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Total Synthesis of the Leucosceptroid Family of Natural Products

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Supporting Information

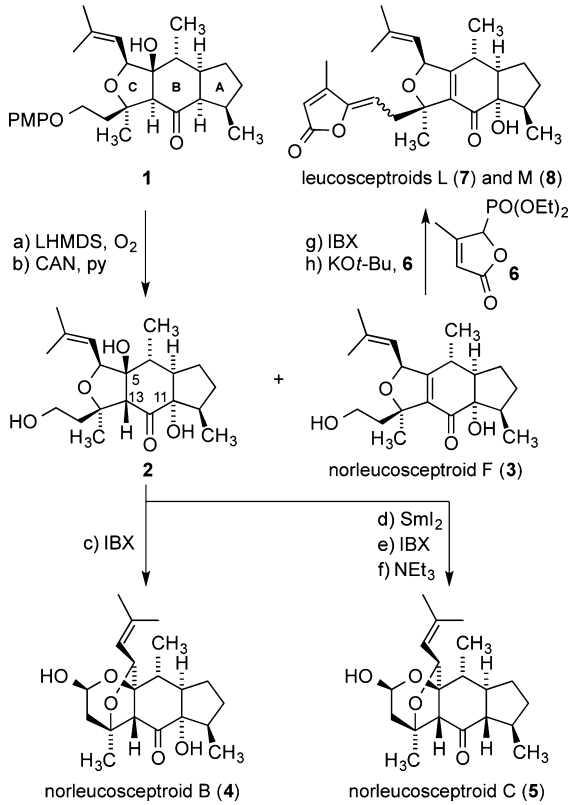
ABSTRACT: A highly efficient strategy enabled the asymmetric total synthesis of 15 antifeedant leucosceptroid natural products. The advanced tricyclic core, available in gram quantity, served as the pivotal intermediate for the preparation of norleucosceptroids B, C, F, and G and leucosceptroids A, B, G, I, J, L, and M. Additionally, the bioinspired oxidative transformation of leucosceptroid A to leucosceptroids C, K, O, and P using singlet oxygen supports the hypothesis that leucosceptroids A and B are most likely the biogenetic precursors of all other members of this natural product family.

Leucosceptroids A−Q and norleucosceptroids A−H are members of families of sesterterpenoids and pentanorsesterterpenoids, respectively, that have been isolated from *Leucosceptrum canum* Smith by Li and co-workers.[1,2] The potent antifeedant activities and novel molecular scaffolds of the leucosceptroids, comprising a 5,6,5-framework with a fully functionalized tetrahydrofuran ring and eight contiguous stereogenic centers, have attracted the attention of several research groups.[3] Concurrent with Ma's work,[3a] we became interested in the biogenetic relationship of the leucosceptroid natural products and hypothesized that two biosynthetic pathways are operative in *L. canum* Smith.[1f] Building upon the previously reported general entry to antifeedant sesterterpenoids,[4] we report the total synthesis of 15 members of the leucosceptroid family. The synthesis of leucosceptroids K (**9**), C (**19**), P (**20**), and O (**23**) was accomplished by the development of experimental conditions that mimic the biosynthetic oxidation, thus corroborating our proposal concerning the metabolic pathway in *L. canum* Smith.

Beginning from the tricyclic core **1**,[4] we first developed an improved route for the synthesis of norleucosceptroid B (**4**), which in the previous approach had been obtained only as a minor byproduct of norleucosceptroid A. As outlined in Scheme 1, we found that α-hydroxylation of **1** prior to cleavage of the *p*-methoxyphenyl ether followed by purification on deactivated silica gel favored the epimerization of H-13 to afford triol **2** together with norleucosceptroid F (**3**). Oxidation (IBX, DMSO, 23 °C)[5] of **2** furnished norleucosceptroid B (**4**), and exposure of **3** to the same conditions afforded norleucosceptroid G (see the Supporting Information for details). The latter was converted to leucosceptroids L (**7**) and M (**8**) (93%, *Z*:*E* = 2:1) by a Horner−Wadsworth−Emmons reaction with phosphonate **6**.[6]

Installation of the AB-*trans*-BC-*cis* ring fusion of norleucosceptroid C (**5**) proved to be unexpectedly challenging. While H-11 and H-13 of tricyclic core **1** were reluctant to undergo epimerization under basic conditions and elimination of OH-5 prevailed, the attempted direct conversion of **4** to **5** failed. Eventually, resorting to triol **2**, where epimerization of H-13 had occurred with ease after the introduction of OH-11,[7] allowed us to prepare the corresponding α-deoxygenated AB-*cis*-BC-*cis* annulated ketone by exposure to samarium(II) iodide.[8] To our surprise, epimerization of H-11 to form the AB-*trans*-BC-*cis* ring system could not be accomplished at this stage. However, oxidation under the established conditions afforded 11-*epi*-norleucosceptroid C, which upon exposure to

Scheme 1. Synthesis of Norleucosceptroids F (3), B (4), and C (5) and Leucosceptroids L (7) and M (8)[a]



[a]Reagents and conditions: (a) LHMDS, O_2, $P(OEt)_3$, THF, −78 to −20 °C; (b) CAN, pyridine, MeCN, H_2O, 0 °C, 21% **2** and 23% **3** over two steps; (c) IBX, DMSO, 23 °C, 56%; (d) SmI_2, THF, MeOH, 23 °C, ≥99%; (e) IBX, DMSO, 23 °C; (f) NEt_3, MeOH, 23 °C, 42% over two steps; (g) IBX, DMSO, 23 °C, 68%; (h) **6**, KO*t*-Bu, 0 to 23 °C, 93%, *Z*:*E* = 2:1.

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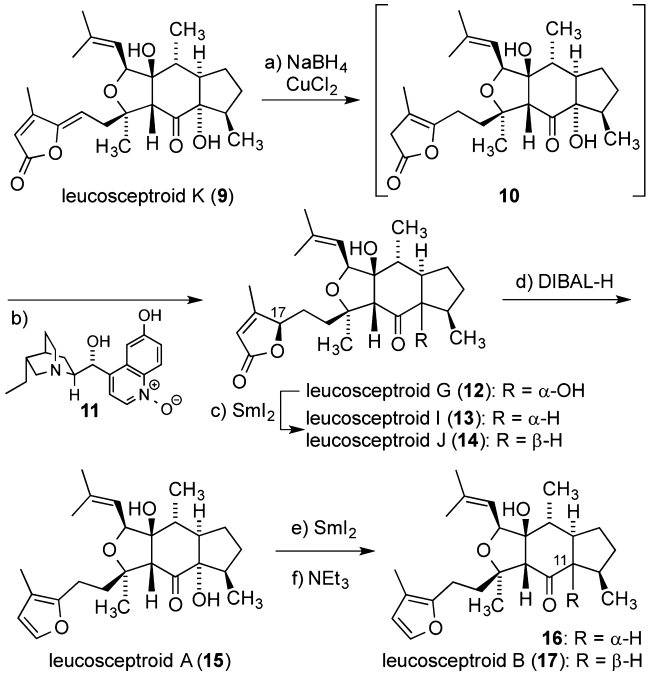
triethylamine in methanol at 23 °C for 24 h was fully converted to norleucosceptroid C (**5**) (42% yield over two steps). Only trace amounts of the 5,13-dehydrated byproduct were formed.

Using our optimized conditions for the extension of norleucosceptroid B,[4] we were able to produce 64 mg of leucosceptroid K (**9**) in a single batch. For its transformation to leucosceptroid G (**12**), we needed to develop a protocol for the selective installation of the remote C-17 stereocenter (Scheme 2). As direct hydrogenation of the C-16/C-17 double bond was

Scheme 2. Preparation of Leucosceptroids A (15), B (17), G (12), I (13), and J (14)[a]



[a]Reagents and conditions: (a) $NaBH_4$, $CuCl_2$, EtOH, 0 °C; (b) **11** (20 mol %), CH_2Cl_2, 0 °C, 70% over two steps, 7:1 d.r.; (c) SmI_2, THF, MeOH, 23 °C, 59%, **13**:**14** = 7:1; (d) DIBAL-H, CH_2Cl_2, −78 °C, then MeOH, aq. 2 M HCl, 23 °C, 75%; (e) SmI_2, THF, MeOH, 23 °C; (f) NEt_3, MeOH, 23 °C, 62%, **16**:**17** = 5:2.

not possible, we were confronted with the challenge of finding conditions to achieve a selective conjugate 1,6-reduction of **9** to *β*,*γ*-unsaturated butenolide **10**. Investigation of conditions reported by Baran[9] (sodium borohydride, cobalt(II) chloride) for the reduction of a somewhat similar system revealed that reduction of **9** under the analogous conditions was nonselective and afforded a mixture of products arising from 1,6- and 1,4-reduction. Further investigations using a combination of sodium borohydride with nickel(II) chloride[10] in ethanol were also unsatisfactory. Although the crude product mixture revealed that the reduction occurred with slightly improved selectivity for the desired 1,6-hydride addition, incomplete conversion of the starting material was observed at low temperatures, while partial hydrogenation of the propenyl side chain took place at temperatures above −25 °C. These difficulties prompted us to investigate the use of sodium borohydride in conjunction with copper(II) chloride, a reagent combination that appears to have received only little attention in the literature to date.[11] To our delight, treating an ethanolic solution of leucosceptroid K (**9**) with excess $CuCl_2$ and $NaBH_4$ at 0 °C resulted in the formation of copper boride (Cu_2B) as a finely divided black precipitate[12] and cleanly furnished *β*,*γ*-unsaturated butenolide **10**. The use of these conditions proved to be remarkable with respect to both the essentially complete 1,6-selectivity and the tolerance of all other functional groups. The installation of the C-17 stereocenter was then realized by employing a methodology developed by Deng[13] for asymmetric olefin isomerization via proton transfer catalysis. Treating crude *β*,*γ*-unsaturated butenolide **10** with cinchona alkaloid-derived catalyst **11** led to the formation of leucosceptroid G (**12**) with good selectivity (7:1 d.r.) in high yield (70% over two steps).[14]

While *α*-deoxygenation of **12** gave rise to leucosceptroid I (**13**) and traces of its H-11 epimer leucosceptroid J (**14**), DIBAL-H reduction followed by acidic workup furnished leucosceptroid A (**15**) in 75% yield.[15,16] For the synthesis of leucosceptroid B (**17**), **15** was *α*-deoxygenated to afford known ketone **16**.[3b] Unfortunately, the epimerization conditions that had efficiently converted the AB-*cis*-BC-*cis* ring system to the AB-*trans*-BC-*cis* one in the synthesis of norleucosceptroid C (**5**) (vide supra) proved to be not as successful in this case. While for **5** the AB-*trans* ring fusion might prevent unfavorable interactions between the lactol moiety and the A ring, the absence of such transannular strain in **16** and **17** leads to a much smaller energetic difference between the two H-11 epimers. Discontinuing the epimerization of **16** after 4.5 h completely avoided the elimination of 5-OH and provided **16** and leucosceptroid B (**17**) as a 5:2 mixture (62% yield).[17]

Having developed an efficient route for the preparation of leucosceptroid A (**15**), our next challenge was its biomimetic photo-oxidation[1f] to access leucosceptroids C (**19**), P (**20**), and O (**23**) (Scheme 3). These studies were also guided by our interest in finding the biosynthetic precursor of the intriguing spirocycle **23**, an issue that raised uncertainty at the outset of our investigations since several members were considered as potential candidates. Initial attempts to convert **15** to **19** showed that the [4 + 2] cycloaddition of singlet oxygen with the furan moiety occurred rapidly.[18] However, the reaction appeared to stall during the ensuing efforts to induce the intramolecular aldol reaction that forms the hydroxycyclopentenone ring in **19**. After a detailed analysis of the reaction mixture, it became apparent that the methoxy acetal intermediate (resulting from nucleophilic addition of methanol to *endo*-peroxide **18** followed by reduction with dimethyl sulfide) was remarkably stable and did not convert to the crucial *γ*-keto aldehyde under the reaction conditions. Hence, an optimized procedure was developed in which the reaction mixture was concentrated at the stage of the methoxy acetal intermediate and the residue was chromatographed on silica gel to unmask the *γ*-keto aldehyde functionality. The subsequent base-induced intramolecular aldol reaction occurred smoothly and produced leucosceptroid C (**19**) and its diastereomer in 78% yield (1:1 d.r.). Next, the synthesis of leucosceptroid P (**20**) could be accomplished by replacing methanol with a non-nucleophilic solvent and conducting the photo-oxidation in the presence of base. Irradiation of a solution of leucosceptroid A (**15**) in oxygen-saturated dichloromethane containing a catalytic amount of tetraphenylporphyrin (TPP) and *N*,*N*-diisopropylethylamine cleanly produced **20** (85% yield), the product of a Kornblum−DeLaMare-type rearrangement[19] of *endo*-peroxide **18**.

Finally, we turned our attention to the challenge of preparing leucosceptroid O (**23**) in a biomimetic manner. The initial plan to hydrolyze the lactone in leucosceptroid K (**9**) to afford the corresponding *γ*-keto acid and effect an acid-mediated

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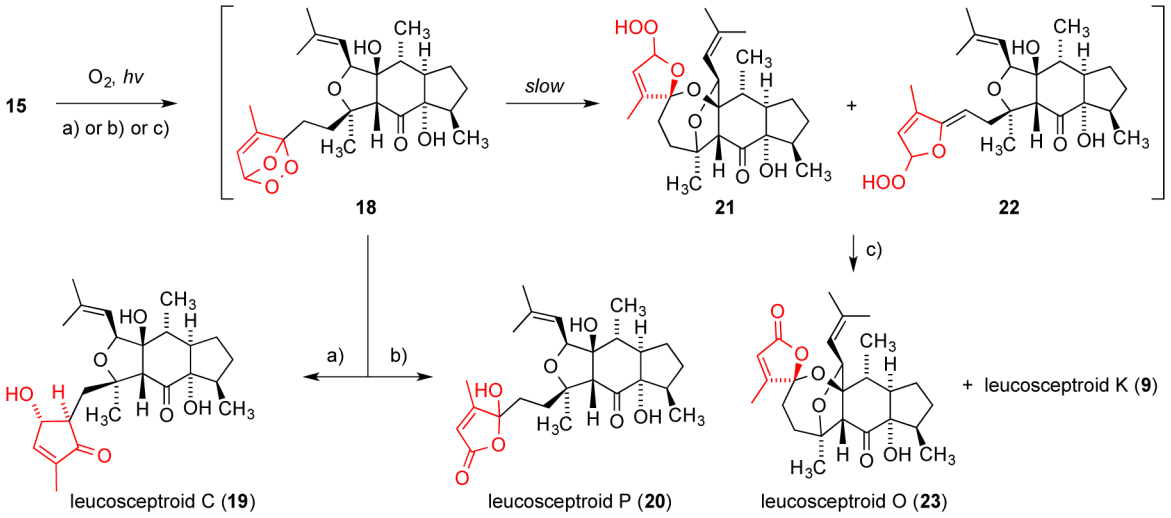
Scheme 3. Bioinspired Photo-oxidation of Leucosceptroid A: Synthesis of Leucosceptroids K (9), C (19), P (20), and O (23)[a]



[a]Reagents and conditions: (a) O_2, *hν*, rose bengal, MeOH, −78 °C, then DMS, 23 °C, then chromatography, then NEt_3, CH_2Cl_2, 23 °C, 78%, 1:1 d.r.; (b) O_2, *hν*, DIPEA, TPP, CH_2Cl_2, −78 °C, 85%; (c) O_2, *hν*, TPP, CD_2Cl_2, −78 to 23 °C, 3 h, then Ac_2O, pyridine, 23 °C, 26% **23** and 34% **9**.

spiroketalization was unsuccessful in our hands.[20] Although leucosceptroid P (**20**) was also regarded as a promising precursor for the synthesis of **23** by virtue of intramolecular ketalization, the envisioned cyclization could not be accomplished under various conditions. After considering several biosynthetic precursors, we hypothesized that all of the leucosceptroid natural products are in fact derived from two parent members, leucosceptroids A (**15**) and B (**17**). Thus, we returned to the biomimetic photo-oxidation and monitored the reaction after exposure of **15** to singlet oxygen by ^{1}H NMR spectroscopy (see the Supporting Information for details). Under strictly anhydrous conditions we were able to observe the clean formation of a 1:1 mixture of diastereomeric *endo*-peroxides **18**.

While standing in solution at 23 °C, **18** slowly (3 h) underwent competing spirocyclization and elimination to afford hydroperoxides **21** and **22**, respectively. Treating this mixture with acetic anhydride and pyridine gave leucosceptroid O (**23**) (26%) and leucosceptroid K (**9**) (34%) after purification by column chromatography on silica gel. Under the assumption that this reaction sequence mimics the biosynthetic oxidation of leucosceptroid A (**15**), it sheds light on the fact that the corresponding *E* isomer of leucosceptroid K (**9**) is unknown. On the basis of a series of optimized structures at the B3LYP/6-31G(d) computational level,[21] we believe that hydrogen bonding between OH-5 and the *endo*-peroxide, as depicted for **18** and **18′** (Figure 1), results in such an orientation that elimination leads to exclusive formation of the *Z* double bond, as observed for leucosceptroid K (**9**). In the case of the photo-oxidation precursor of leucosceptroids L (**7**) and M (**8**),[22] the absence of such a hydrogen-bonding interaction would lead to no preferred orientation of the *endo*-peroxide moiety, resulting in the formation of both double-bond isomers in nature.

In conclusion, our general entry to the synthesis of antifeedant sesterterpenoid natural products enabled the synthesis of 15 complex leucosceptroid members, whose spectroscopic data (^{1}H and ^{13}C NMR, HRMS, $[\alpha]_D$) were in full agreement with those reported for the naturally occurring substances. Additionally, the conducted biomimetic photo-oxidation disclosed that leucosceptroids A and B are most likely the parent members of all other known leucosceptroids.

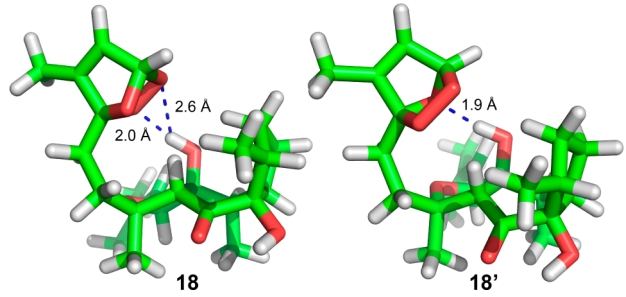


Figure 1. DFT-optimized structures of the diastereomeric *endo*-peroxides **18** and **18′** showing the crucial hydrogen-bonding interaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, NMR spectra of products, comparison of natural and synthetic leucosceptroids, and complete ref 21. 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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(16) Direct reduction of **9** or **10** to give **15** was unsuccessful. DIBAL-H reduction of the lactone in **10** led to the formation of the corresponding γ-keto aldehyde.

(17) Extending the epimerization time to 24 h gave **16** and **17** in a slightly improved ∼3:1 ratio. However, a considerable amount of the OH-5-eliminated product was formed.

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(22) To date, the 5,13-dehydrated analog of leucosceptroid A (**15**), which would constitute the precursor of leucosceptroids L (**7**) and M (**8**), has not been isolated from natural sources, yet its existence is likely.

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