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# Unusual macrocyclic spirocycles from tandem metathesis reactions

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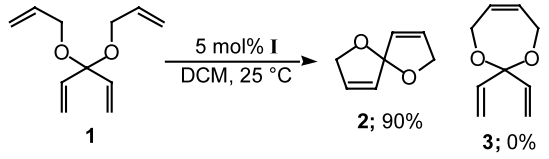
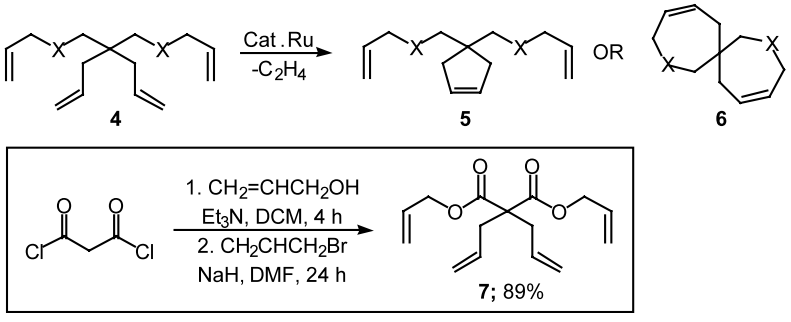
**Abstract**—This letter details the formation of 18-membered macrocyclic spirocyclic esters and ethers from readily prepared tetraene precursors via tandem metathesis reactions. Factors which control the course of these transition metal catalysed processes are discussed and the crystal structures of the novel macrocycles obtained are delineated. 

Tandem ring closing metathesis (RCM) reactions of polyolefinic compounds represent an efficient strategy for multiple carbon–carbon bond formation that provide synthetic intermediates with readily manipulated alkene functionality.[1] Our own research efforts in this area have been directed towards the employment of this methodology for the synthesis of spirocyclic and angularly fused tricyclic compounds.[2] More importantly however, we have largely focused on the utilisation of substrates where a number of possible RCM events can occur in an effort to uncover selective reaction pathways. For example, in an early report we discovered that the tandem RCM reaction of tetraene **1** in the presence of Grubbs' catalyst $Ph(H)C{=}RuCl_2(PCy_3)_2$ **I**[3] selectively furnished spiroacetal **2** exclusively in preference to cyclic acetal **3** (Scheme 1).[2c] More recently, we have been investigating related selectivity issues within the preparation of larger ring spirocyclic compounds; we wish to report herein our progress in this area.




**Scheme 1.**

As outlined in Scheme 2, we were intrigued by the possible regiochemical outcomes of RCM reactions on tetraenes such as **4**. We expected that cyclopentene **5** would be the kinetically preferred product, however, we were confident that this compound would interconvert to the desired spirocycle **6** under more forcing condi-




**Scheme 2.**

*Keywords*: spirocycles; macrocycles; ruthenium; ring closing metathesis.

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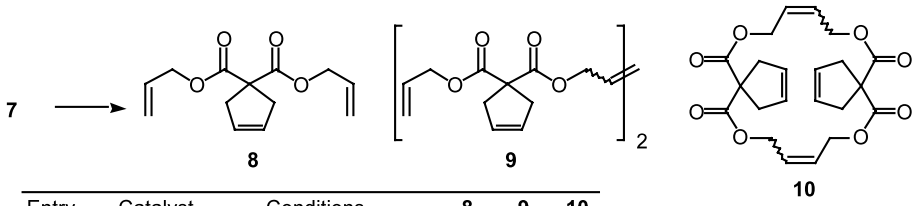
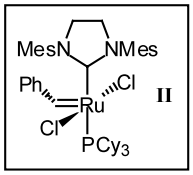
**Table 1.** Tandem RCM reaction of tetraene **7**




| Entry | Catalyst | Conditions | 8 | 9 | 10 |
|---|---|---|---|---|---|
| 1 | 5 mol% **I** | DCM, 20°C, 16 h | 50% | 19% | 19% |
| 2 | 5 mol% **I** | DCE, 60°C, 48 h | 72% | 4% | Trace[a] |
| 3 | 5 mol% **II** | Toluene, 80°C, 24 h | 24% | 13% | 42% |
| 4[b] | 5 mol% **II** | Toluene, 80°C, 5 d | 16% | 11% | 45% |

[a]18% **7** Recovered. [b]Cyclopentene **8** used as starting material.

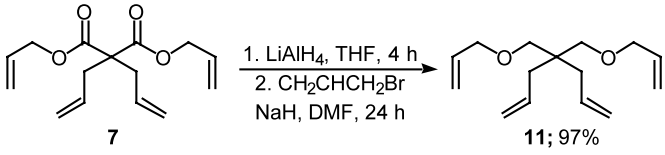



tions after loss of an extra equivalent of ethylene. In the event, we chose to prepare a simple malonate based tetraene **7** through a two step synthesis to determine the feasibility of spirocycle formation in this case versus competing metathesis pathways (Scheme 2). Therefore, treatment of malonyl dichloride with allyl alcohol and $Et_3N$ provided diallyl malonate which was transformed to **7** upon treatment with base and allyl bromide in 89% overall yield.

Subjecting tetraene **7** to 5 mol% of commercially available Grubbs' catalyst **I** rapidly resulted in formation of a new product which was identified as cyclopentene **8**. In an effort to interconvert **8** to the desired spirocyclic product, we allowed the reaction to proceed overnight. TLC analysis indicated that two major new compounds had been formed in that time and the crude reaction mixture was purified chromatographically. As outlined in Table 1, we found that cyclopentene **8** was isolated as the major component, but surprisingly, neither of the two other compounds isolated were the desired spirocyclic product. Instead, these compounds were identified as dimeric compound **9** and 18-membered macrocycle **10**, each of which were isolated as a mixture of olefin isomers.[4] The employment of a higher reaction temperature resulted in cleaner formation of cyclopentene **8** (entry 2), whereas the yield of macrocycle **10** could be improved by subjecting tetraene **7** or cyclopentene **8** to the more active second generation catalyst **II**[3,5] (entries 3 and 4). The macrocycle **10** was isolated as a colourless crystalline solid and slow cooling of a solution of **10** in acetone provided suitable crystals for X-ray analysis, the structure is shown in Fig. 1. A notable feature of the X-ray crystal structure is that it shows that the macrocycle is able to accommodate the more favourable *s*-cis conformation of the ester moieties.[6] Indeed, the reluctance of tetraene **7** or cyclopentene **8** to generate the spirocyclic product is likely a consequence of the ester conformation which precludes a 7-membered ring forming metathesis event.

In considering the rationale that ester conformation was responsible for preventing 7-membered ring closure, we decided to prepare the analogous *ether* substrate. Accordingly, reduction of diester **7** and subsequent base promoted allylation of the resulting 1,3-diol provided the requisite tetraene **11** in excellent overall yield (Scheme 3).

Subjection of tetraene **11** to the first generation Ru-catalyst **I** at room temperature and 60°C resulted in a complex mixture of products, from which compounds derived from RCM of the diallyl moiety were once again predominant with cyclopentene **12**, dimer **13** and




**Scheme 3.**

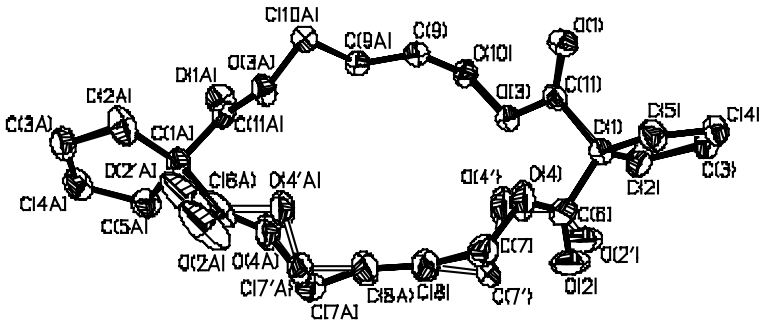
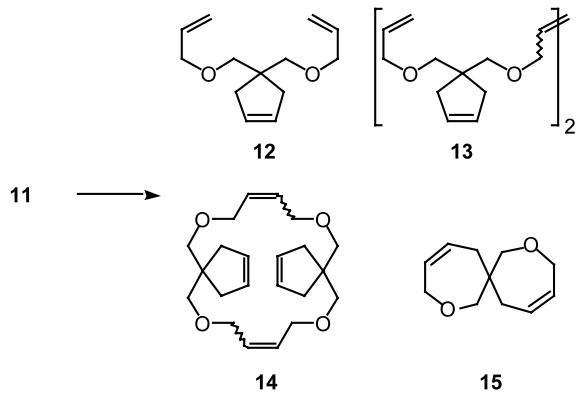
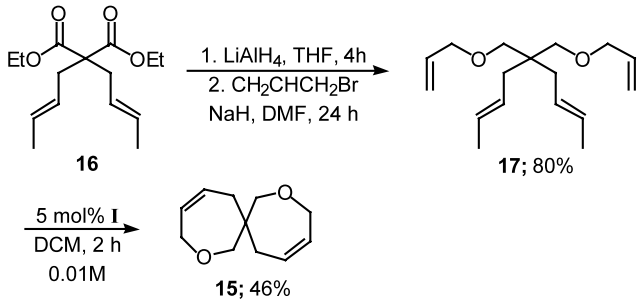


**Figure 1.** ORTEP diagram of macrocyclic ester **10** with thermal ellipsoids shown at 50% probability level, H-atoms omitted for clarity. (O2, O4 and C7 were found to be disordered and refined to a 83:17% occupancy.)




| | 12 | 13 | 14 | 15 |
|---|---|---|---|---|
| 5 mol% **I**, 60 °C, DCE, 30 min. | 43% | 13% | 6% | 21% |
| 5 mol% **I**, RT, DCM, 16 h. | 18% | 13% | 18% | 11% |

**Scheme 4.**




**Scheme 5.**

macrocycle **14** being isolated (Scheme 4).[7] The formation of the macrocyclic ether **14** was unexpected, nonetheless, once again the product was readily characterised by X-ray crystallography (Fig. 2).[8] Although changing from ester **7** to ether **11** did not alter the reaction course substantially, it was notable that in this case a small amount of the desired spirocycle **15** was isolated from the reaction mixture. Unfortunately however, recourse to various reaction conditions failed to improve the yield of this compound.[9] We next examined whether spirocycle **15** resulted from the tandem RCM of tetraene **11** and/or after a ring opening–ring closing metathesis reaction of cyclopentene **12**.[10] Indeed, subjection of cyclopentene **12** to catalyst **I** failed to produce spirocycle **15** and we therefore surmised that the latter product was the result of a kinetically controlled tandem RCM reaction of **11**. Additionally, it appeared likely that 7-membered ring formation would only result after catalyst insertion into the allyl ether alkene moiety, since any catalyst insertion into the alternative alkene would likely result in rapid cyclopentene formation.[11] Accordingly, in an effort to direct catalyst insertion to the allyl ether alkene (and thus direct oxepine formation) we decided to prepare ether tetraene **17** (Scheme 5).

Reduction and allylation of substituted diallyl malonate **16**[12] proceeded without incident to provide the desired substrate **17** in high yield. Unfortunately however, the tandem RCM reaction of **17** again furnished a complex reaction mixture which consisted of polymeric products which appeared to derive from acyclic diene metathesis at the allylic ether alkene moieties. In an effort to attenuate this side reaction, we employed higher dilution conditions. Pleasingly, conducting the reaction in 0.01 M DCM in the presence of 5 mol% **I** provided a much cleaner reaction and furnished spirocyclic ether **15** in a moderate but much improved 46% yield.

In conclusion, we have found that structurally unusual macrocyclic spirocyclic esters and ethers can be formed by tandem metathesis reactions of malonate based tetraene precursors. These compounds appear to be generated after a fast cyclopentene forming RCM reaction followed by acyclic diene metathesis (to form dimeric products) and a final RCM reaction. Finally, spirocyclic oxepine **15** can be generated in moderate yield after two tandem RCM reactions on an appropriately substituted tetraene **17**.

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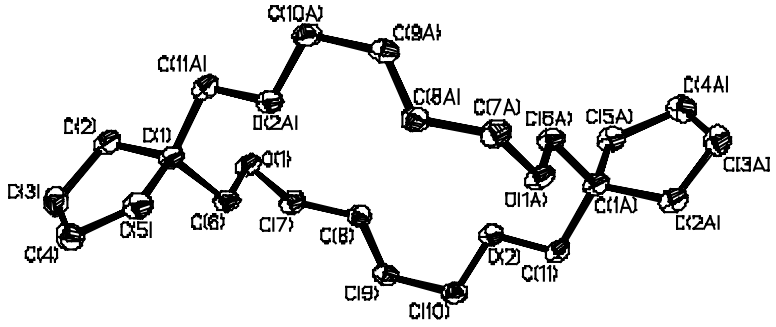


**Figure 2.** ORTEP diagram of macrocyclic ether **14** with thermal ellipsoids shown at 50% probability level, H-atoms omitted for clarity.

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3. For an account of the mechanism and activity of Ru-based metathesis catalysts see: Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.
4. Detailed elucidation of the relative quantities and specific configurations of each olefin isomer was not performed.
5. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
6. For a general discussion see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p. 618.
7. Dimer **13** and macrocycle **14** were isolated as *E*/*Z* mixtures from chromatography as judged by GC MS and $^1$H NMR spectroscopy. Detailed elucidation of the relative quantities and specific configurations of each olefin isomer was not performed.
8. Crystallographic data (excluding structure factors) for the structures **10** and **14** in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 191930 and 191931, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
9. The remaining mass balance of the reaction mixture consisted of high molecular weight polymeric material which was not fully characterised. Additionally, subjecting tetraene **11** to catalyst **II** resulted in substantial isomerisation of the allyl ether moieties to the corresponding vinyl ethers. For a recent example of olefin isomerisation mediated by **II**, see: Bassindale, M. J.; Hamley, P.; Harrity, J. P. A. *Tetrahedron Lett.* **2001**, *42*, 9055 and references cited therein.
10. For a similar class of rearrangement reactions see: Adams, J. A.; Ford, J. G.; Stamatos, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *64*, 9690.
11. Indeed, the example outlined in Scheme 1 represents a case where exclusive 5-membered ring forming RCM takes place at the expense of potentially competing 7-membered ring formation. See Ref. 2c for a discussion.
12. Bhar, S.; Chauhuri, S. K.; Sahu, S. G.; Panja, C. *Tetrahedron* **2001**, *57*, 9011.