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A scalable synthesis of (*R*)-3-(2-aminopropyl)-7-benzyloxyindole via resolution

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Abstract—(±)-3-(2-Aminopropyl)-7-benzyloxyindole **1**, assembled from 7-benzyloxyindole **3** in 59% overall yield, is resolved with *O*,*O*′-di-*p*-toluoyl L-(2*R*,3*R*)-tartaric acid **7** into (*R*)-**1**, a key intermediate of AJ-9677 **2** (selective adrenaline β_3-agonist) in 99.5% e.e. and 36% overall yield. The unwanted enantiomer (*S*)-**1** (61.9% e.e.; recovered in 57% yield from the crystallization filtrate) can be reused in another round of resolution after its enantiomeric purity is lowered to 3.7% by Raney Co treatment under a hydrogen atmosphere.

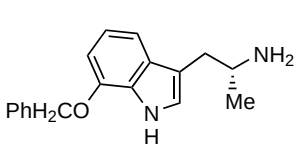
1. Introduction

(*R*)-3-(2-Aminopropyl)-7-benzyloxyindole **1** is a key chiral intermediate of AJ-9677 **2**,[1] which, being a potent and selective adrenaline β_3-agonist, has been nominated as a clinical candidate to treat obesity in those who are suffering from diabetes (Fig. 1).[2] In the stage of drug discovery, (*R*)-**1** was assembled enantioselectively by the chiral pool method.[1] However, this was plagued with the following drawbacks from the practical perspective: (1) relatively expensive *N*-Fmoc D-alanyl chloride, an unnatural α-amino acid derivative, was employed as a chiral source; (2) cryogenic conditions had to be applied to append the *N*-Fmoc D-alanyl group to the 3 position of 7-benzyloxyindole; (3) the acylation proceeded with a reasonably high yield and regioselectivity only in ethyl ether, a solvent of which industrial use is limited due to its high flammability. Hence, we explored more practical and easily scalable processes for (*R*)-**1**, and succeeded in resolving (±)-**1** into (*R*)-**1** via diastereomeric salt formation and making the resolution process enantioconvergent by developing the method to recycle the unwanted enantiomer (*S*)-**1**.

2. Results and discussion

2.1. Preparation of (±)-3-(2-Aminopropyl)-7-benzyloxyindole 1

The starting point of our synthesis was 7-benzyloxyindole **3**, because it could be prepared either from 2-nitrophenol by Bartoli's method[3] or from 3-hydroxy-2-nitrotoluene by Leimgruber-Batcho's method.[4] Vilsmeir reaction ($POCl_3$, DMF) of **3** gave indole-3-carboxaldehyde **4** in 99% yield,[5] which on nitroaldol reaction ($EtNO_2$, AcONa, PhMe) provided nitroolefin **5** in 95% yield (Scheme 1).



(*R*)-**1**

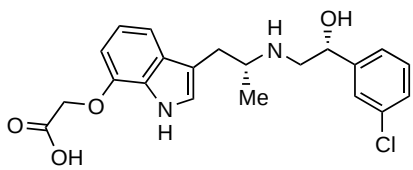


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Figure 1. Structures of (*R*)-3-(2-aminopropyl)-7-benzyloxyindole **1** and AJ-9677 **2**.

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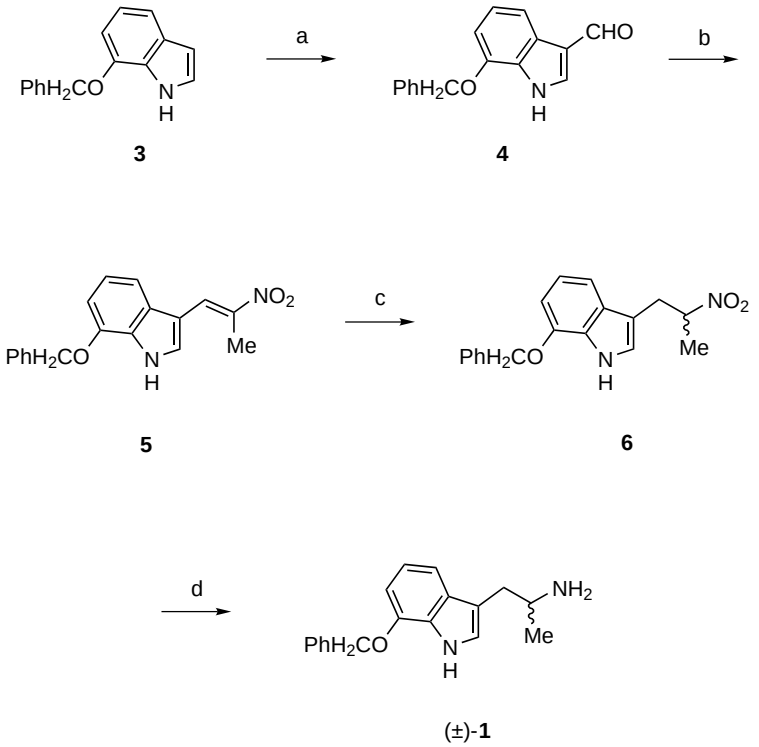


Scheme 1. Preparation of (±)-3-(2-aminopropyl)-7-benzyloxyindole **1**. *Reagents and conditions*: (a) $POCl_3$, DMF, 99%; (b) $EtNO_2$, $AcONH_4$, PhMe, 95%; (c) $NaBH_4$, THF/MeOH (4:1), 79%; (d) H_2 (1 atm), Raney Ni, PhMe, 50°C, 79%.

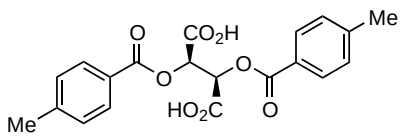
Conjugated nitroolefins such as **5** were reported to be reduced by $LiAlH_4$ directly to saturated primary amines.[5] However, from a practical viewpoint, the $LiAlH_4$-mediated reduction posed the following concerns: (1) $LiAlH_4$ is a rather expensive reagent; (2) it is pyrophoric in its nature; (3) voluminous Al salts generated from the aqueous work-up make the product isolation a tedious process; and (4) the Al salt disposal entails considerable cost. Thus, we investigated synthetic processes that could dispense with $LiAlH_4$, and eventually developed a two-step reduction protocol comprising: (1) 1,4-hydride addition to the olefinic bond in **5**; and (2) hydrogenation of the nitro group in **6** to a primary amine function.

When **5** was treated with $NaBH_4$ in THF-MeOH,[6] the expected 1,4-reduction proceeded uneventfully providing **6** in 79% yield. It was then subjected to Raney Ni-catalyzed hydrogenation to give (±)-**1** in 79% yield (4-step overall yield of 59% from **3**), with its *O*-benzyl group surviving the hydrogenolysis.

2.2. Resolution of (±)-1

With ample quantities of (±)-**1** in hand, we explored a commercially available library of optically active acids for an agent that could resolve (±)-**1** into (*R*)-**1**, which led to identification of *O*,*O*′-di-*p*-toluoyl L-(2*R*,3*R*)-tartaric acid **7** as the resolving agent of choice (Fig. 2).

Experimental parameters affecting the resolution efficiency (a ratio of **7** to (±)-**1**, solvent species, solvent volume, temperature, annealing, etc.) were examined to maximize both the yield and enantiomeric purity of the resolved (*R*)-**1**. Under the optimized conditions, (±)-**1** (1.0 equiv) was combined with **7** (0.5 equiv) in MeOH/H_2O (4:1), and the diastereomeric salt **8** was allowed to crystallize preferentially in 41% yield based on the whole amount of (±)-**1**. The (*R*)-configuration of the



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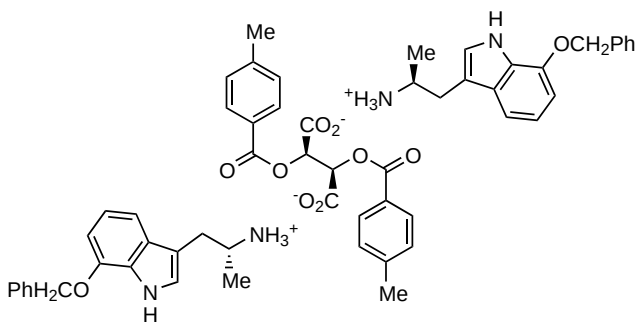

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Figure 2. Structures of *O*,*O*′-di-*p*-toluoyl L-(2*R*,3*R*)-tartaric acid **7** and its diastereomeric salt **8**.

amine contained in the salt was confirmed and its enantiomeric purity was determined to be 94% by chiral HPLC analysis on CHIRALPACK AD column (Daicel) which employed the authentic (*R*)-**1** assembled from *N*-Fmoc D-alanyl chloride[1] as a reference compound. Single recrystallization from MeOH/H_2O (4:1) provided the purified salt **8** in 91% yield, which contained (*R*)-**1** of 99.5% e.e. as determined by the chiral HPLC analysis. Finally, the recrystallized salt **8** was treated with aqueous NaOH solution to liberate (*R*)-**1** of 99.5% e.e. in 97% yield (36% overall yield based on the whole amount of (±)-**1**) (Scheme 2).

2.3. Racemization of the off-enantiomer (*S*)-1

For the above-discussed resolution process to be industrially viable, the off-enantiomer (*S*)-**1** needed to be recouped and racemized for another round of resolution, because preparation of (±)-**1** was highly demanding, whether Bartoli's[3] or Leimgruber–Batcho's method[4] was employed.

Hence, racemization was attempted with (*S*)-**1** that was recovered in 62% e.e. and 57% yield from the crystallization filtrate (Scheme 2). When a PhMe solution of (*S*)-**1** was heated up to 135°C in the presence of Raney Co under a hydrogen atmosphere at an initial pressure of 2 kg/cm,[7] racemization took place. After the reaction time was prolonged to 25 h, the enantiomeric purity of (*S*)-**1** was lowered to 3.7% (70% yield).

As far as this particular incomplete racemization is concerned, no serious problem arises, because (±)-**1** could be easily reconstituted by blending the (*S*)-**1** of 3.7% e.e. (obtained in 40% overall yield from (±)-**1**) with the (*R*)-**1** of 45.1% e.e. (obtained in 4.4% yield from the recrystallization filtrate) (Scheme 2).

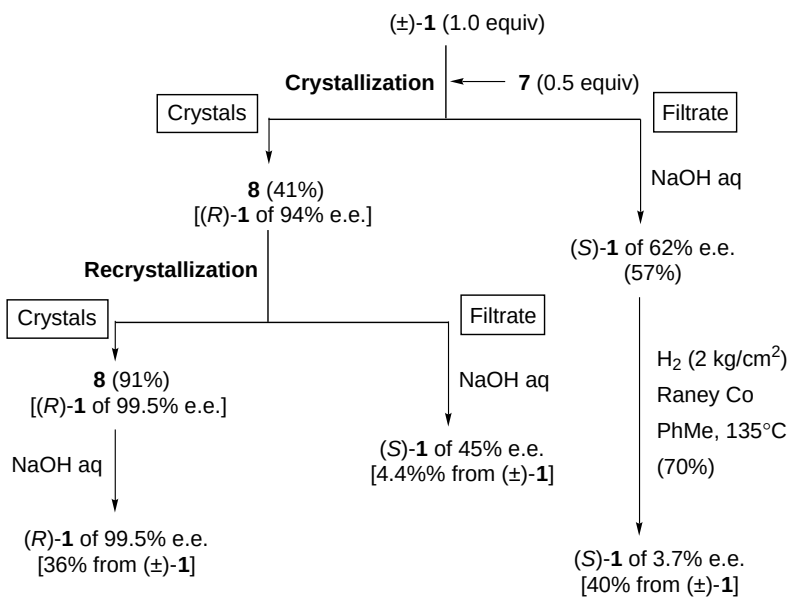
3. Conclusion

Scalable processes for (*R*)-**1**, a key synthetic intermediate of AJ-9677 **2**, have been developed successfully employing resolution of the racemate via diastereomeric salt formation. The features worth mentioning are itemized as follows: (1) (±)-**1** can be prepared from **3** in four steps and 59% overall yield without recourse to expensive intractable reagents and chromatographic purification; (2) (±)-**1** can be resolved by *O*,*O*′-di-*p*-toluoyl L-(2*R*,3*R*)-tartaric acid **7** into (*R*)-**1** of 99.5% e.e. in 36% overall yield based on the whole amount of (±)-**1** after single recrystallization of the diastereomeric salt **8**; (3) (*S*)-**1** of 61.9% e.e. (recovered in 57% yield from the crystallization filtrate) can be recycled for another round of resolution after it is treated with Raney Co catalyst and hydrogen to lower the enantiomeric purity to 3.7% and combined with (*R*)-**1** of 45.1% e.e. (recovered in 4.4% yield from the recrystallization filtrate).

4. Experimental

4.1. General

Melting points were measured on an Electrothermal 1A8104 melting point apparatus and uncorrected. ^{1}H NMR spectra were recorded at 400 MHz on a Varian UNITY-400 spectrometer in a $CDCl_3$ solution with tetramethylsilane as an internal standard. FT-IR spectra were recorded on a Perkin-Elmer 1600 spectrometer. Mass spectra were recorded on a Hitachi M-8000 spectrometer (ESI). Elemental analyses were performed on an Elementar Vario EL analyzer. Optical rotations were measured on a Horiba SEPA-200 polarimeter.



Scheme 2. Resolution of (±)-**1** and lowering the enantiomeric purity of (*S*)-**1**.

4.2. 7-Benzyloxyindole-3-carboxaldehyde 4

To a stirred and ice-cooled DMF (73.1 g) was added dropwise $POCl_3$ (34.5 g, 0.22 mol) between 1 and 5°C over 50 min. The mixture was stirred at the same temperature range for 30 min and a solution of **3** (44.7 g, 0.20 mol) in DMF (50.0 mL) was added dropwise between 3 and 8°C over 50 min. The reaction mixture was gradually warmed to 35°C and stirring was continued at the same temperature for 60 min. To the reaction mixture was added ice (75 g) such that the inner temperature did not exceed 50°C. The mixture was ice-cooled to 35°C and poured into a mixture of water (25 g) and ice (50 g). To the mixture was added 32% (w/w) NaOH aq. solution (93.7 g, 0.74 mol) dropwise between 20 and 34°C. Further 32% (w/w) NaOH aq. solution (187.3 g, 1.37 mol) was added dropwise between 34 and 47°C and the stirred mixture was heated to gentle reflux at 95°C. The mixture was allowed to cool to 40°C and to 0–5°C by ice-cooling. Stirring was continued with ice-cooling for 1 h and the precipitated solids were collected by filtration, and suspended in H_2O (500 mL). The mixture was stirred at ambient temperature for 3 h. The solids were filtered off, washed with H_2O (3×75 mL), and air-dried at 50°C (oven temperature) to give **4** (49.9 g, 99%): mp 156.3–157.3°C; IR ν (KBr) 3120 (m), 3059 (m), 3028 (m), 2877 (m), 1635 (s), 1620 (v.s), 1403 (m), 1263 (m), 1232 (s), 1188 (m), 1128 (s), 783 (m) cm^{-1}; ^1H NMR δ 5.26 (2H, s), 6.93 (1H, d, $J=7.6$ Hz), 7.16 (1H, t, $J=7.6$ Hz), 7.34–7.42 (3H, m), 7.53–7.56 (2H, m), 7.83 (1H, d, $J=7.6$ Hz), 8.12 (1H, s), 10.04 (1H, s), 11.46 (1H, s); MS m/z 250 {[M-H]$^-$}.

4.3. 7-Benzyloxy-3-(2-nitro-1-propenyl)indole 5

A stirred mixture of **4** (22.6 g, 90.0 mmol), $EtNO_2$ (20.3 g, 270 mmol), $AcONH_4$ (3.47 g, 45.0 mmol), and PhMe (100 mL) was heated to 93–105°C and the mixture was heated under reflux for 3 h to remove the generated water azeotropically, during which time it became homogeneous as the inner temperature reached 80°C. The stirred mixture was allowed to cool to ambient temperature, and crystallization was initiated. The mixture was ice-cooled, and it was kept between 0 and 5°C for 2 h. The precipitated solids were collected by filtration, washed with MeOH (2×20 mL), and dried in vacuo to give **5** (25.2 g, 91%). A further amount of **5** (1.16 g) was obtained in 4% yield from the combined filtrate and washings; a total yield of **5**: 26.36 g (95%); mp 147.6–148.5°C; IR ν (KBr) 3410 (m), 3394 (m), 3277 (m), 2850 (w), 1625 (m), 1581 (m), 1475 (m), 1433 (m), 1308 (s), 1277 (s), 1228 (v.s), 1120 (m), 1093 (s), 980 (s) cm^{-1}; ^1H NMR δ 2.51 (3H, s), 5.26 (2H, s), 6.90 (1H, d, $J=8.0$ Hz), 7.15 (1H, t, $J=8.0$ Hz), 7.32–7.46 (4H, m), 7.52–7.58 (2H, m), 7.85 (1H, s), 8.45 (1H, s), 11.46 (1H, s); MS m/z 307 {[M-H]$^-$}.

4.4. 7-Benzyloxy-3-(2-nitropropyl)indole 6

A stirred solution of **5** (15.4 g, 50.0 mmol) in 6:1 THF/MeOH (70 mL) was heated to 40°C and $NaBH_4$ (1.89 g, 50.0 mmol) was added in portions over 6 h maintaining the temperature between 39 and 40°C. The mixture was stirred at the same temperature range for 1 h, it was neutralized by adding AcOH (3.5 g), and concentrated in vacuo. The residue was dissolved in PhMe (100 mL) and the solution was washed with H_2O (1×40 mL, 2×20 mL), dried (Na_2SO_4), and concentrated in vacuo to give a viscous oil (16.7 g). MeOH (30 mL) was added and the mixture was heated to 58–60°C wherein it became homogeneous. To the solution was added activated charcoal, and the mixture was filtered while it was hot. The decolorized filtrate was ice-cooled, and kept between 0 and 5°C for 1 h. The precipitated solids were collected by filtration, washed with a minimum volume of MeOH, and concentrated in vacuo to give **6** (12.3 g, 79%): mp 88.1–90.1°C; IR ν (KBr) 3431 (v.s), 3028 (s), 2902 (m), 2856 (m), 1578 (m), 1543 (v.s), 1500 (s), 1443 (s), 1261 (s), 1090 (s), 1055 (s), 779 (s), 737 (s) cm^{-1}; ^1H NMR δ 1.54 (3H, d, $J=6.8$ Hz), 3.16 (1H, ddd, $J=0.4$, 6.8, 14.6 Hz), 3.45 (1H, ddd, $J=0.4$, 6.8, 14.6 Hz), 4.86 (1H, sextet, $J=6.8$ Hz), 5.16 (2H, s), 6.72 (1H, d, $J=8.0$ Hz), 6.95 (1H, d, $J=2.4$ Hz), 7.04 (1H, dd, $J=8.0$, 8.0 Hz), 7.18 (1H, d, $J=8.0$ Hz), 7.33–7.43 (3H, m), 7.43–7.48 (2H, m), 8.30 (1H, m); MS m/z 311 {[M+H]$^+$}.

4.5. (±)-3-(2-Aminopropyl)-7-benzyloxyindole 1

To a solution of **6** (3.10 g, 10.0 mmol) in PhMe (50 mL) was added Raney Ni (NDHT-95, Kawaken Fine Chemicals Co., Ltd.; about 1.0 mL; washed with MeOH followed by PhMe prior to use). The mixture was stirred under H_2 (atmospheric pressure) with heating between 49 and 50°C for 13 h. The mixture was allowed to cool to ambient temperature and the catalyst was filtered off and washed with warmed PhMe. The combined filtrate and washings were concentrated in vacuo to give a syrupy residue (2.54 g), which was allowed to crystallize after the addition of AcOEt (5.0 mL). The precipitated solids were collected by filtration, washed with AcOEt, and dried in vacuo to give (±)-**1** (2.22 g) in 79.3% yield: mp 129.2–130.5°C; IR ν (KBr) 3361 (m), 3303 (w), 3062 (m), 2951 (m), 2879 (m), 2867 (m), 1575 (m), 1464 (m), 1375 (m), 1621 (m), 1238 (s), 1020 (s), 891 (m), 806 (m), 733 (m), 712 (m), 692 (m) cm^{-1}; ^1H NMR δ 1.14 (3H, d, $J=6.8$ Hz), 1.36 (2H, br.s), 2.60 (1H, ddd, $J=0.8$, 6.8, 14.2 Hz), 2.83 (1H, ddd, $J=0.8$, 4.8, 14.2 Hz), 5.16 (2H, s), 6.70 (1H, d, $J=7.8$ Hz), 6.94 (1H, d, $J=2.0$ Hz), 7.00 (1H, dd, $J=7.8$, 7.8 Hz), 7.22 (1H, d, $J=7.8$ Hz), 7.33–7.43 (3H, m), 7.43–7.48 (2H, d, $J=7.2$ Hz), 8.75 (1H, s); MS 281 {[M+H]$^+$}.

4.6. Bis [(*R*)-2-(7-benzyloxy-3-indolyl)-1-methylethylammonium] *O*,*O*′-di-*p*-toluoyl L-(2*R*,3*R*)-tartrate 8

4.6.1. Formation of the diastereomeric salt 8. A mixture of (±)-**1** (6.80 g, 24.3 mmol) and MeOH–H_2O (4:1; 45 mL) was heated to 70°C wherein it became homogeneous. To the solution was added dropwise a solution of di-*p*-toluoyl L-(2*R*,3*R*)-tartaric acid **7** (4.71 g, 12.2 mmol) in MeOH–H_2O (4:1; 5.0 mL). After the addition was complete, the dropping funnel used was rinsed with MeOH–H_2O (4:1; 8.0 mL). The mixture was allowed to cool to 49°C, and seeded with **8** containing (*R*)-**1** of

95.5% e.e. The stirred mixture was allowed to cool to 30°C, and heated to 45°C. The mixture was allowed to cool to 25°C with stirring and the mixture was then cooled and kept between 15 and 17°C for 1 h. The precipitated solids were collected by filtration, washed with MeOH–H_2O (4:1; 2×10 mL), and dried in vacuo to give **8** (4.71 g, 41% based on the whole amount of (±)-**1**), which was shown to contain (*R*)-**1** of 94% e.e. by the HPLC analysis described in Section 4.6.2.

4.6.2. Recrystallization of the diastereomeric salt 8. To **8** (4.70 g; containing (*R*)-**1** of 94% e.e.) was added MeOH–H_2O (4:1; 47 mL), and the mixture was stirred and heated to 65°C wherein complete dissolution took place. The stirred mixture was allowed to cool to 58°C, and seeded with **8** containing (*R*)-**1** of 99.0% e.e. The stirred mixture was allowed to cool to 35°C, and heated to 55°C. After the stirred mixture was kept at the same temperature for 30 min, it was allowed to cool to 25°C. Stirring was stopped and the mixture was left to stand at ambient temperature overnight. The precipitated solids were collected by filtration, washed with MeOH–H_2O (4:1; 2×5.0 mL) and air-dried at 50°C to give **8** (4.26 g, 91%), which was shown to contain (*R*)-**1** of 99.5% e.e. by HPLC analysis [column, CHIRALPAK AD (Daicel; ∅ 4.6 mm×25 cm); elution, hexane/2-propanol/*N*,*N*-diethylamine (90:10:0.2); flow rate, 1.0 mL/min; detection, UV at 254 nm; 15% (w/w) NaOH aq. solution (0.5 mL) was added to the recrystallized **8** (80 mg), and the precipitated solids were filtered off. After a portion (about 2 mg) of the filtrate was diluted with 2-propanol (2.0 mL), 1.0 μL of the 2-propanol solution was injected; t_R 23.7 min for (*R*)-**1** (99.75%), 32.4 min for (*S*)-**1** (0.25%)]; mp 166.6–168.2°C; $[\alpha]_D^{20}$ −71.8 (*c* 0.50, MeOH); IR ν (KBr) 3412 (s), 3034 (s), 2944 (s), 1715 (s), 1611 (v.s), 1578 (s), 1499 (m), 1443 (m), 1372 (s), 1266 (v.s), 1179 (s), 1096 (s), 1022 (m), 754 (s) cm^{-1}. Anal. calcd for $C_{56}H_{58}N_4O_{10}\cdot 2H_2O$: C, 68.4; H, 6.4; N, 5.7. Found: C, 68.8; H, 6.3; N, 5.6%.

4.7. (*R*)-3-(2-Aminopropyl)-7-benzyloxyindole 1

To a suspension of the recrystallized **8** (4.00 g, 8.45 mmol) in H_2O (20.0 mL) was added dropwise 45% (w/w) NaOH aq. solution (1.65 g, 18.6 mmol) at ambient temperature. After stirring the mixture at ambient temperature for 1 h, the precipitated solids were collected by filtration, washed with H_2O, and air-dried at 50°C to give (*R*)-**1** (2.29 g, 96.6%), the enantiomeric purity of which was determined to be 99.7% e.e. by the HPLC analysis described in Section 4.6.2; mp 123.4–135.3°C; $[\alpha]_D^{20}$ −17.8 (*c* 0.50, MeOH); the IR, ^1H NMR and MS data were identical with those of (±)-**1** recorded in Section 4.5. Anal. calcd for $C_{18}H_{20}N_2O$: C, 77.1; H, 7.2; N, 10.0. Found: C, 77.1; H, 7.2; N, 9.8%.

4.8. (*S*)-3-(2-Aminopropyl)-7-benzyloxyindole 1 of 61.9% e.e.

The filtrate and washings generated in the course of crystallization of **8** (as recorded in Section 4.6.1) were combined and the MeOH was removed by evaporation in vacuo. The syrupy residue (7.5 g) was suspended in H_2O (20 mL), and 45% (w/w) NaOH aq. solution (2.60 g, 29.0 mmol) was added. The mixture was stirred at ambient temperature for 1 h and the precipitated solids were collected by filtration, washed with H_2O, and dried in vacuo to give crude (*S*)-**1** (4.16 g). This was suspended in AcOEt (10 mL), and the mixture was stirred at ambient temperature for 15 min. Stirring was continued with ice-cooling for 30 min and the precipitated solids were collected by filtration, washed with AcOEt, and dried in vacuo to give purified (*S*)-**1** as colorless solids (3.85 g, 56.6% overall yield from (±)-**1**), the enantiomeric purity of which was determined to be 61.9% as determined by HPLC analysis described in Section 4.6.2; all of the spectral data of (*S*)-**1** were identical to those of (±)-**1** recorded in Section 4.5.

4.9. (*R*)-3-(2-Aminopropyl)-7-benzyloxyindole 1 of 45.1% e.e.

The filtrate and washings generated in the course of the recrystallization of **8** (as recorded in Section 4.6.2) were combined, and the MeOH was removed by evaporation in vacuo to give a syrupy residue (0.5 g) from which (*R*)-**1** (0.30 g) of 45.1% e.e. was obtained in 4.4% overall yield from (±)-**1** in the same manner as recorded in Section 4.8; its enantiomeric purity was determined by the HPLC analysis recorded in Section 4.6.2, and its spectral data were identical to those of (±)-**1** recorded in Section 4.5.

4.10. Lowering the enantiomeric excess of (*S*)-1

Raney Co (about 1 mL; DFT-55, Kawaken Fine Chemicals Co., Ltd.) was washed with H_2O (2×6.0 mL), MeOH (3×6.0 mL), 2-propanol (2×6.0 mL), and PhMe (5×6.0 mL) and a portion (0.5 g) of the residue was added to a solution of (*S*)-**1** (61.9% e.e., 0.50 g) in PhMe (40 mL). The mixture was stirred at 135°C under an atmosphere of H_2 (initial pressure: 2 kg/cm^2) for 25 h. After the mixture was allowed to cool to ambient temperature, the supernatant was decanted and filtered. Acetone (20 mL) was added to the residue and the mixture was well mixed by agitation. The mixture was filtered and the filter cake was washed with acetone (5.0 mL). The filtered supernatant, the acetone filtrate and washing were combined and the resulting solution was concentrated in vacuo to give a residue, which was suspended in AcOEt (2.5 mL). The mixture was stirred at ambient temperature for 15 min, and the precipitated solids were collected by filtration, and dried in vacuo to give (*S*)-**1** of 3.7% e.e. as colorless solids (0.35 g, 70%); its enantiomeric purity was determined by the HPLC analysis described in Section 4.6.2, and its spectral data were identical to those of (±)-**1** recorded in Section 4.5.

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