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Samarium diiodide mediated cascade radical cyclisations—synthesis of the eudesmane tricyclic framework

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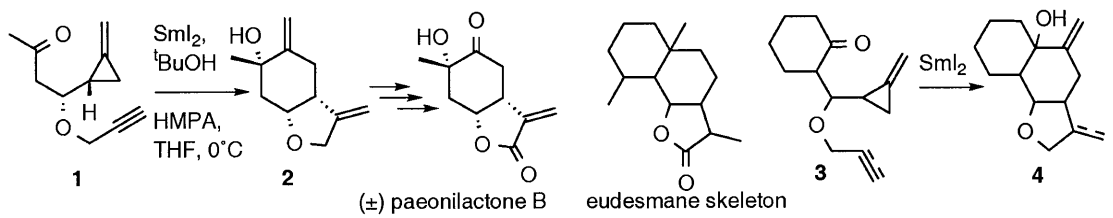
Abstract

Radical cascade cyclisation of methylenecyclopropyl cyclohexanone adducts, using samarium diiodide to generate an initial ketyl radical, provide a short route to tricyclic ethers, and the stereochemical outcome can be influenced by the solvent used for the reaction. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: methylenecyclopropane; samarium diiodide; cascade radical cyclisation.

We recently described the highly stereoselective cascade cyclisation of methyelenecyclopropyl ketone **1**, mediated by samarium diiodide, which led to bicyclic ether **2**, which in turn was used as an intermediate in the synthesis of (±)-paeonilactone B.[1] We wished to extend this methodology to the synthesis of more complex natural products, and in particular, to tricyclic compounds such as the eudesmane sesquiterpenoid lactones, which occur with a range of substitution patterns, stereochemistries and degrees of saturation.[2] In analogy to the preparation of **2** from **1**, we envisaged that the eudesmane skeleton could be accessed via a tricyclic intermediate **4**, which, in turn, could be prepared by cyclisation of a methylenecyclopropyl cyclohexanone adduct **3** (Scheme 1). In this paper we describe our preliminary studies on cyclisations of such adducts.



Scheme 1.

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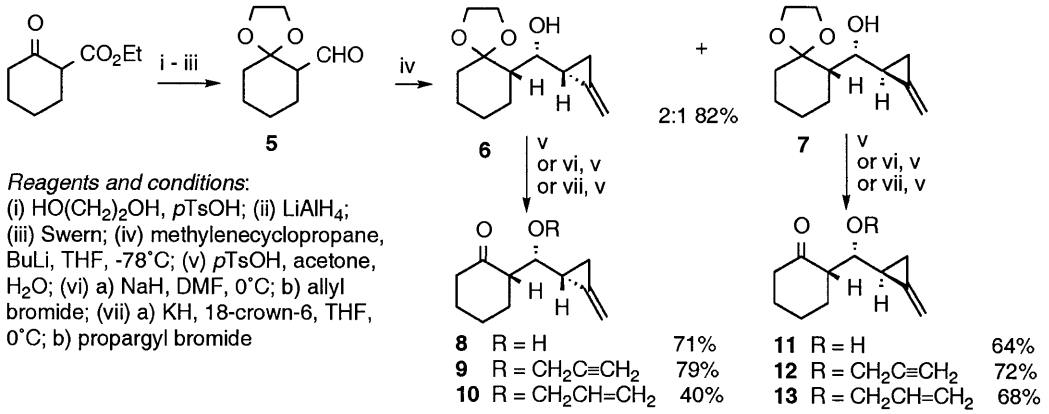
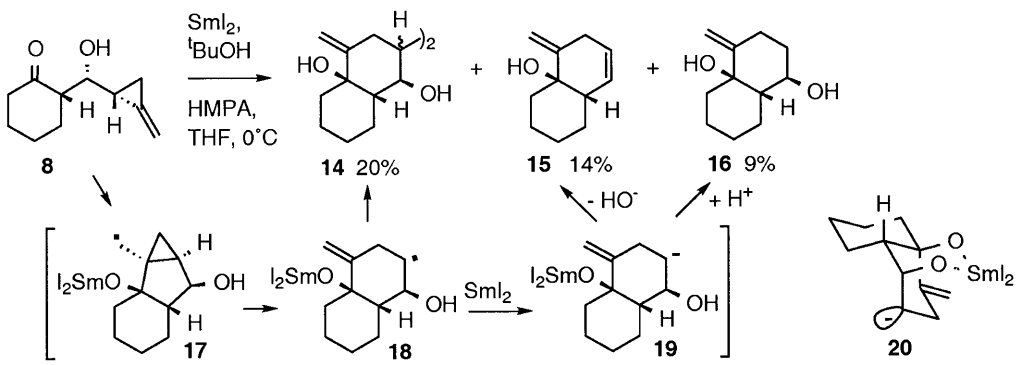
Radical cyclisation precursors were prepared by addition of lithiated methylenecyclopropane to aldehyde **5** to give the two, diastereomeric alcohols **6** and **7** in a 2:1 ratio and in 82% yield. After separation by chromatography, both alcohols could be alkylated to give the corresponding allyl and propargyl ethers, although the alkylation with propargyl bromide required more forcing conditions, reflecting the hindered nature of the alcohols **6** and **7**. Ketal deprotection, using TsOH/acetone/H_2O in each case, gave the corresponding ketones **8**–**13** (Scheme 2).



Scheme 2.

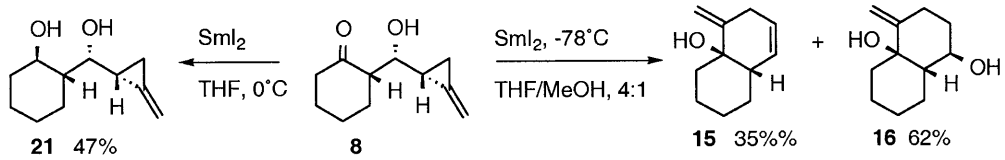
Initially we investigated the SmI_2 mediated cyclisation of the free alcohols **8** and **11**, which we anticipated should cyclise with the stereochemistry controlled by coordination of the alcohol to the samarium bound to the ketyl radical, in analogy to Matsuda's results.[3] Indeed slow addition of ketone **8** to SmI_2, in the presence of ^{t}BuOH (2 equiv.) and HMPA (10 equiv.) in THF at 0°C,[4] gave the expected *cis* diol **16**, but in only 9% yield, and accompanied by the dimer **14** and elimination product **15** (Scheme 3).[5]



Scheme 3.

The formation of **15** can be readily understood since the reaction mechanism presumably proceeds by cyclisation of the ketyl radical onto the methylenecyclopropane and opening of the cyclopropylmethyl radical **17**, to give **18**. Reduction of **18** to the corresponding anion **19** is followed by quenching with a proton from ^{t}BuOH to give diol **16**, or by elimination of HO^-,

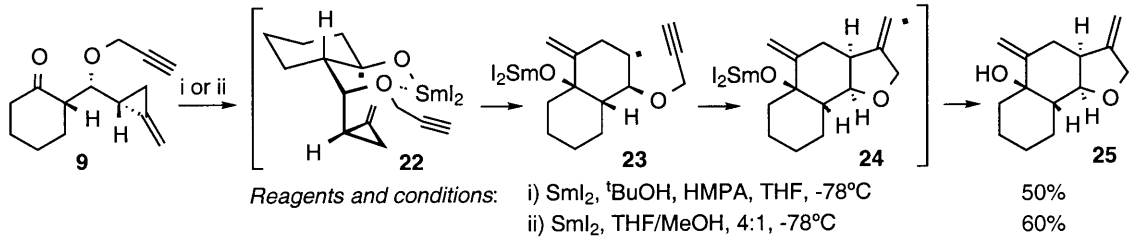
assisted by chelation to Sm(III), which holds the alcohol in a favourable axial orientation (see **20**). Dimerisation to give **14**, while initially surprising, given the high concentration of SmI_2 in the reaction, is precedented by related cyclisations we have observed.[6] The outcome of the reaction, using HMPA/^{t}BuOH, was largely unaffected by altering the temperature, and in the absence of HMPA/^{t}BuOH, using neat THF as solvent, treatment of **8** with SmI_2 yielded diol **21** as the major product. However, using a MeOH/THF (1:4) mixture as solvent in place of HMPA/^{t}BuOH, as described by Procter,[7] at −78°C, gave a much cleaner reaction and diol **16** was isolated in 62% yield along with a 35% yield of the eliminated product **15** (Scheme 4).



Scheme 4.

Cyclisation of alcohol **11** gave similar results, giving bicyclic diol **16** in 50% yield along with **15** in 12% yield, using SmI_2 in MeOH/THF (1:4) at −78°C, but giving a poor reaction when carried out using HMPA/^{t}BuOH.

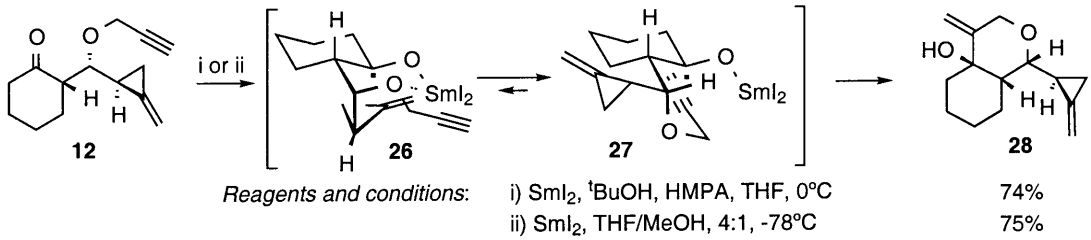
Cyclisation of propargyl ether **9** using SmI_2 with ^{t}BuOH/HMPA in THF (at −78°C) gave the tricyclic ether **25** in 50% yield, and as a single diastereoisomer (Scheme 5). An improved yield of 60% was obtained using the MeOH/THF solvent system.



Scheme 5.

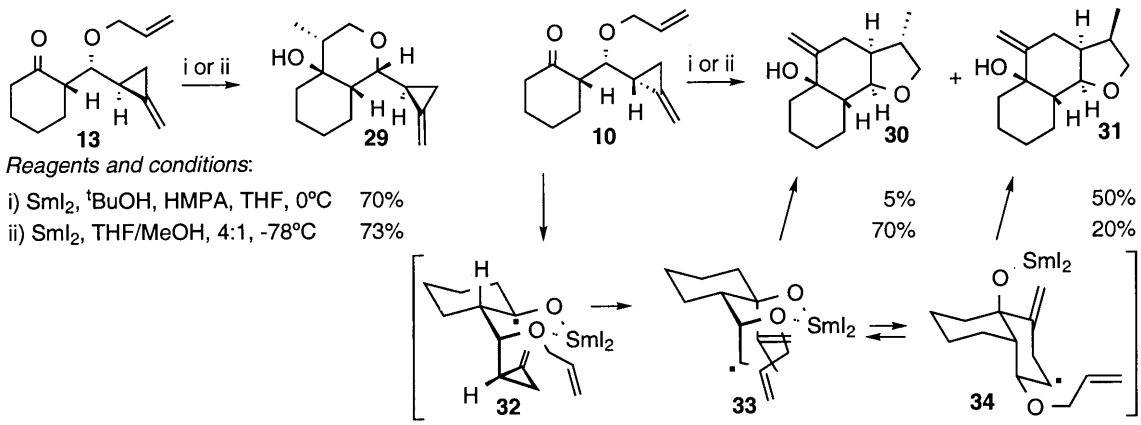
Although chelation of the propargyl ether to the ketyl-bound samarium is not as effective as with the free alcohol **8**, the preferred conformation of the ketyl radical derived from **9** can still be expected to place substituents on the starting cyclohexyl ring in an equatorial orientation as in **22**. After addition to the methylenecyclopropane and ring-opening, radical **23** cyclises on to the propargyl unit to give a *cis*-fused cyclic ether.

Cyclisation of **12**, however, under either set of conditions gave instead the bicyclic ether **28**, indicating that initial cyclisation of the ketyl radical onto the methylenecyclopropane is disfavoured and a 6-*exo* cyclisation onto the alkyne is preferred instead (Scheme 6). Presumably, while cyclisation of **9**, via intermediate **22**, places the cyclopropyl alkene bond in a satisfactory environment, *gauche* to the ketyl C–O bond, the cyclisation of **12**, via intermediate **26**, would require the cyclopropyl alkene bond to be eclipsed with the ketyl C–O bond, which would be unfavourable as a result of electronic repulsion (Scheme 6).[8] Cyclisation instead proceeds via intermediate **27**, although this does require breaking the (weak) chelate to the propargyl ether.



Scheme 6.

Finally, cyclisation of the allyl ethers **10** and **13** introduces an additional chiral centre (Scheme 7). Cyclisation of **13** gave the bicyclic ether **29**, following a 6-*exo* cyclisation onto the allyl ether in preference to the methylenecyclopropane (cf. **12**). However, cyclisation of **10** using HMPA/THF gave predominantly **31** (**30**:**31** = 1:10), whereas using MeOH/THF gave predominantly **30** (**30**:**31** = 3.5:1), and in very good yield. This unexpected reversal of stereoselectivity[9] can be understood with reference to Beckwith's[10] and RajanBabu's[11] detailed studies of the cyclisation of cyclohexyl radicals onto pendant butenyl (or allyloxy) groups. Assuming that **10** cyclises via a weakly chelated intermediate **32**, then the resulting cyclohexyl radical intermediate **33** will have the allyloxy substituent in an *axial* position, which should, according to the Beckwith/Rajan-Babu model, cyclise to give an *anti*-methyl substituent as in **30**. Flipping of conformation **33** (which involves breaking the chelation from the allyl ether oxygen to the samarium metal, and which may be favoured in the presence of HMPA) gives **34** with the allyloxy substituent in an *equatorial* position, which should cyclise to give a *syn*-methyl substituent as in **31**.



Scheme 7.

Thus samarium diiodide mediated cyclisation of methylenecyclopropyl cyclohexanone adducts, under suitable solvent conditions, provides a stereoselective route to tricyclic ethers. Extension of this methodology to the synthesis of eudesmane natural products is ongoing in our research group.

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7. Johnston, D.; McCusker, C. M.; Procter, D. J. *Tetrahedron Lett.* **1999**, *40*, 4913. Note that while a few equivalents of MeOH have been routinely used as a proton donor source in SmI_2 mediated cyclisations, here it is used in large excess as a co-solvent for the reaction.
8. Electronic repulsion between the ketyl oxygen functionality and the alkene π-system is generally accepted as being a major factor determining stereoselectivity in SmI_2 mediated cyclisations of unactivated olefinic ketones: see Ref. 4 and Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.
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