Tetrahedron 65 (2009) 2217–2225

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of chiral threefold and sixfold functionalized macrocyclic imidazole peptides

Áron Pintér, Gebhard Haberhauer *

Institut für Organische Chemie, Fachbereich Chemie, Universität Duisburg-Essen, Universitätsstraße 7, D-45117 Essen, Germany

ARTICLE INFO

Article history:
Received 24 October 2008
Received in revised form 12 January 2009
Accepted 13 January 2009
Available online 20 January 2009

Keywords:
Amino acids
Cyclization
Imidazoles
Macrocycles
Peptidomimetics

ABSTRACT

Starting from 4-oxa- or 4-azasubstituted 2-amino-3-oxoesters and (*S*)-valine, chiral imidazole diamino monocarboxylic acids as well as diamino dicarboxylic acids were prepared in a few synthetic steps. Macrolactamization of the side chain protected imidazole amino acids yields the corresponding 18- and 24-membered ring analogues of the naturally occurring cyclic peptide *Westiellamide* with various anchoring sites. The threefold functionalized scaffolds **2b**–**4b** and the sixfold functionalized scaffold **5** are versatile central modules for artificial receptors and ligands. Structural investigations of threefold functionalized scaffolds based on oxazole and *N*-methylimidazole units by DFT modeling are provided.

1. Introduction

The unique and aesthetic chemical structure of C_3-symmetric molecules inspired chemists to a detailed investigation of the role of threefold rotational symmetry in chiral molecular recognition and catalytic processes.[1] However the importance of C_3-symmetric chiral catalytic systems is still inferior to the ones with rotational axes of lower order and the usefulness of C_3-symmetric receptors concerning enantiodiscrimination was in the beginning a subject of some controversy.[2] Nevertheless, chiral transition metal complexes as well as organocatalysts with threefold symmetry gave rise to promising enantioselectivities in various synthetic operations, such as alkene reduction,[3] direct aldol addition,[4] α-alkylation,[5] allylic substitution,[6] allylic oxidation,[7] cyclopropanation,[8] transesterification,[9] carbonyl addition,[10] sulfide oxidation,[11] α-amination,[12] and ketone reduction.[13] In addition chiral C_3-symmetric host molecules of various chemical structures showed remarkable enantiomeric recognition toward peptides,[14] α-amino acid esters,[15] α-amino acid amides,[16] and ammonium salts.[17] Enantiofacial discrimination of caffeine by C_3-symmetric chiral receptors was also disclosed.[18]

Macrocycles with a constrained conformation and therefore with a fixed considerable diameter offering binding sites for a particular guest substrate or catalytically active metal centre are considered as useful keystones both in supramolecular chemistry and in catalysis. These structural features in addition to chemical stability are characteristic for azole-containing cyclic peptides of the chiral pool.[19,20] The first synthetic analogues of the C_3-symmetric peptide alkaloid *Westiellamide* with oxazole and thiazole units bearing various electrophilic and nucleophilic coupling sites in the aliphatic section of the macrocyclic backbone were developed by Rebek et al.[21] The synthesis of similar cyclohexapeptides with thiazole heterocycles alternating with proteinogenic Glu, Lys, and Orn amino acid residues were reported by others.[22–24] However, no further information was provided to date about the complexation properties of the tubular and conical cages obtained by threefold linking of two macrocycles.

Recently, we reported the synthesis and structure of cyclic peptides having imidazole and oxazole units in the backbone for the control of axial and planar chirality[25,26] and for chirality transfer in C_3-symmetric compounds.[27] For instance, to the imidazole cyclopeptide **1**, three arms can be attached by simple alkylation of the secondary nitrogen atoms of the imidazoles (red arrows in Fig. 1).[28] The resulting tripodal system is able to transfer chiral information via these three arms from its scaffold to a distant metal or non-metal centre.[29] The C_3-symmetric oxazole-containing scaffolds **2a**–**4a** exhibit three easily modifiable functional groups (blue arrows in Fig. 1), which are coupling sites for the synthesis of ligands forming diastereoselective octahedral metal complexes.[30] Moreover, we were able to synthesize the first configurationally

Abbreviations: Bn, benzyl; Boc, *tert*-butyloxycarbonyl; DCM, dichloromethane; DMF, *N*,*N*-dimethylformamide; NMM, *N*-methylmorpholine; PhtN, phthalimido; PyBOP, benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate; THF, tetrahydrofuran; TFA, trifluoroacetic acid; Z, benzyloxycarbonyl.

* Corresponding author. Tel.: +49 201 183 3615; fax: +49 201 183 4252.
E-mail address: gebhard.haberhauer@uni-due.de (G. Haberhauer).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.01.047

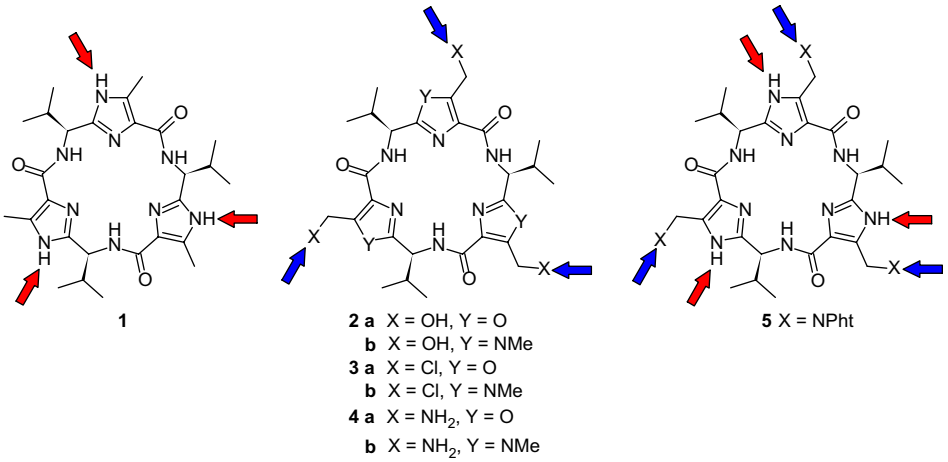


Figure 1. Structural formula of chiral macrocyclic scaffolds with three or six anchoring sites.

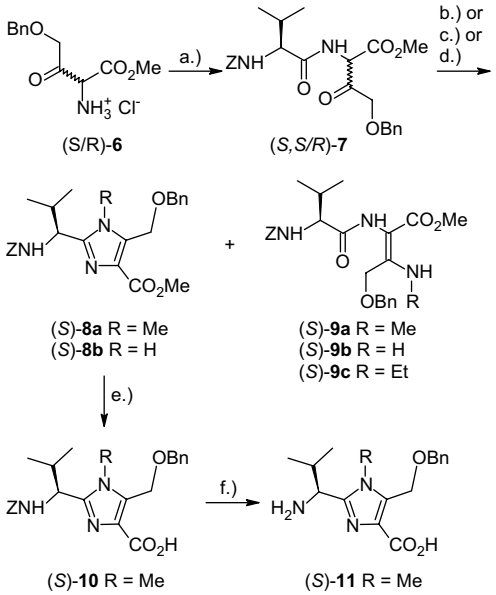
stable, propeller-like triarylphosphine by linking a triphenylphosphine moiety via three peptide bonds to the chiral scaffold **4a**.[31]

Herein we report the synthesis of threefold substitutable *N*-methylimidazole scaffolds **2b**–**4b**, which are insofar of interest as the structure and the flexibility of synthetic analogues of *Westiellamide* depends on the used azole system.[32] Furthermore, the synthesis of the C_3-symmetric scaffold **5** with six anchoring sites for two sets of further substituents (red and blue arrows in Fig. 1) is presented.

2. Results and discussion

2.1. Synthesis

The synthesis of the tripodal imidazole platforms **2b** and **3b** starts from aminoketone **6** (Scheme 1). Peptide coupling of **6** with *Z*-(*S*)-valine using isobutyl chloroformate gave amidoketone **7**, which can smoothly be converted to the *N*-methylimidazole ester **8a** upon treatment with methylamine and trifluoroacetic acid in refluxing xylene. As a side product enamine **9a** could be detected in ESI mass spectra of the reaction mixture, but chromatography gave only **8a**. However, if ammonia along with trifluoroacetic acid were used for intramolecular condensation, a mixture of the corresponding imidazole ester **8b** and the enamine **9b** was obtained, which couldn't be separated upon column chromatography due to their identical polarity. Any attempts to drive imidazole formation to completion failed. Prolongated reaction time resulted in lower total product yield without affecting the **8b**/**9b** ratio of almost 2:3 as judged by ^{1}H NMR spectra. This may be explained by the preferential formation of the (*E*)-configurated enamine, which cannot undergo cyclization due to steric inaccessibility. In addition, we attempted to synthesize the corresponding *N*-ethylimidazole ester. Using ethylamine under the same conditions led to the fast formation of the enamine **9c**, but no imidazole could be isolated.

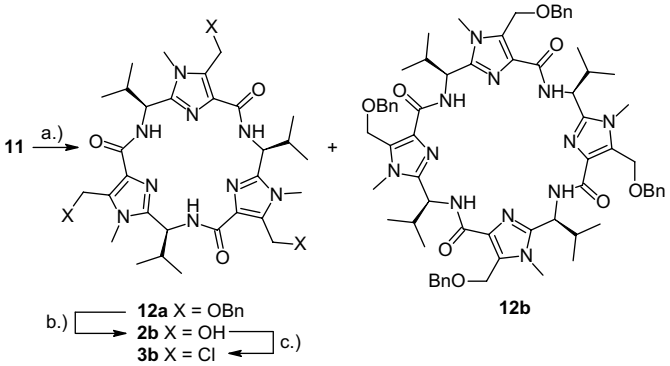


Scheme 1. Reagents and conditions: (a) Z-(*S*)-Val-OH, *i*BuOCOCl, NMM, DCM, −50 °C, 65%; (b) TFA, $MeNH_2$/EtOH, xylene, Δ, 69% for **8a**; (c) TFA, NH_3/MeOH, xylene, Δ, 75% (mixture of **8b** and **9b**); (d) TFA, $EtNH_2$/H_2O, xylene, Δ, 70% for **9c**; (e) aq NaOH, MeOH, dioxane, 20 °C then aq HCl, 99%; (f) 1,4-cyclohexadiene, EtOH, $Pd(OH)_2$/C, 20 °C, 97%.

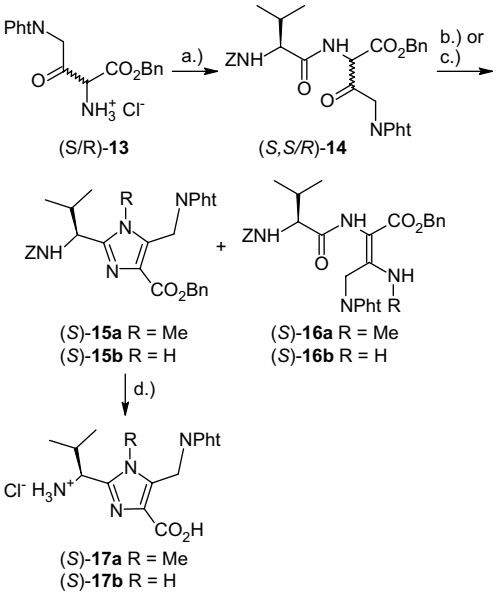
Saponification of *N*-methylimidazole ester **8a** afforded carboxylic acid **10**, which could be selectively deprotected upon reduction with 1,4-cyclohexadiene and palladium(II)hydroxide catalyst.[33]

The unprotected imidazole **11** was treated with PyBOP and Hünig's base in DMF to obtain cyclohexapeptide **12a** and cyclooctapeptide **12b** with moderate total yield (Scheme 2). Debenzylation of **12a** was accomplished by catalytic hydrogenation in dichloromethane to afford the threefold alcohol **2**. The tripodal chloride platform **3** could be obtained upon treatment of **2** with thionyl chloride in chloroform.

The synthesis of chiral imidazole scaffolds **4b** and **5** is based on the phthalimido-substituted aminoketone **13**. Peptide coupling and



Scheme 2. Reagents and conditions: (a) PyBOP, *i*Pr_2NEt, DMF, 20 °C, 21% for **12a** and 9% for **12b**; (b) H_2, Pd/C, DCM, 97%; (c) $SOCl_2$, $CHCl_3$, Δ, 99%.



Scheme 3. Reagents and conditions: (a) Z-(*S*)-Val-OH, *i*BuOCOCl, NMM, DCM, −30 °C, 88%; (b) TFA, $MeNH_2$/EtOH, xylene, Δ, 63% for **15a** and 7% for **16a**; (c) TFA, NH_3/MeOH, xylene, Δ, 34% for **15b** and 44% for **16b**; (d) H_2, Pd/C, MeOH, aq HCl, 99% for **17a**, 99% for **17b**.

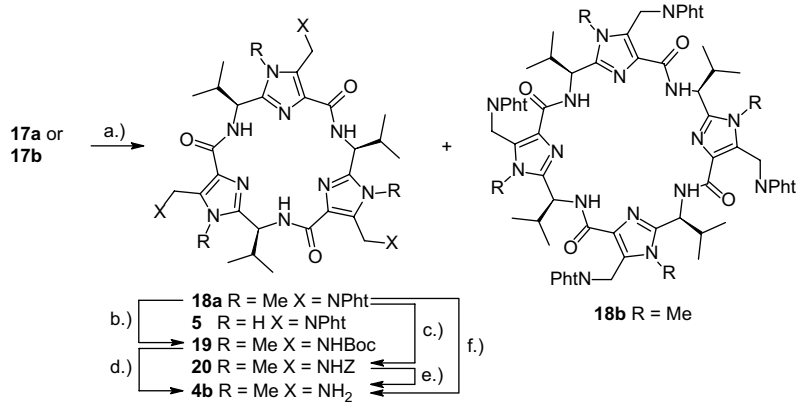
imidazole formation were performed according to standard procedures (Scheme 3). Reaction of amidoketone **14** with methylamine or ammonia gave the corresponding imidazoles **15a**,**b** along with enamines **16a**,**b**. In the case of ammonia the yield of the imidazole ester **15b** remained rather low and enamine **16b** was isolated as major product. Neither longer reaction times nor treatment of the isolated **16b** with different strong acids (TFA, TsOH, H_3PO_4) in refluxing xylene enhanced the yield of **15b**. Hydrogenolytic cleavage of both benzyloxycarbonyl and benzyl ester protective groups in one step afforded the hydrochloride salts **17a** and **17b**, respectively.

Cyclooligomerisation of imidazole **17a** using the same protocol as above led to the cyclic trimer **18a** and cyclic tetramer **18b**, while in the case of **17b** only the cyclic trimer **5** could be isolated (Scheme 4). The yields for the C_3-symmetric platforms are quiet good and vary between 40 and 51%. Hydrazinolysis of platform **18a** followed by acidic work-up afforded the tripodal amine scaffold **4b** as hydrochloride salt. In addition, the threefold Boc and *Z*-protected amine scaffolds **19** and **20** were synthesized. Exchange of the phthalimido side arms with Boc protecting groups followed by the nonaqueous cleavage of **19** proved to be the most convenient method for the preparation of the triamine **4b**.

2.2. Structural investigations

The structures of the imidazole tripodal scaffolds **2b**–**4b** and of the oxazole cyclopeptides **2a**–**4a**[30] were determined by geometry optimizations at B3LYP/6-31G* level of theory.[34] The optimized structures show a bowl-like conformation where the isopropyl groups adopt a quasi-axial orientation on the convex-side of the 18-membered backbone. The conformers of the individual cyclopeptides differ only in the orientation of the CH_2X-group relative to the cycle. The peptide backbone of the conformers is essentially the same, thus suggesting that the cyclic peptides are indeed rigid. For simplicity only the conformers were calculated in which the dihedral angles of the valine side-chains around the C_α–C_β bond have the same values as those found in solid structures obtained for analogous systems.[35] In the case of the tripodal alcohol platforms **2a**,**b** the hydroxyl groups are involved in intramolecular hydrogen bonds with the neighboring amide oxygens of the peptide backbone (Fig. 2). In the case of oxazole platform **2a** the C_3-symmetric conformations with hydrogen bonded side arms are 76–79 kJ mol^{-1} stabilized in favor of the conformations with free hydroxymethyl groups. However, the hydrogen bonded conformations of the imidazole trialcohol **2b** are only stabilized by 51–54 kJ mol^{-1}. This effect is probably due to the different shapes of the scaffolds. In the oxazole platforms **2a**–**4a** the cone angle defined by the plane of the aromatic rings ranges from 113° to 121°, while for the imidazole macrocycles **2b**–**4b** it only varies between 93° and 105°. The change of the cone angle is affected mainly by the dihedral angles $C_{carbonyl}$–N_{amide}–C_α–C_{azole} and N_{amide}–C_α–C_{azole}–Y_{azole} in the 18-membered backbone (definition for the used abbreviations see Fig. 3). This difference in the conformations can be well explained by the strong interaction of the $\pi(C_{azole}–N_{azole})$-orbital of the imidazole ring with the almost parallel $\sigma^*(C_\alpha–N_{amide})$-orbital, while in the case of the oxazoles the interaction of the $\pi^*(C_{azole}–N_{azole})$-orbitals with the $\sigma(C_\alpha–C_\beta)$ and $\sigma(C_\alpha–H_\alpha)$-orbitals is more distinctive, thus resulting in a nearly coplanar arrangement of the oxazole rings.[32]

The H–N_{amide}–C_α–H dihedral angles obtained from the optimized structures are in good agreement with the data obtained from the corresponding $^3J_{H,H}$ coupling constants of the ^{1}H NMR spectra using the Karplus equation[36] (Table 1), which is an evidence that in apolar solvents platforms **2** and **3** exist in a structure quiet similar to that calculated in the gas phase. This also applies to the



Scheme 4. Reagents and conditions: (a) PyBOP, *i*Pr_2NEt, DMF, 20 °C, 51% for **18a** and 8% for **18b** (starting from **17a**); 40% for **5** (starting from **17b**); (b) $N_2H_4·H_2O$, THF/DCM/EtOH then Boc_2O, 20 °C, 97%; (c) (1) $N_2H_4·H_2O$, THF/DCM/EtOH, 20 °C, (2) ZCl, Et_3N, DCM, 20 °C, 77%; (d) HCl/EtOAc, 20 °C, 99%; (e) H_2, Pd/C, aq HCl, MeOH, 88%; (f) $N_2H_4·H_2O$, THF/DCM/EtOH, 20 °C then acidic work-up, 74%.

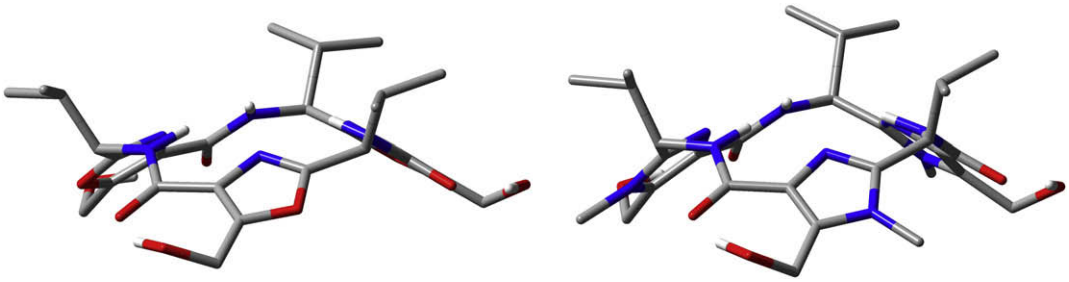


Figure 2. Molecular structures of the energetically preferred conformers of **2a** and **2b** calculated using B3LYP/6-31G*; all non-polar hydrogen atoms have been omitted for clarity.

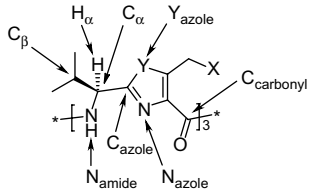


Figure 3. Definition of the used abbreviations.

Table 1
Dihedral angles H–N_{amide}–C_{α}–H and distances in **2**, **3**, and **4**

Scaffold	$^3J_{H,H}$ [Hz]	Dihedral angles [°] calculated by		Distance *a* [Å] between neighboring C_{CH_2X}–C_{CH_2X}
		Karplus equation	B3LYP/6-31G*	
2a	7.8	147	153	9.59
3a	7.9	148	150	9.58
4a	7.9	148	152	9.59
2b	9.5	162	162	9.25
3b	9.1	158	161	9.15
4b	9.4	161	163	9.12

triamine scaffolds **4**, which could be isolated as hydrochloride salts, of which ^{1}H NMR spectra were measured in MeOH-d_4. The slow H/D exchange of the amide protons allowed the evaluation of the coupling constants.

Due to the different shapes, the distance between two adjacent C_{CH_2X}-atoms in the oxazole-containing cyclopeptides **2a**–**4a** is around 9.6 Å, while in the imidazole peptides **2b**–**4b** this distance has a value of only 9.12–9.25 Å (Table 1). This distance is of importance in that the C_{CH_2X}-atoms can serve as anchor groups for further functional units. As a matter of course, the functioning of these groups essentially depends on the distance between each other. Interestingly, the difference in this distance between the oxazole **2a**–**4a** and imidazole cyclopeptides **2b**–**4b** (around 0.3–0.4 Å) is not as large as the difference found for the unsubstituted analogues (X=H), where a value of 1.0 Å was calculated.[32]

3. Conclusion

In summary, we could synthesize the chiral C_3-symmetric macrocyclic imidazoles **2b**–**4b** bearing three functional groups. The distance between the anchoring groups in the imidazole macrocycles **2b**–**4b** is smaller than that calculated for the known corresponding oxazole macrocycles **2a**–**4b**. This expands our toolbox of rigid 18-membered core molecules with various diameters and a variety of anchoring groups. The macrocycle **5** possesses even six anchoring sites, where N-alkylation of the imidazole rings followed by deprotection and N-acylation of the aminomethyl side arms should allow its convenient utilization as a central building block. Applications of the presented scaffolds for the construction of ligands and molecular devices are part of our current investigations.

4. Experimental section

4.1. General remarks

All chemicals were reagent grade and used as purchased. Reactions were monitored by TLC analysis using silica gel 60 F_{254} thin layer plates. Flash chromatography was carried out on silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were measured on Bruker Avance DMX 300 and Avance DRX 500 spectrometers. All chemical shifts (δ) are given in parts per million relative to TMS. The spectra were referenced to deuterated solvents indicated in brackets in the analytical data. HRMS spectra were recorded with a Bruker BioTOF III Instrument. IR spectra were measured on a Varian 3100 FT-IR Excalibur Series spectrometer. UV–vis absorption spectra were obtained with a Varian Cary 300 Bio spectrophotometer.

4.2. Preparation of scaffolds 2b and 3b

*4.2.1. (2RS,2′S)-4-Benzyloxy-2-{[2′-(benzyloxycarbonylamino)-3′-methylbutanoyl]amino}-3-oxobutanoic acid methyl ester (**7**)*

Z-(*S*)-Valine (15.077 g, 60.0 mmol) and NMM (6.069 g, 60.0 mmol) were dissolved in dry DCM (180 mL) under Ar, then cooled to −30 °C and isobutyl chloroformate (8.195 g, 60.0 mmol) in DCM (60 mL) was slowly added. After complete addition the resulting solution was maintained at −30 to −25 °C for 60 min, then cooled down to −50 °C, while aminoketone **6** (16.423 g, 60.0 mmol) was placed in a second round-bottom flask equipped with a mechanical stirrer and cooled to −50 °C. Mixing of the components was achieved by injecting the cold solution via a double-tipped needle to the solid followed by the addition of a second equivalent of NMM (6.069 g, 60.0 mmol) in DCM (30 mL) over a period of 30 min. While stirred vigorously the mixture was allowed to warm up to room temperature within 3 h. The mixture was then diluted with DCM (300 mL) and extracted with water (1×100 mL), 1 M $KHSO_4$ (1×100 mL), and brine (1×100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting thick oil was subjected to column chromatography on silica gel (DCM/EtOAc 95:5→70:30) to yield 18.229 g (65%) of **7** (1:1 mixture of two diastereomers) as a yellowish oil.

TLC: R_f=0.37 (DCM/EtOAc 90:10; silica). ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.36–7.29 (m, 10H, Z and Bn *CH*-2,3,4,5,6), 7.11 (d, $^3J_{H,H}$=5.7 Hz, 1H, amide *NH*), 5.44–5.40 (2×d, 2H, Z *NH* and *CHCO*$_2$*Me*), 5.12 (d, $^2J_{H,H}$=12.2 Hz, 1H, Z *CH*$_2$), 5.08 (d, $^2J_{H,H}$=12.2 Hz, 1H, Z *CH*$_2$), 4.62 (d, $^2J_{H,H}$=12.2 Hz, 1H, *PhCH*$_2$*O*), 4.59 (d, $^2J_{H,H}$=12.2 Hz, 1H, *PhCH*$_2$*O*), 4.42 (d, $^2J_{H,H}$=17.6 Hz, 1H, *BnOCH*$_2$*CO*), 4.35 (d, $^2J_{H,H}$=17.6 Hz, 1H, *BnOCH*$_2$*CO*), 4.19 (dd, $^3J_{H,H}$=8.0 Hz, $^3J_{H,H}$=6.0 Hz, 1H, Val α-*CH*), 3.73 (s, 3H, *CO*$_2$*CH*$_3$), 2.18–2.12 (m, 1H, Val β-*CH*), 0.97 (d, $^3J_{H,H}$=6.8 Hz, 3H, Val *CH*$_3$), 0.92 (d, $^3J_{H,H}$=6.8 Hz,

3H, Val C***H***$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=198.9 (q, ***C***O), 171.2 (q, amide ***C***ONH), 166.0 (q, ***C***O$_2$Me), 156.3 (q, Z ***C***ONH), 136.7 (q, Z ***C***-1), 136.1 (q, Bn ***C***-1), 128.49 (t, Ph ***C***H), 128.14 (t, Ph ***C***H), 128.10 (t, Ph ***C***H), 128.03 (t, Ph ***C***H), 128.00 (t, Ph ***C***H), 127.98 (t, Bn ***C***H), 73.62 (s, BnO***C***H$_2$), 73.49 (s, Ph***C***H$_2$O), 67.1 (s, Z ***C***H$_2$), 59.8 (t, ***C***HCO$_2$Me), 58.8 (t, Val α-***C***H), 53.4 (p, CO$_2$***C***H$_3$), 31.1 (t, Val β-***C***H), 19.0 (p, Val ***C***H$_3$), 17.5 (p, Val ***C***H$_3$) ppm. IR (KBr): ν=3289, 3066, 3035, 2959, 2898, 2872, 1731, 1689, 1651, 1541, 1455, 1436, 1390, 1333, 1291, 1250, 1146, 1044, 970, 912, 860, 842, 733, 695 cm^{-1}. UV–vis (DCM): λ_{max} (log ε)=253 (2.72), 258 (2.77), 264 (2.72), 283 (2.30) nm. ESI-HRMS: *m*/*z* calcd for $[C_{25}H_{31}N_2O_7]^+$ 471.2126, found 471.2113.

4.2.2. (1′S)-2-[1′-(Benzyloxycarbonylamino)-2′-methylpropyl]-5-(benzyloxymethyl)-4-methoxycarbonyl-1-methyl-1H-imidazole (**8a**)

To a slurry of amidoketone **7** (9.410 g, 20.0 mmol) in xylene (300 mL), TFA (6.0 mL, 80.0 mmol) and 8 M methylamine in EtOH (7.5 mL, 60.0 mmol) were added. The mixture was heated under intensive reflux with a Dean–Stark trap for 2 h while the trap was discharged (~10 mL) every 15 min. After completion of the reaction, volatiles were removed in a rotary evaporator. The residual solid was subjected to column chromatography on silica gel (DCM/EtOAc/MeOH 75:25:0→75:25:3) to obtain 6.462 g (69%) of **8a** as a white fluffy solid.

TLC: R_f=0.40 (DCM/EtOAc/MeOH 75:25:0; silica). Mp: 140 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.35–7.28 (m, 10H, Z and Bn C***H***-2,3,4,5,6), 5.61 (d, $^3J_{H,H}$=9.5 Hz, 1H, Z N***H***), 5.10 (d, $^2J_{H,H}$=12.4 Hz, 1H, Z C***H***$_2$), 5.04 (d, $^2J_{H,H}$=12.4 Hz, Z C***H***$_2$), 4.98 (d, $^2J_{H,H}$=12.7 Hz, 1H, C***H***$_2$OBn), 4.93 (d, $^2J_{H,H}$=12.7 Hz, 1H, C***H***$_2$OBn), 4.59 (t, $^3J_{H,H}$=9.2 Hz, 1H, Val α-C***H***), 4.54 (d, $^2J_{H,H}$=11.9 Hz, 1H, PhC***H***$_2$O), 4.52 (d, $^2J_{H,H}$=11.9 Hz, 1H, PhC***H***$_2$O), 3.86 (s, 3H, CO$_2$C***H***$_3$), 3.68 (s, 3H, NC***H***$_3$), 2.30–2.22 (m, 1H, Val β-C***H***), 1.03 (d, 3H, $^3J_{H,H}$=6.7 Hz, Val C***H***$_3$), 0.82 (d, 3H, $^3J_{H,H}$=6.7 Hz, Val C***H***$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=163.7 (q, ***C***O$_2$Me), 156.3 (q, Z ***C***ONH), 149.7 (q, imidazole ***C***-2), 137.6 (q, Bn ***C***-1), 136.3 (q, Z ***C***-1), 134.5 (q, imidazole ***C***-5), 130.0 (q, imidazole ***C***-4), 128.41 (t, Z/Bn ***C***H), 128.40 (t, Z/Bn ***C***H), 128.0 (t, Z/Bn ***C***H), 127.92 (t, Z/Bn ***C***H), 127.87 (t, Z/Bn ***C***H), 127.79 (t, Z/Bn ***C***H), 72.2 (s, Ph***C***H$_2$O), 66.8 (s, Z ***C***H$_2$), 60.4 (s, ***C***H$_2$OBn), 52.7 (t, Val α-***C***H), 51.7 (p, CO$_2$***C***H$_3$), 33.2 (t, Val β-***C***H), 30.9 (p, N***C***H$_3$), 19.5 (p, Val ***C***H$_3$), 18.7 (p, Val ***C***H$_3$) ppm. IR (KBr): ν=3296, 3090, 3066, 3035, 3001, 2980, 2956, 2925, 2869, 2799, 1688, 1578, 1536, 1455, 1414, 1362, 1324, 1302, 1256, 1225, 1199, 1155, 1123, 1092, 1061, 1026, 996, 939, 917, 879, 795, 776, 740, 695, 611, 591, 515 cm^{-1}. UV–vis (DCM): λ_{max} (log ε)=248 (4.68), 289 (3.62) nm. ESI-HRMS: *m*/*z* calcd for $[C_{26}H_{32}N_3O_5]^+$ 466.2336, found 466.2346.

4.2.3. (1′S)-2-[1′-(Benzyloxycarbonylamino)-2′-methylpropyl]-5-(benzyloxymethyl)-1-methyl-1H-imidazole-4-carboxylic acid (**10**)

Imidazole ester **8a** (9.311 g, 20.0 mmol) was dissolved in a mixture of methanol (120 mL) and dioxane (80 mL) followed by slow addition of 2 M NaOH solution (50 mL, 100.0 mmol) at 0 °C. The ice bath was removed and stirring was continued overnight. After TLC showed consumption of the starting material the mixture was diluted with brine (400 mL) and acidified with 2 M HCl (100 mL). The mixture was then repeatedly extracted with DCM (3×100 mL), the organic layers were combined, dried over $MgSO_4$, filtered, and the filtrate was concentrated in vacuo to give 8.962 g (99%) of the free acid **10** as a white powder, which was used without further purification for the next step.

TLC: R_f=0.30 (DCM/EtOAc/MeOH 75:25:5; silica). Mp: 73 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.54 (br s, 1H, CO$_2$***H***), 7.89 (br s, 1H, Z CON***H***), 7.35–7.20 (m, 10H, Z and Bn C***H***-2,3,4,5,6), 5.11 (d, $^2J_{H,H}$=12.5 Hz, 1H, C***H***$_2$OBn), 5.06 (d, $^2J_{H,H}$=13.2 Hz, 1H, Z C***H***$_2$), 4.99 (d, $^2J_{H,H}$=12.5 Hz, 1H, C***H***$_2$OBn), 4.93 (d, $^2J_{H,H}$=13.2 Hz, 1H, Z C***H***$_2$), 4.62 (t, $^3J_{H,H}$=9.6 Hz, 1H, Val α-C***H***), 4.50 (s, 2H, PhC***H***$_2$O), 3.87 (s, 3H, NC***H***$_3$), 2.75–2.67 (m, 1H, Val β-C***H***), 1.15 (d, $^3J_{H,H}$=6.5 Hz, 3H, Val C***H***$_3$), 0.74 (d, $^3J_{H,H}$=6.5 Hz, 3H, Val C***H***$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=157.0 (q, ***C***O$_2$H), 150.0 (q, Z ***C***ONH), 137.0 (q, imidazole ***C***-2), 136.2 (q, Bn ***C***-1), 134.1 (q, Z ***C***-1), 128.51 (t, Z ***C***H-2,6), 128.46 (q, imidazole ***C***-5), 128.35 (t, Bn ***C***H-2,6), 128.14 (t, Z ***C***H-4), 128.06 (t, Bn ***C***H-3,5), 127.86 (t, Bn ***C***H-4), 127.58 (t, Z ***C***H-3,5), 127.0 (q, imidazole ***C***-4), 72.9 (s, Ph***C***H$_2$O), 67.0 (s, Z ***C***H$_2$), 59.6 (s, ***C***H$_2$OBn), 53.4 (t, Val α-***C***H), 32.6 (p, N***C***H$_3$), 32.2 (t, Val β-***C***H), 19.7 (p, Val ***C***H$_3$), 19.4 (p, Val ***C***H$_3$) ppm. IR (KBr): ν=3405, 3242, 3032, 2965, 2874, 1716, 1635, 1518, 1455, 1373, 1317, 1272, 1236, 1191, 1068, 1027, 913, 869, 742, 699 cm^{-1}. ESI-HRMS: *m*/*z* calcd for $[C_{25}H_{30}N_3O_5]^+$ 452.2180, found 452.2182.

4.2.4. (1′S)-2-(1′-Amino-2′-methylpropyl)-5-(benzyloxymethyl)-1-methyl-1H-imidazole-4-carboxylic acid (**11**)

To a solution of imidazole carboxylic acid **10** (4.515 g, 10.0 mmol) in MeOH (200 mL) Pd(OH)$_2$-catalyst (20 wt% Pd on charcoal, 1.000 g) and 1,4-cyclohexadiene (12.020 g, 150.0 mmol) were added at room temperature. The mixture was stirred vigorously for 90 min, then a second portion of 1,4-cyclohexadiene (4.007 g, 50.0 mmol) was added followed by stirring for further 30 min. After completion (control by ESI-MS) the catalyst was filtered off and the filtrate was evaporated to obtain 3.084 g (97%) of **11** as a colorless solid.

Mp: 115 °C. ^{1}H NMR (500 MHz, MeOH-d_4): δ=7.33–7.30 (m, 5H, Ph C***H***-2,3,4,5,6), 4.95 (s, 2H, C***H***$_2$OBn), 4.54 (d, $^2J_{H,H}$=11.7 Hz, 1H, PhC***H***$_2$O), 4.51 (d, $^2J_{H,H}$=11.7 Hz, 1H, PhC***H***$_2$O), 4.40 (d, $^3J_{H,H}$=8.3 Hz, 1H, Val α-C***H***), 3.70 (s, 3H, NC***H***$_3$), 2.40–2.33 (m, 1H, Val β-C***H***), 1.12 (d, $^3J_{H,H}$=6.8 Hz, 3H, Val C***H***$_3$), 0.89 (d, $^3J_{H,H}$=6.8 Hz, 3H, Val C***H***$_3$) ppm. ^{13}C NMR (125 MHz, MeOH-d_4): δ=166.8 (q, ***C***O$_2$H), 146.2 (q, imidazole ***C***-2), 139.3 (q, Ph ***C***-1), 136.2 (q, imidazole ***C***-5), 129.48 (t, Ph ***C***H-2,6), 129.11 (t, Ph ***C***H-3,5), 128.94 (t, Ph ***C***H-4), 132.5 (q, imidazole ***C***-4), 73.5 (s, Ph***C***H$_2$O), 61.4 (s, ***C***H$_2$OBn), 53.3 (t, Val α-***C***H), 33.9 (t, Val β-***C***H), 31.8 (p, N***C***H$_3$), 18.8 (p, Val ***C***H$_3$) ppm. IR (KBr): ν=3425, 3030, 2967, 2877, 1990, 1967, 1706, 1603, 1507, 1476, 1455, 1394, 1376, 1356, 1225, 1193, 1062, 1027, 1007, 934, 869, 822, 802, 771, 743, 699 cm^{-1}. UV–vis (MeOH): λ_{max} (log ε)=209 (4.08), 214 (sh., 4.06), 224 (sh., 3.99) nm. ESI-HRMS: *m*/*z* calcd for $[C_{17}H_{24}N_3O_3]^+$ 318.1812, found 318.1838.

4.2.5. Scaffolds **12a**,**b**

To a solution of the free amino acid **11** (1.587 g, 5.0 mmol) in anhydrous DMF (125 mL), PyBOP (3.903 g, 7.5 mmol) was added at room temperature followed by the addition of *i*Pr$_2$NEt (4.201 g, 32.5 mmol), and the mixture was stirred under Ar for 3 days. For work-up MeOH (20 mL) was added and the solvents were removed in a rotary evaporator. The remaining brown slurry was taken up in EtOAc (500 mL), then washed with 2 M HCl (2×50 mL), water (1×50 mL), concd sodium bicarbonate (1×50 mL), water (1×50 mL), and brine (1×50 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated, and the oily residue was subjected to column chromatography on silica gel (DCM/EtOAc/MeOH 75:25:0→75:25:5). Separation of the products was completed by a second chromatographic step on silica gel using PE/EtOAc (20:80→0:100) to obtain 0.319 g (21%) of imidazole trimer **12a** and 0.128 g (8.5%) of imidazole tetramer **12b** as white powders.

*4.2.5.1. Data for cyclic trimer **12a**.* TLC: R_f=0.60 (DCM/EtOAc/MeOH 75:25:5; silica), R_f=0.55 (EtOAc; silica). Mp: >200 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.52 (d, $^3J_{H,H}$=9.3 Hz, 1H, amide N***H***), 7.29–7.20 (m, 5H, Ph C***H***-2,3,4,5,6), 5.17 (dd, $^3J_{H,H}$=9.3, 5.7 Hz, 1H, Val α-C***H***), 5.12 (d, $^2J_{H,H}$=12.8 Hz, 1H, C***H***$_2$OBn), 5.04 (d, $^2J_{H,H}$=12.8 Hz, 1H, C***H***$_2$OBn), 4.52 (d, $^2J_{H,H}$=11.4 Hz, 1H, PhC***H***$_2$O), 4.48 (d, $^2J_{H,H}$=11.4 Hz, 1H, PhC***H***$_2$O), 3.63 (s, 3H, NC***H***$_3$), 2.17–2.08 (m, 1H, Val β-C***H***), 1.07 (d, $^3J_{H,H}$=6.8 Hz, 3H, Val C***H***$_3$), 1.05 (d, $^3J_{H,H}$=6.8 Hz, 3H, Val C***H***$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=162.5 (q, ***C***ONH), 148.2 (q, imidazole ***C***-2), 138.0 (q, Ph ***C***-1), 131.9 (q, imidazole ***C***-5), 131.2 (q, imidazole ***C***-4), 128.22 (t, Ph ***C***H-2,6), 127.81 (t, Ph ***C***H-3,5), 127.57 (t, Ph ***C***H-4),

72.0 (s, *PhCH$_2$O*), 60.6 (s, *CH$_2$OBn*), 49.4 (t, Val α-*CH*), 34.7 (t, Val β-*CH*), 30.8 (p, *NCH$_3$*), 19.5 (p, Val *CH$_3$*), 17.7 (p, Val *CH$_3$*) ppm. CD (MeOH): λ_{max} ($\Delta\varepsilon$ [dm^3 mol^{-1} cm^{-1}])=220 (+17.3), 239 (0.0), 256 (−62.0) nm. ESI-HRMS: *m*/*z* calcd for $[C_{51}H_{64}N_9O_6]^+$ 898.4970, found 898.5101.

*4.2.5.2. Data for cyclic tetramer **12b**.* TLC: R_f=0.60 (DCM/EtOAc/MeOH 75:25:5; silica), R_f=0.70 (EtOAc; silica). Mp: 158 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.62 (d, $^3J_{H,H}$=9.4 Hz, 1H, amide *NH*), 7.24–7.19 (m, 5H, Ph *CH*-2,3,4,5,6), 5.08 (d, $^2J_{H,H}$=12.6 Hz, 1H, *CH$_2$OBn*), 4.94 (t, $^3J_{H,H}$=9.4 Hz, 1H, Val α-*CH*), 4.89 (d, $^2J_{H,H}$=12.6 Hz, 1H, *CH$_2$OBn*), 4.48 (d, $^2J_{H,H}$=11.6 Hz, 1H, *PhCH$_2$O*), 4.45 (d, $^2J_{H,H}$=11.6 Hz, 1H, *PhCH$_2$O*), 3.73 (s, 3H, *NCH$_3$*), 2.50–2.40 (m, 1H, Val β-*CH*), 1.11 (d, $^3J_{H,H}$=6.7 Hz, 3H, Val *CH$_3$*), 0.87 (d, $^3J_{H,H}$=6.7 Hz, 3H, Val *CH$_3$*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=162.9 (q, *CONH*), 148.5 (q, imidazole *C*-2), 138.0 (q, Ph *C*-1), 131.8 (q, imidazole *C*-4), 131.2 (q, imidazole *C*-5), 128.28 (t, Ph *CH*-2,6), 127.92 (t, Ph *CH*-3,5), 127.67 (t, Ph *CH*-4), 72.2 (s, *PhCH$_2$O*), 60.7 (s, *CH$_2$OBn*), 49.6 (t, Val α-*CH*), 32.6 (t, Val β-*CH*), 30.9 (p, *NCH$_3$*), 19.8 (p, Val *CH$_3$*), 19.1 (p, Val *CH$_3$*) ppm. CD (DCM): λ_{max} ($\Delta\varepsilon$ [dm^3 mol^{-1} cm^{-1}])=231 (+30.7), 243 (0.0), 258 (−63.7) nm. ESI-HRMS: *m*/*z* calcd for $[C_{68}H_{85}N_{12}O_8]^+$ 1197.6608, found 1197.6745.

*4.2.6. Scaffold **2b***

To a solution of **12a** (0.090 g, 0.10 mmol) in DCM (100 mL), palladium–charcoal catalyst (10 wt% Pd, 0.150 g) was added, and the mixture was stirred under hydrogen atmosphere (10^5 Pa) at room temperature for 60 min. Then the catalyst was removed by filtration and the solvent was distilled off in a rotary evaporator to yield 0.057 g (97%) of **2b** as a colorless solid.

Mp: >200 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.46 (d, $^3J_{H,H}$=9.4 Hz, 1H, amide *NH*), 5.66 (t, $^3J_{H,H}$=6.6 Hz, 1H, *CH$_2$OH*), 5.06 (dd, $^3J_{H,H}$=9.4, 6.1 Hz, 1H, Val α-*CH*), 4.97 (dd, $^3J_{H,H}$=14.4, 7.0 Hz, 1H, *CH$_2$OH*), 4.67 (dd, $^2J_{H,H}$=14.4 Hz, $^3J_{H,H}$=6.1 Hz, 1H, *CH$_2$OH*), 3.60 (s, 3H, *NCH$_3$*), 2.14–2.07 (m, 1H, Val β-*CH*), 1.03 (d, $^3J_{H,H}$=6.8 Hz, 6H, Val *CH$_3$*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=163.4 (q, *CONH*), 147.3 (q, imidazole *C*-2), 136.2 (q, imidazole *C*-5), 130.6 (q, imidazole *C*-4), 54.4 (s, *CH$_2$OH*), 49.7 (t, Val α-*CH*), 34.8 (t, Val β-*CH*), 30.8 (s, *NCH$_3$*), 19.4 (p, Val *CH$_3$*), 17.8 (p, Val *CH$_3$*) ppm. CD (MeOH): λ_{max} ($\Delta\varepsilon$ [dm^3 mol^{-1} cm^{-1}])=223 (+15.8), 243 (0.0), 252 (−60.5) nm. ESI-HRMS: *m*/*z* calcd for $[C_{30}H_{45}N_9O_6]^+$ 628.3644, found 628.3566.

*4.2.7. Scaffold **3b***

A solution of **2b** (0.063 g, 0.10 mmol) in $CHCl_3$ (10 mL) was mixed with thionyl chloride (0.119 g, 1.0 mmol) for 15 min, then evaporated and dried in vacuo to give 0.068 g (99%) of **3b** as a colorless solid.

Mp: 145 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.41 (d, $^3J_{H,H}$=9.1 Hz, 1H, amide *NH*), 5.16 (d, $^2J_{H,H}$=12.5 Hz, 1H, *CH$_2$Cl*), 5.15 (dd, $^3J_{H,H}$=9.0, 6.3 Hz, 1H, Val α-*CH*), 5.11 (d, 1H, $^2J_{H,H}$=12.5 Hz, *CH$_2$Cl*), 3.67 (s, 3H, *NCH$_3$*), 2.18–2.11 (m, 1H, Val β-*CH*), 1.06 (d, $^3J_{H,H}$=6.7 Hz, 3H, Val *CH$_3$*), 1.05 (d, 3H, $^3J_{H,H}$=6.7 Hz, Val *CH$_3$*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=162.1 (q, *CONH*), 148.9 (q, imidazole *C*-2), 131.5 (q, imidazole *C*-4), 130.3 (q, imidazole *C*-5), 49.7 (t, Val α-*CH*), 34.8 (t, Val β-*CH*), 33.8 (s, *CH$_2$Cl*), 30.7 (p, *NCH$_3$*), 19.5 (p, Val *CH$_3$*), 18.0 (p, Val *CH$_3$*) ppm. CD (DCM): λ_{max} ($\Delta\varepsilon$ [dm^3 mol^{-1} cm^{-1}])=233 (+10.8), 246 (0.0), 254 (−62.5) nm. ESI-HRMS: *m*/*z* calcd for $[C_{30}H_{42}Cl_3N_9O_3]^+$ 684.2525, found 684.2553.

4.3. Preparation of scaffolds 4b and 5

*4.3.1. (2RS,2′S)-2-{[2′-(Benzyloxycarbonylamino)-3′-methylbutanoyl]amino}-3-oxo-4-phthalimidobutanoic acid benzyl ester (**14**)*

In a round-bottomed flask equipped with a mechanical stirrer, Z-(*S*)-Val-OH (15.077 g, 60.0 mmol) was dissolved in dry DCM (300 mL) and NMM (6.069 g, 60.0 mmol) was added. The solution was cooled to −30 °C and a solution of isobutyl chloroformate (8.195 g, 60.0 mmol) in DCM (60 mL) was added while the inner temperature was maintained at −30 to −25 °C. After further 60 min ketoamine **13** (23.328 g, 60.0 mmol) was added in one portion followed by a solution of NMM (6.069 g, 60.0 mmol) in DCM (30 mL) over a period of 30 min. Stirring was continued for 3 h at −30 °C, then the mixture was allowed to warm up to room temperature resulting in a thick suspension. The white solid was filtered off and the filtrate was evaporated to dryness. The remaining solids were merged and washed on a funnel sequentially with water (1×300 mL), 1 M HCl (2×150 mL), and water (1×300 mL) and dried in vacuo. The crude product was recrystallized from EtOH/*i*PrOH to yield 30.85 g (88%) of **14** (1:1 mixture of two diastereomers) as a white powder.

TLC: R_f=0.62 (DCM/EtOAc 3:1; silica). Mp: 90 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.87–7.83 (2×dd, 2H, PhtN *CH*-2,5), 7.74–7.72 (2×dd, 2H, PhtN *CH*-3,4), 7.40–7.32 (m, 10H, Z and Bn *CH*-2,3,4,5,6), 7.21–7.19 (2×d, $^3J_{H,H}$=5.6 Hz, 1H, amide *NH*), 5.53–5.49 (2×d, $^3J_{H,H}$=7.8 Hz, 1H, *NHCHCO$_2$Bn*), 5.44–5.40 (2×d, $^3J_{H,H}$=9.6 Hz, 1H, Z *NH*), 5.31–5.25 (4×d, 2H, Z *CH$_2$*), 5.12–5.04 (4×d, 2H, *CO$_2$CH$_2$Ph*), 4.85 (d, $^2J_{H,H}$=18.2 Hz, 0.5H, *PhtNCH$_2$*), 4.84 (d, $^2J_{H,H}$=18.2 Hz, 0.5H, *PhtNCH$_2$*), 4.75 (d, $^2J_{H,H}$=18.2 Hz, 0.5H, *PhtNCH$_2$*), 4.71 (d, $^2J_{H,H}$=18.2 Hz, 0.5H, *PhtNCH$_2$*), 4.20 (br d, $^3J_{H,H}$=5.6 Hz, 0.5H, Val α-*CH*), 4.18 (br d, $^3J_{H,H}$=6.6 Hz, 0.5H, Val α-*CH*), 2.20–2.11 (m, 1H, Val β-*CH*), 0.95 (ps t, $^3J_{H,H}$=6.9 Hz, 3H, Val *CH$_3$*), 0.90 (d, $^3J_{H,H}$=6.9 Hz, 3H, Val *CH$_3$*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=193.71 (q, *PhtNCH$_2$CO*), 193.66 (q, *PhtNCH$_2$CO*), 171.2 (q, amide *CO*), 167.1 (q, 2×PhtN *CO*), 164.92 (q, *CO$_2$Bn*), 164.89 (q, *CO$_2$Bn*), 156.4 (q, Z *CO*), 136.13 (q, Z *C*-1), 136.12 (q, Bn *C*-1), 134.21 (t, PhtN *CH*-3,4), 134.20 (t, PhtN *CH*-3,4), 131.92 (q, PhtN *C*-1,6), 131.90 (q, PhtN *C*-1,6), 128.80 (t, Z/Bn *CH*), 128.71 (t, Z/Bn *CH*), 128.67 (t, Z/Bn *CH*), 128.47 (t, Z/Bn *CH*), 128.46 (t, Z/Bn *CH*), 128.11 (t, Z/Bn *CH*), 128.08 (t, Z/Bn *CH*), 128.04 (t, Z/Bn *CH*), 123.60 (t, PhtN *CH*-2,5), 68.92 (s, Z *CH$_2$*), 68.90 (s, Z *CH$_2$*), 67.1 (s, Bn *CH$_2$*), 60.6 (t, *NHCHCO$_2$Bn*), 59.90 (t, Val α-*CH*), 59.88 (t, Val α-*CH*), 45.27 (s, *PhtNCH$_2$*), 45.07 (s, *PhtNCH$_2$*), 31.0 (t, Val β-*CH*), 19.09 (p, Val *CH$_3$*), 19.02 (p, Val *CH$_3$*), 17.52 (p, Val *CH$_3$*), 17.44 (p, Val *CH$_3$*) ppm. IR (KBr): ν=3289, 3065, 3034, 2958, 2935, 2907, 2872, 1778, 1727, 1692, 1653, 1539, 1468, 1455, 1414, 1387, 1273, 1249, 1109, 1041, 950, 843, 732, 714, 696, 531 cm^{-1}. UV–vis (MeOH): λ_{max} (log ε)=217 (4.81), 240 (sh., 4.08), 280 (3.68) nm. ESI-HRMS: *m*/*z* calcd for $[C_{32}H_{32}N_3O_8]^+$ 586.2184, found 586.2180.

*4.3.2. (1′S)-4-(Benzyloxycarbonyl)-2-[1′-(benzyloxycarbonylamino)-2′-methylpropyl]-1-methyl-5-(phthalimidomethyl)-1H-imidazole (**15a**)*

To a slurry of amidoketone **14** (11.712 g, 20.0 mmol) in xylene (300 mL) TFA (6.0 mL, 80.0 mmol) and 8 M methylamine in EtOH (7.5 mL, 60.0 mmol) were added. The mixture was heated under intensive reflux with a Dean–Stark trap for 4 h while the trap was discharged (~10 mL) every 30 min. After the completion of the reaction volatiles were removed in a rotary evaporator. The residual solid was subjected to column chromatography on silica gel (DCM/EtOAc/MeOH 75:25:0→75:25:3) to obtain 7.297 g (63%) of **15a** as a white fluffy solid.

TLC: R_f=0.50 (DCM/EtOAc 75:25; silica). Mp: 71 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.79 (dd, $^3J_{H,H}$=5.5, 3.1 Hz, 2H, PhtN *CH*-2,5), 7.70 (dd, $^3J_{H,H}$=5.5, 3.1 Hz, 2H, PhtN *CH*-3,4), 7.42 (dd, $^3J_{H,H}$=8.1, 1.6 Hz, 2H, Ar *CH*); 7.34–7.24 (m, 8H, Ar *CH*), 5.74 (d, $^3J_{H,H}$=9.5 Hz, 1H, Z *NH*), 5.39 (d, $^2J_{H,H}$=12.3 Hz, 1H, *PhtNCH$_2$*), 5.36 (d, $^2J_{H,H}$=12.3 Hz, 1H, *PhtNCH$_2$*), 5.26 (d, $^2J_{H,H}$=15.6 Hz, 1H, Bn *CH$_2$*), 5.09 (d, $^2J_{H,H}$=12.5 Hz, 1H, Z *CH$_2$*), 5.04 (d, $^2J_{H,H}$=15.6 Hz, 1H, Bn *CH$_2$*), 5.01 (d, $^2J_{H,H}$=12.5 Hz, 1H, Z *CH$_2$*), 4.61 (t, $^3J_{H,H}$=9.0 Hz, 1H, Val α-*CH*), 3.74 (s, 3H, *NCH$_3$*), 2.27–2.20 (m, 1H, Val β-*CH*), 1.01 (d, $^3J_{H,H}$=6.7 Hz, 3H, Val *CH$_3$*), 0.83 (d, $^3J_{H,H}$=6.7 Hz, 3H, Val *CH$_3$*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.5 (q, 2×PhtN *CO*),

162.8 (q, Z ***C***O), 156.3 (q, ***C***O_2*Bn*), 149.5 (q, imidazole ***C***-2), 136.28 (q, Bn ***C***-1), 136.27 (q, Z ***C***-1), 134.1 (t, PhtN ***C***H-3,4), 131.7 (q, PhtN ***C***-1,6), 131.3 (q, imidazole ***C***-4), 130.6 (q, imidazole ***C***-5), 128.48 (t, Z/Bn ***C***H), 128.38 (t, Z/Bn ***C***H), 128.29 (t, Z/Bn ***C***H), 127.93 (t, Z/Bn ***C***H), 127.91 (t, Z/Bn ***C***H), 127.75 (t, Z/Bn ***C***H), 123.4 (t, PhtN ***C***H-2,5), 66.8 (s, Z ***C***H_2), 66.1 (s, Bn ***C***H_2), 52.8 (t, Val α-***C***H), 33.4 (t, Val β-***C***H), 31.57 (s, *PhtN****C***H_2), 31.15 (p, *N****C***H_3), 19.4 (p, Val ***C***H_3), 18.6 (p, Val ***C***H_3) ppm. ESI-HRMS: *m*/*z* calcd for $[C_{33}H_{33}N_4O_6]^+$ 581.2395, found 581.2416.

4.3.3. (1′S)-4(5)-(Benzyloxycarbonyl)-2-[1′-(benzyloxycarbonyl-amino)-2′-methylpropyl]-5(4)-(phthalimidomethyl)-1H-imidazole (**15b**)

To a slurry of amidoketone **14** (11.712 g, 20.0 mmol) in xylenes (300 mL), TFA (4.5 mL, 60.0 mmol) and 7 M NH_3 in MeOH (6.0 mL, 42.0 mmol) were added. The mixture was heated under intensive reflux with a Dean–Stark trap for 12 h. For work-up the mixture was concentrated in a rotary evaporator and the remaining solid was subjected to column chromatography on silica gel (DCM/EtOAc/MeOH 75:25:0→75:25:3) to obtain 3.90 g (34%) of **15b** as a yellowish powder.

TLC: R_f=0.50 (DCM/EtOAc 75:25; silica). Mp: 88 °C. ^{1}H NMR (500 MHz, MeOH-d_4): δ=7.82 (dd, $^3J_{H,H}$=5.5, 3.0 Hz, 2H, PhtN C***H***-2,5), 7.76 (dd, $^3J_{H,H}$=5.5, 3.0 Hz, 2H, PhtN C***H***-3,4), 7.43 (d, $^3J_{H,H}$=7.1 Hz, 1H, Ar C***H***), 7.34–7.26 (m, 8H, Ar C***H***), 5.32 (s, 2H, Bn C***H***$_2$), 5.08 (s, 2H, *PhtNC****H***$_2$), 5.04 (d, $^2J_{H,H}$=12.5 Hz, 1H, Z C***H***$_2$), 4.99 (d, $^2J_{H,H}$=12.5 Hz, 1H, Z C***H***$_2$), 4.47 (d, $^3J_{H,H}$=8.0 Hz, 1H, Val α-C***H***), 2.03–1.96 (m, 1H, Val β-C***H***), 0.89 (d, $^3J_{H,H}$=6.7 Hz, 3H, Val C***H***$_3$), 0.74 (d, $^3J_{H,H}$=6.7 Hz, 3H, Val C***H***$_3$) ppm. ^{13}C NMR (125 MHz, MeOH-d_4): δ=169.4 (q, 2×PhtN ***C***O), 161.2 (q, ***C***O_2*Bn*), 158.3 (q, Z ***C***O), 152.5 (q, imidazole ***C***-2), 144.7 (q, imidazole ***C***-5), 138.1 (q, Z ***C***-1), 137.5 (q, Bn ***C***-1), 135.6 (q, imidazole ***C***-4), 135.4 (t, PhtN ***C***H-3,4), 133.5 (q, PhtN ***C***-1,6), 129.62 (t, Bn ***C***H-2,6), 129.49 (t, Bn ***C***H-4), 129.46 (t, Z ***C***H-2,6), 129.34 (t, Z ***C***H-4), 129.02 (t, Bn ***C***H-3,5), 128.81 (t, Z ***C***H-3,5), 124.2 (t, PhtN ***C***H-2,5), 67.8 (s, Z ***C***H_2), 67.5 (s, Bn ***C***H_2), 56.6 (t, Val α-***C***H), 36.4 (s, *PhtN****C***H_2), 34.2 (t, Val β-***C***H), 19.6 (p, Val ***C***H_3), 19.0 (p, Val ***C***H_3) ppm. IR (KBr): ν=3317, 3064, 3033, 2963, 1773, 1718, 1615, 1569, 1519, 1455, 1425, 1396, 1347, 1278, 1237, 1189, 1116, 1087, 1027, 949, 913, 851, 737, 714, 697 cm^{-1}. UV–vis (MeOH): λ_{max} (log ε)=216 (4.64), 231 (sh., 4.33), 239 (4.29), 248 (sh., 4.17), 291 (3.34) nm. ESI-HRMS: *m*/*z* calcd for $[C_{32}H_{31}N_4O_6]^+$ 567.2238, found 567.2255.

4.3.4. (1′S)-2-(1′-Amino-2′-methylpropyl)-1-methyl-5-(phthalimidomethyl)-1H-imidazole-4-carboxylic acid hydrochloride (**17a**)

Imidazole ester **15a** (5.806 g, 10.0 mmol) was dissolved in methanol (175 mL), acidified with 2 M aqueous HCl (25 mL) and palladium–charcoal catalyst (5 wt % Pd, 0.100 g) was added. Hydrogenation was performed at room temperature and atmospheric pressure with monitoring by TLC. On completion (8 h) the catalyst was filtered off, then the filtrate was evaporated and dried in vacuo to obtain 3.901 g (99%) of the free acid **17a** as a white solid.

Mp: 127 °C. ^{1}H NMR (500 MHz, MeOH-d_4): δ=7.86–7.84 (m, 2H, PhtN C***H***-2,5), 7.82–7.81 (m, 2H, PhtN C***H***-3,4), 5.37 (d, $^2J_{H,H}$=15.8 Hz, 1H, *PhtNC****H***$_2$), 5.22 (d, $^2J_{H,H}$=15.8 Hz, 1H, *PhtNC****H***$_2$), 4.79 (d, $^3J_{H,H}$=9.5 Hz, 1H, Val α-C***H***), 4.02 (s, 3H, *NC****H***$_3$), 2.62–2.54 (m, 1H, Val β-C***H***), 1.24 (d, $^3J_{H,H}$=6.7 Hz, 3H, Val C***H***$_3$), 0.95 (d, $^3J_{H,H}$=6.7 Hz, 3H, Val C***H***$_3$) ppm. ^{13}C NMR (125 MHz, MeOH-d_4): δ=168.9 (q, 2×PhtN ***C***O), 161.5 (q, ***C***O_2H), 145.0 (q, imidazole ***C***-2), 135.8 (q, imidazole ***C***-5), 135.7 (t, PhtN ***C***H-3,4), 133.1 (q, PhtN ***C***-1,6), 127.9 (q, imidazole ***C***-4), 124.5 (t, PhtN ***C***H-2,5), 52.9 (t, Val α-***C***H), 34.1 (p, *N****C***H_3), 33.5 (t, Val β-***C***H), 32.3 (s, *PhtN****C***H_2), 19.1 (p, Val ***C***H_3), 18.8 (p, Val ***C***H_3) ppm. ESI-HRMS: *m*/*z* calcd for $[C_{18}H_{21}N_4O_4]^+$ 357.1557, found 357.1573.

4.3.5. (1′S)-2-(1′-Amino-2′-methylpropyl)-5(4)-(phthalimidomethyl)-1H-imidazole-4(5)-carboxylic acid hydrochloride (**17b**)

Deprotection of imidazole ester **15b** (5.666 g, 10.0 mmol) was performed as for compound **15a** to give 3.732 g (99%) of **17b** as a yellowish powder.

Mp: 105 °C. ^{1}H NMR (500 MHz, MeOH-d_4): δ=7.90–7.88 (m, 2H, PhtN C***H***-2,5), 7.84–7.83 (m, 2H, PhtN C***H***-3,4), 5.22 (s, 2H, *PhtNC****H***$_2$), 4.31 (d, $^3J_{H,H}$=8.5 Hz, 1H, Val α-C***H***), 2.44–2.36 (m, 1H, Val β-C***H***), 1.10 (d, $^3J_{H,H}$=6.7 Hz, 3H, Val C***H***$_3$), 0.90 (d, $^3J_{H,H}$=6.7 Hz, 3H, Val C***H***$_3$) ppm. ^{13}C NMR (125 MHz, MeOH-d_4): δ=169.3 (q, 2×PhtN ***C***O), 161.5 (q, ***C***O_2H), 144.9 (q, imidazole ***C***-2), 143.8 (q, imidazole ***C***-5), 139.3 (q, imidazole ***C***-4), 135.6 (t, PhtN ***C***H-3,4), 133.5 (q, PhtN ***C***-1,6), 124.4 (t, PhtN ***C***H-2,5), 54.7 (t, Val α-***C***H), 34.6 (s, *PhtN****C***H_2), 33.1 (t, Val β-***C***H), 19.1 (p, Val ***C***H_3), 18.7 (p, Val ***C***H_3) ppm. IR (KBr): ν=3420, 2969, 1770, 1617, 1538, 1469, 1423, 1395, 1307, 1213, 1191, 1110, 1034, 944, 797, 716 cm^{-1}. UV–vis (MeOH): λ_{max} (log ε)=220 (4.48), 231 (sh., 4.31), 238 (sh., 4.22), 292 (3.13) nm. ESI-HRMS: *m*/*z* calcd for $[C_{17}H_{19}N_4O_4]^+$ 343.1401, found 343.1492.

4.3.6. Scaffolds ***18a,b***

Starting from amino acid **17a** (1.964 g, 5.0 mmol) preparation and work-up was performed as in the case of macrocycles **12a**,**b**. Isolation of the macrocycles was accomplished by column chromatography on silica gel (EtOAc/MeOH 100:0→100:2) to obtain 0.868 g (51%) of cyclic trimer **18a** and 0.128 g (7.6%) of cyclic tetramer **18b** as light yellowish powders.

*4.3.6.1. Data for cyclic trimer **18a**.* TLC: R_f=0.40 (EtOAc/MeOH 100:2; silica). Mp: >200 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.43 (d, $^3J_{H,H}$=9.1 Hz, 1H, amide *N****H***), 7.78 (dd, $^3J_{H,H}$=5.4, 3.2 Hz, 2H, PhtN C***H***-2,5), 7.66 (dd, $^3J_{H,H}$=5.4, 3.2 Hz, 2H, PhtN C***H***-3,4), 5.37 (d, $^2J_{H,H}$=15.4 Hz, 1H, *PhtNC****H***$_2$), 5.16 (d, $^2J_{H,H}$=15.4 Hz, 1H, *PhtNC****H***$_2$), 5.15 (dd, $^3J_{H,H}$=9.3, 5.8 Hz, 1H, Val α-C***H***), 3.62 (s, 3H, *NC****H***$_3$), 2.12–2.05 (m, 1H, $^3J_{H,H}$=6.6 Hz, Val β-C***H***), 0.98 (ps t, $^3J_{H,H}$=6.6 Hz, 6H, Val C***H***$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.6 (q, 2×PhtN ***C***O), 162.0 (q, ***C***O*NH*), 147.9 (q, imidazole ***C***-2), 133.9 (t, PhtN ***C***H-3,4), 132.2 (q, imidazole ***C***-5), 131.8 (q, PhtN ***C***-1,6), 128.3 (q, imidazole ***C***-4), 123.3 (t, PhtN ***C***H-2,5), 49.4 (t, Val α-***C***H), 34.8 (t, Val β-***C***H), 31.4 (s, *PhtN****C***H_2), 31.1 (p, *N****C***H_3), 19.2 (p, Val ***C***H_3), 17.9 (p, Val ***C***H_3) ppm. IR (KBr): ν=3622, 3476, 3383, 2964, 2934, 2874, 1775, 1718, 1662, 1593, 1521, 1506, 1467, 1388, 1349, 1233, 1204, 1172, 1118, 1086, 1071, 1024, 930, 849, 790, 760, 714 cm^{-1}. UV–vis (MeOH): λ_{max} (log ε)=218 (5.27), 231 (sh., 5.08), 240 (sh., 4.98), 248 (sh., 4.80), 295 (4.03) nm. CD (DCM): λ_{max} (Δε [dm^3 mol^{-1} cm^{-1}])=232 (+11.3), 245 (0.0), 250 (−66.1), 300 (−1.2) nm. ESI-HRMS: *m*/*z* calcd for $[C_{54}H_{55}N_{12}O_9]^+$ 1015.4209, found 1015.4251.

*4.3.6.2. Data for cyclic tetramer **18b**.* TLC: R_f=0.48 (EtOAc/MeOH 100:2; silica). Mp: >200 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.74 (dd, $^3J_{H,H}$=5.4, 3.1 Hz, 2H, PhtN C***H***-2,5), 7.67 (dd, $^3J_{H,H}$=5.4, 3.1 Hz, 2H, PhtN C***H***-3,4), 7.55 (d, $^3J_{H,H}$=9.8 Hz, 1H, amide *N****H***), 5.33 (d, $^3J_{H,H}$=15.4 Hz, 1H, *PhtNC****H***$_2$), 5.18 (d, $^3J_{H,H}$=15.4 Hz, 1H, *PhtNC****H***$_2$), 5.02 (dd, $^3J_{H,H}$=9.1, 9.2 Hz, 1H, Val α-C***H***), 3.69 (s, 3H, *NC****H***$_3$), 2.45–2.37 (m, 1H, Val β-C***H***), 1.09 (d, $^3J_{H,H}$=6.6 Hz, 3H, Val C***H***$_3$), 0.87 (d, $^3J_{H,H}$=6.6 Hz, 3H, Val C***H***$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=167.6 (q, 2×PhtN ***C***O), 162.8 (q, ***C***O*NH*), 148.1 (q, imidazole ***C***-2), 134.0 (t, PhtN ***C***H-3,4), 132.4 (q, imidazole ***C***-4), 131.8 (q, PhtN ***C***-1,6), 128.4 (q, imidazole ***C***-5), 123.3 (t, PhtN ***C***H-2,5), 49.4 (t, Val α-***C***H), 32.6 (t, Val β-***C***H), 31.5 (s, *PhtN****C***H_2), 30.9 (p, *N****C***H_3), 19.7 (p, Val ***C***H_3), 18.7 (p, Val ***C***H_3) ppm. IR (KBr): ν=3638, 3476, 3399, 2963, 2875, 1775, 1718, 1660, 1590, 1505, 1468, 1388, 1349, 1263, 1230, 1201, 1173, 1119, 1070, 1025, 936, 849, 791, 761, 715 cm^{-1}. UV–vis (DCM): λ_{max} (log ε)=240 (sh., 4.90), 248 (sh., 4.66), 295 (3.84) nm. CD (DCM): λ_{max} (Δε

[$dm^3\,mol^{-1}\,cm^{-1}$])=234 (+59.1), 243 (0.0), 257 (−76.4), 277 (0.0), 287 (+1.1) nm. ESI-HRMS: *m*/*z* calcd for $[C_{72}H_{73}N_{16}O_{12}]^+$ 1353.5588, found 1353.5645.

*4.3.7. Scaffold **19***

To a solution of **18a** (0.203 g, 0.20 mmol) in a 2:2:1 mixture of DCM, THF, and EtOH (50 mL) hydrazine monohydrate (0.501 g, 10.0 mmol) was added at room temperature and the mixture was stirred for further 24 h. The resulting suspension was cooled to 0 to 5 °C and a solution of di-*tert*-butyldicarbonate (5.456 g, 25.0 mmol) in DCM (25 mL) was slowly added. After completion of addition the resulting solution was stirred without cooling for further 6 h. Then the solvents were evaporated in vacuo and column chromatography of the residue on silica gel (DCM/EtOAc/MeOH 75:25:0→75:25:3) yielded 0.180 g (97%) of **19** as a colorless solid.

TLC: R_f=0.60 (DCM/EtOAc/MeOH 75:25:5; silica). Mp: >200 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.35 (d, $^3J_{H,H}$=9.4 Hz, 1H, *CONH*), 5.75 (br t, $^3J_{H,H}$=5.4 Hz, 1H, *BocN**H**CH*$_2$), 5.10 (dd, $^3J_{H,H}$=9.5, 6.0 Hz, 1H, Val α-*CH*), 4.59 (dd, $^2J_{H,H}$=15.5, 5.7 Hz, 1H, *BocNHC**H**$_2$*), 4.46 (dd, $^2J_{H,H}$=15.5, 7.3 Hz, 1H, *BocNHC**H**$_2$*), 3.70 (s, 3H, *NCH*$_3$), 2.14–2.07 (m, $^3J_{H,H}$=6.6 Hz, 1H, Val β-*CH*), 1.35 (s, 9H, Boc *C*(*CH*$_3$)$_3$), 1.04 (d, $^3J_{H,H}$=6.6 Hz, 3H, Val *CH*$_3$), 1.03 (d, $^3J_{H,H}$=6.6 Hz, 3H, Val *CH*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=162.9 (q, ***C**ONH*), 156.1 (q, Boc ***C**O*), 147.4 (q, imidazole ***C***-2), 134.0 (q, imidazole ***C***-5), 131.1 (q, imidazole ***C***-4), 79.4 (q, Boc ***C***(*CH*$_3$)$_3$), 49.7 (t, Val α-***C**H*), 34.7 (t, Val β-***C**H*), 33.3 (s, *BocNH**C**H*$_2$), 30.9 (p, *N**C**H*$_3$), 28.3 (p, Boc *C*(***C**H*$_3$)$_3$), 19.5 (p, Val ***C**H*$_3$), 17.9 (p, Val ***C**H*$_3$) ppm. IR (KBr): ν=3385, 2968, 2934, 2875, 1713, 1656, 1592, 1499, 1467, 1417, 1391, 1367, 1328, 1275, 1250, 1170, 1046, 1007, 965, 941, 864, 800, 780, 728, 640 cm^{-1}. CD (MeOH): λ_{max} ($\Delta\varepsilon$ [$dm^3\,mol^{-1}\,cm^{-1}$])=214 (+11.4), 233 (+31.8), 244 (0.0), 258 (−66.6) nm. ESI-HRMS: *m*/*z* calcd for $[C_{45}H_{73}N_{12}O_9]^+$ 925.5618, found 925.5686.

*4.3.8. Scaffold **20***

To a solution of **18a** (0.102 g, 0.10 mmol) in a 2:2:1 mixture of DCM, THF, and EtOH (25 mL) hydrazine monohydrate (0.250 g, 5.0 mmol) was added at room temperature and the mixture was stirred for further 24 h. The resulting suspension was concentrated and dried in vacuo, then covered with DCM (30 mL) followed by the addition of benzyl chloroformate (0.341 g, 2.0 mmol) and Et_3N (0.304 g, 3.0 mmol). After stirring at room temperature for 6 h the mixture was quenched with MeOH (10 mL), concentrated, and the residue was subjected to column chromatography on silica gel (DCM/EtOAc/MeOH 75:25:0→75:25:5) to yield 0.079 g (77%) of **20** as a colorless glassy solid.

TLC: R_f=0.65 (DCM/EtOAc/MeOH 75:25:5; silica). Mp: >200 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.36 (d, $^3J_{H,H}$=9.3 Hz, 1H, *CONH*), 7.29–7.23 (m, 5H, Ph ***C**H*-2,3,4,5,6), 6.23 (t, $^3J_{H,H}$=6.1 Hz, 1H, *ZN**H**CH*$_2$), 5.10 (dd, $^3J_{H,H}$=9.2, 6.1 Hz, 1H, Val α-***C**H*), 5.04 (d, $^2J_{H,H}$=12.3 Hz, 1H, Z *CH*$_2$), 4.95 (d, $^2J_{H,H}$=12.3 Hz, 1H, Z ***C**H*$_2$), 4.54 (dd, $^2J_{H,H}$=15.4 Hz, $^3J_{H,H}$=5.5 Hz, 1H, *ZNHC**H**$_2$*), 4.47 (dd, $^2J_{H,H}$=15.4 Hz, $^3J_{H,H}$=7.1 Hz, 1H, *ZNHC**H**$_2$*), 3.69 (s, 3H, *NCH*$_3$), 2.13–2.07 (m, 1H, Val β-***C**H*), 1.04 (d, $^3J_{H,H}$=6.6 Hz, 3H, Val ***C**H*$_3$), 1.03 (d, $^3J_{H,H}$=6.6 Hz, 3H, Val ***C**H*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=162.7 (q, ***C**ONH*), 156.6 (q, Z ***C**O*), 147.4 (q, imidazole ***C***-2), 136.3 (q, Ph ***C***-1), 133.4 (q, imidazole ***C***-5), 131.1 (q, imidazole ***C***-4), 128.29 (t, Ph ***C**H*-3,5), 127.86 (t, Ph ***C**H*-4), 127.74 (t, Ph ***C**H*-4,6), 66.6 (s, Z ***C**H*$_2$), 49.7 (t, Val α-***C**H*), 34.7 (t, Val β-***C**H*), 33.8 (s, *ZNH**C**H*$_2$), 30.8 (p, *N**C**H*$_3$), 19.4 (p, Val ***C**H*$_3$), 17.8 (p, Val ***C**H*$_3$) ppm. CD (DCM): λ_{max} ($\Delta\varepsilon$ [$dm^3\,mol^{-1}\,cm^{-1}$])=234 (+16.6), 242 (0.0), 256 (−57.3) nm. ESI-HRMS: *m*/*z* calcd for $[C_{54}H_{67}N_{12}O_9]^+$ 1027.4940, found 1027.4972.

*4.3.9. Scaffold **4b***

*4.3.9.1. Preparation from **18a**.* To a solution of **18a** (0.102 g, 0.10 mmol) in a 2:2:1 mixture of DCM, THF, and EtOH (25 mL) hydrazine monohydrate (0.250 g, 5.0 mmol) was added at room temperature and the mixture was stirred for further 24 h. The resulting suspension was concentrated and dried in vacuo, then treated with 2 M HCl (100 mL) and unsoluble phthalylhydrazide was filtered off. The filtrate was extracted with DCM (3×30 mL), then evaporated and dried in vacuo to yield 0.055 g (74%) of **4b**.

*4.3.9.2. Preparation from **19**.* Scaffold **19** (0.093 g, 0.10 mmol) was treated with HCl/EtOAc solution (15%, 20 mL) at room temperature for 3 h. Volatiles were then removed in a rotary evaporator and the resulting white solid was exhaustively dried in vacuo to afford 0.073 g (99.4%) of **4b**.

*4.3.9.3. Preparation from **20**.* Platform **20** (0.103 g, 0.10 mmol) was dissolved in MeOH (40 mL), then treated with 2 M HCl (10 mL) and palladium on charcoal catalyst (5 wt % Pd; 0.050 g) was added. The mixture was hydrogenated at atmospheric pressure for 4 h, then filtered and evaporated to give 0.070 g (95%) of **4b**.

Mp: 155 °C. ^{1}H NMR (500 MHz, MeOH-d_4): δ=5.34 (d, $^3J_{H,H}$=5.4 Hz, 1H, Val α-***C**H*), 4.46 (d, $^2J_{H,H}$=14.8 Hz, 1H, *CH*$_2$*NH*$_3^+$), 4.42 (d, $^2J_{H,H}$=14.8 Hz, 1H, *CH*$_2$*NH*$_3^+$), 3.81 (s, 3H, *NCH*$_3$), 2.27–2.21 (m, $^3J_{H,H}$=6.6 Hz, 1H, Val β-***C**H*), 1.11 (d, $^3J_{H,H}$=6.6 Hz, 3H, Val ***C**H*$_3$), 1.04 (d, $^3J_{H,H}$=6.6 Hz, 3H, Val ***C**H*$_3$) ppm. ^{13}C NMR (125 MHz, MeOH-d_4): δ=164.3 (q, ***C**ONH*), 150.0 (q, imidazole ***C***-2), 133.4 (q, imidazole ***C***-5), 130.3 (q, imidazole ***C***-4), 51.5 (t, Val α-***C**H*), 35.8 (s, *CH*$_2$*NH*$_3^+$), 33.8 (t, Val β-***C**H*), 31.9 (p, *N**C**H*$_3$), 19.8 (p, Val ***C**H*$_3$), 17.8 (p, Val ***C**H*$_3$) ppm. IR (KBr): ν=3430, 3378, 2965, 2621, 1644, 1596, 1529, 1470, 1418, 1390, 1370, 1310, 1287, 1242, 1205, 1150, 1121, 1070, 1020, 982, 939, 878, 811, 778, 747, 658 cm^{-1}. CD (MeOH): λ_{max} ($\Delta\varepsilon$ [$dm^3\,mol^{-1}\,cm^{-1}$])=216 (+10.8), 228 (+12.3), 240 (0.0), 258 (−51.3) nm. ESI-HRMS: *m*/*z* calcd for $[C_{30}H_{49}N_{12}O_3]^+$ 625.4045, found 625.4110.

*4.3.10. Scaffold **5***

Starting from amino acid **17b** (1.894 g, 5.0 mmol) preparation and work-up was performed as in the case of macrocycles **12a**,**b**. Isolation was accomplished by column chromatography on silica gel (DCM/EtOAc/MeOH 75:25:0→75:25:5) to obtain 0.655 g (40%) of cyclic trimer **5** as a light yellowish solid.

TLC: R_f=0.55 (DCM/EtOAc/MeOH 75:25:5; silica). Mp: 95 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=10.15 (br s, 1H, imidazole *NH*), 8.43 (d, 1H, $^3J_{H,H}$=8.7 Hz, amide *NH*), 7.69 (br s, 2H, PhtN ***C**H*-2,5), 7.59 (br s, 2H, PhtN ***C**H*-3,4), 5.52 (d, $^2J_{H,H}$=14.9 Hz, 1H, *PhtNC**H**$_2$*), 5.08 (d, $^2J_{H,H}$=14.9 Hz, 1H, *PhtNC**H**$_2$*), 5.01 (t, $^3J_{H,H}$=6.6 Hz, 1H, Val α-***C**H*), 2.16–2.10 (m, 1H, Val β-***C**H*), 1.00 (d, $^3J_{H,H}$=6.6 Hz, 3H, Val ***C**H*$_3$), 0.94 (d, $^3J_{H,H}$=6.6 Hz, 3H, Val ***C**H*$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=168.3 (q, 2×PhtN ***C**O*), 162.3 (q, ***C**ONH*), 146.7 (q, imidazole ***C***-2), 134.1 (t, PhtN ***C**H*-3,4), 131.6 (q, PhtN ***C***-1,6), 131.0 (q, imidazole ***C***-4), 128.1 (q, imidazole ***C***-5), 123.5 (t, PhtN ***C**H*-2,5), 52.0 (t, Val α-***C**H*), 34.3 (t, Val β-***C**H*), 31.8 (s, *PhtN**C**H*$_2$), 18.6 (p, 2×Val ***C**H*$_3$) ppm. IR (KBr): ν=3555, 3376, 3221, 2964, 2932, 2874, 1774, 1716, 1655, 1603, 1543, 1510, 1408, 1432, 1391, 1350, 1281, 1226, 1188, 1108, 1087, 1037, 1029, 942, 850, 782, 743, 714, 648 cm^{-1}. CD (DCM): λ_{max} ($\Delta\varepsilon$ [$dm^3\,mol^{-1}\,cm^{-1}$])=239 (0.0), 246 (−46.5), 269 (0.0), 303 (+1.6) nm. ESI-HRMS: *m*/*z* calcd for $[C_{51}H_{49}N_{12}O_9]^+$ 973.3740, found 973.3853.

Acknowledgements

This work was generously supported by the Deutsche Forschungsgemeinschaft. The authors thank Dr. Andreea Schuster for helpful discussions.

References and notes

1. (a) Moberg, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 248–268; (b) Gibson, S. E.; Castaldi, M. P. *Chem. Commun.* **2006**, 3045–3062.

2. (a) Moberg, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 4721–4723; (b) Gibson, S. E.; Castaldi, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4718–4720.
3. Burk, M., Jr.; Harlow, R. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1462–1464.
4. Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168–4178.
5. Mase, N.; Ohno, T.; Hoshikawa, N.; Ohishi, K.; Morimoto, H.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 4073–4075.
6. Powell, M. T.; Porte, A. M.; Reibenspies, J.; Burgess, K. *Tetrahedron* **2001**, *57*, 5027–5038.
7. Chuang, T.-H.; Fang, J.-M.; Bolm, C. *Synth. Commun.* **2000**, *30*, 1627–1641.
8. Bellemin-Laponnaz, S.; Gade, L. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3473–3475.
9. Dro, C.; Bellemin-Laponnaz, S.; Welter, R.; Gade, L. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 4479–4482.
10. (a) Bringmann, G.; Pfeifer, R.-M.; Rummey, C.; Hartner, K.; Breuning, M. *J. Org. Chem.* **2003**, *68*, 6859–6863; (b) Fang, T.; Du, D.-M.; Lu, S.-F.; Xu, J. *Org. Lett.* **2005**, *7*, 2081–2084.
11. Suresh, P.; Srimurugan, S.; Babu, B.; Pati, H. N. *Tetrahedron: Asymmetry* **2007**, *18*, 2820–2827.
12. Foltz, C.; Stecker, B.; Marconi, G.; Bellemin-Laponnaz, S.; Wadepohl, H.; Gade, L. H. *Chem.—Eur. J.* **2007**, *13*, 9912–9923.
13. (a) Li, G.-Q.; Yan, Z.-Y.; Niu, Y.-N.; Wu, L.-Y.; Wei, H.-L.; Liang, Y.-M. *Tetrahedron: Asymmetry* **2008**, *19*, 816–821; (b) Fang, T.; Xu, J.; Du, D.-M. *Synlett* **2006**, 1559–1563; (c) Du, D.-M.; Fang, T.; Xu, J.; Zhang, S.-W. *Org. Lett.* **2006**, *8*, 1327–1330.
14. (a) Hong, J. I.; Namgoong, S. K.; Bernardi, A.; Still, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 5111–5112; (b) Liu, R.; Still, W. C. *Tetrahedron Lett.* **1993**, *34*, 2573–2576; (c) Yoon, S. S.; Still, W. C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2458–2460.
15. Howarth, J.; Al-Hashimy, N. A. *Tetrahedron Lett.* **2001**, *42*, 5777–5779.
16. Lee, K. H.; Lee, D. H.; Hwang, S.; Lee, O. S.; Chung, D. S.; Hong, J.-I. *Org. Lett.* **2003**, *5*, 1431–1433.
17. (a) Kim, S.-G.; Kim, K.-H.; Jung, J.; Shin, S. K.; Ahn, K. H. *J. Am. Chem. Soc.* **2002**, *124*, 591–596; (b) Kim, J.; Kim, S.-G.; Seong, H. R.; Ahn, K. H. *J. Org. Chem.* **2005**, *70*, 7227–7231.
18. (a) Schopohl, M. C.; Siering, C.; Kataeva, O.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 2620–2623; (b) Schopohl, M. C.; Faust, A.; Mirk, D.; Froehlich, R.; Kataeva, O.; Waldvogel, S. R. *Eur. J. Org. Chem.* **2005**, 2987–2999.
19. For reviews on the isolation, structure, and synthesis of the *Lissoclinum* cyclic peptides see: (a) Wipf, P. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier: Amsterdam, 1998; Vol. 12, pp 187–228; (b) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115–2134.
20. For a review on cyclic pseudopeptides as new scaffold see: Jolliffe, K. A. *Supramol. Chem.* **2005**, *17*, 81–86.
21. (a) Mink, D.; Mecozzi, S.; Rebek, J., Jr. *Tetrahedron Lett.* **1998**, *39*, 5709–5712; (b) Somogyi, L.; Haberhauer, G.; Rebek, J. *Tetrahedron* **2001**, *57*, 1699–1708; (c) Haberhauer, G.; Somogyi, L.; Rebek, J. *Tetrahedron Lett.* **2000**, *41*, 5013–5016.
22. (a) Pattenden, G.; Thompson, T. *Chem. Commun.* **2001**, 717–718; (b) Singh, Y.; Sokolenko, N.; Kelso, M. J.; Gahan, L. R.; Abbenante, G.; Fairlie, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 333–334.
23. For further westeillamide analouges see: (a) Bertram, A.; Blake, A. J.; González-López de Turiso, F.; Hannam, J. S.; Jolliffe, K. A.; Pattenden, G.; Michael Skae, M. *Tetrahedron* **2003**, *59*, 6979–6990; (b) Wipf, P.; Miller, C. P.; Grant, C. M. *Tetrahedron* **2000**, *56*, 9143–9150; (c) Blake, A. J.; Hannam, J. S.; Jolliffe, K. A.; Pattenden, G. *Synlett* **2000**, 1515–1518.
24. For other C_3-symmetric cyclic pseudopeptides see for example: (a) Chakraborty, T. K.; Tapadar, S.; Raju, T. V.; Annapurna, J.; Singh, H. *Synlett* **2004**, 2484–2488; (b) Heinrichs, G.; Vial, L.; Lacour, J.; Kubik, S. *Chem. Commun.* **2003**, 1252–1253; (c) Choi, K.; Hamilton, A. D. *J. Am. Chem. Soc.* **2003**, *125*, 10241–10249.
25. Haberhauer, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 4397–4399.
26. Haberhauer, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 3635–3638.
27. Haberhauer, G. *Tetrahedron Lett.* **2008**, *49*, 2421–2424.
28. (a) Haberhauer, G.; Oeser, T.; Rominger, F. *Chem.—Eur. J.* **2005**, 6718–6726; (b) Haberhauer, G.; Oeser, T.; Rominger, F. *Chem. Commun.* **2004**, 2044–2045.
29. Haberhauer, G.; Oeser, T.; Rominger, F. *Chem. Commun.* **2005**, 2799–2801.
30. Pintér, Á.; Haberhauer, G. *Eur. J. Org. Chem.* **2008**, 2375–2387.
31. Pintér, Á.; Haberhauer, G.; Hyla-Kryspin, I.; Grimme, S. *Chem. Commun.* **2007**, 3711–3713.
32. Haberhauer, G.; Drosdow, E.; Oeser, T.; Rominger, F. *Tetrahedron* **2008**, *64*, 1853–1859.
33. Bajwa, J. S. *Tetrahedron Lett.* **1992**, *33*, 2299–2302.
34. All computations were performed with the Gaussian 03 program-package: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian: Wallingford, CT, 2004.
35. Haberhauer, G.; Rominger, F. *Tetrahedron Lett.* **2002**, *43*, 6335–6338.
36. Karplus, M. *J. Am. Chem. Soc.* **1963**, *58*, 2870–2871.