



The regioselective outcome of ring rearrangement metathesis transformations performed on bicyclo[2.2.2]oct-2-ene derivatives



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ARTICLE INFO

Article history:

Received 22 April 2013

Revised 14 May 2013

Accepted 24 May 2013

Available online 3 June 2013

Keywords:

Bicyclic

Grignard

Ruthenium

Metathesis

Rearrangement

ABSTRACT

Treatment of bicyclo[2.2.2]oct-2-en-7-one with organometallic reagents gives the addition products in good yield and moderate diastereoselectivities in favour of the *syn*-products. Subsequent exposure of these addition products to ruthenium catalysed ring rearrangement metathesis (RRM) conditions reveals significant product divergence as a consequence of the newly acquired stereocentre.

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Since its first report by Grubbs and co-workers ring rearrangement metathesis (RRM) has become a powerful method for the synthesis of bicyclic systems with defined stereochemical outcomes.^{1,2} Typically, RRM utilises the intrinsic ring strain within a cyclic olefin (e.g., norbornene³) to effect ring opening, which can then subsequently ring close onto an exocyclic double-bond within the same substrate. This can be achieved with complete transfer of stereochemical information with the product outcome being defined by both thermodynamic and kinetic factors. Consequently, RRM strategies involving strained olefins have become an increasingly attractive tactic for the synthesis of sesquiterpenes, alkaloids and carbocyclic scaffolds.²

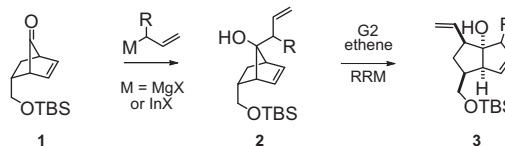
Recently, as part of a study into the total synthesis of natural products containing bicyclic frameworks, we described an efficient approach to *cis*-fused [3.0.3]-carbocycles (Scheme 1 and **1** → **3**). This approach utilised a diastereoselective allylation of a key [2.2.1]-norbornenone (**1**), in conjunction with a thermodynamically controlled and highly regioselective ruthenium catalysed (using Grubbs' 2nd generation catalyst, G2) RRM transformation when performed on the addition products (**2**).⁴

This Letter describes our preliminary studies on this protocol applied to bicyclo[2.2.2]oct-2-en-7-one **4** (Scheme 2). While the allylation of **4** has been described by Snowden and co-workers, the diastereoselectivity of the addition was not reported.⁵

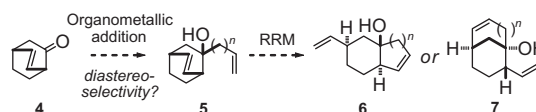
Additionally, of significant interest is the product outcome of the RRM process when performed on alcohols of the type **5**, and

whether the configuration of this alcohol (i.e., *syn* or *anti*) has a significant impact on product outcome (i.e., giving **6** or **7**).

Bicyclo[2.2.2]oct-2-en-7-one **4** was prepared in a three-step sequence and gram quantities in 65% overall yield (Scheme 3).⁶ With **4** in hand the addition of allylmagnesium chloride gave two separable alcohols *syn*-**8a** and *anti*-**8b** in a diastereomeric ratio (dr) of 2:1, and isolated yields of 53% and 24%, respectively.^{7,8a} Similarly, the addition of but-3-enylmagnesium chloride proceeded in a good yield giving the addition products *syn*-**9a** and *anti*-**9b** in a dr of 2.6:1 and in an isolated yield of 45% and 15%, respectively; whereas, 2-methylallylmagnesium chloride gave *syn*-**10a** and *anti*-**10b** in a dr of 2:1 and an overall yield of 62%. The addition of 2-vinylphenyllithium, prepared from the addition of



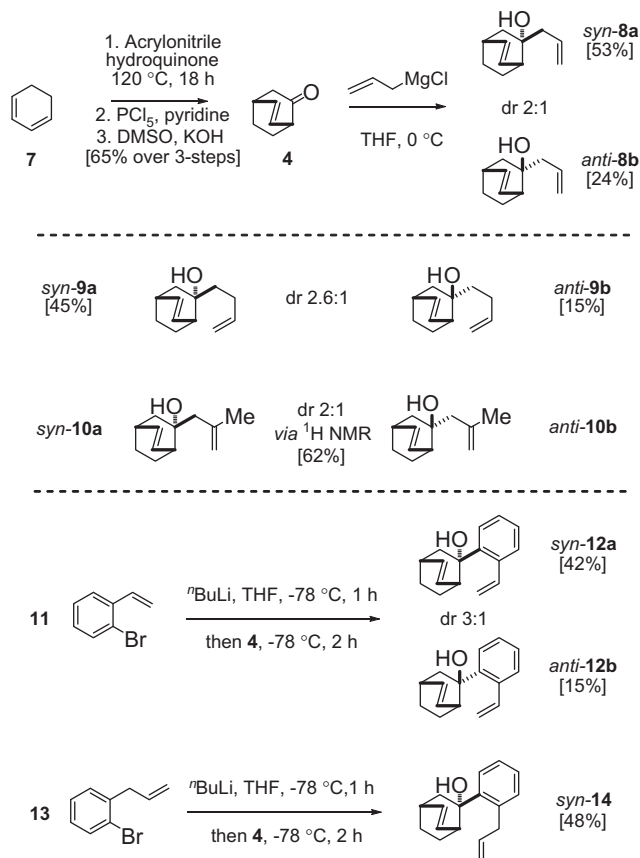
Scheme 1. *cis*-Fused [3.0.3]-carbocycle synthesis from **1**.



Scheme 2. Organometallic addition and subsequent RRM outcome.

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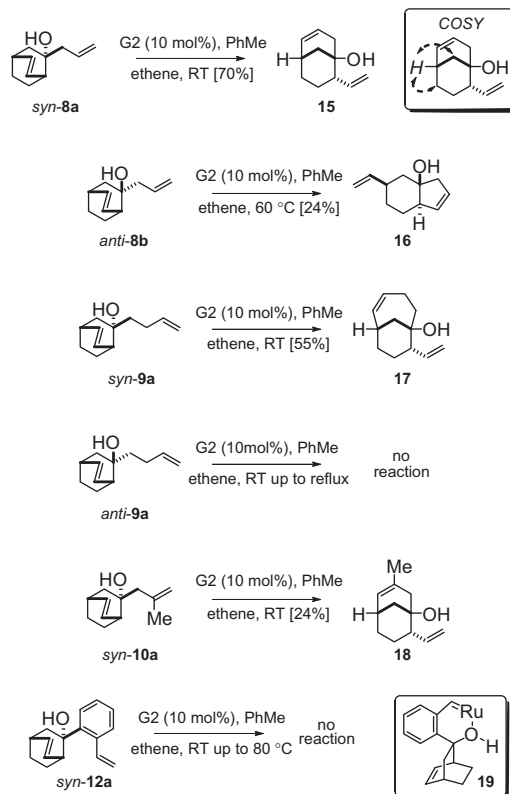
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Scheme 3. The diastereoselectivity of additions to **4**.

n BuLi to 2-bromostyrene (**11**), to **4**, gave the addition products **syn-12a** and **anti-12b** in a dr of 3:1 and in isolated yields of 42% and 15%, respectively.^{8b} Finally, the addition of 2-allylphenyllithium, prepared from the addition of n BuLi to 2-allylbromobenzene (**13**), gave predominantly the addition product **syn-14** in an isolated yield of 48%.

While the addition of Grignard reagents (e.g., methylmagnesium and allylmagnesium bromide) to **4** has been reported previously,^{5,9} the product distributions shown in Scheme 3 indicate a moderate to good degree of diastereoselectivity in favour of the *syn*-alcohol products, and is presumably due to the approach of the nucleophile to the less hindered face of the carbonyl, that is, over the alkene.

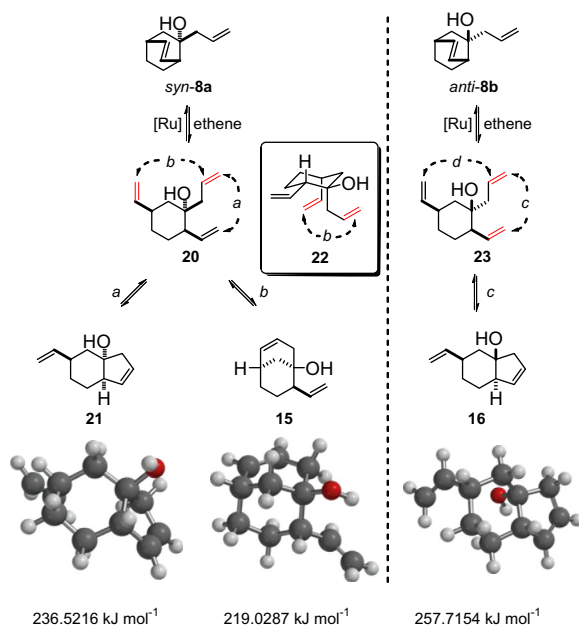
Having investigated the addition of organometallic reagents to **4**, we next explored the RRM transformations on the isolated products (Scheme 4). Consequently, **syn-8a** was exposed to 10 mol % of Grubb's second generation catalyst in PhMe at room temperature, under an atmosphere of ethene,^{4a} and gratifyingly the starting material was consumed within 48 hours to give a new product as detected by TLC. This was subsequently isolated in 70% yield and shown to be the rearranged product **15** by a combination of ^1H and ^{13}C NMR. Specifically, spectroscopic data for **15** showed, inter alia, ^1H NMR signals at 5.73 ppm (ddd, $J = 6.4, 10.4, 17.2$ Hz, 1H), 4.98 ppm (dt, $J = 1.6, 17.2$ Hz, 1H) and 4.90 ppm (dt, $J = 1.6, 10.4$ Hz, 1H), respectively, indicative of the exocyclic olefin. Additionally, signals for the endocyclic double bond were present in the ^1H NMR spectrum at 5.67–5.63 ppm and 5.59–5.55 ppm, respectively. Importantly, the bridgehead proton was shown to couple to two distinct CH_2 environments which provides further proof for the formation of the [3.3.1]-carbocycle **15**.¹⁰ With this result in hand, exposure of diastereoisomer **anti-8b** to these conditions failed to give the rearranged product, with only starting material being isolated. However, upon heating the reaction mix-



Scheme 4. Product outcome for the RRM transformations.

ture to 60 °C for 16 h all the starting material was consumed and the rearranged product **16** was isolated in a moderate yield of 24%. The increase in temperature to effect rearrangement of **anti-8b** is presumably due to the formation of the strained *trans*-fused carbocycle (**16**). The homoallyl analogue, **syn-9a**, readily underwent rearrangement at room temperature to give **17** in 55% isolated yield, but its diastereoisomer **anti-9b** failed under all conditions to undergo RRM. It should be noted that Phillips and co-worker observed difficulty in the cyclisation of similar bicyclo[2.2.2]octene derivatives to indane and decalin systems.^{4f} Due to the poor yield when the RRM transformation was performed on **anti-8b**, along with the failure of **anti-9b** to undergo any rearrangement, all subsequent RRM reactions were performed solely on the *syn*-addition products. The 2-methallyl substrate **syn-10a** gave the rearranged product **18** in a moderate isolated yield; however, the aryl addition product **syn-12a** failed to rearrange under all the tested conditions. The failure of the 2-aryl substituted substrate **syn-12a** to undergo the RRM transformation required further examination. The fact that starting material was returned in all cases implies that the required initial ring-opening of the strained bicyclo[2.2.2]octene, analogous to norbornenes,³ was not occurring. This was further confirmed by performing the reaction in the presence of an excess of styrene to effect cross metathesis (CM), and under these conditions, only starting material was isolated. A possible explanation is the interaction of the ruthenium alkylidene with the tertiary hydroxyl group, reminiscent to the Hoveyda–Grubbs catalysts, giving an intermediate such as **19**.

For **syn-8a** and **anti-8b**, a mechanistic rationale for the formation of each carbocycle is shown in Scheme 5. Reminiscent of [2.2.1]-norbornenyl derivatives,³ the exposure of **syn-8a** to G2 and ethene should deliver **20**. This triene has two possible cyclisation pathways to follow under our reaction conditions; pathway (a) will yield a *cis*-fused [4.0.3]-carbocycle (**21**), while pathway (b) will deliver the observed [3.3.1]-carbocycle **15**. Calculated energies for each regioisomer indicate that [3.3.1]-carbocycle **15** is



Scheme 5. Plausible mechanistic hypothesis and energy minimised conformations of **15**, **16** and **21**.¹¹

approximately $17.49 \text{ kJ mol}^{-1}$ more stable than **21**, indicating that product formation is under thermodynamic control, possibly via the chair conformation depicted in **22**.¹¹ This is further supported by Grubbs^{12a} and Goldring^{12b} who independently demonstrated that similarly substituted precursors undergo RCM to give [3.3.1]-carbocycles.

The exposure of *anti*-**8b** to G2 and ethene will also deliver a triene (**23**), which can cyclise either via pathway *c* or *d*. However, in this case, pathway *c* is the only available avenue for cyclisation, since in pathway *d* the desired olefins involved in the cyclisation are adversely orientated.

Moreover, the increased temperature to effect cyclisation (60°C) via pathway *c* and the moderate yield of the product **16**, can be attributed to the increased strain of having a *trans*-fused 5,6-ring system as reflected in the energy minimisation values shown.

Finally, we utilised the rate difference between the RRM cyclisation of *syn*-**8a** and *anti*-**8b**. Thus, the allylation of **4** gave a diastereomeric mixture of alcohols which was directly exposed to our RRM conditions at room temperature to deliver the bicycle **15**, exclusively, in 56% yield over the two-steps, with none of **16** being detected by ^1H NMR spectroscopy (Scheme 6).

In summary, we have successfully added a range of organometallic reagents to bicyclo[2.2.2]oct-2-en-7-one **4** and demonstrated that a moderate degree of diastereoselectivity was displayed in favour of the *syn*-products. These *syn*-products successfully undergo a ruthenium-catalysed RRM transformation at room temperature to give [3.3.1]- and [4.3.1]-carbocycles, while the *anti*-products (*anti*-**8b**) gave the corresponding *trans*-fused [4.0.3]-carbocycle in moderate yield, and crucially, at elevated temperatures. Further use of this metathesis tactic in the assembly of carbocyclic scaffolds

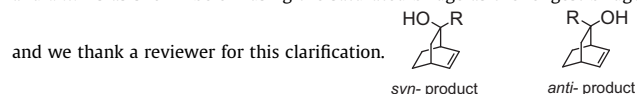
and the use of *ab initio* calculations to determine RRM product outcome will be reported in due course.

Acknowledgments

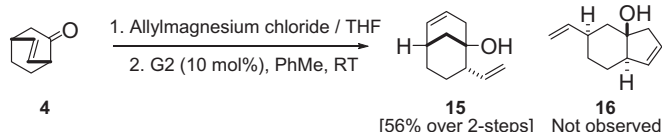
We gratefully acknowledge financial support from the Department of Chemistry at Loughborough University. We also thank Dr. Ben R. Buckley (Loughborough) for performing the energy minimisation calculations contained in Scheme 5, and Dr. Mark Edgar (Loughborough) for help with NMR assignments.

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- The diastereomeric ratio was assigned via ^1H NMR. Assignment of *syn*-**8a** and *anti*-**8b** was achieved using NOE studies and comparison of the ^1H and ^{13}C NMR data as described by Snowden and co-workers. Additionally, assignment of *syn*- and *anti*- is as shown below using the saturated bridge as the longest bridge,



- Representative addition procedures. (a) To a solution of **4** (1.00 g, 8.00 mmol) in anhydrous THF (10.00 mL) cooled to -78°C was added allylmagnesium chloride (2 M in THF, 8.64 mL, 16.0 mmol) and the mixture warmed to room temperature and stirred for a further 12 h. To the mixture was then added saturated NH_4Cl and the resulting solution extracted with EtOAc ($2 \times 50 \text{ mL}$). The combined organic extracts were then dried over MgSO_4 , filtered and the excess volatiles removed under reduced pressure. The crude residue was purified by column chromatography (20:1/petroleum ether/diethyl ether) giving the title compounds as a colourless oil (1.07 g, 82%). Selected data for *syn*-**8a** (53%); IR (CH_2Cl_2) ν_{max} 3419, 2940, 2865 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.24 (dd, $J = 6.4, 7.2 \text{ Hz}$, 1H), 6.19 (dd, $J = 6.4, 7.6 \text{ Hz}$, 1H), 5.94–5.84 (m, 1H), 5.17–5.15 (m, 1H), 5.15–5.10 (m, 1H), 2.60–2.54 (m, 1H), 2.40–2.38 (m, 1H), 2.22–2.07 (m, 3H), 1.66–1.58 (m, 1H), 1.47–1.38 (m, 2H), 1.30–1.24 (m, 1H), 1.11–1.06 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 133.8, 133.2, 119.2, 75.2, 47.8, 41.8, 40.8, 31.1, 24.5, 19.6; MS-ESI found, $\text{C}_{11}\text{H}_{16}\text{O}_2\text{Na}$ found 187.1093, [MNa]⁺ requires 187.1093. Selected data for *anti*-**8b** (24%); ^1H NMR (400 MHz, CDCl_3) δ 6.42 (dd, $J = 7.2, 7.6 \text{ Hz}$, 1H), 6.26 (dd, $J = 6.8, 7.2 \text{ Hz}$, 1H), 6.02–5.91 (m, 1H), 5.17–5.13 (m, 1H), 5.13–5.11 (m, 1H), 2.60–2.57 (m, 2H), 2.43 (dd, $J = 7.2, 13.6 \text{ Hz}$, 1H), 2.30 (dd, $J = 7.2, 13.6 \text{ Hz}$, 1H), 1.71–1.69 (m, 1H), 1.65 (dt, $J = 2.8, 12.4 \text{ Hz}$, 1H), 1.60 (dd, $J = 2.4, 14.0 \text{ Hz}$, 1H), 1.46–1.35 (m, 2H), 1.33–1.14 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.0, 135.5, 132.2, 117.9, 45.0, 44.7, 40.5, 30.9, 23.7, 20.9.
- (b) 2-Bromostyrene (2.0 mL, 16.0 mmol) was dissolved in anhydrous THF (10 mL) in a 25 mL round bottomed flask and cooled to -78°C , to which $n\text{-BuLi}$ (13.0 mL, 64.0 mmol, 2.4 M) was then added dropwise. After stirring for 30 min, the lithiated arene was transferred via cannula to a stirring solution of **4** (1.0 g, 8.0 mmol) in dry THF (10 mL) maintained at -78°C , which was subsequently stirred for a further 1 h at this temperature, then overnight at room temperature. To the mixture was added saturated NH_4Cl and the resulting solution extracted with EtOAc ($3 \times 20 \text{ mL}$). The combined organic extracts were then dried over Na_2SO_4 , filtered and the excess volatiles removed under reduced pressure. The product was purified by column chromatography (20:1/petroleum ether/diethyl ether) to give a clear oil (1.2 g, 66%). Selected data for *syn*-**12a**; IR (CH_2Cl_2) ν_{max} 3395, 2932, 2869 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.60–7.17 (m, 4H), 6.40 (t, $J = 4 \text{ Hz}$, 1H), 6.14 (t, $J = 7.4 \text{ Hz}$, 1H), 5.52 (dd, $J = 1.6, 17.6 \text{ Hz}$, 1H), 5.24 (dd, $J = 1.6, 11.2 \text{ Hz}$, 1H), 3.08–3.06 (m, 1H), 2.64–2.61 (m, 1H), 2.39–2.32 (m, 1H), 2.07–1.93 (m, 2H), 1.78–1.71 (m, 2H), 1.42–1.20 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.0, 138.2, 138.0, 133.2, 133.0, 128.1, 127.1, 126.7, 125.3, 114.9, 78.2, 44.8, 41.1, 31.1, 24.4, 20.3; MS-ESI found 249.1246, $\text{C}_{12}\text{H}_{20}\text{O}_2\text{Na}$ [M+Na]⁺ requires 246.1250.
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Scheme 6. Exploiting reaction rate.

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10. *Representative RRM procedure*
Grubbs second generation catalysts (0.05 g, 0.60 mmol, 10 mol %) was dissolved in anhydrous toluene (4.0 mL) in a 25 mL round bottomed flask. Ethylene was then bubbled through the reaction mixture for 2–3 min. The ethylene atmosphere was maintained and a solution of *syn*-**8a** (0.10 g, 0.21 mmol) in toluene (1.0 mL) was added. The mixture was stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles removed under reduced pressure. The product was purified by column chromatography (20:1/petroleum ether/ethyl acetate) giving **15** as a pale yellow oil (0.07 g, 70 %). IR (CH₂Cl₂) ν_{max} 3455, 3018, 2975 cm⁻¹; ¹H (400 MHz, CDCl₃) δ 5.73 (ddd, *J* = 6.4, 10.4, 17.2 Hz, 1H), 5.67–5.63 (m, 1H), 5.59–5.55 (m, 1H), 4.98 (dt, *J* = 1.6, 17.2 Hz, 1H), 4.90 (dt, *J* = 1.6, 10.4 Hz, 1H), 2.71–2.68 (m, 1H), 2.45 (dq, *J* = 2.4, 15.2 Hz, 1H), 2.25 (dt, *J* = 1.4, 15.3 Hz, 1H), 2.22–2.15 (m, 1H), 1.81–1.72 (m, 3H), 1.68–1.49 (m, 3H); ¹³C (100 MHz, CDCl₃) δ 143.8, 135.4, 129.0, 112.2, 49.9, 48.1, 40.8, 36.1, 29.7, 27.8, 24.4; MS-ESI found 163.1116, C₁₂H₂₀O₄Na [M–H][–] requires 163.1117.
11. Calculated using Spartan'10, version 1.0.1, Wavefunction, Inc Irvine, CA, Values are shown from the MMFF minimisation calculation.
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