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# STEREOSELECTIVE TANDEM RADICAL CYCLISATIONS: SYNTHESIS OF ISOIRIDOMYRMECIN

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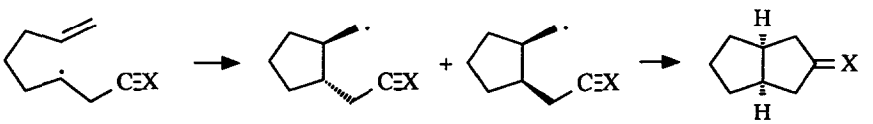
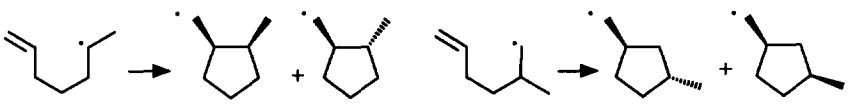
**Abstract.** Tandem radical cyclisation of bromide (**8b**) led to bicyclic ketone (**13**), an intermediate in the synthesis of isoiridomyrmecin (**14**), demonstrating that highly stereoselective tandem cyclisations from acyclic precursors can be achieved if the precursor is suitably substituted.

We have become interested in using tandem radical cyclisations[1] from acyclic precursors (Scheme 1) to synthesise *cis* fused bicyclic products and particularly bicyclo-3.3.0-octan-3-ones.



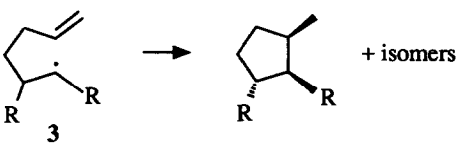

Scheme 1

The limitation of this approach is that the yield of such bicyclic products is controlled by the degree of *cis* selectivity on the first cyclisation, which is often rather modest. Beckwith[2] has reported guidelines for predicting the stereochemical outcome of simple alkyl substituted hexenyl radical cyclisations, so cyclisation of (**1**) gives a predominance of the *cis* product whereas cyclisation of (**2**) gives largely *trans* product. However, despite the investigations of RajanBabu in particular, who has studied the stereochemical outcome of cyclisations of polysubstituted hexenyl radicals derived from carbohydrates[3], it is not clear to what extent simple disubstitution can work cooperatively to control the stereochemistry of the cyclopentane product.



**1** 73 : 27 **2** 65 : 35

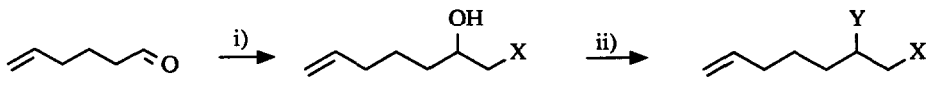
We reasoned that if the cyclisation of disubstituted radicals such as (**3**) followed Beckwith's guidelines and showed high stereoselectivity then an efficient approach to bicyclic products from simple acyclic precursors would be possible.




**3**

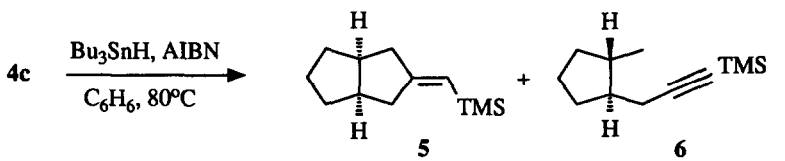
We have tested this idea and in this paper we describe our initial results which show that our expectations have been realised and have allowed a formal synthesis of isoiridomyrmecin (**14**), a member of the monoterpene iridoids.

In an effort to prepare bicyclooctanones directly we first tried using a nitrile group to terminate the second cyclisation[4]. However treatment of either (**4a**) or (**4b**) with $Bu_3SnH$ and catalytic AIBN in refluxing benzene gave no bicyclic products. Using a trimethylsilyl acetylene group to terminate the second cyclisation, reaction of the bromide (**4c**) ($Bu_3SnH$, AIBN) now gave the expected *cis* fused bicyclic product (**5**) and the *trans* substituted cyclopentane (**6**) in 62 % and 16 % yield respectively, although (**5**) appears to be contaminated with approximately 5 % of the *trans* fused bicyclic product. This result mirrors that of Beckwith[5] who found that cyclisation of the bromide (**4d**) gave 58 % of products resulting from *cis* selectivity on the first cyclisation, and 23 % from *trans* selectivity.

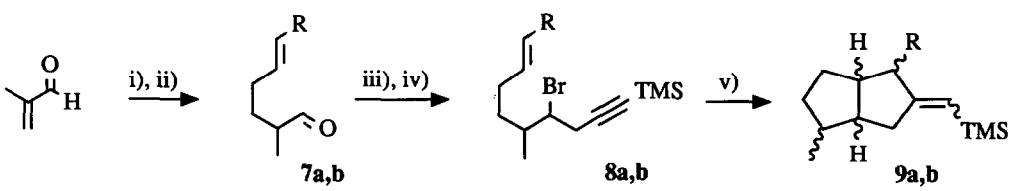



i) $LiCH_2CN$ or $LiCH_2C{\equiv}CSiMe_3$
ii) $CBr_4$, $Ph_3P$ or $Im_2C{=}S$ Im = N N

**4a** X = CN, Y = Br
**4b** X = CN, Y = O.CS.Im
**4c** X = C≡CSiMe$_3$, Y = Br
**4d** X = CH=CH$_2$, Y = Br




We next looked at the effect of introducing a methyl group α to the starting radical. Reductive cyclisation of bromide (**8a**) (prepared in four steps *via* an oxy-Cope rearrangement to give aldehyde (**7a**)) again using the $Bu_3SnH$ method, gave a 71 % yield of four bicyclic products in the ratio 47:44:5:4 (GC analysis).

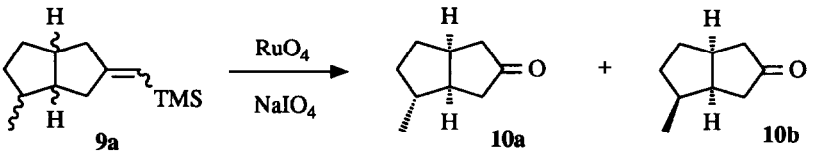



i) R MgBr, 50 - 60 %; ii) KH, THF, reflux, 60 - 70 %;
iii) $LiCH_2C{\equiv}CSiMe_3$, 75 - 80 %; iv) $CBr_4$, $Ph_3P$, 65 - 70 %; v) $Bu_3SnH$, cat. AIBN

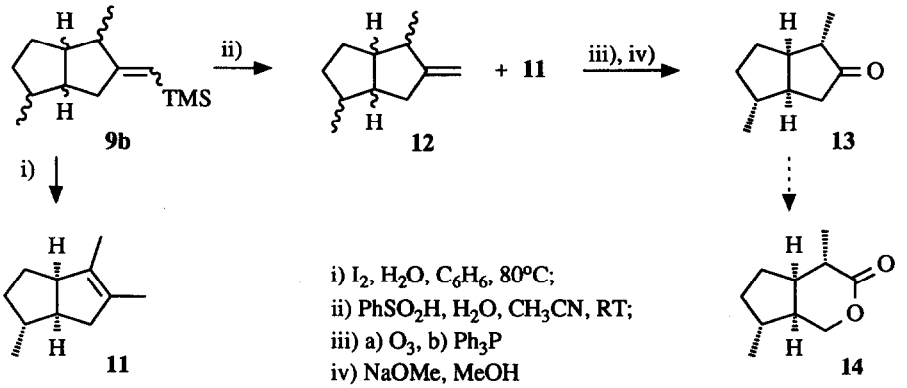
**a**: R = H
**b**: R = Me

Oxidative cleavage ($RuO_4$, $NaIO_4$) of the double bond gave two ketone products in rather low yield (42 %) but in a ratio of 10:1, indicating that, not surprisingly, the vinyl silane moiety was produced stereo randomly. Based on Beckwith's guidelines[2] we believe that ketone (**10a**) is the major isomer and assume (**10b**) to be the minor, although a *trans* fused bicyclic system cannot be ruled out. Thus, further substitution with a

methyl group has, as desired, improved the *cis* selectivity of the first cyclisation, as evidenced by the improved yield of bicyclic material (71 %), and has proceeded with remarkably high control (≥10:1) of the new C-Me stereocentre.

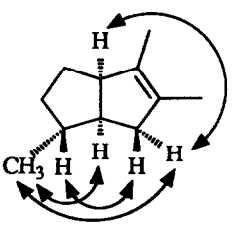



In order to verify the stereochemical outcome of this cyclisation, and to show the utility of this approach to natural product synthesis, we next synthesised the known bicyclic ketone (**13**) which can be converted in two steps to isoiridomyrmecin[6] (**14**).




An oxy-Cope rearrangement gave aldehyde (**7b**) (>95:5 **E**:**Z**) which was converted, as before, to the bromide (**8b**). Treatment with $Bu_3SnH$/AIBN now gave a 73 % yield of bicyclic compounds as a mixture of isomers. Attempted protodesilylation of the isomeric mixture with $I_2/H_2O$ in refluxing benzene gave the bicyclic alkene (**11**), the product of desilylation but with double bond migration into the ring, in 89 % yield. Although not the intended result, (**11**) was obtained as essentially a single product[7] emphasising the excellent control over three stereocentres exhibited by the tandem cyclisation. The well resolved $^1H$ NMR of (**11**) allowed us to confirm the relative stereochemistry using nOe's (see fig. 1).

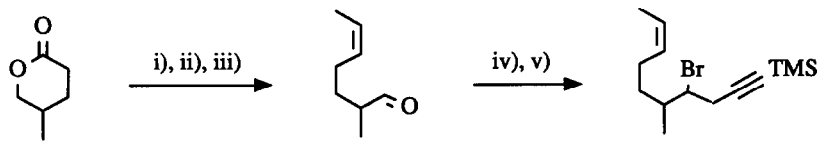
Fig. 1




Relevant nOe's for **11**

Treatment of (**9b**) with the milder $PhSO_2H$ gave the desired exocyclic alkene (**12**) in 70 % yield, as a mixture of largely two isomers in a ratio 3:1, contaminated with ~25 % of (**11**). Ozonolysis and equilibration

with NaOMe/MeOH then gave ketone (**13**), the thermodynamically preferred isomer, which was isolated as essentially a single product[8] in 54 % overall yield from (**9b**). The stereochemistry was further confirmed by the $^{13}C$ NMR which was identical to that reported by Vandewalle[6]. Finally we prepared bromide (**16**) with largely a *cis* double bond (**Z:E**>90:10) from lactone (**15**)[9] to test whether the double bond geometry would influence the stereoselectivity of the first cyclisation as has been suggested elsewhere in the literature[10]. However cyclisation of bromide (**16**) led to bicyclic products (**9b**) with no significant difference in yield or isomer ratio as compared to the cyclisation of (**8b**).




**15** **16**

i) DIBAL, - 78°C; ii) $EtPh_3P^+I^-$, BuLi; iii) PDC; iv) $LiCH_2C{\equiv}CSiMe_3$; v)$CBr_4$, $Ph_3P$

In conclusion a tandem radical cyclisation from an acyclic precursor has led to the preparation of ketone (**13**) in a highly stereoselective manner, completing a formal synthesis of isoiridomyrmecin, but more significantly, demonstrating that disubstitution can act cooperatively to control stereoselectivity in hexenyl radical cyclisations.

**Acknowledgements.** We thank Dr O W Howarth and the SERC NMR Service at the University of Warwick for the nOe experiments, Dr V K Aggarwal and the University of Bath for use of their ozonolysis apparatus, and Glaxo Group Research for supporting this work.

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1. For a review of radical cyclisations in general and tandem cyclisations in particular see D P Curran, *Synthesis*, **1988**, 417 and 489. For tandem cyclisations from linear acyclic precursors see ref 5 and E Kariv-Muller, H Maeda and F Lombardo, *J Org Chem*, **1989**, *54*, 4022.

2. A L J Beckwith and C H Scheisser, *Tetrahedron*, **1985**, *41*, 3925.

3. T V RajanBabu, T Fukunaga, G S Reddy, *J Am Chem Soc*, **1989**, *111*, 1759, and references therein.

4. For the use of nitriles in radical cyclisations see D L J Clive, Beaulieu P L and L J Set, *J Org Chem*, **1984**, *49*, 1313.

5. A L J Beckwith, G Phillipou, A K Serelis, *Tetrahedron Lett*, **1981**, *22*, 2811.

6. P Callant, R Ongena, M Vandewalle, *Tetrahedron*, **1981**, *37*, 2085.

7. >90 % pure by GC and NMR; the major contaminant (~5 %) appears to be the result of double bond migration to the less substituted position in the ring.

8. Any other isomers were present in a total of less than 10 % by GC and NMR.

9. Lactone (**15**) was prepared by the method of J-M Surzur and P Teissier, *Bull Soc Chim Fr*, **1970**, 653.

10. See for example C S Wilcox and L M Thomasco, *J Org Chem*, **1985**, *50*, 546; M Ihara, K Yasui, N Tanaguchi and K Fukumoto, *Tetrahedron Lett*, **1988**, *29*, 4963; A L J Beckwith, D H Roberts, C H Scheisser and A Wallner, *Tetrahedron Lett*, **1985**, *26*, 3349.

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