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(54) **Title:** PROCESSES FOR THE SYNTHESIS OF O-DESMETHYLVENLAFAXINE

(57) **Abstract:** Provides are intermediates and processes for preparation of o- desmethylvenlafaxine.

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PROCESSES FOR THE SYNTHESIS OF O-DESMETHYLVENLAFAXINE

CROSS REFERENCE TO RELATED APPLICATIONS

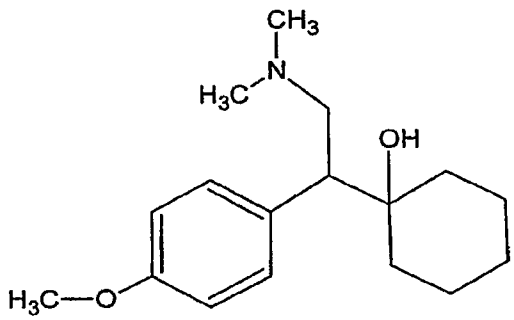
[0001] The present application claims the benefit of the following United States Provisional Patent Application Nos.: 60/833,616, filed July 26, 2006; 60/837,879, filed August 14, 2006; 60/849,216, filed October 3, 2006; 60/843,998, filed September 11, 2006; 60/849,255, filed October 3, 2006; 60/906,639, filed March 12, 2007; and 60/906,879, filed March 13, 2007. The contents of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The invention encompasses a process for the synthesis of O-desmethylvenlafaxine.

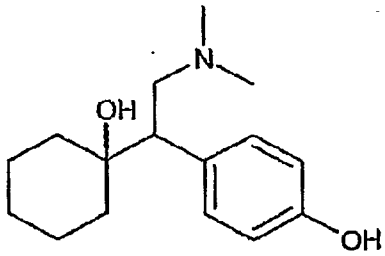
BACKGROUND OF THE INVENTION

[0003] Venlafaxine, (±)-1-[2-(Dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol is the first of a class of anti-depressants. Venlafaxine acts by inhibiting re-uptake of norepinephrine and serotonin, and is an alternative to the tricyclic anti-depressants and selective re-uptake inhibitors. Venlafaxine has the following chemical formula, Formula I:



Formula I

[0004] O-desmethylvenlafaxine, 4-[2-(dimethylamino)-1-(1-hydroxycyclohexyl)ethyl]phenol, is reported to be a metabolite of venlafaxine and has been reported to inhibit norepinephrine and serotonin uptake. *See* Klamerus, K. J. et al., "Introduction of the Composite Parameter to the Pharmacokinetics of Venlafaxine and its Active O-Desmethyl Metabolite," *J. Clin. Pharmacol.* 32:716-724 (1992). O-desmethylvenlafaxine has the following chemical formula, Formula II:

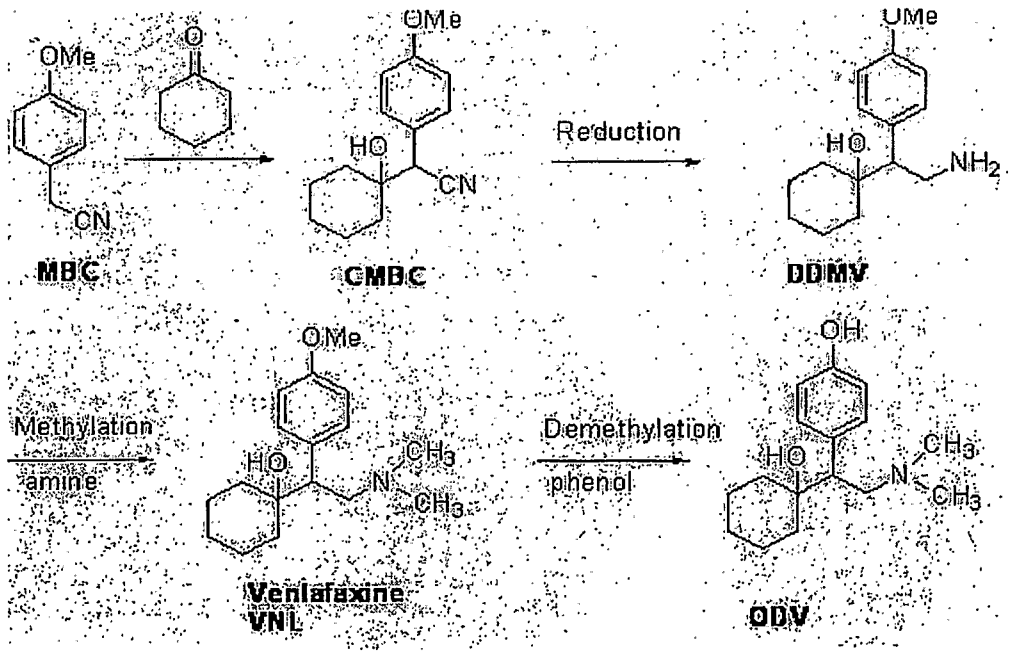


$C_{16}H_{25}NO_2$
Mol. Wt.: 263.38

Formula II

[0005] Processes for the synthesis of O-desmethylvenlafaxine, comprising a step of demethylation of the methoxy group of venlafaxine, are described in U.S. patent No. 7,026,508 and 6,689,912, and in U.S. publication No. 2005/0197392.

[0006] The synthesis disclosed in the above references is performed according to the following scheme:



Wherein "MBC" refers to methyl benzyl cyanide, "CMBC" refers to cyclohexyl methylbenzyl cyanide, "DDMV" refers to didesmethyl venlafaxine, and "ODV" refers to O-desmethylvenlafaxine.

[0007] However, the processes disclosed in the above US patents and US patent applications all remain problematic when applied to industrial scale production. The process in US Patent No. 7,026,508 uses L-selectride, a compound which is very

problematic when scaling up the process for industrial application. Further, the process disclosed in US Application Publication No. 2005/0197392 uses lithiumdiphenyl phosphine, a compound which handling and use in industrial scale processes is extremely dangerous. Also, the process disclosed in US Patent No 6,689,912 uses methanol as a solvent, which use is problematic when traces of methanol remain and in subsequent process steps when high temperatures are applied.

[0008] There is a need in the art for a new synthetic route for obtaining sO-desmethylvenlafaxine, using a precursor of venlafaxine to directly obtain O-desmethylvenlafaxine.

SUMMARY OF THE INVENTION

[0009] In one embodiment, the invention encompasses (4-bromophenyl)(1-hydroxycyclohexyl)acetonitrile (CBBC).

[00010] In one embodiment the present invention provides a process for preparing CBBC comprising reacting BBC with cyclohexanone.

[00011] In another embodiment, the present invention provides a process for preparing (4-bromophenyl)(1-hydroxycyclohexyl)acetonitrile (CBBC) comprising precipitating CBBC from a mixture of: bromophenylacetonitrile (BBC), a dry organic solvent, a base and cyclohexanone.

[00012] In another embodiment, the present invention provides a process for obtaining (4-bromophenyl)(1-hydroxycyclohexyl)acetonitrile (CBBC) from a mixture of bromophenylacetonitrile (BBC), a phase transfer catalyst, a base and cyclohexanone.

[00013] In another embodiment, the present invention provides a process for obtaining O-desmethylvenlafaxine comprising preparing CBBC in any of the methods described above, and further converting the CBBC to O-desmethylvenlafaxine.

[00014] In another embodiment, the invention encompasses 1-[2-amino-1-(4-bromophenyl)ethyl]cyclohexanol (BDDMV).

[00015] In another embodiment, the present invention provides a process for preparing 1-[2-amino-1-(4-bromophenyl)ethyl]cyclohexanol (BDDMV) comprising: combining CBBC, an organic solvent and borane to create a reaction mixture, followed by recovery of the BDDMV from the reaction mixture.

[00016] In another embodiment, the present invention provides a process for obtaining O-desmethylvenlafaxine comprising preparing BDDMV as described above, and further converting the BDDMV to O-desmethylvenlafaxine.

[00017] In another embodiment, the invention encompasses 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV).

[00018] In another embodiment, the present invention provides a process for preparing 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV) comprising: combining BDDMV, formaldehyde and a reducing agent to create a reaction mixture, followed by recovery of the BODV from the reaction mixture.

[00019] In another embodiment, the present invention provides a process for preparing 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV) comprising: combining BDDMV, an organic solvent, and a methylating agent to form a mixture, and recovering the BODV from the mixture.

[00020] In another embodiment, the present invention provides a process for obtaining O-desmethylvenlafaxine comprising preparing BODV in any of the methods described above, and further converting the BODV to O-desmethylvenlafaxine.

[00021] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: combining BODV, a hydroxide donor base and a metal salt to create a reaction mixture, followed by recovery of the O-desmethylvenlafaxine from the reaction mixture.

[00022] In another embodiment, the present invention provides a process for converting BODV to O-desmethylvenlafaxine, using a Grignard reaction or organocuprate reaction.

[00023] In one embodiment the present invention provides a process for preparing O-desmethylvenlafaxine comprising combining BODV with Mg or Cu, and an organic solvent to obtain a grignard reagent or an organocuprate reagent, and combining the reagent with borate and an acid to provide O-desmethylvenlafaxine.

[00024] In another embodiment, the invention encompasses hydroxyprotected-1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV-P).

[00025] In another embodiment, the present invention provides a process for preparing hydroxyprotected-1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV-P) comprising: combining BODV an

organic solvent, a base and a protecting agent to create a reaction mixture, and recovering the BODV-P from the reaction mixture.

[00026] In another embodiment, the present invention provides a process for obtaining O-desmethylvenlafaxine comprising preparing BODV-P as described above, and further converting the BODV-P to O-desmethylvenlafaxine.

[00027] In another embodiment, the present invention provides a process for converting BODV-P to O-desmethylvenlafaxine, using a Grignard reaction or organocuprate reaction.

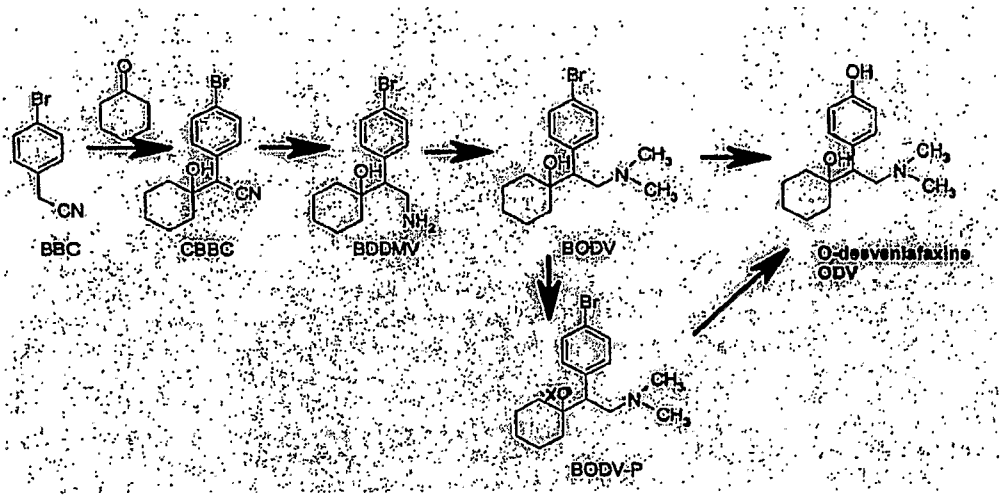
[00028] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: combining BODV-P, hydroxide donor base and a metal salt to create a reaction mixture, followed by recovery of the O-desmethylvenlafaxine from the reaction mixture.

[00029] The present invention further provides processes for preparing O-desmethylvenlafaxine via the intermediates described above.

DETAILED DESCRIPTION OF THE INVENTION

[00030] The invention encompasses a new synthetic route for obtaining O-desmethylvenlafaxine, from 4-bromophenylacetonitrile (BBC), (4-bromophenyl)(1-hydroxycyclohexyl)acetonitrile (CBBC), 1-[2-amino-1-(4-bromophenyl)ethyl]cyclohexanol (BDDMV), 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV) and hydroxyprotected-1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV-P).

[00031] In the process of the invention, the intermediate bromophenylacetonitrile (BBC) is condensed with cyclohexanone to form the intermediate (4-bromophenyl)(1-hydroxycyclohexyl)acetonitrile (CBBC). Further, the cyano group on the CBBC is subjected to reduction, to form the intermediate 1-[2-amino-1-(4-bromophenyl)ethyl]cyclohexanol (BDDMV) which is then subjected to selective alkylation to produce 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV), which is finally converted to O-desmethylvenlafaxine (ODV), by performing halide exchange (optionally, the final conversion step can go via a protected BODV intermediate) as described in the following scheme:



where x is a suitable hydroxy protecting group.

[00032] The use of precursors of venlafaxine which contain a halogen group, in the new synthetic route for obtaining O-desmethylvenlafaxine, highly improves the yield of the reaction.

[00033] In one embodiment, the invention encompasses (4-bromophenyl)(1-hydroxycyclohexyl)acetonitrile (CBBC). Also provided is CBBC in isolated or purified form. Isolated refers to being separated from the reaction mixture in which it forms. The CBBC may have a purity of at least about 50% as measured by HPLC. The compound is characterized by NMR ^{1}H (DMSO-d_6) δ: 1.56 (4H, H cycloheyl), 1.71 (2H, H cyclohexyl), 2.25 (2H, H cyclohexyl), 2.61 (2H, H cyclohexyl), 3.32 (1H, CHCN), 7.27 (2H, H arom.), 7.65 (2H, H arom.).

[00034] The present invention also provides a process for preparing (4-bromophenyl)(1-hydroxycyclohexyl)acetonitrile (CBBC) by reacting BBC with cyclohexanone

[00035] This process can comprise precipitating CBBC from a mixture of: bromophenylacetonitrile (BBC), organic solvent, a base and cyclohexanone. Preferably the organic solvent is dry. An organic solvent is dry if it is essentially free of water such that the amount of residual water, if detectable, does not interfere with the reaction (e.g. by destroying catalysts or reagents) in a manner that prevents the benefits of the present invention from being realized. Typically an organic solvent having less than 1% by water is considered to be dry by one of ordinary skill of art.

[00036] Preferably, the dry organic solvent is selected from the group consisting of: C_{4-8} ethers, polar aprotic solvents (Polarity Index of greater than about 2.0), C_1-C_8 chlorinated aliphatic, C_6-C_{12} aromatic hydrocarbons, and C_{1-6} alcohols.

More preferably, the ethers are selected from the group consisting of: diisopropyl ether, diethyl ether, dioxane, tetrahydrofuran (THF), the polar aprotic solvents are selected from the group consisting of dimethylformamide (DMF), dimethylacetamide (DMA) and dimethylsulfoxide (DMSO), the chlorinated organic solvents are selected from the group consisting of methylene chloride and chlorobenzene or chloroform and the aromatic hydrocarbons are selected from the group consisting of toluene and benzene. Most preferably, the dry organic solvent is selected from the group consisting of: tetrahydrofuran (THF), methanol, methylene chloride and toluene. The organic solvent can be used individually, or in a mixture with another solvent, particularly methanol.

[00037] The base can be an inorganic base, such as an alkali metal or alkaline earth metal. More preferably, the base is selected from the group consisting of: lithium diisopropyl amide (LDA), lithium bis (trimethyl silyl) amide ($LiN[(CH_3)_3Si]_2$), potassium hydroxide (KOH), lithium hydroxide (LiOH), sodium hydride (NaH), potassium tert butoxide (t-BuOK), lithium tert butoxide (t-BuOLi), butyl lithium (BuLi) and sodium methoxide ($NaOCH_3$). The base is preferably present in an amount of about 1 to about 5 moles per mole of BBC.

[00038] The process can be carried out by combining a solution or a slurry of BBC and a dry organic solvent with a base to obtain a reaction mixture, followed by combining the reaction mixture with cyclohexanone, to obtain CBBC. Cyclohexanone can be added to the reaction mixture in a dropwise manner. After combining the reaction mixture with cyclohexanone, the mixture is further maintained, until completion of the reaction.

[00039] CBBC may then be recovered. The solvent can be evaporated and the residue dissolved in a water immiscible solvent such as toluene, EtOAc (ethyl acetate), CH_2Cl_2, diethyl ether, MTBE (methyl-t-butyl ether), MEK (methyl ethyl ketone) washed with water or brine, and evaporated to get an oil. The oil can then be added to an organic solvent such as methanol to obtain a solution and crystallize CBBC.

[00040] In another embodiment, the present invention provides a process for obtaining (4-bromophenyl)(1-hydroxycyclohexyl)acetonitrile (CBBC) from a mixture of bromophenylacetonitrile (BBC), optionally a phase transfer catalyst, a base and cyclohexanone. The reaction may occur with or without the presence of an organic solvent or water. Preferably, the reaction occurs in the presence of water. The use of

water allows for obtaining a product that otherwise would be contaminated with residual organic solvent.

[00041] The phase transfer catalyst can be a tetraalkylammonium, tetraalkylphosphonium, tetraarylammonium or tetraarylphosphonium, preferably wherein the alkyl group can be the same or different and contains from 1 to 10 carbons, and wherein the aryl group can be the same or different and contains from 6 to 8 carbons.

[00042] The phase transfer catalyst can be a tetraalkylammonium halide, preferably wherein the alkyl group can be the same or different and contains from 1 to 6, preferably from 1 to 4 carbon atoms, and the halide is fluoride, chloride, bromide or iodide, preferably chloride, bromide or iodide.

[00043] Preferably, the phase transfer catalyst is selected from the group consisting of: tetrabutylammonium hydrogensulphate, tetrabutylammonium bromide, tetrabutylammonium chloride, tetrabutylammonium iodide, benzyltriethyl ammonium chloride, aliquot, quaternary ammonium salt, quaternary phosphonium salt and crown ether. More preferably, the phase transfer catalyst is tetra butyl ammonium bromide (TBAB).

[00044] The base may be an inorganic base, such as an alkali metal or alkaline earth metal hydroxide or carbonate, preferably, NaOH, KOH, LiOH, CsOH, K_2CO_3 or $NaCO_3$, Cs_2CO_3, $KHCO_3$ or $NaHCO_3$

[00045] BBC, cyclohexanone, the phase transfer catalyst such as TBAB and the base such as NaOH are combined. Preferably, the base is added in an amount of about 0.5 to about 1 mole per mole of BBC. The cyclohexanone is dded in an amount of about 1 to about 1.15 moles per mole of BBC. The reaction is then maintained to get CBBC. The reaction can be maintained from about 1 to about 24 hours. It can also be stirred while maintained.

[00046] In another embodiment, the present invention provides a process for obtaining O-desmethylvenlafaxine comprising preparing CBBC in any of the methods described above, and further converting the CBBC to O-desmethylvenlafaxine.

[00047] In another embodiment, the invention encompasses 1-[2-amino-1-(4-bromophenyl)ethyl]cyclohexanol (BDDMV). Also provided is BDDMV in isolated or purified form. Isolated refers to being separated from the reaction mixture in which it forms. The BDDMV may have a purity of at least about 50% as measured by HPLC.

[00048] BDDMV can be prepared by reacting CBBC with a reducing agent. More specifically, BDDMV can be prepared by combining CBBC an organic solvent such as THF to obtain a solution, to which a reducing agent is added. Preferably the solvent is a dry organic solvent, as described above, more preferably THF. Chlorinated solvents, such as C_1-C_8 chlorinated hydrocarbons and C_4-C_8 ethers can also be used. Preferably the reducing agent is borane or a hydride, more preferably a Borane dimethylsulfide complex, which is added dropwise. Preferably, the borane is present in an amount of about 1 to about 3 moles per mole of CBBC. Alternatively, the reducing agent may be H_2 in presence of catalyst such as Ni or Co or Pt. The resulting reaction mixture can then be maintained, preferably for about 1hr to about 48 hrs, such as about 12 hours. This mixture can then be quenched such as by adding NH_4Cl and hydrogen peroxide.

[00049] The BDDMV can then be recovered. The resulting layers may be separated and the organic layer acidified, such as with citric acid. Optionally, the aqueous phase can be basified such as with NH_4OH and extracted with diethylether to recover more of the product. The organic layer can then be washed with brine or water to remove water soluble impurities, and dried. Drying can be carried out over Na_2SO_4 or under a pressure of less than one atmosphere, or both.

[00050] In another embodiment, the present invention provides a process for obtaining O-desmethylvenlafaxine comprising preparing BDDMV as described above, and further converting the BDDMV to O-desmethylvenlafaxine.

[00051] In another embodiment, the invention encompasses 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV). Also provided is BODV in isolated or purified form. Isolated refers to being separated from the reaction mixture in which it forms. The BODV may have a purity of at least about 50% as measured by HPLC.

[00052] The present invention also provides a process for preparing 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV). BODV may be prepared by reductive amination reaction of BDDMV and a formaldehyde source in the presence of a reducing agent. In one embodiment this process comprises combining BDDMV, formaldehyde and a reducing agent. BODV is then recovered from the obtained reaction mixture.

[00053] BDDMV, such as that prepared above, can be dissolved or suspended (preferably dissolved) in a C_{1-4} alcohol such as MeOH. Formaldehyde,

preferably in the form of a formalin solution is then added to obtain a solution. Formaldehyde in water can also be used as a solvent. A reducing agent, preferably $NaBH_4$ or formic acid is then added. The reaction is an exothermic reaction, so prior to combining the sodium borohydride with the formaldehyde solution, formaldehyde solution is preferably cooled to a temperature of less than about 10°C. Preferably, the reaction mixture is maintained, while stirring, for about 1 to about 24 hours, such as about 12 hours. Preferably, the formaldehyde is present in an amount of from about 1 mole per mole of BDDMV, to an excess amount, such as about 50 moles. Preferably, the sodium borohydride is present in an amount of about 1 mole per mole of BDDMV.

[00054] The BODV can then be recovered. Recovery can be carried out by evaporating the organic solvent, such as under reduced pressure, to obtain a residue. The residue can then be dissolved in a water immiscible organic solvent such as methylene chloride EtOAc, toluene, MEK, TBME, diethyl ether and acidified to a pH of about 2 to about 6. An inorganic acid such as HCl or H2SO4 can be used. Optionally the aqueous phase is basified to a pH of about 8 to about 10 to facilitate extraction of additional amounts of BODC. NH_4OH can be used as a base and methylene chloride as a solvent for extraction. The organic phase can then be evaporated, such as under a pressure of less than about one atmosphere, to obtain BODV.

[00055] BODV can also be prepared by a process which comprises combining BDDMV, an organic solvent, and a methylating agent. BODV is then recovered from the obtained reaction mixture.

[00056] BDDMV, such as that prepared above, is dissolved in an organic solvent, preferably dichloromethane or dimethylsulfoxide. Optionally a base is added to the solution. The base can be BuLi or a C_3-C_9 trialkylamine such as triethylamine. Alkali metal or alkaline earth metal hydrides or hydroxides such as NaH and NaOH can also be used. If an inorganic base is used, an inert organic solvent may also be added. For example, with BuLi can be added as a solution in a C_5-C_{12} saturated (aliphatic) or aromatic hydrocarbon, such as hexane. A methylating agent is added. Preferably the methylating agent is a methyl halide, preferably methyl iodide. Dimethylsulfate can also be used. The reaction can be done as neat reaction, methyliodide being the solvent and the reagent. Preferably, the organic solvent is dichloromethane or dimethylsulfoxide or THF. The mixture can then be maintained

for about 30 minutes to about 16 hours to obtain BODV. The BODV can then be recovered.

[00057] In another embodiment, the present invention provides a process for obtaining O-desmethylvenlafaxine comprising preparing BODV in any of the methods described above, and further converting the BODV to O-desmethylvenlafaxine.

[00058] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: combining BODV, a hydroxide donor base and a metal salt to create a reaction mixture, followed by recovery of the O-desmethylvenlafaxine from the reaction mixture.

[00059] Preferably, the hydroxide donor base is an alkali metal or alkaline earth metal hydroxide, such as potassium hydroxide (KOH), lithium hydroxide (LiOH), sodium hydroxide (NaOH), cesium hydroxide. Preferably, the metal salt is silver nitrate ($AgNO_3$). Optionally, the $AgNO_3$ is employed into the reaction mixture, as a supported $AgNO_3$. The term "supported $AgNO_3$" as used herein refers to Montmorillonite. Silica can also be used as support. Montmorillonite is a very soft phyllosilicate mineral that typically forms in microscopic crystals, forming a clay. Preferably, the hydroxide donor base is present in an amount of about 1 to about 20 moles per mole of BODV. Preferably, the metal salt is present in an amount of about 1 to about 20 by weight of BODV.

[00060] As exemplified, to a solution of $AgNO_3$ in water montmorillonite is added and the resulting mixture is heated. Heating is preferably carried out to a temperature of about 40 to about 150°C, such as about 100°C for 1 hour. The solution can then be dried, such as by heating, or reducing the pressure to less than about one atmosphere. Then, BODV, and a base such as NaOH and the supported $AgNO_3$ are combined. Preferably, the reaction mixture is heated to a temperature of above 20°C; more preferably, the reaction mixture is heated to about 100°C. Preferably, the obtained reaction mixture is maintained, while stirring, for about 18 hours. _ODV can then be extracted from the reaction mixture with an organic solvent, such as with a mixture of chloroform and methanol. Other solvents such as EtOAc, THF, or acetone can also be used.

[00061] The present invention further provides a process for converting BODV to O-desmethylvenlafaxine, using a Grignard reaction or a organocuprate reaction. In one embodiment, BODV is combined with Mg, a halogen (only Mg or

Cu in case of organo cuprate reaction) and a dry organic solvent to provide a Grignard reagent. Such synthetic step is known by one skilled in the art as Grignard reaction. The Grignard reagent is then combined with borate and an acid to provide O-desmethylvenlafaxine.

[00062] In one embodiment, Mg and a halogen such as I_2 are combined with BODV in an inert solvents organic solvent such as THF, CH_2Cl_2, ACN, ethers. The BODV can be added dropwise. The mixture can then be heated, such as to a temperature of about 30 to about reflux, more preferably about reflux. Before adding borate, the mixture is preferably cooled, such as to about -20C to about 10C, preferably about -10C. Trimethylborate is then added. After stirring an organic or inorganic acid, such as glacial acetic acid is added. The reaction mixture can then be quenched, such as by adding hydrogen peroxide. For recovery, a water immiscible solvents organic solvent, such as Diethylether, EtOAc, TBME, toluene, MEK, is added to the reaction mixture to obtain ODV. The solvent can then be rmoved such as by reducing the pressure to less than one atmosphere.

[00063] Optionally, the new synthetic route for obtaining O-desmethylvenlafaxine can go via a protected intermediate of BODV.

[00064] The protected intermediate of BODV may contain any suitable hydroxyl protecting group, such as silyl, acetyl and dihydropyran (DHP).

[00065] In another embodiment, the invention encompasses hydroxyprotected-1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV-P). Preferably, the BODV is protected with an acetyl. Also provided is BODV-P, particularly acetyl protected, in isolated or purified form. Isolated refers to being separated from the reaction mixture in which it forms. The BODV-P including acetyl protected may have a purity of at least about 50% as measured by HPLC.

[00066] In another embodiment, the present invention provides a process for preparing hydroxyprotected-1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV-P) comprising: combining BODV an organic solvent, a base and a protecting agent to create a reaction mixture, and recovering the BODV-P from the reaction mixture.

[00067] Typically, the solvent used can be any organic solvent. Preferably, the organic solvent is ethyl acetate. Other organic solvents such as CH_2Cl_2, ethers such THF, toluene, hexane or ACN can also be used.

[00068] Preferably, the process is performed under basic conditions. Typically, the basic source is organic or inorganic base. Preferably, the basic source is a C_3-C_9 trialkyl amine such as triethylamine or imidazole or lutidine or pyridine. An inorganic base such as an alkali metal or alkaline earth metal carbonate such as K_2CO_3 can also be used,

[00069] Preferably, the protecting agent is selected from the group consisting of: silyl, acetyl, DHP and derivatives thereof. More preferably, the protecting agent is acetyl chloride or acetic anhydride. The reaction mixture is optionally maintained for about 30 minutes to about 24 hours to obtain BODV-P. BODV-P may then be recovered from the reaction mixture by any method known in the art.

[00070] One of ordinary skill of art would appreciate that each of the above processes described for preparation of CBBC, BDDMV, BODV, BODV-P and ODV can be combined. Such combination can be combining the process of of CBBC, with BDDMV to prepare BODV, and further to prepare BODV-P if desired, and further to prepare ODV. Such process can also start with BDDMV, BODV or BODV-P. Such combinations are provided in further detail below.

[00071] In another embodiment, the present invention provides a process for obtaining O-desmethylvenlafaxine comprising preparing BODV-P as described above, and further converting the BODV-P to O-desmethylvenlafaxine.

[00072] In another embodiment, the present invention provides a process for converting BODV-P to O-desmethylvenlafaxine, using a Grignard reaction.

[00073] The conversion can be performed as described above for BODV.

[00074] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: combining BODV-P, a hydroxide donor base and a metal salt. O-desmethylvenlafaxine is then be recovered from the reaction mixture.

[00075] The hydroxide donor base and a metal salt used in the reaction are as described above.

[00076] One of ordinary skill of art would appreciate that each of the above processes described for preparation of CBBC, BDDMV, BODV, BODV-P and ODV can be combined. Such combination can be combining the process of of CBBC, with BDDMV to prepare BODV, and further to prepare BODV-P if desired, and further to prepare ODV. Such process can also start with BDDMV, BODV or BODV-P. Such combinations are provided in further detail below.

[00077] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: precipitating CBBC from a mixture of: BBC, a dry organic solvent, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, formaldehyde and a reducing agent to create a reaction mixture, recovering BODV from the reaction mixture; combining BODV, a hydroxide donor base and a metal salt to create a reaction mixture and recovering O-desmethylvenlafaxine from the reaction mixture.

[00078] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: precipitating CBBC from a mixture of: BBC, a dry organic solvent, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, formaldehyde and a reducing agent to create a reaction mixture, recovering BODV from the reaction mixture; combining BODV an organic solvent, a base and a protecting agent to create a reaction mixture; recovering BODV-P from the reaction mixture; combining BODV-P, a hydroxide donor base and a metal salt to create a reaction mixture and recovering O-desmethylvenlafaxine from the reaction mixture.

[00079] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: precipitating CBBC from a mixture of: BBC, a dry organic solvent, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, formaldehyde and a reducing agent to create a reaction mixture, recovering BODV from the reaction mixture and converting BODV to O-desmethylvenlafaxine, using a Grignard reaction or organocuprate reaction.

[00080] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: precipitating CBBC from a mixture of: BBC, a dry organic solvent, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, formaldehyde and a reducing agent to create a reaction mixture, recovering BODV from the reaction mixture; combining BODV an organic solvent, a base and a protecting agent to create a reaction mixture; recovering BODV-P from the reaction mixture and converting BODV-P to O-desmethylvenlafaxine, using a Grignard reaction or organocuprate reaction.

[00081] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: precipitating CBBC from a mixture of: BBC, a dry organic solvent, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, an organic solvent, and a methylating agent to form a mixture; recovering the BODV from the mixture; combining BODV, a hydroxide donor base and a metal salt to create a reaction mixture and recovering O-desmethylvenlafaxine from the reaction mixture.

[00082] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: precipitating CBBC from a mixture of: BBC, a dry organic solvent, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, an organic solvent, and a methylating agent to form a mixture; recovering the BODV from the mixture; combining BODV an organic solvent, a base and a protecting agent to create a reaction mixture; recovering BODV-P from the reaction mixture; combining BODV-P, a hydroxide donor base and a metal salt to create a reaction mixture and recovering O-desmethylvenlafaxine from the reaction mixture.

[00083] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: precipitating CBBC from a mixture of: BBC, a dry organic solvent, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, an organic solvent, and a methylating agent to form a mixture; recovering the BODV from the mixture and converting BODV to O-desmethylvenlafaxine, using a Grignard reaction.

[00084] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: precipitating CBBC from a mixture of: BBC, a dry organic solvent, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, an organic solvent, and a methylating agent to form a mixture; recovering the BODV from the mixture; combining BODV an organic solvent, a base and a protecting agent to create a reaction mixture; recovering BODV-P from the reaction mixture and converting BODV-P to O-desmethylvenlafaxine, using a Grignard reaction.

[00085] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: obtaining CBBC from a mixture of BBC, a phase transfer catalyst, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, formaldehyde and a reducing agent to create a reaction mixture, recovering BODV from the reaction mixture; combining BODV, a hydroxide donor base and a metal salt to create a reaction mixture and recovering O-desmethylvenlafaxine from the reaction mixture.

[00086] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: obtaining CBBC from a mixture of BBC, a phase transfer catalyst, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, formaldehyde and a reducing agent to create a reaction mixture, recovering BODV from the reaction mixture; combining BODV an organic solvent, a base and a protecting agent to create a reaction mixture; recovering BODV-P from the reaction mixture; combining BODV-P, a hydroxide donor base and a metal salt to create a reaction mixture and recovering O-desmethylvenlafaxine from the reaction mixture.

[00087] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: obtaining CBBC from a mixture of BBC, a phase transfer catalyst, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, formaldehyde and a reducing agent to create a reaction mixture, recovering BODV from the reaction mixture and converting BODV to O-desmethylvenlafaxine, using a Grignard reaction or organocuprate reaction.

[00088] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: obtaining CBBC from a mixture of BBC, a phase transfer catalyst, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, formaldehyde and a reducing agent to create a reaction mixture, recovering BODV from the reaction mixture; combining BODV an organic solvent, a base and a protecting agent to create a reaction mixture; recovering BODV-P from the reaction mixture and converting BODV-P to O-desmethylvenlafaxine, using a Grignard reaction or organocuprate reaction..

[00089] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: obtaining CBBC from a mixture of BBC, a phase transfer catalyst, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, an organic solvent, and a methylating agent to form a mixture; recovering the BODV from the mixture; combining BODV, a hydroxide donor base and a metal salt to create a reaction mixture and recovering O-desmethylvenlafaxine from the reaction mixture.

[00090] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: obtaining CBBC from a mixture of BBC, a phase transfer catalyst, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, an organic solvent, and a methylating agent to form a mixture; recovering the BODV from the mixture; combining BODV an organic solvent, a base and a protecting agent to create a reaction mixture; recovering BODV-P from the reaction mixture; combining BODV-P, a hydroxide donor base and a metal salt to create a reaction mixture and recovering O-desmethylvenlafaxine from the reaction mixture.

[00091] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: obtaining CBBC from a mixture of BBC, a phase transfer catalyst, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, an organic solvent, and a methylating agent to form a mixture; recovering the BODV from the mixture and converting BODV to O-desmethylvenlafaxine, using a Grignard reaction or organocuprate reaction..

[00092] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: obtaining CBBC from a mixture of BBC, a phase transfer catalyst, a base and cyclohexanone; combining CBBC, an organic solvent and borane to create a reaction mixture, recovering BDDMV from the reaction mixture; combining BDDMV, an organic solvent, and a methylating agent to form a mixture; recovering the BODV from the mixture; combining BODV an organic solvent, a base and a protecting agent to create a reaction mixture; recovering BODV-P from the reaction mixture and converting BODV-P to O-desmethylvenlafaxine, using a Grignard reaction or organocuprate reaction..

[00093] The invention in certain of its embodiments is illustrated by the following non-limiting examples.

EXAMPLES

Preparation of CBBC

Example 1

A 250 ml three necked flask equipped with nitrogen inlet, thermometer and mechanical stirrer was charged slowly with MeOH (50 ml) and $NaOCH_3$(10 g, 185 mmol) at ambient temperature. DMF (4 ml) and Bromophenylacetonitrile (20 g, 102 mmol) were added. The reaction mixture was stirred at ambient temperature until complete dissolution. Cyclohexanone (20 g, 203 mmol) was then added dropwise and the reaction was stirred at ambient temperature overnight. The solvent was evaporated and the residue was dissolved in toluene, washed with brine and evaporated to get an oil which on crystallization from MeOH yielded CBBC.

Example 2

A 100 ml three necked flask equipped with, thermometer and mechanical stirrer is charged with BBC (2g, 10 mmol), cyclohexanone (2 g, 20.3 mmol), TBAB (0.2g) and NaOH (6ml 10%). The reaction is stirred at RT overnight to get CBBC.

Preparation of BDDMV

Example 3

A 250ml three necked flask equipped with nitrogen inlet, thermometer and mechanical stirrer was charged with CBBC (7 g, 23.79 mmol) and THF (100 ml). This solution was stirred at ambient temperature. Then a solution of Borane dimethylsulfide complex (20 ml 2M in THF, 39.89mmol) was added dropwise. This mixture was stirred overnight at ambient temperature and poured into saturated solution of NH_4Cl. A 30% solution of hydrogen peroxide was then added. The layers were separated and the organic layer was acidified with citric acid.

The aqueous phase was basified with NH_4OH and extracted with diethylether. The organic layer was then washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to get BDDMV.

Preparation of BODV

Example 4

BDDMV (0.81 g, 2.72 mmol) was dissolved in MeOH (20ml). A formalin solution (1.3 ml, 16.25 mmol) was added and the solution was cooled with an ice bath. To the cold solution $NaBH_4$ (0.25 g, 6.5mmol) was added. The reaction mixture was stirred at ambient temperature overnight and the solvent was then evaporated under reduced pressure. The residue was dissolved in methylene chloride and acidified with 10% HCl. The aqueous phase was basified with NH_4OH and extracted with methylene chloride. The organic phase was then evaporated under reduced pressure to get BODV.

Example 5

BDDMV (0.2g, 0.68 mmol) is dissolved in DMSO (2.5 ml). The solution is cooled into an ice bath causing its solidification. 1.6 M BuLi solution in hexane (0.4 mmol) is added, and the temperature is allowed to heat to room temperature. Then MeI (0.25 mmol) is added. The reaction mixture is stirred until we get BODV (HPLC monitoring).

Example 6

BDDMV (0.5 g, 1.67 mmol) is suspended in CH_2Cl_2. Methyl Iodide (2.65 mmol) and Triethylamine (2.9 mmol) are added. The reaction mixture is stirred under nitrogen atmosphere at room temperature for 6 hours. At this stage MeI (5 mmol) and NEt_3 (3 ml) are added. The addition caused the temperature to rise. After 16 hours, the analysis shows the presence of BODV.

Preparation of ODV from BODV

Example 7

Preparation of supported $AgNO_3$:

To a solution of $AgNO_3$ (3.38g in 100 ml H_2O), montmorillonite K10 (15 g) was added and the mixture was stirred for 30 min. at ambient temperature. The solution was then evaporated to dryness and the residue was dried in an oven at 100°C for 1 hour.

0.4 g of BODV (1.26 mmol), 0.2g of NaOH (5 mmol) and 2 g of supported $AgNO_3$ were mixed thoroughly in a mortar. The mixture was heated to 100°C overnight under mechanical stirring. The mixture was then extracted with chloroform and with methanol to get ODV.

Example 8

A 100ml three-necked flask equipped with nitrogen inlet, thermometer, mechanical stirrer and condenser was charged with Mg (0.2 g, 8.23 mmol) and I_2 (0.1 g 0.39 mmol). BODV (0.3 g, 0.92 mmol) in THF (30 ml) was added dropwise and the mixture was heated to reflux for 1 hour. The mixture was cooled to -10°C and trimethylborate (1 ml, 8.8 mmol) was added. After stirring for 30 min glacial acetic acid (2ml, 34.9 mmol) was added. Then a cold solution of 30% hydrogen peroxide (2ml 19.64mmol) was also added. Diethylether was added and the organic phase was filtered to get ODV.

Preparation of BODV-P

Example 9

A 100ml three-necked flask equipped with Nitrogen inlet, thermometer, mechanical stirred and condenser was charged with BODV (0.37g 1.13mmol), EtOAc (20ml) and Et_3N (1ml 7.16mmol). Acetylchloride (1ml 14mmol) was added slowly. The reaction mixture was stirred 1 hour at ambient temperature and the organic phase was washed with water, dried over magnesium sulfate and evaporated to get BODV-P.

Preparation of ODV from BODV-P

Example 10

A 250ml three-necked flask equipped with Nitrogen inlet, thermometer, mechanical stirred and condenser was charged with Mg (0.7g, 28.80 mmol) and I_2 (0.2 g 0.78 mmol). BODV-P (1g, 2.71 mmol) in THF (30ml) was added dropwise and the mixture was heated to reflux for 2hours. The mixture was then cooled to -10°C and trimethylborate (20ml, 176 mmol) was added. After stirring for 30 min at this temperature glacial acetic acid (15 ml, 261.75 mmol) was added. Then a cold solution of 30%hydrogen peroxide (20 ml 196.4 mmol) was added. The organic phase was washed with saturated ferrous ammonium sulfate, dried over magnesium sulfate and concentrated to get ODV.

Example 11

Preparation of supported $AgNO_3$:

To a solution of $AgNO_3$ (3.38g in 100 ml H_2O), montmorillonite K10 (15 g) is added and the mixture is stirred for 30 min. at ambient temperature. The solution is then evaporated to dryness and the residue is dried in an oven at 100°C for 1 hour.

0.4 g of P-BODV, 0.2g of NaOH (5 mmol) and 2 g of supported $AgNO_3$ are mixed thoroughly in a mortar. The mixture is heated to 100°C overnight under mechanical stirring. The mixture is then extracted with chloroform and with methanol to get ODV.

What is claimed is:

1. (4-bromophenyl)(1-hydroxycyclohexyl)acetonitrile (CBBC).
2. The compound of claim 1, wherein the compound is in isolated or purified form.
3. The compound of any one of claims 1 or 2, wherein the compound has a purity of at least about 50% as measured by HPLC.
4. A process for preparing compound of claim 1, 2 or 3 comprising reacting BBC with cyclohexanone.
5. The process of claim 4, wherein the process comprises combining bromophenylacetonitrile (BBC), an organic solvent, a base and cyclohexanone to precipitating CBBC.
6. The process of claim 5, wherein the organic solvent is selected from the group consisting of: C_{2-8} ethers, polar aprotic solvents (Polarity Index of greater than about 2.0), C_1-C_8 chlorinated aliphatic and aromatic, C_6-C_{12} aromatic hydrocarbons, and C_{1-6} alcohols.
7. The process of claim 5, wherein the organic solvent is selected from the group consisting of diisopropyl ether, diethyl ether, dioxane, tetrahydrofuran (THF), dimethylformamide (DMF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), methylene chloride, chlorobenzene, toluene and benzene.
8. The process of claim 5, wherein the organic solvent is selected from the group consisting of tetrahydrofuran (THF), methanol, methylene chloride and toluene.
9. The process of any one of claims 5-8, wherein the organic solvent contains less than 1% water by volume.
10. The process of any one of claims 5-9, wherein the base is an alkali metal or alkaline earth metal.
11. The process of any one of claims 5-10, wherein the base is selected from the group consisting of: lithium diisopropyl amide (LDA), lithium bis (trimethyl silyl) amide ($LiN[(CH_3)_3Si]_2$), potassium hydroxide (KOH), lithium hydroxide (LiOH), sodium hydride (NaH), potassium tert butoxide (t-BuOK), lithium tert butoxide (t-BuOLi), butyl lithium (BuLi) and sodium methoxide ($NaOCH_3$).
12. The process of any one of claims 5-11, wherein the process is carried out by combining a solution or a slurry of BBC and a dry organic solvent with a base

to obtain a reaction mixture, followed by combining the reaction mixture with cyclohexanone, to obtain CBBC.

13. The process of any one of claims 5-12, further comprising recovering CBBC.
14. The process of any one of claims 13, wherein recovery comprises evaporating the solvent, dissolving the residue in a water immiscible solvent such as toluene, washing with water or brine, and evaporated to get a residue.
15. The process of any one of claims 13-14, further comprising crystallizing CBBC from the residue.
16. The process of any one of claims 4-15, wherein the process comprises combining bromophenylacetonitrile (BBC), a phase transfer catalyst, optionally a base and cyclohexanone.
17. The process of claim 16, wherein the reaction occurs in the presence of water.
18. The process of any one of claims 16-17, wherein the phase transfer catalyst is a tetraalkylammonium, tetraalkylphosphonium, tetraarylammonium or tetraarylphosphonium, wherein the alkyl group can be the same or different and contains from 1 to 10 carbons, and wherein the aryl group can be the same or different and contains from 6 to 8 carbons
19. The process of any one of claims 16-17, wherein the phase transfer catalyst is selected from the group consisting of: tetrabutylammonium hydrogensulphate, tetrabutylammonium bromide, tetrabutylammonium chloride, tetrabutylammonium iodide, benzyltriethyl ammonium chloride, aliquot, quaternary ammonium salt, quaternary phosphonium salt and crown ether.
20. The process of any one of claims 16-18, wherein the phase transfer catalyst is tetra butyl ammonium bromide (TBAB).
21. The process of any one of claims 5-20, wherein the base is an alkali metal or alkaline earth metal hydroxide or carbonate.
22. The process of any one of claims 16-21, wherein the base is NaOH, KOH, LiOH, CsOH, K_2CO_3, $NaCO_3$ or Cs_2CO_3
23. A process for preparing O-desmethylvenlafaxine comprising preparing CBBC as described in any one of claims 4-22, and further converting the CBBC to O-desmethylvenlafaxine.
24. 1-[2-amino-1-(4-bromophenyl)ethyl]cyclohexanol (BDDMV).
25. The compound of claim 24, wherein the compound is in isolated or purified form.

26. The compound of any one of claims 24-25, wherein the compound has a purity of at least about 50% as measured by HPLC.
27. A process for preparing a compound according to any of claims 24 to 26 comprising reacting CBBC with a reducing agent.
28. The process of claim 27, comprising combining CBBC and an organic solvent to obtain a solution, and adding a reducing agent to the solution.
29. The process of claim 28, wherein the solvent is a dry organic solvent.
30. The process of any one of claims 28-29, wherein the reducing agent is Borane or hydride.
31. The process of claim 30, wherein the reducing agent is Borane dimethylsulfide.
32. The process of any one of claims 28-29, wherein the reducing agent is H_2 in presence of catalyst such as Ni, Co or Pt.
33. The process of any one of claims 27-32, wherein the solvent is tetrahydrofuran (THF).
34. The process of claim 31, wherein the borane is present in an amount of about 1 to about 3 moles per mole of CBBC.
35. The process of any one of claims 27-34, further comprising quenching, acidifying resulting organic layer, and extracting CBBC from the organic layer.
36. The process of any one of claims 27-35, further comprising drying the organic layer over Na_2SO_4 or under a pressure of less than one atmosphere, or both.
37. A process for preparing O-desmethylvenlafaxine, comprising preparing BDDMV as described in any one of claims 27-36, and further converting the BDDMV to O-desmethylvenlafaxine.
38. 1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV).
39. The compound of claim 38, wherein BODV is in isolated or purified form.
40. The compound of any one of claims 38-39, wherein BODV has a purity of at least about 50% as measured by HPLC.
41. A process for preparing the compound of any one of claims 38-40 comprising combining BDDMV, formaldehyde and a reducing agent.
42. The process of claim 41, wherein BDDMV is dissolved or suspended in an organic solvent, preferably a C_{1-4} alcohol such as MeOH, followed by addition of formaldehyde and the reducing agent.

43. The process of any one of claims 41-42, wherein the reducing agent is $NaBH_4$.
44. The process of any one of claims 41-42, wherein the reducing agent is formic acid.
45. The process of any one of claims 41-44, further comprising recovering BODV from an organic solvent.
46. The process of any one of claims 41-45, wherein recovery comprises evaporating the organic solvent to obtain a residue, optionally dissolving the residue in a second organic solvent, acidifying, evaporating the second organic solvent.
47. A process for preparing the compound of claim 38 comprising combining BDDMV, an organic solvent, and a methylating agent.
48. The process of claim 47 wherein the process comprises optionally dissolving BDDMV in an organic solvent to obtain a solution, adding a base and a methylating agent to the solution to obtain BODV.
49. The process of any one of claims 47-48, wherein the solvent is dichloromethane or dimethylsulfoxide, THF, ACN or toluene.
50. The process of any one of claims 48-49 wherein the base is BuLi or a C_3-C_9 trialkylamine.
51. The process of claim 50, wherein the base is triethylamine.
52. The process of any one of claims 43-51 wherein the methylating agent is a methyl halide or dimethylsulfate.
53. The process of claim 52 wherein the methylating agent is methyl iodide.
54. The process of claim 53, wherein the NaI is a neat reagent.
55. The process of any one of claims 41-54 further comprising recovering BODV from the obtained reaction mixture.
56. A process for preparing O-desmethylvenlafaxine comprising preparing BODV according to any one of claims 41-55, and further converting the BODV to O-desmethylvenlafaxine.
57. A process for preparing O-desmethylvenlafaxine comprising hydrolyzing BODV of any one of claims 38-40.
58. A process for preparing O-desmethylvenlafaxine comprising: combining BODV of any one of claims 38-40, a hydroxide donor base and a metal salt to obtain a reaction mixture, followed by recovery of the O-desmethylvenlafaxine from the reaction mixture.

59. The process of claim 58, wherein the hydroxide donor base is an alkali metal or alkaline earth metal hydroxide.
60. The process of claim 59, wherein the base is a potassium hydroxide (KOH), lithium hydroxide (LiOH) or sodium hydroxide (NaOH), CsOH.
61. The process of any one of claims 58-60, wherein the metal salt is silver nitrate ($AgNO_3$).
62. The process of claim 61, wherein the metal salt is $AgNO_3$ optionally on a support.
63. The process of any one of claims 56-62, wherein the process comprises combining $AgNO_3$ in water with solid support (montmorillonite or silica) to obtain a reaction mixture, heating the mixture, removing the water to obtain a residue, combining BODV, a base and the residue to obtain ODV.
64. The process of claim 63, further comprising recovering ODV by extracting ODV with an organic solvent.
65. The process of claim 64, wherein the solvent is a mixture of chloroform and methanol.
66. A process for preparing O-desmethylvenlafaxine comprising combining BODV of any one of claims 38-40 with Mg or Cu, and an organic solvent to obtain a grignard reagent or an organocuprate reagent, and combining the reagent with borate and an acid to provide O-desmethylvenlafaxine.
67. The process of claim 66, wherein the process comprises combining Mg or Cu and a halogen when Cu is not used with BODV in an organic solvent such as THF.
68. The process of claim 67, wherein the halogen is I_2.
69. The process of any one of claims 66-68, wherein the borate is trimethylborate.
70. The process of any one of claims 66-69, wherein the acid is glacial acetic acid.
71. The process of any one of claims 66-70, further comprising quenching with hydrogen peroxide.
72. The process of claim 66-71, further comprising adding a water immiscible organic solvent in which O-desmethylvenlafaxine is soluble in, preferably diethylether, to recover O-desmethylvenlafaxine.
73. The process of any of the preceding claims which synthesize O-desmethylvenlafaxine, wherein a hydroxyl protected BODV is used to synthesize O-desmethylvenlafaxine.

74. The process of claim 73, wherein the protected intermediate of BODV has a suitable hydroxyl protecting group selected from the group consisting of silyl, acetyl and dihydropyran (DHP).
75. The process of claim 74, wherein the BODV is protected with an acetyl group.
76. Hydroxyprotected-1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV-P).
77. The BODV-P of claim 76 in isolated or purified form.
78. The BODV-P of claim 76 or 77, wherein the protecting group is acetyl group.
79. The BODV-P of claim 76 or 77, wherein the protecting group is silyl, acetyl or dihydropyran (DHP).
80. The BODV-P of claim 76-79 having a purity of at least about 50% as measured by HPLC.
81. A process for preparing the hydroxyprotected-1-[1-(4-bromophenyl)-2-(dimethylamino)ethyl]cyclohexanol (BODV-P) of claim 76 comprising combining BODV an organic solvent, a base and a protecting agent to create a reaction mixture, and recovering the BODV-P from the reaction mixture.
82. The process of claim 81 wherein the organic solvent is ethyl acetate.
83. The process of claim 81 -82 wherein the process is performed under basic conditions.
84. The process of claim 81-83 wherein the base is a C_3-C_9 trialkyl amine such as triethylamine, or imidazole or lutidine or pyridine or inorganic base such K2CO3.
85. The process of claim 81-84 wherein the protecting agent is selected from the group consisting of: silyl, acetyl, DHP and derivatives thereof.