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

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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.

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)-ΔAla-OMe[6]] with the above nucleophiles in the presence of K_2CO_3, 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 results 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.

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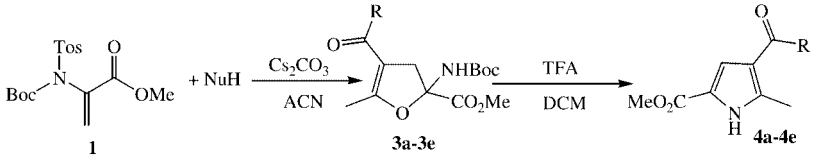
Results and Discussion

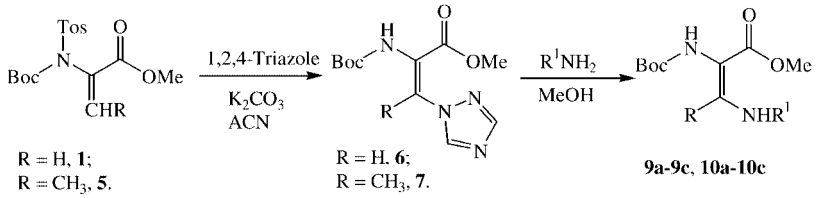
We have reported that the initial products of reactions between Tos(Boc)-ΔAla-OMe[6] (compound **1**) and carbon nucleophiles of the β-dicarbonyl type, with a methyl group bonded to one of the carbonyl groups, undergo spontaneous elimination of tosyl groups with cyclisation to give 5-methyl-2,3-dihydrofuran 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-ΔAla[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.



NuH	R	R
pentane-2,4-dione, **2a**	Me, **3a**[5] (88%)	Me, **4a**[8] (92%)
methylacetoacetate, **2b**	OMe, **3b**[5] (86%)	OMe, **4b** (90%)
benzoylacetone, **2c**	Ph, **3c** (80%)	Ph, **4c**[8] (77%)
benzyloxycarbonyl acetone, **2d**	OBn, **3d**[7] (78%)	OBn, **4d**[7] (79%)
isobutyloxycarbonyl acetone, **2e**	O-*i*Bu, **3e** (82%)	O-*i*Bu, **4e** (88%)

Scheme 1



R^1NH_2: benzylamine, **8a**; propargylamine, **8b**; 1,2-ethylenediamine, **8c**.

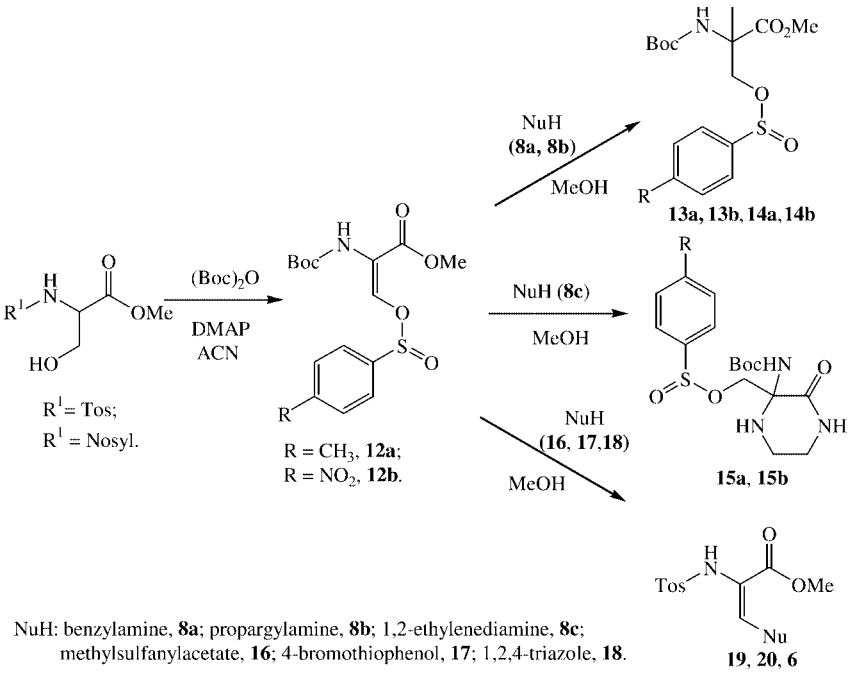
Scheme 2

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

Subst.	R^1NH_2	Product	Yield (%)
6	benzylamine **8a**	(*E*)-Boc-ΔAla(β-benzylamino)-OMe **9a**	87
6	propargylamine **8b**	(*E*)-Boc-ΔAla(β-propargylamino)-OMe **9b**	82
6	1,2-ethylenediamine **8c**	(*E*)-Boc-ΔAla{β-[*N*-(2-aminoethyl)amino]}-OMe **9c**	90
(*E*)-**7**	benzylamine **8a**	(*E*)-Boc-ΔAbu(β-benzylamino)-OMe **10a**[9]	95
(*Z*)-**7**	Ppropargylamine **8b**	(*E*)-Boc-ΔAbu(β-propargylamino)-OMe **10b**	92
(*Z*)-**7**	1,2-ethylenediamine **8c**	(*E*)-Boc-ΔAbu{β-[*N*-(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)-ΔAbu-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-ΔAbu[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-ΔPhe[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

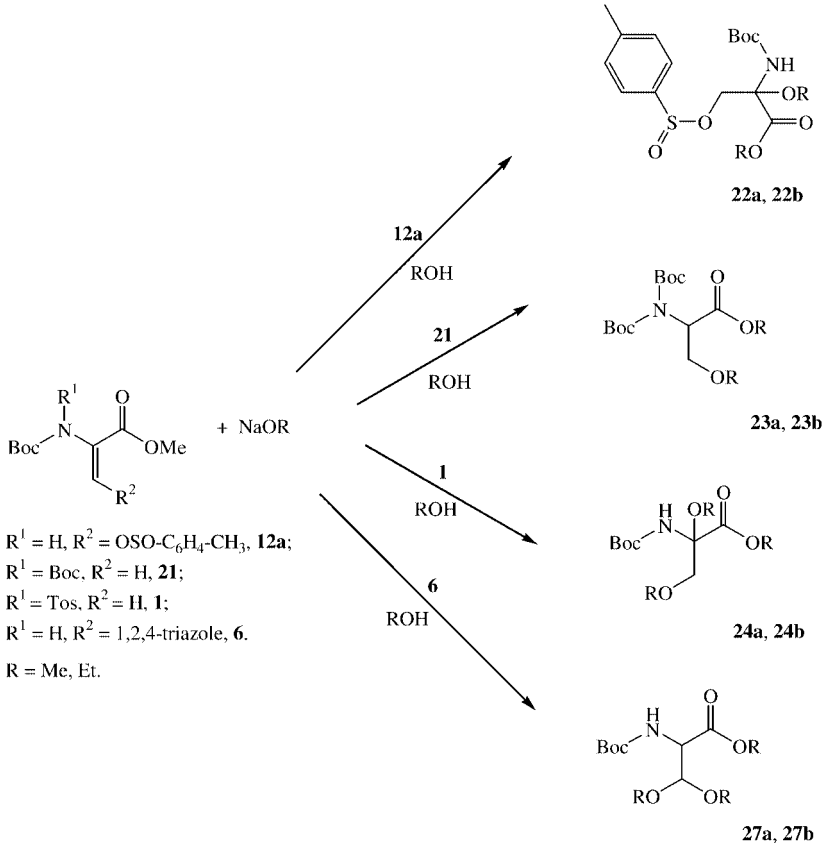
Subst.	NuH	Product	Yield (%)
12a	benzylamine, **8a**	Boc-Ser[α-benzylamino, *O*-(*p*-tolylsulfinyl)]-OMe, **13a**[9]	92
12a	propargylamine, **8b**	Boc-Ser[α-propargylamino, *O*-*p*-(tolylsulfinyl)]-OMe, **13b**	87
12b	benzylamine, **8a**	Boc-Ser[α-benzylamino, *O*-(4-nitrophenylsulfinyl)]-OMe, **14a**	91
12b	propargylamine, **8b**	Boc-Ser[α-propargylamino, *O*-(4-nitrophenylsulfinyl)]-OMe, **14b**	75
12a	1,2-ethylenediamine, **8c**	3-(*tert*-butoxycarbonylamino)-2-oxo-3-[(*p*-tolylsulfinyl)oxymethyl]piperazine, **15a**	89
12b	1,2-ethylenediamine, **8c**	3-(*tert*-butoxycarbonylamino)-2-oxo-3-[(4-nitrophenylsulfinyl)oxymethyl]piperazine, **15b**	59
12a	methylsulfanyl acetate, **16**	(*E*)-Boc-ΔAla(β-methoxycarbonylmethylsulfanyl)-OMe, **19**[5]	54
12a	4-bromothiophenol, **17**	(*E*)-Boc-ΔAla[β-(4-bromophenylsulfanyl)]-OMe, **20**[9]	75
12a	1,2,4-triazole, **18**	(*E*)-Boc-ΔAla(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 (methylsulfanyl 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 Boc_2-ΔAla-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, Boc_2-ΔAbu-OMe[2] and Boc_2-ΔPhe-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)-ΔPhe-OMe[5] (compound **25**), the dehydrophenylalanine analogue of **1**, reacted with sodium methoxide to give the corresponding α,β-dimethoxyphenyalanine derivative (compound **26**) as a racemic mixture. With



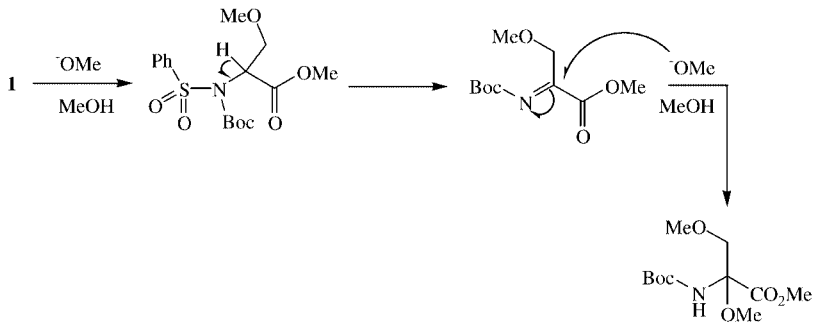
Scheme 4

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

Subst.	NaOR	Product	Yield (%)
12a	NaOMe	Boc-Ser[α-methoxy, *O*-(*p*-tolylsulfinyl)]-OMe **22a**	77
12a	NaOEt	Boc-Ser[α-ethoxy, *O*-(*p*-tolylsulfinyl)]-OEt **22b**	52
21	NaOMe	Boc-Ala(*N*-Boc, β-methoxy)-OMe **23a**	80
21	NaOEt	Boc-Ala(*N*-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
(*E*)-**7**	NaOMe	(*E*)-Boc-ΔAbu(β-methoxy)-OMe **28**	33

Tos(Boc)-ΔAbu-OMe (compound **5**), however, a complex mixture of products that could not be purified was formed, although ^{1}H 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 derivatives (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-ΔAbu[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-



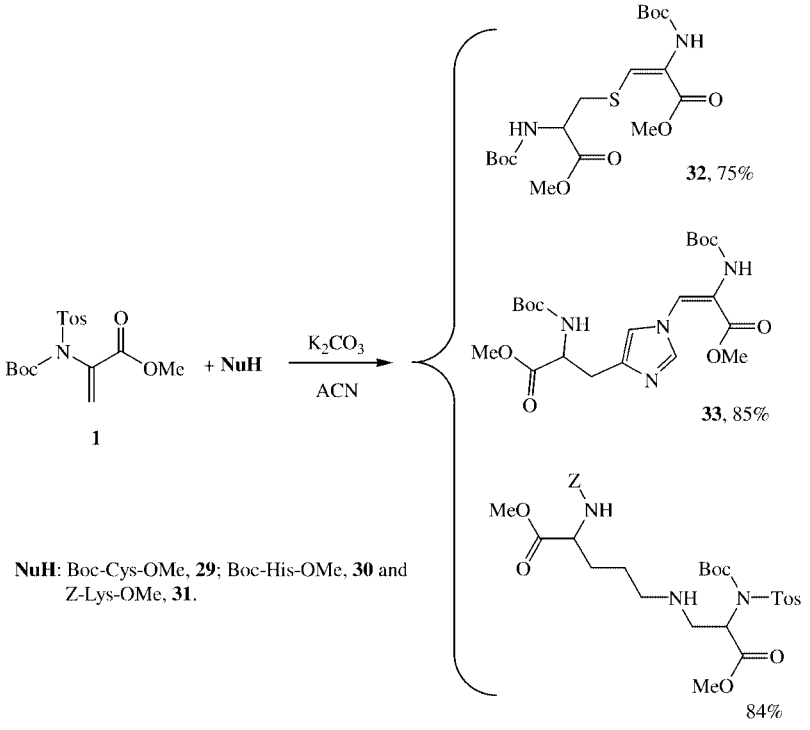
Scheme 5

viously observed with amines, Boc-ΔPhe[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, Tos*N*(Boc)-ΔAla-OMe proved to be an excellent substrate for synthesis of furanic amino acids and, subsequently, tetradehydroproline 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-ΔSer(*p*-tolylsulfinyl)-OMe it was possible to obtain the corresponding α-alkoxy-β-sulfinyl product, while β-alkoxyalanine derivatives were obtained from Boc_2-ΔAla-OMe. Use of Tos(Boc)-ΔAla-OMe gave α,β-dialkoxy compounds, whilst (*E*)-Boc-ΔAla[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 $60F_{254}$) 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 ≈5% $CDCl_3$ solution when not otherwise stated. All shifts are given in δ ppm with δ_H Me_4Si = 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. ^{13}C 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), $C_{17}H_{19}NO_5S$ (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-CH_3 Tos), 2.77 (d, *J* = 3.6 Hz, 1 H, OH), 3.50 (s, 3 H, OCH_3), 4.10 (dd, *J* = 3.9, *J* = 9.9 Hz, 1 H αCH), 5.04 (dd, *J* = 3.6, *J* = 3.9 Hz, 1 H, βCH), 5.43 (d, *J* = 9.9 Hz, 1 H, αNH), 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), $C_{10}H_{12}N_2O_7S$ (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, OCH_3), 3.48−3.61 (m, 2 H, βCH_2), 3.96 (broad s, 1 H, αCH), 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, αNH) 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)-ΔAla-OMe[6] (1), Tos(Boc)-ΔAbu-OMe[2] (5), Boc_2-ΔAla-OMe[12] (21), Tos(Boc)-ΔPhe-OMe[5] (25), Boc_2-ΔAbu-OMe,[2] and Boc_2-ΔPhe-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-ΔAla[β-(1,2,4-triazol-1-yl)]-OMe (6), (*E*)-Boc-ΔAbu[β-(1,2,4-triazol-1-yl)]-OMe [(*E*)-7], (*Z*)-Boc-ΔAbu[β-(1,2,4-triazol-1-yl)]-OMe [(*Z*)-7], (*E*)-Boc-ΔPhe[β-(1,2,4-triazol-1-yl)]-OMe [(*E*)-11] and (*Z*)-Boc-ΔPhe[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-ΔSer(*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 cm^3) and $KHSO_4$ (1 mol·dm^{-3}, 100 cm^3). The organic phase was thoroughly washed with $KHSO_4$ (1 mol·dm^{-3}), $NaHCO_3$ (1 mol·dm^{-3}) and brine (3 × 50 cm^3 each), and dried with $MgSO_4$. Removal of the solvent afforded pure product (1.67 g, 94%), m.p. 102−103.5 °C (from ethyl acetate/*n*-hexane), $C_{16}H_{21}NO_6S$ (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-CH_3), 3.81 (s, 3 H, OCH_3), 5.68 (s, 1 H, βCH), 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, αNH) 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-ΔSer(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), $C_{15}H_{18}N_2O_8S$ (386.37): calcd. C 46.63, H 4.70, N 7.25, S 8.30; found C 46.86, H 4.99, N 7.35, S 8.00%. δ_H = 1.47 (s, 9 H, Boc), 3.95 (s, 3 H, OCH_3), 6.81 (s, 1 H, αNH), 7.16 (s, 1 H, βCH), 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): Cs_2CO_3 (1 equiv.) was added at room temperature with rapid stirring to a solution of Tos(Boc)-ΔAla-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), $C_{19}H_{23}NO_6$ (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, CH_3 Boc), 1.89 (s, 3 H, CH_3), 3.37 (q, *J* = 14.6 Hz, 2 H, CH_2), 3.88 (s, 3 H, OCH_3), 5.88 (s, 1 H, αNH), 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), $C_{17}H_{27}NO_7$ (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 CH_3), 1.45 (s, 9 H, Boc), 1.93−2.01 (m, 1 H, CH), 2.27 (s, 3 H, CH_3), 3.17 (q, *J* = 17.4 Hz, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.90 (d, *J* = 6.9 Hz, 2 H, CH_2), 5.83 (s, 1 H, αNH) 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 cm^3) was added and the solution was washed with $NaHCO_3$ (1 mol·dm^{-3}) and brine (3 × 10 cm^3 each) and dried with $MgSO_4$. Removal of the solvent at reduced pressure afforded **4a** (0.17 g, 92%), m.p. 177.5−179 °C (from diethyl ether/*n*-hexane), $C_9H_{11}NO_3$ (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, CH_3), 2.43 (s, 3 H, CH_3), 3.88 (s, 3 H, OCH_3), 7.21 (d, *J* = 3.0 Hz, 1 H, CH), 9.23 (s, 1 H, αNH) 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), $C_9H_{11}NO_4$ (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, CH_3), 3.82 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 7.24 (d, *J* = 2.7 Hz, 1 H, CH), 9.23 (s, 1 H, αNH) 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), $C_{14}H_{13}NO_3$ (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, CH_3), 3.86 (s, 3 H, OCH_3), 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, αNH) 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-Benzyloxycarbonyl-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, $C_{12}H_{17}NO_4$ (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 CH_3), 1.98−2.17 (m, 1 H, CH), 2.64 (s, 3 H, CH_3), 3.93 (s, 3 H, OCH_3), 4.08 (d, *J* = 6.3 Hz, 2 H, CH_2), 7.26 (d, *J* = 2.7 Hz, 1 H, CH), 9.65 (s, 1 H, αNH) 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-ΔAla(β-benzylamino)-OMe (9a): Benzylamine (2.5 equiv.) was added to solution of (*E*)-Boc-ΔAla[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 cm^3) was added and the organic layer was washed with $KHSO_4$ (1 mol·dm^{-3}) and brine (2 × 30 cm^3 each). Drying with $MgSO_4$ 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), $C_{16}H_{22}N_2O_4$ (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, OCH_3), 4.41 (d, *J* = 6.3 Hz, 2 H, CH_2), 5.68 (s, 1 H, NH), 5.93 (s, 1 H, NH), 7.29−7.41 (m, 6 H, βCH + 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-ΔAla(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), $C_{12}H_{18}N_2O_4$ (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, OCH_3), 3.96 (m, 2 H, CH_2), 5.61 (s, 1 H, NH), 6.05 (s, 1 H, NH), 7.24 (d, *J* = 6.3 Hz, 1 H, βCH) 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-ΔAla{β-[*N*-(2-aminoethyl)amino]}-OMe (9c): 1,2-Ethylenediamine (10 equiv.) was added to a solution of (*E*)-Boc-ΔAla[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 cm^3) and washed with Na_2CO_3 (1 mol·dm^{-3}) (3 × 30 cm^3). The organic phase was dried with $MgSO_4$ 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, CH_2), 3.25 (q, *J* = 5.4 Hz, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 3.46 (broad s, 2 H, NH_2), 5.38 (broad s, 1 H, NH), 5.92 (broad s, 1 H, NH), 7.24 (d, *J* = 13.2 Hz, 1 H, βCH) 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-ΔAbu(β-benzylamino)-OMe (10a): The synthesis of this compound was described in ref.[9]

Synthesis of (*E*)-Boc-ΔAbu(β-propargylamino)-OMe (10b): The same procedure as described for the preparation of **9b** was followed, with substitution of (*E*)-Boc-ΔAbu[β-(1,2,4-triazol-1-yl)]-OMe (1 mmol, 0.28 g) for (*E*)-Boc-ΔAla[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), $C_{13}H_{20}N_2O_4$ (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, γCH_3), 2.28 (t, *J* = 2.4 Hz, 1 H, CH), 3.66 (s, 3 H, OCH_3), 3.98 (2d, *J* = 2.4, *J* = 6.2 Hz, 2 H, CH_2), 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-ΔAbu[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-ΔAbu{β-[*N*-(2-aminoethyl)amino]}-OMe (10c): The same procedure as described for the preparation of **9c** was followed, with substitution of (*E*)-Boc-ΔAbu[β-(1,2,4-triazol-1-yl)]-

OMe (1 mmol, 0.28 g) for (*E*)-Boc-ΔAla[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, γCH_3), 2.87 (t, *J* = 5.7 Hz, 2 H, CH_2), 3.28 (q, *J* = 5.7 Hz, 2 H, CH_2), 3.64 (s, 3 H, OCH_3), 3.90 (d, *J* = 5.7 Hz, 2 H, NH_2), 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-ΔAbu[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-ΔSer(*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 cm^3) was added. The organic phase was then washed with water and brine (2 × 30 cm^3 each) and dried with $MgSO_4$, 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), $C_{19}H_{26}N_2O_6S$ (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-CH_3), 3.09 (s, 1 H, NH), 3.21 (dq, *J* = 2.4, *J* = 16.8 Hz, 2 H, CH_2), 3.89 (d, *J* = 14.7 Hz, 1 H, β-CH_2), 3.90 (s, 3 H, OCH_3), 4.36 (d, *J* = 14.7 Hz, 1 H, CH_2), 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), $C_{17}H_{25}N_3O_5S$ (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-CH_3), 2.90−2.95 (m, 1 H, CH_2), 3.14−3.26 (m, 2 H, CH_2), 3.49 (broad s, 1 H, NH), 3.62−3.71 (m, 1 H, CH_2), 3.95 (d, *J* = 14.4 Hz, 1 H, CH_2), 4.04 (d, *J* = 14.4 Hz, 1 H, CH_2), 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-ΔSer(4-nitrophenylsulfinyl)-OMe (1 mmol, 0.39 g) for (*E*)-Boc-ΔSer(*p*-tolylsulfinyl)-OMe and benzylamine for propargylamine, to afford **14a** (0.45 g, 91%), m.p. 141−143 °C (from diethyl ether), $C_{22}H_{27}N_3O_8S$ (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, CH_2), 3.56 (d, *J* = 12.0 Hz, 1 H, CH_2), 3.88 (s, 3 H, OCH_3), 4.04 (d, *J* = 14.7 Hz, 1 H, CH_2), 4.49 (d, *J* = 14.7 Hz, 1 H, CH_2), 6.08 (s, 1 H, NH), 7.18−7.31 (m, 5 H, ArH Bzl), 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), $C_{18}H_{23}N_3O_8S$ (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, CH_2), 3.96 (s, 3 H, OCH_3), 3.99 (d, *J* = 15.0 Hz, 1 H, CH_2), 4.49 (d, *J* = 15.0 Hz, 1 H, CH_2), 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-ΔSer(4-nitrophenylsulfinyl)-OMe (1 mmol, 0.39 g) for (*E*)-Boc-ΔSer(*p*-tolylsulfinyl)-OMe, to afford **15b** (0.24 g, 59%), m.p. 156−157 °C (from ethyl acetate/*n*-hexane), $C_{16}H_{22}N_4O_7S$ (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 CH_2 + NH), 4.01 (d, *J* = 14.7 Hz, 1 H, CH_2), 4.15 (d, *J* = 14.7 Hz, 1 H, CH_2), 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-ΔAla(β-methoxycarbonylmethylsulfanyl)-OMe (19): The same procedure as described above for the synthesis of **13b** was followed, with substitution of methylsulfanyl acetate (1 equiv.) for propargylamine and addition of triethylamine (2.5 equiv.), to give **19**[5] (0.16 g, 54%).

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

Synthesis of (*E*)-Boc-ΔAla[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 methylsulfanyl 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-ΔSer(*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 cm^3) was added. The organic phase was then washed with water and brine (2 × 30 cm^3 each) and dried with $MgSO_4$, 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), $C_{17}H_{25}NO_7S$ (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-CH_3), 3.11 (s, 3 H, CH_3), 3.83 (d, *J* = 14.7 Hz, 1 H, βCH_2), 3.92 (s, 3 H, OCH_3), 4.68 (d, *J* = 14.7 Hz, 1 H, βCH_2), 6.27 (s, 1 H, αNH), 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), $C_{19}H_{29}NO_7S$ (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, CH_3 OEt), 1.29 (s, 9 H, Boc), 1.39 (t, *J* = 7.2 Hz, 3 H, CH_3 OEt), 2.43 (s, 3 H, Ar-CH_3),

3.21−3.46 (m, 2 H, CH_2 OEt), 3.85 (d, J = 14.7 Hz, 1 H, βCH_2), 4.36 (q, J = 7.2 Hz, 2 H, CH_2 OEt), 4.64 (d, J = 14.7 Hz, 1 H, βCH_2), 6.30 (broad s, 1 H, αNH), 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 Boc_2-Ala(β-methoxy)-OMe (23a): The same procedure as described above for the synthesis of **22a** was followed, with substitution of Boc_2-ΔAla-OMe (1 mmol, 0.30 g) for (*E*)-Boc-ΔSer(*p*-tolylsulfinyl)-OMe, to give **23a** (0.27 g, 80%), oil, $C_{15}H_{27}NO_7$ (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, βOCH_3), 3.74 (s, 3 H, $COOCH_3$), 3.83 (dd, J = 8.4, J = 10.7 Hz, 1 H, βCH_2), 3.99 (dd, J = 5.1, J = 10.7 Hz, 1 H, βCH_2), 5.19 (dd, J = 5.1, J = 8.4 Hz, 1 H, αCH_2) ppm; δ_C = 27.9, 52.2, 57.4, 58.9, 71.1, 83.2, 152.0, 169.6 ppm.

Synthesis of Boc_2-Ala(β-ethoxy)-OEt (23b): The same procedure as described above for the synthesis of **22b** was followed, with substitution of Boc_2-ΔAla-OMe (1 mmol, 0.30 g) for (*E*)-Boc-ΔSer(*p*-tolylsulfinyl)-OMe, to give **23b** (0.14 g, 38%), m.p. 36.5−38 °C, $C_{17}H_{31}NO_7$ (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, CH_3 OEt), 1.27 (t, J = 7.2 Hz, 3 H, CH_3 OEt), 1.51 (s, 18 H, Boc), 3.43−3.59 (m, 2 H, CH_2 OEt), 3.88 (dd, J = 8.4, J = 10.7 Hz, 1 H, βCH_2), 4.03 (dd, J = 4.8, J = 10.7 Hz, 1 H, βCH_2), 4.19 (q, J = 7.2 Hz, 2 H, CH_2 OEt), 5.16 (dd, J = 4.8, J = 8.4 Hz, 1 H, αCH) 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)-ΔAla-OMe (1 mmol, 0.36 g) for (*E*)-Boc-ΔSer(*p*-tolylsulfinyl)-OMe and use of 4 equiv. of NaOEt, to give **24b** (0.18 g, 60%), m.p. 29−30.5 °C, $C_{14}H_{27}NO_6$ (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, CH_3 OEt), 1.20 (t, J = 7.2 Hz, 3 H, CH_3 OEt), 1.31 (t, J = 7.2 Hz, 3 H, CH_3 OEt), 1.45 (s, 9 H, Boc), 3.35−3.63 (m, 4 H, 2 CH_2 OEt), 3.72 (d, J = 9.3 Hz, 1 H, βCH_2), 4.17 (d, J = 9.3 Hz, 1 H, βCH_2), 4.23−4.34 (m, 2 H, CH_2 OEt), 6.04 (broad s, 1 H, αNH) 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)-ΔPhe-OMe (1 mmol, 0.43 g) for (*E*)-Boc-ΔSer(*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), $C_{17}H_{25}NO_6$ (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, αOCH_3 or βOCH_3), 3.36 (s, 3 H, αOCH_3 or βOCH_3), 3.77 (s, 3 H, $COOCH_3$), 4.61 (s, 1 H, βCH), 5.05 (broad s, 1 H, αNH), 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-ΔAla[β-(1,2,4-triazol-1-yl)]-OMe (1 mmol, 0.27 g) for (*E*)-Boc-ΔSer(*p*-tolylsulfinyl)-OMe and use of 3 equiv. of NaOMe, to give **27a** (0.23 g, 88%), oil; $C_{11}H_{21}NO_6$ (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, OCH_3), 3.43 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 4.49−4.57 (m, 2 H, αCH + βCH), 5.24 (d, J = 8.4 Hz, 1 H, αNH) 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-ΔAla(1,2,4-triazol-1-yl)-OMe (1 mmol, 0.27 g) for (*E*)-Boc-ΔSer(*p*-tolylsulfinyl)-OMe, to give **27b** (0.08 g, 27%), oil, $C_{14}H_{27}NO_6$ (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, CH_3 OEt), 1.23 (t, J = 7.2 Hz, 3 H, CH_3 OEt), 1.28 (t, J = 7.2 Hz, 3 H, CH_3 OEt), 1.45 (s, 9 H, Boc), 3.47−3.80 (m, 4 H, 2 CH_2 OEt), 4.16−4.28 (m, 2 H, CH_2 OEt), 4.51 (dd, J = 3.3, J = 9.0 Hz, 1 H, αCH), 4.75 (d, J = 3.3 Hz, 1 H, βCH), 5.26 (d, J = 9.0 Hz, 1 H, αNH) 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-ΔAbu(β-methoxy)-OMe (28): The same procedure as described above for the synthesis of **22a** was followed, with substitution of (*E*)-Boc-ΔAbu[β-(1,2,4-triazol-1-yl)]-OMe (1 mmol, 0.28 g) for (*E*)-Boc-ΔSer(*p*-tolylsulfinyl)-OMe, to give **28** (0.08 g, 33%), m.p. 126−127 °C (from diethyl ether/*n*-hexane), $C_{11}H_{19}NO_5$ (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, γCH_3), 3.74 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 5.64 (s, 1 H, αNH) 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): K_2CO_3 (6 equiv.) was added to a solution of Tos(Boc)-ΔAla-OMe (1 mmol, 0.36 g) in acetonitrile (0.2 $mol \cdot dm^{-3}$), 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, βCH_2 Cys), 3.77 (s, 6 H, $2OCH_3$), 4.62 (m, 1 H, αCH Cys), 5.44 (d, J = 7.2 Hz, 1 H, αNH Cys), 6.07 (broad s, 1 H, αNH ΔAla), 7.17 (s, 1 H, βCH ΔAla) 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, $C_{21}H_{32}N_4O_8$ (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, βCH_2 His), 3.71 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.55−4.58 (m, 1 H, αCH), 5.73 (d, J = 8.1 Hz, 1 H, αNH His), 6.04 (s, 1 H, αNH ΔAla), 7.15 (s, 1 H, βCH ΔAla), 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*)-lysin-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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