Synthetic studies towards the africanane sesquiterpenes via the Cope rearrangement of *gem*-dimethyl substituted divinyl cyclopropanes

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Dedication – To commemorate the 70th birthday of Prof. Steven Ley, FRS; inspirational synthetic organic chemist, mentor and friend .

**Abstract:** The Cope rearrangement of *gem*-dimethyl substituted divinylcyclopropanes has been used to construct functionalised cycloheptadienes. These scaffolds have been further elaborated to furnish advanced intermediates en route to africanane sesquiterpene natural products, most notably pyxidatol C.

**Key words:** Pericyclic reactions, cyclopropanes, natural products, pyxidatol C, africananes.

Pyxidatol C **1** is a tricyclic sesquiterpene recently isolated by Zheng *et al.* from *Clavicorona pyxidata*, a wild mushroom used widely in traditional Chinese medicine for the treatment of gastric pain, dyspepsia, gout and heat toxicity.1 It belongs to a wider family of natural products known as the africananes, which include omphadiol **2**,2 africanol **3**,3 and africanene **4**,4 and are defined by their decahydro-1*H*-cyclopropan[e]azulene core (Figure 1). Several studies concerning their biological activity and biosynthetic origins have been reported.5



**Figure 1** Selected africanane sesquiterpenes.

Interest in the biological properties of the africananes, as well as the challenge of assembling the unusual decahydro-1*H*-cyclopropan[e]azulene core unit, has led to significant efforts from the synthetic community towards their total synthesis. The first synthesis of any member of the africanane family (africanol **3**) was reported in 1980 by Shirahama *et al.*6aand several total syntheses of products **2–4** have since been published.6-8 The most recent africanane to succumb to total synthesis is pyxidatol C, the first synthesis and structural confirmation of which was reported in 2014 by Liang *et al.*7b

As part of an ongoing research program geared towards the development of new tandem/telescoped reaction sequences,9 we recently reported a study into the Cope rearrangement of *gem*-dimethyl divinyl cyclopropanes, as a strategy to generate synthetically useful cycloheptadiene scaffolds (*e.g.* **5** → **6**,Figure 2).10 It was decided to investigate the possibility of using this methodology to generate *gem*-dimethyl substituted cycloheptadienes as precursors for the africananes, leading to the retrosynthetic strategy depicted below (Figure 2). Note that our primary focus was to complete the synthesis of pyxidatol C **1**,as shown (because at the time that this work was performed, no total synthesis has been reported), but it was also considered that with minor modifications, the synthesis of other africananes (*e.g.* **2**–**4**) would be possible. It was planned to construct the fused cyclopentyl ring via a reductive cyclisation reaction of a methyl ketone onto an alkene (*e.g.* using SmI2, disconnection **A**), while the cyclopropyl ring could be formed using a Simmons-Smith cyclopropanation reaction (disconnection **B**).11 It was expected that, following functional group interconversion and alkene isomerism, key building block **7** (or a suitably protected variant)could be formed from a cycloheptadiene of the form **6**; this framework is known be accessible with variable functionality (R1 and R2) from divinyl cyclopropanes **5**,using our published Cope rearrangement methodology.10 Herein, we report preliminary studies leading to the synthesis of building block **7** (where R2 = CO2Et), as well as the installation of the cyclopropyl group (disconnection **B**) on a model system.



**Figure 2** Retrosynthetic strategy, utilizing a key divinyl cyclopropane Cope rearrangement.

Initial work centered on the manipulation of *meso*-diol **11** which was made by heating divinyl cyclopropane **8** (which was itself synthesised in 7 steps from ethyl chrysanthemate)10 to 100 °C in toluene, effecting Cope rearrangement to form cycloheptadiene **10**, which was then reduced with LiAlH4 (Scheme 1). Alternatively, diol **11** could be made directly from divinyl cyclopropane **9**10under the same Cope rearrangement conditions.Next, it was planned to protect one of the alcohol groups of diol **11**,12 before installing a methyl ketone side chain (**14**) via a haloalkane of the form **13**. Unfortunately, we were unable to synthesise the requisite haloalkane; three strategies to mono-protect and iodinate diol **11** were tested, but in each case, cyclic ether **16** was the major product formed, with no evidence for the formation of the requisite iodides **13a–c**. This unexpected product presumably forms via an initial iodination of the mono-protected diols **12a-c** as planned, but then the iodide (**13a**-**c**) cyclises, to generate a cyclic oxycation (**15a-c**), before protecting group cleavage takes place *in situ*. The fact that cyclic ether **16** is formed, despite the use of normally robust protecting groups, indicates that this cyclisation process is particularly favourable. Indeed, when diol **11** was heated at reflux in benzene with *p*-TSA and *p*-anisaldehyde (in an attempt to form a benzylidene acetal) cyclic ether **16** again formed, further highlighting the facility of this cyclisation.



**Scheme 1** Attempts to elaborate diol **11** towards ketone **14**.

The relative ease with which this cyclisation takes place led us to consider an alternative synthetic strategy, in which the steps are ordered such that this problem is avoided (*vide infra*). Nonetheless, concurrent studies performed on alcohol **12a**,an intermediate from this route, provided reassurance that our planned synthetic strategy to install the cyclopropane moiety common in africananes **1–4** via alkene isomerisation and Simons–Smith cyclopropanation (see Figure 2, disconnection **B**) is feasible. The alkene isomerisation was achieved using an efficient three-step telescoped sequence; oxidation with Dess–Martin periodinane, base-mediated alkene isomerisation with DBU and sodium borohydride reduction furnished the isomerised alkene **19** in good overall yield. The Simmons–Smith cyclopropanation was then performed by treating alkene **19** with diiodomethane and diethylzinc in DCM at 0 °C for 40 minutes. Two separable diastereomeric products **20a** and **20b** were isolated in reasonable overall yield and, crucially, the reaction was highly regioselective, which is likely to be a consequence of the cyclopropanation reaction being directed by the alcohol.13,14



**Scheme 2** Cyclopropane installation using a Simmons-Smith reaction.

To avoid the unwanted formation of cyclic ether **16** as described above, it was decided to construct the methyl ketone containing side chain *before* performing the Cope rearrangement (Scheme 3). Thus, starting from known ester **21**,10 reduction with DIBAL afforded alcohol **22**, which was then converted into carbonate **23** upon reaction with ethyl chloroformate, DMAP and pyridine. This was then used, without purification, in a Tsuji–Trost type allylation reaction; the treatment of carbonate **23** with Pd(PPh3)4 and *tert*-butyl 3-oxobutanoate at 50 °C in THF, afforded β-ketoester **24** in an excellent 92% yield over two steps. Silyl cleavage with TBAF was straightforward, furnishing alcohol **25**, which was then converted into diene **27** via a telescoped Dess–Martin periodinane oxidation and Wittig olefination sequence.15 The key Cope rearrangement was then performed by heating diene **27** to 100 °C in toluene for 16 h, furnishing cycloheptadiene **28**. This intermediate was then treated with TFA in refluxing DCM, to effect ester hydrolysis and decarboxylation, furnishing the methyl ketone containing intermediate **29**.16 Finally, base-mediated alkene isomerisation with DBU in THF at 60 °C afforded compound **30** in high yield (Scheme 3).



**Scheme 3** The synthesis of cycloheptadiene **30**.

Next, it was hoped to install the cyclopentane ring via a samarium diiodide mediated cyclisation (*e.g.* **30 → 31**), before completing the synthesis via ester reduction and Simmons–Smith cyclopropanation (**31 → 1**, Scheme 4). Samarium diiodide mediated ketone-olefin coupling reactions are reasonably well established in the literature17,18 and based on this precedent, methyl ketone substrates **30** and **29** (not shown) were each treated with three equivalents of samarium diiodide18 in *tert*-butanol as the solvent, at RT for 18 h.17 Unfortunately, in both cases, no reaction took place and the starting materials were recovered cleanly. The addition of a solution of HMPA in THF is known to increase the reactivity of samarium diiodide17 in related systems, however, its inclusion as an additive in each of the above reactions (both were performed at −78 °C and 0 °C for 10 min) led to the formation of complex product mixtures, from which none of the desired cyclopentyl product (*e.g.* **31**) could be isolated.



**Scheme 4** Planned synthesis of pyxidatol C from advanced intermediates **30** and **32**.

In summary, progress to date towards the synthesis of pyxidatol C is described, culminating in the synthesis of advanced synthetic building block **30**. The utility of our Cope rearrangement methodology to generate complex gem-dimethyl substituted cycloheptadienes has been well demonstrated, and a viable strategy for cyclopropyl installation on related compound **19** has also been developed. In order to complete the synthesis, we envisage a modified synthetic strategy in which the cyclopentyl ring is assembled prior to the Cope reaction, thus avoiding the problematic reductive ring closure (see **32 → 33**, Scheme 4). For example, treating a cyclopentenone-containing divinylcyclopropane (*e.g.* **32**)19under our standard Cope rearrangement conditions is expected to furnish a fused ring system (*e.g.* **33**) closely related to the africanane framework. Subsequent methyl addition, reduction steps, alkene isomerisation and Simmons–Smith cyclopropanation, should then allow for the completion of the total synthesis of pyxidatol C and, ultimately, other members of the africanane family.

**Supporting Information** for this article is available online at <http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083>, including synthetic procedures and full spectral data for all of the novel compounds and processes described above.

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12. It is envisaged that, if required, meso-diol **11** may also be converted into enantioenriched versions of compounds **12a-c**, via an enzymatic desymmetrisation reaction sequence. For a related example of this type of process used in a total synthesis see: Unsworth, W. P.; Gallagher, K. A.; Jean, M.; Schmidt, J. P.; Diorazio, L. J.; Taylor, R. J. K. *Org. Lett*., **2013**, *15*, 262.
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14. To a stirred solution of Et2Zn (170 μL, 1 M in hexanes, 0.170 mmol) in CH2Cl2 (1 mL) at 0 °C was added diiodomethane (27 μL, 0.340 mmol). This was stirred for 10 min before the addition of **19** (25 mg, 0.0850 mmol) in CH2Cl2 (1 mL) via cannula. The reaction was stirred at 0 °C for 30 min before it was quenched by the addition of sat. NH4Cl (aq.) (5 mL). The organic layer was separated and the aqueous layer extracted with further portions of CH2Cl2 (2 × 10 mL). The combined organic extracts were dried (MgSO4), filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:Et2O (15:1) to afford compound **20a** as a colourless oil (8 mg, 32%) and **20b** as a colourless oil (7 mg, 27%); **20a** Rf (4:1 pet. ether:Et2O) 0.21; υmax (thin film)/cm-1 3340, 2909, 2886, 2816; 1H NMR (400 MHz; CDCl3) δ 5.25−5.15 (2H, m), 3.82−3.73 (3H, m), 3.04 (1H, d, *J* 10.5), 2.37−2.31 (1H, m), 1.80−1.74 (1H, m), 1.57−1.43 (1H, m), 1.06 (3H, s), 0.98 (3H, s), 0.92 (9H, s), 0.90−0.88 (1H, m), 0.82−0.77 (2H, m), 0.10 (3H, s), 0.10 (3H, s); 13C NMR (101 MHz; CDCl3) δ 140.9, 125.0, 68.9, 65.3, 48.2, 42.7, 40.2, 39.0, 32.3, 30.7, 27.7, 25.9, 19.3, 18.3, −5.3, −5.3; m/z (ESI): 333 [MNa+]; HRMS: calcd. for C18H34NaO2Si, 333.2220. Found: [MNa+], 333.2220; **20b** Rf (4:1 pet. ether:Et2O) 0.16; υmax (thin film)/cm-1 3354, 2910, 2884, 2814; 1H NMR δ 5.38−5.28 (2H, m), 3.54−3.50 (2H, m), 3.36 (1H, dd, *J* 10.0, 8.5), 3.06 (1H, d, *J* 10.0), 2.93−2.88 (1H, m), 1.84 (1H, ddd, *J* 14.0, 5.0, 2.0), 1.44−1.22 (2H, m), 1.09 (3H, s), 0.93 (3H, s), 0.89 (9H, s), 0.63−0.53 (2H, m), 0.06 (6H, s); 13C NMR (101 MHz; CDCl3) δ 142.5, 124.7, 77.4, 73.5, 66.5, 42.5, 41.4, 38.0, 32.7, 28.4, 27.0, 26.0, 18.3, 16.1, −5.2; m/z (ESI): 333 [MNa+]; HRMS: calcd. for C18H34NaO2Si, 333.2220. Found: [MNa+], 333.2222.
15. Compound **27** exists as a mixture of diastereoisomers and keto/enol tautomers in solution in CDCl3, complicating its NMR spectra such that it was not possible to determine its *E:Z* ratio; based on precedent for similar transformations (see reference 10) and the stereochemical outcome of the subsequent step, it is likely that the *E­-*isomer predominates.
16. A stirred solution of **27** (1.00 g, 2.74 mmol) in toluene (100 mL) was heated to 100 °C for 16 h. After being cooled to RT the solution was concentrated under reduced pressure. The resulting light yellow oil was dissolved in CH2Cl2 (50 mL) and stirred. TFA (2.8 mL) was then added and the reaction mixture was refluxed for a further 16 h before concentrating under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel, eluting with pet. ether:EtOAc (20:1) to afford compound **29** as a colourless oil (369 mg, 51%); Rf (20:1 pet. ether:EtOAc) 0.18; υmax (thin film)/cm-1 2954, 2930, 2858, 1745; 1H NMR (400 MHz; CDCl3) δ 5.83 (1H, dd, *J* 11.5, 6.0), 5.56 (1H, dd, *J* 12.0, 7.0), 5.50 (1H, dt, *J* 11.5, 2.0), 5.33 (1H, d, *J* 12.0), 4.15 (2H, q, *J* 7.0), 3.67−3.58 (1H, m), 2.76−2.65 (1H, m), 2.53−2.35 (2H, m), 2.11 (3H, s), 1.79-1.63 (2H, m), 1.26 (3H, t, J 7.0), 1.13 (3H, s, H-5), 1.10 (3H, s, H-6); 13C NMR (101 MHz; CDCl3) δ 208.9, 173.2, 139.9, 139.2, 128.7, 123.2, 60.9, 47.4, 41.9, 39.4, 39.1, 32.5, 29.9, 29.5, 27.0, 14.4; m/z (ESI): 287 [MNa+]; HRMS: calcd. for C16H24NaO3, 287.1618. Found: [MNa+], 287.1610.
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