#### ORIGINAL ARTICLE

### High yielding synthesis of N-ethyl dehydroamino acids

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Abstract Recently we reported the use of a sequence of alkylation and dehydration methodologies to obtain *N*-ethyl- $\alpha$ ,  $\beta$ -dehydroamino acid derivatives. The application of this N-alkylation procedure to several methyl esters of  $\beta$ , $\beta$ -dibromo and  $\beta$ -bromo,  $\beta$ -substituted dehydroamino acids protected with standard amine protecting groups was subsequently reported. The corresponding N-ethyl,  $\beta$ -bromo dehydroamino acid derivatives were obtained in fair to high yields and some were used as substrates in Suzuki cross-coupling reactions to give N-ethyl,  $\beta$ , $\beta$ -disubstituted dehydroalanine derivatives. Herein, we further explore N-ethylation of  $\beta$ -halo dehydroamino acid derivatives using triethyloxonium tetrafluoroborate as alkylating agent, but substituting N,N-diisopropylethylamine for potassium tert-butoxide as auxiliary base. In these conditions, for all  $\beta$ -halo dehydroamino acid derivatives, reactions were complete and the N-ethylated derivative could be isolated in high yield. This method was also applied for N-ethylation of non-halogenated dehydroamino acids. Again, with all compounds the reactions were complete and the N-ethyl dehydroamino acid derivatives could be isolated in high yields. Some of these N-ethyl dehydroamino acid methyl ester derivatives were converted in high yields to their corresponding acids and coupled to an amino acid methyl ester to give N-ethyl dehydrodipeptide derivatives in good yields. Thus, this method constitutes a general procedure for high yielding synthesis of N-ethylated dehydroamino acids, which can be further applied in peptide synthesis.

**Keywords** Amino acids  $\cdot$  Nonnatural amino acids  $\cdot$  Alkylation  $\cdot$  *N*-ethyl dehydroamino acids  $\cdot$  Protecting groups

#### Introduction

Non-proteinogenic amino acids are an important class of organic compounds with a large application spectrum in medicinal chemistry, since they 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 (Gilon et al. 2003; Kotha 2003; Rilatt et al. 2005). N-Alkylamino acids are constituents of various important naturally occurring peptides and proteins (Gilon et al. 2003; Kotha 2003; Rilatt et al. 2005). Several N-alkylated peptides show antibiotic, anticancer or antiviral activity (Wenger 1985). 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 (Aurelio et al. 2004). Dehydroamino acids are outstanding compounds as they are key intermediates in amino acid and peptide synthesis, having been found in naturally occurring peptides of fungal and microbial origin (Aydin et al. 1985) and from marine organisms (Hamann and Scheuer 1993; Goetz et al. 1997), 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) (Palmer et al. 1992; Jung 1991; Chatterjee et al. 2005).

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Many methods of synthesis of N-alkylamino acids have been developed, most of them are N-methylation (Aurelio et al. 2004). Recently, Belsito et al. (2010) proposed the ethylation of several 4-nitrobenzenesulfonyl (Nosyl) protected amino acids using triethyloxonium tetrafluoroborate (Et<sub>3</sub>OBF<sub>4</sub>) as alkylating agent and N,N-diisopropylethylamine (DIPEA) as a base to give N-ethylamino acid derivatives in high yields. Subsequently, we reported the use of a combination of this alkylation procedure and dehydration methodologies previously developed by us (Ferreira et al. 1999, 2007) to obtain new non-proteinogenic amino acids namely, N-(4-nitrophenylsulfonyl), *N*-ethyl- $\alpha$ , $\beta$ -dehydroamino acids (Monteiro et al. 2010). Thus, it was possible to obtain for the first time, new nonnatural amino acids which incorporate both the N-ethyl and  $\alpha,\beta$ -dehydro moieties.

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  $\beta$ -carbon atom. Thus, we tested the triethyloxonium tetrafluoroborate/N,N-diisopropylethylamine N-alkylation procedure with several methyl esters of  $\beta$ , $\beta$ -dibromo and  $\beta$ -bromo,  $\beta$ -substituted dehydroamino acids protected with standard amine protecting groups such as tert-butyloxycarbonyl (Boc), benzyloxycarbonyl (Z) and 4-nitrobenzyloxycarbonyl [Z(NO<sub>2</sub>)] as well as acyl and sulfonyl amine protecting groups (Monteiro et al. 2011). Depending on the nature of the halogenated dehydroamino acid and of the protecting group, variable ratios of product to reactant were obtained. These ranged from total conversion to product  $[\beta,\beta$ -dibromo, dehydroalanine derivatives protected with  $Z(NO_2)$  and Z,  $\beta$ -bromo dehydroaminobutyric acid and dehydrophenylalanine derivatives protected with Nosyl and Tos] to complete absence of reaction [the methyl ester of N-(*tert*-butyloxycarbonyl),  $\beta$ -bromo dehydroaminobutyric acid]. Some of these N-ethylated dehydroamino acid derivatives were used as substrates in cross-coupling reactions to give the methyl esters of N-protected, N-ethyl,  $\beta$ , $\beta$ -disubstituted dehydroalanines.

Herein, we further explore N-ethylation of  $\beta$ -halo dehydroamino acid derivatives substituting DIPEA for potassium *tert*-butoxide as auxiliary base. Contrary to the reactions carried out using DIPEA in which no reaction or incomplete reactions were observed, with the use of *tert*-butoxide, all reactions were complete giving *N*-ethyl dehydroamino acid derivatives in high yields. The method is further applied to non-halogenated dehydroamino acid derivatives.

#### Materials and methods

Melting points were determined with a Gallenkamp apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded with a Varian Unity Plus spectrometer at 300 and 75.4 MHz, respectively, or with a Bruker Avance II<sup>+</sup> operating at 400 and 100.6 MHz, respectively. <sup>1</sup>H-<sup>1</sup>H spinspin decoupling, DEPT ( $\theta$  45°), HMQC and HMBC were used to attribute some signals. The stereochemistry of the dehydroamino acids derivatives was determined by NOE difference experiments. 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). Petroleum ether refers to fractions with the boiling range 40-60°C. Solvents were used without purification except for acetonitrile and dichloromethane which were dried according to standard procedures.

## Synthesis of the methyl esters of *N*-protected $\beta$ -hydroxyamino acids

Synthesis of compounds  $Z(NO_2)$ -L-Ser-OMe (Ferreira et al. 1999), Z-L-Ser-OMe (Ferreira et al. 1999), Boc-L-Ser-OMe (Ferreira et al. 1999), Z(NO\_2)-L-Thr-OMe (Ferreira et al. 1999), Z-L-Thr-OMe (Ferreira et al. 1999), Boc-L-Thr-OMe (Ferreira et al. 1999), Tos-L-Thr-OMe (Ferreira et al. 1999), Z(NO\_2)-D,L-Phe( $\beta$ -OH)-OMe (Ferreira et al. 1999), Z-D,L-Phe( $\beta$ -OH)-OMe (Monteiro et al. 2011), Boc-D,L-Phe( $\beta$ -OH)-OMe (Ferreira et al. 2007).

The synthesis of these compounds was described in the references given above.

Synthesis of the methyl esters of *N*-protected dehydroamino acids

Synthesis of compounds  $Z(NO_2)$ - $\Delta$ Ala-OMe (1a) (Ferreira et al. 2007), Z- $\Delta$ Ala-OMe (1b) (Bertj et al. 1992), Boc- $\Delta$ Ala-OMe (1c) (Ferreira et al. 1999), Z(NO<sub>2</sub>)-Z- $\Delta$ Abu-OMe (Z-2a) (Ferreira et al. 1999), Z–Z- $\Delta$ Abu-OMe (Z-2b) (Ferreira et al. 1999), Boc-Z- $\Delta$ Abu-OMe (Z-2c) (Ferreira et al. 1999), Tos-Z- $\Delta$ Abu-OMe (Z-2d) (Ferreira et al. 2007), Z(NO<sub>2</sub>)-Z- $\Delta$ Phe-OMe (Z-3a) (Monteiro et al. 2011), Z-Z- $\Delta$ Phe-OMe (Z-3b) (Monteiro et al. 2011), Boc-Z- $\Delta$ Phe-OMe (Z-3c) (Ferreira et al. 2007), Tos-Z- $\Delta$ Phe-OMe (Z-3c) (Ferreira et al. 2007).

The synthesis of these compounds was described in the references given above.

Synthesis of the methyl esters of *N*-protected  $\beta$ -halo dehydroamino acids

Synthesis of compounds Boc- $\Delta$ Ala( $\beta$ , $\beta$ -Br)-OMe (4c) (Silva et al. 2002), Z(NO<sub>2</sub>)-*E*- $\Delta$ Abu( $\beta$ -Br)-OMe (E-5a)

(Ferreira et al. 2007), Z(NO<sub>2</sub>)-Z- $\Delta$ Abu( $\beta$ -Br)-OMe (Z-**5a**) (Ferreira et al. 2007), Z-Z- $\Delta$ Abu-( $\beta$ -Br)OMe (Z-**5b**) (Ferreira et al. 2007), Boc-*E*- $\Delta$ Abu( $\beta$ -Br)-OMe (Z-**5c**) (Silva et al. 2002), Boc-*Z*- $\Delta$ Abu( $\beta$ -Br)-OMe (Z-**5c**) (Silva et al. 2002), Z(NO<sub>2</sub>)-*Z*- $\Delta$ Phe( $\beta$ -Br)-OMe (Z-**6a**) (Monteiro et al. 2011), Z-*Z*- $\Delta$ Phe( $\beta$ -Br)-OMe (Z-**6b**) (Monteiro et al. 2011), Boc-*Z*- $\Delta$ Phe( $\beta$ -Br)-OMe (Z-**6c**) (Abreu et al. 2004), Boc-*Z*- $\Delta$ Phe( $\beta$ -I)-OMe (Z-**7c**) (Queiroz et al. 2008).

The synthesis of these compounds was described in the references given above.

Synthesis of  $Z(NO_2)$ -Z- $\Delta Phe(\beta-I)$ -OMe (Z-7a) Z(NO<sub>2</sub>)-Z- $\Delta$ Phe-OMe (Z-3a) (1.069 g, 3.000 mmol) was dissolved in dichloromethane (0.1 mol dm<sup>-3</sup>) and 1.2 equiv. of *N*-iodosuccinimide was added with vigorous stirring. After reacting for 16 h, triethylamine (1.5 equiv.) was added and stirring continued for an additional hour. An additional 100 cm<sup>3</sup> of dichloromethane was added and the organic phase was washed with KHSO<sub>4</sub> (1 mol dm<sup>-3</sup>), NaHCO<sub>3</sub> (1 mol dm<sup>-3</sup>) and brine (3 times 30 cm<sup>3</sup> each). After drying over MgSO<sub>4</sub> the extract was taken to dryness at reduced pressure to afford Z-7a (1.230 g, 85%) as a light vellow solid. M.p. 135.0-136.0°C (from ethyl acetate/n-hexane). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 3.46$  (br. s, 3H, CH<sub>3</sub> OMe), 5.28 [s, 2H, CH<sub>2</sub> Z(NO<sub>2</sub>)], 6.69 (br. s, 1H NH), 7.27–7.35 (m, 5H, ArH), 7.54 (d, J = 8.4 Hz, 2H, ArH), 8.24 (d, J = 8.4 Hz, 2H, ArH)ppm. <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>):  $\delta = 52.53$  (OCH<sub>3</sub>), 66.33 [CH<sub>2</sub> Z(NO<sub>2</sub>)], 95.39 (C), 123.79 (CH), 128.23 (CH), 128.37 (CH), 128.61 (CH), 129.01 (CH), 132.95 (C), 140.34 (C), 142.53 (C), 147.77 (C), 152.69 (C=O), 163.93 (C=O) ppm. C<sub>18</sub>H<sub>15</sub>N<sub>2</sub>O<sub>6</sub>I (482.23): calcd. C 44.83, H 3.14, N 5.81; found C 44.70, H 3.15, N 6.22.

Synthesis of the methyl esters of *N*-(*tert*-butyloxycarbonyl), *N*-ethyl- $\beta$ ,  $\beta$ -dibromodehydroalanine and *N*-protected, *N*-ethyl,  $\beta$ -substituted,  $\beta$ -halodehydroamino acids

General procedure for the synthesis of the methyl esters of N-(tert-butyloxycarbonyl), N-ethyl- $\beta$ ,  $\beta$ -dibromodehydroalanine and N-protected, N-ethyl,  $\beta$ -substituted,  $\beta$ -halodehydroamino acids

The methyl ester of the *N*-protected,  $\beta$ -halodehydroamino acid was dissolved in anhydrous dichloromethane (0.05 mol dm<sup>-3</sup>) followed by addition of 3.5 equiv. of potassium *tert*-butoxide and 2.5 equiv. of triethyloxonium tetrafluoroborate, under inert atmosphere. The reaction mixture was stirred at room temperature for 30 min. Then dichloromethane was added (50 cm<sup>3</sup>) and the organic phase was washed with KHSO<sub>4</sub> (1 mol dm<sup>-3</sup>), NaHCO<sub>3</sub> (1 mol dm<sup>-3</sup>) and brine (3 times 20 cm<sup>3</sup> each), dried over MgSO<sub>4</sub> and the solvent evaporated at reduced pressure. Synthesis of  $Boc-N(Et)-\Delta Ala(\beta,\beta-Br)-OMe$  (8c) The general procedure described above was followed using Boc- $\Delta Ala(\beta,\beta-Br)$ -OMe (4c) (0.066 g, 0.174 mmol) as reactant to afford 8c (Monteiro et al. 2011) (0.066 g, 93%).

Synthesis of  $Z(NO_2)-N(Et)-E-\Delta Abu(\beta-Br)-OM$ , (*E*-9*a*) The general procedure described above was followed using  $Z(NO_2)-E-\Delta Abu(\beta-Br)$ -OMe (*E*-5*a*) (0.065 g, 0.175 mmol) as reactant to afford *E*-9*a* (Monteiro et al. 2011) (0.066 g, 94%).

Synthesis of  $Z(NO_2)-N(Et)-Z-\Delta Abu(\beta-Br)-OMe$  (Z-9a) The general procedure described above was followed using  $Z(NO_2)-Z-\Delta Abu(\beta-Br)-OMe$  (Z-5a) (0.039 g, 0.105 mmol) as reactant to afford Z-9a (Monteiro et al. 2011) (0.035 g, 82%).

Synthesis of Z-N(Et)-Z- $\Delta$ Abu( $\beta$ -Br)-OMe (Z-9b) The general procedure described above was followed using Z-Z- $\Delta$ Abu( $\beta$ -Br)-OMe (Z-5b) (0.033 g, 0.100 mmol) as reactant to afford Z-9b (Monteiro et al. 2011) (0.031 g, 86%).

Synthesis of Boc-N(*E*t)-*E*- $\Delta$ Abu( $\beta$ -Br)-OMe (*E*-9c) The general procedure described above was followed using Boc-*E*- $\Delta$ Abu( $\beta$ -Br)-OMe (*E*-5c) (0.221 g, 0.750 mmol) as reactant to afford *E*-9c (0.215 g, 89%) as a colorless oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.00-1.21$  (m, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.39–1.48 (m, 9H, CH<sub>3</sub> Boc), 2.40 (s, 3H,  $\gamma$ CH<sub>3</sub>), 3.40 (br. q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.75, 3.77 (2s, 3H, CH<sub>3</sub> OMe) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 12.98$ , 13.47 (CH<sub>3</sub>), 26.80 ( $\gamma$ CH<sub>3</sub>), 28.22 [C(CH<sub>3</sub>)<sub>3</sub>], 43.36 (CH<sub>2</sub>), 52.01, 52.78 (OCH<sub>3</sub>), 80.16, 80.72 [OC(CH<sub>3</sub>)<sub>3</sub>], 130.40 (C), 130.53 (C), 153.78 (C=O), 164.49 (C=O) ppm. m/z (HRESI-MS) 344.04692, ([M + Na]<sup>+</sup>, C<sub>12</sub>H<sub>20</sub>NNaO<sub>4</sub>Br, requires 344.04734).

*Synthesis of Boc-N(Et)-Z-*Δ*Abu*(β-*Br*)-*OMe* (*Z*-**9***c*) The general procedure described above was followed using Boc-*Z*-ΔAbu(β-Br)-OMe (*Z*-**5***c*) (0.147 g, 0.500 mmol) as reactant to afford *Z*-**9***c* (0.137 g, 85%) as a colorless oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta$  = 1.15, 1.17 (2t, *J* = 7.2 Hz, *J* = 7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.39 (s, 9H, CH<sub>3</sub> Boc), 2.79 (s, 3H, γCH<sub>3</sub>), 3.40 (br. q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.75 (s, 3H, CH<sub>3</sub> OMe) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta$  = 13.00, 13.67 (CH<sub>3</sub>), 26.52 (γCH<sub>3</sub>), 27.84, 28.16 [C(*C*H<sub>3</sub>)<sub>3</sub>], 42.99, 44.35 (CH<sub>2</sub>), 52.06, 52.18 (OCH<sub>3</sub>), 80.22, 80.62 [OC(CH<sub>3</sub>)<sub>3</sub>], 130.91, 131.60 (C), 140.10, 140.72 (C), 153.60, 154.15 (C=O), 164.03, 164.23 (C=O) ppm. m/z (HRESI-MS) 344.04679, ([M + Na]<sup>+</sup>, C<sub>12</sub>H<sub>20</sub>NNaO<sub>4</sub>Br, requires 344.04734).

Synthesis of  $Z(NO_2)-N(Et)-Z-\Delta Phe(\beta-Br)-OMe$  (Z-10a) The general procedure described above was followed using Z(NO<sub>2</sub>)-*Z*-ΔPhe( $\beta$ -Br)-OMe (*Z*-**6a**) (0.131 g, 0.300 mmol) as reactant to afford *Z*-**10a** (Monteiro et al. 2011) (0.133 g, 96%).

Synthesis of Z-N(*Et*)-Z- $\Delta$ Phe( $\beta$ -Br)-OMe (Z-10b) The general procedure described above was followed using Z-Z- $\Delta$ Abu( $\beta$ -Br)-OMe (Z-6b) (0.079 g, 0.203 mmol) as reactant to afford Z-10b (Monteiro et al. 2011) (0.069 g, 82%).

Synthesis of Boc-N(Et)-Z-ΔPhe(β-Br)-OMe (Z-10c) 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 Z-10c (0.170 g, 88%) as a light yellow oil. M.p. 59.5–60.0°C (from ethyl acetate/n-hexane). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.28$  (t, J =7.6 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.45, 1.52 (2s, 9H, CH<sub>3</sub> Boc), 3.44, 3.48 (2s, 3H, CH<sub>3</sub> OMe), 3.63 (q, J = 7.5 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 7.32–7.36 (m, 5H, ArH) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta =$  13.29, 13.99 (CH<sub>3</sub>), 28.16 [C(CH<sub>3</sub>)<sub>3</sub>], 42.50, 44.19 (CH<sub>2</sub>), 51.95 (OCH<sub>3</sub>), 80.83, 81.17 [OC(CH<sub>3</sub>)<sub>3</sub>], 128.16 (CH), 128.22 (CH), 129.42 (CH), 132.29 (C), 135.66 (C), 139.18 (C), 153.37 (C=O), 164.66 (C=O) ppm. C<sub>17</sub>H<sub>22</sub>NO<sub>4</sub>Br (384.26): calcd. C 53.14, H 5.77, N 3.65; found C 53.29, H 5.77, N 3.86.

Synthesis of  $Z(NO_2)-N(Et)-Z-\Delta Phe(\beta-I)-OMe$  (Z-11a) The general procedure described above was followed using Z(NO<sub>2</sub>)-Z-ΔPhe( $\beta$ -I)-OMe (Z-7a) (0.121 g, 0.250 mmol) as reactant to afford Z-11a (0.121 g, 95%) as a light yellow solid. M.p. 134.0–135.0°C (from ethyl acetate/n-hexane). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.35$  (t, J =7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 3.40, 3.43 (2s, 3H, CH<sub>3</sub> OMe), 3.68-3.73 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 5.30, 5.35 [2s, 2H, CH<sub>2</sub>  $Z(NO_2)$ ], 7.26–7.34 (m, 5H, ArH), 7.53 (d, J = 8.8 Hz, 2H, ArH), 8.21 (d, J = 8.8 Hz, 2H, ArH) ppm. <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 13.15$  (CH<sub>3</sub>), 44.16, 44.63 (CH<sub>2</sub>), 52.25, 53.68 (OCH<sub>3</sub>), 66.18 [CH<sub>2</sub> Z(NO<sub>2</sub>)], 123.65, 123.79 (CH), 127.53, 127.76 (CH), 127.93, 128.06 (CH), 128.21 (CH), 129.20, 129.36 (CH), 136.20 (C), 142.13 (C), 142.16 (C), 143.71 (C), 147.51 (C), 153.71 (C=O), 162.82 (C=O) ppm. C<sub>20</sub>H<sub>19</sub>N<sub>2</sub>O<sub>6</sub>I (510.28): calcd. C 47.08, H 3.75, N 5.49; found C 46.83, H 4.00, N 5.49.

Synthesis of Boc-N(Et)-Z- $\Delta$ Phe( $\beta$ -I)-OMe (Z-11c) The general procedure described above was followed using Boc-Z- $\Delta$ Phe( $\beta$ -I)-OMe (Z-7c) (0.133 g, 0.328 mmol) as reactant to afford Z-11c (0.134 g, 95%) as a light orange oil. M.p. 69.5–70.0°C (from diethyl ether/*n*-hexane). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.30$  (t, J =7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.48, 1.53 (2s, 9H, CH<sub>3</sub> Boc), 3.46 (s, 3H, CH<sub>3</sub> OMe), 3.61 (q, J = 7.2 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 7.27–7.35 (m, 5H, ArH) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta =$  13.36, 14.08 (CH<sub>3</sub>), 28.24, 28.35 [C(CH<sub>3</sub>)<sub>3</sub>], 42.89, 44.76 (CH<sub>2</sub>), 51.97 (OCH<sub>3</sub>), 81.17  $[OC(CH_3)_3]$ , 117.61 (C), 127.62 (CH), 127.97, 128.10 (CH), 128.94 (CH), 137.16 (C), 142.72 (C), 153.25 (C=O), 163.18 (C=O) ppm.  $C_{17}H_{22}NO_4I$  (431.27): calcd. C 47.34, H 5.14, N 3.25; found C 47.65, H 5.27, N 3.50.

Synthesis of the methyl esters of *N*-protected, *N*-ethyl dehydroamino acids

General procedure for the synthesis of the methyl esters of N-protected, N-ethyl dehydroamino acids

The methyl ester of the *N*-protected dehydroamino acid was dissolved in anhydrous dichloromethane (0.05 mol dm<sup>-3</sup>) followed by addition of 3.5 equiv. of potassium *tert*-butoxide and 2.5 equiv. of triethyloxonium tetrafluoroborate, under inert atmosphere. The reaction mixture was stirred at room temperature for 30 min. Then dichloromethane was added (50 cm<sup>3</sup>) and the organic phase was washed with KHSO<sub>4</sub> (1 mol dm<sup>-3</sup>), NaHCO<sub>3</sub> (1 mol dm<sup>-3</sup>) and brine (3 times 20 cm<sup>3</sup> each), dried over MgSO<sub>4</sub> and the solvent evaporated at reduced pressure.

Synthesis of  $Z(NO_2)-N(Et)-\Delta Ala-OMe$  (12a) The general procedure described above was followed using Z(NO<sub>2</sub>)- $\Delta$ Ala-OMe (1a) (0.211 g, 0.750 mmol) as reactant to afford 12a (0.204 g, 88%) as an orange oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 1.19$  (t, J =6.9 Hz, 3H,  $CH_2CH_3$ ), 3.60 (q, J = 6.9 Hz, 2H,  $CH_2CH_3$ ), 3.72 (s, 3H, CH<sub>3</sub> OMe), 5.21 [s, 2H, CH<sub>2</sub> Z(NO<sub>2</sub>)], 5.63 (s, 1H,  $\beta$ CH<sub>2</sub>), 6.19 (s, 1H,  $\beta$ CH<sub>2</sub>), 7.46 (d, J = 8.4 Hz, 2H, ArH), 8.20 (d, J = 8.4 Hz, 2H, ArH) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta = 13.39$  (CH<sub>3</sub>), 45.02 (CH<sub>2</sub>), 52.44 (OCH<sub>3</sub>), 65.94 [CH<sub>2</sub> Z(NO<sub>2</sub>)], 121.61 ( $\beta$ CH<sub>2</sub>), 123.67 (CH), 127.90 (CH), 138.68 (aC), 143.66 (C), 147.53 (C), 154.19 (C=O), 164.66 (C=O) ppm. C<sub>14</sub>H<sub>16</sub> N<sub>2</sub>NaO<sub>6</sub> (308.29): calcd. C 54.54, H 5.23, N 9.09; found C 54.43, H 5.13, N 9.11. m/z (HRESI-MS) 331.09006,  $([M + Na]^+, C_{14}H_{16}N_2NaO_6, \text{ requires } 331.09060).$ 

Synthesis of Z-N(*Et*)- $\Delta$ Ala-OMe (12b) The general procedure described above was followed using Z- $\Delta$ Ala-OMe (1b) (0.118 g, 0.500 mmol) as reactant to afford 12b (0.119 g, 91%) as a colorless oil that failed to crystallize. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.18$  (t, J = 6.9 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 3.60 (q, J = 6.9 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.63, 3.87 (2s, 3H, CH<sub>3</sub> OMe), 5.13 (s, 2H, CH<sub>2</sub> Z), 5.54 (s, 1H,  $\beta$ CH<sub>2</sub>), 6.09 (s, 1H,  $\beta$ CH<sub>2</sub>), 7.29–7.35 (m, 5H, ArH) ppm. <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 13.43$ , 13.93 (CH<sub>3</sub>), 44.77 (CH<sub>2</sub>), 52.21, 52.94 (OCH<sub>3</sub>), 66.45, 67.39 (CH<sub>2</sub> Z), 120.06 ( $\beta$ CH<sub>2</sub>), 127.85 (CH), 127.96 (CH), 128.36 (CH), 136.18, 136.63 (C), 139.06 ( $\alpha$ C), 154.60 (C=O), 164.90 (C=O) ppm. C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub> (263.29): calcd. C 63.87, H 6.51, N 5.23; found C 63.30, H 6.46, N 5.63. m/z

(HRESI-MS) 286.10537,  $([M + Na]^+, C_{14}H_{17}NNaO_4,$  requires 286.10553).

Synthesis of Boc-N(*E*t)- $\Delta$ Ala-OMe (12c) The general procedure described above was followed using Boc- $\Delta$ Ala-OMe (1c) (0.101 g, 0.500 mmol) as reactant to afford 12c (0.090 g, 79%) as a colorless oil that failed to crystallize. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.17$  (t, J = 7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.43 (s, 9H, CH<sub>3</sub> Boc), 3.54 (br. q, J = 6.9 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.78, 3.88 (2s, 3H, CH<sub>3</sub> OMe), 5.40 (s, 1H,  $\beta$ CH), 5.91, 5.93 (2s, 1H,  $\beta$ CH) ppm. <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 13.47$ , 14.09 (CH<sub>3</sub>), 28.16, 28.38 [C(CH<sub>3</sub>)<sub>3</sub>], 44.32 (CH<sub>2</sub>), 52.15, 52.98 (OCH<sub>3</sub>), 80.67, 80.77 [OC(CH<sub>3</sub>)<sub>3</sub>], 116.96, 117.20 ( $\beta$ CH<sub>2</sub>), 139.94 ( $\alpha$ C), 161.14 (C=O), 165.61 (C=O) ppm. m/z (HRESI-MS) 252.12063, ([M + Na]<sup>+</sup>, C<sub>11</sub>H<sub>19</sub>NNaO<sub>4</sub>, requires 252.12118).

Synthesis of  $Z(NO_2)-N(Et)-Z-\Delta Abu-OMe$  (Z-13a) The general procedure described above was followed using  $Z(NO_2)-Z-\Delta Abu-OMe$  (Z-2a) (0.221 g, 0.750 mmol) as reactant to afford Z-13a (0.217 g, 90%) as an orange oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.14$  (t, J = 7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.81 (d, J = 7.2 Hz, 3H,  $\gamma$ CH<sub>3</sub>), 3.51 (br. q, J = 7.2 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.73, 3.77 (2s, 3H, CH<sub>3</sub> OMe), 5.19, 5.30 [br. s + s, 2H, CH<sub>2</sub> Z(NO<sub>2</sub>)], 7.00, 7.04 (2q, J = 7.2 Hz and J = 7.2 Hz, 1H,  $\beta$ CH), 7.42, 7.55 (2d, J = 8.8 Hz and J = 8.8 Hz, 2H, ArH), 8.20, 8.24 (2d, J = 8.8 Hz and J = 8.8 Hz, 2H, ArH) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 12.94$  (CH<sub>3</sub>), 13.76, 13.91 ( $\gamma$ CH<sub>3</sub>), 44.08 (CH<sub>2</sub>), 52.20 (OCH<sub>3</sub>), 65.68, 65.89 [CH<sub>2</sub> Z(NO<sub>2</sub>)], 123.64, 123.77 (CH), 127.73, 127.92 (CH), 131.59, 131.96 (C), 138.40, 139.07 (βCH), 144.00, 144.09 (C), 147.46 (C), 154.56, 154.75 (C=O), 164.54, 164.87 (C=O) ppm. C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub> (322.31): calcd. C 55.90, H 5.63, N 8.69; found C 55.82, H 5.41, N 8.65. m/z (HRESI-MS) 323.12432, ([M + H]<sup>+</sup>, C<sub>15</sub>H<sub>19</sub>N<sub>2</sub>O<sub>6</sub>, requires 323.12431).

Synthesis of Z-N(*Et*)-Z- $\Delta$ Abu-OMe (Z-13b) The general procedure described above was followed using Z-Z- $\Delta$ Abu-OMe (Z-2b) (0.062 g, 0.250 mmol) as reactant to afford Z-13b (0.064 g, 93%) as a colorless oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.13$  (t, J = 7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.76, 1.80 (2d, J = 7.2 Hz and J = 7.2 Hz, 3H,  $\gamma$ CH<sub>3</sub>), 3.46–3.50 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.66, 3.77 (2s, 3H, CH<sub>3</sub> OMe), 5.11, 5.21 (2s, 2H, CH<sub>2</sub> Z), 6.93, 7.02 (2q, J = 7.2 Hz and J = 7.2 Hz, 1H,  $\beta$ CH), 7.28-7.39 (m, 5H, ArH) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 13.00$  (CH<sub>3</sub>), 13.83, 13.92 ( $\gamma$ CH<sub>3</sub>), 43.80, 43.91 (CH<sub>2</sub>), 52.02, 52.11 (OCH<sub>3</sub>), 67.10, 67.36 (CH<sub>2</sub> Z), 127.66, 127.76 (CH), 127.82, 127.96 (CH), 128.33, 128.46 (CH), 131.77, 132.19 (C), 139.30, 136.66 (C), 138.01, 138.81 ( $\beta$ CH), 155.01, 155.27 (C=O),

164.82, 165.11 (C=O) ppm. m/z (HRESI-MS) 300.12063,  $([M + Na]^+, C_{15}H_{19}NNaO_4, requires 300.12118).$ 

Synthesis of Boc-N(Et)-Z- $\Delta$ Abu-OMe (Z-13c) The general procedure described above was followed using Boc-Z- $\Delta$ Abu-OMe (Z-2c) (0.294 g, 1.364 mmol) as reactant to afford Z-13c (0.304 g, 92%) as a colorless oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.06$  (t, J = 7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.35, 1.46 (2s, 9H, CH<sub>3</sub> Boc), 1.75 (d, J = 7.2 Hz, 3H,  $\gamma$ CH<sub>3</sub>), 3.32, 3.40 (2q, J = 7.2 Hz and J = 7.2 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.71, 3.72 (2s, 3H, CH<sub>3</sub> OMe), 6.79, 6.89 (2q, J = 7.2 Hz and J = 7.2 Hz, 1H,  $\beta$ CH) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 12.99$ , 13.02 (CH<sub>3</sub>), 13.68, 13.81 (yCH<sub>3</sub>), 28.13, 28.25 [C(CH<sub>3</sub>)<sub>3</sub>], 42.84, 43.99 (CH<sub>2</sub>), 51.83, 51.88 (OCH<sub>3</sub>), 79.80, 80.08 [OC(CH<sub>3</sub>)<sub>3</sub>], 132.42, 132.54 (αC), 135.93, 136.17 (βCH), 154.17, 154.38 (C=O), 165.01, 165.45 (C=O) ppm. C<sub>12</sub>H<sub>21</sub>NO<sub>4</sub> (243.30): calcd. C 59.24, H 8.70, N 5.76; found C 59.02, H 8.70, N 5.71. m/z (HRESI-MS) 266.13655,  $([M + Na]^+, C_{12}H_{21}NNaO_4,$ requires 266.13683).

*Synthesis of Tos-N(Et)-Z-*Δ*Abu-OMe* (*Z-13d*) The general procedure described above was followed using Tos-*Z*-ΔAbu-OMe (*Z*-2d) (0.135 g, 0.500 mmol) as reactant to afford *Z*-13d (0.122 g, 82%) as a colorless oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 1.10$  (t, J = 7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.98 (d, J = 7.2 Hz, 3H,  $\gamma$ CH<sub>3</sub>), 2.42 (s, 3H, CH<sub>3</sub> Tos), 3.21, 3.64 (2 br. s, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.51 (s, 3H, CH<sub>3</sub> OMe), 7.28 (d, J = 8.4 Hz, 2H, ArH), 7.32 (q, J = 7.2 Hz, 1H,  $\beta$ CH), 7.70 (d, J = 8.4 Hz, 2H, ArH) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta = 14.01$  (CH<sub>3</sub>), 15.22 ( $\gamma$  CH<sub>3</sub>), 21.49 (Tos CH<sub>3</sub>), 44.06 (CH<sub>2</sub>), 51.76 (OCH<sub>3</sub>), 127.66 (CH), 128.72 (C), 129.18 (CH), 136.99 (C), 143.10 (C), 146.47 (CH), 164.39 (C=O) ppm. m/z (HRESI-MS) 320.09270, ([M + Na]<sup>+</sup>, C<sub>14</sub>H<sub>19</sub>NNaO<sub>4</sub>S, requires 320.09325).

Synthesis of  $Z(NO_2)-N(Et)-Z-\Delta Phe-OMe$  (Z-14a) The general procedure described above was followed using  $Z(NO_2)-Z-\Delta Phe-OMe$  (Z-3a) (0.270 g, 0.758 mmol) as reactant to afford Z-14a (0.283 g, 97%) as a light yellow oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.10, 1.21$  (2t, J = 7.2 Hz and J = 7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 3.29, 3.47, 3.72 (3br. s, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.79, 3.85 (2s, 3H, CH<sub>3</sub> OMe), 5.21, 5.37 [br. s + s, 2H, CH<sub>2</sub> Z(NO<sub>2</sub>)], 7.34–7.58 (m, 8H, ArH +  $\beta$ CH), 8.12, 8.26 [2d, J = 8.8 Hz and J = 8.8 Hz, 2H, Z(NO<sub>2</sub>)] ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 12.76$ , 13.57 (CH<sub>3</sub>), 43.83, 44.16 (CH<sub>2</sub>), 52.53, 52.55 (OCH<sub>3</sub>), 65.90, 66.02 [CH<sub>2</sub> Z(NO<sub>2</sub>)], 123.57, 123.78 (CH), 127.89, 127.99 (CH), 128.73, 128.92 (CH), 129.78 (C), 130.04, 130.09 (CH), 130.43 (CH), 132.58, 132.78 (C), 136.43, 136.81 (CH), 143.83, 144.01 (C), 147.45, 147.62 (C), 154.94, 155.15

(C=O), 165.52, 166.01 (C=O) ppm. m/z (HRESI-MS) 385.13941, ([M + H]<sup>+</sup>, C<sub>20</sub>H<sub>21</sub>N<sub>2</sub>O<sub>6</sub>, requires 385.13996).

Synthesis of Z-N(Et)-Z- $\Delta$ Phe-OMe (Z-14b) The general procedure described above was followed using Z-Z-APhe-OMe (Z-3b) (0.749 g, 2.405 mmol) as reactant to afford Z-14b (0.733 g, 90%) as a yellow oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.07$  $(t, J = 7.2 \text{ Hz}, 3H, CH_2CH_3), 3.24, 3.40$  (2br. s, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.68, 3.84 (s, 3H, CH<sub>3</sub> OMe), 5.17, 5.28 (br. s + s, 2H, CH<sub>2</sub> Z), 7.23–7.52 (m, 10H, ArH +  $\beta$ CH), 7.59 (s, 1H, ArH) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 12.84, 13.58$  (CH<sub>3</sub>), 43.55, 44.00 (CH<sub>2</sub>), 52.33, 52.47 (OCH<sub>3</sub>), 67.37, 67.50 (CH<sub>2</sub> Z), 127.81 (CH), 127.86 (CH), 128.32, 128.50 (CH), 128.67, 128.78 (CH), 129.86 (CH), 130.01 (CH), 130.06 (C), 132.84, 132.94 (C), 135.66 (CH), 136.44, 136.66 (C), 155.52, 155.57 (C=O), 165.81, 166.24 (C=O) ppm. m/z (HRESI-MS) 362.13628,  $([M + Na]^+, C_{20}H_{21}NNaO_4, requires 362.13683).$ 

Synthesis of Boc-N(Et)-Z- $\Delta$ Phe-OMe (Z-14c) The general procedure described above was followed using Boc-Z- $\Delta$ Phe-OMe (Z-3c) (0.206 g, 0.750 mmol) as reactant to afford Z-14c (0.208 g, 92%) as a light vellow oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.04$  (t, J = 7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.40, 1.54 (2s, 9H, CH<sub>3</sub> Boc), 3.10, 3.30, 3.67 (3br. s, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.83 (s, 3H, CH<sub>3</sub> OMe), 7.36–7.39 (m, 4H, ArH +  $\beta$ CH) 7.50–7.53 (m, 2H, ArH) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 12.94$ , 13.54 (CH<sub>3</sub>), 28.17, 28.37 [C(CH<sub>3</sub>)<sub>3</sub>], 42.53, 44.11 (CH<sub>2</sub>), 52.24, 52.31 (OCH<sub>3</sub>), 80.44, 80.60 [OC(CH<sub>3</sub>)<sub>3</sub>], 128.57, 128.71 (CH), 129.63, 129.73 (CH), 129.87, 129.95 (CH), 130.68 (C), 133.23, 133.28 (C), 133.99 (CH), 154.56, 154.78 (C=O), 166.11, 166.68 (C=O) ppm. m/z (HRESI-MS) 328.15193, ([M + Na]<sup>+</sup>, C<sub>17</sub>H<sub>23</sub>NNaO<sub>4</sub>, requires 328.15248).

Synthesis of Tos-N(Et)-Z- $\Delta$ Phe-OMe (Z-14d) The general procedure described above was followed using Tos-Z- $\Delta$ Phe-OMe (Z-3d) (0.166 g, 0.500 mmol) as reactant to afford Z-14d (0.165 g, 92%) as a light yellow oil. M.p. 111.0–112.0°C (from diethyl ether/petroleum ether). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.03$  (t, J = 7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 2.44 (s, 3H, CH<sub>3</sub> Tos), 3.49 (br. s, 2H, CH<sub>2</sub>CH<sub>3</sub>), 3.58 (s, 3H, CH<sub>3</sub> OMe), 7.29 (d, J = 8.1 Hz, 2H, ArH), 7.39–7.41 (m, 3H, ArH), 7.75 (d, J = 8.1 Hz, 2H, ArH), 7.84–7.89 (m, 3H, ArH +  $\beta$ CH) ppm. <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>):  $\delta = 13.38$  (CH<sub>2</sub>CH<sub>3</sub>), 21.53 (Tos CH<sub>3</sub>), 44.13 (CH<sub>2</sub>), 52.08 (OCH<sub>3</sub>), 125.42 (C), 128.04 (CH), 128.62 (CH), 129.17 (CH), 130.80 (CH), 131.15 (CH), 132.51 (C), 136.62 (C), 143.22 (C), 143.32 (CH), 165.76 (C=O) ppm. C<sub>19</sub>H<sub>21</sub>NO<sub>4</sub>S (359.44): calcd. C 63.49, H 5.89, N 3.90, S 8.92; found C 63.55, H 5.97, N 3.96, S 8.73.

Synthesis of N-protected, N-ethyl dehydroamino acids

# *General procedure for the synthesis of N-protected, N-ethyl dehydroamino acids*

The methyl ester of the *N*-protected, *N*-ethyl dehydroamino acid was dissolved in dioxane (0.2 mol dm<sup>-3</sup>), followed by addition of 3 cm<sup>3</sup> of NaOH (1 mol dm<sup>-3</sup>). The solution was stirred at room temperature for 2 h and then acidified to pH 2–3 with KHSO<sub>4</sub> (1 mol dm<sup>-3</sup>) and extracted with ethyl acetate (5 × 10 cm<sup>3</sup>). The organic extracts were collected, dried over MgSO<sub>4</sub> and evaporated at reduced pressure.

Synthesis of Boc-N(*Et*)- $\Delta$ Ala-OH (**15c**) The general procedure described above was followed using Boc-N(Et)- $\Delta$ Ala-OMe (**12c**) (0.134 g, 0.587 mmol) as reactant to afford **15c** (0.115 g, 91%) as a light yellow oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 1.18$  (t, J = 7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.44 (s, 9H, CH<sub>3</sub> Boc), 3.56 (q, J = 6.9 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 5.53 (s, 1H,  $\beta$ CH), 6.07 (s, 1H,  $\beta$ CH) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta = 15.10$  (CH<sub>3</sub>), 28.36 [C(CH<sub>3</sub>)<sub>3</sub>], 44.29 (CH<sub>2</sub>), 81.25 [OC(CH<sub>3</sub>)<sub>3</sub>], 118.90 ( $\beta$ CH<sub>2</sub>), 139.53 ( $\alpha$ C), 156.33 (C=O), 169.13 (C=O) ppm. m/z (HRESI-MS) 216.12374, ([M + H]<sup>+</sup>, C<sub>10</sub>H<sub>17</sub>NO<sub>4</sub>, requires 216.12356).

Synthesis of Z-N(*Et*)-Z- $\Delta$ Abu-OH (Z-16b) The general procedure described above was followed using Z-N(Et)-Z- $\Delta$ Abu-OMe (Z-13b) (0.277 g, 1.000 mmol) as reactant to afford Z-16b (0.249 g, 95%) as a yellow oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.15$  (t, J = 7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.79 (d, J = 7.2 Hz, 3H,  $\gamma$ CH<sub>3</sub>), 3.50 (q, J = 7.2 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 5.11 (br. s, 2H, CH<sub>2</sub>Z), 7.08 (q, J = 7.2 Hz, 1H,  $\beta$ CH), 7.25–7.40 (m, 5H, ArH) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta = 13.03$  (CH<sub>3</sub>), 14.10 ( $\gamma$ CH<sub>3</sub>), 43.75 (CH<sub>2</sub>), 67.27 (CH<sub>2</sub>Z), 127.57 (CH), 127.81 (CH), 128.34 (CH), 131.28 (C), 136.53 (C), 140.67 ( $\beta$ CH), 155.24 (C=O), 169.36 (C=O) ppm. m/z (HRESI-MS) 264.12332, ([M + H]<sup>+</sup>, C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub>, requires 264.12358).

Synthesis of Z-N(*Et*)-Z- $\Delta$ Phe-OH (Z-17b) The general procedure described above was followed using Z-N(Et)-Z- $\Delta$ Phe-OMe (Z-14b) (0.339 g, 1.000 mmol) as reactant to afford Z-17b (0.307 g, 94%) as a light yellow oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): (rotamers)  $\delta = 1.11$  (t, J = 7.2 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>), 3.26, 3.46 (2br. s, 2H, CH<sub>2</sub>CH<sub>3</sub>), 5.16 (s, 2H, CH<sub>2</sub> Z), 7.23–7.25 (m, 3H, ArH), 7.36–7.41 (m, 4H, ArH), 7.52–7.56 (m, 3H, ArH) 7.64 (s, 1H,  $\beta$ CH) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta = 12.89$  (CH<sub>3</sub>), 43.58 (CH<sub>2</sub>), 67.54 (CH<sub>2</sub> Z), 127.62 (CH), 127.79 (CH), 128.30 (CH), 128.40 (C), 128.77 (CH), 128.87 (CH), 130.27 (CH), 132.57 (C), 136.32 (C), 137.75

(CH), 155.52 (C=O), 170.63 (C=O) ppm. m/z (HRESI-MS) 326.13868, ([M + H]<sup>+</sup>, C<sub>19</sub>H<sub>19</sub>NO<sub>4</sub>, requires 326.13923).

Synthesis of the methyl esters of *N*-protected, *N*-ethyl dehydrodipeptides

#### General procedure for the synthesis of the methyl esters of N-protected, N-ethyl dehydrodipeptides

The *N*-protected, *N*-ethyl dehydroamino acid was dissolved in acetonitrile (0.05 mol dm<sup>-3</sup>), followed by addition of 1.0 equiv. of HOBt, 1.1 equiv. of DCC, 1.0 equiv. of HCl.H–L-Phe-OMe and 1.0 equiv. of NEt<sub>3</sub> in an ice bath. After stirring for 16 h at room temperature, the mixture was filtered and the solvent was evaporated at reduced pressure. The residue was dissolved in ethyl acetate (100 cm<sup>3</sup>) and washed with KHSO<sub>4</sub> (1 mol dm<sup>-3</sup>), NaHCO<sub>3</sub> (1 mol dm<sup>-3</sup>) and brine (3 × 30 cm<sup>3</sup> each). The organic layer was dried with MgSO<sub>4</sub> and the solvent evaporated at reduced pressure.

Synthesis of Z-N(Et)-Z- $\Delta$ Abu-L-Phe-OMe (18b) The general procedure described above was followed using Z-N(Et)-Z-ΔAbu-OH (Z-16b) (0.165 g, 0.629 mmol) as reactant to afford 18b (0.233 g, 87%) as a colorless oil that failed to crystallize. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 1.02$  (br. s, 3H, CH<sub>2</sub>CH<sub>3</sub>), 1.62 (d, J = 7.2 Hz, 3H,  $\gamma$ CH<sub>3</sub>), 3.07–3.40 (m, 4H, CH<sub>2</sub>CH<sub>3</sub> +  $\beta$ CH<sub>2</sub>), 3.71 (s, 3H, CH<sub>3</sub> OMe), 4.85–5.20 (m, 3H, CH<sub>2</sub> Z +  $\alpha$ CH), 6.33 (d, J = 7.2 Hz, 1H, NH), 6.87 (q, J = 7.2 Hz, 1H,  $\beta$ CH), 6.99–7.35 (m, 10H, ArH), 7.49 (s, 1H,  $\beta$ CH) ppm. <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 12.91$  (CH<sub>3</sub>), 13.62 ( $\gamma$ CH<sub>3</sub>), 37.50 (βCH<sub>2</sub>), 43.89 (CH<sub>2</sub>), 52.28 (OCH<sub>3</sub>), 53.07 (αCH), 67.37 (CH<sub>2</sub> Z), 127.15 (CH), 127.80 (CH), 128.04 (CH), 128.41 (CH), 128.59 (CH), 129.04 (CH), 133.45 (C), 134.62 (CH), 135.58 (C), 136.23 (C), 155.02 (C=O), 163.79 (C=O), 171.61 (C=O) ppm. m/z (HRESI-MS) 425.20710, ( $[M + H]^+$ ,  $C_{24}H_{28}N_2O_5$ , requires 425.20765).

*Synthesis of Z-N(Et)-Z-ΔPhe-L-Phe-OMe* (**19b**) The general procedure described above was followed using Z-*N*(Et)-*Z*-ΔPhe-OH (*Z*-**17b**) (0.321 g, 0.988 mmol) as reactant to afford **19b** (0.386 g, 80%) as a light yellow oil that failed to crystallize. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 0.95$  (br. s, 3H, CH<sub>2</sub>CH<sub>3</sub>), 2.95–3.21 (m, 4H, CH<sub>2</sub>CH<sub>3</sub> +  $\beta$ CH<sub>2</sub>), 3.71 (s, 3H, CH<sub>3</sub> OMe), 4.82–5.30 (m, 3H, CH<sub>2</sub> Z +  $\alpha$ CH), 6.46 (d, *J* = 7.2 Hz, 1H, NH), 7.01–7.32 (m, 15H, ArH), 7.49 (s, 1H,  $\beta$ CH) ppm. <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 13.07$  (CH<sub>3</sub>), 37.52 ( $\beta$ CH<sub>2</sub>), 43.68 (CH<sub>2</sub>), 52.29 (OCH<sub>3</sub>), 53.48 ( $\alpha$ CH), 67.62 (CH<sub>2</sub> Z), 127.22 (CH), 127.90 (CH), 128.02 (CH), 128.35 (CH), 128.69 (C), 128.78 (CH), 129.09 (CH), 129.43 (CH), 135.51 (C), 136.04 (C), 155.16 (C=O), 164.95 (C=O),

171.60 (C=O) ppm. m/z (HRESI-MS) 487.22309,  $([M + H]^+, C_{29}H_{30}N_2O_5, \text{ requires } 487.22330).$ 

#### **Results and discussion**

An alternative to the use of strong electron withdrawing moieties to enhance the acidity of the NH proton and allow N-ethylation of amino acid derivatives can be the use of a strong base. In the case of amino acids, a strong base will induce racemisation and thus limit the value of the products obtained. With dehydroamino acids this problem does not occur, so the strong base potassium tert-butoxide was tested as auxiliary base in N-ethylation of dehydroamino acid derivatives with triethyloxonium tetrafluoroborate. Initially, the methyl ester of N-(tert-butyloxycarbonyl),  $\beta$ -bromo, dehydroaminobutyric acid, for which no ethylation was observed using the weak base N,N-diisopropylethylamine (Monteiro et al. 2011), was subjected to the treatment with 2.5 equiv. of triethyloxonium tetrafluoroborate using 3.5 equiv. of potassium tert-butoxide as base. In these conditions the reaction was complete in approximately 30 min allowing, the isolation of the N-ethyl dehydroamino acid derivative in 85% yield. Thus, all other substrates that previously had given no alkylation reaction or incomplete reaction using DIPEA (Monteiro et al. 2011) were subjected to ethylation using potassium tert-butoxide as base. Thus, the methyl ester of  $\beta$ , $\beta$ -dibromo dehydroalanine protected with Boc and the Z-isomers of the methyl esters of  $\beta$ -bromo, dehydroaminobutyric acid and dehydrophenylalanine protected with Z(NO<sub>2</sub>), Z and Boc, were reacted with 2.5 equiv. of triethyloxonium tetrafluoroborate using 3.5 equiv. of potassium tert-butoxide as base (compounds 4c, 5a-c, 6a-c, Scheme 1; Table 1).

For all the  $\beta$ -bromo dehydroamino acid derivatives, N-ethylation reactions were complete after approximately 30 min and the corresponding *N*-ethylated derivative could be isolated in high yield (Table 1). In two cases in which *E*-isomers of  $\beta$ -bromo dehydroamino acid derivatives were subjected to N-alkylation, (compounds *E*-**5a** and *E*-**5c**) high yields in *N*-ethyl derivatives were obtained. The same procedure applied to two  $\beta$ -iodo derivatives of dehydrophenylalanine protected with the Z(NO<sub>2</sub>) and Boc groups (compounds *Z*-**7a** and *Z*-**7c**) gave the corresponding *N*-ethylated derivatives in excellent yields (Table 1).

N-Ethylation using the Et<sub>3</sub>OBF<sub>4</sub>/DIPEA procedure of non-halogenated dehydroamino acids with amine protecting groups other than the 4-nitrobenzenesulfonyl group had been completely ineffective, even after several hours of reaction and addition of large excess of alkylating agent (Monteiro et al. 2011). However, the results obtained in ethylation of  $\beta$ -halo dehydroamino acid derivatives using as base potassium *tert*-butoxide, led us to reattempt the

### **Scheme 1** Synthesis of *N*-ethyl dehydroamino acid derivatives



**Table 1** Results obtained in the N-ethylation of the methyl esters of *N*-protected  $\beta$ ,  $\beta$ -dibromo and  $\beta$ -halo,  $\beta$ -substituted dehydroamino acids

Reactant	Product	Yield (%)
Boc- $\Delta$ Ala( $\beta$ , $\beta$ -Br)-OMe, <b>4c</b>	Boc- $N(\text{Et})$ - $\Delta \text{Ala}(\beta,\beta$ -Br)-OMe, <b>8c</b>	93
$Z(NO_2)$ - $E$ - $\Delta Abu(\beta$ -Br)-OMe, E- <b>5a</b>	$Z(NO_2)-N(Et)-E-\Delta Abu(\beta-Br)-OMe \ E-9a$	94
$Z(NO_2)$ -Z- $\Delta Abu(\beta$ -Br)-OMe, Z- <b>5a</b>	$Z(NO_2)-N(Et)-Z-\Delta Abu(\beta-Br)-OMe, Z-9a$	82
Z–Z- $\Delta$ Abu( $\beta$ -Br)-OMe, Z- <b>5b</b>	Z- $N$ (Et)-Z- $\Delta$ Abu( $\beta$ -Br)-OMe, Z- <b>9b</b>	86
Boc- $E$ - $\Delta$ Abu( $\beta$ -Br)-OMe, $E$ - <b>5</b> c	Boc- $N(Et)$ - $E$ - $\Delta$ Abu( $\beta$ -Br)-OMe, $E$ - <b>9c</b>	89
Boc-Z- $\Delta$ Abu( $\beta$ -Br)-OMe, Z- <b>5</b> c	Boc- $N(Et)$ -Z- $\Delta$ Abu( $\beta$ -Br)-OMe, Z- <b>9c</b>	85
$Z(NO_2)$ -Z- $\Delta Phe(\beta$ -Br)-OMe, Z- <b>6a</b>	$Z(NO_2)-N(Et)-Z-\Delta Phe(\beta-Br)-OMe, Z-10a$	96
$Z(NO_2)$ -Z- $\Delta Phe(\beta$ -I)-OMe, Z-7a	$Z(NO_2)-N(Et)-Z-\Delta Phe(\beta-I)-OMe, Z-11a$	95
Z-Z-ΔPhe( $\beta$ -Br)-OMe, Z- <b>6b</b>	Z- $N(Et)$ -Z- $\Delta$ Phe( $\beta$ -Br)-OMe, Z- <b>10b</b>	82
Boc-Z- $\Delta$ Phe( $\beta$ -Br)-OMe, Z- <b>6c</b>	Boc- $N(Et)$ -Z- $\Delta$ Phe( $\beta$ -Br)-OMe, Z-10c	88
Boc-Z- $\Delta$ Phe( $\beta$ -I)-OMe, Z-7c	Boc- $N(Et)$ -Z- $\Delta$ Phe( $\beta$ -I)-OMe, Z- <b>11c</b>	95

alkylation of non-halogenated dehydroamino acids with standard amine protecting groups. Thus, the methyl esters of dehydroalanine, dehydroaminobutyric acid and dehydrophenylalanine protected with Z(NO<sub>2</sub>), Z, Boc and 4-toluenesulfonyl (Tos) were subjected to N-ethylation with triethyloxonium tetrafluoroborate using potassium *tert*butoxide as base (compounds **1a–c**, **2a–d**, **3a–d**, Scheme 1; Table 2). With all the dehydroamino acid derivatives the reactions were complete and the corresponding *N*-ethylated derivative could be isolated in high yield (Table 2).

By removal of the Nosyl protecting group from *N*-Nosyl, *N*-ethyl amino acid methyl esters and reprotection of the amino function with the 9-fluorenylmethoxycarbonyl group (Fmoc), Liguori demonstrated the compatibility of this N-ethylation procedure with standard Fmoc chemistry (Belsito et al. 2010). However, further conversion of the methyl esters to acids is essential for other practical applications of these compounds, such as incorporation into peptides. Thus, representative methyl esters of *N*-ethyl dehydroamino acid derivatives were subjected to cleavage of the methyl ester. Three *N*-ethyl dehydroamino acid derivatives (compounds **12c**, *Z*-**13b** and *Z*-**14b**) were

treated with a mixture of an aqueous solution of NaOH and dioxane, giving in all cases high yields in the corresponding *N*-protected, *N*-ethyl dehydroamino acid (compounds **15c**, *Z*-**16b** and *Z*-**17b**, Scheme 2).

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Two of these dehydroamino acid derivatives (compounds Z-16b and Z-17b) were reacted with phenylalanine methyl ester using the standard DCC/HOBt procedure to give the corresponding *N*-ethyl dehydrodipeptide derivative in good yields (compounds 18b and 19b, Scheme 2).

#### Conclusions

A triethyloxonium tetrafluoroborate/potassium *tert*-butoxide alkylation procedure was applied for N-ethylation of several methyl esters of  $\beta$ , $\beta$ -dibromo dehydroalanine,  $\beta$ -bromo dehydroaminobutyric acid and  $\beta$ -halo dehydrophenylalanine, N-protected with urethane groups. All *N*-ethyl,  $\beta$ -halo dehydroamino acid derivatives could be obtained in high yields. This method was also applied for N-ethylation of non-halogenated dehydroamino acids with urethane amine protecting groups and also the 4-toluenesulfonyl group. With all the dehydroamino acid derivatives,

Reactant	Product	Yield (%)
$Z(NO_2)$ - $\Delta$ Ala-OMe, <b>1a</b>	$Z(NO_2)-N(Et)-\Delta Ala-OMe$ , <b>12a</b>	88
Z- $\Delta$ Ala-OMe, <b>1b</b>	Z- $N(Et)$ - $\Delta$ Ala-OMe, <b>12b</b>	91
Boc- $\Delta$ Ala-OMe, <b>1</b> c	Boc- $N(Et)$ - $\Delta$ Ala-OMe, <b>12c</b>	79
$Z(NO_2)$ -Z- $\Delta$ Abu-OMe, Z- <b>2a</b>	$Z(NO_2)$ - $N(Et)$ - $Z$ - $\Delta$ Abu-OMe, Z- <b>13a</b>	90
Z-Z-∆Abu-OMe, Z- <b>2b</b>	Z-N(Et)-Z-ΔAbu-OMe, Z-13b	93
Boc-Z-∆Abu-OMe, Z- 2c	Boc-N(Et)-Z-AAbu-OMe, Z-13c	92
Tos-Z-∆Abu-OMe, Z-2d	Tos- $N(Et)$ -Z- $\Delta$ Abu-OMe, Z-13d	82
$Z(NO_2)$ -Z- $\Delta$ Phe-OMe, Z- <b>3a</b>	$Z(NO_2)-N(Et)-Z-\Delta Phe-OMe, Z-14a$	97
Z–Z- $\Delta$ Phe-OMe, Z- <b>3b</b>	Z-N(Et)-Z-ΔPhe-OMe, Z-14b	90
Boc-Z-∆Phe-OMe, Z- <b>3c</b>	Boc-N(Et)-Z-ΔPhe-OMe, Z-14c	92
Tos-Z-∆Phe-OMe, Z- <b>3d</b>	Tos- $N(Et)$ -Z- $\Delta$ Phe-OMe, Z-14d	92



 Table 2
 Results obtained in the

 N-ethylation of the methyl
 esters of N-protected

 dehydroamino acids
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the reactions were complete and the corresponding *N*-ethylated derivative could be isolated in high yields. Some of these *N*-ethylated methyl ester derivatives were converted in high yields to their corresponding acids and coupled to an amino acid methyl ester to give *N*-ethyl dehydrodipeptide derivatives in good yields.

Thus, regardless of the nature of the dehydroamino acid and of the amine protecting group, this method constitutes a high yielding procedure for synthesis of *N*-ethylated dehydroamino acid derivatives, which can be further applied in peptide synthesis.

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