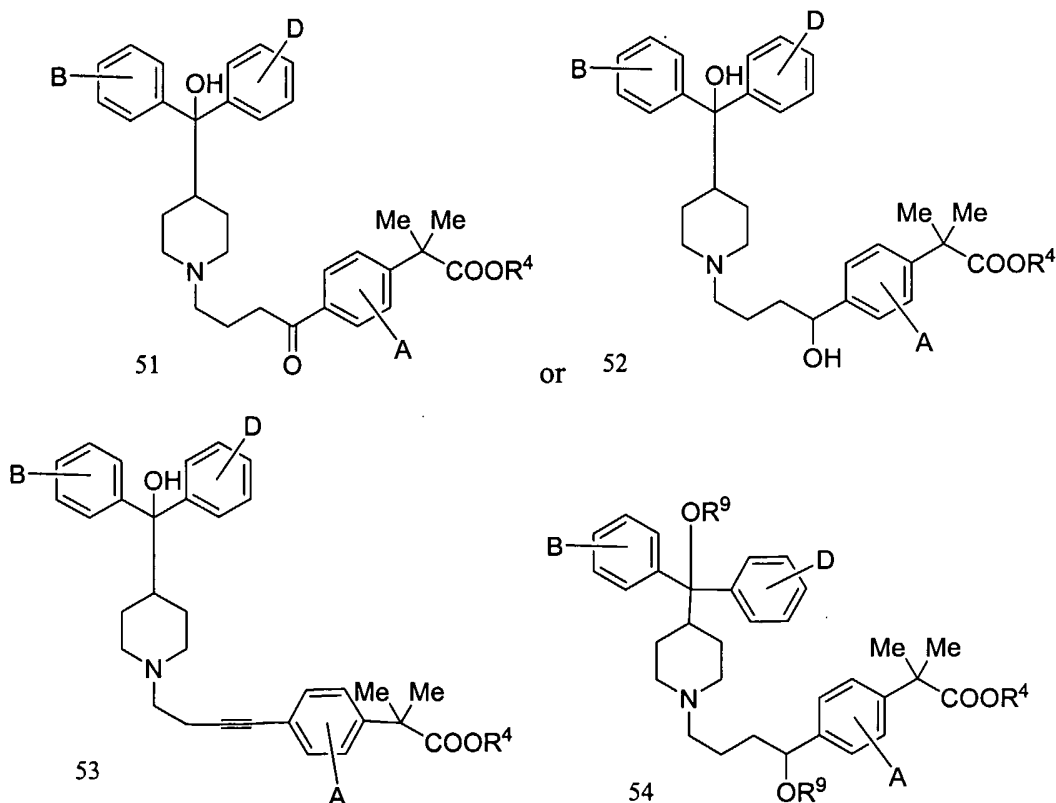
[0026] The term "halogen" means fluorine, chlorine, bromine or iodine.

[0027] Terminology related to "protecting", "deprotecting" and "protected" functionalities occurs throughout this application. Such terminology is well understood by persons of skill in the art and is used in the context of processes which involve sequential treatment with a series of reagents. In that context, a protecting group refers to a group that is used to mask a functionality during a process step in which it would otherwise react, but in which reaction is undesirable. The protecting group prevents reaction at that step, but may be subsequently removed to expose the original functionality. The removal or "deprotection" occurs after the completion of the reaction or reactions in which the functionality would interfere. Thus, when a sequence of reagents is specified, as it is in the processes of the invention, the person of ordinary skill can readily envision those groups that would be suitable as "protecting groups". Suitable groups for that purpose are discussed in standard textbooks in the field of chemistry [See e.g. Protective Groups in Organic Synthesis by T. W. Greene and P.G.M. Wuts, 2nd Edition; John Wiley & Sons, New York (1991)].

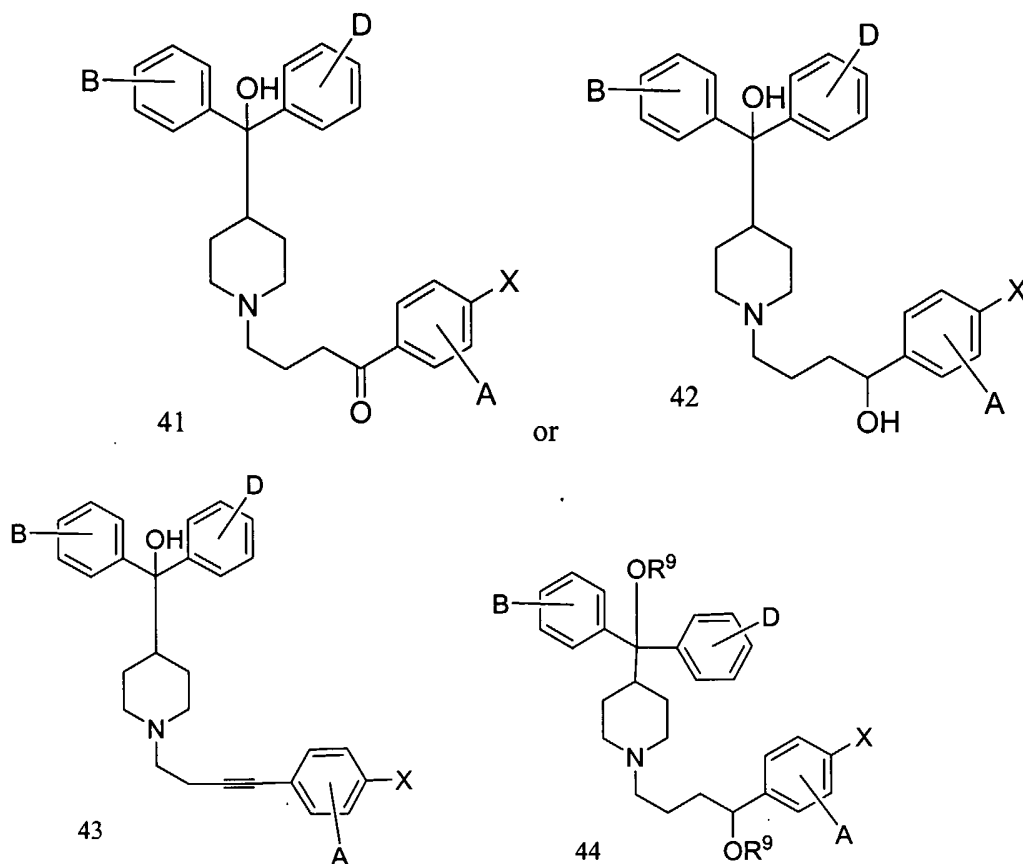
[0028] The abbreviations Me, Et, Ph, Tf, Ts and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, toluenesulfonyl and methanesulfonyl respectively. A comprehensive list of abbreviations utilized by organic chemists (i.e. persons of ordinary skill in the art) appears in the first issue of each volume of the Journal of Organic Chemistry. The list, which is typically presented in a table entitled "Standard List of Abbreviations" is incorporated herein by reference.

[0029] The present invention relates to processes for preparing piperidine derivative compounds of the formula 51, 52, 53 or 54. In these compounds, A, B, and D may be different or the same, and are selected from the group consisting of hydrogen, fluorine, chlorine, alkyl, aryl, hydroxyl, alkoxy, and aryloxy. Examples of compounds of formula 51, 52, 53 or 54 are those in which all of A, B and D are hydrogen and those in which A is hydrogen and B and D are halogens, e.g. fluorine, at the para positions.

[0030] The compounds of formula 51 may be reduced with hydrides, boranes or other reducing agents, as well known in the art, [see e.g. US patents 5,589,487 and 6,743,941] to produce fexofenadine. The compounds of formula 52 in which R⁴ is alkyl or aryl may be hydrolyzed to produce fexofenadine. When R⁴, A, B, and D are all hydrogen, the compound of formula 52 is fexofenadine and is produced by a direct single-step reaction. The compounds of formula 53 may be converted to compounds of formula 51 by the procedure described by Kawai *et al.* J. Org. Chem. **59**, 2620-2622 (1994). The compounds of formula 54 may be converted to compounds of formula 52 by hydrolysis in the case of silyl ethers and acyl derivatives and by hydrogenolysis in the case of benzyl ethers.



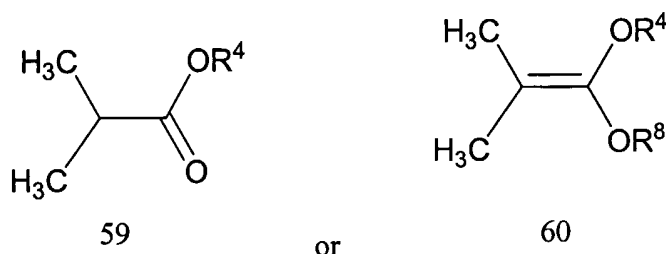
[0031] The compounds of formula 51-54 are prepared by a process in which a compound of formula 41-44:



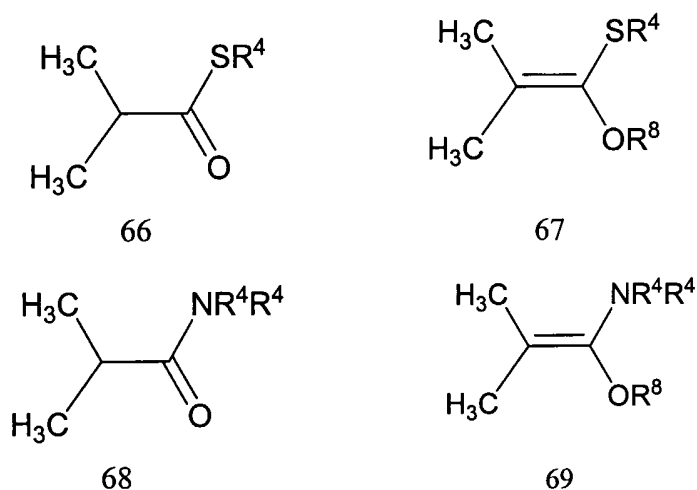
is reacted with isobutyrate or an isobutyrate equivalent. The substituent X may be chlorine, bromine, iodine, $-\text{OSO}_2\text{R}^5$, $-\text{N}_2^+$, $-\text{OP}(\text{O})(\text{OR}^6)(\text{OR}^7)$ or $-\text{B}(\text{OR}^6)(\text{OR}^7)$, wherein

R^5 is chosen from fluoro, alkyl, fluoroalkyl, aryl, heteroaryl and substituted aryl; R^6 and R^7 are chosen from H and C_1 - C_{20} hydrocarbon, including cyclic structures, e.g. dioxaboroles. Compounds in which X is $-OSO_2R^5$, may be prepared from compounds in which X is $-OH$ by sulfonation with the appropriate sulfonyl halide or anhydride in the presence of a base, as well known in the art. Compounds in which X is $-N_2^+$ may be prepared from the corresponding aniline or nitrobenzene by processes well known in the art. [See e.g. Herr *et al.* Org. Proc. Res. Dev. **6**, 677-681 (2002) and Siegrist *et al.* Org. Proc. Res. Dev. **7**, 429-431 (2003).] Compounds in which X is $-B(OR^6)(OR^7)$ may be prepared from the corresponding halides by the method of Ishiyama *et al.* [J. Org. Chem. **60**, 7508-7510 (1995)].

[0032] The isobutyrate or an isobutyrate equivalent may be methyl isobutyrate or a compound of the formula 59 or 60:



wherein R⁸ is a protecting group for a ketene acetal, [See Protective Groups in Organic Synthesis by T.W.Greene, *op. cit.*] The protecting group for a ketene acetal may be a simple alkyl, such as methyl or ethyl, a dialkylphosphoryl or, preferably, a trialkylsilyl group, such as trimethylsilyl or t-butyldimethylsilyl. The compounds of formula 59 are commercially available or are synthesized by procedures well-known in the art. The compounds of formula 60 are also known in the art and may be synthesized as described by Liu and Hartwig [J.Am.Chem.Soc. **126**, 5182-5191 (2004)]. The isobutyrate or isobutyrate equivalent may also be of the formulae 66-69:



although these equivalents are less preferred. As will be evident to the artisan, the conditions for the final hydrolysis of ester to carboxylate to prepare fexofenadine will be modified to accommodate the thioester or amide.

[0033] It has been found in certain circumstances, particularly when the reagent is 59, that compounds in which the carbonyl is protected as a cyclic acetal (e.g. 20a) and compounds in which the hydroxyl is protected as a silyl ether (e.g. 4a) enjoy advantages over their unprotected counterparts in the metal-catalyzed condensation.

[0034] The coupling reactions are carried out in a suitable solvent in the presence of an appropriate catalyst for about 1 to 120 hours and at temperatures of about -78°C to the reflux temperature of the solvent. Suitable solvents for coupling include: hydrocarbon solvents, such as benzene, toluene, xylene, or cyclohexane; halogenated hydrocarbons, such as chlorobenzene, dichloroethane, methylene chloride, chloroform, or carbon tetrachloride; carbon disulfide; dimethylformamide; ethereal solvents, like tetrahydrofuran and diethylether; or dioxane.

[0035] The reaction between the compounds of formulae 51-54 and 59 or 60 is catalyzed by a transition metal. The transition metal catalyst is a Group 8B transition metal selected from iron, cobalt, nickel, palladium, iridium, and platinum. More preferably, the Group 8 metal is palladium, platinum, or nickel, and most preferably, palladium. The Group 8 metal may exist in any oxidation state ranging from the zero-valent state to any higher variance available to the metal. The preferred catalysts for condensations are palladium acetate, palladium chloride, palladium bromide, palladium acetylacetonate, bis(tri-*o*-tolyl)phosphine palladium dichloride, bis(triphenylphosphine)palladium dichloride, tetrakis(triphenylphosphine)palladium $[(\text{Ph}_3\text{P})_4\text{Pd}]$, tris(dibenzylidene-acetone)palladium $[(\text{dba})_3\text{Pd}_2]$ and bis(dibenzylideneacetone) palladium $[(\text{dba})_2\text{Pd}]$.

[0036] The chelating ligand may be a neutral molecule or charged ion. The chelating ligand is also required to contain at least one element from Group 5B of the Periodic Table, preferably, at least one element of nitrogen, phosphorus, or arsenic, and more preferably nitrogen or phosphorus. Examples include tri-(*o*-tolyl)phosphine and triphenylphosphine. Preferred ligands for the coupling with 59 and 60 are 1,1'-bis(di-*o*-tolylphosphino)ferrocene (DTPF); 1,1'-bis(diphenylphosphino)ferrocene (DPPF); 1-di-

t-butylphosphino-2-methylaminoethyl ferrocene; [2'-(diphenylphosphino)[1,1'-binaphthalen]-2-yl]diphenylphosphine oxide (BINAP) 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl (tol-BINAP) and trialkyl or triarylphosphines, such as tri-t-butylphosphine.

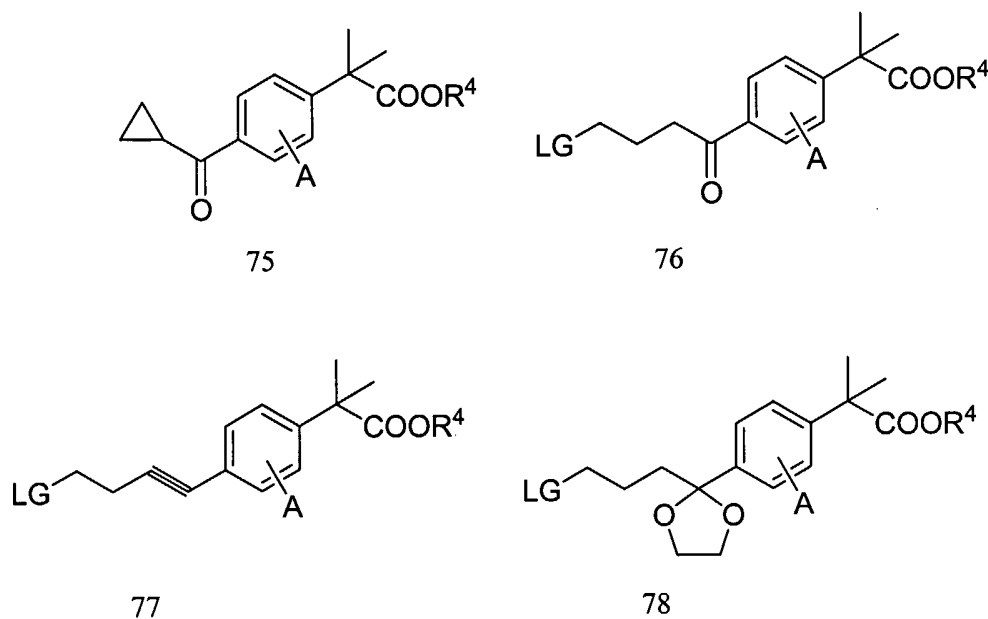
[0037] Conditions for metal catalyzed couplings are described with references in Diederich and Stang, Metal-Catalyzed Cross-Coupling Reactions; Wiley-VCH (1998) and in particular detail in US patent 6,057,456. In addition to palladium catalysts, as described below, one may employ other transition metals.

[0038] In formula 41-44, as well as in 55 and 56 below, X is preferably bromide or triflate, as shown in the examples below, but other substituents suitable for metal catalyzed coupling reactions may be used in their place. For example, diazonium salts may be used as described in Sakakura et al JCSP1 1994, 283-288. It will be apparent to the person of skill that, when A is chlorine, in order to have reasonable yields of single positional isomers, X should be other than chlorine.

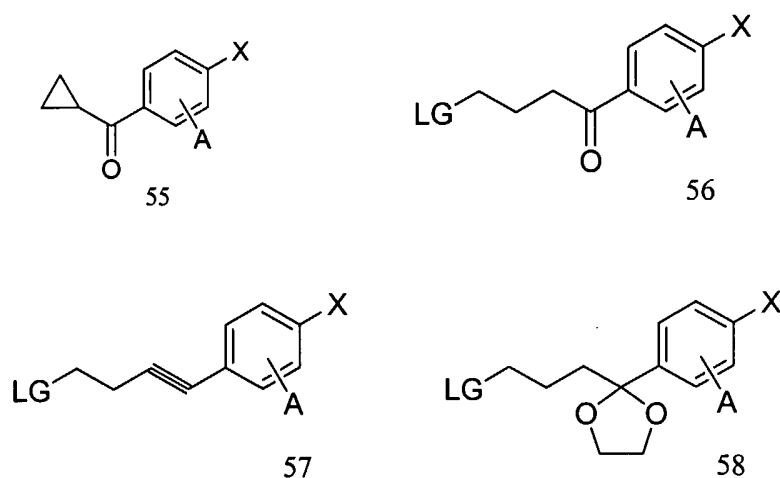
[0039] When the starting material is of the formula 59, a base must be used. Non-limiting examples of suitable bases include alkali metal hydroxides, such as sodium and potassium hydroxides; alkali metal alkoxides, such as sodium t-butoxide; metal carbonates, such as potassium carbonate, cesium carbonate, and magnesium carbonate; alkali metal aryl oxides, such as potassium phenoxide; alkali metal amides, such as lithium amide; tertiary amines, such as triethylamine and tributylamine; (hydrocarbyl)ammonium hydroxides, such as benzyltrimethylammonium hydroxide and tetraethylammonium hydroxide; diaza organic bases, such as 1,8-diazabicyclo[5.4.0]-undec-7-ene and 1,8-diazabicyclo-[2.2.2]-octane, and silyl compounds such as potassium hexamethyldisilazide ($\text{KN}(\text{Si}(\text{CH}_3)_3)_2$). Preferably, the base is a lithium dialkylamide, such as lithium dicyclohexylamide, an alkali alkoxide or a silyl-containing compound. The molar ratio of base to 41, 42, 43 or 44 ranges from about 1:1 to about 3:1, and is usually between about 1:1 and 2:1.

[0040] When the starting material is of the formula 60, a metal salt is used instead of a base. Exemplary salts include ZnF_2 and $\text{Zn}(\text{OtBu})_2$.

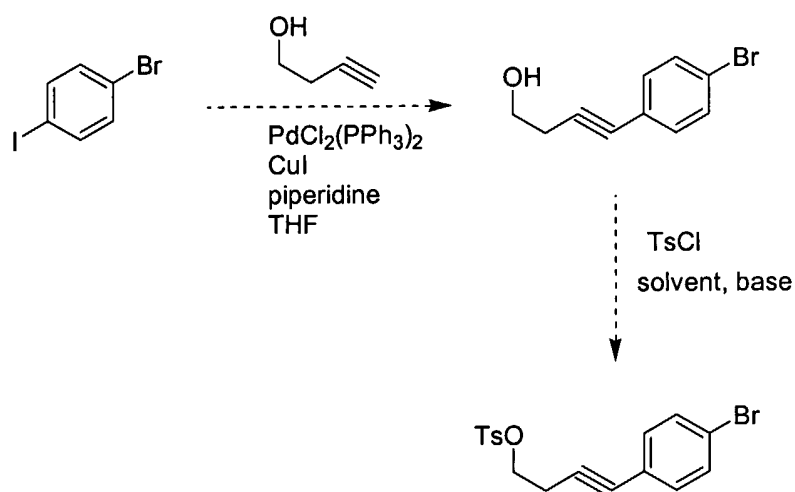
[0041] In another aspect the invention relates to a process for preparing an α,α -dimethylphenylacetate of the formula 75, 76, 77 or 78:



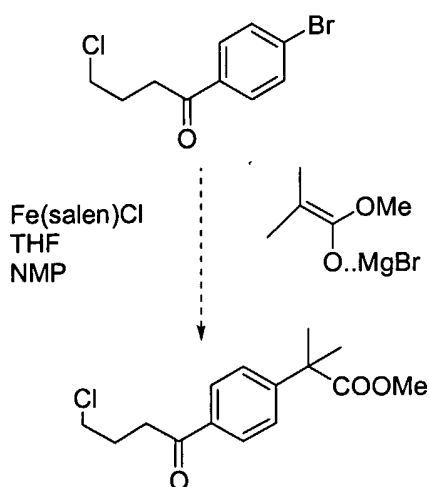
wherein LG is a leaving group displaceable by a secondary amine, particularly a group displaceable by a piperidine, for example a halogen or a sulfonate. LG is preferably bromine, chlorine, methanesulfonate, toluenesulfonate or triflate. The process comprises providing a compound of formula 55-58:



and converting the compound of formula 55-58 to 75-78, respectively, by reacting with isobutyrate or an isobutyrate equivalent. The process parallels the process shown above for 51-54 and 41-44 in that the reaction conditions and reagents are substantially the same. Compounds of formula 55 and 56, in which A is hydrogen are commercially available from Acros Organics, Geel, Belgium. The compounds of formula 57 may be prepared according to the method of Godt [*J.Org.Chem.*, 62, 7471 (1997)]:

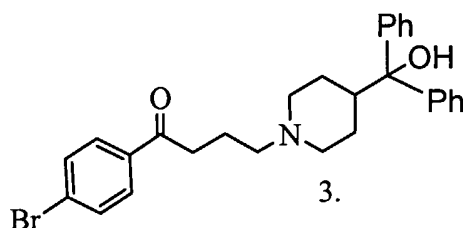


[0042] A useful iron-catalyzed process, which could be used to synthesize any of 51-54, is described by Fürstner et al *J.Am.Chem.Soc.*, 124, 13856-13863 (2002):

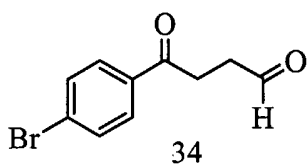


[0043] The α,α -dimethylphenylacetates of the formula 75-78 may be further reacted with a piperidine derivative as described in U.S. patents 4,550,116; 5,750,703; 6,153,754; 6,242,606 and others.

[0044] An additional route for preparing a compound of formula 3 (which is a species within the genus 41)

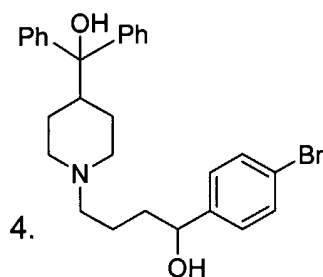


involves reductively aminating a compound of formula 34

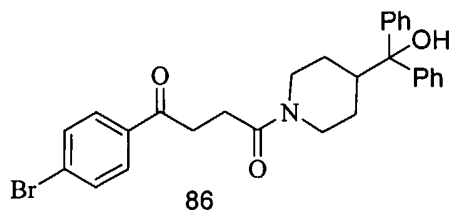
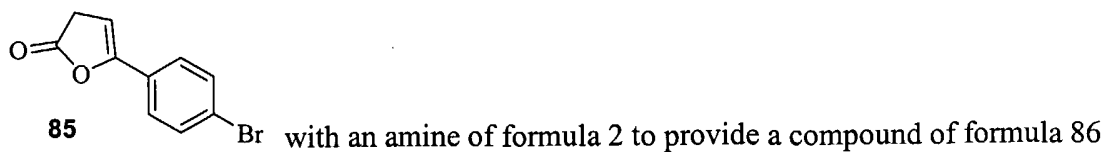


with an amine of formula 2. The reductive amination is typically carried out using a borohydride reducing agent, such as sodium triacetoxyborohydride, but other reductive aminations known in the art may be considered equivalent.

[0045] An additional route to 4 (which is a species in genus 42)



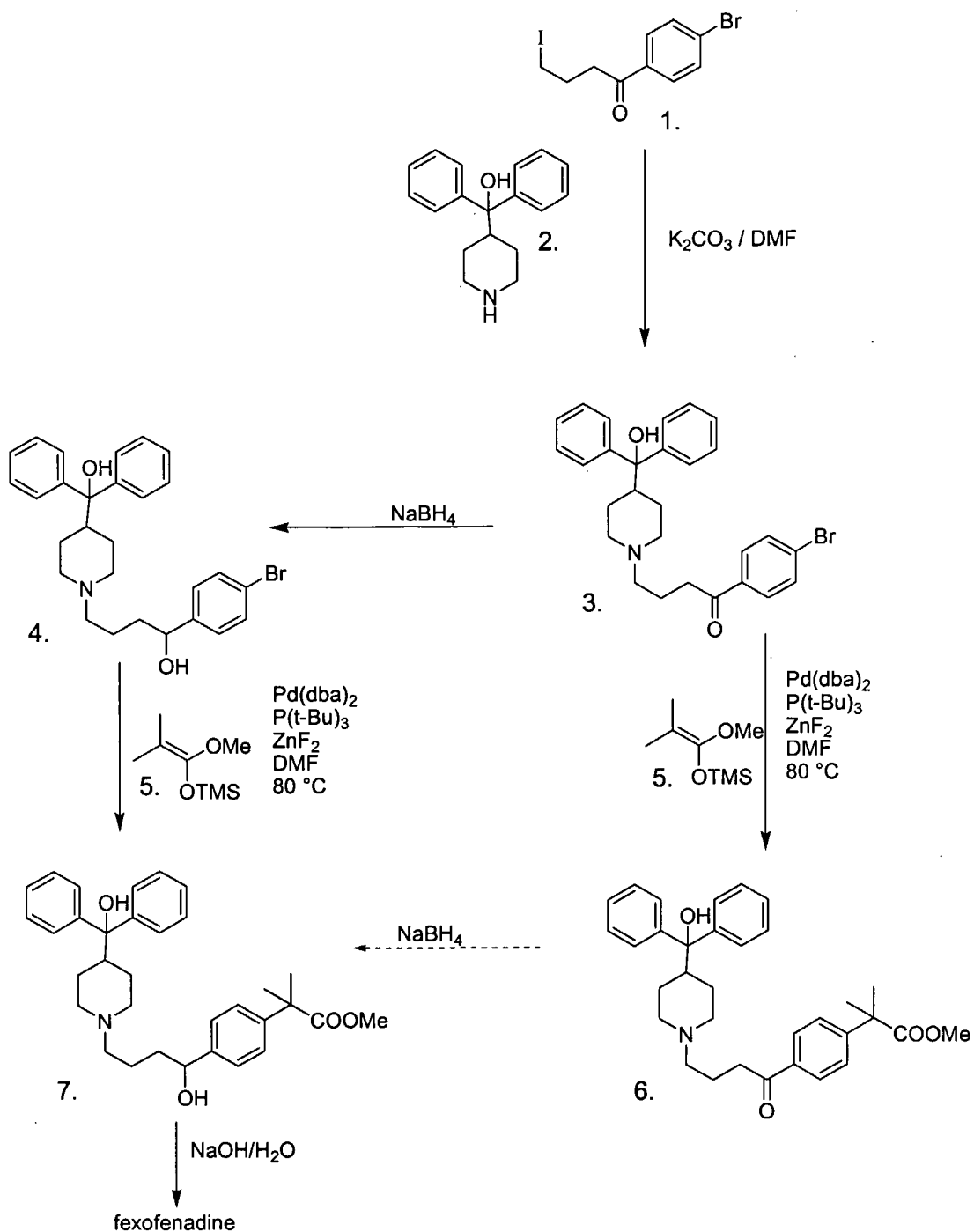
involves reacting a compound of formula 85



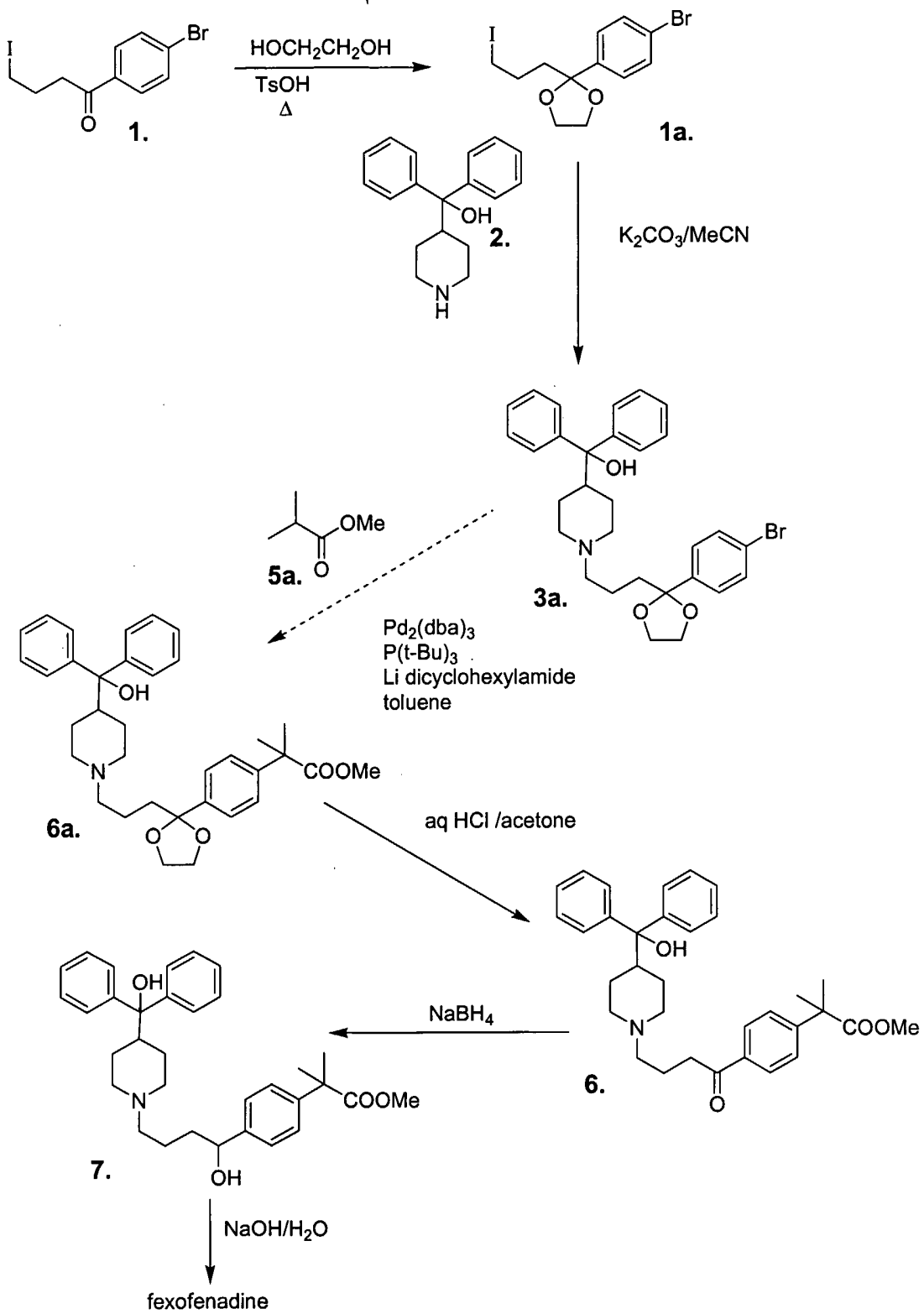
The amide/ketone 86 may be converted to compound 4 by reduction of both amide and ketone (for example with lithium aluminum hydride or diisobutyl aluminum hydride).

[0046] Exemplary processes that fall within the scope of the invention are illustrated in the schemes below for the synthesis of fexofenadine. These schemes also illustrate the interrelatedness of the processes and intermediates. Solid arrows indicate reactions described in the examples.

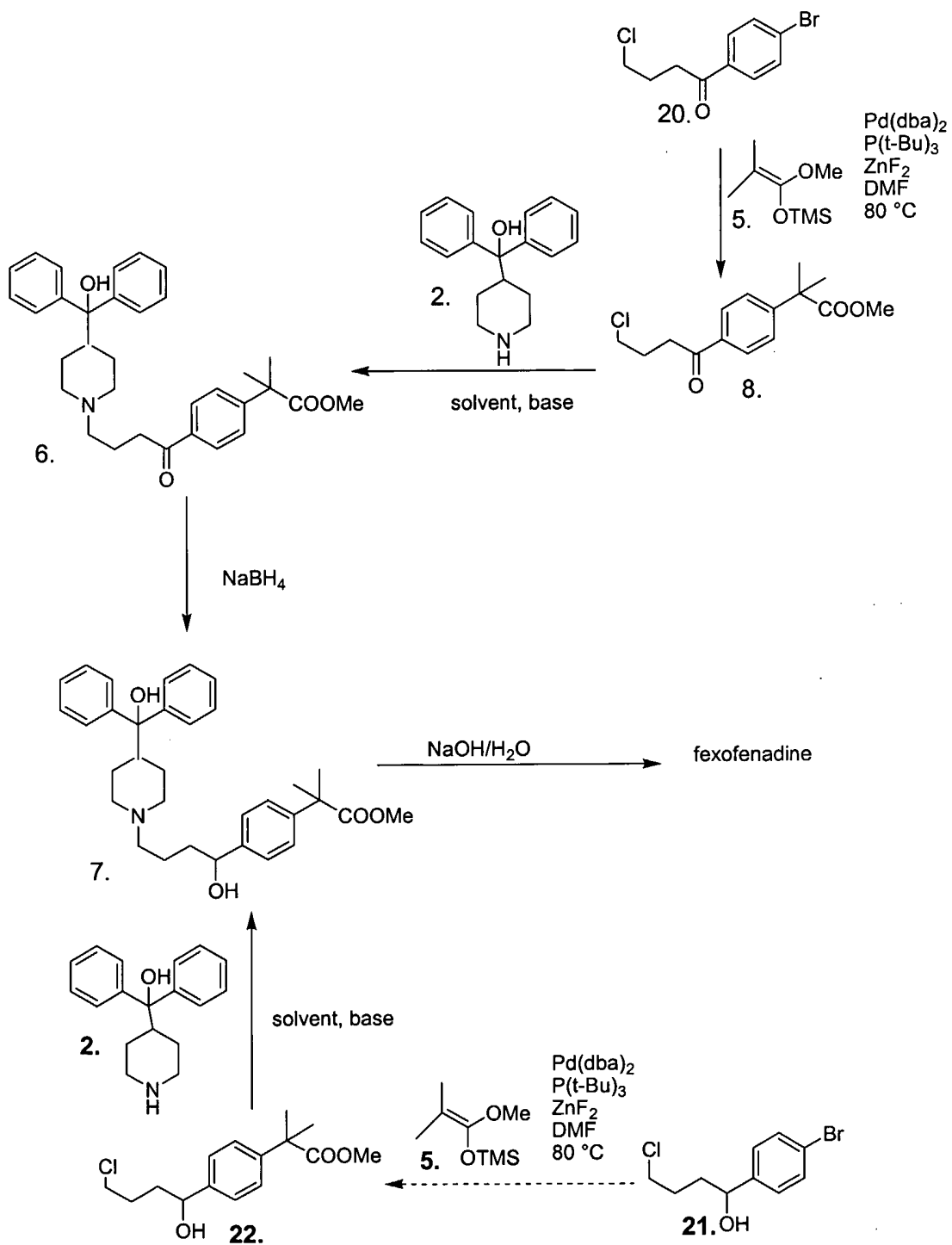
Scheme 1



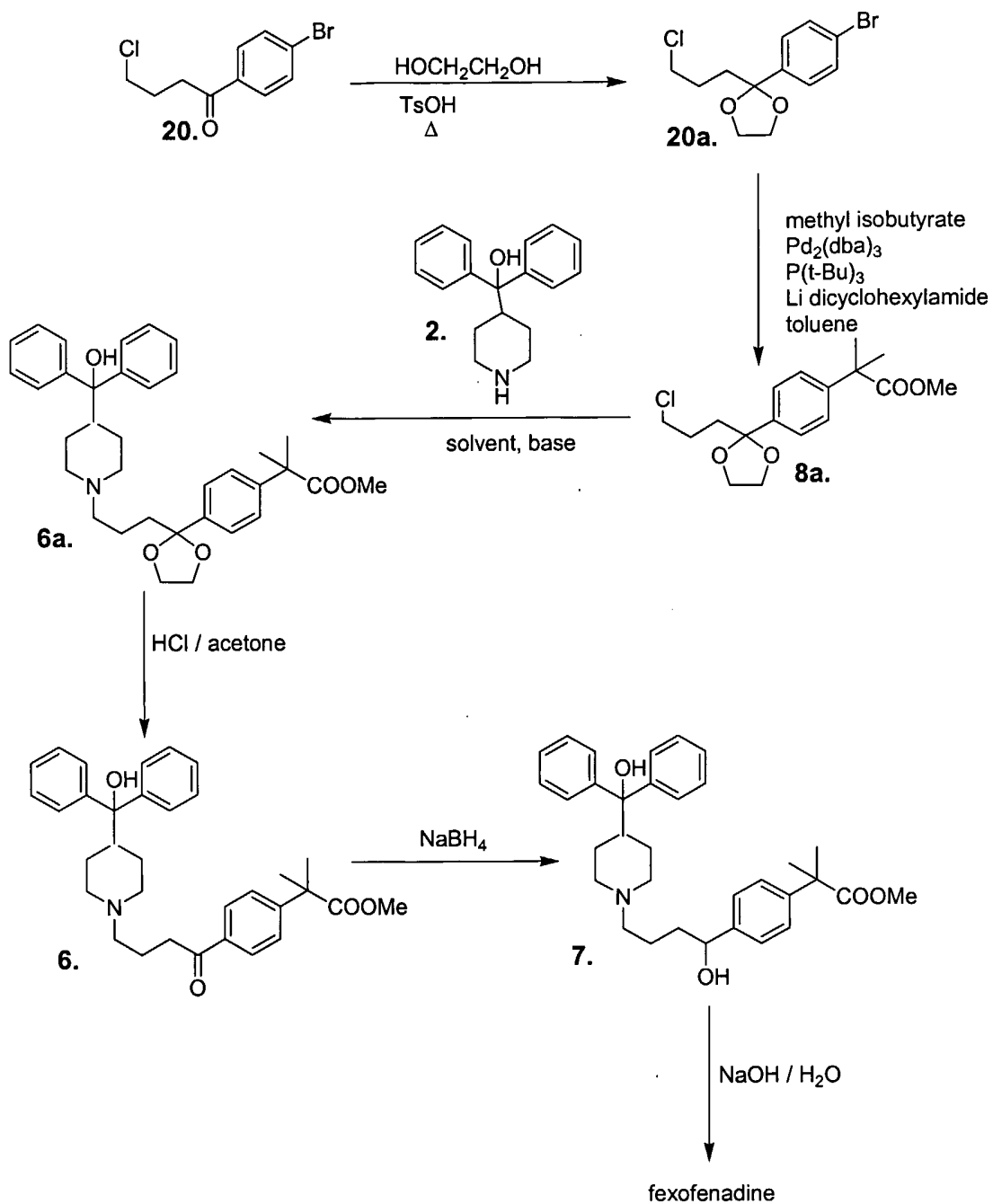
Scheme 1a



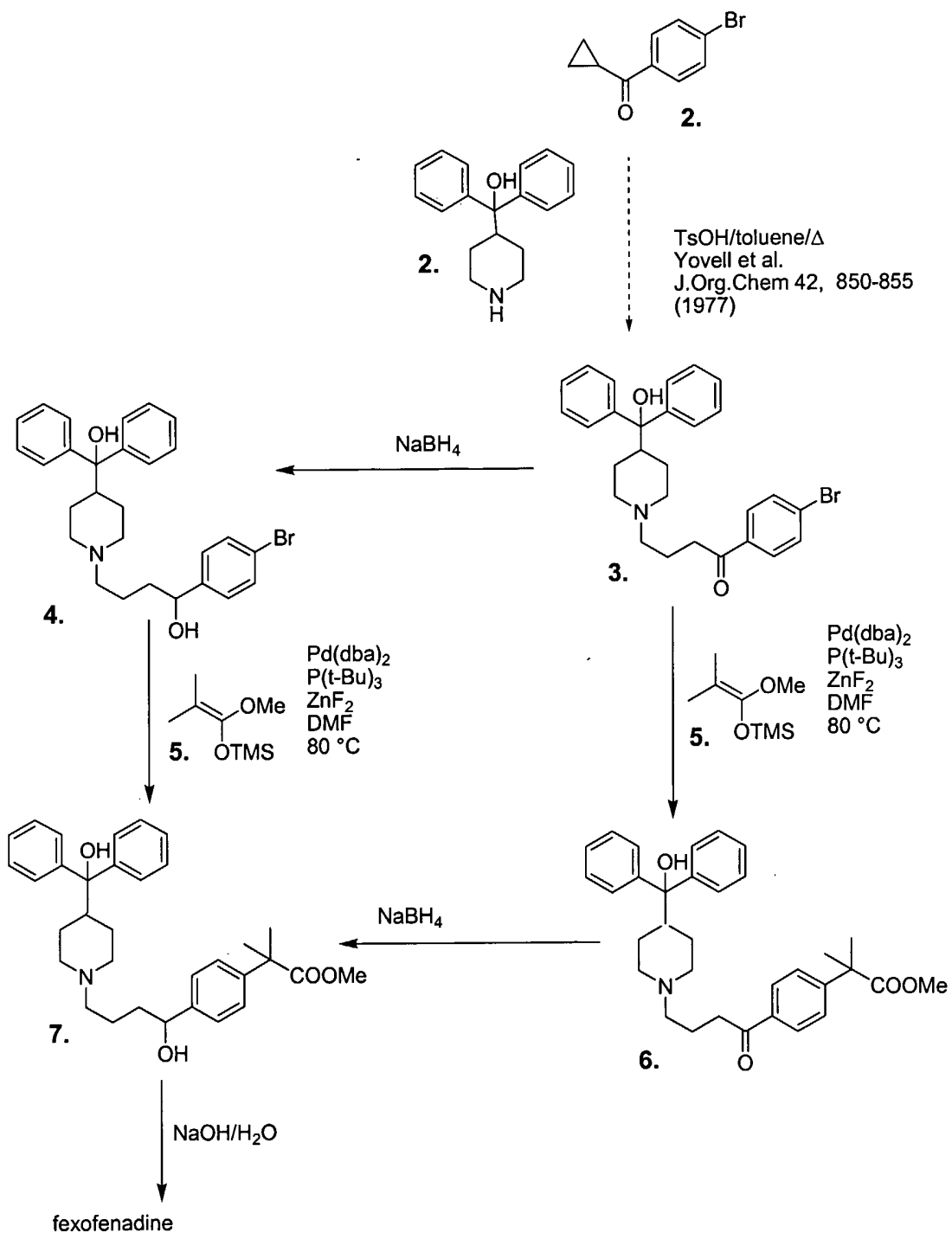
Scheme 2



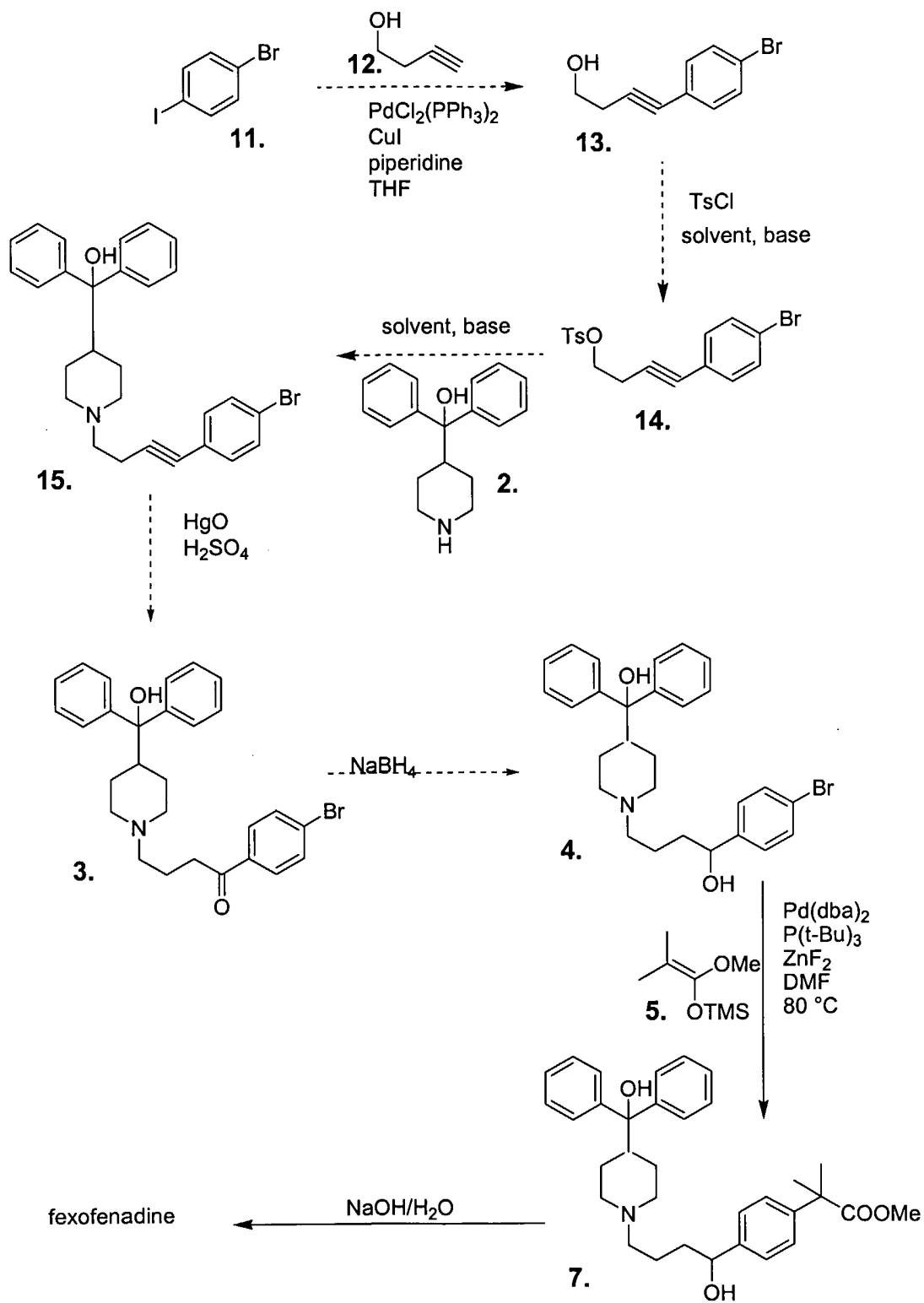
Scheme 2a



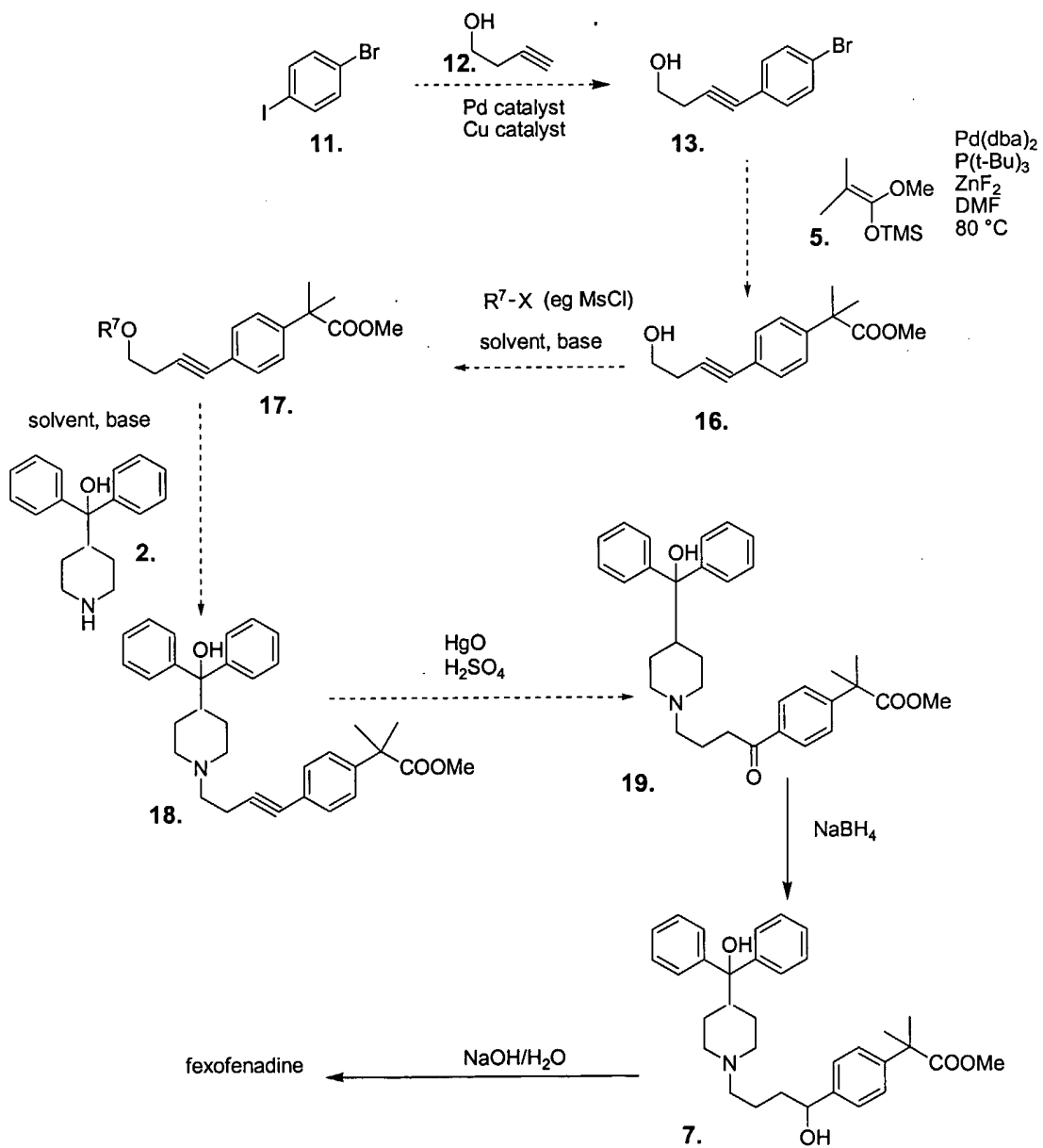
Scheme 3



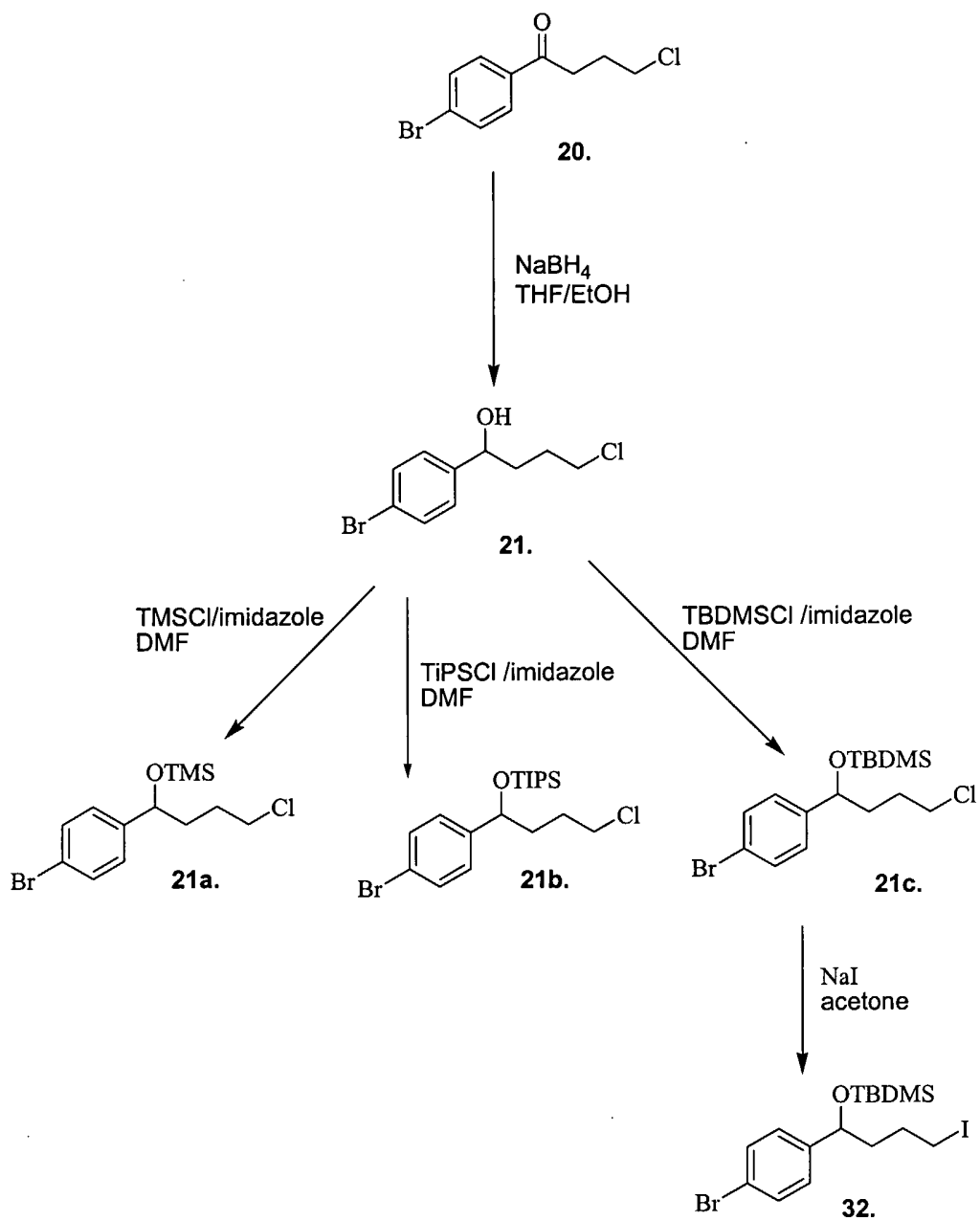
Scheme 5



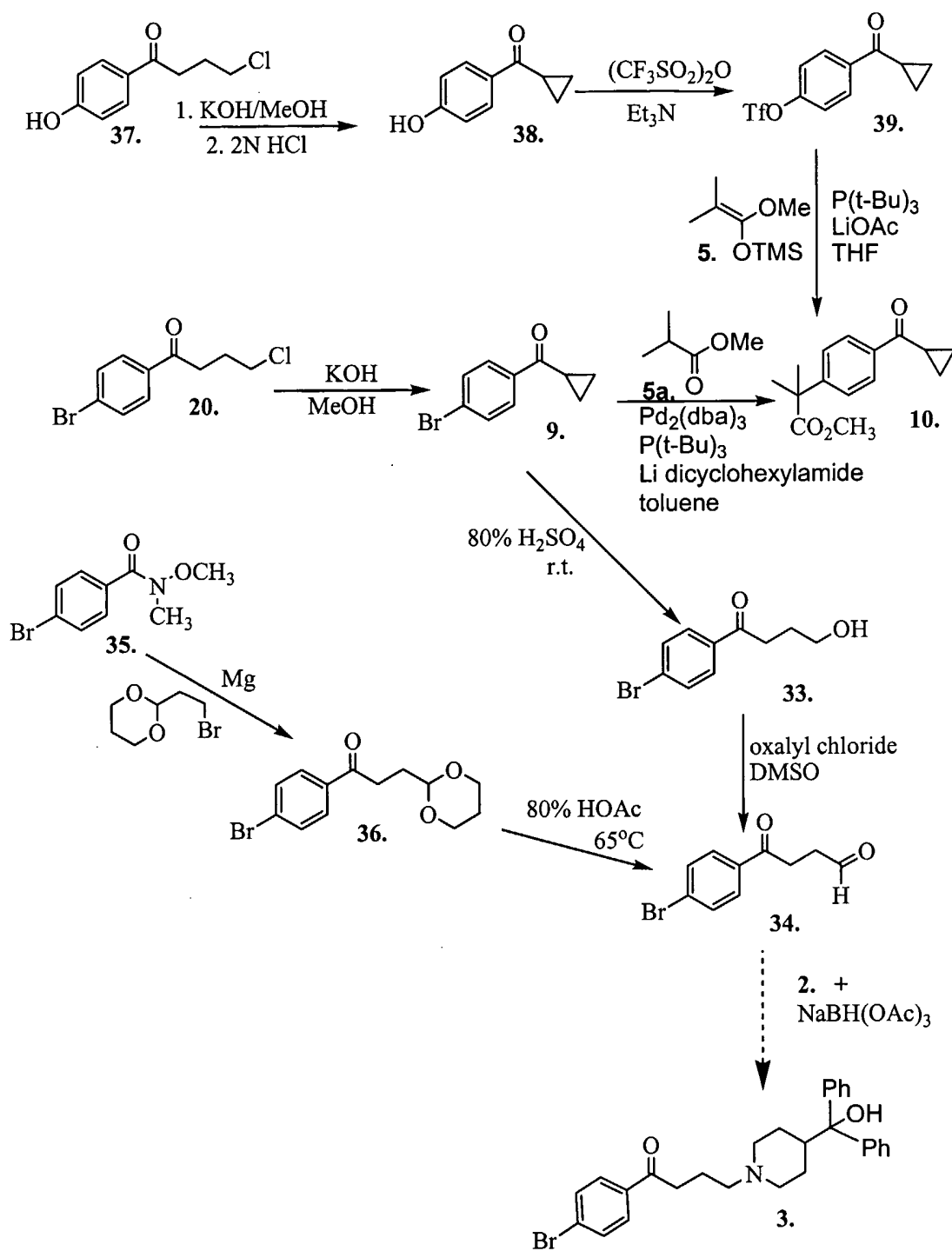
Scheme 6



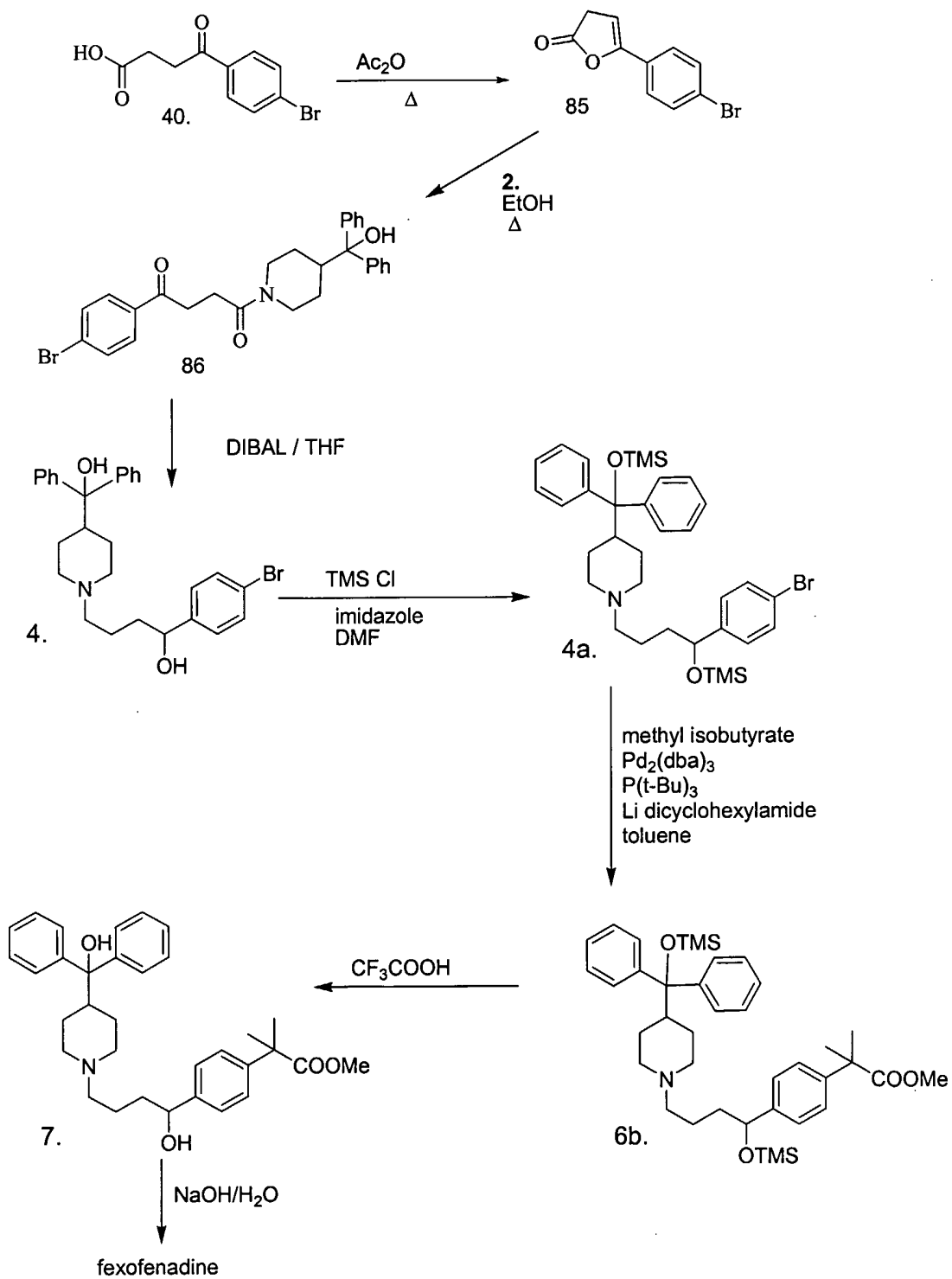
Scheme 7



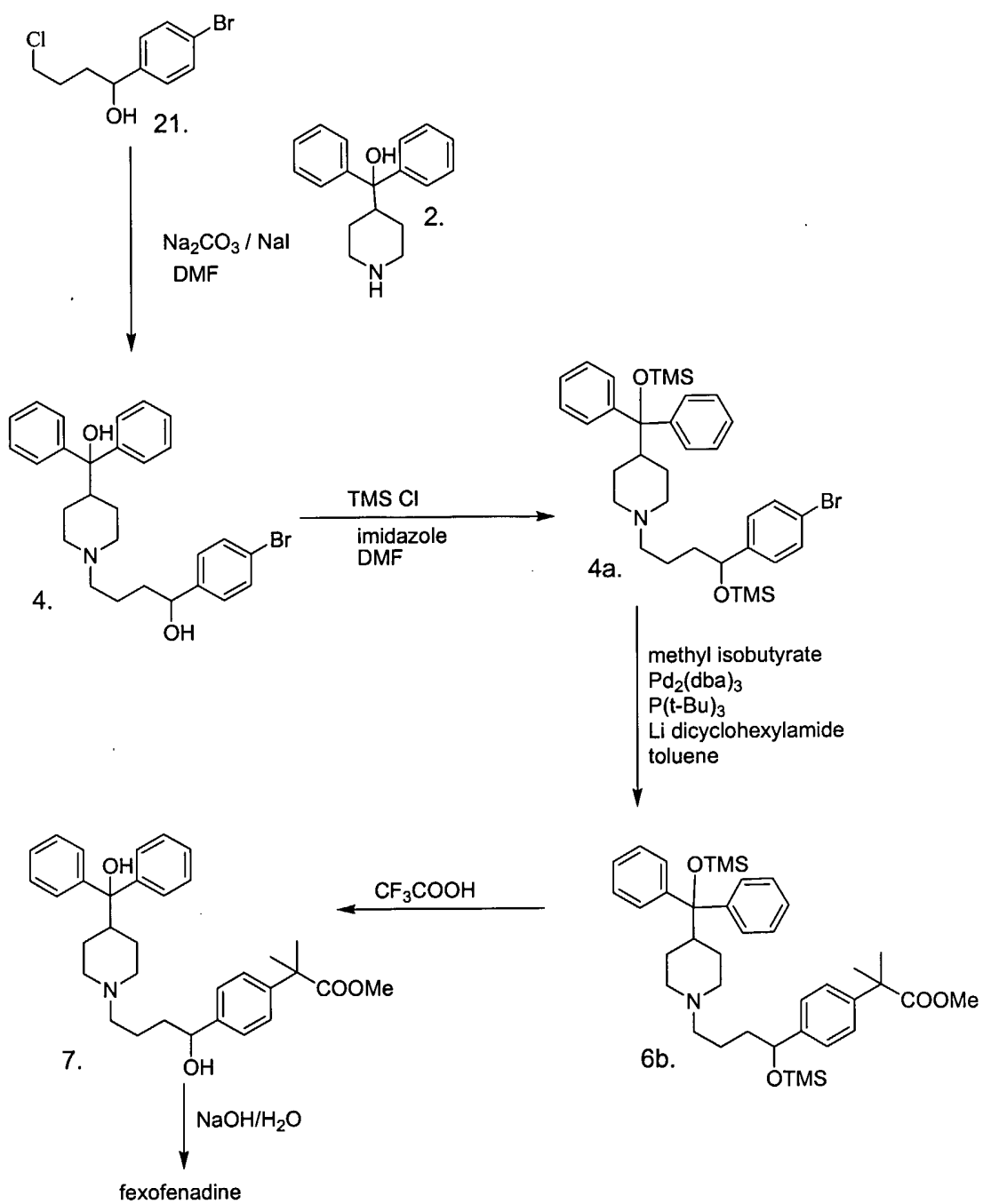
Scheme 8



Scheme 9



Scheme 10



Experimental

[0047] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton and carbon nuclear magnetic resonance spectra were obtained on a Bruker AC 300 or a Bruker AV 300 spectrometer at 300 MHz for proton and 75 MHz for carbon. Spectra are given in ppm (δ) and coupling constants, J , are reported in Hertz. Tetramethylsilane was used as an internal standard for proton spectra and the solvent peak was used as the reference peak for carbon spectra. Mass spectra were obtained on a Perkin Elmer Sciex 100 atmospheric pressure ionization (APCI) mass spectrometer. Thin-layer chromatography (TLC) was performed using Analtech silica gel plates and visualized by ultraviolet (UV) light, iodine, or 20 wt % phosphomolybdic acid in ethanol. HPLC analyses were obtained using a Prevail C18 column (250 x 4.6 mm, Altech) with UV detection at 254 or 236 nm, respectively, using a standard solvent gradient program (Method A) or Luna 5 μ C18(2) column (100 x 4.6 mm, Phenomenex) UV detection at 254 or 236 nm using a standard solvent gradient program (Method B).

Method A:

Time (min)	Flow (mL/min)	%A	%B
0.0	3.0	95.0	5.0
10.0	3.0	0.0	100.0
11.0	3.0	0.0	100.0

A = Water with 0.1% Trifluoroacetic Acid

B = Acetonitrile with 0.1% Trifluoroacetic Acid

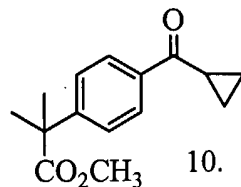
Method B:

Time (min)	Flow (mL/min)	%A	%B
0.0	2.5	95.0	5.0
8.0	2.5	5	95
10.0	2.5	5	95

A = Water with 0.1% Trifluoroacetic Acid

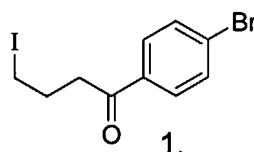
B = Acetonitrile with 0.1% Trifluoroacetic Acid

[0048] Example 1.



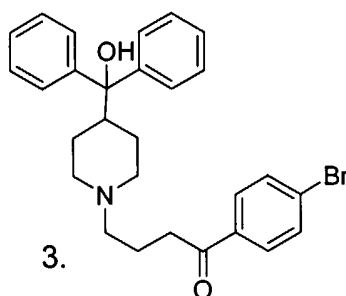
[0049] One gram of 9 was dissolved in 20 mL of DMF and 18 mg of P(tBu)₃, 41 mg of Pd(dba)₂, 230 mg of ZnF₂ and 1.2 g of 5 were added. A mixture was stirred at 80° for 18 hours, cooled to room temperature, diluted with ether and washed with water. The organic layer was dried over sodium sulfate, filtered and stripped *in vacuo*. The resulting product was flash chromatographed on silica gel using 4:1 hexane ethyl acetate to yield 1.0 g (91%) of 10. A repeat of the reaction on larger scale using 15 g of 9 provided 15.2 g (93%) of 10.

[0050] Example 2.



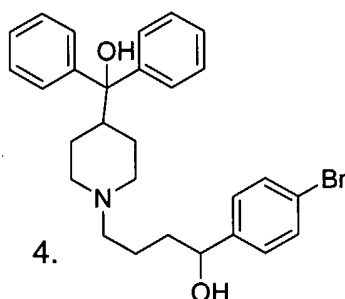
[0051] Five grams of 9 was dissolved in 50 mL of methylene chloride and cooled to 0 °C. To the solution was added 5.78 g of trimethylsilyl iodide. The mixture was stirred for 30 minutes and excess sodium bisulfite solution was added with vigorous stirring at room temperature. The layers were separated and the aqueous layer extracted twice with methylene chloride. Combined organic layers were dried, filtered and stripped *in vacuo* to provide 7.7 g (98%) of 1. The reaction was repeated on a larger scale using 15 g of 9 to produce 22.5 g of 1 (96%) yield.

[0052] Example 3.



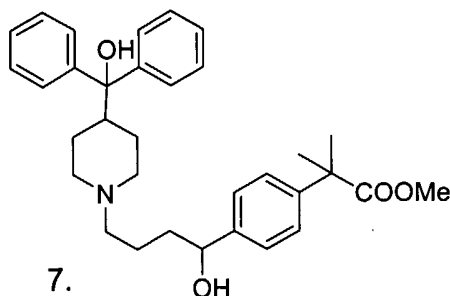
[0053] Six grams of potassium carbonate, 5.8 g of piperidine 2 and 7.6 g of 1 were combined in 100 mL of DMF. The suspension was stirred at room temperature until TLC in 4:1 hexane-ethyl acetate indicated a complete reaction. The reaction mixture was poured into 400 mL of water and extracted three times with methylene chloride. The combined organic extracts were dried, filtered and reduced *in vacuo*. The resulting product was flash chromatographed on silica gel using ethyl acetate containing 10% triethylamine to yield 7.0 g (66%) of 3.

[0054] Example 4.



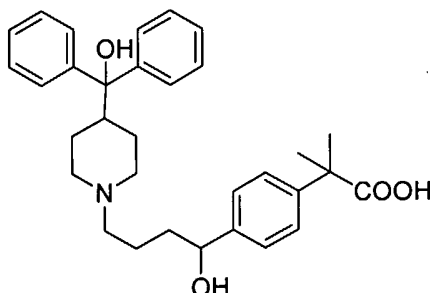
[0055] Seven grams of 3 was dissolved in 100 mL of methanol, cooled to 0 °C and 1.1 g of sodium borohydride was added. The mixture was stirred 1 hour, concentrated and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The bicarbonate layer was extracted twice with ethyl acetate, the combined organic layers were dried over sodium sulfate and the solution was reduced *in vacuo* to provide 7.0 g (100%) of 4.

[0056] Example 5.



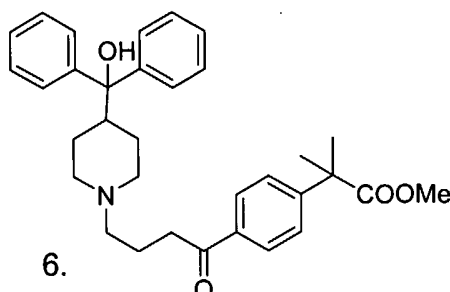
[0057] Two grams of 4 was dissolved in 30 mL of DMF. To this were added 16.2 mg of $P(tBu)_3$, 36.6 mg of $Pd(dba)_2$, 209 mg of ZnF_2 and 1.056 g of 5. The mixture was heated at $80^\circ C$, cooled, diluted with ether and worked up as in example 1. The resulting product was flash chromatographed on silica gel using 9:1 ethyl acetate-triethylamine to provide 450 mg (21.4%) of 7.

[0058] Example 6.



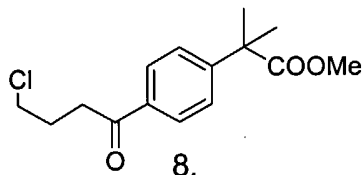
[0059] One hundred fifty milligrams of 7 was slurried in 5 mL of water and 10 mL of methanol. To the slurry was added 175 mg of sodium hydroxide. The slurry was refluxed for one hour, cooled to room temperature and the methanol removed *in vacuo*. The resulting aqueous solution was distributed between water and chloroform, the chloroform layer was discarded, the aqueous layer was adjusted to pH 2.3 and extracted with chloroform. The organic layer was dried, filtered and reduced *in vacuo* to provide fexofenadine.

[0060] Example 7.



[0061] Two grams of 3, 90 mg of $P(tBu)_3$, 300 mg of $Pd(dba)_2$, 250 mg of ZnF_2 and 1.1 g of 5 were dissolved in 330 mL of DMF under argon. The mixture was heated to 80° for two hours, cooled to room temperature, diluted with ether and worked up as described in example 1. The resulting product was filtered through silica to provide 1.3 g (62%) of 6.

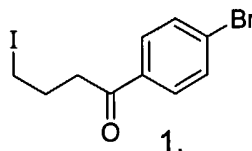
[0062] Example 8.



[0063] Two grams of 20, 170 mg of $P(tBu)_3$, 560 mg of $Pd(acac)_2$, 474 mg of ZnF_2 and 2.0 g of 5 were combined in 50 mL of DMF under argon. The mixture was heated to $80^\circ C$ and monitored by HPLC. When reaction was complete, the mixture was cooled to room temperature and 250 mL of water was added. The mixture was extracted three times with ether, dried, filtered and reduced *in vacuo*. The resulting product was flash chromatographed in 4:1 hexane-ethyl acetate to provide 1.89 g (85%) of 8.

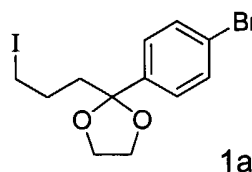
[0064] Example 9. Two grams of the triflate analog of 20 were reacted as in the foregoing example with 134 mg $P(tBu)_3$, 433 mg of $Pd(acac)_2$, 375 mg of ZnF_2 and 1.58 g of 5 to provide 1.56 g (90% yield) of 8.

[0065] Example 10.



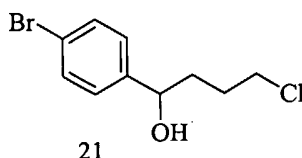
[0066] Seventy-five grams of 20 and 428 g of sodium iodide were refluxed in 600 mL of acetone overnight. The reaction was cooled and filtered and the precipitate rinsed with ethyl acetate. The combined filtrates were concentrated *in vacuo* and rinsed through silica using ethyl acetate. The filtrate was washed with water and the combined ethyl acetate layers dried over sodium sulfate. The solvent was removed *in vacuo* and the residue recrystallized from methanol to yield 75 g (after 3 recyclings of the mother liquors) (75% yield) of product 1 having a melting point 73.5 - 75 °C.

[0067] Example 11.



[0068] A mixture of 75 g of 1, 41.1 g of ethylene glycol and a catalytic amount of toluene sulfonic acid hydrate was refluxed in 1.4 mL of toluene until no further water collected in a Dean-Stark trap. The toluene was removed *in vacuo*, dried onto silica and washed with hexane. The silica was then eluted with 1% ethyl acetate in hexane and the resulting fractions stripped to 65.4 g (78%) of 1a, as a dark brown oil, which NMR indicated to be greater than 95% pure.

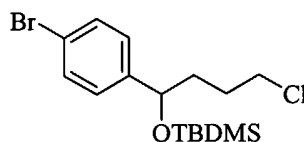
[0069] Example 12. Preparation of 1-(4-bromophenyl)-4-chlorobutan-1-ol



To a stirred solution of 1-(4-bromophenyl)-4-chlorobutan-1-one (20) (40.0 g, 0.15 mol) in THF (675 mL) and EtOH (75 mL) under N₂ was added sodium borohydride (5.80 g,

0.15 mol) and the mixture was stirred for 18 h at room temperature. The solution was passed through a plug of silica gel eluting with EtOAc (500 ml). The filtrate was concentrated under vacuum to provide 39.2 g (99%) of the title compound as an orange oil which was used without further purification: ^1H NMR (300 MHz, CDCl_3) δ 7.42 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.4$ Hz, 2H), 4.56 (t, $J = 5.6$ Hz, 1H), 3.50-3.47 (m, 2H), 2.83 (s, 1H), 1.84-1.67 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.7, 131.9, 128.0, 121.7, 73.4, 45.3, 36.5, 29.1; HPLC (Method A) 71.1% (AUC), $t_R = 7.8$ min.

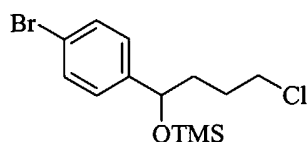
[0070] Example 13. Preparation of (1-(4-bromophenyl)-4-chlorobutoxy)(*tert*-butyl)dimethylsilane



21c

To a stirred solution of 1-(4-bromophenyl)-4-chlorobutan-1-ol (21) (35.0 g, 0.13 mol) in DMF (130 mL) under N_2 was added *t*-butyldimethylsilyl chloride (24.1 g, 0.16 mol) followed by imidazole (22.1 g, 0.33 mol) and the mixture was stirred for 18 h at room temperature. The mixture was diluted with water (500 mL) and extracted with ethyl acetate (2×200 mL). The combined organic extracts were washed with water (5×100 mL), brine (200 mL), dried (MgSO_4), and concentrated under vacuum to provide 47 g (96%) of the title compound as a yellow oil which was used without further purification: ^1H NMR (300 MHz, CDCl_3) δ 7.37 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.4$ Hz, 2H), 4.63 (s, 1H), 3.44-3.41 (m, 2H), 1.77-1.72 (m, 4H), 0.85 (s, 9H), 0.00 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 147.0, 134.1, 130.3, 123.6, 76.5, 47.8, 40.7, 31.3, 28.7, 21.0, -1.7, -2.0; HPLC (Method A) 78.3% (AUC), $t_R = 10.8$ min.

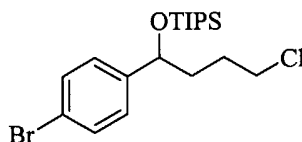
[0071] Example 14. Preparation of (1-(4-bromophenyl)-4-chlorobutoxy)trimethylsilane



21a

(1-(4-bromophenyl)-4-chlorobutoxy)trimethylsilane was prepared as a yellow oil (40.0 g, 92%) following a procedure similar to that described in the synthesis of 21c, starting with 1-(4-bromophenyl)-4-chlorobutan-1-ol (21) (35.0 g, 0.13 mol) and trimethylsilyl chloride (17.4 g, 0.16 mol): ^1H NMR (300 MHz, CDCl_3) δ 7.37 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.5$ Hz, 2H), 4.61 (t, $J = 5.2$ Hz, 1H), 3.48-3.42 (m, 2H), 1.81-1.71 (m, 4H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.9, 131.1, 127.4, 120.6, 73.4, 44.7, 37.6, 28.7, 0.0; HPLC (Method A) 71.9% (AUC), $t_R = 6.6$ min.

[0072] Example 15. Preparation of (1-(4-bromophenyl)-4-chlorobutoxy)triisopropylsilane

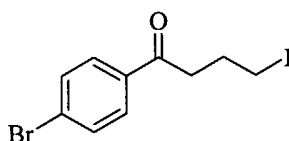


21b

To a stirred solution of 1-(4-bromophenyl)-4-chlorobutan-1-ol (21) (10.0 g, 0.04 mol) and imidazole (6.50 g, 0.09 mol) in DMF (30 mL) was added under nitrogen triisopropylsilyl chloride (9.80 mL, 0.05 mol) and the mixture was stirred for 18 h at room temperature. The reaction mixture was poured into cold water (400 mL) and extracted with toluene (2 x 200 mL, 1 x 100 mL). The combined organic layers were washed with water (500 mL) and brine (500 mL), dried (Na_2SO_4), filtered and concentrated to residue. The crude product was filtered through a plug of silica gel (hexane) to provide 9.20 g (58%) of the title compound as a colorless oil which was used without further purification: ^1H NMR (300 MHz, CDCl_3) δ 7.44 (d, $J = 8.4$ Hz,

2H), 7.19 (d, $J = 8.4$ Hz, 2H), 4.83 (t, $J = 5.5$ Hz, 1H), 3.46 (t, $J = 6.5$ Hz, 2H), 1.89-1.82 (m, 2H), 1.74-1.63 (m, 2H), 1.08-0.96 (m, 21H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.3, 131.5, 128.1, 121.1, 74.0, 45.5, 38.2, 27.9, 18.4, 12.6; HPLC (Method A) >99% (AUC), $t_R = 8.6$ min.

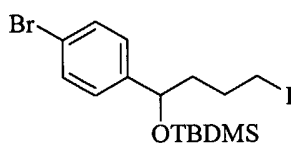
[0073] Example 16: Preparation of 1-(4-bromophenyl)-4-iodobutan-1-one



1

A mixture of 1-(4-bromophenyl)-4-chlorobutan-1-one (20) (75.0 g, 0.29 mol) and anhydrous sodium iodide (428 g, 2.86 mol) in acetone (600 mL) was heated under reflux for 18 h. The reaction mixture was cooled to room temperature and filtered. The filter cake was washed with ethyl acetate (500 mL). The filtrate was washed with water (500 mL). The aqueous layer was extracted with ethyl acetate (2 x 300 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated to dryness. The crude product was recrystallized from methanol to afford 75.0 g (75%) of the title compound as a light brown solid: R_f 0.56 (silica gel, 10:90 ethyl acetate/hexanes); mp 73–75 °C (dec.); ^1H NMR (300 MHz, CDCl_3) δ 7.84 (d, $J = 8.3$ Hz, 2H), 7.62 (d, $J = 8.3$ Hz, 2H), 3.32 (t, $J = 6.6$ Hz, 2H), 3.10 (t, $J = 7.0$ Hz, 2H), 2.25 (p, $J = 6.7$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 197.9, 135.8, 132.3, 129.9, 128.8, 39.2, 27.7, 6.9; HPLC (Method A) >99% (AUC), $t_R = 8.2$ min.

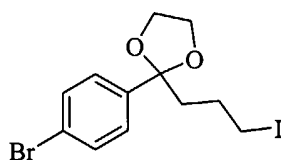
[0074] Example 17: Preparation of (1-(4-bromophenyl)-4-iodobutoxy)(*tert*-butyl)dimethylsilane



32

(1-(4-bromophenyl)-4-iodobutoxy)(*tert*-butyl)dimethylsilane was prepared as orange oil (41.1 g, 87%) following a procedure similar to that described in example 16, starting with 1-(4-bromophenyl)-4-chlorobutoxy)(*tert*-butyl)dimethylsilane (21c): ^1H NMR (300 MHz, CDCl_3) δ 7.38 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 8.4$ Hz, 1H), 4.62 (t, $J = 5.7$ Hz, 1H), 3.13-3.08 (m, 2H), 1.83-1.68 (m, 4H), 0.85 (s, 9H), 0.01 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.5, 131.7, 127.9, 121.2, 73.8, 41.8, 29.7, 26.2, 18.5, 7.2, -4.1, -4.5; HPLC (Method B) 69.9% (AUC), $t_R = 10.1$ min.

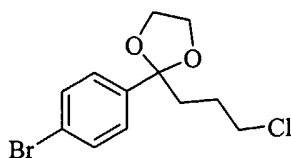
[0075] Example 18. Preparation of 2-(4-bromophenyl)-2-(3-iodopropyl)-1,3-dioxolane



1a

A mixture of 1-(4-bromophenyl)-4-iodobutan-1-one (1) (75.0 g, 0.21 mol), ethylene glycol (37 mL, 0.66 mol), and PTSA (200 mg) in toluene (1.4 L) was heated under azeotropic conditions to reflux until water formation stopped. The reaction mixture was cooled to room temperature and subsequently washed with water (2 x 1 L), saturated sodium bicarbonate (1 x 1 L), water (1 x 1 L), and brine (1 x 1 L). The organic layer was dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by column chromatography (silica gel, hexane to 1:99 Ethyl acetate/Hexanes to afford 65.4 g (78%) of the title compound as a dark brown oil: R_f 0.67 (silica gel, 10:90 ethyl acetate/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.47 (d, $J = 8.6$ Hz, 2H), 7.31 (d, $J = 8.5$ Hz, 2H), 4.03-3.98 (m, 2H), 3.76-3.72 (m, 2H), 3.17 (t, $J = 6.7$ Hz, 2H), 1.96-1.89 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 141.4, 131.3, 127.5, 122.1, 109.4, 64.6, 41.1, 27.8, 6.5; APCI MS m/z 272 [$\text{C}_{12}\text{H}_{14}\text{BrO}_2 + \text{H}$] $^+$.

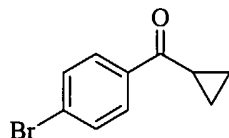
[0076] Example 19. Preparation of 2-(4-bromophenyl)-2-(3-chloropropyl)-1,3-dioxolane)



20a

2-(4-bromophenyl)-2-(3-chloropropyl)-1,3-dioxolane) was prepared as a clear colorless oil (9.80 g, 56%) following a procedure similar to that described in example 21, starting with 1-(4-bromophenyl)-4-chlorobutan-1-one (15.0 g, 0.06 mol): ^1H NMR (300 MHz, CDCl_3) δ 7.47 (d, $J = 8.6$ Hz, 2H), 7.31 (d, $J = 8.5$ Hz, 2H), 7.34-7.29 (m, 2H), 4.03-3.98 (m, 2H), 3.77-3.72 (m, 2H), 3.52 (t, $J = 6.6$ Hz, 2H), 2.02-1.97 (m, 2H), 1.88-1.79 (m, 2H).

[0077] Example 20. Preparation of (4-bromophenyl)(cyclopropyl)methanone

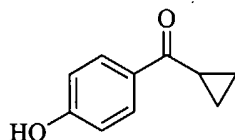


9

To a solution of KOH (42.9 g, 0.76 mol) in MeOH (275 mL) was slowly added at room temperature 1-(4-bromophenyl)-4-chlorobutan-1-one (20) (100 g, 0.382 mol). Once the exothermic reaction cooled back to room temperature, the stirring was stopped and the solids were filtered off. The filtrate is concentrated to dryness. The residue was dissolved in ethyl acetate (250 mL) and washed with H_2O (2 x 250 mL). The organic layer was dried (Na_2SO_4) and filtered through a pad of celite eluting with ethyl acetate. The filtrate was concentrated to give 56 g (99%) of the title compound as an orange oil which was used without further purification: R_f 0.41 (silica gel, 1:20 ethyl acetate/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.87 (d, $J = 8.6$ Hz, 2H), 2.56-2.65 (m, 1H), 7.61 (d, $J = 8.6$ Hz, 2H), 1.22-1.27 (m, 2H), 1.02-1.08 (m, 2H); ^{13}C NMR (75

MHz, CDCl₃) δ 137.08, 132.16, 129.93, 128.20, 17.51, 12.25; APCI MS m/z 226 [C₂₀H₉BrO + H]⁺; HPLC (Method A) >99% (AUC), t_R = 7.255 min.

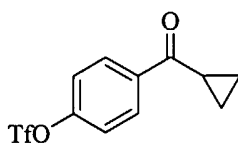
[0078] Example 21. Preparation of cyclopropyl(4-hydroxyphenyl)methanone



38

Cyclopropyl(4-hydroxyphenyl)methanone was prepared as an off-white solid (5.80 g, 72%) following a procedure similar to that described in example 23, starting with 4-chloro-1-(4-hydroxyphenyl)butan-1-one (10.0 g, 0.05 mol): R_f 0.69 (silica gel, 50:50 ethyl acetate/hexanes): mp 106-108 °C (dec.); ¹H NMR (300 MHz, CDCl₃) δ 7.97 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 6.57 (s, 1H), 2.68-2.60 (m, 1H), 1.26-1.21 (m, 2H), 1.06-1.00 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 202.0, 161.9, 131.2, 130.4, 116.0, 17.4, 12.4; HPLC (Method A) >99% (AUC), t_R = 4.5 min.

[0079] Example 22. Preparation of 4-(cyclopropanecarbonyl)phenyl trifluoromethanesulfonate

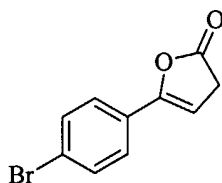


39

To a mixture of cyclopropyl(4-hydroxyphenyl)methanone (38) (2.40 g, 15.1 mmol) and triethylamine (3.20 mL, 22.5 mmol) in CH₂Cl₂ (20 mL) was slowly added drop wise under ice-cooling triflic anhydride (3.8 mL, 22.5 mmol). The reaction mixture was stirred under nitrogen for 3 hours, poured into water (20 mL), and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated to dryness. The crude product was purified by column chromatography (silica gel, hexane to 1:99 to 2:98 ethyl acetate/hexanes) to yield 3.70 g (75%) of the

title compound as a light yellow oil: R_f 0.70 (silica gel, 20:80 ethyl acetate/hexanes; ^1H NMR (300 MHz, CDCl_3) δ 8.11 (d, $J = 8.8$ Hz, 2H), 7.39 (d, $J = 8.8$ Hz, 2H), 2.67-2.58 (m, 1H), 1.30-1.25 (m, 2H), 1.13-1.07 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 199.1, 152.6, 138.2, 131.6, 121.8, 119.1 (q, CF_3), 17.7, 12.4; APCI MS m/z 268 [$\text{C}_{11}\text{H}_9\text{F}_3\text{O}_4\text{S} + \text{H}$] $^+$; HPLC (Method A) >99% (AUC), $t_R = 6.0$ min.

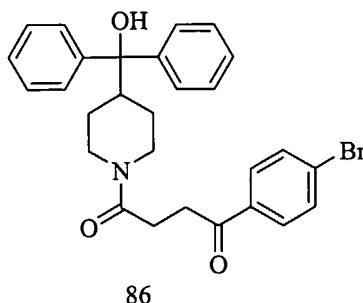
[0080] Example 23. Preparation of 5-(4-bromophenyl)furan-2(3H)-one



85

A mixture of 4-(4-bromophenyl)-4-oxobutanoic acid [prepared by the method of Seed et al. *Organic Syntheses*, Coll. Vol. 10, p.125; Vol. 79, p.204] (10.0 g, 40.0 mmol) (40) and acetic anhydride (80 mL) was heated under reflux for 16 h. After cooling to room temperature the reaction mixture was concentrated to dryness. Triturating of the residue with diethyl ether yielded 4.51 g (48%) of the title compound as an orange solid: R_f 0.25 (silica gel, 1:9 ethyl acetate/hexanes); mp 139-142 °C; ^1H NMR (300 MHz, CDCl_3) δ 7.51 (d, 2H, $J = 8.6$ Hz), 7.46 (d, 2H, $J = 8.6$ Hz), 5.80 (t, 1H, $J = 2.7$ Hz), 3.41 (d, 2H, $J = 2.7$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 175.84, 153.41, 132.02, 127.71, 126.65, 124.13, 98.85, 35.07; APCI MS m/z 240 [$\text{C}_{10}\text{H}_7\text{BrO}_2 + \text{H}$] $^+$; HPLC (Method A) >99% (AUC), $t_R = 7.0$ min.

[0081] Example 24. Preparation of 1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butane-1,4-dione



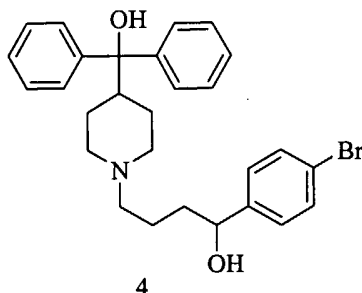
To a suspension of 5-(4-bromophenyl)furan-2(3*H*)-one (85) (447 mg, 1.87 mmol) in ethanol (5 mL) was added diphenyl(piperidin-4-yl)methanol (500 mg, 1.87 mmol). Mixture was stirred for two hours at ambient temperature and the resulting brown slurry was filtered. The filter cake was washed with ice-cold MeOH (10 mL) to yield 563 mg (60%) of the title compound as an off-white solid which was used without further purification: *R_f* 0.46 (silica gel, 50:50 ethyl acetate/hexanes; mp 161-163 °C ; ¹H NMR (300 MHz, CDCl₃) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 4H), 7.33-7.17 (m, 6H), 4.64 (d, *J* = 13.4 Hz, 1H), 3.99 (d, *J* = 13.1 Hz, 1H), 3.35-3.16 (m, 2H), 3.07 (t, *J* = 12.0 Hz, 1H), 2.81-2.68 (m, 2H), 2.66-2.53 (m, 2H), 1.59 (d, *J* = 12.1 Hz, 2H), 1.48-1.21 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 198.7, 170.0, 146.0, 136.0, 132.2, 130.1, 128.6, 127.1, 126.2, 79.8, 46.1, 44.8, 42.7, 33.9, 27.5, 26.6; APCI MS *m/z* 507 [C₂₈H₂₈BrNO₃ + H]⁺; HPLC (Method A) >98% (AUC), *t_R* = 8.0 min.

[0082] Example 25. Alternative preparation of 1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butane-1,4-dione (86)

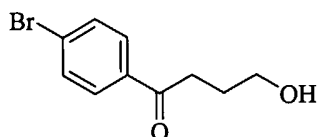
To a mixture of 4-(4-bromophenyl)-4-oxobutanoic acid (1.00 g, 4.00 mmol), diphenyl(piperidin-4-yl)methanol (1.04 g, 4.00 mmol) and HOBT (0.53 g, 4.00 mmol) in CH₂Cl₂ (20 mL) under nitrogen at 0 °C was added EDC (0.75 g, 4.00 mmol), triethylamine (0.90 g, 9.3 mmol), and DMAP (20 mg). The mixture was stirred at 0 °C for 1 h and for 18 h at ambient temperature. The mixture was concentrated to dryness

and the residue was purified by column chromatography (10:90 to 15:85 ethyl acetate/hexanes) to afford 1.07 g (54%) of the title compound as a white solid: R_f 0.35 (silica gel, 1:1 ethyl acetate/hexanes); mp 83-86 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.90 (d, 2H, $J = 8.4$ Hz), 7.73 (d, 2H, $J = 8.4$ Hz), 7.55 (d, 4H, $J = 7.7$ Hz), 7.28 (t, 4H, $J = 7.6$ Hz), 7.13 (t, 2H, $J = 7.2$ Hz), 5.34 (s, 1H), 4.36 (d, 1H, $J = 12.5$ Hz), 3.94 (d, 1H, $J = 13.1$ Hz), 3.16 (dd, 2H, $J = 5.5$ Hz, $J = 11.2$ Hz), 3.03 (dd, 2H, $J = 10.5$ Hz, $J = 22.6$ Hz), 2.80 (dd, 1H, $J = 7.9$ Hz, $J = 11.9$ Hz), 2.49-2.66 (m, 1H), 1.22-1.46 (m, 4H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 198.21, 168.80, 147.02, 146.95, 135.79, 131.59, 129.79, 127.73, 126.88, 125.77, 125.68, 125.59, 78.48, 44.84, 43.21, 41.35, 32.89, 26.77, 26.64, 25.85; APCI MS m/z 507 [$\text{C}_{28}\text{H}_{28}\text{BrNO}_3 + \text{H}$] $^+$; HPLC (Method A) >99% (AUC), $t_R = 8.025$ min.

[0083] Example 26. Preparation of 1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)-piperidin-1-yl)butan-1-ol

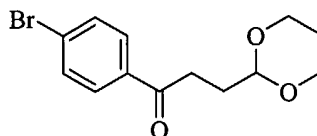


To a solution of 35 mL of 1M solution of lithium aluminum hydride in THF was added dropwise 1-(4-(benzhydryloxy)piperidin-1-yl)-4-(4-bromophenyl)butane-1,4-dione (86) (5g, 9.9 mmol) in 25 mL THF. The solution was heated at 40 °C and then stirred at room temperature for 2 hours. The reaction mixture was quenched with 20 mL of water and extracted with EtOAc (100 mL). The organic layer was washed again with water, dried (Na_2SO_4), filtered, and concentrated to dryness to provide 1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol as a white solid (4.10 g, 84%). The analytical data are identical with the data from example 4.

[0084] Example 27. Preparation of 1-(4-bromophenyl)-4-hydroxybutan-1-one

33

A mixture of (4-bromophenyl)(cyclopropyl)methanone (9) (5.40 g, 24.0 mmol) and 80% sulfuric acid (15 mL) was stirred for 18 h at 50 °C. The reaction was poured into water (500 ml) and stirred for 15 min. The solution was extracted with EtOAc (2 × 200 mL). The combined organic extracts were washed with saturated NaHCO₃ (300 mL), and water (300 ml), and brine (300 mL). The organic layer was dried (MgSO₄) and stirred with activated charcoal for 15 min, filtered, and concentrated under vacuum to produce a yellow oil which was crystallized from hexane to give 4.61 g (77%) of the title compound as white crystals: mp 56-59 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 3.74-3.69 (m, 2H), 3.07 (t, *J* = 7.0 Hz, 2H), 2.47 (t, *J* = 4.7 Hz, 1H), 2.03-1.95 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 199.5, 135.5, 131.8, 129.6, 128.2, 61.9, 35.1, 26.8; HPLC (Method A) >99% (AUC), *t*_R = 5.1 min.

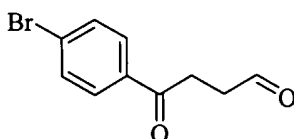
[0085] Example 28. Preparation of 1-(4-bromophenyl)-3-(1,3-dioxan-2-yl)propan-1-one

36

To a mixture of magnesium turnings (1.2 g, 0.05 mol) and anhydrous THF (40 mL) was added at room temperature 2-(2-bromoethyl)-1,3-dioxane [prepared by the method of Krohn et al. *Eur. J. Org. Chem.* **1999**, 12, 3495 - 3500] drop wise over a period of 40 minutes. Once magnesium dissolved, the mixture was cooled to 0 °C and a solution of 4-bromo-*N*-methoxy-*N*-methylbenzamide [prepared by the method of Turnbull et al. *Tetrahedron Lett.* **1998**, 39, 1509-1512] (35) in anhydrous THF (6 mL) was added drop

wise. The reaction was allowed to warm to room temperature and stirred for 16 h. The mixture was quenched with saturated NH_4Cl and extracted with EtOAc (150 mL). The organic layer was washed with water (50 mL), brine (50 mL), and dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified via column chromatography (silica gel, 10:90 to 17:83 ethyl acetate/hexanes) to yield 5.30 g (86%) of the title compound as an colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.85 (d, $J = 8.5$ Hz, 2H), 7.59 (d, $J = 8.5$ Hz, 2H), 4.66 (t, $J = 4.8$ Hz, 1H), 4.06-4.12 (m, 2H), 3.76 (dt, $J = 12.4$ Hz, 2.5 Hz, 2H), 3.07 t, $J = 7.3$ Hz, 2H), 2.01-2.09 (m, 3H), 1.31-1.36 (m, 1H).

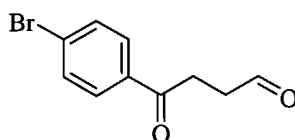
[0086] Example 29. Preparation of 4-(4-bromophenyl)-4-oxobutanal



34

A solution of 1-(4-bromophenyl)-3-(1,3-dioxolan-2-yl)propan-1-one (36) (5.30 g, 18.0 mol) in AcOH (150 mL) was heated to 65 °C under nitrogen. The reaction mixture was diluted with EtOAc (200 mL) and water (50 mL), and neutralized slowly with saturated NaHCO_3 . The organic layer was separated, washed with water (50 mL), and brine (50 mL), and dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified via column chromatography (silica gel, 5:95 to 15:85 ethyl acetate/hexanes) to afford 5.31 g (77%) of the title compound as a white solid: mp 59-62 °C; ^1H NMR (300 MHz, CDCl_3) δ 9.88 (s, 1H), 7.83 (d, $J = 8.5$ Hz, 2H), 7.59 (d, $J = 8.5$ Hz, 2H), 3.72 (t, $J = 6.1$ Hz, 2H), 2.92 (t, $J = 6.4$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 200.7, 197.1, 135.5, 132.3, 129.9, 128.8, 37.9, 31.2; APCI MS m/z 242 [$\text{C}_{10}\text{H}_{11}\text{BrO}_2 + \text{H}$] $^+$; HPLC (Method A) 98.1% (AUC), $t_R = 5.5$ min.

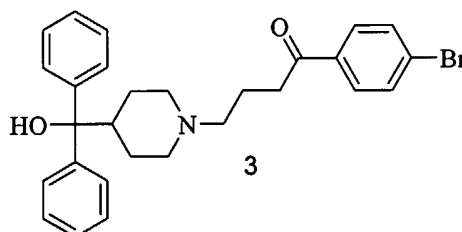
[0087] Example 30. Alternative preparation of 4-(4-bromophenyl)-4-oxobutanal (34)



34

To a solution of DMSO in CH_2Cl_2 under nitrogen was slowly added at -78°C oxalyl chloride and the mixture was stirred for 20 minutes. A solution of 1-(4-bromophenyl)-4-hydroxybutan-1-one (33) (500 mg, 2.08 mmol) in a mixture of DMSO and CH_2Cl_2 (35 mL) was added dropwise over a period of 20 minutes. After the addition was completed, the mixture was stirred at -78°C for 1 hour. DIPEA was added dropwise to the reaction. The reaction mixture was stirred for 1 hour at -78°C and then allowed to warm to ambient temperature and stirred for additional 18 h. The reaction mixture was concentrated to dryness and the residue was partitioned between EtOAc and 2N NaOH. The aqueous layer was washed with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by column chromatography (silica gel, 1:99 $\text{NEt}_3/\text{CH}_2\text{Cl}_2$) followed by trituration with hexanes to provide 4-(4-Bromophenyl)-4-oxobutanal as an off-white solid (450 mg, 90%).

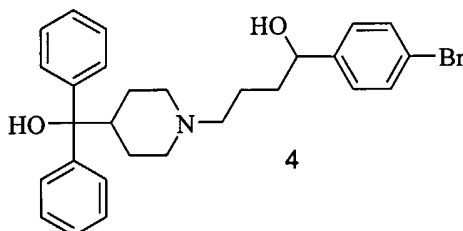
[0088] Example 31. Preparation of 1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-one



To a stirred solution of 4-(4-bromophenyl)-4-oxobutanal (34) (0.5 g, 2.0 mmol) in MeOH (20 mL) and DCM (10 mL) under N_2 was added diphenyl(piperidin-4-yl)methanol (0.83 g, 3.1 mmol) and the mixture was stirred for 1 h at room temperature. Sodium triacetoxyborohydride (0.20 g, 3.10 mmol) was added followed

by AcOH (0.12 mL) and the mixture was stirred for 1 h at room temperature. The mixture was evaporated to dryness. The residue was redissolved in EtOAc (20 mL) and washed with water (2 x 10 mL). The organic layer was dried (MgSO₄), filtered, and concentrated to dryness. The residue was then purified via column chromatography (silica gel, 3:97 MeOH/DCM) to provide 0.18 g (18%) of the title compound as a clear oil: ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.53-7.11 (m, 13H), 3.11 (d, *J* = 10.9 Hz, 2H), 2.93 (t, *J* = 6.8 Hz, 1H), 2.62 (t, *J* = 7.0 Hz, 1H), 2.55-2.51 (m, 2H), 2.30 (t, *J* = 11.4 Hz, 2H), 1.96 (t, *J* = 7.0 Hz, 2H), 1.70-1.48 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ 198.9, 146.3, 132.3, 131.5, 130.0, 128.6, 128.0, 126.9, 126.2, 79.6, 57.4, 53.8, 43.6, 36.3, 25.6, 20.7; APCI MS *m/z* 493 [C₂₈H₃₀BrNO₂ + H]⁺; HPLC (Method A) 97.9% (AUC), *t*_R = 6.2 min.

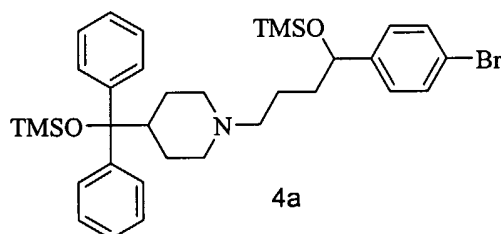
[0089] Example 32. Preparation of 1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)-piperidin-1-yl)butan-1-ol



To a stirred solution of 1-(4-bromophenyl)-4-chlorobutan-1-ol (21), obtained from example 12, (10.0 g, 38.0 mmol) in DMF (130 mL) under nitrogen was added diphenyl(piperidin-4-yl)methanol (15.2 g, 57 mmol) followed by Na₂CO₃ (15.8 g, 114 mmol) and the mixture was stirred for 18 h at 60 °C. The mixture was diluted with water (500 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with water (5 x 150 mL), and brine (200 mL), dried (MgSO₄), filtered, and concentrated under vacuum. The residue was purified by column chromatography (silica gel, 78:19:3 ethyl acetate/hexane/ NEt₃), to provide 9.6 g (51%) of the title compound as a white powder: mp 128-132 °C (dec); ¹H NMR (300 MHz, CDCl₃) δ 7.91 (s, 1H), 7.49-7.15 (m, 14H), 4.53-4.50 (m, 1H), 3.07-2.89 (m, 2H),

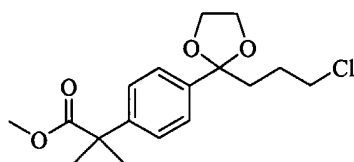
2.63–2.34 (m, 4H), 2.05–1.91 (m, 3H), 1.69–1.46 (m, 6H), 1.27–1.25 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 161.1, 146.7, 146.5, 145.9, 145.8, 145.5, 131.4, 128.6, 128.6, 128.5, 128.5, 127.9, 127.2, 127.1, 126.8, 126.7, 126.4, 126.3, 126.2, 126.1, 120.5, 79.9, 79.6, 77.9, 77.5, 77.1, 73.2, 59.2, 55.1, 53.7, 46.6, 45.1, 44.6, 40.4, 40.3, 27.7, 26.4, 26.3, 24.3; APCI MS m/z 495 [$\text{C}_{28}\text{H}_{32}\text{BrNO}_2 + \text{H}$] $^+$; HPLC (Method A) 98.7% (AUC), $t_R = 6.0$ min.

[0090] Example 33. Preparation of 1-(4-(4-bromophenyl)-4-(trimethylsilyloxy)butyl)-4-(diphenyl(trimethylsilyloxy)methyl)piperidine



To a stirred solution of 1-(4-bromophenyl)-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butan-1-ol (4) (4.00 g, 8.1 mmol) in DMF (10 mL) under N_2 was added trimethylsilyl chloride (2.20 g, 20.2 mmol), followed by imidazole (1.9 g, 28.4 mol) and the mixture was stirred for 18 h at room temperature. The mixture was diluted with water (50 mL) and stirred for 1 h then extracted with ethyl acetate (2×20 mL). The combined organic extracts were washed with water (5×15 mL), brine (20 mL), dried (MgSO_4), filtered, and concentrated under vacuum to provide 4 g (77%) of the title compound as a yellow oil which was used without further purification: ^1H NMR (300 MHz, CDCl_3) δ 7.40–7.37 (d, $J = 8.2$ Hz, 2H), 7.26–7.23 (m, 10H), 7.14–7.11 (d, $J = 8.2$ Hz, 2H), 4.54 (t, $J = 4.4$ Hz, 1H), 2.90–2.87 (m, 2H), 2.39–2.36 (m, 1H), 2.25–2.21 (m, 2H), 1.96–1.82 (m, 4H), 1.61–1.54 (m, 4H), 1.09–1.05 (m, 2H), 0.00 (s, 9H), -0.20 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.3, 130.1, 129.9, 127.8, 127.4, 125.9, 125.8, 119.5, 82.3, 73.1, 57.7, 53.3, 43.9, 37.5, 26.7, 22.1, 0.6, -0.9; APCI MS m/z 640 [$\text{C}_{34}\text{H}_{48}\text{BrNO}_2\text{Si}_2 + \text{H}$] $^+$; HPLC (Method A) 92.0% (AUC), $t_R = 8.1$ min.

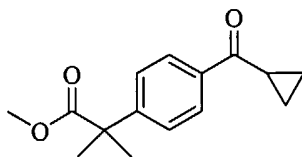
[0091] Example 34. Preparation of methyl 2-(4-(2-(3-chloropropyl)-1,3-dioxolan-2-yl)phenyl)-2-methylpropanoate



8a

To a degassed mixture of dicyclohexylamine (5.1 mL, 26.0 mmol) in toluene (200 mL) was added under nitrogen at -15 °C a 2.5M solution of *n*-butyllithium in hexanes (9.4 mL 24.0 mol) and the mixture was stirred at -5 °C for 20 minutes. Methyl isobutyrate (3.00 g, 29 mmol) was added and the mixture was stirred for an additional 20 minutes as it warmed to room temperature. A degassed suspension of 2-(4-bromophenyl)-2-(3-chloropropyl)-1,3-dioxolane (20a) (6.0 g, 20.0 mmol) and tris(dibenzylideneacetone) dipalladium (0) (180 mg, 1 mol%) in toluene (50 mL) was added via addition funnel, followed by addition of 10% solution of tri-*t*-butylphosphine in hexanes (400 µL, 1 mol%). The reaction mixture was degassed (3 x), stirred at room temperature for 16 h, filtered through a pad of silica eluting with ethyl acetate. The filtrate was concentrated under reduced to dryness. The residue was purified by column chromatography (5:95 ethyl acetate/hexanes) to yield 4.1 g (64%) of the title compounds as a clear yellow oil: *R*_f 0.4 (silica gel, 1:9 ethyl acetate/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 7.39 (d, 2H, *J* = 8.6 Hz), 7.29 (d, 2H, *J* = 8.5 Hz), 3.99 (dd, 2H, *J* = 5.1 Hz, *J* = 8.7 Hz), 3.75-3.79 (m, 2H), 3.65 (s, 3H), 3.52 (t, 2H, *J* = 6.6 Hz), 1.99-2.03 (m, 2H), 1.81-1.90 (m, 2H), 1.57 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 177.42, 144.75, 141.16, 126.04, 125.83, 110.23, 64.95, 52.50, 46.72, 45.48, 38.10, 27.39, 26.96; APCI MS *m/z* 291 [C₁₇H₂₃ClO₄ - Cl]⁺.

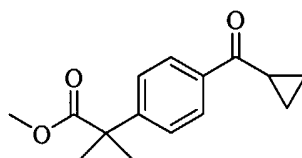
[0092] Example 35. Preparation of methyl 2-(4-(cyclopropanecarbonyl)phenyl)-2-methylpropanoate



10

Methyl 2-(4-(cyclopropanecarbonyl)phenyl)-2-methylpropanoate was prepared as a brown oil (208 mg, 38%) following a procedure similar to that described in example 38 below, starting with (4-bromophenyl)(cyclopropyl)methanone (9) (500 mg, 22.0 mol): R_f 0.30 (silica gel, 1:9 ethyl acetate/hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.98 (d, 2H, $J = 8.4$ Hz), 7.44 (d, 2H, $J = 8.4$ Hz), 3.66 (s, 3H), 2.61-2.71 (m, 1H), 1.61 (s, 6H), 1.17-1.26 (m, 2H), 0.99-1.06 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 177.01, 149.97, 136.86, 129.41, 128.59, 126.27, 52.71, 47.20, 26.79, 17.46, 11.89; APCI MS m/z 247 [$\text{C}_{15}\text{H}_{18}\text{O}_3 + \text{H}$] $^+$; HPLC (Method A) >99% (AUC), $t_R = 6.85$ min.

[0093] Example 36. Alternative preparation of methyl 2-(4-(cyclopropanecarbonyl)phenyl)-2-methylpropanoate (10)

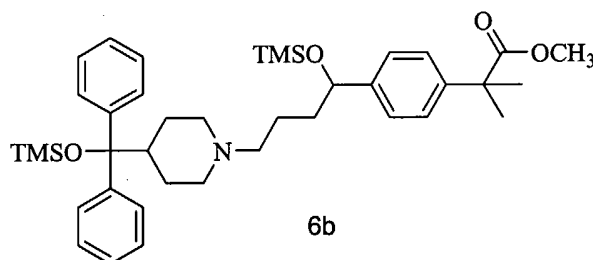


10

A degassed mixture of 4-(cyclopropanecarbonyl)phenyl trifluoromethanesulfonate (39) (276 mg, 1.04 mmol), methyl trimethylsilyl dimethylketene acetal (5) (531 μL , 2.07 mmol), anhydrous lithium acetate (211 mg, 2.07 mmol), and bis(tri-*t*-butylphosphine)palladium (0) (53 mg, 0.10 mmol) in anhydrous THF was heated under reflux for 18 h. The mixture was cooled to ambient temperature and filtered through a pad of silica eluting with ethyl acetate. The filtrate was concentrated under reduced pressure to dryness. The residue was purified by column chromatography (5:95 ethyl acetate/hexanes) to yield 131 mg (52%) of the title compounds as a clear yellow oil: R_f

0.4 (silica gel, 0:100 to 5:95 Ethyl acetate/Hexanes); ^1H NMR (300 MHz, CDCl_3) δ 7.98 (d, 2H, $J = 8.4$ Hz), 7.44 (d, 2H, $J = 8.4$ Hz), 3.65 (s, 3H), 2.61-2.68 (m, 1H), 1.61 (s, 6H), 1.20-1.256 (m, 2H), 0.99-1.06 (m, 2H).

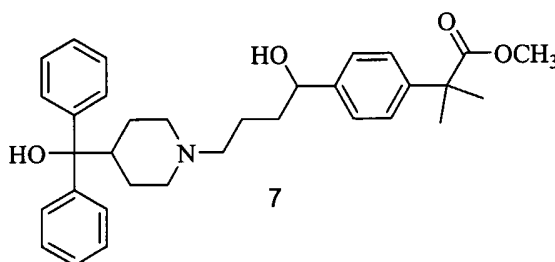
[0094] Example 37. Preparation of methyl 2-(4-(4-(4-(diphenyl(trimethylsilyloxy)methyl)piperidin-1-yl)-1-(trimethylsilyloxy)butyl)phenyl)-2-methylpropanoate



An oven dried 3-neck flask equipped with a magnetic stir bar, addition funnel and N_2 inlet was charged toluene (8 mL) and dicyclohexylamine (183 mg, 1.01 mol) an the mixture was cooled to $-10\text{ }^\circ\text{C}$. A 2.5M solution of *n*-buthyllithium in hexanes (0.38 mL, 0.94 mmol) was added and the mixture was stirred at for 20 minutes. Methyl isobutyrate (120 mg, 1.17 mmol) was added to the round-bottom flask and the mixture was stirred for 20 min. A solution of 1-(4-(4-bromophenyl)-4-(trimethylsilyloxy)butyl)-4-(diphenyl(trimethylsilyloxy)methyl)piperidine (0.50 g, 0.78 mmol) (4a) and tris(dibenzylideneacetone) dipalladium (27 mg, 0.03 mmol, 4 mol %) in toluene (2 mL) was added drop wise, followed by addition of 10% w/w solution of tri-*t*-butylphosphine in hexanes (60 μL , 4 mol%). The reaction mixture was degassed (3 x) warmed to ambient temperature and stirred for 16 h. The reaction was then passed through a silica gel plug and washed with ethyl acetate (50 mL). The filtrate was concentrated to dryness and the residue was purified by column chromatography (silica gel, 4:1 ethyl acetate/hexane) to provide 80 mg (16%) of the title compound as a yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 7.47-7.31 (m, 14H), 4.79-5.75 (m, 1H), 3.83 (s, 3H), 3.11-3.09 (m, 2H), 2.59-2.41 (m, 3H), 2.17-2.02 (m, 4H), 1.82-1.71 (m, 10H), 1.28-1.22 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 175.6, 142.7, 141.9, 141.5, 127.2, 125.5, 125.2, 124.1, 123.6, 81.7, 72.8, 57.2, 52.8, 52.7, 50.4, 44.5, 43.4, 36.9, 26.1,

24.9, 24.8, 21.6, 0.0, -1.5; APCI MS m/z 661 [$C_{39}H_{57}NO_4Si_2 + H$] $^+$; HPLC (Method A) 79.7% (AUC), $t_R = 7.3$ min.

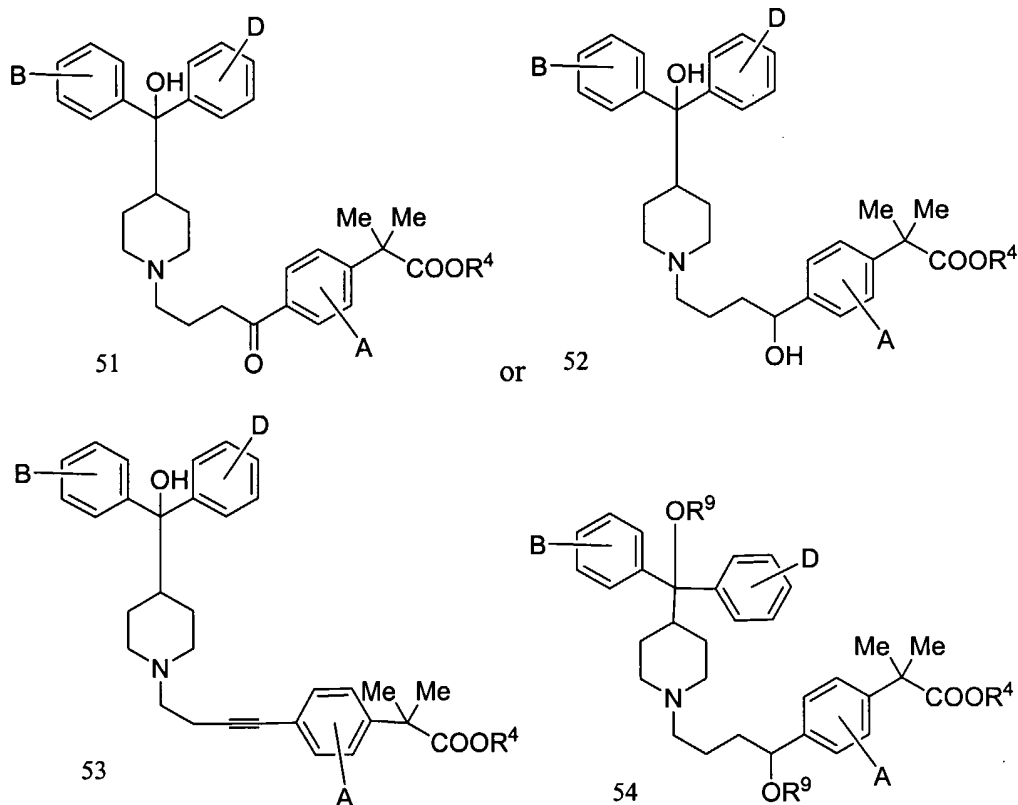
[0095] Example 38. Preparation of methyl 2-(4-(1-hydroxy-4-(4-(hydroxydiphenylmethyl)piperidin-1-yl)butyl)phenyl)-2-methylpropanoate



A mixture of methyl 2-(4-(4-(4-(diphenyl(trimethylsilyloxy)methyl)piperidin-1-yl)-1-(trimethylsilyloxy)butyl)phenyl)-2-methylpropanoate (6b) (12 mg, 0.02 mmol) and trifluoroacetic acid (1 mL) in CH_2Cl_2 (10 mL) was stirred at ambient temperature for 18 h. The mixture was basified with 2M NaOH (5 mL) and the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated to dryness, to afford 6 mg (58%) of the subtitle compound as a white solid, which was characterized by comparison with an authentic sample.

CLAIMS

1. A process for preparing a piperidine derivative compound of the formula 51, 52, 53 or 54:



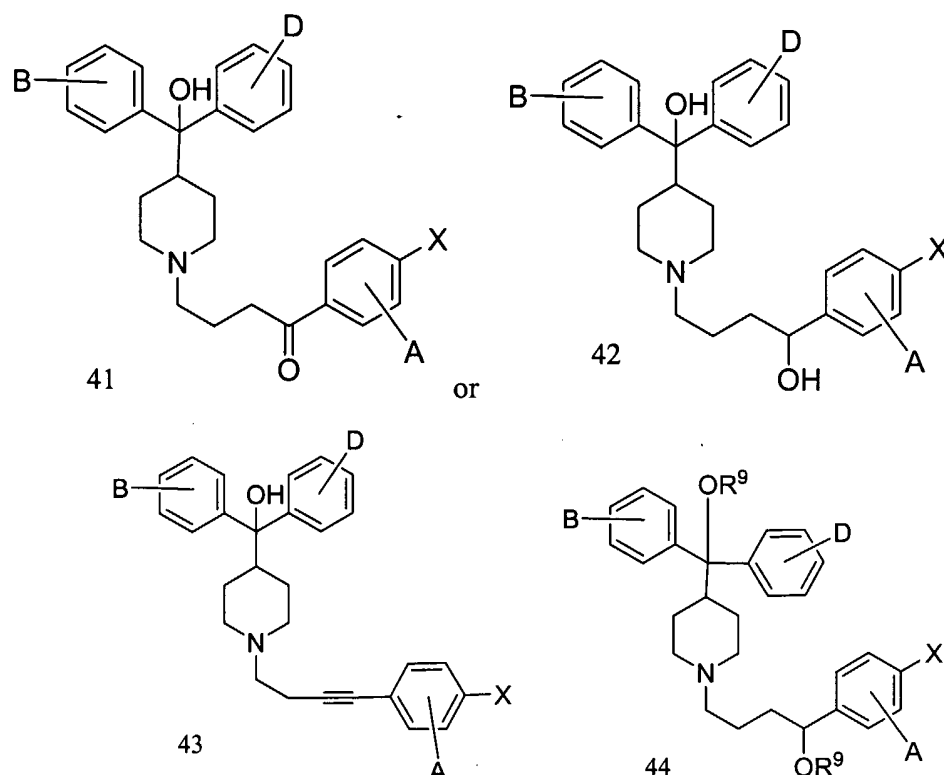
wherein

R^4 is H, alkyl, aryl or substituted aryl;

R^9 is a protecting group for an alcohol chosen from a benzyl ether, a silyl ether and an acyl;

A, B, and D are the substituents of their rings, each of which may be different or the same, and are selected from the group consisting of hydrogen, fluorine, chlorine, alkyl, aryl, hydroxyl, alkoxy, and aryloxy;

said process comprising providing a compound of formula 41, 42, 43 or 44:



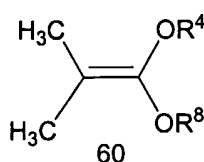
wherein X is a group displaceable via oxidative metallic addition;
and converting the compound of formula 41, 42, 43 or 44 to 51, 52, 53 or 54
respectively by reacting with isobutyrate or an isobutyrate equivalent.

2. A process according to claim 1 wherein 41 and isobutyrate or an isobutyrate equivalent are converted to 51 by reaction in the presence of a trivalent phosphorus compound and a transition metal catalyst.
3. A process according to claim 1 wherein 42 and isobutyrate or an isobutyrate equivalent are converted to 52 by reaction in the presence of a trivalent phosphorus compound and a transition metal catalyst.
4. A process according to claim 1 wherein 43 and isobutyrate or an isobutyrate equivalent are converted to 53 by reaction in the presence of a trivalent phosphorus compound and a transition metal catalyst.

5. A process according to claim 1 wherein 44 and isobutyrate or an isobutyrate equivalent are converted to 54 by reaction in the presence of a trivalent phosphorus compound and a transition metal catalyst and R^9 is a silyl ether.

6. A process according to any of claims 1-5 wherein X is chosen from chlorine, bromine, iodine, $-\text{OSO}_2R^5$, $-\text{N}_2^+$, $-\text{OP}(\text{O})(\text{OR}^6)(\text{OR}^7)$ and $-\text{B}(\text{OR}^6)(\text{OR}^7)$, wherein R^5 is chosen from fluoro, alkyl, fluoroalkyl, aryl, heteroaryl and substituted aryl; R^6 and R^7 are chosen from H and $\text{C}_1\text{-C}_{20}$ hydrocarbon.

7. A process according to any of claims 1-5 wherein said isobutyrate or isobutyrate equivalent is of the formula 60:



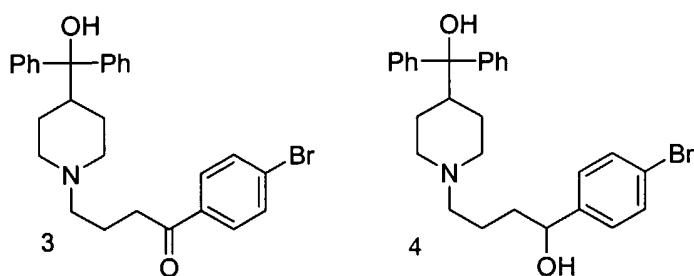
wherein R^8 is a protecting group for a ketene acetal.

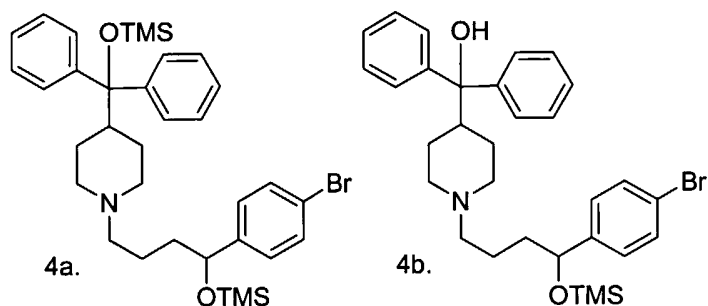
8. A process according to claim 7 wherein R^8 is a trialkylsilyl group.

9. A process according to claim 8 wherein R^8 is a trimethylsilyl group.

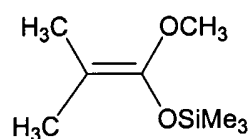
10. A process according to any of claims 1-5 wherein said isobutyrate or isobutyrate equivalent is methyl isobutyrate.

11. A process according to claim 1 for preparing fexofenadine comprising the step of reacting a compound of formula 3, 4, 4a or 4b:



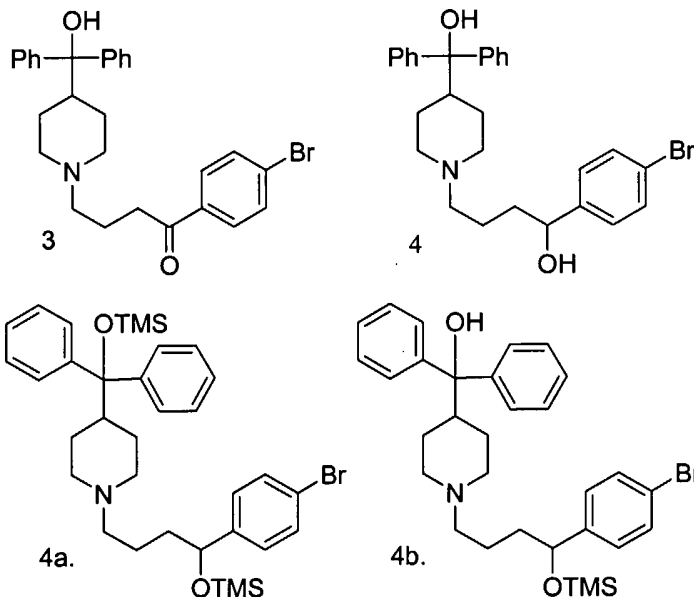


with a silyl ketene acetal of formula:



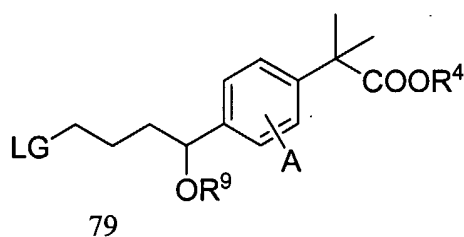
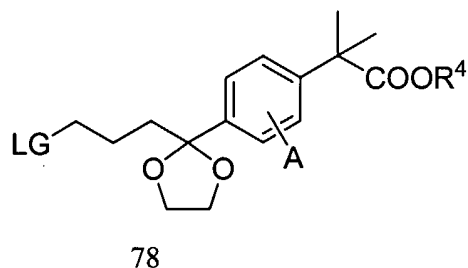
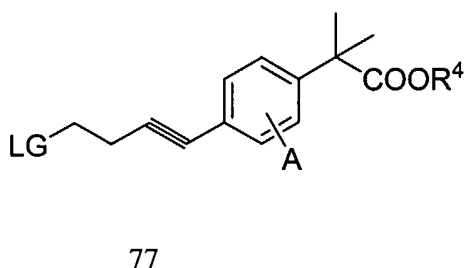
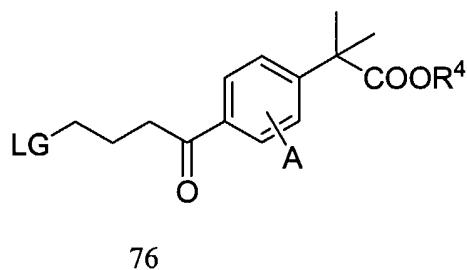
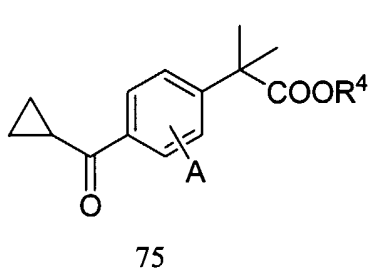
in the presence of a Pd(0) catalyst, a trialkyl or triaryl phosphine and a zinc salt, and carrying out further process steps to provide fexofenadine.

12. A process according to claim 1 for preparing fexofenadine comprising the step of reacting a compound of formula 3, 4, 4a or 4b:



with methyl isobutyrate in the presence of a Pd(0) catalyst, a trialkyl or triaryl phosphine and a lithium dialkylamide, and carrying out further process steps to provide fexofenadine.

13. A process according to claim 11 or 12 wherein said further process steps include reduction of the ketone and saponification of the methyl ester.
14. A process according to claim 11 or 12 wherein said further process steps include cleavage of the alcohol protecting group and saponification of the methyl ester.
15. A process for preparing an α,α -dimethylphenylacetate of the formula 75, 76, 77, 78 or 79:



wherein

R^4 is H, alkyl, aryl or substituted aryl;

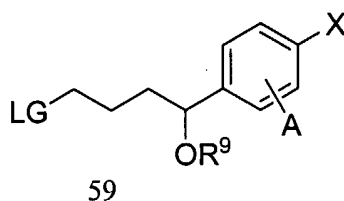
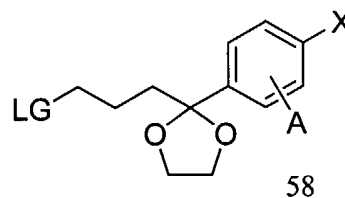
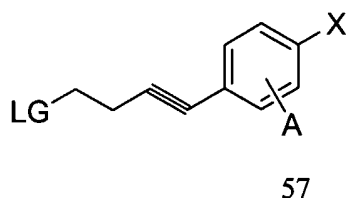
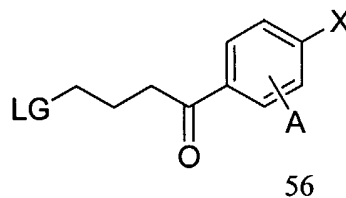
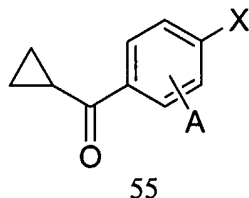
R^9 is a protecting group for an alcohol chosen from a benzyl ether, a silyl ether and an acyl;

A is selected from the group consisting of hydrogen, alkyl, aryl, hydroxyl, alkoxy, and aryloxy;

X is a group displaceable via oxidative metallic addition; and

LG is a leaving group displaceable by a secondary amine;

said process comprising providing a compound of formula 55, 56, 57, 58 or 59:



and converting the compound of formula 55-59 to 75-79 respectively by reacting with isobutyrate or an isobutyrate equivalent.

16. A process according to claim 15 wherein 55 and isobutyrate or an isobutyrate equivalent are converted to 75 by reaction in the presence of a trivalent phosphorus compound and a transition metal catalyst.

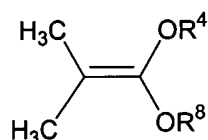
17. A process according to claim 15 wherein 56 and isobutyrate or an isobutyrate equivalent are converted to 76 by reaction in the presence of a trivalent phosphorus compound and a transition metal catalyst.

18. A process according to any of claims 15, 16 or 17 wherein X is chosen from chlorine, bromine, iodine, $-\text{OSO}_2\text{R}^5$, $-\text{N}_2^+$, $-\text{OP}(\text{O})(\text{OR}^6)(\text{OR}^7)$ and $-\text{B}(\text{OR}^6)(\text{OR}^7)$; R^5 is chosen from fluoro, alkyl, fluoroalkyl, aryl, heteroaryl and substituted aryl; and

R^6 and R^7 are chosen from H and C_1 - C_{20} hydrocarbon.

19. A process according to any of claims 15, 16 or 17 wherein LG is chosen from chlorine, bromine, iodine, boronic acid and $-\text{OSO}_2R^5$, wherein R^5 is chosen from fluoro, alkyl, fluoroalkyl, aryl and substituted aryl.

20. A process according to any of claims 15, 16 or 17 wherein said isobutyrate or isobutyrate equivalent is of the formula IV:

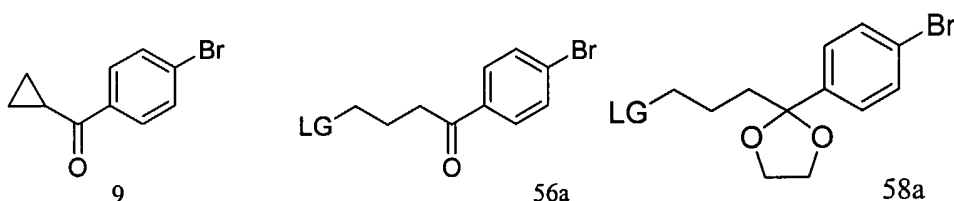


wherein R^8 is a protecting group for a ketene acetal.

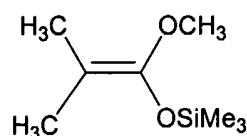
21. A process according to claim 7 or 20 wherein R^8 is a trialkylsilyl or dialkylphosphoryl group.

22. A process according to any of claims 15, 16 or 17 wherein said isobutyrate or isobutyrate equivalent is methyl isobutyrate.

23. A process according to claim 15 for preparing fexofenadine comprising the step of reacting a compound of formula 9, 56a or 58a:

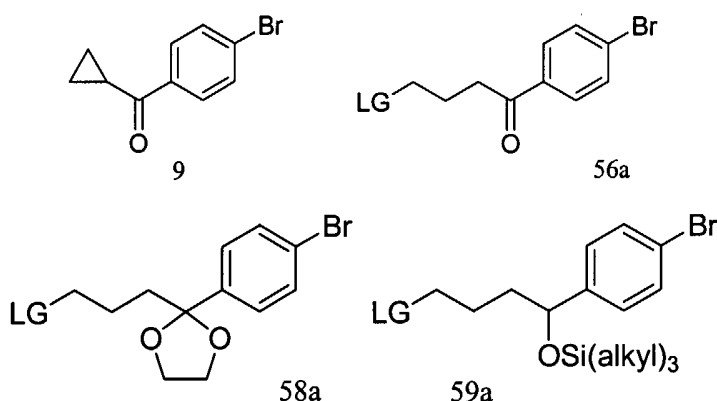


with a silyl ketene acetal of formula:



in the presence of a Pd(0) catalyst, a trialkyl or triaryl phosphine and a zinc salt to provide a compound of formula 75, 76 or 78, and carrying out further process steps to provide fexofenadine.

24. A process according to claim 15 for preparing fexofenadine comprising the step of reacting a compound of formula 9, 56a, 58a or 59a:

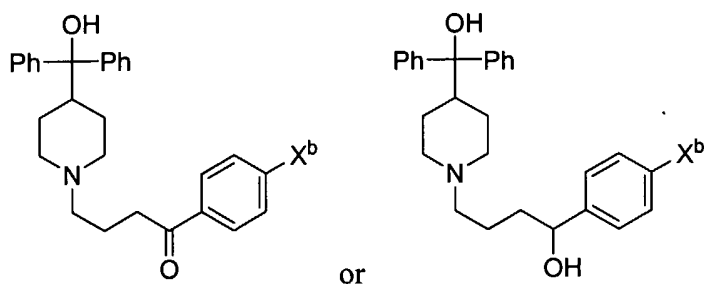


with methyl isobutyrate in the presence of a Pd(0) catalyst, a trialkyl or triaryl phosphine and a lithium amide to provide a compound of formula 75, 76, 78 or 79 and carrying out further process steps to provide fexofenadine.

25. A process according to any of claims 15, 16 or 17 wherein X is chosen from chlorine, bromine, iodine, $-\text{OSO}_2\text{R}^5$, $-\text{N}_2^+$, $-\text{OP}(\text{O})(\text{OR}^6)(\text{OR}^7)$ and $-\text{B}(\text{OR}^6)(\text{OR}^7)$; R^5 is chosen from fluoro, alkyl, fluoroalkyl, aryl, heteroaryl and substituted aryl; and R^6 and R^7 are chosen from H and $\text{C}_1\text{-C}_{20}$ hydrocarbon.

26. A process according to any of claims 15, 16, 17, 23 or 24 wherein LG is chosen from chlorine, bromine, iodine, boronic acid, boronic ester, a diazonium salt, dialkyl phosphate and $-\text{OSO}_2\text{R}^5$, wherein R^5 is chosen from fluoro, alkyl, fluoroalkyl, aryl and substituted aryl.

27. A compound of formula

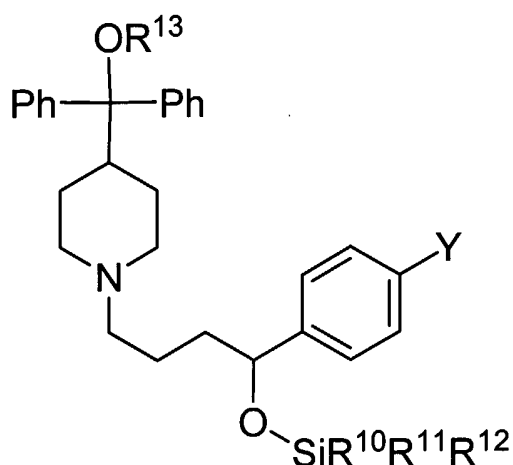


wherein X^b is chosen from $-\text{OSO}_2\text{R}^5$, $-\text{N}_2^+$, $-\text{OH}$, $-\text{OP}(\text{O})(\text{OR}^6)(\text{OR}^7)$ and $-\text{B}(\text{OR}^6)(\text{OR}^7)$, wherein

R^5 is chosen from fluoro, alkyl, fluoroalkyl, aryl, heteroaryl and substituted aryl;

R^6 and R^7 are chosen from H and $\text{C}_1\text{-C}_{20}$ hydrocarbon.

28. A compound of formula



wherein

Y is chosen from Cl, Br, I, $-\text{OSO}_2\text{R}^5$, $-\text{N}_2^+$, $-\text{OH}$, $-\text{B}(\text{OR}^6)(\text{OR}^7)$, $-\text{OP}(\text{O})(\text{OR}^6)(\text{OR}^7)$ and $-\text{C}(\text{CH}_3)_2\text{COOR}^4$;

R^4 is H, alkyl, aryl or substituted aryl;

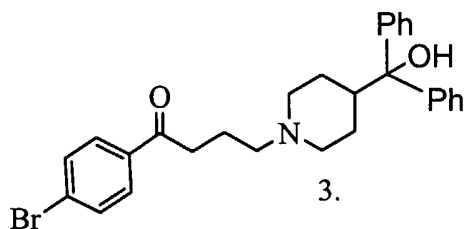
R^5 is chosen from fluoro, alkyl, fluoroalkyl, aryl, heteroaryl and substituted aryl;

R^6 and R^7 are chosen from H and $\text{C}_1\text{-C}_{20}$ hydrocarbon;

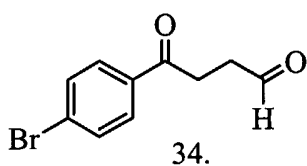
R^{10} , R^{11} and R^{12} are chosen independently from $(\text{C}_1\text{-C}_6)\text{alkyl}$, phenyl and benzyl; and

R^{13} is H or $\text{SiR}^{10}\text{R}^{11}\text{R}^{12}$.

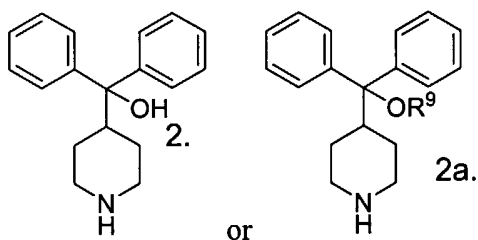
29. A process for preparing a compound of formula 3



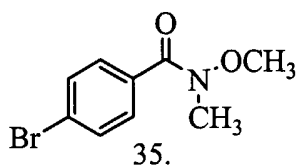
comprising reductively aminating a compound of formula 34



with an amine of formula 2 or 2a

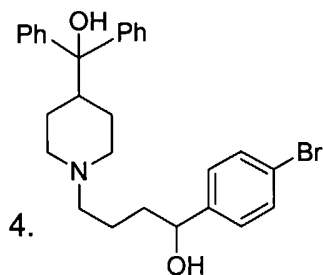


30. A process according to claim 29 wherein compound 34 is provided by reacting a compound of formula 35:



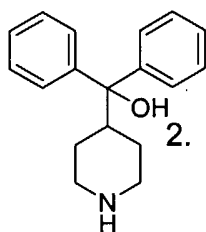
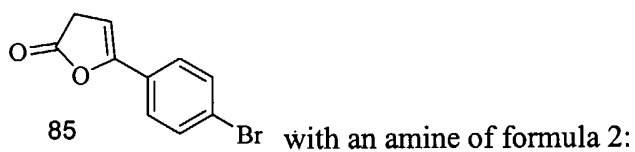
with 2-(2-bromoethyl)-1,3-dioxolane and magnesium followed by hydrolysis of the dioxolane.

31. A process for preparing a compound of formula 4

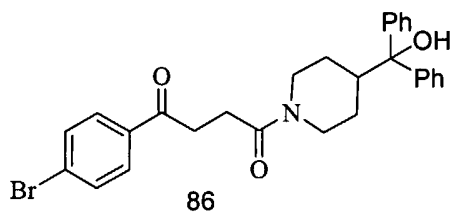


comprising

(a) reacting a compound of formula 85



to provide a compound of formula 86

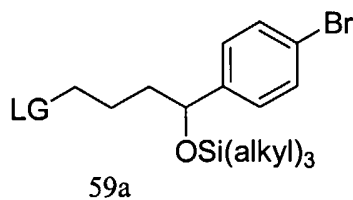


;

(b) converting said compound 86 to compound 4 by reduction.

32. A process according to claim 31 wherein said reduction is carried out with a hydride reagent.

33. A compound of formula 59a



wherein LG is chosen from chlorine, bromine, iodine, boronic acid, boronic ester and OSO_2R^5 , wherein R^5 is chosen from fluoro, alkyl, fluoroalkyl, aryl and substituted aryl.

34. A compound according to claim 33 wherein $\text{OSi}(\text{alkyl})_3$ is chosen from trimethylsilyloxy, t-butyltrimethylsilyloxy and triisopropylsilyloxy.