An Approach to Chiral Trisubstituted Pyrrolidines by Enolate Claisen Rearrangement of Azalactones Derived from α-Amino Acids

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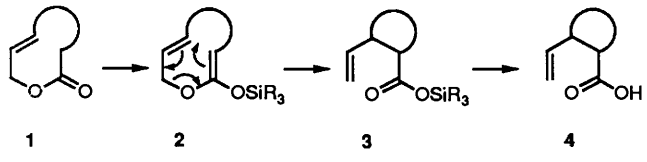
Homologation of the β-amino acid derivatives **17a**, **27a** and **27b** by *N*-alkylation using the *cis*-butenyl chloride **18** has been used to obtain the hydroxy acids **19b**, **28c** and **28d** which were then converted into the 9-membered azalactones **20**, **29a** and **29b** using Mukaiyama's reagent, 2-chloro-1-methylpyridinium iodide. Enolate Claisen rearrangements of these macrolides were then effected using a 'pre-mix' method in which the base (LDA) and the trapping agent (TBDMSCl) were mixed at low temperature before addition of these substrates and took place on warming to ambient temperature. Rearrangement of the azalactone **20** gave only the *cis*-3,4-disubstituted pyrrolidine **21a** while rearrangements of the chiral lactones **29** led to the chiral trisubstituted pyrrolidines **30** in an enantiospecific fashion, *via* a boat-like transition state (*e.g.* **31**).

The enolate Claisen rearrangement, originally developed by Ireland and his colleagues,[1] is probably the most widely applicable version of this extremely useful [3,3] sigmatropic process in which allyl vinyl ethers are converted into γ,δ-unsaturated carbonyl compounds.[2] A major reason for this is that the vinyl ether function, which can often be difficult to prepare, especially in more complex and sensitive substrates, is readily generated by enolisation and *O*-silylation of an allyl ester enolate. The required ether bond is therefore usually prepared by a mild and efficient esterification procedure rather than by a direct method. A bonus is that such rearrangements usually take place at lower temperatures than those required by more conventional Claisen substrates.[1]

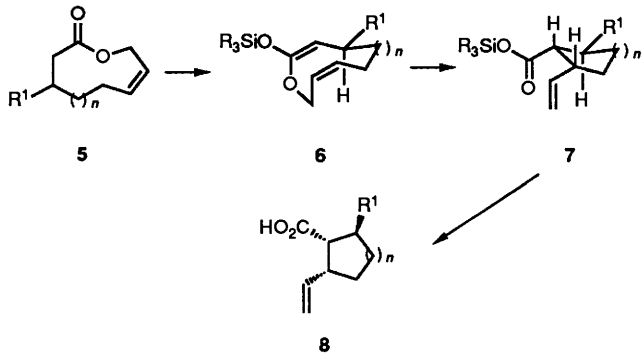
A significant and highly stereoselective development of this methodology, first reported by Danishefsky and his colleagues,[3] involves the use of unsaturated lactones rather than esters as substrates. Specifically, rearrangements of ω-vinyl-valerolactones and -caprolactones were first described leading to cyclohexene- and cycloheptene-carboxylic acids, respectively. The method was subsequently applied to an elegant synthesis of the sesquiterpene widdrol.[4] Interestingly, later studies have shown that in the particular case of rearrangements of ω-vinylvalerolactone *O*-silyl enolates, the mechanism can be a retro hetero Diels–Alder/intramolecular Diels–Alder sequence rather than a direct Claisen rearrangement.[5] The version of the enolate Claisen rearrangement which forms the basis of this present paper is outlined in Scheme 1 and is the extreme



1 2 3 4

Scheme 1

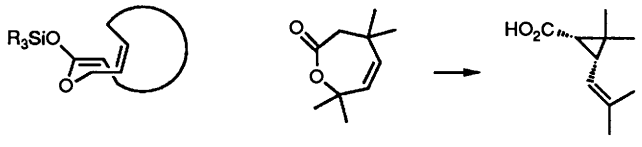
alternative to the original Danishefsky type.[3,4] Thus, enolisation and *O*-silylation of an unsaturated macrolide **1** produces the key rearrangement precursor **2** which on warming is transformed into the carbocyclic system **3**, which is usually isolated as the corresponding acid **4**. A number of studies[6] have demonstrated the viability of this sequence and have revealed a number of useful features which are associated with the scheme. The most significant of these is that if the initial macrolides **1** contain eleven atoms or less, then the rearrangements are stereospecific and lead only to *cis*-β-vinylcycloalkanecarboxylic



5 6 7 8

Scheme 2

acids (i.e. *cis*-**4**). A likely explanation for this (Scheme 2) is that enolisation of such a macrolide (**5**; $n < 4$) leads specifically[6,7] to the *E*-*O*-silyl enolate which can only rearrange by way of a boat-like transition state **6**[3] to give the *cis* products **7**. Furthermore, on the assumption that the remainder of the ring adopts a chair-like conformation, a substituent, R^1, should adopt largely or exclusively a pseudoequatorial position in the transition state **6** and hence control the relative stereochemistry between itself and the two newly created chiral centres, leading finally to at least a preponderance of the diastereoisomers **8**. In general, the Claisen rearrangement proceeds through a chair-like transition state.[2] However, in this type of enolate derived from medium-sized macrolides, the involvement of such a state **9** is clearly precluded by the requirement for a short *trans* diaxial bridge.[3] The most extreme example of this phenomenon is the

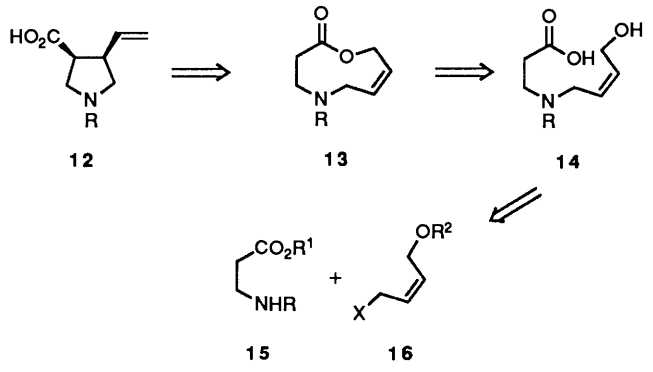


9 10 11

enolisation and rearrangement of the unsaturated caprolactone **10** which leads exclusively to the *cis* cyclopropanecarboxylic acid **11**; clearly, in this case, formation of the *Z*-*O*-silyl enolate or involvement of a chair-like transition state are impossible.[8] The studies detailed in this present paper were aimed at examining two features arising from Scheme 2. Firstly, if a substituent, R^1, was attached to a homochiral carbon, then the rearrangement **6**→**7** should result in the creation of two new chiral centres

with retention of the original. Secondly, if a heteroatom such as nitrogen[9] or oxygen were positioned in the macrolide ring, then the sequence could be used to prepare highly substituted, saturated heterocyclic systems in a stereocontrolled manner.[10]

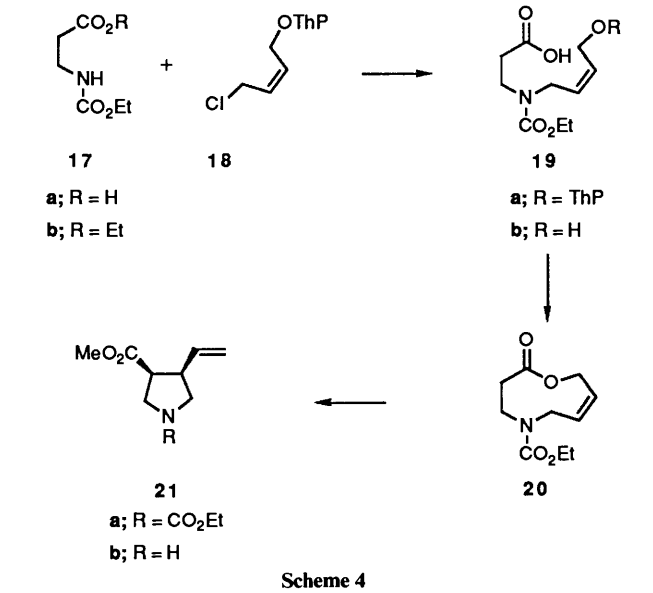
A model sequence to establish the viability of this latter feature in an approach to pyrrolidines is outlined in Scheme 3.



Scheme 3

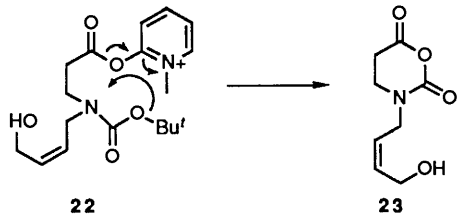
Thus, by extrapolation of Scheme 2, the target pyrrolidines **12** could be formed by enolate Claisen rearrangement of an azalactone **13** which in turn should be available from the corresponding hydroxy acid **14**. Two simple components, a β-alanine derivative **15** and a *cis*-butenol **16**, should then serve as suitable precursors.

The first step, *N*-alkylation of a carbamate derivative of β-alanine by an allylic chloride, proved to be unexpectedly difficult (Scheme 4). Alkylations of both the acid **17a** and the



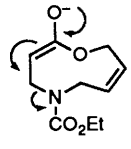
Scheme 4

corresponding ethyl ester **17b** using the readily available allylic chloride **18** uniformly gave poor yields (< 20%) when sodium or potassium hydride were used as base in either tetrahydrofuran (THF) or dimethylformamide (DMF), at a variety of temperatures. Slightly improved yields of the alkylated product **19a** along with unchanged starting materials were obtained by treatment of the dianion derived from acid **17a** using butyllithium or lithium diisopropylamide (LDA) in THF-hexamethylphosphoramide (HMPA) mixtures. The addition of HMPA was essential in order to dissolve the intermediate dianion which was insoluble and unreactive with the chloride **18** in THF alone. Similar moderate yields were obtained from the corresponding *N*-methoxycarbonyl- and *N*-*tert*-butyloxycarbonyl (BOC) derivatives. By contrast, the *N*-phenylsulphonyl and *N*-trifluoroacetyl derivatives of β-alanine gave negligible yields under the foregoing conditions, although both the acid and methyl ester of the trifluoroacetyl derivative gave *ca.* 30% yields of alkylated products when treated with sodium hydride in DMF. Finally, it was found that treatment of the protected acid **17a** with two equivalents of butyllithium in THF at −78 °C followed by warming to ambient temperature, dilution with dimethyl sulphoxide (DMSO) and addition of a slight excess of the allylic chloride **18** led to the desired alkylated product **19a** in 68% isolated yield. The use of DMSO was crucial not only to dissolve the precipitated dianion of acid **17a**, for which purpose HMPA was equally effective, but also to facilitate the alkylation step. Subsequent hydrolysis of the tetrahydropyranyl function to give the hydroxy acid **19b** was effected in excellent yield using pyridinium toluene-*p*-sulphonate (PPTS)[11] in methanol at reflux. Lactonisation of acid **19b** was then carried out using Mukaiyama's procedure in which the acid and triethylamine are added slowly using a syringe pump to a dilute solution of the cyclisation reagent, 2-chloro-1-methylpyridinium iodide, in refluxing acetonitrile.[12] The desired macrolide **20** was obtained in 42% yield after column chromatography over Grade III neutral alumina; the compound decomposed to a considerable degree when chromatographed over silica gel. Only traces of the corresponding diolide were isolated. Attempts to recover the starting hydroxy acid **19b** by saponification of other column fractions, in the hope that these could be ester polymers, failed to produce substantial quantities of the compound. More likely is that much of the substrate was lost by ketene formation as described recently by Funk and and his colleagues.[13] It is also possible that a cyclisation reaction could occur between the carbamate protecting group and the intermediate 2-acyloxypyridinium function, leading to a 2H-1,3-oxazine-2,6(3*H*)-dione.[14] When lactonisation of the corresponding BOC hydroxy acid (**19b**; Bu^t in place of Et) was attempted, none of the expected macrolide was isolated; this may have been due to competition from just such a process in which the reactive intermediate **22** could easily lose isobutene to give an oxazine **23**.[15] This would



probably then undergo polymerisation according to the extensive patent literature on this subject. However, prolonged exposure to triethylamine hydrochloride in hot acetonitrile may also have been responsible for the removal of the *N*-BOC function and the subsequent loss of material. By analogy, PPTS provides sufficient protons to effect the removal of a tetrahydropyran (THP) ether group in refluxing methanol (*vide supra*).

The key Claisen rearrangement was effected by addition of the macrolide **20** to an excess of LDA and *tert*-butyldimethylsilyl chloride (TBDMSCl), crucially, pre-mixed in THF at −100 °C. The rearrangement then took place smoothly as the mixture was warmed to ambient temperature during 0.25 h.



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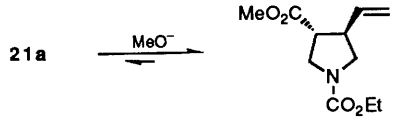
Following desilylation, esterification and finally, column chromatography, the pyrrolidine **21a** was isolated in good yield. The 'pre-mix' method, originally introduced by Ireland,[16] was used to minimise the possibility of ring opening of the macrolide enolate by a retro Michael reaction **24**. Indeed, such a process did appear to occur if the enolisation was carried out at −70 °C in the absence of the trapping agent. It is unclear why the use of excess LDA was necessary; certainly, when less was used, yields of the pyrrolidine **21a** were lower. Perhaps such an excess causes rapid enolisation and thus prevents any interception of the unenolised substrate by Claisen-type condensations.[17] Within the limits of detection, using ^{13}C NMR, the pyrrolidine **21a** was a single diastereoisomer. At first sight, however, this appeared not to be so as each of the four resonances for the pyrrolidine ring carbons appeared as two separate, approximately equally sized lines. That these were due to (pseudo)rotation was confirmed by re-running the spectrum in [$^2H_6$]DMSO at 80 °C, at which temperature all resonances appeared as sharp, single lines. Further convincing evidence for this was obtained by removal of the ethoxycarbonyl protecting group using trimethylsilyl iodide.[18] An optimum set of conditions [55 °C for 5 h] for achieving this were readily found by performing the reaction in deuteriochloroform and following its progress by ^1H NMR. The resulting pyrrolidine ester **21b** was formed in essentially quantitative yield as a single isomer within the limits of detection by ^{13}C NMR. In addition, the latter spectrum showed only eight sharp resonances, indicating that rotation of the carbamate function was probably responsible for the appearance of pairs of resonances in the spectrum of pyrrolidine **21a**. Finally, because the Claisen rearrangement had proceeded smoothly, we assumed that the stereochemistry of the pyrrolidines **21** was *cis* as expected from the likely boat-like transition state involved (Scheme 2).[6] The magnitude of the coupling constants cannot be relied upon to provide definite proof of the stereochemistry in such a five-membered ring system and, in addition, the rotational effects and overlap of signals precluded NOE experiments. Good evidence for the correctness of the stereochemical assignment was obtained by exposing the initial pyrrolidine ester **21a** to a catalytic quantity of sodium methoxide. An equilibrium mixture was obtained in which the alternative, more thermodynamically stable *trans* isomer **25** was present to an extent of 94%. Both isomers were clearly distinguishable by ^1H and especially ^{13}C NMR data.



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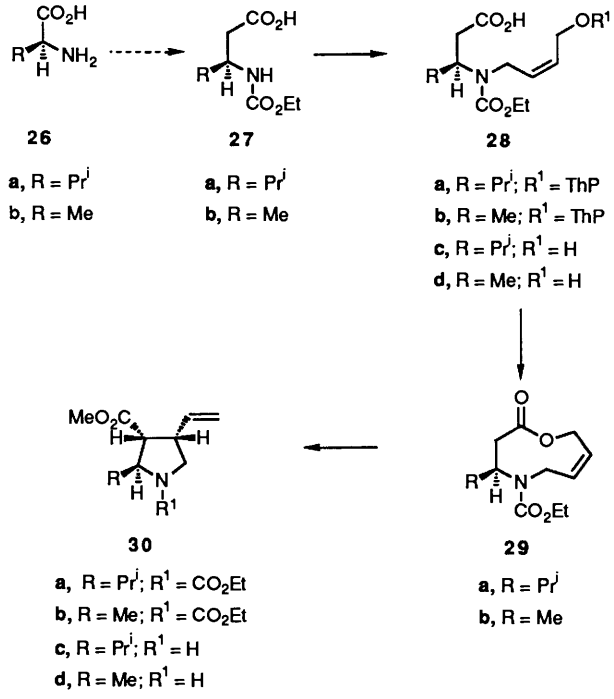
We then turned to the second aspect of these model studies and examined the feasibility of carrying through a chiral centre in the intermediate macrolides and hence effecting chiral induction at the two new asymmetric centres created during the rearrangement step (*cf.* Scheme 2). Starting with (*S*)-valine **26a**, an Arndt–Eistert procedure[19] involving a mixed anhydride intermediate led to the β-amino acid derivative **27a** (Scheme 5). Attempts to form the intermediate diazoketone *via* the acid chloride gave much lower yields. Using procedures identical to those described above, alkylation of the amino acid **27a** using the butenyl chloride **18** led to the homologue **28a** which upon deprotection gave the hydroxy acid **28c**. Subsequent lactonisation using Mukaiyama's reagent[12] then gave the key macrolide **29a** which existed in a number of conformations at ambient temperature according to the broadness of the resonances in the ^1H NMR spectrum.

Subsequent enolate Claisen rearrangement was effected using



26
a, R = Pr^i
b, R = Me

27
a, R = Pr^i
b, R = Me

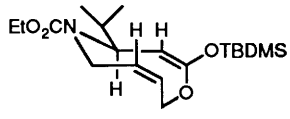
28
a, R = Pr^i; R^1 = ThP
b, R = Me; R^1 = ThP
c, R = Pr^i; R^1 = H
d, R = Me; R^1 = H

30
a, R = Pr^i; R^1 = CO_2Et
b, R = Me; R^1 = CO_2Et
c, R = Pr^i; R^1 = H
d, R = Me; R^1 = H

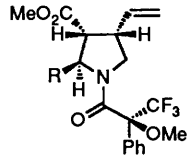
29
a, R = Pr^i
b, R = Me

Scheme 5

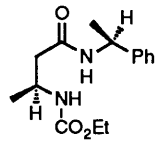
the premixing method outlined above[16] and again, the rearrangement took place on warming the reaction mixture to ambient temperature. Desilylation and esterification of the crude product gave only the pyrrolidine **30a** as a single isomer according to both ^1H and ^{13}C NMR spectra. Again, both spectra were complicated by the presence of rotamers but all signals became sharp when the spectra were obtained at 70 °C in DMSO. No other diastereoisomers were observed, indicating a diastereoselectivity of at least 97%. The stereochemistry of the final product **30a** is consistent with the involvement of the boat-like transition state **31** (*cf.* Scheme 2), in which the isopropyl



31



32
a, R = Pr^i
b, R = Me



33

substituent adopts a pseudoequatorial position. While not unambiguous in the case of a five-membered ring, the proton coupling constants displayed by pyrrolidine **30a** were consistent with the general trend that J_{cis} is usually larger than J_{trans} in such compounds.[20] Also consistent with the assigned stereochemistry is the observation that treatment of pyrrolidine **30a** with sodium methoxide failed to effect any epimerisation of the ester function, in contrast to the almost complete epimerisation of the unsubstituted homologue **21a** under the same conditions. This is presumably due to the considerable

bulk of the isopropyl group relative to the vinyl substituent and confirms the *trans* disposition of the ester and isopropyl groups and hence the overall relative stereochemistry as the vinyl and ester groups would be expected to have a *cis* disposition.[6,21] As the preparation started with pure (*S*)-valine, then the final product **30a** should also be optically pure. The only stage of the sequence where epimerisation was likely to occur was at the Arndt–Eistert step and this is said to proceed with little or no racemisation.[19] That this was the case was confirmed by desilylation of the pyrrolidine **30a** and coupling of the resulting free amine **30c** with (*R*)-Mosher's acid.[22] The resulting amide **32a** was a single diastereoisomer according to ^{1}H NMR spectra, indicating an optical purity of at least 97% for the pyrrolidine **30a**.

As an isopropyl group exerts a relatively large steric effect, the same sequence (Scheme 5) was carried through starting from (*S*)-alanine **26b**, in order to determine if the smallest possible carbon substituent was capable of applying a similar degree of stereocontrol over the rearrangement step. Arndt–Eistert homologation[19] provided the β-amino acid derivative **27b**, the optical purity of which was determined by conversion of a sample into the amide **33** using (*S*)-(−)-α-methylbenzylamine; the product was a single diastereoisomer according to ^{13}C NMR data. *N*-Alkylation then provided the homologue **28b** as before and subsequent hydrolysis to give the hydroxy acid **28d** and lactonisation led to the key macrolide **29b**. Enolate Claisen rearrangement again proceeded smoothly and gave a single isomer **30b** according to NMR spectra which were again complicated by the presence of rotamers. Epimerisation of ester **30b** as described above led to a *ca.* 1:1 mixture of the two epimers about the ester function reflecting the similar steric demands of the methyl and vinyl substituents. Again, a Mosher's amide **32b**[22] derived from the deprotected pyrrolidine **30d** was isolated as a single diastereoisomer, according to both ^{1}H and ^{19}F NMR data, indicating that the initial Claisen product **30b** had been formed with complete chiral induction. The smallest possible carbon substituent is therefore capable of completely controlling the stereochemical outcome of this type of rearrangement.

The method should therefore be widely applicable to the enantiospecific elaboration of a wide variety of trisubstituted pyrrolidines. The one drawback of this otherwise brief sequence is the generally moderate yields obtained at the lactonisation stage. Despite examining a number of alternative lactonisation procedures,[23] the Mukaiyama method[12] proved to be the best in our hands for these particular substrates. Efforts are at present underway aimed at developing alternative and more efficient approaches to the macrolides **29**.

Experimental

General Details.—M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured using an Optical Activity AA-10 polarimeter. IR spectra were recorded using a Pye-Unicam SP3-100 spectrometer for neat liquid films unless otherwise stated, with polystyrene (1601 cm^{-1}) as the standard. ^{1}H NMR spectra were determined using a Perkin-Elmer R32 spectrometer operating at 90 MHz unless otherwise stated. Other spectrometers used were Bruker WM-250 (250 MHz) and Bruker AM-400 (400 MHz) instruments. ^{13}C NMR spectra were determined using the Bruker WM-250 instrument, operating at 62.8 MHz unless otherwise stated; the Bruker AM-400 instrument operating at 100.1 MHz was also used. Dilute solutions in deuteriochloroform were used throughout unless stated otherwise, with tetramethylsilane as the internal standard. ^{19}F NMR spectra were recorded using the Bruker WM-250 spectrometer, operating at 235 MHz. All *J* values are in Hz. Molecular weights and mass spectra were measured using either an A.E.I. MS 902 or VG 7070E spectrometer. All molecular formulae quoted both for molecular ions and fragment ions are correct to within ±3 ppm.

THF was freshly distilled from sodium benzophenone ketyl. Ether and toluene were dried over sodium. Dichloromethane, dimethyl sulphoxide, dimethylformamide, and diisopropylamine were dried over calcium hydride. Pyridine and triethylamine were dried over potassium hydroxide and acetonitrile over phosphorus pentoxide. Methanol was dried using magnesium methoxide and carbon tetrachloride dried using 4 Å sieves. All of the above were distilled onto freshly activated 4 Å molecular sieves prior to use.

Light petroleum refers to the fraction of b.p. 40–60 °C. All reactions were carried out under dry nitrogen. All organic solutions from work-ups were dried by brief exposure to anhydrous magnesium sulphate. Merck No. 9385 flash silica gel was used for column chromatography throughout.

(Z)-4-*Ethoxycarbonyl*-8-(*tetrahydropyran*-2-*yloxy*)-4-*azaoct*-6-*enoic Acid* **19a**.—To a stirred solution of *N*-ethoxycarbonyl-β-alanine **17a** (2.74 g, 17 mmol) in dry THF (35 cm^3) maintained at −78 °C under nitrogen, butyllithium (23.4 cm^3 of a 1.6 mol dm^{-3} solution in hexanes; 37.4 mmol) was added dropwise. The resulting suspension was warmed to ambient temperature, then treated with dry dimethyl sulphoxide (40 cm^3) followed by the dropwise addition of (*Z*)-4-chloro-1-(tetrahydropyran-2-yloxy)-but-2-ene **18** (4.86 g, 25.5 mmol). The resulting solution was stirred at ambient temperature for 20 h, then evaporated. The residue was taken up in water (500 cm^3) and the solution washed with ether (2 × 75 cm^3) then acidified using hydrochloric acid (2 mol dm^{-3}) and extracted with ether (3 × 75 cm^3). The combined extracts were washed with water (2 × 50 cm^3) then dried and evaporated to leave the *acid* **19a** (3.65 g, 68%) as an oil, ν_{max}/cm^{-1} 3430, 1720 and 1692; δ_H 1.26 (3 H, t, *J* 7, OCH_2*Me*), 1.40–1.98 (6 H, m), 2.47–2.77 (2 H, m, CH_2CO_2H), 3.43–4.46 (10 H, m) 4.65–4.77 (1 H, m, OC*H*O), 5.42–5.94 (2 H, m, CH=CH) and 10.04 (1 H, br s, CO_2H); *m/z* 214 (23%, $C_{10}H_{16}NO_4$, M − OTHP), 213 (86, $C_{10}H_{15}NO_4$), 144 (15, $C_6H_{10}NO_3$), 102 (16, $C_4H_8NO_2$), 98 (16, $C_4H_4NO_2$), 85 (100, C_5H_9O), 84 (24, C_5H_8O) and 68 (16, C_4H_6N); (Found: M$^+$, 214.1065. $C_{10}H_{16}NO_4$ requires *M*, 214.1079).

(Z)-4-*Ethoxycarbonyl*-8-*hydroxy*-4-*azaoct*-6-*enoic Acid* **19b**.—A solution of the foregoing tetrahydropyranyl acid **19a** (3.46 g, 11 mmol) in methanol (90 cm^3) containing pyridinium toluene-*p*-sulphonate (PPTS)[11] (0.5 g, 2 mmol) was heated at reflux until TLC analysis indicated that hydrolysis of the ether function was complete (*ca.* 6 h). The solvent was evaporated and the residue partitioned between ethyl acetate (75 cm^3) and half-saturated brine (20 cm^3). The separated organic layer was washed with brine (20 cm^3) then dried and evaporated to leave the *hydroxy acid* **19b** as an oil (2.31 g, 91%), ν_{max}/cm^{-1} 3380, 1720 and 1680; δ_H 1.27 (3 H, t, *J* 7, OCH_2*Me*), 2.50–2.81 (2 H, m, CH_2CO_2H), 3.35–3.80 (3 H, m), 3.91–4.39 (6 H, m), 5.37–6.13 (2 H, m) and 7.93 (*ca.* 2 H, br s, 2 × OH); *m/z* 213 (100%, $C_{10}H_{15}NO_4$, M − H_2O), 144 (28, $C_6H_{10}NO_3$), 116 (25, $C_4H_6NO_3$), 102 (45, $C_4H_8NO_2$), 98 (34, $C_4H_4NO_2$), 82 (41, C_5H_8N), 81 (25, C_5H_7N), 68 (46, C_4H_6N), 55 (33, C_4H_7) and 42 (30, C_2H_4N); (Found: M$^+$, 213.0993. $C_{10}H_{15}NO_4$ requires *M*, 213.1001).

(Z)-4-*Ethoxycarbonyl*-4-*azaoct*-6-*en*-8-*olide* **20**.—A solution of the foregoing hydroxy acid **19b** (2.10 g, 9.1 mmol) in dry acetonitrile (10 cm^3) containing triethylamine (10.1 cm^3, 72 mmol) was added during 8 h, *via* a motor-driven syringe, to a stirred, refluxing solution of 2-chloro-1-methylpyridinium iodide[12] (9.3 g, 36.4 mmol) in dry acetonitrile (1750 cm^3) and

the resulting solution heated at reflux for a further 50 h. The cooled solution was then evaporated and the residue partitioned between water (100 cm^3) and ether (100 cm^3). The separated aqueous layer was extracted with fresh ether (2 × 100 cm^3) and the combined organic extracts washed with saturated brine then dried and evaporated. Chromatography of the residue over neutral alumina (Grade III), eluted with 10% ether in petrol gave the *azalactone* **20** (0.81 g, 42%) as an oil, ν_{max}/cm^{-1} 1738 and 1690; δ_H 1.27 (3 H, t, *J* 7, OCH_2Me), 2.74 (2 H dt, *J* 7 and 3, NCH_2CH_2), 3.65–3.85 (2 H, m, NCH_2CH_2), 3.91 (2 H, d, *J* 8, NCH_2CH), 4.19 (2 H, q, *J* 7, OCH_2Me), 4.89–5.02 (2 H, m, OCH_2CH) and 5.64–6.29 (2 H, m, CH=CH); *m/z* 213 (M^+, 100%, $C_{10}H_{15}NO_4$), 154 (33, $C_8H_{12}NO_2$), 144 (23, $C_6H_{10}NO_3$), 140 (21, $C_7H_{10}NO_2$), 102 (71, $C_4H_8NO_2$), 98 (75, $C_4H_4NO_2$), 82 (51, C_5H_8N), 81 (24, C_5H_7N) and 70 (34, C_4H_6O); (Found: C, 56.0; H, 7.5; N, 6.7; M^+, 213.0995. $C_{10}H_{15}NO_4$ requires C, 56.3; H, 7.1; N, 6.6%; *M*, 213.1001).

Methyl cis-1-*Ethoxycarbonyl*-4-*vinyl-pyrrolidine*-3-*carboxylate* **21a**.—A solution of the azalactone **20** (0.152 g, 0.704 mmol) in dry THF (2 cm^3) was added dropwise during 5 min to a stirred solution of LDA [from diisopropylamine (0.31 cm^3, 2.22 mmol) and butyllithium (1.36 cm^3 of a 1.6 mol dm^{-3} solution in hexanes; 2.11 mmol)] and TBDMSCl (0.32 g, 2.11 mmol) in dry THF maintained at −100 °C under nitrogen.[16] After 0.25 h, the solution was warmed to ambient temperature and stirred for a further 0.25 h. The solvents were then evaporated and the residue partitioned between water (10 cm^3) and ether (10 cm^3). The separated aqueous fraction was extracted with more ether (2 × 10 cm^3) and the combined organic phases washed with brine, then dried and evaporated to leave the crude silyl ester. To a stirred solution of this in THF (5 cm^3) at ambient temperature was added 40% hydrofluoric acid (0.5 cm^3). After 0.25 h, the THF was evaporated, the residue dissolved in ethyl acetate (15 cm^3) and the resulting solution extracted with aqueous sodium hydroxide (2 mol dm^{-3}; 3 × 5 cm^3). The combined alkaline extracts were washed with ethyl acetate (1 × 5 cm^3) then acidified with solid citric acid and extracted with ethyl acetate (4 × 5 cm^3). The combined extracts were dried and evaporated to leave the crude pyrrolidinecarboxylic acid which showed δ_H 1.26 (3 H, t, *J* 7, OCH_2Me), 3.01–3.36 (2 H, m, 3- and 4-H), 3.44–3.90 (4 H, m, 2- and 5-H_2), 4.17 (2 H, q, *J* 7, OCH_2Me), 5.09–5.45 (2 H, m, CH_2=CH), 5.66–6.07 (1 H, m, CH_2=CH) and 9.65 (1 H, br s, CO_2H).

To a solution of this acid in methanol (1 cm^3) and ether (4 cm^3) at 0 °C was added a slight excess of ethereal diazomethane. After 1 h, the solvents were evaporated and the residue was chromatographed over silica gel and eluted with 40% ether in light petroleum to give the *pyrrolidine ester* **21a** (0.099 g, 61%) as an oil, ν_{max}/cm^{-1} 1732 and 1698; δ_H(250 MHz; [$^2H_6$]DMSO) 1.19 (3 H, t, *J* 7.1, OCH_2Me), 3.10–3.31 (2 H, m, 3- and 4-H), 3.44–3.66 (4 H, m, 2- and 5-H_2), 3.60 (3 H, s, OMe), 4.04 (2 H, q, *J* 7.1, OCH_2Me), 5.09 (1 H, ddd, *J* 10.0, 1.6 and 0.8, CH=CH_cH_t), 5.12 (1 H, ddd, *J* 17.2, 1.6 and 1.1, CH=CH_cH_t) and 5.70 (1 H, ddd, *J* 17.2, 10.0 and 7.7, CH=CH_cH_t); δ_C 14.8 (Me), 44.1 and 45.1 (C-4) 46.7 and 47.4 (C-5), 46.9 and 47.8 (C-5), 49.8 and 50.1 (C-2), 51.7 (OMe), 61.1 (OCH_2), 117.6 ($CH=CH_2$), 134.5 ($CH=CH_2$), 155.1 (NCO) and 171.8 (C=O); δ_C([$^2H_6$]DMSO; 297 K) 14.6 (Me), 43.2 and 44.1 (C-4), 46.0 and 46.8 (C-3), 46.6 and 47.1 (C-5), 49.2 and 49.6 (C-2), 51.3 (OMe), 60.4 (OCH_2), 117.2 ($CH=CH_2$), 134.9 ($CH=CH_2$), 154.1 (NCO) and 171.6 (C=O); ([$^2H_6$]DMSO; 353 K) 14.4, 42.7, 46.7, 47.2, 49.3, 51.1, 60.2, 116.9, 134.8, 155.0 and 171.4; *m/z* 227 (M^+, 31%, $C_{11}H_{17}NO_4$), 198 (28, $C_9H_{12}NO_4$), 196 (29, $C_{10}H_{14}NO_3$), 182 (24, $C_9H_{12}NO_3$), 154 (100, $C_8H_{12}NO_2$), 141 (38, $C_8H_{13}O_2$), 138 (35, $C_8H_{10}O_2$), 126 (30, $C_7H_{10}O_2$), 115 (32, $C_5H_9NO_2$), 102 (55, $C_4H_8NO_2$) and 94 (34, C_6H_8N); (Found: C, 58.4; H, 7.2; N, 5.9; M^+, 227.1154. $C_{11}H_{17}NO_4$ requires C, 58.1; H, 7.5; N, 6.2%; *M*, 227.1157).

Methyl cis-4-*Vinylpyrrolidine*-3-*carboxylate* **21b**.—To a solution of the 1-ethoxycarbonyl pyrrolidine **21a** (0.022 g, 0.097 mmol) in deuteriochloroform (0.3 cm^3) was added trimethylsilyl iodide[18] (0.047 g, 34 mm^3; 0.24 mmol) and the resulting solution heated at 55 °C until ^1H NMR showed complete removal of the ethoxycarbonyl function; typically, this took 5 h. The cooled solution was then diluted with chloroform (10 cm^3) and washed with saturated aqueous sodium hydrogen carbonate (3 cm^3) and dilute aqueous sodium thiosulphate (3 cm^3) then dried and evaporated to leave the *pyrrolidine* **21b** (0.014 g, 93%) as an oil which was pure according to TLC and ^{13}C NMR data and which showed ν_{max}/cm^{-1} 3430, 1724, 1630 and 923; δ_H 2.15 (1 H, br s, NH), 2.80–3.52 (6 H, m), 3.68 (3 H, s, OMe), 5.01–5.32 (2 H, m, CH=CH_2) and 5.59–6.03 (1 H, m, CH=CH_2); δ_C 47.5 and 49.0 (CH), 50.0 (CH_2), 51.5 (Me), 52.1 (CH_2), 117.1 (CH=CH_2) 135.9 (CH=CH_2) and 173.7 (C=O); *m/z* 155 (M^+, 4%, $C_8H_{13}NO_2$), 126 (20, $C_7H_{10}O_2$), 124 (21, $C_7H_{10}NO$), 69 (27, C_4H_7N), 67 (38, C_5H_7) and 43 (100, C_2H_5N); (Found: M^+, 155.0937. $C_8H_{13}NO_2$ requires *M*, 155.0946).

Epimerisation of cis-*Pyrrolidine Ester* **21a**.—The *cis*-pyrrolidine ester **21a** (0.020 g, 0.088 mmol) was treated with a catalytic quantity of sodium methoxide (from sodium, *ca.* 1 mg) in methanol (5 cm^3) for 16 h at ambient temperature. After being quenched by the addition of a few drops of aqueous citric acid, the solution was evaporated and the residue partitioned between water (5 cm^3) and ether (5 cm^3). The separated aqueous layer was extracted with more ether (2 × 5 cm^3) and the combined organic solutions were washed with brine (5 cm^3) then dried and evaporated to leave an equilibrium mixture of the *cis* and *trans* pyrrolidine esters **21a** and **25** (0.019 g, 95%) in a ratio of 6:94 according to integration of the respective methyl ester resonances in the ^1H NMR spectrum. The whole sample, an oil, showed ν_{max}/cm^{-1} 1732 and 1698. The major *trans* isomer showed δ_H(250 MHz) 1.26 (3 H, t, *J* 7.1, OCH_2Me), 2.91 (1 H, br quin, *J ca.* 8.1, 3-H), 3.06 (1 H, m, 4-H), 3.21 (1 H, m, 5-H_a), 3.58 (1 H, m, 2-H_a), 3.67–3.84 (2 H, m, 2- and 5-H_b), 3.72 (3 H, s, OMe), 4.14 (2 H, q, *J* 7.1, OCH_2Me), 5.10–5.21 (2 H, m, CH=CH_2) and 5.68–5.82 (1 H, m, CH=CH_2); δ_C 14.8 (OCH_2Me), 45.5 and 46.3 (4-C), 48.2 and 49.0 (3-C), 48.3 and 48.6 (C-5), 50.3 and 50.6 (2-C), 52.1 (OMe), 61.3 (OCH_2Me), 117.2 ($CH=CH_2$), 136.1 ($CH=CH_2$), 154.9 (NCO) and 172.5 (C=O), while the whole sample showed *m/z* 227 (M^+, 21%, $C_{11}H_{17}NO_4$), 198 (32, $C_9H_{12}NO_4$), 196 (30, $C_{10}H_{14}NO_3$), 182 (25, $C_9H_{12}NO_3$), 154 (100, $C_8H_{12}NO_2$), 141 (34, $C_8H_{13}O_2$), 138 (29, $C_8H_{10}O_2$), 126 (30, $C_7H_{10}O_2$), 115 (37, $C_5H_9NO_2$), 102 (59, $C_4H_8NO_2$) and 94 (33, C_6H_8N); (Found: M^+, 227.1149. $C_{11}H_{17}NO_4$ requires *M*, 227.1157).

(R)-3-*Ethoxycarbonylamino*-4-*methylpentanoic Acid* **27a**.—To a stirred solution of *N*-ethoxycarbonyl-(*S*)-valine (14.2 g, 75 mmol) and *N*-methylmorpholine (12.8 g, 128 mmol) in dry THF (250 cm^3) maintained at −10 °C under nitrogen was added ethyl chloroformate (24.3 g, 21.4 cm^3; 225 mmol).[19] After the addition, the reaction mixture was stirred at the same temperature for 20 min, and then filtered and evaporated *in vacuo*. The residual mixed anhydride was treated with an excess of ice-cold, dry ethereal diazomethane. The resulting solution was set aside for 24 h without cooling, then evaporated. The residue was dissolved in ether (150 cm^3) and the resulting solution washed successively with saturated aqueous sodium hydrogen carbonate (30 cm^3) and water (30 cm^3) then dried and evaporated. Chromatography of the residue over silica gel eluted with 50% ether in light petroleum gave the expected *diazoketone* (10.7 g, 67%) as a

yellow oil, ν_{max}/cm^{-1} 3325, 2120 and 1725; δ_H 0.94 (3 H, d, *J* 7, CH*Me*), 1.02 (3 H, d, *J* 7, CH*Me*), 1.27 (3 H, t, *J* 7, CH_2*Me*), 1.95–2.35 (1 H, m, C*H*Me), 4.04–4.35 (1 H, m, NC*H*), 4.20 (2 H, q, *J* 7, CH_2Me), 5.46–5.74 (1 H, br d, NH) and 5.60 (1 H, s, CHN_2); *m/z* 130 (100%, $C_6H_{12}NO_2$), 98 (52, C_5H_8NO), 96 (30, $C_4H_2NO_2$), 71 (37, C_4H_7O) and 59 (54, C_2H_4NO); (Found: M^+, 130.0862. $C_6H_{12}NO_2$ requires *M*, 130.0868). The material was pure according to ^1H NMR and TLC analysis.

To a stirred solution of the foregoing diazoketone (10.5 g, 49 mmol) in dry methanol (150 cm^3) at ambient temperature was added a solution of silver benzoate (0.1 g) in triethylamine (1 cm^3). After 16 h, the mixture was filtered through a pad of Kieselguhr and the filtrate and washings were evaporated. The residue was dissolved in chloroform (150 cm^3) and the solution washed successively with saturated aqueous sodium hydrogen carbonate (30 cm^3) and brine (20 cm^3) then dried and evaporated to leave the expected *methyl ester* (10.5 g, 99%) as a colourless oil, ν_{max}/cm^{-1} 3335 and 1715; δ_H 0.94 (6 H, d, *J* 7, 2 × Me), 1.24 (3 H, t, *J* 7, CH_2*Me*), 1.60–2.06 [1 H, m, C*H*(Me)$_2$], 2.55 (2 H, d, *J* 6, CHCH_2), 3.72 (3 H, s, O*Me*), 3.82–4.08 (1 H, m, NCH), 4.16 (2 H, q, *J* 7, CH_2Me) and 5.47 (1 H, br d, *J ca.* 9, NH); *m/z* 217 (M^+, 1%, $C_{10}H_{19}NO_4$), 174 (100, $C_7H_{12}NO_4$), 144 (21, $C_7H_{14}NO_2$), 102 (22, $C_4H_8NO_2$) and 70 (22, C_3H_4NO); (Found: M^+, 217.1310. $C_{10}H_{19}NO_4$ requires *M*, 217.1314).

The foregoing ester (8.5 g) was added to a solution of potassium hydroxide (4.2 g) in methanol (100 cm^3) and the resulting solution stirred at ambient temperature for 16 h, then evaporated. A solution of the residue in water (150 cm^3) was washed with ethyl acetate (3 × 50 cm^3) then acidified using hydrochloric acid (2 mol dm^{-3}) and extracted with chloroform (3 × 50 cm^3). The combined extracts were washed with saturated brine (30 cm^3), dried and evaporated. Crystallisation of the residue from ether–light petroleum gave the *acid* **27a** (6.6 g, 83%) as a colourless solid, m.p. 70–71 °C, $[\alpha]_D$ − 35.9° (*c* 2; $CHCl_3$), ν_{max}/cm^{-1} 3327 and 1705; δ_H 0.94 (6 H, d, *J* 7, 2 × Me), 1.24 (3 H, t, *J* 7, CH_2*Me*), 1.63–2.08 [1 H, m, C*H*(Me)$_2$], 2.56 (2 H, d, *J* 6, CHCH_2), 3.67–4.01 (1 H, m, NCH), 4.16 (2 H, q, *J* 7, CH_2Me), 5.23 (1 H, br d, *J ca.* 9, NH) and 10.65 (1 H, br s, OH); *m/z* 160 (100%, $C_6H_{10}NO_4$), 144 (14, $C_7H_{14}NO_2$), 114 (18, $C_5H_8NO_2$), 133 (22, $C_5H_7NO_2$), 88 (26, $C_3H_6NO_2$), 87 (33, $C_3H_5NO_2$) and 70 (54, C_3H_4NO); (Found: C, 53.0; H, 8.6; N, 7.1. $C_9H_{17}NO_4$ requires C, 53.2; H, 8.4; N, 6.9%).

(3R,6Z)-4-*Ethoxycarbonyl*-3-*isopropyl*-8-(*tetrahydropyran*-2-*yloxy*)-4-*azaoct*-6-*enoic Acid* **28a**.—The method described above for the preparation of the lower homologue **19a** was used. Thus, treatment of the foregoing protected amino acid **27a** (3.05 g, 15 mmol) in dry THF (40 cm^3) with butyllithium (21.3 ml of a 1.55 mol dm^{-3} solution in hexane; 33 mmol), dry DMSO (10 cm^3) and the allylic chloride **18** (4.3 g, 22.5 mmol) gave the *acid* **28a** (3.5 g, 65%) as an oil, ν_{max}/cm^{-1} 3320 and 1708; δ_H 0.88–1.01 [6 H, m, CH(*Me*)$_2$], 1.24 (3 H, t, *J* 7, OCH_2*Me*), 1.39–2.12 (7 H, m), 2.47–2.82 (2 H, m, CH_2CO_2H), 3.45–4.50 (9 H, m) 4.68–4.82 (1 H, m, OCHO), 5.57–5.95 (2 H, m, CH=CH) and 10.54 (1 H, br s, CO_2H); *m/z* 255 (10%, $C_{13}H_{21}NO_4$, M − OTHP), 188 (100, $C_8H_{14}NO_4$), 133 (12, $C_4H_7NO_4$), 100 (10, $C_5H_8O_2$), 88 (81, C_3H_6NO), 85 (30, C_5H_9O) and 70 (24, C_3H_4NO); (Found: M^+ − OTHP, 255.1465. $C_{13}H_{21}NO_4$ requires *M*, 255.1471).

(3R,6Z)-4-*Ethoxycarbonyl*-8-*hydroxy*-3-*isopropyl*-4-*azaoct*-6-*enoic Acid* **28c**.—As for the preparation of hydroxy acid **19b**, treatment of the ether **28a** (3.0 g, 8.4 mmol) with PPTS[11] (0.43 g, 1.7 mmol) in methanol (70 cm^3) gave the *hydroxy acid* **28c** (2.2 g, 95%) as an oil, ν_{max}/cm^{-1} 3320 and 1705; δ_H 0.96 [6 H, d, *J* 6, CH(*Me*)$_2$], 1.25 (3 H, t, *J* 7, OCH_2*Me*), 1.65–2.15 [1 H, m, C*H*(Me)$_2$], 2.42–2.84 (2 H, m, CH_2CO_2H), 3.69–4.43 (7 H, m), 5.44–6.02 (2 H, m, CH=CH) and 9.97 (*ca.* 2 H, br s, 2 × OH); *m/z* 188 (65%, $C_8H_{14}NO_4$), 160 (9, $C_6H_{10}NO_4$), 116 (10, $C_5H_{10}NO_2$), 88 (100, $C_3H_6NO_2$), 79 (37, C_5H_5N) and 70 (38, C_3H_4NO) (Found: M^+, 188.0934. $C_8H_{14}NO_4$ requires *M*, 188.0923).

(3R,6Z)-4-*Ethoxycarbonyl*-3-*isopropyl*-4-*azaoct*-6-*en*-8-*olide* **29a**.—Treatment of the foregoing hydroxy acid **28c** (1.9 g, 6.9 mmol) with 2-chloro-1-methylpyridinium iodide (7.2 g, 28 mmol) and dry triethylamine (7.9 cm^3, 56 mmol) in refluxing acetonitrile (1500 cm^3) for 50 h as outlined above in the preparation of lactone **20**, gave the *azalactone* **29a** (0.828 g, 46%) as an oil, $[\alpha]_D$ − 38.3° (*c* 1.8; $CHCl_3$), ν_{max}/cm^{-1} 1747 and 1690; δ_H 0.82–1.04 [6 H, m, CH(*Me*)$_2$], 1.12–1.39 (3 H, m, OCH$_2$*Me*), 1.41–1.83 [1 H, m, C*H*(Me)$_2$], 2.43–3.02 (2 H, m, CH_2CO), 3.05–3.71 (2 H, m, NCH_2CH_2), 3.86–4.28 (3 H, m, CH_2Me and NC*H*), 4.37–5.31 (2 H, m, OCH_2CH) and 5.37–6.07 (2 H, m, CH=CH); *m/z* 255 (M^+, 14%, $C_{13}H_{21}NO_4$), 212 (100, $C_{10}H_{14}NO_4$), 202 (18, $C_9H_{16}NO_4$), 170 (34, $C_8H_{12}NO_3$), 116 (13, $C_5H_{10}NO_2$), 113 (20, $C_6H_9O_2$) and 96 (13, C_5H_6NO); (Found: C, 61.7; H, 8.6; N, 5.3; M^+, 255.1464. $C_{13}H_{21}NO_4$ requires C, 61.2; H, 8.3; N, 5.5%; *M*, 255.1470).

Methyl (2S,3R,4S)-1-*Ethoxycarbonyl*-2-*isopropyl*-4-*vinylpyrrolidine*-3-*carboxylate* **30a**.—A procedure identical to that used for the synthesis of the pyrrolidine ester **21** was employed. Thus, treatment of the foregoing macrolide **29a** (0.145 g, 0.57 mmol) with LDA (1.71 mmol) and TBDMSCl (0.26 g, 1.71 mmol) in dry THF (9 cm^3) maintained at −100 °C followed by warming to ambient temperature afforded a crude silyl ester which was desilylated using hydrofluoric acid and the resulting acid esterified with ethereal diazomethane. After column chromatography, the *pyrrolidine methyl ester* **30a** (0.078 g, 51%) was isolated as an oil, $[\alpha]_D$ + 24.5° (*c* 1.1; $CHCl_3$); ν_{max}/cm^{-1} 1733 and 1691; δ_H(250 MHz; [$^2H_6$]DMSO at 297 K; shifts relative to DMSO at δ 2.72) 1.03 [6 H, d, *J* 6.6, CH(*Me*)$_2$], 1.33–1.44 (3 H, m, CH$_2$*Me*), 2.15–2.32 [1 H, m, C*H*(Me)$_2$], 3.18–3.40 (2 H, m, 3- and 4-H), 3.57–3.74 (2 H, m, 5-H), 3.80 (3 H, s, OMe), 4.02–4.12 (1 H, m, 2-H), 4.16–4.34 (2 H, m, CH_2Me), 5.26–5.40 (2 H, m, CH=CH_2) and 5.77–5.89 (1 H, m, C*H*=CH$_2$); δ_H(250 MHz; [$^2H_6$]DMSO at 343 K; shifts relative to DMSO at δ 2.72) 1.07 [6 H, d, *J* 6.8, CH(*Me*)$_2$], 1.13 (3 H, t, *J* 7.3, OCH$_2$*Me*), 2.25 [1 H, sl br oct, *J* 6.8 Hz, C*H*(Me)$_2$], 3.24 (1 H, dd, *J* 7.3 and 3.6, 3-H), 3.36 (1 H, app quin, *J* 7.3, 4-H), 3.64 (1 H, dd, *J* 10.8 and 7.2, 5-H$_a$), 3.71 (1 H, dd, *J* 10.8 and 7.3, 5-H$_b$), 3.66 (3 H, s, OMe), 4.13 (1 H, dd, *J* 6.3 and 3.6, 2-H), 4.27 (2 H, q, *J* 7.3, OCH_2Me), 5.29 (1 H, dt, *J* 10.4 and 1.0, CH=CH_cH$_t$), 5.35 (1 H, dt, *J* 17.1 and 1.0, CH=CH$_c$*H*$_t$) and 5.87 (1 H, ddd, C*H*=CH$_c$H$_t$); δ_C(297 K) 14.7, 17.4, 19.2 (all Me), 30.7 and 31.2 (CH), 44.1 and 44.6 (CH), 48.8 and 49.9 (CH), 50.8 and 51.2 (CH_2), 51.7 (OMe), 61.1 (OCH_2), 64.4 and 65.8 (CH), 117.6 (CH=*C*H_2), 135.0 (*C*H=CH$_2$), 155.9 (NCO) and 172.7 (C=O); δ_C(343 K in [$^2H_6$]DMSO; ref TMS) 14.5, 17.5, 18.9 (all Me), 30.7 (CH), 43.4 (CH), 49.0 (CH), 50.6 (CH_2), 51.3 (OMe), 60.4 (OCH_2), 65.0 (CH), 117.1 (CH=*C*H_2), 135.3 (*C*H=CH$_2$), 155.0 (NCO) and 172.2 (C=O); *m/z* 269 (M^+, 5%, $C_{14}H_{23}NO_4$), 254 (25, $C_{13}H_{20}NO_4$), 227 (11, $C_{11}H_{17}NO_4$), 226 (100, $C_{11}H_{16}NO_4$), 154 (32, $C_8H_{12}NO_2$) and 127 (13, $C_7H_{11}O_2$); (Found: C, 62.3; H, 8.7; N, 5.2; M^+, 269.1617. $C_{14}H_{23}NO_4$ requires C, 62.4; H, 8.6; N, 5.2%; *M*, 269.1627).

Methyl (2S,3R,4S)-2-*Isopropyl*-4-*vinylpyrrolidine*-3-*carboxylate* **30c**.—Treatment of the ester **30a** (0.023 g, 0.085 mmol) with trimethylsilyl iodide (0.042 g, 0.21 mmol) in chloroform (0.4 cm^3) at 55 °C for 5 h, as described above for the preparation of pyrrolidine **21b**, led to the deprotected *pyrrolidine* **30c** (0.014 g, 84%), as an oil, ν_{max}/cm^{-1} 3350 and 1733; δ_H 0.90 (3 H, d, *J* 7, CH*Me*), 0.98 (3 H, d, *J* 7, CH*Me*), 1.41–1.84 [1 H, m, CH(*Me*)$_2$],

2.16 (1 H, br s, NH), 2.73–3.41 (5 H, m), 3.69 (3 H, s, OMe), 5.00–5.29 (2 H, m, CH=CH_2) and 5.57–6.04 (1 H, m, CH=CH$_2$); *m/z* 197 (M$^+$, 0.5%, $C_{11}H_{19}NO_2$), 166 (6, $C_{10}H_{16}NO$), 154 (100, $C_8H_{12}NO_2$), 94 (12, C_6H_8N), 70 (10, C_4H_8N), (6, C_4H_6N), 67 (8, C_5H_7) and 64 (9); (Found M$^+$, 197.1423. $C_{11}H_{19}NO_2$ requires *M*, 197.1416).

Methyl (2S,3R,4S)-2-*Isopropyl*-1-[(R)-α-*methoxy*-α-*trifluoromethylphenylacetyl*]-4-*vinylpyrrolidine*-3-*carboxylate* **32a**.—A solution of (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid[22] (0.025 g, 0.1 mmol) in freshly distilled thionyl chloride (1 cm^3) was heated at reflux for 5 h then cooled and the excess of thionyl chloride was removed *in vacuo*. The residue in dry carbon tetrachloride (0.25 cm^3) was added to a solution of the pyrrolidine ester **30c** (0.01 g, 0.05 mmol) in dry pyridine (0.25 cm^3) and the mixture left at ambient temperature for 20 h, after which period TLC analysis indicated that reaction was complete. The reaction mixture was taken up in water (1 cm^3) and ether (15 cm^3) and the separated ether solution washed successively with hydrochloric acid (5 cm^3; 2 mol dm^{-3}), saturated aqueous sodium carbonate (5 cm^3) and water (5 cm^3). The dried ether solution was then evaporated and the residue chromatographed over silica gel eluted with 50% light petroleum in chloroform to give the *amide* **32a** (0.02 g, 96%) as a colourless solid, m.p. 119–120 °C, ν_{max}/cm^{-1} 1737 and 1650; δ_H(400 MHz) 0.87 (3 H, d, *J* 6.9, CH*Me*), 0.91 (3 H, d, *J* 6.9, CH*Me*), 2.62 [1 H, app dquin, *J* 6.0 and 4.5, C*H*(Me)$_2$], 2.83–2.91 (1 H, m, 4-H), 2.94 (1 H, dd, *J* 7.4 and 5.4, 3-H), 3.05 (1 H, dd, *J* 11.6 and 5.1, 5-H$_a$), 3.44 (1 H, dd, *J* 11.6 and 6.5, 5-H$_b$), 3.58 (3 H, s, OMe), 3.71–3.73 (3 H, m, OMe), 4.61 (1 H, dd, *J* 5.4 and 4.5, 2-H), 4.70 (1 H, ddd, *J* 10.2, 1.2 and 0.3, CH=CH_cH$_t$), 4.74 (1 H, ddd, *J* 17.0, 0.8 and 0.6, CH=CH$_c$*H*$_t$), 5.08 (1 H, ddd, *J* 17.0, 10.2 and 8.7, C*H*=CH$_c$H$_t$) and 7.27–7.60 (5 H, m, Ph); *m/z* 224 [8%, $C_{12}H_{18}NO_3$, M − C(OMe)(CF$_3$)Ph] 210 (76, $C_{11}H_{16}NO_3$), 189 (100, $C_9H_8F_3O$), 164 (7, $C_{10}H_{14}NO$), 154 (6, $C_8H_{12}NO$) and 105 (14, C_7H_5O); [Found: M$^+$ − C(OMe)(CF$_3$)Ph, 224.1277. $C_{12}H_{18}NO_3$ requires *M*, 224.1286].

Examination of the remaining column fractions showed that no other isomers were present.

(S)-3-(*Ethoxycarbonylamino*)*butanoic Acid* **27b**.—*N*-Ethoxycarbonyl-(*S*)-alanine **26b** was homologated to the acid **27b** using the Arndt–Eistert procedure,[19] as described above for the preparation of the acid **27a** from (*S*)-valine on a similar scale and with similar yields. The intermediate diazoketone showed ν_{max}/cm^{-1} 3330, 2120 and 1710; δ_H 1.24 (3 H, t, *J* 7, CH$_2$*Me*), 1.42 (3 H, d, *J* 7, CH*Me*), 4.12 (2 H, q, *J* 7, CH_2Me), 4.20–4.56 (1 H, m, NC*H*), 5.63 (1 H, s, CHN$_2$) and 5.72 (1 H, br s, NH); *m/z* 157 (6%, $C_7H_{11}NO_3$, M − N$_2$), 140 (12, $C_5H_6N_3O_2$), 116 (100, $C_5H_{10}NO_2$), 88 (10, $C_3H_6NO_2$) and 70 (24, C_3H_4NO). (Found: M$^+$, 157.0730. $C_7H_{11}NO_3$ requires *M*, 157.0739). The material was pure according to ^{1}H NMR and TLC analysis. Wolff rearrangement gave the expected *methyl ester*, a colourless oil, ν_{max}/cm^{-1} 3330 and 1715; δ_H(250 MHz) 1.25 (3 H, t, *J* 7.2, CH$_2$*Me*), 1.41 (3 H, d, CH*Me*), 2.53 (2 H, d, *J* 5.4, CHCH_2), 3.69 (3 H, s, O*Me*), 4.04–4.17 (1 H, m, NCH), 4.10 (2 H, q, *J* 7.2, CH_2CH$_3$) and 5.22 (1 H, br d, *J* 9.4, NH); *m/z* 189 (M$^+$, 1%, $C_8H_{15}NO_4$), 174 (6, $C_7H_{12}NO_4$), 129 (8, $C_6H_{11}NO_2$), 116 (100, $C_5H_{10}NO_2$), 102 (16, $C_4H_8NO_2$) and 70 (22, C_3H_4NO). (Found: M$^+$, 189.0984. $C_8H_{15}NO_4$ requires *M*, 189.1001). Saponification then gave the *acid* **27b** as an oil which resisted attempted crystallisation and which showed $[\alpha]_D$ − 19.2° (*c* 2, CHCl$_3$), ν_{max}/cm^{-1} 3330 and 1700; δ_H 1.26 (3 H, t, *J* 7, CH$_2$*Me*), 1.28 (3 H, d, *J* 7, CH*Me*), 2.58 (2 H, d, *J* 6, CHCH_2), 4.19 (2 H, q, *J* 7, CH_2Me), 4.20–4.67 (1 H, m, NCH) and 5.72 (1 H, br s, NH); *m/z* 160 (12%, $C_6H_{10}NO_4$), 116 (94, $C_5H_{10}NO_2$), 102 (30, $C_4H_8NO_2$), 88 (21, $C_3H_6NO_2$), 83 (15, C_4H_5NO) and 70 (100, C_3H_4NO); (Found: M, 160.0607. $C_6H_{10}NO_4$ requires *M*, 160.0610).

(S)-3-*Ethoxycarbonylamino*-N-[(S)-α-*methylbenzyl*]*butanamide* **33**.—To a stirred solution of (*S*)-3-(ethoxycarbonylamino)butanoic acid **27b** (0.045 g, 0.26 mmol) and (*S*)-(−)-α-methylbenzylamine (0.063 g, 0.52 mmol) in dry dichloromethane (1 cm^3) maintained at 0 °C was added *N*,*N*-dicyclohexylcarbodiimide (0.062 g, 0.3 mmol) and 4-dimethylaminopyridine (0.037 g, 0.3 mmol). The reaction mixture was stirred at 0 °C for 0.5 h then at ambient temperature for 16 h. The precipitate was removed by filtration and the filtrates and dichloromethane washings were concentrated under reduced pressure. The residue was dissolved in ether (40 cm^3) and the solution washed successively with hydrochloric acid (15 cm^3; 1 mol dm^{-3}), dilute aqueous sodium hydrogen carbonate (2 × 5 cm^3) and water (5 cm^3), then dried and evaporated. The crude product was purified by chromatography on silica gel eluted with 50% light petroleum in chloroform to give the *amide* **33** (0.068 g, 94%) as a colourless solid, m.p. 159–161 °C, ν_{max}(CHCl$_3$)/cm^{-1} 3434, 3305, 1695 and 1653; δ_H 1.20 (3 H, d, *J* 7, PhCH*Me*), 1.21 (3 H, t, *J* 7, CH$_2$*Me*), 1.45 (3 H, d, *J* 7, CH$_2$CH*Me*), 2.40 (2 H, d, *J* 6, CHCH_2), 3.89–4.23 (1 H, m, C*H*CH$_2$), 4.07 (2 H, q, *J* 7, CH_2Me), 5.16 (1 H, q, *J* 7, C*H*Ph), 5.37 (1 H, br s, N*H*COCH$_2$), 6.09 (1 H, br s, N*H*CO$_2$) and 7.22–7.43 (5 H, m, Ph); δ_C 14.6, 20.6, 21.8 (all Me), 42.7 (CH$_2$), 44.6 (CH), 48.8 (CH), 60.7 (CH$_2$), 126.1 (2 × *m*-CH), 127.4 (*p*-CH), 128.7 (2 × *o*-CH), 143.2 (C), 156.2 (NCO) and 169.8 (CH$_2$CO); *m/z* 278 (M$^+$, 3%, $C_{15}H_{22}N_2O_3$), 232 (17, $C_{13}H_{16}N_2O_2$), 158 (16, $C_7H_{12}NO_3$), 120 (100, $C_8H_{10}N$), 116 (41, $C_5H_{10}NO_2$), 106 (52, C_7H_8N) and 105 (86, C_8H_9); (Found: C, 64.7; H, 7.7; N, 10.0; M$^+$, 278.1639. $C_{15}H_{22}N_2O_3$ requires C, 64.7; H, 8.0; N, 10.1%; *M*, 278.1630).

Examination of the remaining column fractions showed that no other isomers were present.

(3S,6Z)-4-*Ethoxycarbonyl*-3-*methyl*-8-(*tetrahydropyran*-2-*yloxy*)-4-*azaoct*-6-*enoic Acid* **28b**.—Using the above procedure for the preparation of acid **28a**, treatment of (*S*)-3-(ethoxycarbonylamino)butanoic acid **27b** (3.8 g, 21.7 mmol) in dry THF (60 cm^3) with butyllithium (29.8 cm^3 of a 1.6 mol dm^{-3} solution in hexanes; 47.7 mmol), dry DMSO (30 cm^3) and the allylic chloride **18** (5.0 g, 26 mmol) afforded the *ether* **28b** (3.8 g, 53%) as an oil, ν_{max}/cm^{-1} 3400 and 1700; δ_H 1.26 (3 H, t, *J* 7, OCH$_2$*Me*), 1.28 (3 H, d, *J* 7, CH*Me*), 1.40–2.04 (6 H, m), 2.35–2.93 (2 H, m, CH_2CO$_2$H), 3.47–4.53 (9 H, m) 4.66–4.82 (1 H, m, OC*H*O), 5.45–5.93 (2 H, m, CH=C*H*) and 7.01 (1 H, br s, CO$_2$H); *m/z* 227 (51%, $C_{11}H_{17}NO_4$, M − OTHP), 213 (13, $C_{10}H_{15}NO_4$), 140 (9, $C_7H_{10}NO_2$), 116 (29, $C_5H_{10}NO_2$), 102 (12, $C_4H_8NO_2$), 96 (22, $C_6H_{10}N$) and 85 (100, C_5H_9O). (Found: M$^+$ − OTHP, 227.1162. $C_{11}H_{17}NO_4$ requires *M*, 227.1158).

(3S,6Z)-4-*Ethoxycarbonyl*-8-*hydroxy*-3-*methyl*-4-*azaoct*-6-*enoic Acid* **28d**.—Treatment of the foregoing tetrahydropyranyl ether **28b** (3.65 g, 11.1 mmol) with PPTS (0.6 g, 2.2 mmol) in methanol (70 cm^3) as described for the preparation of acid **19b** gave the *hydroxy acid* **28d** (2.5 g, 92%), as an oil, ν_{max}/cm^{-1} 3400 and 1700; δ_H 1.26 (3 H, t, *J* 7, OCH$_2$*Me*), 1.28 (3 H, d, *J* 7, CH*Me*), 2.35–2.90 (2 H, m, CH_2CO$_2$H), 3.76–4.72 (2 H, m, OH and NCH), 3.92 (2 H, d, *J* 7, NCH_2), 4.16 (2 H, q, *J* 7, OCH_2Me), 4.24 (2 H, d, *J* 7, CH_2OH), 5.35–5.95 (2 H, m, CH=CH) and 7.77 (*ca.* 1 H, br s, OH); *m/z* 227 (100%, $C_{11}H_{17}NO_4$, M − H$_2$O), 213 (20, $C_{10}H_{15}NO_4$), 186 (28, $C_9H_{16}NO_3$), 158 (26, $C_7H_{12}NO_3$), 116 (93, $C_5H_{10}NO_2$), 96 (77, $C_6H_{10}N$) and 88 (48, $C_3H_6NO_2$); (Found: M − H$_2$O 227.1140. $C_{11}H_{17}NO_4$ requires *M*, 227.1157).

(3S,6Z)-4-*Ethoxycarbonyl*-3-*methyl*-4-*azaoct*-6-*en*-8-*olide* **29b**.—Treatment of the foregoing hydroxy acid **28d** (2.3 g, 9.4

mmol) with 2-chloro-1-methylpyridinium iodide (10.8 g, 42 mmol) and dry triethylamine (11.9 cm^3, 84 mmol) in refluxing acetonitrile (1700 cm^3) for 26 h, as outlined above in the preparation of lactone **20**, gave the *azalactone* **29b** (0.85 g, 40%) as an oil, $[\alpha]_D$ − 5.3° (*c* 1.0; $CHCl_3$), ν_{max}/cm^{-1} 1740 and 1685; δ_H 1.15–1.55 (6 H, m, 2 × *Me*), 2.49–3.09 (2 H, m, CH_2CO), 3.47–3.77 (2 H, m, NCH_2CH_2), 3.92–4.37 (3 H, m, CH_2Me and NC*H*), 4.59–5.25 (2 H, m, OCH_2CH) and 5.50–6.28 (2 H, m, CH=CH); *m/z* 227 (M^+, 43%, $C_{11}H_{17}NO_4$), 212 (32, $C_{10}H_{14}NO_4$), 168 (34, $C_9H_{14}NO_2$), 154 (33, $C_8H_{12}NO_2$), 116 (80, $C_5H_{10}NO_2$), 113 (100, $C_6H_9O_2$), 96 (27, $C_6H_{10}N$) and 71 (57, C_4H_7O); (Found: C, 58.1; H, 7.7; N, 6.2; M^+, 227.1140. $C_{11}H_{17}NO_4$ requires C, 58.1; H, 7.5; N, 6.2%; *M*, 227.1157).

Methyl (2S,3R,4S)-1-*Ethoxycarbonyl*-2-*methyl*-4-*vinylpyrrolidine*-3-*carboxylate* **30b**.—Following the preparation of pyrrolidine ester **21**, treatment of the foregoing macrolide **29b** (0.23 g, 1.01 mmol) with LDA (2.02 mmol) and TBDMSCl (0.31 g, 2.02 mmol) in dry THF (7 cm^3) at −100 °C followed by warming to ambient temperature, desilylation and esterification gave, after column chromatography, the *pyrrolidine methyl ester* **30b** (0.117 g, 48%) as an oil, $[\alpha]_D$ + 24.9° (*c* 2; $CHCl_3$), ν_{max}/cm^{-1} 1730 and 1690; δ_H(250 MHz) 1.27 (3 H, t, *J* 7.1, CH_2Me), 1.31 (3 H, d, *J* 7, CH*Me*), 2.74–2.86 (1 H, m, 3-H), 3.08–3.20 (1 H, m, 4-H), 3.47–3.68 (2 H, m, 5-CH_2), 3.67 (3 H, s, OMe), 4.07–4.24 (1 H, m, 2-H), 4.13 (2 H, q, *J* 7.1, CH_2Me), 5.11 (1 H, dt, *J* 10.9 and 1.0, CH=CH_cCH_t), 5.15 (1 H, dt, *J* 17.2 and 1.0, CH=CH_cCH_t) and 5.71 (1 H, m, C*H*=CH_cCH_t); δ_C(297 K) 14.8, 20.4, 21.0 (all Me), 42.9 and 43.4 (4-CH), 50.0 and 50.3 (5-CH_2), 51.7 (OMe), 54.6 and 54.9 (3-CH), 55.7 and 55.9 (2-CH), 61.0 (OCH_2), 117.7 (CH=CH_2), 134.5 (*C*H=CH_2), 155.0 (NCO) and 172.2 (C=O); *m/z* 241 (M^+, 16%, $C_{12}H_{19}NO_4$), 226 (29, $C_{11}H_{16}NO_4$), 212 (40, $C_{10}H_{14}NO_4$), 199 (39, $C_9H_{13}NO_4$), 168 (100, $C_9H_{14}NO_2$), 154 (15, $C_8H_{12}NO_2$), 127 (30, $C_7H_{11}O_2$) and 73 (18, C_3H_7NO); (Found: C, 59.9; H, 8.0; N, 6.0; M^+, 241.1312. $C_{12}H_{19}NO_4$ requires C, 59.7; H, 7.9; N, 5.8%; *M*, 241.1314).

Epimerisation of Pyrrolidine Ester **30b**.—Treatment of the ester **30b** (0.034 g, 0.14 mmol) with a catalytic quantity of sodium methoxide in methanol (1.5 cm^3) (*cf.* preparation of **21a** and **25**) gave a 1:1 mixture of the 3α and 3β epimers of **30b** (0.031 g, 91%) as an oil, ν_{max}/cm^{-1} 1735 and 1695. The 3-β epimer showed δ_H 1.27 (3 H, t, *J* 7, CH_2Me), 1.85 (3 H, d, *J* 7, CH*Me*), 2.59–2.94 (1 H, m, 3-H), 3.03–3.39 (1 H, m, 4-H), 3.51–3.90 (2 H, m, 5-CH_2), 3.75 (3 H, s, O*Me*), 4.04–4.37 (1 H, m, NC*H*), 4.18 (2 H, q, *J* 7, CH_2Me), 5.05–5.39 (2 H, m, CH=CH_2), 5.56–6.02 (1 H, C*H*=CH_2), together with resonances for the 3-α epimer **30b** (*vide supra*); *m/z* 241 (M^+, 14%, $C_{12}H_{19}NO_4$), 226 (39, $C_{11}H_{16}NO_4$), 212 (45, $C_{10}H_{14}NO_4$), 199 (11, $C_9H_{13}NO_4$), 168 (100, $C_9H_{14}NO_2$), 154 (49, $C_8H_{12}NO_2$), 127 (43, $C_7H_{11}O_2$) and 116 (61, $C_5H_{10}NO_2$); (Found: M^+, 241.1321. $C_{12}H_{19}NO_4$ requires *M*, 241.1314).

Methyl (2S,3R,4S)-2-*methyl*-4-*vinylpyrrolidine*-3-*carboxylate* **30d**.—In similar fashion to the preparation of pyrrolidine **21b**, treatment of the pyrrolidine ester **30b** (0.02 g, 0.083 mmol) with trimethylsilyl iodide (0.042 g, 0.21 mmol) in chloroform (0.4 cm^3) for 5 h at 55 °C gave the unblocked *pyrrolidine* **30d** (0.013 g, 93%) as an oil, ν_{max}/cm^{-1} 3300–2500 and 1729; δ_H 1.26 (3 H, d, *J* 7, CH*Me*), 2.59–3.83 (5 H, m, 2-, 3-, 4- and 5-H), 2.68 (1 H, s, N*H*), 3.70 (3 H, s, O*Me*), 5.02–5.31 (2 H, m, CH=CH_2) and 5.63–6.07 (1 H, m, C*H*=CH_2); *m/z* 169 (M^+, 11%, $C_9H_{15}NO_2$), 154 (19, $C_8H_{12}NO_2$), 138 (12, $C_8H_{12}NO$), 110 (5, $C_7H_{12}N$), 67 (8, C_5H_7) and 57 (100, C_3H_7N); (Found: M^+, 169.1106. $C_9H_{15}NO_2$ requires *M*, 169.1103).

Methyl (2S,3R,4S)-1-[(R)-α-*Methoxy*-α-*trifluoromethylphenylacetyl*]-2-*methyl*-4-*vinylpyrrolidine*-3-*carboxylate* **32b**.—As for the preparation of the Mosher amide of pyrrolidine **32a**, the foregoing pyrrolidine **30d** (0.01 g, 0.059 mmol) was treated with the acid chloride of (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (0.032 g, 0.12 mmol) in dry carbon tetrachloride (0.25 cm^3) and dry pyridine (0.25 cm^3) for 16 h at ambient temperature, followed by the same work-up and purification method. The *amide* **32b** (0.022 g, 97%) was isolated as an oil, ν_{max}/cm^{-1} 1732 and 1651; δ_H(400 MHz) 1.40 (3 H, d, *J* 6.3, CH*Me*), 2.74 (1 H, dd, *J* 6.8 and 5.3, 3-H), 2.86 (1 H, dd, *J* 11.4 and 5.9, 5-H_a), 2.97 (1 H, m, 4-H), 3.49 (1 H, ddd, *J* 11.5, 6.6 and 0.4, 5-H_b), 3.60 (3 H, s, CO_2Me), 3.68 (3 H, q, J_{C-F} 1.8, COMe), 4.61 (1 H, dq, *J* 6.2 and 5.8, 2-H), 4.78 (1 H, dt, *J* 17.0 and 1.2, CH=CH_cH_t), 4.81 (1 H, ddd, *J* 10.4, 1.4 and 0.8, CH=CH_cH_t), 5.20 (1 H, ddd, *J* 17.0, 10.4 and 8.4, C*H*=CH_cH_t), 7.36–7.39 (3 H, m) and 7.56–7.58 (2 H, m); δ_F − 70.66 ppm (rel. to $CFCl_3$ extn. std. at 0 ppm); *m/z* 385 (M^+, 1%, $C_{19}H_{22}F_3NO_4$), 196 [100, $C_{10}H_{14}NO_3$, M − C(OMe)(CF_3)Ph], 189 (23, $C_9H_8F_3O$), 168 (6, $C_9H_{14}NO_2$), 136 (7, $C_8H_{10}NO$), 105 (11, C_7H_5O) and 93 (17, C_7H_9); (Found: M^+, 385.1514. $C_{19}H_{22}F_3NO_4$ requires *M*, 385.1501).

No other isomers were isolated from the chromatography column.

Acknowledgements

We are very grateful to Drs. Bill Ross and Richard Baker (The Lilly Research Centre Ltd.) and Prof. J. E. Baldwin (Oxford) for their helpful advice and encouragement and to The Lilly Research Centre Ltd. and the SERC for their generous financial support under the CASE award scheme.

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Paper 0/04721J
Received 19*th October* 1990
Accepted 13*th November* 1990