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Chemoenzymatic synthesis of (*R*)- and (*S*)-tembamide, aegeline and denopamine by a one-pot lipase resolution protocol

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Abstract—An efficient synthesis of optically active β-azido alcohols from their ketoazides by a one-pot reduction and an in situ lipase resolution protocol is described. The synthetic utility of this procedure has been illustrated by its application in the practical synthesis of both enantiomers of the natural hydroxyamides, tembamide, aegeline and the cardiac drug denopamine, with high enantioselectivities.

1. Introduction

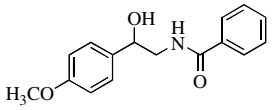
The importance of enantiopure azido alcohols lies in their utility as precursors of nonracemic aziridines[1] and vicinal amino alcohols.[2] The latter compounds are not only important structural elements in pharmaceuticals such as α- or β-adrenergic blockers[3] but also can be widely used as versatile chiral building blocks and chiral catalysts[4] in organic synthesis. In spite of recent advances in drug specificity, many chiral drugs are marketed as racemates. Thus, denopamine[5] [(±)-α,α-(3,4-dimethoxyphenyl ethyl aminomethyl)-4-hydroxy benzyl alcohol] **3** is one of the important β-adrenoceptor agonist marketed as racemates of which the (*R*)-enantiomer is the active component.

In most of the aryl ethanolamine drugs, the biological activity resides only in the (*R*)-enantiomer. The aim of the present study is to demonstrate that the optically active β-azido alcohols can be transformed into chiral natural and non-natural products of high enantiopurity. The synthetic targets are the hydroxyamides, tembamide **1**, aegeline **2** and denopamine **3**.

2. Result and discussion

2.1. Tembamide and aegeline

(−)-Tembamide **1** and (−)-aegeline **2** are naturally occurring hydroxyamides isolated from various members of the Rutaceae family.[6] They have been used in traditional Indian medicines and have been shown to have hypoglycemic activity.[7] These hydroxyamides possess a stereogenic centre and have been isolated as total or partial racemates.[8] One of the aims of this investigation is to develop a one-pot chemoenzymatic synthesis of both enantiomers of tembamide **1** and aegeline **2**. To date only a few methods for the preparation of these compounds have been presented, involving resolution of racemic mixtures[9] and multistep synthesis using optically active cyanohydrins as starting materials.[10] Recently enzymatic[11] as well as chemical asymmetric reduction[12] of α-azido arylketones have been reported for the synthesis of **1** and **2**. In continuation of our one-pot synthesis and resolution of various chiral secondary alcohols,[13] we have developed a one-pot reduction and in situ resolution protocol for the synthesis of



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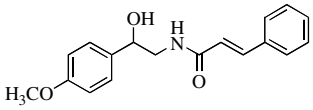

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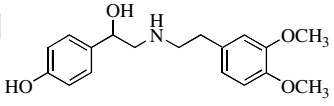

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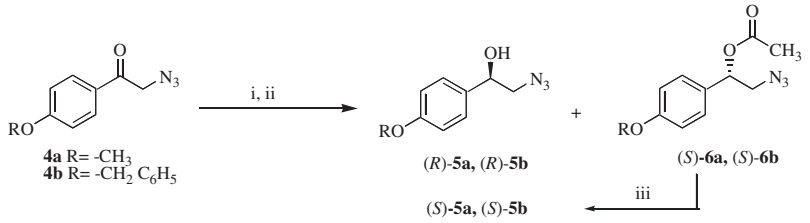


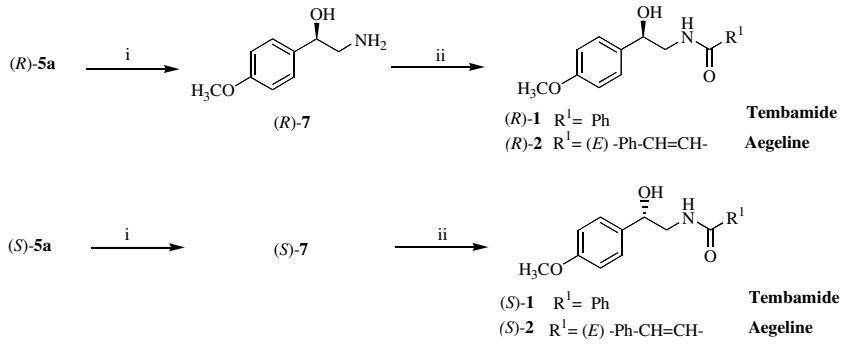
Scheme 1. Reagents and conditions: (i) $NaBH_4$, activated alumina, diisopropyl ether; (ii) lipase PS-C, isopropenyl acetate; (iii) anhydrous K_2CO_3, MeOH.

enantiopure β-azido alcohols.[14] The results encouraged us to extend the application of the method to the synthesis of chiral β-azido alcohol precursors of tembamide, aegeline and denopamine. Therefore, the key step in the synthesis is the one-pot reduction of azidoketone **4a** by employing $NaBH_4$ and active neutral aluminum oxide in diisopropyl ether. The racemic azido alcohol **5a** has been resolved in situ by lipase resolution with *Pseudomonas cepacia* lipase immobilized on ceramic particles (PS-C) and isopropenyl acetate as an acyl donor in 22 h at 40 °C (Scheme 1). The azido alcohol (*R*)-**5a** was obtained in 98% ee whereas (*S*)-**5a** has been obtained in 96% ee by hydrolysis of (*S*)-**6a** with anhydrous potassium carbonate in methanol.

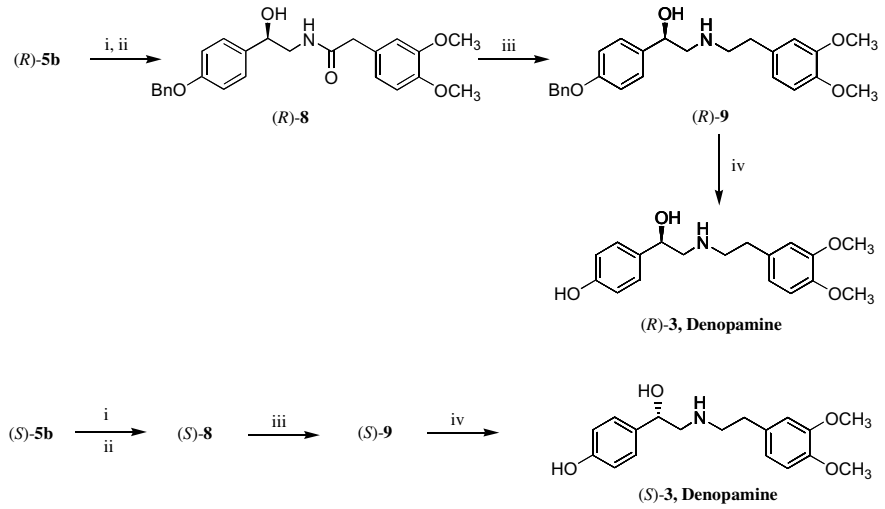
The enantiomeric excesses of the azido alcohols (*R*)-**5a** and (*S*)-**5a** were determined by HPLC analysis employing chiral column (Chiralcel AD-H) with 5:95; isopropanol/hexane mobile phase. Both (*R*)- and (*S*)-tembamide and aegeline have been synthesized from the corresponding azido alcohol (*R*)- and (*S*)-**5a** by sequential transformations as described in Scheme 2. The reduction of azidoalcohol **5a** with 10% Pd/C gives amino alcohol **7**. Condensation of amine **7** with corresponding acid chlorides gives tembamide and aegeline in quantitative yields. The present work represents a chemoenzymatic synthesis of (*R*)- and (*S*)-tembamide and aegeline in three steps from azidoketone **4a** in high enantioselectivity.

2.2. Denopamine

(−)-Denopamine **3** is a relatively new β_1-receptor agonist,[15] which is effective in the treatment of congestive heart failure.[16] It can be administered orally and has reduced toxicity, which are important advantages over many other drugs possessing positive inotropic activity. Prior to 1991 only a few methods had been reported for the enantioselective synthesis of denopamine with maximum enantioselectivity of 60%. Corey et al. have synthesized (*R*)-**3** in 97% ee using the CBS-reduction method. Recently, (*R*)-**3** has been synthesized through reductive biotransformations.[13,17,18] Denopamine (*R*)-**3** have also been synthesized from an optically active cyanohydrin intermediate.[2a,19] The reported methods however suffer from drawbacks such as high cost involvement, long reaction times and poor enantioselectivity. Herein we report the synthesis of both (*R*)- and (*S*)-enantiomers of denopamine **3** via optically active β-azido alcohols obtained by the one-pot reduction and in situ lipase resolution protocol. As described in Scheme 1 the azidoketone **4b** gives (*R*)-**5b** and (*S*)-**6b** under the same conditions described for **4a**. The acetate (*S*)-**6b** on hydrolysis with anhydrous potassium carbonate in methanol gives corresponding azido alcohol (*S*)-**5b**. The azido alcohols (*R*)-**5b** and (*S*)-**5b** have been obtained in >99% ee and in 80% ee, respectively, at 40 °C in 24 h. The enantiopurities of these products were determined by chiral HPLC analysis employing chiral column (Chiralcel OD) with a 5:95; isopropanol/hexane mobile phase. The reduction of azido alcohol (*R*)-**5b** was carried out under mild conditions with triphenylphosphine and the resulted amine on coupling with 3,4-dimethoxyphenylacetylchloride gives hydroxyamide (*R*)-**8**. The amide group of (*R*)-**8** has been reduced with BH_3–DMS to give benzylated denopamine (*R*)-**9**. Finally, the benzyl group deprotection with 10% Pd/C results in denopamine (*R*)-**3**. Denopamine (*S*)-**3** has also been synthesized following the same reaction sequence from resolved azido alcohol (*S*)-**5b** (Scheme 3).



Scheme 2. Reagents and conditions: (i) 10% Pd/C, H_2, MeOH, rt; (ii) R^1COCl, Et_3N, CH_2Cl_2, 0 °C.



Scheme 3. Reagents and conditions: (i) PPh_3, THF/H_2O (1:1), rt; (ii) 3,4-dimethoxyphenylacetylchloride, dry THF; (iii) BH_3–$(CH_3)_2S$, THF, rt; (iv) 10% Pd/C, H_2, MeOH, rt.

3. Conclusion

In summary we have developed a simple and highly efficient synthetic method for optically active β-azido alcohols, which have been utilized towards the preparation of biologically active amino alcohols such as tembamide **1**, aegeline **2** and denopamine **3**. Reduction of ketoazides followed by in situ lipase resolution with *Pseudomonas cepacia* lipase immobilized on ceramic particles (PS-C) gives the corresponding β-azido alcohols in high enantioselectivity. We have described an alternative chemoenzymatic approach for the synthesis of denopamine and hydroxyamides, which is more efficient than the methods previously reported.

4. Experimental

4.1. Material and methods

Enzymatic reactions were carried out on a 'Lab-line environ-shaker' at 150 rpm. Infrared spectra of neat samples are reported in wave numbers (cm^{-1}). ^1H NMR was recorded as solutions in $CDCl_3$ and chemical shifts are reported in parts per million (ppm, δ) on a 200 MHz instrument. Coupling constants are reported in hertz (Hz). LSIMS mass spectra were recorded on Autospec M. with 7 kV acceleration voltage and 25 kV gun voltage. HPLC analysis was performed on an instrument that consisted of a Shimadzu LC-10AT system controller, SPD-10A fixed wavelength UV monitor as detector. Optical rotations were recorded on SEPA-300 Horiba high sensitive polarimeter, fitted with a sodium lamp of wavelength 589 nm.

4.2. Chemicals and enzymes

Sodium borohydride, neutral alumina and solvents were obtained commercially and used without purification. Activated neutral alumina was prepared by homogeneous addition of 1.1 mL water to 10 g of neutral alumina (preheated in oven at 200 °C). *P. cepacia* lipase immobilized on ceramic particles (PS-C) was purchased from Amano (Nagoya, Japan).

4.3. General procedure for the one-pot synthesis of enantiopure azido alcohols 5a,b and acetates 6a,b

To a solution of β-azidoketone (1 mmol) in diisopropyl ether (10 mL) was added activated alumina (1.0 g) and $NaBH_4$ (2 mmol). The suspension was shaken at 150 rpm at 40 °C for 3–4 h and monitored by TLC for the complete reduction to racemic azido alcohol. Then lipase PS-C (1 equiv w/w), isopropenyl acetate (6 mmol) were added to the reaction mixture and monitored on chiral HPLC analysis until it reaches to 50% conversion. The reaction was filtered and the filtrate was washed with water, followed by brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by silica gel column chromatography. The enantiopure products **5** and **6** were analyzed by chiral HPLC and compared with corresponding racemic products.

4.4. Preparation of (*R*)- and (*S*)-tembamide 1

4.4.1. (*S*)-(+)-2-Azido-1-(4-methoxyphenyl)-1-ethyl acetate 6a. One-pot reduction of **4a** and in situ lipase resolution as described above gave acetate **6a**. Yield: 49%; 96% ee [determined by the HPLC analysis using Chiralcel AD-H column (hexane/isopropanol, 95:5) with 0.5 mL/min flow rate (t_R = 15.29 min)]; $[\alpha]_D^{25} = +123.7$ (*c* 1, $CHCl_3$); IR (neat): 2095, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.15 (3H, s), 3.32–3.39 (1H, dd, J = 13.21, 4.15 Hz), 3.55–3.63 (1H, dd, J = 13.21, 8.30 Hz), 3.8 (3H, s), 5.80–5.85 (1H, dd, J = 8.30, 4.15 Hz), 6.85 (2H, d, J = 8.68 Hz), 7.24 (2H, d, J = 8.68 Hz); LSIMS (*m*/*z*): 235 (M^+); Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.11; H, 5.49; N, 17.73%.

4.4.2. (*R*)-(−)-2-Azido-1-(4-methoxyphenyl)-1-ethanol 5a. Prepared from **4a** by above general procedure. Yield: 47%; 98% ee [determined by the HPLC analysis using Chiralcel AD-H column (hexane/isopropanol, 95:5) with 0.5 mL/min flow rate (t_R = 42.32 min)]; $[\alpha]_D^{25} = -116.9$ (*c* 1.2, $CHCl_3$), {lit[12] $[\alpha]_D^{24} = -117.4$ (*c* 1.3, $CHCl_3$), ee 99%}; IR (neat): 3449, 2930, 2105 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.20 (1H, d, *J* = 2.97 Hz), 3.29–3.5 (2H, m), 3.8 (3H, m), 4.72–4.85 (1H, m), 6.85 (2H, d, *J* = 8.17 Hz), 7.25 (2H, d, *J* = 8.17 Hz); Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.89; H, 5.63; N, 21.69%.

4.4.3. (*S*)-(+)-2-Azido-1-(4-methoxyphenyl)-1-ethanol 5a. Prepared from (*S*)-**6a** by deacetylation procedure using anhydrous K_2CO_3 in methanol at room temperature for 2 h to give (*S*)-**5a**. Yield: 100%, 96% ee [determined by the HPLC analysis using Chiralcel AD-H column (hexane/isopropanol, 95:5) with 0.5 mL/min flow rate (t_R = 41.48 min)]; $[\alpha]_D^{25} = +114.3$ (*c* 1.3, $CHCl_3$).

4.4.4. (*R*)-(−)-2-Amino-1-(4-methoxyphenyl)-1-ethanol 7. The azido alcohol (*R*)-**5a** (0.579 g, 3 mmol) was dissolved in methanol (10 mL) and stirred under a hydrogen atmosphere (1 atm) in the presence of 10% Pd/C (50 mg) at room temperature for 3 h. The catalyst was removed by filtration on a Celite pad and the filtrate was concentrated to give 0.5 g amino alcohol **7**. Yield: 99%; $[\alpha]_D^{25} = -38.2$ (*c* 1, EtOH) {lit.[12] $[\alpha]_D^{20}$ −39.9 (*c* 1.03, EtOH)}; IR (neat): 3348, 3078, 1615, 1509 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.68–2.10 (3H, br s), 2.70–3.0 (2H, m), 3.82 (3H, s), 4.60 (1H, br s), 6.89 (2H, d, *J* = 8.68 Hz), 7.28 (2H, d, *J* = 8.68 Hz); LSIMS (*m*/*z*): 137 (M^+−30); Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.59; H, 7.78; N, 8.35%.

4.4.5. (*S*)-(+)-2-Amino-1-(4-methoxyphenyl)-1-ethanol 7. Prepared from azido alcohol (*S*)-**5a** by the same procedure described for (*R*)-**7**. Yield: 99%; $[\alpha]_D^{25} = -37.8$ (*c* 1.1, EtOH).

4.4.6. (*R*)-(−)-Tembamide 1. To a solution of amino alcohol (*R*)-**7** (0.5 g, 3 mmol) in dry CH_2Cl_2 (10 mL) in the presence of Et_3N (0.42 mL, 4 mmol) was added benzoyl chloride (0.38 mL, 3.3 mmol) dropwise at 0 °C and the mixture was stirred at the same temperature for 2 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was separated and washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel to give pure 0.73 g of (*R*)-**1**. Yield: 90%; White crystalline solid; mp 150–151 °C (lit.[11] 154–155 °C); $[\alpha]_D^{25} = -58.7$ (*c* 0.6, $CHCl_3$) {lit.[7a] $[\alpha]_D^{24} = -59.8$ (*c* 0.4, $CHCl_3$)}; IR (neat): 3498, 3390, 1632, 1545, 1243 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.42–3.6 (1H, m), 3.8 (3H, s), 3.81–3.95 (1H, m), 4.9 (1H, dd, *J* = 8.17, 2.97 Hz), 6.6 (1H, m), 6.9 (2H, d, *J* = 8.17 Hz), 7.32 (2H, d, *J* = 8.92 Hz), 7.44 (3H, m), 7.75 (2H, d, *J* = 8.92 Hz); ^{13}C NMR (50 MHz, DMSO-d_6) 47.7, 55.0, 70.8, 113.4, 127.22, 127.25, 128.2, 131.1, 134.6, 135.8, 158.4, 166.5; LSIMS (*m*/*z*): 272 (M^++1); Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.79; H, 6.28; N, 5.09%.

4.4.7. (*S*)-(+)-Tembamide 1. Prepared from the amino alcohol (*S*)-**7** by the same procedure described for (*R*)-**1** to give 0.7 g of (*S*)-**1** in pure form. Yield: 87%; White crystalline solid; mp 150–151 °C (lit.[11] 154–155 °C); $[\alpha]_D^{25} = +56.9$ (*c* 0.54, $CHCl_3$).

4.5. Preparation of (*R*)- and (*S*)-aegeline 2

4.5.1. (*R*)-(−)-Aegeline 2. Acylation of (*R*)-**7** with (*E*)-cinnamoyl chloride under similar above mentioned conditions gave 0.75 g of aegeline (*R*)-**2**. Yield: 85%; White crystalline solid; mp 194–195 °C (lit.[11] 196–197 °C); $[\alpha]_D^{25} = -35.9$ (*c* 0.48, $CHCl_3$) {lit.[7a] $[\alpha]_D^{24} = -35.6$ (*c* 0.4, $CHCl_3$)}; IR (neat): 3460, 3340, 1630, 1093 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.17–3.25 (1H, m), 3.36–3.43 (1H, m), 3.72 (3H, s), 4.6 (1H, m), 5.44 (1H, d, *J* = 4.40 Hz), 6.72 (1H, d, *J* = 15.74 Hz), 6.89 (2H, d, *J* = 8.18 Hz), 7.26 (2H, d, *J* = 8.18 Hz), 7.33–7.43 (3H, m), 7.54 (2H, d, *J* = 6.92 Hz), 8.14 (1H, m); ^{13}C NMR (50 MHz, DMSO-d_6) 46.9, 54.9, 70.9, 113.3, 122.3, 127.0, 127.3, 128.7, 129.2, 134.8, 135.6, 138.4, 158.2, 165.0; LSIMS (*m*/*z*): 298 (M^++1); Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.68; H, 6.38, N, 4.66%.

4.5.2. (*S*)-(+)-Aegeline 2. Prepared from amino alcohol (*S*)-**7** under above mentioned conditions to give 0.69 g of (*S*)-**2**. Yield: 78%; White crystalline solid; mp 194–195 °C (lit.[11] 196–197 °C); $[\alpha]_D^{25} = +34.1$ (*c* 0.4, $CHCl_3$).

4.6. Preparation of (*R*)- and (*S*)-denopamine 3

4.6.1. (*S*)-(+)-2-Azido-1-(4-benzyloxyphenyl) ethyl acetate 6b. Prepared by using the general procedure of one-pot reduction of **4b** and in situ lipase resolution to give acetate (*S*)-**6b**. Yield: 49%; 80% ee [determined by the HPLC analysis using Chiralcel OD column (hexane/isopropanol, 95:5) with 0.5 mL/min flow rate (t_R = 25.56 min)]; $[\alpha]_D^{25} = +80.2$ (*c* 0.9, $CHCl_3$); IR (neat): 2120, 1740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.12 (3H, s), 3.31–3.43 (1H, dd, *J* = 12.63, 3.71 Hz), 3.54–3.68 (1H, dd, *J* = 12.63, 8.17 Hz), 5.06 (2H, m), 5.8–5.89 (1H, dd, *J* = 8.17, 3.71 Hz), 6.93 (2H, d, *J* = 8.92 Hz) 7.26–7.44 (7H, m); LSIMS (*m*/*z*): 255 (M^+−56); Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50, N, 13.50. Found: C, 65.49; H, 5.48; N, 13.46%.

4.6.2. (*R*)-(−)-2-Azido-1-(4-benzoyloxyphenyl)-1-ethanol 5b. Prepared by using the general procedure of one-pot reduction of **4b** and in situ lipase resolution to give azido alcohol (*R*)-**5b**. Yield: 46%; >99% ee [determined by the HPLC analysis using Chiralcel OD column (hexane/isopropanol, 95:5) with 0.5 mL/min flow rate (t_R = 61.57 min)]; $[\alpha]_D^{25} = -72.5$ (*c* 1.3, $CHCl_3$), {lit.[12] $[\alpha]_D^{20} = -72.2$ (*c* 1.1, $CHCl_3$), ee 99%}; IR (neat): 3345, 3142, 2890 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.42–3.52 (2H, m), 4.81 (1H, m) 5.05 (2H, s), 6.95 (2H, d, *J* = 8.78 Hz), 7.25–7.45 (7H, m); LSIMS (*m*/*z*): 213 (M^+−56); Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.79; H, 5.56; N, 15.56%.

4.6.3. (*S*)-(+)-2-Azido-1-(4-benzyloxyphenyl)-1-ethanol 5b. Prepared from **6b** by the deacetylation procedure using anhydrous K_2CO_3 in MeOH at room temperature for 2 h to give **5b**. Yield: 98%; 80% ee [determined by the HPLC analysis using Chiralcel OD column (hexane/isopropanol, 95:5) with 0.5 mL/min flow rate (t_R = 68.67 min)]; $[\alpha]_D^{25} = +69.4$ (*c* 0.9, $CHCl_3$).

4.6.4. Preparation of hydroxyamide (*R*)-8. The azido alcohol (*R*)-**5b** (0.807 g, 3 mmol) was dissolved in THF/H_2O (10:10 mL) and added triphenylphosphine (0.917 g, 3.5 mmol) at room temperature. The resulting mixture was evaporated to remove THF and the residue was extracted with ethyl acetate. The organic layer was separated and washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give crude amino alcohol, which was dissolved in 10 mL of dry THF and Et_3N (0.487 mL, 3.5 mmol) and was added dropwise to the solution of 3,4-dimethoxyphenacetyl chloride[21] in dry THF. The resulting solution was stirred at −78 °C for 30 min and it was allowed to warm to room temperature. After 3 h the reaction mixture was quenched with saturated solution of NH_4Cl and extracted with ethyl acetate (2 × 10 mL). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on silica gel to give 0.985 g of (*R*)-**8** in pure form. Yield: 78%; $[\alpha]_D^{25} = -29.8$ (*c* 1.1, $CHCl_3$); IR (KBr): 3475, 3362, 1639 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.06–3.40 (2H, m), 3.5–3.64 (2H, m) 3.86 (3H, s), 3.89 (3H, s), 4.70–4.77 (1H, m) 5.0 (2H, s) 6.74–6.85 (2H, m), 6.92 (2H, d, J = 8.68), 7.19 (2H, d, J = 8.68 Hz), 7.32–7.45 (6H, m); LSIMS (*m*/*z*): 421 (M^+); Anal. Calcd for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.15; H, 6.39; N, 3.25%.

4.6.5. Preparation of hydroxyamide (*S*)-8. Prepared from the azido alcohol (*S*)-**5b** by the above mentioned conditions to give 0.871 g of (*S*)-**8** in pure form. Yield: 69%; $[\alpha]_D^{25} = +25.6$ (*c* 1.1, $CHCl_3$).

4.6.6. Benzylated denopamine (*R*)-9. To a solution of hydroxyamide (*R*)-**8** (0.9 g, 2.13 mmol) in dry THF (10 mL) a solution of BH_3–DMS (2.43 mL, 2.5 mmol) was added. The resulting mixture was stirred at room temperature for 2 h. The reaction mass was quenched with methanol, upon solvent evaporation to give 0.849 g of (*R*)-**9** in pure form. Yield: 98%; $[\alpha]_D^{25} = -34.8$ (*c* 1.2, $CHCl_3$), {lit.[18] $[\alpha]_D^{20} = -34.3$ (*c* 1.0, $CHCl_3$)}; IR (KBr): 3275, 2920, 1600, 1450 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.70–3.10 (6H, m), 3.74 (3H, s), 3.77 (3H, s), 4.77 (1H, m), 4.94 (2H, s), 6.66 (2H, d, J = 5.12 Hz), 6.83 (2H, d, J = 8.78), 7.1–7.38 (8H, m); LSIMS (*m*/*z*): 408 (M^++1); Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17; N, 3.44. Found: C, 73.57; H, 7.01; N, 3.35%.

4.6.7. Benzylated denopamine (*S*)-9. Prepared from hydroxyamide (*S*)-**8** by above procedure to give 0.85 g of (*S*)-**9**. Yield: 94%; $[\alpha]_D^{25} = +30.4$ (*c* 0.8, $CHCl_3$).

4.6.8. Denopamine (*R*)-3. Benzylated denopamine (*R*)-**9** (0.83 g, 2.07 mmol) was dissolved in MeOH (10 mL) and stirred under hydrogen atmosphere (1 atm) in the presence of 10% Pd/C (80 mg) at room temperature for 6 h. The catalyst was removed by filtration on a Celite pad and the filtrate was concentrated and recrystallized from ethyl acetate/hexane to give 0.661 g of denopamine (*R*)-**3** in pure form. Yield: 96%; White crystalline solid; mp 160–161 °C (lit.[11] 164–165 °C) $[\alpha]_D^{25} = -27.9$ (*c* 1, MeOH), {lit.[20] $[\alpha]_D^{24} = -27.5$ (*c* 0.95, MeOH)} IR (neat): 2935, 1620, 1583 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.02–3.36 (6H, m), 3.79 (3H, s), 3.81 (3H, s), 4.53 (1H, m), 5.16 (1H, m), 6.68–6.88 (5H, m), 7.21 (2H, d, J = 8.78 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 34.88, 50.90, 52.75, 56.09, 72.48, 111.28, 114.43, 119.85, 126.96, 132.08, 134.29, 147.85, 149.18, 158.40, 159.31; LSIMS (*m*/*z*): 318 (M^++1); Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.08; H, 7.23; N, 4.39%.

4.6.9. Denopamine (*S*)-3. Prepared from (*S*)-**9** under similar above mentioned conditions to give 0.647 g of denopamine (*S*)-**3**. Yield: 98%; White crystalline solid; mp 160–161 °C (lit.[11] 164–165 °C) $[\alpha]_D^{25} = +25.4$ (*c* 0.8, MeOH).

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