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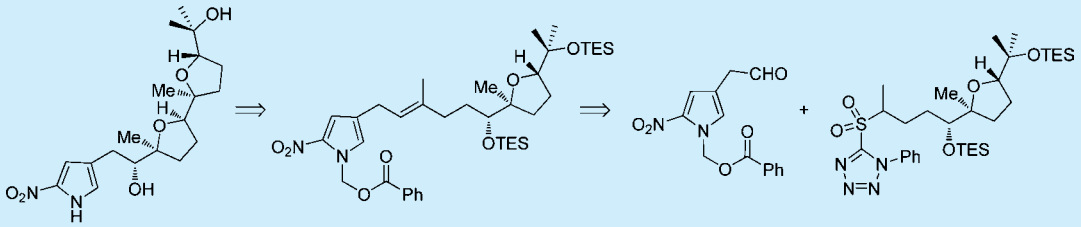
Total Synthesis of Heronapyrrole C

Xiao-Bo Ding,[†] Daniel P. Furkert,[†] Robert J. Capon,[‡] and Margaret A. Brimble*[,†]

[†]School of Chemical Sciences, The University of Auckland, 23 Symonds St., Auckland 1000, New Zealand

[‡]Institute for Molecular Bioscience, The University of Queensland, St. Lucia, QLD 4072, Australia

Supporting Information



(+)-Heronapyrrole C

ABSTRACT: A flexible total synthesis of the 2-nitropyrrole-derived marine natural product, (+)-heronapyrrole C, is reported. The approach is based on regioselective access to key building blocks containing the rare 4-substituted 2-nitropyrrole motif. Sharpless asymmetric epoxidation and dihydroxylation and a Shi epoxidation were used to introduce the five stereogenic centers of the bis-THF-diol side chain. The *N*-benzoyloxymethyl (Boz) protecting group was crucial for functionalization of the 2-nitropyrrole moiety and enabling final deprotection under mild conditions.

Heronapyrroles A–C (**1**–**3**, Figure 1) were isolated in 2010 from a *Streptomyces* sp. (CMB-M0423) culture collected near Heron Island, Australia.[1] These compounds belong to the exceptionally rare family of nitropyrrole natural products, known examples of which are limited to the 3-nitropyrrole pyrrolomycin class of *Streptomyces* antibiotics.[2−4] Together with the almost simultaneously reported nitropyrrolins described by Fenical and co-workers,[5] these compounds are the first documented examples of natural products containing a 2-nitropyrrole ring. Compounds **1**–**3** were found to display promising activity against Gram-positive bacteria without exhibiting cytotoxicity toward mammalian cell lines.

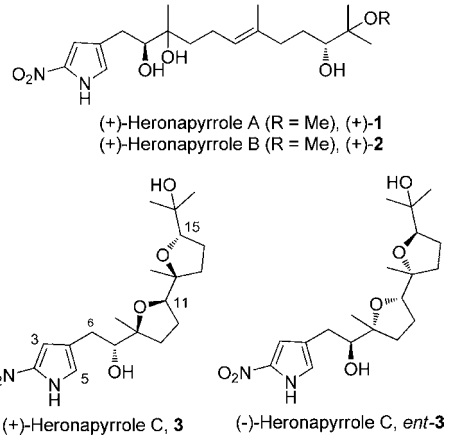
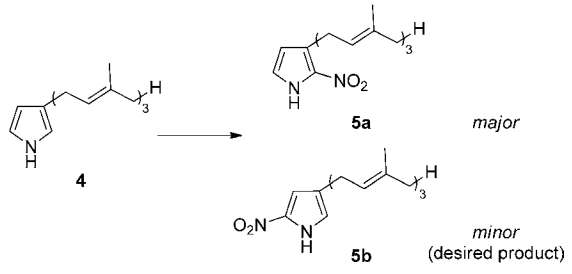


Figure 1. Heronapyrroles A–C.

A synthesis of the enantiomer of **3**, *ent*-**3**, was reported in 2012 by Stark, employing a nonselective and low-yielding nitration of 3-farnesyl pyrrole **4** (Scheme 1).[6] In contrast, we have based our synthetic studies on the regioselective construction of 2-nitropyrrole building blocks that were subsequently elaborated to the natural product scaffold. Herein we report the asymmetric synthesis of naturally occurring (+)-heronapyrrole C **3**, confirming the original stereochemical assignment and enabling rational investigation of structure–activity relationships.

Scheme 1. Poor Regioselectivity in 3-Farnesylpyrrole Nitration



5a/**5b** = 1.7:1 [*Fenical et al.* (Ac_2O, HNO_3)]
5a/**5b** = 1.3:1 [*Stark et al.* ($AcONO_2$, $EtNO_2$)]

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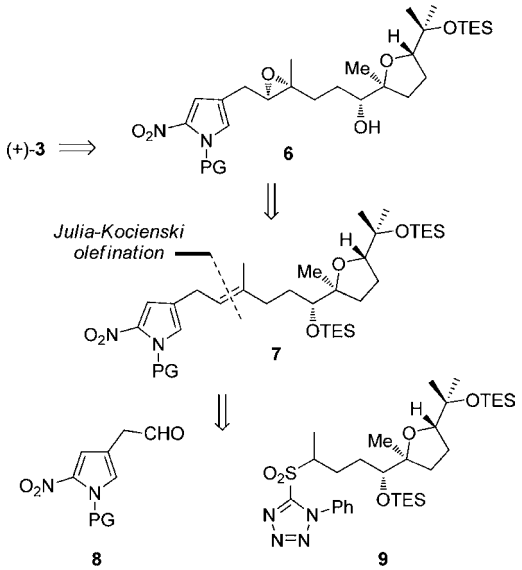
At the outset of our studies, the work of Stark had not been reported and the only stereochemical information about the structure of heronapyrrole C was the C8−C11 *cis*-geometry (ROESY correlation) across one of the THF rings.[1] Hence, instead of using a cascade cyclization to form the two THF rings simultaneously, we decided to construct heronapyrrole C **3**, using a convergent synthesis and form the two THF rings at different stages. The synthesis reported herein is therefore more flexible and enabled access to all possible stereoisomers for structure elucidation purposes.

Nitration of 3-farnesyl pyrrole **4** was reported to be largely nonselective by Fenical and co-workers, giving undesired 2-nitropyrrole **5a** as the major product.[5] Stark and co-workers used the same strategy in their approach, achieving slightly better selectivity for **5b** after optimization.

In light of this poor regioselectivity, we aimed to introduce the 2-nitro group at the start of the synthesis, anticipating that full control of regiochemistry would be achievable. To date, the chemistry of 2-nitropyrroles has remained relatively unexplored, but it was hoped that development of novel synthetic methods would permit investigation of its potential utility in medicinal chemistry.

Retrosynthetically, epoxide **6**, accessible from Shi epoxidation[7] of olefin **7**, constitutes a suitable cyclization precursor for heronapyrrole C **3** (Scheme 2). Intermediate alkene **7**,

Scheme 2. Retrosynthesis of (+)-Heronapyrrole C

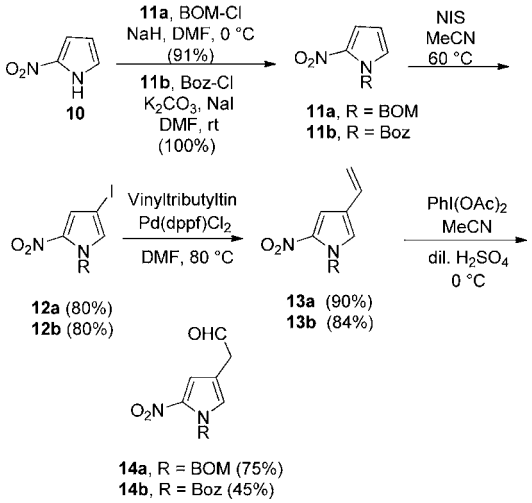


containing the preformed *trans*-THF ring, was envisioned to result from Julia-Kocienski olefination[8] of 2-nitropyrrole aldehyde **8** with advanced sulfone **9**, derived from geraniol.

Our synthetic investigations toward heronapyrrole **3** began with preliminary studies toward the required 2-nitropyrrole building blocks, starting from 2-nitropyrrole **10**[9] itself (Scheme 3). As the feasibility and regioselectivity of subsequent tranformations of the pyrrole nucleus were expected to be dictated by the nature of the pyrrole *N*-substituent, a preliminary screen of suitable protecting groups was undertaken.

Electron-withdrawing groups (Boc, Ts) were readily installed and could also be removed in high yields under standard conditions. A variety of benzyl subsituents could be appended, but these could not be cleanly deprotected. *N*-Silylation (TES,

Scheme 3. Synthesis of Aldehydes 14a and 14b



TIPS) using chlorides or triflates proved unsuccessful. Finally, *N*-benzyloxymethyl (BOM) **11a** and *N*-benzoyloxymethyl (Boz) **11b** derivatives of 2-nitropyrrole were successfully prepared and readily deprotected in excellent yield.[10]

With a range of *N*-protected 2-nitropyrroles in hand, the pivotal regioselective halogenation step was examined (Scheme 3). Attempted iodination of either the *N*-Boc or *N*-Ts derivatives returned only starting material or decomposition products. Direct iodination of unprotected 2-nitropyrrole led to mixtures of mono- and di-iodinated products, which were inseparable by flash chromatography. Pleasingly, however, iodination of the *N*-BOM **11a** and *N*-Boz **11b** 2-nitropyrroles afforded the corresponding 4-iodo-2-nitropyrroles, **12a** and **12b**, respectively, in excellent yield, as the only observable regioisomers. Subsequent Stille coupling with vinyltributyltin proceeded uneventfully to give **13a** and **13b**, which were then oxidized by exposure to iodobenzene diacetate[11] to give the requisite aldehydes **14a** and **14b** for subsequent Julia-Kocienski olefination.

Synthesis of the key sulfone coupling partner **9** was initiated from geraniol **15** (Scheme 4). Sharpless asymmetric epoxidation with (−)-DIPT[12] and subsequent mesylation afforded epoxy mesylate **16** as a single stereoisomer in excellent yield for the two steps.[13] Sharpless asymmetric dihydroxylation of **16** (dr >9:1) followed by acid-catalyzed ring opening of the epoxide, with clean inversion of the quaternary center, gave mesylate **17** containing the required *trans*-tetrahydrofuran ring. Treatment of **17** with potassium carbonate in methanol then led to formation of terminal epoxide **18**.

A direct dihydroxylation/epoxide transposition sequence beginning from **16** provided **18** in a one-pot operation in 80% yield, however the product was contaminated with up to 10% of the undesired stereoisomer.[14,15] As these diastereoisomers were inseparable at this or later stages, the two-step sequence was adopted, such that **18** could be obtained reliably in stereoisomerically pure form after chromatography.

Triethylsilyl protection of the tertiary hydroxy group was effected under standard conditions, followed by ring opening of the epoxide with allyl magnesium bromide in the presence of copper(I) chloride. Silylation of the resultant secondary alcohol, again with TESCl, then afforded alkene **19** in 80% yield. In order to introduce the necessary sulfone unit, the terminal alkene was subjected to Markovnikov oxymercuration-

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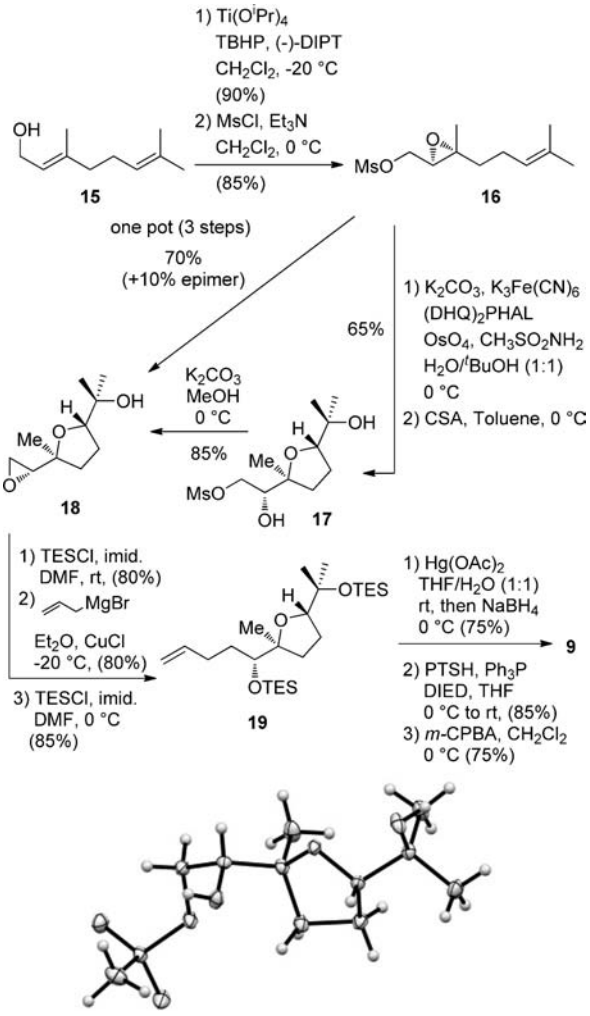
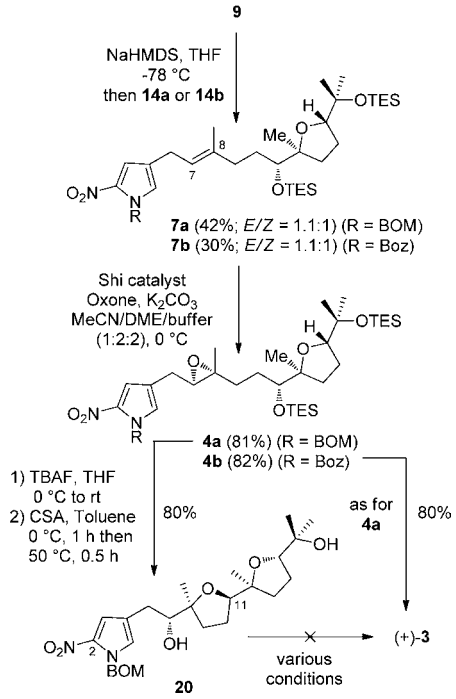
Scheme 4. Synthesis of Sulfone 7; Inset: X-ray Structure of 17



Scheme 5. Fragment Assembly



reduction, followed by installation of the phenyltetrazole sulfide by Mitsunobu inversion. Finally, oxidation to the required olefination partner sulfone **9** was accomplished using *m*-CPBA.

In the final fragment unification, Julia-Kocienski olefination of sulfone **9** with aldehyde **14a** (Scheme 5) afforded a 1.1:1 mixture of the desired *E*-alkene **7a** and its *Z*-isomer in 42% combined yield. Although a survey of alternative bases (LHMDS, KHMDS) and solvents (toluene, DME) failed to improve the reaction outcome, the isomers were separable by chromatography and would both lead to useful heronapyrrole C epimers, enabling unambiguous structural elucidation and future SAR studies.

Asymmetric epoxidation of the C7−C8 olefin of the *E* isomer of **7a**, using the (−)-Shi ketone catalyst derived from D-fructose, under standard biphasic conditions, afforded epoxide **4a** in high yield with excellent stereoselectivity.[16] After deprotection of the triethylsilyl group, the crude product was used directly without purification in the next step, since partial cyclization was observed to occur during workup. The epoxide opening/cyclization step was carried to completion under acid catalysis to afford *N*-BOM heronapyrrole (**20**). To our disappointment, however, despite the early prescreening of conditions for removal of 2-nitropyrrole *N*-protecting groups, it was not possible to convert **20** to the natural product. Investigation of a wide range of conditions returned only starting material or decomposition products.

Eventually, altering the Julia-Kocienski olefination aldehyde coupling partner from *N*-BOM **14a** to *N*-Boz-protected 2-nitropyrrole **14b** (see Scheme 3) allowed an analogous endgame sequence to be carried out. Epoxide **4b** was obtained in excellent yield using the same conditions used for the preparation of **4a**. Deprotection of the TES groups was smoothly effected using TBAF, and the crude diol was directly submitted to the acid-catalyzed epoxide-opening conditions previously employed. To our surprise, we were pleased to find that after completion of the cyclization (TLC), gentle warming of the reaction mixture was enough to promote *N*-deprotection of the *N*-Boz group. Purification by preparative TLC afforded stereoisomerically pure (+)-heronapyrrole C (+)-**3**. Comparison of the ^{1}H and ^{13}C NMR spectra and other data showed that the synthetic material was identical with the natural product in all respects. The measured optical rotation indicated that the synthetic material possessed the same absolute stereochemistry as the natural product; isolated (+)-**3**: $[\alpha]_D$ +6.7, *c* 0.05, MeOH; this work (+)-**3**: $[\alpha]_D$ +7.8, *c* 0.32, MeOH; Stark and co-workers ent-**3**: $[\alpha]_D$ −7.6, *c* 2.3, MeOH.[6] Analytical HPLC of the isolated and synthetic samples of the natural product gave a single peak on co-injection.[17]

In summary, we have completed the total synthesis of the naturally occurring enantiomer of heronapyrrole C (+)-**3** in 14 steps, confirming the earlier structural reassignment by Stark and co-workers. Our synthesis is based upon regiocontrolled access to functionalized 2-nitropyrrole building blocks, which have been little explored in the literature to date. Key steps in the total synthesis include a Julia-Kocienski fragment coupling, Shi epoxidation, and a catalytic epoxide opening reaction to form the bis-THF polyketide side chain possessing five stereogenic centers. Further studies into the synthesis and SAR of heronapyrrole congeners are currently underway in our laboratories.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: m.brimble@auckland.ac.nz.

Notes

The authors declare no competing financial interest.

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(10) See Supporting Information for a full table of the protection/deprotection study and details of reaction conditions.
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(16) A trace amount of the minor diastereomer was observed in the crude ^{1}H NMR of **6a**.
(17) See Supporting Information for HPLC traces.