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Synthetic Endeavors toward 2-Nitro-4-Alkylpyrroles in the Context of the Total Synthesis of Heronapyrrole C and Preparation of a Carboxylate Natural Product Analogue

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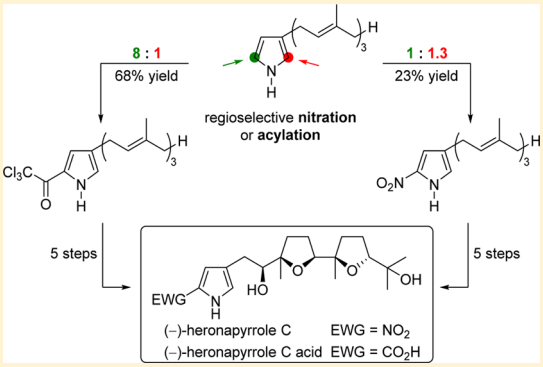
Supporting Information

ABSTRACT: The synthesis of 2-nitro-4-oligoprenyl-substituted pyrrole derivatives relevant to the heronapyrroles and related natural products was investigated. Among numerous approaches, nitration of a 3-farnesyl-substituted unprotected pyrrole using $AcONO_2$ gave the best results, albeit still with unsatisfactory yield and regioselectivity. Therefore, the synthesis of (−)-heronapyrrole C acid, an analogue of the naturally occurring antibiotic heronapyrrole C carrying a bioisosteric carboxylate in place of the nitro group, was examined. In lieu of the unsatisfactory nitration, a regioselective acylation with Cl_3CCOCl was carried out (>8:1 regioselectivity, in contrast to the 1:1.3 ratio for the nitration). The trichloromethyl ketone was converted to the desired acid in a haloform reaction at the final stage of the synthesis. Further key steps of the analogue synthesis involved a position- and stereoselective Corey−Noe−Lin dihydroxylation and an organocatalytic double Shi epoxidation. A biomimetic polyepoxide cyclization cascade established the bis-THF backbone. Thus, (−)-heronapyrrole C acid was synthesized in eight steps (14.5% overall yield) from commercially available starting materials.



INTRODUCTION

Terpenes constitute a widespread and very diverse class of natural products.[1] Because of their biological activity, heterocyclic terpenes are a subgroup of particular interest.[2] Among the compounds with a five-membered aromatic heterocycle, furanoterpenes represent a fairly large class.[3,4] On the other hand, the related pyrroloterpenes are comparably rare yet exhibit an even more exciting spectrum of bioactivities. A representative example of a pyrroloterpene is the lipid peroxidation inhibitor pyrrolostatin (**1**) (Figure 1). It was isolated from *Streptomyces chrestomyceticus* by Mochizuki and co-workers.[5] The first total synthesis was developed by Ono and co-workers in 1999.[6] A key step of their approach is the cyclization of a β-nitroacetate under basic Barton−Zard[7,8] conditions. Thus, the aromatic core is built up during the reaction sequence and not (as usual) present from the beginning of the synthesis. Glaciapyrrole A (**2**) (Figure 1), another example of this class of natural products, was isolated by Potts and co-workers in 2005.[9] A stereoselective synthesis of all possible isomers was recently described by Riclea and Dickschat.[10] Coupling of the aromatic heterocycle with the terpenoid backbone was achieved in an acylation of pyrrol-1-ylmagnesium chloride. The reaction proceeded in good yield but with partial *Z*/*E* isomerization of the conjugated double bond.[10] In addition to these carbonyl-stabilized pyrroloterpenes, the groups of Fenical and Capon independently and almost simultaneously reported the isolation of structurally related and unusual nitropyrroloterpenes, called nitropyrrolins[11] and heronapyrroles,[12] respectively (Figure 1). Both classes of compounds exhibit promising biological activities. Whereas the nitropyrrolins show potency against human colon carcinoma cells (HCT-116), heronapyrroles display antibiotic activity against Gram-positive bacteria such as *Staphylococcus aureus* and *Bacillus subtilis*. Fenical and co-workers were able to determine the 2-nitro-4-sesquiterpenylpyrrole constitution by comparison of NMR and UV data of natural nitropyrrolin A

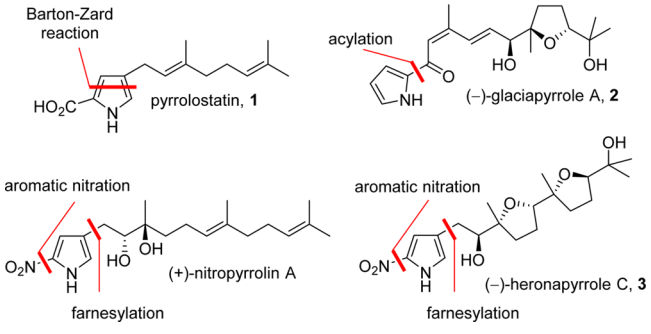


Figure 1. Representative naturally occurring pyrroloterpenes. Red lines indicate crucial synthetic steps around the pyrrole system from published total or partial syntheses.

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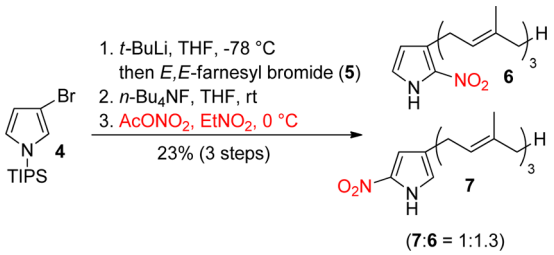
with those of synthetic 2-nitro-4-farnesylpyrrole and 2-nitro-3-farnesylpyrrole.[11] A Barbier-type farnesylation and electrophilic aromatic nitration (HNO_3 in acetic anhydride) yielded sufficient quantities of both isomers as synthetic standards (19% yield over two steps after HPLC separation). Together with the nitropyrrolins,[11] the heronapyrroles[12] are the first naturally occurring 2-nitropyrroloterpenes (Figure 1). The heronapyrroles have been isolated and characterized by Capon and co-workers in late 2010. These metabolites are produced by a *Streptomyces* sp. (CMB-M0423) collected from a sand sample off Heron Island, Australia.[12] As part of our ongoing interest in the development of reaction methodology (e.g., methods for THF[13−16] and THP synthesis[17]) and applications to natural product synthesis,[18] we recently achieved an enantioselective and biomimetic synthesis of heronapyrrole C (**3**) (Figure 1).[19,20] Thus, Capon's original structural assignment was confirmed, and in addition, a suggestion of both the relative and absolute stereochemistry of the natural product was put forward.

During our synthesis of heronapyrrole C, we found that the nitration of the pyrrole moiety is the most challenging step.[11,19] In fact, the putatively simple introduction of the nitro group, rather than the construction of the bis-THF segment with its five stereogenic centers, turned out to be the bottleneck of our approach. Low yields (23% over three steps; Scheme 1) and poor regioselectivities (1.3:1 in favor for the wrong isomer; Scheme 1) were obtained, and product purification was tedious and unsatisfactory.

Scheme 1. Previous Reaction Sequence for the Preparation of 2-Nitro-4-farnesylpyrrole (7)[19]



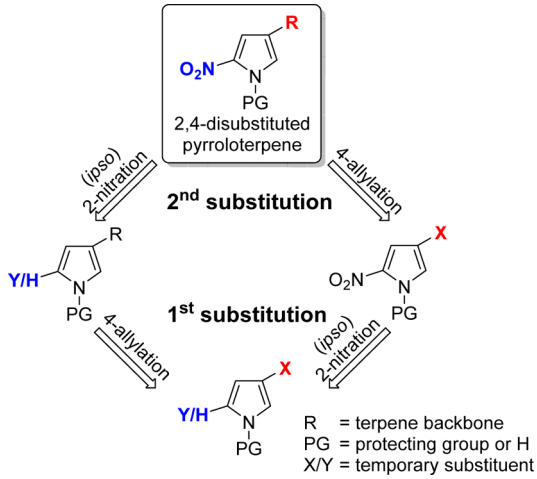
These difficulties hampered access to larger quantities of the natural product and derivatives thereof for biological testing and prompted us to explore the preparation of 2,4-substituted pyrroloterpenes in more detail. We here report investigations into the synthesis of 2-nitro-4-alkylpyrroles and the related and bioisosteric 2-carboxy-substituted analogues.

RESULTS AND DISCUSSION

The analysis of synthetic approaches to π-acceptor-substituted pyrrole natural products (see Figure 1) shows that pyrrole alkylation and the regioselective introduction of a mesomerically stabilizing group are often critical steps of the respective total syntheses. In our recently reported synthesis of (−)-heronapyrrole C (**3**), the requisite substitution motif was obtained starting from 3-bromopyrrole derivative **4** (Scheme 1). Lithium−halogen exchange followed by reaction with farnesyl bromide (**5**) resulted in a regioselective alkylation. Subsequent electrophilic nitration afforded the nitroalkyl-decorated pyrrole core **7** (Scheme 1).[11,19]

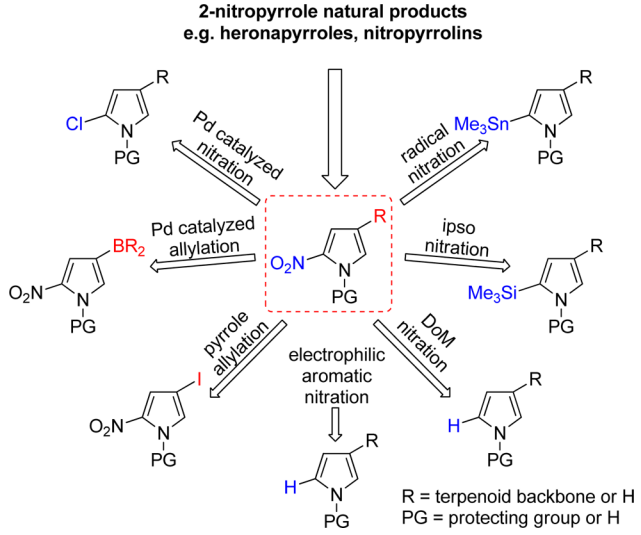
In principle, other scenarios may lead to the same substitution pattern and provide a more efficient entry with higher yields and regioselectivities. In this respect, a "placeholder strategy" (i.e., the use of temporary substituents X and Y as shown in Scheme 2) seems sensible. Thus,

Scheme 2. Possible Approaches for the Regioselective Synthesis of 2-Nitro-4-alkylpyrroles



approaches simply need to deal with the question which substituent is introduced first and which temporary substituent (X or Y in Scheme 2) is used as a placeholder. Scheme 3 summarizes conceivable approaches on the basis of literature precedent.

Scheme 3. Considered Retrosynthetic Precursors for the Synthesis of 2-Nitro-4-(oligo)prenylpyrroles



If the oligoprenyl substituent (R in Scheme 3) is already present or established first, the nitro moiety may be introduced via an electrophilic aromatic substitution as in our original work on heronapyrrole C.[19] In order to improve the regioselectivity, bulkier nitration reagents may be investigated. Alternatively, a directed *ortho*-metalation (DoM) strategy would be expected to result in higher selectivities (Scheme 3). In this respect, an approach where a 2-substituent is simply exchanged in an *ipso*-substitution (Y = $SiMe_3$), a radical displacement (Y = $SnMe_3$), or a palladium-catalyzed nitration (Y = Cl) would obviously be even superior. For the opposite approach, having the nitro

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group present first, a placeholder tactic for the introduction of the sesquiterpene side chain at the 4-position seems to be most appropriate. For instance, the use of a 4-iodo substituent (X = I in Scheme 2) and its conversion in a halogen−metal exchange sequence or a palladium-catalyzed cross-coupling reaction would be reasonable strategies. All of the envisaged retrosynthetic precursors for the preparation of 2-nitro-4-alkylpyrroles are summarized in Scheme 3.

As nitrations of sensitive substrates are a challenging task and the substituted nitropyrrole subunit itself may be of limited stability, we also decided to investigate the synthesis of an analogue where the nitro group is replaced. With regard to accessibility, stability, and pharmacological profile, the bioisosteric carboxylate[21,22] at the 2-position of the pyrrole unit appeared to be a promising additional synthetic target (Figure 2).

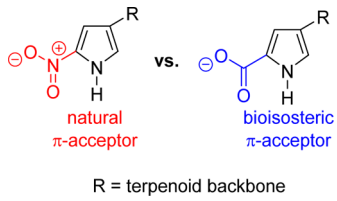
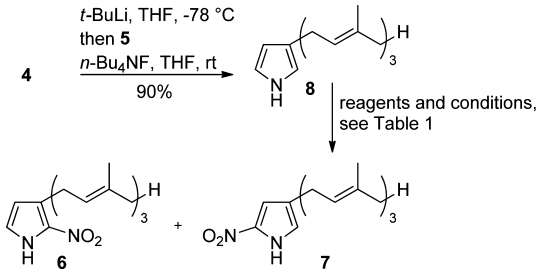


Figure 2. 2-Nitropyrrole and its bioisosteric carboxylate analogue.

At the outset of our studies, we focused on pyrrole nitrations of 3-farnesylated pyrrole derivative **8** using classical conditions (Scheme 4). To develop a reproducible and reliable nitration

Scheme 4. Improved Synthesis of 8 and Subsequent Nitration



protocol, we first optimized the synthesis of the starting material **8**. As before,[19] the oligoprenyl side chain was established by alkylation of a 3-lithiated (*N*-protected) pyrrole using farnesyl bromide (**5**) as the electrophile. It was found that use of highly pure **5** (the purity of the colorless oil was shown to be >99%, as determined by quantitative ^{1}H NMR analysis using 1,4-dimethoxybenzene as an internal standard; see the Supporting Information[23]) and a quick and short chromatographic purification of coupling product **8** (with 5% Et_3N as a coeluent) were necessary to secure an efficient alkylation and isolation. Thus, the desired farnesylated pyrrole **8** could be prepared reproducibly in high yield (90%; see Scheme 4).

With the starting material in hand, several nitration reagents and reaction conditions were investigated. As expected, substrate **8** (Scheme 4 and Table 1) is particularly acid-sensitive. Strongly acidic conditions apparently gave polymerization and other decomposition products with only trace amounts of the desired nitropyrrole **7** (Table 1, entries 1−8). Only the use of weaker (liberated) acids such as acetic acid gave

Table 1. Investigations into the Regioselective Nitration of 8

				yield (%)[a]	
entry	reagent	solvent	temperature (°C)	**6**	7
1	H_2SO_4/HNO_3	neat	0	decomp.	
2	H_2SO_4/HNO_3	$EtNO_2$	0	decomp.	
3	40% HNO_3	neat	0	slow decomp.	
4	40% HNO_3	$EtNO_2$	0	traces	
5	NO_2BF_4	$EtNO_2$	−50 to 0	decomp.	
6	NO_2BF_4 in sulfolane	$EtNO_2$	−50 to 0	decomp.	
7	NO_2BF_4, 2,6-lutidine	$EtNO_2$	−78 to 0	–	
8	NO_2PF_6	$EtNO_2$	−50 to 0	decomp.	
9	$AcONO_2$	Ac_2O	−50 to 0	traces	
10	$AcONO_2$	$EtNO_2$	−50 and 0	13	10
11	Piv_2O/HNO_3	$EtNO_2$	−50 and 0	slow decomp.	
12	$TFAA/HNO_3$	$EtNO_2$	−50 and 0	decomp.	
13	TFAA/EAN[b]	EAN[b]	0	decomp.	
14	Ac_2O/EAN[b]	EAN[b]	0	no conversion	
15	$Ph_2PCl/AgNO_3/I_2$	DCM	−50 and rt	decomp.	

[a]Isolated yields of separated regioisomers (identical isomeric ratios were determined by ^{1}H NMR analysis of the crude mixtures). [b]The ionic liquid ethylammonium nitrate (EAN) was used as the solvent and nitration reagent.

the product as a mixture of the two regioisomers **6** and **7** (Table 1, entry 10). We assumed that the combination of pivalic or trifluoroacetic anhydride and nitric acid [for in situ preparation of $(CH_3)_3COONO_2$ or CF_3COONO_2] as bulkier reagents would provide improved regioisomeric ratios along with comparable yields.[24] However, no product formation could be detected (Table 1, entries 11 and 12). Similarly, the use of a buffered and bulky transfer nitration system (2,6-lutidine, NO_2BF_4; Table 1, entry 7)[25,26] or an ionic liquid (ethylammonium nitrate; Table 1, entries 13 and 14)[27] employed as a reagent and solvent at the same time did not give any product with this sensitive substrate.

With these experiments, we were able to show that improved yields of 3-farnesylated pyrrole **8** (compared with our original procedure[19]) can be achieved. The use of highly pure farnesyl bromide as the starting material and an optimized isolation protocol (vide supra) furnished this key intermediate **8** in 90% yield (see Scheme 4). However, access to the nitro derivative (Table 1, entry 10) could not be improved[19], irrespective of the method of nitration employed. We therefore decided to switch to a different mechanism and investigate other types of reagents and conditions.

In principle, the D*o*M methodology[28] represents another auspicious approach to 2,4-disubstituted pyrroles. The *N*-Boc-protecting group, a well-established substituent for directed metalations, has been shown to be particularly useful for the synthesis of 2,5-substituted pyrroles.[29] Moreover, *N*-sulfonamides as directing groups were reported to allow for a discrimination between the 2- and 5-position of 3-bromo-substituted pyrrole(s) with regioisomeric ratios depending on the base and electrophile used.[30] For our purpose, a combination of the two protocols seemed to be promising. Therefore, we investigated the regioselective deprotonation of *N*-Boc-protected 3-prenylpyrrole (**9**) as a model substrate. The regioselectivity of the deprotonation was determined by NMR analysis after quenching with methanol-d_4. The results are

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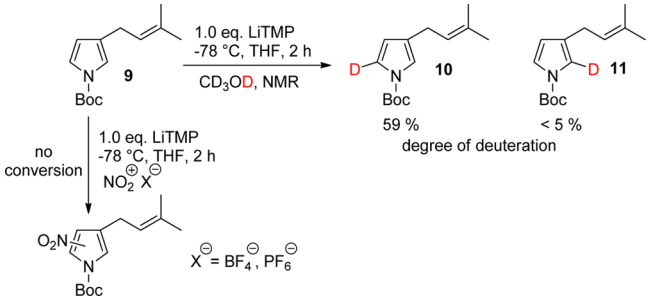
summarized in Scheme 5. With sterically demanding lithium tetramethylpiperidide (LiTMP) on *N*-Boc-protected starting

Scheme 5. Directed *ortho*-Metalation of 9

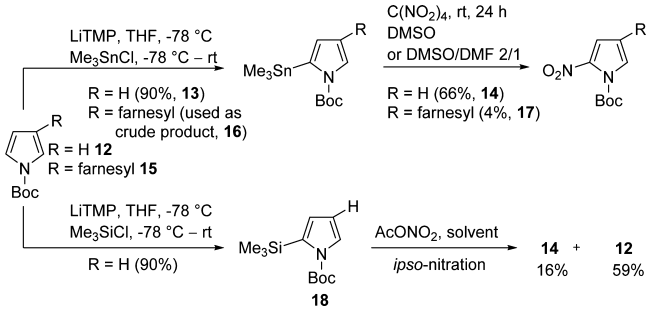


material **9**, up to 59% deuteration with the desired 2,4-substitution pattern (**10**) was obtained (see the Supporting Information for details). Only trace amounts of the opposite regioisomer **11** were detected (Scheme 5).

With optimized and regioselective deprotonation conditions in hand, we next investigated the compatibility of nitronium salts as electrophiles under these basic conditions.[29,32] This deprotonation−nitration sequence was tested in a range of solvents (e.g., THF, hexane, MeCN), at various temperatures and using different procedures for the addition of the electrophile (solid, stock solution). Disappointingly, none of the conditions tested resulted in any conversion.

By means of a similar approach (D*o*M with LiTMP), unsubstituted *N*-Boc-pyrrole (**12**) was selectively stannylated at the 2-position. Gratifyingly, the reaction proceeded in up to 90% yield with this model substrate (Scheme 6). The product,

Scheme 6. Stannylation and Subsequent *ipso*-Nitration of 12 and 15

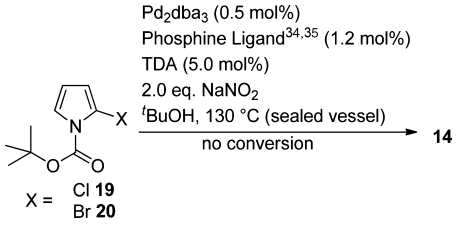


13, was isolated by column chromatography on basic alumina, and careful purification turned out to be essential for the subsequent nitration. Stannylated pyrrole **13** was then subjected to radical nitration with tetranitromethane in DMSO in the dark. Quintard and co-workers reported the nitration of an indole derivative,[33] albeit in low yield. The related nitrodestannylation of pyrrole derivatives has to our knowledge not previously been described. However, a reasonable isolated yield of 66% for compound **14** (Scheme 6) indicates an appropriate HOMO energy level. We next tested the same procedure on substrate **15** with the sesquiterpenyl side chain in place. Thus, stannylation of 3-farnesylated pyrrole **15** was carried out under identical conditions. A similar conversion as for substrate **12** was detected. However, chromatographic purification did not deliver the organotin compound (**16** in Scheme 6) but instead afforded the destannylated starting material **15**. Radical nitration without prior purification yielded only minimal amounts of the desired nitropyrrole **17**[19] (Scheme 6). Variation of the solvent or solvent composition, running the reaction under illumination or in the dark, and the use of different temperatures did not improve the outcome.

Furthermore, nitrodesilylations (*ipso*-nitrations) are well-established methods for the regiospecific synthesis of nitroarenes, and we felt that this methodology may be adaptable to the preparation of nitropyrroles as well.[34] We therefore decided to investigate the reaction of *N*-Boc-2-trimethylsilylpyrrole (**18**) with nitronium acetate ($AcONO_2$). In these experiments, only a minor amount of the desired nitration product **14** (16% yield) was isolated along with the protodesilylation product **12** (59%) as the major component (Scheme 6).

We therefore turned our attention to transition-metal-catalyzed nitrations. Buchwald and co-workers reported the synthesis of nitroarenes (notably heteroaromatics such as indole derivatives) by palladium-catalyzed cross-coupling of aryl chlorides with sodium nitrite.[35,36] With this precedent, we used *N*-Boc-protected 2-halogenated pyrroles **19** and **20** (X = Cl or Br, respectively) as starting materials (Scheme 7). Disappointingly, no conversion was detectable for any pyrrole substrate, possibly because of steric hindrance by the Boc protecting group (Scheme 7).

Scheme 7. Pd-Catalyzed Nitration of 2-Halide-Substituted Pyrroles 19 and 20



As a consequence of the poor nitration reactions of farnesylated pyrrole derivatives, we investigated the opposite strategy: farnesylation of a nitropyrrole substrate. On the basis of some literature precedent,[37] we chose to study the palladium-catalyzed cross-coupling of halogenated heteroarenes with allylboronic acids. First, the halogenation of 2-nitropyrrole to its 4-iododerivative **21** was optimized.[38] Under conditions similar to those reported by the groups of Olah[39] and Colobert,[40] a 92% yield of the regioisomerically pure product **21** was obtained (Scheme 8). Subsequent *N*-Boc protection to give **22** proceeded in 96% yield. We next investigated the cross-coupling reaction to install the side chain at the 4-position using both **21** and **22** as substrates (Scheme 8). Different combinations of oligoprenylboronic acid pinacol esters (with farnesyl and geranyl groups[41]), bases, palladium sources, solvents, and reaction temperatures were tested. Apart from Boc cleavage in some cases, no reaction and, more importantly, no cross-coupling was detectable. Similarly, control experiments with arylboronic acids did not show any conversion. Only the Negishi reaction[42] of phenylzinc chloride with pyrrole **22** gave the aryl−aryl coupling product in moderate yield (57%; Scheme 8). However, the same protocol was not applicable to allylic derivatives. For the converse approach with a π-acceptor-stabilized pyrrole boronic ester, the coupling product could be detected but only as an inseparable mixture of *E* and *Z*

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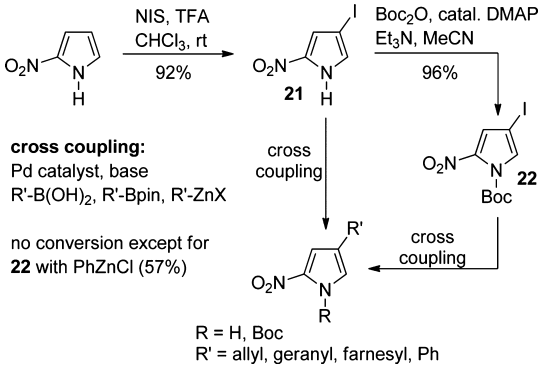
Scheme 8. Regioselective Iodination and Cross-Coupling of 21 and 22



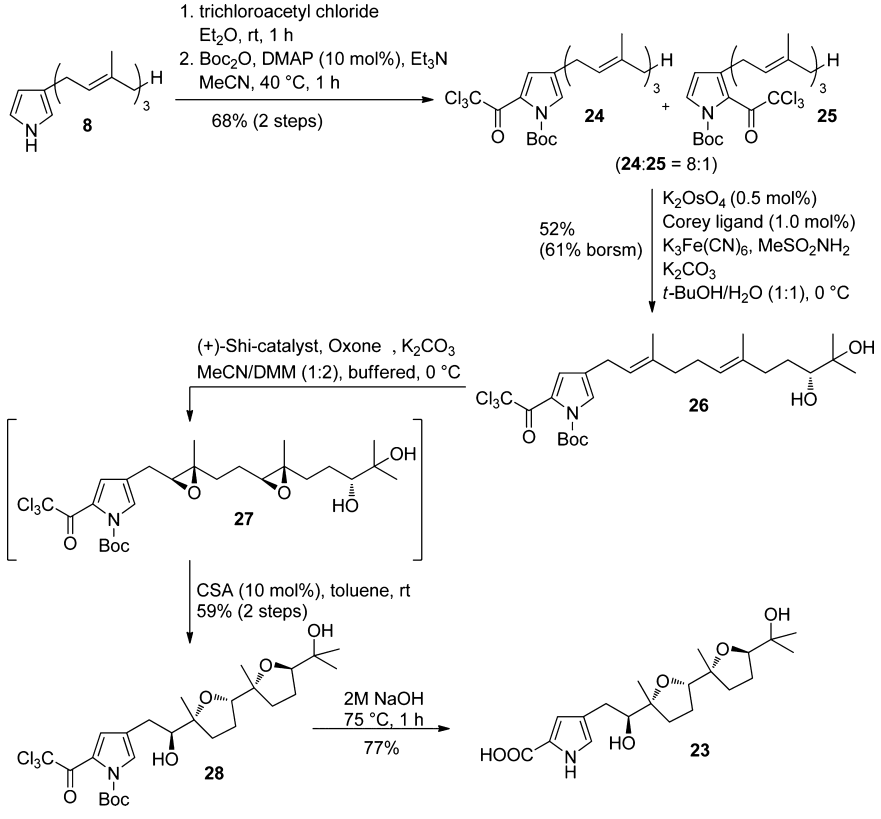
isomers (not shown). For halogen−metal exchange sequences, there are only a few procedures that tolerate labile substituents[43,44] such as nitro groups.[45] Disappointingly, however, these also were not applicable to substrates **21** and **22** (not shown).

Our intense efforts on the preparation of 2-nitro-4-farnesylpyrroles using different strategies under a broad range of conditions show that the synthesis of such sensitive heterocycles with a polyunsaturated side chain is a challenging task. It is important to note that we were indeed able to find conditions for reasonable (and in principle regioselective) pyrrole nitrations and also for the desired 4-farnesylation, but these were not efficient if one of the two substituents was already present in the starting material. It therefore seems that the combination of a nitro group and a polyprenyl side chain is particularly difficult to establish on a pyrrole ring. Interestingly, in the biosynthesis of nitropyrroloterpenes[12,46] (Figure 1), a significantly milder enzymatic pathway[47] for the introduction of these two substituents, in particular the nitro group, has evolved.

Synthesis of a Heronapyrrole C Analogue Carrying a Bioisosteric Carboxylate in Place of the 2-Nitro Group. At this stage, with the aim to provide reasonable amounts of material for biological assays, we decided to replace the natural nitro functionality of heronapyrrole C by a bioisosteric carboxylate group. We expected that its introduction should proceed under milder conditions and with higher regioselectivity.[48] Hence, we focused on the synthesis of heronapyrrole C acid derivative **23** (Scheme 9).

The synthesis commenced with 3-farnesylpyrrole **8** (improved synthesis summarized in Scheme 4; see the Experimental Section for details). Regioselective acylation was envisaged using trichloroacetyl chloride as a reactive and bulky reagent. Pleasingly, when substrate **8** was subjected to this reagent under Friedel−Crafts conditions in the absence of any catalyst, the reaction proceeded smoothly. Without any optimization, product **24** was isolated in good yield (68% yield after subsequent Boc protection) with high regioselectivity of >8:1 (compared with the related nitration, which delivered a 1:1.3 ratio of regioisomers from the same substrate; see Scheme 4 and Table 1). Only small amounts of unreacted starting material **8** were recovered. Subsequent dihydroxylation using the Corey−Noe−Lin catalyst[49,50] provided dienediol **26** in a highly position-[31] and stereoselective[51] manner. Double organocatalytic epoxidation of the two remaining double bonds with (+)-Shi catalyst[52,53] gave **27**, the precursor for the polyepoxide cyclization cascade.[19,50,54] Epoxide opening−cyclization[54−56] to give the corresponding bis-THF **28** was

Scheme 9. Stereoselective Synthesis of Heronapyrrole C Acid Derivative 23



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carried out under acidic conditions [camphorsulfonic acid (CSA) in toluene] (Scheme 9). Minor diastereomers (resulting from the epoxidation) were detected by TLC of the crude reaction mixtures but were readily removed by column chromatography. Finally, heating substrate **28** in an aqueous sodium hydroxide solution led to a smooth *N*-deprotection with simultaneous haloform reaction.[57−59] Thus, heronapyrrole C acid derivative **23** was isolated in 77% yield.

CONCLUSION

We have investigated the preparation of 2-nitro-4-oligoprenyl-substituted pyrroles relevant to the synthesis of heronapyrroles and related natural products. Among various strategies, the nitration using $AcONO_2$ on a 3-substituted pyrrole derivative gave the best results. However, the yield and regioselectivity in favor of the desired product were low. We therefore developed a novel approach to a bioisosteric π-acceptor-stabilized heronapyrrole C carboxylate derivative. In contrast to the nitration sequences, the acylation with a sterically demanding acyl donor (trichloroacetyl chloride) provided high chemo- and regioselectivity for the desired product. The resulting trichloromethyl ketone could be efficiently converted to the expected carboxylic acid at a later stage of the synthesis. Furthermore, a highly stereo- and position-selective dihydroxylation using the Corey−Noe−Lin catalyst[49,50] and an asymmetric double epoxidation of the sesquiterpene side chain with Shi's catalyst[52,53] set the stage for the construction of the bis-THF subunit. A stereoselective polyepoxide cyclization cascade provided the expected product. Finally, a haloform reaction proceeded smoothly by heating the trichloroacetyl precursor under basic aqueous conditions to give the (−)-heronapyrrole C acid derivative. Only eight steps with an overall yield of 14.5% were required to prepare this natural product analogue from commercially available starting materials.

EXPERIMENTAL SECTION

Materials and Methods. All of the reagents were used as purchased from commercial suppliers. All dry solvents were purified using a solvent purification system. All reactions were performed under an atmosphere of dry nitrogen, unless otherwise mentioned. Reactions were monitored by thin layer chromatography using aluminum plates precoated with silica or aluminum oxide and stained with vanillin [vanillin (1 g), conc. H_2SO_4 (10 mL), AcOH (20 mL), ethanol (170 mL)] or ceric ammonium molybdate [phosphomolybdic acid (25 g), $Ce(SO_4)_2{\cdot}2H_2O$ (10 g), conc. H_2SO_4 (60 mL), H_2O (940 mL)]. Chromatographic purification was performed as flash chromatography on silica gel (particle size 0.040−0.063 mm) or aluminum oxide (particle size 0.060−0.200 mm). Yields refer to chromatographically purified and spectroscopically pure compounds. NMR spectra were recorded on a 300 MHz spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C acquisitions), a 400 MHz spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C acquisitions), or a 500 MHz spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C acquisitions). Chemical shifts (δ) are reported in parts per million with tetramethylsilane or the solvent resonance as the internal standard. Coupling constants (J) are given in hertz. Multiplicities are classified as follows: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, or combinations thereof, or m = multiplet or br = broad signal. Two-dimensional NMR (H−COSY, HSQC, HMBC) were used for the assignment of all final compounds. High-resolution mass spectra were obtained on an ESI-TOF mass-spectrometer. IR spectra were recorded on an FT-IR spectroscope by attenuated total reflection (ATR). Absorbance frequencies ($\tilde{\nu}$) are reported in reciprocal centimeters (cm^{-1}). Optical rotation data were obtained at 589 nm using a 100 mm path-length cell in the indicated solvent at the indicated concentration and temperature. The reported melting points are uncorrected. Elemental compositions (anal.) were determined by combustion analysis. All compounds were named according to IUPAC rules. For simplicity, the numbering of the carbon atoms of a given structure does not follow the IUPAC rules (for numbering, see the Supporting Information).

***trans,trans*-Farnesyl Bromide (5).** Phosphorus tribromide (470 μL, 5.00 mmol, 0.50 equiv) was added to a stirred solution of *trans,trans*-farnesol (2.22 g, 10.0 mmol, 1.00 equiv) in dry Et_2O (50 mL) at 0 °C. The solution was stirred for 45 min at 0 °C. After complete conversion was detected (TLC), NaOH (1.24 g, 31.0 mmol, 3.10 equiv) in H_2O (50 mL) was added at 0 °C, and the mixture was stirred for 15 min. The mixture was diluted with hexanes (150 mL) and saturated with NaCl. The layers were separated, and the organic layer was washed with water (50 mL) and brine (2 × 50 mL). The organic layer was dried over Na_2SO_4, and all volatiles were removed under reduced pressure. The residue was filtered through a plug of Na_2SO_4 (elution with 100% hexanes) under vacuum. All volatiles were removed under reduced pressure to give the title compound (2.56 g, 90%) as a colorless oil. The analytical data matched the reported literature data. Quantitative NMR experiments[23] with 1,4-dimethoxybenzene as an internal standard (see the Supporting Information) showed a purity of >99% (Note: the typical purity of commercially available farnesyl bromide is ∼95%, and it is shipped as a yellow to brown oil.). Pure synthetic samples could be stored at −26 °C under a N_2 atmosphere without detectable decomposition for several days.

3-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl)-1*H*-pyrrole (8). 3-Bromo-1-(triisopropysilyl)pyrrole (3.02 g, 10.0 mmol, 1.00 equiv) in dry THF (50 mL) was cooled to −78 °C. *tert*-Butyllithium (1.9 M in heptane, 10.5 mL, 20.0 mmol, 2.00 equiv) was added dropwise, and the yellowish solution was stirred for 5 min. Freshly prepared *trans,trans*-farnesyl bromide (3.42 g, 12.0 mmol, 1.20 equiv) in dry THF (5 mL) was added dropwise over 5 min, and the mixture was stirred for 4 h with warming to −50 °C. The reaction was quenched with brine (50 mL), and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, and the solvents were removed under reduced pressure. The residue was dissolved in THF (50 mL), and tetrabutylammonium fluoride (3.79 g, 12.0 mmol, 1.20 equiv) was added at rt. The mixture was stirred at rt for 30 min, and the solvent was removed under reduced pressure. Flash chromatography (10% ethyl acetate + 5% Et_3N in hexanes, silica) of the residue gave the title compound (2.45 g, 90%) as a yellowish oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01 (br s, 1H, H-1), 6.74 (dd, J = 4.8 Hz, J = 2.5 Hz, 1H, H-2), 6.60−6.57 (m, 1H, H-5), 6.15−6.12 (m, 1H, H-3), 5.47−5.41 (m, 1H, H-7), 5.23−5.13 (m, 2H, H-11/15), 3.28 (d, J = 7.2 Hz, 2H, H-6), 2.21−2.02 (m, 8H, H-9/10/13/14), 1.75 (s, 3H, H-20), 1.74 (s, 3H, H-17), 1.66 (s, 6H, H-18/19). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 135.0 (2C, C-8/12), 131.3 (C-16), 124.6 (C-4), 124.4 (C-11), 124.1 (C-15), 123.6 (C-7), 117.9 (C-2), 115.0 (C-5), 108.7 (C-3), 39.9 (C-9/13), 39.8 (C-9/13), 26.9 (C10/14), 26.8 (C-10/14), 25.8 (C-17), 25.7 (C-6), 17.8 (C-18), 16.12 (C-19), 16.09 (C-20). **IR** (ATR): $\tilde{\nu}$ = 3404, 2960, 2923, 2865, 1451, 1381, 1057, 882, 802, 768, 676 cm^{-1}. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{30}N$ 272.2373; found 272.2371.

***tert*-Butyl 3-(3-Methylbut-2-en-1-yl)-1*H*-pyrrole-1-carboxylate (9).** 3-Bromo-1-(triisopropylsilyl)pyrrole (1.21 g, 4.00 mmol, 1.00 equiv) was converted with 3,3-dimethylallyl bromide (0.69 mL, 6.00 mmol, 1.50 equiv) as described for the synthesis of coupling product **8**. Without further purification, the crude residue was dissolved in dry MeCN (15 mL). Di-*tert*-butyl dicarbonate (1.10 mL, 4.80 mmol, 1.20 equiv) and catalytic amounts of 4-(dimethylamino)pyridine were added, and the solution was stirred at rt for 12 h. After complete conversion, the solvent was removed under reduced pressure. Flash chromatography (2% ethyl ether in hexanes, silica) of the residue gave the title compound (707 mg, 75%) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.16−7.13 (m, 1H, H-5), 6.96 (br s, 1H, H-2), 6.07 (dd, J = 3.1 Hz, J = 1.7 Hz, 1H, H-4), 5.32−5.27 (m, 1H, H-7), 3.12 (d, J = 7.2 Hz, 2H, H-6), 1.73 (s, 3H, H-9/10), 1.68 (s, 3H, H-9/10), 1.57 (s, 9H, H-13). **^{13}C NMR** (100 MHz, $CDCl_3$): δ

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149.1 (C-11), 132.4 (C-8), 127.3 (C-3), 122.8 (C-7), 120.3 (C-5), 116.6 (C-2), 113.0 (C-4), 83.3 (C-12), 28.2 (C-13), 25.8 (C-6, C-9/10), 17.8 (C-9/10). **IR** (ATR): $\tilde{\nu}$ = 2977, 2928, 1737, 1484, 1342, 1286, 1236, 1155, 1065, 969, 769 cm^{-1}. **HRMS** (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{14}H_{21}NNaO_2$ 258.1465; found 258.1464.

***tert*-Butyl 2-(Trimethylstannyl)-1*H*-pyrrole-1-carboxylate (13).** A solution of 2,2,6,6-tetramethylpiperidine (354 μL, 2.10 mmol, 1.05 equiv) in dry THF (10 mL) was cooled to −78 °C, and *n*-butyllithium (1.6 M in hexane, 1.31 mL, 2.10 mmol, 1.05 equiv) was added dropwise. The solution was stirred at 0 °C for 10 min and cooled again to −78 °C. *N*-Boc-pyrrole (334 mg 2.00 mmol, 1.00 equiv) in dry THF (2 mL) was added dropwise, and the solution was stirred at −78 °C for 30 min. A solution of trimethyltin chloride (1.0 M in hexane, 2.20 mL, 2.20 mmol, 1.1 equiv) was added, and the solution was stirred with warming to rt for 12 h (conversion monitored by TLC, Al_2O_3). After complete conversion of the starting material, water (10 mL) was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash chromatography (100% hexanes, basic Al_2O_3) of the residue gave the title compound (595 mg, 90%) as an oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 3.0 Hz, *J* = 1.4 Hz, $^4J_{H,Sn}$ = 10.4 Hz, 1H, H-5), 6.37 (dd, *J* = 3.0 Hz, *J* = 1.4 Hz, $^3J_{H,Sn}$ = 15.6 Hz, 1H, H-3), 6.30 (m, 1H, $^3J_{H,Sn}$ = 8.9 Hz, H-4), 1.58 (s, 9H, H-8), 0.25 (s, 9H, H-9). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 150.6 (C-6), 134.7 (C-2), 123.5 (C-5), 122.4 (C-3), 112.8 (C-4), 83.5 (C-7), 28.1 (C-8), −7.6 (C-9). **IR** (ATR): $\tilde{\nu}$ = 2979, 2918, 1727, 1385, 1334, 1153, 1086, 1046, 980, 773, 724, 525 cm^{-1}. Because of the instability of this compound, no MS data could be obtained.

***tert*-Butyl 2-Nitro-1*H*-pyrrole-1-carboxylate (14).** A solution of pyrrole **13** (165 mg, 0.50 mmol, 1.0 equiv) and tetranitromethane (66 μL, 0.55 mmol, 1.1 equiv) in DMSO (1 mL) was stirred for 24 h in the dark until complete conversion was detected (TLC). Flash chromatography (5% ethyl acetate in hexanes, silica) of the dark-brown solution gave the title compound (70 mg, 66%) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.25 (dd, *J* = 3.2 Hz, *J* = 1.9 Hz, 1H, H-5), 7.07 (dd, *J* = 3.9 Hz, *J* = 1.9 Hz, 1H, H-3), 6.22−6.19 (m, 1H, H-4), 1.58 (s, 9H, H-8). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 147.1 (C-6), 138.6 (C-2), 126.9 (C-5), 117.0 (C-3), 109.6 (C-4), 87.1 (C-7), 27.6 (C-8). **IR** (ATR): $\tilde{\nu}$ = 2983, 1761, 1513, 1366, 1281, 1155, 1109, 806, 742 cm^{-1}. **HRMS** (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_9H_{12}N_2NaO_4$ 235.0689; found 235.0688. Because of its low intensity in the 1D ^{13}C spectrum, the ^{13}C resonance at δ 138.6 was assigned using HMBC and HSQC spectra.

***tert*-Butyl 3-((2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl)-1*H*-pyrrole-1-carboxylate (15).** 3-Bromo-1-(triisopropylsilyl)-pyrrole (302 mg, 1.00 mmol, 1.00 equiv) was converted as described for the preparation of **8**. Without purification, the crude residue was dissolved in dry MeCN (15 mL). Di-*tert*-butyl dicarbonate (276 μL, 1.20 mmol, 1.20 equiv) and catalytic amounts of 4-(dimethylamino)-pyridine were added, and the solution was stirred at rt for 12 h. After complete conversion, the solvent was removed under reduced pressure. Flash chromatography (100% hexanes, silica) of the residue gave the title compound (280 mg, 75%) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.16−7.13 (m, 1H, H-2), 6.96 (br s, 1H, H-5), 6.07 (dd, *J* = 3.1 Hz, *J* = 1.7 Hz, 1H, H-3), 5.34−5.28 (m, 1H, H-7), 5.15−5.05 (m, 2H, H-11/15), 3.13 (d, *J* = 7.2 Hz, 2H, H-6), 2.16−1.93 (m, 8H, H-9/10/13/14), 1.68 (s, 6H, H-17/20), 1.60 (s, 6H, H-18/19), 1.57 (s, 9H, H-23). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 149.1 (C-21), 136.1 (C-8), 135.2 (C-12), 131.4 (C-16), 127.3 (C-4), 124.6 (C-11), 124.3 (C-15), 122.7 (C-7), 120.2 (C-2), 116.7 (C-5), 113.1 (C-3), 83.3 (C-22), 39.9 (C-9/13), 39.8 (C-9/13), 28.2 (C-23), 26.9 (C-10/14), 26.8 (C-10/14), 25.8 (C-17), 25.7 (C-6), 17.8 (C-18), 16.21 (C-19), 16.16 (C-20). **IR** (ATR): $\tilde{\nu}$ = 2976, 2918, 1740, 1482, 1346, 1286, 1236, 1157, 1066, 970, 771 cm^{-1}. **HRMS** (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{38}NO_2$ 372.2897; found 372.2889.

***tert*-Butyl 2-Chloro-1*H*-pyrrole-1-carboxylate (19).** A solution of 2,2,6,6-tetramethylpiperidine (557 μL, 3.30 mmol, 1.10 equiv) in dry THF (10 mL) was cooled to −78 °C, and *n*-butyllithium (1.6 M in hexane, 2.06 mL, 3.30 mmol, 1.10 equiv) was added dropwise. The solution was stirred at 0 °C for 10 min and cooled again to −78 °C. *N*-Boc-pyrrole (502 mg, 3.00 mmol, 1.00 equiv) in dry THF (2 mL) was added dropwise, and the solution was stirred at −78 °C for 45 min. Copper(I) chloride (327 mg, 3.30 mmol, 1.10 equiv) was added at −78 °C, and the suspension was stirred with warming to −45 °C for 1 h (all solids dissolved). The reaction was cooled to −78 °C, and *N*-chlorosuccinimide (441 mg, 3.30 mmol, 1.10 equiv) was added. The mixture was slowly warmed to 0 °C, and after complete conversion, brine (10 mL) was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Short-path distillation (105 °C, 3 × 10^{-2} mbar) of the residue gave the title compound (337 mg, 56%) as an oil. **^{1}H NMR** (400 MHz, CD_2Cl_2): δ 7.21 (dd, *J* = 3.6 Hz, *J* = 2.1 Hz, 1H, H-5), 6.15 (dd, *J* = 3.6 Hz, *J* = 2.1 Hz, 1H, H-3), 6.12 (t, *J* = 3.6 Hz, 1H, H-4), 1.59 (s, 9H, H-8). **^{13}C NMR** (100 MHz, CD_2Cl_2): δ 148.2 (C-6), 121.9 (C-5), 117.2 (C-2), 113.0 (C-4), 110.5 (C-3), 85.1 (C-7), 28.1 (C-8). **IR** (ATR): $\tilde{\nu}$ = 2981, 2934, 1740, 1459, 1320, 1153, 1092, 1052, 994, 845, 712 cm^{-1}. **Anal.** Calcd for $C_9H_{12}ClNO_2$: C, 53.61; H, 6.00; N, 6.95. Found: C, 53.69; H, 6.09; N, 6.91.

4-Iodo-2-nitro-1*H*-pyrrole (21). 2-Nitro-1*H*-pyrrole (224 mg, 2.00 mmol, 1.00 equiv) was dissolved in $CHCl_3$ (20 mL) at rt. *N*-Iodosuccinimide (472 mg 2.10 mmol, 1.05 equiv) and trifluoroacetic acid (168 μL, 2.20 mmol, 1.10 equiv) were added consecutively, and the solution was stirred at rt for 12 h. After complete conversion (TLC), a saturated solution of Na_2SO_3 (10 mL) and water (10 mL) was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash chromatography (10% ethyl acetate in hexanes, silica) of the residue gave the title compound (439 mg, 92%) as an orange crystalline solid. Highly pure samples were obtained by sublimation (115 °C, 2 × 10^{-2} mbar) or recrystallization from MeOH/$CHCl_3$. **Mp**: 156−157 °C. **^{1}H NMR** (400 MHz, MeOH-d_4): δ 7.15 (d, *J* = 1.8 Hz, 1H, H-3), 7.11 (d, *J* = 1.8 Hz, 1H, H-5), 4.84 (br s, 1H, N-H). **^{13}C NMR** (100 MHz, MeOH-d_4): δ 140.0 (C-2), 129.8 (C-5), 117.8 (C-3), 62.3 (C-4). **IR** (ATR): $\tilde{\nu}$ = 3210, 3135, 3120, 1495, 1439, 1325, 1212, 1116, 901, 848, 751, 590 cm^{-1}. **HRMS** (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_4H_3IN_2O_2$ 260.9131; found 260.9130.

***tert*-Butyl 4-Iodo-2-nitro-1*H*-pyrrole-1-carboxylate (22).** Pyrrole **21** (238 mg, 1.00 mmol, 1.00 equiv) was dissolved in MeCN (5 mL) at rt. Di-*tert*-butyl dicarbonate (253 μL, 1.10 mmol, 1.10 equiv) and triethylamine (279 μL, 2.10 mmol, 2.10 equiv) were added consecutively, and the solution was stirred at rt for 3 h. After complete consumption of the starting material (TLC), all volatiles were removed under reduced pressure. Flash chromatography (2% ethyl acetate in hexanes, silica) of the residue gave the title compound (325 mg, 96%) as a light-yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.32 (d, *J* = 2.0 Hz, 1H, H-3), 7.10 (d, *J* = 2.0 Hz, 1H, H-5), 1.56 (s, 9H, H-8). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 145.5 (C-6), 138.9 (C-2), 130.5 (C-5), 122.3 (C-3), 87.8 (C-7), 61.9 (C-4), 27.4 (C-8). **IR** (ATR): $\tilde{\nu}$ = 3133, 2982, 1765, 1514, 1457, 1351, 1274, 1142, 1084, 908, 835, 806, 766, 727, 583 cm^{-1}. **HRMS** (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_9H_{11}IN_2NaO_4$ 360.9656; found 360.9665.

***tert*-Butyl 2-Trichloroacetyl-4-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)-1*H*-pyrrole-1-carboxylate (24).** 3-Farnesylpyrrole (**8**) (1.09 g, 4.00 mmol, 1.00 equiv) was dissolved in dry Et_2O (10 mL) at rt. Trichloroacetyl chloride (0.47 mL, 4.20 mmol, 1.05 equiv) was added dropwise to this solution. After the mixture was stirred for 2 h at rt, the reaction was quenched with brine (10 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was dissolved in dry MeCN (10 mL), and triethylamine (0.67 mL, 4.80 mmol, 1.2 equiv), di-*tert*-butyl dicarbonate (1.10 mL, 4.8 mmol, 1.2 equiv), and a catalytic amount of 4-(dimethylamino)-pyridine were added. The mixture was stirred at 40 °C for 1 h. After complete conversion, the solvent was removed under reduced pressure. Flash chromatography (5% diethyl ether in hexanes, silica) of the residue gave the title compound (1.41 g, 68%) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24−7.22 (m, 1H, H-5), 7.11 (d, J = 1.6 Hz, 1H, H-3), 5.32−5.26 (m, 1H, H-7), 5.25−5.15 (m, 2H, H-11/15), 3.16 (d, J = 7.2 Hz, 2H, H-6), 2.14−1.96 (m, 8H, H-9/10/13/14), 1.67 (br s, 6H, H-17/20), 1.59 (br s, 6H, H-18/19), 1.56 (s, 9H, H-23). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.8 (C-24), 148.5 (C-21), 137.4 (C-8), 135.4 (C-12), 131.4 (C-16), 126.7 (C-5), 125.8 (C-2), 124.9 (C-4), 124.5 (C-3), 124.2 (C-11/15), 124.1 (C-11/15), 121.5 (C-7), 95.7 (C-24), 85.7 (C-22), 39.9 (C-9/13), 39.8 (C-9/13), 27.7 (C-23), 26.9 (C-10/14), 26.7 (C-10/14), 25.8 (C-17), 25.2 (C-6), 17.9 (C-18), 16.3 (C-19), 16.2 (C-20). **IR** (ATR): $\tilde{\nu}$ = 2977, 2923, 2868, 1752, 1718, 1698, 1449, 1396, 1369, 1323, 1288, 1256, 1151, 1115, 988, 838, 729, 681 cm^{-1}. **HRMS** (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{26}H_{36}Cl_3NNaO_3$ 538.1653; found 538.1654.

***tert*-Butyl 4-((10*R*,2*E*,6*E*)-10,11-Dihydroxy-3,7,11-trimethyldodeca-2,6-diene-1-yl)-2-trichloroacetyl-1*H*-pyrrole-1-carboxylate (26).** A solution of **24** (1.00 g, 1.93 mmol, 1.00 equiv) in *t*-BuOH/H_2O (50 mL, 1:1) was cooled to 0 °C, and Corey ligand[49,50] (22.0 mg, 19.0 μmol, 0.01 equiv), methanesulfonamide (184 mg, 1.93 mmol, 1.00 equiv), K_2CO_3 (0.80 g, 5.79 mmol, 3.00 equiv), $K_2OsO_4\cdot 2H_2O$ (3.60 mg, 9.70 μmol, 0.005 equiv), and $K_3Fe(CN)_6$ (1.91 g, 5.79 mmol, 3.00 equiv) were successively added. The suspension was stirred for 24 h at 0 °C. After addition of saturated Na_2SO_3 (50 mL), the solution was stirred for 10 min, diluted with H_2O (100 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Flash chromatography (50% ethyl acetate in hexanes, silica) of the crude product gave the title compound (0.56 g, 52%, 61% brsm) and reisolated starting material **24** (0.15 g, 15%) as yellow oils. $[\alpha]_D^{20}$ +9.8 (c 1.08, MeOH). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23 (br s, 1H, H-5), 7.10 (d, J = 1.4 Hz, 1H, H-3), 5.29 (t, J = 6.8 Hz, 1H, H-7), 5.19 (t, J = 6.2 Hz, 1H, H-11), 3.35 (dd, J = 10.4 Hz, J = 1.6 Hz, 1H, H-15), 3.16 (d, J = 7.3 Hz, 2H, H-6), 2.28−2.05 (m, 6H, H-9/10/13), 1.67 (s, 3H, H-20), 1.62 (s, 3H, H-19), 1.55 (s, 9H, H-23), 1.46−1.40 (m, 2H, H-14), 1.19 (s, 3H, H-17/18), 1.15 (s, 3H, H-17/18). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.9 (C-24), 148.5 (C-21), 137.2 (C-8), 135.4 (C-12), 126.7 (C-5), 125.8 (C-2/4), 124.92 (C-2/4), 124.86 (C-11), 124.2 (C-3), 121.6 (C-7), 95.7 (C-24), 85.8 (C-22), 78.5 (C-15), 73.1 (C-16), 39.7 (C-9), 37.0 (C-13), 29.9 (C-14), 27.7 (C-23), 26.5 (2C, C-10 + C17/18), 25.2 (C-6), 23.5 (C-17/18), 16.2 (C-19), 16.1 (C-20). **IR** (ATR): $\tilde{\nu}$ = 3411, 2978, 2931, 1746, 1697, 1477, 1449, 1397, 1323, 1151, 1118, 909, 839, 768, 728, 682 cm^{-1}. **HRMS** (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{26}H_{38}Cl_3NNaO_5$ 572.1708; found 572.1720.

***tert*-Butyl 4-((2*S*)-Hydroxy-2-((2*S*,2′*R*,5*R*,5′*R*)-5′-(2-hydroxypropan-2-yl)-2′,5-dimethyloctahydro-[2,2′-bifuran]-5-yl)ethyl)-2-trichloroacetyl-1*H*-pyrrole-1-carboxylate (28).** To a stirred solution of (*R*)-diol **26** (226 mg, 0.41 mmol, 1.00 equiv) in MeCN/$(CH_3O)_2CH_2$ (15.6 mL, 1:2) were added $Na_2B_4O_7\cdot 10H_2O$ in 4 × 10^{-4} M Na_2EDTA (0.05 M, 10.4 mL), *n*-Bu_4NHSO_4 (16.0 mg, 0.046 mmol, 0.11 equiv), and (+)-Shi ketone[53] (127 mg, 0.49 mmol, 1.20 equiv). The mixture was cooled to 0 °C, and solutions of Oxone (855 mg, 1.39 mmol, 3.40 equiv) in Na_2EDTA (4 × 10^{-4} M, 6.5 mL) and K_2CO_3 (795 mg, 5.75 mmol, 14.0 equiv) in H_2O (6.5 mL) were added separately via syringe pump over 90 min at 0 °C. The reaction mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude mixture was dissolved in dry toluene (10 mL), and (+)-camphorsulfonic acid (9.5 mg, 0.041 mmol, 0.10 equiv) was added at 0 °C. The solution was stirred for 4 h until complete consumption of the intermediary bis-epoxide was monitored. Triethylamine (2 mL) was added, and all volatiles were removed under reduced pressure. Flash chromatography (50% ethyl acetate in hexanes, silica) of the residue gave the title compound (140 mg, 59%) as a yellowish oil. $[\alpha]_D^{20}$ +7.0 (c 1.00, MeOH). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.39 (d, J = 1.4 Hz, 1H, H-5), 7.29 (d, J = 1.4 Hz, 1H, H-3), 4.05−4.01 (m, 1H, H-11), 3.79−3.75 (m, 2H, H-7, H-15), 2.57 (dd, J = 14.8 Hz, J = 2.0 Hz, 1H, H-6a), 2.43 (dd, J = 14.8 Hz, J = 10.3 Hz, 1H, H-6b), 2.23−2.17 (m, 1H, H-9a), 2.01−1.92 (m, 3H, H-10a, H-14), 1.84−1.77 (m, 2H, H-10b, H-13a), 1.75−1.69 (m, 1H, H-13b), 1.55 (m, 10H, H-9b, H-23), 1.30 (s, 3H, H-19), 1.231 (s, 3H, H-20), 1.228 (s, 3H, H-17), 1.10 (s, 3H, H-18). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.6 (C-24), 148.4 (C-21), 128.0 (C-5), 125.5 (C-3), 124.6 (C-2/4), 123.5 (C-2/4), 95.7 (C-25), 88.2 (C-15), 86.8 (C-8), 85.5 (22), 85.4 (C-12), 84.4 (C-11), 77.8 (C-7), 70.4 (C-16), 34.7 (C-13), 31.4 (C-9), 29.4 (C-6), 28.0 (C-14), 27.9 (C-17/20), 27.7 (C-23), 25.9 (2C, C-10, C-19), 24.8 (C-17/20), 24.4 (C-18). **IR** (ATR): $\tilde{\nu}$ = 3370, 2970, 2933, 2876, 1754, 1696, 1451, 1371, 1257, 1152, 1070, 840, 816, 804, 768, 729 cm^{-1}. **HRMS** (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{26}H_{38}Cl_3NNaO_7$ 604.1601; found 604.1609.

Heronapyrrole C Acid (23). A stirred solution of bis-THF **28** (120 mg, 0.21 mmol, 1.0 equiv) in THF (5 mL) and NaOH (5 mL, 2 M) was heated to 75 °C for 1 h. After complete conversion (TLC), the mixture was cooled to rt, acidified (pH 1.5) with $NaHSO_4$ (1 M) and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and all volatiles were removed under reduced pressure. Flash chromatography (20% ethyl acetate + 5% AcOH in hexanes, silica) of the residue gave the title compound (45 mg, 56%) as an oil. $[\alpha]_D^{20}$ +5.5 (c 1.14, MeOH). **^{1}H NMR** (300 MHz, MeOH-d_4): δ 6.83 (d, J = 1.3 Hz, 1H, H-5), 6.78 (d, J = 1.4 Hz, 1H, H-3), 4.02 (dd, J = 8.6 Hz, J = 6.5 Hz, 1H, H-11), 3.82 (dd, J = 8.5 Hz, J = 6.6 Hz, 1H, H-15), 3.59 (dd, J = 10.1 Hz, J = 2.0 Hz, 1H, H-7), 2.81 (dd, J = 14.8 Hz, J = 1.8 Hz, 1H, H-6a), 2.42 (dd, J = 14.8 Hz, J = 10.1 Hz, 1H, H-6b), 2.18−2.10 (m, 1H, H-9a), 2.03−1.72 (m, 5H, H-10, H-13a, H-14), 1.69−1.57 (m, 2H, H-9b, H-13b), 1.211 (s, 3H, H-19), 1.208 (s, 3H, H-20), 1.16 (s, 3H, H-17/18), 1.13 (s, 3H, H-17/18). **^{13}C NMR** (75 MHz, MeOH-d_4): δ 164.9 (C-21), 124.6 (C-4), 123.5 (C-5), 117.1 (C-3), 88.9 (C-15), 87.1 (C-8), 86.3 (C-12), 86.1 (C-11), 79.4 (C-7), 72.2 (C-16), 35.1 (C-9), 34.7 (C-13), 30.2 (C-6), 28.5 (C-10), 27.6 (C-14), 26.2 (C-17/18), 25.8 (C-17/18), 25.1 (C-19), 22.3 (C-20). **IR** (ATR): $\tilde{\nu}$ = 3378, 2971, 2874, 1678, 1575, 1474, 1413, 1374, 1307, 1215, 1179, 1071, 980, 888, 636 cm^{-1}. **HRMS** (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{20}H_{31}NNaO_6$ 404.2044; found 404.2052. Because of its low intensity in the 1D ^{13}C spectrum, the ^{13}C resonance at δ 164.9 was assigned using HMBC and HSQC spectra. The quaternary carbon atom adjacent to the acid (C-2) could not be detected by either 1D ^{13}C or 2D NMR methods.[60]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of all ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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