

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

Received 6th September 2017

Accepted 14th October 2017

DOI: 10.1039/c7sc03903d

rsc.li/chemical-science

## 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 epoxy polyene cyclization is supported by computational and enzymatic studies.

Triterpenoids constitute an important family of diverse natural products with unique biological activities.<sup>1</sup> Their structural complexity is generated by cyclase enzymes that convert simple acyclic isoprenoid precursors into polycyclic molecules.<sup>2,3</sup> For example, onocerane triterpenes were shown to be biosynthesized from squalene (**1**) or its oxidized derivatives (**2**, **3**) by cyclizations initiated at both termini.<sup>4</sup> 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<sup>5</sup> 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*.<sup>6</sup> 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.<sup>6</sup> Previous synthetic work on the onoceranes<sup>7–10</sup> was focused on the tetracyclic *C*<sub>2</sub>-symmetrical congeners onocerandiol (**5**)<sup>11–14</sup> and α-onocerin (**6**).<sup>15–22</sup> The biosynthesis of onoceranoxide (**7**)<sup>23</sup> and α-onocerin (**6**) *via* **8**<sup>24,25</sup>

was hypothesized to proceed *via* cyclization of squalene and diepoxysqualene, respectively (Scheme 1). This process was elegantly mimicked by Corey's double allylsilane epoxy polyene cyclization.<sup>16</sup> However, the highly substituted oxepane in cupacinoxepin (**4**) and onoceranoxide (**7**)<sup>26,27</sup> required a novel synthetic strategy.

Chemical synthesis of ditertiary ethers is a daunting task.<sup>28–38</sup> Unfortunately, the seemingly obvious approach to form the oxepane from two tertiary alcohols is outpaced by competing cationic pathways.<sup>13,14</sup> Inspired by the cyclization of squalene to **7** *via* **9** catalyzed by *Bacillus megaterium* tetraprenyl-β-curcumen cyclase (BmeTC),<sup>23</sup> we identified myrrhanol C (**11**)<sup>39</sup> or epoxy dienol **12** as potential precursors for the synthesis of **10**. While the actual biosynthetic pathway is unknown, the realization of an epoxy diene 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<sup>40–45</sup> using tertiary alcohols as nucleophiles are known,<sup>46–48</sup> and to the best of our knowledge polyene tricyclizations using tertiary alcohols to form oxepanes have only been achieved enzymatically so far.<sup>23,49</sup> 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**.<sup>50</sup> The two fragments were traced back to the readily available starting materials (+)-sclareolide (**15**) and geranyl chloride (**16**), respectively.<sup>51–53</sup>

The synthesis of fragment **13**<sup>54</sup> started with the conversion of **15** into the corresponding benzyl ether **17** using a one-pot<sup>55,56</sup> reduction/alkylation sequence (Scheme 3). To this end, reduction of (+)-sclareolide with LiAlH<sub>4</sub> in THF at 0 °C<sup>57</sup> was followed by treatment with Rochelle salt, DMF, KOH and 2-Me-C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>Br to afford benzyl ether **17** in excellent yield. A [2,3]-Wittig-type fragmentation mediated by *n*-BuLi directly yielded

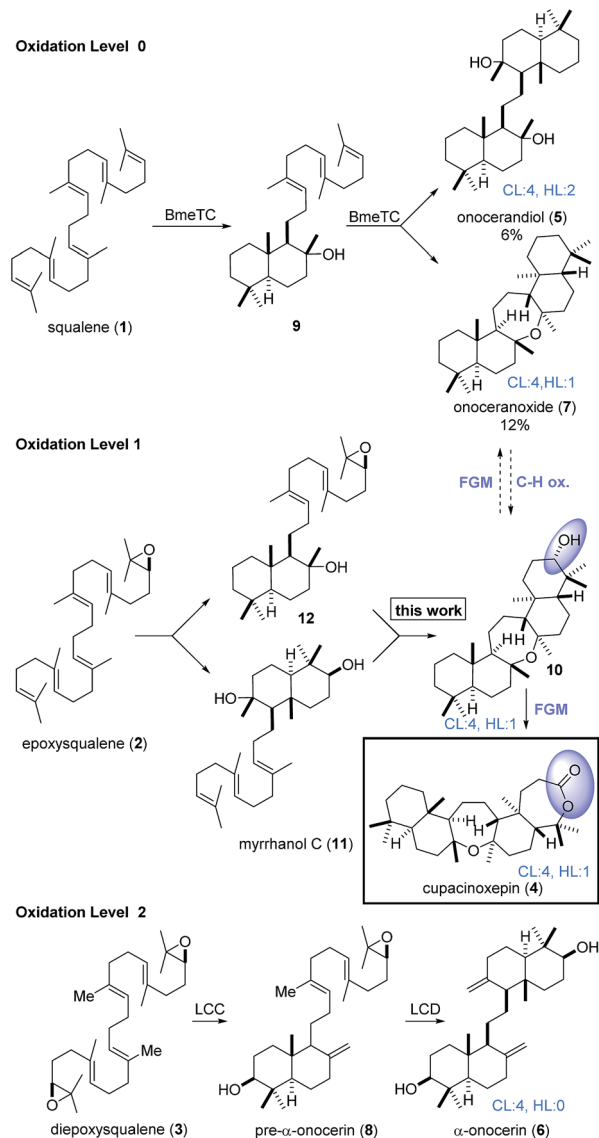
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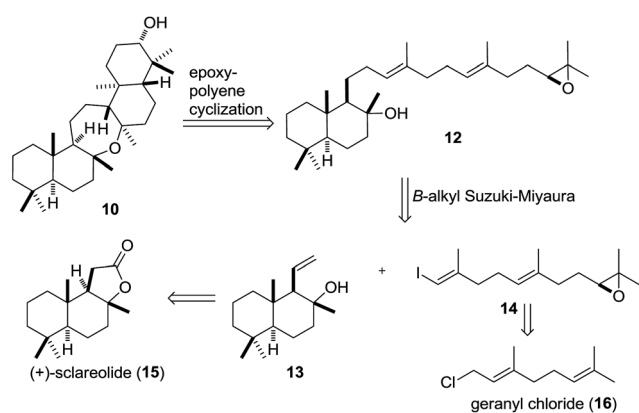
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† Electronic supplementary information (ESI) available: Detailed experimental procedures, spectral data, DFT calculation, X-ray crystallographic data for **4** (CIF), **13** (CIF), **10** (CIF), **22** (CIF). CCDC 1529115–1529118. For ESI and crystallographic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

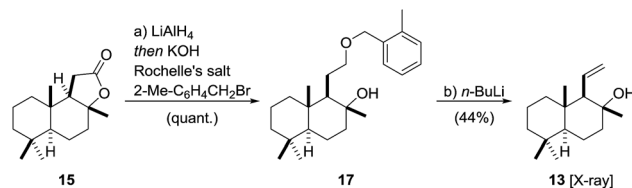




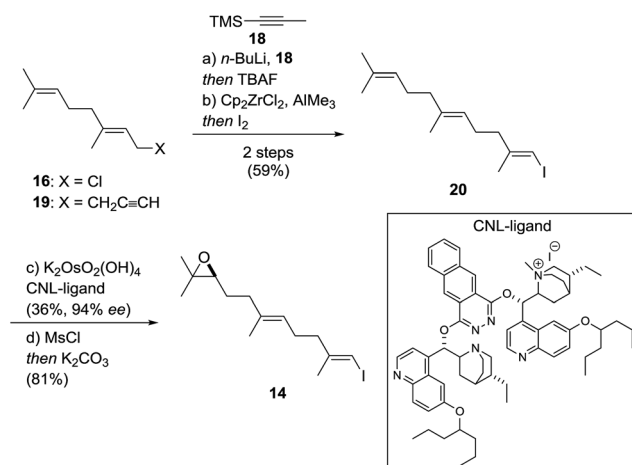
Scheme 1 Core assembly of onocerane triterpenes with regard to the oxidation level (OL), cyclization level (CL) and the hydration level (HL). LCC and LCD = *Lycopodium clavatum* C and D respectively.



Scheme 2 Retrosynthetic analysis of 10 based on an epoxy-polyene cyclization of precursor 12.



Scheme 3 Synthesis of fragment 13. Reagents and conditions: (a)  $\text{LiAlH}_4$  (0.7 eq.), THF, 0 °C, 40 min then 2-Me- $\text{C}_6\text{H}_4\text{CH}_2\text{Br}$  (2.1 eq.), KOH (4.0 eq.), Rochelle's salt (1.2 eq.), DMF, 45 °C, 27 h, quant.; (b)  $n\text{-BuLi}$  (4.0 eq.), THF, -78 °C, 10 min to -13 °C, 90 min, 44% (over 2 steps).

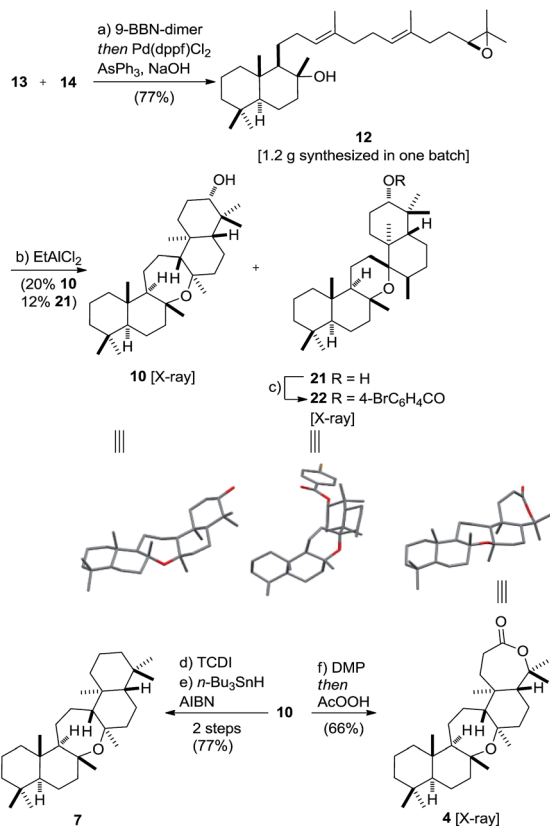


Scheme 4 Synthesis of fragment 14. Reagents and conditions: (a)  $n\text{-BuLi}$  (1.2 eq.), 18 (1.2 eq.), THF, -78 °C, 2.5 h then TBAF (1.3 eq.), -78 °C to 23 °C, 24 h, 82%; (b)  $\text{Cp}_2\text{ZrCl}_2$  (0.25 eq.),  $\text{AlMe}_3$  (3.0 eq.),  $\text{H}_2\text{O}$  (1.0 eq.),  $\text{CH}_2\text{Cl}_2$ , -23 °C, 1 h then  $\text{I}_2$  (1.2 eq.), THF, -23 °C to 23 °C, 16 h, 72%; (c)  $\text{K}_2\text{OsO}_2(\text{OH})_4$  (0.3 mol%), CNL-ligand (0.2 mol%),  $\text{K}_3\text{Fe}(\text{CN})_6$  (3.0 eq.),  $\text{MeSO}_2\text{NH}_2$  (1.0 eq.),  $\text{K}_2\text{CO}_3$  (3.0 eq.),  $t\text{-BuOH}$ ,  $\text{H}_2\text{O}$ , 1 °C, 53 h, 36%, 94% ee, and 49% of 20; (d)  $\text{MsCl}$  (1.1 eq.), pyridine (15 eq.),  $\text{CH}_2\text{Cl}_2$ , 0 °C to 23 °C, 18 h then  $\text{K}_2\text{CO}_3$  (10 eq.), MeOH, 2.5 h, 81%.

fragment 13 in an acceptable yield of 44% over two steps.<sup>58,59</sup> 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.<sup>46</sup> The configuration of 13 was confirmed by X-ray crystallography.<sup>60</sup>

Vinyl iodide 14 was prepared from geranyl chloride *via* nucleophilic substitution with lithiated 18<sup>61</sup> followed by desilylation with TBAF (Scheme 4). Negishi's zirconium-catalyzed carboalumination<sup>62,63</sup> of 19 with  $\text{AlMe}_3$  and subsequent trapping of the vinyl aluminium intermediate with iodine afforded vinyl iodide 20.<sup>64,65</sup> Dihydroxylation of the dimethyl-substituted alkene with the  $(\text{DHQD})_2\text{PHAL}$  ligand<sup>66</sup> (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<sup>67</sup> 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<sub>2</sub> (0.1 eq.), AsPh<sub>3</sub> (0.4 eq.), NaOH (6.0 eq.), 1 °C, 17 h, 77%; (b) EtAlCl<sub>2</sub> (3.0 eq.), CH<sub>2</sub>Cl<sub>2</sub> (1 mM), -78 °C, 1.5 h, 20% **10**, 12% **21**; (c) 4-BrC<sub>6</sub>H<sub>4</sub>COCl (5.0 eq.), 4-DMAP (20 eq.), 50 °C, CH<sub>2</sub>Cl<sub>2</sub>, 3 d, 73%; (d) TCDI (20 eq.), 4-DMAP (20 eq.), CH<sub>2</sub>Cl<sub>2</sub>, 70 °C 13.5 h, 83%; (e) *n*-Bu<sub>3</sub>SnH (3.0 eq.), AIBN (cat.), toluene, 160 °C, 10 min to 120 °C, 20 min then *n*-Bu<sub>3</sub>SnH (3.0 eq.), AIBN (cat.), 160 °C, 10 min to 120 °C, 20 min, 93%; (f) DMP (2.0 eq.), CH<sub>2</sub>Cl<sub>2</sub>, 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.<sup>68</sup> Mesylation of the secondary alcohol and subsequent treatment with K<sub>2</sub>CO<sub>3</sub> afforded epoxide **14** in 81% yield.<sup>69</sup> 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<sup>69–71</sup> to afford epoxy dienol **12** in 77% yield on gram scale. The stage was then set to examine the putative biomimetic tricyclization.<sup>72</sup> We anticipated the formation of the oxepane to be unfavorable both for entropic and enthalpic reasons.<sup>73</sup> A variety of Brønsted and Lewis acids<sup>46</sup> failed to give the desired product, but gratifyingly, treatment of **12** with EtAlCl<sub>2</sub> at -78 °C under high dilution (CH<sub>2</sub>Cl<sub>2</sub>, 1 mM) afforded a separable mixture of target compound **10** (20%) along with another pentacyclic product **21** (12%).<sup>74–76</sup> Spirocyclic motifs similar to **21** have been found in several bioactive natural products.<sup>77–80</sup> Further conditions for the tricyclization of **9** were investigated but no product formation could be observed.<sup>46</sup>

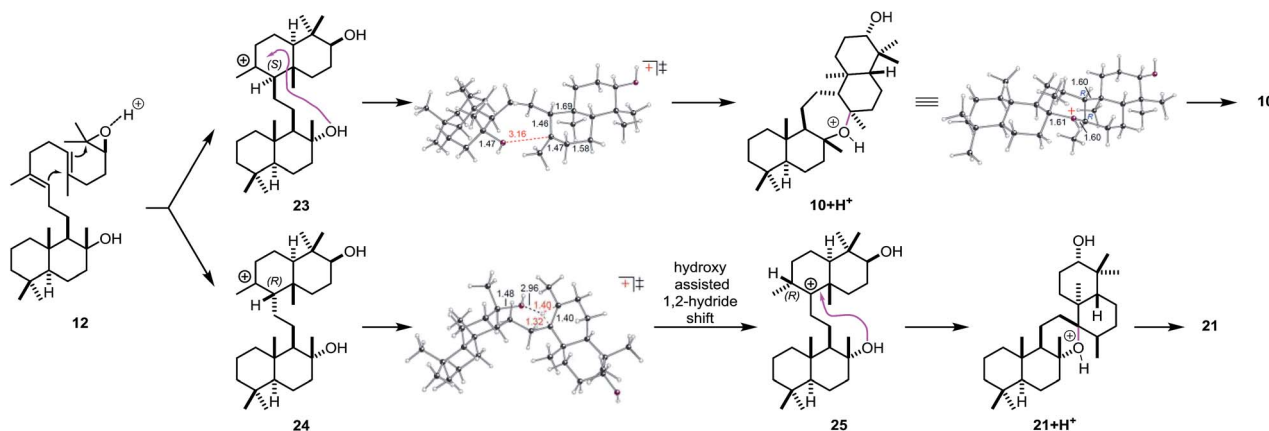
The structures of oxepane **10** and *p*-Br-benzoate derivative **22** were confirmed by X-ray crystallography. Despite its rather low yield, the cyclization generated four stereogenic centers and the remaining carbon skeleton in a single transformation. Additionally, the secondary alcohol in **10** 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.<sup>81,82</sup> 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.<sup>83–90</sup> Next, the major cyclization product **10** was subjected to a one-pot Dess–Martin/Baeyer–Villiger oxidation<sup>91–94</sup> 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.<sup>6</sup> 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**).<sup>95</sup> The spectroscopic data matched those reported in the literature.<sup>26</sup>

In order to investigate the mechanism of the epoxy polyene 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)).<sup>46</sup> 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),<sup>96</sup> to result from epoxy diene cyclization, consistent with previous work by Corey and Shenvi on related systems.<sup>75,97</sup> The predicted major intermediate **23** is derived from a chair–chair conformation, while **24** is derived from a chair–boat conformation.<sup>75,80</sup>

For **23**, 7-membered ring formation was predicted to be preferred over other pathways by several kcal mol<sup>-1</sup>. 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<sup>-1</sup>. 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).<sup>98,99</sup> In addition, the biosynthetic relevance of the epoxy polyene cyclization was probed by incubation of **12** with BmeTC. GC-MS analysis revealed the formation of **10** along with an elimination product.<sup>46</sup> 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 epoxy polyene 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  $\alpha$ -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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