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Structural investigation of westiellamide analogues

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Abstract

The synthesis of westiellamide analogues, wherein the oxazoline units are replaced by oxazole or thiazole units, is presented. The structures of these analogues, and also of an imidazole-based analogue, were investigated using X-ray diffraction and DFT-based molecular modelling calculations. We could show that the oxazole-based peptide is almost planar, whereas the thiazole and the imidazole cyclic peptides have cone-like structures. Furthermore we could show that the flexibility of the systems essentially depends on the type of the azole building block. If oxazole-containing cyclopeptides are used, the scaffold takes an almost planar structure; bending the scaffold towards a cone-like structure, however, requires high energy. Imidazole-containing cyclopeptides show a complementary behaviour: while a planar structure can only be obtained with a high energetic input, a strong bending of the system is energetically favoured.

Keywords: Imidazoles; Macrocycles; Molecular modelling; Marine peptides; Oxazoles; Thiazoles

1. Introduction

The marine genus *Lissoclinum* has been a rich source of cyclopeptide alkaloids featuring multiple oxazolines, thiazolines, oxazoles or thiazoles.[1] These compounds were usually identified as secondary metabolites of algae, fungi and primitive marine organisms with various biological activities, including cytotoxicity, antibacterial and antiviral activities.[2] Examples have been found for their ability to overcome multidrug resistance or to act as antineoplastic agents.[3] The size and conformation of these macrocycles and their functional groups have led to the speculation that they may function as metal complexation and transport agents in vivo.[4] Evidence for metal complexation properties of *Lissoclinum* cyclopeptide alkaloids is given by metal ion binding studies to westiellamide, patellamides and ascidiacyclamide.[5] The direct biological relevance of these metal ion binding properties, however, is still unresolved.

Furthermore, the unique macrocyclic heterocyclic scaffolds present in *Lissoclinum* cyclopeptide offer great opportunities for using them as building blocks in supramolecular chemistry.[6] For example, cyclic peptides with oxazole building blocks in the cyclic backbones have been proposed to be useful structures for the construction of molecular receptors.[7] Macrocycles consisting of three oxazole or thiazole building blocks were used for the synthesis of new tubular and cage structures.[8] Systems having three imidazoles in the scaffold were used as receptors for hydroxybenzenes,[9] or can be used as templates for the chirality transfer of C_2- and C_3-symmetrical compounds.[10] Recently, a system having four oxazole units was used for the selective recognition of pyrophosphate in water.[11] A macrocyclic scaffold, composed of two oxazoles and two thiazoles, was designed to structurally mimic loops of proteins.[12] In all cases, the azole moieties were used as rigid building blocks of the peptidic cycle, thus conferring to the whole system a rigid structure and reducing the number of possible conformers. The knowledge about the structural properties and the flexibility of these systems are of utmost

Abbreviations: Boc, *tert*-butyloxycarbonyl; DPPA, diphenylphosphoryl azide; DCM, dichloromethane; TFA, trifuoroacetic acid.

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importance because this allows the determination of the relative distances of the groups bound to the C_α atoms, which, in most cases, determine the properties necessary for a certain application.

Recently, we reported the synthesis and structure of the imidazole-containing analogues **4**–**6** of westiellamide (**1**; Fig. 1).[13] These macrocycles differ from westiellamide only by having the three oxazoline units replaced by three imidazole moieties, the amino acid side chains (valine units) being the same. Here we describe the synthesis of the analogues **2** and **3** (Fig. 1), wherein the oxazoline units are formally replaced by oxazole and thiazole moieties, respectively.[14,15] We investigated the structures of these analogues using X-ray diffraction and DFT-based molecular modelling calculations. In particular we focused on the question as to what extent the scaffold of the cyclic system and its flexibility depend on the type of azole unit and the size of the side chain.

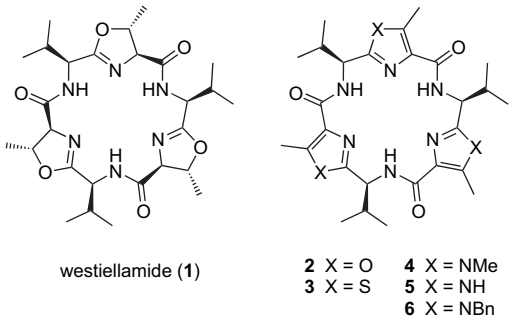
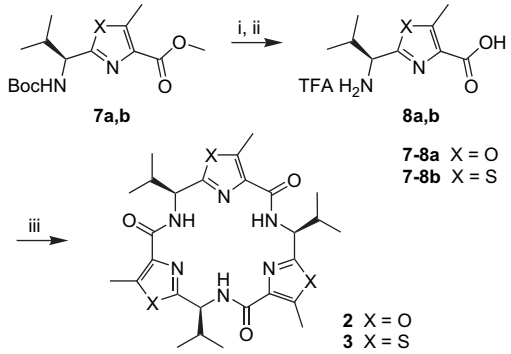


Figure 1. Westiellamide and its analogues **2**–**6**.

2. Results and discussion

2.1. Synthesis

The westiellamide analogues **2** and **3** can be prepared from oxazole building block **7a**[16] and the thiazole building block **7b**,[16] respectively (Scheme 1). Saponification of the methyl esters with NaOH provided the corresponding carbocyclic acids, which were subsequently subjected to amine deprotection using trifluoroacetic acid (TFA) in methylene chloride to give the amino acids **8a**,**b**. Several methods for a one-pot macrocyclization of the monomer building blocks **8a**,**b** were examined. The most advantageous route proved to be the reaction of the monomers with diphenyl phosphorazidate (DPPA) in the presence of an excess of Hünig's base under high dilution conditions at room temperature. This method provided the trimers **2** and **3** in rather good yields (35% for **2** and 25% for **3**).



Scheme 1. Synthesis of the westiellamide analogues **2** and **3**. Reagents: (i) 2 M NaOH, MeOH/dioxane, room temperature, 95%; (ii) TFA, DCM, quant.; (iii) DPPA, *i*-Pr_2NEt, CH_3CN, room temperature, 35% for **2**; DPPA, *i*-Pr_2NEt, THF, room temperature, 25% for **3**.

2.2. Structural investigations

2.2.1. Structural investigations of cyclic peptides 2–4 in solid state

We were able to obtain X-ray structures of the 18-membered cyclic peptides **2** and **3**. In Figure 2, the molecular structures of **2** and **3** are shown together with that of **4**.[13] The obtained X-ray structures show that all 18-membered peptides adopt a molecular triangle conformation in the solid state. As in the case of westiellamide (**1**),[17] all peptide NH groups point to the centre of the ring and the peptide carbonyl functions towards the outside of the ring. The valine side chains of **2**–**4** all lie on the same face of the molecule and adopt axial positions. The most striking difference is that in the case of oxazole peptide **2**, similar to the structures of westiellamide and nostocylamide,[17,18] the azole moieties of the macrocycle are almost coplanar, whereas in the case of the thiazole peptide **3** and the imidazole peptide **4**, the heterocyclic moieties of the macrocycle have a cone-like structure (see Fig. 2). The dihedral angle χ [N_{amide}–C_α–C_{azole}–X] (definition for the used abbreviations see Fig. 3) can be taken to express the extent of deviation from planarity. In the case of complete planarity, this angle is 180°. The oxazole macrocycle **2** shows a dihedral

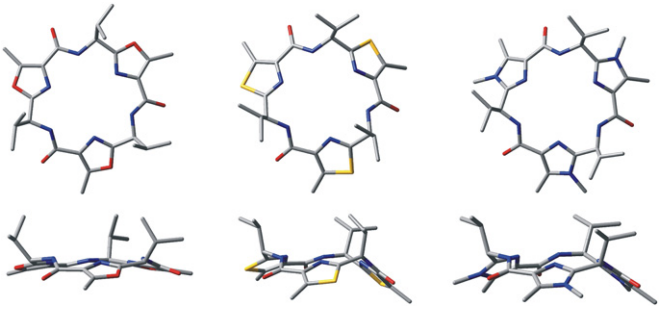


Figure 2. Molecular structures of **2**, **3** and **4** in solid state: top view (upper row) and side view (lower row). All hydrogen atoms and some solvent molecules have been omitted for clarity.

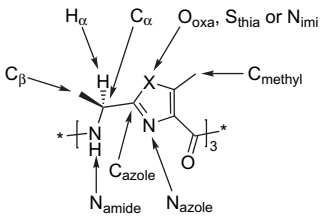


Figure 3. Definition of the used abbreviations.

Table 1
Dihedral angles and distances in **2**, **3** and **4** (mean values)

Method		Dihedral angles [°]		Distance *a* [Å] neighbouring C_{methyl}–C_{methyl}
		φ [H–N_{amide}–C_α–H_α]	χ [N_{amide}–C_α–C_{azole}–X]	
^{1}H NMR	**2**	146		
	3	161		
	4	158		
X-ray	**2**	151	169	10.24
	3	168	138	9.80
	4	171	143	9.64
B3LYP/6-31G*	**2**	139	160	10.12
	3	165	135	9.62
	4	164	135	9.11

angle of 169°, while, contrastingly, **3** and **4** exhibit a dihedral angle of only 138° and 143°, respectively (Table 1). Due to the near-planarity, the distance between the two adjacent C_{methyl}-atoms in the oxazole-containing cyclopeptide **2** is 10.24 Å, while in the peptides **3** and **4** this distance has a value of only 9.80 and 9.64 Å, respectively. This distance is of importance in that the C_{methyl}-atoms can serve as anchor groups for further functional units.[10a] As a matter of course, the functioning of these groups essentially depends on the distance to each other.

The dihedral angles φ [H–N_{amide}–C_α–H_α] (definition for the used abbreviations see Fig. 3) of the three amide linkages in **2**, **3** and **4** were found to be 151°, 168° and 171°, respectively. These values are consistent with those in solution, which can be determined from the vicinal $^3J_{HNCH}$ values of the ^{1}H NMR spectra.[19]

2.2.2. *Gas-phase calculations of cyclic peptides*

To determine the structure of the cyclic peptides **2**–**4** in the gas phase, we performed full geometry optimization computations applying the DFT-B3LYP method[20,21] and the 6-31G* basis set.[22,23] Because of the possible rotation of the isopropyl group around the C_α–C_β-axis a considerable number of conformers must be considered for obtaining a reliable mean value. For a better comparison of the calculated values with those obtained from the solid phase structures, only those conformers were calculated, which have the same conformation of the isopropyl groups as found in the solid state. The thus calculated structural parameters are consistent with the values found in solid state. Especially the fact that **3** and **4** form a distinctly more tapered conus than **2** is confirmed (Table 1).

In order to find an explanation for this behaviour, we had a closer look on the dihedral angle χ [N_{amide}–C_α–C_{azole}–X] in dependence on the azole system on one side and on the size of the amino acid side chains on the other side. As side chains we decided to take the methyl group and the *tert*-butyl group. This selection allows investigating the influence of the group size. Moreover, the isopropyl group has an intermediate position between these two groups, and thus these investigations allow statements about this group, too. Therefore, we chose the model systems **9**–**14** (Fig. 4), where we modified stepwise the dihedral angle χ and simultaneously optimized all the other structural parameters. The thus obtained energy

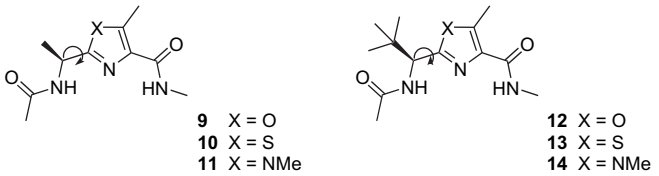


Figure 4. Reference systems **9**–**14** for the determination of the energy profile in relation to the dihedral angle χ [N_{amide}–C_α–C_{azole}–X].

profiles of the reference compounds **9**–**14** in relation to the dihedral angle χ are shown in Figures 5 and 6, respectively.

The reference systems **9** and **11** having methyl side chains show in the region of 0–200° two minima, imidazole **11** having the lowest minimum at 90° and oxazole **9** at about 180°. The reason for this difference can be explained by an NBO analysis of the reference systems **9** und **11**:[24,25] In the imidazole system, the π(C_{azole}–N_{azole})-orbital is energetically much higher than in the corresponding oxazole. Accordingly, the interaction of this π-bond with the σ^*(C_α–N_{amide})-orbital is much stronger than in the oxazole. The optimum interaction between these two orbitals is at an angle of 90°, the σ^*(C_α–N_{amide})-orbital being parallel to the π(C_{azole}–N_{azole})-orbital. In

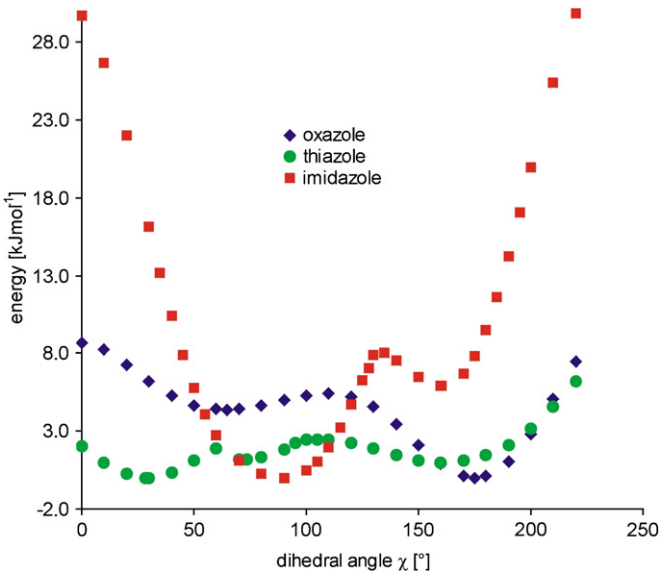


Figure 5. Calculated energy profiles of oxaole **9**, thiazole **10** and imidazole **11**, respectively, in relation to the dihedral angles by use of B3LYP/6-31G**.

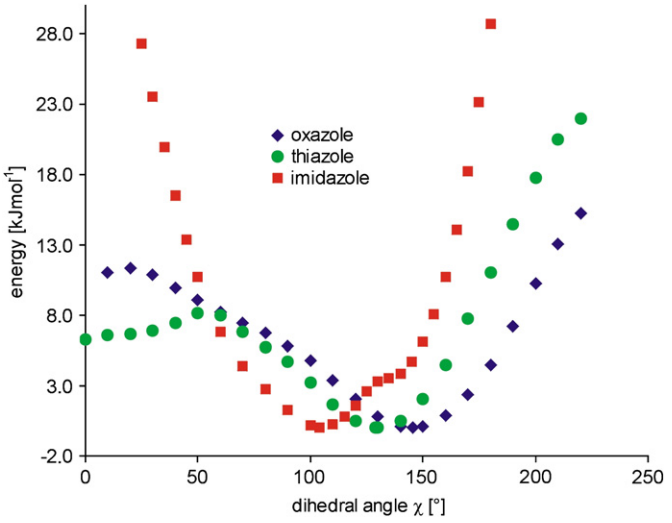


Figure 6. Calculated energy profiles of oxaole **12**, thiazole **13** and imidazole **14**, respectively, in relation to the dihedral angles by use of B3LYP/6-31G*.

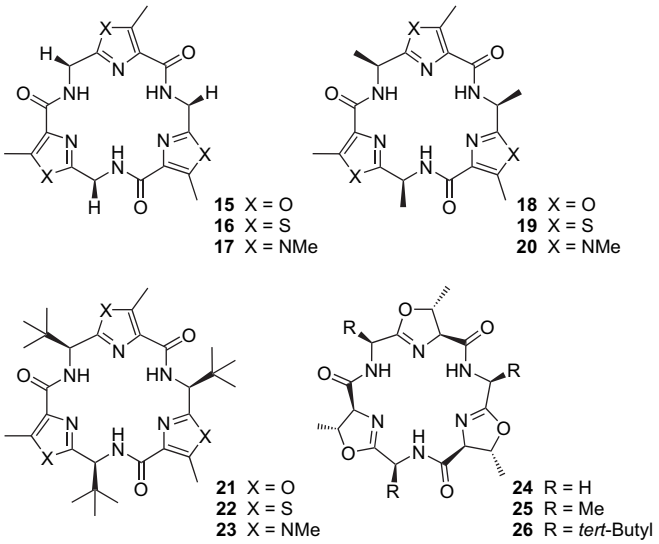


Figure 7. Structures of cyclic peptides investigated by gas-phase calculations.

contrast, the $\pi^*(C_{azole}-N_{azole})$-orbital in the oxazole is of lower energy than in the imidazole and accordingly, the interactions with the highly energetic $\sigma(C_\alpha-C_\beta)$- and $\sigma(C_\alpha-H_\alpha)$-orbitals are of more importance than in the imidazole. The optimum interaction between these two orbitals with the $\pi^*(C_{azole}-N_{azole})$-orbital takes place at an angle of 180°. The thiazole **10** exhibits in the region of 0–200° even three minima, the energy difference between these three minima being very small. Looking only at the minima in the region from 130° to 200°, i.e., in the range where they can be found for the cyclic hexapeptides, it can be seen that in the case of the thiazole **10** and the imidazole **11** the minima are at a dihedral angle χ [$N_{amide}-C_\alpha-C_{azole}-X$] of 160° and of the oxazole **9** of 175°.

When replacing the methyl groups by the sterically more demanding *tert*-butyl groups, i.e., looking at the energy profile of the azoles **12**–**14** (Fig. 6), the results change. Owing to the large groups, the rotation around the dihedral angle has a higher activation barrier. This is most pronounced in the case of the imidazole **14**, which has the most voluminous group in the aromatic ring (NCH_3), followed by the thiazole **13** with the sulfur atom in the aromatic ring. The lowest increase of the activation barrier is found in the oxazole **12**, only having the relatively small oxygen atom in the azole unit.

Due to the increase of the sterical interactions at dihedral angles from 180° to 200° the whole curve form changes and now shows a single minimum in the range from 50 to 200° for all three systems. In the case of the oxazole **12**, the minimum is at 146°, of the thiazole **13** at 129° and of the imidazole **14** at 104°. Additionally, the imidazole has a saddle point at 135°. The preference of the respective azole systems for different dihedral angles corresponds exactly to what is found in the X-ray structures of the cyclic platforms **2**–**4**.

For investigating more precisely the influence of the single azole systems and the size of the side chains on the whole scaffold, we performed full geometry optimization calculations for the cyclic peptides **15**–**23** (Fig. 7). Additionally, the dihedral angles were fixed at 90° and 180°, respectively, and all other parameters were optimized. The focus was on finding out how much energy is required for bringing the aromatic units of the cyclic peptide into a planar form (χ=180°) or into an almost cylindrical form (χ=90°). This energy also reflects the flexibility of the scaffold. The question is highly relevant, in that the distances between the C_{methyl}-atoms of the azole systems are reduced from 10 to 6 Å when passing from the planar to the cylindrical geometry. Since the C_{methyl}-atoms can carry additional groups,[10a] the question about what distances can be obtained with what energy is of high significance. In Table 2, the dihedral angles and the distances in the cyclic peptides **15**–**23** are compiled together with the relative energies.

To compare the flexibility of these azole cyclopeptides with that of westiellamide, the structures of the oxazoline cyclopeptides **24**–**26** were calculated both without geometrical restrictions and with fixed dihedral angles at 120° and 180°.

As expected, the cyclic peptides **15**–**17**, which have only hydrogen atoms as 'side chains', thus being achiral and not having a preferred spatial arrangement, are almost planar. Only the imidazole-containing peptide **17** shows a small deviation from planarity. Of interest is the relative energy of the conformers having a dihedral angle of 90°, i.e., that energy, which is characteristic for the flexibility of the scaffold in respect of bending. In the case of the oxazole peptide **15**, the energy is relatively high (53 kJ mol^{-1}), whereas in the case of the imidazole peptide it is low (14 kJ mol^{-1}). As already stated above, the reason for this is the fact that the best conformation of imidazoles has a dihedral angle of 90°, while in the case of the oxazoles this angle is 180°.

The cyclic peptides having methyl groups as side chains do not differ essentially from those without alkyl side chains; only the deviation from planarity is somewhat stronger. The distances between the methyl groups and the energies required for obtaining a cylinder-like structure are similar and show the same tendencies. In the case of the cyclic peptides **21**–**23** the expected behaviour is found. Due to the large groups, the

Table 2
Dihedral angles and distances in **15**–**26** (mean values) and energy differences calculated using B3LYP/6-31G*

	Dihedral angles [°] χ [N_{amide}–C_{α}–C_{azole}–X]	Distance *a* [Å] neighbouring C_{methyl}–C_{methyl}	ΔE[b] [kJ mol^{-1}]
15	180[a]	10.60	0.0
	179	10.60	0.0
	90[a]	6.21	52.6
16	180[a]	10.84	0.0
	180	10.84	0.0
	90[a]	6.94	33.2
17	180[a]	10.63	0.3
	164	10.64	0.0
	90[a]	6.72	14.0
18	180[a]	10.55	1.7
	172	10.47	0.0
	90[a]	6.17	56.9
19	180[a]	10.79	10.0
	156	10.52	0.0
	90[a]	6.88	36.7
20	180[a]	10.58	11.8
	162	10.39	0.0
	90[a]	6.68	14.7
21	180[a]	10.36	29.1
	149	9.60	0.0
	90[a]	6.09	60.1
22	180[a]	10.58	72.6
	135	9.56	0.0
	90[a]	6.79	46.0
23	180[a]	10.36	85.0
	137	9.21	0.0
	90[a]	6.62	21.1
24	180[a]	10.58	0.7
	184	10.56	0.0
	120[a]	7.60	127.2
25	180[a]	10.46	0.0
	179	10.47	0.0
	120[a]	7.32	121.1
26	180[a]	10.02	3.2
	172	10.01	0.0
	120[a]	7.37	86.9

[a] The dihedral angles χ were fixed to the given values whereas all other structural parameters were optimized.
[b] Relative energy relating to the lowest energy conformer.

dihedral angles of about 180° are strongly disfavoured. Accordingly, the minima of the cycles are at 149°, 135° and 137° (Fig. 8). The question about flexibility, or, in other words, the question about the energy required for reaching the two extremes—planarity and cylinder—is here of interest, too. As expected, in the case of the oxazole, planarity is reached with less energy input (29 kJ mol^{-1}) than the cylinder-like structure (60 kJmol^{-1}). The thiazole requires for both extremes high energy (73 and 46 kJ mol^{-1}). In the case of the imidazole, contrastingly to the oxazole, planarity requires high energy (85 kJ mol^{-1}), while the cylinder-like structure can be reached with an energy of only 21 kJ mol^{-1}.

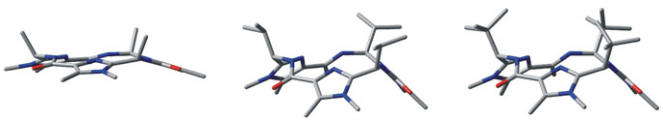


Figure 8. Molecular structures of **20**, **4** and **23** calculated using B3LYP/6-31G*. All hydrogen atoms have been omitted for clarity.

The behaviour of oxazoline cyclopeptides **24**–**26** most resembles that of the oxazole-containing peptides. The tendency to take a dihedral angle of 180° is in this case even stronger. Even the compound with three large substituents (**26**, R=*tert*-butyl) scarcely deviates from this value. Here, a bending is energetically extremely disfavoured. Thus, all three cycles require energies from 86 to 125 kJ mol^{-1} for bringing the angle to a value of 120°.

3. Conclusion

In summary, we described the synthesis and the structures of oxazole, thiazole and imidazole analogues of the naturally occurring cyclopeptide westiellamide. We could show that independently of whether in the solid or gaseous state the aromatic units of the oxazole-based peptide are almost coplanar, whereas in the case of the thiazole and the imidazole cyclic peptides the azole moieties form cone-like structures. As to the flexibility of the cyclic structures, their comportment can be summarized as follows: oxazole-containing peptides are predominantly flexible towards coplanar geometry, i.e., towards a geometry where the distances between C_{methyl}-atoms are large. The imidazole-containing systems behave contrarily, showing flexibility towards a cone-like geometry. They can especially be used when lower distances between the C_{methyl}-atoms are desired. Thus, when building up supramolecular structures the distance between C_{methyl}-atoms can be controlled via the selection of the appropriate azole system.

4. Experimental

4.1. General remarks

The Boc-protected amino acids **7** were prepared according to reported procedures.[16] 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 F_{254} thin layer plates. Flash chromatography was carried out on silica gel 60 (230–400 mesh). Melting points were determined in capillary tubes and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on Bruker Avance DMX 300 and Avance DRX 500 spectrometers. All chemical shifts (δ) are given in parts per million relative to TMS. The spectra were referenced to deuterated solvents indicated in brackets in the analytical data. HRMS spectra were recorded on a JEOL JMS-700 instrument.

4.2. Synthesis of the westiellamide analogue **2**

The Boc-protected amino acid **7a** (298 mg, 1.00 mmol) was dissolved in DCM (20 mL) and the solution was cooled to

0 °C. TFA (4.0 mL) was added at that temperature. The ice bath was removed after 30 min and stirring was continued at room temperature for 2 h. The mixture was concentrated in vacuo to yield quantitatively the amino acid **8a** (312 mg), which was used in the next step without further purification.

To a suspension of **8a** (312 mg, 1.00 mmol) in acetonitrile (100 mL) were added *N*,*N*-diisopropylethylamine (1.16 mL, 7.00 mmol) and DPPA (0.43 mL, 2.00 mmol) and the solution was stirred at room temperature for 2 days. The solvent was evaporated in vacuo and the residue was dissolved in AcOEt and washed with water and brine, then dried over $MgSO_4$ and concentrated in vacuo. Purification was accomplished by chromatography on silica gel (petroleum ether/ethyl acetate: 3:1) to yield **2** (35%) as a white solid; mp=239 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 8.18 (d, $^3J_{H,H}$=7.7 Hz, 3H), 5.03 (dd, $^3J_{H,H}$=4.8, 7.7 Hz, 3H), 2.64 (s, 9H), 2.33 (m, 3H), 1.06 (d, $^3J_{H,H}$=6.9 Hz, 9H), 1.01 (d, $^3J_{H,H}$=6.8 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 161.12, 160.76, 153.48, 128.51, 52.96, 33.48, 18.35, 18.33, 11.59. IR (KBr) 3390, 2966, 2932, 2876, 1682, 1637, 1519, 1370 cm^{-1}. CD (CH_3CN): λ ($\Delta\varepsilon$ [dm^3 mol^{-1} cm^{-1}])=289 (+4.3), 231 (−34.7), 208 (+20.6). HRMS (FAB+) $[M+H]^+$ calculated: 541.2775; observed: 541.2783.

4.3. Synthesis of the westiellamide analogue 3

The Boc-protected amino acid **7b** (230 mg, 0.73 mmol) was dissolved in DCM (15 mL) and the solution was cooled to 0 °C. TFA (3.0 mL) was added at that temperature. The ice bath was removed after 30 min and stirring was continued at room temperature for 2 h. The mixture was concentrated in vacuo to yield quantitatively the amino acid **8b** (240 mg), which was used in the next step without further purification.

To a suspension of **8b** (240 mg, 0.73 mmol) in tetrahydrofuran (40 mL) were added *N*,*N*-diisopropylethylamine (1.30 mL, 7.80 mmol) and DPPA (0.50 mL, 2.20 mmol) at 0 °C. Stirring was continued for 7 days while slowly allowing the reaction mixture to warm to room temperature. The solvent was evaporated in vacuo and the residue was dissolved in AcOEt and washed with water and brine, then dried over $MgSO_4$ and concentrated in vacuo. Purification was achieved by performing chromatography with silica gel (petroleum ether/ethyl acetate: 4:1) to yield **3** (25%) as a white solid; mp=185 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 8.43 (d, $^3J_{H,H}$=9.4 Hz, 3H), 5.27 (dd, $^3J_{H,H}$=5.4, 9.4 Hz, 3H), 2.80 (s, 9H), 2.22 (m, 3H), 1.06 (d, $^3J_{H,H}$=6.7 Hz, 9H), 1.01 (d, $^3J_{H,H}$=7.4 Hz, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 163.78, 161.28, 141.75, 141.05, 54.70, 34.82, 18.83, 18.56, 12.65. IR (KBr) 3411, 2963, 2873, 1672, 1546, 1467 cm^{-1}. CD (MeOH): λ ($\Delta\varepsilon$ [dm^3 mol^{-1} cm^{-1}])=266 (+2.0), 237 (−49.2), 208 (+74.7). HRMS (FAB+) $[M+H]^+$: calculated: 589.2089; observed: 589.2054.

4.4. Crystal data for the westiellamide analogues 2 and 3

Crystal data for **2**: $C_{27}H_{36}N_6O_6$ (crystallization from CH_2Cl_2), M=540.62, monoclinic, space group $P2_1$, dimensions 0.38×0.36×0.28 mm^3, Z=4, a=12.8267(3) Å, b=19.6654(4) Å, c=13.0342(3) Å, β=116.790(1)°, V=2934.88(11) Å^3, ρ=1.224 g cm^{-3}, T=200(2) K, $2\theta_{max}$=27.48°, radiation Mo Kα, λ=0.71073 Å, μ=0.09 mm^{-1}, 30,734 reflections measured, 13,356 unique (R_{int}=0.0265), 10,892 observed ($I>2\sigma(I)$), $R1(F)$=0.043, $wR(F^2)$=0.104.

Crystal data for **3**: $C_{27}H_{36}N_6O_3S_3\cdot CHCl_3$ (crystallization from $CHCl_3$), M=708.17, orthorhombic, space group $P2_12_12_1$, dimensions 0.16×0.13×0.06 mm^3, Z=4, a=8.1781(9) Å, b=9.8364(11) Å, c=41.408(5) Å, $\alpha=\beta=\gamma$=90°, V=3331.0(6) Å^3, ρ=1.412 g cm^{-3}, T=100(2) K, θ_{max}=24.71°, radiation Mo Kα, λ=0.71073 Å, μ=0.50 mm^{-1}, 26,385 reflections measured, 5652 unique (R_{int}=0.0684), 5155 observed ($I>2\sigma(I)$), $R1(F)$=0.056, $wR(F^2)$=0.123. CCDC 611676 and 611677 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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References and notes

1. For reviews on the isolation, structure and synthesis of the *Lissoclinum* cyclic peptides see: (a) Wipf, P. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier: Amsterdam, 1998; Vol. 12, pp 187–228; (b) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115.
2. (a) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249; (b) Wipf, P.; Fritch, P. C.; Geib, S. J.; Sefler, A. M. *J. Am. Chem. Soc.* **1998**, *120*, 4105; (c) Todorova, A. K.; Jüttner, F.; Linden, A.; Plüss, T.; v. Philipsborn, W. *J. Org. Chem.* **1995**, *60*, 789; (d) Li, Y.-M.; Milne, J. C.; Madison, L. L.; Koller, R.; Walsh, C. T. *Science* **1996**, *274*, 1188; (e) Foster, M. P.; Concepción, G. P.; Caraan, G. B.; Ireland, C. M. *J. Org. Chem.* **1992**, *57*, 6671.
3. (a) Ogino, J.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Nat. Prod.* **1996**, *59*, 581; (b) Holzapfel, C. W.; v. Zyl, W. J.; Roos, M. *Tetrahedron* **1990**, *46*, 649.
4. Michael, J. P.; Pattenden, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1.
5. (a) Wipf, P.; Wang, C. *Org. Lett.* **2006**, *8*, 2381; (b) Bernhardt, P. V.; Comba, P.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R.; Lötzbeyer, L. *Chem.—Eur. J.* **2002**, *8*, 1527; (c) Cusack, R. M.; Grøndahl, L.; Abbenante, G.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R.; Hambley, T. W. *J. Chem. Soc., Perkin Trans. 2* **2000**, 323; (d) Freeman, D. J.; Pattenden, G.; Drake, A. F.; Siligardi, G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 129; (e) v. d. Brenk, A. L.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R.; Hambley, T. W. *Inorg. Chem.* **1996**, *35*, 1095; (f) Wipf, P.; Venkatraman, S.; Miller, C. P.; Geib, S. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1516; (g) v. d. Brenk, A. L.; Fairlie, D. P.; Hanson, G. R.; Gahan, L. R.; Hawkins, C. J.; Jones, A. *Inorg. Chem.* **1994**, *33*, 2280; (h) v. d. Brenk, A. L.; Byriel, K. A.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R.; Hawkins, C. J.; Jones, A.; Kennard, C. H. L.; Moubaraki, B.; Murray, K. S. *Inorg. Chem.* **1994**, *33*, 3549.
6. For a review on cyclic pseudopeptides as new scaffold see: Jolliffe, K. A. *Supramol. Chem.* **2005**, *17*, 81.
7. (a) Haberhauer, G.; Somogyi, L.; Rebek, J., Jr. *Tetrahedron Lett.* **2000**, *41*, 5013; (b) Mink, D.; Mecozzi, S.; Rebek, J., Jr. *Tetrahedron Lett.* **1998**, *39*, 5709.
8. (a) Pattenden, G.; Thompson, T. *Tetrahedron Lett.* **2002**, *43*, 2459; (b) Singh, Y.; Sokolenko, N.; Kelso, M. J.; Gahan, L. R.; Abbenante, G.;

Fairlie, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 333; (c) Pattenden, G.; Thompson, T. *Chem. Commun.* **2001**, 717.
9. (a) Haberhauer, G.; Oeser, T.; Rominger, F. *Chem.—Eur. J.* **2005**, 6718; (b) Haberhauer, G.; Oeser, T.; Rominger, F. *Chem. Commun.* **2004**, 2044.
10. (a) Pintér, Á.; Haberhauer, G.; Hyla-Kryspin, I.; Grimme, S. *Chem. Commun.* **2007**, 3711; (b) Haberhauer, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 4397; (c) Haberhauer, G.; Oeser, T.; Rominger, F. *Chem. Commun.* **2005**, 2799.
11. McDonough, M. J.; Reynolds, A. J.; Gladys Lee, W. Y.; Jolliffe, K. A. *Chem. Commun.* **2006**, 2971.
12. (a) Singh, Y.; Stoermer, M. J.; Lucke, A. J.; Guthrie, T.; Fairlie, D. P. *J. Am. Chem. Soc.* **2005**, *127*, 6563; (b) Singh, Y.; Stoermer, M. J.; Lucke, A. J.; Glenn, M. P.; Fairlie, D. P. *Org. Lett.* **2002**, *4*, 3367.
13. Haberhauer, G.; Rominger, F. *Tetrahedron Lett.* **2002**, *43*, 6335.
14. For further westeillamide analogues see: (a) Bertram, A.; Blake, A. J.; González-López de Turiso, F.; Hannam, J. S.; Jolliffe, K. A.; Pattenden, G.; Michael Skae, M. *Tetrahedron* **2003**, *59*, 6979; (b) Wipf, P.; Miller, C. P.; Grant, C. M. *Tetrahedron* **2000**, *56*, 9143; (c) Blake, A. J.; Hannam, J. S.; Jolliffe, K. A.; Pattenden, G. *Synlett* **2000**, 1515.
15. For other C_3-symmetric cyclic pseudopeptides see: (a) Chakraborty, T. K.; Tapadar, S.; Raju, T. V.; Annapurna, J.; Singh, H. *Synlett* **2004**, 2484; (b) Jayaprakash, S.; Pattenden, G.; Viljoen, M. S.; Wilson, C. *Tetrahedron* **2003**, *59*, 6637; (c) Pohl, S.; Goddard, R.; Kubik, S. *Tetrahedron Lett.* **2001**, *42*, 7555.
16. Haberhauer, G.; Rominger, F. *Eur. J. Org. Chem.* **2003**, 3209.
17. Hawkins, J.; Lavin, M. F.; v. d. Brenk, A.; Watters, D. J. *Tetrahedron* **1992**, *48*, 341.
18. Todorova, A. K.; Jüttner, F.; Linden, A.; Plüss, T.; v. Philipsborn, W. *J. Org. Chem.* **1995**, *60*, 7891.
19. Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11.
20. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; (b) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200; (c) Lee, L.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
21. All computations were performed with the Gaussian 03 program-package: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian: Wallingford CT, 2004.
22. (a) Dobbs, K. D.; Hehre, W. J. *J. Comput. Chem.* **1987**, *8*, 880; (b) Dobbs, K. D.; Hehre, W. J. *J. Comput. Chem.* **1987**, *8*, 861; (c) Gordon, M. S.; Binkley, J. S.; Pople, J. A.; Pietro, W. J.; Hehre, W. J. *J. Am. Chem. Soc.* **1982**, *104*, 2797; (d) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.
23. (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724; (b) Blaudeau, J.-P.; McGrath, M. P.; Curtiss, L. A.; Radom, L. *J. Chem. Phys.* **1997**, *107*, 5016; (c) Rassolov, V. A.; Ratner, M. A.; Pople, J. A.; Redfern, P. C.; Curtiss, L. A. *J. Comput. Chem.* **2001**, *22*, 976.
24. Natural Bond Orbital analysis, using NBO version 3: (a) Carpenter, J. E.; Weinhold, F. *J. Mol. Struct. (Theochem)* **1988**, *169*, 41; (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899; (c) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1983**, *78*, 4066.
25. Haberhauer, G.; Pintér, Á.; Oeser, T.; Rominger, F. *Eur. J. Org. Chem.* **2007**, 1779.