

Oxazole Cyclopeptides for Chirality Transfer in C_3 -Symmetric Octahedral Metal Complexes

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A straightforward synthesis of C_3 -symmetric oxazole-containing macrocyclic peptide scaffolds is presented. This type of macrocycles bears three functional groups on the oxazole rings, which allows fixing of various receptor arms on them in an easy manner. The chiral backbone of the macrocycle proved to be a powerful tool for chirality induction, thus pre-determining the configuration of helically coordinated metal

centres. The diastereoselective formation of Co^{II} , Ni^{II} , Cu^{II} and Zn^{II} complexes with tripodal bipyridyl ligand **4** was proved by UV- and CD-absorption spectrophotometric titration experiments.

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Introduction

C_3 -symmetric systems have been studied extensively during the last decade^[1] as they can be used as catalysts^[2] in organic syntheses, ligands^[3] for metal complexes, supramolecular hosts^[4] or nanoscale devices.^[5] Inspired by nature, we turned our attention to the design and synthesis of novel macrocyclic ligands and cages based on the structural motif of *Lissoclinum* cyclopeptide alkaloids like *Westiellamide* and *Bistratamide C*.^[6] Functionalized C_3 -symmetric synthetic analogues of these natural products having three carboxy or aminoalkyl linkers as side chains of the α -C-atoms of the amino acid residues are already known and were applied for the assembly of different cage structures.^[7] The volume of the cavity of such systems can be considerably expanded by introducing additional functionalities in the positions 1 or 5 of the azole rings. In these systems, intramolecular steric interactions and hydrogen bonding contribute to a better preorganisation of planar side chains if attached directly to the conformationally fixed azole rings.

In our earlier work we presented cyclic hexapeptides containing three imidazole units, each carrying on its secondary nitrogen atom various benzyl-type bidental ligand arms.^[8] We showed that this system is able to transfer chiral information from its scaffold to a distant metal or non-metal centre.^[9] Furthermore, we were able to synthesize the first configurationally stable, propeller-like triarylphosphane by linking a triphenylphosphane moiety via three peptide bonds to the chiral oxazole scaffold **1**.^[10]

Herein we report an extended study of the synthesis of oxazole-containing C_3 -scaffolds **1–3** with three easily modifiable functional groups as potential coupling sites for the synthesis of new ligands, supramolecular hosts or container molecules. In particular, we show that the backbone of these macrocycles is a powerful tool for chirality transfer in C_3 -symmetric octahedral metal complexes: The Co^{II} , Ni^{II} , Cu^{II} and Zn^{II} complexes of tripodal bipyridyl ligand **4** are formed diastereoselectively.

Results and Discussion

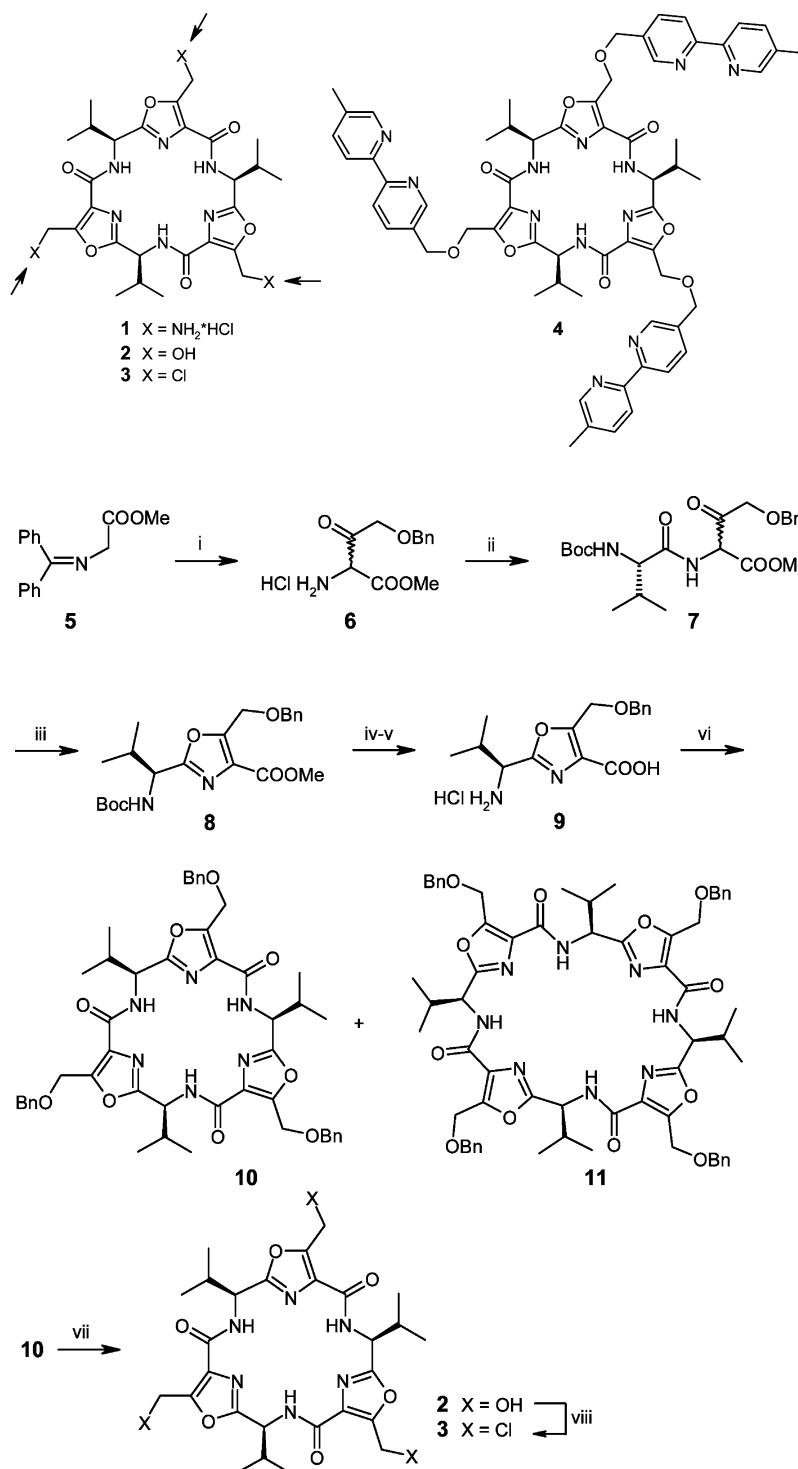
Synthesis of the Scaffolds

In the synthesis of platforms **2** and **3** the oxazole building block **8** bearing orthogonally protected carboxylic acid, amino and hydroxy functions plays a key role (Scheme 1). This compound is available in three steps starting from *N*-(diphenylmethylene)glycine methyl ester (**5**) using a modified procedure of Singh et al.^[11] Deprotonation of **5** with potassium-*tert*-butoxide, followed by the *C*-acylation with benzyloxyacetyl chloride and one-pot hydrolysis afforded keto amine hydrochloride **6** in satisfactory yield and purity. This substrate was coupled with Boc-L-valine using isobutyl chloroformate as activating agent. As compound **6** could only be obtained as an amorphous, tacky solid rather inconvenient to handle, the solution of the mixed anhydride of Boc-L-valine and isobutyl chloroformate in dichloromethane was introduced by Schlenk-technique into the vessel containing the amine salt **6**. By lowering of the reaction temperature from -25°C to -40°C , the yield of keto amide **7** could be enhanced from 30% up to 55% after chromatographic purification.

Cyclodehydration of **7** under Mitsunobu conditions^[11b] with triphenylphosphane, hexachloroethane and triethylamine gave oxazole **8** in 71% yield.

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Scheme 1. Synthesis of scaffolds **2** and **3**: i) BnOCH₂COCl, KO^tBu, THF, then 2 M HCl/H₂O, -60 °C, 76%. ii) Boc-L-Val-OH, *i*BuOCOCl, NMM, DCM, -40 °C → r.t., 55%. iii) PPh₃, Et₃N, C₂Cl₆, DCM, room temp., 71%. iv) 2 M NaOH, MeOH/1,4-dioxane, 97%; v) HCl, EtOAc, 99%; vi) PyBOP, *i*Pr₂NEt, DMF, room temp., 39% for **10** and 13% for **11**. vii) Pd/C, H₂, DCM, 99%. viii) SOCl₂, CHCl₃, Δ, 99%.

Removal of the methyl ester protective group by gentle treatment with sodium hydroxide in methanol/dioxane/water followed by the fast cleavage of the Boc group with hydrochloric gas in ethyl acetate afforded amino acid **9** in almost quantitative amount.

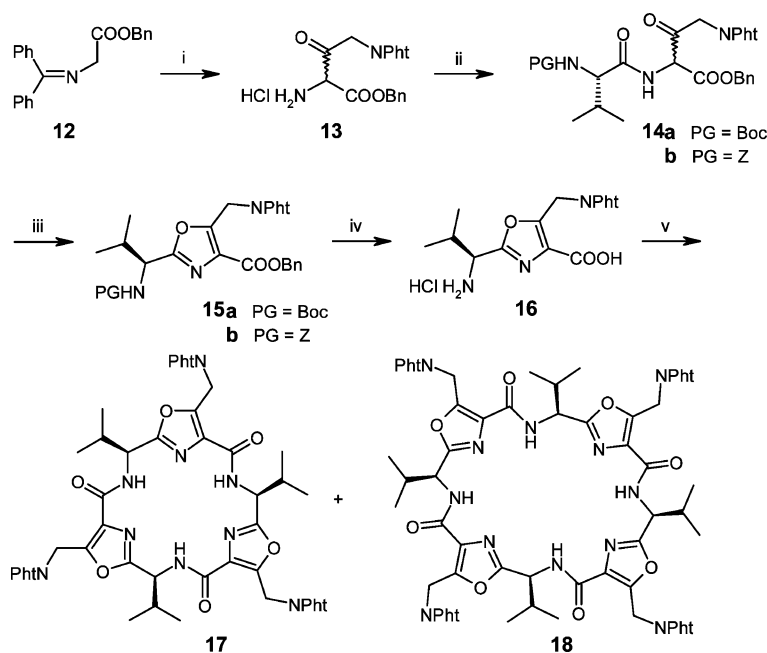
Macrolactamization of **9** with different peptide coupling agents (FDPP, DPPA, PyBOP) under high-dilution conditions ($c_{\text{monomer}} = 0.040$ M) in polar, aprotic solvents (acetonitrile or DMF) in the presence of Hünig's base gave a mixture of cyclic trimer **10** and cyclic tetramer **11**, which were

separated by column chromatography on silica gel. In order to enhance the yield of the cyclohexapeptide **10** at the expense of the cyclooctapeptide **11**, we tried to optimize the reaction parameters for the macrocyclization. Use of FDPP in acetonitrile gave the highest overall yields (34.9% for **10** and 25.1% for **11**, respectively), but the smallest trimer to tetramer product ratio (1.4:1). In the case of DPPA, tetramer **11** could not be isolated, but the yield for trimer **10** remained low (24.1%) even after prolonged reaction time (up to 10 d). The use of PyBOP in DMF proved to be the best choice for our requirements providing the best yield of the cyclic trimer (39.1%) accompanied by less cyclic tetramer (12.5%; product ratio trimer to tetramer: 3.1:1).

In the next step, the benzyloxy protective groups in **10** were cleaved by catalytic hydrogenation. As both carbon–oxygen single bonds of the benzyloxymethyl side arms are weakened by the connected aromatic systems, unwanted cleavage of the (oxazole)CH₂–OBn bond is a serious risk. Indeed, if debenzoylation was conducted in methanol, ethanol or tetrahydrofuran as solvents using 10% Pd/C catalyst under atmospheric pressure of hydrogen, a mixture of products was obtained, containing fully debenzylated platform **2** along with the one-, two- and threefold dehydroxylated macrocycles. While catalytic hydrogenation in ethyl acetate gave no cleavage of the protecting groups, the use of dichloromethane afforded a fast removal of all benzyl ether groups without damaging the desired product **2** even after prolonged (8 h) reaction time. The trihydric alcohol **2** can be easily converted into the corresponding tripodal chloride **3** by treatment with thionyl chloride in chloroform at room temperature.

The key compound for the tripodal amine platform **1** is the oxazole module **15** (Scheme 2). For the protection of its *N*-terminus we chose Boc as well as *Z* groups. For the protection of the side arm, both the Fmoc and the phthalimido group were first taken into consideration. As both protective groups are base labile, we planned the protection of the *C*-terminal function as its benzyl ester which can be selectively cleaved by hydrogenolysis. Unfortunately, the use of the Fmoc group resulted in low yields of the desired oxazole building blocks, accompanied by large amounts of undesired side products. In contrast, the preparation and peptide coupling of phthalimido-protected keto amine hydrochloride **13** with both Boc-L-Val-OH and *Z*-L-Val-OH proceeded smoothly to afford keto amides **14a** (65%) and **14b** (88%), respectively (Scheme 2).

The conversion of the dipeptides **14a,b** to the corresponding oxazoles **15a,b** required uncommonly long reaction times (1–2 weeks at r.t.) to obtain acceptable yields (52% for **15a** and 76% for **15b**, respectively) of the products, which may be the result of the high steric demand of the phthalimidomethyl side chain. On the other hand, TLC and ESI-MS analysis of the reaction mixture indicated the presence of a Ph₃PO adduct of **15a**, in contrast to similar oxazole forming reactions, where a persistent 5-chlorooxazoline was observed.^[12] Column chromatography of the reaction mixture after 3 d on silica gel gave **15a** in low yield, followed by a second uniform substrate as judged by TLC and ESI-MS in larger amount, before eluting pure triphenylphosphane oxide from the column. After evaporating and drying, ¹H NMR spectra of the second fraction showed the peaks of **15a** with minor intensity and those of a major



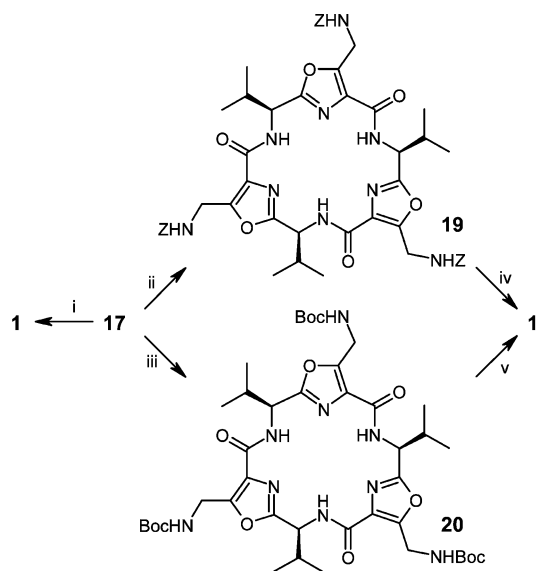
Scheme 2. Synthesis of scaffolds **17** and **18**: i) PhtNCH₂COCl, KO^tBu, THF, then 2 M HCl/H₂O, –60 °C, 84%. ii) Boc-L-Val-OH or *Z*-L-Val-OH, *i*BuOCOC1, NMM, THF or DCM, –25 °C → r.t., 65% for **14a** and 88% for **14b**. iii) PPh₃, Et₃N, C₂Cl₆, DCM, room temp., 52% for **15a** and 76% for **15b**. (iv) **15a**: Pd(OH)₂/C, H₂, MeOH, 98% and HCl, EtOAc, 98%; **15b**: Pd(OH)₂/C, H₂, aq. HCl, MeOH, 99%; (v) PyBOP, *i*Pr₂NEt, DMF, room temp., 32% for **17** and 11% for **18**.

substrate. This indicates that the major compound decomposes to the oxazole **15a**. The attempt to perform the cyclisation of the keto amide **14b** in a more time-saving manner by using POCl₃ in pyridine failed.

Finally, we removed the benzyl ester group in **15a** by catalytic hydrogenolysis followed by elimination of the Boc protecting group with hydrochloric gas in ethyl acetate to afford the free dipeptide **16** in excellent yield. The free amino acid **16** can also be formed in only one step by catalytic hydrogenolysis of **15b**. Macrocyclization of **16** was carried out with PyBOP in dry DMF at room temperature to furnish the cyclic trimer **17** and the cyclic tetramer **18**.

The deprotection of the trimer **17** to the free amine **1** can be performed by three different ways. The shortest one is the deprotection of the phthalimido units using hydrazine in ethanol (Scheme 3). However, the hereby formed

phthalylhydrazide can hardly be separated from the desired amine **1**, and consequently the yield of **1** decreases after several necessary separation steps to 81%. To avoid this costly procedure, we investigated two two-steps procedures. First, the phthalimido groups can be replaced by Z-groups and the so formed scaffold **19** can easily be separated from the phthalylhydrazide. The Z-groups are smoothly removed by hydrogenolysis. The product obtained by this method was very pure, but the overall yield turned out to be even worse (50%) than in the first procedure. However, the second two-step variant, where we replaced the PhtN residues by three Boc groups, proved to be superior. The threefold Boc-protected trimer **20** could be isolated in yields of 92%. The removal of the Boc groups is performed by means of HCl in ethyl acetate which provides the HCl salt of the desired amine **1** in almost quantitative yield.

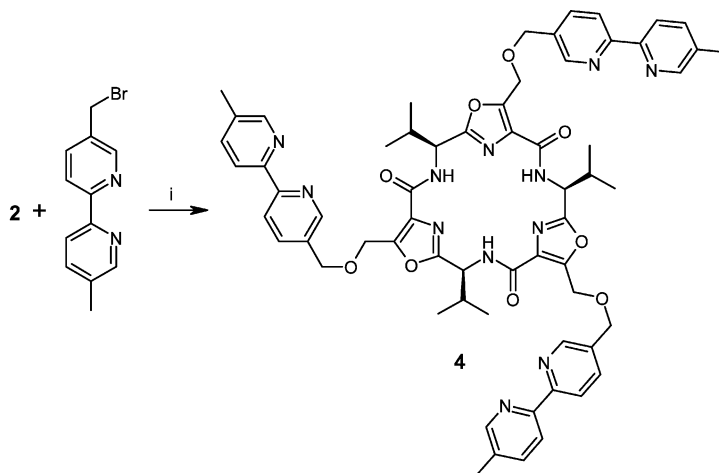


Scheme 3. Synthesis of scaffold **1**: i) NH₂NH₂·H₂O, THF/DCM/EtOH, r.t. then acidic work-up, 81%. ii) 1. NH₂NH₂·H₂O, THF/DCM/EtOH, room temp., 2. Z-Cl, Et₃N, DCM, room temp., 57%. iii) NH₂NH₂·H₂O, THF/DCM/EtOH then Boc₂O, room temp., 92%. iv) Pd/C, H₂, aq. HCl, MeOH, room temp., 88%. v) HCl, EtOAc, room temp., 100%.

Investigation of the Chirality Transfer

The predetermination of the configuration caused by the oxazole scaffold can best be proven by the diastereoselective synthesis of helix-like metal complexes. As model compound we chose the tripodal bipyrindyl ligand **4**, as three bipyridine units tends to form helical octahedral metal complexes with a variety of doubly positive metal ions. The ligand **4** was synthesized by treating the triol **2** with an excess of 5-bromomethyl-5'-methyl-2,2'-bipyridine along with sodium hydride in tetrahydrofuran (Scheme 4).

Ligand **4** was treated with various divalent metal salts and the respective UV and CD spectra were recorded. For all metal ions the formation of the corresponding bipyridyl metal complexes was observed in the UV spectra. In the CD spectra, all metal complexes show a positive Cotton effect at about 318 nm and a negative Cotton effect at about 295 nm (Figure 1 and Table 1). The sign and the magnitude of these values are characteristic for octahedral trisbipyridyl metal complexes exhibiting an *M* helicity.^[13] This clearly indicates that predetermination of the helicity at the metal centre was successful.



Scheme 4. Synthesis of ligand **4**: i) NaH, THF, r.t. → **4**, 33%.

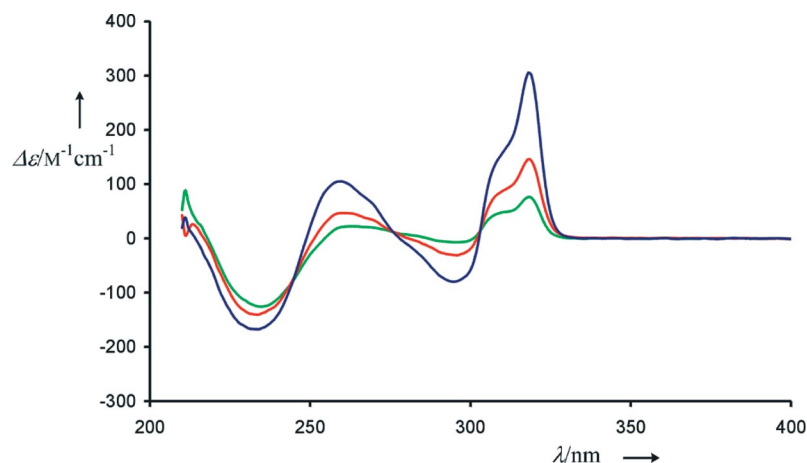


Figure 1. CD spectra of the ligand **4** (green) with CuCl_2 (red) and ZnCl_2 (blue) in $\text{MeOH}/\text{H}_2\text{O}$ (1:1; buffer: 0.10 M TRIS, 0.02 M HCl in H_2O) ($[\mathbf{4}] = 1.6 \times 10^{-5} \text{ M}$ and $\mathbf{4}/\text{M}^{2+} = 1:1$).

Table 1. CD spectra of the complexes of ligand **4** with metal ions in $\text{MeOH}/\text{H}_2\text{O}$ (1:1; buffer: 0.10 M TRIS, 0.02 M HCl in H_2O) ($[\mathbf{4}] = 1.6 \times 10^{-5} \text{ M}$ and $\mathbf{4}/\text{M}^{2+} = 1:1$).

M^{2+}	$\Delta\epsilon [\text{M}^{-1}\text{cm}^{-1}]$ (wavelength [nm])
–	+76.3 (318), –7.3 (295), +22.2 (263), –125.9 (235)
$\text{Co}^{\text{II}}\text{Cl}_2$	+145.6 (318), –30.9 (296), +46.7 (260), –140.5 (234)
$\text{Ni}^{\text{II}}(\text{NO}_3)_2$	+304.9 (318), –79.9 (295), +104.9 (259), –167.5 (234)
$\text{Cu}^{\text{II}}\text{Cl}_2$	+144.4 (318), –26.9 (293), +54.6 (259), –140.3 (230)
$\text{Zn}^{\text{II}}\text{Cl}_2$	+206.6 (316), –44.4 (294), +76.3 (260), –176.0 (230)

For the Cu^{II} and the Zn^{II} complexes we further performed CD titration experiments. In the case of the zinc ion, a singular 1:1 complex is formed, which can be proved by the shape of the titration curve and the location of the maximum in the Job-plot (Figure 2). The association constant of the zinc complex $\mathbf{4}\cdot\text{Zn}^{2+}$ amounts to $2.1 \pm 0.1 \times 10^6 \text{ M}^{-1}$. For copper, the situation is slightly different. Here besides the 1:1 complex at least one complex with a lower coordination number is formed. The shape of

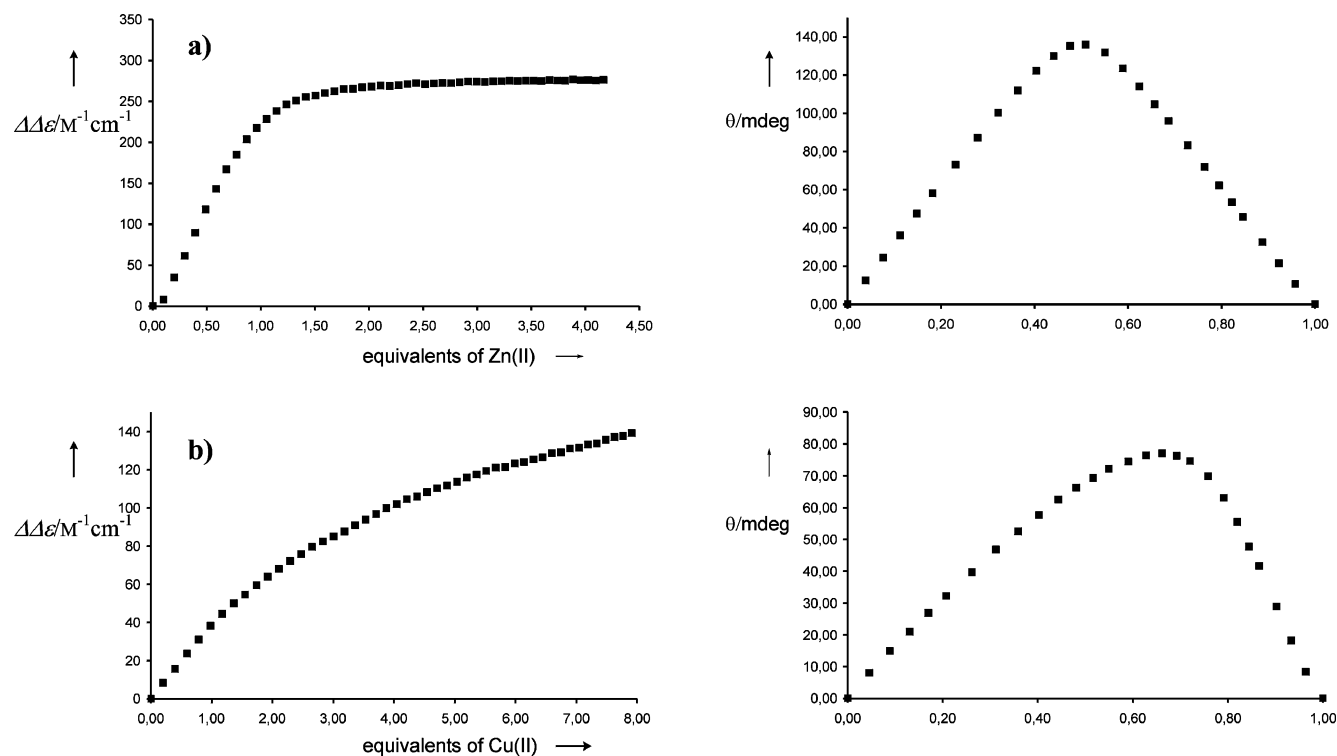


Figure 2. Plot of $\Delta\Delta\epsilon$ vs. equivalents of metal ions and Job-plots $\{y = \theta_{\text{obs}} - \theta_{\text{L}} - (\theta_{\text{M}} - \theta_{\text{L}}) \cdot x \text{ vs. } x = [\text{M}]/([\text{M}] + [\text{L}])\}$ for complexation of **4** with Zn^{II} (a) and Cu^{II} (b), respectively. The values were recorded at 318 nm.

the titration curve does not fit a 1:1 binding curve and the maximum in the Job-plot is about 0.65. This behavior is probably due to the tendency of copper to prefer complexes with a coordination number of 4 rather than 6.

The predetermination of the helicity at the metal centre by the chiral oxazole scaffold was further investigated by molecular modeling studies. The relative stabilities of the stereoisomers of the zinc complex **4**·Zn²⁺ were calculated by Gaussian software program.^[14] The structures were determined by geometry optimizations at HF-level using the 3-21G* basis set. The structures optimized by HF/3-21G* were further used in single-point calculations with B3LYP/6-31G* and BP86/6-31G* methods (Table 2). In principle, the zinc complex **4**·Zn²⁺ can adopt four different conformations (*P1*, *P2*, *M1* and *M2*): on the one side, the three bipyridine rings can be present in two opposite helicities (*P* or *M* isomer), and on the other side, the lone pairs of the ether units connecting the chiral scaffold with the bipyridine rings can adopt two different orientations. Viewing the molecule from the zinc atom along the main C₃-axis, the lone pairs of the three ether units are pointing clockwise in the case of conformers (*M1*)-**4**·Zn²⁺ and (*P1*)-**4**·Zn²⁺ and anticlockwise for isomers (*M2*)-**4**·Zn²⁺ and (*P2*)-**4**·Zn²⁺. All calculations reveal that the *M*-isomers of **4**·Zn²⁺ are stabilized in preference to the *P*-isomers. This is in accordance with the results obtained by the CD measurements.

Table 2. Relative energies of the conformers of **4**·Zn²⁺ calculated with the 6-31G* basis set.

Method ^[a]	ΔE [kJ mol ⁻¹]		<i>P1</i>	<i>P2</i>
	<i>M1</i>	<i>M2</i>		
B3LYP	0.0	0.4	11.6	37.8
BP86	0.0	5.3	28.0	37.9

[a] Single-point calculations employing the indicated method based on the structure optimized with HF/3-21G*.

Conclusions

In summary, we could show that C₃-symmetric oxazole-containing macrocyclic peptidic scaffolds carrying three functional groups on the oxazole rings can be obtained in good yields. Starting from this scaffold, a tripodal bipyridyl ligand can be prepared. Furthermore, we were able to show that the chiral backbone of the macrocycle predetermines the helicity of the metal complexes of this tripodal ligand. This concept of using a chiral oxazole scaffold for the diastereoselective structure formation in supramolecular systems should be applicable to other systems, too.

Experimental Section

General Remarks: All chemicals were of reagent grade and used as purchased. All moisture-sensitive reactions were performed under an inert atmosphere of argon using distilled dry solvents. Reactions were monitored by TLC analysis using silica gel 60 F₂₅₄ thin-layer plates. Flash chromatography was carried out on silica gel 60 (230–400 mesh). ¹H and ¹³C NMR spectra were measured on a Bruker

Avance DMX 300 and Avance DRX 500 spectrometers. All chemical shifts (δ) are given in ppm relative to TMS. The spectra were referenced to deuterated solvents indicated in brackets in the analytical data. HRMS spectra were recorded with a 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, CD-absorption spectra were taken with a Jasco J-815 spectrophotometer equipped with a Jasco ATS-443 automatic titration accessory. Elemental microanalyses were performed at the microanalytical laboratory of the University of Heidelberg.

Abbreviations: Bn: benzyl, Boc: *tert*-butoxycarbonyl, FDPP: pentafluorophenyl diphenylphosphinate, DCM: dichloromethane, DMF: *N,N*-dimethylformamide, DPPA: diphenylphosphoryl azide, NH: *n*-hexane, NMM: *N*-methylmorpholine, PE: petroleum ether, PhtN: phthalimido, PyBOP: benzotriazole-1-ylxytripyrrolidinophosphonium hexafluorophosphate, THF: tetrahydrofuran, TRIS: tris(hydroxymethyl)aminomethane, Z: benzyloxycarbonyl.

***N*-(Diphenylmethylene)glycine Methyl Ester 5:** To a slurry of glycine methyl ester hydrochloride (25.111 g, 200.0 mmol) in DCM (200 mL) was added benzophenone imine (36.247 g, 200.0 mmol) in DCM (200 mL), and the mixture was stirred for 24 h at ambient temperature. Then the white milky mixture was extracted with water (2 × 50 mL) and brine (1 × 50 mL). The organic layer was separated, dried with MgSO₄, then filtered and the solvents evaporated. The solidified raw product was crystallised from petroleum ether to obtain compound **5** (43.045 g, 83.0%) as a white powder. ¹H NMR (300 MHz, CDCl₃): δ = 7.66 (dd, ³J_{H,H} = 8.3, ⁴J_{H,H} = 1.5 Hz, 2 H; *cis* Ph CH-2,6), 7.49–7.42 (m, 3 H), 7.41–7.29 (m, 3 H), 7.17 (m, 2 H), 4.22 (s, 2 H, CH₂), 3.74 (s, 3 H, CO₂CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 171.8 (q, Ph₂C=N), 171.0 (q, CO₂CH₃), 139.1 (q, *cis/trans* Ph C-1), 128.8 (t, *trans* Ph CH-4), 128.7 (t, *trans* Ph CH-3,5), 128.6 (t, *cis* Ph CH-2,6), 128.2 (t, *cis* Ph CH-4), 128.0 (t, *trans* Ph CH-2,6), 127.6 (t, *cis* Ph CH-3,5), 55.5 (s, CH₂), 51.9 (p, CO₂CH₃) ppm. IR (KBr): $\tilde{\nu}$ = 3045, 1756, 1626, 1576, 1491, 1448, 1433, 1386, 1363, 1316, 1290, 1202, 1163, 1065, 993, 785, 773, 713, 694, 679 cm⁻¹. UV/Vis (CH₂Cl₂, *c* = 0.075 mg/mL): $\lambda_{\max}$ (log ϵ) = 250 (0.43) nm. ESI-HRMS: *m/z* calcd. for C₁₆H₁₆NO₂ [MH⁺] 254.1176, found 254.1167. C₁₆H₁₅NO₂ (253.30): calcd. C 75.87, H 5.97, N 5.53; found C 75.81, H 6.03, N 5.67.

Benzyloxyacetic Acid: To a suspension of NaH (16.000 g, 60% dispersion in mineral oil, 400.0 mmol) in dry toluene (100 mL) agitated by a mechanical stirrer a solution of benzyl alcohol (21.628 g, 200.0 mmol) in toluene (40 mL) was added at 0 °C under Ar. After mixing for 1 h at room temperature, a solution of bromoacetic acid (27.790 g, 200.0 mmol) in toluene (100 mL) was added. The resulting slurry was stirred without heating for 60 min, then at 80 °C for 2 h, finally allowed to chill down to room temperature and stirred overnight. Then water (300 mL) was added, and the mixture was washed with diethyl ether (100 mL). The aqueous layer was acidified with concd. HCl (23 mL) to pH 2 and extracted repeatedly with DCM (3 × 100 mL). The combined organic extracts were dried with MgSO₄, filtered, and the solvent was evaporated to give the crude product as a slightly yellow oil. Further purification was accomplished by distillation to obtain 27.920 g (84.0%) of pure product as a colorless liquid; b.p. 146 °C at 1.5 mbar.

TLC: *R*_f = 0.12 (PE/EtOAc, 2:1; silica). ¹H NMR (300 MHz, CDCl₃): δ = 9.09 (br. s, 1 H; CO₂H), 7.39–7.32 (m, 5 H, Ph CH-2,3,4,5,6), 4.65 (s, 2 H, PhCH₂O), 4.15 (s, 2 H, CH₂CO₂H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 175.3 (q, CO₂H), 136.4 (q, Ph C-1), 128.4 (t, Ph CH-4), 128.1 (t, Ph CH-3,5), 128.0 (t, Ph CH-2,6),

73.2 (s, $PhCH_2O$), 66.4 (s, CH_2CO_2H) ppm. IR (film): $\tilde{\nu}$ = 3031, 2927, 1730, 1497, 1455, 1428, 1370, 1209, 1116, 1029, 949, 910, 749, 699, 605, 467 cm^{-1} . UV/Vis (CH_2Cl_2 , c = 0.742 mg/mL): λ_{max} (log ϵ) = 252 (1.07), 258 (1.01), 282 (0.13) nm. EI-MS: m/z = 166.1 $[M]^+$, 122.1, 107.1, 105.1, 91.1, 79.1, 65.2, 60.1, 51.1, 39.2, 32.2, 28.2.

Benzoyloxyacetyl Chloride: Benzoyloxyacetic acid (16.617 g, 100.0 mmol) was dissolved in $CHCl_3$ (50 mL) and thionyl chloride (9.5 mL, 15.466 g, 130.0 mmol) was added at room temperature under Ar. The solution was stirred for 4 h under reflux then the solvent was removed on a rotary evaporator, and the crude product was distilled under reduced pressure to give 16.800 g (91.0%) of acid chloride as a colorless liquid; b.p. 78 °C at 1.0 mbar. 1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.34 (m, 5 H, Ph CH -2,3,4,5,6), 4.67 (s, 2 H, CH_2COCl), 4.44 (s, 2 H, $PhCH_2O$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8 (q, $COCl$), 136.0 (q, Ph C -1), 128.6 (t, Ph CH -2,6), 128.4 (t, Ph CH -3,5), 128.1 (t, Ph CH -4), 74.7 (s, CH_2COCl), 73.5 (s, $PhCH_2O$) ppm. IR (film): $\tilde{\nu}$ = 3065, 3033, 2875, 1802, 1497, 1455, 1412, 1390, 1264, 1211, 1134, 1027, 944, 758, 699, 605, 559, 477, 430 cm^{-1} . UV/Vis (CH_2Cl_2 , c = 0.138 mg/mL): λ_{max} (log ϵ) = 254 (0.15), 258 (0.16), 264 (0.14) nm. EI-MS: m/z = 184.1 $[M]^+$, 121.1, 107.1, 91.1, 79.1, 65.2, 51.1, 39.1, 32.2, 28.2.

Methyl 2-Amino-4-benzoyloxy-3-oxobutanoate Hydrochloride Salt (6): To a solution of $KOtBu$ (13.47 g, 120.0 mmol) in dry THF (250 mL) a solution of **5** (25.33 g, 100.0 mmol) in THF (200 mL) was added dropwise while maintaining the inner temperature below –50 °C. After addition was completed (15 min) the resulting orange mixture was stirred for further 30 min at –60 to –50 °C, then transferred by a long, flexible double-tipped needle to a pre-cooled solution of benzoyloxyacetyl chloride (20.31 g, 110.0 mmol) in dry THF (200 mL) at –60 °C being stirred vigorously by a mechanical stirrer. After completion of the addition (30 min) the mixture was stirred further 60 min at –60 to –50 °C, then quenched by rapidly adding 2 M aqueous HCl solution (200 mL), and stirred at room temperature for 2 h. THF was then removed in a rotary evaporator (150 mbar, 35 °C) and the mixture was extracted with EtOAc (3 $\times$ 100 mL). The organic layers were re-extracted with 2 M HCl (1 $\times$ 50 mL) then discarded. The aqueous layers were combined and the solvents evaporated. The residue solidified upon exhaustive drying in vacuo (< 1.0 mbar, 35 °C, 6–8 h) and this raw product (contains 0.120 mol of KCl; calcd. yield 76.3%; yellow glassy solid) was used without further purification for the next synthetic step. 1H NMR (300 MHz, $[D_6]DMSO$): δ = 9.18 (br. s, 3 H; NH_3^+), 7.37–7.34 (m, 5 H, Ph CH -2,3,4,5,6), 5.34 (s, 1 H, $CHCO_2Me$), 4.58 (s, 2 H, $PhCH_2O$), 4.55 (s, 2 H, $BnOCH_2CO$), 3.76 (s, 3 H, CO_2CH_3) ppm. ^{13}C NMR (75 MHz, $[D_6]DMSO$): δ = 197.0 (q, CO), 164.0 (q, CO_2Me), 137.5 (q, Ph C -1), 128.3 (t, Ph CH -2,6), 127.8 (t, Ph CH -3,4,5), 73.4 (s, $BnOCH_2CO$), 72.4 (s, $PhCH_2O$), 57.9 (t, $CHCO_2Me$), 53.7 (s, CO_2CH_3) ppm. ESI-HRMS: m/z calcd. for $C_{12}H_{16}NO_4$ $[MH]^+$ 238.1085, found 238.1054.

Amido Ketone 7: Boc-L-Val-OH (13.036 g, 60.0 mmol) was dissolved in DCM (120 mL), NMM (6.069 g, 60.0 mmol) was added, and the solution was cooled to –35 °C under Ar. Isobutyl chloroformate (8.195 g, 60.0 mmol) in DCM (30 mL) was slowly added while the inner temperature was maintained at –35 °C. After an hour, the resulting suspension was transferred via cannula into a second round-bottom flask equipped with a mechanical stirrer and containing the amino ketone **6** (16.423 g, 60.0 mmol) covered by DCM (120 mL) and pre-cooled to –40 °C. Right after the transfer was completed, a second equivalent of NMM (6.069 g, 60.0 mmol) in DCM (30 mL) was added to the vigorously stirred mixture at –35 °C. Stirring was continued for 8 h while the mixture was

warmed up to room temperature within a few hours. The mixture was then diluted with DCM (300 mL) and extracted with water (1 $\times$ 100 mL), 1 M $KHSO_4$ (1 $\times$ 100 mL) and brine (1 $\times$ 100 mL). The organic layer was dried with $MgSO_4$, filtered off and the solvent was removed on a rotary evaporator. Purification was accomplished by flash-chromatography on silica gel (PE/EtOAc, 70:30 $\rightarrow$ 50:50) to yield 14.404 g (55.0%) of **7** as a 1:1 mixture of two diastereomers as a yellowish oil. TLC: R_f = 0.40 (PE/EtOAc, 60:40, silica). 1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.32 (m, 5 H, Ph CH -2,3,4,5,6), 7.09 (d, $^3J_{H,H}$ = 6.3 Hz, 1 H; amide NH), 5.41 (d, $^3J_{H,H}$ = 6.3 Hz, 1 H; $CHCO_2Me$), 5.05 (br. d, $^3J_{H,H}$ = 7.5 Hz, 1 H; Boc NH), 4.62 (d, $^2J_{H,H}$ = 11.8 Hz, 1 H; $PhCH_2O$), 4.59 (d, $^2J_{H,H}$ = 11.8 Hz, 1 H; $PhCH_2O$), 4.42 (d, $^2J_{H,H}$ = 17.6 Hz, 0.5 H; $BnOCH_2CO$), 4.41 (d, $^2J_{H,H}$ = 17.6 Hz, 0.5 H; $BnOCH_2CO$), 4.36 (d, $^2J_{H,H}$ = 17.6 Hz, 0.5 H; $BnOCH_2CO$), 4.35 (d, $^2J_{H,H}$ = 17.6 Hz, 0.5 H; $BnOCH_2CO$), 4.07 (br. s, 1 H; Val α -CH), 3.734 (s, 1.5 H; CO_2CH_3), 3.731 (s, 1.5 H; CO_2CH_3), 2.23–2.11 (m, 1 H, Val β -CH), 1.441 (s, 4.5 H; Boc CH_3), 1.438 (s, 4.5 H; Boc CH_3), 0.97 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H; Val CH_3), 0.908 (d, $^3J_{H,H}$ = 6.9 Hz, 1.5 H; Val CH_3), 0.906 (d, $^3J_{H,H}$ = 6.9 Hz, 1.5 H; Val CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.95 (q, CO), 198.84 (q, CO), 171.5 (q, amide $CONH$), 166.09 (q, CO_2Me), 166.06 (q, CO_2Me), 155.75 (q, Boc $CONH$), 155.72 (q, Boc $CONH$), 136.7 (q, Ph C -1), 128.48 (t, Ph CH), 128.09 (t, Ph CH), 128.00 (t, Ph CH), 127.98 (t, Ph CH), 80.1 (q, Boc C), 73.59 (s, $BnOCH_2$), 73.52 (s, $PhCH_2O$), 73.50 (s, $PhCH_2O$), 59.45 (t, Val α -CH), 59.41 (t, Val α -CH), 58.8 (t, $CHCO_2Me$), 53.31 (p, CO_2CH_3), 53.27 (p, CO_2CH_3), 30.83 (t, Val β -CH), 30.74 (t, Val β -CH), 28.2 (p, Boc CH_3), 19.1 (p, Val CH_3), 17.4 (p, Val CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3320, 2968, 2931, 2875, 1700, 1519, 1454, 1392, 1368, 1248, 1166, 1045 (m 1018), 873, 739, 700, 605 cm^{-1} . UV/Vis (CH_2Cl_2 , c = 0.015 mg/mL): λ_{max} (log ϵ) = 236 (4.48), 256 (4.15), 274 (3.97), 322 (3.37) nm. ESI-HRMS: m/z calcd. for $C_{22}H_{32}N_2O_7$ $[MH]^+$ 437.2282, found 437.2306.

Oxazole 8: To a solution of **7** (4.365 g, 10.0 mmol) in anhydrous DCM (100 mL) at 5 °C under Ar a solution of triphenylphosphane (2.885 g, 11.0 mmol) and hexachloroethane (4.735 g, 20.0 mmol) in dry DCM (50 mL) was added followed by immediate addition of a solution of triethylamine (10.119 g, 100.0 mmol) in DCM (50 mL). The cooling bath was removed and the reaction mixture was stirred at ambient temperature for 2 d. The solvent was evaporated and purification was accomplished by flash chromatography on silica gel (DCM/EtOAc, 95:5 $\rightarrow$ 75:25) to yield 2.953 g (70.5%) of **8** as a white foam. TLC: R_f = 0.72 (DCM/EtOAc, 75:25, silica). 1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5 H, Ph CH -2,3,4,5,6), 5.27 (br. d, $^3J_{H,H}$ = 7.6 Hz, 1 H; Boc $CONH$), 4.86 (s, 1 H, CH_2OBn), 4.85 (s, 1 H, CH_2OBn), 4.80 (dd, $^3J_{H,H}$ = 8.8, $^3J_{H,H}$ = 6.4 Hz, 1 H; Val α -CH), 4.58 (s, 2 H, $PhCH_2O$), 3.88 (s, 3 H, CO_2CH_3), 2.20–2.15 (m, 1 H, Val β -CH), 1.42 (s, 9 H, Boc CH_3), 0.92 (d, $^3J_{H,H}$ = 6.7 Hz, 6 H; Val CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.9 (q, CO_2Me), 161.9 (q, oxazole C -5), 155.2 (q, oxazole C -2), 154.4 (q, Boc $CONH$), 137.2 (q, Ph C -1), 129.6 (q, oxazole C -4), 128.4 (t, Ph CH -2,6), 127.9 (t, Ph CH -4), 127.8 (t, Ph CH -3,5), 79.9 (q, Boc C), 72.8 (s, $PhCH_2O$), 61.1 (s, CH_2OBn), 54.1 (t, Val α -CH), 52.2 (p, CO_2CH_3), 32.9 (t, Val β -CH), 28.2 (p, Boc CH_3), 18.7 (p, Val CH_3), 17.8 (p, Val CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3357, 2968, 2933, 2874, 1721, 1620, 1578, 1509, 1454, 1441, 1391, 1367, 1344, 1301, 1244, 1210, 1173, 1094, 1013, 878, 741, 699 cm^{-1} . UV/Vis (CH_2Cl_2 , c = 0.040 mg/mL): λ_{max} (log ϵ) = 236 (4.93), 278 (3.62) nm. ESI-HRMS: m/z calcd. for $C_{22}H_{30}N_2O_6$ $[MH]^+$ 419.2177, found 419.2216.

Oxazolecarboxylic Acid 21: Oxazole **8** (8.370 g, 20.0 mmol) was dissolved in a mixture of methanol (80 mL) and dioxane (20 mL) followed by slow addition of 2 M NaOH solution (20 mL, 40.0 mmol)

at 0 °C. The ice bath was removed and stirring was continued overnight. After TLC showed consumption of all starting material the mixture was diluted with brine (400 mL) and acidified with 2 M HCl (25 mL). The mixture was then repeatedly extracted with DCM (3 × 100 mL), the organic layers were combined, dried with MgSO₄, filtered off, and the filtrate was concentrated in vacuo to give 7.871 g (97.3%) of the free acid **21**, which was used without further purification for the next step. TLC: *R*_f = 0.30 (DCM/EtOAc/MeOH, 75:25:5, silica). ¹H NMR (300 MHz, CDCl₃): δ = 9.00 (br. s, 1 H; CO₂H), 7.35–7.28 (m, 5 H, Ph CH-2,3,4,5,6), 6.45 (br. d, ³*J*_{H,H} = 9.3 Hz, 1 H; Boc CONH), 4.97 (d, ²*J*_{H,H} = 13.8 Hz, 1 H; CH₂O₂), 4.88 (d, ²*J*_{H,H} = 13.8 Hz, 1 H; CH₂O₂), 4.85 (dd, ³*J*_{H,H} = 9.3, ³*J*_{H,H} = 6.6 Hz, 1 H; Val α-CH), 4.61 (s, 2 H, PhCH₂O), 2.28–2.17 (m, 1 H, Val β-CH), 1.39 (s, 9 H, Boc CH₃), 0.98 (d, ³*J*_{H,H} = 6.8 Hz, 3 H; Val CH₃), 0.94 (d, ³*J*_{H,H} = 6.8 Hz, 3 H; Val CH₃) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 165.4 (q, CO₂H), 163.8 (q, oxazole C-5), 155.8 (q, Boc CONH), 155.2 (q, oxazole C-2), 137.2 (q, Ph C-1), 129.3 (q, oxazole C-4), 128.4 (t, Ph CH-2,6), 128.0 (t, Ph CH-3,5), 127.9 (t, Ph CH-4), 79.8 (q, Boc C), 72.9 (s, PhCH₂O), 61.1 (s, CH₂O₂), 54.5 (t, Val α-CH), 32.7 (t, Val β-CH), 28.2 (p, Boc CH₃), 18.9 (p, Val CH₃), 18.1 (p, Val CH₃) ppm. IR (KBr): ν̄ = 3424, 2973, 2933, 1717, 1625, 1573, 1518, 1455, 1393, 1368, 1282, 1246, 1170, 1072, 1014, 877, 738, 698, 604, 463 cm⁻¹. UV/Vis (CH₂Cl₂, *c* = 0.132 mg/mL): λ_{max} (log ε) = 236 (3.87), 294 (2.49) nm. ESI-HRMS: *m/z* calcd. for C₂₁H₂₉N₂O₆ [MH⁺] 405.2020, found 405.2057.

Oxazolecarboxylic Acid Hydrochloride Salt 9: Boc-protected amino acid **21** (6.067 g, 15.0 mmol) was dissolved in EtOAc (60 mL) and concentrated (5 M, 20%) solution of HCl in EtOAc (30 mL, 150.0 mmol) was added. After 30 min the ice bath was removed and stirring was continued at room temperature for two hours. Then the solvent was removed on a rotary evaporator to provide 5.050 g (98.9%) of the hydrochloride salt **9** as a slightly grey hygroscopic powder. ¹H NMR (300 MHz, [D₆]DMSO): δ = 9.10 (br. s, 4 H; CO₂H und NH₃⁺), 7.37–7.26 (m, 5 H, Ph CH-2,3,4,5,6), 4.86 (s, 2 H, CH₂O₂), 4.55 (s, 2 H, PhCH₂O), 4.43 (d, ³*J*_{H,H} = 6.8 Hz, 1 H; Val α-CH), 2.37–2.26 (m, 1 H, Val β-CH), 1.01 (d, ³*J*_{H,H} = 6.8 Hz, 3 H; Val CH₃), 0.86 (d, ³*J*_{H,H} = 6.8 Hz, 3 H; Val CH₃) ppm. ¹³C NMR (75 MHz, [D₆]DMSO): δ = 162.0 (q, oxazole C-5), 159.0 (q, CO₂H), 154.6 (q, oxazole C-2), 137.6 (q, Ph C-1), 130.1 (q, oxazole C-4), 128.2 (t, Ph CH-2,6), 127.7 (t, Ph CH-3,5), 127.6 (t, Ph CH-4), 71.7 (s, PhCH₂O), 60.8 (s, CH₂O₂), 52.8 (t, Val α-CH), 30.6 (t, Val β-CH), 18.5 (p, Val CH₃), 17.3 (p, Val CH₃) ppm. IR (KBr): ν̄ = 3406, 3031, 2969, 2878, 1968, 1718, 1605, 1517, 1455, 1429, 1398, 1361, 1314, 1186, 1097, 1070, 1028, 920, 809, 741, 699 cm⁻¹. UV/Vis (MeOH, *c* = 0.0134 mg/mL): λ_{max} (log ε) = 207 (4.21), 218 (sh, 4.14), 257 (2.71) nm. ESI-HRMS: *m/z* calcd. for C₁₆H₂₁N₂O₄ [MH⁺] 305.1496, found 305.1517.

Scaffolds 10 and 11: To a solution of the free amino acid **9** (1.704 g, 5.0 mmol) in anhydrous DMF (125 mL) at room temperature PyBOP (3.903 g, 7.5 mmol) was added followed by addition of *i*Pr₂NEt (4.201 g, 32.5 mmol) and the mixture was stirred under Ar for 4 d. The solvent was evaporated and the residue was taken up in EtOAc (500 mL), then washed with 2 M HCl (2 × 50 mL), water (2 × 50 mL) and brine (1 × 50 mL). The organic layer was dried with MgSO₄, filtered, concentrated and the residue was subjected to column chromatography on silica gel (PE/EtOAc, 80:20 → 60:40) to obtain 0.490 g (34.5%) of oxazole trimer **10** and 0.340 g (23.8%) of oxazole tetramer **11** as white powders.

Data for 10: TLC: *R*_f = 0.55 (PE/EtOAc, 60:40, silica). ¹H NMR (500 MHz, CDCl₃): δ = 8.24 (d, ³*J*_{H,H} = 7.9 Hz, 1 H; amide NH), 7.34–7.29 (m, 4 H, Ph CH-2,3,5,6), 7.27–7.24 (m, 1 H, Ph CH-4),

5.14 (dd, ³*J*_{H,H} = 7.9, ³*J*_{H,H} = 4.8 Hz, 1 H; Val α-CH), 4.98 (s, 2 H, CH₂O₂), 4.60 (s, 2 H, PhCH₂O), 2.42–2.33 (m, 1 H, Val β-CH), 1.09 (d, ³*J*_{H,H} = 6.9 Hz, 3 H; Val CH₃), 1.05 (d, ³*J*_{H,H} = 6.9 Hz, 3 H; Val CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 162.5 (q, oxazole C-2), 160.0 (q, CONH), 152.1 (q, oxazole C-5), 137.5 (q, Ph C-1), 131.1 (q, oxazole C-4), 128.3 (t, Ph CH-2,6), 127.8 (t, Ph CH-3,5), 127.7 (t, Ph CH-4), 72.9 (s, PhCH₂O), 61.3 (s, CH₂O₂), 53.1 (t, Val α-CH), 33.6 (t, Val β-CH), 18.43 (p, Val CH₃), 18.27 (p, Val CH₃) ppm. IR (KBr): ν̄ = 3390, 3089, 3064, 3032, 2965, 2931, 2873, 1731, 1682, 1575, 1519, 1455, 1435, 1390, 1373, 1316, 1271, 1205, 1140, 1088, 1072, 1028, 1001, 946, 902, 853, 793, 749, 697 cm⁻¹. UV/Vis (CH₂Cl₂, *c* = 0.0115 mg/mL): λ_{max} (log ε) = 235 (sh, 4.58), 292 (3.60) nm. CD (CH₂Cl₂, *c* = 0.0115 mg/mL): λ (Δε) = 230 (–37.6), 256 (0.0) nm (M⁻¹cm⁻¹). ESI-HRMS: *m/z* calcd. for C₄₈H₅₅N₆O₉ [MH⁺] 859.4025, found 859.4127.

Data for 11: TLC: *R*_f = 0.50 (PE/EtOAc, 60:40, silica). ¹H NMR (500 MHz, CDCl₃): δ = 7.31 (d, ³*J*_{H,H} = 9.7 Hz, 1 H; amide NH), 7.27–7.23 (m, 4 H, Ph CH-2,3,5,6), 7.22–7.18 (m, 1 H, Ph CH-4), 5.20 (dd, ³*J*_{H,H} = 9.7, ³*J*_{H,H} = 7.6 Hz, 1 H; Val α-CH), 4.94 (d, ²*J*_{H,H} = 13.1 Hz, 1 H; CH₂O₂), 4.83 (d, ²*J*_{H,H} = 13.1 Hz, 1 H; CH₂O₂), 4.54 (s, 2 H, PhCH₂O), 2.38–2.28 (m, 1 H, Val β-CH), 1.04 (d, ³*J*_{H,H} = 6.7 Hz, 3 H; Val CH₃), 0.97 (d, ³*J*_{H,H} = 6.7 Hz, 3 H; Val CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 162.4 (q, oxazole C-2), 160.2 (q, CONH), 152.1 (q, oxazole C-5), 137.5 (q, Ph C-1), 131.1 (q, oxazole C-4), 128.3 (t, Ph CH-2,6), 127.84 (t, Ph CH-3,5), 127.76 (t, Ph CH-4), 73.1 (s, PhCH₂O), 61.4 (s, CH₂O₂), 51.4 (t, Val α-CH), 32.5 (t, Val β-CH), 19.1 (p, Val CH₃), 18.4 (p, Val CH₃) ppm. IR (KBr): ν̄ = 3412, 3334, 3063, 3032, 2965, 2929, 2873, 1728, 1678, 1531, 1572, 1507, 1468, 1455, 1391, 1372, 1330, 1270, 1204, 1140, 1087, 1072, 1028, 1000, 939, 895, 934, 782, 741, 698 cm⁻¹. UV/Vis (CH₂Cl₂, *c* = 0.0199 mg/mL): λ_{max} (log ε) = 240 (sh, 4.59) nm. CD (CH₂Cl₂, *c* = 0.0199 mg/mL): λ (Δε) = 231 (–53.0), 267 (0.0) nm (M⁻¹cm⁻¹). ESI-HRMS: *m/z* calcd. for C₆₄H₇₃N₈O₁₂ [MH⁺] 1145.5342, found 1145.5465.

Scaffold 2: To a solution of **10** (0.172 g, 0.20 mmol) in DCM (200 mL) Palladium/charcoal catalyst (10%, 0.300 g) was added, and the mixture was stirred under hydrogen atmosphere (10⁵ Pa) at room temperature for 60 min. Then catalyst was removed by filtration and solvent was distilled off in a rotary evaporator to yield 0.117 g (99.4%) of **2** as a colorless solid. TLC: *R*_f = 0.32 (DCM/EtOAc/MeOH, 75:25:5, silica). ¹H NMR (500 MHz, CDCl₃): δ = 8.26 (d, ³*J*_{H,H} = 7.8 Hz, 1 H; amide NH), 5.38 (br. s, 2 H; CH₂OH), 5.07 (dd, ³*J*_{H,H} = 7.7, ³*J*_{H,H} = 4.8 Hz, 1 H; Val α-CH), 4.87 (d, ²*J*_{H,H} = 15.6 Hz, 1 H; CH₂OH), 4.84 (d, ²*J*_{H,H} = 15.6 Hz, 1 H; CH₂OH), 2.40–2.31 (m, 1 H, Val β-CH), 1.06 (d, ³*J*_{H,H} = 6.8 Hz, 3 H; Val CH₃), 1.02 (d, ³*J*_{H,H} = 6.8 Hz, 3 H; Val CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 161.3 (q, oxazole C-2), 160.9 (q, CONH), 156.7 (q, oxazole C-5), 130.0 (q, oxazole C-4), 56.1 (s, CH₂OH), 53.3 (t, Val α-CH), 33.4 (t, Val β-CH), 18.3 (p, 2 Val CH₃) ppm. IR (KBr): ν̄ = 3389, 2966, 2934, 2876, 2513, 1664, 1635, 1577, 1526, 1449, 1392, 1373, 1193, 1139, 1115, 1031, 967, 899, 782, 615, 473 cm⁻¹. ESI-HRMS: *m/z* calcd. for C₂₇H₃₇N₆O₉ [MH⁺] 589.2617, found 589.2686.

Scaffold 3: A solution of **2** (0.029 g, 0.05 mmol) in CHCl₃ (5 mL) was mixed with thionyl chloride (0.060 g, 0.50 mmol) for 15 min, then evaporated and dried in vacuo to give 0.0318 g (98.8%) of **3** as a white solid. ¹H NMR (500 MHz, CDCl₃): δ = 8.20 (d, ³*J*_{H,H} = 7.9 Hz, 1 H; amide NH), 5.12 (dd, ³*J*_{H,H} = 7.9, ³*J*_{H,H} = 4.9 Hz, 1 H; Val α-CH), 5.04 (d, ²*J*_{H,H} = 12.9 Hz, 1 H; CH₂Cl), 4.96 (d, ²*J*_{H,H} = 12.9 Hz, 1 H; CH₂Cl), 2.41–2.34 (m, 1 H, Val β-CH), 1.10 (d, ³*J*_{H,H} = 6.8 Hz, 3 H; Val CH₃), 1.04 (d, ³*J*_{H,H} = 6.8 Hz, 3 H; Val CH₃) ppm. ¹³C NMR (125 MHz, CDCl₃): δ = 162.76 (q,

CONH), 162.72 (q, *CONH*), 159.64 (q, oxazole *C*-2), 159.59 (q, oxazole *C*-2), 150.7 (q, oxazole *C*-5), 130.43 (q, oxazole *C*-4), 130.40 (q, oxazole *C*-4), 53.29 (t, Val α -*CH*), 53.20 (t, Val α -*CH*), 33.67 (t, Val β -*CH*), 33.56 (s, *CH₂Cl*), 18.38 (p, Val *CH₃*), 18.35 (p, Val *CH₃*) ppm. ESI-HRMS: *m/z* calcd. for $C_{27}H_{34}O_6N_6^{35}Cl_2^{37}Cl$ [MH^+] 645.1576, found 645.1609.

***N*-(Diphenylmethylene)glycine Benzyl Ester 12:** To a stirred slurry of glycine benzyl ester 4-toluenesulfonate (67.48 g, 200.0 mmol) in DCM (400 mL) was added benzophenone imine (36.25 g, 200.0 mmol) in DCM (200 mL) over a period of 15 min, and then the mixture was stirred for 24 h at ambient temperature. The resulting white milky mixture was extracted with water (3 $\times$ 200 mL) and brine (100 mL), then the organic layer was separated, dried with $MgSO_4$, filtered and the solvents evaporated. The solidified raw product was grinded and stirred in petroleum ether (200 mL) for a half hour, then filtered and dried to obtain 52.70 g (80.0%) of **12** as a white powder. TLC: R_f = 0.63 (PE/EtOAc, 3:1, silica). 1H NMR (300 MHz, $CDCl_3$): δ = 7.81 (dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.5 Hz, 1 H), 7.67 (dd, $^3J_{H,H}$ = 8.1, $^4J_{H,H}$ = 1.5 Hz, 2 H), 7.50 (dd, $^3J_{H,H}$ = 6.0, $^4J_{H,H}$ = 1.5 Hz, 1 H), 7.44 (d, $^3J_{H,H}$ = 6.6 Hz, 2 H), 7.35 (d, $^3J_{H,H}$ = 6.6 Hz, 2 H), 7.35 (s, 5 H), 7.17 (d, $^3J_{H,H}$ = 6.6 Hz, 1 H), 7.15 (d, $^3J_{H,H}$ = 6.6 Hz, 1 H), 5.20 (s, 2 H, *CO₂CH₂Ph*), 4.27 (q, *Ph₂C=N*), 170.4 (q, *CO₂Bn*), 139.1 (q), 135.9 (q), 135.7 (q), 130.5 (t), 128.8 (t), 128.75 (t, 2 C), 128.65 (t, 2 C), 128.5 (t, 2 C), 128.3 (t, 2 C), 128.2 (t, 2 C), 128.0 (t), 127.6 (t, 2 C), 66.5 (s, *CO₂CH₂Ph*), 55.6 (s, *CH₂CO₂Bn*) ppm. IR (KBr): $\tilde{\nu}$ = 3432, 3060, 2955, 2900, 2870, 1960, 1894, 1829, 1748, 1624, 1596, 1444, 1386, 1351, 1313, 1288, 1220, 1177, 1054, 958, 918, 908, 780, 758, 706, 696, 583 cm^{-1} . UV/Vis (CH_2Cl_2 , c = 0.012 mg/mL): λ_{max} (log ϵ) = 250 (4.164) nm. ESI-HRMS: *m/z* calcd. for $C_{22}H_{20}NO_2$ [MH^+] 330.1489, found 330.1498. $C_{22}H_{19}NO_2$ (329.392): calcd. C 80.22, H 5.81, N 4.25; found C 80.12, H 5.82, N 4.25.

Phthalimidoacetic Acid: In a three-necked round-bottom flask were placed glycine (22.52 g, 300.0 mmol), phthalic anhydride (44.44 g, 300.0 mmol), triethylamine (3.036 g, 30.0 mmol) and toluene (180 mL). The flask was equipped with a stirring bar, a Dean-Stark trap and a reflux condenser. The mixture was heated to reflux temperature and stirred for further 6 h with azeotropic removal of water. After completion of the reaction the solvent was removed in a rotary evaporator. The resulting white solid was taken up in water (450 mL) and the mixture was acidified by adding concd. hydrochloric acid (6.0 mL, 66.0 mmol). The product was collected by filtration, washed with water (2 $\times$ 30 mL) and dried to yield 60.87 g (98.9%) of the carboxylic acid as a white powder. TLC: R_f = 0.12 (PE/EtOAc, 2:1, silica). 1H NMR (300 MHz, $[D_6]DMSO$): δ = 12.80 (br. s, 1 H; *CO₂H*), 7.95–7.85 (m, 4 H, PhtN *CH*-2,3,4,5), 4.32 (s, 2 H, *CH₂CO₂H*) ppm. ^{13}C NMR (75 MHz, $[D_6]DMSO$): δ = 168.7 (q, *CO₂H*), 167.1 (q, 2 PhtN *CO*), 134.7 (t, PhtN *CH*-3,4), 131.3 (q, PhtN *C*-1,6), 123.3 (t, PhtN *CH*-2,5), 38.8 (s, *CH₂CO₂H*) ppm. IR (KBr): $\tilde{\nu}$ = 3433, 2935, 1773, 1724, 1616, 1469, 1418, 1391, 1319, 1248, 1195, 1119, 1087, 957, 800, 738, 715, 623, 563, 531 cm^{-1} . UV/Vis (CH_2Cl_2 , c = 0.147 mg/mL): λ_{max} (log ϵ) = 234 (4.08), 240 (3.97), 294 (3.22) nm. EI-MS: *m/z* (%) = 205.0 (5) [M] $^+$, 165.0 (100) [M – 40u] $^+$. $C_{10}H_7NO_4$ (205.167): calcd. C 58.54, H 3.44, N 6.83; found C 58.30, H 3.51, N 6.87.

Phthalimidoacetyl Chloride: In a round-bottom flask were placed phthalimidoacetic acid (41.03 g, 200.0 mmol) and chloroform (40 mL), then thionyl chloride (20.0 mL, 275.0 mmol) was cautiously added. The flask was equipped with a reflux condenser, flushed with argon, and the mixture was stirred at reflux temperature for 3 h, to obtain a light yellowish, clear solution. Then solvent

and excess of thionyl chloride were removed in a rotary evaporator to obtain 43.92 g (98.2%) of the acid chloride as a slightly grey-brownish solid. 1H NMR (300 MHz, $CDCl_3$): δ = 7.94–7.88 (m, 2 H, PhtN *CH*-2,5), 7.82–7.74 (m, 2 H, PhtN *CH*-3,4), 4.82 (s, 2 H, *CH₂COCl*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1 (q, *COCl*) 166.6 (q, 2 PhtN *CO*), 134.6 (t, PhtN *CH*-3,4), 131.6 (q, PhtN *C*-1,6), 124.0 (t, PhtN *CH*-2,5), 47.6 (p, *CH₂COCl*) ppm. IR (KBr): $\tilde{\nu}$ = 3422, 2979, 2936, 1804, 1774, 1722, 1468, 1418, 1313, 1195, 1117, 1088, 998, 957, 937, 736, 715, 609, 531, 521 cm^{-1} . UV/Vis (CH_2Cl_2 , c = 0.137 mg/mL): λ_{max} (log ϵ) = 240 (3.98), 296 (3.29), 306 (3.21) nm. EI-MS: *m/z* (%) = 223.0 (1) [M] $^+$, 160.0 (100) [M – 63u] $^+$. $C_{10}H_6ClNO_3$ (223.613): calcd. C 53.71, H 2.70, N 6.26; found C 53.86, H 2.81, N 6.29.

Benzyl 2-Amino-3-oxo-4-phthalimidoobutanoate Hydrochloride Salt 13: A solution of KO t Bu (11.22 g, 100.0 mmol) in dry THF (200 mL) was cooled under argon to –60 $^{\circ}C$, and a solution of *N*-(diphenylmethylene)glycine benzyl ester (32.94 g, 100.0 mmol) in THF (200 mL) was added dropwise while maintaining the inner temperature below –50 $^{\circ}C$. After addition was completed (15 min) the resulting orange mixture was stirred for further 30 min at –60 to –50 $^{\circ}C$, then transferred by a long, flexible double-tipped needle to a pre-cooled solution of phthalimidoacetyl chloride (22.36 g, 200.0 mmol) in dry THF (200 mL) at –60 $^{\circ}C$ being stirred vigorously by a mechanical stirrer. After completion of the addition (30 min) the mixture was stirred for further 60 min at –60 to –50 $^{\circ}C$, then quenched by rapidly adding 2 M aqueous HCl solution (100 mL), and stirred at room temperature for 2 h. Then THF was removed in a rotary evaporator (200 $\rightarrow$ 120 mbar, 40 $^{\circ}C$) and the remaining mixture was transferred into a separation funnel. The lower oily layer was separated, then mixed with cold EtOAc (100 mL) to induce precipitation of the product. The resulting white solid was filtered off, washed with cold EtOAc (50 mL) and dried. A second crop of the product could be obtained from the aqueous layer by shaking it with EtOAc (100 mL) followed by filtration. Overall product yield: 32.54 g (83.7%) of **13** as a white powder. 1H NMR (500 MHz, $[D_6]DMSO$): δ = 9.21 (br. s, 3 H; NH_3^+), 7.95–7.92 (m, 2 H, PhtN *CH*-2,5), 7.92–7.88 (m, 2 H, PhtN *CH*-3,4), 7.52 (d, $^3J_{H,H}$ = 7.0 Hz, 2 H; Bn *CH*-2,6), 7.43–7.37 (m, 3 H, Bn *CH*-3,4,5), 5.84 (s, 1 H, $CHNH_3^+$), 5.41 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H; Bn *CH₂*), 5.32 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H; Bn *CH₂*), 4.99 (d, $^2J_{H,H}$ = 18.9 Hz, 1 H; PhtN*CH₂CO*), 4.94 (d, $^2J_{H,H}$ = 18.9 Hz; PhtN*CH₂CO*) ppm. ^{13}C NMR (125 MHz, $[D_6]DMSO$): δ = 193.2 (q, PhtN*CH₂CO*), 166.9 (q, 2 PhtN *CO*), 162.9 (q, *CO₂Bn*), 134.8 (t, PhtN *CH*-3,4), 134.4 (q, Bn *C*-1), 131.2 (q, PhtN *C*-1,6), 128.46 (t, Bn *CH*-4), 128.43 (t, Bn *CH*-3,5), 128.3 (t, Bn *CH*-2,6), 123.4 (t, PhtN *CH*-2,5), 68.5 (s, Bn *CH₂*), 59.5 (t, $CHNH_3^+$), 45.3 (s, PhtN*CH₂CO*) ppm. IR (KBr): $\tilde{\nu}$ = 3474, 3319, 3170, 3125, 3087, 3065, 3031, 2970, 2887, 2818, 2779, 2663, 2593, 1957, 1777, 1761, 1741, 1721, 1578, 1525, 1501, 1468, 1419, 1377, 1329, 1266, 1233, 1196, 1171, 1146, 1103, 1048, 1012, 947, 907, 882, 854, 820, 803, 753, 735, 713, 697, 618 cm^{-1} . UV/Vis (MeOH, c = 0.0058 mg/mL): λ_{max} (log ϵ) = 218 (4.46), 239 (3.88), 268 (4.03) nm. ESI-HRMS: *m/z* calcd. for $[C_{19}H_{17}N_2O_5]^+$ 353.1132, found 353.1108. $C_{19}H_{17}ClN_2O_5$ (388.802): calcd. C 58.69, H 4.41, N 7.21; found C 58.44, H 4.58, N 7.00.

Amido Ketone 14a: In a round-bottomed flask equipped with a mechanical stirrer Boc-L-Val-OH (13.04 g, 60.0 mmol) was dissolved in dry THF (120 mL) and *N*-methylmorpholine (6.069 g, 60.0 mmol) was added. The solution was cooled to –30 $^{\circ}C$ and a solution of isobutyl chloroformate (8.195 g, 60.0 mmol) in THF (30 mL) was added while the inner temperature was maintained at –30 to –25 $^{\circ}C$. After 60 min keto amine **13** (23.33 g, 60.0 mmol) was added in one portion followed by a solution of NMM (6.069 g,

60.0 mmol) in THF (30 mL) over a period of 30 min. Stirring was continued for 3 h at -30°C then the mixture was warmed up to room temperature in further 2 h. The solvent was evaporated and the residue was taken up in water (300 mL) and DCM (300 mL). The mixture was thoroughly shaken and the layers were separated then the aqueous layer was further extracted with DCM (2×100 mL). The collected organic layers were washed with 1 M KHSO_4 (50 mL), concd. NaHCO_3 (50 mL) and brine (50 mL), then dried with MgSO_4 , filtered, and concentrated in vacuo. Purification of the crude product was accomplished by chromatography on silica gel (DCM/EtOAc, 95:5 $\rightarrow$ 70:30) to yield 21.51 g (65.0%) of **14a** as a 1:1 mixture of two diastereomers as a white powder. TLC: R_f = 0.70 (DCM/EtOAc, 3:1, silica). ^1H NMR (300 MHz, CDCl_3): δ = 7.86 (dd, $^3J_{\text{H,H}} = 5.3$, $^4J_{\text{H,H}} = 3.0$ Hz, 2 H; PhtN CH-2,5), 7.73 (dd, $^3J_{\text{H,H}} = 5.3$, $^4J_{\text{H,H}} = 3.0$ Hz, 2 H; PhtN CH-3,4), 7.41–7.33 (m, 5 H, Z CH-2,3,4,5,6), 7.15–7.11 (2 d, $^3J_{\text{H,H}} = 5.5$ Hz, 1 H; amide NH), 5.51–5.47 (2 d, $^3J_{\text{H,H}} = 6.8$ Hz, 1 H; NHCHCO_2Bn), 5.34–5.24 (4 d, 2 H; $\text{CO}_2\text{CH}_2\text{Ph}$), 5.05–5.00 (2 $\times$ br. d, 1 H; Boc NH), 4.89–4.82 (2 d, $^2J_{\text{H,H}} = 18.1$ Hz, 1 H; PhtNCH_2), 4.76–4.69 (2 d, $^2J_{\text{H,H}} = 18.1$ Hz, 1 H; PhtNCH_2), 4.08 (br. m, 1 H; Val α -CH), 2.23–2.13 (m, 1 H, Val β -CH), 1.43–1.42 (2 s, 9 H; Boc CH_3), 0.97–0.94 (2 d, $^3J_{\text{H,H}} = 6.8$ Hz, 3 H; Val CH_3), 0.90–0.87 (2 d, $^3J_{\text{H,H}} = 6.8$ Hz, 3 H; Val CH_3) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 193.76 (q, PhtNCH_2CO), 193.67 (q, PhtNCH_2CO), 171.6 (q, amide CO), 167.13 (q, 2 PhtN CO), 167.10 (q, 2 PhtN CO), 164.9 (q, CO_2Bn), 155.8 (q, Boc CO), 134.8 (q, Bn C-1), 134.22 (t, PhtN CH-3,4), 134.20 (t, PhtN CH-3,4), 132.0 (q, PhtN C-1,6), 128.81 (t, Bn CH), 128.74 (t, Bn CH), 128.72 (t, Bn CH), 123.6 (t, PhtN CH-2,5), 80.19 (q, Boc C(CH_3)₃), 80.16 (q, Boc C(CH_3)₃), 68.93 (s, Bn CH_2), 68.90 (s, Bn CH_2), 60.68 (t, NHCHCO_2Bn), 60.66 (t, NHCHCO_2Bn), 59.51 (t, Val α -CH), 59.47 (t, Val α -CH), 45.28 (s, PhtNCH_2), 45.20 (s, PhtNCH_2), 30.75 (t, Val α -CH), 28.25 (p, Boc CH_3), 19.2 (p, Val CH_3), 19.1 (p, Val CH_3), 17.4 (p, Val CH_3), 17.3 (p, Val CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3420, 2969, 1722, 1500, 1468, 1416, 1392, 1261, 1166, 1111, 948, 716, 698, 531 cm^{-1} . UV/Vis (MeOH, c = 0.0069 mg/mL): λ_{max} (log ϵ) = 219 (4.76), 239 (4.08), 279 (3.65) nm. ESI-HRMS: m/z calcd. for $[\text{C}_{29}\text{H}_{34}\text{N}_3\text{O}_8]^+$ 552.2340, found 552.2316.

Amido Ketone 14b: In a round-bottomed flask equipped with a mechanical stirrer Z-L-Val-OH (15.08 g, 60.0 mmol) was dissolved in dry DCM (300 mL) and *N*-methylmorpholine (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 60 min keto amine **13** (23.33 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 warmed up to room temperature in further 2 h 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) then dried in vacuo. The crude product was recrystallized from EtOH/*i*PrOH to yield 30.85 g (87.8%) of **14b** as a 1:1 mixture of two diastereomers as a white powder. TLC: R_f = 0.62 (DCM/EtOAc, 3:1, silica). ^1H NMR (500 MHz, CDCl_3): δ = 7.87–7.83 (2 dd, 2 H; PhtN CH-2,5), 7.74–7.72 (2 dd, 2 H; PhtN CH-3,4), 7.40–7.32 (m, 10 H, Z and Bn CH-2,3,4,5,6), 7.21–7.19 (2 d, $^3J_{\text{H,H}} = 5.6$ Hz, 1 H; amide NH), 5.53–5.49 (2 d, $^3J_{\text{H,H}} = 7.8$ Hz, 1 H; NHCHCO_2Bn), 5.44–5.40 (2 d, $^3J_{\text{H,H}} = 9.6$ Hz, 1 H; Z NH), 5.31–5.25 (4 d, 2 H; Z CH_2), 5.12–5.04 (4 d, 2 H; $\text{CO}_2\text{CH}_2\text{Ph}$), 4.85 (d, $^2J_{\text{H,H}} = 18.2$ Hz, 0.5 H; PhtNCH_2), 4.84 (d, $^2J_{\text{H,H}} = 18.2$ Hz, 0.5 H; PhtNCH_2), 4.75 (d, $^2J_{\text{H,H}} = 18.2$ Hz, 0.5

H; PhtNCH_2), 4.71 (d, $^2J_{\text{H,H}} = 18.2$ Hz, 0.5 H; PhtNCH_2), 4.20 (br. d, $^3J_{\text{H,H}} = 5.6$ Hz, 0.5 H; Val α -CH), 4.18 (br. d, $^3J_{\text{H,H}} = 6.6$ Hz, 0.5 H; Val α -CH), 2.20–2.11 (m, 1 H, Val β -CH), 0.95 (pst, $^3J_{\text{H,H}} = 6.9$ Hz, 3 H; Val CH_3), 0.90 (d, $^3J_{\text{H,H}} = 6.9$ Hz, 3 H; Val CH_3) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 193.71 (q, PhtNCH_2CO), 193.66 (q, PhtNCH_2CO), 171.2 (q, amide CO), 167.1 (q, 2 PhtN CO), 164.92 (q, CO_2Bn), 164.89 (q, CO_2Bn), 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_2Bn), 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): $\tilde{\nu}$ = 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, c = 0.0051 mg/mL): λ_{max} (log ϵ) = 217 (4.806), 240 (sh, 4.077), 280 (3.684) nm. ESI-HRMS: m/z calcd. for $[\text{C}_{32}\text{H}_{32}\text{N}_3\text{O}_8]^+$ 586.2184, found 586.2180.

Oxazole 15a: To a solution of **14a** (5.516 g, 10.0 mmol) in dry DCM (50 mL) a solution of hexachloroethane (4.735 g, 20.0 mmol) and triphenylphosphane (2.885 g, 11.0 mmol) in DCM (50 mL) was added followed by triethylamine (10.12 g, 100 mmol) in DCM (25 mL) at room temperature. After completion of addition the mixture was stirred for a week. The volatiles were then removed at reduced pressure leaving a viscous, tacky material, which was subjected to column chromatography on silica gel (DCM/EtOAc, 95:5 $\rightarrow$ 75:25) to give 2.775 g (52.0%) of **15a** as a white solid. TLC: R_f = 0.80 (DCM/EtOAc, 3:1, silica). ^1H NMR (300 MHz, CDCl_3): δ = 7.87 (dd, $^3J_{\text{H,H}} = 5.5$, $^4J_{\text{H,H}} = 3.1$ Hz, 2 H; PhtN CH-2,5), 7.75 (dd, $^3J_{\text{H,H}} = 5.5$, $^4J_{\text{H,H}} = 3.1$ Hz, 2 H; PhtN CH-3,4), 7.46 (dd, $^3J_{\text{H,H}} = 7.6$, $^4J_{\text{H,H}} = 1.6$ Hz, 2 H; Bn CH-3,5), 7.38–7.31 (m, 3 H, Bn CH-2,4,6), 5.43 (d, $^2J_{\text{H,H}} = 12.3$ Hz, 1 H; Bn CH_2), 5.38 (d, $^2J_{\text{H,H}} = 12.3$ Hz, 1 H; Bn CH_2), 5.26 (d, $^3J_{\text{H,H}} = 9.4$ Hz, 1 H; Boc NH), 5.24 (d, $^2J_{\text{H,H}} = 16.4$ Hz, 1 H; PhtNCH_2), 5.17 (d, $^2J_{\text{H,H}} = 16.4$ Hz, 1 H; PhtNCH_2), 4.69 (dd, $^3J_{\text{H,H}} = 9.1$, $^3J_{\text{H,H}} = 5.8$ Hz, 1 H; Val α -CH), 2.14–2.03 (m, 1 H, Val β -CH), 1.38 (s, 9 H, Boc CH_3), 0.84 (d, $^3J_{\text{H,H}} = 6.8$ Hz, 6 H; Val CH_3) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ = 167.1 (q, 2 PhtN CO), 163.4 (q, oxazole C-5), 161.2 (q, CO_2Bn), 155.3 (q, oxazole C-2), 151.9 (q, Boc CO), 135.4 (q, oxazole C-4), 134.3 (t, PhtN CH-3,4), 131.8 (q, Bn C-1), 128.81 (q, PhtN C-1,6), 128.59 (t, Bn CH-2,6), 128.57 (t, Bn CH-3,5), 128.39 (t, Bn CH-4), 123.6 (t, PhtN CH-2,5), 79.9 (q, Boc C(CH_3)₃), 67.1 (s, Bn CH_2), 54.0 (t, Val α -CH), 32.9 (t, Val β -CH), 32.9 (s, PhtNCH_2), 28.2 (p, Boc CH_3), 18.5 (p, Val CH_3), 17.7 (p, Val CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3395, 2972, 1775, 1718, 1616, 1499, 1468, 1456, 1421, 1392, 1367, 1248, 1172, 1115, 1068, 941, 753, 715, 699, 530 cm^{-1} . UV/Vis (CH_2Cl_2 , c = 0.077 mg/mL): λ_{max} (log ϵ) = 294 (3.33) nm. ESI-HRMS: m/z calcd. for $[\text{C}_{29}\text{H}_{32}\text{N}_3\text{O}_7]^+$ 534.2235, found 534.2242.

Oxazole 15b: To a solution of **14b** (5.856 g, 10.0 mmol) in dry DCM (50 mL) a solution of hexachloroethane (4.735 g, 20.0 mmol) and triphenylphosphane (2.885 g, 11.0 mmol) in DCM (50 mL) was added followed by triethylamine (10.12 g, 100 mmol) in DCM (25 mL) at room temperature. After completion of addition the mixture was stirred for two weeks. The volatiles were then removed at reduced pressure leaving a viscous, tacky material, which was subjected to column chromatography on silica gel (DCM/EtOAc, 95:5 $\rightarrow$ 75:25) to give 4.297 g (75.7%) of **15b** as a white solid. TLC: R_f = 0.77 (DCM/EtOAc, 3:1, silica). ^1H NMR (300 MHz, CDCl_3):

$\delta = 7.86$ (dd, $^3J_{\text{H,H}} = 5.5$, $^4J_{\text{H,H}} = 3.1$ Hz, 2 H; PhtN *CH*-2,5), 7.74 (dd, $^3J_{\text{H,H}} = 5.5$, $^4J_{\text{H,H}} = 3.1$ Hz, 2 H; PhtN *CH*-3,4), 7.48–7.44 (m, 2 H), 7.39–7.28 (m, 8 H), 5.53 (d, $^3J_{\text{H,H}} = 9.4$ Hz, 1 H; Z *NH*), 5.40 (s, 2 H, Bn *CH*₂), 5.24 (d, $^2J_{\text{H,H}} = 16.2$ Hz, 1 H; *Ph*tN*CH*₂), 5.17 (d, $^2J_{\text{H,H}} = 16.2$ Hz, 1 H; *Ph*tN*CH*₂), 5.08 (d, $^2J_{\text{H,H}} = 12.3$ Hz, 1 H; Z *CH*₂), 5.03 (d, $^2J_{\text{H,H}} = 12.3$ Hz, 1 H; Z *CH*₂), 4.77 (dd, $^3J_{\text{H,H}} = 9.3$, $^3J_{\text{H,H}} = 5.9$ Hz, 1 H; Val α -*CH*), 2.17–2.06 (m, 1 H, Val β -*CH*), 0.86 (d, $^3J_{\text{H,H}} = 6.8$ Hz, 6 H; Val *CH*₃) ppm. ¹³C NMR (75 MHz, CDCl₃): $\delta = 167.1$ (q, 2 PhtN *CO*), 163.0 (q, oxazole *C*-5), 161.1 (q, *CO*₂Bn), 155.9 (q, oxazole *C*-2), 152.0 (q, Z *CO*), 136.1 (q, oxazole *C*-4), 135.3 (q, Bn *C*-1), 134.3 (t, PhtN *CH*-3,4), 131.8 (q, Z *C*-1), 128.8 (q, PhtN *C*-1,6), 128.62 (t, Bn *CH*-2,6), 128.57 (t, Z *CH*-2,6), 128.5 (t, Bn *CH*-3,5), 128.4 (t, Z *CH*-3,5), 128.1 (t, Bn *CH*-4), 128.0 (t, Z *CH*-4), 123.6 (t, PhtN *CH*-2,5), 67.1 (s, Z *CH*₂), 67.0 (s, Bn *CH*₂), 54.6 (t, Val α -*CH*), 32.9 (s, *Ph*tN*CH*₂), 32.85 (t, Val β -*CH*), 18.5 (p, Val *CH*₃), 17.8 (p, Val *CH*₃) ppm. UV/Vis (MeOH, $c = 0.0049$ mg/mL): λ_{max} (log ϵ) = 215 (4.59), 238 (sh, 4.18), 297 (2.96) nm. ESI-HRMS: m/z calcd. for [C₃₂H₃₀N₃O₇]⁺ 568.2078, found 568.2074.

Oxazolecarboxylic Acid 22: Oxazole **15a** (2.668 g, 5.0 mmol) in methanol (50 mL) was hydrogenated at room temperature and atmospheric pressure using Pearlman's catalyst (0.050 g, 20% Pd(OH)₂ on charcoal). The reaction was monitored by TLC, and on completion (3 h) the catalyst was filtered off and washed with several portions of methanol. The filtrate was then evaporated and dried in vacuo to obtain 2.171 g (97.9%) of the free acid **22** as a white solid. ¹H NMR (300 MHz, CDCl₃): $\delta = 8.70$ (br. s, 1 H; *CO*₂H), 7.87 (dd, $^3J_{\text{H,H}} = 5.2$, $^4J_{\text{H,H}} = 3.1$ Hz, 2 H; PhtN *CH*-2,5), 7.74 (dd, $^3J_{\text{H,H}} = 5.2$, $^4J_{\text{H,H}} = 3.1$ Hz, 2 H; PhtN *CH*-3,4), 6.17 (d, $^3J_{\text{H,H}} = 9.5$ Hz, 1 H; Boc *NH*), 5.28 (s, 2 H, *Ph*tN*CH*₂), 4.71 (dd, $^3J_{\text{H,H}} = 9.5$, $^3J_{\text{H,H}} = 6.3$ Hz, 1 H; Val α -*CH*), 2.18–2.03 (m, 1 H, Val β -*CH*), 1.37 (s, 9 H, Boc *CH*₃), 0.86 (t, $^3J_{\text{H,H}} = 6.8$ Hz, 6 H; Val *CH*₃) ppm. ¹³C NMR (75 MHz, CDCl₃): $\delta = 167.1$ (q, 2 PhtN *CO*), 164.5 (q, oxazole *C*-5), 163.8 (q, *CO*₂H), 155.7 (q, oxazole *C*-2), 152.9 (q, Boc *CO*), 134.3 (t, PhtN *CH*-3,4), 131.8 (q, PhtN *C*-1,6), 128.3 (q, oxazole *C*-4), 123.6 (t, PhtN *CH*-2,5), 79.8 (q, Boc *C*(*CH*₃)₃), 54.3 (t, Val α -*CH*), 32.9 (s, *Ph*tN*CH*₂), 32.8 (t, Val β -*CH*), 28.2 (p, Boc *CH*₃), 18.6 (p, Val *CH*₃), 18.0 (p, Val *CH*₃) ppm. IR (KBr): $\tilde{\nu} = 3387, 2973, 2935, 1776, 1726, 1617, 1514, 1468, 1420, 1393, 1368, 1307, 1247, 1171, 1116, 1070, 1015, 941, 715, 530$ cm⁻¹. UV/Vis (CH₂Cl₂, $c = 0.072$ mg/mL): λ_{max} (log ϵ) = 240 (4.259), 296 (3.22) nm. ESI-HRMS: m/z calcd. for [C₂₂H₂₆N₃O₇]⁺ 444.1765, found 444.1773.

Oxazolecarboxylic Acid Hydrochloride Salt 16. Preparation from 15b: To a solution of **15b** (2.838 g, 5.0 mmol) in MeOH (87.5 mL) 2 M aqueous HCl (12.5 mL, 25.0 mmol) and Pd/C catalyst (5%, 0.050 g) were added, and the mixture was stirred under hydrogen atmosphere (10⁵ Pa) at room temperature for 6 h. On completion the catalyst was removed through filtration and evaporation of the filtrate afforded 1.889 g (99.5%) of the hydrochloride salt **16** as a white powder.

Preparation from 22: To a solution of HCl in EtOAc (15%, 30 mL) oxazole carboxylic acid **22** (2.217 g, 5.0 mmol) was added, and the mixture was stirred for 2 h at ambient temperature. The volatiles were then removed in vacuo to provide 1.862 g (98.1%) of the hydrochloride salt **16** as a white powder, which was used in the next step without further purification. ¹H NMR (300 MHz, [D₆]-DMSO): $\delta = 8.98$ (br. s, 4 H; *CO*₂H and *NH*₃⁺), 7.94–7.86 (m, 4 H, PhtN *CH*-2,3,4,5), 5.20 (s, 2 H, *Ph*tN*CH*₂), 4.36 (d, $^3J_{\text{H,H}} = 6.0$ Hz, 1 H; Val α -*CH*), 2.28–2.16 (m, 1 H, Val β -*CH*), 0.91 (d, $^3J_{\text{H,H}} = 6.8$ Hz, 3 H; Val *CH*₃), 0.77 (d, $^3J_{\text{H,H}} = 6.8$ Hz, 3 H; Val *CH*₃) ppm. ¹³C NMR (75 MHz, [D₆]-DMSO): $\delta = 166.9$ (q, oxazole

C-5), 161.9 (q, 2 PhtN *CO*), 158.4 (q, *CO*₂H), 152.7 (q, oxazole *C*-2), 134.7 (q, oxazole *C*-4), 131.3 (t, PhtN *CH*-3,4), 129.0 (q, PhtN *C*-1,6), 123.3 (t, PhtN *CH*-2,5), 52.6 (t, Val α -*CH*), 32.7 (t, Val β -*CH*), 30.5 (s, *Ph*tN*CH*₂), 18.4 (p, Val *CH*₃), 17.0 (p, Val *CH*₃) ppm. IR (KBr): $\tilde{\nu} = 3420, 2967, 1775, 1718, 1613, 1511, 1468, 1421, 1394, 1245, 1190, 1118, 1068, 941, 828, 793, 715, 648, 607, 531$ cm⁻¹. UV/Vis (MeOH, $c = 0.060$ mg/mL): λ_{max} (log ϵ) = 220 (4.63), 240 (4.18), 290 (4.29) nm. ESI-HRMS: m/z calcd. for [C₁₇H₁₈N₃O₅]⁺ 344.1241, found 344.1269.

Scaffolds 17 and 18: To a solution of the free amino acid **16** (1.717 g, 5.0 mmol) in dry DMF (125 mL) were added PyBOP (3.903 g, 7.5 mmol) and *i*Pr₂N*Et* (4.201 g, 32.5 mmol) under argon atmosphere at 0 to 5 °C. After 15 min the cooling bath was removed and stirring was continued at room temperature for further 72 h. The solvent was then evaporated in vacuo, and purification of the product was performed by flash chromatography on silica gel (DCM/EtOAc/MeOH, 75:25:0 → 75:25:3) to yield 0.514 g (31.6%) of oxazole trimer **17** and 0.182 g (11.2%) of oxazole tetramer **18** as white powders.

Data for 17: TLC: $R_f = 0.50$ (DCM/EtOAc, 3:1, silica). ¹H NMR (500 MHz, CDCl₃): $\delta = 8.09$ (d, $^3J_{\text{H,H}} = 7.9$ Hz, 1 H; amide *NH*), 7.83 (dd, $^3J_{\text{H,H}} = 5.5$, $^4J_{\text{H,H}} = 3.1$ Hz, 2 H, 2 H; PhtN *CH*-2,5), 7.71 (dd, $^3J_{\text{H,H}} = 5.5$, $^4J_{\text{H,H}} = 3.1$ Hz, 2 H; PhtN *CH*-3,4), 5.34 (d, $^2J_{\text{H,H}} = 16.3$ Hz, 1 H; *Ph*tN*CH*₂), 5.21 (d, $^2J_{\text{H,H}} = 16.3$ Hz, 1 H; *Ph*tN*CH*₂), 4.99 (dd, $^3J_{\text{H,H}} = 7.9$, $^3J_{\text{H,H}} = 5.0$ Hz, 1 H; Val α -*CH*), 2.27–2.18 (m, 1 H, Val β -*CH*), 0.94 (d, $^3J_{\text{H,H}} = 6.9$ Hz, 3 H, Val *CH*₃), 0.92 (d, $^3J_{\text{H,H}} = 6.9$ Hz, 3 H, Val *CH*₃) ppm. ¹³C NMR (125 MHz, CDCl₃): $\delta = 167.0$ (q, 2 PhtN *CO*), 161.8 (q, oxazole *C*-2), 159.8 (q, *CONH*), 149.3 (q, oxazole *C*-5), 134.1 (t, PhtN *CH*-3,4), 131.8 (q, PhtN *C*-1,6), 130.0 (q, oxazole *C*-4), 123.5 (t, PhtN *CH*-2,5), 52.9 (t, Val α -*CH*), 33.4 (t, Val β -*CH*), 32.4 (s, *Ph*tN*CH*₂), 18.2 (p, Val *CH*₃), 18.1 (p, Val *CH*₃) ppm. IR (KBr): $\tilde{\nu} = 3390, 2966, 2933, 2876, 1776, 1722, 1683, 1637, 1576, 1524, 1468, 1423, 1391, 1197, 1087, 943, 903, 787, 753, 714, 611, 531$ cm⁻¹. UV/Vis (MeOH, $c = 0.0034$ mg/mL): λ_{max} (log ϵ) = 220 (5.189), 294 (3.790) nm. CD (MeOH, $c = 0.0034$ mg/mL): λ ($\Delta\epsilon$ [dm³mol⁻¹cm⁻¹]) = 201 (+16.4), 211 (0.0), 220 (–31.2) nm. ESI-HRMS: m/z calcd. for [C₅₁H₄₆N₉O₁₂]⁺ 976.3260, found 976.3293.

Data for 18: This compound contained even after several chromatographic purifications traces of **17**. TLC: $R_f = 0.47$ (DCM/EtOAc, 3:1, silica). ¹H NMR (500 MHz, CDCl₃): $\delta = 7.83$ (dd, $^3J_{\text{H,H}} = 5.5$, $^4J_{\text{H,H}} = 3.1$ Hz, 2 H, 2 H; PhtN *CH*-2,5), 7.71 (dd, $^3J_{\text{H,H}} = 5.5$, $^4J_{\text{H,H}} = 3.1$ Hz, 2 H; PhtN *CH*-3,4), 7.25 (d, $^3J_{\text{H,H}} = 9.8$ Hz, 1 H; amide *NH*), 5.25 (s, 2 H, *Ph*tN*CH*₂), 5.13 (dd, $^3J_{\text{H,H}} = 9.8$, $^3J_{\text{H,H}} = 7.6$ Hz, 1 H; Val α -*CH*), 2.27–2.17 (m, 1 H, Val β -*CH*), 0.96 (d, $^3J_{\text{H,H}} = 6.8$ Hz, 3 H; Val *CH*₃), 0.88 (d, $^3J_{\text{H,H}} = 6.8$ Hz, 3 H; Val *CH*₃) ppm. ¹³C NMR (125 MHz, CDCl₃): $\delta = 167.1$ (q, 2 PhtN *CO*), 161.8 (q, oxazole *C*-2), 160.1 (q, *CONH*), 149.5 (q, oxazole *C*-5), 134.1 (t, PhtN *CH*-3,4), 131.8 (q, PhtN *C*-1,6), 130.2 (q, oxazole *C*-4), 123.5 (t, PhtN *CH*-2,5), 51.4 (t, Val α -*CH*), 33.1 (t, Val β -*CH*), 32.8 (s, *Ph*tN*CH*₂), 18.6 (p, Val *CH*₃), 18.4 (p, Val *CH*₃) ppm. ESI-HRMS: m/z calcd. for [C₆₈H₆₀N₁₂O₁₆]⁺ 1301.4323, found 1301.4394.

Scaffold 19: To a solution of **17** (0.195 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 concentrated and dried in vacuo, then covered with DCM (50 mL) followed by the addition of benzyl chloroformate (0.341 g, 2.0 mmol) and Et₃N (0.304 g, 3.0 mmol). After stirring at room temperature for 6 h the mixture was concentrated and the residue was subjected to column chromatography on silica gel (DCM/

EtOAc/MeOH, 75:25:0→75:25:5) to yield 0.112 g (57.0%) of **19** as a colorless glassy solid. TLC: R_f = 0.67 (DCM/EtOAc/MeOH, 75:25:3, silica). ^1H NMR (500 MHz, CDCl_3): δ = 8.15 (d, $^3J_{\text{H,H}}$ = 7.9 Hz, 1 H; CONH), 7.35–7.29 (m, 5 H, Ph CH-2,3,4,5,6), 6.34 (br. t, 1 H; ZNHCH₂), 5.14 (d, $^2J_{\text{H,H}}$ = 12.2 Hz, 1 H; Z CH₂), 5.09 (d, $^2J_{\text{H,H}}$ = 12.2 Hz, 1 H; Z CH₂), 5.08 (d, 1 H, Val α -CH), 4.74–4.69 (dd, $^2J_{\text{H,H}}$ = 16.5, $^3J_{\text{H,H}}$ = 6.3 Hz, 1 H; ZNHCH₂), 4.71–4.66 (dd, $^2J_{\text{H,H}}$ = 16.5, $^3J_{\text{H,H}}$ = 6.0 Hz, 1 H; ZNHCH₂), 2.34–2.24 (m, 1 H, Val β -CH), 1.03 (d, $^3J_{\text{H,H}}$ = 6.7 Hz, 3 H; Val CH₃), 0.99 (d, $^3J_{\text{H,H}}$ = 6.7 Hz, 3 H; Val CH₃) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 161.4 (q, oxazole C-2), 160.5 (q, CONH), 156.3 (q, Z CO), 153.3 (q, oxazole C-5), 136.3 (q, Ph C-1), 129.8 (q, oxazole C-4), 128.41 (t, Ph CH-3,4,5), 128.05 (t, Ph CH-2,6), 66.9 (s, Z CH₂), 53.0 (t, Val α -CH), 36.0 (s, ZNHCH₂), 33.4 (t, Val β -CH), 18.36 (t, Val CH₃), 18.15 (t, Val CH₃) ppm. UV/Vis (MeOH, c = 0.0099 mg/mL): λ_{max} [nm] (log ϵ) = 210 (4.792), 225 (4.687), 286 (3.196) nm. CD (MeOH, c = 0.0099 mg/mL): λ [nm] ($\Delta\epsilon$ [$\text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$]) = 208 (+15.4), 217 (0.0), 231 (–35.2) nm. ESI-HRMS: m/z calcd. for $[\text{C}_{51}\text{H}_{58}\text{N}_9\text{O}_{12}]^+$ 988.4199, found 988.3919.

Scaffold 20: To a solution of **17** (0.195 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*-butyl dicarbonate (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 3 h. Then solvents were evaporated in vacuo, and column chromatography of the residue on silica gel (DCM/EtOAc/MeOH, 75:25:0→75:25:4) yielded 0.164 g (92.3%) of **20** as a colorless solid. TLC: R_f = 0.70 (DCM/EtOAc/MeOH, 75:25:3, silica). ^1H NMR (500 MHz, CDCl_3): δ = 8.14 (d, $^3J_{\text{H,H}}$ = 7.9 Hz, 1 H; CONH), 5.82 (br. s, 1 H; BocNHCH₂), 5.03 (dd, $^3J_{\text{H,H}}$ = 7.9, $^3J_{\text{H,H}}$ = 4.7 Hz, 1 H; Val α -CH), 4.63 (dd, $^2J_{\text{H,H}}$ = 16.4, $^3J_{\text{H,H}}$ = 6.6 Hz, 1 H; BocNHCH₂), 4.55 (dd, $^2J_{\text{H,H}}$ = 16.4, $^3J_{\text{H,H}}$ = 5.7 Hz, 1 H; BocNHCH₂), 2.33–2.26 (m, 1 H, Val β -CH), 1.38 (s, 9 H, Boc C(CH₃)₃), 1.02 (d, $^3J_{\text{H,H}}$ = 6.9 Hz, 3 H; Val CH₃), 0.97 (d, $^3J_{\text{H,H}}$ = 6.9 Hz, 3 H; Val CH₃) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 161.20 (q, oxazole C-2), 160.4 (q, CONH), 155.5 (q, Boc CO), 153.7 (q, oxazole C-5), 129.6 (q, oxazole C-4), 79.7 (q, Boc C(CH₃)₃), 53.0 (t, Val α -CH), 35.4 (s, BocNHCH₂), 33.4 (t, Val β -CH), 28.2 (p, Boc C(CH₃)₃), 18.2 (t, 2 Val CH₃) ppm. UV/Vis (MeOH, c = 0.0116 mg/mL): λ_{max} (log ϵ) = 223 (4.545), 297 (2.608) nm. CD (MeOH, c = 0.0116 mg/mL): λ ($\Delta\epsilon$ [$\text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$]) = 207 (+13.3), 217 (0.0), 231 (–28.9) nm. ESI-HRMS: m/z calcd. for $[\text{C}_{42}\text{H}_{64}\text{N}_9\text{O}_{12}]^+$ 886.4669, found 886.4682.

Scaffold 1. Preparation from 17: To a solution of **17** (0.098 g, 0.10 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 concentrated and dried in vacuo, then treated with 2 M HCl (50 mL) and insoluble phthalylhydrazide was filtered off. The filtrate was extracted with DCM (3 × 50 mL), then evaporated and dried in vacuo to yield 0.056 g (80.6%) of **1**.

Preparation from 19: Platform **19** (0.099 g, 0.10 mmol) was dissolved in MeOH (40 mL), then treated with 2 M HCl (10 mL) and palladium on charcoal catalyst (20%; 0.050 g) was added. The mixture was hydrogenated at atmospheric pressure for 4 h, then filtered and evaporated to give 0.061 g (87.8%) of **1**.

Preparation from 20: Scaffold **20** (0.089 g, 0.10 mmol) was treated with HCl/EtOAc solution (15%, 30 mL) at room temperature for 2 h. Volatiles were then removed in a rotary evaporator and the resulting white solid was exhaustively dried in vacuo to afford

0.070 g (quant.) of **1**. ^1H NMR (500 MHz, $[\text{D}_4]\text{MeOH}$): δ = 8.54 (d, $^3J_{\text{H,H}}$ = 7.9 Hz, 1 H; amide NH), 5.24–5.21 (m 1 H; Val α -CH), 4.60 (s, 2 H, CH₂NH₃⁺), 2.45–2.38 (m, 1 H, Val β -CH), 1.09 (d, $^3J_{\text{H,H}}$ = 6.9 Hz, 3 H; Val CH₃), 1.06 (d, $^3J_{\text{H,H}}$ = 6.9 Hz, 3 H; Val CH₃) ppm. ^{13}C NMR (125 MHz, $[\text{D}_4]\text{MeOH}$): δ = 164.4 (q, oxazole C-2), 161.7 (q, CONH), 149.6 (q, oxazole C-5), 133.2 (q, oxazole C-4), 54.7 (t, Val α -CH), 34.9 (s, CH₂NH₃⁺), 34.8 (t, Val β -CH), 18.9 (p, Val CH₃), 18.5 (p, Val CH₃) ppm. IR (KBr): $\tilde{\nu}$ = 3438, 3380, 2967, 2877, 2607, 1661, 1579, 1540, 1474, 1446, 1410, 1373, 1326, 1295, 1275, 1252, 1216, 1200, 1160, 1128, 1079, 1021, 982, 939, 902, 822, 784, 775, 725, 644, 614 cm^{-1} . UV/Vis (MeOH, c = 0.0053 mg/mL): λ_{max} (log ϵ) = 221 (4.661) nm. CD (MeOH, c = 0.0053 mg/mL): λ ($\Delta\epsilon$ [$\text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$]) = 208 (+24.2), 218 (0.0), 232 (–48.6) nm. ESI-HRMS: m/z calcd. for $[\text{C}_{27}\text{H}_{40}\text{N}_9\text{O}_6]^+$ 586.3096, found 586.3077.

Ligand 4: To a slurry of NaH (0.019 g, 0.48 mmol) in dry THF (2 mL) a solution of **2** (0.024 g, 0.04 mmol) in THF (6 mL) was added then stirred for 60 minutes at room temperature under Argon. 5-Bromomethyl-5'-methyl-2,2'-bipyridine (0.042 g, 0.16 mmol) was added and the mixture was refluxed overnight. Solvent was evaporated and the remaining solid was subjected to column chromatography on alumina (Brockmann IV, neutral) using NH/EtOAc, 50:50→10:90 to yield 0.015 g (33.0%) of **4** as a white solid. TLC: R_f = 0.47 (NH/EtOAc, 30:70; Al₂O₃). ^1H NMR (500 MHz, CDCl_3): δ = 8.59 (s, 1 H, Bipy CH-6), 8.47 (s, 1 H, Bipy CH-6'), 8.31 (d, $^3J_{\text{H,H}}$ = 8.1 Hz, 1 H; Bipy CH-3), 8.23 (d, $^3J_{\text{H,H}}$ = 8.1 Hz, 1 H; Bipy CH-3'), 8.19 (d, $^3J_{\text{H,H}}$ = 7.9 Hz, 1 H; amide NH), 7.78 (d, $^3J_{\text{H,H}}$ = 8.1 Hz, 1 H; Bipy CH-4), 7.59 (d, $^3J_{\text{H,H}}$ = 8.1 Hz, 1 H; Bipy CH-4'), 5.13 (dd, $^3J_{\text{H,H}}$ = 7.8, $^3J_{\text{H,H}}$ = 4.8 Hz, 1 H; Val α -CH), 5.01 (s, 2 H, CH₂OCH₂Bipy), 4.68 (s, 2 H, CH₂OCH₂Bipy), 2.39–2.33 (m, 1 H, Val β -CH), 2.38 (s, 3 H, Bipy CH₃), 1.07 (d, $^3J_{\text{H,H}}$ = 6.9 Hz, 3 H; Val CH₃), 1.03 (d, $^3J_{\text{H,H}}$ = 6.9 Hz, 3 H; Val CH₃) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ = 162.6 (q, oxazole C-2), 160.0 (q, CONH), 155.8 (q, Bipy C-2), 153.2 (q, Bipy C-2'), 151.7 (q, oxazole C-5), 149.5 (t, Bipy CH-6'), 148.5 (t, Bipy CH-6), 137.5 (t, Bipy CH-4'), 136.4 (t, Bipy CH-4), 133.5 (q, Bipy C-5'), 132.8 (q, Bipy C-5), 131.4 (q, oxazole C-4), 120.6 (t, Bipy CH-3'), 120.5 (t, Bipy CH-3), 70.3 (s, CH₂OCH₂Bipy), 61.5 (s, CH₂OCH₂Bipy), 53.2 (t, Val α -CH), 33.6 (t, Val β -CH), 18.45 (p, Bipy CH₃), 18.33 (p, 2 Val CH₃) ppm. UV/Vis (MeOH/H₂O, 1:1, c = 0.0114 mg/mL): λ_{max} (log ϵ) = 236 (5.06), 274 (sh, 4.77), 292 (4.98), 300 (sh, 4.91) nm. CD (MeOH/H₂O, 1:1, c = 0.0114 mg/mL): λ ($\Delta\epsilon$ [$\text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$]) = 218 (0), 235 (–125.9), 253 (0), 263 (+22.2), 285 (0), 295 (–7.3), 302 (0), 318 (+76.3) nm. ESI-HRMS: m/z calcd. for $[\text{C}_{63}\text{H}_{67}\text{N}_{12}\text{O}_9]^+$ 1135.5148, found 1135.5112.

UV-Absorption and CD-Spectrophotometric Titrations: For the UV-absorption and CD-spectrophotometric titrations stock solutions of the ligand (10^{-3} M in MeOH) and of the metal salts (10^{-3} – 10^{-2} M in MeOH or H₂O) were prepared. Automatized titrations were performed at 20 °C using 1-cm-path-length quartz cuvettes. To a ligand solution (2.500 mL; c_{ligand} = 10^{-5} M in MeOH/H₂O (1:1), using TRIS/HCl buffer (0.10 M/0.02 M) at pH = 8.90) in the cuvette a ligand-metal solution (up to 0.500 mL; c_{ligand} = 10^{-5} M, $c_{\text{metal ion}}$ = 2×10^{-4} to 5×10^{-4} M, using TRIS/HCl buffer (0.10 M/0.02 M) at pH = 8.90) was added in discrete steps by the titration accessory and after appropriate mixing time (3–10 min) spectra were recorded.

A continuous titration experiment for Job-plot analysis was performed with ligand and metal salt solutions of same concentration (2×10^{-5} M) keeping the total volume constant by removing the same volume of titrated solution from the cuvette before each addition of the titrant.

ESI-HRMS data for the complexes **4**·**M**²⁺:

4·**Zn**²⁺: *m/z* calcd. for [C₆₃H₆₆N₁₂O₉⁶⁴Zn]²⁺ 599.2178, found 599.2233.

4·**Cu**²⁺: *m/z* calcd. for [C₆₃H₆₇N₁₂O₉⁶³Cu]²⁺ 598.7180, found 598.7217.

4·**Co**²⁺: *m/z* calcd. for [C₆₃H₆₆N₁₂O₉⁵⁹Co]²⁺ 596.7198, found 596.7243.

4·**Ni**²⁺: *m/z* calcd. for [C₆₃H₆₇N₁₂O₉⁵⁸Ni]²⁺ 596.2209, found 596.2263.

Supporting Information (see also the footnote on the first page of this article): Schematic representation of the four different conformers *P1*, *P2*, *M1*, and *M2* of the **4**·**Zn**²⁺ complex.

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