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Communications to the Editor

An Improved, Scalable, and Impurity-Free Process for Tolterodine Tartrate†

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Abstract:

Tolterodine tartrate is an anticholinergic muscle relaxant used to treat urinary frequency, urinary urgency, and incontinence in people with unstable bladders. An improved, cost-effective, and impurity-free process for tolterodine tartrate suitable for large-scale commercial production is described here by addressing various scale-up and impurity issues.

Introduction

Tolterodine tartrate (**9**) is a competitive muscarine receptor antagonist used in the treatment of urinary bladder disorders such as urinary urge incontinence.[1] Tolterodine tartrate acts by relaxing the smooth muscle tissue in the wall of the bladder by blocking cholinergic receptors.[2] The first reported synthetic route[3] (Scheme 1) involved acid-catalyzed condensation of cinnamic acid **1**, and 4-methyl phenol **2** in neat sulfuric acid to afford lactone **3**, followed by opening of **3** with potassium carbonate in the presence of methyl iodide in refluxing acetone and methanol to give corresponding methyl ester **4**. Reduction of methyl ester **4** with lithium aluminum hydride in diethyl ether yielded the corresponding alcohol **5**, which on tosylation followed by condensation of obtained tosyl derivative **6** with diisopropylamine in hot acetonitrile gave tertiary amine **7**. Reaction of **7** with boron tribromide in dichloromethane offered hydroxy compound **8**, which upon resolution with L-(+)-tartaric acid yielded tolterodine tartrate (**9**) in overall yield of around 5.5% with several impurities. This process suffers from several drawbacks, such as prolonged reaction time for diisopropylamine condensation (4−6 days) and deprotection of methyl group (2−3 days), usage of hazardous reagents such as lithium aluminum hydride and boron tribromide and unacceptable process solvents such as diethyl ether, pyridine, chloroform, etc. The major disadvantage of this process is the poor yield of the active pharmaceutical ingredient (API) along with the formation of many unwanted impurities, which make this process less viable for commercial production and in producing the regulatory quality product.

The other processes[4] reported in the literature either use hazardous reagents such as diisobutylaluminum hydride (DIBAL) or end up with high production costs. Herein we report an improved route, which is cost-effective, scalable, plant friendly, and impurity free, which has been accomplished by modifying the original synthetic route.

Results and Discussion

In our approach (Scheme 2) we had explored the original route, and we were clear about the disadvantages of the route. Hence, our approach also started with acid-catalyzed condensation of the same starting materials, **1** and **2**, to obtain the intermediate **3**[5] with quantitative yield in pilot plant by eliminating the emulsion problem during the work-up process which involves the separation of the sulfuric acid layer before pH adjustments. Hydrolysis of the lactone ring in **3** with potassium carbonate in acetone and methanol as a solvent system followed by benzyl bromide addition to the reaction mass yielded benzyl derivative **10** with 96% yield and 99.50% purity by HPLC.

As we experienced the problem in the deprotection of the methyl group in the original route (Scheme 1), this small change to benzylation in the modified route (Scheme 2) avoided the usage of the hazardous reagent boron tribromide for the deprotection of the methyl group in the later stage. Also, instead of prolonged reaction time (2−3 days) for deprotection, it took around 4−5 h of reaction time with inexpensive Raney nickel[6]-catalyzed debenzylation. (Scheme 2). This change also benefited us by increasing the yield in the subsequent stages. Reduction of **10** was tried with different reducing agents such as DIBAL and sodium bis(2-methoxyethoxy)aluminum hydride (Vitride)[7] in different solvents such as tetrahydrofuran (THF), cyclohexane, dichloromethane, and toluene under different reaction conditions.

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(6) Raney nickel grade CAT-39 was used for reduction purposes.

(7) Commercially available reagent sodium bis(2-methoxyethoxy)aluminum hydride (Vitride) (65% wt/wt in toluene) is used for this reaction. Procured from Chematek S.P.A. CHEMICAL PRODUCTS, Italy.

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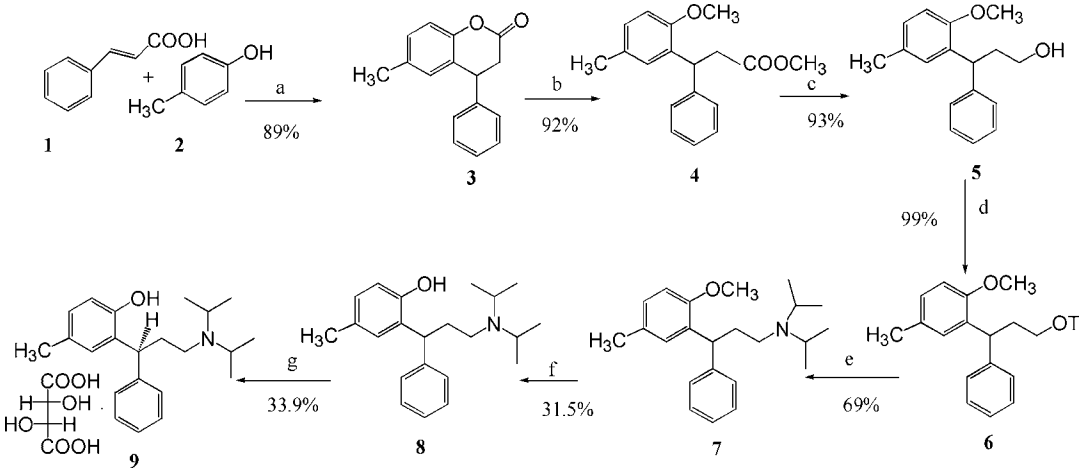
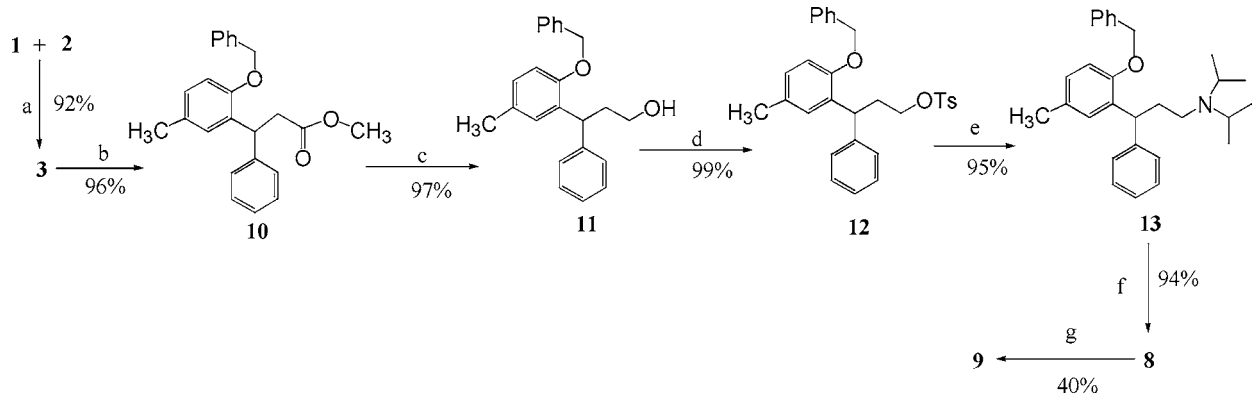
Scheme 1. **Synthetic scheme of tolterodine tartarate**[a]



[a] Reagents and conditions: a) H_2SO_4/120−125 °C. b) MeI/K_2CO_3, acetone, methanol/reflux. c) LAH/dry ether/25−35 °C. d) *p*-Toluene sulfonyl chloride/pyridine, chloroform/−10 to −15 °C. e) Diisopropylamine/acetonitrile/80−85 °C/4−6 days. f) BBR_3/20−25 °C/2−3 days, g) L-(+)-tartaric acid/ethanol.

Scheme 2. **Modified synthetic scheme of tolterodine tartrate**[a]



[a] Reagents and conditions: a) H_2SO_4/120−125 °C. b) Benzyl bromide/K_2CO_3/acetone, methanol/reflux. c) Vitride/THF /25−35 °C. d) *p*-Toluene sufonyl chloride /*N*-ethyldiisopropylamine/dichloromethane/25−35 °C. e) Diisopropylamine/acetonitrile/110−115 °C/12−14 h. f) H_2/Raney Ni/methanol/25−35 °C g) L-(+)-tartaric acid/acetonitrile/methanol.

The reduction was smooth and robust when we employed Vitride in THF at an addition temperature below 40 °C and yielded about 97.8% of alcohol **11** with 99.19% purity by HPLC. The temperature of the Vitride addition was optimized between −30 and +40 °C as it is an exothermic reaction, and addition at below +40 °C is found to be suitable, which is achieved in the plant by controlled addition. This reaction is instantaneous and does not require further maintenance. The byproduct of Vitride, 2-methoxy ethanol, which was formed in the reaction, was completely removed by employing excess water washings in the work-up as it is water-soluble; the absence of this byproduct in the API was confirmed in the organic volatile impurity (OVI) test by GC. Tosylation of alcohol **11** with *p*-toluene sulfonyl chloride in dichloromethane in the presence of *N*-ethyldiisopropylamine as a base afforded the compound **12** in 99% yield with 98.96% purity by HPLC. Condensation of **12** with diisopropylamine in acetonitrile in an autoclave[8] at 110−115 °C under in-built pressure of 2.5−3.0 kg/cm^2 for 10−12 h yielded the product **13** in 95% yield with 95% purity by HPLC. This optimized process enabled us to finish the total reaction in 10−12 h instead of the 4−6 days for completion as mentioned in the original route. During the optimization of this stage, to avoid the pressure reaction, we have explored the reactions with different bases such as potassium carbonate, sodium hydroxide, potassium tertiary butoxide, and sodium carbonate in solvents such as toluene, acetone, 1,4-dioxane, acetonitrile, cyclohexane, DMF, DMSO, and different solvent mixture combinations at their reflux temperature. In all the cases either the reaction did not proceed to completion, or the product is impure. On the other hand, to reduce the time of the reaction further, an experiment was conducted by applying high pressure with nitrogen, wherein the purity of the product was reduced and complete conversion was not achieved. However, the major yield improvement in this stage was achieved during the work-up procedure. Out of several solvents tried for the isolation of **13**, toluene was found to be an apt solvent to enhance the yield to 95% from 75%. As expected, this step was critical with respect to impurities, and two critical impurities of this stage, monomer **14** and dimer **15**, were isolated and characterized and subsequently synthesized as shown in Scheme 3. The formation of impurities **14** and **15** are due to decomposition of the diisopropylamine under the reaction conditions as we are using the pure diisopropylamine with

(8) A 50-L stainless steel autoclave, anchor-type agitator, designed for pressures of 12.0−14.0 kg/cm^2, manufactured by Chemec Equipment Pvt. Ltd., Mumbai, India, was used for the reaction.

Scheme 3. **Synthetic scheme of tolterodine impurities**

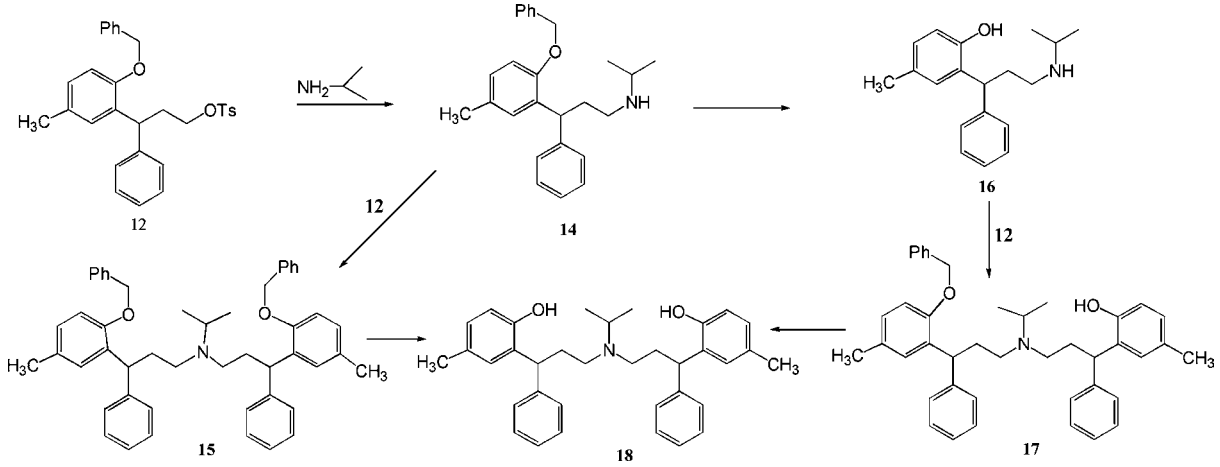


Table 1. **Solubility chart of impurities in various solvents and different pH ranges**

	solvents[a]					pH (acetone)[b]			
cmpd	MeOH	acetone	DCM	ACN	EtOAc	below 1.0	1.0−2.0	2.0−3.0	3.0−4.0
8	++++	+	++	+	+	−	−	−	−
14	++++	++	+++	++++	+	+	+	+	−
15	++++	++	++++	+++	+++	+	+	−	−
16	++++	+++	+++	+++	++	+	+	−	−
17	++++	++++	+++	++	++	+	+	+	−
18	++++	++++	++++	+++	+++	+	+	−	−

[a] Notations used in case of solvents; + = very slightly soluble, ++ = slightly soluble, +++ = sparingly soluble, and ++++ = soluble. [b] Notations used in case of pH: + = soluble, and − = insoluble.

99.77% (by GC) containing 0.01% of isopropylamine in it.[9] Catalytic hydrogenation of **13** using Raney nickel at 25−35 °C for 4−5 h in methanol afforded the desired debenzylated compound **8** in 94% yield with 99% purity by HPLC. The impurities described in the previous step were also sequentially converted to deprotected impurities, viz., **16**, **17**, and **18** (Scheme 3), respectively. Removal of the impurities **14** and **15** could not be achieved efficiently in **13**; however, after deprotection of **13** to its corresponding hydroxyl compound **8**, all the protected and corresponding deprotected impurities were removed efficiently by exploiting solubility differences of their hydrochloride salts.

Hydrochloride salts of compounds **14**, **15**, **16**, **17**, and **18** are highly soluble in acid at a pH range between 1 and 2, whereas **8** is did not. Thus, during the work-up of **8** the pH of the reaction mass was adjusted to between 1 and 2, where all these impurities were washed out in the filtrates, and the thus-obtained tolterodine is substantially free of these impurities. The solubility[10] of the impurities **14**−**18** and **8** in different organic solvents and at different pH ranges in acetone is shown in Table 1.

Further, the racemic tolterodine hydrochloride **8** was hydrolyzed in the presence of base and was subsequently resolved with L-(+)-tartaric acid in the acetonitrile and methanol mixture to get the 100% optically pure tolterodine tartrate (**9**) with 80% yield (with respect to the required isomer) with 99.99% of chemical purity by established and validated HPLC method. Thus, our process produces tolterodine tartrate with overall yield of around 30%. The final process has been validated in the laboratory, and the results of the batches have been reported in Table 2 along with the content of impurities in it.

(9) Alkylamines Chemicals Ltd., Maharashtra, India, supplied diisopropylamine, which is 99.77% pure.

Table 2. **Content of impurities in the tolterodine tartrate (9)**

expt. no	purity by HPLC (**9**) (%)	content of other impurities[a]				
		14	15	16	17	18
01	99.98	ND	ND	ND	ND	ND
02	99.98	ND	ND	0.007	ND	ND
03	99.89	ND	ND	ND	0.006	ND

[a] ND= not detected.

Conclusion

In conclusion, we have provided an improved, cost-effective, and industrially feasible manufacturing process for

(10) The solubility of each compound has been measured in AR&D as per the method of analysis (generally following USP general guidelines for solubility measurement). Solubility has been measured according to the data below in the case of solvents, whereas the solubility of the compounds in case of pH was measured by taking 1 g of each sample in 30 mL of acetone followed by adjusting the pH to the required range. Solubility differences were basically identified by adjusting the pH of the reaction mass (experimental procedure for **8**) to different pH ranges followed by filtration, drying, and HPLC analysis to see the presence of these impurities in the samples at set pH during optimization.

soluble	1 g/30 mL
sparingly soluble	1 g/100 mL
slightly soluble	100 mg/100 mL
very slightly soluble	10 mg/100 mL

tolterodine tartrate that is substantially free from potential impurities and meets the regulatory norms in terms of quality.

Experimental Section

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO, using a Varian Gemini 200 MHz FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The subscript "e" along with multiplicity denotes the merging of the peak with other peaks. The FT-IR spectra were recorded in the solid state as KBr dispersion using Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on HP-5989A LC-MS spectrometer. The CHN analysis was carried out on a Perkin-Elmer model 2400S analyzer. The melting points were determined by using the capillary method on POLMON (model MP-96) melting point apparatus. The solvents and reagents were used without further purification.

Methyl-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropionate (10). A mixture of 6-methyl-4 phenyl-3, 4-dihydrocoumarin (**3**, 7.0 kg, 29.41 mol), benzyl bromide (3.85 L, 32.37 mol), potassium carbonate (5.32 kg, 38.55 mol), acetone (21 L), and methanol (21 L) was heated to reflux temperature for about 3 h. Solvent was distilled off from the reaction mass under reduced pressure, and 70 L of water was added to the crude and stirred for 15 min for dissolution. Reaction mass was extracted with ethyl acetate (35 and 7 L). The combined organic layers were washed with water (2 × 35L), and the solvent was distilled off under reduced pressure. Acetone (35 L) was added to the crude at 50−55 °C, and the solution was stirred at 0−5 °C for about 2 h. The solid was filtered, washed with acetone (7 L), and dried at 50−55 °C for about 2 h under reduced pressure to give compound **10** as a white crystalline powder. Yield: 10.2 kg (96%); mp: 73−75 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.25 (s, 3H), 3.05 (d, J = 3.4, 2H), 3.50 (s, 3H), 4.95 (t_e, 1H), 4.95 (s_e, 2H), 6.60−7.40 (m, Ar−H, 13H); ^{13}C NMR (200 MHz, DMSO): δ 20.2, 38.8, 39.7, 51.1, 69.4, 126.0, 127.5, 128.4, 131.6, 143.1, 153.2, 171.7; MS *m*/*z* 360; Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71; O, 13.32. Found: C, 79.95; H, 6.70; O, 13.31.

3-(2-Benzyloxy-5-methylphenyl)-3-phenylpropanol (11). To a stirred solution of **10** (10.2 kg, 28.33mol) in dry THF (20.5 L) was slowly added Vitride, (10.62 L, 35.37 mol, 65% wt/wt in toluene) at below 40 °C and stirred for about 20−25 min. The reaction mixture was quenched by slowly adding a solution of hydrochloric acid (6 N, 41 L) and extracted with toluene (41 L); the toluene layer was separated, and the aqueous layer was further extracted with toluene (10.2 L). The combined toluene layers were washed with water (51 L), followed by a solution of sodium carbonate (30%, 9.3 L), and finally with water (51 L). The organic layer was distilled off, hexane (41 L) was added to the resultant crude at 40 °C and stirred for 2 h at 40 °C and 1 h at 25−30 °C. The solid obtained was filtered and washed with hexane (10 L), and the solid was dried at 25−30 °C under reduced pressure for 2−3 h to give compound **11** as a crystalline powder. Yield: 9.13 kg (97%); mp: 65−67 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60 (s, 1H), 2.25 (s, 3H), 2.30 (q, J = 10.4, 3.2, 2H), 3.50 (s, 2H), 4.65 (t, J = 16.2, 8.4, 1H), 5.05 (s, 2H), 6.70−7.50 (m, Ar−H, 13H); ^{13}C NMR (200 MHz, DMSO): δ 20.4, 37.7, 39.2, 59.7, 69.4, 127.3, 128.1, 128.6, 132.9, 153.5; MS *m*/*z* 332; Anal. Calcd for $C_{23}H_{24}O_2$: C, 83.10; H, 7.28; O, 9.63. Found: C, 83.08; H, 7.27; O, 9.61

3-(2-Benzyloxy-5-methylphenyl)-3-phenylpropyl-*p*-toluene Sulphonate (12). To a mixture of **11** (9.13 kg, 27.50 mol), dichloromethane (27.4 L), and *N*-ethyl diisopropyl--amine (11.5 L, 66.01 mol) was added a solution of *p*-toluenesulphonyl chloride (6.3 kg, 33.07 mol) in dichloromethane (19 L) slowly, and the contents were stirred at 25−35 °C for about 10−12 h. Hydrochloric acid (1 N, 34.6 L) was added slowly to the above mass and stirred for half an hour before the separation of the organic layer. The organic layer was further washed with water (2 × 35 L) and distilled under reduced pressure to give **12** as syrup, which is directly used in the next step. Yield: 13.28 kg (99%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.15 (s, 3H), 2.30 (m_e, 2H), 2.35 (s_e, 3H), 3.90 (t, J = 9.6, 3.2, 2H), 4.40 (t, J = 16.0, 8.0, 1H), 4.90 (s, 2H), 6.60−7.80 (m, Ar−H, 17H); ^{13}C NMR (200 MHz, DMSO): δ 20.2, 20.8, 33.1, 38.9, 68.9,69.4,127.4, 129.3, 137.2, 143.1, 153.4; MS *m*/*z* 486; Anal. Calcd for $C_{30}H_{30}O_4$ S: C, 74.05; H, 6.21; O, 13.15; S, 6.59. Found: C, 74.02; H, 6.20; O, 13.13; S, 6.56

***N*,*N*-Diisopropyl- 3-(2-benzyloxy-5-methylphenyl)-3-phenylpropylamine (13).** A mixture of **12** (6.0 kg, 12.34 mol), acetonitrile (23 L), and diisopropylamine (6.6 L, 47.18 mol) was heated in an autoclave at 110−115 °C with inbuilt pressure 2.0−3.0 kg/cm^2 for about 12−14 h. The reaction mass was distilled off at 80−85 °C under reduced pressure, and toluene (23 L) was added to the crude. The above organic layer was washed with hydrochloric acid (0.5 N, 14.2 L), then sodium hydroxide solution (2.5%, 9.5 L). followed by water (2 × 23 L). The mixture was then distilled off under reduced pressure to give compound **13** as syrup, which is directly used in the next step. Yield: 4.9 kg (95%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90 (br d, 12H), 2.30 (m_e, 2H), 2.30 (s_e, 3H), 2.98 (t, J = 13.0, 6.8, 2H), 3.10 (m, 2H), 4.40 (t, J = 15.0, 7.6, 1H), 5.00 (s, 2H), 6.70−7.50 (m, Ar−H, 13H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 20.5, 36.7, 41.3, 43.7, 48.4, 69.8, 111.5, 127.1, 128.1, 129.4, 133.4, 144.9, 153.7; MS *m*/*z* 415; Anal. Calcd for $C_{29}H_{37}NO$: C, 83.81; H, 8.97; N, 3.37; O, 3.85. Found: C, 83.80; H, 8.95; N, 3.35; O, 3.83

***N*,*N*-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine Hydrochloride (8).** To the solution of **13** (4.9 kg, 11.80 mol) in methanol (18.8 L) placed in an autoclave was added Raney nickel (0.97 kg) with water (1.67 L) and maintained under hydrogen pressure at 5.0−5.5 kg/cm^2 at 25−35 °C for about 4−5 h. The reaction mass was filtered after cooling to 25−30 °C, and the filter cake was washed with methanol (7.5 L). The pH of the filtrate was adjusted to 1.0−2.0 with concentrated hydrochloric acid (5.2 L) and stirred for 20 min. The solvent was distilled off under reduced pressure, and the obtained crude was crystallized from acetone (18.8 L). The crystalline solid obtained was filtered, washed with chilled acetone (7.5 L), and dried at 60−65 °C for 2−3 h to get the desired compound **8** as a white crystalline powder. Yield: 4.05 kg (94%); mp: 212−216 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10 (br d, 12H), 2.10 (s, 3H), 2.40 (br q, 2H), 2.70 (br t, 2H), 3.25 (m, 2H), 4.30 (t, J = 15.0, 7.6, 1H), 5.30 (s, 1H), 6.40−7.40 (m, Ar−H, 8H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 19.3, 19.7, 20.6,

33.2, 39.4, 42.3, 48.2, 117.8, 125.9, 128.1, 129.0, 144.5, 152.9; MS *m*/*z* 325.

***N*-Isopropyl-3-(2-benzyloxy-5-methylphenyl)-3-phenylpropylamine (14).** The mixture of **12** (60.0 g, 0.123 mol), isopropylamine (53 mL, 0.622 mol), and acetonitrile (300 mL) was stirred at 35−40 °C for 12 h. The reaction mass was distilled off completely, and the obtained residue was crystallized from ethyl acetate (150 mL) to give **14** as a white crystalline powder. Yield: 40.0 g (86%); mp: 137−139 °C: ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (d_e, 6H), 2.18 (s, 3H), 2.51 (q, J = 23.4, 7.6, 2H), 3.18 (t, J = 12.8, 6.4, 2H), 4.11 (m, 1H), 4.38 (t, J = 15.8, 8.0, 1H), 5.00 (s, 2H), 6.70−7.40 (m, Ar−H, 13H), 8.7 (s, 1H); ^{13}C NMR (200 MHz, DMSO): δ 19.1, 20.6, 31.6, 41.4, 44.8, 51.6, 69.8, 116.3, 127.1, 128.7, 128.8, 129.2, 137.2, 144.2, 152.4; MS *m*/*z* 373; Anal. Calcd for $C_{26}H_{31}NO$: C, 83.60; H, 8.37; N, 3.75; O, 4.28. Found: C, 83.58; H, 8.34; N, 3.74; O, 4.26

***N*-Isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine (16).** To a solution of **14** (40.0 g, 0.10 mol) in methanol (200 mL) in an autoclave was added Raney nickel (8.0 g), and the reaction was maintained at 25−30 °C under hydrogen pressure of 3.5 kg/cm^2 for 4−5 h. The reaction mass was filtered through hyflow, the filter cake was washed with 40 mL of methanol, and the filtrates were distilled off completely to give **16** as syrup. Yield: 27.2 g (89%); ^{1}H NMR (200 MHz, DMSO): δ 1.15 (d_e, 6H), 2.18 (s, 3H), 2.5 (br t, 2H), 3.0 (m, 2H), 3.45 (m, 1H), 4.28 (t, J = 15.2, 7.6, 1H), 6.70−7.40 (m, Ar−H, 8H), 8.3 (s, 1H), 9.2 (s, 1H); ^{13}C NMR (200 MHz, DMSO): δ 19.2, 20.6, 31.6, 41.4, 44.8, 51.6, 116.3, 127.1, 128.7, 128.8, 129.2, 130.3, 144.2, 152.4; MS *m*/*z* 283; Anal. Calcd for $C_{19}H_{25}NO$; C, 80.52; H, 8.89; N, 4.94; O, 5.65. Found: C, 80.49; H, 8.87; N, 4.91; O, 5.63.

3-(2-(Benzyloxy)-5-methylphenyl)-*N*-(3-(2-(benzyloxy)-5-methylphenyl)-3-phenylpropyl)-*N*-isopropyl-3-phenylpropan-1-amine (15). A mixture of intermediate **12** (27.0 g, 0.055 mol) and **14** (20.8 g, 0.055 mol) in DMSO (135 mL) was heated at 60−70 °C for 18 h. The reaction mass was cooled to 25−35 °C, decomposed with water (135 mL), and extracted with toluene (135 mL). The toluene layer was washed with hydrochloric acid (1 N, 150 mL), then sodium hydroxide solution (10%, 54 mL), followed by water (135 mL). The organic layer was distilled off completely to obtain **15** as syrup. Yield: 29 g (75%); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97 (d, J = 6.8, 3H), 1.10 (d, J = 7.4, 3H), 2.10 (s, 6H), 2.40 (t_e, 4H), 2.70 (m_e, 4H), 2.98 (m_e, 2H), 3.50 (m_e, 1H), 4.39 (t, J = 15.0, 8.0, 2H), 5.00 (s, 2H), 6.60−7.10 (m, Ar−H, 26 H); ^{13}C NMR (200 MHz, DMSO): δ 20.5, 36.7, 41.3, 43.7, 48.4, 69.8, 111.5, 128.1, 129.4, 133.4, 144.9, 153.7; MS *m*/*z* 687; Anal. Calcd for $C_{49}H_{53}NO_2$: C, 85.55; H, 7.77; N, 2.04; O, 4.65. Found: C, 85.52; H, 7.75; N, 2.01; O, 4.63.

***N*-(3-(2-(Benzyloxy)-5-methylphenyl)-3-phenylpropyl)-*N*-isopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropan-1-amine (17).** A mixture of **16** (15.8 g, 0.055 mol (135 mL) and the intermediate **(12)** (27.0 g, 0.055 mol) in DMF was heated in an autoclave at 60−70 °C under 3.0 kg/cm^2 of nitrogen pressure for 16 h. The reaction mass was cooled to 25−35 °C, decomposed with water (135 mL), and extracted with toluene (135 mL). The toluene layer was washed with hydrochloric acid (1 N, 150 mL), then sodium hydroxide solution (10%, 54 mL) followed by water (135 mL). The organic layer was distilled off completely to obtain crude **17** as syrup. Yield: 27 g (81.40%); ^{1}H NMR (200 MHz, DMSO): δ 1.10 (d, J = 5.6, 3H), 1.15 (d, J = 6.2,3H), 2.10 (s, 6H), 2.30 (t, J = 3.2, 3.4, 4H), 2.80 (br q, 4H), 3.55 (m, 1H), 4.30 (br t, 2H), 5.05 (s, 2H), 6.60−7.10 (m, Ar−H, 21H), 7.40 (s, 1H); ^{13}C NMR (200 MHz, DMSO): δ 16.3, 20.2, 28.5, 40.7, 47.9, 53.7, 69.8,127.6, 128.1, 143,152; MS *m*/*z* 597; Anal. Calcd for $C_{42}H_{47}NO_2$: C, 84.38; H, 7.92; N, 2.34; O, 5.35. Found: C, 84.36; H, 7.90; N, 2.31; O, 5.32

Bis{4-methyl-2-(3-phenylpropyl)phenol} (18). To a mixture of **17** (25.0 g, 0.041 mol) in methanol (125 mL) was added 5.0 g of Raney nickel with the reaction mass maintained under 3.0 kg/cm^2 of hydrogen pressure at 25−35 °C for 5 h. Reaction mass was filtered over hyflow, the filter cake was washed with methanol (25 mL), and the filtrate was evaporated completely under vacuum to obtain the residue, which was crystallized from hexanes (125 mL) to give **18** as a crystalline solid. Yield: 15 g (70.65%); mp: 152−155 °C; ^{1}H NMR (200 MHz, DMSO): δ 1.10 (d, J = 6.8, 3H), 1.20 (d, J = 6.7, 3H), 2.05 (s, 6H), 2.30 (br t, 4H), 2.85 (br q, 4H), 3.35 (m, 1H), 4.30 (t, J = 15.0, 8.0, 2H), 6.60−7.10 (m, Ar−H, 16 H), 7.40 (s, 2H); ^{13}C NMR (200 MHz, DMSO): δ 16.3, 20.2, 28.5, 40.7, 47.9, 53.7, 115.1, 127.6, 128.1, 143.9, 152.3; MS *m*/*z* 507; Anal. Calcd for $C_{35}H_{41}NO_2$: C, 82.80; H, 8.14; N, 2.76; O, 6.30. Found: C, 82.78; H, 8.11; N, 2.74; O, 6.28.

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