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A quadruple ring-closing metathesis reaction in the synthesis of bis-spirocyclic compounds: extending the scope of metathesis chemistry

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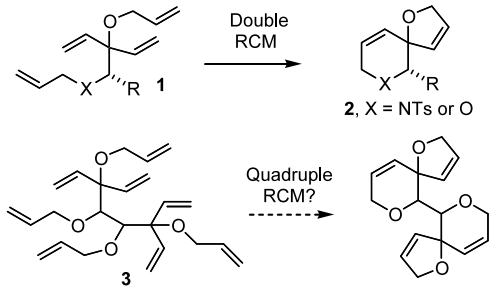
Abstract—The first example of a quadruple ring-closing metathesis reaction is reported. The reaction of the C2 symmetric octaene **3** afforded bis-spirocyclic compounds in high yield.

In the past decade the ring-closing metathesis (RCM) reaction has evolved to become a major tool for synthetic organic chemists and has been applied to the synthesis of heterocyclic, carbocyclic and macrocyclic molecules.[1] Recently, the use of double RCM reactions of tetraenes has been exploited to provide annulated,[2] spirocyclic,[3] and other bicyclic systems[4] from acyclic precursors in a single step.[5,6] Additionally, Heck et al. have now reported a triple RCM reaction of a hexaene to give a triadjacent cyclic ether.[7] We recently published the double RCM reaction of tetraenes **1** which afforded spirocycles such as **2** with a high degree of stereoselectivity (Scheme 1).[8]

As part of an ongoing interest in multiple RCM reactions we considered extending this strategy to a quadruple ring-closing reaction. In this paper the preliminary results on this reaction are reported.



Scheme 1.

Octaene **3** was considered a viable target for the quadruple RCM study. Ring-closing reactions of this substrate could generate both C2 symmetric and desymmetrized tetracycles providing an interesting range of novel products. The synthesis of this compound could also be envisaged starting from a readily available tartrate ester using comparable chemistry to that developed in our previous work. Hence, using the conditions developed for the dibenzylation of dimethyl L-tartrate,[9] the diallyl ether **4** was obtained in 46% yield (Scheme 2). Unfortunately, the cerium-mediated addition of vinylmagnesium bromide to this substrate failed to afford the desired product, yielding solely the lactone **5**.[10] In the absence of cerium chloride the desired diol **6** was formed as the minor component in an inseparable mixture also containing the conjugate addition product **7**. Fortunately, subjection of this mixture to forcing alkylation conditions gave compounds **3** and **8** which could then be separated by column chromatography to give the desired octaene **3** (13% yield over the two steps) and hexaene **8** (45% yield from **4**). A similar synthetic route starting from the acetonide of dimethyl L-tartrate failed when the protecting group could not be removed without decomposition of the molecule. Despite the modest yields sufficient quantities of octaene **3** were generated from the above route to study the key RCM reaction.[11]

Treatment of octaene **3** with the Grubbs' catalyst **9**[12] (20 mol%) in a portionwise manner led to complete consumption of starting material and generation of several new compounds as assessed by TLC analysis. After 24 hours the reaction had reached an apparent resting state consisting of just two products, both of which resulted from quadruple RCM reactions. These

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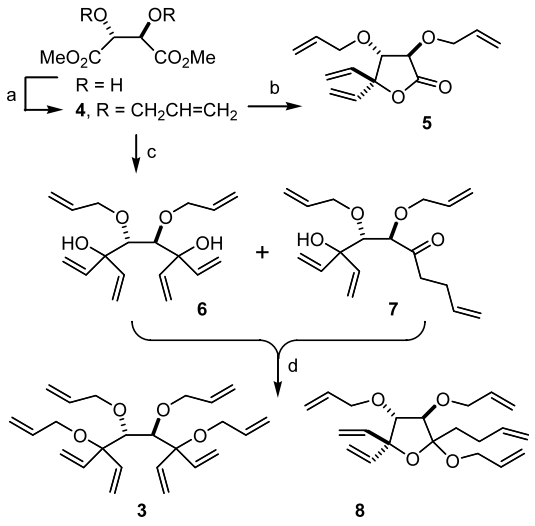
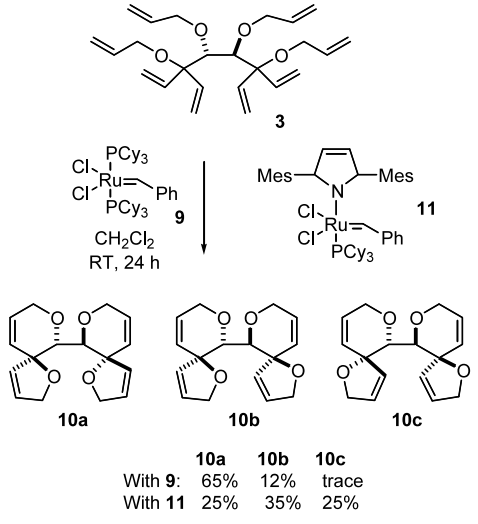


Scheme 2. *Reagents and conditions*: (a) NaH, THF, 0°C, then 18-C-6, Bu_4NI, allylbromide, rt, 16 h. (b) CH_2=CHMgBr, $CeCl_3$, THF, 0°C to rt, 16 h. (c) CH_2=CHMgBr, THF, 0°C to rt, 16 h. (d) NaH, THF, DMPU, allylbromide, rt, 24 h.

were easily separated by column chromatography and isolated in a combined yield of 77% (94% yield per ring-closing step!), indicating a surprising lack of oligomerisation (Scheme 3).

In addition to the observed regioselectivity for bis-spirocycles, the reaction also proceeded in a stereoselective manner, and gave predominantly the C2 symmetric compound **10a** with a small amount of the desymmetrized material **10b** (Scheme 3), and only trace amounts of the other C2 isomer **10c**. Use of the more reactive second generation catalyst **11**[13] also afforded bis-spirocyclic compounds in high yield, but in this case the reaction was found to be stereorandom affording all three possible isomers in a near equimolar mixture.[14]



Scheme 3.

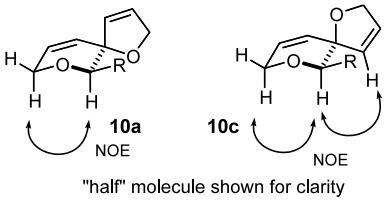


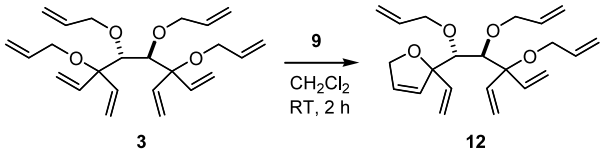
Figure 1.

Identification of **10b** was straightforward as it is the only possible non-symmetric bis-spirocycle. Discrimination of the two C2 symmetric isomers **10a** and **10c** was achieved by NMR methods. An NOE interaction in **10c** between the axial CH and the alkene proton (Fig. 1), was lacking in **10a** and allowed for stereochemical assignment. It should be noted that due to the C2 symmetry of the system certain conformers of **10a** might conceivably show a similar NOE interaction between the axial CH and the alkene of the other spirocycle. However, as all realistic conformations of **10c** would be expected to have the relevant protons in close proximity we are confident in our assignment.[15,16] This stereochemical outcome is also in accord with that expected based on previous work in related systems.[3c,8b]

Many mechanistic pathways can be envisaged for this reaction, indeed both TLC and HPLC analysis indicate the generation of several intermediates prior to production of the final compounds. However at low conversions (40% recovered starting material, 5 mol% catalyst **9** used) the major isolable compound, **12**, is one in which a single five-membered ring has been formed (30% yield) (Scheme 4). With no other compound present in an amount greater than 10% we conclude that initial formation of a five-membered ring is a favorable process.[17]

We also observed that re-subjection of any one of the isolated bis-spirocycles to the reaction conditions did not lead to any equilibration of the final products. The same result was obtained with both ruthenium catalysts and also under an ethylene atmosphere, suggesting that these species are stable to the reaction conditions. This observation, in conjunction with the different product ratios obtained for the two different catalysts, may suggest an element of kinetic control in these multiple ring-closing reactions, however further investigations are required to elucidate a detailed reaction mechanism.

In conclusion, we have demonstrated the first example of a quadruple RCM reaction, which regioselectively afforded bis-spirocyclic molecules in high yields. The



Scheme 4.

stereochemical outcome was found to be dependent on the catalyst used. Further studies on the mechanism of the reaction are in progress and a full account of this work including RCM reactions of intermediate polyenes will be published in due course.

Acknowledgements

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10. All new compounds gave satisfactory spectroscopic and HRMS or microanalytical data.
11. Diene **4** had: rotation α_D +61.1 (*c* 0.7, $CHCl_3$); IR (film) 1762, 1669, 1641 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 5.80 (m, 2H), 5.19 (dq, $J=17.6$, 1.4 Hz, 2H), 5.14 (dq, $J=10.3$, 1.2 Hz, 2H), 4.37 (s, 2H), 4.25 (ddt, $J=12.8$ 5.3, 1.3 Hz, 2H), 3.92 (ddt, $J=12.8$, 6.5, 1.1 Hz, 2H), 3.74 (s, 6H); ^{13}C (100.6 MHz, $CDCl_3$) δ 169.7, 133.6, 118.1, 78.4, 72.5, 52.1: MS (281.1, (*M*+Na)); Anal. calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 56.12; H, 6.79. Octaene **3** had: rotation α_D −28.0 (*c* 0.9, $CHCl_3$); IR (film) 1651 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6.10 (dd, $J=17.7$, 10.9 Hz, 2H), 5.98 (dd, $J=17.8$, 10.5 Hz, 2H), 5.91 (m, 2H), 5.83 (m, 2H), 5.36–5.30 (m, 6H), 5.25 (dq, $J=17.2$, 1.8 Hz, 2H), 5.22 (dd, $J=17.7$, 1.6 Hz, 2H), 5.18 (dq, $J=17.3$, 1.7 Hz, 2H), 5.08 (dq, $J=10.5$, 1.7 Hz, 2H), 5.40 (m, 2H), 4.32 (ddt, $J=12.8$, 5.7, 1.2 Hz, 2H), 4.06 (ddt, $J=12.8$, 7.0, 1.1 Hz, 2H), 3.81 (ddt, $J=13.2$, 4.8, 1.6 Hz, 2H), 3.78 (ddt, $J=13.2$, 5.1, 1.5 Hz, 2H), 3.69 (s, 2H); ^{13}C (100.6 MHz, $CDCl_3$) δ 137.1, 136.9, 135.9, 135.8, 117.3, 117.1, 115.7, 115.0, 85.4, 84.5, 74.5, 64.3; MS (409.2, (*M*+Na)); HRMS, calcd for $C_{24}H_{34}O_4Na$ (*M*+Na) 409.2355, found 409.2375.
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14. To a solution of octaene **3** (75 mg, 0.203 mmol) in dichloromethane (6.0 mL) was added catalyst **11** (18.0 mg, 0.02 mmol), the mixture was de-gassed and stirred for 3 h whereupon a further 10 mol% of catalyst was added and stirring continued for 24 h. Concentration and column chromatography (EtOAc:hexanes 1:1 increasing to EtOAc and then EtOAc:MeOH 4:1) afforded **10a** (14.0 mg, 25%), **10b** (19.5 mg, 35%) and **10c** (14.0 mg, 24%). **10a** had: $R_f=0.3$ (EtOAc:hexanes 1:1); Rotation α_D −36.3 (*c* 0.5, $CHCl_3$); ^1H (400 MHz, $CDCl_3$) δ 5.99 (dt, $J=6.1$, 2.4 Hz, 2H), 5.88 (dt, $J=6.1$, 1.3 Hz, 2H), 5.76 (ddd, $J=10.1$, 3.3, 1.4 Hz, 2H), 5.66 (dt, $J=10.1$, 2.1 Hz, 2H), 4.70 (m, 4H), 4.18 (ddd, $J=16.4$, 3.3, 1.6 Hz, 2H), 3.98 (ddd, $J=16.4$, 2.4, 1.6 Hz, 2H), 3.58 (s, 2H); ^{13}C (100.6 MHz, $CDCl_3$) δ 130.2, 129.8, 126.2, 124.4, 86.8, 77.2, 74.9, 66.0; MS (297.0, (*M*+Na)); HRMS, calcd for $C_{16}H_{18}NaO_4$ (*M*+Na) 297.1103, found 297.1089. **10b** had: $R_f=0.4$ (EtOAc:MeOH 9:1); ^1H (400 MHz, $CDCl_3$) δ 6.11 (dt, $J=6.1$, 1.5 Hz, 1H), 6.05 (dt, $J=6.1$, 24. Hz, 1H), 5.92 (ddd, $J=10.0$, 3.8, 1.3 Hz, 1H), 5.87 (m, 1H), 5.77 (ddd, $J=10.1$, 3.2, 1.5 Hz, 1H), 5.69 (dt, $J=10.0$, 1.9 Hz, 1H), 5.64, (dt, $J=10.1$, 1.9 Hz, 1H), 5.56, (dt, $J=6.1$,

2.4 Hz, 1H), 4.80 (dt, $J=13.3$, 1.9 Hz, 1H), 4.70 (ddd, $J=12.7$, 2.3, 1.6 Hz, 1H), 4.64 (dt, $J=13.3$, 1.8 Hz, 1H), 4.62 (dt, $J=12.7$, 1.9 Hz, 1H), 4.33 (ddd, $J=16.7$, 3.1, 1.6 Hz, 1H), 4.25 (ddd, $J=16.5$, 3.7, 1.5 Hz, 1H), 4.16 (dt, $J=16.7$, 1.7 Hz, 1H), 3.89 (dt, $J=16.5$, 1.5 Hz, 1H), 3.68 (s, 1H), 3.37 (s, 1H); ^{13}C (100.6 MHz, $CDCl_3$) δ 130.7, 130.3, 129.9, 129.4, 128.9, 128.3, 128.2, 126.5, 124.3, 87.2, 86.9, 76.3, 76.0, 75.8, 74.9, 67.0, 65.7; MS (297, (M+Na)); HRMS, calcd for $C_{16}H_{18}NaO_4$ (M+Na) 297.1103, found 297.1109. **10c** had $R_f=0.2$ (EtOAc:MeOH 8:2); ^1H (400 MHz, $CDCl_3$) δ 6.06 (dt, $J=6.1$, 1.5 Hz, 2H), 5.93 (ddd, $J=10.1$, 3.8, 1.5 Hz, 2H), 5.67 (dt, $J=10.1$, 2.0 Hz, 2H), 5.50 (dt, $J=6.1$, 2.4 Hz, 2H), 4.82 (dt, $J=13.4$, 1.9 Hz, 2H), 4.66 (dt, $J=13.6$, 1.9 Hz, 2H), 4.43 (ddd, $J=16.7$, 3.7, 1.6 Hz, 2H), 4.07 (dt, $J=16.7$, 1.9 Hz, 2H), 3.53 (s, 2H); ^{13}C (100.6 MHz, $CDCl_3$) δ 130.5, 129.3, 129.0, 127.6, 86.9, 76.1, 75.6, 66.3; MS (297.0, (M+Na)); HRMS, calcd for $C_{16}H_{18}O_4Na$ (M+Na) 297.1103, found 297.1104.

15. Preliminary molecular modeling calculations suggest that **10c** would be the more polar molecule which is in line with experimental observation based on R_f value.
16. Modeling studies performed using PC Sparton Pro suggest dipole moments: **10a** = 0.53 debye, **10b** = 2.46 debye and **10c** = 4.26 debye. More rigorous molecular modeling studies are planned and will be presented in a full paper.
17. The rapid formation of five membered rings in RCM reactions has been noted before, see inter alia, Refs. 3a, 3c, 5a, 8c.