The synthesis of angularly fused tricyclic compounds *via* tandem ring closing metathesis reactions†

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A novel and highly efficient approach to angularly fused tricycles has been developed through the employment of selective tandem ring closing metathesis reactions.

Angularly fused tricycles represent a structurally intriguing unit present in many natural products and have attracted the attention of synthetic chemists for a number of years.[1] Amongst prominent targets of this class of compounds are triquinanes and marine alkaloids, of which there are a plethora of examples with a variety of biological activities. In the process of our investigations into the scope of tandem ring closing metathesis (RCM) reactions[2] for the synthesis of functionalised carbon skeleta,[3,4] we have turned our attention to the application of this technique to the formation of angularly fused tricycles by employing the general strategy outlined in Fig. 1. Specifically, we were interested in observing the relative ease of tricycle formation (mode a cyclisation) *versus* that of spirocyclisation (mode b cyclisation), and additionally, whether spirocycles would themselves participate in tricycle formation. In this regard, the groups of Grubbs[4a] and Mioskowski[4e] have shown that tandem metathesis (mode a type) cyclisation products are highly favoured, and can indeed be generated by ring opening/closing metathesis of mode b type substrates.

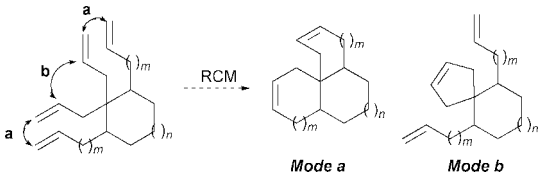
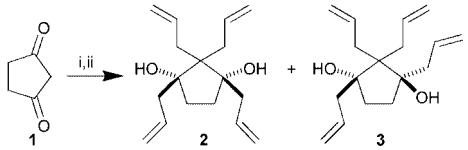


Fig. 1

We prepared a suitable model system through a routine two step procedure, which provided both *syn*- and *anti*-diols **2** and **3** which were readily separated by column chromatography (Scheme 1).

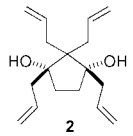
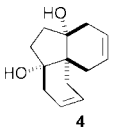
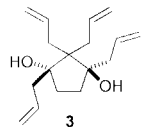
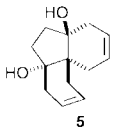
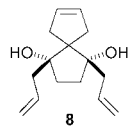
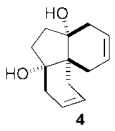
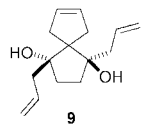
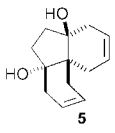
With the desired tetraenes in hand, we turned our attention to the tandem RCM reaction paying particular regard to the selectivity of tricycle *versus* spirocycle formation. Subjection of *syn*-tetraene **2** to 20 mol% Grubbs' catalyst PhCH=Ru(P-$Cy_3)_2Cl_2$ **I** for 48 h gave a complex reaction mixture[5] from



Scheme 1 *Reagents and conditions*: i, CH_2=$CHCH_2OAc$, 0.8% $Pd(PPh_3)_4$, DBU, 74%; ii, CH_2=$CHCH_2MgCl$, 73%, 6:1 *syn*:*anti*.

† Electronic supplementary information (ESI) available: general experimental and synthetic and spectral data for the new compounds. See http://www.rsc.org/suppdata/cc/b0/b002136i/

Table 1 Ru-catalysed preparation of angularly fused tricycles[a]

Entry	Substrate	Product	Yield (%)
1	 **2**	 **4**	38[b]
2	 **3**	 **5**	72
3	 **8**	 **4**	40[c]
4	 **9**	 **5**	85

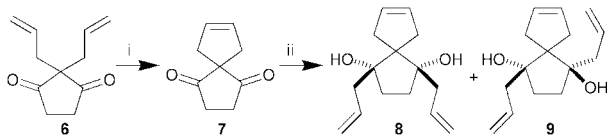
[a] All reactions carried out in dichloroethane at 60 °C for 48 h using 10 mol% **I**. [b] Reaction required 20 mol% **I**. [c] 49% of **8** recovered.

which the desired tricycle **4** could be isolated in 38% yield as a stable crystalline solid (Table 1, entry 1). In contrast to **2**, the *anti*-diol **3** underwent smooth and selective cyclisation to tricycle **5** in high yield (Table 1, entry 2).[6]‡

We were intrigued that the potentially competing spirocyclisation process was not evident under any of the reaction conditions employed, however, we could not rule out the possibility that the spirocycles were formed transiently and reacted *in situ* to furnish the observed tricyclic products. In an attempt to further clarify this issue, we prepared the appropriate spirocycles by the route shown in Scheme 2.

Surprisingly, RCM of diene **6** was rather sluggish and required extensive heating and relatively high catalyst loadings to achieve useful product yield.[7] Nonetheless, the subsequent Grignard alkylation reaction proceeded smoothly to provide a mixture of *syn*- and *anti*-diols in good yield.

Both spirocyclic substrates **8** and **9** were stable to the Ru-catalyst at 25 °C but provided the corresponding tricycles in



Scheme 2 *Reagents and conditions*: i, 10 mol% **I**, 60 °C, DCE, 48 h, 67%; ii, CH_2=$CHCH_2MgCl$, 66%, 5:1 *syn*:*anti*.

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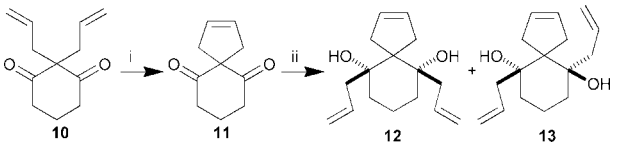


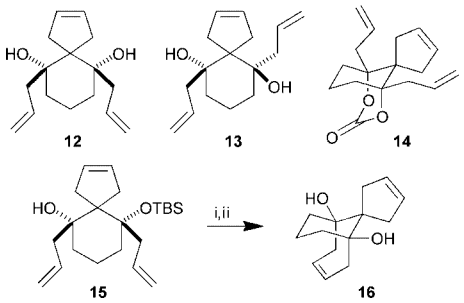
Scheme 3 *Reagents and conditions*: i, 2 mol% **I**, 25 °C, CH_2Cl_2, 16 h, 92%; ii, CH_2=$CHCH_2MgCl$, 85%, 2 : 1 *syn* : *anti*.

comparable yields to those from the appropriate tetraenes in the presence of 10 mol% **I** at elevated temperatures (entries 3 and 4 of Table 1). These results demonstrate that whilst spirocycles **8** and **9** have not been observed in the RCM reactions of **2** and **3**, they cannot be ruled out as intermediates in the reaction process.

In extending this chemistry to six-membered ring analogues we encountered some surprising differences in reactivity. Firstly, all attempts to add allyl magnesium halides to 2,2-diallylcyclohexa-1,3-dione (**10** in Scheme 3) failed to furnish the desired tetraene substrate. We therefore turned our attention to the preparation of the corresponding spirocyclic substrates as outlined in Scheme 3.

In sharp contrast to the RCM reaction of diene **6**, cyclohexane analogue **10** underwent smooth ring closure at room temperature in the presence of 2 mol% **I** to provide the spirocycle **11** in excellent yield. Additionally, this substrate was readily alkylated to give the expected diols **12** and **13** in good yield.

Once again, in contrast to the cyclopentanedione spirocycles, we have found the corresponding cyclohexane analogues to be extremely unreactive towards Ru-catalysed tricycle formation. As outlined in Scheme 4, the *syn*- and *anti*-spirocycles **12** and **13** were inert to metathesis even on prolonged heating with 20 mol% Ru-catalyst. Protection of the diol unit as mono-silyl ether **15** provided bridged bicycle **16** in 64% overall yield, after removal of the TBS-group, as the only metathesis reaction product. In this particular case, it is likely that the increased steric demands of the OTBS unit provides a greater concentration of the diaxial diene conformation and facilitates seven-membered ring closure. We therefore tethered the diol units in the axial position by the preparation of cyclic carbonate **14**,[8] however, once again this substrate was found to be unreactive.



Scheme 4 *Reagents and conditions*: i, 15 mol% **I**, 80 °C, C_6H_6, 48 h; ii, TBAF, 64% overall yield.

The notable difference in reactivity of the cyclopentane-derived spirocycles in comparison to the cyclohexane analogues is unclear at present, however, the relative ease of RCM of diene **10** in comparison to **6** and the ready conversion of spirocycles **8** and **9** *versus* that of **12** and **13** suggests that these differences may originate from the relative strain in the respective cyclopentene moieties.[9] Nonetheless, we have shown that tandem RCM is a viable method for the rapid assembly of *cis,trans*- and *cis,cis*-fused tricyclic skeleta.[10] The application of this methodology in target orientated synthesis and the further study of the selectivity issues raised in this communication are currently under investigation.

We are grateful to the EPSRC for studentships (M. J. B. and A. S. E.) and to AstraZeneca for financial support.

Notes and references

‡ *Crystal data* for $C_{13}H_{18}O_2$ **5** at 150 K: M = 206.27, orthorhombic, space group *Pbca* (no. 61), a = 8.6041(5), b = 13.1932(7), c = 19.0521(10) Å, U = 2162.7(2) Å^3, Z = 8, D_c = 1.267 g cm^{-3}. Mo-Kα radiation (λ = 0.71073 Å), μ(Mo-Kα) = 0.083 mm^{-1}, F(000) = 896. Data were collected in the range 3.02 < θ < 28.27°, 2624 independent reflections (R_{int} = 0.0679), final R = 0.0572, with allowance for the thermal anisotropy of all non-hydrogen atoms.

CCDC 182/1621. See http://www.rsc.org/suppdata/cc/b0/b002136i/ for crystallographic files in .cif format.

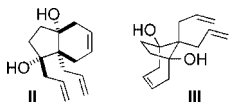
1 For representative alkaloid examples, see: K. M. Werner, J. M. de los Santos and S. M. Weinreb, *J. Org. Chem.*, 1999, **64**, 686; W. H. Pearson and Y. Ren, *J. Org. Chem.*, 1999, **64**, 688; C. Sha, F. Lee and C. Chang, *J. Am. Chem. Soc.*, 1999, **121**, 9875; for synthetic approaches to triquinanes, see: G. Mehta and S. Srikrishna, *Chem. Rev.*, 1997, **97**, 671.

2 For recent reviews on the ring closing metathesis reaction in organic synthesis see: S. K. Armstrong, *J. Chem. Soc., Perkin Trans. 1*, 1998, 371; R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413; M. Schuster and S. Blechert, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2036.

3 M. J. Bassindale, P. Hamley, A. Leitner and J. P. A. Harrity, *Tetrahedron Lett.*, 1999, **40**, 3247.

4 For other examples of tandem diene metathesis reactions, see: (*a*) W. J. Zuercher, M. Hashimoto and R. H. Grubbs, *J. Am. Chem. Soc.*, 1996, **118**, 6634; (*b*) S. D. Burke, K. J. Quinn and V. J. Chen, *J. Org. Chem.*, 1998, **63**, 8626; (*c*) W. J. Zuercher, M. Scholl and R. H. Grubbs, *J. Org. Chem.*, 1998, **63**, 4291; (*d*) M. Lautens and G. Hughes, *Angew. Chem., Int. Ed.*, 1999, **38**, 129; (*e*) C. Baylon, M. Heck and C. Mioskowski, *J. Org. Chem.*, 1999, **64**, 3354; (*f*) A. H. Hoveyda, in *Topics in Organometallic Chemistry*, ed. A. Furstner, Springer-Verlag, Berlin, 1998, vol. 1, pp. 105–132.

5 We have isolated and tentatively assigned (NMR and mass spectrometry) compounds **II** and **III** from the reaction mixture. Their rigorous characterisation is currently underway and will form part of a full account.



6 The stereochemical assignment of **5** is based on the significant stability of the *cis,cis*-isomer over the alternative *trans,trans*-isomer, calculated to be *ca*. 30 kcal mol^{-1} using AM1 semiempirical methods implemented using Spartan™ software. The assignment of **4** was based on X-ray crystallographic analysis.

7 In the course of this study the RCM reaction of diene **6** was reported to proceed in good yield (77%) at room temperature: S. Kotha, E. Manivannan, T. Ganesh, N. Sreenivasachary and A. Deb, *Synlett*, 1999, 1618. This result could not be reproduced in our hands.

8 Prepared by addition of diol **12** to oxalyl chloride in the presence of pyridine and DMAP catalyst.

9 Additionally, the poor reactivity of the cyclohexane system may originate from the inability of the appropriate alkene units to attain sufficient alignment for metathesis. We thank a referee for this suggestion.

10 All compounds exhibited satisfactory analytical and spectral data.