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Tamar [IL/IL]; Rechov Weizman 53/40, 56238 Yehud (IL).

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(74) Agents: **BIRDE, Patrick, J.** et al.; Kenyon & Kenyon LLP, One Broadway, New York, NY 10004-1050 (US).

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(71) Applicant (*for all designated States except BB, US*): **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O. Box 3190, 49131 Petah Tiqva (IL).

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(71) Applicant (*for BB only*): **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454 (US).

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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **NIDDAM-HILDESHEIM, Valerie** [IL/IL]; P.O. Box 3948, 60920 Kadima (IL). **SHENKAR, Natalia** [UY/IL]; 11/1 Hashofet Brandes, Street, Petach Tiqva (IL). **NIDAM,**

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

(57) Abstract: The present invention describes processes for the preparation of O-desmethylvenlafaxine and the intermediates cyclohexylbenzylcyanide and tridesmethylvenlafaxine, which may be used as intermediates in preparing O-desmethylvenlafaxine.



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PROCESSES FOR THE SYNTHESIS OF O-DESMETHYLVENLAFAXINE

CROSS REFERENCE TO RELATED APPLICATIONS

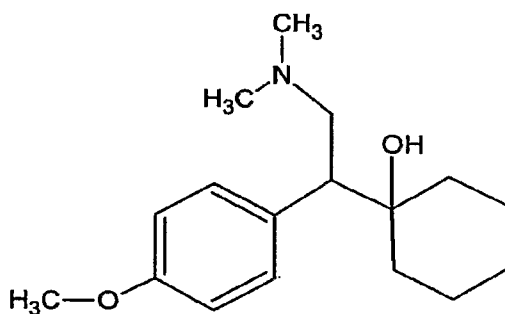
[1] The present application claims the benefit of the following United States Provisional Patent Application Nos.: 60/833,616, filed July 26, 2006; 60/837,879, filed August 14, 2006; 60/849,216, filed October 3, 2006; 60/843,998, filed September 11, 2006; 60/849,255, filed October 3, 2006; 60/906,639, 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

[2] The invention encompasses processes for the synthesis of O-desmethylenlafaxine.

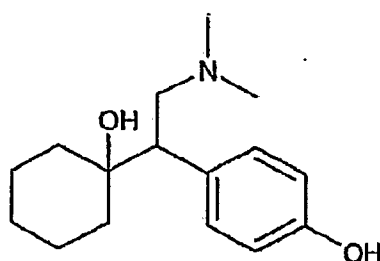
BACKGROUND OF THE INVENTION

[3] 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

[4] O-desmethylenlafaxine, 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-desmethylenlafaxine has the following chemical formula, Formula II:

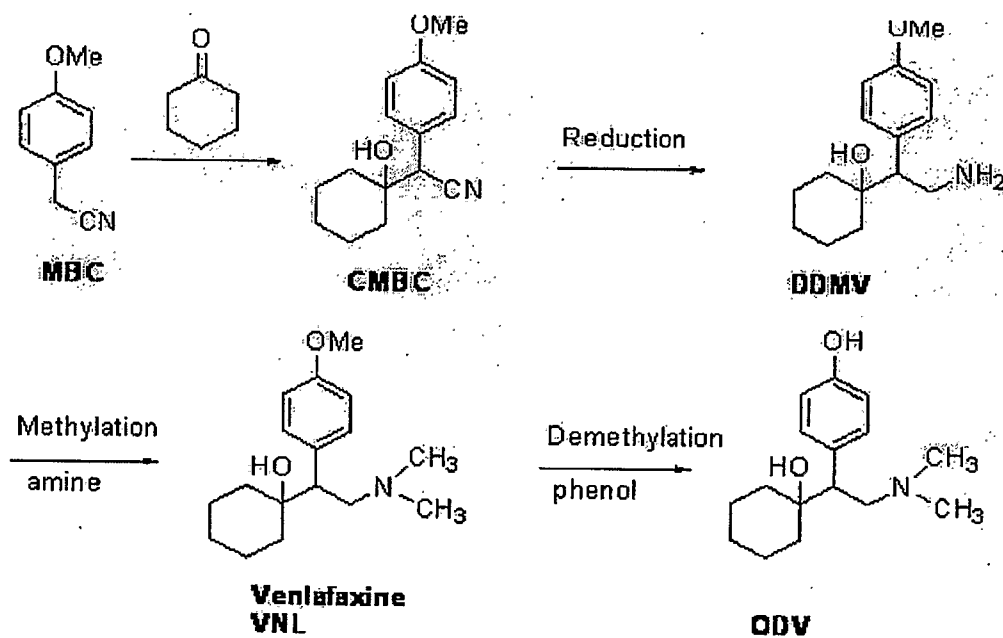


$C_{16}H_{25}NO_2$
Mol. Wt.: 263.38

Formula II

[5] 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.

[6] 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.

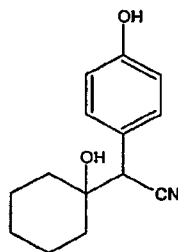
[7] However, the processes disclosed in the above US patents and US patent applications all remain problematic when applied to industrial scale production. Further, the process disclosed in US Application Publication No. 2005/0197392 uses

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.

[8] There is a need in the art for a new synthetic route for obtaining O-desmethylvenlafaxine, using a precursor of venlafaxine to obtain O-desmethylvenlafaxine rather than by preparing venlafaxine and subsequently demethylating venlafaxine to obtain O-desmethyl venlafaxine.

SUMMARY OF THE INVENTION

[9] In one embodiment, there is provided cyclohexylbenzylcyanide (COBC) of the formula:



COBC

[10] In another embodiment, the present invention provides a process for preparing cyclohexylbenzylcyanide (COBC) comprising reacting hydroxybenzylcyanide (OBC) with cyclohexanone, preferably the reaction comprises combining OBC, an organic solvent, preferably a dry organic solvent, a base and cyclohexanone.

[11] In another embodiment, the present invention provides a process for obtaining cyclohexylbenzylcyanide (COBC) comprising reacting hydroxybenzylcyanide (OBC) with cyclohexanone in the presence of a phase transfer catalyst and a base.

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

[13] In another embodiment, the present invention provides a process for preparing tridesmethyl venlafaxine (TDMV) comprising: reducing COBC, preferably the step of reducing COBC comprises combining COBC, a reducing agent, an organic solvent and a Lewis acid catalyst, preferably boron trifluoride (BF₃), to create a

reaction mixture, optionally followed by recovery of the TDMV from the reaction mixture.

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

[15] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: reacting hydroxybenzylcyanide (OBC) with cyclohexanone, preferably the step of reacting with cyclohexanone comprises combining OBC, an organic solvent, a base and cyclohexanone; reducing COBC, preferably the step of reducing COBC comprises combining a reducing agent, an organic solvent and a Lewis acid catalyst, preferably boron trifluoride (BF₃), to create a reaction mixture; optionally recovering TDMV from the reaction mixture and converting the TDMV to O-desmethylvenlafaxine.

[16] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: providing a mixture of hydroxybenzylcyanide (OBC), a phase transfer catalyst, a base and cyclohexanone, to obtain COBC; reducing COBC, preferably the step of reducing COBC comprises combining a reducing agent, an organic solvent and a Lewis acid catalyst, preferably boron trifluoride (BF₃), to create a reaction mixture; optionally recovering TDMV from the reaction mixture and converting the TDMV to O-desmethylvenlafaxine.

[17] In another embodiment, the present invention provides a process of preparing O-desmethyl venlafaxine (ODV) comprising combining hydroxybenzylcyanid (OBC) with a protecting reagent to obtain a hydroxyl protected hydroxybenzylcyanide (POBC), converting POBC to hydroxy protected O-desmethylvenlafaxine (PODV), and deprotecting PODV to form ODV.

[18] In yet another embodiment there is provided a hydroxyl protected hydroxybenzylcyanide (POBC). Also provided is a process of preparing POBC from hydroxybenzyl cyanide (OBC).

[19] In another embodiment there is provided a hydroxyl protected cyclcohexylbenzylcyanide (PCOBC). Also provided is a process of preparing PCOBC.

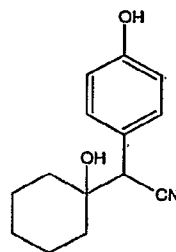
[20] In another embodiment there is provided a hydroxyl protected tridesmethyl venlafaxine (PTDMV). Also provided is a process of preparing PTDMV).

[21] In another embodiment there is provided a hydroxyl protected O-desmethyl venlafaxine (PODV).

[22] In yet other embodiments of the invention each of the other embodiments provide one of each of the following compounds in isolated form: cyclohexylbenzylcyanide (COBC), hydroxyl protected 4-hydroxybenzylcyanide (POBC), hydroxyl protected cyclohexylbenzylcyanide (PCOBC), hydroxyl protected tridesmethyl venlafaxine (PTDMV), and hydroxyl protected O-desmethyl venlafaxine (PODV).

DETAILED DESCRIPTION OF THE INVENTION

[23] In one embodiment of the invention there is provided a cyclohexylbenzylcyanide compound COBC of the following formula



COBC

COBC may be obtained by any of the processes described below. Preferably, COBC is substantially pure, preferably at least 95% pure, more preferably at least 99% pure.

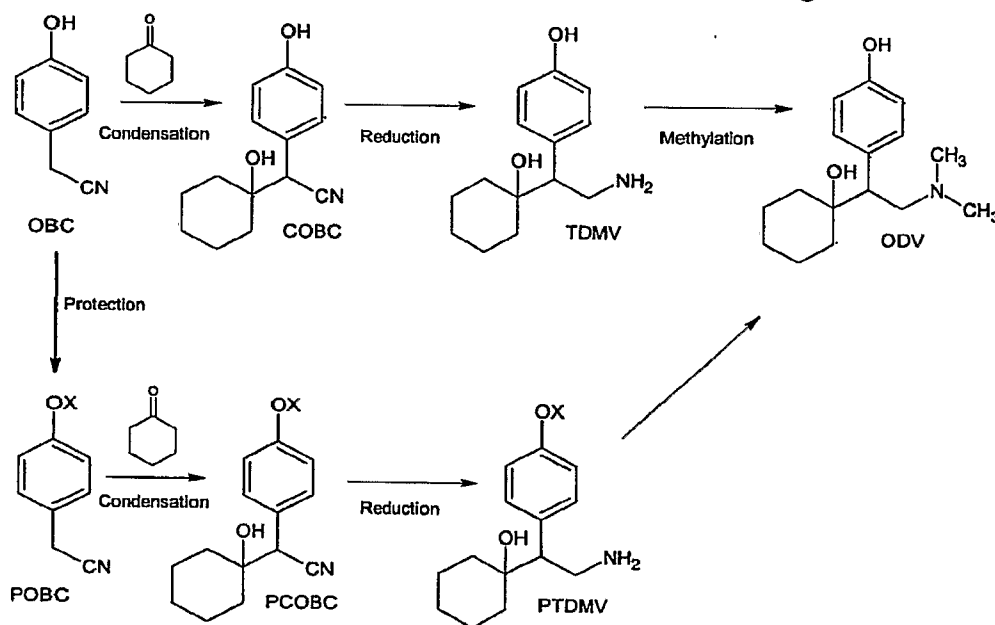
[24] The invention encompasses a synthetic route for obtaining O-desmethylvenlafaxine, from hydroxybenzylcyanide (OBC) and cyclohexylbenzylcyanide (COBC). As used herein, hydroxybenzylcyanide or OBC refers to the compound 4-hydroxybenzylcyanide and cyclohexylbenzylcyanide or COBC refers to the compound 4-[1-cyano-1-(1-hydroxycyclohexyl)methyl]phenol.

[25] As used herein, the term "reduced pressure" refers to a pressure less than atmospheric pressure. As used herein, the term "substantially pure" means a compound of very high purity as is understood by one of skill in the art, such as a purity of about 95%, or greater, as determined, for example, by HPLC area percent. As used herein the term "room temperature" or "RT" means the ambient temperature of an typical laboratory, which is usually about that of Standard Temperature and Pressure (STP). As used herein, an "isolated" compound means the compound has been separated from the reaction mixture in which it was formed.

[26] In the process of the invention, the intermediate hydroxybenzylcyanide (OBC) is condensed with cyclohexanone to form the intermediate (hydroxy)cyclohexylbenzylcyanide (COBC). Further, the cyano group on the COBC is subjected to reduction, to form the intermediate tridesmethyl venlafaxine (TDMV) which is then subjected to selective alkylation to produce O-desmethylvenlafaxine (ODV).

[27] Alternatively, a protected hydroxybenzylcyanide (POBC) intermediate is condensed with cyclohexanone to form the protected intermediate (hydroxy)cyclohexylbenzylcyanide (PCOBC). Further, the cyano group on the PCOBC is subjected to reduction, to form the protected intermediate tridesmethyl venlafaxine (PTDMV) which is then subjected to selective alkylation to produce O-desmethylvenlafaxine (ODV).

[28] The two pathways are as described in the following scheme:



wherein X is a hydroxyl protecting group.

[29] In one embodiment, the present invention provides a process for preparing cyclohexylbenzylcyanide (COBC) comprising reacting hydroxybenzylcyanide (OBC) with cyclohexanone, preferably in the presence of an organic solvent and/or a base. The organic solvent is preferably a “dry organic solvent.” As used herein the term “dry organic solvent” refers to an organic solvent that 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) in a manner that prevents the benefits of the present invention from being realized. Such dry organic

solvent useful in the process of the present invention preferably comprises less about 1% by weight, more preferably less than about 0.1% by weight water, such as about 0.05% by weight to about 0.1% by weight of water.

[30] A suitable organic solvent is selected from the group consisting of: ethers, polar aprotic solvents, aromatic hydrocarbons, and alcohols, acetonitrile, and mixtures thereof. More preferably, the ethers contain 2-8 carbon atoms, more preferably 4-8 carbon atoms, or are selected from the group consisting of: diisopropyl ether, diethyl ether, dioxane, tetrahydrofuran (THF); preferably, the polar aprotic solvents are selected from the group consisting of dimethylformamide (DMF), dimethylacetamide (DMA) and dimethylsulfoxide (DMSO); and the aromatic hydrocarbons are selected from the group consisting of toluene, xylene, and benzene; preferably the aromatic hydrocarbons contain 6-14 carbon atoms, more preferably from 6-10 carbon atoms, even more preferably toluene, xylene or benzene; preferably, the alcohols contain 1-6 carbon atoms, more preferably 1-4 carbon atoms or are selected from the group consisting of methanol, ethanol, isopropanol (IPA), and butanol. Most preferably, the organic solvent is selected from the group consisting of: tetrahydrofuran (THF), dimethylformamide (DMF), dimethylacetamide (DMA) and dimethylsulfoxide (DMSO). Preferably, the organic solvent is a dry organic solvent.

[31] The organic solvent can be employed as such, or it can be employed in mixture with another organic solvent such as methanol or toluene.

[32] Preferably, the cyclohexanone is present in an amount of about 1 to about 2 moles per mole of OBC, more preferably from about 1.1 mole to about 1.5 mole per mole of OBC.

[33] Preferably, the base is an inorganic base. More preferably, the inorganic base is an alkali metal base. A suitable base for use in the process of the present invention is selected from the group consisting of: lithium diisopropyl amide (LDA), lithium bis (trimethyl silyl) amide ($\text{LiN}[(\text{CH}_3)_3\text{Si}]_2$), sodium hydroxide (NaOH), potassium hydroxide (KOH), lithium hydroxide (LiOH), cesium hydroxide (CsOH), sodium hydride (NaH), potassium hydride (KH), cesium hydride (CsH), potassium tert butoxide (t-BuOK), lithium tert butoxide (t-BuOLi), butyl lithium (BuLi) and sodium methoxide (NaOMe). When the organic solvent is tetrahydrofuran (THF), the base is preferably lithium diisopropyl amide (LDA), and when the organic solvent is a polar aprotic solvent, such as for example DMSO, the base is preferably sodium methoxide (NaOMe).

[34] Preferably, the base is present in an amount of about 1 to about 5 moles per mole of OBC, more preferably in an amount of about 1.5 to about 3.5 moles per mole of OBC, even more preferably the amount is from about 2 to about 3 moles per mole of OBC.

[35] In one embodiment of the invention, a solution or a slurry of hydroxybenzylcyanide (OBC) and an organic solvent may be first combined with a base, followed by combining the obtained reaction mixture with cyclohexanone, to obtain COBC. The initial reaction mixture may be cooled prior to adding cyclohexanone, preferably cooling is to a temperature of about -50°C to about -80°C, preferably about -65°C. Preferably, cyclohexanone is added to the reaction mixture in a dropwise manner.

[36] After combining the reaction mixture with cyclohexanone, the mixture may be further maintained, preferably at a constant temperature of about -40°C to about 35°C, preferably with stirring, for a sufficient time to obtain a useful amount of COBC, which is generally at least 10 minutes, preferably at least 45 min, more preferably from about 1 hour to an overnight period (about 8 to 18 hours), even more preferably from about 2 hours to about 5 hours.

[37] COBC may be further recovered from the reaction mixture by any method known in the art. In one embodiment, recovery of COBC from the reaction mixture comprises the steps of extracting COBC from the reaction mixture, preferably with ethylacetate, washing the obtained organic layer, preferably with a saturated ammonium chloride solution and brine, and evaporating the solvent, preferably under reduced pressure, to obtain crude COBC. Such recovery may further comprise the steps of slurrying the crude COBC in a chlorinated hydrocarbon, preferably methylene chloride, filtering the slurry, washing the solid with methylene chloride, and drying to obtain substantially pure COBC.

[38] In another embodiment, the present invention provides a process for obtaining cyclohexylbenzylcyanide (COBC) from a mixture of hydroxybenzylcyanide (OBC), a phase transfer catalyst, a base and cyclohexanone.

[39] Preferably, the phase transfer catalyst is selected from the group consisting of: tetrabutylammonium hydrogensulphate; a tetraalkylammonium halide wherein the alkyl group can be the same or different and contains from 1 to 6, such as for example tetrabutylammonium bromide, tetrabutylammonium chloride, or tetrabutylammonium iodide; benzyltriethyl ammonium chloride; a quaternary

ammonium salt; a quaternary phosphonium salt and a crown ether. More preferably, the phase transfer catalyst is tetrabutylammonium bromide (TBAB).

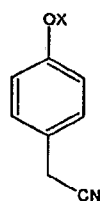
[40] The base in this embodiment is preferably an inorganic base. Suitable inorganic bases are, for example, metal oxides and metal carbonates. Preferably, the inorganic base is selected from the group consisting of: NaOH, KOH, LiOH, CsOH, K_2CO_3 , Na_2CO_3 , and Cs_2CO_3 . Other bases suitable for use in the process of the invention are, for example, metal alkanoxides such as sodium methoxide (NaOMe) or sodium ethanoxide (NaOEt). Preferably, the base is present in an amount of about 0.5 to about 3 mole per mole of OBC, more preferably from about 1 mole to about 2 mole per mole of OBC.

[41] Preferably, the cyclohexanone is present in an amount of about 1 to about 2 moles per mole of OBC, more preferably from about 1.1 mole to about 1.5 mole per mole of OBC.

[42] The reaction may occur with or without the presence of an organic solvent or water. Preferably, the reaction occurs in the presence of water.

[43] Preferably, the reaction mixture is maintained, preferably with stirring, for a sufficient period of time to obtain a useful amount of COBC. A sufficient period of time may be from about 1 hour to about 24 hours, preferably an overnight period (about 8 to about 18 hours). One of ordinary skill in the art could easily monitor the reaction to determine whether a sufficient period of time has elapsed.

[44] The present invention also provides hydroxyl protected hydroxybenzylcyanide (POBC) of the following formula:



POBC

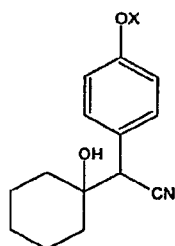
wherein X is a hydroxyl protecting group. The hydroxyl protecting group may be removed by deprotection.

[45] The hydroxyl group on the 4-hydroxybenzylcyanide (OBC) may be prepared by a process comprising combining OBC with a protecting reagent to form a reaction mixture, optionally in an organic solvent and in the presence of a catalyst, a base or both, to obtain the hydroxyl protected POBC.

[46] A suitable protecting agent can be any known hydroxyl protecting agent. Suitable hydroxyl protecting groups are listed in T.W. Greene, *Protecting Groups in Organic Synthesis*, (2nd Ed.), which is incorporated herein by reference. Preferably, the hydroxyl protecting group can be a silyl, acetyl, or 3,4-dihydro-2H-puran (DHP). The silyl protecting group is preferably tert-butyldimethylsilyl (TBDMS). The protection reaction may be carried out at any suitable temperature depending on reagent used, preferably the temperature is between about 0°C to about 100°C, more preferably between about room temperature to about 55°C. A preferred base added to the reaction mixture is selected from the group selected from imidazole, pyridine, triethylamine, lutidine, and dimethylaminopyridine. A catalyst may be added to the mixture, such as for example Pyridinium p-toluene sulfonate (PPTS).

[47] Preferably, POBC is substantially pure, preferably at least 95% pure, more preferably at least 99% pure.

[48] The present invention also provides hydroxyl protected cyclohexylbenzylcyanide (PCOBC). of the following formula:



PCOBC

wherein X is as described above. Preferably, PCOBC is substantially pure, preferably at least 95% pure, more preferably at least 99% pure.

[49] In another embodiment, the present invention provides a process for preparing a hydroxyl protected COBC (PCOBC), according to the processes for preparing COBC, wherein the starting material 4-hydroxybenzylcyanide (OBC) is a hydroxyl protected OBC (POBC) as described in the scheme above.

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

[51] In another embodiment of the process of the present invention O-desmethyl venlafaxine, salts thereof or hydroxyl protected derivatives thereof may be prepared from hydroxybenzylcyanide by first protecting the hydroxyl group on the

hydroxybenzylcyanide (OBC). The hydroxyl protected hydroxybenzylcyanide (POBC) may then be condensed with cyclohexanone to obtain a hydroxyl protected cyclohexylbenzylcyanide (PCOBC) which is reduced to form the hydroxyl protected tridesmethyl venlafaxine (PTDMV) and methylated to form a hydroxyl protected O-desmethyl venlafaxine (PODV) as is shown in the schematic above.

[52] The protected POBC may be converted by any of the above processes to a hydroxyl protected PCOBC, which can be reduced to a hydroxyl protected PTDMV by a process described above, and the protected PTDMV may be methylated to obtain the hydroxyl protected PODV. Subsequently, the PODV is preferably deprotected with an appropriate deprotecting agent depending on the protecting group used. Preferably such deprotection agent can be an acid, such as for example methanesulfonic acid.

[53] The present invention also provides a process for preparing tridesmethyl venlafaxine (TDMV). TDMV may be prepared by reducing COBC. Preferably, COBC is combined with a reducing agent in the presence of an organic solvent and/or a Lewis acid catalyst, preferably boron trifluoride (BF₃) to create a reaction mixture. TDMV may be further recovered from the reaction mixture.

[54] In one embodiment, a solution of COBC, a reducing agent and an organic solvent are combined with a Lewis acid catalyst to obtain a reaction mixture, followed by recovery of the TDMV from the reaction mixture.

[55] Preferably, the solution of COBC, reducing agent and organic solvent is cooled prior to combining it with a Lewis acid catalyst. A preferred temperature to which the mixture is cooled is to a temperature of less than about 10⁰C, more preferably from about -10⁰C to about 10⁰C.

[56] A preferred Lewis acid catalyst is boron trifluoride (BF₃). When BF₃ is used, it is preferably added as a complex in ether (BF₃Et₂O), or else the complex may be formed *in situ*.

[57] In some embodiments, COBC may be prepared by precipitation from a mixture of hydroxybenzylcyanide (OBC), an organic solvent, a base and cyclohexanone; or from a mixture of hydroxybenzylcyanide (OBC), a phase transfer catalyst, a base and cyclohexanone.

[58] Preferably, the reducing agent is selected from the group consisting of: sodium borohydride (NaBH₄), lithium borohydride (LiBH₄), lithium aluminum

hydride (LiAlH_4), L-selectride (lithium tri-sec-butylborohydride), and borane. More preferably, the reducing agent is NaBH_4 .

[59] Alternatively, the reduction can be performed by hydrogenation in the presence of a catalyst, e.g. Ni, Co, Pd/C, or Pt catalyst.

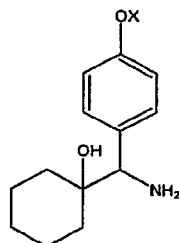
[60] Preferably, the organic solvent is a dry organic solvent. The organic solvent is as described above. More preferably, the organic solvent is THF.

[61] Preferably, the reducing agent is present in an amount of about 1 to about 10 moles per mole of COBC, more preferably in an amount of about 4 to about 10 moles per mole of COBC. A preferred amount of the Lewis acid catalyst, such as BF_3 , is an amount of about 1 to about 5 moles per mole of COBC, more preferably from about 2 to about 3 mole per mole of COBC.

[62] The reaction mixture in the process of the present invention may be maintained, preferably at a constant temperature, such as at room temperature, preferably while stirring, for a sufficient period of time to obtain TDMV. A preferred period of time is from about 1 hour to about 24 hours, more preferably from about 3 hours to about 12 hours, even more preferably, from about 8 hours to about 10 hours.

[63] TDMV may then be recovered from the reaction mixture by any method known in the art. In one embodiment, recovery of TDMV from the reaction mixture comprises the steps of basifying and optionally extracting TDMV from the reaction mixture, preferably with ethylacetate, washing the obtained organic solution, preferably with water and/or brine, and drying to obtain TDMV, preferably by evaporating the solvent for example under reduced pressure.

[64] The present invention also provides the hydroxyl protected tridesmethyl venlafaxine (PTDMV) of the following formula:



PTDMV

wherein X is as described above. Preferably, PCOBC is substantially pure, preferably at least 95% pure, more preferably at least 99% pure.

[65] In another embodiment, the present invention provides a process for preparing hydroxyl protected tridesmethyl venlafaxine (PTDMV), according to the

preparation of TDMV, wherein the starting material the hydroxyl protected PCOBC as described above.

[66] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising preparing TDMV or PTDMV as described above, and further converting them to O-desmethylvenlafaxine.

[67] The conversion of TDMV to O-desmethylvenlafaxine can be performed, for example as described in co-pending United States Patent Application No. --/---,---, filed July 26, 2007, entitled "Processes for the Synthesis of O-Desmethylvenlafaxine"(Atty Docket No 1662/03304), which is incorporated herein by reference. For example, TDMV may be combined with an organic solvent and a methylating agent to form a mixture, and recovering the O-desmethylvenlafaxine from the mixture. Also, TDMV may be subjected to selective reductive amination to produce O-desmethylvenlafaxine ("ODV"). PTDMV is converted to PO-desmethylvenlafaxine in a similar manner.

[68] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: reacting hydroxybenzylcyanide (OBC) with cyclohexanone, preferably the step of reacting with cyclohexanone comprises combining OBC, an organic solvent, a base and cyclohexanone; reducing COBC, preferably the step of reducing COBC comprises combining a reducing agent, an organic solvent and boron trifluoride (BF₃) to create a reaction mixture; recovering TDMV from the reaction mixture and converting the TDMV to O-desmethylvenlafaxine.

[69] In another embodiment, the present invention provides a process for preparing O-desmethylvenlafaxine comprising: providing a mixture of hydroxybenzylcyanide (OBC), a phase transfer catalyst, a base and cyclohexanone, to obtain COBC; reducing COBC, preferably the step of reducing COBC comprises combining a reducing agent, an organic solvent and boron trifluoride (BF₃) to create a reaction mixture; recovering TDMV from the reaction mixture and converting the TDMV to O-desmethylvenlafaxine.

[70] In another embodiment of the present invention a hydroxyl protected O-desmethyl venlafaxine (PODV) may be prepared by any of the above processes wherein the starting material is a hydroxyl protected intermediate as described above. The present invention also provides the hydroxyl protected O-desmethyl venlafaxine (PODV).

[71] The O-desmethyl venlafaxine prepared by any of above process can be prepared in the form of a salt, preferably a succinate salt.

[72] Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the synthesis of the compound COBC, tridesmethyl venlafaxine and further their conversion to O-desmethylvenlafaxine. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

EXAMPLES

HPLC Method:

Column & Packing: Zorbax SB C-18 4.6*250mm Part No.28105-020 or equivalent column

Column Temperature: 25°C

Buffer Add 4.0ml of trifluoroacetic acid and 7.0ml of triethylamine to 1L of water adjust the pH to 3.0 with triethylamine.

Eluent:

Reservoir A 30%Acetonitrile and 70% Buffer

Reservoir B To a mixture of 700ml Acetonitrile and 300ml buffer add 1.6ml of trifluoroacetic acid and 2.9ml of triethylamine measure the pH it should be about 3.0 (correct the pH with triethylamine or trifluoroacetic acid if necessary).

<i>Gradient</i>	Time	Reservoir A	Reservoir B
	0	100%	0%
	21 min	100%	0%
	55 min	45%	55%
	Equilibrium time: 10min		
Flow Rate:	1.0 ml/min		
Detector:	230 nm		
Sample Volume:	10 µl		

Diluent: Eluent A

Mobile phase composition and flow rate may be varied in order to achieve the required system suitability.

Sample Preparation

Weigh accurately about 10 mg of sample in a 20ml amber volumetric flask. Dissolve with eluent A.

Method

Inject the sample solutions into the chromatograph, continuing the chromatogram of sample up to the end of the gradient. Determine the areas for each peak in each solution using a suitable integrator.

Calculation

Impurity Profile Determination

$$\% \text{ impurity} = \frac{\text{area impurity in sample}}{\text{Total area}} \times 100$$

Preparation of COBC

Example 1:

A 100 ml, three necked flask equipped with Nitrogen inlet, thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol) and THF (15 ml). This solution was cooled to -78°C and LDA (2M in THF, 16.5 ml, 33 mmol) was added slowly, keeping temperature under -65°C. A white solid precipitated during LDA addition. After the end of the addition, the mixture was stirred for 30 minutes. Cyclohexanone (1.62 g, 16.5 mmol) was then added, and the mixture continued in the same conditions for 5 hours. The reaction was quenched by pouring it into 100 ml of a saturated ammonium chloride solution containing ice.

The product was extracted to EtOAc (3x30 ml). The organic layer was washed with a saturated ammonium chloride solution and brine. Finally the solvent was evaporated under reduced pressure to get 3.5 g of a mixture of OBC (30%) and COBC (60%) (Yield =60%).

This mixture was suspended in 10 ml methylene chloride, where a solid precipitated. The slurry was stirred at room temperature for 2 hours, the solid filtered,

washed with methylene chloride and vacuum dried at room temperature, to get 1.9g COBC (purity 99% by HPLC area, yield=55%).

Example 2:

A 100 ml, three necked flask equipped with Nitrogen inlet, thermometer and magnetic stirrer was charged with OBC (5g, 37.5 mmol) and DMSO (5 ml). The contents of the flask were stirred to complete dissolving (brown color). KOH (3.2g, 56 mmol) was added and the reaction mixture stirred vigorously (exothermic).

Cyclohexanone (5.52 g, 56 mmol) was then added dropwise. The reaction was quenched with HCl 5% and methylene chloride was added. The layers were separated and a solid precipitated. The solid was then filtered under reduced pressure and washed with a small amount of methylene chloride to yield 3.2g of COBC.

Example 3:

A 100 ml three necked flask equipped with nitrogen inlet, thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol), toluene (15 ml) and DMF (2ml). The reaction mixture was stirred at about room temperature (RT) until dissolution was complete and NaH (1.2g, 30 mmol) was added. Cyclohexanone (1.7 g, 17.3 mmol) was then added dropwise. The reaction was stirred at RT for an additional 1hr to get 21% COBC (% area HPLC).

Example 4:

A 100 ml three necked flask equipped with nitrogen inlet, thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol), THF (30 ml) and DMF (2ml). The reaction mixture was stirred at RT until dissolution was complete and t-BuOK (3.3 g, 30 mmol) was added. Cyclohexanone (1.65 g, 16.8 mmol) was then added dropwise and the reaction was stirred at RT for an additional 3.5hrs to get 19%COBC (% area HPLC).

Example 5:

A 100 ml three necked flask equipped with nitrogen inlet, thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol), THF (15 ml) and DMF (2ml). The mixture was stirred at RT until complete dissolution and NaH (1.2g, 30 mmol) was added. Cyclohexanone (1.7 g, 17.3 mmol) was then added dropwise and the reaction was stirred at RT for an additional 2hrs to get 34%COBC (% area HPLC).

Example 6:

A 100 ml three necked flask equipped with nitrogen inlet, thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol) MeOH (15 ml) and DMF (2ml). The reaction mixture was stirred at RT until complete dissolution and NaOCH₃ (1.7g, 30 mmol) was added. Cyclohexanone (1.7 g, 17.3 mmol) was then added dropwise and the reaction was stirred at RT overnight to obtain 30% COBC (% area HPLC).

Example 7:

A 100 ml three necked flask equipped with nitrogen inlet, thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol), MeOH (10 ml) and DMSO (10ml). The reaction mixture was stirred at RT until complete dissolution and NaOCH₃ (1.7g, 30 mmol) was added. Cyclohexanone (1.7 g, 17.3 mmol) was added dropwise. The reaction was stirred at RT overnight to obtain 32% COBC (% area HPLC).

Example 8:

A 100 ml, three necked flask equipped with nitrogen inlet, thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol) and DMSO (10ml). The reaction mixture was stirred at RT until complete dissolution and NaOCH₃ (2.65g, 47 mmol) was added. Cyclohexanone (2 g, 20.37 mmol) was then added dropwise. The reaction was stirred at RT 10 min to get 43% COBC (% area HPLC).

Example 9:

A 100 ml three necked flask equipped with nitrogen inlet, thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol) and DMSO (10ml). The reaction mixture was stirred at RT until complete dissolution and NaOCH₃ (1g, 17.6 mmol) was added. Cyclohexanone (2 g, 20.37 mmol) was then added dropwise. The reaction was stirred at RT 45 min to get 55% of COBC (% area HPLC).

Example 10:

A 100 ml three necked flask equipped with nitrogen inlet, thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol) and DMSO (10ml). The reaction mixture was stirred at RT until complete dissolution and LiOH (1g, 23.8

mmol) was added. Cyclohexanone (2 g, 20.37 mmol) was then added dropwise. The reaction was stirred at RT 8.5hrs to get 35% of COBC (% area HPLC).

Example 11:

A 100 ml three necked flask equipped with, thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol), cyclohexanone (1.7 g, 17.3 mmol), TBAB (0.26g) and NaOH (6ml 10%). The reaction was stirred at RT overnight to get 44% COBC (HPLC).

Example 12:

A 100 ml three necked flask equipped with nitrogen inlet, thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol) and THF (15ml). The reaction mixture was stirred at RT until complete dissolution and t-BuOLi (2g, 25 mmol) was added. Cyclohexanone (2 g, 20.37 mmol) was then added dropwise. The reaction was stirred at RT 45min to get 19% COBC (% area HPLC).

Example 13:

A 100 ml three necked flask equipped with nitrogen inlet, thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol), THF(15ml) and DMF (1.5ml). The reaction mixture was stirred at RT until complete dissolution and t-BuOLi (2.5g, 30 mmol) was added. Cyclohexanone (2 g, 20.37 mmol) was then added dropwise. The reaction was stirred at RT 1.15 hr to get 23.5% COBC (% area HPLC).

Example 14:

A 100 ml three necked flask equipped with thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol) and cyclohexanone (2 g, 20.37 mmol), TBAB (0.5g) and NaOH (13ml 10%) were added. The reaction was stirred at RT overnight to get 40%COBC (% area HPLC).

Example 15:

A 100 ml three necked flask equipped with thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol) and cyclohexanone (2.2g, 22.4 mmol). Water (10ml), TBAB (0.3g) and KOH (1.9g, 30.5 mmol) were then added. The reaction was stirred at RT overnight to get 39% COBC (% area HPLC).

Example 16:

A 100 ml three necked flask equipped with thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol) and cyclohexanone (2.2g, 22.4 mmol). Water (10ml), TBAB(0.3gr) and LiOH (2g, 47.6mmol) were then added. The reaction was stirred at RT overnight to get 39% COBC (% area HPLC).

Example 17:

A 100 ml three necked flask equipped with thermometer and mechanical stirrer was charged with OBC (2g, 15 mmol), DMA (10ml) and LiOH (2g, 47.7 mmol). Cyclohexanone (2.2g, 22.4 mmol) was then added dropwise. The reaction mixture was stirred at RT overnight to get 10% COBC (% area HPLC).

Preparation of TDMV**Example 18:**

A 100 ml three necked flask equipped with nitrogen inlet thermometer and mechanical stirrer was charged with COBC (2 g, 8.64 mmol), MeOH (50 ml) and CoCl anhydrous (2.25 g, 17.32 mmol). The resulting solution was cooled to -10°C with an ice-bath. NaBH₄ (3.35 g, 88.62mmol) was added portionwise at this temperature. The ice-bath was removed one hour after the end of addition.

The reaction mixture was stirred 3 hours at room temperature and then quenched with 10% HCl. MeOH was removed under reduced pressure and the aqueous phase was basified with ammonium hydroxide (25%) and extracted with EtOAc. The organic phase was washed with water, brine, dried over Na₂SO₄ and evaporated under reduced pressure to get 0.4 g of TDMV.

Example 19:

A 100 ml three necked flask equipped with nitrogen inlet thermometer and mechanical stirrer was charged with NaBH₄ (1.2 g, 31.74 mmol) THF (10ml). This solution was cooled to 10°C with an ice-bath. BF₃Et₂O (3.95g, 27.86mmol) and COBC (2 g, 8.64 mmol) were then added. The reaction mixture was stirred at room temperature overnight.

The reaction mixture was quenched with formic acid and water. The organic phase was basified with NaOH (25%), washed with water and evaporated under reduced pressure to get TDMV.

Preparation of O-désmethylvenlafaxine**Example 20:**

TDMV (0.5 g, 2.12 mmol) was suspended in CH_2Cl_2 . Methyl iodide (0.26 ml, 4.3 mmol) and triethylamine (0.66 ml, 4.73 mmol) were added. The reaction mixture was stirred under nitrogen atmosphere at room temperature for 6 hours. At this stage methyl iodide (0.5 ml) and NEt_3 (1.2 ml) were added. The addition caused the temperature to rise. After 16 hours, HPLC analysis indicated the presence of ODV.

Preparation of POBC**Example 21:** Preparation of OBC-DHP

OBC (0.5g, 3.7 mmol) was dissolved at room temperature in 3,4-dihydro-2H-pyran (DHP) (approx. 2 ml) under N_2 . Pyridinium p-toluene sulfonate (PPTS, catalytic amount) was added and heated to 55°C for 45 min. The end of reaction was determined by TLC (eluent EtOAc:Hex 1:1). The product was extracted in EtOAc, washed with brine and dried over MgSO_4 . A pale yellow powder was obtained (0.74g, purity= 98% by area % of HPLC, yield= 91%)

Example 22: Preparation of OBC-TBDMS

OBC (5g, 37 mmol), 11 g of TBDMS-Cl, 12g of imidazole and 25ml of CH_2Cl_2 were stirred together for 2 hours at ambient temperature under N_2 atmosphere. The product was washed with brine, a 10% aqueous solution of citric acid, brine and dried over MgSO_4 . After removal of the solvent 4g of product was obtained.

Preparation of PCOBC**Example 23:** Preparation of COBC-DHP

OBC-DHP (0.74g, 3.4 mmol), cyclohexanone (0.5 g), TBAB (0.15g) and a 10% aqueous solution of NaOH (4 ml) were mixed and stirred at room temperature, forming two phases. After 30 minutes of stirring, the organic phase was analyzed by HPLC, containing 46% COBC-DHP and 48% unreacted OBC-DHP.

Example 24:

OBC-DHP (3.25g, 15 mmol) was dissolved in dry THF under N_2 and cooled to -80°C . LDA 2M in THF/heptane/ethyl benzene (8 ml, 16 mmol) was added

dropwise, keeping the temperature under -60°C . The mixture was stirred at -80°C for 30 minutes. Cyclohexanone (1.65g, 16.5 mmol) was added dropwise. After 1 hour stirring a sample was analyzed by HPLC, containing 41% COBC-DHP and 42% unreacted OBC-DHP.

Preparation of PTDMV

Example 25:

A 100 ml three necked flask equipped with nitrogen inlet thermometer and mechanical stirrer is charged with PCOBC (8.64 mmol), MeOH (50 ml) and CoCl anhydrous (17.32 mmol). The resulting solution is cooled to -10°C with an ice-bath. NaBH_4 (88.62mmol) is added portionwise at this temperature. The ice-bath is removed one hour after the end of addition.

The reaction mixture is stirred 3 hours at room temperature and then quenched with 10% HCl. MeOH is removed under reduced pressure and the aqueous phase is basified with ammonium hydroxide (25%) and extracted with EtOAc. The organic phase is washed with water, brine, dried over Na_2SO_4 and evaporated under reduced pressure to get PTDMV.

Example 26:

A 100 ml three necked flask equipped with nitrogen inlet thermometer and mechanical stirrer is charged with NaBH_4 (31.74 mmol) and THF (10ml). This solution is cooled to 10°C with an ice-bath. $\text{BF}_3\text{Et}_2\text{O}$ (27.86mmol) and PCOBC (8.64 mmol) are then added. The reaction mixture is stirred at room temperature overnight.

The reaction mixture is quenched with formic acid and water. The organic phase is basified with NaOH (25%), washed with water and evaporated under reduced pressure to get PTDMV.

Preparation of PODV

Example 27:

P-TDMV (2.12 mmol) is suspended in CH_2Cl_2 . Methyl iodide (4.3 mmol) and triethylamine (4.73 mmol) are added. The reaction mixture is stirred under nitrogen atmosphere at room temperature for 6 hours. At this stage methyl iodide (0.5 ml) and

NEt₃ (1.2 ml) are added. After 16 hours, HPLC analysis indicated the presence of PODV.

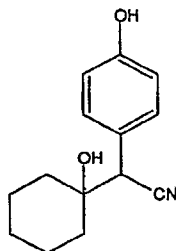
Preparation of O-desmethylvenlafaxine

Example 28:

PODV (2.12 mmol) is suspended in THF in presence of methanesulfonic acid (6 mmol). The reaction is stirred at ambient temperature overnight. To the mixture so-obtained is first added EtOAc and the organic phase is washed with brine, Na₂CO₃ saturated and water. The organic phase is then concentrated under reduced pressure to get ODV.

What is claimed is:

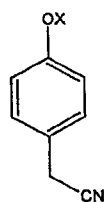
1. Cyclohexylbenzylcyanide (COBC) of the following formula



2. The cyclohexylbenzylcyanide compound of claim **Error! Reference source not found.**1, wherein the cyclohexylbenzylcyanide is at least 95% pure.
3. A process of preparing cyclohexylbenzylcyanide (COBC) of claim 1 or claim 2 comprising reacting hydroxybenzylcyanide (OBC) with cyclohexanone.
4. The process of claim 3, wherein the reaction comprises combining OBC, an organic solvent, a base and cyclohexanone.
5. The process of claim 4, wherein the organic solvent is selected from the group consisting of: C₂₋₈ ethers, polar aprotic solvents, aromatic hydrocarbons, C₁₋₆ alcohols, and acetonitrile.
6. The process of claim 5, wherein the organic solvent is selected from the group consisting of: diisopropyl ether, diethylether, dioxane, tetrahydrofuran (THF), dimethylformamide (DMF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), toluene, xylene, benzene, methanol, ethanol, isopropanol, butanol and acetonitrile.
7. The process of claim 6, wherein the organic solvent is selected from the group consisting of: diisopropyl ether, dioxane, tetrahydrofuran (THF), dimethylformamide (DMF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), xylene, benzene, methanol, ethanol, isopropanol, butanol and acetonitrile.
8. The process of claim 7, wherein the organic solvent is selected from the group consisting of: THF, DMF, DMA, and DMSO.
9. The process of any of claims 4 to 8, wherein the organic solvent is a dry organic solvent.

10. The process of any of claims 3 to 9, wherein the cyclohexanone is present in an amount of about 1 to about 2 moles per mole of OBC.
11. The process of claim 10, wherein the cyclohexanone is present in an amount of about 1.1 to about 1.5 moles per mole OBC.
12. The process of any of claims 4 to 11, wherein the base is an inorganic base.
13. The process of any of claims 4 to 11, wherein the base is selected from the group consisting of: lithium diisopropyl amide (LDA), lithium bis (trimethyl silyl) amide ($\text{LiN}[(\text{CH}_3)_3\text{Si}]_2$), sodium hydroxide (NaOH), potassium hydroxide (KOH), lithium hydroxide (LiOH), cesium hydroxide (CsOH), sodium hydride (NaH), potassium hydride (KH), cesium hydride (CsH), potassium tert butoxide (t-BuOK), lithium tert butoxide (t-BuOLi), butyl lithium (BuLi) and sodium metoxide (NaOMe).
14. The process of any of claims 4 to 13, wherein the base is present in an amount of about 1 to about 5 moles per mole of OBC.
15. The process of claim 14, wherein the base is present in an amount of about 1.5 to about 3.5 moles per mole of OBC.
16. The process of any of claims 4 to 15, wherein the combining step comprises combining a solution or a slurry of OBC, the organic solvent and the base, followed by combining the obtained reaction mixture with cyclohexanone.
17. The process of claim 16, wherein the cyclohexanone is added to the reaction mixture in a dropwise manner.
18. The process of any of claims 4 to 17, wherein the reaction mixture is maintained for a period of at least 10 minutes.
19. The process of claim 18, wherein the period is from about 1 hour to about 18 hours.
20. The process of claim 19, wherein the mixture is maintained at a temperature of about -40°C to about 35°C .
21. The process of any of claims 3 to 20, comprising reacting OBC and cyclohexanone in the presence of a phase transfer catalyst and a base.
22. The process of claim 21, wherein the phase transfer catalyst is selected from the group consisting of: tetrabutylammonium hydrogensulphate, a

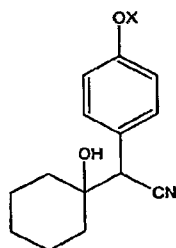
- tetraalkylammonium halide wherein the alkyl group can be the same or different and contains from 1 to 6, benzyltriethyl ammonium chloride, a quaternary ammonium salt, a quaternary phosphonium salt and a crown ether.
23. The process of claim 22, wherein the phase transfer catalyst is tetrabutyl ammonium bromide (TBAB).
 24. The process of any of claims 21 to 23, wherein the base is an inorganic base.
 25. The process of any of claims 21 to 23, wherein the base is selected from the group consisting of: NaOH, KOH, LiOH, CsOH, K₂CO₃, Na₂CO₃, Cs₂CO₃, sodium metoxide (NaOMe), and sodium ethoxide (NaOEt).
 26. The process of any of claims 21 to 25, wherein the base is present in an amount of about 0.5 to about 3 mole per mole of OBC.
 27. The process of claim 26, wherein cyclohexanone is present in an amount of about 1 to about 2 moles per mole of OBC.
 28. The process of any of claims 21 to 27, wherein the reaction mixture is maintained for a sufficient period of time to obtain COBC.
 29. The process of claim 28, wherein the period of time is from about 1 hour to about 24 hours.
 30. The process of claim 29, wherein the period of time is from about 8 hours to about 18 hours.
 31. The process of claim 30, wherein the mixture is maintained at a temperature of about -40°C to about 35°C.
 32. The process of any of claims 3 to 31, further comprising converting COBC to O-desmethylvenlafaxine or a salt thereof.
 33. The process of claim 32, wherein the O-desmethyl vanlafaxine salt is a succinic acid salt.
 34. The process of any of claims 3 to 33, wherein the hydroxybenzylcyanide (OBC) is a hydroxyl protected hydroxybenzylcyanide (POBC) to obtain hydroxyl protected cyclohexylbenzylcyanide (PCOBC).
 35. Hydroxyl protected hydroxybenzylcyanide (POBC) of the following formula:



POBC

wherein X is a hydroxyl protecting group.

36. The hydroxyl protected hydroxybenzylcyanide (POBC) of claim 35, wherein the protecting reagent is selected from the group consisting of dihydropuran and TBDMS.
37. The hydroxyl protected hydroxybenzylcyanide (POBC) of any of claims 35 or 36, having a purity of at least 95%.
38. A process for preparing the hydroxyl protected hydroxybenzylcyanide (POBC) of any of claims 35 to 37 comprising combining OBC with a protecting reagent.
39. Hydroxyl protected cyclobenzylcyanide (PCOBC) of the following formula:



PCOBC

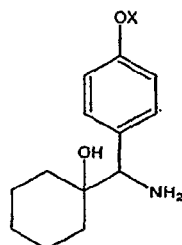
wherein X is a hydroxyl protecting group.

40. The hydroxyl protected cyclobenzylcyanide of claim 39, wherein the protecting reagent is selected from the group consisting of dihydropuran and TBDMS.
41. The hydroxyl protected cyclobenzylcyanide (PCOBC) of any of claim 39 or 40, having a purity of at least 95%.
42. A process of preparing the hydroxyl protected cyclobenzylcyanide (PCOBC) of any of claims 39 to 41 comprising reacting hydroxyl protected hydroxybenzylcyanide (POBC) with cyclohexanone.

43. The process of claim 42, wherein the reaction comprises combining POBC, an organic solvent, a base and cyclohexanone.
44. The process of claim 42, comprising reacting POBC and cyclohexanone in the presence of a phase transfer catalyst and a base.
45. The process of any of claims 42 to 44, further comprising converting PCOBC to O-desmethylvenlafaxine or a salt thereof.
46. The process of claim 45, wherein the O-desmethylvenlafaxine salt is a succinic acid salt.
47. A process for preparing tridesmethyl venlafaxine (TDMV) comprising reducing COBC.
48. The process of claim 47, wherein the reduction of COBC comprises combining COBC with a reducing agent, an organic solvent and a Lewis acid catalyst.
49. The process of claim 48, wherein the combining step comprises combining COBC, a reducing agent and an organic solvent to form a solution, followed by combining the solution with the Lewis acid catalyst.
50. The process of claim 49, wherein the solution is cooled to a temperature less than about 10°C prior to combining the solution with the Lewis acid catalyst.
51. The process of any of claims 48 to 50, wherein the Lewis acid catalyst is boron trifluoride (BF₃).
52. The process of any of claims 48 to 51, wherein the reducing agent is selected from the group consisting of: sodium borohydride (NaBH₄), lithium borohydride (LiBH₄), lithium aluminum hydride (LiAlH₄), L-selectride, and borane.
53. The process of claim 52, wherein the reducing agent is NaBH₄.
54. The process of any of claims 48 to 53, wherein the organic solvent is selected from the group consisting of: C₂₋₈ ethers, polar aprotic solvents, aromatic hydrocarbons, and C₁₋₆ alcohols, and acetonitrile.
55. The process of claim 54, wherein the organic solvent is selected from the group consisting of: diisopropyl ether, dioxane, tetrahydrofuran (THF),

dimethylformamide (DMF), dimethylacetamide (DMA), dimethylsulfoxide (DMSO), xylene and benzene.

56. The process of claim 55, wherein the organic solvent is THF.
57. The process of any of claims 48 to 56, wherein the organic solvent is a dry organic solvent.
58. The process of any of claims 48 to 57, wherein the reducing agent is present in an amount of about 1 to about 10 moles per mole of COBC and the Lewis acid catalyst is BF_3 , present in an amount of about 1 to about 5 moles per mole of COBC.
59. The process of any of claims 48 to 58, wherein the reaction mixture is maintained for a sufficient period of time to obtain TDMV.
60. The process of claim 59, wherein the period of time is from about 1 hour to about 24 hours.
61. The process of claim 60, wherein the mixture is maintained at a temperature of about 15°C to about 35°C .
62. The process of any of claims 47 to 61, wherein the reduction is carried out by hydrogenation in the presence of a catalyst.
63. The process of claim 62, wherein the catalyst is a Ni, Co, Pd/C, or Pt catalyst.
64. The process of any of claims 47 to 63, further comprising converting TDMV to O-desmethylvenlafaxine or a salt thereof.
65. The process of claim 64, wherein the O-desmethylvenlafaxine salt is a succinic acid salt.
66. Hydroxyl protected tridesmethyl venlafaxine (PTDMV) of the following formula:



PTDMV

wherein X is a hydroxyl protecting group.

67. The hydroxyl protected tridesmethyl venlafaxine of claim 66, wherein the protecting group is selected from the group consisting of dihydropuran and TBDMS.
68. The hydroxyl protected tridesmethyl venlafaxine (PTDMV) of any of claim 66 or 67, having a purity of at least 95%.
69. A process of preparing the hydroxyl protected tridesmethyl venlafaxine (PTDMV) of any of claims 66 to 68 comprising reducing PCOBC.
70. The process of claim 69, further comprising converting PTDMV to O-desmethylvenlafaxine or a salt thereof.
71. The process of claim 70, wherein the O-desmethylvenlafaxine salt is a succinic acid salt.
72. A process of preparing O-desmethyl venlafaxine (ODV) comprising:
 - a) reacting hydroxybenzylcyanide (OBC) with cyclohexanone to obtain cyclohexylbenzylcyanide (COBC);
 - b) reducing the cyano group of COBC to obtain tri-desmethyl venlafaxine (TDMV); and
 - c) converting TDMV to ODV.
73. The process of claim 72, wherein the reaction of step a) comprises combining OBC, an organic solvent, a base, and cyclohexanone.
74. The process of claim 72, wherein the reaction of step a) comprises providing a mixture of hydroxybenzylcyanide (OBC), a phase transfer catalyst, a base and cyclohexanone, to obtain COBC.
75. The process of any of claims 72 to 74, wherein reducing COBC in step b) comprises combining COBC with a reducing agent, an organic solvent and a Lewis acid catalyst to create a reaction mixture.
76. The process of claim 75, wherein the Lewis acid catalyst is boron fluoride (BF₃).
77. The process of any of claims 72 to 76, wherein converting TDMV to ODV comprises selectively alkylating TDMV.

78. The process of claim 77, wherein converting TDMV to ODV comprises combining TDMV with a methylating agent.
79. The process of claim 78, wherein converting TDMV to ODV is in the presence of a base.
80. The process of claim 79, wherein the base is triethylamine.
81. The process of any of claims 72 to 80, further comprising converting ODV to a ODV salt.
82. The process of claim 81, wherein the ODV salt is succinic acid salt.
83. A process of preparing O-desmethyl venlafaxine (ODV) comprising combining hydroxybenzylcyanid (OBC) with a protecting reagent to obtain a hydroxyl protected hydroxybenzylcyanide (POBC), reacting POBC with cyclohexanone to obtain hydroxyl protected cyclohexylbenzylcyanide (PCOBC), reducing PCOBC to obtain hydroxyl protected tridesmethyl venlafaxine (PTDMV), converting PTDMV to hydroxyl protected O-desmethylvenlafaxine (PODV), and deprotecting PODV to form ODV.
84. The process of claim 83, wherein OBC and the protecting reagent are provided in a mixture further comprising an organic solvent, a catalyst, a base or a mixture thereof.
85. The process of any of claims 83 or 84, wherein the protecting reagent is selected from the group consisting of dihydropuran and TBDMS-Cl.
86. Use of OBC or COBC, either in a hydroxyl protected or unprotected form, in a process for the preparation of TDMV or for the preparation of O-desmethylvenlafaxine (ODV).
87. Use of PTDMV for the preparation of O-desmethylvenlafaxine (ODV).