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Process Development of the Synthetic Route to (*R*)-6-Amino-1-ethyl-4-methylhexahydro-1,4-diazepine

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Abstract:

The optically active (*R*)-6-amino-1-ethyl-4-methylhexahydro-1,4-diazepine (1) is the amine moiety of a novel and potent dopamine (D_2 and D_3) and 5-HT_3 receptors antagonist AS-8112, which is a clinical candidate expected to be a broad antiemetic agent. Process development of an effective synthetic route to the optically active amine 1 from *N*-Cbz- and *N*-Ts-L-serine methyl esters was undertaken. In two potential scale-up processes, the route from *N*-Ts-L-serine methyl ester (21) was chosen because of its better overall yield (>30% yield for seven steps) and handling. The optically active amine 1 with high purity (>99.5% ee) was prepared via the reaction of the key intermediate *N*-Ts-aziridine 23 with $EtNH_2$ and successive $LiAlH_4$ reduction without racemization. Moderate scale-up synthesis of the amine 1 and AS-8112 by condensation of 1 and 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid is described.

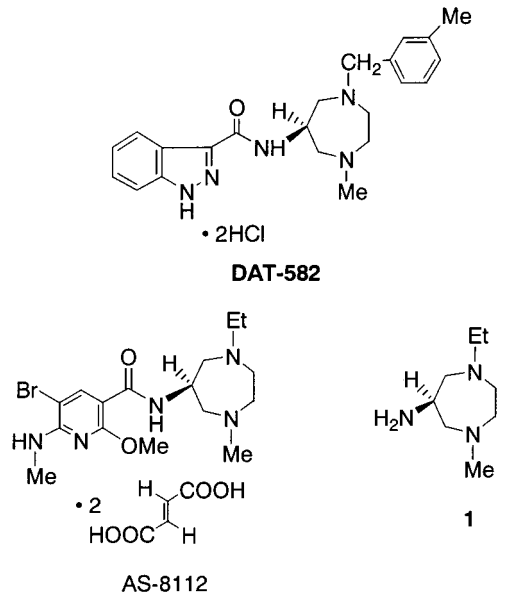

Figure 1.

Introduction

Potent and selective 5-HT_3 receptor antagonists are known to be effective for the control of chemotherapy- or radiation-induced nausea and vomiting.[1] On the other hand, selective dopamine D_2 receptor antagonists have been shown to be effective for the treatment of symptoms of chronic upper gastrointestinal distress and for the prevention of nausea and vomiting resulting from a variety of causes.[2a,b] Thus, dual inhibitors at 5-HT_3 and dopamine D_2 receptors are expected to be broad antiemetic agents. In the course of our studies on the structure−activity relationships of a potent and selective 5-HT_3 receptor antagonist DAT-582,[3] novel benzamides with an alkyl group at the 1- and 4-nitrogen atoms in the 6-aminohexahydro-1,4-diazepine ring of the amine moiety were found to show dopamine D_2 receptor inhibitory activity along with a potent 5-HT_3 receptor inhibitory activity and to cause only weak central nervous system depression and extrapyramidal syndromes.[4] Finally, AS-8112, (*R*)-5-bromo-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-2-methoxy-6-methylaminopyridine-3-carboxamide difumarate, was selected as a promising clinical candidate.[4−6] The production of a large amount of AS-8112 was required for development needs of toxicology, formulation, and pharmacology. To meet these production requirements, process development of a scalable synthetic route to the amine moiety, (*R*)-6-amino-1-ethyl-4-methylhexahydro-1,4-diazepine (**1**), and the carboxylic acid part, 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid,[7] of AS-8112 was essential. This work describes an efficient synthetic route to optically active **1** from L-serine methyl ester hydrochloride (**10**).

Results and Discussion

Synthesis of (*R*)-6-Amino-1-ethyl-4-methylhexahydro-1,4-diazepine (1) from *N*-Benzyloxycarbonyl-l-serine Methyl Ester. We have reported the several synthetic methods of the structurally novel hexahydro-1,4-diazepine derivatives **2**. The reaction of the ethylendiamines **3** with the activated C3 components **4**−**9** gave **2** in low overall yield, but that with 1,3-dichloroacetone was unsuccessful. In addition, attempts at resolution of **2** (R = Me, R_1 = Et, X = NH_2, Y = H) into its enantiomers using various resolving agents also failed (Scheme 1).[8]

On the other hand, we previously reported the other synthetic method of (*R*)-6-amino-1-methyl-4-(3-methylbenz-

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(2) (a) Brogden, R. N.; Carmine, A. A.; Heel, R. C.; Speight, T. H.; Avery, G. S. *Drugs* **1982**, *24*, 360. (b) Davis, R. H.; Clench, M. H.; Mathiae, J. R. *Dig. Dis. Sci.* **1988**, *33*, 1505.
(3) Harada, H.; Morie, T.; Hirokawa, Y.; Yoshida, N.; Kato, S. *Chem. Pharm. Bull.* **1995**, *43*, 1364.
(4) Hirokawa, Y.; Yoshida, N.; Kato, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1551.
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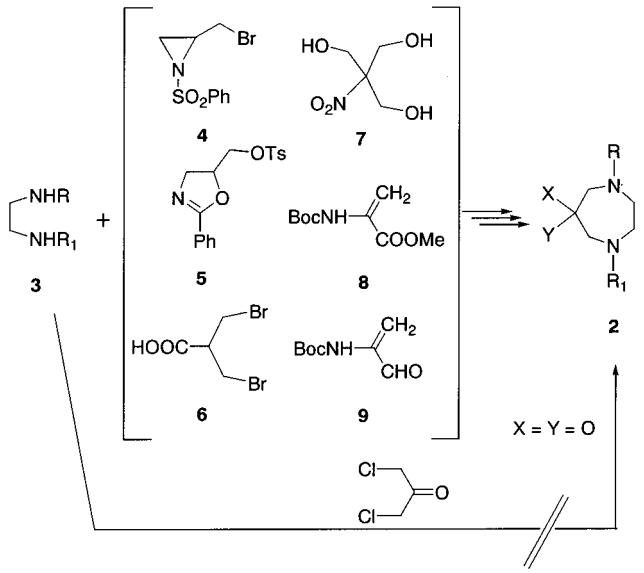
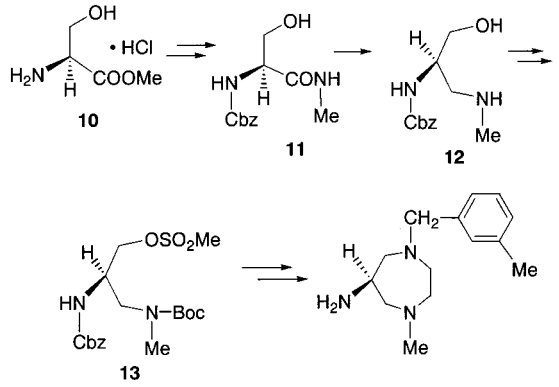
Scheme 1

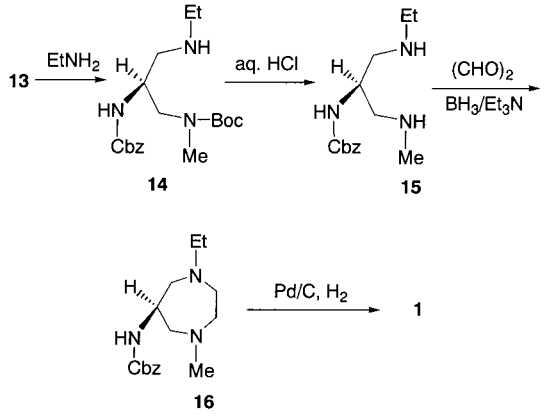


Scheme 2

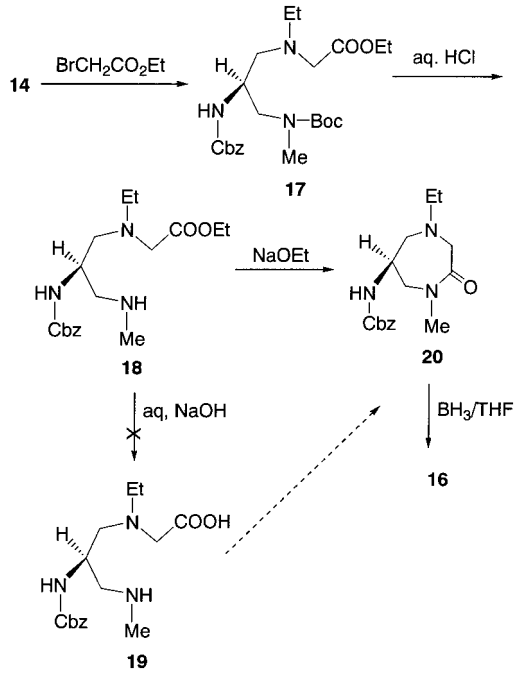


yl)hexahydro-1,4-diazepine, which is the amine moiety of DAT-582, from **10**, through the *N*-Cbz-amide **11** and the 2,3-diaminopropanes **12** and **13** (Scheme 2).[9] As in this synthesis the nucleophilic substitution reaction of **13** with 1.04 mol equiv of 3-methylbenzylamine gave the corresponding 1-(3-methylbenzyl)aminopropane derivative in only 27% yield (see Scheme 2); reaction of **13** with $EtNH_2$ was investigated. The process of this reaction was optimized using ca. 5 mol equiv of 70% aqueous $EtNH_2$ solution in EtOH, and (*S*)-2-Cbz-amino-3-(*N*-Boc-*N*-methyl)amino-1-ethylaminopropane (**14**) was obtained in 95% yield. Acid hydrolysis of **14** produced the 1,2,3-trisubstituted aminopropane **15**. Cyclization of **15** into the hexahydro-1,4-diazepine ring was carried out as described before.[10] Namely, **15** was treated with glyoxal in the presence of BH_3•Et_3N complex or $NaBH_3$-CN directly to give 6-Cbz-amino-1-ethyl-4-methylhexahydro-1,4-diazepine (**16**) in 66% yield. Hydrogenolysis of **16** over Pd/C afforded the desired optically active (*R*)-6-aminodiazepine **1** in quantitative yield (Scheme 3). This compound

Scheme 3



Scheme 4



was identified with the sample obtained from (*R*)-6-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1,4-diazepine,[11] on the basis of ^1H NMR comparison.

On the other hand, reaction of **14** with ethyl bromoacetate gave the aminoacetate **17** in 87% yield. After deprotection of Boc group of **17**, intramolecular cyclization of the resultant aminoacetate **18** into the hexahydro-1,4-diazepin-3-one ring via the corresponding aminoacetic acid **19** was examined. Unfortunately, alkaline hydrolysis of **18** did not give the aminoacetic acid **19**. Treatment of **18** with NaOEt in EtOH at room temperature produced the hexahydro-1,4-diazepin-3-one **20** as crystals in 44% yield. Finally, borane reduction of **20** gave the hexahydro-1,4-diazepine **16** in 51% yield (Scheme 4).

Although a sequence of this process from L-serine methyl ester with Cbz group was sufficient for small-scale synthesis of **1**, it was inefficient for the preparation of large amounts. Particularly, borane reduction of **11** to **12** on kilogram-scale caused a considerable decrease in yield (<30%). Our interest

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(11) Hirokawa, Y.; Morie, T.; Yamazaki, H.; Yoshida, N.; Kato, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 619.

Table 1. **Reaction conditions for amidation of 21**

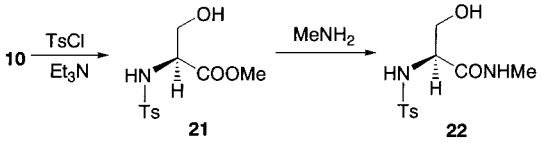
run	reagent[a] (equiv)	solvent[b]	temperature	reaction time (h)	optical purity of **22**[c] (% ee)
1	$MeNH_2$·HCl (1.1) + Et_3N	MeOH	rt	20	no reaction
2	40% aq NH_2Me (5)	MeOH	rt	2	89
3	40% aq NH_2Me (5)	MeOH	ca. −5 °C	4	*d*
4	40% aq NH_2Me (5)	MeOH	ca. 5 °C	2	95
5	40% aq NH_2Me (5)	MeOH	reflux	1	43
6	40% aq NH_2Me (3)	MeOH	rt	4	76
7	40% aq NH_2Me (5)	THF	rt	1.5	91
8	40% aq NH_2Me (5)	THF	ca. 5 °C	4	98

[a] 1.0 g (3.7 mmol) of *N*-(*p*-toluenesulfonyl)-L-serine methyl ester (**21**) with 98% ee was used. [b] 5 mL was used. [c] Measured by HPLC analysis of the crude reaction mixture without work-up. Product was not isolated. [d] **21** did not react under these conditions.

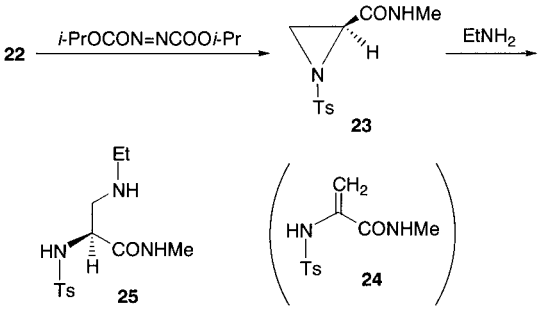
has then focused on the discovery of an alternative synthetic route which could eventually be used for the manufacture of the optically active amine **1**.

Large-Scale Synthesis of (*R*)-6-Amino-1-ethyl-4-methylhexahydro-1,4-diazepine (1) from *N*-(*p*-Toluenesulfonyl)-l-serine Methyl Ester (21). To improve the yield in reduction of the amide functionality, the *N*-protecting group of L-serine methyl ester was changed from a Cbz group into a Ts group. This change did not affect the reduction conditions. Treatment of L-serine methyl ester hydrochloride (**10**, >99.5% ee) with TsCl in the presence of Et_3N gave *N*-Ts-L-serine methyl ester (**21**)[12] in a quantitative yield without racemization. The reaction conditions for the preparation of the *N*-methylcarboxamide **22** from **21** were then examined (Table 1). Reaction of **21** with 1.1 mol equiv of $MeNH_2$ generated by $MeNH_2$·HCl and Et_3N in MeOH as a solvent did not proceed (run 1). On the other hand, in the reaction with 5 mol equiv of 40% aqueous $MeNH_2$ solution in MeOH at room temperature, **21** reacted smoothly (2 h) and the target product **22** was produced although slight racemization was detected by HPLC (89% ee, run 2). Several recrystallizations of **22** with 89% ee from AcOEt did not cause any increase in enantiomeric excess. To obtain optically pure **22**, details of the reaction conditions were examined (runs 3−8). Reaction of **21** at lower temperature (ca. −5 °C) needed longer time (4 h) to proceed completely (run 3). At ca. 5 °C, the reaction smoothly proceeded (2 h) giving **22** with 95% ee (run 4). Although the reaction of **21** under reflux temperature was fast, it resulted in considerable racemization (43% ee, run 5). A decrease in mol equivalency (5 to 3) of $MeNH_2$ needed longer reaction time (4 h) and reduced enantiomeric excess (89% to 76% ee, run 6). In a similar reaction in THF instead of MeOH at room temperature, **21** reacted completely after 1.5 h affording **22** with 91% ee (run 7). Finally, a similar reaction in run 7 at ca. 5 °C provided **22** with 98% ee (run 8). Compound **22** did not racemize in THF under reflux temperature in the presence of 5.0 mol equiv of 40% aqueous $MeNH_2$ solution. Among the reaction conditions studies, we selected the reaction under ice-cooling in THF (run 8) as the best condition. A large-scale synthesis of **22** without isolation of **21** starting from **10** gave a similar result to that described above, and **22** with ca. 99% ee was obtained in 80% yield as crystals (Scheme 5).

Scheme 5



Scheme 6



We previously reported that Mitsunobu-type reaction of *N*-Ts-ethanolamine derivative prepared from N^2-Ts-L-asparagine occurred in an intramolecular cyclization fashion to afford the corresponding activated *N*-Ts-aziridine derivative in a good yield without racemization and formed the dehydroalanine[13] as a by-product.[14] Mitsunobu-type reaction of **22** with 84% ee at lower temperature (<5 °C) gave the *N*-Ts-aziridine derivative **23** in a good yield without formation of methyl 2-Ts-aminoacrylate (**24**). However, when the inner temperature was elevated to >0 °C, **24** was formed. Addition of **24** to $EtNH_2$ resulted in racemization of **25**. Thus, a Mitsunobu-type reaction was performed at <−5 °C to avoid racemization. The exothermic Mitsunobu-type reaction could be easily controlled by the rate of addition of diisopropyl azodicarboxylate. Without isolation of the optically active *N*-Ts-aziridine **23**, the THF solution was treated with 2.0 mol equiv of 70% aqueous $EtNH_2$ solution at room temperature for 4 h to provide the C_3−N aziridine ring-opened product **25** as crystals. In this reaction, the formation of the C_2−N aziridine ring-opened product and racemization were not detected by HPLC. Fortunately, a single recrystallization of the crude product **25** from AcOEt gave the enantiomerically pure **25** (>99.5% ee) in 56% yield in two steps. When **22** with 95% ee was used as a starting material, the yield of **25** was elevated to 70% (Scheme 6).

The optically active aziridine **23** was obtained from the nonactivated *N*-tritylaziridine derivative **26** via **27** in a manner similar to that described in our previous report (Scheme 7).[10]

Reduction of the amide functionality of **25** with several reductants (BH_3·THF complex, $LiAlH_4$, sodium bis(2-methoxyethoxy)aluminum hydride, DIBALH) was next examined. Reaction of **25** with $LiAlH_4$ and DIBALH provided the desired 1,2,3-trisubstituted amine derivative **28** in good yield, although the reaction with DIBALH needed a longer time (ca. 3 d). As a result, $LiAlH_4$ was selected as

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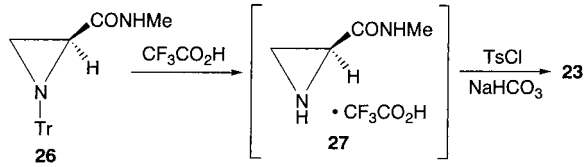
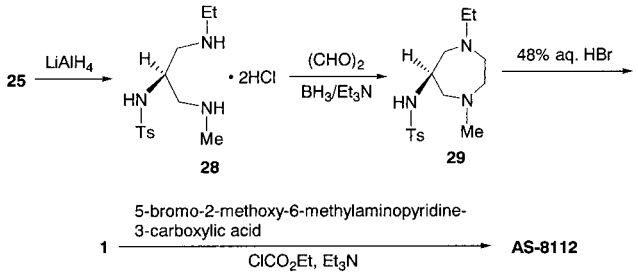
(14) Kato, S.; Harada, H.; Morie, T. *J. Heterocycl. Chem.* **1997**, *34*, 1460.

Scheme 7



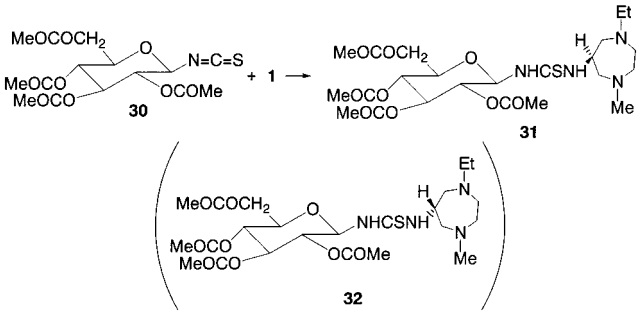
Scheme 8



the best reductant of **25**. Treatment of **25** with $LiAlH_4$ at ca. 10 °C followed by careful decomposition of excess $LiAlH_4$ using saturated aqueous Rochelle salt (potassium sodium tartarate tetrahydrate) solution gave the 1,2,3-trisubstituted aminopropane derivative (the free base of **28**) as a water-soluble pale yellow oil. The oil was then converted into the crystalline dihydrochloride **28** in 87% yield. It is worth noting that in the reduction of **25** no racemization was detected by chiral HPLC and that in the work-up water use must be strictly limited due to the complete solubility of the free base of **28** in H_2O. Cyclization of the 1,2,3-trisubstituted aminopropane **28** into the hexahydro-1,4-diazepine ring was carried out according to our previously described method.[10] Reaction of **28** with 40% aqueous glyoxal solution in the presence of $BH_3 \cdot Et_3N$ complex, $BH_3 \cdot Me_3N$ complex, or $NaBH_3CN$ directly gave the target (*R*)-1-ethyl-4-methyl-6-(*p*-toluenesulfonylamino)hexahydro-1,4-diazepine (**29**) as a pale yellow oil in quantitative yield. The oil was used in the next step without further purification. Finally, we examined the detosylation of **29** using HI,[15] HBr in AcOH,[16] aqueous HBr solution,[17] aqueous HBr solution/P,[18] and sodium bis(2-methoxyethoxy)aluminum hydride.[19] As a result, a solution of **29** in aqueous HBr solution was vigorously heated to reflux for 3 h, and the crude oil was distilled to produce (*R*)-6-amino-1-ethyl-4-methylhexahydro-1,4-diazepine (**1**) as a considerably water-soluble pale yellow oil in 77% yield in >99.5% ee (Scheme 8).

The enantiomeric excess of **1** was measured by the 1-[(*R*)-1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (**31**). Compound **31** and 1-[(*S*)-1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (**32**) were prepared by treatment of **1** and (*S*)-6-amino-1-ethyl-4-methylhexahydro-1,4-diazepine with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (**30**), respectively (Scheme 9).

Scheme 9



Preparation of AS-8112. Condensation of 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid[7] with **1** prepared above using acid anhydride method in AcOEt proceeded smoothly, and the desired free base of AS-8112 was obtained in good yield. The free base of AS-8112 was converted into the corresponding difumarate (AS-8112) without serious problems (see Scheme 8).

Summary

Effective and convergent process for a large-scale preparation of the optically active amine, (*R*)-6-amino-1-ethyl-4-methylhexahydro-1,4-diazepine (**1**) was examined. Synthesis of **1** by a sequence containing (1) methylamidation of *N*-Ts-L-serine methyl ester (**21**) obtained from the commercially available L-serine methyl ester hydrochloride (**10**), (2) formation of the aziridine derivative using Mitsunobu-type reaction, (3) nucleophilic substitution reaction with $EtNH_2$, (4) reduction with $LiAlH_4$, (5) reductive cyclization into the hexahydro-1,4-diazepine ring, and (6) deprotection of *N*-Ts group was accomplished. Although the step for the reaction of **21** with methylamine caused a slight decrease of enantiomeric excess, fortunately, a single recrystallization of the aziridine-opened product **25** gave this compound in an optically pure form. Amine **1** which is considerably soluble in water and is highly pure (>99.5% ee) was prepared in seven steps from **10** in >30% overall yield. This synthetic process, thus devised, could dispense with chromatographic purification and required neither expensive reagents nor special equipment. Therefore, it should be practical enough to be operated on an industrial scale. AS-8112, which is a clinical candidate expected to be a broad antiemetic agent, was prepared from **1** and the corresponding pyridine-3-carboxylic acid using acid anhydride method in good yield.

Experimental Section

General Procedures. All melting points were determined on a Yanagimoto micromelting point apparatus without correction. IR spectra were recorded on a Shimadzu FTIR-8200PC spectrometer with KBr disks. Atmospheric pressure chemical ionization and secondary ion mass spectra were obtained on a Hitachi M-1000 spectrometer. ^1H NMR spectra were recorded on a Varian Gemini-200 (200 MHz) or a JEOL JNM-LA300 (300 MHz) spectrometer using dilute solution in $CDCl_3$ unless otherwise stated. Chemical shifts

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are expressed as δ (ppm) values from Me_4Si as an internal standard. Optical rotations were measured at 589 nm with a Jasco P-1020 digital polarimeter. Organic extracts were dried over anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure.

(*S*)-2-Benzyloxycarbonylamino-3-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)amino-1-ethylaminopropane (14). Methanesulfonyl chloride (3.8 g, 33 mmol) was added dropwise to a mixture of (*R*)-2-benzyloxycarbonylamino-3-[*N*-(*tert*-butoxycarbonyl)-*N*-methyl]amino-1-propanol[9] (9.3 g, 28 mmol), Et_3N (4.2 g, 42 mmol), DMAP (0.19 g, 1.6 mmol), and CH_2Cl_2 (100 mL) at ca. 5 °C. The mixture was stirred at the same temperature for 0.5 h, washed with water, and concentrated to dryness. The oily residue including (*R*)-2-benzyloxycarbonylamino-3-[*N*-(*tert*-butoxycarbonyl)-*N*-methyl]amino-1-methanesulfonyloxypropane (**13**) was dissolved in EtOH (50 mL), and then 70% aqueous $EtNH_2$ solution (8.8 g, 137 mmol) was added. The solution was heated to reflux for 2 h and cooled to room temperature. The volatiles were evaporated, and the residue was diluted with 25% aqueous K_2CO_3 solution and extracted with $CHCl_3$. The extract was concentrated to dryness to afford 9.5 g (95%) of crude **14** as a viscous oil. ^{1}H NMR δ 1.06 (t, 3H, J = 7.1 Hz, CH_2*Me*), 1.43 (s, 9H, CMe_3), 2.5−2.7 (m, 2H), 2.73 (dd, 1H, J = 3.9 Hz, 11.2 Hz), 2.88 (s, 3H, NMe), 3.2−3.4 (m, 3H), 3.87 (m, 1H), 5.09 (s, 2H, *CH*$_2$Ph), 7.2−7.4 (m, 5H, Ph); MS *m*/*z* 366 (MH^+).

(*R*)-2-Benzyloxycarbonylamino-1-(ethylamino)-3-methylaminopropane (15). A mixture of **14** (7.2 g, 20 mmol), EtOH (25 mL), and 30% HCl in EtOH (25 mL) was stirred at room temperature for 3 h. After evaporation of the solvent, the residue was dissolved in 25% aqueous K_2CO_3 solution and extracted with $CHCl_3$. The extract was concentrated to dryness to give 5.0 g (96%) of **15** as an oil. An analytical sample was obtained by conversion to the fumarate: mp 156−157 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ 1.06 (t, 3H, J = 7.1 Hz, CH_2*Me*), 2.39 (s, 3H, NMe), 2.6−2.9 (m, 6H), 3.86 (m, 1H), 5.02 (s, 2H, *CH*$_2$Ph), 6.45 (s, 2H, fumaric acid), 7.2−7.4 (m, 5H, Ph), 7.61 (m, 1H, NH); MS *m*/*z* 266 (MH^+). Anal. Calcd for $C_{14}H_{23}N_3O_2 \cdot C_4H_4O_4$: C, 56.68: H, 7.14: N, 11.02. Found: C, 56.48: H, 7.19: N, 10.95.

(*R*)-6-Benzyloxycarbonylamino-1-ethyl-4-methylhexahydro-1,4-diazepine (16). (a) 40% aqueous glyoxal solution (32.7 g, 0.23 mol) and $BH_3 \cdot Et_3N$ complex (82.2 g, 0.71 mol) were added successively to a solution of **15** (46.0 g, 0.17 mol) in MeOH (460 mL) at ca. 5 °C. The mixture was stirred at room temperature for 24 h. After addition of 10% aqueous HCl solution (500 mL) at ca. 5 °C, the whole was heated to reflux for 1 h and cooled to room temperature. The mixture was concentrated, and the resulting aqueous solution was washed with AcOEt (200 mL × 2), basified with K_2CO_3(s), and extracted with $CHCl_3$. The extract was concentrated to dryness, and the oily residue was chromatographed on silica gel with $CHCl_3$/MeOH = 30/1 to afford 33.5 g (66%) of **16** as a pale yellow oil. ^{1}H NMR δ 1.01 (t, 3H, J = 7.0 Hz, NCH_2*Me*), 2.34 (s, 3H, NMe), 2.3−2.85 (m, 10H), 3.82 (m, 1H, 6-CH), 5.10 (s, 2H, C*H*$_2$Ph), 5.86 (br d, 1H, J = 10 Hz, NH), 7.25−7.4 (m, 5H, Ph); MS *m*/*z* 292 (MH^+). An analytical sample was obtained by conversion to the oxalate: mp 142−144 °C (EtOH). Anal. Calcd for $C_{16}H_{25}N_3O_2 \cdot 2C_2H_2O_4 \cdot 0.25H_2O$: C, 50.47: H, 6.25: N, 8.83. Found: C, 50.55: H, 6.44: N, 8.66.

(b) 1.0 M $BH_3 \cdot$THF complex (33 mL, 33 mmol) was added dropwise to a solution of **20** (3.4 g, 11 mmol) in THF (34 mL) at ca. 5 °C. The mixture was stirred at room temperature for 18 h. After addition of 2N aqueous HCl solution (17 mL, 34 mmol), the whole was heated to reflux for 1 h and cooled to room temperature. The reaction mixture was concentrated to dryness, and the resulting aqueous solution was washed with AcOEt, basified with solid K_2CO_3(s), and extracted with $CHCl_3$ (100 mL × 3). The extract was concentrated, and the residue was chromatographed on silica gel with $CHCl_3$/MeOH = 30/1 to give 1.8 g (51%) of **16** as a pale yellow oil. The resulting **16** was identified with the sample obtained above, on the basis of HPLC and ^{1}H NMR comparison.

Ethyl (*S*)-*N*-{2-Benzyloxycarbonylamino-3-[*N*-(*tert*-butoxycarbonyl)-*N*-methyl]amino-1-propyl}-*N*-ethylaminoacetate (17). A mixture of **14** (10.0 g, 27 mmol), ethyl bromoacetate (5.5 g, 33 mmol), K_2CO_3 (11.3 g, 82 mmol), and methyl ethyl ketone (150 mL) was heated to reflux for 4 h and cooled to room temperature. The reaction mixture was concentrated to dryness, and the residue was dissolved in H_2O (200 mL) and $CHCl_3$ (100 mL). The organic layer was separated and washed with brine. The solvent was dried over anhydrous $MgSO_4$ and evaporated. The oily residue was chromatographed on silica gel with $CHCl_3$/AcOEt = 9/1 to give 10.8 g (87%) of **17** as a colorless oil. ^{1}H NMR δ 1.01 (t, 3H, J = 7.1 Hz, NCH_2*Me*), 1.25 (t, 3H, J = 7.1 Hz, OCH_2*Me*), 1.43 (s, 9H, CMe_3), 2.5−2.8 (m, 4H), 2.89 (s, 3H, NMe), 3.33 (s, 2H, NCH_2CO), 3.2−3.7 (m, 2H), 3.79 (m, 1H, 6-H), 4.14 (q, 2H, J = 7.1 Hz, *CH*$_2$Me), 5.09 (s, 2H, C*H*$_2$Ph), 5.84 (br, 1H, NH), 7.25−7.4 (m, 5H, Ph); MS *m*/*z* 452 (MH^+).

Ethyl (*R*)-*N*-(2-Benzyloxycarbonylamino-3-methylamino-1-propyl)-*N*-ethylaminoacetate (18). A mixture of **17** (16.2 g, 36 mmol) and 10% HCl in EtOH (150 mL) was stirred at room temperature for 18 h. After evaporation of the volatiles, the residue was dissolved in H_2O (200 mL). The aqueous solution was then washed with AcOEt (100 mL), basified with K_2CO_3(s), and extracted with $CHCl_3$ (200 mL × 2). The extract was washed with brine and concentrated to dryness to give 11.4 g (90%) of **18** as a brown oil, which was used in the next step without further purification. ^{1}H NMR δ 1.01 (t, 3H, J = 7.1 Hz, NCH_2*Me*), 1.25 (t, 3H, J = 7.1 Hz, OCH_2*Me*), 2.42 (s, 3H, NMe), 2.62 (q, 2H, J = 7.1 Hz, *CH*$_2$Me), 2.55−2.8 (m, 4H), 3.03 (s, 2H, CH_2CO), 3.76 (m, 1H, 6-H), 4.15 (q, 2H, J = 7.1 Hz, *CH*$_2$Me), 5.10 (s, 2H, C*H*$_2$Ph), 5.65 (br, 1H, NH), 7.25−7.45 (m, 5H, Ph); MS *m*/*z* 352 (MH^+).

(*S*)-6-Benzyloxycarbonylamino-1-ethyl-4-methylhexahydro-1,4-diazepin-3-one (20). NaOEt (4.5 g, 66 mmol) was added to a solution of **18** (25.0 g, 71 mmol) in EtOH (250 mL) at ca. 5 °C, and the mixture was stirred at room temperature for 6 h. After acidification with 30% aqueous HCl solution, the mixture was concentrated. The aqueous

solution was then washed with AcOEt (100 mL × 2), basified with $NaHCO_3$(s), and extracted with AcOEt (200 mL × 2). The extract was washed with brine and concentrated to dryness. The residue was chromatographed on silica gel with $CHCl_3$/MeOH = 30/1 to give a solid, which was recrystallized from Et_2O to afford 9.6 g (44%) of **20** as a colorless prism: mp 85−87 °C. $[\alpha]^{27}_D = -11.9°$ (c = 1.07, MeOH). ^{1}H NMR δ 1.00 (t, 3H, J = 7 Hz, CH_2*Me*), 2.61 (q, 2H, J = 7 Hz, *CH_2*Me), 2.69 (dd, 1H, J = 12 Hz, 3 Hz, 5-CH_2), 2.88 (s, 3H, NMe), 2.92 (m, 1H, 5-CH_2), 3.18 (d, 1H, J = 14 Hz, 2-CH_2), 3.39 (dd, 1H, J = 14 Hz, 1.5 Hz, 2-CH_2), 3.62−3.46 (m, 2H), 3.9 (m, 1H, 6-CH), 5.08 (d, 1H, J = 12 Hz, C*H_2*Ph), 5.12 (d, 1H, J = 12 Hz, C*H_2*Ph), 5.4 (br d, 1H, J = 7.5 Hz, NH), 7.3−7.4 (m, 5H, Ph); MS m/z 306 (MH^+), 198 ($M^+ - OCH_2Ph$); IR 3281, 2955, 1713, 1620, 1541, 1288, 1234, 1030 cm^{-1}. Anal. Calcd for $C_{16}H_{23}N_3O_3$: C, 62.93: H, 7.59: N, 13.76. Found: C, 62.73; H, 7.61; N, 13.73.

(*S*)-3-Hydroxy-*N*-methyl-2-(*p*-toluenesulfonyl)aminopropionamide (22). To a suspension of L-serine methyl ester hydrochloride (**10**, 500 g, 3.2 mol, >99.5% ee) in $CHCl_3$ (2500 mL) was added dropwise Et_3N (683 g, 6.8 mol) at <−5 °C. The mixture was cooled to ca. −20 °C, and TsCl (613 g, 3.2 mol) was added portionwise at <−12 °C. The whole was warmed to ca. 10 °C, stirred at the same temperature for 1.5 h, and poured into ice−water. After addition of 35% aqueous HCl solution (150 mL), the resulting crystals were collected by filtration to give *N*-(*p*-toluenesulfonyl)-L-serine methyl ester (**21**) as a solid, which was used in the next step without further purification. A portion of the crude **21** was purified by recrystallization from AcOEt: mp 90−91 °C [Lit.[12] 92−93 °C (Et_2O)]. $[\alpha]^{27}_D$ = −11.3° (c = 1.52, MeOH). ^{1}H NMR δ 2.42 (s, 3H, C_6H_4*Me*), 3.62 (s, 3H, CO_2Me), 3.88 (d, 2H, J = 5.0 Hz, *CH_2*OH), 3.98 (m, 1H), 5.61 (d, 1H, J = 7.5 Hz, NH), 7.31 (d, 2H, J = 7.5 Hz, arom H), 7.75 (d, 2H, J = 7.5 Hz, arom H); MS m/z 274 (MH^+); IR 3491, 3273, 1749, 1331, 1165 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_5S$: C, 48.34: H, 5.53: N, 5.12; S, 11.73. Found: C, 48.31; H, 5.60; N, 5.17; S, 11.63. Chiral HPLC [column, CHIRALCEL AS (Daicel Chemical Industries, Ltd., Japan); 4.6 mm ϕ × 250 mm; eluent, hexane/*i*-PrOH/Et_2NH = 60/40/0.2; flow rate, 1.0 mL/min; column temperature, 25 °C; detection, 254 nm]; the retention times of **21** and its enantiomer were 10.0 and 8.2 min, respectively.

To a solution of **21** thus obtained in THF (2500 mL) was added dropwise 40% aqueous $MeNH_2$ solution (1245 g, 16 mol) at ca. 5 °C. The mixture was stirred at the same temperature for 2 h and concentrated. After addition of ice−water, the resulting precipitate was collected by filtration and recrystallized from AcOEt to give 697 g (80%, ca. 99% ee) of **22** as a crystal: mp 113−115 °C. $[\alpha]^{27}_D = -31.2°$ (c = 1.18, MeOH). ^{1}H NMR δ 2.42 (s, 3H, C_6H_4*Me*), 2.77 (d, 3H, J = 5.0 Hz, NH*Me*), 3.33 (dd, 1H, J = 5.0 Hz, 11.0 Hz, *CH_2*OH), 3.73 (m, 1H), 3.90 (dd, 1H, J = 3.5 Hz, 11.0 Hz, *CH_2*OH), 6.07 (br, 1H, N*H*Me), 6.92 (br, 1H), 7.32 (d, 2H, J = 9.0 Hz, arom H), 7.76 (d, 2H, J = 7.5 Hz, arom H); MS m/z 273 (MH^+); IR 1659, 1331, 1163 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52: H, 5.92: N, 10.29; S, 11.77. Found: C, 48.47; H, 5.98; N, 10.42; S, 11.61. Chiral HPLC [column, CHIRALCEL OD (Daicel Chemical Industries, Ltd., Japan); 4.6 mm ϕ × 250 mm; eluent, hexane/*i*-PrOH/CF_3CO_2H = 90/10/0.2; flow rate, 0.8 mL/min; column temperature, 25 °C; detection, 254 nm]; the retention times of **22** and its enantiomer were 24.9 and 29.2 min, respectively.

(*S*)-*N*-Methyl-1-(*p*-toluenesulfonyl)aziridine-2-carboxamide (23). To a solution of (*S*)-*N*-methyl-1-tritylaziridine-2-carboxamide[10] (**26**, 10.0 g, 29 mmol) in a mixture of $CHCl_3$ (30 mL) and MeOH (30 mL) was added dropwise CF_3CO_2H (20 mL) kept at 0 °C. The mixture was stirred for 5 h at <5 °C and kept at ca. 5 °C overnight. The solvent was evaporated <40 °C, and the white solid was dissolved in a mixture of AcOEt (40 mL) and ice−water (50 mL). The aqueous layer containing (*S*)-*N*-methylaziridine-2-carboxamide trifluoroacetate (**27**) was separated and basified with $NaHCO_3$(s) (9.8 g, 0.12 mol). After successive addition of CH_2Cl_2 (50 mL) and 1,4-dioxane (100 mL), TsCl (4.5 g, 24 mmol) was added portionwise under ice-cooling. The mixture was stirred at the same temperature for 5 h, and the volatiles were evaporated. The resulting precipitate was collected by filtration to give a wet white solid, which was dissolved in $CHCl_3$. The solution was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to give 4.7 g (63%) of **23**, which was recrystallized from acetone to afford pure **23** as a colorless crystal: mp 144−145.5 °C. $[\alpha]^{27}_D = -63.4°$ (c = 1.05, MeOH). ^{1}H NMR δ 2.38 (d, 1H, J = 4 Hz, 3-CH_2), 2.48 (s, 3H, C_6H_4*Me*), 2.73 (d, 1H, J = 6 Hz, 3-CH_2), 2.75 (d, J = 5 Hz, NH*Me*), 3.28 (dd, 1H, J = 4 Hz, 7 Hz, 2-CH), 6.3 (br, 1H), 7.39 (d, 2H, J = 7 Hz, arom H), 7.81 (d, 2H, J = 7 Hz, arom H); MS m/z 255 (MH^+); IR 3248, 3096, 1682, 1651, 1574, 1342, 1323, 1157 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.95: H, 5.55: N, 11.02; S, 12.61. Found: C, 52.00; H, 5.58; N, 11.02; S, 12.48.

(*S*)-3-Ethylamino-*N*-methyl-2-(*p*-toluenesulfonyl)aminopropionamide (25). Diisopropyl azodicarboxylate (892 g, 4.4 mol) was added dropwise to a solution of **22** (1200 g, 4.4 mol, 84% ee) and Ph_3P (1150 g, 4.4 mol) in THF (7000 mL) kept at <−5 °C. The reaction mixture was stirred at the same temperature for 0.5 h. Then, 70% aqueous $EtNH_2$ solution (567 g, 8.8 mol) was added dropwise at −5 °C to the solution containing (*S*)-*N*-methyl-1-(*p*-toluenesulfonyl)-aziridine-2-carboxamide (**23**), and the mixture was stirred at room temperature for 4 h. After concentration of the reaction mixture, the oily residue was dissolved in $CHCl_3$ (4000 mL). Cold (ca. 10 °C) aqueous citric acid solution [citric acid (700 g, 3.6 mol)/H_2O (2500 mL)] was added to the solution at 5 °C, and the mixture was stirred at room temperature for 3 h. The aqueous solution was separated and basified with 48% aqueous NaOH solution. K_2CO_3(s) (about 1500 g) was added, and the mixture was extracted with $CHCl_3$ (3000 mL + 200 mL). The combined extract was concentrated to dryness to give 1080 g of a white solid, which was recrystallized from AcOEt/hexane to afford 734 g (56%, >99.5% ee) of **25**: mp 123−124.5 °C. $[\alpha]^{27}_D = -10.9°$ (c = 1.06, MeOH). ^{1}H NMR δ 1.00 (t, 3H, J = 7.5 Hz, NCH_2*Me*), 2.25−2.65 (m, 2H), 2.44 (s, 3H, C_6H_4*Me*), 2.78

(d, 3H, J = 5.0 Hz, NH*Me*), 3.11 (dd, 1H, J = 5.0 Hz, 12.5 Hz, *CH*$_2$N), 3.50 (m, 1H), 3.53 (dd, 1H, J = 5.0 Hz, 7.5 Hz, *CH*$_2$N), 7.32 (d, 2H, J = 9.0 Hz, arom H), 7.45 (br, 1H), 7.75 (d, 2H, J = 7.5 Hz, arom H); MS m/z 300 (MH^+); IR 3337, 3242, 1651, 1329, 1165 cm^{-1}. Anal. Calcd for $C_{13}H_{21}N_3O_3S$: C, 52.15: H, 7.07: N, 14.04; S, 10.71. Found: C, 52.06; H, 7.15; N, 13.93; S, 10.56. Chiral HPLC [column, SUMICHIRAL OA-4900 (Sumika Chemical Analysis Service, Ltd., Japan); 4.6 mm ϕ × 250 mm; eluent, hexane/CH_2Cl_2/EtOH = 60/30/10; flow rate, 1.0 mL/min; column temperature, room temperature; detection, 254 nm]; the retention times of **25** and its enantiomer were 10.6 and 17.8 min, respectively.

(*R*)-1-Ethylamino-3-methylamino-2-(*p*-toluenesulfonyl)aminopropane Dihydrochloride (28). To a suspension of $LiAlH_4$ (pellet, 256 g, 6.7 mol) in anhydrous THF (6000 mL) was added portionwise **25** (920 g, 3.1 mol) at ca. 10 °C. The reaction mixture was stirred at ca. 20 °C for 18 h. Aqueous Rochelle salt solution [potassium sodium tartarate tetrahydrate (1380 g)/H_2O (920 mL)] was carefully added dropwise to the reaction mixture at ca. 5 °C. After addition of AcOEt (8000 mL) and Celite (2000 g), the mixture was stirred at room temperature for 3 h. The insoluble materials were filtered off and washed with AcOEt. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness to leave a pale yellow oil, which was dissolved in a mixture of *i*-PrOH (1000 mL) and acetone (1500 mL). HCl (20%, 1404 g) in *i*-PrOH was added at ca. 5 °C, and the solution was allowed to stand at 10 °C overnight. The resulting precipitate was collected by filtration, washed with acetone, and dried to give 955 g (87%, >99.5% ee) of **28** as a white powder: mp 223−228 °C. $[\alpha]^{27}_D$ = −8.1° (c = 2.12, H_2O). ^{1}H NMR (DMSO-d_6) δ 1.13 (t, 3H, J = 7.5 Hz, CH_2*Me*), 2.42 (s, 3H, C_6H_4*Me*), 2.46 (s, 3H, Me), 2.6−3.25 (m, 6H), 3.93 (m, 1H), 7.44 (d, 2H, J = 8.5 Hz, arom H), 7.85 (d, 2H, J = 7.5 Hz, arom H), 9.16 (br, 2H); MS m/z 286 (MH^+); IR 2982, 2775, 2718, 1331, 1153 cm^{-1}. Anal. Calcd for $C_{13}H_{23}N_3O_2S$·2HCl: C, 43.57: H, 7.03: N, 11.73; S, 8.95; Cl, 19.79. Found: C, 43.45; H, 7.10; N, 11.67; S, 8.74; Cl, 19.57. Chiral HPLC [column, SUMICHIRAL OA-4900; 4.6 mm ϕ × (250 mm × 2); eluent, hexane/THF/MeOH/CF_3CO_2H = 50/45/5/0.5; flow rate, 1.0 mL/min; column temperature, room temperature; detection, 235 nm]; the retention times of **28** and its enantiomer were 41.2 and 48.3 min, respectively.

(*R*)-1-Ethyl-4-methyl-6-(*p*-toluenesulfonyl)aminohexahydro-1,4-diazepine (29). Glyoxal solution (40% aqueous, 105.4 g, 0.73 mol) and BH_3·Et_3N complex (257.1 g, 2.2 mol) was added successively dropwise to a suspension of **28** (200 g, 0.56 mol) in MeOH (2000 mL) at room temperature. The mixture was stirred at the same temperature for 16 h. HCl solution (6 N aqueous, 559 mL) was added at <5 °C, and the mixture was heated to reflux for 2 h and cooled to room temperature. After evaporation of MeOH, the resulting aqueous solution was washed with AcOEt, basified with $NaHCO_3$(s), and extracted with AcOEt. The extract was then concentrated to dryness to give 173 g (quantitative yield) of **29** as an oil, which was used in the next step without further purification. ^{1}H NMR δ 0.97 (t, 3H, J = 7.5 Hz, CH_2*Me*), 2.25 (s, 3H, C_6H_4*Me*), 2.42 (s, 3H, Me), 2.3−2.85 (m, 10H), 3.45 (m, 1H), 7.29 (d, 2H, J = 8.4 Hz, arom H), 7.76 (d, 2H, J = 8.4 Hz, arom H); MS m/z 311 (MH^+).

(*R*)-6-Amino-1-ethyl-4-methylhexahydro-1,4-diazepine (1). (a) A mixture of crude **29** (173 g) and 48% aqueous HBr solution (1000 mL) was vigorously heated to reflux for 3 h and cooled to room temperature. The aqueous solution was washed with $CHCl_3$ (400 mL × 2) and basified with 48% aqueous NaOH solution. After addition of K_2CO_3(s) (200 g), the mixture was extracted with $CHCl_3$ (700 mL × 3). The extract was concentrated to dryness to give ca. 90 g of **1** as an yellow oil, which was distilled to afford 67.8 g (77%, >99.5% ee) of **1** as a colorless oil: bp 85−102 °C/5−18 Torr. $[\alpha]^{27}_D$ = −2.0° (c = 2.65, MeOH). ^{1}H NMR δ 1.04 (t, 3H, J = 7.0 Hz, CH_2*Me*), 2.38 (s, 3H, Me), 2.3−2.9 (m, 10H), 3.05 (m, 1H); MS m/z 158 (MH^+). $C_8H_{19}N_3$·$0.1H_2O$: C, 60.41: H, 12.17: N, 26.42. Found: C, 60.60; H, 12.06; N, 26.11.

Compound **1** (3.0 mg) was dissolved in 0.2% Et_3N in CH_3CN solution (0.2 mL in 100 mL; 0.6 mL). To the solution (100 μL) was added successively H_2O (50 μL) and 0.2% 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (**30**) in CH_3CN solution (30 mg in 15 mL; 100 μL), the mixture was vigorously stirred at room temperature for ca. 1 min. After standing at room temperature for 15 min, the reaction mixture was analyzed by chiral HPLC. Chiral HPLC [column, DEVELOSIL ODS-HG-5 (Nomura Chemical Co., Ltd., Japan); 4.6 mm ϕ × 250 mm; eluent, 50 mM NaH_2PO_4 + H_3PO_4 (pH = 3.5)/CH_3CN/*i*-PrOH = 80/15/5; flow rate, 1.0 mL/min; column temperature, 40 °C; detection, 254 nm]; the retention times of 1-[(*R*)-1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (**31**) and 1-[(*S*)-1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiourea (**32**) were 11.5 and 12.5 min, respectively.

(b) A solution of **16** (33.5 g, 0.12 mol) in a mixture of EtOH (300 mL) and H_2O (30 mL) was hydrogenated over 10% Pd−C (3.35 g) at room temperature until TLC indicated almost no starting material remained. The catalyst was filtered off, and the filtrate was concentrated to give 18.0 g (quantitative yield, >99% ee) of **1** as a pale brown oil. The resulting **1** was identified with the sample obtained above, on the basis of ^{1}H NMR comparison.

(*R*)-5-Bromo-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-2-methoxy-6-methylaminopyridine-3-carboxamide Difumarate (AS-8112). Ethyl chloroformate (46.9 g, 0.43 mol) and a solution of **1** (65.0 g, 0.41 mol) in AcOEt (130 mL) were successively added dropwise to a mixture of 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid[7] (102.5 g, 0.39 mol), Et_3N (43.7 g, 0.43 mol), and AcOEt (975 mL) at kept ca. 3 °C. The mixture was stirred at the same temperature for 0.5 h. The insoluble materials were filtered off, and the filtrate was washed with H_2O and dried over anhydrous $MgSO_4$. The solvent was evaporated to give 160 g of (*R*)-5-bromo-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-2-methoxy-6-methylaminopyridine-3-carboxamide as a solid, which was converted into the difumarate in

the usual manner [fumaric acid (95 g)/EtOH (800 mL)] to afford 192.0 g (77%) of AS-8112: mp 149−151 °C. $[\alpha]^{27}_{D} = -4.4°$ ($c = 2.13$, MeOH). ^{1}H NMR (DMSO-d_6) δ 1.05 (t, 3H, $J = 7$ Hz, CH_2*Me*), 2.48 (s, 3H, Me), 2.52 (m, 1H), 2.58−3.07 (m, 10H), 2.93 (d, 3H, $J = 5$ Hz), 3.99 (s, 3H), 4.18 (m, 1H), 6.59 (s, 4H, fumaric acid), 6.99 (d, 1H, $J = 5$ Hz, N*H*Me), 8.10 (s, 1H, Py-4), 8.37 (d, 1H, $J = 8.5$ Hz, CONH); MS *m*/*z* 401 (MH^+); IR 3360, 1666, 1601, 1512, 1275 cm^{-1}. Anal. Calcd for $C_{16}H_{26}BrN_5O_2 \cdot 2C_4H_4O_4$: C, 45.58: H, 5.42: N, 11.07; Br, 12.63. Found: C, 45.78; H, 5.43; N, 11.11; Br, 12.62.

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