Efficient synthesis of (6*R*)-6-amino-1-methyl-4-(3-methylbenzyl)-hexahydro-1*H*-1,4-diazepine from methyl (2*R*)- and (2*S*)-1-benzyloxycarbonylaziridine-2-carboxylates

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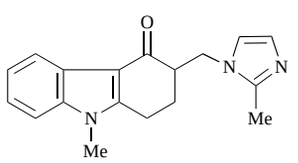
An efficient and practical method for the synthesis of (6*R*)-6-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepine 2, which serves as the amine part of DAT-582, a potent and selective 5-HT$_3$ receptor antagonist, is described. The key intermediates, the chiral 2,3-diaminopropionic esters 20 and 26, are prepared by treatment of the optically active aziridines (*R*)-13 and (*S*)-13, obtained from D- and L-serine methyl ester hydrochlorides (*R*)-9 and (*S*)-9, with the ethylenediamine 19 and its protected derivative 18, respectively. Intramolecular reductive cyclization of 20 gives the chiral 6-benzyloxycarbonylaminohexahydro-1*H*-1,4-diazepine 22 with high optical purity *via* the corresponding iminium salt. Deprotection of 22 affords the desired chiral amine 2. As an alternative method, intramolecular amidation of the 2,3-diaminopropionic acids 23 and 28, which are prepared from 20 and 26, gives the 6-benzyloxycarbonylaminohexahydro-1*H*-1,4-diazepin-5-one 24 and the 7-oxo analogue 29. After removal of the benzyloxycarbonyl group, the resultant compounds 25 and 30 are reduced with diisobutylaluminium hydride to produce the optically active amine 2.

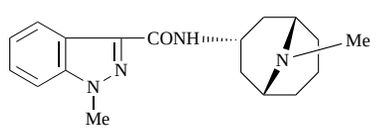
Introduction

Serotonin (5-HT) is a neurotransmitter involved in a wide range of pharmacological effects in several peripheral as well as central nervous tissues.[1] 5-HT receptors are subdivided into four major categories designated '5-HT$_1$-like', 5-HT$_2$, 5-HT$_3$ and 5-HT$_4$.[2] The 5-HT$_3$ receptor is of special interest due to its involvement in various pathophysiological processes.[3] Recently, a number of potent 5-HT$_3$ receptor antagonists, typified by granisetron and ondansetron, have been reported,[4] and several 5-HT$_3$ receptor antagonists are used clinically as antiemetics in cancer chemotherapy. Furthermore, 5-HT$_3$ receptor antagonists are currently being investigated for use in the treatment of various centrally mediated disorders such as anxiety, drug abuse and schizophrenia.[5]

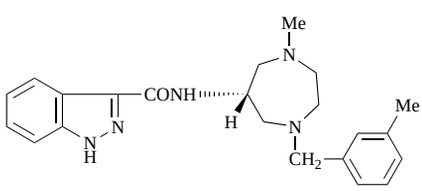
To identify novel 5-HT$_3$ receptor antagonists, we prepared earlier a series of *N*-(hexahydro-1*H*-1,4-diazepin-6-yl)benzamides and carboxamides.[6] Among them, (6*R*)-(−)-*N*-[1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-6-yl]-1*H*-indazole-3-carboxamide **1** (DAT-582 as its dihydrochloride) showed the most potent 5-HT$_3$ receptor antagonistic activity and was selected as a promising candidate for potential clinical use.[7] DAT-582 is structurally novel and unrelated to any other potent 5-HT$_3$ receptor antagonists reported, and the free base was prepared from (6*R*)-6-amino-1-methyl-4-(3-methylbenzyl)-hexahydro-1*H*-1,4-diazepine **2** and 1*H*-indazole-3-carboxylic acid.[8] Therefore, a general route which would allow the preparation of the optically active amine **2** in quantities of the order of several hundred grams was required. Our interest has focused on the discovery of an efficient method for the asymmetric synthesis of **2**. Earlier, we reported the original formation of the racemic 6-(substituted amino)hexahydro-1*H*-1,4-diazepine ring; reduction of the protected 2,3-diaminopropionic esters **5** prepared from the known 2-(substituted amino)propenic esters **3** and *N*-benzyl-*N*′-methylethylenediamine **4** with diisobutylaluminium hydride (DIBAL-H) at −70 °C followed by rapid sodium borohydride reduction of the iminium salts **7** derived from the amino aldehydes **6** provided the hexahydro-1*H*-1,4-diazepine derivatives **8** in good overall yields (Scheme 1).[9] On the basis of these results, we hoped



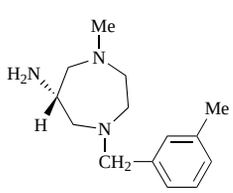
ondansetron



granisetron



1 (2HCl salt; DAT-582)



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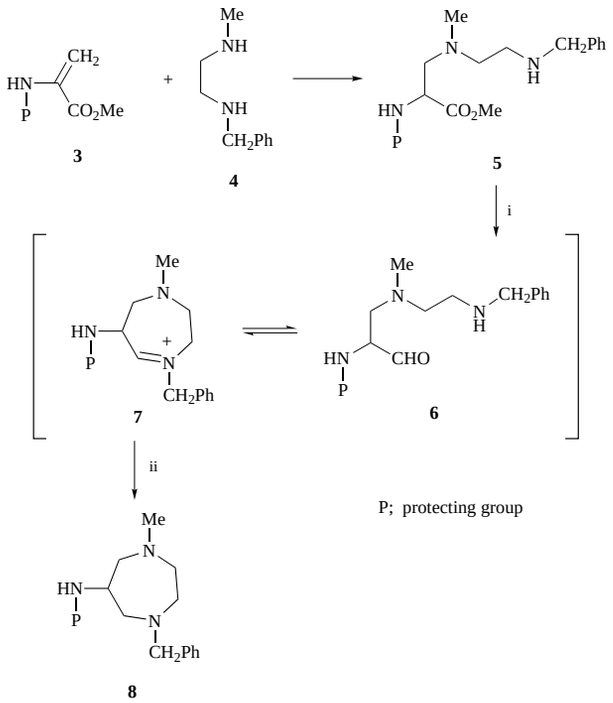
that reaction of the chiral 2,3-diaminopropionic esters with DIBAL-H at low temperature followed by sodium borohydride reduction of the chiral iminium salts would produce the chiral 6-(substituted amino)hexahydro-1*H*-1,4-diazepines without racemization. Here, we describe an efficient and practical synthesis of the optically active amine **2** from D- and L-serine methyl ester hydrochlorides (*R*)-**9a** and (*S*)-**9a** *via* methyl (2*R*)-



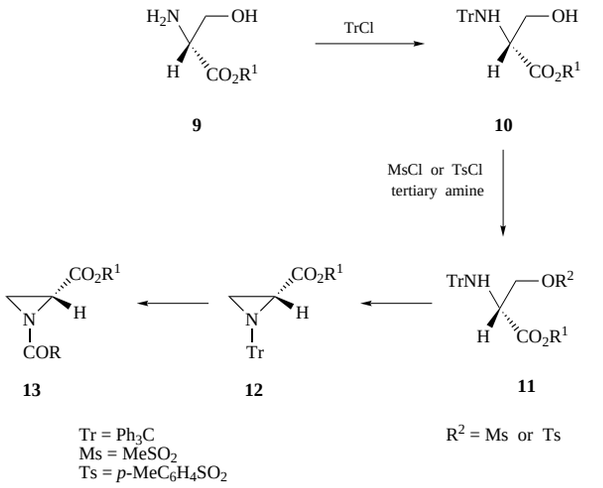
Scheme 1 *Reagents*: i, diisobutylaluminium hydride; ii, sodium borohydride

and (2*S*)-1-benzyloxycarbonylaziridine-2-carboxylates (*R*)-**13** and (*S*)-**13**.

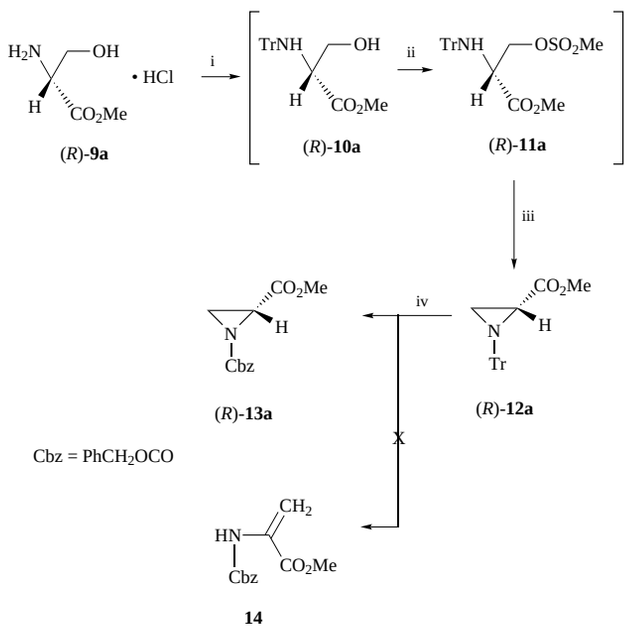
Results and discussion

Synthesis of (6*R*)-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepine from D-serine *via* methyl (2*R*)-1-benzyloxycarbonylaziridine-2-carboxylate

Preparation of the optically active form of the 2,3-diaminopropionic ester intermediates such as **5** was first examined. There have been a number of reports demonstrating the utility of the activated aziridine-2-carboxylic esters in the preparation of α- and β-amino acids.[10] We chose the chiral 1-substituted aziridine-2-carboxylic esters as chiral equivalents of **3**. The reaction of 1-substituted aziridine-2-carboxylic esters with an ethylenediamine such as **4** would give the expected chiral 2,3-diaminopropionic esters by C_3-N aziridine ring opening. For the success of this strategy, the enantiopure 1-substituted aziridine-2-carboxylic esters need to be obtained. The optically active forms of the activated aziridine-2-carboxylic esters can be readily obtained from the optically active serine ester as a source of chirality; the hydroxy group in the optically pure *N*-triphenylmethyl (trityl) serine esters **10** derived from the readily available amino acid serines **9** was converted into the corresponding *O*-mesyl or *O*-tosyl derivatives **11** which, in turn, were subjected to intramolecular cyclization in the presence of a tertiary amine as auxiliary base to afford the 1-tritylaziridine-2-carboxylic esters **12**. Compounds **12** were converted into the activated aziridine-2-carboxylic esters **13** (Scheme 2).[11] Although this route provided enough material for preliminary investigations, it is too lengthy and low yielding for efficient multigram scale preparation. Accordingly, a more direct route was developed in which the optically pure aziridine **13a** was prepared in 2 steps from D-serine methyl ester hydrochloride (*R*)-**9a** (Scheme 3).† Thus,



Scheme 2



Scheme 3 *Reagents*: i, trityl chloride, triethylamine; ii, methanesulfonyl chloride, triethylamine, 4-dimethylaminopyridine; iii, triethylamine; iv, trifluoroacetic acid then benzyl chloroformate

reaction of (*R*)-**9a** with trityl chloride in the presence of triethylamine in chloroform, without isolation, followed by mesylation of *N*-trityl-D-serine methyl ester (*R*)-**10a** using methanesulfonyl chloride in the presence of an excess of triethylamine and 4-dimethylaminopyridine and successive treatment of the mixture containing the mesylate (*R*)-**11a** in refluxing chloroform for 14 h gave the chiral methyl 1-tritylaziridine-2-carboxylate (*R*)-**12a** in 88% overall yield. Compound (*R*)-**12a** thus isolated was shown to be more than 99% pure according to HPLC and ^{1}H NMR spectral analysis, whilst its optical rotation {$[\alpha]_D^{27}$ +87.9 (*c* 2.0, in chloroform)} was in good agreement with the reported value[11a] {$[\alpha]_D^{20}$ +95.0 (*c* 2, in chloroform)}. A benzyloxycarbonyl (Cbz) group was selected for protection of the nitrogen atom in the aziridine ring. Deprotection of the trityl group of (*R*)-**12a** by an excess of trifluoroacetic acid at low temperature followed by reprotection of the unstable aziridine trifluoroacetate salt employing benzyl chloroformate under basic conditions afforded (*R*)-**13a** (74%), without formation of methyl 2-benzyloxycarbonylaminoacrylate[12] **14**.

N-Methyl-*N*′-(3-methylbenzyl)ethylenediamine **19** was prepared as follows. After protection of 2-methylaminoethanol **15** by a *tert*-butoxycarbonyl (Boc) group, oxidation of the result-

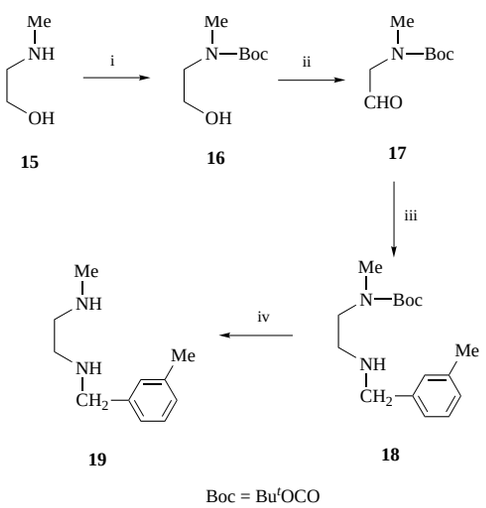
† After we completed this work, Willems *et al*. recently reported a multigram one-pot method for the synthesis of methyl (2*S*)-1-tritylaziridine-2-carboxylate (*S*)-**12a** as an intermediate of (2*S*)-1-tritylaziridin-2-yl(diphenyl)methanol. Thus, the mesylation of (*S*)-**10a** followed by the aziridine ring closure in the presence of triethylamine in refluxing tetrahydrofuran for 48 h produced (*S*)-**12a** in almost quantitative yield (*J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 963).

Table 1 Conditions and yield of **20**

Entry	Reaction conditions	Yield of **20** (%)[a]
1	Tetrahydrofuran, reflux, 15 h	62
2	Chloroform, reflux, 8 h	51
3	Methanol, reflux, 20 h	11
4	Neat, room temperature, 20 h	49
5	Neat, 70 °C, 20 h	44

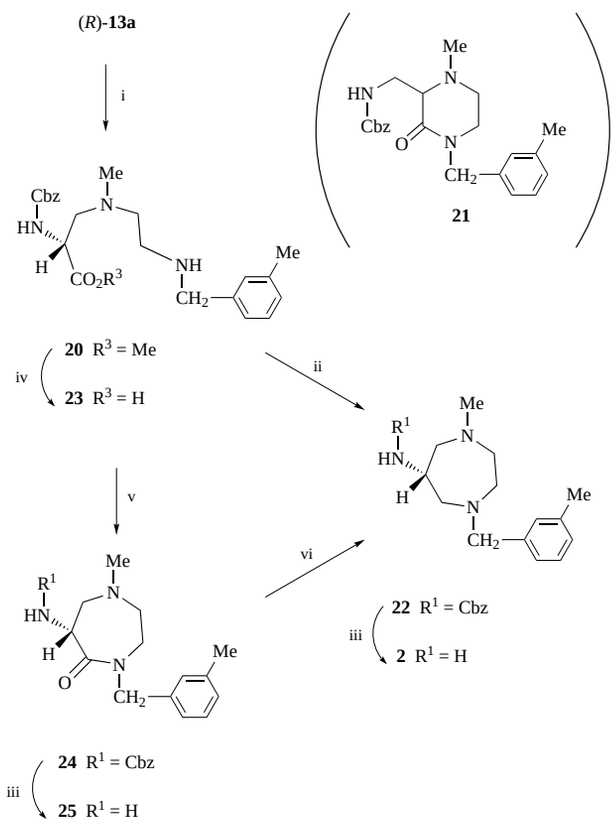
[a] Isolated yields based on (*R*)-**13** after silica gel column chromatography.

ant compound **16** was carried out using pyridine sulfur trioxide, dimethyl sulfoxide and triethylamine to give the corresponding aldehyde **17** (63%). Reaction of **17** with 3-methylbenzylamine followed by sodium borohydride reduction produced the ethylenediamine **18** (75%). Finally, deprotection of **18** by trifluoroacetic acid afforded the desired ethylenediamine **19** (Scheme 4).



Scheme 4 *Reagents*: i, di-*tert*-butyl dicarbonate; ii, pyridine sulfur trioxide, dimethyl sulfoxide, triethylamine; iii, 3-methylbenzylamine, sodium hydrogen carbonate then sodium borohydride; iv, trifluoroacetic acid

Reaction of the optically active aziridine-2-carboxylic ester (*R*)-**13a** with the ethylenediamine **19** thus obtained was initially carried out in refluxing tetrahydrofuran for 15 h followed by purification using silica gel column chromatography to give the expected C_3-N aziridine ring-opened product **20** (62%), together with the known 2-aminoacrylate **14** (12%) resulting from decomposition of the starting material (*R*)-**13a** and the unexpected piperazinone derivative **21** (12%), which would be formed by C_2-N aziridine ring opening and successive cyclization. The structures of **14**, **20** and **21** were assigned by analysis of their ^{1}H NMR and mass spectra. Without determination of the enantiomeric excess (ee) of the chiral 2,3-diaminopropionic ester **20**, its treatment with DIBAL-H at −70 °C, followed by reduction with sodium borohydride, gave the optically active hexahydro-1*H*-1,4-diazepine **22** (80%). The enantiomeric purity of **22** was determined to be practically 92% ee on the basis of chiral high-performance liquid chromatography (HPLC). Isolation of the 2-aminoacrylate **14** indicated a decrease in the optical purity of **20** because the reaction of **14** with **19** gave the racemic 2,3-diaminopropionate ester. To improve the yield of **20** and avoid formation of **14** and **21**, we investigated the reaction conditions of (*R*)-**13a** and **19** (Table 1). Although the reaction was performed in refluxing chloroform (entry 2) and without solvent at room temperature and at 70 °C (entries 4 and 5, respectively), the yield of **20** was essentially the same as that of refluxing tetrahydrofuran described above (entry 1). On the other hand, use of methanol resulted in a low yield (entry 3). Unfortunately, in all cases, the 2-aminoacrylate **14** and the piperazinone **21** were still detected by TLC analysis. Furthermore, to examine the influence of the reactivity of the methyl ester moiety and *N*-protecting group of (*R*)-**13a**, the optically active benzyl 1-benzyloxycarbonylaziridine-2-carboxylate[13] and the chiral methyl 1-acetyl,[14] 1-benzoyl,[13a] 1-(*tert*-butoxycarbonyl),[13a,15] and 1-(*p*-tolylsulfonyl)aziridine-2-carboxylates[16] were prepared and then allowed to react with **19** without solvent at 70 °C. However, none of these reactions afforded a satisfactory result; the yields of the corresponding C_3-N aziridine ring-opened products were 45–60%, and the 2-aminoacrylic esters and the piperazinone derivatives were also obtained in 10–15% yield. Therefore, variation of the ester and *N*-protecting groups failed to effect marked changes in product distributions in the reaction of the aziridine-2-carboxylic esters with the nitrogen nucleophile. Finally, acid hydrolysis of **22** afforded the desired (6*R*)-6-aminohexahydro-1*H*-1,4-diazepine **2** with 92% ee (Scheme 5).‡ The hexahydro-1*H*-1,4-diazepine



Scheme 5 *Reagents*: i, **19**; ii, diisobutylaluminium hydride then sodium borohydride; iii, 47% aqueous hydrobromic acid; iv, 2 M aqueous sodium hydroxide; v, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride; vi, diisobutylaluminium hydride

ring formation described above is a very efficient method in amounts of the order of several grams. However, the intramolecular reductive cyclization of **20** was found to be not applicable for such large-scale production of **22** because obvious racemization was observed (60%–70% ee). This suggests that the instability of iminium salts such as **7** in the solution causes racemization.

Next, we investigated the development of an alternative synthetic route to the chiral hexahydro-1*H*-1,4-diazepine **2** from the 2,3-diaminopropionic ester **20**. Based on our earlier results,[9b] we adopted the method involving intramolecular amidation. Hydrolysis of **20** with 2 M aqueous sodium hydroxide gave the 2,3-diaminopropionic acid **23**, which was then treated

‡ The enantiomerically pure carboxamide **1** (>99% ee) was obtained by several recrystallizations of the crystals which were prepared from the chiral amine **2** (92% ee) and 1*H*-indazole-3-carboxylic acid in the presence of a coupling reagent.[17]

Table 2 Conditions and yield of **26**

Entry	Reaction conditions	Yield of **26** (%)[a]
1	Chloroform, room temperature, 20 h[b]	0
2	Chloroform, reflux, 20 h[b]	42
3	Neat, 80 °C, 18 h	50
4	Toluene, reflux, 72 h	43
5	Xylene, reflux, 24 h	43

[a] Isolated yields based on (*S*)-**13** after silica gel column chromatography. [b] Addition of boron trifluoride–diethyl ether (1 mol equiv.).

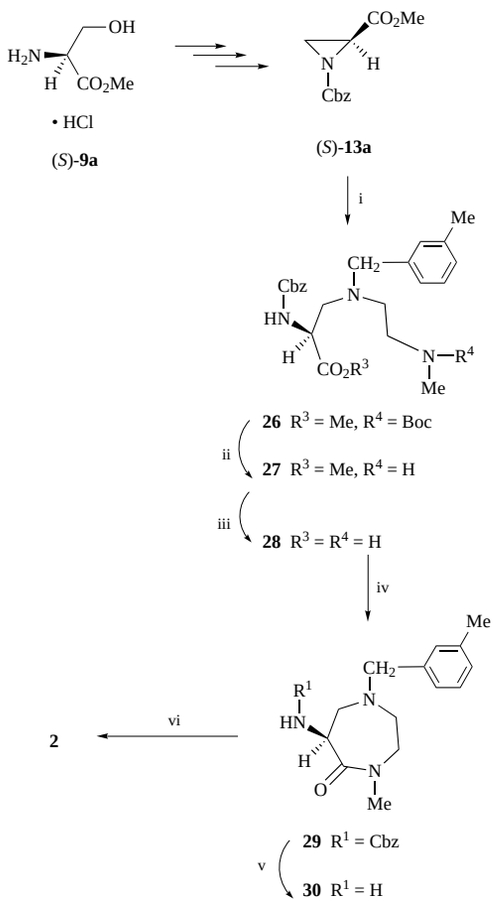
with 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSC) to afford the hexahydro-1*H*-1,4-diazepin-5-one **24** (52%) in two steps. Although the use of diphenylphosphoryl azide[18] instead of WSC as a coupling reagent resulted in the same yield, the use of *N*,*N*′-carbonyldiimidazole furnished **24** in poor yield. Reduction of **24** with DIBAL-H gave **22** in only 33% yield. Thus, after deprotection of the Cbz group by 47% aqueous hydrobromic acid, the resulting 6-aminohexahydro-1*H*-1,4-diazepinone **25** was reduced with DIBAL-H to afford the amine **2** (60%) with 89% ee. A large-scale synthesis *via* the hexahydro-1*H*-1,4-diazepin-5-one **24** produced the desired amine **2** in *ca*. 90% ee. This result indicates that no racemization occurred in either process (Scheme 5).

Synthesis of (6*R*)-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepine from L-serine *via* methyl (2*S*)-1-benzyloxycarbonylaziridine-2-carboxylate

We finally examined the route to **2** from the more readily available starting material L-serine methyl ester hydrochloride (*S*)-**9a**. Compound (*S*)-**9a** was sequentially converted into methyl (2*S*)-1-benzyloxycarbonylaziridine-2-carboxylate (*S*)-**13a** as well as (*R*)-**13a** in 65% overall yield. To obtain the *R* form of 6-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepine, the benzylamine moiety instead of the methylamino moiety of the ethylenediamine **19** must attack the C-3 position in the aziridine ring of (*S*)-**13a**. Thus, the ethylenediamine **18** with a Boc group was selected. First, the aziridine (*S*)-**13a** was treated with **18** in chloroform in the presence of boron trifluoride–diethyl ether at room temperature for 20 h, but the expected 2,3-diaminopropionic ester derivative **26** was not obtained (Table 2, entry 1). On the other hand, a similar reaction in refluxing chloroform for 20 h afforded **26** (42%) with approximately 90% ee, along with the 2-aminoacrylate **14** and the starting (*S*)-**13a** and **18** (entry 2).§ Although the reaction without solvent at 80 °C and in refluxing toluene and xylene was investigated, the yield of **26** did not increase, and compounds (*S*)-**13a**, **14** and **18** were also detected by HPLC analysis (entries 3–5). After deprotection of the Boc group of **26**, saponification of the 2,3-diaminopropionic ester **27** followed by intramolecular cyclization of the resulting 2,3-diaminopropionic acid **28** using WSC produced the hexahydro-1*H*-1,4-diazepin-7-one **29** in 54% overall yield from **26** with 90% ee. In a similar manner to that described for the pathway from **24** to **2**, after deprotection of **29**, the resulting 6-aminohexahydro-1*H*-1,4-diazepin-7-one **30** was reduced with DIBAL-H to give the amine **2** (58%) in 2 steps without racemization (Scheme 6).

In conclusion, an efficient and practical method for synthesis of (6*R*)-6-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepine **2** has been developed from D- and L-serine methyl esters (*R*)-**9a** and (*S*)-**9a** as a source of chirality *via* methyl (2*R*)- and (2*S*)-1-benzyloxycarbonylaziridine-2-carboxylates (*R*)-**13a** and (*S*)-**13a** in approximately 10–30% overall yield with high enantiomeric purity.

§ From HPLC analysis of the crude reaction mixture [column, CAPCELL PAK C_{18} (Shiseido, Japan); 4.6 diam. × 150 mm; eluent, water (including 0.5% trifluoroacetic acid)–acetonitrile, 1:1; flow rate, 1.0 cm^3 min^{-1}; column temperature; 25 °C, detection; 215 nm], the starting materials (*S*)-**13a** and **18**, methyl 2-benzyloxycarbonylaminoacrylate **14** and **26** were observed. The retention times for **18**, (*S*)-**13a**, **26** and **14** were 2.0, 4.2, 6.0 and 6.1 min, respectively.



Scheme 6 *Reagents*: i, **18**; ii, 30% hydrochloric acid in ethanol; iii, 2 M aqueous sodium hydroxide; iv, 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride; v, 47% aqueous hydrobromic acid; vi, **18**; vii, diisobutylaluminium hydride

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus without correction. IR spectra were recorded on a Hitachi 260-10 or a Shimadzu FTIR-8200PC spectrometer. Secondary ion mass spectra were measured with a Hitachi M-80-B spectrometer. ^{1}H NMR spectra were recorded using a Varian Gemini-200 spectrometer (200 MHz), and chemical shifts are expressed as δ (ppm) values from tetramethylsilane as an internal standard; *J* values are given in Hz. All spectra were obtained in deuteriochloroform solution. Optical rotations were measured at 589 nm with a Jasco DIP-4 digital polarimeter and are recorded as 10^{-1} deg cm^2 g^{-1}. 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. Merck silica gel 60 (70–230 mesh) was used for column chromatography.

Methyl (2*S*)-1-tritylaziridine-2-carboxylate (*S*)-12a

The method of Smrt *et al*. was applied.[11a,b] Trityl chloride (1793 g, 6.4 mol) was added portionwise to a stirred suspension of L-serine methyl ester hydrochloride (*S*)-**9a** (1000 g, 6.4 mol) and triethylamine (1564 g, 15.5 mol) in chloroform (8000 cm^3) over a period of 2 h at 0–10 °C. The mixture was stirred at the same temperature for 1 h and then washed successively with water and brine. To the dry chloroform solution containing *N*-trityl-L-serine methyl ester[16b] (*S*)-**10a** was added triethylamine (1759 g, 17.4 mol) and 4-dimethylaminopyridine (79 g, 0.65 mol).

Methanesulfonyl chloride (1029 g, 9.0 mol) was then added dropwise to the mixture during *ca*. 2 h at 20–50 °C. The solution containing methyl 2-tritylamino-3-methylsulfonyloxypropionate (*S*)-**11a**, triethylamine and 4-dimethylaminopyridine was heated to reflux for 14 h, cooled to room temperature and washed successively with water and brine. The solvent was evaporated to leave a solid, which was recrystallized from ethanol to give (*S*)-**12a** (1740 g, 79% for 3 steps), mp 130–131 °C; $[\alpha]_D^{27}$ −87.7 (*c* 1.0, in chloroform) {lit.,[11a] mp 123–125 °C, $[\alpha]_D^{20}$ −94.2 (*c* 1, in chloroform), lit.,[16b] mp 114–116 °C (from diethyl ether), $[\alpha]_D^{20}$ −89.2 (*c* 2.68, in tetrahydrofuran), lit.,[19] $[\alpha]_D^{22}$ −95.4 (*c* 1.1, in methanol)}; δ_H 1.41 (1H, dd, *J* 7.0 and 1.8, 3-CH_2), 1.89 (1H, dd, *J* 7.0 and 3.0, 2-CH), 2.55 (1H, dd, *J* 3.0, and 1.8, 3-CH_2), 3.75 (3H, s, CO_2Me) and 7.17–7.55 (15H, m, ArH); *m*/*z* 344 (MH^+) (Found: C, 80.6; H, 6.1; N, 4.2. $C_{23}H_{21}NO_2$ requires C, 80.44; H, 6.16; N, 4.08%).

In a similar manner to that described above, the enantiomer (*R*)-**12a**[11a,b] was prepared from D-serine methyl ester hydrochloride (*R*)-**9a** *via* (*R*)-**10a** and (*R*)-**11a** in 88% overall yield, mp 129–131 °C (from ethanol); $[\alpha]_D^{27}$ +87.9 (*c* 2.0, in chloroform) {lit.,[11a] mp 123–124 °C, $[\alpha]_D^{20}$ +95.0 (*c* 2, in chloroform)} (Found: C, 80.2; H, 6.1; N, 4.2. $C_{23}H_{21}NO_2$ requires C, 80.44; H, 6.16; N, 4.08%).

Methyl (2*S*)-1-benzyloxycarbonylaziridine-2-carboxylate (*S*)-13a

Compound (*S*)-**13a** was prepared by a modification of the method of Sato and Kozikowski.[13a] Trifluoroacetic acid (3000 g, 26.3 mol) was added dropwise to a solution of (*S*)-**12a** (1372 g, 4.0 mol) in a mixture of methanol (2700 cm^3) and chloroform (2700 cm^3) over a period of *ca*. 2 h at 0–5 °C. The mixture was stirred at the same temperature for 1 h and then concentrated at *ca*. 5 °C until a precipitate was deposited. After dilution of the mixture with cold water (4000 cm^3), the precipitate was filtered off. The filtrate was washed with diethyl ether (2000 cm^3) and neutralized with sodium hydrogen carbonate at 5 °C. Additional sodium hydrogen carbonate (500 g, 6.0 mol) and diethyl ether (4000 cm^3) were added to the aqueous solution, followed by benzyl chloroformate (612 g, 3.6 mol), added dropwise over a period of 2 h at 0–10 °C. The mixture was vigorously stirred at the same temperature for 2 h, after which the organic layer was separated, washed with brine and evaporated at *ca*. 40 °C to leave a pale yellow oil. This was distilled to give (*S*)-**13** (771 g, 82%) as a colourless oil, bp 160–165 °C (2 mmHg); δ_H 2.48 (1H, dd, *J* 5.5 and 1, 3-CH_2), 2.60 (1H, dd, *J* 3 and 1, 2-CH), 3.11 (1H, dd, *J* 5.5 and 3, 3-CH_2), 3.72 (3H, s, CO_2Me), 5.15 (2H, s, CH_2Ph) and 7.35–7.40 (5H, m, ArH); ν_{max}(neat)/cm^{-1} 1732; *m*/*z* 236 (MH^+) (Found: C, 61.5; H, 5.7; N, 5.95. $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.65; N, 5.95%).

The enantiomer (*R*)-**13a**[13a] was prepared from (*R*)-**12a** in a similar manner to that described above in 74% yield, bp 162–163 °C (2 mmHg) (Found: C, 61.1; H, 5.9; N, 5.7. $C_{12}H_{13}NO_4$ requires C, 61.27; H, 5.65; N, 5.95%).

2-[*N*-(*tert*-Butoxycarbonyl)-*N*-methylamino]ethanol 16

A solution of di-*tert*-butyl dicarbonate (594 g, 2.7 mol) in chloroform (500 cm^3) was added dropwise to a solution of 2-methylaminoethanol **15** (204 g, 2.7 mol) in chloroform (1000 cm^3) at *ca*. 5 °C. The mixture was stirred at room temperature for 15 h and then concentrated to dryness. The residue was distilled to give **16** (475 g, quantitative yield) as a colourless oil, bp 117–120 °C (4–5 mmHg); δ_H 1.47 (9H, s, Me_3C), 2.92 (3H, s, Me), 3.13 (1H, br s, OH), 3.38 (2H, t, *J* 5, C$H_2$$CH_2$) and 3.73 (2H, t, *J* 5, CH_2CH_2); ν_{max}(neat)/cm^{-1} 3439 and 1674; *m*/*z* 176 (MH^+).

2-[*N*-(*tert*-Butoxycarbonyl)-*N*-methylamino]acetaldehyde 17

To a mixture of **16** (108.0 g, 0.62 mol), triethylamine (124.6 g, 1.23 mol), dichloromethane (1500 cm^3) and dimethyl sulfoxide (378 cm^3) was added portionwise pyridine sulfur trioxide (98%; 200.0 g, 1.23 mol) kept at *ca*. 15 °C. The mixture was stirred at room temperature for 2 h and then washed successively with water (1000 cm^3 × 3), 10% aqueous citric acid (300 cm^3), water (300 cm^3) and brine. Concentration of the mixture afforded an oily residue which was distilled to give **17** (67.5 g, 63%) as a colourless oil, bp 87–89 °C (3 mmHg); δ_H 1.46 (9H, br s, Me_3C), 2.96 (3H, br s, Me), 3.98 (2H, br s, CH_2) and 9.61 (1H, s, CHO); ν_{max}(neat)/cm^{-1} 1734 and 1693; *m*/*z* 174 (MH^+).

N-(*tert*-Butoxycarbonyl)-*N*-methyl-*N*′-(3-methylbenzyl)-ethylenediamine 18

A mixture of **17** (19.0 g, 0.11 mol), 3-methylbenzylamine (13.3 g, 0.11 mol), sodium hydrogen carbonate (18.5 g, 0.22 mol) and methanol (250 cm^3) was heated to reflux for 2 h and then cooled to *ca*. 5 °C. After sodium borohydride (8.3 g, 0.22 mol) had been added portionwise to the mixture kept at *ca*. 5 °C it was stirred at room temperature for 2 h and then concentrated to dryness. The residue was partitioned between a mixture of chloroform and water after which the organic layer was separated, washed with brine and evaporated. The oily residue was distilled to give **18** (22.8 g, 75%) as a pale yellow oil, bp 145–148 °C (0.5 mmHg); δ_H 1.44 (9H, s, Me_3C), 2.34 (3H, s, Me), 2.78 (2H, t, *J* 6), 2.86 (3H, s, Me), 3.36 (2H, t, *J* 6), 3.77 (2H, s, C$H_2C_6H_4$) and 7.01–7.30 (5H, m, ArH and NH); ν_{max}(neat)/cm^{-1} 1680; *m*/*z* 279 (MH^+).

N-Methyl-*N*′-(3-methylbenzyl)ethylenediamine 19

A mixture of **18** (27.8 g, 0.10 mol), trifluoroacetic acid (60 cm^3) and chloroform (10 cm^3) was stirred at room temperature for 15 h after which it was concentrated to dryness to leave a residue. A solution of this in water (20 cm^3) was basified with an excess of potassium carbonate and then extracted with chloroform. The extract was evaporated to leave an oily residue, which was distilled to give **19** (12.3 g, 69%), bp 102–106 °C (2 mmHg); δ_H 1.62 (2H, s, NH), 2.34 (3H, s, Me), 2.46 (3H, s, Me), 2.66–2.84 (4H, m), 3.77 (2H, s, C$H_2C_6H_4$) and 7.03–7.27 (4H, m, ArH); ν_{max}(neat)/cm^{-1} 2831, 2788 and 1440; *m*/*z* 179 (MH^+).

Methyl (2*R*)-2-benzyloxycarbonylamino-3-{*N*-methyl-*N*-[2-(3-methylbenzyl)aminoethyl]}aminopropionate 20

A mixture of (*R*)-**13a** (10.0 g, 43 mmol), **19** (9.1 g, 51 mmol) and tetrahydrofuran (50 cm^3) was heated to reflux for 15 h and then cooled to room temperature. Evaporation of the mixture left an oily residue, which was chromatographed on silica gel with a gradient of chloroform to chloroform–methanol (50:1) to give methyl 2-benzyloxycarbonylaminopropenate **14** (1.2 g, 12%) as an oil, 2-benzyloxycarbonylaminomethyl-1-methyl-4-(3-methylbenzyl)piperazin-3-one **21** (2.0 g, 12%) as an oil and **20** (10.9 g, 62%) as an oil.

Compound **20**: δ_H 2.22 (3H, s), 2.32 (3H, s), 2.4–2.9 (7H, m), 3.70 (3H, s, CO_2Me), 3.78 (2H, s, C$H_2C_6H_4$), 4.35 (1H, m), 5.10 (2H, s, CH_2Ph), 6.40 (1H, m) and 7.0–7.4 (9H, m, ArH); ν_{max}(neat)/cm^{-1} 1720 and 1710; *m*/*z* 414 (MH^+). The oil was converted into the oxalate in the usual manner, mp 197–200 °C (from ethanol) (Found: C, 55.1; H, 6.5; N, 7.4. $C_{23}H_{31}N_3O_4 \cdot 1.5C_2H_2O_4 \cdot H_2O$ requires C, 55.12; H, 6.40; N, 7.42%).

Compound **21**: δ_H 2.30 (3H, s), 2.42 (3H, s), 2.55 (1H, dd, *J* 12 and 5), 2.82–3.11 (3H, m), 3.33–3.52 (2H, m), 3.92 (1H, m), 4.48 (1H, d, *J* 15, C$H_2C_6H_4$), 4.62 (1H, d, *J* 15, C$H_2C_6H_4$), 5.10 (2H, s, CH_2Ph), 5.55 (1H, m) and 6.95–7.41 (9H, m, ArH); ν_{max}(neat)/cm^{-1} 1715; *m*/*z* 382 (MH^+) and 217 (M^+ − $CbzNHCH_2$).

The ^1H NMR spectrum of **14** was identical with that described in the literature.[12]

(6*R*)-6-Benzyloxycarbonylamino-1-methyl-4-(3-methylbenzyl)-hexahydro-1*H*-1,4-diazepine 22

Diisobutylaluminium hydride (DIBAL-H: 1 mol dm^{-3} solution in toluene; 105 cm^3, 0.11 mol) was added dropwise to a solution of **20** (10.8 g, 26 mmol) in anhydrous tetrahydrofuran (108 cm^3)

at −70 °C. The mixture was stirred at the same temperature for 0.5 h after which the excess of reagent was decomposed with methanol (216 cm^3) at −70 °C. The reaction mixture was warmed to −10 °C after which sodium borohydride (1.5 g, 40 mmol) was gradually added to it. After the mixture had been stirred at room temperature for 15 h, it was concentrated to dryness and the residue dissolved in chloroform. The resulting solution was washed successively with water and brine and then evaporated to leave an oil. This was chromatographed on silica gel with chloroform–methanol (50:1) to give **22** (7.7 g, 80%) as a pale yellow oil. The optical purity of **22** (92% ee), thus obtained, was analysed by chiral HPLC [column, CHIRALCEL OD (Daicel Chemical Industries, Ltd., Japan); 4.6 diam. × 250 mm; eluent, hexane–propan-2-ol (7:3, including 0.1% diethylamine); flow rate, 1.0 $cm^3\ min^{-1}$; column temperature; 20 °C, detection; 215 nm]. The retention times for **22** and the enantiomer were 5.6 and 9.2 min, respectively; $[a]_D^{25}$ +4.2 (*c* 1.0, in methanol); δ_H 2.29 (3H, s), 2.34 (3H, s), 2.2–2.9 (8H, m), 3.50 (1H, d, *J* 15, CH_2C$_6$H$_4$), 3.65 (1H, d, *J* 15, CH_2C$_6$H$_4$), 3.80 (1H, m), 5.05 (2H, s, CH_2Ph), 5.78 (1H, d, *J* 8) and 7.0–7.4 (9H, m, ArH); ν_{max}(neat)/cm^{-1} 1715; *m*/*z* 368 (MH^+) (Found: C, 71.3; H, 7.9; N, 11.3. $C_{22}H_{29}N_3O_2$·0.25H_2O requires C, 71.03; H, 7.99; N, 11.30%).

(6*R*)-6-Benzyloxycarbonylamino-1-methyl-4-(3-methylbenzyl)-hexahydro-1*H*-1,4-diazepin-5-one 24

A mixture of **20** (8.9 g, 22 mmol), 2 M aqueous sodium hydroxide (11 cm^3, 22 mmol) and ethanol (9 cm^3) was stirred at room temperature for 2 h. After removal of the ethanol from the mixture by evaporation, the resulting aqueous solution was acidified with 2 M aqueous hydrochloric acid and extracted with chloroform. The extract containing (2*R*)-2-benzyloxycarbonylamino-3-{*N*-methyl-*N*-[2-(3-methylbenzyl)aminoethyl]}aminopropionic acid **23** was washed with brine, after which 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSC; 2.9 g, 15 mmol) was added to it. The mixture was stirred at room temperature for 15 h and then washed successively with water and brine and finally evaporated to leave a residue. This was chromatographed on silica gel with chloroform–methanol (50:1) to give **24** (4.3 g, 52%) as an oil; δ_H 2.07 (1H, dd, *J* 12 and 12), 2.29 (1H, dd, *J* 12 and 12), 2.34 (3H, s), 2.38 (3H, s), 2.78 (1H, dd, *J* 12 and 5), 3.10 (1H, d-like, *J* 12), 3.19 (1H, dd, *J* 15 and 5), 3.70 (1H, dd, *J* 15 and 12), 4.43 (1H, d, *J* 15, CH_2C$_6$H$_4$), 4.65 (1H, m, 6-CH), 4.75 (1H, d, *J* 15, CH_2C$_6$H$_4$), 5.15 (2H, s, CH_2Ph), 6.28 (1H, d, *J* 7, CONH) and 6.75–7.50 (9H, m, ArH); *m*/*z* 382 (MH^+).

The oil was converted into the hydrochloride in the usual manner, mp 120–122 °C (from acetone) (Found: C, 59.9; H, 6.9; Cl, 8.1; N, 9.5. $C_{22}H_{27}N_3O_3$·HCl·1.25H_2O requires C, 59.99; H, 6.98; Cl, 8.05; N, 9.54%).

Methyl (2*S*)-2-benzyloxycarbonylamino-3-[*N*-(3-methylbenzyl)-*N*-{2-[*N*-(*tert*-butoxycarbonyl)-*N*-methylamino]ethyl}amino]-propionate 26

A solution of (*S*)-**13a** (10.0 g, 43 mmol) and **18** (10.6 g, 38 mmol) in xylene (100 cm^3) was heated to reflux for 24 h and then cooled to room temperature. The mixture was evaporated to leave an oily residue, which was chromatographed on silica gel with chloroform to give **26** [9.4 g, 43% yield from (*S*)-**13a**] as a viscous oil. The optical purity of **26** (90% ee) thus obtained was analysed by chiral HPLC [column, CHIRALCEL AS (Daicel Chemical Industries, Ltd., Japan); 4.6 diam. × 250 mm; eluent, hexane–ethanol (9:1); flow rate, 1.0 $cm^3\ min^{-1}$; column temperature; 25 °C, detection; 254 nm]. The retention times for **26** and its enantiomer were 5.5 and 6.4 min, respectively; δ_H 1.40 and 1.55 (9H, s, Me_3C), 2.30 (3H, s), 2.5–3.8 (11H, m), 3.73 (3H, s), 4.38 (1H, m), 5.10 (2H, s, CH_2Ph), 6.50 (1H, m) and 6.9–7.5 (9H, m, ArH); ν_{max}(neat)/cm^{-1} 1740, 1700 and 1690; *m*/*z* 514 (MH^+) (Found: C, 65.1; H, 7.6; N, 7.9. $C_{28}H_{39}N_3O_6$·0.25H_2O requires C, 64.91; H, 7.68; N, 8.11%).

Methyl (2*S*)-2-benzyloxycarbonylamino-3-[*N*-(3-methylbenzyl)-*N*-(2-methylaminoethyl)]aminopropionate 27

A mixture of **26** (8.5 g, 17 mmol), 30% hydrochloric acid in ethanol (28 cm^3) and ethanol (50 cm^3) was stirred at room temperature for 2 h. The mixture was evaporated at <40 °C to give an oily residue which was dissolved in water. The solution was washed with diethyl ether and then neutralised with potassium carbonate and extracted with chloroform. The extract was washed with brine and concentrated to leave an oil, which was chromatographed on silica gel with chloroform–methanol (30:1) to give **27** (6.0 g, 88%) as an oil; δ_H 2.32 (7H, br s), 2.64 (4H, br s), 2.7–3.0 (2H, m), 3.58 (2H, s, CH_2C$_6$H$_4$), 3.71 (3H, s, CO_2Me), 4.34 (1H, m), 5.08 (1H, d, *J* 10, CH_2Ph), 5.17 (1H, d, *J* 10, CH_2Ph) and 7.0–7.4 (10H, m, CONH and ArH); ν_{max}(neat)/cm^{-1} 1735 and 1710; *m*/*z* 414 (MH^+).

The oil was converted into the oxalate in the usual manner, mp 185–190 °C (from ethanol–diethyl ether) (Found: C, 59.6; H, 6.6; N, 8.3. $C_{23}H_{31}N_3O_4$·$C_2H_2O_4$·0.25H_2O requires C, 59.63; H, 6.61; N, 8.34%).

(2*S*)-2-Benzyloxycarbonylamino-3-[*N*-(3-methylbenzyl)-*N*-(2-methylaminoethyl)amino]propionic acid 28

A mixture of **27** (191 g, 0.46 mol), ethanol (280 cm^3) and 2 M aqueous sodium hydroxide (277 cm^3, 0.55 mol) was stirred at room temperature for 16 h. After evaporation of the mixture, the resulting aqueous solution was acidified with 35% aqueous hydrochloric acid and then extracted with chloroform. The extract was washed with brine and concentrated to give **28** (146 g, 79%) as a solid. An analytical sample was obtained by recrystallization of the solid from diethyl ether, mp 170–175 °C; δ_H 2.07 (3H, s), 2.34 (3H, s), 2.4–3.1 (7H, m), 3.49 (1H, d, *J* 15, CH_2C$_6$H$_4$), 4.15 (1H, d, *J* 15, CH_2C$_6$H$_4$), 4.10 (1H, m), 5.04 (1H, d, *J* 10, CH_2Ph), 5.12 (1H, d, *J* 10, CH_2Ph), 6.07 (1H, d, *J* 7, NHCO), 7.0–7.4 (9H, m, ArH) and 9.7 (1H, br s, CO_2H); ν_{max}(KBr)/cm^{-1} 1705; *m*/*z* 400 (MH^+) (Found: C, 65.5; H, 7.1; N, 10.4. $C_{22}H_{29}N_3O_4$·0.25H_2O requires C, 65.41; H, 7.36; N, 10.40%).

(6*S*)-6-Benzyloxycarbonylamino-1-methyl-4-(3-methylbenzyl)-hexahydro-1*H*-1,4-diazepin-7-one 29

A mixture of **28** (22.0 g, 55 mmol), WSC (11.7 g, 61 mmol) and dichloromethane (440 cm^3) was stirred at room temperature for 15 h after which it was washed successively with water, 10% aqueous sodium hydroxide and brine and then evaporated to leave a residue. This was chromatographed on silica gel with a gradient of chloroform to chloroform–methanol (20:1) to give **29** (16.1 g, 77%) as a solid. An analytical sample was obtained by recrystallization from diethyl ether, mp 70–71 °C. The optical purity of **29** (90% ee) thus obtained was analysed by chiral HPLC [column, CHIRALCEL OJ (Daicel Chemical Industries, Ltd., Japan); 4.6 diam. × 250 mm; eluent, hexane–propan-2-ol (8:2, including 0.1% diethylamine); flow rate, 1.0 $cm^3\ min^{-1}$; column temperature; 25 °C, detection; 254 nm]. The retention times for **29** and its enantiomer were 10.0 and 12.5 min, respectively; δ_H 2.34 (3H, s), 2.1–2.4 (2H, m), 2.87 (1H, m), 3.00 (3H, s), 3.0–3.25 (2H, m), 3.55 (1H, d, *J* 15, CH_2C$_6$H$_4$), 3.80 (1H, d, *J* 15, CH_2C$_6$H$_4$), 3.88 (1H, m), 4.69 (1H, m), 5.10 (2H, s, CH_2Ph), 6.21 (1H, d, *J* 7, NHCO) and 7.05–7.40 (9H, m, ArH); ν_{max}(KBr)/cm^{-1} 1718 and 1650; *m*/*z* 382 (MH^+) (Found: C, 68.6; H, 7.1; N, 11.1. $C_{22}H_{27}N_3O_3$·0.25H_2O requires C, 68.46; H, 7.18; N, 10.89%).

(6*S*)-6-Amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-7-one 30

A mixture of **29** (8.0 g, 21 mmol) and 47% aqueous hydrobromic acid (40 cm^3) was heated at 60 °C for 1 h and then cooled to room temperature. After dilution of the reaction mixture with water it was washed with diethyl ether (20 cm^3 × 3), basified with 20% aqueous sodium hydroxide and extracted with chloroform. The extract was washed successively with

water and brine and then concentrated to leave a pale brown oil, which was chromatographed on silica gel with chloroform–methanol (30:1) to give **30** (4.5 g, 87%) as a pale yellow oil; δ_H 1.85 (2H, s, NH_2), 2.12–2.32 (2H, m), 2.35 (3H, s), 2.77–2.93 (2H, m), 3.02 (3H, s), 3.12 (1H, m), 3.50 (1H, d, *J* 15, $CH_2C_6H_4$), 3.61 (1H, d, *J* 15, $CH_2C_6H_4$), 3.60–3.88 (2H, m) and 7.00–7.30 (4H, m, ArH); ν_{max}(neat)/cm^{-1} 1640; *m*/*z* 248 (MH^+) [Found: C, 67.8; H, 8.65; N, 16.6%; M (EI), 247.1681. $C_{14}H_{21}N_3O$ requires C, 67.98; H, 8.56; N, 16.99%; *M*, 247.1683].

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

(i) From 22. In a similar manner to that described for the conversion of **29** into **30**, **22** was treated with 47% aqueous hydrobromic acid to give **2** (86%), bp 128–140 °C (1 mmHg). The optical purity of **2** (92% ee) thus obtained was analysed by chiral HPLC [column, CROWN PAK CR(+) (Daicel Chemical Industries, Ltd., Japan); 4.6 diam. × 150 mm; eluent, perchloric acid in water (pH 1.5)–methanol (9:1); flow rate, 0.7 cm^3 min^{-1}; column temperature, 25 °C; detection, 220 nm]. The retention times for **2** and its enantiomer were 10.8 and 12.3 min, respectively; δ_H 1.72 (2H, br s, NH_2), 2.34 (3H, s), 2.30–2.74 (6H, m), 2.36 (3H, s), 2.76–2.90 (2H, m), 3.03 (1H, m), 3.60 (2H, s, $CH_2C_6H_4$) and 7.00–7.30 (4H, m, ArH); ν_{max}(neat)/cm^{-1} 3250, 1595, 1450 and 1340; *m*/*z* 234 (MH^+).

(ii) From 30. To a solution of **30** (28.0 g, 0.11 mol) in toluene (140 cm^3) was added dropwise DIBAL-H (1 mol dm^{-3} solution in toluene; 800 cm^3, 0.80 mol) at 0–10 °C. The mixture was stirred at room temperature for 15 h, after which the excess of reagent was decomposed with water (30 cm^3). After addition of 10% aqueous sodium hydroxide (30 cm^3), the mixture was stirred at room temperature for 0.5 h. The organic layer was separated, washed with brine and concentrated to leave an oily residue, which was distilled to give **2** (17.8 g, 67%, 89% ee).

(iii) From 24. In a similar manner to that described for the conversion of **29** into **2**, **24** was treated with 47% aqueous hydrobromic acid and DIBAL-H to afford **2** *via* (6*R*)-6-amino-1-methyl-4-(3-methylbenzyl)hexahydro-1*H*-1,4-diazepin-5-one **25** in 60% overall yield with 89% ee.

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