Stereochemistry of an Allyl Cyanate-to-isocyanate Rearrangement

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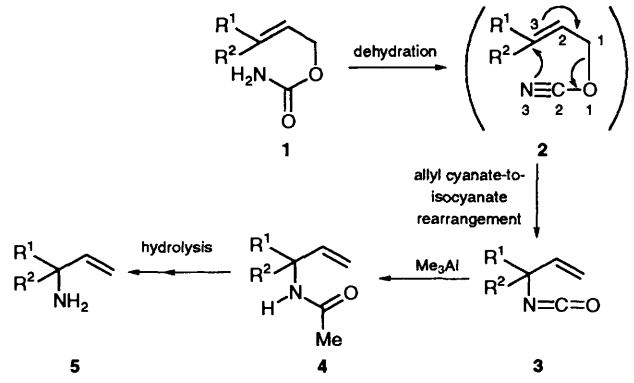
The stereochemistry of an allyl cyanate-to-isocyanate rearrangement has been investigated by employing a chiral allyl carbamate. The rearrangement has been found to be stereospecific and the chirality of an allyl cyanate is transformed into that of an allyl isocyanate. This result shows that an allyl cyanate-to-isocyanate rearrangement is a concerted reaction involving a cyclic transition state.

In a previous paper, we have demonstrated that an allyl cyanate-to-isocyanate rearrangement provides a useful method for the construction of allylamines, especially at stereochemically congested positions as shown in Scheme 1.[1] This reaction is

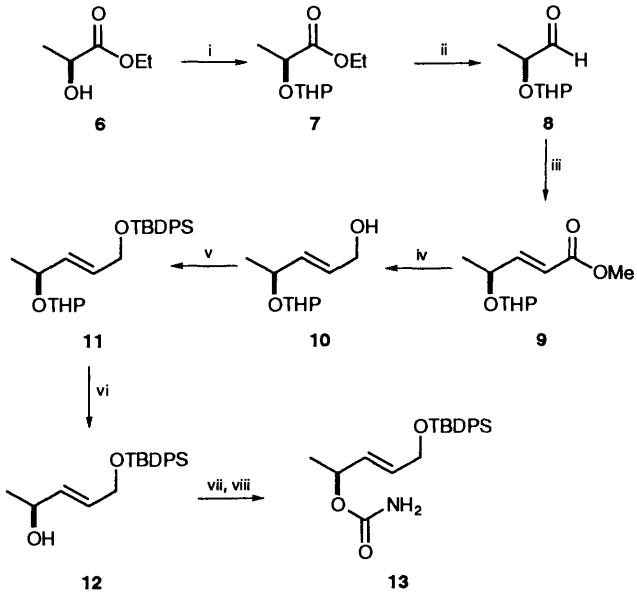


Scheme 1

initiated by dehydration of the allyl carbamates **1**, and the resulting allyl cyanates **2** undergo [3,3] sigmatropic rearrangement below ambient temperature to provide the allyl isocyanates **3**. Subsequent treatment of the resulting allyl isocyanates **3** with trimethylaluminium results in the formation of the acetamides **4**, which are hydrolysed to the allylamines **5**.

When we started to develop this reaction for the asymmetric synthesis of allylamines, it was found that data for this rearrangement had not as yet been reported and its stereochemistry as well as the mechanism remained largely undefined.[2] In this context, we planned to clarify these points, and report here for the first time the stereochemistry of an allyl cyanate-to-isocyanate rearrangement.

In order to probe the stereochemistry of this rearrangement, we prepared the chiral allyl carbamate **13** from ethyl (*S*)-(−)-lactate **6** as shown in Scheme 2. The hydroxy group of ethyl (*S*)-(−)-lactate **6** was protected quantitatively as the tetrahydropyranyl (THP) ether [dihydropyran, pyridinium toluene-*p*-sulfonate (PPTS), dichloromethane, room temperature, overnight]. Selective reduction of the ester **7** [diisobutylaluminium hydride, (DIBAL), dichloromethane, −78 °C] followed by chain extension using a Horner–Emmons reaction {methyl diethylphosphonoacetate [$(EtO)_2P(O)CH_2CO_2Me$], sodium hydride, tetrahydrofuran, −78–room temperature} furnished the unsaturated ester **9** with high selectivity (*E*:*Z* = 98:2) in 70% overall yield from the ester **7**. Reduction of the ester **9** (DIBAL, dichloromethane, −78 °C) afforded the allyl alcohol **10**, which was protected as the silyl ether [*tert*-butylchlorodiphenylsilane (TBDPSCl), imidazole, *N*,*N*-dimethylformamide]. Removal of the THP ether (PPTS, methanol, 55 °C) furnished the allyl alcohol **12** in 76% overall yield from the

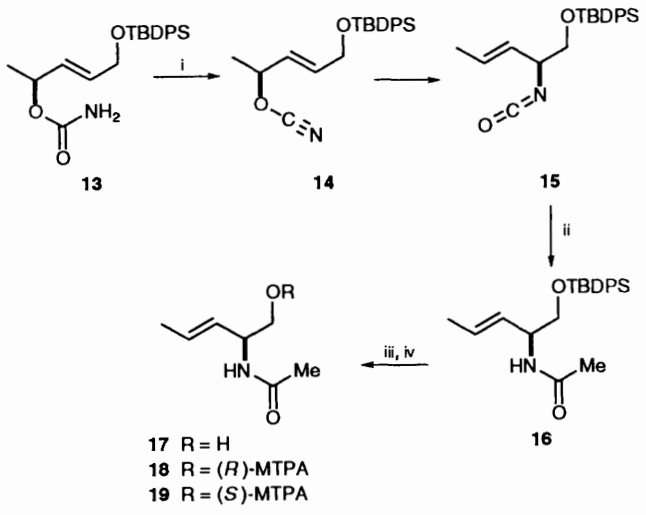


Scheme 2 *Reagents and conditions:* i, dihydropyran, PPTS; ii, DIBAL, −78 °C; iii, $(EtO)_2P(O)CH_2CO_2Me$, NaH, −78–0 °C; iv, DIBAL, −78 °C; v, TBDPSCl, imidazole; vi, PPTS, MeOH, 55 °C; vii, CCl_3CONCO; viii, K_2CO_3, aq. MeOH

unsaturated ester **9**. At this stage, the allyl alcohol **12** was converted into (*R*)- and (*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) esters,[3] and the enantiomeric purity was checked and shown to be 98% suggesting that no apparent epimerization had occurred during these transformations. Finally, treatment of the allyl alcohol **12** with trichloroacetyl isocyanate (dichloromethane, 0 °C, 30 min) and subsequent hydrolysis (potassium carbonate, aqueous methanol, room temperature, 100 min) provided the chiral allyl carbamate **13** in 99% yield. The resulting carbamate **13** was purified by recrystallization.

Having obtained chiral allyl carbamate **13**, we next focused our attention on the stereochemistry of the rearrangement. We have already reported two methods for dehydration of carbamates: method A (trifluoromethanesulfonic anhydride, diisopropylethylamine, −78 °C) and method B [triphenylphosphine; PPh_3, tetrahalogenomethane (CX_4, X = Cl, Br), triethylamine]. Method B requires laborious chromatography to remove the triphenylphosphine oxide by-product and, therefore, we have previously recommended method A because of its simpler work-up.[4] In spite of this drawback, however, we employed method B for the dehydration of the chiral allyl carbamate **13** because it gave higher yields under milder reaction conditions (Scheme 3). Dehydration of carbamate **13** using method B [PPh_3 (2.5 equiv.), CBr_4 (2.8 equiv.), Et_3N

(2 equiv.)] went smoothly at −20 °C for 60 min to provide the unstable allyl isocyanate **15**. Treatment of the resulting allyl isocyanate **15** with trimethylaluminium (8 equiv., −20 °C, 60 min) furnished the acetamide **16** in 93% yield.



Scheme 3 *Reagents and conditions:* i, PPh_3, CBr_4, Et_3N; ii, Me_3Al; iii, Bu_4NF; iv, (*R*)- and (*S*)-MTPA chlorides

The rearrangement of the allyl cyanate **14** proceeded stereoselectively with highly effective transfer of chirality. In fact, in the high field (270 MHz) ^1H NMR spectrum of the allyl acetamide **16** only the diastereoisomer with the (*E*)-double bond could be detected. Moreover, enantiomeric purity was determined to be 98% after converting the allyl acetamide **16** into the (*R*)- and (*S*)-MTPA esters **18** and **19** through desilylation (tetrabutylammonium fluoride, tetrahydrofuran, room temperature, 30 min) and acylation [(*S*)- and (*R*)-MTPACl, triethylamine, 4-dimethylaminopyridine]. Fig. 1 shows methyl signals of acetamides **18** and **19** in the 270 MHz ^1H NMR spectra.

The next problem was the determination of the absolute configuration of the allyl acetamide **16**. Initially, we transformed the amide **16** into the known *N*-Boc-protected (*E*)-dehydronorvaline **22**, the synthesis of which had been reported by Williams and Zhai.[5] Thus, amide **16** was converted into the *tert*-butyl carbamate **20** by the following sequence. (i) Treatment of **16** with freshly prepared triethyloxonium tetrafluoroborate;[6] (ii) hydrolysis of the resulting imino ether with aqueous acetic acid[7] and (iii) protection of the resulting amine with di-*tert*-butyl dicarbonate. Treatment of the carbamate **20** with tetrabutylammonium fluoride afforded *N*-Boc-protected amino alcohol **21** (Scheme 4). Oxidation of the alcohol **21** to the carboxylic acid **22** proved to be a more difficult task than expected. Oxidation using pyridinium dichromate (PDC) in the

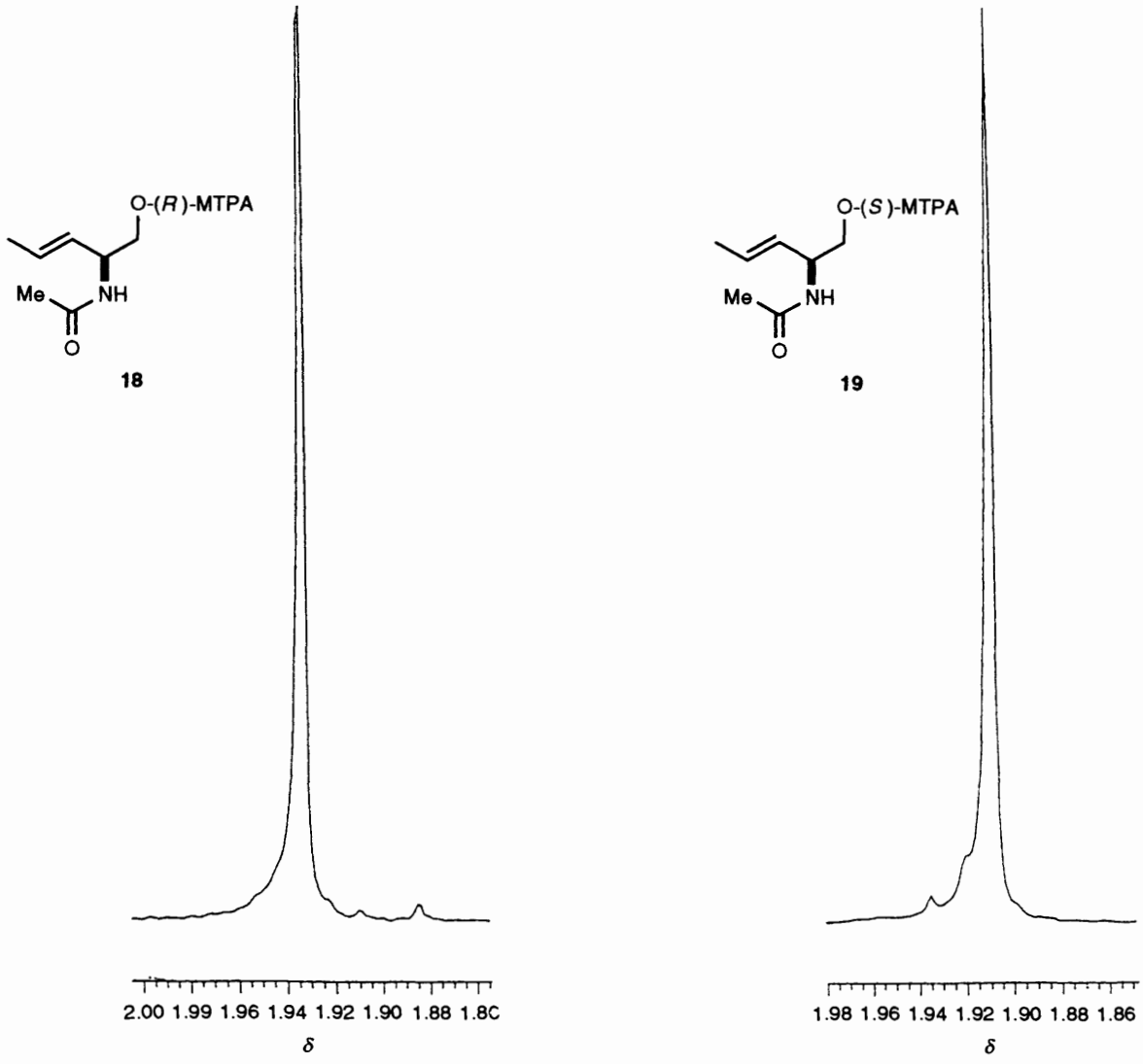
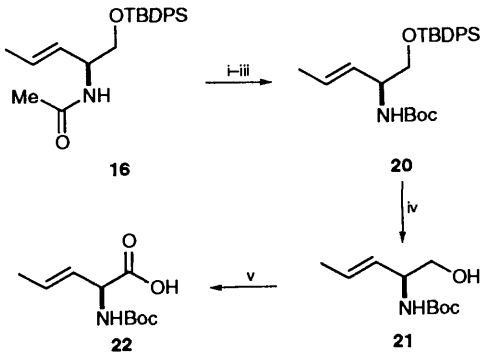
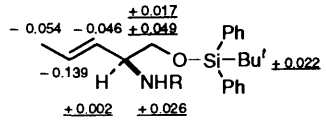


Fig. 1 ^1H NMR ($CDCl_3$) spectra of the MTPA esters **18** and **19**



Scheme 4 *Reagents and conditions:* i, $Et_3O^+ \cdot BF_4^-$, Na_2CO_3; ii, AcOH, H_2O; iii, $(Boc)_2O$, Et_3N; iv, Bu_4NF; v, PDC, DMF, 4 Å MS



$\Delta\delta = \delta_S - \delta_R$ **23** R = (*R*)-MTPA
24 R = (*S*)-MTPA

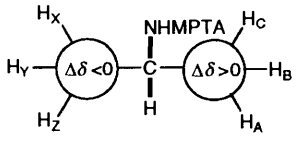


Fig. 2

presence of activated powdered 4 Å molecular sieves (MS) seemed to be one of the most promising conditions found in the literature.[8] This procedure did indeed provide the desired *N*-Boc-protected (*E*)-dehydronorvaline **22** but in variable and often low yields (8–12%). In addition, the optical rotation of the product **22** was $[\alpha]_D^{26}$ +22.8, while Williams and Zhai reported $[\alpha]_D^{25}$ +61 for **22**. The sign of rotation clearly defined the stereogenic centre of the amino alcohol **21** to be the *S* configuration, however, the value was smaller than that of Williams and Zhai. This result suggested that partial racemization had occurred during the PDC oxidation step. Efforts to improve the oxidation conditions were unsuccessful, and as a consequence, an alternative method for determining the stereochemistry of the amide **16** was elaborated.

A modification of Mosher's method for the elucidation of the absolute configuration of amines[9] seemed to be the method of choice, because this method does not suffer from epimerization at the stereogenic centre to be determined. Accordingly, amide **16** was transformed into the (*R*)- and (*S*)-MTPA amides **23** and **24** by a three step sequence. (i) Alkylation with triethyloxonium tetrafluoroborate; (ii) hydrolysis of the resulting imino ether with aqueous acetic acid and (iii) acylation with (*S*)- and (*R*)-MTPA chlorides to set up the ^{1}H NMR analysis. Examination of the $\Delta\delta$ values ($\delta_S - \delta_R$) obtained for the (*R*)- and (*S*)-MTPA amides **23** and **24** are summarized in Fig. 2. These $\Delta\delta$ values clearly showed the stereogenic centre to be in the *S* configuration based on the model of MTPA plane as depicted.[10]

Conclusions

We have shown that an allyl cyanate-to-isocyanate rearrangement involves the highly selective transfer of chirality to the newly developing asymmetric centre. This result may be taken as strong evidence for a concerted cyclic transition state in an allyl cyanate-to-isocyanate rearrangement. Fig. 3 shows

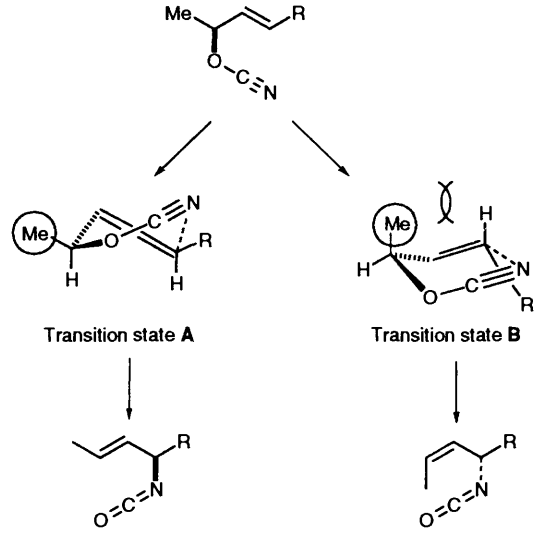


Fig. 3

two possible transition-state conformations resembling six-membered rings. The *E*-configuration at the newly formed double bond and the stereochemistry of the resulting C–N bond are those predicted by transition state **A** with the methyl group occupying a pseudo-equatorial position. Transition state **B** is less favoured because of the pseudo-axial placement of the methyl substituent which destabilizes transition state **B**.

In summary, this work has opened up an approach to the asymmetric synthesis of allylamines by an allyl cyanate-to-isocyanate rearrangement starting from chiral allyl alcohols. Further studies using a variety of chiral allyl alcohols as well as the access to optically active natural products are now underway.

Experimental

M.p.s were determined on a hot stage melting apparatus and are uncorrected. IR spectra were recorded using a JASCO FT/IR-7000S in KBr discs unless otherwise stated. ^{1}H NMR spectra were determined using a JEOL EX 270 spectrometer operating at 270 MHz unless otherwise stated. ^{13}C NMR spectra were determined using the JEOL EX 270 instrument, operating at 67.80 MHz unless otherwise stated. Dilute solutions in [$^2H_6$]chloroform were used throughout unless stated otherwise, with tetramethylsilane as the internal standard. *J*-Values are given in Hz. Optical rotations were measured on a JASCO DIP-0181 digital polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. All organic solutions from work-ups were dried by brief exposure to anhydrous sodium sulfate. Column chromatography was performed on silica gel supplied by Fuji Davison (BW-820MH). Preparative TLC was performed on plates prepared with a 2 mm layer of silica gel PF_{254} obtained from E. Merck (Art # 7747). Ether refers to diethyl ether.

(2S)-*Ethyl* 2-(*Tetrahydropyran-2-yloxy*)*propanoate* **7**.—A solution of ethyl (*S*)-(−)-lactate **6** (5 g, 42.3 mmol), pyridinium toluene-*p*-sulfonate (1.06 g, 4.23 mmol) and 3,4-dihydro-2*H*-pyran (8.47 cm^3, 93 mmol) in dichloromethane (50 cm^3) was stirred at room temperature overnight. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate. The separated aqueous phase was extracted with dichloromethane. The combined extracts were dried and then concentrated under reduced pressure to give the crude product. Purification by silica gel (100 g) chromatography eluting with a mixture of ether–hexane (4:1, v/v) afforded the

tetrahydropyranyl ether **7** as a chromatographically inseparable diastereoisomeric mixture (8.59 g, quantitative).

(4S)-(E)-*Methyl* 4-(*Tetrahydropyran-2-yloxy*)*pent-2-enoate* **9**.—To a solution of the ester **7** (4.18 g, 20.7 mmol) in dichloromethane (50 cm^3) cooled to −78 °C under a nitrogen atmosphere was added a solution of diisobutylaluminium hydride (1 mol dm^{-3} solution in hexane; 19 cm^3, 19 mmol) *via* a dropping funnel over 60 min. After being stirred for 10 min, the reaction mixture was cautiously treated with methanol until the evolution of gas had ceased. The resulting mixture was poured into aqueous sodium potassium tartrate (35 g dissolved in 100 cm^3 of water). The aqueous phase was extracted with dichloromethane (4 times). The combined organic phases were dried and then concentrated under reduced pressure to afford the crude aldehyde (4.07 g). Purification by silica gel (200 g) chromatography, eluting with a mixture of ether–hexane (1:2, v/v) afforded the aldehyde **8** (2.58 g, 79%) which was immediately used for subsequent reactions.

To a suspension of sodium hydride (60% dispersion in mineral oil; 850 mg, 21.3 mmol, washed with hexane before use) in tetrahydrofuran (THF) (30 cm^3) under a nitrogen atmosphere was added methyl diethyl phosphonoacetate (4.1 cm^3, 22.4 mmol) dropwise. After being stirred at room temperature for 30 min, the resulting homogeneous solution was cooled to −78 °C. A solution of aldehyde **8** (2.35 g, 14.9 mmol) dissolved in THF (10 cm^3) was added, and the reaction mixture was stirred for 15 min at −78 °C. The cooling bath was removed, and stirring was continued at room temperature for 2 h. Water was added to the mixture and the resulting aqueous phase was extracted with ether (3 times). The combined organic phases were washed with water and brine and then dried. The solvent was evaporated under reduced pressure to give a residue (3.40 g) which was purified by silica gel (100 g) chromatography, eluting with a mixture of ether–hexane (1:2, v/v) to afford the unsaturated ester **9** as a diastereoisomeric mixture (2.80 g, 88%).

(2S)-(*E*)-5-(tert-*Butyldiphenylsilyloxy*)*pent-3-en-2-ol* **12**.—A three-necked round-bottomed flask (300 cm^3) equipped with a nitrogen inlet, a pressure-equalizing dropping funnel and a magnetic stirring bar was charged with unsaturated ester **9** (2.50 g, 11.7 mmol) and dichloromethane (70 cm^3). To this solution cooled to −78 °C was added diisobutylaluminium hydride (1 mol dm^{-3} solution in hexane; 27 cm^3, 27 mmol) *via* the dropping funnel over 20 min and then stirring was continued for 10 min. Methanol was added to the mixture until the evolution of gas had ceased. The reaction mixture was poured into ice-cooled aqueous potassium sodium tartrate (40 g in 100 cm^3 of water). The separated aqueous phase was extracted with dichloromethane (4 times), and the combined organic extracts were dried and then concentrated under reduced pressure to provide the allyl alcohol **10** (2.49 g) which was used in the next reaction without further purification.

To a solution of the allyl alcohol **10** (2.49 g) and imidazole (1.6 g, 23.6 mmol) dissolved in *N*,*N*-dimethylformamide (DMF) (30 cm^3) was added *tert*-butylchlorodiphenylsilane (3.08 cm^3, 11.8 mmol) dropwise. After being stirred at room temperature for 2 h, the reaction mixture was poured into water. The separated aqueous layer was extracted with ether (3 times). The combined extracts were washed with water and brine, dried and then concentrated under reduced pressure to provide the silyl ether **11** (5.02 g).

A solution of the resulting silyl ether **11** (5.02 g) and pyridinium toluene-*p*-sulfonate (0.45 g, 1.77 mmol) dissolved in methanol (70 cm^3) was stirred at 55 °C for 90 min. The reaction mixture was then diluted with water and concentrated to a low volume under reduced pressure. The resulting aqueous phase was extracted with ether (3 times). The combined organic phases were washed with water and brine, dried and then concentrated under reduced pressure. Purification of the resulting residue (4.37 g) by silica gel (200 g) chromatography eluting with a mixture of ether–hexane (1:3, v/v) afforded the allyl alcohol **12** (2.65 g, 76% overall yield from **9**, three steps), $[\alpha]_D^{24}$ −3.6 (*c* 2.07 in $CHCl_3$) (Found: C, 74.0; H, 8.4. $C_{21}H_{28}O_2Si$ requires C, 74.07; H, 8.29%); ν_{max}(KBr)/cm^{-1} 3400 (OH); δ_H(270 MHz; $CDCl_3$) 1.06 (9 H, s, Bu^t), 1.25 (3 H, d, *J* 6, CH_3), 1.50 (1 H, br s, OH), 4.21 (2 H, d, *J* 4, CH_2OTBDPS), 4.30 [1 H, qd, *J* 6 and 5, CH_3CH(OH)], 5.71 (1 H, dt, *J* 16 and 4, CH=CH), 5.79 (1 H, dd, *J* 16 and 5, CH=CH), 7.3–7.5 (6 H, m) and 7.6–7.7 (4 H, m).

Esterification of the Allyl Alcohol **12** *with* (R)- *and* (S)-2-*Methoxy-2-phenyl-2-(trifluoromethyl)acetic Acid* (*MTPA*) *Chlorides*.[11]—A solution of the allyl alcohol **12** (6 mg, 0.018 mmol), 4-dimethylaminopyridine (2 mg, 0.016 mmol) and triethylamine (0.007 cm^3, 0.053 mmol) in dichloromethane (0.3 cm^3) was treated with (*S*)-MTPA chloride (0.010 cm^3, 0.053 mmol) at room temperature for 30 min. TLC analysis showed that the starting material had been consumed. *N*,*N*-Dimethylpropane-1,3-diamine (0.01 cm^3) was added to it, and the reaction mixture was purified by silica gel (2 g) chromatography, eluting with a mixture of ether–hexane (1:8, v/v) to provide (*R*)-MTPA ester (9 mg, 92%), $[\alpha]_D^{22}$ +17.7 (*c* 0.37 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1748 (OC=O); δ_H(270 MHz; $CDCl_3$) 1.05 (9 H, s, Bu^t), 1.42 (3 H, d, *J* 8, CH_3), 3.57 (3 H, q, *J* 1, CH_3), 4.17 (2 H, br, CH_2O), 5.58–5.7 [1 H, m, CH(OMTP)Me], 5.78 (2 H, m, CH=CH) and 7.3–7.7 (15 H).

Starting from the allyl alcohol **12** (5 mg, 0.015 mmol), 4-dimethylaminopyridine (2 mg, 0.016 mmol), triethylamine (0.006 cm^3, 0.044 mmol), dichloromethane (0.3 cm^3), (*R*)-MTPA chloride (0.083 cm^3, 0.044 mmol) and *N*,*N*-dimethylpropane-1,3-diamine (0.01 cm^3), (*S*)-MTPA ester (8 mg) was isolated in 98% yield, $[\alpha]_D^{22}$ −37.3 (*c* 0.36 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1748 (OC=O); δ_H(270 MHz; $CDCl_3$) 1.06 (9 H, s, Bu^t), 1.35 (3 H, d, *J* 6, CH_3), 3.55 (3 H, q, *J* 1, CH_3), 4.21 (2 H, d, *J* 1, CH_2O), 5.58–5.7 [1 H, m, CH(OMTP)Me], 5.88 (2 H, m, CH=CH) and 7.31–7.7 (15 H).

(2S)-(E)-5-(tert-*Butyldiphenylsilyloxy*)*pent-3-en-2-yl Carbamate* **13**.—To a solution of the allyl alcohol **12** (201 mg, 0.59 mmol) in dichloromethane (5 cm^3) was added trichloroacetyl isocyanate (0.11 cm^3, 0.89 mmol) dropwise at 0 °C. After being stirred for 30 min, the solvent was removed by evaporation under reduced pressure. The resulting residue was dissolved in a mixture of methanol (4 cm^3) and water (2 cm^3). To this solution cooled to 0 °C was added potassium carbonate (0.25 g, 18.1 mmol) portionwise. After being stirred at 0 °C for 100 min, the cooling bath was removed, and stirring was continued at room temperature for a further 100 min. The methanol was evaporated under reduced pressure and the resulting aqueous phase was extracted with dichloromethane (3 times). The combined organic phases were washed with aqueous sodium chloride (a 1:1 mixture of saturated aqueous sodium chloride and water, v/v) and then dried. Concentration under reduced pressure afforded a residue (231 mg) which was purified by silica gel (10 g) chromatography, eluting with a mixture of ether–hexane (1:1, v/v) to afford the carbamate **13** (223 mg, 99%), m.p. 84–85 °C (from ether–hexane) (Found: C, 68.9; H, 7.6; N, 3.6. $C_{22}H_{29}NO_3Si$ requires C, 68.89; H, 7.62; N, 3.65%); $[\alpha]_D^{27}$ −14.8 (*c* 0.202 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1670 ($OCONH_2$); δ_H(270 MHz; $CDCl_3$) 1.06 (9 H, s, Bu^t), 1.31 [3 H, d, *J* 6, CH_3CH(OH)], 4.18–4.23 (2 H, CH_2OTBDPS), 4.66 (2 H, br s, NH_2), 5.27 [1 H, m, CH_3CH($OCONH_2$)], 5.76–5.81 (2 H, CH=CH) and 7.3–7.5 (6 H, m) and 7.6–7.7 (4 H, m); δ_C(67.80

MHz; $CDCl_3$) 19.2, 20.5, 26.8, 63.6, 71.2, 127.6, 129.4, 129.6, 130.6, 133.6, 135.5 and 156.3.

(2S)-(E)-N-(1-tert-*Butyldiphenylsilyloxypent*-3-*en*-2-*yl*)*acetamide* **16**.—To a solution of allyl carbamate **13** (100 mg, 0.26 mmol), triphenylphosphine (170 mg, 0.65 mmol) and triethylamine (0.07 cm^3, 0.52 mmol) in dichloromethane (2 cm^3) was added to a solution of carbon tetrabromide (242 mg, 0.73 mmol) in dichloromethane (1.4 cm^3) dropwise at −20 °C. After stirring at −20 °C for 60 min, a solution of trimethylaluminium (1 mol dm^{-3} solution in hexane; 2.1 cm^3, 2.1 mmol) was added dropwise to the mixture. After being stirred for 60 min, methanol was added to it cautiously. The reaction mixture was poured into saturated aqueous potassium sodium tartrate (20 cm^3) and the aqueous phase was extracted with dichloromethane (3 times). The combined organic phases were dried and then concentrated under reduced pressure. Purification of the resulting residue (424 mg) by silica gel (20 g) chromatography eluting with a mixture of ether–hexane (3:1, v/v) provided acetamide **16** (93 mg, 93%), m.p. 79–81 °C (from ether–hexane) (Found: C, 72.3; H, 8.05; N, 3.6. $C_{23}H_{31}NO_2Si$ requires C, 72.40; H, 8.19; N, 3.67%); $[\alpha]_D^{20}$ −11.2 (*c* 1.2 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3276 (NH) and 1645 (CON); δ_H(270 MHz; $CDCl_3$) 1.07 (9 H, s, Bu^t), 1.69 (3 H, dt, *J* 6, 1, CH_3CH=CH), 1.94 (3 H, s, CH_3CO), 3.64–3.78 (2 H, CH_2OTBDPS), 4.50 [1 H, m, CH(NHCOCH$_3$)], 5.44 (1 H, ddq, *J* 15, 6 and 1, CH=CH), 5.64 (1 H, dqd, *J* 15, 6 and 1, CH=CH), 5.77 (1 H, br d, *J* 8, NH), 7.3–7.5 (6 H, m) and 7.6–7.7 (4 H, m); δ_C(67.80 MHz; $CDCl_3$) 17.7, 19.3, 23.4, 26.8, 52.3, 66.1, 127.3, 127.7, 128.6, 129.8, 133.1, 133.3, 135.5, 135.6 and 169.2.

(2S)-(E)-N-(1-*Hydroxypent*-3-*en*-2-*yl*)*acetamide* **17**.—To a solution of the acetamide **16** (31 mg, 0.081 mmol) in THF (1 cm^3) was added a solution of tetrabutylammonium fluoride in THF (1 mol dm^{-3} solution in THF; 0.1 cm^3, 0.1 mmol) dropwise. The reaction mixture was stirred at room temperature for 30 min and then concentrated under reduced pressure to afford the crude product (84 mg). Purification by silica gel (5 g) chromatography eluting with a mixture of dichloromethane–methanol (10:1, v/v) provided the alcohol **17** (12 mg, quantitative), $[\alpha]_D^{24}$ +13.7 (*c* 0.52 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3281 (OH) and 1652 (CON); δ_H(270 MHz; $CDCl_3$) 1.72 (3 H, br d, *J* 6, CH_3CH=CH), 2.03 (3 H, s, CH_3CO), 3.58–3.73 (2 H), 4.48 [1 H, m, CH(NHCOCH$_3$)-CH$_2$], 5.43 (1 H, ddq, *J* 15, 6, 2, CH=CH), 5.71 (1 H, dqt, *J* 15, 6, 1, CH=CH) and 6.02 (1 H, br, NH); δ_C(67.80 MHz; $CDCl_3$) 17.7, 23.0, 53.3, 64.9, 127.6, 128.0 and 170.9.

Preparation of Mosher's Esters from Allyl Alcohol **17**.[11]—To a solution of the alcohol **17** (25 mg, 0.175 mmol), 4-dimethylaminopyridine (10 mg, 0.082 mmol) and triethylamine (0.035 cm^3) in dichloromethane (0.8 cm^3) was added (*S*)-MTPA chloride (0.04 cm^3, 0.21 mmol). After being stirred at room temperature for 90 min, TLC analysis showed the absence of alcohol **17**. The solvent was removed by evaporation, and the residue was purified by silica gel (5 g) chromatography eluting with a mixture of ethyl acetate–hexane (1:1, v/v) to provide (*R*)-MTPA ester **18** (57 mg, 91%), $[\alpha]_D^{26}$ +23.3 (*c* 0.57 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3278 (NH), 1751 (COO) and 1655 (CON); δ_H(270 MHz; $CDCl_3$) 1.66 [3 H, dt, *J* 6 and 2, CH_3CH(OH)], 1.94 (3 H, s, CH_3CO), 3.52 (3 H, q, *J* 1, OCH_3), 4.36 (2 H, m, CH_2OMTPA), 4.74 [1 H, m, CH_3CH(OMTPA)], 5.34 (1 H, ddq, *J* 15, 6 and 2, CH=CH), 5.58 (1 H, br d, NH), 5.68 (1 H, dqd, *J* 15, 6, 1, CH=CH) and 7.3–7.5 (5 H, m).

Starting from alcohol **17** (20 mg, 0.140 mmol), 4-dimethylaminopyridine (9 mg, 0.099 mmol), triethylamine (0.028 cm^3), dichloromethane (0.8 cm^3) and (*R*)-MTPA chloride (0.039 cm^3, 0.21 mmol), (*S*)-MTPA ester **19** was obtained by the procedure described before (46 mg, 92%), $[\alpha]_D^{24}$ −33.5 (*c* 0.45 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3278 (NH), 1751 (COO) and 1654 (CON); δ_H(270 MHz; $CDCl_3$) 1.67 [3 H, dt, *J* 6 and 2, CH_3CH(OH)], 1.90 (3 H, s, CH_3CO), 3.54 (3 H, q, *J* 1, OCH_3), 4.36 (2 H, m, CH_2OMTPA), 4.76 [1 H, m, CH_3CH(OMTPA)], 5.36 (1 H, ddq, *J* 15, 6, 2, CH=CH), 5.56 (1 H, br d, NH), 5.69 (1 H, dqd, *J* 15, 6 and 1, CH=CH) and 7.35–7.55 (5 H, m).

tert-*Butyl* (2S)-(E)-N-(1-tert-*Butyldiphenylsilyloxypent*-3-*en*-2-*yl*)*carbamate* **20**.—To a solution of acetamide **16** (471 mg, 1.24 mmol) and sodium carbonate (800 mg) in dichloromethane (8 cm^3) under a nitrogen atmosphere was added a solution of freshly prepared triethyloxonium tetrafluoroborate (1 mol dm^{-3} solution in dichloromethane; 6.2 cm^3, 6.2 mmol) dropwise. After being stirred at room temperature for 90 min, the reaction mixture was poured into water. The separated aqueous phase was extracted with dichloromethane, and the combined organic phases were dried and then concentrated under reduced pressure to afford crude imino ether (568 mg). This imino ether was immediately dissolved in a mixture of acetic acid (0.8 cm^3), water (0.8 cm^3) and THF (9 cm^3). The solution was stirred at room temperature overnight, and then neutralized with saturated aqueous sodium hydrogen carbonate. The aqueous phase was extracted with dichloromethane, and the combined extracts were dried and then concentrated under reduced pressure. Purification of the residue (457 mg) by silica gel (15 g) chromatography eluting with a mixture of dichloromethane–methanol (10:1, v/v) provided the corresponding amine (389 mg).

The resulting amine (389 mg) was dissolved in dichloromethane (10 cm^3). Triethylamine (0.3 cm^3, 2.3 mmol) and a solution of di-*tert*-butyl dicarbonate (300 mg, 1.38 mmol) in dichloromethane (3 cm^3) was added dropwise to this solution. After being stirred at room temperature for 165 min, *N*,*N*-dimethylpropane-1,3-diamine (0.15 cm^3, 1.15 mmol) was added to it. The reaction mixture was poured into water, and the aqueous phase was extracted with ether. The combined organic phases were washed with aqueous ammonium chloride, water and brine, dried and then concentrated under reduced pressure. Purification of the resulting oil (483 mg) by silica gel (24 g) chromatography eluting with a mixture of ether–hexane (1:1, v/v) afforded *tert*-butyl carbamate **20** (423 mg, 84%), m.p. 50–51 °C (from ether–hexane) (Found: C, 71.0; H, 8.5; N, 3.1. $C_{26}H_{37}NO_3Si$ requires C, 71.03; H, 8.48; N, 3.19%); $[\alpha]_D^{27}$ −17.8 (*c* 0.52 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3343 (NH) and 1691 (CON); δ_H(270 MHz; $CDCl_3$) 1.06 (9 H, s, Bu^{t}Si), 1.45 (9 H, s, Bu^{t}O), 1.68 (3 H, dt, *J* 6, 2, CH_3CH=CH), 3.55–3.75 (2 H, CH_2OTBDPS), 4.16 [1 H, br, CH(NHBoc)], 4.78 (1 H, br d, *J* 7, NH), 5.41 (1 H, ddq, *J* 16, 6, 1, CH=CH), 5.63 (1 H, dq, *J* 16, 6, CH=CH), 7.3–7.5 (6 H, m) and 7.6–7.7 (4 H, m).

(2S)-(E)-(tert-*Butoxycarbonylamino*)*pent*-3-*en*-1-*ol* **21**.—A solution of tetrabutylammonium fluoride (1 mol dm^{-3} solution in THF; 0.55 cm^3, 0.55 mmol) was added to a solution of carbamate **20** (201 mg, 0.46 mmol) dissolved in THF (7 cm^3) at room temperature. The resulting reaction mixture was stirred for 50 min and then was poured into aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane (3 times). The combined organic phases were dried and then concentrated under reduced pressure. Purification of the resulting residue (263 mg) by silica gel (13 g) chromatography eluting with a mixture of ether–hexane (1:1, v/v) afforded amino alcohol **21** (80 mg, 87%), m.p. 57–59 °C (from ether–hexane) (Found: C, 59.8; H, 9.3; N, 6.9. $C_{10}H_{19}O_3N$ requires C, 59.68; H, 9.52; N, 6.96%); $[\alpha]_D^{27}$ −3.6 (*c* 0.51 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3600–3100 (NH, OH) and 1695 (CON); δ_H(270 MHz; $CDCl_3$) 1.45 (9 H, s, Bu^{t}O), 1.71 (3 H, dt, *J* 6, 1, CH_3CH=CH),

2.71 (1 H, br, OH), 3.53–3.71 (2 H, CH_2OTBDPS), 4.16 [1 H, br, CH(NHBoc)], 4.92 (1 H, br d, *J* 7, NH), 5.41 (1 H, ddq, *J* 15, 6, 1, CH=CH) and 5.70 (1 H, dqd, *J* 15, 6 and 1, CH=CH); δ_C(67.80 MHz; $CDCl_3$) 17.8, 28.3, 54.3, 65.6, 79.7, 128.0, 128.1 and 156.1.

(2S)-(E)-(tert-*Butoxycarbonylamino*)*pent*-3-*enoic Acid* **22**.—To a solution of the amino alcohol **21** (130 mg, 0.65 mmol) and 4 Å molecular sieves (6 g) in DMF (10 cm^3) was added a solution of pyridinium dichromate (2.4 g, 6.4 mmol) in DMF (50 cm^3) dropwise over 165 min. After being stirred at room temperature for 16 h, the DMF was removed under reduced pressure using a vacuum pump. The residue was taken up in ether and water, and then filtered over Celite. The aqueous layer was extracted with ether (3 times). The combined organic phases were extracted with saturated aqueous sodium hydrogen cabonate (3 times). The combined aqueous layers were adjusted to pH 4 by the addition of acetic acid. The resulting aqueous layer was extracted with ethyl acetate (3 times). The combined extracts were washed with water and brine, dried and then concentrated under reduced pressure to afford the acid **22** (11 mg, 8%), $[\alpha]_D^{26}$ +22.8 (*c* 0.35 in CH_2Cl_2) {lit.,[5] $[\alpha]_D^{25}$ +61 (*c* 0.23 in CH_2Cl_2}; ν_{max}(KBr)/cm^{-1} 3335 (OH), 2980 and 1718 (CO) (lit.,[5] 3320, 2980 and 1720); δ_H(270 MHz; $CDCl_3$) 1.45 (9 H, s, Bu^{t}O), 1.74 (3 H, dd, *J* 7, 1, CH_3CH=CH), 4.78 (1 H, br s, CHNHBoc), 5.10 (1 H, br, NH), 5.52 (1 H, br dd, *J* 15 and 5, CH=CH) and 5.85 (1 H, dqd, *J* 15, 7 and 1, CH=CH) [lit.,[5] 1.5 (9 H, s), 1.72 (3 H, d, *J* 6.5), 4.8 (0.5 H, br), 5.15 (0.5 H, br), 5.48–5.55 (1 H, m) and 5.79–5.85 (1 H, m, *J* 14.5, decoupling)].

Treatment of a portion of the acid **22** (3 mg) with diazomethane in ether at room temperature provided the corresponding methyl ester (3 mg), ν_{max}(KBr)/cm^{-1} 3382 (NH), 1746 (CO_2Me) and 1720 (NHCO); δ_H(270 MHz; $CDCl_3$) 1.45 (9 H, s, Bu^{t}O), 1.72 (3 H, br d, *J* 6, CH_3CH=CH), 3.76 (3 H, s, CO_2CH_3), 4.77 (1 H, br, CHNHBoc), 5.12 (1 H, br, NH), 5.47 (1 H, br dd, *J* 15 and 6, CH=CH) and 5.79 (1 H, dqd, *J* 15, 6 and 1, CH=CH).

Preparation of (R)-**23** *and* (S)-**24** *MTPA Amides of Acetamide* **16**.—(2S)-(E)-1-*tert*-Butyldiphenylsilyloxyaminopent-3-ene was prepared from acetamide **16** by an identical procedure to that of carbamate **20**. The resulting crude (2*S*)-(*E*)-1-*tert*-butyldiphenylsilyloxyaminopent-3-ene (10 mg, 0.029 mmol) was treated with 0.1 mol dm^{-3} HCl at 0 °C for 20 min. The aqueous layer was extracted with ethyl acetate (4 times). The combined organic phases were washed with water and brine, dried and then concentrated under reduced pressure to afford the corresponding amine hydrochloride (9 mg).

The amine hydrochloride (17 mg, 0.045 mmol) dissolved in pyridine (0.2 cm^3) was treated with (*S*)-MTPA-Cl (0.025 cm^3, 0.135 mmol) at room temperature for 40 min. TLC analysis showed that the starting material had been consumed. *N*,*N*-Dimethylpropane-1,3-diamine (0.017 cm^3, 0.14 mmol) was added to the mixture and stirring continued for 10 min. The solution was diluted with ether, and washed with 0.1 mol dm^{-3} HCl and brine, dried and then concentrated under reduced pressure. Purification of the resulting residue by preparative TLC afforded (*R*)-MTPA amide **23** (7 mg, 26%), $[\alpha]_D^{22}$ −11.6 (*c* 0.38 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3422 (NHCOO) and 1701 (NHCO); δ_H(270 MHz; $CDCl_3$) 1.03 (9 H, s, Bu^{t}Si), 1.70 (3 H, br d, *J* 6, 2, CH_3CH=CH), 3.40 (3 H, q, *J* 1, OCH_3), 3.62–3.76 (2 H, m, CH_2OTBDPS), 4.54 [1 H, m, CH(NHMTPA)], 5.46 (1 H, ddq, *J* 15, 6 and 2, CH=CH), 5.70 (1 H, dqd, *J* 15, 6 and 1, CH=CH), 7.3–7.75 (15 H, m) and 7.55 (1 H, br, NH).

A portion of amine hydrochloride (12 mg, 0.032 mmol) was also transformed into (*S*)-MTPA amide **24** (7 mg, 31%) by using (*R*)-MTPA-Cl (0.018 cm^3, 0.094 mmol), pyridine (0.2 cm^3) and *N*,*N*-dimethylpropane-1,3-diamine (0.012 cm^3, 0.10 mmol), $[\alpha]_D^{27}$ −9.7 (*c* 0.35 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3422 (NHCOO) and 1701 (NHCO); δ_H(270 MHz; $CDCl_3$) 1.05 (9 H, s, Bu^{t}Si), 1.65 (3 H, br d, *J* 6, CH_3CH=CH), 3.42 (3 H, q, *J* 1, OCH_3), 3.63–3.81 (2 H, m, CH_2OTBDPS), 4.54 [1 H, m, CH(NHMTPA)], 5.42 (1 H, ddq, *J* 15, 6 and 2, CH=CH), 5.56 (1 H, dqd, *J* 15, 6 and 1, CH=CH), 7.3–7.75 (15 H, m) and 7.55 (1 H, br, NH).

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