Syntheses and Structures of Imidazole Analogues of *Lissoclinum* Cyclopeptides

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The syntheses of the cyclic peptides **3**–**7**, which contain imidazole units in their backbones and resemble naturally occurring marine cyclopeptides such as westiellamide and ascidiacyclamide, are described. Structural investigations on the trimer **3** reveal a molecular triangle conformation with all lone pairs of the imidazole nitrogen atoms and the hydrogen atoms of the secondary amides directed to the center of the macrocycle. The structures of the tetramers **4** and **6** display distorted molecular square conformations with the heterocycles (**4**) and the αCH groups (**6**) placed at the corners of the rectangle, respectively.

Introduction

A wide variety of unusual cyclopeptide alkaloids have been isolated from marine sources in recent years.[1] These compounds have usually been identified as secondary metabolites of algae, fungi, and primitive marine organisms, possessing various biological activities, including cytotoxicity, antibacterial activities, and antiviral activities.[2] Examples of their ability to overcome multidrug resistance or to act as antineoplastic agents have been found.[3] The *Lissoclinum* class of cyclic peptides, such as westiellamide (**1**)[4] or ascidiacyclamide (**2**),[5] belongs to these alkaloids and is characterized by an alternating sequence of oxazole, thiazole, oxazoline, and thiazoline moieties with hydrophobic standard amino acid residues.[6] These five-membered heterocyclic rings result from condensation of serine, threonine, and cysteine side chains with the preceding carbonyl groups in a peptide sequence. The unique macrocyclic heterocyclic scaffolds in *Lissoclinum* cyclopeptides have prompted the speculation that they may function in vivo as metal complexation and transport agents.[7] Evidence for metal complexation properties of *Lissoclinum* cyclopeptide alkaloids has been obtained by metal ion binding studies to westiellamide, patellamides, and ascidiacyclamide.[8] Additionally, intensive investigations concerning the application of properties resulting from this particularly rigid structure have been conducted.[9]

The imidazole unit, as part of the side chain of histidine, plays a major role in the biological functions of many peptides and proteins. Imidazoles, for example, are well known as ligands in many metalloenzymes (e.g. metalloproteases),[10] and due to their basicity, have proven to be key structural elements in basic active sites of enzymes.[11] However, no cyclopeptides containing imidazole units in the scaffold have yet been isolated from nature. This may be due to the fact that the diaminopropanoic acid (Dap), formally the amino analogue of serine, rarely occurs in natural sources.[12] This prompted us to synthesize the peptides **3**−**7** (Figure 1), which contain imidazole units in their backbones and resemble naturally occurring marine cyclopeptides such as westiellamide and ascidiacyclamide, and also

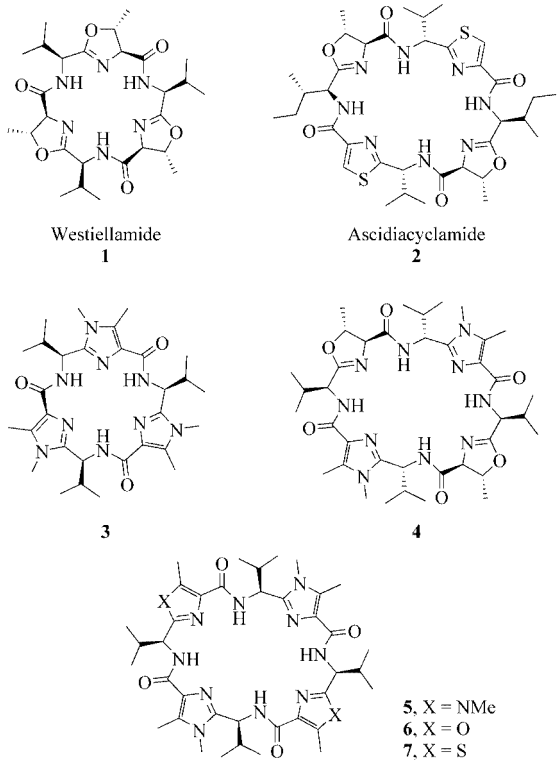

Figure 1. *Lissoclinum* cyclopeptides and their imidazole analogues

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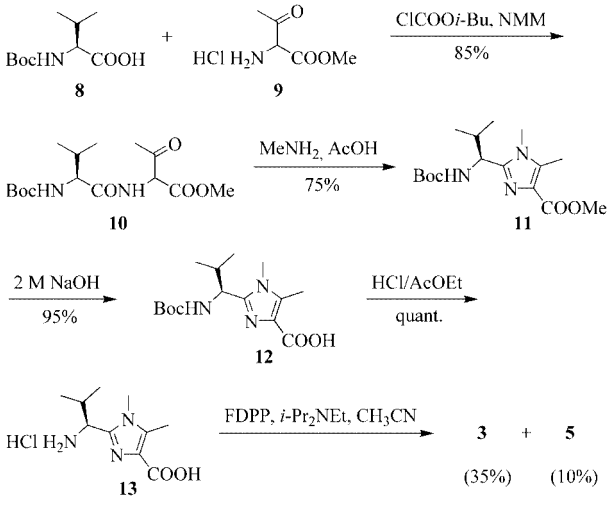
to investigate the structure modifications caused by the introduction of these imidazole moieties.

Results and Discussion

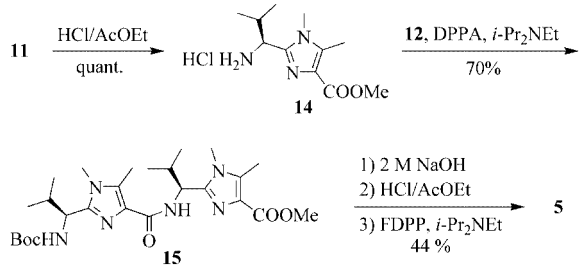
Synthesis

A straightforward synthesis for the 18-membered cyclohexapeptide **3** and the 24-membered cyclooctapeptide **5** is summarized in Scheme 1.[13] It started with the activation of the Boc-protected valine **8** as a mixed anhydride by treatment with isobutyl chloroformate and coupling to the keto ester **9**[14] at −20 °C. The resulting amidoketone **10** was transformed into the imidazole **11** with methylamine in the presence of acetic acid in refluxing xylenes with azeotropic removal of water.[15] Deprotection of the carboxyl residue by saponification and removal of the Boc group with HCl in ethyl acetate afforded the amino acid **13**. The one-pot macrocyclization of the imidazole **13** was carried out through pentafluorophenyl diphenylphosphinate (FDPP)[16] activation and addition of Hünig's base in acetonitrile, and yielded the trimer **3** in 35% yield and the tetrameric compound **5** in 10% yield.



Scheme 1

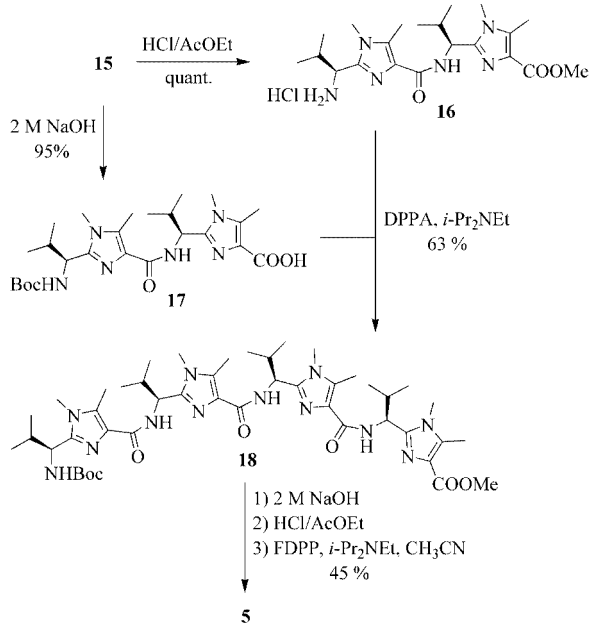
Because of the difficulties occurring during the separation of the tetramer **5** from the trimer **3**, we also elaborated alternative synthetic routes, which provided the tetramer **5** in significantly increased yields and in higher purity. An appropriate way is presented in Scheme 2.



Scheme 2

Removal of the Boc group of **11** with HCl in ethyl acetate provided the hydrochloride **14**, which was coupled to the free acid building block **12** by use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI)[17] and benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP)[18] as activation reagents. However, both routes resulted in low yields of the desired product **15**, often accompanied by large amounts of undesired side products. The use of diphenyl phosphorazidate (DPPA)[19] in the presence of Hünig's base in acetonitrile proved superior, finally providing **15** in 70% yield. The protected linear dimer **15** was successively subjected to methyl and Boc deprotection to give the corresponding free amino acid, which was dimerized by FDPP activation in acetonitrile to afford the tetramer **5** in 44% yield. Overall, the yield of this route is 29% starting from imidazole **11**.

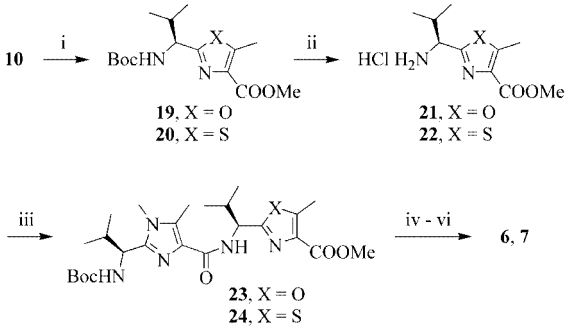
Another route for a stepwise preparation of the 24-membered cyclooctapeptide **5** is summarized in Scheme 3. Here, the protected linear tetramer **18** was synthesized by coupling of the dimeric modules **16** and **17** with DPPA and Hünig's base in acetonitrile. After basic and acidic protective group cleavages, macrolactamization with FDPP as coupling reagent gave the desired cyclic peptide **5** in 45% yield. The overall yield amounts to 18% starting from the monomeric module **11**. From comparison of the three synthetic routes to the tetramer **5**, it is evident that the cyclodimerization (Scheme 2) is the most convenient.



Scheme 3

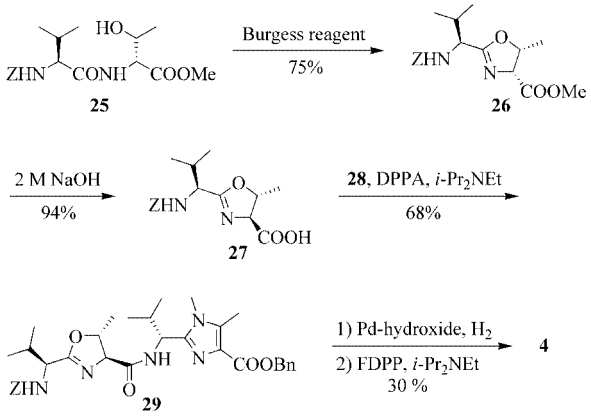
We therefore also chose the cyclodimerization route for the syntheses of the C_2-symmetric cyclooctapeptides **6** and **7** (Scheme 4). The amidoketone **10** was transformed either into the oxazole module **19** or into the thiazole module **20** by use of PPh_3 in the presence of CCl_4 and Et_3N[20] or Lawesson's reagent,[21] respectively. After acid cleavage of

the Boc group, the resulting hydrochlorides **21** and **22** were coupled to the imidazole acid **12** with DPPA and Hünig's base in acetonitrile to afford the dimers **23** and **24** in 65% and 60% yields, respectively. Protective groups were removed from the carboxylic acid and amino termini and the dimeric modules were subjected to cyclization by FDPP activation in the presence of Hünig's base in acetonitrile. After two days, the reaction mixtures were worked up and the macrocycles **6** and **7** could be isolated in 35% and 56% yields, respectively.



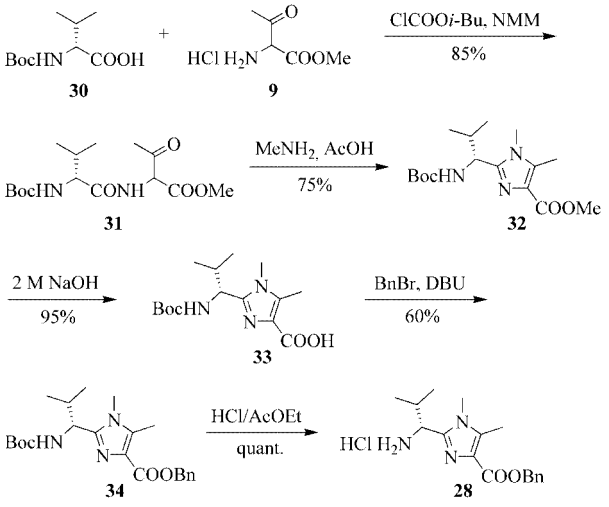
Scheme 4. i) PPh_3, Et_3N, CCl_4, 86% for **19**; Lawesson's reagent, 75% for **20**. ii) HCl/EtOAc, quant. iii) **12**, DPPA, iPr$_2$NEt, 65% for **23**, 60% for **24**. iv) 2 M NaOH. v) HCl/EtOAc. vi) FDPP, iPr$_2$NEt, CH_3CN, 35% for **6**, 56% for **7**

A challenging aspect in the preparation of the macrocycle **4** is the presence of *trans*-4,5-disubstituted oxazoline, which turned out to be an acid-sensitive and readily opened moiety, in the peptide backbone (Scheme 5).[22] For this reason, in earlier works on peptide macrocycles the oxazoline ring-closure was delayed until the final step.[23] Additionally, preliminary studies in our lab have shown that the oxazoline moiety is not stable under the reaction and workup conditions necessary for the cleavage of a methyl ester at an imidazole ring. However, there are particular cases in which the preconstructed oxazoline was employed successfully.[24] We chose to follow this strategy, since we expected that the incorporation of a further rigid moiety (the oxazoline) into the tetrapeptide sequence of **29** in addition to the presence of the imidazole ring should significantly facilitate the ring-closure process through backbone bending. Moreover, as protecting groups in **29** we decided to use the Z group for the amine and the benzyl ester for the acid, since both should be removable under non-acidic conditions. The D-valine-derived imidazole **32** (Scheme 6) was prepared in the same way as its enantiomer (**11**, Scheme 1). Transesterification of the methyl ester **32** to the benzyl ester **34** was accomplished by saponification with sodium hydroxide and subsequent alkylation with benzyl bromide and DBU (1,8-diazabicyclo[5.4.0.]undec-7-ene)[25] in acetonitrile. The benzyl ester **34** was then subjected to amine deprotection with HCl in ethyl acetate, providing the hydrochloride salt **28** in essentially quantitative yield. The oxazoline **27** was obtained as follows, by the procedure reported by Wipf



Scheme 5

(Scheme 5).[26] Condensation of oxazoline acid **27** with hydrochloride salt **28** with the aid of DPPA in the presence of Hünig's base in acetonitrile gave the dimer **29** in 68% yield. Removal of the Z group and the benzyl ester in **29** was achieved by catalytic hydrogenation with $Pd(OH)_2$ in methanol. The final cyclodimerization step was successfully implemented by treatment of the crude amino acid with FDPP and Hünig's base in acetonitrile. Isolation of the product afforded the desired macrocycle **4** in 30% yield.



Scheme 6

Structural Investigations

The NMR spectra (^{1}H, ^{13}C) for the 18-membered peptide **3** and the 24-membered peptide **5** indicate that they are C_3- and C_4-symmetric, respectively. The ^{1}H NMR spectra for **3** and **5** are similar, although the doublets of the amide NH resonances in **3** are shifted about $\delta = 0.8$ ppm further downfield than those in **5**, suggesting that the interaction between the lone pairs of the imidazole nitrogen and the

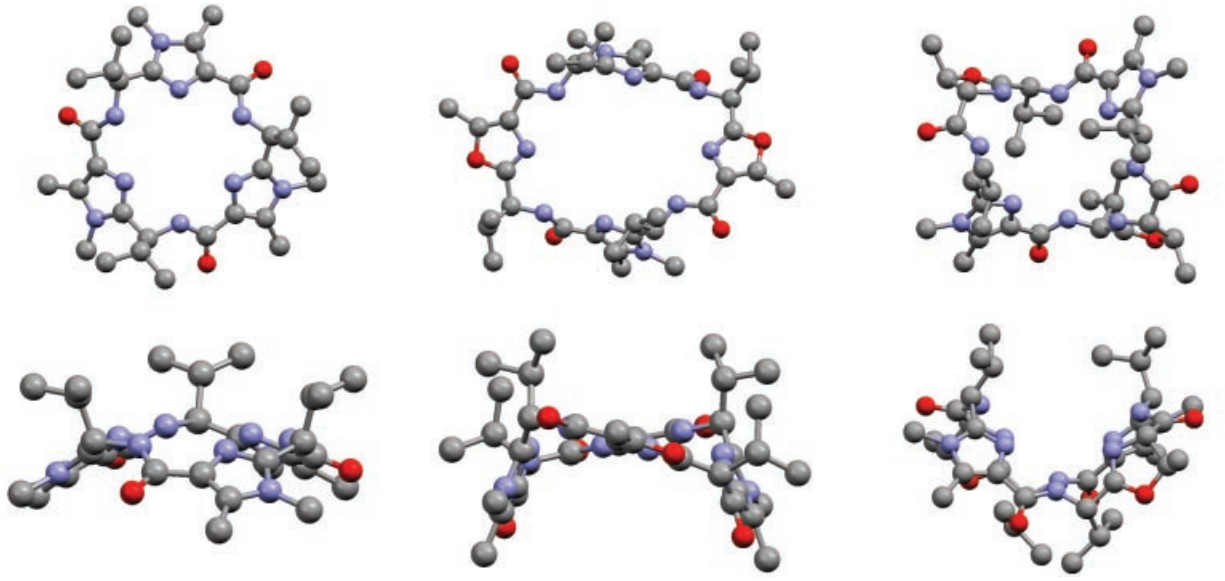


Figure 2. Molecular structures of **3**, **6**, and **4**: top view (upper row) and side view (lower row); all hydrogen atoms have been omitted for clarity

hydrogen of the secondary amides are probably stronger in **3** than in **5**. The vicinal $^3J_{NHCH}$ values of 8.9 Hz and 9.1 Hz for **3** and **5**, respectively, correspond to dihedral angles of $160° < \theta < 180°$ in both macrocycles.[27]

In the case of **3** we were able to obtain single crystals by crystallization from acetone (Figure 2).[13] The 18-membered peptide **3** adopts a molecular triangle conformation in the solid state. As in the case of the X-ray analyses of the closely related westiellamide[4] (**1**) and nostocylamide,[28] there are no intra- or intermolecular hydrogen bonds, their formation being prevented by the disposition of the peptide NH groups into the center of the ring and peptide carbonyl functions toward the outside of the ring. The valine side chains of **3** all lie on the same face of the molecule and adopt axial positions. Unlike in the structures of westiellamide and nostocylamide, the azole moieties of the macrocycle **3** do not form a single plane but have a cone-like structure, their deviation from the coplanar structure amounting to about 33°. The NHαCH dihedral angles of the three amide linkages in **3** were found to be between 168 and 173°, which is consistent with the values determined by ^{1}H NMR spectroscopy.

The NMR spectra of **6** and **7** indicate that they are C_2-symmetric. The values for the NH amide resonances (δ = 7.32 ppm and 7.65 ppm for **6**; δ = 7.65 ppm and 7.92 ppm for **7**) and for the vicinal coupling $^3J_{NHCH}$ (9.9 Hz and 9.0 Hz for **6**; 9.2 Hz and 9.1 Hz for **7**) are similar to those of the tetramer **5** (δ = 7.53 ppm; 9.1 Hz), thus suggesting that all three 24-membered peptides adopt similar conformations in solution. Single crystals of **6** could be obtained by crystallization from dichloromethane/petroleum ether at room temperature. Tetramer **6** displays a distorted molecular square conformation with the αCH groups placed at the corners of the rectangle (Figure 2). The imidazole and the oxazole moieties are tilted about 70° and 15° out of the macrocycle plane, respectively. The distances between the opposite heterocycles amount to 6.3 Å for the imidazoles and 7.8 Å for the oxazoles. The L-valine side chains are in pseudoaxial orientation and are all directed from the same face of the macrocycle. The NHαCH dihedral angles of the amide linkages in **6** are between 164° and 173°, which is in agreement with the values determined by ^{1}H NMR spectroscopy.

The macrocycle **4** shows NMR spectra consistent with a C_2-symmetric structure in solution. The vicinal coupling constants ($^3J_{NHCH}$) amount to 8.7 Hz and 9.9 Hz. It is known that thiazole- and oxazoline-containing cyclic octapeptide patellamides, which resemble the octapeptide **4** regarding the oxidation states of the azoles and configurations of the adjacent side chains, exist in one of two conformations (square and folded forms) depending on the side chains present in the molecule.[29] However, it became apparent that the values of the vicinal coupling constants ($^3J_{NHCH}$) are not an appropriate means for distinguishing the two conformers of symmetric patellamides.[30] Accordingly, the observed NMR spectroscopic data are not sufficient for unambiguous determination of the conformation of **4** in solution. X-ray diffraction analysis of a single crystal of **4** revealed that two crystallographically independent molecules of **4** exist in the asymmetric unit, and their conformations are similar to each other. Therefore, only one molecule is shown in Figure 2. The macrocycle displays a molecular square or saddle-shaped conformation in which the imidazole and oxazoline rings are separated from each other and located at the corners of the backbone ring. The valine side chains are in pseudoaxial orientation, the D-valine groups adjacent to the imidazole ring and the L-valine groups adjacent to the oxazoline ring protruding over and under the ring chain, respectively. These features are similar to the square form of ascidiacyclamide.[31]

Conclusion

In conclusion, we have demonstrated that the preparation of 18- and 24-membered cyclic peptides containing imidazole moieties in their backbones can be achieved in satisfactory yields in few steps. The observed structures resemble corresponding naturally occurring marine cyclopeptides such as westiellamide and ascidiacyclamide. This means that the modification of the structures caused by the exchange of oxazoline or thiazoline moieties by imidazole rings is minimal. Future studies will aim at determining how the imidazole unit influences further properties of the macrocycles, such as metal complexation and biological activity.

Experimental Section

General Remarks: Amino ketone **9**[14] and oxazoline **27**[26] were prepared by reported procedures. All chemicals were reagent grade and used as purchased. All moisture-sensitive reactions were performed under argon in distilled dry solvents. Reactions were monitored by TLC analysis with silica gel 60 F_{254} thin layer plates. Flash chromatography was carried out on silica gel 60 (230−400 mesh). Melting points were determined in capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured with Bruker WH 300, Avance 300, and Avance 500 instruments. All chemical shifts (δ) are given in ppm relative to TMS. The spectra were referenced to deuterated solvents indicated in brackets in the analytical data. HRMS spectra were recorded with a JEOL JMS-700 instrument. IR spectra were measured with a Bruker Vector 22 FT-IR spectrometer. Elemental microanalyses were performed by the microanalytical laboratory of the University of Heidelberg.

Abbreviations: Boc: *tert*-butoxycarbonyl; FDPP: pentafluorophenyl diphenylphosphinate; DBU: 1,8-diazabicyclo[5.4.0.]undec-7-ene; DCM: dichloromethane; DMF: *N*,*N*-dimethylformamide; DPPA: diphenylphosphoryl azide; NMM: *N*-methylmorpholine; THF: tetrahydrofuran; Z: benzyloxycarbonyl.

General Procedure for the Cleavage of the Methyl Ester Group: The protected compound (1 equiv.) was dissolved in methanol/dioxane (10:7, 0.08 M), followed by slow addition of 2 M NaOH solution (10 equiv.) at 0 °C. Stirring was continued until TLC showed the consumption of all starting material, and then brine, 1 M HCl solution, and DCM were added. The aqueous phase was repeatedly extracted with DCM; the organic layers were combined, dried with $MgSO_4$, and concentrated in vacuo to give the acid compound, which was used in the next step without further purification.

General Procedure for the Cleavage of the Boc Group: The Boc-protected compound (1 equiv.) was dissolved in ethyl acetate (0.1 M) and the solution was cooled to 0 °C. HCl in EtOAc (10 ml/mmol starting material) was added at that temperature. The ice bath was removed after 30 min and stirring was continued at room temperature for two hours. The mixture was concentrated in vacuo to provide a quantitative yield of the hydrochloride, which was used in the next step without further purification.

Methyl 2-{[(*S*)-2-(*tert*-Butoxycarbonylamino)-3-methylbutanoyl]-amino}-3-oxobutanoate (10): (*S*)-Boc−Val−OH (**8**; 9.78 g, 45.0 mmol) was dissolved in THF (250 mL), NMM (4.95 mL, 45.0 mmol) was added, and the solution was cooled to −25 °C. Isobutyl chloroformate (5.91 mL, 45.0 mmol) was added while the reaction mixture was maintained at −25 °C. After 35 min, amino ketone **9** (7.54 g, 45.0 mmol) followed by a second equivalent of NMM (4.95 mL, 45.0 mmol) were added at −25 °C. Stirring was continued for 20 h while the mixture was warmed to room temperature. The solvent was evaporated and the residue was dissolved in EtOAc, and then washed with water and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. Purification was accomplished by chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) to yield **7** (12.71 g; 85%) as a white solid; m.p. 109−112 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CHMe_2), 0.92 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CHMe_2), 0.97 (d, $^3J_{H,H}$ = 6.8 Hz, 6 H, CHMe_2), 1.43 (s, 9 H, CMe_3), 1.44 (s, 9 H, CMe_3), 2.24−2.11 (m, 2 H, C*H*Me_2), 2.38 (s, 6 H, COMe), 3.80 (s, 6 H, CO_2Me), 4.06 (m, 2 H, C*H*CONH), 5.02 (m, 2 H, $NHCO_2$), 5.23 (m, 2 H, C*H*CO_2Me), 7.06 (d, $^3J_{H,H}$ = 6.1 Hz, 1 H, NH), 7.13 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.3, 17.5, 19.1, 19.2, 27.9, 28.0, 28.3, 30.7, 30.9, 53.2, 53.3, 59.5, 62.86, 62.90, 80.2, 155.7, 166.25, 166.33, 171.4, 197.92, 197.99 ppm. IR (KBr): ṽ = 3440, 3323, 2959, 2873, 1751, 1727, 1687, 1656, 1524 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{15}H_{27}N_2O_6$ [MH^+] 331.1869, found 331.1864. $C_{15}H_{26}N_2O_6$ (330.38): calcd. C 54.53, H 7.93, N 8.48; found C 54.54, H 7.92, N 8.45.

Methyl 2-[(*S*)-1-*tert*-Butoxycarbonylamino-2-methylpropyl]-1,5-dimethyl-1*H*-imidazole-4-carboxylate (11): Acetic acid (13 mL) and $MeNH_2$ in MeOH (8 M, 13 mL, 105 mmol) were added at room temperature to a solution of **10** (11.56 g, 35.0 mmol) in xylenes (220 mL). The solution was stirred at 150 °C with azeotropic removal of water for 3.5 h and then cooled down to room temperature. $MeNH_2$ in MeOH (8 M, 5 mL, 40.0 mmol) and acetic acid (10 mL) were added and the mixture was stirred at reflux with azeotropic removal of water for 5 h. The solution was cooled, the solvent was concentrated, and the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) to provide **11** (8.58 g, 75%) as a white solid and in > 96% *ee* as determined by HPLC analysis [Chiralpak AD-H, hexane/*iso*-propanol, 90:10, 0.5 mL/min, *t*(minor) = 9.8 min, *t*(major) = 12.8 min); m.p. 130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CHMe_2), 0.99 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CHMe_2), 1.38 (s, 9 H, CMe_3), 2.15−2.27 (m, 1 H, C*H*Me_2), 2.51 (s, 3 H, C_{Het}Me), 3.54 (s, 3 H, NMe), 3.86 (s, 3 H, CO_2Me), 4.51 (m, 1 H, CHC_{Het}), 5.32 (d, $^3J_{H,H}$ = 9.5 Hz, 1 H, $NHCO_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.2, 18.5, 19.6, 28.3, 30.3, 33.2, 51.4, 52.2, 79.5, 127.6, 135.9, 148.4, 155.7, 164.3 ppm. IR (KBr): ṽ = 3447, 3341, 2968, 1694, 1678, 1573, 1525 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{16}H_{27}N_3O_4Na$ [MNa^+] 348.1899, found 348.1904. $C_{16}H_{27}N_3O_4$ (325.40): calcd. C 59.06, H 8.36, N 12.91; found C 58.86, H 8.37, N 12.71.

***N*-Boc-Protected Aminoimidazolecarboxylic Acid 12:** Compound **11** (4.88 g, 15.0 mmol) was converted into **12** as described above in the general procedure for the cleavage of the methyl ester group. Yield: 4.44 g (95%); m.p. 99−102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CHMe_2), 1.12 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CHMe_2), 1.39 (s, 9 H, CMe_3), 2.48−2.62 (m, 1 H, C*H*Me_2), 2.59 (s, 3 H, C_{Het}Me), 3.70 (s, 3 H, NMe), 4.54 (m, 1 H, CHC_{Het}), 7.40 (s, 1 H, $NHCO_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.9, 19.5, 19.6, 28.3, 31.1, 32.5, 52.8, 79.5, 125.7, 135.2, 148.9, 156.4, 163.5 ppm. IR (KBr): ṽ = 3431, 2973, 1704, 1635, 1511 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{15}H_{26}N_3O_4$ [MH^+] 312.1923, found 312.1918. $C_{15}H_{25}N_3O_4{\cdot}(H_2O)$ (329.39): calcd. C 54.69, H 8.26, N 12.76; found C 54.95, H 7.95, N 12.43.

Hydrochloride of Aminoimidazole-carboxylic Acid 13: Compound **12** (2.80 g, 9.00 mmol) was converted into **13** as described above in the general procedure for the cleavage of the Boc group. Yield: quantitative; m.p. 182 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.80 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CH*Me*$_2$), 1.06 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH*Me*$_2$), 2.39−2.48 (m, 1 H, C*H*Me$_2$), 2.51 (s, 3 H, C$_{Het}$Me), 3.73 (s, 3 H, NMe), 4.58 (m, 1 H, CHC$_{Het}$), 9.16 (s, 3 H, NH$_3$), 11.17−12.16 (s, 1 H, CO$_2$H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 9.7, 18.1, 18.7, 31.3, 31.8, 50.6, 124.0, 136.9, 143.5, 161.8 ppm. IR (KBr): ṽ = 3431, 2968, 1995, 1722, 1632, 1510 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for C$_{10}$H$_{18}$N$_3$O$_2$ [MH$^+$] 212.1399, found 212.1370.

Hydrochloride of Aminoimidazole Methyl Ester 14: Compound **11** (2.93 g, 9.00 mmol) was converted into **14** as described above in the general procedure for the cleavage of the Boc group. Yield: quantitative; m.p. 67 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.80 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH*Me*$_2$), 1.00 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CH*Me*$_2$), 2.25−2.37 (m, 1 H, C*H*Me$_2$), 2.49 (s, 3 H, C$_{Het}$Me), 3.64 (s, 3 H, NMe), 3.76 (s, 3 H, CO$_2$Me), 4.45 (m, 1 H, CHC$_{Het}$), 8.85 (s, 3 H, NH$_3$) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 9.8, 18.0, 18.4, 31.0, 31.5, 50.7, 51.0, 125.5, 137.1, 143.9, 162.4 ppm. IR (KBr): ṽ = 3432, 2963, 1733, 1633, 1511 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for C$_{11}$H$_{20}$N$_3$O$_2$ [MH$^+$] 226.1556, found 226.1565.

***N*-Boc-Protected Methyl Ester 15:** *i*Pr$_2$NEt (2.96 mL, 17.0 mmol) and DPPA (1.63 mL, 7.50 mmol) were added at room temperature to acid **12** (1.56 g, 5.00 mmol) and aminohydrochloride **14** (1.44 g, 5.50 mmol) in acetonitrile (50 mL), and the mixture was stirred at room temperature for 4 days. The solvent was evaporated, and the residue was dissolved in EtOAc, and then extracted with water and brine, dried with MgSO$_4$, and concentrated in vacuo. Flash chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:2) gave **15** (1.82 g, 70%) as a white solid; m.p. 84 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 0.89 (m, 6 H, CH*Me*$_2$), 1.02 (m, 6 H, CH*Me*$_2$), 1.37 (s, 9 H, CMe$_3$), 2.19−2.43 (m, 2 H, C*H*Me$_2$), 2.51 (s, 3 H, C$_{Het}$Me), 2.52 (s, 3 H, C$_{Het}$Me), 3.59 (s, 3 H, NMe), 3.66 (s, 3 H, NMe), 3.76 (s, 3 H, CO$_2$Me), 4.54 (m, 1 H, CHC$_{Het}$), 5.03 (m, 1 H, CHC$_{Het}$), 6.32 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, NHCO$_2$), 7.52 (d, $^3J_{H,H}$ = 9.7 Hz, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 10.7, 11.2, 19.9, 20.2, 21.05, 21.15, 29.5, 31.7, 34.1, 34.2, 51.2, 51.9, 54.0, 80.0, 129.1, 130.9, 134.2, 137.9, 148.7, 150.0, 157.5, 164.8, 165.9 ppm. IR (KBr): ṽ = 3404, 2965, 2873, 1705, 1653, 1592, 1506 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for C$_{26}$H$_{43}$N$_6$O$_5$ [MH$^+$] 519.3295, found 519.3312. C$_{26}$H$_{42}$N$_6$O$_5$·(H$_2$O)$_{0.5}$ (527.66): calcd. C 59.18, H 8.21, N 15.93; found C 59.43, H 8.25, N 15.69.

Hydrochloride of Methyl Ester 16: Compound **15** (441 mg, 0.85 mmol) was converted into **16** as described above in the general procedure for the cleavage of the Boc group. Yield: quantitative; m.p. 198 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.80 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CH*Me*$_2$), 0.89 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH*Me*$_2$), 0.98 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH*Me*$_2$), 1.06 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, CH*Me*$_2$), 2.25−2.35 (m, 1 H, C*H*Me$_2$), 2.43 (s, 3 H, C$_{Het}$Me), 2.39−2.47 (m, 1 H, C*H*Me$_2$), 2.53 (s, 3 H, C$_{Het}$Me), 3.56 (s, 3 H, NMe), 3.81 (s, 3 H, NMe), 3.83 (s, 3 H, CO$_2$Me), 4.43 (m, 1 H, CHC$_{Het}$), 5.07 (m, 1 H, CHC$_{Het}$), 8.36 (m, 1 H, CONH), 8.71 (s, 3 H, NH$_3$) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 9.3, 9.6, 17.9, 18.1, 18.8, 19.2, 30.4, 31.2, 31.5, 31.7, 49.9, 51.0, 51.9, 128.1, 133.9, 137.3, 142.4, 148.3, 162.7, 166.1, 169.6 ppm. IR (KBr): ṽ = 3426, 2966, 2021, 1728, 1637, 1511 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for C$_{21}$H$_{35}$N$_6$O$_3$ [MH$^+$] 419.2771, found 419.2788.

***N*-Boc-Protected Amino Acid 17:** Compound **15** (830 mg, 1.60 mmol) was converted into **17** as described above in the general procedure for the cleavage of the methyl ester group. Yield: 770 mg (95%); m.p. 204 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 0.90 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CH*Me*$_2$), 0.95 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CH*Me*$_2$), 1.10 (d, $^3J_{H,H}$ = 6.5 Hz, 3 H, CH*Me*$_2$), 1.21 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CH*Me*$_2$), 1.39 (s, 9 H, CMe$_3$), 2.62 (s, 3 H, C$_{Het}$Me), 2.65 (s, 3 H, C$_{Het}$Me), 2.75−2.52 (m, 2 H, C*H*Me$_2$), 3.94 (s, 3 H, NMe), 3.99 (s, 3 H, NMe), 4.89 (d, $^3J_{H,H}$ = 9.2, 1 H, CHC$_{Het}$), 5.24 (d, $^3J_{H,H}$ = 9. 6 Hz, 1 H, CHC$_{Het}$) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 10.81, 10.84, 20.2, 20.5, 20.6, 21.1, 29.5, 32.8, 33.5, 33.7, 34.1, 54.1, 54.3, 81.2, 123.5, 124.1, 138.3, 139.1, 148.8, 149.6, 157.5, 160.6, 161.8 ppm. IR (KBr): ṽ = 3429, 2970, 1711, 1664, 1636, 1511 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for C$_{25}$H$_{40}$N$_6$O$_5$ [MH$^+$] 505.3138, found 505.3117.

***N*-Boc-Protected Methyl Ester 18:** *i*Pr$_2$NEt (233 mg, 1.80 mmol) and DPPA (124 mg, 0.45 mmol) were added at room temperature to acid **17** (151 mg, 0.30 mmol) and aminohydrochloride **16** (205 mg, 0.45 mmol) in acetonitrile (12 mL) and the mixture was stirred at room temperature for 3 days. The solvent was evaporated and the residue was dissolved in EtOAc, and then extracted with water and brine, dried with MgSO$_4$, and concentrated in vacuo. The residue was then purified by chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:3) to provide 172 mg (63%) of **18** as a white solid; m.p. 146 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 0.84 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CH*Me*$_2$), 0.90−1.00 (m, 15 H, CH*Me*$_2$), 1.04−1.08 (m, 6 H, CH*Me*$_2$), 1.30 (s, 9 H, CMe$_3$), 2.10−2.22 (m, 1 H, C*H*Me$_2$), 2.34−2.50 (m, 3 H, C*H*Me$_2$), 2.51 (s, 6 H, C$_{Het}$Me), 2.52 (s, 3 H, C$_{Het}$Me), 2.53 (s, 3 H, C$_{Het}$Me), 3.56 (s, 3 H, NMe), 3.59 (s, 3 H, NMe), 3.62 (s, 3 H, NMe), 3.67 (s, 3 H, NMe), 3.68 (s, 3 H, CO$_2$Me), 4.51 (m, 1 H, CHC$_{Het}$), 4.95−5.08 (m, 3 H, CHC$_{Het}$), 6.26 (d, $^3J_{H,H}$ = 9.4 Hz, 1 H, NHCO$_2$), 7.44 (m, 2 H, CONH), 7.58 (d, $^3J_{H,H}$ = 9.7 Hz, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 10.69, 10.72, 10.75, 11.3, 19.9, 20.1, 20.2, 20.3, 21.1, 21.2, 21.39, 21.40, 29.5, 31.7, 31.4, 33.5, 33.7, 33.9, 34.2, 51.17, 51.28, 51.30, 51.8, 54.0, 79.9, 129.2, 130.8, 130.9, 131.6, 134.2, 134.4, 134.6, 137.8, 148.4, 148.5, 148.6, 149.9, 157.5, 164.81, 164.83, 165.9 ppm. IR (KBr): ṽ = 3404, 2963, 2873, 1705, 1656, 1592, 1500 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for C$_{46}$H$_{73}$N$_{12}$O$_7$ [MH$^+$] 905.5725, found 905.5724.

Imidazole Trimer 3 and Imidazole Tetramer 5: *i*Pr$_2$NEt (0.84 mL, 4.80 mmol) and FDPP (922 mg, 2.40 mmol) were added at room temperature to a suspension of **13** (396 mg, 1.60 mmol) in acetonitrile (34 mL) and the mixture was stirred at room temperature for 3 days. The solvent was evaporated and the residue was dissolved in EtOAc, then extracted with water and brine, dried with MgSO$_4$, and concentrated in vacuo. Flash chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:6) gave **3** (109 mg, 35%) as a white solid, followed by **5** (39 mg, 10%) as a white solid.

Alternatively, **5** can be prepared as follows:

1) Dimer **15** (182 mg, 0.35 mmol) was successively subjected to methyl and Boc deprotection to give the corresponding free amino acid. *i*Pr$_2$NEt (0.24 mL, 1.40 mmol) and FDPP (211 mg, 0.55 mmol) were added at room temperature to the stirred solution of this compound in acetonitrile (10 mL) and the mixture was stirred at that temperature for 3 days. The solvent was evaporated, and the residue was dissolved in EtOAc, and then extracted with water and brine, dried with MgSO$_4$, and concentrated in vacuo. Purification was accomplished by chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:7) to yield **5** (59 mg, 44%) as a white solid.

2) Tetramer **18** (72 mg, 0.08 mmol) was subjected successively to methyl and Boc deprotection to give the corresponding free amino

acid. *i*Pr$_2$NEt (65 mg, 0.50 mmol) and FDPP (58 mg, 0.15 mmol) were added at room temperature to the stirred solution of this compound in acetonitrile (10 mL) and the mixture was stirred for 24 h. The solvent was evaporated, and the residue was dissolved in EtOAc, extracted with water and brine, dried with $MgSO_4$, and concentrated in vacuo. Purification was accomplished by chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:6) to yield **5** (28 mg, 45%) as a white solid.

Data for 3: M.p. > 250 °C. $[\alpha]_D^{20} = -114$ (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 0.95 (d, $^3J_{H,H}$ = 6.7 Hz, 9 H, CHMe_2), 1.01 (d, $^3J_{H,H}$ = 6.8 Hz, 9 H, CHMe_2), 2.05−2.13 (m, 3 H, CHMe$_2$), 2.52 (s, 9 H, C_{Het}Me), 3.62 (s, 9 H, NMe), 5.14 (m, 3 H, CHC_{Het}), 8.36 (d, $^3J_{H,H}$ = 8.9 Hz, 3 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 10.6, 19.0, 20.8, 31.7, 36.4, 51.1, 131.3, 134.0, 148.7, 164.6 ppm. IR (KBr): $\tilde{\nu}$ = 3385, 2963, 2874, 1661, 1595, 1510, 1465 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{30}H_{46}N_9O_3$ [MH$^+$] 580.3724, found 580.3707. $C_{30}H_{45}N_9O_3\cdot(H_2O)_{2/3}$ (591.75): calcd. C 60.89, H 7.89, N 21.30; found C 61.15, H 7.92, N 20.92.

Data for 5: M.p. 150−152 °C. $[\alpha]_D^{20} = -185$ (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 0.87 (d, $^3J_{H,H}$ = 6.6 Hz, 12 H, CHMe_2), 1.10 (d, $^3J_{H,H}$ = 6.7 Hz, 12 H, CHMe_2), 2.35−2.46 (m, 4 H, CHMe$_2$), 2.47 (s, 12 H, C_{Het}Me), 3.67 (s, 12 H, NMe), 4.90 (m, 4 H, CHC_{Het}), 7.53 (d, $^3J_{H,H}$ = 9.1 Hz, 4 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 10.7, 20.5, 21.0, 31.4, 34.2, 51.4, 131.1, 133.8, 149.3, 164.8 ppm. IR (KBr): $\tilde{\nu}$ = 3409, 2962, 2873, 1656, 1593, 1502 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{40}H_{61}N_{12}O_4$ [MH$^+$] 773.4939, found 773.4896.

Methyl 2-[(*S*)-1-(*tert*-Butoxycarbonylamino)-2-methylpropyl]-5-methyloxazole-4-carboxylate (19): Triethylamine (6.75 mL, 48.4 mmol) was added at 0 °C to a solution of amidoketone **10** (4.00 g, 12.1 mmol), triphenylphosphane (6.35 g, 24.2 mmol), and CCl_4 (2.36 mL, 24.2 mmol) in anhydrous DCM (150 mL). The ice bath was removed after 10 min and the mixture was stirred at room temperature for 5 days. The solvent was evaporated and purification was accomplished by flash chromatography on silica gel (petroleum ether/EtOAc, 3:1) to yield **19** (3.26 g, 86%) as a white solid; m.p. 57 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CHMe_2), 0.90 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CHMe_2), 1.41 (s, 9 H, CMe_3), 2.08−2.20 (m, 1 H, CHMe$_2$), 2.59 (s, 3 H, C_{Het}Me), 3.88 (s, 3 H, CO_2Me), 4.71 (m, 1 H, CHC_{Het}), 5.25 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, $NHCO_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.9, 17.9, 18.7, 28.2, 32.8, 51.9, 54.1, 79.9, 127.2, 155.3, 156.2, 162.1, 162.7 ppm. IR (KBr): $\tilde{\nu}$ = 3399, 3346, 2969, 2933, 1720, 1621, 1580, 1521 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{15}H_{25}N_2O_5$ [MH$^+$] 313.1763, found 313.1782. $C_{15}H_{24}N_2O_5$ (312.36): calcd. C 57.68, H 7.74, N 8.97; found C 57.53, H 7.71, N 8.87.

Hydrochloride of Aminooxazole Methyl Ester 21: Compound **19** (1.00 g, 3.20 mmol) was converted into **21** as described above in the general procedure for the cleavage of the Boc group. Yield: quantitative; m.p. 73−76 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.85 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CHMe_2), 1.00 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CHMe_2), 2.23−2.36 (m, 1 H, CHMe$_2$), 2.60 (s, 3 H, C_{Het}Me), 3.81 (s, 3 H, CO_2Me), 4.36 (m, 1 H, CHC_{Het}), 9.02 (s, 3 H, NH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 11.7, 17.3, 18.5, 30.4, 51.6, 52.7, 126.7, 156.9, 157.5, 161.6 ppm. IR (film): $\tilde{\nu}$ = 3408, 2967, 2360, 2024, 1717, 1616, 1520 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{10}H_{17}N_2O_3$ [MH$^+$] 213.1239, found 213.1258.

***N*-Boc-Protected Methyl Ester 23:** The procedure applied for the coupling of acid **12** (623 mg, 2.00 mmol) to the hydrochloride **21** (547 mg, 2.20 mmol) was the same as that used in the case of the synthesis of **15**. Flash chromatography on silica gel (DCM/EtOAc/MeOH,75:25:2) provided **23** (659 mg, 65%) as a solid; m.p. 57−59 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 0.90 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CHMe_2), 0.93 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CHMe_2), 0.99 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CHMe_2), 1.03 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CHMe_2), 1.39 (s, 9 H, CMe_3), 2.20−2.34 (m, 2 H, CHMe$_2$), 2.51 (s, 3 H, C_{Het}Me), 2.59 (s, 3 H, C_{Het}Me), 3.60 (s, 3 H, NMe), 3.82 (s, 3 H, CO_2Me), 4.57 (m, 1 H, CHC_{Het}), 5.08 (m, 1 H, CHC_{Het}), 6.30 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, $NHCO_2$), 7.66 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 10.7, 13.0, 19.6, 19.9, 20.4, 21.1, 29.6, 31.4, 34.07, 34.15, 52.7, 53.3, 54.1, 80.1, 129.2, 130.9, 134.5, 148.7, 157.5, 157.9, 163.8, 164.2, 164.9 ppm. IR (KBr): $\tilde{\nu}$ = 3406, 2965, 2874, 1713, 1665, 1621, 1592, 1503 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{25}H_{40}N_5O_6$ [MH$^+$] 506.2979, found 506.3007. $C_{25}H_{39}N_5O_6\cdot(H_2O)_{1/3}$ (511.61): calcd. C 58.69, H 7.81, N 13.69; found C 59.01, H 7.83, N 13.39.

Imidazole−Oxazole Tetramer 6: Dimer **23** (178 mg, 0.35 mmol) was successively subjected to methyl and Boc deprotection to give the corresponding free amino acid. *i*Pr$_2$NEt (0.24 mL, 1.40 mmol) and FDPP (211 mg, 0.55 mmol) were added at room temperature to the stirred solution of this compound in acetonitrile (10 mL), and the mixture was stirred at that temperature for 2 days. The solvent was evaporated and the residue was dissolved in EtOAc, extracted with water and brine, dried with $MgSO_4$, and concentrated in vacuo. Purification was accomplished by chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:5) to yield **23** (46 mg, 35%) as a white solid; m.p. 145 °C. $[\alpha]_D^{20} = -153$ (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 0.94 (d, $^3J_{H,H}$ = 6.6 Hz, 6 H, CHMe_2), 0.95 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H, CHMe_2), 1.00 (d, $^3J_{H,H}$ = 6.8 Hz, 6 H, CHMe_2), 1.11 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H, CHMe_2), 2.17−2.31 (m, 2 H, CHMe$_2$), 2.43 (s, 6 H, C_{Het}Me), 2.48−2.61 (m, 2 H, CHMe$_2$), 2.62 (s, 6 H, C_{Het}Me), 3.58 (s, 6 H, NMe), 4.96−5.09 (m, 4 H, CHC_{Het}), 7.32 (d, $^3J_{H,H}$ = 9.9 Hz, 2 H, CONH), 7.65 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 10.6, 12.6, 19.5, 20.2, 20.4, 21.3, 31.4, 33.4, 34.3, 51.2, 53.3, 130.5, 130.9, 134.9, 148.0, 154.6, 162.5, 164.2, 164.7 ppm. IR (KBr): $\tilde{\nu}$ = 3414, 2963, 2930, 2874, 1668, 1638, 1594, 1515 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{38}H_{55}N_{10}O_6$ [MH$^+$] 747.4306, found 747.4302.

Methyl 2-[(*S*)-1-*tert*-Butoxycarbonylamino-2-methylpropyl]-5-methylthiazole-4-carboxylate (20): Lawesson's reagent (7.08 g, 17.5 mmol) was added at room temperature to a solution of amido ketone **10** (3.87 g, 11.7 mmol) in anhydrous THF (120 mL). The mixture was stirred at reflux for 8 h. The solvent was removed and the residue was dissolved in EtOAc, washed with water, 1 M HCl, saturated $NaHCO_3$ solution and brine, dried with $MgSO_4$, and concentrated in vacuo. Purification was accomplished by flash chromatography on silica gel (petroleum ether/EtOAc: 3:1) to yield **20** (2.87 g, 75%) as a solid; m.p. 88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CHMe_2), 0.95 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CHMe_2), 1.42 (s, 9 H, CMe_3), 2.28−2.47 (m, 1 H, CHMe$_2$), 2.71 (s, 3 H, C_{Het}Me), 3.90 (s, 3 H, CO_2Me), 4.78 (m, 1 H, CHC_{Het}), 5.24 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, $NHCO_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, 17.2, 19.4, 28.3, 33.0, 52.0, 57.8, 80.0, 140.9, 144.3, 155.3, 162.8, 168.5 ppm. IR (KBr): $\tilde{\nu}$ = 3434, 2971, 1715, 1638, 1510 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{15}H_{25}N_2O_4S$ [MH$^+$] 329.1535, found 329.1519.

Hydrochloride of Aminothiazole Methyl Ester 22: Compound **20** (1.05 g, 3.20 mmol) was converted into **22** as described above in the general procedure for the cleavage of the Boc group. Yield: quantitative; m.p. 145 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.84 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CHMe_2), 1.01 (d, $^3J_{H,H}$ = 6.8 Hz, 3

H, CHMe_2), 2.22−2.36 (m, 1 H, CHMe$_2$), 2.72 (s, 3 H, C_{Het}Me), 3.82 (s, 3 H, CO_2Me), 4.50 (m, 1 H, CHC_{Het}), 8.95 (s, 3 H, NH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 12.6, 17.9, 18.6, 31.7, 51.6, 56.3, 140.2, 145.8, 161.0, 161.9 ppm. IR (KBr): ṽ = 3435, 2963, 2572, 2021, 1718, 1698, 1598 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{10}H_{17}N_2O_2S$ [MH$^+$] 229.1011, found 229.1019.

***N*-Boc-Protected Methyl Ester 24:** The procedure applied for the coupling of acid **12** (623 mg, 2.00 mmol) to the hydrochloride **22** (582 mg, 2.20 mmol) was the same as that used in the case of the synthesis of **15**. Flash chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:2) provided **24** (629 mg, 60%) as a solid; m.p. 64−66 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 0.91 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CHMe_2), 0.97−1.04 (m, 9 H, CHMe_2), 1.39 (s, 9 H, CMe_3), 2.21−2.35 (m, 1 H, CHMe$_2$), 2.41−2.51 (m, 1 H, CHMe$_2$), 2.52 (s, 3 H, C_{Het}Me), 2.70 (s, 3 H, C_{Het}Me), 3.61 (s, 3 H, NMe), 3.84 (s, 3 H, CO_2Me), 4.58 (m, 1 H, CHC_{Het}), 5.12 (m, 1 H, CHC_{Het}), 6.28 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, $NHCO_2$), 7.78 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 10.7, 14.0, 19.1, 19.9, 21.0, 21.0, 29.6, 31.4, 34.1, 34.4, 52.8, 54.1, 57.2, 80.1, 130.8, 134.5, 143.0, 145.8, 148.7, 157.5, 164.5, 165.1, 170.2 ppm. IR (KBr): ṽ = 3400, 2964, 2873, 1714, 1664, 1592, 1501 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{25}H_{40}N_5O_5S$ [MH$^+$] 522.2750, found 522.2753. $C_{25}H_{39}N_5O_5S\cdot(H_2O)_{0.5}$ (530.68): calcd. C 56.58, H 7.60, N 13.20; found C 56.76, H 7.47, N 13.10.

Imidazole−Thiazole Tetramer 7: The procedure applied for the macrocyclization of **24** (157 mg, 0.30 mmol) to the tetramer **7** was the same as that used in the case of the synthesis of **6**. Flash chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:3) provided **7** (66 mg, 56%) as a solid; m.p. 205−207 °C. $[\alpha]_D^{20}$ = −138 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 0.94 (d, $^3J_{H,H}$ = 6.6 Hz, 6 H, CHMe_2), 0.99 (d, $^3J_{H,H}$ = 6.6 Hz, 6 H, CHMe_2), 1.08−1.13 (m, 12 H, CHMe_2), 2.49 (s, 6 H, C_{Het}Me), 2.40−2.55 (m, 4 H, CHMe$_2$), 2.73 (s, 6 H, C_{Het}Me), 3.67 (s, 6 H, NMe), 4.95−5.10 (m, 4 H, CHC_{Het}), 7.65 (d, $^3J_{H,H}$ = 9.2 Hz, 2 H, CONH), 7.92 (d, $^3J_{H,H}$ = 9.1 Hz, 2 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 10.7, 13.5, 20.0, 21.11, 21.13, 31.5, 33.8, 34.4, 51.9, 56.0, 130.9, 134.6, 142.5, 143.8, 148.4, 163.5, 164.5, 167.9 ppm. IR (KBr): ṽ = 3407, 2961, 2928, 2873, 1666, 1593, 1546, 1504 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{38}H_{55}N_{10}O_4S_2$ [MH$^+$] 779.3849, found 779.3880.

Methyl 2-[(*R*)-2-*tert*-Butoxycarbonylamino-3-methylbutanoylamino]-3-oxobutanoate (31): The applied procedure, workup, and purification were the same as those used in the case of the synthesis of **10**. The NMR and IR spectra were identical to those described for **10**. FAB-HRMS: *m*/*z* calcd. for $C_{15}H_{27}N_2O_6$ [MH$^+$] 331.1869, found 331.1879. $C_{15}H_{26}N_2O_6$ (330.38): calcd. C 54.53, H 7.93, N 8.48; found C 54.38, H 7.87, N 8.44.

Methyl 2-[(*R*)-1-*tert*-Butoxycarbonylamino-2-methylpropyl]-1,5-dimethyl-1*H*-imidazole-4-carboxylate (32): The applied procedure, workup and purification were the same as those used in the case of the synthesis of **11**. The NMR and IR spectra were identical to those described for **11**, and the enantiomeric purity of **32** was also > 96% *ee*. FAB-HRMS: *m*/*z* calcd. for $C_{16}H_{28}N_3O_4$ [MH$^+$] 326.2080, found 326.2068. $C_{16}H_{27}N_3O_4$ (325.40): calcd. C 59.06, H 8.36, N 12.91; found C 59.04, H 8.31, N 12.79.

***N*-Boc-Protected Amino Acid 33:** The applied procedure and workup were the same as those used in the case of the synthesis of **12**. The NMR and IR spectra were identical to those described for **12**. FAB-HRMS: *m*/*z* calcd. for $C_{15}H_{26}N_3O_4$ [MH$^+$] 312.1923, found 312.1940.

Benzyl 2-[(*R*)-1-*tert*-Butoxycarbonylamino-2-methylpropyl]-1,5-dimethylimidazole-4-carboxylate (34): DBU (0.94 mL, 6.30 mmol) and BnBr (1.00 mL, 8.40 mmol) were added at room temperature to a solution of **33** (1.96 g, 6.30 mmol) in acetonitrile and the mixture was stirred at that temperature for 6 days. The solvent was evaporated and the residue was dissolved in EtOAc, extracted with water and brine, dried with $MgSO_4$, and concentrated in vacuo. Purification was accomplished by chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) to yield **34** (1.53 g, 60%) as a white solid; m.p. 80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CHMe_2), 1.00 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CHMe_2), 1.40 (s, 9 H, CMe_3), 2.16−2.29 (m, 1 H, CHMe$_2$), 2.48 (s, 3 H, C_{Het}Me), 3.53 (s, 3 H, NMe), 4.53 (m, 1 H, CHC_{Het}), 5.34−5.41 (m, 3 H, $NHCO_2$, PhCH_2), 7.27−7.46 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.5, 18.5, 19.6, 28.3, 30.3, 33.2, 52.2, 65.7, 79.4, 127.7, 127.9, 128.1, 128.4, 135.8, 136.7, 148.5, 155.7, 163.7 ppm. IR (KBr): ṽ = 3340, 2966, 1700, 1572, 1521 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{22}H_{32}N_3O_4$ [MH$^+$] 402.2393, found 402.2390. $C_{22}H_{31}N_3O_4$ (401.50): calcd. C 65.81, H 7.78, N 10.47; found C 65.71, H 7.72, N 10.40.

Hydrochloride of Aminoimidazole Benzyl Ester 28: Compound **34** (0.88 g, 2.20 mmol) was converted into **28** as described above in the general procedure for the cleavage of the Boc group. Yield: quantitative; m.p. 137 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 0.80 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CHMe_2), 0.98 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CHMe_2), 2.19−2.32 (m, 1 H, CHMe$_2$), 2.49 (s, 3 H, C_{Het}Me), 3.61 (s, 3 H, NMe), 4.41 (m, 1 H, CHC_{Het}), 5.22−5.34 (m, 2 H, PhCH_2), 7.47−7.29 (m, 5 H, ArH), 8.69 (s, 3 H, NH_3) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 9.9, 18.1, 30.8, 31.5, 50.7, 65.1, 126.1, 128.0, 128.2, 128.4, 136.3, 137.4, 144.0, 162.3 ppm. IR (KBr): ṽ = 3436, 2965, 2019, 1729, 1631, 1504 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{17}H_{24}N_3O_2$ [MH$^+$] 302.1869, found 302.1858.

Z-Protected Aminoimidazole Benzyl Ester 29: The procedure applied for the coupling of acid **27** (350 mg, 1.90 mmol) to the hydrochloride **28** (642 mg, 1.90 mmol) was the same as that used in the case of the synthesis of **15**. Flash chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:2) provided **29** (802 mg, 68%) as a solid; m.p. 153 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.62 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, CHMe_2), 0.79 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, CHMe_2), 0.83 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, CHMe_2), 1.03 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CHMe_2), 1.44 (d, *J* = 6.3 Hz, 3 H, C_{Oxa}HMe), 1.98−2.06 (m, 1 H, CHMe$_2$), 2.34−2.42 (m, 1 H, CHMe$_2$), 2.47 (s, 3 H, C_{Imi}Me), 3.51 (s, 3 H, NMe), 4.17 (d, $^3J_{H,H}$ = 7.0 Hz, 1 H, $C_{Oxa}HCO_2$Me), 4.36 (m, 1 H, $C_{Oxa}H$Me), 4.69 (m, 1 H, CHC_{Het}), 4.84 (m, 1 H, CHC_{Het}), 5.07−5.18 (m, 2 H, PhCH_2), 5.29−5.35 (m, 2 H, PhCH_2), 5.62 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, $NHCO_2$), 7.20−7.45 (m, 11 H, CONH, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.4, 16.9, 18.7, 18.9, 19.7, 21.8, 30.3, 31.3, 32.9, 50.5, 54.4, 65.7, 66.8, 74.1, 80.4, 127.8, 128.0, 128.3, 128.40, 128.42, 135.8, 136.5, 136.6, 147.5, 156.3, 163.5, 168.7, 170.9 ppm. IR (KBr): ṽ = 3305, 3260, 2964, 1696, 1655, 1572, 1524 cm^{-1}. FAB-HRMS: *m*/*z* calcd. for $C_{34}H_{44}N_5O_6$ [MH$^+$] 618.3292, found 618.3262. $C_{34}H_{43}N_5O_6$ (617.74): calcd. C 66.11, H 7.02, N 11.34; found C 65.87, H 6.98, N 11.12.

Imidazole−Oxazoline Tetramer 4: Palladium hydroxide (200 mg) was added at room temperature to a solution of dimer **29** (297 mg, 0.48 mmol) in methanol. The mixture was stirred under H_2 for 20 h, filtered, and concentrated in vacuo. The residue was dissolved in acetonitrile (25 mL), *i*Pr$_2$NEt (0.35 mL, 2.00 mmol) and FDPP (327 mg, 0.85 mmol) were added at room temperature, and the mixture was stirred for 3 days. The solvent was evaporated, and the residue was dissolved in EtOAc, extracted with water and brine,

dried with $MgSO_4$, and concentrated in vacuo. Purification was accomplished by chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:5) to yield **4** (55 mg, 30%) as a white solid; m.p. > 250 °C. $[\alpha]_D^{20}$ = +132 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.65 (d, $^3J_{H,H}$ = 6.9 Hz, 6 H, CH*Me*$_2$), 0.83 (d, $^3J_{H,H}$ = 6.9 Hz, 6 H, CH*Me*$_2$), 0.93 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H, CH*Me*$_2$), 1.04 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H, CH*Me*$_2$), 1.44 (d, $^3J_{H,H}$ = 6.3 Hz, 6 H, C_{Oxa}H*Me*), 2.07−2.30 (m, 4 H, C*H*Me$_2$), 2.54 (s, 6 H, C_{Imi}Me), 3.54 (s, 6 H, NMe), 4.23 (m, 2 H, C_{Oxa}*H*CO), 4.78−4.86 (m, 4 H, CHC_{Het}, C_{Oxa}*H*Me), 5.03 (m, 2 H, CHC_{Het}), 7.69 (d, $^3J_{H,H}$ = 9.9 Hz, 2 H, CONH), 7.98 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, CONH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 9.8, 17.3, 18.4, 18.7, 19.1, 21.9, 30.2, 31.9, 33.9, 49.3, 51.5, 73.5, 80.8, 129.7, 132.3, 146.1, 163.4, 169.1, 170.7 ppm. IR (KBr): $\tilde{\nu}$ = 3397, 2964, 2930, 2874, 1672, 1652, 1592, 1511 cm^{-1}. FAB-HRMS: *m/z* calcd. for $C_{38}H_{59}N_{10}O_6$ [MH^+] 751.4619, found 751.4609.

X-ray Crystallographic Study: Data were collected with a Bruker Smart CCD-diffractometer at 200 K. Relevant crystal and data collection parameters are given below. CCDC-207161 (**4**) and CCDC-207162 (**6**) contain the supplementary crystallographic data for the structures in this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

Crystal Data for 4: $C_{38}H_{58}N_{10}O_6\cdot(CHCl_3)_{0.5}\cdot H_2O$, colorless crystal (polyhedron), dimensions 0.43 × 0.36 × 0.19 mm^3, crystal system orthorhombic, space group $P2_12_12_1$, Z = 8, a = 15.5026(3) Å, b = 20.5167(3) Å, c = 27.5323(4) Å, α = 90°, β = 90°, γ = 90°, V = 8757.0(2) Å^3, ρ = 1.257 g/cm^3, T = 200(2) K, $2\theta_{max}$ = 21.48°, radiation Mo-K_α, λ = 0.71073 Å, 0.3° ω-scans, covering a whole sphere in reciprocal space, 54375 reflections measured, 10026 unique (R_{int} = 0.0446), 8665 observed [$I > 2\sigma(I)$], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied by use of SADABS[32] based on the Laue symmetry of the reciprocal space, μ = 0.17 mm^{-1}, $T_{min.}$ = 0.93, $T_{max.}$ = 0.97, structure solved by direct methods and refined against F^2 with a full-matrix, least-squares algorithm by use of the SHELXTL-PLUS (5.10) software package,[33] 1042 parameters refined, hydrogen atoms were treated by appropriate riding models, Flack absolute structure parameter 0.0(3), goodness of fit 1.07 for observed reflections, final residual values $R(F)$ = 0.055, $wR(F^2)$ = 0.143 for observed reflections, residual electron density −0.45 to 0.62 e·Å^{-3}.

Crystal Data for 6: $C_{38}H_{54}N_{10}O_6$, colorless crystal (polyhedron), dimensions 0.42 × 0.27 × 0.25 mm^3, crystal system orthorhombic, space group $P2_12_12_1$, Z = 4, a = 12.7473(2) Å, b = 17.2917(3) Å, c = 22.0819(3) Å, α = 90°, β = 90°, γ = 90°, V = 4867.35(13) Å^3, ρ = 1.019 g/cm^3, T = 200(2) K, $2\theta_{max}$ = 23.23°, radiation Mo-$K\alpha$, λ = 0.71073 Å, 0.3° Ω-scans, covering a whole sphere in reciprocal space, 35807 reflections measured, 6977 unique (R_{int} = 0.0403), 5882 observed [$I > 2\sigma(I)$], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied by use of SADABS[32] based on the Laue symmetry of the reciprocal space, μ = 0.07 mm^{-1}, $T_{min.}$ = 0.97, $T_{max.}$ = 0.98, structure solved by direct methods and refined against F^2 with a full-matrix, least-squares algorithm by use of the SHELXTL-PLUS (5.10) software package[33], 519 parameters refined, hydrogen atoms were treated by appropriate riding models, Flack absolute structure parameter 0.5(16), goodness of fit 1.06 for observed reflections, final residual values $R(F)$ = 0.056, $wR(F^2)$ = 0.153 for observed reflections, residual electron density −0.20 to 0.49 e·Å^{-3}.

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