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TETRAHEDRON

Efficient Synthesis of (*R*)-6-Benzyloxycarbonylamino-1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepine. 2.[1] Novel Formation of Hexahydro-1,4-diazepine Ring using 1,2,3-Trisubstituted Aminopropane Derivative and Glyoxal

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Abstract: An efficient and practical method for synthesis of the optically active hexahydro-1,4-diazepine **2**, which is a key intermediate of DAT-582, a potent and selective serotonin-3 receptor antagonist, is described. Treatment of the (*R*)-1,2,3-trisubstituted aminopropane dihydrochloride **5b** prepared from methyl (*S*)-1-tritylaziridine-2-carboxylate (**4**) *via* the (*S*)-1-benzyloxycarbonylaziridine-2-carboxamide **8** with glyoxal in the presence of $NaBH_3CN$ or boran-triethylamine complex directly gave **2** in good yield without racemization.

INTRODUCTION

(*R*)-(-)-*N*-[1-Methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide [(*R*)-**1**, DAT-582 as its dihydrochloride] has shown a highly potent and selective 5-HT_3 receptor antagonistic activity and was selected as a promising candidate for potential antiemetic agent against the emesis induced by anticancer drugs.[2] DAT-582 is structurally novel and unrelated to any other potent 5-HT_3 receptor antagonists reported.[3]

In our earlier study, (*R*)-**1** was provided by optical resolution of the racemates.[4,5] We then focused our efforts on the discovery of an efficient method for the asymmetric synthesis of the hexahydro-1,4-diazepine **2**. As a result, we developed an original synthetic method[1] of **2** involving an intramolecular reductive cyclization of the chiral aminoaldehyde **3** derived from D-serine (Scheme 1, path *a*). However, this route was unamenable to large-scale production as it requires low temperature (–70 °C) for the preparation of **3** and uses the expensive D-serine. We then planned an alternative synthetic route using (*S*)-aziridine-2-carboxylate **4**[6,7] prepared from the more readily available L-serine. We expected that the treatment of the chiral 1,2,3-trisubstituted aminopropane **5a** prepared *via* regioselective aziridine ring-opening with glyoxal would give an intermolecular reductive cyclization product **2** (Scheme 1, path *b*). To our knowledge, there has been no report on the hexahydro-1,4-diazepine ring formation using glyoxal thus far.

This paper describes an efficient and practical synthetic route to the optically active amine **2** from L-serine.

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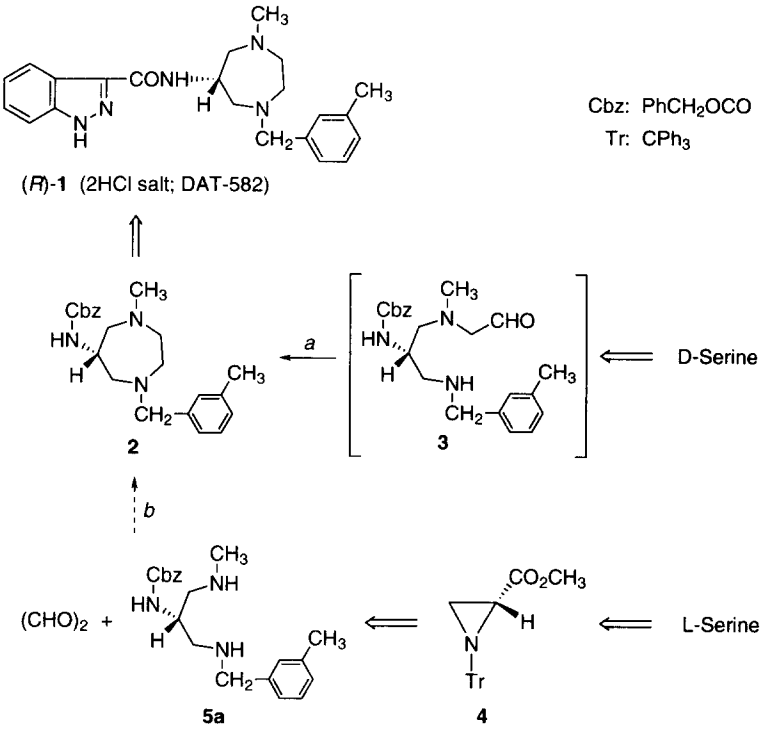
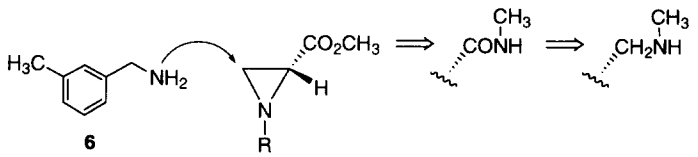


Scheme 1

RESULTS AND DISCUSSION

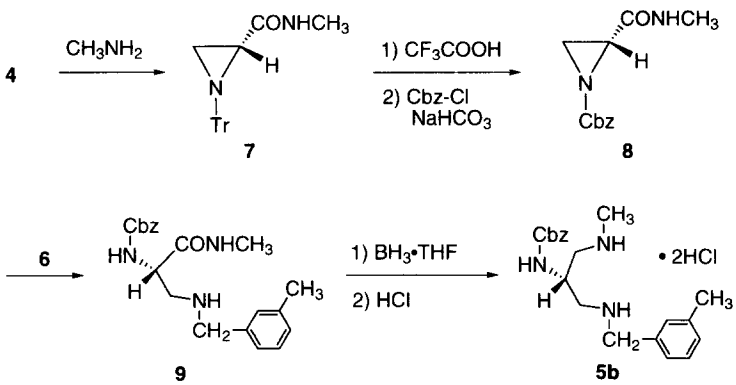
We first examined the preparation of the chiral 1,2,3-trisubstituted aminopropane **5a** from the known aziridine-2-carboxylate **4** derived from L-serine methyl ester hydrochloride. To obtain **5a** with three different amino groups, two points were at issue: the conversion of **4** to the corresponding *N*-methylamide without aziridine ring-opening and the regioselective aziridine ring-opening reaction with 3-methylbenzylamine (**6**). The *N*-methylamide moiety was reduced to produce the *N*-methylamino group (Scheme 2). In general,



Scheme 2

nonactivated aziridine derivatives contain a basic nitrogen atom like **4**, aziridine ring-opening reactions usually occur only after protonation, quaternization, or formation of a Lewis acid adduct.[8] Thus, treatment of **4** with

40% methylamine in EtOH at room temperature gave the aziridine-2-carboxamide **7** in 95% yield without ring-opening reaction products (Scheme 3). The enantiomeric purity of **7** was determined to be practically >99% enantiomeric excess (ee) on the basis of chiral HPLC. Activated aziridines containing an electrophilic group on nitrogen considerably increase the reactivity of the aziridine ring. Thus, the aziridine ring-opening reaction with **6** was achieved by using *N*-benzyloxycarbonyl (Cbz) aziridine. According to a previous report[9], the trityl group of **7** was changed to the Cbz group (giving **8**) in 67% yield. Reaction of **8** with **6** in toluene at 80 °C gave the C_3-N aziridine ring-opened product **9** in 79% yield. In this reaction, the unwanted C_2-N aziridine ring-opening product was not detected by TLC analysis. Reduction of the amide moiety of **9** with borane in THF followed by treatment with 10% HCl-EtOH afforded the desired (*R*)-1,2,3-triaminopropane dihydrochloride **5b** in 51% yield. This synthetic route to **5b** is suitable for large-scale production as none of its steps involve column chromatography.



Scheme 3

We next investigated the formation of a hexahydro-1,4-diazepine ring using **5b** and glyoxal. The results are summarized in Table. Reduction of **5b** with 1.3 equiv. of 40% aqueous glyoxal solution in the presence of $NaBH_3CN$ (1 equiv.) as a reducing agent in MeOH at room temperature proceeded smoothly, and the desired hexahydro-1,4-diazepine **2** was isolated in 53% yield (entry 1). Spectroscopic data of **2** thus obtained were identical with those prepared by a different route. Furthermore, the enantiomeric purity of **2** was determined to be practically >99% ee on the basis of chiral HPLC. In order to improve the yield of **2**, the reducing agent and the reaction conditions were examined. Increasing the amount of $NaBH_3CN$ to 2 equiv. improved the yield of **2** to 71% (entry 2). However, use of 3 equiv. of glyoxal resulted in a decrease in yield (entry 3). The reaction using $NaBH_4$ instead of $NaBH_3CN$ provided no favorable influence on yield (entry 4). The addition of triethylamine caused a slight increase in yield (*ca.* 55%, entries 5 and 6). Next, the reaction under catalytic hydrogenation using PtO_2 was performed. In both cases without triethylamine and with 2 equiv. of triethylamine, the desired **2** was not isolated (entries 7 and 8). On the other hand, **2** was isolated in 54% yield when a small amount of acetic acid was added (entry 9). Finally borane-triethylamine complex was used as a reducing agent (entries 10-12). Entries 10 and 11 had comparable yields to that of entry 5, and entry 12 conferred the highest yield (79%). Thus, the use of 4 equiv. of borane-triethylamine complex and 1.3 equiv. of glyoxal were found to be the optimum conditions. The present method can be easily scaled up and provides a practical route to **2**.

Table. Reductive Cyclization of **5b** with Glyoxal[a]

Entry	Reducing agent (equiv.)	Et_3N (equiv.)	glyoxal (equiv.)	yield[b] **3** (%)
1	$NaBH_3CN$ (1)	none	1.3	53
2	$NaBH_3CN$ (2)	none	1.3	71
3	$NaBH_3CN$ (2)	none	3.0	53
4	$NaBH_4$ (4)	none	2.0	45
5	$NaBH_4$ (3)	2	1.3	56
6	$NaBH_4$ (5)	2	3.0	54
7	PtO_2 / H_2	none	2.0	0
8	PtO_2 / H_2	2	2.0	0
9[c]	PtO_2 / H_2	2	2.0	54
10	$BH_3 \cdot Et_3N$ (2)	2	1.3	56
11	$BH_3 \cdot Et_3N$ (3)	none	1.3	56
12	$BH_3 \cdot Et_3N$ (4)	none	1.3	79

[a]See experimental section. [b]Isolated yield. [c]A small amount of acetic acid was added.

In conclusion, an efficient and practical method for synthesis of (*R*)-6-benzyloxycarbonylamino-1-methyl-4-(3-methylbenzyl)-hexahydro-1,4-diazepine (**2**), which has served as an intermediate of DAT-582, from L-serine methyl ester hydrochloride as a source of chirality *via* the (*R*)-1,2,3-triaminopropane dihydrochloride **5b** was developed with high enantiomeric purity. This method comprises the novel hexahydro-1,4-diazepine ring formation by reductive cyclization of **5b** and glyoxal in the presence of a reducing agent.

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.

(*S*)-(-)-*N*-Methyl-1-tritylaziridine-2-carboxamide (7) To a solution of methyl (*S*)-1-tritylaziridine-2-carboxylate[6,7] (**4**, 200 g, 0.58 mol) in $CHCl_3$ (400 ml) was added dropwise 40% methylamine in EtOH (323 g, 2.91 mol) at room temperature. The reaction mixture was stirred at room temperature for 6 days. The solvent was evaporated and the residual solid was recrystallized from 2-propanol to give 189 g (95%) of **7**, mp 178—180 °C. $[\alpha]_D^{25}$ -96.5° (*c* = 1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (d, *J* = 7, 1H, 3-CH_2), 1.95 (d, *J* = 3, 1H, 3-CH_2), 2.03 (dd, *J* = 7, 3, 1H, 2-CH), 2.92 (d, *J* = 5, 3H, CH_3), 6.76 (m, 1H,

NH), 7.18—7.44 (m, 15H, arom. H). IR (KBr) ν cm^{-1}: 1665, 1640. *Anal.* Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.46; H, 6.45; N, 8.09. The enantiomeric excess (>99%) of **7** was analyzed by chiral HPLC [column, URTRON ES-OVM (Shinwa Chemical Industries, Ltd., Japan); 6.0 ϕ × 250 mm; eluent, 20 mM KH_2PO_4 (pH 4.6)—2-propanol (19 : 1); flow rate, 1.0 ml/min; column temperature; 25 °C, detection; 220 nm]. The retention time for **7** and the enantiomer was 15.3 min and 18.1 min, respectively.

(*S*)-(-)-*N*-Methyl-1-benzyloxycarbonyaziridine-2-carboxamide (8) To a solution of **7** (80.0 g, 0.23 mol) in a mixture of $CHCl_3$ (240 ml) and MeOH (240 ml) was added dropwise trifluoroacetic acid (267 g, 2.34 mol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then concentrated to dryness. The residue was dissolved in water and washed with ethyl acetate. The aqueous solution including (*S*)-*N*-methyl-aziridine-2-carboxamide was neutralized with solid Na_2CO_3 (39.3 g, 0.47 mol), and then $CHCl_3$ (400 ml) was added. After addition of benzyl chloroformate (35.8 g, 0.21 mol) at 0—10 °C, the reaction mixture was stirred at room temperature for 5 h. The organic layer was separated and concentrated to dryness. The solid residue was recrystallized from ethyl acetate—hexane to give 36.6 g (67%) of **8**, mp 100—102 °C. $[\alpha]_D^{25}$ -42.2° (*c* = 1.1, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (d, *J* = 4, 1H, 3-CH_2), 2.48 (d, *J* = 7, 1H, 3-CH_2), 2.80 (d, *J* = 5, 3H, CH_3), 3.30 (dd, *J* = 7, 4, 1H, 2-CH), 5.16 (s, 2H, OCH_2Ph), 6.22 (m, 1H, NH), 7.38 (s, 5H, arom. H). IR (KBr) ν cm^{-1}: 1720, 1640. *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.27; H, 5.98; N, 11.82.

(*S*)-(+)-2-Benzyloxycarbonylamino-*N*-methyl-3-(3-methylbenzyl)aminopropionamide (9) To a solution of **8** (40.0 g, 0.17 mol) in toluene (160 ml) was added dropwise 3-methylbenzylamine (**6**, 20.8 g, 0.17 mol) at room temperature. The reaction mixture was stirred at 80 °C for 6 h, and a mixture of toluene (80 ml) and hexane (320 ml) was added to the solution. After cooling at *ca.* 0 °C, the resulting precipitates were collected by filtration to afford 47.8 g (79%) of **9**, mp 132—134 °C (toluene). $[\alpha]_D^{25}$ +3.4° (*c* = 1.5, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.34 (s, 3H, 3-C<u>H</u>$_3$C$_6$H$_4$), 2.65 (dd, *J* = 12, 8, 1H, CHC<u>H</u>$_2$N), 2.79 (d, *J* = 5, 3H, NCH_3), 3.25 (dd, *J* = 12, 4, 1H, CHC<u>H</u>$_2$N), 3.68 and 3.81(each d, *J* = 14, each 1H, NC<u>H</u>$_2$C$_6$H$_4$), 4.09 (m, 1H, $CHNCO_2$), 5.12 (s, 2H, OCH_2Ph), 5.98 (m, 1H, $NHCO_2$), 7.04—7.51 (m, 9H, arom. H). IR (KBr) ν cm^{-1}: 1715, 1642. *Anal.* calcd for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.44; H, 7.06; N, 11.79.

(*R*)-(-)-2-Benzyloxycarbonylamino-1-methylamino-3-(3-methylbenzyl)aminopropane dihydrochloride (5b) To a solution of **9** (14.2 g, 40 mmol) in anhydrous THF (280 ml) was added dropwise 1M solution of BH_3-THF complex (200 ml, 200 mmol) at 10 °C. The reaction mixture was stirred at room temperature for 72 h. After addition of 1N aqueous H_2SO_4 solution (100 ml), the mixture was heated to reflux for 2 h and cooled to room temperature. Most of THF was evaporated, and the resulting aqueous solution was basified with 10% aqueous NaOH solution and extracted with $CHCl_3$. The extract was concentrated to dryness. 10 % HCl in EtOH (36 g, 100 mmol) was added to the residue, and the resulting precipitates were collected by filtration to afford 7.8 g (51%) of **5b**, mp 191—193 °C (EtOH). $[\alpha]_D^{25}$ -7.5° (*c* = 1.0, MeOH). ^{1}H-NMR (DMSO-d_6) δ: 2.32 (s, 3H, 3-C<u>H</u>$_3$C$_6$H$_4$), 2.52 (s, 3H, NCH_3) , 2.92—3.29 (m, 4H, CHC<u>H</u>$_2$N), 3.35 (s, 2H, NH), 3.35 (s, 2H, NC<u>H</u>$_2$C$_6$H$_4$), 4.28 (m, 1H, $CHNCO_2$), 5.07 (s, 2H, OCH_2Ph), 7.20—7.45 (m, 9H, arom. H), 7.66 (br, 1H, $NHCO_2$) , 9.10 and 9.49 (each br, each 1H, HCl). IR (KBr) ν cm^{-1}: 1680, 1635. *Anal.* calcd for $C_{20}H_{27}N_3O_2 \cdot 2HCl$: C, 57.97; H, 7.05; N, 10.14; Cl, 17.11. Found: C, 57.77; H, 7.12; N, 10.09; Cl, 16.98.

(*R*)-6-Benzyloxycarbonylamino-1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepine (2) General procedure (Table, Entry 2)

Sodium cyanoborohydride (0.3 g, 4.8 mmol) was added portionwise to a mixture of **5b** (1.0 g, 2.4 mmol), 40% glyoxal (0.46 g, 3.2 mmol) and MeOH (10 ml) at 5 °C. The reaction mixture was stirred at room temperature for 6 h and then concentrated. The residue was dissolved in $CHCl_3$, and the solution was washed with saturated $NaHCO_3$ solution and brine. The solvent was evaporated to give the oily residue,[10] which was chromatographed on silica gel with $CHCl_3$ — MeOH (50 : 1) to give 0.63 g (71%) of **2** as a pale yellow oil. This compound was identical with the sample obtained by the alternative synthesis[7] by comparison of IR and ^{1}H-NMR spectra. The enantiomeric excess (>99%) of **2** thus obtained was analyzed by chiral HPLC.[1]

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10. The pure carboxamide (*R*)-**1** was obtained by several crystallizations of the crystals which were prepared from the crude amine **2** without column chromatography.