Synthesis of optically active azetidine-2,4-dicarboxylic acid and related chiral auxiliaries for asymmetric synthesis

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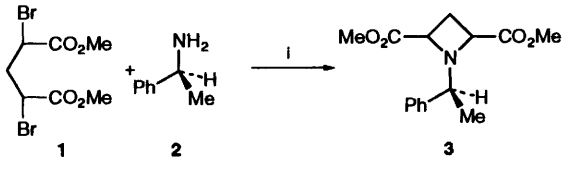
(*S*)-1-Phenylethylamine has been used as a chiral auxiliary as well as a nitrogen atom donor in the synthesis of an enantiomeric pair of azetidine-2,4-dicarboxylic acids, the absolute configuration of one of which has been assigned on the basis of the X-ray structure and the known absolute configuration of the (*S*)-1-phenylethylamine moiety. Chiral auxiliaries of related C_2-symmetric azetidines have also been prepared and their propionamides have been asymmetrically alkylated. The stereochemistry of the resulting products was compared with their analogues having different ring sizes.

(+)-(2*S*,3*S*)-Aziridine-2,3-dicarboxylic acid [1] and (−)-(2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid,[2] naturally occurring non-protein heterocyclic amino acids with C_2-symmetry, have been synthesised in optically active forms.[3,4] *trans*-Azetidine-2,4-dicarboxylic acid having an analogous structure to the above compounds is not found in nature and its optically active form has not been reported, despite neurobiological interest in it as a modulator of the *N*-methyl-D-aspartate receptor.[5] Here we report a facile synthesis of an enantiomeric pair of *trans*-azetidine-2,4-dicarboxylic acids based on our recent synthesis of optically active pyrrolidine-2,5-dicarboxylic acid.[3]

A diastereoisomeric mixture of the azetidine derivative **3** was obtained by heating dimethyl 2,4-dibromopentanedioate **1** [6] with (*S*)-1-phenylethylamine **2** in a mixutre of toluene and aqueous potassium carbonate (Scheme 1).[7] TLC analysis of this



1 2 3

Scheme 1 *Reagents and conditions:* i, K_2CO_3, toluene, reflux

mixture showed the presence of three components, R_{fSS} 0.40, R_{fRR} 0.31 and R_{fcis} 0.23,† which were readily separated by conventional flash chromatography to give (*S*,*S*)-**3** (22%), (*R*,*R*)-**3** (22%) and *cis*-**3** (44%). The absolute configuration of one of them was assigned from the X-ray analysis of the diol (*R*,*R*)-**5** (Fig. 1), which was derived from the diester (*R*,*R*)-**3** (*vide infra*). The azetidine ring formation and the following transformation to (*R*,*R*)-**5** do not affect the stereogenic centre of (*S*)-1-phenylethylamine.[8] The *R*,*R*-configuration of the azetidine ring was not assigned experimentally but chosen on the basis of that of the (*S*)-1-phenylethylamine moiety.‡ Hydrogenolysis of the diester (*S*,*S*)-**3** over palladium hydroxide on carbon followed by hydrolysis in hot water afforded (2*S*,4*S*)-

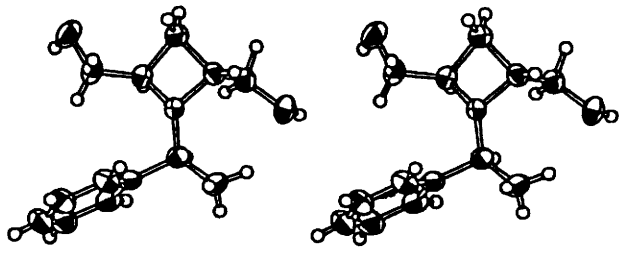


Fig. 1 A stereoview of compound (*R*,*R*)-**5**

azetidine-2,4-dicarboxylic acid **4** (Scheme 2).§ The (*R*,*R*)-isomer was also prepared by following the same reaction sequence from the diester (*R*,*R*)-**3**.

C_2-Symmetric cyclic amines bearing bis(alkoxymethyl) substituents on carbons adjacent to the nitrogen have been efficiently employed for substrate-controlled asymmetric syntheses.[9,10] A chiral auxiliary of this type having a 4-membered ring has not been described. We now describe its synthesis and application for asymmetric alkylation and compare the stereo-course thereof with other cyclic amines.

The diester (*S*,*S*)-**3** was reduced with lithium aluminium hydride to give the diol (*S*,*S*)-**5**. *O*-Methylation of (*S*,*S*)-**5** with sodium hydride and methyl iodide followed by hydrogenolysis over palladium hydroxide on carbon gave the azetidine (*S*,*S*)-**6a** (Scheme 2). Similarly, the azetidine (*R*,*R*)-**6a** was obtained from the diester (*R*,*R*)-**3**. The diol (*R*,*R*)-**5** was converted into the azetidine (*R*,*R*)-**6b** by successive hydrogenolysis, *N*-formylation with ethyl formate, *O*-benzylation and alkaline hydrolysis.

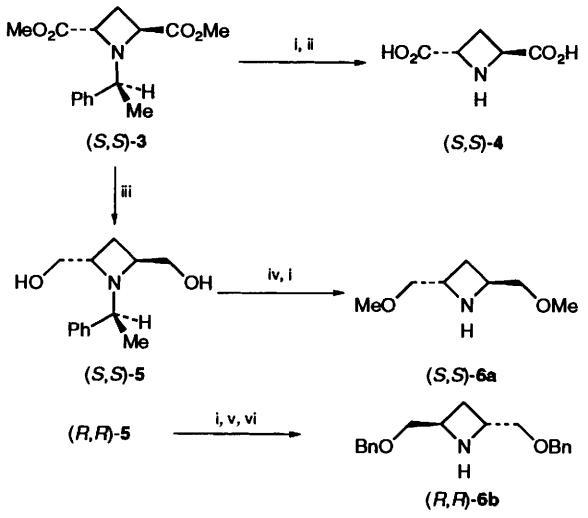
In order to compare the azetidine obtained here with the known chiral auxiliaries differing in ring size, the following cyclic amines were prepared. The aziridine (*R*,*R*)-**7b** was synthesised according to methods described by Nicolaou [11] and Tanner.[12] The aziridine (*R*,*R*)-**7a** could not be synthesised by the same method,¶ but was successfully prepared from the cyclic sulfate (*S*,*S*)-**18**, which was obtained from (2*S*,3*S*)-1,4-dimeth-

† Selective hydrolysis of the *cis* isomer was carried out but the *trans* counterparts were not recovered in a satisfactory yield as for the pyrrolidine analogue.[3]

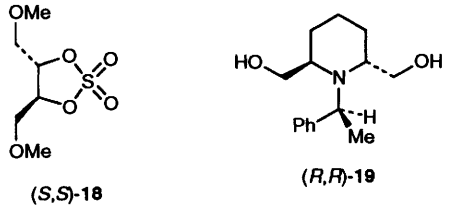
‡ We deduced the same *R*,*R*-configuration of the azetidine by a CD analysis; the tris(*p*-nitrobenzoyl) derivative of the azetidinediol, derived from (*R*,*R*)-**5** by hydrogenolysis, showed the same Cotton effect as that of the derivative of the pyrrolidinediol to which the *R*,*R*-configuration has been assigned.[3]

§ This methodology was also successfully applied to the synthesis of the enantiomeric pair of azetidine-2-carboxylic acid. The *S*-form is a naturally occurring amino acid, constituting a component of mugineic acid which is a typical phytosiderophore.

¶ The action of phosphorus pentachloride on the dimethyl analogue of cyclic orthoformate resulted in the formation of a complex mixture of products.

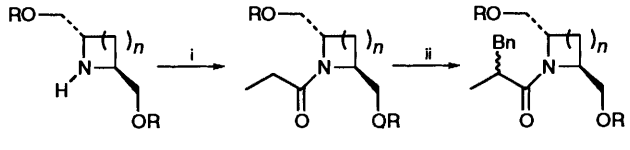


Scheme 2 i, H_2–$Pd(OH)_2$; ii, H_2O, reflux; iii, $LiAlH_4$; iv, MeI–NaH; v, HCO_2Et; vi, BnBr–NaH then NaOH



oxybutane-2,3-diol.[13] The pyrrolidines **8a**, **b** were synthesised by our previously published method.[3] The piperidines **9a**, **b** were prepared using the azetidine synthesis described in this paper. A diastereoisomeric mixture of the corresponding diesters could not be separated but was directly reduced to the diol **19**. The (*R*,*R*)-isomer of **19** was isolated and converted into the piperidine (*R*,*R*)-**9a** by a similar method to that for the azetidine (*S*,*S*)-**6a**. The piperidine (*R*,*R*)-**9b** was prepared similarly.[14] The propionamides **10**–**13** of the cyclic amines were obtained by reaction with propionic anhydride in the presence of triethylamine and 4-dimethylaminopyridine (DMAP).

The asymmetric alkylation of the propionamides **10**–**13** with benzyl bromide was effected in tetrahydrofuran (THF) at −78 °C using lithium diisopropylamide (LDA) or lithium hexamethyldisilazane (LHMDS) to give the products in good yields (Scheme 3). The products **14**–**17** were also prepared



7 *n* = 0	**10**	**14**
6 *n* = 1	**11**	**15**
8 *n* = 2	**12**	**16**
9 *n* = 3	**13**	**17**

a R = Me, **b** R = Bn

Scheme 3 *Reagents:* i, $(EtCO)_2O$–DMAP; ii, LDA or LHMDS then BnBr

from (*S*)-(+)-2-benzylpropionic acid[15] and used as reference compounds for the determination of the diastereoisomeric excesses (des) and absolute configurations of the asymmetric alkylation products.

The results of the asymmetric alkylation are shown in Table 1. For ease of understanding and comparison, the product configurations are uniformly formulated as those observed when *S*,*S* auxiliaries are employed although *R*,*R* auxiliaries are actually used in entries 7–10 and 13–16. Stereoselectivity is irrelevant for the alkyl substituents on the oxygen atoms (Me or Bn) throughout all entries. For the azetidines **11a**, **b** (entries 5–8), the benzyl group is introduced from the opposite direction to the side arm with high selectivity‖ (Fig. 2, Model **A**). This stereochemistry is identical with that proposed for the pyrrolidines **12a**, **b** (entries 9–12) by Katsuki[10] and it is also followed by the piperidines **13a**, **b** (entries 13–16). Of them, the pyrrolidines **12a**, **b** exhibit the highest selectivity. In the cases of the aziridines **10a**, **b** the stereochemistry through the transition state model (Fig. 2, Model **B**) by Tanner[12] is reproduced when LHMDS is used (entries 2 and 4). A drastic drop in stereoselectivity is observed with LDA (entries 1 and 3). The fact that high selectivity is achieved only with LHMDS which produces the poorer complexing hexamethyldisilazane in the deprotonation step[16] seems to support the chelation model, because diisopropylamine liberated from LDA is considered to disturb the model.

Table 1 Asymmetric alkylation of amides having C_2-auxiliaries

Entry	Substrate	Base[a]	% de (config.)
1	**10a**	1	18 (*S*)
2	**10a**	2	93 (*R*)
3	**10b**	1	13 (*S*)
4	**10b**	2	93 (*R*)
5	**11a**	1	79 (*S*)
6	**11a**	2	79 (*S*)
7[b]	**11b**	1	78 (*S*)
8[b]	**11b**	2	81 (*S*)
9[b]	**12a**	1	99 (*S*)
10[b]	**12a**	2	97 (*S*)
11	**12b**	1	98 (*S*)
12	**12b**	2	97 (*S*)
13[b]	**13a**	1	89 (*S*)
14[b]	**13a**	2	89 (*S*)
15[b]	**13b**	1	83 (*S*)
16[b]	**13b**	2	82 (*S*)

[a] 1: LDA; 2: LHMDS. [b] For ease of understanding the product configurations are uniformly formulated as those observed when *S*,*S* auxiliaries are employed although *R*,*R* auxiliaries are actually used in entries 7–10 and 13–16.

Whilst the spectrometric properties of the propionamides of azetidine, pyrrolidine and piperidine are similar, they differ from those of the corresponding aziridine compounds. Thus, the carbonyl chemical shifts of the azetidine propionamides **11a**, **b** (174.6 and 174.5 ppm) are comparable with those of pyrrolidine and piperidine (173.2–174.3 ppm) and are significantly smaller than those of aziridine (184.7 and 184.5 ppm). In the IR spectra higher frequencies for the carbonyl bond absorptions of the aziridines **10a**, **b** (1700 cm^{-1}) are observed, whilst those of the azetidines **11a**, **b** (1650 cm^{-1}) are almost the same as those of pyrrolidine and piperidine (1640–1650 cm^{-1}). These facts both confirm the planarity of azetidine amides as well as their similarity to pyrrolidine and piperidine amides.

Experimental

All mps (measured on a Yanagimoto micro melting point apparatus) and bps are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL-JNM-EX-270 spectrometer (at 270 MHz for ^1H, 68 MHz for ^{13}C). *J* Values are given in Hz. IR spectra were recorded with a Hitachi 215 spectrophotometer. Optical rotations were measured with a Perkin-Elmer R-241

‖ The change of the oxygen atom substituents to *tert*-butyldiphenylsilyl group decreased the des to 47–57%.

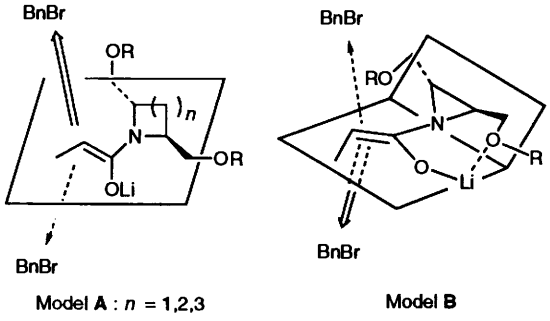


Fig. 2 Transition state models for asymmetric alkylation

polarimeter (with a 1 dm cell) and are given in units of 10^{-1} deg cm^2 g^{-1}. HPLC analyses were run on a JASCO 880-PU chromatographic system with an 875-UV detector (220 nm) and a silica gel column (Finepack Sil, 4 mm × 25 cm). GC analyses were performed on a Shimadzu 14A apparatus equipped with a capillary column DB-1 (J & W Scientific, Inc.).

Synthesis of diastereoisomeric isomers of dimethyl 1-[(*S*)-1-phenylethyl]azetidine-2,4-dicarboxylate 3

A mixture of the dibromide **1** (83.0 g, 261 mmol) and (*S*)-(−)-1-phenylethylamine **2** (31.6 g, 261 mmol), K_2CO_3 (43.3 g, 313 mmol), toluene (230 cm^3) and water (78 cm^3) was refluxed for 20 h. After cooling, the layers were separated and the aqueous layer was extracted with Et_2O (2 × 100 cm^3). The combined organic layer and extracts were washed with saturated aqueous NaCl (2 × 100 cm^3) and dried (Na_2SO_4). Evaporation gave a diastereoisomeric mixture of the diesters **3** (59.8 g, 83%), a portion of which (27.0 g) was separated by flash column chromatography (silica gel, 15–30% EtOAc in hexane) to afford the diesters (*S,S*)-**3** (5.8 g, 22%), (*R,R*)-**3** (5.8 g, 22%) and *cis*-**3** (11.9 g, 44%).

Compound (*S,S*)-**3**, colourless oil; bp 122 °C (0.05 mmHg) (Found: C, 64.65; H, 7.0; N, 5.0. Calc. for $C_{15}H_{19}NO_4$: C, 64.95; H, 6.90; N, 5.07%); $[\alpha]_D^{25}$ −222.2 (*c* 1.0, $CHCl_3$); R_f 0.40 (silica gel, 20% EtOAc in hexane); $\delta_H(CDCl_3)$ 1.17 (d, *J* 6.6, 3 H, $CHCH_3$), 2.41 (t, *J* 7.0, 2 H, CH_2), 3.62 (s, 6 H, 2 × OCH_3), 4.00 (q, *J* 6.6, 1 H, $CHCH_3$), 4.17 (t, *J* 7.0, 2 H, 2 × $CHCO_2$) and 7.16–7.34 (m, 5 H, Ph); $\delta_C(CDCl_3)$ 21.8, 25.0, 51.6, 60.7, 61.0, 127.4, 127.4, 128.3, 142.5 and 173.6.

Compound (*R,R*)-**3**, colourless oil; bp 125 °C (0.05 mmHg) (Found: C, 64.9; H, 7.2; N, 5.3. Calc. for $C_{15}H_{19}NO_4$: C, 64.95; H, 6.90; N, 5.07%); $[\alpha]_D^{20}$ +22.5 (*c* 1.0, $CHCl_3$); R_f 0.31 (silica gel, 20% EtOAc in hexane); $\delta_H(CDCl_3)$ 1.22 (d, *J* 6.6, 3 H, $CHCH_3$), 2.39 (t, *J* 7.0, 2 H, CH_2), 3.51 (s, 6 H, 2 × OCH_3), 3.93 (q, *J* 6.6, 1 H, $CHCH_3$), 4.29 (t, *J* 7.0, 2 H, 2 × $CHCO_2$) and 7.16–7.34 (m, 5 H, Ph); $\delta_C(CDCl_3)$ 19.6, 24.9, 51.6, 60.7, 61.6, 127.7, 128.1, 128.4, 141.4 and 173.0.

Compound *cis*-**3**, colourless solid; mp 37–38 °C (Found: C, 65.1; H, 7.0; N, 5.2. Calc. for $C_{15}H_{19}NO_4$: C, 64.95; H, 6.90; N, 5.07%); $[\alpha]_D^{20}$ −0.1 (*c* 10.0, $CHCl_3$); R_f 0.23 (silica gel, 20% EtOAc in hexane); $\delta_H(CDCl_3)$ 1.33 (d, *J* 6.6, 3 H, $CHCH_3$), 2.24–2.44 (m, 2 H, CH_2), 3.39 (s, 3 H, OCH_3), 3.49–3.73 (m, 3 H, $CHCH_3$ and 2 × $CHCO_2$), 3.77 (s, 3 H, OCH_3) and 7.18–7.36 (m, 5 H, Ph); $\delta_C(CDCl_3)$ 19.9, 24.3, 51.7, 52.1, 59.7, 60.1, 66.4, 127.7, 128.2, 128.2, 140.8, 172.1 and 172.6.

(2*S*,4*S*)-Azetidine-2,4-dicarboxylic acid (*S,S*)-4

The diester (*S,S*)-**3** (0.79 g, 2.85 mmol) dissolved in MeOH (20 cm^3) was hydrogenated over 26% $Pd(OH)_2$ on carbon (0.80 g) in a Paal apparatus at 3 atm for 24 h. The catalyst was filtered off and washed with MeOH (30 cm^3). The filtrate was concentrated under reduced pressure and the residue was dissolved in EtOAc (20 cm^3). The solution was washed with 2% aqueous NaOH (10 cm^3) and saturated aqueous NaCl (10 cm^3), dried (Na_2SO_4) and evaporated. The residue was refluxed in water (10 cm^3) for 15 h and, on evaporation, gave the amino acid (*S,S*)-**4** (0.19 g, 46%). An analytical sample was obtained by recrystallisation from water–EtOH. The same procedure afforded the amino acid (*R,R*)-**4** (43%) from the diester (*R,R*)-**3**.

Compound (*S,S*)-**4**, colourless solid; mp *ca.* 220 °C (decomp.) [lit.,[5] mp *ca.* 200 °C (decomp.) for the racemate] (Found: C, 40.85; H, 4.9; N, 9.5. Calc. for $C_5H_7NO_4$: C, 41.38; H, 4.86; N, 9.65%); $[\alpha]_D^{20}$ −185 (*c* 0.1, H_2O); $\delta_H(D_2O)$ 2.34 (t, *J* 8.1, 2 H, CH_2) and 3.78 (t, *J* 8.1, 2 H, 2 × $CHCO_2$); $\delta_C(D^2O)$ 31.0, 57.0 and 183.4.

Compound (*R,R*)-**4**, colourless solid; mp *ca.* 220 °C (decomp.) (Found: C, 41.1; H, 4.9; N, 9.55. Calc. for $C_5H_7NO_4$: C, 41.38; H, 4.86; N, 9.65%); $[\alpha]_D^{20}$ +190 (*c* 0.1, H_2O); δ_H and $\delta_C(D_2O)$ are identical with those of (*S,S*)-**4**.

(2*S*,4*S*)-1-[(*S*)-1-Phenylethyl]-2,4-bis(hydroxymethyl)azetidine (*S,S*)-5

A solution of the diester (*S,S*)-**3** (6.10 g, 22 mmol) in THF (60 cm^3) was added dropwise to a suspension of $LiAlH_4$ (1.67 g, 44 mmol) in THF (60 cm^3). The mixture was refluxed for 1.5 h and then cooled. Water (1.7 cm^3), 15% aqueous NaOH (1.7 cm^3) and water (5.1 cm^3) were added successively with ice-cooling, after which the mixture was filtered and the precipitate was washed with CH_2Cl_2 (2 × 50 cm^3). The combined filtrate and washings were concentrated and the residue was dissolved in EtOAc (100 cm^3). The solution was washed with saturated aqueous NaCl (50 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the diol (*S,S*)-**5** (4.76 g, 98%). An analytical sample was obtained by recrystallisation from Et_2O–hexane. The same procedure afforded the diol (*R,R*)-**5** (88%) from the diester (*R,R*)-**3**.

Compound (*S,S*)-**5**, colourless solid; mp 66–67 °C (Found: C, 70.6; H, 8.6; N, 6.3. Calc. for $C_{13}H_{19}NO_2$: C, 70.53; H, 8.65; N, 6.36%); $[\alpha]_D^{25}$ −92.1 (*c* 1.0, MeOH); $\delta_H(CD_3OD$–$CDCl_3$; 1:1) 1.16 (d, *J* 6.5, 3 H, $CHCH_3$), 2.15 (t, *J* 6.2, 2 H, $CHCH_2CH$), 2.88–3.10 (br s, 2 H, 2 × OH), 3.37–3.76 (m, 6 H, 2 × $CHCH_2O$), 4.18 (q, *J* 6.5, 1 H, $CHCH_3$) and 7.14–7.39 (m, 5 H, Ph); $\delta_C(CD_3OD$–$CDCl_3$; 1:1) 21.2, 23.1, 53.8, 60.6, 63.0, 126.3, 127.0, 128.7 and 145.0.

Compound (*R,R*)-**5**, colourless solid; mp 140–141 °C (Found: C, 70.6; H, 8.9; N, 6.5. Calc. for $C_{13}H_{19}NO_2$: C, 70.53; H, 8.65; N, 6.36%); $[\alpha]_D^{25}$ −18.3 (*c* 1.0, MeOH); $\delta_H(CD_3OD$–$CDCl_3$; 1:1) 1.37 (d, *J* 6.5, 3 H, $CHCH_3$), 2.03 (t, *J* 6.6, 2 H, $CHCH_2CH$), 3.16–3.38 (m, 4 H, 2 × CH_2O), 3.58–3.73 (m, 2 H, 2 × $CHCH_2$), 3.97 (q, *J* 6.5, 1 H, $CHCH_3$), 4.55 (s, 2 H, 2 × OH) and 7.19–7.39 (m, 5 H, Ph); $\delta_C(CD_3OD$–$CDCl_3$; 1:1) 20.8, 23.0, 59.1, 61.6, 62.5, 128.2, 128.3, 128.7 and 143.1.

(2*S*,4*S*)-2,4-Bis(methoxymethyl)azetidine (*S,S*)-6a

A solution of the diol (*S,S*)-**5** (3.97 g, 17.9 mmol) in THF (60 cm^3) and MeI (14.2 g, 100 mmol) were added dropwise with ice-cooling to a suspension of NaH (60%; 4.0 g, 100 mmol) [previously washed with hexane (3 × 10 cm^3)] in THF (40 cm^3). The mixture was stirred at room temperature for 0.5 h and then refluxed for 1.5 h. After the mixture had cooled, water (1.7 cm^3) was added dropwise to it with ice-cooling. It was then extracted with Et_2O (2 × 50 cm^3). The extracts were combined and washed with saturated aqueous NaCl (50 cm^3) and dried (Na_2SO_4). Distillation gave the dimethyl ether of (*S,S*)-**5** (4.15 g, 92%), bp 110 °C (0.04 mmHg). A solution of the dimethyl ether (1.80 g, 7.20 mmol) in MeOH (18 cm^3) was hydrogenated over 26% $Pd(OH)_2$ on carbon (0.90 g) in a Paal apparatus at 5 atm for 24 h. The catalyst was filtered off and washed with MeOH (30 cm^3). Distillation of the filtrate gave the azetidine

(*S,S*)-**6a** (0.74 g, 71%) with an enantiomeric excess >98%, shown by GC analysis (250 °C), of its (1*S*)-camphanyl amide. The same procedure afforded the azetidine (*R,R*)-**6a** (53%) from the diol (*R,R*)-**5**.

Compound (*S,S*)-**6a**, colourless oil; bp 107–110 °C (18 mmHg); $[\alpha]_D^{25}$ +10.0 (*c* 1.2, $CHCl_3$); $\delta_H(CDCl_3)$ 2.12 (t, *J* 7.0, 2 H, $CHCH_2CH$), 2.59 (s, 1 H, NH), 3.38 (s, 6 H, 2 × OCH_3), 3.40–3.48 (m, 4 H, 2 × CH_2O) and 3.80–3.98 (m, 2 H, 2 × CH); $\delta_C(CDCl_3)$ 25.7, 54.7, 59.0 and 76.4. The picrate salt of (*S,S*)-**6a** crystallised from Et_2O–MeOH, mp 98–100 °C (Found: C, 41.7; H, 4.9; N, 14.9. Calc. for $C_{13}H_{18}NO_9$: C, 41.68; H, 4.84; N, 15.03%).

Compound (*R,R*)-**6a**, colourless oil; bp 107–110 °C (18 mmHg); $[\alpha]_D^{25}$ −11.0 (*c* 1.2, $CHCl_3$); δ_H and $\delta_C(CDCl_3)$ are identical with those of (*S,S*)-**6a**. The picrate salt of (*R,R*)-**6a** crystallised from Et_2O–MeOH, mp 98–100 °C (Found: C, 41.8; H, 4.9; N, 15.0. Calc. for $C_{13}H_{18}NO_9$: C, 41.68; H, 4.84; N, 15.03%).

(2*R*,4*R*)-2,4-Bis(benzyloxymethyl)azetidine (*R,R*)-6b

A solution of the diol (*R,R*)-**5** (2.00 g, 9.03 mmol) in MeOH (50 cm^3) was hydrogenated over 26% $Pd(OH)_2$ on carbon (1.22 g) in a Paal apparatus at 5 atm for 24 h. The catalyst was filtered off and washed with MeOH (30 cm^3). The filtrate was concentrated, and the residue was dissolved in MeOH–ethyl formate (20 cm^3; 1:1). The solution was set aside for 48 h, after which it was evaporated to give the *N*-formyl derivative (1.3 g). This was dissolved in THF (20 cm^3). A suspension of NaH in THF (60%; 0.98 g, 24.4 mmol), previously washed with hexane, and benzyl bromide (3.6 g, 20.5 mmol) were added portionwise with ice-cooling to the solution which was then stirred at room temperature for 0.5 h, finally refluxed for 3 h. After cooling, water (20 cm^3) was added to the mixture with ice-cooling. The mixture was extracted with Et_2O (2 × 50 cm^3) and the combined extracts were washed with saturated aqueous NaCl (50 cm^3) and dried (Na_2SO_4). This solution was concentrated and the residue was dissolved in a mixture of MeOH (50 cm^3) and 15% aqueous NaOH (2 cm^3). The mixture was refluxed for 30 h and then concentrated. The residue was dissolved in EtOAc (100 cm^3). The solution was washed with saturated aqueous NaCl (50 cm^3) and dried (Na_2SO_4). Purification by flash column chromatography (silica gel, 2% Et_3N, 50% EtOAc in hexane–2% Et_3N in EtOAc) gave the azetidine (*R,R*)-**6b** (1.78 g, 66%) as a pale yellow oil (Found: C, 76.1; H, 7.8; N, 4.8. Calc. for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71%); $[\alpha]_D^{20}$ +13.9 (*c* 1.14, $CHCl_3$); $\delta_H(CDCl_3)$ 2.25 (t, *J* 7.0, 2 H, $CHCH_2CH$), 2.43 (br s, 1 H, NH), 3.61–3.73 (m, 4 H, 2 × $CHCH_2O$), 3.98–4.10 (m, 2 H, 2 × CH), 4.67 (m, 4 H, 2 × CH_2Ph) and 7.32–7.49 (m, 10 H, 2 × Ph); $\delta_C(CDCl_3)$ 26.1, 54.8, 73.1, 74.6, 127.5 (2 signals), 128.3 and 138.2.

(2*S*,3*S*)-2,3-Bis(methoxymethyl)aziridine (*S,S*)-7a

To a solution of (2*S*,3*S*)-1,4-dimethoxybutane-2,3-diol (5.37 g, 35.8 mmol) in CCl_4 (35 cm^3), $SOCl_2$ (5.1 g, 42.5 mmol) was added dropwise with ice-cooling. The mixture was refluxed for 0.5 h, then cooled, when $RuCl_3 \cdot H_2O$ (74 mg, 0.36 mmol), $NaIO_4$ (11.5 g, 53.8 mmol), MeCN (35 cm^3) and water (54 cm^3) were added successively to the mixture with ice-cooling. The mixture was stirred at room temperature for 1 h and then diluted with Et_2O (100 cm^3). The mixture was filtered and the aqueous layer was separated and extracted with Et_2O (2 × 50 cm^3). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100 cm^3) and saturated aqueous NaCl (100 cm^3), dried (Na_2SO_4) and evaporated to give the cyclic sulfate (*S,S*)-**8**, 7.60 g, (97%) as a colourless oil; $[\alpha]_D^{20}$ −33.7 (*c* 10, $CHCl_3$); $\delta_H(CDCl_3)$ 3.45 (s, 6 H, 2 × CH_3), 3.74 (d, *J* 3.5, 4 H, 2 × CH_2) and 4.92 (s, 2 H, 2 × CH); $\delta_C(CDCl_3)$ 59.7, 69.8 and 81.4.

A mixture of the cyclic sulfate (*S,S*)-**8** (1.00 g, 4.70 mmol), LiN_3 (0.46 g, 9.40 mmol) and THF (50 cm^3) was refluxed for 6 h. After cooling, $LiAlH_4$ (0.36 g, 9.50 mmol) was added portionwise to it with ice-cooling and the mixture was refluxed for 48 h. After cooling, water (0.34 cm^3), 15% aqueous NaOH (0.34 cm^3) and water (1.0 cm^3) were added successively with ice-cooling. The mixture was filtered and the precipitate was washed with Et_2O (2 × 50 cm^3). The filtrate and washings were combined and concentrated. Distillation of the residue gave the aziridine (*S,S*)-**7a** (0.38 g, 61%) as a colourless oil; bp 115–120 °C (13 mmHg) (Found: C, 54.5; H, 10.2; N, 10.3. Calc. for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68%); $[\alpha]_D^{20}$ +55.6 (*c* 10, Et_2O); $\delta_H(CDCl_3)$ 0.52–1.03 (br s, 1 H, NH), 2.09 (t, *J* 3.8, 2 H, 2 × CH), 3.34–3.56 (m, 4 H, 2 × CH_2) and 3.37 (s, 6 H, 2 × CH_3); $\delta_C(CDCl_3)$ 33.3, 58.7 and 73.4.

(2*R*,6*R*)-2,6-Bis(methoxymethyl)piperidine (*R,R*)-9a

A diastereoisomeric mixture of 1-[(*S*)-1-phenylethyl]-2,6-bis(hydroxymethyl)piperidine **19** was derived from dimethyl 2,6-dibromoheptanedioate in the manner described for the azetidine (*S,S*)-**5** and was separated with flash column chromatography (silica gel, 3% MeOH in CH_2Cl_2) to give the diol (*R,R*)-**19** (15% overall yield) as an amorphous solid; $[\alpha]_D^{20}$ −13.4 (*c* 1.0, $CHCl_3$); $\delta_H(CDCl_3)$ 0.84–1.16 and 1.24–1.43 (m, 6 H, $CH_2CH_2CH_2$), 1.47 (d, *J* 6.9, 3 H, CH_3), 2.60–3.65 (br s, 2 H, 2 × OH), 3.19–3.37 (m, 2 H, 2 × $CHCH_2$), 3.41–3.52 and 3.75–3.90 (m, 4 H, 2 × CH_2O), 4.44 (q, *J* 6.9, 1 H, $CHCH_3$) and 7.22–7.42 (m, 5 H, Ph); $\delta_C(CDCl_3)$ 19.5, 20.6, 22.2, 53.5, 53.8, 60.1, 126.6, 127.4, 127.7 and 142.0.

The piperidine (*R,R*)-**9a** was obtained from the diol (*R,R*)-**19** in the same manner as for the azetidine (*S,S*)-**6a** in 77% yield.

Compound (*R,R*)-**9a** was a colourless oil; bp 128 °C (13 mmHg) (Found: C, 62.1; H, 11.25; N, 7.9. Calc. for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08%); $[\alpha]_D^{20}$ −3.2 (*c* 1.06, $CHCl_3$); $\delta_H(CDCl_3)$ 1.29–1.71 (m, 6 H, $CH_2CH_2CH_2$), 2.49 (br s, 1 H, NH), 3.07–3.18 (m, 2 H, 2 × $CHCH_2$), 3.25–3.49 (m, 4 H, 2 × CH_2O) and 3.37 (s, 6 H, 2 × OCH_3); $\delta_C(CDCl_3)$ 19.9, 27.3, 49.8, 59.0 and 74.9.

General procedure for preparation of propionamides of C_2-symmetric cyclic amines

To a mixture of the amine (4.00 mmol), Et_3N (0.81 g, 8.00 mmol), DMAP (49 mg, 0.40 mmol) and CH_2Cl_2 (5 cm^3), propionic anhydride (0.62 g, 4.80 mmol) was added with ice-cooling. After being stirred at room temperature for 3 h, the mixture was diluted with EtOAc (50 cm^3) and washed successively with 1 mol dm^{-3} aqueous HCl (2 × 20 cm^3), saturated aqueous $NaHCO_3$ (2 × 20 cm^3) and saturated aqueous NaCl (20 cm^3) and then dried (Na_2SO_4). Evaporation under reduced pressure gave the corresponding amides **10a, b**–**13a, b** quantitatively.

General procedure of asymmetric alkylation

To a solution of LDA [prepared from Pr^i_2NH (294 mg, 2.91 mmol) and BuLi (1.6 mol dm^{-3} in hexane; 1.33 cm^3, 2.13 mmol)] or LHMDS (1.0 mol dm^{-3} in hexane; 2.16 cm^3, 2.16 mmol) in dry THF (3 cm^3), a solution of the amide **10a, b**–**13a, b** (1.94 mmol) in dry THF (3 cm^3) was added at −78 °C under an argon atmosphere. After the mixture had been stirred for 45 min at −78 °C, benzyl bromide (398 mg, 2.33 mmol) was added to it and the whole was stirred at −78 °C for 1 h, and then at room temperature for 1 h. Acetic acid (1.2 cm^3) was added dropwise to the mixture which was then diluted with Et_2O (50 cm^3), washed successively with 1 mol dm^{-3} aqueous HCl (2 × 10 cm^3), saturated aqueous $NaHCO_3$ (20 cm^3) and saturated aqueous NaCl (20 cm^3) and dried (Na_2SO_4).

Purification by flash column chromatography (silica gel, 20% EtOAc in hexane) gave the corresponding amides **14a, b–17a, b**.

Determination of the des and the absolute configurations of the asymmetric alkylation products

The following analyses were employed for the determination of des and absolute configurations of **14a,b–17a, b**.

14a: $\delta_C(CDCl_3)$ 186.1 for (*S,S*)-(*S*)-form, 186.3 for (*S,S*)-(*R*)-form. **14b**: $\delta_C(CDCl_3)$ 185.9 for (*S,S*)-(*S*)-form, 186.2 for (*S,S*)-(*R*)-form. **15a:** GC (170 °C) (retention time) t_R/min: 61.3 for (*S,S*)-(*R*)-form, 62.9 for (*S,S*)-(*S*)-form. **15b**: GC (290 °C) t_R/min: 30.0 for (*R,R*)-(*R*)-form, 30.7 for (*R,R*)-(*S*)-form. **16a**: GC (190 °C) t_R/min: 38.0 for (*R,R*)-(*S*)-form, 39.1 for (*R,R*)-(*R*)-form. **16b**: GC (300 °C) t_R/min: 25.3 for (*S,S*)-(*S*)-form, 25.9 for (*S,S*)-(*R*)-form. **17a**: GC (250 °C) t_R/min 34.9 for (*R,R*)-(*R*)-form, 36.6 for (*R,R*)-(*S*)-form. **17b**: HPLC (5% propan-2-ol in hexane, 0.5 cm^3 min^{-1}) t_R/min 9.0 for (*R,R*)-(*S*)-form, 10.0 for (*R,R*)-(*R*)-form.

Single-crystal X-ray diffraction analysis of (2*R*,4*R*)-1-[(*S*)-1-phenylethyl]-2,4-bis(hydroxymethyl)azetidine (*R,R*)-5

Crystals of the diol (*R,R*)-**5** for X-ray diffraction studies were recrystallised from Et_2O–hexane. A colourless plate having approximate dimensions of 0.05 × 0.20 × 0.20 mm was mounted on a glass fibre. Intensity measurements were performed on a Rigaku AFC7R diffractometer using Ni-filtered Cu-Kα radiation from a rotating anode X-ray generator run at 40 kV-200 mA. Cell constants and an orientation matrix for data collection, obtained by a least-squares refinement using the setting angles of 25 carefully centred reflections in the range $77.10 < 2\theta < 79.93°$, corresponded to a primitive orthorhombic cell with dimensions: $a = 9.265(1)$ Å, $b = 16.892(1)$ Å, $c = 7.748(1)$ Å and $V = 1212.6(2)$ Å^3. For $Z = 4$ and $M = 221.30$, the calculated density is 1.21 g cm^{-3}. The systematic absences of $h00$: $h = 2n + 1$, $0k0$: $k = 2n + 1$ and 001: $l = 2n + 1$ uniquely determine the space group to be $P2_12_12_1$ (No. 19). The data were collected at a temperature of 24 ± 1 °C using $\omega - 2\theta$ scan technique to a maximum 2θ value of 120.1°. The ω scans width of $(1.63 + 0.30 \tan \theta)°$ was scanned for each reflection at a speed of 8.0 deg min^{-1} (in omega). A total of 1092 reflections were collected. The structure was solved by direct methods[17] and expanded using Fourier technique.[18] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement was based on 1051 observed reflections $[I > 3.00\sigma(I)]$ and 222 variable parameters and converged with $R = 0.036$ and $R_w = 0.052$. The weighting scheme ω was $1/[\sigma^2(F_o) + 0.0025F_o^2]$. All calculations were performed using the teXsan[19] crystallographic software package. The absolute structure was assigned on the basis of the known absolute configuration of (*S*)-1-phenylethylamine, the synthetic route and the relative configuration as determined by this X-ray analysis. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.††

†† For full details of the deposition scheme, see 'Instructions for Authors (1995)', *J. Chem. Soc., Perkin Trans. 1*, Issue 1.

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