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Synthesis and Structural Investigation of C_4- and C_2-Symmetric Molecular Scaffolds Based on Imidazole Peptides

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Dedicated to Professor Rolf Gleiter on the occasion of his 70th birthday

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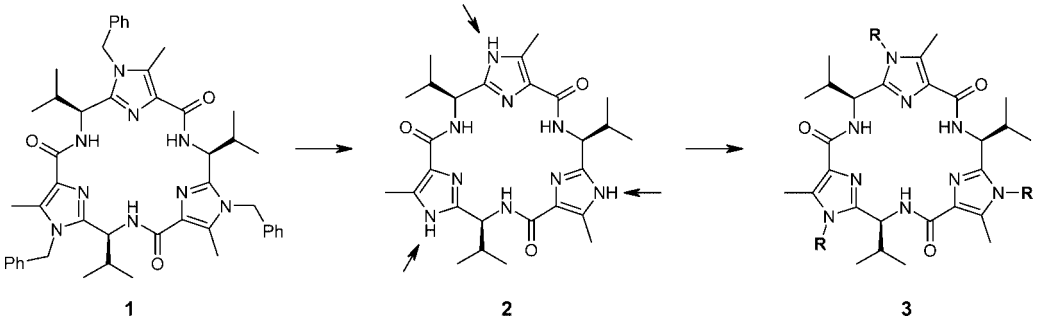
The syntheses of a C_4- and a C_2-symmetric scaffold are presented. The first is composed of four imidazole units, while the second contains two imidazole and two oxazole moieties. The synthesis of the key building block for both systems has been fundamentally improved. Starting from these scaffolds, various platforms possessing two or four arms can easily be prepared. The structures of the scaffolds, together with that of a C_4-symmetric oxazole scaffold, were investigated in the solid state and in the gas phase. We found that these 24-membered cyclic peptides exist as two different structure types. In one case (type I), the nitrogen atoms of the azole units pointing into the interior of the macrocycle form a square, whereas in the second case (type II), they form a parallelogram. The type of molecular structure does not depend on the symmetry of the system, but on the type of azole used. Cyclic systems composed of four imidazole units are present in the type I structure, whereas systems consisting of four oxazole units exhibit the type II nature. Structure type II is also present in cycles composed of two oxazole units and two imidazole units. The existence of the different structure types can be explained in terms of the different orbital energies of the imidazole and oxazole systems.

Introduction

During the last few years, an emerging number of molecular platforms consisting of several arms fixed on a rigid platform have been reported.[1] These arms can be used as, for example, recognition sites of a receptor.[2] For smaller systems – such as the benzene ring – a concept allowing the synthesis of numerous receptors by making simple modifications has been developed. Larger platforms, though, are generally synthesized stepwise from three subunits that already carry their recognition sites,[3] so modification of the recognition sites is only possible through transformation of these functional groups, which is not always easy to achieve.

Recently, we were able to synthesize the C_3-symmetric scaffold **2**, on which we can attach a large variety of arms.[4,5] The scaffold consists of three imidazole units linked through *trans* amide bonds, making the macrocycle rigid. A variety of arms can be attached to the scaffold **2** by treatment of the secondary nitrogen atoms of the imidazole units with alkyl halides (Scheme 1). By this method we were able to synthesize platform species **3**, which act as



Scheme 1. Synthesis of the C_3-symmetric molecular scaffold **2**.

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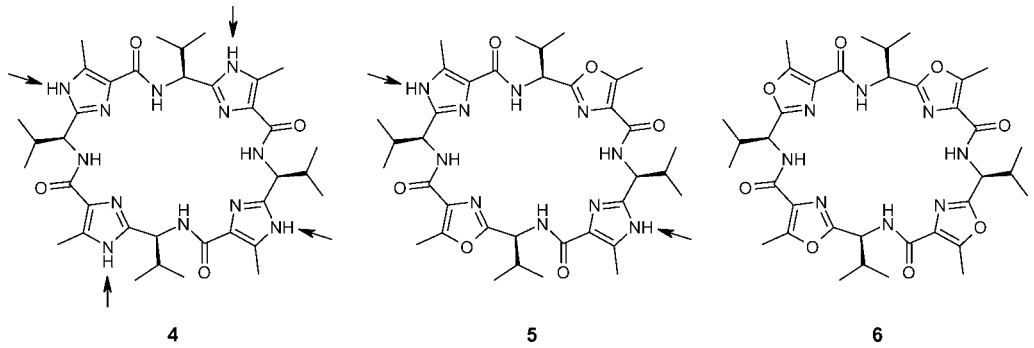


Figure 1. Structures of C_4- and C_2-symmetric molecular scaffolds.

receptors for hydroxybenzenes[4] that can further be used for predetermining configurations at metal centres or nitrogen atoms.[6]

Our intention was to apply this concept – a rigid scaffold to which various arms can be attached – not only to C_3-symmetric systems, but to extend it to the synthesis of platforms with four or as few as two arms.[7]

Here we describe the syntheses of the C_4-symmetric scaffold **4** and of the C_2-symmetric scaffold **5** and show that four and two arms, respectively, can be introduced by simple alkylation of the imidazole units (Figure 1). In addition, we investigate the structural properties of these 24-membered systems and compare them with the structure of the C_4-symmetric oxazole platform **6**, which was also synthesized.

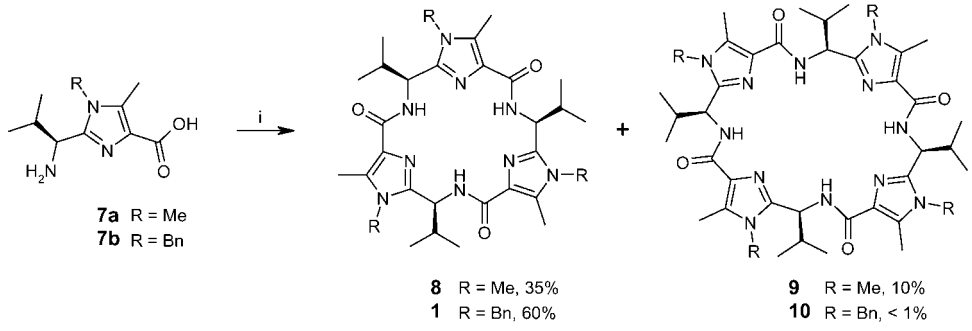
Results and Discussion

Synthesis

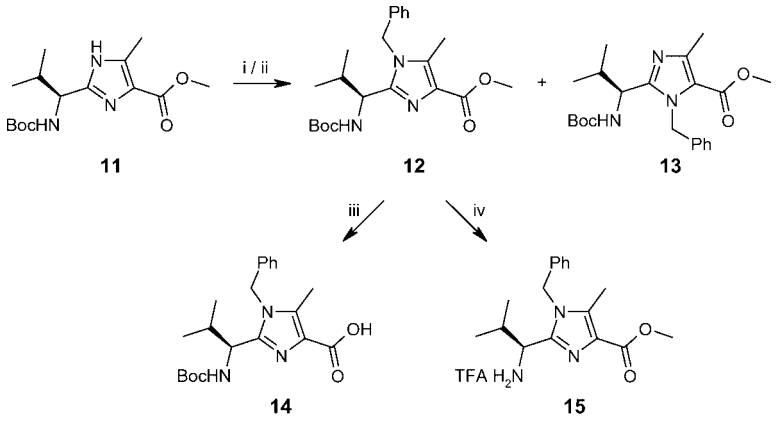
The most efficient synthetic route to the molecular scaffold **2** is by synthesizing a platform with three benzylic arms and removing these arms by hydrogenolysis (Scheme 1).[4] This method not only provides the highest yields of **2** but also affords the purest product. For this reason, we also set out to apply this method to the preparation of the C_4- and C_2-symmetric systems. Thus, the simplest way to synthesize the C_4-symmetric cyclic peptide **10** appeared to be a cyclotetramerization of the corresponding imidazole building block **7b** (Scheme 2). While the tetramer **9** had been formed from the imidazole building block **7a** in at least 10% yield,[8] however, the cyclization of **7b** under the same reaction conditions afforded only traces of the cycle **10**, the predominant product being the trimer **1**. The cyclization yields in these systems thus strongly depend on the substituents R used.

We therefore decided to apply a stepwise method. The starting material was the doubly protected benzyl-substituted imidazole **12**, obtainable from the imidazole **11** by alkylation with benzyl bromide in the presence of K_2CO_3 in acetonitrile (Scheme 3). Because of the presence of a tautomeric form of **11**, not only the desired product **12** was formed (32% yield), but also the undesired alkylation product **13** in a yield of 51%.[4] Since compound **12** is a building block of utmost importance, we examined different methods for optimizing the ratio in favour of the desired isomer **12**. Indeed, the yield of **12** could be enhanced from 32 to 72% by carrying out the alkylation in DMF at 0 °C in the presence of NaH as base. The benzyl-substituted imidazole **12** can easily be deprotected to give two singly protected building blocks **14** and **15**.

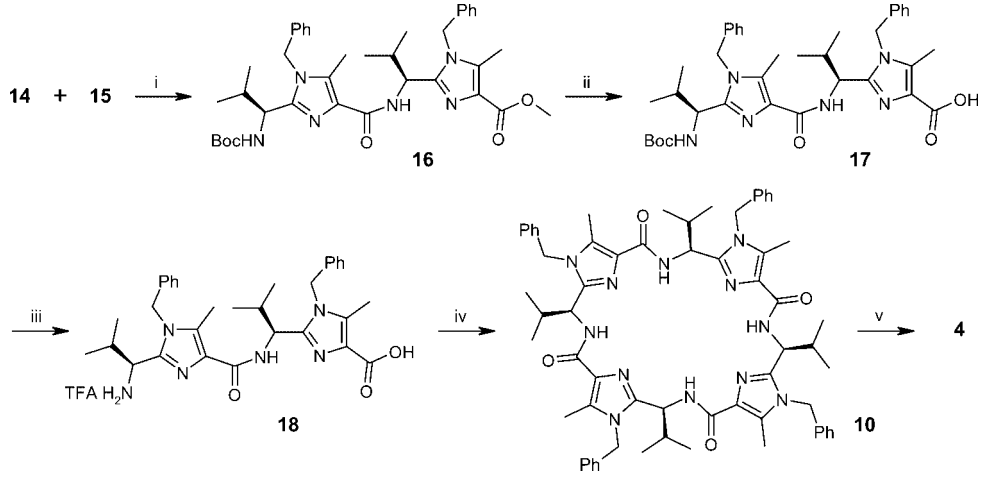
From these building blocks (**14** and **15**), we succeeded in preparing the platform **10** (Scheme 4): The two building blocks **14** and **15** were coupled with pentafluorophenyl diphenylphosphinate (FDPP)[9] to provide the dimer **16**, and deprotection of the carboxyl residue by saponification afforded the acid **17**. Subsequent removal of the Boc group provided the free amino acid **18**, which was subjected to a cyclodimerization with FDPP to give the tetramer **10** in yields as good as 65%. The removal of the benzyl groups



Scheme 2. i) FDPP, iPr$_2$NEt, CH_3CN, room temp.



Scheme 3. i) BnBr, K_2CO_3, CH_3CN, Δ, 32% for **12**, 51% for **13**. ii) BnBr, NaH, DMF, 0 °C, 72% for **12**, < 5% for **13**. iii) 2 M NaOH, MeOH/dioxane, 95%. iv) TFA, DCM, quant.

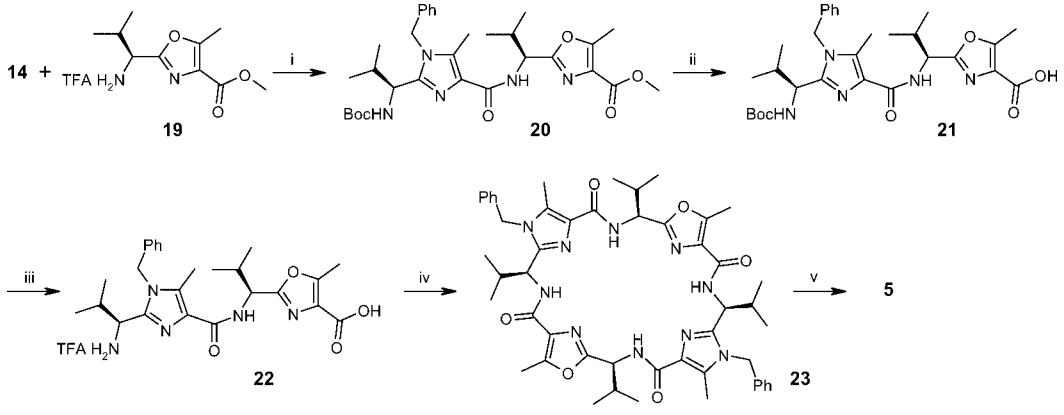


Scheme 4. Synthesis of scaffold **4**: i) FDPP, *i*Pr_2NEt, CH_3CN, room temp., 78%. ii) 2 M NaOH, MeOH/dioxane, 95%. iii) TFA, DCM, quant. iv) FDPP, *i*Pr_2NEt, CH_3CN, room temp., 65%. v) H_2, $Pd(OH)_2$, MeOH/DCM, 97%.

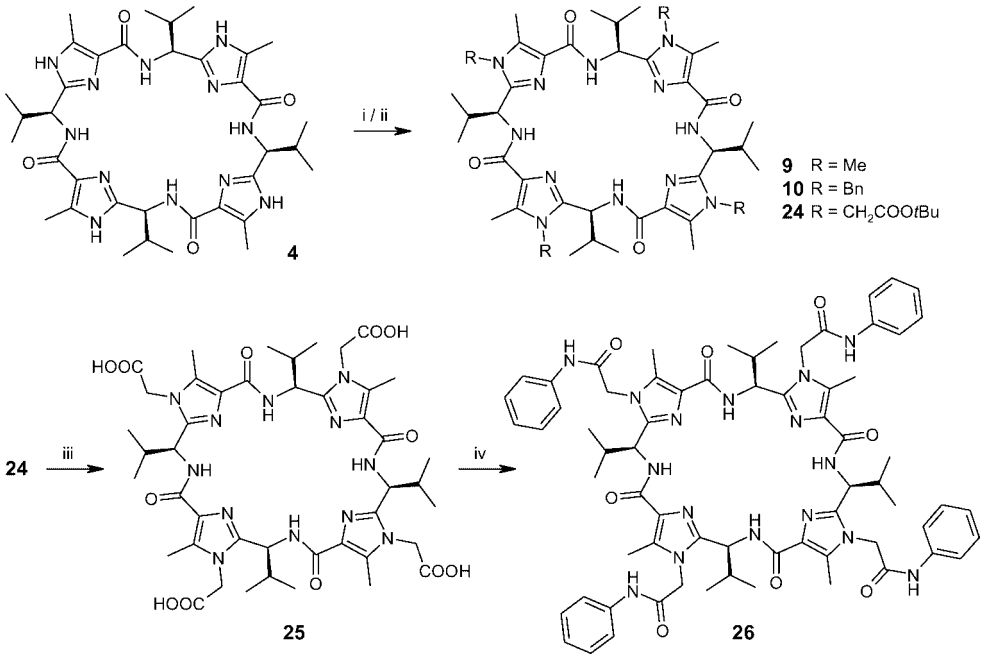
with palladium hydroxide yielded the desired C_4-symmetric scaffold. Since this route requires only a few reaction steps and the yields are relatively high, the scaffold **4** is available in quite large quantities.

A similar concept was applied to the preparation of the scaffold **5**, the successful synthesis of which is shown in Scheme 5. Coupling of the imidazole **14** with the oxazole **19** afforded the dimer **20**, which could be deprotected in two steps to give the free amino acid **22**. The dimerization of **22** gave the cyclic peptide **23**, also in good yields, whilst in a final step the two benzyl arms were removed to yield the C_2-symmetric scaffold **5**.

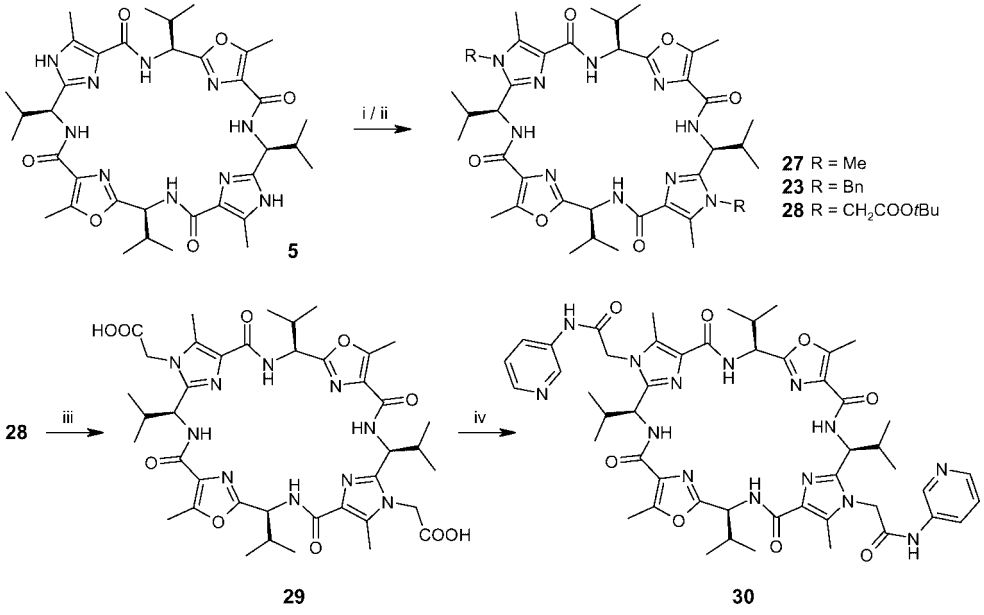
In the next step, different arms could be attached to the successfully prepared scaffolds **4** and **5** through simple alky-



Scheme 5. Synthesis of scaffold **5**: i) FDPP, *i*Pr_2NEt, CH_3CN, room temp., 87%. ii) 2 M NaOH, MeOH/dioxane, 98%. iii) TFA, DCM, quant. iv) FDPP, *i*Pr_2NEt, CH_3CN, room temp., 55%. v) H_2, $Pd(OH)_2$, MeOH/DCM, 95%.

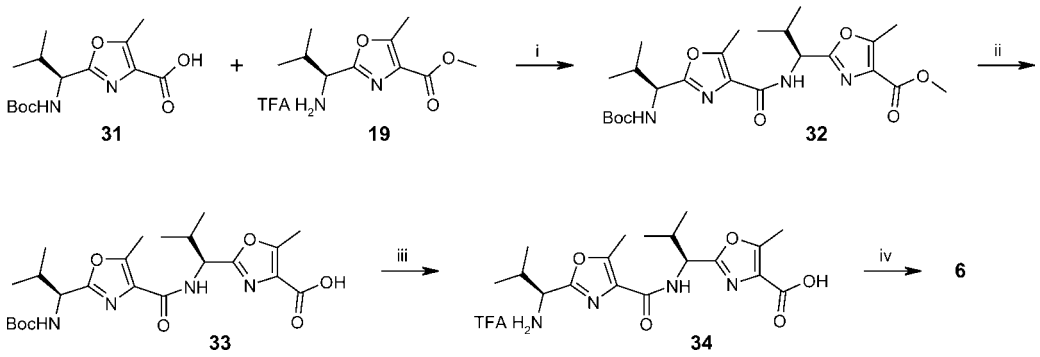


Scheme 6. i) RX, K_2CO_3, CH_3CN, Δ. ii) RX, NaH, DMF, 0 °C → room temp. iii) TFA, DCM, quant. iv) DMC, aniline, Et_3N, DCM, 0 °C → room temp., 44%.



Scheme 7. i) RX, K_2CO_3, CH_3CN, Δ. ii) RX, NaH, DMF, 0 °C → room temp. iii) TFA, DCM, quant. iv) DMC, 3-aminopyridine, Et_3N, DCM, 0 °C → room temp., 87%.

lation reactions, and the platforms **9**,[8a] **10** and **24** on the one hand and platforms **23**, **27**[8a] and **28** on the other were synthesized by this route (see Schemes 6 and 7). The best reaction mode proved to be the use of the alkyl halide together with K_2CO_3 as base in acetonitrile under reflux. Lower yields were obtained when NaH was used at 0 °C in DMF. From the tetraester **24** and from the diester **28**, the corresponding acids **25** and **29** could be obtained in quantitative yields by treatment of the esters with trifluoroacetic acid (TFA). The thus-formed acid functionalities have the advantage that the arms can be modified further, such as by conversion into the amides. Astonishingly, though, numerous conventional coupling agents failed in the conversions of **25** to **26** and **29** to **30**: the use of, for example, diphenylphosphoryl azide (DPPA),[10] FDPP, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI)[11] or [(benzotriazol-1-yl)oxy]tripyrrolidinophosphonium hexafluorophosphate (PyBOP)[12] afforded only traces of the desired compounds, with large amounts of nonisolable by-products being formed instead. The best



Scheme 8. Synthesis of cyclopeptide **6**. i) FDPP, *i*Pr_2NEt, CH_3CN, room temp., 74%. ii) 2 M NaOH, MeOH/dioxane, 95%. iii) TFA, DCM, quant. iv) FDPP, *i*Pr_2NEt, CH_3CN, room temp., 72%.

coupling agent proved to be 2-chloro-1,3-dimethylimidazolinium chloride (DMC),[13] the use of which gave the amides **26** and **30** in yields of 44% and 87%, respectively.

The synthesis of the C_4-symmetric cyclic peptide **6**, which contains four oxazole units, is shown in Scheme 8. The two building blocks **31** and **19** were coupled with pentafluorophenyl diphenylphosphinate (FDPP) to give the dimer **32**, and deprotection of the carboxyl residue by saponification afforded the acid **33**. Subsequent removal of the Boc group provided the free amino acid **34**, which was subjected to a cyclodimerization with FDPP to give the tetramer **6** in yields as good as 72%.

Structural Investigations

In Solution

The NMR spectra (^1H, ^{13}C) of the cyclic peptides **4**, **6**, **10** and **24**–**26** indicate that they are C_4-symmetric in solution. The vicinal $^3J_{HNCH}$ values, of 9.7 and 9.4 Hz for **6** and **10**, respectively, correspond to dihedral angles of $155° < |\theta| < 165°$ in both macrocycles.[14]

The NMR spectra of the cyclic peptides **5**, **23** and **28**–**30** are all consistent with C_2-symmetrical structures in solution. The vicinal $^3J_{HNCH}$ values of 8.6 and 10.2 Hz for **23** correspond to dihedral angles of $150° < |\theta| < 180°$ in the macrocycle.

In the Solid State

We were able to obtain X-ray structures of the 24-membered cyclic peptides **6**, **10** and **30**. Figure 2 shows the molecular structures of **6** and **10**, together with that of **27**.[8a] Comparison of the structural data for the four compounds shows that two structural types are present: type I is represented by the C_4-symmetric tetramer **10** and type II by the C_2-symmetric peptides **27** and **30**. Surprisingly, the C_4-symmetric tetramer **6** also exists as the structural type II. In structural type I, the nitrogen atoms of the imidazole rings pointing into the interior of the macrocycle form the corners of a square with edge lengths of approximately 5.3 Å (distance *a* in Table 1). The diagonal distance in this square amounts to 7.5 Å. The imidazole rings do not form a single plane but adopt a cone-like structure. Their deviation from a coplanar structure, defined as the average angle between

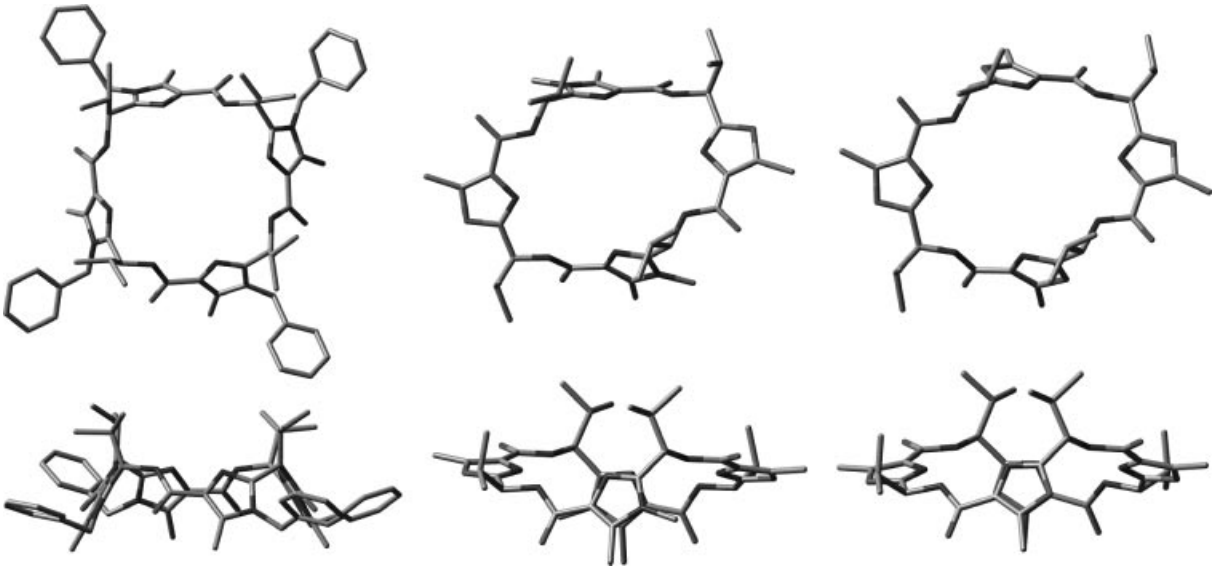


Figure 2. Molecular structures of **10**, **27** and **6**: top view (upper row) and side view (lower row); all hydrogen atoms and all solvent molecules have been omitted for clarity.

Table 1. Measured (X-ray) dihedral angles and distances in **6**, **10** and **27**.[8a]

	Structure	Dihedral angle [°] φ [H–N_{amide}–C_α–H_α]	χ [N_{amide}–C_α–C_{azole}–N_{imi}]	χ [N_{amide}–C_α–C_{azole}–O_{oxa}]	Distance *a* [Å] neighbouring N_{azole}–N_{azole}
10	type I	–152	104.6		5.285
		–155	106.7		5.258
		–162	105.8		5.299
		–155	102.9		5.254
27	type IIa	166	84.7		4.602
		167		188.0	5.446
		164	79.5		4.592
		172		181.5	5.427
6	type II	168		79.4	4.586
		158		187.6	5.446
		168		79.4	4.586
		158		187.6	5.446

the imidazole ring planes and the plane of the macrocycle, is 58°. All dihedral angles χ [N_{amide}–C_α–C_{azole}–N_{imi}] are approximately 100° (definition for the used abbreviations see Figure 3). The L-valine side chains are in pseudoaxial orientation and are all directed from the same face of the macrocycle.

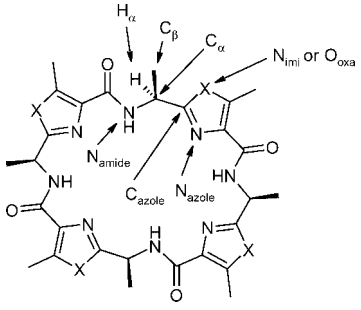


Figure 3. Definition of the abbreviations used.

In the structure type II as present in the solid-phase structures of **6**, **27** and **30**, in contrast, the nitrogen atoms of the azoles pointing into the macrocycle form a parallelogram with edge lengths of 4.6 and 5.4 Å (distance *a* in Table 1) and acute angles of approximately 78° in **27** and 82° in **6**. The distances between the nitrogen atoms of opposite azoles differ markedly and amount to 6.3 and 7.8 Å for **27** and 6.6 and 7.6 Å for **6**. In the macrocycles **27** and **30** the oxazoles are positioned at the corners with acute angles and the imidazoles are positioned at the corners with obtuse angles of the parallelogram. The L-valine side chains on the azole rings forming the obtuse angle of the parallelogram are in pseudoaxial orientations, whereas the L-valine side chains on the azole rings forming the acute angle are arranged rather pseudoequatorially. The dihedral angles φ [H–N_{amide}–C_α–H_α], however, are quite similar in all azole systems. The most striking difference is the dihedral angle χ: in the case of the azole rings forming the obtuse angle of the parallelogram this angle amounts to 80°, whereas in case of the azole rings forming the acute angle it is more than 180°.

Gas-Phase Calculations

For determination of the structures of the 24-membered oxazole- and imidazole-based cyclic peptides in the gas phase, compounds **35**–**37** were investigated (Figure 4). These advantageously have only methyl groups as side chains, so rotation around the C_α–C_β axis does not have to be taken into consideration, the number of possible conformers thus being reduced. To determine the preferred conformations of the cycles **35**–**37**, we performed full geometry optimization by applying the HF and the DFT-B3LYP method.[15,16] As basis sets, we used the 3-21G* and the 6-31G* basis set for the HF and the 6-31G* and the 6-31G** basis set for the DFT-B3LYP procedure.[17,18] Figure 5 shows the lowest-energy structures of the conformers of **35**–**37**.

The calculations also afforded only two structural types; these two structure types are identical with those already found in the solid state (for data see also Table 2). We fur-

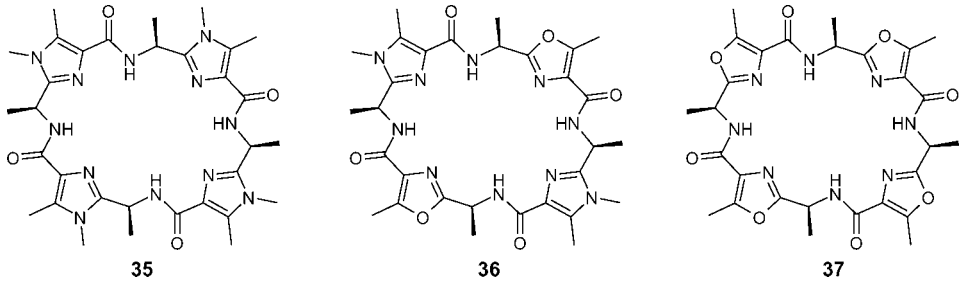


Figure 4. Structures of the cyclic peptides investigated by gas-phase calculations.

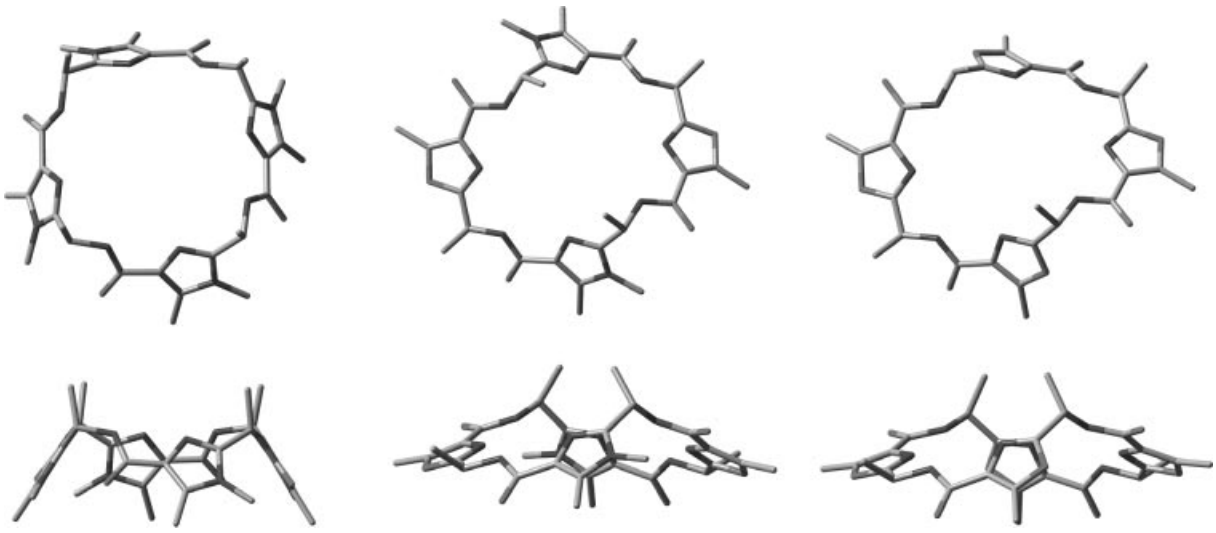


Figure 5. Molecular structures of the energetically preferred conformers of **35** (type I), **36** (type IIa) and **37** (type II) calculated with B3LYP/6-31G**: top views (upper row) and side views (lower row); all hydrogen atoms have been omitted for clarity.

ther found that the energetically lowest conformation of the imidazole tetramer is of type I, which correlates with the findings in the solid state. For the imidazole tetramer, type II is of much higher energy, independently of the method and the basis set used (see Table 3). In the case of **36**, which is the cycle containing two oxazole and two imidazole units, only two structures of type II were found, the type I structure of **36** not being a minimum on the potential energy hypersurface. Of the two minimum structures of type II, structure type IIb, in which the oxazoles are positioned at the corners forming the obtuse angle of the parallelogram, is of much higher energy than structure type IIa, which is in perfect correlation with the fact that only structure types IIa were found for compounds **27** and **30** in the solid phase. In the case of the tetrameric oxazole **37**, only structure type II was found as a minimum on the potential energy hypersurface, which also correlates with the crystal structure data for **6**.

Explanation

In order to find an explanation for this behaviour, we took a closer look at those structural parameters that produce the most striking difference between the two structure types: namely the dihedral angles χ. In structure type I,

Table 2. Calculated (B3LYP/6-31G**) dihedral angles and distances in **35**, **36** and **37**.

	Structure	Dihedral angle [°]			Distance *a* [Å]
		φ [H–N_{amide}–C_α–H_α]	χ [N_{amide}–C_α–C_{azole}–N_{imi}]	χ [N_{amide}–C_α–C_{azole}–O_{oxa}]	neighbouring N_{azole}–N_{azole}
35	type I	–158.6	101.9		5.290
		–158.6	101.9		5.290
		–158.6	101.9		5.290
		–158.6	101.9		5.290
35	type II	–161.0	93.1		4.590
		146.5	164.3		5.510
		–161.0	93.1		4.600
		146.5	164.3		5.510
36	type IIa	–168.1	89.4		4.560
		139.5		178.8	5.460
		–168.1	89.4		4.560
		139.5		178.8	5.460
36	type IIb	–171.3		90.0	4.560
		144.9	166.9		5.480
		–171.3		90.0	4.560
		144.9	166.9		5.480
37	type II	179.5		86.3	4.570
		142.1		182.3	5.460
		179.5		86.3	4.570
		142.2		182.3	5.460

Table 3. Calculated energy differences (ΔE_1), estimated strain energies (E_2) and strain energy differences (ΔE_2).

	Structure	ΔE_1[a] [kJ mol^{-1}]				E_2[b] [kJ mol^{-1}]	ΔE_2[c] [kJ mol^{-1}]
		HF		B3LYP		B3LYP	B3LYP
		3-21G*	6-31G*	6-31G*	6-31G**	6-31G**	6-31G**
35	type I	0.0	0.0	0.0	0.0	1.8	0.0
	type II	25.2	12.6	18.5	19.1	19.0	17.2
36	type I	–[d]	–[d]	–[d]	–[d]	11.5	11.3
	type IIa	0.0	0.0	0.0	0.0	0.2	0.0
	type IIb	46.6	23.0	27.1	28.0	30.0	29.8
37	type I	–[d]	–[d]	–[d]	–[d]	21.2	11.0
	type II	0.0	0.0	0.0	0.0	10.2	0.0

[a] Relative energy relative to the lowest-energy conformer. [b] Estimated strain energy caused by the deviation from the optimum dihedral angle with the following assumptions: type I: χ = 100°; type II: χ = 90 and 180°. [c] Relative strain energy relative to the lowest-energy conformer. [d] No minimum found.

these angles are around 100° for all azole rings, whereas in structure type II they amount to approximately 90° in two of the azole rings and to 180° in the other two. We chose the two model systems **38** and **39** (Figure 6), in which we modified the dihedral angle χ stepwise and simultaneously optimized all the other structural parameters. The obtained energy profiles of the reference compounds **38** and **39** in relation to the dihedral angle χ are shown in Figure 7.

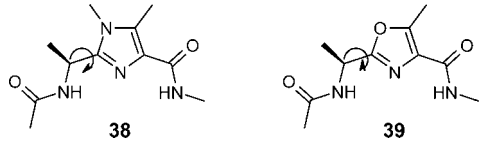


Figure 6. Reference systems **38** and **39** for the determination of the energy profiles in relation to the dihedral angles χ [N_{amide}–C_α–C_{azole}–N_{imi}] and χ [N_{amide}–C_α–C_{azole}–O_{oxa}], respectively.

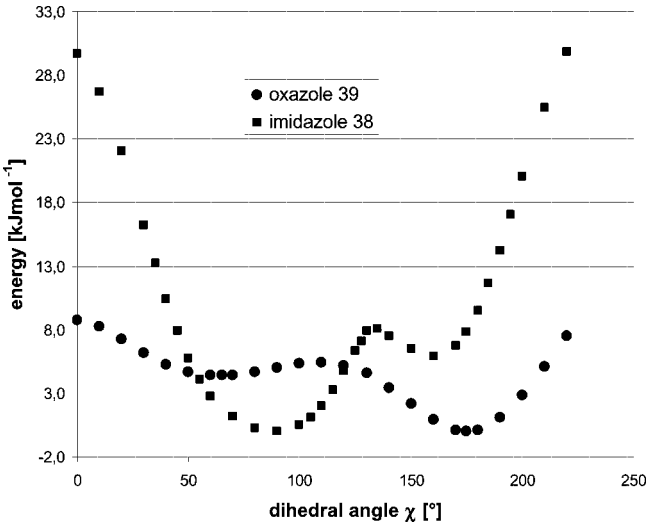


Figure 7. Calculated energy profiles in relation to the dihedral angles by use of B3LYP/6-31G**.

Both reference systems show two minima in the region of 20 to 200°, imidazole **38** having the lowest minimum at 90° and oxazole **39** at about 180°. The reason for this difference can be explained by NBO analysis of the reference systems **38** and **39**:[15,19] in the imidazole system, the $\pi(C_{azole}–N_{azole})$ orbital is energetically much higher (–0.29908 au at χ = 90°) than in the corresponding oxazole (–0.33246 au at χ = 90°). Accordingly, the interaction of this π-bond with the $\sigma^*(C_\alpha–N_{amide})$ orbital is much stronger than in the oxazole. The optimum interaction between these two orbitals is at an angle of 90°, the $\sigma^*(C_\alpha–N_{amide})$ orbital then being parallel to the $\pi(C_{azole}–N_{azole})$ orbital (18.5 kJ mol^{-1} for the imidazole vs. 16.4 kJ mol^{-1} for the oxazole at χ = 90°). In contrast, the $\pi^*(C_{azole}–N_{azole})$ orbital in the oxazole is of lower energy (–0.00352 au at χ = 180°) than in the imidazole (+0.00875 au at χ = 180°), so the interactions with the higher-energy $\sigma(C_\alpha–C_\beta)$ and $\sigma(C_\alpha–H_\alpha)$ orbitals are accordingly of more importance than in the imidazole. The optimum interaction between these two orbitals with the $\pi^*(C_{azole}–N_{azole})$ orbital takes place at an angle of 180° (25.1 kJ mol^{-1} for the imidazole vs. 30.3 kJ mol^{-1} for the oxazole at χ = 180°).

That this angle is indeed the decisive parameter for the presence of the distinct structure types can be substantiated as follows: an estimated strain energy (E_2) is defined to be the energy caused by the deviation from the optimum dihedral angle in the cycle at each of the four azole units under the assumption that in type I the angle is 100° for all of the azoles, whilst in type II it amounts to 90° in two of the azole units, but to 180° in the other two (see Table 3). In view, then, of the relative strain energies in relation to the energetically favoured conformer (ΔE_2 in Table 3), it can be seen that this corresponds almost perfectly to the calculated energy differences (ΔE_1) at the same level of theory (B3LYP/6-31G**) and thus explains very well why the specific structure types were found in the specific molecules.

Conclusions

We have been able to show that C_4- and C_2-symmetric scaffolds can both be obtained in good yields. The synthesis of the key building block required for their preparation has been significantly improved. Starting from these scaffolds, various platforms with four or two arms can easily be prepared. Furthermore, we were able to show that 24-mem-

bered cycles composed of oxazoles and imidazoles are present in the forms of two different structure types. The type of molecular structure does not depend on the symmetry of the system, but on the type of azole used, the reason for this being the different energy profiles of oxazoles and imidazoles for the rotation around the dihedral angle χ. It can be generalized that structure type I will predominate in systems containing four azole units with high-energy π-orbitals, whereas in systems having four azole units with low-energy π*-orbitals, this will be the case for structure type II. If a C_2-symmetric system is composed both of azoles possessing high-energy π-orbitals and azoles possessing low-energy π*-orbitals, structure type IIa will predominate, with the azoles with high-energy π-orbitals being arranged at the corners of the parallelogram with obtuse angles.

In further studies we will investigate the use of these C_4- and a C_2-symmetric platforms as receptors and for the predetermination of configurations at C_4- and C_2-symmetric centres.

Experimental Section

General Remarks: Imidazole **11** and oxazoles **19** and **31** were prepared according to reported procedures.[8] All chemicals were of 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 deuteriated solvents indicated in brackets in the analytical data. HRMS data were recorded with a JEOL JMS-700 instrument. IR spectra were measured with a Bruker Vector 22 FT-IR spectrometer. Elemental microanalyses were performed in the microanalytical laboratory of the University of Heidelberg.

Abbreviations: Bn: benzyl; Boc: *tert*-butoxycarbonyl; FDPP: pentafluorophenyl diphenylphosphinate; DCM: dichloromethane; DMC: 2-chloro-1,3-dimethylimidazolinium chloride; DMF: *N*,*N*-dimethylformamide; TFA: trifluoroacetic acid.

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), and this was followed by the slow addition of an NaOH solution (2 M, 10 equiv.) at 0 °C. Stirring was continued until TLC showed the consumption of all starting material, after which brine, HCl solution (1 M) and DCM were added. The aqueous phase was repeatedly extracted with DCM, and 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 DCM (20 ml/mmol starting material) and the solution was cooled to 0 °C. TFA (1.5 mL/10 mL DCM) was added at that temperature. The ice bath was removed after 30 min and stirring was continued at room temperature for 3 h. The mixture was concentrated in vacuo to provide a quantitative yield of the TFA salt, which was used in the next step without further purification.

General Procedure for the Cleavage of the Benzyl Group: The Bn-protected compound (1 equiv.) was dissolved in MeOH (20 mL/mmol starting material) at room temperature. $Pd(OH)_2$ (50 mg/mmol starting material) was added and the solution was stirred under H_2 at room temperature for 1 d. The solution was filtered and the solvent was removed in vacuo to give the free imidazole, which was used in the next step without further purification.

***N*-Boc-benzylimidazole Methyl Esters 12 and 13:** NaH (60 wt-%, 0.51 g, 12.9 mmol) and BnBr (1.70 mL, 13.9 mmol) were added at 0 °C to a solution of **11** (3.33 g, 10.7 mmol) in DMF (100 mL). The mixture was stirred at that temperature for 2 h and at room temperature overnight. The mixture was poured into water (700 mL) and the precipitated white solid was washed several times with water. The crude product was dissolved in DCM, 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 3:1 to 1:1) to yield **13** (3.08 g, 72%) and **12** (0.22 g, 5%) as white solids.

Aminoimidazole Methyl Ester (TFA Salt) 15: Compound **12** (2.01 g, 5.00 mmol) was converted into **15** as described above in the General Procedure for the cleavage of the Boc group. Yield: quantitative; m.p. 48 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.40 (br. s, 3 H), 7.42–7.35 (m, 3 H), 7.13–7.04 (m, 2 H), 5.59–5.31 (m, 2 H), 4.53 (m, 1 H), 3.94 (s, 3 H), 2.63 (s, 3 H), 2.57–2.46 (m, 1 H), 1.06 (d, $^3J_{H,H}$ = 5.26 Hz, 3 H), 0.33 (d, $^3J_{H,H}$ = 6.14 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.65, 144.06, 137.81, 132.77, 129.56, 129.22, 126.38, 123.85, 52.63, 51.70, 48.67, 31.62, 18.81, 18.29, 9.95 ppm. IR (KBr): $\tilde{\nu}$ = 3587, 3567, 3419, 3400, 3035, 2969, 2931, 1716, 1679, 1635, 1558, 1517, 1507, 1499, 1457, 1440, 1394, 1354, 1204, 722 cm^{-1}. FAB-HRMS: calcd. for $C_{17}H_{24}N_3O_2$ [M + H]$^+$ 302.1856; found 302.1867.

***N*-Boc-imidazole–imidazole Methyl Ester 16:** *i*Pr_2NEt (4.40 mL, 25.0 mmol) and FDPP (1.54 g, 4.00 mmol) were added at room temperature to acid **14** (1.39 g, 3.60 mmol) and ammonium salt **15** (1.66 g, 4.00 mmol) in acetonitrile (80 mL) and the mixture was stirred at room temperature for 2 d. The solvent was removed by evaporation and the residue was dissolved in AcOEt and then extracted with water and brine, dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) gave **16** (1.88 g, 78%) as a white solid; m.p. 80 °C. ^{1}H NMR (500 MHz, [D_6]acetone): δ = 7.51 (d, $^3J_{H,H}$ = 9.83 Hz, 1 H), 7.38–7.02 (m, 10 H), 6.35 (d, $^3J_{H,H}$ = 9.40 Hz, 1 H), 5.55 (d, $^3J_{H,H}$ = 17.10 Hz, 1 H), 5.37–5.28 (m, 3 H), 4.98 (t, $^3J_{H,H}$ = 9.40 Hz, 1 H), 4.51 (t, $^3J_{H,H}$ = 8.98 Hz, 1 H), 3.80 (s, 3 H), 2.47 (s, 3 H), 2.45–2.40 (m, 1 H), 2.39 (s, 3 H), 2.29–2.22 (m, 1 H), 1.32 (s, 9 H), 0.97 (d, $^3J_{H,H}$ = 6.84 Hz, 3 H), 0.95 (d, $^3J_{H,H}$ = 6.41 Hz, 3 H), 0.71 (d, $^3J_{H,H}$ = 6.84 Hz, 6 H) ppm. ^{13}C NMR (125 MHz, [D_6]acetone): δ = 165.83, 164.59, 157.46, 150.35, 149.19, 138.73, 138.67, 137.94, 134.05, 131.28, 130.55, 130.51, 129.68, 129.33, 129.22, 128.27, 128.10, 80.04, 54.02, 51.99, 51.25, 48.22, 48.10, 33.78, 33.52, 29.49, 21.43, 21.25, 20.21, 19.87, 11.40, 10.93 ppm. IR (KBr): $\tilde{\nu}$ = 3400, 2964, 2933, 2873, 1707, 1654, 1592, 1498, 1469, 1455, 1436, 1391, 1366, 1345, 1307, 1221, 1170, 1085, 730, 696, 582 cm^{-1}. FAB-HRMS: calcd. for $C_{38}H_{51}N_6O_5$ [M + H]$^+$ 671.3921; found 671.3889. $C_{38}H_{50}N_6O_5$·MeOH (702.88): calcd. C 66.64, H 7.74, N 11.96; found C 66.77, H 7.66, N 11.83.

***N*-Boc-imidazole–imidazolecarboxylic Acid 17:** Compound **16** (2.01 g, 3.00 mmol) was converted into **17** as described above in the General Procedure for the cleavage of the methyl ester group. Yield: 1.87 g (95%); m.p. 114 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 7.71 (d, $^3J_{H,H}$ = 7.89 Hz, 1 H), 7.39–7.18 (m, 6 H), 7.11–6.95 (m, 4 H), 5.42 (m, 2 H), 5.29 (m, 2 H), 4.94 (t, $^3J_{H,H}$ = 9.32 Hz, 1 H),

4.38 (t, $^3J_{H,H}$ = 9.21 Hz, 1 H), 2.38 (s, 3 H), 2.35–2.16 (m, 2 H), 2.28 (s, 3 H), 1.27 (s, 9 H), 0.94–0.85 (m, 6 H), 0.66–0.59 (m, 6 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 163.80, 162.24, 155.39, 147.90, 147.22, 136.42, 135.98, 135.73, 132.44, 128.64, 128.58, 128.17, 127.45, 127.37, 126.15, 77.97, 52.13, 49.14, 46.46, 46.05, 31.40, 31.02, 28.01, 19.71, 19.50, 18.73, 9.97, 9.50 ppm. IR (KBr): $\tilde{\nu}$ = 3437, 3415, 3399, 2969, 2931, 2873, 1706, 1655, 1591, 1500, 1467, 1455, 1427, 1391, 1366, 1331, 1308, 1230, 1171, 731 cm^{-1}. FAB-HRMS: calcd. for $C_{37}H_{49}N_6O_5$ [M + H]$^+$ 657.3764; found 657.3769.

Aminoimidazole–imidazolecarboxylic Acid (TFA Salt) 18: Compound **17** (1.97 g, 3.00 mmol) was converted into **18** as described above in the General Procedure for the cleavage of the Boc group. Yield: quantitative; m.p. 148 °C. ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 7.33–7.17 (m, 6 H), 7.09–6.94 (m, 4 H), 5.53–5.39 (m, 2 H), 5.28–5.17 (m, 2 H), 4.97 (d, $^3J_{H,H}$ = 9.70 Hz, 1 H), 4.25 (d, $^3J_{H,H}$ = 6.69 Hz, 1 H), 2.43 (s, 3 H), 2.38–2.31 (m, 1 H), 2.35 (s, 3 H), 2.19–2.10 (m, 1 H), 0.94 (d, $^3J_{H,H}$ = 6.61 Hz, 3 H), 0.91 (d, $^3J_{H,H}$ = 6.78 Hz, 3 H), 0.76 (d, $^3J_{H,H}$ = 6.86 Hz, 3 H), 0.55 (d, $^3J_{H,H}$ = 6.61 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_4$]methanol): δ = 165.06, 164.35, 164.11, 150.09, 144.18, 137.92, 136.98, 136.65, 136.55, 136.27, 130.99, 130.24, 130.18, 129.30, 129.23, 127.65, 127.31, 53.54, 51.78, 47.95, 33.30, 19.92, 19.52, 19.02, 17.82, 10.38, 10.09 ppm. IR (KBr): $\tilde{\nu}$ = 3446, 2970, 1674, 1593, 1509, 1500, 1203, 1138, 722 cm^{-1}. FAB-HRMS: calcd. for $C_{32}H_{41}N_6O_3$ [M + H]$^+$ 557.3240; found 557.3217.

Cyclic Peptide 10: *i*Pr$_2$NEt (2.40 mL, 13.5 mmol) and FDPP (1.53 g, 3.98 mmol) were added at room temperature to a suspension of **18** (1.41 g, 2.10 mmol) in acetonitrile (200 mL) and the mixture was stirred at room temperature for 2 d. The solvent was removed by evaporation and the residue was dissolved in AcOEt and then extracted with water and brine, dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:2) gave **10** (735 mg, 65%) as a white solid; m.p. >250 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (d, $^3J_{H,H}$ = 9.37 Hz, 4 H), 7.31–7.23 (m, 12 H), 7.11–7.08 (m, 8 H), 5.81 (d, $^2J_{H,H}$ = 16.73 Hz, 4 H), 5.11 (d, $^2J_{H,H}$ = 16.73 Hz, 4 H), 4.75 (t, $^3J_{H,H}$ = 9.37 Hz, 4 H), 2.48 (m, 12 H), 2.42–2.35 (m, 4 H), 1.00 (d, $^3J_{H,H}$ = 6.69 Hz, 12 H), 0.47 (d, $^3J_{H,H}$ = 6.69 Hz, 12 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.71, 147.76, 136.67, 131.89, 129.74, 128.70, 127.57, 126.50, 49.93, 46.57, 32.12, 19.74, 19.33, 9.93 ppm. IR (KBr): $\tilde{\nu}$ = 3454, 3448, 3414, 2964, 2930, 1650, 1592, 1501, 1467, 1457, 1434, 1389, 1356, 1332, 1225, 730, 698, 581, 525, 513 cm^{-1}. FAB-HRMS: calcd. for $C_{64}H_{77}N_{12}O_4$ [M + H]$^+$ 1077.6191; found 1077.6189.

Scaffold 4: Cyclic peptide **10** (539 mg, 0.50 mmol) was converted into **4** as described above in the General Procedure for the cleavage of the benzyl group. Yield: 348 mg (97%); m.p. > 250 °C. ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 4.88 (d, $^3J_{H,H}$ = 9.23 Hz, 4 H), 2.52–2.38 (m, 4 H), 2.48 (s, 12 H), 1.10 (d, $^3J_{H,H}$ = 6.62 Hz, 12 H), 0.93 (d, $^3J_{H,H}$ = 6.62 Hz, 12 H) ppm. ^{13}C NMR (75 MHz, [D$_4$]methanol): δ = 162.77, 147.56, 134.81, 127.02, 53.93, 33.46, 19.76, 19.61, 10.79 ppm. IR (KBr): $\tilde{\nu}$ = 3400, 3048, 3038, 2965, 2932, 2875, 2763, 2663, 1656, 1601, 1543, 1518, 1470, 1390, 1370, 1343, 1035, 577 cm^{-1}. FAB-HRMS: calcd. for $C_{36}H_{53}N_{12}O_4$ [M + H]$^+$ 717.4313; found 717.4304.

***N*-Boc-imidazole–oxazole Methyl Ester 20:** *i*Pr$_2$NEt (1.50 mL, 8.50 mmol) and FDPP (692 mg, 1.80 mmol) were added at room temperature to acid **14** (465 mg, 1.20 mmol) and ammonium salt **19** (587 mg, 1.80 mmol) in acetonitrile (45 mL) and the mixture was stirred at room temperature for 2 d. The solvent was removed by evaporation and the residue was dissolved in AcOEt and then extracted with water and brine, dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) gave **20** (604 mg, 87%) as a white solid; m.p. 64 °C. ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 7.73 (br. s, 1 H), 7.38–7.25 (m, 3 H), 7.13–7.04 (m, 2 H), 6.35 (br. s, 1 H), 5.37 (m, 2 H), 5.10 (m, 1 H), 4.55 (m, 1 H), 3.83 (s, 3 H), 2.60 (s, 3 H), 2.43 (s, 3 H), 2.35–2.26 (m, 1 H), 1.33 (s, 9 H), 1.01 (d, $^3J_{H,H}$ = 6.84 Hz, 3 H), 0.98 (d, $^3J_{H,H}$ = 6.84 Hz, 3 H), 0.95 (d, $^3J_{H,H}$ = 6.41 Hz, 3 H), 0.76 (d, $^3J_{H,H}$ = 6.41 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 164.73, 164.13, 163.77, 157.89, 157.47, 149.21, 138.67, 134.49, 131.29, 130.58, 129.34, 129.12, 128.20, 80.11, 54.05, 53.40, 52.75, 48.17, 34.09, 33.69, 29.47, 21.34, 20.34, 19.91, 19.65, 13.02, 10.89 ppm. IR (film): $\tilde{\nu}$ = 3400, 2966, 2872, 1708, 1663, 1620, 1590, 1498, 1444, 1389, 1365, 1351, 1307, 1246, 1173, 1098, 1014, 810, 785, 730 cm^{-1}. FAB-HRMS: calcd. for $C_{31}H_{44}N_5O_6$ [M + H]$^+$ 582.3292; found 582.3264. $C_{31}H_{43}N_5O_6$·MeOH (613.74): C 62.62, H 7.72, N 11.41; found C 62.66, H 7.40, N 11.45.

***N*-Boc-imidazole–oxazolecarboxylic Acid 21:** Compound **20** (582 mg, 1.00 mmol) was converted into **21** as described above in the General Procedure for the cleavage of the methyl ester group. Yield: 570 mg (98%); m.p. 201 °C. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 7.77 (br. s, 1 H), 7.38–7.22 (m, 3 H), 7.06–6.95 (m, 2 H), 5.26 (m, 2 H), 4.94 (m, 1 H), 4.36 (t, $^3J_{H,H}$ = 9.21 Hz, 1 H), 2.49 (s, 3 H), 2.30 (s, 3 H), 2.27–2.11 (m, 2 H), 1.26 (s, 9 H), 0.93–0.81 (m, 6 H), 0.74 (d, $^3J_{H,H}$ = 6.36 Hz, 3 H), 0.63 (d, $^3J_{H,H}$ = 6.36 Hz, 3 H) ppm. ^{13}C NMR (300 MHz, [D$_6$]DMSO): δ = 165.12, 162.68, 160.09, 155.39, 147.04, 136.52, 132.38, 128.69, 128.58, 127.32, 126.10, 77.89, 52.13, 51.25, 45.92, 31.81, 31.76, 30.84, 27.99, 19.82, 18.80, 18.73, 18.30, 11.03, 9.43 ppm. IR (KBr): $\tilde{\nu}$ = 3400, 2965, 2931, 2874, 1710, 1653, 1593, 1498, 1455, 1426, 1392, 1367, 1327, 1307, 1251, 1227, 1171, 1111, 729, 696, 582 cm^{-1}. ESI-HRMS: calcd. for $C_{30}H_{40}N_5O_6$ [M – H]$^-$ 566.2979; found 566.2980.

Aminoimidazole–oxazolecarboxylic Acid (TFA Salt) 22: Compound **21** (454 mg, 0.80 mmol) was converted into **22** as described above in the General Procedure for the cleavage of the Boc group. Yield: quantitative; m.p. 97 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.56 (s, 3 H), 7.80 (d, $^3J_{H,H}$ = 9.21 Hz, 1 H), 7.39–7.25 (m, 3 H), 7.12–7.05 (m, 2 H), 5.39 (d, $^2J_{H,H}$ = 17.10 Hz, 1 H), 5.27 (d, $^2J_{H,H}$ = 17.10 Hz, 1 H), 4.97 (dd, $^3J_{H,H}$ = 7.02, 9.10 Hz, 1 H), 4.42 (br. s, 1 H), 2.55 (s, 3 H), 2.35 (s, 3 H), 2.29–2.08 (m, 2 H), 0.95 (d, $^3J_{H,H}$ = 6.91 Hz, 3 H), 0.91 (d, $^3J_{H,H}$ = 6.58 Hz, 3 H), 0.89 (d, $^3J_{H,H}$ = 6.47 Hz, 3 H), 0.77 (d, 3 H, $^3J_{H,H}$ = 6.80 Hz) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 162.96, 162.21, 161.18, 155.51, 143.03, 136.03, 133.52, 129.34, 128.73, 127.64, 127.39, 126.35, 51.27, 50.89, 46.36, 31.74, 31.61, 18.86, 18.20, 18.16, 17.50, 11.75, 9.53 ppm. IR (KBr): $\tilde{\nu}$ = 3420, 3066, 2972, 2933, 2881, 1676, 1592, 1544, 1516, 1469, 1456, 1436, 1395, 1377, 1355, 1203, 1143, 800, 723, 698 cm^{-1}. FAB-HRMS: calcd. for $C_{25}H_{34}N_5O_4$ [M + H]$^+$ 468.2611; found 468.2620.

Cyclic Peptide 23: *i*Pr$_2$NEt (1.20 mL, 6.75 mmol) and FDPP (765 mg, 1.99 mmol) were added at room temperature to a suspension of **22** (581 mg, 1.00 mmol) in acetonitrile (100 mL) and the mixture was stirred at room temperature for 2 d. The solvent was removed by evaporation and the residue was dissolved in AcOEt and then extracted with water and brine, dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography on silica gel (DCM/AcOEt/MeOH, 75:25:0.5) gave **23** (247 mg, 55%) as a white solid; m.p. 153 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.75 (d, $^3J_{H,H}$ = 8.55 Hz, 2 H), 7.35 (d, $^3J_{H,H}$ = 10.19 Hz, 2 H), 7.27–7.17 (m, 6 H), 6.97–6.91 (m, 4 H), 5.43 (d, $^3J_{H,H}$ = 16.99 Hz, 2 H), 5.24 (d, $^3J_{H,H}$ = 17.10 Hz, 2 H), 5.04–4.93 (m, 4 H), 2.68–2.56 (m, 2 H), 2.53 (s, 6 H), 2.43 (s, 6 H), 2.28–2.17 (m, 2 H), 1.02 (d, $^3J_{H,H}$ =

6.80 Hz, 6 H), 1.01 (d, $^3J_{H,H}$ = 6.69 Hz, 6 H), 0.96 (d, $^3J_{H,H}$ = 6.80 Hz, 6 H), 0.79 (d, $^3J_{H,H}$ = 6.58 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 164.69, 164.06, 162.40, 154.37, 148.43, 138.50, 135.01, 131.28, 130.49, 130.31, 129.19, 127.66, 53.66, 51.23, 47.91, 34.16, 32.71, 21.48, 20.38, 20.18, 19.68, 12.59, 10.73 ppm. IR (KBr): $\tilde{\nu}$ = 3400, 2963, 2930, 2874, 1670, 1637, 1594, 1509, 1468, 1454, 1390, 1371, 1353, 1220, 1189, 1148, 1126, 1113, 731, 696, 583 cm^{-1}. FAB-HRMS: calcd. for $C_{50}H_{63}N_{10}O_6$ [M + H]$^+$ 899.4932; found 899.4943. $C_{50}H_{62}N_{10}O_6{\cdot}CH_3OH{\cdot}H_2O$ (948.15): calcd. C 64.54, H 7.22, N 14.76; found C 64.68, H 6.92, N 14.71.

Scaffold 5: Cyclic peptide **23** (360 mg, 0.40 mmol) was converted into **5** as described above in the General Procedure for the cleavage of the benzyl group. Yield: 274 mg (95%); m.p. > 250 °C. ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 5.04 (d, $^3J_{H,H}$ = 7.78 Hz, 2 H), 4.99 (d, $^3J_{H,H}$ = 9.76 Hz, 2 H), 2.59–2.47 (m, 2 H), 2.54 (s, 6 H), 2.50 (s, 6 H), 2.40–2.27 (m, 2 H), 1.10 (d, $^3J_{H,H}$ = 6.69 Hz, 6 H), 1.04 (d, $^3J_{H,H}$ = 6.80 Hz, 6 H), 0.93 (m, 12 H) ppm. ^{13}C NMR (75 MHz, [D$_4$]methanol): δ = 163.19, 162.37, 155.03, 147.41, 134.74, 129.61, 53.46, 53.33, 33.69, 33.08, 19.81, 19.78, 19.31, 19.18, 11.72, 10.85 ppm. IR (KBr): $\tilde{\nu}$ = 3411, 3041, 2965, 2932, 2875, 2735, 1660, 1635, 1602, 1514, 1469, 1444, 1391, 1372, 1347, 1208, 1189, 1150, 1117, 579 cm^{-1}. FAB-HRMS: calcd. for $C_{36}H_{51}N_{10}O_6$ [M + H]$^+$ 719.3993; found 719.4026. $C_{36}H_{50}N_{10}O_6{\cdot}CH_2Cl_2{\cdot}CH_3OH$ (835.82): calcd. C 54.61, H 6.75, N 16.76; found C 54.58, H 6.87, N 17.02.

General Procedure for the Syntheses of Four-Armed Platforms 9, 10 and 24 and Two-Armed Platforms 23, 27 and 28: K_2CO_3 (207 mg, 1.50 mmol) and RX (1.00 mmol for **4** and 2.00 mmol for **5**) were added at room temperature to a solution of **4** or **5** (0.20 mmol) in acetonitrile (40 mL) and the mixture was stirred at reflux for 8 h. The solvent was removed by evaporation and the residue was dissolved in AcOEt, extracted with water and brine, dried with $MgSO_4$ and concentrated in vacuo. Purification was accomplished by chromatography on silica gel (DCM/AcOEt/MeOH, 75:25:0.5) to yield the four-armed platforms **9** (90%), **10** (85%) and **24** (91%) and the two-armed platforms **23** (85%), **27** (92%) and **28** (73%), respectively, as white solids.

Data for Receptor 24: M.p. 146 °C. ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.61 (d, $^3J_{H,H}$ = 8.66 Hz, 4 H), 5.48 (d, $^2J_{H,H}$ = 18.31 Hz, 4 H), 4.70 (d, $^2J_{H,H}$ = 18.20 Hz, 4 H), 4.64 (m, 4 H), 2.57–2.45 (m, 4 H), 2.43 (s, 12 H), 1.48 (s, 36 H), 1.14 (d, $^3J_{H,H}$ = 6.80 Hz, 12 H), 0.87 (d, $^3J_{H,H}$ = 6.58 Hz, 12 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-acetone): δ = 168.86, 164.81, 149.78, 134.03, 131.02, 83.96, 51.55, 47.13, 33.67, 29.10, 21.40, 20.75, 10.55 ppm. IR (KBr): $\tilde{\nu}$ = 3407, 2965, 2936, 2874, 1746, 1654, 1597, 1503, 1456, 1394, 1371, 1286, 1237, 1223, 1157, 1107, 608, 579 cm^{-1}. FAB-HRMS: calcd. for $C_{60}H_{93}N_{12}O_{12}$ [M + H]$^+$ 1173.7036; found 1173.6993.

Data for Receptor 28: M.p. 147 °C. ^{1}H NMR (500 MHz, [D$_6$]acetone): δ = 7.74 (br. s, 2 H), 7.47 (br. s, 2 H), 5.12–4.99 (m, 4 H), 4.89 (t, $^3J_{H,H}$ = 9.92 Hz, 2 H), 4.79 (d, $^2J_{H,H}$ = 18.24 Hz, 2 H), 2.71–2.63 (m, 2 H), 2.62 (s, 6 H), 2.40 (s, 6 H), 2.27–2.19 (m, 2 H), 1.42 (s, 18 H), 1.11 (d, $^3J_{H,H}$ = 6.66 Hz, 6 H), 1.01 (d, $^3J_{H,H}$ = 6.74 Hz, 6 H), 0.95 (d, $^3J_{H,H}$ = 6.51 Hz, 6 H), 0.94 (d, $^3J_{H,H}$ = 6.74 Hz, 6 H) ppm. ^{13}C NMR (125 MHz, [D$_6$]acetone): δ = 168.53, 164.44, 164.13, 162.66, 154.53, 148.47, 135.03, 130.45, 84.13, 53.39, 51.17, 47.14, 34.41, 32.93, 29.03, 21.50, 20.54, 20.13, 19.56, 12.63, 10.46 ppm. IR (KBr): $\tilde{\nu}$ = 3411, 2965, 2933, 2875, 1746, 1671, 1637, 1598, 1510, 1457, 1393, 1371, 1352, 1282, 1238, 1222, 1192, 1156, 1114, 582 cm^{-1}. FAB-HRMS: calcd. for $C_{48}H_{71}N_{10}O_{10}$ [M + H]$^+$ 947.5355; found 947.5323. $C_{48}H_{70}N_{10}O_{10}{\cdot}H_2O$ (965.15): calcd. C 59.73, H 7.52, N 14.51; found C 59.86, H 7.45, N 14.29.

Tetraacid 25: The tetra-*tert*-butyl ester **24** (153 mg, 0.13 mmol) was dissolved in DCM (10 mL) and the solution was cooled to 0 °C. TFA (3.0 mL) was added at that temperature. The ice bath was removed after 30 min and stirring was continued at room temperature for 1 d. The mixture was concentrated in vacuo to provide a quantitative yield of the tetraacid **25**, which was used in the next step without further purification; m.p. > 250 °C. ^{1}H NMR (500 MHz, [D$_4$]methanol): δ = 5.21 (d, $^2J_{H,H}$ = 18.39 Hz, 4 H), 4.81–4.76 (m, 8 H), 2.44–2.36 (m, 4 H), 2.35 (s, 12 H), 1.05 (d, $^3J_{H,H}$ = 6.51 Hz, 12 H), 0.83 (d, $^3J_{H,H}$ = 6.51 Hz, 12 H) ppm. ^{13}C NMR (125 MHz, [D$_4$]methanol): δ = 170.30, 164.23, 149.03, 135.84, 128.75, 51.42, 46.07, 33.28, 20.13, 19.54, 9.71 ppm. IR (KBr): $\tilde{\nu}$ = 3400, 2965, 2937, 1739, 1642, 1598, 1511, 1453, 1389, 1376, 1348, 1221, 1206, 600, 572, 520, 470 cm^{-1}. FAB-HRMS: calcd. for $C_{44}H_{61}N_{12}O_{12}$ [M + H]$^+$ 949.4532; found 949.4566.

Tetraamide 26: DMC (51 mg, 0.30 mmol) and NEt_3 (0.20 mL, 1.40 mmol) were added at room temperature to a solution of **25** (48 mg, 0.05 mmol) and aniline (38 mg, 0.40 mmol) in DCM (20 mL) and the mixture was stirred at room temperature for 1 d. The solvent was removed by evaporation and the residue was dissolved in DCM and then extracted with water and brine, dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography on silica gel (DCM/AcOEt/MeOH, 75:25:9) gave **26** (28 mg, 44%) as a white solid; m.p. > 250 °C. ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 7.51–7.45 (m, 8 H), 7.33–7.24 (m, 8 H), 7.12–7.05 (m, 4 H), 5.12 (d, $^2J_{H,H}$ = 17.42 Hz, 4 H), 4.89–4.85 (m, 8 H), 2.54–2.41 (m, 4 H), 2.37 (s, 12 H), 1.12 (d, $^3J_{H,H}$ = 6.62 Hz, 12 H), 0.94 (d, $^3J_{H,H}$ = 6.62 Hz, 12 H) ppm. ^{13}C NMR (300 MHz, [D$_4$]methanol): δ = 166.73, 165.35, 149.03, 139.37, 135.54, 129.96, 129.92, 125.5, 121.26, 51.42, 47.58, 33.40, 20.33, 19.36, 9.92 ppm. IR (KBr): $\tilde{\nu}$ = 3428, 3421, 3141, 3088, 2964, 2930, 1682, 1639, 1599, 1554, 1501, 1446, 1390, 1374, 1312, 1258, 1228, 758, 694, 612 cm^{-1}. FAB-HRMS: calcd. for $C_{68}H_{81}N_{16}O_8$ [M + H]$^+$ 1249.6423; found 1249.6423.

Diacid 29: The di-*tert*-butyl ester **28** (66 mg, 0.07 mmol) was dissolved in DCM (5 mL) and the solution was cooled to 0 °C. TFA (1.5 mL) was added at that temperature. The ice bath was removed after 30 min and stirring was continued at room temperature for 1 d. The mixture was concentrated in vacuo to provide a quantitative yield of the diacid **29**, which was used in the next step without further purification; m.p. 164 °C. ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 5.02–4.94 (m, 4 H), 4.87–4.77 (m, 4 H), 2.65–2.55 (m, 2 H), 2.50 (s, 6 H), 2.31 (s, 6 H), 2.23–2.12 (m, 2 H), 1.01 (d, $^3J_{H,H}$ = 6.58 Hz, 6 H), 0.89 (d, $^3J_{H,H}$ = 6.58 Hz, 6 H), 0.86 (d, $^3J_{H,H}$ = 6.69 Hz, 6 H), 0.84 (d, $^3J_{H,H}$ = 6.58 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, [D$_4$]methanol): δ = 170.26, 164.52, 163.14, 162.91, 155.65, 148.11, 136.30, 129.44, 129.10, 53.34, 51.09, 45.97, 34.14, 31.84, 20.67, 19.68, 19.18, 18.38, 11.77, 9.67 ppm. IR (KBr): $\tilde{\nu}$ = 3403, 3396, 3390, 3333, 3311, 2970, 2939, 2879, 1743, 1669, 1657, 1634, 1597, 1511, 1468, 1391, 1375, 1351, 1196, 1145 cm^{-1}. FAB-HRMS: calcd. for $C_{40}H_{55}N_{10}O_{10}$ [M + H]$^+$ 835.4103; found 835.4121.

Diamide 30: DMC (40 mg, 0.21 mmol) and NEt_3 (0.15 mL, 1.00 mmol) were added at room temperature to a solution of **29** (58 mg, 0.07 mmol) and 3-aminopyridine (26 mg, 0.28 mmol) in DCM (30 mL) and the mixture was stirred at room temperature for 1 d. The solvent was removed by evaporation and the residue was dissolved in DCM and then extracted with water and brine, dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography on silica gel (DCM/MeOH, 5:1) gave **30** (60 mg, 87%) as a white solid; m.p. > 250 °C. ^{1}H NMR (300 MHz, [D$_4$]methanol/$CDCl_3$): δ = 10.30 (s, 2 H), 8.56 (m, 4 H), 8.24 (m, 4 H), 8.12 (m, 4 H), 7.85 (m, 2 H), 7.31 (m, 2 H), 5.18–4.97 (m, 4 H), 4.78–4.62 (m, 4 H), 2.69–2.56 (m, 2 H), 2.43 (s, 6 H), 2.42 (s, 6 H), 2.25–2.13

(m, 2 H), 1.04 (d, $^3J_{H,H}$ = 6.78 Hz, 6 H), 0.95–0.87 (m, 18 H) ppm. ^{13}C NMR (75 MHz, [D$_4$]methanol/CDCl$_3$): δ = 165.11, 163.24, 161.73, 161.61, 153.50, 146.28, 143.53, 139.43, 135.47, 134.01, 128.94, 127.92, 127.88, 124.23, 51.60, 49.95, 45.96, 32.65, 30.87, 19.96, 19.07, 18.51, 17.81, 11.38, 9.40 ppm. IR (KBr): $\tilde{\nu}$ = 3414, 2965, 2936, 1711, 1650, 1636, 1600, 1554, 1515, 1485, 1461, 1425, 1391, 1372, 1286, 1200, 708, 630 cm^{-1}. FAB-HRMS: calcd. for $C_{50}H_{63}N_{14}O_8$ [M + H]$^+$ 987.4953; found 987.4942.

***N*-Boc-oxazole–oxazolecarboxylic Acid *((<=AUTHOR: Change ok?))* Methyl Ester 32:** *i*Pr$_2$NEt (4.40 mL, 25.0 mmol) and FDPP (1.54 g, 4.00 mmol) were added at room temperature to acid **31** (1.07 g, 3.60 mmol) and ammonium salt **19** (1.31 g, 4.00 mmol) in acetonitrile (80 mL) and the mixture was stirred at room temperature for 3 d. The solvent was removed by evaporation and the residue was dissolved in AcOEt and then extracted with water and brine, dried with MgSO$_4$ and concentrated in vacuo. Flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) gave **32** (1.32 g, 74%) as a white solid; m.p. 52 °C. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.38 (d, $^3J_{H,H}$ = 9.54 Hz, 1 H), 5.13–5.05 (m, 2 H), 4.66 (m, 1 H), 3.85 (m, 3 H), 2.57 (s, 3 H), 2.55 (s, 3 H), 2.32–2.25 (m, 1 H), 2.15–2.07 (m, 1 H), 1.42 (s, 9 H), 0.99 (d, $^3J_{H,H}$ = 6.69 Hz, 3 H), 0.92–0.87 (m, 9 H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 162.60, 161.61, 161.44, 160.83, 156.22, 155.28, 153.37, 128.36, 127.37, 80.00, 54.03, 52.07, 51.90, 32.66, 32.58, 28.27, 19.05, 18.68, 18.54, 17.89, 11.97, 11.61 ppm. IR (film): $\tilde{\nu}$ = 3411, 3328, 2967, 2933, 1718, 1672, 1633, 1581, 1511, 1469, 1457, 1442, 1391, 1367, 1351, 1293, 1246, 1204, 1174, 1099, 989, 735 cm^{-1}. FAB-HRMS: calcd. for $C_{24}H_{37}N_4O_7$ [M + H]$^+$ 493.2662; found 493.2643. $C_{24}H_{36}N_4O_7$·1/2H$_2$O (501.57): calcd. C 57.47, H 7.44, N 11.17; found C 57.25, H 7.23, N 10.94.

***N*-Boc-Protected Amino Acid 33:** Dimer **32** (850 mg, 1.73 mmol) was dissolved in methanol/dioxane (35 mL/25 mL), and this was followed by the slow addition of an NaOH solution (2 M, 9.00 mL, 17.3 mmol) at 0 °C. Stirring was continued until TLC showed the consumption of all starting material, after which brine, HCl solution (1 M) and DCM were added. The aqueous phase was repeatedly extracted with DCM and the organic layers were combined, dried with MgSO$_4$ and concentrated in vacuo to give the acid **33** as a white solid (790 mg, 95%), which was used in the next step without further purification; m.p. 82 °C. ^{1}H NMR (75 MHz, [D$_6$]-DMSO): δ = 8.08 (d, $^3J_{H,H}$ = 8.77 Hz, 1 H), 7.47 (d, $^3J_{H,H}$ = 8.33 Hz, 1 H), 4.90 (t, $^3J_{H,H}$ = 8.33 Hz, 1 H), 4.42 (t, $^3J_{H,H}$ = 8.33 Hz, 1 H), 2.54 (s, 3 H), 2.53 (s, 3 H), 2.39–2.27 (m, 1 H), 2.17–2.05 (m, 1 H), 1.37 (s, 9 H), 0.97–0.89 (m, 6 H), 0.85 (d, $^3J_{H,H}$ = 6.80 Hz, 3 H), 0.80 (d, $^3J_{H,H}$ = 6.91 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 162.89, 161.15, 160.80, 160.64, 155.49, 155.32, 152.59, 127.94, 127.26, 78.26, 54.37, 51.86, 31.09, 30.77, 28.07, 19.01, 18.95, 18.59, 11.71, 11.27 ppm. IR (KBr): $\tilde{\nu}$ = 3428, 2952, 2920, 2867, 1702, 1664, 1631, 1508, 1241, 1159, 1095, 720 cm^{-1}. FAB-HRMS: calcd. for $C_{23}H_{35}N_4O_7$ [M + H]$^+$ 501.2325; found 501.2314.

TFA Amino Acid 34: The Boc-protected amino acid **33** (766 mg, 1.60 mmol) was dissolved in DCM (35 mL) and the solution was cooled to 0 °C. TFA (5.0 mL) was added at that temperature. The ice bath was removed after 30 min and stirring was continued at room temperature for 2 h. The mixture was concentrated in vacuo to provide a quantitative yield of the amino acid **34** (787 mg), which was used in the next step without further purification. ^{1}H NMR (300 MHz, [D$_4$]methanol): δ = 4.91 (d, $^3J_{H,H}$ = 7.49 Hz, 1 H), 4.38 (d, $^3J_{H,H}$ = 6.62 Hz, 1 H), 2.58 (s, 3 H), 2.56 (s, 3 H), 2.39–2.24 (m, 2 H), 1.07 (d, $^3J_{H,H}$ = 6.79 Hz, 3 H), 0.98 (d, $^3J_{H,H}$ = 6.62 Hz, 3 H), 0.97 (d, $^3J_{H,H}$ = 6.97 Hz, 3 H), 0.90 (d, $^3J_{H,H}$ = 6.62 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_4$]methanol): δ = 164.72, 162.92, 158.26, 157.83, 156.60, 130.14, 128.73, 55.32, 53.91, 33.29, 32.41, 19.41, 18.86, 18.75, 18.24, 12.03, 11.69 ppm. IR (KBr): $\tilde{\nu}$ = 3446, 3286, 3017, 2946, 2888, 1727, 1675, 1636, 1529, 1203, 1189, 1139 cm^{-1}. FAB-HRMS: calcd. for $C_{18}H_{27}N_4O_5$ [M + H]$^+$ 379.1982; found 379.1962.

Cyclic Peptide 6: *i*Pr$_2$NEt (1.60 mL, 9.00 mmol) and FDPP (1.02 g, 2.65 mmol) were added at room temperature to a suspension of **34** (690 mg, 1.40 mmol) in acetonitrile (175 mL) and the mixture was stirred at room temperature for 2 d. The solvent was removed by evaporation and the residue was dissolved in AcOEt and then extracted with water and brine, dried with MgSO$_4$ and concentrated in vacuo. Flash chromatography on silica gel (DCM/AcOEt/MeOH, 75:25:0.5) gave **6** (361 mg, 72%) as a white solid; m.p. 133 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.31 (d, $^3J_{H,H}$ = 9.65 Hz, 4 H), 5.14 (dd, $^3J_{H,H}$ = 7.67, 9.65 Hz, 4 H), 2.60 (s, 12 H), 2.41–2.27 (m, 4 H), 1.06 (d, $^3J_{H,H}$ = 6.80 Hz, 12 H), 0.98 (d, $^3J_{H,H}$ = 6.69 Hz, 12 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 161.13, 160.89, 153.57, 128.49, 51.25, 32.40, 19.11, 18.50, 11.68 ppm. IR (KBr): $\tilde{\nu}$ = 3448, 3417, 2965, 1679, 1634, 1578, 1512, 1470, 1391, 1373, 1203, 1193, 1141, 1115 cm^{-1}. ESI-HRMS: calcd. for $C_{36}H_{49}N_8O_8$ [M + H]$^+$ 743.3493; found 743.3509. $C_{36}H_{48}N_8O_8$·1/2H$_2$O·1/2MeOH (745.38): calcd. C 58.78, H, 6.89, N, 15.02; found C 58.72, H 6.71, N 14.71.

X-ray Crystal Structure Analysis

Data for 10: $C_{64}H_{76}N_{12}O_4$·3CHCl$_3$ (crystallization from CHCl$_3$); M = 1435.47, colourless crystal (polyhedron), dimensions 0.52 × 0.45 × 0.20 mm, crystal system orthorhombic, space group $P2_12_12_1$, Z = 4, a = 16.1337(3), b = 17.4146(3), c = 26.1804(2) Å, $\alpha = \beta = \gamma$ = 90°, V = 7355.7(2) Å^3, ρ = 1.296 g cm^{-3}, T = 200(2) K, θ_{max} = 21.49°, radiation Mo-K_α, λ = 0.71073 Å, 0.3° ω-scans with CCD area detector, covering a whole sphere in the reciprocal space, 45790 reflections measured, 8442 unique (R_{int} = 0.0431), 7047 observed [$I > 2\sigma(I)$], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied by use of SADABS[20] based on the Laue symmetry of the reciprocal space, μ = 0.40 mm^{-1}, T_{min} = 0.82, T_{max} = 0.92, structure solved by direct methods and refined against F^2 with a full-matrix, least-squares algorithm with use of the SHELXTL-PLUS (5.10) software package,[21] 991 parameters refined, hydrogen atoms were treated by use of appropriate riding models, Flack absolute structure parameter 0.03(9), goodness of fit 1.09 for observed reflections, final residual values $R_1(F)$ = 0.050, $wR(F^2)$ = 0.125 for observed reflections, residual electron density –0.26/0.53 e·Å^{-3}.

Data for 30: $C_{50}H_{62}N_{14}O_8$·3.3CH$_3$CN (crystallization from CH$_3$CN); M = 1122.61, colourless crystal (columns), dimensions 0.50 × 0.14 × 0.14 mm, crystal system orthorhombic, space group $P2_12_12_1$, Z = 4, a = 17.3820(3), b = 18.8274(3), c = 20.5823(3) Å, $\alpha = \beta = \gamma$ = 90°, V = 6735.7(2) Å^3, ρ = 1.107 g cm^{-3}, T = 200(2) K, θ_{max} = 22.22°, radiation Mo-K_α, λ = 0.71073 Å, 0.3° ω-scans with CCD area detector, covering a whole sphere in the reciprocal space, 44732 reflections measured, 8465 unique (R_{int} = 0.0507), 7302 observed [$I > 2\sigma(I)$], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied by use of SADABS[20] based on the Laue symmetry of the reciprocal space, μ = 0.08 mm^{-1}, T_{min} = 0.96, T_{max} = 0.99, structure solved by direct methods and refined against F^2 with a full-matrix, least-squares algorithm with use of the SHELXTL (6.12) software package,[21] 821 parameters refined, hydrogen atoms were treated by use of appropriate riding models, Flack absolute structure parameter –1.3(14), goodness of fit 1.09 for observed reflections, final residual

values $R_1(F) = 0.056$, $wR(F^2) = 0.145$ for observed reflections, residual electron density –0.24/0.57 e·Å^{-3}.

Data for 6: $C_{36}H_{48}N_8O_8$; $M = 720.82$, colourless crystal (polyhedron), dimensions $0.38 \times 0.34 \times 0.12$ mm, crystal system orthorhombic, space group $C222$, $Z = 4$, $a = 17.6317(7)$, $b = 21.5974(9)$, $c = 12.2646(5)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 4670.3(3)$ Å^3, $\rho = 1.025$ g cm^{-3}, $T = 298(2)$ K, $2\theta_{max} = 21.99°$, radiation Mo-K_α, $\lambda = 0.71073$ Å, 0.3° ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 10162 reflections measured, 2882 unique ($R_{int} = 0.0413$), 2159 observed [$I > 2\sigma(I)$], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied by use of SADABS[20] based on the Laue symmetry of the reciprocal space, $\mu = 0.17$ mm^{-1}, $T_{min} = 0.97$, $T_{max} = 0.99$, structure solved by direct methods and refined against F^2 with a full-matrix, least-squares algorithm with use of the SHELXTL-PLUS (5.10) software package,[21] 272 parameters refined, hydrogen atoms were treated by use of appropriate riding models, Flack absolute structure parameter –1(3), goodness of fit 1.03 for observed reflections, final residual values $R_1(F) = 0.064$, $wR(F^2) = 0.166$ for observed reflections, residual electron density –0.25/0.45 e·Å^{-3}.

CCDC-625516, -625517 and -625790 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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