Asymmetric Synthesis of (*R*)-6-Amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepine from L-Asparagine

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An efficient asymmetric synthesis of (*R*)-6-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepine [(*R*)-**2**] which serves as the amine part of (*R*)-**1**, a potent and selective 5-HT_3 receptor antagonist, is described. Formation of the hexahydro-1*H*-1,4-diazepine ring was achieved by the intramolecular amidation of the optically active aminocarboxylic acid **18** or reductive cyclization of the optically active aminoaldehyde **25**. Compounds **18** and **25** were prepared from L-asparagine *via* the key aziridine derivatives **15** and **22**, respectively, with retention of the configuration. The intramolecular aziridine ring opening reaction of **29** gave the C_2-N bond cleavage product of the aziridine ring, the piperazin-5-one **30**, as the main product along with the desired 7-membered ring, the hexahydro-1*H*-1,4-diazepine product **19**.

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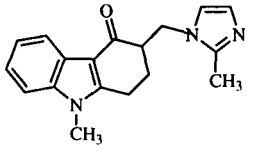
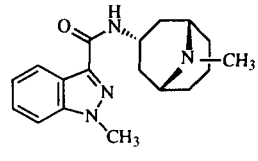
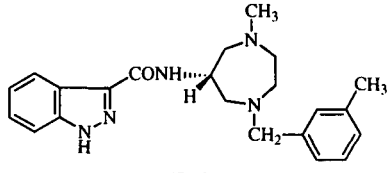
Serotonin 5-HT_3 receptor antagonists, for example ondansetron and granisetron, have been shown to be clinically effective for the blockade of chemotherapy-induced emesis in cancer patients [1,2]. In addition, 5-HT_3 receptor antagonists have been investigated for use in the treatment of various centrally mediated disorders such as anxiety, drug abuse, and schizophrenia [2]. Among the 5-HT_3 receptor antagonists reported previously, a number of compounds possess the quinuclidine, tropane, and granatane rings as a basic moiety. We previously reported that the structurally novel compound (*R*)-(-)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide [(*R*)-**1**] is a potent 5-HT_3



ondansetron



granisetron



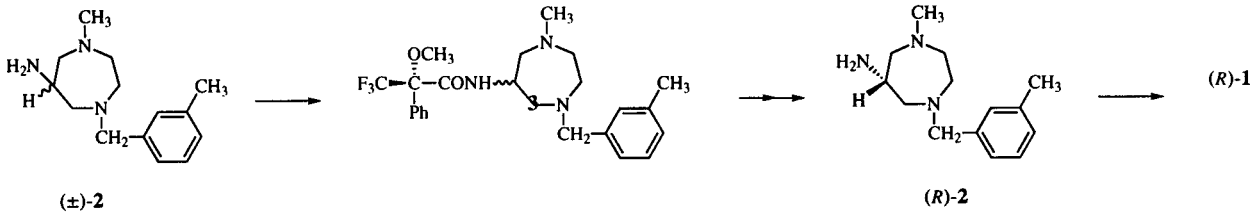
(*R*)-**1**

receptor antagonist as evidenced by inhibition of the von Bezold-Jarisch reflex in rats and of cisplatin-induced emesis in ferrets and dogs [3]. Small quantities of the optically active amine 6-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepine [(*R*)-**2**] were prepared involving the separation of the Mosher's amide **3** derived from the racemic amine (±)-**2**, and condensation of (*R*)-**2** with 1*H*-indazole-3-carboxylic acid [4] produced the carboxamide (*R*)-**1** (Scheme 1) [5]. However, the method was not practical because of the low yield and the requirement of the expensive Mosher's acid. Our interest has been in the discovery of an alternative synthetic route which could eventually be used for the manufacture of the optically active amine (*R*)-**2**. In this paper, we present our results on asymmetric synthesis of (*R*)-**2** from L-asparagine as a starting material.

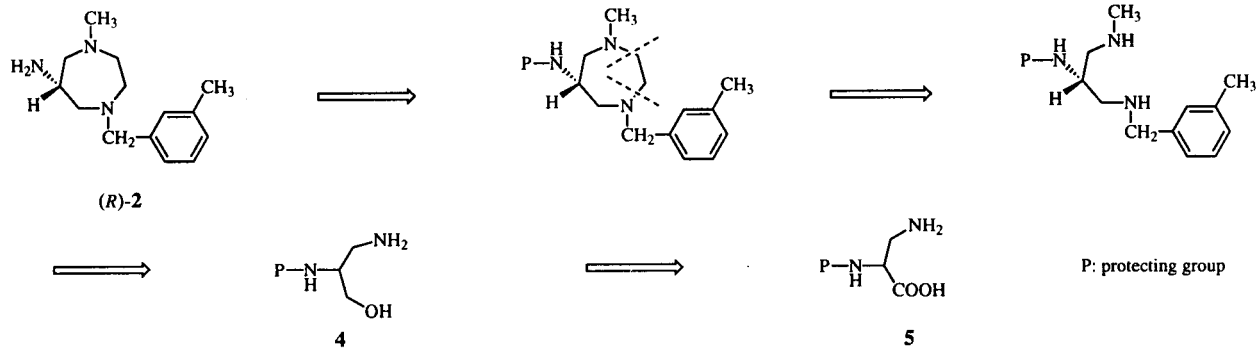
On the basis of *retro*-synthetic consideration for the optically active (*R*)-**2**, we planned to prepare firstly the protected 2,3-diamino-1-propanol **4** as a key intermediate *via* N^2-protected L-2,3-diaminopropionic acid **5** (Scheme 2). As L-2,3-diaminopropionic acid is a constituent amino acid of several antibiotics, a number of preparations of L-2,3-diaminopropionic acid and closely related analogs from asparagine, aspartic acid, serine, and lactone have been reported [6]. Among them, we adopted the conversion of N^2-[4-toluenesulfonyl(tosyl)]-L-asparagine (**6**) to N^2-tosyl-L-2,3-diaminopropionic acid (**7**) by means of the Hofmann rearrangement [7-10]. This method seems to be amenable to large-scale production.

N^2-Tosyl-L-asparagine (**6**) obtained from L-asparagine monohydrate as described previously [8] was added to aqueous sodium hypobromide solution, which was prepared from aqueous sodium hydroxide solution and bromine below 0°. The mixture was then heated at *ca.* 80° followed by acidification with 35% aqueous hydrochloric acid to give N^2-tosyl-L-2,3-diaminopropionic acid (**7**) in 78% yield, without formation of the cyclic urea, imidazolidin-2-one, which was obtained by intramolecular addition to the intermediate isocyanate of the amide moiety at the α-position [6f]. After protection of the β-amino group with a *tert*-butoxycarbonyl (Boc) group, treatment of the resulting N^2,N^3-diprotected 2,3-diaminopropionic acid **8** with methyl iodide in the presence of sodium hydrogen

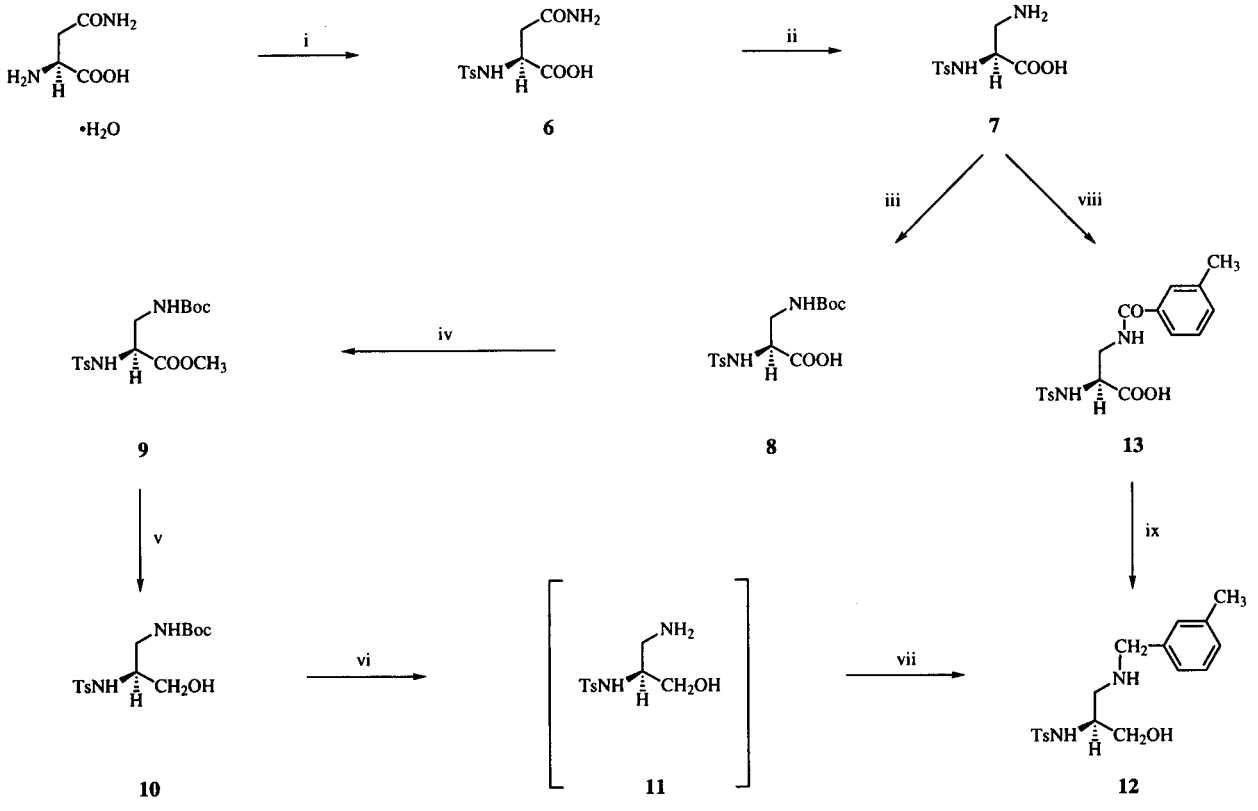
Scheme 1



Scheme 2



Scheme 3



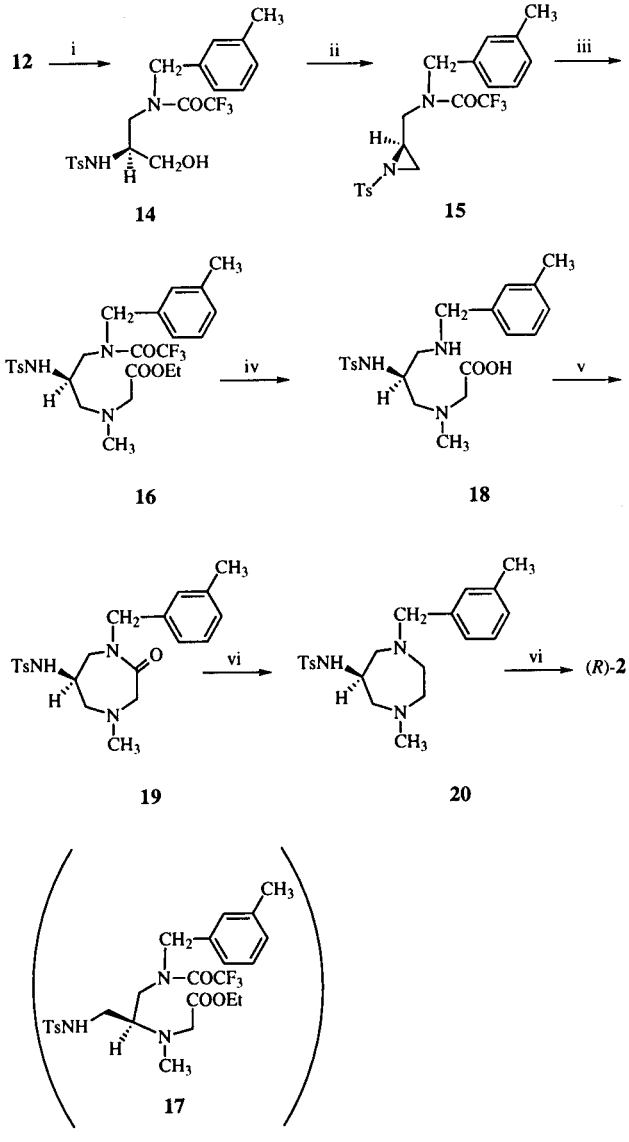
i, TsCl; ii, Br_2/NaOH; iii, Boc_2O; iv, CH_3I; v, $LiBH_4$; vi, CF_3COOH; vii, 3-MeC_6H_4CHO/$NaBH_4$; viii, 3-MeC_6H_4COCl; ix, $NaBH_4$/BF_3•Et_2O.

Ts: 4-$MeC_6H_4SO_2$
Boc: COO-*t*-Bu

carbonate in *N,N*-dimethylformamide afforded the corresponding ester **9** in excellent yield. Then, the 2,3-diaminopropionic ester **9** was reduced by lithium borohydride to produce the 2,3-diamino-1-propanol **10** in 89% yield. Deprotection of the N^3-Boc group of **10** using trifluoroacetic acid, followed by treatment of the resultant aminopropanol **11** with 3-tolualdehyde in the presence of sodium hydrogen carbonate and successive sodium borohydride reduction of the iminium salt gave the propanol **12** in almost quantitative yield. As an alternative route to **12**, reaction of the carboxylic acid **7** with 3-toluoyl chloride in an alkaline solution provided the benzamide **13**, which was subsequently reduced with diborane generated *in situ* (sodium borohydride and borontrifluoride diethyl etherate [11]) to afford **12** in 51% overall yield (Scheme 3).

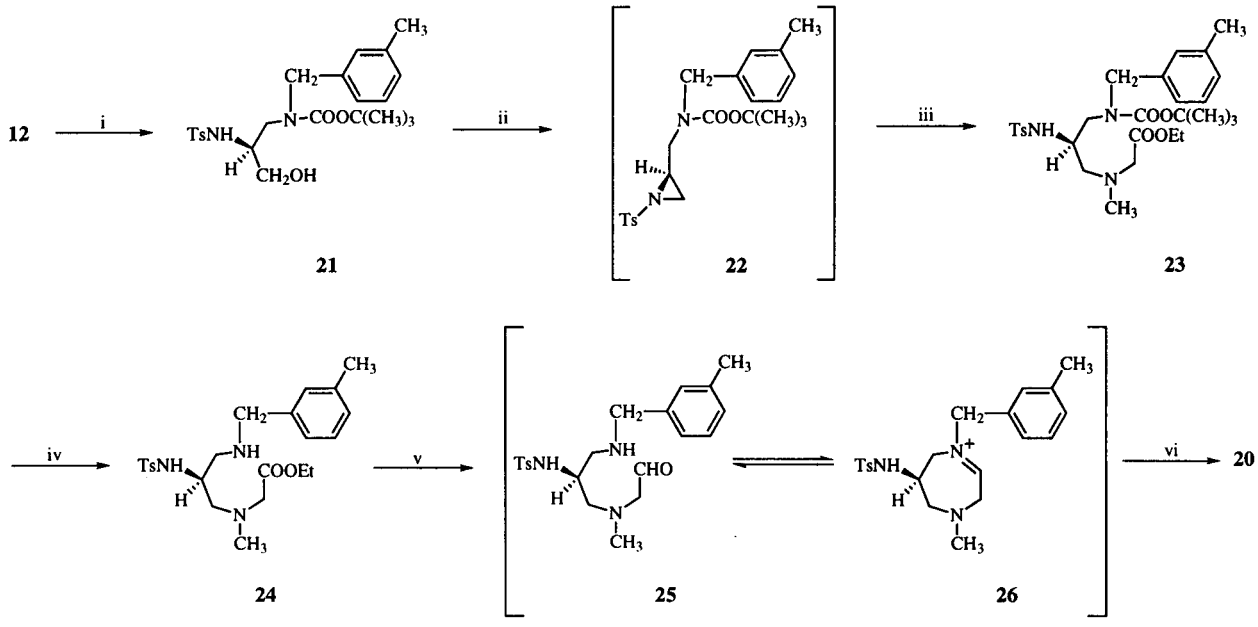
After protection of the amino group of **12** using a trifluoroacetyl group, the resulting propanol **14** was allowed to react under Mitsunobu conditions (diisopropyl azodicarboxylate/triphenylphosphine) to give the *N*-tosylaziridine derivative **15** in 61% yield. Solomon *et al.* reported that Mitsunobu reaction of *N*-tosyl serine methyl ester afforded the dehydroamino acid methyl ester as the major product instead of the expected aziridine derivative [12]. However, in Mitsunobu reaction of **14**, formation of the dehydrodiamine by-product was not detected. In addition, treatment of **14** with triphenylphosphine/bromine in the presence of triethylamine [13] also produced the *N*-tosylaziridine **15** in 73% yield. Reaction of the *N*-tosylaziridine **15** with sarcosine ethyl ester hydrochloride in the presence of triethylamine gave the C_3-N aziridine ring opening product **16** in 86% yield. The structure was assigned by analysis of its ^{1}H-nmr and mass spectra. In this reaction, a trace of the C_2-N aziridine ring opening product **17**, whose structure was proposed on the basis of the mass spectrum, was isolated. Treatment of **16** thus obtained with aqueous sodium hydroxide solution resulted in simultaneous deprotection of the trifluoroacetyl group and hydrolysis of the ester group, giving the amino acid **18** in quantitative yield. Intramolecular condensation of **18** using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride as a coupling agent smoothly proceeded to afford the expected hexahydro-1*H*-1,4-diazepin-3-one **19** as a crystal in 72% yield. Reduction of **19** with sodium bis(2-methoxyethoxy)aluminum hydride (Vitride®) produced the hexahydro-1*H*-1,4-diazepine **20** in quantitative yield. Finally, conversion of the sulfonamide **20** to the desired amine (*R*)-**2** was attempted. The *N*-tosyl group is one of the most stable protecting groups. As a method amenable to large-scale production of (*R*)-**2**, we attempted the detosylation of **20** using hydroiodic acid [14], hydrobromic acid in acetic acid [15], and aqueous hydrobromic acid/phosphorus [16]. Unfortunately, acid hydrolysis of **20** gave a complex mixture from which the amine (*R*)-**2** could be isolated in a yield of less than 5% or large amounts of unchanged starting material. Gold and Babad reported that Vitride® is a useful reagent for the regeneration of primary and secondary aliphatic amines from the corresponding sulfonamides [17]. We applied their method; treatment of **20** with Vitride® in refluxing xylene produced the desired amine (*R*)-**2** in 39% yield. When compound **19** was allowed to react with excess amounts of Vitride®, reduction of the carbonyl group of **19** and successive detosylation of **20** occurred to produce the amine (*R*)-**2**. This one-pot reaction may be a useful method for the preparation of (*R*)-**2** (Scheme 4).

Scheme 4



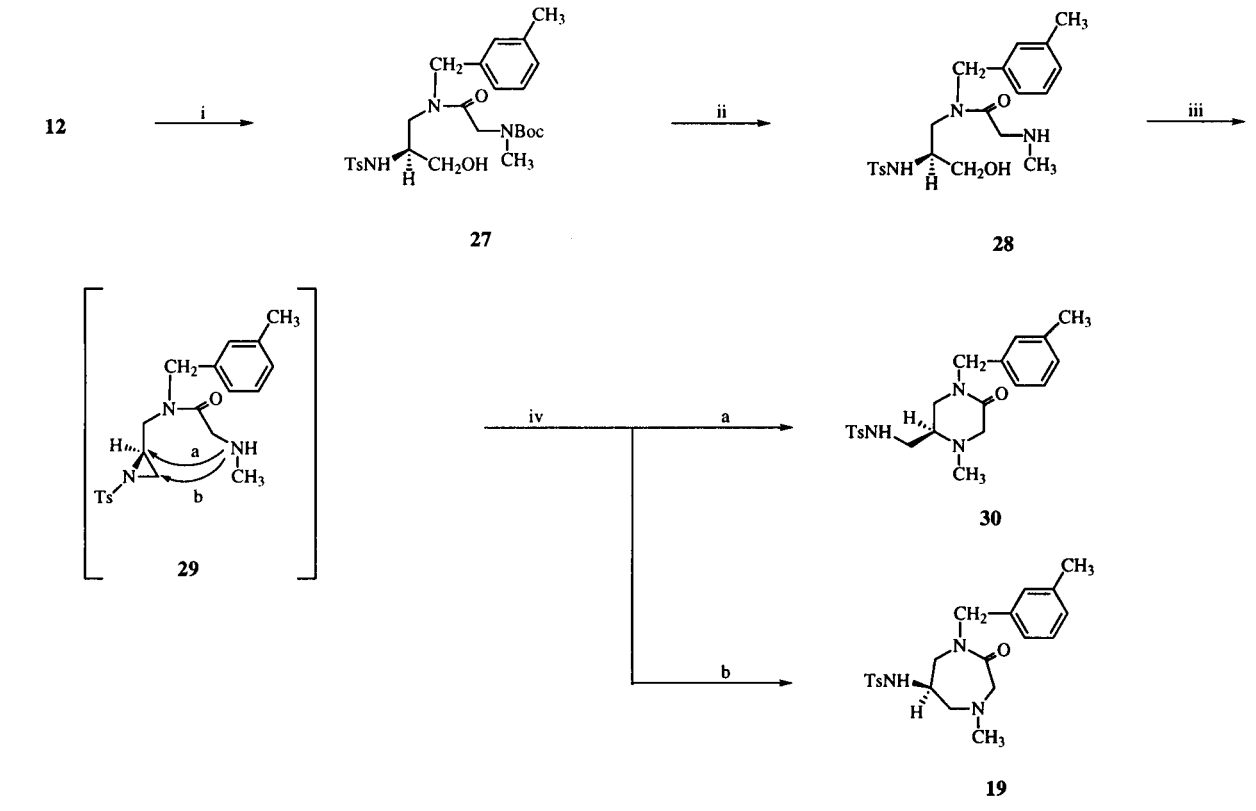
i, $(CF_3CO)_2O$; ii, PPh_3, *i*-PrOOCN=NCOO*i*-Pr or PPh_3, Br_2; iii, $EtOOCCH_2NHCH_3$•HCl; iv, NaOH; v, 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride; vi, $[(CH_3OCH_2CH_2O)_2AlH_2]Na$ (Vitride®).

Scheme 5



i, Boc_2O; ii, PPh_3, *i*-PrOOCN=NCOO*i*-Pr; iii, $EtOOCCH_2NHCH_3$•HCl; iv, HCl; v, $[(CH_3)_2CHCH_2]_2AlH$; vi, $NaBH_4$.

Scheme 6



i, $HOOCCH_2N(Boc)CH_3$/WSC; ii, CF_3COOH; iii, PPh_3, *i*-PrOOCN=NCOO*i*-Pr; iv, heat.

An alternative formation of hexahydro-1*H*-1,4-diazepine ring was next examined. Treatment of **12** obtained as described above with di-*tert*-butyl dicarbonate afforded the *N*-Boc aminopropanol **21**, which was subsequently treated by Mitsunobu reaction to give the corresponding aziridine **22**. The aziridine ring opening reaction of **22** with sarcosine ethyl ester hydrochloride in the presence of triethylamine provided the *N*-Boc aminoester **23** in approximately 41% overall yield for 3 steps. After deprotection of the Boc group of **23**, formation of a hexahydro-1*H*-1,4-diazepine ring from the aminoester **24** was performed by our original method [18]; treatment of **24** with diisobutylaluminum hydride at -70° followed by rapid sodium borohydride reduction of the iminium salt **26** derived from the aminoaldehyde **25** produced the hexahydro-1*H*-1,4-diazepine **20** in 55% yield from **23** (Scheme 5).

Intramolecular aziridine ring opening reaction was finally investigated. Treatment of **12** with *N*-Boc sarcosine [19] in the presence of 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride gave the amide **27** in 68% yield. After deprotection of the Boc group, the resulting aminopropanol **28** was allowed to react under Mitsunobu conditions to afford the aziridine **29**, which was subsequently treated in refluxing toluene to produce an inseparable mixture of the desired **19** and the unexpected isomer piperazin-5-one **30** in 46% yield at a ratio of *ca.* 2:5. The structure of **30** was determined by analysis of its ^{1}H-nmr and mass spectra, and the ratio of the products was determined from the relative intensity of the benzyl methylene signal of **30** (δ 4.39 and 4.60) and C_2 methylene signal of the hexahydro-1*H*-1,4-diazepine ring of **19** (δ 3.93 and 5.06) in the ^{1}H-nmr spectrum. This result indicated that the cleavage of C_2-N (path a) bond of the aziridine ring dominantly occurred compared with C_3-N bond cleavage (path b) in the case of intramolecular aziridine ring opening reaction like **29** (Scheme 6).

In summary, an efficient synthesis of (*R*)-6-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepine [(*R*)-**2**] from L-asparagine as a chirality source was developed. The method involved the key intermediate 2,3-diaminopropanol derivative **12**, and overall yield was 5-10%. Reaction of the aziridines **15** and **22** with the nitrogen nucleophile such as sarcosine dominantly afforded the C_3-N aziridine ring opening products **16** and **23**, respectively. On the other hand, intramolecular aziridine ring opening reaction of **29** resulted in C_2-N bond cleavage, giving the piperazin-5-one **30** as the main product.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus without correction. The ir spectra were recorded on a Hitachi 260-10 spectrometer and a Shimadzu FTIR-8200PC spectrometer. Secondary ion mass spectra were obtained on a Hitachi M-80B spectrometer. The ^{1}H-nmr spectra were taken at 200 MHz with a Varian Gemini-200 spectrometer. Chemical shifts are expressed as δ (ppm) values from tetramethylsilane as an internal standard. Optical rotation was measured at 589 nm with a Jasco DIP-4 digital polarimeter. Organic extracts were dried over anhydrous magnesium sulfate or anhydrous sodium sulfate. The solvent was evaporated under reduced pressure. Merck silica gel 60 (70-230 mesh) was used for column chromatography.

N^2-(4-Toluenesulfonyl)-L-asparagine (**6**).

The method of Piper *et al.* was applied [8]. To a stirred solution of L-asparagine monohydrate (600 g, 4.0 mole) in a mixture of 2*N* aqueous sodium hydroxide solution (2400 ml) and 1,4-dioxane (5000 ml) was added 2*N* aqueous sodium hydroxide solution (2400 ml) and pulverized *p*-toluenesulfonyl chloride (840 g, 4.4 moles) portionwise over a period of 30 minutes under ice cooling. The mixture was stirred at the same temperature for 1 hour and then at room temperature for 3 hours. The solution was diluted with water (10000 ml) and acidified with 35% aqueous hydrochloric acid solution (400 ml). The resulting precipitates were collected by filtration, washed with water, and dried to give 1042 g (91%) of **6**. An analytical sample was obtained by recrystallization from water, mp 200-201°; $[\alpha]_D^{30}$ -64.6° (c = 0.765, in 2*N* aqueous sodium hydroxide solution) [lit mp 189-191° dec [8], lit mp 187-188° dec, $[\alpha]_D^{25}$ +9.8° (c = 2, in 1 equivalent of potassium hydroxide-water) [9], lit mp 182-183°, $[\alpha]_D^{23}$ +5.8° (c = 0.572, in potassium salt in water at *p*H 7.5), $[\alpha]_D^{25}$ -68.54° (c = 0.77, in 2*M* aqueous sodium hydroxide solution) [10], lit mp 175°, $[\alpha]_D^{20}$ +6.8° (in potassium salt in water) [20], lit mp 191° (from water), $[\alpha]_D^{20}$ +9.7 ± 0.5° (c = 5.4, in 1 equivalent of potassium hydroxide-water) [21], lit mp 182°, $[\alpha]_D^{22}$ -10.7° (c = 2, in 1.0 equivalent of sodium hydroxide-water) [22]]; ir (potassium bromide): 3390, 3230, 3120, 1730, 1718, 1660, 1590, 1330, 1150 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): 2.24 (dd, J = 6.5, 15.5 Hz, 1H, CH_2CO), 2.37 (s, 3H, $MeC_6H_4SO_2$), 2.46 (dd, J = 6.5, 15.5 Hz, 1H, CH_2CO), 4.07 (ddd, J = 6.5, 6.5, 8.5 Hz, 1H, 2-CH), 6.88 (s, 1H, $CONH_2$), 7.32 (s, 1H, $CONH_2$), 7.35 (d, J = 8.0 Hz, 2H, ArH), 7.67 (d, J = 8.0 Hz, 2H, ArH), 7.92 (d, J = 8.5 Hz, 1H, $NHSO_2$), 12.59 (br s, 1H, COOH); ms: m/z 287 (MH^+)

Anal. Calcd. for $C_{11}H_{14}N_2O_5S$: C, 46.15; H, 4.93; N, 9.78; S, 11.20. Found: C, 46.03; H, 4.95; N, 9.76; S, 11.15.

N^2-(4-Toluenesulfony)-L-2,3-diaminopropionic Acid (**7**).

Compound **7** was prepared by a modification of the method of Rudinger *et al.* [7]. Bromine (167.0 g, 1.0 mole) was added slowly to a stirred solution of sodium hydroxide (87.0 g, 2.2 moles) in water (250 ml) at such a rate as to keep the temperature below 0°. A cooled (*ca.* 0°) solution of **6** (250 g, 0.87 mole) in 15% aqueous sodium hydroxide solution (1500 ml) was added to a solution including sodium hypobromide as rapidly as possible while keeping the temperature of the mixture below 5°. The mixture was then quickly heated to *ca.* 80°, stirred at the same temperature for 15 minutes and recooled to room temperature. After the *p*H of the solution was adjusted to *ca.* 6 with 35% aqueous hydrochloric acid solution, the resulting precipitates were collected by filtration, washed with cold water, and dried to give 176.0 g (78%) of **7**. An analytical sample was obtained

by recrystallization from water, mp 226-227° dec; $[\alpha]_D^{27}$ -64.1° (c = 1.0, in 1*N* aqueous sodium hydroxide solution) [lit mp 218-219° (from aqueous acetic acid solution), $[\alpha]_D^{23}$ +17.1 ±0.5° (c = 2.4, in 5*N* aqueous hydrochloric acid solution), $[\alpha]_D^{23}$ -52.5 ±0.5° (c = 4, in 1*N* aqueous sodium hydroxide solution) [7], lit mp 210-212° [8], lit mp 215-218° (from water), $[\alpha]_D^{25}$ +19.8° (c = 2.5, in 5*M* aqueous hydrochloric acid solution), $[\alpha]_D^{25}$ -60.6° (c = 1, in 1*N* aqueous sodium hydroxide solution) [9], lit mp 189-191°, $[\alpha]_D^{23}$ -57.7° (c = 1.05, in 1*M* aqueous sodium hydroxide solution), $[\alpha]_D^{25}$ -68.54° (c = 0.765, in 2*M* aqueous sodium hydroxide solution) [10]); ir (potassium bromide): 3500, 3300, 3000, 1630, 1345, 1155 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): 2.38 (s, 3H, $MeC_6H_4SO_2$), 2.81 (dd, J = 9.5, 11.5 Hz, 1H, CH_2NH_2), 3.04 (dd, J = 4.5, 11.5 Hz, 1H, CH_2NH_2), 3.10 (dd, J = 4.5, 9.5 Hz, 1H, 2-CH), 3.33 (br s, 1H, SO_2NH), 7.40 (d, J = 8.0 Hz, 2H, ArH), 7.72 (d, J = 8.0 Hz, 2H, ArH), 7.85 (br s, 3H).

Anal. Calcd. for $C_{10}H_{14}N_2O_4S$: C, 45.50; H, 5.46; N, 10.85; S, 12.41. Found: C, 45.25; H, 5.49; N, 10.72; S, 12.31.

N^3-(*tert*-Butoxycarbonyl)-N^2-(4-toluenesulfony)-L-2,3-diaminopropionic Acid (**8**).

The method of Piper *et al.* was applied [8]. Di-*tert*-butyl dicarbonate (279.5 g, 1.3 moles) was added dropwise to a solution of **7** (300 g, 1.2 moles) and sodium hydroxide (51.2 g, 1.3 moles) in a mixture of water (1160 ml) and 1,4-dioxane (2200 ml) at such a rate as to keep the temperature below 5°. The mixture was stirred at room temperature for 3 hours. After acidification with 20% aqueous citric acid solution, most of the 1,4-dioxane was removed by evaporation. The resulting oil was extracted with chloroform, and the extract was washed with brine and concentrated to dryness. The residue was crystallized from ethyl acetate-ligroin to give 399 g (96%) of **8**, mp 126-127°; $[\alpha]_D^{30}$ -72.0° (c = 4.0, in 1*N* aqueous sodium hydroxide solution) [lit mp 127-128° dec (dec from ethyl acetate-ligroin) [8], lit mp 125-129° (dec, from ethyl acetate-light petroleum), $[\alpha]_D^{22}$ -71.1° (c = 4.0, in 1*N* aqueous sodium hydroxide solution) [23], lit mp 129-131° (from ethyl acetate-light petroleum), $[\alpha]_D^{20}$ -71.2° (c = 4.0, in 1*N* aqueous sodium hydroxide solution) [24], lit D-enantiomer, mp 213-214° (from diethyl ether), $[\alpha]_D^{20}$ +68.5° (c = 4.0, in 1*N* aqueous sodium hydroxide solution) [25]]; ir (potassium bromide): 3294, 1684, 1632, 1522, 1421, 1335, 1169 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): 1.32 (br s, 9H, COO-*t*-Bu), 2.37 (s, 3H, $MeC_6H_4SO_2$), 2.94-3.25 (m, 2H), 3.82 (dd, J = 5, 15 Hz, 1H, 2-CH), 6.74 (t, J = 5 Hz, 1H, NHCO), 7.35 (d, J = 8.0 Hz, 2H, ArH), 7.66 (d, J = 8.0 Hz, 2H, ArH), 7.95 (br d, J = 8 Hz, 1H, SONH), 12.55 (br s, 1H, COOH); ms: m/z 359 (MH^+), 329, 303, 259, 91.

Anal. Calcd. for $C_{15}H_{22}N_2O_6S$: C, 50.27; H, 6.19; N, 7.82; S, 8.95. Found: C, 50.33; H, 6.17; N, 7.79; S, 9.16.

Methyl N^3-(*tert*-Butoxycarbonyl)-N^2-(4-toluenesulfony)-L-2,3-diaminopropionate (**9**).

A mixture of **8** (399 g, 1.1 moles), sodium hydrogen carbonate (187 g, 2.2 moles), 98% methyl iodide (258 g, 1.8 moles), and *N,N*-dimethylformamide (1300 ml) was stirred at room temperature for 18 hours. The reaction mixture was poured into ice-water (4000 ml) and then extracted with ethyl acetate-toluene (1:1). The extract was washed with brine and evaporated to leave a residual solid, which was triturated with toluene to give 409 g (99%) of **9**, mp 91-93°, $[\alpha]_D^{28}$ +11.8° (c = 1.0, in methyl alcohol); ir (potassium bromide): 3366, 3260, 1742, 1693, 1522, 1340, 1167 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.41 (s, 9H, COO-*t*-Bu), 2.42 (s, 3H, $MeC_6H_4SO_2$), 3.4-3.55 (m, 2H, 3-CH_2), 3.57 (s, 3H, COOMe), 3.97 (m, 1H, 2-CH), 4.93 (br s, 1H, NHCO), 5.57 (br s, 1H, $NHSO_2$), 7.29 (d, J = 8.0 Hz, 2H, ArH), 7.72 (d, J = 8.0 Hz, 2H, ArH); ms: m/z 373 (MH^+), 317, 273, 161, 88.

Anal. Calcd. for $C_{16}H_{24}N_2O_6S$: C, 51.60; H, 6.50; N, 7.52; S, 8.61. Found: C, 51.57; H, 6.45; N, 7.52; S, 8.75.

(*S*)-3-(*tert*-Butoxycarbonyl)amino-2-(4-toluenesulfony)amino-1-propanol (**10**).

Anhydrous ethyl alcohol (1300 ml) was added dropwise to a suspension of **9** (210 g, 0.56 mole), sodium borohydride (42.7 g, 1.1 moles), and lithium chloride (47.9 g, 1.1 moles) in anhydrous tetrahydrofuran (1300 ml) at room temperature. The mixture was stirred at the same temperature for 18 hours and then concentrated to dryness. The residue was dissolved in chloroform and water, and the organic layer was separated and washed with brine. The solvent was evaporated to afford 173.0 g (89%) of **10** as an amorphous solid. An analytical sample was obtained by crystallization from toluene-hexane, mp 110-111°, $[\alpha]_D^{25}$ +1.4° (c = 1.1, in methyl alcohol); ir (potassium bromide): 3466, 3396, 1684, 1522, 1157 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.42 (s, 9H, COO-*t*-Bu), 1.65 (br s, 1H, OH), 2.42 (s, 3H, $MeC_6H_4SO_2$), 3.15-3.35 (m, 4H), 3.48 (br d, J = 10 Hz, 1H), 4.90 (br t, J = 6 Hz, 1H, NHCO), 5.27 (br d, J = 7 Hz, 1H, $NHSO_2$), 7.30 (d, J = 8.0 Hz, 2H, ArH), 7.75 (d, J = 8.0 Hz, 2H, ArH); ms: m/z 345 (MH^+), 289, 245, 191, 135, 91.

Anal. Calcd. for $C_{15}H_{24}N_2O_5S$: C, 52.31; H, 7.02; N, 8.13; S, 9.31. Found: C, 52.31; H, 6.98; N, 8.13; S, 9.40.

N^3-(3-Methylbenzoyl)-N^2-(4-toluenesulfony)-L-2,3-diaminopropionic Acid (**13**).

3-Toluoyl chloride (56.1 g, 0.36 mole) was added dropwise to a mixture of **7** (93.7 g, 0.36 mole), 48% aqueous sodium hydroxide solution (90.8 g, 1.1 moles), water (200 ml), and 1,4-dioxane (300 ml) at *ca.* 5°. The reaction mixture was stirred at the same temperature for 1 hour and then at room temperature for 2 hours. After evaporation of 1,4-dioxane, the resulting aqueous solution was washed with chloroform, acidified with 35% aqueous hydrochloric acid solution, and extracted with chloroform. The extract was washed with brine and evaporated to leave a residue as an amorphous solid. The residue was crystallized from toluene-*iso*-propyl alcohol to give 86.8 g (64%) of **13** as a colorless crystalline, mp 164-166°, $[\alpha]_D^{30}$ -41.8° (c = 1.0, in 2*N* aqueous sodium hydroxide solution); ir (potassium bromide): 3275, 1720, 1638, 1528, 1330, 1328, 1150 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): 2.27 (s, 3H, Me), 2.34 (s, 3H, Me), 3.34 (m, 1H), 3.52 (m, 1H), 4.00 (dd, J = 7.5, 15.0 Hz, 1H, 2-CH), 7.23 (d, J = 8.0 Hz, 2H, ArH), 7.29-7.39, 7.46-7.58 (m, 4H, ArH), 7.63 (d, J = 8.0 Hz, 2H, ArH), 8.08 (d, J = 9 Hz, 1H, $NHSO_2$), 8.36 (t, J = 5.5 Hz, 1H, NHCO), 12.74 (1H, s, COOH); ms: m/z 377 (MH^+), 177, 157.

Anal. Calcd. for $C_{18}H_{20}N_2O_5S$: C, 57.34; H, 5.34; N, 7.40; S, 8.62. Found: C, 57.43; H, 5.36; N, 7.44; S, 8.52.

(*S*)-3-(3-Methylbenzyl)amino-2-(4-toluenesulfony)amino-1-propanol (**12**).

a) Compound **10** (335 g, 0.97 mole) was added portionwise to trifluoroacetic acid (1100 ml), and the mixture was stirred at

room temperature for 1 hour. Trifluoroacetic acid was evaporated to leave an oil containing (*S*)-3-amino-2-(4-toluenesulfonyl)amino-1-propanol (**11**), which was dissolved in methyl alcohol (3000 ml). After addition of sodium hydrogen carbonate (817 g, 9.7 moles), 3-tolualdehyde (122.5 g, 1.0 mole) was added. The mixture was heated to reflux for 4.5 hours and then cooled to *ca.* 10°. Sodium borohydride (55.2 g, 1.5 moles) was added portionwise to the reaction mixture, followed by stirring at room temperature for 4 hours. The solvent was evaporated to leave a residue, which was dissolved in water and chloroform. The organic layer was separated, washed with brine, and evaporated to give 332 g (98%) of **12** as a colorless oil; ^{1}H-nmr (deuteriochloroform): 2.35 (s, 3H, Me), 2.40 (s, 3H, Me), 2.72 (dd, J = 5.0, 12.0 Hz, 1H, CH_2CHCH_2), 2.86 (ddd, J = 1.0, 4.2, 12.0 Hz, 1H, CH_2CHCH_2), 3.23 (m, 1H), 3.5 (br s, 3H), 3.52 (ddd, J = 1.0, 4.2, 12.0 Hz, 1H, CH_2CHCH_2), 3.60 (d, J = 1.5 Hz, 2H, $CH_2C_6H_4$), 3.62 (dd, J = 3.5, 12.0 Hz, 1H, CH_2CHCH_2), 6.95-7.35 (m, 6H, ArH), 7.75 (d, J = 8, 2H, ArH); ms: m/z 349 (MH^+), 105.

The oily **12** was converted to the oxalate in the usual manner, mp 201-203° (from methyl alcohol), $[\alpha]_D^{30}$ +13.6° (c = 1.0, in dimethyl sulfoxide); ir (potassium bromide): 3320, 1710, 1620, 1585, 1325, 1210 1150 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 2.31 (s, 3H, Me), 2.38 (s, 3H, Me), 2.65-2.90, 2.90-3.30 (m, 4H), 3.40 (m, 1H), 4.02 (s, 2H, $CH_2C_6H_4$), 7.15-7.35 (m, 4H, ArH), 7.39 (d, J = 8.0 Hz, 2H, ArH), 7.72 (d, J = 8.0 Hz, 2H, ArH), 8.40 (br s, 2H, NH).

Anal. Calcd. for $C_{20}H_{26}N_2O_7S$: C, 54.78; H, 5.98; N, 6.39; S, 7.31. Found: C, 54.83; H, 5.91; N, 6.37; S, 7.24.

b) Boron trifluoride diethyl etherate (47%, 27 ml) was added dropwise to a suspension of sodium borohydride (2.9 g, 77 mmoles) in anhydrous tetrahydrofuran (100 ml) at 10° for 1 hour. After addition of a solution of **13** (6.4 g,17 mmoles) in anhydrous tetrahydrofuran (50 ml), the mixture was stirred at room temperature for 18 hours. Methyl alcohol (10 ml) and 1*N* aqueous hydrochloric acid solution (10 ml) were carefully added, and then the mixture was heated to reflux for 1 hour. The reaction mixture was cooled to room temperature and concentrated to leave an aqueous solution, which was basified with 2*N* aqueous sodium hydroxide solution and extracted with chloroform. The extract was washed successively with water and brine. The solvent was evaporated to give 4.7 g (79%) of **12** as a colorless oil, which was identical with the sample described above, based on comparisons of tlc behavior and ir and ^{1}H-nmr spectra.

(*S*)-3-[*N*-(3-Methylbenzyl)-*N*-trifluoroacetyl]amino-2-(4-toluene sulfony)amino-1-propanol (**14**).

Trifluoroacetic anhydride (28.5 g, 0.14 mole) was added dropwise to a solution of **12** (44.9 g, 0.13 mole) and triethylamine (26.0 g, 0.26 mole) in chloroform (400 ml) kept at *ca.* 5°. The mixture was stirred at the same temperature for 1 hour and at room temperature for 2 hours. The reaction mixture was washed successively with water, 1*N* aqueous hydrochloric acid solution, and brine. The solvent was evaporated to give 55.3 g (97%) of **14** as an oil, ir (neat): 3250, 1670, 1440, 1320, 1200, 1145 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 2.37 (s, 3H, Me), 2.42 (s, 3H, Me), 2.58 (br s, 1H, OH), 3.1-3.4 (m, 4H), 3.62 (dd, J = 8.0, 13.0 Hz, 1H), 4.51 (d, J = 16 Hz, 1H, $CH_2C_6H_4$), 4.64 (d, J = 16 Hz, 1H, $CH_2C_6H_4$), 5.32 (d, J = 8 Hz, 1H, $NHSO_2$), 6.91-7.05 (m, 2H, ArH), 7.14-7.40 (m, 4H, ArH), 7.62 (d, J = 8, 2H, ArH); ms: m/z 445 (MH^+), 105.

(*S*)-3-[*N*-(3-Methylbenzyl)-*N*-trifluoroacetylaminomethyl]-1-(4-toluenesulfony)aziridine (**15**).

a) Diisopropyl azodicarboxylate (95%, 3.4 g, 16 mmoles) was added dropwise to a solution of **14** (7.0 g, 16 mmoles) and triphenylphosphine (4.2 g, 16 mmoles) in anhydrous tetrahydrofuran (100 ml) at *ca.* 5°. The mixture was stirred at room temperature for 15 hours and concentrated to dryness. The residue was chromatographed on silica gel with a gradient of ethyl acetate-hexane (1:5) to ethyl acetate to give 4.1 g (61%) of **15**, as an unstable colorless oil, ir (neat): 3250, 1680, 1445, 1330, 1200, 1145 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 2.02 (dd, J = 4.5, 14 Hz, 1H), 2.31 and 2.33 (each s, 3H, Me), 2.45 and 2.46 (each s, 3H, Me), 2.65 (dd, J = 7, 14 Hz, 1H), 2.80-3.10 (m, 2H), 3.78 (dd, J = 4.5, 14 Hz, 1H), 4.20 (dd, J = 15, 24 Hz, 1H, $CH_2C_6H_4$), 4.62 (dd, J = 15, 29 Hz, 1H, $CH_2C_6H_4$), 6.85-6.96 (m, 2H, ArH), 7.05-7.25 (m, 2H, ArH), 7.34-7.44 (m, 2H, ArH), 7.80-7.90 (m, 2H, ArH); ms: m/z 427 (MH^+), 105.

b) A solution of bromine (1.6 g, 10 mmoles) in acetonitrile (20 ml) was added dropwise to a suspension of triphenylphosphine (2.6 g, 10 mmoles) in acetonitrile (30 ml) at room temperature. The mixture was stirred at the same temperature for 20 minutes and then cooled to *ca.* 0°. A solution of **14** (4.3 g, 9.7 mmoles) in acetonitrile (30 ml) and triethylamine (2.0 g, 20 mmoles) was added successively to the mixture kept at *ca.* 0°. This mixture was stirred at room temperature for 3.5 hours and concentrated to dryness. The residue was chromatographed on silica gel with chloroform to give 3.0 g (73%) of **15**, which was identical with the sample above, based on comparisons of tlc behavior and ir and ^{1}H-nmr spectra.

Ethyl (*S*)-*N*-Methyl-*N*-{3-[*N*-(3-methylbenzyl)-*N*-trifluoroacetyl]amino-2-(4-toluenesulfony)amino-1-propyl}aminoacetate (**16**).

A mixture of **15** (4.1 g, 9.6 mmoles), sarcosine ethyl ester hydrochloride (1.8 g, 12 mmoles), triethylamine (1.9 g,19 mmoles), and toluene (50 ml) was heated to reflux for 15 hours and then cooled to room temperature. The reaction mixture was washed successively with water, 10% aqueous hydrochloric acid solution, and brine and concentrated to dryness. The residue was chromatographed on silica gel with ethyl acetate to give 4.5 g (86%) of **16** as a pale yellow viscous oil, ir (neat): 3300, 1720, 1680, 1445, 1330, 1200, 1150 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.26 (t, J = 7.0 Hz, 3H, $COOCH_2Me$), 1.69 (s, 3H), 2.35 (s, 3H), 2.2-2.5 (m, 2H), 2.40 (s, 3H, Me), 2.95-3.05 (m, 2H), 2.98 (d, J = 17 Hz, 1H, $CH_2C_6H_4$), 3.06 (d, J = 17 Hz, 1H, $CH_2C_6H_4$), 3.15-3.42 (m, 2H), 3.62 (m, 1H), 4.17 (q, J = 7.0 Hz, 2H, $COOCH_2Me$), 4.80 (s, 2H, NCH_2COO), 6.26 (d, J = 4 Hz, 1H, $NHSO_2$), 6.95-7.10 (m, 2H, ArH), 7.10-7.20 (m, 2H, ArH), 7.20-7.36 (m, 2H, ArH), 7.60-7.75 (m, 2H, ArH); ms: m/z 544 (MH^+), 130, 105.

(*S*)-*N*-Methyl-*N*-[3-(3-methylbenzyl)amino-2-(4-toluenesulfony)amino-1-propyl]aminoacetic Acid (**18**).

A solution of **16** (4.5 g, 8.3 mmoles) in a mixture of 2*N* aqueous sodium hydroxide solution (20 ml) and ethyl alcohol (30 ml) was stirred at room temperature for 16 hours. After evaporation of ethyl alcohol, the resulting aqueous solution was acidified with 20% aqueous hydrochloric acid solution and extracted with chloroform. The extract was washed successively with water and brine and evaporated to give 3.6 g (quantitative yield) of **18** as a pale yellow viscous oil, ir (neat): 1570, 1450, 1400, 1325,

1150 cm^{-1}; ^1H-nmr (deuteriochloroform): 1.90-3.30 (m, 5H), 2.08 (s, 3H, Me), 2.30 (s , 3H, Me), 2.39 (s, 3H, Me), 3.65 (m, 1H), 4.01 (s, 2H), 7.10-7.30 (m, 2H, ArH), 7.65-7.85 (m, 7H, ArH), 8.35 (br s, 1H); ms: m/z 420 (MH^+), 105.

(*R*)-1-Methyl-4-(3-methylbenzyl)-3-oxo-6-(4-toluenesulfony)-aminohexahydro-1*H*-1,4-diazepine (**19**).

A mixture of **18** (3.6 g, 8.6 mmoles), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (1.9 g, 9.9 mmoles), and dichloromethane (50 ml) was stirred at room temperature for 4 hours. The reaction mixture was washed successively with water and brine and concentrated to dryness. The resulting amorphous solid was crystallized from toluene to give 2.4 g (72%) of **19**, mp 155-156°; $[\alpha]_D^{30}$ +25.9° (c = 1.0, in methyl alcohol); ir (potassium bromide): 3279, 1651, 1609, 1443, 1317, 1161 cm^{-1}; ^1H-nmr (deuteriochloroform): 2.33 (s, 6H, Me x 2), 2.44 (dd, J = 2.5, 13.0 Hz, 1H, CH_2CH), 2.45 (s, 3H, Me), 2.58 (dd, J = 2.5, 13.0 Hz, 1H, CH_2CH), 3.20 (d, J = 14.5 Hz, 1H, $CH_2C_6H_4$), 3.25-3.4 (m, 2H), 3.42 (d, J = 14.5 Hz,1H, $CH_2C_6H_4$), 3.47 (m, 1H), 3.94 (d, J = 14.5 Hz, 1H, NCH_2CO), 5.07 (d, J = 14.5 Hz, 1H, NCH_2CO), 5.21 (d, J = 8 Hz, 1H, $NHSO_2$), 6.9-7.25 (m, 4H, ArH), 7.32 (d, J = 8.0 Hz, 2H, ArH), 7.72 (d, J = 8.0 Hz, 2H, ArH); ms: m/z 402 (MH^+), 343, 246.

Anal. Calcd. for for $C_{21}H_{27}N_3O_3S$: C, 62.82; H, 6.78; N, 10.47; S, 7.99. Found: C, 62.81; H, 6.72; N, 10.38; S, 7.87.

(*S*)-3-[*N*-(*tert*-Butoxycarbonyl)-*N*-(3-methylbenzyl)]amino-2-(4-toluenesulfony)amino-1-propanol (**21**).

Di-*tert*-butyl dicarbonate (26.2 g, 0.12 mole) was added to a mixture of the oxalate of **12** (44.8 g, 0.10 mole), triethylamine (20.2 g, 0.20 mole), and chloroform (500 ml) at room temperature. This mixture was stirred at the same temperature for 3 hours and washed successively with water, 10% aqueous citric acid solution, and brine. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with ethyl acetate-chloroform (1:1) to give 46 g (quantitative yield) of **21** as a colorless oil; ir (potassium bromide): 3273, 1668, 1418, 1161 cm^{-1}; ^1H-nmr (deuteriochloroform): 1.46 (s, 9H, COO-*t*-Bu), 2.35 (s, 3H, $MeC_6H_4CH_2$), 2.41 (s, 3H, Me), 3.02-3.22 (m, 3H), 3.30-3.56 (m, 2H), 3.64 (m, 1H), 4.21 (d, J = 12 Hz, 1H, $CH_2C_6H_4$), 4.32 (d, J = 12 Hz, 1H, $CH_2C_6H_4$), 5.26 (br d, J = 8 Hz, 1H, $NHSO_2$), 6.92-7.05 (m, 2H, ArH), 7.05-7.30 (m, 4H, ArH), 7.61-7.74 (m, 2H, ArH); ms: m/z 449 (MH^+), 349.

Ethyl (*S*)-*N*-Methyl-*N*-{3-[*N*-(*tert*-butoxycarbonyl)-*N*-(3-methylbenzyl)]amino-2-(4-toluenesulfony)amino-1-propyl}aminoacetate (**23**).

A solution of diisopropyl azodicarboxylate (95%, 21.8 g, 0.10 mole) in anhydrous tetrahydrofuran (100 ml) was added dropwise to a mixture of triphenylphosphine (26.8 g, 0.10 mole), **21** (46.3 g, 0.10 mole), and anhydrous tetrahydrofuran (400 ml) at room temperature. The mixture was stirred at the same temperature for 0.5 hour and then concentrated to dryness. The residue containing the corresponding aziridine **22** was dissolved in toluene (600 ml), and then sarcosine ethyl ester hydrochloride (17.5 g, 0.11 mole) and triethylamine (31.3 g, 0.31 mole), were added. This mixture was heated to reflux for 18 hours and cooled to room temperature. The reaction mixture was washed successively with water (100 ml x 3), 10% aqueous citric acid solution (100 ml x 2), water (100 ml), and brine and concentrated to dryness. The oily residue was dissolved in diethyl ether (500 ml), and the solution was stood at *ca.* 5° overnight. The deposited triphenylphosphine oxide was filtered off, and the filtrate was evaporated to leave a pale orange oil, which was chromatographed on silica gel with ethyl acetate-chloroform (1:9) to give 23.1 g (41%) of **23** as a pale yellow oil; ir (neat): 3233, 1732, 1693, 1163 cm^{-1}; ^1H-nmr (deuteriochloroform): 1.26 (t, J = 7 Hz, 3H, $COOCH_2Me$), 1.45 (s, 9H, COO-*t*-Bu), 1.81 (br s, 3H, Me), 2.31 (br s, 3H, Me), 2.40 (s, 3H, Me), 2.43 (m, 1H), 3.04 (s, 2H, $CH_2C_6H_4$), 3.1 (m, 1H), 3.42 (t, J = 5 Hz, 2H), 4.16 (q, J = 7 Hz, 2H, $COOCH_2Me$), 4.2 (m, 1H), 4.3 (m, 1H), 5.93 and 6.26 (each br s, 1H), 6.95-7.11 (m, 3H, ArH), 7.11-7.36 (m, 3H, ArH), 7.62-7.80 (m, 2H, ArH); ms: m/z 548 (MH^+), 492, 448, 376, 133.

Anal. Calcd. for $C_{28}H_{41}N_3O_6S$: C, 61.40; H, 7.55; N, 7.67; S, 5.85. Found: C, 61.28; H, 7.56; N, 7.67; S, 5.65.

Ethyl (*S*)-*N*-Methyl-*N*-[3-(3-methylbenzyl)amino-2-(4-toluenesulfony)amino-1-propyl]aminoacetate (**24**).

Trifluoroacetic acid (100 ml) was added dropwise to **23** (18.7 g, 34 mmoles) at room temperature. The mixture was stirred at the same temperature for 1 hour and concentrated to dryness. The residue was dissolved in water and chloroform, and the mixture was basified with 20% aqueous sodium hydroxide solution. The organic layer was separated and washed with brine. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with ethyl acetate-chloroform (2:5) to give 13.5 g (88%) of **24** as a colorless oil, ir (neat): 3234, 1732, 1456, 1333, 1163 cm^{-1}; ^1H-nmr (deuteriochloroform): 1.26 (t, J = 7 Hz, 3H, $COOCH_2Me$), 1.9 (m, 1H), 1.98 (br s, 3H, Me), 2.33 (s, 3H, Me), 2.40 (s, 3H, Me), 2.4-2.60 (m, 2H), 2.68 (d, J = 4 Hz, 2H), 3.10 (s, 2H, $CH_2C_6H_4$), 3.12 (m, 1H), 3.65 (s, 2H), 4.18 (q, J = 7, 2H, $COOCH_2Me$), 5.90 (br s, 1H), 7.00-7.11 (m, 3H, ArH), 7.13-7.28 (m, 3H, ArH), 7.68-7.78 (m, 2H, ArH); ms: m/z 448 (MH^+), 105.

(*R*)-1-Methyl-4-(3-methylbenzyl)-6-(4-toluenesulfonyl)aminohexahydro-1*H*-1,4-diazepine (**20**).

a) A solution of **19** (1.0 g, 2.5 mmoles) in anhydrous tetrahydrofuran (20 ml) was added to a mixture of Vitride® (70% solution in toluene, 8.3 g, 29 mmoles) and xylene (30 ml) at room temperature. This mixture was heated to reflux for 25 hours and then cooled to room temperature. The reaction mixture was poured into ice-water, and the insoluble materials were removed by filtration. The filtrate was washed with brine and evaporated to leave an oil, which was chromatographed on silica gel with ethyl acetate-methyl alcohol (9:1) to give 0.9 g (quantitative yield) of **20** as a pale yellow oil; ir (neat): 3255, 1450, 1320, 1145 cm^{-1};^1H-nmr (deuteriochloroform): 2.27 (s, 3H, Me), 2.38 (s, 3H, Me), 2.39 (s, 3H, Me), 2.30-2.52 (m, 4H), 2.58-2.85 (m, 4H), 3.33 (m, 1H), 3.36 (d, J = 13.0 Hz, 1H, $CH_2C_6H_4$), 3.56 (d, J = 13.0 Hz, 1H, $CH_2C_6H_4$), 5.80 (br s, 1H, SO_2NH), 7.02-7.28 (m, 6H, ArH), 7.50 (d, J = 8.0, 2H, ArH); ms: m/z 388 (MH^+), 217, 105.

b) Diisobutylaluminum hydride (1*M* solution in toluene, 192 ml, 0.19 mole) was added dropwise to a solution of **24** (22.0 g, 49 mmoles) in tetrahydrofuran (250 ml) at -70°. The mixture was stirred at the same temperature for 1.5 hours, and the excess of reagent was decomposed with methyl alcohol (500 ml) at -70°. After warming to *ca.* 0°, sodium borohydride (2.7 g, 71 mmoles) was gradually added to the mixture. This mixture was stirred at room temperature for 15 hours and then concentrated to dryness.

The residue was dissolved in chloroform and water, and the organic layer was separated. The aqueous layer was extracted with chloroform, and the combined organic layer was washed with brine. The solvent was evaporated to leave a pale yellow oil, which was chromatographed on silica gel with chloroform-ethyl acetate (1:1) to give 9.8 g (62%) of **20** as a colorless viscous oil. This was identical with the sample obtained above, based on comparisons of tlc behavior and ir and ^{1}H-nmr spectra.

(*R*)-6-Amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepine [(*R*)-**2**].

a) A solution of **20** (9.0 g, 23 mmoles) in xylene (20 ml) was added to a mixture of Vitride® (70% solution in toluene, 75 g, 0.26 mole) and xylene (230 ml) at room temperature. The mixture was heated to reflux for 63 hours and then cooled to room temperature. The reaction mixture was poured into ice-water, and the insoluble materials were removed by filtration. The filtrate was washed with brine and evaporated to leave an oily residue, which was distilled to give 2.1 g (39%) of (*R*)-**2**, bp 146-148°/2 mmHg; ir (neat): 3250, 1595, 1450, 1340 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.72 (2H, br s, NH_2), 2.34 (3H, s, $MeC_6H_4CH_2$), 2.36 (3H, s, NMe), 2.30-2.74 (6H, m), 2.76-2.90 (2H, m), 3.03 (1H, m), 3.60 (2H, s, $CH_2C_6H_4$), 7.00-7.30 (4H, m, ArH); m/z 234 (MH^+). The enantiomeric excess (>99%) of (*R*)-**2**, thus obtained, was analyzed by chiral hplc [column, CROWNPAK CP (+) (Daicel Chemical Industries, Ltd., Japan); 4.6 ϕ x 150 mm; eluent, perchloric acid (*p*H = 1.5)-methyl alcohol (9:1); flow rate, 0.7 ml/minute column temperature, 25°, detection, 220 nm]. The retention times of (*R*)-**2** and (*S*)-**2** were 10.8 minutes and 12.3 minutes, respectively.

b) A solution of **19** (12.0 g, 30 mmoles) in anhydrous tetrahydrofuran (100 ml) was added dropwise to a solution of Vitride® (70% solution in toluene, 85 g, 0.29 mole) in a mixture of xylene (300 ml) and anhydrous tetrahydrofuran (200 ml) at room temperature. The mixture was heated to reflux for 24 hours and then cooled to room temperature. After evaporation of tetrahydrofuran, the resulting xylene solution including **20** was reheated to reflux for 24 hours and cooled to room temperature. A similar workup afforded 3.1 g (44%) of (*R*)-**2** as a pale yellow oil.

(*S*)-3-[[*N*-(*N*-*tert*-Butoxycarbonyl-*N*-methyl)aminoacetyl]-*N*-(3-methylbenzyl)]amino-2-(4-toluenesulfonyl)amino-1-propanol (**27**).

A mixture of **12** (40.5 g, 0.12 mole), *N*-*tert*-butoxycarbonylsarcosine [19] (23.6 g, 0.12 mole), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (32.5 g, 0.17 mole), and chloroform (500 ml) was stirred at room temperature for 2.5 hours. The reaction mixture was washed successively with water, 10% aqueous sodium hydroxide solution, 10% aqueous hydrochloric acid solution, and brine. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with ethyl acetate to give 41.1 g (68%) of **27** as a colorless amorphous solid, ir (potassium bromide): 3393, 1690, 1651, 1159 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 1.42 (s, 9H, COO-*t*-Bu), 2.36 (s, 3H, Me), 2.40 (s, 3H, Me), 2.90 (s, 3H, Me), 3.00-3.70 (m, 5H), 3.70-3.90 (m, 2H), 3.75 (d, J = 15 Hz, 1H), 3.80 (m, 1H), 4.19 (d, J = 15 Hz, 1H), 4.45 (s, 2H), 5.31 (br d, J = 7 Hz, 1H, SO_2NH), 6.90-7.05 (m, 2H, ArH), 7.10-7.30 (m, 4H, ArH), 7.65 (d, J = 8 Hz, 2H, ArH); ms: m/z 520 (MH^+), 420, 349.

(*S*)-3-[*N*-(*N*-Methylaminoacetyl)-*N*-(3-methylbenzyl)]amino-2-(4-toluenesulfonyl)amino-1-propanol (**28**).

A mixture of **27** (41.0 g, 79 mmoles), *ca.* 30% hydrochloric acid in ethyl alcohol (50 ml), and ethyl alcohol (500 ml) was stirred at room temperature for 2 hours and concentrated to dryness. After addition of water, the aqueous solution was basified with 20% aqueous sodium hydroxide solution and extracted with chloroform. The extract was washed successively with water and brine. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with chloroform-methyl alcohol (9:1) to give 24.2 g (73%) of **28** as a pale yellow amorphous solid; ir (potassium bromide): 3315, 3179, 1638, 1421, 1327, 1159 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 2.34 (s, 3H, Me), 2.39 (s, 6H, Me x 2), 3.15-3.55 (m, 8H), 3.70 (m, 1H), 4.36 (s, 2H), 6.87-6.98 (m, 2H, ArH), 7.02-7.35 (m, 5H, ArH, $NHSO_2$), 7.63-7.75 (m, 2H, ArH); ms: m/z 420 (MH^+), 349.

(*S*)-1-Methyl-4-(3-methylbenzyl)-2-[(4-toluenesulfonyl)aminomethyl]-5-oxopiperazine (**30**) and **19**.

Diisopropyl azodicarboxylate (95%, 1.7 g, 8.0 mmoles) was added dropwise to a solution of **28** (3.3 g, 7.9 mmoles) and triphenylphosphine (2.1 g, 8.0 mmoles) in tetrahydrofuran (100 ml) at room temperature. The mixture was stirred at the same temperature for 1 hour and concentrated to dryness. The residue containing **29** was dissolved in toluene (100 ml), and the solution was heated to reflux for 4 hours and then cooled to room temperature. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with ethyl acetate-methyl alcohol (9:1) to give 2.0 g (63%) of a mixture of **30** and **19** as an amorphous solid, ir (potassium bromide): 1638, 1331, 1161 cm^{-1}; ^{1}H-nmr (deuteriochloroform): 2.15 (s, Me of **30**), 2.32 (s, Me x 2 of **19**), 2.33 (s, Me of **30**), 2.43 (s, Me of **30**), 2.45 (Me of **19**), 3.93 (d, J = 15 Hz, NCH_2CO of **19**), 4.39 (d, J = 14 Hz, $C_6H_4CH_2$ of **30**), 4.60 (d, J = 14 Hz, $C_6H_4CH_2$ of **30**), 4.85 (br s, $NHSO_2$ of **30**), 5.06 (d, J = 15 Hz, NCH_2CO of **19**), 5.21 ($NHSO_2$ of **19**); ms: m/z 402 (MH^+), 299.

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