DOI: 10.1002/ejoc.201100907

Synthesis of New *N*-Ethyl Dehydroamino Acid Derivatives: *N*-Ethyl β,β-Dibromo, *N*-Ethyl β-Bromo β-Substituted, and *N*-Ethyl β,β-Disubstituted *N*-Protected Dehydroamino Acid Methyl Esters

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Keywords: Amino acids / Nonnatural amino acids / Alkylation / Cross-coupling / Protecting groups

Recently, we reported the use of a sequence of alkylation and dehydration methodologies to obtain new non-proteinogenic amino acids (*N*-ethyl α,β-dehydroamino acids) from the methyl esters of *N*-(4-nitrophenylsulfonyl) β-hydroxy amino acids. Thus, it was possible to obtain for the first time, non-natural amino acids that incorporate both *N*-ethyl and α,β-dehydro moieties. Herein, we report the application of this *N*-alkylation procedure to several methyl esters of β,β-dibromo and β-bromo β-substituted dehydroamino acids protected with standard amine protecting groups such as *tert*-butyloxycarbonyl, benzyloxycarbonyl, and (4-nitrobenzyl)-oxycarbonyl, as well as acyl and sulfonyl groups. The procedure allows the synthesis of the methyl esters of *N*-protected *N*-ethyl β,β-dibromo and *N*-ethyl β-bromo β-substituted dehydroamino acids in fair to high yields. Some of these *N*-ethylated dehydroamino acid derivatives were used as substrates in cross-coupling reactions to give β,β-disubstituted *N*-ethyldehydroalanine derivatives.

Introduction

Non-proteinogenic amino acids are an important class of organic compounds that can have intrinsic biological activity or can be found in peptides with antiviral, antitumor, anti-inflammatory, or immunosuppressive activities. Among the non-proteinogenic amino acids are *N*-alkyl amino acids and dehydroamino acids, both of which can be found in many biologically important peptides.[1]

N-Alkyl amino acids are constituents of various important naturally occurring peptides and proteins.[1] They have been isolated from plant strains, microorganisms, and marine species. *N*-Alkylation of the peptide bond causes changes in volume and conformation of peptides, resulting in reduced flexibility, increase of permeability for the membrane (increased lipophilicity), and prevention of cleavage by proteolytic enzymes.[2] Several *N*-alkylated peptides show antibiotic, anticancer, or antiviral activity.[3] The incorporation of *N*-alkyl amino acids in peptides has been used in medicinal chemistry to change conformation and restrict flexibility, thus increasing receptor selectivity, and also improving oral activity and duration of action.[4]

Many methods for the synthesis of *N*-alkyl amino acids have been developed, mostly involving *N*-methylation reactions.[2] Many of these approaches require treatment of the amino acids with strong bases to form anionic nucleophiles that are then reacted with alkyl halides, which can result in racemization. Fewer methods for the synthesis of *N*-ethylated amino acids and their derivatives are available in the literature.[5] Chen and Benoiton prepared *N*-ethyl amino acids by reaction of *N*-acetyl amino acids with trimethyloxonium tetrafluoroborate (Meerwein's reagent) in a two-step procedure.[6] Initially, an imino ether fluoroborate is formed and then reduced by treatment with sodium borohydride. McDermott and Benoiton were able to carry out complete *N*-methylations of *N*-(benzyloxycarbonyl)amino acids using methyl iodide and sodium hydride[7] but *N*-ethylations with ethyl iodide were far from complete.[6] More recently, Stodulski and Mlynarski tried the same strategy to obtain *N*-benzyloxycarbonyl-*N*-ethylalanine by substituting lithium bis(trimethylsilyl)amide or cesium carbonate for sodium hydride, but were also unsuccessful.[8] However, by carrying out the original protocol (ethyl iodide and NaH in tetrahydrofuran) at elevated temperatures they were able to obtain *N*-benzyloxycarbonyl *N*-ethyl amino acids in moderate to high yields. Papaioannou and co-workers described a Mitsunobu-type *N*-ethylation of tosylamino esters with excess ethanol.[9] Difficulties found in the chemical detosylation step could be overcome by reductive electrochemical cleavage of the protecting group.[10] The stronger electron-withdrawing effect of nitroarylsulfonamides further enhances the acidity of the α-amide hydrogen, making these groups unique for the preparation of *N*-alkyl peptides.[11] Recently, Liguori et al. proposed the ethylation of several 4-nitrophenylsulfonyl (Nosyl) protected amino acids using triethyloxonium tetrafluoroborate (Et_3OBF_4) as alkylating agent and *N*,*N*-diisopropylethylamine (DIPEA) as base to give *N*-ethyl amino acid derivatives in high yields.[12] These authors demonstrated the compatibility of the procedure with standard Fmoc chemistry.[12]

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Dehydroamino acids have been found in naturally occurring peptides of fungal and microbial origin[13] and from marine organisms,[14] in which they play a catalytic role in the active sites of some enzymes. They are also found in a variety of peptide antibiotics of bacterial origin that include the lantibiotics (nisin, epidermin, subtilin, gallidermin).[15] Because they affect both chemical reactivity and conformation, dehydroamino acids have been introduced into peptides for structure–function relationship studies, and can also be used as precursors to obtain new non-proteinogenic amino acids.[16] In our laboratories, an efficient method for the synthesis of *N*,*N*-diacyl α,β-dehydroamino acid derivatives from *N*-acyl β-hydroxy amino acid derivatives was developed by treatment with two equivalents of *tert*-butyl pyrocarbonate and 4-(dimethylamino)pyridine as catalyst in anhydrous acetonitrile.[17] To allow the synthesis of *N*-acyl α,β-dehydroamino acid derivatives, a modification of this method was subsequently reported.[18]

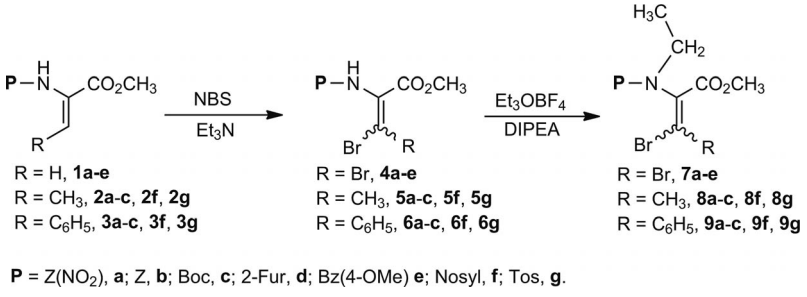
Recently, we reported the use of a combination of the alkylation procedure reported by Liguori et al.[12] and our dehydration methodologies[17,18] to obtain new non-proteinogenic amino acids, namely, *N*-(4-nitrophenylsulfonyl) *N*-ethyl α,β-dehydroamino acids.[19] Thus, it was possible to obtain for the first time, new non-natural amino acids that incorporate both the *N*-ethyl and the α,β-dehydro moieties. Herein, we report the application of this *N*-alkylation procedure to several methyl esters of β,β-dibromo and β-bromo β-substituted dehydroamino acids protected with standard amine protecting groups such as *tert*-butyloxycarbonyl (Boc), benzyloxycarbonyl (Z), and (4-nitrobenzyl)oxycarbonyl [Z(NO_2)], as well as acyl and sulfonylamine protecting groups. The procedure allows the synthesis of *N*-protected, *N*-ethyl β,β-dibromo and *N*-ethyl β-bromo β-substituted dehydroamino acid methyl esters. Some of these *N*-ethylated dehydroamino acid derivatives are used as substrates in cross-coupling reactions to give the methyl esters of *N*-protected, β,β-disubstituted *N*-ethyldehydroalanines. Thus, this methodology opens the possibility of obtaining a large range of new β,β-disubstituted *N*-ethyldehydroalanines.

Results and Discussion

To expand the scope of the procedure for *N*-ethylation of dehydroamino acid derivatives previously reported,[19] attempts at alkylating dehydroamino acids with amine protecting groups other than the 4-nitrophenylsulfonyl group were carried out. Thus, the methyl esters of *N*-(*tert*-butyloxycarbonyl)dehydroalanine (Boc-ΔAla-OMe) and of *N*-(4-nitrobenzyloxycarbonyl)dehydroalanine [Z(NO_2)-ΔAla-OMe] were subjected to *N*-ethylation with triethyloxonium tetrafluoroborate. However, after several hours of reaction and addition of a large excess of alkylating agent, no *N*-ethylated dehydroalanine derivative could be detected. The ^{1}H NMR chemical shift of the NH proton of Boc-ΔAla-OMe and Z(NO_2)-ΔAla-OMe in dimethyl sulfoxide (DMSO) solutions were determined (δ_{NH} = 8.35 and 9.13 ppm, respectively) and compared with a dehydroamino acid derivative in which alkylation under the same conditions was complete, such as the methyl ester of *N*-(4-nitrophenylsulfonyl)dehydroaminobutyric acid (Nosyl-ΔAbu-OMe, δ_{NH} = 9.66 ppm). Thus, the strong electron-withdrawing effect of the nitroarylsulfonamide group was confirmed to be essential for *N*-ethylation even of the more conjugated dehydroalanine derivatives.

In the case of *N*-alkylation of dehydroamino acids, an alternative to the electron-withdrawing effect of the amine protecting group could be the presence of electron-withdrawing substituents on the β-carbon atom. In our laboratories, we have been synthesizing β-halogenated dehydroamino acid derivatives and using them as substrates in Suzuki–Miyaura cross-coupling reactions with aryl and heteroarylboronic acids to obtain new dehydroamino acid derivatives.[20] Thus, we decided to study how the presence of bromine substituents on the β-C atom of dehydroalanine derivatives affects *N*-ethylation.

The methyl esters of dehydroalanine that are *N*-protected with the (4-nitrobenzyl)oxycarbonyl, benzyloxycarbonyl, *tert*-butyloxycarbonyl, 2-furanoyl (2-Fur), or 4-methoxybenzoyl [Bz(4-OMe)] groups (compounds **1a**–**e**, Scheme 1) were prepared from the corresponding *N*-protected serine methyl ester, according to the dehydration procedure previously developed by us.[18] The *N*-protected dehydroalanine derivatives were treated with 2.2 equiv. of *N*-bromosuccinimide (NBS) followed by treatment with triethylamine to give the corresponding *N*-protected β,β-dibromodehydroalanine derivatives (**4a**–**e**; Scheme 1).[18] These compounds were subjected to *N*-ethylation using the previously established conditions[12] [2.5 equiv. of triethyloxonium tetrafluoroborate, 3.5 equiv. of *N*,*N*-diisopropyl-



Scheme 1. Synthesis of the methyl esters of *N*-acyl-*N*-ethyl-β,β-dibromodehydroalanines and of *N*-acyl *N*-ethyl β-bromo β-substituted dehydroamino acids.

Table 1. Results obtained in the *N*-ethylation of the methyl esters of *N*-acyl-β,β-dibromodehydroalanines and of *N*-acyl β-bromo β-substituted dehydroamino acids.

Reactant		^{1}H NMR δ_{NH} [ppm][a]	Product		Ratio prod./reac.[b]	Yield [%]
Z(NO_2)-ΔAla(β,β-Br)-OMe	**4a**	9.85	Z(NO_2)-*N*(Et)-ΔAla(β,β-Br)-OMe	**7a**	100:0	85
Z-ΔAla(β,β-Br)-OMe	**4b**	9.69	Z-*N*(Et)-ΔAla(β,β-Br)-OMe	**7b**	100:0	82
Boc-ΔAla(β,β-Br)-OMe	**4c**	9.20	Boc-*N*(Et)-ΔAla(β,β-Br)-OMe	**7c**	48:52	44
2-Fur-ΔAla-(β,β-Br)-OMe	**4d**	10.16	2-Fur-*N*(Et)-ΔAla(β,β-Br)-OMe	**7d**	82:18	80
Bz(4-OMe)-ΔAla(β,β-Br)-OMe	**4e**	10.07	Bz(4-OMe)-*N*(Et)-ΔAla(β,β-Br)-OMe	**7e**	64:36	47
Z(NO_2)-*E*-ΔAbu(β-Br)-OMe	*E*-**5a**	9.58	Z(NO_2)-*N*(Et)-*E*-ΔAbu(β-Br)-OMe	*E*-**8a**	80:20	75
Z(NO_2)-*Z*-ΔAbu(β-Br)-OMe	*Z*-**5a**	9.42	Z(NO_2)-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe	*Z*-**8a**	37:63	33
Z-(*Z*)-ΔAbu(β-Br)-OMe	*Z*-**5b**	9.26	Z-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe	*Z*-**8b**	43:57	40
Boc-*Z*-ΔAbu(β-Br)-OMe	*Z*-**5c**	9.01	Boc-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe	*Z*-**8c**	0:100	–
Nosyl-*Z*-ΔAbu(β-Br)-OMe	*Z*-**5f**	10.24	Nosyl-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe	*Z*-**8f**	100:0	93
Tos-*Z*-ΔAbu(β-Br)-OMe	*Z*-**5g**	9.69	Tos-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe	*Z*-**8g**	100:0	78
Z(NO_2)-*Z*-ΔPhe(β-Br)-OMe	*Z*-**6a**	9.82	Z(NO_2)-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe	*Z*-**9a**	45:55	30
Z-(*Z*)-ΔPhe(β-Br)-OMe	*Z*-**6b**	9.65	Z-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe	*Z*-**9b**	38:62	36
Boc-*Z*-ΔPhe(β-Br)-OMe	*Z*-**6c**	9.15	Boc-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe	*Z*-**9c**	15:85	–
Nosyl-*Z*-ΔPhe(β-Br)-OMe	*Z*-**6f**	10.66	Nosyl-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe	*Z*-**9f**	100:0	90
Tos-*Z*-ΔPhe(β-Br)-OMe	*Z*-**6g**	10.08	Tos-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe	*Z*-**9g**	100:0	89

[a] ^{1}H NMR shift of the amide hydrogen measured in DMSO. [b] Ratio of product to reactant determined by ^{1}H NMR spectroscopic analysis.

ethylamine (DIPEA) in anhydrous dichloromethane] to give the corresponding *N*-protected *N*-ethyl-β,β-dibromodehydroalanine derivative (**7a**–**e**; Scheme 1, Table 1).

The reactions were complete with the urethane protecting groups Z(NO_2) and Z, giving the corresponding *N*-acyl- and *N*-ethyl-β,β-dibromodehydroalanine derivatives in 85 and 82% yields, respectively (compounds **7a** and **7b**). With Boc as protecting group, the reaction could not be taken to completion, giving an approximately 1:1 mixture of product and starting material. The product **7c** could be isolated by column chromatography. Thus, the β,β-dibromodehydroalanine derivatives protected with the more electron-withdrawing groups Z(NO_2) and Z, gave complete reactions with good yields of the *N*-ethylated product, whereas the reaction could not be taken to completion with the dehydroalanine derivative containing the less electron-withdrawing Boc group. The ^{1}H NMR shifts of the NH proton of compounds **4a**–**c** in DMSO solutions were measured (Table 1). Compounds **4a** and **4b** showed higher chemical shifts than compound **4c**. Thus, a correlation could be observed between the chemical shift of the nitrogen protons and reaction yields.

With the acyl-protected derivatives **4d** and **4e**, the *N*-ethylation reactions were also incomplete, but the desired products **7d** and **7e** could be isolated after column chromatography. For the reaction with **4d**, a ratio of approximately 8:2 of product to reactant was obtained, whereas for **4e** this ratio was approximately 6:4. These ratios could be correlated with the ^{1}H NMR chemical shift of the nitrogen protons (δ_{NH} = 10.16 and 10.07 ppm for **4d** and **4e**, respectively).

The results obtained in the *N*-alkylation of β,β-dibromodehydroalanine derivatives led us to attempt to expand the scope of this methodology to other dehydroamino acid derivatives, namely β-bromo β-substituted dehydroamino acids. Because β,β-dibromodehydroalanine derivatives that were *N*-protected with urethane-type protecting groups gave the best results in *N*-alkylation, threonine and phenylserine methyl esters protected with Z(NO_2), Z, and Boc, and also with the strong electron-withdrawing sufonyl derivatives Nosyl and 4-toluenesulfonyl (Tos) were prepared. With the exception of the Nosyl derivatives, these compounds were subject to dehydration with 1 equiv. of *tert*-butyl pyrocarbonate,[18] to give the corresponding *N*-protected derivatives of dehydroaminobutyric acid and of dehydrophenylalanine (**2a**–**c**, **2g**, **3a**–**c**, and **3g**; Scheme 1). For the Nosyl derivatives, dehydration had to be carried out using 2 equiv. of *tert*-butyl pyrocarbonate to give the corresponding *N*-Boc and *N*-Nosyl dehydroamino acid derivatives, followed by treatment with a 4% solution of trifluoroacetic acid in dichloromethane to give compounds **2f** and **3f**.[19] The dehydroamino acid derivatives were treated with 1.2 equiv. NBS followed by triethylamine to give *N*-protected β-bromodehydroaminobutyric acid and dehydrophenylalanine derivatives (**5a**–**c**, **5f**, **5g**, **6a**–**c**, **6f**, and **6g**; Scheme 1). The β-bromo β-substituted dehydroamino acid derivatives were subject to *N*-ethylation under identical conditions to those described previously for the β,β-dibromodehydroalanine derivatives.

N-Ethylation of dehydroaminobutyric acid derivatives protected with Z(NO_2) and Z (*E*-**5a**, *Z*-**5a**, and *Z*-**5b**) could not be taken to completion, in contrast to the reaction with β,β-dibromodehydroalanine derivatives protected with the same groups (**4a** and **4b**). However, the *N*-ethylated product could be isolated after column chromatography. The ^{1}H NMR chemical shifts of the NH proton of compounds *E*-**5a**, *Z*-**5a**, and *Z*-**5b** in DMSO solutions were measured (Table 1). It was observed that the substitution of a β-methyl group of the dehydroamino acids for a bromine atom reduces the ^{1}H NMR chemical shift. Comparison of the chemical shift of the NH proton of both diastereomers of compounds **5a** shows that the *E* isomer exhibits a higher chemical shift than the *Z* isomer. For compound *E*-**5a**, a ratio of 8:2 product to reactant was obtained, whereas for *Z*-**5a** a ratio was of approximately 4:6 was found. For the Boc-protected dehydroaminobutyric acid derivative *Z*-**5c**,

Table 2. Results obtained in the Suzuki cross-coupling reactions of *N*-ethyl β,β-dibromo and *N*-ethyl β-bromo β-substituted dehydroamino acid derivatives with phenylboronic acid.

Reactant		Product		Yield [%]
Z(NO_2)-*N*(Et)-ΔAla(β,β-Br)-OMe	**7a**	Z(NO_2)-*N*(Et)-ΔPhe(β-C_6H_5)-OMe	**10a**	81
Z-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe	***Z*-8b**	Z-*N*(Et)-*Z*-ΔAbu(β-C_6H_5)-OMe	***Z*-10b**	50
Z(NO_2)-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe	***Z*-9a**	Z(NO_2)-*N*(Et)-ΔPhe(β-C_6H_5)-OMe	**10a**	63
Nosyl-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe	***Z*-9f**	Nosyl-*N*(Et)-ΔPhe(β-C_6H_5)-OMe	**10f**	95

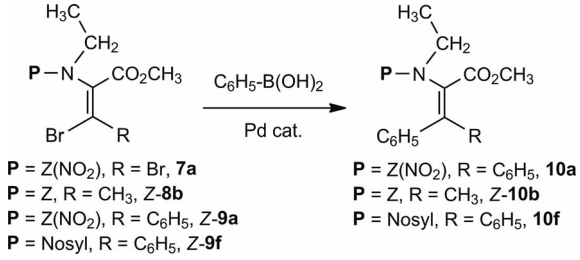
no *N*-ethylation was observed. The ^{1}H NMR chemical shift of the NH proton was again significantly lower than for the Z(NO_2) and Z-protected dehydroaminobutyric acid derivatives, and was also lower than for the *N*-Boc-β,β-dibromodehydroalanine derivative.

Both *N*-sulfonamide derivatives of dehydroaminobutyric acid ***Z*-5f** and ***Z*-5g** gave rise to higher ^{1}H NMR chemical shifts for their respective NH proton, and the *N*-ethylation reactions were complete, giving the *N*-ethylated products ***Z*-8f** and ***Z*-8g** in yields of 93 and 78%, respectively.

N-Ethylation of dehydrophenylalanine derivatives protected with Z(NO_2) and Z (compounds ***Z*-6a** and ***Z*-6b**) could not be taken to completion. Again, the *N*-ethylated product could be isolated after column chromatography. The ratio of *N*-ethylated dehydrophenylalanine derivative to starting material was comparable to those obtained from the corresponding β-bromodehydroaminobutyric acid derivatives. However, the ^{1}H NMR chemical shifts for the NH proton of compounds ***Z*-6a** and ***Z*-6b** were higher than those of the corresponding dehydroaminobutyric acid derivatives, as would be expected from the electron-withdrawing effect of the β-phenyl ring compared to the electron-donating effect of the β-methyl group. Thus, it is possible that the more extended conjugation of the dehydrophenylalanine derivatives counteracts the higher acidity of the NH proton in this ethylation reaction. For the *N*-Boc derivative ***Z*-6a**, a 15:85 ratio of product to reactant was obtained, however the product could not be isolated by chromatography.

N-Ethylation of the *N*-sulfonamide derivatives of dehydrophenylalanine (***Z*-6f** and ***Z*-6g**) were complete, giving ***Z*-9f** and ***Z*-9g** in yields of 90 and 89%, respectively.

To demonstrate the applicability of these *N*-ethyl β,β-dibromo and *N*-ethyl β-bromo β-substituted dehydroamino acid derivatives as substrates for the synthesis of new *N*-ethylated dehydroamino acids, compounds **7a**, ***Z*-8b**, ***Z*-9a**, and ***Z*-9f** were reacted with phenylboronic acid under Suzuki–Miyaura cross-couplings conditions (Scheme 2).



P = Z(NO_2), R = Br, **7a**
P = Z, R = CH_3, ***Z*-8b**
P = Z(NO_2), R = C_6H_5, ***Z*-9a**
P = Nosyl, R = C_6H_5, ***Z*-9f**

P = Z(NO_2), R = C_6H_5, **10a**
P = Z, R = CH_3, ***Z*-10b**
P = Nosyl, R = C_6H_5, **10f**

Scheme 2. Suzuki cross-coupling reactions of *N*-ethyl β,β-dibromo and *N*-ethyl β-bromo β-substituted dehydroamino acid derivatives with phenylboronic acid.

The corresponding *N*-ethyl β-phenyl β-substituted dehydroamino acid derivatives were obtained in moderate to high yields (**10a**, ***Z*-10b**, and **10f**; Scheme 2, Table 2).

Conclusions

The triethyloxonium tetrafluoroborate/*N*,*N*-diisopropylethylamine alkylation procedure was applied in the *N*-ethylation of several derivatives of β,β-dibromodehydroalanine, β-bromodehydroaminobutyric acid, and β-bromodehydrophenylalanine, *N*-protected with urethane, acyl, and sufonyl groups. Depending on the nature of the halogenated dehydroamino acid and of the protecting group, variable ratios of product to reactant were obtained. These varied from total conversion into product [β,β-dibromodehydroalanine derivatives protected with Z(NO_2) and Z, β-bromodehydroaminobutyric acid and dehydrophenylalanine derivatives protected with Nosyl and Tos] to complete absence of reaction (β-bromodehydroaminobutyric acid protected with Boc). A correlation between the ^{1}H NMR chemical shift of the NH proton and the extent of the *N*-ethylation reaction can be established within the same type of dehydroamino acid with protecting groups also of the same type. With the exception of the *N*-ethyl-β-bromodehydroaminobutyric acid and dehydrophenylalanine derivatives protected with the Boc group, all other *N*-ethyl β-bromo dehydroamino acid derivatives could be obtained in yields ranging from 30 to 93%. Some of these new non-proteinogenic amino acids were used successfully as substrates in Suzuki–Miyaura cross-coupling reactions. Thus, in addition to their intrinsic potential interest, these compounds also constitute important substrates for the synthesis of new β,β-disubstituted *N*-ethyldehydroalanine derivatives.

Experimental Section

General: Melting points were determined with a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Unity Plus spectrometer operating at 300 and 75.4 MHz, respectively, or with a Bruker Avance II$^+$ operating at 400 and 100.6 MHz, respectively. ^{1}H–^{1}H spin–spin decoupling, DEPT (θ 45°), HMQC, and HMBC were used to attribute some signals. Chemical shifts are given in ppm and coupling constants (*J*) in Hz. HRMS data were obtained by the mass spectrometry service of the University of Vigo, Spain. Elemental analysis was

performed with a LECO CHNS 932 elemental analyzer. The reactions were monitored by thin layer chromatography (TLC). Column chromatography was performed with Macherey–Nagel silica gel 230–400 mesh. Petroleum ether refers to fractions with the boiling range 40–60 °C. When solvent gradients were used, the increase of polarity was made from neat petroleum ether to mixtures of diethyl ether/petroleum ether, increasing 10% of diethyl ether each time until isolation of the product was complete. Solvents were used without purification except for acetonitrile and dichloromethane, which were dried according to standard procedures.

Methyl Esters of *N*-Protected β-Hydroxy Amino Acids: Z(NO$_2$)-L-Ser-OMe,[17] Z-L-Ser-OMe,[17] Boc-L-Ser-OMe,[17] 2-Fur-L-Ser-OMe,[21] Bz(4-OMe)-L-Ser-OMe,[21] Z(NO$_2$)-L-Thr-OMe,[17] Z-L-Thr-OMe,[17] Boc-L-Thr-OMe,[17] Nosyl-L-Thr-OMe,[19] Tos-L-Thr-OMe,[17] Z(NO$_2$)-D,L-Phe(β-OH)-OMe,[17] Boc-D,L-Phe(β-OH)-OMe,[22] Nosyl-D,L-Phe(β-OH)-OMe,[19] Tos-D,L-Phe(β-OH)-OMe;[18] the synthesis of these compounds has been described previously.

Z-D,L-Phe(β-OH)-OMe: HCl,H-D,L-Phe(β-OH)-OMe (1.158 g, 5.000 mmol) was dissolved in dichloromethane (0.2 mol dm^{-3}) and triethylamine (2.2 equiv.) was added. Benzyl chloroformate (1.1 equiv.) was slowly added with vigorous stirring and cooling in an ice bath. After stirring at 0 °C for 30 min, the solution was stirred at room temperature for 3 h. The reaction mixture was then evaporated and partitioned between of ethyl acetate (200 mL) and KHSO$_4$ (1 mol dm^{-3}, 100 mL) and washed with KHSO$_4$ (1 mol dm^{-3}, 3 × 50 mL), NaHCO$_3$ (1 mol dm^{-3}, 3 × 50 mL), and brine (3 × 50 mL). After drying over MgSO$_4$, the extract was taken to dryness at reduced pressure to afford Z-D,L-Phe(β-OH)-OMe (1.548 g, 94%) as a white solid; m.p. 87.0–88.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.60 (br. s, 1 H, OH), 3.76 (s, 3 H, CH$_3$ OMe), 4.61–4.63 (m, 1 H, αCH), 5.00 (s, 2 H, CH$_2$ Z), 5.28 (d, *J* = 2.0 Hz, 1 H, βCH), 5.66 (br. d, *J* = 8.8 Hz, 1 H, NH), 7.31–7.35 (m, 10 H, ArH) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$): δ = 52.63 (OCH$_3$), 59.80 (αCH), 66.97 (CH$_2$ Z), 73.57 (βCH), 125.85 (CH), 127.88 (CH), 128.05 (CH), 128.11 (CH), 128.41 (2CH), 136.13 (C), 139.52 (C), 156.24 (C=O), 171.11 (C=O) ppm. C$_{18}$H$_{19}$NO$_5$ (329.35): calcd. C 65.64, H 5.81, N 4.25; found C 65.49, H 5.89, N 4.41.

Methyl Esters of *N*-(*tert*-Butoxycarbonyl) *N*-(4-Nitrophenylsulfonyl) α,β-Dehydroamino Acids: The synthesis of Nosyl-*Z*-ΔAbu(*N*-Boc)-OMe[19] and Nosyl-*Z*-ΔPhe(*N*-Boc)-OMe[19] have been described previously.

Methyl Esters of *N*-Protected Dehydroamino Acids: Z(NO$_2$)-ΔAla-OMe (**1a**),[18] Z-ΔAla-OMe (**1b**),[18] Boc-ΔAla-OMe (**1c**),[17] 2-Fur-ΔAla-OMe (**1d**),[21] Bz(4-OMe)-ΔAla-OMe (**1e**),[21] Z(NO$_2$)-*Z*-ΔAbu-OMe (**2a**),[17] *Z*-*Z*-ΔAbu-OMe (**2b**),[17] Boc-*Z*-ΔAbu-OMe (**2c**),[17] Nosyl-*Z*-ΔAbu-OMe (**2f**),[19] Tos-*Z*-ΔAbu-OMe (**2g**),[18] Boc-*Z*-ΔPhe-OMe (**3c**),[22] Nosyl-*Z*-ΔPhe-OMe (**3f**),[19] Tos-*Z*-ΔPhe-OMe (**3g**);[18] the synthesis of these compounds has been described previously.

General Procedure: The methyl ester of the *N*-protected β-hydroxy amino acid was dissolved in anhydrous acetonitrile (0.5 mol dm^{-3}), and DMAP (0.1 equiv.) was added followed by *tert*-butyl pyrocarbonate (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, *N*,*N*,*N*′,*N*′-tetramethylguanidine (2% by volume) was added, and stirring was continued for an additional 6 h. Evaporation under reduced pressure gave a residue that was partitioned between diethyl ether (100 mL) and KHSO$_4$ (1 mol dm^{-3}, 30 mL). The organic phase was thoroughly washed with KHSO$_4$ (1 mol dm^{-3}, 3 × 30 mL), NaHCO$_3$ (1 mol dm^{-3}, 3 × 30 mL), and brine (3 × 30 mL), and dried with MgSO$_4$. Removal of the solvent afforded the corresponding methyl ester of the *N*-protected α,β-dehydroamino acid.

Z(NO$_2$)-*Z*-ΔPhe-OMe (3a): The general procedure described above was followed using Z(NO$_2$)-D,L-Phe(β-OH)-OMe (1.608 g, 4.300 mmol) as reactant to afford **3a** (1.166 g, 76%) as an orange oil; m.p. 108.0–109.0 °C (ethyl acetate/petroleum ether). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.86 (s, 3 H, CH$_3$ OMe), 5.20 [s, 2 H, CH$_2$ Z(NO$_2$)], 6.40 (br. s, 1 H NH), 7.27–7.41 (m, 6 H, ArH, βH), 7.55 (d, *J* = 8.4 Hz, 2 H, ArH), 8.23 (d, *J* = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$): δ = 52.77 (OCH$_3$), 65.92 [CH$_2$ Z(NO$_2$)], 123.67 (CH), 126.95 (C), 128.23 (CH), 128.47 (CH), 128.66 (CH), 129.67 (CH), 132.52 (CH), 133.46 (C), 143.21 (C), 147.63 (C), 153.45 (C=O), 165.56 (C=O) ppm. C$_{18}$H$_{16}$N$_2$O$_6$ (356.33): calcd. C 60.67, H 4.53, N 7.86; found C 60.36, H 4.69, N 8.09.

Z-*Z*-ΔPhe-OMe (3b): The general procedure described above was followed using Z-D,L-Phe(β-OH)-OMe (1.028 g, 3.120 mmol) as reactant to afford **3b** (0.795 g, 82%) as a yellowish oil that failed to crystallize. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.82 (s, 3 H, CH$_3$ OMe), 5.13 (s, 2 H, CH$_2$ Z), 6.39 (br. s, 1 H NH), 7.33–7.37 (m, 9 H, ArH, βH), 7.51–7.52 (m, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, CDCl$_3$): δ = 52.63 (OCH$_3$), 67.50 (CH$_2$), 128.17 (CH), 128.22 (CH), 128.33 (C), 128.47 (CH), 128.59 (CH), 129.45 (CH), 129.70 (CH), 131.71 (CH), 133.57 (C), 135.89 (C), 153.80 (C=O), 165.71 (C=O) ppm. HRMS (ESI): calcd. for C$_{18}$H$_{17}$NNaO$_4$ 334.10553; found 334.10553.

Methyl Esters of *N*-Protected β-Bromo Dehydroamino Acids: Z(NO$_2$)-ΔAla(β,β-Br)-OMe (**4a**),[18] Z-ΔAla(β,β-Br)-OMe (**4b**),[18] Boc-ΔAla(β,β-Br)-OMe (**4c**),[20a] 2-Fur-ΔAla(β,β-Br)-OMe (**4d**),[23] Bz(4-OMe)-ΔAla(β,β-Br)-OMe (**4e**),[23] Z(NO$_2$)-*E*-ΔAbu(β-Br)-OMe (***E*-5a**),[18] Z(NO$_2$)-*Z*-ΔAbu(β-Br)-OMe (***Z*-5a**),[18] Z-*Z*-ΔAbu-(β-Br)OMe (***Z*-5b**),[18] Boc-*Z*-ΔAbu(β-Br)-OMe (***Z*-5c**),[24] Tos-*Z*-ΔAbu(β-Br)-OMe (***Z*-5g**),[18] Boc-*Z*-ΔPhe(β-Br)-Ome (***Z*-6c**),[20b] Tos-*Z*-ΔPhe(β-Br)-OMe (***Z*-6g**);[18] the syntheses of these compounds have been described previously.

General Procedure: The methyl ester of the *N*-protected α,β-dehydroamino acid was dissolved in dichloromethane (0.1 mol dm^{-3}) and *N*-bromosuccinimide (1.2 equiv.) was added with vigorous stirring. After reacting for 16 h, triethylamine (1.5 equiv.) was added and stirring was continued for 1 h. Additional dichloromethane (100 mL) was added and the organic phase was washed with KHSO$_4$ (1 mol dm^{-3}, 3 × 30 mL), NaHCO$_3$ (1 mol dm^{-3}, 3 × 30 mL), and brine (3 × 30 mL). After drying over MgSO$_4$, the extract was taken to dryness under reduced pressure. When necessary, the diastereomers were separated by column chromatography (petroleum ether to diethyl ether/petroleum ether, 40%) to afford the corresponding methyl ester of the *N*-protected β-bromo α,β-dehydroamino acid.

Nosyl-*Z*-ΔAbu(β-Br)-OMe (*Z*-5f): The general procedure described above was followed using Nosyl-*Z*-ΔAbu-OMe (**2f**; 0.660 g, 2.200 mmol) as reactant to afford ***Z*-5f** (0.746 g, 89%) as a light-yellow solid; m.p. 116.0–117.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.60 (s, 3 H, γCH$_3$), 3.80 (s, 3 H, CH$_3$ OMe), 6.46 (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. ^{13}C NMR (100.6 MHz, CDCl$_3$): δ = 25.75 (γCH$_3$), 52.96 (OCH$_3$), 124.22 (CH), 125.78 (C), 128.64 (CH), 133.37 (C), 144.96 (C), 150.38 (C), 162.72 (C=O) ppm. C$_{11}$H$_{11}$BrN$_2$O$_6$S (379.18): calcd. C 34.84, H 2.92, N 7.39, S 8.46; found C 34.82, H 3.02, N 7.33, S 8.22.

Z(NO$_2$)-*Z*-ΔPhe(β-Br)-OMe (*Z*-6a): The general procedure described above was followed using Z(NO$_2$)-*Z*-ΔPhe-OMe (**3a**;

1.003 g, 2.816 mmol) as reactant to afford *Z*-**6a** (1.137 g, 93%) as a white solid; m.p. 151.0–152.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.51 (br. s, 3 H, CH_3 OMe), 5.29 [s, 2 H, CH_2 Z(NO_2)], 6.80 (br. s, 1 H NH), 7.35 (s, 5 H, ArH), 7.55 (d, J = 8.4 Hz, 2 H, ArH), 8.25 (d, J = 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 52.64 (OCH_3), 66.40 [CH_2 Z(NO_2)], 117.09 (C), 123.85 (CH), 128.34 (CH), 128.45 (CH), 128.48 (C), 128.83 (CH), 129.50 (CH), 137.03 (C), 142.53 (C), 147.85 (C), 152.50 (C=O), 163.12 (C=O) ppm. $C_{18}H_{15}BrN_2O_6$ (435.23): calcd. C 49.67, H 3.47, N 6.44; found C 50.07, H 3.69, N 6.34. HRMS (ESI): calcd. for $C_{18}H_{15}N_2NaO_6Br$ 457.00112; found 457.00224.

Z-*Z*-ΔPhe(β-Br)-OMe (*Z*-6b): The general procedure described above was followed using Z-*Z*-ΔPhe-OMe (**3b**; 0.970 g, 3.119 mmol) as reactant to afford *Z*-**6b** (1.045 g, 86%) as a white solid; m.p. 87.0–88.0 °C (diethyl ether/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.53 (br. s, 3 H, CH_3 OMe), 5.19 (s, 2 H, CH_2 Z), 6.76 (br. s, 1 H, NH), 7.33–7.39 (m, 10 H, ArH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 52.55 (OCH_3), 68.14 (CH_2 Z), 115.61 (C), 128.27 (CH), 128.46 (CH), 128.58 (CH), 128.63 (CH), 128.86 (C), 128.91 (CH), 129.30 (CH), 135.18 (C), 137.17 (C), 152.86 (C=O), 163.24 (C=O) ppm. $C_{18}H_{16}BrNO_4$ (390.23): calcd. C 55.40, H 4.13, N 3.59; found C 55.60, H 4.15, N 3.62.

Nosyl-*Z*-ΔPhe(β-Br)-OMe (*Z*-6f): The general procedure described above was followed using Nosyl-*Z*-ΔPhe-OMe (**3f**; 1.011 g, 2.794 mmol) as reactant to afford *Z*-**6f** (1.027 g, 83%) as a yellow solid; m.p. 187.0–188.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.58 (s, 3 H, CH_3 OMe), 6.74 (s, 1 H, NH), 7.24–7.26 (m, 2 H, ArH), 7.33–7.38 (m, 3 H, ArH), 8.16 (d, J = 8.7 Hz, 2 H, ArH Nosyl), 8.43 (d, J = 8.7 Hz, 2 H, ArH Nosyl) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 53.03 (OCH_3), 124.30 (CH), 125.41 (C), 127.50 (C), 128.45 (CH), 128.49 (CH), 128.77 (CH), 130.07 (CH), 136.64 (C), 144.67 (C), 150.55 (C), 162.99 (C=O) ppm. $C_{16}H_{13}BrN_2O_6S$ (441.25): calcd. C 43.55, H 2.97, N 6.35, S 7.27; found C 43.54, H 3.02, N 6.31, S 7.16.

Methyl Esters of *N*-Protected *N*-Ethyl-β,β-dibromodehydroalanines and *N*-Protected *N*-Ethyl β-Substituted β-Bromo Dehydroamino Acids

General Procedure: The methyl ester of the *N*-protected β-bromo dehydroamino acid was dissolved in anhydrous dichloromethane (0.05 mol dm^{-3}) followed by addition of *N*,*N*-diisopropylethylamine (3.5 equiv.) and triethyloxonium tetrafluoroborate (2.5 equiv.) under an inert atmosphere. The reaction mixture was stirred at room temperature for 30 min. In cases where TLC indicated some starting material remained, *N*,*N*-diisopropylethylamine (1 equiv.) and triethyloxonium tetrafluoroborate (1 equiv.) were added and stirring was continued for 1 h. Dichloromethane (50 mL) was added and the organic phase was washed with $KHSO_4$ (1 mol dm^{-3}, 3 × 30 mL), $NaHCO_3$ (1 mol dm^{-3}, 3 × 30 mL), and brine (3 × 30 mL), and dried with $MgSO_4$. Removal of the solvent generally afforded an oil, which was either subjected to column chromatography (diethyl ether/petroleum ether) or crystallized.

Z(NO_2)-*N*(Et)-ΔAla(β,β-Br)-OMe (7a): The general procedure described above was followed using Z(NO_2)-ΔAla(β,β-Br)-OMe (**4a**; 0.764 g, 1.745 mmol) as reactant to afford **7a** (0.687 g, 85%) as a yellowish oil; m.p. 58.0–59.0 °C (diethyl ether/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 3.57 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.75 (s, 3 H, CH_3 OMe), 5.25 [s, 2 H, CH_2 Z(NO_2)], 7.48 (d, J = 8.8 Hz, 2 H, ArH), 8.23 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.89 (CH_3), 44.11 (CH_2), 52.86 (OCH_3), 66.23 [CH_2 Z(NO_2)], 108.16 (C), 123.73 (CH), 127.98 (CH), 134.32 (C), 143.42 (C), 147.62 (C), 153.29 (C=O), 162.83 (C=O) ppm. $C_{14}H_{14}Br_2N_2O_6$ (466.08): calcd. C 36.08, H 3.03, N 6.01; found C 36.02, H 3.12, N 6.01. HRMS (ESI): calcd. for $C_{14}H_{14}N_2NaO_6Br_2$ 486.91163; found 486.91108.

Z-*N*(Et)-ΔAla(β,β-Br)-OMe (7b): The general procedure described above was followed using Z-ΔAla(β,β-Br)-OMe (**4b**; 0.158 g, 0.400 mmol) as reactant to afford **7b** (0.138 g, 82%) as a colorless oil that failed to crystallize. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 3.57 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.62 (s, 3 H, CH_3 OMe), 5.16 (s, 2 H, CH_2 Z), 7.31–7.38 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.96 (CH_3), 43.91 (CH_2), 52.61 (OCH_3), 66.69 (CH_2 Z), 107.25 (C), 127.91 (CH), 128.08 (CH), 128.42 (CH), 134.62 (C), 136.08 (C), 153.79 (C=O), 162.92 (C=O) ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NNaO_4Br_2$ 441.92655; found 441.92600.

Boc-*N*(Et)-ΔAla(β,β-Br)-OMe (7c): The general procedure described above was followed using Boc-ΔAla(β,β-Br)-OMe (**4c**; 0.180 g, 0.500 mmol) as reactant to afford a colorless oil (0.176 g) consisting of a mixture of product and reactant in a 48:52 ratio. Purification by column chromatography (diethyl ether/petroleum ether) afforded **7c** (0.084 g, 44%) as a colorless oil that failed to crystallize. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 1.42 (s, 9 H, CH_3 Boc), 3.50 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.80 (s, 3 H, CH_3 OMe) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.05 (CH_3), 28.11 [$C(CH_3)_3$], 42.96 (CH_2), 52.56 (OCH_3), 81.25 [$OC(CH_3)_3$], 105.08 (C), 135.40 (C), 152.71 (C=O), 163.35 (C=O) ppm. HRMS (ESI): calcd. for $C_{11}H_{17}NNaO_4Br_2$ 407.94220; found 407.94198.

2-Fur-*N*(Et)-ΔAla(β,β-Br)-OMe (7d): The general procedure described above was followed using 2-Fur-ΔAla(β,β-Br)-OMe (**4d**; 0.177 g, 0.500 mmol) as reactant to afford a yellow oil (0.185 g) consisting of a mixture of product and reactant in a 82:18 ratio. Purification by column chromatography (diethyl ether/petroleum ether) afforded **7d** (0.152 g, 80%) as a colorless oil; m.p. 74.0–75.0 °C (diethyl ether/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 3.69 (br. q, 2 H, CH_2CH_3), 3.78 (s, 3 H, CH_3 OMe), 6.45 (dd, J = 1.8, J = 3.3 Hz, 1 H, ArH), 7.06 (d, J = 3.3 Hz, 1 H, ArH), 7.46 (s, 1 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.64 (CH_3), 43.71 (CH_2), 52.97 (OCH_3), 108.75 (C), 111.48 (CH), 116.80 (CH), 135.73 (C), 144.95 (CH), 147.25 (C), 158.37 (C=O), 162.91 (C=O) ppm. $C_{11}H_{11}Br_2NO_4$ (381.02): calcd. C 34.67, H 2.91, N 3.68; found C 34.73, H 2.94, N 3.72.

Bz(4-OMe)-*N*(Et)-ΔAla(β,β-Br)-OMe (7e): The general procedure described above was followed using Bz(4-OMe)-ΔAla(β,β-Br)-OMe (**4e**; 0.118 g, 0.300 mmol) as reactant to afford a colorless oil (0.093 g) consisting of a mixture of product and reactant in a 64:36 ratio. Purification by column chromatography (diethyl ether/petroleum ether) afforded **7e** (0.060 g, 47%) as a colorless oil; m.p. 68.0–70.0 °C (diethyl ether/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 3.59 (br. s, 2 H, CH_2CH_3), 3.78 (s, 3 H, CH_3 OMe), 3.83 (s, 3 H, CH_3 OMe), 6.86 (d, J = 8.8 Hz, 2 H, ArH), 7.56 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.83 (CH_3), 43.49 (CH_2), 52.98 (OCH_3), 55.27 (OCH_3), 105.52 (C), 113.34 (CH), 127.73 (C), 129.63 (CH), 137.33 (C), 161.54 (C), 163.33 (C=O), 169.98 (C=O) ppm. $C_{14}H_{15}Br_2NO_4$ (421.08): calcd. C 39.93, H 3.59, N 3.33; found C 40.38, H 3.86, N 3.33.

Z(NO_2)-*N*(Et)-*E*-ΔAbu(β-Br)-OMe (*E*-8a): The general procedure described above was followed using Z(NO_2)-*E*-ΔAbu(β-Br)-OMe (*E*-**5a**; 0.118 g, 0.315 mmol) as reactant to afford a colorless oil (0.119 g) consisting of a mixture of product and reactant in a 80:20 ratio. Purification by column chromatography (diethyl ether/petroleum ether) afforded *E*-**8a** (0.095 g, 75%) as a white solid; m.p.

59.0–60.0 °C (diethyl ether/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.42 (s, 3 H, γCH_3), 3.49 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.73 (s, 3 H, CH_3 OMe), 5.23 [br. s, 2 H, CH_2 Z(NO_2)], 7.46 (d, J = 8.7 Hz, 2 H, ArH), 8.22 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 12.84 (CH_3), 27.00 (γCH_3), 44.43 (CH_2), 52.32 (OCH_3), 66.03 [CH_2 Z(NO_2)], 123.73 (CH), 127.88 (CH), 129.45 (C), 132.95 (C), 143.61 (C), 147.57 (C), 154.22 (C=O), 164.00 (C=O) ppm. $C_{15}H_{17}BrN_2O_6$ (401.21): calcd. C 44.90, H 4.27, N 6.98; found C 45.23, H 4.40, N 7.07.

Z(NO_2)-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe (*Z*-8a): The general procedure described above was followed using Z(NO_2)-*Z*-ΔAbu(β-Br)-OMe (*Z*-**5a**; 0.187 g, 0.500 mmol) as reactant to afford a yellowish oil (0.178 g) consisting of a mixture of product and reactant in a 37:63 product/reactant ratio. Purification by column chromatography (diethyl ether/petroleum ether) afforded *Z*-**8a** (0.066 g, 33%) as a colorless oil; m.p. 73.0–73.5 °C (diethyl ether/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.85 (s, 3 H, γCH_3), 3.55 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.71 (s, 3 H, CH_3 OMe), 5.21 [s, 2 H, CH_2 Z(NO_2)], 7.45 (d, J = 8.7 Hz, 2 H, ArH), 8.19 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.83 (CH_3), 26.83 (γCH_3), 44.17 (CH_2), 52.36 (OCH_3), 65.78 [CH_2 Z(NO_2)], 123.61 (CH), 127.81 (CH), 130.02 (C), 142.90 (C), 143.99 (C), 147.47 (C), 154.00 (C=O), 163.64 (C=O) ppm. $C_{15}H_{17}BrN_2O_6$ (401.21): calcd. C 44.90, H 4.27, N 6.98; found C 44.89, H 4.40, N 7.03.

Z-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe (*Z*-8b): The general procedure described above was followed using Z-*Z*-ΔAbu(β-Br)-OMe (*Z*-**5b**; 0.318 g, 0.970 mmol) as reactant to afford a colorless oil (0.322 g) consisting of a mixture of product and reactant in a 43:57 ratio. Purification by column chromatography (diethyl ether/petroleum ether) afforded *Z*-**8b** (0.138 g, 40%) as a colorless oil that failed to crystallize. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.84 (s, 3 H, γCH_3), 3.52 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 3.59 (s, 3 H, CH_3 OMe), 5.22 (s, 2 H, CH_2 Z), 7.28–7.39 (m, 5 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.91 (CH_3), 26.74 (γCH_3), 43.95 (CH_2), 52.12 (OCH_3), 67.19 (CH_2 Z), 127.72 (CH), 127.84 (CH), 128.31 (CH), 130.30 (C), 136.50 (C), 142.11 (C), 154.53 (C=O), 163.82 (C=O) ppm. HRMS (ESI): calcd. for $C_{15}H_{18}NNaO_4Br$ 378.03169; found 378.03114.

Nosyl-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe (*Z*-8f): The general procedure described above was followed using Nosyl-*Z*-ΔAbu(β-Br)-OMe (*Z*-**5f**; 0.081 g, 0.214 mmol) as reactant to afford *Z*-**8f** (0.081 g, 93%) as a light-yellow solid; m.p. 108.0–109.0 °C (diethyl ether/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.85 (s, 3 H, γCH_3), 3.58 (br. m, 2 H, CH_2CH_3), 3.67 (s, 3 H, CH_3 OMe), 8.04 (d, J = 8.7 Hz, 2 H, ArH), 8.35 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.82 (CH_2CH_3), 27.64 (γCH_3), 45.20 (CH_2), 52.43 (OCH_3), 123.91 (CH), 128.11 (C), 128.96 (CH), 145.74 (C), 147.09 (C), 149.99 (C), 163.72 (C=O) ppm. $C_{13}H_{15}BrN_2O_6S$ (407.24): calcd. C 38.34, H 3.71, N 6.88, S 7.87; found C 38.76, H 3.85, N 6.92, S 7.85.

Tos-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe (*Z*-8g): The general procedure described above was followed using Tos-*Z*-ΔAbu(β-Br)-OMe (*Z*-**5g**; 0.085 g, 0.244 mmol) as reactant to afford *Z*-**8g** (0.072 g, 78%) as a colorless oil; m.p. 93.0–94.0 °C (diethyl ether/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.43 (s, 3 H, CH_3 Tos), 2.82 (s, 3 H, γCH_3), 3.46 (br. m, 2 H, CH_2CH_3), 3.60 (s, 3 H, CH_3 OMe), 7.29 (d, J = 8.8 Hz, 2 H, ArH), 7.73 (d, J = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.79 (CH_2CH_3), 21.51 (Tos CH_3), 27.45 (γCH_3), 44.63 (CH_2), 52.10 (OCH_3), 127.76 (CH), 128.51 (C), 129.23 (CH), 137.23 (C), 143.30 (C), 146.02 (C), 164.12 (C=O) ppm. $C_{14}H_{18}BrNO_4S$ (376.27): calcd. C 44.69, H 4.82, N 3.72, S 8.52; found C 45.02, H 4.89, N 3.87, S 8.32.

Z(NO_2)-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe (*Z*-9a): The general procedure described above was followed using Z(NO_2)-*Z*-ΔPhe(β-Br)-OMe (*Z*-**6a**; 0.109 g, 0.250 mmol) as reactant to afford a colorless oil (0.076 g) consisting of a mixture of product and reactant in a 45:55 ratio. Purification by column chromatography (diethyl ether/petroleum ether) afforded *Z*-**9a** (0.034 g, 30%) as a yellowish solid; m.p. 117.0–118.0 °C (from ethyl acetate/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.6 Hz, 3 H, CH_2CH_3), 3.42 (s, 3 H, CH_3 OMe), 3.71 (br. m, 2 H, CH_2CH_3), 5.28 [s, 2 H, CH_2 Z(NO_2)], 7.30–7.40 (m, 5 H, ArH), 7.50 (d, J = 8.4 Hz, 2 H, ArH), 8.21 (d, J = 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.13 (CH_2CH_3), 43.85 (CH_2), 52.26 (OCH_3), 66.20 [CH_2 Z(NO_2)], 123.67 (CH), 127.90 (CH), 128.16 (CH), 128.31 (CH), 129.90 (CH), 131.28 (C), 138.32 (C), 138.60 (C), 143.71 (C), 147.56 (C), 153.89 (C=O), 164.19 (C=O) ppm. $C_{20}H_{19}BrN_2O_6$ (463.28): calcd. C 51.85, H 4.13, N 6.05; found C 51.91, H 4.15, N 6.12.

Z-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe (*Z*-9b): The general procedure described above was followed using Z-*Z*-ΔPhe(β-Br)-OMe (*Z*-**6b**; 0.133 g, 0.341 mmol) as reactant to afford a colorless oil (0.135 g) consisting of a mixture of product and reactant in a 38:62 ratio. Purification by column chromatography (diethyl ether/petroleum ether) afforded *Z*-**9b** (0.051 g, 36%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.5 Hz, 3 H, CH_2CH_3), 3.33 (s, 3 H, CH_3 OMe), 3.72 (q, J = 7.5 Hz, 2 H, CH_2CH_3), 5.19 (s, 2 H, CH_2 Z), 7.30–7.37 (m, 10 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.08 (CH_2CH_3), 43.54 (CH_2), 52.06 (OCH_3), 67.66 (CH_2 Z), 127.85 (CH), 127.94 (CH), 128.15 (CH), 128.20 (CH), 128.32 (CH), 129.57 (CH), 131.64 (C), 136.22 (C), 137.43 (C), 138.87 (C), 154.39 (C=O), 164.17 (C=O) ppm. HRMS (ESI): calcd. for $C_{20}H_{20}NNaO_4Br$ 440.04734; found 440.04658.

Attempted Synthesis of Boc-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe (*Z*-9c): The general procedure described above was followed using Boc-*Z*-ΔPhe(β-Br)-OMe (*Z*-**6c**; 0.178 g, 0.500 mmol) as reactant to afford a colorless oil (0.175 g) consisting of a mixture of product and reactant in a 15:85 ratio that could not be separated.

Nosyl-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe (*Z*-9f): The general procedure described above was followed using Nosyl-*Z*-ΔPhe(β-Br)-OMe (*Z*-**6f**; 0.309 g, 0.700 mmol) as reactant to afford *Z*-**9f** (0.294 g, 90%) as a colorless oil; m.p. 118.0–119.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 3.41 (s, 3 H, CH_3 OMe), 3.66 (br. m, 2 H, CH_2CH_3), 7.31–7.41 (m, 5 H, ArH), 8.14 (d, J = 8.7 Hz, 2 H, ArH Nosyl), 8.39 (d, J = 8.7 Hz, 2 H, ArH Nosyl) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.06 (CH_2CH_3), 44.74 (CH_2), 52.39 (OCH_3), 124.02 (CH), 128.13 (CH), 128.34 (CH), 129.13 (CH), 129.19 (C), 130.20 (CH), 138.47 (C), 142.26 (C), 145.35 (C), 150.17 (C), 164.58 (C=O) ppm. $C_{18}H_{17}BrN_2O_6S$ (469.31): calcd. C 46.07, H 3.65, N 5.97, S 6.83; found C 45.98, H 3.72, N 5.98, S 6.85.

Tos-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe (*Z*-9g): The general procedure described above was followed using Tos-*Z*-ΔPhe(β-Br)-OMe (*Z*-**6g**; 0.205 g, 0.500 mmol) as reactant to afford *Z*-**9g** (0.194 g, 89%) as a colorless oil; m.p. 99.0–100.0 °C (diethyl ether/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.45 (s, 3 H, CH_3 Tos), 3.39 (s, 3 H, CH_3 OMe), 3.62 (br. q, J = 7.2 Hz, 2 H, CH_2CH_3), 7.31–7.38 (m, 7 H, ArH), 7.83 (d, J = 8.4 Hz, 2 H, ArH Tos) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.00 (CH_2CH_3), 21.57 (Tos CH_3), 44.11 (CH_2), 52.16 (OCH_3), 127.88 (CH), 128.17 (CH), 128.21 (CH), 129.36 (CH), 129.82 (CH), 129.90 (C), 136.80 (C), 138.86 (C), 140.48 (C), 143.63 (C), 164.89

(C=O) ppm. $C_{19}H_{20}BrNO_4S$ (438.34): calcd. C 52.06, H 4.60, N 3.20, S 7.32; found C 51.97, H 4.53, N 3.25, S 7.35.

Suzuki Cross-Coupling of the Methyl Esters of *N*-Protected *N*-Ethyl β-Bromo α,β-Dehydroamino Acids with Phenylboronic Acid

General Procedure: To a solution of the methyl ester of *N*-protected *N*-ethyl β-bromo α,β-dehydroamino acid in THF/H_2O (1:1, 0.05 mol dm^{-3}), phenylboronic acid (1.5 equiv.), [$PdCl_2$dppf]·CH_2Cl_2 (1:1, 10 mol-%), and Cs_2CO_3 (1.4 equiv.) were added. The reaction mixture was heated at 90 °C and the reaction was monitored by TLC until all the *N*-ethyl β-brominated dehydroamino acid derivative was consumed (1–3 h). The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with water (2 × 30 mL) and brine (2 × 30 mL), dried with $MgSO_4$, and the solvent was removed. The residue was purified by column chromatography (diethyl ether/petroleum ether).

Z(NO_2)-*N*(Et)-ΔPhe(β-C_6H_5)-OMe (10a): The general procedure described above was followed using Z(NO_2)-*N*(Et)-ΔAla(β,β-Br)-OMe (**7a**; 0.093 g, 0.200 mmol) and phenylboronic acid (3.0 equiv.) as reactant to afford **10a** (0.075 g, 81%) as a colorless oil; m.p. 92.0–93.0 °C (diethyl ether/*n*-hexane). ^{1}H NMR (300 MHz, DMSO): δ = 1.00 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 3.02 (br. m, 2 H, CH_2CH_3), 3.32 (s, 3 H, CH_3 OMe), 5.26 [s, 2 H, CH_2 Z(NO_2)], 7.06–7.11 (m, 4 H, ArH), 7.34–7.37 (m, 6 H, ArH), 7.58 (d, J = 8.7 Hz, 2 H, ArH), 8.22 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, DMSO): δ = 12.79 (CH_3), 43.37 (CH_2), 51.58 (OCH_3), 65.87 [CH_2 Z(NO_2)], 123.53 (CH), 127.94 (CH), 128.06 (CH), 128.18 (CH), 128.51 (CH), 128.67 (CH), 128.83 (CH), 129.01 (CH), 139.19 (C), 139.84 (C), 143.94 (C), 144.39 (C), 145.84 (C), 147.12 (C), 154.29 (C=O), 166.89 (C=O) ppm. $C_{26}H_{24}N_2O_6$ (460.48): calcd. C 67.82, H 5.25, N 6.08; found C 67.74, H 5.27, N 6.13.

Z-*N*(Et)-ΔAbu(β-C_6H_5)-OMe (*Z*-10b): The general procedure described above was followed using Z-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe (*Z*-**8b**; 0.122 g, 0.344 mmol) as reactant to afford *Z*-**10b** (0.060 g, 50%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 2.46 (s, 3 H, γCH_3), 3.50 (br. s, 2 H, CH_2CH_3), 3.53 (s, 3 H, CH_3 OMe), 5.18 (s, 2 H, CH_2 Z), 7.28–7.39 (m, 10 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.53 (CH_3), 21.66 (γCH_3), 44.53 (CH_2), 51.59 (OCH_3), 67.18 (CH_2 Z), 126.83 (CH), 127.68 (CH), 127.84 (CH), 128.03 (CH), 128.35 (CH), 128.44 (CH), 136.67 (C), 141.18 (C), 148.07 (C), 155.65 (C), 156.31 (C=O), 166.43 (C=O) ppm. HRMS (ESI): calcd. for $C_{21}H_{23}NNaO_4$ 376.15248; found 376.15193.

Z(NO_2)-*N*(Et)-ΔPhe(β-C_6H_5)-OMe (10a): The general procedure described above was followed using Z(NO_2)-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe (*Z*-**9a**; 0.093 g, 0.200 mmol) as reactant to afford **10a** (0.058 g, 63%).

Nosyl-*N*(Et)-ΔPhe(β-C_6H_5)-OMe (10f): The general procedure described above was followed using Nosyl-*N*(Et)-ΔPhe(β-Br)-OMe (*Z*-**9f**; 0.215 g, 0.458 mmol) as reactant to afford **10f** (0.203 g, 95%) as a white solid; m.p. 155.0–156.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, J = 7.2 Hz, 3 H, CH_2CH_3), 3.00 (br. m, 2 H, CH_2CH_3), 3.40 (s, 3 H, CH_3 OMe), 7.12–7.16 (m, 2 H, ArH), 7.30–7.37 (m, 8 H, ArH), 8.05 (d, J = 9.0 Hz, 2 H, ArH Nosyl), 8.34 (d, J = 9.0 Hz, 2 H, ArH Nosyl) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.08 (CH_2CH_3), 43.27 (CH_2), 51.96 (OCH_3), 123.89 (CH), 124.76 (C), 128.22 (CH), 128.36 (CH), 128.82 (CH), 129.03 (CH), 129.23 (CH), 123.47 (CH), 129.59 (CH), 138.65 (C), 140.46 (C), 144.81 (C), 150.10 (C), 150.73 (C), 167.77 (C=O) ppm. $C_{24}H_{22}N_2O_6S$ (466.51): calcd. C 61.79, H 4.75, N 6.00, S 6.87; found C 61.67, H 4.90, N 6.00, S 6.70.

Acknowledgments

The Portuguese Foundation for Science and Technology (FCT) and the Fundo Europeu de Desenvolvimento Regional (FEDER) are thanked for financial support to the Chemistry Centre of University of Minho. The Bruker Avance II$^+$ 400 NMR spectrometer is part of the National NMR Network and was purchased in the framework of the National Program for Scientific Re-equipment, REDE/1517/RMN/2005, with funds from POCI 2010, FEDER and FCT.

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Received: June 21, 2011
Published Online: September 19, 2011

