Efficient Synthesis of (R)-6-Benzylloxycarbonylamino-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-benzylloxycarbonylamino-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 (±)S 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.

Keywords: (R)-6-amino-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. Recently several 5-HT₃ receptor antagonists have been used clinically as antiemetics in cancer chemotherapy. Furthermore, 5-HT₃ receptor antagonists are currently being investigated for use in the treatment of gastrointestinal disorders or various centrally mediated disorders.

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]-1H-indazole-3-carboxamide dihydrochloride (I, DAT-582). For further pharmacological and toxicological studies, large scale production of DAT-582 was needed. Our previous paper 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 of the chiral 2,3-diaminopropionic ester R-4 to the 6-benzylloxycarbonylamino-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-diaminopropylaminoacetae 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-Benzylloxycarbonyl-L-serine
Preparation of the chiral 2,3-diaminopropylaminoacetate S-5 from the commercially available N-benzylloxycarbonyl-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-benzylloxycarbonyl-L-serine methyl ester with 30% methylamine in EtOH gave (S)-2-benzylloxycarbonylamino-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-benzylloxycarbonylamino-3-methylaminopropanol (R-7) in 64% yield. Reaction of R-7 with ethyl bromoacetate gave the corresponding amine 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 (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 amine R-8 in 85% 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 diisobutyldiamidohydrid (DIBAL-H) followed by reduction with sodium borohydride to produce 6-benzylloxycarbonylamino-1-methyl-4-(3-methylbenzyl)hexahydro-1,4-dia-
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-amino- propane 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 azetidinon cation 12. As a result, an efficient and practical preparation of S-5 from N-benzylxycarbonyl-t-serine was unsuccessful.

**Synthesis of Chiral 2,3-Diaminopropylaminocacete S-5 from N-Benzylxycarbonyl-d-serine (Chart 3)**. Condensation of R-6 with 3-methylbenzylamine in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]-carboximidide hydrochloride as a coupling reagent gave (R)-2-benzylxycarbonylaminopropano-3-hydoxy-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-amino propanol S-17 in 72% yield. Protection of the benzylamine 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 aminocacete R-20 using 10% hydrochloric acid in EtOH gave the desired S-5 in excellent yield. Overall yield of S-5 from starting N-benzylxycarbonyl-d-serine was 36% in 7 steps. We finally performed intramolecular reductive cyclization of the chiral 2,3-diaminopropylaminocacete S-5 according to the previously reported method.21 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-benzylxycarbonylaminol-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepine (R-3) was developed from N-benzylxycarbonyl-t-serine as a source of chirality via the chiral precursor 2,3-diaminopropylaminocacete 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. 1H-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 F60 (purchased from Fuji Silysia Co., Ltd.) was used for column chromatography.

(R)-2-Benzylxycarboonylaminol-3-methylaminol-1-propanol [R (++)-7]

A mixture of N-benzylxycarbonyl-t-serine (5.6, 47.8 g, 0.2 mol), NaHCO3 (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-benzylxycarbonyl-t-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-benzylxycarbonyl-t-serine methyl ester (48.0 g, 0.19 mol) in anhydrous THF (760 ml) was added dropwise a 1 N solution of THF of BH3·THF complex (452 ml, 0.45 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-benzylxycarbonylamino-3-hydoxy-N-methylpropiolamide (S-23), mp 116–117 °C. To a solution of S-23 (38.0 g, 0.15 mol) in anhydrous MeOH (180 ml) was added dropwise a 1 N solution of THF of BH3·THF complex (452 ml, 0.45 mol) at 5 °C. The reaction mixture was stirred at room temperature for 16 h. 1H NMR (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 CH2Cl2. 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. [α]25D +13.6° (c = 1, MeOH). 1H-NMR (CDCl3): δ 4.24 (s, 3H, NCH3), 2.67 (m, 2H, OH, NHCH2), 2.75 (dd, J = 12, 4, 1H, CH2N), 2.98 (dd, J = 12, 5, 1H, CH2N), 3.65–3.95 (3H, 3H, CH2CH2OH), 5.11 (s, 2H, CH2Ph), 5.52 (m, 1H, NHCO2), 7.37 (s, 7H, arom. H). IR (KBr) cm⁻¹: 1685, 1625. Anal. Calcd for C16H17NO3: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.39; H, 7.56; N, 11.80.

(S)-4-(N-Ethoxycarbonylamino)-2,2-dimethylxazolidin-3-carboxylic acid [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-dimethylxazolidin-3-carboxylic acid8 (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 recrystallized from ethyl acetate on silica gel with n-hexane:ethyl acetate (1:1) to give 4.7 g (68%) of R-(-)-10 as a pale brown oil. [α]25D +41.0° (c = 1.0, MeOH). 1H-NMR (CDCl3) δ: 1.25 (t, J = 7, 3H, CO2CH2CH3), 1.40–1.75 (m, 6H, CH2CH2N), 2.29 (s, 3H, NCH3), 2.4–2.8 (m, 2H, CH2CCHN), 3.1–3.4 (m, 2H, CH2CO), 3.85–4.25 (m, 5H, 4H, CH2CH2N), 5.10 (s, 2H, CH2Ph), 7.35 (s, 3H, arom. H). IR (neat) cm⁻¹: 1725, 1695. Anal. Calcd for C16H18NO3: C, 62.62; H, 7.82; N, 7.75. 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-HPLC [Shinwa Chemical Industries, Ltd., Japan]; 40 °C, 100 mm; eluent, 20 ml/ min, MeOH:CH2Cl2 = 90:10). 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.

(i) From R-(-)-10: A mixture of R-(-)-10 (3.2 g, 8.7 mmol), 10% Pd/C (32 ml) and THF (32 ml) was heated at 60 °C for 4 h. After evaporation of the solvent, the residue was made basic with aqueous NaHCO3 solution and then extracted with ethyl acetate. The extract was concentrated to give a crude product, which was chromatographed on silica gel with CHCl3 to afford 2.4 g (86%, >99% ee) of R-(-)-8 as a pale brown oil.

(ii) From R-(-)-10: A mixture of N-benzylxycarbonyl-3-methylaminol-1-propanol [R (++)-7] Methanesulfonfyl 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 CH2Cl2 (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 K2CO3 (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 10 g of silica gel (32-60 mesh, with CH₂Cl₂ as eluent) with a gradient (for 30 min) to give 15.7 (84%) of (±)-5 as a pale yellow oil, which was converted to the furamate in the usual manner, mp 131.7 °C (EtOH-diethyl ether). [α]D +3.3° (c = 1.0, MeOH). 

**1H-NMR (DMSO-d₆) δ**: 1.18 (t, J = 7.7, 3H, CO₂CH₃), 2.30, 2.32 (each, s, each 3H, NCH₃, 3-C₆H₅CH₂), 2.41-2.87 (m, 4H, CH₂CH₃CH₂), 3.22 (d, J = 17.1, 1H, CH₂CH₂CO₂H), 3.34 (d, J = 17.1, 1H, CH₂CO₂H), 3.81 (m, 1H, CH₂CO₂H), 3.83 (s, 2H, NCH₂CH₂), 4.07 (q, J = 7.2, CO₂CH₃CH₂), 5.02 (s, 2H, OCH₂Ph), 6.54 (s, 2H, CO₂CH₃), 7.05-7.38 (m, 10H, arom. H, NH₂CO₂H), 9.90 (m, 3H, NH₂CH₂CO₂H) [IR (KBr) ν cm⁻¹: 1730, 1690]. Anal. Caled for C₈H₁₄N₂O₄·C₄H₆O₂: C, 61.86; H, 6.86; N, 7.73. Found: C, 61.78; H, 6.76; N, 7.70.

**2-(Benzyloxy)benzylamine-3-[(N-tert-butoxycarbonyl)-N-methyl]-amino-1-propanol** [Re]+[13] Di-tert-butyl carbamate (0.58 g, 2.7 mmol) was added to a solution of the crude product from (±)-5 (0.25 g, 1.1 mmol) in 15 ml of CHCl₃ (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 CHCl₃ to give 0.8 g (94%) of (R)+[13] as an oil. [α]D +18.3° (c = 0.5, MeOH). 

**1H-NMR (CDCl₃) δ**: 1.45 (s, 9H, C(CH₃)₃), 2.89 (s, 3H, NCH₃), 3.04 (dd, J = 6, 2.1, 1H, OCH₂), 3.45-3.91 (m, 5H, 3H, CH₂OCH₂CH₂), 5.11 (s, 2H, PhCH), 5.42 (d, J = 15.9, 1H, C₆H₅CH₂), 7.43-7.55 (m, 5H, PhCH), 7.74, 8.29. Found: C, 72.20; H, 7.81; N, 8.24.

**2-(Benzyloxy)benzylamine-3-[(N-tert-butoxycarbonyl)-N-methyl]-amino-1-(3-methylbenzyl)laminopropane [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 CH₂Cl₂ (10 ml) at 0 °C, and the reaction mixture was stirred at room temperature for 3 h, washed with water and concentrated to dryness. The residue was chromatographed on silica gel with CH₂Cl₂ to give 0.5 g (93%) of the product as a pale yellow oil. [α]D +15.0° (c = 0.9, MeOH). 

**1H-NMR (CDCl₃) δ**: 1.24 (t, J = 7.7, 3H, CO₂CH₃), 1.3-1.7 (m, 9H, C(CH₃)₃), 2.21 (s, 3H, NCH₃), 2.35-2.37 (m, 2H, CH₂CH₃), 2.35-2.70 (m, 2H, CH₂NCH₂CH₂), 3.12 (s, 2H, NCH₂CO₂H), 3.20-3.35 (m, 2H, CH₂CH₂NCH₂), 3.79 (m, 1H, OCH₂Ph), 4.15 (q, J = 7.2, CO₂CH₃CH₂), 4.30 (d, J = 15.1, NH₂CO₂H), 4.55 (d, J = 15.1, NH₂CO₂H), 5.04 (d, J = 13.1, OCH₂Ph), 5.14 (d, J = 13.1, OCH₂Ph), 5.90 (m, 1H, NH₂CO₂H), 6.19 (m, 1H, arom. H, NH₂CO₂H), 7.84 (s, 1H, O(CH₃)₂), 8.04 (s, 1H, N(CH₃)₂). Found: C, 75.91; H, 7.31; N, 5.92. Anal. Caled for C₃₁H₃₀N₄O₂·H₂O: C, 56.00; H, 5.54; N, 4.54.

**Ethyl (S)-[N-2-(Benzyloxy)benzylamine-3-[(N-tert-butoxycarbonyl)-N-methyl]-amino]-propyl-N-methylaminoacetate [R]+[20] A mixture of (R)-[19] (5.4 g, 122 mmol), K₂CO₃ (8.4 g, 61 mmol), ethyl bromocacetate (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 CHCl₃ to give 0.9 g (93%) of the product as a yellow oil. [α]D +15.0° (c = 0.9, MeOH). 

**1H-NMR (CDCl₃) δ**: 1.24 (t, J = 7.7, 3H, CO₂CH₃), 1.3-1.7 (m, 9H, C(CH₃)₃), 2.21 (s, 3H, NCH₃), 2.35-2.37 (m, 2H, CH₂CH₃), 2.35-2.70 (m, 2H, CH₂NCH₂CH₂), 3.12 (s, 2H, NCH₂CO₂H), 3.20-3.35 (m, 2H, CH₂CH₂NCH₂), 3.79 (m, 1H, OCH₂Ph), 4.15 (q, J = 7.2, CO₂CH₃CH₂), 4.30 (d, J = 15.1, NH₂CO₂H), 4.55 (d, J = 15.1, NH₂CO₂H), 5.04 (d, J = 13.1, OCH₂Ph), 5.14 (d, J = 13.1, OCH₂Ph), 5.90 (m, 1H, NH₂CO₂H), 6.19 (m, 1H, arom. H, NH₂CO₂H), 7.84 (s, 1H, O(CH₃)₂), 8.04 (s, 1H, N(CH₃)₂). Found: C, 75.91; H, 7.31; N, 5.92. Anal. Caled for C₃₁H₃₀N₄O₂·H₂O: C, 56.00; H, 5.54; N, 4.54.
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.

References