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Enantioselective Synthesis of Guaianolides in the Osmitopsin Family by Domino Metathesis

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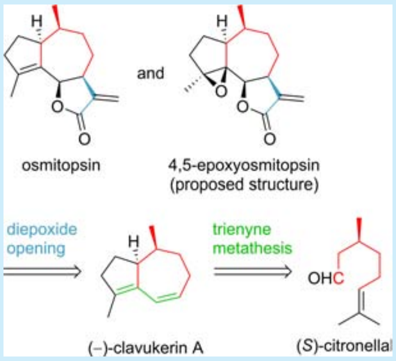
Ⓢ *Supporting Information*

ABSTRACT: Relay metathesis enabled an improved access from (*S*)-citronellal to the marine trisnorguaiane (−)-clavukerin A. This hydroazulene was applied as an advantageously functionalized building block for the asymmetric synthesis of the sesquiterpene lactone osmitopsin and the proposed structure of 4,5-epoxyosmitopsin using a chemo-, regio-, and diastereoselective diepoxide opening as the key step.



Sesquiterpene lactones of the guaianolide type are often associated with interesting biological properties[1] and have recently attracted much interest from the synthetic community.[2,3] The guaianolides osmitopsin (**1**) and 4,5-epoxyosmitopsin (**2**) were isolated from the aerial parts of *Osmitopsis asteriscoides*,[4] a South African medicinal plant known for its antimicrobial activity (Figure 1).[5]

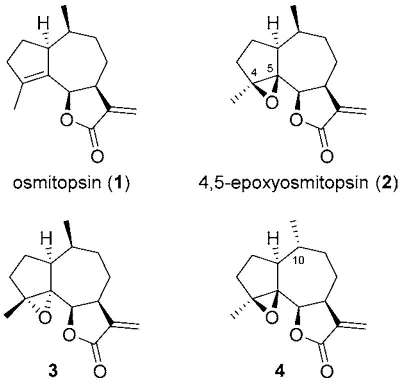
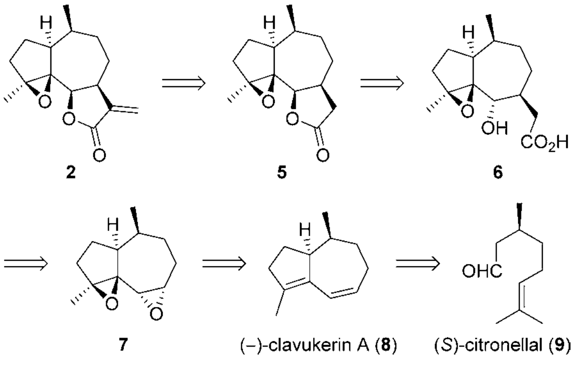


Figure 1. Naturally occurring guaianolides **1** and **2** (proposed structure) and non-natural diastereomers **3** and **4** of **2**.

Assignment of the relative configuration depicted for **1** and **2** was mainly based on ^{1}H NMR arguments, while the absolute configuration was unknown. In particular, experiments using the shift reagent Eu(fod)$_3$ with epoxy lactone **2** and the isomeric compound **3** obtained by epoxidation of **1** with *meta*-chloroperbenzoic acid led Bohlmann to propose a *cis* relationship between the epoxide oxygen and the γ-lactone attached to the hydroazulene core in **2**.[4a] Whereas the bioactivity of **1** and **2** has not yet been investigated, the racemic C-10 epimer **4** of **2** synthesized by Posner shows significant activity against schistosomal cercariae,[6] worm larvae that cause bilharziosis.[7] Herein we report a concise synthesis of osmitopsin (**1**) and the proposed structure of 4,5-epoxyosmitopsin (**2**) from (*S*)-citronellal (**9**).

We first focused on the synthesis of 4,5-epoxyosmitopsin (**2**), and Scheme 1 illustrates our original retrosynthetic analysis for this structure. Since many methods are known for attachment of an *exo* methylene unit to a γ-butyrolactone,[8] we selected the saturated lactone **5** as a precursor to **2** that should be available by intramolecular Mitsunobu reaction with inversion of configuration[9] from hydroxy acid **6**. Carboxylic acid **6** in turn might be obtained by selective nucleophilic opening of

Scheme 1. Retrosynthesis of 4,5-Epoxyosmitopsin (2)



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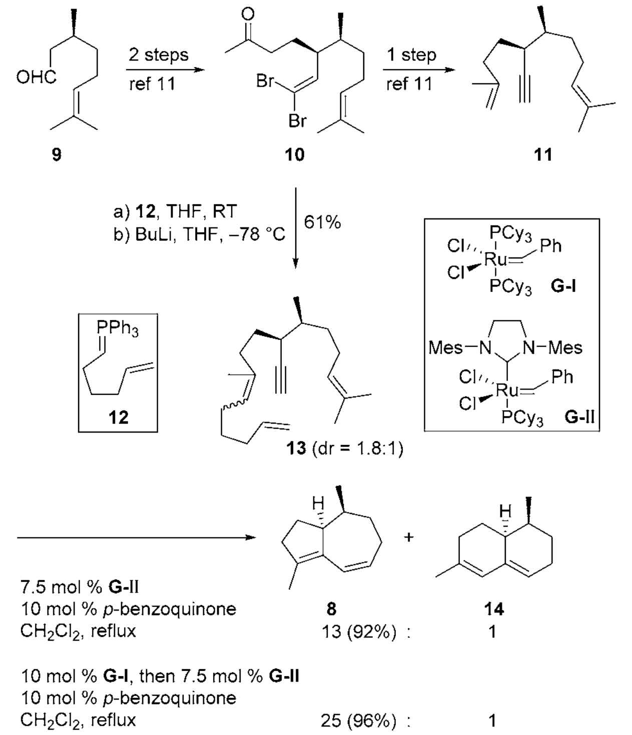
diepoxide **7** that was reported to be formed by epoxidation of the marine natural product (−)-clavukerin A (**8**).[10] Hydroazulene **8** can be prepared from (*S*)-citronellal (**9**) in only four steps using a combined organocatalytic/metal-catalyzed strategy.[11]

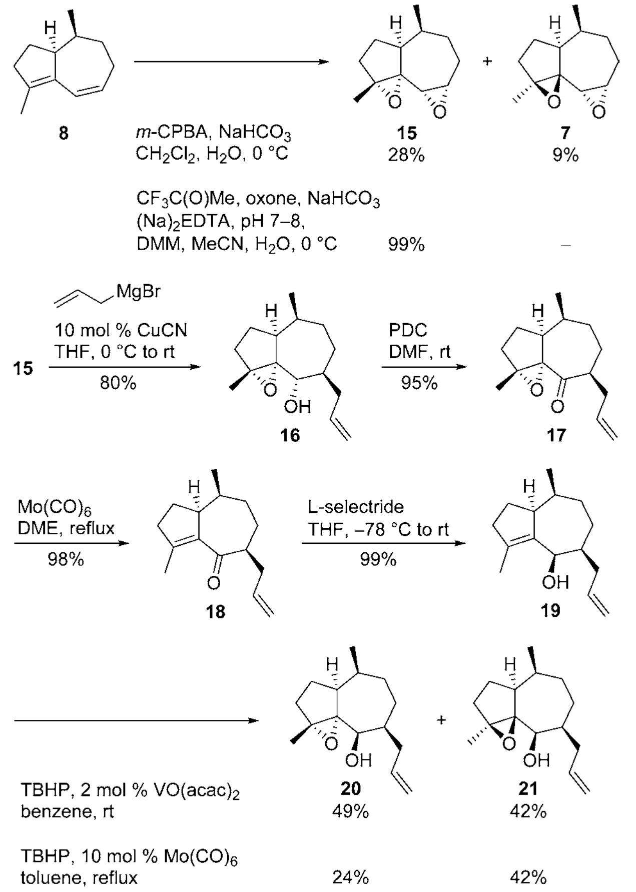
Since the chemoselectivity of the domino metathesis reaction of dienyne **11** to give hydroazulene **8** and hexalin **14** was only moderate (**8**:**14** = 2:1) so far,[11] we tried to improve this issue by application of a relay strategy (Scheme 2).[12] As before, asymmetric organocatalytic Michael addition of **9** to methyl vinyl ketone and subsequent chemoselective dibromoolefination efficiently led to ketone **10**,[11] which now was subjected to a Wittig reaction with unsaturated ylide **12**[13] followed by alkyne formation with butyllithium in a one-pot procedure.[14,15] The monosubstituted olefin of the resulting trienyne **13** was envisioned to react preferably with a ruthenium carbene complex to place the metal left to the triple bond after release of cyclopentene. Thus, higher selectivity for production of the desired hydroazulene was anticipated.[16] Indeed, using the Grubbs-II catalyst **G-II** in the presence of *p*-benzoquinone,[17] an efficient relay metathesis succeeded to give a 13:1 mixture of hydroazulene and hexalin, from which pure (−)-clavukerin A (**8**) was isolated in 92% yield. If the Grubbs catalysts **G-I** and **G-II** were used successively, the isomer ratio was even improved to 25:1, and the isolated yield of **8** increased to 96%.

Scheme 2. Improved Access to (−)-Clavukerin A (8) through Relay Metathesis



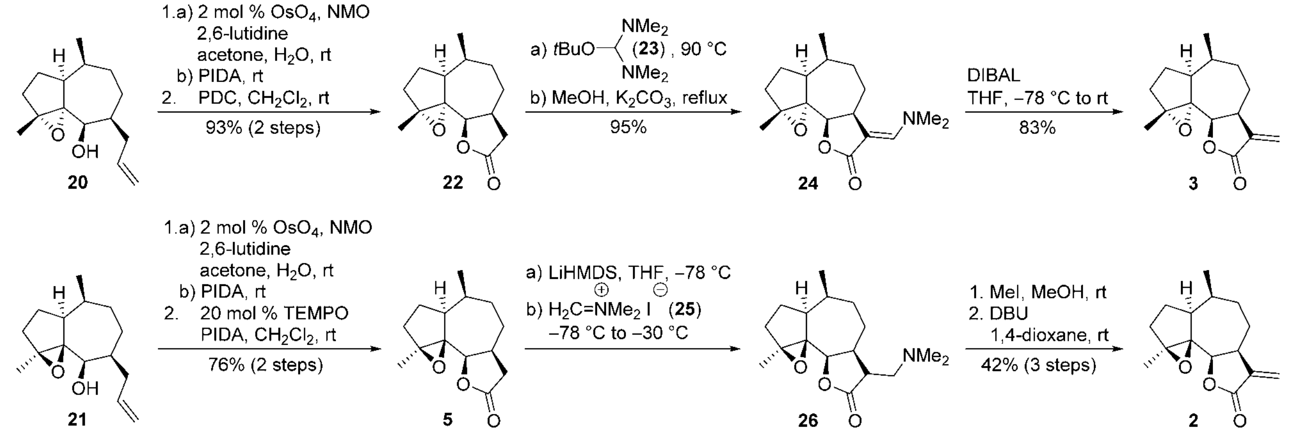
With this more selective access to (−)-clavukerin A (**8**), we then studied bisepoxidation of the 1,3-diene (Scheme 3). To our surprise, using *meta*-chloroperbenzoic acid we obtained the *anti* diepoxide **7** reported by Kitagawa and secured by X-ray diffraction analysis[10] only in small amounts next to the *syn* diepoxide **15** as the major product, while the total epoxide yield was rather low. Finally, we found that methyl(trifluoromethyl)-dioxirane[18] produces only **15** in nearly quantitative yield, and we could also confirm the relative configuration of this compound by X-ray diffraction analysis.[19] Due to the undesired configuration of the epoxide at the five-membered ring of **15**, we had to modify our synthetic strategy. As originally intended, we first studied opening of the diepoxide with different carbon nucleophiles. Whereas experiments with dilithiated acetic acid,[20] diethylethoxyalkynylalane,[20c,21] or a vinylcuprate[22] were not successful, reaction with an allylcopper species from allylmagnesium bromide and catalytic amounts of copper cyanide[23] afforded the desired product **16** cleanly in a completely chemo-, regio-, and diastereoselective fashion. Deoxygenation of the remaining epoxide then proceeded with high efficiency by oxidation of **16** with pyridinium dichromate[24] followed by reaction of the resultant epoxy ketone **17** with molybdenum hexacarbonyl[25] to give dienone **18**. Reduction of this substrate with the bulky hydride lithium selectride provided the desired *β*-alcohol **19** as a single stereoisomer. Unexpectedly, vanadium-catalyzed hydroxyl-directed epoxidation[26] of this alcohol with *tert*-butylhydroperoxide not only furnished the desired *β*-epoxide **21** but led to a 1.2:1 mixture of diastereomers **20** and **21**. Under catalysis with molybdenum hexacarbonyl,[26b] the *β*-epoxide **21** was formed preferentially, albeit with a lower total epoxide yield. As the unwanted *α*-epoxide **20** can be oxidized quantitatively with PDC in DMF to return epoxy ketone **17**, vanadium catalysis is overall more efficient, especially since separation of the diastereomeric epoxides **20** and **21** succeeds without problems.

Scheme 3. Conversion of (−)-Clavukerin A (8) into Epoxy Alcohol 21



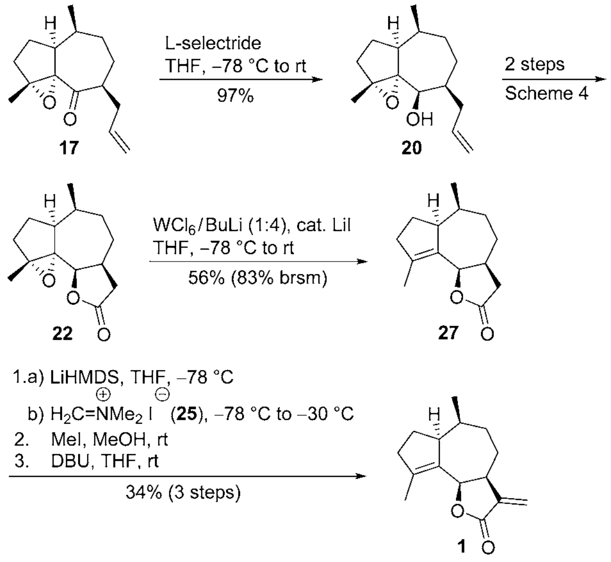
Before proceeding with *β*-epoxide **21** to the target molecule **2**, we tested a range of conditions for *α*-methylene *γ*-

Scheme 4. Completion of the Synthesis of Guaianolide 2 and Its C-4/C-5 Bisepimer 3



butyrolactone construction commencing with α-epoxy diastereomer **20** (Scheme 4). The optimum conditions found for conversion of this substrate to lactone **22** involved catalytic dihydroxylation with osmium tetroxide and subsequent 1,2-diol cleavage with (diacetoxyiodo)benzene[27] to give a mixture of cyclic hemiacetals followed by pyridinium dichromate oxidation.[28] The relative configuration of epoxy lactone **22** was unambiguously established by X-ray diffraction analysis.[19] Condensation of **22** with Bredereck's reagent **23**[29] then delivered enamino lactone **24** in high yield that was readily converted to α-methylene lactone **3** by DIBAL reduction.[30] Compound **3** turned out to be identical to the epoxy lactone obtained by Bohlmann through epoxidation of the guaianolide osmitopsin (**1**) with *meta*-chloroperbenzoic acid.[4a,31] Transformation of β-epoxide **21** into lactone **5** was best carried out by oxidative scission of the terminal olefin via dihydroxylation/1,2-diol cleavage as for **20** followed by oxidation with TEMPO and (diacetoxyiodo)benzene.[32] Epoxy lactone **5** also provided suitable crystals for X-ray diffraction analysis that unequivocally proved its relative configuration.[19] While condensation of **5** with Bredereck's reagent **23** led to the corresponding enamino lactone in high yield (91%), DIBAL reduction of this compound did not proceed as smoothly as for **24**, and furnished the target molecule **2** in 44% yield next to a presumed overreduction product, the separation of which was not trivial.[33] After considerable experimentation, we found that *exo* methylenation of **5** was best achieved by alkylation of the lactone enolate with Eschenmoser's salt **25**[6,34] under strict temperature control followed by quaternization of the resultant tertiary amine **26** with methyl iodide and β-elimination with DBU.[35] From this reaction sequence we finally isolated compound **2** in good overall yield. Surprisingly, the data obtained for this compound showed significant deviation from the values reported in the literature.[4a,36] Thus, we have to conclude that the structural assignment for 4,5-epoxyosmitopsin has been disproved by our synthesis of **2**. The natural product is most likely a diastereomer of structure **2**, and current efforts are devoted to identifying the correct stereochemistry.

Scheme 5. Streamlined Access to Epoxy Alcohol 20 and Synthesis of Guaianolide 1



For the synthesis of osmitopsin (**1**) the route depicted in Scheme 5 eventually turned out to give optimal results. Epoxy ketone **17** available in three steps from clavukerin A (**8**) was directly converted into epoxy alcohol **20** by L-selectride reduction, which saved two steps compared to its preparation from **8** according to Scheme 3. Transformation of **20** to epoxy lactone **22** as before then allowed a chemoselective epoxide deoxygenation with a lower valent tungsten halide to give olefinic lactone **27**.[37,38] Finally, *exo* methylenation of **27** was accomplished as for **5** using Eschenmoser's salt **25** to yield α-methylene lactone **1** as a colorless oil. This compound had ^1H NMR data identical to those reported for the guaianolide osmitopsin and furnished epoxy lactone **3** upon reaction with *meta*-chloroperbenzoic acid as described by Bohlmann.[4a,31,39]

Due to the relay metathesis strategy and the highly selective diepoxide opening reaction as the crucial elements of our synthetic route, only 14 steps were required to arrive at the sesquiterpene lactone osmitopsin (**1**) and 15 steps to secure the proposed structure of 4,5-epoxyosmitopsin (**2**) from (*S*)-citronellal (**9**). Moreover, with the improved access to (−)-clavukerin A (**8**) developed in the course of this synthesis, further applications of this compound as an advanced enantiomerically pure building block for structurally more complex hydroazulenes are easily foreseeable.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01619.

X-ray structure of **15** (CIF)
X-ray structure of **5** (CIF)
X-ray structure of **22** (CIF)
Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(19) CCDC 1449721 (**5**), CCDC 1449720 (**15**), and CCDC 1449722 (**22**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(36) Synthetic **2**: $[\alpha]_D^{22}$ −85.1 (*c* 0.52, CHCl$_3$), mp 85.4 °C, ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.59 (s, 3H, C-4 Me); natural **2**: $[\alpha]_D^{22}$ −203 (*c* 0.8, CHCl$_3$), mp 119.3 °C, ^{1}H NMR (100 MHz, CDCl$_3$): δ 1.34 (s, 3H, C-4 Me).[4a] ^{1}H NMR measurements with synthetic **2** in the presence of 20 mol % Eu(fod)$_3$ did not reproduce the shifts listed in ref 4a.

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(38) Subjecting α-methylene lactone **3** to these conditions failed to give **1**.

(39) CD measurements with more highly oxygenated derivatives of **1** also isolated from *Osmitopsis asteriscoides* indicate that the absolute configuration of synthetic **1** corresponds to the naturally occurring enantiomer.[4b]