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Bioinspired synthesis of pentacyclic onocerane triterpenoids†

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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.[1] Their structural complexity is generated by cyclase enzymes that convert simple acyclic isoprenoid precursors into polycyclic molecules.[2,3] For example, onocerane triterpenes were shown to be biosynthesized from squalene (**1**) or its oxidized derivatives (**2**, **3**) by cyclizations initiated at both termini.[4] 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[5] 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*.[6] 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.[6] Previous synthetic work on the oncerranes[7–10] was focused on the tetracyclic C_2-symmetrical congeners onocerandiol (**5**)[11–14] and α-onocerin (**6**).[15–22] The biosynthesis of onoceranoxide (**7**)[23] and α-onocerin (**6**) *via* **8**[24,25] 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.[16] However, the highly substituted oxepane in cupacinoxepin (**4**) and onoceranoxide (**7**)[26,27] required a novel synthetic strategy.

Chemical synthesis of ditertiary ethers is a daunting task.[28–38] Unfortunately, the seemingly obvious approach to form the oxepane from two tertiary alcohols is outpaced by competing cationic pathways.[13,14] Inspired by the cyclization of squalene to **7** *via* **9** catalyzed by *Bacillus megaterium* tetraprenyl-β-curcumene cyclase (BmeTC),[23] we identified myrrhanol C (**11**)[39] or epoxy dienol **12** as potential precursors for the synthesis of **10**. While the actual biosynthetic pathway is unknown, the realization of an epoxydiene tricyclization appeared more feasible in a laboratory setting. Finally, oxidation of the secondary alcohol **10** to cupacinoxepin (**4**) (*via* the intermediacy of a ketone) completes the putative biosynthesis. Only a few examples of polyene cyclizations[40–45] using tertiary alcohols as nucleophiles are known,[46–48] and to the best of our knowledge polyene tricyclizations using tertiary alcohols to form oxepanes have only been achieved enzymatically so far.[23,49] 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 **14**.[50] The two fragments were traced back to the readily available starting materials (+)-sclareolide (**15**) and geranyl chloride (**16**), respectively.[51–53]

The synthesis of fragment **13**[54] started with the conversion of **15** into the corresponding benzyl ether **17** using a one-pot[55,56] reduction/alkylation sequence (Scheme 3). To this end, reduction of (+)-sclareolide with $LiAlH_4$ in THF at 0 °C [57] was followed by treatment with Rochelle salt, DMF, KOH and 2-Me-$C_6H_4CH_2Br$ to afford benzyl ether **17** in excellent yield. A [2,3]-Wittig-type fragmentation mediated by *n*-BuLi directly yielded

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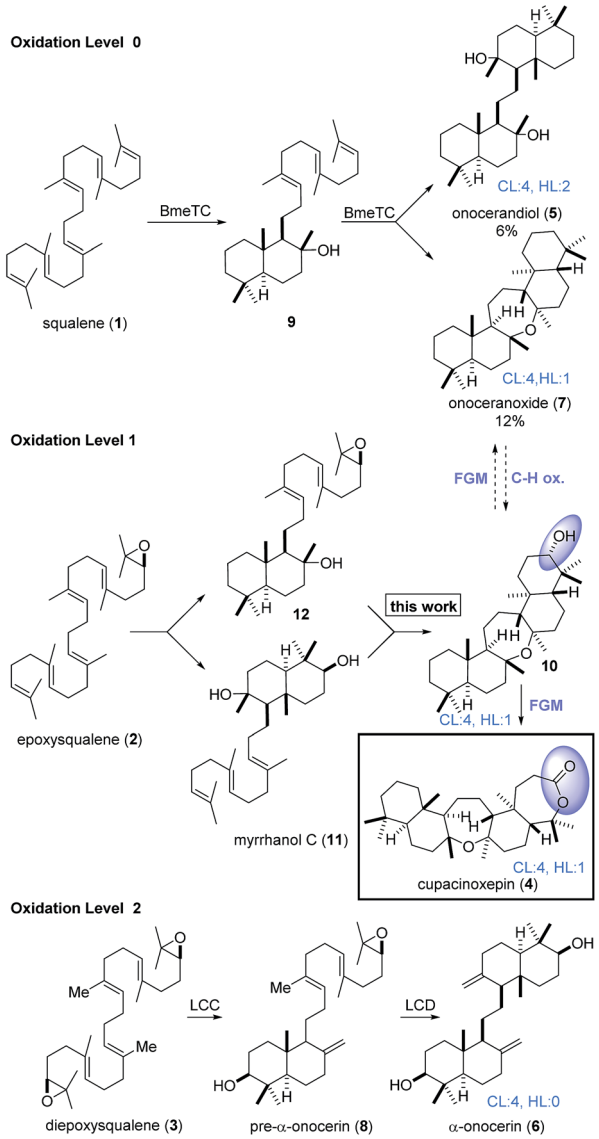
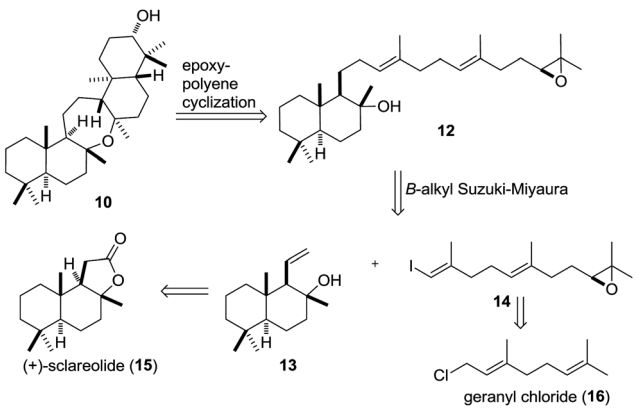
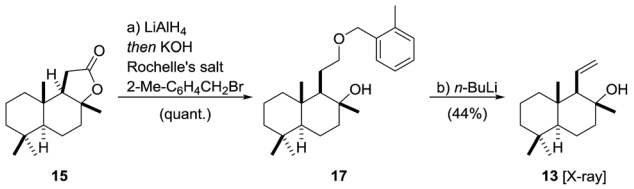


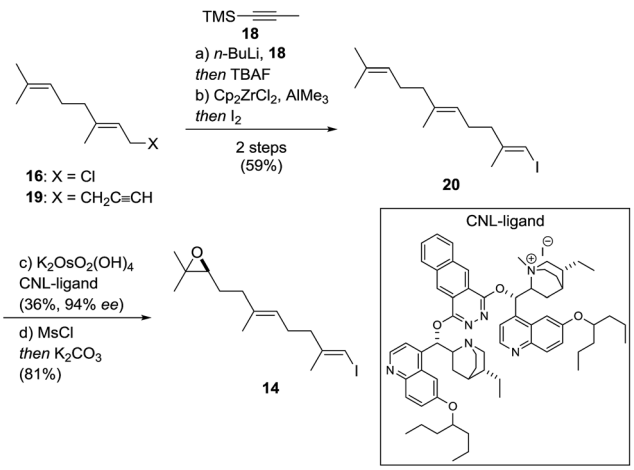
Scheme 1 Core assembly of onocerane triterpenes with regard to the oxidation level (OL), cyclization level (CL) and the hydration level (HL). LCC and LCD = *Lycopodium clavatum* C and D respectively.



Scheme 2 Retrosynthetic analysis of **10** based on an epoxypolyene cyclization of precursor **12**.



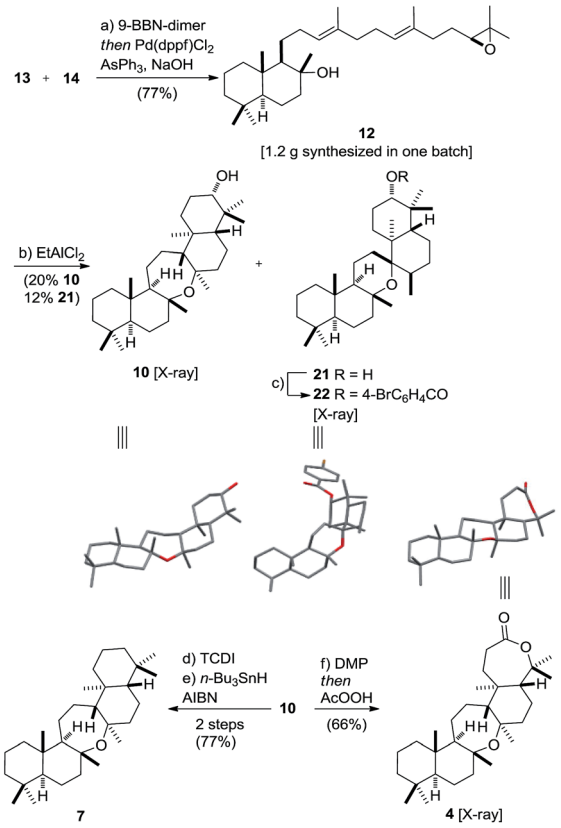
Scheme 3 Synthesis of fragment **13**. Reagents and conditions: (a) $LiAlH_4$ (0.7 eq.), THF, 0 °C, 40 min then 2-Me-$C_6H_4CH_2Br$ (2.1 eq.), KOH (4.0 eq.), Rochelle's salt (1.2 eq.), DMF, 45 °C, 27 h, quant.; (b) *n*-BuLi (4.0 eq.), THF, −78 °C, 10 min to −13 °C, 90 min, 44% (over 2 steps).



Scheme 4 Synthesis of fragment **14**. Reagents and conditions: (a) *n*-BuLi (1.2 eq.), **18** (1.2 eq.), THF, −78 °C, 2.5 h then TBAF (1.3 eq.), −78 °C to 23 °C, 24 h, 82%; (b) Cp_2ZrCl_2 (0.25 eq.), $AlMe_3$ (3.0 eq.), H_2O (1.0 eq.), CH_2Cl_2, −23 °C, 1 h then I_2 (1.2 eq.), THF, −23 °C to 23 °C, 16 h, 72%; (c) $K_2OsO_2(OH)_4$ (0.3 mol%), CNL-ligand (0.2 mol%), $K_3Fe(CN)_6$ (3.0 eq.), $MeSO_2NH_2$ (1.0 eq.), K_2CO_3 (3.0 eq.), *t*-BuOH, H_2O, 1 °C, 53 h, 36%, 94% ee, and 49% of **20**; (d) MsCl (1.1 eq.), pyridine (15 eq.), CH_2Cl_2, 0 °C to 23 °C, 18 h then K_2CO_3 (10 eq.), MeOH, 2.5 h, 81%.

fragment **13** in an acceptable yield of 44% over two steps.[58,59] 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 °C.[46] The configuration of **13** was confirmed by X-ray crystallography.[60]

Vinyl iodide **14** was prepared from geranyl chloride *via* nucleophilic substitution with lithiated **18**[61] followed by desilylation with TBAF (Scheme 4). Negishi's zirconium-catalyzed carboalumination[62,63] of **19** with $AlMe_3$ and subsequent trapping of the vinyl aluminium intermediate with iodine afforded vinyl iodide **20**.[64,65] Dihydroxylation of the dimethyl-substituted alkene with the $(DHQD)_2PHAL$ ligand[66] (33% yield, 97% ee) proceeded with low position-selectivity which is reflected by the small amount of recovered starting material (25%). Using the Corey–Noe–Lin (CNL) ligand[67] increased the position-selectivity to give the terminal diol in 36% yield (94% ee) with 49% of



Scheme 5 Synthesis of cupacinoxepin **4** and onoceranoxide **7**. Reagents and conditions: (a) **13** (1.4 eq.), 9-BBN dimer (2.8 eq.), 85 °C, 4 h then **14** (1.0 eq.), $Pd(dppf)Cl_2$ (0.1 eq.), $AsPh_3$ (0.4 eq.), NaOH (6.0 eq.), 1 °C, 17 h, 77%; (b) $EtAlCl_2$ (3.0 eq.), CH_2Cl_2 (1 mM), −78 °C, 1.5 h, 20% **10**, 12% **21**; (c) 4-BrC_6H_4COCl (5.0 eq.), 4-DMAP (20 eq.), 50 °C, CH_2Cl_2, 3 d, 73%; (d) TCDI (20 eq.), 4-DMAP (20 eq.), CH_2Cl_2, 70 °C 13.5 h, 83%; (e) *n*-Bu_3SnH (3.0 eq.), AIBN (cat.), toluene, 160 °C, 10 min to 120 °C, 20 min then *n*-Bu_3SnH (3.0 eq.), AIBN (cat.), 160 °C, 10 min to 120 °C, 20 min, 93%; (f) DMP (2.0 eq.), CH_2Cl_2, 23 °C, 4 h then AcOOH (10 eq.), NaOAc (20 eq.), 17 h then AcOOH (10 eq.), NaOAc (20 eq.), 5 h, 66%. DMP = Dess–Martin periodinane, TCDI = 1,1′-thiocarbonyldiimidazole, AIBN = azobisisobutyronitrile.

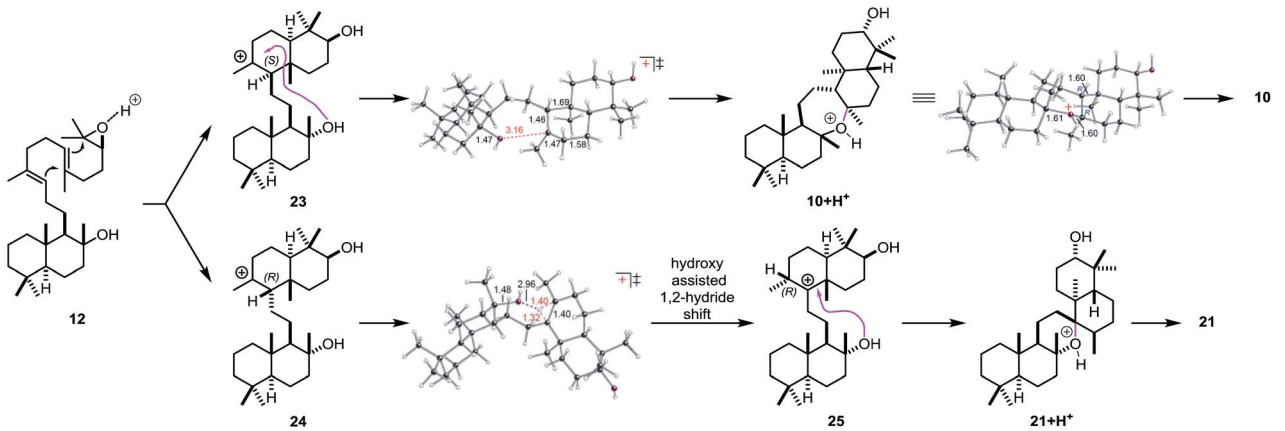
recovered alkene.[68] Mesylation of the secondary alcohol and subsequent treatment with K_2CO_3 afforded epoxide **14** in 81% yield.[69] With alkene **13** and vinyl iodide **14** in hand, the crucial coupling was investigated (Scheme 5). Treatment of alkene **13** (neat) with 9-BBN dimer at 85 °C for 4 h led to the expected borane, which was directly used in the *B*-alkyl Suzuki–Miyaura reaction[69–71] to afford epoxy dienol **12** in 77% yield on gram scale. The stage was then set to examine the putative biomimetic tricyclization.[72] We anticipated the formation of the oxepane to be unfavorable both for entropic and enthalpic reasons.[73] A variety of Brønsted and Lewis acids[46] failed to give the desired product, but gratifyingly, treatment of **12** with $EtAlCl_2$ at −78 °C under high dilution (CH_2Cl_2, 1 mM) afforded a separable mixture of target compound **10** (20%) along with another pentacyclic product **21** (12%).[74–76] Spirocyclic motifs similar to **21** have been found in several bioactive natural products.[77–80] Further conditions for the tricyclization of **9** were investigated but no product formation could be observed.[46]

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.[81,82] In addition, recent work in the field of C–H functionalization has demonstrated the sclareolide scaffold to be amenable for the selective introduction of other functional groups.[83–90] Next, the major cyclization product **10** was subjected to a one-pot Dess–Martin/Baeyer–Villiger oxidation[91–94] 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.[6] 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**).[95] The spectroscopic data matched those reported in the literature.[26]

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 (mPW1PW91/6-31+G(d,p)//B3LYP/6-31+G(d)).[46] 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),[96] to result from epoxydiene cyclization, consistent with previous work by Corey and Shenvi on related systems.[75,97] The predicted major intermediate **23** is derived from a chair–chair conformation, while **24** is derived from a chair–boat conformation.[75,80]

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).[98,99] 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.[46] 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 tricyclization as the key step, we were able to rapidly assemble the



Scheme 6 Carbocation rearrangements leading to **10** and **21**, modeled with H^+ in place of Lewis acid (LA).

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.

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