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 (±)-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-aminohexahydro-1,4-diazepine; DAT-582; (*S*)-2,3-diaminopropyl-aminoacetate; intramolecular reductive cyclization

The serotonin-3 (5-HT_3) receptor is of special interest due to its involvement in various pathophysiological processes.[1] Recently several 5-HT_3 receptor antagonists have been used clinically as antiemetics in cancer chemotherapy.[2] Furthermore, 5-HT_3 receptor antagonists are currently being investigated for use in the treatment of gastrointestinal disorders[3] or various centrally mediated disorders.[4]

We have found a highly potent and selective 5-HT_3 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 paper[6] 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 cyclization[7] 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 $NaHCO_3$ 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-oxazolidinecarboxylate[8] (*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 Et_3N 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-

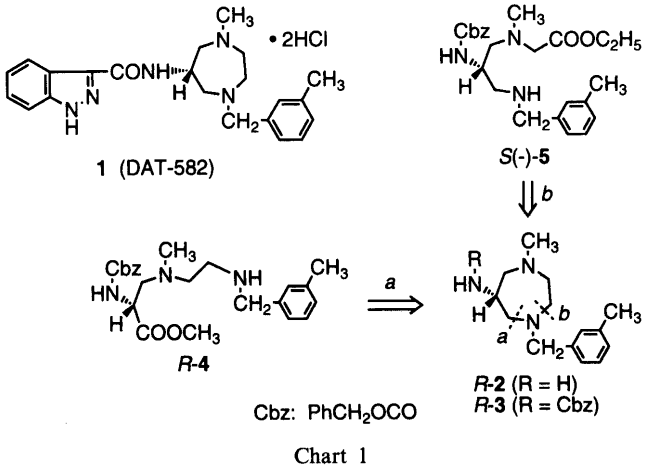

Chart 1

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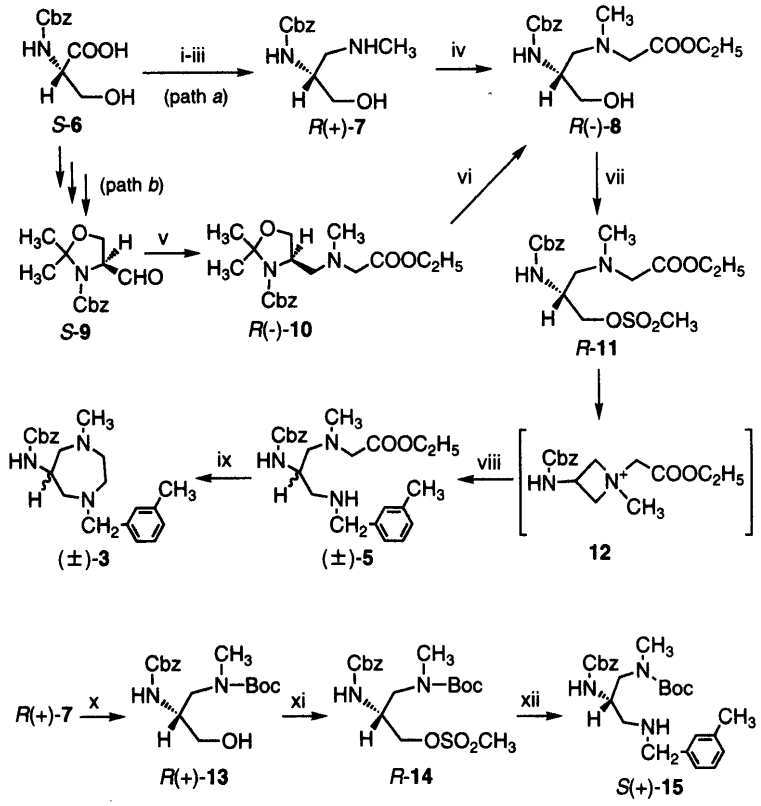
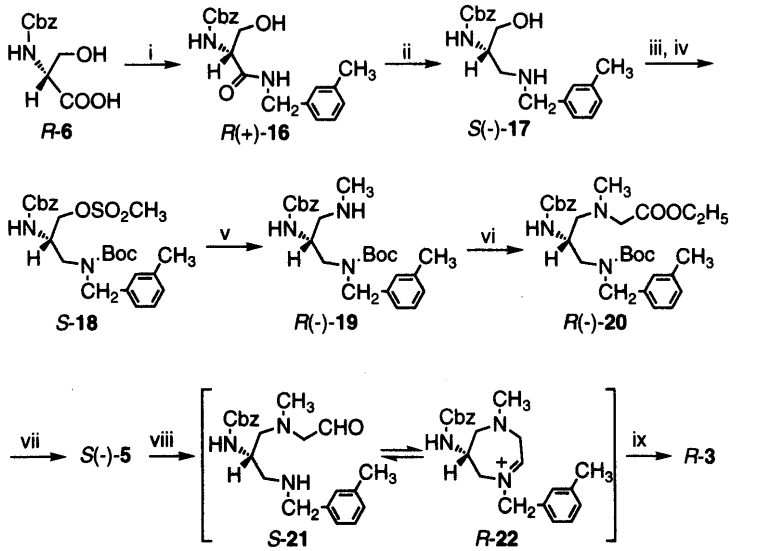


Boc: *tert*-BuOCO

i) MeI, $NaHCO_3$; ii) CH_3NH_2; iii) BH_3•THF; iv) $BrCH_2CO_2C_2H_5$, K_2CO_3; v) $NaBH_3CN$, $CH_3NHCH_2CO_2C_2H_5$•HCl; vi) HCl; vii) CH_3SO_2Cl, Et_3N; viii) 3-$CH_3C_6H_4CH_2NH_2$; ix) $[(CH_3)_2CHCH_2]_2AlH$ then $NaBH_4$; x) $(Boc)_2O$; xi) CH_3SO_2Cl, Et_3N; xii) 3-$CH_3C_6H_4CH_2NH_2$

Chart 2



i) 3-$CH_3C_6H_4CH_2NH_2$, $C_2H_5N{=}C{=}N(CH_2)_3N(CH_3)_2$•HCl; ii) BH_3•THF; iii) $(Boc)_2O$; iv) CH_3SO_2Cl, Et_3N; v) CH_3NH_2; vi) $BrCH_2COOC_2H_5$, K_2CO_3; vii) HCl; viii) $[(CH_3)_2CHCH_2]_2AlH$; ix) $NaBH_4$

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 $-70\,^{\circ}C$, 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}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—117 °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 BH_3–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—121 °C. $[\alpha]_D^{25}$ +13.6° (c=1.0, MeOH). ^{1}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 $C_{12}H_{18}N_2O_3$: 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*-methyl)amino]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-carboxylate[8] (*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° (c=1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, J=7, 3H, $CO_2CH_2CH_3$), 1.40—1.75 (m, 6H, $CH(CH_3)_2$), 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, $CO_2CH_2CH_3$), 5.10 (s, 2H, CH_2Ph), 7.35 (s, 5H, arom. H). IR (neat) ν cm^{-1}: 1725, 1695. *Anal.* Calcd for $C_{19}H_{28}N_2O_5$: 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° (c=1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, J=7, 3H, $CO_2CH_2CH_3$), 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, $CO_2CH_2CH_3$), 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 $C_{16}H_{24}N_2O_5$: 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 ϕ × 100 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 (±)-**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° (c=1.0, MeOH). ^{1}H-NMR (DMSO-d_6) δ: 1.18 (t, J=7, 3H, $CO_2CH_2C\underline{H}_3$), 2.30, 2.32 (each s, each 3H, NCH_3, 3-$C\underline{H}_3C_6H_4$), 2.41—2.87 (m, 4H, $CHC\underline{H}_2N$), 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, $NC\underline{H}_2C_6H_4$), 4.07 (q, J=7, 2H, $CO_2C\underline{H}_2CH_3$), 5.02 (s, 2H, OCH_2Ph), 6.54 (s, 2H, $C\underline{H}CO_2H$), 7.05—7.38 (m, 10H, arom. H, $NHCO_2$), 9.90 (m, 3H, $N\underline{H}CH_2$, CO_2H). IR (KBr) ν cm^{-1}: 1730, 1690. *Anal.* Calcd for $C_{24}H_{33}N_3O_4 \cdot C_4H_4O_4$: C, 61.86; H, 6.86; N, 7.73. Found: C, 61.78; H, 6.76; N, 7.70.

(*R*)-2-Benzyloxycarbonylamino-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° (c=0.5, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.45 (s, 9H, $C(CH_3)_3$), 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 $C_{17}H_{26}N_2O_5$: C, 60.34; H, 7.74; N, 8.28. Found: C, 60.12; H, 7.81; N, 8.24.

(*S*)-2-Benzyloxycarbonylamino-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° (c=1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (s, 9H, $C(CH_3)_3$), 2.32 (s, 3H, 3-$C\underline{H}_3C_6H_4$), 2.48—2.83 (m, 2H, $CHC\underline{H}_2NCH_2C_6H_4$), 2.83 (s, 3H, NCH_3), 3.25—3.41 (m, 2H, $CHC\underline{H}_2NCH_3$), 3.72 (s, 2H, $NC\underline{H}_2C_6H_4$), 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, $N\underline{H}CH_2$). *Anal.* Calcd for $C_{25}H_{35}N_3O_4$: C, 68.00; H, 7.99; N, 9.52. Found: C, 67.77; H, 8.14; N, 9.54.

(*R*)-2-Benzyloxycarbonylamino-3-hydroxy-*N*-(3-methylbenzyl)propion-amide [R(+)-16] A mixture of *N*-benzyloxycarbonyl-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° (c=0.5, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.34 (s, 3H, CH_3), 2.65 (s, 1H, OH), 3.68 (dd, J=11, 5, 1H, $C\underline{H}_2OH$), 4.13 (dd, J=11, 3, 1H, $C\underline{H}_2OH$), 4.25 (m, 1H, $CHNCO_2$), 4.39 (d, J=6, 2H, $NC\underline{H}_2C_6H_4$), 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 $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.41; H, 6.42; N, 8.17.

(*S*)-2-Benzyloxycarbonylamino-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° (c=1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.75 (s, 1H, OH), 2.32 (s, 3H, NCH_3), 2.40 (dd, J=13, 4, 1H, $CHC\underline{H}_2N$), 3.02 (dd, J=13, 5, 1H, $CHC\underline{H}_2N$), 3.65—3.92 (m, 3H, $C\underline{H}C\underline{H}_2OH$), 3.73 (s, 2H, $NC\underline{H}_2C_6H_4$), 5.10 (s, 2H, OCH_2Ph), 5.49 (m, 1H, $NHCO_2$), 7.03—7.40 (m, 10H, arom. H, $N\underline{H}CH_2$). IR (KBr) ν cm^{-1}: 1675. *Anal.* Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.25; H, 7.35; N, 8.51.

(*R*)-2-Benzyloxycarbonylamino-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-benzyloxycarbonylamino-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° (c=1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (s, 9H, $C(CH_3)_3$), 2.32, 2.37 (each s, each 3H, NCH_3, 3-$C\underline{H}_3C_6H_4$), 2.50 (dd, J=11, 4, 1H, $C\underline{H}_2NCH_3$), 2.67 (dd, J=11, 4, 1H, $C\underline{H}_2NCH_3$), 3.12—3.53 (m, 2H, CH_2NBoc), 3.88 (m, 1H, $CHNCO_2$), 4.32 (d, J=16, 1H, $NC\underline{H}_2C_6H_4$), 4.49 (d, J=16, 1H, $NC\underline{H}_2Ph$), 5.09 (s, 2H, OCH_2Ph), 5.66 (m, 1H, $NHCO_2$), 6.90—7.41 (m, 10H, arom. H, $N\underline{H}CH_2$). IR (neat) ν cm^{-1}: 1710, 1680. *Anal.* Calcd for $C_{25}H_{35}N_3O_4$:C, 68.00; H, 7.99; N, 9.52. Found: C, 67.64; H, 8.06; N, 9.58.

Ethyl (*R*)-*N*-[2-Benzyloxycarbonylamino-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° (c=0.9, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (t, J=7, 3H, $CO_2CH_2C\underline{H}_3$), 1.3—1.7 (m, 9H, $C(CH_3)_3$), 2.31 (s, 6H, NCH_3, 3-$C\underline{H}_3C_6H_4$), 2.35—2.70 (m, 2H, $CHC\underline{H}_2NCH_2C_6H_4$), 3.21 (s, 2H, $NC\underline{H}_2CO_2$), 3.20—3.65 (m, 2H, $CHC\underline{H}_2NCH_3$), 3.79 (m, 1H, $CHNCO_2$), 4.15 (q, J=7, 2H, $CO_2C\underline{H}_2CH_3$), 4.30 (d, J=15, 1H, $NC\underline{H}_2C_6H_4$), 4.55 (d, J=15, 1H, $NC\underline{H}_2C_6H_4$), 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 $C_{29}H_{41}N_3O_6$: C, 66.01; H, 7.83; N, 7.96. Found: C, 65.91; H, 7.96; N, 7.89.

Ethyl (*S*)-*N*-[2-Benzyloxycarbonylamino-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° (c=1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, J=7, 3H, $CO_2CH_2C\underline{H}_3$), 2.32, 2.35 (each s, each 3H, NCH_3, 3-$C\underline{H}_3C_6H_4$), 2.58 (d, J=7, 2H, $CHC\underline{H}_2NCH_3$), 2.77 (dd, J=14, 5, 1H, $CHC\underline{H}_2NCH_2C_6H_4$), 2.90 (dd, J=14, 5, 1H, $CHC\underline{H}_2NCH_2C_6H_4$), 3.24 (s, 2H, NCH_2CO_2), 3.80 (s, 2H, $NC\underline{H}_2C_6H_4$), 3.82 (m, 1H, $CHNCO_2$), 4.15 (q, J=7, 2H, $CO_2C\underline{H}_2CH_3$), 5.10 (s, 2H, OCH_2Ph), 5.78 (m, 1H, $NHCO_2$), 7.03—7.41 (m, 10H, arom. H, $N\underline{H}CH_2$). IR (neat) ν cm^{-1}: 1710. *Anal.* Calcd for $C_{24}H_{33}N_3O_4$: C, 67.42; H, 7.78; N, 9.83. Found: C, 67.38; H, 7.72; N, 9.82.

(*R*)-6-Benzyloxycarbonylamino-1-methyl-4-(3-methylbenzyl)hexa-hydro-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}H-NMR) with the sample[6] 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 × 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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