Pergamon

Tetrahedron Letters 43 (2002) 6335–6338

TETRAHEDRON LETTERS

Synthesis of a new class of imidazole-based cyclic peptides

Gebhard Haberhauer* and Frank Rominger

Organisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany

Received 19 June 2002; accepted 8 July 2002

Abstract—A new class of cyclic peptides based on dipeptidyl imidazoles is presented. Their structure consists of imidazole units alternating with standard amino acid residues and resembles naturally occurring marine cyclopeptides such as westiellamide and ascidiacyclamide.

In recent years a number of cyclopeptides incorporating five-membered heterocyclic rings have been isolated from marine sources.[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]

In *Lissoclinum* cyclopeptide alkaloids, oxazole, thiazole, oxazoline and thiazoline moieties alternate with standard amino acid residues (Fig. 1).[1] These five-membered heterocyclic rings result from condensation of serine, threonine and cysteine side chains with the preceding carbonyl groups in a peptide sequence. The size and conformation of these macrocycles and the functional groups they possess 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] and by metal-catalyzed templated assemblies of oxazole and thiazole-based amino acids.[6] The unique macrocyclic heterocyclic scaffolds present in *Lissoclinum* cyclopeptide offer great opportunities for molecular recognition[7] and the preparation of new tubular and cage structures.[8]

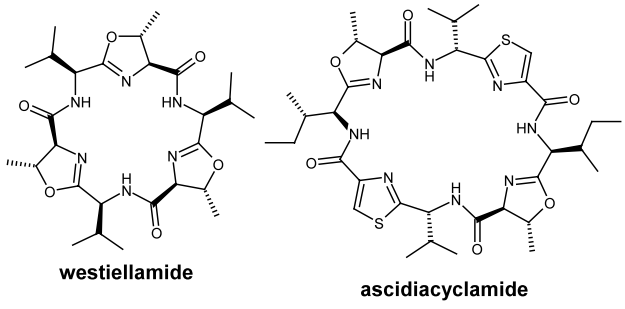


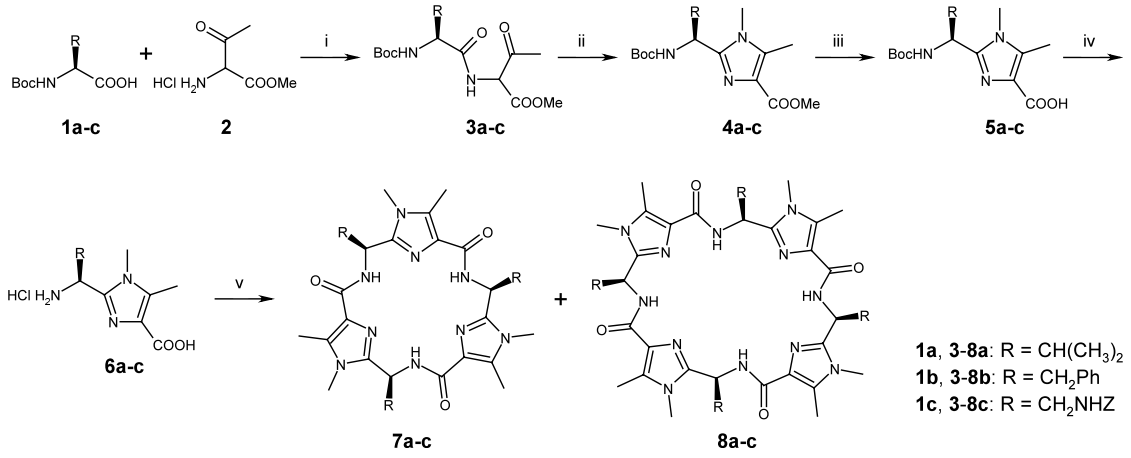
Figure 1. Natural marine cyclopeptides with heterocyclic scaffolds.

Cyclopeptides containing imidazole units in the scaffold have not been isolated from nature yet. This may be due to the fact that the diaminopropanoic acid (Dap), which is formally the amino analogue of serine, occurs rarely in natural sources.[9] Moreover, non-natural cyclopeptides incorporating dipeptidyl imidazoles in the backbone have not been described in literature, neither. We consider the unique feature of imidazoles, constrained into an asymmetric macrocyclic peptidylic framework, to be highly promising for the development of new classes of metal chelators and asymmetric catalysts. For example, imidazoles are well known as ligands in many metalloenzymes (e.g. metalloproteases) as well as in non-natural metal complexes.[10] Furthermore, the basicity of imidazoles is significantly higher than that of the corresponding oxazoles and thiazoles.[11] For this reason, imidazoles have been proven to be a key structural element in basic active sites of asymmetric catalysts.[12]

We now wish to report the synthesis of the cyclic peptides **7a–c** and **8a–c** (see Scheme 1) based on the dipeptidyl imidazoles **4a–c**. The synthesis starts with the activation of the Boc-protected valine (**1a**), the Boc-protected phenylalanine (**1b**) or the bis-*N*-protected β-aminoalanine derivative **1c** as the mixed anhydride using isobutyl chloroformate and their coupling to the

* Corresponding author. Tel.: +49 (0)6221 546239; fax: +49 (0)6221 544205; e-mail: gebhard.haberhauer@urz.uni-heidelberg.de

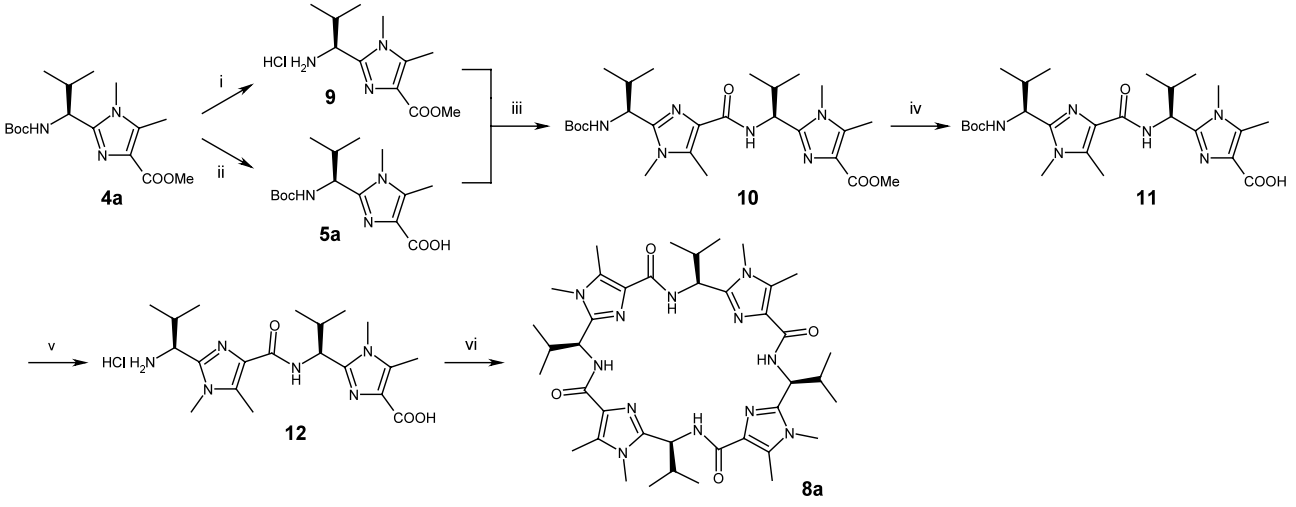
0040-4039/02/$ - see front matter
PII: S0040-4039(02)01365-5



Scheme 1. *Reagents and conditions*: (i) isobutyl chloroformate, NMM, THF, –20°C, 85%; (ii) $MeNH_2$, AcOH, xylenes, reflux, 70%; (iii) 2 M NaOH, MeOH/dioxane, rt, 95%; (iv) HCl/AcOEt, rt, quant.; (v) DPPA, $i Pr_2NEt$, CH_3CN, rt, 25–35% for **7a**–**c**, 5–10% for **8a**,**b**.

keto ester **2**[13] at –20°C. The resulting amidoketones **3a**–**c** were condensed to the imidazoles **4a**–**c** with methylamine in the presence of acetic acid in refluxing xylenes with azeotropic removal of water.[14] Saponification of the methyl esters **4a**–**c** with NaOH provided the corresponding carbocyclic acids **5a**–**c**, which were subsequently subjected to amine deprotection using HCl in ethyl acetate, leading to the amino acids **6a**–**c**. Several methods for a one-pot macrocyclization of the imidazoles **6a**–**c** were examined. The most advantageous route proved to be reacting the monomers with diphenyl phosphorazidate (DPPA) in the presence of an excess of Hünig's base in acetonitrile under high dilution conditions (0.05 M) at room temperature.[15] This method provided the trimers **7a**–**c** in rather good yields (25–35%).[16] The tetrameric compounds **8a** and **8b** were obtained in lower yields (5–10%)[17] whereas the yield for the tetramer **8c** was so poor that it could not be isolated but only observed by FAB mass spectrometry.

Due to the low yields of the tetramers and to the difficulties occurring during the separation of the tetramers from the trimers, we also elaborated an alternative synthetic route which could provide the tetramers in significantly increased yields and in higher purity. An appropriate way for the improved preparation of the tetramer **8a** is presented in Scheme 2. Acid cleavage of the Boc group of **4a** with HCl in ethyl acetate provided the ammonium salt **9** which was coupled to the free acid building block **5a** via DPPA activation to give the protected linear dimer **10** in a 70% yield. Deprotection of the carboxyl group by saponification and removal of the Boc group with HCl in ethyl acetate afforded the completely deprotected linear dimer **12**. The macrodimerization was carried out by pentafluorophenyl diphenylphosphinate (FDPP) activation and addition of Hünig's base in acetonitrile, and yielded the tetramer **8a** in 40%.



Scheme 2. *Reagents and conditions*: (i) HCl/AcOEt, rt, quant.; (ii) 2 M NaOH, MeOH/dioxane, rt, 95%; (iii) DPPA, $i Pr_2NEt$, CH_3CN, rt, 70%; (iv) 2 M NaOH, MeOH/dioxane, rt, 95%; (v) HCl/AcOEt, rt, quant.; (vi) FDPP, $i Pr_2NEt$, CH_3CN, rt, 40%.

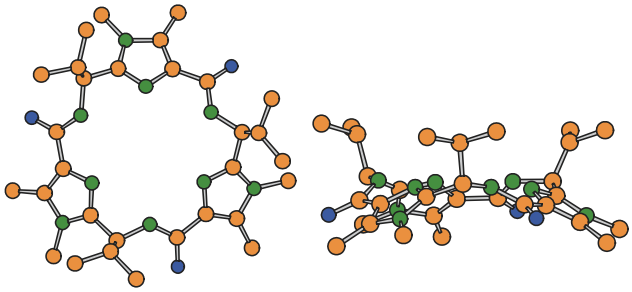


Figure 2. X-Ray structure of **7a**: top view (left) and side view (right).

X-Ray quality crystals of **7a** were obtained by crystallization in acetone-d_6.[18] The X-ray structure indicates that **7a** is a rigid molecule in which all lone pairs of the imidazole nitrogens and the hydrogens of the secondary amides point towards the center of the macrocycle (Fig. 2). The valine side chains all lie on the same face of the molecule and adopt axial positions. The imidazole moieties do not form a single plane but a cone-like structure.

Investigations concerning metal complexation properties of this new class of imidazole-based cyclic peptides and their application in asymmetric synthesis are ongoing in our lab.

Acknowledgements

Financial support from the Deutsche Forschungsgemeinschaft is gratefully acknowledged. The authors would also like to express their special thanks to Professor Rolf Gleiter (University of Heidelberg) and Dr. Rolf Roers (Bayer AG) for advice and encouragement.

References

1. (a) Wipf, P.; Uto, Y. *J. Org. Chem.* **2000**, *65*, 1037; (b) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155; (c) Wipf, P. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1998; pp. 187–228; (d) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115; (e) Pettit, G. R. *Pure Appl. Chem.* **1994**, *66*, 2271; (f) Fusetani, N.; Matsunoga, S. *Chem. Rev.* **1993**, *93*, 1793; (g) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771; (h) Garson, M. J. *Chem. Rev.* **1993**, *93*, 1699.
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.; van 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. N.; van Zyl, W. J. *Tetrahedron* **1990**, *46*, 649.
4. Michael, J. P.; Pattenden, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1.
5. (a) Bernhardt, P. V.; Comba, P.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R.; Lötzbeyer, L. *Chem. Eur. J.* **2002**, *8*, 1527; (b) 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; (c) Freeman, D. J.; Pattenden, G.; Drake, A. F.; Siligardi, G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 129; (d) van der Brenk, A. L.; Fairlie, D. P.; Gahan, L. R.; Hanson, G. R.; Hambley, T. W. *Inorg. Chem.* **1996**, *35*, 1095; (e) Wipf, P.; Venkatraman, S.; Miller, C. P.; Geib, S. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1516; (f) van der Brenk, A. L.; Fairlie, D. P.; Hanson, G. R.; Gahan, L. R.; Hawkins, C. J.; Jones, A. *Inorg. Chem.* **1994**, *33*, 2280; (g) van der 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. (a) Bertram, A.; Pattenden, G. *Synlett* **2001**, 1873; (b) Blake, A. J.; Hannam, J. S.; Jolliffe, K. A.; Pattenden, G. *Synlett* **2000**, 1515.
7. (a) Somogyi, L.; Haberhauer, G.; Rebek, J., Jr. *Tetrahedron* **2001**, *57*, 1699; (b) Haberhauer, G.; Somogyi, L.; Rebek, J., Jr. *Tetrahedron Lett.* **2000**, *41*, 5013; (c) Boss, C.; Rasmussen, P. H.; Wartini, A. R.; Waldvogel, S. R. *Tetrahedron Lett.* **2000**, *41*, 6327; (d) 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) Ikegami, F.; Murakoshi, I. *Phytochemistry* **1994**, *35*, 1089; (b) Wang, M.; Gould, S. J. *J. Org. Chem.* **1993**, *58*, 5176.
10. For examples, see: (a) Navarro, J. A. R.; Lippert, B. *Coord. Chem. Rev.* **2001**, *222*, 219; (b) Sénèque, O.; Giorgi, M.; Reinaud, O. *Chem. Commun.* **2001**, 984; (c) Kondo, S.; Shinbo, K.; Yamaguchi, T.; Yoshida, K.; Yano, Y. *J. Chem. Soc., Perkin Trans. 2* **2001**, 128; (d) Buncel, E.; Clement, O.; Onyido, I. *Acc. Chem. Res.* **2000**, *33*, 672; (e) Ašperger, S.; Cetina-Čižmek, B. *Croat. Chem. Acta* **1996**, *69*, 1305; (f) Arena, G.; Impellizzeri, G.; Maccarrone, G.; Pappalardo, G.; Rizzarelli, E. *J. Chem. Soc., Dalton Trans.* **1994**, 1227; (g) Mani, F. *Coord. Chem. Rev.* **1992**, *120*, 325.
11. Gupta, R. R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry II*; Springer: Berlin, 1999; pp. 357–486.
12. (a) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134; (b) Jarvo, E. R.; Vasbinder, M. M.; Miller, S. J. *Tetrahedron* **2000**, *56*, 9773; (c) Copeland, G. T.; Jarvo, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784; (d) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181; (e) Oku, J.-I.; Inoue, S. *J. Chem. Soc. Chem. Commun.* **1981**, 229.
13. Singh, J.; Gordon, T. D.; Earley, W. G.; Morgan, B. A. *Tetrahedron Lett.* **1993**, *34*, 211.
14. Gordon, T. D.; Singh, J.; Hansen, P. E.; Morgan, B. A. *Tetrahedron Lett.* **1993**, *34*, 1901.
15. General procedure for the oligomerization: To a suspension of **6a–c** (1 equiv.) in acetonitrile (0.05 M) were added *N*,*N*-diisopropylethylamine (4 equiv.) and DPPA (1.5 equiv.) 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.

16. Spectroscopic data for **7a**: ^{1}H NMR (300 MHz, acetone-d_6): 8.36 (d, 3H, $J=8.9$ Hz), 5.14 (dd, 3H, $J=9.2$, 5.5 Hz), 3.62 (s, 9H), 2.52 (s, 9H), 2.09 (m, 3H), 1.01 (d, 9H, $J=6.6$ Hz), 0.95 (d, 9H, $J=6.6$ Hz). ^{13}C NMR (75 MHz, acetone-d_6): 163.42, 147.51, 132.88, 130.14, 49.92, 35.24, 30.45, 19.67, 17.85, 9.43. HRMS (FAB+) $[M+H]^+$ calculated: 580.3724; observed: 580.3707.
17. Spectroscopic data for **8a**: ^{1}H NMR (300 MHz, acetone-d_6): 7.53 (d, 4H, $J=9.2$ Hz), 4.90 (m, 4H), 3.67 (s, 12H), 2.47 (s, 12H), 2.41 (m, 4H), 1.10 (d, 12H, $J=6.6$ Hz), 0.87 (d, 12H, $J=6.6$ Hz). ^{13}C NMR (75 MHz, acetone-d_6): 164.83, 149.35, 133.81, 131.06, 51.39, 34.18, 31.43, 20.98, 20.47, 10.69. HRMS (FAB+) $[M+H]^+$ calculated: 773.4939; observed: 773.4896.
18. Crystal data for **7a**: $C_{33}H_{54}N_9O_{5.50}$, $M=664.85$, crystal dimensions $5.00\times0.34\times0.22$ mm^3, crystal system monoclinic, space group $C2$, $Z=4$, $a=22.7890(5)$, $b=13.5759(3)$, $c=12.2504(3)$ Å, $\beta=92.005(1)°$, $V=3787.72(15)$ Å^3, $\rho=1.166$ g cm^{-3}, $2\theta_{max}=48.2°$, radiation Mo Kα, $\lambda=0.71073$ Å, 0.3° ω-scans with CCD area detector, $T=298$ K, 14917 reflections measured, 5973 unique ($R_{int}=0.0305$), 5109 observed ($I>2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption and crystal oversize correction was applied using SADABS[19] based on the Laue symmetry of the reciprocal space, $\mu=0.081$ mm^{-1}, T_{min}/T_{max} ratio = 0.64, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the SHELXTL-PLUS (5.10) software package,[20] methylgroup C52 is disordered over two positions with similar occupancy, leading to two different orientations of the corresponding isopropylgroup, 1 mol of acetone and 1.5 mol of water were found, 449 parameters refined, hydrogen atoms were treated using appropriate riding models, final residual values $R(F)=0.060$, $wR(F^2)=0.162$ for observed reflections, residual electron density –0.16 to 0.19 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 187958. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
19. Sheldrick, G. M., unpublished work, 1996, based on the method described in: Blessing, R. H. *Acta Crystallogr., Sect. A* **1995**, *51*, 33.
20. Sheldrick, G. M. Bruker Analytical X-ray Division, Madison, WI, 1995.