Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 8669

www.rsc.org/obc

PAPER

The stereochemical outcome of allyl magnesium and indium additions to 5-substituted norbornen-7-ones and its application to *cis* fused carbocycle formation *via* ring rearrangement metathesis†

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Received 11th September 2012, Accepted 21st September 2012
DOI: 10.1039/c2ob26784e

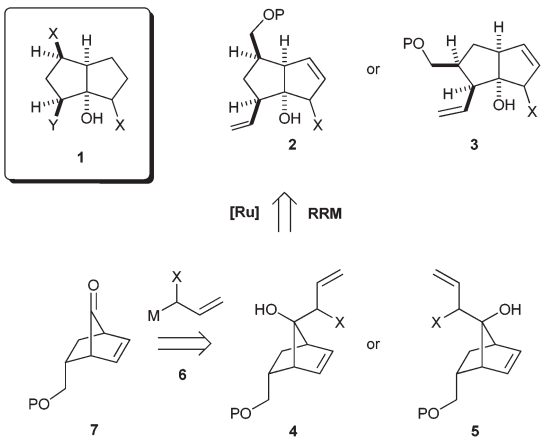
The addition of allyl magnesium and allyl indium reagents to a key TBS protected norbornenyl building block, synthesised in 6-steps from commercially available 1,1-dimethoxy-2,3,4,5-tetrachlorocyclopentadiene, has been achieved providing the *syn* addition products with high diastereoselectivity. The subsequent exposure of the addition products to metathesis conditions, in the presence of ethene, then provided *cis* fused[3.0.3]-carbocycles with very high regioselectivity, *via* a Ring Rearrangement Metathesis (RRM) transformation.

Introduction

The *cis* fused carbocycle (**1**) is a common structural motif contained within a variety of natural product scaffolds (Scheme 1). For example the [3.0.3]-bicyclic is a widespread subunit present within a number of hirsutane and capnellane sesquiterpenoids as well as daphniphyllum alkaloids.[1] Upon close inspection, the all *cis* fused configuration of this carbocycle and the substitution pattern (**2** and substituents X, Y and Z) presents itself as a synthetic challenge which we believed could be met using the 2-step sequence set out in Scheme 1.

We envisaged that **2** could be ideally accessed *via* a Ring Rearrangement Metathesis (RRM) transformation[2] performed on a suitably substituted norbornenyl derivative **4**; which in turn would be obtained from the addition of an allyl organometallic reagent (**6**) to a key norbornenone building block of the type **7**. However, within this approach lies two significant challenges; (1) the diastereoselectivity of the allyl addition (giving either **4** or **5**) with the stereochemical outcome being determined by the nature of the organometallic reagent[3] along with the electronics of the norbornenone itself;[4] and (2) the regioselectivity of the RRM transformation giving potentially **2** or **3**.

The pioneering reports of Bly[5] in 1963 and Berson[6] in 1964, on the stereoselective addition of organometallic reagents to norbornenones (**8**), indicate that Grignard reagents (**9**) will provide



Scheme 1

the desired product **10** *via* stereoselective *syn* addition (Scheme 2). While both Paquette[7] and Warkentin[8a] showed the organolithiums were less selective and in some cases (*e.g.* vinyl lithium and phenyl lithium) even favoured the formation of the undesired *anti* addition product **11**. Moreover, subsequent expansion of the addition of Grignard reagents to norbornenones by Warkentin[8b] also indicated that the nature of the reagent is crucial as the reduction product (**12**) can be formed in some cases, *e.g.* Et, ^{i}Pr and ^{t}Bu Grignard reagents predominantly give the *anti*-reduction product **12** compared to methyl and vinyl Grignard reagents.

In regard to the planned RRM transformation on norbornenyl derivatives, two notable examples must be considered (Scheme 3). Hoveyda and co-workers reported in 2004[2a] that a tandem asymmetric RRM sequence on norbornenyl **13** using a chiral Mo catalyst gave rise to a [3.0.5]-bicycle **14**, a key intermediate in the

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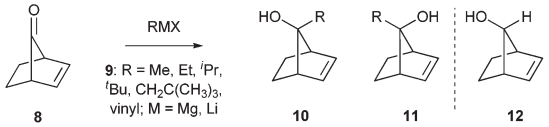
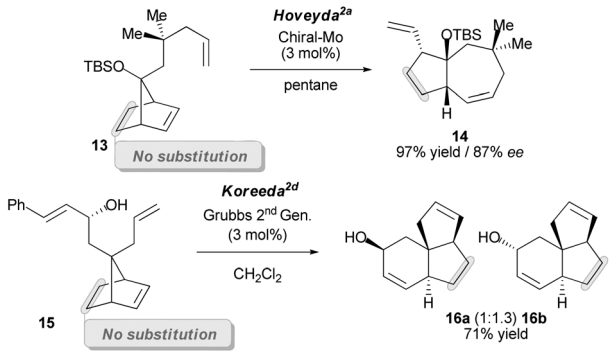
†Electronic supplementary information (ESI) available: Experimental procedures for **18**, **19** and **20**; NMR spectra and characterization for all new materials, and the crystal structure data of **25**. CCDC 893728. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26784e



Scheme 2 Organometallic addition to norbornenones.



Scheme 3 Relevant RRM transformations.

synthesis of (+)-africanol in 97% yield and 87% ee. Whereas Koreeda[2d] established that substituted norbornenyl substrate such as **15** could participate in a RRM sequence giving rise to tricycles (**16**) using Grubbs 2nd generation catalyst. However, in both of these studies, no further substitution on the norbornene skeleton on the major bridge was explored in relation to the RRM process.

Results and discussion

Therefore with these transformations in mind, we first of all investigated the addition of hitherto unused allyl Grignards, as well as allyl indium reagents, to a key norbornenone building block (**22**) which was assembled as outlined in Scheme 4.[9] The synthesis of **22** saw commercially available 1,1-dimethoxy-2,3,4,5-tetrachlorocyclopentadiene **17** being converted to **19** in 3-steps and then reduced to the primary alcohol **21** under standard conditions. Initial protection of **21** as its TBS-ether was achieved in high yield but subsequent attempts to unmask the protected ketone consistently resulted in removal. Consequently, acid mediated hydrolysis of **21** followed by TBS protection gave our desired key norbornenone **22** in an overall yield of 46% over 6-steps.

With **22** in hand, addition of allyl magnesium chloride gave exclusively the desired *syn* addition product **23** and in an excellent yield of 91% (Conditions A). We also explored the use of indium mediated allylations of 22.[10] Using allyl bromide and stoichiometric indium metal in a 1 : 1 mixture of THF and water (Conditions B) we found that the allylated product **23** was formed in 95% yield and as a single diastereoisomer. All NMR data fully supported the proposed structure of **23**, with a signal for the *endo*-H_7 proton occurring at 0.50 ppm possibly due to the shielding effects of the TBS group. However, to confirm the relative stereochemistry it was subsequently deprotected under standard conditions to give the diol **25**. This product proved to be crystalline and we were able to obtain small crystals suitable for single X-ray analysis at a synchrotron source which definitely defined the *syn*-stereochemistry, relative to the endocyclic olefin and the allylic side chain within the norbornenyl ring system (Fig. 1).[11]

Likewise, we also found that the addition of (2-methylallyl) magnesium chloride (Conditions A) gave the norbornenyl **27** stereoselectively in a reduced yield of 61%, while but-3-en-2-ylmagnesium chloride (Conditions A) gave the *syn* product 28 in 74% isolated yield (Scheme 5). This later product was isolated as an inseparable 1 : 1 mixture of diastereoisomers, a

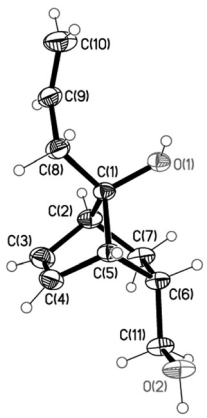
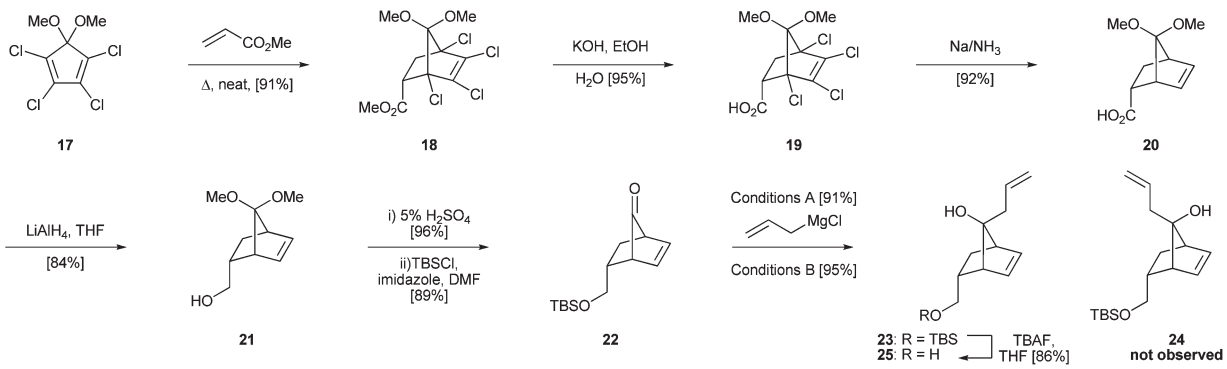
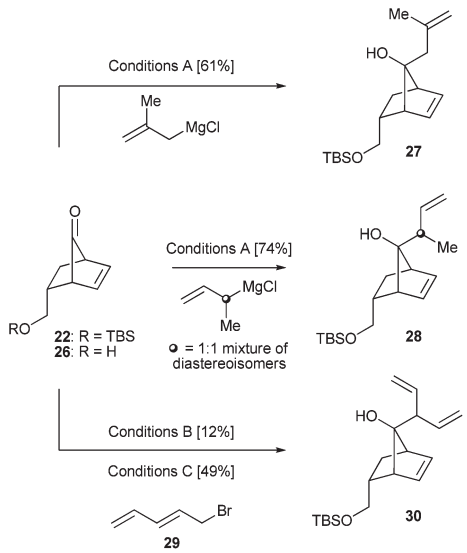


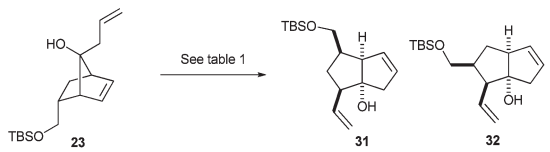
Fig. 1 ORTEP depiction of **25**.



Scheme 4 Synthesis of key building block **22** and its diastereoselective allylation. **Conditions A**: Grignard reagent (2 eq.), THF, N_2; **Conditions B**: In^0, allyl bromide THF–H_2O (1 : 1).



Scheme 5 **Conditions A**: Grignard reagent (2 eq.), THF, N_2; **Conditions B**: In^0, allyl bromide or **29**, THF–H_2O (1 : 1); **Conditions C**: In^0, **29**, DMF, RT.



Scheme 6

Table 1 Ru catalyzed ROM-RCM sequence performed on **23**[a]

Entry	Solvent	Time (h)	Temp. (°C)	Cat. (mol%)	Additive	Yield[b] (%)
1	CH_2Cl_2	24	R.T.	G1 (5)	—	—
2	CH_2Cl_2	48	R.T.	G2 (10)	Styrene[c]	—
3	PhMe	24	R.T.	G2 (5)	Styrene[c]	—
4	PhMe	24	35	G2 (10)	Styrene[c]	**31** (20)[d]
5	PhMe	24	60	G2 (10)	Styrene[c]	—[e]
6	PhMe	48	R.T.	G2 (5)	Ethylene[f]	**31** (86)
7	PhMe	24	R.T.	G2 (10)	—	—

[a] All reactions were performed under an atmosphere of N_2 unless otherwise stated. [b] Isolated yield. [c] 3.0 equivalents. [d] No **32** detected by ^1H NMR or isolated. [e] Stilbene isolated. [f] Performed under 1 atmosphere.

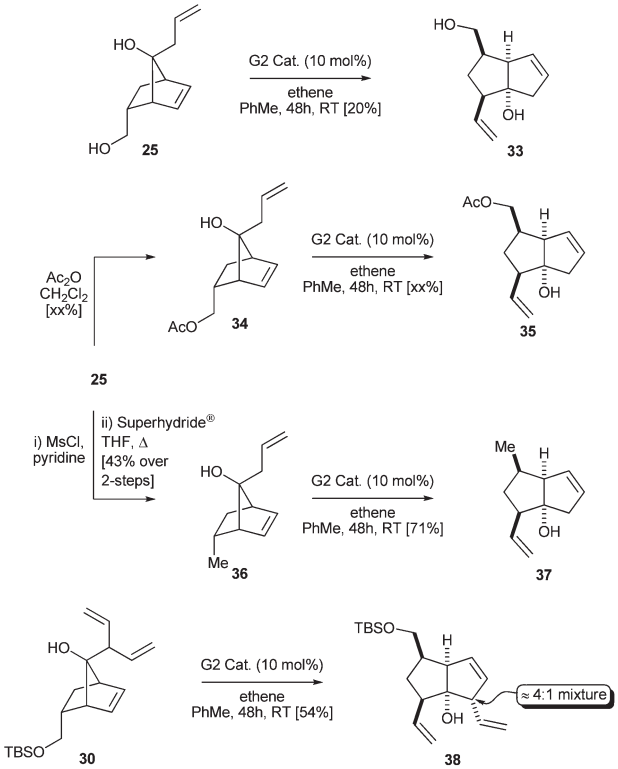
consequence of the starting Grignard reagent, but does indicate that an *alpha* substituent on the organometallic reagent is tolerated.

Fallis and co-workers[12a] in 1999 demonstrated the use of (*E*)-5-bromopenta-1,3-diene (**29**)[13] and its indium mediated addition to aldehydes and ketones. Accordingly, treatment of **22** with bromide **29** and stoichiometric indium metal in a 1 : 1 mixture of THF and H_2O (Conditions B) gave only modest amounts (12%) of the desired addition product **30**. However, using the further modified conditions of Fallis, namely performing the reaction in DMF for a 48 h period (Conditions C) gave the addition product **30** in a yield of 49% and importantly as a single diastereoisomer.[12b] This result is significant as it now incorporates an *alpha* substituent on the organometallic reagent without compromising diastereoselectivity, as well as providing a potential synthetic handle on the reaction product. Lastly, when the indium allylations conditions were use on the alcohol **26**, the addition product **25** was obtained as a single diastereoisomer but in a modest yield of 21%.

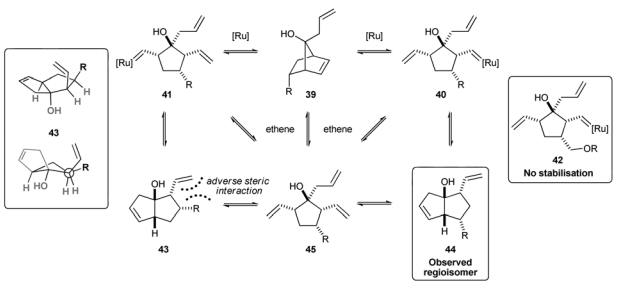
Having established that allyl magnesium and indium reagents add with high diastereoselectivity we next examined the regioselectivity of RRM transformation when performed on substrate **23** (Scheme 6) (Table 1).

Initial work centred on performing the RRM sequence on **23** in the presence of Grubbs 1st generation catalyst (G1) (5 mol%) in CH_2Cl_2 at room temperature, which proved unsuccessful with only starting material being isolated (entry 1). The addition of styrene,[14] along with a switch to Grubbs 2nd generation catalyst (G2), in both CH_2Cl_2 (entry 2) and toluene (entry 3) also proved unsuccessful. Heating the reaction mixture to 35 °C in toluene in the presence of styrene and G2 resulted in isolation of the **31**[15] albeit in a low isolated yield of 20% (entry 4), while increasing the temperature to 60 °C in the presence of styrene, resulted in the isolation of stilbene (entry 5). However, the omission of styrene and undertaking the reaction under an atmosphere of ethene at room temperature gave the rearranged product in 86% yield with the product being identified as **31** (entry 6). Finally, to prove the requirement of ethene for this RRM process the reaction was done in the absence of ethene in toluene with 10 mol% of G2 resulting in no product formation and only the isolation of starting material (entry 7).

Noteworthy, is the apparent regioselectivity of this reaction, with the crude ^1H NMR showing very little of the regioisomer **32**, and the tolerance of the tertiary hydroxyl group at the 7-position, which is contrast to Hoveyda and co-workers molybdenum catalysed transformation.[2a] We also exposed diol **25** to our optimised conditions which gave the rearranged product **33** in a modest isolated yield of 20%; with the lower yield for **33**, as compared to **31**, possibly being due to the presence of the primary hydroxyl group (Scheme 7). The regioselectivity of this RRM transformation and deserved further investigation, and therefore the role in which the OTBS group plays within this transformation was probed. We accordingly replaced the TBS with an acetate protecting group, which was achieved *via* acylation of **25** under standard conditions to give **34**. Analysis of the crude ^1H NMR after the exposure of **34** to our RRM conditions indicated that the predominant product was **35** but in an approximate ratio of 4 : 1 with its regioisomer.[16] Complete removal of the OTBS group was also accomplished in two steps from **25** involving mesylation followed by reduction in refluxing Superhydride® to the parent alkane **36** in an overall yield 43% over the 2-steps. Subsequent exposure of **36** to our RRM conditions then provided the rearranged product **37** in a yield of 71%; however, it must be noted that the only regioisomer detected within the crude ^1H and ^{13}C NMR was that shown in Scheme 7.[16] This later result indicates that the formation of the observed regioisomer in our RRM reaction is *not* a result of any chelation effects from the OTBS group. Finally, we exposed **30** to our RRM conditions which delivered the rearranged product **38** predominantly, but as an inseparable 4 : 1 mixture of diastereoisomers in a respectable yield of 54%.



Scheme 7



Scheme 8

A credible reaction pathway for this transformation and an explanation for the formation of the observed product **44** from norbornenyl **39** are described in Scheme 8. Due to the inherent ring strain within norbornenes[17] ruthenium catalysed ring opening of **39** can give either intermediate **40** or **41**, respectively; with **41** giving rise to **43** and **40** giving rise to the observed regioisomer **44**. Only **40** will lead to the formation of the observed product **44**; however stabilisation of this intermediate (*e.g.* **42**) by the –OR group is unlikely and furthermore is not supported by the cyclisation selectivity observed for substrate **36**. Conversely, under the RRM reaction conditions the inter-conversion of **43** and **44**, presumably *via* **45**, is plausible, with **43** being disfavoured compared to **44** possibly due to an adverse steric interaction.[18]

Conclusions

We have stereoselectively allylated norbornenones to give the *syn* addition products exclusively, and this was achieved with both allyl Grignard reagents and allyl indium reagents with no discernable drop in isolated yield or diastereoselectivity. Additionally, we were able to demonstrate that the products of these additions successfully undergo a regioselective ruthenium catalysed RRM transformation to give [3.0.3]-carbocycles common to natural product scaffolds. Furthermore, the regioselectivity of the RRM transformation is thought to derive from the thermodynamic stability of the observed product under the reaction conditions. The further use of this diastereoselective allylation/RRM transformation tactic will be reported on in due course.

Experimental

General

Commercially available reagents and solvents were used throughout without further purification, except tetrahydrofuran (benzophenone/Na) and dichloromethane (CaH) which were freshly distilled. Diethyl ether were purchased dry from commercial suppliers. Light petroleum refers to the fraction with bp 40–60 °C. Thin layer chromatography was carried out on Merck Kieselgel 60 GF254 aluminum foil backed plates. The plates were visualized under UV light and/or anisaldehyde stain. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrix silica 60, with the eluent specified. IR spectra were recorded using Perkin Elmer FTIR Spectrometer (Paragon 100) as solutions using chloroform as solvent. ^{1}H and ^{13}C NMR spectra were recorded using Bruker 400 MHz NMR machine (^{1}H 400 MHz, ^{13}C frequencies 100 MHz, respectively); chemical shifts are quoted in ppm and coupling constants, *J*, are quoted in Hz; d-Chloroform was used throughout unless otherwise stated. Spectra were calibrated to residual solvent peaks. High and low resolution mass spectra were carried out on a Thermofisher exactive (orbi) resolution mass spectrometer. Melting points were recorded on a Stuart Scientific apparatus and are uncorrected.

7,7-Dimethoxybicyclohept-5-en-2-yl methanol 21

7,7-Dimethoxyhept-5-ene-2-*endo*-carboxylic acid (1.40 g, 6.90 mmol) was added to dry glassware and dissolved in anhydrous THF (30 mL). The reaction mixture was then cooled to 0 °C and a solution of $LiAlH_4$ (6.9 mL, 2 M, 13.8 mmol) added drop wise over 30 min. The reaction mixture was then left to warm to room temperature and stirred for 12 h. The reaction was then cooled to 0 °C and a solution of sodium potassium tartrate solution added and the reaction mixture allowed too warm to room temperature. The aqueous layer was then extracted with diethyl ether and the combined organic layers dried over magnesium sulphate and excess volatiles were removed under reduced pressure. The crude mixture was then purified by column chromatography which furnished the titled compound as a colourless oil (1.10 g, 84%); IR (CH_2Cl_2) ν_{max} 3405, 2934, 2076, 1636 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (dd, J = 3.2, 6.0 Hz, 1H), 6.04 (dd, J = 3.2, 6.0 Hz, 1H), 3.38–3.28 (m, 2H), 3.22 (s, 3H), 3.16 (s, 3H), 2.97–2.95 (m, 1H), 2.80–2.78 (m, 1H), 2.52–2.48 (m, 1H), 2.05–1.97 (m, 1H), 0.54 (dd, J = 4.0, 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 133.7,

119.3, 64.4, 51.9, 50.8, 46.3, 44.6, 39.0, 27.0; MS-ESI found 207.1201, $C_8H_{10}O_3$ $[M + Na]^+$ requires 207.0992.

Key TBS protected norbornenone 22

7,7-Dimethoxybicyclohept-5-en-2-yl methanol (1.10 g, 5.10 mmol) was dissolved in 5% H_2SO_4 (30 mL) and heated to 65 °C for 72 h. The aqueous layer was then extracted with diethyl ether and the combined organic layers dried over magnesium sulphate and excess volatiles were removed under reduced pressure. This crude product was purified by column chromatography to give the alcohol as a yellow oil (0.98 g, 96%); IR (CH_2Cl_2) ν_{max} 3387, 2931, 1771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.59 (dd, J = 3.6, 6.4 Hz, 1H), 6.44 (dd, J = 3.2, 6.4 Hz, 1H), 3.44 (dd, J = 6.0, 10.4 Hz, 1H), 3.35 (dd, J = 9.2, 10.8 Hz, 1H), 3.08 (t, J = 3.6 Hz, 1H), 2.88 (t, J = 3.2 Hz, 1H), 2.56–2.49 (m, 1H), 2.16–2.07 (m, 1H), 0.74 (dd, J = 5.6, 12.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 133.7, 130.1, 64.5, 48.6, 46.3, 36.2, 25.8; MS-ESI found 161.0571, $C_8H_{10}O_2$ $[M + Na]^+$ requires 161.0573. The alcohol was immediately protected as follows. Imidazole (0.20 g, 3.60 mmol) and TBDMSCl (0.26 g, 7.50 mmol) were added to a 3-necked round bottomed flask fitted with a reflux condenser. To this mixture was added the alcohol (0.20 g, 1.40 mmol) in anhydrous DMF (20 mL) and resulting solution heated to 35 °C and stirred for 48 h. The aqueous layer was then extracted with ethyl acetate and the combined organic layers dried over magnesium sulphate and excess volatiles were removed under reduced pressure and the crude product purified by column chromatography which furnished the titled compound as a colourless yellow oil (0.31 g, 89%); IR (CH_2Cl_2) ν_{max} 3384, 2930, 2856, 1778, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.54 (dd, J = 3.6, 6.8 Hz, 1H), 6.38 (dd, J = 3.6, 7.2 Hz, 1H), 3.38 (dd, J = 6.0, 10.4 Hz, 1H), 3.23 (t, J = 9.6 Hz, 1H), 3.04 (t, J = 3.6 Hz, 1H), 2.83 (t, J = 3.6 Hz, 1H), 2.51–2.46 (m, 1H), 2.05 (ddd, J = 4.0, 10.0, 12.4 Hz, 1H), 0.88 (s, 9H), 0.66 (dd, J = 5.6, 12.0 Hz, 1H), 0.04 (s, 6H); δ_C (100 MHz, $CDCl_3$) 204.7, 133.6, 130.2, 64.3, 48.6, 46.3, 36.2, 25.7, 25.4, 18.0, −3.6; MS-ESI found 275.1461, $C_{14}H_{24}O_2Si$ $[M + Na]^+$ requires 275.1438.

7-Allyl-5-(^{t}butyl-dimethyl-silanyloxymethyl)bicyclo[2.2.1]hept-2-en-7-ol 23

Conditions A. To a solution of **22** (0.20 g, 0.80 mmol) in anhydrous THF (10 mL) cooled to −78 °C was added the Grignard reagent (2 M, 1.60 mL, 1.60 mmol) and the reaction mixture allowed to warm to room temperature and stirred for 16 h. To the reaction mixture was then added 2 M HCl and the resultant solution extracted with ethyl acetate. The combined organic extracts were then dried over magnesium sulphate and the excess volatiles removed under reduced pressure. The crude product was purified by column chromatography giving the title compound as a clear yellow oil. **Conditions B.** Into a stirring solution of tetrahydrofuran : water (10 mL 1 : 1) was added indium powder (0.015 g, 0.13 mmol), allyl bromide (0.017 g, 0.14 mmol) and ketone **22** (0.020 g, 0.007 mmol). The reaction was then heated to 50 °C for 12 h. Upon completion the reaction mixture was extracted with diethyl ether, and washed sequentially with water and brine. The organic fraction was then dried over magnesium sulphate and the excess volatiles removed under reduced pressure. The crude product was then purified by column chromatography (10 : 1, petroleum ether : ethyl acetate) giving the title compound as a clear yellow oil (**Conditions A**: 0.22 g, 91%; **Conditions B**: 0.20 g, 95%). IR (CH_2Cl_2) ν_{max} 3398, 2856, 1955, 1638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 (ddd, J = 0.8, 3.2, 6.4 Hz, 1H), 5.93 (dd, J = 3.2, 6.0 Hz, 1H), 5.84–5.74 (m, 1H), 5.13–5.06 (m, 2H), 3.38 (dd, J = 6.4, 10.0 Hz, 1H), 3.22 (t, J = 9.6 Hz, 1H), 2.68–2.63 (m, 1H), 2.59 (t, J = 3.6 Hz, 1H), 2.51–2.41 (m, 2H), 2.39 (t, J = 3.6 Hz, 1H), 2.12 (ddd, J = 4.0, 8.8, 11.6 Hz, 1H), 0.89 (s, 9H), 0.50 (dd, J = 4.4, 11.6 Hz, 1H), 0.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.5, 132.7, 118.5, 92.1, 65.4, 50.6, 48.9, 39.6, 37.8, 27.2, 26.0, 18.3, −5.3, −5.4; MS-ESI found 317.1897, $C_{17}H_{30}O_2Si$ $[M + Na]^+$ requires 317.1913.

7-Allyl-5-(methanol)-bicyclo[2.2.1]hept-2-en-7-ol 25

TBAF (1 M, 0.05 mmol, 0.50 mL) was added to a stirring reaction mixture of tetrahydrofuran (10 mL) and **23** (0.08 g, 0.027 mmol) under anhydrous conditions. Upon completion the reaction mixture was extracted using diethyl ether, and washed with water and brine. The organic fraction was then dried over magnesium sulphate and the excess volatiles removed under reduced pressure. Product was then purified by column chromatography (10 : 1, petroleum ether : ethyl acetate) giving the title compound as a colourless crystalline solid (0.07 g, 72%) M.P. 96–97 °C (from ethyl acetate–petroleum ether); IR (CH_2Cl_2) ν_{max} 3398, 2856, 1955, 1638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.12 (dd, J = 3.6, 6.4 Hz, 1H), 5.97 (dd, J = 3.2, 6.0 Hz, 1H), 5.83–5.73 (m, 1H), 5.15–5.13 (m, 1H), 5.13–5.09 (m, 1H), 3.42 (dd, J = 6.4, 10.4 Hz, 1H), 3.34 (dd, J = 9.2, 10.4 Hz, 1H), 2.71–2.67 (m, 1H), 2.62–2.60 (m, 1H), 2.53–2.41 (m, 2H), 2.45–2.43 (m, 1H), 2.22–2.16 (m, 1H), 0.60 (dd, J = 4.4, 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1 (CH), 135.2 (CH), 132.3 (CH), 118.8 (CH_2), 92.1 (C), 65.5 (CH_2), 50.5 (CH), 48.9 (CH), 39.8 (CH), 37.7 (CH_2), 27.4 (CH_2); MS-ESI found 203.1040, $C_{11}H_{16}O_2$ $[M + Na]^+$ requires 204.1048.

5-[(^{t}Butyldimethylsilyloxy)methyl]-7-(2-methylallyl)bicyclehept-2-en-7-ol 27

To a solution of **22** (0.20 g, 0.80 mmol) in anhydrous THF (10 mL) cooled to −78 °C was added the Grignard reagent (2 M, 1.60 mL, 1.60 mmol) and the reaction mixture allowed to warm to room temperature and stirred for 16 h. To the reaction mixture was then added 2 M HCl and the resultant solution extracted with ethyl acetate. The combined organic extracts were then dried over magnesium sulphate and the excess volatiles removed under reduced pressure. The crude product was purified by column chromatography giving the title compound as a colourless oil (0.14 g, 61%); IR (CH_2Cl_2) ν_{max} 3434, 2928, 2856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (dd, J = 3.6, 6.4 Hz, 1H), 5.94 (dd, J = 3.2, 6.4 Hz, 1H), 4.89–4.88 (m, 1H), 4.76–4.75 (m, 1H), 3.38 (dd, J = 6.4, 10.0 Hz, 1H), 3.22 (t, J = 9.6 Hz, 1H), 2.72–2.68 (m, 1H), 2.60 (t, J = 3.6 Hz, 1H),

2.16–2.09 (m, 1H), 1.76 (s, 3H), 0.88 (s, 9H), 0.50 (dd, J = 4.0, 11.6 Hz, 1H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 134.9, 132.7, 114.3, 91.5, 65.6, 50.5, 49.6, 39.7, 38.6, 30.9, 27.3, 25.6, 23.8, 23.8, 18.3, −5.3; MS-ESI found 331.2051, $C_{18}H_{32}O_2Si$ $[M + Na]^+$ requires 331.2064.

7-(But-3-en-2-yl)-5-((*tert*-butyldimethylsilyloxy)methyl)bicyclo-[2.2.1]hept-2-en-7-ol 28

To a solution of **22** (0.20 g, 0.80 mmol) in anhydrous THF (10 mL) cooled to −78 °C was added the Grignard reagent (2 M, 1.60 mL, 1.60 mmol) and the reaction mixture allowed to warm to room temperature and stirred for 16 h. To the reaction mixture was then added 2 M HCl and the resultant solution extracted with ethyl acetate. The combined organic extracts were then dried over magnesium sulphate and the excess volatiles removed under reduced pressure. The crude product was purified by column chromatography giving the title compound as a colourless oil (0.18 g, 74%); IR (CH_2Cl_2) ν_{max} 3468, 3069, 2929, 2857 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07–6.04 (m, 1H), 5.91–5.85 (m, 2H), 5.14 (t, J = 1.4 Hz, 1H), 5.12–5.00 (m, 1H), 3.38–3.35 (m, 1H), 3.25–3.19 (t, J = 4.8 Hz, 1H), 2.99–2.94 (m, 1H), 2.70–2.261 (m, 2H), 2.51–2.48 (m, 1H), 2.13–2.06 (m, 1H), 1.56 (d, J = 6.8 Hz, 1H), 0.97–0.94 (t, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 135.7, 132.9, 115.6, 94.7, 65.4, 50.2, 47.5, 39.7, 36.6, 29.7, 25.9, 18.3, 14.1, −5.2; MS-ESI found 331.2051, $C_{18}H_{32}O_2Si$ $[M + Na]^+$ requires 331.2064.

5-((*t*Butyldimethylsilyloxy)methyl)-7-(penta-1,4-dien-3-yl)bicyclo-[2.2.1]hept-2-en-7-ol 30 (Conditions C)

The TBS protected ketone **22** (0.20 g, 0.84 mmol) and 5-bromo-1,3-pentadiene (0.29 g, 1.99 mmol) were dissolved in DMF (0.30 mL). Indium powder (0.13 g, 1.13 mmol) was added slowly to the reaction mixture and the subsequently stirred for 48 h at room temperature. The reaction mixture was then diluted with CH_2Cl_2 (5 mL) and then added to diethyl ether (25 mL) and the resultant mixture filtered through a pad of silica. The silica was washed with additional diethyl ether, and the filtrate concentrated *in vacuo*. This afforded a yellow oil which was then purified by column chromatography (R_f = 0.51, ethyl acetate–light petroleum 10 : 1) to give the title compound as a colourless oil (0.13 g, 49%); IR (CH_2Cl_2) ν_{max} 3368, 2851, 1950, 1631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (ddd, J = 0.8, 3.6, 6.4 Hz, 1H), 5.96–5.85 (m, 2H), 5.18–5.11 (m, 2H), 5.07–5.00 (m, 2H), 3.53–3.49 (m, 1H), 3.63 (dd, J = 6.4, 10.0 Hz, 1H), 3.23 (t, J = 8.0 Hz, 1H), 2.69–2.62 (m, 2H), 2.47 (t, J = 3.6 Hz, 1H), 2.12–2.06 (m, 1H), 0.89 (s, 9H), 0.52 (dd, J = 4.0, 11.0 Hz, 1H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 137.5, 135.3, 132.4, 117.1, 116.9, 94.4, 65.4, 49.7, 48.0, 47.9, 39.7, 27.2, 26.0, 22.6, −5.3, −5.4; MS-ESI found 343.2057, $C_{19}H_{32}O_2Si$ $[M + Na]^+$ requires 343.2069.

TBS protected [3.0.3]-bicycle 31

Grubbs second generation catalysts (10 mol%) was dissolved in anhydrous toluene (5 mL) in a 25 mL round bottomed flask. Ethene was then bubbled through the reaction mixture for 2–3 min. The ethene atmosphere was then maintained and a solution of **23** (67 mg, 0.21 mmol) in toluene (1 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 products was then purified by column chromatography (R_f 0.46, 10 : 1 petroleum ether : ethyl acetate) giving the title compound as a pale yellow oil (36 mg, 54%); IR (CH_2Cl_2) ν_{max} 3420, 2845, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddd, J = 6.4, 10.8, 17.2 Hz, 1H), 5.79–5.70 (m, 2H), 5.54 (d, J = 6.0 Hz, 1H), 5.21–4.94 (m, 4H), 3.43 (d, J = 7.2 Hz, 1H), 3.41 (d, J = 5.6 Hz, 1H), 3.31 (d, J = 7.6 Hz, 1H), 3.02 (d, J = 8.8 Hz, 1H), 2.67 (dt, J = 6.0, 13.2 Hz, 1H), 2.47–2.36 (m, 1H), 1.77 (dt, J = 5.6, 12.0 Hz, 1H), 1.03 (q, J = 12.4 Hz, 1H), 0.85 (s, 9H), −0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.5, 132.3, 131.1, 1108.2, 116.3, 90.2, 64.4, 60.1, 54.2, 53.9, 43.4, 32.4,25.9, 18.2, −5.3, −5.4; MS-ESI found 343.3055, $C_{19}H_{32}O_2Si$ $[M + Na]^+$ requires 343.2069.

7-Allyl-7-hydroxybicyclo[2.2.1]hept-5-en-2-ylmethyl acetate 34

7-Allyl-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-ol (0.10 g, 0.1 mmol) dissolved in CH_2Cl_2 (10 mL) was added to a 25 mL round bottomed flask. Acetic anhydride (0.10 mL, 0.1 mmol) and triethylamine (0.15 mL, 0.1 mmol) were added and the reaction mixture stirred at room temperature for 5 days. The organic layer was washed with water and brine and then dried over magnesium sulphate, and the filtrate concentrated *in vacuo*. The product was the purified by column chromatography (2 : 1 petrol : ethyl acetate) and a clear yellow oil was obtained (0.16 g, 65%); IR (CH_2Cl_2) 3464, 3060, 2967, 2865, 1741, 1718, 1638, 1573 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (dd, J = 0.8, 3.2 Hz, 1H), 5.95 (dd, J = 3.2, 6.4 Hz, 1H), 5.82–5.72 (m, 1H), 5.15–5.08 (m, 2H), 3.88–3.72 (m, 2H), 2.84–2.76 (m, 1H), 2.55 (t, J = 3.4 Hz, 1H), 2.49–2.43 (s, 3H), 2.25–2.19 (m, 1H), 0.64–0.60 (dd, J = 4.0, 11.6 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.1, 136.4, 135.0, 132.2, 118.8, 92.0, 66.8, 50.7, 48.9, 37.6, 35.9, 27.7, 21.0; MS-ESI found 245.1140, $C_{13}H_{18}O_3Na$ $[M + Na]^+$ requires 245.1148.

7-Allyl-5-methylbicyclo[2.2.1]hept-2-en-7-ol 36

To CH_2Cl_2 (5 mL) in a 10 mL round bottomed flask under nitrogen, was added 7-allyl-5-(hydroxymethyl)bicyclo[2.2.1]hept-2-en-7-ol (0.1 g, 0.55 mmol) and triethylamine (0.12 mL, 0.86 mmol). The reaction mixture was then cooled to 0 °C and methanesulfonyl chloride (0.05 mL, 0.66 mmol) was added drop wise and the reaction mixture stirred for a further 30 min. To the reaction mixture was washed using ice-cold water (10 mL), HCl (5 M 10 mL), $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was then dried over magnesium sulphate and excess volatiles removed under reduced pressure. The crude mesylate was the purified by column chromatography (2 : 1 petrol : ethyl acetate) and a clear oil was obtained (0.09 g, 70%); IR (CH_2Cl_2) ν_{max} 3531, 3061, 2973, 2940, 2867, 1638 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 6.10 (dd, J = 0.8, 3.6 Hz, 1H), 5.92 (dd, J = 3.2, 6.4 Hz, 1H), 5.74–5.64 (m, 1H), 5.10–5.02 (m, 2H),

3.96–3.81 (m, 2H), 2.93 (s, 3H), 2.87–2.82 (m, 1H), 2.57 (t, J = 3.4 Hz, 1H), 2.46–2.32 (m, 3H), 2.22–2.16 (m, 1H), 1.90 (s, 1H), 0.54 (dd, J = 4.4, 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 133.7, 130.7, 118.1, 91.0, 71.2, 51.0, 49.4, 36.5, 36.2, 35.9, 26.3. MS-ESI found 282.0964, $C_{12}H_{20}O_4SNa$ $[M + Na]^+$ requires 282.0975. Into a 100 mL 3-necked round bottomed flask was added the mesylate (0.1 g, 0.38 mmol) in THF (20 mL). Superhydride® (1 M in THF 3.8 mL, 0.38 mmol) was then added drop wise and the reaction mixture brought to reflux overnight. Excess Superhydride® was then quenched using ice-cold water and the organoboranes were oxidised by the addition of 3 M aqueous NaOH and cold 30% H_2O_2. The mixture was then heated to reflux for a further 1.5 h. The reaction mixture was then extracted using hexane. The organic layer was washed with water and brine, and dried over magnesium sulphate. Excess volatiles were removed under reduced pressure. The product was the purified by column chromatography (2 : 1 petrol : ethyl acetate) and a clear oil was obtained (0.05 g, 62%); IR (CH_2Cl_2) ν_{max} 3646, 3379, 3060, 2955, 2925, 2985 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (dd, J = 1.0, 3.0 Hz, 1H), 5.87 (dd, J = 3.0 6.0 Hz, 1H), 5.76–5.65 (m, 1H), 5.08–4.99 (m, 2H), 2.49–2.41 (m, 1H), 2.40–2.37 (m, 2H), 2.27 (dt, J = 3.8, 7.4 Hz, 2H), 2.17–2.11 (m, 1H), 1.21–1.16 (m, 3H), 0.85–0.79 (m, 1H), 0.44 (dd, J = 4.0, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 135.6, 118.3, 61.3, 53.2, 40.8, 31.6, 27.8, 17.5; MS-ESI found 163.1116, $C_{11}H_{15}O$ $[M - H]^-$ requires 163.1117.

1-Methyl-3-vinyl-1,2,3,3a,4,6a-hexahydropentalen-3a-ol 37

Grubbs' second generation catalysts (0.01 g, 0.003 mmol) was dissolved in anhydrous toluene (5 mL) in a 5 mL round bottomed flask. Ethylene was then bubbled through the reaction mixture for 2–3 min. The ethylene atmosphere was then maintained and **36** (0.05 g, 0.03 mmol) 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. Product was then purified by column chromatography (10 : 1 petrol : ethyl acetate) giving the title compound. A clear yellow oil was obtained (0.035 g, 71%); IR (CH_2Cl_2) ν_{max} 3647, 3381, 3050, 2965, 2925, 2913 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94–5.86 (m, 1H), 5.68–5.66 (m, 1H), 5.58–5.52 (m, 1H), 5.11–5.03 (m, 2H), 2.92–2.90 (d, J = 8 Hz, 1H), 2.65–2.58 (m, 2H), 2.38–2.25 (m, 1H), 2.18–2.08 (m, 1H), 1.29–1.20 (m, 3H), 0.91–0.89 (d, J = 12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 137.7, 129.6, 115.9, 92.2, 61.7, 51.2, 44.4, 37.2, 35.1, 16.1; MS-ESI found 163.1121, $C_{11}H_{15}O$ $[M - H]^+$ requires 163.1117.

TBS protected [3.0.3]-bicycle 38

Grubbs second generation catalysts (10 mol%) was dissolved in anhydrous toluene (5 mL) in a 25 mL round bottomed flask. Ethene was then bubbled through the reaction mixture for 2–3 min. The ethene atmosphere was then maintained and a solution of **30** (67 mg, 0.21 mmol) in toluene (1 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 products was then purified by column chromatography (R_f 0.46, 10 : 1 petroleum ether : ethyl acetate) giving the title compound as a pale yellow oil (36 mg, 54%); IR (CH_2Cl_2) ν_{max} 3420, 2845, 1452 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddd, J = 6.4, 10.8, 17.2 Hz, 1H), 5.79–5.70 (m, 2H), 5.54 (d, J = 6.0 Hz, 1H), 5.21–4.94 (m, 4H), 3.43 (d, J = 7.2 Hz, 1H), 3.41 (d, J = 5.6 Hz, 1H), 3.31 (d, J = 7.6 Hz, 1H), 3.02 (d, J = 8.8 Hz, 1H), 2.67 (dt, J = 6.0, 13.2 Hz, 1H), 2.47–2.36 (m, 1H), 1.77 (dt, J = 5.6, 12.0 Hz, 1H), 1.03 (q, J = 12.4 Hz, 1H), 0.85 (s, 9H), −0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.5, 132.3, 131.1, 1108.2, 116.3, 90.2, 64.4, 60.1, 54.2, 53.9, 43.4, 32.4, 25.9, 18.2, −5.3, −5.4; MS-ESI found 343.3055, $C_{19}H_{32}O_2Si$ $[M + Na]^+$ requires 343.2069.

Acknowledgements

We gratefully acknowledge financial support from the Department of Chemistry at Loughborough University, as well as NMR analysis by Dr Mark Edgar (Department of Chemistry, Loughborough University). The Advanced Light Source is supported by the Director, Office of Science, Office of Basic Energy Sciences, of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231.

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