Diastereoselective synthesis of 2-alkylated 4-silyloxyproline esters

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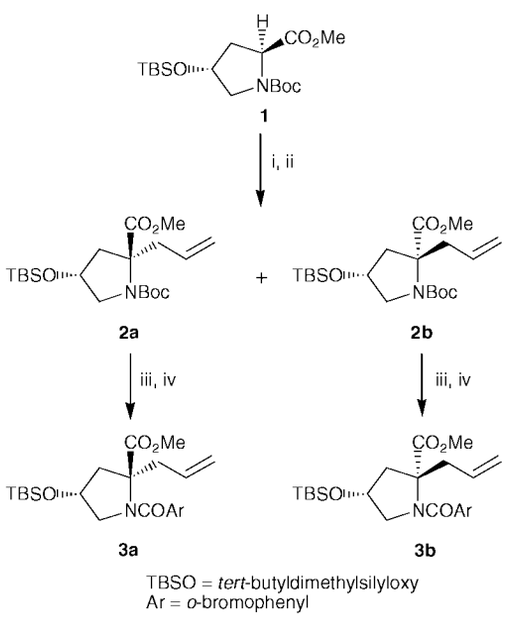
Treatment of the 4-silyloxy-*N*-Boc-L-proline methyl ester **1** with allyl bromide in the presence of LDA in THF at −78 °C gives a mixture of the (2*S*,4*R*)- and (2*R*,4*R*)-2-(prop-2-enyl)-4-silyloxy-*N*-Boc-L-proline esters **2a** and **2b** in 75% combined yield in the ratio 53 : 47. In contrast, similar treatment of the (−)- and (+)-menthyl esters **5** and **6** gives a mixture of allylated products **7a**,**b** and **8a**,**b** in the ratio 75 : 25 and 89 : 11, respectively. Reaction of **6** with methyl iodide and propyl iodide also give the corresponding 2-alkylated esters **16a** and **16b** in a highly diastereoselective manner (94 : 6 and 93 : 7, respectively).

Introduction

Optically active 2-alkylprolines and related compounds are important intermediates in the syntheses of alkaloids[1] as well as of conformationally restricted peptides[2] which have been of great interest in the field of medicinal chemistry in recent years. Although several methods for the synthesis of such compounds have been developed,[3] there had been only a few general methods reported for the synthesis of 2-alkylated 4-hydroxyprolines which involve either alkylation of *O*-protected *N*-Boc-4-hydroxyproline methyl esters[4] or benzylation of *O*-silylated *N*-benzoyl-4-hydroxyproline methyl esters.[5] The former method proceeds with low diastereomeric excess during alkylation (de < 20%). Although the latter proceeds in a highly diastereoselective manner (de ≈ 90%) affording *N*-benzoyl-2-benzyl-4-hydroxyproline esters, harsh conditions might be required for a cleavage of the *N*-protecting group (a tertiary amide) to liberate the free amino acids from the alkylation products. For practical purposes the 4-hydroxyproline derivatives carrying the carbamate protecting group such as a Boc instead of a benzoyl group on the nitrogen atom would be desirable. In connection with our studies on the total synthesis of alkaloids,[6] optically active 2-(prop-2-enyl)-4-silyloxyproline esters were required. Therefore, we have examined the diastereoselectivity in alkylation of *trans*-4-silyloxy-*N*-Boc-L-proline esters.



Scheme 1 *Reagents and conditions*: i, LDA, THF; ii, allyl bromide; iii, TMSI, MeCN; iv, ArCOCl, Et_3N, benzene.

Results and discussion

We initiated our investigation by examining allylation of the methyl ester **1**. Treatment of **1**[4] with allyl bromide in the presence of LDA in THF at −78 °C gave two diastereomeric 2-(prop-2-enyl)proline methyl esters **2a** and **2b** in 75% yield in the ratio 53 : 47, which could be separated by column chromatography. The stereochemistry of **2a**,**b** was determined by conversion of each ester into the known *N*-(*o*-bromobenzoyl)-prolines **3a**,**b**[7] (Scheme 1).

To improve the diastereoselectivity of this reaction, we next examined the allylation of 4-silyloxy-*N*-Boc-proline (−)- and (+)-menthyl esters **5** and **6**, which were prepared by hydrolysis of **1** with lithium hydroxide in aq. methanol followed by re-esterification of the acid **4** with (−)- and (+)-menthol in the presence of DCC and DMAP in methylene dichloride.

Treatment of **5** with allyl bromide in the presence of LDA in THF at −78 °C gave an inseparable mixture of 2-(prop-2-enyl)-4-silyloxyproline esters **7a** and **7b** in 93% combined yield (Scheme 2). The diastereomeric ratio was determined to be 75 : 25 by HPLC analysis after reduction of the mixture with $LiAlH_4$ to the corresponding alcohols **9a**,**b**, whose stereochemistries were separately confirmed by a direct comparison with authentic samples prepared by $LiAlH_4$ reduction of **2a**,**b**. The major isomer was the (2*S*)-isomer **7a**; that is, the allylation took place preferentially from the same side as the 4-silyloxy group.

On the other hand, similar treatment of **6** with allyl bromide gave a mixture of the proline esters **8a** and **8b** in 98% combined yield, and the diastereomeric ratio increased to 89 : 11. The major product was again assigned to be the (2*S*)-isomer **8a**.

For comparison, we then examined the diastereoselectivity of *N*-Boc-L-proline (+)-menthyl ester **10**. Treatment of **10**, which was prepared by condensation of *N*-Boc-L-proline with (+)-menthol by use of DCC, with allyl bromide in the presence of LDA in THF at −78 °C gave an inseparable mixture of

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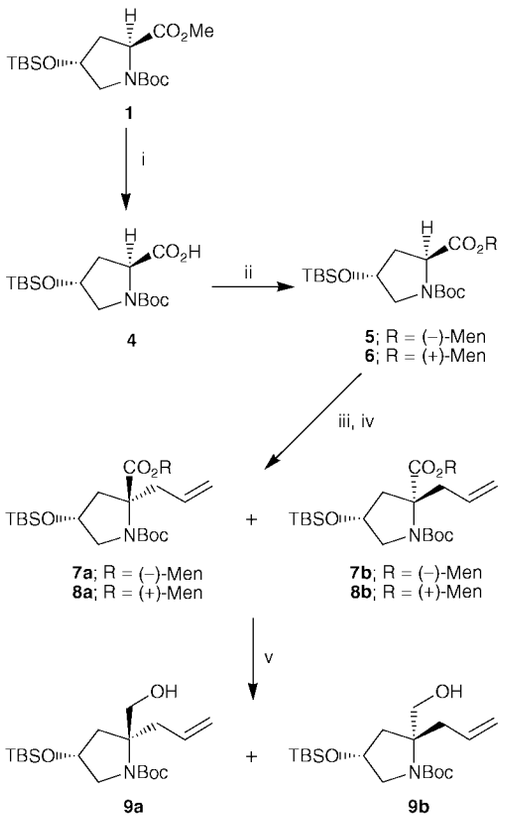
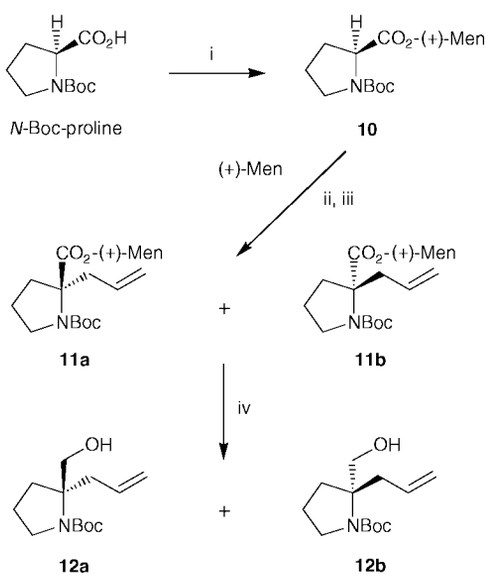


Scheme 2 *Reagents and conditions*; i, LiOH, aq. MeOH; ii, (−)- or (+)-menthol, DCC, DMAP, CH_2Cl_2; iii, LDA, THF, −78 °C; iv, allyl bromide; v, $LiAlH_4$, Et_2O, 0 °C.

2-(prop-2-enyl)proline (+)-menthyl esters **11a** and **11b** in 93% combined yield (Scheme 3). The diastereomeric ratio of the

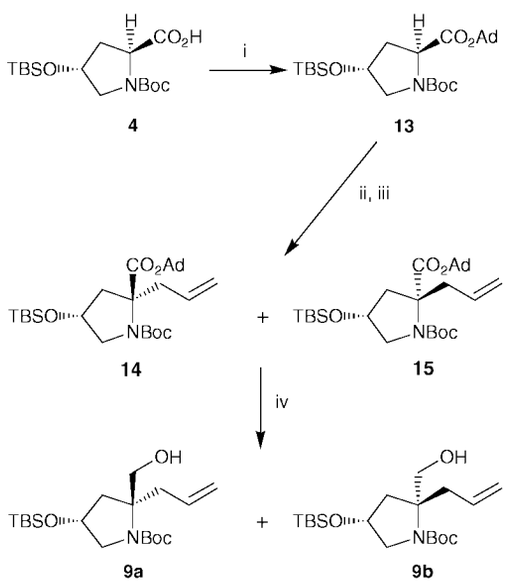


Scheme 3 *Reagents and conditions*: i, (+)-menthol, DCC, DMAP, CH_2Cl_2; ii, LDA, THF, −78 °C; iii, allyl bromide; iv, $LiAlH_4$, Et_2O, 0 °C.

mixture and the stereochemistry of each isomer were determined as follows. $LiAlH_4$ reduction of the mixture gave a mixture of the alcohols **12a** and **12b**, whose enantiomeric ratio was shown to be 66 : 34 by HPLC analysis on a chiral column (CHIRALPAK AD-RH, DAICEL). The absolute configuration of the major isomer of **12a**,**b** was deduced from a comparison of the specific optical rotation of the mixture of **12a**,**b** {$[\alpha]_D^{26}$ +16.4 (*c* 1.29, $CHCl_3$)} with that of an authentic sample of **12b** {$[\alpha]_D^{20}$ −31.8 (*c* 2.00, $CHCl_3$)} prepared from D-proline using Seebach's procedure.[3b] Thus, the allylation took place again on the α-face of the enolate derived from **10** to afford preferentially **11a**. These results indicate that the 4-silyloxy group enhances the diastereoselectivity in the allylation of **5** and **6** to some extent.

Interestingly, in all cases the electrophile attacks the intermediate enolate from the same direction to afford allylated products bearing the same stereochemistry (*S* configuration for **7a** and **8a**, *R* configuration for **11a**) at the C-2 position, suggesting that the steric bulkiness of the ester group rather than the absolute configuration of the chiral auxiliary might play a crucial role in enhancing the selectivity, and that there might be a so-called 'matching' character for the (+)-menthyl group with the 4-silyloxy group and a 'mismatching' one for the (−)-menthyl group in directing the electrophile to attack, although the exact reason for this interaction is obscure at the moment.

In order to evaluate the steric factor of the menthyl group of the ester **6** in amplifying the diastereoselectivity in the alkylation, we then examined the allylation of compound **13** bearing a sterically demanding adamantyl group in place of the menthyl group. When the ester **13**, which was prepared from **4** and 1-adamantyl bromide in the presence of silver(I) oxide, was subjected to the allylation under similar conditions to those described above, a diastereomeric mixture of **14** and **15** was obtained in 78% yield, together with 14% recovery of **13** (Scheme 4). The diastereomeric ratio of the mixture was deter-



Scheme 4 *Reagents and conditions*: i, 1-adamantyl bromide, Ag_2O, Et_2O; ii, LDA, THF; iii, allyl bromide; iv, $LiAlH_4$, Et_2O, 0 °C.

mined as the corresponding alcohols **9a** and **9b** after $LiAlH_4$ reduction and shown to be 64 : 36. To our surprise the diastereoselectivity in the allylation of **13** is extremely low, contrary to our expectation, and this result led us to assume that the steric requirement of the ester group might not be the only critical factor in controlling the diastereoselectivity in the alkylation.

This selectivity in the allylation of the (+)-menthyl ester **6** has been further investigated by molecular modelling. The conformation of the intermediate enolate was optimised using semi-empirical PM3 calculations,[8,9] in which the carbamate nitrogen atom has a slightly pyramidal structure, and is shown in Fig. 1. The optimal conformer with the *N*-Boc group *trans* to the silyloxy group (**A**) is the lowest in energy. It appears from the conformer **A** that the steric and/or electronic factor of the *N*-Boc group would be more crucial rather than that of the silyloxy or ester moieties in the attack on the electrophilic

Table 1 Reaction of **6** with various electrophiles

Entry	R-X	Products	Yield (%)	Ratio [a]
1	CH_2=$CHCH_2Br$	**8a** and **8b**	98	89 : 11 [b]
2	MeI	**16a** and **17a**	96	94 : 6
3	PrI	**16b** and **17b**	94	93 : 7 [b]
4	BnBr	**16c** and **17c**	93	53 : 47 [c]
5	$EtOCOCH_2Br$	**16d** and **17d**	96	69 : 31 [b]

[a] Determined as the corresponding alcohols **18a–d** and **19a–d** after $LiAlH_4$ reduction. [b] The absolute stereochemistry at the 2-position was unambiguously determined by comparison with authentic samples. [c] The stereochemistry was not determined.

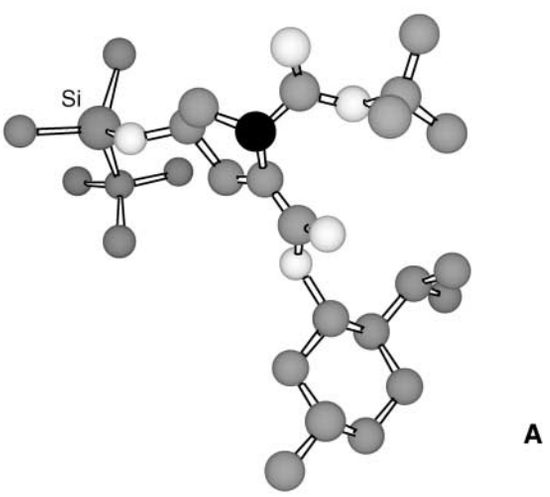
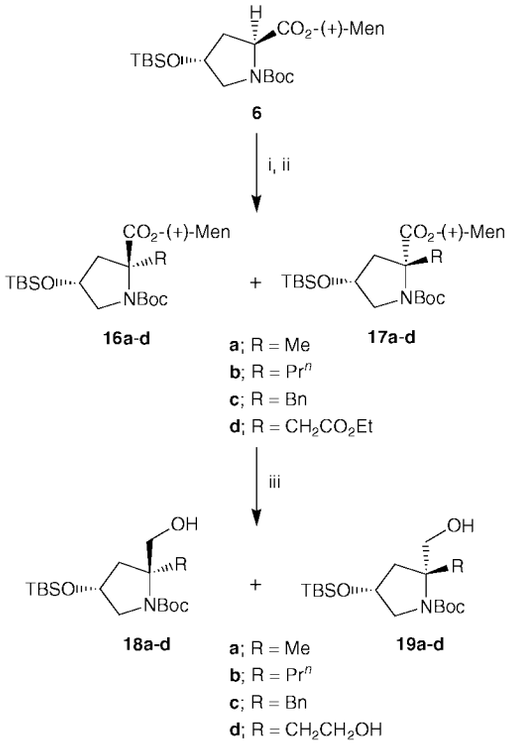


Fig. 1 The optimised structure (**A**) of the enolate with 1,4-*trans* configuration. Grey circles, carbon; black circles, nitrogen; white circles, oxygen. Only silicon is labelled by a symbol.

carbon centre. The preferential formation of **8a** might be thus due to a shielding of the *syn*-face (*si* face) of the enolate by the *N*-Boc group.

Finally, we investigated the reaction of the 4-silyloxyproline (+)-menthyl ester **6** with other electrophiles under the same conditions as described above. The results are summarised in Table 1 in which the diastereomeric ratios were again determined as the corresponding alcohols **18** and **19**, after $LiAlH_4$ reduction of the mixture of esters **16** and **17**, by either HPLC analysis or chromatographic separation (Scheme 5). For entries 3 and 5, the structures of **16b**,**d** and **17b**,**d** were unambiguously confirmed by comparison with authentic samples synthesised separately from **2a** and **2b** (see Experimental section). Reaction of **6** with methyl iodide gave a mixture of the (2*S*,4*R*)- and (2*R*,4*R*)-2-methyl-4-silyloxy-*N*-Boc-proline esters **16a** and **17a** in 96% combined yield in the ratio 94 : 6 (entry 2). Similar treatment with propyl iodide gave a mixture of **16b** and **17b** also in a highly diastereoselective manner (93 : 7) (entry 3). On the other hand, alkylation with ethyl bromoacetate and with benzyl bromide showed lower or no diastereoselectivity (entries 4 and 5).[10] In other words, the reaction with electrophiles bearing no π-electron system proceeds with high diastereoselectivity (entries 2 and 3), whereas with electrophiles containing a π-electron system the diastereoselectivity in alkylation decreased either to some extent or significantly (entries 1, 4 and 5), suggesting that there might be an n–π or π–π repulsive interaction between the lone pair of the nitrogen or carbamate π-electron system and that of the electrophile.

In summary, we have shown that the 4-silyloxy-*N*-Boc-L-proline (+)-menthyl ester **6**, on treatment with LDA in THF and then with simple electrophiles such as allyl bromide, methyl iodide, and propyl iodide, gave (2*S*,4*R*)-2-alkyl-4-silyloxy-*N*-Boc-proline esters in a highly diastereoselective manner almost quantitatively. Application of (2*S*,4*R*)-2-alkyl-4-silyloxy-*N*-Boc-proline esters to the synthesis of optically active alkaloids is now in progress.



Scheme 5 *Reagents and conditions*: i, LDA, THF, −78 °C; ii, RX; iii, $LiAlH_4$, Et_2O, 0 °C.

Experimental

Mps are uncorrected. IR spectra were recorded on a JASCO-IR-A-100 or a JASCO FT/IR-410 spectrophotometer. ^{1}H NMR (60, 300 and 400 MHz) and ^{13}C NMR (75.4 and 100.5 MHz) spectra were measured on a JEOL JNM-PMX 60, a Varian XL-300, or a Varian UNITY INOVA 400NB spectrometer for solutions in $CDCl_3$. δ-Values quoted are relative to tetramethylsilane (δ 0) and $CDCl_3$ (δ_C 77.02) for ^{1}H and ^{13}C NMR, respectively, and *J*-values are given in Hz. Column chromatography was performed on Silica gel 60 PF_{254} (Nacalai Tesque) under pressure. Optical rotations were measured on a JASCO DIP-360 polarimeter; $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Exact mass determinations (FAB mass spectra) were obtained on a JEOL-SX 102A instrument using 3-NOBA as matrix.

Methyl (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)pyrrolidine-2-carboxylate [*trans*-4-(*tert*-butyldimethylsilyloxy)-*N*-Boc-L-proline methyl ester] 1

To a suspension of *trans*-4-hydroxy-L-proline methyl ester hydrochloride (10.6 g, 458.1 mmol) in methylene dichloride (50 cm^3) was added triethylamine (8.82 g, 87.2 mmol) at room temperature and then the mixture was stirred for 10 min. DMAP (709 mg, 5.8 mmol) and a solution of di-*tert*-butyl dicarbonate (13.95 g, 63.9 mmol) in methylene dichloride (15 cm^3) were then added at 0 °C to this mixture which was allowed to warm to room temperature and stirred overnight. After filtration to remove the precipitate the filtrate was evaporated to give a residue, which was dissolved in ethyl acetate (50 cm^3) and washed successively with 3% aq. HCl, saturated aq. $NaHCO_3$, and brine and dried ($MgSO_4$). Concentration of the mixture gave the N-protected ester (11.3 g, 79%) which was used for the next step without further purification, δ_H(60 MHz) 1.44 (9 H, s, OBu^t), 1.9–2.4 (2 H, m, 3-H_2), 3.4–3.8 (2 H, m, 5-H_2), 3.75 (3 H, s, OMe) and 4.2–4.6 (2 H, m, 2- and 4-H).

The Boc-protected ester (11.3 g, 46.1 mmol) thus obtained was dissolved in DMF (50 cm^3) and to this solution were added imidazole (6.27 g, 92.2 mmol) and *tert*-butyldimethylsilyl chloride (7.47 g, 50.8 mmol) at room temperature. The mixture was stirred overnight, then diluted with AcOEt (50 cm^3), washed successively with water and saturated aq. NH_4Cl, dried ($MgSO_4$), and concentrated. The crude material was chromatographed on silica gel to give **1**[4] (16.6 g, quant.) as a colourless oil, δ_H(60 MHz) 0.07 (6 H, s, $SiMe_2$), 0.88 and 0.91 (total 9 H, both s, $SiBu^t$), 1.44 (9 H, s, OBu^t), 1.9–2.3 (2 H, m, 3-H_2), 3.3–3.8 (2 H, m, 5-H_2), 3.73 (3 H, s, OMe) and 4.2–4.6 (2 H, m, 2- and 4-H).

Allylation of 1

General procedure. To a stirred solution of LDA [3.34 mmol, prepared from diisopropylamine (338 mg, 3.34 mmol) and a 1.6 mol dm^{-3} solution of *n*-butyllithium in hexane (2.09 cm^3, 3.34 mmol) at 0 °C] in THF (5 cm^3) at −78 °C was added a solution of **1** (500 mg, 1.39 mmol) in THF (5 cm^3) and the whole was stirred at −20 to −30 °C for 1 h. After cooling of the mixture again to −78 °C, allyl bromide (337 mg, 2.78 mmol) was added dropwise to the solution, and the mixture was stirred for 2 h during which time the bath was allowed to warm to room temperature. After dilution with diethyl ether, the reaction mixture was quenched with 5% aq. HCl, then the organic phase was separated and washed successively with saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel [hexane–AcOEt (7 : 1)]. The first eluate gave *methyl* (2R,4R)-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)-2-(*prop*-2-*enyl*)*pyrrolidine*-2-*carboxylate* **2b** (196 mg, 35%) as a colourless oil [Found: $(M + H)^+$, 400.2510. $C_{20}H_{38}NO_5Si$ requires MH^+, 400.2519]; $[\alpha]_D^{24}$ −15.8 (*c* 3.0, $CHCl_3$); $\nu_{max}(CCl_4)/cm^{-1}$ 1745 and 1700; δ_H(300 MHz; $CDCl_3$, a mixture of two rotamers in the ratio 60 : 40) 0.01 (6 H × 6/10, s, $SiMe_2$), 0.02 (6 H × 4/10, s, $SiMe_2$), 0.84 (9 H × 6/10, s, $SiBu^t$), 0.85 (9 H × 4/10, s, $SiBu^t$), 1.40 (9 H × 6/10, s, OBu^t), 1.44 (9 H × 4/10, s, OBu^t), 2.04 (0.4 H, dd, *J* 12.9 and 6.1, one of 3-H_2), 2.11 (0.6 H, dd, *J* 12.9 and 6.1, one of 3-H_2), 2.17 (0.6 H, dd, *J* 12.9 and 6.1, one of 3-H_2), 2.22 (0.4 H, dd, *J* 12.9 and 6.1, one of 3-H_2), 2.52 (1 H, dd, *J* 14.0 and 8.8), 2.89 (0.6 H, br dd, *J* 14.1 and 6.0), 3.09 (0.4 H, br dd, *J* 14.1 and 6.0), 3.27 (0.4 H, dd, *J* 10.5 and 6.2, one of 5-H_2), 3.36 (0.6 H, dd, *J* 10.9 and 5.8, one of 5-H_2), 3.58 (0.4 H, dd, *J* 10.5 and 6.2, one of 5-H_2), 3.64 (0.6 H, dd, *J* 10.9 and 6.2, one of 5-H_2), 3.69 (3 H × 4/10, s, OMe), 3.70 (3 H × 6/10, s, OMe), 4.29 (1 H, quintet, *J* 6.1, 4-H), 5.08–5.16 (2 H, m, CH=CH_2) and 5.61–5.72 (1 H, m, C*H*=CH_2). The second eluate gave *methyl* (2S,4R)-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)-2-(*prop*-2-*enyl*)*pyrrolidine*-2-*carboxylate* **2a** (222 mg, 40%) as a colourless oil [Found: $(M + H)^+$, 400.2513]; $[\alpha]_D^{23}$ +37.2 (*c* 2.65, $CHCl_3$); $\nu_{max}(CCl_4)/cm^{-1}$ 1745 and 1700; δ_H(300 MHz; $CDCl_3$, a mixture of two rotamers in the ratio 70 : 30) 0.050 (6 H × 7/10, s, $SiMe_2$), 0.055 (6 H × 3/10, s, $SiMe_2$), 0.87 (9 H × 7/10, s, $SiBu^t$), 0.88 (9 H × 3/10, s, $SiBu^t$), 1.41 (9 H × 7/10, s, OBu^t), 1.44 (9 H × 3/10, s, OBu^t), 2.01–2.21 (2 H, m, 3-H_2), 2.69 (1 H, br dd, *J* 14.3 and 7.5), 2.86 (0.7 H, dd, *J* 14.3 and 7.3), 3.03 (0.3 H, dd, *J* 14.3 and 6.9), 3.10 (1 H, dd, *J* 10.8 and 6.6), 3.71 (3 H, s, OMe), 3.78 (0.3 H, dd, *J* 10.8 and 6.9), 3.90 (0.7 H, dd, *J* 10.8 and 6.6), 4.40 (0.3 H, quintet, *J* 7.0, 4-H), 4.41 (0.7 H, quintet, *J* 7.0, 4-H), 5.09–5.18 (2 H, m, CH=CH_2) and 5.76–5.94 (1 H, m, C*H*=CH_2).

Methyl (2*S*,4*R*)-1-(*o*-bromobenzoyl)-4-(*tert*-butyldimethylsilyloxy)-2-(prop-2-enyl)pyrrolidine-2-carboxylate 3a

To a solution of **2a** (50 mg, 0.12 mmol) in acetonitrile (3 cm^3) was added trimethylsilyl iodide (31 mg, 0.15 mmol) at 0 °C and, after the mixture had been stirred for 15 min, methanol (0.3 cm^3) and saturated aq. $NaHCO_3$ (6 cm^3) were added; the mixture was then extracted with methylene dichloride. The extract was dried ($MgSO_4$) and concentrated *in vacuo* to give the amine, which was dissolved in benzene (4 cm^3). This solution was treated with triethylamine (32 mg, 0.31 mmol), DMAP (1.5 mg, 0.01 mmol) and a solution of *o*-bromobenzoyl chloride (30 mg, 0.14 mmol) in benzene (4 cm^3) at 0 °C, and the whole was stirred at room temperature overnight. The mixture was then diluted with diethyl ether (10 cm^3) and the organic layer was washed successively with 5% aq. HCl, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (10 : 1)] to give **3a**[7] (9 mg, 18%).

Methyl (2*R*,4*R*)-1-(*o*-bromobenzoyl)-4-(*tert*-butyldimethylsilyloxy)-2-(prop-2-enyl)pyrrolidine-2-carboxylate 3b

Following the same procedure described above for the preparation of **3a**, **2b** (50 mg, 0.12 mmol) was treated with trimethylsilyl iodide (31 mg, 0.03 mmol) and the resulting crude amine was acylated with *o*-bromobenzoyl chloride (30 mg, 0.14 mmol) in the presence of triethylamine (32 mg, 0.31 mmol) and DMAP (1.5 mg, 0.01 mmol) to give **3b**[7] (18 mg, 30%).

(2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-pyrrolidine-2-carboxylic acid 4

To a solution of **1** (5.879 g, 16.35 mmol) in MeOH (30 cm^3) was added a solution of $LiOH·H_2O$ (1.029 g, 24.53 mmol) in water (10 cm^3) and the solution was heated at 45 °C for 1 h. After cooling of the mixture to 0 °C and acidification with 5% aq. HCl the precipitate was extracted with diethyl ether. The extract was dried ($MgSO_4$) and concentrated to give (2S,4R)-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)*pyrrolidine*-2-*carboxylic acid* **4** (5.411 g, 96%), which was used for the next step without further purification.

(−)-Menthyl (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)pyrrolidine-2-carboxylate 5

To a solution of the carboxylic acid **4** (1.03 g, 3.00 mmol) in methylene dichloride (10 cm^3) were added sequentially (−)-menthol (469 mg, 3.00 mmol) and DMAP (367 mg, 3.00 mmol) at room temperature, then a solution of DCC (681 mg, 3.30 mmol) in methylene dichloride (5 cm^3) at 0 °C, and the whole was stirred at room temperature overnight. The precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was redissolved in ethyl acetate, washed successively with 5% aq. HCl and saturated aq. $NaHCO_3$, and dried ($MgSO_4$). After evaporation of the mixture the crude material was chromatographed on silica gel [hexane–AcOEt (12 : 1)] to give **5** (1.13 g, 78%) as a colourless oil [Found: $(M + H)^+$, 484.3449. $C_{26}H_{50}NO_5Si$ requires MH^+, 484.3458]; $[\alpha]_D^{23}$ −62.3 (*c* 1.77, $CHCl_3$); $\nu_{max}(CCl_4)/cm^{-1}$ 1750 and 1705; δ_H(300 MHz; $CDCl_3$, a mixture of two rotamers in the ratio 69 : 31) 0.05 (6 H, s, $SiMe_2$), 0.74–1.14 (2 H, m), 0.76 (3 H, d, *J* 7.0, CMe), 0.87 (9 H, s, $SiBu^t$), 0.88 (6 H × 31/100, d, *J* 7.0), 0.90 (6 H × 69/100, d, *J* 7.0), 1.32–1.57 (2 H, m), 1.43 (9 H × 69/100, s), 1.46 (9 H × 31/100, s), 1.63–2.30 (7 H, m), 3.26 (0.31 H, dd, *J* 10.5 and 4.1), 3.39 (0.69 H, dd, *J* 10.8 and 4.0), 3.59 (0.31 H, dd, *J* 10.5 and 5.8), 3.62 (0.69 H, dd, *J* 10.8 and 5.5), 4.31–4.45 (2 H, m, 2- and 4-H) and 4.64–4.77 (1 H, m, 1′-H).

(+)-Menthyl (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)pyrrolidine-2-carboxylate 6

Following the procedure described for the preparation of **5**, **6** (6.82 g, 86%) was obtained from the carboxylic acid **4** (5.65 g, 16.4 mmol), (+)-menthol (2.56 g, 16.4 mmol), DCC (3.71 g, 18.0 mmol) and DMAP (2.00 g, 16.4 mmol) as a colourless oil [Found: $(M + H)^+$, 484.3453]; $[\alpha]_D^{23}$ −1.7 (*c* 1.55, $CHCl_3$); $\nu_{max}(CCl_4)/cm^{-1}$ 1740 and 1700; δ_H(300 MHz; $CDCl_3$, a mixture of two rotamers in the ratio 62 : 38) 0.06 (6 H, s, $SiMe_2$), 0.74

(3 H × 38/100, d, *J* 6.8), 0.75 (3 H × 62/100, d, *J* 6.8), 0.82–1.14 (2 H, m), 0.87 (9 H, s, SiBu^t), 0.90 (6 H × 62/100, d, *J* 6.8), 0.91 (6 H × 38/100, d, *J* 6.8), 1.32–1.57 (3 H, m), 1.42 (9 H × 62/100, s), 1.46 (9 H × 38/100, s), 1.62–1.74 (2 H, m), 1.86 (1 H, d of septet, *J* 7.0 and 2.8), 1.93–2.07 (2 H, m), 2.11–2.25 (1 H, m), 3.28 (0.38 H, br dd, *J* 10.9 and 4.0), 3.40 (0.62 H, br dd, *J* 10.9 and 4.0), 3.58 (0.38 H, dd, *J* 10.9 and 5.1), 3.61 (0.62 H, dd, *J* 10.9 and 5.1), 4.28–4.44 (2 H, m, 2- and 4-H) and 4.65–4.78 (1 H, m, 1′-H).

Allylation of 5

Following the general procedure, **5** (300 mg, 0.62 mmol) was treated with LDA [1.49 mmol, prepared from diisopropylamine (151 mg, 1.49 mmol) and a 1.59 mol dm^{-3} solution of *n*-butyllithium in hexane (0.94 cm^3, 1.49 mmol) at 0 °C] and then allyl bromide (135 mg, 1.12 mmol). The crude product was purified by column chromatography on silica gel [hexane–AcOEt (10 : 1)] to give an inseparable mixture of (−)-*menthyl* (2S,4R)- and (2R,4R)-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)-2-(*prop*-2-*enyl*)*pyrrolidine*-2-*carboxylate* **7a** and **7b** (301 mg, 93%) as a colourless oil [Found: (M + H)$^+$, 524.3779. $C_{29}H_{54}NO_5Si$ requires *M*H$^+$, 524.3771]; ν_{max}(film)/cm^{-1} 1738 and 1703. The presence of at least two rotamers for each diastereomer makes the ^{1}H NMR spectrum highly complex and the mixtute was directly reduced with $LiAlH_4$ to the corresponding alcohols **9a** and **9b** to determine the diastereomeric ratio in the allylation.

(2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-2-(prop-2-enyl)pyrrolidine-2-methanol 9a

To a suspension of $LiAlH_4$ (19 mg, 0.50 mmol) in diethyl ether (2 cm^3) was added dropwise a solution of **2a** (50 mg, 0.13 mmol) in diethyl ether (4 cm^3) at 0 °C and the mixture was stirred at the same temperature for 20 min. Water was carefully added to decompose excess of reagent. The inorganic material was filtered off and washed with diethyl ether. The filtrate was dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (7 : 1)] to give **9a** (38 mg, 80%) as a colourless oil [Found: (M + H)$^+$, 372.2574. $C_{19}H_{38}NO_4Si$ requires *M*H$^+$, 372.2570]; $[\alpha]_D^{26}$ +9.8 (*c* 1.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 3404, 1695 and 1672; δ_H(400 MHz; $CDCl_3$) 0.068 (3 H, s, one of $SiMe_2$), 0.070 (3 H, s, one of $SiMe_2$), 0.90 (9 H, s, SiBu^t), 1.46 (9 H, s, OBu^t), 1.59 (1 H, dd, *J* 13.4 and 5.9, one of 3-H_2), 2.00 (1 H, ddd, *J* 13.4, 4.0 and 1.1, one of 3-H_2), 2.71 (1 H, dd, *J* 13.1 and 8.6), 2.90 (1 H, dd, *J* 13.1 and 6.4), 3.28 (1 H, ddd, *J* 11.7, 3.7 and 1.1, one of 5-H_2), 3.56 (1 H, dd, *J* 11.7 and 5.5, one of 5-H_2), 3.57 and 3.62 (1 H each, ABq, *J* 11.7, CH_2O), 4.23–4.28 (1 H, m, 4-H), 5.11 (1 H, dd, *J* 10.1 and 2.2, one of CH=CH_2), 5.16 (1 H, br d, *J* 17.2, one of CH=CH_2) and 5.84 (1 H, dddd, *J* 17.2, 10.1, 8.6 and 6.4, C*H*=CH_2).

(2*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-2-(prop-2-enyl)pyrrolidine-2-methanol 9b

Following the procedure described for the preparation of **9a**, **9b** (46 mg, 77%) was obtained from **2b** (65 mg, 0.16 mmol) and $LiAlH_4$ (24 mg, 0.66 mmol) as a colourless oil [Found: (M + H)$^+$, 372.2567]; $[\alpha]_D^{25}$ −35.7 (*c* 1.3, $CHCl_3$); ν_{max}(film)/cm^{-1} 3406, 1695 and 1670; δ_H(400 MHz; $CDCl_3$, a mixture of two rotamers in the ratio 67 : 33) 0.07 (6 H × 67/100, s, $SiMe_2$), 0.11 (6 H × 33/100, s, $SiMe_2$), 0.89 (9 H × 67/100, s, SiBu^t), 0.90 (9 H × 33/100, s, SiBu^t), 1.46 (9 H × 67/100, s, OBu^t), 1.50 (9 H × 33/100, s, OBu^t), 1.60 (0.67 H, ddd, *J* 13.6, 4.4 and 1.5, one of 3-H_2), 1.91 (0.33 H, br d, *J* 13.6, one of 3-H_2), 2.16 (1 H, dd *J* 13.6 and 5.7, one of 3-H_2), 2.33 (0.33 H, dd, *J* 14.1 and 5.1), 2.44 (0.67 H, dd, *J* 13.6 and 7.5), 2.68 (0.33 H, br dd, *J* 13.6 and 5.9), 2.76 (0.67 H, dd, *J* 13.6 and 7.3), 3.32 (0.67 H, ddd, *J* 11.7, 3.7 and 1.5, one of 5-H_2), 3.42 (0.33 H, dd, *J* 11.7 and 4.2, one of 5-H_2), 3.45 (1 H, dd, *J* 11.7 and 5.5, one of 5-H_2), 3.63 (0.33 H, br d, *J* 12.0, one of CH_2O), 3.70 (0.67 H, dd, *J* 11.5 and 9.7, one of CH_2O), 3.83 (0.67 H, d, *J* 11.5, one of CH_2O), 3.98 (0.33 H, dd, *J* 10.0 and 8.5, one of CH_2O), 4.22–4.28 (1 H, m, 4-H), 5.08–5.15 (2 H, m, CH=CH_2) and 5.59–5.77 (1 H, m, C*H*=CH_2).

Reduction of a mixture of 7a and 7b

Following the procedure described for the preparation of **9a**, a mixture of **7a** and **7b** (109 mg, 0.21 mmol) was treated with $LiAlH_4$ (32 mg, 0.83 mmol) in diethyl ether (4 cm^3) to afford a crude product (116 mg, quant.) containing **9a**, **9b**, and (−)-menthol, which was subjected to HPLC analysis carried out on an ODS-AM-302 column (5 μm; 4.6 × 150 mm, YMC) using an acetonitrile–water (80 : 20) system as eluent. The diastereomeric ratio of **9a** : **9b** was shown to be 75 : 25.

Allylation of 6

Following the general procedure, **6** (332 mg, 0.69 mmol) was treated with LDA [1.66 mmol, prepared from diisopropylamine (168 mg, 1.66 mmol) and a 1.59 mol dm^{-3} solution of *n*-butyllithium in hexane (1.04 cm^3, 1.49 mmol) at 0 °C] and then allyl bromide (149 mg, 1.24 mmol). The crude product was purified by column chromatography on silica gel [hexane–AcOEt (10 : 1)] to give an inseparable mixture of (+)-*menthyl* (2S,4R)- and (2R,4R)-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)-2-(*prop*-2-*enyl*)*pyrrolidine*-2-*carboxylate* **8a** and **8b** (353 mg, 98%) as a colourless oil [Found: (M + H)$^+$, 524.3765. $C_{29}H_{54}NO_5Si$ requires *M*H$^+$, 524.3771]; ν_{max}(film)/cm^{-1} 1738 and 1703. The presence of at least two rotamers for each diastereomer makes the ^{1}H NMR spectrum highly complex and the diastereomeric ratio of **8a** and **8b** was determined as for a mixture of **7a** and **7b**.

Reduction of a mixture of 8a and 8b

Following the procedure described for the preparation of **9a**, a mixture of **8a** and **8b** (95 mg, 0.18 mmol) was treated with $LiAlH_4$ (28 mg, 0.73 mmol) in diethyl ether (4 cm^3) to afford a crude product (100 mg, quant.) containing **9a**, **9b**, and (+)-menthol, which was subjected to HPLC analysis carried out on an ODS-AM-302 column (5 μm; 4.6 × 150 mm, YMC) using an acetonitrile–water (80 : 20) system as eluent. The diastereomeric ratio of **9a** : **9b** was determined to be 89 : 11. Furthermore, the crude mixture was chromatographed on silica gel [hexane–AcOEt (15 : 1)]. The first fraction gave a mixture of **9b** and (+)-menthol (35 mg). The second fraction gave **9a** (57 mg, 85%).

(+)-Menthyl (*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylate 10

To a solution of *N*-Boc-L-proline (2.00 g, 9.29 mmol) and (+)-menthol (1.45 g, 9.29 mmol) in methylene dichloride (30 cm^3) were added DMAP (1.14 g, 9.29 mmol) and a solution of DCC (2.11 g, 10.22 mmol) in methylene dichloride (10 cm^3) at 0 °C and the whole was stirred at room temperature for 16 h. The precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was redissolved in ethyl acetate, washed successively with 5% aq. HCl and saturated aq. $NaHCO_3$, and dried ($MgSO_4$). After evaporation of the mixture the crude material was chromatographed on silica gel [hexane–AcOEt (15 : 1)] to give **10** (1.60 g, 49%) as a white solid, mp 66.5–67.2 °C [from light petroleum (30–70 °C)] (Found: C, 67.87; H, 10.01; N, 4.26. $C_{20}H_{35}NO_4$ requires C, 67.95; H, 9.98; N, 3.96%); $[\alpha]_D^{24}$ −6.6 (*c* 0.68, $CHCl_3$); ν_{max}(film)/cm^{-1} 1743 and 1703; δ_H(400 MHz; $CDCl_3$, a mixture of two rotamers in the ratio 69 : 31) 0.74 (3 H × 31/100, d, *J* 6.8, CMe), 0.76 (3 H × 69/100, d, *J* 6.8, CMe), 0.87, 0.89 and 0.91 (total 6 H, all d, *J* 7.0, 2 × CMe), 0.85–1.11 (2 H, m), 1.33–1.58 (3 H, m), 1.43

(9 H × 69/100, s, OBu^t), 1.46 (9 H × 31/100, s, OBu^t), 1.63–1.73 (2 H, m), 1.81–2.05 (5 H, m), 2.13–2.28 (1 H, m), 3.34–3.58 (2 H, m, 5-H_2), 4.22 (0.69 H, dd, *J* 8.9 and 3.2), 4.30 (0.31 H, *J* 8.9 and 3.2) and 4.66–4.74 (1 H, m, 1′-H).

Allylation of 10

Following the general procedure, **10** (100 mg, 0.28 mmol) was treated with LDA [0.68 mmol, prepared from diisopropylamine (69 mg, 0.68 mmol) and a 1.6 mol dm^{-3} solution of *n*-butyllithium in hexane (0.43 cm^3, 0.68 mmol) at 0 °C] and then allyl bromide (62 mg, 0.51 mmol). The crude product was purified by column chromatography on silica gel [hexane–AcOEt (10 : 1)] to give an inseparable mixture of (+)-*menthyl* (R)- and (S)-1-(tert-*butoxycarbonyl*)-2-(*prop*-2-*enyl*)*pyrrolidine*-2-*carboxylate* **11a** and **11b** (103 mg, 93%) as a colourless oil [Found: (M + H)$^+$, 394.2948. $C_{23}H_{40}NO_4$ requires *M*H$^+$, 394.2957]; ν_{max}(film)/cm^{-1} 1734 and 1699. The presence of at least two rotamers for each diastereomer makes the ^{1}H NMR spectrum highly complex and the diastereomeric ratio of **11a** and **11b** was determined as for a mixture of **7a** and **7b**.

Reduction of a mixture of 11a and 11b

Following the procedure described for the preparation of **9a**, a mixture of **11a** and **11b** (50 mg, 0.13 mmol) was treated with $LiAlH_4$ (20 mg, 0.53 mmol) in diethyl ether (4 cm^3) to afford a crude product (49 mg), which was chromatographed on silica gel [hexane–AcOEt (7 : 1)] to give 1-tert-*butyl* 2-*hydroxymethyl*-2-(*prop*-2-*enyl*)*pyrrolidine*-1-*carboxylate* **12a**,**b**[1e] (23 mg, 74%) as a colourless oil, $[\alpha]_D^{26}$ +16.4 (*c* 1.29, $CHCl_3$). HPLC analysis performed on a CHIRALPAK AD-RH (4.6 × 150 mm, DAICEL) using an acetonitrile–water (80 : 20) system as eluent showed that the enantiomeric ratio of **12a** and **12b** was 66 : 34.

1-Adamantyl (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)pyrrolidine-2-carboxylate 13

To a solution of **4** (962 mg, 2.78 mmol) and 1-adamantyl bromide (897 mg, 4.17 mmol) in diethyl ether (10 cm^3) was added portionwise silver(I) oxide (774 mg, 3.34 mmol) at 0 °C and the whole was stirred at room temperature for 30 h. The insoluble materials were filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel [hexane–AcOEt (10 : 1)] to give ester **13** (1.42 g, quant.) as a colourless oil (Found: C, 64.10; H, 9.42; N, 3.18. $C_{26}H_{45}NO_5Si\cdot 1/2\ H_2O$ requires C, 63.90; H, 9.49; N, 2.87%) [Found: (M + H)$^+$, 480.3141. $C_{26}H_{46}NO_5Si$ requires *M*H$^+$, 480.3145]; $[\alpha]_D^{24}$ −31.8 (*c* 0.83, $CHCl_3$); ν_{max}(film)/cm^{-1} 1739 and 1705; δ_H(400 MHz; $CDCl_3$, a mixture of two rotamers in the ratio 67 : 33) 0.056 and 0.060 (total 6 H, both s, $SiMe_2$), 0.87 (9 H, s, SiBu^t), 1.44 (9 H × 67/100, s, OBu^t), 1.46 (9 H × 33/100, s, OBu^t), 1.63–1.68 (6 H, unresolved m), 1.96–2.04 (1 H, m), 2.08–2.21 (10 H, unresolved m), 3.26 (0.33 H, br dd, *J* 11.0 and 3.8, one of 5-H_2), 3.35 (0.67 H, ddd, *J* 11.0, 3.8 and 0.9, one of 5-H_2), 3.56 (0.33 H, dd, *J* 11.0 and 5.3, one of 5-H_2), 3.60 (0.67 H, dd, *J* 11.0 and 5.3, one of 5-H_2), 4.19 (0.67 H, dd, *J* 8.1 and 6.1, 2-H), 4.27 (0.33 H, dd, *J* 8.1 and 5.6, 2-H) and 4.40 (1 H, dtd, *J* 5.8, 5.3 and 3.8, 4-H).

Allylation of 13

Following the general procedure, **13** (100 mg, 0.20 mmol) was treated with LDA [0.50 mmol, prepared from diisopropylamine (51 mg, 0.50 mmol) and a 1.6 mol dm^{-3} solution of *n*-butyllithium in hexane (0.31 cm^3, 0.50 mmol) at 0 °C] and then allyl bromide (46 mg, 0.38 mmol). The crude product was purified by column chromatography on silica gel [hexane–AcOEt (15 : 1)]. The first fraction gave an inseparable mixture of 1-*adamantyl* (2S,4R)- and (2R,4R)-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)-2-(*prop*-2-*enyl*)*pyrrolidine*-2-*carboxylate* **14** and **15** (84 mg, 78%) as a colourless oil [Found: (M + H)$^+$, 520.3463. $C_{29}H_{50}NO_5Si$ requires *M*H$^+$, 520.3458]; ν_{max}(film)/cm^{-1} 1736 and 1703. The presence of at least two rotamers for each diastereomer makes the ^{1}H NMR spectrum highly complex and the diastereomeric ratio of **14** and **15** was determined as for a mixture of **7a** and **7b**.

Reduction of a mixture of 14 and 15

Following the procedure described for the preparation of **9a**, a mixture of **14** and **15** (115 mg, 0.22 mmol) was treated with $LiAlH_4$ (34 mg, 0.88 mmol) in diethyl ether (4 cm^3) to afford a crude product (120 mg, quant.) containing **9a**, **9b** and adamantan-1-ol, which was subjected to HPLC analysis carried out on an ODS-AM-302 column (5 μm; 4.6 × 150 mm, YMC) using an acetonitrile–water (80 : 20) system as eluent. The diastereomeric ratio of **9a** : **9b** proved to be 64 : 36. In addition, the mixture was further chromatographed on silica gel [hexane–AcOEt (15 : 1)]. The first fraction gave **9b** (23 mg, 28%). The second fraction gave an inseparable mixture of **9a** and adamantan-1-ol (74 mg).

Alkylation of 6

With methyl iodide. Following the general procedure, **6** (400 mg, 0.83 mmol) was treated with LDA [1.66 mmol, prepared from diisopropylamine (200 mg, 1.98 mmol) and a 1.60 mol dm^{-3} solution of *n*-butyllithium in hexane (1.24 cm^3, 1.98 mmol) at 0 °C] and then methyl iodide (940 mg, 6.62 mmol). The crude product was purified by column chromatography on silica gel [hexane–AcOEt (12 : 1)] to give an inseparable mixture of (+)-*menthyl* (2S,4R)- and (2R,4R)-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)-2-*methylpyrrolidine*-2-*carboxylate* **16a** and **17a** (396 mg, 96%) as a colourless oil [Found: (M + H)$^+$, 498.3608. $C_{27}H_{52}NO_5Si$ requires *M*H$^+$, 498.3615]; ν_{max}(film)/cm^{-1} 1738 and 1703; δ_H for **16a** (300 MHz; $CDCl_3$, a mixture of two rotamers in the ratio 60 : 40) 0.058 (6 H × 3/5, s, $SiMe_2$), 0.064 (6 H × 2/5, s, $SiMe_2$), 0.74 (3 H × 2/5, d, *J* 7.1, CMe), 0.77 (3 H × 3/5, d, *J* 7.1, CMe), 0.80–1.55 (11 H, m), 0.88 (9 H × 3/5, s, SiBu^t), 0.89 (9 H × 2/5, s, SiBu^t), 1.43 (9 H × 3/5, s, OBu^t), 1.44 (9 H × 2/5, s, OBu^t), 1.60–1.74 (2 H, m), 1.64 (3 H × 3/5, s, 2-Me), 1.67 (3 H × 2/5, s, 2-Me), 1.84–2.16 (3 H, m), 2.25 (1 H, ddd, *J* 13.2, 8.0 and 5.9), 3.31 (0.4 H, ddd, *J* 11.0, 4.2 and 0.8, one of 5-H_2), 3.39 (0.6 H, ddd, *J* 11.0, 4.7 and 0.8, one of 5-H_2), 3.68 (0.4 H, dd, *J* 11.0 and 5.9, one of 5-H_2), 3.77 (0.6 H, dd, *J* 11.0 and 5.9, one of 5-H_2), 4.32–4.42 (1 H, m, 4-H) and 4.60–4.74 (1 H, m, 1′-H).

With propyl iodide. Following the general procedure, **6** (500 mg, 1.03 mmol) was treated with LDA [2.48 mmol, prepared from diisopropylamine (251 mg, 2.48 mmol) and a 1.60 mol dm^{-3} solution of *n*-butyllithium in hexane (1.60 cm^3, 2.48 mmol) at 0 °C] and then propyl iodide (1.41 g, 8.27 mmol). The crude product was purified by column chromatography on silica gel [hexane–AcOEt (15 : 1)] to give an inseparable mixture of (+)-*menthyl* (2S,4R)- and (2R,4R)-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)-2-*propylpyrrolidine*-2-*carboxylate* **16b** and **17b** (504 mg, 94%) as a colourless oil [Found: (M + H)$^+$, 526.3931. $C_{29}H_{56}NO_5Si$ requires *M*H$^+$, 526.3928]; ν_{max}(film)/cm^{-1} 1736 and 1703; δ_H for **16b** (400 MHz; $CDCl_3$, a mixture of two rotamers in the ratio 60 : 40) 0.04 (6 H × 3/5, s, $SiMe_2$), 0.06 (6 H × 2/5, s, $SiMe_2$), 0.74 (3 H × 3/5, d, *J* 7.0, CMe), 0.77 (3 H × 2/5, d, *J* 7.0, CMe), 0.82–1.60 (13 H, m), 0.87 (9 H × 3/5, s, SiBu^t), 0.89 (9 H × 2/5, s, SiBu^t), 1.41 (9 H × 3/5, s, OBu^t), 1.44 (9 H × 2/5, s, OBu^t), 1.62–2.33 (11 H, m), 3.07 (0.4 H, dd, *J* 10.4 and 7.5, one of 5-H_2), 3.09 (0.6 H, dd, *J* 10.4 and 7.7, one of 5-H_2), 3.78 (0.4 H, br dd, *J* 10.4 and 7.1, one of 5-H_2), 3.91 (0.6 H, br dd, *J* 10.4 and 7.1, one of 5-H_2), 4.26–4.45 (1 H, m, 4-H) and 4.59–4.74 (1 H, m, 1′-H).

With benzyl bromide. Following the general procedure, **6** (522 mg, 1.14 mmol) was treated with LDA [2.74 mmol,

prepared from diisopropylamine (277 mg, 2.74 mmol) and a 1.60 mol dm^{-3} solution of *n*-butyllithium in hexane (1.71 cm^3, 2.74 mmol) at 0 °C] and then benzyl bromide (390 mg, 2.28 mmol). The crude product was purified by column chromatography on silica gel [hexane–AcOEt (50 : 1)] to give an inseparable mixture of (+)-*menthyl* (2S,4R)- and (2R,4R)-2-*benzyl*-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)-*pyrrolidine*-2-*carboxylate* **16c** and **17c** (610 mg, 93%) as a colourless oil [Found: $(M + H)^+$, 574.3937. $C_{33}H_{56}NO_5Si$ requires MH^+, 574.3928]; ν_{max}(film)/cm^{-1} 1737 and 1700. The presence of at least two rotamers for each diastereomer makes the ^1H NMR spectrum highly complex and the diastereomeric ratio of **16c** and **17c** was determined after the reduction to **18c** and **19c** as for a mixture of **7a** and **7b**.

With ethyl bromoacetate. Following the general procedure, **6** (500 mg, 1.03 mmol) was treated with LDA [2.48 mmol, prepared from diisopropylamine (251 mg, 2.48 mmol) and a 1.60 mol dm^{-3} solution of *n*-butyllithium in hexane (1.60 cm^3, 2.48 mmol) at 0 °C] and then ethyl bromoacetate (311 mg, 1.86 mmol). The crude product was purified by column chromatography on silica gel [hexane–AcOEt (50 : 1)] to give an inseparable mixture of *ethyl* (2S,4R)- and (2R,4R)-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)-2-((+)-*menthyloxycarbonyl*)*pyrrolidine*-2-*acetate* **16d** and **17d** (570 mg, 96%) as a colourless oil [Found: $(M + H)^+$, 570.3831. $C_{30}H_{56}NO_7Si$ requires MH^+, 570.3826]; ν_{max}(film)/cm^{-1} 1737 and 1703. The presence of at least two rotamers for each diastereomer makes the ^1H NMR spectrum highly complex and the diastereomeric ratio of **16d** and **17d** was determined after the reduction to **18d** and **19d** as for a mixture of **7a** and **7b**.

Determination of the diastereomeric ratios of 16a–d and 17a–d

Reduction of a mixture of 16a and 17a. Following the procedure described for the preparation of **9a**, a mixture of **16a** and **17a** (120 mg, 0.24 mmol) was treated with $LiAlH_4$ (37 mg, 0.96 mmol) in diethyl ether (4 cm^3) to afford a crude product (121 mg, quant.) containing **18a**, **19a** and (+)-menthol, which was subjected to HPLC analysis carried out on an ODS-AM-302 column (5 μm; 4.6 × 150 mm, YMC) using an acetonitrile–water (80 : 20) system as eluent. The diastereomeric ratio of **18a** : **19a** proved to be 94 : 6. Furthermore, the mixture was chromatographed on silica gel [hexane–AcOEt (15 : 1)]. The first fraction gave an inseparable mixture of **19a** and (+)-menthol (39 mg). The second fraction gave (2S,4R)-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)-2-*methylpyrrolidine*-2-*methanol* **18a** (69 mg, 83%) as a colourless oil [Found: $(M + H)^+$, 346.2405. $C_{17}H_{36}NO_4Si$ requires MH^+, 346.2413]; $[\alpha]_D^{24}$ −15.3 (*c* 2.7, $CHCl_3$); ν_{max}(film)/cm^{-1} 3419, 1695 and 1671; δ_H(400 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiBu^t$), 1.46 (9 H, s, OBu^t), 1.48 and 1.54 (total 3H, both s, 2-Me), 1.74 (1 H, ddd, *J* 13.2, 2.8 and 1.7, one of 3-H_2), 1.83 (1 H, dd, *J* 13.2 and 5.1, one of 3-H_2), 3.40 (1 H, br d, *J* 11.9, one of 5-H_2), 3.52 (1 H, dd, *J* 11.9 and 5.0, one of 5-H_2), 3.58 (2 H, s) and 4.23–4.33 (1 H, br, 4-H); δ_C(100 MHz; $CDCl_3$) −4.92, −4.81, 17.9, 20.8, 25.7 (3 × Me), 28.6 (3 × Me), 46.1, 57.4, 64.8, 69.1, 70.6, 80.1 and 155.8.

(2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-2-propylpyrrolidine-2-methanol 18b

A solution of **2a** (53 mg, 0.13 mmol) in ethyl acetate (5 cm^3) was hydrogenated in the presence of 10% Pd–C (50 mg) under pressure (4.8 kg cm^{-2}) for 2 h. After the catalyst had been removed by filtration, the filtrate was concentrated to afford the crude product (44 mg), which was directly reduced with $LiAlH_4$ (10 mg, 0.26 mmol) according to the same procedure as that for the preparation of **9a**. The crude product was purified by column chromatography on silica gel [hexane–AcOEt (5 : 1)] to give alcohol **18b** (37 mg, 75%) as a colourless oil [Found: $(M + H)^+$, 374.2722. $C_{19}H_{40}NO_4Si$ requires MH^+, 374.2727]; $[\alpha]_D^{22}$ −2.2 (*c* 1.15, $CHCl_3$); ν_{max}(film)/cm^{-1} 3404, 1695 and 1670; δ_H(400 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.89 (9 H, s, $SiBu^t$), 0.94 (3 H, t, *J* 7.3, CMe), 1.12–1.30 (2 H, m), 1.46 (9 H, s, OBu^t), 1.62 (1 H, dd, *J* 13.4 and 5.8, one of 3-H_2), 1.88 (1 H, td, *J* 12.7 and 4.4), 1.92 (1 H, ddd, *J* 13.4, 4.3 and 0.7, one of 3-H_2), 2.07 (1 H, td, *J* 12.7 and 4.5), 3.25 (1 H, ddd, *J* 11.7, 3.8 and 0.7, one of 5-H_2), 3.54 (1 H, br d, *J* 11.5, one of CH_2O), 3.57 (1 H, dd, *J* 11.7 and 5.8, one of 5-H_2), 3.64 (1 H, dd, *J* 11.5 and 9.5, one of CH_2O), 4.25 (1 H, tt, *J* 5.8 and 4.0, 4-H) and 5.15 (1 H, br d, *J* 9.5, OH).

(2*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-2-propylpyrrolidine-2-methanol 19b

Following the procedure described for the synthesis of **18b**, **2b** (64 mg, 0.16 mmol) was hydrogenated and then treated with $LiAlH_4$ (13 mg, 0.34 mmol). The crude product was purified by column chromatography on silica gel [hexane–AcOEt (5 : 1)] to give alcohol **19b** (59 mg, 95%) as a colourless oil [Found: $(M + H)^+$, 374.2719]; $[\alpha]_D^{25}$ −3.3 (*c* 2.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3394, 1691 and 1672; δ_H(400 MHz; $CDCl_3$, a mixture of mainly two rotamers in the ratio ≈73 : 27) 0.07 (6 H × 73/100, s, $SiMe_2$), 0.11 (6 H × 27/100, s, $SiMe_2$), 0.89 (9 H × 73/100, s, $SiBu^t$), 0.90 (9 H × 27/100, s, $SiBu^t$), 0.94 (3 H, t, *J* 6.9, CMe), 1.06–1.51 (2 H, m), 1.45 (9 H × 73/100, s, OBu^t), 1.49 (9 H × 27/100, s, OBu^t), 1.63 (0.73 H, ddd, *J* 13.6, 4.2 and 1.3, one of 3-H_2), 1.70–1.90 (2 H, m), 1.95 (0.27 H, br d, *J* 14.0, one of 3-H_2), 2.10 (0.73 H, dd, *J* 13.6 and 5.5, one of 3-H_2), 2.27 (0.27 H, dd, *J* 14.0 and 5.3, one of 3-H_2), 3.34 (0.73 H, ddd, *J* 11.7, 3.4 and 1.5, one of 5-H_2), 3.43–3.51 (0.27 H, m, one of 5-H_2), 3.47 (1 H, dd, *J* 11.7 and 5.0, one of 5-H_2), 3.63 (0.27 H, br d, *J* 11.5, CH_2O), 3.69 (0.73 H, dd, *J* 11.5 and 9.9, CH_2O), 3.82 (0.73 H, d, *J* 11.5, CH_2O), 3.94 (0.27 H, dd, *J* 10.2 and 8.2), 4.21–4.28 (1 H, m, 4-H) and 5.18 (1 H, br d, *J* 10.2, OH).

Reduction of a mixture of 16b and 17b

Following the procedure described for the preparation of **9a**, a mixture of **16b** and **17b** (100 mg, 0.19 mmol) was treated with $LiAlH_4$ (29 mg, 0.76 mmol) in diethyl ether (4 cm^3) to afford the crude product (104 mg, quant.) containing **18b**, **19b**, and (+)-menthol, which was subjected to HPLC analysis carried out on an ODS-AM-302 column (5 μm; 4.6 × 150 mm, YMC) using an acetonitrile–water (80 : 20) system as eluent. The diastereomeric ratio of **18b** : **19b** proved to be 93 : 7. Furthermore, the mixture was chromatographed on silica gel [hexane–AcOEt (15 : 1)]. The first fraction gave an inseparable mixture of **19b** and (+)-menthol (34 mg). The second fraction gave **18b** (55 mg, 77%).

(2*S*,4*R*)-2-Benzyl-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)pyrrolidine-2-methanol 18c

Following the general procedure, **1** (500 mg, 1.39 mmol) was treated with LDA [3.34 mmol, prepared from diisopropylamine (338 mg, 3.34 mmol) and a 1.60 mol dm^{-3} solution of *n*-butyllithium in hexane (2.09 cm^3, 3.34 mmol) at 0 °C] and then benzyl bromide (476 mg, 2.78 mmol). The crude product was purified by column chromatography on silica gel [hexane–AcOEt (10 : 1)] to give an inseparable mixture of *methyl* (2S,4R)- and (2R,4R)-2-*benzyl*-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)*pyrrolidine*-2-*carboxylate* (554 mg, 80%) as a colourless oil. A portion of the diastereomeric mixture was further purified by column chromatography on silica gel (chloroform) to afford the single diastereomer (polar one) *methyl* (2S,4R)-2-*benzyl*-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)-*pyrrolidine*-2-*carboxylate* (50 mg) [Found: $(M + H)^+$, 450.2684. $C_{24}H_{40}NO_5Si$ requires MH^+, 450.2676]; $[\alpha]_D^{25}$ −57.0 (*c* 2.05, $CHCl_3$); ν_{max}(film)/cm^{-1} 1745 and 1701; δ_H(400 MHz; $CDCl_3$, a mixture of two rotamers in the ratio 63 : 37) −0.23 (3 H ×

63/100, s, one of $SiMe_2$), −0.21 (3 H × 63/100, s, one of $SiMe_2$), −0.20 (3 H × 37/100, s, one of $SiMe_2$), −0.18 (3 H × 37/100, s, one of $SiMe_2$), 0.71 (9 H × 63/100, s, $SiBu^t$), 0.74 (9 H × 37/100, s, $SiBu^t$), 1.49 (9 H × 63/100, s, OBu^t), 1.51 (9 H × 37/100, s, OBu^t), 1.98 (0.37 H, dd, *J* 12.2 and 8.6, one of 3-H_2), 2.05 (0.63 H, ddd, *J* 12.7, 9.0 and 0.7, one of 3-H_2), 2.14–2.20 (0.37 H, m, one of 3-H_2), 2.18 (0.63 H, dd, *J* 12.7 and 6.5, one of 3-H_2), 2.87–3.01 (1 H, m, 4-H), 3.01 (0.37 H, d, *J* 13.7, one of CH_2Ph), 3.02 (0.67 H, d, *J* 13.9, one of CH_2Ph), 3.04 (0.37 H, dd, *J* 9.7 and 7.9, one of 5-H_2), 3.09 (0.67 H, dd, *J* 10.1 and 8.1, one of 5-H_2), 3.23 (0.37 H, ddd, *J* 9.7, 6.7 and 1.1, one of 5-H_2), 3.36 (0.63 H, ddd, *J* 10.1, 7.1 and 0.7, one of 5-H_2), 3.51 (0.63 H, d, *J* 13.9, one of CH_2Ph), 3.69 (0.37 H, d, *J* 13.7, one of CH_2Ph), 3.75 (3 H × 37/100, s, OMe), 3.76 (3 H × 67/100, s, OMe), 7.10–7.14 (2 H, m, ArH) and 7.23–7.33 (3 H, m, ArH).

This ester (38 mg, 0.08 mmol) was treated with $LiAlH_4$ (13 mg, 0.34 mmol) in diethyl ether (5 cm^3) following the procedure described for the preparation of **9a** and the resulting crude product was purified by column chromatography on silica gel [hexane–AcOEt (7 : 1)] to give (2S,4R)-2-*benzyl*-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)*pyrrolidine*-2-*methanol* **18c** (37 mg, quant.) as a colourless oil [Found: $(M + H)^+$, 422.2733. $C_{23}H_{40}NO_4Si$ requires MH^+, 422.2726]; $[\alpha]_D^{25}$ −93.0 (*c* 1.4, $CHCl_3$); ν_{max}(film)/cm^{-1} 3394, 1693 and 1670; δ_H(400 MHz; $CDCl_3$, a mixture of two rotamers in the ratio 79 : 21) −0.09 (3 H × 79/100, s, one of $SiMe_2$), −0.08 (3 H × 79/100, s, one of $SiMe_2$), −0.01 (6 H × 21/100, br s, $SiMe_2$), 0.80 (9 H × 79/100, s, $SiBu^t$), 0.84 (9 H × 21/100, $SiBu^t$), 1.52 (9 H × 79/100, s, OBu^t), 1.55 (0.79 H, dd, *J* 13.4 and 6.4, one of 3-H_2), 1.59 (9 H × 21/100, s, OBu^t), 1.86 (0.21 H, br d, *J* 14.0, one of 3-H_2), 2.11 (0.79 H, dd, *J* 13.4 and 6.1, one of 3-H_2), 2.21 (0.21 H, dd, *J* 13.7 and 5.4, one of 3-H_2), 2.50 (0.21 H, d, *J* 13.6), 2.69 (0.79 H, d, *J* 13.6), 3.08 and 3.09 (1 H each, both s), 3.38 (0.21 H, d, *J* 13.6), 3.44 (0.79 H, quintet, *J* 6.0, 4-H), 3.55 (0.79 H, d, *J* 13.6), 3.56 (0.21 H, d, *J* 10.8), 3.70–3.75 (0.21 H, m, 4-H), 3.77 and 3.87 (0.79 H each, ABq, *J* 11.5), 4.08 (0.21 H, d, *J* 10.8), 7.10–7.13 (2 H × 21/100, m, ArH), 7.14–7.18 (2 H × 79/100, m, ArH) and 7.21–7.31 (3 H, m, ArH); δ_C(100 MHz; $CDCl_3$, for a major rotamer) −5.1, −5.0, 17.9 (quaternary), 25.7 (3 × Me), 28.5 (3 × Me), 38.2, 43.2, 56.4, 67.4, 68.4, 70.4, 80.3, 126.5, 128.3, 130.4, 138.0 and 155.9.

Reduction of a mixture of 16c and 17c

Following the procedure described for the preparation of **9a**, a mixture of **16c** and **17c** (200 mg, 0.34 mmol) was treated with $LiAlH_4$ (27 mg, 0.70 mmol) in diethyl ether (5 cm^3) to afford a crude product (210 mg, quant.) containing **18c**, **19c** and (+)-menthol, which was subjected to HPLC analysis carried out on an ODS-AM-302 column (5 μm; 4.6 × 150 mm, YMC) using an acetonitrile–water (80 : 20) system as eluent. The diastereomeric ratio of **18c** : **19c** proved to be 53 : 47. Furthermore, the mixture was chromatographed on silica gel [hexane–AcOEt (20 : 1)]. The first fraction gave (+)-menthol (55 mg, 100% recovery). The second fraction gave a mixture of (2S,4R)- and (2R,4R)-2-*benzyl*-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)*pyrrolidine*-2-*methanol* **18c** and **19c** (125 mg, 87%).

(2*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-2-(hydroxymethyl)pyrrolidine-2-ethanol 18d

A stream of ozone-enriched oxygen was passed through a solution of **2a** (50 mg, 0.12 mmol) in methanol (5 cm^3) at −78 °C for 10 min. After purging of unchanged excess ozone by nitrogen flow, sodium iodide (38 mg, 0.25 mmol) and acetic acid (0.1 cm^3) were added simultaneously to the reaction mixture. The whole was allowed to warm to room temperature after which 10% aq. $Na_2S_2O_3$ was added until the colour of the liberated iodine disappeared. Methanol was evaporated off and the resulting solution was extracted with AcOEt. The extract was washed with saturated aq. $NaHCO_3$, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel [hexane–AcOEt (5 : 1)] to give *methyl* (2R,4R)-2-*formylmethyl*-1-(tert-*butoxycarbonyl*)-4-(tert-*butyldimethylsilyloxy*)*pyrrolidine*-2-*carboxylate* (45 mg, 90%) as a colourless oil.

This aldehyde (45 mg, 0.11 mmol) was then reduced with $LiAlH_4$ (13 mg, 0.34 mmol) following the procedure described for the preparation of **9a**. The crude product was chromatographed on silica gel [hexane–AcOEt (3 : 2)] to afford diol **18d** (37 mg, 75% from **2a**) as a colourless oil [Found: $(M + H)^+$, 376.2513. $C_{18}H_{38}NO_5Si$ requires MH^+, 376.2519]; $[\alpha]_D^{22}$ −3.7 (*c* 2.0, $CHCl_3$); ν_{max}(film)/cm^{-1} 3408 and 1668; δ_H(400 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.88 (9 H, s, $SiBu^t$), 1.46 (9 H, s, OBu^t), 1.69 (1 H, dd, *J* 13.2 and 5.2, one of 3-H_2), 1.80 (1 H, ddd, *J* 14.6, 5.1 and 4.7), 2.16 (1 H, dd, *J* 13.2 and 5.6, one of 3-H_2), 2.45 (1 H, ddd, *J* 14.6, 7.7 and 5.1), 3.31 (1 H, dd, *J* 11.5 and 4.0, one of 5-H_2), 3.52 (1 H, dd, *J* 11.5 and 5.3, one of 5-H_2), 3.64–3.75 (3 H, m), 3.90 (1 H, d, *J* 12.0) and 4.24–4.30 (1 H, m, 4-H).

(2*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-2-(hydroxymethyl)pyrrolidine-2-ethanol 19d

Following the procedure described for the preparation of **18d**, **2b** (50 mg, 0.12 mmol) was subjected to ozonolysis followed by treatment with $LiAlH_4$ (28 mg, 0.73 mmol). The crude product was purified by column chromatography on silica gel [hexane–AcOEt (3 : 2)] to afford diol **19d** (26 mg, 58%) as a colourless oil [Found: $(M + H)^+$, 376.2526]; $[\alpha]_D^{23}$ −14.3 (*c* 2.2, $CHCl_3$); ν_{max}(film)/cm^{-1} 3398 and 1668; δ_H(400 MHz; $CDCl_3$) 0.066 (3 H, s, one of $SiMe_2$), 0.070 (3 H, s, one of $SiMe_2$), 0.88 (9 H, s, $SiBu^t$), 1.46 (9 H, s, OBu^t), 1.70 (1 H, dd, *J* 13.7 and 5.4, one of 3-H_2), 2.03 (1 H, br d, *J* 13.7, one of 3-H_2), 2.27 (1 H, ddd, *J* 14.6, 5.4 and 3.4), 2.51 (1 H, ddd, *J* 14.6, 8.5 and 4.2), 3.38 (1 H, br d, *J* 12.2, one of 5-H_2), 3.57 (1 H, dd, *J* 12.2 and 5.1, one of 5-H_2), 3.63 and 3.69 (1 H each, ABq, *J* 12.3), 3.66–3.77 (2 H, m) and 4.25–4.30 (1 H, m, 4-H).

Reduction of a mixture of 16d and 17d

Following the procedure described for the preparation of **9a**, a mixture of **16d** and **17d** (100 mg, 0.17 mmol) was treated with $LiAlH_4$ (20 mg, 0.53 mmol) in diethyl ether (5 cm^3) to afford a crude product (105 mg, quant.) containing **18d**, **19d**, and (+)-menthol, which was subjected to HPLC analysis carried out on an ODS-AM-302 column (5 μm; 4.6 × 150 mm, YMC) using an acetonitrile–water (80 : 20) system as eluent. The diastereomeric ratio of **18d** : **19d** proved to be 69 : 31.

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10 Quite recently, Ishibashi has reported that the benzylation of the enolate derived from (2*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-*N*-(benzyloxycarbonyl)proline methyl ester with *o*-bromobenzyl bromide proceeded stereoselectively to afford the (2*R*,4*R*)-2-(*o*-bromobenzyl)-4-(silyloxy)proline ester in 96% yield, carrying the *o*-bromobenzyl group at the 2 position *trans* to the 4-silyloxy group. This selectivity might be attributed to the π–π stacking interaction between the Cbz group and *o*-bromobenzyl bromide (H. Ishibashi, personal communication).