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New Routes to Polysubstituted Cycloheptenones

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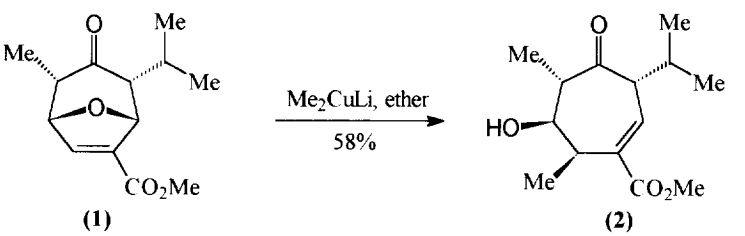
Abstract: We describe the synthesis of stereochemically-defined 2,3,6,7-substituted cyclohept-4-enones and 2,5,6,7-substituted cyclohept-3-enones *via* reaction of 2,4-disubstituted-8-oxabicyclo[3.2.1]oct-6-en-3-ones with organometallic species, and 6,7-disubstituted cyclohept-2-enones *via* reaction of 8-oxabicyclo[3.2.1]octan-3-one with BF_3. etherate and sodium iodide. Copyright © 1996 Elsevier Science Ltd

In 1987 we described the first cleavage of the ether bridge of an 8-oxabicyclo[3.2.1]oct-6-en-3-one (**1**) using a cuprate[1] to produce the polysubstituted cycloheptenone **2** (Figure 1). Lautens and coworkers subsequently demonstrated the scope and synthetic utility of this type of reaction[2], and in this paper we provide details of our methods which are similar (though non-identical) together with an alternative approach to polysubstituted cycloheptenones which involves direct cleavage of the ether bridge.



(1) (2)

Figure 1

Our two organometallic routes to cycloheptenones are shown in Figure 2. They are exemplified by the reaction between 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**3**) and methyl magnesium iodide in conjunction with cuprous iodide (ratio 1:1) in ether to provide 2α,6α,7α-trimethylcyclohept-4-en-3β-ol-1-one (**4**) (58% isolated yield); and by reaction between **3** and methyl lithium in conjunction with cuprous iodide (ratio 1:1) in toluene to provide 2α,5α/β,7α-trimethylcyclohept-3-en-6β-ol-1-one (**5**) (75%). Interestingly, if the methyl lithium/cuprous iodide reaction was carried out in THF a poor yield (15%) of **5** was obtained together with the hydroxytropone **6** (10%). In addition, when cuprous iodide was omitted from either system, only the 1,2-addition product **7** was obtained in yields of up to 85%. All of these reactions can be carried out on the multigram scale and given the accessibility of polysubstituted 8-oxabicyclo[3.2.1]oct-6-en-3-ones using oxyallyl cycloadditions[3], this chemistry provides a general route to polysubstituted cycloheptenones. However, the subsequent more comprehensive studies carried out by Lautens[2], persuaded us to investigate alternative routes to polysubstituted cycloheptenones.

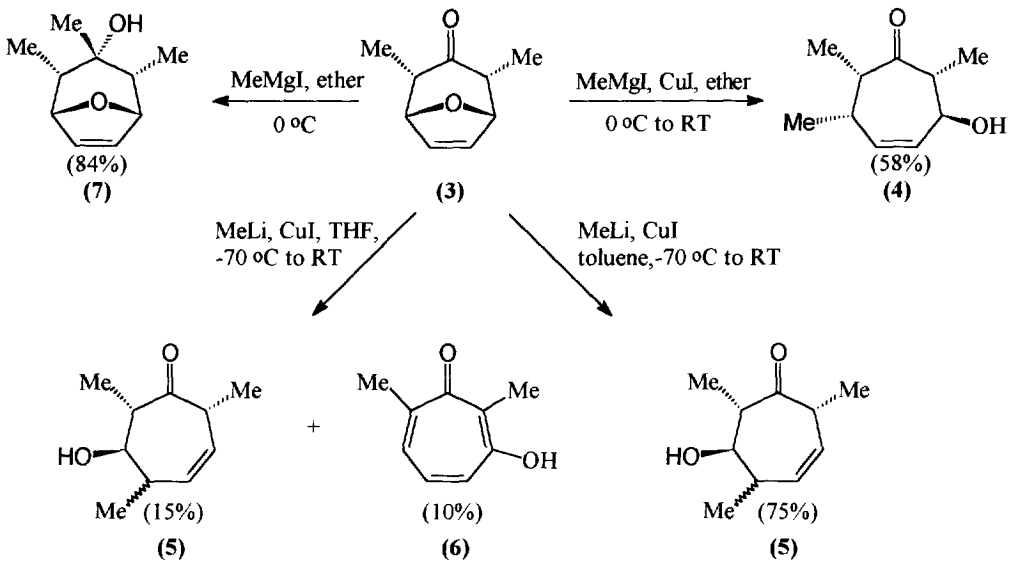


Figure 2

For our second route to polysubstituted cycloheptenones we envisaged that the side-chain ester of cycloadduct **8**[4] would participate in a Lewis acid mediated ether cleavage to yield the fused lactone **9** as shown in Figure 3. In the event, reaction of **8** with $BF_3.Et_2O$ in conjunction with KI provided only the two 2-substituted furans **10** and **11** (48 and 18% yields respectively). Prior formation of the enol silyl ether **12** using DBU and TMS chloride (95% yield) followed by reaction with $BF_3.Et_2O$ and KI yielded the same furans (60 and 11%). Interestingly, reaction of the corresponding *tert*-butyl ester **13** with trimethylsilyl triflate in the presence of triethylamine - a method introduced by Föhlisch for the cleavage of the ether bridge in similar cycloadducts[5] - produced 33% of the 2-*tert*-butoxycarbonylmethyltropone **14a** and 15% of the acid **14b.**

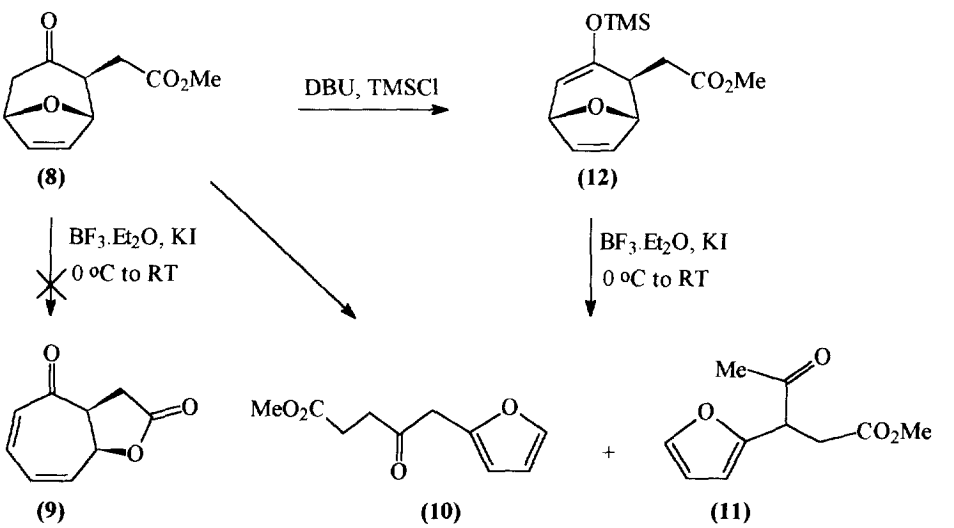
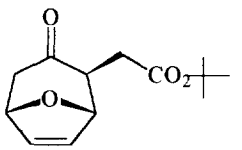


Figure 3

Reaction of the ester **15a**[6] with lithium diisopropylamide and trimethylsilyltriflate (5 eq.) in tetrahydrofuran, at -78 °C provided a 40% yield of the desired lactone **16**. Use of smaller amounts of the triflate (1 eq.) and a basic work-up, provided the cleavage compounds **19 - 21** instead. Treatment of **15a** with zirconium(IV) chloride and triethylamine in dichloromethane (a modification of the method introduced by Hoffman[7]) or with titanium(IV) chloride (*via* silyl enol ether **18**[8]) provided **16** and **17** in poorer yields.



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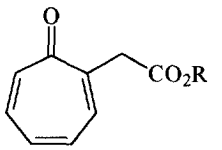
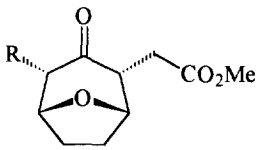
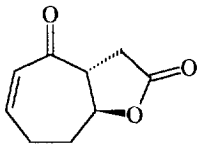


(14a): R = t-Bu
(14b): R = H



(15a): R=H
(15b): R=Me



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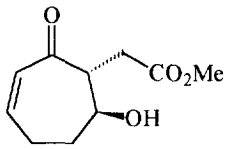

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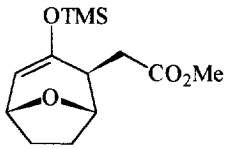

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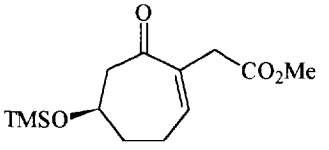

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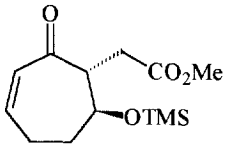

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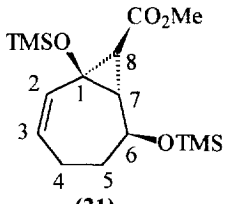

(21)

The structure of the bicyclic product **21** is particularly intriguing but is fully consistent with the spectroscopic data. In particular, the proton spectrum showed the presence of two TMS groups, a carbomethoxy group and a non-conjugated double bond (two alkene hydrogens at δ= 5.48 and 5.82, J = 11.6Hz). H2 signal showed two other small correlations (J = 1.8 and 2.6 Hz) due to W type couplings with H4 and H7. H3 was also coupled with H4 (J = 7.5 Hz) and H4'(J = 3.5 Hz). The ^{13}C spectrum showed quite clearly the presence of a tetrasubstituted carbon, two CH_2's and five CH's and one signal in the carbonyl region. NOE experiments suggested the positions assigned to the siloxy groups. Furthermore, no NOE was observed between H7 and H8 and an enhancement of the OMe signal was observed upon irradiation at H7 frequency. The 2D COSY, HETCOR and the mass spectrum were also consistent with the structure, and we suggest the mechanism shown in Fig. 4 for the production of this interesting product.

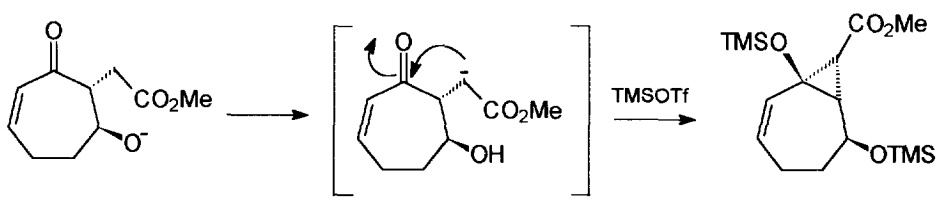

Figure 4

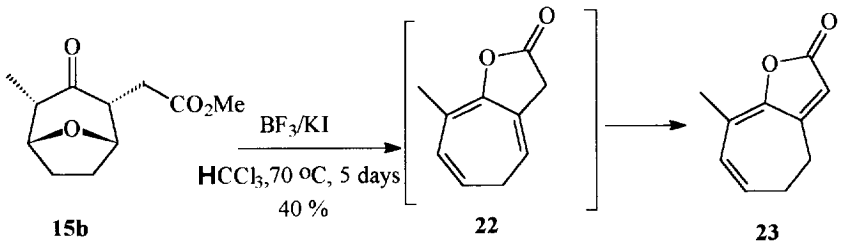

Figure 5

Finally, reaction of the ester **15b** with Me_2BBr in chloroform at 60 °C for 24 hours[9] resulted in partial recovery of the starting material and no product was isolated. Treatment of this ester **15b** with BF_3/KI in chloroform at 70 °C for 5 days afforded the lactone **23** in 40% yield. We suggest that lactone **23** was formed from isomerization of the intermediate **22** catalysed by acid.

EXPERIMENTAL

Reagents and solvents were purified when necessary according to the usual procedures described in the literature[10]. Flash column chromatography was performed using Crosfield Sorbil C60 (32-63μm). Rfs were determined by Analytical Thin Layer Chromatography on a 0.25 mm film of silica gel containing fluorescent indicator UV_{254} supported on a plastic sheet (Camlab plc.). The melting points were determined on a Electrothermal digital apparatus without correction. Infrared Spectra were recorded on a Perkin Elmer 881 grating spectrometer, scanning from 625 to 4000 cm^{-1}. The samples were diluted in chloroform or dichloromethane and run against a reference cell with the same solvent. Mass Spectra were recorded at the SERC Mass Spectrometry Centre at University of Swansea. Alternatively spectra were recorded on a MICROMASS 7070F at Reading University. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX400 (400 and 100.53MHz). Alternatively they were recorded on a Bruker WM400 at the Chemistry Department at University of Warwick. Samples were dissolved in $CDCl_3$ and tetramethylsilane was used as the internal standard. All the NMR analysis was supported by NOE, DEPT, COSY and HETCOR spectral data. Compounds **15a** and **15b** were prepared according to the procedures described in references 6 and 11 respectively.

2α,3β,4α-Trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3α-ol (7): A solution of methylmagnesium iodide (3.0 M in dry ether, 2 ml, 6 mmol) was added to a solution of the ketone **3** (0.304 g, 2 mmol), ar 0 °C under argon. The white solid deposited was allowed to stand at 0 °C for 1 h, and saturated aqueous ammonium chloride (50 ml) was added. The mixture was extracted with ether (2x 50 ml), and the extracts were dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica gel with elutant ethyl acetate:hexane, 2:3, to give the alcohol **7** (0.28 g, 84%) as a yellow oil. A colourless solid analytical sample was prepared by Kugelrohr distillation , bp 60-140 °C/7 mmHg *IR (paraffin liquid film)* ν_{max} *(cm^{-1})*:3532, 1046, 931 and 904. *^1H NMR (400MHz, $CDCl_3$)* 0.92 (d, 6H, J= 7.3 Hz, C-Me), 1.08 (d, 3H, J= 1.1 Hz, C-Me), 1.70 (d, 1H, J= 1.0 Hz, OH), 2.04 (dq, 2H, J= 3.6 and 7.3 Hz, MeC-H), 4.49 (d, 2H, J= 3.6 Hz, OCH), 6.56 (s, 2H, C=CH). *^{13}C NMR (100MHz, $CDCl_3$)* 10.5, 27.1, 42.5, 73.0, 83.0 and 135.35. Found: C 71.3; H 9.4 %. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.6%).

Reaction of the ketone (3) with methylmagnesium iodide in ether in the presence of copper (I) iodide: A solution of methylmagnesium iodide (3.0 M in ether, 10 ml, 30 mmol) was added dropwise, maintaining the temperature below 10 °C, to a stirred suspension of copper (I) iodide (6.28 g, 33 mmol) in dry ether (180 ml) under argon. The bright yellow suspension was stirred at 0 °C for 30 min, and a solution of the ketone **3** (1.52 g, 10 mmol) in dry ether (10 ml) was added. The yellow suspension was stirred at 20 °C for 18 h, and a purple/brown solid complex was formed. The suspension was diluted with ether (200 ml), and was quenched by dropwise addition of saturated aqueous solution of ammonium chloride (50 ml). The mixture was stirred for 1 h and water (50 ml) was added. The layers were separated and the aqueous phase was extracted with ether (2x 100 ml). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica gel (ethyl acetate:hexane 2:3), to give 3β-hydroxy-2α,6α,7α-trimethylcyclohept-4-en-1-one **(4)** (0.98g, 58%) as a colourless oil, b.p. 110-130 °C/ 0.1 mmHg. *IR (thin film)* ν_{max} *(cm^{-1}):* 3411, 2969, 1697 and 1009; *^{1}H NMR (400MHz, CDCl$_3$)* 1.03 (d, 3H, J= 7.2 Hz, 6-Me), 1.04 (d, 3H, J= 6.9 Hz, 7-Me), 1.19 (d, 3H, J= 6.5 Hz, 2-Me), 2.13 (m, 1H, OH), 2.80 (dq, 1H, J= 4.1 and 6.9 Hz, H7), 3.21 (m, 1H, J= 7.2 Hz, H6), 3.35 (m, 1H, J= 6.5 Hz, H2), 3.84 (m, 1H, H3), 5.66 (m, 2H, H4 and H5); *^{13}C NMR (100MHz, CDCl$_3$)* 11.15, 13.80, 17.40, 33.10, 50.80, 51.00, 72.20, 130.40, 137.30 and 213.40; *Accurate Mass Peak Match (m/z):* 186.1494 ($[M+NH_4]^+$, $C_{10}H_{20}NO_2$ requires 186.1494).

Reaction of ketone 3 with methyllithium in toluene in the presence of copper (I) iodide: A solution of methyllithium (1.54 M in ether, 39 ml, 60 mmol) was added dropwise over 5 min *via* syringe, maintaining the temperature below 5 °C, to a stirred suspension of copper (I) iodide (6.28g, 33 mmol) in dry toluene (160 ml) under argon. The near colourless solution was stirred at 0 °C for 1 h, and was cooled to -70 °C. A solution of the ketone **3** (1.53 g, 10 mmol) in dry toluene (15 ml) was added, mantaining the temperature below -65 °C, and the yelow solution was stirred at -70 °C for 5 min and was allowed to warm to 20 °C. The yellow suspension was stirred for a further 18 h, and a dark green suspension was formed. The mixture was diluted with toluene (200 ml), and was quenched by the dropwise addition of a saturated aqueous ammonium chloride (100 ml). The mixture was stirred for 1 h, and water (100 ml) was added. The layers were separated, and the aqueous phase was extracted with ether (2x 100 ml). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica eluting with ethyl acetate:hexane 2:3, to give 6β-hydroxy-2α,5,7α-trimethylcyclohept-3-en-1-one (1.26 g, 75% as a 2:1 mixture of 5β and 5α diastereomers respectively and as a colourless oil, b.p. 115-130 °C/ 0.3 mmHg; *IR (thin film)* ν_{max} *(cm^{-1}):* 3437, 2967, 1701 and 978; 5β diastereomer: *^{1}H NMR (400MHz, CDCl$_3$)* 1.13 (d, 3H, J= 7.1 Hz, 5-Me), 1.16 (d, 3H, J= 7.0 Hz, 2-Me), 1.21 (d, 3H, J= 6.7 Hz, 7-Me), 1.78 (d, 1H, J= 6.5 Hz, OH), 2.36 (m, 1H, H5), 3.00 (m, 1H, J= 6.6 Hz, H7), 3.07 (m, 1H, H2), 3.49 (m, 1H, H6), 5.43 (dd, 1H, J= 5.4 and 10.5 Hz, H4), 5.79 (ddd, 1H, J= 2.2, 6.4 and 10.5, H3); *Accurate Mass Peak Match (m/z):* 186.1494 ($[M+NH_4]^+$, $C_{10}H_{20}NO_2$ requires 186.1494).

Reaction of ketone 3 with methyllithium in THF in the presence of copper (I) iodide: A solution of methyllithium (1.54 M in ether, 39 ml, 60 mmol) was added dropwise over 10 min *via* syringe, maintaining the temperature below 10 °C, to a stirred suspension of copper (I) iodide (6.28g, 33 mmol) in dry THF (160 ml) under argon. The colourless solution was stirred at 0 °C for 1 h, and was cooled to -70 °C., and a white suspension was formed. A solution of the ketone **3** (1.53 g, 10 mmol) in dry THF (15 ml) was added,

maintaining the temperature below -65 °C, and the yellow suspension was stirred at -70 °C for 5 min and was allowed to warm to 20 °C. The orange solution was stirred for a further 18 h, and a dark green suspension was formed. The mixture was diluted with THF (200 ml), and was quenched by the dropwise addition of saturated aqueous ammonium chloride (50 ml). The mixture was stirred for 1 h, and water (50 ml) was added. The layers were separated, and the aqueous phase was extracted with ether (2x 100 ml). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude product was chromatographed on silica eluting with ethyl acetate:hexane 2:3→1:0, to give predominantly 6β-hydroxy-2α,5α,7α-trimethylcyclohept-3-en-1-one **(5)** (0.258 g, 15%) as a yellow oil. *IR (thin film)* ν_{max} *(cm^{-1}):* 3446, 2967, 1702 and 1451; *^{1}H NMR (400MHz, $CDCl_3$)* 1.18 (d, 3H, J= 6.9 Hz, 2-Me), 1.20 (d, 3H, J= 6.8 Hz, 5-Me), 1.23 (d, 3H, J= 6.5 Hz, 7-Me), 2.21 (d, 1H, J= 7.4 Hz, OH), 2.76 (m, 2H, H5 and H7), 3.15 (t, 1H, J= 8.9 Hz, H6), 3.57 (m, 1H, H2), 5.32 (ddd, 1H, J= 1.9, 4.85 and 10.25 Hz, H4), 5.53 (ddd, 1H, J= 2.4, 5.4 and 10.3, H3); and 3-hydroxy-2,7-dimethylcyclohepta-2,4,6-trien-1-one **(6)** (0.156g, 10%) as a yellow brown solid after recrystalization from acetonitrile, m.p. 212-213 °C; λ_{max} (EtOH)/nm 249.8 (ε/dm^3 mol^{-1} cm^{-1} 29710), 256 (29519) and 274.2 (11884); *IR (paraffin film)* ν_{max} *(cm^{-1}):* 1511, 1244, 1066 and 796; *^{1}H NMR (400MHz, DMSO)* 2.04 (s, 3H, 7-Me), 2.14 (s, 3H, 2-Me), 6.81 (dd, 1H, J= 8.4 and 11.8 Hz, H5), 6.97 (d, 1H, J= 11.5 Hz, H4), 7.18 (d, 1H, J= 8.4 Hz, H6), 10.34 (brs, 1H, OH); *^{13}C NMR (100MHz, DMSO)* 14.1, 23.45, 128.40, 129.90, 132.40, 149.30 and 161.10. Found: C 71.8, H 6.5%. $C_9H_{10}O_2$ requires C 72.0, H 6.7%.

2-(*t*-Butoxycarbonylmethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-one (13): Methyllithium (1.4 M in ether, 14.3 ml, 20 mmol) was added to a stirred solution of 3-trimethylsilyloxy-8-oxabicyclo[3.2.1]octa-2,6-diene[12] (3.92 g, 20 mmol) in DME (35 ml), at -40 °C, under nitrogen atmosphere. The suspension formed was stirred for 1.5 h and *t*-butyl bromoacetate (5.75 g, 30 mmol) was added over a period of 15 min. The resultant mixture was allowed to warm to room temperature and stirred for 15 h. Water (80 ml) was added extractions with ethyl acetate were performed (4x 80 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated to an orange oil. This oil was chromatographed on silica using ethyl acetate:hexane (1:2) as elutant, to afford the product **13** as a colourless oil in 48% yield (2.3 g ,9.6 mmol). *IR (thin film)* ν_{max} *(cm^{-1}):* 3084, 2977, 1724 (ester and ketone), 1368, 1240, 1155 and 721; *^{1}H NMR (60MHz, $CDCl_3$)* 1.38 (2s, 9H, -CMe_2), 2.00-3.50 (m, 5H, 2x CH_2 and H2), 4.90-5.10 (m, 2H, H1 and H5), 6.35 (2s, 2H, H6 and H7);. Found: C 65.38, H 7.63%. $C_{13}H_{18}O_4$ requires C 65.53, H 7.61%.

2-(*t*-Butoxycarbonylmethyl)cyclohepta-2,4,6-trien-1-one (14a): Trimethylsilyl triflate (1.87 ml, 11.62 mmol) was added dropwise to an ice cooled solution of **13** (1.3 g, 5.75 mmol) and TEA (1.68 ml, 11.7 mmol) in CCl_4 (4 ml), under nitrogen. After stirring at room temperature for 2 h the reaction was quenched by addition of saturated aqueous solution of $NaHCO_3$ (30 ml), and the product extracted with DCM (3x 30 ml). The combined organic extract was dried ($MgSO_4$) and concentrated to give an orange oil. This oil was purified by column chromatography (ethyl acetate:hexane 2:3) to provide the ester **14a** as an yellow oil (33%, 0.42g, 1.91 mmol) and the acid **14b** (15%, 0.14 g, 0.86 mmol). Data for **14a:***IR (thin film)* ν_{max} *(cm^{-1}):* 3020, 2978, 2932, 1727, 1632, 1578, 1522, 1469, 1392, 1219, 1154 and 775; *^{1}H NMR (60MHz, $CDCl_3$)* 1.40 (s, 9H, CMe_3), 3.40 (s, 2H, CH_2), 6.70-7.20 (m, 5H). Found: C 70.82, H 7.30%. $C_{13}H_{16}O_3$ requires C 70.89, H 7.32%.

Data for **14b**: White solid, m.p. 123-125 °C; *IR ($CHCl_3$) ν_{max} (cm^{-1}):* 3200-2550, 1703, 1620, 1596, 1509, 1467, 1601 and 770; *^1H NMR (60MHz, $CDCl_3$):* 3.50 (s, 2H, CH_2), 3.00-5.00 (brs, 1H, OH), 6.60-7.30 (m, 5H). Found: C 65.46, H 4.87%. $C_9H_8O_3$ requires C 65.84, H 4.91%.

8-Oxabicyclo[5.3.0]dec-3-en-2,9-dione (16) and 2α-methoxycarbonylmethyl-3β-hydroxycyclohept-6-en-1-one (17):

***Method a** (TMSOTf)*: To a stirring solution of diisopropylamine (0.82ml, 6mmol) in dry THF (15ml) under a nitrogen atmosphere at -78°C was added n-butyllithium (2.4ml, 6mmol, 2.5M in hexane). After 5 minutes the reaction mixture was allowed to warm up to room temperature and after a further 20 minutes the mixture was cooled to -78°C. Then, a solution of **15a** (779mg, 4mmol) in dry THF (39ml) was added and the resultant mixture was stirred at -78°C for 1.5 hours. A solution of trimethylsilyltrifluoromethanesulphonate (TMSOTf) (3.82 ml, 20mmol) in dry THF (15ml) was added and the reaction mixture was stirred at -78°C for a further 2.5 hours. A saturated aqueous solution of ammonium chloride (60ml) was added and extractions with diethyl ether (4 x 40ml) were performed. The combined organic extracts were dried over $MgSO_4$, concentrated and submitted to flash column chromatography on silica gel eluting with a mixture of petroleum spirit and diethyl ether (1:3 to 1:4) to give **16** (129mg, 20%) and some recovered starting material (390mg, 50%).

***Method b** ($ZrCl_4$ / Et_3N)*: To a suspension of zirconium tetrachloride (1.05g, 4.5mmol) in dry DCM (15ml) at -78°C under a nitrogen atmosphere was added triethylamine (0.63ml, 4.5mmol). This mixture was stirred for 10 minutes at -78°C prior to the addition of **15a** (300mg, 1.5mmol) in dry DCM (6 ml). The reaction mixture was stirred at -78°C for 5 hours. Then a saturated aqueous solution of ammonium chloride (10ml) was added, the 2 phases were separated and the aqueous layer was extracted with DCM (3 x 10ml). The combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure. Flash column chromatography of the crude reaction mixture on silica gel with petroleum spirit and ethyl acetate (3:1 to 1:1) as eluants gave two main products : **16** (36mg, 14% yield) and **17** (48mg, 16% yield) and some starting material was recovered (55mg, 18%).

***Method c** ($TiCl_4$, via Silyl Enol Ether* **18**): To a solution of diisopropylamine (2.12ml, 15mmol) in dry THF (47ml) at -78°C under a nitrogen atmosphere was added dropwise n-butyllithium (5.96ml, 15mmol, 2.5M in hexane). After 5 minutes, the solution was allowed to warm to room temperature and after a further 15 minutes it was cooled to -78°C. Trimethylsilyl chloride (6.62ml, 50mmol) was added and after 2 minutes a solution of **15** (2.0g, 10mmol) in dry THF (19ml) was added. The mixture was stirred at -78°C for 3:5hours. Then, a saturated aqueous solution of sodium bicarbonate (30ml) was added and extractions with petroleum spirit (3 x 30ml) and diethyl ether (2 x 20ml) performed. The combined organic extracts were washed with a saturated aqueous solution of cupric sulphate (10ml), dried over magnesium sulphate and concentrated to a colourless oil. Flash chromatography on silica gel with a mixture of petroleum spirit and diethyl ether (2:1 to 1:1) as eluants gave **18** (1.636g, 60%) and some starting material was recovered (0.599g, 30%).

To a solution of the enol silane **18** (371mg, 1.37mmol) in dry DCM (5ml) under a nitrogen atmosphere at -78°C was added titanium tetrachloride (1.37ml, 1.37mmol, 1M in THF). After stirring at -78°C for 3 hours, a saturated aqueous solution of sodium bicarbonate (10ml) was added and extractions with DCM (4 x 10ml) were performed. The mixture was immediately purified by flash column chromatography on silica gel with a mixture

of petroleum spirit and diethyl ether (1:2) as eluants and **16** (15mg, 7%), **17** (45mg, 17%) and **15** (196mg, 72%) were obtained. Obs.: When the reaction mixture was stirred at -78°C for 8 hours and at room temperature for 2 days the yields were as follows: **16** (36%), **17** (14%) and **15** (25%).

Compound 16 ($C_9H_{10}O_3$, white crystals): *m.p.* 121-122 °C; *Rf:* 0.26 (ethyl acetate / petroleum spirit 1:1); *IR (paraffin liquid film)* ν_{max} *(cm^{-1}):* 1773 (bS), 1666 (S), 1557, 1257, 1220, 1195, 1170 (M); 1130, 1075 (W); 1040, 1015 (M); 965, 945, 895, 870, 850 (W); 825 (M); 785, 770 (W); *^{1}H NMR (400MHz, $CDCl_3$)* 2.06-2.16 (m, 1H, H6); 2.51-2.63 (m, 2H, H5 and H6'); 2.62-2.80 (m/dd, 2H, J=8.43 and 17.95Hz, H5' and H10); 2.99 (dd, 1H, J= 11.72 and 17.95Hz, H10'); 3.39-3.47 (m, 1H, H1); 4.37-4.43 (m, 1H, H7); 6.10 (d, 1H, J=12.46Hz, H3); 6.63-6.69 (m, 1H, H4); *^{13}C NMR (100MHz, $CDCl_3$) (DEPT):* 25.07 (CH_2, C5), 30.03 (CH_2, C6), 30.72 (CH_2, C10), 54.50 (CH, C1), 78.25 (CH, C7), 131.67 (CH, C3), 145.32 (CH, C4), 174.57 (C, C9=O), 195.32 (C, C2=O), *MS m/z (%):* 166 (M^+, 18), 149 (40), 138 (6), 121 (13), 107 (9), 94 (13), 91 (12), 81 (43), 68 (62), 65 (11), 55 (56), 53 (42), 39 (100).

Compound 17 ($C_{10}H_{14}O_4$, white crystals): *IR* $\nu_{max.}$ *(cm^{-1}):* 3457 (bS); 2952, 1738, 1678, 1440 (S); 1411, 1377, 1343 (M); 1205, 1157, 1058 (S); 988, 953, 920, 896, 879, 825, 759, 735 (M); *^{1}H NMR (400MHz, $CDCl_3$)* 1.73-1.81 (m, 1H, H4); 2.07 (bdd, 1H, J=6.8 and 15.2Hz, H4'); 2.38-2.47 (m, 1H, H5); 2.59* (b, 1H, OH); 2.70-2.80 (m/dd, 2H, J=5.3 and 17.0Hz, H5' and H8); 3.00 (dd, 1H, J=8.1 and 16.9Hz, H8'); 3.27 (td, 1H, J= 5.1, 8.1 and 8.1Hz, H2); 3.68 (s, 3H, OMe); 3.85-3.86 (m, 1H, H3); 6.11 (dd, 1H, J= 3.5 and 11.5Hz, H7); 6.83 (m, 1H, H6); *^{13}C NMR (100MHz, $CDCl_3$) (DEPT):* 24.59 (CH_2, C5), 33.57 (CH_2, C8), 37.10 (CH_2, C4), 51.95 (CH_3, OMe), 55.29 (CH, C2), 70.69 (CH, C3), 132.74 (CH, C7), 148.25 (CH, C6), 173.89 (C, ester C=O), 200.37 (C, ketone C=O); *MS m z (%):* 199 (50); 181 (22); 167 (56); 149 (100); 138 (34); 125 (24); 121 (30); 120 (42); 107 (22); 93(36); 81 (28); 71 (32); 68 (28); 55 (73); 49 (34); *Accurate Mass Peak Match (m/z):* 199.0970 ($[M+H]^+$, $C_{10}H_{15}O_4$ requires 199.0966)

*This signal presents different chemical shifts when sample concentration varies

Compound 18 ($C_{13}H_{22}SiO_4$, colourless oil): *Rf:* 0.5 (diethyl ether / petroleum spirit 2:1); *^{1}H NMR (400MHz, $CDCl_3$)* 0.13 (s, $OSiMe_3$); 1.83-1.84 (m, 4H, H7, H6, H6' and H7'); 2.06 (dd, 1H, J=7.9 and 15.9Hz, H8); 2.54 (dd, 1H, J= 7.2 and 15.9Hz, H8'), 3.23-3.28 (m, 1H, H4); 3.64 (s, 3H, OMe); 4.43-4.44 (m, 2H, H1 and H5); 4.88-4.90 (m, 1H, H2); *^{13}C NMR (100MHz, $CDCl_3$) (DEPT):* -0.64 (CH_3, $OSiMe_3$), 22.92 (CH_2, C7), 31.46 (CH_2, C8), 34.20 (CH_2, C6), 41.53 (CH, C4), 50.95 (CH_3, OMe), 72.42 (CH, C1), 75.91 (CH, C5), 106.13 (C, C2), 148.54 (C, C3), 172.27 (C, ester C=O), *MS m/z (%):* 270 (16); 241 (22); 211 (9); 197 (22); 183 (10); 169 (26); 155 (12); 89 (17); 73 (100); 59 (12); 45 (19); *Accurate Mass Peak Match (m/z):* 270.1283 (M^+, $C_{13}H_{22}SiO_4$ requires 270.1281).

2-Methoxycarbonylmethyl-6-trimethylsilyloxy-cyclohept-2-en-1-one (19), 2α-methoxycarbonyl methyl-3β-trimethylsilyloxycyclohept-6-en-1-one (20) and 1β,6β-bis(trimethylsilyloxy)-8-methoxycarbonyl-bicyclo[5.1.0]-oct-2-ene (21): To a solution of diisopropylamine (1.06ml, 7.5mmol) in dry THF (16ml) at -78°C under a nitrogen atmosphere was added, dropwise, n-butyllithium (3ml, 7.5 mmol, 2.5M in hexane). After 5 minutes the solution was allowed to warm to room temperature and then cooled down to -78°C, stirring for

further 15 minutes. A solution of **15a** (1.0g, 5.05mmol) in dry THF (14ml) was added and the mixture stirred at -78°C for 1.5 hours. Then, trimethylsilyltrifluoromethanesulphonate (1ml, mmol) was added and the mixture stirred for 2 hours at -78°C. A saturated aqueous solution of sodium bicarbonate (20ml) was added and extractions with diethyl ether (4 x 20ml) were performed. The combined organic extracts were washed with cupric sulphate saturated aqueous solution, dried over magnesium sulphate, concentrated under reduced presure to leave an yellow oil. This oil was submitted to a flash column chromatography on silica gel eluting with a mixture of petroleum spirit and diethyl ether (2:1 to 1:1) to afford compounds **19** (78mg, 6%), **20** (111mg, 8.%) and **21** (262mg, 15.%) were obtained and some starting material (493mg, 49%).

Compound 19 ($C_{13}H_{22}SiO_4$, colourless oil): *^1H NMR (400MHz, $CDCl_3$)* 0.09 (s, ca. 9H, OTMS), 1.83-1.87 (m, 2H, H4 and H4'), 2.25-2.36 (m, 1H, H5), 2.58-2.63 (m, 1H, H5'), 2.85 (d, 2H, J= 6.6Hz, H7 and H7'), 3.23(s, 2H, H8 and H8'), 3.63 (s, 3H, OMe), 4.17-4.21 (m, 1H, H6), 6.63 (dd, 1H, J= 4.76 and 7.33Hz, H3).

Compound 20 ($C_{13}H_{22}SiO_4$, colourless oil): *^1H NMR (400MHz, $CDCl_3$)* 0.09 (s, 9H, OTMS), 1.61-1.68 (m, 1H, H4), 1.95 (d, 1H, J= 6.8 and 14.8Hz, H4'), 2.29-2.38 (m, 1H, H5), 2.55 (dd, 1H, J= 3.5 and 16.8Hz, H8), 2.66-2.74 (m, 1H, H5'), 2.86 (dd, 1H, J= 10.26 and 16.85Hz, H8'), 3.25-3.31 (m, 1H, H2), 3.61 (s, 3H, OMe), 3.70-3.75 (m, 1H, H3), 6.06 (dd, 1H, J= 3.30 and 11.73Hz, H7), 6.74-6.80 (m, 1H, H6). Obs.: **20** can be transformed into **17** upon reaction with tetrabutylammonium fluoride in THF, at room temperature.

Compound 21 ($C_{16}H_{30}Si_2O_4$, colourless oil): *Rf:* 0.67 (petroleum spirit/diethyl ether 1:1); *IR ν_{max} (cm^{-1}):* 3219 (M); 2955 (S); 2857 (M); 1737 (S); 1665 (M); 1444 (S); 1410, 1370, 1352, 1334 (M); 1316, 1252, 1227, 1175 (S); 1127 (MS); 1098, 1070, 1014, 998 (S); 964, 944 (M); 918, 893, 844 (S); 788 (M); 757 (S); 717, 690, 639 (M); *^1H NMR (400MHz, $CDCl_3$)* 0.10 (s, 9H, OTMS a), 0.10 (s, 9H, OTMS b), 1.37-1.44 (m, 1H, H5), 1.51 (d, 1H, J= 7.3Hz, H8), 1.79-1.86 (m, 1H, H5'), 1.86-1.96 (m, 1H, H4), 2.40-2.45 (m, 1H, H7), 2.49 (ddd, 1H, J = 13.7, 6.6, 3.5, H4'), 3.65 (s, 3H, OMe), 3.94-3.98 (m, 1H, H6), 5.49 (ddd, 1H, J = 11.6, 7.5, 3.5, H3), 5.82 (ddd, 1H, J = 11.6, 2.6, 1.8, H2); *^{13}C NMR (100MHz, $CDCl_3$) (DEPT):* 0.00 (CH_3, OTMS a), 0.73 (CH_3, OTMS b), 23.26 (CH_2, C4), 32.85 (CH_2, C5), 34.78 (CH, C8), 41.08 (CH, C7), 51.54 (CH_3, OMe), 64.06 (CH, C1), 69.75 (CH, C6), 128.73 (CH, C3), 131.49 (CH, C2), 169.22 (C, ester C=O); *MS m/z (%):* 343($[M+H]^+$, 1), 252 (6), 237 (11), 226 (21), 211 (13), 193 (14), 179 (8), 167 (100), 151 (40), 122 (8), 89 (13), 73 (93), 59 (14), 45 (25); *Accurate Mass Peak Match m/z:* 342.1663 (M^+, $C_{16}H_{30}Si_2O_4$ requires 342.1674) and 343.1761 ($[M+H]^+$, $C_{16}H_{31}Si_2O_4$ requires 343.1752).

6-Methyl-8-oxabicyclo[5.3.0]dec-4,6,10(1)trien-9-one (23): To a stirrred solution of the ester **15b** (273 mg, 1.3 mmol) and potassium iodide (622 mg, 3.8 mmol) in dry chloroform (8 mL), under a nitrogen atmosphere, was added boron trifluoride etherate (0.92 mL, 7.5 mol). The reaction mixture was refluxed at 70 °C for five days, at wich time all the starting material had disappeared (t.l.c. analysis). The reaction was worked up by quenching with saturated aqueous solution of $NaHCO_3$ (50 mL), and extracting the crude product into dichloromethane (3x 30 mL). The combined organic extracts were then washed with $Na_2S_2O_5$ (2M, 30 mL) and water (30 mL), followed by drying over $MgSO_4$. Concentration gave a brown oil wich was subsequently purified by column chromatography (1:1 petroleum: ether) to afford the lactone **23** in 40% yield (85 mg, 0.52 mmol) as a

pale yellow solid. *Rf:* 0.29 (Petroleum spirit/diethyl ether 1:1); *m.p.* 65-67 °C, *IR* ν_{max} *(cm^{-1}):* 3009 (M), 2934 (M), 1742 (S), 1673 (W), 1642 (M), 1580 (W), 1553 (M), 1431 (M), 1219 (S), 1089 (M), 932 (S), 840 (S), and 668 (S).; *^{1}H NMR (400MHz, $CDCl_3$)* 2.05 (s, 3H, CH_3), 2.40-2.50 (m, 4H, CH_2CH_2), 5.85 (s, 1H, H10), 6.30-6.40 (m , 1H, H4), 6.43 (d, 1H, J= 11 Hz, H5). *MS m/z (%):* 163($[M+H]^+$, 100), 149(10), 133(25), 119(18), 105(20), 91(50), 65(20), *Accurate Mass Peak Match m/z*: 163.0758 ($[M+H]^+$, $C_{10}H_{11}O_2$ requires 163.0759).

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