

Synthesis of Non-Natural Amino Acids from *N*-(*p*-Tolylsulfonyl)- α,β -didehydroamino Acid Derivatives

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Keywords: Amino acids / Synthesis design / Nitrogen heterocycles / α,β -Didehydroamino acids / Dihydrofurans

Carbon nucleophiles, amines, and oxygen nucleophiles were treated with the methyl ester of *N*-(*tert*-butoxycarbonyl)-*N*-(*p*-tolylsulfonyl)- α,β -didehydroalanine, and also with the methyl esters of *N*-(*tert*-butoxycarbonyl)-*O*-(*p*-tolylsulfinyl)- α,β -didehydroserine and *N*-(*tert*-butoxycarbonyl)- β -(1,2,4-triazol-1-yl)- α,β -didehydroalanine, both of which were obtained from the former substrate. Carbon nucleophiles of the β -dicarbonyl type gave furanic amino acids, which were converted into the corresponding pyrrole derivatives (dehydroprolines) in high yields, while use of amines allowed the

synthesis of α,α -diamino acids and β -amino- α,β -didehydroamino acids. Different types of alkoxyamino acids were obtained by treatment of the above substrates with oxygen nucleophiles. The reactivities of the α,β -didehydroaminobutyric and α,β -didehydrophenylalanine analogues were also tested. Some of the methods developed were applied to the synthesis of cross-linked amino acids, namely didehydrolanthionine and histidino- α,β -didehydroalanine derivatives.

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Introduction

Research towards new practical methods for the preparation of non-natural amino acids that can serve as building blocks in combinatorial chemistry and drug discovery has become a major field in peptide chemistry.^[1] In recent years we have developed an efficient synthesis of *N,N*-diacyl- α,β -didehydroamino acids^[2] and promoted their subsequent use as precursors of other novel amino acids.^[3–5] We found that *N,N*-diacyl- α,β -didehydroamino acid derivatives are excellent substrates in Michael addition reactions, allowing the preparation of a variety of new β -substituted amino acids.^[3] When one of the protecting groups is *p*-tolylsulfonyl, addition of several types of nucleophile (nitrogen heterocycles, thiols, carbon nucleophiles, and amines) enables the synthesis not only of β -substituted amino acid derivatives but also, in some cases, of β -substituted α,β -didehydroamino acid derivatives.^[4,5] Therefore, on treatment of the methyl ester of *N*-(*tert*-butoxycarbonyl)-*N*-(*p*-tolylsulfonyl)- α,β -didehydroalanine [Tos(Boc)- Δ Ala-OMe^[6]] with the above nucleophiles in the presence of K₂CO₃, addition to the β -carbon atom occurs in all cases to give β -substituted alanine derivatives. When the nucleophile is a nitrogen heterocycle or a thiol, the obtained β -substituted alanine undergoes elimination of *p*-tolylsulfinic acid with regeneration of the α,β -double bond to yield the corresponding β -substituted α,β -didehydroalanine derivative.^[4,5] With certain carbon nucleophiles the addition product undergoes cyclization to give 2,3-dihydrofuran derivatives.^[5] These re-

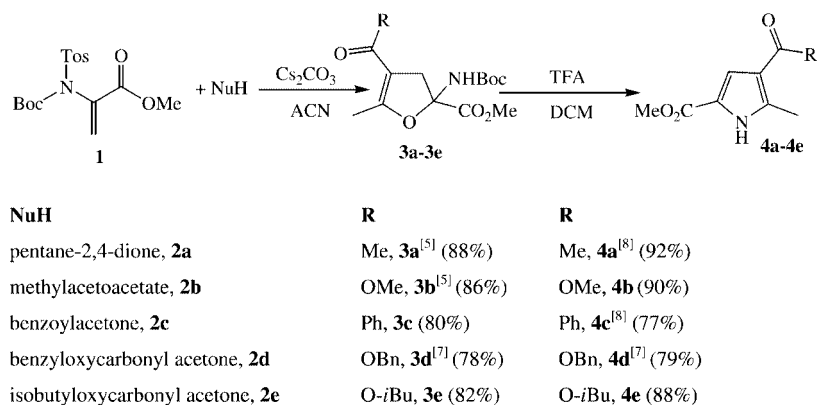
sults encouraged us to investigate the reactivities of *N*-(*p*-tolylsulfonyl)- α,β -didehydroamino acids further in order to obtain new non-natural amino acids, as described below.

Results and Discussion

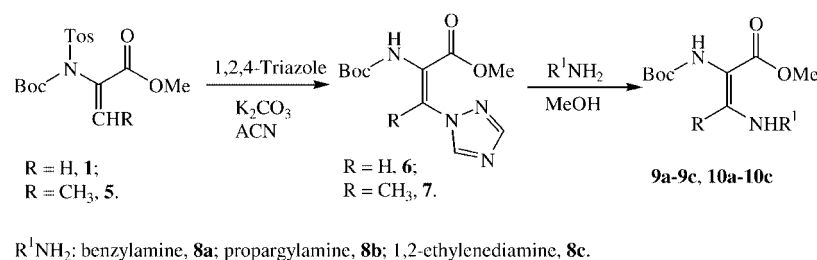
We have reported that the initial products of reactions between Tos(Boc)- Δ Ala-OMe^[6] (compound **1**) and carbon nucleophiles of the β -dicarbonyl type, with a methyl group bonded to one of the carbonyl groups, undergo spontaneous elimination of tosyl groups with cyclisation to give 5-methyl-2,3-dihydrofuran derivatives in good yields.^[5,7] We now report the synthesis of a few more such compounds, which were carried out with the aim of exploring possible applications for these adducts (compounds **3a–3e**, Scheme 1). Deprotection of dihydrofurans **3a–3e** with trifluoroacetic acid (TFA) resulted in a new rearrangement followed by elimination of a water molecule to give the corresponding pyrrole derivatives **4a–4e** (Scheme 1) in high yields.

It had previously been found that reactions between compound **1** and amines proceed as typical Michael additions without elimination of tosyl groups, thus affording the expected β -substituted alanines.^[5] We now report the synthesis of the *E* isomers of the corresponding α,β -didehydro analogues (compounds **9a–9c**, Scheme 2, Table 1) by treatment of the *E* isomer of Boc- Δ Ala[β -(1,2,4-triazol-1-yl)]-OMe^[4] (compound **6**) with amines. These reactions proceed with replacement of the triazole group by the amines, giving the *E* isomers of the corresponding β -amino- α,β -didehydroalanine derivatives.

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Scheme 1



Scheme 2

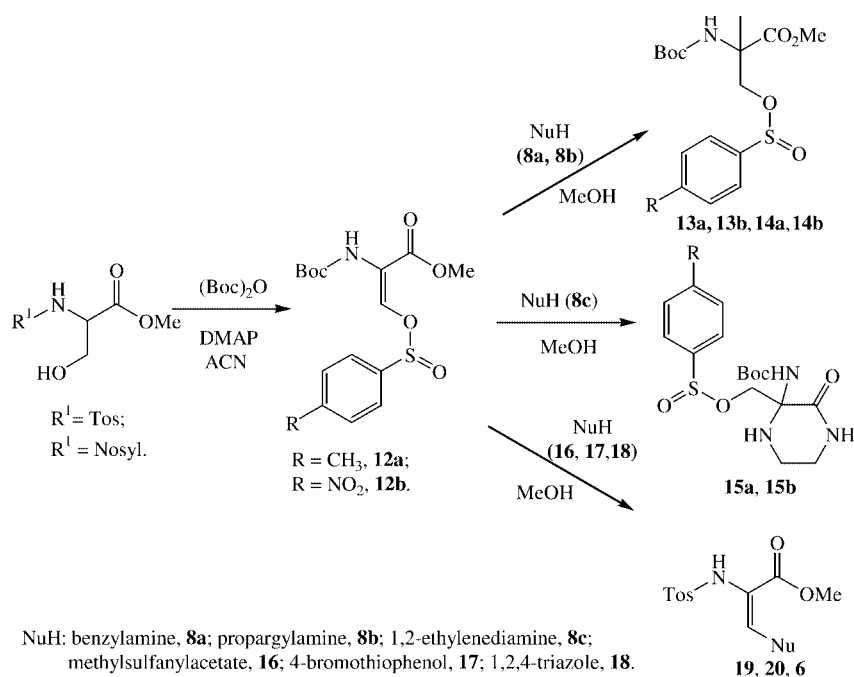
Table 1. Yields obtained in the synthesis of β -aminodehydroamino acid derivatives

Subst.	R^1NH_2	Product	Yield (%)
6	benzylamine 8a	(<i>E</i>)-Boc- Δ Ala(β -benzylamino)-OMe 9a	87
6	propargylamine 8b	(<i>E</i>)-Boc- Δ Ala(β -propargylamino)-OMe 9b	82
6	1,2-ethylenediamine 8c	(<i>E</i>)-Boc- Δ Ala{ β -[<i>N</i> -(2-aminoethyl)amino]}-OMe 9c	90
(<i>E</i>)- 7	benzylamine 8a	(<i>E</i>)-Boc- Δ Abu(β -benzylamino)-OMe 10a ^[9]	95
(<i>Z</i>)- 7	Propargylamine 8b	(<i>E</i>)-Boc- Δ Abu(β -propargylamino)-OMe 10b	92
(<i>Z</i>)- 7	1,2-ethylenediamine 8c	(<i>E</i>)-Boc- Δ Abu{ β -[<i>N</i> -(2-aminoethyl)amino]}-OMe 10c	49

In attempts to induce reactions between amines and *N*-(*tert*-butoxycarbonyl)-*N*-(*p*-tolylsulfonyl)- α,β -dehydroaminobutyric acid [Tos(Boc)- Δ Abu-OMe,^[2] **5**] no products could be obtained, which we have attributed to the low reactivity of the substrate.^[5] However, by taking advantage of Boc- Δ Abu[β -(1,2,4-triazol-1-yl)]-OMe^[4] (compounds (*E*)-**7** and (*Z*)-**7**), we were able to synthesize several α,β -diamino- α,β -didehydroaminobutyric acid derivatives (compounds **10a**,^[9] **10b** and **10c**, Scheme 2, Table 1). The reactions were stereoselective, yielding only the *E* isomers either from the *E* or from the *Z* isomer of the starting material. Unfortunately, neither the *E* nor the *Z* isomer of Boc- Δ Phe[β -(1,2,4-triazol-1-yl)]-OMe^[4] [compounds (*E*)-**11** and (*Z*)-**11**] reacted with amines under these conditions, possibly due to stabilization of the substrate through conjugation with the aromatic ring.

In previous work it had been found that compound **1**, in the presence of dimethylaminopyridine (DMAP), underwent a rearrangement to give the fully protected *E* isomer

of (*p*-tolylsulfinyl)- α,β -didehydroserine^[4,5] (compound **12a**, Scheme 3). By extending the reaction time during the dehydration of Tos-Ser-OMe,^[2] it was possible to obtain this sulfinyl derivative as the major product. This compound was treated with amines **8a** and **8b**, yielding the corresponding α -amino-*O*-(*p*-tolylsulfinyl)serine derivatives (compounds **13a** and **13b**, Scheme 3, Table 2). We believe that the attack at the α -carbon atom is due to the strongly electron-withdrawing effect of the sulfinyl group, which would render the α -carbon less negative than the β -carbon atom. With 1,2-ethylenediamine (**8c**), addition to the α -carbon atom was followed by intramolecular aminolysis to give the lactone **15a** (Scheme 3, Table 2) in high yield. The same reactions as above were carried out with substrates in which a 4-nitrophenylsulfonyl (nosyl, Nos) moiety substituted for *p*-tolylsulfonyl. Thus, treatment of **12b** with amines **8a** and **8b** gave the corresponding α -amino-*O*-(4-nitrophenylsulfinyl)serine derivatives (compounds **14a** and **14b**, Scheme 3, Table 2). With 1,2-ethylenediamine, compound **12b** gave the corre-



Scheme 3

Table 2. Results obtained on treatment of *O*-(*p*-tolylsulfinyl)- α,β -didehydroserine derivatives with nitrogen nucleophiles

Subst.	NuH	Product	Yield (%)
12a	benzylamine, 8a	Boc-Ser[α -benzylamino, <i>O</i> -(<i>p</i> -tolylsulfinyl)]-OMe, 13a ^[9]	92
12a	propargylamine, 8b	Boc-Ser[α -propargylamino, <i>O</i> - <i>p</i> -(tolylsulfinyl)]-OMe, 13b	87
12b	benzylamine, 8a	Boc-Ser[α -benzylamino, <i>O</i> -(4-nitrophenylsulfinyl)]-OMe, 14a	91
12b	propargylamine, 8b	Boc-Ser[α -propargylamino, <i>O</i> -(4-nitrophenylsulfinyl)]-OMe, 14b	75
12a	1,2-ethylenediamine, 8c	3-(<i>tert</i> -butoxycarbonylamino)-2-oxo-3-[(<i>p</i> -tolylsulfinyl)oxymethyl]piperazine, 15a	89
12b	1,2-ethylenediamine, 8c	3-(<i>tert</i> -butoxycarbonylamino)-2-oxo-3-[(4-nitrophenylsulfinyl)oxymethyl]piperazine, 15b	59
12a	methylsulfonyl acetate, 16	(<i>E</i>)-Boc- Δ Ala[β -methoxycarbonylmethylsulfinyl]-OMe, 19 ^[5]	54
12a	4-bromothiophenol, 17	(<i>E</i>)-Boc- Δ Ala[β -(4-bromophenylsulfinyl)]-OMe, 20 ^[9]	75
12a	1,2,4-triazole, 18	(<i>E</i>)-Boc- Δ Ala(1,2,4-triazol-1-yl)-OMe, 6	83

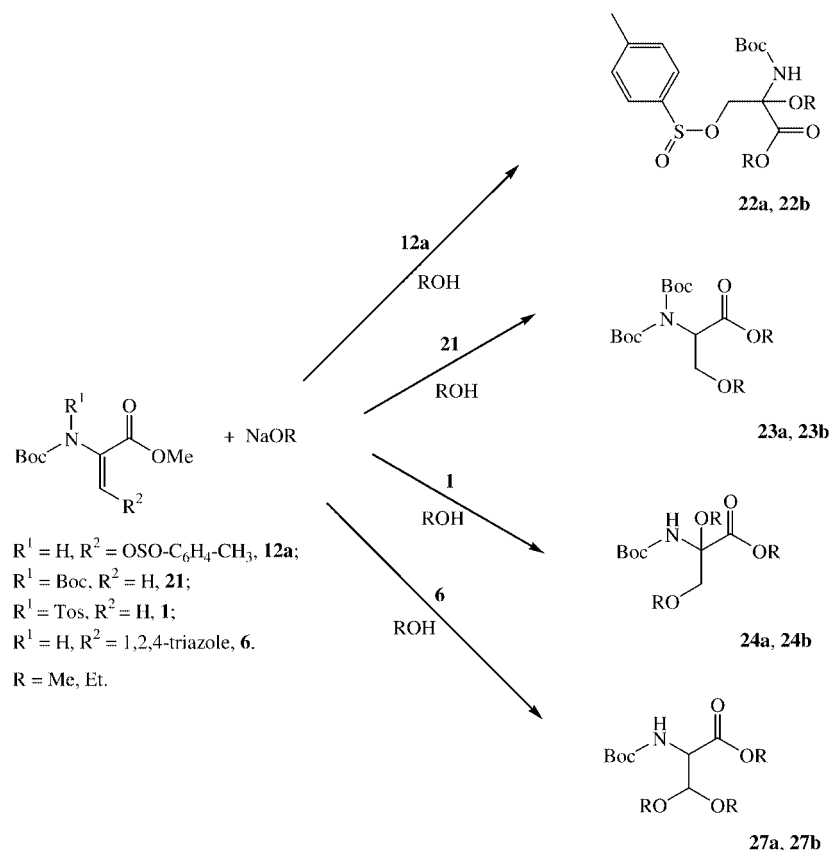
sponding lactone (compound **15b**, Scheme 3, Table 2). These results differ from those reported by Nakazawa et al.,^[10,11] who found that treatment of an *O*-(*p*-tolylsulfonyl)- α,β -didehydroserine derivative with amines gave the corresponding β -amino- α,β -didehydroalanine derivatives.

Treatment of **12a** with sulfur nucleophiles (methylsulfonyl acetate **16** and 4-bromothiophenol **17**) as well as with 1,2,4-triazole (**18**) resulted in substitution of the *O*-sulfinyl group to give the corresponding β -substituted α,β -didehydroalanine derivatives (compounds **19**, **20** and **6**; Scheme 3, Table 2). These results seem to indicate that attack at the β -carbon atom of substrate **12a** requires powerful nucleophiles, whilst amines add at the α -carbon atom.

With oxygen nucleophiles (sodium methoxide and sodium ethoxide), in a pattern similar to that observed in the case of the reactions with amines, sulfinyl derivative **12a** underwent addition of alkoxide at the α -carbon atom to give the α -alkoxyamino acid derivatives **22a** and **22b**, respectively (Scheme 4, Table 3). Treatment of Boc₂- Δ Ala-

OMe^[12] (compound **21**) with sodium methoxide and sodium ethoxide under similar conditions resulted in a typical Michael addition to give the corresponding β -alkoxyalanine derivatives **23a** and **23b** (Table 3).

Being poor Michael substrates, Boc₂- Δ Abu-OMe^[2] and Boc₂- Δ Phe-OMe^[5] reacted differently with sodium methoxide, undergoing competitive nucleophilic cleavage of one of the Boc groups, which prevented addition from taking place. Treatment of compound **1** with the oxygen nucleophile sodium methoxide gave the methyl ester of *N*-(*tert*-butoxycarbonyl)- α,β -dimethoxyalanine (compound **24a**,^[9] Scheme 4, Table 3). The same reaction but with sodium ethoxide gave the ethyl ester of *N*-(*tert*-butoxycarbonyl)- α,β -diethoxyalanine (compound **24b**, Scheme 4, Table 3). Differently from what was reported above for the case of amines, Tos(Boc)- Δ Phe-OMe^[5] (compound **25**), the dehydrophenylalanine analogue of **1**, reacted with sodium methoxide to give the corresponding α,β -dimethoxyphenylalanine derivative (compound **26**) as a racemic mixture. With



Scheme 4

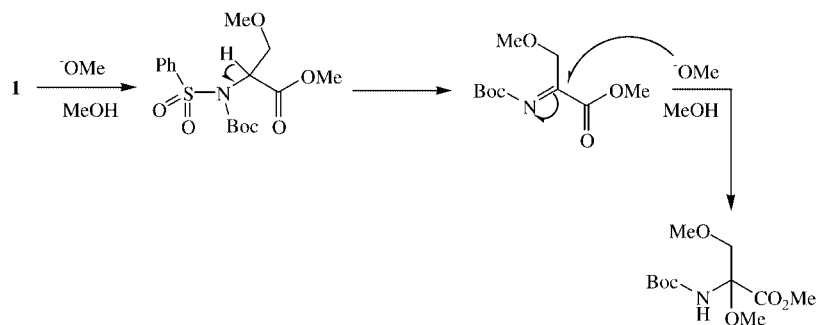
Table 3. Yields obtained on treatment of several dehydroamino acid derivatives with oxygen nucleophiles

Subst.	NaOR	Product	Yield (%)
12a	NaOMe	Boc-Ser[α -methoxy, <i>O</i> -(<i>p</i> -tolylsulfinyl)]-OMe 22a	77
12a	NaOEt	Boc-Ser[α -ethoxy, <i>O</i> -(<i>p</i> -tolylsulfinyl)]-OEt 22b	52
21	NaOMe	Boc-Ala(<i>N</i> -Boc, β -methoxy)-OMe 23a	80
21	NaOEt	Boc-Ala(<i>N</i> -Boc, β -ethoxy)-OEt 23b	38
1	NaOMe	Boc-Ala(α,β -dimethoxy)-OMe 24a ^[9]	91
1	NaOEt	Boc-Ala(α,β -diethoxy)-OEt 24b	60
25	NaOMe	Boc-Phe(α,β -dimethoxy)-OMe 26	87
6	NaOMe	Boc-Ala(β,β -dimethoxy)-OMe 27a	88
6	NaOEt	Boc-Ala(β,β -diethoxy)-OEt 27b	27
(<i>E</i>)-7	NaOMe	(<i>E</i>)-Boc- Δ Abu(β -methoxy)-OMe 28	33

Tos(Boc)- Δ Abu-OMe (compound **5**), however, a complex mixture of products that could not be purified was formed, although ^1H NMR indicated that it contained diastereomers of the expected α,β -dimethoxy derivative. We believe that the above reactions involve the initial addition of a methoxy group at the β -carbon atom, followed by elimination of tosyl and subsequent attack at the α -carbon of the resulting imine by a methoxide ion (Scheme 5).

Finally, treatment of the triazole derivative **6** with either sodium methoxide or sodium ethoxide in the corresponding alcohol gave the corresponding β,β -dialkoxyalanine deriva-

tives (compound **27a** and **27b**, respectively). These products suggest that in this case 1,2,4-triazole is replaced by an alkoxide ion, leaving a α,β -double bond, which allows addition of a second alkoxide ion. Treatment of the *E* isomer of Boc- Δ Abu[β -(1,2,4-triazol-1-yl)]-OMe with sodium methoxide in methanol gave the corresponding β -methoxy- α,β -didehydroaminobutyric acid derivative (compound **28**) but in a low yield (33%). The fact that this product did not undergo addition of a second alkoxide ion shows that it is not a sufficiently strong Michael acceptor and reflects the electron-donating effect of the β -methyl group. As pre-



Scheme 5

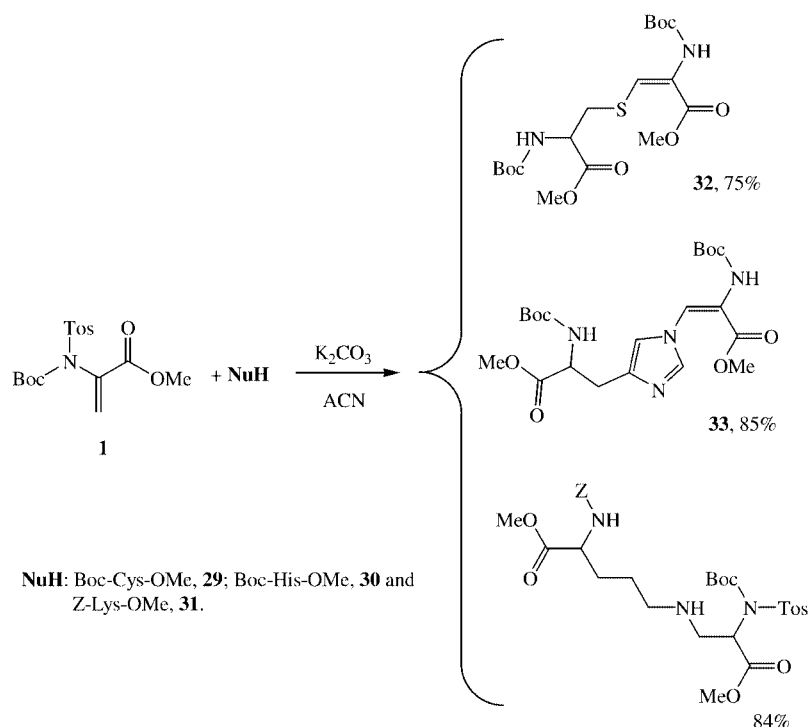
viously observed with amines, Boc- Δ Phe[β -(1,2,4-triazol-1-yl)]-OMe also did not react with sodium methoxide, again possibly due to stabilization by conjugation with the phenyl group.

These results suggested the possibility of using a similar approach in order to obtain cross-linked amino acids. Cross-linking in peptides causes conformational constraints, resulting in increased molecular rigidity and thus determining the final shape of these molecules. By using amino acid derivatives containing thiol, imidazole, and amine side chains as nucleophiles – namely, Boc-Cys-OMe (**29**), Boc-His-OMe (**30**), and Z-Lys-OMe (**31**) – and by treating them with compound **1** we were able to obtain several cross-linked amino acids in good yields. Treatment of compound **1** with nucleophiles **29** and **30** resulted in the formation of didehydrolanthionine and histidino- α,β -didehydroalanine derivatives (compounds **32** and **33**, respectively, Scheme 6). Addition of nucleophile **31** to compound

1 gave the corresponding lysinoalanine derivative as a diastereomeric mixture.

The above results show that *N*-(*tert*-butoxycarbonyl)-*N*-(*p*-tolylsulfonyl)- α,β -didehydroamino acid esters and their triazole and tolylsulfinyl derivatives are versatile reagents for the synthesis of a variety of non-proteinogenic amino and dehydroamino acids. Thus, TosN(Boc)- Δ Ala-OMe proved to be an excellent substrate for synthesis of furanic amino acids and, subsequently, tetrahydroproline derivatives. This method may have great synthetic importance, since most approaches to pyrrole derivatives are multistep and low-yielding.^[13–15]

Treatment of amines with the above triazole and tolylsulfinyl substrates allowed the synthesis of different diamino acid derivatives. The use of the dehydroaminobutyric acid analogue of the above triazole substrate allowed the synthesis of several β -amino- α,β -didehydroaminobutyric acid derivatives. In a similar way, sulfanylamino acid derivatives



Scheme 6

were obtained from treatment of the tolylsulfinyl substrate with sulfur nucleophiles. Taking advantage of the above substrates, we were able to develop a strategy enabling the synthesis of a variety of alkoxy and dialkoxyalanine derivatives. Thus, from (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe it was possible to obtain the corresponding α -alkoxy- β -sulfinyl product, while β -alkoxyalanine derivatives were obtained from Boc₂- Δ Ala-OMe. Use of Tos(Boc)- Δ Ala-OMe gave α,β -dialkoxy compounds, whilst (*E*)-Boc- Δ Ala[β -(1,2,4-triazol-1-yl)]-OMe yielded the corresponding β,β -dialkoxy isomers. β,β -Dimethoxyalanine derivatives have been used in a variety of synthetic transformations, namely the synthesis of ifetroban, a cardiovascular drug, and of several capreomycins and tuberactinomycins.^[16,17]

The application of the methods described in this work to provision of cross-linked amino acids was demonstrated by the syntheses of didehydrolanthionine and histidino- α,β -didehydroalanine derivatives in good yields.

Experimental Section

General Remarks: All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel 60F₂₅₄) and spots were viewed either under UV light or through exposure to vaporized iodine. Preparative chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). ¹H NMR spectra were recorded on a Varian Unit Plus spectrometer at 300 MHz at 25 °C in $\approx$ 5% CDCl₃ solution when not otherwise stated. All shifts are given in δ ppm with δ_{H} Me₄Si = 0 as reference. *J* Values are given in Hz. Spin-spin decoupling techniques were used to attribute the signals. The stereochemistries of the products were determined by NOE experiments. ¹³C NMR spectra were recorded with the same instrument at 75.4 MHz and with use of the solvent peak as internal reference (DEPT θ 45°). The elemental analyses of crystalline compounds and of some oils were carried out on a Leco CHNS 932 instrument.

Preparation of *N*-Acyl Amino Acid Esters

Synthesis of Tos-Ser-OMe, Boc-Ser-OMe, and Tos-Thr-OMe: The syntheses of these compounds were described in ref.^[2]

Synthesis of Tos-Phe(β -OH)-OMe: This compound was prepared from HCl·H-Phe(β -OH)-OMe (10 mmol, 3.23 g) and *p*-tolylsulfonyl chloride according to the procedure described in ref.^[2] for the compounds above (2.72 g, 78%), m.p. 175–177 °C (from ethyl acetate), C₁₇H₁₉NO₅S (349.40): calcd. C 58.44, H 5.48, N 4.01, S 9.18; found C 58.39, H 5.60, N 4.07, S 9.16%. δ_{H} = 2.39 (s, 3 H, 4-CH₃ Tos), 2.77 (d, *J* = 3.6 Hz, 1 H, OH), 3.50 (s, 3 H, OCH₃), 4.10 (dd, *J* = 3.9, *J* = 9.9 Hz, 1 H α CH), 5.04 (dd, *J* = 3.6, *J* = 3.9 Hz, 1 H, β CH), 5.43 (d, *J* = 9.9 Hz, 1 H, α NH), 7.16 (d, *J* = 8.4 Hz, 2 H, ArH Tos), 7.28 (broad s, 5 H, ArH), 7.51 (d, *J* = 8.4 Hz, 2 H, ArH Tos) ppm; δ_{C} = 21.5, 52.6, 61.8, 74.2, 126.1, 127.0, 128.3, 128.4, 129.5, 136.4, 138.5, 143.5, 170.4 ppm.

Synthesis of Nosyl-Ser-OMe: This compound was prepared from HCl·H-Ser-OMe (10 mmol, 2.47 g) and 4-nitrophenylsulfonyl chloride according to the procedure described elsewhere for the compounds above (2.70 g, 89%), m.p. 172.5–173.5 °C (from methanol), C₁₀H₁₂N₂O₇S (304.27): calcd. C 39.47, H 3.97, N 9.21, S 10.54; found C 39.62, H 4.08, N 9.24, S 10.59%. δ_{H} (DMSO) = 3.41 (s,

3 H, OCH₃), 3.48–3.61 (m, 2 H, β CH₂), 3.96 (broad s, 1 H, α CH), 5.10 (t, *J* = 5.7 Hz, 1 H, OH), 8.03 (d, *J* = 9.0 Hz, 2 H, ArH), 8.39 (d, *J* = 9.0 Hz, 2 H, ArH), 8.71 (s, 1 H, α NH) ppm; δ_{C} (DMSO) 51.9, 58.1, 61.9, 124.4, 128.1, 146.7, 149.5, 170.2 ppm.

Preparation of α,β -Didehydroamino Acid Derivatives

Synthesis of Tos(Boc)- Δ Ala-OMe^[6] (1), Tos(Boc)- Δ Abu-OMe^[2] (5), Boc₂- Δ Ala-OMe^[12] (21), Tos(Boc)- Δ Phe-OMe^[5] (25), Boc₂- Δ Abu-OMe,^[2] and Boc₂- Δ Phe-OMe:^[5] The syntheses of these compounds were described in refs.^[2,5,6,12]

Preparation of β -Substituted α,β -Didehydroamino Acid Derivatives

Synthesis of (*E*)-Boc- Δ Ala[β -(1,2,4-triazol-1-yl)]-OMe (6), (*E*)-Boc- Δ Abu[β -(1,2,4-triazol-1-yl)]-OMe [(*E*)-7], (*Z*)-Boc- Δ Abu[β -(1,2,4-triazol-1-yl)]-OMe [(*Z*)-7], (*E*)-Boc- Δ Phe[β -(1,2,4-triazol-1-yl)]-OMe [(*E*)-11] and (*Z*)-Boc- Δ Phe[β -(1,2,4-triazol-1-yl)]-OMe [(*Z*)-11]: The syntheses of these compounds were described in ref.^[4]

Preparation of *O*-Sulfinyl- α,β -didehydroserine Derivatives

Synthesis of (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe (12a): DMAP (0.1 equiv.) was added at room temperature with rapid stirring to a solution of Tos-Ser-OMe (5 mmol, 1.37 g) in acetonitrile (1 mol·dm⁻³), followed by *tert*-butyl pyrocarbonate (2.2 equiv.). The reaction mixture was stirred for 36 hours with monitoring by TLC (diethyl ether/*n*-hexane, 1:1). Evaporation at reduced pressure gave a residue that was partitioned between diethyl ether (200 cm³) and KHSO₄ (1 mol·dm⁻³, 100 cm³). The organic phase was thoroughly washed with KHSO₄ (1 mol·dm⁻³), NaHCO₃ (1 mol·dm⁻³) and brine (3 $\times$ 50 cm³ each), and dried with MgSO₄. Removal of the solvent afforded pure product (1.67 g, 94%), m.p. 102–103.5 °C (from ethyl acetate/*n*-hexane), C₁₆H₂₁NO₆S (355.41): calcd. C 54.07, H 5.96, N 3.94, S 9.02; found C 53.93, H 6.11, N 4.01, S 8.83%. δ_{H} = 1.48 (s, 9 H, Boc), 2.45 (s, 3 H, Ar-CH₃), 3.81 (s, 3 H, OCH₃), 5.68 (s, 1 H, β CH), 7.35 (d, *J* = 8.4 Hz, 2-H, ArH), 7.77 (d, *J* = 8.4 Hz, 2 H, ArH), 8.86 (s, 1 H, α NH) ppm; δ_{C} = 21.7, 28.0, 53.3, 83.2, 109.3, 127.2, 130.1, 137.8, 139.9, 145.2, 150.7, 163.3 ppm.

Synthesis of (*E*)-Boc- Δ Ser(4-nitrophenylsulfinyl)-OMe (12b): The same procedure as described above for the synthesis of 12a was followed, with substitution of Nosyl-Ser-OMe (5 mmol, 1.52 g) for Tos-Ser-OMe to afford 12b (1.24 g, 64%), m.p. 128.5–130 °C (from diethyl ether/*n*-hexane), C₁₅H₁₈N₂O₈S (386.37): calcd. C 46.63, H 4.70, N 9.725, S 8.30; found C 46.86, H 4.99, N 9.735, S 8.00%. δ_{H} = 1.47 (s, 9 H, Boc), 3.95 (s, 3 H, OCH₃), 6.81 (s, 1 H, α NH), 7.16 (s, 1 H, β CH), 8.15 (d, *J* = 9.0 Hz, 2 H, ArH), 8.38 (d, *J* = 9.0 Hz, 2 H, ArH) ppm; δ_{C} = 27.9, 53.8, 83.7, 110.3, 124.2, 128.6, 141.4, 147.8, 150.2, 150.6, 162.3 ppm.

Synthesis of 2,3-Dihydrofuran Derivatives

Synthesis of 4-Acetyl-2-(*tert*-butoxycarbonylamino)-2-methoxycarbonyl-5-methyl-2,3-dihydrofuran^[5] (3a), 2-(*tert*-Butoxycarbonylamino)-2,4-bis(methoxycarbonyl)-5-methyl-2,3-dihydrofuran^[5] (3b), and 2-(*tert*-Butoxycarbonylamino)-4-benzyloxycarbonyl-2-methoxycarbonyl-5-methyl-2,3-dihydrofuran^[7] (3d): The synthesis of these compounds was described in refs.^[5,7]

Synthesis of 4-Benzoyl-2-(*tert*-butoxycarbonylamino)-2-methoxycarbonyl-5-methyl-2,3-dihydrofuran (3c): Cs₂CO₃ (1 equiv.) was added at room temperature with rapid stirring to a solution of Tos(Boc)- Δ Ala-OMe (2 mmol, 0.71 g) in acetonitrile (0.1 mol·dm⁻³), followed by benzoyl acetone (1 equiv.). The reaction was monitored by TLC and when no starting material was detected, the solution was filtered and the solvent was evaporated at reduced pressure to

give **3c** (0.58 g, 80%), m.p. 120–121 °C (from diethyl ether/*n*-hexane), C₁₉H₂₃NO₆ (361.39): calcd. C 63.15, H 6.41, N 3.88; found: 62.92, H 6.20, N 3.86%. δ_{H} = 1.47 (s, 9 H, CH₃ Boc), 1.89 (s, 3 H, CH₃), 3.37 (q, J = 14.6 Hz, 2 H, CH₂), 3.88 (s, 3 H, OCH₃), 5.88 (s, 1 H, α NH), 7.40–7.61 (m, 5 H, ArH) ppm; δ_{C} = 28.0, 39.8, 53.4, 67.1, 81.3, 91.2, 100.6, 128.0, 128.3, 128.4, 128.5, 129.8, 136.2, 153.2, 164.7, 167.0, 168.7 ppm.

Synthesis of 2-(*tert*-Butoxycarbonylamino)-4-isobutoxycarbonyl-2-methoxycarbonyl-5-methyl-2,3-dihydrofuran (3e): The same procedure as used above for the synthesis of **3c** was followed, with substitution of isobutoxycarbonyl acetone for benzoyl acetone to afford **3e** (0.59 g, 82%), m.p. 109.5–111 °C (from diethyl ether/*n*-hexane), C₁₇H₂₇NO₇ (357.40): calcd. C 57.13, H 7.61, N 3.92; found C 57.13, H 7.61, N 3.99%. δ_{H} = 0.95 (d, J = 6.9 Hz, 6 H, 2 CH₃), 1.45 (s, 9 H, Boc), 1.93–2.01 (m, 1 H, CH), 2.27 (s, 3 H, CH₃), 3.17 (q, J = 17.4 Hz, 2 H, CH₂), 3.85 (s, 3 H, OCH₃), 3.90 (d, J = 6.9 Hz, 2 H, CH₂), 5.83 (s, 1 H, α NH) ppm; δ_{C} = 14.1, 19.2, 28.1, 30.9, 40.0, 53.5, 70.1, 81.5, 91.1, 101.1, 153.3, 165.0, 166.2, 168.9 ppm.

Synthesis of Pyrrole Derivatives

Synthesis of 4-Acetyl-2-methoxycarbonyl-5-methylpyrrole^[8] (4a): TFA (10%) was added at room temperature with rapid stirring to a solution of **3a** (1 mmol, 0.30 g) in dichloromethane (0.1 mol·dm⁻³). The reaction was monitored by TLC and when no starting material was detected, dichloromethane (30 cm³) was added and the solution was washed with NaHCO₃ (1 mol·dm⁻³) and brine (3 × 10 cm³ each) and dried with MgSO₄. Removal of the solvent at reduced pressure afforded **4a** (0.17 g, 92%), m.p. 177.5–179 °C (from diethyl ether/*n*-hexane), C₉H₁₁NO₃ (181.19): calcd. C 59.66, H 6.12, N 7.73; found C 59.55, H 6.11, N 7.77%. δ_{H} = 1.62 (s, 3 H, CH₃), 2.43 (s, 3 H, CH₃), 3.88 (s, 3 H, OCH₃), 7.21 (d, J = 3.0 Hz, 1 H, CH), 9.23 (s, 1 H, α NH) ppm; δ_{C} = 14.0, 28.2, 51.7, 117.4, 119.9, 122.5, 139.5, 161.5, 194.8 ppm.

Synthesis of 2,4-Bis(methoxycarbonyl)-5-methylpyrrole (4b): This compound was prepared from compound **3b** (1 mmol, 0.32 g) by the same procedure as described above for **4a**, to give **4b** (0.18 g, 90%), m.p. 175–176 °C (from diethyl ether/*n*-hexane), C₉H₁₁NO₄ (197.19): calcd. C 54.82, H 5.62, N 7.10; found C 54.75, H 5.62, N 7.11%. δ_{H} = 2.58 (s, 3 H, CH₃), 3.82 (s, 3 H, OCH₃), 3.86 (s, 3 H, OCH₃), 7.24 (d, J = 2.7 Hz, 1 H, CH), 9.23 (s, 1 H, α NH) ppm; δ_{C} = 13.3, 51.0, 51.7, 113.8, 117.5, 120.3, 140.0, 161.7, 165.1 ppm.

Synthesis of 4-Benzoyl-2-methoxycarbonyl-5-methylpyrrole^[8] (4c): This compound was prepared from compound **3c** (1 mmol, 0.36 g) by the same procedure as described for **4a**, to give **4c** (0.19 g, 77%), m.p. 153–154.5 °C (from diethyl ether/*n*-hexane), C₁₄H₁₃NO₃ (243.26): calcd. C 69.13, H 5.39, N 5.76; found C 69.39, H 5.39, N 5.62%. δ_{H} = 2.38 (s, 3 H, CH₃), 3.86 (s, 3 H, OCH₃), 7.36 (d, J = 3.0 Hz, 1 H, CH), 7.44–7.46 (m, 3 H, ArH), 7.58–7.61 (m, 2 H, ArH), 9.48 (s, 1 H, α NH) ppm; δ_{C} = 28.9, 51.9, 117.9, 121.8, 123.0, 128.4, 129.1, 129.4, 131.0, 139.8, 161.3, 193.8 ppm.

Synthesis 4-Benzoyloxycarbonyl-2-methoxycarbonyl-5-methylpyrrole (4d): The synthesis of this compound was described in ref.^[7]

Synthesis of 4-Isobutoxycarbonyl-2-methoxycarbonyl-5-methylpyrrole (4e): This compound was prepared from compound **3e** (1 mmol, 0.36 g) by the same procedure as described above for **4a**, to give **4e** (0.21 g, 88%) as an oil, which solidified on standing m.p. 137–138.5 °C, C₁₂H₁₇NO₄ (239.27): calcd. C 60.24, H 7.16, N 5.85; found C 60.15, H 7.12, N 5.91%. δ_{H} = 1.06 (d, J = 6.9 Hz, 6 H, 2 CH₃), 1.98–2.17 (m, 1 H, CH), 2.64 (s, 3 H, CH₃), 3.93 (s, 3 H,

OCH₃), 4.08 (d, J = 6.3 Hz, 2 H, CH₂), 7.26 (d, J = 2.7 Hz, 1 H, CH), 9.65 (s, 1 H, α NH) ppm; δ_{C} = 13.5, 19.2, 27.9, 51.7, 70.0, 114.3, 117.4, 120.3, 139.4, 164.7, 170.8 ppm.

Synthesis of β -Amino- α,β -didehydroamino Acid Derivatives

Synthesis of (*E*)-Boc- Δ Ala(β -benzylamino)-OMe (9a): Benzylamine (2.5 equiv.) was added to solution of (*E*)-Boc- Δ Ala[β -(1,2,4-triazol-1-yl)]-OMe (1 mmol, 0.27 g) in methanol (0.1 mol·dm⁻³). After overnight stirring, TLC still indicated some starting material, so a further 2.5 equiv. of benzylamine were added. When no starting material was detected, ethyl acetate (100 cm³) was added and the organic layer was washed with KHSO₄ (1 mol·dm⁻³) and brine (2 × 30 cm³ each). Drying with MgSO₄ and evaporation of the solvent at reduced pressure afforded **9a** (0.27 g, 87%), m.p. 90–91.5 °C (from diethyl ether/*n*-hexane), C₁₆H₂₂N₂O₄ (306.36): calcd. C 62.73, H 7.24, N 9.14; found C 62.75, H 7.18, N 9.03%. δ_{H} = 1.46 (s, 9 H, Boc), 3.70 (s, 3 H, OCH₃), 4.41 (d, J = 6.3 Hz, 2 H, CH₂), 5.68 (s, 1 H, NH), 5.93 (s, 1 H, NH), 7.29–7.41 (m, 6 H, β CH + ArH) ppm; δ_{C} = 28.2, 51.3, 52.0, 80.2, 98.3, 127.0, 127.2, 127.57, 127.63, 128.7, 138.6, 141.7, 166.6 ppm.

Synthesis of (*E*)-Boc- Δ Ala(β -propargylamino)-OMe (9b): The same procedure as described for the preparation of **9a** was followed, with substitution of propargylamine for benzylamine, to afford **9b** in (0.21 g, 82%), m.p. 60–61.5 °C (from diethyl ether), C₁₂H₁₈N₂O₄ (254.28): calcd. C 56.68, H 7.13, N 11.02; found C 56.43, H 7.12, N 10.70%. δ_{H} = 1.45 (s, 9 H, Boc), 2.35 (m, 1 H, CH), 3.70 (s, 3 H, OCH₃), 3.96 (m, 2 H, CH₂), 5.61 (s, 1 H, NH), 6.05 (s, 1 H, NH), 7.24 (d, J = 6.3 Hz, 1 H, β CH) ppm; δ_{C} = 28.5, 37.4, 51.8, 73.2, 79.8, 80.7, 100.2, 139.6, 150.3, 166.6 ppm.

Synthesis of (*E*)-Boc- Δ Ala[β -[*N*-(2-aminoethyl)amino]]-OMe (9c): 1,2-Ethylenediamine (10 equiv.) was added to a solution of (*E*)-Boc- Δ Ala[β -(1,2,4-triazol-1-yl)]-OMe (1 mmol, 0.27 g) in methanol (0.1 mol·dm⁻³). The solution was heated at reflux for 2 hours and the solvent was then evaporated at reduced pressure. The residue was dissolved in dichloromethane (100 cm³) and washed with Na₂CO₃ (1 mol·dm⁻³) (3 × 30 cm³). The organic phase was dried with MgSO₄ and the solvents were evaporated at reduced pressure to afford **9c** (0.23 g, 90%), oil; δ_{H} = 1.47 (s, 9 H, Boc), 2.85 (t, J = 5.4 Hz, 2 H, CH₂), 3.25 (q, J = 5.4 Hz, 2 H, CH₂), 3.70 (s, 3 H, OCH₃), 3.46 (broad s, 2 H, NH₂), 5.38 (broad s, 1 H, NH), 5.92 (broad s, 1 H, NH), 7.24 (d, J = 13.2 Hz, 1 H, β CH) ppm; δ_{C} = 28.2, 31.5, 42.8, 51.2, 80.2, 97.9, 128.2, 144.2, 166.7 ppm.

Synthesis of (*E*)-Boc- Δ Abu(β -benzylamino)-OMe (10a): The synthesis of this compound was described in ref.^[9]

Synthesis of (*E*)-Boc- Δ Abu(β -propargylamino)-OMe (10b): The same procedure as described for the preparation of **9b** was followed, with substitution of (*E*)-Boc- Δ Abu[β -(1,2,4-triazol-1-yl)]-OMe (1 mmol, 0.28 g) for (*E*)-Boc- Δ Ala[β -(1,2,4-triazol-1-yl)]-OMe, to afford **10b** (0.24 g, 90%), m.p. 75–77 °C (from diethyl ether/*n*-hexane), C₁₃H₂₀N₂O₄ (268.31): calcd. C 58.19, H 7.51, N 10.44; found C 57.85, H 7.36, N 10.07%. δ_{H} = 1.46 (s, 9 H, Boc), 2.09 (s, 3 H, γ CH₃), 2.28 (t, J = 2.4 Hz, 1 H, CH), 3.66 (s, 3 H, OCH₃), 3.98 (2d, J = 2.4, J = 6.2 Hz, 2 H, CH₂), 5.39 (broad s, 1 H, NH), 9.11 (s, 1 H, NH) ppm; δ_{C} = 14.0, 28.0, 32.8, 54.0, 72.0, 79.6, 84.0, 94.2, 109.7, 156.0, 168.1 ppm. The same procedure with (*Z*)-Boc- Δ Abu[β -(1,2,4-triazol-1-yl)]-OMe again gave the *E* isomer of **10b**, in 92% yield (0.25 g).

Synthesis of (*E*)-Boc- Δ Abu[β -[*N*-(2-aminoethyl)amino]]-OMe (10c): The same procedure as described for the preparation of **9c** was followed, with substitution of (*E*)-Boc- Δ Abu[β -(1,2,4-triazol-1-yl)]-

OMe (1 mmol, 0.28 g) for (*E*)-Boc- Δ Ala[β -(1,2,4-triazol-1-yl)]-OMe, to afford **10c** (0.11 g, 39%), oil; δ_{H} = 1.45 (s, 9 H, Boc), 2.01 (s, 3 H, γ -CH₃), 2.87 (t, J = 5.7 Hz, 2 H, CH₂), 3.28 (q, J = 5.7 Hz, 2 H, CH₂), 3.64 (s, 3 H, OCH₃), 3.90 (d, J = 5.7 Hz, 2 H, NH₂), 5.11 (broad s, 1 H, NH), 5.40 (broad s, 1 H, NH) ppm; δ_{C} = 14.4, 28.2, 42.0, 46.3, 52.2, 79.4, 92.6, 143.7, 151.3, 162.2 ppm. The same procedure with (*Z*)-Boc- Δ Abu[β -(1,2,4-triazol-1-yl)]-OMe again gave the *E* isomer of **10c**, in 49% yield (0.13 g).

Synthesis of α -Amino-*O*-Sulfinylserine Derivatives

Synthesis of Boc-Ser[α -benzylamino, *O*-(*p*-tolylsulfinyl)]-OMe (13a**):** The synthesis of this compound was described in ref.^[9]

Synthesis of Boc-Ser[α -propargylamino, *O*-(*p*-tolylsulfinyl)]-OMe (13b**):** Propargylamine (2.5 equiv.) was added at room temperature, with rapid stirring, to a solution of (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe (1 mmol, 0.36 g) in methanol (0.1 mol·dm⁻³). The reaction was monitored by TLC and when no starting material was detected, ethyl acetate (100 cm³) was added. The organic phase was then washed with water and brine (2 $\times$ 30 cm³ each) and dried with MgSO₄, and the solvents were evaporated at reduced pressure to afford **13b** (0.36 g, 87%), m.p. 117–119 °C (from diethyl ether/*n*-hexane), C₁₉H₂₆N₂O₆S (410.49): calcd. C 55.59, H 6.38, N 6.82, S 7.81; found C 55.52, H 6.39, N 6.73, S 7.69%. δ_{H} = 1.27 (s, 9 H, Boc), 2.17 (t, J = 2.4 Hz, 1 H, CH), 2.43 (s, 3 H, Ar-CH₃), 3.09 (s, 1 H, NH), 3.21 (dq, J = 2.4, J = 16.8 Hz, 2 H, CH₂), 3.89 (d, J = 14.7 Hz, 1 H, β -CH₂), 3.90 (s, 3 H, OCH₃), 4.36 (d, J = 14.7 Hz, 1 H, CH₂), 6.02 (s, 1 H, NH), 7.32 (d, J = 8.1 Hz, 2 H, ArH), 7.73 (d, J = 8.1 Hz, 2 H, ArH) ppm; δ_{C} = 21.6, 28.0, 31.4, 53.8, 59.5, 71.7, 80.4, 128.2, 129.8, 137.1, 144.6, 153.7, 169.1 ppm.

Synthesis of 3-(*tert*-Butoxycarbonylamino)-2-oxo-3-[(*p*-tolylsulfinyl)oxymethyl]piperazine (15a**):** The same procedure as described for the preparation of **13b** was followed, with substitution of 1,2-ethylenediamine for benzylamine, to afford **15a** (0.34 g, 89%), m.p. 118–119.5 °C (from methanol/diethyl ether), C₁₇H₂₅N₃O₅S (383.47): calcd. C 53.25, H 6.57, N 10.96, S 8.36; found C 53.27, H 6.42, N 11.08, S 8.37%. δ_{H} = 1.41 (s, 9 H, Boc), 2.44 (s, 3 H, Ar-CH₃), 2.90–2.95 (m, 1 H, CH₂), 3.14–3.26 (m, 2 H, CH₂), 3.49 (broad s, 1 H, NH), 3.62–3.71 (m, 1 H, CH₂), 3.95 (d, J = 14.4 Hz, 1 H, CH₂), 4.04 (d, J = 14.4 Hz, 1 H, CH₂), 5.46 (s, 1 H, NH), 6.15 (broad s, 1 H, NH), 7.32 (d, J = 8.1 Hz, 2 H, ArH), 7.82 (d, J = 8.1 Hz, 2 H, ArH) ppm; δ_{C} = 21.6, 28.2, 37.2, 42.3, 60.5, 71.5, 80.6, 128.3, 129.4, 138.4, 144.2, 154.5, 167.4 ppm.

Synthesis of Boc-Ser[α -benzylamino, *O*-(4-nitrophenylsulfinyl)]-OMe (14a**):** The same procedure as described for the preparation of **13b** was followed, with substitution of (*E*)-Boc- Δ Ser(4-nitrophenylsulfinyl)-OMe (1 mmol, 0.39 g) for (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe and benzylamine for propargylamine, to afford **14a** (0.45 g, 91%), m.p. 141–143 °C (from diethyl ether), C₂₂H₂₇N₃O₈S (493.53): calcd. C 53.54, H 5.51, N 8.51, S 6.50; found C 53.63, H 5.49, N 8.86, S 6.90%. δ_{H} = 1.25 (s, 9 H, Boc), 2.94 (s, 1 H, NH), 3.33 (d, J = 12.0 Hz, 1 H, CH₂), 3.56 (d, J = 12.0 Hz, 1 H, CH₂), 3.88 (s, 3 H, OCH₃), 4.04 (d, J = 14.7 Hz, 1 H, CH₂), 4.49 (d, J = 14.7 Hz, 1 H, CH₂), 6.08 (s, 1 H, NH), 7.18–7.31 (m, 5 H, ArH Bz), 8.07 (d, J = 9.0 Hz, 2 H, ArH), 8.38 (d, J = 9.0 Hz, 2 H, ArH) ppm; δ_{C} = 28.0, 46.4, 53.9, 59.7, 71.9, 80.8, 124.2, 127.5, 128.3, 128.5, 128.6, 129.8, 138.0, 145.5, 150.7, 153.5, 169.2 ppm.

Synthesis of Boc-Ser[α -propargylamino, *O*-(4-nitrophenylsulfinyl)]-OMe (14b**):** The same procedure as described for the preparation of **14a** was followed, with substitution of propargylamine for benzylamine, to afford **14b** (0.33 g, 75%), m.p. 131–133 °C (from diethyl ether), C₁₈H₂₃N₃O₈S (441.46): calcd. C 48.97, H 5.25, N 9.52,

S 7.26; found C 49.04, H 5.38, N 9.48, S 7.14%. δ_{H} = 1.23 (s, 9 H, Boc), 2.20 (t, J = 2.4 Hz, 1 H, CH), 3.05 (s, 1 H, NH), 3.19–3.24 (m, 2 H, CH₂), 3.96 (s, 3 H, OCH₃), 3.99 (d, J = 15.0 Hz, 1 H, CH₂), 4.49 (d, J = 15.0 Hz, 1 H, CH₂), 6.02 (s, 1 H, NH), 8.07 (d, J = 8.7 Hz, 2 H, ArH), 8.38 (d, J = 8.7 Hz, 2 H, ArH) ppm; δ_{C} = 28.0, 31.4, 54.0, 59.6, 71.6, 71.9, 80.2, 81.0, 124.3, 129.9, 145.4, 150.8, 153.6, 168.7 ppm.

Synthesis of 3-(*tert*-Butoxycarbonylamino)-2-oxo-3-[(4-nitrophenylsulfinyl)oxymethyl]piperazine (15b**):** The same procedure as described for the preparation of **15a** was followed, with substitution of (*E*)-Boc- Δ Ser(4-nitrophenylsulfinyl)-OMe (1 mmol, 0.39 g) for (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe, to afford **15b** (0.24 g, 59%), m.p. 156–157 °C (from ethyl acetate/*n*-hexane), C₁₆H₂₂N₄O₇S (414.44): calcd. C 46.37, H 5.35, N 13.52, S 7.74; found C 46.30, H 5.44, N 13.34, S 7.66%. δ_{H} = 1.33 (s, 9 H, Boc), 2.63–3.22 (m, 5 H, 2 CH₂ + NH), 4.01 (d, J = 14.7 Hz, 1 H, CH₂), 4.15 (d, J = 14.7 Hz, 1 H, CH₂), 7.38 (s, 1 H, NH), 7.90 (s, 1 H, NH), 8.13 (d, J = 9.0 Hz, 2 H, ArH), 8.40 (d, J = 9.0 Hz, 2 H, ArH) ppm; δ_{C} = 28.0, 36.4, 41.1, 59.7, 70.0, 79.1, 123.9, 130.0, 146.5, 150.1, 154.4, 164.9 ppm.

Synthesis of β -Sulfanyl α,β -Didehydroalanine Derivatives

Synthesis of (*E*)-Boc- Δ Ala(β -methoxycarbonylmethylsulfinyl)-OMe (19**):** The same procedure as described above for the synthesis of **13b** was followed, with substitution of methylsulfinyl acetate (1 equiv.) for propargylamine and addition of triethylamine (2.5 equiv.), to give **19**^[5] (0.16 g, 54%).

Synthesis of (*E*)-Boc- Δ Ala[β -(4-bromophenylsulfinyl)]-OMe (20**):** The same procedure as described above for the synthesis of **19** was followed, with substitution of 4-bromothiophenol for methylsulfinyl acetate, to give **20**^[9] (0.29 g, 75%).

Synthesis of (*E*)-Boc- Δ Ala[β -(1,2,4-triazol-1-yl)]-OMe: The same procedure as described above for the synthesis of **19** was followed, with substitution of 1,2,4-triazole for methylsulfinyl acetate, to give **6**^[4] (0.12 g, 42%).

Synthesis of Alkoxyamino Acid Derivatives

Synthesis of Boc-Ser[α -methoxy-*O*-(*p*-tolylsulfinyl)]-OMe (22a**):** NaOMe (2 equiv.) was added with rapid stirring at room temperature to a solution of (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe (1 mmol, 0.36 g) in methanol (0.1 mol·dm⁻³). The reaction was monitored by TLC and, when no starting material was detected, ethyl acetate (100 cm³) was added. The organic phase was then washed with water and brine (2 $\times$ 30 cm³ each) and dried with MgSO₄, and the solvents were evaporated at reduced pressure to give **22a** (0.30 g, 77%), m.p. 89.5–90.5 °C (from diethyl ether/*n*-hexane), C₁₇H₂₅NO₇S (387.45): calcd. C 52.70, H 6.50, N 3.62, S 8.28; found C 52.43, H 6.58, N 3.66, S 7.75%. δ_{H} = 1.30 (s, 9 H, Boc), 2.44 (s, 3 H, Ar-CH₃), 3.11 (s, 3 H, CH₃), 3.83 (d, J = 14.7 Hz, 1 H, β -CH₂), 3.92 (s, 3 H, OCH₃), 4.68 (d, J = 14.7 Hz, 1 H, β -CH₂), 6.27 (s, 1 H, α NH), 7.33 (d, J = 8.1 Hz, 2 H, ArH), 7.75 (d, J = 8.1 Hz, 2 H, ArH) ppm; δ_{C} = 21.5, 27.9, 50.2, 53.7; 58.3, 80.5, 83.6, 128.3, 129.6, 136.8, 144.6, 152.6, 168.0 ppm.

Synthesis of Boc-Ser[α -ethoxy, *O*-(*p*-tolylsulfinyl)]-OEt (22b**):** The same procedure as described above for the synthesis of **22a** was followed, with substitution of NaOEt (3 equiv.) for NaOMe and ethanol for methanol, to give **22b** (0.22 g, 52%), m.p. 81.5–82.5 °C (from diethyl ether/*n*-hexane), C₁₉H₂₉NO₇S (415.50): calcd. C 54.92, H 7.03, N 3.37, S 7.72; found C 54.96, H 6.89, N 3.39, S 7.72%. δ_{H} = 1.08 (t, J = 7.2 Hz, 3 H, CH₃ OEt), 1.29 (s, 9 H, Boc), 1.39 (t, J = 7.2 Hz, 3 H, CH₃ OEt), 2.43 (s, 3 H, Ar-CH₃),

3.21–3.46 (m, 2 H, CH₂ OEt), 3.85 (d, J = 14.7 Hz, 1 H, β CH₂), 4.36 (q, J = 7.2 Hz, 2 H, CH₂ OEt), 4.64 (d, J = 14.7 Hz, 1 H, β CH₂), 6.30 (broad s, 1 H, α NH), 7.32 (d, J = 8.1 Hz, 2 H, ArH), 7.75 (d, J = 8.1 Hz, 2 H, ArH) ppm; δ_C = 14.0, 14.8, 21.6, 28.0, 58.6, 63.1, 80.3, 83.1, 109.7, 128.3, 129.6, 137.1, 144.5, 152.7, 167.9 ppm.

Synthesis of Boc₂-Ala(β -methoxy)-OMe (23a): The same procedure as described above for the synthesis of **22a** was followed, with substitution of Boc₂- Δ Ala-OMe (1 mmol, 0.30 g) for (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe, to give **23a** (0.27 g, 80%), oil, C₁₅H₂₇NO₇ (333.38): calcd. C 54.04, H 8.16, N 4.20; found C 53.83, H 7.97, N 4.53%. δ_H = 1.51 (s, 9 H, Boc), 3.37 (s, 3 H, β OCH₃), 3.74 (s, 3 H, COOCH₃), 3.83 (dd, J = 8.4, J = 10.7 Hz, 1 H, β CH₂), 3.99 (dd, J = 5.1, J = 10.7 Hz, 1 H, β CH₂), 5.19 (dd, J = 5.1, J = 8.4 Hz, 1 H, α CH₂) ppm; δ_C = 27.9, 52.2, 57.4, 58.9, 71.1, 83.2, 152.0, 169.6 ppm.

Synthesis of Boc₂-Ala(β -ethoxy)-OEt (23b): The same procedure as described above for the synthesis of **22b** was followed, with substitution of Boc₂- Δ Ala-OMe (1 mmol, 0.30 g) for (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe, to give **23b** (0.14 g, 38%), m.p. 36.5–38 °C, C₁₇H₃₁NO₇ (361.43): calcd. C 56.49, H 8.64, N 3.88; found C 56.33, H 8.35, N 3.96%. δ_H = 1.17 (t, J = 7.2 Hz, 3 H, CH₃ OEt), 1.27 (t, J = 7.2 Hz, 3 H, CH₃ OEt), 1.51 (s, 18 H, Boc), 3.43–3.59 (m, 2 H, CH₂ OEt), 3.88 (dd, J = 8.4, J = 10.7 Hz, 1 H, β CH₂), 4.03 (dd, J = 4.8, J = 10.7 Hz, 1 H, β CH₂), 4.19 (q, J = 7.2 Hz, 2 H, CH₂ OEt), 5.16 (dd, J = 4.8, J = 8.4 Hz, 1 H, α CH) ppm; δ_C = 14.1, 15.1, 27.9, 57.7, 61.2, 66.3, 68.9, 82.9, 152.1, 169.2 ppm.

Synthesis of Boc-Ala(α,β -dimethoxy)-OMe (24a): The synthesis of this compound was described in ref.^[9]

Synthesis of Boc-Ala(α,β -diethoxy)-OEt (24b): The same procedure as described above for the synthesis of **22b** was followed, with substitution of Tos(Boc)- Δ Ala-OMe (1 mmol, 0.36 g) for (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe and use of 4 equiv. of NaOEt, to give **24b** (0.18 g, 60%), m.p. 29–30.5 °C, C₁₄H₂₇NO₆ (305.37): calcd. C 55.07, H 8.91, N 4.59; found C 55.42, H 8.88, N 4.43%. δ_H = 1.15 (t, J = 7.2 Hz, 3 H, CH₃ OEt), 1.20 (t, J = 7.2 Hz, 3 H, CH₃ OEt), 1.31 (t, J = 7.2 Hz, 3 H, CH₃ OEt), 1.45 (s, 9 H, Boc), 3.35–3.63 (m, 4 H, 2 CH₂ OEt), 3.72 (d, J = 9.3 Hz, 1 H, β CH₂), 4.17 (d, J = 9.3 Hz, 1 H, β CH₂), 4.23–4.34 (m, 2 H, CH₂ OEt), 6.04 (broad s, 1 H, α NH) ppm; δ_C = 14.1, 14.9, 15.2, 28.2, 59.3, 62.2, 67.1, 71.0, 80.0, 86.7, 153.4, 169.6 ppm.

Synthesis of Boc-Phe(α,β -dimethoxy)-OMe (26): The same procedure as described above for the synthesis of **22a** was followed, with substitution of Tos(Boc)- Δ Phe-OMe (1 mmol, 0.43 g) for (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe and use of 3 equiv. of NaOMe, to give **26** (0.30 g, 87%), m.p. 80–81 °C (from diethyl ether/*n*-hexane), C₁₇H₂₅NO₆ (339.39): calcd. C 60.16, H 7.42, N 4.13; found C 59.92, H 7.30, N 4.07%. δ_H = 1.42 (s, 9 H, Boc), 3.21 (s, 3 H, α OCH₃ or β OCH₃), 3.36 (s, 3 H, α OCH₃ or β OCH₃), 3.77 (s, 3 H, COOCH₃), 4.61 (s, 1 H, β CH), 5.05 (broad s, 1 H, α NH), 7.38–7.47 (m, 5 H, ArH) ppm; δ_C = 28.1, 52.1, 52.6, 57.5, 68.9, 86.6, 87.5, 128.3, 128.9, 129.1, 134.8, 153.9, 169.1 ppm.

Synthesis of Boc-Ala(β,β -dimethoxy)-OMe (27a): The same procedure as described above for the synthesis of **22a** was followed, with substitution of (*E*)-Boc- Δ Ala[β -(1,2,4-triazol-1-yl)]-OMe (1 mmol, 0.27 g) for (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe and use of 3 equiv. of NaOMe, to give **27a** (0.23 g, 88%), oil; C₁₁H₂₁NO₆ (263.29): calcd. C 50.18, H 8.04, N 5.32; found C 50.16, H 7.85, N 5.31%. δ_H = 1.44 (s, 9 H, Boc), 3.41 (s, 3 H, OCH₃), 3.43 (s, 3 H, OCH₃), 3.76 (s, 3 H, OCH₃), 4.49–4.57 (m, 2 H, α CH + β CH),

5.24 (d, J = 8.4 Hz, 1 H, α NH) ppm; δ_C = 28.2, 52.5, 55.3, 55.5, 55.7, 80.0, 103.7, 155.6, 170.2 ppm.

Synthesis of Boc-Ala(β,β -diethoxy)-OEt (27b): The same procedure as described above for the synthesis of **22b** was followed, with substitution of (*E*)-Boc- Δ Ala(1,2,4-triazol-1-yl)-OMe (1 mmol, 0.27 g) for (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe, to give **27b** (0.08 g, 27%), oil, C₁₄H₂₇NO₆ (305.37): calcd. C 55.07, H 8.91, N 4.59; found C 55.22, H 8.64, N 4.50%. δ_H = 1.17 (t, J = 7.2 Hz, 3 H, CH₃ OEt), 1.23 (t, J = 7.2 Hz, 3 H, CH₃ OEt), 1.28 (t, J = 7.2 Hz, 3 H, CH₃ OEt), 1.45 (s, 9 H, Boc), 3.47–3.80 (m, 4 H, 2 CH₂ OEt), 4.16–4.28 (m, 2 H, CH₂ OEt), 4.51 (dd, J = 3.3, J = 9.0 Hz, 1 H, α CH), 4.75 (d, J = 3.3 Hz, 1 H, β CH), 5.26 (d, J = 9.0 Hz, 1 H, α NH) ppm; δ_C = 14.1, 14.8, 15.0, 28.2, 56.0, 61.3, 63.5, 63.6, 79.8, 101.1, 155.7, 169.7 ppm.

Synthesis of (*E*)-Boc- Δ Abu(β -methoxy)-OMe (28): The same procedure as described above for the synthesis of **22a** was followed, with substitution of (*E*)-Boc- Δ Abu[β -(1,2,4-triazol-1-yl)]-OMe (1 mmol, 0.28 g) for (*E*)-Boc- Δ Ser(*p*-tolylsulfinyl)-OMe, to give **28** (0.08 g, 33%), m.p. 126–127 °C (from diethyl ether/*n*-hexane), C₁₁H₁₉NO₅ (245.27): calcd. C 53.87, H 7.81, N 5.71; found C 53.84, H 7.94, N 5.69%. δ_H = 1.46 (s, 9 H, Boc), 2.38 (s, 3 H, γ CH₃), 3.74 (s, 3 H, OCH₃), 3.76 (s, 3 H, OCH₃), 5.64 (s, 1 H, α NH) ppm; δ_C = 13.7, 28.2, 51.6, 55.3, 80.0, 109.2, 154.1, 166.5 ppm.

Synthesis of Cross-linked Amino Acid Derivatives

Synthesis of *N,N'*-Bis-Boc-cysteino-(*E*)- α,β -didehydroalanine Dimethyl Ester (32): K₂CO₃ (6 equiv.) was added to a solution of Tos(Boc)- Δ Ala-OMe (1 mmol, 0.36 g) in acetonitrile (0.2 mol·dm^{−3}), followed by Boc-L-Cys-OMe (1 equiv.), with fast stirring at room temperature. The reaction was monitored by ¹H NMR and when no starting material was detected, the solution was filtered and the solvent was evaporated at reduced pressure to give **32** (0.33 g, 75%), oil; δ_H = 1.45 (s, 9 H, Boc), 1.47 (s, 9 H, Boc), 3.29 (d, J = 4.2 Hz, 2-H, β CH₂ Cys), 3.77 (s, 6 H, 2OCH₃), 4.62 (m, 1 H, α CH Cys), 5.44 (d, J = 7.2 Hz, 1 H, α NH Cys), 6.07 (broad s, 1 H, α NH Δ Ala), 7.17 (s, 1 H, β CH Δ Ala) ppm; δ_C = 28.1, 28.2, 37.2, 52.3, 52.7, 59.0, 80.4, 80.9, 122.8, 134.9, 144.4, 154.9, 163.3, 170.4 ppm.

Synthesis of *N,N'*-Bis-Boc-histidino-(*E*)- α,β -didehydroalanine Dimethyl Ester (33): The same procedure as described above for the synthesis of **32** was followed, with substitution of Boc-L-His-OMe (1 mmol, 0.27 g) for Boc-L-Cys-OMe, to give **33** (0.40 g, 85%), m.p. 70–71.5 °C, C₂₁H₃₂N₄O₈ (468.50): calcd. C 53.84, H 6.88, N 11.96; found C 53.51, H 6.88, N 11.68%. δ_H = 1.41 (s, 9 H, Boc), 1.43 (s, 9 H, Boc), 3.00–3.12 (m, 2 H, β CH₂ His), 3.71 (s, 3 H, OCH₃), 3.85 (s, 3 H, OCH₃), 4.55–4.58 (m, 1 H, α CH), 5.73 (d, J = 8.1 Hz, 1 H, α NH His), 6.04 (s, 1 H, α NH Δ Ala), 7.15 (s, 1 H, β CH Δ Ala), 7.63 (s, 1 H, 2-H or 4-H imid.), 7.76 (s, 1 H, 2-H or 4-H imid.) ppm; δ_C = 28.0, 29.3, 52.3, 52.6, 52.8, 53.2, 79.7, 81.8, 116.1, 126.6, 136.9, 138.3, 139.1, 152.9, 165.2, 172.3 ppm.

Synthesis of Tos-Ala[*N*-Boc- β -{(Z)-lysino- ω -yl]-OMe]-OMe: The same procedure as described above for the synthesis of **32** was followed, with substitution of (Z)-L-Lys-OMe (1 mmol, 0.29 g) for Boc-L-Cys-OMe, to give a mixture of diastereomers (0.55 g, 84%) that could not be separated by column chromatography.

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Received February 18, 2003