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Biomimetic Synthesis and Proposal of Relative and Absolute Stereochemistry of Heronapyrrole C

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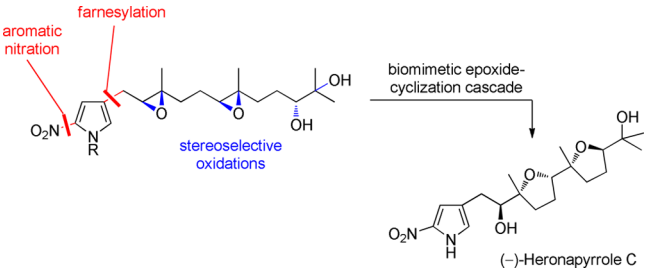
ABSTRACT



The first synthesis of (−)-heronapyrrole C, the enantiomer of a unique farnesylated 2-nitropyrrole natural product is described. With none of the chiral centers of heronapyrrole C originally assigned, we proposed the most likely natural configuration on the basis of a putative biosynthetic pathway. The key step of the synthesis is a biomimetic polyepoxide cyclization cascade to establish the bis-THF moiety. Thus, (−)-heronapyrrole C is synthesized in eight steps from commercially available starting materials.

Terpenoid natural products are a diverse family of compounds with a broad spectrum of bioactivities.[1] Pyrroloterpenes constitute a small subgroup in which a terpenoid backbone is connected to a differently substituted pyrrole ring.[2] Examples such as pyrrolostatin[3] and the glaciapyrroles A−C[3] were found to be highly active as lipid peroxidation inhibitors and exhibit moderate cytotoxicity against different tumor cell lines.[3,4]

Recently, Capon and co-workers reported the isolation and characterization of three structurally unique 2-nitropyrroloterpenes named heronapyrroles A−C (Figure 1).[5] These compounds are produced by a *Streptomyces* sp. (CMB-M0423) derived from a sand sample off Heron Island (Australia). Together with the almost simultaneously reported nitropyrrolins,[6] described by Fenical and co-workers, these natural products are the first examples of nitropyrroloterpenes. The heronapyrroles and nitropyrrolins are structurally closely related hybrid natural products sharing a previously unknown 2-nitropyrrole aromatic core to which a differently oxidized sesquiterpene unit is attached in the 4 position of the heterocycle. Heronapyrroles A−C show significant activity against Gram-positive bacteria without adverse effects on mammalian cell lines.[5]

Based on our interest in the development of reaction methodology for the construction of substituted oxygen

(1) For an overview, see: Breitmaier, E. *Terpenes*; Wiley-VCH: Weinheim, 2006.

(2) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517.

(3) Isolation: Kato, S.; Shindo, K.; Kawai, H.; Odagawa, A.; Matsuoka, M.; Mochizuki, J. *J. Antibiot.* **1993**, *46*, 892. Synthesis: Fumoto, Y.; Eguchi, T.; Uno, H.; Ono, N. *J. Org. Chem.* **1999**, *64*, 6518.

(4) Isolation: Macherla, V. R.; Liu, J.; Bellows, C.; Teisan, S.; Nicholson, B.; Lam, K. S.; Potts, B. C. M. *J. Nat. Prod.* **2005**, *68*, 780. Synthesis and determination of absolute configuration: Riclea, R.; Dickschat, J. S. *Chem.−Eur. J.* **2011**, *17*, 11930.

(5) Raju, R.; Piggott, A. M.; Barrientos Diaz, L. X.; Khalil, Z.; Capon, R. J. *Org. Lett.* **2010**, *12*, 5158.

(6) Kwon, H. C.; Espindola, A. P. D. M.; Park, J.-S.; Prieto-Davó, A.; Rose, M.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2010**, *73*, 2047.

(7) (a) Roth, S.; Göhler, S.; Cheng, H.; Stark, C. B. W. *Eur. J. Org. Chem.* **2005**, 4109. (b) Göhler, S.; Stark, C. B. W. *Org. Biomol. Chem.* **2007**, *5*, 1605. (c) Göhler, S.; Roth, S.; Cheng, H.; Göksel, H.; Rupp, A.; Haustedt, L. O.; Stark, C. B. W. *Synthesis* **2007**, 2751. (d) Cheng, H.; Stark, C. B. W. *Angew. Chem.* **2010**, *122*, 1632. *Angew. Chem., Int. Ed.* **2010**, *49*, 1587.

(8) Roth, S.; Stark, C. B. W. *Angew. Chem.* **2006**, *118*, 6364. *Angew. Chem., Int. Ed.* **2006**, *45*, 6218.

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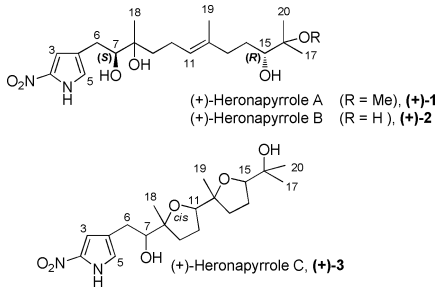
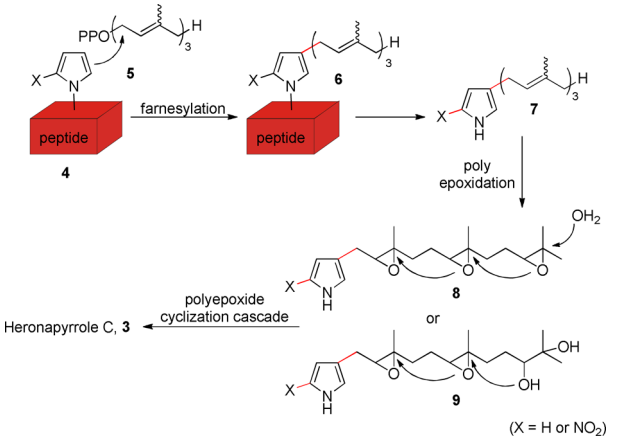


Figure 1. Structures of heronapyrroles A−C.

heterocycles (THFs[7] and THPs[8]) and applications to natural product synthesis,[9] we decided to investigate a synthetic approach to the bis-THF natural product heronapyrrole C. In this particular case, our strategy is centered on a putative biomimetic polyepoxide cyclization cascade.[10,11]

Capon and co-workers originally isolated 0.5 mg of heronapyrrole C and were able to assign the overall structure and the *cis*-geometry (ROESY) across one of the THF rings (see Figure 1).[5] None of the other stereocenters, neither absolute nor relative stereochemistry, were established. With five chiral centers in natural heronapyrrole C one needs to synthesize up to 32 stereoisomers (or 16 diastereoisomers) to unambiguously determine the configuration of the natural product. In order to narrow down this number and select our initial target stereostructure, we decided to follow a putative biomimetic pathway. Whereas the timing and manner of the introduction of the nitro group during heronapyrrole biosynthesis may be a matter of some debate,[12] other key steps appear somewhat less speculative. Thus, after polyprenylation[13] of (a potentially peptide bound[2]) pyrrole system the acyclic terpenoid subunit is oxidatively converted to the bis-THF substructure (Scheme 1). In close correlation to the biosynthesis of polyether antibiotics[14] and the presumed biogenesis of acetogenines[15] as well as terpenoid oligo-THF's[16b] one may suspect a polyepoxide cascade cyclization[10] pathway (Scheme 1).[16]

Scheme 1. Possible Biosynthesis of Heronapyrrole C



On the basis of this biosynthetic scheme and a set of further assumptions, we derived the structure of the most likely natural stereoisomer of heronapyrrole C (Scheme 2). The starting point of this chain of assumptions is the putative biosynthetic relation of heronapyrrole C to heronapyrrole A already suggested by Capon and co-workers.[5] Accordingly, the absolute stereochemistry at C7 and C15, originally determined for heronapyrrole A[17] only (see Figure 1), would be identical in heronapyrrole C (7*S*,15*R*; red in Scheme 2). Moreover, with the hypothesis that the bis-THF backbone is biosynthetically derived from an (*E*,*E*)-farnesol derivative[13] (blue in Scheme 2) via an epoxide cyclization cascade[10] the stereocenter at C8 has to be *S*-configured. The relative configuration between C8 and C11 (*cis*-THF;[5] see Figure 1) results in the secondary center at C11 to be likewise *S*-configured (orange in Scheme 2). The same reasoning as before (*E*,*E*-triene precursor) leads to the *S*-configuration of the neighboring tertiary center at C12 (blue in Scheme 2). We therefore propose heronapyrrole C **3** as depicted in Scheme 2 as the most likely natural stereoisomer (relative and absolute stereochemistry) and decided to synthesize this compound.

(9) Göksel, H.; Stark, C. B. W. *Org. Lett.* **2006**, *8*, 3433.

(10) For reviews, see: (a) Koert, U. *Synthesis* **1995**, 115. (b) McDonald, F. E.; Tong, R.; Valentine, J. C.; Bravo, F. *Pure Appl. Chem.* **2007**, *79*, 281. (c) Vilotijevic, I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250. *Angew. Chem.* **2009**, *121*, 5352.

(11) For selected examples from natural product synthesis, see: (a) Koert, U.; Wagner, H.; Stein, M. *Tetrahedron Lett.* **1994**, *35*, 7629. (b) Lindel, T.; Franck, B. *Tetrahedron. Lett.* **1995**, *36*, 9465. (c) Xiong, Z.; Corey, E. J. J. *Am. Chem. Soc.* **2000**, *122*, 4831. (d) Morimoto, Y.; Okita, T.; Takaishi, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 1132. *Angew. Chem.* **2007**, *119*, 1150. (e) Marshall, J. A.; Hann, R. K. *J. Org. Chem.* **2008**, *73*, 6753. (f) Morimoto, Y.; Okita, T.; Kambara, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2538. *Angew. Chem.* **2009**, *121*, 2576. (g) Clausen, D. J.; Wan, S.; Floreanicig, P. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 5178. *Angew. Chem.* **2011**, *123*, 5284. For examples prior to 1994, see ref 10a.

(12) See, for instance: (a) Ratnyake, A. S.; Haltli, B.; Feng, X.; Bernan, V. S.; Singh, M. P.; He, H.; Carter, G. T. *J. Nat. Prod.* **2008**, *71*, 1923. (b) Kers, J. A.; Wach, M. J.; Krasnoff, S. B.; Widom, J.; Cameron, K. D.; Bukhalid, R. A.; Gibson, D. M.; Crane, B. R.; Loria, R. *Nature* **2004**, *429*, 79.

(13) (a) Wessjohann, L. A.; Sontag, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1697. *Angew. Chem.* **1996**, *108*, 1821. (b) Wessjohann, L. A. ; Sontag, B.; Dessoy, M. A. *Organic Chemistry Highlights IV*; Schmalz, H.-G., Ed.; Wiley-VCH: Weinheim, 1999; p 79.

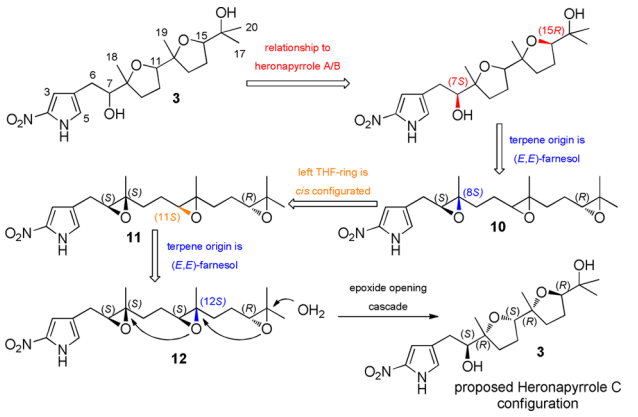
(14) (a) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594. (b) Bhatt, A.; Stark, C. B. W.; Harvey, B. M.; Gallimore, A. R.; Demydchuk, Y. A.; Spencer, J. B.; Staunton, J.; Leadlay, P. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 7075. *Angew. Chem.* **2005**, *117*, 7237. See also ref 16.

(15) (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. (b) Bermejo, A.; Figadère, B.; Zafra-Polo, M. C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269.

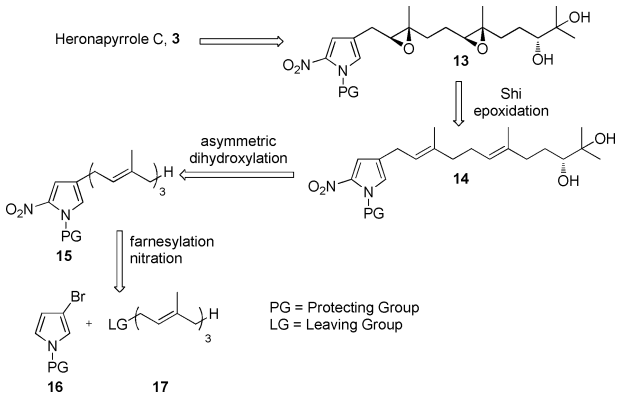
(16) For general reviews on the biosynthesis of oligo-THF and related natural products, see: (a) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 298. *Angew. Chem.* **1995**, *107*, 326. (b) Fernández, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235. (c) Gallimore, A. R.; Spencer, J. B. *Angew. Chem., Int. Ed.* **2006**, *44*, 4406. *Angew. Chem.* **2006**, *118*, 4514. (d) Gallimore, A. R. *Nat. Prod. Rep.* **2009**, *26*, 266. (e) de María, P. D.; van Gemert, R. W.; Straathof, A. J. J.; Hanefeld, U. *Nat. Prod. Rep.* **2010**, *27*, 370. (f) Ueberbacher, B. T.; Hall, M.; Faber, K. *Nat. Prod. Rep.* **2012**, *29*, 337.

(17) The configuration of these chiral centers was assigned using the Mosher method; see ref 5 for details; see also ref 23.

Scheme 2. Derivation of a Likely Relative and Absolute Stereochemistry of Heronapyrrole C



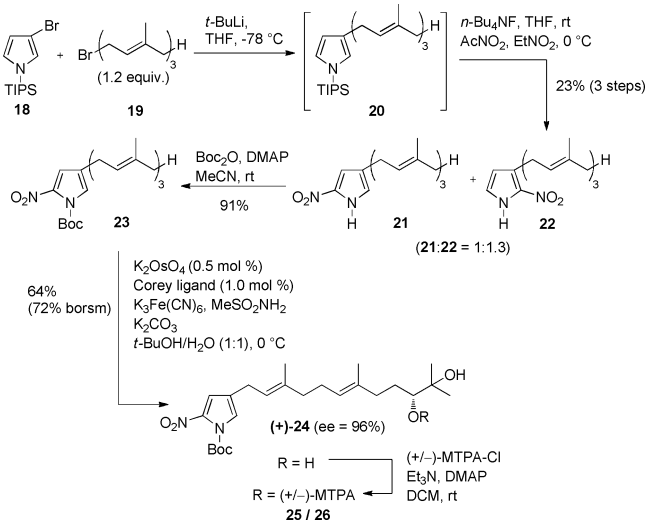
Scheme 3. Heronapyrrole C: Retrosynthetic Analysis



As summarized in the retrosynthetic scheme we decided to construct the bis-THF backbone at the end of the synthesis (Scheme 3). Accordingly, dihydroxybisepoxide **13** is regarded as the precursor of (an *N*-protected) heronapyrrole C. The required functional groups and stereochemistry were intended to be established in a sequence of a position- and stereoselective dihydroxylation followed by a double Shi-epoxidation[18] leading to farnesylated nitropyrrole **15**. Due to the somewhat rough reaction conditions required for aromatic nitration,[19] we chose to introduce the nitro group at an early stage of the synthesis directly after farnesylation of the pyrrole ring. This strategy seems to be in accord with the biosynthesis of the heronapyrroles as the less oxidized natural congeners also contain the same nitro group (in the same position).[2,12] Therefore, known 3-bromopyrrole[20] and *E*,*E*-farnesyl derivative containing a leaving group at C1 (LG in Scheme 3) represent the starting materials of our synthetic strategy.

The synthesis commences with the coupling of commercially available *N*-TIPS-protected 3-bromopyrrole to farnesyl bromide followed by *N*-deprotection and nitration of the aromatic heterocycle (Scheme 4). Nitration under standard reaction conditions (H_2SO_4/HNO_3)[19] produced the desired product only in minute amounts and lead to significant problems during purification. The use of $AcNO_2$[21] proved more reliable and reproducible, albeit the desired nitropyrrole was still isolated with low selectivity. However, the isomers were separable by standard flash chromatography. Subsequent Boc protection of the 2,4-substituted regioisomer delivered the precursor for the oxidation/cyclization sequence in 91% yield. Asymmetric dihydroxylation using the Corey–Noe–Lin catalyst[22] provided the dienediol (+)-**24** in a clean and highly position- and stereoselective reaction. The enantiomeric excess was determined to be 96% ee after conversion to the Mosher-ester[23] and by chiral HPLC.

Scheme 4. Heronapyrrole C Synthesis: Pyrrole Farnesylation and Nitration



Double organocatalytic asymmetric epoxidation using the (+)-Shi catalyst[18] produced the precursor for the cascade cyclization in high yield and good diastereoselectivity (Scheme 5). Minor diastereoisomers were detectible by TLC and NMR analysis of samples taken from crude reaction mixtures. Also, partial cyclization seems to occur under the buffered and slightly basic reaction conditions and/or during workup (TLC analysis). The diepoxide **27** was therefore not purified but directly used for the next step.

(18) (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (b) Zhao, M.-X.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 5377. For a review, see: Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.

(19) (a) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanism*; VCH: New York, 1989. (b) Schofield, K. *Aromatic Nitration*; Cambridge University Press: Cambridge, 1980.

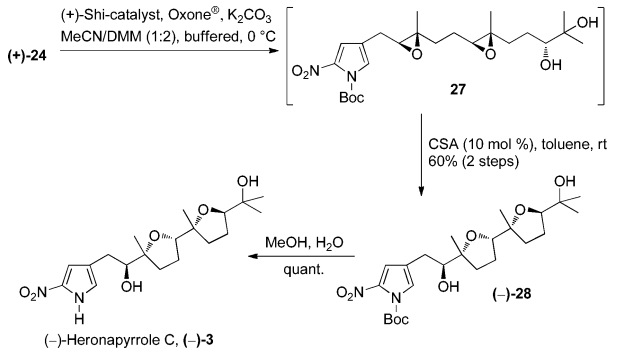
(20) Stefan, K.-P.; Schuhmann, W.; Parlar, H.; Korte, F. *Chem. Ber.* **1989**, *122*, 169.

(21) Bordwell, F. G.; Garbish, E. W., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 3588.

(22) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741.

(23) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Seco, J. M.; Quinoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17. (c) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451.

Scheme 5. Heronapyrrole C: Completion of the Total Synthesis



Acid catalyzed (CSA; camphorsulfonic acid) epoxide-opening cascade reaction yielded, after column chromatography, a stereoisomerically pure product. Finally, heating of compound (−)-**28** in a mixture of methanol and water led to a smooth *N*-deprotection, the product was isolated in quantitative yield. Close inspection of NMR data including correlation and NOESY spectra revealed identity of our synthetic sample with the natural product (see the Supporting Information for details). In addition, the synthetic compound was found to coelute with natural (+)-heronapyrrole C when compared by HPLC analysis.[24] To our surprise, however, the optical rotation showed a comparable absolute value but the opposite sign (natural heronapyrrole C: $[\alpha]_D = +7.6$, $c = 0.05$, MeOH,[5] synthetic heronapyrrole C: $[\alpha]_D = -6.7$, $c = 2.3$, MeOH), clearly indicating that we prepared the mirror image of natural heronapyrrole C. Apparently, the first assumption of our stereochemical derivation (Scheme 2, red) is wrong. An equally obvious and intriguing explanation would be that there is no such biogenetic relation between heronapyrrole A and C. On the other hand, the assumption of a polyepoxide cyclization cascade and an *E*,*E*-configured triene precursor may still be correct. Based on the close correlation of NMR data and the coelution of our synthetic material with natural (+)-heronapyrrole C we do not believe that we prepared a diastereoisomer but rather the enantiomer of the natural product. In order to corroborate this assertion, we currently focus on the synthesis of other stereoisomers of heronapyrrole C as well as heronapyrrole A.

In summary, we have presented the first synthesis of (−)-heronapyrrole C and proposed the relative and absolute stereochemistry of the natural product. On the basis of a putative biosynthesis we suggested a likely stereostructure of the bis-THF pyrroloterpene. Intriguingly, the synthesized compound appears to match the relative but not the absolute stereochemistry. Further, substantiation of these findings would rise questions on the origin of differences in the biosynthesis of the heronapyrroles. Key steps of our approach to heronapyrrole C are a pyrrole farnesylation and nitration followed by a two-step sequence of stereoselective oxidations introducing five stereogenic centers. Finally, a biomimetic polyepoxide cyclization cascade[10,11] is used to establish the bis-THF moiety.

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Supporting Information Available. Experimental procedures, spectral and analytical data, as well as comparisons between natural (+)-heronapyrrole C and synthetic material. This material is available free of charge via the Internet at http://pubs.acs.org.

(24) These experiments were carried out in the laboratories of Prof. Dr. Robert J. Capon at the University of Queensland (Australia). See the Supporting Informations for details.

The authors declare no competing financial interest.