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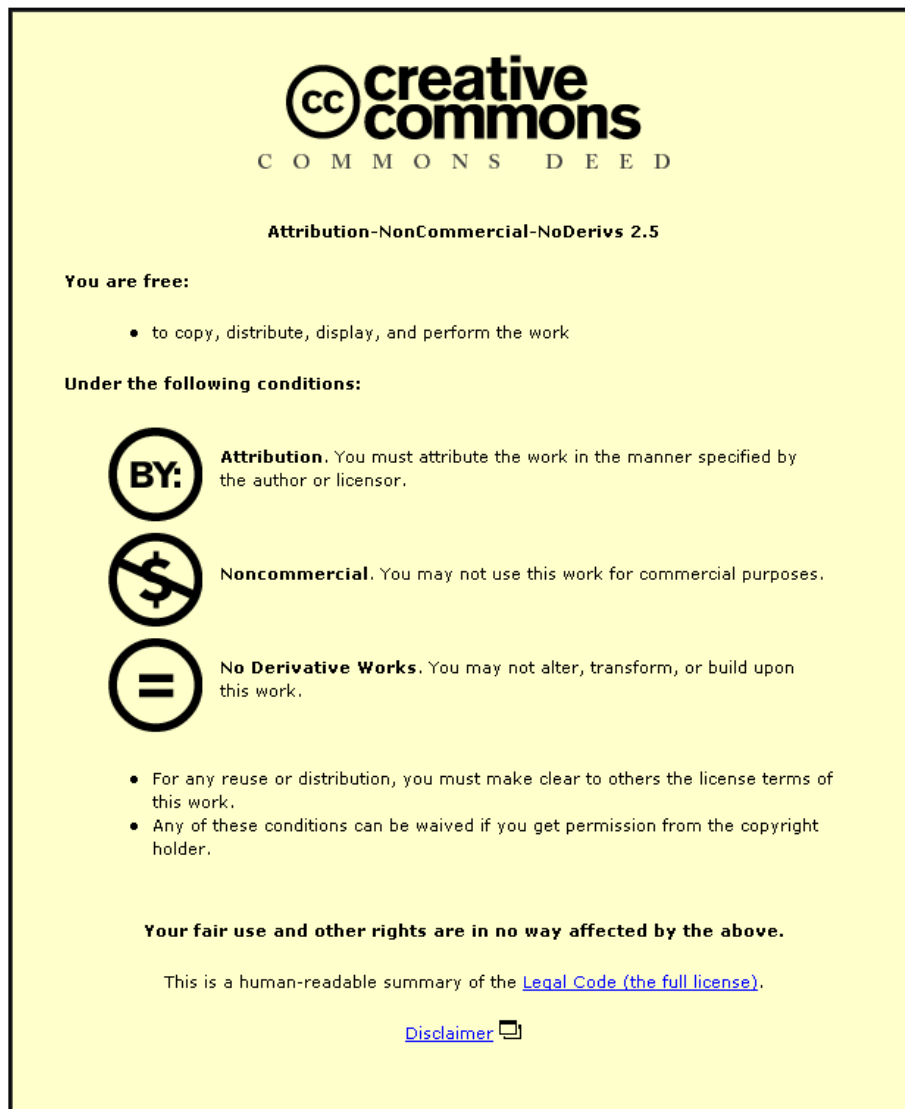
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The regioselective outcome of ring rearrangement metathesis transformations when performed on bicyclo-[2.2.2]-oct-2-ene derivatives

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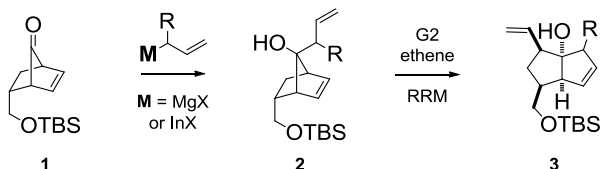
ABSTRACT

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 *exo*-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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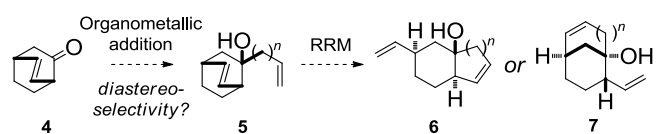
Since its first report by Grubbs and co-workers Ring Rearrangement Metathesis (RRM) has become a powerful method for the synthesis of bicyclic systems with defined stereochemical outcomes.^{1,2} Typically, RRM utilises the intrinsic ring strain within a cyclic olefin (e.g. norbornene³) to affect ring 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, **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 catalyzed (using Grubbs' second generation catalyst **G2**) RRM transformation when performed on the addition products (**2**).⁴



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

This letter will describe our preliminary studies when this protocol is applied to bicyclic-[2.2.2]-oct-2-en-7-one **4** (Scheme 2). While the allylation of **4** has been described by Snowdon and co-workers the diastereoselectivity of the addition was not reported.⁵

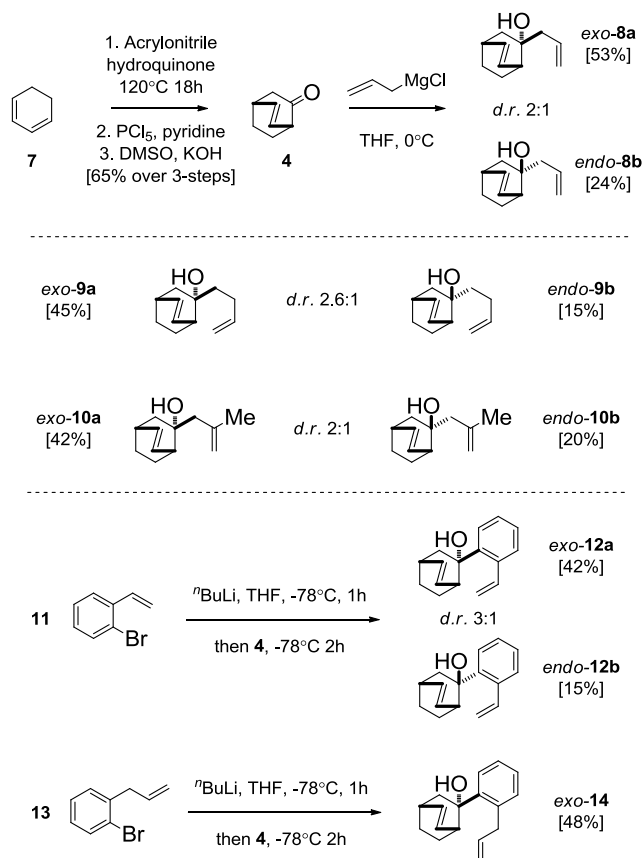


Scheme 2. Organometallic addition and subsequent RRM outcome.

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. *exo* or *endo*) 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 3-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 *exo*-**8a** and *endo*-**8b** in a diastereomeric ratio (*d.r.*) of 2:1, and isolated yields of 53% and 24%, respectively.^{7,8a} Similarly, the addition of homoallylmagnesium chloride proceeded in a good yield giving the addition products *exo*-**9a** and *endo*-**9b** in a *d.r.* of 2.6:1 and in an isolated yield of 45% and 15%, respectively; whereas, 2-methylallyl magnesium chloride gave *exo*-**10a** and *endo*-**10b** in yields of 42% and 20%, and a *d.r.* of 2:1. The addition of ⁿBuLi to 2-bromostyrene (**11**) to **4**, gave the addition products *exo*-**12a** and *endo*-**12b** in a *d.r.* of 3:1 and in isolated

yields of 42% and 15%, respectively.^{8b} Finally, the addition of 2-allyl phenyllithium, prepared from the addition of ⁿBuLi to 2-allylbromobenzene (**13**), gave predominantly the addition product *exo*-**12** in an isolated yield of 48%.

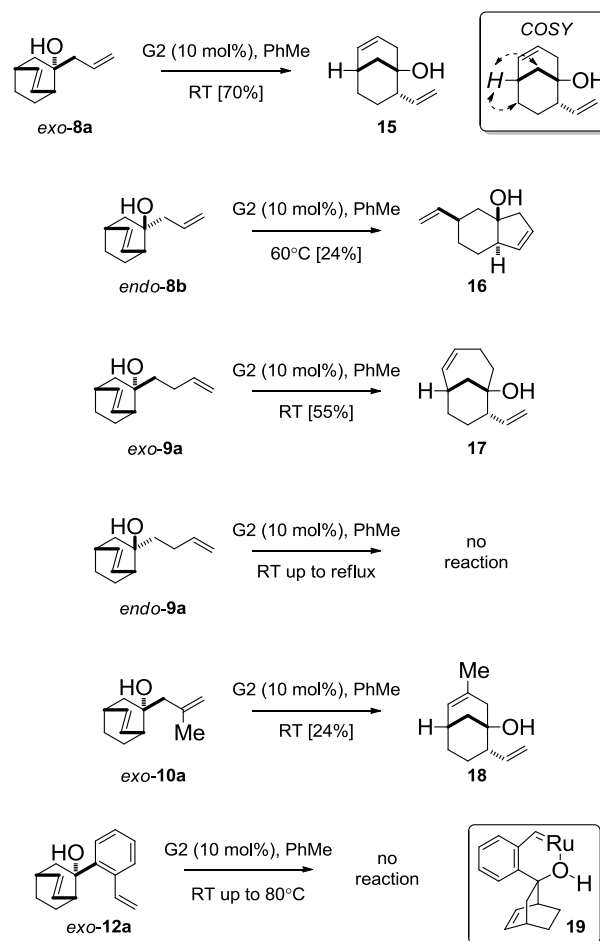


Scheme 3. The diastereoselectivity of the addition to **4**.

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 *exo*-addition product, and is presumably due to the approach of the nucleophile to the less hindered face of the carbonyl, i.e. over the alkene.

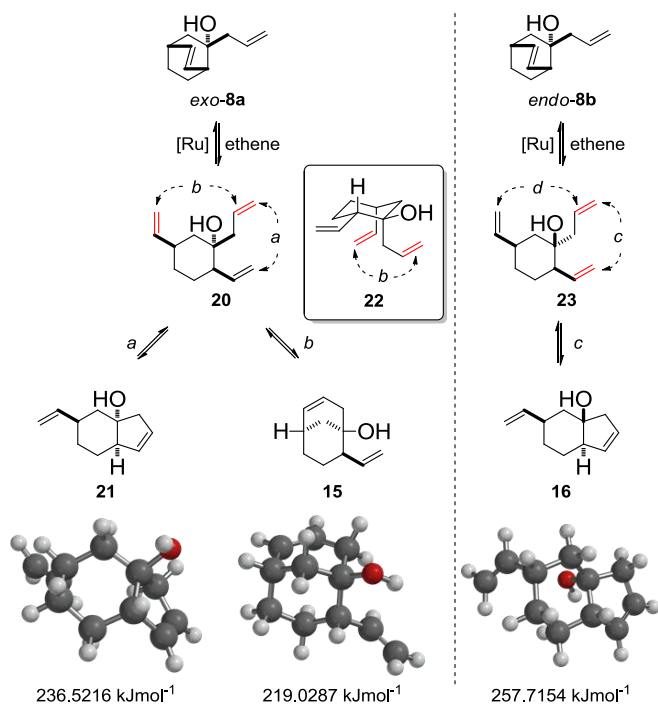
Having investigated the addition of organometallic reagents to **4** next we explored the RRM transformations on the isolated products (Scheme 4). Consequently, *exo*-**8a** was exposed to 10 mol% of Grubb's second generation catalyst in PhMe at room temperature, under an atmosphere of ethene^{4a} and gratifyingly the starting material was consumed within 48h 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 ¹³C NMR. Specifically, spectroscopic data for **15** showed, *inter alia*, ¹H NMR signals at 5.73 ppm (ddd, *J* = 6.4, 10.4, 17.2Hz, 1H), 4.98 ppm (dt, *J* = 1.6, 17.2Hz, 1H) and 4.90 ppm (dt, *J* = 1.6, 10.4Hz, 1H), respectively, indicative of the exocyclic olefin. Additionally, signals for the endocyclic double bond were present within the ¹H NMR spectrum at 5.65 ppm and 5.57 ppm, respectively. Importantly, the bridge head proton was shown to couple to two distinct CH₂ environments which provides further proof for the formation of the [3.3.1]-carbocycle **15**.¹⁰ With this result in-hand the exposure of diastereoisomer *endo*-**8b** to these conditions failed to give the rearranged product, with only starting material being isolated. However, upon heating the reaction mixture to 60° C for 16h all 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 *endo*-**8b** is presumably due to the formation of the strained *trans*-fused carbocycle (**16**). The homoallyl analogue *exo*-**9a** readily underwent rearrangement at room temperature to give **17** in 55% isolated yield but its diastereoisomer *endo*-**9b** failed under all conditions to undergo RRM. It must be noted that Phillips and co-workers 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 *endo*-**8b**, along with the failure of *endo*-**9b** to undergo any rearrangement, all subsequent RRM reactions were performed solely on the *exo*-addition products. The 2-methallyl substrate *exo*-**10a** gave the rearranged product **18** in a moderate isolated yield; however, the aryl addition product *exo*-**12a** failed to rearrange under all conditions. The failure of the 2-aryl substituted substrate *exo*-**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**.



Scheme 4. Product outcome for the RRM transformation.

For *exo-8a* and *endo-8b* a mechanistic rationale for the formation of each carbocycle is shown below in scheme 5. Reminiscent of [2.2.1]-norbornenyl derivatives,³ the exposure of *exo-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 the [3.3.1]-carbocycle **15** is some 17.49 kJmol⁻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.



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

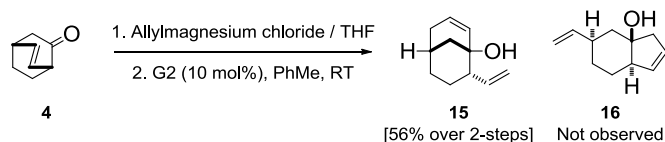
The exposure of *endo-8b* to G2 and ethene will also deliver a triene (**23**) which can cyclise either *via* pathway *c* and *d*. However in this case pathway *c* is the only available avenue for cyclisation, since in pathway *d* the desired olefins involved in the cyclisation are adversely orientated.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

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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 minimization value shown.

Finally, we utilised the rate difference between the RRM cyclisation of *exo-8a* and *endo-8b*. Consequently, the allylation of **4** gave a diastereomeric mixture of alcohols which were directly exposed to our RRM conditions at room temperature to deliver the bicycle **15** exclusively in 56% yield over the 2-steps, with none of **16** being detected by ¹H NMR (Scheme 6).



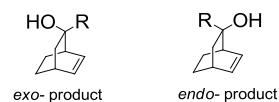
Scheme 6. Exploiting reaction rate.

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 is displayed in favour of the *exo*-addition products. These *exo*-addition products successfully undergo a ruthenium catalyzed RRM transformation at room temperature to give [3.3.1]- and [4.3.1]-carbocycles, while the *endo*-addition product (*endo-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

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 - The diastereomeric ratio was assigned *via* ¹H NMR. Assignment of *exo-8a* and *endo-8b* was achieved using NOE studies and comparison of the ¹H and ¹³C NMR data as described by Snowden and co-workers. Additionally, we have adopted the *exo*- and *endo*-product assignment described by the same authors.



8. *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 allyl magnesium chloride (2M in THF, 8.64 mL, 16.0 mmol) and the reaction mixture warmed to room temperature and stirred for a further 12h. To the reaction mixture was then added a solution of saturated NH_4Cl and the resultant solution extracted with ethyl acetate (2x50 mL). The combined organic extracts were then dried over magnesium sulfate, filtered and the excess volatiles removed under reduced pressure. The crude product was then purified by column chromatography giving the title compounds as a colourless oil (1.07 g, 82%). Selected data for *exo-8a* (53%); IR (CH_2Cl_2) ν_{max} 3419, 2940, 2865 cm^{-1} ; ^1H (400 MHz, CDCl_3) δ 6.24 (dd, $J = 6.4, 7.2$ Hz, 1H), 6.19 (dd, $J = 6.4, 7.6$ 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 (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, $\text{C}_{11}\text{H}_{16}\text{ONa}$ found 187.1093, $[\text{MNa}]^+$ requires 187.1093. Selected data for *endo-8b* (24%); ^1H (400 MHz, CDCl_3) δ 6.42 (dd, $J = 7.2, 7.6$ Hz, 1H), 6.26 (dd, $J = 6.8, 7.2$ Hz, 1H), 6.02 – 5.91 (m, 1H), 5.17 – 2.13 (m, 1H), 5.13 – 5.11 (m, 1H), 2.60 – 2.57 (m, 2H), 2.43 (dd, $J = 7.2, 13.6$ Hz, 1H), 2.30 (dd, $J = 7.2, 13.6$ Hz, 1H) 1.71- 1.69 (m, 1H), 1.65 (dt, $J = 2.8, 12.4$ Hz, 1H), 1.60 (dd, $J = 2.4, 14.0$ Hz, 1H), 1.46 – 1.35 (m, 2H), 1.33 – 1.14 (m, 3H); ^{13}C (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 $^t\text{BuLi}$ (13.0 mL, 64.0 mmol, 2.4 M) was then added dropwise. After stirring for 30 min. the lithiated arene was then 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 reaction mixture was then added a solution of saturated NH_4Cl and the resultant solution extracted with ethyl acetate (3x20 mL). The combined organic extracts were then dried over Na_2SO_4 , filtered and the excess volatiles removed under reduced pressure. The product was then purified by column chromatography to give a clear oil (1.2 g, 66 %). Selected data for *exo-12a*; IR (CH_2Cl_2) ν_{max} 3395, 2932, 2869 cm^{-1} ; ^1H (400 MHz, CDCl_3) δ 7.60 – 7.17 (m, 4H), 6.40 (t, $J = 4$ Hz, 1H), 6.14 (t, $J = 7.4$ Hz, 1H), 5.52 (dd, $J = 1.6, 17.6$ Hz, 1H), 5.24 (dd, $J = 1.6, 11.2$ 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 (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, $\text{C}_{12}\text{H}_{20}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ requires 246.1250.
9. For related diastereoselective organometallic additions to norbornenones *see*, (b) Bly, R. K.; Bly, R. S. *J. Org. Chem.*, **1963**, 28, 3165; (c) Berson, J. A.; Jones Jr. M. *J. Am. Chem. Soc.*, **1964**, 86, 5019; (d) Paquette, L. A.; Pierre, F.; Cottrell, C. E.; *J. Am. Chem. Soc.*, **1987**, 109, 5731; (e) Paquette, L. A.; DeRussy, D. T. *Tetrahedron*, **1988**, 44, 3139; (f) Warkentin, J. *Can. J. Chem.*, **1970**, 48, 1970; (g) Clark, F. R. S.; Warkentin, J. *Can. J. Chem.*, **1971**, 49, 2223.
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 then maintained and a solution of *exo-8a* (0.10 g, 0.21 mmol) in toluene (1.0 mL) was added. The reaction mixture was then stirred at room temperature for 48 h with monitoring by TLC. The excess volatiles removed under reduced pressure. The product was then purified by column chromatography giving **15** as a pale yellow oil (0.07 g, 70 %). IR (CH_2Cl_2) ν_{max} 3455, 3018, 2975 cm^{-1} ; ^1H (400 MHz, CDCl_3) 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); ^{13}C (100 MHz, CDCl_3) 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, $\text{C}_{12}\text{H}_{20}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ requires 163.1117.
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