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Synthesis of Substituted Oxazoles from *N*-Acyl-β-hydroxyamino Acid Derivatives

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Several *N*-acyl-β-hydroxyamino acids were prepared and treated with di-*tert*-butyl dicarbonate in the presence of 4-(dimethylamino)pyridine, followed by treatment with *N*,*N*,*N*′,*N*′-tetramethylguanidine to give the corresponding *N*-acyldehydroamino acids in good to high yields. These were then treated with I_2/K_2CO_3 followed by 1,8-diazabicyclo[5.4.0]undec-7-ene. The methyl esters of *N*-acyldehydroaminobutyric acid gave the corresponding substituted oxazoles in good to high yields. The *N*-acyldehydrophenylalanines gave 5-phenyloxazole derivatives in low to moderate yields together with β-iododehydrophenylalanines.
Under the same conditions, *N*-acyldehydroalanines failed to give the corresponding oxazoles. However, when the reaction was carried out in the absence of DBU, it was possible to isolate the β,β-diiododehydroalanine derivatives. Although the reason for the different reactivities of the *N*-acyldehydroamino acids is not completely clear to us, cyclic voltammetry studies showed that the less-reactive derivatives have higher reduction potentials. This suggests that the double bonds in dehydroaminobutyric acid derivatives are more susceptible to electrophilic attack by iodine.

Introduction

Oxazoles are important structural motifs of a wide range of biologically active molecules. Natural products containing the oxazole ring have been isolated from marine invertebrates and microorganisms.[1] This heterocyclic ring system is biosynthesized from serine, threonine and cysteine precursors by enzyme-catalysed cyclodehydration and redox reactions.[2] There have been many synthetic efforts to develop efficient and mild methodologies for the preparation of oxazoles. These include, among others, the Cornforth protocol,[3] catalytic decomposition of α-diazocarbonyl compounds,[4] photolysis and pyrolysis of *N*-acylisoxazolones[5] and modified Robinson–Gabriel reactions.[6] Wipf and co-workers[7] reported the synthesis of oxazoles by treatment of serine derivatives with diethylaminosulfur trifluoride (DAST) followed by bromotrichloromethane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Morwick et al. prepared 2,4-disubstituted oxazoles from *N*-acylamino acids by cyclodehydration of the intermediate α-acylamino aldehydes.[8] Recently, Buchwald et al.[9] described the synthesis of oxazoles by a sequential copper-catalysed amidation of vinyl halides, followed by iodine-promoted cyclization.

In our group, we developed an efficient synthesis of *N*-acyldehydroamino acid derivatives.[10] The high reaction yields and the simple workup procedures allowed the preparation of large quantities of these compounds, which were used as substrates in several types of reactions, giving a wide range of nonproteinogenic amino acids.[11] Here we report the synthesis of substituted oxazoles from *N*-acyl-β-hydroxyamino acids by a sequence involving a dehydration reaction followed by an intramolecular cyclization promoted by iodine.

Results and Discussion

Several *N*-acyldehydroaminobutyric acid derivatives were prepared by treating the corresponding threonine derivatives with one equivalent of di-*tert*-butyl dicarbonate (Boc_2O) and 4-(dimethylamino)pyridine (DMAP), followed by treatment with *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) (Scheme 1, conditions i; Table 1).[10b] The stereochemistry of the dehydroaminobutyric acid derivatives was determined by NOE difference experiments, through irradiation of the α-NH proton and observation of a NOE enhancement on the γ-methyl protons. These *N*-acyldehydroaminobutyric acids were then treated with iodine in the presence of K_2CO_3 followed by DBU to give the corresponding 2-substituted methyl 5-methyloxazole-4-carboxylates (**3a**–**f**; Scheme 1, conditions ii; Table 1) in good to high yields.

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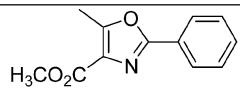
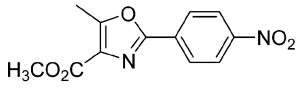
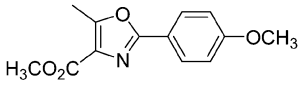
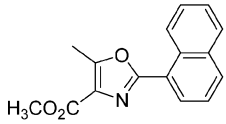
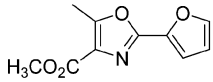
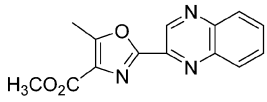
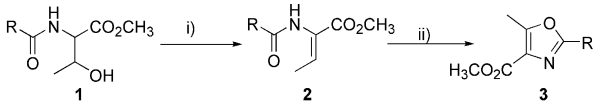
Table 1. Synthesis of *N*-acylthreonine, *N*-acyldehydroaminobutyric acid and methyl oxazole-4-carboxylate derivatives.

N-acyl-L-threonine methyl ester	% Yield	*N*-acyldehydroaminobutyric acid methyl ester	% Yield	5-methyl oxazole derivatives	% Yield
Bz-L-Thr-OMe (**1a**)	77	Bz-*Z*-ΔAbu-OMe (**2a**)	83	 (**3a**)	91
Bz(4-NO_2)-L-Thr-OMe (**1b**)	30	Bz(4-NO_2)-*Z*-ΔAbu-OMe (**2b**)	71	 (**3b**)	71
Bz(4-OMe)- L-Thr-OMe (**1c**)	81	Bz(4-OMe)-*Z*-ΔAbu-OMe (**2c**)	82	 (**3c**)	73
1-Naph- L-Thr-OMe (**1d**)	88	1-Naph-*Z*-ΔAbu-OMe (**2d**)	88	 (**3d**)	85
2-Fur- L-Thr-OMe (**1e**)	57	2-Fur-*Z*-ΔAbu-OMe (**2e**)	88	 (**3e**)	90
2-Qnx-L-Thr-OMe (**1f**)	78	2-Qnx-*Z*-ΔAbu-OMe (**2f**)	84	 (**3f**)	38



1 **2** **3**

R = C_6H_5, **a**; (4-NO_2)C_6H_4, **b**; (4-OCH_3)C_6H_4, **c**; Naph-1-yl, **d**; Fur-2-yl, **e**; Qnx-2-yl, **f**.
i) 1. Boc_2O (1 equiv.), DMAP (0.1 equiv.) in dry ACN. 2. TMG (2% in volume).
ii) 1. I_2 (1.2 equiv.), K_2CO_3 (2 equiv.) in THF at 80 °C. 2. DBU (2 equiv.) at 80 °C.

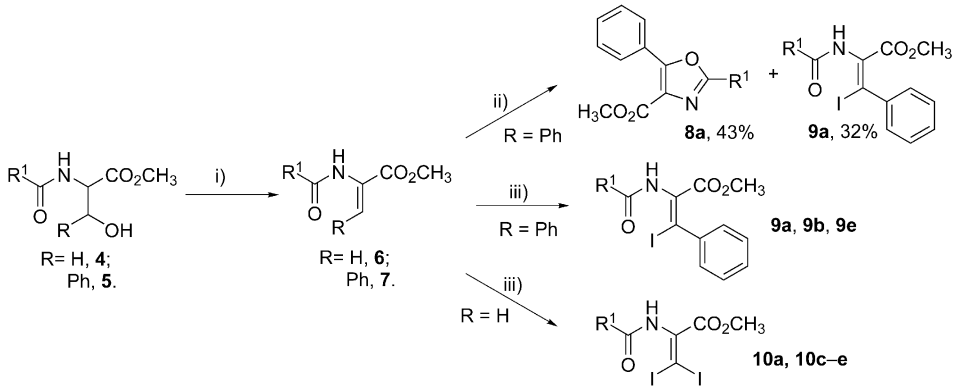
Scheme 1.

The cyclization reaction was tested with the methyl ester of *tert*-(butoxycarbonyl)dehydroaminobutyric acid as substrate. However, the only product isolated was the *Z* isomer of the corresponding β-iodo derivative, in 87% yield. Recently, Licini et al. described the iodocyclization of allylalanine derivatives to γ-lactones and oxazolinones in good yields.[12] According to the authors, the efficiencies of I_2 and *N*-iodosuccinimide (NIS) as I^+ sources appear to be comparable in terms of reactivity. However, when compound **2a** was treated with NIS, the *Z* isomer of the methyl ester of *N*-benzoyl-β-iododehydroaminobutyric acid was obtained in 81% yield.

The dehydration/cyclization protocol was also applied to serine and β-hydroxyphenylalanine derivatives. The methyl esters of *N*-acyl dehydroalanines and dehydrophenylalanines were prepared in good yields (Scheme 2, Table 2). As expected in the case of dehydrophenylalanine derivatives the dehydration reaction was stereoselective for the *Z* isomers.[10b] These compounds were then treated with I_2/K_2CO_3 followed by DBU. The *N*-acyldehydroalanine derivatives (**6a**, **6c**–**e**) failed to give the corresponding 2-substituted methyl oxazole 4-carboxylates, and the starting materials were the only products isolated. When *N*-benzoyldehydrophenylalanine (**7a**) was used as a substrate, it was possible to obtain the corresponding 2,5-diphenyloxazole in moderate yield (**8a**; Scheme 2, conditions ii), together with the *Z* isomer of the β-iododehydrophenylalanine derivative (**9a**). In the cases of compounds **7b** and **7e** the oxazoles were detectable in the ^1H NMR spectra of the reaction mixtures, together with the starting materials and the corresponding β-iododehydrophenylalanine derivatives. Treatment of compounds **6a**, **6c**–**e**, **7a**, **7b** and **7e** with I_2/K_2CO_3 in THF, without addition of DBU, afforded the corresponding β,β-diiododehydroalanines (**10a**, **10c**–**e**) or β-iododehydrophenylalanines (**9a**, **9b**, **9e**) in good yields (Scheme 2, conditions iii; Table 2). These reaction conditions were also applied to compound **2a**, giving the *Z* isomer of the methyl ester of *N*-benzoyl-β-iododehydroaminobutyric acid (**11**).

The stereochemistries of compounds **9** and **11** were determined by irradiation of the methyl ester protons and observation of NOE enhancements on the C_6H_5 or β-CH_3 protons, respectively.

The reason for the good yields obtained in the synthesis of 5-methyloxazoles, relative to those for 5-phenyloxazoles, and the impossibility of obtaining 5-unsubstituted oxazoles from dehydroalanine derivatives is not clear to us. However, cyclic voltammetry studies of compounds **2a**, **2c**, **6a**, **6c**, **7a** and **7c** (Table 3) show that the *N*-acyldehydroaminobutyric acid derivatives have lower reduction peak potentials. This might suggest that in this case the double bond can undergo electrophilic attack by iodine more easily.



R^1 = C_6H_5, **a**; (4-NO_2)C_6H_4, **b**; (4-OCH_3)C_6H_4, **c**; Naph-1-yl, **d**; Fur-2-yl, **e**.

i) 1. Boc_2O (1 equiv.), DMAP (0.1 equiv.) in dry ACN; 2. TMG (2% in volume).

ii) 1. I_2 (1.2 equiv.), K_2CO_3 (2 equiv.) in THF at 80 °C; 2. DBU (2 equiv.) at 80 °C.

iii) I_2 (1.2 equiv.), K_2CO_3 (2 equiv.) in THF at 80 °C.

Scheme 2.

Table 2. Synthesis of *N*-acyldehydroamino acid and *N*-acyl-β-iododehydroamino acid derivatives.

N-Acyldehydroamino acids	% Yield	*N*-Acyl-β-iododehydroamino acids	% Yield
Bz-ΔAla-OMe (**6a**)[13]	71	Bz-ΔAla(β,β-I)-OMe (**10a**)	40
Bz(4-OMe)-ΔAla-OMe (**6c**)	50	Bz(4-OMe)-ΔAla(β,β-I)-OMe (**10c**)	42
1-Naph-ΔAla-OMe (**6d**)	72	1-Naph-ΔAla(β,β-I)-OMe (**10d**)	47
2-Fur-ΔAla-OMe (**6e**)	67	2-Fur-ΔAla(β,β-I)-OMe (**10e**)	53
Bz-*Z*-ΔPhe-OMe (**7a**)	90	Bz-*Z*-ΔPhe(β-I)-OMe (**9a**)[a]	87
Bz(4-NO_2)-*Z*-ΔPhe-OMe (**7b**)	87	Bz(4-NO_2)-Z-ΔPhe(β-I)-OMe (**9b**)[a]	85
2-Fur-*Z*-ΔPhe-OMe (**7e**)	91	2-Fur-*Z*-ΔPhe(β-I)-OMe (**9e**)	83
Bz-*Z*-ΔAbu-OMe (**2a**)	83	Bz-*Z*-ΔAbu(β-I)-OMe (**11**)	81

[a] The reaction was carried out under conditions ii (Scheme 2) at room temperature.

Table 3. Peak potentials obtained by cyclic voltammetry of *N*-acyldehydroamino acid derivatives.[a]

Compound	$-E_p$ [V] (vs. SCE[b])
Bz-ΔAla-OMe (**6a**)	1.91[13]
Bz-*Z*-ΔAbu-OMe (**2a**)	2.21[13]
Bz-*Z*-ΔPhe-OMe (**7a**)	1.87[13]
Bz(OMe)-ΔAla-OMe (**6c**)	2.03
Bz(OMe)-*Z*-ΔAbu-OMe (**2c**)	2.39
Bz(OMe)-*Z*-ΔPhe-OMe (**7c**)	1.74

[a] Cathode: vitreous carbon. Solvent: DMF. Supporting electrolyte: Bu_4NBF_4 0.1 M. Substrate conc. = 0.005 M. [b] SCE: standard calomel electrode.

Conclusions

The reactivities of several *N*-acyldehydroamino acid derivatives – namely, dehydroalanine, dehydroaminobutyric acid and dehydrophenylalanine – towards iodine-induced cyclization were studied, with the goal of obtaining oxazole-4-carboxylate derivatives. With dehydroaminobutyric acid derivatives good to high yields of methyl 5-methyloxazole-4-carboxylate derivatives were obtained, whereas with dehydrophenylalanine derivatives the yields ranged from poor to moderate. With dehydroalanine derivatives no cyclization occurred. A modification of the reaction conditions allowed the preparation of β,β-diiododehydroalanines in moderate yields and of (*Z*)-β-iododehydroaminobutyric acid and dehydrophenylalanine derivatives in high yields.

The higher reactivities of dehydroaminobutyric acid derivatives towards iodocyclization seem to be related to the more strongly electrophilic characters of the double bonds in these dehydroamino acid derivatives relative to those in dehydroalanine and dehydrophenylalanine derivatives.

Experimental Section

General Methods: Melting points were determined with a Gallenkamp apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a Varian Unity Plus instrument at 300 and 75.4 MHz, respectively, or with a Bruker Avance II$^+$ instrument at 400 and 100.6 MHz, respectively. ^1H–^1H spin-spin decoupling and DEPT θ 45° were used. MS and HRMS data were recorded by the mass spectrometry service of the University of Vigo, Spain; elemental analysis was performed with a LECO CHNS 932 elemental analyser. 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 °C. When solvent gradients were used, the increase in polarity was made from neat petroleum ether to mixtures of diethyl ether/petroleum ether, with diethyl ether being increased by 10% each time until the isolation of the product. Cyclic voltammetry experiments were carried out with a Hi-Tek potentiostat type DT 2101 and a Hi-Tek wave generator type PPRl, connected to a Philips recorder type PM 8043 and to a three-electrode, home-built glass cell.

General Procedure for the Synthesis of *N*-Acylamino Acid Methyl Esters: Triethylamine (2.2 equiv.) was added to a solution of a β-

hydroxyamino acid methyl ester hydrochloride (5 mmol) in dichloromethane (0.1 M), and the corresponding acyl chloride (1.1 equiv.) was then slowly added with vigorous stirring and cooling in an ice bath. After stirring at 0 °C for 30 min the solution was stirred at room temperature for 3 h. The reaction mixture was then concentrated and partitioned between ethyl acetate (200 mL) and $KHSO_4$ (1 M, 100 mL) and washed with $KHSO_4$ (1 M), $NaHCO_3$ (1 M) and brine (3 × 50 mL). After drying over $MgSO_4$ the extract was taken to dryness at reduced pressure to afford the corresponding *N*-acylamino acid methyl ester.

Bz-L-Ser-OMe (4a) and Boc-L-Thr-OMe: The synthesis of these compounds has been described elsewhere.[10a]

Bz-L-Thr-OMe (1a): The general procedure described above was followed with HCl·H-L-Thr-OMe and benzoyl chloride to give compound **1a** (0.913 g, 77%) as a white solid. M.p. 94.0–95.5 °C (ethyl acetate/diethyl ether). ^{1}H NMR ($CDCl_3$): δ = 1.31 (d, J = 6.6 Hz, 3 H, γCH_3), 2.30 (br. s, 1 H, OH), 3.81 (s, 3 H, CH_3 CO_2Me), 4.47 (dd, J = 2.4 Hz, J = 6.6 Hz, 1 H, βCH), 4.83 (dd, J = 2.4 Hz, J = 8.7 Hz, 1 H, αCH), 6.96 (br. s, 1 H, αNH), 7.53–7.59 (m, 3 H, ArH), 7.85–7.87 (m, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.96 (γCH_3), 52.57 (OCH_3), 57.73 (αC), 68.01 (βC), 127.16 (CH), 128.52 (CH), 131.86 (CH), 133.51 (C), 168.05 (C=O), 171.55 (C=O) ppm. $C_{12}H_{15}NO_4$ (237.26): calcd. C 60.75, H 6.37, N 5.90; found C 60.82, H 6.46, N 5.99.

Bz(4-NO_2)-L-Thr-OMe (1b): The general procedure described above was followed with HCl·H-L-Thr-OMe and 4-nitrobenzoyl chloride to give compound **1b** (0.428 g, 30%) as a white solid. M.p. 122.0–123.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 1.33 (d, J = 6.6 Hz, 3 H, γCH_3), 3.84 (s, 3 H, CH_3 CO_2Me), 4.50–4.53 (m, 1 H, βCH), 4.83 (dd, J = 2.1 Hz, J = 8.6 Hz, 1 H, αCH), 6.97 (d, J = 8.1 Hz, 1 H, NH), 8.03 (d, J = 8.7 Hz, 2 H, ArH), 8.33 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.18 (γCH_3), 52.86 (OCH_3), 57.74 (αCH), 68.05 (βCH_2), 123.82 (CH), 128.44 (CH), 139.20 (C), 149.81 (C), 165.90 (C=O), 171.26 (C=O) ppm. $C_{12}H_{14}N_2O_6$ (282.25): calcd. C 51.07, H 5.00, N 9.93; found C 51.06, H 5.03, N 9.85.

Bz(4-OMe)-L-Thr-OMe (1c): The general procedure described above was followed with HCl·H-L-Thr-OMe and 4-methoxybenzoyl chloride to give compound **1c** (1.072 g, 81%) as a white solid. M.p. 108.0–109.0 °C (ethyl acetate/diethyl ether). ^{1}H NMR ($CDCl_3$): δ = 1.25 (d, J = 6.3 Hz, 3 H, γCH_3), 2.92 (br. s, 1 H, OH), 3.75 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.38–4.45 (m, 1 H, βCH), 4.76–4.80 (m, 1 H, αCH), 6.88 (d, J = 9.0 Hz, 2 H, ArH), 7.07 (d, J = 9.0 Hz, 1 H, NH), 7.80 (d, J = 9.0 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.95 (CH_3), 52.53 (OCH_3), 55.33 (OCH_3), 57.72 (CH), 68.12 (CH), 113.69 (CH), 125.76 (C), 129.07 (CH), 162.43 (C), 167.53 (C=O), 171.75 (C=O) ppm. $C_{13}H_{17}NO_5$ (267.28): calcd. C 58.42, H 6.41, N 5.24; found C 58.57, H 6.47, N 5.23.

1-Naph-L-Thr-OMe (1d): The general procedure described above was followed with HCl·H-L-Thr-OMe and 1-naphthaloyl chloride to give compound **1d** (1.26 g, 88%) as a white solid. M.p. 110.0–111.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 1.37 (d, J = 6.6 Hz, 3 H, γCH_3), 3.85 (s, 3 H, CH_3 CO_2Me), 4.48–4.55 (m, 1 H, βCH), 4.93 (dd, J = 2.4 Hz, J = 9.0 Hz, 1 H, αCH), 6.80 (br. d, J = 8.7 Hz, 1 H, NH), 7.45–7.60 (m, 3 H, ArH), 7.60–7.74 (m, 1 H, ArH), 7.87–7.96 (m, 2 H, ArH), 8.36–8.39 (m, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.06 (γCH_3), 52.59 (OCH_3), 57.68 (αC), 67.85 (βC), 124.56 (CH), 125.26 (CH), 125.27 (CH), 126.39 (CH), 127.17 (CH), 128.23 (CH), 130.02 (C), 130.90 (CH), 133.51 (C), 133.55 (C), 170.05 (C=O), 171.36 (C=O) ppm. $C_{16}H_{17}NO_4$ (287.31): calcd. C 66.89, H 5.96, N 4.88; found C 66.88, H 5.79, N 5.03.

2-Fur-L-Thr-OMe (1e): The general procedure described above was followed with HCl·H-L-Thr-OMe and 2-furanoyl chloride to give compound **1e** (0.65 g, 57%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ = 1.23 (d, J = 6.0 Hz, 3 H, γCH_3), 3.73 (s, 3 H, CH_3 CO_2Me), 4.38–4.45 (m, 1 H, βCH), 4.70–4.74 (m, 1 H, αCH), 6.46–6.48 (m, 1 H, ArH), 7.11–7.12 (m, 1 H, ArH), 7.20 (br. d, J = 8.7 Hz, 1 H, NH), 7.43–7.44 (m, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.89 (γCH_3), 52.48 (OCH_3), 57.00 (αC), 67.79 (βC), 112.09 (CH), 114.96 (CH), 144.36 (CH), 147.12 (C), 158.68 (C=O), 171.18 (C=O) ppm. $C_{10}H_{13}NO_5$ (227.21): calcd. C 52.86, H 5.77, N 6.16; found C 52.56, H 5.66, N 5.92.

2-Qnx-L-Thr-OMe (1f): The general procedure described above was followed with HCl·H-L-Thr-OMe and 2-quinoloyl chloride to give compound **1f** (1.10 g, 78%) as a light yellow solid. M.p. 130.0–131.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 1.34 (d, J = 6.3 Hz, 3 H, γCH_3), 3.83 (s, 3 H, CH_3 CO_2Me), 4.53–4.61 (m, 1 H, βCH), 4.89 (dd, J = 6.9, J = 9.3 Hz, 1 H, αCH), 7.82–7.91 (m, 2 H, ArH), 8.15–8.20 (m, 2 H, ArH), 8.67 (d, J = 9.0 Hz, 1 H, NH), 9.66 (s, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.03 (γCH_3), 52.76 (OCH_3), 57.37 (αC), 68.09 (βC), 129.39 (CH), 129.86 (CH), 130.87 (CH), 131.80 (CH), 140.30 (C), 142.79 (C), 143.75 (CH), 143.94 (C), 163.85 (C=O), 171.12 (C=O) ppm. $C_{14}H_{15}N_3O_4$ (289.29): calcd. C 58.13, H 5.23, N 14.53; found C 58.30, H 5.25, N 14.19.

Bz(4-OMe)-L-Ser-OMe (4c): The general procedure described above was followed with HCl·H-L-Ser-OMe and 4-methoxybenzoyl chloride to give compound **4c** (1.222 g, 97%) as a white solid. M.p. 41.5–43.0 °C (methanol/diethyl ether). ^{1}H NMR ($CDCl_3$): δ = 3.84 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.07 (d, J = 3.6 Hz, 2 H, βCH_2), 4.85–4.90 (m, 1 H, αCH), 6.95 (d, J = 9.0 Hz, 2 H, ArH), 7.20 (br. d, J = 6.6 Hz, 1 H, NH), 7.80 (d, J = 9.0 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.63 (COO*C*H_3), 55.06 (αC), 55.30 (OCH_3), 63.03 (βC), 113.65 (CH), 125.53 (C), 129.02 (CH), 162.43 (C), 167.30 (C=O), 171.20 (C=O) ppm.

1-Naph-L-Ser-OMe (4d): The general procedure described above was followed with HCl·H-L-Ser-OMe and 1-naphthaloyl chloride to give compound **4d** (1.243 g, 91%) as a white solid. M.p. 82.5–83.0 °C (ethyl acetate/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 3.84 (s, 3 H, CH_3 CO_2Me), 4.06–4.17 (m, 2 H, βCH_2), 4.94–4.99 (m, 1 H, αCH), 7.00 (br. d, J = 9.0 Hz, 1 H, NH), 7.43–7.59 (m, 3 H, ArH), 7.59–7.71 (m, 1 H, ArH), 7.86–7.95 (m, 2 H, ArH), 8.35–8.38 (m, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.76 (OCH_3), 55.01 (αC), 63.13 (βC), 124.58 (CH), 125.20 (CH), 125.45 (CH), 126.42 (CH), 127.23 (CH), 128.27 (CH), 130.01 (C), 131.02 (CH), 133.23 (C), 133.57 (C), 169.83 (C=O), 170.84 (C=O) ppm. $C_{15}H_{15}NO_4$ (273.29): calcd. C 65.93, H 5.53, N 5.13; found C 66.00, H 5.55, N 5.27.

2-Fur-L-Ser-OMe (4e): The general procedure described above was followed with HCl·H-L-Ser-OMe and 2-furanoyl chloride to give compound **4e** (0.49 g, 46%) as a light yellow oil. ^{1}H NMR ($CDCl_3$): δ = 3.76 (s, 3 H, CH_3 CO_2Me), 3.92–4.07 (m, 2 H, βCH_2), 4.76–4.81 (m, 1 H, αCH), 6.45–6.47 (m, 1 H, ArH), 7.10–7.12 (m, 1 H, ArH), 7.39 (br. d, J = 7.5 Hz, 1 H, NH), 7.43–7.44 (m, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.68 (OCH_3), 54.33 (αC), 62.84 (βC), 112.10 (CH), 115.03 (CH), 144.49 (CH), 147.01 (C), 158.46 (C=O), 170.76 (C=O) ppm.

Bz-D,L-Phe(β-OH)-OMe (5a): The general procedure described above was followed with HCl·H-D,L-Phe(β-OH)-OMe and benzoyl chloride to give compound **5a** (1.332 g, 89%) as a white solid. M.p.

124.0–125.0 °C (ethyl acetate/diethyl ether). ^{1}H NMR ($CDCl_3$): δ = 3.78 (s, 3 H, CH_3 CO_2Me), 5.07 (dd, J = 3.0, J = 8.7 Hz, 1 H, αCH), 5.40 (d, J = 3.0 Hz, 1 H, βCH), 6.92 (d, J = 8.7 Hz, 1 H, αNH), 7.27–7.72 (m, 10 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.63 (OCH_3), 58.53 (αC), 73.53 (βC), 125.69 (CH), 127.04 (CH), 128.00 (CH), 128.35 (CH), 128.44 (CH), 131.72 (C), 133.51 (C), 139.66 (C), 167.71 (C=O), 170.95 (C=O) ppm. $C_{17}H_{17}NO_4$ (299.30): calcd. C 68.22, H 5.72, N 4.68; found C 68.22, H 5.73, N 4.73.

Bz(4-NO_2)-D,L-Phe(β-OH)-OMe (5b): The general procedure described above was followed with HCl·H-D,L-Phe(β-OH)-OMe and 4-nitrobenzoyl chloride to give compound **5b** (0.671 g, 39%) as a white solid. M.p. 153.0–155.0 °C (ethyl acetate/diethyl ether). ^{1}H NMR (DMSO): δ = 3.60 (s, 3 H, CH_3 CO_2Me), 4.85 (br. s, 1 H, αCH), 5.22 (br. s, 1 H, βCH), 5.94 (d, J = 6.0 Hz, 1 H, OH), 7.18–7.42 [m, 5 H, ArH Phe(β-OH)], 7.96 [d, J = 8.7 Hz, 2 H, ArH Bz(NO_2)], 8.27 [d, J = 8.7 Hz, 2 H, ArH Bz(NO_2)], 8.95 (d, J = 8.7 Hz, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.96 (OCH_3), 58.43 (αC), 73.45 (βC), 123.80 (CH), 125.55 (CH), 128.24 (CH), 128.43 (CH), 128.61 (C), 139.26 (C), 149.68 (C), 165.51 (C=O), 170.53 (C=O) ppm. $C_{17}H_{16}N_2O_6$ (344.33): calcd. C 59.30, H 4.68, N 8.14; found C 59.04, H 4.80, N 8.03.

2-Fur-D,L-Phe(β-OH)-OMe (5e): The general procedure described above was followed with HCl·H-D,L-Phe(β-OH)-OMe and 2-furanoyl chloride to give compound **5e** (1.24 g, 86%) as a white solid. M.p. 126.0–127.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 3.33 (br. s, 1 H, OH), 3.73 (s, 3 H, CH_3 CO_2Me), 4.98 (dd, J = 9.0, 3.0 Hz, 1 H, αCH), 5.34 (d, J = 3.0 Hz, 1 H, βCH), 6.43–6.45 (m, 1 H, ArH), 7.00 (d, J = 3.6 Hz, 1 H, ArH), 7.18 (d, J = 9.0 Hz, 1 H, NH), 7.24–7.42 (m, 6 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.62 (OCH_3), 57.82 (βCH), 73.43 (αCH), 112.06 (CH), 115.00 (CH), 125.74 (CH), 128.02 (CH), 128.35 (CH), 139.60 (C), 144.33 (CH), 147.00 (C), 158.38 (C=O), 170.72 (C=O) ppm. $C_{15}H_{15}NO_5$ (289.28): calcd. C 62.28, H 5.23, N 4.84; found C 62.23, H 5.25, N 4.90.

General Procedure for the Synthesis of *N*-Acyldehydroamino Acid Methyl Esters: DMAP (0.1 equiv.) was added to a solution of the *N*-acylamino acid methyl ester (2 mmol) in dry acetonitrile (1 M), followed by di-*tert*-butyl dicarbonate (1.0 equiv.) with rapid stirring at room temperature. The reaction was monitored by TLC (diethyl ether/*n*-hexane, 1:1) until all the reactant had been consumed. TMG (2% in volume) was then added, stirring was continued, and the reaction was followed by TLC. When all the reactant had been consumed, evaporation at reduced pressure gave a residue that was partitioned between diethyl ether (100 mL) and $KHSO_4$ (1 M, 30 mL). The organic phase was thoroughly washed with $KHSO_4$ (1 M), $NaHCO_3$ (1 M) and saturated brine (2 × 30 mL) and dried with $MgSO_4$. Removal of the solvent afforded the corresponding *N*-acyldehydroamino acid methyl ester.

Bz-ΔAla-OMe (6a) and Boc-*Z*-ΔAbu-OMe: The synthesis of these compounds has been described elsewhere.[10a,13]

Bz-*Z*-ΔAbu-OMe (2a): The general procedure described above was followed with compound **1a** as substrate to give **2a** (0.34 g, 83%) as a white solid. M.p. 78.0–79.0 °C (diethyl ether/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 2.76 (d, J = 7.5 Hz, 3 H, γCH_3), 3.77 (s, 3 H, CO_2CH_3), 6.88 (q, J = 7.5 Hz, 1 H, βCH), 7.41–7.55 (m, 3 H, ArH), 7.69 (br. s, 1 H, NH), 7.85–7.88 (m, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.86 (γCH_3), 52.32 (OCH_3), 126.07 (C), 127.35 (CH), 128.56 (CH), 131.90 (CH), 133.80 (CH), 133.83 (C), 165.06 (C=O), 165.41 (C=O) ppm. $C_{12}H_{13}NO_3$ (219.24): calcd. C 65.74, H 5.98, N 6.39; found C 65.30, H 5.93, N 6.48.

Bz(4-NO_2)-*Z*-ΔAbu-OMe (2b): The general procedure described above was followed with compound **1b** as substrate to give **2b** (0.375 g, 71%) as a white solid. M.p. 122.5–123.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 1.88 (d, J = 7.2 Hz, 3 H, γCH_3), 3.82 (s, 3 H, CH_3 CO_2Me), 6.97 (q, J = 7.2 Hz, 1 H, βCH), 7.62 (br. s, 1 H, NH), 8.04 (d, J = 9.0 Hz, 2 H, ArH), 8.34 (d, J = 9.0 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.04 (γCH_3), 52.59 (OCH_3), 123.84 (CH), 125.60 (αC), 128.61 (CH), 134.85 (βCH), 139.38 (C), 149.80 (C), 163.45 (C=O), 164.86 (C=O) ppm. $C_{12}H_{12}N_2O_5$ (264.24): calcd. C 54.55, H 4.58, N 10.60; found C 54.52, H 4.43, N 10.57.

Bz(4-OMe)-*Z*-ΔAbu-OMe (2c): The general procedure described above was followed with compound **1c** (3 mmol, 0.804 g) as substrate to give **2c** (0.409 g, 82%) as a white solid. M.p. 112.0–113.0 °C (diethyl ether/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.82 (d, J = 5.4 Hz, 3 H, γCH_3), 3.77 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 6.85 (q, J = 5.4 Hz, 1 H, βCH), 6.93 (d, J = 6.6 Hz, 2 H, ArH), 7.58 (br. s, 1 H, NH), 7.83 (d, J = 6.6 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.87 (γCH_3), 52.32 (OCH_3), 55.36 (OCH_3), 113.77 (CH), 126.07 (C), 126.20 (C), 129.27 (CH), 133.40 (CH), 162.51 (CO), 164.96 (C), 165.22 (CO) ppm. $C_{13}H_{15}NO_4$ (249.26): calcd. C 62.64, H 6.07, N 5.62; found C 62.05, H 6.00, N 5.63.

1-Naph-*Z*-ΔAbu-OMe (2d): The general procedure described above was followed with compound **1d** as substrate to give **2d** (0.473 g, 88%) as a white solid. M.p. 139.5–140.5 °C (ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 1.97 (d, J = 6.9 Hz, 3 H, γCH_3), 3.83 (s, 3 H, CH_3 CO_2Me), 6.98 (q, J = 6.9 Hz, 1 H, βCH), 7.40 (br. s, 1 H, NH), 7.47–7.62 (m, 4 H, ArH), 7.79 (d, J = 6.9 Hz, 1 H, ArH), 7.88–7.98 (m, 2 H, ArH), 8.44 (d, J = 7.8 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.11 (γCH_3), 52.44 (OCH_3), 124.62 (CH), 125.36 (CH), 125.62 (CH), 126.01 (βCH), 126.51 (CH), 127.35 (CH), 128.34 (CH), 130.22 (C), 131.25 (CH), 133.50 (C), 133.72 (C), 134.40 (αC), 165.02 (C=O), 167.30 (C=O) ppm. $C_{16}H_{15}NO_3$ (269.30): calcd. C 71.36, H 5.61, N 5.20; found C 71.13, H 5.44, N 5.33.

2-Fur-*Z*-ΔAbu-OMe (2e): The general procedure described above was followed with compound **1e** as substrate to give **2e** (0.37 g, 88%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84 (d, J = 7.2 Hz, 3 H, γCH_3), 3.78 (s, 3 H, CH_3), 6.51–6.53 (m, 1 H, ArH), 6.90 (q, J = 7.2 Hz, 1 H, βCH), 7.18–7.19 (m, 1 H, ArH), 7.49–7.50 (m, 1 H, ArH), 7.76 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.93 (γCH_3), 52.39 (OCH_3), 112.33 (CH), 115.43 (CH), 125.10 (C), 134.67 (CH), 144.44 (CH), 156.00 (C=O), 164.86 (C=O) ppm.

2-Qnx-*Z*-ΔAbu-OMe (2f): The general procedure described above was followed with compound **1f** as substrate to give **2f** (0.455 g, 84%) as a light yellow solid. M.p. 106.0–107.5 °C (ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 1.93 (d, J = 7.2 Hz, 3 H, γCH_3), 3.83 (s, 3 H, CH_3), 7.00 (q, J = 7.2 Hz, 1 H, βCH), 7.84–7.92 (m, 3 H, ArH), 8.15–8.22 (m, 1 H, ArH), 9.37 (br. s, 1 H, NH) 9.69 (s, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 15.04 (γCH_3), 52.46 (OCH_3), 125.58 (αC), 129.34 (CH), 129.76 (CH), 130.92 (CH), 131.84 (CH), 134.89 (βCH), 140.17 (C), 142.87 (C), 143.83 (CH), 143.98 (C), 161.17 (C=O), 164.75 (C=O) ppm. $C_{14}H_{13}N_3O_3$ (271.27): calcd. C 61.99, H 4.83, N 15.49; found C 62.17, H 4.90, N 14.88.

Bz(4-OMe)-ΔAla-OMe (6c): The general procedure described above was followed with compound **4c** as substrate to give **6c** (0.235 g, 50%) as a white solid. M.p. 39.5–41.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 3.86 (s, 3 H, CH_3), 3.89 (s, 3 H, CH_3), 5.63 (d, J = 1.8 Hz, 1 H, βCH), 6.77 (s, 1 H, βCH), 6.96 (d,

J = 9.0 Hz, 2 H, ArH), 7.81 (d, *J* = 9.0 Hz, 2 H, ArH), 8.46 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 53.02 (OCH_3), 55.40 (OCH_3), 108.38 (βCH_2), 113.94 (CH), 126.46 (C), 128.82 (CH), 131.05 (C), 162.61 (C), 164.87 (C=O), 165.24 (C=O) ppm. $C_{12}H_{13}NO_4$ (235.24): calcd. C 61.27, H 5.57, N 5.95; found C 61.31, H 5.44, N 6.07.

1-Naph-ΔAla-OMe (6d): The general procedure described above was followed with compound **4d** as substrate to give **6d** (0.365 g, 72%) as a colourless oil that solidified on standing. M.p. 58.0–59.0 °C. ^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3 H, CH_3 CO_2Me), 6.08 (d, *J* = 1.5 Hz, 1 H, βCH), 6.92 (s, 1 H, βCH), 7.49–7.62 (m, 4 H, ArH), 7.70–7.73 (m, 1 H, ArH), 7.89–8.00 (m, 2 H, ArH), 8.32 (br. s, 1 H, NH), 8.35–8.38 (m, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 53.08 (OCH_3), 109.35 (βC), 124.69 (CH), 125.18 (CH), 125.27 (CH), 126.60 (CH), 127.45 (CH), 128.43 (CH), 130.04 (C), 131.28 (αC), 131.38 (CH), 133.74 (C), 134.78 (C), 164.56 (C=O), 167.90 (C=O) ppm. $C_{15}H_{13}NO_3$ (255.27): calcd. C 70.58, H 5.13, N 5.49; found C 70.65, H 5.29, N 5.61.

2-Fur-ΔAla-OMe (6e): The general procedure described above was followed with compound **4e** as substrate to give **6e** (0.260 g, 67%) as a white solid. M.p. 55.0–56.0 °C (diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3 H, OCH_3), 5.96 (d, *J* = 1.5 Hz, 1 H, βCH), 6.52–6.45 (m, 1 H, ArH), 6.72 (s, 1 H, βCH), 7.19–7.21 (m, 1 H, ArH), 7.50–7.51 (m, 1 H, ArH), 8.68 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 53.04 (OCH_3), 109.14 (βCH_2), 112.50 (CH), 115.41 (CH), 130.56 (C), 144.50 (CH), 146.87 (C), 147.30 (C=O), 164.34 (C=O) ppm.

Bz-*Z*-ΔPhe-OMe (7a): The general procedure described above was followed with compound **5a** as substrate to give **7a** (0.51 g, 90%) as a white solid. M.p. 126.0–127.0 °C (diethyl ether/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 3.88 (s, 3 H, CO_2CH_3), 7.28–7.35 (m, 3 H, ArH), 7.42–7.57 (m, 6 H, ArH, βCH), 7.86–7.90 (m, 2 H, ArH), 8.03 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.66 (OCH_3), 124.30 (C), 127.45 (CH), 128.53 (CH), 128.63 (CH), 129.39 (CH), 129.62 (CH), 132.06 (CH), 133.40 (C), 133.70 (C), 165.83 (C=O) ppm.

Bz(4-NO_2)-*Z*-ΔPhe-OMe (7b): The general procedure described above was followed with compound **5b** as substrate to give **7b** (0.568 g, 87%) as a light yellow solid. M.p. 186.5–187.5 °C (ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 3.89 (s, 3 H, CH_3 CO_2Me), 7.34–7.36 (m, 3 H, ArH), 7.47–7.50 (m, 2 H, ArH), 7.55 (s, 1 H, βCH), 8.00 (br. s, 1 H, NH), 8.02 [d, *J* = 8.4 Hz, 2 H, ArH Bz(NO_2)], 8.31 [d, *J* = 8.4 Hz, 2 H, ArH Bz(NO_2)] ppm. ^{13}C NMR ($CDCl_3$): δ = 52.95 (OCH_3), 123.84 (CH), 123.44 (αC), 123.97 (CH), 128.64 (CH), 128.72 (CH), 129.58 (CH), 129.83 (CH), 132.92 (C), 133.54 (αC), 138.98 (C), 149.95 (C), 163.75 (C=O), 165.49 (C=O) ppm. $C_{17}H_{14}N_2O_5$ (326.31): calcd. C 62.58, H 4.32, N 8.59; found C 62.43, H 4.13, N 8.64.

2-Fur-Z-ΔPhe-OMe (7e): The general procedure described above was followed with compound **5e** as substrate to give **7e** (0.493 g, 91%) as a white solid. M.p. 122.0–123.0 °C (diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 3.86 (s, 3 H, CH_3 OMe), 6.53–6.55 (m, 1 H, ArH), 7.19–7.21 (m, 1 H, ArH), 7.33–7.40 (m, 3 H, ArH), 7.47 (s, 1 H, βCH), 7.50–7.53 (m, 3 H, ArH), 7.94 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.69 (OCH_3), 112.42 (CH), 115.81 (CH), 123.25 (C), 128.56 (CH), 129.46 (CH), 129.66 (CH), 132.32 (CH), 133.61 (C), 144.60 (CH), 147.20 (C), 156.24 (C), 165.50 (CH) ppm. $C_{15}H_{13}NO_4$ (271.27): calcd. C 66.42, H 4.83, N 5.16; found C 66.41, H 4.94, N 5.19.

General Procedure for the Synthesis of Oxazole Derivatives: A dried Schlenk tube was charged with the dehydroamino acid derivative (0.44 mmol), K_2CO_3 (2 equiv.) and THF (2 mL). A solution of I_2 (1.2 equiv.) in THF (1 mL) was added at 0 °C. The tube was sealed, and the reaction mixture was stirred at 80 °C for ≈3 h. After the system had cooled to room temperature, DBU (2 equiv.) was added and the tube was heated for ≈3 h at 80 °C. The reaction mixture was quenched with a saturated solution of $Na_2S_2O_3$ (2 mL). The organic phase was separated and dried with $MgSO_4$, and the solvent was evaporated. The residue was subjected to column chromatography.

Oxazole 3a:[14] The general procedure described above was used with **2a** (97.0 mg, 0.44 mmol) to give compound **3a** (87.0 mg, 91%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:1) . M.p. 88.0–89.0 °C (diethyl ether/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 2.70 (s, 3 H, CH_3), 3.94 (s, 3 H, CH_3 CO_2Me), 7.42–7.45 (m, 3 H, ArH), 8.04–8.07 (m, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.04 (CH_3), 51.93 (OCH_3), 126.45 (CH), 128.43 (C), 128.64 (CH), 130.68 (CH), 156.31 (C), 159.58 (C), 162.77 (C=O) ppm. $C_{12}H_{11}NO_3$ (217.22): calcd. C 66.35, H 5.10, N 6.45; found C 66.54, H 5.12, N 6.46.

Oxazole 3b: The general procedure described above was used with **2b** (116 mg, 0.44 mmol) to give compound **3b** (82.0 mg, 71%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:1). M.p. 169.0–170.0 °C (diethyl ether/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 2.77 (s, 3 H, CH_3), 3.98 (s, 3 H, CH_3 CO_2Me), 8.26 (d, *J* = 9.0 Hz, 2 H, ArH), 8.34 (d, *J* = 9.0 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.21 (CH_3), 52.10 (OCH_3), 124.11 (CH), 127.26 (CH), 129.37 (C), 131.88 (C), 148.86 (C), 157.48 (C), 157.68 (C), 162.31 (C=O) ppm. HRMS (EI): calcd. for $C_{12}H_{10}N_2O_5$ 262.0590; found 262.0591.

Oxazole 3c: The general procedure described above was used with **2c** (110 mg, 0.44 mmol) to give compound **3c** (79.4 mg, 73%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:1). M.p. 105.0–106.0 °C (diethyl ether/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 2.70 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.97 (d, *J* = 9.0 Hz, 2 H, ArH), 8.02 (d, *J* = 9.0 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.01 (CH_3), 51.90 (OCH_3), 55.30 (OCH_3), 114.07 (CH), 119.20 (C), 128.19 (CH), 155.82 (C), 159.70 (C), 161.58 (C), 162.93 (C=O) ppm. HRMS (EI): calcd. for $C_{13}H_{13}NO_4$ 247.0845; found 247.0840.

Oxazole 3d: The general procedure described above was used with **2d** (118 mg, 0.44 mmol) to give compound **3d** (100 mg, 85%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:1). M.p. 78.0–79.0 °C (diethyl ether/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 2.78 (s, 3 H, CH_3), 3.99 (s, 3 H, CH_3 CO_2Me), 7.52–7.70 (m, 3 H, ArH), 7.91 (d, *J* = 8.1 Hz, 1 H, ArH), 7.98 (d, *J* = 8.1 Hz, 1 H, ArH), 8.20 (dd, *J* = 7.2, 1.2 Hz, 1 H, ArH), 9.20 (d, *J* = 7.2 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.14 (CH_3), 51.95 (OCH_3), 123.09 (C), 124.76 (CH), 126.03 (CH), 126.36 (CH), 127.77 (CH), 128.12 (CH), 128.49 (CH), 128.56 (C), 130.04 (C), 131.60 (CH), 133.80 (C), 156.15 (C), 159.54 (C), 162.97 (C=O) ppm. HRMS (EI): calcd. for $C_{16}H_{13}NO_3$ 267.0895; found 267.0899.

Oxazole 3e: The general procedure described above was followed with **2e** as substrate to give compound **3e** (82.0 mg, 90%) as a white solid. M.p. 110.0–111.0 °C (diethyl ether/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 2.71 (s, 3 H, CH_3), 3.95 (s, 3 H, CO_2CH_3), 6.54–6.56 (m, 1 H, ArH), 7.11–7.12 (m, 1 H, ArH), 7.56–7.57 (m, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.92 (CH_3), 51.96 (OCH_3), 111.89 (CH), 112.25 (CH), 128.22 (C), 141.97 (C), 144.64 (CH), 152.28 (C), 155.81 (C), 162.55 (C=O) ppm. $C_{10}H_9NO_4$ (207.18): calcd. C 57.97, H 4.38, N 6.76; found C 57.69, H 4.42, N 6.65.

Oxazole 3f: The general procedure described above was used with **2f** (119 mg, 0.44 mmol) to give compound **3f** (45 mg, 38%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:1). M.p. 176.0–177.0 °C (diethyl ether/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 2.86 (s, 3 H, CH_3), 4.01 (s, 3 H, CH_3 CO_2Me), 7.84–7.90 (m, 2 H, ArH), 8.18–8.28 (m, 2 H, ArH), 9.75 (s, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 12.46 (CH_3), 52.28 (OCH_3), 129.46 (CH), 129.80 (CH), 131.02 (CH), 131.29 (CH), 139.97 (C), 141.49 (C), 142.71 (C), 143.66 (CH), 156.84 (C), 158.79 (C), 162.26 (C=O) ppm. $C_{14}H_{11}N_3O_3$ (269.26): calcd. C 62.45, H 4.12, N 15.61; found C 62.66, H 4.18, N 15.24.

Oxazole 8a: The general procedure described above was used with **7a** (124 mg, 0.44 mmol) to give compound **8a** (53.0 mg, 43%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:1). M.p. 74.0–75.0 °C (diethyl ether/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.99 (s, 3 H, CH_3 CO_2Me), 7.49–7.52 (m, 6 H, ArH), 8.15–8.18 (m, 4 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 52.38 (OCH_3), 126.30 (C), 126.83 (CH), 126.97 (C), 127.91 (C), 128.43 (CH), 128.45 (CH), 128.82 (CH), 130.36 (CH), 131.11 (CH), 130.74 (C), 155.20 (C), 159.79 (C), 162.69 (C=O) ppm. HRMS (EI): calcd. for $C_{17}H_{13}NO_3$ 279.0895; found 279.0895. Bz-*Z*-ΔPhe(β-I)-OMe (**9a**) was also isolated in 32% yield.

Bz-*Z*-ΔPhe(β-I)-OMe (9a): The same procedure as described above but at room temperature afforded **9a** as a white solid (156 mg, 87%). M.p. 136.0–137.0 °C (diethyl ether/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (s, 3 H, CH_3 CO_2Me), 7.30–7.39 (s, 5 H, ArH), 7.50–7.63 (s, 3 H, ArH), 7.88 (br. s, 1 H, NH), 7.92–7.94 (m, 2 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 52.61 (OCH_3), 95.69 (C), 127.45 (CH), 128.24 (CH), 128.85 (CH), 128.93 (CH), 129.03 (CH), 132.24 (C), 132.73 (CH), 133.65 (C), 140.17 (C), 162.11 (C=O), 164.78 (C=O) ppm. $C_{17}H_{14}INO_3$ (407.20): calcd. C 50.14, H 3.47, N 3.44; found C 50.55, H 3.52, N 3.80. Compound **9a** was also obtained from compound **3a** in 86% yield by treatment with NIS (2.5 equiv.) in dichloromethane followed by triethylamine (1.5 equiv.).

Bz-ΔAla(β,β-I)-OMe (10a): The general procedure described above was followed with **6a** (90.3 mg, 0.44 mmol) as substrate, but without addition of DBU, to give compound **10a** (80.4 mg, 40%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:1). M.p. 138.0–139.0 °C (diethyl ether/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, CH_3 CO_2Me), 7.51–7.61 (m, 3 H, ArH), 7.85–7.87 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 6.01 (C), 53.16 (OCH_3), 127.45 (CH), 128.52 (C), 129.08 (CH), 131.68 (C), 132.97 (CH), 139.53 (C), 162.62 (C=O), 163.24 (C) ppm.

Bz(4-OMe)-ΔAla(β,β-I)-OMe (10c): The general procedure described above was followed with **6c** (104 mg, 0.44 mmol) as substrate, but without addition of DBU, to give compound **10c** (90.0 mg, 42%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:1). M.p. 151.0–152.0 °C (diethyl ether/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, 3 H, CH_3 OMe), 3.94 (s, 3 H, CH_3 OMe), 6.97 (d, *J* = 8.7 Hz, 2 H, ArH), 7.82 (d, *J* = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 5.32 (C), 53.11 (OCH_3), 55.52 (OCH_3), 114.24 (CH), 123.70 (C), 128.61 (C), 129.48 (CH), 139.71 (C), 162.70 (C=O), 163.35 (C=O) ppm. HRMS (EI): calcd. for $C_{12}H_{11}NO_4I_2$ 486.8777; found 486.8771.

1-Naph-ΔAla(β,β-I)-OMe (10d): The general procedure described above was followed with **6d** (112 mg, 0.44 mmol) as substrate, but without addition of DBU, to give compound **10d** (105 mg, 47%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:1). M.p. 165.0–166.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 4.00 (s, 3 H, CH_3 OMe), 7.51–7.64 (m, 5 H, ArH, NH), 7.81 (d, *J* = 7.2 Hz, 1 H, ArH), 7.90–7.93 (m, 1 H, ArH), 8.03 (d, *J* = 8.1 Hz, 1 H, ArH), 8.42 (d, *J* = 8.1 Hz, 1 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 8.40 (C), 53.20 (OCH_3), 124.61 (CH), 125.20 (CH), 126.03 (CH), 126.87 (CH), 127.83 (CH), 128.48 (CH), 130.18 (C), 130.95 (C), 132.33 (CH), 133.76 (C), 139.54 (C), 165.05 (C=O), 163.35 (C=O) ppm. HRMS (ESI): calcd. for $C_{15}H_{12}NO_3I_2$ 507.8901; found 507.8828.

2-Fur-ΔAla(β,β-I)-OMe (10e): The general procedure described above was followed with **6e** (86.0 mg, 0.44 mmol) as substrate, but without addition of DBU, to give compound **10e** (104 mg, 53%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:1). M.p. 135.0–136.0 °C (diethyl ether/petroleum ether). ^{1}H NMR ($CDCl_3$): δ = 3.94 (s, 3 H, CH_3 OMe), 6.58–6.59 (m, 1 H, ArH), 7.25–7.27 (m, 1 H, ArH), 7.56–7.58 (m, 1 H, ArH), 8.06 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 6.12 (C), 53.13 (OCH_3), 112.96 (CH), 117.20 (CH), 138.73 (C), 145.38 (CH), 145.60 (C), 153.78 (C=O), 162.54 (C=O) ppm.

Bz(4-NO_2)-*Z*-ΔPhe(β-I)-OMe (9b): The general procedure described above was followed with **7b** (144 mg, 0.44 mmol) as substrate, but without addition of DBU, to give compound **9b** (169 mg, 85%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:2). M.p. 157.0–158.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 3.55 (s, 3 H, OCH_3), 7.35 (br. s, 5 H, ArH), 7.94 (br. s, 1 H, NH), 8.09 (d, *J* = 8.7 Hz, 2 H, ArH), 8.37 (d, *J* = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.76 (OCH_3), 98.88 (C), 124.12 (CH), 128.33 (CH), 128.44 (CH), 128.67 (CH), 129.33 (CH), 132.94 (C), 137.70 (C), 139.95 (C), 150.20 (C), 161.89 (C=O), 162.93 (C=O) ppm. HRMS (ESI): calcd. for $C_{17}H_{14}N_2O_5I$ 452.9942; found 452.9869.

2-Fur-*Z*-ΔPhe(β-I)-OMe (9e): The general procedure described above was followed with **7e** (119 mg, 0.44 mmol) as substrate, but without addition of DBU, to give compound **9e** (145 mg, 83%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:2). M.p. 130.0–131.0 °C (ethyl acetate/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 3.54 (s, 3 H, OCH_3), 6.58–6.60 (m, 1 H, ArH), 7.26–7.37 (m, 6 H, ArH), 7.58–7.59 (m, 1 H, ArH), 8.06 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 52.60 (OCH_3), 95.51 (C), 112.82 (CH), 116.68 (CH), 128.23 (CH), 128.85 (CH) 129.02 (CH), 132.87 (C), 140.22 (C), 145.17 (CH), 146.31 (C), 155.41 (C=O), 162.02 (C=O) ppm.

Bz-*Z*-ΔAbu(β-I)-OMe (11): The general procedure described above was followed with **2a** (96.5 mg, 0.44 mmol) as substrate, but without addition of DBU, to give compound **11** (123 mg, 81%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:2). M.p. 155.0–156.0 °C (diethyl ether/*n*-hexane). ^{1}H NMR ($CDCl_3$): δ = 2.82 (s, 3 H, γCH_3), 3.86 (s, 3 H, CH_3 CO_2Me), 7.46–7.60 (m, 3 H, ArH), 7.64 (s, 1 H, NH), 7.85–7.89 (m, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.88 (γCH_3), 52.72 (OCH_3), 101.82 (C), 127.33 (CH), 128.82 (CH), 131.58 (C), 132.46 (CH), 132.55 (C), 161.47 (C=O), 164.98 (C=O) ppm. $C_{12}H_{12}NO_3I$(345.13): calcd. C 41.76, H 3.50, N 4.07; found C 41.89, H 3.56, N 4.42. Compound **11** was also obtained from compound **2a** in a 87% yield by treatment with NIS (2.5 equiv.) in dichloromethane followed by triethylamine (1.5 equiv.).

Boc-Z-ΔAbu(β-I)-OMe: The general procedure described above was followed with Boc-ΔAbu-OMe (94.7 mg, 0.44 mmol) as substrate, but without addition of DBU, to give Boc-*Z*-ΔAbu(β-I)-OMe (131 mg, 87%) as a white solid after column chromatography in diethyl ether/petroleum ether (1:2). M.p. 67.0–68.0 °C (diethyl ether/*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9 H,

CH_3 Boc), 2.73 (s, 3 H, γCH_3), 3.83 (s, 3 H, OCH_3), 6.15 (s, 1 H, NH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 28.07 [$(CH_3)_3C$], 52.44 (OCH_3), 81.51 [$(CH_3)_3C$], 98.62 (C), 131.69 (C), 152.48 (C=O), 161.72 (C=O) ppm. $C_{10}H_{16}NO_4I$ (341.01): calcd. C 35.21, H 4.73, N 4.11; found C 35.44, H 4.67, N 4.12.

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[1] a) N. Lindquist, W. Fenical, G. D. Van Duyne, J. Clardy, *J. Am. Chem. Soc.* **1991**, *113*, 2303–2304; b) J. Kobayashi, M. Tsuda, H. Fuse, T. Sasaki, Y. Mikami, *J. Nat. Prod.* **1997**, *60*, 150–154; c) J. R. Lewis, *Nat. Prod. Rep.* **1999**, *16*, 389–416; d) Z. Cruz-Monserrate, H. C. Vervoort, R. Bai, D. J. Newman, S. B. Howell, G. Los, J. T. Mullaney, M. D. Williams, G. R. Pettit, W. Fenical, E. Hamel, *Mol. Pharmacol.* **2003**, *63*, 1273–1280.

[2] a) Y. Li, J. C. Milne, L. L. Madison, R. Kolter, C. T. Walsh, *Science* **1996**, *274*, 1188–1190; b) R. S. Roy, A. M. Gehring, J. C. Milne, P. J. Belshaw, C. T. Wash, *Nat. Prod. Rep.* **1999**, *16*, 249–263.

[3] J. W. Cornforth, R. H. Cornforth, *J. Chem. Soc.* **1947**, 96–102.

[4] M. P. Doyle, W. E. Buhro, J. G. Davidson, R. C. Elliot, J. W. Hoekstra, M. Oppenhuizen, *J. Org. Chem.* **1980**, *45*, 3657–3664.

[5] R. H. Prager, J. A. Smith, B. Weber, C. M. Williams, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2665–2672.

[6] a) P. Wipf, C. P. Miller, *J. Org. Chem.* **1993**, *58*, 3604–3606; b) M. Pulici, F. Quartier, E. R. Felder, *J. Comb. Chem.* **2005**, *7*, 463–473; c) M. Keni, J. J. Tepe, *J. Org. Chem.* **2005**, *70*, 4211–4213.

[7] A. J. Phillips, Y. Uto, P. Wipf, M. J. Reno, D. R. Williams, *Org. Lett.* **2000**, *2*, 1165–1168.

[8] T. Morwick, M. Hrapchak, M. DeTuir, S. Campbell, *Org. Lett.* **2002**, *4*, 2665–2668.

[9] R. Martín, A. Cuenca, S. L. Buchwald, *Org. Lett.* **2007**, *9*, 5521–5524.

[10] a) P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, J. Sacramento, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3697–3703; b) P. M. T. Ferreira, L. S. Monteiro, G. Pereira, L. Ribeiro, J. Sacramento, L. Silva, *Eur. J. Org. Chem.* **2007**, 5934–5949.

[11] a) P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, J. Sacramento, J. Sebastião, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3317–3324; b) P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, J. Sacramento, *J. Chem. Soc. Perkin Trans. 1* **2001**, 3167–3174; c) P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, *Eur. J. Org. Chem.* **2003**, 2635–2644; 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) P. M. T. Ferreira, L. S. Monteiro, *Eur. J. Org. Chem.* **2006**, 3226–3234.

[12] M. Pattarozzi, C. Zonta, Q. B. Broxterman, B. Kaptein, R. De Zorzi, L. Randaccio, P. Scrimin, G. Licini, *Org. Lett.* **2007**, *9*, 2365–2368.

[13] P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro, *Tetrahedron Lett.* **2003**, *44*, 2137–2139.

[14] B. Clapham, C. Spanka, K. D. Janda, *Org. Lett.* **2001**, *3*, 2173–2176.

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