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Synthesis of Cyclopeptide Alkaloids by Cyclooligomerization of Dipeptidyl Oxazolines

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Abstract—Cyclodehydration of Cbz-valylthreonine methyl esters with Burgess reagent provides access to *cis*- and *trans*-oxazoline segments for cyclooligomerization reactions. The ratio of 12-, 18-, 24-, and larger-ring macrocycles obtained in this process is kinetically controlled and dependent on the relative stereochemistry of the backbone α-carbons. A network of bifurcated hydrogen bonds rigidifies the peptidyl oxazoline strand and positions the valine side chains in either pseudoaxial or pseudoequatorial orientations. In the former case, transannular strain prevents the formation of 12-membered cyclopeptide alkaloids. Several X-ray structures illustrate the conformational preferences in this family of marine natural product analogs.

Introduction

Since 1986, a large number of cyclic oxazole- and thiazole-containing secondary metabolites have been isolated from cyanobacteria, ascidians, and other predominantly marine sources (Fig. 1).[1,2] The structural variety of these natural products and their biological activities has attracted strong synthetic interest.[2,3] Generally, very little is known about the biological mode of action of these cyclopeptide alkaloids, and they are not available in sufficient quantities from natural sources for a thorough evaluation of their pharmacological potential.

In *Lissoclinum* cyclopeptide alkaloids, oxazolines, oxazoles, thiazolines, and thiazoles alternate with standard amino acid residues (Fig. 1).[1,2] The majority of these ascidian-derived marine metabolites show moderate to strong cytotoxic activities, ulithiacyclamide and lissoclinamide 7 being the most potent (IC_{50} values of <50 ng/mL in SV40-transformed fibroblasts cell lines (MRC5CV1)). Patellamide D has been reported to reverse multidrug resistance in human leukemia cells.[4] There has been considerable speculation linking marine natural products in general and *Lissoclinum* peptides specifically, to metal ion chelation and transport functions.[5] In a series of systematic metal ion binding studies to synthetic westiellamide, we have demonstrated a unique selectivity and affinity of the natural product to silver(I) ions.[6] Additional evidence for metal complexation properties of *Lissoclinum* peptides comes from studies of copper(II) binding to the cyclooctapeptides patellamide D and ascidiacyclamide.[7] We consider the unique features of polyazoles, constrained into a macrocyclic framework, to be highly promising for the development of new classes of high-affinity metal chelators. An exceptionally broad range of applications for selective metal binders in organic synthesis, materials, and environmental sciences can be envisioned. For example, oxazolines have been used as ligands in copper-, palladium-, and zinc-catalyzed asymmetric C,C-bond formations.[8] Still unanswered is the question of the biological relevance of azole–metal complexes.[5] Further studies are needed to acquire a deeper understanding of the biological role of many heterocyclic marine natural products and the mode of action of *Lissoclinum* peptides.

The macrocyclic heterocyclic scaffolds present in *Lissoclinum* peptides offer great opportunities for molecular recognition and the preparation of new metal complexes with applications in metal metabolism, ion transport and delivery, and asymmetric catalysis.[8–10] It is not unrealistic to compare *Lissoclinum* peptides with ring-expanded porphyrins[11] due to their alternating five-membered heterocyclic ligands. However, *Lissoclinum* peptides are not fully conjugated, and α-chiral centers provide a powerful asymmetric environment for the metal ligand that critically influences all metal-complex properties.

The key to studying the bioinorganic and preparative chemistry of *Lissoclinum*-type macrocycles is a concise synthetic approach to these compounds. We have developed a cyclooligomerization strategy that leads to a narrow ring-size distribution from diastereomerically pure dipeptide oxazolines (Fig. 2).[3,12,13] The cyclooligomerization of peptidyl-oxazolines, -oxazoles, -thiazolines, and -thiazoles, can provide libraries of metal-binding macrocyclic ligands that are likely to reveal novel ion-binding and transport

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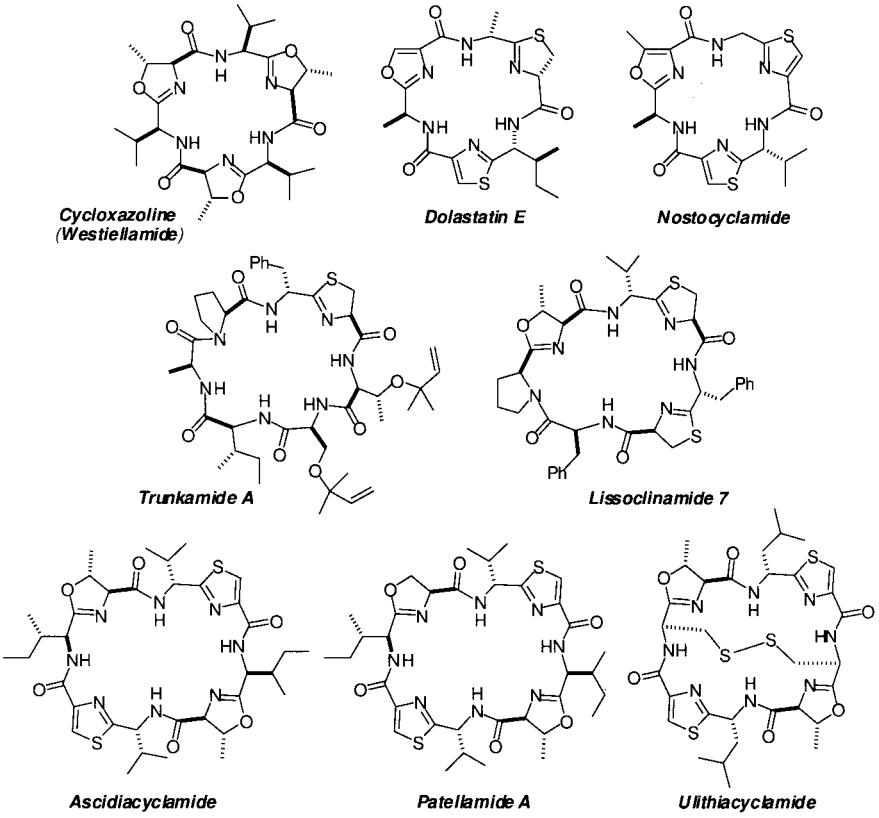


Figure 1. Representative oxazole- and thiazole-containing cyclopeptide alkaloids.

interactions and can serve as scaffolds for supramolecular and combinatorial chemistry.[9,10] Unlike dipeptide segments of natural amino acids which undergo diketopiperazine formation upon *N*-deprotection and carboxyl group activation,[14] diketopiperazine formation is inaccessible for oxazoline-containing segments due to the rigid *trans*-orientation of the imidate linkage fused into the five-membered ring. These building blocks are therefore ideally suited for cyclooligomerization strategies and macrocycle formation (Fig. 3).

We now report an application of this strategy toward the preparation of the natural product westiellamide and several ring-size and configurational analogs.

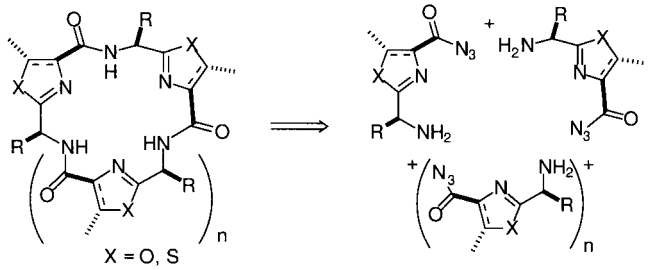


Figure 2. Cyclooligomerization approach toward *Lissoclinum* macrocycles.

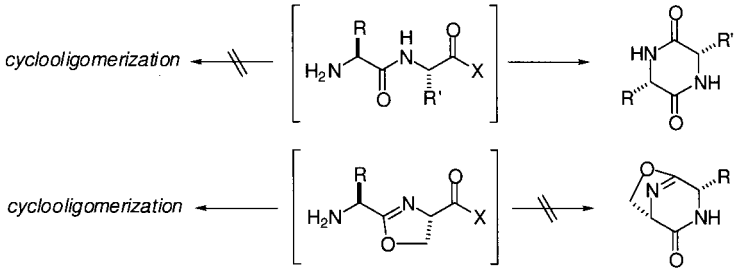
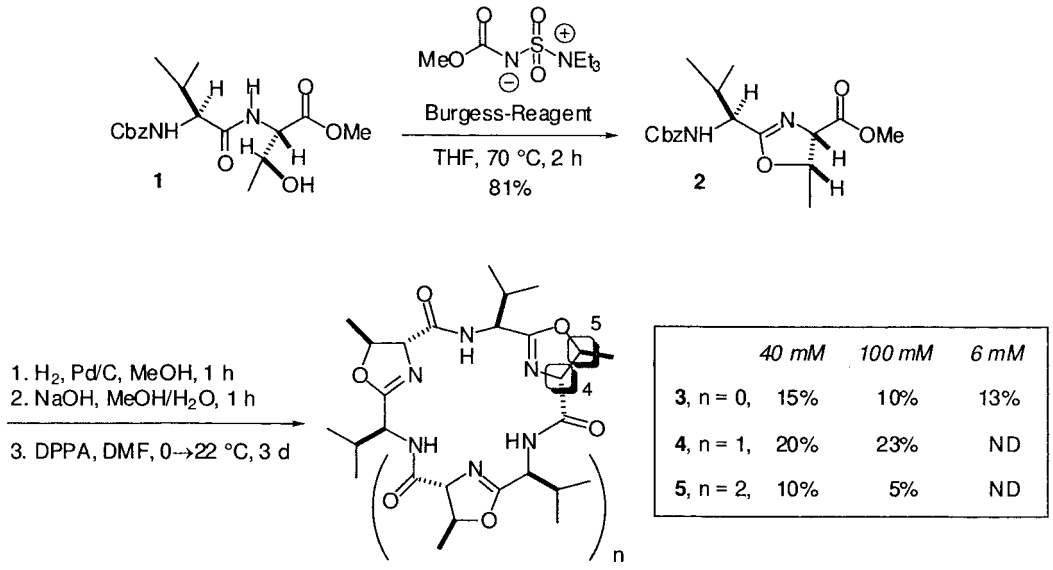


Figure 3. Amide bond modification prevents cyclization and promotes cyclooligomerization.



	40 mM	100 mM	6 mM
3, n = 0,	15%	10%	13%
4, n = 1,	20%	23%	ND
5, n = 2,	10%	5%	ND

Scheme 1.

Results and Discussion

The C_3-symmetric cytotoxic 18-membered *Lissoclinum* peptide westiellamide was first isolated from the ascidian *Lissoclinum bistratum* by Watters and coworkers, who named the compound cycloxazoline.[15] Interestingly, the terrestrial blue-green alga *Westiellopsis prolifica* yielded an identical compound, characterized independently by Moore and co-workers and named westiellamide.[16] There is strong structural resemblance between westiellamide and the bistratamides, another group of cyclohexapeptides isolated from *L. bistratum*.[2,17] Due to the inherent symmetry of the macrocycle, westiellamide represented an ideal target to develop the cyclooligomerization strategy toward cyclopeptide alkaloids.

Treatment of the readily available Cbz-L-valine-L-threonine (**1**) with Burgess reagent provided oxazoline **2** in 81% yield (Scheme 1).[18] Subsequent hydrogenolytic cleavage of the *N*-Cbz group of **2**, followed by saponification and treatment of the dipeptidyl oxazoline with diphenylphosphoryl azide (DPPA)[19] initiated the cyclooligomerization reaction. In the concentration range 6–100 mM, chain extension competed with cyclization, and various ratios of 12-, 18-, and 24-membered macrocycles were isolated by chromatography on SiO_2. The highest yield of cyclopeptide alkaloids was achieved at a 40 mM concentration of dipeptidyl oxazoline, and 15% of the cyclotetrapeptide **3**, 20% of the cyclohexapeptide **4**, and 10% of the cyclooctapeptide **5** were obtained. The structure of **3** was confirmed by X-ray analysis (Fig. 4). The relative distribution of these ring isomers reflects the conformational properties of the linear dipeptidyl oxazolines, which favor β-turn structures that considerably facilitate ring closure.[20] Therefore, high dilution conditions are generally not required in the cyclization of short peptide segments containing these heterocycles. In addition, the conversion of the *C*-terminus by DPPA into an acyl azide that is only a mild acylating agent appears to strike an ideal compromise between chain extension and macrocyclization. More activated derivatives that can be obtained with HATU[21] or FDPP[22] coupling reagents provided lower overall yields of cyclopeptides and larger amount of linear oligomers, albeit at greatly reduced reaction times.

The 12-membered cyclotetrapeptide **3** was an unexpected product of the cyclooligomerization process. Factors that discourage ring closure, such as steric hindrance, kinetic competition with the oligomerization reaction, and transition state energy are generally particularly severe for tetrapeptide segments that lack *N*-substituted amino acids that would establish a rapid transoid–cisoid equilibrium.[23] In this context, it is interesting to analyze the solid state structure of **3** in more detail. While the two oxazoline imidates are obviously restricted to the *trans*-configuration, both amide bonds in **3** also remain in the transoid form, in spite of the large strain associated with the 12-membered ring. However, the amides are highly distorted from planarity and

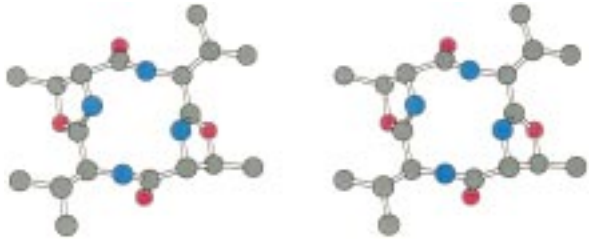


Figure 4. Stereoview of the X-ray structure of cyclotetrapeptide alkaloid **3**.

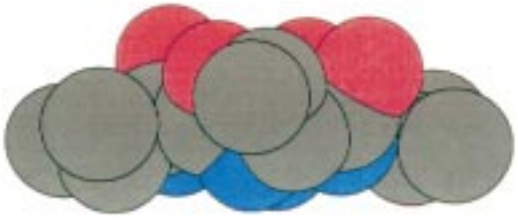
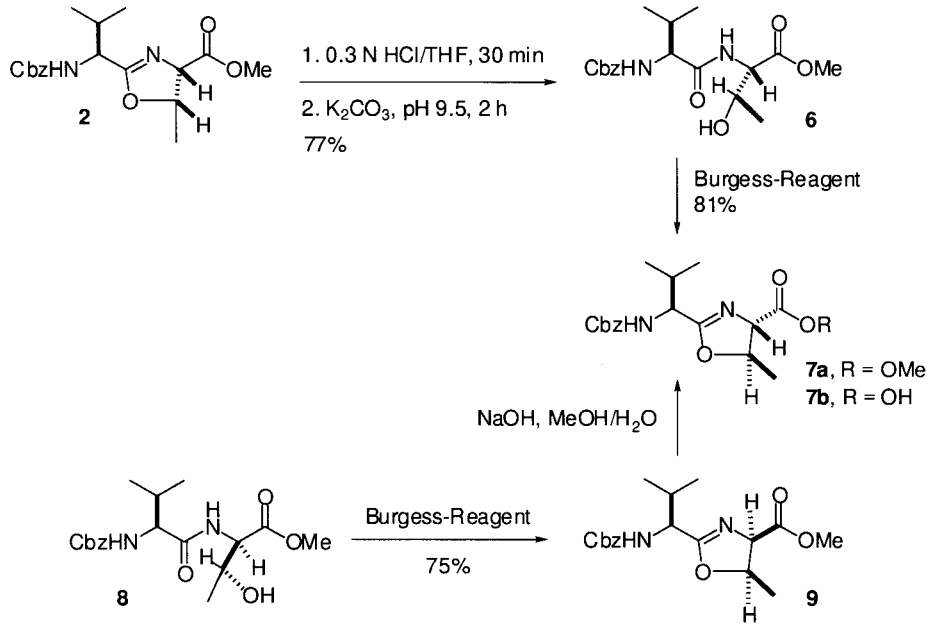


Figure 5. CPK-model of the X-ray structure of **3**.

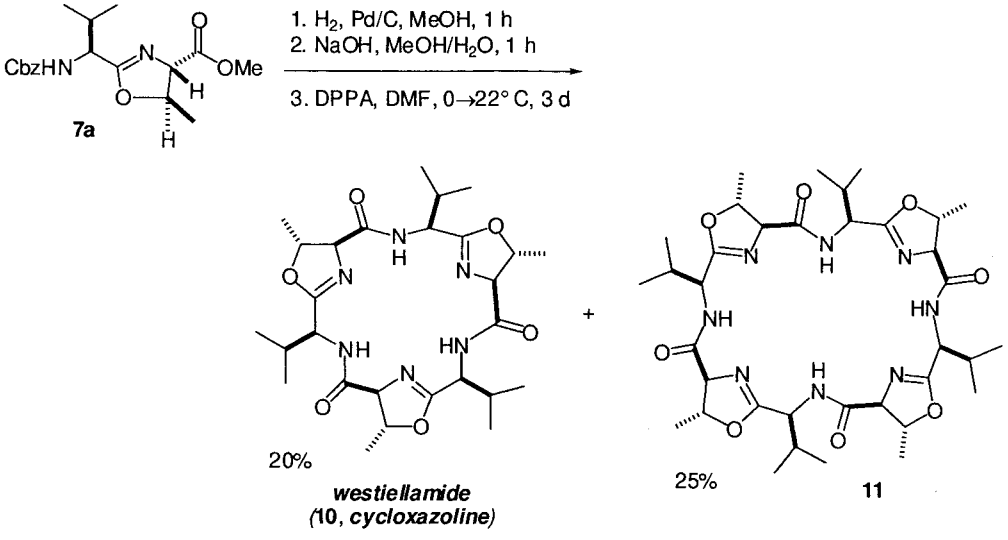


Scheme 2.

show a dihedral angle of 154.5°.[24] The overall shape of **3** is saucer-like, with an equatorial disposition of the isopropyl and methyl side chains; the four nitrogens are closely compressed to van der Waals contacts across the bottom of the saucer, and the four oxygens spread slightly further apart on the top (Fig. 5).

Since the configuration at the L-threonine C(3) was inverted in the Burgess cyclo-dehydration and the resulting *cis*-oxazoline **2** was epimerized at the α-carbon of the ester carbonyl group to give a *trans*-oxazoline intermediate during the saponification reaction,[3,25] cyclooligomers **3**–**5** are doubly epimeric to westiellamide at all oxazoline C(4) and C(5) positions. In earlier studies, we developed two complementary synthetic strategies to prepare oxazoline building blocks of natural configuration.[3,12,26] Hydrolysis of **2** with dilute acid gave an *O*-acyl amine, which was rearranged in situ to the *N*-acyl alcohol to give Cbz-L-valine-L-*allo*-threonine **6** (Scheme 2).[26] Subsequent cyclodehydration of **6** led to the desired *trans*-oxazoline ester **7a**. A more direct approach for the preparation of this oxazoline in two steps and in high yields from Cbz-L-valine-D-threonine **8** involved oxazoline formation (which inverted the stereochemistry at the threonine β-carbon) and room temperature ester hydrolysis with 2 equiv. of sodium hydroxide, which also quantitatively led to inversion of stereochemistry at the former threonine α-carbon in **7b**.[3,25]

After removal of the *N*-Cbz protective group in **7a** by hydrogenolysis and saponification, activation of the *C*-terminal carboxylate with DPPA in a 15 mM solution in DMF led in good overall yields to a complementary series of



Scheme 3.

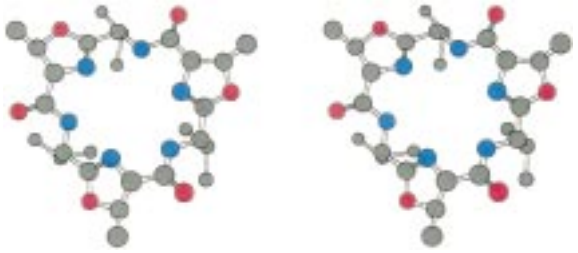


Figure 6. Stereoview of the X-ray structure of westiellamide (**10**).

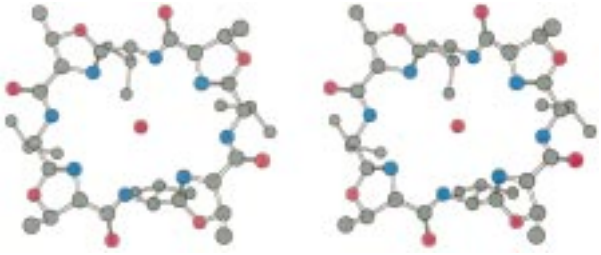


Figure 7. Stereoview of the X-ray structure of cyclotetramer **11**.

macrocyclic peptides (Scheme 3). Westiellamide (**10**) and the 24-membered cyclotetramer **11** were isolated in high overall yields of 20 and 25%, respectively. While traces of a 30-membered cyclopentamer were also detected, no cyclodimer analogous to **3** could be isolated. The X-ray structure of westiellamide shown in Fig. 6 has been determined by Moore and coworkers.[16] We were able to grow crystals of the cyclotetramer **11** from $CHCl_3$ (Fig. 7). Both compounds display an aza-crown ether motif, with all nitrogens oriented toward the inside of the macrocycle; the isopropyl side chains are in a pseudoaxial orientation. The cavity of the cyclotetramer measures ca. 7 Å across and is large enough to extract a water molecule from the residual moisture in the solvent ($CHCl_3$) that was used for crystallization. The saddle shape of cyclotetramer **11** that places the azole heterocycles at the corners of the molecular square is closely reminiscent of the solid state and solution structures of ascidiacyclamide and patellamide A.[2] The pseudoaxial attachment of the side-chains on the macrocycle is clearly visible in the stereoviews. The C_4-symmetric structure for **11** observed in the crystal appears to be essentially the same as the solution structure based on NMR experiments.

It is interesting to consider what conformational effects determine the formation of different ring size isomers in the cyclooligomerization of the L–D dipeptidyl oxazoline derived from **2** vs the L–L epimer derived from **7**. In the former case, significant amounts of the 12-membered macrocycle are formed along with 18-membered and some 24-membered ring system. The L–L-epimer has the natural configuration at the C(4)- and C(5)-positions of the oxazoline heterocycle, and only 18- and 24-membered macrocycles are produced, along with traces of the 30-membered ring. Since the cyclooligomerization cascade is kinetically controlled, we postulate that the timing of the ring formation is a function of the folding of the oligooxazoline strand which in turn is controlled by non-bonding interactions between the valine side chains. As the X-ray

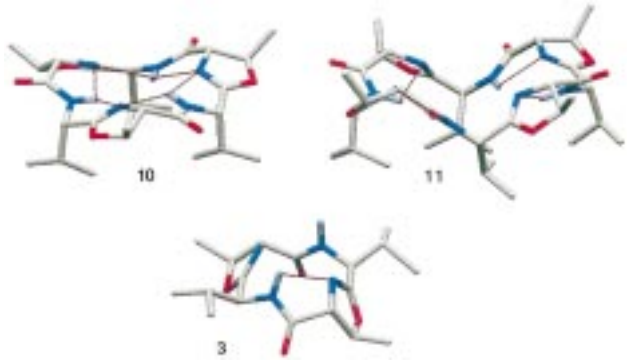


Figure 8. Side views of the X-ray structures of epimers **3**, **10**, and **11** that highlight steric interactions between the valine side chains and the bifurcated hydrogen bonding network.

structure of the cyclodimer **3** shows, the valine side chains are in a pseudoequatorial orientation and there is little or no steric repulsion between them, thus favoring a smaller ring size. In contrast, the pseudoaxial orientation of the isopropyl groups in westiellamide and **11** disfavors small ring sizes by transannular repulsions and favors the larger 18- and 24-membered macrocycles. With both diastereomeric building blocks, cyclization is ultimately facilitated by the reverse turn conformation of the dipeptide oxazoline segments which is stabilized by intramolecular bifurcated hydrogen bond formation between the oxazoline nitrogens and the amide NH (Fig. 8).[20] The 18-membered macrocycles maximize the stabilization through bifurcated hydrogen bonding that can be achieved within the cyclic polyoxazoline scaffold. As a further consequence of the hydrogen bonding array, the conformational flexibility of these cyclopeptide alkaloids is restricted, and the relative positions of the isopropyl side chains in pseudoaxial or pseudoequatorial orientations with respect to the macrocycle are determined by the relative stereochemistry at the backbone α-carbons. Accordingly, stereochemistry determines conformation which in turn determines the kinetic selectivity for macrocycle formation in the cyclooligomerization of dipeptidyl oxazolines.

In conclusion, the formation of epimeric dipeptidyl oxazolines by cyclodehydration of β-hydroxy amides provides an efficient entry toward natural (westiellamide) and unnatural cyclopeptide alkaloids of the *Lissoclinum* class of marine natural products. The relative ring size of the macrocycles is determined by kinetic control effected by the relative configurations of the backbone stereogenic carbons. As a consequence of an intramolecular bifurcated hydrogen bonding network, amino acid side chains are forced into pseudoaxial or pseudoequatorial orientations, and steric interactions in the former case discourage the formation of tight 12-membered macrocycles and favor larger 18- and 24-membered ring systems. As the steric requirements decrease from the branched, valine-derived isopropyl groups to linear side chains such as alanine-derived methyl or phenylalanine-derived benzyl groups, it is to be expected that kinetic preference will shift back in favor of smaller ring sizes. In contrast, the use of *tert*-valine-derived building blocks should allow for the spontaneous formation of even larger macrocycles. Studies to test these hypotheses, as well as investigations of the metal-complexation properties of

the new cyclopeptide alkaloid scaffolds, will be reported in due course.

Experimental

General

All moisture-sensitive reactions were performed under an atmosphere of N_2 or Ar and all glassware was dried in an oven at 140°C prior to use. THF and Et_2O were dried by distillation over Na/benzophenone under a nitrogen atmosphere. Dry CH_2Cl_2 was obtained by distillation from CaH_2. Dry DMF was obtained by distillation from alumina under reduced pressure. Dry CF_3CH_2OH was obtained by distillation from $CaSO_4$. Unless otherwise stated, solvents or reagents were used without further purification. NMR spectra were recorded at either 300/75 MHz ($^1H/^{13}C$ NMR) or 500/125 MHz ($^1H/^{13}C$ NMR) in $CDCl_3$ unless stated otherwise. Flash silica gel chromatography was used to separate and purify the crude reaction mixtures.

Cbz-Val-Thr-OMe (1). A solution of Cbz-Val-OH (4.7 g, 17 mmol) in 40 mL of CH_2Cl_2 was treated with *N*-methyl morpholine (3.1 mL, 25.5 mmol, 1.5 equiv.) and cooled to −15°C. Isobutyl chloroformate (2.4 mL, 17 mmol, 1 equiv.) was added dropwise. After stirring for 3 min, the mixture was treated with a solution of threonine methyl ester hydrochloride (2.8 g, 17 mmol) and Et_3N (2.5 mL, 17 mmol) in 10 mL of DMF. The reaction mixture was warmed to 22° C, stirred for 30 min, and diluted to 100 mL by addition of CH_2Cl_2. After extraction with 1N HCl (2×50 mL), 1N NaOH (150 mL), and brine (1×50 mL), the organic layer was dried ($MgSO_4$), filtered, and concentrated (10 mL). After addition of hexane, dipeptide **1** precipitated from the solution and was filtered off, washed with hexane, and dried in vacuo to yield 4.7 g (68%) of colorless solid: mp 135–137° C; $[\alpha]_D^{23}=-14.4$ (c=1.0, EtOH); IR (neat) 3310, 3060, 3030, 2970, 1740, 1720, 1710, 1660, 1530, 1460, 1450, 1300, 1248, 1220, 1150, 1100, 1030, 670 cm^{-1}; ^1H NMR δ 7.42–7.31 (m, 5H),6.78 (d, 1H, J=8.9 Hz), 5.48 (d, 1H, J=8.8 Hz), 5.09 (s, 2H), 4.60(dd, 1H, J=8.8, 2.0 Hz), 4.36 (dq, 1H, J=6.4, 2.3 Hz), 4.08 (dd, 1H, J=6.7, 1.9 Hz), 3.75 (s, 3H), 2.25–2.10 (m, 1H), 1.18 (d, 3H, J=6.3 Hz), 0.99 (d, 3H, J=6.7 Hz), 0.95 (d, 3H, J=6.8 Hz), ^{13}C NMR δ 172.2, 171.3, 156.7, 136.3, 128.5, 128.2, 128.0, 68.1, 67.1, 60.5, 57.5, 52.6, 31.2, 19.9, 19.1, 18.1; MS (CI) m/z (relative intensity) 367 ($[M+H]^+$, 12), 349 (6), 323 (10), 259 (8), 224 (6), 206 (16), 162 (30), 116 (10), 91 (100), 72 (15).

(4*S*,5*S*)-2-((1*S*)-1-Benzyloxycarbonylamino-2-methylpropyl)-5-methyl-4,5-dihydro-oxazole-4-carboxylic acid methyl ester (2). A solution of Cbz-Val-Thr-OMe (**1**, 250 mg, 0.68 mmol) in 4 mL of dry THF was treated with Burgess reagent (175 mg, 0.73 mmol, 1.1 equiv.) and heated at 75° C for 2.5 h. The reaction mixture was evaporated onto silica gel and chromatographed (EtOAc/Hexanes, 1:1) to yield *cis*-oxazoline **2** (165 mg, 81%) as an oil: $[\alpha]_D^{23}=-6.2$ (c=1.4, EtOH); IR (neat) 3330, 3260, 3050, 1748, 1725, 1660, 1530, 1460, 1370, 1255, 1220, 1195, 1100, 1050, 1030, 710 cm^{-1}; ^1H NMR δ 7.40–7.25 (m, 5H), 5.59 (d, 1H, J=8.0 Hz), 5.13, 5.08 (AB, 2H, J=12.2 Hz), 5.02–4.94 (m, 1H), 4.79 (d, 1H, J=10.1 Hz), 4.40 (dd, 1H, J=8.0, 4.6 Hz), 3.75 (s, 3H), 2.24–2.18 (m, 1H), 1.31 (d, 3H, J=6.4 Hz), 1.02 (d, 3H, J=6.9 Hz), 0.98 (d, 3H, J=6.9 Hz); ^{13}C NMR δ 170.0, 169.7, 156.2, 136.3, 128.4, 128.0, 78.5, 70.6, 66.9, 54.3, 52.0, 31.4, 18.8, 17.0, 16.1; MS (EI) m/z (relative intensity) 348 (M^+, 11), 184 (10), 108 (10), 91 (100); HRMS calcd for $C_{18}H_{24}N_2O_5$: 348.1685, found 348.1684.

Cbz-Val-*allo*Thr-OMe (6). A solution of **2** (228 mg, 0.66 mmol) in 10 mL of dry THF was treated with 5 mL of 1 M HCl. The reaction mixture was stirred for 30 min at 22°C and then the pH was adjusted to 9.5 by the addition of solid K_2CO_3. The reaction was complete after 2 h (TLC). The organic solvent was evaporated and the aqueous layer extracted with EtOAc (2×30 mL). The combined organic extracts were washed with brine (1×20 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation in vacuo yielded **6** (184 mg, 77%) as a colorless solid: mp 122–125° C; $[\alpha]_D^{23}=-22$ (c=0.8, EtOH); IR (neat) 3090, 3050, 2960, 1750, 1710, 1680, 1535, 1455, 1445, 1380, 1360, 1290, 1240, 1150, 1090, 1050, 770, 735, 700 cm^{-1}; ^1H NMR δ 7.33–7.26 (m, 5H), 7.16 (d, 1H, J=7.3 Hz), 5.55 (d, 1H, J=8.4 Hz), 5.11, 5.06 (AB, 2H, J=11.7 Hz), 4.67–4.65 (m, 1H), 4.13–4.08 (m, 2H), 3.77 (s, 3H), 2.11–2.04 (m, 1H), 1.18 (d, 3H, J=6.0 Hz), 0.98–0.92 (m, 6H); ^{13}C NMR δ 172.2, 170.5, 156.7, 136.1, 128.6, 128.3, 128.1, 68.7, 67.2, 60.5, 58.2, 52.6, 31.1, 19.2, 18.9, 18.0; MS (CI) m/z (relative intensity) 367 ($[M+H]^+$, 20), 323 (16), 259 (12), 215 (10), 206 (20), 162 (25), 108 (10), 91 (100), 72 (20).

(4*S*,5*R*)-2-((1*S*)-1-Benzyloxycarbonylamino-2-methylpropyl)-5-methyl-4,5-dihydro-oxazole-4-carboxylic acid methyl ester (7a). This compound was prepared analogously to the *cis*-isomer **2** in 81% yield by heating Cbz-Val-*allo*Thr-OMe (**6**) with Burgess Reagent at 70–75° C for 1 h: $[\alpha]_D^{24}=47.6$ (c=0.2, CH_2Cl_2); IR (neat) 3239, 3034, 2965, 1723, 1661, 1535, 1454, 1372, 1238, 1206, 1094, 1026, 868, 741, 698 cm^{-1}; ^1H NMR δ 7.45–7.25 (m, 5H), 5.51 (d, 1H, J=9.1 Hz), 5.12, 5.07 (AB, 2H, J=12.2 Hz), 4.88–4.80 (m, 1H), 4.41 (dd, 1H, J=9.1, 4.5 Hz), 4.26 (d, 1H, J=6.9 Hz), 3.76 (s, 3H), 2.17–2.11 (m, 1H), 1.41 (d, 3H, J=6.4 Hz), 0.97 (d, 3H, J=6.8 Hz), 0.91 (d, 3H, J=6.8 Hz); ^{13}C NMR δ 171.3, 169.1, 156.2, 136.3, 128.5, 128.1, 79.8, 74.0, 67.0, 54.4, 52.7, 31.7, 20.9, 18.8, 17.2; MS (EI) m/z (relative intensity) 348 (M^+, 10), 305 (4), 261 (4), 198 (10), 181 (6), 108 (10), 91 (100); HRMS calcd for $C_{18}H_{24}N_2O_5$: 348.1685, found: 348.1714.

Westiellamide (10) and Cyclotetramer (11). A solution of **7a** in 50 mL of MeOH was hydrogenated over catalytic 10% Pd/C. After 1 h, the reaction mixture was filtered through celite and treated with 1 M NaOH solution (7.0 mL, 1.2 equiv.). The reaction mixture was stirred at 22°C for 1 h, treated with $NaHCO_3$ (2.5 g, 5 equiv.), and evaporated to dryness by azeotropic distillation with benzene at 22°C. The solid residue was diluted with 440 mL of DMF, treated with DPPA (1.9 mL, 8.8 mmol, 1.5 equiv.) at 0°C, and stirred for 23 h at 0°C, 48 h at 4°C, and 24 h at 22°C. The reaction mixture was quenched by addition of 50 mL of saturated aqueous $NaHCO_3$ solution and stirring was continued for an additional 1 h. The solution was evaporated to dryness under reduced pressure (T<65° C), and the residue

was partitioned between 60 mL of H_2O and 150 mL of CH_2Cl_2. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2×50 mL). The combined CH_2Cl_2 extracts were washed with brine (1×40 mL) and dried over Na_2SO_4. Chromatography on silica gel (EtOAc/Hexanes, 1:1, followed by EtOAc) afforded westiellamide (**10**, 214 mg, 20%) and cyclotetramer **11** (266 mg, 25%) as amorphous solids.

10. Mp 168° C (dec.); $[\alpha]_D^{23}$=130.0 (c=0.1, MeOH); IR (neat) 3376, 2965, 1694, 1651, 1526, 1456, 1372, 1202, 1038 cm^{-1}; ^1H NMR δ 7.76 (d, 1H, J=7.9 Hz), 4.80 (dq, 1H, J=8.7, 6.3 Hz), 4.65 (ddd, 1H, J=7.9, 3.1, 2.1), 4.22 (dd, 1H, J=8.7 Hz, 2.1 Hz), 2.32–2.26 (m, 1H), 1.58 (d, 3H, J=6.3 Hz), 0.89 (d, 3H, J=7.0 Hz), 0.81 (d, 3H, J=7.0 Hz); ^{13}C NMR δ 170.6, 168.5, 82.7, 73.8, 52.4, 31.5, 22.0, 18.7, 16.9; MS (EI) m/z (relative intensity) 546 (M^+, 7), 531 (2), 503 (3), 462 (4), 447 (2), 363 (2), 308 (3), 280 (4), 252 (2), 183 (3), 168 (2), 153 (2), 138 (15), 69 (15); HRMS calcd for $C_{27}H_{42}N_6O_6$: 546.3166, found: 546.3158.

11. Mp 242° C (dec.); $[\alpha]_D^{21}$=69.0 (c=0.1, MeOH); IR 3389, 2965, 2932, 1715, 1684, 1653, 1576, 1516, 1456, 1379, 1277, 1202, 1146, 1038, 864 cm^{-1}; ^1H NMR δ 7.31 (d, 1H, J=9.7 Hz), 4.81 (dq, 1H, J=7.6, 6.3 Hz), 4.69 (dd, 1H, J=9.7, 5.0 Hz), 4.22 (d, 1H, J=7.6 Hz), 2.17–2.04 (m, 1H), 1.50 (d, 3H, J=6.3 Hz), 0.92–0.88 (m, 6H); ^{13}C NMR δ 171.2, 169.4, 81.1, 74.4, 51.7, 31.7, 21.9, 18.9, 17.6; MS (EI) m/z (relative intensity) 728 (M^+, 100), 713 (20), 685 (40), 670 (30), 657 (30), 644 (40), 628 (20), 545 (24), 462 (20), 363 (14), 322 (12), 280 (30), 252 (20), 223 (20), 138 (90), 124 (30), 98 (40), 84 (55), 72 (100); HRMS calcd for $C_{36}H_{56}N_8O_{8:}$ 728.4221, found: 728.4286.

Cyclotetrapeptide 3, cyclohexapeptide 4, and cyclooctapeptide 5. According to the procedure described for westiellamide, **3**, **4**, and **5** were obtained in 15, 20, and 10% yield, respectively, from **2**, when a 40 mM concentration in DMF was used for the cyclooligomerization step.

3. Mp 149–152°C; $[\alpha]_D$=−433 (c=0.6, CH_2Cl_2, 23°C); IR (neat) 3343, 2965, 1728, 1680, 1644, 1566, 1555, 1516, 1468, 1453, 1375, 1225, 1192, 1142, 1074, 1017 cm^{-1}; ^1H NMR δ 6.79 (d, 1H, J=10.3 Hz), 5.15 (dq, 1H, J=6.5, 2.7 Hz), 4.15 (dd, 1H, J=10.3, 9.8 Hz), 4.15 (d, 1H, J=2.7 Hz), 2.12–2.00 (m, 1H), 1.28 (d, 3H, J=6.6 Hz), 1.05 (d, 3H, J=6.7 Hz), 0.99 (d, 3H, J=6.7 Hz); ^{13}C NMR δ 173.2, 172.5, 79.3, 72.8, 54.5, 31.7, 20.1, 19.1, 19.0; MS (EI) m/z (relative intensity) 364 (M^+, 8), 321 (12), 308 (60), 280 (80), 252 (25), 234 (20), 183 (20), 170 (25), 138 (25), 124 (30), 84 (20), 72 (45); HRMS m/z calcd for $C_{18}H_{28}N_4O_4$: 364.2111, found: 364.2112.

4. Mp 209°C (dec.); $[\alpha]_D$=−207 (c=0.7, CH_2Cl_2, 23°C); IR (neat) 3400, 2967, 2934, 2877, 1655, 1517, 1378, 1198, 10005, 845 cm^{-1}; ^1H NMR δ 7.24 (d, 1H, J=7.9 Hz), 4.88 (dq, 1H, J=9.0, 6.1 Hz), 4.52 (dd, 1H, J=7.7, 4.8 Hz), 4.19 (d, 1H, J=9.0 Hz), 2.35–2.26 (m, 1H), 1.51 (d, 3H, J=6.2 Hz), 1.01 (d, 3H, J=7.0 Hz), 0.94 (d, 3H, J=6.9 Hz); ^{13}C NMR δ 169.4, 167.2, 79.1, 74.8, 52.5, 32.0, 21.88, 18.6, 17.8; MS (EI) m/z (relative intensity) 546 (M^+, 70), 503 (100), 488 (50), 462 (70), 363 (20), 308 (30), 138 (75), 72 (80); HRMS calcd for $C_{27}H_{42}N_6O_6$: 546.3166, found: 546.3175.

5. $[\alpha]_D$=−131 (c=0.66, CH_2Cl_2, 23°C); IR (neat) 3393, 2966, 2933, 2875, 1683, 1653, 1521, 1457, 1378, 1204, 1037, 736 cm^{-1}; ^1H NMR δ 6.78 (d, 1H, J=9.6 Hz), 4.77–4.67 (m, 2H), 4.18 (d, 1H, J=6.6 Hz), 2.35–2.26 (m, 1H), 1.45 (d, 3H, J=6.3 Hz), 1.04 (d, 3H, J=6.9 Hz), 0.98 (d, 3H, J=6.8 Hz); ^{13}C NMR δ 170.9, 168.2, 80.3, 74.7, 51.9, 31.4, 21.9, 19.4, 17.4; MS (EI) m/z (relative intensity) 728 (M^+, 100), 713 (20), 685 (20), 670 (30), 644 (20), 545 (25), 504 (15), 462 (35), 422 (15), 322 (20), 280 (30), 138 (90); HRMS calcd for $C_{36}H_{56}N_8O_8$: 728.4221, found: 728.4178.

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