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Synthesis of Natural Product Derivatives Containing 2,4-Concatenated Oxazoles

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Herein is described the synthesis of several oxazole-containing derivatives of IB-01211. The macrocyclization reaction of peptide **14** containing a concatenated triazole was successful and afforded **3** by amide bond formation. However, for those compounds containing quaterazoles or quinqueazoles, the oxazole ring had to be formed during macrocyclization.

Introduction

Oxazole rings are present in a large amount of natural products possessing a wide range of pharmacological activities. Several marine natural products with 2,4-concatenated azoles have been isolated and synthesized during the past few years.[1] Hennoxazoles[2] (potent antiherpes virus agents and peripheral analgesics) contain a bioxazole unit; muscoride A[3] (an antibacterial agent) features a bioxazole with methyl substituents at the 5-position of both oxazole rings; the macrolactams ulapualides,[4] kabiramides,[5] mycalolides,[6] and halichondramides[7] all contain a teroxazole unit; and the structurally complex diazonamides,[8] telomestatin,[9] YM-216391,[10] and IB-01211[11] all feature 2,4-concatenated polyoxazoles linked to other heterocycles and/or peptidic fragments (Figure 1).

Following our studies on the synthesis of marine natural products containing concatenated azoles,[12,13] we synthesized IB-01211 analogs containing three, four, or five oxazole rings tethered by a peptidic chain to give the macrocycle.

Compound **1** contains a phenylquinqueoxazole system that differs from IB-01211 in its azole system: it contains an oxazole rather than a thiazole moiety. Compound **2** has one oxazole less than **1** and a hydroxymethyl group as a precursor of the exocyclic methylidene group. Finally, only three oxazole rings are present in compound **3**, which also has a hydroxymethyl group as a precursor of the exocyclic methylidene unit. In order to obtain the same size macrocycle as that in IB-01211, the peptide chains of **2** and **3** were conveniently modified by substitution of L-Val with (*S*)-β-Leu[14] or by addition of β-Ala, respectively.

The preparations of quinque-, quater-, and teroxazoles followed by introduction of the peptidic chain and final macrocyclization by formation of the amide bond indicated in Figure 2 were examined. The number of oxazole rings is crucial in the macrocyclization step and is only possible for compound **3**. Alternative methods of macrocyclization have been essayed.

Results and Discussion

Synthesis of Peptides and Peptidic Bonds

The peptides used in the syntheses of **1**–**3**, and the amide bond used to prepare the oxazoles, were formed in solution by condensation of the appropriate acid and amine with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBT) as activating agents in dichloromethane (DCM) as solvent. For all syntheses, the protecting groups for the amine, hydroxy alcohol, and carboxylic acid were *N*-*tert*-butoxycarbonyl (*N*-Boc), *O*-*tert*-butyl (*O*-*t*Bu), and methyl ester, respectively. The *N*-Boc and *O*-*t*Bu groups were simultaneously cleaved with 95% trifluoroacetic acid (TFA), whereas the methyl ester functionalities were hydrolyzed by using LiOH, as detailed in the Experimental Section.

Synthesis of 2,4-Concatenated Azoles

Quinqueazole **4**, quaterazole **5**, and terazole **6** were prepared by cyclization of a Ser/oxazol-containing peptide (OH from the Ser side chain and the carboxylamide of the same Ser unit) to give an oxazoline, which was then oxid-

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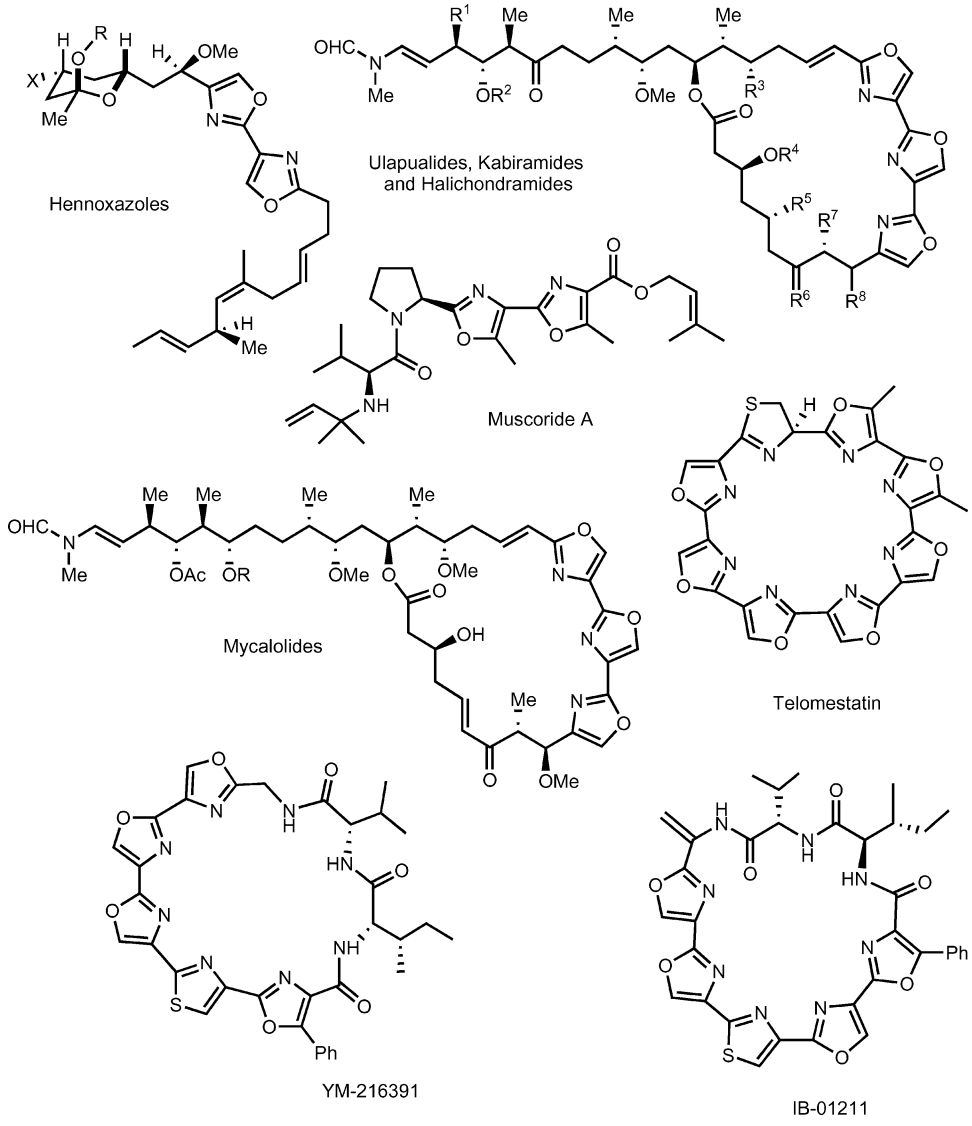


Figure 1. Oxazole-containing natural products: hennoxazoles, ulapualides, kabiramides, mycalolides, halichondramides, telomestatin, YM-216391, and IB-01211.

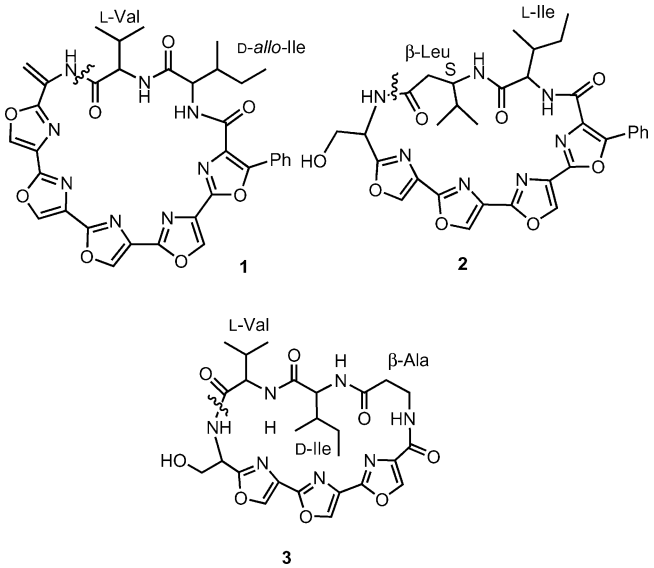
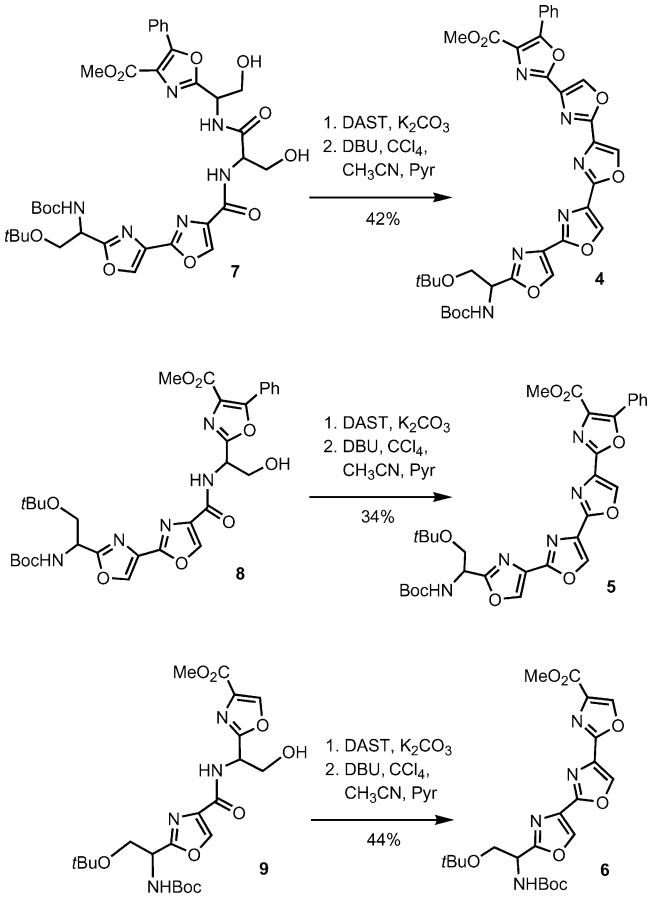


Figure 2. Structures of peptide–azoles **1**–**3**.

ized to the oxazole. The cyclization agent was (diethylamino)sulfur trifluoride (DAST) and potassium carbonate in DCM at low temperature, and the oxidation was performed with 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU)/CCl_4 in MeCN/pyridine at room temperature.[15] Interestingly, quinqueoxazole **4** was obtained in 42% yield by simultaneous formation of two oxazole rings from compound **7**. Quaterazole **5** and terazole **6** were obtained in yields of 34 and 44%, respectively, by formation of one oxazole ring from compounds **8** and **9**, respectively (Scheme 1).

The synthetic precursors of **7**–**9** were the previously described oxazoles **10** and **11** (Figure 3).[12,13] Compound **7** was obtained by coupling the deprotected amine of **10b** with *N*-Boc-*O*-*t*Bu-Ser-OH, followed by *N*- and *O*-deprotection and, finally, by coupling the resulting free amine with the acid of **11a** (R^1 = H). Oxazole derivative **8** was obtained by coupling the free amine of **10b** with the acid of **11a** (R^2 = H). Likewise, compound **9** was obtained by intermolecular peptide coupling between the free amino of **10a** and the deprotected acid of **10a**.



Scheme 1. Synthesis of concatenated azoles **4**–**6**.

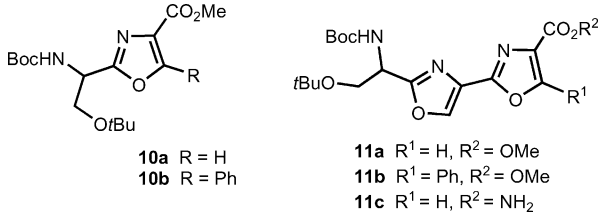


Figure 3. Structures of oxazoles **10** and **11**.

For compound **4**, simultaneous assembly of two oxazole rings is advantageous over their sequential formation; this involves fewer steps and provides greater yields. This procedure was developed for the synthesis of **11a**, but could not be used to prepare phenyl derivative **11b**. The phenyl ring favors elimination of water over cyclization and thus formation of a conjugated vinylic system instead of an oxazoline ring.[12] As an alternative strategy, formation of three oxazole rings by cyclization and subsequent oxidation of a tetraserine peptide was also evaluated. However, after several tests with the same reagents and various reaction times and temperatures, only trace amounts of teroxazole **6** were obtained (as detected by HPLC–MS and ^{1}H NMR spectroscopy).

Macrocyclization Studies

Introduction of the peptide chain into oxazoles **4**–**6** to give the corresponding peptide–heterocycles **12**–**14** (Scheme 2) was afforded by amide coupling of the acid at the 4-position of the oxazole with the free amine of the appropriate peptide, as described above. Macrocycle **3** was obtained in 15% yield (global from **6**) through cyclization of **14** by using *N*,*N*′-diisopropylcarbodiimide (DIPCDI) and 1-hydroxy-7-azabenzotriazole (HOAt) as activating agents in DCM as solvent.

Attempts at macrocyclization of peptides **12** and **13** under the same conditions, and also by using either 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium hexafluorophosphate 3-oxide (HATU) and *N*,*N*-diisopropylethylamine (DIEA) or EDC and HOAt as cyclization agents were unsuccessful.

Macrocyclization of the more flexible heterocyclic peptides **16**[16,17] and **17**[18] was tested under the aforementioned conditions, but gave only complex mixtures. However, cyclic compound **18**[19] (Scheme 3) was detected by HPLC–MS in the crude mixture formed from treatment of **17** with (7-azabenzotriazol-1-yloxy)tris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP) and 1-hydroxy-7-azabenzotriazole (HOAt) in DMF/DCM.

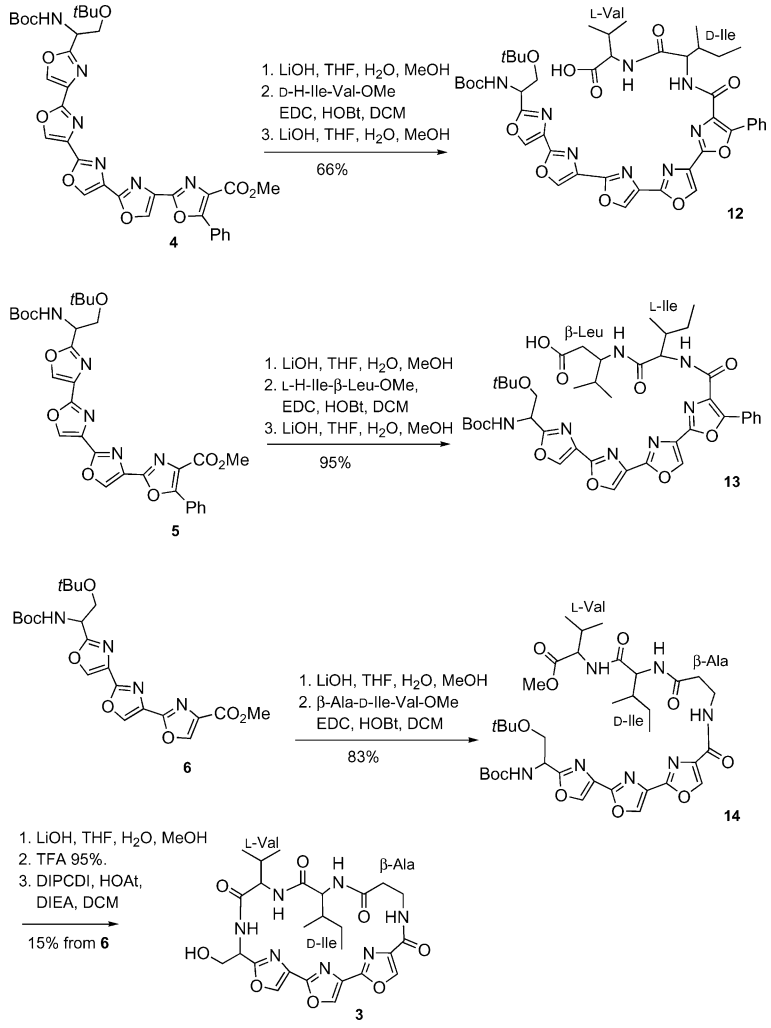
The poor results obtained for the macrocyclization based on amide coupling prompted us to change our strategy to one similar to that used for the macrocyclization of IB-01211.[12] Thus, heterocyclic peptide **20** obtained from coupling of **11c** to **19** was deprotected with formic acid. The resulting α-bromo ketone was used for intramolecular oxazole formation by reaction with the terminal amide under Hantzsch synthesis conditions with simultaneous macrocyclization and water elimination to give the exocyclic double bond.

IB-01211 analog **1** (Scheme 4), whose central azole is a thiazole instead of an oxazole as in the parent compound, was obtained in 16% yield after deprotection, macrocyclization, and elimination.

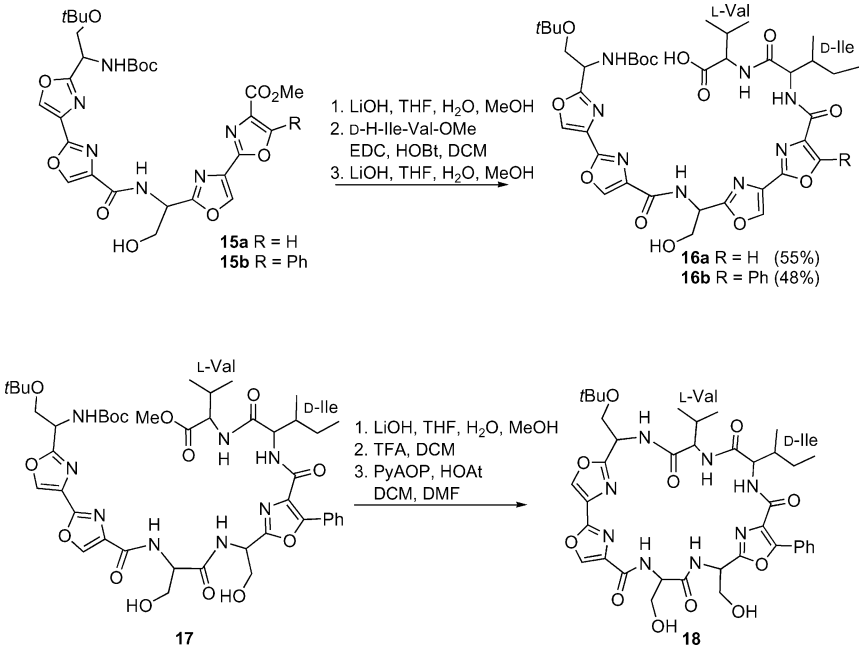
Conclusions

Quinqueazole **4**, quaterazole **5**, and terazole **6** were synthesized from their corresponding serine-derived, *N*-substituted 2-hydroxyethylamides. Simultaneous formation of two oxazole rings was the preferred route to **4**, as it gave similar results to those previously obtained for **11a**. However, simultaneous formation of three oxazole rings could not be achieved.

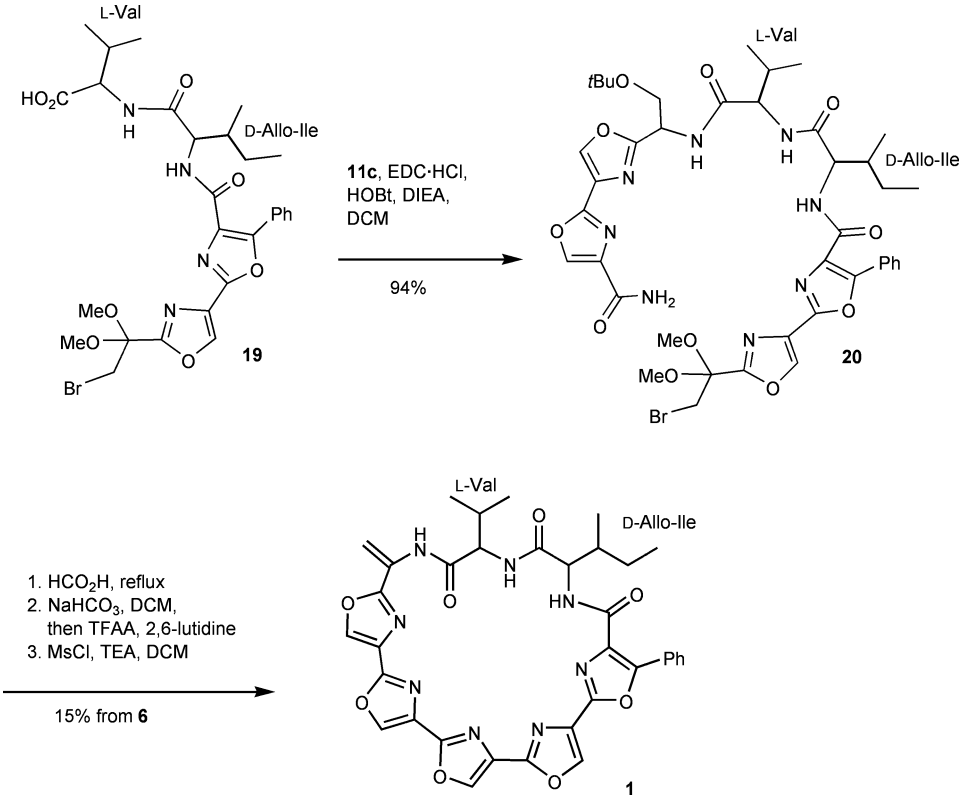
Studies on the macrocyclization of **12**, **13**, and **14** corroborate our earlier results from the total synthesis of IB-01211 and its epimer, in which the synthetic precursors were peptides containing a rigid quinqueazole system.[13] Whereas macrocyclization of **14** was readily achieved, attempts at macrocyclization of **12** and **13** failed by using the same reaction conditions or by employing more active coupling agents. The use of more flexible precursors of **1** (compounds **16** and **17**) only led to trace amounts of **18**.



Scheme 2. Synthesis of peptides **12**–**14** and macrocycle **3**.



Scheme 3. Synthesis of peptides **16** and macrocycle **18**.



Scheme 4. Synthesis of compound **1**.

Finally, compound **1** was obtained from **20** by using a similar strategy to that used for the synthesis of IB-01211, which is based on assembly of the central oxazole ring during macrocyclization reaction (Scheme 3).

Experimental Section

General: Melting points were determined with a Büchi Melting Point B540 in open capillaries and are uncorrected. Microwave-assisted reactions were carried out in a CEM Discover microwave. Purifications were performed on a Teledyne Isco module Companion with a C18-RediSep column, a photodiode array absorbance detector, and H_2O (0.04% TFA) and MeCN (0.04% TFA) as eluents. Analytical HPLC was performed with a Waters Alliance separation module 2695 by using a Waters Xterra MS C18 column (150 × 4.6 mm, 5 mm) and a Waters 996 PDA detector at 254 nm (using gradients of MeCN–0.036 TFA and H_2O–0.045 TFA). Polarimetry studies were performed with a Perkin–Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded with a Varian Mercury 400 MHz spectrometer. Multiplicity of the carbon atoms was assigned with DEPT and gHSQC experiments. Spectra were referenced to appropriate residual solvent peaks ($CDCl_3$ or MeOD). MS (MALDI-TOF or ES) were performed with a PerSeptive Biosystems Voyager DE RP by using an ACH matrix or a Waters alliance 2795 HPLC equipped with a 2487 UV/Vis detector and coupled to a ZQ electrospray mass detector. The samples were run with MeCN (0.07% HCO_2H) and H_2O (0.1% HCO_2H). HRMS was performed with a Bruker Autoflex high-resolution mass spectrometer by the Mass Spectrometry Service of the University of Santiago de Compostela. Compounds **10a**, **10b**, **11a**, **11b**, **11c**, and **19** were synthesized as described in the literature.[12,13]

Peptide Bond Formation: The free carboxylic acid (1 mmol), EDC·HCl (1.1 mmol), HOBt (1.1 mmol), and DIEA (2 mmol) were added to a solution of the free amine (1 mmol) in dry DCM (10 mL) at 0 °C. The mixture was stirred at room temperature for 20 h. The organic solution was washed with 5% aqueous $NaHCO_3$ and aqueous NH_4Cl, dried, and concentrated.

Hydrolysis of Me Esters: LiOH (2 M, 9 mmol) was added to a solution of methyl ester (3 mmol) in THF/H_2O/MeOH (50:6:0.2 mL), and the reaction mixture was stirred at room temperature for 1 h. After this time, HCl (1 M) was added until pH 3, and the solution was extracted with EtOAc. The organic solution was dried and concentrated to afford the acid as a white solid.

Elimination of the *N*-Boc and O-*t*Bu Protecting Groups by TFA: TFA (95%, 10 mL) was added to the oxazole (1.8 mmol), and the solution was stirred at room temperature for 5 h. After this time, the TFA was removed in vacuo. The crude material was used in the following reaction without purification.

Oxazoline Formation: DAST (1.05 equiv.) was added dropwise to a solution of peptidyl-Ser (1 equiv.) in DCM (13 mL) and cooled to –78 °C under N_2. The reaction mixture was stirred for 2 h. Anhydrous K_2CO_3 (2 equiv.) was then added in one portion, and the reaction mixture was stirred for 15 min at –78 °C and then warmed to room temperature and stirred for 20 min. The organic solution was poured into saturated aqueous $NaHCO_3$ and extracted with DCM, dried, and concentrated to give the oxazoline as oil.

Oxidation of Oxazoline: DBU (4 mmol) was added to a cold –30 °C solution of the oxazoline (1 mmol) in CCl_4/MeCN/Pyr (2.2:3.2:3.2 mL), and the solution was stirred for 48 h at room temperature. The solvents were removed in vacuo, and the residue was purified by column chromatography on silica gel.

Boc-β-Ala-D-Ile-L-Val-OMe: H-D-Ile-Val-OMe (70 mg, 0.290 mmol) was coupled to Boc-β-Ala-OH (57.0 mg, 0.304 mmol) following the general peptide synthesis procedure to give the title compound (107.6 mg, 90%) as a white solid. Column chromatography (DCM/EtOAc, 9:1) gave the peptide as a white solid. R_f = 0.57 (DCM/MeOH, 95:5). M.p. 158–160 °C ($CHCl_3$). $[a]_D$ = +27.0 (c = 0.78, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89–0.95 (m, 12 H), 1.07–1.19 (m, 1 H), 1.41 (s, 9 H), 1.47–1.57 (m, 1 H), 1.84–1.92 (m, 1 H), 2.12–2.22 (m, 1 H), 2.37–2.49 (m, 2 H), 3.34–3.46 (m, 2 H), 3.73 (s, 3 H), 4.36 (dd, J = 6.8 and 8.6 Hz, 1 H), 4.51 (dd, J = 4.8 and 8.4 Hz, 1 H), 5.29 (br. s, 1 H), 6.25 (d, J = 8.8 Hz, 1 H), 6.57 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 (q), 15.5 (q), 17.8 (q), 18.9 (q), 24.7 (t), 28.3 (q), 30.9 (d), 36.2 (t), 36.8 (t), 36.9 (d), 52.1 (q), 57.2 (d), 57.5 (d), 79.0 (s), 155.9 (s), 171.3 (s), 171.7 (s), 172.2 (s) ppm. MS (MALDI): m/z (%) = 454 (50) [M + 39], 438 (100) [M + 23]. HRMS: calcd. for $C_{20}H_{38}N_3O_6$ 416.2755; found 416.2748.

Cyclic Peptide–Quinqueoxazole 1: A solution of **20** (500 mg, 0.53 mmol) in HCO_2H (98%, 10 mL) in a sealed tube was warmed at 85 °C over 15 min in a microwave. The cooled reaction mixture was poured into a solution of $NaHCO_3$ and extracted with DCM. The organic solution was dried and concentrated under reduced pressure to give the deprotected hydroxy ketone as a yellow oil. A solution of the oil in DCM (10 mL) and $NaHCO_3$ (181 mg, 2.15 mmol) was stirred at room temperature for 5 h. The mixture was filtered over alumina, and the solid was washed with DCM/MeOH (4:1). The mixed organic solutions were concentrated to give a crude material, which was dissolved in dry DCM (10 mL) and cooled to –10 °C. Lutidine (0.76 mL, 5.39 mmol) and TFAA (0.31 mL, 2.69 mmol) were added over the cold solution, and the reaction mixture was stirred at 50 °C in a microwave for 30 min. The reaction mixture was cooled, poured into a solution of $NaHCO_3$, extracted with DCM, dried, and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (silica gel; CH_2Cl_2/MeOH, 99:1) to give **1** as an yellow solid (60 mg, 16%). $[a]_D$ = +10.8 (c = 0.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.26 (m, 12 H), 1.28–1.31 (m, 2 H), 2.02–2.13 (m, 2 H), 3.94–3.99 (m, 1 H), 4.78–4.91 (m, 1 H), 6.06 (s, 1 H), 6.69 (s, 1 H), 7.52–7.57 (m, 3 H), 7.86 (s, 1 H), 8.03–8.10 (m, 2 H), 8.21 (s, 1 H), 8.26 (s, 1 H), 8.27 (s, 1 H), 8.31 (s, 1 H), 8.34 (s, 1 H), 8.45 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (q), 15.0 (q), 26.8 (q), 27.2 (q), 28.2 (t), 31.8 (d), 42.2 (d), 57.8 (d), 61.6 (d), 109.3 (t), 120.2 (s), 125.1 (s), 125.8 (2 d), 128.3 (s), 128.8 (2 d), 129.3 (s), 129.7 (d), 131.8 (s), 134.4 (s), 137.4 (s), 142.3 (d), 142.8 (s), 143.4 (s), 149.9 (d), 146.2 (d), 146.3 (d), 150.5 (s), 152.1 (s), 154.5 (s), 156.9 (s), 162.6 (s), 168.9 (s), 169.7 (s) ppm. MS (MALDI-TOF): m/z = 716 (100) [M + Na].

Cyclic Peptide–Teroxazole 3: A solution of the carboxylic acid of **14** (19 mg, 18.2 μmol) in dry DCM/DMF (91 mL and 1 mL) was cooled to 0 °C. HOAt (7.4 mg, 54.6 μmol), DIEA (3.0 μL, 18.2 μmol), and DIPCDI (8.5 mg, 54.6 μmol) were then added. The mixture was stirred at room temperature for 120 h. The solvents were removed, and the crude was purified by preparative silica gel chromatography (DCM/MeOH, 6:1) to give **3** (2.5 mg, 15%) as a white solid. R_f = 0.61 (DCM/MeOH, 9:1). $[a]_D$ = –34.8 (c = 0.13, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89–0.98 (m, 12 H), 1.49–1.68 (m, 1 H), 1.54–1.61 (m, 1 H), 2.27–2.35 (m, 1 H), 2.38–2.47 (m, 1 H), 2.60–2.68 (m, 2 H), 3.33–3.43 (m, 1 H), 3.84–3.92 (m, 1 H), 4.09 (d, J = 11.6 Hz, 1 H), 4.25–4.32 (m, 1 H), 4.80 (dd, J = 4.0 and 10.2 Hz, 1 H), 4.93 (dd, J = 3.2 and 9.0 Hz, 1 H), 5.44 (d, J = 7.2 Hz, 1 H), 6.77 (d, J = 7.6 Hz, 1 H), 7.75 (d, J = 7.6 Hz, 1 H), 7.97 (s, 1 H), 8.03 (d, J = 7.6 Hz, 1 H), 8.06 (s, 1 H), 8.21 (s, 1 H), 8.25 (d, J = 7.6 Hz, 1 H) ppm. MS (MALDI-TOF): m/z (%) = 610 (28) [M + 39], 594 (100) [M + 23], 572 (13), 413 (15), 388 (18), 304 (9), 295 (5). HRMS: calcd. for $C_{26}H_{34}N_7O_8$ [M + 1] 572.2452; found 572.2463.

Quinqueoxazole 4: Compound **7** (296 mg, 0.41 mmol) was cyclized by using the general procedure with DAST/K_2CO_3 and DBU/CCl_4 for the oxidation. The reaction crude was purified by column chromatography (silica gel) to give **4** (42%) as a white solid. R_f = 0.65 (DCM/EtOAc, 1:1). M.p. 171–173 °C ($CHCl_3$). $[a]_D$ = –12.05 (c = 0.7, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 9 H), 1.47 (s, 9 H), 3.73 (dd, J = 4.0 and 9.2 Hz, 1 H), 3.85–3.88 (m, 1 H), 3.97 (s, 3 H), 5.07 (br. s, 1 H), 5.58 (d, J = 9.2 Hz, 1 H), 7.48–7.51 (m, 3 H), 8.15–8.17 (m, 2 H), 8.33 (s, 1 H), 8.44 (s, 1 H), 8.45 (s, 1 H), 8.48 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.2 (q), 28.2 (q), 51.0 (d), 52.3 (q), 62.8 (t), 73.7 (s), 80.2 (s), 126.4 (s), 127.6 (s), 128.4 (2 d), 128.6 (2 d), 129.7 (s), 130.6 (d), 130.7 (d), 130.8 (s), 130.9 (s), 139.3 (s), 139.4 (d), 139.5 (d), 139.6 (d), 152.8 (s), 155.6 (s), 155.7 (s), 155.9 (s), 156.2 (s), 162.2 (s), 164.7 (s), 170.8 (s) ppm. MS (ES): m/z = 704 [M + 18], 575, 527, 121. HRMS: calcd. for $C_{34}H_{38}N_7O_{10}$ [M + NH_4] 704.2674; found 704.2665.

Quateroxazole 5: Compound **8** (164 mg, 0.25 mmol) was cyclized by using the general procedure with DAST/K_2CO_3 and DBU/CCl_4 for the oxidation. The reaction crude was purified by column chromatography (silica gel; DCM/EtOAc, 6:1) to give **5** (34%) as a white solid. R_f = 0.37 (DCM/EtOAc, 2:1). M.p. 199–201 °C ($CHCl_3$). $[a]_D$ = –20.1 (c = 0.79, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, 9 H), 1.47 (s, 9 H), 3.72 (dd, J = 4.0 and 9.0 Hz, 1 H), 3.85–3.88 (m, 1 H), 3.97 (s, 3 H), 5.06–5.09 (m, 1 H), 5.58 (d, J = 8.2 Hz, 1 H), 7.47–7.52 (m, 3 H), 8.15–8.17 (m, 2 H), 8.34 (s, 1 H), 8.42 (s, 1 H), 8.47 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.2 (q), 28.3 (q), 50.0 (d), 52.4 (q), 62.8 (t), 73.7 (s), 80.2 (s), 126.4 (s), 127.6 (s), 128.4 (2 d), 128.6 (2 d), 129.7 (s), 130.6 (d), 130.8 (s), 130.9 (s), 139.2 (d), 139.3 (d), 139.5 (d), 152.8 (s), 155.3 (s), 155.6 (s), 155.8 (s), 156.2 (s), 162.3 (s), 164.6 (s) ppm. MS (FAB): m/z (%) = 642 (25) [M + 23], 508 (100), 231 (63). HRMS: calcd. for $C_{31}H_{33}N_5NaO_9$ [M + 1] 620.2356; found 620.2356.

Teroxazole 6: Compound **9** (215 mg, 0.43 mmol) was cyclized by using the general procedure with DAST/K_2CO_3 and DBU/CCl_4 for the oxidation. The reaction crude was purified by column chromatography (silica gel; hexane/EtOAc, 2:1) to give **6** (90.5 mg, 44%) as a white solid. R_f = 0.28 (hexane/EtOAc, 1:1). M.p. 205–207 °C ($CHCl_3$). $[a]_D$ = –62.35 (c = 0.51, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 9 H), 1.44 (s, 9 H), 3.70 (dd, J = 4.0 and 9.2 Hz, 1 H), 3.80–3.88 (m, 1 H), 3.93 (s, 3 H), 5.05 (br. s, 1 H), 5.56 (d, J = 8.0 Hz, 1 H), 8.29 (s, 1 H), 8.30 (s, 1 H), 8.40 (s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.2 (q), 28.2 (q), 50.0 (d), 52.3 (q), 62.8 (t), 73.7 (s), 80.2 (s), 129.7 (s), 130.7 (s), 134.3 (s), 139.2 (d), 139.5 (d), 143.8 (d), 155.3 (s), 155.4 (s), 156.2 (s), 161.2 (s), 164.7 (s) ppm. MS (ES): m/z (%) = 499 [M + 23], 494 [M + 18], 421, 365, 121. HRMS: calcd. for $C_{22}H_{32}N_5O_8$ [M + NH_4] 494.2245; found 494.2242.

Peptide 7: The title compound was obtained as a yellow oil (86%). R_f = 0.35 (DCM/MeOH, 95:5). $[a]_D$ = –8.2 (c = 0.21, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 9 H), 1.45 (s, 9 H), 3.49–3.55 (m, 2 H), 3.63–3.77 (m, 2 H), 3.84 (s, 3 H), 3.97–4.10 (m, 1 H), 4.16–4.32 (m, 1 H), 4.70–4.81 (m, 1 H), 5.01–5.11 (m, 1 H), 5.33–5.43 (m, 1 H), 5.58 (br. s, 1 H), 7.32 (br. s, 1 H), 7.39–7.50 (m, 3 H), 7.79 (br. s, 1 H), 7.92–8.01 (m, 2 H), 8.18 (s, 1 H), 8.22 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.3 (q), 27.1 (q), 50.0 (q), 52.2 (d), 52.3 (d), 62.7 (t), 62.8 (t), 62.9 (t), 64.1 (d), 73.7 (s), 80.3 (s), 126.1 (s), 126.5 (s), 128.4 (2 d), 128.5 (2 d), 129.4 (s), 129.8 (s), 130.8 (d), 133.3 (s), 139.8 (d), 141.6 (s), 144.5 (d), 155.4

(s), 160.0 (s), 160.4 (s), 162.2 (s), 164.9 (s), 169.0 (s) ppm. MS (MALDI-TOF): *m*/*z* = 745 [M + 18]. HRMS: calcd. for $C_{34}H_{43}N_6O_{12}$ 727.2933; found 727.2940.

Peptide 8: The title compound was obtained as a yellow oil (296 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 9 H), 1.45 (s, 9 H), 3.68–3.74 (m, 1 H), 3.80–3.87 (m, 1 H), 3.91 (s, 3 H), 4.12 (dd, *J* = 4.4 and 11.4 Hz, 1 H), 4.30 (dd, *J* = 4.4 and 11.4 Hz, 1 H), 5.06 (br. s, 1 H), 5.56–5.61 (m, 2 H), 7.43–7.47 (m, 3 H), 7.87 (d, *J* = 8.8 Hz, 1 H), 7.98–8.02 (m, 2 H), 8.20 (s, 1 H), 8.27 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.2 (q), 28.2 (q), 48.9 (q), 50.0 (d), 52.2 (d), 62.8 (t), 63.2 (t), 73.7 (s), 80.2 (s), 126.4 (s), 128.3 (2 d), 128.4 (2 d), 129.6 (s), 129.8 (s), 130.4 (d), 136.5 (s), 139.3 (d), 141.5 (d), 154.9 (s), 155.3 (s), 155.9 (s), 159.8 (s), 160.2 (s), 162.1 (s), 164.8 (s) ppm. MS (MALDI-TOF): *m*/*z* = 678 [M + 39], 662 [M + 23]. HRMS: calcd. for $C_{31}H_{37}N_5NaO_{10}$ 662.2433; found 662.2435.

Methyl 2-(1-{[2-(2-*tert*-Butoxy-1-*tert*-butoxycarbonylaminoethyl)oxazole-4-carbonyl]amino}-2-hydroxyethyl)oxazole-4-carboxylate (9): The title compound was obtained as a white solid (407 mg, 85%). M.p. 81–83 °C ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 9 H), 1.38 (s, 9 H), 3.57–3.63 (m, 1 H), 3.65–3.71 (m, 1 H), 3.81 (s, 3 H), 3.96–4.07 (m, 1 H), 4.09–4.21 (m, 1 H), 4.88 (br. s, 1 H), 5.36–5.46 (m, 1 H), 5.62 (br. s, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 8.09 (s, 1 H), 8.17 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.1 (q), 28.1 (q), 48.9 (d), 49.7 (d), 52.0 (q), 62.4 (t), 62.7 (t), 73.6 (s), 80.1 (s), 132.9 (s), 135.2 (s), 141.6 (d), 144.3 (d), 155.2 (s), 160.5 (s), 161.2 (s), 162.8 (s), 162.9 (s) ppm. MS (ES): *m*/*z* = 514 [M + 18], 497, 441, 385, 341, 323. HRMS: calcd. for $C_{22}H_{36}N_5O_9$ [M + NH_4] 514.2507; found 514.2502.

Peptide–Quinqueoxazole 12: The title compound was obtained as a yellow solid (35 mg, 66%). M.p. 220–222 °C ($CHCl_3$). $[\alpha]_D$ = –6.8 (*c* = 0.67, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD): δ = 0.90 (d, *J* = 6.8 Hz, 3 H), 0.97 (dd, *J* = 6.8 and 11.4 Hz, 6 H), 1.05 (d, *J* = 6.8 Hz, 3 H), 1.16 (s, 9 H), 1.17–1.34 (m, 1 H), 1.46 (s, 9 H), 1.57–1.72 (m, 1 H), 2.02–2.10 (m, 1 H), 2.13–2.24 (m, 1 H), 3.81 (d, *J* = 5.6 Hz, 2 H), 4.30 (d, *J* = 4.8 Hz, 1 H), 4.59 (d, *J* = 5.6 Hz, 1 H), 7.46–7.52 (m, 3 H), 8.29–8.32 (m, 2 H), 8.65 (s, 1 H), 8.77 (s, 1 H), 8.81 (s, 1 H), 8.85 (s, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 11.9 (q), 16.3 (q), 18.4 (q), 20.2 (q), 27.6 (q), 28.7 (q), 32.6 (d), 39.1 (t), 59.6 (d), 61.0 (d), 63.8 (t), 71.6 (s), 82.2 (s), 121.3 (s), 121.6 (s), 128.7 (d), 129.4 (2 d), 129.5 (2 d), 129.7 (s), 130.8 (s), 131.4 (d), 131.8 (d), 131.9 (s), 141.8 (d), 141.9 (d), 142.3 (s), 149.5 (s), 149.7 (s), 151.3 (s), 153.6 (s), 154.0 (s), 157.7 (s), 157.8 (s), 162.8 (s), 171.4 (s), 177.5 (s) ppm. MS (ES): *m*/*z* = 922.4 [M + 39], 902.4 [M + 18], 680, 563, 338, 282, 121. HRMS: calcd. for $C_{44}H_{56}N_9O_{12}$ [M + NH_4] 902.4042; found 902.4033.

Peptide–Quateroxazole 13: The title compound was obtained as a yellow solid (57 mg, 95%). M.p. 130–132 °C ($CHCl_3$). $[\alpha]_D$ = –27.59 (*c* = 0.54, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–0.98 (m, 12 H), 1.10 (s, 9 H), 1.17–1.26 (m, 2 H), 1.46 (s, 9 H), 1.57–1.67 (m, 1 H), 1.89–2.03 (m, 2 H), 2.63 (dd, *J* = 4.4 and 16.8 Hz, 1 H), 2.73 (dd, *J* = 4.4 and 16.8 Hz, 1 H), 3.72 (dd, *J* = 4.0 and 9.2 Hz, 1 H), 3.82–3.90 (m, 1 H), 3.94–4.03 (m, 1 H), 4.78 (t, *J* = 8.0 Hz, 1 H), 5.08 (br. s, 1 H), 5.61 (d, *J* = 8.4 Hz, 1 H), 7.42–7.49 (m, 3 H), 7.61 (d, *J* = 9.6 Hz, 1 H), 8.05 (d, *J* = 10.0 Hz, 1 H), 8.21–8.26 (m, 2 H), 8.35 (s, 1 H), 8.40 (s, 1 H), 8.46 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.7 (q), 15.3 (q), 19.5 (q), 19.6 (q), 25.1 (t), 27.2 (q), 28.2 (q), 30.6 (d), 35.4 (t), 37.4 (d), 50.0 (d), 51.4 (d), 57.6 (d), 62.8 (t), 73.7 (s), 80.2 (s), 126.6 (s), 128.8 (2 d), 128.5 (s), 128.6 (2 d), 129.4 (s), 129.7 (s), 130.2 (s), 130.7 (d), 130.9 (d), 139.3 (d), 139.6 (d), 151.8 (s), 153.2 (s), 155.3 (s), 155.9 (s), 156.2 (s), 161.0 (s), 164.7 (s), 170.5 (s), 174.6 (s) ppm. MS (ES): *m*/*z* = 849 [M + 18], 832, 776, 282, 137. HRMS: calcd. for $C_{42}H_{57}N_8O_{11}$ [M + NH_4] 849.4141; found 849.4122.

Peptide–Teroxazole 14: The title compound was obtained as a yellow solid (81 mg, 83%). R_f = 0.4 (DCM/MeOH, 95:5). M.p. 163–165 °C ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83–0.92 (m, 12 H), 1.08 (s, 9 H), 1.08–1.14 (m, 1 H), 1.45 (s, 9 H), 1.45–1.53 (m, 1 H), 1.81–1.89 (m, 1 H), 2.11–2.19 (m, 1 H), 2.57 (t, *J* = 6.1 Hz, 2 H), 3.69 (s, 3 H), 3.70–3.77 (m, 3 H), 3.84 (br. s, 1 H), 4.39 (dd, *J* = 7.3 and 8.5 Hz, 1 H), 4.51 (dd, *J* = 5.2 and 8.4 Hz, 1 H), 5.05 (br. s, 1 H), 5.58 (d, *J* = 8.0 Hz, 1 H), 6.39 (d, *J* = 8.4 Hz, 1 H), 6.50 (d, *J* = 8.4 Hz, 1 H), 7.59 (br. s, 1 H), 8.25 (s, 1 H), 8.30 (s, 1 H), 8.32 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2 (q), 15.4 (q), 17.8 (q), 19.0 (q), 24.8 (t), 27.2 (q), 28.2 (q), 30.9 (d), 35.5 (t), 35.8 (t), 36.7 (d), 50.0 (d), 52.2 (q), 57.2 (d), 57.7 (d), 62.8 (t), 73.7 (s), 80.1 (s), 129.7 (s), 130.9 (s), 137.1 (s), 138.9 (d), 139.5 (d), 141.1 (d), 154.3 (s), 155.2 (s), 156.2 (s), 160.4 (s), 164.6 (s), 171.1 (s), 171.3 (s), 172.2 (s) ppm. MS (ES): *m*/*z* = 777 [M + 18], 760 [M + 1]. HRMS: calcd. for $C_{36}H_{57}N_8O_{11}$ [M + 18] 777.4138; found 777.4141.

Compound 15a: The title compound was obtained as a yellow solid (188 mg, 97%). M.p. 133–135 °C. $[\alpha]_D$ = –16.2 (*c* = 0.52, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (s, 9 H), 1.45 (s, 9 H), 3.71 (dd, *J* = 4.4 and 9.2 Hz, 1 H), 3.82–3.87 (m, 1 H), 3.97 (s, 3 H), 4.11 (dd, *J* = 4.0 and 11.6 Hz, 1 H), 4.31 (dd, *J* = 4.0 and 11.6 Hz, 1 H), 5.06 (br. s, 1 H), 5.53–5.62 (m, 2 H), 7.87 (d, *J* = 8.8 Hz, 1 H), 8.21 (s, 1 H), 8.27 (s, 1 H), 8.29 (s, 1 H), 8.33 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.0 (q), 28.1 (q), 49.0 (d), 49.8 (d), 52.1 (d), 62.6 (t), 73.6 (s), 80.0 (s), 129.4 (s), 133.9 (s), 136.3 (s), 139.3 (d), 139.9 (d), 141.5 (d), 143.7 (d), 154.7 (s), 155.2 (s), 155.3 (s), 160.2 (s), 161.0 (s), 163.0 (s), 164.6 (s), 170.8 (s) ppm. MS (ES): *m*/*z* = 648.2 [M + 18], 519, 475, 121. HRMS: calcd. for $C_{28}H_{38}N_7O_{11}$ [M + NH_4] 648.2623; found 648.2615.

Peptide–Heterocycle 16a: The title compound was obtained as a yellow solid (76 mg, 55%). M.p. 162–164 °C ($CHCl_3$). $[\alpha]_D$ = +25.1 (*c* = 0.52, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–0.96 (m, 12 H), 1.09 (s, 9 H), 1.15–1.22 (m, 1 H), 1.44 (s, 9 H), 1.53–1.65 (m, 1 H), 1.92–2.02 (m, 1 H), 2.18–2.26 (m, 1 H), 3.67–3.77 (m, 1 H), 3.79–3.91 (m, 1 H), 4.11–4.24 (m, 1 H), 4.26–4.40 (m, 1 H), 4.53–4.69 (m, 2 H), 5.08 (br. s, 1 H), 5.56–5.64 (m, 1 H), 5.66–5.78 (m, 1 H), 7.35 (br. s, 1 H), 7.77 (br. s, 1 H), 8.09 (br. s, 1 H), 8.23 (s, 1 H), 8.27 (s, 1 H), 8.29 (s, 1 H), 8.31 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0 (q), 15.3 (q), 17.8 (q), 19.0 (q), 25.0 (t), 27.2 (q), 28.3 (q), 31.0 (d), 37.2 (d), 49.3 (d), 50.0 (d), 57.3 (d), 57.7 (d), 62.9 (t), 63.0 (t), 73.8 (s), 80.3 (s), 129.6 (s), 129.7 (s), 136.4 (s), 136.6 (s), 139.5 (d), 140.0 (d), 141.7 (d), 141.8 (d), 154.5 (s), 154.9 (s), 155.4 (s), 160.4 (s), 163.3 (s), 164.8 (s), 171.4 (s), 173.9 (s) ppm. MS (ES): *m*/*z* = 846 [M + 18], 829, 773, 729, 282, 254, 149, 109. HRMS: calcd. for $C_{38}H_{56}N_9O_{13}$ [M + NH_4] 846.3992; found 846.3979.

Peptide–Heterocycle 16b: The title compound was obtained as a yellow solid (35 mg, 48%). M.p. 148–150 °C ($CHCl_3$). $[\alpha]_D$ = +24.9 (*c* = 0.53, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–1.03 (m, 12 H), 1.09 (s, 9 H), 1.19–1.30 (m, 1 H), 1.45 (s, 9 H), 1.56–1.68 (m, 1 H), 1.95–2.06 (m, 1 H), 2.13–2.25 (m, 1 H), 3.67–3.76 (m, 1 H), 3.78–3.88 (m, 1 H), 4.07–4.22 (m, 1 H), 4.24–4.37 (m, 1 H), 4.46–4.64 (m, 1 H), 4.78 (br. s, 1 H), 5.08 (br. s, 1 H), 5.53–5.61 (m, 1 H), 5.65–5.76 (m, 1 H), 7.22 (br. s, 1 H), 7.34–7.47 (m, 3 H), 8.0 (br. s, 1 H), 8.09–8.18 (m, 2 H), 8.22–8.36 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4 (q), 15.8 (q), 18.1 (q), 19.2 (q), 25.2 (t), 27.5 (q), 28.5 (q), 29.9 (d), 37.7 (d), 49.4 (d), 50.3 (d), 57.7 (d), 57.8 (d), 63.0 (t), 63.2 (t), 74.0 (s), 80.5 (s), 126.7 (s), 128.5 (2 d), 128.6 (2 d), 129.7 (s), 129.8 (d), 130.4 (s), 130.6 (s), 136.7 (s),

139.8 (d), 140.0 (d), 142.0 (d), 152.0 (s), 153.0 (s), 155.2 (s), 155.6 (s), 160.6 (s), 161.5 (s), 163.6 (s), 165.0 (s), 171.7 (s), 174.0 (s) ppm. MS (ES): *m*/*z* = 904 [M], 805, 388, 282. HRMS: calcd. for $C_{44}H_{60}N_9O_{13}$ [M + NH_4] 922.4305; found 922.4280.

Peptide 17: The title compound was obtained as a yellow oil (748 mg, 50%). R_f = 0.4 (DCM/MeOH, 95:5). $[\alpha]_D$ = +8.9 (*c* = 0.62, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90–1.0 (m, 12 H), 1.10 (s, 9 H), 1.15–1.25 (m, 2 H), 1.46 (s, 1 H), 1.98–2.10 (m, 1 H), 2.13–2.23 (m, 1 H), 3.40–3.61 (m, 2 H), 3.67 (s, 3 H), 3.69–3.77 (m, 2 H), 3.81–3.97 (m, 2 H), 4.42–4.60 (m, 1 H), 4.73–4.81 (m, 1 H), 5.03–5.16 (m, 1 H), 5.31–5.44 (m, 1 H), 5.59 (br. s, 1 H), 6.64 (br. s, 1 H), 7.37–7.47 (m, 3 H), 7.82 (br. s, 1 H), 8.16–8.23 (m, 2 H), 8.24 (s, 1 H), 8.29 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5 (q), 15.9 (q), 18.1 (q), 19.2 (q), 25.2 (t), 27.5 (q), 28.5 (q), 31.4 (d), 37.1 (d), 49.8 (d), 50.3 (d), 52.4 (q), 53.3 (d), 57.4 (d), 58.1 (d), 61.6 (t), 63.1 (2t), 73.9 (s), 80.4 (s), 126.9 (s), 127.6 (s), 128.5 (2 d), 128.8 (2 d), 130.1 (s), 130.3 (d), 136.9 (s), 139.8 (s), 141.6 (d), 141.7 (d), 155.1 (s), 155.5 (s), 160.5 (s), 160.7 (s), 161.3 (s), 165.0 (s), 170.4 (s), 171.1 (s), 172.2 (s) ppm. MS (MALDI-TOF): *m*/*z* (%) = 977 (80) [M + 39], 961 (100) [M + 23].

Peptide–Heterocycle 20: The title compound was formed by coupling of the acid of **19** (406 mg, 0.639 mmol) to the free amine of **11c** (197 mg, 0.671 mmol) by using the general procedure for peptide synthesis. After 20 h, crude **20** was obtained as an oil. Purification by column chromatography (silica gel; hexane/EtOAc, 8:2 to 4:6) afforded pure **20** (547 mg, 94%) as a yellow oil. R_f = 0.37 (DCM/MeOH, 95:5). $[\alpha]_D$ = +6.5 (*c* = 0.97, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89–1.03 (m, 12 H), 1.06 (s, 9 H), 1.20–1.30 (m, 1 H), 1.47–1.58 (m, 1 H), 2.07–2.16 (m, 1 H), 2.20–2.28 (m, 1 H), 3.37 (s, 6 H), 3.68–3.75 (m, 1 H), 3.81 (dd, *J* = 4.6 and 9.4 Hz, 1 H), 3.89 (s, 2 H), 4.41–4.55 (m, 1 H), 4.59–4.70 (m, 1 H), 5.29–5.43 (m, 1 H), 5.98 (br. s, 1 H), 6.96–7.20 (m, 2 H), 7.38–7.46 (m, 3 H), 7.78–7.88 (m, 1 H), 8.07 (s, 1 H), 8.11 (s, 1 H), 8.22–8.33 (m, 3 H), 8.35 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5 (q), 14.8 (q), 17.8 (q), 19.2 (q), 26.3 (t), 27.2 (q), 30.6 (d), 31.7 (t), 37.2 (d), 48.6 (d), 50.3 (2q), 57.2 (d), 58.4 (d), 62.3 (t), 73.9 (s), 99.3 (s), 126.6 (s), 127.2 (s), 128.3 (2 d), 128.5 (2 d), 129.6 (s), 130.2 (d), 136.7 (s), 139.3 (d), 140.0 (d), 141.6 (d), 151.7 (s), 153.0 (s), 154.7 (s), 161.3 (s), 161.4 (s), 162.3 (s), 163.9 (s), 170.8 (s), 171.1 (s), 171.3 (s), 171.4 (s) ppm. MS (MALDI-TOF): *m*/*z* (%) = 935 (42) [MBr^{81} + Na], 933 (100) [MBr^{79} + Na]. HRMS: calcd. for $C_{41}H_{52}BrN_8O_{11}$ 911.2933 and 913.2943; found 911.2951 and 913.2923.

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[17] Compound **16a**, which has the same structure as that of **16b** but without the phenyl ring, did not undergo macrocyclization under the conditions tested for **16b**.
[18] Peptide **17** was obtained from the free acid of **7** and H-D-Ile-L-Val-OMe by using the general procedure described for peptide bond formation.
[19] The high polarity of macrocycle **18** with two hydroxy groups precluded its purification from a complex crude reaction mixture in which HPLC shows **18** with an area of around 8% (t_R = 7.56 min; MS: *m*/*z* = 845 [M + K], 829 [M + Na]).

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