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Cascade radical cyclisations of methylenecyclopropyl ketones—synthesis of bicyclo-[3.2.1]-octanes

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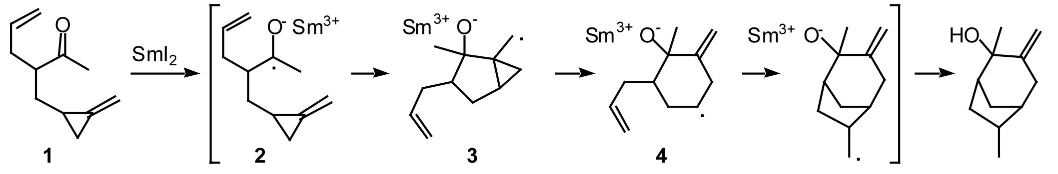
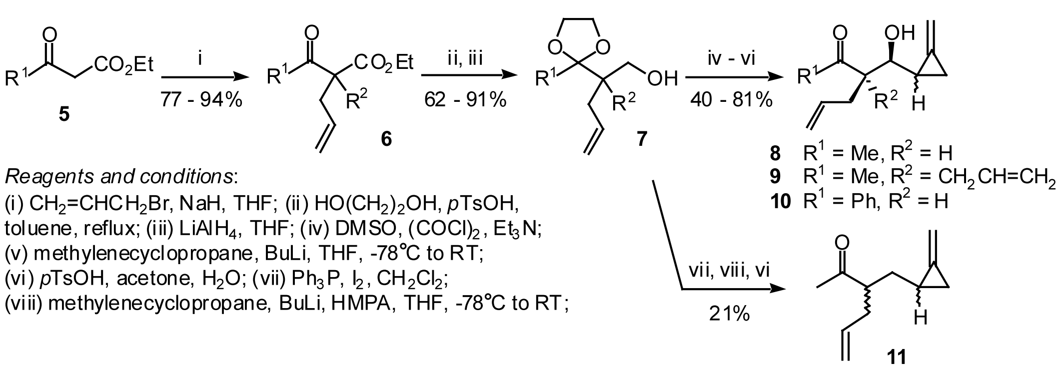
Abstract—Samarium diiodide mediated cyclisation of methylenecyclopropyl ketones, readily prepared from β-ketoesters provides a simple route to bicyclo-[3.2.1]-octanes. © 2002 Elsevier Science Ltd. All rights reserved.

We have previously shown that cyclisations of methylenecyclopropylpropyl radicals provides an efficient method for the generation of methylenecyclohexyl radicals, via a 5-*exo* cyclisation and '*endo*' opening of the resulting cyclopropylmethyl radical (e.g. **2**→**4**).[1] The methylenecyclohexyl radicals so formed can be used in further radical cyclisations leading to bicyclic products.[2] Radical cascades of this type, initiated by ketyl radicals, can be particularly efficient and can be highly diastereoselective.[3] We reasoned that cyclisations of methylenecyclopropyl ketones, such as **1**, with a suitably placed alkene radical trap could provide a route to bicyclo-[3.2.1]-octanes,[4] a common structural component of many natural products such as the kaurenoids and gibberellins (Scheme 1).

The required methylenecyclopropyl ketones were readily prepared from simple β-ketoesters by mono- or dialkylation with allyl bromide, protection of the ketone, conversion of the ester to an aldehyde, addition of methylenecyclopropyl lithium, and finally deprotection of the ketal. Using this sequence the methylenecy-



Scheme 1.



8 R^1 = Me, R^2 = H
9 R^1 = Me, R^2 = $CH_2CH{=}CH_2$
10 R^1 = Ph, R^2 = H

Reagents and conditions:
(i) $CH_2{=}CHCH_2Br$, NaH, THF; (ii) $HO(CH_2)_2OH$, *p*TsOH, toluene, reflux; (iii) $LiAlH_4$, THF; (iv) DMSO, $(COCl)_2$, Et_3N;
(v) methylenecyclopropane, BuLi, THF, -78°C to RT;
(vi) *p*TsOH, acetone, H_2O; (vii) Ph_3P, I_2, CH_2Cl_2;
(viii) methylenecyclopropane, BuLi, HMPA, THF, -78°C to RT;

Scheme 2.

Keywords: methylenecyclopropane; samarium diiodide; cyclisation.

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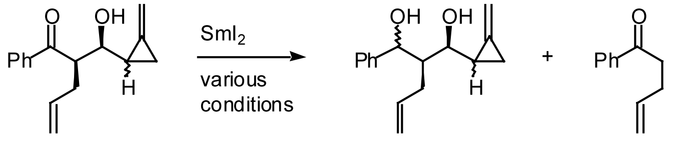
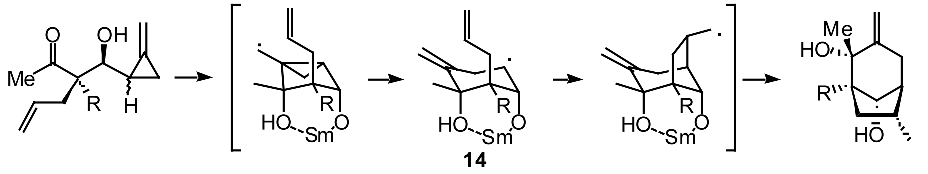


10 **12** (17 - 83%) **13** (12 - 70%)

Scheme 3.



	Reagents and conditions:	
8 R = H	2 equivs. SmI$_2$, HMPA, ^{t}BuOH, THF, 0°C	**15** R = H 71% (9:1 ratio of diastereoisomers)
9 R = CH$_2$CH=CH$_2$	4 equivs. SmI$_2$, HMPA, ^{t}BuOH, THF, -78°C	**16** R = CH$_2$CH=CH$_2$ 53% (6:1 ratio of diastereoisomers)

Scheme 4.

clopropyl ketoalcohols **8**–**10** were prepared in good overall yields (Scheme 2). Ketoalcohols **8** and **10** were both obtained as a mixture of four diastereoisomers (~9:9:1:1), from which the two major diastereoisomers, having a *syn* relationship between the resulting hydroxy and allyl groups, could be separated. Ketoalcohol **9** was obtained as a 1:1 mixture, of two diastereoisomers. Alcohol **7** was also converted to the corresponding iodide, which was displaced with methylenecyclopropyl lithium and deprotected, to give ketone **11** as a 3:1 mixture of diasteroisomers.

Cyclisation of phenyl ketone **10** was not successful under any of the conditions tried[5] (slow addition of ketone to SmI$_2$, in the presence of ^{t}BuOH (2 equiv.) and HMPA (10 equiv.) in THF[6] at 0 or −78°C; slow addition to SmI$_2$ in THF/MeOH (4:1)[7] at 0 or −78°C; reverse addition of SmI$_2$ to the ketone under similar solvent conditions) and led only to the reduced diol **12** and ketone **13** (Scheme 3), presumably formed by a retroaldol reaction, catalysed by Lewis acidic Sm^{3+}. Similarly, attempted cyclisation of **11**, led to a complex mixture of products from which no bicyclic product could be identified.

The methyl ketones **8** and **9**, however, cyclised efficiently to produce the desired bicyclooctanes **15** and **16**, with almost complete control of the stereochemistry (Scheme 4). Cyclisation of ketone **8** was best carried out by slow addition of the ketone to 2 equiv. of SmI$_2$, in the presence of ^{t}BuOH (2 equiv.) and HMPA (10 equiv.) in THF at 0°C and gave **15** in 71% yield and as a 9:1 ratio of diastereoisomers. Cyclisation of ketone **9**, on the other hand was best carried out with 4 equiv. of SmI$_2$ at −78°C to give bicyclic product **16** in 53% yield and as a 6:1 ratio of diastereoisomers.

The structure of the major diastereoisomer of **15** was determined by X-ray crystallography[8] (Fig. 1) and the structure of the major diastereoisomer of **16** was determined by comparison of NMR data and NOE experiments with that obtained for **15**.[9] The stereoselectivity can be understood by assuming chelation of the Sm^{3+} by both the ketyl oxygen and the alcohol[10] leading to the chair intermediate **14** with an allyl group held axial, and in the appropriate orientation for further cyclisation (Scheme 4).

In conclusion, methyl ketones incorporating a methylenecyclopropane can be used in SmI$_2$ mediated cascade cyclisations to provide the bicyclooctane skeleton with excellent stereocontrol, although the presence of an alcohol group in the substrate, to chelate to the ketyl samarium, appears to be essential for efficient cyclisation.

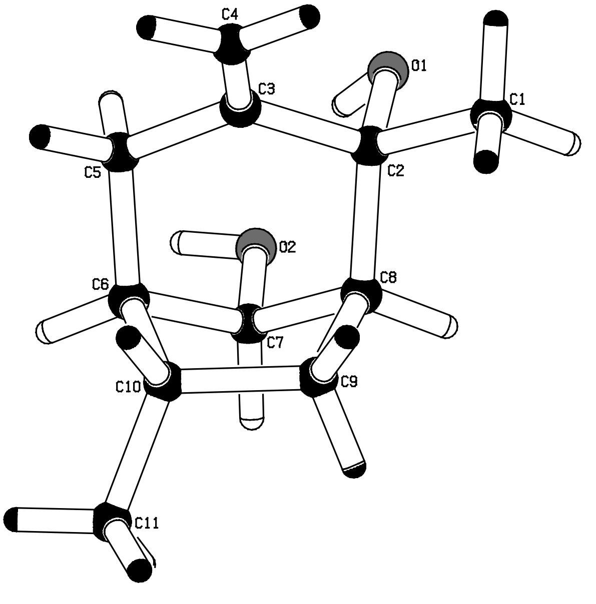


Figure 1. X-Ray crystal structure of **15**.

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