JOC Article

An Efficient Synthesis of *N*-Methyl Amino Acids by Way of Intermediate 5-Oxazolidinones

Luigi Aurelio, John S. Box, Robert T. C. Brownlee, Andrew B. Hughes,* and Marianne M. Sleebs

Department of Chemistry, La Trobe University, Melbourne, Victoria 3086, Australia

a.hughes@latrobe.edu.au

Received November 15, 2002

N-Methyl amino acids occur in many natural products. Experimental strategies are presented for a unified approach to the synthesis of *N*-methyl derivatives through 5-oxazolidinones of the 20 common L-amino acids. The amino acids with reactive side chains that required protecting groups or devoted syntheses for side chain construction for *N*-methylation to proceed included serine, threonine, tyrosine, cysteine, methionine, tryptophan, asparagine, histidine, and arginine. The studies have provided improved methods for the preparation of *N*-methyl serine, threonine, and tyrosine. All 20 of the common L-amino acids are now available in suitable forms for solid or solution-phase peptide synthesis.

Introduction

The synthesis of *N*-methyl amino acids[1] in suitable form for further solution or solid-phase transformation attracts the attention of chemists due to the demonstrable biological activity associated with these subunits as part of larger peptidic natural products or lead compounds.[2] *N*-Methyl amino acids are well-known to increase pharmacokinetically useful parameters such as membrane permeability,[2,3] proteolytic stability,[2,4] and conformational rigidity.[2,5]

In a previous paper[6] we reported the synthesis, via the carbamates **1** and the 5-oxazolidinones **2**, of a number of new *N*-methyl α-amino acids in the form of their benzyl carbamates and free amino acids (Scheme 1). A focus of that study was the endeavor to demonstrate the general applicability of 5-oxazolidinones to the generation of *N*-methyl derivatives of the 20 common natural α-amino acids in the absence (e.g. glutamic acid and tyrosine) of or the presence (e.g. glutamine and aspartic acid) of side chain protecting groups. This approach was designed to emphasize the efficiency of the 5-oxazolidinone route, its mildness, as measured by the lack of racemization of the α-center, and its chemoselectivity. Indeed, the selectivity of the oxazolidination reaction for the α-amino acid backbone aza and carboxylic functionalities often allowed the subsequent manipulation of reactive side chains.

However, in that previous paper,[6] the simple strategy was not applicable to the α-amino acids bearing basic side chains such as histidine, tryptophan, arginine, and asparagine. The successful syntheses of the *N*-methyl derivatives of these amino acids with 5-oxazolidinone intermediates was recently communicated.[7] In this paper we report the successful syntheses of the outstanding *N*-methyl targets and improved procedures for some substrates.

Results and Discussion

In general, *N*-methyl amino acids were synthesized previously by the reactions in Scheme 1. However, the amino acids with reactive side chains (with hydroxy, sulfur, or amino groups) either did not react to form oxazolidinones or the reductive cleavage was not successful. For each of these groups of amino acids, different strategies of side chain protection or assembly were adopted to facilitate successful synthesis by the template shown in Scheme 1, and these are discussed in detail below.

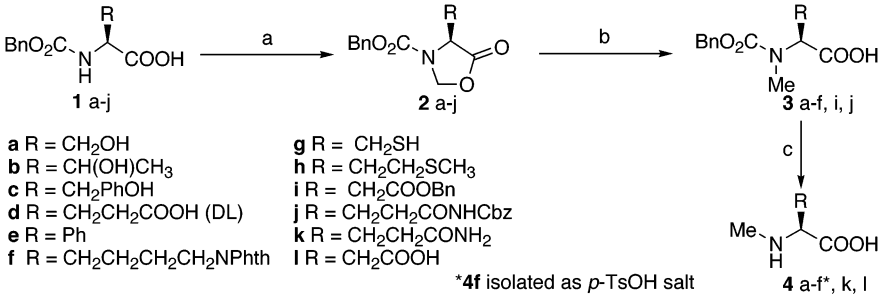
Serine, Threonine, and Tyrosine. Previously we reported the formation of the 5-oxazolidinones of serine and threonine is complicated by participation of the side chain hydroxyls to form oxazolidines as shown in structures **5** and **6** and, in the case of threonine, this intermediate was also produced in the attempted reductive cleavage.[6] Thus, for side chain protection, several strategies were considered.

While a number of protected derivatives of serine and threonine are known[8−11] and were considered, in the end,

(1) See references in ref 6.
(2) Fairlie, D. P.; Abbenante, G.; March, D. R. *Curr. Med. Chem.* **1995**, *2*, 654.
(3) Cody, W. L.; He, J. X.; Reily, M. D.; Haleen, S. J.; Walker, D. M.; Reyner, E. L.; Stewart, B. H.; Doherty, A. M. *J. Med. Chem.* **1997**, *40*, 2228.
(4) Haviv, F.; Fitzpatrick, T. D.; Swenson, R. E.; Nichols, C. J.; Mort, N. A.; Bush, E. U.; Diaz, G.; Bammert, G.; Nguyen, A.; Nellans, H. N.; Hoffman, D. J.; Johnson, E. S.; Greer, J. *J. Med. Chem.* **1993**, *36*, 363.
(5) Vitoux, B.; Aubry, A.; Cung, M. T.; Marraud, M. *Int. J. Pept. Prot. Res.* **1986**, *27*, 617.
(6) Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B.; Sleebs, B. E. *Aust. J. Chem.* **2000**, *53*, 425.
(7) Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B. *Org. Lett.* **2002**, *4*, 3767.
(8) Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Tetrahedron Lett.* **1998**, *39*, 1985.
(9) Mizoguchi, T.; Levin, G.; Woolley, D. W.; Stewart, J. M. *J. Org. Chem.* **1968**, *33*, 903.

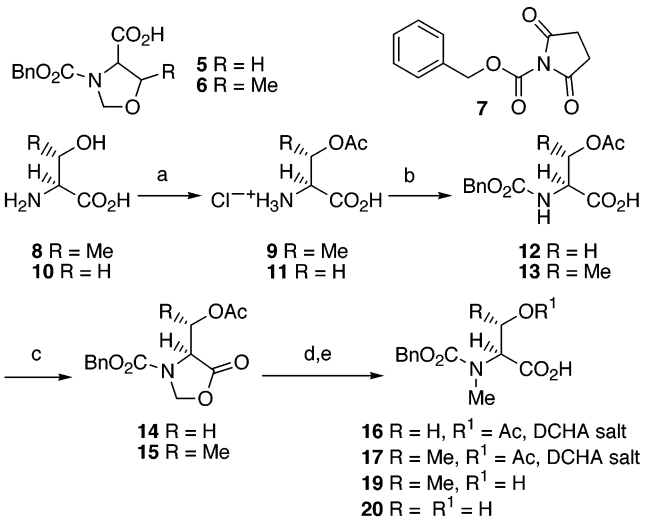
10.1021/jo026722l CCC: $25.00
Published on Web 03/07/2003

SCHEME 1[a]



[a] Reagents and conditions: (a) C_6H_6, CSA (cat.), $(CH_2O)_n$, reflux; (b) CF_3CO_2H, Et_3SiH, $CHCl_3$; (c) H_2, EtOH, 10% Pd-on-C.

SCHEME 2. *N*-Methyl Serine and Threonine[a]



[a] Reagents and conditions: (a) HCl, CH_3CO_2H, CH_3COCl, 0 °C; (b) **7**, Et_3N, DMF; (c) $(CH_2O)_n$, C_6H_6, *p*TsOH, reflux; (d) Et_3SiH, $CHCl_3$, CF_3CO_2H; (e) 2 M HCl, dioxane, 60 °C, 30 h.

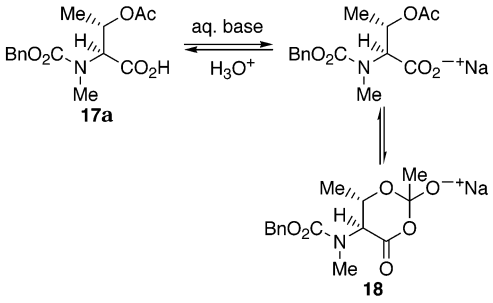
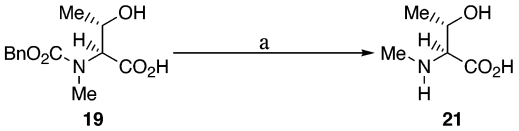


FIGURE 1. Formation of intermediate **18**. In situ protection of the acetate in attempted base hydrolysis.

SCHEME 3[a]



[a] Reagents and conditions: (a) H_2, 10% Pd−C, EtOH.

the simple expedient of acetylation fulfilled all the objectives. L-Threonine **8** was used to prepare *O*-acetyl threonine **9** in high yield according to the method of Wilchek and Patchornik (Scheme 2).[12] This procedure was equally successful with L-serine **10** and provided the acetate **11**.

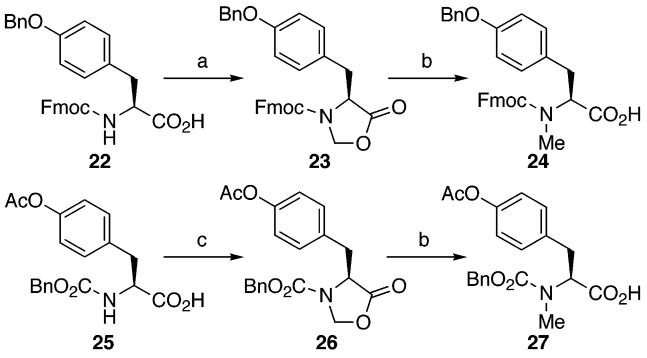
The formation of the new 5-oxazolidinones **14** (87%) and **15** (91%) from the intermediates **12** and **13**, respectively, proceeded in high yield. Reductive cleavage gave the *N*-methyl-*O*-acetyl amino acids **16** (74%) and **17** (80%) as their dicyclohexylamine salts. These acetates are in suitable form for use in solution and solid-phase coupling procedures but the deprotection procedure required additional examination. Hydrolysis of the acetate esters under basic conditions has been reported in relation to serine derivatives[13] but was unsuccessful in this study with the threonine acetate **17a**. Attempted base hydrolyses of the threonine acetate **17a** always resulted in isolation of the starting material and this was attributed to the in situ formation of the tetrahedral intermediate **18** (Figure 1) that survived the hydrolytic conditions and returned the starting material upon acidic workup.

Conversely, aqueous acidic conditions and mild heating (Scheme 2) removed the acetate in high yield to give the alcohol **19** (88%). The same sequence of reactions works well for the serine intermediates **14**, **16**, and **20**. Confirmation that this synthetic sequence did not reduce the optical purity was obtained by hydrogenolysis of the threonine carbamate **19** (Scheme 3). The isolated *N*-methyl-L-threonine **21** had an optical rotation of $[\alpha]_D$ −14° (*c* 1, 6 M HCl), which matched previously reported values.[6] Thus, *N*-methyl serine and threonine, with and without side chain protection, are available by a side chain *O*-acetyl protection strategy.

Tyrosine formed the expected oxazolidinone without side chain protection but the yields for its formation (37%) and subsequent reductive cleavage (60%) were lower than desired. Given the success of side chain acetylation in the serine and threonine manipulations, a similar strategy was attempted with tyrosine. Solubility problems were encountered with the Fmoc carbamate of tyrosine and its conversion to the corresponding acetate. The commercially available tyrosine benzyl ether **22** suited the oxazolidinone chemistry, and the oxazolidinone **23** was isolated in 86% yield (Scheme 4). Reductive cleavage then gave the *N*-methyl tyrosine **24** in 70% yield: a substantial improvement compared with the

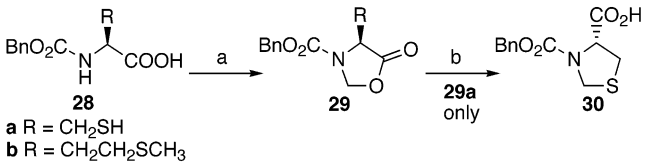
(10) Chen, S.-T.; Wu, S.-H.; Wang, K.-T. *Synth. Commun.* **1989**, *19*, 3589.
(11) Wang, J.; Okada, Y.; Li, W.; Yokoi, T.; Zhu, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 621.
(12) Wilchek, M.; Patchornik, A. *J. Org. Chem.* **1964**, *29*, 1629.
(13) Ondetti, M. A. *J. Med. Chem.* **1963**, *6*, 10.

SCHEME 4[a]



[a] Reagents and conditions: (a) CSA (cat.), $(CH_2O)_n$, C_6H_6, reflux; (b) CF_3CO_2H, Et_3SiH, CH_2Cl_2; (c) CSA (cat.), $(CH_2O)n$, $PhCH_3$, reflux.

SCHEME 5[a]



[a] Reagents and conditions: (a) CSA (cat.), $(CH_2O)_n$, C_6H_6, reflux; (b) CF_3CO_2H, Et_3SiH, $CHCl_3$.

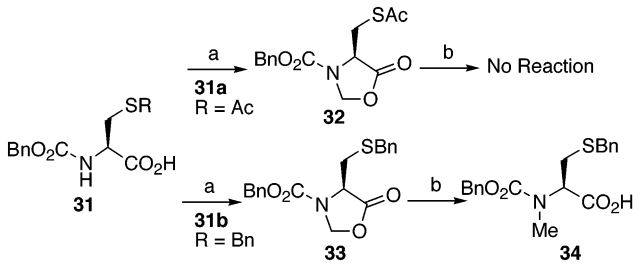
previous sequence in which the hydroxy group was unprotected.

The tyrosine benzyl carbamate **25**[14] was also converted to the oxazolidinone **26** (89%) and reductive cleavage afforded the *N*-methyl tyrosine *O*-acetate **27** (88%). Formation of **27** represents a 40% improvement compared to the tyrosine sequence in which the hydroxy group was unprotected.

Cysteine and Cystine. The synthesis of the sulfur bearing *N*-methyl amino acids gave mixed results using our 5-oxazolidinone route (Scheme 5).[6] The cysteine carbamate **28a** gave the oxazolidinone **29a** in only 3% yield. Methionine, on the other hand, gave the oxazolidinone **29b** in 91%. The reductive cleavage of the oxazolidinone **29a** gave the thiazolidine **30** exclusively, indicating the requisite iminium ion had been formed and was then intercepted intramolecularly by the thiol. The methionine intermediate **29b** gave a mixture of products.

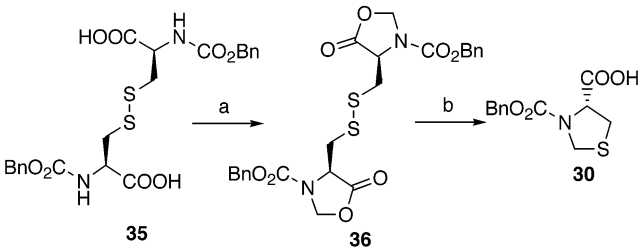
To lessen the nucleophilicity of the thiol, the *S*-acetyl cysteine derivative **31a**[15,16] was prepared and this underwent oxazolidination in moderate yield (51%) (Scheme 6). However, attempted reductive cleavage of the oxazolidinone **32** gave no *N*-methyl products upon workup. Thus the *S*-benzyl cysteine **31b**[17] was converted to the oxazolidinone **33** in high yield (89%) and subsequent reductive cleavage with trifluoroacetic acid and triethylsilane gave the expected *N*-methyl amino acid **34** (70%). Removal of the *S*-benzyl group in any subsequent sequence may present problems given that the preferred

SCHEME 6[a]



[a] Reagents and conditions: (a) CSA (cat.), $(CH_2O)_n$, C_6H_6, reflux; (b) CF_3CO_2H, Et_3SiH, $CHCl_3$.

SCHEME 7[a]



[a] Reagents and conditions: (a) CSA (cat.), $(CH_2O)_n$, C_6H_6, reflux; (b) CF_3CO_2H, Et_3SiH, $CHCl_3$.

method for debenzylation involves treatment with HF.[18] Thus protection using a *S*-PMB (*p*-methoxybenzyl) ether was proposed, as the ultimate removal of the PMB ether can be effected with refluxing trifluoroacetic acid.[18] The ether was prepared but attempts to convert it to the corresponding oxazolidinone resulted in decomposition.

However, the formation of *N*-methyl cysteine can be performed efficiently by the related method of Yamashiro et al.,[17] which involves the reaction of cysteine with paraformaldehyde to give a thiazolidine carboxylic acid. A dissolving metal reductive cleavage of the thiazolidine ring generates *N*-methyl cysteine, which can then be converted in many ways to a range of synthetically useful intermediates including the *S*-benzyl carbamate **34**.

During the studies to solve the cysteine manipulation problems, the use of the cystine carbamate **35** (Scheme 7) was also trialed. Oxazolidinone formation gave the dimeric structure **36** as a solid (33%). However, the reductive cleavage resulted in isolation of the thiazolidine **30**. Evidently, the disulfide bridge was cleaved initially giving the cysteine oxazolidinone **29a** in situ. This was then transformed into the expected iminium ion, which reacted with the thiol, as before, to give the thiazolidine **30**.

In the previous paper,[6] we reported that oxazolidination of cysteine led to the formation of the dimeric structure **37**. In reality this dimeric structure is a proton-sharing aggregate of two thiazolidines **30** that forms in the ESMS. The proposal of structure **37** was based on the observance in the electrospray mass spectrum of *m*/*z* 535. However, further analysis of the cysteine product revealed the appearance of the *m*/*z* 535 peak was concentration dependent. And furthermore, while the ESMS of the putative aggregate also exhibited peaks at

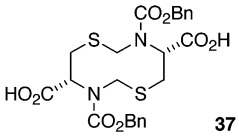
(14) Dawson, J. R.; Dory, Y. L.; Mellor, J. M.; McAleer, J. F. *Tetrahedron* **1996**, *52*, 1361. Davies, J. S.; Hassall, C. H.; Hopkins, K. H. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2614.

(15) Zervas, L.; Photaki, I.; Ghelis, N. *J. Am. Chem. Soc.* **1963**, *85*, 1337.

(16) Clark, D. G.; Cordes, E. H. *J. Org. Chem.* **1973**, *38*, 270.

(17) Yamashiro, D.; Aanning, H. L.; Branda, L. A.; Cash, W. D.; Murti, V. V. S.; Du Vigneaud, V. *J. Am. Chem. Soc.* **1968**, *90*, 4141.

(18) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley-Interscience: New York, 1991.



37

FIGURE 2. Previously reported cysteine dimer **37**.

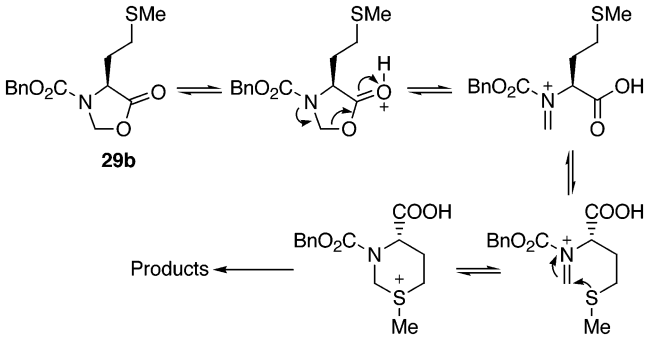


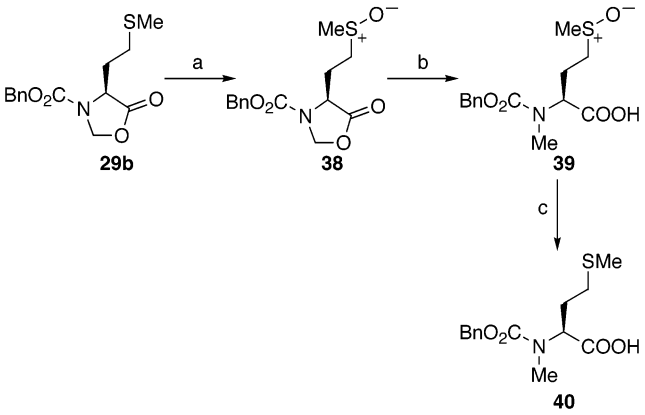
FIGURE 3. Mechanism for cation scavenging by the methionine side chain.

m/*z* 557 and 268 corresponding to M + Na and M + 2/2, that same spectrum did not show a peak at *m*/*z* 279 for M + Na + H/2. Thus *m*/*z* 535 fits only the aggregate and is not consistent with structure **37**. The *m*/*z* 268 peak is revealed as the M + H ion for the thiazolidine **30**. Thus, the dimer **37** is not formed in the cysteine oxazolidination; only the thiazolidine **30** is formed in that reaction.

Methionine. The methionine carbamate reacted well to form the oxazolidinone **29b** (Scheme 5), but the reductive cleavage was not successful and gave a mixture of products. This was attributed to the side chain thioether acting as a cation scavenger (Figure 3), a phenomenon that is known in peptide chemistry through the use of dimethyl sulfide.[19]

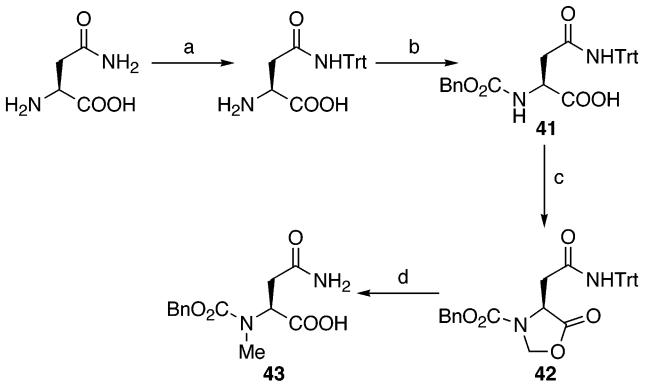
As with cysteine, the nucleophilicity of the thiomethyl group needed to be ameliorated to prevent its participation in the reductive cleavage. The corresponding sulfoxide **38**[20] (98%) was easily prepared (Scheme 8) by reaction of the oxazolidinone **29b** with *m*-chloroperoxybenzoic acid (mCPBA). Initial attempts to convert the methionine carbamate **28b** to its sulfoxide[21] were successful but the subsequent oxazolidination was compromised by its poor solubility. The sulfoxide **38** was then reductively cleaved in high yield (92%) to give the *N*-methyl amino acid **39**. It was evident this procedure caused a small amount of deoxygenation of the sulfoxides **38** or **39** and so the procedure included treatment with hydrogen peroxide to reoxidize the thioether **40**. The *N*-methyl methionine **40**[22] was formed in 81% yield in a one-pot procedure, which included the ammonium iodide/dimethyl sulfide treatment.

SCHEME 8[a]



[a] Reagents and conditions: (a) mCPBA, CH_2Cl_2; (b) Et_3SiH, CF_3CO_2H, $CHCl_3$; (c) NH_4I, Me_2S.

SCHEME 9[a]



[a] Reagents and conditions: (a) Ph_3COH, H_2SO_4, AcOH, Ac_2O; (b) Et_3N, DMF, $BnOCO_2Succ$; (c) C_6H_6, $(CH_2O)_n$, cat. CSA, reflux; (d) Et_3SiH, $CHCl_3$, CF_3CO_2H.

Asparagine. Although it has been shown that carbamoylation of the side chain of glutamine allows its conversion to *N*-methyl glutamine,[6] this protection strategy was not possible with asparagine and so an alternative was sought. Tritylation (Trt) of the asparagine amide side chain was achieved under acidic conditions (Scheme 9).[23] Carbamoylation with *N*-(benzyloxycarbonyl-oxy)-succinimide ($BnOCO_2Succ$) then gave **41**,[23] and subsequent oxazolidination afforded **42** (83%). The solubility of the asparagine carbamate **41** was not high and a minimal amount of DMF was included in the reaction protocol to improve substrate solubility and reaction yield. Reductive cleavage of the oxazolidinone **42** gave a 86% yield of the desired *N*-methyl product **43**.[23] In this reaction the *N*-methyl group forms with concomitant removal of the trityl group under the acidic conditions. The low solubility of the *N*-methyl intermediate **43** necessitated workup by concentration of the reaction mixture and column chromatography of the residue rather than the normal aqueous procedure.

Arginine and Homoarginine. The guanidine group of arginine presents several problems for the oxazolidinone chemistry. But *N*-methyl arginine is an attractive target given the key role arginine plays in many enzy-

(19) (a) Tam, J. P.; Heath, W. F.; Merrifield, R. B. *J. Am. Chem. Soc.* **1983**, *105*, 6442. (b) Ogawa, H.; Sasaki, T.; Irie, H.; Yajima, H. *Chem. Pharm. Bull.* **1978**, *26*, 3144. (c) Yajima, H.; Takeyama, M.; Kanaki, J.; Nishimura, O.; Fujino, M. *Chem. Pharm. Bull.* **1978**, *26*, 3752. (d) Yajima, H.; Futaki, S.; Otaka, A.; Yamashita, T.; Funakoshi, S.; Bessho, K.; Fujii, N.; Kenichi, A. *Chem. Pharm. Bull.* **1986**, *34*, 4356.

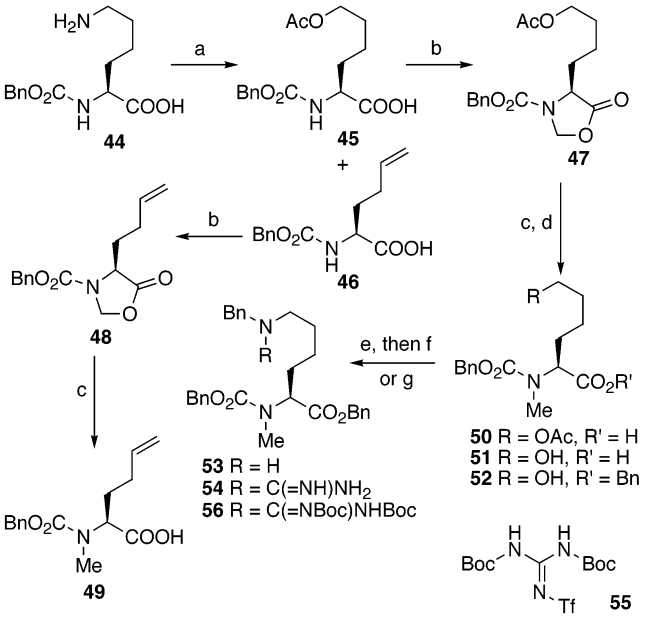
(20) Mzengeza, S.; Whitney, R. A. *J. Org. Chem.* **1988**, *53*, 4074.

(21) (a) Fujii, N.; Sasaki, T.; Funakoshi, S.; Irie, H.; Yajima, H. *Chem. Pharm. Bull.* **1978**, *26*, 650. (b) Holland, H. L.; Andreana, P. R.; Brown, F. M. *Tetrahedron: Asymmetry* **1999**, *10*, 2833. (c) Strazzolini, P.; Scuccato, M.; Giumanini, A. G. *Tetrahedron* **2000**, *56*, 3625.

(22) Nicolás, E.; Vilaseca, M.; Giralt, E. *Tetrahedron* **1995**, *51*, 5701.

(23) Sieber, P.; Riniker, B. *Tetrahedron Lett.* **1991**, *32*, 739.

SCHEME 10. Attempted Formation of *N*-Methyl Homoarginine[a]



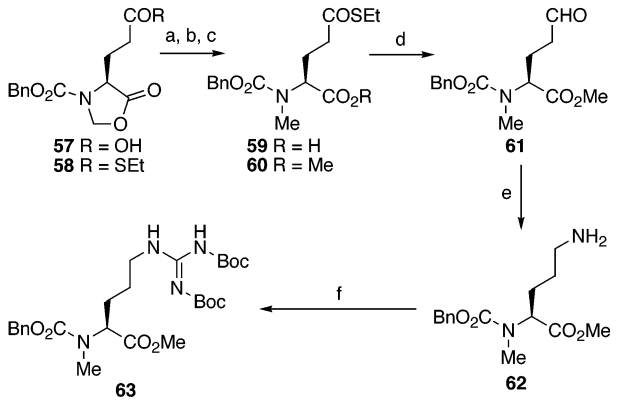
[a] Reagents and conditions: (a) $NaNO_2$, AcOH, NaOAc, 40 °C; (b) C_6H_6, $(CH_2O)_n$, CSA (cat.), reflux; (c) Et_3SiH, CF_3CO_2H, CH_2Cl_2; (d) NaOH, H_2O then K_2CO_3, DMF, BnBr; (e) Tf_2O, $BnNH_2$; (f) $HO_3SC(=NH)NH_2$; (g) **55**.

matic transformations. The lysine carbamate **44** was readily available in our laboratory and so the sequence in Scheme 10 leading to the *N*-methyl-lysine **53** was investigated as a trial for the preparation of *N*-methyl homoarginine. Diazotization of the carbamate **44** and its decomposition with sodium acetate led to the formation of the acetate **45** as a mixture with the elimination product **46**. These compounds were not separated prior to oxazolidination. Oxazolidination of the mixture gave the expected oxazolidinones **47** and **48**, which were separated by column chromatography.

Reductive cleavage of the butenyl oxazolidinone **48** gave the expected *N*-methyl amino acid **49** (64%). Reductive cleavage of the oxazolidinone **47** afforded the *N*-methyl compound **50** (82%). Then the acetate group was hydrolyzed with aqueous base to give the alcohol **51** and the carboxylic acid was esterified to give the benzyl ester **52**. Treatment of the benzyl ester **52** with triflic anhydride formed the triflate ester in situ. Benzylamine was added to the triflate and displacement provided the fully protected *N*-methyl lysine **53**. The secondary amine **53** was then treated with aminoiminomethanesulfonic acid[24] but this failed to afford the *N*-methyl homoarginine **54**. In addition, reaction with the triflylguanidine **55**[25] also failed to give the desired homoarginine **56**. It was evident the secondary amine was insufficiently nucleophilic for these guanylation reactions. A similar sequence with ornithine intermediates also failed for the same reasons.

We then pursued the reactions depicted in Scheme 11, which offered a synthesis of *N*-methyl arginine via direct and less demanding transformations. The glutamic ox-

SCHEME 11. Synthesis of *N*-Methyl Arginine 63[a]



[a] Reagents and conditions: (a) EtSH, DMAP, DCC, CH_2Cl_2; (b) Et_3SiH, CF_3CO_2H, CH_2Cl_2; (c) CH_2N_2; (d) 10% Pd-on-C, Et_3SiH, acetone; (e) $NH_4^+AcO^-$, MeOH, $NaCNBH_3$; (f) $CHCl_3$, **55**, $EtNiPr_2$.

azolidinone **57** was converted to the thioester **58** (92%) by DCC coupling with ethanethiol. Reductive cleavage then proceeded smoothly to give the *N*-methyl amino acid **59** (87%). The carboxylic acid was protected as the methyl ester **60** by diazomethylation[26] in quantitative yield. The resulting thioester was converted into the aldehyde **61** by treatment with palladium catalyst in the presence of triethylsilane.[27] This material was not purified but was submitted directly to the next series of reactions for generating the target arginine. Reductive amination with ammonium acetate then afforded the *N*-methyl ornithine **62**. Reaction of this with the guanylating reagent **55** gave the desired *N*-methyl arginine **63** in 49% yield from the methyl ester **60**.

In addition, conversion of the commercial Fmoc L-nitroarginine **64** was attempted. The oxazolidination reaction did not give the expected compound. Electrospray mass spectrometry and NMR analysis indicated the product had a molecular weight of 495, which required the presence of extra methylene groups. It is proposed that the novel heterocycle **66** was prepared (Scheme 12). Similar chemistry on nitroguanidino compounds in which there is a second nucleophilic reagent, a primary amine, included in the reaction results in intermolecular condensation of the guanidine, the amine, and 2 equiv of the formaldehyde.[28] We propose in the current reaction that there is no second nucleophilic reactant and so the weakly nucleophilic nitro group is able to intercept a reactive iminium intermediate and form the isolated product.

There are potentially two possible routes that the reaction can take: to produce initially either **65** or **66** and then **67** or **68**. It was shown that the reaction proceeded via **66** from a detailed analysis of the NMR spectra and comparison with the data expected for structure **65**. Initially, the NMR spectra of compound **66** were run in $CDCl_3$; however, broad peaks in both the ^1H and the ^{13}C NMR spectra were seen as a result of

(24) Kim, K.; Lin, Y.-T.; Mosher, H. S. *Tetrahedron Lett.* **1988**, *29*, 3183.

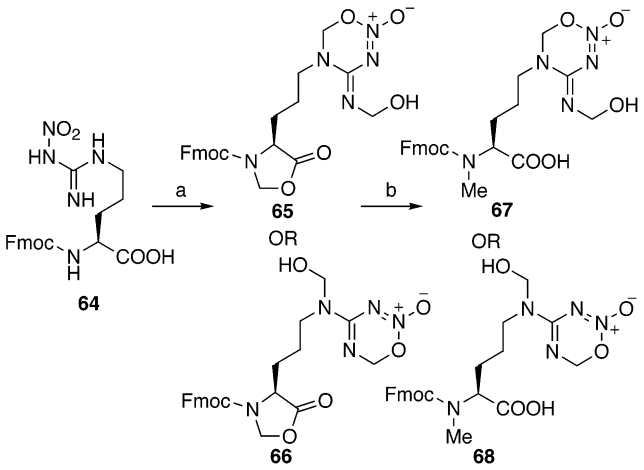
(25) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432.

(26) De Boer, T. J.; Backer, H. J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 250.

(27) (a) Fukuyama, T.; Liu, G.; Linton, S. D.; Lin, S.-C.; Nishino, H. *Tetrahedron Lett.* **1993**, *34*, 2577. (b) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

(28) Maienfisch, P.; Huerlimann, H.; Haettenschwiler, J. *Tetrahedron Lett.* **2000**, *41*, 7187.

SCHEME 12[a]



[a] Reagents and conditions: (a) C_6H_6, $(CH_2O)_n$, CSA (cat.), reflux; (b) Et_3SiH, CF_3CO_2H, CH_2Cl_2.

TABLE 1. ^{13}C and ^{1}H NMR Data for Compound 66 at 300 MHz and 333 K in DMSO

carbon	carbon shift	proton shift	no. of protons	multiplicity	*J* coupling
2[a]	77.34	5.26	2	dd	20.0, 4.1
4	53.98	4.05	1H	t	6.3
5	171.95				
1′	26.69	1.58−1.39	2H	m	
2′	22.17	1.58−1.39	2H	m	
3′	44.79	3.24−3.18	2H	m	
5′	77.34	4.84	2H	s	
4″	153.84				
6″ [a]	72.99	4.90−4.89	2	d	1.2
1‴ (8‴)	126.85	7.63−7.61	2H	d	7.13
2‴ (7‴)	124.59	7.31	2H	t	7.34
3‴ (6‴)	119.73	7.39	2H	t	7.31
4‴ (5‴)	127.39	7.86−7.84	2H	d	7.42
4a‴ (4b‴)	143.41				
8a‴ (9a‴)	140.62				
9‴	46.49	4.28	1H	t	5.6
10‴	66.57	4.54	2H	m	
11‴	152.44				
OH		9.6	1	s	

[a] Overlapping signals.

conformational mobility. Thus, in this solvent there were a number of missing peaks in the 2D spectra. In DMSO at 333 K the peaks were sharper and provided satisfactory 2D spectra.

An accurate assignment of all the protons and carbons in the molecule was obtained by using a combination of COSY, DEPT, HSQC, and the HMBC experiments. The complete assignment is presented in Table 1.

The HMBC experimental data were critical in differentiating between structures **65** and **66**. Long-range correlations from the (C4″) at δ 153.84 to the protons of (H3′) (δ 3.24−3.18), (H5′) (δ 4.84), and (H6″) (δ 4.90−4.89) would be seen in both. The assignment as **66** was determined from the long-range correlation between the (C3′) at δ 44.79 and the (H5′) at δ 4.84 of the γ-position of the propyl chain and the hydroxymethyl group, marked B in Figure 4. This is not possible in structure **65**.

The conclusion depends on the accurate assignment of the carbons and protons for the 1′, 2′, and 3′ positions. Proton assignments for these positions were obtained

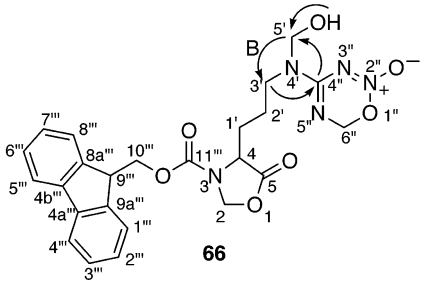
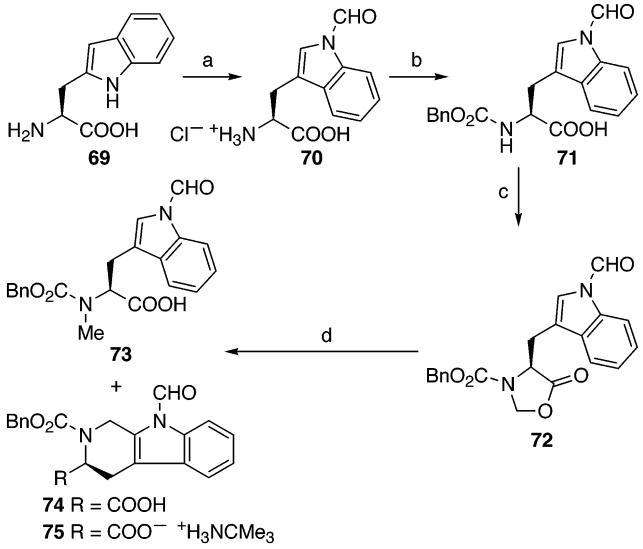


FIGURE 4. HMBC correlations for compound **66**.

SCHEME 13[a]



[a] Reagents and conditions: (a) HCO_2H, HCl (g); (b) Et_3N, DMF, $BnOCO_2Succ$; (c) C_6H_6, CSA (cat.), $(CH_2O)_n$, reflux; (d) Et_3SiH, CF_3CO_2H, $CHCl_3$.

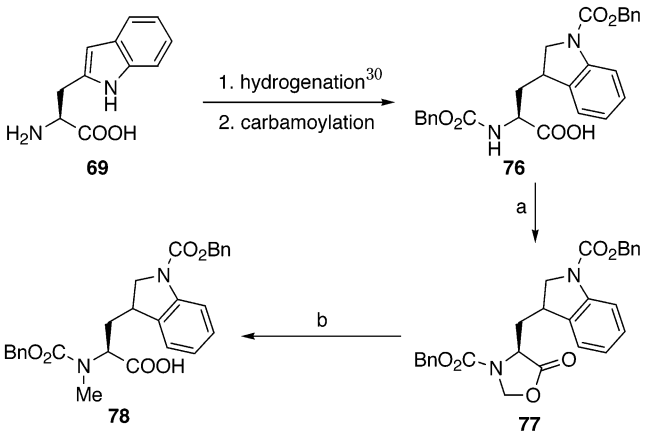
from the mCOSY experiment, and HSQC and HMBC experiments were used for the carbon assignments.

The reductive cleavage produced a single product **68** that has a molecular weight of 497 (ESMS). The ^{1}H and ^{13}C NMR spectra clearly indicate the presence of the *N*-methyl group and a methylene group associated with the oxatriazine. The reduction of the oxazolidinone **66** to the acid **68** shows the disappearance of the H2 proton peaks at δ 5.35 and appearance of the expected NCH_3 at δ 2.72, indicating that only the oxazolidinone ring is reductively cleaved. It is apparent that the triethylsilane/trifluoroacetic acid is able to reduce the 5-oxazolidinone but not the new heterocyclic ring formed from the nitroguanidine.

Tryptophan. Attempted oxazolidination of the carbamate of tryptophan resulted in decomposition. This is presumably due to side reactions of the indole nitrogen. An electron-withdrawing protecting group was anticipated to solve this problem and accordingly the *N*-formyl tryptophan **70**[29] (Scheme 13) was prepared in quantitative yield from L-tryptophan **69**. Carbamoylation then gave the precursor **71** for oxazolidination. The oxazolidination proceeded in good yield (86%) and the oxazolidinone **72** was isolated as an oil. The following reductive

(29) Previero, A.; Coletti-Previero, M. A.; Cavadore, J.-C. *Biochim. Biophys. Acta* **1967**, *147*, 453.

SCHEME 14[a]



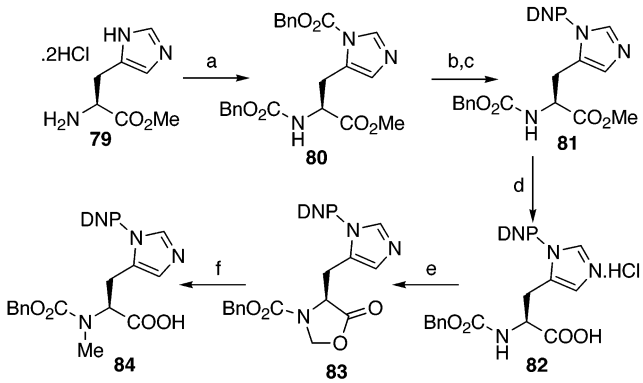
[a] Reagents and conditions: (a) C_6H_6, $(CH_2O)_n$, CSA (cat.), reflux; (b) Et_3SiH, CF_3CO_2H, $CHCl_3$.

cleavage did not proceed as planned. In all cases two products were isolated. The minor product (22%) was the expected *N*-methyl tryptophan **73**. The major product was the *β*-carboline **74**. The *β*-carboline arises by reaction of the intermediate iminium ion with the indole in an intramolecular electrophilic aromatic substitution. The resulting carboxylic acid **74** was isolated as its *tert*-butylammonium salt **75**.

To further substantiate this role of the indole, the electrophilic aromatic substitution can be eliminated by reducing the pyrrole ring double bond. Accordingly, tryptophan **69** was converted to dihydrotryptophan (Scheme 14).[30] This material underwent bis-carbamoylation to give the precursor **76**. Oxazolidination proceeded smoothly to afford the mixture of diastereoisomers **77**. The key reductive cleavage proceeded as expected to afford the *N*-methyl dihydrotryptophan **78** in 83% yield.

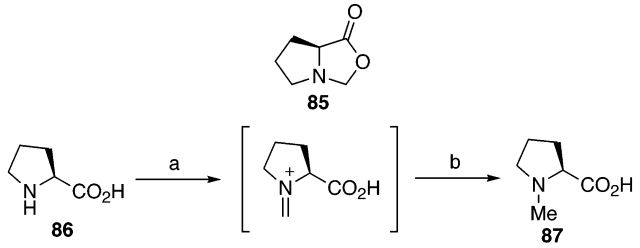
Histidine. Again the basic and highly nucleophilic nature of the histidine side chain caused problems in the initial attempts to form *N*-methyl histidine. Selective formation of the α-amino carbamate is difficult too, so the sequence in Scheme 15 was adopted. Histidine methyl ester dihydrochloride salt **79** was carbamoylated with 2 equiv of (benzyloxycarbonyloxy)succinimide to give the bis-carbamate **80**. Treatment of this with propylamine effected removal of the imidazole carbamate. The reaction mixture was then evaporated under reduced pressure and the residue in acetonitrile was treated with 2,4-dinitrofluorobenzene, which underwent a nucleophilic aromatic substitution to afford the dinitrophenyl (DNP) imidazole **81**. Treatment of this compound with a mixture of acetic acid and 2 M hydrochloric acid resulted in hydrolysis of the methyl ester to afford the acid as a hydrochloride salt **82**. This acid is the precursor for the oxazolidinone, but standard conditions for its formation could not be used due to the insolubility of **82**. This was overcome by dissolving the hydrochloride **82** in acetic acid and acetic anhydride in the presence of camphorsulfonic acid catalyst. Treatment of this mixture with paraformaldehyde afforded the required oxazolidinone **83** in 66% yield. Reductive cleavage then gave the *N*-methyl histidine carbamate **84** with the side chain imidazole still protected with the dinitrophenyl group.

SCHEME 15[a]



[a] Reagents and conditions: (a) $BnOCO_2Succ$, Et_3N, CH_3CN; (b) $C_3H_7NH_2$; (c) Et_3N, CH_3CN, 2,4-dinitrofluorobenzene; (d) AcOH, 2 M HCl, 3 d; (e) AcOH, Ac_2O, $(CH_2O)_n$, CSA (cat.); (f) Et_3SiH, CF_3CO_2H, $CHCl_3$.

SCHEME 16[a]



[a] Reagents and conditions: (a) MeOH, aq CH_2O; (b) 10% Pd-on-C, H_2.

Proline. Due to the tertiary substitution of the α-amino nitrogen in *N*-methyl proline there was limited interest on our part in its synthesis as it cannot be readily incorporated in peptide sequences except at the *N*-terminus. The formation of the proline oxazolidinone **85** has been reported[31] though its synthesis is not high yielding. The isolation of the oxazolidinone **85** can be avoided by the simple expedient of combining aqueous formaldehyde and proline **86** in methanol (Scheme 16). This mixture was then subjected to hydrogenating conditions to afford the *N*-methyl proline **87** in near quantitative yield. This approach was employed by Lin et al.[32] to prepare an *N*-methyl proline ester from a proline ester.

Conclusion

5-Oxazolidinone chemistry has been applied to the 20 common α-amino acids (and some others) in the formation of *N*-methyl derivatives and it is possible to classify the compounds according to their ease of manipulation. In the first group are those α-amino acids with side chains that do not interfere with the oxazolidination and subsequent reductive cleavage. Into this group fits glycine, alanine, valine, leucine, isoleucine, phenylalanine,

(30) Daly, J. W.; Mauger, A. B.; Yonemitsu, O.; Antonov, V. K.; Takase, K.; Witkop, B. *Biochemistry* **1967**, *6*, 648.

(31) Joucla, M.; Mortier, J. *Bull. Soc. Chim. France* **1988**, 579.

(32) Lin, N.-H.; He, Y.; Elliott, R. L.; Chorghade, M. S.; Wittenberger, S. J.; Bunnelle, W. H.; Narayanan, B. A.; Singam, P. R.; Esch, T. K.; Beer, D. O.; Witzig, C. C.; Herzig, T. C.; Rao, A. V. R. PCT Int. Appl. 1995, WO9507277; *Chem. Abstr. 123*, 9432.

aspartic acid, glutamic acid, proline, and tyrosine (and, in addition, phenylglycine). Historically, it is these amino acids that have been concentrated on by other workers.[33] Methionine gives one of the highest yields of the corresponding 5-oxazolidinone but does not react well in the reductive cleavage. The second category includes those α-amino acids for which a simple side chain protection reaction that is also compatible with standard solid-phase deprotection conditions allows their participation in the oxazolidinone chemistry. These amino acids are serine, threonine, cysteine, tyrosine, lysine, asparagine, and glutamine (and ornithine). Tyrosine has been included in both categories because, while the *N*-methylation sequence works in moderate to low yield without the phenolic hydroxyl protected, side chain benzylation substantially improves the yield. The third category is those amino acids that require devoted synthetic schemes and more exotic functional group protection. This group currently consists of the problematic α-amino acids arginine (and homoarginine), histidine, tryptophan, and methionine. These amino acids have collectively formed the substance of this paper.

The study has been highly successful in generating novel amino acid derivatives for inclusion in wide-ranging target synthesis projects and our results in these areas will be reported in due course. Elaboration of the chemistry to encompass new conditions for the oxazolidination and reductive cleavage that allows the generation of novel lipoamino acids, esters, peptide coupling chemistry, surfactants, *β*-amino acid derivatives, and target syntheses is underway.

Experimental Section

General. All melting points are uncorrected and were recorded on a microscope hot-stage apparatus. Infrared spectra were recorded on a FTIR spectrometer, using a diffuse reflectance accessory with KBr background. Standard pulse sequences (HMBC, HSQC, COSY, and DEPT) were used to identify compound **66**. Electrospray mass spectra (ESMS) were obtained on a triple quadrupole mass spectrometer, 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. Other low and high-resolution mass spectra (l.s.i.m.s.) were measured at the University of Tasmania by Dr. Noel Davies and co-workers. 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[34] 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.[34]

(*S*)-3-Benzyloxycarbonyl-4-acetoxymethyloxazolidin-5-one (14). To a sample of the carbamate **12** (1.11 g, 3.9 mmol) in toluene (50 mL) was added camphorsulfonic acid (70 mg) and dry paraformaldehyde (1.0 g). The reaction mixture was then heated to reflux for 30−60 min [monitored by TLC (40% ethyl acetate−hexane)]. The mixture was cooled, filtered to remove solids, and diluted with ether (150 mL). The ethereal solution was washed with 2.5% aqueous sodium bicarbonate solution (4 × 30 mL). The combined aqueous layers were extracted with ether (30 mL) and the combined ethereal layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the oxazolidinone **14** as an oil (1.01 g, 87%). A small sample was further purified by flash chromatography on silica, eluting with 30% ethyl acetate−hexane. $[\alpha]^{24}_D$ +110.7° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 5H), 5.51 (br s, 1H), 5.20 (d, 1H, J = 3.8 Hz), 5.16 (s, 2H), 4.61−4.58 (m, 1H), 4.42−4.32 (m, 2H), 1.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.85, 152.30, 135.07, 128.57, 128.25, 78.39, 68.04, 62.19, 54.41, 20.44. IR (NaCl) ν 3090, 3065, 3034, and 3010 (CH, aromatic), 3000−2900 (CH, saturated), 1807 (C=O, oxazolidinone), 1746 (C=O, acetate), 1719 (C=O, carbamate), 1500, 1452, 1419, 1359, 1315, 1290, 1234, 1170, 1130, 1060, 1034, 969, 945, 765, 699 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.54; H, 5.26; N, 4.96.

(4*S*)-3-Benzyloxycarbonyl-4-[(1*S*)-acetoxyethyl]oxazolidin-5-one (15). To a sample of the carbamate **13** (1.47 g, 4.9 mmol) in toluene (50 mL) was added camphorsulfonic acid (70 mg) and dry paraformaldehyde (1.0 g). The reaction mixture was then heated to reflux for 30−60 min [monitored by TLC (40% ethyl acetate−hexane)]. The mixture was cooled, filtered to remove solids, and diluted with ether (150 mL). The ethereal solution was washed with 2.5% aqueous sodium bicarbonate solution (4 × 30 mL). The combined aqueous layers were extracted with ether (30 mL) and the combined ethereal layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the oxazolidinone **15** as an oil (1.39 g, 91%). A small sample was further purified by flash chromatography on silica, eluting with 30% ethyl acetate−hexane. $[\alpha]^{24}_D$ +120.7° (*c* 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 5H), 5.70 (br s, 1H), 5.29−5.18 (m, 4H), 4.41 (br s, 1H), 1.97 (s, 3H), 1.34−1.31 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 170.14, 169.19, 153.83, 134.98, 128.59, 128.37, 78.98, 70.59, 68.34, 59.11, 20.76, 16.63. IR (NaCl) ν 3092, 3066 and 3033 (CH, aromatic), 3000−2900 (CH, saturated), 1808 (C=O, oxazolidinone), 1742 (C=O, acetate), 1719 (C=O, carbamate), 1498, 1454, 1409, 1360, 1328, 1232, 1169, 1124, 1041, 955, 897, 753, 700 cm^{-1}. MS (l.s.i.m.s.) *m*/*z* 308 (M + 1, 90), 289, (50), 264 (100). HRMS calcd for $C_{15}H_{18}NO_6$ (M + 1) 308.1134, found 308.1142. Anal. Calcd for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.62; H, 5.63; N, 4.71.

***N*-Benzyloxycarbonyl-*N*-methyl-L-serine-*O*-acetate (16).** A sample of the oxazolidinone **14** (1.18 g, 4.0 mmol) was dissolved in chloroform (20 mL) at room temperature and triethylsilane (1.89 mL) was added followed by trifluoroacetic acid (20 mL) and the reaction mixture was left to stand for 3−4 d. The reaction mixture was concentrated under reduced pressure. To the residue was added toluene (50 mL) and the mixture was again concentrated in vacuo. This procedure was repeated with more toluene (50 mL). The residue was then diluted with ether and extracted with saturated aqueous sodium bicarbonate solution (4 × 30 mL). The combined aqueous extracts were washed with ether and then acidified to pH 2 with 5 M hydrochloric acid. The aqueous phase was then extracted with ether (3 × 50 mL). The combined ethereal extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to approximately 20 mL volume. Dicyclohexylamine (DCHA) (0.8 mL) was added and any solid, which formed immediately, was filtered off. The clear filtrate was left to stand overnight during which the *N*-methyl serine acetate **16** precipitated as its DCHA salt (1.42 g, 74%). Mp 135−147 °C. $[\alpha]^{25}_D$ −8.0° (*c* 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (br s, 2H), 7.33−7.24 (m, 5H), 5.21−4.99 (m, 2H), 4.84 (td, 1H, J = 10.0, 4.2 Hz), 4.55 (dt, 1H, J = 11.8, 3.8 Hz), 4.42−4.26 (m, 1H), 2.97−2.88 (m, 5H), 1.97−1.13 (m, 23H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 172.30, 172.14, 170.85, 156.97, 156.77, 137.01, 128.37, 127.81, 127.58, 127.52, 66.97, 66.89, 62.54, 62.48, 59.99, 59.75, 52.75, 31.14, 28.95, 25.04, 24.67, 20.83, 20.74. IR (KBr disk) ν 3062, 3034 and 3005 (CH, aromatic), 3000−2800 (CH, saturated), 2476 and 2417 (NH_2^+), 1738 (C=O, acetate), 1693 (C=O, carbamate), 1641 (CO_2^-), 1566, 1441, 1392, 1370, 1345, 1312, 1286, 1250, 1149, 1075, 696 cm^{-1}. Anal. Calcd for $C_{26}H_{40}N_2O_6$: C, 65.52; H, 8.46; N, 5.88. Found: C, 65.52; H, 8.65; N, 5.86.

(33) See refs 1−27 in ref 6.

(34) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, UK, 1988.

***N*-Benzyloxycarbonyl-*N*-methyl-L-threonine-*O*-acetate (17).** A sample of the oxazolidinone **15** (1.22 g, 4.0 mmol) was dissolved in chloroform (20 mL) at room temperature and triethylsilane (1.89 mL) was added followed by trifluoroacetic acid (20 mL) and the reaction mixture was left to stand for 3−4 d. The reaction mixture was concentrated under reduced pressure. To the residue was added toluene (50 mL) and the mixture was again concentrated in vacuo. This procedure was repeated with more toluene (50 mL). The residue was then diluted with ether and extracted with saturated aqueous sodium bicarbonate solution (4 × 30 mL). The combined aqueous extracts were washed with ether and then acidified to pH 2 with 5 M hydrochloric acid. The aqueous phase was then extracted with ether (3 × 50 mL). The combined ethereal extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to approximately 20 mL volume. Dicyclohexylamine (DCHA) (0.8 mL) was added and any solid, which formed immediately, was filtered off. The filtrate solution was left to stand overnight during which the *N*-methyl threonine acetate **17** precipitated as its DCHA salt (1.57 g, 80%). Mp 114−118 °C. $[\alpha]^{25}_D$ +5.6° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 9.50 (br s, 2H), 7.33−7.24 (m, 5H), 5.51−5.43 (quintet, 1H, J = 6.5 Hz), 5.22−4.99 (m, 2H), 4.68 and 4.57 (2d, 1H, J = 6.7 Hz), 2.99−2.87 (m, 5H), 1.94−1.02 (m, 26H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 172.27, 172.15, 169.94, 157.34, 156.90, 137.04, 136.94, 128.35, 127.79, 127.60, 70.37, 69.94, 67.00, 66.92, 64.32, 52.45, 32.03, 31.79, 28.84, 28.79, 25.06, 24.65, 21.05, 17.81, 17.66. IR (KBr disk) ν 3200−2800 (CH, saturated), 2525 and 2456 (NH_2^+), 1729 (C=O, acetate), 1704 (C=O, carbamate), 1625 (CO_2^-), 1570, 1496, 1453, 1372, 1308, 1249, 1203, 1178, 1160, 1140, 1100, 1055, 735 cm^{-1}. Anal. Calcd for $C_{27}H_{42}N_2O_6$: C, 66.10; H, 8.63; N, 5.71. Found: C, 66.05; H, 8.74; N, 5.49.

***N*-Benzyloxycarbonyl-*N*-methyl-L-serine (20).** A sample of the serine DCHA salt **16** (970 mg, 2.0 mmol) was suspended in a mixture of dioxane and 2 M hydrochloric acid (20 mL, 1:1) with stirring. The mixture was then heated to 60 °C for ca. 30 h (TLC). The reaction mixture was then diluted with water (300 mL) and extracted with ether (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give the *N*-methyl serine **20** as an oil (455 mg, 88%), which was identical in all respects with previously reported material.[6]

***N*-Benzyloxycarbonyl-*N*-methyl-L-threonine (19).** A sample of the threonine DCHA salt **17** (1.04 g, 2.1 mmol) was suspended in a mixture of dioxane and 2 M hydrochloric acid (20 mL, 1:1) with stirring. The mixture was then heated to 60 °C for ca. 30 h (TLC). The reaction mixture was then diluted with water (300 mL) and extracted with ether (3 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give the *N*-methyl threonine **19** as an oil (498 mg, 88%), which was identical in all respects with previously reported material.[6]

***N*-Methyl-L-threonine (21).** A small sample of the carbamate **19** was hydrogenolysed over 10% palladium on charcoal catalyst.[6] The material isolated had $[\alpha]^{25}_D$ −14° (*c* 0.5, 6 M HCl), which was identical with authentic material.[6]

(*S*)-3-(Carbonyl-9*H*-fluoren-9-ylmethoxy)-4-(4-benzyloxybenzyl)oxazolidin-5-one (23). To a sample of the carbamate **22** (470 mg, 0.9 mmol) in toluene (150 mL) was added camphorsulfonic acid (66 mg). The reaction mixture was then heated to reflux for 4 h during which dry paraformaldehyde (500 mg) was added in small portions down the condenser. The mixture was then cooled and filtered to remove solids and the filtrate was evaporated under reduced pressure. The residue was taken up in ethyl acetate and washed with saturated aqueous sodium bicarbonate solution (3 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica, eluting with 25% ethyl acetate−hexane to give the oxazolidinone **23** as a foam (405 mg, 86%). $[\alpha]^{22}_D$ +132.5° (*c* 1.0, Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 7.77−6.60 (m, 17H), 5.11 (br s, 1H), 4.99−4.95 (m, 1H), 4.73−4.64 (m, 1H), 4.47 (m, 0.5H), 4.27−4.19 (m, 1H), 4.10 (m, 1H), 3.94 (m, 0.5H), 3.32−2.35 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 171.54, 157.84, 151.84, 143.09, 141.12, 136.50, 126.19, 130.31, 128.25, 127.67, 127.17, 126.93, 124.20, 119.87, 119.80, 114.76, 77.49, 69.56, 67.10, 66.31, 56.05, 46.93, 34.20. IR (KBr disk) ν 3034 (CH, aromatic), 3000−2800 (CH, saturated), 1800 (C=O, oxazolidinone), 1717 (C=O, carbamate), 1610, 1511, 1451, 1422, 1357, 1300, 1242, 1177, 1159, 1129, 1052, 1024, 830, 759, 741, 696 cm^{-1}. HRMS calcd for $C_{32}H_{27}NO_5$ (M^+) 505.1968, found 505.1891.

(*S*)-3-Benzyloxycarbonyl-4-(4-acetoxybenzyl)oxazolidin-5-one (26). To a sample of the carbamate **25** (2.90 g, 8.1 mmol) in toluene (50 mL) was added camphorsulfonic acid (200 mg). To the reaction mixture was added dry paraformaldehyde (3.0 g) and the mixture was heated to reflux for 1 h. The mixture was then cooledand filtered to remove solids and the filtrate was evaporated under reduced pressure. The residue was taken up in ether (100 mL). The ether layer was washed with 5% sodium carbonate solution (3 × 50 mL) followed by water and then brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue (2.80 g) was purified by flash chromatography on silica, eluting with 20% ethyl acetate−hexane to give the oxazolidinone **26** as a clear colorless oil (2.66 g, 89%). $[\alpha]^{24}_D$ +172.3° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.29 and 7.21−6.91 (2m, 9H), 5.28−5.14 (m, 3H), 4.49 (br s, 1H), 4.32 (d, 1H, J = 3.9 Hz), 3.42−3.08 (m, 2H), 2.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.51, 168.95, 152.06, 149.93, 135.37, 131.91, 130.42, 128.51, 128.25, 121.70, 77.78, 67.62, 56.11, 35.33, 34.31, 20.85. IR (NaCl) ν 3100, 3062 and 3034 (CH, aromatic), 3000−2800 (CH, saturated), 1800 (C=O, oxazolidinone), 1760 (C=O, acetate), 1716 (C=O, carbamate), 1604, 1506, 1416, 1361, 1310, 1202, 1126, 1049, 1013, 912, 843, 754 cm^{-1}. Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 64.89; H, 5.35; N, 3.87.

***N*-(Carbonyl-9*H*-fluoren-9-ylmethoxy)-*N*-methyl-L-tyrosine-*O*-benzyl Ether (24).** A sample of the oxazolidinone **23** (95 mg, 0.2 mmol) was dissolved in dichloromethane (5 mL) at room temperature and triethylsilane (270 μL, 1.7 mmol) was added followed by trifluoroacetic acid (1.2 mL, 10.5 mmol) and the reaction mixture was left to stand for 2 d. The reaction mixture was concentrated under reduced pressure. To the residue was added dichloromethane (5 mL) and the mixture was again concentrated in vacuo. This procedure was repeated with toluene (5 mL) until traces of trifluoroacetic acid were removed. The residue was then diluted with ethyl acetate and extracted with saturated aqueous sodium bicarbonate solution (3 × 30 mL). The combined aqueous extracts were washed with ether and then acidified to pH 2 with 2 M hydrochloric acid. The aqueous phase was then extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography, eluting with 95:4:1 dichloromethane/methanol/acetic acid to yield the *N*-methyl acid **24** as a white foam (67 mg, 70%). $[\alpha]^{24}_D$ −1.6° (*c* 0.5, Et_2O). R_f 0.3 (95:4:1 dichloromethane/methanol/acetic acid). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 7.74−6.46 (m, 17H), 4.90−4.07 (m, 6H), 3.27 and 3.08−2.96 and 2.66−2.63 (dd and 2m, 1H and 2H, J = 4.8, 14.4 Hz), 2.78 and 2.74 (2s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 174.21, 156.70, 155.85, 154.28, 143.41, 143.31, 140.93, 129.57, 128.24, 127.55, 126.73, 124.64, 124.31, 119.62, 115.20, 67.62, 67.10, 60.59, 60.26, 46.81, 46.69, 33.61, 33.46, 31.92.

***N*-Benzyloxycarbonyl-*N*-methyl-L-tyrosine-*O*-acetate (27).** A sample of the oxazolidinone **26** (1.50 g, 4.1 mmol) was dissolved in chloroform (20 mL) at room temperature and triethylsilane (1.9 mL) was added followed by trifluoroacetic acid (20 mL) and the reaction mixture was left to stand for 4 d. The reaction mixture was diluted with toluene and concentrated under reduced pressure. This procedure was repeated with a further aliquot of toluene (50 mL). The residue was then

diluted with ether and extracted with 5% sodium carbonate solution (4 × 20 mL). The combined aqueous extracts were washed with ether and then acidified to pH 2 with 5 M hydrochloric acid. The aqueous phase was then extracted with dichloromethane (3 × 50 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford a clear oil (1.33 g, 88%). A sample of the oil was converted to the *tert*-butylamine salt by dissolution in ether and addition of *tert*-butylamine (1.1 equiv) followed by hexane until the solution turned slightly cloudy. The turbid solution was then left to stand at room temperature for 4 h and then at 0 °C overnight during which the *N*-methyl tyrosine acetate **27** precipitated as its *tert*-butylammonium salt. Mp 54−60 °C. $[\alpha]^{24}_D$ −34.3° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 7.74 (br s, 3H), 7.29−6.88 (m, 9H), 5.01−4.64 (m, 3H), 3.38−3.28 and 3.00−2.77 (2m, 5H), 2.26 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 175.95, 169.51, 156.89, 156.50, 148.99, 136.78, 136.66, 136.60, 136.50, 129.68, 128.35, 127.76, 127.45, 121.32, 66.97, 66.86, 62.64, 62.34, 51.23, 35.51, 35.05, 31.90, 31.08, 27.51, 21.10. IR (KBr disk) ν 3121, 3064 and 3033 (CH, aromatic), 3000−2800 (CH, saturated), 2622 and 2529 (NH_3^+), 1760 (C═O, acetate), 1674 (C═O, carbamate), 1592 (CO_2^-), 1507, 1448, 1377, 1314, 1209, 1194, 1134, 750, 695, 639 cm^{-1}. Anal. Calcd for $C_{24}H_{32}N_2O_6$: C, 64.85; H, 7.26; N, 6.30. Found: C, 64.71; H, 7.39; N, 6.41.

(*R*)-3-Benzyloxycarbonyl-4-(acetylthiomethyl)oxazolidin-5-one (32). In a round-bottomed flask fitted with a Dean−Stark apparatus, a mixture of the *S*-acetyl cysteine **31a** (1.0 g, 3.4 mmol), paraformaldehyde (450 mg), and camphorsulfonic acid (40 mg) was suspended in benzene (30 mL). The mixture was heated to reflux for 3 h (monitored by TLC). The reaction mixture was then concentrated at reduced pressure. The residue was taken up in ethyl acetate and the organic layer was washed with saturated aqueous sodium bicarbonate solution to remove acidic material. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography, eluting with 50% ethyl acetate−hexane to afford the oxazolidinone **32** as an oil (540 mg, 51%). $[\alpha]^{25}_D$ +101.0° (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.30 (m, 5H), 5.44 (br s, 1H), 5.22−5.14 (m, 3H), 4.52 (br s, 1H), 3.65 (dd, 1H, J = 4.7, 14.2 Hz), 3.41−3.30 (m, 1H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.03, 170.28, 152.39, 135.17, 128.51, 128.45, 128.24, 127.82, 78.39, 68.03, 54.60, 30.36, 29.36. IR (NaCl) ν 3110, 3090, 3065 and 3034 (CH, aromatic), 3000−2800 (CH, saturated), 1804 (C═O, oxazolidinone), 1714 (C═O, carbamate, acetate), 1500, 1412, 1357, 1290, 1215, 1168, 1129, 1051, 1020, 966, 884, 764, 699, 620 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_5S$: C, 54.36; H, 4.89; N, 4.53; S, 10.37. Found: C, 54.47; H, 4.94; N, 4.32; S, 10.29.

(*R*)-3-Benzyloxycarbonyl-4-(phenylmethylthiomethyl)oxazolidin-5-one (33). In a round-bottomed flask fitted with a Dean−Stark apparatus, a mixture of the *S*-benzyl cysteine **31b** (1.0 g, 2.9 mmol), paraformaldehyde (450 mg), and camphorsulfonic acid (50 mg) was suspended in benzene (30 mL). The mixture was heated to reflux (monitored by TLC for disappearance of starting material). The reaction mixture was then concentrated at reduced pressure. The residue was taken up in ethyl acetate and the organic layer was washed with saturated aqueous sodium bicarbonate solution to remove acidic material. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. The pale yellow syrupy residue was purified by column chromatography, eluting with 20% ether−hexane then 20−50% ethyl acetate−hexane to afford the oxazolidinone **33** as a clear colorless oil (920 mg, 89%). $[\alpha]^{24}_D$ +102.3° (*c* 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.20 (m, 10H), 5.50 (br s, 1H), 5.35 (d, 1H, J = 4.1 Hz), 5.16 (s, 2H), 4.50 (br s, 1H), 3.69 (d, 1H, J_{AB} = 13.3 Hz), 3.65 (d, 1H, J_{AB} = 13.3 Hz), 3.37−2.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.28, 152.38, 137.45, 135.23, 128.95, 128.69, 128.55, 128.32, 127.28, 78.77, 68.01, 56.04, 37.24, 31.86, 31.42. IR (NaCl) ν 3086, 3062, 3030 and 3006 (CH, aromatic), 3000−2800 (CH, saturated), 1801 (C═O, oxazolidinone), 1717 (C═O, carbamate), 1495, 1452, 1413, 1357, 1290, 1257, 1212, 1165, 1127, 1052, 1019, 961, 764, 699 cm^{-1}. Anal. Calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.59; H, 5.62; N, 4.07.

***N*-Benzyloxycarbonyl-*N*-methyl-*S*-phenylmethyl-L-cysteine (34).**[35] The oxazolidinone **33** (850 mg, 2.4 mmol) was taken up in chloroform (20 mL). Triethylsilane (1.5 mL) was added followed by trifluoroacetic acid (20 mL) and the resulting mixture was left to stand for 2 d. The reaction mixture was concentrated under reduced pressure. The residue was diluted with excess saturated aqueous sodium bicarbonate solution. The aqueous phase was washed with ether and then acidified to pH 2 with 2 M hydrochloric acid. The acidic layer was then extracted with ether. The ethereal extracts were dried ($MgSO_4$) and then treated with dicyclohexylamine (2.4 mmol) and the solution was stored overnight at 0 °C. The crystalline precipitate that formed was filtered off at the pump and dried to give the *N*-methyl-*S*-benzyl cysteine **34** as its DCHA salt (900 mg, 70%). Mp 105−107 °C. $[\alpha]^{26}_D$ −56.0° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) 7.35−7.17 (m, 10H), 5.25−5.03 (m, 2H), 4.76 (dd, 1H, J = 4.9, 10.6 Hz), 4.61 (dd, 1H, J = 4.9, 10.5 Hz), 3.73−3.61 (m, 2H), 3.12−3.05 (m, 1H), 2.89−2.83 (m, 5H), 2.71−2.65 (m, 1H), 1.91−1.03 (m, 20H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 173.99, 173.66, 157.07 156.78, 138.49, 137.04, 136.85, 128.92, 128.73, 128.27, 127.70, 127.46, 126.69, 67.04, 66.83, 60.31, 59.79, 52.37, 36.17, 35.76, 32.21, 31.75, 30.62 30.29, 28.93, 28.81, 25.11, 24.67. IR (KBr disk) ν 3059 and 3029 (CH, aromatic), 3000−2800 (CH, saturated), 2525 and 2466 (H_2N^+), 1692 (C═O, carbamate), 1624 (CO_2^-), 1563, 1496, 1476, 1453, 1382, 1311, 1293, 1169, 1128, 1024, 760, 700 cm^{-1}. Anal. Calcd for $C_{31}H_{44}N_2O_4S$: C, 68.85; H, 8.20; N, 5.18; S, 5.93. Found: C, 68.91; H, 8.39; N, 5.05; S, 5.85.

(4*R*,4′*R*)-3,3′-Bis-benzyloxycarbonyl-4,4′-[dithiobis(methylene)]bis-oxazolidin-5-one (36). A mixture of the cystine carbamate **35** (3.0 g, 5.9 mmol), camphorsulfonic acid (40 mg), paraformaldehyde (2.0 g), and toluene (100 mL) was heated to reflux (ca. 1.5 h, TLC). The reaction mixture was then concentrated under reduced pressure and the residue was filtered through a short column or plug of silica gel, eluting with dichloromethane. The filtrate was concentrated in vacuo and the residual syrup was refrigerated at ∼5 °C overnight to initiate crystallization. The mixture of syrup and most of the solid was taken up in hot ether solution (small amounts of ethyl acetate can be added to facilitate dissolution). The solution was concentrated by boiling to ca. 15 mL and then hexane (10 mL) was added. The solution was left to stand overnight at 0 °C. The precipitate that formed was filtered off at the pump and dried to give the oxazolidinone **36** as a crystalline solid (1.05 g, 33%). Mp 86−88 °C. $[\alpha]^{23}_D$ +99.4° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.29 (m, 10H), 5.49−5.46 (m, 2H), 5.30 (br s, 2H), 5.15−5.12 (m, 4H), 4.51 (br s, 2H), 3.47−3.12 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.62, 152.15, 135.19, 128.66, 128.42, 78.43, 68.04, 55.07, 38.86, 37.85. IR (KBr disk) ν 3090, 3065, and 3033 (CH, aromatic), 3000−2800 (CH, saturated), 1796 (C═O, oxazolidinone), 1704 (C═O, carbamate), 1500, 1453, 1431, 1362, 1296, 1268, 1213, 1175, 1159, 1125, 1055, 761, 700 cm^{-1}. Anal. Calcd for $C_{24}H_{24}N_2O_8S_2$: C, 54.12; H, 4.54; N, 5.26; S, 12.04. Found: C, 54.11; H, 4.46; N, 5.17; S, 11.96.

Attempted Reductive Cleavage of the Cystine Oxazolidinone (36). The cystine oxazolidinone **36** (300 mg, 0.6 mmol) was taken up in chloroform (5 mL). Triethylsilane (750 μL) was added followed by trifluoroacetic acid (5 mL) and the reaction mixture was left to stand for 2 d. Workup of the reaction mixture as described for the *N*-methyl cysteine (**33**) afforded the thiazolidine (**30**) as an oil (241 mg, 80%) identical in all respects with material previously reported.[6,35]

(35) (a) Yamashiro, D.; Aanning, H. L.; Branda, L. A.; Cash, W. D.; Murti, V. V. S.; Du Vigneaud, V. *J. Am. Chem. Soc.* **1968**, *90*, 4141. (b) See also: Ratner, S.; Clarke, H. T. *J. Am. Chem. Soc.* **1937**, *59*, 200.

(*S*)-3-Carbonylbenzyloxy-4-(2-methanesulfinylethyl)-oxazolidin-5-one (38).[20] To a solution of the methionine oxazolidinone **29b** (3.0 g, 10.2 mmol) in dichloromethane (135 mL) was slowly added *m*-CPBA (1.74 g) and the reaction mixture was stirred at room temperature for 15 min. The solution was washed with sodium carbonate solution (3 × 40 mL, 10% w/v). The aqueous washings were extracted with dichloromethane (2 × 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the sulfoxides **38** as a clear colorless gum (3.1 g, 98%). This material was sufficiently pure to be used directly in the next step. A sample was further purified by column chromatography, eluting with chloroform to afford a diastereoisomeric mixture of the sulfoxides **38** as a colorless gum. ^{1}H NMR (300 MHz, $CDCl_3$) 7.32 (s, 5H), 5.48−5.47 (m, 1H), 5.22−5.08 (m, 3H), 4.38 (t, 1H, J = 6.0 Hz), 2.75 (br s, 2H), 2.47 (s, 3H), 2.38−2.27 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.09, 152.89, 152.83, 135.00, 128.61, 128.33, 77.74, 68.13, 53.79, 53.68, 49.28, 38.54, 38.47, 24.37, 24.08. IR (NaCl) ν 3038 (CH, aromatic), 3000−2900 (CH, saturated), 1796 (C═O, oxazolidinone), 1714 (C═O, carbamate), 1502, 1413, 1356, 1317, 1247, 1132, 1049, 753 cm^{-1}. HRMS calcd for $C_{14}H_{17}NO_5S$ (M^+) 311.0827, found 311.0832.

***N*-Benzyloxycarbonyl-*N*-methyl-L-methionine-d-sulfoxide (39a) and *N*-Benzyloxycarbonyl-*N*-methyl-L-methionine-l-sulfoxide (39b).** To a solution of the sulfoxides **38** (1.3 g, 4.2 mmol) in chloroform (22 mL) was added triethylsilane (2.0 mL) and trifluoroacetic acid (22 mL). The reaction mixture was stirred at room temperature for 2 d and it was then concentrated at reduced pressure. The residue was taken up in ethyl acetate and extracted with sodium carbonate solution (10% w/v, 4 × 15 mL). The combined aqueous extracts were washed with ethyl acetate and then acidified with 5 M hydrochloric acid. The aqueous layer was then extracted with dichloromethane (3 × 20 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue (1.22 g) was taken up in methanol (12 mL). To the methanolic solution was added concentrated hydrochloric acid (20 μL). Hydrogen peroxide (30%) was added dropwise until TLC indicated the presence of a single compound. The reaction mixture was concentrated at reduced pressure and the residue was taken up in dichloromethane and washed with water. The dichloromethane phase was then dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue (1.22 g) was recrystallized from ethyl acetate−ether to give the sulfoxide **39a** as a solid (210 mg, 16%). Mp 145−148 °C. $[\alpha]^{25}_D$ +21.0° (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) (d_6-DMSO) δ 7.39−7.28 (m, 5H), 5.10−5.02 (m, 2H), 4.60−4.53 (m, 1H), 2.82−2.70 (m, 3H), 2.67−2.58 (m, 2H), 2.51−2.47 (m, 3H), 2.22−2.20 (m, 1H), 2.06−1.97 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 171.81, 156.08, 155.59, 136.72, 128.43, 128.36, 127.84, 127.38, 66.48, 58.44, 49.99, 38.11, 31.86, 31.30, 22.18, 21.50. IR (KBr) ν 3600−3200 (CO_2H), 3063 and 3031 (CH, aromatic), 3000−2800 (CH, saturated), 1721 (CO, acid), 1691 (CO, carbamate), 1629, 1492, 1456, 1407, 1366, 1303, 1222, 1146, 987 cm^{-1}. Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47; S, 10.23. Found: C, 53.56; H, 6.25; N, 4.39; S, 10.35. The mother liquor was concentrated at reduced pressure to afford the sulfoxide **39b** as a colorless gum (1.00 g, 76%). $[\alpha]^{25}_D$ −53.2° (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) (d_6-DMSO) δ 7.37−7.29 (m, 5H), 5.10−5.03 (m, 2H), 4.63−4.56 (m, 1H), 2.83−2.70 (m, 4H), 2.59−2.49 (m, 4H), 2.25−2.20 (m, 1H), 2.10−1.97 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 171.87, 156.12, 155.65, 136.81, 128.44, 128.37, 127.81, 127.38, 66.50, 57.94, 57.76, 49.68, 49.48, 37.83, 31.62, 31.15, 21.54, 21.23. IR (NaCl) ν 3500−3200 (COOH), 3063 and 3023 (CH, aromatic), 3000−2800 (CH, saturated), 1700 (CO, acid), 1550, 1455, 1404, 1317, 1222, 1169, 1132, 1001, 823, 742, 693 cm^{-1}. HRMS calcd for $C_{14}H_{19}NO_5S$ (M^+) 314.1062, found 314.1074.

***N*-Benzyloxycarbonyl-*N*-methyl-L-methionine (40).**[36] To a solution of the sulfoxides **38** (1.3 g, 4.2 mmol) in chloroform (22 mL) was added triethylsilane (2.0 mL) and trifluoroacetic acid (22 mL). The reaction mixture was stirred at room temperature for 2 d. The solution was then cooled to 0 °C and ammonium iodide (3.02 g) and dimethyl sulfide (1.53 mL) were added. The reaction mixture was stirred vigorously for 1 h at 0 °C and then it was diluted with toluene and evaporated at reduced pressure. The residue was taken up in ether and extracted with sodium carbonate solution (10% w/v, 4 × 15 mL). The combined aqueous extracts were washed with ether and then acidified to pH 2 with 5 M hydrochloric acid. The aqueous layer was then extracted with dichloromethane (3 × 20 mL) and the combined organic extracts were washed with 5% sodium thiosulfate solution, dried ($MgSO_4$), filtered, and concentrated in vacuo to give the methionine **40** as a clear colorless oil (1.01 g, 81%). For analytical purposes this material can be taken up in ether and treated with dicyclohexylamine (1 equiv) to give the DCHA salt. Mp 97−99 °C. $[\alpha]^{23}_D$ −17.0° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 9.47 (br s, 2H), 7.34−7.22 (m, 5H), 5.15−4.95 (m, 2H), 4.59−4.51 (m, 1H), 2.88−2.82 (m, 5H), 2.53−2.22 (m, 3H), 2.03 and 1.99 (2 × s, 3H), 1.90−1.02 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 174.68, 174.60, 156.83, 136.96, 136.83, 128.18, 127.56, 127.38, 66.78, 66.65, 60.44, 60.16, 52.29, 31.56, 30.54, 30.15, 29.70, 29.66, 28.94, 28.69, 25.07, 24.61, 15.40. IR (KBr) ν 3037 (CH, aromatic), 3000−2800 (CH, saturated), 2525 and 2452 (NH_2^+), 1702 (CO, carbamate), 1631 (CO_2^-), 1546, 1517, 1483, 1440, 1390, 1320, 1268, 1170, 1121, 1062, 740 cm^{-1}. Anal. Calcd for $C_{26}H_{42}N_2O_4S$: C, 65.24; H, 8.84; N, 5.85. Found, C, 65.32; H, 8.54; N, 5.99.

(*S*)-3-Carbonylbenzyloxy-4-(triphenylmethylamino-acetoyl)oxazolidin-5-one (42). The carbamate **41** (2.54 g, 5.0 mmol) was dissolved in a minimum of DMF (ca. 2−3 mL). The solution was then added to toluene (120 mL), followed by camphorsulfonic acid (50 mg) and paraformaldehyde (5 g). The mixture was heated to reflux until the reaction was complete, ca. 2 h (monitored by TLC, 40% ethyl acetate−hexane). The reaction mixture was concentrated under reduced pressure, and the residue was taken up in ethyl acetate, and the organic layer was washed with saturated aqueous sodium bicarbonate solution to remove acidic material. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography, eluting with 40% ethyl acetate−hexane to afford the oxazolidinone **42** as a foam (2.16 g, 83%). A sample of the foam was recrystallized from hot ether−ethyl acetate to give a solid. Mp 122−123 °C. $[\alpha]^{23}_D$ +60.3° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.04 (m, 20H), 6.77 and 6.53 (2m, 1H), 5.46−4.89 (m, 3H), 4.63−4.20 (m, 2H), 3.30−2.92 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 171.68, 167.90, 152.40, 144.03, 135.33, 128.63, 128.48, 128.27, 127.95, 127.04, 77.83, 77.45, 70.95, 67.70, 52.17, 37.79, 36.82. IR (KBr disk) ν 3352 (CONH), 3088, 3060, 3031 and 3007 (CH, aromatic), 3000−2800 (CH, saturated), 1797 (C═O, oxazolidinone), 1710 (C═O, carbamate), 1685 (C═O, amide), 1519, 1494, 1449, 1417, 1360, 1319, 1256, 1210, 1165, 1130, 1055, 755, 721, 700 cm^{-1}. Anal. Calcd for $C_{32}H_{28}N_2O_5$: C, 73.83; H, 5.42; N, 5.38. Found: C, 73.94; H, 5.39; N, 5.24.

***N*-Benzyloxycarbonyl-*N*-methyl-L-asparagine (43).**[37] The oxazolidinone **42** (1.0 g, 1.9 mmol) was dissolved in chloroform (12 mL) and to this solution was added triethylsilane (1.2 mL) followed by trifluoroacetic acid (12 mL) and the reaction mixture was left to stir at room temperature for 2 d. The reaction mixture was concentrated in vacuo and the residue was chromatographed on silica, eluting with 90:10:0.5 chloroform−methanol−water. The appropriate fractions were combined and concentrated under reduced pressure. The residue was triturated with ether to give the *N*-methyl asparagine **43** as a colorless solid (463 mg, 86%). Mp 134−136 °C. $[\alpha]^{23}_D$ −60.8° (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, CD_3-

(36) Reddy, G. V.; Iyengar, D. S. *Chem. Lett.* **1999**, 299.
(37) Sokolov, V. V.; Kozhushkov, S. I.; Nikolskaya, S.; Belov, V. N.; Es-Sayed, M.; De Meijere, A. *Eur. J. Org. Chem.* **1998**, 777.

OD) δ 7.34−7.25 (m, 5H), 5.11 (s, 2H), 4.89−4.82 (m, 1H), 2.97−2.89 (m, 4H), 2.79−2.66 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD) (rotamers) δ 175.33, 175.11, 173.66, 158.09, 137.96, 137.76, 129.52, 129.05, 128.98, 128.68, 68.68, 68.45, 59.11, 58.53, 36.79, 36.29, 34.05, 33.95. IR (KBr disk) ν 3500−3200 (CO_2H), 3427 and 3219 ($CONH_2$), 3115, 3092, 3067, 3033 and 3009 (CH, aromatic), 3000−2800 (CH, saturated), 1714 (CO_2H), 1679 (C=O, carbamate), 1590, 1484, 1451, 1403, 1370, 1340, 1256, 1228, 1201, 1169, 1011, 773, 739 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.65; H, 5.83; N, 9.93.

Preparation of the Lysine-Derived Oxazolidinones 47 and 48. Deamination via diazotization of the lysine carbamate **44** (870 mg, 3.1 mmol) according to the method of Hutton[38] afforded the acetate **45** and the alkene **46** as a mixture (861 mg) that was not purified. The crude acetate **45** was taken up in benzene (30 mL) and camphorsulfonic acid (35 mg) and paraformaldehyde (3 g) were added. The mixture was heated to reflux for 2 h and then allowed to cool. The mixture was concentrated at reduced pressure, the residue was taken up in ethyl acetate, and the organic layer was washed with saturated aqueous sodium bicarbonate solution to remove acidic material. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography, eluting with 30% ethyl acetate−hexane, to afford first the oxazolidinone **48** as a clear colorless oil (113 mg, 13%). $[\alpha]^{25}_D$ +112.6° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.29 (m, 5H), 5.70 (br s, 1H), 5.49 (br s, 1H), 5.31−4.95 (m, 5H), 4.31 (br s, 1H), 2.12−1.59 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 172.10, 152.68, 136.36, 135.35, 128.58, 128.50, 128.19, 127.69, 115.79, 77.77, 67.80, 67.67, 55.16, 54.96, 54.24, 29.60, 28.43. IR (NaCl) ν 3076 and 3034 (CH, aromatic), 3000−2800 (CH, saturated), 1801 (C=O, oxazolidinone), 1716 (C=O, carbamate), 1506, 1413, 1357, 1316, 1251, 1164, 1128, 1050, 919, 754, 693 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.42; H, 6.31; N, 5.07. Further elution gave the oxazolidinone **47** as a colorless oil (478 mg, 46%). $[\alpha]^{25}_D$ +86.6° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 5H), 5.48 (br s, 1H), 5.23−5.09 (m, 3H), 4.27 (t, 1H, J = 5.2 Hz), 3.97 (t, 2H, J = 6.2 Hz), 2.04−1.76 (m, 2H), 1.98 (s, 3H), 1.61−1.32 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.03, 170.84, 152.78, 135.29, 128.56, 128.49, 128.16, 77.80, 67.80, 63.71, 54.64, 30.18, 27.99, 20.79, 20.76. IR (NaCl) ν 3067 and 3033 (CH, aromatic), 3000−2800 (CH, saturated), 1801 (C=O, oxazolidinone), 1724 (2 × C=O), 1506, 1413, 1361, 1318, 1244, 1167, 1131, 1047, 755, 696 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.80; H, 6.41; N, 4.26.

(*S*)-*N*-Benzyloxycarbonyl-*N*-methyl-2-(3-butenyl)-glycine (49). The oxazolidinone **48** (300 mg, 1.1 mmol) was taken up in chloroform (6 mL), triethylsilane (540 μL) was added followed by trifluoroacetic acid (6 mL), and the mixture was left to stand at room temperature for 2 d. The reaction mixture was diluted with toluene and then concentrated in vacuo and the residue was taken up in ether and extracted with aqueous sodium carbonate solution (4 × 2 mL). The combined aqueous extracts were washed with ether and then acidified to pH ∼2 with 5 M hydrochloric acid. The aqueous phase was then extracted with dichloromethane (3 × 5 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated to give a yellow oil (230 mg). The oil was chromatographed on silica, eluting with 94:5.5:0.5 chloroform−methanol−water, to provide the *N*-methyl amino acid **49** as a clear colorless oil (200 mg, 64%). $[\alpha]^{24}_D$ −16.6° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 10.02 (br s, 1H), 7.34−7.30 (m, 5H), 5.86−5.50 (m, 1H), 5.19−4.63 (m, 5H), 2.89−2.88 (m, 3H), 2.12−1.60 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 176.66, 157.14, 156.45, 136.64, 136.47, 136.32, 136.15, 128.39, 127.97, 127.80, 127.68, 116.03, 115.85, 67.61, 58.06, 57.80, 31.02, 30.63, 30.10, 29.95, 27.96, and 27.69. IR (NaCl) ν 3600−3000 (COOH), 3077 and 3038 (CH, aromatic), 3000−2800 (CH, saturated), 1705 (C=O), 1548, 1451, 1402, 1321, 1210, 1153, 1035, 916, 854, 740, 692 cm^{-1}. HRMS calcd for $C_{15}H_{19}NO_4$ (M + H) 278.1392, found 278.1384.

(*S*)-*N*-Benzyloxycarbonyl-*N*-methyl-2-(4-acetoxybutanyl)-glycine (50). The oxazolidinone **47** (3.26 g, 9.7 mmol) was taken up in dichloromethane (50 mL), triethylsilane (5.0 mL) was added followed by trifluoroacetic acid (50 mL), and the mixture was left to stand at room temperature for 2 d. The reaction mixture was concentrated in vacuo and the residue was taken up in aqueous sodium bicarbonate solution and washed with ether. The aqueous was then acidified with 5 M hydrochloric acid and extracted with dichloromethane. The organic phase was dried ($MgSO_4$), filtered, and evaporated to give a yellow oil (2.69 g, 82%) that was used directly in the next step.

(*S*)-*N*-Benzyloxycarbonyl-*N*-methyl-2-(4-hydroxybutanyl)-glycine (51). The crude acetate 50 (1.67 g, 4.9 mmol) was treated with 1 M sodium hydroxide solution (10.8 mL) at 0 °C and left to stir at that temperature for 1.5 h. The solution was then acidified with dilute hydrochloric acid and extracted with chloroform (6 × 30 mL). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was triturated with ether to afford the alcohol **51** as a colorless solid (1.21 g, 83%). Mp 122−124 °C. $[\alpha]^{24}_D$ −22.3° (*c* 1.0, acetone). ^{1}H NMR [300 MHz, CD_3COCD_3] (rotamers) δ 7.38−7.31 (m, 5H), 5.14−5.12 (m, 2H), 4.76 (dd, 0.5H, J = 4.7, 10.9 Hz), 4.65 (dd, 0.5H, J = 4.7, 10.7 Hz), 3.55 (t, 2H, J = 4.9 Hz), 2.89−2.87 (m, 3H), 1.95−1.35 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 172.99, 157.51, 156.85, 138.06, 129.18, 128.56, 128.34, 67.49, 62.14, 59.03, 32.94, 31.05, 30.57, 29.45, 29.06, 23.37. IR (KBr disk) ν 3600−3200 (CO_2H and OH), 3095 and 3030 (CH, aromatic), 3000−2800 (CH, saturated), 1738 (C=O, acid), 1650 (C=O, carbamate), 1490, 1405, 1322, 1258, 1206, 1162, 1101, 1024, 763 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.87; H, 7.34; N, 4.65.

(*S*)-*N*-Benzyloxycarbonyl-*N*-methyl-2-(4-hydroxybutanyl)-glycine Benzyl Ester (52). The acid **51** (300 mg, 1.0 mmol) was dissolved in dimethylformamide (10 mL). Anhydrous potassium carbonate (210 mg) was added and the mixture was vigorously stirred while benzyl bromide (121 μL) was added. The resulting mixture was stirred at room temperature under a nitrogen atmosphere overnight. It was then diluted with water (150 mL) and extracted with ethyl acetate (3 × 20 mL) and the combined extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give the benzyl ester **52** as a clear gum (343 mg, 87%). A sample was further purified by column chromatography, eluting with 30% ethyl acetate−hexane, to give the pure ester **52**. $[\alpha]^{25}_D$ −23.4° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 7.32−7.24 (m, 10H), 5.18−5.08 (m, 4H), 4.85 (dd, 0.5H, J = 4.9, 10.8 Hz), 4.62 (dd, 0.5H, J = 4.9, 10.5 Hz), 3.59−3.51 (m, 2H), 2.86−2.83 (m, 3H), 2.04−1.30 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 171.34, 171.18, 156.99, 156.23, 136.46, 136.33, 135.49, 135.38, 128.45, 128.35, 128.16, 127.94, 127.79, 127.58, 67.33, 66.67, 62.22, 58.64, 58.36, 31.85, 30.87, 30.21, 28.57, 28.18, 22.24, 22.16. IR (NaCl) ν 3600−3200 (OH), 3094, 3065 and 3036 (CH, aromatic), 3000−2800 (CH, saturated), 1739 (C=O, ester), 1699 (C=O, carbamate), 1456, 1401, 1320, 1257, 1212, 1151, 1069, 909, 742, 693 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.28; H, 7.24; N, 3.72.

N^{α}-Benzyloxycarbonyl-N^{α}-methyl-N^{ϵ}-benzyl-L-lysine Benzyl Ester (53). The alcohol **52** (740 mg, 1.9 mmol) was dissolved in dry dichloromethane (9 mL) and the solution was cooled to −50 °C. Triethylamine (460 μL) was added followed by trifluoromethanesulfonic anhydride (490 μL). After 15 min at −50 °C TLC analysis indicated complete conversion to the corresponding triflate. Benzylamine (0.82 mL) was then added in one portion at −50 °C and the reaction mixture was stirred at this temperature for 30 min and then at room temperature

(38) (a) Hutton, G. E. PCT Int. Appl. 1996, WO9611181; *Chem. Abstr. 125*, 115135. (b) Adger, B.; Dyer, U.; Hutton, G.; Woods, M. *Tetrahedron Lett.* **1996**, *37*, 6399.

overnight. The reaction mixture was diluted with ether (100 mL) and the organic phase was washed with water (3 × 300 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated at reduced pressure. The crude residue was purified by column chromatography, eluting first with 60% ethyl acetate−hexane and then 8% methanol−ethyl acetate, to afford the lysine **53** as a clear oil (710 mg, 78%). $[\alpha]^{25}_D$ −18.6° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 7.34−7.22 (m, 15H), 5.19−5.10 (m, 4H), 4.88 (dd, 0.5H, J = 4.9, 10.7 Hz), 4.64 (dd, 0.5H, J = 4.8, 10.4 Hz), 3.76 (br s, 2H), 2.88−2.85 (m, 3H), 2.61 (br s, 2H), 2.05−1.23 (m, 7H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 171.31, 171.13, 156.85, 156.14, 140.04, 136.49, 136.33, 135.49, 135.37, 128.39, 128.29, 128.21, 128.08, 127.97, 127.88, 127.81, 127.69, 127.53, 126.77, 67.23, 66.56, 58.54, 58.34, 53.74, 48.80, 30.77, 30.12, 29.23, 28.69, 28.33, 23.68. IR (NaCl) ν 3092, 3064 and 3033 (CH, aromatic), 3000−2800 (CH, saturated), 1740 (C=O, ester), 1702 (C=O, carbamate), 1533, 1455, 1399, 1318, 1208, 1145, 1030, 739, 693 cm^{-1}. Anal. Calcd for $C_{29}H_{34}N_2O_4$: C, 73.39; H, 7.22; N, 5.90. Found: C, 73.30; H, 7.35; N, 5.99.

(*S*)-3-Carbonylbenzyloxy-4-(2-ethylsulfanylcarbonyl-ethyl)oxazolidin-5-one (58). To a sample of the glutamic acid oxazolidinone **57** (2.0 g, 6.8 mmol) in dichloromethane (8 mL) was added ethanethiol (1.01 mL, 13.6 mmol) and DMAP (20 mg) and the solution was cooled to 0 °C. DCC (1.69 g, 8.2 mmol) was added in one portion and the reaction mixture was stirred at 0 °C for 30 min. Acetic acid (0.8 mL) was then added and stirring was continued for 10 min. The mixture was diluted with ether (50 mL) and suction filtered. The filtrate was washed sequentially with 10% sodium carbonate solution (2 × 20 mL), water, 0.5 M hydrochloric acid (20 mL), water, and brine. The ethereal solution was then dried ($MgSO_4$), filtered, and concentrated in vacuo to give the thioester **58** as an oil (2.13 g, 92%). A sample was further purified for analytical purposes by column chromatography on silica, eluting with 50% ether−hexane. $[\alpha]^{25}_D$ +99.2° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 5H), 5.42 (br s, 1H), 5.14 (d, 1H, J = 4.5 Hz), 5.12 (s, 2H), 4.27 (t, 1H, J = 5.7 Hz), 2.79 (q, 2H, J = 7.4 Hz), 2.65−2.49 and 2.36−2.11 (2m, 4H), 1.16 (t, 3H, J = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.34, 171.36, 152.64, 135.12, 128.39, 128.29, 128.04, 77.59, 67.72, 53.71, 38.49, 25.95, 23.10, 14.44. IR (NaCl) ν 3097, 3063 and 3033 (CH, aromatic), 3000−2800 (CH, saturated), 1800 (C=O, oxazolidinone), 1718 (C=O, carbamate and thioester), 1500, 1412, 1356, 1317, 1252, 1169, 1131, 1052, 998, 840, 756, 696 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_5S$: C, 56.96; H, 5.68; N, 4.15. Found: C, 56.72; H, 5.57; N, 4.30.

(*S*)-2-(Benzyloxycarbonyl-methyl-amino)-4-ethylsulfanylcarbonyl-butyric Acid (59). A sample of the oxazolidinone **58** (1.0 g, 2.9 mmol) was dissolved in dichloromethane (15 mL), triethylsilane (1.4 mL) was added followed by trifluoroacetic acid (15 mL), and the mixture was left to stand for 3 d at room temperature. The solution was then taken up in toluene (50 mL) and evaporated to dryness under reduced pressure. The residue was then taken up in ether and extracted with 10% sodium carbonate solution. The aqueous layer was washed with ether and then acidified to pH ∼2 with 5 M hydrochloric acid. The aqueous phase was then extracted with dichloromethane (4 × 20 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residual oil (920 mg) slowly crystallized. The solid was recrystallized from ether−hexane to afford the carboxylic acid **59** as a colorless solid (880 mg, 87%). Mp 94−96 °C. $[\alpha]^{24}_D$ −15.6° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.22 (br s, 1H), 7.32−7.27 (m, 5H), 5.14 (s, 2H), 4.85−4.56 (m, 1H), 2.88−2.81 (m, 5H), 2.65−2.05 (m, 4H), 1.21 (t, 3H, J = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 198.17, 175.29, 157.11, 156.27, 136.36, 128.50, 128.08, 127.83, 67.84, 58.46, 40.31, 31.47, 24.49, 23.37, 14.57. IR (KBr disk) ν 3700−3200 (CO_2H), 3134, 3097, 3069 and 3033 (CH, aromatic), 3000−2800 (CH, saturated), 1736, 1687 and 1648 (3 × C=O), 1492, 1455, 1411, 1374, 1325, 1254, 1222, 1174, 1096, 1069, 1017, 989, 767, 739 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24; N, 4.13. Found: C, 56.75; H, 6.30; N, 4.29.

(*S*)-2-(Benzyloxycarbonyl-methyl-amino)-4-ethylsulfanylcarbonyl-butyric Acid Methyl Ester (60). The title compound **60** was prepared by diazomethylation of the carboxylic acid **59** by the standard method.[26] The methyl ester **60** was isolated in 100% yield. $[\alpha]^{24}_D$ −21.8° (*c* 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 7.26−7.17 (m, 5H), 5.06−5.04 (m, 2H), 4.67 and 4.49 (2dd, 1H, J = 5.0, 10.5 Hz), 3.59−3.52 (m, 3H), 2.77−2.71 (m, 5H), 2.58−2.40 and 2.31−1.91 (2m, 4H), 1.12 (t, 3H, J = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 197.68, 170.71, 170.59, 156.42, 155.65, 136.18, 136.03, 128.08, 127.63, 127.49, 127.34, 67.09, 57.90, 51.79, 39.96, 39.68, 31.32, 30.57, 24.29, 23.99, 22.92, 14.34. IR (NaCl) ν 3095, 3063 and 3029 (CH, aromatic), 3000−2800 (CH, saturated), 1743 and 1700 (3 × C=O), 1448, 1403, 1316, 1219, 1180, 1141, 1057, 1007, 907, 742, 695. Anal. Calcd for $C_{17}H_{23}NO_5S$: C, 57.77; H, 6.56; N, 3.96. Found: C, 58.05; H, 6.74; N, 4.15.

(*S*)-2-(Benzyloxycarbonyl-methyl-amino)-5-[*tert*-butoxycarbonylamino-(*tert*-butoxycarbonylimino)methyl]-pentanoic Acid Methyl Ester (63). To a sample of the thioester **60** (200 mg, 0.56 mmol) in acetone (1.0 mL) was added triethylsilane (300 μL) followed by 10% palladium-on-charcoal catalyst (50 mg) and the reaction mixture was stirred vigorously for 1 h. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue aldehyde (61) was purified by chromatography on a short silica column, eluting with 20% ethyl acetate−hexane to remove the triethylsilane. The fractions collected were concentrated in vacuo, the residue was taken up in methanol (4 mL) and ammonium acetate (222 mg) was added followed by sodium cyanoborohydride (71 mg), and the mixture was stirred at room temperature for 30 min. The solution was concentrated at reduced pressure to about 1 mL and it was then diluted with saturated aqueous sodium bicarbonate solution (10 mL). The aqueous phase was then extracted with dichloromethane (3 × 5 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the primary amine **62**. The amine **62** was taken up in chloroform (filtered through neutral alumina, 2 mL), di-boc-triflylguanidine **55** (221 mg, 0.56 mmol) was added followed by diisopropylethylamine (0.15 mL, 0.85 mmol), and the mixture was stirred at room temperature for 2 h. The solution was concentrated under reduced pressure and the residue was purified by chromatography on silica, eluting with chloroform. The material isolated was further purified by chromatography, eluting with 50% ether−hexane, to give the protected *N*-methyl arginine **63** as a clear colorless oil (149 mg, 49%). $[\alpha]^{19}_D$ −13.0° (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 11.45 (br s, 1H), 8.28 (br s, 1H), 7.31−7.23 (m, 5H), 5.12 (d, 1H, J_{AB} = 12.3 Hz), 5.07 (d, 1H, J_{AB} = 12.3 Hz), 4.76 and 4.57 (2dd, 1H, J = 4.8, 10.5 Hz), 3.65−3.58 (m, 3H), 3.43−3.33 (m, 2H), 2.82 (s, 3H), 2.02−1.37 (m, 22H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 171.53, 171.35, 163.30, 156.81, 156.00, 153.12, 136.41, 136.31, 128.84, 128.32, 127.84, 127.58, 82.98, 79.07, 67.34, 58.37, 58.19, 51.99, 40.17, 39.97, 31.07, 30.26, 28.12, 27.89, 26.12, 25.84, 25.73. IR (NaCl) ν 3335 and 3290 (sh, 2 × NH), 3133, 3104, 3076 and 3033 (CH, aromatic), 3000−2800 (CH, saturated), 1712 and 1633 (4 × C=O), 1574, 1446, 1411, 1364, 1327, 1238, 1229, 1141, 1053, 866, 809, 762, 746 cm^{-1}. Anal. Calcd for $C_{26}H_{40}N_4O_8$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.32; H, 7.56; N, 10.22.

(4*S*)-4-{4-[4-Hydroxymethylimino-2-oxy-4*H*-(1,2,3,5)-oxatriazin-5-yl]-propyl}oxazolidin-5-one-3-carboxylic Acid 9*H*-Fluoren-9-ylmethyl ester (66). The nitroarginine carbamate **64** (1.0 g, 2.3 mmol) was dissolved in toluene (50 mL) in a round-bottomed flask fitted for reflux. To the solution was added camphorsulfonic acid (10 mg) and paraformaldehyde (1.5 g) and the mixture was heated to reflux for 1.5 h. The reaction mixture was cooled and the solvent was decanted from residual solid material. The solvent was concentrated in vacuo

and the residue was purified by column chromatography, eluting with 80% ethyl acetate−dichloromethane to afford the oxazolidinone **66** as a colorless foam (750 mg, 67%). $[\alpha]^{22}_D$ +117.8° (*c* 1.0, CH_2Cl_2). ^{1}H NMR [300 MHz, d_6-DMSO, 298 K] δ 9.76 (s, 1H), 7.93−7.34 (m, 8H), 5.35 (s, 2H), 4.94−4.93 (m, 4H), 4.52 (br s, 2H), 4.32 (t, 1H, J = 5.4 Hz), 3.57−3.44 (m, 2H), 3.27 (s, 1H), 1.90−1.25 (br s, 4H). ^{1}H NMR [300 MHz, d_6-DMSO, 333 K] 9.60 (s, 1H), 7.86−7.31 (m, 8H), 5.26 (dd, 2H, J = 20.0, 4.1 Hz), 4.90 (d, 2H, J = 1.2 Hz), 4.84 (s, 2H), 4.54 (m, 2H), 4.28 (t, 1H, J = 5.6 Hz), 4.04 (t, J = 6.4 Hz), 3.24−3.18 (m, 2H), 1.58−1.39 (m, 4H). ^{13}C NMR [75 MHz, d_6-DMSO, 298 K] δ 172.45, 153.74, 152.75, 143.67, 143.59, 140.87, 127.73, 127.21, 124.98, 120.14, 77.75, 77.55, 73.26, 66.82, 54.33, 46.61, 44.98, 26.87, 22.38. ^{13}C NMR [75 MHz, d_6-DMSO, 333 K] δ 171.95, 153.84, 152.44, 143.41 and 143.32, 140.62, 127.39, 126.85, 124.59, 124.56, 119.73, 77.34, 72.99, 66.57, 53.98, 46.49, 44.79, 26.69, 22.17. IR (KBr disk) ν 3289 (OH), 3066, 3041, 3015 and 3007 (CH, aromatic), 3000−2800 (CH, saturated), 1798 (C=O, oxazolidinone), 1713 (C=O, carbamate), 1588, 1557, 1412, 1346, 1196, 1136, 1048, 940, 742, 709 cm^{-1}. HRMS calcd for $C_{24}H_{26}N_5O_7$ (M + H) 498.1842, found 496.1816.

(2*S*)-2-[(9*H*-Fluoren-9-ylmethylmethoxycarbonyl)-methyl-amino]-5-[hydroxymethyl-(2-oxy-6*H*-[1,2,3,5]oxatriazin-4-yl-amino)pentanoic Acid (68). The oxazolidinone **66** (100 mg, 0.2 mmol) was dissolved in dichloromethane (4 mL), triethylsilane (0.3 mL) was added followed by trifluoroacetic acid (4 mL), and the reaction mixture was stirred under a nitrogen atmosphere overnight. The mixture was concentrated at reduced pressure. The residue was purified by column chromatography, eluting with 10% methanol-dichloromethane, to afford the *N*-methyl compound **68** as a colorless foam (60 mg, 60%). $[\alpha]^{22}_D$ −12.9° (*c* 1.0, CH_2Cl_2). ^{1}H NMR [300 MHz, d_6-DMSO, 300 K] δ 9.60 (s, 1H), 7.84−7.26 (m, 8H), 4.90 (s, 2H), 4.88 (s, 2H), 4.35−3.97 (m, 4H), 3.30 (s, 2H), 2.72 (s, 3H), 1.70−1.40 (m, 4H). ^{13}C NMR [75 MHz, d_6-DMSO, 300 K] δ 171.97, 155.63, 153.90, 143.64 and 143.59, 140.54, 127.30, 126.76, 124.65, 119.70, 77.41, 73.04, 66.56, 57.94, 46.62, 44.95, 30.16, 25.10, 24.05. IR (KBr disk) ν 3700−2700 (COOH), 3300−3200 (=NH), 3064, 3039, 3018 and 3009 (CH, aromatic), 1739 (C=O), 1696 (C=O, carbamate), 1589, 1555, 1451, 1409, 1315, 1263, 1195, 1158, 1131, 1028, 992, 760, 741 cm^{-1}. HRMS calcd for $C_{24}H_{28}N_5O_7$ (M + H) 498.1989, found 498.1969.

(*S*)-3-Carbonylbenzyloxy-4-(1-formyl-1*H*-indol-3-ylmethyl)oxazolidin-5-one (72). A mixture of the tryptophan carbamate **71** (3.0 g, 8.2 mmol), benzene (200 mL), camphorsulfonic acid (100 mg), and paraformaldehyde (5 g) was heated to reflux for 1.5 h. The reaction mixture was concentrated under reduced pressure and the residue was taken up in ether. The ethereal layer was washed with saturated aqueous sodium bicarbonate solution, dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil. The oil was further purified by column chromatography, eluting with 60% ether−hexane, to give the oxazolidinone **72** as a colorless foam (2.67 g, 86%). $[\alpha]^{25}_D$ +154.0° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31, 8.89 and 8.33−8.31 (2 × br s and m, 2H), 7.58−7.04 (m, 9H), 5.21 (br s, 3H), 4.59−4.46 (m, 2H), 3.57−3.22 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.73, 159.13, 155.53, 152.36, 135.25, 134.07, 130.74, 128.65, 125.40, 124.67, 124.27, 120.91, 119.68, 118.70, 116.69, 115.91, 109.49, 77.81, 67.86, 55.64, 26.11, 25.06. IR (KBr disk) ν 3100 and 3063 (CH, aromatic), 3000−2800 (CH, saturated), 1801 (C=O, oxazolidinone), 1712 (C=O, carbamate), 1604, 1459, 1417, 1370, 1241, 1198, 1163, 1127, 1047, 1001, 753, 696 cm^{-1}. Anal. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.87; H, 5.06; N, 7.50.

(*S*)-*N*-Carbonylbenzyloxy-*N*-methyl-*N*′-formyl-L-tryptophan (73) and (*S*)-2-Carbonylbenzyloxy-9-formyl-1,3,4,9-tetrahydro-*β*-carboline-3-carboxylic Acid *tert*-Butyl Ammonium Salt (75). To a mixture of the oxazolidinone **72** (500 mg, 1.3 mmol), chloroform (8 mL), and triethylsilane (0.6 mL) was added trifluoroacetic acid (8 mL) and the whole was left to stand at room temperature for 2 d. The mixture was then concentrated at reduced pressure and the residue was taken up in ether. The ethereal solution was extracted with saturated aqueous sodium bicarbonate solution (3 × 10 mL). The combined aqueous extracts were acidified with dilute hydrochloric acid and extracted with dichloromethane (3 × 20 mL). The extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was purified by column chromatography, eluting with 95:5:0.5:0.2 chloroform−methanol−water−acetic acid to give first the *β*-carboline **74** as an oil (340 mg, 68%). The *β*-carboline can be converted to the *tert*-butylammonium salt **75** by taking it up in ether and adding an equivalent of *tert*-butylamine. The precipitated *tert*-butylammonium salt **75** can be recrystallized from hot methanol. Mp 162−165 °C. $[\alpha]^{24}_D$ +41.3° (*c* 1.0, MeOH). ^{1}H NMR [300 MHz, d_6-DMSO] δ 9.68, 9.32 and 8.21−7.93 (2 × br s and m, 4H), 7.48−7.23 (m, 9H), 5.17−4.71 (m, 5H), 3.44−3.39 (m, 1H), 2.78−2.72 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 172.56, 159.08, 155.94, 155.77, 137.14, 136.06, 135.27, 130.34, 128.33, 127.70, 127.62, 127.42, 127.18, 123.75, 118.41, 114.77, 110.76, 66.07, 54.19, 50.06, 42.12, 27.19, 23.44, 23.21. IR (KBr disk) ν 3000−2800 (CH, saturated), 2743, 2636 and 2554 (NH_3^+), 1711 (C=O, carbamate), 1637 (CO_2^-), 1568, 1422, 1386, 1358, 1301, 1222, 1102, 1066, 748, 697 cm^{-1}. Anal. Calcd for $C_{25}H_{29}N_3O_5$: C, 66.50; H, 6.47; N, 9.31. Found: C, 66.67; H, 6.54; N, 9.20. Further elution afforded the *N*-methyl tryptophan **73** as a solid (110 mg, 22%). Mp 129−130 °C. $[\alpha]^{25}_D$ −49.6° (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) (rotamers) δ 9.35, 8.83 and 8.38−8.36 (2 × br s and m, 2H), 7.63−6.94 (m, 9H), 5.14−5.01 (m, 3H), 3.50−3.09 (m, 2H), 2.89−2.83 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 175.25, 159.41, 156.88, 155.94, 136.29, 135.92, 134.33, 130.96, 128.52, 128.19, 127.79, 125.55, 124.89, 124.67, 124.21, 122.75, 119.75, 118.58, 116.26, 109.71, 67.83, 67.71, 58.66, 58.39, 31.97, 31.81, 24.68, 24.16. IR (KBr disk) ν 3600−3200 (CO_2H), 3091 and 3056 (CH, aromatic), 3000−2800 (CH, saturated), 1749 (C=O, acid), 1675 (CO, carbamate), 1605, 1459, 1392, 1319, 1251, 1191, 1135, 983, 795, 755, 699 cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.20; H, 5.39; N, 7.16.

(*S*)-3-Carbonylbenzyloxy-4-[1-carbonylbenzyloxy-2,3-dihydroindol-3(*R*,*S*)-ylmethyl]oxazolidin-5-one (77). The dihydrotryptophan **76**[30] (2.0 g, 4.2 mmol) was dissolved in toluene (100 mL) and the solution was treated with camphorsulfonic acid (60 mg) and paraformaldehyde (5 g) and heated at reflux for 1 h. The clear solution was concentrated in vacuo and the residue was taken up in ethyl acetate and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give a tan oil (1.56 g). The oil was purified by column chromatography, eluting with 20% ethyl acetate−hexane, to give the oxazolidinone **77** as a colorless oil (1.38 g, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89−6.93 (m, 14H), 5.53 (br s, 1H), 5.26−5.09 (m, 5H), 4.22−4.18 and 3.78−3.35 (2 × m, 4H), 2.31−2.12 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.71, 153.18, 152.78, 142.01, 136.16, 135.01, 132.87, 128.65, 128.49, 128.32, 128.12, 127.98, 123.86, 122.70, 114.84, 77.63, 68.21, 68.11, 66.92, 53.56, 53.16, 36.76, 36.38, 35.66. IR (NaCl) ν 3000−2800 (CH, saturated), 1798 (C=O, oxazolidinone), 1712 (CO, carbamate), 1599, 1457, 1412, 1347, 1261, 1140, 1032, 752 cm^{-1}. Anal. Calcd for $C_{28}H_{26}N_2O_6$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.37; H, 5.67; N, 5.57.

***N*,*N*′-Bis-carbonylbenzyloxy-3(*R*,*S*)-3-[2(*S*)-2-carboxy-2-methylamino-ethyl]-*N*-methyl-2,3-dihydroindole (78).** To a solution of the dihydrotryptophan oxazolidinone **77** (1.2 g, 2.5 mmol) in chloroform (13 mL) was added triethylsilane (1.2 mL) and trifluoroacetic acid (13 mL). The mixture was left to stand for 2 d and then diluted with toluene and concentrated under reduced pressure. The greenish residue was chromatographed on a short silica gel column, eluting with chloroform−methanol−water 93:6.5:0.5. The appropriate fractions were collected and the solvent was removed in vacuo. The residue was further purified by chromatography, eluting with the same solvent system, to give the *N*-methyl dihydro-

tryptophan **78** as a clear pale yellow oil (1.0 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−6.94 (m, 14H), 5.26−5.11 (m, 4H), 5.00−4.90 and 4.77−4.69 (2 × m, 1H), 4.18−3.96 and 3.79−3.22 (2 × m, 3H), 2.95−2.88 (m, 3H), 2.42−1.95 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.75, 174.48, 157.03, 156.21, 152.87, 141.84, 136.11, 135.87, 133.36, 128.49, 128.43, 128.14, 128.03, 127.69, 124.38, 123.52, 122.78, 114.96, 67.77, 67.02, 57.03, 56.74, 53.21, 36.28, 34.54, 34.06, 31.07. IR (NaCl) ν 3500−3200 (CO_2H), 3064 and 3038 (CH, aromatic), 3000−2800 (CH, saturated), 1703 (C═O), 1600, 1487, 1456, 1411, 1321, 1214, 1146, 1089, 1035, 971, 911, 856, 746, 697 cm^{-1}. HRMS calcd for $C_{28}H_{28}N_2O_6$ (M^+) 488.1947, found 488.1944.

***N*,*N*^{imid}-Biscarbonylbenzyloxy-L-histidine Methyl Ester (80).** A sample of the methyl ester **79** (1.0 g, 4.1 mmol) in acetonitrile (25 mL) was cooled to 0 °C with vigorous stirring and triethylamine (2.3 mL) was added followed by BnOCO$_2$-Succ (2.16 g, 8.7 mmol). The reaction mixture was stirred at 0 °C for 30 min and then at room temperature overnight. The solution was concentrated at reduced pressure and the residue was taken up in ethyl acetate and washed with water (3 × 25 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated in vacuo to give a pale yellow oil (1.57 g). The oil was purified by column chromatography on silica, eluting with 40% ethyl acetate−hexane, to give the carbamate **80** as a colorless oil, which slowly crystallized on standing (1.3 g, 72%). Mp 63−65 °C. $[\alpha]^{22}_D$ +28.0° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.41−7.24 (m, 10H), 7.17 (s, 1H), 6.10 (d, 1H, J = 8.1 Hz), 5.35 (s, 2H), 5.07 (s, 2H), 4.67−4.61 (m, 1H), 3.68 (s, 3H), 3.12−2.99 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.68, 155.83, 148.13, 138.76, 136.82, 136.25, 133.78, 129.04, 128.71, 128.58, 128.29, 127.89, 114.51, 69.74, 66.71, 53.36, 52.25, 29.80. IR (KBr disk) ν 3342 (CONH), 3175, 3139, 3108 and 3040 (CH, aromatic), 3000−2800 (CH, saturated), 1755 (C═O, ester), 1695 (C═O, carbamate), 1531, 1447, 1409, 1257, 1015, 871, 736, 697 cm^{-1}. Anal. Calcd for $C_{23}H_{23}N_3O_6$: C, 63.15; H, 5.30; N, 9.61. Found: C, 63.35; H, 5.26; N, 9.78.

***N*-Carbonylbenzyloxy-*N*^{imid}-(2,4-dinitrophenyl)-L-histidine Methyl Ester (81).** The bis-carbamate **80** (1.0 g, 2.3 mmol) was dissolved in propylamine (30 mL) and the solution was left to stir at room temperature for 1 h. The solvent was removed by evaporation at reduced pressure. The residue was taken up in ethyl acetate (100 mL) and the solution was again concentrated under reduced pressure. The residue was taken up in acetonitrile (20 mL) and triethylamine (0.64 mL) was added in one portion followed by 1-fluoro-2,4-dinitrobenzene (336 μL) and the solution was left to stir in the dark overnight. The solution was concentrated in vacuo and the residue was taken up in ethyl acetate and washed with water (3 × 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to provide a crude yellow oil (1.5 g). The oil was chromatographed on silica, eluting with 88:10:2 dichloromethane−acetone−methanol, to give the methyl ester **81** as a yellow gum (0.9 g, 84%). $[\alpha]^{23}_D$ +23.7° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, 1H, J = 2.4 Hz), 8.53 (dd, 1H, J = 2.4, 8.7 Hz), 7.76 (s, 1H), 7.67 (d, 1H, J = 8.7 Hz), 7.31−7.24 (m, 5H), 6.84 (s, 1H), 6.12 (d, 1H, J = 8.1 Hz), 5.07 (s, 2H), 4.69−4.66 (m, 1H), 3.71 (s, 3H), 3.15 (d, 2H, J = 3.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.71, 155.97, 146.98, 144.32, 139.15, 134.68, 136.46, 129.31, 128.43, 128.30, 128.05, 121.28, 117.44, 66.89, 53.48, 52.54, 29.85. IR (NaCl) ν 3348 (CONH), 3109, 3067 and 3021 (CH, aromatic), 3000−2800 (CH, saturated), 1717 (C═O), 1609, 1536 and 1346 (NO_2), 1449, 1255, 1214, 1055, 911, 835, 743 cm^{-1}.

***N*-Carbonylbenzyloxy-*N*^{imid}-(2,4-dinitrophenyl)-L-histidine Hydrochloride Salt (82).**[40] The methyl ester **81** (900 mg, 1.9 mmol) was dissolved in a mixture of glacial acetic acid (10 mL) and 2 M hydrochloric acid (10 mL) and the solution was left in the dark at room temperature for 3 d. The mixture was then concentrated at reduced pressure. The residue crystallized on standing and was purified by recrystallization from methanol−ether to afford the hydrochloride salt **82** as a pale yellow solid (870 mg, 92%). Mp 169−171 °C. $[\alpha]^{30}_D$ −8.1° (*c* 1.0, MeOH). ^{1}H NMR [300 MHz, d_6-DMSO] δ 9.48 (s, 1H), 9.00 (s, 1H), 8.81 (d, 1H, J = 8.7 Hz), 8.15 (d, 1H, J = 8.7 Hz), 7.81−7.78 (m, 2H), 7.38−7.27 (m, 5H), 5.03 (d, 1H, J_{AB} = 12.5 Hz), 4.99 (d, 1H, J_{AB} = 12.6 Hz), 4.46−4.39 (m, 1H), 3.28−3.05 (m, 2H). ^{13}C NMR [75 MHz, d_6-DMSO] δ 172.20, 156.06, 148.12, 143.87, 136.83, 136.75, 132.99, 131.86, 131.52, 129.45, 128.34, 127.82, 127.69, 121.53, 120.56, 65.61, 52.90, 26.51. IR (KBr disk) ν 3403 (CONH), 3200−2500, (CO_2H), 3112 and 3064 (CH, aromatic), 3000−2800 (CH, saturated), 2604, ($^+$NH Cl$^-$), 1705 (C═O), 1614, 1542 and 1345 (NO_2), 1447, 1389, 1241, 1056, 911, 843, 745, 697, 633 cm^{-1}. Anal. Calcd for $C_{20}H_{18}ClN_5O_8$: C, 48.84; H, 3.69; N, 14.24. Found: C, 48.87; H, 3.83; N, 14.23.

(*S*)-3-Carbonylbenzyloxy-4-[3*H*-3-(2,4-dinitrophenyl)-imidazol-4-ylmethyl]oxazolidin-5-one (83). To a solution of the carbamate **82** (200 mg, 0.4 mmol) in glacial acetic acid (5 mL) was added camphorsulfonic acid (10 mg), acetic anhydride (50 mL), and paraformaldehyde (50 mg). The mixture was heated with stirring at 85 °C for 2.5 h under a nitrogen atmosphere. The mixture was cooled to room temperature and then concentrated at reduced pressure. The residue was taken up in ethyl acetate and washed with aqueous sodium carbonate solution (10% w/v, 3 × 20 mL). The ethyl acetate phase was dried ($MgSO_4$), filtered and evaporated to dryness. The residual material was further purified by column chromatography, eluting with ethyl acetate, to give the oxazolidinone **83** as a yellow foam (133 mg, 66%). $[\alpha]^{25}_D$ +148.3° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (d, 1H, J = 2.5 Hz), 8.54 (dd, 1H, J = 2.5, 8.7 Hz), 7.66 (d, 1H, J = 8.7 Hz), 7.62 (s, 1H), 7.32−7.24 (m, 5H), 6.84−6.64 (m, 1H), 5.37 (br s, 1H), 5.26−5.10 (m, 2H), 4.89 (d, 1H, J = 3.7 Hz), 4.51−4.49 (m, 1H), 3.49−3.37 (m, 1H), 3.18 (dd, 1H, J = 2.4, 14.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.03, 152.31, 146.95, 144.35, 138.27, 136.69, 135.64, 134.88, 129.36, 128.53, 128.39, 128.29, 121.24, 117.95, 78.10, 67.69, 54.61, 28.57, 27.77. IR (KBr disk) ν 3110 (CH, aromatic), 3000−2800 (CH, saturated), 1800 (C═O, oxazolidinone), 1714 (C═O, carbamate), 1611, 1540 and 1352 (NO_2), 1503, 1419, 1253, 1132, 1051, 835, 748, 699 cm^{-1}. Anal. Calcd for $C_{21}H_{17}N_5O_8$: C, 53.96; H, 3.67. Found: C, 53.82; H, 3.72.

***N*-Carbonylbenzyloxy-*N*-methyl-*N*′-(2,4-dinitrophenyl)-L-histidine (84).** To a solution of the oxazolidinone **83** (460 mg, 1.0 mmol) in chloroform (5 mL) was added triethylsilane (470 mL) and trifluoroacetic acid (5 mL) and the reaction mixture was left to stand for 2 d. The solution was then concentrated under reduced pressure. The residue was taken up in a minimum of 95% chloroform−methanol and the precipitate, which formed, was filtered off at the pump to give the *N*-methyl amino acid **84** (225 mg). The filtrate was concentrated in vacuo and the residue was purified by column chromatography, eluting with 92:7.5:0.5 chloroform−methanol−water, to afford the *N*-methyl amino acid **84** (150 mg). The combined solids were recrystallized from methanol−ether to give the title compound **84** as a solid (375 mg, 81%). Mp 165−167 °C. $[\alpha]^{25}_D$ −24.7° (*c* 1.0, MeOH). ^{1}H NMR [300 MHz, d_6-DMSO] (rotamers) δ 8.92−8.91 (m, 1H), 8.65−8.62 (m, 1H), 7.98 (br s, 1H), 7.92−7.88 (m, 1H), 7.28−7.19 (m, 6H), 5.04−4.95 (m, 2H), 4.88−4.79 (m, 1H), 3.13−2.99 (m, 2H), 2.82−2.79 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) (rotamers) δ 172.14, 155.80, 155.47, 146.22, 143.52, 139.72, 137.03, 136.85, 134.63, 129.36, 128.69, 128.32, 127.67, 127.21, 127.11, 121.32, 117.06, 116.94, 66.29, 66.18, 58.93, 58.79, 31.83, 31.64, 27.61, 27.14. IR (KBr disk) ν 3600−3200 (CO_2H), 3185, 3130 and 3041 (CH, aromatic), 3000−2800 (CH, saturated), 1734 (C═O, acid), 1680 (C═O, carbamate), 1618, 1545 and 1347 (CNO_2), 1492, 1460, 1402, 1308, 1187, 1143, 1087, 842 cm^{-1}. Anal. Calcd for $C_{21}H_{19}N_5O_8$: C, 53.73; H, 4.08; N, 14.92. Found: C, 53.55; H, 4.07; N, 14.65.

(39) Walter, M. W.; Adlington, R. M.; Baldwin, J. E.; Schofield, C. J. *J. Org. Chem.* **1998**, *63*, 5179.
(40) Siepmann, E.; Zahn, H. *Biochim. Biophys. Acta* **1964**, *82*, 412.

***N*-Methyl-L-proline (87).** L-Proline **86** (2.0 g, 17.4 mmol) was dissolved in methanol (20 mL) and to this solution was added 40% aqueous formaldehyde solution (1.4 mL, 19.1 mmol). This was followed by the addition of 10% palladium-on-charcoal catalyst (500 mg) and the resulting slurry was stirred in a hydrogen atmosphere overnight. The slurry was then filtered through a Celite pad to remove the catalyst. The pad was washed with methanol and the combined filtrates were concentrated under reduced pressure. The residue was taken up in ethanol−benzene (1:1, 100 mL) and concentrated a second time to provide a solid, which was recrystallized from methanol−diethyl ether. In this way *N*-methyl proline **87** was isolated as fine needles (2.2 g, 98%). Mp 142−145 °C. $[\alpha]^{23}_{D}$ −78.0° (*c* 2.0, MeOH). ^{1}H NMR (300 MHz, D_2O) δ 3.71−3.65 and 3.55−3.51 (2m, 1H), 3.00−2.91 (m, 1H), 2.74 (s, 3H), 2.34−2.28 (m, 1H), 1.99−1.78 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.06, 70.18, 55.83, 40.26, 28.34, 22.37. IR (KBr disk) ν 3000−2800 (CH, saturated), 2675 and 2605 (ammonium ion), 1669 (CO_2H), 1612 (CO_2^-), 1468, 1401, 1354, 1327, 1234, 1183, 1112, 1056, 1025, 808, 775 cm^{-1}. HRMS calcd for $C_6H_{11}NO_2$ (M^+) 129.0790, found 129.0784.

Acknowledgment. We thank La Trobe University and the Australian Government for the provision of Post-Graduate scholarships. This research was supported by an Australian Research Council Small Grant.

JO026722L