

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  $\mu$ M) 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  $C_{22}$ -symmetrical congeners onocerandiol (**5**)<sup>11–14</sup> and  $\alpha$ -onocerin (**6**).<sup>15–22</sup> The biosynthesis of onoceranoxide (**7**)<sup>23</sup> and  $\alpha$ -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- $\beta$ -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**  $\rightarrow$  **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>

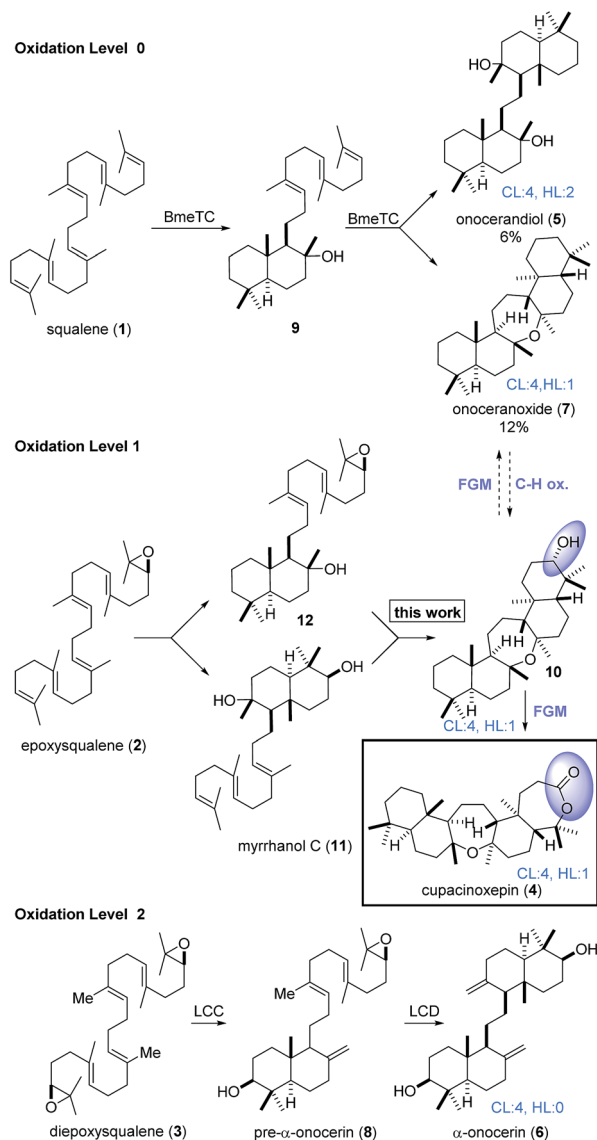
The synthesis of fragment **13**<sup>54</sup> started with the conversion of **15** into the corresponding benzyl ether **17** using a one-pot<sup>55,56</sup> reduction/alkylation sequence (Scheme 3). To this end, reduction of (+)-sclareolide with  $\text{LiAlH}_4$  in THF at 0 °C<sup>57</sup> was followed by treatment with Rochelle salt, DMF, KOH and 2-Me- $\text{C}_6\text{H}_4\text{CH}_2\text{Br}$  to afford benzyl ether **17** in excellent yield. A [2,3]-Wittig-type fragmentation mediated by *n*-BuLi directly yielded

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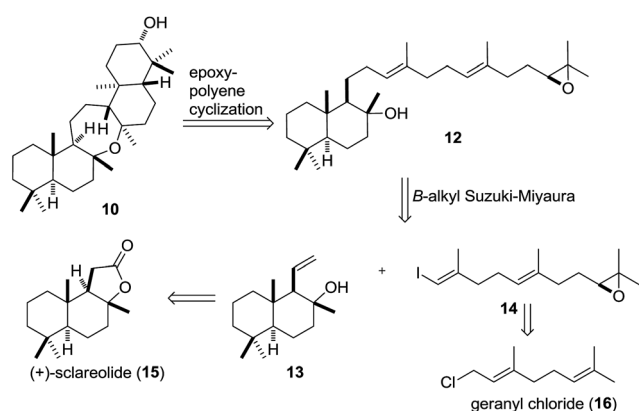
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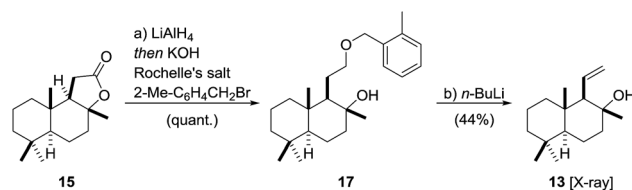
† Electronic supplementary information (ESI) available: Detailed experimental procedures, spectral data, DFT calculation, X-ray crystallographic data for **4** (CIF), **13** (CIF), **10** (CIF), **22** (CIF). CCDC 1529115–1529118. For ESI and crystallographic data in CIF or other electronic format see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



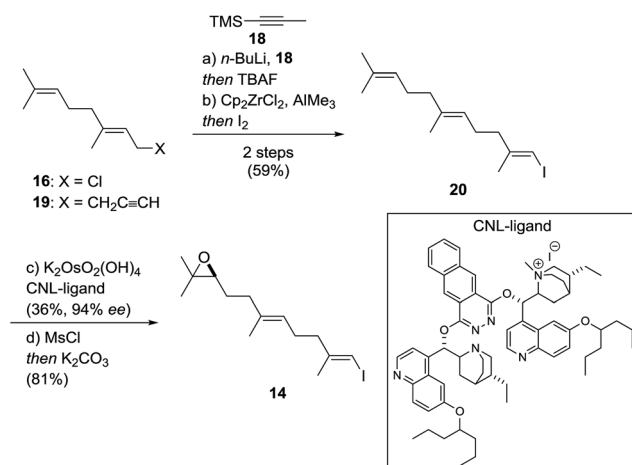
Scheme 1 Core assembly of onocerane triterpenes with regard to the oxidation level (OL), cyclization level (CL) and the hydration level (HL). LCC and LCD = *Lycopodium clavatum* C and D respectively.



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



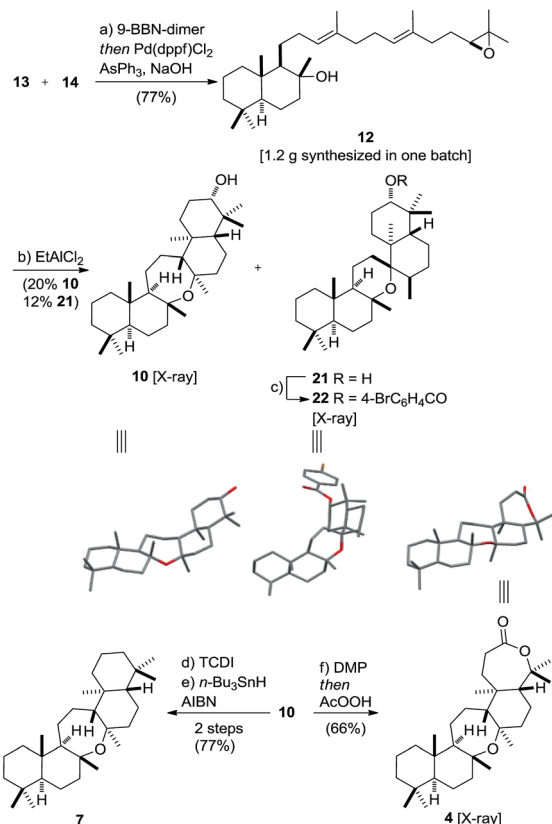
Scheme 3 Synthesis of fragment 13. Reagents and conditions: (a)  $\text{LiAlH}_4$  (0.7 eq.), THF, 0 °C, 40 min then 2-Me- $\text{C}_6\text{H}_4\text{CH}_2\text{Br}$  (2.1 eq.), KOH (4.0 eq.), Rochelle's salt (1.2 eq.), DMF, 45 °C, 27 h, quant.; (b)  $n\text{-BuLi}$  (4.0 eq.), THF, -78 °C, 10 min to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

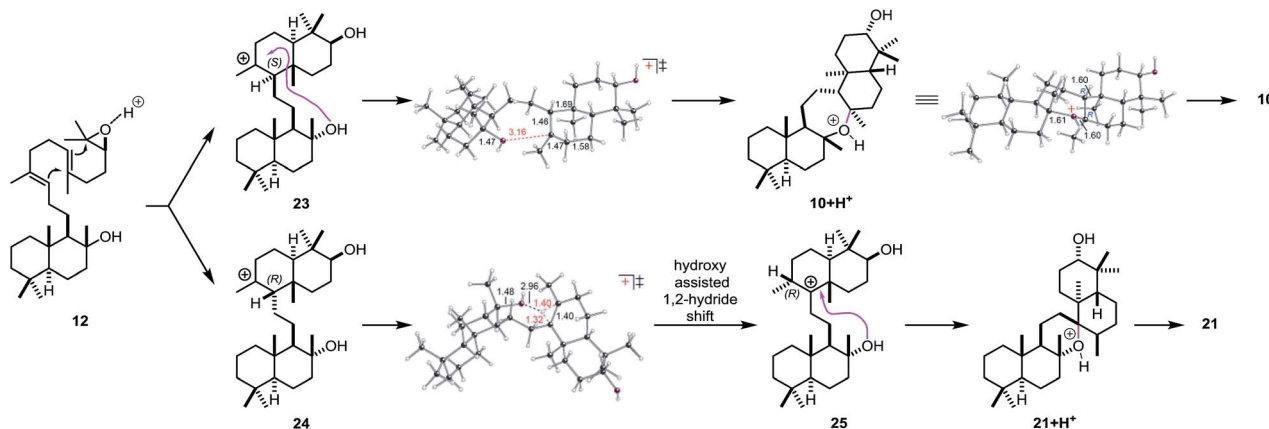
The structures of oxepane **10** and *p*-Br-benzoate derivative **22** were confirmed by X-ray crystallography. Despite its rather low yield, the cyclization generated four stereogenic centers and the remaining carbon skeleton in a single transformation. Additionally, the secondary alcohol in **10** 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 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)).<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 epoxidiene 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 epoxypolyene 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 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<sup>+</sup> 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.).

## Notes and references

- J. Gershenzon and N. Dudareva, *Nat. Chem. Biol.*, 2007, **3**, 408–414.
- R. Xu, G. C. Fazio and S. P. T. Matsuda, *Phytochemistry*, 2004, **65**, 261–291.
- R. Thimmappa, K. Geisler, T. Louveau, P. O'Maille and A. Osbourn, *Annu. Rev. Plant Biol.*, 2014, **65**, 225–257.
- V. Domingo, J. F. Arteaga, J. F. Quilez del Moral and A. F. Barrero, *Nat. Prod. Rep.*, 2009, **26**, 115–134.
- B. Meunier, S. P. de Visser and S. Shaik, *Chem. Rev.*, 2004, **104**, 3947–3980.
- M. S. Gachet, O. Kunert, M. Kaiser, R. Brun, M. Zehl, W. Keller, R. A. Muñoz, R. Bauer and W. Schuehly, *J. Nat. Prod.*, 2011, **74**, 559–566.
- A. F. Barrero, M. M. Herrador, J. F. Quilez del Moral, P. Arteaga, J. F. Arteaga, M. Piedra and E. M. Sánchez, *Org. Lett.*, 2005, **7**, 2301–2304.
- M. Nishizawa, H. Nishide and Y. Hayashi, *Tetrahedron Lett.*, 1984, **25**, 5071–5074.
- R. Carman and H. Deeth, *Aust. J. Chem.*, 1971, **24**, 1099–1102.
- E. E. van Tamelen, M. A. Schwartz, E. J. Hessler and A. Storni, *Chem. Commun.*, 1966, 409–411.
- P. F. Vlad, K. I. Kuchkova, A. N. Aryku and K. Deleanu, *Russ. Chem. Bull.*, 2005, **54**, 2656–2658.
- E. Romann, A. J. Frey, P. A. Stadler and A. Eschenmoser, *Helv. Chim. Acta*, 1957, **40**, 1900–1917.
- E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.*, 1957, **79**, 3925–3926.
- E. J. Corey and R. R. Sauers, *J. Am. Chem. Soc.*, 1959, **81**, 1739–1743.
- D. H. R. Barton and K. H. Overton, *J. Chem. Soc.*, 1955, 2639–2652.
- Y. Mi, J. V. Schreiber and E. J. Corey, *J. Am. Chem. Soc.*, 2002, **124**, 11290–11291.
- Y. Tsuda, N. Kashiwaba, M. Kajitani and J. Yasui, *Chem. Pharm. Bull.*, 1981, **29**, 3424–3426.
- G. Stork, A. Meisels and J. E. Davies, *J. Am. Chem. Soc.*, 1963, **85**, 3419–3425.
- N. Danieli, Y. Mazur and F. Sondheimer, *Tetrahedron*, 1967, **23**, 509–514.
- J. Kokosi and C. Schmidt, *Synth. Commun.*, 1985, **15**, 341–354.
- R. F. Church, R. E. Ireland and J. A. Marshall, *Tetrahedron Lett.*, 1961, **2**, 34–38.
- S. Berger and D. Sicker, *Classics in Spectroscopy: Isolation and Structure Elucidation of Natural Products*, Wiley-VCH, Weinheim, 2009.
- D. Ueda, T. Hoshino and T. Sato, *J. Am. Chem. Soc.*, 2013, **135**, 18335–18338.
- M. G. Rowan, P. D. G. Dean and T. W. Goodwin, *FEBS Lett.*, 1971, **12**, 229–232.





- 25 T. Araki, Y. Saga, M. Marugami, J. Otaka, H. Araya, K. Saito, M. Yamazaki, H. Suzuki and T. Kushiro, *ChemBioChem*, 2016, **17**, 288–290.
- 26 H. Ageta, K. Shiojima and K. Masuda, *Chem. Pharm. Bull.*, 1982, **30**, 2272–2274.
- 27 Y. Arai, M. Yamaide, S. Yamazaki and H. Ageta, *Phytochemistry*, 1991, **30**, 3369–3377.
- 28 A. S. Kleinke, D. Webb and T. F. Jamison, *Tetrahedron*, 2012, **68**, 6999–7018.
- 29 H. Bouanou, J. A. Gil, R. Alvarez-Manzaneda, R. Chahboun and E. Alvarez-Manzaneda, *J. Org. Chem.*, 2016, **81**, 10002–10008.
- 30 M. T. Corbett and J. S. Johnson, *Chem. Sci.*, 2013, **4**, 2828–2832.
- 31 E. J. Alvarez-Manzaneda, R. Chahboun, E. Alvarez, E. Cabrera, R. Alvarez-Manzaneda, A. Haidour and J. M. Ramos, *Synlett*, 2006, **2006**, 1829–1834.
- 32 M. Maemoto, A. Kimishima and T. Nakata, *Org. Lett.*, 2009, **11**, 4814–4817.
- 33 H. Shigehisa, M. Hayashi, H. Ohkawa, T. Suzuki, H. Okayasu, M. Mukai, A. Yamazaki, R. Kawai, H. Kikuchi, Y. Satoh, A. Fukuyama and K. Hiroya, *J. Am. Chem. Soc.*, 2016, **138**, 10597–10604.
- 34 S. Pan, J. Xuan, B. Gao, A. Zhu and H. Ding, *Angew. Chem., Int. Ed.*, 2015, **54**, 6905–6908.
- 35 L. Catti and K. Tiefenbacher, *Chem. Commun.*, 2015, **51**, 892–894.
- 36 G. A. Olah, A. P. Fung and R. Malhotra, *Synthesis*, 1981, **1981**, 474–476.
- 37 L. Fang, Y. Chen, J. Huang, L. Liu, J. Quan, C.-c. Li and Z. Yang, *J. Org. Chem.*, 2011, **76**, 2479–2487.
- 38 O. Piva, in *Synthesis of Saturated Oxygenated Heterocycles II: 7- to 16-Membered Rings*, ed. J. Cossy, Springer Berlin Heidelberg, Berlin, Heidelberg, 2014, pp. 283–320, DOI: 10.1007/978-3-642-41470-1\_1.
- 39 R. B. Boar, L. A. Couchman, A. J. Jaques and M. J. Perkins, *J. Am. Chem. Soc.*, 1984, **106**, 2476–2477.
- 40 R. A. Yoder and J. N. Johnston, *Chem. Rev.*, 2005, **105**, 4730–4756.
- 41 L. F. Tietze, G. Brasche and K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006.
- 42 S. A. Snyder and A. M. Levinson, in *Comprehensive Organic Synthesis II*, ed. P. Knochel and G. A. Molander, Elsevier, Amsterdam, 2nd edn, 2014, p. 268, DOI: 10.1016/B978-0-08-097742-3.00309-8.
- 43 M. Baunach, J. Franke and C. Hertweck, *Angew. Chem., Int. Ed.*, 2015, **54**, 2604–2626.
- 44 V. K. Aggarwal, P. A. Bethel and R. Giles, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3315–3321.
- 45 T. N. Barrett and A. G. M. Barrett, *J. Am. Chem. Soc.*, 2014, **136**, 17013–17015.
- 46 See ESI† for details.
- 47 S. Nakamura, K. Ishihara and H. Yamamoto, *J. Am. Chem. Soc.*, 2000, **122**, 8131–8140.
- 48 M. Uyanik, H. Ishibashi, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2005, **7**, 1601–1604.
- 49 T. Abe and T. Hoshino, *Org. Biomol. Chem.*, 2005, **3**, 3127–3139.
- 50 D. Urabe, T. Asaba and M. Inoue, *Chem. Rev.*, 2015, **115**, 9207–9231.
- 51 J. Mulzer, *Nat. Prod. Rep.*, 2014, **31**, 595–603.
- 52 Z. G. Brill, M. L. Condakes, C. P. Ting and T. J. Maimone, *Chem. Rev.*, 2017, **117**, 11753–11795.
- 53 T. Newhouse, P. S. Baran and R. W. Hoffmann, *Chem. Soc. Rev.*, 2009, **38**, 3010–3021.
- 54 For an attempted synthesis, see: J. H. George, M. McArdle, J. E. Baldwin and R. M. Adlington, *Tetrahedron*, 2010, **66**, 6321–6330.
- 55 C. Vaxelaire, P. Winter and M. Christmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 3605–3607.
- 56 Y. Hayashi, *Chem. Sci.*, 2016, **7**, 866–880.
- 57 K. K. W. Kuan, H. P. Pepper, W. M. Bloch and J. H. George, *Org. Lett.*, 2012, **14**, 4710–4713.
- 58 M. Matsushita, Y. Nagaoka, H. Hioki, Y. Fukuyama and M. Kodama, *Chem. Lett.*, 1996, **25**, 1039–1040.
- 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.†
- 61 E. J. Corey and H. A. Kirst, *Tetrahedron Lett.*, 1968, **9**, 5041–5043.
- 62 T. Yoshida and E. Negishi, *J. Am. Chem. Soc.*, 1981, **103**, 4985–4987.
- 63 P. Wipf and S. Lim, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1068–1071.
- 64 D. J. Clausen, S. Wan and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2011, **50**, 5178–5181.
- 65 V. Domingo, L. Lorenzo, J. F. Quilez del Moral and A. F. Barrero, *Org. Biomol. Chem.*, 2013, **11**, 559–562.
- 66 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483–2547.
- 67 (a) E. J. Corey, M. C. Noe and S. Lin, *Tetrahedron Lett.*, 1995, **36**, 8741–8744; (b) J. Schmidt and C. B. W. Stark, *Org. Lett.*, 2012, **14**, 4042–4045.
- 68 Determination of the absolute configuration by Mosher ester analysis.
- 69 K. Surendra and E. J. Corey, *J. Am. Chem. Soc.*, 2008, **130**, 8865–8869.
- 70 V. Domingo, L. Silva, H. R. Diéguez, J. F. Arteaga, J. F. Quílez del Moral and A. F. Barrero, *J. Org. Chem.*, 2009, **74**, 6151–6156.
- 71 D. T. Hog, F. M. E. Huber, G. Jiménez-Osés, P. Mayer, K. N. Houk and D. Trauner, *Chem.–Eur. J.*, 2015, **21**, 13646–13665.
- 72 M. Razzak and J. K. De Brabander, *Nat. Chem. Biol.*, 2011, **7**, 865–875.
- 73 C. Galli and L. Mandolini, *Eur. J. Org. Chem.*, 2000, 3117–3125.
- 74 S. V. Pronin and R. A. Shenvi, *Nat. Chem.*, 2012, **4**, 915–920.
- 75 R. A. Shenvi and E. J. Corey, *Org. Lett.*, 2010, **12**, 3548–3551.



- 76 E. J. Corey and M. Sodeoka, *Tetrahedron Lett.*, 1991, **32**, 7005–7008.
- 77 W. H. Gerwick and W. Fenical, *J. Org. Chem.*, 1981, **46**, 22–27.
- 78 A. Abad, C. Agulló, M. Arnó, A. C. Cuñat, B. Meseguer and R. J. Zaragoza, *J. Org. Chem.*, 1998, **63**, 5100–5106.
- 79 A. Grube, M. Assmann, E. Lichte, F. Sasse, J. R. Pawlik and M. Köck, *J. Nat. Prod.*, 2007, **70**, 504–509.
- 80 A. W. Markwell-Heys and J. H. George, *Org. Biomol. Chem.*, 2016, **14**, 5546–5549.
- 81 B. T. Grimberg and R. K. Mehlotra, *Pharmaceuticals*, 2011, **4**, 681.
- 82 E. L. Flannery, A. K. Chatterjee and E. A. Winzeler, *Nat. Rev. Microbiol.*, 2013, **11**, 849–862.
- 83 C. R. Shugrue and S. J. Miller, *Chem. Rev.*, 2017, **117**, 11894–11951.
- 84 R. K. Quinn, Z. A. Könst, S. E. Michalak, Y. Schmidt, A. R. Szklarski, A. R. Flores, S. Nam, D. A. Horne, C. D. Vanderwal and E. J. Alexanian, *J. Am. Chem. Soc.*, 2016, **138**, 696–702.
- 85 M. S. Chen and M. C. White, *Science*, 2010, **327**, 566–571.
- 86 Y. Kawamata, M. Yan, Z. Liu, D.-H. Bao, J. Chen, J. T. Starr and P. S. Baran, *J. Am. Chem. Soc.*, 2017, **139**, 7448–7451.
- 87 W. Liu, X. Huang, M.-J. Cheng, R. J. Nielsen, W. A. Goddard and J. T. Groves, *Science*, 2012, **337**, 1322–1325.
- 88 K. Chen, A. Eschenmoser and P. S. Baran, *Angew. Chem., Int. Ed.*, 2009, **48**, 9705–9708.
- 89 V. A. Schmidt, R. K. Quinn, A. T. Brusoe and E. J. Alexanian, *J. Am. Chem. Soc.*, 2014, **136**, 14389–14392.
- 90 O. F. Jeker, A. G. Kravina and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2013, **52**, 12166–12169.
- 91 D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155–4156.
- 92 A. Baeyer and V. Villiger, *Ber. Dtsch. Chem. Ges.*, 1899, **32**, 3625–3633.
- 93 R. R. Sauers, *J. Am. Chem. Soc.*, 1959, **81**, 925–927.
- 94 J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.*, 1960, **82**, 5235–5239.
- 95 M. Göhl and K. Seifert, *Eur. J. Org. Chem.*, 2014, 6975–6982.
- 96 D. J. Tantillo, *Angew. Chem., Int. Ed.*, 2017, **56**, 10040–10045.
- 97 E. J. Corey and B. E. Roberts, *Tetrahedron Lett.*, 1997, **38**, 8921–8924.
- 98 M. W. Lodewyk, D. Willenbring and D. J. Tantillo, *Org. Biomol. Chem.*, 2014, **12**, 887–894.
- 99 S. R. Hare, R. P. Pemberton and D. J. Tantillo, *J. Am. Chem. Soc.*, 2017, **139**, 7485–7493.

