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SYNTHESIS OF NONPROTEINOGENIC AMINO ACIDS PART 3:[1] CONVERSION OF GLUTAMIC ACID INTO γ,δ-UNSATURATED α-AMINO ACIDS.

JACK E. BALDWIN,* MICHAEL NORTH, ANTHONY FLINN, AND MARK G. MOLONEY

The Dyson Perrins Laboratory, University of Oxford,
South Parks Road, Oxford OX1 3QY, U.K.

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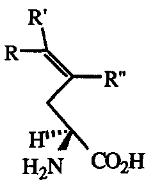
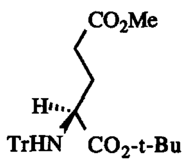
Abstract: A general procedure for the asymmetric synthesis of γ,δ-unsaturated α-amino acids (7) from the γ-anion derived from (S)-glutamic acid is described.

Many naturally occurring non-proteinogenic α-amino acids possess unsaturation within their side chains, and those having general structure (1), with a double bond between the γ and δ positions are common.[2] In addition, double bonds can be converted into many other types of functionality,[3] making the asymmetric synthesis of these amino acids of considerable value.



(1)



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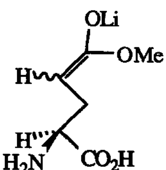


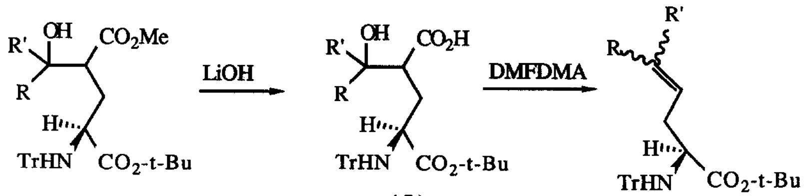
(3)

In the preceding paper,[1] we described the preparation of α-t-butyl γ-methyl N-trityl-(S)-glutamate (2), and its use in asymmetric amino acid synthesis, by deprotonation to give ester enolate (3). Thus the reaction of diester (2) with LICA followed by carbonyl compounds gave hydroxydiesters (4a-i). In this paper, the conversion of these hydroxydiesters (4) into γ,δ-unsaturated amino acids (7) is described.

Our methodology, shown in Scheme 1, involved reaction of hydroxydiesters (4) with lithium hydroxide in aqueous methanol/THF,[4] to give hydroxyacids (5) in good yield. Only in the case of acetone adduct (4c) was this reaction found to be problematic, since without THF present the reaction was very slow and gave only 17% of (5c) after 4 weeks. When THF was added to the reaction mixture, a homogeneous solution was obtained, but the only isolated product was α-t-butyl N-trityl-(S)-glutamate (8), resulting from a retro-aldol reaction. These hydroxyacids could not be purified by silica chromatography, and were used directly.

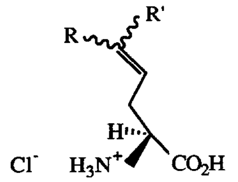
Of the various procedures for converting hydroxyacids into alkenes,[5,6,7] the most promising appeared to be reaction with triphenylphosphine and diethyl azodicarboxylate.[5] Although this reaction was reported to be stereospecific, and to occur under mild conditions, when hydroxyacid (5a) was treated with these reagents, none of the desired reaction occurred, and only starting material was recovered.

An alternative procedure[6] involves reaction of the hydroxyacid with benzenesulphonyl chloride and pyridine to give a β-lactone, followed by heating to give the alkene. Again this process was reported to be stereospecific. Treatment of hydroxyacid (5a) with benzene-



(4) (5) (6)

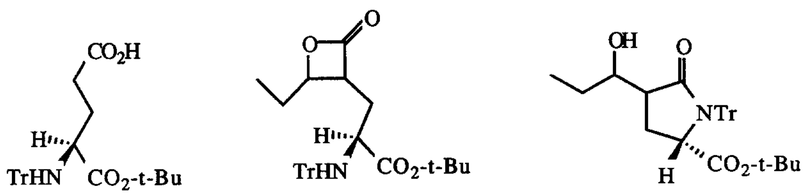
SCHEME 1



(7)

a	R = Et	R' = H
b	R = Ph	R' = H
c	R = Me	R' = Me
d	R = ^{i}Pr	R' = H
e	R = p-O_2N-C_6H_4	R' = H
f	R = H	R' = H
g	R = ^{n}Pr	R' = H
h	R = Me	R' = H
i	R = p-MeO-C_6H_4	R' = H

sulphonyl chloride and pyridine gave a product, the ^1H and ^{13}C nmr and mass spectrum of which were consistent with the required β-lactone (9). However, the structure was assigned as pyroglutamate derivative (10), since the i.r. spectrum showed no β-lactone carbonyl stretch (1810-1840 cm^{-1}), and heating to 140°C gave no olefinic products.



(8) (9) (10)

A third procedure for converting hydroxyacids into alkenes is heating with dimethyl formamide dimethyl acetal (DMFDMA),[7] which has been shown[8-9] not to be stereospecific. When hydroxyacid (5a) was treated with DMFDMA at 100°C in toluene, alkene (6a) was formed in 60% yield, as a mixture of (E)- and (Z)-isomers. The results obtained when this reaction was extended to other hydroxyacids are shown in Table 1. These results provide support for Mulzer's proposed mechanisms for this reaction[9] for the following reasons. Firstly, comparison of the diastereomeric ratio of the hydroxyacids (5) and the isomer ratio of the alkenes (6) show that the reaction cannot be stereospecific. This is particularly clear in the case of (5i) where a single diastereomer of the hydroxyacid gave both (E)- and (Z)-alkenes. Also, the two diastereomers of hydroxyester (4b) were separated by HPLC as previously described.[1] Each diastereomer of (4b) was saponified without epimerisation of any chiral centre as detected by ^1H nmr, and subjected to the elimination conditions. In both cases the same ratio of (E)- and (Z)-alkenes was obtained.

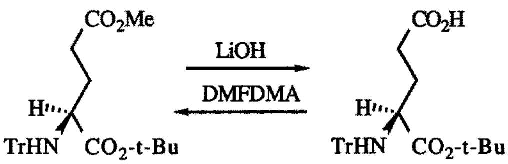
Table 1. **Formation of Alkenes (6) by treatment of hydroxyacids (5) with DMFDMA.**

HYDROXYACID	DIASTEREOMERIC RATIO	YIELD (%) of (6)	ISOMER RATIO[a]
5a	3:3:2:2	60	3:2
5b	5:2:0:0	50	11:5
5c	2:1	40	-
5d	3:3:3:2	30	1:1
5e	6:4:2:1	9	4:1
5f	3:2	0	-
5g	3:3:1:1	52	5:1
5h	6:3:3:1	38	2:1
5i	1:0:0:0	48	4:1

a. In the case of aromatic alkenes (5b,e,i), the major isomer was identified as the (E)-isomer on the basis of the ^{1}H coupling constant between the 2 vinyl protons. The isomer ratio was determined by integration of suitable peaks in the ^{1}H nmr spectrum.

Secondly, the failure of the reaction with formaldehyde adduct (5f) and the very low yield obtained with 4-nitrobenzaldehyde adduct (5e), is consistent with a cationic contribution, as proposed by Mulzer.[9]

Protected alkenes (6a-c) were deprotected with trifluoroacetic acid (TFA) to give the free amino acids (7a-c), completing a total synthesis of these amino acids, and an investigation of the optical purity of these products was made. It had previously been established that no racemisation occurred during the hydroxyalkylation.[1] To show that in principle no racemisation should occur during the saponification or elimination steps, the following procedure was adopted. Saponification of diester (2) under the conditions used for hydroxydiesters (4) gave acid (8). Treatment of acid (8) with DMFDMA under the conditions used for the elimination reactions, resulted in re-esterification,[10] giving recovered diester (2), Scheme 2. The optical rotation of recovered (2) (+ 22.5°) was identical to that recorded before the saponification.



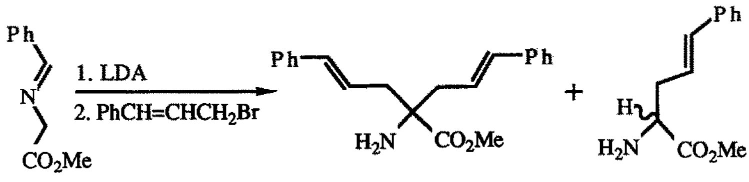
(2) (8)

SCHEME 2

This showed that in principle, no racemisation should occur, and further evidence that no racemisation occurred during the basic saponification was obtained by re-esterification of hydroxyacid (5b) with diazomethane,[11] giving hydroxydiester (4b). We had previously shown that the chiral shift reagent tris [3-(trifluoromethylhydroxymethylene)-(+)-camphorato] europium (III) [Eu(TFC)$_3$][12] would resolve both diastereomers of racemic diester (4b).[1] When the ^{1}H nmr spectrum of diester (4b) obtained by re-esterification of hydroxyacid (5b) was obtained in the presence of Eu(TFC)$_3$, there was no evidence of the presence of any (R)-isomer. The minimum enantiomeric excess was calculated as 99% based on the observed signal to noise ratio.

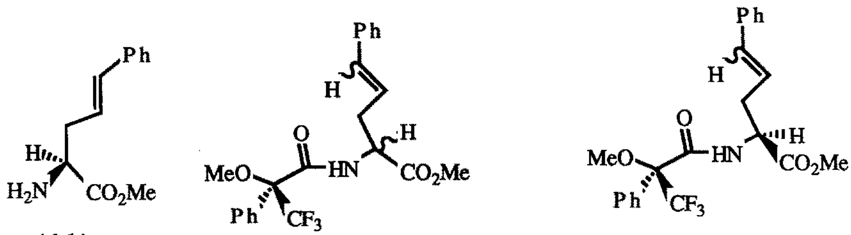
It remained to show that no racemisation occurred during the acidic deprotection. Initially it was hoped to achieve this by synthesising allylglycine (7f), and comparing its' optical rotation with that reported in the literature. However the failure of hydroxyacid (5f) to undergo elimination to protected alkene (6f) under any of the literature conditions prevented this. 2-Amino-5-methyl-(S)-4-hexenoic acid (7c) is also a known amino acid,[13] however the facile retro-aldol reaction observed in the conversion of hydroxyacid (5c) to alkene (6c) prevented the synthesis of sufficient (7c) to obtain an accurate optical rotation.

Schollkopf et al.[14] had reported that the chiral shift reagents Eu(TFC)$_3$ and Pr(TFC)$_3$ would resolve the methyl esters of a range of unsaturated amino acids, including methyl 2-amino-5-phenyl-4-pentenoate. Thus amino acid (7b) was re-esterified with methanolic hydrogen chloride, giving methyl 2-amino-5-phenyl-(S)-4-pentenoate (11). This work also required the corresponding racemic amino acid (12), which was prepared from N-benzylidene-glycine methyl ester (13).[15] Treatment of (13) with one equivalent of LDA in THF/HMPA followed by addition of cinnamyl bromide (1 eq, or excess), gave, after acidic workup, dialkylated amino acid (14) as the major product, and just 1% of the required mono-alkylated amino acid (12) (Scheme 3). Racemic amino ester (12) prepared via both routes was used in the following work.



(13) (14) (12)

SCHEME 3



(11) (16) (15)

When the ^{1}H nmr spectrum of (12) was recorded in the presence of either Eu(TFC)$_3$, or Pr(TFC)$_3$, line broadening occurred, masking any resolution of the two enantiomeric methyl esters.

Mosher et al.[16] had reported that (+) or (-)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoic acid (Mosher's acid) could be used to resolve chiral amines by formation of diastereomeric amides, which could be distinguished by ^{1}H or ^{19}F nmr, HPLC, or GC.[17] Treatment of amino esters (11) and (12) with Mosher's acid chloride,[16] gave amides (15) and (16) respectively. The ^{1}H nmr spectra of (15) and (16) were too complex to interpret, but the ^{19}F nmr spectra showed that the diastereomers were being distinguished, and that in the case of (15), the enantiomeric excess was at least 96%. This was confirmed by HPLC, which gave an enantiomeric excess of greater than 95%. It is possible that at least some of this racemisation occurs during the acidic re-esterification, and during the prolonged exposure of the amides to pyridine whilst the enantiomeric excess was determined.[18]

In conclusion, a stereospecific synthesis of γ,δ-unsaturated (S)-amino acids from (S)-glutamic acid has been achieved, and the low cost of (R)-glutamic acid should also make this a viable synthesis of unsaturated (R)-amino acids. Also, evidence in support of Mulzer's mechanism for the DMFDMA induced elimination of β-hydroxyacids has been obtained.

EXPERIMENTAL

Melting points were determined with a Buchi 510 capillary apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 Polarimeter. Ir spectra were recorded on a Perkin-Elmer 681 spectrophotometer; only selected resonances are reported, and are reported as (s) strong, (m) medium, (w) weak, or (br) broad. ^{1}H nmr spectra were recorded on a Bruker WH300 (300 MHz), AM 250 (250 MHz), or when stated AM 500 (500 MHz) spectrometer. The residual solvent peak was used as an internal standard, spectra were recorded in $CDCl_3$ unless otherwise stated, for compounds (5a-i) only selected resonances are reported. Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (dt) double triplet etc. ^{13}C nmr spectra were recorded at 62.85 MHz on a Bruker AM 250 spectrometer unless otherwise stated, using the residual solvent peak as an internal reference. For compounds (5), (6), and (10), the DEPT sequence[19] was used, but spectra are reported as if they had been recorded as off-resonance spectra. ^{19}F nmr spectra were recorded at 235.2 MHz on a Bruker AM 250 spectrometer and are externally referenced to $CFCl_3$. Mass spectra were recorded on VG analytical Ltd. ZAB1F, or MM30F mass spectrometers using the techniques of (DCI) ammonia desorption chemical impact, (FAB) positive argon fast atom bombardment, or (FD) field desorption. Microanalyses were performed by Mrs. V. Lamburn, Dyson Perrins Laboratory, University of Oxford. All solvents were distilled before use, THF was distilled over sodium/ benzophenone. Flash chromatography,[20] and dry flask chromatography[21] were performed on silica. Chiral HPLC was performed on a Waters M-6000A pump, Rheodyne 7125 injector, Pye Unicam LC3 UV detector set at 254nm, and a semi-preparative column (250 x 11mm internal diameter) packed with *N*-(3,5-dinitrobenzoyl)-(R)-phenylglycine ionically bound to a silicon polymer. A flow rate of 1 ml per minute was used.

t-Butyl 2-tritylamino-4-carboxy-5-hydroxy-(2S)-heptanoate (5a)

To diester (4a) (5.0 g, 10.0 mMol) in MeOH (200 ml) was added a saturated solution of lithium hydroxide in $MeOH/H_2O$ (9:1) (100 ml). The solution was stirred at RT for 5 days, and the MeOH evaporated *in vacuo*. The residue was acidified with aqueous citric acid and extracted with ether (3 x 100 ml). The combined organic phases were dried ($MgSO_4$) and evaporated to give (5a) as a white foam which was used without further purification. An analytical sample was obtained by flash chromatography (1:1 Et_2O/CH_2Cl_2). Yield 4.0 g (80%); (Found: C, 73.8; H, 7.3; N, 3.0. $C_{31}H_{37}NO_5$ requires: C, 74.0; H, 7.35; N, 2.8%); ν_{max} (nujol) 3370 br, 1730 m, 1600 m, and 1155 cm^{-1} s; δ_H (500 MHz) 0.9-1.0 (3H, m, CH_3CH_2), 1.22, 1.24, 1.26, and 1.30 (4 x 9H, s, $OC(CH_3)_3$), 1.4-1.6 (2H, m, $MeCH_2$), 2.5-2.7 (3H, m, CH_2CHCO_2), 3.4-3.5 (1H, m, NCH), 3.5-3.8 (1H, m, CH-O), 7.1-7.6 (15H, m, ArH); δ_C (125 MHz) (DEPT) 10.04, 10.19, 10.43, and 10.49 (4 x q, CH_3CH_2), 26.24, 26.96, 27.87, and 28.09 (4 x t, $CHCH_2CH$), 27.76, and 27.84 (2 x q, $OC(CH_3)_3$), 30.28, 32.85, 33.60, and 34.41, (4 x t, $MeCH_2$), 45.80, 46.26, 46.73, and 46.93 (4 x d, $CHCO_2H$), 55.19, 55.39, 55.40, and 55.51 (4 x d, NCH), 71.52, 71.60, 72.31, and 72.51, (4 x s, $NCPh_3$), 73.60, 73.64, 73.74, and 74.64 (4 x d , CH-O), 81.53, 81.65, 82.04, and 82.84 (4 x s, $OCMe_3$), 126.53, 126.56, 126.80, 127.76, 127.82, 127.86, 127.98, 128.10, 128.23, 128.66, 128.75, and 128.79 (12 x d, ArCH), 144.30, 144.85, 145.50, and 145.63 (4 x s, ArC), 172.94, 173.07, 173.77, 173.82, 177.60, 177.69, 177.76, and 178.20 (8 x s, CO_2); m/z (FD) 504 (MH^+), 485.

t-Butyl 2-tritylamino-4-carboxy-5-hydroxy-5-phenyl-(2S)-pentanoate (5b).

The method was as described for (5a) using diester (4b) (3.5 g, 6.0 mMol). The reaction was complete in 2 days. Acidic work up gave (5b) as a white solid which was used without further purification. Yield 2.9 g (88%); ν_{max} ($CHCl_3$) 3600-2400 br, 3060 w, 3000 m, 1728 s, 1600 w, and 1154 cm^{-1} s; δ_H 1.23, and 1.28 (2 x 9H, s, $OC(CH_3)_3$), 3.0-3.5 (1H, m, $NCHCO_2$), 4.0-4.3 (1H, m, PhCH-O), 7.0-7.6 (20H, m, ArH); δ_C (DEPT) 27.83, and 27.92 (2 x q, $OC(CH_3)_3$), 30.03, and 31.06 (2 x t, CH_2), 48.85, and 48.91 (2 x d, $CHCO_2H$), 55.63, and 57.18 (2 x d, $NCHCO_2$), 72.85, and 73.26 (2 x d, PhCH-O), 74.27, and 74.70 (2 x s, $NCPh_3$), 82.17, and 83.06 (2 x s, $OCMe_3$), 126.59, 126.93, 127.23, 127.37, 127.76, 127.90, 127.98, 128.10, 128.28, 128.61, 128.70, and 128.87 (12 x d, ArCH), 143.56, 144.61, 146.38, and 146.85 (4 x s, ArC), 172.46, 174.23, 174.36, and 179.10 (4 x s, CO_2); m/z (FD) 552 (MH^+).

t-Butyl 2-tritylamino-4-carboxy-5-hydroxy-5-methyl-(2S)-hexanoate (5c).

The method was as described for (5a) using diester (4c) (1.5 g, 3.0 mMol). The reaction mixture remained hetrogenous, and the reaction was worked up after 4 weeks. Flash chromatography (10% Et_2O/CH_2Cl_2) gave recovered diester (4c) (1.2 g, 80%) and (5c) as a white foam. Yield 250 mg (17%, 86% based on recovered starting material); (Found: C, 74.05; H, 7.4; N, 2.7. $C_{31}H_{37}NO_5$ requires: C, 74.0; H, 7.4; N, 2.8%); ν_{max} ($CHCl_3$) 3600-3300 br, 3020 w, 2980 w, 1720 s, and 1154 cm^{-1} s; δ_H 1.13, 1.19, 1.22, and 1.25 (2 x 9H + 2 x 3H, s, $OC(CH_3)_3$ + $(CH_3)_2C$), 1.7-2.1 (2H, m, CH_2), 2.2-2.6 (2H, m, $CHCO_2H$ + NH), 3.4-3.6 (2H, m, $NCHCO_2$ + OH), 7.1-7.5 (15H, m, ArH); m/z (DCI) 504 (MH^+, 2.1), 243 (100%).

t-Butyl 2-tritylamino-4-carboxy-5-hydroxy-6-methyl-(2S)-heptanoate (5d).

The method was as described for (5a) using diester (4d) (250 mg, 0.5 mMol). The reaction took 5 days and gave (5d) as a white foam. Yield 190 mg (74%); δ_H 0.8-1.1 (6H, m, $(CH_3)_2$), 1.15, 1.23, 1.25, and 1.28 (4 x 9H, s, $OC(CH_3)_3$), 7.0-7.7 (15H, m, ArH); δ_C (DEPT) 18.67, 19.36, 19.81, and 20.99 (4 x q, $(CH_3)_2CH$), 24.53, 25.33, 30.28, and 30.79 (4 x t, CH_2), 27.89 (q, $OC(CH_3)_3$), 32.31, 32.87, 33.88, and 35.20 (4 x d, Me_2CH), 42.25, 43.47, and 44.92 (3 x d, $CHCO_2H$), 54.86, 55.21, and 55.57 (3 x d, $NCHCO_2$), 71.10, 71.33, 72.28, and 73.14 (4 x s, $NCPh_3$), 77.07, 77.26, 78.35, and 79.37 (4 x d, CH-O), 81.86, 82.05, 82.17, and 82.43 (4 x s, $OCMe_3$), 126.38, 126.76, 127.23, 127.79, 127.92, 128.03, 128.80, and 130.41 (8 x d, ArCH), 145.99, 146.47, 146.90, and 147.33 (4 x s, ArC), 173.52, and 174.38 (2 x s, CO_2); m/z (FD) 517 (M^+).

t-Butyl 2-tritylamino-4-carboxy-5-hydroxy-5-(4-nitrophenyl)-(2S)-pentanoate (5e).

The method was as described for (5a) using diester (4e) (300 mg, 0.5 mMol). The reaction took 24 hours and gave (5e) as a white foam. Yield 250 mg (85%). This crude material was used immediately without further purification.

t-Butyl 2-tritylamino-4-carboxy-5-hydroxy-(2S)-pentanoate (5f).

The method was as described for (5a) using diester (4f) (500 mg, 1.0 mMol). The reaction took 24 hours and gave (5f) as a white solid, which was used without further purification Yield 450 mg (95%); (Found: C, 73.5; H, 7.0; , 2.7. $C_{29}H_{33}NO_5$ requires: C, 73.3; H, 6.9; N, 2.9%); ν_{max} (nujol) 3600-2400 br, 1725 s, 1600 s, and 1150 cm^{-1} s; δ_H 1.28, and 1.40 (2 x 9H, s, $OC(CH_3)_3$), 1.3-1.7 (2H, m, CH_2), 2.2-2.5 (1H, m, $CHCO_2H$), 3.5-3.9 (3H, m, $NCHCO_2$ + CH_2-O), 7.1-7.5 (15H, m, ArH); δ_C (DEPT) 27.86, (q, $OC(CH_3)_3$), 30.87, and 33.59 (2 x t, $CHCH_2CH$), 42.76, and 43.92 (2 x d, $CHCO_2H$), 55.63, and 55.74 (2 x d, $NCHCO_2$), 63.40, and 64.27 (2 x t, CH_2OH), 71.97, and 72.94 (2 x s, $NCPh_3$), 82.33, and 83.51 (2 x s, $OCMe_3$), 127.23, 127.91, 128.14, 128.38, 128.64, and 128.88 (6 x d, ArCH), 143.52, and 144.84 (2 x s ArC), 172.48, 173.92, 176.19, and 177.31 (4 x s, CO_2); m/z (FD) 476 (MH^+).

t-Butyl 2-tritylamino-4-carboxy-5-hydroxy-(2S)octanoate (5g).

The method was as described for (5a) using diester (4 g) (160 mg, 0.3 mMol). The reaction took 2 weeks and gave (5g) as a colourless oil, which was used without further purification. Yield 150 mg (97%); δ_H 0.8-1.0 (3H, m, $CH_3CH_2CH_2$), 1.11, 1.17, 1.24, and 1.29 (4 x 9H, s, $OC(CH_3)_3$), 1.3-1.5 (2H, m, $MeCH_2$), 3.3-3.5 (1H, m, $NCHCO_2$), 3.7-3.9 (1H, m, CH-O), 7.1-7.6 (15H, m, ArH); m/z (FD) 518 (MH^+).

t-Butyl 2-tritylamino-4-carboxy-5-hydroxy-(2S)-hexanoate (5h).

The method was as described for (5a) using diester (4h) (250 mg, 0.5 mMol). The reaction took 2 weeks and gave (5h) as a colourless oil, which was used without further purification. Yield 170 mg (70%); δ_H 1.10, 1.12, 1.23, and 1.28 (4 x 9H, s, $OC(CH_3)_3$), 1.2-1.4 (3H, m, CH_3CH-O), 7.1-7.6 (15H, m, ArH); m/z (FD) 490 (MH^+).

t-Butyl 2-tritylamino-4-carboxy-5-hydroxy-5-(4-methoxyphenyl)-(2S)-pentanoate (5i).

The method was as described for (5a) using diester (4i) (340 mg, 0.6 mMol). The reaction took 3 days and gave (5i) as a white solid, which was used without further purification. Yield 310 mg (89%); ν_{max} ($CHCl_3$) 3100 br, 3002 m, 1720 s, 1248 s, 1152 s, and 708 cm^{-1} s; δ_H 1.17 (9H, s, $OC(CH_3)_3$), 3.5-3.6 (1H, m, $NCHCO_2$), 3.76 (3H, s, $ArOCH_3$) 4.6-4.7 (1H, m, ArCH-O), 6.7-6.9 (2H, m, ArH, ortho OMe), 7.1-7.5 (17H, m, ArH); δ_C 27.69 (q, $OC(CH_3)_3$), 32.45 (t, CH_2), 48.58 (d, $CHCO_2$), 55.23 (d, $NCHCO_2$), 55.30 (q, $ArOCH_3$), 72.53 (s, $NCPh_3$), 75.21 (d, ArCH-O), 82.36 (s, $OCMe_3$) 107.94 (d, ArCH ortho OMe), 113.80 (ArCH meta OMe), 127.66, 127.88, and 128.73 (3 x d, ArCH), 133.82, 144.51, and 159.19 (3 x s, ArC), 172.63, and 177.64 (2 x s, CO_2); m/z (DCI) 599 (M + NH_4^+), 582 (MH^+), 564, 243.

t-Butyl 2-tritylamino-4-carboxy-5-hydroxy-(2S)-heptanoate γ-lactam (10).

To hydroxyacid (5a) (250 mg, 0.5 mMol) in pyridine (0.5 ml) at 0°C was added benzenesulphonyl chloride (380 mg, excess). The solution was shaken, kept at 4°C for 18 hours, and poured into water (10 ml). The products were extracted with ether, dried ($MgSO_4$), and the solvents evaporated in vacuo. Flash chromatography (CH_2Cl_2) gave (10) as a white foam. Yield 200 mg (82%); ν_{max} (nujol) 1740 (m, lactam C=O), and 1710 cm^{-1} (s, ester C=O); δ_H 0.61, 0.63, 0.82, and 0.85 (4 x 3H, t, CH_3CH_2), 1.22, 1.30, and 1.36 (3 x 9H, s, $OC(CH_3)_3$), 1.4-1.8 (2H, m, $MeCH_2$), 1.9-2.9 (2H, m, $CHCH_2CH$), 3.0-3.6 (1H, m, $CHCO_2$), 4.0-4.4 (1H, m, NCH), 4.4-5.2 (1H, m, CH-O), 7.25 (15H, s, ArH); δ_C (125 MHz) (DEPT) 7.67, 8.88, 9.65, and 10.14 (4 x q, CH_3CH_2), 22.94, 23.07, 23.80, and 25.01 (4 x t, CH_2), 25.69, 27.09, 27.35, and 27.46 (4 x t, CH_2), 27.63, 27.67, 27.70, and 27.77 (4 x q, $OC(CH_3)_3$), 43.77, 44.43, 45.36, and 45.71 (4 x d, CHCON), 60.12, 60.21, 60.40, and 60.80 (4 x d, NCH), 75.02, 75.12, 75.15, and 75.18 (4 x s, $NCPh_3$), 81.66, 81.69, 81.89, and 82.28 (4 x s, $OCMe_3$), 83.17, 83.83, 84.33, and 84.69 (4 x d, CH-O), 127.03, 127.11, 127.38, 127.42, 128.89, 128.99, 129.09, 129.17, 130.29, 130.36, 130.39, and 131.44 (12 x d, ArCH), 142.17, 142.22, and 142.35 (3 x s, ArC), 171.22, 171.48, 171.88, 172.41, 172.77, 173.00, 173.13, and 173.39 (8 x s, CO_2 + C(O)N); m/z (FD) 485 (M^+), 467.

t-Butyl 2-tritylamino(S)-4-heptenoate (6a).

To hydroxyacid (5a) (3.0 g, 6.0 mMol) in toluene (60 ml) was added DMFDMA (12.0 ml, excess). The solution was stirred at RT for 1 hour, then heated at 100°C for 18 hours. The solvent was evaporated in vacuo and the residue subjected to flash chromatography (40% hexane/ CH_2Cl_2) to give (6a) as a colourless oil. Yield 1.6 g (60%); Found: C, 81.6; H, 7.9; N, 3.2. $C_{30}H_{35}NO_2$ requires C, 81.6; H, 7.9; N, 3.2%); ν_{max} (neat) 3320 w, 3060 m, 3020 m, 2970 m, 1730 s, 1600 m, and 1150 cm^{-1} s; δ_H 1.00, and 1.01 (2 x 3H, t, CH_3CH_2), 1.18, and 1.19 (2 x 9H, s, $OC(CH_3)_3$), 1.9-2.2 (2H, m, $MeCH_2$), 2.2-2.5 (2H, m, $CHCH_2CH$), 2.71 (1H, br, NH), 3.2-3.4 (1H, m, NCH), 5.3-5.6 (2H, m, CH=CH), 7.1-7.6 (15H, m, ArH); δ_C 13.71, and 14.19 (2 x q, CH_3CH_2)

24.72, and 25.62 (2 x t, $MeCH_2$), 27.92, and 27.98 (2 x q, $OC(CH_3)_3$), 33.51, and 39.06 (2 x t, $NCHCH_2$), 56.27, and 56.44 (2 x d, NCH), 71.21 (s, $NCPh_3$), 80.19, and 80.31 (2 x s, $OCMe_3$), 123.93, and 124.14 (2 x d, C=CH), 126.26, 127.73, and 128.81 (3 x d, ArCH), 134.02, and 135.34 (2 x d, C=CH), 146.40 (s, ArC), 173.64, and 173.75 (2 x s, CO_2); m/z (FD) 441 (M^+).

t-Butyl 2-tritylamino-5-phenyl-(S)-4-pentenoate (6b).

The method was as described for alkene (6a) using (5b) (950 mg, 1.7 mMol). Flash chromatography (15% hexane/CH_2Cl_2) gave (6b) as a colourless oil. Yield 420 mg (50%); (Found: C, 83.5; H, 7.4; N, 2.6. $C_{34}H_{35}NO_2$ requires: C, 83.4; H, 7.2; N, 2.9%); ν_{max} (neat) 3310 w, 3030 m, 2980 m, 1725 s, 1598 m, and 1150 cm^{-1} s; δ_H 1.11, and 1.18 (2 x 9H, s, $OC(CH_3)_3$), 2.5-3.0 (2H, m, CH_2), 3.4-3.5 (1H, m, $NCHCO_2$), 5.76 (1H, dt, J 11.7, and 6.8 Hz , $=CHCH_2$ (Z)-isomer), 6.21 (1H, dt, J 15.8, and 7.3 Hz, $=CHCH_2$ (E)-isomer), 6.42 (1H, d, J 15.8 Hz, PhCH= (E)-isomer), 6.58 (1H, d, J 11.8 Hz, PhCH= (Z)-isomer), 7.1-7.6 (20H, m, ArH); δ_C (DEPT) 27.86, and 27.98 (2 x q, $OC(CH_3)_3$), 39.72 (t, CH_2), 56.40, and 56.73 (2 x d, $NCHCO_2$), 71.33 (s, $NCPh_3$), 80.58 (s, $OCMe_3$), 126.05, 126.13, 126.37, 126.67, 127.09, 127.82, 128.13, 128.47, and 128.86 (9 x d, ArCH + $C=CHCH_2$), 131.15, and 132.60 (2 x d, PhCH=0), 137.68, and 138.21 (2 x s, ArC), 146.32, and 146.37 (2 x s, ArC), 173.63 (s, CO_2); m/z (FD) 489 (M^+).

t-Butyl 2-tritylamino-5-methyl-(S)-4-hexenoate (6c).

The method was as described for alkene (6a) using (5c) (200 mg, 0.4 mMol). Flash chromatography (1:1 hexane/CH_2Cl_2) gave (6c) as a white oil. Yield 70 mg (40%); (Found: C, 81.8; H, 7.7; N, 3.1. $C_{30}H_{35}NO_2$ requires: C, 81.6; H. 7.9; N, 3.2%); $[\alpha]_D^{20}$ + 28.9° (c 2.14 in $CHCl_3$); ν_{max} (neat) 3315 br, 3030 w, 2980 m, 2930 m, 1730 s, 1598 w, and 1150 cm^{-1} s; δ_H 1.14 (9H, s, $OC(CH_3)_3$), 1.64, and 1.71 (2 x 3H, s, $(CH_3)_2C=$), 2.36 (2H, t, J 6.6 Hz, $CH_2CH=$), 3.29 (1H, t, J 5.9 Hz, $NCHCO_2$), 5.13 (1H, t, J 7.4 Hz, C=CH), 7.1-7.6 (15H, m, ArH); δ_C (DEPT) 18.08, and 25.97 (2 x q, $(CH_3)_2C=$), 27.96 (q, $OC(CH_3)_3$), 34.85 (t, CH_2), 56.75 (d, $NCHCO_2$), 71.31 (s, $NCPh_3$), 80.19 (s, $OCMe_3$), 120.08 (d,C=CH), 126.35, 127.83, and 128.94 (3 x d, ArCH), 133.73 (s, C=C), 146.56 (s, ArC), 174.14 (s, CO_2); m/z (FD) 441 (M^+).

t-Butyl 2-tritylamino-6-methyl-(S)-4-heptenoate (6d).

The method was as described for alkene (6a) using (5d) (115 mg, 0.22 mMol). Flash chromatography (1:1 hexane/CH_2Cl_2) gave (6d) as a colourless oil. Yield 30 mg (30%); (Found: C, 81.6; H, 8.4; N, 2.85. $C_{31}H_{37}NO_2$ requires: C, 81.8; H, 8.1; N, 3.1%); ν_{max} ($CHCl_3$) 3320 w, 3060 w, 3004 m, 2964 s, 1725 s, 1598 m, 1155 s, and 708 cm^{-1} s; δ_H 0.87 and 0.91 (2 x 6H, d, J 6.7, and 6.6 Hz, $(CH_3)_2CH$), 1.08 (9H, s, $OC(CH_3)_3$), 2.2-2.8 (4H, m, $CHMe_2$ + CH_2 + NH), 3.2-3.4 (1H, m, $NCHCO_2$), 5.1-5.6 (2H, m, CH=CH), 7.0-7.8 (15H, m, ArH); δ_C (125 MHz) (DEPT) 22.53, and 23.10 (2 x q, $(CH_3)_2CH$), 26.59 (d, Me_2CH), 27.98 (q, $OC(CH_3)_3$), 31.15, and 33.71 (2 x t, CH_2), 56.35, and 56.41 (2 x d, $NCHCO_2$), 71.24 (s, $NCPh_3$), 80.20, and 80.38 (2 x s, $OCMe_3$), 122.08, and 122.20 (2 x d,C=CH), 126.30, 127.76, and 127.87 (3 x d, ArCH), 139.87, and 141.00 (2 x s, ArC), 146.43, and 146.48 (2 x d, C=CH), 173.63, and 173.84 (2 x s, CO_2); m/z (FD) 455 (M^+).

t-Butyl 2-tritylamino-5-(4-nitrophenyl)-(S)-4-pentenoate (6e).

The method was as described for alkene (6a) using (5e) (250 mg, 0.4 mMol). Flash chromatography (20% hexane/CH_2Cl_2) gave (6e) as a colourless oil. Yield 20 mg (9%); δ_H 1.10, and 1.14 (2 x 9H, s, $OC(CH_3)_3$), 2.4-2.7 (2H, m, CH_2), 3.3-3.5 (1H, m, $NCHCO_2$), 5.9-6.1, and 6.3-6.6 (2 x 1H, m, $=CHCH_2$), 6.3-6.4 (1H, m, ArCH=C), 7.1-8.2 (19H, m, ArH); m/z (FD) 534 (M^+).

t-Butyl 2-tritylamino-(S)-4-octenoate (6g).

The method was described for alkene (6a) using (5g) (180 mg, 0.4 mMol). Flash chromatography (1:1 hexane/$CHCl_2$) gave (6g) as a colourless oil. Yield 95 mg (52%); (Found: C, 81.3; H, 8.0; N, 3.1. $C_{31}H_{37}NO_2$ requires: C, 81.8; H, 8.1; N, 3.1%); ν_{max} ($CHCl_3$) 3410 w, 2980 s, 2965 s, 1722 s, 1152 s, and 706 cm^{-1} s; δ_H 0.8-1.0 (3H, m, $CH_3CH_2CH_2$), 1.17, and 1.27 (2 x 9H, s, $OC(CH_3)_3$), 1.3-1.5 (2H, m, $MeCH_2$), 1.9-2.1, and 2.2-2.4 (2 x 2H, m, $CH_2CH=CHCH_2$), 2.68 (1H, br, NH), 3.2-3.4 (1H, m, $NCHCO_2$), 5.3-5.6 (2H, m, CH=CH), 7.1-7.6 (15H, m, ArH); δ_C (DEPT) (major diastereomer only, peaks for minor diastereomer of lower intensity than the signal to noise ratio) 13.72 (q, $CH_3CH_2CH_2$), 22.60 (t, $MeCH_2$), 28.01 (q, $OC(CH_3)_3$), 34.77, and 39.03 (2 x t, $CH_2CH=$), 56.44 (d, $NCHCO_2$), 71.25 (s, $NCPh_3$), 80.21 (s, $OCMe_3$), 125.21 (d, CH=C), 126.28, 127.76, and 128.85 (3 x d, ArCH), 133.73 (d, CH=C), 146.49 (s, ArC), 173.66 (s, CO_2); m/z (FD) 455 (M^+).

t-Butyl 2-tritylamino-(S)-4-hexenoate (6h).

The method was as described for alkene (6a) using (5h) (150 mg, 0.3 mMol). Flash chromatography (1:1 hexane/CH_2Cl_2) gave (6h) as a colourless oil. Yield 50 mg (38%); (Found: C, 81.2; H, 8.0; N, 3.1. $C_{29}H_{33}NO_2$ requires C, 81.5; H, 7.7; N, 3.3%); ν_{max} ($CHCl_3$) 3320 w, 3000 m, 2990 m, 1722 s, 1151 s, and 706 cm^{-1} s; δ_H 1.67, and 1.77 (2 x 9H, s, $OC(CH_3)_3$), 1.66, and 1.68 (2 x 3H, s, $CH_3CH=C$), 2.2-2.5 (2H, m, $CH_2CH=C$), 2.69 (1H, br, NH) 3.2-3.4 (1H, m, NCH), 5.3-5.7 (2H, m, CH=CH), 7.1-7.7 (15H, m, ArH); δ_C (125 MHz) (DEPT) 13.06, and 15.22 (2 x q, $CH_3CH=$), 27.87, and 27.94 (2 x q, $OC(CH_3)_3$), 33.23, and 39.07 (2 x t, CH_2), 56.29, and 56.44 (d, $NCHCO_2$), 71.29, and 71.31 (2 x s, $NCPh_3$), 80.19, and 80.27 (2 x s, $OCMe_3$), 126.25, 126.43, 127.73, 127.89, 128.07, and 128.80 (6 x d, ArCH), 133.92 (s, ArC), 174.51 (s, CO_2); m/z (FD) 427 (M^+).

t-Butyl 2-tritylamino-5-(4-methoxyphenyl)-(S)-4-pentenoate (6i).

The method was as described for alkene (6a) using (5i) (220 mg, 0.4 mMol). Flash chromatography (40% CH_2Cl_2/hexane) gave (6i) as a colourless oil. Yield 100 mg (48%);

(Found: C, 81.1; H, 7.05; N, 2.8. $C_{35}H_{37}NO_3$ requires C, 80.9; H, 7.1; N, 2.7%); ν_{max} ($CHCl_3$) 3001 w, 1725 m, 1510 s, 1245 s, 1152 s, and 704 cm^{-1} s; δ_H 1.11, and 1.16 (2 x 9H, s, $OC(CH_3)_3$), 2.4-2.9 (3H, m, CH_2 + NH), 3.3-3.5 (1H, m, $NCHCO_2$), 3.81, and 3.83 (2 x s, CH_3OAr), 5.66 (1H, dt, J 11.7, and 7.4 Hz, $C=CHCH_2$ (Z)-isomer), 6.05 (1H, dt, J 15.7, and 7.6 Hz, $C=CHCH_2$ (E)-isomer), 6.36 (1H, d, J 15.7 Hz, ArCH=C (E)-isomer), 6.50 (1H, d, J 11.6 Hz, ArCH=C (Z)-isomer), 6.8-7.6 (19H, m, ArH), δ_C (DEPT) 27.87, and 27.98 (2 x q, $OC(CH_3)_3$), 33.95, and 39.71 (2 x t, CH_2), 55.27 (q, OCH_3), 56.48, and 56.82 (2 x d, NCH), 71.31 (s, $NCPh_3$), 80.48 (s, $OCMe_3$), 113.62, and 113.96 (2 x d, $C=CHCH_2$), 123.79, 126.33, 127.23, 127.79, 127.93, 128.87, 130.03, 130.45, and 131.98 (9 x d, ArCH + ArCH=); 146.40, 146.93, and 158.92 (3 x s, ArC), 173.71 (s, CO_2); m/z (DCI) 520 (MH^+, 2%), 243 (100%).

2-Amino-(S)-4-heptenoic acid hydrochloride (7a)[22].

To alkene (6a) (400 mg, 1.0 mMol) in CH_2Cl_2 v(5 ml) was added 90% aqueous TFA (5 ml, excess), the yellow solution was stirred at RT for 1 hour, diluted with CH_2Cl_2, and the products extracted into 1M hydrochloric acid. The aqueous layer was thoroughly washed with CH_2Cl_2 and evaporated *in vacuo* as an azeotrope with ethanol to give (7a) as a white powder. Yield 155 mg (95%) ν_{max} (KBr) 3500-2300 br, 1730 s, 1680 m, and 1475 cm^{-1} s; δ_H (D_2O) 0.74, and 0.75 (2 x 3H, t, J 7.5 Hz, CH_3CH_2), 1.7-1.9 (2H, m, $MeCH_2$), 2.3-2.5 (2H, m, $CHCH_2CH$), 3.7-3.9 (1H, m, $NCHCO_2$), 5.0-5.2 (1H, m, CH=C), 5.4-5.6 (1H, m, CH=C); m/z (DCI) 144 (MH^+, 100%), 98 (66).

2-Amino-5-phenyl-(S)-4-pentenoic acid hydrochloride (7b)[23].

The method was as described for alkene (7a) using protected amino acid (6b) (250 mg, 0.5 mMol). Yield 110 mg (95%); δ_H (D_2O) 2.6-2.9 (2H, m, CH_2), 3.8-4.1 (1H, m, $NCHCO_2$), 5.49 (1H, dt, J 10.7, and 5.8 Hz, $C=CHCH_2$, (Z)-isomer), 6.02 (1H, dt, J 16.4, and 6.8 Hz, $C=CHCH_2$ (E)-isomer), 6.48 (1H, d, J 16.4 Hz, PhCH=C, (E)-isomer), 6.60 (1H, d, J 10.8 Hz, PhCH=C (Z)-isomer); m/z (DCI) 192 (MH^+, 100%), 148 (43).

2-Amino-5-methyl-(S)-4-hexenoic acid hydrochloride (7c)[13].

The method was as described for alkene (7a) using protected amino acid (6c) (30 mg, 0.05 mMol). Yield 6 mg (49%); δ_H (D_2O) 1.50, and 1.59 (2 x 3H, s, $(CH_3)_2C=C$), 2.4-2.6 (2H, m, CH_2), 3.8-3.9 (1H, m, $NCHCO_2$), 4.9-5.0 (1H, m, C=CH); m/z (DCI) 144 (MH^+).

α-t-Butyl γ-methyl N-trityl-(S)-glutamate (2) from α-t-butyl N-trityl-(S)-glutamate (8).

To acid (8)[1] (150 mg, 0.3 mMol) in toluene (5 ml) was added DMFDMA (0.5 ml, excess). The solution was heated at 100°C for 18 hours, the solvents were evaporated *in vacuo* and the residue subjected to flash chromatography (CH_2Cl_2), to give (2) as a white solid. Yield 50 mg (30%); $[\alpha]_D^{20}$ + 22.5° (c 7.5 in $CHCl_3$). This product was identical to an authentic sample of (2)[1] as shown by t.l.c. (CH_2Cl_2) and ^1H n.m.r. spectroscopy.

t-Butyl 2-tritylamino-4-carbomethoxy-5-hydroxy-5-phenyl-(2S)-pentanoate (4b) from t-butyl 2-tritylamino-4-carboxy-5-hydroxy-5-phenyl-(S)-pentanoate (5b).

Diazomethane dissolved in ether[11] (excess) was added to a flask containing hydroxy-acid (5b) (170 mg, 0.3 mMol) dissolved in ether (10 ml) and cooled to 0°C. The yellow solution was allowed to stand for 30 minutes at 0°C, then acetic acid was added dropwise until the yellow colour was quenched. The solvents were evaporated *in vacuo* and the residue subjected to flash chromatography (2% Et_2O/CH_2Cl_2) to give (4b) as a white foam. Yield 30 mg (16%). This product was identical to an authentic sample of (4b)[1], as shown by t.l.c. and ^1H n.m.r. spectroscopy.

Methyl 2-amino-5-phenyl-(S)-4-pentenoate (11)[14].

Amino acid (7b) (80 mg, 0.4 mMol) was added to a saturated solution of hydrogen chloride in methanol (5 ml). The solution was stirred at RT for 18 hours, the MeOH was evaporated *in vacuo*, and the residue redissolved in Et_2O and washed with saturated aqueous sodium carbonate. The organic phase was dried ($MgSO_4$), and evaporated *in vacuo* to give (11) as a colourless oil. Yield 40 mg (50%); δ_H 2.02 (2H, br, NH_2), 2.5-2.9 (2H, m, CH_2), 3.5-3.8 (1H, m, $NCHCO_2$), 3.70, and 3.78 (2 x 3H, s, OCH_3), 5.69 (1H, dt, J 11.4, and 5.9 Hz, $C=CHCH_2$ (Z)-isomer), 6.15 (1H, dt, J 16.2, and 6.5 Hz, $C=CHCH_2$, (E)-isomer), 6.52 (1H, d, J 16.2 Hz, PhCH=C, (E)-isomer), 6.61 (1H, d, J 11.4 Hz, PhCH=C, (Z)-isomer), 7.2-7.5 (5H, m, ArH); m/z (CI) 206 (MH^+).

Methyl 2-amino-5-phenyl-(RS)-(E)-4-pentenoate (11) from N-benzylidene glycine methyl ester (13).

To N-benzylidene glycine methyl ester[15] (13) (2.0 g, 11.0 mMol) in THF (10 ml) under argon at -78°C was added a solution of LDA (1,3 g, 12.1 mMol) in THF (10 ml) followed by HMPA (2 ml). The resulting red solution was stirred at -78°C for 1 hour, then cinnamyl bromide (2.3 g, 12 mMol) dissolved in THF (10 ml) was added and the solution allowed to warm to RT over a period of three hours. The THF was evaporated *in vacuo*, and the residue dissolved in Et_2O and washed with 1M hydrochloric acid. The organic phase was dried ($MgSO_4$), and the solvent evaporated *in vacuo*. The resulting oil was absorbed onto a silica column and allowed to stand for 1 hour, in order to hydrolyse the imine, and then subjected to flash chromatography (CH_2Cl_2 then Et_2O, then 5% MeOH/Et_2O) to give (E,E)-dicinnamyl-glycine methyl ester (14) (500 mg, 14%), and (11) as a colourless oil. Yield 16 mg (1%); δ_H (500 MHz) 1.79 (2H, br, NH_2), 2.5-2.6, and 2.6-2.7 (2 x 1H, m, CH_2), 3.64 (1H, dd, J 6.9, and 5.4 Hz, $NCHCO_2$), 3.76 (3H, s, OCH_3), 6.15 (1H, dt, J 15.7, and 7.5 Hz, $C=CHCH_2$), 6.50 (1H, d, J 15.7 Hz, PhCH=C), 7.2-7.4 (5H, m, ArH); m/z (CI) 206 (MH^+).

Methyl N-((R)-2-methoxy-2-phenyl-3,3,3-trifluoropropionoyl)-2-amino-5-phenyl-(S)-4-pentenoate (15).

To (S)-amino ester (11) (8 mg, 0.03 mMol) in $CDCl_3$ (0.5 ml) was added (R)-Mosher's acid chloride[16] (11 mg, 0.04 mMol) and pyridine (1 drop, excess). The resulting solution was analysed by ^{19}F nmr. The solvents were evaporated *in vacuo* and the residue analysed by chiral HPLC using a solvent system of 10% $^{i}PrOH$/hexane. The enantiomeric excess of the amino ester was found to be at least 96%; δ_F -70.96; retention time 30.5 min.

Methyl N-((R)-2-methoxy-2-phenyl-3,3,3-trifluoropropionoyl)-2-amino-5-phenyl-(RS)-4-pentenoate (16)

The method was as described for amino ester (15) using (12) (8 mg, 0.03 mMol). The product was analysed as for (15). δ_F -70.74, and -70.96; retention time 30.5 min, and 32.3 min.

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