Flash vacuum pyrolysis of stabilised phosphorus ylides. Part 17.[1] Preparation of aliphatic amino acid derived γ-alkoxycarbonyl-amino-β-oxo ylides and pyrolysis to give α,β-acetylenic γ-amino acid and GABA analogues

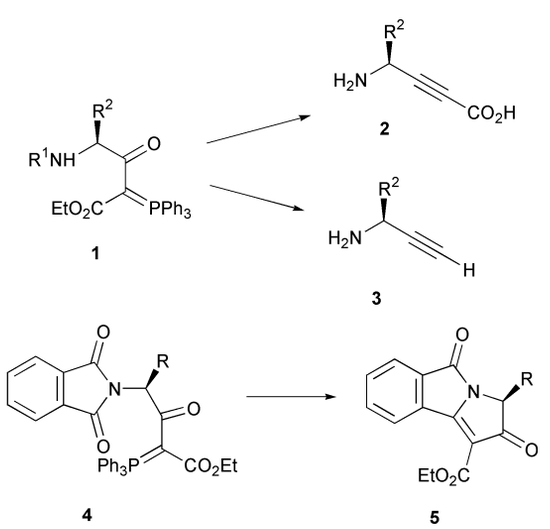
R. Alan Aitken,*[a] Nazira Karodia,[a] Tracy Massil[a] and Robert J. Young[b]

[a] *School of Chemistry, University of St. Andrews, North Haugh, St. Andrews, Fife, UK KY16 9ST*
[b] *GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, UK SG1 2NY*

Received (in Cambridge, UK) 12th November 2001, Accepted 19th December 2001
First published as an Advance Article on the web 21st January 2002

A series of eleven α-aminoacyl stabilised phosphorus ylides **9**–**19** have been prepared by condensation of *N*-alkoxycarbonyl protected amino acids with $Ph_3P{=}CHCO_2Et$ using a carbodiimide peptide coupling reagent. Upon flash vacuum pyrolysis at 600 °C, these undergo extrusion of Ph_3PO to give the corresponding α,β-acetylenic γ-amino esters **21**–**29**, **33** and **34** in moderate yield. In two cases the terminal alkynes **30** and **31** are also formed. The β-aminoacyl ylide **20** from β-alanine similarly gives the α,β-acetylenic δ-amino ester **35** upon pyrolysis. Regioselective addition of HBr to the triple bond of one acetylenic ester **25** was observed giving a mixture of *E* and *Z* α-bromoacrylates **36**. Hydrogenation of the *N*-Cbz acetylenic esters **21**–**23** and **33** results in *N*-deprotection and hydrogenation of the triple bond to afford the chiral GABA analogues **37**–**40** in 70 –>95% ee as determined by ^{19}F NMR of their Mosher amides. Fully assigned ^{13}C NMR spectra of all the ylides and acetylenic ester derivatives are presented.

In previous Parts of this series we have shown that flash vacuum pyrolysis (FVP) of oxo stabilised phosphorus ylides provides a useful route for synthesis of a wide variety of alkynes.[2] Since the ylides are readily formed by acylation with an acid chloride or the equivalent we were interested to extend the method to ylides **1** derived from amino acids. As shown, this is expected to give chiral amino acid analogues in which the acid group is either spaced out from the α-centre by a C≡C unit as in **2** or, using our previous discovery that higher temperature FVP results in loss of the ester group,[3] replaced by C≡CH as in **3**. In Part 7, we described the synthesis of aminoacyl ylides **4** with nitrogen protected in the form of the thermally robust phthalimide but these underwent loss of Ph_3PO in an unexpected way upon FVP to give the pyrroloisoindolediones **5**.[4]



Relatively few compounds of structure **2** and **3** have been prepared before,[5] but they are of considerable importance as potential mechanism-based inhibitors of medicinally important enzymes.[6] In particular, **2** (R^2 = H) and a number of *N*-substituted analogues have been shown to be effective GABA mimics,[7] and related compounds have been proposed for the therapeutic treatment of alcoholism and as anti-tumour agents.[8] The propargylamine (prop-2-ynylamine) **3** ($R^2 = (CH_2)_3NH_2$) and analogues have been shown to be selective irreversible inhibitors of ornithine decarboxylase and thus to have potential anti-tumour activity,[9] while **3** ($R^2 = (CH_2)_2CO_2H$) and related compounds effectively inhibit GABA aminotransferase and may be used for the treatment of epilepsy.[10]

We describe here the synthesis of aminoacyl ylides with the amino function protected by apparently more labile alkoxycarbonyl groups and their successful transformation using FVP into a range of acetylenic amino ester products.[11]

Results and discussion

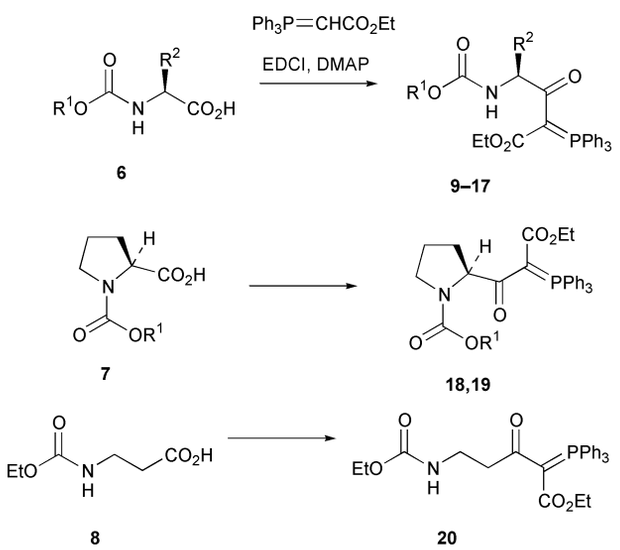
Using the method developed by Wasserman,[12] a range of *N*-benzoxycarbonyl and *N*-ethoxycarbonyl amino acids **6**–**8** were reacted with (ethoxycarbonylmethylene)triphenylphosphorane and the peptide coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) in the presence of a catalytic quantity of DMAP. Standard work-up followed by chromatographic purification afforded the desired ylides **9**–**20** in moderate yield (Table 1). As expected these were stable crystalline solids which gave satisfactory analytical data and ^{31}P NMR signals in the range δ_P +17–18. The ^1H and particularly ^{13}C NMR spectra were rather complex both due to phosphorus coupling and, in the cases of **16**, **18** and **19**, the presence of rotamers due to restricted rotation about the carbamate function. The fully assigned spectra of the starting *N*-protected

DOI: 10.1039/b110243e

Table 1 Preparation and properties of ylides **9**–**20**

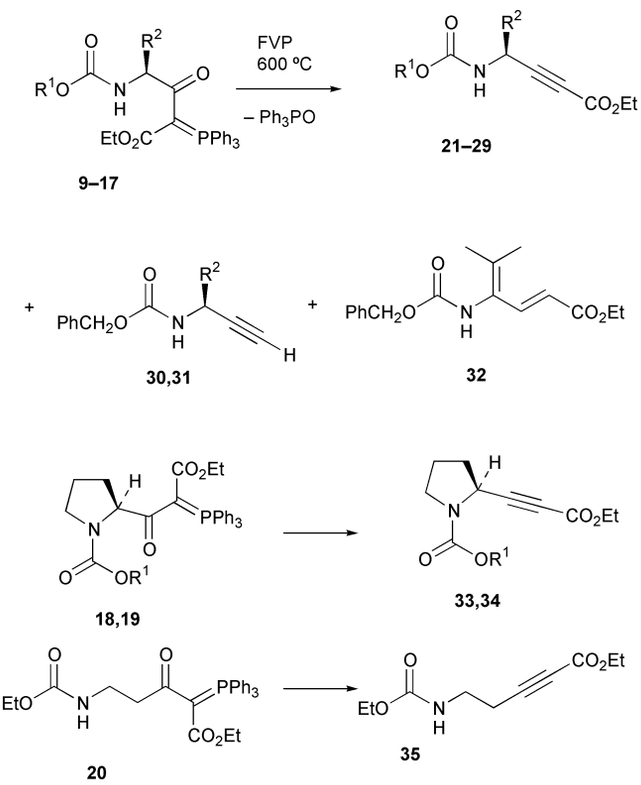
	Amino acid	R^1	R^2	Yield (%)	Mp/°C	δ_P	$[\alpha]_D$
9	Ala	Bn	Me	46	140–142	+17.5	+20.3
10	Val	Bn	Pr^i	49	88–91	+17.8	+28.7
11	Leu	Bn	Bu^i	44	152–154	+17.5	+21.7
12	Gly	Et	H	51	147–149	+17.8	—
13	Ala	Et	Me	50	68–69	+18.0	+17.5
14	Val	Et	Pr^i	45	128–129	+17.8	+22.6
15	Leu	Et	Bu^i	45	105–107	+17.9	+17.1
16	Ile	Et	Bu^s	48	148–149	+18.7/18.6	+5.9
17	Ala	Bu^i	Me	45	103–104	+18.0	+13.8
18	Pro	Bn	—	49	129–130	+17.6/17.4	−45.0
19	Pro	Et	—	44	112–114	+17.4/17.2	−33.8
20	β-Ala	—	—	52	94–95	+18.1	—

amino acids, some of which are reported here for the first time, were of considerable assistance in allowing complete assignment of the ^{13}C NMR data for the new ylides **9**–**20** (Table 2). As we have noted previously, the low value (≤3 Hz) for $^2J_{P\text{–keto }C(=O)}$ bodes well for the successful extrusion of Ph_3PO. As shown in Tables 1 and 2, both the isoleucine derived ylide **16** and the two proline derived ylides **18** and **19** showed separate ^{31}P and ^{13}C NMR signals for the two carbamate rotamers. For ylides **16** and **19** variable temperature ^{31}P NMR studies gave activation energies $\Delta G^{\ddagger}$ of 74.8 and 70.9 kJ mol^{-1}, respectively, for the rotation processes.



The ylides were now subjected to FVP at 600 °C and 1–5 × 10^{-2} Torr in a conventional flow system and this led to the desired extrusion of Ph_3PO to give the acetylenic esters **21**–**29** and **33**–**35** in moderate yield after chromatographic separation from the Ph_3PO (Table 3). These gave the expected analytical and spectroscopic data and in the majority of cases separate ^{13}C NMR signals were observed for the two carbamate rotamers (Table 4). For **9** and **10** additional minor products were obtained from the chromatography which proved to be the terminal alkynes **30** and **31** resulting from the known[3] loss of the ethoxycarbonyl group under these conditions. Attempts to increase the proportion of these products by performing the pyrolyses at higher temperatures were frustrated by an increasing degree of decomposition to give intractable products. The rather interesting functionalised 1,3-diene product **32** was also obtained as a minor product from **10** and its formation is probably explained by two consecutive 1,3-hydrogen shifts in the primary product **22**.

As noted in Tables 1 and 3, both the chiral acetylenic esters and their ylide precursors showed substantial optical rotations. However no satisfactory method for direct determination of the ee of these compounds has yet been found. For **16** and its



pyrolysis product **28** where an additional stereogenic centre is present the absence of diastereomer signals in the NMR spectra indicated that no significant degree of racemisation had occurred. An alternative to the method reported here is provided by the work of Reetz and coworkers[13] who treated suitably protected α-amino aldehydes with CBr_4–Ph_3P followed by BuLi in the so-called Corey–Fuchs procedure and then intercepted the aminoalkynyllithiums with CO_2 to give α,β-acetylenic γ-amino acids after deprotection.

With the acetylenic products in hand, we were anxious to examine the further reactivity of these potentially versatile synthetic intermediates. Treatment of **25** with HBr in acetic acid resulted in clean regioselective addition of HBr across the triple bond to give the α-bromoacrylate **36** as a 1 : 1 mixture of *E* and *Z* isomers. It seems likely that a wide variety of other additions to the triple bond could be carried out and this is currently being examined. In order to obtain GABA analogues, we subjected the Cbz protected compounds **21**–**23** and **33** to catalytic hydrogenation. This resulted in removal of the Cbz group and complete hydrogenation of the triple bond to give the chiral γ-amino esters **37**–**40** in 70–80% yield. These again showed significant optical rotations and the ee could now be determined by conversion to the corresponding Mosher amides[14] which gave good separation of ^{19}F NMR signals in each case leading to values for the ee of 76% (**37**), 85% (**38**), >85% (**39**)

Table 2 ^{13}C NMR spectra of ylides **9**–**20**, δ_C ($J_{P\text{-}C}$)

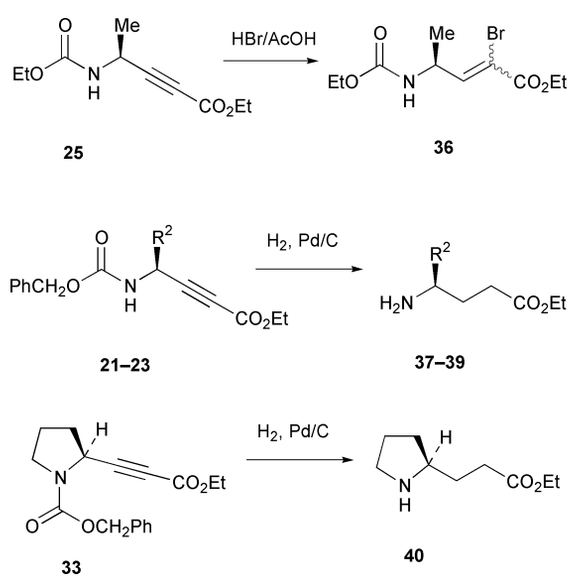
	CHN	P=C	*C*OCN	CO_2Et	NCO_2R^1 signals[b]		P-Phenyl				R^2 signals
					CO	R^1	C-1	C-2	C-3	C-4	
9	52.5 (8)	68.8 (111)	194.8	166.7 (14), 58.7, 13.8	155.5	137.1 (4ry), 128.3, 127.7 (3C), 65.9	126.0 (93)	133.0 (10)	128.6 (12)	131.8 (<2)	20.4
10	60.4 (8)	69.8 (111)	194.1	166.8 (14), 58.6, 13.8	156.6	137.1 (4ry), 128.2, 127.6 (3C), 66.0	126.0 (94)	133.0 (10)	128.5 (12)	131.8 (<2)	32.3, 20.7, 15.9
11	55.1 (8)	69.3 (111)	195.2	166.8 (15), 58.7, 13.9	156.6	137.1 (4ry), 128.3, 127.7 (3C), 66.1	126.2 (94)	133.1 (10)	128.5 (12)	131.8 (2)	43.6, 25.1, 21.9, 21.8
12	49.2 (8)	68.9 (112)	190.6	167.4 (15), 58.7, 13.9	156.6	60.4, 14.7	125.9 (94)	133.2 (10)	128.6 (13)	131.9 (2)	—
13	52.4 (8)	68.8 (111)	195.1	166.8 (15), 58.7, 13.8	155.9	60.2, 14.7	126.2 (94)	133.1 (10)	128.6 (13)	131.8 (2)	20.5
14	60.3 (8)	70.0(110)	194.4	166.9 (15), 58.8, 13.9	157.0	60.4, 14.6	126.1 (94)	133.2 (10)	128.5 (13)	131.8 (2)	32.3, 20.7, 15.9
15	54.9 (8)	69.2 (110)	195.4	166.8 (15), 58.7, 13.9	156.6	60.3, 14.6	126.3 (94)	133.1 (10)	128.5 (13)	131.7 (2)	43.7, 25.1, 24.0, 21.8
16[a]	60.5 (8)	70.3 (110)	194.5	166.8 (14), 58.7, 13.8	156.9	60.3, 14.6	126.2 (93)	133.1 (10)	128.5 (12)	131.6 (<2)	39.4, 27.8, 16.8, 12.1
	57.2 (8)	69.8 (110)		166.7 (14)			126.15 (93)				38.8, 22.8 12.9
17	51.9 (8)	68.4 (110)	194.5	166.4 (14), 58.2, 13.3	155.5	69.9, 27.5, 18.6 (2C)	125.5 (93)	132.5 (10)	128.1 (13)	131.5 (<2)	20.6
18[a]	62.9 (8)	69.2 (111)	195.6(3)	167.51 (15), 58.4, 13.7	154.54	137.4 (4ry), 128.2, 127.6 (3C), 66.3	126.4 (93)	133.3 (10)	128.8 (13)	131.6 (4)	46.9, 30.7, 23.8
	62.4 (8)	68.9 (111)	195.1(3)	167.46 (15), 58.3	154.51	66.0	126.2 (94)	132.9 (10)		131.5 (4)	47.4, 31.8, 23.0
19[a]	62.7 (8)	69.3 (110)	195.5	167.54 (15), 58.4, 13.8	155.0	60.6, 14.8	126.7 (94)	133.4 (10)	128.5 (13)	131.6 (2)	47.2, 31.7, 22.9
	62.4 (8)	68.9 (111)	195.4	167.49 (15), 58.3, 13.7	154.9	60.5		133.1 (10)	128.4 (13)	131.5 (<2)	46.9, 30.7, 23.8
20	—	71.4 (111)	196.0	167.9 (15), 58.5, 13.7	156.6	60.2, 14.8	126.5 (94)	133.0 (10)	128.6 (12)	131.7 (2)	40.0 (6), 37.4

[a] For **16**, **18** and **19** the signals for both carbamate rotamers are given where they differ. [b] 4ry refers to quaternary carbon atoms.

Table 3 Pyrolysis of ylides **9**–**20**

Ylide	Product(s)	R^1	R^2	Yield (%)	$[\alpha]_D$
9	**21**	Bn	Me	29	−30.3
	30	—	Me	15	−3.4
10	**22**	Bn	Pr^i	58	−34.4
	31	—	Pr^i	10	−2.7
	32	—	—	11	—
11	**23**	Bn	Bu^i	30	−26.7
12	**24**	Et	H	39	—
13	**25**	Et	Me	32	−91.0
14	**26**	Et	Pr^i	34	−49.5
15	**27**	Et	Bu^i	36	−74.5
16	**28**	Et	Bu^s	38	+9.1
17	**29**	Bu^i	Me	38	−9.1
18	**33**	Bn	—	48	−114.4
19	**34**	Et	—	48	−137.7
20	**35**	—	—	49	—

and >95% (**40**). Thus it seems likely that the FVP process does not involve a major degree of racemisation. While this work was in progress a valuable alternative route from α-amino acids to γ-substituted γ-amino acid derivatives involving condensation with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione), reduction and thermolysis was described.[15] Although this may be preferable to the route described here for access to saturated GABA analogues, when we come to γ-amino alkynoic and alkenoic acid derivatives, the latter of which have been of recent interest as conformationally restricted GABA analogues,[16] the present route has much to offer and further applications to the preparation of more highly functionalised chiral products will be reported shortly.



25 36 21–23 37–39 33 40

Experimental †

Melting points were recorded on a Reichert hot-stage microscope and are uncorrected. Infra red spectra were recorded as Nujol mulls for solids and as thin films for liquids on a Perkin Elmer 1420 instrument. NMR spectra were obtained for ^{1}H at 300 MHz, for ^{13}C at 75 MHz, for ^{31}P at 121 MHz and for ^{19}F at 282 MHz using a Bruker AM300 instrument. All spectra were run on solutions in $CDCl_3$ with internal Me_4Si as reference for ^{1}H and ^{13}C, external 85% H_3PO_4 as reference for ^{31}P and external $CFCl_3$ as reference for ^{19}F. Chemical shifts are reported in ppm to high frequency of the reference and coupling constants J are in Hz. Mass spectra were obtained on an A. E. I.

† In the spectroscopic data the signals due to the minor carbamate rotamer are denoted by * where these can be identified.

Table 4 ^{13}C NMR spectra of alkyne products **21**–**31** and **33**–**35**, δ_C (J_{P-C}). The signals for both carbamate rotamers are given where they differ

	–*C*≡O	C–CO_2Et	*C*HN	R^2	N*C*O_2R^1	R^1 signals
21	74.4, 86.8	14.0, 62.2, 155.0	38.8	21.6	153.2	67.2, 128.2 (2C), 128.3, 128.6 (2C), 136.0 (4ry)
30	70.6, 84.1	—	38.9	22.5	155.2	67.0, 128.1 (2C), 128.2, 128.5 (2C), 136.2 (4ry)
22	76.0, 85.2	14.0, 62.1, 155.5	49.2	17.9, 18.6, 33.0	153.3	67.3, 128.2 (2C), 128.3, 128.6 (2C), 136.1 (4ry)
	75.8, 81.6					
31	72.1, 81.6	—	49.1	17.5, 18.6, 32.8	155.5	67.0, 125.5, 128.2 (2C), 128.5 (2C), 136.2 (4ry)
23	75.0, 86.5	14.0, 62.1, 155.3	41.8	22.1, 22.4, 24.9, 44.3	153.3	67.2, 128.2 (2C), 128.3, 128.6 (2C), 136.1 (4ry)
	71.2, 83.4					
24	75.1, 83.5	14.0, 62.2, 156.0	30.7	—	153.2	14.6, 61.5
	75.0, 83.3		29.8			
25	74.2, 87.1	14.0, 62.1, 155.3	38.6	21.6	153.3	14.5, 61.4
26	75.9, 85.6	14.0, 62.1, 156.0	49.7	18.0, 18.6, 33.2	153.4	14.5, 60.1
	75.2, 86.9	14.0, 62.0, 156.6	47.7	17.8, 18.8, 33.3	153.6	14.5, 61.4
27	74.8, 86.9	14.0, 62.1, 155.7	40.2	22.1, 22.3, 24.8, 44.3	153.4	14.5, 61.9
	74.4, 88.2	60.0, 156.0	41.6	22.1, 22.5, 24.9, 44.6	153.6	61.4
28	75.6, 86.1	14.0, 62.1, 155.9	47.6	11.5, 15.1, 25.2, 39.4	153.4	14.5, 61.9
	76.0, 85.3	62.0, 155.7	47.8	11.4, 14.7, 25.8, 39.6	153.3	62.0
29	74.3, 87.1	14.0, 62.1, 155.5	38.7	21.6	153.3	19.0 (2C), 28.0, 71.6
33	74.3, 87.0	14.0, 62.0, 154.4	48.4	24.6, 33.2, 46.3	153.4	67.0, 127.9, 128.0, 128.4 (2C), 136.5(4ry)
	70.3, 86.8		47.9	23.8, 33.2, 45.9	154.1	
34	74.1, 81.1	14.0, 62.0, 154.7	47.7	23.8, 33.2, 46.1	153.5	14.7, 61.5
	70.1	154.5	48.2	24.6, 32.4, 45.8		
35	74.3, 86.1	14.0, 62.0, 156.5	38.9	20.3	153.5	14.6, 61.1
	74.2, 87.1					

MS-902 spectrometer using electron impact at 70 eV or on a VG Autospec using chemical ionisation with isobutane as the ionising gas. Optical rotations were measured on an Optical Activity AA1000 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Dry CH_2Cl_2 was prepared by storage over P_2O_5.

Preparation of *N*-protected amino acids

To a stirred solution of the appropriate amino acid (10.0 g) in 2 M NaOH (1.0 equiv.) at 0 °C were added simultaneously benzyl or ethyl chloroformate (1.0 equiv.) and 2 M NaOH (1.0 equiv.) dropwise. The mixture was stirred at 0 °C for 3 h then washed with ether (20 cm^3). The aqueous phase was acidified with 2 M HCl and extracted with ethyl acetate (3 × 50 cm^3). The combined organic phase was dried and the solvent evaporated to furnish the product. Properties of the products are summarised in Table 5.

Preparation of β-aminoacyl phosphorus ylides

To a stirred solution of (ethoxycarbonylmethylene)triphenylphosphorane (1.82 g, 5.2 mmol) and the appropriate *N*-protected amino acid (5.2 mmol) in dry CH_2Cl_2 (25 cm^3) at 0 °C was added EDCI (1.0 g, 5.2 mmol) and DMAP (0.03 g, 0.26 mmol). The mixture was stirred at this temperature for 30 min then allowed to warm up to RT. Once all the starting material was consumed (indicated by TLC) the mixture was poured into brine, extracted with CH_2Cl_2 (3 × 20 cm^3) and the combined organic extracts dried and evaporated. The crude product was purified by chromatography (SiO_2, ethyl acetate–hexane, 1 : 2) followed by recrystallisation from ethyl acetate.

Ethyl (4*S*)-4-benzoxycarbonylamino-3-oxo-2-triphenylphosphoranylidenepentanoate 9. From *N*-benzoxycarbonyl-(*S*)-alanine as colourless crystals (1.21 g, 46%), mp 140–142 °C (Found: C, 71.9; H, 5.7; N, 2.5. $C_{33}H_{32}NO_5P$ requires C, 71.6; H, 5.7; N, 2.5%); $[a]_D^{20}$ +20.3 (*c* 1.005 in CH_2Cl_2); ν_{max}/cm^{-1} 3450, 1700, 1645, 1560, 1475, 1270, 1220, 1090, 1080, 1040, 750 and 690; δ_H 7.78–7.61 (5 H, m, Ph), 7.55–7.41 (10 H, m, Ph), 7.41–7.25 (5 H, m, Ph), 5.88 (1 H, d, *J* 7, NH), 5.51 (1 H, m, CH), 5.05 (2 H, s, OC*H*$_2$Ph), 3.79 (2 H, m, OCH_2), 1.54 (3 H, d, *J* 6, CHC*H*$_3$) and 0.74 (3 H, t, *J* 7, Me); δ_C see Table 2; δ_P +17.5; *m*/*z* (CI) 554 (M + H^+, 100%), 508 (20), 446 (18), 375 (31), 279 (11), 263 (17), 184 (8) and 91 (10).

The racemic compound was prepared using *N*-benzoxycarbonyl-(±)-alanine and had mp 142–143 °C.

Ethyl (4*S*)-4-benzoxycarbonylamino-5-methyl-3-oxo-2-triphenylphosphoranylidenehexanoate 10. From *N*-benzoxycarbonyl-(*S*)-valine as colourless crystals (1.48 g, 49%), mp 88–91 °C (Found: C, 72.4; H, 6.4; N, 2.35. $C_{35}H_{36}NO_5P$ requires C, 72.3; H, 6.2; N, 2.4%); $[a]_D^{20}$ +28.7 (*c* 0.995 in CH_2Cl_2); ν_{max}/cm^{-1} 3390, 1710, 1640, 1550, 1275, 1220, 1090, 1065, 1000, 740, 710 and 680; δ_H 7.80–7.63 (5 H, m, Ph), 7.51–7.40 (10 H, m, Ph), 7.39–7.20 (5 H, m, Ph), 5.68 (1 H, d, *J* 9, NH), 5.54 (1 H, m, C*H*NH), 5.06 (2 H, s, OC*H*$_2$Ph), 3.74 (2 H, m, OCH_2), 2.44 (1 H, br m, CH), 1.09 (3 H, d, *J* 6, CH*Me*), 0.72 (3 H, t, *J* 7, CH_2*Me*) and 0.68 (3 H, d, *J* 7, CH*Me*); δ_C see Table 2; δ_P +17.8; *m*/*z* (FAB) 582 (M + H^+, 16%), 492 (5), 375 (100), 303 (39), 262 (14) and 183 (14).

Ethyl (4*S*)-4-benzoxycarbonylamino-6-methyl-3-oxo-2-triphenylphosphoranylideneheptanoate 11. From *N*-benzoxycarbonyl-(*S*)-leucine as colourless crystals (1.36 g, 44%), mp 152–154 °C (Found: C, 72.8; H, 6.5; N, 2.3. $C_{34}H_{34}NO_5P$ requires C, 72.6; H, 6.4; N, 2.4%); $[a]_D^{20}$ +21.7 (*c* 0.975 in CH_2Cl_2); ν_{max}/cm^{-1} 3390, 3300, 1695, 1655, 1535, 1500, 1290, 1250, 1094, 1080, 1045, 730 and 680; δ_H 7.67–7.61 (5 H, m, Ph), 7.64–7.44 (10 H, m, Ph), 7.30–7.26 (5 H, m, Ph), 5.61 (2 H, m, NH and CH), 5.07 (2 H, s, OC*H*$_2$Ph), 3.81 (2 H, m, OCH_2), 1.77 (2 H, m, C*H*$_2$CH), 1.36 (1 H, m, CH_2C*H*), 1.12 (3 H, d, *J* 6, CH*Me*), 0.94 (3 H, d, *J* 6, CH*Me*) and 0.72 (3 H, t, *J* 7, CH_2*Me*); δ_C see Table 2; δ_P +17.5; *m*/*z* (CI) 596 (M + H^+, 100%), 550 (44), 506 (6), 488 (19), 416 (30), 375 (23), 319 (7), 292 (12), 279 (17), 263 (41), 225 (36), 187 (11), 156 (12) and 91 (19).

Ethyl 4-ethoxycarbonylamino-3-oxo-2-triphenylphosphoranylidenebutyrate 12. From *N*-ethoxycarbonylglycine as colourless crystals (1.27 g, 51%), mp 147–149 °C (Found: C, 68.2; H, 6.0; N, 2.8. $C_{27}H_{28}NO_5P$ requires C, 67.9; H, 5.9; N, 2.9%); ν_{max}/cm^{-1} 3400, 1700, 1650, 1570, 1510, 1300, 1235, 1170, 1105, 1090, 770 and 690; δ_H 7.70–7.61 (6 H, m, Ph), 7.60–7.50 (3 H, m, Ph), 7.49–7.43 (6 H, m, Ph), 5.68 (1 H, br m, NH), 4.56 (2 H, d, *J* 3, CH_2), 4.09 (2 H, m, OCH_2), 3.78 (2H, m, OCH_2), 1.17 (3 H, t, *J* 7, Me) and 0.76 (3 H, t, *J* 7, Me); δ_C see Table 2; δ_P +17.8; *m*/*z* (CI) 478 (M + H^+, 100%), 432 (52), 386 (8), 375 (19), 365 (11), 319 (6), 279 (26), 263 (29), 218 (14), 187 (9), 172 (20) and 47 (8).

Ethyl (4*S*)-4-ethoxycarbonylamino-3-oxo-2-triphenylphosphoranylidenepentanoate 13. From *N*-ethoxycarbonyl-(*S*)-alanine as colourless crystals (1.09 g, 50%), mp 68–69 °C

Table 5 Properties of *N*-protected amino acids **6**–**8** The signals for both carbamate rotamers are given where they differ

							δ_H					δ_H				
	R^1	R^2	Yield (%)	Mp/°C	Lit. mp/°C	Ref.	OH	NH	CHN	R^1 signals	R^2 signals	CO_2H	NCO	CHN	R^1 signals	R^2 signals
6	Bn	Me	68	82–84	83–84	17	10.84	5.58 6.69	4.41	7.38, 5.17	0.74	177.5	155.9	49.4	136.0, 128.5, 128.2, 128.0, 67.1	18.2
6[a]	Bn	Me	68	114–115	114–115	18										
6	Bn	Pr^i	58	60–62	66–67	19	10.90	5.60 6.64	4.43 4.22	7.41, 5.18	2.18, 1.12, 0.98	176.4	156.5	58.8	136.0, 128.4, 128.2, 128.1, 67.2	31.0, 19.0, 17.3
6	Bn	Bu^i	61	(Oil)	(Oil)	19	10.15	5.28 6.33	4.43 4.25	7.34, 5.11	1.61, 0.94, 0.93	178.0	156.2	52.3	136.0, 128.5, 128.2, 128.1, 67.1	41.4, 24.7, 22.8, 21.7
6	Et	H	70	(Oil)	67–69	20	9.66	5.50 6.85	4.33	4.15, 1.25 4.00	—	174.4 173.7	157.2	42.6 43.2	61.8, 14.6 62.4	—
6	Et	Me	71	(Oil)	(Oil)	21	10.26	5.58 6.77	4.33	4.07, 1.19	1.40	177.2	156.5	49.4	61.4, 14.5	18.4
6[a]	Et	Me	71	80–82	84	22										
6	Et	Pr^i	70	(Oil)	37	23	10.80	5.52 6.54	4.33	4.16, 1.25	2.23, 1.00, 0.94	176.3	157.0	58.8	61.5, 14.5	31.1, 19.0, 17.4
6	Et	Bu^i	69	(Oil)	(Oil)	24	11.11	5.31 6.38	4.37	4.13, 1.25	1.64, 0.96	178.0	156.6	52.3	61.4, 14.5	41.4, 24.7, 22.9, 21.7
6	Et	Bu^s	72	(Oil)	—	—	9.47	5.32 6.36	4.36	4.13, 1.26	1.95, 1.49, 0.98, 0.93	176.7	156.6	58.2	61.4, 14.5	37.8, 24.8, 15.5, 11.6
6	Bu^i	Me	69	83–85	—	—	10.15	5.45 7.01	4.25	3.91, 1.94[b]	1.48	177.3 177.9	156.9 157.9	50.5 49.9	72.6, 28.2, 19.4 72.0	18.9
7	Bn	—	77	60–61	77	19	10.01	—	4.35	7.31, 5.09 7.26	3.46, 2.05	176.7 176.3	155.4 154.7	59.1 58.7	67.3, 136.3, 128.4, 127.9, 127.8 67.2	46.6, 30.7, 24.1 128.3,127.5
7	Et	—	77	59–60	57–58	25	10.68	—	4.24	4.07, 1.13	3.39, 2.11, 1.80	177.0 176.4	155.9 155.1	59.1 58.7	61.8, 14.7 61.7, 14.6	46.8, 30.9, 24.3 46.5, 29.7, 23.5
8	—	—	62	57–59	57–59	26	10.88	6.42 7.17	3.46	4.14, 1.28	—[c]	177.2	157.4	36.7	61.5, 14.9	—[c]

[a] Data for racemic compound. [b] Additional signal at δ_H 0.96 (6 H). [c] Additional signal at δ_H 2.52 and δ_C 34.6 (CH_2CO).

(Found: C, 68.4; H, 5.8; N, 2.8. $C_{28}H_{30}NO_5P$ requires C, 68.4; H, 6.2; N, 2.9%); $[\alpha]_D^{20}$ +17.5 (*c* 0.98 in CH_2Cl_2); ν_{max}/cm^{-1} 3400, 1710, 1650, 1570, 1340, 1280, 1230, 1100, 1070 and 690; δ_H 7.81–7.62 (6 H, m, Ph), 7.60–7.53 (3 H, m, Ph), 7.53–7.42 (6 H, m, Ph), 5.66 (1 H, br d, *J* 9, NH), 5.48 (1 H, br m, CHN), 4.06 (2 H, q, *J* 7, OCH_2), 3.79 (2 H, m, OCH_2), 1.45 (3 H, d, *J* 6, CH*Me*), 1.16 (3 H, t, *J* 7, CH_2*Me*) and 0.75 (3 H, t, *J* 7, CH_2*Me*); δ_C see Table 2; δ_P +18.0; *m*/*z* (CI) 492 (M + H^+, 100%), 446 (76), 375 (54), 303 (8), 279 (9), 263 (34), 232 (8), 186 (21), 116 (8) and 47 (11).

The racemic compound was prepared using *N*-ethoxycarbonyl-(±)-alanine and had mp 80–82 °C.

Ethyl (4*S*)-4-ethoxycarbonylamino-5-methyl-3-oxo-2-triphenylphosphoranylidenehexanoate 14. From *N*-ethoxycarbonyl-(*S*)-valine as colourless crystals (1.23 g, 45%), mp 128–129 °C (Found: C, 69.3; H, 6.5; N, 2.6. $C_{30}H_{34}NO_5P$ requires C, 69.4; H, 6.6; N, 2.7%); $[\alpha]_D^{20}$ +22.6 (*c* 0.975 in CH_2Cl_2); ν_{max}/cm^{-1} 3385, 1730, 1660, 1575, 1380, 1290, 1220, 1100, 1070 and 690; δ_H 7.74–7.61 (6 H, m, Ph), 7.59–7.51 (3 H, m, Ph), 7.49–7.42 (6 H, m, Ph), 5.69 (1 H, br d, NH), 5.17 (1 H, br m, C*H*NH), 4.06 (2 H, q, *J* 7, OCH_2), 3.79 (2 H, m, OCH_2), 2.41 (1 H, br s, C*H*Me_2), 1.18 (3 H, t, *J* 7, CH_2*Me*), 1.06 (3H, d, *J* 7, CH*Me*), 0.75 (3 H, t, *J* 7, CH_2*Me*) and 0.62 (3 H, d, *J* 7, CH*Me*); δ_C see Table 2; δ_P +17.8; *m*/*z* (CI) 520 (M + H^+, 100%), 474 (31), 375 (34) and 263 (31).

Ethyl (4*S*)-4-ethoxycarbonylamino-6-methyl-3-oxo-2-triphenylphosphoranylideneheptanoate 15. From *N*-ethoxycarbonyl-(*S*)-leucine as colourless crystals (1.23 g, 45%), mp 105–107 °C (Found: C, 69.6; H, 7.0; N, 2.5. $C_{30}H_{34}NO_5P$ requires C, 69.8; H, 6.8; N, 2.6%); $[\alpha]_D^{20}$ +17.1 (*c* 0.935 in CH_2Cl_2); ν_{max}/cm^{-1} 3360, 3260, 1720, 1670, 1580, 1260, 1100, 1050 and 690; δ_H 7.75–7.61 (6 H, m, Ph), 7.56–7.50 (3 H, m, Ph), 7.48–7.42 (6 H, m, Ph), 5.56 (1 H, m, NH), 5.41 (1 H, m, C*H*NH), 4.04 (2 H, q, *J* 7, OCH_2), 3.72 (2 H, m, OCH_2), 1.78 (2 H, m, CH_2CH), 1.34 (1 H, m, C*H*Me_2), 1.17 (3 H, t, *J* 7, CH_2*Me*), 1.11 (3 H, d, *J* 5, CH*Me*), 0.93 (3 H, d, *J* 6, CH*Me*) and 0.73 (3 H, t, *J* 7, CH_2*Me*); δ_C see Table 2; δ_P +17.9; *m*/*z* (CI) 534 (M + H^+, 100%), 488 (93), 431 (14), 412 (7), 375 (30), 319 (5), 274 (20), 263 (39), 228 (28), 185 (8), 158 (8) and 47 (9).

Ethyl (4*S*,5*S*)-4-ethoxycarbonylamino-5-methyl-3-oxo-2-triphenylphosphoranylideneheptanoate 16. From *N*-ethoxycarbonyl-(*S,S*)-isoleucine as colourless crystals (1.34 g, 48%), mp 148–149 °C (Found: C, 69.4; H, 6.8; N, 2.5. $C_{31}H_{36}NO_5P$ requires C, 69.8; H, 6.8; N, 2.6%); $[\alpha]_D^{20}$ +5.9 (*c* 1.0 in CH_2Cl_2); ν_{max}/cm^{-1} 3390, 1695, 1650, 1580, 1470, 1440, 1340, 1298, 1280, 1220, 1098, 1065, 750 and 690; δ_H 7.78–7.61 (6 H, m, Ph), 7.59–7.50 (3 H, m, Ph), 7.47–7.31 (6 H, m, Ph), 5.55 (1 H, m, NH), 5.46 (1 H, m, CHN), 4.03 (3 H, q, *J* 7, OCH_2), 3.78 (2 H, m, OCH_2), 1.68 (1 H, m, CH), 1.17 (3 H, t, *J* 7, OCH_2*Me*), 1.10–0.91 (3 H, m, CH_2*Me*), 0.87 (2 H, m, $CHCH_2$), 0.74 (3 H, t, *J* 7, OCH_2*Me*) and 0.58 (3 H, d, *J* 7, CH*Me*); δ_C see Table 2; δ_P +18.7, 18.6*; *m*/*z* (CI) 534 (M + H^+, 75%), 458 (9), 412 (6), 375 (11), 326 (17), 312 (11), 294 (5), 281 (22), 266 (23), 215 (48) and 236 (100).

Ethyl (4*S*)-4-isobutoxycarbonylamino-3-oxo-2-triphenylphosphoranylidenepentanoate 17. From *N*-isobutyloxycarbonyl-(*S*)-alanine as colourless crystals (1.2 g, 45%), mp 103–104 °C (Found: C, 69.1; H, 6.5; N, 2.7. $C_{30}H_{34}NO_5P$ requires C, 69.4; H, 6.6; N, 2.7%); $[\alpha]_D^{20}$ +13.8 (*c* 0.5 in CH_2Cl_2); ν_{max}/cm^{-1} 3490, 1710, 1650, 1545, 1320, 1255, 1230, 1120, 1105, 1100, 1090, 1050, 750 and 690; δ_H 7.81–7.62 (6 H, m, Ph), 7.57–7.52 (3 H, m, Ph), 7.49–7.42 (6 H, m, Ph), 5.76 (1 H, br d, *J* 7, NH), 5.46 (1 H, m, CH), 3.77 (4 H, m, 2 × CH_2), 1.83 (1 H, m, CH), 1.46 (3 H, d, *J* 7, CH*Me*), 0.85 (6 H, d, *J* 6, CHMe_2) and 0.75 (3 H, t, *J* 7, Me); δ_C see Table 2; δ_P +18.0; *m*/*z* (CI) 520 (M + H^+, 100%), 474 (10), 444 (13), 375 (12), 263 (19) and 187 (15).

(*N*-Benzoxycarbonyl-(*S*)-prolinoyl(ethoxycarbonyl)methylene)triphenylphosphorane 18. From *N*-benzoxycarbonyl-(*S*)-proline as colourless crystals (1.40 g, 49%), mp 129–130 °C (Found: C, 72.5; H, 6.15; N, 2.3. $C_{34}H_{34}NO_5P$ requires C, 72.5; H, 5.9; N, 2.4%); $[\alpha]_D^{20}$ −45.0 (*c* 1.03 in CH_2Cl_2); ν_{max}/cm^{-1} 3350, 1675, 1650, 1580, 1440, 1295, 1100, 760 and 690; δ_H 7.88–7.14 (20 H, m, Ph), 5.71 and 5.64* (1 H, dd, *J* 9, 3, CH), 5.08 (2 H, m, OCH_2Ph), 3.72 (2 H, m, OCH_2), 3.49 (2 H, m, CH_2), 2.40 and 2.04 (2 H, 2 × m, CH_2), 1.73 (2 H, m, CH_2) and 0.66 (3 H, t, *J* 7, Me); δ_C see Table 2; δ_P +17.6 and 17.4*; *m*/*z* 567 (M^+, 0.7%), 553 (2.8), 525 (8), 465 (2.3), 375 (27), 279 (20), 181 (23), 149 (25), 105 (29) and 91 (100).

(*N*-Ethoxycarbonyl-(*S*)-prolinoyl(ethoxycarbonyl)methylene)-triphenylphosphorane 19. From *N*-ethoxycarbonyl-(*S*)-proline as colourless crystals (1.19 g, 44%), mp 112–114 °C (Found: C, 69.8; H, 6.5; N, 2.4. $C_{30}H_{32}NO_5P$ requires C, 69.6; H, 6.2; N, 2.7%); $[\alpha]_D^{20}$ −33.8 (*c* 0.96 in CH_2Cl_2); ν_{max}/cm^{-1} 1650, 1560, 1440, 1290, 1095, 1080, 750 and 690; δ_H 7.68–7.55 (6 H, m, Ph), 7.55–7.38 (9 H, m, Ph), 5.52 and 5.61 (1 H, ddd, *J* 13, 9, 2, CH), 4.04 (2 H, m, OCH_2), 3.72 (2 H, m, OCH_2), 3.40 (2 H, m, CH_2), 2.36 and 2.04 (2 H, 2 × m, CH_2), 1.71 (2 H, m, CH_2), 1.18 (3 H, m, Me) and 0.68 (3 H, t, *J* 7, Me); δ_C see Table 2; δ_P +17.4 and 17.2*; *m*/*z* (CI) 518 (M + H^+, 100%), 472 (95), 449 (9), 400 (42), 375 (71), 319 (9), 290 (58), 279 (73), 244 (14), 212 (49), 187 (32), 142 (52) and 47 (16).

Ethyl 5-ethoxycarbonylamino-3-oxo-2-triphenylphosphoranylidenepentanoate 20. From *N*-ethoxycarbonyl-β-alanine as colourless crystals (1.34 g, 52%), mp 94–95 °C (Found: C, 68.1; H, 6.1; N, 2.8. $C_{28}H_{30}NO_5P$ requires C, 68.4; H, 6.2; N, 2.9%); ν_{max}/cm^{-1} 3230, 1700, 1650, 1535, 1320, 1255, 1230, 1120, 1105, 1100, 1080, 1030, 750 and 690; δ_H 7.80–7.42 (15 H, m, Ph), 5.31 (1 H, br m, NH), 4.08 (2 H, q, *J* 7, OCH_2), 3.72 (2 H, q, *J* 7, OCH_2), 3.42 (2 H, m, CH_2N), 3.12 (2 H, t, *J* 7, CH_2), 1.25 (3 H, t, *J* 7, Me) and 0.69 (3 H, t, *J* 7, Me); δ_C see Table 2; δ_P +18.1; *m*/*z* (CI) 492 (M + H^+, 100%), 446 (12), 391 (29), 279 (39) and 263 (5).

Flash vacuum pyrolysis of ylides

The apparatus used was as described previously.[27] All pyrolyses were conducted at 600 °C and at pressures in the range 1–5 × 10^{-2} Torr. Under these conditions the contact time in the hot zone was estimated to be ~10 ms. In each case a mixture of solid and oil collected at the furnace exit which was shown by ^1H and ^{31}P NMR to be a mixture of Ph_3PO and the desired product. Chromatography on silica (diethyl ether–hexane, 1 : 2) gave the pure products as follows.

Ethyl (4*S*)-4-(benzoxycarbonylamino)pent-2-ynoate 21. FVP of the ylide **9** (500 mg) gave the title compound (72 mg, 29%) as a yellow oil (Found: C, 65.7; H, 6.6; N, 5.4; M + H^+, 276.1226. $C_{15}H_{17}NO_4$ requires C, 65.4; H, 6.2; N, 5.1%; *M* + *H*, 276.1236); $[\alpha]_D^{23}$ −30.3 (*c* 0.615 in CH_2Cl_2); ν_{max}/cm^{-1} 3318, 2983, 2245, 1709, 1526, 1254, 1064, 770 and 708; δ_H 7.38 (5 H, s, Ph), 5.11 (2 H, s, O*CH*$_2$Ph), 4.99 (1 H, br d, N*H*), 4.70 (1 H, m, C*H*), 4.22 (2 H, q, *J* 7, OCH_2), 1.47 (3 H, d, *J* 7, CH*Me*) and 1.30 (3 H, t, *J* 7, Me); δ_C see Table 4; *m*/*z* (CI) 276 (M + H^+, 26%), 232 (100), 147 (8) and 91 (9).

An additional minor product obtained from the chromatography was compound **30**.

(3*S*)-3-(Benzoxycarbonylamino)but-1-yne 30. Compound **30** as a yellow oil (28 mg, 15%) (Found: M^+, 203.0954. $C_{12}H_{13}NO_2$ requires M^+, 203.0946); $[\alpha]_D^{22}$ −3.43 (*c* 0.84 in CH_2Cl_2); ν_{max}/cm^{-1} 3405, 2926, 2253, 1708, 1525, 1224, 1049, 752 and 698; δ_H 7.40 (5 H, s, Ph), 5.14 (2 H, s, O*CH*$_2$Ph), 5.06 (1 H, br d, NH), 4.72 (1 H, m, NHC*H*), 2.62 (1 H, d, *J* 2, –CH) and 1.48 (3 H, d, *J* 7, CH*Me*); δ_C see Table 4; *m*/*z* (EI) 203 (M^+, 8%), 149 (9), 112 (5), 108 (80), 91 (100), 79 (16) and 65 (14).

Ethyl (4*S*)-4-benzoxycarbonylamino-5-methylhex-2-ynoate 22. FVP of the ylide **10** (300 mg) gave the title compound (91 mg, 58%) as colourless crystals, mp 60–62 °C (Found: M + H^+, 304.1551. $C_{17}H_{21}NO_4$ requires *M* + *H*, 304.1549); $[\alpha]_D^{23}$ −34.4 (*c* 0.545 in CH_2Cl_2); ν_{max}/cm^{-1} 3330, 2970, 2240, 1715, 1535, 1302, 1260, 1050, 750 and 690; δ_H 7.38 (5 H, s, Ph), 5.14 (2 H, s, OC*H*$_2$Ph), 5.02 (1 H, br d, NH), 4.55 (1 H, m, NHC*H*), 4.24 (2 H, q, *J* 7, OCH_2), 1.99 (1 H, m, C*H*Me_2), 1.33 (3 H, t, *J* 7, Me) and 1.03 (6 H, d, *J* 7, CH*Me*$_2$); δ_C see Table 4; *m*/*z* (CI) 304 (M + H^+, 51%), 260 (92), 232 (100), 188 (14) and 171 (16).

Additional minor products obtained from the chromatography were as follows.

(3*S*)-3-Benzoxycarbonylamino-4-methylpent-1-yne 31. Compound **31** was isolated as a colourless oil (13 mg, 10%) (Found: M^+, 231.1253. $C_{14}H_{17}NO_2$ requires *M*, 231.1259); $[\alpha]_D^{22}$ −2.7 (*c* 0.25 in CH_2Cl_2); ν_{max}/cm^{-1} 3307, 2963, 2243, 1708, 1526, 1467, 1238, 1028, 754 and 697; δ_H 7.37 (5 H, s, Ph), 5.11 (2 H, s, OC*H*$_2$), 4.92 (1 H, br s, NH), 4.37 (1 H, m, NHC*H*), 2.28 (1 H, d, *J* 2, –CH), 1.92 (1 H, m, C*H*Me_2) and 0.98 (6 H, d, *J* 8, CH*Me*$_2$); δ_C see Table 4; *m*/*z* (EI) 231 (M^+, 3%), 188 (8), 144 (11), 108 (13), 91 (100) and 65 (6).

(*E*)-Ethyl 4-benzoxycarbonylamino-5-methylhexa-2,4-dienoate 32. Compound **32** was isolated as a yellow oil (18 mg, 11%) (Found: M^+ − $PhCH_2$, 212.0931. $C_{17}H_{21}NO_4$ requires *M* − *PhCH*$_2$, 212.0923); ν_{max}/cm^{-1} 3322, 2981, 1728, 1625, 1371, 1279, 1176, 1029, 747 and 699; δ_H 7.80 (1 H, d, *J* 15, HC=), 7.38 (5 H, s, Ph), 5.88 (1 H, d, *J* 15, HC=), 5.68 (1 H, br s, NH), 5.16 (2 H, s, C*H*$_2$Ph), 4.20 (2 H, q, *J* 7, OC*H*$_2$Me), 2.03 (3 H, s, Me), 1.86 (3 H, s, Me) and 1.32 (3 H, t, *J* 7, OCH_2*Me*); δ_C 167.3 (CO_2), 154.3 (NHCO), 144.3 (NH*C*=), 138.8 (=CH), 136.2 (Ph C-1), 128.6 (2 C), 128.2 (2 C), 127.6 (Ph C-4), 125.9 (=*C*Me_2), 116.7 (=CH), 67.2 (O*C*H$_2$Ph), 60.4 (O*C*H$_2$Me), 21.5 (CH*Me*), 20.3 (CH*Me*) and 14.3 (Me); *m*/*z* (EI) 212 (M^+ − $PhCH_2$, 42%), 127 (10), 109 (16) and 91 (100).

Ethyl (4*S*)-4-benzoxycarbonylamino-6-methylhept-2-ynoate 23. FVP of the ylide **11** (360 mg) gave the title compound (68 mg, 30%) as a yellow oil (Found: M + H^+, 318.1707. $C_{18}H_{23}NO_4$ requires *M* + *H*, 318.1705); $[\alpha]_D^{22}$ −26.7 (*c* 0.49 in CH_2Cl_2); ν_{max}/cm^{-1} 3320, 2960, 2240, 1710, 1530, 1245, 1030, 750 and 700; δ_H 7.35 (5 H, s, Ph), 5.12 (2 H, s, OC*H*$_2$Ph), 4.93 (1 H, br s, NH), 4.68 (1 H, m, NHC*H*), 4.22 (2 H, q, *J* 7, OCH_2), 1.78 (1 H, m, CH_2C*H*), 1.62 (2 H, m, CHC*H*$_2$), 1.30 (3 H, t, *J* 7, Me) and 0.94 (6 H, d, *J* 7, CH*Me*$_2$); δ_C see Table 4; *m*/*z* (CI) 318 (M + H^+, 26%), 274 (100), 246 (13) and 202 (10).

Ethyl 4-(ethoxycarbonylamino)but-2-ynoate 24. FVP of the ylide **12** (200 mg) gave the title compound (33 mg, 39%) as a yellow oil (Found: C, 54.0; H, 6.9; N, 7.0; M + H^+, 200.0913. $C_9H_{13}NO_4$ requires C, 54.3; H, 6.5; N, 7.0%; *M* + *H*, 200.0922); ν_{max}/cm^{-1} 3340, 2980, 2240, 1705, 1520, 1360, 1240, 750 and 720; δ_H 4.25 (7 H, m, 3 × CH_2 and NH), 1.28 (3 H, t, *J* 7, Me) and 1.23 (3 H, t, *J* 7, Me); δ_C see Table 4; *m*/*z* (EI) 199 (M^+, 7%), 171 (6), 154 (45), 127 (100), 98 (83), 84 (82), 66 (47), 54 (68) and 49 (93).

Ethyl (4*S*)-4-(ethoxycarbonylamino)pent-2-ynoate 25. FVP of the ylide **13** (475 mg) gave the title compound (78 mg, 32%) as a yellow oil (Found: C, 56.6; H, 7.2; N, 6.6; M + H^+, 214.1083. $C_{10}H_{15}NO_4$ requires C, 56.3; H, 7.1; N, 6.6%; *M* + *H*, 214.1079); $[\alpha]_D^{20}$ −91.0 (*c* 0.695 in CH_2Cl_2); ν_{max}/cm^{-1} 3300, 2960, 2210, 1695, 1520, 1430, 1355, 1235, 1165, 1109 and 1044; δ_H 4.99 (1 H, br s, N*H*CH), 4.69 (1 H, m, NHC*H*), 4.23 (2 H, q, *J* 7, OCH_2), 4.14 (2 H, q, *J* 7, OCH_2), 1.47 (3 H, d, *J* 7, CH*Me*), 1.31 (3 H, t, *J* 7, CH_2*Me*) and 1.25 (3 H, t, *J* 7, CH_2*Me*); δ_C see Table 4; *m*/*z* (CI) 214 (M + H^+, 79%), 168 (100) and 142 (16).

Ethyl (4*S*)-4-ethoxycarbonylamino-5-methylhex-2-ynoate 26. FVP of the ylide **14** (500 mg) gave the title compound (79 mg, 34%) as a yellow oil (Found: M + H^+, 242.1400. $C_{12}H_{19}NO_4$ requires *M* + *H*, 242.1392); $[\alpha]_D^{20}$ −49.5 (*c* 0.91 in CH_2Cl_2); ν_{max}/cm^{-1} 3350, 2960, 2240, 1700, 1540, 1460, 1360, 1240, 1090, 1030 and 740; δ_H 4.92 (1 H, br d, *J* 8, N*H*CH), 4.51 (1 H, m, NHC*H*), 4.22 (2 H, q, *J* 7, OCH_2), 4.14 (2 H, q, *J* 7, OCH_2), 1.96 (1 H, m, CH), 1.31 (3 H, t, *J* 7, Me), 1.26 (3 H, t, *J* 7, Me) and 1.02 (6 H, d, *J* 7, CH*Me*$_2$); δ_C see Table 4; *m*/*z* (CI) 242 (M + H^+, 92%), 224 (9), 213 (21), 196 (100), 170 (27), 153 (21) and 57 (44).

Ethyl (4*S*)-4-ethoxycarbonylamino-6-methylhept-2-ynoate 27. FVP of the ylide **15** (450 mg) gave the title compound (77 mg, 36%) as a yellow oil (Found: M + H^+, 256.1556. $C_{13}H_{21}NO_4$ requires *M* + *H*, 256.1549); $[\alpha]_D^{20}$ −74.5 (*c* 0.865 in CH_2Cl_2); ν_{max}/cm^{-1} 3340, 2460, 2240, 1700, 1530, 1370, 1245, 1050 and 760; δ_H 5.15 and 5.31 (1 H, 2 × br d, N*H*CH), 4.64 and 4.81 (1 H, m, NHC*H*), 4.22 (2 H, q, *J* 7, OCH_2), 4.17 (2 H, q, *J* 7, OCH_2), 1.78 (1 H, m, CH_2C*H*), 1.48 (2 H, t, *J* 7, CH_2), 1.31 (3 H, t, *J* 7, Me), 1.26 (3 H, t, *J* 7, Me) and 0.95 (6 H, d, *J* 7, CH*Me*$_2$); δ_C see Table 4; *m*/*z* (CI) 256 (M + H^+, 98%), 228 (11), 210 (100), 198 (12), 167 (15) and 57 (23).

Ethyl (4*S*,5*S*)-4-ethoxycarbonylamino-5-methylhept-2-ynoate 28

FVP of the ylide **16** (440 mg) gave the title compound (80 mg, 38%) as a yellow oil (Found: C, 61.3; H, 8.3; N, 5.7; M + H^+, 256.1547. $C_{13}H_{21}NO_4$ requires C, 61.2; H, 8.3; N, 5.5%; *M* + *H*, 256.1549); $[\alpha]_D^{20}$ +9.1 (*c* 0.52 in CH_2Cl_2); ν_{max}/cm^{-1} 3310, 2960, 2230, 1710, 1530, 1240, 1040 and 750; δ_H 5.34 and 5.06 (1 H, 2 × m, N*H*CH), 4.79 and 4.62 (1 H, 2 × m, NHC*H*), 4.24 (2 H, m, OCH_2), 4.15 (2 H, m, OCH_2), 1.76–1.58 (1 H, m, *H*CH), 1.27 (5 H, m, *Me*CHC*H*$_2$), 1.00 (3 H, d, *J* 7, Me) and 0.94 (3 H, t, *J* 7, Me); δ_C see Table 4; *m*/*z* (CI) 256 (M + H^+, 67%), 228 (37), 210 (31) and 184 (11).

Ethyl (4*S*)-4-(isobutoxycarbonylamino)pent-2-ynoate 29. FVP of the ylide **17** (500 mg) gave the title compound (77 mg, 33%) as a pale yellow oil (Found: M + H^+, 242.1392. $C_{12}H_{19}NO_4$ requires *M* + *H*, 242.1401); $[\alpha]_D^{23}$ −9.1 (*c* 0.615 in CH_2Cl_2); ν_{max}/cm^{-1} 3320, 2970, 2250, 1715, 1530, 1470, 1370, 1255, 1055, 1025, 780 and 755; δ_H 4.97 (1 H, m, NH), 4.69 (1 H, m, NCH), 4.23 (2 H, q, *J* 7, OCH_2), 3.86 (2 H, d, *J* 6, C*H*$_2$CH), 2.92 (1H, m, C*H*Me_2), 1.48 (3 H, d, *J* 7, CH*Me*), 1.31 (3 H, t, *J* 7, CH_2*Me*) and 0.93 (6 H, d, *J* 7, Me); δ_C see Table 4; *m*/*z* (CI) 242 (M + H^+, 100%).

Ethyl (*S*)-3-(1-benzoxycarbonylpyrrolidin-2-yl)propynoate 33. FVP of the ylide **18** (352 mg) gave the title compound (90 mg, 48%) as a pale yellow oil (Found: C, 68.0; H, 6.6; N, 4.6. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4; N, 4.7%); $[\alpha]_D^{22}$ −114.4 (*c* 1.01 in CH_2Cl_2); ν_{max}/cm^{-1} 3400, 2980, 2240, 1705, 1410, 1355, 1250, 1180, 1120, 1090, 750 and 700; δ_H 7.34 (5 H, m, Ph), 5.18 (2 H, m, OC*H*$_2$Ph), 4.68 (1 H, m, CHN), 4.22 (2 H, q, *J* 7, OCH_2), 3.44 (2 H, m, CHC*H*$_2$), 2.12 (4 H, m, CH_2CH_2) and 1.30 (3 H, t, *J* 7, Me); δ_C see Table 4; *m*/*z* (CI) 302 (M + H^+, 61%), 272 (11), 258 (33), 168 (12), 147 (27), 111 (28), 97 (53), 86 (32), 71 (37) and 59 (100).

Ethyl (*S*)-3-(1-ethoxycarbonylpyrrolidin-2-yl)propynoate 34. FVP of the ylide **19** (500 mg) gave the title compound (110 mg, 48%) as a yellow oil (Found: M + H^+, 240.1226. $C_{12}H_{17}NO_4$ requires *M* + *H*, 240.1236); $[\alpha]_D^{20}$ −137.7 (*c* 0.535 in CH_2Cl_2); ν_{max}/cm^{-1} 2960, 2220, 1700, 1410, 1330, 1250, 1120, 1090, 770 and 750; δ_H 4.68 (1 H, m, NCH), 4.59 (2 H, m, OCH_2), 4.16 (2 H, m, OCH_2), 3.44 (2 H, m, CH_2), 2.13 (4 H, m, CH_2CH_2) and 1.29 (6 H, t, *J* 7, 2 × Me); δ_C see Table 4; *m*/*z* (CI) 240 (M + H^+, 55%), 212 (98), 194 (70), 167 (100), 138 (77), 94 (33) and 70 (39).

Ethyl 5-(ethoxycarbonylamino)pent-2-ynoate 35. FVP of the ylide **20** (505 mg) gave the title compound (107 mg, 49%) as a pale yellow oil (Found: C, 56.6; H, 7.3; N, 6.4. $C_{10}H_{15}NO_4$ requires C, 56.3; H, 7.1; N, 6.6%); ν_{max}/cm^{-1} 3330, 2980, 2240, 1700, 1540, 1360, 1250, 1070, 1030 and 750; δ_H 5.16 (1 H, br s, NH), 4.22 (2 H, q, *J* 7, OCH_2), 4.12 (2 H, q, *J* 7, OCH_2), 3.38 (2 H, q, *J* 7, $NHCH_2$), 2.57 (2 H, t, *J* 7, CH_2), 1.31 (3 H, t, *J* 7, Me) and 1.24 (3 H, t, *J* 7, Me); δ_C see Table 4; *m/z* 213 (M^+, 15%), 185 (20), 168 (40), 141 (14), 122 (31), 102 (100), 84 (29) and 66 (22).

Reactions of acetylenic amino acid esters

Hydrobromination. *(E) and (Z)-Ethyl (4S)-2-bromo-4-(ethoxycarbonylamino)pent-2-enoate* ***36***. To a solution of ethyl (4*S*)-4-(ethoxycarbonylamino)pent-2-ynoate **25** (0.12 g, 0.56 mmol) in dry CH_2Cl_2 (5 cm^3) was added a solution of hydrobromic acid in acetic acid (45% w/v, 0.20 cm^3, 1.1 mmol) and the mixture stirred overnight at RT. The solvent was evaporated under vacuum and the residue was chromatographed (SiO_2, ethyl acetate–hexane, 1 : 1) to give the product (0.13 g, 80%) as a yellow oil (Found: $^{79}Br - M + H^+$, 294.0347. $C_{10}H_{16}{}^{79}BrNO_4$ requires *M* + *H*, 294.0340); ν_{max}/cm^{-1} 3320, 2980, 1710, 1625, 1520, 1445, 1330, 1300, 1250, 1170, 1090, 1050, 1030, 865 and 750; δ_H 6.57 and 6.36 (1 H, 2 × s, =CH), 5.74 and 5.61 (1 H, 2 × s, NH), 5.73 and 4.49 (1 H, 2 × s, NHC*H*), 4.14 and 4.10 (2 H, m, OCH_2), 4.041 and 4.042 (2 H, m, OCH_2), 1.29 (3 H, d, *J* 7, Me), 1.21 and 1.16 (3 H, t, *J* 7, Me) and 1.14 (3 H, t, *J* 7, Me); δ_C 164.1 and 163.6 (CO_2Et), 155.4 (2 × NHCO), 151.7 and 143.4 (=CBr), 123.5 and 119.6 (=CH), 61.2 and 61.0 (OCH_2), 54.9 and 48.6 (NCH), 20.3 and 19.6 (CH*Me*), 14.6 (CH_2Me) and 14.2 (CH_2Me); *m/z* 296/294 ($^{81/79}Br - M + H^+$, 94/94%), 146 (26), 116 (35), 99 (34), 90 (48), 73 (85), 59 (53) and 46 (5).

Hydrogenation: preparation of GABA analogues. *Ethyl (4S)-4-aminopentanoate* ***37***. To a solution of ethyl (4*S*)-4-(benzoxycarbonylamino)pent-2-ynoate **21** (80 mg, 0.29 mmol) in methanol (10 cm^3) was added Pd/C catalyst (80 mg) and the mixture was stirred under a hydrogen atmosphere. After 12 h the mixture was filtered through a Celite pad and the solvent removed. Chromatography on silica (methanol–diethyl ether, 2 : 1) gave the pure product (31 mg, 74%) as a yellow oil (Found: $M + H^+$, 146.1179. $C_7H_{15}NO_2$ requires *M*+ H, 146.1181); $[\alpha]_D^{25.5}$ −2.5 (*c* 0.50 in MeOH); ν_{max}/cm^{-1} 3400, 1730, 1600, 1505, 1275, 1188 and 1020; δ_H 7.52 (2 H, br s, NH_2), 4.14 (2 H, q, *J* 7, OCH_2), 3.47 (1 H, m, CH), 2.51 (2 H, t, *J* 7, $COCH_2$), 2.17 and 1.98 (1 H, 2 × m, CH_2), 1.43 (3 H, d, *J* 5, CH*Me*) and 1.25 (3 H, t, *J* 7, OCH_2Me); δ_C 172.7 (CO_2), 60.8 (OCH_2), 47.8 (CH), 30.4 ($COCH_2$), 29.7 (CH_2CH), 18.5 (CH*Me*) and 14.2 (Me); *m/z* (CI) 146 ($M + H^+$, 100%).

(±)-Ethyl 4-aminopentanoate. This was prepared as above using ethyl (±)-4-(benzoxycarbonylamino)pent-2-ynoate, the racemic analogue of **21** (100 mg, 0.36 mmol) and Pd/C catalyst (100 mg) to give the title compound (38 mg, 72%) as an oil. Spectroscopic properties were identical to the non-racemic compound.

Ethyl (4R)-4-amino-5-methylhexanoate ***38***. This was prepared as above using ethyl (4*S*)-4-benzoxycarbonylamino-5-methylhex-2-ynoate **22** (88 mg, 0.29 mmol) and Pd/C catalyst (88 mg) to give the title compound (40 mg, 72%) as colourless crystals, mp 101–102 °C (Found: $M + H^+$, 174.1498. $C_9H_{19}NO_2$ requires *M* + *H*, 174.1494); $[\alpha]_D^{25}$ +7.2 (*c* 0.50 in MeOH); ν_{max}/cm^{-1} 3340, 1725, 1640, 1540, 1260, 1180, 1100, 1040 and 800; δ_H 7.96 (2 H, br s, NH_2), 4.13 (2 H, q, *J* 7, CH_2), 3.14 (1 H, m, NCH), 2.62 (2 H, t, *J* 7, $COCH_2$), 2.02 (3 H, m, CH + CH_2), 1.25 (3 H, t, *J* 7, OCH_2Me), 1.10 (3 H, d, *J* 5, CH*Me*) and 1.08 (3 H, d, *J* 5, CH*Me*); δ_C 172.5 (CO_2), 60.7 (OCH_2), 57.3 (NCH), 30.52 (CH), 30.48 ($COCH_2$), 25.0 (CH_2CH), 18.1 (CH*Me*), 18.0 (CH*Me*) and 14.2 (OCH_2Me); *m/z* (CI) 174 ($M + H^+$, 100%), 128 (8) and 102 (6).

Ethyl (4R)-4-amino-6-methylheptanoate ***39***. This was prepared as above using ethyl (4*S*)-4-benzoxycarbonylamino-6-methylhept-2-ynoate **23** (94 mg, 0.30 mmol) and Pd/C catalyst (94 mg) to give the title compound (39 mg, 70%) as colourless crystals, mp 124–125 °C (Found: $M + H^+$, 188.1644. $C_{10}H_{21}NO_2$ requires *M* + H, 188.1650); $[\alpha]_D^{25}$ +6.9 (*c* 0.50 in MeOH); ν_{max}/cm^{-1} 3390, 1730, 1600, 1510, 1275, 1190 and 1020; δ_H 8.93 (2 H, br s, NH_2), 4.14 (2 H, q, *J* 7, OCH_2), 3.37 (1 H, m, NCH), 2.59 (2 H, t, *J* 7, $COCH_2$), 2.04 (2 H, m, CH_2), 1.88 and 1.70 (2 H, 2 × m, CH_2), 1.49 (1 H, m, CH), 1.25 (3 H, t, *J* 7, OCH_2Me) and 0.95 (6 H, d, *J* 7, $CHMe_2$); δ_C 172.5 (CO_2), 60.7 (OCH_2), 50.2 (NCH), 42.1 ($CHCH_2$), 30.1 ($COCH_2$), 28.2 (CH_2), 24.4 (CH), 22.4 (CH*Me*), 22.2 (CH*Me*) and 14.2 (OCH_2Me); *m/z* (CI) 188 ($M + H^+$, 100%).

Ethyl (S)-3-(pyrrolidin-2-yl)propanoate ***40***. This was prepared as above using ethyl (*S*)-3-(1-benzoxycarbonylpyrrolidin-2-yl)propynoate **33** (90 mg, 0.30 mmol) and Pd/C catalyst (90 mg) to give the title compound (40 mg, 78%) as a yellow oil (Found: $M + H^+$, 172.1339. $C_9H_{17}NO_2$ requires *M* + H, 172.1338); $[\alpha]_D^{25}$ −8.6 (*c* 1.0 in MeOH); ν_{max}/cm^{-1} 3440, 2960, 2750, 2500, 1730, 1630, 1450, 1420, 1375, 1280, 1190 and 1025; δ_H 8.90 (1 H, br s, NH), 4.09 (2 H, q, *J* 7, OCH_2), 3.61 (1 H, m, NCH), 3.40 (2 H, m, CH_2), 2.57 (2 H, t, *J* 8, $COCH_2$), 2.05 (5 H, m, 2 × CH_2 and 1 H of CH_2CH), 1.71 (1 H of CH_2CH, m) and 1.26 (3 H, t, *J* 7, Me); δ_C 172.3 (CO_2), 60.8 (OCH_2), 59.8 (NCH), 44.6 (CH_2), 31.5 (CH_2), 30.3 (CH_2), 27.1 (CH_2), 23.4 (CH_2) and 14.2 (Me); *m/z* (CI) 172 ($M + H^+$, 100%); *m/z* (EI) 170 ($M - H^+$, 6%), 126 (14), 84 (6) and 70 (100).

Preparation of Mosher amides

These derivatives were prepared by a modification of the method by Mosher and co-workers[14] as illustrated by the example below. In the spectra * denotes the minor diastereomer.

Derivative of ethyl (4*S*)-4-aminopentanoate 37. A solution of (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (156 mg, 0.62 mmol) in dry toluene (2 cm^3) under a nitrogen atmosphere was cooled to 0 °C. DMAP (76 mg, 0.62 mmol) and **37** (30 mg, 0.21 mmol) in dry toluene (2 cm^3) were then added and the mixture stirred at RT for 2 h. The reaction mixture was recooled to 0 °C and washed successively with 1 M HCl (1 cm^3) and saturated $NaHCO_3$ (1 cm^3). The organic phase was dried and concentrated under vacuum to give the Mosher amide derivative which was analysed without further purification; δ_H 7.59 (2 H, m, Ph), 7.50 (3 H, m, Ph), 6.81 and 6.74* (1 H, 2 × d, *J* 8, NH), 4.05 (3 H, m, NCH + OCH_2), 3.41 and 3.38* (3 H, 2 × q, *J* 2, OMe), 2.28 (2 H, m, $COCH_2$), 1.81 (2 H, m, CH_2), 1.25 (3 H, t, *J* 7, OCH_2Me) and 1.20 and 1.17* (3 H, 2 × d, *J* 6, CH*Me*); δ_C 173.3 and 173.2 (CO), 165.83 and 165.78 (CO_2), 132.8 and 132.6 (C-1 of Ph), 129.5 (C-4 of Ph), 128.59 and 128.54 (2 C, Ph), 127.72 and 127.65 (2 C, Ph), 124.0 (q, *J* 290, CF_3), 84.1 (q, *J* 26, CCF_3), 60.6 (OCH_2), 54.9 (OMe), 45.4 (NCH), 31.4 and 31.3 (CH_2), 31.0 (CH_2), 20.85 and 20.77 (CH*Me*) and 14.2 (OCH_2Me); δ_F −70.46 and −70.51*; de = 76%.

Derivative of ethyl (4*R*)-4-amino-5-methylhexanoate 38. This was prepared as above using **38** to give the Mosher amide derivative as an oil; δ_H 7.56 (2 H, m, Ph), 7.40 (3 H, m, Ph), 6.69 and 6.56* (1 H, 2 × br d, *J* 8, NH), 4.06 (2 H, m, OCH_2), 3.82 (1 H, m, CHN), 3.44 and 3.39* (3 H, 2 × q, *J* 2, OMe), 2.20 (2 H, m, $COCH_2$), 1.84 (2 H, m, CH_2), 1.63 (1 H, m, CH), 1.20 (3 H, t, *J* 7, Me), 0.94 (3 H, d, *J* 6, CH*Me*) and 0.92 (3 H, d, *J* 6, CH*Me*); δ_C 173.6 (CO), 166.4 (CO_2), 133.1 (d, *J* 17, C-1 of Ph), 129.6 (Ph), 128.7 (2 C, d, *J* 4, Ph), 127.7 (2 C, d, *J* 5, Ph), 124.0 (q, *J* 290, CF_3), 84.2 (q, *J* 26, CCF_3), 60.6 (OCH_2), 55.2 (NCH), 54.2 (OMe), 39.5 (CH), 32.0 (CH_2), 29.8 (CH_2), 19.0 (CH*Me*), 17.8 (CH*Me*) and 14.2 (OCH_2Me); δ_F −69.68 and −69.86*; de = 85%.

Derivative of ethyl (4*R*)-4-amino-6-methylheptanoate 39. This was prepared as above **39** to give the Mosher amide derivative as an oil; δ_H 7.53 (2 H, m, Ph), 7.31 (3 H, m, Ph), 6.64 (1 H, br s, NH), 4.07 (3 H, m, CHN and OCH_2), 3.39 and 3.38* (3 H, 2 × q, *J* 2, OMe), 2.32 (1 H, m, $COCH_2$), 1.89 (2 H, m, CH_2), 1.64 (1 H, m, CH), 1.41 (2 H, m, CH_2), 1.21 (3 H, t, *J* 7, OCH_2*Me*), 0.94 (3 H, d, *J* 6, CH*Me*) and 0.92 (3 H, d, *J* 6, CH*Me*); δ_C 173.99* and 173.86 (CO), 166.3 (CO_2), 132.4 (C-1 of Ph), 129.4 (C-4 of Ph), 128.6* and 128.5 (2 C, Ph), 127.6* and 127.4 (2 C, Ph), 123.8* and 123.2 (2 × q, *J* 288, CF_3), 84.1 (q, *C*CF_3, *J* 26), 60.8 (OCH_2), 55.5 (OMe), 47.6 (NCH), 44.4 (CH*C*H_2), 30.8 (CH_2), 30.3 (CH_2), 24.9 (CH), 23.0 (CH*Me*), 22.0 (CH*Me*) and 14.1 (OCH_2*Me*); δ_F −69.68 and −69.86*; de >85%.

Derivative of ethyl (*S*)-3-(pyrrolidin-2-yl)propanoate 40. This was prepared as above using **40** to give the Mosher amide derivative as an oil; δ_H 7.54 (2 H, m, Ph), 7.34 (3 H, m, Ph), 4.18 (3 H, m, CHN and OCH_2), 3.46 (1 H, m, CH), 3.42 (3 H, d, *J* <2, OMe), 2.36 (4 H, m), 1.85 (2 H, m), 1.70 (2 H, m), 1.59 (2 H, m) and 1.26 (3 H, t, *J* 7, Me); δ_C 173.6 (CO), 164.6 (CO_2), 132.3 (C-1 of Ph), 130.6 (Ph), 128.7 (2 C, d, *J* 4, Ph), 127.9 (2 C, d, *J* 5, Ph), 124.1 (q, *J* 290, CF_3), 84.3 (q, *J* 26, *C*CF_3), 60.8 (OCH_2), 58.4 (NCH), 55.4 (OMe), 46.1 (CH*C*H_2), 31.5 (CH_2), 28.5 (CH_2), 27.5 (CH_2), 24.4 (CH_2) and 14.2 (Me); δ_F −71.96; de >95%.

Acknowledgements

We thank EPSRC and GlaxoSmithKline for a CASE studentship (T. M.)

References

1 Part 16: R. A. Aitken, M. J. Drysdale, L. Hill, K. W. Lumbard, J. R. MacCallum and S. Seth, *Tetrahedron*, 1999, **55**, 11039.
2 Review, R. A. Aitken and A. W. Thomas, in *Chemistry of the functional groups*, Supplement A3, ed. S. Patai, Wiley, New York, 1997, 473.
3 R. A. Aitken, C. E. R. Horsburgh, J. G. McCreadie and S. Seth, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1727.
4 R. A. Aitken, H. R. Cooper and A. P. Mehrotra, *J. Chem. Soc., Perkin Trans. 1*, 1996, 475.
5 S. A. Abdulganeeva and K. B. Erzhanov, *Russ. Chem. Rev.*, 1991, **60**, 676.
6 C. Walsh, *Tetrahedron*, 1982, **38**, 871.
7 P. M. Beart and G. A. R. Johnston, *Aust. J. Chem.*, 1972, **25**, 1359.
8 A. G. Doutheau, J. Gore and G. Quash, EP 133 407, 1985.
9 B. W. Metcalf, P. Bey, C. Danzin, M. J. Jung, P. Casara and J. P. Vevert, *J. Am. Chem. Soc.*, 1978, **100**, 2551; P. Casara, C. Danzin, B. W. Metcalf and M. J. Jung, *J. Chem. Soc., Chem. Commun.*, 1982, 1190; P. Casara, C. Danzin, B. Metcalf and M. Jung, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2201.
10 B. W. Metcalf and P. Casara, *Tetrahedron Lett.*, 1975, 3337; A. B. Tabor, A. B. Holmes and R. Baker, *J. Chem. Soc., Chem. Commun.*, 1989, 1025; J. R. Burke and R. B. Silverman, *J. Am. Chem. Soc.*, 1991, **113**, 9329.
11 Preliminary communication: R. A. Aitken and N. Karodia, *Chem. Commun.*, 1996, 2079.
12 H. H. Wasserman, D. S. Ennis, C. A. Blum and V. M. Rotello, *Tetrahedron Lett.*, 1992, **33**, 6003; H. H. Wasserman, D. S. Ennis, P. L. Power and M. J. Ross, *J. Org. Chem.*, 1993, **58**, 4785.
13 M. T. Reetz, T. J. Strack, J. Kanand and R. Goddard, *Chem. Commun.*, 1996, 733.
14 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543; H. Niwa, T. Ogawa, O. Okamoto and K. Yamada, *Tetrahedron*, 1992, **48**, 10531.
15 M. Smrcina, P. Majer, E. Majerová, T. A. Guerassina and M. A. Eissenstat, *Tetrahedron*, 1997, **53**, 12867.
16 J.-N. Denis, S. Tchertchian, A. Tomassini and Y. Vallée, *Tetrahedron Lett.*, 1997, **38**, 5503.
17 K. Yamada, M. Takeda and T. Iwakuma, *J. Chem. Soc., Perkin Trans. 1*, 1983, 265.
18 M. Bergmann and L. Zervas, *Ber. Dtsch. Chem. Ges.*, 1932, **65**, 1192.
19 W. Grassmann and E. Wünsch, *Chem. Ber.*, 1958, **91**, 462.
20 A. Hantzsch and W. V. Metcalf, *Ber. Dtsch. Chem. Ges.*, 1896, **29**, 1680.
21 K. Freudenberg and M. Meister, *Liebigs Ann. Chem.*, 1935, **518**, 86.
22 E. Fischer and W. Axhausen, *Liebigs Ann. Chem.*, 1905, **340**, 123.
23 F. M. F. Chen and N. L. Benoiton, *Can. J. Chem.*, 1987, **65**, 1224.
24 M. R. Vernsten and M. B. Moore, *J. Am. Chem. Soc.*, 1953, **75**, 1320.
25 Y. Kita, J. Haruta, H. Tagawa and Y. Tamura, *J. Org. Chem.*, 1980, **45**, 4519.
26 L. L. Braun and J. H. Looker, *J. Am. Chem. Soc.*, 1958, **80**, 359.
27 R. A. Aitken and J. I. Atherton, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1281.