FULL PAPER

DOI: 10.1002/ejoc.200700669

Reactivity of Dehydroamino Acids and Dehydrodipeptides Towards *N*-Bromosuccinimide: Synthesis of β-Bromo- and β,β-Dibromodehydroamino Acid Derivatives and of Substituted 4-Imidazolidinones

Paula M. T. Ferreira,^{*[a]} Luís S. Monteiro,^{*[a]} Goreti Pereira,^[a] Liliana Ribeiro,^[a] Joana Sacramento,^[b] and Liseta Silva^[a]

Keywords: Amino acids / Peptides / Bromination reactions / Imidazolidinones

We have developed a modification of our previously reported high-yielding method for the synthesis of N₁N-diacyldehydroamino acid derivatives to prepare N-monoprotected dehydroamino acids and dehydrodipeptides. Thus, several dehydroalanine, dehydroaminobutyric acid and dehydrophenylalanine derivatives have been prepared by treating the corresponding L-serine, L-threonine and D,L-3-phenylserine (threo-type) derivatives with 1 equiv. of di-tert-butyl dicarbonate and 4-(dimethylamino)pyridine. The reaction proceeded with the initial formation of an O-tert-butyl carbonate which, by treament with $N_1N_1N'_1N'$ -tetramethylguanidine, underwent β elimination to give the corresponding dehydroamino acid derivative. This two-step method can be carried out as a one-pot procedure and is stereoselective, giving only the Z isomer. The N-monoprotected dehydroamino acids were treated with N-bromosuccinimide and thereafter

Introduction

In our laboratories we have developed an efficient method for the synthesis of N,N-diacyldehydroamino acid derivatives by using di-tert-butyl dicarbonate (Boc₂O) and 4-(dimethylamino)pyridine (DMAP) as catalyst in dry acetonitrile at room temperature.^[1,2] Owing to the high reaction yields and to the simple work-up procedures we were able to prepare these compounds in large amounts and to use them as substrates in other types of reactions to obtain new amino acids such as β -substituted alanines,^[3] α -aminoglycines,^[4] furanic amino acids^[5] and β , β -diaryl- or heteroaryl-dehydroamino acids.^[6] These dehydroamino acids were synthesized by Suzuki cross-coupling reactions of a β,β-dibromodehydroalanine^[6a] or β-bromodehydrophenylalanines^[6b] with several aryl- or heteroarylboronic acids. However, to prepare brominated dehydroamino acids from N,N-diacyldehydroamino acid derivatives it was always nec-

[a] Department of Chemistry, University of Minho, Gualtar, 4710-057 Braga, Portugal Fax: +351-253604382
E-mail: pmf@quimica.uminho.pt monteiro@quimica.uminho.pt
[b] Faculdade de Ciências, University Agostinho Neto, Av. 4 de Fevereiro no. 71, Luanda, Angola creased stereoselectivity towards the formation of the Z isomer was observed with dehydrophenylalanine and when 4tolylsulfonyl was used as the *N*-protecting group. In the case of dehydrodipeptides, the reaction with NBS and triethylamine afforded the corresponding brominated dehydrodipeptides when the *N*-protecting group was other than 4-tolylsulfonyl. However, when the reagent was a peptide with a dehydroamino acid as the second residue and an *N*-(4-tolylsulfonyl) group the corresponding 2,2-disubstituted 1-(4-tolylsulfonyl)imidazolidin-4-ones were obtained in good-tohigh yields. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2007)

with triethylamine to afford several β , β -dibromodehydroalanines or β -bromo-, β -alkyl- or β -aryldehydroalanines. The

latter were obtained as mixtures of *E* and *Z* isomers. An in-

essary to remove one of the *N*-protecting groups before the reaction with *N*-bromosuccinimide (NBS). Usually a *tert*-butyloxycarbonyl group (Boc) was cleaved by treatment with trifluoroacetic acid.^[6b] Thus, it was clear to us that a modification of our method for the synthesis of *N*,*N*-diprotected dehydroamino acids allowing the preparation of *N*-monosubstituted compounds would be an advantage in the synthesis of halogenated dehydroamino acids.

The reaction sequence leading to N,N-diacyldehydroamino acids proceeds with the initial formation of a tertbutyl carbonate which undergoes β elimination to the final product after a tert-butyloxycarbonyl group has been bound to the amine function. In this case the second acyl group is the driving force for the elimination process.^[1] Bearing this in mind and the fact that the β elimination of O-(4-tolylsulfonyl)- and O-dichloroacetyl-β-hydroxyamino acids to yield the corresponding dehydroamino acid derivatives with bases such as DBU, DABCO or triethylamine has already been reported,^[7a-7f] we decided to use the base N, N, N', N'-tetramethylguanidine (TMG) to induce elimination of the tert-butyl carbonate group from the O-(tertbutyloxycarbonyl)-β-hydroxyamino acid derivatives. The Nmonoprotected dehydroamino acid derivatives were obtained in good yields and in the case of β -substituted β -

WILEY

hydroxyamino acid derivatives (*threo* configuration) the only products isolated were the Z isomers.

Thus, we report herein the synthesis of *N*-monoprotected dehydroamino acids and dehydrodipeptides by two strategies. 1) The treatment of β -hydroxyamino acid derivatives with 2 equiv. of Boc₂O in the presence of DMAP followed by cleavage of a *tert*-butyloxycarbonyl group with TFA. 2) The synthesis of *O*-*tert*-butyl carbonates by using 1 equiv. of Boc₂O in the presence of DMAP followed by treatment with TMG.

The *N*-monoprotected dehydroamino acids and dehydrodipeptides obtained were then treated with *N*-bromosuccinimide (NBS) and triethylamine^[8] to afford the corresponding β , β -dibromo- and β -bromo β -substituted dehydroalanine derivatives in good yields. It was found that when the *N*-protecting group was 4-tolylsulfonyl the dipeptides containing a dehydroamino acid in the C-terminal position gave by treatment with NBS and NEt₃, *N*-(4-tolylsulfonyl)imidazolidin-4-ones. The imidazolidinone ring is part of a series of matrix metalloproteinase inhibitors that have great potential in the treatment of a variety of diseases including arthritis and cancer.^[9]

Results and Discussion

Several methyl esters of *N*-protected β -hydroxyamino acids [L-serine, L-threonine and D,L-3-phenylserine (*threo* type)] were treated with 1 equiv. of Boc₂O and DMAP in dry acetonitrile to give the corresponding *O*-tert-butyl carbonates (Scheme 1, Table 1). These compounds were then treated with a 2% solution of TMG in acetonitrile to afford the *N*-monoprotected dehydroamino acids in good yields (Scheme 1, Table 1). This two-step method can also be carried out as a one-pot procedure (Scheme 1, Table 1). In the case of β -substituted- β -hydroxyamino acids it was found that *O*-tert-butyloxycarbonyl-L-threonine and D,L-3-phenylserine (*threo* configuration) underwent elimination to yield only the Z isomer. This stereoselectivity is in agreement with a *trans* E_2 elimination which was also considered by Olsen and co-workers^[7d] to be the mechanism involved in the synthesis of dehydroaminobutyric acid derivatives from *O*-(4-tolylsulfonyl)threonines (*threo* type). The stereochemistry of these β -substituted dehydroamino acids was determined by NOE difference experiments by irradiating the α -NH and OCH₃ protons and observing the effect on the β -methyl and β -phenyl protons.



Scheme 1. Synthesis of the dehydroamino acid derivatives.

Olsen co-workers^[7d] reported the synthesis of Z-Z- Δ Abu-OMe (**3f**) and Tos-Z- Δ Abu-OMe (**3h**) by the reaction of Z-Thr(*O*-Tos)-OMe and Tos-Thr(*O*-Tos)-OMe with DABCO. The reaction yields (85 and 81%, respectively) are similar to those obtained by us when Z-Thr(*O*-Boc)-OMe and Tos-Thr(*O*-Boc)-OMe were treated with TMG (84 and 91%, respectively). However, the yields reported for the synthesis of the *O*-(4-tolylsulfonyl)threonines were smaller (71 and 79%, respectively) than those obtained by us in the synthesis of *O*-(*tert*-butyloxycarbonyl)threonines (86 and 90%, respectively). Thus, the overall yields were 60 and 64%,

Table 1. Yields obtained in synthesis of N-monoprotected dehydroamino acid esters from L-serine, L-threonine and D,L-3-phenylserine (*threo* type).

Reagent	2	% Yield	3	% Yield
Boc-Ser-OMe (1a)	Boc-Ser(O-Boc)-OMe (2a)	80	Boc- Δ Ala-OMe (3a) ^[1]	87
Boc-Ser-OMe (1a)	_	_	Boc- Δ Ala-OMe (3a) ^[1]	82
Z-Ser-OMe (1b)	Z-Ser(<i>O</i> -Boc)-OMe (2b)	86	Z- Δ Ala-OMe (3b) ^[10]	82
Z-Ser-OMe (1b)	-	_	Z- Δ Ala-OMe (3b) ^[10]	90
$Z(NO_2)$ -Ser-OMe (1c)	$Z(NO_2)$ -Ser(O-Boc)-OMe (2c)	83	$Z(NO_2)$ - ΔAla -OMe (3c)	85
$Z(NO_2)$ -Ser-OMe (1c)	_	_	$Z(NO_2)$ - Δ Ala-OMe (3c)	90
Tos-Ser-OMe (1d)	Tos-Ser(O-Boc)-OMe (2d)	81	Tos- Δ Ala-OMe (3d)	_
Tos-Ser-OMe (1d)	_	_	Tos- Δ Ala-OMe (3d)	65
Boc-Thr-OMe (1e)	Boc-Thr(O-Boc)-OMe (2e)	87	Boc-Z- Δ Abu-OMe (3e) ^[1]	98
Boc-Thr-OMe (1e)	_	_	Boc-Z- Δ Abu-OMe (3e) ^[1]	82
Z-Thr-OMe (1f)	Z-Thr(O -Boc)-OMe (2f)	86	$Z-Z-\Delta Abu-OMe (3f)^{[1]}$	84
Z-Thr-OMe (1f)	_	_	$Z-Z-\Delta Abu-OMe (3f)^{[1]}$	83
$Z(NO_2)$ -Thr-OMe (1g)	$Z(NO_2)$ -Thr(O-Boc)-OMe (2g)	89	$Z(NO_2)$ -Z- Δ Abu-OMe (3g) ^[1]	95
$Z(NO_2)$ -Thr-OMe (1g)	-	_	$Z(NO_2)$ -Z- Δ Abu-OMe (3g) ^[1]	91
Tos-Thr-OMe (1h)	Tos-Thr(O-Boc)-OMe (2h)	90	Tos- Z - Δ Abu-OMe (3h)	91
Tos-Thr-OMe (1h)	_	_	Tos- Z - Δ Abu-OMe (3h)	86
Boc-Phe(β -OH)-OMe (1i)	Boc-Phe(β -O-Boc)-OMe (2i)	82	Boc-Z- Δ Phe-OMe (3i) ^[3b]	88
Boc-Phe(β-OH)-OMe (1i)	-	_	Boc-Z- Δ Phe-OMe (3i) ^[3b]	81
Tos-Phe(β -OH)-OMe (1j)	Tos-Phe(β -O-Boc)-OMe (2j)	73	Tos- Z - Δ Phe-OMe (3j)	_
Tos-Phe(β-OH)-OMe (1j)	_	-	Tos- Z - Δ Phe-OMe ($3j$)	81

respectively, by using the Tos-Cl/pyridine/DABCO method and 72 and 82% by using our $Boc_2O/DMAP/TMG$ procedure. These latter results are similar to those reported by us using 2.2 equiv. of Boc_2O in the presence of DMAP followed by treatment with TFA (72 and 74%, respectively).^[1]

FULL PAPER

When the reagent was Tos-Ser-OMe (1d) we were able to prepare the corresponding *tert*-butyl carbonate in good yield (81%). This compound, when treated with TMG, gave immediately the corresponding dehydroalanine derivative (3d), however, the product was found to be highly unstable in the presence of base giving 4-toluenesulfonamide.

The *N*-monoprotected dehydroamino acids were treated with 2.2 equiv. of NBS and then with NEt₃ to give β , β dibromodehydroalanines in yields of between 52 and 86% depending on the *N*-protecting group (Scheme 2, Table 2). Compound **4a** had already been prepared by us and used together with aryl- and heteroarylboronic acids in Suzuki cross-coupling reactions to synthesize aryl- or heteroaryldehydroalanine derivatives.^[6a,11]



Scheme 2. Synthesis of β , β -dibromodehydroalanines.

The Z isomers of dehydroaminobutyric acid and dehydrophenylalanine derivatives were treated with 1.1 equiv. of NBS and NEt₃ to give the corresponding β -substituted β bromodehydroalanine (compounds 5e-h and 6i,j, respectively) in yields ranging from 78 to 97% (Scheme 3, Table 2). According to the mechanism proposed^[8] for this reaction the dehydroamino acid reacts with NBS to give a β -bromo β -imino ester which upon treatment with NEt₃ yields the β-bromo enamine. In all cases except for Tos- $\Delta Phe(\beta-Br)$ -OMe (6j), a mixture of E and Z isomers were obtained which could be separated by column chromatography. It was found that there is an increase in stereoselectivity towards the Z isomer with the dehydrophenylalanine derivative. This result is in agreement with those obtained by Nunami and co-workers^[12a] who reported a 1:2 E/Z ratio for the bromination of the methyl ester of N-formyl-Zdehydrophenylalanine and a 1:1 E/Z ratio for the bromination of the methyl ester of N-formyl-Z-dehydroaminobutyric acid. An increase in Z stereoselectivity was also found when the 4-tolylsulfonyl group was used as the N-protecting group (5h). In the case of compound 6j, which has an N-(4-tolylsulfonyl) group and is a derivative of dehydrophenylalanine, only the Z isomer was obtained.



Scheme 3. Synthesis of β -bromo- β -substituted dehydroamino acids.

The stereochemistry of the β -bromodehydroamino acids was determined by NOE difference experiments by irradiating the α -NH and OCH₃ protons and observing the effect on the β -methyl and β -phenyl protons. As reported by other authors,^[12a,12b] we found that for compounds with an alkyl substituent at the β position (**5e**–**g**) the chemical shift of the γ -CH₃ protons of the *E* isomers is observed at a higher field relative to that of the corresponding *Z* isomer (Table 3). However, in the case of Tos- Δ Abu(β -Br)-OMe (**5h**), the chemical shift of the γ -CH₃ protons of the *E* isomer appears at a lower field ($\delta = 2.63$ ppm in CDCl₃) which is probably due to the proximity of the 4-tolylsulfonyl group.

Several dehydrodipeptides were prepared from the corresponding dipeptides containing L-serine, L-threonine and D,L-3-phenylserine by using 3.3 equiv. of Boc₂O in the presence of DMAP followed by cleavage of the Boc groups with TFA (Scheme 4, Table 4).

The *O-tert*-butyl carbonates of dipeptides containing β -hydroxyamino acids were obtained by using 1 equiv. of Boc₂O in the presence of DMAP. These compounds in the presence of TMG afforded the corresponding dehydrodipeptides in good yields (Scheme 5, Table 5).

Compound **9f** was obtained in a 77% yield by using $Boc_2O/DMAP$ followed by TMG which is slightly less than that obtained by using 3.3 equiv. of $Boc_2O/DMAP$ and

Table 2. Results obtained in the synthesis of β-brominated dehydroamino acid derivatives.

Reagent	Product	% Yield	E/Z
Boc-ΔAla-OMe (3a)	Boc- Δ Ala(β , β -Br)-OMe (4) ^[6a]	52 ^[6a]	_
$Z-\Delta Ala-OMe(3b)$	$Z-\Delta Ala(\beta,\beta-Br)-OMe$ (4b)	86	_
$Z(NO_2)$ - Δ Ala-OMe (3c)	$Z(NO_2)-\Delta Ala(\beta,\beta-Br)-OMe$ (4c)	75	_
Boc- Δ Abu-OMe (3e)	Boc- $\Delta Abu(\beta$ -Br)-OMe (5 e) ^[13]	92 ^[13]	$1:1^{[13]}$
$Z-\Delta Abu-OMe$ (3f)	$Z-\Delta Abu(\beta-Br)-OMe$ (5f)	89	1:1
$Z(NO_2)$ - Δ Abu-OMe (3g)	$Z(NO_2)$ - $\Delta Abu(\beta$ -Br)-OMe (5g)	80	1:1
Tos- ΔAbu -OMe (3h)	Tos- $\Delta Abu(\beta$ -Br)-OMe (5h)	94	1:9
Boc- Δ Phe-OMe (3i)	Boc- Δ Phe(β -Br)-OMe (6i) ^[6b]	97 ^[6b]	$1:2^{[6b]}$
Tos- Δ Phe-OMe 3j)	Tos- Z - Δ Phe(β -Br)-OMe (6j)	78	only Z



(Z)-5	$\delta(\gamma$ -CH ₃) [ppm]	(E)- 5	$\delta(\gamma$ -CH ₃) [ppm]
Boc- Δ Abu(β -Br)-OMe [(Z)-5e]	2.52	Boc- Δ Abu(β -Br)-OMe [(<i>E</i>)- 5 e]	2.41
$Z-\Delta Abu(\beta-Br)-OMe[(Z)-5f]$	2.56	$Z-\Delta Abu(\beta-Br)-OMe[(E)-5f]$	2.41
$Z(NO_2)-\Delta Abu(\beta-Br)-OMe[(Z)-5g]$	2.59	$Z(NO_2)-\Delta Abu(\beta-Br)-OMe [(E)-5g]$	2.44
Tos- $\Delta Abu(\beta - Br)$ -OMe [(Z)-5h]	2.54	Tos- $\Delta Abu(\beta - Br)$ -OMe [(E)-5h]	2.63

TFA (82%). However, the overall yield obtained in the synthesis of compound **9h** by using $Boc_2O/DMAP$ followed by TMG is higher (84%) than that obtained by using 3.3 equiv. of $Boc_2O/DMAP$ and TFA (71%). When compound **7b** was treated with 3.3 equiv. of Boc_2O in the presence of DMAP it was found that the reagent was consumed but failed to give the corresponding Tos-Ala(*N*-Boc)- Δ Ala(*N*-Boc)-OMe and thus it was impossible to prepare compound **9b** by this route. The latter was synthesized in high yield (93%) by treatment of **7b** with Boc₂O/DMAP and TMG.



Scheme 4. Synthesis of dehydrodipeptides using Boc₂O/DMAP followed by treatment with TFA.



Scheme 5. Synthesis of dehydrodipeptides using $Boc_2O/DMAP$ followed by treatment with TMG.

In the case of *N*-(4-tolylsulfonyl)dipeptides (compounds **7a** and **7c**) the reaction with 1 equiv. of $Boc_2O/DMAP$ and TMG gave the corresponding piperazine derivatives (Scheme 6). In the case of piperazine **11c**, the ¹H NMR analysis showed that only one stereoisomer was formed. This cyclization results from the nucleophilic attack of the sulfonamide nitrogen on the β -carbon atom of the β -hydroxyamino acid derivative. It was possible to prepare the dehydrodipeptides **9a** and **9c** by using Boc₂O (3.3 equiv.)/DMAP followed by treatment with TFA (Table 4).

Table 4. Yields obtained in the synthesis of dehydrodipeptide derivatives on treatment of the corresponding dipeptides with Boc₂O/DMAP followed by TFA.

Reagent	8	% Yield	9	% Yield
7a	Tos-Gly(N -Boc)- Δ Ala(N -Boc)-OMe (8a) ^[3a]	96	Tos-Gly- Δ Ala-OMe (9a)	96
7c	Tos-Gly(N -Boc)- Z - Δ Abu(N -Boc)-OMe (8c)	91	Tos-Gly- Z - Δ Abu-OMe (9c)	96
7d	Tos-Ala(N -Boc)- Z - Δ Abu(N -Boc)-OMe (8d)	52	Tos-Ala- Z - Δ Abu-OMe (9d)	47
7e	Tos-Gly(N -Boc)- Z - Δ Phe(N -Boc)-OMe (8e)	96	Tos-Gly- Z - Δ Phe-OMe (9e)	92
7f	Tos-Ala(N -Boc)- Z - Δ Phe(N -Boc)-OMe (8f)	94	Tos-Ala- Z - Δ Phe-OMe (9f)	87
7g	Boc-Ala(N -Boc)- Δ Ala(N -Boc)-OMe (8g) ^[1]	91 ^[1]	Boc-Ala- Δ Ala-OMe (9g)	92
7h	$Boc-Gly(N-Boc)-Z-\Delta Abu(N-Boc)-OMe$ (8h)	82	Boc-Gly-Z-ΔAbu-OMe (9h)	87

Table 5. Yields obtained in the synthesis of dehydrodipeptides upon treatment of dipeptides with Boc₂O/DMAP followed by TMG.

Reagent	10	% Yield	9	% Yield
7b	Tos-Ala-Ser(O-Boc)-OMe (10b)	85	Tos-Ala-ΔAla-OMe (9b)	_
7b	Tos-Ala-Ser(O-Boc)-OMe (10b)	_	Tos-Ala- Δ Ala-OMe (9b)	93
7f	Tos-Ala-Phe(β-O-Boc)-OMe (10f)	_	Tos-Ala- Δ Phe-OMe (9f)	77
7h	Boc-Gly-Thr(O-Boc)-OMe (10h)	79	Boc-Gly- Z - Δ Abu-OMe (9h)	92
7h	Boc-Gly-Thr(O-Boc)-OMe (10h)	_	Boc-Gly- Z - Δ Abu-OMe (9h)	84
7i	Boc-Gly-Ser(O-Boc)-OMe (10i)	67	Boc-Gly- Δ Ala-OMe (9i)	65
7i	Boc-Gly-Ser(O-Boc)-OMe (10i)	_	Boc-Gly- Δ Ala-OMe (9i)	59
7j	_	_	Boc-Gly- Z - Δ Phe-OMe (9j)	82
71	-	_	Z-Gly- Δ Ala-OMe (9l)	61

FULL PAPER

Scheme 6. Reaction of Tos-Gly-L-Ser-OMe and Tos-Gly-L-Thr-OMe with Boc_2O (1 equiv.)/DMAP followed by TMG.

In order to prepare brominated peptides, the dehydrodipeptides were treated with NBS and then with NEt₃. It was found that when the N-protecting group was other than 4tolylsulfonyl the corresponding β,β-dibromodehydrodipeptide and β-bromo-β-substituted dehydrodipeptide derivatives were obtained (Scheme 7, compounds 12g, 13h and 13j). A 1:1 E/Z mixture was formed in the case of the β bromo β -substituted dehydrodipeptides. However, when the N-protecting group was 4-tolylsulfonyl the reaction of dehydrodipeptides with NBS afforded the 2,2-disubstituted 1-(4-tolylsulfonyl)imidazolidin-4-one in good-to-high yields (Scheme 8, compounds 14a-f). We believe that the initial step in the formation of these compounds is the bromination of the dehydroamino acid residue by NBS. This is followed by cyclization which occurs by nucleophilic attack of the nitrogen atom of the sulfonamide moiety on the α -carbon atom of the second amino acid residue. The results show that the presence of the 4-tolylsulfonyl group is essential for the intramolecular cyclization. Also, NOESY experiments performed on Boc-Gly-AAbu-OMe (9c) showed a correlation between the γ -CH₃ protons of the Δ Abu residue and the aromatic protons of the 4-tolylsulfonyl group. With Boc-Gly- Δ Abu-OMe (9h) it is not possible to observe a similar correlation with the CH₃ protons of the Boc group. These results suggest that the NH proton of the 4tolylsulfonylamide moiety in compound 9c is closer to the Δ Abu residue than that of the *tert*-butyloxycarbonylamide in compound 9h.



Scheme 7. Synthesis of β -bromodehydrodipeptides.

In the synthesis of compounds 14a–f at least one stereocentre is generated which leads to the possibility of obtaining two diastereomers for compounds 14b, 14c and 14e and four diastereomers in the case of compounds 14d and 14f. The reaction of compound 9b with NBS and NEt₃ gave as expected compound 14b as a mixture of two diastereomers each one presenting a quartet in the ¹H NMR spectrum ($\delta = 4.36$ and 4.07 ppm) corresponding to the C5– CH₃ resonance. The same reaction with the dehydrophenyl-



Scheme 8. Yields obtained in the synthesis of imidazolidin-4-ones from dehydrodipeptides.

alanine derivatives 9e and 9f gave compounds 14e and 14f as a mixture of two and four diastereomers, respectively. The ¹H NMR spectra of these reaction mixtures showed two singlets at $\delta = 6.37$ and 6.18 ppm for compound 14e and four singlets at 6.64, 6.45, 6.16 and 6.13 ppm for compound 14f corresponding to the CHBrPh resonances. The dehydroaminobutyric acid derivatives behaved differently. Thus, the reaction of compound 9c gave only one diastereomer of compound 14c although two stereocentres were generated. In the case of compound 14d, four diastereomers were anticipated, however, only two diastereomers were formed (1:1), each one presenting a quartet (5.51 and 5.22 ppm) corresponding to a CHBrCH₃ resonance and a singlet (3.57 and 3.39 ppm) corresponding to a OCH_3 resonance. These results suggest stereoselectivity in the cyclization of the dehydroaminobutyric acid derivatives.

In order to test this reaction with larger peptides, a tripeptide (compound 9k) was synthesized in a 71% overall yield by saponification of the dipeptide 9a (98%) followed by coupling with the methyl ester of glycine using the DCC/



Scheme 9. Synthesis of imidazolidin-4-one (14k) from a dehydrotripeptide derivative.

Eurjoean Journal

HOBt method (72%). This compound was then treated with NBS and NEt₃ to give the corresponding imidazolidinone **14k** in 82% yield (Scheme 9) thus showing that this reaction can also be applied to tripeptides containing a β dehydroamino acid as the second residue and an *N*-(4-tolyl-sulfonyl) group.

Conclusions

Several N-monoprotected dehydroamino acids and dehydrodipeptides have been prepared by a modification of our previously described method for the synthesis of N,Ndiacyldehydroamino acid derivatives. This modification involves treating the β -hydroxyamino acid with 1 equiv. of Boc₂O in the presence of DMAP to give the corresponding *tert*-butyl carbonates which undergo β elimination in the presence of TMG to give the dehydroamino acid derivatives. With threenine and β -hydroxyphenylserine the reaction is stereoselective giving only the Z isomer. This method for the preparation of N-monoprotected dehydroamino acid derivatives has advantages, namely good yields and the possibility of performing these reactions in a one-pot procedure. The compounds prepared were treated with NBS followed by NEt₃ to give the corresponding β , β -dibromodehydroalanines and β-bromo β-substituted dehydroamino acids. In the case of dehydroaminobutyric acid and dehydrophenylalanine the corresponding brominated derivatives were obtained as mixtures of Z and E isomers. An increased Z stereoselectivity was observed with dehydrophenylalanine and when 4-tolylsulfonyl was used as the N-protecting group. Treatment of N-(tert-butyloxycarbonyl)dehydrodipeptides with NBS and NEt₃ afforded the corresponding brominated dehydrodipeptides. However, when the reagent was a peptide with a β -dehydroamino acid as the second residue and an N-(4-tolylsulfonyl) group the corresponding 1-(4-tolylsulfonyl)imidazolidin-4-ones were obtained in good-to-high yields.

Experimental Section

General Methods: Melting points were determined with a Gallenkamp apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded on a Varian Unity Plus spectrometer at 300 and 75.4 MHz, respectively. ¹H–¹H spin-spin decoupling and DEPT θ 45° were used. Chemical shifts are given in ppm and coupling constants in Hz. MS and HRMS data were recorded by the mass spectrometry service of the University of Vigo, Spain. Elemental analysis was performed on a LECO CHNS 932 elemental analyser. Reactions were monitored by thin-layer chromatography (TLC). Column chromatography was performed on Macherey–Nagel silica gel 230–400 mesh. Petroleum ether refers to the boiling range 40– 60 °C. When a solvent gradient was used, the polarity was increased from neat petroleum ether to mixtures of diethyl ether/petroleum ether by increasing in steps of 10% diethyl ether each time until the product was isolated.

Synthesis of the Methyl Esters of *N*-Protected β -Hydroxyamino Acids 1a–j: The synthesis of these compounds has been described elsewhere.^[1]

Synthesis of the N-Acyl-O-(tert-butyloxycarbonyl)hydroxyamino Acid Esters 2a-j

Boc-Ser(O-Boc)-OMe (2a): DMAP (0.1 equiv.) was added to a solution of Boc-L-Ser-OMe (5 mmol, 1.10 g) in dry acetonitrile (1 moldm⁻³) followed by di-tert-butyl dicarbonate (1.0 equiv.) under rapid stirring at room temperature. The reaction was monitored by TLC (diethyl ether/n-hexane, 1:1) until all the reactant had been consumed. Evaporation at reduced pressure gave a residue that was partitioned between diethyl ether (100 mL) and KHSO₄ (30 mL, 1 moldm⁻³). The organic phase was thoroughly washed with KHSO₄ (1 moldm⁻³), NaHO₃ (1 moldm⁻³) and brine (2×30 mL, each), and dried with MgSO₄. Removal of the solvent afforded pure 2a (1.28 g, 80%). M.p. 101.0-102.0 °C (from ethyl acetate/n-hexane). ¹H NMR (CDCl₃): δ = 5.35 (br. d, J = 8.1 Hz, 1 H, NH), 4.57–4.52 (m, 1 H, α CH), 4.48 (dd, J = 3.6, J = 11.1 Hz, 1 H, β CH₂), 4.30 (dd, J = 3.6, J = 11.1 Hz, 1 H, β CH₂), 3.77 (s, 3 H, CH₃ CO₂Me), 1.47 (s, 9 H, CH₃ Boc), 1.45 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 170.13 (C=O), 155.13 (C=O), 152.98 (C=O), 82.77 [C(CH₃)₃], 80.22 [C(CH₃)₃], 66.34 (βCH₂), 52.95 (aCH), 52.71 (OCH₃), 28.24 [C(CH₃)₃], 27.63 [C(CH₃)₃] ppm. C14H25NO7 (319.35): calcd. C 52.65, H 7.89, N 4.39; found C 52.51, H 7.94, N 4.48.

Z-Ser(*O***-Boc)-OMe (2b):** The same procedure described for the preparation of **2a** was followed substituting Z-L-Ser-OMe (5 mmol, 1.27 g) for Boc-L-Ser-OMe to give **2b** (1.52 g, 86%). M.p. 52.0–53.0 °C (from ethyl acetate/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.36 (s, 5 H, ArH), 5.64 (br. d, *J* = 8.4 Hz, 1 H, NH), 5.13 (s, 2 H, CH₂ Z), 4.65–4.61 (m, 1 H, α CH), 4.44 (dd, *J* = 3.6, *J* = 11.1 Hz, 1 H, β CH₂), 4.34 (dd, *J* = 3.6, *J* = 11.1 Hz, 1 H, β CH₂), 4.34 (dd, *J* = 3.6, *J* = 11.1 Hz, 1 H, β CH₂), 3.78 (s, 3 H, CH₃ CO₂Me), 1.47 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 169.74 (C=O), 155.71 (C=O), 152.93 (C=O), 136.01 (C), 128.50 (CH), 128.19 (CH), 128.08 (CH), 82.88 [*C*(CH₃)₃], 67.15 (CH₂), 66.10 (β CH₂), 53.39 (α CH), 52.83 (OCH₃), 27.59 [C(*C*H₃)₃] ppm. C₁₇H₂₃NO₇ (353.37): calcd. C 57.78, H 6.56, N 3.96; found C 58.18, H 6.58, N 4.13.

Z(NO₂)-Ser(*O***-Boc)-OMe (2c):** The same procedure described for the preparation of **2a** was followed substituting Z(NO₂)-L-Ser-OMe (5 mmol, 1.49 g) for Boc-L-Ser-OMe to give **2c** (1.65g, 83%) as an oil. ¹H NMR (CDCl₃): δ = 8.22 (d, *J* = 8.7 Hz, 2 H, ArH), 7.51 (d, *J* = 8.7 Hz, 2 H, ArH), 5.75 (br. d, *J* = 8.1 Hz, 1 H, NH), 5.22 [s, 2 H, CH₂ Z(NO₂)], 4.62–4.57 (m, 1 H, αCH), 4.49 (dd, *J* = 3.9, *J* = 11.1 Hz, 1 H, βCH₂), 4.36 (dd, *J* = 3.9, *J* = 11.1 Hz, 1 H, βCH₂), 3.79 (s, 3 H, CH₃ CO₂Me), 1.46 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 169.55 (C=O), 155.27 (C=O), 152.93 (C=O), 147.60 (C), 143.49 (C), 128.04 (CH), 123.71 (CH), 83.05 [*C*(CH₃)₃], 65.93 (βCH₂), 65.52 (CH₂), 53.52 (αCH), 52.94 (OCH₃), 27.57 [C(CH₃)₃] ppm. C₁₇H₂₂N₂O₉ (398.37): calcd. C 51.26, H 5.57, N 7.03; found C 51.60, H 5.40, N 7.00.

Tos-Ser(*O***-Boc)-OMe (2d):** The same procedure described for the preparation of **2a** was followed substituting Tos-L-Ser-OMe (5 mmol, 1.37 g) for Boc-L-Ser-OMe to give **2d** (1.51 g, 81%). M.p. 67.5–68.5 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.74 (d, *J* = 8.1 Hz, 2 H, ArH), 7.30 (d, *J* = 8.1 Hz, 2 H, ArH), 5.41 (br. d, *J* = 8.1 Hz, 1 H, NH), 4.41–4.35 (m, 1 H, βCH₂), 4.25–4.21 (m, 2 H, βCH₂ + αCH), 3.60 (s, 3 H, CH₃ CO₂Me), 2.43 (s, 3 H, CH₃ Tos), 1.46 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 169.09 (C=O), 152.72 (C=O), 143.78 (C), 136.73 (C), 129.06 (CH), 127.12 (CH), 82.99 [*C*(CH₃)₃], 66.62 (βCH₂), 54.81 (αCH), 52.97 (OCH₃), 27.60 [C(CH₃)₃], 21.49 (CH₃ Tos) ppm. C₁₆H₂₃NO₇S (373.42): calcd. C 51.46, H 6.21, N 3.75, S 8.59; found C 51.31, H 6.06, N 3.97, S 8.62.

Boc-Thr(*O***-Boc)-OMe (2e):** The same procedure described for the preparation of **2a** was followed substituting Boc-L-Thr-OMe (5 mmol, 1.17 g) for Boc-L-Ser-OMe to give **2e** (1.45 g, 87%) as an oil. ¹H NMR (CDCl₃): δ = 5.28–5.19 (m, 2 H, βCH + NH), 4.40 (dd, J = 2.1, J = 9.9 Hz, 1 H, αCH), 3.73 (s, 3 H, CH₃ CO₂Me), 1.44 (s, 9 H, CH₃ Boc), 1.41 (s, 9 H, CH₃ Boc), 1.32 (d, J = 6.3 Hz, 3 H, γCH₃) ppm. ¹³C NMR (CDCl₃): δ = 170.59 (C=O), 156.00 (C=O), 152.39 (C=O), 82.54 [C(CH₃)₃], 80.04 [C(CH₃)₃], 73.05 (βCH), 56.96 (αCH), 52.51 (OCH₃), 28.20 [C(CH₃)₃], 27.60 [C(CH₃)₃], 17.00 (γCH₃) ppm. C₁₅H₂₇NO₇ (333.38): calcd. C 54.04, H 8.16, N 4.20; found C 54.22, H 7.83, N 4.27.

Z-Thr(O-Boc)-OMe (2f): The same procedure described for the preparation of **2a** was followed substituting Z-L-Thr-OMe (5 mmol, 1.34 g) for Boc-L-Ser-OMe to give **2f** (1.58 g, 86%) as an oil that solidified on standing. M.p. 65.5–66.5 °C. ¹H NMR (CDCl₃): δ = 7.30 (s, 5 H, ArH), 5.53 (br. d, *J* = 9.9 Hz, 1 H, NH), 5.30–5.23 (m, 1 H, β CH), 5.14 (s, 2 H, CH₂ Z), 4.48 (dd, *J* = 2.4, *J* = 9.8 Hz, 1 H, α CH), 3.75 (s, 3 H, CH₃ CO₂Me), 1.45 (s, 9 H, CH₃ Boc), 1.34 (d, *J* = 6.3 Hz, 3 H, γ CH₃) ppm. ¹³C NMR (CDCl₃): δ = 170.28 (C=O), 156.47 (C=O), 152.34 (C=O), 136.07 (C), 128.49 (CH), 128.16 (CH), 127.97 (CH), 82.66 [*C*(CH₃)₃], 72.80 (β CH), 67.18 (CH₂), 57.50 (α CH), 52.65 (OCH₃), 27.58 [C(CH₃)₃], 17.06 (γ CH₃) ppm. C₁₈H₂₅NO₇ (367.40): calcd. C 58.85, H 6.86, N 3.81; found C 59.05, H 6.80, N 4.05.

Z(NO₂)-Thr(*O***-Boc)-OMe (2g): The same procedure described for the preparation of 2a** was followed substituting Z(NO₂)-L-Thr-OMe (5 mmol, 1.56 g) for Boc-L-Ser-OMe to give **2g** (1.84 g, 89%) as an oil. ¹H NMR (CDCl₃): δ = 8.23 (d, *J* = 8.7 Hz, 2 H, ArH), 7.52 (d, *J* = 8.7 Hz, 2 H, ArH), 5.62 (br. d, *J* = 9.6 Hz, 1 H, NH), 5.32–5.25 (m, 1 H, βCH), 5.23 [s, 2 H, CH₂ Z(NO₂)], 4.46 (dd, *J* = 2.4, *J* = 9.6 Hz, 1 H, αCH), 3.76 (s, 3 H, CH₃ CO₂Me), 1.46 (s, 9 H, CH₃ Boc), 1.35 (d, *J* = 6.3 Hz, 3 H, γCH₃) ppm. ¹³C NMR (CDCl₃): δ = 170.13 (C=O), 156.04 (C=O), 152.28 (C=O), 147.62 (C), 143.52 (C), 127.98 (CH), 123.75 (CH), 82.87 [*C*(CH₃)₃], 72.68 (βCH), 65.61 (CH₂), 57.61 (αCH), 52.77 (OCH₃), 27.59 [C(*C*H₃)₃], 17.10 (γCH₃) ppm. C₁₈H₂₄N₂O₉ (412.39): calcd. C 52.43, H 5.87, N 6.79; found C 52.59, H 5.93, N 6.89.

Tos-Thr(*O***-Boc)-OMe (2h):** The same procedure described for the preparation of **2a** was followed substituting Tos-L-Thr-OMe (5 mmol, 1.44 g) for Boc-L-Ser-OMe to give **2h** (1.74 g, 90%) as an oil. ¹H NMR (CDCl₃): δ = 7.70 (d, *J* = 8.7 Hz, 2 H, ArH), 7.27 (d, *J* = 8.7 Hz, 2 H, ArH), 5.33 (br. d, *J* = 7.8 Hz, 1 H, NH), 5.16–5.08 (m, 1 H, CH), 3.97 (br. d, *J* = 5.7 Hz, 1 H, CH), 3.49 (s, 3 H, CH₃ CO₂Me), 2.41 (s, 3 H, CH₃ Tos), 1.43 (s, 9 H, CH₃ Boc), 1.34 (d, *J* = 6.3 Hz, 3 H, γCH₃) ppm. ¹³C NMR (CDCl₃): δ = 169.49 (C=O), 152.32 (C=O), 143.69 (C), 136.68 (C), 129.56 (CH), 127.15 (CH), 82.77 [*C*(CH₃)₃], 72.59 (CH), 59.62 (CH), 52.67 (OCH₃), 27.55 [*C*(CH₃)₃], 21.48 (CH₃), 17.00 (γCH₃) ppm. C₁₇H₂₅NO₇S (387.45): calcd. C 52.70, H 6.50, N 3.62, S 8.28; found C 53.26, H 6.67, N 3.67, S 8.15.

Boc-Phe(β-O-Boc)-OMe (2i): The same procedure described for the preparation of **2a** was followed substituting Boc-D,L-Phe(β-OH)-OMe (5 mmol, 1.48 g) for Boc-L-Ser-OMe to give **2i** (1.62 g, 82%). M.p. 85.0–86.0 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.37–7.33 (m, 5 H, ArH), 6.08 (d, *J* = 3.0 Hz, 1 H, βCH), 5.32 (d, *J* = 9.9 Hz, 1 H, NH), 4.69 (dd, *J* = 3.0, *J* = 9.9 Hz, 1 H, αCH), 3.76 (s, 3 H, CH₃ CO₂Me), 1.45 (s, 9 H, CH₃ Boc), 1.32 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 170.16 (C=O), 155.01 (C=O), 152.19 (C=O), 136.17 (C), 128.39 (CH), 128.31 (CH), 126.08 (CH), 83.05 [*C*(CH₃)₃], 82.99 [*C*(CH₃)₃], 79.96 (βCH), 57.89 (αCH), 52.66 (OCH₃), 28.09 [*C*(CH₃)₃], 27.57 [C-

 $(CH_3)_3$] ppm. C₂₀H₂₉NO₇ (395.45): calcd. C 60.75, H 7.39, N 3.54; found C 60.63, H 7.31, N 3.62.

Tos-Phe(β-O-Boc)-OMe (2j): The same procedure described for the preparation of **2a** was followed substituting Tos-D,L-Phe(β-OH)-OMe (5 mmol, 1.75 g) for Boc-L-Ser-OMe to give **2j** (1.64g, 73%). M.p. 119.5–120.5 °C (from ethyl acetate/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.46 (d, *J* = 8.1 Hz, 2 H, ArH), 7.27 (s, 5 H, ArH), 7.13 (d, *J* = 8.1 Hz, 2 H, ArH), 5.95 (d, *J* = 3.3 Hz, 1 H, βCH), 5.36 (d, *J* = 10.2 Hz, 1 H, NH), 4.26 (dd, *J* = 10.2, *J* = 3.3 Hz, 1 H, aCH), 3.57 (s, 3 H, CH₃ CO₂Me), 2.38 (s, 3 H, CH₃ Tos), 1.44 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 169.34 (C=O), 152.13 (C=O), 143.35 (C), 136.61 (C), 135.43 (C), 129.40 (CH), 128.48 (CH), 128.42 (CH), 126.97 (CH), 126.34 (CH), 83.26 [*C*(CH₃)₃], 77.00 (βCH₂), 60.32 (aCH), 52.81 (OCH₃), 27.57 [C(CH₃)₃], 21.45 (CH₃ Tos) ppm. C₂₂H₂₇NO₇S (449.52): calcd. C 58.78, H 6.05, N 3.12, S 7.13; found C 58.86, H 6.12, N 3.21, S 7.13.

Synthesis of N-Acyldehydroamino Acid Esters 3a-c,e-i from N-Acyl-O-(tert-butyloxycarbonyl)hydroxyamino Acid Esters

Boc- Δ **Ala-OMe (3a):** TMG (2% in volume) was added to a solution of Boc-L-Ser(*O*-Boc)-OMe (1 mmol, 0.320 g) in acetonitrile (1 mol dm⁻³). The reaction was monitored by TLC (diethyl ether/ *n*-hexane, 1:1) until all the reactant had been consumed. Evaporation at reduced pressure gave a residue that was partitioned between diethyl ether (100 mL) and KHSO₄ (30 mL, 1 mol dm⁻³). The organic phase was thoroughly washed with KHSO₄ (1 mol dm⁻³), NaHCO₃ (1 mol dm⁻³) and saturated brine (2 × 30 mL, each), and dried with MgSO₄. Removal of the solvent afforded pure **3a** (0.175 g, 87%).^[1]

Z-AAla-OMe (3b): The same procedure described for the preparation of **3a** was followed substituting Z-L-Ser(*O*-Boc)-OMe (1 mmol, 0.353 g) for Boc-L-Ser(*O*-Boc)-OMe to give **3b** (0.193 mg, 82%) as an oil.^[10] ¹H NMR (CDCl₃): δ = 7.40–7.37 (m, 5 H, ArH), 7.26 (br. s, 1 H, NH), 6.26 (s, 1 H, β CH₂), 5.80 (s, 1 H, β CH₂), 5.18 (s, 2 H, CH₂ Z), 3.84 (s, 3 H, CH₃ CO₂Me) ppm.

Z(NO₂)-AAla-OMe (3c): The same procedure described for the preparation of **3a** was followed substituting Z(NO₂)-L-Ser(*O*-Boc)-OMe (1 mmol, 0.398 g) for Boc-L-Ser(*O*-Boc)-OMe to give **3c** (0.238 g, 85%). M.p. 93.5–94.5 °C (from ethyl acetate/*n*-hexane). ¹H NMR (CDCl₃): δ = 8.23 (d, *J* = 8.4 Hz, 2 H, ArH), 7.54 (d, *J* = 8.4 Hz, 2 H, ArH), 7.33 (s, 1 H, NH), 6.24 (s, 1 H, βCH₂), 5.82 (d, *J* = 1.5 Hz, 1 H, βCH₂), 5.26 [s, 2 H, CH₂ Z(NO₂)], 3.86 (s, 3 H, CH₃ CO₂Me) ppm. ¹³C NMR (CDCl₃): δ = 164.08 (C=O), 152.59 (C=O), 147.71 (C), 143.18 (C), 130.72 (αC), 128.25 (CH), 123.80 (CH), 106.54 (βCH₂), 65.41 (CH₂), 53.04 (OCH₃) ppm. C₁₂H₁₂N₂O₆ (280.24): calcd. C 51.43, H 4.32, N 10.00; found C 51.48, H 4.21, N 9.88.

Boc-Z-AAbu-OMe (3e): The same procedure described for the preparation of **3a** was followed substituting Boc-L-Thr(*O*-Boc)-OMe (1 mmol, 0.333 g) for Boc-L-Ser(*O*-Boc)-OMe to give **3e** (0.211 g, 98%).^[1]

Z-Z-ΔAbu-OMe (3f): The same procedure described for the preparation of **3a** was followed substituting Z-L-Thr(*O*-Boc)-OMe (1 mmol, 0.367 g) for Boc-L-Ser(*O*-Boc)-OMe to give **3f** (0.209 g, 84%).^[1,7d]

Synthesis of $Z(NO_2)$ -Z- Δ Abu-OMe (3g): The same procedure described for the preparation of 3a was followed substituting $Z(NO_2)$ -L-Thr(*O*-Boc)-OMe (1 mmol, 0.412 g) for Boc-L-Ser(*O*-Boc)-OMe to give 3g (0.280 g, 95%).^[1]



Tos-Z-AAbu-OMe (3h): The same procedure described for the preparation of **3a** was followed substituting Tos-L-Thr(*O*-Boc)-OMe (1 mmol, 0.387 g) for Boc-L-Ser(*O*-Boc)-OMe to give **3h** (0.245 g, 91%). M.p. 118.5–119.5 °C (from ethyl acetate/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.67 (d, *J* = 8.7 Hz, 2 H, ArH), 7.27 (d, *J* = 8.7 Hz, 2 H, ArH), 6.99 (q, *J* = 7.2 Hz, 1 H, βCH), 6.06 (s, 1 H, NH), 3.43 (s, 3 H, CH₃ CO₂Me), 2.41 (s, 3 H, CH₃ Tos), 2.04 (d, *J* = 7.2 Hz, 3 H, γCH₃) ppm. ¹³C NMR (CDCl₃): δ = 164.32 (C=O), 143.82 (C), 140.32 (βCH), 136.15 (C), 129.35 (CH), 127.48 (CH), 125.65 (αC), 52.20 (OCH₃), 21.50 (CH₃ Tos), 15.00 (γCH₃) ppm. C₁₂H₁₅NO₄S (269.32): calcd. C 53.52, H 5.61, N 5.20, S 11.91; found C 53.30, H 5.63, N 5.33, S 11.82.

Boc-Z-ΔPhe-OMe (3i): The same procedure described for the preparation of **3a** was followed substituting Boc-L-Phe(*O*-Boc)-OMe (1 mmol, 0.395 g) for Boc-L-Ser(*O*-Boc)-OMe to give **3i** (0.244 g, 88%).^[3b]

One-Pot Synthesis of N-Acyldehydroamino Acid Esters 3a-j from N-Acyl-β-hydroxyamino Acid Esters

Boc-AAla-OMe (3a): DMAP (0.1 equiv.) was added to a solution of Boc-L-Ser-OMe (1 mmol, 0.219 g) in dry acetonitrile (1 mol dm⁻³) followed by di-*tert*-butyl dicarbonate (1.0 equiv.) under rapid stirring at room temperature. The reaction was monitored by TLC (diethyl ether/*n*-hexane, 1:1) until all the reactant had been consumed. Then TMG (2% in volume) was added and stirring was continued and the reaction followed by TLC. When all the reactant had been consumed evaporation at reduced pressure gave a residue that was partitioned between diethyl ether (100 mL) and KHSO₄ (30 mL, 1 moldm⁻³). The organic phase was thoroughly washed with KHSO₄ (1 moldm⁻³), NaHCO₃ (1 moldm⁻³) and saturated brine (2 × 30 mL, each), and dried with MgSO₄. Removal of the solvent afforded pure **3a** (0.165 g, 82%).^[1]

Z-\DeltaAla-OMe (3b): The same procedure described for the preparation of **3a** was followed substituting Z-L-Ser-OMe (1 mmol, 0.254 g) for Boc-L-Ser-OMe to give **3b** (0.212 g, 90%).^[10]

Z(NO₂)-ΔAla-OMe (3c): The same procedure described for the preparation of 3a was followed substituting Z(NO₂)-L-Ser-OMe (1 mmol, 0.298 g) for Boc-L-Ser-OMe to give 3c (0.252 g, 90%).

Tos-ΔAla-OMe (3d): The same procedure described for the preparation of 3a was followed substituting Tos-L-Ser-OMe (1 mmol, 0.273 g) for Boc-L-Ser-OMe and stopping the reaction 5 min after the addition of TMG to give 3d (0.166 g, 65%) as a white solid. M.p. 101.5–102.5 °C (diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.76 (d, J = 8.7 Hz, 2 H, ArH), 7.30 (d, J = 8.7 Hz, 2 H, ArH), 7.14 (s, 1 H, NH), 5.67 (d, J = 1.2 Hz, 1 H, β CH₂), 5.65 (t, J =1.5 Hz, 1 H, βCH₂), 3.76 (s, 3 H, CH₃ CO₂Me), 2.42 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (CDCl₃): δ = 163.64 (C=O), 144.32 (C), 135.35 (C), 130.77 (αC), 129.68 (CH), 127.56 (CH), 106.87 (βCH₂), 53.18 (OCH₃), 21.56 (CH₃ Tos) ppm. C₁₁H₁₃NO₄S (255.29): calcd. C 51.75, H 5.13, N 5.49, S 12.56; found C 51.74, H 5.13, N 5.67, S 12.60. The other product isolated was Tos-NH₂. M.p. 125.5-126.5 °C (ref. $^{[14]}$ 137.0–138.0 °C) (from diethyl ether/n-hexane). $^1\mathrm{H}$ NMR (CDCl₃): δ = 7.83 (d, J = 8.4 Hz, 2 H, ArH), 7.33 (d, J = 8.4 Hz, 2 H, ArH), 4.77 (br. s, 2 H, NH₂), 2.45 (s, 9 H, CH₃ Tos) ppm.

Boc-Z-AAbu-OMe (3e): The same procedure described for the preparation of **3a** was followed substituting Boc-L-Thr-OMe (1 mmol, 0.233 g) for Boc-L-Ser-OMe to give **3e** (0.177 g, 82%).^[1]

Z-Z-\DeltaAbu-OMe (3f): The same procedure described for the preparation of **3a** was followed substituting Z-L-Thr-OMe (1 mmol, 0.267 g) for Boc-L-Ser-OMe to give **3f** (0.207 g, 83%).^[1]

Z(NO₂)-Z-ΔAbu-OMe (3g): The same procedure described for the preparation of 3a was followed substituting Z(NO₂)-L-Thr-OMe (1 mmol, 0.312 g) for Boc-L-Ser-OMe to give 3g (0.268 g, 91%).^[1]

Tos-Z-ΔAbu-OMe (3h): The same procedure described for the preparation of **3a** was followed substituting Tos-L-Thr-OMe (1 mmol, 0.287 g) for Boc-L-Ser-OMe to give **3h** (0.232 g, 86%).

Boc-Z-ΔPhe-OMe (3i): The same procedure described for the preparation of **3a** was followed substituting Boc-D,L-Phe-OMe (1 mmol, 0.295 g) for Boc-L-Ser-OMe to give **3i** (0.240 g, 81%).^[3b]

Tos-Z-ΔPhe-OMe (3j): The same procedure described for the preparation of **3a** was followed substituting Tos-D,L-Phe(β-OH)-OMe (1 mmol, 0.349 g) for Boc-L-Ser-OMe to give **3j** (0.268 g, 81%). M.p. 147.5–148.5 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.88–7.85 (m, 2 H, ArH), 7.67 (d, *J* = 8.4 Hz, 2 H, ArH), 7.53 (s, 1 H, βCH), 7.38–7.36 (m, 3 H, ArH), 7.29–7.23 (m, 2 H, ArH), 6.20 (br. s, 1 H, NH), 3.54 (s, 3 H, CH₃ CO₂Me), 2.41 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (CDCl₃): δ = 165.35 (C=O), 143.88 (C), 137.73 (CH), 136.25 (C), 132.64 (C), 131.05 (CH), 130.36 (CH), 129.32 (CH), 128.39 (CH), 127.50 (CH), 122.61 (C), 52.54 (OCH₃), 21.51 (CH₃ Tos) ppm. C₁₇H₁₇NO₄S (331.39): calcd. C 61.61, H 5.17, N 4.23, S 9.68; found C 61.59, H 5.17, N 4.29, S 9.61.

Synthesis of the Methyl Esters of *N*-Protected β -Brominated Dehydroamino Acids 4a–c, 5e–h and 6i,j

Boc-ΔAla(β , β -Br)-OMe (4a): The synthesis of this compound has been described elsewhere.^[6a]

Z-ΔAla(β,β-Br)-OMe (4b): Z-ΔAla-OMe (5 mmol, 1.18 g) was dissolved in dichloromethane (0.1 mol dm⁻³) and N-bromosuccinimide (2.5 equiv.) was added with vigorous stirring. After reacting for 16 h, triethylamine (1.5 equiv.) was added and stirring was continued for an additional hour. The solvent was then evaporated at reduced pressure and the residue partitioned between dichloromethane (100 mL) and KHSO₄ (50 mL, 1 moldm⁻³). The organic phase was washed with KHSO₄ (1 mol dm⁻³), NaHCO₃ (1 mol dm^{-3}) and brine $(3 \times 30 \text{ mL}, \text{ each})$. After drying with MgSO₄ the extract was taken to dryness at reduced pressure to afford 4b (1.69 g, 86%). M.p. 103.5-104.5 °C (from ethyl acetate/nhexane). ¹H NMR (CDCl₃): δ = 7.38–7.35 (m, 5 H, ArH), 6.54 (br. s, 1 H, NH), 5.16 (s, 2 H, CH₂), 3.82 (s, 3 H, CH₃ CO₂Me) ppm. ¹³C NMR (CDCl₃): δ = 162.17 (C=O), 151.93 (C=O), 135.10 (C), 132.40 (C), 128.67 (CH), 128.48 (CH), 119.72 (C), 68.39 (CH₂), 52.96 (OCH₃) ppm. C₁₂H₁₁NO₄ (393.03): C 36.67, H 2.82, N 3.56; found C 36.66, H 2.90, N 3.93.

Z(NO₂)-ΔAla(β,β-Br)-OMe (4c): The same procedure described for the preparation of **4b** was followed substituting **3c** (5 mmol, 1.40 g) for **3b** to give **4c** (1.64 g, 75%). M.p. 153.5–154.5 °C (from ethyl acetate/*n*-hexane). ¹H NMR (CDCl₃): δ = 8.25 (d, *J* = 9.0 Hz, 2 H, ArH), 7.53 (d, *J* = 9.0 Hz, 2 H, ArH), 6.62 (br. s, 1 H, NH), 5.26 (s, 2 H, CH₂), 3.87 (s, 3 H, CH₃ CO₂Me) ppm. ¹³C NMR (CDCl₃): δ = 162.10 (C=O), 151.59 (C=O), 147.87 (C), 142.19 (C), 131.73 (C), 128.50 (CH), 123.84 (CH), 82.06 (C), 66.58 (CH₂), 53.18 (OCH₃) ppm. C₁₂H₁₀N₂O₆Br₂ (438.03): C 32.90, H 2.30, N 6.40; found C 33.35, H 2.41, N 6.63.

Boc- Δ **Abu(** β **-Br)-OMe (5e):** The synthesis of this compound has been described elsewhere.^[13]

Z-AAbu(\beta-Br)-OMe (5f): The same procedure described for the preparation of **4b** was followed substituting **3f** (5 mmol, 1.25 g) for **3b** and by using 1.2 equiv. of NBS to give (*E*)-**5f** and (*Z*)-**5f** as a 1:1 *E/Z* mixture (1.46 g, 89%). The diastereomers were separated by column chromatography using a solvent gradient of neat petro-

leum ether to 40% diethyl ether/petroleum ether. (E)-5f: M.p. 141.5–142.0 °C (from ethyl acetate/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.36–7.33 (m, 5 H, ArH), 6.30 (br. s, 1 H, NH), 5.15 (s, 2 H, CH₂ Z), 3.81 (br. s, 3 H, CH₃ CO₂Me), 2.41 (s, 3 H, γCH₃) ppm. ¹³C NMR (CDCl₃): δ = 164.06 (C=O), 153.53 (C=O), 135.53 (C), 128.57 (CH), 128.43 (CH), 128.28 (CH), 125.66 (C), 124.14 (C), 67.76 (CH₂), 52.37 (OCH₃), 25.92 (γCH₃) ppm. C₁₃H₁₄NO₄Br (328.16): C 47.58, H 4.30, N 4.27; found C 47.74, H, 4.44, N 4.45. (Z)-5f: M.p. 97.5–98.0 °C (from ethyl acetate/n-hexane). ¹H NMR $(CDCl_3): \delta = 7.41-7.32 \text{ (m, 5 H, ArH)}, 6.46 \text{ (br. s, 1 H, NH)}, 5.16$ (s, 2 H, CH₂ Z), 3.81 (br. s, 3 H, CH₃ CO₂Me), 2.56 (s, 3 H, γ CH₃) ppm. ¹³C NMR (CDCl₃): δ = 162.91 (C=O), 153.25 (C=O), 135.47 (C), 128.57 (CH), 128.44 (CH), 128.32 (CH), 126.90 (C), 122.47 (C), 67.77 (CH₂), 52.59 (OCH₃), 24.69 (γCH₃) ppm. C13H14NO4Br (328.16): C 47.58, H 4.30, N 4.27; found C 47.56, H 4.38, N 4.47.

 $Z(NO_2)-\Delta Abu(\beta-Br)-OMe$ (5g): The same procedure described for the preparation of **5f** was followed substituting **3g** (5 mmol, 1.47 g) for **3f** to give (*E*)-**5g** and (*Z*)-**5g** as a 1:1 mixture (1.49 g, 80%). The diastereomers were separated by column chromatography using a solvent gradient of neat petroleum ether to 30% diethyl ether/petroleum ether. (E)-5g: M.p. 140.5-141.0 °C (from ethyl acetate/n-hexane). ¹H NMR (CDCl₃): δ = 8.22 (d, J = 8.4 Hz, 2 H, ArH), 7.52 (d, J = 8.4 Hz, 2 H, ArH), 6.34 (br. s, 1 H, NH), 5.24 [s, 2 H, CH₂ Z(NO₂)], 3.81 (br. s, 3 H, CH₃ CO₂Me), 2.44 (s, 3 H, γCH₃) ppm. ¹³C NMR (CDCl₃): δ = 163.95 (C=O), 152.90 (C=O), 147.74 (C), 142.89 (C), 128.26 (CH), 125.40 (C), 125.25 (C), 123.79 (CH), 66.08 (CH₂), 52.48 (OCH₃), 26.18 (γCH₃) ppm. C₁₃H₁₃N₂O₆Br (373.16): C 41.84, H 3.51, N 7.51, found C 41.85, H 3.59, N 7.74. (Z)-5g: M.p. 143.5-144.0 °C (from ethyl acetate/n-hexane). ¹H NMR (CDCl₃): δ = 8.22 (d, J = 8.4 Hz, 2 H, ArH), 7.52 (d, J = 8.4 Hz, 2 H, ArH), 6.52 (br. s, 1 H, NH), 5.24 [s, 2 H, CH₂ Z(NO₂)], 3.79 (br. s, 3 H, CH₃ CO₂Me), 2.59 (s, 3 H, γCH₃) ppm. ¹³C NMR (CDCl₃): δ = 162.70 (C=O), 152.87 (C=O), 147.71 (C), 142.88 (C), 128.24 (CH), 126.49 (C), 124.68 (C), 123.75 (CH), 66.04 (CH₂), 52.65 (OCH₃), 24.88 (γCH₃) ppm. C₁₃H₁₃N₂O₆Br (373.16): C 41.84, H 3.51, N 7.51; found C 41.78, H 3.57, N 7.68.

Tos- Δ Abu(β -Br)-OMe (5h): The same procedure described for the preparation of 5f was followed substituting 3h (5 mmol, 1.35 g) for **3f** to give (*E*)-**5h** and (*Z*)-**5h** as a 1:9 *E*/*Z* mixture (1.64 g, 94%). The diastereomers were separated by column chromatography using a solvent gradient of neat petroleum ether to 40% diethyl ether/petroleum ether. (*E*)-**5h**: Oil. ¹H NMR (CDCl₃): δ = 7.68 (d, *J* = 8.4 Hz, 2 H, ArH), 7.31 (d, J = 8.4 Hz, 2 H, ArH), 6.13 (s, 1 H, NH), 3.37 (s, 3 H, CH₃ CO₂Me), 2.63 (s, 3 H, γCH₃), 2.43 (s, 3 H, CH₃) Tos) ppm. ¹³C NMR (CDCl₃): δ = 166.39 (C=O), 137.36 (C), 135.75 (C), 129.70 (C), 129.47 (CH), 127.32 (CH), 123.55 (C), 52.09 (OCH₃), 28.21 (γCH₃), 21.55 (CH₃ Tos) ppm. (Z)-5h: M.p. 112.0-113.0 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.73 $(d, J = 8.4 \text{ Hz}, 2 \text{ H}, \text{ArH}), 7.31 (d, J = 8.4 \text{ Hz}, 2 \text{ H}, \text{ArH}), 6.29 (s, J = 8.4 \text{ Hz}, 2 \text$ 1 H, NH), 3.77 (s, 3 H, CH₃ CO₂Me), 2.55 (s, 3 H, γCH₃), 2.44 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (CDCl₃): δ = 163.06 (C=O), 144.21 (C), 136.14 (C), 130.86 (C), 129.61 (CH), 127.31 (CH), 126.53 (C), 52.76 (OCH₃), 25.45 (γ CH₃), 21.60 (CH₃ Tos) ppm. C12H14NO4SBr (348.22): C 41.39, H 4.05, N 4.02, S 9.21; found C 41.56, H 4.05, N 4.11, S 9.19.

Boc- Δ **Phe(\beta-Br)-OMe (6i):** The same procedure described for the preparation of **5f** was followed substituting **3i** for **3f** to give (*E*)-**6i** and (*Z*)-**6i** as a 1:2 mixture (97%).^[6b]

Tos-Z-ΔPhe(β-Br)-OMe (6j): The same procedure described for the preparation of **5f** was followed substituting **3j** (2 mmol, 0.66 g) for **3f** to give (*Z*)-**6j** (0.64 g, 78%). M.p. 133.0–134.0 °C (from diethyl

ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.83 (d, *J* = 8.4 Hz, 2 H, ArH), 7.38–7.22 (m, 7 H, ArH), 6.63 (s, 1 H, NH), 3.58 (s, 3 H, CH₃ CO₂Me), 2.48 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (CDCl₃): δ = 163.26 (C=O), 144.49 (C), 137.00 (C), 135.95 (C), 129.68 (CH), 129.65 (CH), 128.46 (CH), 128.37 (C), 128.30 (CH), 127.36 (CH), 123.65 (βC), 52.82 (OCH₃), 21.66 (CH₃ Tos) ppm. C₁₇H₁₆NO₄SBr (410.28): C 49.77, H 3.93, N 3.41, S 7.82; found C 49.63, H 4.16, N 3.51, S 7.65.

Synthesis of the Methyl Esters of *N*-Acyldipeptides 7a–j,l: In all cases the *N*-protected amino acid was treated with the corresponding amino acid methyl ester in acetonitrile using the standard DCC/ HOBt procedure.

Tos-Gly-L-Ser-OMe (7a): The procedure referred to above was followed using Tos-Gly-OH (10 mmol) and HCl·H-L-Ser-OMe (10 mmol) giving **7a** as a white solid (2.35 g, 71%). M.p. 102.0–103.0 °C (from ethyl acetate). ¹H NMR (CDCl₃): δ = 7.75 (d, *J* = 7.8 Hz, 2 H, ArH), 7.42 (d, *J* = 7.8 Hz, 1 H, NH), 7.33 (d, *J* = 7.8 Hz, 2 H, ArH), 6.05 (br. s, 1 H, NH), 4.65–4.63 (m, 1 H, α-CH), 4.02–3.83 (m, 2 H, CH₂), 3.78 (s, 3 H, CH₃ CO₂Me), 3.66–3.64 (m, 2 H, CH₂), 3.35 (br. s, 1 H, OH), 2.43 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (DMSO): δ = 170.80 (C=O), 167.74 (C=O), 142.79 (C), 137.33 (C), 129.58 (CH), 126.70 (CH), 61.16 (αCH), 54.49 (CH₂), 51.99 (OCH₃), 45.02 (CH₂), 21.01 (CH₃ Tos) ppm. C₁₃H₁₈N₂O₆S (330.30): calcd. C 47.27, H 5.49, N 8.48, S 9.69; found C 47.40, H 5.49, N 8.24, S 9.48.

Tos-L-Ala-L-Ser-OMe (7b): The procedure referred to above was followed using Tos-L-Ala-OH (10 mmol) and HCl·H-L-Ser-OMe (10 mmol) giving **7b** (2.48 g, 72%). M.p. 152.5–154.0 °C (from ethyl acetate/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.77 (d, *J* = 8.1 Hz, 2 H, ArH), 7.46 (d, *J* = 7.5 Hz, 1 H, NH), 7.30 (d, *J* = 8.1 Hz, 2 H, ArH), 6.14 (d, *J* = 7.8 Hz, 1 H, NH), 4.58–4.53 (m, 1 H, αCH Ser), 3.97–3.79 (m, 3 H, αCH Ala + βCH₂ Ser), 3.75 (s, 3 H, CH₃ CO₂Me), 2.41 (s, 3 H, CH₃ Tos), 1.23 (d, *J* = 6.9 Hz, 3 H, βCH₃ Ala) ppm. ¹³C NMR (CDCl₃): δ = 172.16 (C=O), 170.68 (C=O), 143.91 (C), 136.62 (C), 129.78 (CH), 127.24 (CH), 62.47 (CH₂), 54.81 (CH), 52.76 (OCH₃), 52.40 (CH), 21.51 (CH₃ Tos), 18.73 (βCH₃) ppm. C₁₄H₂₀N₂O₆S (344.39): calcd. C 40.83, H 5.85, N 8.13, S 9.31; found C 49.12, H 5.85, N 8.13, S 9.31.

Tos-Gly-L-Thr-OMe (7c): The procedure referred to above was followed using Tos-Gly-OH (10 mmol) and HCl·H-L-Thr-OMe (10 mmol) giving **7c** as a white solid (2.27 g, 66%). M.p. 75.0–76.5 °C (from ethyl acetate/diethyl ether). ¹H NMR (CDCl₃): δ = 7.76 (d, *J* = 8.1 Hz, 2 H, ArH), 7.32 (d, *J* = 8.1 Hz, 2 H, ArH), 7.25 (br. s, 1 H, NH Thr), 5.99 (br. t, 1 H, NH Gly), 4.57–4.53 (m, 1 H, βCH Thr), 4.38–4.35 (m, 1 H, αCH Thr), 3.77 (s, 3 H, CH₃ CO₂Me), 3.69 (d, *J* = 6.6 Hz, 2 H, CH₂ Gly), 2.43 (s, 3 H, CH₃ Tos), 1.21 (d, *J* = 6.6 Hz, 3 H, γCH₃ Thr) ppm. ¹³C NMR (CDCl₃): δ = 171.49 (C=O), 169.02 (C=O), 144.04 (C), 135.58 (C), 129.88 (CH), 127.19 (CH), 67.87 (CH), 57.58 (CH), 52.76 (OCH₃), 45.66 (CH₂), 21.52 (CH₃ Tos), 19.89 (γCH₃) ppm. C₁₄H₂₀N₂O₆S (344.33): calcd. C 48.83, H 5.85, N 8.14, S 9.29; found C 48.68, H 5.98, N 8.06, S 9.35.

Tos-L-Ala-L-Thr-OMe (7d): The procedure referred to above was followed using Tos-L-Ala-OH (10 mmol) and HCl·H-L-Thr-OMe (10 mmol) giving **7d** as a white solid (3.44 g, 96%). M.p. 140.0–141.0 °C (from ethyl acetate/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.77 (d, *J* = 8.1 Hz, 2 H, ArH), 7.29 (d, *J* = 8.1 Hz, 2 H, ArH), 7.20 (d, *J* = 9.0 Hz, 1 H, NH Ala), 6.02 (d, *J* = 8.1 Hz, 1 H, NH Thr), 4.50–4.46 (m, 1 H, βCH Thr), 4.33–4.30 (m, 1 H, αCH Thr), 3.97–3.89 (m, 1 H, αCH Ala), 3.74 (s, 3 H, CH₃ CO₂Me), 2.41 (s, 3 H, CH₃ Tos), 1.28 (d, *J* = 6.9 Hz, 3 H, γCH₃ Ala), 1.08 (d, *J* = 6.3 Hz, 3 H, γCH₃ Thr) ppm. ¹³C NMR (CDCl₃): δ = 172.45 (C=O),



171.18 (C=O), 143.72 (C), 136.71 (C), 129.75 (CH), 127.16 (CH), 67.92 (aCH Thr), 57.47 (β CH Thr), 52.62 (OCH₃), 52.32 (aCH Ala), 21.47 (CH₃ Tos), 19.67 (γ CH₃), 19.34 (β CH₃) ppm. MS (FAB): *m*/*z* (%) = 359.08 (100) [M + 1]⁺, 299.07 (25.17), 198.11 (56.09). HRMS (FAB): calcd. for C₁₅H₂₃N₂O₆S [M + 1] 359.1277; found 359.1278. C₁₅H₂₃N₂O₆S (358,41): calcd. C 50.27, H 6.19, N 7.82, S 8.95; found C 50.18, H 6.12, N 7.80, S 8.73.

Tos-Gly-D,L-Phe(**β**-OH)-OMe (7e): The procedure referred to above was followed using Tos-Gly-OH (10 mmol) and HCl·H-D,L-Phe(β-OH)-OMe (10 mmol) giving 7e as a white solid (3.05 g, 75%). M.p. 118.0–120.0 °C (from ethyl acetate/diethyl ether). ¹H NMR (CDCl₃): δ = 7.71 (d, *J* = 8.4 Hz, 2 H, ArH Tos), 7.36–7.28 [m, 7 H, ArH Tos + ArH Phe(β-OH)], 5.51 (br. s, 1 H, NH Gly), 5.29 (d, *J* = 3.3 Hz, 1 H, βCH), 4.78 [dd, *J* = 3.3, *J* = 8.7 Hz, 1 H, αCH Phe(β-OH)], 3.73 (s, 3 H, CH₃ CO₂Me), 3.55–3.53 (m, 2 H, CH₂ Gly), 2.42 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (CDCl₃): δ = 170.92 (C=O), 168.67 (C=O), 143.85 (C), 139.41 (C), 135.68 (C), 129.79 (CH), 128.38 (CH), 128.12 (CH), 127.09 (CH), 125.91 (CH), 73.36 (CH), 58.44 (CH), 52.72 (OCH₃), 45.46 (CH₂), 21.48 (CH₃ Tos) ppm. C₁₉H₂₂N₂O₆S (406.40): calcd. C 56.15, H 5.46, N 6.89, S 7.87; found C 55.80, H 5.60, N 6.84, S 7.49.

Tos-L-Ala-D,L-Phe(β-OH)-OMe (7f): The procedure referred to above was followed using Tos-L-Ala-OH (10 mmol) and HCl· H-D,L-Phe(β -OH)-OMe (10 mmol) giving 7f as a diastereomeric mixture (4.01 g, 95%). Crystallization from ethyl acetate/n-hexane allowed the isolation of one of the diastereomers as a white solid. M.p. 173.0–174.0 °C. ¹H NMR (DMSO): $\delta = 8.15$ [d, J = 9.0 Hz, 1 H, NH Phe(β -OH)], 7.77 (d, J = 8.1 Hz, 1 H, NH Ala), 7.61 (d, J = 8.1 Hz, 2 H, ArH Tos), 7.34–7.18 [m, 7 H, ArH Tos + ArH Phe(β -OH)], 5.89 [d, J = 4.5 Hz, 1 H, OH Phe(β -OH)], 5.11–5.09 [m, 1 H, β CH Phe(β -OH)], 4.46 [dd, J = 2.7, J = 9.0 Hz, 1 H, αCH Phe(β-OH)], 3.94–3.84 (m, 1 H, αCH Ala), 3.65 (s, 3 H, CH₃) CO_2Me), 2.35 (s, 3 H, CH₃ Tos), 0.68 (d, J = 7.2 Hz, 3 H, β CH₃ Ala) ppm. ¹³C NMR (DMSO): $\delta = 171.36$ (C=O), 170.38 (C=O), 142.34 (C), 141.41 (C), 138.45 (C), 129.35 (CH), 127.66 (CH), 127.14 (CH), 126.48 (CH), 126.20 (CH), 72.18 [BCH Phe(B-OH)], 57.90 [αCH Phe(β-OH)], 52.00 (OCH₃), 51.28 (αCH Ala), 20.96 (CH₃ Tos), 18.85 (βCH₃ Ala) ppm. C₂₀H₂₄N₂O₆S (420.48): calcd. C 57.13, H 5.75, N 6.66, S 7.63; found C 57.13, H 5.69, N 6.63, S 7.62. The other diastereomer was obtained from the mother liquor as an oil. ¹H NMR (CDCl₃): δ = 7.69 (d, J = 8.4 Hz, 2 H, ArH Tos), 7.33–7.22 [m, 8 H, ArH Tos + ArH Phe(β-OH) + NH], 5.51 (br. d, J = 7.5 Hz, 1 H, NH), 5.25 [d, J = 3.3 Hz, 1 H, β CH Phe(β -OH)], 4.74 [dd, J = 3.3, J = 8.6 Hz, 1 H, α CH Phe(β -OH)], 3.83– 3.76 (m, 1 H, αCH Ala), 3.70 (s, 3 H, CH₃ CO₂Me), 3.42 (br. s, 1 H, OH), 2.41 (s, 3 H, CH₃ Tos), 1.11 (d, J = 6.9 Hz, 3 H, β CH₃ Ala) ppm. ¹³C NMR (CDCl₃): δ = 171.85 (C=O), 170.57 (C=O), 143.63 (C), 139.57 (C), 136.55 (C), 129.71 (CH), 128.27 (CH), 127.94 (CH), 127.03 (CH), 125.92 (CH), 73.41 [\$CH Phe(\$-OH)], 58.35 [αCH Phe(β-OH)], 52.58 (OCH₃), 52.34 (αCH Ala), 21.47 (CH₃ Tos), 18.82 (βCH₃ Ala) ppm.

Boc-L-Ala-L-Ser-OMe (7g): The procedure referred to above was followed using Boc-L-Ala-OH (10 mmol) and HCl·H-L-Ser-OMe (10 mmol of) giving **7g** as an oil (2.35 g, 81%).^[15]

Boc-Gly-L-Thr-OMe (7h): The procedure referred to above was followed using Boc-Gly-OH (10 mmol) and HCl·H-L-Thr-OMe (10 mmol) giving **7h** as an oil (2.12 g, 73%). ¹H NMR (CDCl₃): δ = 7.00 (d, *J* = 9.0 Hz, 1 H, NH Thr), 5.37 (br. s, 1 H, NH Gly), 4.61 (dd, *J* = 2.7, *J* = 9.0 Hz, 1 H, αCH Thr), 4.36–4.32 (m, 1 H, βCH Thr), 3.88 (d, *J* = 6.0 Hz, 2 H, CH₂ Gly), 3.77 (s, 3 H, CH₃ CO₂Me), 1.45 (s, 9 H, CH₃ Boc), 1.22 (d, *J* = 6.3 Hz, 3 H, γCH₃ ΔAbu) ppm. ¹³C NMR (CDCl₃): δ = 171.45 (C=O), 170.40 (C=O),

156.18 (C=O), 80.12 [*C*(CH₃)₃], 67.74 (CH), 57.46 (CH), 52.51 (OCH₃), 43.88 (CH₂), 28.17 [C(*C*H₃)₃], 19.80 (γCH₃) ppm.

Boc-Gly-L-Ser-OMe (7i): The procedure referred to above was followed using Boc-Gly-OH (10 mmol) and HCl·H-L-Ser-OMe (10 mmol) giving **7i** as an oil (2.04 g, 74%). ¹H NMR (CDCl₃): *δ* = 7.32 (d, *J* = 7.5 Hz, 1 H, NH Thr), 5.60 (s, 1 H, NH Gly), 4.66–4.62 (m, 1 H, αCH Ser), 3.93 (br. t, *J* = 5.1 Hz, 2 H, βCH₂ Ser), 3.84 (br. s, 2 H, CH₂ Gly), 3.76 (s, 3 H, CH₃ CO₂Me), 3.34 (br. s, 1 H, OH), 1.43 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): *δ* = 170.89 (C=O), 170.00 (C=O), 156.36 (C=O), 80.42 [*C*(CH₃)₃], 62.48 (CH₂), 54.69 (CH), 52.67 (OCH₃), 40.01 (CH₂), 28.21 [C(CH₃)₃] ppm.

Boc-Gly-D,L-Phe(β-OH)-OMe (7j): The procedure referred to above was followed using Boc-Gly-OH (10 mmol) and HCl·H-D,L-Phe(β-OH)-OMe (10 mmol) giving **7j** as a white solid (3.03 g, 86%). M.p. 132.5–133.5 °C (from diethyl ether/diethyl ether). ¹H NMR (CDCl₃): δ = 7.35–7.24 (m, 5 H, ArH), 7.16 (br. d, *J* = 8.1 Hz, 1 H, NH), 5.30 (br. s, 1 H, NH), 5.25 (d, *J* = 3.3 Hz, 1 H, β-CH), 4.83 (dd, *J* = 3.3, *J* = 8.7 Hz, 1 H, α-CH), 3.73–3.69 (m, 5 H, CH₃ CO₂Me + CH₂ Gly), 1.42 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 170.85 (C=O), 169.87 (C=O), 155.96 (C=O), 139.64 (C), 128.31 (CH), 128.00 (CH), 125.79 (CH), 80.14 [Cinline style="font-weight: bold; vertical-align: sub;"(CH₃)₃], 73.35 (CH), 58.18 (CH), 52.60 (OCH₃), 43.75 (CH₂), 28.19 [C(CH₃)₃] ppm. C₁₇H₂₄N₂O₆ (352.38): calcd. C 57.94, H 6.86, N 7.95; found C 58.43, H 7.16, N 8.41.

Z-Gly-L-Ser-OMe (71): The procedure referred to above was followed using Z-Gly-OH (10 mmol) and HCl·H-L-Ser-OMe (10 mmol) giving **71** as a white solid (2.82 g, 91%). M.p. 93.0–94.0 °C (from ethyl acetate/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.34–7.30 (m, 5 H, ArH), 7.21 (d, *J* = 7.5 Hz, 1 H, NH Ser), 5.79 (br. s, 1 H, NH Gly), 5.11 (s, 2 H, CH₂ Z), 4.67–4.62 (m, 1 H, αCH Ser), 3.98–3.92 (m, 4 H, βCH₂ Ser + CH₂ Gly), 3.75 (s, 3 H, CH₃ CO₂Me) ppm. ¹³C NMR (DMSO): δ = 170.88 (C=O), 169.54 (C=O), 156.89 (C=O), 135.99 (C), 128.53 (CH), 128.24 (CH), 128.05 (CH), 67.29 (CH₂), 62.61 (αCH), 54.69 (CH₂), 52.76 (OCH₃), 44.29 (CH₂) ppm. C₁₄H₁₈N₂O₆ (310.30): calcd. C 54.19, H 5.85 N 9.03; found C 54.26, H 5.84, N 9.21.

Synthesis of the Methyl Esters of *N*-Protected *N*,*N'*-Bis(*tert*-butyloxycarbonyl)dehydrodipeptides 8a,c-h

Tos-Gly(*N*-**Boc**)- Δ **Ala**(*N*-**Boc**)-**OMe** (8a): The synthesis of this compound has been described elsewhere.^[3a]

Tos-Gly(N-Boc)-Z-ΔAbu(N-Boc)-OMe (8c): DMAP (0.3 equiv.) was added to a solution of 7c (5 mmol, 1.72 g) in dry acetonitrile (1 moldm⁻³) followed by di-tert-butyl dicarbonate (3.3 equiv.) under rapid stirring at room temperature. The reaction was stirred for 12 h while monitored by TLC (diethyl ether/n-hexane, 2:1). Evaporation at reduced pressure gave a residue that was partitioned between diethyl ether (200 mL) and KHSO₄ (100 mL, 1 mol dm^{-3}). The organic phase was thoroughly washed with KHSO₄ (1 mol dm⁻³), NaHCO₃ (1 mol dm⁻³) and saturated brine $(3 \times 50 \text{ mL}, \text{ each})$, and dried with MgSO₄. Removal of the solvent afforded 8c as an oil (2.40 g, 91%). M.p. 61.0-62.0 °C (from diethyl ether/petroleum ether). ¹H NMR (CDCl₃): δ = 7.92 (d, J = 8.1 Hz, 2 H, ArH), 7.28 (d, J = 8.1 Hz, 2 H, ArH), 7.06 (q, J = 7.2 Hz, 1 H, CH ΔAbu), 5.34 (d, J = 18.9 Hz, 1 H, CH₂ Gly), 5.26 (d, J =18.9 Hz, 1 H, CH₂ Gly), 3.77 (s, 3 H, CH₃ CO₂Me), 2.43 (s, 3 H, CH₃ Tos), 1.73 (d, J = 7.2 Hz, 3 H, γ CH₃ Δ Abu), 1.48 (s, 9 H, CH₃ Boc), 1.31 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 169.61 (C=O), 163.70 (C=O), 151.41 (C=O), 150.55 (C=O), 144.13 (C), 138.69 (C), 136.82 (C), 129.21 (CH), 128.97 (CH), 128.71 (CH),

84.49 [(CH₃)₃CO], 84.22 [(CH₃)₃CO], 52.18 (OCH₃), 51.06 (CH₂), 27.79 [C(CH₃)₃], 27.73 [C(CH₃)₃], 21.62 (CH₃ Tos), 13.52 (CH₃) ppm. $C_{24}H_{34}N_2O_9S$ (526.55): calcd. C 54.75, H 6.51, N 5.32, S 6.08; found C 54.71, H 6.53, N 5.25, S 5.98.

Tos-L-Ala(N-Boc)-Z-AAbu(N-Boc)-OMe (8d): The same procedure described above was used substituting compound 7d (5 mmol, 1.79g) for compound 7c giving 8d as an oil (1.41g, 52%). ¹H NMR (CDCl₃) doubling of signals due to the presence of two conformers:^[16] δ = 7.86–7.81 (m, 4 H, ArH), 7.29–7.24 (m, 4 H, ArH), 7.06 $(q, J = 7.2 \text{ Hz}, 1 \text{ H}, \text{ CH } \Delta \text{Abu}), 7.00 (q, J = 6.9 \text{ Hz}, 1 \text{ H}, \text{ CH})$ Δ Abu), 6.42 (q, J = 7.2 Hz, 1 H, α CH Ala), 6.03 (q, J = 6.9 Hz, 1 H, αCH Ala), 3.77 (s, 3 H, CH_3 $CO_2Me),$ 3.75 (s, 3 H, CH_3 CO₂Me), 2.42 (s, 3 H, CH₃ Tos), 2.41 (s, 3 H, CH₃ Tos), 1.93 (d, J = 7.2 Hz, 3 H, CH₃ Δ Abu), 1.74 (d, J = 7.2 Hz, 3 H, CH₃ Δ Abu), 1.50 (s, 9 H, CH₃ Boc), 1.48 (s, 9 H, CH₃ Boc), 1.33 (s, 9 H, CH₃ Boc), 1.31 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃) doubling of signals due to the presence of two conformers: $\delta = 172.14$ (C=O), 171.59 (C=O), 163.96 (C=O), 151.23 (C=O), 151.09 (C=O), 150.69 (C=O), 150.58 (C=O), 144.07 (C), 143.82 (C), 138.81 (C), 138.06 (C), 137.19 (C), 136.97 (C), 129.50 (CH), 129.21 (CH), 129.11 (CH), 129.03 (CH), 128.29 (CH), 128.16 (CH), 84.38 [(CH₃)₃CO], 84.21 [(CH₃)₃CO], 84.18 [(CH₃)₃CO], 83.71 [(CH₃)₃CO], 57.93 (CH), 57.04 (CH), 52.18 (OCH₃), 27.77 [C(CH₃)₃], 27.70 [Cinline style="font-weight: bold; vertical-align: sub;"(CH₃)₃], 22.59 (CH₃) Tos), 21.58 (CH₃ Tos), 18.52 (CH₃ Ala), 17.09 (CH₃ Ala), 13.62 (CH₃ Δ Abu), 13.45 (CH₃ Δ Abu) ppm. C₂₅H₃₆N₂O₉S (540.63): calcd. C 55.54, H 6.71, N 5.18, S 5.93; found C 55.86, H 6.69, N 5.12, S 5.63.

Tos-Gly(*N***-Boc)-***Z***-ΔPhe(***N***-Boc)-OMe (8e): The same procedure described above was used substituting compound 7e** (5 mmol, 2.03 g) for compound **7c** giving **8e** as an oil (2.83 g, 96%). M.p. 64.0–66.0 °C (from ethyl acetate/*n*-hexane). ¹H NMR (CDCl₃): $\delta = 7.75$ (d, J = 8.1 Hz, 2 H, ArH), 7.74 (s, 1 H, CH ΔPhe), 7.42–7.38 (m, 5 H, ArH), 7.17 (d, J = 8.1 Hz, 2 H, ArH), 5.30 (d, J = 6.6 Hz, 2 H, CH₂ Gly), 3.83 (s, 3 H, CH₃ CO₂Me), 2.38 (s, 3 H, CH₃ Tos), 1.31 (s, 9 H, CH₃ Boc), 1.30 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): $\delta = 170.22$ (C=O) 164.42 (C=O), 151.07 (C=O), 150.41 (C=O), 144.06 (C), 137.98 (C), 132.61 (C), 130.23 (C), 129.33 (CH), 129.01 (CH), 128.91 (CH), 128.78 (CH), 125.99 (CH), 84.40 [(CH₃)₃CO], 84.32 [(CH₃)₃CO], 52.55 (OCH₃), 51.25 (CH₂), 27.68 [C(CH₃)₃], 27.51 [C(CH₃)₃], 21.62 (CH₃ Tos) ppm. C₂₉H₃₆N₂O₉S (588.62): calcd. C 59.17, H 6.16, N 4.76, S 5.44; found C 59.27, H 6.33, N 4.62, S 5.18.

Tos-L-Ala(N-Boc)-Z-ΔPhe(N-Boc)-OMe (8f): The same procedure described above was used substituting compound 7f (5 mmol, 2.10g) for compound 7c giving 8f as an oil (2.83 mg, 94%). M.p. 59.0-60.5 °C (from diethyl ether/petroleum ether). ¹H NMR (CDCl₃) doubling of signals due to the presence of two conformers:^[16] δ = 7.84–7.70 (m, 6 H, ArH + CH Δ Phe), 7.44–7.37 (m, 10 H, ArH), 7.25–7.20 (m, 4 H, ArH), 6.46 (q, J = 6.9 Hz, 1 H, α CH Ala), 5.76 (br. d, J = 6.0 Hz, 1 H, α CH Ala), 3.85 (s, 3 H, CH₃ CO₂Me), 3.84 (s, 3 H, CH₃ CO₂Me), 2.40 (s, 3 H, CH₃ Tos), 2.38 (s, 3 H, CH₃ Tos), 1.81 (d, J = 6.9 Hz, 3 H, CH₃ Ala), 1.63–1.61 (m, 3 H, CH₃ Ala), 1.46 (s, 9 H, CH₃ Boc), 1.37 (s, 9 H, CH₃ Boc), 1.33 (s, 9 H, CH₃ Boc), 1.17 (s, 9 H, CH₃ Boc) ppm. 13 C NMR (CDCl₃) doubling of signals due to the presence of two conformers: δ = 172.13 (C=O), 171.56 (C=O), 164.60 (C=O), 151.01 (C=O), 150.88 (C=O), 150.52 (C=O), 150.33 (C=O), 144.09 (C), 143.72 (C), 137.80 (C), 137.34 (C), 136.86 (C), 136.60 (C), 132.55 (C), 132.51 (C), 130.17 (CH), 129.98 (CH), 129.54 (CH), 129.38 (CH), 129.03 (CH), 129.00 (CH), 128.95 (CH), 128.65 (CH), 128.48 (CH), 128.31 (CH), 127.21 (C), 126.84 (C), 84.66 [(CH₃)₃CO], 84.48

[(CH₃)₃CO], 83.99 [(CH₃)₃CO], 83.85 [(CH₃)₃CO], 57.70 (CH), 56.53 (CH), 52.52 (OCH₃), 27.71 [C(CH₃)₃], 27.62 [C(CH₃)₃], 27.56 [C(CH₃)₃], 27.52 [C(CH₃)₃], 21.55 (CH₃ Tos), 18.20 (CH₃ Ala), 16.86 (CH₃ Ala) ppm. $C_{30}H_{38}N_2O_9S$ (602,70): calcd. C 59.79, H 6.35, N 4.65, S 5.32; found C 59.84, H 6.37, N 4.84, S 5.14.

Boc-L-Ala(N-Boc)-ΔAla(N-Boc)-OMe (8g): The synthesis of this compound has been described elsewhere.^[1]

Boc-Gly(*N***-Boc)-***Z***-ΔAbu(***N***-Boc)-OMe (8h): The same procedure described above was used substituting compound 7h** (5 mmol, 1.45 g) for compound **7c** giving **8h** as an oil (1.94 g, 82%). M.p. 91.0–92.0 °C (*n*-hexane). ¹H NMR (CDCl₃): δ = 7.03 (q, *J* = 7.2 Hz, 1 H, βCH ΔAbu), 5.04 (d, *J* = 18.3 Hz, 1 H, CH₂ Gly), 4.89 (d, *J* = 18.3 Hz, 1 H, CH₂ Gly), 3.75 (s, 3 H, CH₃ CO₂Me), 1.71 (d, *J* = 7.2 Hz, 3 H, γCH₃ ΔAbu), 1.49 (s, 18 H, CH₃ Boc), 1.46 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 169.92 (C=O), 163.81 (C=O), 152.18 (C=O), 151.52 (C=O), 138.34 (C), 128.80 (CH), 83.82 [(CH₃)₃CO], 82.59 [(CH₃)₃CO], 52.10 (OCH₃), 51.41 (CH₂), 27.93 [C(CH₃)₃], 27.77 [C(CH₃)₃], 13.51 (CH₃) ppm. C₂₂H₃₆N₂O₉ (472.54): calcd. C 55.92, H 7.68, N 5.93; found C 55.65, H 7.53, N 5.98.

Synthesis of the Methyl Esters of *N*-Protected Dehydrodipeptides 9a,c-h by Deprotection of the Methyl Esters of *N*-Protected *N*,*N*'-Bis(*tert*-butyloxycarbonyl)dehydrodipeptides

Tos-Gly-AAla-OMe (9a): A 10% solution of TFA was added to a solution of **8a** (3 mmol, 1.54 g) in dichloromethane (0.1 mol dm⁻³) with vigorous stirring. The reaction was monitored by TLC and when no starting material was detected additional dichloromethane (50 mL) was added. The organic phase was then washed with NaHCO₃ (1 moldm⁻³) and brine (3 \times 30 mL). After drying with MgSO₄ the extract was taken to dryness at reduced pressure to afford compound 9a as an oil (0.90 g, 96%). Crystallization from diethyl ether afforded white crystals. M.p. 122.5-124.0 °C. 1H NMR (DMSO): δ = 9.23 (s, 1 H, NH), 8.11 (br. s, 1 H, NH), 7.68 (d, J = 8.1 Hz, 2 H, ArH), 7.38 (d, J = 8.1 Hz, 2 H, ArH), 6.22 (s, J = 0.1 Hz, 2 H, ArH)1 H, β-CH₂), 5.71 (s, 1 H, β-CH₂), 3.76 (s, 3 H, CH₃ CO₂Me), 3.60 (d, J = 5.4 Hz, 2 H, CH₂), 2.37 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (CDCl₃): δ = 166.64 (C=O), 164.04 (C=O), 144.14 (C), 135.61 (C), 130.40 (C), 129.91 (CH), 127.16 (CH), 109.90 (=CH₂), 53.09 (OCH₃), 46.34 (CH₂), 21.51 (CH₃ Tos) ppm. C₁₃H₁₆N₂O₅S (312.28): calcd. C 50.00, H 5.16, N 8.97, S 10.25; found C 49.83, H 5.19, N 8.96, S 10.39.

Tos-Gly-Z-ΔAbu-OMe (9c): The procedure described above was used substituting compound **8c** (3 mmol, 1.58 g) for **8a** to give **9c** as an oil (0.94 g, 96%). M.p. 111.5–113.0 °C (from diethyl ether). ¹H NMR (CDCl₃): δ = 7.77 (d, *J* = 8.1 Hz, 2 H, ArH), 7.51 (s, 1 H, NH ΔAbu), 7.34 (d, *J* = 8.1 Hz, 2 H, ArH), 6.87 (q, *J* = 7.5 Hz, 1 H, βCH ΔAbu), 5.34 (t, *J* = 6.3 Hz, 1 H, NH Gly), 3.77 (s, 3 H, CH₃ CO₂Me), 3.72 (d, *J* = 6.3 Hz, 2 H, CH₂ Gly), 2.45 (s, 3 H, CH₃ Tos), 1.73 (d, *J* = 7.5 Hz, 3 H, γCH₃ ΔAbu) ppm. ¹³C NMR (CDCl₃): δ = 166.89 (C=O), 164.73 (C=O), 144.04 (C), 135.83 (C), 135.60 (C), 129.87 (CH), 127.18 (CH), 125.52 (CH), 52.42 (OCH₃), 45.91 (CH₂), 21.50 (CH₃ Tos), 14.36 (CH₃) ppm. C₁₄H₁₈N₂O₅S (326.31): calcd. C 51.53, H 5.56, N 8.58, S 9.81; found C 51.21, H 5.50, N 8.47, S 9.85.

Tos-L-Ala-Z-ΔAbu-OMe (9d): The procedure described above was used substituting compound **8d** (3 mmol, 2.70 g) for **8a** to give **9d** as an oil (0.48 mg, 47%). M.p. 118.5–119.5 °C (from diethyl ether). ¹H NMR (CDCl₃): δ = 7.77 (d, *J* = 8.1 Hz, 2 H, ArH), 7.59 (s, 1 H, NH ΔAbu), 7.32 (d, *J* = 8.1 Hz, 2 H, ArH), 6.83 (q, *J* = 7.2 Hz, 1 H, βCH ΔAbu), 5.37 (d, *J* = 7.5 Hz, 1 H, NH Ala), 3.93 (m, 1 H, αCH Ala), 3.76 (s, 3 H, CH₃ CO₂Me), 2.43 (s, 3 H, CH₃ Tos),

1.68 (d, J = 7.2 Hz, 3 H, γCH₃ ΔAbu), 1.32 (d, J = 7.2 Hz, 3 H, βCH₃ Ala) ppm. ¹³C NMR (CDCl₃): $\delta = 170.05$ (C=O), 164.63 (C=O), 143.97 (C), 136.34 (C), 135.31 (C), 129.88 (CH), 127.19 (CH), 125.57 (CH), 52.68 (CH), 52.37 (OCH₃), 21.51 (CH₃ Tos), 19.02 (CH₃), 14.34 (CH₃) ppm. C₁₅H₂₀N₂O₅S (340.40): calcd. C 52.93, H 5.92, N 8.23, S 9.42; found C 52.49, H 6.14, N 8.17, S 9.06.

Tos-Gly-Z-ΔPhe-OMe (9e): The procedure described above was used substituting compound **8e** (3 mmol, 1.77 g) for **8a** to give **9e** as an oil (1.07 g, 92%). M.p. 132.0–134.0 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 8.20 (s, 1 H, NH ΔPhe), 7.73 (d, J = 8.1 Hz, 2 H, ArH Tos), 7.53–7.30 (m, 8 H, ArH + βCH), 6.06 (t, J = 6.6 Hz, 1 H, NH Gly), 3.77 (s, 3 H, CH₃ CO₂Me), 3.65 (d, J = 6.6 Hz, 2 H, CH₂), 2.41 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (CDCl₃): δ = 167.52 (C=O), 165.44 (C=O), 144.01 (C), 135.71 (C), 134.12 (C), 133.01 (CH), 129.92 (CH), 129.88 (CH), 129.81 (CH), 128.69 (CH), 127.14 (CH), 123.29 (C), 52.74 (OCH₃), 46.04 (CH₂), 21.49 (CH₃ Tos) ppm. C₁₉H₂₀N₂O₅S (388.44): calcd. C 58.75, H 5.19, N 7.21, S 8.26; found C 58.50, H 5.27, N 7.32, S 8.12. HRMS (FAB): calcd. for C₁₉H₂₁N₂O₅S 389.1171 [M + 1]; found 389.1186.

Tos-L-Ala-Z-ΔPhe-OMe (9f): The procedure described above was used substituting compound **8f** (3 mmol, 1.81 g) for **8a** to give **9f** as an oil (1.05 g, 87%). M.p. 133.5–134.5 °C (from diethyl ether). ¹H NMR (CDCl₃): δ = 7.95 (br. s, 1 H, NH ΔPhe), 7.72 (d, *J* = 8.1 Hz, 2 H, ArH Tos), 7.50–7.30 (m, 8 H, ArH + βCH ΔPhe), 5.35 (d, *J* = 7.5 Hz, 1 H, NH Ala), 3.90 (m, 1 H, αCH Ala), 3.82 (s, 3 H, CH₃ CO₂Me), 2.43 (s, 3 H, CH₃ Tos), 1.26 (d, *J* = 7.2 Hz, 3 H, βCH₃ Ala) ppm. ¹³C NMR (CDCl₃): δ = 170.19 (C=O), 165.36 (C=O), 143.99 (C), 136.35 (C), 133.49 (C), 133.20 (CH), 129.89 (CH), 129.84 (CH), 129.69 (CH), 128.62 (CH), 127.14 (CH), 123.49 (C), 52.77 (CH), 52.67 (OCH₃), 21.52 (CH₃ Tos), 18.33 (CH₃) ppm. C₂₀H₂₂N₂O₅S (402.47): calcd. C 59.69, H 5.51, N 6.96, S 7.97; found C 59.63, H 5.45, N 6.89, S 7.81.

Boc-L-Ala-ΔAla-OMe (9g): The procedure described above was used substituting compound **8g** (3 mmol, 1.42 g) for **8a** to give **9g** as a white solid (0.751 g, 92%). M.p. 81.0–82.5 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 8.45 (s, 1 H, NH ΔAla), 6.61 (s, 1 H, βCH₂ ΔAla), 5.91 (d, *J* = 1.5 Hz, 1 H, βCH₂ ΔAla), 4.97 (br. s, 1 H, NH Ala), 4.27–4.25 (m, 1 H, αCH Ala), 3.85 (s, 3 H, CH₃ CO₂Me), 1.46 (s, 9 H, CH₃ Boc), 1.41 (d, *J* = 7.2 Hz, 3 H, βCH₃ Ala) ppm. ¹³C NMR (CDCl₃): δ = 171.50 (C=O), 164.24 (C=O), 155.40 (C=O), 130.79 (C), 109.22 (βCH₂), 80.52 [(CH₃)₃CO], 52.93 (OCH₃), 50.94 (αCH), 28.23 [C(CH₃)₃], 17.95 (βCH₃) ppm. C₁₂H₂₀N₂O₅ (272.30): calcd. C 52.93, H 7.40, N 10.29; found C 52.77, H 7.07, N 10.17.

Boc-Gly-Z-ΔAbu-OMe (9h): The procedure described above was used substituting compound **8h** (3 mmol, 1.42 g) for **8a** to give **9h** as a white solid (0.71 g, 87%). M.p. 100.0–101.5 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.52 (s, 1 H, NH ΔAbu), 6.85 (q, *J* = 7.2 Hz, 1 H, βCH ΔAbu), 5.26 (br. s, 1 H, NH Gly), 3.93 (d, *J* = 5.4 Hz, 2 H, CH₂ Gly), 3.76 (s, 3 H, CH₃ CO₂Me), 1.78 (d, *J* = 7.2 Hz, 3 H, γCH₃ ΔAbu), 1.46 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 168.21 (C=O), 164.75 (C=O), 156.11 (C=O), 134.86 (C), 125.77 (CH), 80.13 [(CH₃)₃CO], 52.21 (OCH₃), 44.28 (CH₂), 28.14 [C(CH₃)₃], 14.32 (γCH₃) ppm. C₁₂H₂₀N₂O₅ (272.30): calcd. C 52.93, H 7.40, N 10.29; found C 53.11, H 7.15, N 9.95.

Synthesis of N-Acyl-O-(tert-butyloxycarbonyl)dipeptide Esters 10b, 10h and 10i

Tos-L-Ala-L-Ser(*O*-Boc)-OMe (10b): DMAP (0.1 equiv.) was added to a solution of Tos-L-Ala-L-Ser-OMe (7b) (5 mmol, 1.72 g) in dry

acetonitrile (1 moldm⁻³) followed by di-tert-butyl dicarbonate (1.0 equiv.) under rapid stirring at room temperature. The reaction was monitored by TLC (diethyl ether/n-hexane, 1:1) until all the reactant had been consumed. Evaporation of the solvent at reduced pressure gave a residue that was partitioned between diethyl ether (100 mL) and KHSO₄ (30 mL, 1 mol dm⁻³). The organic phase was thoroughly washed with KHSO₄ (1 mol dm⁻³), NaHCO₃ (1 mol dm^{-3}) and saturated brine $(2 \times 30 \text{ mL}, \text{ each})$, and dried with MgSO₄. Removal of the solvent afforded Tos-L-Ala-L-Ser(O-Boc)-OMe (10b) (0.378 g, 85%) as a white solid. M.p. 114.5-116.5 °C (from diethyl ether/petroleum ether). ¹H NMR (CDCl₃): $\delta = 7.74$ (d, J = 8.4 Hz, 2 H, ArH), 7.29 (d, J = 8.4 Hz, 2 H, ArH), 6.88(br. d, J = 7.8 Hz, 1 H, NH), 5.44 (br. d, J = 7.8 Hz, 1 H, NH), 4.68–4.63 (m, 1 H, α CH Ser), 4.40 (dd, J = 11.3, J = 3.9 Hz, 1 H, β CH₂ Ser), 4.10 (dd, J = 11.3, J = 3.6 Hz, 1 H, β CH₂ Ser), 3.91– 3.85 (m, 1 H, aCH Ala), 3.76 (s, 3 H, CH₃ CO₂Me), 2.41 (s, 3 H, CH₃ Tos), 1.48 (s, 9 H, CH₃ Boc), 1.31 (d, J = 6.6 Hz, 3 H, β CH₃ Ala) ppm. ¹³C NMR (CDCl₃): δ = 171.31 (C=O), 169.14 (C=O), 152.98 (C=O), 143.80 (C), 136.58 (C), 129.74 (CH), 127.22 (CH), 80.05 [C(CH₃)₃], 65.62 (βCH₂ Ser), 52.92 (OCH₃), 52.28 (αCH Ala), 51.86 (aCH Ser), 27.61 [C(CH₃)₃], 21.47 (CH₃ Tos), 19.54 (βCH₃ Ala) ppm. C₁₉H₂₈N₂O₈S (444.50): calcd. C 51.34, H 6.35, N 6.30, S 7.21; found C 51.77, H 6.28, N 6.56, S 7.39.

Boc-Gly-L-Thr(*O***-Boc)-OMe (10h):** The procedure described above was used substituting compound **7h** (5 mmol, 1.38 g) for **7b** to give **10h** as a white solid (1.54 g, 79%). M.p. 101.0–102.5 °C (from ethyl acetate/*n*-hexane) ¹H NMR (CDCl₃): $\delta = 6.64$ (d, J = 7.5 Hz, 1 H, NH), 5.30–4.26 (m, 1 H, βCH), 5.12 (br. s, 1 H, NH), 4.79 (dd, J = 2.4, J = 9.3 Hz, 1 H, αCH), 3.91–3.86 (m, 2 H, CH₂ Gly), 3.75 (s, 3 H, CH₃ CO₂Me), 1.48 (s, 9 H, CH₃ Boc), 1.47 (s, 9 H, CH₃ Boc), 1.30 (d, J = 6.3 Hz, 3 H, γCH₃) ppm. ¹³C NMR (CDCl₃): $\delta = 169.44$ (C=O), 155.84 (C=O), 152.97 (C=O), 82.92 [*C*(CH₃)₃], 80.20 [*C*(CH₃)₃], 65.91 (βCH₂), 52.87 (OCH₃), 51.71 (αCH), 44.06 (CH₂), 28.22 [*C*(CH₃)₃], 27.58 [*C*(CH₃)₃] ppm. C₁₇H₃₀N₂O₈ (390.43): calcd. C 52.30, H 7.74, N 7.18; found C 53.43, H 7.61, N 7.42.

Boc-Gly-L-Ser(*O***-Boc)-OMe (10i):** The procedure described above was used substituting compound 7i (5 mmol, 1.38 g) for 7b to give **10i** (1.26 g, 67%) as a white solid. M.p. 71.5–73.0 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 6.95 (d, *J* = 7.5 Hz, 1H, NH), 5.23 (br. s, 1 H, NH), 4.85–4.80 (m, 1 H, CH Ser), 4.47 (dd, *J* = 11.4, *J* = 3.6 Hz, 1 H, CH₂ Ser), 4.31 (dd, *J* = 11.4, *J* = 3.3 Hz, 1 H, CH₂ Ser), 3.86–3.82 (m, 2 H, CH₂ Gly), 3.76 (s, 3 H, CH₃ CO₂Me), 1.45 (s, 18 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 169.44 (C=O), 155.84 (C=O), 152.97 (C=O), 82.92 [*C*(CH₃)₃], 80.20 [*C*(CH₃)₃], 65.91 (βCH₂ Ser), 52.87 (OCH₃), 51.71 (αCH Ser), 44.06 (CH₂ Gly), 28.22 [*C*(CH₃)₃], 27.58 [*C*(CH₃)₃] ppm. C₁₆H₂₈N₂O₈ (376.40): calcd. C 51.05, H 7.50, N 7.44; found C 51.35, H 7.12, N 7.52.

Synthesis of *N*-Acyldehydrodipeptide Esters 9h and 9i from *N*-Acyl-*O*-(*tert*-Butyloxycarbonyl)Dipeptide Esters

Boc-Gly-Z-AAbu-OMe (9h): TMG (2% in volume) was added to a solution of Boc-Gly-L-Thr(*O*-Boc)-OMe (**10h**) (2 mmol, 0.78 g) in acetonitrile (0.1 moldm⁻³) and stirring was continued and the reaction followed by TLC. When all the reactant had been consumed evaporation at reduced pressure gave a residue that was partitioned between diethyl ether (50 mL) and KHSO₄ (30 mL, 1 moldm⁻³). The organic phase was thoroughly washed with KHSO₄ (1 moldm⁻³), NaHCO₃ (1 moldm⁻³) and saturated brine (2 × 30 mL, each), and dried with MgSO₄. Removal of the solvent afforded **9h** (0.50 g, 92%).



Boc-Gly-AAla-OMe (9i): The procedure described above was used substituting compound **10i** (1 mmol, 0.376 g) for **10h** to give **9i** (0.168 g, 65%) as a white solid. M.p. 155.0–156.5 °C (from diethyl ether/petroleum ether). ¹H NMR (CDCl₃): δ = 8.32 (br. s, 1 H, NH), 6.61 (s, 1 H, CH₂ ΔAla), 5.93 (d, *J* = 1.5 Hz, 1 H, CH₂ ΔAla), 5.16 (br. s, 1 H, NH), 3.90 (d, *J* = 7.8 Hz, 2 H, CH₂ Gly), 3.85 (s, 3 H, CH₃ CO₂Me), 1.47 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 168.27 (C=O), 164.24 (C=O), 156.92 (C=O), 130.56 (C), 109.39 (CH₂), 80.05 [(CH₃)₃C], 52.98 (OCH₃), 45.16 (CH₂), 21.48 [(CH₃)₃C] ppm. C₁₁H₁₈N₂O₅ (258.27): calcd. C 51.15, H 7.02, N 10.85; found C 51.08, H 7.00, N 10.89.

One-Pot Synthesis of N-Acyldehydrodipeptide Esters 9b,f,h-l

Tos-L-Ala-AAla-OMe (9b): DMAP (0.1 equiv.) was added to a solution of Tos-L-Ala-L-Ser-OMe (7b) (5 mmol, 1.72 g) in dry acetonitrile (1 mol dm⁻³) followed by di-tert-butyl dicarbonate (1.0 equiv.) under rapid stirring at room temperature. The reaction was monitored by TLC (diethyl ether/n-hexane, 1:1) until all the reactant had been consumed. Then TMG (2% in volume) was added, stirring was continued and the reaction followed by TLC. When all the reactant had been consumed evaporation at reduced pressure gave a residue that was partitioned between diethyl ether (50 mL) and KHSO₄ (30 mL, 1 moldm⁻³). The organic phase was thoroughly washed with KHSO₄ (1 mol dm⁻³), NaHCO₃ (1 mol dm^{-3}) and saturated brine $(2 \times 30 \text{ mL}, \text{ each})$, and dried with MgSO₄. Removal of the solvent afforded **9b** (1.21 g, 93%) as a white solid. M.p. 113.5–114.5 °C (from diethyl ether/n-hexane). ¹H NMR (CDCl₃): δ = 8.50 (s, 1 H, NH), 7.77 (d, J = 8.1 Hz, 2 H, ArH), 7.29 (d, J = 8.1 Hz, 2 H, ArH), 6.46 (s, 1 H, β CH₂), 5.86 (br. d, J = 1.5 Hz, 1 H, β CH₂), 5.63 (br. d, J = 7.5 Hz, 1 H, NH), 3.91-3.86 (m, 1 H, αCH Ala), 3.83 (s, 3 H, CH₃ CO₂Me), 2.41 (s, 3 H, CH₃ Tos), 1.31 (d, J = 6.6 Hz, 3 H, β CH₃ Ala) ppm. ¹³C NMR (CDCl₃): δ = 170.18 (C=O), 164.03 (C=O), 143.99 (C), 136.20 (C), 130.55 (C), 129.86 (CH), 127.27 (CH), 109.51 (βCH₂), 53.02 (OCH₃), 53.01 (αCH Ala), 21.50 (CH₃ Tos), 18.86 (βCH₃ Ala) ppm. C₁₄H₁₈N₂O₅S (326.37): calcd. C 51.52, H 5.56, N 8.58, S 9.82; found C 51.72, H 5.70, N 8.43, S 9.44.

Tos-Ala-Z-\DeltaPhe-OMe (9f): The procedure described above was used substituting compound **7f** (1 mmol, 0.420 g) for **7b** to give **9f** (0.309 g, 77%).

Boc-Gly-Z-\DeltaAbu-OMe (9h): The procedure described above was used substituting compound **7h** (1 mmol, 0.290 g) for **7b** to give **9h** (0.229 g, 84%).

Boc-Gly-AAla-OMe (9i): The procedure described above was used substituting compound **7i** (1 mmol, 0.376 g) for **7b** to give **9i** (0.152 g, 59%).

Boc-Gly-Z-ΔPhe-OMe (9j): The procedure described above was used substituting compound **7j** (1 mmol, 0.376 g) for **7b** to give **9j** (1.10 g, 82%) as a white solid. M.p. 62.5–64.0 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 8.03 (br. s, 1 H, NH), 7.49–7.32 (m, 6 H, βCH ΔPhe + ArH), 5.50 (br. s, 1 H, NH), 3.92 (d, *J* = 3.6 Hz, 2 H, CH₂), 3.79 (s, 3 H, CH₃ CO₂Me), 1.42 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 168.65 (C=O), 165.44 (C=O), 156.14 (C=O), 133.28 (C), 129.75 (CH), 129.54 (CH), 128.58 (CH), 123.64 (C), 80.24 [(CH₃)₃C], 52.59 (OCH₃), 44.50 (CH₂), 28.19 [(CH₃)₃C] ppm. C₁₇H₂₂N₂O₅ (334.37): calcd. C 61.07, H 6.63, N 8.38; found C 60.83, H 6.74, N 8.65.

Z-Gly-AAla-OMe (91): The procedure described above was used substituting compound **71** (1 mmol, 0.310 g) for **7b** to give **91** (0.178 g, 61%) as a white solid. M.p. 74.0–74.5 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 8.26 (br. s, 1 H, NH), 7.35–7.31 (m, 5 H, ArH), 6.60 (s, 1 H, β CH₂ Δ Ala), 5.92 (d, *J* = 1.2 Hz,

1 H, βCH₂ ΔAla), 5.60 (br. s, 1 H, NH), 5.15 (s, 2 H, CH₂ Z), 3.97 (d, J = 5.4 Hz, 2 H, CH₂ Gly), 3.83 (s, 3 H, CH₃ CO₂Me) ppm. ¹³C NMR (CDCl₃): $\delta = 167.76$ (C=O), 164.21 (C=O), 156.59 (C=O), 135.99 (C), 130.46 (C), 128.50 (CH), 128.20 (CH), 128.07 (CH), 109.55 (CH₂), 67.29 (CH₂), 53.00 (OCH₃), 45.26 (CH₂) ppm. C₁₃H₁₆N₂O₆ (296.28): calcd. C 57.53, H 5.52, N 9.58; found C 57.44, H 5.47, N 9.66.

Synthesis of Piperazine Derivatives 11a,c

1-*tert***-Butyl 2-Methyl 6-Oxo-4-(4-tolylsulfonyl)piperazine-1,2-dicarboxylate (11a):** The procedure described above for the preparation of **9b** was used substituting compound **7a** (1 mmol, 0.376 g) for **7b** to give **11a** (0.231 g, 56%) as a white solid. M.p. 113.0–114.0 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.64 (d, *J* = 8.1 Hz, 2 H, ArH), 7.36 (d, *J* = 8.1 Hz, 2 H, ArH), 4.80 (t, *J* = 3.6 Hz, 1 H, CH), 4.15–4.10 (m, 2 H, 2CH₂), 3.79 (s, 3 H, CH₃ CO₂Me), 3.46 (d, *J* = 15.9 Hz, 1 H, CH₂), 2.99 (dd, *J* = 12.6, *J* = 3.6 Hz, 1 H, CH₂), 2.44 (s, 3 H, CH₃ Tos), 1.48 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 168.88 (C=O), 163.41 (C=O), 150.59 (C=O), 144.80 (C), 131.67 (C), 130.05 (CH), 127.79 (CH), 84.90 [*C*(CH₃)₃], 57.11 (CH), 53.15 (OCH₃), 50.00 (CH₂), 45.48 (CH₂), 27.73 [*C*(CH₃)₃], 21.52 (CH₃ Tos) ppm. C₁₈H₂₄N₂O₇S (412.46): calcd. C 52.42, H 5.86, N 6.79, S 7.77; found C 52.36, H 6.00, N 6.81, S 7.68.

1-*tert*-**Butyl 2-Methyl 3-Methyl-6-oxo-4-(4-tolylsulfonyl)piperazine-1,2-dicarboxylate (11c):** The procedure described above was used substituting compound **7c** (1 mmol, 0.376 g) for **7b** to give **11c** (0.222 g, 52%) as a white solid. M.p. 134.0–135.0 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.64 (d, *J* = 8.1 Hz, 2 H, ArH), 7.31 (d, *J* = 8.1 Hz, 2 H, ArH), 4.69 (qd, *J* = 6.9, *J* = 2.1 Hz, 1 H, CH), 4.60 (d, *J* = 2.1 Hz, 1 H, CH), 4.12 (d, *J* = 17.4 Hz, 1 H, CH₂), 3.80 (d, *J* = 17.4 Hz, 1 H, CH₂), 3.63 (s, 3 H, CH₃ CO₂Me), 2.42 (s, 3 H, CH₃ Tos), 1.49 (s, 9 H, CH₃ Boc), 1.20 (d, *J* = 6.9 Hz, 3 H, CH₃) ppm. ¹³C NMR (CDCl₃): δ = 169.14 (C=O), 163.53 (C=O), 151.09 (C=O), 144.24 (C), 135.37 (C), 129.86 (CH), 127.25 (CH), 84.90 [*C*(CH₃)₃], 62.62 (CH), 52.90 (OCH₃), 49.82 (CH₂), 45.75 (CH₂), 27.73 [C(CH₃)₃], 21.47 (CH₃ Tos), 15.19 (CH₃) ppm. C₁₉H₂₆N₂O₇S (426.48): calcd. C 53.51, H 6.14, N 6.57, S 7.52; found C 53.56, H 6.26, N 6.39, S 7.29.

Synthesis of the Methyl Esters of N-Protected β -Brominated Dehydropeptides 12g and 13h,j

Boc-Ala-ΔAla(β-Br,Br)-OMe (12g): The same procedure described for the preparation of **4b** was followed substituting **9g** (1 mmol, 0.272 g) for **3b** to give **12g** (0.327 g, 76%) as an oil. ¹H NMR (CDCl₃): δ = 8.60 (br. s, 1 H, NH ΔAla), 5.04 (d, *J* = 6.0 Hz, 1 H, NH), 4.28 (br. t, *J* = 5.1 Hz, 1 H, CH Ala), 3.85 (s, 3 H, CH₃ CO₂Me), 1.45 (s, 9 H, CH₃ Boc), 1.36 (d, *J* = 6.9 Hz, 3 H, βCH₃ Ala) ppm. ¹³C NMR (CDCl₃): δ = 169.93 (C=O), 162.56 (C=O), 156.03 (C=O), 132.27 (C), 85.47 (C), 81.00 [*C*(CH₃)₃], 53.00 (OCH₃), 49.46 (αCH), 28.25 [*C*(*C*H₃)₃], 16.49 (βCH₃) ppm. C₁₂H₁₈Br₂N₂O₅ (430.09): calcd. C 33.51, H 4.22, N 6.51; found C 33.77, H 4.36, N 6.39.

Boc-Gly-AAbu(β-Br)-OMe (13h): The same procedure described for the preparation of **5f** was followed substituting **9h** (1 mmol, 0.272 g) for **3f** to give (*E*)- and (*Z*)-**13h** as a 1:1 *E/Z* mixture (0.316 g, 90%). The diastereomers were separated by column chromatography using a solvent gradient of neat petroleum ether to 40% diethyl ether/petroleum ether. (*E*)-**13h**: M.p. 93.0–95.0 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): $\delta = 8.11$ (br. s, 1 H, NH ΔAbu), 5.37 (br. t, J = 5.1 Hz, 1 H, NH Gly), 3.86 (d, J =6.0 Hz, 2 H, CH₂), 3.81 (s, 3 H, CH₃ CO₂Me), 2.38 (s, 3 H, γCH₃), 1.46 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): $\delta = 168.10$ (C=O),



164.24 (C=O), 156.53 (C=O), 125.66 (C), 122.82 (C), 80.73 [*C*(CH₃)₃], 52.49 (OCH₃), 44.33 (CH₂), 28.21 (CH₃ Boc), 25.61 (γCH₃) ppm. C₁₂H₁₉BrN₂O₅ (351.19): calcd. C 41.04, H 5.45, N 7.98; found C 41.52, H 5.37, N 7.98. (*Z*)-**13h**: M.p. 83.0–85.0 °C (from diethyl ether/*n*-hexane). ¹H NMR (CDCl₃): δ = 7.92 (br. s, 1 H, NH ΔAbu), 5.27 (s, 1 H, NH Gly), 3.88 (d, *J* = 6.0 Hz, 2 H, CH₂), 3.80 (s, 3 H, CH₃ CO₂Me), 2.57 (s, 3 H, γCH₃), 1.46 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 167.94 (C=O), 162.84 (C=O), 156.18 (C=O), 126.51 (C), 124.88 (C), 80.66 [*C*(CH₃)₃], 52.63 (OCH₃), 44.37 (CH₂), 28.24 [*C*(*C*H₃)₃], 24.70 (γCH₃) ppm. C₁₂H₁₉BrN₂O₅ (351.19): calcd. C 41.04, H 5.45, N 7.98; found C 40.93, H 5.40, N 8.05.

Boc-Gly- Δ Phe(β -Br)-OMe (13j): The same procedure described for the preparation of 5f was followed substituting 9j (1 mmol, 0.344 g) for 3f to give 13j as a 1:1 E/Z mixture (0.359 g, 87%) that could not be separated by column chromatography. ¹H NMR (CDCl₃): δ = 8.28 (s, 1 H, NH Δ Phe), 7.90 (s, 1 H, NH Δ Phe), 7.41 (br. s, 5 H, ArH), 7.36 (br. s, 5 H, ArH), 5.36 (br. t, J = 5.7 Hz, 1 H, NH Gly), 5.16 (br. s, 1 H, NH Gly), 3.93 (d, J = 5.7 Hz, 2 H, CH₂), 3.90 (s, 3 H, CH₃ CO₂Me), 3.72 (d, J = 6.0 Hz, 2 H, CH₂), 3.51 (s, 3 H, CH₃ CO₂Me), 1.48 (s, 9 H, CH₃ Boc), 1.34 (s, 9 H, CH₃ Boc) ppm. ¹³C NMR (CDCl₃): δ = 167.98 (C=O), 167.27 (C=O), 164.42 (C=O), 163.33 (C=O), 156.26 (C=O), 155.98 (C=O), 137.00 (C), 136.15 (C), 129.68 (CH), 129.40 (CH), 128.98 (CH), 128.83 (CH), 128.51 (C), 128.33 (C), 128.24 (CH), 127.53 (C), 125.88 (C), 80.85 [C(CH₃)₃], 80.61 [C(CH₃)₃], 52.72 (OCH₃), 52.56 (OCH₃), 44.53 (CH₂), 44.13 (CH₂), 28.27 [C(CH₃)₃], 28.14 [C(CH₃)₃] ppm. C₁₇H₂₁BrN₂O₅ (413.26): calcd. C 49.41, H 5.12, N 6.78; found C 49.35, H 5.19, N 7.00.

Synthesis of 1-(4-Tolylsulfonyl)imidazolidin-4-one Derivatives 14af,k

Methyl 2-(Bromomethyl)-4-oxo-1-(4-tolylsulfonyl)imidazolidine-2carboxylate (14a): N-Bromosuccinimide (1.1 equiv., 0.55 mmol) was added to a solution of Tos-Gly-AAla-OMe (9a) (0.5 mmol) in dichloromethane (0.1 moldm⁻³). The reaction was stirred at room temperature for 18 h and then triethylamine (1.1 equiv.) was added. After 4 h at room temperature, dichloromethane (25 mL) was added and the organic phase washed with water and brine $(3 \times 10 \text{ mL})$. After drying with MgSO₄ the extract was taken to dryness at reduced pressure to afford compound 14a as a white solid (0.18 g, 92%). M.p. 150.0-151.0 °C (from ethyl acetate/n-hexane). ¹H NMR (CDCl₃): δ = 7.75 (d, J = 8.1 Hz, 1 H, ArH), 7.35 (d, J = 8.1 Hz, 1 H, ArH), 7.27 (br. s, 1 H, NH), 4.23 (d, J =12.0 Hz, 1 H, CH₂), 4.13 (d, J = 12.0 Hz, 1 H, CH₂), 4.06 (d, J = 14.1 Hz, 1 H, CH₂), 3.89 (d, J = 14.1 Hz, 1 H, CH₂), 3.77 (s, 3 H, CH₃ CO₂Me), 2.46 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (CDCl₃): δ = 169.64 (C=O), 167.28 (C=O), 144.77 (C), 135.07 (C), 129.76 (CH), 127.50 (CH), 78.98 (C), 53.72 (OCH₃), 36.49 (CH₂), 21.57 (CH₃ Tos) ppm. MS (FAB): *m*/*z* (%) = 392.97 (26.21) and 390.97 (27.24) [M + 1]⁺, 332.94 (12.46), 330.95 (12.41) [M - CO₂Me]⁺. HRMS (FAB): calcd. for C13H15BrN2O5S 389.9885 [M + 1]; found 390.9952. C₁₃H₁₅BrN₂O₅S (391.24): calcd. C 39.91, H 3.86, N 7.16, S 8.20; found C 39.66, H 4.00, N 7.03, S 8.00.

Methyl 2-(Bromomethyl)-5-methyl-4-oxo-1-(4-tolylsulfonyl)imidazolidine-2-carboxylate (14b): The procedure described above was used substituting compound **9b** for **9a** to give **14b** (0.357 mg, 88%) as a diastereomeric mixture. ¹H NMR (CDCl₃): $\delta = 7.78$ (d, J =8.1 Hz, 2 H, ArH), 7.67 (s, 1 H, NH), 7.34 (d, J = 8.1 Hz, 2 H, ArH), 4.36 (q, J = 6.6 Hz, 1H, CH), 4.33 (d, J = 12.0 Hz, 1 H, CH₂), 4.19 (d, J = 12.3 Hz, 1 H, CH₂), 4.15 (d, J = 12.0 Hz, 1 H, CH₂), 4.12 (d, J = 12.3 Hz, 1 H, CH₂), 4.07 (q, J = 6.6 Hz, 1 H, CH), 3.82 (s, 3 H, CH₃ CO₂Me), 3.80 (s, 3 H, CH₃ CO₂Me), 2.45 (s, 3 H, CH₃ Tos), 1.58 (d, J = 6.6 Hz, 3 H, CH₃), 1.34 (d, J = 6.6 Hz, 3 H, CH₃) ppm. ¹³C NMR (CDCl₃): $\delta = 173.06$ (C=O), 172.69 (C=O), 168.07 (C=O), 167.57 (C=O), 144.73 (C), 144.57 (C), 136.68 (C), 136.36 (C), 129.73 (CH), 129.66 (CH), 127.88 (CH), 127.61 (CH), 78.70 (C), 78.06 (C), 57.12 (CH), 56.52 (CH), 53.92 (OCH₃), 53.64 (OCH₃), 37.19 (CH₂), 35.92 (CH₂), 21.58 (CH₃ Tos), 18.54 (CH₃), 17.09 (CH₃) ppm. C₁₄H₁₇BrN₂O₅S (405.26): calcd. C 41.49, H 4.23, N 6.91, S 7.91; found C 41.95, H 4.37, N 6.99, S 7.76.

Methyl 2-(1-Bromoethyl)-4-oxo-1-(4-tolylsulfonyl)imidazolidine-2carboxylate (14c): The procedure described above was used substituting compound 9c for 9a to give 14c as a white solid (0.19 g, 94%). M.p. 161.0-162.0 °C (from ethyl acetate/n-hexane). ¹H NMR $(CDCl_3)$: $\delta = 7.66$ (d, J = 8.4 Hz, 2 H, ArH), 7.37 (d, J = 8.4 Hz, 2 H, ArH), 6.41 (s, 1 H, NH), 5.32 (q, J = 7.5 Hz, 1 H, CH), 4.15 (d, J = 14.4 Hz, 1 H, CH₂), 3.91 (d, J = 14.4 Hz, 1 H, CH₂), 3.44 (s, 3 H, CH₃ CO₂Me), 2.46 (s, 3 H, CH₃ Tos), 1.86 (d, J = 7.5 Hz, 3 H, CH₃) ppm. ¹³C NMR (CDCl₃): δ = 168.11 (C=O), 166.17 (C=O), 145.04 (C), 133.97 (C), 129.78 (CH), 127.69 (CH), 81.37 (C), 53.08 (OCH₃), 50.73 (CH₂), 48.80 (CH), 21.58 (CH₃ Tos), 18.74 (CH₃) ppm. MS (FAB): m/z (%) = 407.02 (40.70), 405.02 (40.99) [M + 1]⁺, 346.99 (19.76), 344.99 (19.31) [M - CO₂Me]⁺. HRMS (FAB): calcd. for $C_{14}H_{17}BrN_2O_5S$ 404.0042 [M + 1]; found 405.0105. C₁₄H₁₇BrN₂O₅S (405.26): calcd. C 41.49, H 4.23, N 6.91, S 7.91; found C 41.64, H 4.39, N 6.91, S 8.00.

2-(1-Bromoethyl)-5-methyl-4-oxo-1-(4-tolylsulfonyl)imid-Methyl azolidine-2-carboxylate (14d): The procedure described above was used substituting compound 9d for 9a to give 14d as a diastereomeric mixture (0.16 g, 74%). The diastereomers were isolated by column chromatography through silica using diethyl ether/petroleum ether as eluent. Diastereomer 1: m.p. 180.0-181.0 °C. 1H NMR (CDCl₃): δ = 7.72 (d, J = 8.1 Hz, 2 H, ArH), 7.33 (d, J = 8.1 Hz, 2 H, ArH), 6.59 (br. s, 1 H, NH), 5.51 (q, J = 6.6 Hz, 1 H, CH), 4.37 (q, J = 6.9 Hz, 1 H, CH), 3.57 (s, 3 H, CH₃ CO₂Me), 2.45 (s, 3 H, CH₃ Tos), 1.84 (d, J = 6.6 Hz, 3 H, CH₃), 1.42 (d, J = 6.9 Hz, 3 H, CH₃) ppm. ¹³C NMR (CDCl₃): δ = 170.95 (C=O), 167.40 (C=O), 144.62 (C), 137.47 (C), 129.24 (CH), 127.62 (CH), 81.17 (C), 58.59 (CH), 53.25 (OCH₃), 50.63 (CH), 21.56 (CH₃ Tos), 18.74 (CH₃), 17.94 (CH₃) ppm. C₁₅H₁₉BrN₂O₅S (419.29): calcd. C 42.97, H 4.57, N 6.68, S 7.65; found C 43.01, H 4.62, N 6.66, S 7.47. Diastereomer 2: ¹H NMR (CDCl₃): δ = 7.62 (d, J = 8.1 Hz, 2 H, ArH), 7.36 (d, J = 8.1 Hz, 2 H, ArH), 6.54 (br. s, 1 H, NH), 5.22 (q, J = 6.6 Hz, 1 H, CH), 4.06 (q, J = 6.9 Hz, 1 H, CH), 3.39(s, 3 H, CH₃ CO₂Me), 2.46 (s, 3 H, CH₃ Tos), 1.82 (d, J = 6.6 Hz, $3 \text{ H}, \text{CH}_3$, 1.69 (d, $J = 6.9 \text{ Hz}, 3 \text{ H}, \text{CH}_3$) ppm. ¹³C NMR (CDCl₃): δ = 171.43 (C=O), 166.36 (C=O), 145.02 (C), 133.87 (C), 129.74 (CH), 127.91 (CH), 80.63 (C), 58.00 (CH), 48.91 (OCH₃), 52.98 (CH), 21.60 (CH₃ Tos), 19.36 (CH₃), 19.21 (CH₃) ppm. C₁₅H₁₉BrN₂O₅S (419.29): calcd. C 42.97, H 4.57, N 6.68, S 7.65; found C 42.61, H 4.59, N 6.60, S 7.30.

Methyl 2-[Bromo(phenyl)methyl]-4-oxo-1-(4-tolylsulfonyl)imidazolidine-2-carboxylate (14e): The procedure described above was used substituting compound 9e for 9a to give 14e as a diastereomeric mixture (0.20 g, 86%). ¹H NMR (CDCl₃): δ = 7.80–7.29 (m, 20 H, ArH + NH), 7.08 (s, 1 H, NH), 6.37 (s, 1 H, CH), 6.19 (s, 1 H, CH), 4.20 (d, *J* = 14.1 Hz, 1 H, CH₂), 3.98 (d, *J* = 14.1 Hz, 1 H, CH₂), 3.69 (d, *J* = 14.7 Hz, 1 H, CH₂), 3.60 (s, 3 H, CH₃ CO₂Me), 3.42 (s, 3 H, CH₃ CO₂Me), 3.12 (d, *J* = 14.7 Hz, 1 H, CH₂), 2.45 (s, 3 H, CH₃ Tos), 2.42 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (CDCl₃): δ = 169.02 (C=O), 168.56 (C=O), 166.11 (C=O), 165.14 (C=O), 144.80 (C), 144.67 (C), 135.73 (C), 134.99 (C), 134.83 (C), 134.46 (C), 130.98 (CH), 130.04 (CH), 129.67 (CH), 129.42 (CH), 128.62 (CH), 128.46 (CH), 127.48 (CH), 127.34 (CH), 82.56 (C), 81.96 (C), 58.50 (CH), 53.47 (CH), 53.47 (OCH₃), 53.16 (OCH₃), 50.28 (CH₂), 50.19 (CH₂), 21.57 (CH₃ Tos), 21.56 (CH₃ Tos) ppm. MS FAB: m/z (%) =469.03 (16.38), 467.03 (15.96) [M + 1]⁺, 297.05 (15.5) [M - CHBrPh]⁺. HRMS (FAB): calcd. for C₁₉H₁₉BrN₂O₅S 466.0198 [M + 1]; found 467.0288. C₁₉H₁₉BrN₂O₅S (467.33): calcd. C 48.83, H 4.10, N 5.99, S 6.86; found C 48.76, H 4.38, N 6.05, S 6.71.

Methyl 2-[Bromo(phenyl)methyl]-5-methyl-4-oxo-1-(4-tolylsulfonyl)imidazolidine-2-carboxylate (14f): The procedure described above was used substituting compound 9f for 9a to give 14f as a diastereomeric mixture (0.22 g, 91%). The diastereomers were isolated by column chromatography through silica using diethyl ether/petroleum ether as eluent. Diastereomer 1 (0.041 g, 17%): m.p. 172.5-173.5 °C. ¹H NMR (CDCl₃): δ = 7.78–7.75 (m, 2 H, ArH Phe), 7.48–7.41 (m, 5 H, ArH Tos + ArH Phe), 7.24 (d, J = 8.1 Hz, 2 H, ArH Tos), 7.01 (s, 1 H, NH), 6.45 (s, 1 H, CH ΔPhe), 3.74 (s, 3 H, $CH_3 CO_2Me$), 3.15 (q, J = 14.7 Hz, 1 H, CH_2), 2.41 (s, 3 H, CH_3 Tos), 1.26 (d, J = 6.9 Hz, 3 H, β CH₃ Ala) ppm. ¹³C NMR (CDCl₃): $\delta = 171.27$ (C=O), 167.24 (C=O), 144.41 (C), 137.59 (C), 134.32 (C), 130.75 (CH), 129.68 (CH), 129.60 (CH), 128.59 (CH), 127.34 (CH), 81.51 (C), 57.96 (CHBr), 54.58 (αCH Ala), 53.66 (OCH₃), 21.50 (CH₃ Tos), 17.40 (CH₃) ppm. C₂₀H₂₁BrN₂O₅S (481.36): calcd. C 49.90, H 4.40, N 5.82, S 6.66; found C 50.10, H 4.56, N 5.73, S 6.69. Mixture of diastereomers (0.118 g, 49%): ¹H NMR (CDCl₃): δ = 7.86 (d, J = 8.1 Hz, 2 H, ArH Tos), 7.80 (d, J = 8.1 Hz, 2 H, ArH Tos), 7.62-7.52 (4m, 5 H, ArH), 7.38-7.33 (m, 10 H, ArH), 6.64 (s, 1 H, CHBr), 6.61 (s, 1 H, NH), 6.42 (s, 1 H, NH), 6.16 (s, 1 H, CHBr), 4.43 (q, J = 6.9 Hz, 1 H, α CH Ala), 4.24 (q, J = 6.9 Hz, 1 H, α CH Ala), 3.47 (s, 3 H, CH₃ CO₂Me), 3.42 (s, 3 H, CH₃ CO₂Me), 2.46 (s, 3 H, CH₃ Tos), 2.45 (s, 3 H, CH₃ Tos), 1.69 (d, J = 6.9 Hz, 3 H, β CH₃ Ala), 1.46 (d, J = 6.9 Hz, 3 H, β CH₃ Ala) ppm. ¹³C NMR (CDCl₃): δ = 172.17 (C=O), 171.56 (C=O), 165.96 (C=O), 165.56 (C=O), 144.90 (C), 144.38 (C), 137.90 (C), 135.89 (C), 135.37 (C), 134.79 (C), 130.56 (CH), 129.92 (CH), 129.63 (CH), 129.60 (CH), 129.56 (CH), 129.24 (CH), 128.86 (CH), 128.53 (CH), 128.17 (CH), 127.68 (CH), 82.55 (C), 81.20 (C), 58.87 (CHBr), 56.86 (αCH Ala), 53.21 (OCH₃), 53.12 (OCH₃), 21.63 (CH₃ Tos), 21.56 (CH₃ Tos), 18.36 (βCH₃ Ala), 18.33 (βCH₃ Ala) ppm. Diastereomer 2 (0.034 g, 14%): ¹H NMR $(CDCl_3): \delta = 7.68-7.63 \text{ (m, 2 H, ArH)}, 7.54 \text{ (d, } J = 8.1 \text{ Hz}, 2 \text{ H},$ ArH Tos), 7.42–7.39 (m, 3 H, ArH), 7.32 (d, J = 8.1 Hz, 2 H, ArH Tos), 6.80 (br. s, 1 H, NH), 6.13 (s, 1 H, CHBr), 3.89 (q, J = 6.9 Hz, 1 H, αCH Ala), 3.48 (s, 3 H, CH₃ CO₂Me), 2.44 (s, 3 H, CH₃ Tos), 0.68 (d, J = 6.9 Hz, 3 H, β CH₃ Ala) ppm. ¹³C NMR (CDCl₃): $\delta =$ 171.12 (C=O), 166.23 (C=O), 144.83 (C), 134.71 (C), 134.54 (C), 130.84 (CH), 129.66 (CH), 129.47 (CH), 128.29 (CH), 127.69 (CH), 81.50 (C), 57.91 (aCH Ala), 54.35 (CHBr), 53.30 (OCH₃), 21.59 (CH₃ Tos), 18.17 (β CH₃ Ala) ppm. HRMS (FAB): calcd. for $C_{20}H_{22}BrN_2O_5S$ 480.0433 [M + 1]; found 481.0435.

Synthesis of the Tripeptide Tos-Gly- Δ Ala-Gly-OMe (9k)

Tos-Gly-AAla-OH: NaOH (1 equiv., 1 moldm⁻³) was added to a solution of Tos-Gly-AAla-OMe (**9a**) (0.34 mmol) in dioxane (3 mL). The solution was stirred for 18 h at room temperature (the reaction was followed by TLC until no starting material was detected). The reaction mixture was acidified to pH 2–3 with KHSO₄ (1 moldm⁻³) and the solid formed filtered. Crystallization from ethyl acetate/*n*-hexane afforded Tos-Gly-AAla-OH (0.10 g, 98%) as a white solid. M.p. 159.5–161.0 °C. ¹H NMR (DMSO): δ = 13.60 (s, 1 H, COOH), 9.11 (s, 1 H, NH AAla), 8.16 (t, *J* = 6.3 Hz, 1 H, NH Gly), 7.68 (d, *J* = 8.1 Hz, 2 H, ArH), 7.38 (d, *J* = 8.1 Hz, 2 H, ArH), 6.27 (s, 1 H, CH₂ AAla), 5.70 (s, 1 H, CH₂ AAla), 3.58

(d, J = 6.3 Hz, 2 H, CH₂ Gly), 2.37 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (DMSO): $\delta = 167.47$ (C=O), 164.73 (C=O), 143.04 (C), 137.03 (C), 132.20 (C), 129.69 (CH), 126.70 (CH), 107.70 (β CH₂), 45.85 (CH₂), 21.01 (CH₃ Tos) ppm. C₁₂H₁₄N₂O₅S (298.26): calcd. C 48.32, H 4.73, N 9.39, S 10.73; found C 48.09, H 4.86, N 9.20, S 10.69.

Tos-Gly-AAla-Gly-OMe (9k): HOBt (0.22 mmol, 0.034 mg) and DCC (0.22 mmol, 0.044 mg) were added to a solution of Tos-Gly- Δ Ala-OH (0.20 mmol) in acetonitrile (5 mL) with vigorous stirring at 0 °C. After 15 min, HCl·H-Gly-OMe (0.2 mmol) and Et₃N (0.2 mmol, 0.03 mL) were added. The reaction was stirred for 18 h at room temperature. The urea was removed by filtration and the solvent removed at reduced pressure. The oily residue was dissolved in ethyl acetate (15 mL) and the solution washed with KHSO₄ (1 moldm⁻³), NaHCO₃ (1 moldm⁻³) and brine (3×5 mL, each). The organic layer was dried with MgSO₄ and the solvent removed at reduced pressure giving an oil which was purified by column chromatography with diethyl ether/petroleum ether (2:1). Compound 9k was isolated as a white solid (0.053 g, 72%). M.p. 114.0-115.5 °C (from ethyl acetate/diethyl ether). ¹H NMR (CDCl₃): δ = 8.59 (s, 1 H, NH Δ Ala), 7.76 (d, J = 8.4 Hz, 2 H, ArH), 7.31 (d, J= 8.4 Hz, 2 H, ArH), 6.83 (s, 1 H, NH Gly), 6.37 (s, 1 H, CH₂ ΔAla), 5.60 (s, 1 H, NH Gly), 5.40 (s, 1 H, CH₂ ΔAla), 4.12 (d, J = 5.4 Hz, 2 H, CH₂ Gly), 3.80 (s, 3 H, CH₃ CO₂Me), 3.70 (s, 2 H, CH₂ Gly), 2.42 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (CDCl₃): δ = 170.22 (C=O), 167.04 (C=O), 163.94 (C=O), 143.97 (C), 135.72 (C), 133.29 (C), 129.86 (CH), 127.23 (CH), 104.41 (βCH₂), 52.59 (OCH₃), 46.36 (CH₂), 41.60 (CH₂), 21.50 (CH₃ Tos) ppm. C₁₅H₁₉N₃O₆S (369.34): calcd. C 48.78, H 5.18, N 11.38, S 8.72; found C 48.93, H 5.27, N 11.40, S 8.72.

Methyl 2-[2-(Bromomethyl)]-4-oxo-1-(4-tolylsulfonyl)imidazolidine-2-carboxamidoacetate (14k): The procedure described above for the synthesis of 14a was used substituting compound 9k (0.1 mol) for 9a to give 14k as a white solid (0.036 g, 82%). M.p. 161.0-162.0 °C (from ethyl acetate/*n*-hexane). ¹H NMR (CDCl₃): $\delta = 8.36-8.22$ (m, 1 H, NH), 8.20 (s, 1 H, NH), 7.74 (d, J = 7.8 Hz, 2 H, ArH), 7.35 $(d, J = 7.8 \text{ Hz}, 2 \text{ H}, \text{ArH}), 4.42 (d, J = 12.3 \text{ Hz}, 1 \text{ H}, \text{CH}_2), 4.35$ (dd, J = 7.5, J = 17.9 Hz, 1 H, CH₂), 4.06 (d, J = 12.3 Hz, 1 H, CH₂), 4.03 (d, J = 13.8 Hz, 1 H, CH₂), 3.93 (d, J = 13.8 Hz, 1 H, CH₂), 3.74 (s, 3 H, CH₃ CO₂Me), 3.55 (dd, J = 4.5, J = 17.9 Hz, 1 H, CH₂), 2.46 (s, 3 H, CH₃ Tos) ppm. ¹³C NMR (CDCl₃): δ = 172.24 (C=O), 170.94 (C=O), 167.56 (C=O), 144.75 (C), 135.08 (C), 129.77 (CH), 127.53 (CH), 79.35 (C), 53.05 (OCH₃), 49.98 (CH₂), 41.00 (CH₂), 38.54 (CH₂), 21.65 (CH₃ Tos) ppm. C₁₅H₁₈BrN₃O₆S (448.29): calcd. C 40.19, H 4.05, N 9.37, S 7.15; found C 40.01, H 4.16, N 9.39, S 7.03.

Acknowledgments

The Portuguese Fundação para a Ciência e Tecnologia (FCT) and Fundo Europeu de Desenvolvimento Regional (FEDER) are acknowledged for financial support through the Centro de Química of University of Minho and through project POCI/QUI/59407/ 2004.

- [1] P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, J. Sacramento, J. Chem. Soc. Perkin Trans. 1 1999, 3697–3703.
- [2] For a review on dehydroamino acids, see; C. Bonauer, T. Walenzyk, B. König, *Synthesis* **2006**, 1–20.
- [3] a) P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, J. Sacramento, J. Sebatião, J. Chem. Soc. Perkin Trans. 1 2000, 3317–3324; b) P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, J. Sacramento, J. Chem. Soc. Perkin Trans. 1 2001, 3167–3174.



- [4] P. M. T. Ferreira, L. S. Monteiro, Eur. J. Org. Chem. 2006, 3226–3234.
- [5] a) P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, *Tetrahedron Lett.* 2002, 43, 4491–4493; b) P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, *Eur. J. Org. Chem.* 2003, 2635–2644.
- [6] a) N. O. Silva, A. S. Abreu, P. M. T. Ferreira, M. J. R. P. Queiroz, *Tetrahedron Lett.* 2003, 44, 3377–3379; b) A. S. Abreu, P. M. T. Ferreira, L. S. Monteiro, M. J. R. P. Queiroz, I. C. F. R. Ferreira, R. C. Calhelha, L. M. Estevinho, *Tetrahedron* 2004, 60, 11821–11828.
- [7] a) I. Photaki, J. Am. Chem. Soc. 1963, 85, 1123–1126; b) Y. Nakagawa, T. Tsuno, K. Nakajima, M. Iwai, H. Kawai, K. Okawa, Bull. Chem. Soc. Jpn. 1972, 45, 1162–1167; c) A. Srinivasan, R. W. Stephenson, R. K. Olsen, J. Org. Chem. 1977, 42, 2253–2256; d) A. Srinivasan, R. W. Stephenson, R. K. Olsen, J. Org. Chem. 1977, 42, 2256–2260; e) K. Goodall, A. F. Parsons, Tetrahedron Lett. 1995, 36, 3259–3260; f) W. A. Nugent, PCT Int. Appl. W09616021 (Cl C07C231/14), US Appl. 34078117, 1996 [Chem. Abstr. 1996, 143302k].
- [8] R. Danion-Bougot, D. Danion, G. Francis, *Tetrahedron Lett.* 1990, 31, 3739–3742.
- [9] R. P. Robinson, E. R. Laird, K. M. Donahue, L. L. Lopresti-Morrow, P. G. Mitchell, M. P. Reese, L. M. Reeves, A. J.

Rouch, I. J. Stam, I. S. A. Yocum, *Bioorg. Med. Chem. Lett.* 2001, 11, 1211–1213.

- [10] F. Bertj, C. Ebert, L. Gardossi, *Tetrahedron Lett.* 1992, 33, 8145–8148.
- [11] a) A. S. Abreu, P. M. T. Ferreira, M. J. R. P. Queiroz, M. Venanzi, *Eur. J. Org. Chem.* **2003**, 4792–4796; b) M. J. R. P. Queiroz, A. S. Abreu, E. Coutinho, P. M. T. Ferreira, *Tetrahedron* **2007**, 63, 2215–2222.
- [12] a) M. Yamada, K. Nakao, T. Fukui, K. Nunami, *Tetrahedron* 1996, 52, 5751–5764; b) A. G. Brown, T. C. Smale, *J. Chem. Soc. C* 1969, 1489–1490.
- [13] N. O. Silva, A. S. Abreu, P. M. T. Ferreira, L. S. Monteiro, M. J. R. P. Queiroz, *Eur. J. Org. Chem.* **2002**, 2524–2528.
- [14] N. Puttaswamy, R. Suresha, V. Jagadeesh, V. Nirmala, Synth. React. Inorg. Met-Org. Nano-Met. Chem. 2005, 35, 845–854.
- [15] L. Sannama, T. Kanmera, H. Aoyagi, N. Izumiya, Int. J. Pept. Protein Res. 1979, 13, 207.
- [16] L. Grehn, U. Ragnarsson, Angew. Chem. 1985, 97, 519–520; Angew. Chem. Int. Ed. Engl. 1985, 24, 510–511.

Received: July 20, 2007 Published Online: October 11, 2007