Tetrahedron Vol. 45, No. 5, pp. 1453 to 1464, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00
Pergamon Press plc

SYNTHESIS OF NONPROTEINOGENIC AMINO ACIDS PART 2:[1] PREPARATION OF A SYNTHETIC EQUIVALENT OF THE γ ANION SYNTHON FOR ASYMMETRIC AMINO ACID SYNTHESIS

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

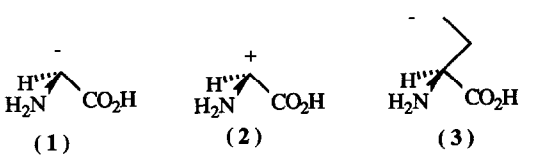
The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, OX1 3QY, U.K.

(*Received in UK* 25 *November* 1988)

Abstract: The synthesis of α-t-butyl γ-methyl N-trityl-(S)-glutamate (12) from (S)-glutamic acid (6) is described. Diester (12), on treatment with lithium isopropylcyclohexylamide followed by the addition of carbonyl compounds, reacts to give the γ-substituted glutamic acid derivatives (13a-i) with retention of optical purity at the α centre.

The α-amino acids[2] are an important group of natural products. In addition to the twenty amino acids commonly found in proteins, over 700 non-proteinogenic α-amino acids are known. Recently there has been much interest in the synthesis of both non-proteinogenic and unnatural amino acids because of their importance in biosynthesis,[3] their use as enzyme inhibitors,[4] their application to the investigation of enzyme mechanisms,[5] and their medicinal properties.[6]

The synthesis of α-amino acids is complicated both by the diverse range of side groups found in natural amino acids, and by the presence of at least one chiral centre. Early syntheses ignored the latter problem and produced racemic amino acids, which have been shown, at least in some cases, to have limited pharmaceutical application.[7] Amongst the first successful asymmetric amino acid syntheses was the asymmetric hydrogenation of prochiral dehydro-amino acids,[8] and although much used, this method suffers both from the limited range of side chains which are acceptable, and from variable enantiomeric excesses. More recently, some proteinogenic amino acids have been stereospecifically transformed into non-proteinogenic amino acids. Most work in this field has concentrated on the glycine enolate (or α-anion synthon) (1).[10,11] In particular, Schollkopf *et.al.* have developed a powerful, and general, method using the bis-lactim ether derived from valine and glycine.[11] A number of groups have also studied the α-cation synthon (2), although this method has not yet achieved the generality of the α-anion synthon.[12,13]

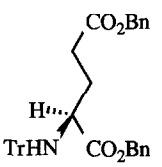


(1) (2) (3)

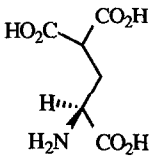
It seemed to us however that an alternative approach would be to start with a chiral amino acid and to carry out carbon-carbon bond forming reactions at a position other than the α-centre. This would mean that the chirality of the α-centre need only be preserved, not created. A number of workers have already synthesised amino acids using this methodology, but their methods were either not general or have not been widely adopted.[14]

We decided to examine the γ-anion synthon (3), since there are many naturally occurring γ-substituted α-amino acids. In this paper, the synthesis of a synthetic equivalent to the γ-anion synthon is described, and in the following paper, its use in the synthesis of γ,δ-unsaturated α-amino acids is described. Preliminary results from this work have already been published.[1]

A survey of the literature revealed one previous report of an amino acid synthesis *via* a γ-anion synthon.[15] It was reported that treatment of dibenzyl *N*-trityl-(S)-glutamate (4) with lithium di-isopropylamide (LDA), followed by benzyl chloroformate, gave after hydrogenation, γ-carboxyglutamic acid (5), the optical rotation of which was identical to that of the natural product. It appeared that the bulky trityl group, which prevented α-deprotonation, was responsible for maintaining the optical integrity at the α-centre. Rapoport *et al.* had also reported that *N*-trityl-α-amino acids were not racemised by strong bases.[16] In view of this precedent, an investigation of the use of *N*-trityl-glutamic acid derivatives for non-proteinogenic amino acid synthesis was undertaken.

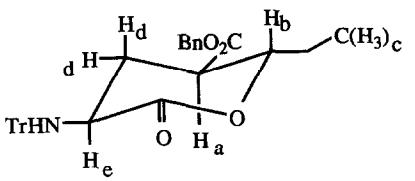


(4)



(5)

Diester (4) was synthesised from (S)-glutamic acid (6) in two steps by the literature procedure,[17] but treatment of (4) with LDA followed by a range of electrophiles (MeI, BnBr, PhCHO, EtCHO) lead only to decomposition. Only once, using propanal on the electrophile, was a 40% yield of lactone (7) obtained, as a single diastereomer by ^{1}H and ^{13}C nmr spectroscopy. The all-equatorial stereochemistry of (7) was shown by decoupling experiments (Table 1), and in particular by noting that irradiation of the multiplet at 2.5-2.7 ppm (due to H_a), caused the ddd signal at 3.78 ppm (due to H_b), to collapse to a dd in which the 9.9 Hz coupling constant had disappeared. This implied that H_a and H_b were both axial.



(7)

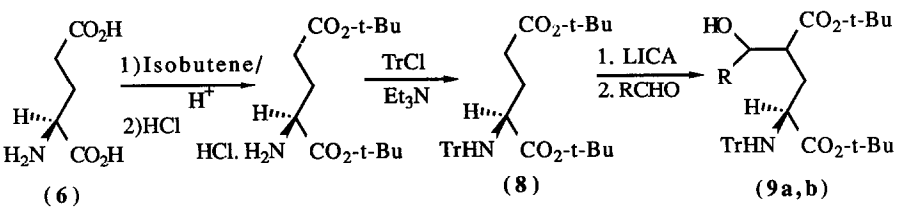
Table 1. 500 MHz Decoupling Experiments on Lactone (7)

Affect (δ_H)	1.35	1.51	1.65	2.55	3.78	4.40
Irradiate (δ_H)						
0.95 (H_c)	Y	Y	N	N	N	N
2.55 (H_a + H_d)	N	N	Y	-	Y	Y
3.78 (H_b)	Y	Y	N	Y	-	N
4.40 (H_e)	N	N	Y	Y	N	-

Y = affected, N = no effect

Lactone (7) was obviously formed by the intramolecular cyclisation of the intermediate alkoxide onto a supposedly hindered α-ester. This led us to suspect that alternative pathways involving intramolecular cyclisation may have been responsible for our inability to isolate any products from the attempted hydroxyalkylation reactions.

In an attempt to prevent intra- and inter-molecular self condensation of the Y-enolate, di-t-butyl N-trityl-(S)-glutamate (8) was synthesised from (S)-glutamic acid (6), since there was literature precedent for t-butyl esters preventing self condensation in similar systems.[18] When diester (8) was treated with LDA followed by propanal in THF, the Y-hydroxyalkylated product (9a) was indeed isolated in 20% yield as a mixture of the four possible diastereomers. In an attempt to improve the yield of this reaction lithium-isopropylcyclohexylamide (LICA), a more hindered base, which had previously been used to form ester enolates,[19] was used instead of LDA. This resulted in the yield of propanal adduct (9a) increasing to 68%. The Y-enolate of diester (8) also reacted with benzaldehyde, giving adduct (9b) in 40% yield (Scheme 1).



a R= Et

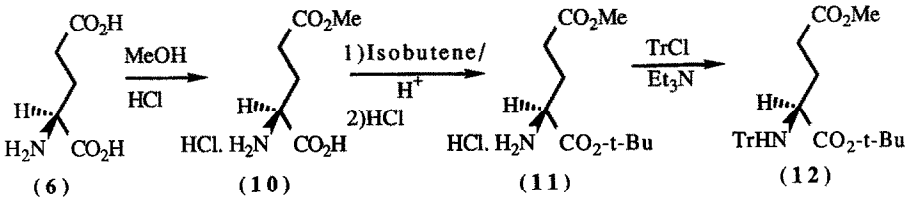
b R= Ph

SCHEME 1

Diester (8) therefore, proved to be a useful synthetic equivalent to the Y-anion and it was desired to further manipulate the hydroxyalkylated adducts (9). However, this required selective deprotection of the Y-ester, which it was anticipated would not be possible with the di-t-butyl compound (8). Hence the synthesis of α-t-butyl Y-methyl N-trityl-(S)-glutamate (12) was undertaken.

This synthesis required the selective esterification of the Y-ester of glutamic acid. A number of procedures have been developed for achieving this reaction,[20] but most appeared unattractive owing to the low yields or low selectivity obtained. However, as long ago as 1951, Coleman described a solution to this problem[21] which appears to have been universally ignored but which worked excellently in our hands. His method is reproduced within the experimental section of this paper. Treatment of (S)-glutamic acid (6) with one equivalent of HCl in methanol gave Y-methyl (S)-glutamate hydrochloride (10) in 95% yield (Scheme 2).

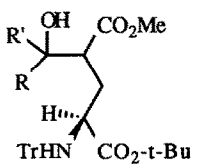
Reaction of (10) with isobutene and conc. sulphuric acid in THF gave α-t-butyl γ-methyl (S)-glutamate hydrochloride (11) in 60% yield. Diester (11) was found to have properties identical to those reported for (11) prepared via a longer route[22] and avoided the use of perchloric acid.[23] Treatment of diester (11) with trityl chloride and triethylamine gave (12) in 35% overall yield. In view of the very low cost of (S)-(or (R))-glutamic acid, and the suitability of this synthesis for large scale reactions, the yield of diester (12) was felt to be satisfactory for our needs.



SCHEME 2

When diester (12) was reacted with LICA in THF followed by propanal, γ-hydroxyalkylated product (13a) was obtained in 68% yield. When the hydroxyalkylation of (12) was extended to other carbonyl compounds, it was found that hexane was a better solvent than THF, both in terms of yield and diasterioselectivity. The results for nine carbonyl compounds (giving 13a-i) are shown in Table 2.

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



(13a-i)

The results with benzaldehyde deserve particular note, since in THF the reaction would appear to be reversible under the reaction conditions (Entries 3 and 4). On changing the solvent to hexane, there is a large increase in yield and the reaction becomes more selective since only two diastereomers are formed (Entry 5).

Attempts to react the γ-enolate of diester (12) with electrophiles other than carbonyl compounds (AcOD, D_2O, MeI, BnBr) were unsuccessful. Lack of, or incomplete deuteration of, enolates formed from nitrogen bases has previously been reported,[24] and Seebach *et al.*[25] have proposed an explanation based on selective reaction of the electrophile with the nitrogen base which is in equilibrium with the enolate.

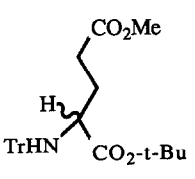
Having shown that diester (12) was a synthetic equivalent to the γ-anion synthon, it remained to show that the optical purity of the α-centre had not been compromised during the synthesis. Treatment of diester (12) with LICA in hexane followed by quenching with acetic acid gave recovered diester (12), the optical rotation of which (+22.5°) was identical to that recorded before treatment with LICA. However since this experiment did not prove that enolate formation had occurred, it was decided to show that one of the hydroxydiesters was also optically pure. This was achieved by the use of a chiral shift reagent.

TABLE 2. Reaction of (12) with LICA and carbonyl compounds.

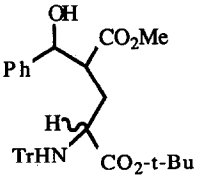
ENTRY	PRODUCT	SOLVENT	YIELD of (13) (%)	WORK UP TEMP. (g)	DIASTEREOMERIC RATIO (a)
1.	13a	THF	68	RT	3:3:2:2
2.	13a	HEXANE	70	RT	3:3:2:2
3.	13b	THF	10	RT	1:1:1:1
4.	13b	THF	10	-78°C	1:5:1:1
5.	13b	HEXANE	39	RT	5:2:0:0 (b)
6.	13c	THF	20	RT	2:1
7.	13c	HEXANE	42	RT	2:1
8.	13d	THF	25	RT	2:3:3:3
9.	13d	HEXANE	50	RT	2:3:3:3
10.	13e	HEXANE	95	RT	6:4:2:1 (c)
11.	13f (d)	THF	17 (e)	RT	1:1
12.	13f (d)	HEXANE	30 (e)	RT	3:2
13.	13g	THF	30 (e)	RT	3:3:1:1
14.	13h	THF	50	RT	6:3:3:1
15.	13i	HEXANE	32 (f)	RT	3:4:0:0

(a) Ratio determined by ^{1}H NMR. (b) Ratio of separated diastereomers. (c) The four diastereomers were separated into two sets of two by flash chromatography. (d) Gaseous formaldehyde was bubbled through a solution of the anion. (e) Recovered starting material also obtained. (f) Yield and Ratio for product whilst still slightly impure with 4-methoxybenzylalcohol; the yield is based on ^{1}H nmr analysis of the mixture. Trituration with ether removed the impurity and gave a single diastereomer of (13i) in 25% yield. (g) In each case the carbanion of (12) was formed and quenched with the carbonyl compound at -78°C.

α-t-Butyl γ-methyl N-trityl-(S)-glutamate (14) was synthesised from (RS)-glutamic acid exactly as described for the (S)-isomer (12). The benzaldehyde adducts were chosen for this work, since having only two diastereomers present simplified the nmr spectra. Hence racemic diester (14) was converted into racemic hydroxydiester (15) as described for the (S)-isomer (13b). In the absence of shift reagent, the ^{1}H nmr spectrum of (15) was identical to that of (13b). However when the chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium (III) [Eu(TFC)$_3$][26] was added, both methyl ester resonances of racemic hydroxydiester (15) split into two peaks indicating that the enantiomers were being distinguished by the shift reagent. When this experiment was repeated with hydroxydiester (13b), no splitting of the methyl esters was observed, showing that within the detection limits of 500 MHz nmr, the hydroxyalkylated products (13) were obtained without loss of optical purity at the α-centre. The minimum enantiomeric excess was calculated as 99% based on the observed signal to noise ratio.



(14)



(15)

In conclusion the synthesis of diester (12) has been achieved, and it has been shown that the Y-enolate of (12) can be formed without loss of optical purity at the α-centre. The use of diester (12) in the synthesis of non-proteinogenic α-amino acids is currently being investigated.

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 WH 300 (300 MHz), AM 250 (250 MHz), or when stated AM 500 (500 MHz) spectrometer. The residual solvent peak was used as an internal standard, and spectra were recorded in $CDCl_3$ unless otherwise stated. For compounds (13a-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 (9) and (13), the DEPT sequence[28] was used, but spectra are reported as if they had been recorded as off-resonance spectra. Mass spectra were recorded on VG Analytical Ltd., ZAB1F, or MM3OF 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, di-isopropylamine was distilled over calcium hydride and stored over 4A molecular sieves. n-BuLi was used as a solution in hexane and standardised[29] prior to use. Flash chromatography,[30] and dry flash chromatography[31] were performed on silica. Chiral HPLC was performed using a Waters M-6000A pump, Rheodyne 7125 injector, Pye Unicam LC3 UV detector set at 254 nm, and an analytical column (250 x 4.9 mm 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.

2-Tritylamino-4-benzyloxycarbonyl-5-hydroxy-(2S,4R,5S)-heptanoic acid lactone (7).

To di-isopropylamine (1.5 g, 15.0 mMol; 2.1 ml) at 0°C in THF (30 ml) under argon was added BuLi (1.5 M, 12.0 mMol; 8.0 ml). The solution was stirred at RT for 30 minutes, cooled to -78°C, and a solution of dibenzyl N-trityl-(S)-glutamate[17] (4) (5.7 g, 10.0 mMol) in THF (30 ml) was added. After stirring for 2 hours at -78°C, propanal (4.0 ml, excess) was added and the solution allowed to warm to RT over 3 hours. The THF was evaporated *in vacuo* and the product redissolved in CH_2Cl_2 and washed with saturated ammonium chloride solution. The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to give an orange oil which was subjected to flash chromatography (5% EtOAC/CH_2Cl_2) to give (7) as a white foam. Yield 2.5 g (48%); mp 65°C (decomp.); (Found: C,78.4; H,6.5; N, 2.7. $C_{34}H_{33}NO_4$ requires: C, 78.6; H, 6.4; N, 2.7%); $[\alpha]_D^{\circ}$ -72.2° (c 0.4 in $CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3450 w, 1770 s, 1680 s, 1170 s, and 700 cm^{-1} s; δ_H (500 MHz) 0.95 (3H, t, J 7.3 Hz, CH_3); 1.3 - 1.4 (1H, m, $MeCH_2$); 1.51 (1H, ddd, J 14.4, 7.5, and 2.9 Hz, $MeCH_2$); 1.6 - 1.7 (1H, m, $NCHCH_2$), 2.5 - 2.6 (3H, m, $NCHCH_2CHCO_2Bn$); 3.78 (1H, ddd, J 9.9 Hz, 7.1, and 2.9 Hz, EtCH-O); 4.35 - 4.45 (2H, m, (collapses to 1H, on addition of D_2O), NH+ NCH); 4.59, and 4.83 (2 x 1H, d, J 12.0 Hz, CH_2Ph), 7.1 - 7.7 (20H, m, ArH); δ_C 8.93 (q, CH_3), 26.75 (t, CH_2), 27.39 (t, CH_2), 46.04 (d, $CHCO_2$), 60.80 (d, NCH), 67.05 (t, CH_2Ph), 73.09 (d, CH-O), 75.30 (s, Ph_3C), 127.31, 127.55, 128.06, 128.59, 128.78, and 130.43 (6 x d, ArCH), 134.70, and 141.95 (2 x s, ArC), 172.83, and 178.28 (2 x s, CO_2); m/z (FD) 519 (M^+).

Di-t-butyl N-trityl-(S)-glutamate (8).

To di-t-butyl (S)-glutamate hydrochloride[27] (4.3 g, 14.6 mMol) in CH_2Cl_2 (40 ml) was added triethylamine (10 ml, excess) and trityl chloride (4.1 g, 14.7 mMol). The solution was stirred at RT for 18 hours, washed with saturated aqueous sodium carbonate, and water, dried ($MgSO_4$), and the solvent evaporated *in vacuo* to give an orange oil which was purified by flash chromatography (30% hexane/CH_2Cl_2) to give a white solid containing the product and trityl alcohol. The trityl alcohol was crystallised out of the mixture by dissolving the solid in the minimum amount of CH_2Cl_2 and adding hexane. After filtration, the solution was evaporated *in vacuo* to give (8) as a colourless oil. Yield 1.5 g (21%); R_f (CH_2Cl_2) 0.5. (Found: C, 76.3; H, 8.0; N, 2.7. $C_{32}H_{39}NO_4$ requires: C, 76.6; H, 7.8; N, 2.8%); $[\alpha]_D^{\circ}$ + 16.9° (c 2.5 in $CHCl_3$); $\nu_{max.}$ (neat) 3305 w, 3060 m, 2950 m, 1730 s, and 1150 cm^{-1} s; δ_H 1.17 (9H, s, α-OC(CH_3)$_3$), 1.47 (9H, s, Y-OC(CH_3)$_3$), 1.9 - 2.2 (3H, m, $CH_2CH_2CO_2$), 2.4 - 2.6 (1H, m, CH), 2.76 (1H, br, NH), 3.3 - 3.4 (1H, m, NCH), 7.1 - 7.6 (15H, m, ArH); δ_C 27.89, and 28.15 (2 x q, OC(CH_3)$_3$), 30.83, and 31.21 (2 x t, CH_2CH), 55.50 (d, NCH), 71.33 (s, Ph_3CN), 80.20, and 80.71 (2 x s, $OCMe_3$), 126.37, 127.81, and 128.85 (3 x d, ArCH), 146.27 (s, ArC), 172.69, and 173.78 (2 x s, CO_2); m/z (FD) 502 (MH^+).

t-Butyl 2-tritylamino-4-carbo-t-butyloxy-5-hydroxy-(2S)-heptanoate (9a).

To cyclohexylisopropylamine (3.0 ml, 15.0 mMol) in hexane (50 ml) at 0°C under argon was added BuLi (2.2 M, 5.0 ml, 11.0 mMol). The solution was stirred at RT for 30 minutes, cooled to -78°C and diester (8) (5.0 g, 10.0 mMol) dissolved in hexane (50 ml) was added all at once. The resulting white slurry was stirred at -78°C for 30 minutes, then propanal (5.0 ml, excess) was added. The slurry was allowed to warm to RT over 3 hours, during which time the precipitate dissolved forming a yellow solution. The solution was poured into aqueous ammonium chloride (30 ml) and the products extracted with ether (3 x 50 ml). The combined organic phases were dried ($MgSO_4$) and the solvent evaporated in vacuo. The resulting yellow oil was subjected to flash chromatography (10 % EtOAc/CH_2Cl_2) to give (9a) as a white foam. Yield 2.8 g (50%); R_f = 0.35 (Found: C, 75.2; H, 8.0; N, 2.3. $C_{35}H_{45}NO_5$ requires: C, 75.1; H, 8.05; N, 2.5%); $\nu_{max.}$ ($CHCl_3$) 3550 w, 3060 w, 2990 m, 1720 s, 1150 s, and 708 cm^{-1} m; δ_H (500 MHz) 0.9 - 1.0 (3H, m, CH_3CH_2), 1.15, 1.16, 1.19 and 1.21 (4 x 9H, s, α-$OC(CH_3)_3$), 1.34, 1.35, 1.48, and 1.49 (4 x 9H, s, γ-$OC(CH_3)_3$), 1.4 - 1.5 (2H, m, $MeCH_2$), 2.1 - 2.3 (2H, m, $CHCH_2CH$), 2.35 - 2.65 (1H, m, $CHCO_2$), 2.5 - 3.2 (1H, br, NH), 3.25 - 3.45 (1H, m, NCH), 3.5 - 3.65 (1H, m, EtCH-O), 7.1 - 7.5 (15H, m, ArH); δ_C (125 MHz) (DEPT) 9.92, 10.26, and 10.45 (3 x q, CH_3CH_2), 27.04, 27.26, 28.28, and 28.52 (4 x t, $CHCH_2CH$) 27.80, 27.85, 27.94, 27.99, 28.06, 28.13, and 28.14 (7 x 9H, s, $OC(CH_3)_3$), 32.89, 33.93, 35.23, and 35.39 (4 x t, $MeCH_2$), 46.44, 47.31, 47.72, and 48.09 (4 x d, $CHCO_2$), 54.96, 55.20, 55.28, and 55.35 (4 x d, NCH), 71.32, 71.38, 71.42, and 71.50 (4 x s, $NCPh_3$), 73.78, 74.07, 74.18, and 74.32 (4 x d, EtCH-O), 80.71 80.76, 80.85, 80.94, 81.10, 81.18, and 81.34 (7 x s, $OCMe_3$), 126.31, 126.35, 126.41, 126.61, 127.68, 127.71, 127.74, 127.79, 128.79, 128.82, 128.85, and 128.89 (12 x d, ArCH), 145.94, 146.07, 146.11, and 146.12 (4 x s, ArC), 173.77, 173.92, 173.94, 174.08, 174.17, 174.31, and 174.51 (7 x s, CO_2); m/z (DCI) 560 (MH^+, 4%), 318 (30), 243 (100%).

t-Butyl 2-tritylamino-4-carbo-t-butyloxy-5-hydroxy-5-phenyl-(2S)-pentanoate (9b).

The method was as described for (9a) using diester (8) (1.0 g, 2.0 mMol) and benzaldehyde (0.3 ml, 3.0 mMol). Flash chromatography (2% EtOAc/CH_2Cl_2) gave (9b) as a white foam. Yield 500 mg (41 %); R_f = 0.4 (Found: C, 77.15; H, 7.65; N, 2.0. $C_{39}H_{45}NO_5$ requires C, 77.1; H, 7.4; N, 2.0 %); $\nu_{max.}$ (nujol) 3400 br, 1722 s, and 1150 cm^{-1} s; δ_H 1.10, 1.15, 1.21, 1.27, 1.28, 1.33, and 1.37 (7 x 9H, s, $OC(CH_3)_3$), 1.6 - 1.9 (1H, br, NH), 2.1 - 2.4 (1H, m, CH_2), 2.8 -3.1 (2H, m, CH_2CH), 3.2 - 3.4 (1H, m, NCH), 3.53 (1H, br, OH), 4.6 - 5.0 (1H, m, PhCH-O), 7.1 - 7.7 (20H, m, ArH); δ_C (125 MHz) (DEPT) 27.71, 27.80, 27.86, 27.91, 27.96, and 28.09 (6 x q, $OC(CH_3)_3$), 33.01, 34.16, 35.21, and 35.44 (4 x t, CH_2), 48.82, 49.82, 49.77, and 50.63 (4 x d, $CHCO_2$), 54.97, 55.10, 55.22, and 55.42 (4 x d, $NCHCO_2$), 71.30, 71.43, and 71.52 (3 x s, $NCPh_3$), 74.34, 74.80, 75.28, and 75.81 (4 x d, PhCH-O), 80.68, 80.77, 80.94, 81.30, 81.34, and 81.52 (6 x s, $OCMe_3$), 126.11, 126.27, 126.32, 126.39, 126.42, 126.58, 126.68 126.99, 127.25, 127.36, 127.63, 127.70, 127.78, 127.85, 127.93, 127.96, 128.11, 128.15, 128.23, 128.26, 128.83, 128.88, 128.93, and 129.02 (23 x d, ArCH), 141.32, 141.68, 142.08, 142.32, 145.69, 146.11, 146.15, and 146.91 (8 x s, ArC), 173.59, 173.84, 173.89, 174.02, 174.08, and 174.47 (6 x s, CO_2); m/z (FD) 607 (M^+).

γ-Methyl (S)-glutamate hydrochloride (10)[21].

The following is the method of Coleman:[21] HCl gas (15.0 g, 0.41 Mol) was dissolved in redistilled (but not necessarily dry) methanol (200 ml), and (S)-glutamic acid (6) (56.0 g, 0.38 Mol) (the monohydrate salt is not adequate for this reaction) was added with vigorous stirring. As soon as all the solid dissolved (c.a. 20s), the solution was poured into ether (1500 ml) and the product allowed to crystallise at 4°C for 1 hour. The resulting white solid was filtered and dried under high vacuum. Ester (10) obtained in this way contains about 2% of the di-ester as an impurity. This can be removed by recrystallisation from ethanol, but this was not necessary for the following reactions. Yield 71.5 g (95 %); $\nu_{max.}$ (nujol) 2900 br, 1725 s, and 1605 cm^{-1} m; δ_H (DMSO-d_6) 1.9 - 2.1 (2H, m, CH_2CO_2), 2.4 - 2.6 (2H, m, $CH_2CH_2CO_2$), 3.65 (3H, s, OCH_3), 3.83 (1H, t, J 6.4 Hz, NCH), 8.52 (4H, br, NH_3 + CO_2H).

α-t-Butyl γ-methyl (S)-glutamate hydrochloride (11).

Conc. sulphuric acid (48 ml) was added dropwise to THF (150 ml) at 0°C, the solution was transferred to a pressure bottle and γ-methyl (S)-glutamate hydrochloride (10) (51.0 g, 0.26 Mol) was added followed by isobutene (90 ml, excess). The bottle was tightly stoppered and the solution stirred at RT for 18 hours. The bottle was opened and the contents poured into aqueous sodium carbonate (600 ml) and extracted with ether (3 x 300 ml). The ether layer was dried ($MgSO_4$), and concentrated in vacuo to ca 60 ml. HCl gas was bubbled through the solution and the product precipitated as a white solid. (Occasionally no precipitate formed, so the solution was evaporated in vacuo and allowed to crystallise under high vacuum.) The precipitate was filtered, and dried under vacuum to give (11) as a white solid. Yield 34.2 g (60 %); mp 130 - 131°C; $\nu_{max.}$ ($CHCl_3$) 2900 s, 1740 s, and 1730 cm^{-1} s; δ_H 1.49 (9H, s, $OC(CH_3)_3$), 2.37 (2H, t, J 7.0 Hz, CH_2CO_2), 2.5 - 2.8 (2H, m, $NCHCH_2$), 3.67 (3H, s, OCH_3), 4.12 (1H, t, J 6.2 Hz, NCH), 8.75 (3H, br, NH_3); m/z (CI) 218 (MH^+, 100%), 162 (82), 116 (43).

α-t-Butyl γ-methyl N-trityl-(S)-glutamate (12).

The method was as described for diester (8) using diester (11) (25.0 g, 115.0 mMol). Dry flash chromatography (hexane to CH_2Cl_2) gave (12) as a colourless oil. Yield 31.3 g (59%); R_f (CH_2Cl_2) 0.6 (Found: C, 75.8; H, 7.4; N, 2.8. $C_{29}H_{33}NO_4$ requires: C, 75.8; H, 7.2; N, 3.05 %); $[\alpha]_D^{\circ}$ + 22.5° (c 0.75 in $CHCl_3$); $\nu_{max.}$ (neat) 3305 w, 3030 m, 2980 m, and 1730 cm^{-1} s; δ_H 1.18 (9H, s, $OC(CH_3)_3$), 2.0 - 2.4 (3H, m, CH_2CHCO_2), 2.5 - 2.7 (1H, m, CH_2), 2.79 (1H, br, NH), 3.41 (1H, t, J 4.5 Hz, NCH), 3.72 (3H, s, OCH_3), 7.1 - 7.6 (15H, m, ArH); δ_C 27.83 (q, $OC(CH_3)_3$), 29.61 and 30.61 (2 x t, CH_2CH_2), 51.50 (q, OCH_3), 55.35 (d, NCH), 71.32 (s, $NCPh_3$), 80.77 (s, $OCMe_3$), 126.35, 127.78, and 128.77 (3 x d, ArCH), 146.14 (s, ArC), 173,57, and 173.74 (2 x s, CO_2); m/z (FD) 459 (M^+).

t-Butyl 2-tritylamino-4-carbomethoxy-5-hydroxy-(2S)-heptanoate (13a).

To cyclohexylisopropylamine (3.3 ml, 16.5 mMol) in hexane (55 ml) at 0°C was added BuLi (2.2 M, 5.5 ml, 12.1 mMol). The solution was stirred at RT for 30 minutes, cooled to -78°C and diester (12) (5.0g, 11.0 mMol) dissolved in hexane (55 ml) was added all at once. The resulting white slurry was stirred at -78°C for 30 minutes, then propanal (4.0 ml, excess) was added. The slurry was allowed to warm to RT over 3 hours, during which time the precipitate dissolved forming a yellow solution. The solution was poured into aqueous ammonium chloride (250 ml) and the products extracted with ether (3 x 250 ml). The combined organic phases were dried ($MgSO_4$) and the solvent evaporated in vacuo. The resulting yellow oil was subjected to flash chromatography (3 % EtOAc/CH_2Cl_2) to give (13a) as a white foam. Yield 4.0 g (70 %); (Found: C, 74.0; H, 7.7; N, 2.4. $C_{32}H_{39}NO_5$ requires: C, 74.3; H, 7.5; N, 2.7 %); $\nu_{max.}$ (nujol) 3400 br, 1730 s, and 1160 cm^{-1} s; δ_H 0.95 - 1.00 (3H, m, CH_3CH_2), 1.15, 1.16, 1.18, and 1.19 (4 x 9H, s, $OC(CH_3)_3$), 1.4 - 1.5 (2H, m, $MeCH_2$), 3.3 - 3.5 (1H, m, NCH), 3.59, 3.60, 3.82, and 3.83 (4 x 3H, s, OCH_3), 3.5 - 3.9 (1H, m, EtCH-O), 7.0 -7.5 (15H, m, ArH); δ_C (DEPT) (125 MHz) 9.93, 10.05, 10.07, and 10.16 (4 x q, CH_3CH_2), 27.21, 27.37, 28.13, and 28.51 (4 x t, $CHCH_2CH$), 27.67, 27.68, 27.71, and 27.75 (4 x q, $OC(CH_3)_3$), 32.36, 33.42, 35.11, and 35.19 (4 x t, $MeCH_2$), 46.19, 46.60, 46.88, and 46.98 (4 x d, $CHCO_2Me$), 51.33, 51.39, 51.50, and 51.65 (4 x q, OCH_3), 54.85, 54.91, 55.08, and 55.17 (4 x d, NCH), 71.27, 71.39, 71.60, and 71.63 (4 x s, $NCPh_3$), 73.73, 73.82, 74.22, and 74.63 (4 x d, EtCH-O), 80.61, 80.66, 80.87, and 81.03 (4 x s, $OCMe_3$), 126.21, 126.22, 126.27, 126.31, 127.60, 127.62, 127.66, 127.68, 127.70, 127.82, 128.66, and 128.67 (12 x d, ArCH), 145.85, 145.86, 145.89, and 145.93 (4 x s, ArC), 173.32, 173.47, 173.68, 173.76, 174.67, 174.80, 175.55, and 175.79 (8 x s, CO_2); m/z (FD) 517 (M^+).

When the above experiment was repeated using THF as the solvent, compound (13a) was obtained in 68% yield.

t-Butyl 2-tritylamino-4-carbomethoxy-5-hydroxy-5-phenyl-(2S)-pentanoate (13b).

The method was as described for (13a) using benzaldehyde (4.0 ml, excess). Flash chromatography (2 % Et_2O/CH_2Cl_2) gave (13b) as a white foam. Yield 2.4 g (39 %). The two diastereomers were separated by chiral HPLC, using a solvent system of 10 % ^iPrOH/hexane and injections of 1.6 mg in 0.1 ml of solvent. In total 75 mg of material was injected, giving 50 mg of the major diastereomer (retention time 8.3 min) and 20 mg of the minor diastereomer (retention time 6.8 min); (Found: C, 76.7; H, 7.0; N, 2.3. $C_{36}H_{39}NO_5$ requires: C, 76.5; H, 6.9; N, 2.5 %); $\nu_{max.}$ (nujol) 3400 br, 1730 m, 1150 s, and 700 cm^{-1} s; δ_H (500 MHz) (major diastereomer) 0.99 (9H, s, $OC(CH_3)_3$), 1.75 (1H, dt, J 14.1, and 3.1 Hz, CH_2), 2.45 (1H, ddd, J 14.1, 10.3, and 6.3 Hz, CH_2), 2.7 - 2.9 (3H, m, (reduces to 1H, ddd, J 10.4, 6.2, and 3.1 Hz, on addition of D_2O), $CHCO_2Me$+ NH+ OH), 3.42 (1H, ddd, J 8.9, 6.3, and 3.0 Hz, $NCHCO_2$), 3.81 (3H, s, OCH_3), 4.73 (1H, dd, J 7.2, and 6.1 Hz, PhCH-O), 7.1 - 7.5 (20H, m, ArH); (minor diastereomer) 1.12 (9H, s, $OC(CH_3)_3$), 1.70 (1H, ddd, J 12.0, 8.5, and 3.4 Hz, CH_2), 2.11 (1H, m, CH_2), 2.9 (2H, br, disappears on addition of D_2O, NH+ OH), 3.15 - 3.35 (2H, m, $CHCO_2Me$+ $NCHCO_2$), 3.59 (3H, s, OCH_3), 4.81 (1H, d, J 8.1 Hz, PhCH-O), 7.0 - 7.5 (20H, m, ArH) (For both isomers, the assignments were confirmed by 2D proton COSY experiments); δ_C (DEPT) (major diastereomer) 27.63 (q, $OC(CH_3)_3$), 34.84 (t, CH_2), 49.26 (d, $CHCO_2Me$), 51.79 (q, OCH_3), 55.06 (d, $NCHCO_2$), 71.87 (s, $NCPh_3$), 80.74 (s, $OCMe_3$), 126.36, 127.79, 127.94, 128.42, 128.59, and 128.74 (6 x d, ArCH), 142.01, and 145.98 (2 x s, ArC), 173.04, and 175.57 (2 x s, CO_2); (minor diastereomer) 27.76 (q, $OC(CH_3)_3$), 34.52 (t, CH_2), 49.08 (d, $CHCO_2Me$), 51.67 (q, OCH_3), 54.35 (d, $NCHCO_2$), 71.44 (s, $NCPh_3$), 80.97 (s, $OCMe_3$), 126.62, 126.94, 127.11, 127.74, 128.15, and 128.84, (6 x d, ArCH), 141.86, and 145.98 (2 x s, ArC), 173.42, and 174.86 (2 x s, CO_2); m/z (FD) 565 (M^+).

When the above experiment was repeated in THF as the solvent, compound (13b) was obtained in 10% yield.

t-Butyl 2-tritylamino-4-carbomethoxy-5-hydroxy-5-methyl-(2S)-hexanoate (13c).

The method was as described for (13a) using diester (12) (3.4 g, 7.4 mMol) and acetone (3.5 ml, excess). Flash chromatography (5 % Et_2O/CH_2Cl_2) gave (13c) as a white foam.

Yield 1.6 g (42 %); (Found: C, 74.2; H, 7.8; N, 2.6. $C_{32}H_{39}NO_5$ requires: C, 74.3; H, 7.5; N, 2.7 %); $\nu_{max.}$ ($CHCl_3$) 3520 br, 3060 w, 2980 m, 1720 s, 1150 s, and 708 cm^{-1} s; δ_H 1.14, and 1.18 (2 x 9H, s, $OC(CH_3)_3$), 1.21, and 1.23 (2 x 6H, s, $(CH_3)_2CO$), 3.2 - 3.3, and 3.4 - 3.5 (2 x 1H, m, $NCHCO_2$), 3.60, and 3.90 (2 x 3H, s, OCH_3), 7.1 - 7.6 (15H, m, ArH); δ_C (DEPT) 26.94, and 28.18 (2 x q, $(CH_3)_2CO$), 27.71 (q, $OC(CH_3)_3$), 32.84, and 33.72 (2 x t, CH_2), 51.20, and 51.58 (2 x d, $CHCO_2Me$), 51.35 (q, OCH_3), 54.77, and 55.19 (2 x d, $NCHCO_2$), 71.03, 71.26, and 71.72 (3 x s, $NCPh_3$ + Me_2C-O), 80.55, and 80.79 (2 x s, $OCMe_3$), 126.16, 127.53, 127.61, 128.60, and 128.81 (5 x d, ArCH), 145.80, and 145.92 (2 x s, ArC), 173.12, 173.61, 175.04, and 175.90 (4 x s, CO_2); m/z (FD) 517 (M^+).

When the above experiment was repeated in THF as the solvent, compound (13c) was obtained in 20% yield.

t Butyl 2-tritylamino-4-carbomethoxy-5-hydroxy-6-methyl-(2S)-heptanoate (13d).

The method was as described for (13a) using diester (12) (460 mg, 1.0 mMol), and isobutyraldehyde (0.5 ml, excess). Flash chromatography (2 % EtOAc/CH_2Cl_2) gave (13d) as a white foam. Yield 266 mg (50 %); (Found: C, 74.3; H, 7.7; N, 2.4. $C_{33}H_{41}NO_5$ requires: C, 74.6; H, 7.7; N, 2.6 %); $\nu_{max.}$ ($CHCl_3$) 3515 br, 3060 w, 2975 m, 1720 s, 1150 s, and 705 cm^{-1} s; δ_H 0.8 - 1.1 (6H, m, $(CH_3)_2CH$), 1.11, 1.12, 1.15, and 1.17 (4 x 9H, s, $OC(CH_3)_3$), 3.81, 3.94, and 3.95 (3 x 3H, s, OCH_3), 7.0 -7.6 (15H, m, ArH); δ_C (DEPT) 16.63, 18.54, 19.33, and 20.30 (4 x q, $(CH_3)_2CH$), 27.78 (q, $OC(CH_3)_3$), 32.23, 32.39, 32.66, and 32.83 (4 x d, Me_2CH), 36.33, 36.44, and 36.92 (3 x t, CH_2), 43.39, 44.28, and 45.00 (3 x d, $CHCO_2Me$), 51.62, 51.64, 51.71, and 51.80 (4 x q, OCH_3), 54.99, 55.21, and 55.36 (3 x d, $NCHCO_2$), 71.38, and 71.77 (2 x s, $NCPh_3$), 78.79, 79.38, and 80.80 (3 x s, $OCMe_3$), 126.34, 127.17, 127.73, 128.47, 128.76, and 130.35 (6 x d, ArCH), 145.93, and 145.99 (2 x s, ArC), 173.45, 173.70, 173.81, 175.52, and 176.16 (5 x s, CO_2); m/z (FD) 531 (M+).

When the above experiment was repeated in the THF as the solvent, compound (13d) was obtained in 25% yield.

t-Butyl 2-tritylamino-4-carbomethoxy-5-hydroxy-5-(4-nitrophenyl)-(2S)-pentanoate (13e)

The method was as described for (13a) using diester (12) (460 mg, 1.0 mMol), and 4-nitrobenzaldehyde (500 mg, excess) added as a solid. Flash chromatography (CH_2Cl_2 then 5 % EtOAc/CH_2Cl_2) gave two components each of which contained two diastereomers of (13e). Combined yield 580 mg (95 %); (Found: C, 70.6; H, 6.4; N, 4.3. $C_{36}H_{36}N_2O_7$ requires: C, 70.8; H, 6.2; N, 4.6 %); $\nu_{max.}$ ($CHCl_3$) 3450 br, 3010 w, 2980 w, 1720 s, 1155 s, and 708 cm^{-1} s; δ_H (higher R_f component) 0.94, and 1.22 (2 x 9H, s, $OC(CH_3)_3$), 3.2 - 3.3, and 3.4 -3.5 (2 x 1H, m, $NCHCO_2$), 3.40, and 3.75 (2 x 3H, s, OCH_3), 4.79, and 5.02 (2 x 1H, d, J 7.5, and 4.2 Hz, ArCH-O), 7.1 - 7.6 (17H, m, ArH), 8.1 - 8.3 (2H, m, ArH ortho to NO_2); (lower R_f component) 1.07, and 1.24 (2 x 9H, s, $OC(CH_3)_3$), 3.3 - 3.4 (1H, m, $NCHCO_2$), 3.69, and 3.70 (2 x 3H, s, OCH_3), 4.81, and 5.02 (2 x 1H, d, J 6.3, and 4.6 Hz, ArCH-O), 7.1 - 7.6 (17H, m, ArH), 8.1 - 8.3 (2H, m, ArH ortho to NO_2); δ_C (DEPT) (higher R_f component) 27.64, and 27.75 (2 x q, $OC(CH_3)_3$), 31.84, and 33.77 (2 x t, CH_2), 48.68, and 49.80 (2 x d, $CHCO_2Me$), 51.68, and 52.15 (2 x q, OCH_3), 54.96, and 55.11 (2 x d, $NCHCO_2$), 71.76, and 71.88 (2 x s, $NCPh_3$), 73.42, and 74.44 (2 x d, ArCH-O), 80.98, and 82.03 (2 x s, $OCMe_3$), 123.40, 126.46, 126.62, 127.20, 127.47, 127.78, 128.05, 128.68, and 128.80 (9 x d, ArCH), 145.28, 145.81, 147.47, 148.41, and 149.31 (5 x s, ArC), 173.08, 173.25, 173.98, and 175.39 (4 x s, CO_2); (lower R_f component) 27.73 (q, $OC(CH_3)_3$), 33.55, and 34.98 (2 x t, CH_2), 48.40 (d, $CHCO_2Me$), 51.82, and 51.96 (2 x q, OCH_3), 54.80, and 55.00 (2 x d, $NCHCO_2$), 71.73 (s, $NCPh_3$), 73.78, and 74.31 (2 x d, ArCH-O), 81.19, and 81.58 (2 x s, $OCMe_3$), 123.49, 123.67, 126.48, 126.66, 126.95, 127.04, 127.66, 127.82, 128.09, and 128.74 (10 x d, ArCH), 145.64, 145.82, 147.48, 149.24, and 149.36 (5 x s, ArC), 173.17, 173.35, 174.89, and 175.04 (4 x s, CO_2); m/z (FD) 611 (MH^+), 610 (M^+).

t-Butyl 2-tritylamino-4-carbomethoxy-5-hydroxy-(2S)-pentanoate (13f).

The general method was as described for (13a) using diester (12) (460 mg, 1.0 mMol). The reaction flask was fitted with a gas inlet tube connected to a flask containing paraformaldehyde and fitted with an argon inlet tube. After formation of the carbanion, the paraformaldehyde was heated to 180°C and the resulting formaldehyde gas allowed to pass into the reaction vessel as a stream in argon for 30 minutes, keeping the external temperature at -78°C. The flow of formaldehyde was then stopped and the solution allowed to warm to RT,

filtered (to remove paraformaldehyde), and worked up as for (13a). Flash chromatography (10 % EtOAc/CH_2Cl_2) gave (13f) as a white oil. Yield 147 mg (30 %); (Found: C, 73.7; H, 7.2; N, 2.7. $C_{30}H_{35}NO_5$ requires: C, 73.6; H, 7.2; N, 2.9 %); $\nu_{max.}$ (neat) 3460 br, 3060 w, 2936 m, 1730 s, and 1155 cm^{-1} s; δ_H 1.15, and 1.21 (2 x 9H, s, $OC(CH_3)_3$), 3.3 - 3.5 (1H, m, $NCHCO_2$ 3.62, and 3.80 (2 x 3H, s, OCH_3), 3.6 - 3.8 (2H, m, CH_2O), 7.1 - 7.5 (15H, m, ArH); δ_C (DEPT) 27.78 (q, $OC(CH_3)_3$), 34.07, and 34.19 (2 x t, $CHCH_2CH$), 43.95, and 44.00 (2 x d, $CHCO_2Me$), 51.71, and 51.85 (2 x q, OCH_3), 54.92, and 55.03 (2 x d, $NCHCO_2$), 63.35, and 63. 67 (2 x t, CH_2O), 71.56 (s, $NCPh_3$), 80.95, and 81.36 (2 x s, $OCMe_3$), 126.36, 126.52, 127.41, 127.52, 127.76, and 127.87 (6 x d, ArCH), 145.97, and 146.31 (2 x s, ArC), 173.60, 174.72, and 175.48 (3 x s, CO_2); m/z (FD) 490 (MH^+), 489 (M^+).

When the above experiment was repeated in THF as the solvent, compound (13f) was obtained in 17% yield.

t-Butyl 2-tritylamino-4-carbomethoxy-5-hydroxy-(2S)-octanoate (13g).

The general method was as described for (13a) using THF as the solvent, diester (12) (460 mg, 1.0 mMol), and n-butanal (0.7 ml, excess). Flash chromatography (5 % EtOAc/CH_2Cl_2) gave (13g) as a colourless oil. Yield 160 mg (30 %); (Found: C, 74.4; H, 7.9; N, 2.3. $C_{33}H_{41}NO_5$ requires: C, 74.6; H, 7.7; N, 2.6 %); $\nu_{max.}$ (neat) 3500 br, 3060 w, 2960 m, 1730 s, and 1154 cm^{-1} s; δ_H 0.8 - 1.0 (3H, m, CH_3CH_2), 1.15, 1.20, and 1.21 (3 x 9H, s, $OC(CH_3)_3$), 3.3 - 3.5 (1H, m, $NCHCO_2$), 3.60, 3.63, 3.85, and 3.86 (4 x 3H, s, OCH_3), 3.6 - 3.8 (1H, m, CHO), 7.0 - 7.5 (15H, m, ArH); δ_C (DEPT) 13.83, and 13.95 (2 x t, $MeCH_2$), 18.96, and 19.01 (2 x q, CH_3CH_2), 27.82 (q, $OC(CH_3)_3$), 32.43, 33.41, 36.52, 36.71, 35.11, 35.28, 37.61, and 38.05 (8 x t, CH_2CH-O and CH_2CHCO_2), 46.58, 47.02, 47.22, and 47.31 (4 x d, $CHCO_2Me$), 51.58, and 51.85 (2 x q, OCH_3), 55.03, and 55.28 (2 x d, $NCHCO_2$), 71.55, 71.73, 72.71, and 73.09 (4 x s, $NCPh_3$), 72.23, and 72.44 (2 x d, CHO), 80.82, 81.23, and 81.95 (3 x s, $OCMe_3$), 126.39, 126.48, 127.28, 127.59, 127.78, 127.88, 128.83, and 130.27 (8 x d, ArCH), 146.01, and 146.06 (2 x s, ArC), 173.65, 173.80, 175.10, and 176.04 (4 x s, CO_2); m/z (FD) 531 (M^+).

t-Butyl 2-tritylamino-4-carbomethoxy-5-hydroxy-(2S)-hexanoate (13h).

The general method was as described for (13a) using THF as the solvent, diester (12) (460 mg, 1.0 mMol), and ethanal (0.7 ml, excess). Flash chromatography (7 % EtOAc/CH_2Cl_2) gave (13h) as a white oil. Yield 250 mg (50 %); (Found: C, 73.75; H, 7.55 N, 2.7. $C_{31}H_{37}NO_5$ requires: C, 73.95; H, 7.35; N, 2.8 %); $\nu_{max.}$ (neat) 3450 br, 3060 w, 2980 m, 1730 s, and 1154 cm^{-1} s; δ_H 1.15, 1.18, and 1.23 (3 x 9H, s, $OC(CH_3)_3$), 1.1 - 1.2 (3H, m, CH_3CH-O), 3.3 -.3.5 (1H, m, $NCHCO_2$), 3.59, 3.61, 3.70, and 3.84 (4 x 3H, s, OCH_3), 3.7 - 4.0 (1H, m, CH-O), 7.0 - 7.5 (15H, m, ArH); δ_C (DEPT) 20.43, 20.64, 21.16, and 21.68 (4 x q, CH_3CH-O), 27.83 (q, $OC(CH_3)_3$), 34.03, 34.46, and 34.90 (3 x t, CH_2), 48.31, 48.43, and 48.87 (3 x d, $CHCO_2Me$), 51.57, and 51.86 (2 x q, OCH_3), 54.92, 55.13, and 55.25 (3 x d, $NCHCO_2$) 68.50, 68.68, 69.00, and 69.49 (4 x d, CH-O), 71.50, 71.62, and 71.77 (3 x s, $NCAr_3$), 80.87, 81.17, and 81.49 (3 x s, $OCMe_3$), 126.41, 126.50, 126.59, 127.24, 127.32, 127.62, 127.80, 127.96, 128.80, and 130.28 (10 x d, ArCH), 145.82, and 146.03 (2 x s, ArC), 173.63, 173.83, and 174.81 (3 x s, CO_2); m/z (FD) 503 (M^+).

t-Butyl 2-tritylamino-4-carbomethoxy-5-hydroxy-5-(4-methoxyphenyl)-(2S)-pentanoate (13i).

The method was as described for (13a) using diester (12) (1.0 g, 2.2 mMol), and 4-methoxybenzaldehyde (0.5 ml, excess). Flash chromatography (2 % Et_2O/CH_2Cl_2) gave a colourless oil which was trituated with ether, to give (13i) as a white solid. Yield 415 mg (32 %); mp 183 - 184°C; (Found: C, 74.5; H, 7.0; N, 2.5. $C_{37}H_{41}NO_6$ requires: C, 74.6; H, 6.9; N, 2.35 %); δ_H 0.99 (9H, s, $OC(CH_3)_3$), 1.72 (1H, dt, J 14.1, and 3.1 Hz, $CHCO_2Me$), 2.3 - 2.9 (4H, m, CH_2+ NH+ OH), 3.28 (1H, m, $NCHCO_2$), 3.78, and 3.81 (2 x 3H, s, $ArOCH_3$ + CO_2CH_3), 4.6 - 4.8 (1H, m, ArCH-O), 6.82 (2H, d, J 8.6 HZ, ArH ortho to OMe), 7.1 - 7.6 (17H, m, ArH); δ_C 27.65 (q, $OC(CH_3)_3$), 34.88 (t, CH_2), 49.39 (d, $CHCO_2$), 51.86 (d, $NCHCO_2$), 55.04 and 55.25 (2 x q, $ArOCH_3$ and CO_2CH_3), 71.85 (s, $NCPh_3$), 75.88 (d, ArCH-O), 80.75 (s, $OCMe_3$), 113.86, 126.38, 127.78, and 128.88 (4 x d, ArCH-O), 134.17, 146.03, and 159.42 (3 x s, ArC), 173.13, and 175.76 (2 x s, CO_2); m/z (FAB) 596 (MH^+, 0.4%), 494 (1.2), 444 (1.1), 243 (100), 165 (22).

Reaction of diester (12) with LICA and acetic acid.

The general method was as described for hydroxydiester (13a) using diester (12) (460 mg, 1.0 mMol), $[\alpha]_D^{\circ}$ + 22.5° (c 7.5 in $CHCl_3$). The reaction was quenched with acetic acid (0.5 ml, excess) and worked up without warming to RT. Flash chromatography (CH_2Cl_2) gave recovered (12) contaminated with trityl alcohol. The crude product was dissolved in hot hexane, the solution allowed to cool, filtered, the solvent evaporated in vacuo and the process repeated to remove trityl alcohol and give (12) as a colourless oil. Yield 220 mg (48 %); $[\alpha]_D^{\circ}$ +22.5° (c 7.5 in $CHCl_3$). This product was identical to the pure starting material (12) by t.l.c. and ^1H n.m.r. spectroscopy.

α-t-Butyl γ-methyl N-trityl-(RS)-glutamate (14).
This was prepared in three steps from (RS)-glutamic acid in 36% overall yield using the method described above for the corresponding (S)-isomer (12). This material was identical to the optically pure (S)-isomer (12) by t.l.c. and ^{1}H n.m.r. spectroscopy.

t-Butyl 2-tritylamino-4-carbomethoxy-5-hydroxy-5-phenyl-(2RS)-pentanoate (15).
The method was as described for (13b) using racemic diester (14) (5.0 g, 11 mMol), to give the product (15) as an oil (33%). This material was identical to the optically pure (S)-isomer (13b) by t.l.c. and ^{1}H n.m.r. spectroscopy.

Acknowledgements
We thank the S.E.R.C. for a quota award to M.N., Glaxo Group (U.K.) Ltd., for financial support to M.G.M., Dr. A.E. Derome for help with the nmr work, Dr. W.J. Norris for help with the HPLC work, and Mrs. D.G. Shirley for typing this manuscript.

References

1. Part 1 in this series is J.E. Baldwin, M. North, A. Flinn and M.G. Moloney, J.Chem.Soc.,Chem.Commun., 1988, 828.

2. For reviews see: G.C. Barrett (Ed.) 'Chemistry and Biochemistry of the Amino Acids', Chapman and Hall, London, 1985; I. Wagner and H. Musso, Angew.Chem.,Int.Ed.Engl., 1983, 22, 816.

3. R.A. Herbert 'The Biosynthesis of Secondary Metabolites', Chapman and Hall, London, 1981.

4. For example: G.K. Farrington, A. Kumar and F.C. Wedler, J.Med.Chem., 1987, 30, 2062 and references therein.

5. For example: J.E. Baldwin, 'Procedings of the 3rd International Symposium on Recent Advances in the Chemistry of β-Lactam Antibiotics', A.G. Brown and S.M. Roberts (Eds.), The Royal Society of Chemistry, London, 1985, 62.

6. A. Osol (Ed.), 'Remington's Pharmaceutical Sciences, 16th Ed', Mack Publishing, Easton P.A, 1980, 1170.

7. G.W. Mellin and K. Katzenstein, New Engl.J.Med., 1962, 267, 1184.

8. For a recent review see: J.D. Morrison, 'Asymetric Synthesis, Chiral Catalysts', Academic, Orlando, 1985, Vol.5.

9. See for example: H. Kunz and W. Suger, Angew.Chem.,Int.Ed.Engl., 1987, 26, 557; W. Oppolzer, R. Pedrosa and R. Moretti, Tetrahedron Lett., 1986, 27, 831.

10. For some recent examples see: R. Fitzi and D. Seebach, Angew.Chem.,Int.Ed.Engl., 1986, 25, 345; D.A. Evans and A.E. Weber, J.Am.Chem.Soc., 1986, 108, 6757; J.M. McIntosh and R.K. Leavitt, Tetrahedron Lett., 1986, 27 3839; S. Ikegami, T. Hayama, T. Katsuki and M. Yamaguchi, Tetrahedron Lett., 1986, 27, 3403; J.P. Genet, S. Ferroud, S. Juge and J.R. Montes, Tetrahedron Lett., 1986 27, 4573; D.A. Evans, E.B. Sjogren, A.E. Weber and R.E. Conn, Tetrahedron Lett., 1987, 28, 39; D. Seebach, E. Juaristi, D.D. Miller, C. Schickli and T. Weber, Helv.Chim.Acta, 1987, 70, 237; H. Kuzuhara, N. Watanabe and M. Ando, J.Chem.Soc.,Chem.Commun., 1987, 95.

11. U. Schollkopf, Pure Appl.Chem., 1983, 55, 1799 and references therein.

12. U. Schollkopf, H.J. Neubauer and M. Hauptreif, Angew.Chem.,Int.Ed.Engl., 1985, 24, 1066; R.M. Williams, P.J. Sinclair, D. Zhai and D. Chen, J.Am.Chem.Soc., 1988, 110, 1547 and references therein.

13. P. Munster and W. Steglich, Synthesis, 1987, 223; Y. Yamamoto, W. Ito and K. Maruyama, J.Chem.Soc., Chem.Commun., 1985, 1131; P. Ermert, J. Meyer, C. Stucki, J. Schneebeli and J.P. Obrecht, Tetrahedron Lett., 1988, 29, 1265; K.E. Harding, and C.S. Davis, Tetrahedron Lett., 1988, 29, 1891.

14. For some recent examples: L.D. Arnold, T.H. Kalantar and J.D. Vederas, J.Am.Chem.Soc., 1985, 107, 7105; L.D. Arnold, T.H. Kalantar and J.D. Vederas, J.Am.Chem.Soc., 1987, 109, 4649; D.H.R. Barton, Y. Herve, P. Potier and J. Thierry, J.Chem.Soc.,Chem.Commun., 1984, 1298; D.H.R. Barton, Y. Herve, P. Potier and J. Thierry, Tetrahedron, 1987, 43, 4297; L.D. Arnold, R.G. May and J.C. Vederas, J.Am.Chem.Soc., 1988, 110, 2237.

15. R.K.Y. Zee-Cheng and R.E. Olsen, Biochem.Biophys.Res.Commun., 1980, 94, 1128.

16. B.D. Christie and H. Rapoport, J.Org.Chem., 1985, 50, 1239.

17. G. Amiard, R. Heymes and L. Velluz, Bull.Soc.Chim.Fr., 1956, 97.

18. D. Seebach and D. Wasmuth, Angew.Chem.,Int.Ed.Engl., 1981, 20, 971; M.W. Rathke and D.F. Sullivan, J.Am.Chem.Soc., 1973, 95, 3050.

19. M.W. Rathke and J. Deitch, Tetrahedron Lett., 1971, 12, 2953.

20. R. Albert, J. Danklmaier, H. Honig and H. Kandolf, Synthesis, 1987, 635 and references therein; R.L. Prestidge, D.R.K. Harding, J.E. Battersby and W.S. Hancock, J.Org.Chem., 1975, 40, 3287.

21. D. Coleman, J.Chem.Soc.(C)., 1951, 2294.

22. J. Tomasz, Acta.Chim.Acad.Sci.Hung., 1971, 70, 255; P.M. Hardy, J.C. Haylock and H.N. Rydon, J.Chem.Soc.,Perkin Trans. 1, 1972, 605.

23. A. Rosowsky, R. Forsch, J. Uren and M. Wick, J.Med.Chem., 1981, 24, 1450.

24. M.W. Rathke and A. Lindert, J.Am.Chem.Soc., 1971, 93, 2318; P.L. Creger, J.Am.Chem.Soc., 1970, 92, 1396.

25. T. Laube, J.D. Dunitz and D. Seebach, Helv.Chim.Acta, 1985, 68, 1373.

26. K. Kime and R. Sievers, Aldrichimica Acta, 1977, 10, 54.

27. G.W. Anderson and F.M. Callahan, J.Am.Chem.Soc., 1960, 82, 3359.

28. A.E. Derome 'Modern NMR Techniques for Chemistry Research', Pergamon, Oxford, 1987, Chapter 6.

29. W.G. Kofron and L.M. Baclawski, J.Org.Chem., 1976, 41, 1879.

30. W.C. Still, M. Kahn and A. Mitra, J.Org.Chem., 1978, 43, 2923.

31. L.M. Harwood, Aldrichimica Acta, 1985, 18, 25.