Bioinspired synthesis of pentacyclic onocerane triterpenoids†

Florian Bartels, a, b Young J. Hong, b Daijiro Ueda, c, * Manuela Weber, a, * Tsutomu Sato, a, c Dean J. Tantillo, a, b and Mathias Christmann, a, *

The first chemical synthesis of pentacyclic onocerane triterpenoids has been achieved. A putative biomimetic tricyclization cascade is employed to forge a fused decalin-/oxepane ring system. The synthetic route proceeds to (+)-cupacinoxepin in seven steps and to (+)-onoceranoxide in eight steps in the longest linear sequence, when starting from geranyl chloride and (+)-sclareolide. The bioinspired epoxypolyene cyclization is supported by computational and enzymatic studies.

Triterpenoids constitute an important family of diverse natural products with unique biological activities. Their structural complexity is generated by cyclase enzymes that convert simple acyclic isoprenoid precursors into polycyclic molecules. For example, onocerane triterpenes were shown to be biosynthesized from squalene (1) or its oxidized derivatives (2, 3) by cyclizations initiated at both termini. The intermediates and products can be distinguished by their oxidation level (OL), (carbo-)cyclization level (CL), and the hydration level (HL), i.e. the number of incorporated water molecules. Following core assembly, functional group modifications (FGMs) or C–H-oxidations may occur (Scheme 1). In a bioassay-guided screening for anti-malarial compounds, Schuehly and coworkers reported the isolation of a novel triterpenoid from the bark of Cupania cinerea. Cupacinoxepin (4) showed moderate activity against the Plasmodium falciparum K1 strain (8.7 µM) and features a novel fused pentacyclic onocerane scaffold composed of three six-membered carbocycles and two oxepanes. Although data from a single crystal suitable for X-ray crystallography was obtained, the absolute configuration could not be determined. Previous synthetic work on the onoceranes was focused on the tetracyclic C22-symmetrical congeners onocerandiol (5) and α-onocerin (6). The biosynthesis of onoceranoxide (7) and α-onocerin (6) via 8 was hypothesized to proceed via cyclization of squalene and diepoxysqualene, respectively (Scheme 1). This process was elegantly mimicked by Corey’s double allylsilane epoxypolyene cyclization. However, the highly substituted oxepane in cupacinoxepin (4) and onoceranoxide (7) required a novel synthetic strategy.

Chemical synthesis of ditertiary ethers is a daunting task. Unfortunately, the seemingly obvious approach to form the oxepane from two tertiary alcohols is outpaced by competing cationic pathways. Inspired by the cyclization of squalene to 7 via 9 catalyzed by Bacillus megaterium tetraprenyl-β-curname cyclase (BmεTC), we identified myrrhanol C (11) or epoxy dienol 12 as potential precursors for the synthesis of 10. While the actual biosynthetic pathway is unknown, the realization of an epoxypolyene tricyclization appeared more feasible in a laboratory setting. Finally, oxidation of the secondary alcohol 10 to cupacinoxepin (4) (via the intermediary of a ketone) completes the putative biosynthesis. Only a few examples of polynene cyclizations using tertiary alcohols as nucleophiles are known, and to the best of our knowledge polynene tricyclizations using tertiary alcohols to form oxepanes have only been achieved enzymatically so far. In order to probe this key cyclization (12 → 10) in the laboratory, we selected epoxy dienol 12 as our retrosynthetic target (Scheme 2).

We envisioned the cyclization precursor 12 to be generated in a B-alkyl Suzuki-Miyaura coupling between an alkylborane derived from 13 and vinyl iodide. The two fragments were traced back to the readily available starting materials (+)-sclareolide (15) and geranyl chloride (16), respectively.

The synthesis of fragment 13 started with the conversion of 15 into the corresponding benzyl ether 17 using a one-pot reduction/alkylation sequence (Scheme 3). To this end, reduction of (+)-sclareolide with LiAlH₄ in THF at 0 °C was followed by treatment with Rochelle salt, DMF, KOH and 2-MeC₆H₄CH₂Br to afford benzyl ether 17 in excellent yield. A [2,3]-Wittig-type fragmentation mediated by n-BuLi directly yielded
The subtle deviation of the ether group from the literature-known benzyl ether to its 2-Me-benzyl derivative increased the yield from 21% to 44%. A screening of different ether derivatives showed alkyl substituents with benzylic hydrogen atoms in the 2-position of the aromatic ring to give higher yields of 13. Moreover, we observed a temperature dependence of the fragmentation yield, maximizing at \( \frac{1}{C_0} \text{C} \) to \( \frac{1}{C_0} \text{C} \text{C} \). The conformation of 13 was confirmed by X-ray crystallography.

Vinyl iodide 14 was prepared from geranyl chloride via nucleophilic substitution with lithiated \( \text{CH}_3\text{C}_2\text{H}_5\) followed by desilylation with TBAF (Scheme 4). Negishi’s zirconium-catalyzed carboalumination of 19 with \( \text{AlMe}_3 \) and subsequent trapping of the vinyl aluminium intermediate with iodine afforded vinyl iodide 20. Dihydroxylation of the dimethyl-substituted alkene with the \( \text{(DHQD)}_2\text{PHAL} \) ligand \( \text{33\% yield, 97\% ee} \) proceeded with low position-selectivity which is reflected by the small amount of recovered starting material \( \text{25\%} \). Using the Corey–Noe–Lin (CNL) ligand \( \text{49\% of} \) increased the position-selectivity to give the terminal diol in \( \text{36\% yield (94\% ee)} \) with \( \text{49\% of} \) fragment 13 in an acceptable yield of 44% over two steps. The subtle deviation of the ether group from the literature-known benzyl ether to its 2-Me-benzyl derivative increased the yield from 21% to 44%. A screening of different ether derivatives showed alkyl substituents with benzylic hydrogen atoms in the 2-position of the aromatic ring to give higher yields of 13. Moreover, we observed a temperature dependence of the fragmentation yield, maximizing at \( -13 \text{°C} \). The configuration of 13 was confirmed by X-ray crystallography. Vinyl iodide 14 was prepared from geranyl chloride via nucleophilic substitution with lithiated followed by desilylation with TBAF (Scheme 4). Negishi’s zirconium-catalyzed carboalumination of 19 with \( \text{AlMe}_3 \) and subsequent trapping of the vinyl aluminium intermediate with iodine afforded vinyl iodide 20. Dihydroxylation of the dimethyl-substituted alkene with the \( \text{(DHQD)}_2\text{PHAL} \) ligand \( \text{33\% yield, 97\% ee} \) proceeded with low position-selectivity which is reflected by the small amount of recovered starting material \( \text{25\%} \). Using the Corey–Noe–Lin (CNL) ligand \( \text{49\% of} \) increased the position-selectivity to give the terminal diol in \( \text{36\% yield (94\% ee)} \) with \( \text{49\% of} \).
The structures of oxepane 10 and p-Br-benzoate derivative 22 were confirmed by X-ray crystallography. Despite its rather low yield, the cyclization generated four stereogenic centers and the remaining carbon skeleton in a single transformation. Additionally, the secondary alcohol in 10 might serve as a handle in future SAR studies and enable the evaluation of this class of pentacyclic onocerane triterpenoids as potential antimalarial drug leads. In addition, recent work in the field of C–H functionalization has demonstrated the scarelolide scaffold to be amenable for the selective introduction of other functional groups. Next, the major cyclization product 10 was subjected to a one-pot Dess–Martin/Baeyer–Villiger oxidation to afford cupacinoxepin in 66% yield (1.7% overall yield starting from 16). The spectroscopic data, including the optical rotation, matched those reported in the literature, thereby determining the absolute configuration of (+)-cupacinoxepin. In addition, we were able to obtain a crystal suitable for the direct determination of the absolute configuration of 4 by X-ray crystallography. Onoceranoxide 7 was formed from 10 via formation of the thiocarbamate and subsequent reduction with tributyltin hydride in 77% yield (2 steps) (2.0% overall yield starting from 16). The spectroscopic data matched those reported in the literature.

In order to investigate the mechanism of the epoxypolyene cyclization in more detail and to get insight into the low selectivity for the desired trans–anti–trans pathway, well established density functional theory (DFT) methods were applied (mpPW1PW91/6-31+G(d,p)/B3LYP/6-31+G(d)). Two epimeric trans-decalin-type structures (S-epimer 23 and R-epimer 24, Scheme 6) were predicted, based on inherent reactivity preferences (i.e., in the absence of solvent or enzyme), to result from epoxypolyene cyclization, consistent with previous work by Corey and Shenvi on related systems. The predicted major intermediate 23 is derived from a chair–chair conformation, while 24 is derived from a chair–boat conformation.

For 23, 7-membered ring formation was predicted to be preferred over other pathways by several kcal mol⁻¹. For 24, 1,2-hydride shift to form 25/6-membered ring formation was predicted to be preferred over formation of a 7-membered ring by several kcal mol⁻¹. As shown in the transition state structure for formation of 25, the hydride shift appears to be assisted by the tertiary hydroxyl group (via a favorable electrostatic interaction between the partially negatively charged oxygen and the partially positively charged migrating hydrogen; related interactions have been described previously). In addition, the biosynthetic relevance of the epoxypolyene cyclization was probed by incubation of 12 with BmeTC. GC-MS analysis revealed the formation of 10 along with an elimination product. The absence of 21 indicates the influence of BmeTC in overriding inherent reactivity and enforcing the chair–chair conformation leading to 10.

In conclusion, we have provided access to a new class of pentacyclic onocerane triterpenoids. Additionally, we have completed the first asymmetric synthesis of antiprotozoal agent (+)-cupacinoxepin and (+)-onoceranoxide and determined their absolute configuration. By using an epoxypolyene cascade cyclization as the key step, we were able to rapidly assemble the recovered alkene. Mesylation of the secondary alcohol and subsequent treatment with K₂CO₃ afforded epoxydien 14 in 81% yield. With alkene 13 and vinyl iodide 14 in hand, the crucial coupling was investigated (Scheme 5). Treatment of alkene 13 (neat) with 9-BBN dimer at 85 °C for 4 h led to the expected borane, which was directly used in the B-aryl Suzuki–Miyaura reaction to afford epoxydien 12 in 77% yield on gram scale. The stage was then set to examine the putative biometric tricyclization. We anticipated the formation of the oxepane to be unfavorable both for entropic and enthalpic reasons. A variety of Brønsted and Lewis acids failed to give the desired product, but gratifyingly, treatment of 12 with EtAlCl₂ at −78 °C under high dilution (CH₂Cl₂, 1 mM) afforded a separable mixture of target compound 10 (20%) along with another pentacyclic product 21 (12%). Spiroyclic motifs similar to 21 have been found in several bioactive natural products. Further conditions for the tricyclization of 9 were investigated but no product formation could be observed.
fused pentacyclic structure in a single synthetic operation. The putative biosynthetic precursor was assembled from two terpene derived fragments using a B-alkyl Suzuki–Miyaura reaction. Our synthetic route to cupacinoxepin consists of seven steps from geranyl chloride, four of which are C–C bond formations.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Studienstiftung des deutschen Volkes for a doctoral Fellowship [F. B.], Buchler GmbH (Braunschweig) for a generous donation of dihydrochinidin–hydrochloride, Joanna Najdek, Anna Timofeeva, Lucine V. Gabriel, Ryan Allen for experimental assistance with the [2,3]-Wittig-type fragmentation, Tobias Olbrisch for the isolation of cupacinoxepin, and CHE-030089 [Ported by the US National Science Foundation (CHE-1565933 and 16K14911 (to T. S.).

Notes and references

46 See ESI† for details.
59 Direct conversion of the primary alcohol into a leaving group and subsequent elimination was outcompeted by intramolecular substitution forming ambroxide.
60 CCDC 1529115 (13), 1529116 (4), 1529117 (22), 1529118 (10) contain the supplementary crystallographic data for this paper.†
68 Determination of the absolute configuration by Mosher ester analysis.
Chemical Science