Chiral C_2-symmetric 2,5-disubstituted pyrrolidine derivatives as catalytic chiral ligands in the reactions of diethylzinc with aryl aldehydes

Min Shi,* Yukihiro Satoh and Yukio Masaki

Gifu Pharmaceutical University, 5-6-1 Mitahora-Higashi, Gifu 502, Japan

Two kinds of chiral C_2-symmetric 2,5-disubstituted pyrrolidine derivatives having a β-aminoalcohol moiety have been successfully synthesized and their catalytic abilities of chiral induction have been examined in the reactions of diethylzinc with aryl aldehydes. The production of *sec*-alcohols having *R*-absolute configuration could be achieved in very high chemical yield (85–95%) and very high enantiomeric excess (ee) (70–96%) when *N*-(2′,2′-diphenyl-2′-hydroxyethyl)-(2*R*,5*R*)-bis(methoxymethyl)-pyrrolidine is used as a chiral ligand. On the other hand, when an *N*-methyl-(2*R*,5*R*)-bis(diarylhydroxy-methyl)pyrrolidine is used as a catalyst ligand, the ee of the corresponding *sec*-alcohols decreases to 20–45% and an interesting inversion of the enantioselectivity is observed in the addition reaction of *m*-chloro-, *p*-chloro- and *m*-fluoro-benzaldehyde with diethylzinc under the same reaction conditions. In the meantime, we have also synthesized some chiral C_2-symmetric *N*-(β-hydroxyethyl)pyrrolidine derivatives which have differently steric sized bulky substituents on the 2,5-position of the pyrrolidine ring and their chiral induction abilities have also been examined under the same reaction conditions. Furthermore, we have prepared a simple chiral C_2-symmetric β-aminothiol pyrrolidine derivative. It has also been employed as a chiral ligand for the same addition reaction.

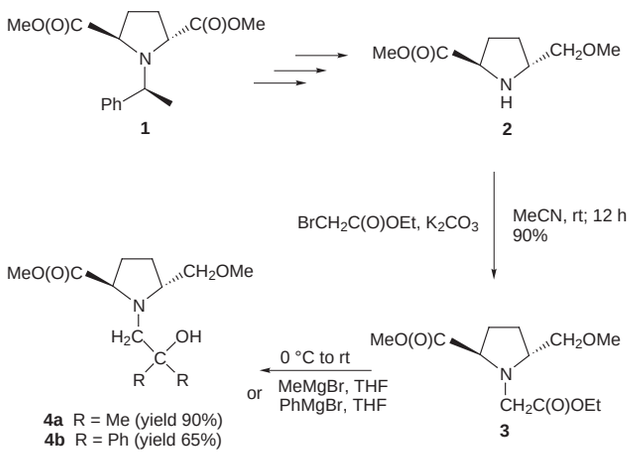
Introduction

High efficiencies of C_2-symmetric chiral reagents, including chiral auxiliaries and catalyst ligands, in asymmetric induction have attracted much attention in asymmetric synthesis.[1] Previously, we reported a short synthesis of homochiral C_2-symmetric 2,3,4,5-tetrasubstituted pyrrolidines from D-mannitol and their use as catalytic chiral ligands in the reaction of diethylzinc with benzaldehyde.[2] A dramatic change of enantioselectivity was observed between the bis(benzylideneacetal) ligands which favoured the production of the (*S*)-alcohol and the methoxylated ones which preferentially afforded the (*R*)-alcohol. These results imply that the flexibility of the substituents on the pyrrolidine ring may play an important role in the enantioselectivity for this addition reaction. In order to gain more insight into this inversion phenomenon of enantioselectivity between the two chiral pyrrolidines, recently we also reported chiral C_2-symmetric 2,5-disubstituted *N*-(β-hydroxyethyl)pyrrolidine derivatives **4a**,**b** and chiral C_2-symmetric *N*-methyl-2,5-bis(diarylhydroxymethyl)pyrrolidines **7a**,**b** as catalytic chiral ligands in the reaction of diethylzinc with arylaldehydes.[3] We found that the chiral C_2-symmetric 2,5-disubstituted *N*-(β-hydroxyethyl)pyrrolidines **4a** and **4b** have very similar chiral-induction abilities to those of the corresponding 2,3,4,5-tetrasubstituted ones in the reaction of diethylzinc with benzaldehyde; that is, the substituents at the 3,4-position of the pyrrolidine ring have no effect on the chiral induction for this addition reaction.[3] On the other hand, when an *N*-methyl-(2*R*,5*R*)-bis(diarylhydroxymethyl)pyrrolidine **7a** or **7b** was used as a catalyst ligand, inversion of the enantioselectivity was observed in the addition reaction of *m*-chloro-, *p*-chloro- and *m*-fluoro-benzaldehyde with diethylzinc under the same conditions.[3] In this paper we disclose full details of the catalytic chiral-induction abilities of chiral C_2-symmetric, 2,5-disubstituted *N*-(β-hydroxyethyl)pyrrolidine derivatives **4a,b** and chiral C_2-symmetric *N*-methyl-2,5-bis(diarylhydroxymethyl)pyrrolidines **7a,b** in the reaction of diethylzinc with arylaldehydes in order to clearly elucidate the effect of the substituents at the 2,5- and 3,4-positions of pyrrolidine ring on the enantioselectivity. We will also disclose the catalytic abilities of some chiral C_2-symmetric *N*-(β-hydroxyethyl)pyrrolidine derivatives **13a–d** having bulky substituents of different steric size on the 2,5-position of the pyrrolidine ring and a corresponding simple β-aminothiol **14** in this addition reaction.

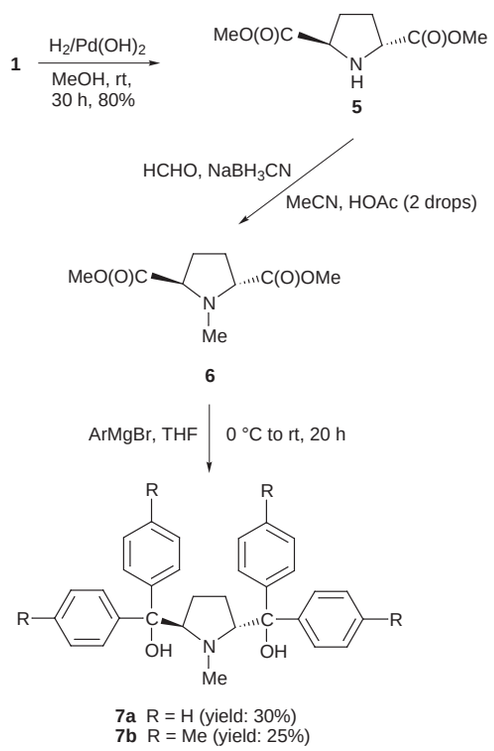
Results and discussion

Chiral C_2-symmetric 2,5-disubstituted pyrrolidines have long been recognized as useful chiral auxiliaries for asymmetric synthesis.[4] These compounds were prepared first by resolution of *trans*-1-benzylpyrrolidine-2,5-dicarboxylic acid,[5] and then were synthesized from homochiral starting materials: D-mannitol,[6] (*S*)-O-benzylglycidol[7] and L-proline[8] by means of relatively long reaction sequences. Recently, Yamamoto reported a convenient and reliable synthesis of each enantiomer of the 2,5-disubstituted pyrrolidines by the reaction of dimethyl 2,5-dibromoadipate with (*S*)-(−)-1-phenylethylamine and chromatographic separation.[9] According to this method 1-[(*S*)-1′-phenylethyl]-(2*R*,5*R*)-bis(methoxycarbonyl)pyrrolidine **1** and a *N*-unsubstituted pyrrolidine **2** were easily obtained. Compound **2** was treated with ethyl bromoacetate to give the *N*-(ethoxycarbonylmethyl)pyrrolidine derivative **3**. The *N*-(β-hydroxyethyl)pyrrolidines **4a** and **4b** were then obtained from the reaction of ester **3** with methylmagnesium bromide and phenylmagnesium bromide, respectively (Scheme 1). On the other hand, the synthesis of chiral C_2-symmetric *N*-methyl-(2*R*,5*R*)-bis(diarylhydroxymethyl)pyrrolidines **7a** and **7b** was carried out starting from precursor **1** through an *N*-unsubstituted pyrrolidine **5** which was obtained by removal of the *N*-1-phenylethyl group by using catalytic hydrogenolysis over palladium hydroxide in methanol, and successively *N*-methylation using formaldehyde to give an *N*-methylpyrrolidine derivative **6**, followed by treatment with the corresponding arylmagnesium bromides (Scheme 2).

* Current address and for any correspondence: Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fengline Lu, Shanghai 200032, China.



Scheme 1

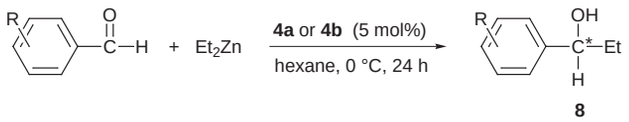


Scheme 2

It is well known that the reaction of aldehydes with diethylzinc giving *sec*-alcohols **8** takes place in the presence of a catalytic amount of *β*-aminoalcohol.[10] Excellent chiral inductions including asymmetric amplifications[11] by use of chiral *β*-aminoalcohols in this reaction have been reported.[11] Thus we also examined this addition reaction by using the two kinds of chiral C_2-symmetric pyrrolidine derivatives **4a**,**b** and **7a**,**b**. The ees of the product **8** were determined by HPLC analysis using chiral stationary-phase column (CHIRALCEL OD) or ^{1}H NMR analysis of the corresponding (+)-methoxy(trifluoromethyl)phenylacetate [(+)-MTPA] ester, and the absolute configuration of the major enantiomer was assigned according to the sign of its specific rotation.[11,12] Their results are summarized in Tables 1 and 2, respectively. As shown in Table 1, high yields (85–95%) and high ees (75–95%) of the corresponding *sec*-alcohols **8** were obtained by using 5 mol% of compound **4b** as a chiral catalyst ligand. The product's configuration (*R*), chemical yield, and ee in this addition reaction of diethylzinc with benzaldehyde are very similar to those reported previously in which the corresponding chiral C_2-symmetric 2,3,4,5-tetrasubstituted pyrrolidine derivatives was used as a chiral catalyst ligand.[2] Thus the chiral-ligand characters for the C_2-symmetric 2,5-disubstituted and 2,3,4,5-tetrasubstituted pyrrolidines appear to be very similar in the reaction of diethylzinc with benzaldehyde and, therefore, the substituents at the 3- and 4-position of the pyrrolidine ring have no effect on the enantioselectivity of this addition reaction. On the other hand, when compound **7a** or **7b** was used as a catalyst, the ee of product **8** decreased to 20–45% and inversion of the enantioselectivity affording the (*S*)-configuration preferentially was observed in the reaction of *m*-chloro-, *p*-chloro- and *m*-fluoro-benzaldehyde with diethylzinc under the same reaction conditions (Table 2). This result is particularly interesting in view of the fact reported by Soai[13] that, when *N*-methyl-(2*S*)-(diphenylhydroxymethyl)-pyrrolidine derived from (*S*)-proline was used as a chiral ligand, no inversion phenomenon in enantioselectivity by changing the substitution mode of the substrate arylaldehydes from *o*-chloro- to *m*-chloro- and *p*-chloro-benzaldehyde could be observed. At present the detailed mechanism of this inversion phenomenon remains obscure and work along these lines is in progress.

In order to elucidate the dominant factors of chiral induction and catalytic ability in this addition reaction, we also syn-

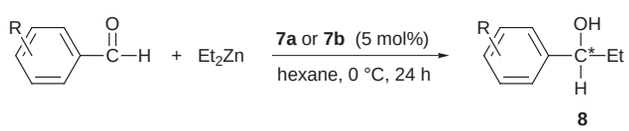
Table 1 Asymmetric addition reaction of diethylzinc with arylaldehydes in the presence of chiral pyrrolidine (**4a** or **4b**). All products had *R*-configuration.



R	Cat.	Yield (%)[a]	ee (%)
H	**4a**	90	61[b]
H	**4b**	99	91[b]
p-Me	**4b**	99	96[b]
o-OMe	**4b**	85	83[b]
p-OMe	**4b**	85	73[b]
p-F	**4b**	96	70[c]
m-F	**4b**	88	85[d]
p-Cl	**4b**	92	76[b]
m-Cl	**4b**	96	90[b]
o-Cl	**4b**	86	92[d]

[a] Isolated yields. [b] Determined by chiral HPLC. [c] Determined by comparison of the optical rotation value with the literature value. [d] Determined by ^{1}H NMR analysis of the corresponding (+)-MTPA ester.

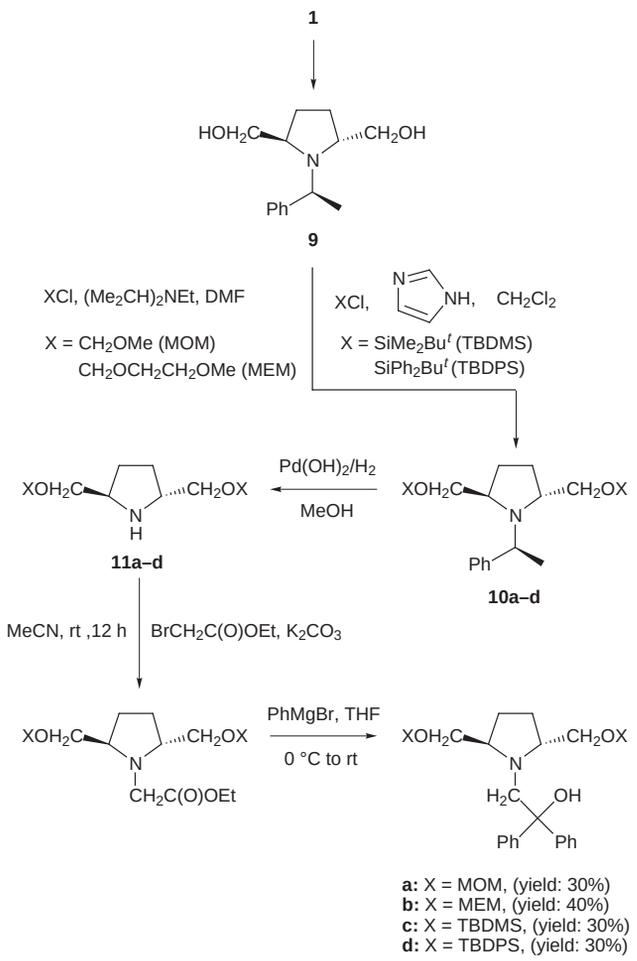
Table 2 Asymmetric addition reaction of diethylzinc with arylaldehydes in the presence of chiral pyrrolidine (5 mol%) (**7a** or **7b**)



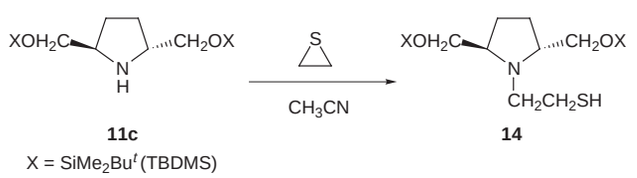
R	Cat.	Yield (%)[a]	ee (%)	Configuration
H	**7a**	82	16[b]	*R*
H	**7b**	82	15[b]	*R*
p-Me	**7a**	70	53[b]	*R*
p-Me	**7b**	70	52[b]	*R*
o-OMe	**7a**	73	42[b]	*R*
p-OMe	**7a**	72	43[b]	*R*
p-F	**7b**	50	16[c]	*R*
m-F	**7b**	45	15[d]	*S*
p-Cl	**7a**	71	13[b]	*S*
m-Cl	**7a**	90	40[b]	*S*
m-Cl	**7b**	90	38[b]	*S*
o-Cl	**7a**	76	10[d]	*R*

[a–d] As in Table 1.

thesized some chiral C_2-symmetric *N*-(*β*-hydroxyethyl)pyrrolidine derivatives having bulky substituents of different steric size on the 2,5-position of pyrrolidine ring. As shown in Scheme 3, compound **9** can be readily obtained from 1-[(*S*)-1′-phenylethyl]-(2*R*,5*R*)-bis(methoxycarbonyl)pyrrolidine **1** by reduction with lithium aluminium hydride. From compound **9** according to the standard procedures for protection of hydroxy groups, we can easily introduce a MOM, a MEM, a TBDMS and a *tert*-butyldiphenylsilyl group (TBDPS) on the 2,5-position of pyrrolidine ring, respectively. Then, in the same reaction procedure as described above, we can successfully synthesize the corresponding chiral C_2-symmetric *N*-(*β*-hydroxyethyl)pyrrolidine derivatives **13a–d** (Scheme 3). Furthermore, recently we have reported that a chiral C_2-symmetric *N*-(*β*-mercaptoethyl)pyrrolidine bearing a 6-membered benzylidene acetal functional group fused at the 2,3,4,5-position was found to exhibit very high efficiency as a chiral ligand in the asymmetric addition reaction of aldehyde with diethylzinc to give extremely high ee (99%) of the product **8**.[14] Therefore, we synthesized a simple *β*-aminothiol **14** from the reaction of chiral C_2-symmetric pyrrolidine derivative **11c** with ethylene sulfide and expected this ligand to have very high asymmetric induction ability as well (Scheme 4).

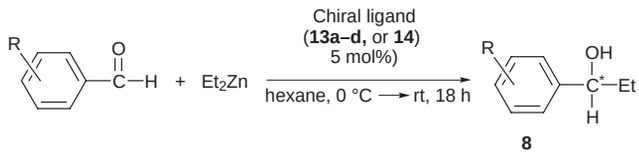


Scheme 3



Scheme 4

Table 3 Asymmetric addition reaction of diethylzinc with arylaldehyde in the presence of chiral pyrrolidine (5 mol%) (**13a–d** or **14**). All products had *R*-configuration.

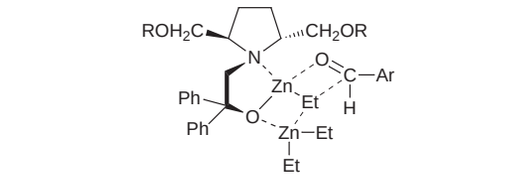


R	Chiral ligand	Yield (%)[a]	ee (%)
H	**13a**	88	60[b]
o-OCH_3	**13a**	69	62[b]
p-OCH_3	**13a**	56	60[b]
p-F	**13a**	67	63[c]
m-F	**13a**	60	60[d]
m-Cl	**13a**	97	74[b]
H	**13b**	74	55[b]
p-CH_3	**13b**	50	63[b]
o-OCH_3	**13b**	42	55[b]
p-OCH_3	**13b**	44	40[b]
m-Cl	**13b**	79	56[d]
p-Cl	**13b**	40	48[b]
H	**13c**	74	43[b]
p-CH_3	**13c**	70	48[b]
o-OCH_3	**13c**	75	49[b]
p-OCH_3	**13c**	63	54[b]
m-Cl	**13c**	96	48[b]
p-Cl	**13c**	87	44[b]
H	**13d**	70	40[b]
p-CH_3	**13d**	72	42[b]
H	**14**	58	9[b]

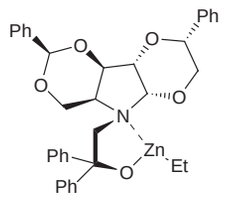
[a–d] As in Table 1.

The results using chiral pyrrolidines **13a–d**, **14** as catalyst ligands in the asymmetric addition reaction of diethylzinc to aryl aldehydes are summarized in Table 3. High chemical yields (50–90%) and moderate ees (40–70%) could be achieved by use of the chiral ligands **13a–d**. However, the enantioselectivities apparently decrease compared with the corresponding chiral pyrrolidine **4b**. In particular, when the bulky chiral pyrrolidine **13c** or **13d** was employed as a chiral ligand, the ee of the formed corresponding *sec*-alcohol is only 40%. Using *β*-aminothiol **14** as chiral ligand gave only very poor ee (9%). These results suggest that the enhancement of the bulkiness of chiral ligand does not always increase the enantioselectivity in some cases, and that appropriate adjustment of the bulkiness of the chiral ligand is very subtle and important.

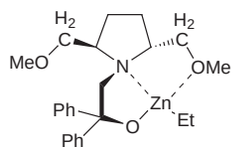
The mechanism and nonlinear effects of enantioselective addition of dialkylzinc to aldehydes promoted by chiral aminoalcohols have been clearly disclosed by Noyori.[11,15] The ethylation proceeds *via* a dinuclear zinc species **A** containing the chiral C_2-symmetric pyrrolidine auxiliary, an aldehyde ligand, and three ethyl groups, where the bridging ethyl group migrates from zinc to the aldehyde carbon. The opposite enantioselectivity between chiral C_2-symmetric *N*-(*β*-hydroxyethyl)pyrrolidine bearing a 6-membered benzylidene acetal functional group fused at the 2,3,4,5-position and the methoxylated ones[2] could be attributed to an additional coordination to the zinc atom by the methoxy group on the side chain of compound **4a** or **4b** which might enhance the Lewis acidity of the *β*-aminoalcohol-chelated zinc complex and influence the approach of aldehyde (complex **C**), whereas the fixed structure of complex **B** does not have such flexibility for this kind of coordination. At present, we postulate that this additional coordination is responsible for the opposite enantioselectivity. In order to verify this point, we tried to synthesize the pyrrolidine derivative **D**, which does not have an oxygen atom on the side chain, as a chiral ligand for the reaction of aryl aldehyde with diethylzinc. Unfortunately, we have failed in the preparation of this simple compound by



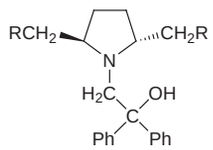
A



Complex **B**



Complex **C**



D

the usual synthetic methodology. Further work is in progress to prepare this compound.

Experimental

Mps were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were determined in a solution of $CHCl_3$ or EtOH at 20 °C by using a JASCO DIP-360 digital polarimeter; $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra were determined for solutions in $CDCl_3$ with tetramethylsilane (TMS) as internal standard on a JNM-GX270 spectrometer; *J*-values are in Hz. Mass spectra were recorded with a JMS D-300 instrument. FAB Mass spectra [in *m*-nitrobenzyl alcohol (NBA) or glycerine (Gly)] were recorded on a JEOL JMS-HX100 mass spectrometer. All solid compounds reported in this paper gave satisfactory CHN microanalyses with a Perkin-Elmer Model 240 analyzer. Hexane was distilled from calcium hydride under nitrogen. The preparations of compounds **1**, **2**, **5** and **9** were reported in a previous paper.[9] All ethylation experiments were performed under argon using standard Schlenk techniques. The optical purities of *sec*-alcohols were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. CHIRALCEL OD; eluent, 100 : 0.5–2 hexane–propan-2-ol mixture; flow rate, 1.0 ml min^{-1}; detection, 254 nm light) or ^{1}H NMR analysis of the corresponding (+)-MTPA ester, and the absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation.

Preparation of the corresponding (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester [(+)-MTPA ester]

Oxalyl dichloride (144.7 mg, 1.14 mmol) was added to a hexane solution (10 ml) of (+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (56.2 mg, 0.24 mmol) and DMF (17.5 mg, 0.24 mmol) at rt and the reaction mixture was stirred for 1 h. After filtration, and removal of the solvent under reduced pressure, the residue was added to a dichloromethane solution of the obtained *sec*-alcohol (0.2 mmol), triethylamine (60.7 mg, 0.6 mmol) and DMAP (10 mg, 0.08 mmol) at rt. The reaction mixture was also stirred at rt for 1 h. After usual work-up, the residue was purified by TLC (20 cm × 20 cm. Developer 4 : 1 hexane–ethyl acetate mixture) to give the corresponding (+)-MTPA ester.

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***N*-Ethoxycarbonylmethyl-(2*R*,5*R*)-bis(methoxymethyl)-pyrrolidine 3**

An acetonitrile solution (20 ml) of (2*R*,5*R*)-bis(methoxymethyl)pyrrolidine **2** (637 mg, 4.0 mmol) and ethyl bromoacetate (802 mg, 4.8 mmol) was stirred at rt in the presence of potassium carbonate (553 mg, 4.0 mmol) for 12 h. After usual work-up, the residue was chromatographed on a flash column (SiO_2) to give *title ester* **3** as an oil (880 mg, 90%); $[\alpha]_D$ +43.9 (*c* 1.2, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.3), 1.48–1.62 (2 H, m), 1.89–2.05 (2 H, m), 3.28 (6 H, s), 3.25–3.45 (4 H, m), 3.35–3.49 (2 H, m), 3.70 (2 H, d, *J* 1.46) and 4.16 (2 H, q, *J* 7.32); MS (FAB$^+$/Gly) *m*/*z* (%) 246 (10, M$^+$ + H), 216 (100, M$^+$ − 30) and 200 (60, M$^+$ − 46). $C_{12}H_{23}NO_4$ (245) (Found: C, 58.7; H, 9.4; N, 5.8. $C_{12}H_{23}NO_4$ requires C, 58.75; H, 9.45; N, 5.71%).

***N*-(2-Hydroxy-2-methylpropyl)-(2*R*,5*R*)-bis(methoxymethyl)-pyrrolidine 4a**

Compound **4a** was prepared from the reaction of ester **3** (245 mg, 1.0 mmol) with methylmagnesium bromide (1 M; 5 ml, 5 mmol) in THF (10 ml) at rt for 3 h. After usual work-up, the residue was chromatographed on a flash column (SiO_2) to give *title compound* **4a** as an oil (208 mg, 90%); $[\alpha]_D$ +57.8 (*c* 1.62, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.14 (3 H, s), 1.18 (3 H, s), 1.60–1.73 (2 H, m), 1.84–1.98 (2 H, m), 2.45 (1 H, d, *J* 14.2), 2.97 (1 H, d, *J* 14.16), 3.18–3.29 (2 H, m), 3.33 (6 H, s) and 3.34–3.38 (4 H, m) [Found: C, 62.3; H, 10.8; N, 6.0%; HR-MS (FAB$^+$/NBA) *m*/*z* 232.1906 (M$^+$ + H). $C_{12}H_{25}NO_3$ requires C, 62.31; H, 10.89; N, 6.06%; *M* + H, 232.1914].

***N*-(2-Hydroxy-2,2-diphenylethyl)-(2*R*,5*R*)-bis(methoxymethyl)-pyrrolidine 4b**

Compound **4b** was prepared from the reaction of compound **3** (134 mg, 0.55 mmol) with phenylmagnesium bromide (1 M; 5.5 ml, 5.5 mmol) in THF (20 ml) at rt for 20 h. After usual work-up, the residue was chromatographed on a flash column (SiO_2) to give *title alcohol* **4b** as a solid (127 mg, 65%); mp 78–79 °C; $[\alpha]_D$ +11.7 (*c* 1.17, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.53–1.70 (2 H, m), 1.75–1.90 (2 H, m), 2.79 (2 H, br), 3.18 (2 H, dd, *J* 9.76 and 3.42), 3.27 (6 H, s), 3.24–3.32 (3 H, m), 3.95 (1 H, d, *J* 14.16), 5.37 (1 H, br) and 7.14–7.60 (10 H, m, ArH); MS (EI) *m*/*z* (%) 354 (8, M$^+$ − 1) and 337 (100, M$^+$ − 18) (Found: C, 74.1; H, 8.3; N, 3.95. $C_{22}H_{29}NO_3$ requires C, 74.33; H, 8.22; N, 3.94%).

(2*R*,5*R*)-Bis(methoxycarbonyl)-*N*-methylpyrrolidine 6

Sodium cyanoborohydride (200 mg, 3.22 mmol) and two drops of acetic acid were added to a solution of (2*R*,5*R*)-bis(methoxycarbonyl)pyrrolidine **5** (300 mg, 1.61 mmol) in acetonitrile (5 ml) containing aq. formaldehyde (30%; 78.3 μl) and the reaction mixture was stirred for *ca*. 2 h at rt. After usual work-up, the residue was chromatographed on a flash column (SiO_2) to give *title compound* **6** as an oil (259 mg, 80%); $[\alpha]_D$ +100.3 (*c* 1.0, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.51–2.0 (4 H, m), 3.20 (3 H, s, NMe), 3.64 (6 H, s, OMe) and 4.10–4.40 (2 H, m); MS (EI) *m*/*z* (%) 201 (10, M$^+$), 142 (100, M$^+$ − 59) and 59 (60, M$^+$ − 142) (Found: C, 53.5; H, 7.5; N, 6.9. $C_9H_{15}NO_4$ requires C, 53.72; H, 7.51; N, 6.96%).

(2*R*,5*R*)-Bis(hydroxydiphenylmethyl)-*N*-methylpyrrolidine 7a

Compound **7a** was prepared from the reaction of **6** (200 mg, 1.0 mmol) with an excess of phenylmagnesium bromide in THF (30 ml) at rt for 3 h and under reflux for 3 h. After usual work-up, the residue was chromatographed on a flash column (SiO_2) to give *title diol* **7a** as a solid (250 mg, 50%), mp 246–248 °C; $[\alpha]_D$ +71.6 (*c* 0.5, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.51–2.0 (4 H, m), 2.84 (3 H, s, NMe), 4.10–4.40 (2 H, m) and 7.0–7.60 (20 H, m, ArH); MS (EI) *m*/*z* (%) 449 (10, M$^+$) and 266 (100, M$^+$ − 183) (Found: C, 82.8; H, 6.9; N, 3.1. $C_{31}H_{31}NO_2$ requires C, 82.82; H, 6.94; N, 3.12%).

(2*R*,5*R*)-Bis[hydroxybis(4-methylphenyl)methyl]-*N*-methylpyrrolidine 7b

Compound **7b** was prepared in the same manner as that described above, with 4-methylphenylmagnesium bromide (152 mg, 35%), mp 195–197 °C; $[\alpha]_D$ +60.8 (*c* 0.5, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.51–2.0 (4 H, m), 2.30 (12 H, s, Me), 2.84 (3 H, s, NMe), 4.10–4.40 (2 H, m) and 7.0–7.60 (16 H, m, ArH); MS (EI) *m*/*z* (%) 505 (10, M^+) and 294 (100, $M^+ - 211$) (Found: C, 83.0; H, 7.78; N, 2.7. $C_{35}H_{39}NO_2$ requires C, 83.13; H, 7.77; N, 2.77%).

(2*R*,5*R*)-Bis(methoxymethoxymethyl)-*N*-[(1*S*)-phenylethyl]pyrrolidine 10a

Compound **10a** was prepared from the reaction of (2*R*,5*R*)-bis(hydroxymethyl)-*N*-[(1*S*)-phenylethyl]pyrrolidine **9** (200 mg, 0.85 mmol) with methoxymethyl chloride (360 mg, 4.5 mmol) in the presence of *N*,*N*-diisopropylethylamine (DIPEA) (1.30 g, 10 mmol) in DMF (20 ml). After usual work-up, the residue was chromatographed on a flash column (SiO_2) to give *title compound* **10a** as an oil (247 mg, 90%); δ_H(270 MHz; $CDCl_3$) 1.49 (3 H, d, *J* 6.4, CH_3), 1.60–1.90 (2 H, m), 1.90–2.20 (2 H, m), 3.05 (2 H, dd, *J* 8.3 and 8.3, CH_2), 3.27 (6 H, s, OMe), 3.10–3.40 (4 H, m), 3.96 (1 H, q, *J* 6.4), 4.45 (4 H, s, OCH_2O) and 7.20–7.60 (5 H, m, ArH) [Found: C, 66.8; H, 9.0; N, 4.3%; HRMS (EI) *m*/*z* 323.2096 (M^+). $C_{18}H_{29}NO_4$ requires C, 66.85; H, 9.04; N, 4.33%; *M*, 323.2098].

(2*R*,5*R*)-Bis(methoxyethoxymethyl)-*N*-[(1*S*)-phenylethyl]pyrrolidine 10b

Compound **10b** was prepared in the same manner as that described above, with MEMCl, DIPEA and DMF (279 mg, 80%); δ_H(270 MHz; $CDCl_3$) 1.48 (3 H, d, *J* 6.8, CH_3), 1.70–1.90 (2 H, m), 1.90–2.10 (2 H, m), 3.06 (2 H, dd, *J* 8.3 and 8.3, CH_2), 3.20–3.35 (4 H, m), 3.38 (6 H, s, CH_3), 3.50–3.70 (8 H, m, OCH_2CH_2O), 3.95 (1 H, q, *J* 6.8), 4.55 (4 H, s, OCH_2O) and 7.20–7.50 (5 H, m, ArH) [Found: C, 64.1; H, 9.05; N, 3.4%; HRMS (EI) *m*/*z* 411.2617 (M^+). $C_{22}H_{37}NO_6$ requires C, 64.21; H, 9.06; N, 3.40%; *M*, 411.2622].

(2*R*,5*R*)-Bis(*tert*-butyldimethylsiloxymethyl)-*N*-[(1*S*)-phenylethyl]pyrrolidine 10c

Compound **10c** was prepared in the same manner as that described above, with TBDMSCl, DIPEA and DMF (373 mg, 95%); $[\alpha]_D^{20}$ +25.1 (*c* 1.0, CH_2Cl_2); δ_H(270 MHz; $CDCl_3$) −0.07 (6 H, s, CH_3), −0.09 (6 H, s, CH_3), 0.83 [18 H, s, $C(CH_3)_3$], 1.45 (3 H, d, *J* 6.8, CH_3), 1.60–1.70 (2 H, m), 1.80–2.0 (2 H, m), 3.10–3.20 (4 H, m, CH_2), 3.23 (2 H, dd, *J* 5.86 and 3.2), 4.02 (1 H, q, *J* 6.8) and 7.20–7.50 (5 H, m, ArH) [Found: C, 67.2; H, 10.5; N, 3.0%; HRMS (EI) *m*/*z* 463.3301 (M^+). $C_{26}H_{49}NO_2Si_2$ requires C, 67.33; H, 10.65; N, 3.02%; *M*, 463.3304].

(2*R*,5*R*)-Bis(*tert*-butyldiphenylsiloxymethyl)-*N*-[(1*S*)-phenylethyl]pyrrolidine 10d

Compound **10d** was prepared in the same manner as that described above, with TBDPSCl, DIPEA and DMF (513 mg, 85%); $[\alpha]_D^{20}$ +13.4 (*c* 1, CH_2Cl_2); δ_H(270 MHz; $CDCl_3$) 0.99 [18 H, s, $(CH_3)_3C$], 1.15 [3 H, d, *J* 6.8], 1.50–1.60 (2 H, m), 1.90–2.0 (2 H, m), 3.10–3.50 (6 H, m), 3.80 (1 H, q, *J* 6.4) and 7.0–7.80 (25 H, m, ArH) [Found: C, 77.5; H, 8.1; N, 1.9%; HRMS (EI) *m*/*z* 711.3920 (M^+). $C_{46}H_{57}NO_2Si_2$ requires C, 77.59; H, 8.07; N, 1.97%; *M*, 711.3930].

(2*R*,5*R*)-Bis(methoxymethyl)pyrrolidine 11a

Compound **11a** was prepared by catalytic hydrogenolysis of compound **10a** (200 mg, 0.62 mmol) over palladium hydroxide in methanol (30 ml) (125 mg, 92%); $[\alpha]_D$ −6.4 (*c* 1.0, CH_2Cl_2); δ_H(270 MHz; $CDCl_3$) 1.60–1.90 (2 H, m), 1.90–2.20 (2 H, m), 3.05 (2 H, dd, *J* 8.3 and 8.3, CH_2), 3.27 (6 H, s, OCH_3), 3.10–3.40 (4 H, m) and 4.45 (4 H, s, OCH_2O) [Found: C, 54.7; H, 9.5; N, 6.35%; HRMS (EI) *m*/*z* 219.1470 (M^+). $C_{10}H_{21}NO_4$ requires C, 54.78; H, 9.65; N, 6.39%; *M*, 219.1471].

(2*R*,5*R*)-Bis(methoxyethoxymethyl)pyrrolidine 11b

Compound **11b** was prepared in the same manner as that described above, from compound **10b** (175 mg, 92%); $[\alpha]_D$ −4.4 (*c* 1.0, CH_2Cl_2); δ_H(270 MHz; $CDCl_3$) 1.40–1.60 (2 H, m), 1.90–2.10 (2 H, m), 3.40 (6 H, s, CH_3), 3.34–3.70 (6 H, m), 3.40–3.70 (8 H, m, OCH_2CH_2O) and 4.75 (4 H, s, OCH_2O) [Found: C, 54.7; H, 9.5; N, 4.5%; HRMS (EI) *m*/*z* 307.1990 (M^+). $C_{14}H_{29}NO_6$ requires C, 54.70; H, 9.51; N, 4.56%; *M*, 307.1996].

(2*R*,5*R*)-Bis(*tert*-butyldimethylsiloxymethyl)pyrrolidine 11c

Compound **11c** was prepared in the same manner as that described above, from compound **10c** (178 mg, 80%); $[\alpha]_D$ +10.4 (*c* 1.17, CH_2Cl_2); δ_H(270 MHz; $CDCl_3$) 0.10 (12 H, s, CH_3), 0.90 [18 H, s, $(CH_3)_3C$], 1.30–1.50 (2 H, m), 1.80–1.95 (2 H, m), 1.96 (1 H, s), 3.25 (2 H, qu), 3.45 (4 H, dd, *J* 5.86 and 3.20) [Found: C, 60.15; H, 11.45; N, 3.9%; HRMS (EI) *m*/*z* 359.2668 (M^+). $C_{18}H_{41}NO_2Si_2$ requires C, 60.11; H, 11.49; N, 3.90%; *M*, 359.2677].

(2*R*,5*R*)-Bis(*tert*-butyldiphenylsiloxymethyl)pyrrolidine 11d

Compound **11d** was prepared in the same manner as that described above, from compound **10d** (188 mg, 50%); $[\alpha]_D$ +1.5 (*c* 1.0, CH_2Cl_2); δ_H(270 MHz; $CDCl_3$) 1.0 [18 H, s, $(CH_3)_3C$], 1.70–2.0 (4 H, m), 3.30–3.50 (2 H, m), 3.60–3.80 (4 H, m) and 7.30–7.80 (20 H, m, ArH) [Found: C, 75.05; H, 8.05; N, 2.3%; HRMS (EI) *m*/*z* 607.3301 (M^+). $C_{38}H_{49}NO_2Si_2$ requires C, 75.07; H, 8.12; N, 2.30%; *M*, 607.3304].

***N*-Ethoxycarbonylmethyl-(2*R*,5*R*)-bis(methoxymethyl)pyrrolidine 12a**

Compound **12a** was prepared from the reaction of compound **11a** (323 mg, 2.04 mmol) with ethyl bromoacetate (417 mg, 2.5 mmol) in the presence of potassium carbonate (345 mg, 2.5 mmol) in acetonitrile (20 ml) at rt for 24 h. After usual work-up, the residue was purified by means of flash column chromatography (eluent: ethyl acetate–hexane 1:4) to give *title compound* **12a** as an oil (214 mg, 35%); $[\alpha]_D$ +52.5 (*c* 0.5, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 6.4, CH_3), 1.52–1.80 (2 H, m), 2.0–2.20 (2 H, m), 3.35 (6 H, s, OCH_3), 3.40–3.55 (6 H, m), 3.70 (1 H, d, *J* 15.2), 3.73 (1 H, d, *J* 15.2), 4.14 (2 H, q, *J* 6.8, CH_2) and 4.58 (4 H, s, OCH_2O) [Found: C, 55.0; H, 8.95; N, 4.6%; HRMS (EI) *m*/*z* 305.1835 (M^+). $C_{14}H_{27}NO_6$ requires C, 55.07; H, 8.91; N, 4.59%; *M*, 305.1839].

***N*-Ethoxycarbonylmethyl-(2*R*,5*R*)-bis(methoxyethoxymethyl)pyrrolidine 12b**

Compound **12b** was prepared in the same manner as that described above, from compound **11b** (281 mg, 35%); $[\alpha]_D$ +60.1 (*c* 0.5, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.34 (3 H, t, *J* 6.4, CH_3), 1.60–1.80 (2 H, m), 2.0–2.20 (2 H, m), 3.47 (6 H, s, OCH_3), 3.50–3.80 (12 H, m), 3.70–3.85 (4 H, m), 4.23 (2 H, q, *J* 6.8, CH_2) and 4.75 (4 H, s, OCH_2O) (Found: C, 54.85; H, 8.95; N, 3.6%; HRMS (EI) *m*/*z* 393.2360 (M^+). $C_{18}H_{35}NO_8$ requires C, 54.95; H, 8.97; N, 3.56%; *M*, 393.2364).

(2*R*,5*R*)-Bis(*tert*-butyldimethylsiloxymethyl)-*N*-(ethoxycarbonylmethyl)pyrrolidine 12c

Compound **12c** was prepared in the same manner as that described above, from compound **11c** (318 mg, 35%); $[\alpha]_D$ +40.3 (*c* 0.5, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.08 (6 H, s, CH_3), 0.085 (6 H, s, CH_3), 1.24 (3 H, t, *J* 6.4, CH_3), 1.50–1.70 (2 H, m), 1.85–2.10 (2 H, m), 3.20–3.28 (2 H, m), 3.55 (4 H, dd, *J* 5.6 and 3.4, CH_2), 3.68 (1 H, d, *J* 17.8), 3.79 (1 H, d, *J* 17.8) and 4.14 (2 H, q, *J* 6.4, CH_2) [Found: C, 59.25; H, 10.65; N, 3.1%; HRMS (EI) *m*/*z* 445.3043 (M^+). $C_{22}H_{47}NO_4Si_2$ requires C, 59.28; H, 10.63; N, 3.14%; *M*, 445.3045].

(2*R*,5*R*)-Bis(*tert*-butyldiphenylsiloxymethyl)-*N*-ethoxycarbonylmethylpyrrolidine 12d

Compound **12d** was prepared in the same manner as that described above, from compound **11d** (495 mg, 35%); $[\alpha]_D$ +43.6 (*c* 0.5, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.05 [18 H, s, $(CH_3)_3C$], 1.14 (3 H, t, *J* 6.8, CH_3), 1.50–1.70 (2 H, m), 1.90–2.10 (2 H, m), 3.40–3.55 (2 H, m), 3.50–3.75 (4 H, m), 3.80–3.90 (2 H, m), 4.25 (2 H, q, *J* 6.4, CH_2) and 7.30–7.80 (20 H, m, ArH) [Found: C, 72.65; H, 7.95; N, 2.1%; HRMS (EI) *m*/*z* 693.3670 (M^+). $C_{42}H_{55}NO_4Si_2$ requires C, 72.68; H, 7.99; N, 2.02%; *M*, 693.3672].

***N*-(2-Hydroxy-2,2-diphenylethyl)-(2*R*,5*R*)-bis(methoxymethyl)pyrrolidine 13a**

Compound **13a** was prepared from the reaction of compound **12a** (100 mg, 0.35 mmol) with phenylmagnesium bromide (1 M; 1.2 ml) in THF (15 ml) at rt for 24 h under nitrogen. After usual work-up, the residue was purified by means of flash column chromatography (eluent: ethyl acetate–hexane 1:4) to give title compound **13a** as an oil (51 mg, 35%); $[\alpha]_D$ +10.4 (*c* 0.95, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.55–1.80 (2 H, m), 1.85–2.10 (2 H, m), 2.80–3.0 (2 H, m), 3.31 (1 H, d, *J* 13.7), 3.34 (6 H, s, OCH_3), 3.96 (1 H, d, *J* 13.7), 4.56 (4 H, s, OCH_2O) and 7.10–7.70 (10 H, m, ArH) [Found: C, 69.35; H, 7.95; N, 3.3%; HRMS (EI) *m*/*z* 415.2355 (M^+). $C_{24}H_{33}NO_5$ requires C, 69.37; H, 8.01; N, 3.37%; *M*, 415.2360].

***N*-(2-Hydroxy-2,2-diphenylethyl)-(2*R*,5*R*)-bis(methoxyethoxymethyl)pyrrolidine 13b**

Compound **13b** was prepared in the same manner as that described above, from compound **12b** (62 mg, 35%); $[\alpha]_D$ +6.9 (*c* 1.05, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.51–1.80 (2 H, m), 1.80–2.0 (2 H, m), 2.80–2.95 (2 H, m), 3.31 (1 H, d, *J* 10.2), 3.30–3.50 (4 H, m), 3.38 (6 H, s, OCH_3), 3.54–3.62 (4 H, m), 3.70–3.80 (5 H, m), 4.0 (1 H, d, *J* 10.2), 4.66 (4 H, s, OCH_2O) and 7.15–7.80 (10 H, m, ArH) [Found: C, 66.75; H, 8.15; N, 2.76%; HRMS (EI) *m*/*z* 503.2881 (M^+). $C_{28}H_{41}NO_7$ requires C, 66.78; H, 8.21; N, 2.78%; *M*, 503.2884].

(2*R*,5*R*)-Bis(*tert*-butyldimethylsiloxymethyl)-*N*-(2-hydroxy-2,2-diphenylethyl)pyrrolidine 13c

Compound **13c** was prepared in the same manner as that described above, from compound **12c** (68 mg, 35%); $[\alpha]_D$ −3.9 (*c* 0.87, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.05 (6 H, s, CH_3), 0.10 (6 H, s, CH_3), 0.85 [18 H, s, $(CH_3)_3C$], 1.40–1.75 (2 H, m), 1.80–2.0 (2 H, m), 2.70–2.90 (2 H, m), 3.28 (1 H, d, *J* 13.2), 3.50 (2 H, dd, *J* 10.3 and 3.4), 3.51 (2 H, dd, *J* 10.3 and 3.4), 4.0 (1 H, d, *J* 13.2) and 7.10–7.60 (10 H, m, ArH) [Found: C, 69.05; H, 9.65; N, 2.5%; HRMS (EI) *m*/*z* 555.3560 (M^+). $C_{32}H_{53}NO_3Si_2$ requires C, 69.13; H, 9.61; N, 2.52%; *M*, 555.3566].

(2*R*,5*R*)-Bis(*tert*-butyldiphenylsiloxymethyl)-*N*-(2-hydroxy-2,2-diphenylethyl)pyrrolidine 13d

Compound **13d** was prepared in the same manner as that described above, from compound **12d** (98 mg, 35%); $[\alpha]_D$ −6.4 (*c* 0.5, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.05 [18 H, s, $(CH_3)_3C$], 1.60–1.90 (2 H, m), 1.90–2.10 (2 H, m), 2.75–2.90 (2 H, m), 3.10 (1 H, d, *J* 13.7), 3.26 (2 H, dd, *J* 10.4 and 3.7, CH_2), 3.52 (2 H, dd, *J* 10.4 and 4.4, CH_2), 3.74 (1 H, d, *J* 13.7) and 7.0–7.80 (30 H, m, ArH) [Found: C, 77.65; H, 7.6; N, 1.8%; HRMS (EI) *m*/*z* 803.4192 (M^+). $C_{52}H_{61}NO_3Si_2$ requires C, 77.66; H, 7.65; N, 1.74%; *M*, 803.4192].

(2*R*,5*R*)-Bis(*tert*-butyldimethylsiloxymethyl)-*N*-(2-mercaptoethyl)pyrrolidine 14

Compound **14** was prepared from the reaction of free amine **11c** (200 mg, 0.56 mmol) with excess of ethylene sulfide in acetonitrile (20 ml) at rt. After evaporation under reduced pressure, the residue was purified by means of flash column chromatography (eluent: ethyl acetate–hexane 1:4) to give title compound **14** as an oil (152 mg, 65%); $[\alpha]_D$ +12.6 (*c* 0.5, $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.01 (12 H, s, CH_3), 0.85 (18 H, s, CH_3), 1.50–1.70 (2 H, m), 1.80–2.0 (2 H, m), 2.45–2.95 (4 H, m), 3.0–3.20 (3 H, m), 3.42 (2 H, dd, *J* 10.0 and 5.37) and 3.52 (2 H, *J* 10.0 and 5.37) [Found: C, 57.2; H, 10.75; N, 3.4%; HRMS (EI) *m*/*z* 419.2710 (M^+). $C_{20}H_{45}NO_2SSi_2$ requires C, 57.22; H, 10.80; N, 3.34%; *M*, 419.2712].

Typical reaction procedure

To a suspension of *β*-aminoalcohol **4b** (18.0 mg, 0.050 mmol) in hexane (2.0 ml) was added diethylzinc (2.2 mmol, 2.2 ml of 1 M hexane solution) at 0 °C. After stirring of the mixture for 0.5 h, benzaldehyde (106.0 mg, 1.0 mmol) was added and the reaction mixture was stirred for 24 h at 0 °C. The reaction was quenched by 3% aq. HCl and the product was extracted with ethyl acetate. The extract was dried over $MgSO_4$, and then evaporated under reduced pressure. The residue was purified by silica gel TLC to give optically active 1-phenylpropan-1-ol **8** (134.2 mg, 99%).

References

1 H. B. Kagan and T. P. Dang, *J. Am. Chem. Soc.*, 1972, **94**, 6429; J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581.
2 Y. Masaki, H. Oda, K. Kazuta, A. Usui, A. Itoh and F. Xu, *Tetrahedron Lett.*, 1992, **33**, 5089.
3 M. Shi, Y. Satoh, T. Makihara and Y. Masaki, *Tetrahedron: Asymmetry*, 1995, **6**, 2109.
4 T. Katsuki and M. Yamaguchi, *J. Synth. Org. Chem. Jpn.*, 1986, **44**, 532; S. Ikegami, H. Uchiyama, T. Hayama, T. Katsuki and M. Yamaguchi, *Tetrahedron*, 1988, **44**, 5333 and references cited therein; V. Gouverneur and L. Ghosez, *Tetrahedron: Asymmetry*, 1990, **1**, 363; *Tetrahedron Lett.*, 1991, **32**, 5349.
5 Y. Kawanami, Y. Ito, T. Kitagawa, Y. Taniguchi, T. Katsuki and M. Yamaguchi, *Tetrahedron Lett.*, 1984, **25**, 857.
6 M. Marzi and D. Misiti, *Tetrahedron Lett.*, 1989, **30**, 6075.
7 S. Takano, M. Moriya, Y. Iwabuchi and K. Ogasawara, *Tetrahedron Lett.*, 1989, **30**, 3805.
8 K. Izawa, S. Nishi and S. Asada, *Jpn. Kokai Tokkyo Koko*, 6229, 569 [8729, 569] (*Chem. Abstr.*, 1987, **106**, 213 770v).
9 Y. Yamamoto, J. Hoshino, Y. Fujimoto, J. Ohmoto and S. Sawada, *Synthesis*, 1993, 298.
10 E. J. Corey, P.-W. Yuen, F. J. Hannon and D. A. Wierda, *J. Org. Chem.*, 1990, **55**, 784; R. Noyori and M. Kitamura, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 49 and references cited therein.
11 N. Oguni, Y. Matsuda and T. Kaneko, *J. Am. Chem. Soc.*, 1988, **110**, 7877; M. Kitamura, S. Okada, S. Suga and R. Noyori, *ibid.*, 1989, **111**, 4028.
12 J. Kang, J. W. Lee and J. I. Kim, *J. Chem. Soc., Chem. Commun.*, 1994, 2009.
13 K. Soai, A. Ookawa, K. Ogawa and T. Kaba, *J. Chem. Soc., Chem. Commun.*, 1987, 467.
14 Y. Masaki, Y. Satoh, T. Makihara and M. Shi, *Chem. Pharm. Bull.*, 1996, **44**, 454.
15 M. Kitamura, S. Suga, M. Niwa and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 4832.

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