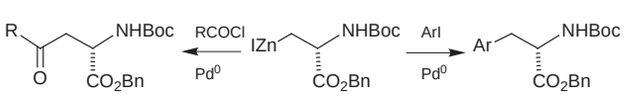
Synthesis of α-amino acids using amino acid γ-anion equivalents: synthesis of 5-oxo α-amino acids, homophenylalanine derivatives and pentenylglycines

Richard F. W. Jackson,*[,a] Joanne L. Fraser,[a] Neil Wishart,[a] Barry Porter[b] and Martin J. Wythes[c]

[a] *Department of Chemistry, Bedson Building, The University of Newcastle, Newcastle upon Tyne, UK NE1 7RU*
[b] *Dagenham Research Centre, Rhône-Poulenc Rorer Ltd., Rainham Road South, Dagenham, Essex, UK RM10 7XS*
[c] *Pfizer Central Research, Sandwich, Kent, UK CT13 9NJ*

Treatment of protected iodohomoalanine 7 with Rieke copper leads to the formation of an organocopper reagent 10 which reacts with electrophiles in moderate yield to give enantiomerically pure α-amino acid derivatives 11, 12 and 13. Alternatively, reaction of the fully protected iodohomoalanine derivative 15 with activated zinc gives the corresponding alkylzinc iodide 14, which reacts under palladium catalysis with a range of electrophiles (aryl iodides and acid chlorides) to give the corresponding adducts 19 and 22. While the reactions with aryl iodides provide acceptable yields in THF as solvent, the corresponding reactions with acid chlorides requires dimethoxyethane or, preferably, a combination of toluene and dimethylacetamide under ultrasonication, for good results. The alkylzinc iodide 14 can be transformed into a zinc–copper reagent 16 which reacts with allylic halides, and with reactive acid chlorides, to give the corresponding adducts 22l, 24–26 in reasonable yields.

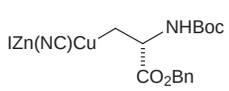
Over recent years, we have developed the use of iodoalanine-derived organometallic reagents for the synthesis of non-proteinogenic amino acids in enantiomerically pure form. For example, the organozinc reagent **1**, prepared by treatment of appropriately protected iodoalanine with activated zinc in benzene–dimethylacetamide using sonochemical activation, reacts under palladium catalysis with acid chlorides to give 4-oxo α-amino acids **2**, and also with aryl iodides to give 3-aryl α-amino acids **3** (Scheme 1).[1]



2 **1** **3**

Scheme 1

The synthetic applicability of this approach has been significantly extended by the demonstration that the zinc–copper reagent **4**, prepared from **1** by transmetallation, can react with

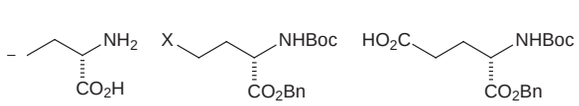


4

allylic halides (and a range of other electrophiles) to give enantiomerically pure amino acid derivatives.[2] The successful demonstration that the zinc reagent **1** and the zinc–copper reagent **4** behave as direct synthetic equivalents for the simple unstabilised amino acid β-anion synthon prompted us to explore the generality of this approach. In this paper we report in full the results of our initial efforts to generate synthetic equivalents for the amino acid γ-anion synthon **5**.†

† The work described in this paper has been published in preliminary form.[3–5]

Efficient access to a synthetic equivalent for the amino acid γ-anion synthon **5** would allow the direct preparation of enantiomerically pure 5-oxo α-amino acids by reaction with acid chlorides, homophenylalanine derivatives by coupling with aryl iodides, and pentenylglycines by reaction with allylic halides. Previous routes to 5-oxo α-amino acids have included reaction of nucleophiles with pyroglutamic acid derivatives,[6–10] treatment of activated glutamic acid derivatives with diazoalkanes[11,12] and acylation of glutamic acid derived enolates.[13,14] Homophenylalanines, which are important as components of ACE inhibitors (*e.g.* Enalapril), have been prepared by a variety of methods. These include use of the chiral pool, for example by reaction of diarylcopper lithium reagents with analogues of iodohomoalanine **7**.[15,16] Use of chiral glycine anion equivalents[17] and of chiral glycine cation equivalents[18] has also been explored. An indirect approach, based on catalytic asymmetric reduction of trichloromethyl ketones followed by reaction with azide anion and hydrogenation, has been developed,[19] and catalytic asymmetric hydrogenation has also been exploited.[20] Pentenylglycines have been prepared by both chemical[21] and enzymatic methods.[22]



5 **6** X = ZnI, **7** X = I, **8** X = H **9**

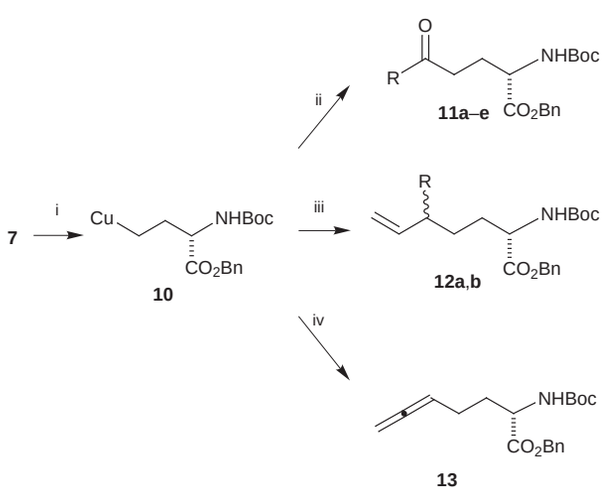
Earlier indirect approaches to the γ-anion equivalent **5** have relied on the use of differentially protected glutamic acid derivatives[23–25] or the use of pyroglutamic acid.[26,27] Since the reagent **1** is viable,[1] despite the presence of an acidic proton on nitrogen,[28] we decided to investigate whether a similarly protected homologous reagent **6** could be prepared using the conditions that we had developed for the preparation of zinc reagent **1**. The required iodohomoalanine derivative **7** was prepared from commercially available Boc-glutamic acid α-benzyl

ester **9** in 68% overall yield by the use of the Barton decarboxylative iodination procedure.[29] Photolytic decomposition of the intermediate *N*-hydroxy-2-thiopyridone ester,[30,31] rather than the use of thermolysis, resulted in slightly higher yields. Unfortunately, reaction of iodide **7** with zinc–copper couple under the sonochemical conditions[1] which we have developed for preparation of the serine derived reagent **1**, resulted in the formation not only of the zinc reagent **6** but also significant amount of protected 2-aminobutanoic acid **8**, formed by protonation of the carbon–zinc bond. Similarly, use of activated zinc in THF as solvent was also inefficient. After we had completed these preliminary experiments, it was reported that provided a four-fold excess of the zinc reagent **6** is used, satisfactory yields of coupled product may be obtained in the palladium catalysed reaction with an iodohistidine derivative, provided the yield is based on the iodohistidine derivative.[32] Given the higher cost, in general, of the amino acid derived-iodide compared with most simple electrophiles, we have chosen to explore alternatives which make more efficient use of the amino acid component.

We have therefore pursued two strategies for the development of alternative synthetic equivalents for the amino acid γ-anion synthon **5**. The first of these involved direct formation of an organocopper reagent **10** by treatment of the iodide **7** with Rieke copper at low temperature,[33] under which conditions we hoped that protonation of the carbon–metal bond would be less likely to occur. The second strategy involved complete nitrogen protection, so as to prevent protonation of the carbon–zinc bond by the acidic NH.

Preparation of an amino acid derived copper reagent

The alkylcopper reagent **10** was prepared by treatment of the iodide **7** with Rieke copper, prepared by reduction of the THF-soluble salt CuCN·2 LiCl.[33,34] After significant experimentation, it was established that the most effective conditions involved the use of an excess of Rieke copper (6 equiv.) at −78 °C, which allowed conversion of the iodide **7** into the copper reagent **10** within 30 minutes.‡ Reaction of **10** with acid chlorides gave 5-oxo α-amino acids **11a–e** in moderate yield (Scheme 2). In all cases, the only isolated by-product was



Scheme 2 *Reagents and conditions*: i, Rieke Cu (6 equiv.), THF, −78 °C, 30 min; ii, RCOCl (6 equiv.), THF, −30 °C, 3 h; iii, RCH=CHCH$_2$Cl (6 equiv.), THF, −30 °C, 3 h; iv, HC≡CCH$_2$Cl (6 equiv.), THF, −30 °C, 3 h

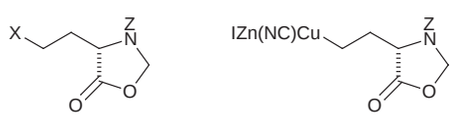
‡ The precise structure of the organocopper reagent **10** is a matter for further investigation. One can speculate that the reagent is a lower order lithiocyanocuprate [RCu(CN)Li], since Rieke has established that free LiCN is not present in simpler cases.[33] The reactivity of this reagent towards electrophiles is substantially higher than the analogous zinc–copper reagent **16**.

Table 1 Reactions of organocopper reagent **10** with electrophiles

Electrophile	Product	R	Yield (%)
PhCOCl	**11a**	Ph	46
MeCOCl	**11b**	Me	52
n-C_5H_{11}COCl	**11c**	*n*-C_5H_{11}	44
c-C_5H_9COCl	**11d**	*c*-C_5H_9	55
2-furylCOCl	**11e**	2-furyl	40
CH_2=$CHCH_2Cl$	**12a**	H	42
PhCH=$CHCH_2Cl$	**12b**	Ph	62

protected 2-aminobutanoic acid **8**. In two cases, **11c** and **11d**, the enantiomeric purity of the products could be established by direct comparison with literature data. Use of allylic halides gave the corresponding allylated derivatives **12a** and **12b**. Isolation of **12b** established that the predominant reaction pathway of the copper reagent with allylic substrates was S_N2'. Our results are summarised in Table 1. Consistent with this observation, reaction of **10** with prop-2-ynyl chloride gave the terminal allene **13** (36%).[12] A differently protected analogue of this allene has been prepared previously by means of radical chemistry,[35] as well as by conventional enzymatic resolution.[36]

Having established that it was possible to prepare the organocopper reagent **10**, attention was then directed towards the formation of an organozinc reagent so as to explore its palladium catalysed coupling reactions with a range of electrophiles. At the outset of our work in this area, the fully protected organozinc reagent **14** had been prepared from the corresponding iodide **15**, and two examples of an efficient copper-catalysed



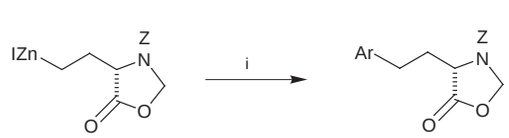
14 X = IZn
15 X = I
17 X = HO_2C
18 X = H

16

conjugate addition reaction of reagent **14** with enones had been reported.[37] This reagent therefore appeared to be an ideal choice for exploring the scope of palladium catalysed coupling reactions with a range of electrophiles. It was also clear that a stoichiometric transmetallation into the zinc–copper reagent **16** would broaden the scope of the amino acid derivatives which were accessible.[38] The iodide **15** was prepared in an analogous manner to the iodide **7**, using the protected glutamic acid derivative **17** as starting material, using the general literature procedure[29] which had been applied to this particular substrate and reported in preliminary form.[37]

Synthesis of homophenylalanine derivatives

The zinc reagent **14** was prepared by treatment of the iodide **15** with zinc dust under the conditions developed by Knochel.[39] This allowed the preparation of the reagent under more convenient conditions than those previously reported.[37] Coupling[40] of the zinc reagent **14** with aryl iodides in the presence of the palladium(0) catalyst prepared by reaction of tris(dibenzylideneacetone)dipalladium with tri-*o*-tolylphosphine, proceeded as expected to give the homophenylalanine derivatives **19** in moderate yields (Scheme 3). The major by-product in all cases

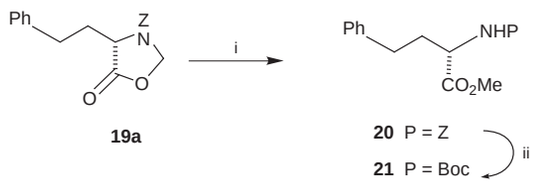


14 **19a–h**

Scheme 3 *Reagents and conditions*: i, ArI, $Pd_2(dba)_3$ (0.625 mol%), P(*o*-tol)$_3$ (2.5 mol%), THF, 50 °C, 1 h

was the 2-aminobutyric acid derivative **18** formed by protonation of the zinc reagent **14**. Our results are summarised in Table 2.

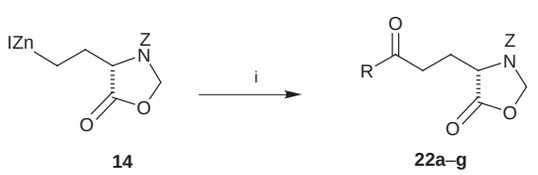
Treatment of **19a** with lithium methoxide in methanol[12] gave Z-protected homophenylalanine methyl ester **20** in excellent yield, establishing the utility of these derivatives for the synthesis of homophenylalanine derivatives. The enantiomeric purity of **20** was established by conversion into the corresponding known Boc derivative **21**[15] using triethylsilane, di-*tert*-butyl dicarbonate and catalytic palladium(II) acetate (Scheme 4).[41]



Scheme 4 *Reagents and conditions*: i, LiOMe (1 equiv.), MeOH, −10 °C, 1 h; ii, Et_3SiH, Boc_2O, $Pd(OAc)_2$, Et_3N, EtOH, 60 °C, 7 d

Synthesis of 5-oxo α-amino acid derivatives by palladium-catalysed cross-coupling reactions

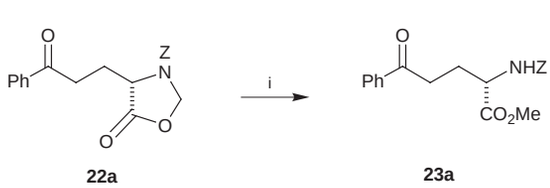
Mindful of our previous observations concerning the incompatibility of acid chlorides with alkylzinc iodides generated in THF, presumably due to the well-established tendency of zinc salts to promote the cleavage of THF by acid chlorides,[42] we screened a range of solvents for the coupling of the zinc reagent **14** with acid chlorides. We established that use of dimethoxyethane (DME) as solvent allowed efficient formation of the zinc reagent **14** from the iodide **15** using activated zinc dust.[39] Addition of a range of acid chlorides, together with catalytic bis(triphenylphosphine)palladium(II) chloride, gave the 5-oxo amino acid derivatives **22a**–**g** in moderate to good yields. Our results are summarised in Table 3 (Scheme 5). The



Scheme 5 *Reagents and conditions*: i, RCOCl, $PdCl_2(PPh_3)_2$ (5 mol%), DME, 35 °C, 1 h

adducts **22d**[11,12] and **22e**[11] have been prepared previously by treatment of the acid chloride derived from protected glutamic acid **17** with diazoalkanes[11,12] or by palladium catalysed coupling with organotin derivatives.[11]

A minimum value for the enantiomeric purity of **22a** was established by chiral phase HPLC analysis of the corresponding methyl ester **23a**, prepared by treatment of **22a** with lithium methoxide in methanol (Scheme 6).[12] This analysis indicated



Scheme 6 *Reagents and conditions*: i, LiOMe (1 equiv.), MeOH, −10 °C, 1 h

that **23a** possessed an enantiomeric excess of 96%. We suspect that the small amount of racemisation detected occurred during the ring-cleavage process with lithium methoxide.

The main drawback to the use of DME as solvent is that reaction of zinc reagent **14** with functionalised acid chlorides

Table 2 Synthesis of homophenylalanine derivatives

Aryl iodide	Product	Ar	Yield (%)
PhI	**19a**	Ph	61
4-Br-C_6H_4I	**19b**	4-Br-C_6H_4	42
4-F-C_6H_4I	**19c**	4-F-C_6H_4	65
2-MeO-C_6H_4I	**19d**	2-MeO-C_6H_4	26
3,4-$(MeO)_2$-C_6H_3I	**19e**	3,4-$(MeO)_2$-C_6H_3	41
2-NO_2-C_6H_4I	**19f**	2-NO_2-C_6H_4	28
4-NO_2-C_6H_4I	**19g**	4-NO_2-C_6H_4	54
1-naphthyl iodide	**19h**	1-naphthyl	53

Table 3 Reaction of zinc reagent **14** with acid chlorides in DME

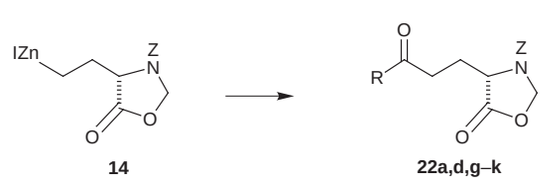
Acid chloride	Product	R	Yield (%)
PhCOCl	**22a**	Ph	64
2-furylCOCl	**22b**	2-furyl	78
m-Me-C_6H_4COCl	**22c**	*m*-Me-C_6H_4	55
CH_3COCl	**22d**	CH_3	60
C_2H_5COCl	**22e**	C_2H_5	50
$C_5H_{11}COCl$	**22f**	C_5H_{11}	86
$AcOCH_2COCl$	**22g**	$AcOCH_2$	18

Table 4 Reaction of zinc reagent **14** with acid chlorides in benzene–dimethylacetamide or toluene–dimethylacetamide

Acid chloride	Product	R	Yield (%)
PhCOCl	**22a**	Ph	76[a]
CH_3COCl	**22d**	CH_3	73[a]
$AcOCH_2COCl$	**22g**	$AcOCH_2$	77[b]
CH_2=CHCOCl	**22h**	CH_2=CH	52[b]
$ClCH_2COCl$	**22i**	$ClCH_2$	49[b]
$PhthNCH_2COCl$	**22j**	$PhthNCH_2$	77[b]
$PhthNCH(CH_3)COCl$	**22k**	$PhthNCH(CH_3)$	73[b]

[a] Benzene–DMA. [b] Toluene–DMA.

(specifically acetoxyacetyl chloride) gives the corresponding adducts in poor yield. Given our success in coupling the serine-derived organozinc reagent with functionalised acid chlorides, provided the zinc reagent was prepared by sonication in benzene–dimethylacetamide (DMA) (15 : 1) as solvent,[1] we have also employed these conditions. Zinc reagent **14** was prepared efficiently in benzene–DMA using our sonochemical conditions, and subsequent palladium catalysed reaction with functionalised acid chlorides gave the expected functionalised 5-oxo amino acid derivatives **22g** and **22h** in much improved yield, emphasising the importance of proper choice of solvent in reactions of organozinc reagents. Preparation of the zinc reagent **14** in toluene–dimethylacetamide was also possible, thus obviating the need to use benzene (Scheme 7). As further

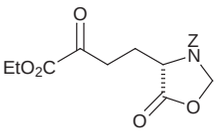


Scheme 7 *Reagents and conditions*: i, RCOCl, $PdCl_2(PPh_3)_2$ (5 mol%), benzene–DMA or toluene–DMA, 35 °C, 1 h

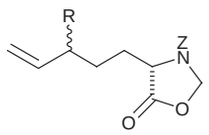
examples, reaction with *N*-phthaloylglycine acid chloride, and *N*-phthaloylalanine acid chloride, gave the corresponding adducts **22j** and **22k**, respectively. Reaction of **14** with simple acid chlorides also proceeded well in toluene–DMA. Thus, reaction with benzoyl chloride gave ketone **22a** (76%), while reaction with acetyl chloride gave **22d** (73%). Our results are summarised in Table 4.

Use of the zinc–copper reagent 16

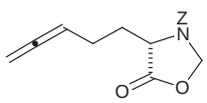
Given the success we had achieved using the zinc reagent **14** in palladium-catalysed coupling reactions with aryl iodides, it was appropriate to explore the reactivity of the zinc–copper reagent **16**. This reagent was prepared from the zinc reagent **14** by addition of CuCN·2 LiCl (as a solution in THF).[2,39] Subsequent reaction with ethyl oxalyl chloride gave the keto ester **22l** in



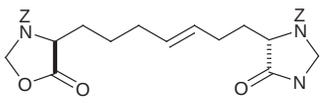
22l



24a R = H
24b R = CH_2Cl



25



26

good yield, indicating that, at least with very reactive acid chlorides, good yields of adducts may be obtained even in the presence of THF. The zinc–copper reagent **16** also reacts with a range of allylic halides to give the corresponding products of S_N2' substitution, specifically **24a** (66%), **24b** (52%), **25** (63%) and **26** (18%).

In summary, we have established that the copper reagent **10**, the zinc reagent **14** and the zinc–copper reagent **16**, which each function as synthetic equivalents for the α-amino acid γ-anion synthon, are useful intermediates for the preparation of non-proteinogenic α-amino acids in enantiomerically pure form.

Experimental

General experimental procedures and instrumentation are as previously described.[1] *J* Values are given in Hz. $[a]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Light petroleum refers to that fraction with boiling point range 40–60 °C. All organic extracts were dried over anhydrous $MgSO_4$, and solvent was removed using a rotary evaporator. Protected glutamic acid derivatives **17** and *ent*-**17** were prepared by the literature method.[43]

Benzyl (2*S*)-*tert*-butoxycarbonylamino-4-iodobutanoate 7

N-Methylmorpholine (1.1 cm^3, 10 mmol) and isobutyl chloroformate (1.4 cm^3, 10 mmol) were added to a nitrogen purged 250 cm^3 round bottomed flask, covered with aluminium foil, containing a stirred solution of α-benzyl (L)-*N*-(*tert*-butoxycarbonyl)glutamic acid (3.37 g, 10 mmol) in dry THF (50 cm^3) at −15 °C. After stirring for 30 min at −15 °C the mixed anhydride had formed, as judged by TLC analysis using dichloromethane–methanol (10:1) as the eluent. A solution of dry triethylamine (1.7 cm^3, 12 mmol) and *N*-hydroxythiopyridine (1.52 g, 12 mmol) in dry THF (20 cm^3) (prepared by stirring at room temperature, under an inert atmosphere and in the absence of light) was added to the reaction flask. The resulting solution was stirred for 1 h at −15 °C to yield the 2-thiopyridyl ester [a yellow spot judged by TLC analysis using toluene–ethyl acetate (1:1) as the eluent]. The solution was filtered under reduced pressure in the absence of light and concentrated under reduced pressure. The resulting yellow liquid was dissolved in carbon tetrachloride (130 cm^3) and transferred to a 1000 cm^3 round bottomed flask containing a solution of iodoform (7.88 g, 20 mmol) in carbon tetrachloride (200 cm^3) under a nitrogen atmosphere. The reaction mixture was irradiated for approximately 3 h using a 150 W tungsten bulb. This was carried out without the use of an external cooling bath until all the 2-thiopyridyl ester had been consumed, as judged by TLC analysis using toluene–ethyl acetate (10:1) as the eluent. The solvent was removed under reduced pressure. Purification was performed by initially applying the crude product to a silica gel pad and eluting with a toluene–ethyl acetate (5:1) solvent system. The resulting yellow crystalline solid was further purified by flash chromatography over silica gel using toluene–ethyl acetate (20:1) as the eluent, to afford a colourless oil which solidified on standing. Recrystallisation from cyclohexane yielded benzyl (2*S*)-2-*tert*-butoxycarbonylamino-4-iodobutanoate as white needles, mp 54–55 °C (from pentane) (lit.,[29] 54 °C) (2.87 g, 5 mmol, 68%) (Found: C, 46.05; H, 5.05; N, 3.35. $C_{16}H_{22}INO_4$ requires C, 45.85; H, 5.3; N, 3.35%); $[a]_D^{24}$ −33.4 (*c* 1.0 in MeOH) {lit.,[29] $[a]_D^{24}$ −33.0 (*c* 1.0 in MeOH)}; ν_{max}(KBr disc)/cm^{-1} 3355, 1756, 1680 and 1516; δ_H(200 MHz, $CDCl_3$) 1.44 [9 H, s, $OC(CH_3)_3$], 2.15–2.27 [1 H, m, C(3)H], 2.35–2.52 [1 H, m, C(3)H], 3.14 [2 H, t, *J* 8, C(4)H_2], 4.34–4.40 [1 H, m, C(2)H], 5.12 (1 H, br d, *J* 8, NH), 5.14 (1 H, d, *J* 12, CH_aH_bPh), 5.20 (1 H, d, *J* 12, CH$_a$$H_b$Ph) and 7.36 (5 H, s, Ph); *m*/*z* (EI) 284 (M^+ − CO_2Bn, 53.2%), 236 [72, M^+ − $(CH_3)_2C{=}CH_2$ − HI] and 228 [73, M^+ − CO_2Bn − $(CH_3)_2C{=}CH_2$].

General procedure for the preparation of the copper reagent 10 and subsequent reaction with electrophiles

A solution of CuCN (0.417 g, 4.65 mmol) and anhydrous LiCl (0.420 g, 9.9 mmol) in dry THF (4.5 cm^3) at −40 °C was added by syringe to a solution of lithium naphthalenide [prepared by reaction of lithium (0.035 g, 5.0 mmol) and naphthalene (0.75 g, 5.85 mmol) in dry THF (5 cm^3)] cooled to −100 °C under argon. The resulting solution was stirred for 10 min at −100 °C, warmed to −78 °C, when a solution of iodide **7** (0.314 g, 0.75 mmol) in THF (2.5 cm^3) was added, during which the temperature of the reaction mixture rose transiently to −65 °C. The mixture was stirred at −78 °C for 30 min, at which point TLC analysis (5:1 light petroleum–ethyl acetate) indicated no remaining iodide **7**, and the electrophile (4.5 mmol, 6 equiv.) was then added. The reaction mixture was warmed to −30 °C, and stirred at this temperature for 3 h, and then treated with sat. aq. NH_4Cl (5 cm^3). The mixture was extracted with EtOAc (60 cm^3), and the organic extract was washed with sat. aq. $NaHCO_3$ (2 × 40 cm^3), distilled water (2 × 40 cm^3), dried and solvent was removed. The residue was then purified by flash chromatography using gradient elution with toluene–EtOAc to give the products **11**, **12** or **13**; protected 2-aminobutanoic acid **8** was also isolated.

Benzyl (2*S*)-2-*tert*-butoxycarbonylamino-5-oxo-5-phenylpentanoate 11a

Treatment with benzoyl chloride (0.52 cm^3, 4.5 mmol) yielded the product as white crystals (0.138 g, 46%), mp 88–89 °C (from EtOH) (Found: C, 69.6; H, 6.8; N, 3.5. $C_{23}H_{27}NO_5$ requires C, 69.5; H, 6.85; N, 3.5%); $[a]_D^{24}$ −0.7 (*c* 1 in CH_2Cl_2); ν_{max}(KBr disc)/cm^{-1} 3366, 2986, 1752, 1684, 1597 and 1514; δ_H(200 MHz, $CDCl_3$) 1.41 [9 H, s, $OC(CH_3)_3$], 2.01–2.22 [1 H, m, C(3)H], 2.25–2.38 [1 H, m, C(3)H], 2.88–3.16 [2 H, m, C(4)H_2], 4.41–4.48 [1 H, m, C(2)H], 5.13 (1 H, d, *J* 12, CH_aH_bPh), 5.22 (1 H, d, *J* 12, CH$_a$$H_b$Ph), 5.23 (1 H, br s, NH), 7.34 (5 H, s, Ph), 7.43 (2 H, dd, *J* 8, 7, *m*-PhCO), 7.53 (1 H, dd, *J* 7, 1, *p*-PhCO) and 7.88 (2 H, dd, *J* 8, 1, *o*-PhCO); *m*/*z* (EI) 341 [M^+ − $(CH_3)_2C{=}CH_2$, 11%], 206 [67, MH^+ − $(CH_3)_2C{=}CH_2$ − $PhCH_3$ − CO_2] and 162 [85, MH^+ − $(CH_3)_2C{=}CH_2$ − $PhCH_3$ − $2CO_2$).

Benzyl (2*S*)-2-*tert*-butoxycarbonylamino-5-oxohexanoate 11b

Treatment with acetyl chloride (0.352 g, 0.32 cm^3, 4.5 mmol) yielded the product as an oil (0.130 g, 52%) (Found: C, 64.4; H, 7.5; N, 4.0. $C_{18}H_{25}NO_5$ requires C, 64.45; H, 7.5; N, 4.2%); $[a]_D^{20}$ −5.3 (*c* 5.7 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3368, 2978, 2934, 1728, 1715 and 1514 (br); δ_H(200 MHz, $CDCl_3$) 1.43 [9 H, s, $OC(CH_3)_3$], 1.79–2.02 [1 H, m, C(3)H], 2.06–2.21 [1 H, m, C(3)H], 2.09 [3 H, s, C(6)H_3], 2.43–2.58 [2 H, m, C(4)H_2],

4.27–4.33 [1 H, m, C(2)H], 5.11 (1 H, d, *J* 12, CH_aH_bPh), 5.19 (1 H, d, *J* 12, CH$_a$$H_b$Ph), 5.19 (1 H, br s, NH), and 7.34 (5 H, s, Ph); *m*/*z* (EI) 336 (MH^+, 1%), 280 [15, $MH^+ - (CH_3)_2C{=}CH_2$], 236 [10, $MH^+ - (CH_3)_2C{=}CH_2 - CO_2$], 200 (38, $MH^+ - PhCH_3 - CO_2$), 144 [77, $MH^+ - (CH_3)_2C{=}CH_2 - PhCH_3 - CO_2$] and 100 [84, $MH^+ - (CH_3)_2C{=}CH_2 - PhCH_3 - 2CO_2$].

Benzyl (2*S*)-2-*tert*-butoxycarbonylamino-5-oxodecanoate 11c

Treatment with hexanoyl chloride (0.606 g, 0.63 cm^3, 4.5 mmol) yielded the product as an oil (0.130 g, 44%) (Found: C, 67.25; H, 8.55; N, 3.3. $C_{22}H_{33}NO_5$ requires C, 67.5; H, 8.5; N, 3.6%); $[a]_D^{18}$ −22.0 (*c* 2.0 in MeOH) {lit.,[13] $[a]_D^{27}$ −22.3 (*c* 8.1 in MeOH)}; ν_{max}(film)/cm^{-1} 3368, 2959, 2934, 1728, 1713 and 1501 (br); δ_H(200 MHz, $CDCl_3$) 0.88 [3 H, t, *J* 6.7, C(10)H$_3$], 1.10–1.35 [4 H, m, C(8)H$_2$ and C(9)H$_2$], 1.43 [9 H, s, OC(CH$_3$)$_3$], 1.46–1.60 [2 H, m, C(7)H$_2$], 1.80–2.02 [1 H, m, C(3)H], 2.06–2.19 [1 H, m, C(3)H], 2.33 [2 H, t, *J* 7.4, C(6)H$_3$], 2.40–2.54 [2 H, m, C(4)H$_2$], 4.24–4.35 [1 H, m, C(2)H], 5.11 (1 H, d, *J* 12, CH_aH_bPh), 5.12 (1 H, br s, NH), 5.20 (1 H, d, *J* 12, CH$_a$$H_b$Ph) and 7.35 (5 H, s, Ph); *m*/*z* (EI) 392 (MH^+, 1.6%), 336 [12, $MH^+ - (CH_3)_2C{=}CH_2$], 256 [33, $MH^+ - (CH_3)_2C{=}CH_2 - CO_2$], 200 [75, $MH^+ - (CH_3)_2C{=}CH_2 - PhCH_3 - CO_2$] and 156 [87, $MH^+ - (CH_3)_2C{=}CH_2 - 2CO_2$].

Benzyl (2*S*)-2-*tert*-butoxycarbonylamino-5-oxo-5-cyclopentylpentanoate 11d

Treatment with cyclopentanecarbonyl chloride (0.597 g, 0.55 cm^3, 4.5 mmol) yielded the product as an oil (0.160 g, 55%) (Found: C, 68.0; H, 8.05; N, 3.95. $C_{22}H_{31}NO_5$ requires C, 67.85; H, 8.0; N, 3.6%); $[a]_D^{18}$ −22.1 (*c* 6.7 in MeOH) {lit.,[13] $[a]_D^{27}$ −23.3 (*c* 8.3 in MeOH)}; ν_{max}(film)/cm^{-1} 3370, 2961, 1728, 1713 and 1501; δ_H(200 MHz, $CDCl_3$) 1.43 [9 H, s, OC(CH$_3$)$_3$], 1.53–1.79 [8 H, m, C(2′)H$_2$, C(3′)H$_2$, C(4′)H$_2$ and C(5′)H$_2$], 1.82–2.01 [1 H, m, C(3)H], 2.03–2.19 [1 H, m, C(3)H], 2.45–2.55 [2 H, m, C(4)H$_3$], 2.71–2.86 [1 H, m, C(1′)H$_2$], 4.25–4.36 [1 H, m, C(2)H], 5.12 (1 H, d, *J* 12, CH_aH_bPh), 5.18 (1 H, br s, NH), 5.20 (1 H, d, *J* 12, CH$_a$$H_b$Ph) and 7.35 (5 H, s, Ph); *m*/*z* (EI) 390 (MH^+, 11%), 334 [35, $MH^+ - (CH_3)_2C{=}CH_2$], 254 (59, $MH^+ - PhCH_3 - CO_2$), 198 [76, $MH^+ - (CH_3)_2C{=}CH_2 - PhCH_3 - CO_2$] and 154 [86, $MH^+ - (CH_3)_2C{=}CH_2 - 2CO_2$].

Benzyl (2*S*)-2-*tert*-butoxycarbonylamino-5-oxo-5-(2′-furyl)-pentanoate 11e

Treatment with 2-furoyl chloride (0.587 g, 0.444 cm^3, 4.5 mmol) yielded the product as white crystals (0.120 g, 40%), mp 118 °C (from EtOH) (Found: C, 65.15; H, 6.45; N, 3.8. $C_{21}H_{25}NO_6$ requires C, 65.1; H. 6.5; N, 3.6%); $[a]_D^{20}$ −9.8 (*c* 2.8 in $CHCl_2$); ν_{max}(KBr disc)/cm^{-1} 3368, 2978, 2932, 1738, 1713, 1672, 1501, 1254 and 1028; δ_H(200 MHz, $CDCl_3$) 1.41 [9 H, s, OC(CH$_3$)$_3$], 1.99–2.19 [1 H, m, C(3)H], 2.21–2.33 [1 H, m, C(3)H], 2.75–2.99 [2 H, m, C(4)H], 4.34–4.45 [1 H, m, C(2)H], 5.00–5.24 (3 H, m, CH$_2$Ph and NH), 6.51 [1 H, dd, *J* 3.6, 1.7, C(4′)H], 7.13 [1 H, dd, *J* 3.6, 0.7, C(3′)H], 7.34 (5 H, s, Ph) and 7.55 [1 H, dd, *J* 1.7, 0.7, C(5′)H]; *m*/*z* (EI) 388 (MH^+, 20%), 332 5, $MH^+ - (CH_3)_2C{=}CH_2$], and 252 (64 $MH^+ - PhCH_3 - CO_2$).

Benzyl (2*S*)-2-(*tert*-butoxycarbonylamino)hept-6-enoate 12a

Treatment with allyl chloride (0.344 g, 0.37 cm^3, 4.5 mmol) yielded the product as an oil (0.104 g, 42%) (Found: $MH^+ - PhCH_3 - CO_2$, 198.1496. $C_{11}H_{20}NO_2$ requires 198.1494); $[a]_D^{20}$ −5.5 (*c* 1.4 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3370, 3067, 3034, 2978, 2932, 1732, 1717 and 1501; δ_H(200 MHz, $CDCl_3$) 1.43 [9 H, s, OC(CH$_3$)$_3$], 1.48–1.88 [4 H, m, C(3)H$_2$ and C(4)H$_2$], 1.97–2.09 [2 H, m, C(5)H$_2$], 4.29–4.39 [1 H, m, C(2)H], 4.92–5.02 [3 H, m, C(7)H$_2$ and NH], 5.12 (1 H, d, *J* 12, CH_aH_bPh), 5.21 (1 H, d, *J* 12, CH$_a$$H_b$Ph), 5.62–5.82 [1 H, m, C(6)H] and 7.35 (5 H, s, Ph); *m*/*z* (FAB) 334 (MH^+, 8%), 278 [48, $MH^+ - (CH_3)_2C{=}CH_2$], and 234 [63, $MH^+ - (CH_3)_2C{=}CH_2 - CO_2$]; *m*/*z* (EI) 198.

Benzyl (2*S*,5*RS*)-2-*tert*-butoxycarbonylamino-5-phenylhept-6-enoate 12b

Treatment with cinnamyl chloride (0.687 g, 0.61 cm^3, 4.5 mmol) yielded the product as an inseparable mixture of diastereoisomers as an oil (0.189 g, 62%) (Found: C, 73.3; H, 7.15; N, 3.55. $C_{25}H_{31}NO_4$ requires C, 73.3; H, 7.65; N, 3.4%); ν_{max}(film)/cm^{-1} 3380, 3063, 3031, 2978, 2932, 1727, 1715 and 1499; δ_H(300 MHz, $CDCl_3$) (both isomers, ratio not determined) 1.42 [9 H, s, OC(CH$_3$)$_3$], 1.64–1.72 [4 H, m, C(3)H$_2$ and C(4)H$_2$], 3.16–3.29 [1 H, m, C(5)H], 4.30–4.40 [1 H, m, C(2)H], 4.94–5.26 [5 H, m, NH, CH$_2$Ph, C(7)H$_2$], 5.81–5.94 [1 H, m, C(6)H], 7.10–7.40 (10 H, m, Ph); *m*/*z* (EI) 410 (MH^+, 3%), 354 [13, $MH^+ - (CH_3)_2C{=}CH_2$], 310 [53, $MH^+ - (CH_3)_2C{=}CH_2 - CO_2$], and 174 [74, $MH^+ - (CH_3)_2C{=}CH_2 - PhCH_3 - 2CO_2$].

Benzyl (2*S*)-2-(*tert*-butoxycarbonylamino)hept-5,6-dienoate 13

Treatment with prop-2-ynyl chloride (0.335 g, 0.322 cm^3, 4.5 mmol) yielded the product as an oil (0.090 g, 36%) (Found: C, 68.6; H, 7.6; N, 4.25. $C_{19}H_{25}NO_4$ requires C, 68.85; H, 7.6; N, 4.25%); $[a]_D^{20}$ +2.5 (*c* 3.7 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3370, 3067, 3034, 2978, 2932, 1735, 1716 and 1501; δ_H(200 MHz, $CDCl_3$) 1.43 [9 H, s, OC(CH$_3$)$_3$], 1.65–1.80 [1 H, m, C(3)H], 1.92–2.10 [3 H, m, C(3)H and C(4)H$_2$], 4.35–4.44 [1 H, m, C(2)H], 4.64–4.70 [2 H, m, C(7)H$_2$], 5.01–5.09 [2 H, m, C(5)H and NH], 5.12 (1 H, d, *J* 12, CH_aH_bPh), 5.20 (1 H, d, *J* 12, CH$_a$$H_b$Ph) and 7.35 (5 H, s, Ph); δ_C(50 MHz, $CDCl_3$) 24.07, 28.34, 31.96, 53.14, 67.04, 75.67, 79.93, 88.73, 128.27–128.64 (5 signals), 135.44, 155.09, 171.86 and 208.38; *m*/*z* (EI) 332 (MH^+, 48%), 276 [61, $MH^+ - (CH_3)_2C{=}CH_2$], 232 [95, $MH^+ - (CH_3)_2C{=}CH_2 - CO_2$] and 140 [42, $MH^+ - (CH_3)_2C{=}CH_2 - PhCH_3 - CO_2$].

(4*S*)-3-Benzyloxycarbonyl-4-(2′-iodoethyl)oxazolidin-5-one 15

N-Methylmorpholine (1.9 cm^3, 17.2 mmol) and isobutyl chloroformate (2.4 cm^3, 17.2 mmol) were added to a nitrogen purged 250 cm^3 round bottomed flask (covered with foil) containing a stirred solution of 3-[(4*S*)-3-benzyloxycarbonyl-5-oxooxazolidin-4-yl]propanoic acid **17** (5.04 g, 17.2 mmol) in dry THF (50 cm^3) at −15 °C. After stirring for 30 min at −15 °C the mixed anhydride had formed as judged by TLC analysis using dichloromethane–methanol (10 : 1) as the eluent. A solution of triethylamine (2.9 cm^3, 20.5 mmol) and *N*-hydroxythiopyridine (2.6 g, 20.5 mmol) in dry THF (20 cm^3) (prepared by stirring at room temperature, under an inert atmosphere and in the absence of light) was added to the reaction flask. The resulting solution was stirred for 1 h at −15 °C to yield the 2-thiopyridyl ester [a yellow spot judged by TLC analysis using toluene–ethyl acetate (1 : 1) as the eluent]. The solution was filtered under reduced pressure in the absence of light and concentrated under reduced pressure. The resulting yellow liquid was dissolved in 1,1,1-trichloroethane (100 cm^3) and transferred to a 1000 cm^3 round bottomed flask containing a solution of iodoform (13.5 g, 34 mmol) in 1,1,1-trichloroethane (400 cm^3) under a nitrogen atmosphere. The reaction mixture was irradiated for approximately 3 h using a 150 W tungsten bulb. This was carried out without the use of an external cooling bath until all the 2-thiopyridyl ester had been consumed, as judged by TLC analysis using toluene–ethyl acetate (10 : 1) as the eluent. The solvent was removed under reduced pressure. Purification was performed by initially applying the crude product to a silica gel pad and eluting with a toluene–ethyl acetate (5 : 1) solvent system. The resulting yellow crystalline solid was further purified by flash chromatography over silica gel using toluene–ethyl acetate (50 : 1) as the eluent, to afford a colourless oil which solidified on standing. Recrystallisation from cyclohexane yielded (4*S*)-3-benzyloxycarbonyl-4-(2′-iodoethyl)oxazolidin-5-one as white needles, mp 80–81 °C (from cyclohexane) (3.31 g, 8.85 mmol, 51%) (Found: C, 41.6; H, 3.54; N, 3.7. $C_{13}H_{14}INO_4$ requires C, 41.6; H, 3.76; N, 3.7%); $[a]_D^{17}$ +86.5 (*c* 1.04 in CH_2Cl_2); ν_{max}(KBr disc)/cm^{-1} 2922, 1778, 1718, 1415 and 501; δ_H(200 MHz,

$CDCl_3$) 2.38–2.52 [2 H, m, C(1′)H_2], 3.20 [2 H, t, *J* 7, C(2′)H_2], 4.35 [1 H, t, *J* 7, C(4)H], 5.15 (2 H, s, CH_2Ph), 5.20 [1 H, d, *J* 4, C(2)H], 5.60 [1 H, m, C(2)H] and 7.37 (5 H, s, Ph); *m*/*z* (EI) 375 (M^+, 4%), 240 (40, MH$^+$ − CO_2 − PhCH_3) and 91 (100, $C_7H_7^+$).

(4*R*)-3-Benzyloxycarbonyl-4-(2′-iodoethyl)oxazolidin-5-one *ent*-15

The title compound was prepared from *ent*-**17** using the procedure described for the preparation of (4*S*)-3-benzyloxycarbonyl-4-(2′-iodoethyl)oxazolidin-5-one **15**. Recrystallisation from cyclohexane yielded the product as white needles, mp 80–81 °C (from cyclohexane), $[\alpha]_D^{17}$ −86.9 (*c* 1.05 in CH_2Cl_2).

General procedure for the preparation of 4-aryl α-amino acids 19a–h

Zinc dust (325 mesh, 0.300 g, 4.5 mol) was added to a nitrogen purged flask, to which distilled THF (0.34 cm^3) and 1,2-dibromoethane (19 μl, 0.225 mmol) were then added. The flask was heated with a heat gun until reflux of the solvent was observed, and the zinc suspension was stirred for a few minutes. This process was repeated five times. The flask was allowed to cool to room temperature, and trimethylsilyl chloride (6 μl, 0.046 mmol) was added. The resultant mixture was stirred under nitrogen for 30 min. (4*S*)-3-Benzyloxycarbonyl-4-(2′-iodoethyl)oxazolidin-5-one **15** (0.280 g, 0.75 mmol) in THF (0.75 cm^3) was added to the flask and the resultant mixture stirred at 35 °C (typically 15 min) generating (4*S*)-3-benzyloxycarbonyl-4-(2′-iodozincethyl)oxazolidin-5-one **14**, *in situ*, as judged by disappearance of the iodide using TLC with light petroleum–ethyl acetate (5:1) as the eluent. The aromatic iodide (1 mmol) was added, followed by *tris*(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] (0.004 g, 0.005 mmol) and tri(*o*-tolylphosphine) (0.006 g, 0.02 mmol) and the reaction mixture was stirred for 1 h at 50 °C. After allowing the reaction mixture to reach ambient temperature, ethyl acetate (50 cm^3) was added and the contents were filtered into a separating funnel. The organic layer was washed with dilute hydrochloric acid (20 cm^3, 1 M), washed with water (3 × 20 cm^3), dried and concentrated under reduced pressure to give the crude product as an oil. Flash chromatography over silica gel (light petroleum–ethyl acetate—gradient, typically 50:1 to 50:4) yielded the pure protected amino acid. In each case, the protonated zinc reagent **18** was isolated from each subsequent experiment employing zinc reagent **14** in varying yields, together with the desired product.

(4*S*)-3-Benzyloxycarbonyl-4-ethyloxazolidin-5-one 18

This compound was isolated as an oil (Found: M^+, 249.1007. $C_{13}H_{15}NO_4$ requires 249.1001); $[\alpha]_D^{24}$ +57.0 (*c* 0.8 in MeOH) {lit.,[44] $[\alpha]_D^{24}$ +58 (*c* 0.8 in MeOH)}; ν_{max}(film)/cm^{-1} 2972, 1805, 1716 and 1417; δ_H(200 MHz; $CDCl_3$) 0.95 [3 H, t, *J* 8, C(2′)H_3], 1.83–2.25 [2 H, m, C(1′)H_2], 4.30–4.35 [1 H, m, C(4)H], 5.13–5.26 [3 H, m, CH_2Ph and C(2)H], 5.48–5.58 [1 H, m, C(2)H] and 7.36 (5 H, s, Ph); *m*/*z* (EI) 249 (M^+, 24%).

(4*S*)-3-Benzyloxycarbonyl-4-(2′-phenethyl)oxazolidin-5-one 19a

Treatment with iodobenzene (112 μl, 1 mmol) yielded the product as a white solid (0.150 g, 0.46 mmol, 61%), mp 46–47 °C (from cyclohexane) (Found: M^+, 325.1322. $C_{19}H_{19}NO_4$ requires 325.1314); $[\alpha]_D^{16}$ +101.1 (*c* 0.19 in CH_2Cl_2); ν_{max}(KBr disc)/cm^{-1} 2924, 1802, 1717 and 1418; δ_H(200 MHz; $CDCl_3$) 2.08–2.23 [2 H, m, C(1′)H_2], 2.55–2.78 [2 H, m, C(2′)H_2], 4.25–4.40 [1 H, m, C(4)H], 5.10–5.20 [3 H, m, CH_2Ph and C(2)H], 5.40–5.53 [1 H, m, C(2)H], 7.00–7.20 (5 H, m, Ar) and 7.36 (5 H, s, Ph); *m*/*z* (EI) 325 (M^+, 1.9%), 281 (29, M^+ − CO_2) and 233 (61, M^+ − CO_2 − PhCH_3).

(4*S*)-3-Benzyloxycarbonyl-4-[2′-(4″-bromophenyl)ethyl]-oxazolidin-5-one 19b

Treatment with 1-bromo-4-iodobenzene (0.283 g, 1 mmol) yielded the product as a white solid (0.127 g, 0.31 mmol, 42%), mp 73–74 °C (from cyclohexane) (Found: C, 56.1; H, 4.3; N, 3.3. $C_{19}H_{18}BrNO_4$ requires C, 56.4; H, 4.5; N, 3.5%); $[\alpha]_D^{22}$ +62.6 (*c* 1.08 in CH_2Cl_2); ν_{max}(KBr disc)/cm^{-1} 2963, 1784, 1684, 1425 and 698; δ_H(200 MHz; $CDCl_3$) 2.05–2.40 [2 H, m, C(1′)H_2], 2.53–2.75 [2 H, m, C(2′)H_2], 4.25–4.40 [1 H, m, C(4)H], 5.10–5.23 [3 H, m, PhCH_2 and C(2)H], 5.43–5.58 [1 H, m, C(2)H], 6.89–7.15 [2 H, m, C(2″)H and C(6″)H] and 7.36 [7 H, m, Ph, C(3″)H and C(5″)H]; *m*/*z* (EI) 404 (M^+, 0.2%), 360 (52, M^+ − CO_2) and 268 (80, M^+ − CO_2 − PhCH_3).

(4*S*)-3-Benzyloxycarbonyl-4-[2′-(4″-fluorophenyl)ethyl]-oxazolidin-5-one 19c

Treatment with 1-fluoro-4-iodobenzene (115 μl, 1 mmol) yielded the product as a white solid (0.167 g, 65%), mp 64–65 °C (from cyclohexane) (Found: MH$^+$, 344.1285. $C_{19}H_{19}NO_4F$ requires 344.1298); $[\alpha]_D^{22}$ +100.8 (*c* 1.00 in CH_2Cl_2); ν_{max}(KBr disc)/cm^{-1} 2937, 1778, 1687, 1521, 1423, 1223 and 1180; δ_H(200 MHz; $CDCl_3$) 2.08–2.43 [2 H, m, C(1′)H_2], 2.53–2.80 [2 H, m, C(2′)H_2], 4.25–4.40 [1 H, m, C(4)H], 5.09–5.26 [3 H, m, CH_2Ph and C(2)H], 5.43–5.60 [1 H, m, C(2)H], 6.85–6.97 [2 H, m, C(3″)H and C(5′)H], 7.00–7.23 [2 H, m, C(2″)H and C(6″)H] and 7.37 (5 H, s, Ph); *m*/*z* (EI) 344 (MH$^+$, 0.2%), 300 (8, MH$^+$ − CO_2) and 208 (58, M^+ − CO_2 − PhCH_3).

(4*S*)-3-Benzyloxycarbonyl-4-[2′-(2″-methoxyphenyl)ethyl]-oxazolidin-5-one 19d

Treatment with 2-iodoanisole (130 μl, 1 mmol) yielded the product as an oil (0.069 g, 0.20 mmol, 26%) (Found: M^+, 355.1406. $C_{20}H_{21}NO_5$ requires 355.1420); $[\alpha]_D^{22}$ +95.3 (*c* 1.14 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2926, 1801, 1716, 1601 and 1417; δ_H(200 MHz; $CDCl_3$) 2.08–2.45 [2 H, m, C(1′)H_2], 2.53–2.85 [2 H, m, C(2′)H_2], 3.75 (3 H, s, OMe), 4.30–4.40 [1 H, m, C(4)H], 5.10–5.23 [3 H, m, CH_2Ph and C(2)H], 5.45–5.58 [1 H, m, C(2)H], 6.73–6.88, [2 H, m, C(3″)H and C(5″)H], 7.00–7.08 [1 H, m, C(4″)H], 7.13–7.23 [1 H, m, C(6″)H] and 7.35 (5 H, s, *Ph*CH_2O); *m*/*z* (EI) 355 (M^+, 9%), 311 (2, M^+ − CO_2) and 219 (60, M^+ − CO_2 − PhCH_3).

(4*S*)-3-Benzyloxycarbonyl-4-[2′-(3″,4″-dimethoxyphenyl)ethyl]-oxazolidin-5-one 19e

Treatment with 3,4-dimethoxyiodobenzene (0.246 g, 1 mmol) yielded the product as an oil (0.118 g, 0.31 mmol, 41%) (Found: C, 65.5; H, 6.0; N, 3.3. $C_{21}H_{23}NO_6$ requires C, 65.4; H, 6.0; N, 3.6%); $[\alpha]_D^{22}$ +95.7 (*c* 0.985 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2924, 1802, 1717 and 1418; δ_H(200 MHz; $CDCl_3$) 2.08–2.33 [2 H, m, C(1′)H_2], 2.50–2.73 [2 H, m, C(2′)H_2], 3.84 (6 H, s, CH_3O at 3″ and CH_3O at 4″), 4.28–4.40 [1 H, m, C(4)H], 5.13–5.23 [3 H, m, CH_2Ph and C(2)H], 5.45–5.55 [1 H, m, C(2)H], 6.65–6.80 [3 H, m, C(2″)H, C(5″)H and C(6″)H] and 7.36 (5 H, s, Ph); *m*/*z* (EI) 385 (M^+, 100%), 341 (44, M^+ − CO_2) and 249 (62, M^+ − CO_2 − PhCH_3).

(4*S*)-3-Benzyloxycarbonyl-4-[2′-(2″-nitrophenyl)ethyl]-oxazolidin-5-one 19f

Treatment with 1-iodo-2-nitrobenzene (0.249 g, 1 mmol) yielded the product as an oil (0.079 g, 0.21 mmol) (Found: M^+ − CO_2H, 325.1195. $C_{18}H_{17}N_2O_4$ requires 325.1188); $[\alpha]_D^{22}$ +79.8 (*c* 0.5 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2925, 1801, 1717, 1526, 1416 and 1355; δ_H(200 MHz; $CDCl_3$) 2.15–2.48 [2 H, m, C(1′)H_2], 2.78–3.00 [1 H, m, C(2′)H_2], 3.03–3.18 [1 H, m, C(2′)H], 4.33–4.48 [1 H, m, C(4)H], 5.21 (2 H, s, CH_2Ph), 5.08 [1 H, d, *J* 4, C(2)H], 5.55 [1 H, d, *J* 4, C(2)H], 7.36 [7 H, s, Ph, C(4″)H and C(6″)H], 7.4–7.58 [1 H, m, C(5″)H] and 7.93 [1 H, dd, *J* 8 and 1, C(3″)H]; *m*/*z* (EI) 325 (M^+ − CO_2H, 6.8%), 281 (18, M^+ − CO_2H − CO_2) and 189 (23, M^+ − CO_2H − CO_2 − PhCH_3).

(4*S*)-3-Benzyloxycarbonyl-4-[2′-(4″-nitrophenyl)ethyl]-oxazolidin-5-one 19g

Treatment with 1-iodo-4-nitrobenzene (0.249 g, 1 mmol) yielded

the product as a solid (0.154 g, 0.41 mmol, 54%), mp 82–84 °C (from light petroleum and ethyl acetate) (Found: $M^+ - CO_2H$, 325.1176. $C_{18}H_{17}N_2O_4$ requires 325.1188); $[\alpha]_D^{22}$ +92.1 (*c* 1.0 in CH_2Cl_2); ν_{max}(KBr disc)/cm^{-1} 2927, 1792, 1513, 1420 and 1350; δ_H(200 MHz; $CDCl_3$) 2.08–2.40 [2 H, m, C(1′)H_2], 2.65–2.88 [2 H, m, C(2′)H_2], 4.23–4.45 [1 H, m, C(4)H], 5.05–5.23 [3 H, m, CH_2Ph and C(2)H], 5.43–5.55 [1 H, m, C(2)H], 7.35 [7 H, m, Ph, C(2″)H and C(6″)H] and 8.07 [2 H, m, C(3″)H and C(5″)H]; *m*/*z* (EI) 325 ($M^+ - CO_2H$, 47%), 281 (31, $M^+ - CO_2H - CO_2$) and 189 (40, $M^+ - CO_2H - CO_2 - PhCH_3$).

(4*S*)-3-Benzyloxycarbonyl-4-[2′-(1″-naphthyl)ethyl]oxazolidin-5-one 19h

Treatment with 1-iodonaphthalene (146 μl, 1 mmol) yielded the product as an oil (0.149 g, 0.40 mmol, 53%) (Found: M^+, 375.1452. $C_{23}H_{21}NO_4$ requires 375.1470); $[\alpha]_D^{16}$ +94.0 (*c* 0.705 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3065, 2924, 1799, 1716 and 1415; δ_H(200 MHz; $CDCl_3$) 2.00–2.38 [2 H, m, C(1′)H_2], 2.98–3.30 [2 H, m, C(2′)H_2], 4.33–4.48 [1 H, m, C(4)H], 5.15 (2 H, s, CH_2Ph), 5.23 [1 H, d, *J* 4, C(2)H], 5.45–5.60 [1 H, m, C(2)H], 7.33 (5 H, s, Ph) 7.40–7.50 [3 H, m, C(2″)H, C(3″)H and C(4″)H] and 7.70–8.00 [4 H, m, C(5″)H, C(6″)H, C(7″)H and C(8″)H]; *m*/*z* (EI) 375 (M^+, 8.8%), 331 (0.3, $M^+ - CO_2$) and 239 (7, $M^+ - CO_2 - PhCH_3$).

Methyl (2*S*)-2-benzyloxycarbonylamino-4-phenylbutanoate 20

(4*S*)-3-Benzyloxycarbonyl-4-(2′-phenylethyl)oxazolidin-5-one **19a** (0.060 g, 0.18 mmol) in methanol (1 cm^3) was added to a stirred solution of lithium methoxide (0.016 g, 0.41 mmol) in methanol (2 cm^3) at −10 °C under an atmosphere of nitrogen. The reaction mixture was stirred at −10 °C of 1.5 h. After allowing the reaction mixture to reach ambient temperature, ethyl acetate (10 cm^3) was added and the contents were filtered into a separating funnel. The organic phase was washed with dilute hydrochloric acid (10 cm^3, 1 M) and water (3 × 10 cm^3), dried and concentrated under reduced pressure to give the crude product as an oil. Flash chromatography over silica gel using toluene–ethyl acetate (30 : 1) as the eluent yielded methyl (2*S*)-2-benzyloxycarbonylamino-4-phenylbutanoate **20** as an oil (0.054 g, 0.16 mmol, 92%) (Found: MH^+, 328.1542. $C_{19}H_{22}NO_4$ requires 328.1549); $[\alpha]_D^{22}$ +14.4 (*c* 0.5 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3341, 2953, 1724, 1527 and 1498; δ_H(200 MHz; $CDCl_3$) 1.83–2.01 [1 H, m, C(3)H], 2.05–2.30 [1 H, m, C(3)H], 2.62 [2 H, t, *J* 8, C(4)H_2], 3.66 (3 H, s, OCH_3), 4.38 [1 H, m, C(2)H], 5.07 (2 H, s, OCH_2Ph), 5.33 (1 H, br d, *J* 8, NH), 7.00–7.27 (5 H, m, Ph) and 7.31 (5 H, s, OCH_2*Ph*); *m*/*z* (EI) 328 (MH^+, 0.9%) and 284 (41, $MH^+ - CO_2$).

Methyl (2*S*)-2-*tert*-butoxycarbonylamino-4-phenylbutanoate 21

A solution of methyl (2*S*)-2-benzyloxycarbonylamino-4-phenylbutanoate **20** (0.070 g, 0.215 mmol) in ethanol (1 cm^3) was added dropwise to a nitrogen purged flask, covered with aluminium foil, containing a stirred solution of triethylsilane (69 μl, 0.43 mmol), di-*tert*-butyl dicarbonate (59 μl, 0.26 mmol), palladium acetate (0.005 g, 0.02 mmol) and triethylamine (10 μl, 0.07 mmol) in dry ethanol (1 cm^3) at 60 °C. The reaction mixture was stirred for 7 d at 60 °C. The reaction mixture was then allowed to reach ambient temperature, filtered under reduced pressure in the absence of light and concentrated under reduced pressure to give the crude product as an oil. Flash chromatography over silica gel using light petroleum–diethyl ether (4 : 1) as the eluent yielded methyl (2*S*)-2-*tert*-butoxycarbonylamino-4-phenylbutanoate **21** as an oil (0.024 g, 0.08 mmol, 38%) [Found: $M^+ - (CH_3)_2C{=}CH_2$, 237.1013 $C_{12}H_{15}NO_4$ requires 237.1001]; $[\alpha]_D^{22}$ −14.7 (*c* 1.2 in MeOH) [lit.,[15] $[\alpha]_D^{20}$ −15.0 (*c* 1.6 in MeOH)]; ν_{max}(film)/cm^{-1} 3362, 2977, 1744, 1716 and 1516; δ_H(200 MHz; $CDCl_3$) 1.45 [9 H, s, $OC(CH_3)_3$], 1.87–2.02 [1 H, m, C(3)H], 2.06–2.21 [1 H, m, C(3)H], 2.67 [2 H, t, *J* 8, C(4)H_2], 3.72 (3 H, s, OCH_3), 4.36 [1 H, m, C(2)H], 5.08 (1 H, br d, *J* 8, NH) and 7.22–7.32 (5 H, m, Ph); *m*/*z* (EI) 237 [$M^+ - (CH_3)_2C{=}CH_2$, 18.5%] and 133 [93, $M^+ - (CH_3)_2C{=}CH_2 - CO_2 - CO_2Me$).

General procedure for the preparation of 5-oxo α-amino acids 22

Method A. Zinc dust (325 mesh, 0.300 g, 4.5 mmol) was added to a nitrogen purged flask to which distilled 1,2-dimethoxyethane (0.34 cm^3) and 1,2-dibromoethane (19 μl, 0.225 mmol) were then added. The flask was heated with a heat gun until reflux of the solvent was observed and the zinc suspension was stirred for a few minutes. This process was repeated five times. The flask was allowed to cool to room temperature, and trimethylsilyl chloride (6 μl, 0.046 mmol) was added. The resultant mixture was stirred under nitrogen for 15 min. (4*S*)-3-Benzyloxycarbonyl-4-(2′-iodoethyl)oxazolidin-5-one **15** (0.280 g, 0.75 mmol) in 1,2-dimethoxyethane (0.75 cm^3) was added to the flask and the resultant mixture stirred at 35 °C (typically 15 min) generating (4*S*-3-benzyloxycarbonyl-4-(2′-iodozincethyl)-oxazolidin-5-one *in situ*, as judged by disappearance of the iodide by TLC analysis using light petroleum–ethyl acetate (5 : 1) as the eluent. The freshly distilled acid chloride (1 mmol) was added, followed by bis(triphenylphosphine)palladium dichloride [$(Pd(PPh_3)_2Cl_2)$] (0.028 g, 0.0375 mmol, 5 mol%) and the reaction mixture was stirred for 1 h at 35 °C. After allowing the reaction mixture to reach ambient temperature, ethyl acetate (50 cm^3) was added and the contents were filtered into a separating funnel. The organic phase was washed with dilute hydrochloric acid (20 cm^3, 1 M), water (3 × 20 cm^3), dried and concentrated under reduced pressure to give the crude product as an oil. Flash chromatography over silica gel (light petroleum–ethyl acetate–gradient, typically 50 : 1 to 50 : 16) yielded the pure protected amino acid.

Method B. (4*S*)-3-Benzyloxycarbonyl-4-(2′-iodoethyl)oxazolidin-5-one[15] (0.280 g, 0.75 mmol) and zinc–copper couple (0.090 g) were added to a nitrogen purged flask, to which dry toluene (1.5 cm^3) and anhydrous DMA (0.2 cm^3) were then added. The reaction mixture was irradiated in an ultrasonic cleaning bath according to the procedure described previously,[1] typically for 30 min, generating (4*S*)-3-benzyloxycarbonyl-4-(2′-iodozincethyl)oxazolidin-5-one, *in situ*, as judged by disappearance of the iodide by TLC analysis using light petroleum–ethyl acetate (5 : 1) as the eluent. $Pd(PPh_3)_2Cl_2$ (0.028 g, 0.0375 mmol, 5 mol%) and the freshly distilled acid chloride were added and the reaction mixture was sonicated for a further 1 h (25–35 °C). Ethyl acetate (50 cm^3) was added and the contents were filtered into a separating funnel. The organic phase was washed with dilute hydrochloric acid (20 cm^3, 1 M), water (3 × 20 cm^3), dried and concentrated under reduced pressure to give the crude product as an oil. Flash chromatography over silica gel (light petroleum–ethyl acetate–gradient, typically 50 : 1 to 50 : 16) yielded the pure protected amino acid.

(4*S*)-3-Benzyloxycarbonyl-4-(3′-oxo-3′-phenylpropyl)-oxazolidin-5-one 22a

Treatment with benzoyl chloride (0.141 g, 116 μl, 1 mmol) using Method B yielded the product as an oil (0.202 g, 0.57 mmol, 76%) (Found: $MH^+ - PhCH_3 - CO_2$, 218.0827. $C_{12}H_{12}NO_3$ requires 218.0817); $[\alpha]_D^{20}$ +26.3 (*c* 0.695 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2924, 1801, 1716, 1603, 1450 and 1417; δ_H(200 MHz; $CDCl_3$) 2.30–2.50 [2 H, m, C(1′)H_2], 3.00–3.20 [2 H, m, C(2′)H_2], 4.45 [1 H, t, *J* 7, C(4)H], 5.10 (2 H, s, PhCH_2), 5.20 [1 H, d, *J* 4, C(2)H], 5.60 [1 H, br s, C(2)H], 7.33 (5 H, s, *Ph*CH_2O), 7.40–7.60 (3 H, m, *m*-PhCO and *p*-PhCO) and 7.90 (2 H, dd, *J* 7 and 1, *o*-PhCO); *m*/*z* (EI) 218 ($MH^+ - PhCH_3 - CO_2$, 0.9%).

(4*R*)-3-Benzyloxycarbonyl-4-(3′-oxo-3′-phenylpropyl)-oxazolidin-5-one *ent*-22a

The above compound was prepared using Method B with (4*R*)-3-benzyloxycarbonyl-4-(2′-iodoethyl)oxazolidin-5-one as

starting material. Treatment with benzoyl chloride (0.141 g, 116 μl, 1 mmol) yielded the product as an oil, $[\alpha]_D^{20}$ −24.6 (*c* 0.88 in CH_2Cl_2).

(4*S*)-3-Benzyloxycarbonyl-4-[3′-oxo-3′-(2″-furyl)propyl]-oxazolidin-5-one 22b

Treatment with 2-furoyl chloride (0.131 g, 98 μl, 1 mmol) using Method A yielded the product as an oil (0.203 g, 0.59 mmol, 78%) (Found: MH^+, 344.1116. $C_{18}H_{18}NO_6$ requires 344.1134); $[\alpha]_D^{16}$ +74.6 (*c* 0.84 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2926, 1799, 1716, 1676, 1469, 1415; δ_H(200 MHz; $CDCl_3$) 2.20–2.88 [2 H, m, C(1′)H_2], 2.96–2.98 [2 H, m, C(2′)H_2], 4.42 [1 H, t, *J* 7, C(4)H], 5.15 (2 H, s, PhCH_2), 5.22 [1 H, d, *J* 4, C(2)H], 5.51–5.60 [1 H, m, C(2)H], 6.52 [1 H, dd, *J* 3.6 and 1.7, C(4″)H], 7.16 [1 H, br d, *J* 3.6, C(3″)H], 7.35 (5 H, s, Ph) and 7.56 [1 H, dd, *J* 1.7 and 0.7, C(5″)H]; *m*/*z* (EI) 344 (MH^+, 4.4%), 300 (21, $MH^+ - CO_2$), 252 (19, $MH^+ - PhCH_3$) and 208 (63, $MH^+ - CO_2$).

(4*S*)-3-Benzyloxycarbonyl-4-[3′-oxo-3′-(3″-methylphenyl)-propyl]oxazolidin-5-one 22c

Treatment with *m*-toluoyl chloride (0.155 g, 132 μl, 1 mmol) using Method A yielded the product as an oil (0.151 g, 0.41 mmol, 55%) (Found: M^+, 367.1406. $C_{21}H_{21}NO_5$ requires 367.1419); $[\alpha]_D^{20}$ +81.6 (*c* 0.3 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3034, 2922, 1799, 1718, 1604, 1587 and 1415; δ_H(200 MHz; $CDCl_3$) 2.40 [5 H, m, C(1′)H_2 and CH_3], 3.01–3.18 [2 H, m, C(2′)H_2], 4.45 [1 H, t, *J* 7, C(4)H], 5.22 [1 H, d, *J* 4, C(2)H], 5.29 (2 H, s, PhCH_2), 5.43–5.60 [1 H, m, C(2)H], 7.33–7.44 [7 H, m, C(4″)H, C(5″)H and Ph] and 7.65–7.75 [2 H, m, C(2″)H and C(6″)H]; *m*/*z* (EI) 367 (M^+, 2.7%), 323 (2.0, $M^+ - CO_2$) and 231 (63, $M^+ - PhCH_3 - CO_2$).

(4*S*)-3-Benzyloxycarbonyl-4-(3′-oxobutyl)oxazolidin-5-one 22d

Treatment with acetyl chloride (0.0785 g, 71 μl, 1 mmol) using Method B yielded the product as an oil (0.159 g, 0.55 mmol, 73%) (Found: MH^+, 292.1199). $C_{15}H_{18}NO_5$ requires 292.1185); $[\alpha]_D^{16}$ +75.4 (*c* 0.19 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2924, 1802, 1717 and 1416; δ_H(200 MHz; $CDCl_3$) 2.09 (3 H, br 2, CH_3), 2.10–2.17 [2 H, m, C(1′)H_2], 2.48–2.68 [2 H, m, C(2′)H_2], 4.34 [1 H, t, *J* 7, C(4)H], 5.19 [3 H, m, C(2)H and PhCH_2], 5.43–5.52 [1 H, br d, *J* 4, C(2)H] and 7.37 (5 H, s, Ph); *m*/*z* (EI) 292 (MH^+, 1.9%), 248 (43, $MH^+ - CO_2$) and 156 (81, $MH^+ - CO_2 - PhCH_3$). There is a significant inconsistency in the reported mps for this compound; lit.,[11] mp 64–65 °C and lit.,[12] mp 102–103 °C. Our sample did not crystallise, but exhibited spectroscopic data which were consistent with the data reported in the literature.[12]

(4*S*)-3-Benzyloxycarbonyl-4-(3′-oxopentyl)oxazolidin-5-one 22e

Treatment with propanoyl chloride (0.0925 g, 87 μl, 1 mmol) using Method A yielded the product as an oil (0.116 g, 0.38 mmol, 50%) (Found: $M^+ - CO_2$, 261.1357. $C_{15}H_{19}NO_3$ requires 261.1365); $[\alpha]_D^{16}$ +34.8 (*c* 0.33 in CH_2Cl_2) {lit.,[11] $[\alpha]_D^{25}$ +82.5 (*c* unspecified, MeOH)}; ν_{max}(film)/cm^{-1} 2922, 1801, 1716 and 1416; δ_H(200 MHz; $CDCl_3$) 1.25 [3 H, t, *J* 8, C(5′)H_3], 2.13–2.26 [2 H, m, C(4′)H_2], 2.32–2.43 [2 H, m, C(1′)H_2], 2.48–2.63 [2 H, m, C(2′)H_2], 4.33 [1 H, t, *J* 4, C(4)H], 5.17 (2 H, s, PhCH_2), 5.21 [1 H, br d, *J* 4, C(2)H], 5.50–5.59 [1 H, m, C(2)H] and 7.36 (5 H, s, Ph); *m*/*z* (EI) 261 ($M^+ - CO_2$, 1.4%) and 169 (6, $M^+ - CO_2 - PhCH_3$). This compound has reported mp 45–46 °C,[11] but no spectroscopic data were included.

(4*S*)-3-Benzyloxycarbonyl-4-(3′-oxooctyl)oxazolidin-5-one 22f

Treatment with hexanoyl chloride (0.135 g, 171 μl, 1 mmol) using Method A yielded the product as an oil (0.225 g, 0.65 mmol, 86%) (Found: M^+, 347.1744. $C_{19}H_{25}NO_5$ requires 347.1733); $[\alpha]_D^{16}$ +70.0 (*c* 0.51 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2957, 2932, 1801, 1716 and 1415; δ_H(200 MHz; $CDCl_3$) 0.81 [3 H, t, *J* 7, C(8′)H_3], 1.17 [4 H, m, C(6′)H_2 and C(7′)H_2], 1.46 (2 H, m, C(5′)H_2], 2.09–2.16 [2 H, m, C(4′)H_2], 2.24–2.31 [2 H, m, C(1′)H_2], 2.40–2.46 [2 H, m, C(2′)H_2], 4.26 [1 H, t, *J* 6, C(4)H], 5.04–5.18 [3 H, m, C(2)H and PhCH_2], 5.46 [1 H, br d, *J* 4, C(2)H] and 7.29 (5 H, s, Ph); *m*/*z* (EI) 347 (M^+, 5.8%), 303 (37, $M^+ - CO_2$) and 211 (85, $M^+ - CO_2 - PhCH_3$).

(4*S*)-3-Benzyloxycarbonyl-4-(4′-acetoxy-3′-oxobutyl)-oxazolidin-5-one 22g

Treatment with acetoxyacetyl chloride (0.137 g, 107 μl, 1 mmol) using Method B yielded the product as an oil (0.202 g, 0.58 mmol, 77%) (Found: M^+, 349.1168. $C_{17}H_{19}NO_7$ requires 349.1161); $[\alpha]_D^{16}$ +78.0 (*c* 0.595 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3433, 1801, 1718, 1653 and 1419; δ_H(200 MHz; $CDCl_3$) 2.15–2.19 [5 H, m, C(1′)H_2 and CH_3CO], 2.23–2.60 [2 H, m, C(2′)H_2], 4.34 [1 H, t, *J* 7, C(4)H], 4.34–4.37 (2 H, m, AcOCH_2CO), 5.18–5.22 [3 H, m, C(2)H and PhCH_2], 5.50–5.58 [1 H, m, C(2)H] and 7.37 (5 H, s, Ph); *m*/*z* (EI) 349 (M^+, 2.0%), 305 (2.5, $M^+ - CO_2$) and 213 (56, $M^+ - CO_2 - PhCH_3$).

(4*S*)-3-Benzyloxycarbonyl-4-(3′-oxopent-4′-enyl)oxazolidin-5-one 22h

Treatment with acryloyl chloride (0.091 g, 81 μl, 1 mmol) using Method B yielded the product as an oil (0.118 g, 0.39 mmol, 52%) (Found: $MH^+ - PhCH_3$, 212.0550. $C_9H_{10}NO_5$ requires 212.0559); $[\alpha]_D^{16}$ +100.9 (*c* 1.06 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2901, 1802, 1722, 1653 and 1415; δ_H(200 MHz, $CDCl_3$) 2.18–2.31 [2 H, m, C(1′)H_2], 2.65–2.80 [2 H, m, C(2′)H_2], 4.38 [1 H, t, *J* 6, C(4)H], 5.20–5.22 [3 H, m, C(2)H and PhCH_2], 5.48–5.58 [1 H, m, C(2)H], 5.82 [1 H, dd, *J* 10 and 2, C(5′)H], 6.12–6.38 [2 H, m, C(4′)H and C(5′)H] and 7.37 (5 H, s, Ph); *m*/*z* (EI) 212 ($MH^+ - PhCH_3$, 6.9%) and 168 (83, $M^+ - CO_2 - PhCH_3$).

(4*S*)-3-Benzyloxycarbonyl-4-(4′-chloro-3′-oxobutyl)oxazolidin-5-one 22i

Treatment with chloroacetyl chloride (0.113 g, 80 μl, 1 mmol) using Method B yielded the product as an oil (0.120 g, 0.37 mmol, 49%) (Found: M^+, 325.0715. $C_{15}H_{16}NO_5Cl$ requires 325.0717); $[\alpha]_D^{16}$ +57.1 (*c* 0.14 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3034, 2934, 1798, 1716, 1454 and 1416; δ_H(200 MHz, $CDCl_3$) 2.09–2.21 [2 H, m, C(1′)H_2], 2.44–2.57 [1 H, m, C(2′)H], 2.74–2.81 [1 H, m, C(2′)H], 4.03–4.27 (2 H, s, $ClCH_2CO$), 4.35 [1 H, t, *J* 7, C(4)H], 5.11–5.23 [3 H, m, C(2)H and PhCH_2], 5.52–5.58 [1 H, m, C(2)H] and 7.37 (5 H, s, Ph); *m*/*z* (EI) 325 (M^+, 2.4%), 233 (3, $M^+ - PhCH_3$) and 189 (65, $M^+ - PhCH_3 - CO_2$).

(4*S*)-3-Benzyloxycarbonyl-4-(3′-oxo-4′-phthalimidobutyl)-oxazolidin-5-one 22j

Treatment with freshly prepared *N*-phthaloylglycine acid chloride (0.75 mmol) [prepared by adding oxalyl chloride (67 μl, 0.098 g, 0.717 mmol) to a stirred solution of *N*-phthaloylglycine (0.154 g, 0.75 mmol) in dry toluene (2 cm^3), followed by the addition of dry *N*,*N*-dimethylformamide (25 μl) and stirring for 30 min] using Method B gave the crude product as an oil. Flash chromatography over silica gel (light petroleum–ethyl acetate, 10:1 to 1:1) yielded the product as an oil (0.173 g, 0.41 mmol, 77%) (Found: $MH - C_9H_6NO_2$, 277.0958. $C_{14}H_{15}NO_5$ requires 277.0950; $[\alpha]_D^{16}$ +63.9 (*c* 1.04 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2926, 1800, 1717, 1686, 1449 and 1415; δ_H(200 MHz; $CDCl_3$) 2.22–2.29 [2 H, m, C(1′)H_2], 2.60–2.80 [2 H, m, C(2′)H_2], 4.53 [1 H, t, *J* 7, C(4)H], 4.37–4.54 (2 H, m, NCH_2CO), 5.16–5.21 [3 H, m, C(2)H and PhCH_2], 5.52 [1 H, br d, *J* 4, C(2)H], 7.36 (5 H, s, Ph), 7.42 [2 H, dd, *J* 5.5 and 3.1, C(2″)H and C(3″)H phthaloyl] and 7.82 [2 H, dd, *J* 5.5 and 3.1, C(1″)H and C(4″)H phthaloyl]; *m*/*z* (EI) 277 ($MH^+ - C_9H_6NO_2$, 0.1%).

(4*S*)-3-Benzyloxycarbonyl-4-[(4′*S*)-3′-oxo-4′-phthalimido-pentyl]oxazolidin-5-one 22k

Treatment with *N*-phthaloyl-L-alanine acid chloride[45] (0.472 g, 2 mmol) according to Method B (double scale) gave the crude product as an oil. Flash chromatography over silica gel (light petroleum–ethyl acetate–gradient, 10:1 to 1:1) yielded the product as an oil (0.494 g, 1.095 mmol, 73%) (Found: M^+,

450.1417. $C_{24}H_{22}N_2O_7$ requires 450.1426); $[\alpha]_D^{16}$ +48.9 (*c* 1.115 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2922, 1799, 1778, 1714, 1414 and 1388; δ_H(200 MHz, $CDCl_3$) 1.61 (3 H, d, *J* 6.5, CH_3), 2.11–2.25 [2 H, m, C(1′)H_2], 2.62–2.67 [2 H, m, C(2′)H_2], 4.31 [1 H, t, *J* 4, C(4)H], 4.70–4.98 [1 H, m, C(4′)H], 5.15–5.21 [3 H, m, PhCH_2 and C(2)H], 5.43–5.58 [1 H, m, C(2)H], 7.36 (5 H, s, Ph), 7.63–7.77 [2 H, m, C(2″)H and C(3″)H phthaloyl] and 7.78–7.87 [2 H, m, C(1″)H and C(4″)H phthaloyl]; *m*/*z* (EI) 450 (M^+, 4.1%), 406 (12, $M^+ - CO_2$) and 314 (52, $M - CO_2 - PhCH_3$).

Methyl (2*S*)-2-[benzyloxycarbonylamino-5-oxo-5-phenylpentanoate 23a

(4*S*)-3-Benzyloxycarbonyl-4-(3′-oxo-3′-phenylpropyl)oxazolidin-5-one **22a** (0.120 g, 0.34 mmol) was added to a stirred solution of LiOMe from lithium (0.030 g, 0.77 mmol) in methanol (4 cm^3) at −10 °C under an atmosphere of nitrogen. The reaction mixture was stirred at −10 °C for 1 h. After allowing the reaction mixture to reach ambient temperature, ethyl acetate (10 cm^3) was added and the contents were filtered into a separating funnel. The organic phase was washed with dilute hydrochloric acid (10 cm^3, 1 M) and water (3 × 10 cm^3), dried and concentrated under reduced pressure to give the crude product as an oil. Flash chromatography over silica gel using toluene–ethyl acetate (10:1) as the eluent yielded methyl (2*S*)-2-benzyloxycarbonylamino-5-oxo-5-phenylpentanoate as a solid (0.095 g, 0.27 mmol, 79%), mp 74–75 °C (Found: C, 67.7; H, 6.13; N, 3.9. $C_{20}H_{21}NO_5$ requires C, 67.6; H, 6.13; N, 3.9%); $[\alpha]_D^{17}$ +4.5 (*c* 0.635 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3340, 3037, 2916, 1743, 1689, 1524 and 1446; δ_H(200 MHz, $CDCl_3$) 2.01–2.20 [1 H, m, C(3)H], 2.26–2.43 [1 H, m, C(3)H], 2.94–3.22 [2 H, m, C(4)H_2], 3.74 (3 H, s, OCH_3], 4.45 [1 H, m, C(2)H], 5.08 (2 H, s, PhCH_2), 5.57 (1 H, d, *J* 8, NH), 7.33 (5 H, s, Ph), 7.40–7.48 [2 H, m, C(3′)H and C(5′)H], 7.52–7.61 [1 H, m, C(4′)H] and 7.92 [2 H, d, *J* 7, C(2′)H and C(5′)H]; *m*/*z* (EI) 296 ($M^+ - CO_2Me$, 17.1%), 252 (51, $M^+ - CO_2Me - CO_2$) and 160 (10, $M^+ - CO_2Me - CO_2 - PhCH_3$).

Methyl (2*R*)-2-benzyloxycarbonylamino-5-oxo-5-phenylpentanoate *ent*-23a

The compound was prepared from *ent*-**22a** using the above procedure, and the product was isolated as a solid, mp 74–75 °C; $[\alpha]_D^{18}$ −4.3 (*c* 0.9 in CH_2Cl_2). The enantiomeric purities of compounds **23a** and *ent*-**23a** were determined to be 96% ee by chiral phase HPLC using a Daicel Chiralpak AS column.

Reactions of the zinc–copper reagent 16

A solution of (4*S*)-3-benzyloxycarbonyl-4-(2′-iodozincethyl)-oxazolidin-5-one **14** in dry THF (1.09 cm^3) (prepared as described previously) was cooled to −10 °C and a solution of CuCN·2 LICl [prepared from reaction of anhydrous copper(I) cyanide (0.67 g, 0.75 mmol) and anhydrous lithium chloride (0.64 g, 1.5 mmol) in dry THF (2 cm^3)] was added dropwise. The reaction mixture was warmed to 0 °C and stirred for 10 min prior to re-cooling to −25 °C, and the electrophile added. The reaction mixture was then warmed to 0 °C and stirred for 3 h. After allowing the reaction mixture to reach ambient temperature, ethyl acetate (50 cm^3) was added and the contents were filtered into a separating funnel. The organic phase was washed with saturated aqueous sodium hydrogen carbonate (2 × 20 cm^3), water (3 × 20 cm^3), dried and concentrated under reduced pressure to give a crude product as an oil. Flash chromatography over silica gel using a light petroleum–ethyl acetate-gradient, typically 50:1 to 50:4 as the eluent (except where stated otherwise) yielded the pure protected amino acid.

Ethyl 2-oxo-4-[(4′*S*)-3′-benzyloxycarbonyl-5′-oxooxazolidin-4-yl]butanoate 22l

Ethyl oxalyl chloride (0.137 g, 112 μl, 1 mmol) was used as the electrophile, and the reaction was conducted according to the general procedure. Flash chromatography over silica gel (light petroleum–ethyl acetate, 10:1 to 1:1) yielded the pure protected amino acid as an oil (0.186 g, 0.53 mmol, 71%) (Found: M^+, 349.1150. $C_{17}H_{19}NO_7$ requires 349.1162); $[\alpha]_D^{16}$ +64.8 (*c* 1.015 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3034, 2984, 2934, 1801, 1724, 1446 and 1415; δ_H(200 MHz, $CDCl_3$) 1.36 (3 H, t, *J* 7.1, OCH_2CH_3), 2.00–2.39 [2 H, m, C(1′)H_2], 3.03–3.12 [2 H, m, C(2′)H_2], 4.25–4.35 [3 H, m, C(4)H and OCH_2CH_3], 5.00 [3 H, m, C(2)H and PhCH_2], 5.51–5.59 [1 H, m, C(2)H] and 7.36 (5 H, s, Ph); *m*/*z* (EI) 349 (M^+, 1.2%), 305 (31, $M^+ - CO_2$) and 213 (22, $M^+ - CO_2 - PhCH_3$).

(4*S*)-3-Benzyloxycarbonyl-4-(pent-4-enyl)oxazolidin-5-one 24a

Treatment with allyl chloride (0.765 g, 81 μl, 1 mmol) yielded the product as an oil (0.145 g, 0.50 mmol, 66%) (Found: M^+, 289.1302. $C_{16}H_{19}NO_4$ requires 289.1314); $[\alpha]_D^{24}$ +101.5 (*c* 1.075 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3402, 3067, 3036, 2926, 1803, 1718 and 1417; δ_H(200 MHz, $CDCl_3$) 1.30–1.63 [2 H, m, C(1′)H_2], 1.75–2.18 [4 H, m, C(2′)H_2 and C(3′)H_2], 4.28–4.40 [1 H, m, C(4)H], 4.90–5.05 [2 H, m, C(5′)H_2], 5.11–5.29 [3 H, m, PhCH_2 and C(2)H], 5.45–5.60 [1 H, m, C(2)H], 5.63–5.90 [1 H, m, C(4′)H], and 7.37 (5 H, s, Ph); *m*/*z* (EI) 289 (M^+, 1.6%), 245 (6, $M^+ - CO_2$) and 153 (61, $M^+ - CO_2 - PhCH_3$).

(4*S*)-3-Benzyloxycarbonyl-4-[(3′*RS*)-3-(chloromethyl)pent-4′-enyl]oxazolidin-5-one 24b

Treatment with 1,4-dichlorobut-2-ene (0.125 g, 106 μl, 1 mmol) yielded the products (an inseparable mixture of diastereoisomers) as an oil (0.131 g, 0.39 mmol, 52%) (Found: M^+, 337.1095. $C_{17}H_{20}NO_4Cl$ requires 337.1081); ν_{max}(film)/cm^{-1} 3419, 3067, 3034, 2954, 2925, 1801, 1717 and 1417; δ_H(200 MHz, $CDCl_3$) 1.18–2.10 [4 H, m, C(1′)H_2 and C(2′)H_2], 2.25–2.48 [1 H, m, C(3′)H], 3.43 (2 H, d, *J* 6, CH_2Cl), 4.28–4.38 [1 H, m, C(4)H], 5.03–5.25 [5 H, m, C(5′)H_2, PhCH_2 and C(2)H], 5.43–5.70 [2 H, m, C(2)H and C(4′)H] and 7.37 (5 H, s, Ph); *m*/*z* (EI) 337 (M^+, 1.3%), 293 (3, $M^+ - CO_2$) and 201 (58, $M^+ - CO_2 - PhCH_3$).

(4*S*)-3-Benzyloxycarbonyl-4-(penta-3′,4′-dienyl)oxazolidin-5-one 25

Treatment with prop-2-ynyl chloride (0.0745 g, 72 μl, 1 mmol) yielded the product as an oil (0.136 g, 0.47 mmol, 63%) (Found: $M^+ - CO_2H$, 242.1187. $C_{15}H_{16}NO_2$ requires 242.1181); $[\alpha]_D^{24}$ +67.6 (*c* 1.05 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3034, 2957, 2926, 1801, 1716 and 1525; δ_H(200 MHz, $CDCl_3$) 1.95–2.25 [4 H, m, C(1′)H_2 and C(2′)H_2], 4.30–4.38 [1 H, m, C(4)H], 4.66–4.73 [2 H, m, C(5′)H_2], 5.00–5.13 [1 H, m, C(3′)H], 5.18–5.26 [3 H, m, PhCH_2 and C(2)H], 5.45–5.63 [1 H, m, C(2)H] and 7.37 (5 H, s, Ph); *m*/*z* (EI) 242 ($M^+ - CO_2H$, 7.7%), 198 (20, $M^+ - CO_2H - CO_2$) and 106 (60, $M^+ - CO_2H - CO_2 - PhCH_3$).

1,7-Bis[(4′*S*)-3′-benzyloxycarbonyl-5′-oxooxazolidin-4′-yl]hept-3-ene 26

Treatment with 1,3-dichloropropene (0.055 g, 46 μl, 0.5 mmol) yielded the product as an oil (0.072 g, 0.14 mmol, 18%) (Found: $MH^+ - CO_2 - PhCH_3$, 401.1730. $C_{21}H_{25}N_2O_6$ requires 401.1713); $[\alpha]_D^{24}$ +99.9 (*c* 0.99 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3403, 3065, 3033, 2925, 1801, 1717 and 1417; δ_H(200 MHz, $CDCl_3$) 1.23–1.50 [4 H, m, C(1)H_2 and C(7)H_2], 1.65–2.50 [6 H, m, C(2)H_2, C(5)H_2 and C(6)H_2], 4.25–4.35 [2 H, m, 2 × C(4′)H], 5.11–5.26 [6 H, m, 2 × PhCH_2 and 2 × C(2′)H], 5.30–5.40 [2 H, m, C(3)H and C(4)H], 5.48–5.60 [2 H, m, 2 × C(2′)H] and 7.37 (10 H, s, Ph); *m*/*z* (EI) 401 ($MH^+ - CO_2 - PhCH_3$, 18.5%) and 357 (37, $MH^+ - CO_2 - PhCH_3 - CO_2$).

Acknowledgements

We thank the EPSRC for CASE awards (N. W. and J. L. F.), and Pfizer Central Research and Rhône-Poulenc Rorer for support through the CASE scheme.

References

1 R. F. W. Jackson, N. Wishart, A. Wood, K. James and M. J. Wythes, *J. Org. Chem.*, 1992, **57**, 3397.
2 M. J. Dunn, R. F. W. Jackson, J. Pietruszka and D. Turner, *J. Org. Chem.*, 1995, **60**, 2210.
3 R. F. W. Jackson, N. Wishart and M. J. Wythes, *Synlett*, 1993, 219.
4 J. L. Fraser, R. F. W. Jackson and B. Porter, *Synlett*, 1994, 379.
5 J. L. Fraser, R. F. W. Jackson and B. Porter, *Synlett*, 1995, 819.
6 T. Ohta, A. Hosoi, T. Kimura and S. Nozoe, *Chem. Lett.*, 1987, 2091.
7 T. Ohta, T. Kimura, N. Sato and S. Nozoe, *Tetrahedron Lett.*, 1988, **29**, 4303.
8 T. Ohta, N. Sato, T. Kimura, S. Nozoe and K. Izawa, *Tetrahedron Lett.*, 1988, **29**, 4305.
9 J. Ackermann, M. Matthes and C. Tamm, *Helv. Chim. Acta*, 1990, **73**, 122.
10 J. Ezquerra, J. de Mendoza, C. Pedregal and C. Ramirez, *Tetrahedron Lett.*, 1992, **33**, 5589.
11 T. L. Ho, B. Gopalan and J. J. Nestor, *J. Org. Chem.*, 1986, **51**, 2405.
12 J. M. Scholtz and P. A. Bartlett, *Synthesis*, 1989, 542.
13 N. Aubry, R. Plante and R. Déziel, *Tetrahedron Lett.*, 1990, **31**, 6311.
14 H. H. Ibrahim and W. D. Lubell, *J. Org. Chem.*, 1993, **58**, 6438.
15 J. A. Bajgrowicz, A. El Hallaoui, R. Jacquier, C. Pigiere and P. Viallefont, *Tetrahedron*, 1985, **41**, 1833.
16 A. El Marini, M.-L. Roumestant, L. Pappalardo and P. Viallefont, *Bull. Soc. Chim. Fr.*, 1989, **4**, 554.
17 R. Fitzi and D. Seebach, *Tetrahedron*, 1988, **44**, 5277.
18 R. M. Williams, P. J. Sinclair, D. Zhai and D. Chen, *J. Am. Chem. Soc.*, 1988, **110**, 1547.
19 E. J. Corey and J. O. Link, *J. Am. Chem. Soc.*, 1992, **114**, 1906.
20 D. G. Melillo, R. D. Larsen, D. J. Mathre, W. F. Shukis, A. W. Wood and J. R. Colleluori, *J. Org. Chem.*, 1987, **52**, 5143.
21 J. E. Baldwin, R. M. Adlington, A. Basak, S. L. Flitsch, A. K. Forrest and H.-H. Ting, *J. Chem. Soc., Chem. Commun.*, 1986, 273.
22 H. K. Chenault, J. Dahmer and G. M. Whitesides, *J. Am. Chem. Soc.*, 1989, **111**, 6354.
23 J. E. Baldwin, M. North, A. Flinn and M. G. Moloney, *Tetrahedron*, 1989, **45**, 1453.
24 J. E. Baldwin, M. North, A. Flinn and M. G. Moloney, *Tetrahedron*, 1989, **45**, 1465.
25 M. Delbosco, A. N. C. Johnstone, G. Bazza, S. Lopatriello and M. North, *Tetrahedron*, 1995, **51**, 8545.
26 J. E. Baldwin, T. Miranda, M. G. Moloney and T. Hokelek, *Tetrahedron* 1989, **45**, 7459.
27 M. R. Attwood, M. G. Carr and S. Jordan, *Tetrahedron Lett.*, 1990, **31**, 283.
28 H. P. Knoess, M. T. Furlong, M. J. Rozema and P. Knochel, *J. Org. Chem.*, 1991, **56**, 5974.
29 D. H. R. Barton, Y. Hervé, P. Potier and J. Thierry, *Tetrahedron*, 1988, **44**, 5479.
30 D. H. R. Barton, Y. Hervé, P. Potier and J. Thierry, *Tetrahedron*, 1987, **43**, 4297.
31 W. G. Dauben, B. A. Kowalczyk and D. P. Bridon, *Tetrahedron Lett.*, 1989, **30**, 2461.
32 D. A. Evans and T. Bach, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1326.
33 D. E. Stack, B. T. Dawson and R. D. Rieke, *J. Am. Chem. Soc.*, 1992, **114**, 5110.
34 D. E. Stack, B. T. Dawson and R. D. Rieke, *J. Am. Chem. Soc.*, 1991, **113**, 4672.
35 J. E. Baldwin, R. M. Adlington, A. Basak and H.-H. Ting, *J. Chem. Soc., Chem. Commun.*, 1986, 1280.
36 N. J. S. Huby, R. G. Kinsman, D. Lathbury, P. G. Vernon and T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, 1991, 145.
37 Y. Tamaru, H. Tanigawa, T. Yamamoto and Z.-i. Yoshida, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 351.
38 P. Knochel and R. D. Singer, *Chem. Rev.*, 1993, **93**, 2117.
39 P. Knochel, M. C. P. Yeh, S. C. Berk and J. Talbert, *J. Org. Chem.*, 1988, **53**, 2390.
40 E.-i. Negishi, A. O. King and N. Okukado, *J. Org. Chem.*, 1977, **42**, 1821.
41 M. Sakaitani, K. Hori and Y. Ohfune, *Tetrahedron Lett.*, 1988, **29**, 2983.
42 S. Bhar and B. C. Ranu, *J. Org. Chem.*, 1995, **60**, 745.
43 M. Itoh, *Chem. Pharm. Bull.*, 1969, **17**, 1679.
44 D. H. R. Barton, Y. Hervé, P. Potier and J. Thierry, *J. Chem. Soc., Chem. Commun.*, 1984, 1298.
45 K. Balenovic, D. Cerar and Z. Fuks, *J. Chem. Soc.*, 1952, 3316.

Paper 8/02142B
Received 18*th March* 1998
Accepted 20*th April* 1998