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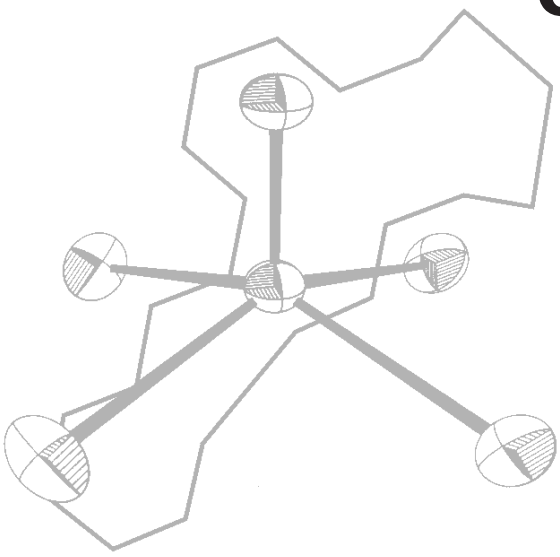

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The Facile Production of *N*-Methyl Amino Acids via Oxazolidinones

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A range of oxazolidinones derived from *N*-carbamoyl α-amino acids were prepared by an efficient method as key intermediates in the synthesis of *N*-methyl amino acids and peptides. The method was readily applied to most α-amino acids except those with basic side chains. The oxazolidinones were converted by reductive cleavage into *N*-methyl α-amino acids.

Keywords. Oxazolidinones; *N*-methyl amino acids; synthesis; reductive cleavage.

Introduction

N-Methylated peptides are secondary metabolites that display a remarkable range of biological activities and consequently are the subject of considerable interest. The manufacture of these compounds and derivatives by solid phase techniques is a natural extension of the methods for standard or unmodified peptides. There are two problems associated with the preparation of these compounds: firstly, the limited availability of *N*-methyl amino acid residues for synthesis and, secondly, the poor efficiency of the coupling of such residues, particularly on resin or solid phase procedures. This paper is concerned primarily with the former problem, the facile production of *N*-methyl amino acids and certain derivatives in suitable forms for solution and solid phase (SPPS) elaboration.

In our research program, a wide range of functionalized α-amino acid residues were required that could be converted efficiently into *N*-methylated residues and/or subsequently employed in the solution and SPPS of target peptides. The α-amino acids of most interest are those with reactive side chains and include such amino acids as serine, threonine, aspartic acid, glutamine, tyrosine and cysteine.

A range of methods has been employed to prepare *N*-alkylated (methyl) amino acids. These include methods for direct methylation,[1–5] reductive amination,[6–12] alternative methods[13–18] and through the generation of oxazolidinones and their subsequent transformation to the *N*-methyl (alkyl) product.[19–23] In addition, there are strategies involving the use of immonium ions in Diels–Alder/retro-Diels–Alder sequences,[24] the nucleophilic displacement of triflates,[25] the hydroxyamination of chiral enolates[26] and the Mitsunobu reaction.[27] Some of these methods suffer from limitations in the range of amino acids to which they are applicable, some utilize rather long synthetic sequences and some cause at least partial racemisation of the substrate. This paper seeks to exploit oxazolidinone chemistry to generate a range of *N*-methyl amino acids (with retained optical purity) in reasonable yields.

In general, the methods above are relevant to the preparation of *N*-methyl aliphatic amino acids with limited application to *N*-methyl amino acids with functionalized or reactive side chains and the few isolated examples reported usually required side-chain protection. Certainly, it seemed there was no general strategy that could cope with a range of amino acids, natural or unnatural, with unprotected, functionalized side chains.

In this paper we report studies directed toward the synthesis of *N*-methyl amino acids with high optical purity, with protection regimes in accord with solution or solid phase chemistry and by methods that have been shown to be efficient. In searching for this transformation strategy, we were attracted to a series of papers[19–23] that accomplished the synthesis of *N*-methyl amino acids via oxazolidinone intermediates.

In the first paper, Ben-Ishai[20] showed a limited range of *N*-benzyloxycarbonyl (*N*-Cbz) amino acids underwent acid-catalysed oxazolidinone formation in reaction with paraformaldehyde or trioxan.[28] This acid-catalysed procedure is operationally simple, the reaction conditions are mild, it employs cheap reagents, the products are free of racemisation and they are produced in high chemical yields. Formation of oxazolidinones also has the advantage that it does not require the separate protection/deprotection of the carboxylic acid. Ben-Ishai was able to elaborate the glycine oxazolidinone (1) using 1 equiv. of benzyl amine to give the *N*-hydroxymethyl benzylamide (2). Hydrogenolysis of the *N*-hydroxymethyl group gave the *N*-methyl compound (3), a derivative of sarcosine. Later Itoh[21] prepared the oxazolidinones of *N*-Cbz aspartic and glutamic acids (and other dipeptidal compounds based on glutamine and asparagine) and

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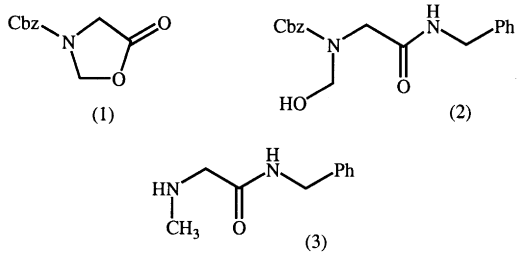
showed that hydrogenolysis of the oxazolidinone caused removal of the Cbz group and complete excision of the formyl methylene. Itoh[21] commented it was important for rapid cleavage reactions to have the *N*-carbamoyl group removed and an NH present which raised the possibility the oxazolidinone cleavage was not hydrogenolytic.



Freidinger *et al.*[19] made an important advance in this area in their paper addressing the preparation of *N*-methyl-*N*-fluorenylmethoxycarbonyl (*N*-Fmoc) amino acids via oxazolidinones for applications in peptide synthesis. Freidinger's work employed a subsequent triethylsilane/trifluoroacetic acid reductive cleavage to form the *N*-methyl group while retaining the Fmoc protection.

More recently, Reddy *et al.*[22] described the preparation of *N*-t-butoxycarbonyl (*N*-Boc) protected oxazolidinones and the production of *N*-methyl amino acids from *N*-Cbz and *N*-Boc oxazolidinones by hydrogenolysis. Their results with *N*-Cbz compounds (from aliphatic amino acids) contradict the results of Williams and Yuan[23] and Itoh.[21] Williams and Yuan have described the hydrogenolysis of the *N*-Cbz protected glutamic acid oxazolidinone (4) which gave the product (5) (Fig. 1), exhibiting no *N*- or *O*-methylation, also in accord with the results of Itoh. Furthermore, based on Itoh's work, *N*-Boc oxazolidinones might not be expected to give *N*-methyl products from hydrogenolysis, since the *N*-Boc group is stable to the neutral hydrogenolytic conditions employed by Reddy *et al.*

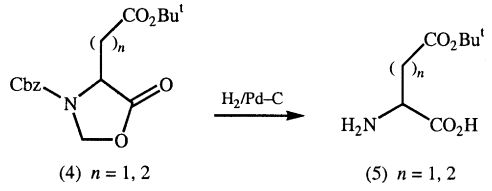


Fig. 1. Hydrogenolysis of oxazolidinones by Williams and Yuan.[23]

The work described in this paper exploits the oxazolidinone route[19–23] to generate a range of *N*-methyl amino acids by using simple reproducible chemistry. The reaction plan presented in this paper is depicted by the general diagram in Fig. 2, where protected amino acids are cyclized efficiently to oxazolidinones. These oxazolidinones may be reductively cleaved by complementary procedures that give *N*-methyl or *N*-methyl, *N*-carbamoylated amino acids.

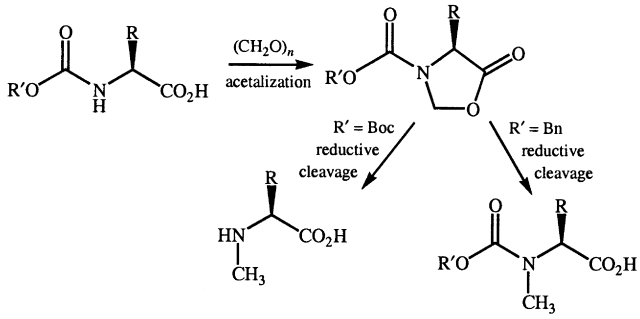


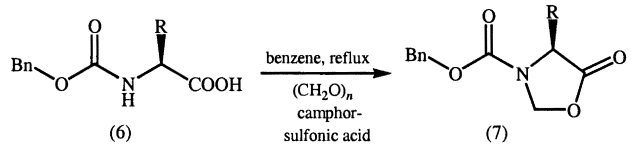
Fig. 2. General reaction plan.

Results and Discussion

Acetalization Reactions to Form Oxazolidinones

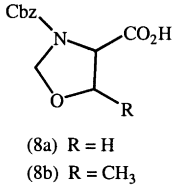
In the first series of reactions, *N*-Cbz amino acids (6a–j) were converted into the corresponding oxazolidinones (7a–j) by reaction with paraformaldehyde (Scheme 1). The potential exists with the side chains, of say serine and threonine, for acetalizing side reactions to occur, either intra- or intermolecularly, to give products like structures (8) and (9). Some precedent exists for this in the reactions of asparagine reported by Ben-Ishai.[20] Presumably, it is this concern that caused Reddy *et al.*[22] to prepare the t-butyldiphenylsilyl ether of serine.

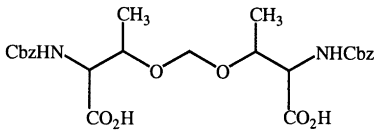
This assumption of reactivity was tested by reaction of *N*-Cbz L-threonine (6b) with excess paraformaldehyde in

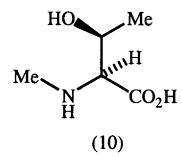


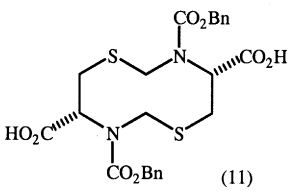
(a) R = CH_2OH	(h) R = CH_2SH
(b) R = $CH(OH)CH_3$	(i) R = $CH_2CH_2SCH_3$
(c) R = $CH_2C_6H_4OH$	(j) R = $CH_2CH_2CH_2CH_2NPhth$
(d) R = $CH_2CH_2CONHCbz$	(k) R = $CH_2CH_2CH_2CH_2NHCbz$
(e) R = CH_2CH_2COOH (DL)	(l) R = $R'CH_2$ (R' = indol-3-yl)
(f) R = CH_2COOBn	(m) R = $R''CH_2$ (R'' = *N*-Cbz imidazol-4-yl)
(g) R = C_6H_5	(n) R = CH_2CONH_2
	(o) R = $CH_2CH_2CONH_2$

Scheme 1









refluxing benzene in the presence of catalytic camphorsulfonic acid (Scheme 1). Two products were isolated from this reaction [and also that of *N*-Cbz L-serine (6a)]. The reaction gave the desired oxazolidinone (7b), albeit in only 21% yield, showing a characteristic i.r. absorption (1805 cm^{-1}),[20] together with the oxazolidine (8a) (55%). Subsequent hydrogenolysis of the oxazolidinone (7b), gave *N*-methyl-L-threonine (10) (see below). The corresponding reaction with *N*-Cbz L-serine (6a) gave the oxazolidinone (7a) in similar yield (15%). In both the serine and threonine reactions, the major products were the oxazolidines (8a) (55%) and (8b) (50%), respectively, resulting from cyclization of the intermediate iminium ion with the side-chain hydroxyl. Thus protection of the side-chain hydroxyls of serine and threonine is a prudent step.

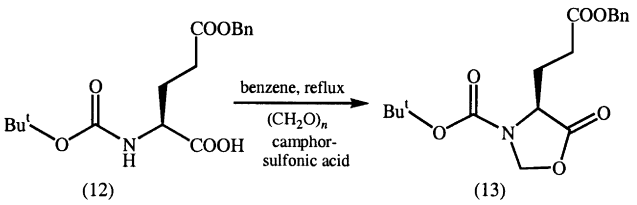
The paraformaldehyde reaction to form the oxazolidinones was applied to several α-amino acids with 'reactive' or functionalized side chains and so the compounds (7a–j) derived from L-serine, L-threonine, L-tyrosine, L-glutamine, DL-glutamic acid, L-aspartic acid, L-phenylglycine, L-cysteine, L-methionine and L-lysine have all been prepared in poor to high yields. In certain cases, (6d), (6f) and (6j), side-chain protection was employed and in these cases the protecting group also facilitated handling of the compounds by improving compound solubility. In both cases (7d) and (7f), the side-chain benzylic protecting groups were removed in the same hydrogenolysis reaction that was to generate the *N*-methyl group. The phthalimido group present in compound (7j) can be removed by a variety of techniques.[29]

Oxazolidinone formation with *N*-Cbz cysteine (6h) gave a mixture of products. The desired oxazolidinone (7h) was isolated in only 3% yield. The major compound from this reaction exhibited a M+H peak (electrospray mass spectrum) at *m/z* 535, which, together with the ^1H and ^{13}C n.m.r. spectra, was suggestive of the dimeric structure (11) (65% conversion). Consistent with this suggested structure is the fact that the compound was isolated during workup by extraction into sodium bicarbonate solution. *N*-Cbz methionine (6i) formed the required oxazolidinone (7i) in high yield (91%).

Results for the amino acids with basic or amido side chains (6k–o) were uniformly poor, though the problematic reaction with lysine was solved by use of the side-chain phthalimido derivative (6j). All reactions of the compounds with free amino side chains were unsuccessful. This was still the case with the derivatives of lysine (6k) and histidine (6m) in which the side-chain amino group was carbamoylated.

It was also noted that Reddy *et al.*[22] had shown that *N*-Boc amino acids would form oxazolidinones. The *N*-Boc glutamic acid derivative (12) was available in our laboratory and it underwent reaction in the same manner as the *N*-Cbz amino acids (Scheme 1) to give the oxazolidinone (13) in 60% yield (Scheme 2).

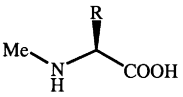
Analysis of all the oxazolidinones was made simple by the diagnostic signals in the infrared and ^1H n.m.r. spectra. The compounds (7a–j) and (13) typically have a strong C=O stretch 1790–1810 cm^{-1}.[20] In the ^1H n.m.r. spectrum, the value of the *J* coupling of the oxazolidinone methylene group is 4–5 Hz.[30] It is known that the geminal coupling constant is sensitive to both α- and β-substituents with electronegative substituents leading to a positive change in the coupling constant. Thus the absolute value of the coupling constant changes from a typical *J* of about –15 Hz to the smaller absolute value seen here.



Scheme 2

Reductive Cleavages of Oxazolidinones; Hydrogenolysis

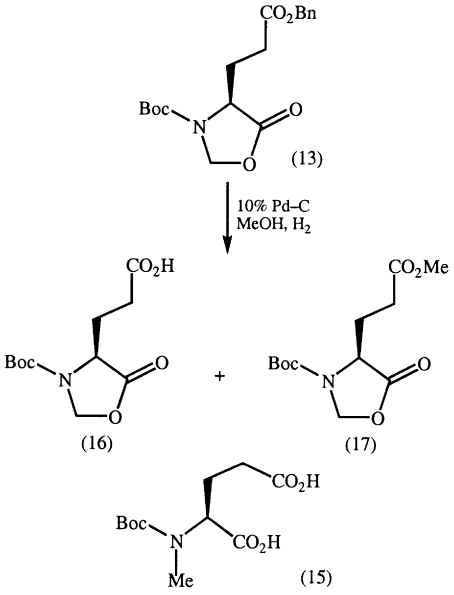
In the next phase of the study, the oxazolidinones were to be reductively cleaved to afford the *N*-methyl amino acids. Initially, hydrogenolysis was the procedure adopted. The reaction protocol followed was that reported by Reddy *et al.*[22] Such hydrogenolysis reactions are a simple and potentially efficient method for the conversion of the oxazolidinones (7a–g) and (7j) into the corresponding *N*-methyl amino acids (14a–g) and (14j). Hydrogenolyses of the oxazolidinones (7a–g) and (7j) were performed and the initial results were encouraging. Detailed examination (^1H n.m.r.) of the hydrogenolysis products showed in all cases the presence of varying amounts of deformylated amino acids (namely the product observed by Itoh[21]). The occurrence in the hydrogenolyses of this side product (the free α-amino acid), which on occasion was the major product, was not commented on by previous workers.[22] It would seem the hydrogenolytic conditions are able to cleave the formyl carbon from the oxazolidinone and this effect is accentuated when the amino acid has reactive functionality in its side chain. Thus, with side-chain functionalized amino acids, the derived oxazolidinones undergo hydrogenolysis with varying efficiencies and this has necessitated the use of alternative reductive cleavage conditions.



(14a) R = CH_2OH
(14b) R = $CH(OH)CH_3$
(14c) R = $CH_2C_6H_4OH$
(14d) R = $CH_2CH_2CONH_2$
(14e) R = CH_2CH_2COOH (DL)
(14f) R = CH_2COOH
(14g) R = C_6H_5
(14j) R = $CH_2CH_2CH_2CH_2NPhth$

Additionally, Reddy *et al.*[22] reported their *N*-Boc oxazolidinones were hydrogenolytically cleaved to give the expected *N*-Boc, *N*-methyl compounds and this might be a useful alternative to the hydrogenolyses of the *N*-Cbz compounds. However, application of this method to the hydrogenolysis of the glutamic acid derivative (13) gave two compounds (Scheme 3), neither of which was the expected *N*-Boc, *N*-methyl glutamic acid (15). One of the products is the carboxylic acid (16) (7%), in which only the side-chain benzyl ester has been hydrogenolysed. The carboxylic acid

(16) result is in accord with Itoh's theory[21] that the oxazolidinone NH must be present for hydrogenolysis to occur. The other product is the methyl ester (17) (59%), the result of a transesterification. Intriguingly, the oxazolidinone rings remain untouched (1801 cm^{-1}) in the hydrogenolysis of the *N*-Boc oxazolidinones. This observation lends support to the literature,[21] which proposes the cleavage of oxazolidinones is not hydrogenolytic and the successful cleavage requires the N–H be present. The *N*-Boc protection, unlike the *N*-Cbz, is stable to the hydrogenolytic conditions used and so according to Itoh's theory would remain intact, as observed.

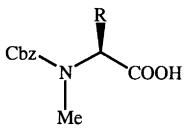


Scheme 3

Reductive Cleavages of Oxazolidinones; Trifluoroacetic Acid/Triethylsilane

Attention was turned to the oxazolidinone reductive cleavage reported by Freidinger *et al*.[19] (see above). This triethylsilane/trifluoroacetic acid reaction gave the required *N*-Cbz *N*-methyl amino acids (18a, c–g and j)[31] in high yield and purity with no evidence of side-reaction. It is thus the preferred method for the production of *N*-methyl amino acids from oxazolidinones.

In the case, however, of the threonine oxazolidinone (7b), the triethylsilane reduction led to approximately equal yields of the required *N*-Cbz *N*-methyl amino acid (18b) (35%) and the side-product (8b) (R = Me, 32%).[32] Evidently, in this case the intermediate iminium ion from initial cleavage of the oxazolidinone ring can be intercepted intramolecularly by the side-chain hydroxyl to form the new oxazolidinine (8b), which is stable under these reaction conditions. The same reaction with the serine oxazolidinone (7a) did not produce any of the analogous side-product (8a).



(18a) R = CH_2OH
(18b) R = $CH(OH)CH_3$
(18c) R = $CH_2C_6H_4OH$
(18d) R = $CH_2CH_2CONH_2$
(18e) R = CH_2CH_2COOH (DL)
(18f) R = CH_2COOBn
(18g) R = C_6H_5
(18h) R = CH_2SH
(18i) R = $CH_2CH_2SCH_3$
(18j) R = $CH_2CH_2CH_2CH_2NPhth$

The glutamine substrate (7d) which bears benzyloxycarbonyl protection on both the α-amino and side-chain nitrogens was smoothly converted into the *N*-methyl compound (18d) (62%). Notably, it also suffered selective removal of the side-chain benzyloxycarbonyl group.

Conclusion

In conclusion, we have shown that side-chain functionalized *N*-protected α-amino acids can form oxazolidinones in poor to excellent yields, without the need for side-chain protection in some cases. Consistent with the experience of other workers, the amino or nitrogen based acids (lysine, histidine, tryptophan) were not good candidates for oxazolidinone formation. A protection strategy for overcoming this problem was successful in the case of lysine (*N*-phthalimido). The chief purpose in preparing these oxazolidinones was to convert them into *N*-methyl amino acids by reductive cleavage. A literature method for this transformation is hydrogenolysis. However, the studies described in this paper have highlighted the occurrence of a side-reaction in this transformation, which in some cases becomes the major pathway and leads to deformylation of the substrate oxazolidinone, giving the free amino acid as the reaction product. It was due to this deficiency that the triethylsilane/trifluoroacetic acid reductive cleavage employed, in particular by Freidinger *et al*.,[19] was the reaction of first resort for the oxazolidinone reductive cleavage. By using this procedure, several *N*-Cbz *N*-methyl amino acids have been prepared in moderate chemical yields and will be used in research projects aimed at the synthesis of *N*-methylated peptides by solution and solid phase techniques.

Experimental

General Instructions

All melting points are uncorrected and were recorded on a Reichert 'Thermopan' microscope hot-stage apparatus. Infrared spectra were recorded on a Perkin–Elmer 1720X FTIR spectrometer, using a diffuse reflectance accessory with KBr background. N.m.r. spectra including the DEPT experiments were recorded in (D)chloroform solution unless otherwise stated on a Brüker AM-300 Spectrometer (^1H at 300.13 MHz and ^{13}C at 75.47 MHz) or on a Brüker DRX 400 MHz machine. Chemical shifts are reported as δ values in parts per million (ppm) and coupling constants (*J*) in Hz relative to residual solvent. Electrospray mass spectra (e.s.m.s.) were obtained on a VG Bio-Q triple quadrupole mass spectrometer by using water/methanol/acetic acid (0 : 99 : 1 or 50 : 50 : 1) mixtures as the mobile phase. Low resolution mass spectra (e.i.) were performed at La Trobe University by Dr John Traeger, on a Shimadzu GCMS-QP5050A mass spectrometer fitted with a direct insertion probe at 70 eV, with a transfer line temperature of 250°C. Other low and high resolution mass spectra (l.s.i.m.s.) were measured at the University of Tasmania by Dr Noel Davies and coworkers, on a Kratos concept mass spectrometer at 70 eV with a source temperature of 200°C. Optical rotations were obtained on a Perkin–Elmer 141 Polarimeter. Flash column chromatography was carried out using silica gel (silica gel 60, 230–400 mesh ASTM) supplied by Merck Chemicals (Darmstadt). Ethyl acetate and hexane used for chromatography were distilled prior to use. All solvents were purified by distillation. For dry

solvents, procedures from Perrin and Armarego[33] were followed. Dry dichloromethane was distilled and stored over Linde type 4 Å molecular sieves. All other reagents and solvents were purified or dried as described by Perrin and Armarego.[33]

Preparation of *N*-Benzyloxycarbonyl Oxazolidinones

General Procedure

A mixture of the *N*-benzyloxycarbonyl amino acid (6) (7.5 mmol), camphorsulfonic acid (88 mg, 3.8 mmol) and benzene (60 ml) was placed in a 250 ml round-bottom flask set for reflux. To the refluxing solution was added paraformaldehyde (1.13 g, 38 mmol) in five equal portions, allowing for the solution to clear before each subsequent addition. After the last addition, the mixture was heated at reflux until the solution was clear. The benzene solution was concentrated and the residue was dissolved in ethyl acetate (100 ml). The organic layer was washed with 5% aqueous sodium bicarbonate solution, dried over magnesium sulfate, filtered and concentrated under vacuum. Residual solids were recrystallized from dichloromethane/hexane and oils were purified by silica gel chromatography, with 30–50% ethyl acetate/hexane as the eluting solvent.

(S)-*3-Benzyloxycarbonyl-4-hydroxymethyloxazolidin-5-one (7a)*

This was an *oil* (15% yield) (Found: C, 57.2; H, 5.3; N, 5.2. $C_{12}H_{13}NO_5$ requires C, 57.4; H, 5.2; N, 5.6%). $[\alpha]_D^{23}$ +88.6° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3472 (OH), 3094, 3069, 3035 (CH, aromatic), 3000–2900 (CH, saturated), 1801 (C=O, oxazolidinone), 1717 (C=O, carbamate), 1499, 1423, 1359, 1307, 1212, 1172, 1132, 1078, 976, 918, 765 and 699. *m/z* (e.s.m.s.) 252 (M+1, 100%). δ_H 7.31, s, 5H, ArH; 5.43 and 5.27, each m, 1H, NCH_2O; 5.17, d, J_{AB} 12.2 Hz, 1H, ArC**H**H; 5.13, d, J_{AB} 12.2 Hz, 1H, ArCH**H**; 4.24, s, 1H, NCHCO; 4.11–3.96, m, 2H, CHC**H**$_2$OH; 2.92, s, 1H, OH. δ_C 170.88, C 5; 152.74, OCON; 135.20, quaternary ArC; 128.69, 128.29, 5×ArC; 78.43, C 2; 68.04, $ArCH_2$; 61.47, CH_2OH; 57.64, C 4.

N-*Cbz-(4S)-1,3-Oxazolidine-4-carboxylic Acid (8a)*[32]

This compound was isolated by acidification of the 5% bicarbonate wash described in the general procedure. The combined bicarbonate washings were acidified with 5 M hydrochloric acid. The aqueous acidic layer was extracted with ethyl acetate and the organic layers were dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was flash column chromatographed by eluting with 5% methanol/chloroform to give the oxazolidine (8a) as an oil (55%). $[\alpha]_D^{23}$ –64.0° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3700–2700 (CO_2H), 3113, 3091, 3054 and 3033 (CH, aromatic), 3000–2800 (CH, saturated), 1712 (C=O), 1500, 1425, 1358, 1215, 1136, 1109, 1052, 937, 840, 752, 699, and 602. δ_H 10.67, s, 1H, CO_2H; 7.31, s, 5H, ArH; 5.14, s, 2H, $ArCH_2$; 4.95, s, 2H, NCH_2O; 4.53–4.46, m, 1H, NCHCO; 4.17–4.16, m, 2H, CHC**H**$_2$O. δ_C (rotamers) 173.99, COOH; 153.38, 152.76, OCON; 135.53, quaternary ArC; 128.31, 128.05, 127.73, ArC; 79.55, 78.95, NCH_2O; 70.79, 69.98, CH**C**H$_2$O; 68.07, 67.64, $ArCH_2$; 56.84, C 4.

(4S)-3-Benzyloxycarbonyl-4-[(1S)-hydroxyethyl]oxazolidin-5-one (7b)

This was an *oil* (21% yield) (Found: M+H, 266.1026. $C_{13}H_{16}NO_5$ requires M+H, 266.1028). $[\alpha]_D^{23}$ +78.4° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3477 (OH), 3094, 3069 and 3044 (CH, aromatic), 3000–2900 (CH, saturated), 1805 (C=O, oxazolidinone), 1714 (C=O, carbamate), 1498, 1414, 1360, 1240, 1167, 1123, 1026, 968, 756, 699. *m/z* (l.s.i.m.s.) 266 (M+1, 100%), 222 (63). δ_H 7.31, s, 5H, ArH; 5.60, 5.18, each m, 1H, NCH_2O; 5.19–5.05, m, 2H, $ArCH_2$; 4.30, m, 1H, CH_3C**H**OH; 4.23, s, 1H, NCHCO; 3.08, s, 1H, OH; 1.21, d, *J* 6.5 Hz, 3H, C**H**$_3$CHOH. δ_C 172.00, C 5; 153.95, OCON; 134.99, quaternary ArC; 128.41, 128.25, 128.13, 127.91, 127.67, 5×ArC; 79.20, C 2; 68.20, HO**C**HCH$_3$; 68.03, $ArCH_2$; 60.92, C 4; 19.76, HOCH**C**H$_3$.

N-*Cbz-5-Methyl-1,3-oxazolidine-4-carboxylic Acid (8b)*[32]

This compound was isolated by acidification of the 5% bicarbonate wash described in the general procedure. The combined bicarbonate washings were acidified with 5 M hydrochloric acid. The aqueous acidic layer was extracted with ethyl acetate and the organic layers were dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was flash column chromatographed by eluting with 5% acetic acid/chloroform to give the oxazolidine (8b) as an oil (50%). This compound was the same as that produced as a by-product from the reductive cleavage of the threonine oxazolidinone (7b).

(S)-*3-Benzyloxycarbonyl-4-(4-hydroxyphenyl)methyloxazolidin-5-one (7c)*

This compound was a *solid* (37% yield), m.p. 110–112° (Found: C, 66.3; H, 5.3; N, 4.1. $C_{18}H_{17}NO_5$ requires C, 66.0; H, 5.2; N, 4.3%). $[\alpha]_D^{23}$ +206.0° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (KBr) 3352 (OH), 3090, 3064 and 3033 (CH, aromatic), 3000–2900 (CH, saturated), 1796 (C=O, oxazolidinone), 1665 (C=O, carbamate), 1615, 1593, 1517, 1463, 1352, 1227, 1168, 1105, 1057, 1005, 967, 915, 836, 759, 698, 615, 587. *m/z* (e.i.) 327 (M^+, 6%), 107 (100%), 91 (35), 77 (7), 65 (7). δ_H [300 MHz, (D_6)dimethyl sulfoxide] 9.31, s, 1H, OH; 7.39, s, 5H, ArH; 6.77, d, *J* 8.3 Hz, 2H, H 3′; 6.61, d, *J* 8.3 Hz, H 4′; 5.25, d, *J* 3.9 Hz, 1H, NCH**H**O; 5.18, s, 2H, $ArCH_2$; 4.54, m, 1H, NCHCO or NC**H**HO; 4.44, m, 1H, NCHCO or NC**H**HO; 3.08, m, 1H, CHCH**H**; 2.90, dd, *J* 2.8, 2.7 Hz, 1H, CHC**H**H. δ_C 173.19, C 5; 155.35, C 5′; 152.68, 152.16, OCON; 135.30, 2×quaternary ArC; 130.76, C 3′; 128.72, 125.80, 5×ArC; 115.66, C 4′; 78.16, C 2; 68.14, 67.85, $ArCH_2$; 56.59, C 4; 35.26, 34.22 C 1′.

(S)-*3-Benzyloxycarbonyl-4-(benzyloxycarbonylaminopropanoyl)-oxazolidin-5-one (7d)*

This was an *oil* (68% yield) (Found: M+H, 427.1490. $C_{22}H_{23}N_2O_7$ requires M+H, 427.1505). $[\alpha]_D^{27}$ +69.0° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3286 (CONHCO), 3094, 3069 and 3032 (CH, aromatic), 3000–2900 (CH, saturated), 1797 (C=O, oxazolidinone), 1763 (C=O), 1711 (C=O, carbamate), 1498, 1454, 1416, 1359, 1198, 1130, 1057, 915, 751, 698. *m/z* (e.s.m.s.) 449 (M + Na, 68%), 427 (M+1, 46), 396 (5), 383 (5), 295 (4), 282 (12), 260 (10). δ_H 8.16, bs, 1H, CONHCO; 7.32, s, 10H, ArH; 5.46, s, 1H, NC**H**HO; 5.15, s, 1H, NCH**H**O; 5.11, s, 4H, $ArCH_2$×2; 4.37, t, *J* 6.1 Hz, 1H, NCHCO; 2.92–2.76, m, 2H, CH_2C**H**$_2$CO; 2.29–2.13, m, 2H, C**H**$_2$CH$_2$CO. δ_C 172.99, 171.80, 2×CO_2; 152.99, 151.49, 2×CONH; 135.16, 134.82, 2×quaternary ArC; 128.51, 128.18, 10×ArC; 77.62, C 2; 67.89, 67.61, 2×$ArCH_2$; 53.72, C 4; 31.15, CH_2**C**H$_2$CO; 25.02, **C**H$_2$CH$_2$CO.

3-Benzyloxycarbonyl-4-(2-hydroxycarbonylethyl)oxazolidin-5-one (7e)[21,34]

This was an *oil* (86% yield) (Found: M+H, 294.0964. Calc. for $C_{14}H_{16}NO_6$: M+H, 294.0978). ν_{max}/cm^{-1} (NaCl) 3500–2750 (CO_2H), 3094, 3069 and 3044 (CH, aromatic), 3000–2900 (CH, saturated), 1800 (C=O, oxazolidinone), 1710 (C=O), 1499, 1417, 1359, 1247, 1168, 1054, 765, 699. *m/z* (e.s.m.s.) 310 (14%), 308 (12), 294 (M+1, 46), 264 (38), 250 (100). δ_H 10.54, bs, 1H, CO_2H; 7.31, s, 10H, ArH; 5.46, s, 1H, NC**H**HO; 5.14, s, 1H, NCH**H**O; 5.09, s, 4H, $ArCH_2$×2; 4.34, t, *J* 5.6 Hz, 1H, NCHCO; 2.44, m, 2H, C**H**$_2$CO$_2$H; 2.28–2.19, m, 1H, C**H**HCH$_2$CO; 2.15–2.10, m, 1H, CH**H**CH$_2$CO. δ_C 177.35, CO_2H; 171.61, C 5; 152.93, OCON; 135.00, quaternary ArC; 128.39, 128.32, 128.01, 5×ArC; 77.60, C 2; 67.86, $ArCH_2$; 53.65, C 4; 28.84, CH_2**C**H$_2$CO$_2$H; 25.42, **C**H$_2$CH$_2$CO$_2$H.

(S)-*3-Benzyloxycarbonyl-4-(benzyloxycarbonylmethyl)oxazolidin-5-one (7f)*

This compound was an *oil* (58% yield) (Found: C, 65.3; H, 5.3; N, 3.6. $C_{20}H_{19}NO_6$ requires C, 65.0; H, 5.2; N, 3.8%). $[\alpha]_D^{23}$ +111.1° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3090, 3064 and 3033 (CH, aromatic), 3000–2900 (CH, saturated), 1803 (C=O, oxazolidinone), 1731 (C=O, amide), 1498, 1454, 1414, 1358, 1259, 1176, 1131, 1052, 994, 749, 698. δ_H 7.33, s, 10H, ArH; 5.45, 5.23, m, 2H, NCH_2O; 5.20–5.04, m, 4H,

$ArCH_2$×2; 4.34, s, 1H, NCHCO; 3.31, 3.11–3.01, m, 2H, C**H**$_2CO_2$Bn.* δ_C 171.58, 169.78, C 5, C 2′; 152.59, OCON; 135.23, 134.93, 2×quaternary ArC; 128.61, 128.38, 128.25, 10×ArC; 78.30, NCH_2O; 67.96, 67.17, 2×Ar**C**H_2; 51.58, C 4; 35.20, 34.32, C 1′.

(S)-*3-Benzyloxycarbonyl-4-phenyloxazolidin-5-one (7g)*

This compound was a *solid* (70% yield), m.p. 126–128° (Found: C, 68.5; H, 5.0; N, 4.4. $C_{17}H_{15}NO_4$ requires C, 68.7; H, 5.1; N, 4.7%). $[\alpha]_D^{30}$ +167.8° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (KBr) 3094 and 3069 (CH, aromatic), 1783 (C=O, oxazolidinone), 1695 (C=O, carbamate), 1507, 1421, 1361, 1243, 1169, 1052, 964, 917, 771, 739, 697, 626, 592, 547. *m/z* (e.s.m.s.) 298 (M+1, 34%), 288 (34), 254 (45), 250 (63), 206 (100). δ_H 7.36, s, 10H, ArH; 5.69, d, *J* 4.0 Hz, 1H, NC**H**HO; 5.44, d, *J* 4.0 Hz, 1H, NCH**H**O; 5.29, m, 1H, NCHCO; 5.11, m, 2H, $ArCH_2$. δ_C 170.37, C 5; 152.75, OCON; 135.23, quaternary ArC; 134.23, quaternary ArC; 129.10, 128.94, 128.57, 126.36, ArC; 78.18, C 2; 68.01, $ArCH_2$; 58.21, C 4.

(S)-*3-Benzyloxycarbonyl-4-(2-methylthioethyl)oxazolidin-5-one (7i)*

This compound was an *oil* (91% yield) (Found: C, 56.9; H, 5.9; N, 4.8. $C_{14}H_{17}NO_4S$ requires C, 56.9; H, 5.8; N, 4.7%). $[\alpha]_D^{31}$ +127.3° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3096, 3071 and 3033 (CH, aromatic), 3000–2900 (CH, saturated), 1798 (C=O, oxazolidinone), 1714 (C=O, carbamate), 1498, 1415, 1358, 1314, 1246, 1128, 1053, 917, 765, 699, 611, 575. *m/z* (e.i.) 296 (M+1, 1.7%), 295 (M^+, 9), 160 (26), 131 (6), 112 (5), 91 (100), 75 (12), 65 (17), 61 (62). δ_H 7.32, s, 5H, ArH; 5.47, s, 1H, NCH**H**O; 5.21, d, *J* 4.3 Hz, 1H, NC**H**HO; 5.17, d, J_{AB} 12.2 Hz, 1H, ArC**H**H; 5.11, d, J_{AB} 12.2 Hz, 1H, ArCH**H**; 4.34, t, *J* 5.2 Hz, 1H, NCHCO; 2.48, m, 2H, CHC**H**$_2CH_2S$; 2.16, m, 2H, C**H**$_2SCH_3$; 1.97, s, 1H, CH_3. δ_C 171.99, C 5; 152.67, OCON; 135.16, quaternary ArC; 128.45, 128.39, 128.09, 5×ArC; 77.65, C 2; 67.72, $ArCH_2$; 53.39, C 4; 28.64, CH**C**H_2**C**H_2SCH_3; 14.60, CH_3.

(S)-*3-Benzyloxycarbonyl-4-(4-phthalimidobutyl)oxazolidin-5-one (7j)*

This compound was a *solid* (81% yield), m.p. 75–76° (Found: C, 65.3; H, 5.2; N, 6.5. $C_{23}H_{22}N_2O_6$ requires C, 65.4; H, 5.2; N, 6.6%). $[\alpha]_D^{23}$ +75.1° (*c*, 1.0 in $CHCl_3$); ν_{max}/cm^{-1} (KBr) 3092, 3067 and 3033 (CH, aromatic), 3000–2800 (CH, saturated), 1797 (C=O, oxazolidinone), 1784 (C=O, Phth†), 1704 (C=O, carbamate), 1507, 1445, 1400, 1367, 1333, 1290, 1244, 1216, 1172, 1127, 1109, 1049, 936, 775, 718, 698, 530. δ_H 7.83–7.87, 7.71–7.67, m, 4H, Phth.; 7.33, s, 5H, ArH; 5.50, m, 1H, NC**H**HO; 5.19, d, *J* 4.6 Hz, 1H, NCH**H**O; 5.18–5.13, m, 2H, $ArCH_2$; 4.30, m, 1H, NCHCO; 3.62, m, 2H, NCHC**H**$_2$; 2.01–1.89, m, 2H, CH_2; 1.67–1.58, m, 2H, CH_2; 1.45-1.38, m, 2H, CH_2. δ_C 171.99, C 5; 168.08, C=O, Phth; 152.70, OCON; 135.22, quaternary ArC; 133.72, CH, Phth; 131.85, quaternary ArC, Phth; 128.45, 128.36, 128.11, 5×ArC; 122.97, CH, phth.; 77.75, C 2; 67.67, $ArCH_2$; 54.49, C 4; 37.21, CH_2; 30.06, CH_2; 27.84, CH_2; 21.51, CH_2.

(S)-*3-t-Butoxycarbonyl-4-(2-benzyloxycarbonylethyl)oxazolidin-5-one (13)*

This compound was an *oil* (60% yield) (Found: C, 61.7; H, 6.7; N, 3.8. $C_{18}H_{23}NO_6$ requires C, 61.9; H, 6.6; N, 4.0%). $[\alpha]_D^{23}$ +76.9° (*c*, 1.0 in $CHCl_3$). ν_{max}/cm^{-1} (NaCl) 3094, 3069 and 3035 (CH, aromatic), 3000–2900 (CH, saturated), 1801 (C=O, oxazolidinone), 1737 (C=O, ester), 1709 (C=O, carbamate), 1498, 1477, 1456, 1392, 1259, 1166, 1052, 911, 879, 852, 753, 699. δ_H 7.28, s, 5H, ArH; 5.37, m, 1H, NCH**H**O; 5.04, m, 3H, NC**H**HO, $ArCH_2$; 4.24, t, *J* 5.5 Hz, 1H, NCHCO; 2.45–2.40, m, 2H, C**H**$_2CO_2$Bn; 2.23–2.21, m, 1H, C**H**HCH_2CO_2; 2.15–2.13, m, 1H, CH**H**CH_2CO_2; 1.41, s, 9H, $(CH_3)_3C$. δ_C 171.94, 171.65, C 5, C 3′; 151.96, OCON; 135.44, quaternary ArC; 128.23, 127.95, 5×ArC; 81.82, $(CH_3)_3$**C**; 77.58, C 2; 66.13, $ArCH_2$; 53.69, C 4; 29.07, C 2′; 27.85, ($\mathbf{C}H_3)_3C$; 25.65, C 1′.

* Bn represents benzyl.
† Phth represents phthaloyl.

Oxazolidinone Formation Reaction of *N*-Benzyloxycarbonyl-DL-cysteine (6h)

A mixture of *N*-benzyloxycarbonyl-DL-cysteine (6h) (2.66 g, 10.5 mmol), camphorsulfonic acid (121 mg, 5.25 mmol) and benzene (85 ml) was placed in a 250 ml round-bottom flask set for reflux. To the refluxing solution was added paraformaldehyde (1.56 g, 52.5 mmol) in five equal portions by allowing the solution to clear between additions. After the last addition, the mixture was heated at reflux until the solution was clear. The benzene solution was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (150 ml). The organic layer was extracted with 5% sodium bicarbonate solution and the aqueous layer was put aside. The ethyl acetate layer was dried ($MgSO_4$) and evaporated under vacuum. The resulting oil was purified by silica gel chromatography, with 30% ethyl acetate/hexane as the eluting solvent, to afford the required oxazolidinone (7h**)** (90 mg, 3%). ν_{max}/cm^{-1} (NaCl) 3089, 3065 and 3034 (CH, aromatic), 3000–2900 (CH, saturated), 1801 (C=O, oxazolidinone), 1714 (C=O, carbamate), 1498, 1410, 1357, 1290, 1165, 1128, 1052, 963, 763, 698, 609; δ_H 7.34, s, 5H, ArH; 5.48, 5.30, m, 2H, NCH_2O; 5.18, m, 2H, $ArCH_2$; 4.50, s, 1H, NCHCO; 3.22–3.08, m, 2H, C**H**$_2$SH. δ_C (rotamers) 170.87, 170.58, 169.59, C 5; 153.75, 152.34, OCON; 135.83, 135.13, quaternary ArC; 128.60, 128.42, 128.25, 127.90, 127.36, 5×ArC; 78.55, C 2; 68.40, 67.98, 67.67, $ArCH_2$; 55.60, 54.99, C 4; 32.88, 31.23, CH_2SH. The set-aside bicarbonate extract was acidified with 5 mol dm^{-3} HCl and extracted with ethyl acetate (3×20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under vacuum to give the dimer (11) as a clear oil (1.8 g, 65% conversion). ν_{max}/cm^{-1} (NaCl) 3250–2700 (CO_2H), 3097, 3068 and 3032 (CH, aromatic), 3000–2900 (CH, saturated), 1705 (C=O), 1414, 1355, 1212, 1112, 1009, 763, 698. δ_H (rotamers) 10.51, s, 2H, CO_2H; 7.34–7.30, m, 10H, ArH; 5.16, m, 4H, $ArCH_2$×2; 4.97 and 4.83, m, 2H, NCHCO×2; 4.69–4.46, m, 4H, NCH_2S×2; 3.29, m, 4H, CHC**H**$_2$S×2. δ_C (rotamers) 174.60, 174.26, CO_2H; 154.10, 153.82, carbamate CO; 135.51, quaternary ArC; 128.31, 128.06, 127.78, 127.68, ArC; 67.83, $ArCH_2$; 61.59, 60.86, N**C**HCO; 49.05, 47.86, NCH_2S; 34.07, 32.78, CH**C**H_2S.

Formation of *N*-Cbz *N*-Methyl Amino Acids[19]

General Procedure

The oxazolidinone (1 mmol) was dissolved in chloroform (5 ml) in a round-bottom flask followed by addition of trifluoroacetic acid (5 ml) and triethylsilane (0.48 ml, 3.0 mmol) and the mixture was left to stir. Oxazolidinones without functionalized side chains were stirred for 24 h, those with carboxylic acids for 5 days and those with alcoholic side chains for 3 days. After the solutions were stirred, they were concentrated to give residues which were reconcentrated under reduced pressure from ethanol three times. The residue was taken up in a mixture of ether (15 ml) and 5% sodium bicarbonate solution (30 ml). The ethereal solution was extracted with 5% sodium bicarbonate solution (2×10 ml). The combined aqueous layers were washed with ether (2×10 ml) and the aqueous layer was then acidified with 5 mol dm^{-3} HCl to pH 2 and extracted with ethyl acetate (3×15 ml). The combined ethyl acetate layers were dried ($MgSO_4$), filtered and concentrated to give an oil. The oil was further purified by silica gel chromatography with solvent systems ranging from $CHCl_3$/MeOH/acetic acid (90 : 9.9 : 0.1) to $CHCl_3$/MeOH (95 : 5).

N-*Benzyloxycarbonyl*-N-*methyl-L-serine (18a)*

The compound was isolated as an *oil* (79% yield) (Found: M+H, 254.1030. $C_{12}H_{16}NO_5$ requires M+H, 254.1028). ν_{max}/cm^{-1} (NaCl) 3600–3250 (CO_2H), 3094, 3069 and 3044 (CH, aromatic), 3000–2900 (CH, saturated), 1750–1640 (C=O), 1454, 1404, 1324, 1218, 1157, 1041, 753, 698, 609; $[\alpha]_D^{30}$ –18.2° (*c*, 1.0 in $CHCl_3$). *m/z* (e.s.m.s.) 268 (10%), 254 (M+1, 100%), 210 (36). δ_H (rotamers) 7.31, s, 5H, ArH; 5.11, s, 2H, $ArCH_2$; 4.65–4.61, m, 1H, NCHCO; 4.09–3.90, m, 2H, CHC**H**$_2$OH; 2.96, s, 3H, NCH_3. δ_C (rotamers) 173.02, CO_2H; 157.53,

CO carbamate; 135.90, quaternary ArC; 128.48, 128.13, 127.73 5×ArC; 67.90, $ArCH_2$; 61.56, $CHCH_2OH$; 60.98, 60.45, N**C**HCO; 33.20, NCH_3.

N-*Benzyloxycarbonyl*-N-*methyl*-L-*tyrosine (18c)*

The compound was isolated as an *oil* (60% yield) (Found: M+H, 330.1352. $C_{18}H_{20}NO_5$ requires M+H, 330.1341). ν_{max}/cm^{-1} (NaCl) 3400–2700 (CO_2H), 3092, 3067 and 3034 (CH, aromatic), 3000–2900 (CH, saturated), 1760 (C=O), 1708 (C=O, carbamate), 1509, 1454, 1402, 1218, 1018, 738, 698. $[\alpha]_D^{27}$ –47.2° (*c*, 1.0 in $CHCl_3$). *m/z* (e.s.m.s.) 344 (25%), 330 (M+1, 8%), 316 (14), 288 (16), 279 (54), 214 (100), 129 (24). δ_H [300 MHz, (D_6)dimethyl sulfoxide, 333 K] 7.45–7.27, m, 5H, ArH; 7.24, d, J_{AB} 8.3 Hz, 2H, ArH; 7.10, d, *J* 8.3 Hz, 2H, ArH; 5.04, d, J_{AB} 10.0 Hz, 1H, ArC**H**H; 5.01, d, J_{AB} 10.0 Hz, 1H, ArCH**H**; 4.84–4.77, m, 1H, NCHCO; 3.29–3.01, m, 2H, C**H**$_2$PhOH; 2.78, s, 3H, NCH_3. δ_C [75 MHz, (D_6)dimethyl sulfoxide, 333 K, rotamers] 171.07, CO_2H; 155.24, 152.39, 149.14, carbamate CO, C 6; 136.43, 135.34, 134.76, 2×quaternary ArC; 129.35, 129.08, 128.02, 127.94, 127.76, 127.59, 127.13, 126.75, 5×ArC; 120.08, C 4; 114.83, C 5; 65.96, $ArCH_2$; 59.83, N**C**HCO; 33.40, **C**H_2PhOH; 31.28, NCH_3.

N-*Benzyloxycarbonyl*-N-*methyl*-L-*glutamine (18d)*

The compound was isolated as an *oil* (62% yield) (Found: M+H, 295.1296. $C_{14}H_{19}N_2O_5$ requires M+H, 295.1294). ν_{max}/cm^{-1} (NaCl) 3500–3000 (CO_2H), 3349 and 3220 (NH_2), 3094, 3069 and 3044 (CH, aromatic), 3000–2900 (CH, saturated), 1680 (C=O), 1612, 1454, 1403, 1321, 1187, 1145, 771, 698. $[\alpha]_D^{28}$ –17.6° (*c*, 1.0, $CHCl_3$). *m/z* (e.s.m.s.) 296 (M+2, 22%), 295 (M+1, 100), 277 (14), 251 (18), 204 (23), 186 (13), 161 (17). δ_H (rotamers) 9.70, s, 1H, CO_2H; 7.30, s, 5H, ArH; 6.80, 6.35, 6.04, 3s, 2H, $CONH_2$; 5.09, s, 2H, $ArCH_2$; 4.73, 4.62, 2m, 1H, NCHCO; 2.80, s, 3H, NCH_3; 2.24, 2.04, 2m, 4H, C**H**$_2$C**H**$_2$CONH$_2$. δ_C (rotamers) 176.78, 176.41, CO_2H; 174.40, $CONH_2$; 157.40, C=O, carbamate; 136.19, quaternary ArC; 128.51, 128.14, 127.95, 127.73, ArC; 67.79, $ArCH_2$; 58.48, N**C**HCO; 32.18, 31.07, NCH_3; 24.36, **C**H_2CONH$_2$; 20.76, **C**H_2CH$_2$CONH$_2$.

N-*Benzyloxycarbonyl*-N-*methyl*-DL-*glutamic Acid (18e)*[35]

The compound was isolated as an *oil* (63% yield) (Found: M+H, 296.1126. Calc. for $C_{14}H_{18}NO_6$: M+H, 296.1134). ν_{max}/cm^{-1} (NaCl) 3500–2750 (CO_2H), 3093, 3066 and 3035 (CH, aromatic), 3000–2900 (CH, saturated), 1710 (C=O), 1486, 1453, 1405, 1322, 1189, 1143, 770, 698. *m/z* (e.s.m.s.) 296 (M+1, 100%), 277 (23), 252 (41), 204 (37), 160 (26). δ_H (rotamers) 10.42, s, 2H, 2×CO_2H; 7.20, s, 5H, ArH; 4.99, s, 2H, $ArCH_2$; 4.65–4.61, 4.52–4.49, 2m, 1H, NCHCO; 2.74, s, 3H, NCH_3; 2.24–2.17, 1.92–1.86, 2m, 4H, C**H**$_2$C**H**$_2$CO$_2$H. δ_C (rotamers) 175.13, 174.98, 172.85, 2×CO_2H; 156.60, 156.00, CO carbamate; 136.06, quaternary ArC; 128.01, 127.49, 127.13, 5×ArC; 66.96, $ArCH_2$; 57.78, N**C**HCO; 30.95, 30.41, 30.24, NCH_3; 23.75, 23.45, **C**H_2**C**H$_2$CO$_2$H.

4-Benzyl Hydrogen N-*Benzyloxycarbonyl*-N-*methyl*-L-*aspartate (18f)*

The compound was isolated as an *oil* (65% yield) (Found: M+H, 372.1439. $C_{20}H_{22}NO_6$ requires M+H, 372.1447). ν_{max}/cm^{-1} (NaCl) 3600–3250 (CO_2H), 3092, 3064 and 3033 (CH, aromatic), 3000–2900 (CH, saturated), 1735 (C=O, acid), 1702, 1681 (C=O), 1454, 1401, 1316, 1261, 1167, 1001, 737, 697. *m/z* (e.s.m.s.) 372 (M+1, 12%), 342 (12), 288 (57), 274 (44), 218 (100), 188 (67), 174 (33). δ_H 7.25, 7.24, 2s, 10H, ArH; 5.11–4.39, 4.75, 2m, 5H, NCHCO, 2×$ArCH_2$; 3.12–3.07, 2.84–2.73, 2m, 5H, C**H**$_2$CO$_2$Bn, NCH_3. δ_C (rotamers) 176.07, CO_2H; 171.34, 170.91, **C**OOCH$_2$; 157.16, C=O, carbamate; 136.18, 135.61, 2×quaternary ArC; 128.33, 128.09, 127.86, 127.69, 10×ArC; 67.67, 67.41, 66.48, 2×$ArCH_2$; 58.46, 57.37, N**C**HCO; 35.19, 34.46, **C**H_2CO$_2$Bn; 33.23, NCH_3.

N-*Benzyloxycarbonyl*-N-*methyl*-L-*phenylglycine (18g)*

The compound was isolated as an *oil* (64% yield). ν_{max}/cm^{-1} (NaCl) 3400–2750 (CO_2H), 3094, 3069, 3033 (CH, aromatic), 3000–2900 (CH, saturated), 1746 (C=O, acid), 1697 and 1674 (C=O), 1586, 1454, 1399, 1361, 1311, 1149, 1080, 1049, 972, 916, 769, 699, 649, 616. $[\alpha]_D^{28}$ +120.1° (*c*, 1.0 in $CHCl_3$). *m/z* (e.s.m.s.) 322 (M+Na, 13%), 300 (M+1, 82), 288 (43), 274 (32), 256 (35), 235 (26), 218 (100), 188 (33), 174 (42). δ_H (rotamers) 10.52, s, 1H, CO_2H; 7.34, s, 10H, ArH; 6.18, 6.02, 2m, 1H, NCHCO; 5.23, s, 2H, $ArCH_2$; 2.78, s, 3H, NCH_3. δ_C (rotamers) 175.30, CO_2H; 157.35, CO, carbamate; 136.01, 133.58, 2×quaternary ArC; 129.09, 128.76, 128.62, 128.45, 128.07, 127.79, 10×ArC; 67.95, 2×$ArCH_2$; 62.46, N**C**HCO; 31.43, 30.97, NCH_3.

N$^{\alpha}$–*Benzyloxycarbonyl*-N$^{\alpha}$-*methyl*-N$^{\varepsilon}$-*phthaloyl*-L-*lysine (18j)*[33]

The compound was isolated as an *oil* (79% yield) (Found: M+H, 425.1724. Calc. for $C_{23}H_{25}N_2O_6$: M+H, 425.1713). ν_{max}/cm^{-1} (NaCl) 3700–3200 (CO_2H), 3091, 3064 and 3032 (CH, aromatic), 3000–2800 (CH, saturated), 1770 (C=O, Phth), 1711 (C=O, carbamate), 1439, 1398, 1368, 1326, 1213, 1154, 1088, 1046, 965, 870, 753, 721, 698. $[\alpha]_D^{25}$ –13.7° (*c*, 1.0 in $CHCl_3$). δ_H (rotamers) 8.13, m, 1H, CO_2H; 7.75–7.74, 7.63–7.60, m, 4H, Phth.; 7.32–7.19, m, 5H, ArH; 5.13–5.02, m, 2H, $ArCH_2$; 4.74–4.72, 4.59–4.57, m, 1H, NCHCO; 3.62–3.54, m, 2H, NCHC**H**$_2$; 2.82, s, 3H, NCH_3; 1.99–1.94, 1.75–1.57, m, 4H, 2×CH_2; 1.33–1.29, m, 2H, CH_2. δ_C (rotamers) 175.46, 175.23, C 5; 168.21, C=O, Phth; 157.06, 156.29, OCON; 136.13, 136.03, quaternary ArC; 133.74, CH, Phth; 131.73, quaternary ArC, Phth; 128.22, 127.76, 127.60, 127.45, 5×ArC; 122.98, CH, Phth; 67.39, $ArCH_2$; 58.21, C 4; 37.30, CH_2; 30.75, 30.33, NCH_3; 27.98, CH_2; 27.70, CH_2; 23.14, CH_2.

CF_3COOH/Et_3SiH Reductive Cleavage of the Threonine Oxazolidinone (7b)

The oxazolidinone (7b) (1.71 g, 6.4 mmol) was dissolved in chloroform (32 ml) in a round-bottom flask followed by addition of trifluoroacetic acid (32 ml) and triethylsilane (3.0 ml, 19.2 mmol) and the mixture was left to stir for 3 days. The reaction mixture was concentrated from ethanol (×3) under reduced pressure. The residue was taken up in a mixture of ether (50 ml) and 5% sodium bicarbonate solution (50 ml). The ethereal solution was extracted with 5% sodium bicarbonate solution (2×20 ml). The combined aqueous layers were washed with ether (2×20 ml) and the aqueous layer was then acidified with 5 mol dm^{-3} HCl to pH 2 and extracted with ethyl acetate (3×20 ml). The combined ethyl acetate layers were dried ($MgSO_4$), filtered and concentrated to give an oil. The oil was further purified by silica gel chromatography, with $CHCl_3$/MeOH/Acetic acid (95 : 4.9 : 0.1) as the eluting solvent to afford firstly the by-product (8b)[32] as an oil (540 mg, 32%). ν_{max} (NaCl)/cm^{-1} 3400–2700 (CO_2H), 3094, 3064 and 3035 (CH, aromatic), 3000–2800 (CH, saturated), 1715 (C=O), 1500, 1424, 1358, 1219, 1150, 1107, 973, 766, 698; $[\alpha]_D^{29}$ –70.9° (*c*, 1.0 in $CHCl_3$). *m/z* (e.s.m.s.) 288 (M+Na, 74%), 266 (M+1, 100), 238 (17), 222 (24), 219 (19). δ_H 10.30, s, 1H, CO_2H; 7.32, m, 5H, ArH; 5.16, m, 3H, $ArCH_2$, NC**H**HO; 4.84, m, 1H, NCH**H**O; 4.29–4.21, m, 1H, CH_3C**H**OH; 4.05–4.01, m, 1H, NCHCO; 1.44, d, *J* 6.1 Hz, 3H, CH_3. δ_C (rotamers) 174.29, 173.77, CO_2H; 153.54, 152.91, carbamate CO; 135.58, quaternary ArC; 128.39, 128.18, 127.95, 127.61, 5×ArC; 79.28, 79.04, 78.44, NCH_2O; 67.75, $ArCH_2$; 67.50, CH_3**C**HOH; 63.26, N**C**HCO; 18.32, CH_3. Further elution gave *N*-Cbz *N*-methyl-L-threonine (18b) as an oil (600 mg, 35%). ν_{max}/cm^{-1} (NaCl) 3600–3250 (CO_2H), 3094, 3069 and 3035 (CH, aromatic), 3000–2900 (CH, saturated), 1725 (C=O, acid), 1680 (C=O, carbamate), 1454, 1403, 1310, 1157, 1028, 981, 881, 771, 698. $[\alpha]_D^{30}$ –28.2° (*c*, 1.0 in $CHCl_3$). *m/z* (e.s.m.s.) 268 (M+1, 100%), 224 (28), 214 (13). δ_H (rotamers) 7.56, s, 1H, CO_2H; 7.36, s, 5H, ArH; 5.14, s, 2H, $ArCH_2$; 4.61, s, 1H, C**H**OHCH$_3$; 4.48–4.39, m, 1H, NCHCO; 3.04, m, 3H, NCH_3; 1.27–1.17, m, 3H, CH_3. δ_C (rotamers) 172.86, CO_2H; 157.88, 156.70, CO carbamate; 135.94, quaternary ArC; 128.33, 127.93, 127.70, 127.47, 5×ArC; 67.82, $ArCH_2$; 66.95, **C**HOH; 64.56, 63.40, N**C**HCO; 33.94, 33.19, NCH_3; 19.29, CH_3.

Hydrogenolysis of the *N*-t-Butoxycarbonyloxazolidin-5-one (13)

A sample of the oxazolidinone (13) (2.21 g, 6.3 mmol) was dissolved in methanol (150 ml) and 10% Pd-on-charcoal catalyst (165 mg) was added, and the resulting solution was stirred in a hydrogen atmosphere for 3 days. Only half the theoretical amount of hydrogen was absorbed. The solution was filtered through a sintered glass funnel to remove the catalyst and the filtrate was concentrated under vacuum to give an oil, which contained two compounds by t.l.c.. The mixture was

subjected to flash column chromatography by eluting with 30% ethyl acetate/hexane to afford, firstly, the *methyl ester* (17) as a clear oil (880 mg, 51%). (Found: $M^{+\bullet}$, 273.1215. $C_{12}H_{19}NO_6$ requires $M^{+\bullet}$, 273.1212). ν_{max}/cm^{-1} (NaCl) 3000–2900 (CH, saturated), 1801 (C=O, oxazolidinone), 1737 (C=O, ester), 1709 (C=O, carbamate), 1476, 1439, 1393, 1258, 1168, 1052, 880, 769. *m/z* (e.s.m.s.) 288 (100%), 274 (M+1, 34%), 218 (72), 188 (93), 174 (24). $[\alpha]_D^{20}$ +78.3° (*c*, 1.0 in $CHCl_3$). δ_H 5.17, m, 1H, NC**H**HO; 4.86, d, *J* 4.1 Hz, 1H, NCH**H**O; 4.02, t, *J* 5.7 Hz, 1H, NCHCO; 3.35, s, 3H, CO_2CH_3; 2.14, t, *J* 7.7 Hz, 2H, C**H**$_2CO_2CH_3$; 2.03–1.80, m, 2H, C**H**$_2CH_2CO_2$; 1.18, s, 9H, $(CH_3)_3$. δ_C 171.90, 171.65, 2×CO_2; 151.66, CO carbamate; 81.13, **C**$(CH_3)_3$; 77.42, NCH_2O; 53.39, N**C**HCO; 50.89, CO_2**C**H_3; 28.48, **C**$H_2CO_2CH_3$; 27.38, C(**C**$H_3)_3$; 25.33, **C**$H_2CH_2CO_2$. Further elution gave the carboxylic acid (16) as a clear oil (110 mg, 7%). ν_{max}/cm^{-1} (NaCl) 3500–2700 (CO_2H), 3000–2900 (CH, saturated), 1801 (C=O, oxazolidinone), 1737 (C=O, ester), 1710 (C=O, carbamate), 1395, 1257, 1166, 1053, 881, 769. *m/z* (e.s.m.s.) 260 (M+1, 100%), 204 (66), 160 (18). δ_H 9.84, m, 1H, CO_2H; 5.42, m, 1H, NC**H**HO; 5.10, d, *J* 4.5 Hz, 1H, NCH**H**O; 4.27, t, *J* 5.8 Hz, 1H, NCHCO; 2.47–2.06, m, 4H, C**H**$_2$C**H**$_2CO_2H$; 1.14, s, 9H, $(CH_3)_3$. δ_C 177.17, CO_2H; 172.18, CO_2 oxazolidinone; 152.29, CO carbamate; 82.41, **C**$(CH_3)_3$; 77.80, NCH_2O; 53.85, N**C**HCO; 29.02, **C**H_2CO_2H; 28.01, C(**C**$H_3)_3$; 25.62, **C**$H_2CH_2CO_2$.

Hydrogenolysis of *N*-Benzyloxycarbonyl-*N*-methyl Amino Acids

General Procedure

To a mixture of the *N*-benzyloxycarbonyl-*N*-methyl amino acid (18) 1 mmol) and ethanol (30 ml) in a 100 ml round-bottom flask was added 10% Pd-on-C catalyst (20 mg). The mixture was stirred at room temperature in an atmosphere of H_2 until the required amount of hydrogen gas was absorbed. The mixture was then concentrated under reduced pressure. The residue was taken up in hot distilled water (15 ml) and filtered through celite. The filter cake was washed with hot water (2 × 10 ml) and the combined filtrates were evaporated under vacuum to afford a white solid. The solid was then dissolved in a minimum of hot distilled water and crystallized by the addition of ethanol to afford the pure *N*-methyl amino acid.

N-*Methyl-L-serine (14a)*[9,11]

The compound was isolated as a solid (64% yield), m.p. 198–200°C. ν_{max}/cm^{-1} (KBr) 3353 (OH), 3600–3100 (CO_2H), 2940 and 2905 (CH, saturated), 2474 and 2420 ($CH_3NH_2^+$), 1625 (CO_2H), 1601 (CO_2^-), 1509, 1460, 1366, 1328, 1300, 1259, 1166, 1100, 1073, 1038, 864, 798, 604, 584, 525. $[\alpha]_D^{25}$ +8.9° (*c*, 1.0 in 6 mol dm^{-3} HCl). *m/z* (e.s.m.s.) 134 (100%), 120 (M+1, 28). δ_H (300 MHz, D_2O) 3.91–3.80, m, 2H, C**H**$_2$OH; 3.53, t, *J* 4.0 Hz, 1H, NCHCO; 2.61, s, 3H, NCH_3. δ_C (75 MHz, D_2O) 171.50, CO_2H; 64.29, CH_2OH; 58.59, N**C**HCO; 31.39, NCH_3.

N-*Methyl-L-threonine (10)*[9,10]

The compound was isolated as a solid (62% yield), m.p. 224°C subl. (Found: C, 44.9; H, 8.5; N, 10.24. Calc. for $C_5H_{11}NO_3$: C, 45.1; H, 8.3; N, 10.5%). ν_{max}/cm^{-1} (KBr) 3224 (OH), 3600–2970 (CO_2H), 2933 and 2893 (CH, saturated), 2525 ($CH_3NH_2^+$), 1649 (CO_2H), 1595 and 1573 (CO_2^-), 1503, 1454, 1429, 1380, 1352, 1310, 1181, 1127, 1058, 983, 931, 854, 755, 735, 541. $[\alpha]_D^{20}$ –14.2° (*c*, 1.0 in 6 mol dm^{-3} HCl). *m/z* (e.s.m.s.) 148 (100%), 134 (M+1, 79), 116 (12). δ_H (300 MHz, D_2O) 3.94–3.85, m, 1H, HOC**H**; 3.22, d, *J* 7.4 Hz, 1H, NCHCO; 2.59, s, 3H, NCH_3; 1.18, d, *J* 6.3 Hz, 3H, HOCHC**H**$_3$. δ_C (75 MHz, D_2O) 171.43, CO_2H; 70.10, CHOH; 66.10, N**C**HCO; 32.35, NCH_3; 19.50, HOCH**C**H_3.

N-*Methyl-L-tyrosine (14c)*[1,9]

The workup for this compound was different to that used for other compounds in this series. Upon completion of the hydrogenolysis, the reaction mixture was evaporated to dryness under reduced pressure. The grey solid was taken up in hot distilled water (120 ml) and filtered through a celite pad. The celite cake was further washed with hot distilled water (3×10 ml). The combined filtrates were reduced (*c*. 70 ml) under vacuum and ethanol (1 ml) was added and the solution was left to stand at 0°C overnight. The precipitate was filtered off at the pump, washed with cold methanol and dried to give *N*-methyl-L-tyrosine (14c) as a colourless solid (180 mg, 47%), m.p. 238–241°C (Found: C, 61.4; H, 6.8; N, 6.9. Calc. for $C_{18}H_{19}NO_5$: C, 61.5; H, 6.7; N, 7.2%). ν_{max}/cm^{-1} (KBr) 3600–3250 (CO_2H), 3206 (OH), 3097, 3039 and 3012 (CH, aromatic), 2966, 2923 and 2896 (CH, saturated), 2619 ($CH_3NH_2^+$), 1588 (CO_2^-), 1515, 1477, 1440, 1416, 1388, 1319, 1258, 1177, 1145, 1105, 1056, 945, 864, 827, 647, 578, 541; $[\alpha]_D^{25}$ +29.9° (*c*, 1.0 in 6 mol dm^{-3} HCl/acetic acid, 1 : 1). *m/z* (e.s.m.s.) 210 (52%), 196 (M+1, 100), 178 (7), 146 (18). δ_H (300 MHz, D_2O/D_2SO_4, 25000 : 1 v/v) 6.69, d, J_{AB} 7.1 Hz, 2H, H 5; 6.40, d, J_{AB} 7.1 Hz, 2H, H 4; 3.74, t, *J* 5.2 Hz, 1H, NCHCO; 2.83–2.70, m, 2H, CH_2Ar; 2.27, s, 3H, NCH_3. δ_C (75 MHz, D_2O/D_2SO_4, 25 000:1 v/v) 170.18, CO_2H; 154.89, C 6; 130.52, C 4; 124.72, C 3; 115.64, C 5; 61.72, N**C**HCO; 33.59, CH**C**H_2; 31.63, NCH_3.

N-*Methyl-L-glutamine (14d)*

The compound was isolated as a *solid* (56% yield), m.p. 147–152°C (Found: M+H, 161.0919. $C_6H_{13}N_2O_3$ requires M+H, 161.0926). ν_{max}/cm^{-1} (KBr) 3500–3250 (CO_2H), 3222 and 3093 ($CONH_2$), 2929, 2940 and 2870 (CH, saturated), 2361 ($CH_3NH_2^+$), 1668, 1618 ($CONH_2$), 1576 (CO_2^-), 1476, 1449, 1392, 1354, 1309, 1155, 1045, 846, 761, 654, 511. $[\alpha]_D^{25}$ +12.7° (*c*, 1.0 in H_2O). *m/z* (e.s.m.s.) 161 (M+1, 100%), 144 (27). δ_H (300 MHz, D_2O) 3.46, t, *J* 5.8 Hz, 1H, NCHCO; 2.58, s, 3H, NCH_3; 2.29, t, *J* 7.5 Hz, 2H, CH_2C**H**$_2CONH_2$; 2.10–1.19, m, 2H, C**H**$_2CH_2CONH_2$. δ_C (75 MHz, D_2O) 177.28, CO_2H; 172.79, $CONH_2$; 62.77, N**C**HCO; 31.60, NCH_3; 30.43, **C**H_2CONH_2; 24.72, **C**$H_2CH_2CONH_2$.

N-*Methyl-DL-glutamic Acid (14e)*[9]

The compound was isolated as a solid (63% yield), m.p. 172–176°C. ν_{max}/cm^{-1} (KBr) 3600–3250 (CO_2H), 3300–3000, 2970, 2950, 2853, 2710 (m, $CH_3NH_2^+$), 1723 (CO_2H), 1618, 1571 (CO_2^-), 1504, 1480, 1450, 1392, 1330, 1301, 1257, 1218, 1198, 1058, 1000, 846, 653, 532. *m/z* (e.s.m.s.) 176 (100%), 162 (M+1, 18), 144 (12), 130 (9). δ_H (300 MHz, D_2O) 3.47, t, *J* 6.0 Hz, 1H, NCHCO; 2.56, s, 3H, NCH_3; 2.36, t, *J* 7.3 Hz, 2H, C**H**$_2CO_2H$; 2.07–1.89, m, 2H, C**H**$_2CH_2CO_2H$. δ_C (75 MHz, D_2O) 176.88, 172.75, 2×CO_2H; 62.53, N**C**HCO; 31.65, NCH_3; 29.79, **C**H_2CO_2H; 24.25, **C**$H_2CH_2CO_2H$.

N-*Methyl-L-aspartic Acid (14f)*[9,26]

The compound was isolated as a solid (65% yield), m.p. 186–192°C. ν_{max}/cm^{-1} (KBr) 3600–3250 (CO_2H), 3174, 2945 (CH, saturated), 2600–2400 ($CH_3NH_2^+$), 1709 (CO_2H), 1637, 1610 (CO_2^-), 1465, 1373, 1248, 1158, 1077, 935, 880, 820, 786, 686, 646, 573. $[\alpha]_D^{25}$ +24.9° (*c*, 1.0 in 6 mol dm^{-3} HCl). *m/z* (e.s.m.s.) 162 (100%), 148 (M+1, 18), 144 (18), 131 (16), 116 (18), 102 (17), 91 (23). δ_H (300 MHz, D_2O) 3.71, t, *J* 5.4 Hz, 1H, NCHCO; 2.89–2.74, m, 2H, C**H**$_2CO_2H$; 2.63, s, 3H, NCH_3. δ_C (75 MHz, D_2O) 174.74, CO_2H; 172.28, CO_2H; 59.49, N**C**HCO; 33.72, **C**H_2COOH; 31.85, NCH_3.

N-*Methyl-L-phenylglycine (14g)*[12]

The compound was isolated as a solid (72% yield), m.p. 204°C subl. (Found: C, 65.6; H, 7.0; N, 8.4. Calc. for $C_9H_{11}NO_2$: C, 65.4; H, 6.7; N, 8.5%). ν_{max}/cm^{-1} (KBr) 3200–2750 (CO_2H), 3026 (CH, aromatic), 2411 ($CH_3NH_2^+$), 1624 (CO_2H), 1592 (Ar ring), 1580 (CO_2^-), 1458, 1384, 1358, 1255, 1134, 1050, 850, 758, 736, 697, 597, 506. $[\alpha]_D^{22}$ +180.9° (*c*, 1.0 in 6 mol dm^{-3} HCl). *m/z* (e.s.m.s.) 180 (16%), 166 (M+1, 100), 135 (8). δ_H (300 MHz, D_2O) 7.33–7.31, m, 5H, ArH; 4.43, s, 1H, NCHCO; 2.42, s, 3H, NCH_3. δ_C (75 MHz, D_2O) 172.22, CO_2H; 131.96, quaternary ArC; 129.81, 129.39, 128.37, ArC; 66.58, N**C**HCO; 30.84, NCH_3.

N$^{\alpha}$-*Methyl*-N$^{\varepsilon}$-*phthalimido-L-lysine* p-*Toluenesulfonate (14j)*

The benzyl carbamate (18j) (910 mg, 2.14 mmol) was dissolved in 10% aqueous acetic acid (20 ml). *p*-Toluenesulfonic acid monohydrate (407 mg, 1 equiv.) was added followed by 10% Pd on charcoal catalyst (50 mg). The reaction mixture was connected to a hydrogenator and hydrogen gas was admitted. Reaction was continued until t.l.c. analysis

indicated the reaction was complete. The mixture was filtered through celite and the filter cake was washed with further glacial acetic acid (5 ml). The combined filtrates were concentrated under reduced pressure to yield a clear residue which was kept overnight under reduced pressure. The resulting foam was dissolved in a minimum of methanol and crystallized by the addition of diethyl ether to give the p-*toluenesulfonate* salt monohydrate (14j) (693 mg, 67%), m.p. 132–134°. (Found: C, 55.5; H, 5.9; N, 5.8. $C_{22}H_{26}N_2O_7S.H_2O$ requires C, 55.0; H, 5.9; N, 5.8%). ν_{max}/cm^{-1} (KBr) 3200–2500 (CO_2H), 3029 (CH, aromatic), 3000–2800 (CH, saturated), 2500–2400 ($CH_3NH_2^+$), 1770 (C=O, Phth), 1700 (C=O), 1589 (Ar ring), 1467, 1438, 1402, 1374, 1280, 1191, 1125, 1036, 1011, 958, 824, 720, 684, 565. $[\alpha]_D^{23}$ +14.7° (*c*, 1.0 in MeOH). δ_H (300 MHz, D_2O) 7.52–7.45, m, 6H, ArH; 7.10–7.08, m, 2H, ArH; 3.76, t, *J* 5.6 Hz, 1H, NCHCO; 3.35, t, 2H, *J* 5.3 Hz, NCH_2; 2.60, s, 3H, NCH_3; 2.14, s, 3H, $ArCH_3$; 1.83–1.80, m, 2H, CH_2; 1.47–1.42, m, 2H, CH_2; 1.28–1.16, m, 2H, CH_2. δ_C (75 MHz, D_2O) 171.03, COOH; 169.93, C=O, Phth; 141.93, 139.51, 2×quaternary ArC; 134.55, Aryl CH, Phth; 130.70, quaternary ArC, Phth; 129.14, 125.19, ArC; 123.02, Aryl CH, Phth; 60.74, NCH; 36.91, NCH_2; 31.35, NCH_3; 27.78, CH_2; 27.09, CH_2; 21.21, CH_2; 20.32, $ArCH_3$.

References

[1] Fischer, E., and Lipschitz, W., *Ber. Dtsch. Chem. Ges.*, 1915, **48**, 360.

[2] Coggins, J. R., and Benoiton, N. L., *Can. J. Chem.*, 1971, **49**, 1968; McDermott, J. R., and Benoiton, L. N., *Can. J. Chem.*, 1973, **51**, 1915, 2555, 2562; Benoiton, L. N., Kuroda, K., Cheung, S. T., and Chen, F. M. F., *Can. J. Biochem.*, 1979, **57**, 776.

[3] Hlavácek, J., Poduska, K., Sorm, F., and Slama, K., *Collect. Czech. Chem. Commun.*, 1976, **41**, 2079; Hlavácek, J., Fric, I., Budesinsky, M., and Blaha, K., *Collect. Czech. Chem. Commun.*, 1988, **53**, 2473.

[4] Olsen, R. K., *J. Org. Chem.*, 1970, **35**, 1912.

[5] Okamoto, K., Abe, H., Kuromizu, K., and Izumiya, N., *Mem. Fac. Sci. Kyushu Univ. Ser. C*, 1974, **9**, 131.

[6] Ohfune, Y., Kurokawa, N., Higuchi, N., Saito, M., Hashimoto, M., and Tanaka, T., *Chem. Lett.*, 1984, 441.

[7] Ramanjulu, J. M., and Joullié, M. M., *Synth. Commun.*, 1996, **26**, 1379.

[8] Chruma, J. J., Sames, D., and Polt, R., *Tetrahedron Lett.*, 1997, **38**, 5085.

[9] Quitt, P., Hellerbach, J., and Vogler, K., *Helv. Chim. Acta*, 1963, **46**, 327; Ebata, M., Takahashi, Y., and Otsuka, H., *Bull. Chem. Soc. Jpn*, 1966, **39**, 2535.

[10] Brockmann, H., and Lackner, H., *Chem. Ber.*, 1967, **100**, 353.

[11] Peter, H., Brugger, M., Schreiber, J., and Eschenmoser, A., *Helv. Chim. Acta*, 1963, **46**, 577.

[12] O'Donnell, M. J., Bruder, W. A., Daugherty, B. W., Liu, D., and Wojciechowski, K., *Tetrahedron Lett.*, 1984, **25**, 3651; O'Donnell, M. J., and Polt, R. L., *J. Org. Chem.*, 1982, **47**, 2663.

[13] Auerbach, J., Zamore, M., and Weinreb, S. M., *J. Org. Chem.*, 1976, **41**, 725.

[14] Dorow, R. L., and Gingrich, D. E., *J. Org. Chem.*, 1995, **60**, 4986.

[15] Wisniewski, K., and Kolodziejczyk, A. S., *Tetrahedron Lett.*, 1997, **38**, 483.

[16] Coulton, S., Moore, G. A., and Ramage, R., *Tetrahedron Lett.*, 1976, 4005.

[17] Luke, R. W. A., Boyce, P. G. T., and Dorling, E. K., *Tetrahedron Lett.*, 1996, **37**, 263.

[18] Spengler, J., and Burger, K., *Synthesis*, 1998, 67.

[19] Freidinger, R. M., Hinkle, J. S., Perlow, D. S., and Arison, B. H., *J. Org. Chem.*, 1983, **48**, 77.

[20] D. Ben-Ishai, *J. Am. Chem. Soc.*, 1957, **79**, 5736.

[21] Itoh, M., *Chem. Pharm. Bull.*, 1969, **17**, 1679.

[22] Reddy, G. V., Rao, G. V., and Iyengar, D. S., *Tetrahedron Lett.*, 1998, **39**, 1985.

[23] Williams, R. M., and Yuan, C., *J. Org. Chem.*, 1994, **59**, 6190.

[24] Grieco, P. A., and Bahsas, A., *J. Org. Chem.*, 1987, **52**, 5746.

[25] Effenberger, F., Burkard, U., and Willfahrt, J., *Liebigs Ann. Chem.*, 1986, 314.

[26] Oppolzer, W., Cintas-Moreno, P., Tamura, O., and Cardinaux, F., *Helv. Chim. Acta*, 1993, **76**, 187.

[27] Papaioannou, D., Athanassopoulos, C., Magafa, V., Karamanos, N., Stavropoulos, G., Napoli, A., Sindona, G., Aksnes, D. W., and Francis, G. W., *Acta Chem. Scand.*, 1994, **48**, 324.

[28] Loffet, A., Galeotti, N., Jouin, P., and Castro, B., *Tetrahedron Lett.*, 1989, **30**, 6859.

[29] Greene, T. W., and Wuts, P. G. M., in 'Protective Groups in Organic Synthesis' 2nd Edn (John Wiley: New York 1991).

[30] Gunther, H. 'NMR Spectroscopy. An Introduction' p. 101 (John Wiley: New York 1980).

[31] Holladay, M. W., Kopecka, H., Miller, T. R., Bednarz, L., Nikkel, A. L., Bianchi, B. R., Witte, D. G., Shiosaki, K., Lin, C. W., Asin, K. E., and Nadzan, A. M., *J. Med. Chem.*, 1994, **37**, 630.

[32] Falorni, M., Conti, S., Giacomelli, G., Cossu, S., and Soccolini, F., *Tetrahedron Asymmetry*, 1995, **6**, 287.

[33] Perrin, D. D., and Armarego, W. L. F., 'Purification of Laboratory Chemicals' 3rd Edn (Pergamon: Oxford 1988).

[34] Sawayama, T., Tsukamoto, M., Sasagawa, T., Nishimura, K., Yamamoto, R., Deguchi, T., Takeyama, K., and Hosoki, K., *Chem. Pharm. Bull.*, 1989, **37**, 2417.

[35] Bavetsias, V., Jackman, A. L., Marriott, J. H., Kimbell, R., Gibson, W., Boyle, F. T., and Bisset, G. M. F., *J. Med. Chem.*, 1997, **40**, 1495.