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Synthesis of new oxazole-containing peptidomimetics

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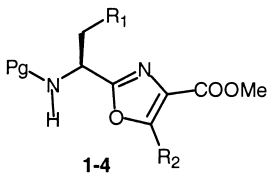
Abstract

Enantiospecific syntheses of optically active amino acids containing an oxazole moiety are described. Two different strategies for their insertion in a peptidomimetic chain are also discussed. The procedures presented are based on materials readily available in multigram quantities.

1. Introduction

The synthesis of optically active amino acids is an area that is currently attracting considerable interest, mainly due to the commercial importance of biologically active peptides that incorporate synthetic amino acids.[1] In continuing our studies directed towards the preparation of unnatural amino acids,[2] we have considered oxazole-containing amino acids. Oxazoles are important compounds as precursors of peptidomimetic structures[3] and constituents of biologically active natural marine metabolites,[4] therefore some methods that effect their preparation from α-amino acids have been proposed. However, several of these methods suffer from one or more drawbacks, such as low overall yield, use of hazardous or expensive reagents and failure in large-scale preparation.[5] Here we wish to report the synthesis of optically active oxazole amino acids **1**–**4** along with two different strategies for their insertion into peptidomimetic chains.



1-4

	R_1	R_2	Pg
1	Ph	OMe	Cbz
2	Ph	Me	Cbz
3	COOBn	OMe	Boc
4	COOBn	Me	Cbz

The preparation of compounds **1**–**4** has been approached through the retrosynthetic correlation of the oxazole ring with a β-carbonyl amide that could be prepared from *N*-protected α-amino acid amide by rhodium(II) catalysed N–H insertion of a diazocarbonyl compound[6] (Scheme 1).

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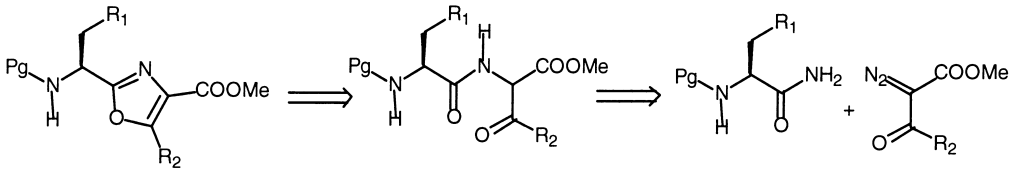
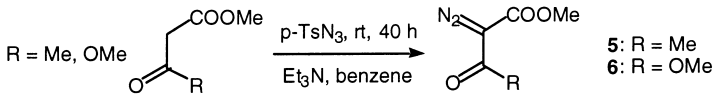


Scheme 1.

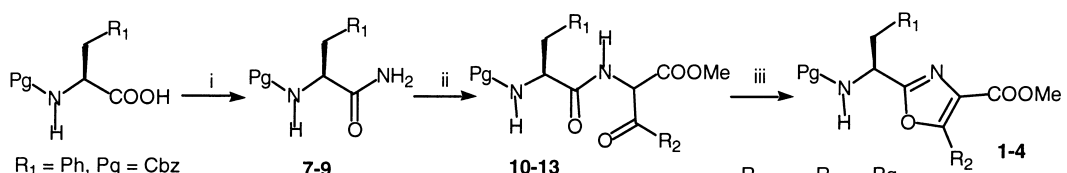
2. Results and discussion

We have prepared the diazoderivatives **5** and **6** by treatment of *p*-toluenesulphonyl azide (*p*-TsN_3)[7] with methyl acetoacetate and dimethylmalonate respectively in benzene/Et_3N at room temperature (Scheme 2); the crude diazocompounds **5**–**6** were separated from unreacted products by flash chromatography. Compounds **5** and **6** were obtained in 81–88% yield as stable liquids that could be further purified by vacuum distillation. In our experience, no hazard was apparent during preparation and handling of these diazocompounds; however, due to the general explosive nature of diazo and azide compounds, the experiments were conducted behind an auxiliary safety shield in a closed fume hood.[7]



Scheme 2.

The amides Cbz–Phe–NH_2 **7**, Boc–Asp(OBn)–NH_2 **8** and Cbz–Asp(OBn)–NH_2 **9** were prepared following standard methods[8] (Scheme 3). When the amide **7** was treated with diazocompounds **5** or **6** in $CHCl_3$ in the presence of a catalytic amount of Rh(II) acetate dimer, the reaction proceeded very smoothly to the formation of the corresponding derivatives **10** and **11** in excellent yield. By the same procedure, starting from amides **8** and **9**, we have thus obtained the intermediates **12** and **13**, respectively. During these processes, any trace of water and alcohols should be avoided since the O–H insertion reaction was competitive with the desired N–H insertion in the C=N_2 bond: we recovered derivatives **10**–**13** in high yield only when dry ethanol-free $CHCl_3$ was used. The cyclodehydration of amides **10**–**13** was carried out with PPh_3 and I_2 in the presence of Et_3N in CH_2Cl_2: after removal of any volatile product and purification of the crude products we obtained the oxazoles **1**–**4** in satisfactory yields.

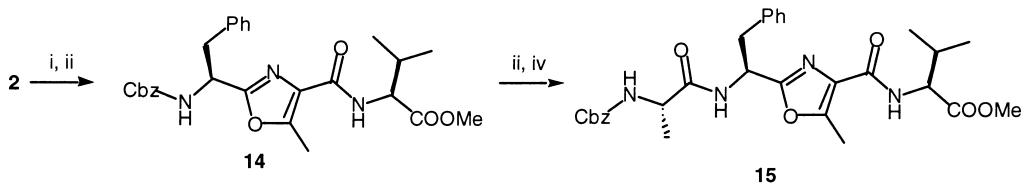


	R_1	R_2	Pg
7	Ph	-	Cbz
8	COOBn	-	Boc
9	COOBn	-	Cbz
10	Ph	OMe	Cbz
11	Ph	Me	Cbz
12	COOBn	OMe	Boc
13	COOBn	Me	Cbz

Scheme 3.

Oxazole-containing amino acids **2** and **3** were inserted into a peptidic frame following two different strategies. As a first approach, we prepared the peptoid **14** starting from **2** and carrying out the methylester cleavage with 2 N NaOH/MeOH followed by amide coupling with H–Val–OMe (Scheme 4) using the mixed anhydride protocol. The hydrogenolysis of product **14** in the presence of 10% Pd/C provided the

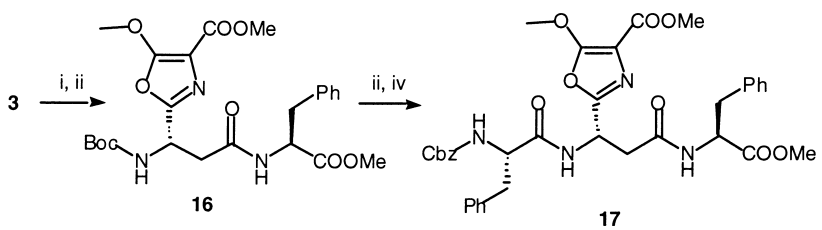
removal of Cbz group; a successive amide coupling with Cbz–Ala–OH afforded compound **15** in good yield. In this manner the complete incorporation of compound **2** in a peptidomimetic chain was realised.



Reagents and conditions: i) NaOH 2N/MeOH 1/2, 35°C, 1 h. ii) Bu^{i}OCOCl, 4-methylmorpholine, -15°C, H-Val-OMe, then rt12 h. iii) H_2, 10% Pd/C, MeOH, rt, 40 min. iv) Cbz-Ala-OH, Bu^{i}OCOCl, 4-methylmorpholine, -15°C then rt12 h.

Scheme 4.

The incorporation of compound **3** in a peptoid chain (Scheme 5) was also realised in a different way. The sequence adopted started with the removal of the β-benzyl ester group from oxazole **3**. The subsequent amide coupling with H–Phe–OMe afforded product **16**. The cleavage of the Boc group in the structure **16** was carried out with HCl/EtOAc and the next amide coupling with Cbz–Phe–OH afforded compound **17** in which the oxazole structure is in a side branch of the main peptoid chain.



Reagents and conditions: i) H_2, 10% Pd/C, MeOH, rt, 40 min. ii) Bu^{i}OCOCl, 4-methylmorpholine, -15°C, H-Phe-OMe, then rt12 h. iii) HCl 4N in EtOAc, rt, 1 h. iv) Cbz-Val-OH, Bu^{i}OCOCl, 4-methylmorpholine, -15°C then rt12 h.

Scheme 5.

Compounds **15** and **17** are currently under investigation as to their biological activity while oxazole amino acids **3** and **4** are being checked as possible substrates for the preparation of new peptide dendrimers.[9]

3. Experimental section

Boiling points are uncorrected. Elemental analyses were performed on a Perkin–Elmer 420 B analyser. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter in a 1 dm tube. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were obtained with a Varian VXR-300 spectrometer from $CDCl_3$ solutions. All reactions involving air sensitive materials were carried out under an N_2 atmosphere; all reagents and solvents employed were reagent grade materials purified by standard methods and distilled before use. The $CHCl_3$ was washed with H_2O seven times, dried over $CaCl_2$ overnight, filtered and stored over molecular sieves at 5°C. As chiral starting material, (*S*)-aspartic acid, (*S*)-phenylalanine, (*S*)-valine and (*S*)-alanine of 'BioChemika' grade (chemical and enantiomeric purity >99%) purchased from Fluka Chemie AG were used.

3.1. General procedure for diazocompounds **5** and **6**

A solution of *p*-TsN_3 (20 g, 101 mmol), Et_3N (16 mL, 114 mmol) and dimethylmalonate (14.1 g, 107 mmol) or methylacetoacetate (12.4 g, 107 mmol) in dry benzene (90 mL) was allowed to stand at rt for 2 h, at which time a solid precipitated. After standing for 48 h at rt, the solvent was removed under reduced pressure and the residue was separated from by-products by flash chromatography on silica and further purified by vacuum distillation.

3.1.1. 2-Diazodimethylmalonate, **5**

TLC: EtOAc:petroleum ether (3:7); 88% yield; bp 40–45°C/0.05 mbar. Calculated for $C_5H_6N_2O_4$: C, 37.98; H, 3.82; N, 17.72. Found: C, 37.89; H, 3.87; N, 17.77.

3.1.2. 2-Diazomethylacetoacetate, **6**

TLC: EtOAc:petroleum ether (1.5:8.5); 81% yield; bp 38–40°C/0.05 mbar. Calculated for $C_5H_6N_2O_3$: C, 42.26; H, 4.26; N, 19.71. Found: C, 42.27; H, 4.30; N, 19.65.

3.2. General procedure for **7**–**9**

Ethyl chloroformate (1.05 mL, 11 mmol) in CH_2Cl_2 (20 mL) at −15°C, was added slowly and under vigorous stirring to 4-methylmorpholine (1.21 mL, 11 mmol) and carboxylic acid [Z–Phe–OH, Boc–Asp(OBn)–OH or Cbz–Asp(OBn)–OH] (10 mmol) in CH_2Cl_2 (80 mL). The mixture was stirred at −15°C for 20 min, then saturated with $NH_{3(g)}$. The mixture was allowed to warm to rt. After 12 h stirring at rt, the solvent was eliminated in vacuo; to the residue H_2O (50 mL) and EtOAc (100 mL) were added and the aqueous layer was separated. The organic solution was washed with 10% aq. $KHSO_4$, sat. aq. NaCl, 10% aq. $NaHCO_3$, sat. aq. NaCl (20 mL of each), in that order, and dried (Na_2SO_4). The solvent was removed under reduced pressure affording pure amides.

3.2.1. (S)-N-*Benzyloxycarbonyl phenylalanylamide*, **7**

TLC: EtOAc:petroleum ether:Et_3N (7:3:0.1); 87% yield, ^{1}H NMR δ: 7.40–7.13 (m, 10H, Ar), 5.81 (bs, 1H, NH), 5.59 (bs, 1H, NH), 5.43 (d-like, 1H, NH), 5.07 (s, 2H, OC*H*$_2$Ph), 4.44 (m, 1H, C*H*CH$_2$Ph), 3.15–2.99 (m, 2H, CHC*H*$_2$Ph). Calculated for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.39; H, 6.04; N, 9.44.

3.2.2. (S)-β-*Benzylester*-N-tert-*butoxycarbonyl aspartylamide*, **8**

TLC: EtOAc:petroleum ether:Et_3N (7:3:0.1); 99% yield. ^{1}H NMR δ: 7.40–7.30 (m, 5H, Ph), 6.46 (bs, 1H, NH), 5.70 (d-like, 1H, NH), 5.44 (bs, 1H, NH), 5.14 (AB system, 2H, OC*H*$_2$Ph), 4.60–4.50 (m, 1H, CH), 3.08 (dd, 1H, J_1=4.3, J_2=17, CHC*H*$_2$COO), 2.72 (dd, 1H, J_1=6, J_2=17, CHC*H*$_2$COO), 1.44 (s, 9H, *t*-Bu). Calculated for: $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.55; H, 6.91; N, 8.72.

3.2.3. (S)-β-*Benzylester*-N-*benzyloxycarbonyl aspartylamide*, **9**

TLC: EtOAc:petroleum ether (6:4), 69% yield. ^{1}H NMR δ: 7.45–7.29 (m, 10H, Ar), 6.50 (bs, 1H, NH), 6.07 (d-like, 1H, NH), 5.87 (bs, 1H, NH), 5.21–5.08 (m, 4H, OC*H*$_2$Ph), 4.70–4.56 (m, 1H, C*H*CH2COO), 3.07 (dd, 1H, J_1=4.5, J_2=17, CHC*H*$_2$COO). Calculated for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.12; H, 5.61; N, 7.82.

3.3. General procedure for **10**–**13**

A solution of the diazocompound **5** or **6** (7 mmol) in dry chloroform (35 mL) was added dropwise over 3 h to a refluxing solution of the suitable amide **7**–**9** (5 mmol) and $Rh_2(OAc)_4$ (44 mg, 0.1 mmol) in dry chloroform (130 mL). The mixture was refluxed for a further 24 h, allowed to cool, evaporated in vacuo and the crude product purified by flash chromatography on silica.

3.3.1. (RS)-N-[(S)-N-Benzyloxycarbonylphenylalanyl]-2-amino dimethylmalonate, **10**

TLC: EtOAc:petroleum ether (5:7); 80% yield, ^{1}H NMR δ: 7.40–7.15 (m, 11H, Ar+NH), 6.80 (bs, 1H, NH), 5.30–5.20 (m, 1H, CHCOO), 5.14–5.06 (m, 2H, OC*H*$_2$Ph), 4.60–4.47 (m, 1H, C*H*CH$_2$Ph), 3.79 (s, 6H, OCH$_3$), 3.11 (d-like, 2H, C*H*$_2$Ph). Calculated for $C_{22}H_{24}N_2O_7$: C, 61.67; H, 5.65; N, 6.54. Found: C, 61.61; H, 5.61; N, 6.61.

3.3.2. (RS)-N-[(S)-N-Benzyloxycarbonylphenylalanyl]-2-amino methylacetoacetate, **11**

TLC: EtOAc:petroleum ether (5:7); 92% yield, ^{1}H NMR δ: 7.40–7.15 (m, 10H, Ar), 7.02–6.85 (m, 1H, NH), 5.41–5.02 (m, 3H, C*H*COOCH$_3$+OC*H*$_2$Ph+NH), 4.67–4.42 (m, 1H, NH), 3.90–3.82 (m, 1H, C*H*CH$_2$Ph) 3.78 (s, 3H, OCH$_3$) 3.10 (d-like, 2H, CHC*H*$_2$Ph), 2.31 (s, 3H, COCH$_3$). Calculated for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 64.13; H, 5.88; N, 6.71.

3.3.3. (RS)-N-[(S)-β-Benzylester-N-tert-butoxycarbonylaspartyl]-2-amino dimethylmalonate, **12**

TLC: EtOAc:petroleum ether (1:1); 74% yield, ^{1}H NMR δ: 7.55 (d-like, 1H, NH), 7.31–7.15 (m, 5H, Ph), 5.8 (d-like, 1H, NH), 5.10–4.98 (m, 3H, CHCOO+OC*H*$_2$Ph), 4.65–4.49 (m, 1H, C*H*CH$_2$COO), 3.67 (s, 6H, COOCH$_3$), 2.79 (AB part of an ABX system, 2H, CHC*H*$_2$COO), 1.36 (s, 9H, *t*-Bu). Calculated for $C_{21}H_{28}N_2O_9$: C, 55.75; H, 6.24; N, 6.19. Found: C, 55.81; H, 6.22; N, 6.23.

3.3.4. (RS)-N-[(S)-β-Benzylester-N-benzyloxycarbonylaspartyl]-2-amino methylacetoacetate, **13**

TLC: EtOAc:petroleum ether (1:1); 79% yield, ^{1}H NMR δ: 7.57 (bs, 1H, NH), 7.40–7.25 (m, 10H, Ar), 5.95 (d-like, 1H, NH), 5.21–5.05 (m, 5H, OC*H*$_2$Ph+C*H*COCH$_3$), 4.77–4.61 (m, 1H, C*H*CH$_2$COO), 3.79 (s, 3H, COOCH$_3$), 3.16–3.00 (m, 1H, CHC*H*$_2$COO), 2.85–2.69 (m, 1H, CHC*H*$_2$COO), 2.35 (s, 3H, COC*H*$_3$). Calculated for $C_{24}H_{26}N_2O_8$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.31; H, 5.60; N, 5.90.

3.4. General procedure for **1**–**4**

To a stirred solution of PPh_3 (1.6 g, 6 mmol) and I_2 (1.5 g, 6 mmol) in dry dichloromethane (40 mL) at rt, Et_3N (1.7 mL, 12 mmol) and the ketoamide **10**–**13** (3 mmol), in dry dichloromethane (10 mL) were added sequentially. The mixture was stirred overnight, evaporated in vacuo, and the crude product purified by flash chromatography on silica.

3.4.1. (S)-1-N-Benzyloxycarbonylamino-1-(4′′-carboxymethyl-5′′-methoxy-2′′-oxazolyl)-2-phenylethane, **1**

TLC: EtOAc:petroleum ether (8:2); 34% yield, $[\alpha]_D^{20}$ −18.7 (c 0.5, CH_2Cl_2); ^{1}H NMR δ: 7.39–7.12 (m, 10H, Ar), 7.03 (bs, 1H, NH), 5.46–4.87 (m, 3H, CH+OC*H*$_2$Ph), 3.91 (s, 3H, OCH$_3$), 3.83 (s, 3H, OCH$_3$), 3.30–3.18 (m, 2H, CHC*H*$_2$Ph). ^{13}C NMR δ: 163.2, 160.7, 156.3, 155.5, 140.1, 136.1, 135.6, 128.6, 128.2, 128.0, 127.9, 127.4, 126.3, 66.0, 52.4, 51.2, 39.1, 26.8. Calculated for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.45; H, 5.39; N, 6.79.

*3.4.2. (S)-1-*N*-Benzyloxycarbonylamino-1-(4′′-carboxymethyl-5′′-methyl-2′′-oxazolyl)-2-phenylethane,* ***2***

TLC: EtOAc:petroleum ether (8:2); 84% yield, $[\alpha]_D^{19}$ −29.9 (c 1.4, CH_2Cl_2); ^{1}H NMR δ: 7.42–7.13 (m, 10H, Ar), 7.05 (bs, 1H, NH), 5.51–4.95 (m, 3H, CH+OC*H*$_2$Ph), 3.90 (s, 3H, OCH_3), 3.33–3.10 (m, 2H, CHC*H*$_2$Ph), 2.56 (s, 3H, oxazole-CH_3). ^{13}C NMR δ: 162.4, 161.2, 156.7, 155.7, 136.0, 135.4, 129.1, 128.5, 128.3, 128.0, 127.9, 127.3, 126.9, 66.9, 51.9, 50.3, 40.0, 11.8. Calculated for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 67.04; H, 5.59; N, 7.12.

*3.4.3. (S)-1-*N*-tert-Butoxycarbonylamino-1-(4′-carboxymethyl-5′-methoxy-2′-oxazolyl)benzyl propionate,* ***3***

TLC: EtOAc:petroleum ether (1:1), 35% yield, $[\alpha]_D^{19}$ −17.3 (c 2.15, CH_2Cl_2); ^{1}H NMR δ: 7.38–7.23 (m, 5H, Ph), 5.61 (d-like, 1H, NH), 5.21–5.15 (m, 1H, CH), 5.05 (s, 2H, C*H*$_2$Ph), 4.04 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.02 (AB part of an ABX system, 2H, CHC*H*$_2$COO), 1.40 (s, 9H, *t*-Bu). ^{13}C NMR δ: 169.9, 165.8, 161.6, 154.7, 151.6, 135.2, 128.6, 128.2, 128.1, 73.6, 66.6, 59.6, 51.6, 45.3, 37.3, 27.8. Calculated for $C_{21}H_{26}N_2O_8$: C, 58.06; H, 6.03; N, 6.45. Found: C, 57.99; H, 6.10; N, 6.40.

*3.4.4. (S)-3-*N*-Benzyloxycarbonylamino-3-(4′-carboxymethyl-5′-methyl-2′-oxazolyl)benzyl propionate,* ***4***

TLC: EtOAc:petroleum ether (1:1), 45% yield, $[\alpha]_D^{18}$ −14.4 (c 1.0, CH_2Cl_2); ^{1}H NMR δ: 7.44–7.11 (m, 10H, Ar), 5.87 (d-like, 1H, NH), 5.35–5.24 (m, 1H, CH), 5.11 (s, 2H, OC*H*$_2$Ph), 5.03 (s, 2H, OC*H*$_2$Ph), 3.89 (s, 3H, OCH_3), 3.19 (dd, 1H, J_1=5, J_2=16, CH_2COO), 3.04 (dd, 1H, J_1=5.6, J_2=16, CH_2COO), 2.55 (s, 3H, oxazole-CH_3). ^{13}C NMR δ: 170.0, 162.4, 160.3, 156.8, 155.6, 135.9, 135.2, 128.5, 128.4, 128.3, 128.2, 128.1, 127.5, 67.2, 66.8, 51.9, 45.9, 37.6, 12.0. Calculated for $C_{24}H_{24}N_2O_7$: C, 63.71; H, 5.35; N, 6.19. Found: C, 63.78; H, 5.31; N, 6.21.

*3.5. (S)-1-*N*-(Benzyloxycarbonylamino)-1-{4′′-[carboxyamido-(S)-valinemethylester]-5′′-methyl-2′′-oxazolyl}-2-phenylethane,* ***14***

Compound **2** (0.3 g, 0.76 mmol), was stirred in the presence of 2 N NaOH:MeOH (1:2; 2.3 mL) at 35°C for 1 h. The MeOH was evaporated under vacuum and the remaining aqueous solution was washed with ether (2×2 mL), cooled (0°C), and brought to pH 2 with 4 N HCl. The aqueous phase was extracted with EtOAc (3×3 mL), the combined extracts were dried (Na_2SO_4), and the solvent was removed in vacuo giving the crude product which was employed without any further purification. ^{1}H NMR δ: 9.83 (bs, 1H, COOH), 7.41–7.03 (m, 11H, Ar+NH), 5.27 (m, 1H, C*H*CH$_2$Ph), 5.02 (AB system, 2H, OC*H*$_2$Ph), 3.24 (d-like, 2H, C*H*$_2$Ph), 2.49 (s, 3H, oxazole-C*H*$_3$). ^{13}C NMR δ: 164.4, 163.4, 157.1, 156.1, 136.1, 135.7, 129.1, 128.5, 128.2, 127.8, 127.7, 126.9, 66.8, 50.7, 40.4, 11.6.

Isobutyl chloroformate (0.17 mL 1.32 mmol) in CH_2Cl_2 (10 mL) at −15°C, was added slowly and under vigorous stirring to the crude acid (456 mg, 1.2 mmol) and 4-methylmorpholine (0.28 mL, 2.6 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred at −15°C for 20 min, then H–Val–OMe·HCl was added (200 mg, 1.2 mmol). After stirring at rt for 12 h, the solvent was evaporated in vacuo; H_2O (50 mL) and EtOAc (50 mL) were added to the residue and the aqueous layer was discarded. The organic solution was washed with 10% aq. $KHSO_4$, sat. aq. NaCl, 10% aq. $NaHCO_3$, sat. aq. NaCl (30 mL of each), in that order, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure affording pure [TLC: EtOAc:MeOH (8:1)] peptoid **14** (544 mg, 92% yield), $[\alpha]_D^{16}$ −13.9 (c 1.43, CH_2Cl_2); ^{1}H NMR δ: 7.57–7.20 (m, 10H, Ar), 7.05 (bs, 1H, NH), 5.61 (d-like, 1H, NH), 5.38–5.0 (m, 2H, O*CH*$_2$Ph), 4.68–4.59 (dd, 1H, J_1=6, J_2=13, C*H*CH$_2$Ph), 3.95–3.79 (m, 1H, NHC*H*CO), 3.73 (s, 3H, OCH_3), 3.20 (AB part of an ABX system, 2H, C*H*$_2$Ph), 2.53 (s, 3H, oxazole-CH_3), 2.30–2.16 [m, 1H, C*H*$(CH_3)_2$],

1.03–0.93 [m, 6H, CH(C*H*$_3$)$_2$]. ^{13}C NMR δ: 172.2, 161.6, 159.9, 155.6, 153.5, 140.1, 136.2, 135.7, 129.6, 129.4, 129.2, 128.9, 128.7, 128.1, 67.1, 56.7, 52.1, 50.3, 39.8, 31.3, 19.1, 18.0, 11.6. Calculated for $C_{27}H_{31}N_3O_6$: C, 65.71; H, 6.33; N, 8.51. Found: C, 65.79; H, 6.30; N, 8.55.

*3.6. (*S*)-1-*N-*[*N*-Benzyloxycarbonyl-(*S*)-alanilamino]-1-{4′′-[carboxyamido-(*S*)-valinemethylester]-5′′-methyl-2′′-oxazolyl}-2-phenylethane, **15***

To a solution of the compound **14** (0.59 g, 1.2 mmol) in MeOH (20 mL) was added 10% Pd/C catalyst (90 mg). The mixture was kept in H_2 atmosphere with vigorous stirring for 40 min. The catalyst was removed by Celite filtration and the solvent removed in vacuo affording the crude amine (0.4 g, 92% yield) that was employed without any further purification. Isobutyl chloroformate (0.15 mL, 1.2 mmol) in CH_2Cl_2 (20 mL) at −15°C, was added slowly and under vigorous stirring to a solution of Cbz–Ala–OH (0.25 g, 1.12 mmol) and 4-methylmorpholine (0.13 mL, 1.2 mmol) in CH_2Cl_2 (80 mL). The mixture was stirred at −15°C for 20 min, then the deprotected crude amine was added (0.4 g, 1.1 mmol). After 12 h stirring at rt, the solvent was removed in vacuo; to the residue H_2O (50 mL) and EtOAc (50 mL) were added and the aqueous layer was discarded. The organic solution was washed with 10% aq. $KHSO_4$, sat. aq. NaCl, 10% aq. $NaHCO_3$, sat. aq. NaCl (50 mL), in that order, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure affording pure [TLC: EtOAc:petroleum ether (6:4)] peptoid **15** (0.59 g, 94% yield), $[\alpha]_D^{20}$ −23.3 (c 1.58, CH_2Cl_2); ^{1}H NMR δ: mixture of conformers at amide bond, 7.66–7.41 (m, 10H, Ar), 7.08–6.99 (d-like, 1H, NH), 6.6 (bs, 0.4H, NH), 5.58–5.20 (m, 1.6H, NH), 5.09 (AB system, 2H, OC*H*$_2$Ph), 4.61 (dd, 1H, J_1=5, J_2=9, C*H*CH$_2$Ph), 4.35–4.22 (m, 1H, C*H*CH$_3$), 4.04 [d, 1H, C*H*CH(CH$_3$)$_2$], 3.72 (s, 3H, COOCH$_3$), 3.17 (AB part of an ABX system, 2H, CHC*H*$_2$Ph), 2.54 (s, 3H, oxazole-CH$_3$), 2.30–2.16 [m, 1H, C*H*(CH$_3$)$_2$], 1.36 (m, 1.2H, CHC*H*$_3$) 1.21 (m, 1.8H, CHC*H*$_3$), 1.00–0.85 [m, 6H, CH(C*H*$_3$)$_2$]. ^{13}C NMR δ: 172.4, 172.3, 167.9, 161.7, 159.9, 153.7, 148.8, 137.0, 136.0, 129.5, 128.8, 128.6, 128.2, 128.1, 127.1, 75.9, 67.2, 67.1, 56.9, 52.3, 39.4, 31.4, 27.7, 18.1, 17.7, 11.7. Calculated for $C_{30}H_{36}N_4O_7$: C, 63.82; H, 6.43; N, 9.92. Found: C, 63.91; H, 6.40; N, 9.88.

*3.7. (*S*)-1-*N-tert-*Butoxycarbonylamino-1-(4′-carboxymethyl-5′-methoxy-2′-oxazolyl)-(*S*)-phenylalaninemethylester propionamide, **16***

To a solution of the compound **3** (1.2 g, 2.7 mmol) in MeOH (30 mL) was added 10% Pd/C catalyst (0.3 g). The mixture was kept under an H_2 atmosphere with vigorous stirring for 40 min. The catalyst was removed by Celite filtration and the solvent removed in vacuo affording the crude acid (0.72 g, 77% yield) that was employed without any further purification. To the crude acid (0.41 g, 1.2 mmol) dissolved in dichloromethane (40 mL), at −15°C under vigorous stirring 4-methylmorpholine (0.29 mL, 2.64 mmol) and isobutyl chloroformate (0.17 mL, 1.32 mmol) were added slowly. The mixture was stirred at −15°C for 20 min, then the H–Phe–OMe·HCl was added (0.26 g, 1.2 mmol). After 12 h of stirring at rt, the solvent was evaporated in vacuo; to the residue H_2O (50 mL) and EtOAc (50 mL) were added and the aqueous layer was discarded. The organic solution was washed with 10% aq. $KHSO_4$, sat. aq. NaCl, 10% aq. $NaHCO_3$, sat. aq. NaCl (30 mL), in that order, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure affording pure [TLC: EtOAc:MeOH (8:1)] peptoid **16** (0.52 g, 85% yield), $[\alpha]_D^{19}$ +36.9 (c 1.5, CH_2Cl_2); ^{1}H NMR δ: mixture of conformers at amide bond, 7.35–7.11 (m, 5H, Ph), 7.0 (d-like, 1H, NH), 6.23 (d-like, 0.6H, NH), 5.46 (d-like, 0.4H, NH), 4.80 (m, 1H, CH), 4.61 (m, 1H, CH), 3.78 (s, 3H, OCH$_3$), 3.68 (s, 3H, OCH$_3$), 3.64 (s, 3H, OCH$_3$), 3.19–2.77 (m, 4H, CHC*H*$_2$CO+CHC*H*$_2$Ph), 1.43 (s, 9H, *t*-Bu). ^{13}C NMR δ: 171.8, 171.4, 169.1, 165.6, 161.3, 161.2, 155.7, 135.6, 128.8, 127.9, 126.4, 70.4, 59.9, 54.4, 52.8, 51.7, 51.0, 37.4, 27.8, 18.5. Calculated for $C_{24}H_{31}N_3O_9$: C, 57.02; H, 6.18; N, 8.31. Found: C, 57.12; H, 6.12; N, 8.25.

3.8. (S)-1-N-[N-Benzyloxycarbonyl-(S)-phenylalanilamino]-1-(4′-carboxymethyl-5′-methoxy-2′-oxazolyl)-(S)-phenylalaninemethylester propionamide, ***17***

The protected product **16** (0.28 g, 0.5 mmol) was treated at rt with 3 N HCl in EtOAc (4 mL). After 30 min, the solvent was removed under reduced pressure, affording pure (TLC) crude amine hydrochloride (0.22 g, 90% yield) that was employed without any further purification.

To a solution of Cbz–Phe–OH (0.14 g, 0.5 mmol) in dichloromethane (20 mL) at −15°C, were added slowly and under vigorous stirring 4-methylmorpholine (0.17 mL, 1.5 mmol) and isobutyl chloroformate (0.1 mL, 0.55 mmol). The mixture was stirred at −15°C for 20 min, then the crude amine hydrochloride was added (0.22 g, 0.45 mmol). After 12 h of stirring at rt, the solvent was evaporated in vacuo; to the residue H_2O (20 mL) and EtOAc (20 mL) were added and the aqueous layer was discarded. The organic solution was washed with 10% aq. $KHSO_4$, sat. aq. NaCl, 10% aq. $NaHCO_3$, sat. aq. NaCl (15 mL), in that order, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude peptoid **17** was purified by flash cromatography on silica [EtOAc:petroleum ether (2:7)] affording pure product **17** (0.2 g, 48% yield), $[\alpha]_D^{19}$ +25.0 (c 0.2, CH_2Cl_2); ^{1}H NMR δ: 7.45–7.1 (m, 17H, Ar+NH), 7.03 (m, 1H, NH) 5.26–4.92 (m, 3H, OC*H*$_2$Ph+CH), 4.73–4.62 (m, 1H, CH), 4.59–4.50 (m, 1H, CH), 3.92 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.23–3.01 (m, 6H, C*H*$_2$CONH+C*H*$_2$Ph). ^{13}C NMR δ: 172.1, 171.8, 171.4, 169.1, 165.6, 161.3, 156.2, 155.2, 135.6, 135.7, 129.5, 129.0, 128.8, 128.7, 128.4, 128.2, 127.8, 127.1, 126.7, 71.3, 61.6, 54.7, 52.3, 45.5, 38.3, 29.7, 27.9, 27.5, 14.1. Calculated for $C_{36}H_{38}N_4O_{10}$: C, 62.96; H, 5.58; N, 8.16. Found: C, 62.91; H, 5.57; N, 8.14.

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