FULL PAPER

DOI: 10.1002/ejoc.200((will be filled in by the editorial staff))

Synthesis of new *N*-ethyl dehydroamino acid derivatives: *N*-ethyl β,β-dibromo, *N*-ethyl β-bromo β-substituted, *N*-ethyl β,β-disubstituted *N*-protected dehydroamino acid methyl esters

Luís S. Monteiro,*[a] Juliana J. Andrade[a] and Ana C. Suárez[a]

Keywords: Amino acids / Alkylation / *N*-Ethyl dehydroamino acids / *N*-Ethyl β-bromo dehydroamino acids / Suzuki cross-coupling

Recently we reported the use of a sequence of alkylation and dehydration methodologies to obtain from the methyl esters of *N*-(4-nitrophenylsulfonyl)-β-hydroxyamino acids, new non-proteinogenic amino acids, namely, *N*-ethyl-α,β-dehydroamino acids. Thus, it was possible to obtain for the first time, non-natural amino acids which incorporate both the *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-nitrobenzyloxycarbonyl 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 *N*-ethyl, β,β-disubstituted dehydroalanine derivatives.

[a] Chemistry Centre, University of Minho, Gualtar, 4710-057 Braga, Portugal.
Fax: +351 253604382
E-mail: monteiro@quimica.uminho.pt

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 non-proteinogenic amino acids are *N*-alkylamino acids and dehydroamino acids, both of which can be found in many biologically important peptides.[1]

N-Alkylamino acids are constituents of various important naturally occurring peptides and proteins.[1] They have been isolated from plant strains, microorganism 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 of synthesis of *N*-alkylamino acids have been developed, most of them are *N*-methylations.[2] Many of these methods require treatment of 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*-ethylamino acids by reaction of *N*-acetylamino 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*-benzyloxycarbonylamino 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 substituting lithium bis(trimethylsilyl)amide or cesium carbonate for sodium hydride but were also unsuccessful.[8] However, carrying out the original protocol (ethyl iodide and NaH in THF) at elevated temperatures they were able to obtain *N*-benzyloxycarbonyl, *N*-ethylamino 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-nitrobenzenesulfonyl (Nosyl) protected amino acids using triethyloxonium tetrafluoroborate (Et_3OBF_4) as alkylating agent and *N*,*N*-diisopropylethylamine (DIPEA) as base to give *N*-ethylamino acid derivatives in high yields.[12] These authors demonstrated the compatibility of the procedure with standard Fmoc chemistry.[12]

Dehydroamino acids have been found in naturally occurring peptides of fungal and microbial origin[13] and from marine organisms,[14] in which they contribute with 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] Since 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 we developed an efficient method for the synthesis of *N*,*N*-diacyl-α,β-dehydroamino acid derivatives from *N*-acyl-β-hydroxyamino acid derivatives by reacting them with two equiv. of *tert*-butylpyrocarbonate and 4-dimethylaminopyridine as catalyst in dry acetonitrile.[17] In order to allow the synthesis of *N*-acyl-α,β-dehydroamino acid derivatives, a modification of this method was subsequently reported.[18]

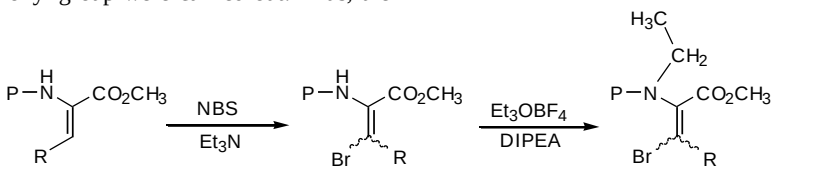
Recently we reported the use of a combination of the alkylation procedure reported by Liguori et al.[12] and our dehydration

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 which 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-nitrobenzyloxycarbonyl [Z(NO_2)] as well as acyl and sulfonyl amine 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, *N*-ethyl, β,β-disubstituted dehydroalanines. Thus, this methodology opens the possibility of obtaining a large range of new *N*-ethyl, β,β-disubstituted dehydroalanines.

Results and Discussion

In order 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-nitrobenzenesulfonyl 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 subject to *N*-ethylation with triethyloxonium tetrafluoroborate. However, after several hours of reaction and addition of large excess of alkylating agent no *N*-ethylated dehydroalanine derivative could be detected. The chemical shift of the NH proton of Boc-ΔAla-OMe and Z(NO_2)-ΔAla-OMe in DMSO solutions was determined (δ_{NH}=8.35 ppm and δ_{NH}=9.13 ppm, respectively) and compared with a dehydroamino acid derivative in which alkylation in the same conditions is 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 continues 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-couplings with aryl and heteroaryl boronic acids to obtain new dehydroamino acid derivatives.[20] Thus, we decided to study how the presence of bromine substituents on the β-carbon of dehydroalanine derivatives affects *N*-ethylation.



R = H, **1a-e**; R = CH_3, **2a-c**, **2f**, **2g**; R = C_6H_5, **3a-c**, **3f**, **3g**.

R = Br, **4a-e**; R = CH_3, **5a-c**, **5f**, **5g**; R = C_6H_5, **6a-c**, **6f**, **6g**.

R = Br, **7a-e**; R = CH_3, **8a-c**, **8f**, **8g**; R = C_6H_5, **9a-c**, **9f**, **9g**.

P = Z(NO_2), **a**; Z, **b**; Boc, **c**; 2-Fur, **d**; Bz(4-OMe) **e**; Nosyl, **f**; Tos, **g**.

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

Reactant	**δ NH[a] (ppm)**	**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] Chemical shift of the amide hydrogen measured in DMSO solutions. [b] Ratio of product to reactant determined by HNMR.

The methyl esters of dehydroalanine *N*-protected with the 4-nitrobenzyloxycarbonyl, benzyloxycarbonyl, *tert*-butyloxycarbonyl, 2-furanoyl (2-Fur) and 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 reacted with 2.2 equiv. of *N*-bromosuccinimide (NBS) followed by treatment with triethylamine to give *N*-protected β,β-dibromodehydroalanine derivatives (compounds **4a-e**, Scheme 1).[18] These compounds were subject to *N*-ethylation using the conditions previously established[12] [2.5 equiv. of triethyloxonium tetrafluoroborate, 3.5 equiv. of *N*,*N*-diisopropylethylamine (DIPEA) in dry dichloromethane] to give the corresponding *N*-protected, *N*-ethyl

β,β-dibromodehydroalanine derivative (compounds **7a-e**, Scheme 1, Table 1).

With the urethane protecting groups Z(NO_2) and Z the reactions were complete giving the corresponding *N*-acyl, *N*-ethyl β,β-dibromodehydroalanine derivative in yields of 85% and 82%, 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 could be isolated by column chromatography (compound **7c**). Thus, the β,β-dibromodehydroalanine derivatives protected with the more electron withdrawing groups Z(NO_2) and Z, gave complete reactions with good yields in *N*-ethylated product, while for the dehydroalanine derivative with the less electron withdrawing Boc group, the reaction could not be taken to completion. The chemical shift of the NH proton of compounds **4a-c** in DMSO solutions was measured (Table 1). Compounds **4a** and **4b** show 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 (compounds **4d** and **4e**) the *N*-ethylation reactions were also incomplete but the wanted product could be isolated after column chromatography (compounds **7d** and **7e**). For the reaction with compound **4d** a ratio of approximately 8/2 of product to reactant was obtained, whilst for **4e** this ratio was of approximately 6/4. These ratios can be correlated with the chemical shift of the nitrogen protons which were 10.16 and 10.07 for compounds **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. Since β,β-dibromodehydroalanine derivatives *N*-protected with the 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*-butylpyrocarbonate,[18] to give *N*-protected derivatives of dehydroaminobutyric acid and of dehydrophenylalanine, (compounds **2a-c**, **2g**, **3a-c** and **3g**, Scheme 1). For the Nosyl derivatives, dehydration had to be carried out using 2 equiv. of *tert*-butylpyrocarbonate to give the corresponding *N*-Boc, *N*-Nosyl-dehydroamino acid derivative, followed by treatment with a 4% solution of trifluoroacetic acid in dichloromethane to give compounds **2f** and **3f**.[19] The dehydroamino acid derivatives were reacted with 1.2 equiv. of NBS followed by treatment with triethylamine to give *N*-protected β-bromo dehydroaminobutyric acid and dehydrophenylalanine derivatives (compounds **8a-c**, **8f**, **8g**, **9a-c**, **9f**, and **9g**, Scheme 1). The β-bromo, β-substituted dehydroamino acid derivatives were subject to *N*-ethylation in identical conditions as described previously for the β,β-dibromodehydroalanine derivatives.

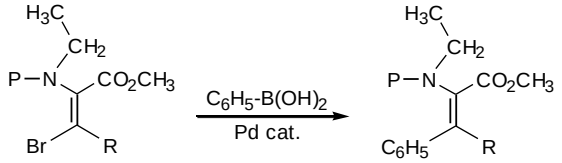
N-Ethylation of dehydroaminobutyric acid derivatives protected with Z(NO_2) and Z (compounds *E*-**5a**, *Z*-**5a** and *Z*-**5b**) could not be taken to completion, contrary to what had occurred with the β,β-dibromodehydroalanine derivatives protected with the same groups (**4a** and **4b**). However, the *N*-ethylated product could be isolated after column chromatography. The chemical shift of the NH proton of compounds *E*-**5a**, *Z*-**5a** and *Z*-**5b** in DMSO solutions was measured (Table 1). It can be observed that the substitution of a β-methyl group of the dehydroamino acids for a bromine atom reduces the chemical shift. Comparison of the chemical shift of the NH proton of both the 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 of product to reactant was obtained, whilst for *Z*-**5a** the ratio was of approximately 4/6. For the Boc protected dehydroaminobutyric acid derivative (compound *Z*-**5c**) no *N*-ethylation was observed. The chemical shift of the NH proton was again significantly lower than for the Z(NO_2) and Z protected dehydroaminobutyric acid derivatives and also lower than for the *N*-Boc β,β-dibromodehydroalanine derivative.

Both *N*-sulfonamide derivatives of dehydroaminobutyric acid (compounds *Z*-**5f** and *Z*-**5g**) show high chemical shift for their NH proton and in fact the *N*-ethylation reactions were complete, giving the *N*-ethylated products (compounds *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 are comparable to those obtained from the corresponding β-bromo dehydroaminobutyric acid derivatives. However, the chemical shifts for the NH proton of compounds *Z*-**6a** and *Z*-**6b** are higher than those of the corresponding dehydroaminobutyric acid derivatives, as would be expected due to the electron withdrawing effect of the β-phenyl ring as opposed to the electron donating effect of the β-methyl group. Thus, possibly the more extended conjugation of the dehydrophenylalanine derivatives counter balances the higher acidity of the NH proton in this ethylation reaction. For the *N*-Boc derivative (compound *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 (compounds *Z*-**6f** and *Z*-**6g**) were complete, giving compounds *Z*-**9f** and *Z*-**9g** in yields of 90% and 89%, respectively.

In order 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 made to react with phenyl boronic 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 couplings of *N*-ethyl, β,β-dibromo and *N*-ethyl, β-bromo, β-substituted dehydroamino acid derivatives with phenyl boronic acid.

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

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

Conclusions

The triethyloxonium tetrafluoroborate/*N,N*-diisopropylethylamine alkylation procedure was applied for *N*-ethylation of several derivatives of β,β-dibromo, dehydroalanine, β-bromo, dehydroaminobutyric acid and β-bromo, dehydrophenylalanine, 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 to product (β,β-dibromo, dehydroalanine derivatives protected with Z(NO_2) and Z, β-bromo dehydroaminobutyric acid and dehydrophenylalanine derivatives protected with Nosyl and Tos) to complete absence of reaction (β-bromo dehydroaminobutyric acid protected with Boc). A correlation between the chemical shift of the NH proton and the extension 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-bromo dehydroaminobutyric 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-couplings. Thus, in addition to their intrinsic potential interest, these compounds also constitute important substrates for the synthesis of new *N*-ethyl β,β-disubstituted dehydroalanine derivatives.

Experimental Section

Melting points (ºC) were determined in a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus at 300 and 75.4 MHz, respectively or on a Bruker Avance II$^+$ at 400 and 100.6 MHz, respectively. ^{1}H-^{1}H spin-spin decoupling, DEPT θ 45º, HMQC and HMBC were used to attribute some signals. Chemical shifts are given in ppm and coupling constants in Hz. HRMS data were recorded by the mass spectrometry service of the University of Vigo, Spain; elemental analysis was performed on a LECO CHNS 932 elemental analyzer. The reactions were monitored by thin layer chromatography (TLC). Column chromatography was performed on Macherey-Nagel silica gel 230-400 mesh. Petroleum ether refers to the boiling range 40-60 ºC. When solvent gradient was 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. Solvents were used without purification except for acetonitrile and dichloromethane which were dried using standard procedures.

Synthesis of the Methyl Esters of *N*-Protected β-Hydroxyamino 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 in the references given above.

Synthesis of 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 2.2 equiv. of triethylamine added, then 1.1 equiv. of benzyl chloroformate was slowly added with vigorous stirring and cooling in an ice bath. After stirring at 0 ºC for 30 minutes the solution was stirred at room temperature for 3 hours. The reaction mixture was then evaporated and partitioned between 200 cm^3 of ethyl acetate and 100 cm^3 of $KHSO_4$ (1 mol dm^{-3}) and washed with $KHSO_4$ (1 mol dm^{-3}), $NaHCO_3$ (1 mol dm^{-3}) and brine (3 times 50 cm^3 each). 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 ºC (from ethyl acetate/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.60 (br. s, 1H, OH), 3.76 (s, 3H, CH_3 OMe), 4.61-4.63 (m, 1H, αCH), 5.00 (s, 2H, CH_2 Z), 5.28 (d, *J* = 2.0 Hz, 1H, βCH), 5.66 (br. d, *J* = 8.8 Hz, 1H, NH), 7.31-7.35 (m, 10H, 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.

Synthesis of the Methyl Esters of *N*-(*tert*-Butoxycarbonyl)-*N*-(4-nitrophenylsulfonyl)-α,β-dehydroamino Acids: Nosyl-*Z*-ΔAbu(*N*-Boc)-OMe,[19] **Nosyl-*Z*-ΔPhe(*N*-Boc)-OMe**[19]**;** The synthesis of these compounds has been described in the reference given above.

Synthesis of the 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 in the references given above.

General procedure: The methyl ester of the *N*-protected β-hydroxyamino acid was dissolved in dry acetonitrile (0.5 mol dm^{-3}), and 0.1 equiv. of DMAP was added followed by 1.0 equiv. of *tert*-butylpyrocarbonate 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 2% in volume of TMG was added and stirring was continued and the reaction followed by TLC. When all the reactant had been consumed, evaporation at reduced pressure gave a residue that was partitioned between 100 cm^3 of diethyl ether and 30 cm^3 of $KHSO_4$ (1 mol dm^{-3}). The organic phase was thoroughly washed with $KHSO_4$ (1 mol dm^{-3}), $NaHCO_3$ (1 mol dm^{-3}) and brine (3 times 30 cm^3 each), and dried over $MgSO_4$. Removal of the solvent afforded the corresponding methyl ester of the *N*-protected α,β-dehydroamino acid.

Synthesis of Z(NO_2)-*Z*-ΔPhe-OMe (compound 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 a orange oil. M.p. 108.0-109.0 °C (from ethyl acetate/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (s, 3H, CH_3 OMe), 5.20 [s, 2H, CH_2 Z(NO_2)], 6.40 (br. s, 1H NH), 7.27-7.41 (m, 6H, ArH + βH), 7.55 (d, *J* = 8.4 Hz, 2H, ArH), 8.23 (d, *J* = 8.7 Hz, 2H, 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. $C_{18}H_{16}N_2O_6$ (356.33): calcd. C 60.67, H 4.53, N 7.86; found C 60.36, H 4.69, N 8.09.

Synthesis of Z-*Z*-ΔPhe-OMe (compound 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, 3H, CH_3 OMe), 5.13 (s, 2H, CH_2 Z), 6.39 (br. s, 1H NH), 7.33-7.37 (m, 9H, ArH + βH), 7.51-7.52 (m, 2H, 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.

Synthesis of the 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

synthesis of these compounds has been described in the references given above.

General procedure: The methyl ester of the *N*-protected α,β-dehydroamino acid was dissolved in dichloromethane (0.1 mol dm^{-3}) and 1.2 equiv. of *N*-bromosuccinimide were added with vigorous stirring. After reacting for 16 hours, triethylamine (1.5 equiv.) was added and stirring continued for an additional hour. An additional 100 cm^3 of dichloromethane were added and the organic phase was washed with $KHSO_4$ (1 mol dm^{-3}), $NaHCO_3$ (1 mol dm^{-3}) and brine (3 times 30 cm^3 each). After drying over $MgSO_4$ the extract was taken to dryness at reduced pressure. When necessary the diastereomers obtained were separated by column chromatography using solvent gradient from neat petroleum ether to 40% diethyl ether/petroleum ether to afford the corresponding methyl ester of the *N*-protected, β-bromo-α,β-dehydroamino acid.

Synthesis of Nosyl-*Z*-ΔAbu(β-Br)-OMe (compound *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 (from ethyl acetate/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60 (s, 3H, γCH_3), 3.80 (s, 3H, CH_3 OMe), 6.46 (s, 1H, NH), 8.07 (d, *J* = 8.7 Hz, 2H, ArH), 8.38 (d, *J* = 8.7 Hz, 2H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): 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. $C_{11}H_{11}N_2O_6SBr$ (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.

Synthesis of Z(NO_2)-*Z*-ΔPhe(β-Br)-OMe (compound *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 (from ethyl acetate/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.51 (br. s, 3H, CH_3 OMe), 5.29 [s, 2H, CH_2 Z(NO_2)], 6.80 (br. s, 1H NH), 7.35 (s, 5H, ArH), 7.55 (d, *J* = 8.4 Hz, 2H, ArH), 8.25 (d, *J* = 8.4 Hz, 2H, 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. $C_{18}H_{15}N_2O_6Br$ (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.

Synthesis of Z-*Z*-ΔPhe(β-Br)-OMe (compound *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 (from diethyl ether/*n*-hexane).^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.53 (br. s, 3H, CH_3 OMe), 5.19 (s, 2H, CH_2 Z), 6.76 (br. s, 1H, NH), 7.33-7.39 (m, 10H, 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. $C_{18}H_{16}NO_4Br$ (390.23): calcd. C 55.40, H 4.13, N 3.59; found C 55.60, H 4.15, N 3.62.

Synthesis of Nosyl-*Z*-ΔPhe(β-Br)-OMe (compound *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 (from ethyl acetate/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.58 (s, 3H, CH_3 OMe), 6.74 (s, 1H, NH), 7.24-7.26 (m, 2H, ArH), 7.33-7.38 (m, 3H, ArH), 8.16 (d, *J* = 8.7 Hz, 2H, ArH Nosyl), 8.43 (d, *J* = 8.7 Hz, 2H, 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. $C_{16}H_{13}N_2O_6SBr$ (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.

Synthesis of the Methyl Esters of *N*-Protected, *N*-Ethyl-β,β-dibromodehydroalanines and *N*-Protected, *N*-Ethyl-β-substituted β-bromodehydroamino Acids

General procedure: The methyl ester of the *N*-protected, β-bromodehydroamino acid was dissolved in dry dichloromethane (0.05 mol dm^{-3}) followed by addition 3.5 equiv. of *N*,*N*-diisopropylethylamine and 2.5 equiv. triethyloxonium tetrafluoroborate under inert atmosphere. The reaction mixture was stirred at room temperature for 30 min. In cases where TLC still indicated some starting material, 1 equiv. of both *N*,*N*-diisopropylethylamine and triethyloxonium tetrafluoroborate were added and stirring continued for another hour. Then dichloromethane was added (50 cm^3) and the organic phase was washed with $KHSO_4$ (1 mol dm^{-3}), $NaHCO_3$ (1 mol dm^{-3}) and brine (3 times 30 cm^3 each) and dried over $MgSO_4$. Removal of the solvent generally afforded and oil that was subject to column chromatography using diethyl ether/petroleum ether as eluent or crystallized.

Synthesis of Z(NO_2)-*N*(Et)-ΔAla(β,β-Br)-OMe (compound 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 (from diethyl ether/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 3.57 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 3.75 (s, 3H, CH_3 OMe), 5.25 [s, 2H, CH_2 Z(NO_2)], 7.48 (d, *J* = 8.8 Hz, 2H, ArH), 8.23 (d, *J* = 8.8 Hz, 2H, 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. $C_{14}H_{14}N_2O_6Br_2$ (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.

Synthesis of Z-*N*(Et)-ΔAla(β,β-Br)-OMe (compound 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, 3H, CH_2CH_3), 3.57 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 3.62 (s, 3H, CH_3 OMe), 5.16 (s, 2H, CH_2 Z), 7.31-7.38 (m, 5H, 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.

Synthesis of Boc-*N*(Et)-ΔAla(β,β-Br)-OMe (compound 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 0.176 g of a colorless oil consisting of a mixture of product and reactant in a 48/52 ratio. Column chromatography using diethyl ether/petroleum ether as eluent 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, 3H, CH_2CH_3), 1.42 (s, 9H, CH_3 Boc), 3.50 (q, 2H, *J* = 7.2 Hz, CH_2CH_3), 3.80 (s, 3H, 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 [O*C*(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.

Synthesis of 2-Fur-*N*(Et)-ΔAla(β,β-Br)-OMe (compound 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 0.185 g of a yellow oil consisting of a mixture of product and reactant in a 82/18 ratio. Column chromatography using diethyl ether/petroleum ether as eluent afforded **7d** (0.152 g, 80%) as a colorless oil. M.p. 74.0-75.0 °C (from diethyl ether/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 3.69 (br. q, 2H, CH_2CH_3), 3.78 (s, 3H, CH_3 OMe), 6.45 (dd, *J* = 1.8 Hz, *J* = 3.3 Hz, 1H, ArH), 7.06 (d, *J* = 3.3 Hz, 1H, ArH), 7.46 (s, 1H, 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. $C_{11}H_{11}NO_4Br_2$ (381.02): calcd. C 34.67, H 2.91, N 3.68; found C 34.73, H 2.94, N 3.72.

Synthesis of Bz(4-OMe)-*N*(Et)-ΔAla(β,β-Br)-OMe (compound 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 0.093 g of a colorless oil consisting of a mixture of product and reactant in a 64/36 ratio. Column chromatography using diethyl ether/petroleum ether as

eluent afforded **7e** (0.060 g, 47%) as a colorless oil. M.p. 68.0-70.0 °C (from diethyl ether/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 3.59 (br. s, 2H, CH_2CH_3), 3.78 (s, 3H, CH_3 OMe), 3.83 (s, 3H, CH_3 OMe), 6.86 (d, *J* = 8.8 Hz, 2H, ArH), 7.56 (d, *J* = 8.8 Hz, 2H, 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. $C_{14}H_{15}NO_4Br_2$ (421.08): calcd. C 39.93, H 3.59, N 3.33; found C 40.38, H 3.86, N 3.33.

Synthesis of Z(NO_2)-*N*(Et)-*E*-ΔAbu(β-Br)-OMe (compound *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 0.119 g of a colorless oil consisting of a mixture of product and reactant in a 80/20 ratio. Column chromatography using diethyl ether/petroleum ether as eluent afforded *E*-**8a** (0.095 g, 75%) as a white solid. M.p. 59.0-60.0 °C (from diethyl ether/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 2.42 (s, 3H, γCH_3), 3.49 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 3.73 (s, 3H, CH_3 OMe), 5.23 [br. s, 2H, CH_2 Z(NO_2)], 7.46 (d, *J* = 8.7 Hz, 2H, ArH), 8.22 (d, *J* = 8.7 Hz, 2H, 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. $C_{15}H_{17}N_2O_6Br$ (401.21): calcd. C 44.90, H 4.27, N 6.98; found C 45.23, H 4.40, N 7.07.

Synthesis of Z(NO_2)-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe (compound *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 0.178 g of a yellowish oil consisting of a mixture of product and reactant in a 37/63 product/reactant ratio. Column chromatography using diethyl ether/petroleum ether as eluent afforded *Z*-**8a** (0.066 g, 33%) as a colorless oil. M.p. 73.0-73.5 °C (from diethyl ether/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 2.85 (s, 3H, γCH_3), 3.55 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 3.71 (s, 3H, CH_3 OMe), 5.21 [s, 2H, CH_2 Z(NO_2)], 7.45 (d, *J* = 8.7 Hz, 2H, ArH), 8.19 (d, *J* = 8.7 Hz, 2H, 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. $C_{15}H_{17}N_2O_6Br$ (401.21): calcd. C 44.90, H 4.27, N 6.98; found C 44.89, H 4.40, N 7.03.

Synthesis of Z-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe (compound *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 0.322 g of a colorless oil consisting of a mixture of product and reactant in a 43/57 ratio. Column chromatography using diethyl ether/petroleum ether as eluent 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, 3H, CH_2CH_3), 2.84 (s, 3H, γCH_3), 3.52 (q, *J* = 7.2 Hz, 2H, CH_2CH_3), 3.59 (s, 3H, CH_3 OMe), 5.22 (s, 2H, CH_2 Z), 7.28-7.39 (m, 5H, 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.

Synthesis of Nosyl-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe (compound *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 (from diethyl ether/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 2.85 (s, 3H, γCH_3), 3.58 (br m, 2H, CH_2CH_3), 3.67 (s, 3H, CH_3 OMe), 8.04 (d, *J* = 8.7 Hz, 2H, ArH), 8.35 (d, *J* = 8.7 Hz, 2H, 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. $C_{13}H_{15}N_2O_6SBr$ (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.

Synthesis of Tos-*N*(Et)-*Z*-ΔAbu(β-Br)-OMe (compound *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 (from diethyl ether/*n*-hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 2.43 (s, 3H, CH_3 Tos), 2.82 (s, 3H, γCH_3), 3.46 (br m, 2H, CH_2CH_3), 3.60 (s, 3H, CH_3 OMe), 7.29 (d, *J* = 8.8 Hz, 2H, ArH), 7.73 (d, *J* = 8.8 Hz, 2H, 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. $C_{14}H_{18}NO_4SBr$ (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.

Synthesis of Z(NO_2)-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe (compound *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 0.076 g of a colorless oil consisting of a mixture of product and reactant in a 45/55 ratio. Column chromatography using diethyl ether/petroleum ether as eluent 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, 3H, CH_2CH_3), 3.42 (s, 3H, CH_3 OMe), 3.71 (br m, 2H, CH_2CH_3), 5.28 [s, 2H, CH_2 Z(NO_2)], 7.30-7.40 (m, 5H, ArH), 7.50 (d, *J* = 8.4 Hz, 2H, ArH), 8.21 (d, *J* = 8.4 Hz, 2H, 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. $C_{20}H_{19}N_2O_6Br$ (463.28): calcd. C 51.85, H 4.13, N 6.05; found C 51.91, H 4.15, N 6.12.

Synthesis of Z-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe (compound *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 0.135 g of a colorless oil consisting of a mixture of product and reactant in a 38/62 ratio. Column chromatography using diethyl ether/petroleum ether as eluent 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, 3H, CH_2CH_3), 3.33 (s, 3H, CH_3 OMe), 3.72 (q, *J* = 7.5 Hz, 2H, CH_2CH_3), 5.19 (s, 2H, CH_2 Z), 7.30-7.37 (m, 10H, 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 (compound *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 0.175 g of a colorless oil consisting of a mixture of product and reactant in a 15/85 ratio that could not be separated.

Synthesis of Nosyl-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe (compound *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 (from ethyl acetate/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 3.41 (s, 3H, CH_3 OMe), 3.66 (br m, 2H, CH_2CH_3), 7.31-7.41 (m, 5H, ArH), 8.14 (d, *J* = 8.7 Hz, 2H, ArH Nosyl), 8.39 (d, *J* = 8.7 Hz, 2H, 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. $C_{18}H_{17}N_2O_6SBr$ (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.

Synthesis of Tos-*N*(Et)-*Z*-ΔPhe(β-Br)-OMe (compound *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 (from diethyl ether/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 2.45 (s, 3H, CH_3 Tos), 3.39 (s, 3H, CH_3 OMe), 3.62 (br q, *J* = 7.2 Hz, 2H, CH_2CH_3), 7.31-7.38 (m, 7H, ArH), 7.83 (d, *J* = 8.4 Hz, 2H, 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. $C_{19}H_{20}NO_4SBr$ (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 Phenyl Boronic 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}), 1.5 equiv. of phenyl boronic acid, $PdCl_2dppf{\cdot}CH_2Cl_2$ (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 cm^3). The organic layer was washed with water and brine (2 times 30 cm^3 each), dried with $MgSO_4$, and the solvent was removed. The residue was submitted to column chromatography using diethyl ether/petroleum ether as eluent.

Synthesis of Z(NO_2)-*N*(Et)-ΔPhe(β-C_6H_5)-OMe (compound 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 3.0 equiv. of phenyl boronic acid as reactant to afford **10a** (0.075 g, 81%) as a colorless oil. M.p. 92.0-93.0 °C (from diethyl ether/*n*-hexane). ^{1}H NMR (300 MHz, DMSO): δ = 1.00 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 3.02 (br. m, 2H, CH_2CH_3), 3.32 (s, 3H, CH_3 OMe), 5.26 [s, 2H, CH_2 Z(NO_2)], 7.06-7.11 (m, 4H, ArH), 7.34-7.37 (m, 6H, ArH), 7.58 (d, *J* = 8.7 Hz, 2H, ArH), 8.22 (d, *J* = 8.7 Hz, 2H, 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.

Synthesis of Z-*N*(Et)-ΔAbu(β-C_6H_5)-OMe (compound *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 cloudless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 2.46 (s, 3H, γCH_3), 3.50 (br. s, 2H, CH_2CH_3), 3.53 (s, 3H, CH_3 OMe), 5.18 (s, 2H, CH_2 Z), 7.28-7.39 (m, 10H, 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.

Synthesis of Z(NO_2)-*N*(Et)-ΔPhe(β-C_6H_5)-OMe (compound 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%).

Synthesis of Nosyl-*N*(Et)-ΔPhe(β-C_6H_5)-OMe (compound 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 (from ethyl acetate/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 3.00 (br m, 2H, CH_2CH_3), 3.40 (s, 3H, CH_3 OMe), 7.12-7.16 (m, 2H, ArH), 7.30-7.37 (m, 8H, ArH), 8.05 (d, *J* = 9.0 Hz, 2H, ArH Nosyl), 8.34 (d, *J* = 9.0 Hz, 2H, 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

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

[1] a) T. Goodman, L. Moroder in *Synthesis of Peptides and Peptidomimetics*, Houben-Weyl, Thieme, Stuttgart, Germany, **2003**, vol. E22c, pp. 215–271. b) S. Kotta, *Acc. Chem. Res.* **2003**, *36*, 342-351. c) I. Rilatt, L. Caggiano, R.F.W Jackson, *Synlett*, **2005**, 2701-2719.

[2] L. Aurelio, R. T. C. Brownlee, A. B. Hughes, *Chem. Rev.* **2004**, *104*, 5823–5846, and references cited therein.

[3] R. M. Wenger, *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 77-85.

[4] a) K. S. Chu, G. R. Negrete, J. P. Konopelski, *J. Org. Chem.* **1991**, *56*, 5196-5202. b) D. L. Boger, S. Teramoto, H. Cai, *Bioorg. Med. Chem.* **1997**, *5*, 1577-1589. c) D. L. Boger, D. Yohannes, *J. Org. Chem.* **1988**, *53*, 487-499.

[5] a) H. Schedel, K. Burger, *Monatsh. Chem.* **2000**, *131*, 1011-1018. b) T. Ruckle, B. Dubray, F. Hubler, M. J. Mutter, *Pept. Sci.* **1999**, *5*, 56-58.

[6] F. M. F. Chen, N. L. Benoiton, *Can. J. Chem.* **1977**, *55*, 1433-1435.

[7] J. R. McDermott, N. L. Benoiton, *Can. J. Chem.* **1973**, *51*, 1915-1915.

[8] M. Stodulski, J. Mlynarski, *Tetrahedron: Asymmetry* **2008**, *19*, 970-975.

[9] D. Papaioannou, C. Athanassopoulos, V. Magafa, N. Karamanos, G. Stavropoulos, A. Napoli, G. Sindona, D. W. Aksnes, G. W. Francis, *Acta Chem. Scand*. **1994**, *48*, 324–333.

[10] C. Athanassopoulos, H. L. S. Maia, L. S. Monteiro, D. Papaioannou *Peptides 1996: Proceedings of the 24th European Peptide Symposium*, (Eds.: R. Ramage, R. Epton), Mayflower Scientific Ltd., Kingswinford, U. K., **1998**, pp. 219-220.

[11] I. Chataigner, C. Panel, H. Gérard, S. R. Piettre, *Chem. Commun.*, **2007**, 3288-3290.

[12] E. L. Belsito, R. De Marco, M. L. Di Gioia, A. Liguori, F. Perri, M. C. Viscomi, *Eur. J. Org. Chem*. **2010**, 4245-4252.

[13] M. Aydin, N. Lucht, W. A. Koenig, R. Lupp, G. Jung, G. Winkelmann, *Liebigs Ann. Chem.* **1985**, 2285-2300.

[14] a) M. T. Hamann, P. J. Scheuer, *J. Am. Chem. Soc* **1993**, *115*, 5825-5826. b) G. Goetz, Y. Nakao, P. J. Scheuer, *J. Nat. Prod*. **1997**, *60*, 562-567.

[15] a) D. E. Palmer, C. Pattaroni, K. Nunami, R. K. Chadha, M. Goodman, T. Wakamiyia, K. Fukase, S. Horimoto, M. Kitazawa, H. Fujita, A. Kubo, T. Shiba, *J. Am. Chem. Soc*. **1992**, *114*, 5634-5642. b) G. Jung, *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1051-1068. c) C. Chatterjee, M. Paul, L. Xie, W. A. Van Der Donk, *Chem. Rev.* **2005**, *105*, 633-684.

[16] a) U. Schmidt, J. Hausler, E. Olher, H. Poisel, *Fortschr. Chem. Org. Naturst.* **1977**, *37*, 251-300. b) K. Noda, Y. Shimohigashi, N. Izumiya, *The Peptides, Analysis, Synthesis, Biology*; Academic Press: New York, 1983, Vol. 5, pp. 286. c) U. Schmidt, A. Lieberknecht, J. Wild, *Synthesis* **1988**, 159-172. d) S. Nomoto, A. Sano, T. Shiba, *Tetrahedron Lett.* **1979**, *20*, 521-522. e) R. H. Mazur, D. R. Pilipauskas, *Peptides 1982*; (Ed.: W. de Gruyter), Berlin, **1983**, pp. 319. f) C. Bonauer, T. Walenzyk, B. König, *Synthesis*, **2006**, *1*, 1-20.

[17] P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, J. Sacramento, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3697-3703.

[18] P. M. T. Ferreira, L. S. Monteiro, G. Pereira, L. Silva, L. Ribeiro, J. Sacramento, *Eur. J. Org. Chem*. **2007**, 5934-5949.

[19] L. S. Monteiro, J. Kołomańska, A. C. Suarez, *Eur. J. Org. Chem*. **2010**, 6731-6735.

[20] a) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.*, **2005**, *44*, 4442-4489. b) S. Kotta, K. Lahiri, *Eur. J. Org. Chem.* **2007**, 1221-1236. c) N. O. Silva, A. S. Abreu, P. M. T. Ferreira, M. J. R. P. Queiroz, *Tetrahedron Lett.* **2003**, *44*, 3377-3379. d) A. S. Abreu, P. M. T. Ferreira, L. S. Monteiro, M. J. R. P. Queiroz, I. C. F. R. Ferreira, R. C. Calhelha, L. M. Estevinho, *Tetrahedron* **2004**, *60*, 11821-11828. e) A. S. Abreu, E. M. S. Castanheira, Ferreira, P. M. T. Ferreira, M. J. R. P. Queiroz, *Tetrahedron* **2007**, *63*, 2215-2222. f) M. J. R. P. Queiroz, A. S. Abreu, R. C. Calhelha, M. S. D. Carvalho, P. M. T. Ferreira, *Tetrahedron*, **2008**, *64*, 5139-5146.

[21] P. M. T. Ferreira, L. S. Monteiro, G. Pereira, *Eur. J. Org. Chem.* **2008**, 4676–4683.

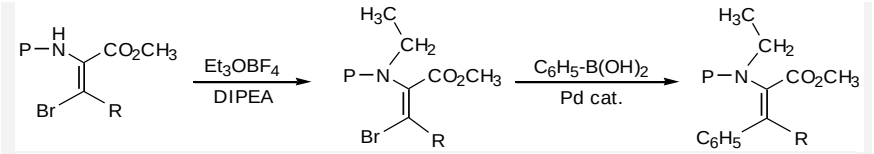
[22] P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, J. Sacramento, *J Chem. Soc. Perkin Trans 1* **2001**, 3167–3173.

[23] P. M. T. Ferreira, L. S. Monteiro, G. Pereira, *Amino Acids* **2010**, *39*, 499–513.

[24] N. O. Silva, A. S. Abreu, P. M. T. Ferreira, L. S. Monteiro, M. J. R. P. Queiroz, *Eur. J. Org. Chem.* **2002**, 2524–2528.

Received: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))

Layout 2:



N-Ethylation of the methyl esters of β,β-dibromo and β-bromo, β-substituted dehydroamino acids protected with standard amine protecting groups is reported. The procedure allows the synthesis of *N*-ethyl, β,β-dibromo and *N*-ethyl, β-bromo, β-substituted dehydroamino acid derivatives in fair to high yields. These substrates can be applied in cross coupling reactions, constituting valuable synthons for the synthesis of *N*-ethyl, β,β-disubstituted dehydroamino acids.

Luís S. Monteiro*, Juliana J. Andrade, Ana C. Suárez ... Page No. – Page No.

Synthesis of new *N*-ethyl dehydroamino acid derivatives: *N*-ethyl β,β-dibromo, *N*-ethyl β-bromo β-substituted, *N*-ethyl β,β-disubstituted *N*-protected dehydroamino acid methyl esters

Keywords: Amino acids / Alkylation / *N*-Ethyl dehydroamino acids / *N*-Ethyl β-bromo dehydroamino acids / Suzuki cross-coupling