Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2989–2997

TETRAHEDRON: *ASYMMETRY*

Practical synthesis of (3*S*,4*S*)-3-methoxy-4-methylaminopyrrolidine

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Received 24 October 2001; accepted 8 November 2001

Abstract—Three synthetic methods for the preparation of (3*S*,4*S*)-3-methoxy-4-methylaminopyrrolidine, an important intermediate in the synthesis of the novel quinolone antitumor agent, AG-7352, have been developed. By one route, an efficient and large-scale preparation of the chiral pyrrolidine could be achieved through resolution of (±)-1-Boc-3-benzylamino-4-hydroxypyrrolidine, which is prepared from either 3-pyrroline or 1,4-dichloro-2-butene. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Chiral, non-racemic pyrrolidines are common structural subunits found in many natural and unnatural products with interesting and important biological activities.[1] One such compound is AG-7352 **1**, which is a novel antitumor agent created at our laboratories and is now under development. AG-7352 **1** shows antitumor activities equal or superior to those of cisplatin and etoposide against human breast, ovarian and colon cancers implanted in nude mice.[2] It has recently been reported that some quinolone-related compounds show antitumor activity with inhibition of eukaryotic topoisomerase II.[3] While those reported compounds have in common a quinolone structure as their basic framework, the basic structure of **1** is 4-oxo-1,8-naphthyridine-3-carboxylic acid. Thus, in terms of the chemical structure, **1** is a new type of antitumor agent.

As shown in Fig. 1, AG-7352 **1** has an optically active 3-methoxy-4-methylaminopyrrolidinyl group at C(7) of the naphthyridine ring. Thus, it is very important to establish a practical synthetic method for homochiral **2** because **1** is synthesized by the reaction of **2** with the 7-chloro-1,8-naphthyridine derivative. While a synthesis of (±)-**2** is known,[4] no asymmetric synthesis of **2** has been reported to date. We have previously reported the stereospecific synthesis of **2** via two S_N2 displacement reactions, and the result allowed us to deduce the absolute structure of diastereomerically pure **2** as (3*S*,4*S*).[5] Herein, we describe three methods for the synthesis of the pyrrolidine (*S*,*S*)-**2**, including our original synthesis. Using one route, (*S*,*S*)-**2** was derived successfully from 3-pyrroline or 1,4-dichloro-2-butene through resolution of racemic 1-Boc-3-benzylamino-4-hydroxypyrrolidine on a large scale. Furthermore, the absolute configuration of this chiral pyrrolidine was unambiguously confirmed as (3*S*,4*S*) by X-ray crystallographic analysis.

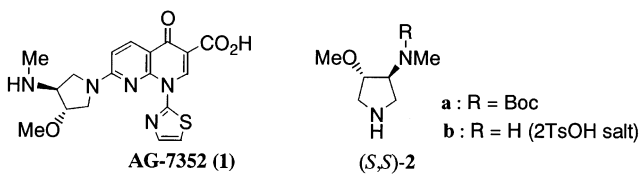

Figure 1.

2. Results and discussion

The key challenge of the synthesis is the effective generation of two stereogenic centers at positions 3 and 4 of the pyrrolidine ring. Based on retrosynthetic analysis, we designed three routes to (*S*,*S*)-**2** (Routes A–C, Scheme 1). Each route includes a key intermediate (±)-**3**, (±)-**4** or (±)-**5** which give (*S*,*S*)-**2** via classical resolution or separation of diastereoisomers. To prepare these intermediates, 3-pyrroline **6** or 1,4-dichloro-2-butene **7** are regarded as a common starting material, of these, **7** is preferable since it is more easily available. The synthesis of (*S*,*S*)-**2** could be readily achieved in

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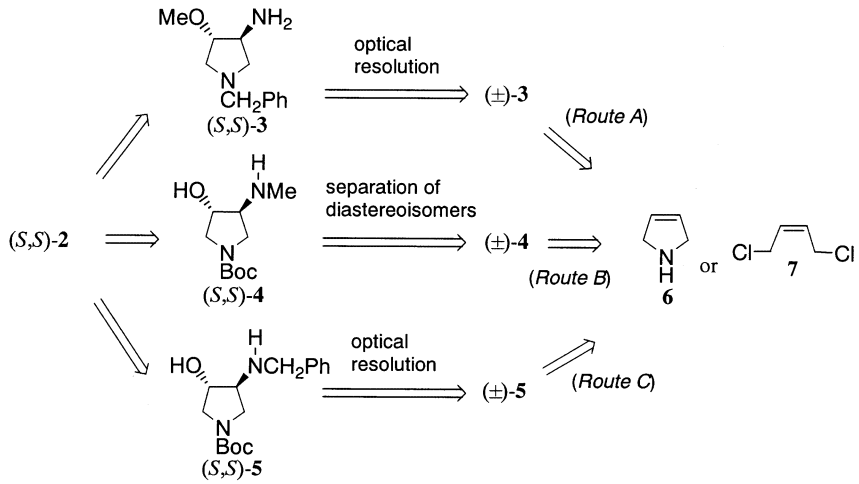
PII: S0957-4166(01)00530-4



Scheme 1.

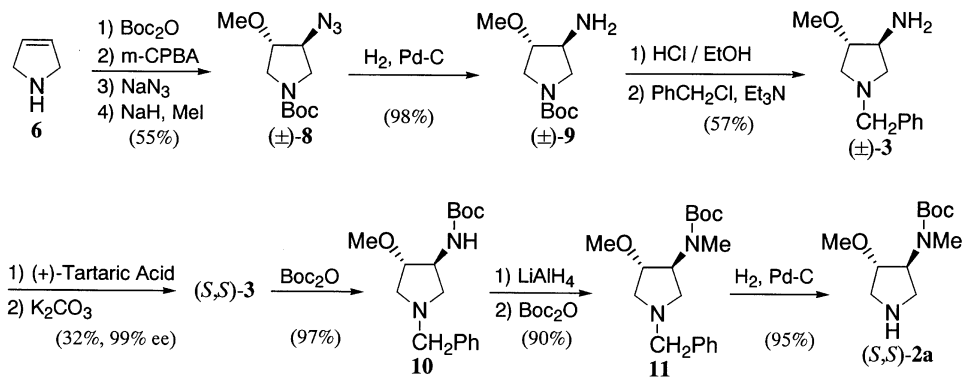
several steps from the resolved compounds (*S*,*S*)-**3**, (*S*,*S*)-**4** or (*S*,*S*)-**5**.

2.1. Route A

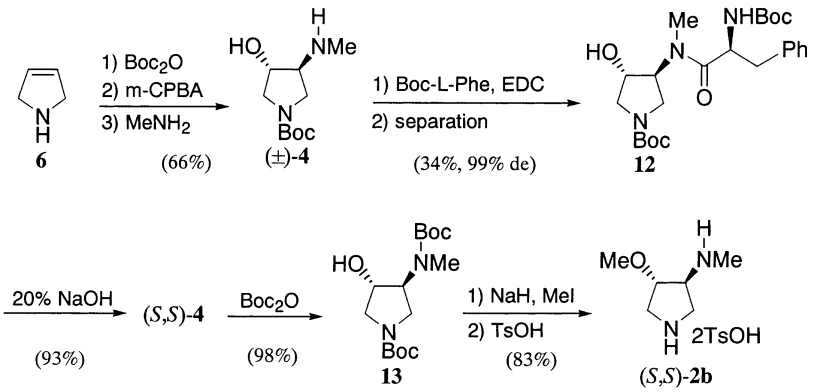
The first synthesis of (*S*,*S*)-**2** was achieved by Route A (Scheme 2). (±)-*trans*-3-Amino-1-Boc-4-methoxy pyrrolidine (±)-**9** was readily prepared in five steps from 3-pyrroline **6** via azide compound (±)-**8**, but attempted resolution of (±)-**9** with various resolving agents was not successful. On the other hand, after removal of the Boc group from (±)-**9**, the resulting secondary amine selectively reacted with benzyl chloride to give compound (±)-**3**, and resolution of (±)-**3** with (+)-tartaric acid in MeOH–H_2O afforded (*S*,*S*)-**3** in 32% yield. Compound (*S*,*S*)-**3** was treated with Boc_2O to give compound **10** in 97% yield. Compound **10** was converted to compound **11** in 90% yield by reduction of the Boc group with $LiAlH_4$ and successive treatment with Boc_2O. Debenzylation of **11** was effected by hydrogenation in the presence of Pd–C then afforded the desired (*S*,*S*)-**2a** in 95% yield. However, this route has several drawbacks: it requires 13 steps and the use of NaN_3 and $LiAlH_4$, unsuitable materials for large-scale synthesis.

2.2. Route B

We examined more practical routes to (*S*,*S*)-**2** than the above method. (±)-*trans*-3-Hydroxy-4-methylaminopyrrolidine (±)-**4** was obtained in three steps from 3-pyrroline **6**. Attempts to resolve compound (±)-**4** with various resolving agents were unsuccessful. We therefore tried to obtain (*S*,*S*)-**4** by diastereomeric separation via *N*-acylation with an amino acid (Scheme 3).[6] The condensation of (±)-**4** with *N*-Boc-L-Phe by means of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) in CH_2Cl_2 gave a 1:1 mixture of diastereomers (TLC: high $R_f = 0.37$ and low $R_f = 0.21$, $CHCl_3$:MeOH = 50:1), which were easily separated by column chromatography to obtain pure **12** with 99% d.e. as the higher R_f component in 34% yield. Cleavage of the amide of **12** with 20% NaOH in EtOH at 50°C smoothly afforded (*S*,*S*)-**4** in 93% yield and protection of (*S*,*S*)-**4** with Boc_2O afforded **13** in 98% yield. Compound **13** was methylated with NaH and MeI in DMF, followed by removal of both Boc groups with *p*-toluenesulfonic acid (TsOH) in *i*-PrOH to give the desired (*S*,*S*)-3-methoxy-4-methylaminopyrrolidine di-*p*-toluenesulfonate salt (*S*,*S*)-**2b** in 83% yield.[7]



Scheme 2.



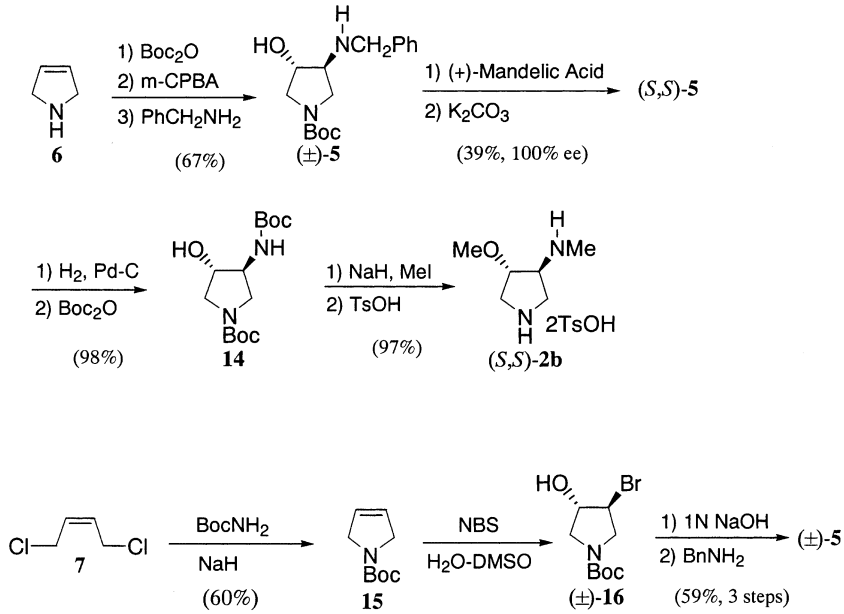
Scheme 3.

This method is better than the Route A because it consists of less steps and does not require the use of dangerous materials. Also, this approach could be readily applicable to the general synthesis of optically active 3,4-disubstituted pyrrolidine derivatives. However, this method does involve separation of the diastereoisomers by column chromatography, and thus, it is unsuitable for the large-scale preparation of (*S*,*S*)-**2b**.

2.3. Route C

We examined another route to (*S*,*S*)-**2** that did not require chromatographic purifications. Replacement of the *N*-methyl group of (±)-**4** with an *N*-benzyl group was first completed because the *N*-benzyl derivative (±)-**5** was expected to give crystals of its salts in a racemate resolution process. In fact, resolution of (±)-*trans*-3-benzylamino-4-hydroxylpyrrolidine (±)-**5** derived from 3-pyrroline **6** successfully afforded (*S*,*S*)-**5** with high enantiomeric purity (100% e.e.) in 39% yield on reaction with (+)-mandelic acid in CH_3CN–H_2O (Scheme 4). Debenzylation of (*S*,*S*)-**5** with Pd–C was followed by treatment with Boc_2O to give crystalline compound **14** in 98% yield. Compound **14** was then methylated with NaH (2.5 equiv.) and MeI (3.0 equiv.) in DMF to afford the *N*,*O*-dimethylated product.[8] Removal of both Boc groups from the intermediate by treatment with TsOH completed the synthesis of (*S*,*S*)-**2b** (99.8% purity and 100% e.e.[9]) in 97% yield. Thus, the desired (*S*,*S*)-**2b** was obtained from **6** via crystalline compound (±)-**5**, (*S*,*S*)-**5** and **14** without the need for column chromatography.

In order to manufacture (*S*,*S*)-**2**, we needed to develop an efficient process for the important intermediate **5**, avoiding the use of expensive 3-pyrroline **6**[10] and hazardous *m*-chloroperbenzoic acid (*m*-CPBA). We took advantage of *cis*-1,4-dichloro-2-butene **7** as a commercially available and inexpensive starting material. Compound **7** was treated with NaH and *tert*-butyl carbamate,[11] which was prepared from Boc_2O and NH_3 in 98% yield, in DMF at 50°C to generate 1-Boc-3-pyrroline **15** in 60% yield. Reaction of **15** with *N*-bromosuccinimide (NBS) in DMSO–H_2O yielded bromohydrin (±)-**16**. Under basic conditions, the bromohydrin (±)-**16** was converted to the epoxide, followed by treatment with benzylamine to give the desired intermediate (±)-**5** in 59% yield. These two steps could be carried out more conveniently in a one-pot operation without isolation of the epoxide. Thus, the



Scheme 4.

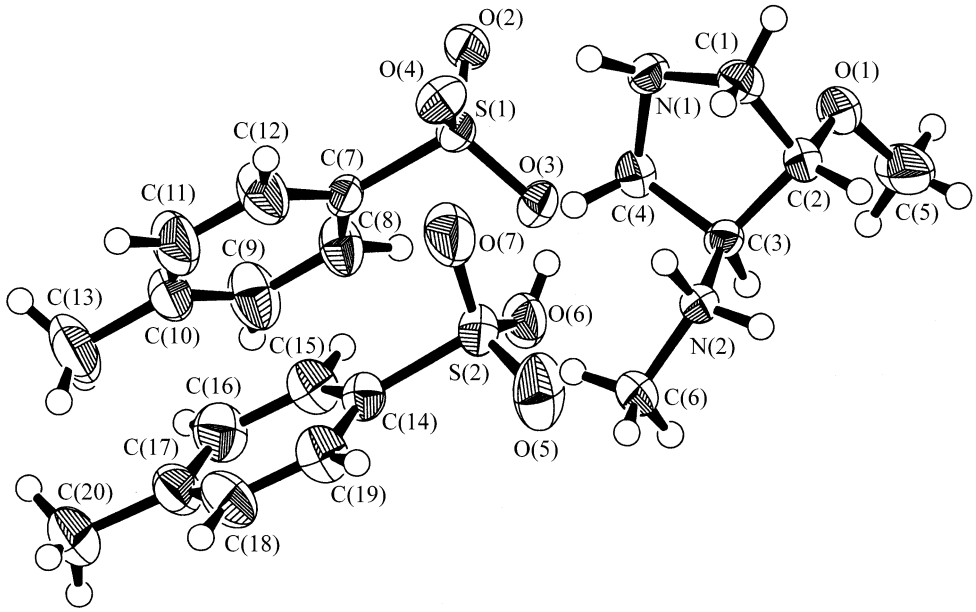


Figure 2. ORTEP drawing of **2b**.

intermediate (±)-**5** was prepared from 1,4-dichloro-2-butene **7** via 1-Boc-3-pyrroline **15** in four steps without using the expensive starting material **6** and hazardous peracid. The synthetic method for (*S*,*S*)-**2** from **7** via (*S*,*S*)-**5** is much improved over the two former methods and is highly suited to large-scale preparation.

The absolute configuration of (*S*,*S*)-**2** was unambiguously confirmed by X-ray crystallographic analysis. Fig. 2 shows the crystal structure of (*S*,*S*)-**2b**. As can be seen from Fig. 2, the absolute configuration of this chiral pyrrolidine is (3*S*,4*S*) and thus AG-7352 is found to have (3′*S*,4′*S*) absolute configuration from this data.

3. Conclusions

In summary, three different synthetic methods for the preparation of (*S*,*S*)-**2** were achieved in excellent purity through resolution or separation of diastereoisomers. The second route is good to obtain gram quantities of (*S*,*S*)-**2** because of short steps and a convenient synthetic method. The third route is the most attractive in terms of practical, economical and large-scale process. The process is free of chromatography and affords high purity (99.8%, 100% e.e.). We have demonstrated the efficient process to provide the key intermediate for a novel quinolone antitumor agent, AG-7352.

4. Experimental

4.1. General

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer 1600 Series FT-IR spectrophotometer. ^{1}H NMR spectra were recorded at 200 MHz on a Varian Gemini-200 spectrometer. Chemical shifts are expressed in ppm (δ) with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a Hitachi M-80B or Hitachi M-1000 spectrometer. Optical rotations were measured on Jasco DIP-370 or P-1020 digital polarimeter. HPLC analyses were performed with Shimadzu LC-6AD or LC-10AS.

4.2. Route A

4.2.1.(±)-*trans*-3-Azido-1-*tert*-butoxycarbonyl-4-methoxypyrrolidine ((±)-8). Di-*tert*-butyl dicarbonate (314 g, 1.44 mol) was added dropwise to a solution of 3-pyrroline **6** (100 g, 0.940 mol, purity of 65%) in MeOH (400 mL) over a period of 30 min at 0°C. The reaction mixture was then stirred at room temperature for 15 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (1.3 L). The mixture was cooled to 0°C and *m*-CPBA (278 g, 1.12 mol, purity of 70%) was added over a period of 6 h. After stirring the mixture at room temperature for 2 days, the precipitate was filtered off and the filtrate was successively washed with saturated $NaHSO_3$, 5% aqueous K_2CO_3 and saturated NaCl, dried over Na_2SO_4 and then concentrated in vacuo. The resulting residue was chromatographed on silica gel with hexane–AcOEt (10:1) to give the epoxide (134 g). The epoxide was dissolved in 1,4-dioxane (1.25 L) and water (250 mL). Sodium azide (141 g, 2.17 mol) was added at room temperature. After the reaction mixture was stirred at 100°C for 15 h, water was added at 0°C and the mixture was extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4 and concentrated in vacuo. A solution of the residue in dry THF (1 L) was added to a suspension of NaH (60% dispersion in oil, 31.8 g, 0.796 mol, washed with dry hexane before use) in dry THF (2 L). After stirring at room temperature for 1 h, the mixture

was allowed to gradually warm to 50°C over 3 h. MeI (118 g, 0.833 mol) was added to the mixture at 0°C which was then stirred at room temperature for 15 h. After evaporation of the solvent, AcOEt and water were added to the residue. The organic layer was washed with saturated NaCl, dried over Na_2SO_4 and then concentrated in vacuo. The resulting residue was chromatographed on silica gel with hexane–AcOEt (10:1) to give (±)-**8** as a colorless oil (124 g, 55%): ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 3.33–3.63 (m, 4H), 3.39 (s, 3H), 3.74–3.79 (m, 1H), 3.95–4.00 (m, 1H); MS m/z 243 (M^++1); IR (neat) 2105, 1695 cm^{-1}. Anal. calcd for $C_{10}H_{18}N_4O_3 \cdot 0.25H_2O$: C, 48.67; H, 7.56; N, 22.70. Found: C, 48.98; H, 7.47; N, 22.44%.

4.2.2. (±)-*trans*-3-Amino-1-*tert*-butoxycarbonyl-4-methoxypyrrolidine (±)-9. A solution of (±)-**8** (76.0 g, 0.317 mol) in EtOH (370 mL) was hydrogenated over 5% Pd–C (7.0 g) at room temperature for 10 h. The mixture was filtered and then concentrated in vacuo to give (±)-**9** as a colorless oil (67.0 g, 98%): ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.58 (br s, 2H), 3.05–3.48 (m, 3H), 3.35 (s, 3H), 3.50–3.69 (m, 3H); MS m/z 203 (M^++1); IR (neat) 2950, 1690 cm^{-1}. Anal. calcd for $C_{10}H_{20}N_2O_3$: C, 55.53; H, 9.32; N, 12.95. Found: C, 55.58; H, 9.33; N, 13.02%.

4.2.3. (±)-*trans*-3-Amino-1-benzyl-4-methoxypyrrolidine (±)-3. A solution of 35% HCl–EtOH (80.2 mL) was added to a solution of (±)-**9** (50.0 g, 0.231 mol) in EtOH (180 mL) over a period of 1 h at 0°C and the reaction mixture was stirred at room temperature for 8 h. The mixture was cooled to 0°C and the resultant precipitates were collected by filtration, washed with EtOH and dried to give 39.6 g of white crystals. Benzyl chloride (25.2 g, 0.199 mol) was added into a mixture of the intermediate, Et_3N (93.9 g, 0.993 mol), CH_3CN (1.5 L) and water (15 mL) over a period of 1 h at 0°C. The mixture was allowed to warm gradually to room temperature for 15 h. After neutralization with 2% K_2CO_3 at 0°C, AcOEt was added. The organic layer was washed with saturated NaCl, dried over Na_2SO_4 and then concentrated in vacuo. The resulting residue was chromatographed on silica gel with hexane–AcOEt (50:1) to give (±)-**3** as a colorless oil (27.0 g, 57%): ^{1}H NMR ($CDCl_3$) δ 1.63 (br s, 2H), 2.34 (dd, 1H, J=9.7, 4.6 Hz), 2.48 (dd, 1H, J=10.4, 4.0 Hz), 2.85 (dd, 1H, J=9.7, 6.3 Hz), 2.95 (dd, 1H, J=10.4, 6.3 Hz), 3.32 (s, 3H), 3.34 (ddd, 1H, J=6.3, 4.6, 2.4 Hz), 3.53 (ddd, 1H, J=6.3, 4.0, 2.4 Hz), 3.56 (d, 1H, J=12.8 Hz), 3.65 (d, 1H, J=12.8 Hz), 7.21–7.34 (m, 5H); MS m/z 207 (M^++1); IR (neat) 2950, 1600 cm^{-1}. Anal. calcd for $C_{12}H_{18}N_2O \cdot 0.2H_2O$: C, 68.67; H, 8.87; N, 13.35. Found: C, 68.82; H, 8.78; N, 13.48%.

4.2.4. (3*S*,4*S*)-3-Amino-1-benzyl-4-methoxypyrrolidine (*S*,*S*)-3. A mixture of (±)-**3** (25.0 g, 121 mmol) and (+)-tartaric acid (25.4 g, 169 mmol) in MeOH (395 mL) and H_2O (5 mL) was heated at 65°C and cooled to room temperature. The resultant crystalline precipitates were collected by filtration, washed with MeOH and recrystallized from MeOH–H_2O, giving 18.8 g of (*S*,*S*)-**3**·1.5(+)-tartaric acid as white crystals: mp 206–208°C (dec.); $[\alpha]_D^{29}$ +33.0 (*c* 1.00, H_2O); ^{1}H NMR (DMSO-d_6) δ 2.39 (dd, 1H, J=9.9, 3.5 Hz), 2.48–2.58 (m, 1H), 2.75 (dd, 1H, J=10.1, 6.6 Hz), 2.96 (dd, 1H, J=9.9, 6.4 Hz), 3.25 (s, 3H), 3.44–3.53 (m, 1H), 3.57 (d, 1H, J=13.1 Hz), 3.67 (d, 1H, J=13.1 Hz), 3.76–3.84 (m, 1H), 4.00 (s, 3H), 7.24–7.35 (m, 5H), 8.20 (br s, 8H); MS m/z 207 (M^++1); IR (KBr) 3370, 2925, 1735, 1600 cm^{-1}. Anal. calcd for $C_{12}H_{18}N_2O \cdot 1.5C_4H_6O_6$: C, 50.11; H, 6.31; N, 6.49. Found: C, 49.85; H, 6.26; N, 6.27%.

The crystals were treated with 3% K_2CO_3 and the liberated amine was extracted three times with AcOEt. The combined organic layer was washed with saturated NaCl and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave 7.94 g (32%) of (*S*,*S*)-**3** as a colorless oil: $[\alpha]_D^{27}$ +32.2 (*c* 1.05, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.55 (br s, 2H), 2.33 (dd, 1H, J=9.6, 4.5 Hz), 2.47 (dd, 1H, J=10.0, 4.0 Hz), 2.85 (dd, 1H, J=9.6, 6.3 Hz), 2.95 (dd, 1H, J=10.0, 6.3 Hz), 3.31 (s, 3H), 3.34 (ddd, 1H, J=6.3, 4.6, 2.4 Hz), 3.56 (ddd, 1H, J=6.3, 4.0, 2.4 Hz), 3.56 (d, 1H, J=12.8 Hz), 3.65 (d, 1H, J=12.8 Hz), 7.20–7.33 (m, 5H); MS m/z 207 (M^++1); IR (neat) 2935, 1605 cm^{-1}. Anal. calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.90; H, 8.81; N, 13.68%; e.e. 99% (*S*,*S*); HPLC analysis using CHIRALCEL OJ-H 4.6×250 mm (hexane:*i*-PrOH, 85:15), 0.4 mL/min; (*S*,*S*)-**3** t_r=17.97 min; (*R*,*R*)-**3** t_r=18.98 min.

4.2.5. (3*S*,4*S*)-1-Benzyl-3-(*N*-*tert*-butoxycarbonyl)-amino-4-methoxypyrrolidine 10. Di-*tert*-butyl dicarbonate (7.15 g, 32.8 mmol) was added dropwise to a solution of (*S*,*S*)-**3** (6.42 g, 31.2 mmol) in MeOH (80 mL) at 0°C. The reaction mixture was stirred at room temperature for 4 h and then concentrated in vacuo to leave a residue. The resulting residue was chromatographed on silica gel with $CHCl_3$–MeOH (100:1) to give **10** as white crystals (9.26 g, 97%): mp 44–45°C; $[\alpha]_D^{29}$ +9.5 (*c* 1.04, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.75 (br s, 1H), 2.24 (dd, 1H, J=10.5, 4.1 Hz), 2.55 (dd, 1H, J=10.0, 4.8 Hz), 2.70 (dd, 1H, J=9.9, 5.8 Hz), 3.15 (dd, 1H, J=10.5, 6.6 Hz), 3.39 (s, 3H), 3.60 (s, 2H), 3.90–4.04 (m, 1H), 4.85–5.00 (m, 1H), 7.20–7.32 (m, 5H); MS m/z 307 (M^++1); IR (KBr) 2975, 1710, 1530 cm^{-1}. Anal. calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.49; H, 8.51; N, 9.28%.

4.2.6. (3*S*,4*S*)-1-Benzyl-3-(*N*-*tert*-butoxycarbonyl)-methylamino-4-methoxypyrrolidine 11. A solution of **10** (8.20 g, 27.5 mmol) in dry THF (60 mL) was added to a suspension of $LiAlH_4$ (3.13 g, 82.5 mmol) in dry THF (120 mL) at room temperature. After stirring the mixture at room temperature for 1 h, the mixture was heated under reflux for 5 h. After cooling to 0°C, water was added and the mixture was filtered. The filtrate was extracted with AcOEt and the organic layer was washed with saturated NaCl, dried over Na_2SO_4 and then concentrated in vacuo. Di-*tert*-butyl dicarbonate (6.00 g, 27.5 mmol) was added to a solution of the residue in CH_2Cl_2 (100 mL) at 0°C. The reaction mixture was stirred at room temperature for 2 h and then concentrated in vacuo. The resulting residue was chro-

matographed on silica gel with $CHCl_3$–MeOH (150:1) to give **11** as a colorless oil (7.93 g, 90%): $[\alpha]_D^{29}$ +9.9 (*c* 1.00, MeOH); ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 2.44 (dd, 1H, $J=10.0$, 5.2 Hz), 2.54 (dd, 1H, $J=10.0$, 4.8 Hz), 2.70–2.79 (m, 1H), 2.87 (s, 3H), 2.91–3.02 (m, 1H), 3.34 (s, 3H), 3.50 (d, 1H, $J=12.8$ Hz), 3.65 (d, 1H, $J=12.8$ Hz), 3.84–3.92 (m, 1H), 4.40–4.53 (m, 1H), 7.19–7.32 (m, 5H); MS *m*/*z* 321 (M^++1); IR (neat) 2975, 1695, 1540 cm^{-1}. Anal. calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.09; H, 8.78; N, 8.76%.

4.2.7. (3*S*,4*S*)-3-(*N*-*tert*-Butoxycarbonyl)methylamino-4-methoxypyrrolidine ((*S*,*S*)-2a)[12]. A solution of **11** (7.15 g, 22.3 mmol) in EtOH (70 mL) was hydrogenated over 5% Pd–C (700 mg) at 50°C. The mixture was filtered and then concentrated in vacuo to give of (*S*,*S*)-**2a** as a colorless oil (4.87 g, 95%): $[\alpha]_D^{29}$ +12.5 (*c* 1.05, MeOH); ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.86 (br s, 1H), 2.74–2.84 (m, 1H), 2.84 (s, 3H), 2.96 (dd, 1H, $J=12.0$, 3.1 Hz), 3.07 (dd, 1H, $J=11.9$, 5.2 Hz), 3.28 (dd, 1H, $J=12.0$, 8.6 Hz), 3.34 (s, 3H), 3.81–3.85 (m, 1H), 4.19–4.31 (m, 1H); MS *m*/*z* 231 (M^++1); IR (neat) 2975, 1695 cm^{-1}. Anal. calcd for $C_{11}H_{22}N_2O_3$: C, 57.37; H, 9.63; N, 12.16. Found: C, 57.09; H, 9.60; N, 12.05%. It was confirmed that AG-7352·HCl {$[\alpha]_D^{28}$ +50.1 (*c* 1.00, 1N NaOH)} derived from (*S*,*S*)-**2a** had >99% e.e. based on HPLC analysis.

4.3. Route B

4.3.1. (±)-*trans*-1-*tert*-Butoxycarbonyl-3-hydroxy-4-methylaminopyrrolidine (±)-4. Di-*tert*-butyl dicarbonate (314 g, 1.44 mmol) was added dropwise to a solution of 3-pyrroline **6** (100 g, 0.940 mol, purity of 65%) in MeOH (1 L) over a period of 30 min at 0°C and the reaction mixture was stirred at room temperature for 15 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (1.8 L). The mixture was cooled to 0°C and then *m*-CPBA (240 g, 1.12 mol, purity of 80%) was added over a period of 6 h. After stirring at room temperature for 2 days, the precipitated solid was filtered off and the filtrate was successively washed with saturated $NaHSO_3$, 5% K_2CO_3 and saturated NaCl, dried over Na_2SO_4 and then concentrated in vacuo. A solution of 40% methylamine–water (1 L) was added into the residue and the reaction mixture was stirred at room temperature for 15 h. After evaporation of the solvent, the residue was triturated with *i*-Pr_2O to give (±)-**4** as white crystals (133 g, 66%): mp 98–100°C; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.29 (br s, 2H), 2.47 (s, 3H), 3.01–3.36 (m, 3H), 3.57–3.76 (m, 2H), 4.08–4.17 (m, 1H); MS *m*/*z* 217 (M^++1); IR (KBr) 3295, 2970, 1695 cm^{-1}. Anal. calcd for $C_{10}H_{20}N_2O_3$: C, 55.53; H, 9.32; N, 12.95. Found: C, 55.66; H, 9.31; N, 13.05%.

4.3.2. (3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-(*N*-*tert*-butoxycarbonyl-L-phenylalanyl)methylamino-4-hydroxy pyrrolidine 12. L-Boc-Phe (10.3 g, 38.9 mmol) and EDC (8.07 g, 42.1 mmol) were added successively to a solution of (±)-**4** (7.00 g, 32.4 mmol) in CH_2Cl_2 (200 mL) at 0°C. After stirring for 20 h at room temperature, water and $CHCl_3$ were added. The organic phase was washed with saturated NaCl, dried over Na_2SO_4 and then concentrated in vacuo to leave a residue. The resulting residue was chromatographed on silica gel with $CHCl_3$ to give a higher R_f diastereomer **12** as a colorless oil (5.11 g, 34%): $[\alpha]_D^{25}$ +52.0 (*c* 0.15, MeOH); ^1H NMR ($CDCl_3$) δ 1.41 (s, 9H), 1.46 (s, 9H), 1.85 (br s, 2H), 2.57(s, 1H), 2.73 (s, 3H), 2.91–3.10 (m, 3H), 3.43–3.77 (m, 2H), 4.02–4.45 (m, 2H), 4.78–4.92 (m, 1H), 5.28–5.42 (m, 1H), 7.15–7.31 (m, 5H); MS *m*/*z* 464 (M^++1); IR (neat) 3335, 1690, 1635, 1600 cm^{-1}. Anal. calcd for $C_{24}H_{37}N_3O_6$: C, 62.18; H, 8.04; N, 9.06. Found: C, 61.89; H, 7.94; N, 9.03%; d.e. 99.0%; HPLC analysis using CAPCELL PAK SG120 4.6×250 mm (CH_3CN:0.05% aq. TFA, 43:57), 1.0 mL/min; **12** t_r = 19.36 min; isomer of **12** t_r = 20.34 min.

4.3.3. (3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-hydroxy-4-methylaminopyrrolidine (*S*,*S*)-4. A mixture of **12** (4.70 g, 10.2 mmol) and 20% NaOH (50 mL) in EtOH (75 mL) was heated at 50°C for 7 h and concentrated in vacuo. The residue was poured into water and the mixture was extracted with AcOEt. The extract was washed with saturated NaCl, dried over Na_2SO_4 and then concentrated in vacuo. The residue was triturated with *i*-Pr_2O to give (*S*,*S*)-4 as white crystals (2.05 g, 93%): mp 105–107°C; $[\alpha]_D^{26}$ −8.7 (*c* 1.00, MeOH); ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.90 (br s, 2H), 2.47 (s, 3H), 2.99–3.35 (m, 3H), 3.57–3.75 (m, 2H), 4.07–4.17 (m, 1H); MS *m*/*z* 217 (M^++1); IR (KBr) 3290, 2970, 1695 cm^{-1}. Anal. calcd for $C_{10}H_{20}N_2O_3$: C, 55.53; H, 9.32; N, 12.95. Found: C, 55.39; H, 9.39; N, 12.96%.

4.3.4. (3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-(*N*-*tert*-butoxycarbonyl)methylamino-4-hydroxypyrrolidine 13. Di-*tert*-butyl dicarbonate (2.12 g, 9.72 mmol) was added dropwise to a solution of (*S*,*S*)-**4** (2.00 g, 9.26 mmol) in MeOH (40 mL) at 0°C. The reaction mixture was stirred at room temperature for 4 h and then concentrated in vacuo to leave a residue. The resulting residue was chromatographed on silica gel with $CHCl_3$–MeOH (50:1) to give 2.87 g (98%) of **13** as a colorless oil: $[\alpha]_D^{25}$ +21.7 (*c* 0.60, MeOH); ^1H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.47 (s, 9H), 2.81 (s, 3H), 3.15–3.39 (m, 2H), 3.58–3.77 (m, 2H), 4.23–4.43 (m, 3H); MS *m*/*z* 317 (M^++1); IR (neat) 3335, 1695 cm^{-1}. Anal. calcd for $C_{15}H_{28}N_2O_5$: C, 56.94; H, 8.92; N, 8.85. Found: C, 56.75; H, 8.93; N, 8.55%.

4.3.5. (3*S*,4*S*)-3-Methoxy-4-methylaminopyrrolidine di-*p*-toluenesulfonic acid (*S*,*S*)-2b[5]. A solution of **13** (2.80 g, 8.86 mmol) in dry DMF (25 mL) was added to a suspension of NaH (60% dispersion in oil, 444 mg, 11.1 mmol, washed with dry hexane before use) in dry DMF (25 mL) and MeI (1.89 g, 13.3 mmol) over a period of 10 min at 0°C. After stirring at 0°C for 1 h, the mixture was stirred at room temperature for 5 h. After neutralization with 2% AcOH under ice-cooling, toluene was added. The organic layer was separated and the aqueous layer was extracted with toluene. The combined organic layer was washed with saturated NaCl, dried over Na_2SO_4 and then concentrated in vacuo. The residue was dissolved in *i*-PrOH (42 mL) and then *p*-toluenesulfonic acid (3.44 g, 18.1 mmol) was added. The reaction mixture was stirred at 65°C for 3 h and

then cooled to 0°C. The resultant precipitates were collected by filtration, washed with *i*-PrOH and dried to give (*S*,*S*)-**2b** as white crystals (3.44 g, 83%): mp 163–164°C (lit. 163–164°C); $[\alpha]_D^{29}$ +10.3 (*c* 1.00, MeOH) (lit. $[\alpha]_D^{29}$ +10.4 (*c* 1.00, MeOH)); ^{1}H NMR (DMSO-d_6) δ 2.31 (s, 6H), 2.70 (s, 3H), 3.22–3.40 (m, 3H), 3.32 (s, 3H), 3.60–3.72 (m, 1H), 3.80–3.90 (m, 1H), 4.19–4.26 (m, 1H), 7.14 (d, 4H, J=9.9 Hz), 7.50 (d, 4H, J=9.9 Hz), 9.02 (br s, 4H); MS m/z 131 (M^++1); IR (KBr) 3050, 1615, 1570 cm^{-1}. Anal. calcd for $C_6H_{14}N_2O\cdot 2C_7H_8O_3S$: C, 50.62; H, 6.37; N, 5.90; S, 13.51. Found: C, 50.59; H, 6.38; N, 5.99; S, 13.40%. It was confirmed that AG-7352·HCl {$[\alpha]_D^{27}$ +50.4 (*c* 1.01, 1N NaOH)} derived from (*S*,*S*)-**2b** had more than 99% e.e. based on HPLC analysis.

4.4. Route C

4.4.1. (±)-1-*tert*-Butoxycarbonyl-*trans*-3-benzylamino-4-hydroxypyrrolidine (±)-5. Di-*tert*-butyl dicarbonate (1.51 kg, 6.93 mol) was added dropwise to a solution of 3-pyrroline **6** (486 g, 6.60 mol, purity of 93.9%) in $CHCl_3$ (5.8 L) over a period of 1.5 h at 0°C and the reaction mixture was stirred at room temperature for 17 h. The whole was cooled to 0°C and then *m*-CPBA (1.67 kg, 7.26 mol, purity of 75%) was added over a period of 6 h. After stirring at room temperature for 2 days, the precipitate that formed was filtered off and the filtrate was successively washed with saturated $NaHSO_3$ (5 L), 5% K_2CO_3 (5 L) and saturated NaCl (3 L), dried over Na_2SO_4 and then concentrated in vacuo. The residue was dissolved in water (1.8 L) and then benzylamine (1.8 L, 16.5 mol) was added at room temperature. After stirring at room temperature for 2 h, the reaction mixture was stirred at 65°C for 3 h, water (2 L) was added and the mixture was extracted with AcOEt. The organic layer was washed with water and then concentrated in vacuo. The residue was triturated with *i*-Pr_2O to give (±)-**5** as white crystals (1.29 kg, 67%): mp 140–141°C; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 1.65 (br s, 2H), 3.10–3.35 (m, 3H), 3.57–3.75 (m, 2H), 3.82 (d, 2H, J=5.0 Hz), 4.06–4.15 (m, 1H), 7.21–7.38 (m, 5H); MS m/z 293 (M^++1); IR (KBr) 3250, 1670, 1605 cm^{-1}. Anal. calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.76; H, 8.31; N, 9.65%.

4.4.2. (3*S*,4*S*)-3-Benzylamino-1-*tert*-butoxycarbonyl-4-hydroxypyrrolidine (*S*,*S*)-5. A mixture of (±)-**5** (714 g, 2.45 mol) and (+)-mandelic acid (411 g, 2.70 mol) in CH_3CN (7.5 L) and water (62 mL) was heated at 70°C for 30 min and cooled to room temperature during 4 h. The resultant crystalline precipitates were collected by filtration, washed with CH_3CN and recrystallized from CH_3CN–H_2O (20: 1), giving 439 g of (*S*,*S*)-**5**·(+)-mandelic acid: mp 189–191°C; $[\alpha]_D^{26}$ +59.8 (*c* 0.51, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.39 (s, 9H), 2.95–3.18 (m, 3H), 3.28–3.50 (m, 4H), 3.73 (s, 2H), 3.95–4.02 (m, 1H), 4.97 (s, 1H), 5.05 (br s, 2H), 7.19–7.44 (m, 10H); MS m/z 293 (M^++1); IR (KBr) 3415, 3215, 1685, 1670, 1575 cm^{-1}. Anal. calcd for $C_{16}H_{24}N_2O_3\cdot C_8H_8O_3$: C, 64.85; H, 7.26; N, 6.30. Found: C, 64.79; H, 7.45; N, 6.29%.

The crystals were treated with 3% K_2CO_3 (3 L) and the liberated amine was extracted three times with AcOEt. The combined organic layer was washed with saturated NaCl and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure left a residual oil, which was crystallized from *i*-Pr_2O. The resultant crystals were collected by filtration, washed with *i*-Pr_2O and dried to give (*S*,*S*)-**5** as white crystals (275 g, 39%); mp 69–70°C; $[\alpha]_D^{29}$ +18.0 (*c* 0.50, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.03 (br s, 2H), 3.08–3.33 (m, 3H), 3.57–3.75 (m, 2H), 3.82 (d, 2H, J=5.0 Hz), 4.06–4.15 (m, 1H), 7.22–7.39 (m, 5H); MS m/z 293 (M^++1); IR (KBr) 3250, 1670, 1605 cm^{-1}. Anal. calcd for $C_{16}H_{24}N_2O_3$; C, 65.73; H, 8.27; N, 9.58. Found: C, 65.54; H, 8.41; N, 9.59%; e.e. 100% (*S*,*S*); HPLC analysis using CHIRALCEL OJ 4.6×250 mm (hexane:EtOH, 95:5), 0.8 mL/min; (*S*,*S*)-**5** t_r=14.39 min; (*R*,*R*)-**5** t_r=19.00 min.

4.4.3. (3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-*tert*-butoxycarbonylamino-4-hydroxypyrrolidine 14.[5] A solution of (*S*,*S*)-**5** (274 g, 0.938 mol) in BuOH (1.2 L) was hydrogenated over 5% Pd–C (13.7 g) at 40°C for 5 h. The mixture was filtered and EtOH (0.8 L) was added to the filtrate. Di-*tert*-butyl dicarbonate (215 g, 0.985 mol) was added to the mixture over a period of 10 min at 0°C. The reaction mixture was stirred at room temperature for 15 h and then concentrated in vacuo. The residue was triturated with *i*-Pr_2O to give 278 g (98%) of **14** as white crystals: mp 148–149°C (lit. 147–148°C); $[\alpha]_D^{29}$ +1.80 (*c* 1.00, MeOH) (lit. $[\alpha]_D^{24}$ +1.50 (*c* 1.00, MeOH)); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.46 (s, 9H), 3.10–3.38 (m, 2H), 3.61–4.01 (m, 3H), 4.16–4.29 (m, 1H), 4.70 (br s, 2H); MS m/z 303 (M^++1); IR (KBr) 3470, 3300, 1670 cm^{-1}. Anal. calcd for $C_{14}H_{26}N_2O_5$: C, 55.61; H, 8.67; N, 9.26. Found: C, 55.80; H, 8.74; N, 9.27%.

4.4.4. (3*S*,4*S*)-3-Methoxy-4-methylaminopyrrolidine di-*p*-toluenesulfonic acid (*S*,*S*)-2b.[13] A solution of **14** (177 g, 0.586 mol) in dry DMF (0.7 L) was added into the suspension of NaH (58.8 g of 60% oil suspension, 1.47 mol, washed with dry hexane before use) in dry DMF (1.4 L) and MeI (250 g, 1.76 mol) over a period of 1 h at 0°C. After stirring at 0°C for 1 h, the reaction mixture was stirred at room temperature for 15 h. After neutralization with 2% AcOH (2.5 L) under ice-cooling, toluene (2.5 L) was added. The organic layer was separated and the aqueous layer was extracted with toluene. The combined organic layer was washed with saturated NaCl, dried over Na_2SO_4 and then concentrated in vacuo. The residue was dissolved in THF–MeOH (3: 1, 2.9 L) and then *p*-toluenesulfonic acid (257 g, 1.35 mol) was added. After stirring at room temperature for 30 min, the reaction mixture was stirred at 60°C for 3 h and then cooled to 0°C. The resultant precipitates were collected by filtration, washed with THF and dried to give (*S*,*S*)-**2b** as white crystals (270 g, 97%): mp 163–164°C; $[\alpha]_D^{29}$ +10.5 (*c* 1.00, MeOH). Anal. calcd for $C_6H_{14}N_2O\cdot 2C_7H_8O_3S$: C, 50.62; H, 6.37; N, 5.90; S, 13.51. Found: C, 50.60; H, 6.41; N, 5.98; S, 13.37%. It was confirmed that AG-7352·HCl {$[\alpha]_D^{27}$ +51.0 (*c* 1.00, 1N NaOH)} derived from (*S*,*S*)-**2b** had more than 99.8% e.e. based on HPLC analysis.

4.4.5. *tert*-Butyl carbamate.[11] A solution of di-*tert*-butyl dicarbonate (400 g, 1.83 mol) in EtOH (500 mL) was added to a solution of saturated ammonia–EtOH (500 mL) in EtOH (500 mL) over a period of 1 h at 0°C. The reaction mixture was stirred at room temperature for 15 h and then concentrated in vacuo. Hexane (1.6 L) was added to the resulting solid, the mixture was stirred at 65°C for 30 min and cooled to 0°C. The resultant precipitates were collected by filtration, washed with hexane and dried to give the title compound as white crystals (210 g, 98%): mp 106–107°C (lit. 107–109°C); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 4.42 (br s, 2H); MS m/z 118 (M^++1); IR (KBr) 2985, 1685 cm^{-1}. Anal. calcd for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96. Found: C, 51.20; H, 9.44; N, 11.90%.

4.4.6. 1-*tert*-Butoxycarbonyl-3-pyrroline 15. *cis*-1,4-Dichloro-2-butene (36.0 g, 0.288 mol) was added to a suspension of NaH (60% dispersion in oil, 19.2 g, 0.48 mol, washed with dry hexane before use) in dry DMF (200 mL). A solution of *tert*-butyl carbamate (22.5 g, 0.192 mol) in dry DMF (200 mL) was added to the mixture. After being stirred at room temperature for 40 min, the reaction mixture was stirred at 50°C for 5 h. After neutralization with saturated NH_4Cl at 0°C, AcOEt was added. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with saturated NaCl, dried over Na_2SO_4 and then concentrated in vacuo to give **15** as a colorless oil (19.4 g, 60%): ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 4.03–4.18 (m, 4H), 5.70–5.82 (m, 2H).

4.4.7. (±)-*trans*-3-Bromo-1-*tert*-butoxycarbonyl-4-hydroxypyrrolidine (±)-16. To a stirred mixture of **15** (17.3 g, 0.102 mol), DMSO (120 mL) and H_2O (6 mL), NBS (21.7 g, 0.122 mol) was gradually added over 15 min at 0°C. After stirring at room temperature for 2 h, water (140 mL) was added and the mixture was extracted with AcOEt. The organic layer was washed with saturated NaCl, dried over Na_2SO_4 and then concentrated in vacuo to give crude (±)-**16** as an oil (27.8 g): ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.23 (br s, 1H), 3.32–3.48 (m, 1H), 3.68–3.94 (m, 2H), 3.96–4.11 (m, 1H), 4.12–4.20 (m, 1H), 4.43–4.53 (m, 1H); MS m/z 266 (M^++1), 268 (M^++3); IR (neat) 3350, 1655 cm^{-1}.

4.4.8. (±)-*trans*-3-Benzylamino-1-*tert*-Butoxycarbonyl-4-hydroxypyrrolidine (±)-5. A mixture of crude (±)-**16** (27.8 g) and aqueous NaOH (1N, 128 mL, 0.128 mol) was stirred at room temperature for 1 h. The mixture was treated with benzylamine (27.3 g, 0.255 mol) and stirred at 65°C for 2 h, then cooled to 0°C. The resultant precipitates were collected by filtration, washed with water and *i*-Pr_2O and dried to give (±)-**5** as white crystals (17.5 g, 59% based on **15**). The spectral data were identical to that of an authentic sample of (±)-**5**.

4.4.9. X-Ray crystallographic analysis. The colorless prismatic crystals of (*S*,*S*)-**2b** having approximate dimensions of 1.00×0.40×0.2 mm were obtained from MeOH solution by slow evaporation at room temperature. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated CuKα radiation. The structure was solved by direct methods and refined by full-matrix least-squares methods with anisotropic temperature factors for non-H atoms. All H atoms found from difference Fourier maps were included in the calculation of the structure factors. The crystal data are as follows: $C_{20}H_{30}O_7N_2S_2$, M_r=474.59, orthorhombic, $P2_12_12_1$, a=11.620(2), b=26.562(2), c=7.421(1) Å, V=2290.5(5) Å^3, Z=4, D_{calcd}=1.376 g/cm^3, $F(000)$=1008.00, μ(CuKα)=24.34 cm^{-1}, T=293 K, R=0.038, S=1.07. Flack's χ parameter (–0.02 (3)) indicated that the absolute structure of **2b** was (*S*,*S*). Crystallographic details have been deposited at the Cambridge Crystallographic Data Centre (deposition number 167835).

Acknowledgements

We are grateful to Dr. K. Hino for his encouragement throughout this work. Thanks are also due to members of the Department of Physico Chemical Analysis of these laboratories for elemental analyses and spectral measurements.

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7. By the study of a variety of acids, *p*-toluenesulfonic acid was selected because only (*S*,*S*)-**2b** was non-hygroscopic. It is not necessary to protect the methylamino group of (*S*,*S*)-**2** because it was found that the methylamino group was less nucleophilic than the pyrrolidine for the nucleophilic substitution reaction with 1,8-naphthyridone derivative.
8. When **13** was methylated with NaH (1.2 equiv.) and MeI (1.1 equiv.) in THF, it gave an *O*-methylated product solely. This result implies that optically active 3-amino-4-methoxypyrrolidine could be prepared by this method.
9. The purity of (*S*,*S*)-**2b** was determined based on HPLC analyses of 2-(3-methoxy-4-methylamino pyrrolidinyl)-3-nitropyridine derived from the reaction with 2-chloro-3-nitropyridine.
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11. *tert*-Butyl carbamate is commercially available but expensive. *tert*-Butyl carbamate could be obtained from the reaction of hazardous sodium cyanate and *t*-BuOH with TFA, see: Loev, B.; Kormendy, M. F.; Goodman, M. M. *Org. Synth*. **1968**, *48*, 32.
12. Following the procedure described for (*S*,*S*)-**2a**, compound (±)-**3** was converted to (*R*,*R*)-**2a** by the use of (−)-tartaric acid via (*R*,*R*)-**3**, (*R*,*R*)-**10** and (*R*,*R*)-**11**; (*R*,*R*)-**3**·1.5(−)-tartaric acid, $[\alpha]_D^{29}$ −33.4 (*c* 1.02, MeOH); (*R*,*R*)-**3**, $[\alpha]_D^{27}$ −32.7 (*c* 1.02, MeOH); (*R*,*R*)-**10**, $[\alpha]_D^{29}$ −9.5 (*c* 1.08, MeOH), (*R*,*R*)-**11**, $[\alpha]_D^{29}$ −10.1 (*c* 1.05, MeOH); (*R*,*R*)-**2a**, $[\alpha]_D^{29}$ −12.2 (*c* 1.00, MeOH).
13. Following the procedure described for (*S*,*S*)-**2b**, compound (±)-**5** was converted to (*R*,*R*)-**2b** by the use of (−)-mandelic acid via (*R*,*R*)-**5** and (*R*,*R*)-**14**; (*R*,*R*)-**5**·(−)-mandelic acid, $[\alpha]_D^{26}$ −60.0 (*c* 0.50, MeOH); (*R*,*R*)-**5**, $[\alpha]_D^{29}$ −18.5 (*c* 0.52, MeOH); (*R*,*R*)-**14**, $[\alpha]_D^{28}$ −1.4 (*c* 1.01, MeOH); (*R*,*R*)-**2b**, $[\alpha]_D^{26}$ −10.2 (*c* 1.00, MeOH).