Pergamon

Tetrahedron Vol. 51, No. 11, pp. 3303-3318, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00052-6

Intramolecular Palladium Catalysed [3+2] Cycloadditions of Methylenecyclopropanes with Acetylenic Acceptors

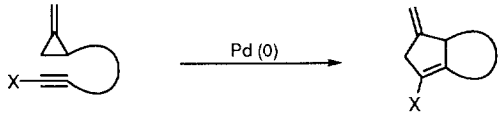
Hervé Corlay, Richard T. Lewis, William B. Motherwell,¶* and Michael Shipman§

Department of Chemistry, Imperial College of Science, Technology and Medicine, London, SW7 2AY, U.K.

Abstract: The synthesis and intramolecular palladium catalysed cycloaddition reactions of eight methylenecyclopropanes containing alkyne acceptors are described. Bicyclo[3.3.0]octane and bicyclo[4.3.0]nonane rings systems can be successfully accessed using this chemistry. The nature of the substituents attached to the alkyne acceptor play a key role in the efficiency of the cycloaddition.

INTRODUCTION

In 1988, we reported the first examples of the palladium catalysed intramolecular [3+2] cycloaddition of diphenylmethylenecyclopropanes with electron deficient olefinic and acetylenic acceptors.[1] While these substrates displayed good reactivity in the palladium catalysed reactions, they were nevertheless more difficult to prepare and the incorporation of the diarylidene unit in the cycloadducts limited their synthetic utility. Since that time, further studies by ourselves[2] and others[3] have extended this methodology to the corresponding methylenecyclopropanes which are generally easier to prepare and yield more synthetically versatile cycloadducts. In this paper, we wish to disclose in detail our findings on such palladium catalysed cycloadditions using acetylenic acceptors and outline the scope and limitations of this approach to fused bicyclic systems (Scheme 1). Specifically, the investigations we describe focus on how the length of the linking tether between the methylenecyclopropane and the acceptor, and the nature of the acetylenic substituent, X, influence the outcome of these reactions. Additional studies examining how heteroatom substituents in the tether can influence the outcome of these cyclisations are also presented.



Scheme 1

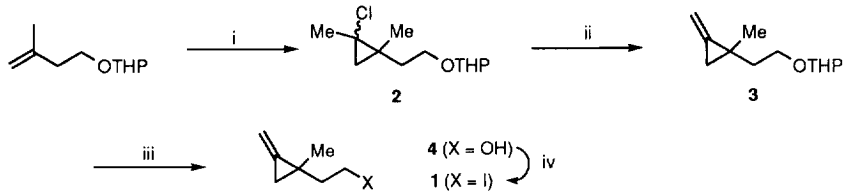
RESULTS AND DISCUSSION

Cycloadditions Using Different Linking Tether Lengths.

Synthesis of Cyclisation Precursors. We envisaged that a variety of carbocyclic ring systems could be accessed using this methodology by simply varying the number of atoms contained within the linking tether. To test this hypothesis we synthesised cyclisation precursors anticipated to provide entry to bicyclo[3.3.0]octane,

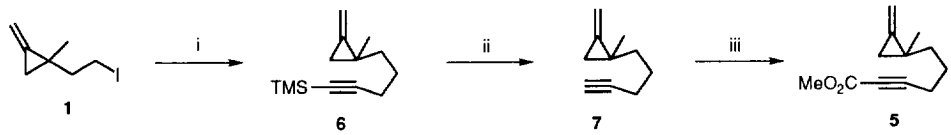
¶ Present address: Christopher Ingold Laboratories, Department of Chemistry, University College, London, WC1H 0AJ, U.K.
§ Present address: Department of Chemistry, Loughborough University of Technology, Loughborough, Leics., LE11 3TU, U.K.

bicyclo[4.3.0]nonane and bicyclo[5.3.0]decane ring systems. In each case, the same methylenecyclopropane building block **1** was utilised. This material was prepared in a concise and efficient fashion from a protected form of 3-methyl-3-buten-1-ol (Scheme 2). Thus, treatment of tetrahydro-2-[(3-methyl-3-butenyl)oxy]-2H-pyran[4] with methyl chlorocarbene, generated from 1,1-dichloroethane and butyllithium at -35°C, gave chlorocyclopropane **2**.[5] Dehydrohalogenation to methylenecyclopropane **3** was achieved in a straightforward manner using potassium *tert*-butoxide in dimethyl sulphoxide. Removal of the hydroxyl protecting group with tosic acid, gave **4** which was subsequently converted to the desired iodide.[6]



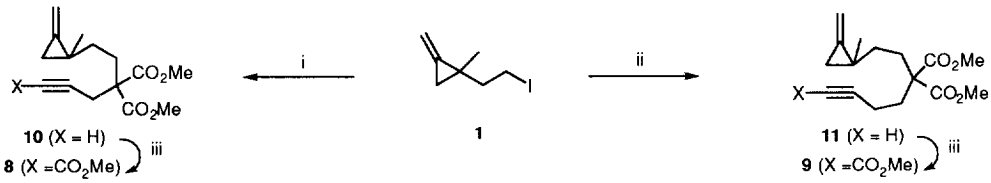
Scheme 2. (i) 1,1-dichloroethane, n-BuLi, -35°C, Et_2O, 82%; (ii), ^tBuOK, DMSO, 80°C, 88%; (iii), p-TsOH, MeOH, 85%; (iv), I_2, PPh_3, MeCN, 86%.

The bicyclo[3.3.0]octane precursor **5** was prepared from **1** using the sequence outlined in Scheme 3. Deprotonation of 1-trimethylsilyl-1-propyne with butyllithium in the presence of tetramethylethylenediamine and subsequent alkylation with **1** provided methylenecyclopropane **6**.[7] Removal of the trimethylsilyl group using tetrabutylammonium fluoride proceeded uneventfully to give the corresponding terminal acetylene **7**. Deprotonation of this material with butyllithium and subsequent quenching of the anion with methyl chloroformate afforded cyclisation precursor **5** in 53% overall yield.



Scheme 3. (i) $H_3CC{\equiv}CTMS$, n-BuLi, TMEDA, Et_2O, 0°C, 73%; (ii) TBAF, THF, rt, 77%; (iii) n-BuLi, THF, -78°C, MeO_2CCl, 95%.

Iodide **1** was also converted to the bicyclo[4.3.0]nonane and bicyclo[5.3.0]decane precursors **8** and **9** using simple malonate chemistry (Scheme 4). Thus, alkylation with dimethyl 3-butyne-1,1-dicarboxylate gave terminal acetylene **10** which was further alkylated with methyl chloroformate to provide precursor **8**. Higher homologue **9** was synthesised using a similar sequence *via* **11** using dimethyl 4-pentyne-1,1-dicarboxylate.



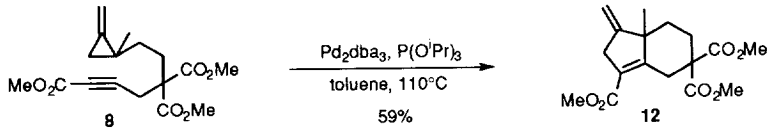
Scheme 4. (i) NaH, DMF, dimethyl 3-butyne-1,1-dicarboxylate, 77%; (ii) NaH, DMF, dimethyl 4-pentyne-1,1-dicarboxylate, 68%; (iii) BuLi, THF, MeO_2CCl, 86% for **10**, 80% for **11**.

Cyclisation Studies. Before discussing the outcome of specific cycloadditions some general comments concerning the cyclisation reactions are appropriate. All of the cycloaddition studies described in this paper utilised the same convenient catalyst system prepared *in situ* from either bis(dibenzylideneacetone) palladium or tris(dibenzylideneacetone) dipalladium by addition of four equivalents of triisopropyl phosphite. The

cyclisations were performed by simply refluxing the substrate in toluene in the presence of 5-20 mol% of this catalyst mixture.

It is important to note that whilst all the cyclisations described in this paper involve geminally disubstituted methylenecyclopropanes, we have successfully accomplished intramolecular cycloadditions with both monosubstituted[2a] and 1,2-disubstituted methylenecyclopropanes.[8] Our selection of the methyl substituted derivatives for these studies stems in part from the fact that many important polyquinane and related natural products contain such angular substituents.[9] These systems possess an additional attribute from a practical point of view insofar as they contain a useful nmr 'handle' for structural elucidation work.

Our initial cyclisation studies focused on the bicyclo[4.3.0]nonane system. Thus, palladium catalysed cycloaddition of acetylenic ester **8** gave cycloadduct **12** in a regiospecific fashion *via* cleavage of the distal bond (C2-C3) of the cyclopropane ring (Scheme 5).[2a] This mode of cycloaddition is in complete agreement with previous intermolecular precedent.[10]



Scheme 5

The structure of **12** was unambigously determined using a series of nmr studies. The bicyclic nature of the adduct and the connectivity patterns within the structure were established using ^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY and selective decoupling experiments. These results were further supported by nOe measurements which confirmed the location of the exocyclic double bond (Figure 1). Irradiation of the angular methyl group produced an nOe enhancement of one of the exomethylene hydrogens assigned as H_{cis}. Irradition of this olefinic hydrogen gave an enhancement of the one of the hydrogens attached to C-7, while irradiation of the other olefinic hydrogen, H_{trans}, enhanced only the downfield methylene grouping of C-2. These results establish that the exomethylene double bond is located next to the ring junction confirming that cycloaddition occurred *via* distal cleavage of the methylenecyclopropane.

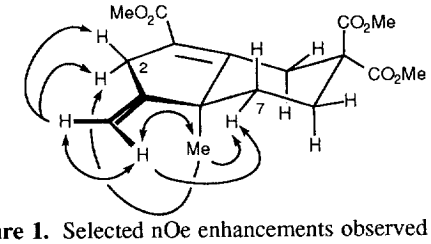
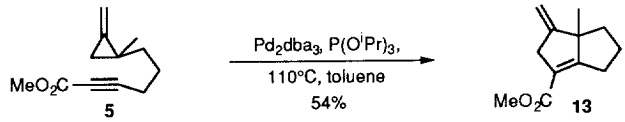


Figure 1. Selected nOe enhancements observed for **12**

In an analogous fashion, acetylenic ester **5** provided the bicyclo[3.3.0]octane derivative **13** in 54% yield (Scheme 6). Again, all spectroscopic evidence was consistent with cycloaddition across the distal bond of the methylenecyclopropane.

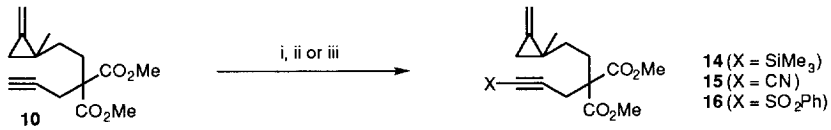


Scheme 6

In contrast to the successes accomplished with **5** and **8**, all attempts to cyclise **9** to the hydroazulene skeleton under similar conditions were unsuccessful. The only identifiable product from the complex reaction mixture was recovered starting material, isolated in 50% yield. The simplest explanation for the failure of this reaction is that it probably involves the development of unfavourable transannular interactions which prevent the two reaction centres from approaching one another. Interestingly, Trost and coworkers experienced a similar lack of success in attempting to prepare bicyclo[5.3.0]decanes using palladium trimethylenemethane species (Pd-TMM's) derived from 2-trimethylsilylmethyl substituted allylic acetates.[11,12]

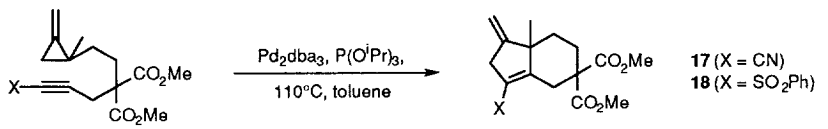
Cycloaddition Studies Employing Different Acetylenic Acceptors.

Synthesis of Cyclisation Precursors. In contrast to Pd-TMM's derived from 2-trimethylsilylmethyl substituted allylic acetates, the species derived from methylenecyclopropanes have been shown to undergo cycloadditions with simple olefins as well as electron deficient alkenes.[10] However, much less information has been obtained concerning the intermolecular reactions of methylenecyclopropanes with acetylenic acceptors. In the presence of phosphine modified nickel catalysts, it has been established that efficient cycloadditions can be accomplished with silyl substituted acetylenes *via* cleavage of the distal bond of the cyclopropane ring.[13] In order to assess what types of alkyne can be tolerated in the intramolecular reaction and to gain some mechanistic insight into the cyclisation process we have undertaken a series of reactions using different acetylenic acceptors. Alkyne **10** was selected for these studies since it had already been shown that this material undergoes efficient cyclisation to the bicyclo[4.3.0]nonane system when activated by a carbomethoxyl group. Furthermore, it was anticipated that little new synthetic chemistry would be required to introduce a variety of different acetylenic acceptors. Indeed, quenching of the lithio anion of this material with trimethylsilyl chloride and tosyl cyanide afforded cyclisation precursors **14** and **15** respectively. The preparation of the analogous sulphone **16** proved somewhat problematic. Attempts to prepare this material by quenching the lithio anion of acetylene **10** with phenyl tosylate failed.[14] However, the desired sulphone precursor could be synthesised by quenching the lithio anion of the acetylene with diphenyl disulphide to yield the acetylenic sulphide, which could be subsequently oxidised to the corresponding sulphone using Oxone® albeit in rather poor overall yield.



Scheme 7. (i) n-BuLi, -78°C, THF, TMSCl, 96%; (ii) n-BuLi, -78°C, THF, TsCN, 55%; (iii) n-BuLi, -78°C, THF, PhSSPh then Oxone®, MeOH/THF/H_2O, 33%.

Cyclisation Studies. The palladium catalysed cycloadditions of nitrile **15** and sulphone **16** proceeded smoothly yielding bicycles **17** and **18** in unoptimised yields of 44% and 41% respectively. To our surprise, all attempts to cyclise the silyl substituted acetylene **14** were unsuccessful. Cycloaddition studies using this type of catalyst system with terminal acetylenes have also proven equally fruitless.[15]



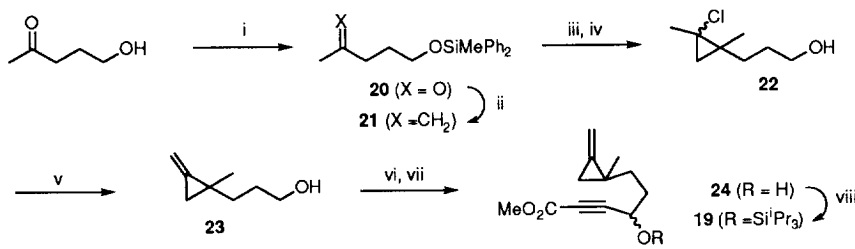
Scheme 8

While the requirement for an electronwithdrawing group to faciliate these cyclisations is clearly a limitation of this methodology it is apparent that a variety of electronegative substituents can nevertheless be tolerated. Particulary noteworthy is the success achieved using the phenylsulphonyl group (**16** to **18**) since reductive removal of this functionality could, in principle, provide access to the parent hydrocarbon. Mechanistically, these results suggest that the cycloaddition reactions may be considered to proceed in a stepwise fashion *via* conjugate addition of the Pd-TMM species to the β-carbon of the alkyne followed by a subsequent ring closure step.[16]

Cycloadditions Involving Heteroatom Functionalised Tethers.

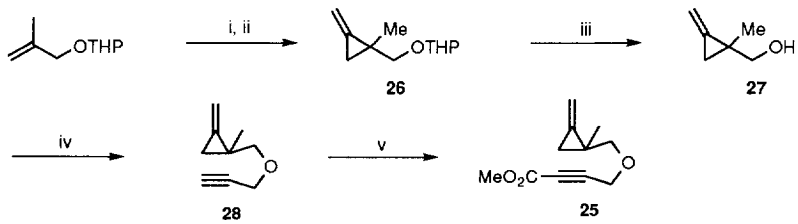
Synthesis of Cyclisation precursors. The utility of this intramolecular cycloaddition protocol would be significantly enhanced if heteroatoms could be tolerated in this reaction either as simple substituents or indeed as part of the linking chain. In order to gain some preliminary data on this subject we have examined the cycloaddition reactions of two further precursors which incorporate oxygen substituents.

Silyloxy substituted bicyclo[3.3.0]octane precursor **19** was readily prepared from 5-hydroxy-2-pentanone according to the following sequence (Scheme 9). Protection of the hydroxyl group as the diphenylmethylsilyl ether gave **20** and subsequent Wittig olefination provided alkene **21**.[17] Introduction of the cyclopropane ring was again accomplished *via* the already established methylchlorocarbene addition protocol. Removal of the silicon protecting group at this stage was necessary in order to facilitate separation of the product from traces of unreacted olefin. Treatment of purified **22** with potassium *tert*-butoxide then introduced the exocyclic double bond furnishing **23**. Oxidation of this alcohol under Swern conditions gave the corresponding aldehyde, which, due to its volatility, was used without purification. Low temperature addition of the lithium anion of methyl propiolate to this aldehyde gave acetylenic alcohol **24**, in 51% yield over the two steps. Interestingly, the initial alkoxide anion produced in the addition reaction proved quite unstable and it was necessary to quench this reaction at low temperature with acetic acid to prevent extensive decomposition. Finally, treatment of **24** with triisopropylsilyl chloride gave **19**, as a 1:1 mixture of diastereomers.



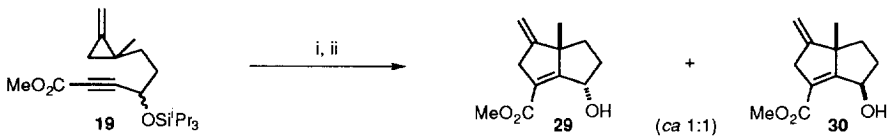
Scheme 9. (i) $Ph_2MeSiCl$, Et_3N, 59%; (ii) $MePPh_3^+Br^-$, n-BuLi, THF, 77%; (iii) 1,1-dichloroethane, n-BuLi, -35°C, Et_2O; (iv) TBAF, THF, 80% from **21**; (v) ^tBuOK, DMSO, 80°C, 60%; (vi) $(COCl)_2$, DMSO, Et_3N, -78°C, DCM; (vii) $LiC{\equiv}CCO_2Me$, THF, -78°C, 51% from **23**; (viii) $^iPr_3SiCl$, imidazole, DMF, 73%.

The second precursor, ether **25** was prepared in a straightforward fashion using the following synthetic sequence (Scheme 10). Alcohol **27** was derived from tetrahydro-2-[(2-methyl-2-propenyl)oxy]-2H-pyran[18] using an analogous protocol to that previously described for the preparation of **4**. Treatment of **27** with sodium hydride and subsequent alkylation with propargyl bromide led to the formation of terminal acetylene **28**. The synthesis of a suitably functionalised cyclisation precursor was completed by introduction of the electronwithdrawing carbomethoxyl group.



Scheme 10. (i) 1,1-dichloroethane, n-BuLi, -35°C, Et_2O, 64%; (ii) ^tBuOK, DMSO, 80°C, 78%; (iii), p-TsOH, MeOH, 89%; (iv) NaH, THF, propargyl bromide, 74%; (v) n-BuLi, MeO_2CCl, THF, -78°C, 89%.

Cyclisation Studies. Treatment of methylenecyclopropane **19** with tris(dibenzylideneacetone) dipalladium and triisopropylphosphite, in refluxing toluene, gave a chromatographically inseparable mixture of products. ^1H nmr analysis of this material revealed the formation of two products in an essentially 1:1 ratio. Deprotection of this mixture with tetrabutylammonium fluoride enabled the separation of bicyclo[3.3.0]octanes **29** and **30** in 29% and 32% yields respectively from methylenecyclopropane **19**. As in the case of the diphenylmethylenecyclopropane cyclisations,[1] the product ratio closely parallels the diastereomeric ratio of the starting material. The structures of these bicycles were again elucidated by nmr studies and their relative stereochemistry tentatively assigned on the basis of nOe measurements. Clearly suitably protected hydroxyl substituents can be introduced into this cyclisation protocol without detrimental effects.[19,20] To our surprise however, attempts to cyclise **25** to the corresponding tetrahydrofuran derivative using our standard catalyst system were unsuccessful and instead led to the formation of complex mixture of products. Nmr analysis suggested that ring opening of the methylenecyclopropane to conjugated dienes had occurred, a side reaction which we have observed previously.[2b]



Scheme 11. (i) Pd_2dba_3, $P(O^iPr)_3$, toluene, 110°C; (ii) TBAF, THF, 61% from **19**.

The foregoing examples clearly highlight that the intramolecular variant of the palladium catalysed [3+2] cycloaddition process is a useful strategy for controlling regioselectivity and minimising unwanted dimerisation reactions. It is also evident however that subtle changes particularly in the nature of the tethering chain may have a profound effect on the efficiency of these cyclisation reactions.

EXPERIMENTAL

General. ^1H and ^{13}C nmr spectra were recorded at 90 MHz on a Jeol FX-90Q instrument, at 250 MHz on a Bruker WM-250 instrument, at 270 MHz and 67.9 MHz respectively 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. Cycloaddition reactions were carried out in glassware washed with sodium hydroxide solution, water and finally acetone prior to drying.

2-[2-(2-Chloro-1,2-dimethyl-1-cyclopropyl)ethyloxyltetrahydro-2H-pyran (2). To tetrahydro-2-[(3-methyl-3-butenyl)oxy]-2H-pyran[4] (23.6 g, 139 mmol) and 1,1-dichloroethane (3.25 ml, 38.7 mmol) in diethyl ether (80 ml) at -35°C was added butyllithium (2.5M solution in hexanes, 55.5 ml, 139 mmol) dropwise over 4.5 hours, by means of a syringe pump. Further portions of 1,1-dichloroethane (2.25 ml, 26.8 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 addition repeated. The solution was again warmed to room temperature and stirred overnight. The reaction mixture was poured into water (100 ml) and the organic phase separated and dried over $MgSO_4$. Removal of the solvent under reduced pressure and subsequent distillation of the residue gave **2** (26.4 g, 82%) as a clear liquid (b.p. 112-115°C / 6 mmHg) and as a mixture of diastereomers. ν_{max} (film) 2941, 2871, 1440, 1381, 1352, 1201, 1183, 1136, 1079, 1032, 986 cm^{-1} ; ^1H NMR (270 MHz; $CDCl_3$) 4.60 (1H, m), 3.99-3.82 (2H, m), 3.64-3.44 (2H, m), 2.06-1.47 (8H, m), 1.70, 1.69, 1.65, 1.32, 1.31 and 1.13 (6H, 6 x s, 2 x CH_3), 0.92-0.56 (2H, m); *m / z* 197 (M^+-Cl), 179 (M^+-Cl-H_2O), 159, 85 ($C_5H_9O^+$); Found: C 61.77, H 9.14%; $C_{12}H_{21}O_2Cl$ requires: C 61.93, H 9.09%.

Tetrahydro-2-[2-(1-methyl-2-methylene-1-cyclopropyl)ethyloxy]-2H-pyran (3). To a stirred solution of potassium *tert*-butoxide (24.0 g, 214 mmol) in DMSO (35 ml) at 70°C was added **2** (26.3 g, 113 mmol) dropwise. After heating for 5.5 hours the resulting dark brown solution was cooled, poured into ice-cold water and extracted with ether (3 x 150 ml). The combined organic layers were washed with water and dried over $MgSO_4$. Removal of the solvent under reduced pressure and subsequent distillation of the residue gave **3** (19.5 g, 88%) as a clear liquid (b.p. 82-850C / 4 mmHg) and as a 1:1 mixture of diastereomers. ν_{max} (film) 2938, 2870, 1201, 1122, 1078, 1033, 983, 884, 871 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.39 (0.5H, dt, 1.0, 2.4 Hz), 5.38 (0.5H, dt, 1.0, 2.4 Hz), 5.29 (0.5H, bs), 5.28 (0.5H, bs), 4.59 (1H, m), 3.93-3.78 (2H, m), 3.55-3.40 (2H, m), 1.95-1.45 (8H, m), 1.17 (3H, s), 1.02 (1H, dt, 8.5, 2.0 Hz), 0.98 (1H, dq, 8.5, 2.0 Hz); *m / z* 196 (M^+), 165, 151, 123, 115, 94, 85 ($C_5H_9O^+$); Found: C 73.60, H 10.51%; $C_{12}H_{20}O_2$ requires: C 73.43, H 10.27%.

1-Methyl-2-methylenecyclopropane-ethanol (4). To a stirred solution of **3** (19.5 g, 99.4 mmol) in MeOH (300 ml) was added *p*-toluenesulphonic acid (4.14 g, 21.8 mmol). After 2 days, the reaction mixture was neutralised by addition of potassium carbonate, and the methanol removed by distillation at atmospheric pressure. The residue was diluted with water (250 ml), extracted with ether (3 x 150 ml) and the combined organic layers dried over $MgSO_4$. Removal of the solvent under reduced pressure at 5°C, and subsequent distillation of the residue gave **4** (9.58 g, 85%) as a colourless liquid (b.p. 76-78°C / 25 mmHg). ν_{max} (film) 3331, 3065, 2927, 1443, 1376, 1086, 1055, 1029, 885 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.41 (1H, dt, 1.0, 2.4 Hz), 5.34 (1H, bs), 3.74 (2H, dt, 5.6, 6.6 Hz), 1.80 (1H, dt, 13.9 Hz, 6.6 Hz), 1.58 (1H, dt, 13.9, 6.8 Hz), 1.33 (1H, t, 5.6 Hz), 1.17 (3H, s), 1.04 (1H, dt, 8.8, 2.2 Hz), 0.95 (1H, dt, 8.6, 2.2 Hz); *m / z* 97 (M^+-CH_3), 94 (M^+-H_2O), 83, 79, 67; Found: C 74.75, H 10.85%; $C_7H_{12}O$ requires: C 74.95, H 10.78%.

1-(2-Iodoethyl)-1-methyl-2-methylenecyclopropane (1). To a stirred solution of **4** (0.82 g, 7.31 mmol) in ether (60 ml) and acetonitrile (20 ml) was added triphenylphosphine (2.85 g, 10.9 mmol), imidazole (0.83 g, 12.2 mmol) and finally iodine (2.91 g, 11.5 mmol). After stirring for 15 minutes, the resulting red solution was diluted with ether (100 ml), washed with 5% sodium thiosulphate solution (75 ml), then water (75 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue triturated with petrol and filtered through a short plug of silica. Removal of the solvent under reduced pressure and distillation

of the residue gave **1** (1.40 g, 86%) as a colourless liquid (b.p. 60-64°C / 6 mmHg). ν_{max} (film) 3065, 3036, 2964, 2923, 1746, 1443, 1376, 1171, 889 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.43 (1H, dt, 1.1, 2.6 Hz), 5.33 (1H, bs), 3.20 (2H, m), 2.07 (1H, ddd, 13.9, 10.3, 6.1 Hz), 1.92 (1H, ddd, 13.9, 10.5, 6.1 Hz), 1.16 (3H, s), 1.05 (1H, dt, 8.9, 2.1 Hz), 0.97 (1H, dt, 8.8, 2.1 Hz); *m / z* 222 (M^+), 221 (M^+-H), 95 (M^+-I), 79, 41; Observed (M^+): 221.9901; $C_7H_{11}I$ requires 221.9906.

5-(1-Methyl-2-methylene-1-cyclopropyl)-1-trimethylsilyl-pent-1-yne (6). To a solution of trimethylsilyl propyne (1.0 g, 9.1 mmol) in ether (25 ml) under argon at -5°C was added tetramethylethylenediamine (1.5 ml, 9.9 mmol) and n-butyllithium (1.6 M in hexanes, 6.2 ml, 10.0 mmol). The pale yellow solution was stirred at -5°C for 30 minutes and a solution of iodide **1** (1.78 g, 8.0 mmol) in ether (8 ml) was added. The mixture was stirred at 0°C for 15 hours, poured into water (50 ml), extracted with hexane, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by column chromatography (pentane) gave **6** (1.19 g, 73%) as a colourless oil. ν_{max} (film) 2955, 2865, 2174, 1744, 1452, 1400, 1375, 1325, 1249, 1037, 914, 843, 696 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.3 (2H, m), 2.2 (2H, m), 1.6-1.3 (4H, m), 1.1 (3H, s), 0.9 (2H, m), 0.1 (9H, s); ^{13}C NMR (125.8 MHz; $CDCl_3$) 142.9, 107.5, 101.4, 84.5, 37.0, 26.2, 21.5, 19.9, 19.5, 16.8, 0.1; *m / z* 206 (M^+), 191 (M^+-Me), 133, 117, 73; Observed (M^+-Me): 191.1253; $C_{12}H_{19}Si$ requires 191.1256.

1-(1-Methyl-2-methylene-1-cyclopropyl)-pent-4-yne (7). To a solution of **6** (0.57 g, 2.8 mmol) in THF (2 ml) at room temperature was added a solution of tetrabutylammonium fluoride (1.0 M in THF, 6.5 ml, 6.5 mmol). After 2 hours the mixture was poured into water (50 ml), extracted with hexane (3 x 50 ml) and the combined extracts were dried over $MgSO_4$. The solvent was distilled off and the residue distilled at atmospheric pressure to give **7** (0.29 g, 77%) as a colourless liquid, bp 135-145°C. ν_{max} (film) 3307, 2950, 2864, 2797, 2119, 1743, 1454, 1375, 1110, 1084, 885, 631 cm^{-1} ; ^1H NMR (270 MHz; $CDCl_3$) 5.3 (2H, m), 2.1 (2H, m), 1.9 (1H, t, 1.7 Hz), 1.7-1.3 (4H, m), 1.1 (3H, s), 0.9 (1H, dt, 2.0, 8.6 Hz) and 0.8 (1H, dt, 2.0, 8.6 Hz); ^{13}C NMR (125.8 MHz; $CDCl_3$) 142.9, 101.4, 84.5, 68.3, 36.9, 26.0, 21.6, 19.5, 18.4, 16.8; *m / z* 133 (M^+-H), 119 (M^+-Me), 105, 91; Observed (M^+-Me): 119.0859; C_9H_{11} requires 119.0860.

Methyl 5-(1-methyl-2-methylene-1-cyclopropyl)-pent-1-yne-1-carboxylate (5). To a solution of **7** (106.2 mg, 0.79 mmol) in THF (3 ml) stirred at -78°C under argon was added n-butyllithium (1.6 M in hexanes, 0.65 ml, 1.04 mmol) dropwise. The resulting pale yellow solution was stirred at -78°C for 45 minutes then methyl chloroformate (0.2 ml, 2.59 mmol) was added. After 2 hours, the mixture was allowed to warm to room temperature, poured into water (20 ml) and extracted with ether (3 x 20 ml). The combined extracts were washed with brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure to give **5** (145 mg, 95%) as a colourless oil which required no further purification. ν_{max} (film) 2950, 2236, 1714, 1432, 1256, 1076, 886, 752 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.3 (1H, dt, 1.4, 1.0 Hz), 5.2 (1H, bd, 0.7 Hz), 3.7 (3H, s), 2.3 (2H, dt, 7.1, 6.8 Hz), 1.7-1.3 (4H, m), 1.1 (3H, s), 0.9-0.7 (2H, m); ^{13}C NMR (125.8 MHz; $CDCl_3$) 154.2, 142.5, 101.7, 89.6, 73.0, 52.5, 36.9, 25.0, 21.5, 19.3, 18.7, 16.8; *m / z* 191 (M^+-H), 177 (M^+-Me), 133 (M^+-CO_2Me), 117, 105, 91; Observed (M^+-Me): 177.0916; $C_{11}H_{13}O_2$ requires 177.0916.

Dimethyl 1-(1-methyl-2-methylene-1-cyclopropyl)-5-hexyne-3,3-dicarboxylate (10). To sodium hydride (60% dispersion in mineral oil, 181 mg, 4.53 mmol) in DMF (1 ml) at 0°C was added dimethyl 3-butyne-1,1-dicarboxylate[21] (760 mg, 4.47 mmol) in DMF (2 ml). The resulting solution was warmed to room temperature and **1** (827 mg, 3.73 mmol) in DMF (2.5 ml) added. After stirring for 2.5 days, the reaction

was quenched by addition of saturated NH_4Cl solution (2 ml). The mixture was diluted with water (100 ml) and extracted with ether (3 x 50 ml). The combined organic layers were washed with brine (50 ml) and dried over Na_2SO_4. Removal of the solvent *in vacuo* and subsequent column chromatography (10% ether / petrol) gave **10** (761 mg, 77%) as a colourless oil. ν_{max} (film) 3290, 2954, 1735, 1435, 1285, 1230, 1202 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.38 (1H, dt, 1.0, 2.4 Hz), 5.26 (1H, m), 3.74 (3H, s), 3.73 (3H, s), 2.79 (2H, d, 2.7 Hz), 2.26-2.06 (2H, m), 2.01 (1H, t, 2.7 Hz), 1.32-1.13 (2H, m), 1.16 (3H, s), 0.93 (2H, m); *m / z* 232 (M^+-MeOH), 225, 217, 204, 193, 189, 145, 144; Found: C 67.93, H 7.66%; $C_{15}H_{20}O_4$ requires: C 68.16, H 7.63%.

Trimethyl 6-(1-methyl-2-methylene-1-cyclopropyl)-1-hexyne-1,4,4-tricarboxylate (8). To **10** (334 mg, 1.26 mmol) in THF (5 ml) stirred at -78°C was added butyllithium (2.2M in hexanes, 600 µl, 1.32 mmol) dropwise. The resulting pale yellow solution was stirred for 30 minutes at -78°C, then methyl chloroformate (295 µl, 3.82 mmol) was added. After stirring for 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 layers were washed with water (50 ml), dried over Na_2SO_4 and the solvent removed under reduced pressure. Column chromatography (10% ether / petrol) gave **8** (351 mg, 86%) as a colourless oil. ν_{max} (film) 2955, 2242, 1737, 1718, 1433, 1260, 1078, 752 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.39 (1H, dt, 0.9, 2.5 Hz), 5.27 (1H, m), 3.75 (3H, s), 3.74 (6H, s), 2.94 (2H, s), 2.26-2.06 (2H, m), 1.33-1.12 (2H, m), 1.16 (3H, s), 0.94 (2H, m); *m / z* 307 (M^+-Me), 289, 275, 231, 193, 79; Found: C 63.60, H 7.10%; $C_{17}H_{22}O_6$ requires: C 63.34, H 6.88%.

Dimethyl 4-pentyne-1,1-dicarboxylate. To sodium hydride (60%, 502 mg, 12.6 mmol) in DMF (5 ml) was added a solution of dimethyl malonate (1.66 g, 12.6 mmol) in DMF (10 ml) dropwise with stirring. After 20 minutes, 4-iodo-1-butyne[22] (2.14 g, 11.9 mmol) in DMF (5 ml) was added. After stirring overnight, the mixture was poured into water (100 ml) and extracted with ether (3 x 100 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (10% ether / petrol) gave dimethyl 4-pentyne-1,1-dicarboxylate (1.38 g, 63%) as a colourless oil. ν_{max} (film) 3287, 2954, 1732, 1433, 1350, 1248, 1202, 1157, 1049, 644 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 3.75 (6H, s), 3.62 (1H, t, 7.3 Hz), 2.33-2.26 (2H, m), 2.19-2.08 (2H, m), 1.99 (1H, t, 2.7 Hz); *m / z* 184 (M^+),169 (M^+-Me) 153, 132, 125, 113, 100; Found: C 58.66, H 6.56%; $C_9H_{12}O_4$ requires: C 58.69, H 6.57%.

Dimethyl 1-(1-methyl-2-methylene-1-cyclopropyl)-6-heptyne-3,3-dicarboxylate (11). To sodium hydride (60%, 79 mg, 1.97 mmol) in DMF (0.2 ml) at 0°C was added a solution of dimethyl 4-pentyne-1,1-dicarboxylate (335 mg, 1.82 mmol) in DMF (1.5 ml). The resulting solution was warmed to room temperature and **1** (323 mg, 1.45 mmol) in DMF (2 ml) added. After stirring for 2.5 days, the resulting orange solution was poured into water (50 ml) and extracted with ether (3 x 50 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (10% ether / petrol) gave **11** (274 mg, 68%) as a colourless oil. ν_{max} (film) 3294, 2953, 2924, 2120, 1730, 1432, 1274, 1222, 1198, 637 cm^{-1}. ^1H NMR (270 MHz; $CDCl_3$) 5.37 (1H, dt, 1.0, 2.6 Hz), 5.27 (1H, m), 3.72 (3H, s), 3.71 (3H, s), 2.18-1.89 (7H, m,), 1.33-1.11 (2H, m, 2 x H-1), 1.14 (3H, s), 0.91 (2H, m); *m / z* 278 (M^+), 263 (M^+-Me), 246 (M^+-MeOH), 159, 145, 119, 79; Found: C 68.78, H 7.76%; $C_{16}H_{22}O_4$ requires: C 69.04, H 7.97%.

Trimethyl 7-(1-methyl-2-methylene-1-cyclopropyl)-1-heptyne-1,5,5-tricarboxylate (9). To **11** (133 mg, 0.478 mmol) in THF (4 ml) stirred at -78°C was added n-butyllithium (2.5M in hexanes, 200 µl, 0.50 mmol) dropwise. The solution was stirred for 30 minutes at -78°C, then methyl chloroformate (95 µl, 1.23 mmol) was added. After 1 hour, the solution was allowed to warm to room temperature and quenched with saturated ammonium chloride solution. The mixture was diluted with water (50 ml) and extracted with ether (3 x 50 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (10-20% ether petrol) gave **11** (129 mg, 80%) as a colourless oil. ν_{max} (film) 2954, 2239, 1730, 1433, 1258, 1199, 1076, 752 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.37 (1H, dt, 1.0, 2.4 Hz), 5.27 (1H, m), 3.75 (3H, s), 3.73 (3H, s), 3.72 (3H, s), 2.35-1.87 (6H, m), 1.33-1.09 (2H, m), 1.13 (3H, s), 0.91 (2H, m); *m / z* 321 (M^+-Me), 289 (M^+-MeOH-Me), 261, 245, 217, 145; Found: C 64.31, H 7.16%; $C_{18}H_{24}O_6$ requires: C 64.27, H 7.19%.

Trimethyl 2,4,5,6,7,7a-hexahydro-7a-methyl-1-methylene-1H-indene-3,5,5-tricarboxylate (12). To bis(dibenzylideneacetone) palladium (5.3 mg, 9.2 µmol) was added a solution of triisopropyl phosphite (9 µl, 37 µmol) in toluene (0.75 ml). The mixture was sonicated for 15 minutes to give a green homogenous solution, and then heated to reflux. A solution of **8** (31.7 mg, 98 µmol) in toluene (1.25 ml) was added and the mixture refluxed for 2 days. On cooling, the reaction mixture was diluted with ether and filtered through a plug of silica. Removal of the solvent under reduced pressure and subsequent column chromatography (20% ether / petrol) afforded **12** (18.6 mg, 59%) as a colourless oil. ν_{max} (film) 2953, 1734, 1668, 1433, 1289, 1230, 1194, 1131, 1104 cm^{-1} ; ^1H NMR (500 MHz; $CDCl_3$) 4.93 (1H, t, 2.2 Hz, $=CH_{cis}$), 4.83 (lH, t, 2.5 Hz, $=CH_{trans}$), 4.14 (1H, dd, 14.4, 2.3 Hz, H-4β), 3.76 (3H, s, CO_2CH_3), 3.73 (3H, s, CO_2CH_3), 3.65 (3H, s, CO_2CH_3), 3.42-3.32 (2H, m, 2 x H-2), 2.49 (1H, ddd, 14.5, 3.7, 2.7 Hz, H-4α), 2.33 (1H, m, H-6β), 2.09 (1H, dt, 4.0, 14.1 Hz, H-6α), 1.80 (1H, ddd, 13.7, 3.7, 3.1 Hz, H-7α), 1.60 (1H, dt, 3.9, 14.0 Hz, H-7β), 1.22 (3H, s, (α-CH_3); ^{13}C NMR (67.9 MHz; $CDCl_3$) 172.2 (s), 170.5 (s), 165.9 (s), 156.8 (s), 156.5 (s), 124.8 (s), 105.7 (t), 56.5 (s), 52.9 (q), 52.5 (q), 51.3 (q), 50.3 (s), 38.6 (t), 35.0 (t), 29.8 (t), 27.7 (t), 24.7 (q); *m / z* 322 (M^+), 290 (M^+-MeOH), 275, 231, 203, 143; Found: C 63.43, H 6.92%; $C_{17}H_{22}O_6$ requires: C 63.34, H 6.88%.

Methyl 2,3,3a,4,5,6-hexahydro-3a-methyl-3-methylene-1-pentalenecarboxylate (13). A solution of $Pd_2(dba)_3$ (14.8 mg, 16 µmol) and triisopropyl phosphite (34 µl, 138 µmol) in toluene (1.0 ml) turned green upon sonication for 20 minutes. A solution of **5** (36.4 mg, 0.19 mmol) in toluene (2.5 ml) was added and the mixture refluxed for 2 days. Removal of the solvent under reduced pressure and subsequent purification of the residue on silica gel (2% ether / hexane) afforded **13** (18.5 mg, 51%) as a colourless oil. ν_{max} (film) 2955, 1691, 1432, 1320, 1291, 1244, 1109, 1037, 999, 887 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 4.85 (1H, t, 1.7 Hz), 4.80 (1H, m), 3.7 (3H, s), 3.7-3.6 (1H, m), 3.4-3.3 (1H, m), 2.8-2.6 (1H, m), 2.5-2.4 (1H, m), 1.9-2.2 (2H, m), 1.7 (1H, ddd, 1.7, 7.6, 12.2 Hz), 1.5 (1H, m), 1.2 (3H, s); ^{13}C NMR (125.8 MHz; $CDCl_3$) 172.5 , 166.0, 156.8, 120.0, 105.6, 60.7, 51.1 , 41.6, 34.7, 25.6, 24.7, 24.6; *m / z* 191 (M^+-H), 177 (M^+-Me), 161, 133, 117, 105, 91; Observed (M^+-Me): 177.0917; $C_{11}H_{13}O_2$ requires 177.0916.

Dimethyl 1-(1-methyl-2-methylene-1-cyclopropyl)-6-(trimethylsilyl)-5-hexyne-3,3-dicarboxylate (14). To **10** (330 mg, 1.25 mmol) in THF (5 ml) stirred at -78°C was added butyllithium (2.5M in hexanes, 525 µl, 1.31 mmol) dropwise. The resulting pale yellow solution was stirred for 30 minutes at -78°C, then trimethylsilyl chloride (500 µl, 3.94 mmol) was added. After stirring for 20 minutes, the reaction

was quenched by addition of saturated NH_4Cl solution (2 ml) and allowed to warm to room temperature. The mixture was diluted with water (50 ml) and extracted with ether (3 x 50 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatogaphy (10% ether / petrol) gave **14** (405 mg, 96%) as a colourless oil. ν_{max} (film) 2955, 2179, 1739, 1433, 1375, 1284, 1251, 1229, 1198, 1181, 1033, 845, 761 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.38 (1H, dt, 1.1, 2.6 Hz), 5.26 (1H, m), 3.71 (6H, s), 2.79 (2H, s), 2.24-2.05 (2H, m), 1.30-1.00 (2H, m), 1. 15 (3H, s), 0.92 (2H, m), 0. 12 (9H, s); *m / z* 321 (M^+-Me), 304 (M^+-MeOH), 203, 189, 173, 145, 73; Observed (M^+-Me): 321.1521; $C_{17}H_{25}O_4Si$ requires 321.1522.

Dimethyl 6-cyano-1-(1-methyl-2-methylene-1-cyclopropyl)-5-hexyne-3,3-dicarboxylate (15). To **10** (70.0 mg, 0.26 mmol) in THF (2.5 ml) stirred at -78°C was added butyllithium (2.5M in hexanes, 130 µl, 0.33 mmol) dropwise. The solution was stirred for 30 minutes at -78°C, then *p*-toluenesulphonyl cyanide (80 mg, 0.44 mmol) in THF (1 ml) was added. After stirring for 45 minutes, the reaction mixture was warmed to room temperature and quenched by addition of 0.88 ammonia solution (1 ml). The mixture was poured into water (25 ml), extracted with ether (3 x 25 ml) and the combined organic layers dried over $MgSO_4$. Removal of the solvent *in vacuo* and subsequent column chromatography (10% ether / petrol) gave less polar **10** (9.6 mg, 14%) as a colourless oil; and more polar **15** (42.1 mg, 55%) as a colourless oil. ν_{max} (film) 2955, 2314, 2264, 1736, 1433, 1285, 1230, 1151, 1059 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.39 (1H, dt, 0.9, 2.6 Hz), 5.29 (1H, bs), 3.76 (3H, s), 3.75 (3H, s), 2.95 (2H, s), 2.20-2.01 (2H, m), 1.32-1.11 (2H, m), 1.15 (3H, s), 0.94 (2H, m); *m / z* 288 (M^+-H), 274 (M^+-Me), 257, 242, 170, 79; Observed (M^+) 289.1312; $C_{16}H_{19}NO_4$ requires 289.1314.

Dimethyl 1-(1-methyl-2-methylene-1-cyclopropyl)-6-(phenylsulphonyl)-5-hexyne-3,3-dicarboxylate (16). To **10** (227 mg, 0.86 mmol) in THF (8 ml) stirred at -78°C was added butyllithium (2.5M in hexanes, 410 µl, 1.03 mmol) dropwise. The resulting pale yellow solution was stirred for 30 minutes at -78°C, then diphenyl disulphide (265 mg, 1.21 mmol) in THF (2 ml) was added dropwise. The solution was stirred for a further 15 minutes at -78°C and then warmed to room temperature. The reaction mixture was diluted with water (50 ml), extracted with ether (3 x 50 ml) and the combined organic layers dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded the crude sulphide (246 mg) as a yellow oil. To a portion of this sulphide (148 mg, 0.40 mmol) in THF (6 ml), MeOH (6 ml) and pH 4 buffered water (6 ml) was added Oxone® (890 mg, 2.86 mmol). After stirring for 2 days, the mixture was poured into water (50 ml), extracted with DCM (3 x 25 ml), and the combined organic layers dried over $MgSO_4$. Removal of the solvent under reduced pressure and subsequent column chromatography (30% ether / petrol) gave **16** (68 mg, 33%) as a colourless oil. ν_{max} (film) 2954, 2206, 1735, 1331, 1285, 1230, 1161, 1088, 729, 686 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 8.01-7.96 (2H, m), 7.71-7.54 (3H, m), 5.32 (1H, dt, 1.0, 2.6 Hz), 5.24 (1H, m), 3.69 (6H, s), 2.95 (2H, s), 2.12-1.93 (2H, m), 1.25-1.05 (2H, m), 1.06 (3H, s), 0.92-0.82 (2H, m); *m / z* 404 (M^+), 263, 231, 203, 143, 77; Observed (M^+): 404.1286; $C_{21}H_{24}O_6S$ requires 404.1294.

Dimethyl 3-cyano-2,4,5,6,7,7a-hexahydro-7a-methyl-1-methylene-1H-indene-5,5-dicarboxylate (17). To tris(dibenzylideneacetone) dipalladium (7.6 mg, 8.3 µmol) in toluene (1 ml) was added triisopropyl phosphite (18 µl, 73 µmol). The mixture was sonicated for 15 minutes to give a green homogenous solution. **15** (36.4 mg, 126 µmol) in toluene (1.5 ml) was added and the mixture refluxed for 2 days. On cooling, the reaction mixture was diluted with ether, and filtered through a plug of silica. Removal of the solvent under reduced pressure and subsequent column chromatography (10-20% ether / petrol) afforded **17**

(16.0 mg, 44%) as a colourless oil. ν_{max} (film) 2955, 2218, 1733, 1666, 1432, 1308, 1287 1250, 1196, 1131, 1106 1054, 1028 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 4.99 (1H, t, 2.2 Hz), 4.91 (1H, dd, 2.7, 2.2 Hz), 3.75 (3H, s), 3.74 (3H, s), 3.47-3.35 (2H, m, H-2), 3.25 (1H, dq, 20.4, 2.2 Hz), 2.61 (1H, ddd, 14.2, 4.2, 2.4 Hz), 2.36 (1H, ddt, 14.3, 3.7, 2.5 Hz), 2.05 (1H, dt, 3.9, 14.2 Hz), 1.81 (1H, ddd, 13.9, 3.9, 2.9 Hz), 1.56 (1H, dt, 3.8, 13.9 Hz), 1.22 (3H, s); *m / z* 289 (M^+), 229, 214, 170, 145; Observed (M^+): 289.1312; $C_{16}H_{19}NO_4$ requires 289.1314.

Dimethyl 2,4,5,6,7,7a-hexahydro-7a-methyl-1-methylene-3-(phenylsulphonyl)-1H-indene-5,5-dicarboxylate (18). To tris(dibenzylideneacetone) dipalladium (7.7 mg, 8.4 μmol) in toluene (0.3 ml) was added triisopropyl phosphite (18 μl, 73 μmol). The mixture was sonicated for 15 minutes to give a green homogenous solution, and then **16** (27.4 mg, 68 μmol) in toluene (1.7 ml) was added. The mixture was subsequently refluxed for 2 days, during which time further portions of toluene were added to maintain the solvent level. On cooling, the reaction mixture was diluted with ether, and filtered through a plug of silica. Removal of the solvent under reduced pressure and subsequent column chromatography (20-30% ether / petrol) afforded **17** (11.1 mg, 41%) as a colourless oil. ν_{max} (film) 2954, 1730, 1633, 1627, 1318, 1288, 1250, 1195, 1150, 719, 690 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) 8.01-7.98 (2H, m), 7.64-7.53 (3H, m), 4.85 (1H, dd, 2.3, 1.9 Hz), 4.82 (1H, dd, 2.9, 2.0 Hz), 4.39 (1H, dd, 15.0, 2.2 Hz), 3.76 (3H, s), 3.71 (3H, s), 3.37 (1H, ddt, 20.1, 4.2, 2.7 Hz), 3.13 (1H, ddd, 20.1, 4.0, 1.9 Hz,), 2.55 (1H, ddd, 15.0, 4.3, 2.4 Hz), 2.35 (1H, m), 2.09 (1H, dt, 4.0, 14.3 Hz), 1.82 (1H, dt, 13.7, 3.4 Hz), 1.60 (1H, dt, 4.0, 14.0 Hz), 1.20 (3H, s); *m / z* 404 (M^+), 389 (M^+-Me), 344, 312, 203, 125; Observed (M^+): 404.1286; $C_{21}H_{24}O_6S$ requires 404.1294.

3-(2-Chloro-1,2-dimethyl-1-cyclopropyl)propan-1-ol (22). To a solution of **21** (2.59 g, 8.74 mmol) and 1,1-dichloroethane (1.12 g, 11.36 mmol) in ether (4 ml) at -35°C was added n-butyllithium (2.1 M in hexanes, 9.4 ml, 19.7 mmol) dropwise with stirring over 3 hours using a syringe pump. Two further portions of 1,1-dichloroethane (0.5 ml, 5.9 mmol) were added during the the course of this addition. After completion of the addition the reaction was allowed to warm to room temperature, poured into water and extracted with petrol. The organic phase was dried over $MgSO_4$ and concentrated. The residue was dissolved in THF (5 ml) and tetrabutylammonium fluoride (1.1 M in THF, 10.0 ml, 11 mmol) was added. After stirring for 18 hours, the mixture was poured into water, extracted with ether and dried over $MgSO_4$. Removal of the solvent under reduced pressure and subsequent distillation of the residue gave **22** (1.13 g, 80%) as a colourless liquid (70°C / 1 mmHg). ν_{max} (film) 3338, 2937, 1438, 1381, 1130, 1057, 796, 738, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) 3.64 (2H, t, 6.0 Hz) 2.0-1.0 (5H, m), 1.62 (3H, s), 1.32 (3H, s), 0.80 (1H, d, 6.5 Hz), 0.59 (1H, d, 6.5 Hz); *m / z* 145, 127, 126, 116, 81, 67, 55, 41; Observed (M^+-HCl): 126.1044; $C_8H_{14}O$ requires: 126.1045.

1-Methyl-2-methylenecyclopropane-propanol (23). To potassium *tert*-butoxide (6.43 g, 57.3 mmol) in DMSO (15 ml) at 70°C was added **22** (3.77 g, 23.2 mmol). After 2 hours, more potassium *tert*-butoxide (1.40 g, 12.5 mmol) in DMSO (5 ml) was added and heating continued for a further 1.5 hours. The mixture was poured into ice, diluted with water (50 ml) and extracted with ether (3 x 50 ml). The combined organic layers were washed with water (50 ml) and dried over $MgSO_4$. Removal of the solvent under reduced pressure at 0°C gave an inseperable mixture of cyclopropanes. This mixture (2.45 g) was again treated with potassium *tert*-butoxide (7.19 g, 64.1 mmol) in DMSO (12 ml) at 90°C. After 2 hours, a further portion of base (3.64 g, 32.4 mmol) was added and heating continued for a further 3 hours. On cooling, the reaction was worked up as described above. Column chromatography (30% ether / petrol) and subsequent distillation gave **23** (1.76 g,

60%) as a colourless liquid. ν_{max} (film) 3340, 3063, 2938, 2867, 1448, 1374, 1058, 884 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.36 (1H, dt, 1.0, 2.6 Hz), 5.28 (1H, bs), 3.65 (2H, t, 6.5 Hz), 1.73-1.21 (5H, m), 1.15 (3H, s), 0.98-0.88 (2H, m); *m / z* 111 (M^+-Me), 93, 82, 67, 41; Observed (M^+-Me): 111.0805; $C_7H_{11}O$ requires: 111.0810.

Methyl 4-hydroxy-6-(1-methyl-2-methylene-1-cyclopropyl)-2-hexynoate (24). To a solution of oxalyl chloride (0.24 ml, 2.75 mmol) in DCM (10 ml) cooled to -78°C, was added DMSO (0.39 ml, 5.50 mmol) dropwise. The solution was stirred for 5 minutes, then **23** (284 mg, 2.25 mmol) in DCM (4 ml) was added dropwise giving a dense white precipitate. The mixture was stirred for 20 minutes, triethylamine (1.05 ml, 7.53 mmol) 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 (50 ml) and extracted with DCM (3 x 50 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure at 0°C. The residue was passed through a plug of silica with ether, and the solvent removed *in vacuo* to give the semi-purified aldehyde (297 mg) as a yellow liquid. To methyl propiolate (0.30 ml, 3.37 mmol) in THF (12 ml) at -78°C was added n-butyllithium (2.5M in hexanes, 1.34 ml, 3.35 mmol) dropwise. The mixture was stirred for 30 minutes, then the aldehyde prepared previously (297 mg) in THF (5 ml) was added. After stirring for 45 minutes, glacial acetic acid (0.5 ml) in THF (5 ml) was added and the reaction mixture allowed to warm slowly to room temperature overnight. The resulting red solution was poured into water (50 ml) and extracted with ether (3 x 50 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatogaphy (25% ether / petrol) gave **24** (241 mg, 51%) as a pale yellow oil and as a 1:1 mixture of diastereomers. ν_{max} (film) 3412, 2953, 2864, 2236, 1715, 1434, 1254, 1060, 888, 752 cm^{-1}; ^1H NMR (250 MHz; $CDCl_3$) 5.36 (1H, dt, 0.7, 2.5 Hz), 5.29 (1H, bs), 4.50 (1H, bs), 3.78 (3H, s), 2.00 (1H, bs), 1.95-1.74 (2H, m), 1.70-1.40 (2H, m), 1.15 (3H, s), 1.02-0.88 (2H, m); m / z 208 (M^+), 193 (M^+-Me), 175 (M^+-Me-H_2O), 147, 93, 91, 79; Observed (M^+): 208.1100; $C_{12}H_{16}O_3$ requires: 208.1099.

Methyl 6-(1-methyl-2-methylene-1-cyclopropyl)-4-[tris(methylethyl)silyloxy]-2-hexynoate (19). To triisopropylsilyl chloride (190 µl, 0.89 mmol) and imidazole (105 mg, 1.54 mmol) was added **24** (154 mg, 0.74 mmol) in DMF (1 ml). After stirring for 14 hours, the mixture was poured into water (25 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. Column chromatography (2% ether / petrol) gave **19** (198 mg, 73%) as a colourless oil and as a 1:1 mixture of diastereomers. ν_{max} (film) 2946, 2866, 2235, 1719, 1250, 1103, 1068, 883, 682 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 5.37 (0.5H, dt, 1.0, 2.4 Hz), 5.36 (0.5H, dt, 1.0, 2.4 Hz), 5.27 (1H, bs), 4.60 (0.5H, t, 6.0 Hz), 4.59 (0.5H, t, 6.0 Hz), 3.77 (3H, s), 1.88-1.40 (4H, m), 1.30-0.88 (5H, m), 1.14 (3H, s), 1.08 (18H, d, 3.2 Hz); *m / z* 349 (M^+-Me), 321 (M^+-C_3H_7), 131, 103, 93, 75; Found: C 69.17, H 10.10%; $C_{21}H_{36}O_3Si$ requires: C 69.18, H 9.95%.

Tetrahydro-2-[1-(1-methyl-2-methylenecyclopropyl)methyloxy]-2H-pyran (26). To a solution of tetrahydro-2-[(2-methyl-2-propenyl)oxy-2H-pyran[18] (30.0 g, 192 mmol) in ether (100 ml) cooled to -35°C under argon was added 1,1-dichloroethane (4.7 ml, 55 mmol). Then n-butyllithium (1.6 M in hexanes, 122 ml, 195 mmol) was added dropwise over 4 hours. Further portions of 1,1-dichloroethane (3.0 ml, 35 mmol) were added after 0.5, 1.5, 2.5 and 3.5 hours of the addition. The mixture was allowed to reach room temperature, stirred overnight, recooled to -35°C and the same proceedure repeated. The reaction mixture was again warmed to room temperature, poured into water (100 ml), the organic phase separated, dried over $MgSO_4$ and

concentrated under reduced pressure. Distillation afforded the desired chlorocyclopropane (26.9 g, 64%) as a colourless liquid (bp 80°C / 1.3 mmHg). This material was dissolved in DMSO (20 ml) and added dropwise to a stirred solution of potassium *tert*-butoxide (26.1 g, 0.23 mol) in DMSO (35 ml) stirred at 70°C. After stirring for 20 hours, the solution was cooled to 0°C, poured into ice cold water (200 ml) and extracted with ether (2 x 200 ml). The combined organic layers were washed with water (4 x 50 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Distillation of the residue afforded **26** (17.5 g, 78%) as a colourless liquid (bp 43°C / 0.9 mmHg). ν_{max} (film) 2940, 2868, 1200, 1137, 1120, 1077, 1056, 1031, 981, 905, 887cm^{-1} ; ^{1}H NMR (270 MHz; $CDCl_3$) 5.4-5.3 (2H, m), 4.6 (1H, m), 3.9-3.1 (4H, m), 1.9-1.4 (6H, m), 1.2 (3H, bs), 1.1-0.9 (2H, m); *m / z* 156, 143, 115, 101, 85, 67; Observed (M^+-OTHP): 81.0704; C_6H_9 requires 81.0704.

1-Methyl-2-methylene-1-cyclopropane-methanol (27). To a solution of **26** (14.0 g, 77 mmol) in methanol (250 ml) stirred at room temperature was added *p*-toluenesulphonic acid (3.2 g, 17 mmol). The mixture was stirred for 19 hours, potassium carbonate (1 g) was added and the mixture was stirred for a further 20 minutes. The solvent was removed by distillation at atmospheric pressure, then the residue was dissolved in ether (400 ml), washed with water (2 x 100 ml), dried over $MgSO_4$ and carefully concentrated under reduced pressure at 0°C. Distillation of the residue gave **27** (6.7 g, 89%) as a colourless liquid (bp 46°C / 25 mmHg). ν_{max} (film) 3353, 2928, 2867, 1745, 1440, 1376, 1126, 1032, 888 cm^{-1}; ^{1}H NMR (270 MHz; $CDCl_3$) 5.45 (1H, m), 5.35 (1H, m), 3.5 (2H, bs), 1.35 (1H, t, OH, 6.2 Hz), 1.25 (3H, s), 1.1 (1H, m), 1.0 (1H, m); *m / z* 97 (M^+-H), 83, 69 (M^+-CH_2OH), 55, 41; Observed (M^+-Me): 83.0497; C_5H_7O requires 83.0497.

1-(1-Methyl-2-methylene-1-cyclopropyl)-methyloxy-prop-2-yne (28). To a stirred suspension of sodium hydride (0.38 g, 9.5 mmol) in THF (10 ml) was added **27** (0.77 g, 7.8 mmol) in THF (5 ml). The mixture was stirred at room temperature for 90 minutes then cooled to 0°C and propargyl bromide (80% in toluene, 2.5 ml, 22.4 mmol) added. The mixture was stirred for 1 hour warmed to room temperature and stirred for a further 3 hours. The mixture was poured into water (50 ml) and extracted with ether (3 x 50 ml). The combined extracts were washed with water (2 x 20 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue on silica gel (20% ether / petrol) gave **28** (0.72 g, 74%) as a colourless oil. ν_{max} (film) 2924, 2853, 1459, 1351, 1263, 1091, 1032, 890 cm^{-1}; ^{1}H NMR (270 MHz; $CDCl_3$) 5.45 (1H, m), 5.35 (1H, bs), 4.2 (2H, t, 2.4 Hz), 3.4 (2H, s), 2.4 (1H, t, 2.4 Hz), 1.25 (3H, s), 1.2-1.0 (2H, m); *m / z* 135 (M^+-H), 105, 97, 81, 69, 53; Observed (M^+-H): 135.0814; $C_9H_{11}O$ requires 135.0810.

Methyl 5-(1-methyl-2-methylene-1-cyclopropyl)-4-oxapent-1-yne-1-carboxylate (25). To a solution of **28** (50.0 mg, 0.37 mmol) in THF (3 ml) stirred at -78°C was added n-butyllithium (2.5 M in hexanes, 0.18 ml, 0.45 mmol) dropwise. The resulting dark brown-red solution was stirred at -78°C for 1 hour then methyl chloroformate (0.1 ml, 1.29 mmol) was added. After 2 hours, the mixture was warmed to room temperature, poured into water (20 ml) and extracted with ether (3 x 20 ml). The combined extracts were washed with brine (10 ml), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue on silica gel (10% ether / petrol) afforded **25** (63.4 mg, 89%) as a colourless oil. ν_{max} (film) 2954, 2237, 1716, 143 3, 1254, 1096, 1060, 751 cm^{-1}; ^{1}H NMR (270 MHz; $CDCl_3$) 5.4 (1H, t, 2.4 Hz), 5.3 (1H, bs), 4.3 (2H, m), 3.8 (3H, s), 3 .4 (2H, s), 1.2 (3H, s), 1.0 (1H, m), 1.1 (1H, m); *m / z* 193 (M^+-H), 179 (M^+-Me), 163, 97; Found 179.0706; $C_{10}H_{11}O_3$ (M^+-Me) requires 179.0708.

(3aα, 6β)-Methyl 2,3,3a,4,5,6-hexahydro-6-hydroxy-3a-methyl-3-methylene-1-pentalenecarboxylate (29) and (3aα, 6α)-methyl 2,3,3a,4,5,6-hexahydro-6-hydroxy-3a-methyl-3-methylene-1-pentalenecarboxylate (30). To tris(dibenzylidineacetone) dipalladium (12.8 mg, 14 μmol) in toluene (1 ml) was added triisopropyl phosphite (30 μl, 122 μmol). The resulting mixture was sonicated for 20 minutes, giving a pale green solution. A solution of **19** (56.7 mg, 156 μmol) in toluene (2 ml) was added, and the resulting solution refluxed for 42 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 partially separable mixture of silylated adducts (50 mg). To this mixture in THF (1 ml) at 0°C was added tetrabutylammonium fluoride (1.1M in THF, 160 μl, 176 μmol) dropwise. After stirring for 30 minutes, the purple solution was warmed to room temperature and stirred for a further 3 hours. The mixture was poured into water (25 ml) and extracted with ether (3 x 25 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (20-40% ether / petrol) gave less polar **29** (9.4 mg, 29%) as a colourless oil; ν_{max} (film) 3432, 2955, 1687, 1436, 1319, 1290, 1244, 1201, 1116, 1039, 1002, 887 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) 5.12 (1H, s), 4.97 (1H, m), 4.86 (1H, dd, 2.4, 1.4 Hz), 4.79 (1H, dd, 2.9, 1.6 Hz), 3.78 (3H, s), 3.67 (1H, dq, 19.7, 3.0 Hz), 3.38 (1H, dq, 19.7, 1.5 Hz), 2.56 (1H, m), 2.01 (1H, m), 1.87 (1H, dt, 12.2, 9.9 Hz), 1.71 (1H, ddd, 12.2, 8.1, 2.2 Hz), 1.20 (3H, s) ; *m / z* 208 (M^+), 193 (M^+-Me), 176, 148, 119, 105, 91; Observed (M^+): 208.1100; $C_{12}H_{16}O_3$ requires: 208.1099; and more polar **30** (10.3 mg, 32%) as a colourless oil. ν_{max} (film) 3478, 2953, 1705, 1672, 1435, 1329, 1293, 1240, 1112, 1027, 885 cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) 4.87 (1H, bt, 7.3 Hz), 4.83 (1H, dd, 2.3, 1.3 Hz), 4.78 (1H, dd, 2.9, 1.5 Hz), 3.77 (3H, s), 3.68 (1H, ddd, 19.7, 4.5, 2.4 Hz), 3.34 (1H, dt, 21.0, 1.3 Hz), 2.80 (1H, bs), 2.49-2.43 (1H, m), 2.20-2.12 (1H, m), 1.84 (1H, dd, 12.3, 7.6 Hz), 1.45 (1H, dt, 7.8, 12.3 Hz), 1.34 (3H, s); *m / z* 208 (M^+), 193 (M^+-Me), 149, 148, 133, 119, 105, 91; Observed (M^+): 208.1100; $C_{12}H_{16}O_3$ requires: 208.1099.

ACKNOWLEDGEMENTS

We gratefully acknowledge the receipt of studentships from the SERC (to R.T.L. and M.S.), Johnson Matthey plc for the generous loan of palladium salts, and Glaxo Group Research Ltd for additional financial support. We are indebted to Dick N Sheppard for his help and expertise in performing the nOe experiments.

REFERENCES AND NOTES

1 Lewis, R.T.; Motherwell, W.B.; Shipman, M.; *J. Chem. Soc. Chem. Commun.*, **1988**, 948. A more detailed account of this work can be found in the preceding paper in this issue of *Tetrahedron*.

2 (a) Bapuji, S.A.; Motherwell, W.B.; Shipman, M.; *Tetrahedron Lett.*, **1989**, *30*, 7117; (b) Motherwell, W.B.; Shipman, M.; *Tetrahedron Lett.*, **1991**, *32*, 1103.

3 Yamago, S.; Nakamura, E.; *J. Chem. Soc. Chem. Commun.*, **1988**, 1112; Yamago, S.; Nakamura, E.; *Tetrahedron*, **1989**, *45*, 2887.

4 Ladlow, M.; Pattenden, G.; *J. Chem. Soc., Perkin Trans 1*, **1988**, 1107.

5 Baldwin, J.E.; Parker, D.W.; *J. Org. Chem.*, **1987**, *52*, 1475.

6 Garreg, P.J.; Samuelsson, B.; *J. Chem. Soc., Perkin Trans 1*, **1980**, 2866.

7 Corey, E.J.; Kirst, H.A.; *Tetrahedron Lett.*, **1968**, 5041.

8 Corlay, H.; PhD thesis, University of London, 1992.

9 Paquette, L.A.; *Top. Curr. Chem.*, **1984**, *119*, 1; Paquette, L.A.; Doherty, A.M.; *Polyquinane Chemistry: Synthesis and Reactions*, Springer-Verlag, Berlin, 1987.

10 For a comprehensive review on the intermolecular reaction, see Binger, P.; Buch, H.M.; *Top. Curr. Chem.*, **1987**, *135*, 77.

11 Trost, B.M.; Grese, T.A.; Chan, D.M.T.; *J. Am. Chem. Soc.*, **1991**, *113*, 7350.

12 Recent studies have shown that the perhydroazulene skeleton can be accessed using this chemistry by employing a Pd-TMM intermediate stabilised by an adjacent acyl substituent, see Trost, B.M.; Grese, T.A.; *J. Org. Chem.*, **1992**, *57*, 686.

13 Binger, P.; Lü, Q.-H.; Wedemann, P.; *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 316.

14 Baarschers, W.H.; *Can. J. Chem.*, **1976**, *54*, 3056.

15 Bapuji, S.A.; PhD thesis, University of London, 1989.

16 We have previously proposed an asynchronous mechanism to account for some of the unusual stereochemical facets of this cycloaddition reaction, see ref 2b.

17 Experimental details for the preparation of **20** and **21** can be found in the preceding paper in this issue of *Tetrahedron*.

18 Kao, L.-C.; Staken, F.G.; Patel, B.A.; Heck, R.F.; *J. Org. Chem.*, **1982**, *47*, 1267.

19 Cyclisation of alcohol **24** was also examined, however substantially lower yields were obtained.

20 Benzyl protected alcohols have been utilised in some related cycloaddition studies, see ref 2b.

21 Dötz, K.H.; Popall, M.; *Tetrahedron*, **1985**, *41*, 5797.

22 Eglington, G.; Whiting, W.C.; *J. Chem. Soc.*, **1950**, 3650.

(*Received in UK* 7 *December* 1994; *accepted* 13 *January* 1995)