

Efficient Synthesis of (*R*)-6-Benzyloxycarbonylamino-1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepine. I

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An efficient and practical method for large scale synthesis of (*R*)-6-benzyloxycarbonylamino-1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepine (*R*-3), which is a key intermediate in the synthesis of DAT-582, a potent and selective serotonin-3 receptor antagonist, is described. The precursor of *R*-3, the (*S*)-2,3-diaminopropylaminoacetate *S*-5, was obtained from the chiral triaminopropane derivative *R*-19. Nucleophilic reaction of the chiral mesylate *R*-11 with 3-methylbenzylamine gave the racemic 2,3-diaminopropylaminoacetate ($\pm$)-5 via the achiral azetidinium cation 12, while the reaction of the *N*-protected mesylate *R*-14 produced the desired triamine *S*-15 but in poor yield. However, reaction of the *N*-protected mesylate *S*-18 with a large excess of methylamine proceeded smoothly to afford *R*-19 in good yield. *S*-5 was converted into *R*-3 with >99% enantiomeric excess using an intramolecular reductive cyclization method.

Key words (*R*)-6-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepine; DAT-582; (*S*)-2,3-diaminopropyl-aminoacetate; intramolecular reductive cyclization

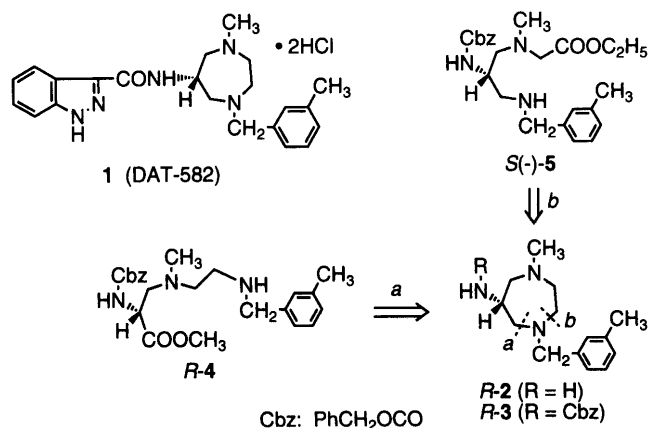
The serotonin-3 (5-HT₃) receptor is of special interest due to its involvement in various pathophysiological processes.¹⁾ Recently several 5-HT₃ receptor antagonists have been used clinically as antiemetics in cancer chemotherapy.²⁾ Furthermore, 5-HT₃ receptor antagonists are currently being investigated for use in the treatment of gastrointestinal disorders³⁾ or various centrally mediated disorders.⁴⁾

We have found a highly potent and selective 5-HT₃ receptor antagonist, (*R*)-(-)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide dihydrochloride (1, DAT-582).⁵⁾ For further pharmacological and toxicological studies, large scale production of DAT-582 was needed. Our previous paper⁶⁾ reported the chiral synthesis of (*R*)-6-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepine (*R*-2), a key intermediate in the synthesis of DAT-582 (Chart 1, path *a*). This route involves an intramolecular reductive cyclization⁷⁾ of the chiral 2,3-diaminopropionic ester *R*-4 to the 6-benzyloxycarbonylamino-1,4-diazepine *R*-3. This reaction is very useful, but in the case of large scale synthesis of *R*-3, the enantiomeric excess of *R*-3 was reduced. We thought that intramolecular reductive cyclization of the chiral 2,3-diaminopropylaminoacetate *S*-5 would proceed without racemization (Chart 1, path *b*). Here, we describe an efficient and practical synthetic method of the novel chiral 2,3-diaminopropylaminoacetate *S*-5, which is a precursor of *R*-3, and the conversion of *S*-5 to the optically active amine *R*-3.

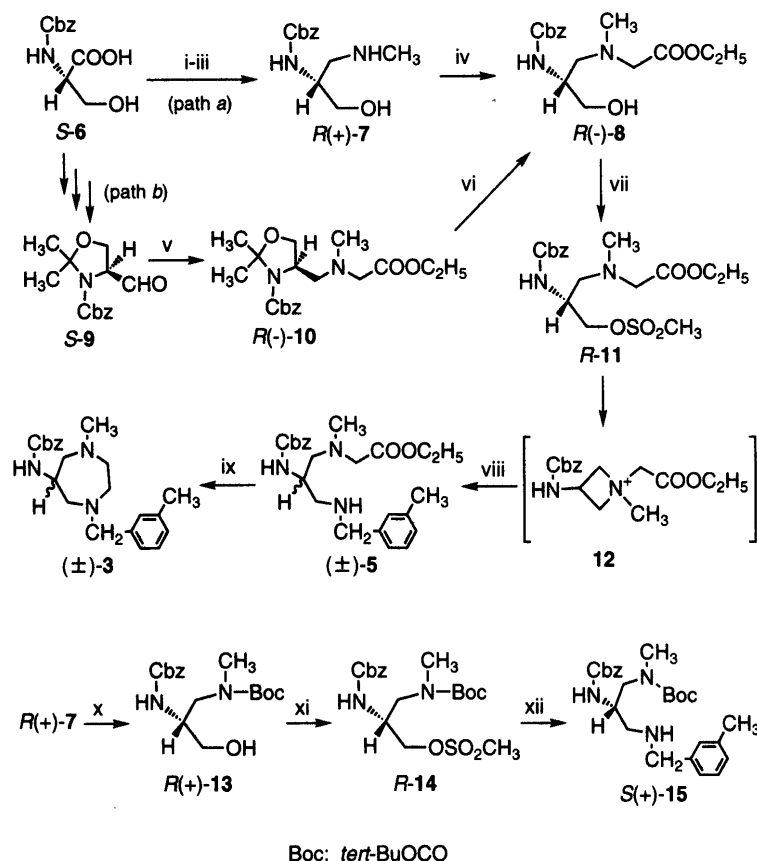
Synthetic Studies on the Chiral 2,3-Diaminopropylaminoacetate *S*-5 from *N*-Benzyloxycarbonyl-L-serine
Preparation of the chiral 2,3-diaminopropylaminoacetate *S*-5 from the commercially available *N*-benzyloxycarbonyl-L-serine (*S*-6) was examined first (Chart 2). Reaction of *S*-6 with methyl iodide in the presence of NaHCO₃ in *N,N*-dimethylformamide (DMF) followed by treatment of the resulting *N*-benzyloxycarbonyl-L-serine methyl ester with 30% methylamine in EtOH gave (*S*)-2-benzyloxycarbonylamino-3-hydroxy-*N*-methylpropionamide in 75% yield from *S*-6. Reduction of the amide with borane

in tetrahydrofuran (THF) followed by treatment with 1*N* aqueous hydrochloric acid at refluxing temperature afforded (*R*)-2-benzyloxycarbonylamino-3-methylaminopropanol (*R*-7) in 64% yield. Reaction of *R*-7 with ethyl bromoacetate gave the corresponding aminoacetate *R*-8 in 84% yield (path *a*). As an alternative route to *R*-8 (path *b*), treatment of benzyl (*S*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate⁸⁾ (*S*-9), which is a protected chiral serine equivalent and readily available from *S*-6, with sarcosine ethyl ester hydrochloride in the presence of sodium cyanoborohydride produced the oxazolidine derivative *R*-10 in 68% yield. Acid hydrolysis of *R*-10 afforded the aminoacetate *R*-8 in 86% yield. The enantiomeric purity of *R*-8 was determined to be >99% enantiomeric excess (ee) by chiral high-performance liquid chromatography (HPLC).

Reaction of *R*-8 with methanesulfonyl chloride in the presence of Et₃N gave the mesylate *R*-11, which without purification was treated with 3-methylbenzylamine to give the 2,3-diaminopropylaminoacetate 5 in 84% yield. Compound 5 was allowed to react with diisobutylaluminum hydride (DIBAL-H) followed by reduction with sodium borohydride to produce 6-benzyloxycarbonylamino-1-methyl-4-(3-methylbenzyl)hexahydro-1,4-dia-

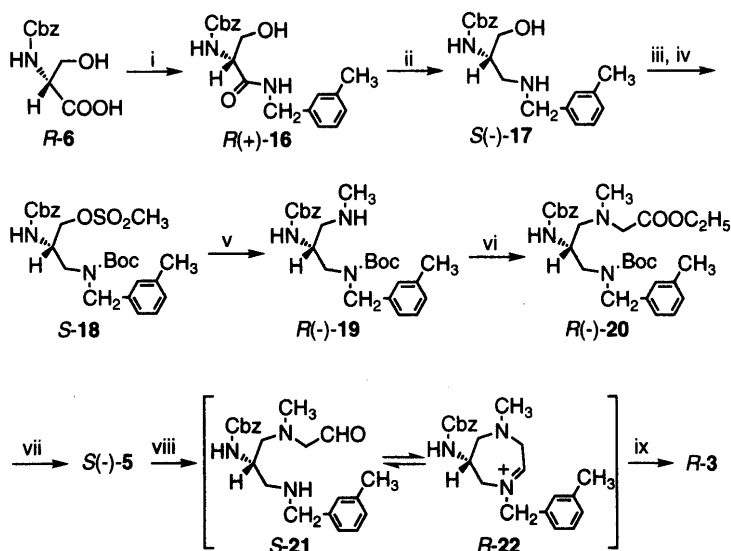


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i) MeI, NaHCO₃; ii) CH₃NH₂; iii) BH₃·THF; iv) BrCH₂CO₂C₂H₅, K₂CO₃; v) NaBH₃CN, CH₃NHCH₂CO₂C₂H₅·HCl; vi) HCl; vii) CH₃SO₂Cl, Et₃N; viii) 3-CH₃C₆H₄CH₂NH₂; ix) [(CH₃)₂CHCH₂]₂AlH then NaBH₄; x) (Boc)₂O; xi) CH₃SO₂Cl, Et₃N; xii) 3-CH₃C₆H₄CH₂NH₂

Chart 2



i) 3-CH₃C₆H₄CH₂NH₂, C₂H₅N=C=N(CH₂)₃N(CH₃)₂·HCl; ii) BH₃·THF; iii) (Boc)₂O; iv) CH₃SO₂Cl, Et₃N; v) CH₃NH₂; vi) BrCH₂COOC₂H₅, K₂CO₃; vii) HCl; viii) [(CH₃)₂CHCH₂]₂AlH; ix) NaBH₄

Chart 3

zepine (**3**) in good yield. Unfortunately, the product was found to be the racemate by chiral HPLC analysis. The postulated mechanism for the racemization in the reaction of *R*-**11** with 3-methylbenzylamine involves formation of

the achiral azetidinium cation **12** as an intermediate. Therefore, in order to avoid formation of **12**, a *tert*-butoxycarbonyl (Boc) group as a protecting group was introduced onto the amino group. Reaction of *R*-**7** with

di-*tert*-butyl dicarbonate afforded the *N*-Boc-3-aminopropanol **R-13** in 94% yield. In a similar manner to that described above, compound **R-13** was mesylated and successive treatment of the resulting *N*-protected mesylate **R-14** with 3-methylbenzylamine gave the 1,2,3-triaminopropane derivative **S-15**. However, the yield was poor (27% from **R-13**) because of the low reactivity of **R-14** compared with azetidinium cation **12**. As a result, an efficient and practical preparation of **S-5** from *N*-benzyloxycarbonyl-L-serine was unsuccessful.

Synthesis of Chiral 2,3-Diaminopropylaminoacetate S-5 from *N*-Benzyloxycarbonyl-D-serine We next examined a route to **S-5** from *N*-benzyloxycarbonyl-D-serine (**R-6**) (Chart 3). Condensation of **R-6** with 3-methylbenzylamine in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride as a coupling reagent gave (*R*)-2-benzyloxycarbonylamino-3-hydroxy-*N*-(3-methylbenzyl)propionamide (**R-16**) in 78% yield. Reduction of **R-16** with borane followed by treatment with 10% aqueous hydrochloric acid afforded the 3-aminopropanol **S-17** in 72% yield. Protection of the benzylamino moiety of **S-17** by a Boc group and subsequent mesylation of the hydroxy group gave the mesylate **S-18**, which was used in the next step without further purification. Reaction of **S-18** with a large excess of methylamine in refluxing EtOH proceeded smoothly to provide the expected triamine **R-19** in 73% yield from **S-17**. Reaction of **R-19** with ethyl bromoacetate followed by deprotection of the Boc group of the resulting aminoacetate **R-20** using 10% hydrochloric acid in EtOH gave the desired **S-5** in excellent yield. Overall yield of **S-5** from starting *N*-benzyloxycarbonyl-D-serine was 36% in 7 steps. We finally performed intramolecular reductive cyclization of the chiral 2,3-diaminopropylaminoacetate **S-5** according to the previously reported method.⁶⁾ Treatment of **S-5** with DIBAL-H at -70°C , followed by reduction of the iminium salt **R-22** derived from the aminoaldehyde **S-21** with sodium borohydride, gave the optically active hexahydro-1,4-diazepine **R-3** in 86% yield. The enantiomeric purity of **R-3** was $>99\%$ ee by chiral HPLC.

In conclusion, a novel and practical method for synthesis of (*R*)-6-benzyloxycarbonylamino-1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepine (**R-3**) was developed from *N*-benzyloxycarbonyl-D-serine as a source of chirality *via* the chiral precursor 2,3-diaminopropylaminoacetate **S-5** in 31% overall yield with high enantiomeric purity.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Hitachi 260-10 or a Shimadzu FTIR-8200PC spectrometer. $^1\text{H-NMR}$ spectra were recorded using a Varian Gemini-200 spectrometer (200 MHz). Chemical shifts are expressed as δ (ppm) values from tetramethylsilane as an internal standard and coupling constants (*J*) are given in Hz. Optical rotations were measured at 589 nm with a Jasco DIP-4 digital polarimeter. Analytical HPLC was performed with Shimadzu LC-6A and SPD-6A instruments. Organic extracts were dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. Silica gel FL60D (purchased from Fuji Silysia Co., Ltd.) was used for column chromatography.

(*R*)-2-Benzyloxycarbonylamino-3-methylamino-1-propanol [R(+)-7] A mixture of *N*-benzyloxycarbonyl-L-serine (**S-6**, 47.8 g, 0.2 mol), NaHCO_3 (33.6 g, 0.4 mol), methyl iodide (28.4 g, 0.4 mol) and DMF (250 ml) was stirred at room temperature for 16 h. The reaction mixture

was poured into ice-water and then extracted with ethyl acetate. The extract was washed successively with water and brine. The solvent was evaporated to give *N*-benzyloxycarbonyl-L-serine methyl ester (48.0 g) as a pale yellow oil, which was used in the next step without further purification. To a solution of *N*-benzyloxycarbonyl-L-serine methyl ester (48.0 g, 0.19 mol) in EtOH (100 ml) was added dropwise 30% methylamine in EtOH (62 g, 0.57 mol) at 5°C . The reaction mixture was stirred at room temperature for 16 h and then concentrated to dryness. The solid residue was recrystallized from ethyl acetate to give 38.0 g (75% for 2 steps) of (*S*)-2-benzyloxycarbonylamino-3-hydroxy-*N*-methylpropionamide (**S-23**), mp $116\text{--}117^{\circ}\text{C}$. To a solution of **S-23** (38.0 g, 0.15 mol) in anhydrous THF (760 ml) was added dropwise a 1 M solution in THF of $\text{BH}_3\text{-THF}$ complex (452 ml, 0.45 mol) at 5°C . The reaction mixture was stirred at room temperature for 16 h. 1 N HCl (226 ml) was added to the reaction mixture, and the mixture was heated at reflux for 1 h. After cooling to room temperature, the solvent was evaporated. The aqueous solution was made basic with 10% NaOH and then extracted with CHCl_3 . The extract was concentrated to dryness. The solid residue was recrystallized from ethyl acetate to give 25.7 g (64%) of **R(+)-7**, mp $120\text{--}121^{\circ}\text{C}$. $[\alpha]_D^{25} + 13.6^{\circ}$ ($c=1.0$, MeOH). $^1\text{H-NMR}$ (CDCl_3) δ : 2.42 (s, 3H, NCH_3), 2.67 (m, 2H, OH, NHCH_3), 2.75 (dd, $J=12$, 4, 1H, CHCH_2N), 2.98 (dd, $J=12$, 5, 1H, CHCH_2N), 3.65–3.95 (m, 3H, CHCH_2OH), 5.11 (s, 2H, CH_2Ph), 5.52 (m, 1H, NHCO_2), 7.37 (s, 5H, arom. H). IR (KBr) ν cm^{-1} : 1685, 1625. Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.39; H, 7.56; N, 11.80.

Benzyl (*R*)-4-[(*N*-Ethoxycarbonylmethyl-*N*-methylamino)methyl-2,2-dimethyloxazolidine-3-carboxylate [R(–)-10] Sodium cyanoborohydride (0.59 g, 9.5 mmol) was added portionwise to a mixture of sarcosine ethyl ester hydrochloride (5.9 g, 0.038 mol), benzyl (*S*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate⁸⁾ (**S-9**, 5.0 g, 0.019 mol) and MeOH (50 ml) at 5°C . The reaction mixture was stirred at room temperature for 16 h and then concentrated to dryness. The residue was chromatographed on silica gel with *n*-hexane–ethyl acetate (1:1) to give 4.7 g (68%) of **R(–)-10** as a pale brown oil. $[\alpha]_D^{25} - 41.0^{\circ}$ ($c=1.0$, MeOH). $^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (t, $J=7$, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.40–1.75 (m, 6H, $\text{CH}(\text{CH}_3)_2$), 2.29 (s, 3H, NCH_3), 2.4–2.8 (m, 2H, CHCH_2N), 3.1–3.4 (m, 2H, CH_2CO_2), 3.85–4.25 (m, 5H, 4-CH, 5- CH_2 , $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.10 (s, 2H, CH_2Ph), 7.35 (s, 5H, arom. H). IR (neat) ν cm^{-1} : 1725, 1695. Anal. Calcd for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_5$: C, 62.62; H, 7.82; N, 7.75. Found: C, 62.62; H, 7.74; N, 7.69.

Ethyl (*R*)-*N*-(2-Benzyloxycarbonylamino-3-hydroxy)propyl-*N*-methylaminoacetate [R(–)-8] (i) From **R(+)-7**: A mixture of **R(+)-7** (13.4 g, 56 mmol), K_2CO_3 (23 g, 167 mmol), ethyl bromoacetate (9.4 g, 56 mmol) and MeCN (268 ml) was heated at reflux for 2 h and cooled to room temperature. The insoluble materials were filtered off, and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel with CHCl_3 to give 15.2 g (84%) of **R(–)-8** as a pale yellow oil. $[\alpha]_D^{25} - 4.6^{\circ}$ ($c=1.0$, MeOH). $^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (t, $J=7$, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.38 (3H, s, NCH_3), 2.4–2.7 (m, 2H, CHCH_2N), 3.25 (d, $J=6$, 2H, CH_2CO_2), 3.11 (dd, $J=11$, 4, 1H, CH_2OH), 3.78 (m, 2H, CHNCO_2 , OH), 3.90 (dd, $J=11$, 4, 1H, CH_2OH), 4.18 (q, $J=7$, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.10 (s, 2H, CH_2Ph), 5.63 (m, 1H, NHCO_2), 7.35 (s, 5H, arom. H). IR (neat) ν cm^{-1} : 1710. Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.03; H, 7.35; N, 8.77. The enantiomeric excess ($>99\%$) of **R(–)-8**, thus obtained, was determined by chiral HPLC [column, chiral-AGP (Shinwa Chemical Industries, Ltd., Japan); $4.0\phi \times 100\text{ mm}$; eluent, 20 mM KH_2PO_4 (pH 7.0)–2-propanol (19:1); flow rate, 0.8 ml/min; column temperature, 25°C ; detection, 210 nm]. The retention time for **R(–)-8** and its enantiomer was 3.5 and 2.8 min, respectively.

(ii) From **R(–)-10**: A mixture of **R(–)-10** (3.2 g, 8.7 mmol), 10% HCl (32 ml) and THF (32 ml) was heated at 60°C for 4 h. After evaporation of solvent, the residue was made basic with aqueous NaHCO_3 solution and then extracted with ethyl acetate. The extract was concentrated to give a crude product, which was chromatographed on silica gel with CHCl_3 to afford 2.4 g (86%, $>99\%$ ee) of **R(–)-8** as a pale brown oil.

Ethyl *N*-[2-Benzyloxycarbonylamino-3-(3-methylbenzyl)amino]propyl-*N*-methylaminoacetate [(±)-5] Methanesulfonyl chloride (6.0 g, 53 mmol) was added dropwise to a mixture of **R(–)-8** (14.2 g, 44 mmol), triethylamine (5.8 g, 57 mmol) and CH_2Cl_2 (280 ml) at -5°C . The reaction mixture was stirred at room temperature for 1 h, washed with water, and concentrated to dryness. The residue including **R-11** was dissolved in MeCN (450 ml), and then K_2CO_3 (18.2 g, 138 mmol) and 3-methylbenzylamine (5.6 g, 46 mmol) were added. The mixture was

heated at reflux for 3 h and cooled to room temperature. The insoluble materials were filtered off, and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel with CHCl_3 -MeOH (30:1) to give 15.7 g (84%) of ($\pm$)-**5** as a pale yellow oil, which was converted to the fumarate in the usual manner, mp 137–139 °C (EtOH-diethyl ether). $[\alpha]_D^{25} + 0.3^\circ$ ($c = 1.0$, MeOH). $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.18 (t, $J = 7$, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.30, 2.32 (each s, each 3H, NCH_3 , $3\text{-CH}_3\text{C}_6\text{H}_4$), 2.41–2.87 (m, 4H, CHCH_2N), 3.22 (d, $J = 17$, 1H, CH_2CO_2), 3.34 (d, $J = 17$, 1H, CH_2CO_2), 3.81 (m, 1H, CHNCO_2), 3.83 (s, 2H, $\text{NCH}_2\text{C}_6\text{H}_4$), 4.07 (q, $J = 7$, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.02 (s, 2H, OCH_2Ph), 6.54 (s, 2H, CHCO_2H), 7.05–7.38 (m, 10H, arom. H, NHCO_2), 9.90 (m, 3H, NHCH_2 , CO_2H). IR (KBr) ν cm^{-1} : 1730, 1690. Anal. Calcd for $\text{C}_{24}\text{H}_{33}\text{N}_3\text{O}_4 \cdot \text{C}_4\text{H}_4\text{O}_4$: C, 61.86; H, 6.86; N, 7.73. Found: C, 61.78; H, 6.76; N, 7.70.

(R)-2-Benzylloxycarbonylamino-3-[N-(tert-butoxycarbonyl)-N-methyl]amino-1-propanol [R(+)-13] Di-tert-butyl dicarbonate (0.58 g, 2.7 mmol) was added dropwise to a solution of *R*(+)-**7** (0.6 g, 2.5 mmol) in CHCl_3 (12 ml) at 5 °C. The reaction mixture was stirred at room temperature for 2 h, washed with water, and concentrated to dryness. The residue was chromatographed on silica gel with CHCl_3 to give 0.8 g (94%) of *R*(+)-**13** as an oil. $[\alpha]_D^{25} + 18.3^\circ$ ($c = 0.5$, MeOH). $^1\text{H-NMR}$ (CDCl_3) δ : 1.45 (s, 9H, $\text{C}(\text{CH}_3)_3$), 2.89 (s, 3H, NCH_3), 3.04 (dd, $J = 6$, 2, 1H, OH), 3.45–3.91 (m, 5H, CH_2CHCH_2), 5.11 (s, 2H, CH_2Ph), 5.42 (d, $J = 3$, 1H, NHCO_2), 7.35 (s, 5H, arom. H). Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}_5$: C, 60.34; H, 7.74; N, 8.28. Found: C, 60.12; H, 7.81; N, 8.24.

(S)-2-Benzylloxycarbonylamino-3-[N-(tert-butoxycarbonyl)-N-methyl]amino-1-(3-methylbenzyl)aminopropane [S(+)-15] Methanesulfonyl chloride (0.34 g, 3.0 mmol) was added dropwise to a mixture of *R*(+)-**13** (0.8 g, 2.4 mmol), triethylamine (0.38 g, 3.7 mmol) and CH_2Cl_2 (10 ml) at –5 °C. The reaction mixture was stirred at room temperature for 1 h, washed with water and concentrated to dryness. The residue including *R*-**14** was dissolved in MeCN (40 ml) and then K_2CO_3 (1.0 g, 7.2 mmol) and 3-methylbenzylamine (0.31 g, 2.5 mmol) were added. The reaction mixture was heated at reflux for 3 h and cooled to room temperature. The insoluble materials were filtered off, and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel with CHCl_3 to give 0.3 g (27%) of *S*(+)-**15** as a pale yellow oil. $[\alpha]_D^{25} + 0.7^\circ$ ($c = 1.0$, MeOH). $^1\text{H-NMR}$ (CDCl_3) δ : 1.42 (s, 9H, $\text{C}(\text{CH}_3)_3$), 2.32 (s, 3H, $3\text{-CH}_3\text{C}_6\text{H}_4$), 2.48–2.83 (m, 2H, $\text{CHCH}_2\text{NCH}_2\text{C}_6\text{H}_4$), 2.83 (s, 3H, NCH_3), 3.25–3.41 (m, 2H, $\text{CHCH}_2\text{NCH}_3$), 3.72 (s, 2H, $\text{NCH}_2\text{C}_6\text{H}_4$), 3.86 (m, 1H, CHNCO_2), 5.08 (s, 2H, OCH_2Ph), 5.65 (m, 1H, NHCO_2), 7.02–7.42 (m, 10H, arom. H, NHCH_2). Anal. Calcd for $\text{C}_{25}\text{H}_{35}\text{N}_3\text{O}_4$: C, 68.00; H, 7.99; N, 9.52. Found: C, 67.77; H, 8.14; N, 9.54.

(R)-2-Benzylloxycarbonylamino-3-hydroxy-N-(3-methylbenzyl)propionamide [R(+)-16] A mixture of *N*-benzylloxycarbonyl-D-serine (*R*-**6**, 300 g, 1.26 mol), 3-methylbenzylamine (167 g, 1.38 mol), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (266 g, 1.38 mol) and CHCl_3 (9000 ml) was stirred at room temperature for 16 h, washed with water and concentrated to dryness. The residue was dissolved in DMF and poured into ice-water. The resulting precipitates were collected by filtration and washed with water to afford 334 g (78%) of *R*(+)-**16** as white crystals, mp 132–134 °C. $[\alpha]_D^{25} + 4.2^\circ$ ($c = 0.5$, MeOH). $^1\text{H-NMR}$ (CDCl_3) δ : 2.34 (s, 3H, CH_3), 2.65 (s, 1H, OH), 3.68 (dd, $J = 11$, 5, 1H, CH_2OH), 4.13 (dd, $J = 11$, 3, 1H, CH_2OH), 4.25 (m, 1H, CHNCO_2), 4.39 (d, $J = 6$, 2H, $\text{NCH}_2\text{C}_6\text{H}_4$), 5.10 (s, 2H, OCH_2Ph), 5.85 (d, $J = 8$, 1H, NHCO_2), 6.90 (m, 1H, CONH), 7.08–7.51 (m, 9H, arom. H). IR (KBr) ν cm^{-1} : 1680, 1635. Anal. Calcd for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.41; H, 6.42; N, 8.17.

(S)-2-Benzylloxycarbonylamino-3-(3-methylbenzyl)amino-1-propanol [S(-)-17] To a solution of *R*(+)-**16** (195 g, 0.57 mol) in anhydrous THF (3900 ml) was added dropwise a 1 M solution of BH_3 -THF complex (1710 ml, 1.71 mol) at 5 °C. The reaction mixture was stirred at room temperature for 16 h. After addition of 1 N HCl (1700 ml), the mixture was heated at reflux for 4 h and cooled to room temperature. The THF was evaporated, and the resulting aqueous solution was made basic with 10% NaOH and extracted with CHCl_3 . The extract was concentrated to dryness. The residue was recrystallized from diethyl ether to give 135 g (72%) of *S*(-)-**17**, mp 83–84 °C. $[\alpha]_D^{25} - 3.9^\circ$ ($c = 1.0$, MeOH). $^1\text{H-NMR}$ (CDCl_3) δ : 1.75 (s, 1H, OH), 2.32 (s, 3H, NCH_3), 2.40 (dd, $J = 13$, 4, 1H, CHCH_2N), 3.02 (dd, $J = 13$, 5, 1H, CHCH_2N), 3.65–3.92 (m, 3H, CHCH_2OH), 3.73 (s, 2H, $\text{NCH}_2\text{C}_6\text{H}_4$), 5.10 (s, 2H, OCH_2Ph), 5.49 (m, 1H, NHCO_2), 7.03–7.40 (m, 10H, arom. H, NHCH_2). IR (KBr) ν cm^{-1} : 1675. Anal. Calcd for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_3$: C, 69.49; H, 7.37;

N, 8.53. Found: C, 69.25; H, 7.35; N, 8.51.

(R)-2-Benzylloxycarbonylamino-3-[N-tert-butoxycarbonyl-N-(3-methylbenzyl)]amino-1-methylaminopropane [R(-)-19] Di-tert-butyl dicarbonate (12.4 g, 57 mmol) was added dropwise to a solution of *S*(-)-**17** (17 g, 52 mmol) in CHCl_3 (170 ml) at 5 °C. The reaction mixture was stirred at room temperature for 2 h, washed with water, and concentrated to dryness to give 25 g of (*S*)-2-benzylloxycarbonylamino-3-[*N*-tert-butoxycarbonyl-*N*-(3-methylbenzyl)]amino-1-propanol (*S*-**24**) as an oil. To a mixture of *S*-**24** (25 g), triethylamine (7.8 g, 78 mmol) and CH_2Cl_2 (250 ml) was added dropwise methanesulfonyl chloride (7.1 g, 62 mmol) at –5 °C. The reaction mixture was stirred at room temperature for 1 h, washed with water, and concentrated to dryness. The residue including the mesylate *S*-**18** was dissolved in 30% methylamine in EtOH (200 ml), and the solution was heated at reflux for 6 h. After cooling to room temperature, the solvent was evaporated. The residue was chromatographed on silica gel with CHCl_3 to give 16.6 g (73%) of *R*(-)-**19** as a pale yellow oil. $[\alpha]_D^{25} - 8.0^\circ$ ($c = 1.0$, MeOH). $^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (s, 9H, $\text{C}(\text{CH}_3)_3$), 2.32, 2.37 (each s, each 3H, NCH_3 , $3\text{-CH}_3\text{C}_6\text{H}_4$), 2.50 (dd, $J = 11$, 4, 1H, CH_2NCH_3), 2.67 (dd, $J = 11$, 4, 1H, CH_2NCH_3), 3.12–3.53 (m, 2H, CH_2NBoc), 3.88 (m, 1H, CHNCO_2), 4.32 (d, $J = 16$, 1H, $\text{NCH}_2\text{C}_6\text{H}_4$), 4.49 (d, $J = 16$, 1H, NCH_2Ph), 5.09 (s, 2H, OCH_2Ph), 5.66 (m, 1H, NHCO_2), 6.90–7.41 (m, 10H, arom. H, NHCH_2). IR (neat) ν cm^{-1} : 1710, 1680. Anal. Calcd for $\text{C}_{25}\text{H}_{35}\text{N}_3\text{O}_4$: C, 68.00; H, 7.99; N, 9.52. Found: C, 67.64; H, 8.06; N, 9.58.

Ethyl (R)-N-[2-Benzylloxycarbonylamino-3-[N-tert-butoxycarbonyl-N-(3-methylbenzyl)]aminopropyl]-N-methylaminoacetate [R(-)-20] A mixture of *R*(-)-**19** (5.4 g, 122 mmol), K_2CO_3 (8.4 g, 610 mmol), ethyl bromoacetate (2.1 g, 122 mmol) and MeCN (270 ml) was heated at reflux for 2 h and cooled to room temperature. The insoluble materials were filtered off, and the filtrate was concentrated to dryness. The residue was chromatographed on silica gel with CHCl_3 to give 5.6 g (88%) of *R*(-)-**20** as a pale yellow oil. $[\alpha]_D^{25} - 15.0^\circ$ ($c = 0.9$, MeOH). $^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (t, $J = 7$, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.3–1.7 (m, 9H, $\text{C}(\text{CH}_3)_3$), 2.31 (s, 6H, NCH_3 , $3\text{-CH}_3\text{C}_6\text{H}_4$), 2.35–2.70 (m, 2H, $\text{CHCH}_2\text{NCH}_2\text{C}_6\text{H}_4$), 3.21 (s, 2H, NCH_2CO_2), 3.20–3.65 (m, 2H, $\text{CHCH}_2\text{NCH}_3$), 3.79 (m, 1H, CHNCO_2), 4.15 (q, $J = 7$, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.30 (d, $J = 15$, 1H, $\text{NCH}_2\text{C}_6\text{H}_4$), 4.55 (d, $J = 15$, 1H, $\text{NCH}_2\text{C}_6\text{H}_4$), 5.04 (d, $J = 13$, 1H, OCH_2Ph), 5.14 (d, $J = 13$, 1H, OCH_2Ph), 5.80 (m, 1H, NHCO_2), 6.91–7.40 (m, 9H, arom. H). IR (neat) ν cm^{-1} : 1710, 1680. Anal. Calcd for $\text{C}_{29}\text{H}_{41}\text{N}_3\text{O}_6$: C, 66.01; H, 7.83; N, 7.96. Found: C, 65.91; H, 7.96; N, 7.89.

Ethyl (S)-N-[2-Benzylloxycarbonylamino-3-(3-methylbenzyl)amino]propyl-N-methylaminoacetate [S(-)-5] A mixture of *R*(-)-**20** (5.6 g, 106 mmol) and 10% HCl in EtOH (56 ml) was stirred at room temperature for 3 h. After evaporation of the solvent, the residue was made basic with aqueous NaHCO_3 solution and then extracted with CHCl_3 . The extract was concentrated to give a crude product, which was chromatographed on silica gel with CHCl_3 to afford 4.5 g (99%) of *S*(-)-**5** as a pale brown oil. $[\alpha]_D^{25} - 11.3^\circ$ ($c = 1.0$, MeOH). $^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (t, $J = 7$, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.32, 2.35 (each s, each 3H, NCH_3 , $3\text{-CH}_3\text{C}_6\text{H}_4$), 2.58 (d, $J = 7$, 2H, $\text{CHCH}_2\text{NCH}_3$), 2.77 (dd, $J = 14$, 5, 1H, $\text{CHCH}_2\text{NCH}_2\text{C}_6\text{H}_4$), 2.90 (dd, $J = 14$, 5, 1H, $\text{CHCH}_2\text{NCH}_2\text{C}_6\text{H}_4$), 3.24 (s, 2H, NCH_2CO_2), 3.80 (s, 2H, $\text{NCH}_2\text{C}_6\text{H}_4$), 3.82 (m, 1H, CHNCO_2), 4.15 (q, $J = 7$, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.10 (s, 2H, OCH_2Ph), 5.78 (m, 1H, NHCO_2), 7.03–7.41 (m, 10H, arom. H, NHCH_2). IR (neat) ν cm^{-1} : 1710. Anal. Calcd for $\text{C}_{24}\text{H}_{33}\text{N}_3\text{O}_4$: C, 67.42; H, 7.78; N, 9.83. Found: C, 67.38; H, 7.72; N, 9.82.

(R)-6-Benzylloxycarbonylamino-1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepine (R-3) DIBAL-H (1 M solution in toluene, 41 ml, 41 mmol) was added dropwise to a solution of *S*-**5** (2.5 g, 5.9 mmol) in anhydrous THF (108 ml) at –70 °C. The mixture was stirred at the same temperature for 0.5 h, and the excess reagent was decomposed with MeOH (40 ml) at –70 °C. The reaction mixture was warmed to –10 °C, and then sodium borohydride (440 mg, 11.7 mmol) was added in small portions. The mixture was stirred at room temperature for 15 h and concentrated to dryness. The residue was dissolved in CHCl_3 , and the solution was washed successively with water and brine. The solvent was evaporated to leave an oil, which was chromatographed on silica gel with CHCl_3 -MeOH (50:1) to give 1.8 g (86%) of *R*-**3** as a pale yellow oil. This compound was identical (IR, $^1\text{H-NMR}$) with the sample⁶⁾ obtained by an alternative synthesis. The enantiomeric excess (>99%) of *R*-**3** thus obtained was determined by chiral HPLC [column, Chiralcel OD (Daicel Chemical Industries, Ltd., Japan); 4.6 ϕ $\times$ 250 mm; eluent, hexane-2-propanol (7:3, including 0.1% diethylamine); flow rate,

1.0 ml/min; column temperature; 20 °C, detection; 215 nm]. The retention time for *R*-3 and the enantiomer was 5.6 and 9.2 min, respectively.

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