Studies Towards the Total Synthesis of Cycloaraneosene and Ophiobolin M: A General Strategy for the Construction of the 5−8 Bicyclic Ring System

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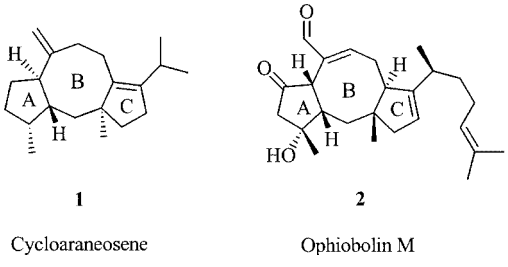
The synthesis of the core unit of cycloaraneosene and ophiobolin M has been investigated, following a general strategy applicable to both 5–8 bicyclic systems. The synthetic strategy includes a ring-closing metathesis reaction to generate the central eight-membered ring as well as a palladium-mediated coupling of a Grignard reagent to introduce the exocyclic side-chain. The stereochemistry of the ring junction is also discussed and moderate diastereoselectivity has been achieved.

Introduction

Ophiobolins and fusicoccin diterpenes are distinct classes of natural compounds containing the same 5-8-5 tricyclic carbon backbone. The construction of this unusual ring system has inspired considerable synthetic effort.[1] Ophiobolin M **2** and the fusicoccin cycloaraneosene **1** are typical examples (Figure 1). These natural products show a variety of biological activities such as a potential treatment for parasitic diseases in both humans and animals.[2]



1 Cycloaraneosene **2** Ophiobolin M

Figure 1. Cycloaraneosene and ophiobolin M

The synthetic challenge is not only due to the stereochemistry of these natural compounds but also arises from the carbon skeleton itself: eight-membered rings have often proven difficult to synthesise.[3] However, the last decade has seen the rapid development of ring-closing metathesis (RCM) reactions, applicable to a wide range of substrates.[4] We anticipated that RCM could be an appropriate solution to the problematic construction of the central eight-membered ring.

Examining both structures in more detail, one can consider that ring A is an exocyclic group, attached to the central eight-membered ring B. Then, both bicyclic ring systems B-C are rather structurally similar, the major differences being the exocyclic isopropyl or dimethylhexenyl alkyl chain and the position of the double bond in ring C. Therefore, a general strategy towards the synthesis of these 5−8 ring systems seems to be applicable to both molecules (Figure 1). We propose to design a general synthetic strategy applicable to the synthesis of the core ring system of natural compounds **1** and **2**.

Results and Discussion

Our general synthetic strategy relies on a convergent approach (Scheme 1).

The exocyclic chain R could be attached via a palladium-catalysed coupling reaction between vinyl triflates **5** and **6** and the corresponding organometallic RM. Trapping the kinetic or the thermodynamic enolate of **7** by literature procedures[5] should afford **5** and **6**. The bicyclic methylated ketone **7** could be obtained from the action of a methyl cuprate on the bicyclic enone **8**. Key intermediate **8** results from a ring-closing metathesis performed on triene **9** which can be generated from methyl ether **10**. Palladium-catalysed allylation of the commercially available 1,3-cyclopentanedione **11** would be the starting point of the synthesis.

The synthesis of the ring-closing metathesis precursor **9** was achieved in three steps (Scheme 2).

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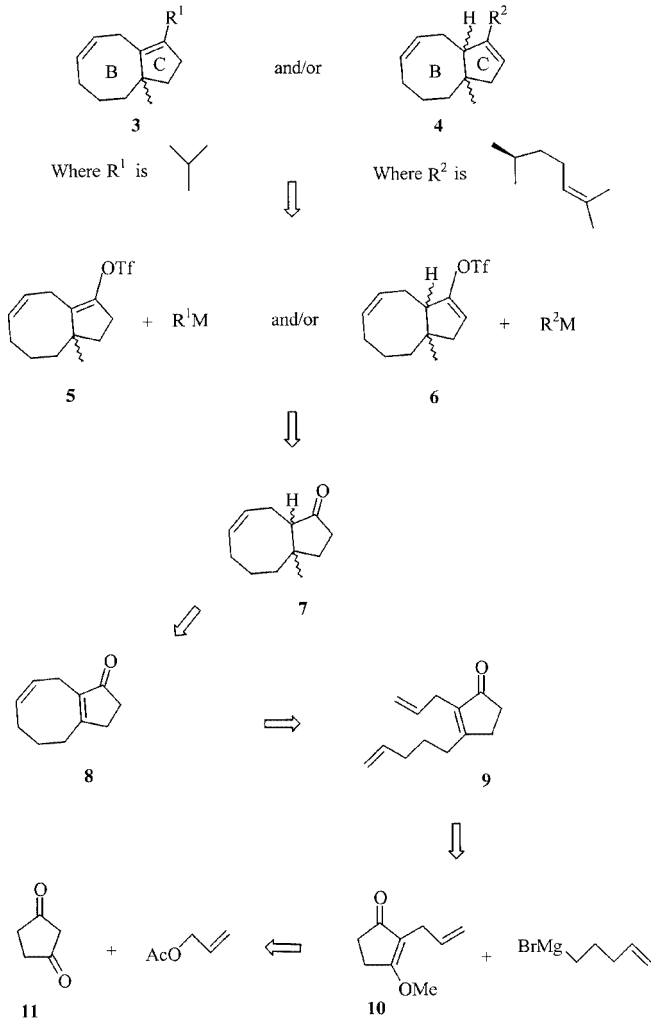
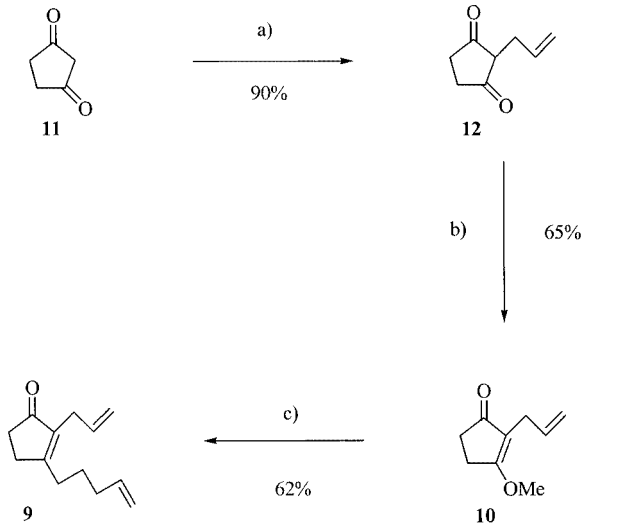


Scheme 1. Retrosynthetic analysis of the core units of cycloaraneosene and ophiobolin M



Scheme 2. Synthesis of RCM precursor **9**; reagents and conditions: a) allyl acetate, $[Pd(C_3H_5)Cl_2]_2$, BSA [BSA = $Me_3SiN{=}C(CH_3)O\text{-}SiMe_3$], cat. NaOAc, THF, reflux 24 h; b) $(MeO)_3CH$, conc. H_2SO_4, MeOH, reflux 1 h; c) (i) pentenylmagnesium bromide, Et_2O, 0 °C to room temp. 12 h, (ii) 2 M HCl, room temp. 30 min.

First, 1,3-cyclopentanedione **11** was allylated in good yields following a one-step palladium-catalysed reaction. The literature procedure for the synthesis of 2-allyl-1,3-cyclopentanedione **12** usually involves cyclisation of an acyclic precursor and direct alkylations of 1,3-cyclopentanedione give low to moderate yields.[6]

The allylated cyclopentanedione **12** was then converted into the methyl enol ether **10** in refluxing methanol in the presence of acid and trimethyl orthoformate.[7]

The methyl enol ether **10** was then reacted with the Grignard reagent derived from pentenyl bromide. Initial investigative reactions showed that low yields of the product formed when the Grignard reagent was added to the enol ether. This was also the case when more than a stoichiometric amount of the enol ether was used or when the reaction was performed at −78 °C. The protocol used in the reaction[8] required that a solution of the enol ether **10** in diethyl ether was added to a solution of two equivalents of the pentenylmagnesium bromide at 0 °C. The mixture was warmed to room temperature and stirred overnight before quenching with acid. Following this procedure, yields of up to 62% of the desired triene intermediate **9** could be obtained.

The next step in the synthesis was the generation of the eight-membered ring B.

Construction of eight-membered rings by traditional methods of ring formation has proven to be challenging, probably due to the various conformations and energies associated with the cyclooctanoid system. The synthesis of these eight-membered carbocycles and applications to natural product synthesis has been summarised in two key reviews.[9]

In the present synthesis, it was hoped to use ring-closing metathesis to form ring B. Initially, the commercially available Grubbs' ruthenium catalyst, **13**, was used (Figure 2).

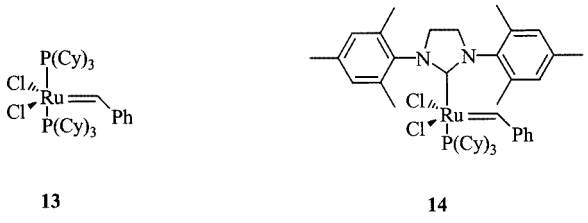
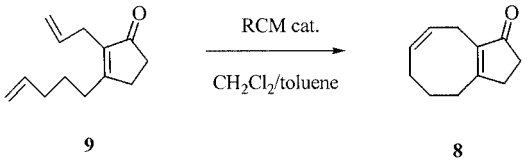


Figure 2. Ruthenium catalysts for ring-closing metathesis

A series of reactions was performed varying the temperature and concentration in either toluene or dichloromethane to obtain optimal condition for this ring closure. The conversion of the precursor **9** into the bicycle **8** (Scheme 3) was determined by ^1H NMR spectroscopy. The signal from the alkenyl proton nearest the carbonyl in the cyclised product **8** appears as a multiplet in the $\delta = 5.43-5.51$ ppm region of the spectrum. The four protons of the terminal alkenes of the starting material **9** appear as a separate mul-

tiplet in the δ = 4.95−5.07 ppm region of the spectrum. Results from these reactions are summarised in Table 1.



Scheme 3. Ring-closing metathesis: general scheme

Table 1. Ring-closing metathesis with catalyst **13**

Entry	Solvent	mol % **13**	Temp. (°C)	Conc. (M)	Time	B:M[a]	Yield (%)[b]
1	CH_2Cl_2	6	rt	0.02	24 h	29:71	23
2	CH_2Cl_2	8	45	0.02	24 h	62:38	38
3	CH_2Cl_2	8	45	0.01	2.5 d	96:4	34
4	CH_2Cl_2	10	45	0.01	3 d	92:8	48
5	toluene	8	rt	0.02	24 h	22:78	11
6	toluene	8	65	0.02	24 h	78:22	43
7	toluene	8	65	0.01	4 d	83:17	61
8	toluene	8	65	0.075	4 d	91:9	30
9	toluene	8	103	0.01	3 d	97:3	49

[a] B:M = bicycle:monocycle ratio. [b] Yield of bicycle before separation.

In general, a higher rate of conversion from the monocycle into the bicycle occurred at elevated temperatures. At 103 °C, the ratio was 97:3 in favour of the bicycle (entry **9**). Reactions in dichloromethane proceeded more cleanly and were easier to workup than those in toluene due to the volatility of the product. Therefore the conditions of choice were refluxing dichloromethane with a catalyst loading of 8−10 mol %.

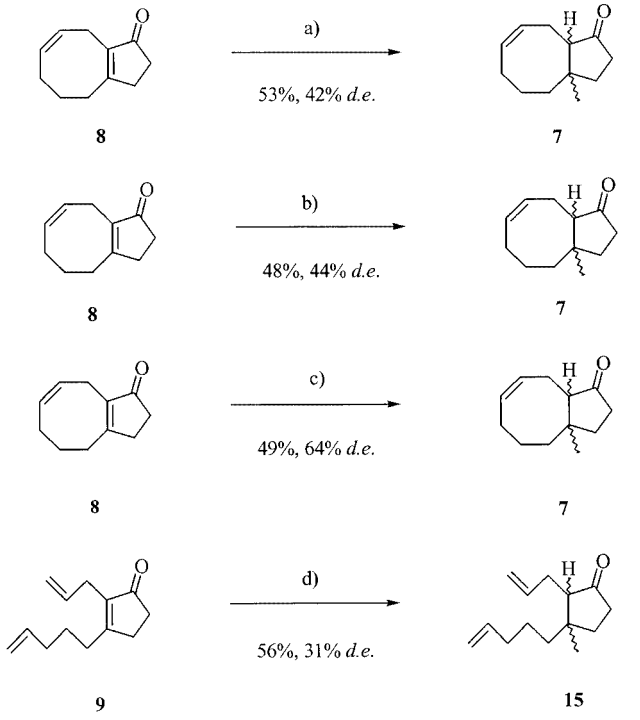
Attempts with the recently developed ruthenium catalyst **14**[10] did not lead to any improvement. Lower conversions and a lower bicycle:monocycle ratio were observed.

About 10% of a by-product was isolated in most of the reactions studied, arising probably from isomerisation of the allylic bond in the triene **9**.

Once the bicyclic enone **8** had been prepared, the introduction of the methyl group at the ring junction was investigated using a methyl cuprate reagent.

1,4-Conjugate addition of organocuprate reagents to α,β-unsaturated enones is now a well-established synthetic procedure for the formation of C−C bonds.[11−13] However, a universal protocol that can be successfully applied to any substrate is not available. Various copper sources, solvents, Lewis acid activation and stoichiometries of reagents have to be explored, especially in the case of highly hindered β,β-disubstituted enones such as bicyclic compounds, where reagent reactivity is usually low. In such cases, Yamamoto's method of BF_3·Et_2O-organocopper reagent has often proven to be successful.[14,15] Trimethylchlorosilane has been used by Nakamura et al. to mediate 1,4-conjugate additions to hindered enones, although not bicyclic enones.[16]

In the present synthesis, methyl addition at the B/C ring junction was accomplished by using either Nakumura and co-workers[16] method of chlorosilane-mediated addition, or by Yamamoto's[15] method with a BF_3·Et_2O-organocopper system; the chlorosilane reaction gave similar yields to other 1,4-conjugate addition reactions on bicyclic enones (Scheme 4).[15]



Scheme 4. Diastereomeric excess after 1,4-addition; reagents and conditions: a) MeMgBr $CuBrMe_2S$, DMPU, TMSCl, THF, −78 °C, 5 h; b) MeLi, CuI, BF_3·Et_2O, THF, −78 °C, 5 h; c) (i) MeLi, CuI, BF_3·Et_2O, THF, −78 °C, (ii) MeLi, (iii) 2,4,6-tri-*tert*-butylphenol, (d) MeMgBr, CuBr·Me_2S, DMPU, TMSCl, THF, −78 °C, 6 h

Moderate diastereomeric control was achieved in this reaction (44% *de* by ^{1}H NMR spectroscopy), although yields were not consistent. More accurately, the four isomers could be separated by GC; lower diastereomeric excess could then be confirmed (30% *de*). A change of solvent from THF to diethyl ether led to the failure of the reaction.

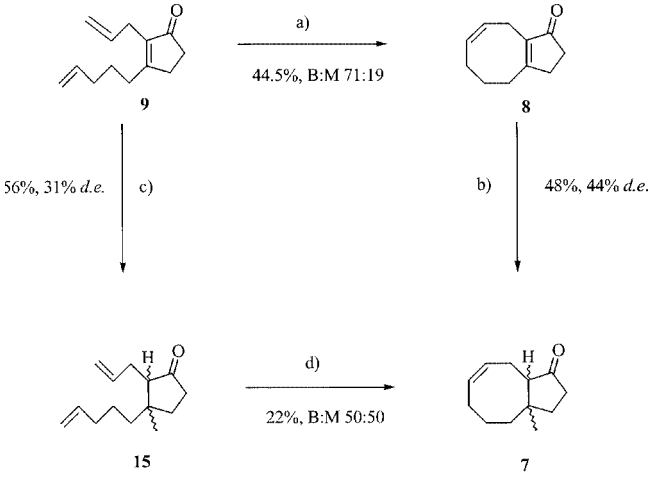
Yamamoto's procedure using BF_3·Et_2O leads to more consistent yields (Scheme 4). Yields up to 58% were obtained. The *de* of the methyl addition product (42% by ^{1}H NMR spectroscopy) was similar to those obtained using Nakamura's procedure.

We also tried a slight modification to Yamamoto's procedure: after transmetallation with methyllithium, the resulting enolate was trapped in situ with a hindered source of proton (2,4,6-tri-*tert*-butylphenol). As a result, the diastereocontrol of the reaction was greatly improved (64% *de* by ^{1}H NMR spectroscopy) and the same major set of isomers persisted. Unfortunately, the diastereoisomers could not be separated and ^{1}H NMR spectroscopy could not confirm the conformation of the predominant set of isomers. However, we hope to achieve their separation on a more functionalised product at a later stage of the synthesis

(hopefully, once the exocyclic side chains have been coupled).

1,4-Conjugate addition was also performed on the monocyclic enone **9** (Scheme 4). The ^{1}H NMR spectrum again showed two signals for the newly introduced methyl at δ = 0.83 and 1.12 ppm. The *de* was lower than that observed in the case of the bicyclic enone **8**, and, interestingly, the diastereoselectivity was opposite. The signal due to the major set of isomers (65.5%) occurred at δ = 0.83 ppm and that for the minor set (34.5%) appeared at δ = 1.12 ppm. Again, the diastereoisomers could not be separated and the conformation of the major set of isomers was not elucidated. The addition product **7** could also be obtained if a ring-closing metathesis reaction was carried out on the moncyclic diene **15**. An unoptimised RCM reaction on monocyclic diene **15** in refluxing dichloromethane (0.01 M/ 10% cat. loading) yielded only a 50% conversion.

A summary scheme leading to the addition product **7**, via the two routes discussed so far, is given in Scheme 5.

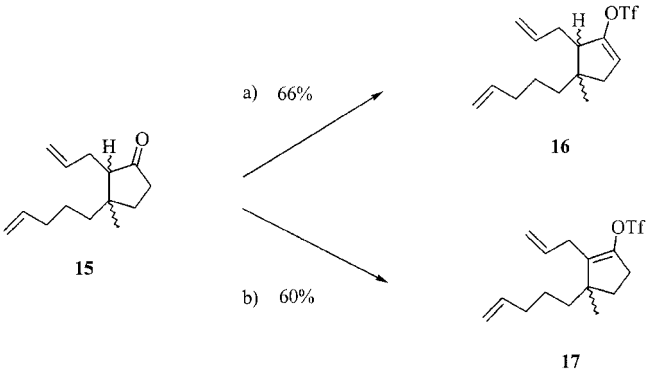


Scheme 5. Synthesis of the bicyclic ketone **7**; reagents and conditions: a) **13** (6 mol%), CH_2Cl_2, 45 °C 24 h; b) MeMgBr, CuBr·Me_2S, DMPU, TMSCl, THF, −78 °C 5 h; c) MeMgBr, CuBr·Me_2S, DMPU, TMSCl, THF, −78 °C 5 h; d) **13** (10 mol%), CH_2Cl_2, 45 °C, 24 h; B:M = Bicycle:monocycle ratio

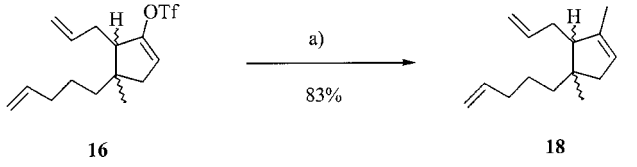
The next step in the synthesis was to attach the exocyclic side-chain to the bicyclic core. This could be achieved by a metal-mediated reaction between an organometallic precursor of the side-chain and a vinyl triflate derived from bicyclic ketone. Initially, the reaction was done on the more readily available monocyclic ketone **15**. Both kinetic and thermodynamic enolates of **15** could be trapped as their corresponding vinyl triflate **16** and **17** (Scheme 6).

Once vinyl triflates **16** and **17** had been formed, different coupling reactions were investigated. Attempts with organocopper reagents, following the method developed by McMurry,[17] were unsuccessful.

On the other hand, product **18** was obtained in 83% yield when the monocyclic triflate **16** was reacted with methylmagnesium bromide in the presence of $Pd(PPh_3)_4$ for 1 hour (Scheme 7). It is hoped that the same method can be successfully applied to triflate **17** and will also allow the coupling of both exocylic side-chains *via* their respective Grignard reagent derivative.

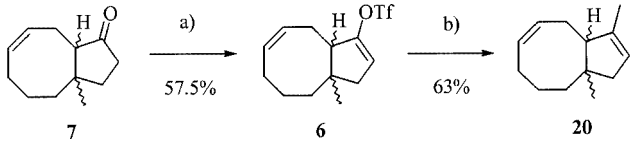


Scheme 6. Synthesis of monocyclic triflates **16** and **17**; reagents and conditions a) LDA, $PhNTf_2$, THF; b) (i) KHMDS (ii) $PhNTf_2$, THF



Scheme 7. Synthesis of coupled products **18**; reagents and conditions: a) $Pd(PPh_3)_4$, MeMgBr, THF, reflux

Finally, the same synthetic pathway was applied to bicyclic ketone **7** (Scheme 8): vinyl triflate **6** was obtained in a similar yield to **16**, and subsequent coupling reaction with methylmagnesium bromide in the presence of $Pd(PPh_3)_4$ gave the methyl-coupled product **20**. Surprisingly, the *de* varied considerably along the synthetic pathway, from 64% *de* (by ^{1}H NMR spectroscopy) for ketone **7** to 57% *de* (by ^{1}H NMR spectroscopy) for triflate **6** to 78% *de* (by ^{1}H NMR spectroscopy) for product **20**.



Scheme 8. Synthesis of bicyclic compound **20**; reagents and conditions: a) LDA, DMPU, $PhNTf_2$, THF; b) $Pd(PPh_3)_4$, MeMgBr, THF, reflux

Conclusion

We have proposed a successful synthetic strategy towards the synthesis of the 5−8 bicyclic core of cycloaraneosene and ophiobolin M. Construction of the central eight-membered ring has been achieved by means of a ring-closing metathesis reaction. Palladium coupling of the dimethylhexenyl exocylic side chain of ophiobolin M has yet to be achieved; however we have demonstrated that the simple Grignard reagent methylmagnesium bromide could be easily coupled. Further investigations will hopefully allow us

to apply our strategy to the total synthesis of cycloaraneosene and ophiobolin M.

Experimental Section

General Remarks: All reactions that required an inert atmosphere were performed under nitrogen. Solvents for these reactions were dried and purified prior to use. Commercial reagents were purified when required. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with either a JEOL GX 270 MHz or JEOL GX 400 MHz instrument. IR spectra were recorded mainly as liquid films or KBr discs on a Perkin−Elmer FT1000 spectrometer. Mass spectra were recorded with a Finnigan MAT 8340 instrument. Elemental analysis was carried out on a Carbo Erba Stamentazione EA 1506 analyser. Separation of diastereoisomers was achieved by chiral GC on a SUPELCO™ Betadex 120 column.

2-Allyl-1,3-cyclopentanedione (12):[18] $[Pd(C_3H_5)Cl]_2$ (0.09 g, 0.25 mmol, 2.5 mol %) was added to dppe (0.40 g, 1.0 mmol) in a reaction flask equipped with a nitrogen line and a water condenser (NB The commercially available greenish-yellow Pd dimer was purified by dissolving in a small quantity of warm CH_2Cl_2. This solution was then passed through a small column of silica, which was rinsed several times with CH_2Cl_2. The combined washings were then evaporated to give a bright yellow solid.). The reaction flask was purged twice with nitrogen. The solid reagents were dissolved in THF (25 mL) and allyl acetate (1.08 mL, 10.0 mmol) added. To the yellow-orange solution were added sequentially 1,3-cyclopentanedione **11** (1.50 g, 15.0 mmol), BSA (3.70 mL, 15.0 mmol) and NaOAc (0.05 g, 0.25 mmol). The mixture was refluxed for 24 h, after which it was cooled, diluted with MeOH (20 mL) and stirred for 15 min. A cream solid precipitated which was removed by filtering the suspension through a pad of celite. The pad was washed with more MeOH (3 × 10 mL) and the combined washings were reduced to about a third of the original volume under reduced pressure. Silica (4 g) was then added to the concentrate and the solvent evaporated. The pre-adsorbed crude mixture was chromatographed (silica, 98:2 CH_2Cl_2/MeOH) to isolate allylated cyclopentanedione **12** as an off-white solid that was recrystallised from hot EtOAc as shiny white needles (1.19 g, 90%). M.p. 152.9−153.3 °C. R_f (95:5 CH_2Cl_2/MeOH) = 0.27. IR (KBr): $\tilde{\nu}$ = 3414 cm^{-1} (w, OH), 3077 (=CH), 2970 and 2929 (CH), 2400 (broad, strong), 1868 (broad, strong), 1675 (C=O), 1640 (C=C). ^{1}H NMR (270 MHz, CD_3OD): δ = 2.58 (s, 4 H, CH_2CH_2CO), 2.92 (d, J = 6.0 Hz, 2 H, CH_2=CHCH_2C), 4.99−5.08 (m, 2 H, CH_2=CHCH_2C), 5.10 (broad s, 1 H, OH), 5.87 (ddt, J = 6.0, 10.0, 17.2 Hz, 1 H, CH_2=CHCH$_2$C). ^{13}C NMR (68 MHz, CD_3OD): δ = 26.2 (CH_2, CH_2CO), 31.5 (CH_2), 115.1 (=CH_2), 116.6 (quaternary), 136.4 (=CH), 199.2 (quaternary, CO). MS (EI): *m*/*z* = 138 (100) [M$^+$], 95 (47); $C_8H_{10}O_2$ requires M$^+$ = 138.0681; found 138.0680. $C_8H_{10}O_2$ (138.2): calcd. C 69.5, H 7.3; found C 69.3, H 7.3.

2-Allyl-3-methoxy-2-cyclopenten-1-one (10):[18] Conc. H_2SO_4 (4.0 mL) was added to a solution of 2-allyl-1,3-cyclopentanedione (**12**; 10.0 g, 0.07 mol) and $(MeO)_3CH$ (45.9 mL, 0.4 mol) in MeOH (140 mL). The mixture was refluxed for 1 h and, after cooling, most of the MeOH was carefully removed under vacuum. The residue was brought to pH 8 with saturated sodium hydrogen carbonate solution and extracted with Et_2O (6 × 200 mL). The combined extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure. The residual brown oil was flushed quickly with Et_2O through a column of silica and basified with Et_3N, to afford the methyl enol ether **10** as a yellow brown oil (7.10 g, 64.5%) which was stored under an atmosphere of nitrogen in the refrigerator. R_f (Et_2O) = 0.12. IR (film): $\tilde{\nu}$ = 3483 cm^{-1} (w), 3078 (=CH), 2952 (CH), 1686 (C=O), 1625 (C=C), 1360 (s), 1261 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45−2.47 (m, 2 H, CH_2), 2.68 (t, J = 4.6 Hz, 2 H, CH_2), 2.90 (d, J = 6.4 Hz, 2 H, H_2C=CHCH_2C), 3.96 (s, 3 H, OMe), 4.93−5.03 (m, 2 H, CH_2CH=CH_2), 5.83 (ddt, J = 6.3, 10.0, 17.1 Hz, 1 H, CH_2CH=CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (CH_2), 25.5 (CH_2), 33.3 (CH_2), 56.4 (CH_3), 114.7 (=CH_2), 118.0 (quaternary), 134.9 (=CH), 184.9 (quaternary), 204.2 (quaternary). MS (EI): *m*/*z* (%) = 152 (100) [M$^+$], 137 (47) [M$^+$ − Me], 95 (43), 43 (44); $C_9H_{12}O_2$ requires M$^+$ = 152.0837; found 152.0833.

2-Allyl-3-(4-pentenyl)-2-cyclopenten-1-one (9): Magnesium turnings (84.0 mg, 3.4 mmol) in a three-necked, 25-mL round bottom flask equipped with a nitrogen line and water condenser were mechanically stirred under nitrogen for 2 h and then suspended in dry Et_2O (7.0 mL). Bromopentene (0.39 mL, 3.3 mmol) was then added dropwise. Initially, about 0.1 mL was added and the mixture gently refluxed for about 5 min, after which the reflux was maintained simply by the addition of more bromopentene. After the addition was complete, the reagent mixture was stirred at room temperature for 15 min, cooled to 0 °C, and a solution of methylenol ether **10** (0.25 g, 1.6 mmol) was added dropwise. The resulting yellow-brown suspension was stirred at room temperature for 8 h, then quenched very carefully with 2 M HCl (10 mL) solution and stirred at room temperature for a further 30 min. The mixture was poured into water and extracted with Et_2O (4 × 15 mL). The extract was dried (Na_2SO_4), the solvent evaporated under reduced pressure and the residue chromatographed (silica, CH_2Cl_2) to afford the triene **9** as a yellow oil (0.19 g, 62%). R_f (9:1 CH_2Cl_2) = 0.2. IR (film): $\tilde{\nu}$ = 3078 cm^{-1} (=CH), 2928 (CH), 1698 (CO), 1641 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59−1.71 (m, 2 H, CH_2), 2.07−2.16 (m, 2 H), 2.39−2.41 (m, 2 H), 2.44 (t, J = 7.8 Hz, 2 H), 2.53 (t, J = 4.6 Hz, 2 H), 2.95 (d, J = 6.4 Hz, 2 H, H_2C=CHCH_2C), 4.95−5.07 (m, 4 H, CH_2CH=CH_2), 5.72−5.85 (m, 2 H, CH_2CH=CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.5 (CH_2), 27.3 (CH_2), 29.2 (CH_2), 30.6 (CH_2), 33.6 (CH_2), 34.2 (CH_2), 115.2 (=CH_2), 115.4 (=CH_2), 134.9 (=CH), 137.7 (=CH), 138.0 (quaternary), 174.8 (quaternary), 209.2 (quaternary, CO). MS (FAB): *m*/*z* (%) = 191 (100) [M$^+$ + H]; $C_{13}H_{18}O$ requires [M + H] = 191.1436; found 191.1439.

Bicyclo-[6.3.0]-undecane (8)

Note: Preparation[19] *of silver nitrate-impregnated silica for the chromatographic separation of monocyclic and bicyclic compounds from RCM reaction:* Silica, MeCN and $AgNO_3$, were used in a ratio of 3:3:1, w:v:w, respectively. A solution of $AgNO_3$ (for example, 5 g) in MeCN (15 mL) was added to silica (15 g). The moist silica was mixed thoroughly for 5 min, the vessel covered with aluminium foil and dried in a hot oven (70 °C) for 4 h. The dry, silver-doped silica was stored in a dark place. *Preparation of silver nitrate-impregnated silica TLC plates:* Reagent ratio was $AgNO_3$:MeCN, 1:3 w:v. Glass-backed silica TLC plates, cut to appropriate sizes, were soaked in a solution of $AgNO_3$ (for example, 1 g) in MeCN (3 mL) for 5 min and then dried in a hot oven for 5−10 min. The dry, silver-doped plates were covered in aluminium foil and stored in the dark. Compounds on the TLC plate were revealed with potassium permanganate followed by gentle heating.

A solution of $[RuCl_2(=CHPh)(PCy_3)_2]$ (95.0 mg, 0.115 mmol, 10 mol %) in dry, degassed CH_2Cl_2 (0.50 mL), was added with a cannula to a solution of triene **9** (0.22 g, 1.15 mmol) in dry, degassed CH_2Cl_2 (114 mL). The reaction flask was placed in an oil bath and the light purple solution (0.01 M) refluxed for 72 h. The solvent was

removed under reduced pressure and the dark residue was chromatographed (silica, 92:8 petroleum ether/Et_2O) to afford a mixture of monocycle and bicycle as an oil [yield: 97.0 mg; ratio monocycle: bicycle 8:92); R_f (8:2 petroleum ether/Et_2O) = 0.11]. The mixture of compounds was separated by further chromatography (1 × 10 cm silver-doped silica column) using 1:1 petroleum ether/Et_2O as eluent to isolate the bicycle **8** as a pale yellow oil (83.0 mg, 44.5%) and Et_2O as eluent to recover unchanged triene (6.0 mg, 3%). R_f (Et_2O, silver-doped silica TLC plate) = bicycle 0.68, monocycle 0.42.

Bicycle **8**: IR (film): $\tilde{\nu}$ = 3015 cm^{-1} (=CH), 2934 (CH), 1697 (C=O), 1640 (C=C). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.61−1.67 (m, 2 H, H_2), 2.09−2.17 (m, 2 H, H_3), 2.35−2.38 (m, 2 H, H_9), 2.46−2.49 (m, 2 H, H_{10}), 2.62 (t, J = 6.2 Hz, 2 H, H_1), 2.98 (dd, J = 1.9, 5.0 Hz, 2 H, H_6), 5.43−5.51 (m, 1 H, H_4), 5.77 (quintet, J = 5.4 Hz, 1 H, H_5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3 (C_2, CH_2), 24.3 (C_6, CH_2), 25.5 (C_3, CH_2), 29.2 (C_1, CH_2), 31.6 (C_{10}, CH_2), 34.2 (C_9, CH_2), 127.9 (C_5, =CH), 128.6 (C_4, =CH), 140.2 (C_{11}, quaternary), 172.6 (C_7, quaternary), 209.1 (C_8, quaternary). MS (FAB): *m/z* (%) = 325 (7) [$2M^+$ + H], 163 (100) [M^+ + H]; $C_{11}H_{14}O$ requires [M + H] = 163.1123; found 163.1127.

Methylated Bicycle 7. Method A:[15] MeLi (0.37 mL of a 1.5 M solution in Et_2O, 0.55 mmol) was added dropwise to a stirred suspension of CuI (105.0 mg, 0.55 mmol) in Et_2O (0.60 mL) under nitrogen at −40 °C. After stirring at this temperature for 5 min, the yellow slurry was cooled to −78 °C and $BF_3{\cdot}Et_2O$ (71.0 μL, 0.57 mmol) was added. The thick, deep-yellow slurry was stirred for a further 5 min before the dropwise addition of a solution of pre-dried (over 4 Å molecular sieves pellets) enone **8** (30.0 mg, 0.18 mmol) in Et_2O (0.2 mL). The mixture was stirred at −78 °C for 5 h, quenched with saturated NH_4Cl solution (3 mL), the phases separated and the aqueous layer re-extracted with Et_2O (5 × 2 mL). The combined organic extracts were dried (Na_2SO_4), the solvent evaporated under reduced pressure and the residue chromatographed (silica). Elution with 99:1 petroleum ether/Et_2O afforded the addition product **7** as a yellow oil (17.0 mg, 53%) and with 92:8 petroleum ether/Et_2O, the unchanged enone **8** (13.0 mg, 43%). The addition product was isolated as a mixture of isomers with a *de* of 42% (by ^1H NMR spectroscopy) and 30% by chiral GC. R_f (9:1 petroleum ether/Et_2O) =: 0.48. IR (film): $\tilde{\nu}$ = 3015 cm^{-1} (=CH), 2933 (CH), 1739 (C=O). ^1H NMR (270 MHz, $CDCl_3$): δ = 0.91 (Me, minor − 29%, s), 1.14 (Me, major − 71%, s), 1.34−1.61 (m, 2 H), 1.63−1.86 (m, 5 H), 1.93−2.17 (m, 1 H), 2.20−2.49 (m, 5 H, CHC=CHCH_2C*H*COCH_2), 5.54−5.60 (m, 1 H, C*H*C=CHCH$_2$CHCO), 5.70−5.76 (m, 1 H, CHC=C*H*CH$_2$CHCO). ^{13}C NMR (68 MHz, $CDCl_3$): δ = (major isomer) 20.3 (CH_2), 24.6 (CH_2), 24.7 (CH_2), 25.3 (CH_3), 33.8 (CH_2), 34.4 (CH_2), 38.3 (CH_2), 42.3 (quaternary), 59.7 (CH), 128.2 (=CH), 129.4 (=CH), 221.9 (quaternary, C=O); (minor isomer) 16.8 (CH_3), 24.5 (CH_2), 25.0 (CH_2), 26.6 (CH_2), 34.3 (CH_2), 36.7 (CH_2), 37.7 (CH_2), 42.1 (quaternary), 63.9 (CH), 129.2 (=CH), 130.7 (=CH), 217.6 (quaternary, C=O). MS (EI): *m/z* (%) = 178 (100) [M^+], 163 (54) [M^+ − Me]; $C_{12}H_{18}O$ requires [M^+] =178.1358; found 178.1356. GC (155 °C, 2 mg/mL in CH_2Cl_2): retention time (% area), 38.47 (3.415), 38.92 (3.435), 39.49 (1.847), 40.38 (1.801).

Method B:[16] The same procedure as for the monocyclic enone was followed using $CuBrMe_2S$ (8.0 mg, 0.036 mmol), MeMgBr (0.10 mL of a 2.5 M solution in Et_2O, 0.25 mmol) in THF (0.70 mL), DMPU (54.0 μL, 0.44 mmol), a mixture of enone **8** (30.0 mg, 0.18 mmol) and TMSCl (46.0 μL, 0.36 mmol) in THF (0.20 mL) to generate the methyl addition product **7** (16.0 mg, 48%, 44% *de* by ^1H NMR spectroscopy). A small amount of starting enone was also recovered (1.0 mg, 3%).

Method C: MeLi (0.37 mL of a 1.5 M solution in Et_2O, 0.55 mmol) was added dropwise to a stirred suspension of CuI (105.0 mg, 0.55 mmol) in Et_2O (0.60 mL) under nitrogen at −40 °C. After stirring at this temperature for 5 min, the yellow slurry was cooled to −78 °C and $BF_3{\cdot}Et_2O$ (71.0 μL, 0.57 mmol) was added. The thick, deep-yellow slurry was stirred for a further 5 min before the dropwise addition of a solution of pre-dried (over 4 Å molecular sieves pellets) enone **8** (30.0 mg, 0.18 mmol) in Et_2O (0.2 mL). One more equivalent of MeLi (0.37 mL of a 1.5 M solution in Et_2O, 0.55 mmol) was slowly added. The mixture was stirred for 15 min before 2,4,6-tri-*tert*-butylphenol (0.24 g, 0.90 mmol) was introduced. The reaction mixture was stirred for an additional 6 h, and then diluted with Et_2O (5 mL) and saturated NH_4Cl (5 mL). The organics were separated, washed with water (2 × 2 mL) and brine (2 × 2 mL), dried over $MgSO_4$ and concentrated in vacuo. Same purification method as in method a), to yield **7** (49%, 64% *de*).

2-Allyl-3-methyl-3-(4-pentenyl)-2-cyclopentanone (15): $CuBrMe_2S$ (0.21 g, 1 mmol) was added in one portion to MeMgBr (2.90 mL of a 2.5 M solution in Et_2O, 7.3 mmol) in THF (20 mL) under nitrogen at −78 °C, followed by the slow dropwise addition of DMPU (1.50 mL, 12.6 mmol). The cream coloured, gelatinous mixture was stirred at −78 °C for 5 min and then stirred at 0 °C for 15 min. During this time the mixture became more mobile and translucent. It was then cooled down to −78 °C, and after 10 min a mixture of enone **9** (1.0 g, 5.2 mmol) and TMSCl (1.30 mL, 10.5 mmol) in THF (4 mL) was added dropwise. The yellow suspension was stirred at −78 °C for 6 h, quenched with saturated ammonium chloride solution and the phases separated. The aqueous phase was re-extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4), the solvent evaporated under reduced pressure and the residue chromatographed (silica, 98:2 petroleum ether/Et_2O) to afford the 1,4-addition product **15** (0.60 g, 56%) as a yellow oil as a mixture of isomers (*de* 31% by ^1H NMR spectroscopy). [Some starting enone **9**, was also recovered (eluent: 9:1 petroleum ether/Et_2O; yield: 0.117 g, 12%).] R_f (9:1 petroleum ether/Et_2O) = 0.4. IR (film): $\tilde{\nu}$ = 3076 cm^{-1} (=CH), 2932 (CH), 1739 (C=O), 1640 (C=C). ^1H NMR (270 MHz, $CDCl_3$): δ = 0.83 (Me, major isomer − 65.5%, s), 1.12 (Me, minor isomer − 34.5%, s), 1.25−1.56 (m, 4 H), 1.59−1.75 (m, 2 H), 1.94−2.10 (m, 5 H), 2.14−2.33 (m, 1 H), 2.35−2.41 (m, 1 H), 4.95−5.09 (m, 4 H, H_2C=), 5.72−5.99 (m, 2 H, H_2C=C*H*CH$_2$). ^{13}C NMR (68 MHz, $CDCl_3$): δ = (major isomer) 19.7 (CH_3), 23.3 (CH_2), 29.2 (CH_2), 32.6 (CH_2), 34.2 (CH_2), 34.7 (CH_2), 40.9 (CH_2), 42.3 (quaternary), 58.9 (CH), 114.6 (=CH_2), 115.4 (=CH_2), 137.4 (=CH), 138.7 (=CH), 219.6 (quaternary), (minor isomer) 23.5 (CH_2), 26.2 (CH_3), 28.9 (CH_2), 31.5 (CH_2), 33.3 (CH_2), 34.3 (CH_2), 34.8 (CH_2), 42.0 (quaternary), 61.1 (CH), 114.7 (=CH_2), 115.5 (=CH_2), 137.3 (=CH), 138.4 (=CH). MS (EI): *m/z* (%) = 206 (11) [M^+], 191 (6) [M^+ − Me], 137 (47) [M^+ − pentenyl], 96 (100); $C_{14}H_{22}O$ requires [M^+] 206.1671; found 206.1667.

5-Allyl-4-methyl-4-(4-pentenyl)-1-cyclopenten-1-yl trifluoromethanesulfonate (16): A cold (−78 °C) solution of ketone **15** (0.30 g, 1.45 mmol) in THF (3.0 mL plus 0.20 mL for rinses) was transferred via cannula into a reaction flask containing LDA (0.79 mL of a 2.0 M solution in hexane and THF, 1.6 mmol) in THF (3.20 mL) under nitrogen at −78 °C. After stirring for 1.5 h, a cold (−20 °C) solution of *N*-phenyltrifluoromethanesulfonimide (0.57 g, 1.6 mmol) in THF (3.0 mL plus 0.20 mL for rinses) was added to the mixture. This was allowed to warm up slowly to room temperature and stirred overnight. The reaction mixture was then directly pre-adsorbed onto silica and chromatographed (silica basified with Et_3N, petroleum ether) to afford the vinyl triflate **16** as a colourless

oil (0.33 g, 66.4%) as mixture of isomers with a *de* of 41% (by ^{1}H NMR spectroscopy). [Some ketone **15**, was also recovered (eluent: 99:1 petroleum ether/Et_2O; yield: 96.0 mg, 32%).] R_f (98:2 petroleum ether/Et_2O) = 0.25. IR (film): $\tilde{\nu}$ = 3079 cm^{-1} (=CH), 2932 (CH), 1421 and 1210 (-SO_2-O-). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.02 (s, Me, major), 1.10 (s, Me, minor), 1.31−1.50 (m, 4 H), 1.95−2.08 (m, 3 H), 2.17−2.34 (m, 3 H), 2.37−2.44 (m) and 2.55−2.63 (m) (1 H, ratio of 2:1), 4.94−5.13 (m, 4 H, 2 × H_2C=CHCH$_2$), 5.57−5.59 [m, 1 H, C*H*=C(OTf)], 5.72−5.87 (m, 2 H, 2 × H_2C=C*H*CH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = (major isomer) 22.3 (CH_3), 24.1 (CH_2), 32.7 (CH_2), 34.6 (CH_2), 41.1 (CH_2), 42.3 (CH_2), 43.9 (quaternary), 51.6 (CH), 114.8 (=CH_2), 115.7 (CH, TfOC=CH) 116.9 (=CH_2), 136.3 (=CH), 138.8 (=CH), 150.6 (quaternary); (minor isomer) 24.5 (CH_2), 27.7 (CH_3), 33.4 (CH_2), 34.8 (CH_2), 36.6 (CH_2), 40.4 (CH_2), 43.5 (quaternary), 53.8 (CH), 114.9 (=CH_2), 116.1 (CH, TfOC=CH), 117.1 (=CH_2), 135.9 (=CH), 138.7 (=CH), 151.8 (quaternary). ^{19}F NMR (254 MHz, $CDCl_3$): δ = −74.0 (CF_3, major isomer), −73.9 (CF_3, minor isomer). MS (EI): *m*/*z* (%) = 338 (25) [M$^+$], 323 (14) [M$^+$ − Me], 297 (65) [M$^+$ − allyl], 269 (100) [M$^+$ − pentenyl]. $C_{15}H_{21}F_3O_3S$ requires [M$^+$] = 338.1164; found 338.1155.

2-Allyl-3-methyl-3-(4-pentenyl)-1-cyclopenten-1-yl Trifluoromethanesulfonate (17): KHMDS (1.60 mL of a 0.5 M solution in hexane, 0.8 mmol) was added to a cold (0 °C) solution of ketone **15** (0.17 g, 0.8 mmol) in THF (5 mL). The reaction mixture was then allowed to warm up to room temperature and stirred for 12 h. *N*-phenyltrifluoromethanesulfonimide (0.32 g, 0.9 mmol) in THF (2 mL) was subsequently added and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was pre-adsorbed on silica and chromatographed (0.5 mL of Et_3N, petroleum ether as eluent) to yield 0.28 g, 60% of vinyl triflate **17** as a colourless oil. IR(film): $\tilde{\nu}$ = 3079 cm^{-1} (=CH), 2932 (CH), 1419 and 1212 (-SO_2-O-). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (Me, s), 1.30−1.44 (m, 4 H), 1.64.1.94 (m, 2 H), 1.98−2.06 (m, 2 H), 2.53−2.59 (m, H_2C=CH-C*H*$_2$-CH$_2$), 2.71−2.91 [CH$_2$=CH-C*H*$_2$-C=C(OTf)], 4.92−5.66 (m, 2 × *H*$_2$C=CH), 5.68−5.84 (m, 2 × H_2C=C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.97 (CH_3), 26.89 (CH_2), 28.95 (CH_2), 29.38 (CH_2), 33.78 (CH_2), 34.53 (CH_2), 47.17 (quaternary), 114.91 (=CH_2), 116.94 (quaternary), 117.00 (=CH_2), 134.39 (=CH), 135.87 (quaternary), 138.73 (=CH), 143.38 (quaternary). ^{19}F NMR (254 MHz, $CDCl_3$): δ = −74.94.

Bicyclic Vinyl Triflate 6: A cold (−78 °C) solution of ketone **7** (64.0 mg, 0.36 mmol) in THF (0.7 mL) was transferred with a cannula into a reaction flask containing LDA (0.56 mL of a 1.6 M solution in hexane and THF, 0.9 mmol) in THF (1.6 mL) under nitrogen at −78 °C. After stirring for 30 min, DMPU (0.14 mL, 1.07 mmol) was added, the mixture stirred for a further 15 min and a cold (−20 °C) solution of *N*-phenyltrifluoromethanesulfonimide (0.64 g, 1.8 mmol) in THF (3.0 mL) was added. The reaction mixture was allowed to warm slowly to room temperature, stirred overnight and then directly pre-adsorbed onto silica and chromatographed (silica basified with Et_3N, petroleum ether) to afford the vinyl triflate **6** as a colourless oil (64 mg, 57.5%, 78% *de* by ^{1}H NMR). [Further elution of the column with 99.5:0.5 petroleum ether/Et_2O gave a UV-active impurity, and with 99:1 petroleum ether/Et_2O the unchanged ketone (10 mg, 15.6%, *de*: 30% ^{1}H NMR spectrum).] R_f (98:2 petroleum ether/Et_2O) = 0.5. IR (film): $\tilde{\nu}$ = 3012 cm^{-1} (=CH), 2936 (CH), 1661 (C=C), 1422 and 1209 (-SO_2-O-), 1142 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, Me, minor), 1.17 (s, Me, major), 1.35−1.48 (m, 2 H), 1.71−1.91 (m, 2 H), 1.96 (dd, *J* = 3.2, 16.1 Hz, 2 H), 2.06 (dd, *J* = 12.1, 18.3 Hz, 1 H), 2.20−2.32 (m, 2 H), 2.43 (d, *J* = 18.2 Hz, *1 H)*, 2.75 (dt, *J* = 2.3, 12.0 Hz, 1 H), 5.51 [t, *J* = 2.6 Hz, *1 H,* C(OTf)=C*H*], 5.55−5.58 (m, 2 H, C*H*=C*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1 (CH_2), 25.7 (CH_2), 26.3 (CH_3), 26.7 (CH_3), 30.8 (CH_2), 33.4 (CH_2), 42.5 (CH_2), 43.9 (quaternary), 52.3 (CH), 114.4 [C(OTf)=*C*H], 127.0 (=CH), 129.1 (=CH), 152.9 (quaternary). ^{19}F NMR (254 MHz, $CDCl_3$): δ = −74.1 (CF_3, minor), −74.0 (CF_3, major). MS (EI): *m*/*z* (%) = 310 (14) [M$^+$], 160 (53) [M$^+$ − CF_3SO_3H], 55 (100); $C_{13}H_{17}F_3O_3S$ requires [M$^+$] = 310.0851; found 310.0843.

5-Allyl-1,4-dimethyl-4-(4-pentenyl)-2-cyclopentene (18): A solution of vinyl triflate **16** (34.0 mg, 0.1 mmol) and Pd(PPh$_3$)$_4$ (11.0 mg, 0.01 mmol) in THF (1.0 mL) was stirred for 5 min at room temperature under nitrogen. MeMgBr (0.12 mL of a 2.5 M solution in Et_2O, 0.3 mmol) was added and the mixture refluxed for 1 h. The mixture was cooled and pre-adsorbed directly on to silica. The pre-adsorbed material was chromatographed (silica, petroleum ether) to afford the coupled product **17** as a colourless oil (17.0 mg, 83%) as mixture of isomers (38% *de* by ^{1}H NMR spectroscopy). R_f (petroleum ether) = 0.78. IR (film): $\tilde{\nu}$ = 3075 cm^{-1} (=CH), 2929 (CH), 1639 (C=C), 908 (s). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.92 (s, Me, major), 0.98 (s, Me, minor), 1.25−1.38 (m, 4 H), 1.65 (broad s, 3 H, =CMe), 1.8−2.09 (m, 4 H), 2.08−2.21 (m, 3 H), 4.91−5.06 (m, 4 H, 2 × *H*$_2$C=CHCH$_2$), 5.24 (s, 1 H, C*H*=CMeCH), 5.76−5.89 (m, 2 H, 2 × H$_2$C=C*H*CH$_2$). ^{13}C NMR (68 MHz, $CDCl_3$): δ = (major isomer) 16.1 (CH_3), 21.8 (=C*C*H$_3$), 24.4 (CH_2), 33.2 (CH_2), 34.6 (CH_2), 42.4 (CH_2), 44.9 (CH_2), 45.0 (quaternary), 55.5, 114.1 (=CH_2), 114.93 (=CH_2), 123.3 (=CH, CH=CMe), 139.0 (=CH, CH=CH$_2$), 139.2 (=CH, CH=CH$_2$), 141.9 (quaternary); (minor isomer) 16.4 (CH_3), 24.8 (CH_2), 27.6 (=C*C*H$_3$), 33.4 (CH_2), 34.8 (CH_2), 36.5 (CH_2), 44.3 (CH_2), 45.2 (quaternary), 57.6 (CH), 114.2 (=CH_2), 114.9 (=CH_2), 123.1 (=CH, CH=CMe), 139.2 (=CH, CH=CH$_2$), 139.4 (=CH, CH=CH$_2$), 142.6 (quaternary). MS (EI): *m*/*z* (%) = 204 (6) [M$^+$], 163 (100) [M$^+$ − allyl], 135 (36) [M$^+$ − pentenyl]; $C_{15}H_{24}$ requires [M$^+$] = 204.1878; found 204.1858.

Methyl-Coupled Bicycle 20: A solution of vinyl triflate **6** (14.0 mg, 0.045 mmol) and Pd(PPh$_3$)$_4$ (5.0 mg, 4.5 μmol) in THF (1.0 mL) was stirred for 5 min at room temperature under nitrogen. MeMgBr (52.0 μL of a 2.6 M solution in Et_2O, 0.13 mmol) was added and the mixture refluxed for 2 h. The mixture was cooled and pre-adsorbed directly on to silica. The pre-adsorbed material was chromatographed (silica, pentane) to afford the coupled product **20** as a colourless oil (5.0 mg, 63%, 57% *de* by ^{1}H NMR spectroscopy and 52% by chiral GC) [Some starting vinyl triflate was also recovered (1.0 mg, 7%).] R_f (pentane) = 0.82. IR (film): $\tilde{\nu}$ = 3003 cm^{-1} (=CH), 2929 (CH), 1659 (C=C), 1453. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (s, Me, minor), 1.03 (s, Me, major), 1.34−1.46 (m, 2 H), 1.62 (=CMe, minor, s), 1.67 (=CMe, major, s), 1.69−1.96 (m, 4 H), 2.00−2.37 (m, 3 H), 2.4 (d, *J* = 11.7 Hz, 2 H), 5.15 (s, 1 H, C*H*=CMe, major), 5.22 (s, 1 H, C*H*=CMe, minor), 5.47−5.61 (m, 2 H, C*H*=C*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 15.6 (CH_3, minor), 15.8 (CH_3, major), 23.9 (CH_2), 25.7 (CH_2), 26.5 (=C*C*H$_3$, minor), 29.7 (CH_2), 32.8 (CH_2), 34.1 (=C*C*H$_3$, major), 45.4 (quaternary), 46.8 (CH_2), 55.9 (CH), 121.4 (=CH), 126.1 (=CH), 131.0 (=CH), 144.7 (quaternary). MS (EI): *m*/*z* (%) = 176 (48) [M$^+$], 161 (64) [M$^+$ − Me], 107 (100); $C_{13}H_{20}$ requires [M$^+$] 176.1565; found 176.1562. GC (120 °C, 2 mg/mL in CH_2Cl_2): retention time (% area), 37.01(2.238), 37.89(2.230), 47.41(0.688), 49.80(0.689).

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