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Asymmetric transfer hydrogenation of 2-tosyloxy-1-(4-hydroxyphenyl)ethanone derivatives: synthesis of (*R*)-tembamide, (*R*)-aegeline, (*R*)-octopamine, and (*R*)-denopamine

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Abstract—Catalytic transfer hydrogenation of 2-tosyloxy-1-(4-hydroxyphenyl)ethanone derivatives leads to efficient synthesis of β-adrenergic agonists, (*R*)-tembamide, (*R*)-aegeline, (*R*)-octopamine, and (*R*)-denopamine.

1. Introduction

The 1,2-aminoalcohol functionality is a rich resource in organic and medicinal chemistry.[1] The functional group is often found not only in the structural unit of many building blocks, chiral auxiliaries, and ligands in organic transformation, but also in the structural motif of many biologically active compounds. In particular, optically active 2-amino-1-arylethanols are of great importance as β-adrenergic agonists in the therapy of asthma, bronchitis, and congestive heart failure.[2] Even though many β-agonists, such as tembamide **1**, aegeline **2**, octopamine **3**, and denopamine **4**, as shown in Figure 1, are currently available as racemates, recent studies have demonstrated that the pharmacological efficacy and drug specificity resides mainly in the (*R*)-enantiomers.

Much attention has been paid to the enantioselective synthesis of β-adrenergic agonists under catalytic enantioselective synthesis, classical/enzymatic resolution and biotransformative pathway. The oxazaborolidine-catalyzed reduction represents a reliable and industrially popular choice for the enantioselective reduction of ketones with its versatility and high enantioselectivity. Indeed, this

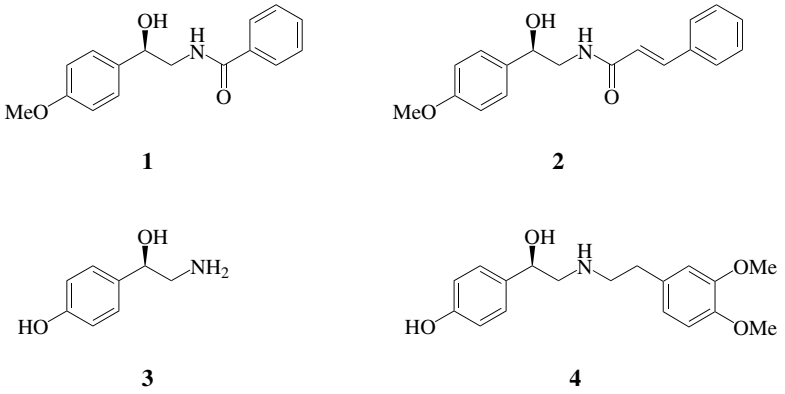

Figure 1. Single enantiomers of β-adrenergic agonists.

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approach have been intensively applied to the synthesis of many aminoalcohols via the utilization of common precursors, such as α-chloro, -bromo, and -tosyloxyacetophenones.[3] Recently, the β-agonists have been prepared through microbial reduction of α-azido and -bromoketones[4] or lipase-mediated resolution of α-azidoalcohols.[5] It has been also noted that enantiomerically enriched cyanohydrin or nitroaldol products lead to the synthesis of the β-agonists from the corresponding benzaldehydes.[6] Interestingly, most of the reported methods involve a unique feature, such as an easy access to versatile synthetic intermediates, thus securing their wide application to the synthesis of aminoalcohols.

Asymmetric transfer hydrogenation has broadened its application to the enantioselective hydrogenation of unsaturated carbonyl and imine groups.[7] The asymmetric transfer hydrogenation offers operational simplicity, since the reaction does not involve molecular hydrogen and is insensitive to air oxidation. Generally, catalysts consist of bidentate ligands based on 1,2-aminoalcohols or monosulfonylated diamines, bound to ruthenium, iridium or rhodium. It has been proven that (1*S*,2*S*)- or (1*R*,2*R*)-*N*-(*p*-toluenesulfony)-1,2-diphenylethylenediamine (TsDPEN) is an excellent ligand for the catalytic transfer hydrogenation of aryl ketones, where the reaction can be routinely carried out under azeotopic mixtures of formic acid/triethylamine as hydrogen donors. A wide range of α-functionalized aromatic ketones were subjected to transfer hydrogenation producing enantiopure alcohols for establishing chirality within target molecules.[8] It shows that the Rh(III) catalysts are preferable, notably in the reduction of α-chloroketones. The α-sulfonyloxyketone is also particularly interesting as a versatile intermediate for the preparation of a large group of anti-depressants and α- and β-adrenergic drugs,[9] however, to date, it has not found much attention in asymmetric transfer hydrogenation.[10] Herein, we report a catalytic transfer hydrogenation of 2-tosyloxy-1-(4-hydroxyphenyl)ethanone derivatives leading to efficient and practical synthesis of β-adrenergic agonists, (*R*)-tembamide, (*R*)-aegeline, (*R*)-octopamine, and (*R*)-denopamine.

2. Results and discussion

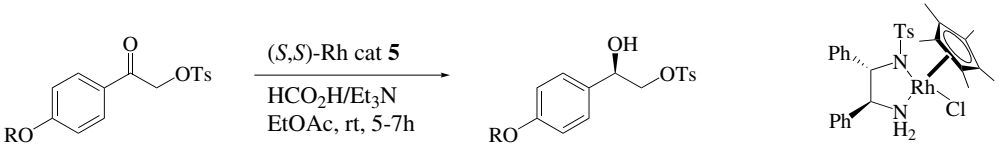
2.1. Asymmetric transfer hydrogenation of 2-tosyloxy-1-(4-hydroxyphenyl)ethanone derivatives

The 2-tosyloxyacetophenones **6a** and **6b** were prepared by tosyloxylation of aryl methyl ketones with [hydroxy(tosyloxy)iodo]benzene[11] in refluxing acetonitrile. The well-defined (*S*,*S*)-Rh catalyst **5** [(*S*,*S*)-TsDPEN–RhClCp*, where $Cp^* =$ pentamethylcyclopentadienyl][12] also effectively performed in asymmetric transfer hydrogenation of tosyloxyketones **6a** and **6b** (substrate/catalyst ratio = 1000) with azeotopic mixtures of formic acid/triethylamine (molar ratio = 5:2)[13] in ethyl acetate to produce (*R*)-1-aryl-2-tosyloxyethanols **7a** {$[\alpha]_D^{25} = -50.7$ (*c* 0.79, $CHCl_3$); lit.[10b] $[\alpha]_D^{20} = -18$ (*c* 0.74, $CHCl_3$), 15% ee} and **7b** {$[\alpha]_D^{25} = -42.5$ (*c* 0.79, $CHCl_3$); lit.[9f] $[\alpha]_D^{20} = -41.9$ (*c* 1.08, $CHCl_3$)}, in 92% and 87% yield with 94% and 95% ee, respectively. The ee values were similar to those reported for α-chloroketones,[8b] and thus the represented α-tosyloxyketones are also good substrates for transfer hydrogenation, as shown in Scheme 1. However, this observation was in contrast to the previous report, presumably, an in situ preparation of the catalyst in a neat formic acid/triethylamine media and the simultaneous contact with substrate may deteriorate the catalytic activity.[10]

The absolute configuration was determined by comparing the sign of the specific rotation with the literature data, the ee values were measured by chiral HPLC analysis using Daicel Chiralcel OD-H chiral column. Racemic alcohols (±)-**7** were prepared by sodium borohydride reduction of **6** in THF, and used as standards for ee determination.

2.2. (*R*)-Tembamide and (*R*)-aegeline

With (*R*)-1-aryl-2-tosyloxyethanols **7a** and **7b** in hand, we were able to access aminoethanols containing the 4′-hydroxylphenyl subunit, as shown in Figure 1. (*R*)-Tembamide and (*R*)-aegeline, which have been used in traditional Indian medicines, are naturally occurring hydroxyamides possessing hypoglycemic activity. As already established, (*R*)-tembamide **1** and (*R*)-aegeline **2** were easily prepared from methoxy-tosylate **7a** according to the precedent, as shown in Scheme 2.[4b,5,9e] Tosylate **7a** was converted to azide **8** by heating in DMSO with sodium azide, which was then reduced under hydrogen over 5% Pd/C in MeOH using Parr apparatus to give hydroxyamine **9**. Selective acylation on the amino group of **9** was conveniently performed utilizing the Schotten–Baumann protocol. Thus, the reaction of **9** with benzoyl chloride in aqueous NaOH gave 92% yield of (*R*)-tembamide **1** {$[\alpha]_D^{25} = -59.4$ (*c* 0.57, $CHCl_3$); lit.[9e] $[\alpha]_D^{20} = -57.6$ (*c* 0.3, $CHCl_3$), 99% ee}, after recrystallization. Similarly, (*R*)-aegeline **2** {$[\alpha]_D^{25} = -49.1$ (*c* 0.27, MeOH); lit.[9e] $[\alpha]_D^{20} = -35.7$ (*c* 0.5, $CHCl_3$), >99% ee} was obtained in 84% yield, by treatment with (*E*)-cinnamoyl chloride. The

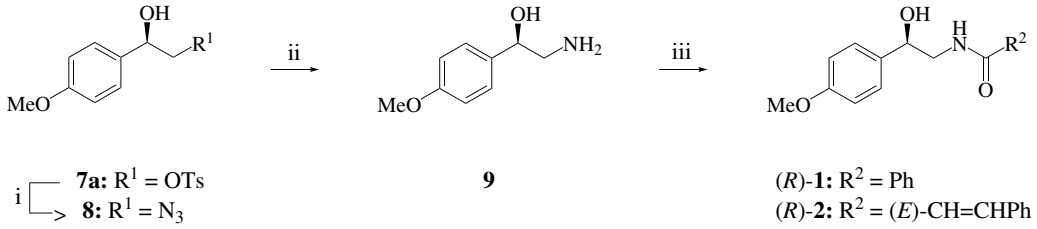


6a: R = OMe
6b: R = OBn

7a (94% *ee*)
7b (95% *ee*)

5

Scheme 1.



Scheme 2. Reagents and conditions: (i) NaN_3, DMSO, 80 °C, 2 h, 91%; (ii) 5% Pd/C, H_2 (30 psi), MeOH, rt, 2 h, 95%; (iii) BzCl (for **1**, 92%); (*E*)-cinnamoyl chloride (for **2**, 84%), aq NaOH, CH_2Cl_2–PhMe, 4–10 °C, 1 h.

spectral and specific rotation data of **1** and **2** were in agreement with those reported in the literature.

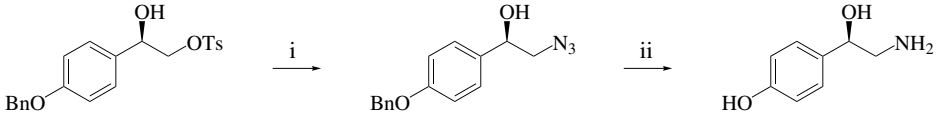
2.3. (*R*)-Octopamine and (*R*)-denopamine

(*R*)-Octopamine, a biogenic hydroxyamine with a similar action to dopamine, has a β-adrenergic activity and is currently used as a circulatory stimulant. As usual, access to (*R*)-octopamine **3** was readily achieved from benzyloxy-tosylate **7b**, as shown in Scheme 3.[9e,14] Tosylate **7b** converted to azide **10**, followed by hydrogenation, along with sequential debenzylation, over 20% $Pd(OH)_2/C$ to afford (*R*)-octopamine **3** {$[\alpha]_D^{25} = -37.3$ (*c* 1.02, H_2O); lit.[14] $[\alpha]_D^{25} = -37.4$ (*c* 1.0, H_2O)} in 81% yield, after recrystallization.

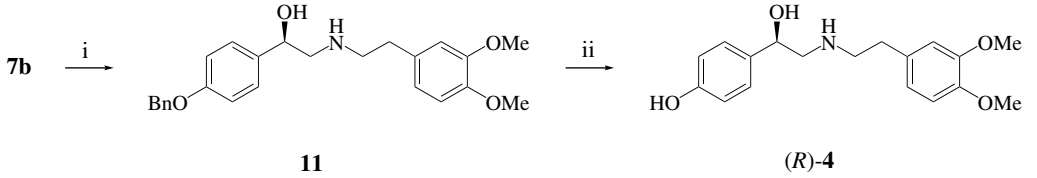
(*R*)-Denopamine, a selective β-adrenergic agonist that is currently being used in the treatment of congestive heart failure, is also available from **7b** as shown in Scheme 4.[3b,4a,b,5,6c,9f] Previous approaches to the destination depend highly on the precursor available. So far, α-azido compounds, such as **10**, have been transformed to an amine. Subsequent acylation with an acyl halide and reduction of the corresponding amide carbonyl,[4b,5,6c] or α-halo precursor routinely gives the epoxide followed by subsequent regioselective ring-opening with amine.[4a] These approaches work very effectively for the synthesis of 1,2-aminoalcohols, it has been secured that direct displacement of **7b** with an amine would offer a more concise alternative. By treating tosylate **7b** with 3,4-dimethoxyphenethylamine, it was converted to hydroxylamine **11** in 82% yield, without protection of the secondary alcohol.[3b] Final installation was accomplished with removal of the benzyl group in **11** to afford enantiomerically pure (*R*)-denopamine **4** {$[\alpha]_D^{25} = -27.7$ (*c* 0.91, MeOH); lit.[5] $[\alpha]_D^{25} = -27.9$ (*c* 1.0, MeOH)} in 86% yield, after recrystallization.

3. Conclusion

The optically active 2-amino-1-arylethanols are of great importance as β-adrenergic agonists in the therapy of asthma, bronchitis, and congestive heart failure. To date, many α-functionalized acetophenones have been successfully applied toward the synthesis of aminoalcohols. In this study, we have represented a simple and highly efficient procedure for the preparation of chiral alcohols from α-tosyloxyketones under catalytic transfer hydrogenation, as an alternative. Central to this approach is the demonstration of α-tosyloxy alcohols as versatile precursors for the synthesis of β-adrenergic agonists, (*R*)-tembamide, (*R*)-aegeline, (*R*)-octopamine, and (*R*)-denopamine. It is noteworthy that α-tosyloxyalcohols are particularly interesting since they have wide scope and would offer an alternative route to the synthesis of a number of chiral aminoalcohols. Currently, their scope and applications are under investigation.



Scheme 3. Reagents and conditions: (i) NaN_3, DMSO, 80 °C, 2 h, 91%; (ii) 20% $Pd(OH)_2/C$, H_2 (60 psi), EtOH, rt, 9 h, 81%.



Scheme 4. Reagents and conditions: (i) 3,4-dimethoxyphenethylamine, Et_3N, THF, 100 °C, 5 h, 82%; (ii) 20% $Pd(OH)_2/C$, H_2 (60 psi), EtOH, rt, 2 h, 86%.

4. Experimental

4.1. General

The catalytic reactions were carried out under an argon atmosphere with oven-dried glassware. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (230–400 mesh). Melting points were measured on an electrothermal apparatus and are uncorrected. NMR spectra were recorded at 300 MHz for ^{1}H and 75 or 125 MHz for ^{13}C. Mass spectra were recorded on a GC/MS operating system at an ionization potential of 70 eV. Optical rotations were measured on a high resolution digital polarimeter. Enantiomeric excess (ee) values of the samples were determined by HPLC analysis using Daicel Chiralcel OD-H chiral column.

4.2. Materials

The starting α-tosyloxyketones were prepared by α-tosyloxylation of the corresponding acetophenones with [hydroxy(tosyloxy)iodo]benzene in refluxing acetonitrile, according to the literature procedure.[10b] The (*S*,*S*)-Rh catalyst was prepared from the reaction of dichloro(pentamethylcyclopentadienyl)rhodium(III) dimer (99%) and (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (98%) in dichloromethane in the presence of triethylamine, according to the literature procedure.[12a] The formic acid/triethylamine (molar ratio = 5:2) azeotrope was prepared by the double distillation of the mixtures.[13b] All reagent-grade chemicals and anhydrous solvents were purchased from commercial suppliers and used without further purification.

4.3. General procedure for the preparation of 2-tosyloxy-1-(4-hydroxyphenyl)ethanones

According to the literature procedure, compounds **6a** and **6b** were conveniently prepared by α-tosyloxylation of the corresponding acetophenones with [hydroxy(tosyloxy)-iodo]benzene in refluxing acetonitrile.[10b]

4.3.1. 1-(4-Methoxyphenyl)-2-(*p*-tolylsulfonyloxy)ethanone 6a. 85% yield; mp 117–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.80 (4H, m), 7.34 (2H, d, $J = 8.1$ Hz), 6.93 (2H, d, $J = 8.7$ Hz), 5.20 (2H, s), 3.87 (3H, s), 2.44 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 164.2, 145.2, 132.6, 130.4, 129.8, 128.1, 126.7, 114.0, 69.7, 55.5, 21.6; EIMS (70 eV) *m*/*z* (rel intensity) 320 (M^+, 6), 135 (100), 121 (3), 107 (5), 91 (9), 77 (10), 65 (4).

4.3.2. 1-(4-Benzyloxyphenyl)-2-(*p*-tolylsulfonyloxy)ethanone 6b. 86% yield; mp 131–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.80 (4H, m), 7.41–7.32 (7H, m), 7.00 (2H, d, $J = 7.0$ Hz), 5.19 (2H, s), 5.14 (2H, s), 2.44 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 163.6, 145.4, 136.1, 132.9, 130.6, 130.1, 128.9, 128.5, 128.3, 127.7, 127.2, 115.2, 70.4, 70.0, 21.9; EIMS (70 eV) *m*/*z* (rel intensity) 396 (M^+, 12), 211 (100), 91 (65).

4.4. General procedure for asymmetric transfer hydrogenation of 2-tosyloxy-1-(4-hydroxyphenyl)ethanones

4.4.1. (*R*)-1-(4-Methoxyphenyl)-2-(*p*-tolylsulfonyloxy)ethanol 7a. Onto a mixture of (*S*,*S*)-Rh catalyst **5** (3.98 mg, 0.005 mmol) and **6a** (1.60 g, 5.0 mmol) was charged ethyl acetate (35 mL), and then an azeotopic mixture of formic acid/triethylamine (molar ratio = 5:2, 1.0 mL). The reaction mixture was stirred at room temperature for 18 h. After dilution with ethyl acetate (20 mL), the mixture was washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give a residue. The residue was purified by column chromatography on silica gel (EtOAc/$CHCl_3$ = 1:20) to give 1.48 g (92% yield) of **7a**. Mp 71–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (2H, d, $J = 8.3$ Hz), 7.33 (2H, d, $J = 8.1$ Hz), 7.23 (2H, d, $J = 6.9$ Hz), 6.86 (2H, d, $J = 6.8$ Hz), 4.92 (1H, dd, $J = 8.4$ and 3.5 Hz), 4.11 (1H, dd, $J = 10.3$ and 3.5 Hz), 4.03 (1H, dd, $J = 10.4$ and 8.5 Hz), 3.79 (3H, s), 2.45 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 145.0, 132.6, 130.3, 129.9, 127.9, 127.4, 114.0, 74.2, 71.4, 55.2, 21.6; EIMS (70 eV) *m*/*z* (rel intensity) 322 (M^+, 44), 304 (69), 172 (89), 155 (83), 108 (100), 90 (99), 79 (88); $[\alpha]_D^{25} = -50.7$ (*c* 0.79, $CHCl_3$) {lit.[10b] $[\alpha]_D^{20} = -18$ (*c* 0.74, $CHCl_3$), 15% ee}; HPLC analysis (Chiralcel OD-H, 250 × 4.6 mm, ethanol/hexane = 2:98, 1.2 mL/min), 94% ee.

4.4.2. (*R*)-1-(4-Benzyloxyphenyl)-2-(*p*-tolylsulfonyloxy)ethanol 7b. 85% yield; mp 91–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (2H, d, $J = 8.4$ Hz), 7.43–7.32 (6H, m), 7.26–7.20 (3H, m), 6.93 (2H, d, $J = 8.8$ Hz), 5.05 (2H, s), 4.95 (1H, dt, $J = 8.3$ and 3.0 Hz), 4.13–3.99 (2H, m), 2.44 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.9, 145.0, 136.7, 132.6, 130.5, 129.9, 128.5, 128.0, 127.9, 127.4, 127.4, 114.9, 74.2, 71.4, 69.9, 21.6; EIMS (70 eV) *m*/*z* (rel intensity) 398 (M^+, 1), 213 (56), 91 (100); $[\alpha]_D^{25} = -42.5$ (*c* 0.79, $CHCl_3$) {lit.[9f] $[\alpha]_D^{20} = -41.9$ (*c* 1.08, $CHCl_3$)}; HPLC analysis (Chiralcel OD-H, 250 × 4.6 mm, ethanol/hexane = 2:98, 1.2 mL/min), 95% ee.

4.5. Preparation of (*R*)-tembamide, (*R*)-aegeline, (*R*)-octopamine, and (*R*)-denopamine

4.5.1. (*R*)-(−)-2-Azido-1-(*p*-methoxyphenyl)ethanol 8. A mixture of **7a** (1.73 g, 5.38 mmol) and sodium azide (0.7 g, 10.7 mmol) in DMSO (12 mL) was heated at 80 °C for 2 h and then cooled to room temperature. To this was added water (15 mL) and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined extract was dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:7) to give 0.95 g (91%) of **8**. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (2H, d, $J = 8.5$ Hz), 6.91 (2H, d, $J = 8.8$ Hz), 4.86–4.81 (1H, m), 3.48 (1H, dd, $J = 12.5$ and 8.0 Hz), 3.81 (3H, s), 3.40 (1H, dd, $J = 12.5$ and 4.1 Hz), 2.29 (1H, d, $J = 3.1$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 132.6, 127.1, 114.0, 73.0, 58.0, 55.2; EIMS (70 eV) *m*/*z* (rel intensity) 193 (M^+, 5), 137 (39), 109 (70), 94 (97), 77 (100); $[\alpha]_D^{25} = -86.1$ (*c* 1.39, $CHCl_3$) {lit.[4b] $[\alpha]_D^{25} = -40.1$

(c 1.0, $CHCl_3$), 99% ee; lit.[5] $[\alpha]_D^{25} = -116.9$ (c 1.2, $CHCl_3$), 98% ee; lit.[9e] $[\alpha]_D^{20} = -117.4$ (c 1.30, $CHCl_3$), 99% ee}.

4.5.2. (*R*)-(−)-2-Amino-1-(*p*-methoxyphenyl)ethanol 9. Azidoalcohol **8** (0.71 g, 3.68 mmol) was dissolved in MeOH (6 mL) and the solution shaken using a Parr apparatus under a hydrogen atmosphere (30 psi) in the presence of 5% Pd/C (20 mg) for 2 h. The reaction mixture was filtered on a pad of Celite and the filtrate was concentrated to give 0.59 g (95%) of aminoalcohol **9**. Mp 100–102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (2H, d, $J = 6.70$ Hz), 6.89 (2H, d, $J = 6.67$ Hz), 4.57 (1H, dd, $J = 7.8$ and 4.0 Hz), 3.80 (3H, s), 2.96 (1H, dd, $J = 12.7$ and 4.1 Hz), 2.79 (1H, dd, $J = 12.7$ and 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 134.6, 127.0, 113.3, 74.1, 55.0, 50.2; EIMS (70 eV) m/z (rel intensity) 167 (M^+, 8), 136 (91), 109 (100), 94 (86); $[\alpha]_D^{25} = -38.3$ (c 0.49, EtOH) {lit.[9e] $[\alpha]_D^{20} = -39.9$ (c 1.0, EtOH), 99% ee}.

4.5.3. (*R*)-(−)-Tembamide (*R*)-1. To a solution of **9** (0.16 g, 1.0 mmol) in dry CH_2Cl_2 (3 mL), a solution of NaOH (0.24 g, 3.0 mmol) in water (3 mL) was added at ice bath temperature and the mixture was stirred vigorously for 10 min. A solution of benzoyl chloride (1.2 mmol) in anhydrous toluene (1 mL) was added dropwise to the reaction mixture, while vigorously stirring. After the addition was complete, the reaction mixture was stirred for a further 1 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was separated and washed with brine. The solvent was evaporated and then the resulting solid was recrystallized from ethanol/water (v/v = 80:20) to afford 0.27 g (92%) of (*R*)-(−)-tembamide (*R*)-**1**. Mp 145–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, d, $J = 6.9$ Hz), 7.51 (1H, t, $J = 7.3$ Hz), 7.43 (2H, t, $J = 7.5$ Hz), 7.33 (2H, d, $J = 8.7$ Hz), 6.90 (2H, d, $J = 8.7$ Hz), 6.58 (1H, br s), 4.94–4.89 (1H, m), 3.93–3.85 (1H, m), 3.81 (3H, s), 3.56–3.48 (1H, m), 3.09 (1H, d, $J = 3.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 159.3, 134.1, 133.8, 131.6, 128.6, 127.0, 126.9, 113.9, 73.3, 55.2, 47.7; EIMS (70 eV) m/z (rel intensity) 254 (M^+−OH, 17), 150 (7), 134 (29), 105 (60), 77 (100); $[\alpha]_D^{25} = -59.4$ (c 0.57, $CHCl_3$) {lit.[4b] $[\alpha]_D^{25} = -59.6$ (c 0.52, $CHCl_3$); lit.[5] $[\alpha]_D^{25} = -58.7$ (c 0.6, $CHCl_3$); lit.[9e] $[\alpha]_D^{20} = -57.6$ (c 0.3, $CHCl_3$), 99% ee}.

4.5.4. (*R*)-(−)-Aegeline (*R*)-2. Acylation of aminoalcohol **9** (0.16 g, 1.0 mmol) with (*E*)-cinnamoyl chloride (1.2 mmol) under the aforementioned conditions gave 0.25 g (84%) of (*R*)-(−)-aegeline (*R*)-**2**. Mp 194–195 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (1H, t, $J = 5.6$ Hz), 7.54 (2H, d, $J = 6.4$ Hz), 7.44–7.35 (3H, m), 7.27 (2H, d, $J = 8.6$ Hz), 6.89 (2H, d, $J = 8.7$ Hz), 6.72 (1H, d, $J = 15.8$ Hz), 5.44 (1H, d, $J = 4.3$ Hz), 4.63–4.58 (1H, m), 3.44–3.36 (1H, m), 3.26–3.17 (1H, m); ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.0, 158.3, 138.4, 135.7, 134.9, 129.3, 128.9, 127.4, 127.1, 122.3, 113.4, 70.9, 55.0, 47.0; EIMS (70 eV) m/z (rel intensity) 297 (M^+, 3), 285 (21), 103 (15), 71 (56), 57 (100); $[\alpha]_D^{25} = -49.1$ (c 0.27, MeOH) {lit.[4b] $[\alpha]_D^{24} = -36.1$ (c 0.45, $CHCl_3$); lit.[5] $[\alpha]_D^{25} = -35.9$ (c 0.48, $CHCl_3$); lit.[9e] $[\alpha]_D^{20} = -35.7$ (c 0.5, $CHCl_3$), >99% ee}.

4.5.5. (*R*)-(−)-2-Azido-1-(*p*-benzyloxyphenyl)ethanol 10. A mixture of **7b** (3.39 g, 8.51 mmol) and sodium azide (1.11 g, 17.0 mmol) in DMSO (15 mL) was heated at 80 °C for 2 h and then cooled to room temperature. To this was added water (20 mL) and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined extract was dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The residue was purified by column chromatography on silica gel (EtOAc/hexane = 1:5) to give 2.09 g (91%) of **10**. Mp 69–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.27 (7H, m), 6.98 (2H, d, $J = 8.8$ Hz), 5.07 (2H, s), 4.86–4.81 (1H, m), 3.48 (1H, dd, $J = 12.6$ and 8.0 Hz) 3.40 (1H, dd, $J = 12.6$ and 4.1 Hz), 2.26 (1H, d, $J = 3.2$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.7, 136.7, 132.9, 128.5, 128.0, 127.4, 127.2, 114.9, 72.9, 70.0, 57.9; EIMS (70 eV) m/z (rel intensity) 267 (M^+, 3), 213 (37), 91 (100); $[\alpha]_D^{25} = -70.3$ (c 1.09, $CHCl_3$) {lit.[5] $[\alpha]_D^{25} = -72.5$ (c 1.3, $CHCl_3$), >99% ee; lit.[9e] $[\alpha]_D^{20} = -72.2$ (c 1.1, $CHCl_3$), 99% ee}.

4.5.6. (*R*)-(−)-Octopamine (*R*)-3. Azidoalcohol **10** (0.54 g, 2 mmol) was dissolved in EtOH (10 mL) and the solution shaken using a Parr apparatus under a hydrogen atmosphere (60 psi) in the presence of 20% $Pd(OH)_2$/C (150 mg) for 9 h. The reaction mixture was filtered on a pad of Celite and the filtrate was concentrated to give a solid residue. The resulting solid was recrystallized from water to afford 248 mg (81%) of (*R*)-**3**. Mp 245–246 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.16 (2H, d, $J = 8.5$ Hz), 6.76 (2H, d, $J = 8.5$ Hz), 4.38 (1H, dd, $J = 7.4$ and 4.7 Hz), 2.69–2.56 (2H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.5, 124.9, 117.3, 104.9, 64.5, 40.5; EIMS (70 eV) m/z (rel intensity) 153 (M^+, 4), 136 (11), 123 (100), 95 (30), 77 (23); $[\alpha]_D^{25} = -37.3$ (c 1.02, H_2O) {lit.[9e] $[\alpha]_D^{20} = -37.6$ (c 0.56, H_2O), 100% ee; lit.[14] $[\alpha]_D^{25} = -37.4$ (c 1.0, H_2O)}.

4.5.7. (*R*)-1-(*p*-Benzyloxyphenyl)-2-[2-(3,4-dimethoxyphenyl)ethylamino]ethanol 11. A mixture of **10** (0.40 g, 1.0 mmol), 3,4-dimethoxyphenethylamine (0.54 g, 3.0 mmol), triethylamine (0.20 g, 2.0 mmol) in THF (20 mL) was stirred at 100 °C for 5 h. After cooling to room temperature, the reaction mixture was poured onto water (3 mL), and then extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to give a residue. The residue was purified by column chromatography on silica gel (MeOH/EtOAc = 2:1) to give 0.33 g (82%) of **11**. Mp 119–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.28 (5H, m), 7.21 (2H, d, $J = 8.7$ Hz), 6.92 (2H, d, $J = 8.6$ Hz), 6.84–6.69 (3H, m), 5.06 (2H, s), 4.67 (1H, dd, $J = 8.1$ and 5.0 Hz), 3.79 (3H, s), 3.77 (3H, s), 2.86–2.68 (6H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.5, 149.3, 147.8, 137.5, 135.4, 132.4, 128.3, 127.6, 127.3, 127.0, 120.8, 114.6, 112.4, 112.0, 71.7, 69.7, 56.4, 55.3, 55.2, 50.4, 34.9; EIMS (70 eV) m/z (rel intensity) 407 (M^+, 2), 194 (35), 91 (100); $[\alpha]_D^{25} = -19.2$ (c 1.1, MeOH) {lit.[5] $[\alpha]_D^{25} = -34.8$ (c 1.2, $CHCl_3$); lit.[9f] $[\alpha]_D^{20} = -17.5$ (c 1.09, MeOH)}.

4.5.8. (*R*)-(−)-Denopamine (*R*)-4. The benzylated denopamine **11** (0.20 g, 0.49 mmol) was dissolved in EtOH

(20 mL) and the solution was shaken using a Parr apparatus under a hydrogen atmosphere (60 psi) in the presence of 20% $Pd(OH)_2/C$ (50 mg) for 2 h. The reaction mixture was filtered on a pad of Celite and the filtrate was concentrated to give a solid residue. The resulting solid was recrystallized from *n*-hexane/ethyl acetate (v/v = 7:3) to afford 134 mg (86%) of (*R*)-**4**. Mp 162–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (2H, d, $J = 8.5$ Hz), 6.83 (1H, d, $J = 8.2$ Hz), 6.79 (1H, d, $J = 1.7$ Hz), 6.73–6.69 (3H, m), 4.64 (1H, d, $J = 8.2$ and 4.9 Hz), 3.80 (3H, s), 3.79 (3H, s), 2.86–2.68 (6H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.9, 149.3, 147.8, 133.8, 132.4, 127.1, 120.8, 114.9, 112.4, 112.0, 71.8, 56.4, 55.3, 55.2, 50.5, 34.9; EIMS (70 eV) *m*/*z* (rel intensity) 317 (M^+, 1), 165 (37), 121 (34), 107 (63), 91 (86) 77 (100); $[\alpha]_D^{25} = -27.7$ (*c* 0.91, MeOH) {lit.[4b] $[\alpha]_D^{25} = -27.8$ (*c* 1.02, MeOH); lit.[5] $[\alpha]_D^{25} = -27.9$ (*c* 1.0, MeOH); lit.[9f] $[\alpha]_D^{20} = -28.5$ (*c* 0.98, MeOH)}.

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