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Stereochemical Aspects of Intramolecular Palladium Catalysed [3+2] Cycloadditions of Methylenecyclopropanes

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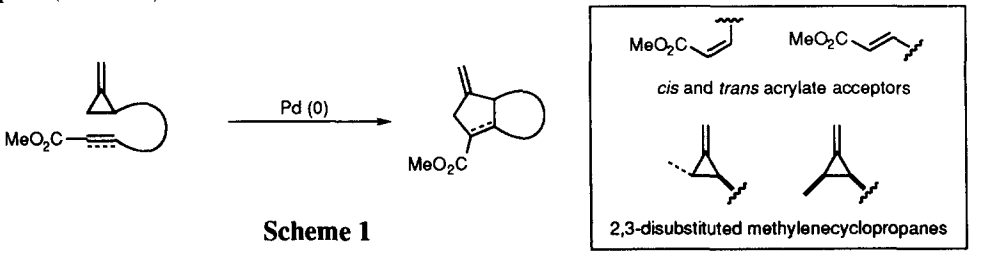
Abstract: The preparation and intramolecular palladium catalysed [3+2] cycloaddition reactions of a range of substrates containing either stereochemically defined 2,3-disubstituted methylenecyclopropanes **3** or acrylate acceptors **12-15** are described. Evidence is presented which supports the hypothesis that these cycloaddition reactions proceed *via* palladium-trimethylenemethane type intermediates and that the two carbon-carbon bonds are formed in a highly asynchronous manner.

INTRODUCTION

The transition metal catalysed [3+2] cycloaddition of methylenecyclopropanes with olefinic and acetylenic acceptors has been shown to be a useful method for cyclopentanoid synthesis.[1] The essentially simultaneous introduction of the intramolecular variant of this reaction by ourselves[2a] and by the Nakamura group[3a] has considerably enhanced the inherent synthetic potential of such cyclisations by providing a greatly enhanced level of regiocontrol, and led to a series of systematic studies, both within our own group,[2] and by others.[3] In this paper, we now report in full detail on the key stereochemical issues which are associated with palladium catalysed intramolecular [3+2] cycloaddition reactions and focus, in particular, on the cycloadditions of various substrates which contain either 2,3-disubstituted methylenecyclopropanes or geometrically defined acrylate acceptors (Scheme 1).



Scheme 1

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RESULTS AND DISCUSSION

Cycloadditions Using Geometrically Defined 2,3-Disubstituted Methylenecyclopropanes. Precursor Design & Synthesis. The utility of the palladium catalysed intramolecular [3+2] cycloaddition reactions of methylenecyclopropanes would be further enhanced if the stereochemical information associated with substituents attached to the cyclopropane could be successfully relayed into the cycloadducts. In order to ascertain whether this could be accomplished, we required precursors containing geometrically defined 2,3-disubstituted methylenecyclopropanes. Since a previous investigation had established that methylenecyclopropane **1** can readily be prepared from 3-buten-1-ol and cyclised to bicyclo[4.3.0]nonane **2** using palladium catalysts (Figure 1),[2e] we elected to study the related cycloaddition reactions of **3a** and **3b**. We anticipated that these precursors could be prepared in an analogous fashion from suitably protected forms of *cis* and *trans* 3-penten-1-ol.

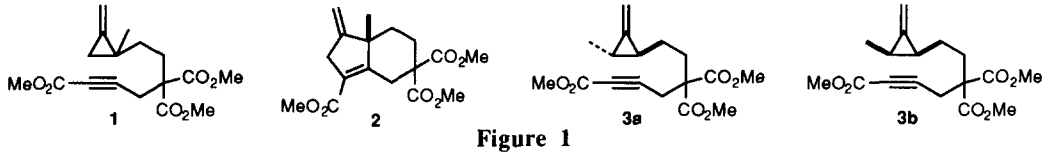
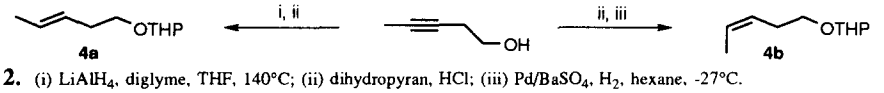


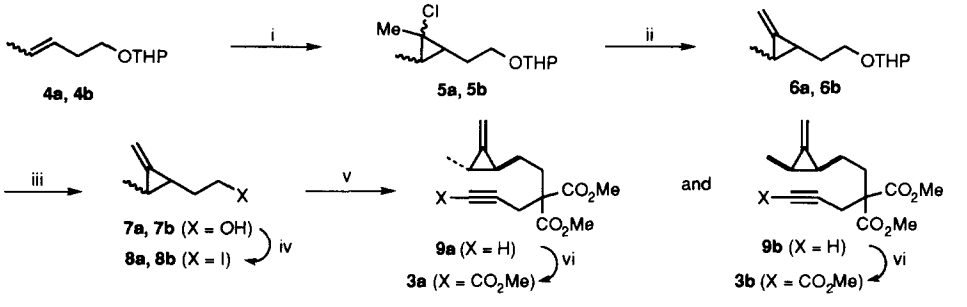
Figure 1

Treatment of 3-pentyn-1-ol according to a published procedure with lithium aluminium hydride in diglyme at 140°C and subsequent protection with dihydropyran provided isomerically pure *trans* **4a** in a modest 30% overall yield.[4] *Cis* alkene **4b** was prepared in a simple two step sequence involving protection of 3-pentyn-1-ol as its tetrahydropyranyl ether and subsequent hydrogenation with palladium on barium sulfate (Scheme 2). This hydrogenation step was not completely stereospecific and furnished **4b**, contaminated with a small amount of **4a** (*ca* 5%), which was carried through the reaction sequence.



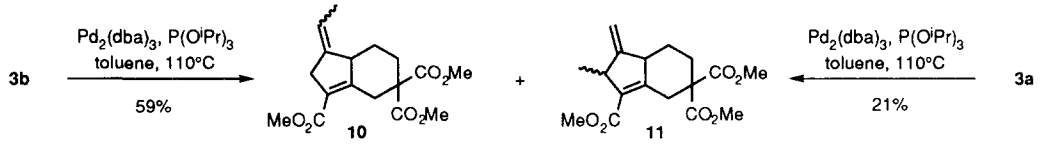
Scheme 2. (i) $LiAlH_4$, diglyme, THF, 140°C; (ii) dihydropyran, HCl; (iii) $Pd/BaSO_4$, H_2, hexane, -27°C.

The sequence outlined below was used separately for the conversion of both *trans* and *cis* alkenes **4a** and **4b** into the cyclisation precursors **3a** and **3b** respectively (Scheme 3). Thus, chlorocarbene addition using 1,1-dichloroethane and *n*-butyllithium in diethyl ether at -35°C furnished cyclopropane **5**. Dehydrohalogenation to **6** was then achieved in a straightforward fashion using potassium *tert*-butoxide in dimethyl sulfoxide and subsequent removal of the tetrahydropyranyl ether afforded **7** which was converted into iodide **8**. Alkylation of **8** with dimethyl 3-butyne-1,1-dicarboxylate gave acetylene **9** which was further alkylated to furnish **3a** and **3b**.



Scheme 3. (i) 1,1-dichloroethane, *n*-BuLi, -35°C, Et_2O, 95% (**5a**), 80% (**5b**); (ii), ^tBuOK, DMSO, 80°C, 60% (**6a**), 95% (**6b**); (iii), *p*-TsOH, MeOH, 66% (**7a**), 87% (**7b**); (iv), I_2, PPh_3, MeCN; (v) NaH, DMF, dimethyl 3-butyne-1,1-dicarboxylate, 43% (**9a** from **7a**), 44% (**9b** from **7b**); (vi) *n*-BuLi, THF, MeO_2CCl, 95% (**3a**), 93% (**3b**).

Cyclisation Studies. Treatment of the *cis* isomer **3b** with tris(dibenzylidineacetone) dipalladium and triisopropylphosphite in refluxing toluene furnished an inseparable 3:1 mixture of **10** and **11** respectively in 59% yield (Scheme 4). Spectroscopic comparisons with **2** confirmed that both of these materials were indeed bicyclo[4.3.0]nonane derivatives. Careful analysis of the ^{1}H nmr spectrum established that the major cycloadduct **10** consisted of two geometric isomers in a 5:1 ratio. Interestingly, the minor cycloadduct **11** was formed as a single stereoisomer as ascertained by ^{13}C nmr spectroscopy. However, no attempts were made to ascertain the relative configuration at this position. A similar mixture of cycloadducts was obtained when the *trans* isomer **3a** was subjected to the same cyclisation conditions albeit in a somewhat lower yield. In this instance, ring opening of the cyclopropane to dienes appeared to be the dominant reaction pathway (*Vide Infra*).



Scheme 4

Clearly, the anticipated rate enhancements in such intramolecular cyclisations are insufficient to prevent "memory loss" and hence regiochemical scrambling of the C-3 substituent of the methylenecyclopropane on to the exocyclic double bond is observed. Indeed, these results can be succintly rationalised in terms of a relatively long-lived palladium-trimethylenemethane (Pd-TMM) type intermediate and are consistent with the results obtained in related intermolecular reactions.[1] It is nevertheless interesting to note that the cyclisation of the *trans* isomer **3a** is significantly less efficient than that of corresponding *cis* isomer **3b**. Such differences in reactivity may be due, in part, to the relative ease with which the metal can coordinate to the methylenecyclopropanes **3a** and **3b** prior to ring opening. However, such an explanation cannot account for the fact that 2,2-disubstituted methylenecyclopropanes *eg* **1** which also possess substituents projecting out from both sides of the cyclopropane undergo efficient cycloaddition reactions. It can be concluded from these studies that cyclisations involving 2,3-disubstituted methylenecyclopropanes are of limited synthetic utility.

Cycloadditions Using Geometrically Defined Acrylates as Acceptors.

Precursor Design & Synthesis. By analogy with the intramolecular variant of the Diels-Alder reaction,[5] we envisaged that the stereochemical outcome of cycloadditions involving acrylate acceptors may be dependant not only on the initial alkene geometry but also on the conformational preference of the linking tether. In order to test this hypothesis, we have synthesised a variety of different cyclisation precursors **12-15** which possess differences both in the alkene geometry and also in the nature of the linking tether (Figure 2). Using these compounds, we hoped to develop an understanding of the factors which dictate the efficiency and stereochemical outcome of intramolecular cycloadditions involving acrylate acceptors.

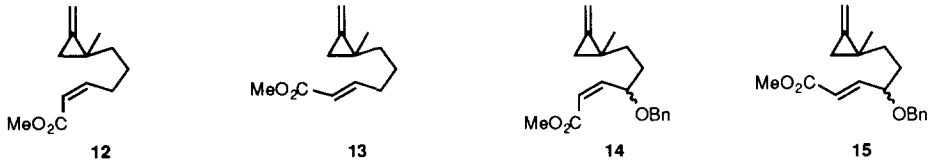
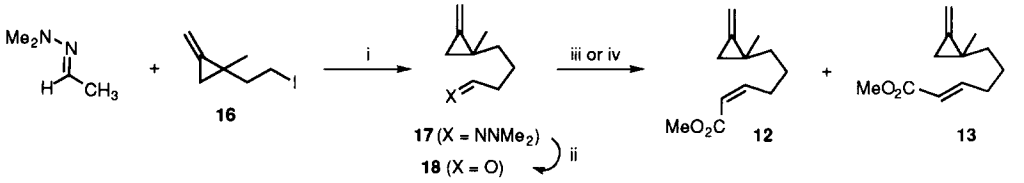


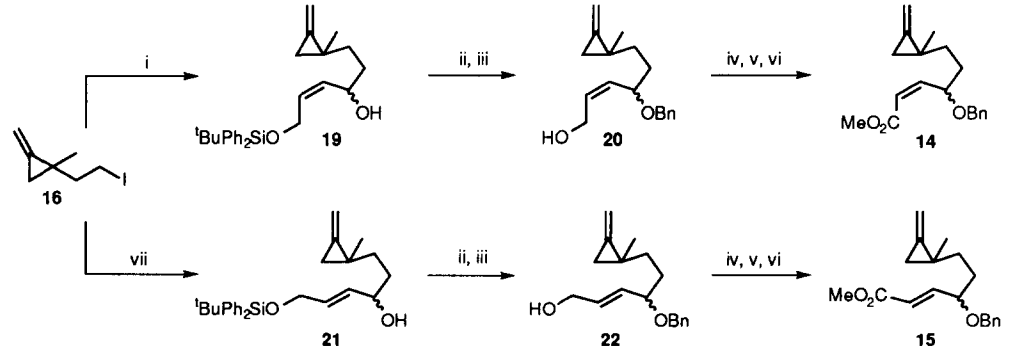
Figure 2

Cis and *trans* precursors **12** and **13** were synthesised from the known methylenecyclopropane **16**[2e] as depicted below (Scheme 5). thus, acetaldehyde dimethylhydazone[6] was alkylated with this iodide according to the procedure of Corey and Enders.[7] Hydrolysis of the resultant hydrazone **17** using periodic acid yielded the homologated aldehyde **18**. A modified procedure, using two equivalents of the oxidant was found to improve the yield of this reaction. Methods for the stereoselective formation of the desired *cis* and *trans* α,β-unsaturated esters were then investigated. The geometrically pure *trans* ester **13** was readily prepared using the Masamune and Roush olefination protocol.[8] Thus, treatment of **18** with trimethyl phosphonoacetate in the presence of lithium chloride and Hünig's base gave **13** in 83% yield. The corresponding *cis* isomer **12** was prepared using the method described by Still and Gennari.[9] Thus, treatment of the aldehyde **18** with trimethyl phosphonoacetate using a strongly dissociated base system gave a mixture of the *Z* and *E* isomers in a 5:2 ratio in 86% yield. Fortunately, the desired *cis* isomer could be readily separated from the unwanted *trans* compound by flash chromatography and hence no attempts were made to improve the selectivity of this reaction.



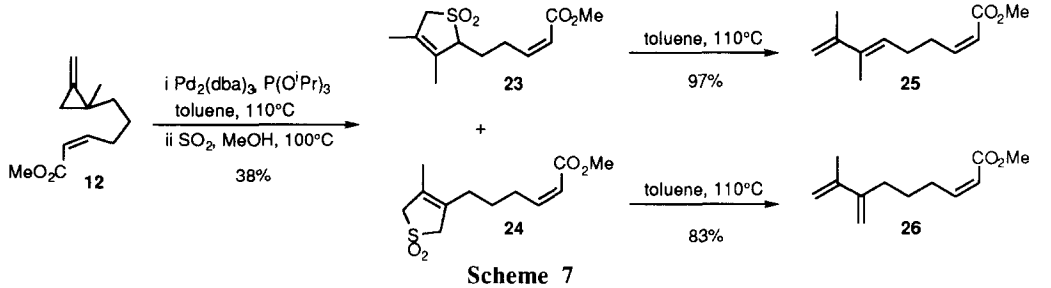
Scheme 5. (i) LDA, THF, 0°C then **16** 74%; (ii) HIO_4, THF, H_2O, pH4, 73%; (iii) $MeO_2CCH_2PO(OMe)_2$, LiCl, $^iPr_2EtN$, MeCN, 83% (**12**); (iv) $MeO_2CCH_2PO(OMe)_2$, 18-crown-6, $KN(SiMe_3)_2$, -78°C, 61% (**12**), 25% (**13**).

The more functionalised precursors **14** and **15** were also prepared using iodide **16** (Scheme 6). Conversion of this compound into the corresponding lithio species using two equivalents of *tert*-butyllithium and subsequent addition of (*Z*)-4-(*tert*-butyldiphenylsilyloxy)-2-butenal[10] gave the *cis* allylic alcohol **19** as a 1:1 mixture of diastereomers. Benzylation of the secondary hydroxyl group followed by removal of silyl ether protection then furnished the primary alcohol **20**. Oxidation to the corresponding aldehyde was accomplished using manganese dioxide which was further oxidised to the carboxylic acid with sodium chlorite.[11] Subsequent esterification[12] furnished the *cis* acrylate **14** as a 1:1 mixture of diasteromers. An identical reaction sequence employing (*E*)-4-(*tert*-butyldiphenylsilyloxy)-2-butenal[10] was then employed to prepare **21** which was converted *via* **22** into the *trans* acrylate **15**.



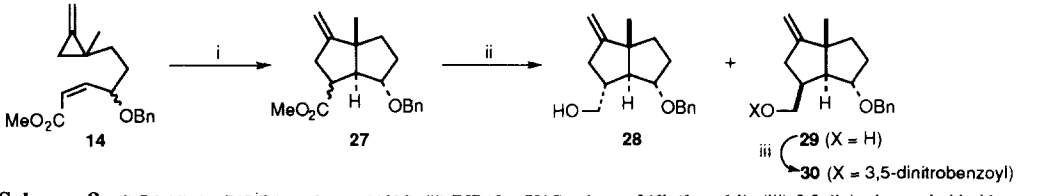
Scheme 6. (i) ^{t}BuLi, petrol, -78°C then (*Z*)-*tert*-$BuPh_2SiOCH_2CH{=}CHCHO$, 73%; (ii) NaH, BnBr, THF; (iii) TBAF, THF, 77% (**20** from **19**), 87% (**22** from **21**); (iv) MnO_2, CH_2Cl_2; (v) $NaClO_2$, 2-methyl-butene, ^{t}BuOH, H_2O; (vi) DCC, MeOH, DMAP, CH_2Cl_2, 78% (**14** from **20**), 72% (**15** from **22**); (vii) ^{t}BuLi, petrol, -78°C then (*E*)-*tert*-$BuPh_2SiOCH_2CH{=}CHCHO$, 87%.

Cyclisation Studies. Treatment of *cis* ester **12** with tri(dibenzylideneacetone) dipalladium and triisopropyl phosphite in refluxing toluene gave a chromatographically inseparable mixture of products. ^{1}H nmr analysis of this mixture revealed that no bicyclic products had been produced. The presence of several new olefinic signals suggested that ring opening to dienes had occurred. To test this hypothesis, the mixture was treated with sulfur dioxide in a pressure bottle.[13] Cyclic sulfones **23** and **24** were isolated in 13% and 25% yields respectively from methylenecyclopropane **12** (Scheme 7). Thermal extrusion of the sulfur dioxide from these sulfones produced trienes **25** and **26** respectively.[14] Reexamination of the ^{1}H nmr spectrum of the mixture isolated from the initial palladium reaction confirmed that these trienes were indeed the major constituents. Similar results were obtained when attempts were made to effect cycloadditions using *trans* acrylate **13**.



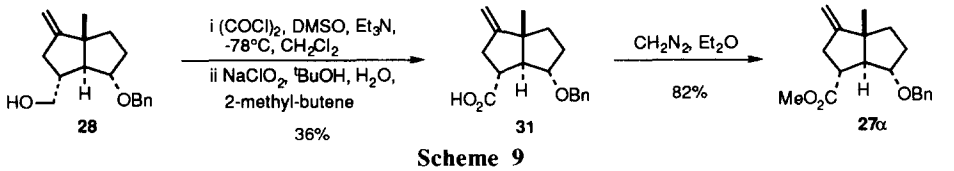
Scheme 7

In sharp contrast to the disappointing results obtained above with substrates **12** and **13**, substituted *cis* ester **14** which differs only by the presence of an additional benzyl ether functionality in the tethering chain furnished bicyclic adduct **27** in 43% yield upon treatment with palladium catalysts. Careful analysis of the ^{1}H nmr spectrum of the material obtained indicated that it consisted of two epimers in a 6:1 ratio. Reduction of this mixture with DIBAL enabled chromatographic separation of the derived primary alcohols **28** and **29** in 30% and 6% yields respectively from **14** (Scheme 8). The minor alcohol **29** was converted into its corresponding crystalline dinitrobenzoyl derivative **30**.



Scheme 8. (i) $Pd_2(dba)_3$, $P(O^iPr)_3$, toluene, 110°C; (ii) DIBAL, -78°C, toluene, 36% (from **14**); (iii) 3,5-dinitrobenzoyl chloride, DMAP, Et_3N, CH_2Cl_2, 63%.

In order to confirm that no epimerisation of the stereochemistry occurred in the derivitisation sequence, alcohol **28** was oxidized to carboxylic acid **31** and subsequently esterified with diazomethane (Scheme 9). Ester **27α** prepared in this manner was identical by ^{1}H nmr with the major diastereomer isolated from the initial palladium catalysed cyclisation reaction confirming that no epimerisation had occured during the DIBAL reduction which was used to separate **28** and **29**.



Scheme 9

The structures of the two bicyclic adducts formed in the initial palladium catalysed cyclisation reaction were unequivocally established by X-ray crystallographic analyses on the dinitrobenzoyl ester **30** and the carboxylic acid **31** (Figure 3). Examination of the structures reveals that both these cycloadducts possess the thermodynamically less favoured *trans* fused bicyclo[3.3.0]octanes. The relative configuration of the benzyl ether and methyl substituents in both of these materials are the same, the only difference being in the relative configuration at the position formerly occupied by the ester moiety. The hydroxymethyl substituent of **30** is *anti* to the bridgehead hydrogen atom while the carboxyl group of **31** is located *syn* to this substituent. At this stage, it is also appropriate to issue a caveat on the dangers of attempting to rely solely on nOe measurements, even in relatively rigid systems, when other stereoisomers are unavailable for comparitive measurements. Thus, as indicated below, significant nOe enhancements were detected between many of the *trans* diaxial substituents within **27α**. On the basis of such ^{1}H NMR measurements, one may incorrectly conclude that this compound possesses a *cis* ring junction.

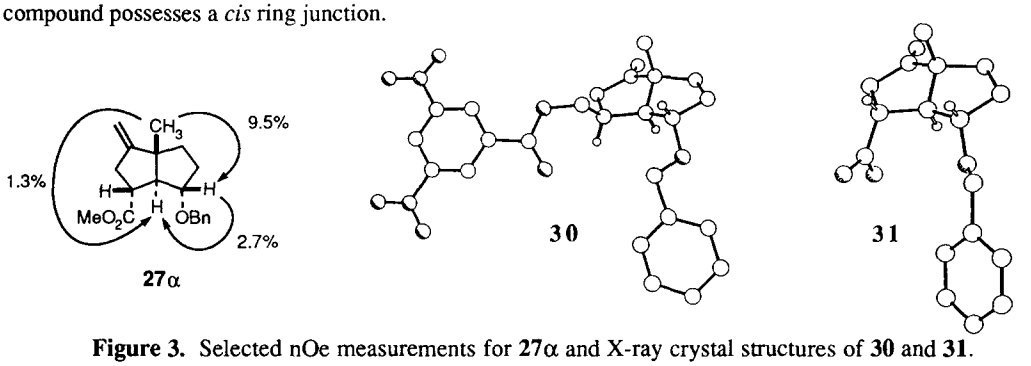
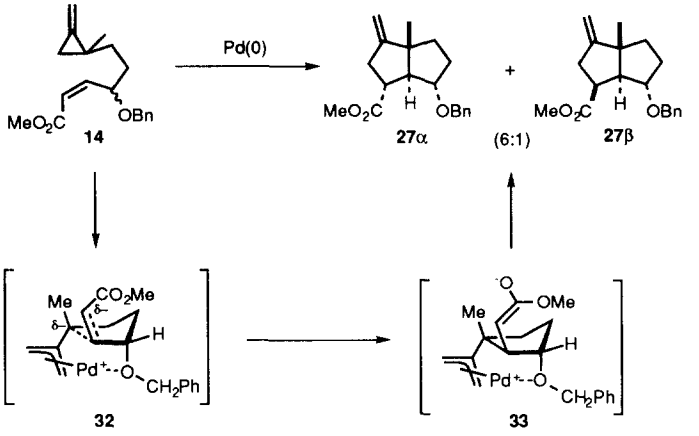


Figure 3. Selected nOe measurements for **27α** and X-ray crystal structures of **30** and **31**.

Under identical reaction conditions to those described for **14**, the *trans* isomer **15** failed to yield any bicyclic products. Thus, this cyclisation reaction appears to be highly sensitive to substitution patterns. This observation is reinforced by the fact that we have been able to successfully accomplish palladium catalysed [3+2] cycloadditions using substrates very similar to **13**.[15] The reaction dichotomies uncovered for **12-15** can be rationalised using the following model (Scheme 10). Oxidative addition of the palladium into the distal bond of the methylenecyclopropane results in formation of a palladium-trimethylenemethane type intermediate. We believe that the initial ring closure to form the first cyclopentane ring proceeds through intermediate **32** in which the ether oxygen atom adopts a pseudo-axial orientation, enabling it to complex and stabilise the cationic π-allyl palladium intermediate. This type of interaction is likely to assist formation of cycloadducts by bringing the reaction partners together. Two pieces of evidence can be presented in support of this type of chelation process. Substrates **12** and **13** which do not possess the benzyl ether substituent fail to cyclise under the same reaction conditions. Furthermore, no bicyclic adducts were obtained from **14** in which the benzyl ether substituent possessed the opposite β-stereochemistry. Examination of molecular models reveals that the diastereomeric Pd-TMM complex derived from **14** cannot adopt a suitable conformation for cyclisation if the oxygen atom is chelated to the palladium. We speculate that the acrylate substituent lies away from the palladium centre during the bond forming process in order to minimise non-bonding interactions. This may explain why **15** fails to produce cycloadducts. Subsequent ring closure of zwitterion **33** would then account for the formation of **27α** and **27β**. It is notable that the major isomer produced arises from net inversion of the stereochemistry encoded in the *cis* double bond. This loss of stereochemical integrity during the cycloaddition provides further support that this reaction involves a highly asynchronous process.



Scheme 10

The foregoing results provide good evidence that the intramolecular variant of these [3+2] cycloaddition reactions of methylenecyclopropanes proceed *via* palladium-trimethylenemethane type intermediates and that the two carbon-carbon bonds are formed in a highly asynchronous if not stepwise manner. It is apparent that the fate of a particular reaction is highly dependant not only on the nature of the ancillary ligands around palladium, but also on the exact nature of the substrate. The unexpected and unusual formation of the *trans* fused bicyclo[3.3.0]octanes from **14** in which the stereochemical outcome is dictated by the presence of ancillary functionality in the tethering chain and in which the initial geometry of the acrylate acceptor is not preserved in the adduct, serves as a good illustration of this point. Consequently, simple generalisations concerning these reactions cannot be made with any degree of certainty at the present time and further research is required to unravel the subtleties and devise a predictive rationale for such reactions.

EXPERIMENTAL

General. ^{1}H and ^{13}C nmr spectra were recorded at 250 MHz on a Bruker WM-250 instrument, at 270 MHz and 67.9 MHz on a Jeol GSX-270 instrument, and at 500 MHz and 125.8 MHz respectively on a Bruker AM-500 instrument, with either tetramethylsilane or residual protic solvent as the internal standard. Infrared spectra were recorded on a Perkin Elmer 983G spectrometer. Mass Spectra were recorded on VG 7070B, VG 12-253 and VG ZAB-E instruments under EI conditions. Diethyl ether, and tetrahydrofuran were distilled from sodium - benzophenone ketyl under argon immediately prior to use. Toluene was distilled from sodium under argon immediately prior to use. All other solvents and reagents were purified by standard means. All reactions were performed using oven dried glassware under an atmosphere of argon unless otherwise stated.

(Z)-Tetrahydro-2-[(pent-3-enyl)oxy]-2H-pyran (4b). Palladium on barium sulphate (105 mg, 5% palladium) in hexane (2 ml) poisoned with quinoline (3 drops) was activated at room temperature by passing through hydrogen for 30 minutes. The suspension was cooled to -27°C and a solution of tetrahydro-2-[(pent-3-ynyl)oxy]-2H-pyran (1.0 g, 6.0 mmol) in hexane (10 ml) added. The reaction was monitored by glc. After 11 hours, the catalyst was filtered off and the solution was concentrated under reduced pressure to give **4b** (1.0 g, 99%) as a colourless liquid which was used without further purification. ν_{max} (film) 3015, 2940, 2869, 1654,

1439, 1351, 1200, 1138, 1122, 1033 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.4 (2H, m), 4.5 (1H, m), 3.8-3.2 (4H, m), 2.3-2.2 (2H, m), 1.6-1.4 (9H, m); *m / z* 115, 85, 69, 43; Found: C 70.73, H 10.86%; $C_{10}H_{18}O_2$ requires: C 70.55, H 10.66%.

(*E*)-Tetrahydro-2-[(penten-3-yl)oxy]-2H-pyran (4a). A flask equipped with a condenser was charged with lithium aluminium hydride (5.1 g, 0. 13 mol), THF (10 ml) and diglyme (80 ml). The mixture was heated and a low boiling fraction was distilled off. Upon cooling to room temperature, a solution of 3-pentyn-1-ol (3.2 g, 38 mmol) in diglyme (10 ml) was added and the mixture heated to 140°C for 70 hours. After cooling to 0°C the mixture was slowly hydrolysed with cold water (10 ml) and extracted with pentane (3 x 100 ml). The combined organic extracts were washed with water (30 ml), brine (2 x 50 ml) and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave (*E*)-pent-3-en-1-ol (1.0 g). To this alcohol was added 3,4-dihydro-2H-pyran (8.4 g, 0.10 mol). The mixture was cooled to 0°C and concentrated HCl (1 drop) was added. After the initial exotherm the solution was warmed to room temperature and stirred for 24 hours. Removal of the solvent under reduced pressure and subsequent bulb-to-bulb distillation of the residue afforded **4a** (1.74 g, 27% overall) as a colourless liquid (bp 160-162°C). ν_{max} (film) 2939, 1439, 1351, 1322, 1260, 1200, 1121, 1079, 1032, 968, 908, 869, 815 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.4 (2H, m), 4.5 (1H, m), 3.2-3.8 (4H, m), 2.2-2.3 (2H, m), 1.6-1.4 (9H, m); *m / z* 170 (M^+), 140, 115, 101, 85, 69, 57, 41, 29; Found: C 70.59, H 10.67%; $C_{10}H_{18}O_2$ requires: C 70.55, H 10.66%.

***cis*-2-[2-(2-Chloro-2,3-dimethyl-1-cyclopropyl)ethyloxy]tetrahydro-2H-pyran (5b).** To a solution of **4b** (9.76 g, 57.4 mmol) and 1,1-dichloroethane (1.05 ml, 12.2 mmol) in ether (30 ml) at -35°C was added *n*-butyllithium (2.5 M in hexanes, 23.3 ml, 58.3 ml) dropwise over a period of 4 hours, by means of a syringe pump. Further portions of 1,1-dichloroethane (1.0 ml, 12.0 mmol) were added after 0.5, 1.5, 2.5 and 3.5 hours of the addition. The solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was recooled to -35°C and the above procedure repeated. The solution was again warmed to room temperature and stirred overnight. The reaction mixture was poured into water (50 ml), the organic phase was separated and dried over $MgSO_4$. Removal of the solvent under reduced pressure and subsequent distillation of the residue gave **5b** (10.7 g, 80%) as a colourless liquid (bp 100-102°C / 0.7 mbar) as a 1:1 mixture of stereoisomers. ν_{max} (film) 2940, 1450, 1381, 1351, 1201, 1121, 1076, 1033, 986, 907, 871, 814 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 4.6 (1H, t, 3.2 Hz), 3.9-3.4 (4H, m), 1.50 and 1.55 (3H, 2 x s), 2.0-1.0 (8H, m), 1.05 (3H, d, 5.9 Hz), 0.9-0.5 (2H, m); *m / z* 231 (M^+-H), 197 (M^+-Cl), 167, 130, 112, 101, 85, 67, 41.

***trans*-2-[2-(2-Chloro-2,3-dimethyl-1-cyclopropyl)ethyloxy]tetrahydro-2H-pyran (5a).** Using **4a** (5.5 g, 32.3 mmol), the above procedure afforded **5a** (7.1 g, 95%) as a colourless liquid (bp 99-101°C / 0.6 mbar) as a 1:1 mixture of stereoisomers. ν_{max} (film) 2940, 1449, 1380, 1349, 1201, 1120, 1076, 1033, 907, 814 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 4.6 (1H, t, 3.2 Hz), 3.9-3.4 (4H, m), 2.0-1.0 (8H, m), 1.50 and 1.55 (3H, 2 x s), 1.05 (3H, d, 5.9 Hz), 0.9-0.5 (2H, m).

***cis*-Tetrahydro-2-[2-(3-methyl-2-methylene-1-cyclopropyl)ethyloxy]-2H-pyran (6b).** To a solution of potassium *tert*-butoxide (1.46 g, 13.1 mmol) in DMSO (3 ml) stirred at 70°C was added a solution of **5b** (2.0 g, 8.6 mmol) in DMSO (1 ml) dropwise over a period of 30 minutes. After 6 hours, the solution

was cooled to 0°C, poured into cold water (100 ml) and extracted with ether (3 x 100 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Bulb-to bulb distillation of the residue afforded **6b** (1.60 g, 95%) as a colourless liquid (bp 110°C / 0.3 mbar). ν_{max} (film) 2945, 2868, 1736, 1439, 1352, 1200, 1162, 1121, 1034, 883 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.4-5.3 (2H, m), 4.6 (1H, t, 3.2 Hz), 3.9-3.6 (4H, m), 1.9-1.5 (8H, m), 1.2-1.0 (2H, m), 1.0 (3H, d, 5.8 Hz); *m/z* 196 (M^+), 167, 149, 115, 101, 85, 67, 41; Found: C 73.08, H 10.50%; $C_{12}H_{20}O_2$ requires: C 73.43, H 10.27%.

***trans*-Tetrahydro-2-[2-(3-methyl-2-methylene-1-cyclopropyl)ethyloxy]-2H-pyran (6a).** Using **5a** (7.0 g, 30.0 mmol) the above procedure afforded **6a** (3.6 g, 60%) as a colourless liquid (bp 72-75°C / 0.1 mbar). ν_{max} (film) 3062, 2942, 2866, 1351, 1200, 1138, 1121, 1077, 1035, 885 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.3 (2H, m), 4.5 (1H, t, 3.2 Hz), 3.8-3.3 (4H, m), 1.8-1.1 (8H, m), 1.0 (3H, d, 5.9 Hz), 1.0-0.8 (2H, m); *m / z* 195 (M^+-H), 181, 143, 129, 115, 101, 85, 57, 41; Observed (M^+): 196.1457; $C_{12}H_{20}O_2$ requires: 196.1463.

***cis*-3-Methyl-2-methylenecyclopropane-ethanol (7b).** To **6b** (2.40 g, 12.2 mmol) in MeOH (30 ml) stirred at room temperature was added a solution of *p*-toluenesulphonic acid (0.62 g, 3.3 mmol) in MeOH (5 ml). The solution was stirred for 3 hours then anhydrous potassium carbonate (2.0 g) was added. After 10 minutes, the solvent was distilled off at atmospheric pressure. The residue was partitioned between water (200 ml) and ether (200 ml). The aqueous layer was extracted with ether (2 x 100 ml), and the combined organic extracts washed with brine (50 ml), dried over $MgSO_4$ and concentrated at atmospheric pressure to give a yellow liquid. Subsequent distillation of the residue under reduced pressure yielded **7b** (1.20 g, 87%) as a colourless liquid (bp 61°C / 0.05 mbar). ν_{max} (film) 3320, 2982, 2928, 2869, 1377, 1143, 1053, 965, 884 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.3 (2H, m), 3.7 (2H, m), 1.8-1.5 (2H, m), 1.4 (1H, bs), 1.1 (3H, d, 5.8 Hz), 1.2-1.1 (2H, m); ^{13}C (67.9 MHz; $CDCl_3$) 142.4, 101.2, 62.4, 30.1, 15.8, 13.3, 11.6; *m / z* 111 (M^+-H), 79, 67, 41; Found: C 74.67, H 10.94%; $C_7H_{12}O$ requires: C 74.95, H 10.78%.

***trans*-3-Methyl-2-methylenecyclopropane-ethanol (7a).** Using **6a** (3.29 g, 16.8 mmol), the above procedure afforded **7a** (1.78 g, 66%) as a colourless liquid (bp 67°C / 0.05 mbar). ν_{max} (film) 3320, 3062, 2982, 2928, 1744, 1377, 1186, 1142, 1050, 963, 812 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.4 (2H, m), 3.7 (2H, t, 5.4 Hz), 1.5-1.8 (2H, m), 1.4 (1H, bs), 1.1 (3H, d, 5.9 Hz), 1.1-1.0 (2H, m); *m / z* 111 (M^+-H), 79, 67, 41; Found: C 75.00, H 11.06%; $C_7H_{12}O$ requires: C 74.95, H 10.78%.

***cis*-Dimethyl 1-(3-methyl-2-methylene-1-cyclopropyl)hex-5-yne-3,3-dicarboxylate (9b).** To a solution of **7b** (1.28 g, 11.4 mmol) in ether (50 ml) and acetonitrile (20 ml) was added triphenylphosphine (4.3 g, 16.4 mmol), imidazole (1.4 g, 20.5 mmol) and finally iodine (4.63 g, 18.2 mmol). The red solution was stirred vigorously at room temperature for 30 minutes. The mixture was diluted with ether (100 ml), washed with a 5% aqueous sodium thiosulphate (2 x 100 ml), then water (100 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Filtration of the residue through a pad of silica eluting with hexane and subsequent bulb-to-bulb distillation of the filtrate at atmospheric pressure afforded **8b** (1.53 g, 60%) as a colourless liquid (bp 150-152°C) which was used without delay. To a solution of sodium hydride (0.33 g, 8.4 mmol) in DMF (2 ml) was added dimethyl but-3-yne-1,1-dicarboxylate[16] (1.40 g, 8.2 mmol) in DMF (4 ml) at 0°C. After 1

hour, a solution of **8b** (1.53 g, 6.9 mmol) in DMF (6 ml) was added. The solution was allowed to warm to room temperature and stirred for 70 hours. The mixture was poured into cold water (100 ml) and extracted with ether (3 x 50 ml). The combined extracts were washed with water (2 x 100 ml) then brine (50 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (15% ether / petrol) afforded **9b** (1.33 g, 44% from **7b**) as a colourless oil. ν_{max} (film) 2954, 1735, 1436, 1273, 1236, 1202, 1093, 1031, 888, 645 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.3 (2H, m), 3.75 (3H, s), 3.70 (3H, s), 2.80 (2H, d, 3.0 Hz), 2.2 (2H, m), 2.0 (1H, t, 3.0 Hz), 1.6-1.1 (4H, m), 1.05 (3H, d, 5.9 Hz); ^{13}C NMR (67.9 MHz; $CDCl_3$) 170.4, 142.2, 101.2, 78.6, 71.3, 56.6, 52.5, 31.9, 22.6, 21.8, 18.8, 13.6, 11.3; *m / z* 264 (M^+), 204, 189, 173, 145, 129, 105, 79; Found: C 68.10, H 7.92%; $C_{15}H_{20}O_4$ requires: C 68.16, H 7.63%.

***trans*-Dimethyl 1-(3-methyl-2-methylene-1-cyclopropyl)hex-5-yne-3,3-dicarboxylate (9a).** Using **7a** (0.52 g, 4.64 mmol) as substrate the above procedure afforded **8a** (0.64g, 63%) as a colourless liquid, which gave **9a** (0.51 g, 43% from **7a**) as a colourless oil. ν_{max} (film) 2954, 1735, 1434, 1270, 1236, 1204, 1105, 1030, 890, 644 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.4-5.3 (2H, m), 3.8 (3H, s), 3.70 (3H, s), 2.80 (2H, d, 3.0 Hz), 2.2 (2H, m), 2.0 (1H, t, 3.0 Hz), 1.3-1.1 (2H, m), 1.1 (3H, bs), 1.1-0.9 (2H, m); ^{13}C NMR (125.8 MHz; $CDCl_3$) 170.6, 143.0, 102.1, 78.7, 71.3, 56.6, 52.7, 31.7, 27.3, 23.0, 22.7, 17.4, 17.0; *m / z* 264 (M^+), 232, 217, 193, 145, 105, 79; Found: C 67.84, H 7.75%; $C_{15}H_{20}O_4$ requires: C 68.16, H 7.63%.

***cis*-Trimethyl 6-(3-methyl-2-methylene-1-cyclopropyl)-1-hexyne-1,4,4-tricarboxylate (3b).** To a solution of **9b** (320 mg, 1.21 mmol) in THF (5 ml) stirred at -78°C was added *n*-butyllithium (2.5 M in hexanes, 0.53 ml, 1.33 mmol) dropwise. The resulting pale yellow solution was stirred for 30 minutes at -78°C, then methyl chloroformate (0.30 ml, 3.83 mmol) was added. After 1 hour, the solution was allowed to warm to room temperature, diluted with water (50 ml) and extracted with ether (3 x 50 ml). The combined organic extracts were washed with water (50 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (10% ether/hexane) gave **3b** (363 mg, 93%) as a colourless liquid. ν_{max} (film) 2954, 2867, 2242, 1735, 1433, 1378, 1326, 1259, 1203, 1125, 1076, 1030, 955, 889, 823, 788, 752 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.3 (2H, m), 3.8-3.7 (9H, m), 2.95 (2H, s), 2.2 (2H, m), 1.6-1.1 (4H, m), 1.1 (3H, d, 6.5 Hz); *m / z* 322 (M^+), 307 (M^+-Me), 290, 275, 231, 143, 105, 79; Found: C 63.24, H 6.77%; $C_{17}H_{22}O_6$ requires: C 63.34, H 6.88%.

***trans*-Trimethyl 6-(3-methyl-2-methylene-1-cyclopropyl)-1-hexyne-1,4,4-tricarboxylate (3a).** Using **9a** (384 mg, 1.45 mmol) as substrate the above procedure afforded **3a** (445 mg, 95%) as a colourless liquid. ν_{max} (film) 2955, 2241, 1735, 1716, 1433, 1260, 1202, 1077, 752 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.3 (2H, m), 3.8-3.7 (9H, m), 2.95 (2H, s), 2.2 (2H, m), 1.2 (2H, m), 1.1 (3H, s), 1.1-0.8 (2H, m); *m / z* 307 (M^+-Me), 275, 247, 231, 203, 187, 171, 143, 79; Found: C 63.34, H 6.88%; $C_{17}H_{22}O_6$ requires: C 63.34, H 6.88%.

Palladium catalysed cyclisation of *cis*-trimethyl 6-(3-methyl-2-methylene-1-cyclopropyl)-1-hexyne-1,4,4-tricarboxylate (9b). A purple solution of tris(dibenzylidineacetone) dipalladium (16.2 mg, 17.7 µmol) and triisopropyl phosphite (37 µl, 150 µmol) in toluene (1.0 ml) was sonicated for 20 minutes giving a green homogeneous solution. **9b** (66.7 mg, 0.21 mmol) in toluene (2.75 ml) was added and the

mixture refluxed for 24 hours. On cooling to room temperature the mixture was filtered through a short plug of silica and the solvent removed under reduced pressure. Column chromatography of the residue (5-20% ether/hexane) afforded an inseparable mixture of **10** and **11** (39.3 mg, 59%) in a 3:1 ratio. ν_{max} (film) 2953, 2926, 2856, 1734, 1668, 1433, 1324, 1289, 1230, 1194, 1131, 1104, 1023 cm^{-1}; *m / z* 322 (M^+), 290 (M^+-MeOH), 275 (M^+-Me-MeOH), 263 (M^+-CO_2Me), 231, 203, 143; Found: C 63.43, H 6.92%; $C_{17}H_{22}O_6$ requires: C 63.34, H 6.88%; **10** ^1H NMR (270 MHz; $CDCl_3$) 5.3 (1H, m), 4.2 (1H, dd, 2.5, 12.0 Hz), 3.8-3.6 (9H, 3 x s), 3.3 (2H, m), 3.1-3.0 (1H, m), 2.45-2.35 (2H, m), 2.1-2.0 (1H, m), 2.0-1.8 (1H, m), 1.55 (3H, m, 2.0, 7.0 Hz), 1.35-1.32 (1H, m); ^{13}C NMR (125.8 MHz; $CDCl_3$) 172.1, 170.6, 165.8, 153.8, 140.4, 125.6, 116.8, 56.2, 52.8, 51.1, 50.8, 50.7, 36.6, 32.6, 30.6, 29.9, 14.5 and **11** ^1H NMR (270 MHz; $CDCl_3$) 4.95-4.95 (2H, t, 2.3 Hz), 4.15 (1H, dd, 2.5, 12.0 Hz), 3.9-3.6 (9H, 3 x s), 3.2 (1H, m), 3.1 (1H, m), 2.4-2.3 (2H, m), 2.1-2.0 (1H, m), 2.0-1.8 (1H, m), 1.40-1.25 (1H, m), 1.2 (3H, m); ^{13}C NMR (125.8 MHz; $CDCl_3$) 172.1, 170.6, 165.8, 155.9, 144.4, 118.5, 106.6, 65.8, 56.3, 52.4, 52.3, 51.0, 49.9, 32.7, 30.9, 30.9, 15.2.

Palladium catalysed cyclisation of *trans*-trimethyl 6-(3-methyl-2-methylene-1-cyclopropyl)-1-hexyne-1,4,4-tricarboxylate (9a). A purple solution of tris(dibenzylidineacetone) dipalladium (12.0 mg, 12.4 μmol) and triisopropyl phosphite (27 μl, 110 μmol) in toluene (1.0 ml) was sonicated for 20 minutes giving a green homogeneous solution. **9a** (51.0 mg, 0.16 mmol) in toluene (2.25 ml) was added and the mixture refluxed for 24 hours. On cooling to room temperature, the mixture was filtered through a plug of silica and the solvent removed under reduced pressure. Column chromatography (5-20% ether/hexane) afforded an inseparable mixture of **10** and **11** (10.8 mg, 21%) in a 3:1 ratio. All spectroscopic data was identical with that previously described.

1-Methyl-2-methylenecyclopropanebutanal dimethylhydrazone (17). To diisopropylamine (0.98 ml, 6.99 mmol) at 0°C was added *n*-butyllithium (2.5M solution in hexanes, 2.75 ml, 6.88 mmol) dropwise. The resulting sticky oil was diluted with THF (6 ml) and after stirring for 30 minutes, added *via* a cannula to acetaldehyde dimethylhydrazone[6] (562 mg, 6.52 mmol) in THF (3 ml) at 0°C. After 30 minutes, **16**[2e] (1.60 g, 7.20 mmol) in THF (6 ml) was added and the solution stirred for a further hour. The reaction mixture was poured into water (50 ml), extracted with DCM (3 x 50 ml) and the combined layers dried over Na_2SO_4. Removal of the solvent under reduced pressure and subsequent column chromatography (20% ether / petrol) gave **17** (875 mg, 74%) as a clear liquid. ν_{max} (film) 3062, 2949, 2779, 1743, 1608, 1459, 1399, 1374, 1255, 1138, 1031, 882 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 6.64 (1H, t, 5.6 Hz), 5.35 (1H, dt, 1.1, 2.5 Hz), 5.26 (1H, m), 2.72 (6H, s), 2.21 (2H, dt, 5.6, 7.5 Hz), 1.65-1.25 (4H, m), 1.13 (3H, s), 0.90 (2H, m); *m / z* 180 (M^+), 165 (M^+-Me), 151, 85, 59, 44; Found: C 73.36, H 11.43, N 15.40%; $C_{11}H_{20}N_2$ requires: C 73.28, H 11.18, N 15.44%.

4-(1-Methyl-2-methylenecyclopropane)-butanal (18). To a stirred solution of **17** (405 mg, 2.25 mmol) in THF (1 0 ml) and water (10 ml) buffered with acetic acid / sodium acetate to pH4 was added periodic acid (1.05 g, 4.61 mmol). The mixture was stirred for 40 minutes, during which time a dense white precipitate formed, poured into water (50 ml) and extracted with DCM (3 x 25 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure with the water bath temperature maintained below 10°C. Column chromatography (4% ether / petrol) gave **18** (227 mg, 73%) as a clear liquid. ν_{max} (film)

2946, 2866, 2719, 1723, 1454, 1376, 1115, 885 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 9.77 (1H, t, 1.7 Hz), 5.36 (1H, dt, 1.1, 2.5 Hz), 5.28 (1H, m), 2.43 (2H, dt, 1.7, 7.4 Hz), 1.80-1.27 (4H, m), 1.15 (3H, s), 0.93 (2H, m); *m / z* 139 (MH^+), 123 (M^+-Me), 109, 79, 67.

(*E*)-Methyl 6-(1-methyl-2-methylene-1-cyclopropyl)-2-hexenoate (13). To a stirred solution of lithium chloride (20 mg, 470 µmol), trimethyl phosphonoacetate (60 µl, 370 µmol) and diisopropylethylamine (57 µl, 330 µmol) in acetonitrile (2 ml) was added **18** (41 mg, 297 µmol) in acetonitrile (1 ml). After stirring for 3.5 hours, the mixture was poured into water (25 ml) and extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (2-4% ether / petrol) gave **13** (48 mg, 83%) as a colourless liquid. ν_{max} (film) 2934, 1723, 1654, 1433, 1270, 1195, 1177 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 6.96 (1H, dt, 15.6, 7.0 Hz), 5.81 (1H, dt, 15.6, 1.6 Hz), 5.34 (1H, dt, 1.1, 2.6 Hz), 5.26 (1H, m), 3.72 (3H, s), 2.24-2.14 (2H, m), 1.66-1.24 (4H, m), 1.12 (3H, s), 0.91 (2H, m); *m / z* 194 (M^+), 179 (M^+-Me), 162, 135, 93, 79, 67; Observed (M^+): 194.1309; $C_{12}H_{18}O_2$ requires: 194.1307.

(*Z*)-Methyl 6-(1-methyl-2-methylene-1-cyclopropyl)-2-hexenoate (12) and (*E*)-methyl 6-(1-methyl-2-methylene-1-cyclopropyl)-2-hexenoate (13). To a stirred solution of trimethyl phosphonoacetate (310 µl, 1.92 mmol) and 18-crown-6.CH_3CN (1.98 g, 6.48 mmol) in THF (35 ml) at -78°C was added potassium bis(trimethylsilyl)amide (0.5 M in toluene, 3.8 ml, 1.90 mmol). After stirring for 15 minutes, a precooled solution of **18** (222 mg, 1.61 mmol) in THF (8 ml) was added dropwise *via* a lagged cannula. After stirring for a further 45 minutes, saturated ammonium chloride solution (10 ml) was added and the mixture allowed to warm to room temperature. The solution was diluted with water (50 ml) and extracted with ether (3 x 25 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (2% ether / petrol) gave less polar **12** (191 mg, 61%) as a colourless liquid; ν_{max} (film) 2948, 2926, 1723, 1644, 1436, 1174, 885, 818 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 6.22 (1H, dt, 11.5, 7.4 Hz), 5.77 (1H, dt, 11.5, 1.7 Hz), 5.35 (1H, dt, 1.1, 2.5 Hz), 5.26 (1H, m), 3.70 (3H, s), 2.69-2.60 (2H, m), 1.60-1.28 (4H, m), 1.13 (3H, s), 0.91 (2H, m); *m / z* 194 (M^+), 179 (M^+-Me), 135, 134, 95; Found: C 74.37, H 9.54%; $C_{12}H_{18}O_2$ requires: C 74.19, H 9.34%; and more polar **13** (78 mg, 25%) as a colourless liquid, identical with the material previously described.

(*Z*)-4-(*tert*-Butyldiphenylsilyloxy)-2-buten-1-ol. To *cis*-2-butene-1,4-diol (14.1 g, 160 mmol) in DMF (25 ml) was added a solution of imidazole (4.93 g, 72.4 mmol) and *tert*-butyldiphenylsilyl chloride (8.99 g, 32.7 mmol) in DMF (15 ml) dropwise over 3 hours *via* a syringe pump. After stirring for a further 18 hours, the mixture was diluted with water (150 ml) and extracted with ether (3 x 100 ml). The combined organic layers were washed with brine (100 ml), dried over Na_2SO_4 and solvent removed under reduced pressure. Column chromatography (25-40% ether / petrol) gave the *title compound* (6.55 g, 61%) as a colourless oil. ν_{max} (film) 3339, 3069, 2931, 2857, 1461, 1427, 1388, 1112, 824, 741, 706, 613 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 7.74-7.66 (4H, m), 7.50-7.36 (6H, m), 5.68 (2H, m), 4.28-4.25 (2H, m), 4.02 (2H, t, 5.6 Hz), 1.46 (1H, t, 5.8 Hz), 1.05 (9H, s); *m / z* 308 (M^+-H_2O), 295, 269 (M^+-C_4H_9), 199; Found: C 73.41, H 8.10%; $C_{20}H_{26}O_2Si$ requires: C 73.57, H 8.03%

(Z)-4-(*tert*-Butyldiphenylsilyloxy)-2-butenal. To a solution of (Z)-4-(*tert*-butyldiphenylsilyloxy)-2-buten-1-ol (6.55 g, 20.1 mmol) in DCM (50 ml) was added manganese dioxide (26.2 g, 301 mmol). After stirring in air overnight, t.l.c. indicated that the reaction had not proceeded to completion. A further portion of manganese dioxide (3.0 g, 34.5 mmol) was added and stirring continued for 5 hours. The mixture was filtered through a plug of celite with DCM and the solvent removed under reduced pressure. Column chromatography (2-5% ether / petrol) gave the *title compound* (5.0 g, 77%) as a white crystalline solid (m.p. 48-50°C). ν_{max} (film) 2957, 2931, 2891, 2857, 1683, 1608, 1589, 1427, 1112, 823, 742, 704, 612 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 9.98 (1H, d, 7.1 Hz), 7.76-7.64 (4H, m), 7.51-7.36 (6H, m), 6.63 (1H, dt, 11.6, 5.5 Hz), 5.95 (1H, ddt, 11.5, 7.1, 2.0 Hz), 4.67 (2H, dd, 5.4, 2.0 Hz), 1.08 (9H, s); *m / z* 324 (M^+), 295, 281, 267 (M^+-C_4H_9), 199, 189, 139; Found: C 73.85, H 7.41%; $C_{20}H_{24}O_2Si$ requires C 74.03, H 7.46%.

(Z)-6-(*tert*-Butyldiphenylsilyloxy)-1-(1-methyl-2-methylene-1-cyclopropyl)-4-hexen-3-ol (19). To a solution of **16** (1.37 g, 6.17 mmol) in 30-40°C petrol (60 ml) at -78°C, was added *tert*-butyllithium (1.7M in pentane, 8.0 ml, 13.6 mmol) dropwise, and the resulting solution stirred for 1.5 hours. A solution of (Z)-4-(*tert*-butyldiphenylsilyloxy)-2-butenal (1.01 g, 3.12 mmol) in THF (22 ml), precooled to -78°C, was then added *via* a lagged cannula. After stirring for 30 minutes, saturated ammonium chloride solution (10 ml) was added and the mixture allowed to warm to room temperature. The solution was poured into water (100 ml), extracted with ether (3 x 50 ml) and the combined organic layers dried over $MgSO_4$. Removal of the solvent under reduced pressure and subsequent column chromatography (10-20% ether / petrol) gave **19** (957 mg, 73%) as a colourless oil and as a 1:1 mixture of diastereomers. ν_{max} (film) 3366, 2930, 2857, 1589, 1427, 1112, 1082, 740, 703, 612 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 7.73-7.66 (4H, m), 7.49-7.35 (6H, m), 5.72-5.63 (1H, m), 5.47-5.38 (1H, m), 5.32 (0.5H, dt, 1.1, 2.5 Hz), 5.30 (0.5H, dt, 1.1, 2.6 Hz), 5.24 (1H, m), 4.34-4.10 (3H, m), 1.65-1.10 (5H, m), 1.09 (3H, s), 1.04 (9H, s), 0.93-0.80 (2H, m); *m / z* 363 (M^+-C_4H_9), 345 (M^+-C_4H_9-H_2O), 267, 255, 199; Found: C 77.01, H 8.87%; $C_{27}H_{36}O_2Si$ requires C 77.09, H 8.63%.

(Z)-6-(1-Methyl-2-methylene-1-cyclopropyl)-4(phenylmethoxy)-2-hexen-1-ol (20). To sodium hydride (60% dispersion in mineral oil, 66 mg, 1.65 mmol) and tetrabutylammonium iodide (12 mg, 32 µmol) was added a solution of **19** (490 mg, 1.16 mmol) in THF (5.5 ml). After 5 minutes, benzyl bromide (220 µl, 1.85 mmol) was added and the mixture stirred in the dark for 24 hours. More benzyl bromide (250 µl, 2.10 mmol) was added, and the solution stirred for a further 3 days. The reaction mixture was poured into water (50 ml) and extracted with ether (3 x 50 ml). The combined organic layers were washed with water (50 ml) and dried over Na_2SO_4. Column chromatography (0-2% ether / petrol) gave the benzylated material (588 mg) as a clear oil. To a stirred solution of this material in THF (3 ml) was added tetrabutylammonium fluoride (1.1 M in THF, 2.1 ml, 2.31 mmol). After 2 hours, the green solution was poured into water (50 ml) and extracted with ether (3 x 50 ml). The combined organic layers were washed with water (50 ml) and dried over Na_2SO_4. Column chromatography (2-4% ethyl acetate / dichloromethane) gave **20** (245 mg, 77%) as a colourless oil and as a 1:1 mixture of diastereomers. ν_{max} (film) 3383, 2942, 2863, 1451, 1028, 886, 736, 698 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 7.40-7.24 (5H, m), 5.85-5.76 (1H, m), 5.51-5.42 (1H, m), 5.35 (0.5H, dt, 1.0, 2.4 Hz), 5.34 (0.5H, dt, 1.1, 2.5 Hz), 5.26 (1H, m), 4.57 (0.5H, d, 12.0 Hz), 4.57 (0.5H, d, 12.0 Hz), 4.35 (1H, d, 11.7 Hz), 4.24-4.02 (3H, m), 1.88-1.22 (5H, m), 1.13 (3H, s), 0.96-0.85 (2H, m);

m / z 272 (M^+), 257 (M^+-Me), 239 (M^+-Me-H_2O), 131, 91 ($C_7H_7^+$); Found: C 79.16, H 8.82%; $C_{18}H_{24}O_2$ requires: C 79.37, H 8.88%.

(*Z*)-6-(1-Methyl-2-methylene-1-cyclopropyl)-4-(phenylmethoxy)-2-hexenal. To **20** (397 mg, 1.46 mmol) in DCM (10 ml), vigorously stirred in air was added manganese dioxide (2.54 g, 29.2 mmol). After 5 hours, the mixture was filtered through a plug of celite with DCM, and the solvent removed under reduced pressure. Column chromatography (5% ether petrol) gave the *title compound* (382 mg, 97%) as a colourless oil and as a 1:1 mixture of diastereomers. ν_{max} (film) 2946, 2862, 1681, 1451, 1070, 887, 738, 698 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 9.97 (0.5H, d, 7.6 Hz), 9.97 (0.5H, d, 7.8 Hz), 7.38-7.28 (5H, m), 6.48 (1H, dd, 11.4, 8.8 Hz), 6.09 (1H, ddd, 11.4, 7.6, 1.0 Hz), 5.34 (1H, m), 5.27 (1H, bs), 4.73-4.60 (1H, m), 4.60 (0.5H, d, 12.0 Hz), 4.59 (0.5H, d, 11.7 Hz), 4.41 (1H, d, 11.7 Hz), 1.94-1.23 (4H, m), 1.15 (3H, s), 0.98-0.86 (2H, m); *m / z* 255 (M^+-Me), 179, 161, 139, 105, 91 ($C_7H_7^+$); Found: C 79.67, H 8.43%; $C_{18}H_{22}O_2$ requires: C 79.96, H 8.20%.

(*Z*)-Methyl 6-(1-methyl-2-methylene-1-cyclopropyl)-4-(phenylmethoxy)-2-hexenoate (14). To (*Z*)-6-(1-methyl-2-methylene-1-cyclopropyl)-4-(phenylmethoxy)-2-hexenal (419 mg, 1.55 mmol), potassium dihydrogen phosphate (647 mg, 4.75 mmol) and 2-methyl-2-butene (1.0 ml, 9.4 mmol) in *tert*-butanol (5 ml) and water (5 ml) was added sodium chlorite (420 mg, 4.64 mmol). The resulting mixture was stirred for 2 hours, cooled to 0°C and saturated sodium sulphite solution (10 ml) added. After 5 minutes, the mixture was poured into water (50 ml) and extracted with DCM (5 x 50 ml). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure to give the crude acid (517 mg). To a stirred solution of this acid and DMAP (10 mg, 82 µmol) in DCM (4 ml) and MeOH (1.25 ml, 30.9 mmol) at 0°C, was added 1,3-dicyclohexylcarbodiimide (390 mg, 1.89 mmol) in DCM (3 ml). After stirring for 10 minutes, the solution was allowed to warm to room temperature and stirred for a further 2 hours. The solvent was removed under reduced pressure, and the residue filtered and washed with petrol. Removal of the solvent *in vacuo*, and subsequent column chromatography (0-4% ether / petrol) gave **14** (372 mg, 80%) as a colourless oil and as a 1:1 mixture of diastereomers. ν_{max} (film) 2949, 2861, 1722, 1646, 1402, 1198, 1068, 697 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 7.38-7.23 (5H, m), 6.18 (0.5H, dd, 11.7, 8.6 Hz), 6.17 (0.5H, dd, 11.8, 8.6 Hz), 5.91 (1H, m), 5.36 (1H, m), 5.25 (1H, bs), 5.07-4.99 (1H, m), 4.51 (0.5H, d, 11.7 Hz), 4.51 (0.5H, d, 11.5 Hz), 4.41 (0.5H, d, 11.5 Hz), 4.40 (0.5H, d, 11.7 Hz), 3.71 (3H, s), 1.85-1.24 (4H, m), 1.13 (3H, s), 0.98-0.84 (2H, m); *m / z* 300 (M^+), 285 (M^+-Me), 267 (M^+-Me-H_2O), 209, 192, 169, 91 ($C_7H_7^+$); Found: C 75.78, H 8.23%; $C_{19}H_{24}O_3$ requires: C 75.97, H 8.05%.

(*E*)-4-(*tert*-Butyldiphenylsilyloxy)-2-buten-1-ol. To dimethyl fumarate (3.18 g, 22.1 mmol) in toluene (50 ml) at -78°C was added DIBAL (1.5M in toluene, 60 ml, 90 mmol). After 90 minutes, the mixture was warmed to 0°C and stirred for a further 30 minutes. The solution was recooled to -78°C, quenched with water (10 ml) and ethyl acetate (50 ml) and allowed to warm to room temperature. Ethyl acetate and Na_2SO_4 were added and the mixture stirred for 30 minutes. Filtration and subsequent removal of the solvent under reduced pressure gave crude diol (1.58 g). To a stirred solution of this diol and imidazole (1.39 g, 20.4 mmol) in DMF (9 ml) was added *tert*-butyldiphenylsilyl chloride (5.18 g, 18.8 mmol) in DMF (7 ml) dropwise over 16 hours *via* syringe pump. The mixture was poured into water (100 ml) and extracted with ether (3 x 100 ml). The combined organic layers were washed with water (100 ml), dried over Na_2SO_4 and the solvent removed *in*

vacuo. Column chromatography (30-50% ether / petrol) gave the *title compound* (2.21g, 31%) as a colourless oil. ν_{max} (film) 3332, 2955, 2930, 2890, 2856, 1469, 1461, 1427, 1112, 1057, 997, 985, 823, 740, 702, 613 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 7.70-7.67 (4H, m), 7.47-7.35 (6H, m), 5.99-5.88 (1H, m), 5.83-5.74 (1H, m), 4.24-4.21 (2H, m), 4.15 (2H, m), 1.25 (1H, t, 6.0 Hz), 1.06 (9H, s); *m / z* 308 (M^+-H_2O), 269 (M^+-C_4H_9), 251 (M^+-C_4H_9-H_2O), 239, 227, 223, 199; Found: C 73.56, H 8.23%; $C_{20}H_{26}O_2Si$ requires: C 73.57, H 8.03%.

(*E*)-4-(*tert*-Butyldiphenylsilyloxy)-2-butenal. To (*E*)-4-(*tert*-butyldiphenylsilyloxy)-2-buten-1-ol (2.18 g, 6.68 mmol) in DCM (50 ml) was added manganese dioxide (11.6 g, 133 mmol). After 18 hours, stirring in air, the mixture was filtered through a plug of celite with DCM and the solvent removed under reduced pressure. Column chromatography (5-10% ether / petrol) gave the *title compound* (1.81 g, 84%) as a white crystalline solid (m.p. 38-41°C). ν_{max} (film) 2956, 2930, 2856, 1686, 1427, 1145, 1113, 967, 823, 742, 703, 631 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 9.61 (1H, d, 8.1 Hz), 7.68-7.64 (4H, m), 7.49-7.36 (6H, m), 6.86 (1H, dt, 15.4, 3.2 Hz), 6.58 (1H, ddt, 15.4, 8.1, 2.2 Hz), 4.46 (2H, dd, 3.2, 2.2 Hz), 1.09 (9H, s); *m / z* 325 (MH^+), 324 (M^+), 267 (M^+-C_4H_9), 256, 249 (M^+-C_4H_9-H_2O), 241, 199; Found: C 74.31, H 7.65%; $C_{20}H_{24}O_2Si$ requires: C 74.03, H 7.46%.

(*E*)-6-(*tert*-Butyldiphenylsilyloxy)-1-(1-methyl-2-methylene-1-cyclopropyl)-4-hexen-3-ol (21). To a solution of **16** (640 mg, 2.88 mmol) in 30-40°C petrol (28 ml) at -78°C, was added *tert*-butyllithium (1.7M in pentane, 3.72 ml, 6.32 mmol) dropwise, and the resulting solution stirred for 1.5 hours. A solution of (*E*)-4-(*tert*-butyldiphenylsilyloxy)-2-butenal (455 mg, 1.40 mmol) in THF (10 ml), precooled to -78°C was then added *via* a lagged cannula. After stirring for 30 minutes, the mixture was warmed to -20°C and stirred for a further hour. Saturated ammonium chloride solution (5 ml) was added and the solution allowed to warm to room temperature. The mixture was poured into water (50 ml) and extracted with ether (3 x 50 ml). The combined extracts were washed with water (50 ml), dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography(10-20% ether / petrol) gave **21** (510 mg, 87%) as a colourless oil and as a 1:1 mixture of diastereomers. ν_{max} (film) 3347, 2930, 2856, 1427, 1112, 1057, 1009, 970, 823, 740, 703, 613 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 7.70-7.66 (4H, m), 7.47-7.35 (6H, m), 5.74-5.72 (2H, m), 5.37 (1H, dt, 1.0, 2.4 Hz), 5.28 (1H, bs), 4.21 (2H, m), 4.13-4.03 (1H, m), 1.70-1.25 (5H, m), 1.14 (3H, s), 1.06 (9H, s), 0.97-0.88 (2H, m); *m / z* 363 (M^+-C_4H_9), 345 (M^+-C_4H_9-H_2O), 285, 267, 255, 239, 229, 225, 199; Found: 77.38, H 8.65%; $C_{27}H_{36}O_2Si$ requires: C 77.09, H 8.63%.

(*E*)-6-(1-Methyl-2-methylene-1-cyclopropyl)-4-(phenylmethoxy)-2-hexen-1-ol (22). To sodium hydride (60% dispersion in mineral oil, 168 mg, 4.20 mmol) and a trace of tetrabutylammonium iodide was added a solution of **21** (862 mg, 2.05 mmol) in THF (8 ml). Benzyl bromide (1.0 ml, 8.4 mmol) was added and the mixture stirred in the dark for 3 days. The solution was poured into water (100 ml) and extracted with ether (3 x 100 ml). The combined organic layers were washed with water (100 ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (2% ether / petrol) gave the benzylated adduct (1.03 g) as a clear oil. To this material in THF (8 ml) was added tetrabutylammonium fluoride (1.1M in THF, 3.65 ml, 4.02 mmol). After 2 hours, the mixture was poured into water (100 ml) and extracted with ether (3 x 100 ml). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. Column chromatogaphy (2-4% EtOAc / DCM) gave **22** (483 mg, 87%) as a colourless oil and as a

1:1 mixture of diastereomers. ν_{max} (film) 3377, 2941, 2861, 1450, 1374, 1069, 974, 885, 736, 697 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 7.38-7.24 (5H, m), 5.86-5.76 (1H, m), 5.66-5.56 (1H, m), 5.34 (1H, m), 5.25 (1H, m), 4.57 (0.5H, d, 12.0 Hz), 4.56 (0.5H, d, 12.0 Hz), 4.36 (1H, d, 11.7 Hz), 4.18 (2H, bt, 5.4 Hz), 3.81-3.73 (1H, m), 1.80-1.25 (5H, m), 1.13 (1.5H, s), 1.12 (1.5H, s), 0.96-0.85 (2H, m); *m / z* 257 (M^+-Me), 241, 223, 186, 181, 131, 105, 93, 91 ($C_7H_7^+$); Observed (M^+-Me): 257.1545; $C_{17}H_{21}O_2$ requires: 257.1542.

(*E*)-6-(1-Methyl-2-methylene-1-cyclopropyl)-4-(phenylmethoxy)-2-hexenal. To **22** (483 mg, 1.77 mmol) in DCM (10 ml) vigorously stirred in air was added manganese dioxide (3.05 g, 35.1 mmol). After 18 hours, the mixture was filtered through a plug of celite with DCM and the solvent removed under reduced pressure. Column chromatography (5% ether / petrol) gave the *title compound* (440 mg, 92%) as a colourless oil and as a 1:1 mixture of diastereomers. ν_{max} (film) 2945, 2925, 2862, 1689, 1450, 1132, 1096, 979, 737, 698 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 9.59 (0.5H, d, 7.8 Hz), 9.59 (0.5H, d, 7.8 Hz), 7.39-7.29 (5H, m), 6.72 (0.5H, dd, 15.9, 6.3 Hz), 6.72 (0.5H, dd, 15.9, 6.3 Hz), 6.27 (0.5H, dd, 15.9, 7.8 Hz), 6.27 (0.5H, dd, 15.9, 7.8 Hz), 5.36 (0.5H, dt, 1.1, 2.5 Hz), 5.34 (0.5H, dt, 1.0, 2.5 Hz), 5.27 (1H, m), 4.58 (0.5H, d, 11.7 Hz), 4.56 (0.5H, d, 11.7 Hz), 4.41 (1H, d, 11.7 Hz), 4.09-4.04 (1H, m), 1.83-1.26 (4H, m), 1.13 (1.5H, s), 1.11 (1.5H, s), 0.98-0.83 (2H, m); *m / z* 255 (M^+-CH_3),185, 179, 170, 161, 139, 105, 91 ($C_7H_7^+$); Found: C 80.06, H 8.11%; $C_{18}H_{22}O_2$ requires: C 79.96, H 8.20%.

(*E*)-Methyl 6-(1-methyl-2-methylene-1-cyclopropyl)-4-(phenylmethoxy)-2-hexenoate (15). To (*E*)-6-(1-methyl-2-methylene-1-cyclopropyl)-4-(phenylmethoxy)-2-hexenal (440 mg, 1.63 mmol), potassium dihydrogen phosphate (678 mg, 4.98 mmol) and 2-methyl-2-butene (1.5 ml, 14.2 mmol) in *tert*-butanol (5 ml) and water (5 ml) was added sodium chlorite (439 mg, 4.85 mmol). The resulting mixture was stirred for 2.5 hours, cooled to 0°C and saturated sodium sulphite solution added. After 5 minutes, the mixture was poured into water (50 ml) and extracted with DCM (5 x 50 ml). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure to give the acid (535 mg). To a stirred solution of this acid and DMAP (10 mg, 82 μmol) in DCM (4 ml) and MeOH (1.30 ml, 32.1 mmol) at 0°C, was added 1,3-dicyclohexylcarbodiimide (410 mg, 1.99 mmol) in DCM (3 ml). After 10 minutes, the solution was warmed to room temperature at which point a white precipitate formed. After 2 hours, the solvent was removed under reduced pressure, and the residue filtered and washed with petrol. Removal of the solvent *in vacuo* and subsequent column chromatography (0-5% ether / petrol) gave **15** (382 mg, 78%) as a colourless oil and as a 1:1 mixture of diastereomers. ν_{max} (film) 2947, 2861, 1723, 1433, 1300, 1275, 1194, 1168, 1095, 1072, 1028, 736, 698 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 7.38-7.28 (5H, m), 6.86 (0.5H, dd, 15.6, 6.6 Hz), 6.86 (0.5H, dd, 15.6, 6.6 Hz), 6.01 (1H, m), 5.35 (0.5H, dt, 1.0, 2.4 Hz), 5.33 (0.5H, dt, 1.0, 2.4 Hz), 5.26 (1H, m), 4.58 (0.5H, d, 11.7 Hz), 4.57 (0.5H, d, 12.0 Hz), 4.36 (1H, d, 11.7 Hz), 3.98-3.91 (1H, m), 3.76 (3H, s), 1.781.23 (4H, m), 1.12 (1.5H, s), 1.11 (1.5H, s), 0.95-0.85 (2H, m); *m / z* 300 (M^+), 285 (M^+-Me), 268 (M^+-MeOH), 267, 209, 185, 177, 169, 91 ($C_7H_7^+$); Found: C 75.91, H 7.90%; $C_{19}H_{24}O_3$ requires: C 75.97, H 8.05%.

(*Z*)-Methyl 5-(2,5-dihydro-3,4-dimethyl-2-thienyl)-2-pentenoate S,S-dioxide (23) and (*Z*)-methyl 6-(2,5-dihydro-4-methyl-3-thienyl)-2-hexenoate S,S-dioxide (24). To tris(dibenzylidineacetone) dipalladium (21.2 mg, 23 μmol) in toluene (2 ml) was added triisopropyl phosphite

(46 µl, 186 µmol). The resulting mixture was sonicated for 20 minutes, giving a pale green solution. **12** (55.2 mg, 284 µmol) in toluene (3.7 ml) was added, and the solution refluxed for 48 hours. On cooling, the mixture was filtered through a plug of silica with ether, and the solvent removed under reduced pressure. Column chromatography (2% ether / petrol) gave a mixture of dienes (47.9 mg) as a clear oil. To this mixture and a trace of hydroquinone in MeOH (5 ml) cooled to -78°C was added sulphur dioxide (2.5 ml). The solution was sealed in a pressure bottle and heated to 100°C for 5 hours. After allowing to cool overnight, the vessel was opened and the solvent removed under reduced pressure. Extensive column chromatogaphy (50% ether / petrol) gave less polar **23** (9.6 mg, 13%) as a colourless oil; ν_{max} (film) 2919, 1716, 1643, 1439, 1405, 1302, 1246, 1201, 1175, 1108, 824 cm^{-1}; ^1H NMR (250 MHz; $CDCl_3$) 6.26 (1H, dt, 11.4, 7.7 Hz), 5.83 (1H, dt, 11.4, 1.5 Hz), 3.71 (3H, s), 3.65 (2H, m), 3.57 (1H, m), 2.85 (2H, dq, 1.3, 7.8 Hz), 2.02-1.91 (2H, m), 1.78 (6H, s); *m / z* 258 (M^+), 227, 194 (M^+-SO_2), 162 (M^+-SO_2-MeOH), 147, 110, 95, 68; Observed (M^+): 258.0931; $C_{12}H_{18}O_4S$ requires: 258.0926; and more polar **24** (18.6 mg, 25%) as a colourless oil. ν_{max} (film) 2947, 1716, 1641, 1439, 1405, 1308, 1249, 1202, 1175, 1109, 818 cm^{-1}; ^1H NMR (250 MHz; $CDCl_3$) 6.20 (1H, dt, 11.5, 7.6 Hz), 5.81 (1H, dt, 11.5, 1.6 Hz), 3.74 (4H, s), 3.70 (3H, s), 2.66 (2H, dq, 1.5, 7.6 Hz), 2.23 (2H, t, 7.7 Hz), 1.78 (3H, s), 1.54 (2H, quintet, 7.7 Hz); *m / z* 258 (M^+), 227, 194 (M^+-SO_2), 162 (M^+-SO_2-MeOH), 161, 100, 95, 81; Observed (M^+): 258.0931; $C_{12}H_{18}O_4S$ requires: 258.0926.

(2*Z*,6*E*)-Methyl 7,8-dimethyl-2,6,8-nonatrienoate (25). A solution of **23** (6.6 mg, 25.5 µmol) in toluene (2 ml) was refluxed for 36 hours. On cooling, the solvent was removed under reduced pressure. Repeated column chromatography (5% ether / petrol then 0-2% ether / petrol) gave **25** (4.8 mg, 97%) as a colourless liquid. ν_{max} (film) 2947, 1722, 1641, 1436, 1171, 819 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 6.24 (1H, dt, 11.5, 7.5 Hz), 5.80 (1H, dt, 11.5, 1.6 Hz), 5.60 (1H, bt, 7.1 Hz), 4.99 (1H, m), 4.89 (1H, bs), 3.71 (3H, s), 2.77 (2H, dq, 1.7, 7.6 Hz), 2.30 (2H, q, 7.5 Hz), 1.89 (3H, d, 1.0 Hz), 1.81 (3H, s).

(*Z*)-Methyl 8-methyl-7-methylene-2,8-nonadienoate (26). A solution of **24** (14.3 mg, 55.4 µmol) in toluene (2 ml) was refluxed for 50 hours. On cooling, the solvent was removed under reduced pressure. Column chromatography (5% ether / petrol) gave **26** (8.9 mg, 83%) as a colourless liquid. ν_{max} (film) 2946, 1722, 1641, 1596, 1436, 1405, 1198, 1174, 891, 818 cm^{-1}; ^1H NMR (250 MHz; $CDCl_3$) 6.24 (1H, dt, 11.5, 7.5 Hz), 5.79 (1H, dt, 11.5, 1.8 Hz), 5.09 (1H, d, 0.7 Hz), 5.07 (1H, m), 4.96 (2H, m), 3.71 (3H, s), 2.68 (2H, dq, 1.7, 7.5 Hz), 2.32 (2H, t, 7.7 Hz), 1.90 (3H, s), 1.63 (2H, quintet, 7.8 Hz); *m / z* 194 (M^+), 179 (M^+-Me), 151, 81; Observed (M^+): 194.1309; $C_{12}H_{18}O_2$ requires: 194.1307.

(1α, 3aβ, 6α, 6aα)-Octahydro-3a-methyl-3-methylene-6-(phenylmethoxy)-1-pentalenemethanol (28) and (1α, 3aα, 6β, 6aβ)-octahydro-3a-methyl-3-methylene-6-(phenylmethoxy)-1-pentalenemethanol (29). To tris(dibenzylidineacetone) dipalladium (86.3 mg, 94 µmol) in toluene (7 ml) was added triisopropyl phosphite (190 µl, 0.77 mmol). The resulting mixture was sonicated for 20 minutes, giving a pale green solution. Ester **14** (380 mg, 1.26 mmol) in toluene (8 ml) was added, and the resulting solution refluxed for 10 days. On cooling, the solvent was removed under reduced pressure. Column chromatography (0-10% ether / petrol) gave a diastereomeric mixture of bicycles (165 mg, 43%) as a yellow oil. To this mixture in toluene (10 ml) cooled to -78°C, was added DIBAL (1.5M in toluene, 810 µl, 1.22 mmol) dropwise. After 30 minutes, the solution was warmed to room temperature and quenched with water (1 ml), ethyl acetate (10 ml) and Na_2SO_4. The mixture was filtered with ethyl acetate and the solvent

removed under reduced pressure. Column chromatography (20-40% ether / petrol) gave less polar **28** (104 mg, 30%) as a colourless oil. ν_{max} (film) 3463, 2930, 2870, 1656, 1450, 1374, 1079, 1051, 1028, 738, 698 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) 7.37-7.30 (5H, m), 4.64 (1H, m), 4.61 (1H, m), 4.56 (1H, d, 11.1 Hz), 4.45 (1H, d, 11.1 Hz), 3.93 (1H, ddd, 10.3, 8.1, 4.9 Hz), 3.68 (1H, ddd, 12.0, 10.8, 4.4 Hz), 3.57 (1H, dd, 12.0, 1.1 Hz), 3.26 (1H, bt, 10.5 Hz), 2.87 (1H, ddt, 17.2, 8.9, 2.5 Hz), 2.55 (1H, ddd, 16.8, 13.9, 8.3 Hz), 2.25 (1H, m), 2.13 (1H, ddt, 17.2, 7.5, 1.9 Hz), 2.05 (1H, m), 1.81 (1H, t, 10.3 Hz), 1.72 (1H, m), 1.55 (1H, ddd, 11.8, 8.8, 2.1 Hz), 0.96 (3H, s); ^{13}C NMR (67.9 MHz; $CDCl_3$) 155.1 (s), 137.4 (s), 128.7 (d), 128.2 (d), 128.1 (d), 102.1 (t), 77.1 (d), 72.2 (t), 67.4 (t), 65.4 (d), 55.3 (s), 38.4 (d), 37.6 (t), 34.1 (t), 31.3 (t), 20.8 (q); *m / z* 272 (M^+), 243, 197, 181, 163, 151, 135, 91 ($C_7H_7^+$); Observed (M^+): 272.1779; $C_{18}H_{24}O_2$ requires: 272.1776; and more polar **29** (19.1 mg, 6%) as a colourless oil. ν_{max} (film) 3390, 2927, 1658, 1450, 1028, 736, 698 cm^{-1}; ^1H NMR (500 MHz; C_6D_6) 7.34-7.07 (5H, m), 4.65 (1H, m), 4.62 (1H, m), 4.39 (1H, d, 11.7 Hz), 4.30 (1H, d, 11.7 Hz), 3.89 (1H, ddd, 10.7, 8.3, 4.5Hz), 3.70 (1H, dd, 10.3, 8.2 Hz), 3.36 (1H, dd, 10.3, 7.7 Hz), 2.64-2.59 (1H, m), 2.54-2.48 (1H, m), 2.33 (1H, dd, 10.7, 8.8 Hz), 2.27 (1H, ddd, 17.1, 13.9, 8.6 Hz), 2.23-2.18 (1H, m), 1.94-1.88 (1H, m), 1.60 (1H, m), 1.25 (1H, ddd, 11.4, 8.7, 1.6 Hz), 0.82 (3H, s), 0.46 (1H, bs); *m / z* 272 (M^+), 257 (M^+-Me), 254 (M^+-H_2O), 243, 107, 91 ($C_7H_7^+$); Observed (M^+): 272.1779; $C_{18}H_{24}O_2$ requires: 272.1776.

(1α,3aβ,6α,6aα)-Octahydro-3a-methyl-3-methylene-6-(phenylmethoxy)-1-pentalene-carboxylic acid (31). To a solution of oxalyl chloride (20 µl, 230 µmol) in DCM (1 ml) cooled to -78°C, was added DMSO (33 µl, 470 µmol) dropwise. The solution was stirred for 5 minutes, then **28** (43.6 mg, 160 µmol) in DCM (1.5 ml) was added dropwise giving a white precipitate. The mixture was stirred for 20 minutes, triethylamine (100 µl, 720 µmol) was added and, after stirring for a further 5 minutes at -78°C, allowed to warm to room temperature. The reaction mixture was poured into water (10 ml) and extracted with DCM (3 x 10 ml). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. Column chromatography (10% ether / petrol) gave the aldehyde (39.7 mg). To this material in *tert*-butanol (0.5 ml) and water (0.5 ml) was added potassium dihydrogen phosphate (65 mg, 480 µmol), 2-methyl-2-butene (100 µl, 940 µmol) and sodium chlorite (38 mg, 420 µmol). The resulting mixture was stirred for 1 hour, cooled to 0°C and saturated sodium sulphite solution (2 ml) added. After 5 minutes, the mixture was poured into water (10 ml) and extracted with DCM (6 x 10 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (ether) gave **31** (16.3 mg, 36%) as a white solid. Recrystallisation from acetone / water gave needles suitable for x-ray diffraction (m.p. 128-129°C). ν_{max} (film) 2959, 1690, 1439, 1337, 1309, 1240, 1111, 695 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) 7.36-7.28 (5H, m), 4.69 (2H, m), 4.60 (1H, d, 11.6 Hz), 4.50 (1H, d, 11.6 Hz), 3.98 (1H, ddd, 10.3, 8.3, 4.9 Hz), 3.19 (1H, ddt, 17.3, 9.5, 2.4 Hz), 2.99-2.87 (2H, m), 2.55 (1H, ddd, 16.9, 14.1, 8.4 Hz), 2.35 (1H, dd, 12.1, 10.3 Hz), 2.05 (1H, m), 1.76 (1H, m), 1.55 (1H, ddd, 12.0, 8.9, 2.0 Hz), 0.93 (1H, s); *m / z* (ACE, NH_3) 304 (M^++NH_3), 287 (MH^+), 269 (MH^+-H_2O), 251, 91 ($C_7H_7^+$); Observed (MH^+): 287.1647; $C_{18}H_{23}O_3$ requires 287.1647.

(1α,3aβ,6α,6aα)-Methyl octahydro-3a-methyl-3-methylene-6-(phenylmethoxy)-1-pentalenecarboxylate (27). An ethereal solution of diazomethane was added portionwise to a stirred solution of **31** (5.6 mg, 19.6 µmol) in ether (1 ml). On complete consumption of the starting material, the

solvent was removed *in vacuo*. Column chromatography gave **27** (4.8 mg, 82%) as a colourless oil. ν_{max} (film) 2958, 1733, 1657, 1433, 1273, 1201, 1171, 1099 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) 7.34-7.24 (5H, m), 4.67 (2H, m), 4.47 (1H, d, 11.9 Hz), 4.39 (1H, d, 11.9 Hz), 3.88 (1H, ddd, 9.9, 8.6, 4.6 Hz), 3.66 (3H, s), 3.07 (1H, ddt, 17.2, 9.1, 2.4 Hz), 2.96 (1H, ddt, 17.2, 7.6, 2.0 Hz), 2.82 (1H, ddd, 12.0, 9.1, 7.6 Hz), 2.53 (1H, m), 2.42 (1H, dd, 12.0, 9.9 Hz), 2.02 (1H, m), 1.72 (1H, m), 1.49 (1H, ddd, 11.7, 8.9, 1.8 Hz), 0.92 (3H, s); *m / z* (ACE, NH_3) 301 (MH^+), 283 (MH^+-H_2O), 251 (MH^+-H_2O-MeOH), 91 ($C_7H_7^+$); Observed (MH^+): 301.1804; $C_{19}H_{25}O_3$ requires 301.1804.

[1(1α,3aα,6β,6aβ)]-[[Octahydro-3a-methyl-3-methylene-6-(phenylmethoxy)-1-pentalenyl]-methyl]-3,5-dinitrobenzoate (30). To a stirred solution of 3,5-dinitrobenzoyl chloride (21 mg, 92 μmol), triethylamine (20 μl, 140 μmol) and a trace of DMAP in DCM (0.3 ml) at 0°C was added **29** (19.1 mg, 70 μmol) in DCM (1.7 ml). After 10 minutes, the mixture was poured into water (10 ml) and extracted with DCM (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. Repeated column chromatography (20% ether / petrol then 10-15% ether / petrol) gave **30** (20.7 mg, 63%) as a white solid. Recrystallisation from EtOAc / petrol gave clear prisms suitable for x-ray diffraction (mp. 126-128°C). ν_{max} (film) 2957, 1726, 1540, 1459, 1343, 1278, 1164, 1113, 1074, 720 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) 9.03 (1H, d, 2.2 Hz), 8.95 (2H, t, 2.1 Hz), 7.147.10 (3H, m), 7.01 (2H, m), 4.76 (1H, dd, 10.8, 8.6 Hz), 4.68 (2H, m), 4.50 (1H, d, 12.2 Hz), 4.47 (1H, dd, 10.8, 7.2 Hz), 4.19 (1H, d, 12.2 Hz), 4.08 (1H, ddd, 10.8, 8.3, 4.5 Hz), 3.02-2.96 (1H, m), 2.81-2.72 (2H, m), 2.57 (1H, ddd, 17.1, 14.0, 8.6 Hz), 2.43 (1H, dd, 10.8, 8.5 Hz), 2.00 (1H, m), 1.71 (1H, m), 1.50 (1H, ddd, 11.8, 8.7, 1.6 Hz), 1.14 (3H, s); *m / z* 466 (M^+), 437, 225, 195, 163, 149, 91 ($C_7H_7^+$); Observed (M^+): 466.1734; $C_{25}H_{26}O_7N_2$ requires 466.1740.

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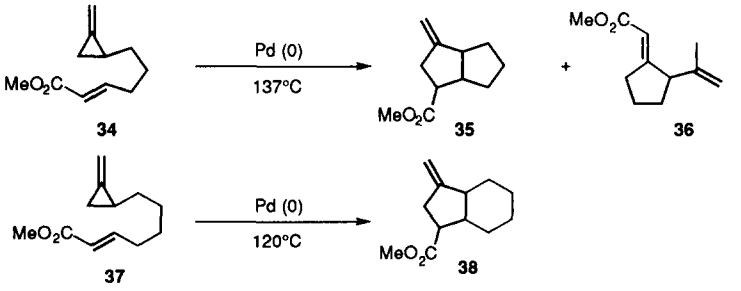
14. The (2*Z*, 6*E*) geometry of triene **25** was been tentatively assigned using a combination of decoupling and nOe experiments. Allylic coupling to the methyl groups resulted in broadening of these signals. Decoupling of each of the olefinics attached to C-9 (δ 4.99, δ 4.89) resulted in considerable sharpening of the downfield methyl group (δ 1.89). No change to the resonance associated with the upfield methyl group was observed (δ 1.81). Decoupling of H-6 produced the opposite effect: whilst the downfield methyl group remained unchanged, significant sharpening of the upfield methyl group occurred. From these decouplings, δ 1.89 and δ 1.81 were assigned to C-8-Me and C-7-Me respectively. Irradiation of the C-7-Me gave a nOe enhancement (1.5%) to the geminal CH_2 of C-5 suggesting the *E* geometry of this double bond. All other nOe measurements were consistent with this assignment.
15. We have effected the palladium catalysed cyclisations of two substrates closely related to **13** using modified cyclisation conditions (η^3-allyl-η^5-cyclopentadienylpalladium, P^iPr_3, *o*-xylene). Using this procedure, methylenecyclopropane **34** furnished the corresponding bicyclo[3.3.0]octane **35** in 30% yield. An additional product, tentatively assigned as the cyclopentene **36** (21%) was isolated from the reaction mixture. Cyclisation of homologue **37** furnished the corresponding bicyclo[4.3.0]nonane **38** in 87% yield as a 65:35 mixture of two stereoisomers. Unfortunately, exhaustive NMR studies failed to unambiguously establish the relative stereochemical relationships within the bicycles **35** and **38**.



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