Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue



Cite this: *Chem. Sci.*, 2017, **8**, 8285

# Bioinspired synthesis of pentacyclic onocerane triterpenoids†

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Received 6th September 2017
Accepted 14th October 2017

DOI: 10.1039/c7sc03903d

rsc.li/chemical-science

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 oncerianes[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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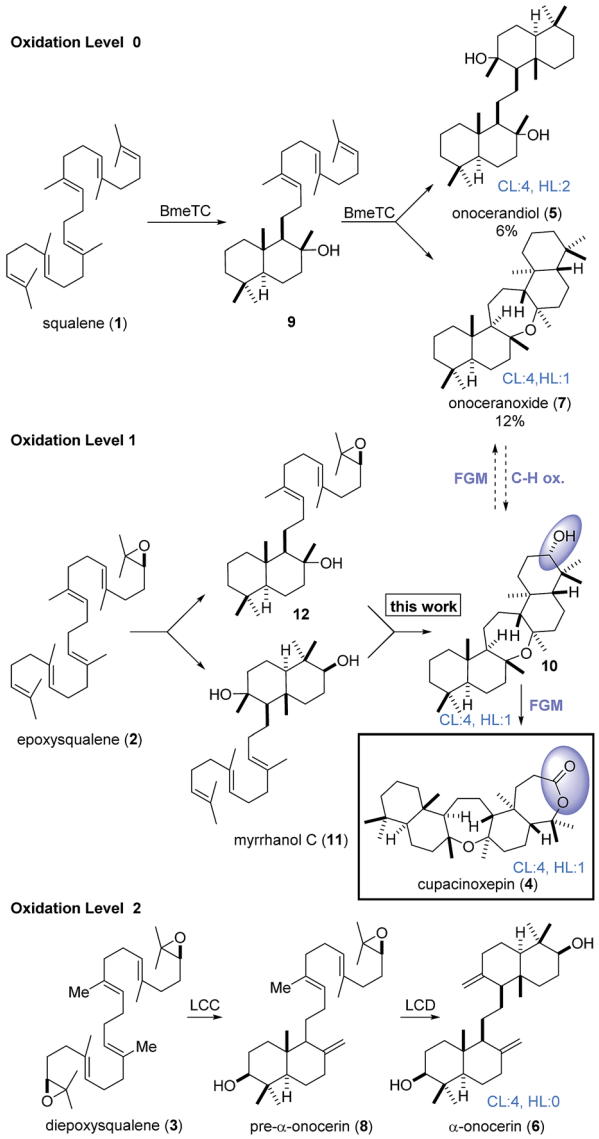
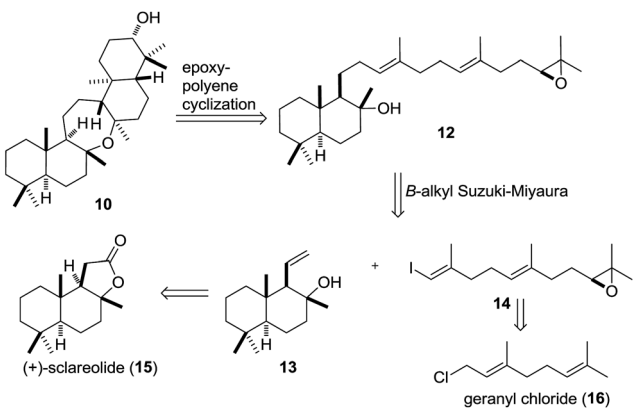
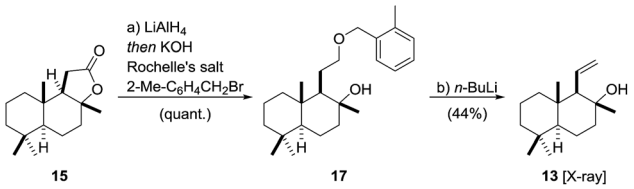
† Electronic supplementary information (ESI) available: Detailed experimental procedures, spectral data, DFT calculation, X-ray crystallographic data for **4** (CIF), **13** (CIF), **10** (CIF), **22** (CIF). CCDC 1529115–1529118. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7sc03903d



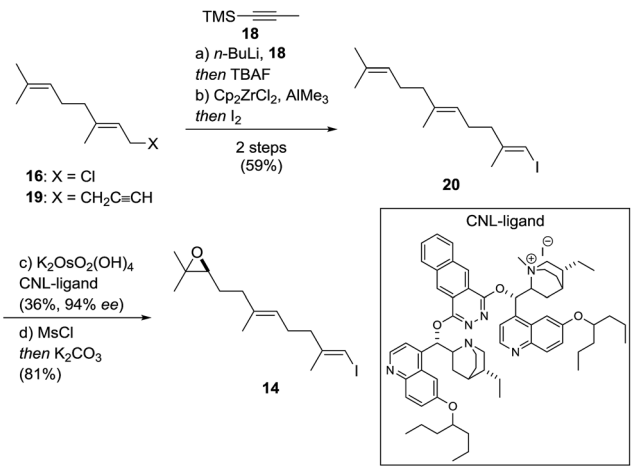

Scheme 1 Core assembly of onocerane triterpenes with regard to the oxidation level (OL), cyclization level (CL) and the hydration level (HL). LCC and LCD = *Lycopodium clavatum* C and D respectively.




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



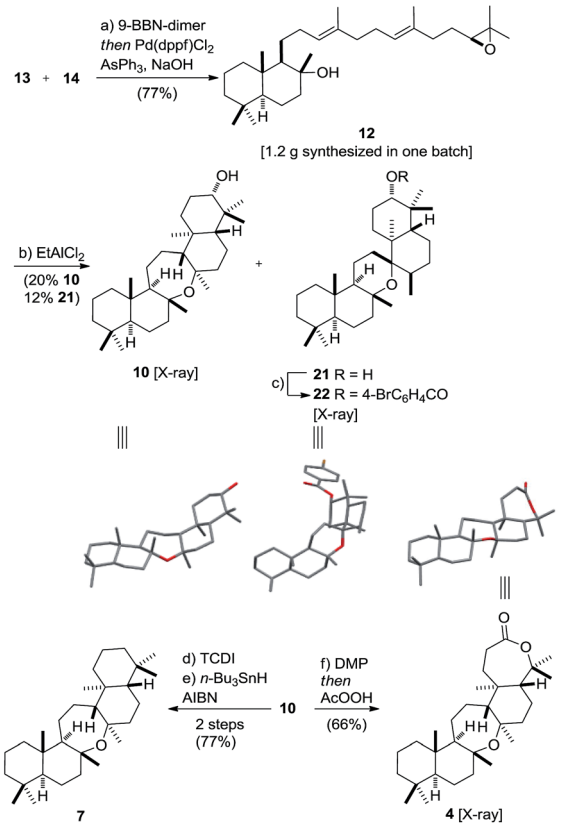

Scheme 3 Synthesis of fragment **13**. Reagents and conditions: (a) $LiAlH_4$ (0.7 eq.), THF, 0 °C, 40 min then 2-Me-$C_6H_4CH_2Br$ (2.1 eq.), KOH (4.0 eq.), Rochelle's salt (1.2 eq.), DMF, 45 °C, 27 h, quant.; (b) *n*-BuLi (4.0 eq.), THF, −78 °C, 10 min to −13 °C, 90 min, 44% (over 2 steps).




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.

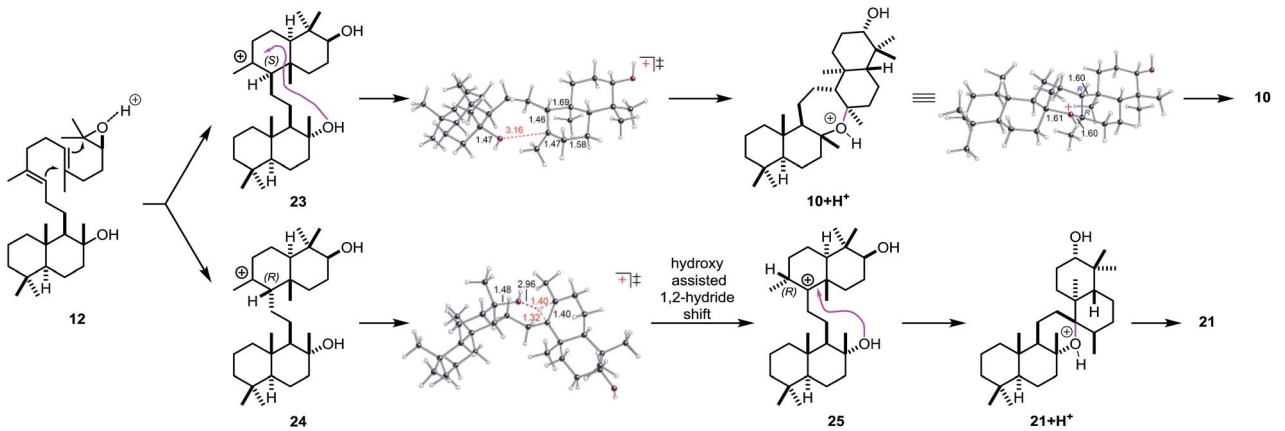
recovered alkene.[68] Mesylation of the secondary alcohol and subsequent treatment with $K_2CO_3$ afforded epoxide **14** in 81% yield.[69] With alkene **13** and vinyl iodide **14** in hand, the crucial coupling was investigated (Scheme 5). Treatment of alkene **13** (neat) with 9-BBN dimer at 85 °C 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.

## 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, Luciné V. Gabriel, Ryan Allen for experimental assistance with the [2,3]-Wittig-type fragmentation, Tobias Olbrisch for the isolation of α-onocerin and Dr Jens Schmidt and Prof. Dr Christian B. W. Stark (Universität Hamburg) for experimental data and a generous donation of the Corey–Noe–Lin catalyst. The computational work was supported by the US National Science Foundation (CHE-1565933 and CHE-030089 [*via* XSEDE] to D. J. T.). This work was supported by JSPS KAKENHI Grant Numbers 25450149 and 16K14911 (to T. S.).

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