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Synthetic studies on CP-225,917 and CP-263,114: concise synthesis of the bicyclic core using an intramolecular Mukaiyama aldol reaction †

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A concise synthesis of the bicyclo[4.3.1]dec-1(9)-en-10-one core of the natural products CP-225,917 and CP-263,114 is reported, employing an intramolecular Mukaiyama aldol cyclisation as a key step.

Introduction

The natural products CP-225,917 **1** and CP-263,114 **2** were isolated by Pfizer workers in the mid-1990s from the fermentation products of an unidentified fungus.[1a,1b] They were identified as moderate inhibitors of squalene synthase and *ras*-farnesyl protein transferase, enzymes of interest in the cholesterol-lowering and anti-cancer areas respectively. A major stimulus for the synthetic chemist to study these two compounds is their highly novel structure. Common to both is a highly functionalised bicyclo[4.3.1]dec-1(9)-en-10-one core containing an anti-Bredt, bridgehead alkene. Further synthetic challenges are presented by the fused maleic anhydride unit and a quaternary stereocentre at C14 (natural product numbering) which is part of a lactone acetal array. Compounds **1** and **2** display very similar structural features, the only difference being the acetal linkage in **2** joining the sidechain C7-hydroxy group to the bridgehead carbonyl. Interconversion of **1** and **2** has been shown to be feasible.[1c] The synthetic community has risen admirably to the challenges posed by the synthesis of these compounds: as well as many inventive model studies,[2,3] monumental total syntheses have been recorded by the groups of Nicolaou,[4] Danishefsky,[5] Shair,[6] and Fukuyama.[7] Asymmetric total synthesis has allowed the absolute configuration of the natural products to be revised to that shown in Fig. 1.[4–7]

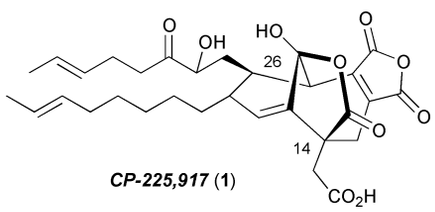
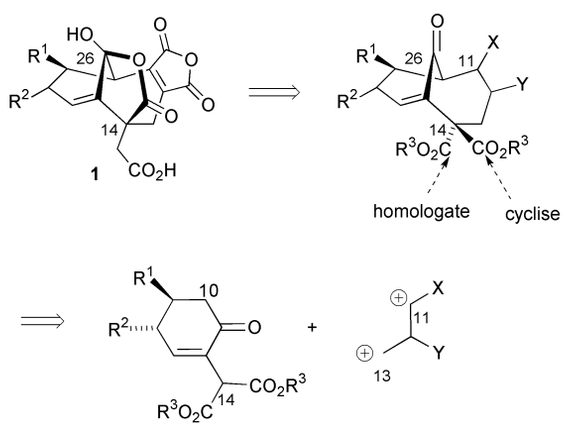


Fig. 1

When our own interest in these compounds began, no synthetic studies of CP-225,917 had been reported. We hoped to develop a route that would allow the rapid preparation of the bicyclo[4.3.1]dec-1(9)-en-10-one core and a range of analogues. Since we were concerned by the potential sensitivity of the anhydride unit, we envisaged its introduction at a late stage in the synthesis. Having simplified the polycyclic system by removing the anhydride group (Scheme 1), the next problem was how we were to construct the γ-lactone acetal moiety and the C14 quaternary stereocentre. The natural product displays a carboxylic acid at C14 cyclised onto a ketone at C26, and we hoped to utilise this feature in the construction of the C14 stereocentre, allowing differentiation of two diastereotopic ester groups *via* the derived carboxylic acids. Having a *gem*-diester at C14 was in turn a useful pointer to further facile bond disconnections. It was envisaged that the anion-stabilising properties of such a diester could be used to create the C13–C14 bond *via* attack of a C14 anion onto a suitably activated



Scheme 1

† Electronic supplementary information (ESI) available: crystal data for **13a**. See http://www.rsc.org/suppdata/p1/b2/b202752f/

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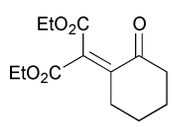
electrophilic centre at C13. A further bond disconnection between C10 and C11 was suggested by the anion stabilising properties of the C26 carbonyl group, *i.e.* an anion at C10 would attack a suitably activated C11. These latter two disconnections led to a simple cyclohexenone-malonate derivative **3** and a suitable bis-electrophile (Scheme 1).

Having devised a synthetic strategy, we began our investigations by looking at a model synthesis of the core bicyclic system lacking the side chains (*i.e.* $R^1 = R^2 = H$ in Scheme 1). Here we report in full the realisation of this goal,[8] resulting in the development of a highly concise synthesis of the key bicyclo[4.3.1]dec-1(9)-en-10-one core.

Results and discussion

Our first challenge was the synthesis of the requisite bis-nucleophile component, cyclohexenone **3**. Since our actual requirement was for an allylic anion that would act as a C14-nucleophile, we initially reasoned that it would not matter if we were to synthesise either endocyclic olefin **3**, or exocyclic isomer **4**, since treatment of either with base should generate the same allylic anion. In line with precedent for deconjugative alkylation of α,β-unsaturated esters,[9] we anticipated that alkylation of such an anion would occur α to the diester, leading to an endocyclic enone. Thus, our first explorations were aimed at establishing a synthetic route to ketone **4**, which we anticipated being easier to prepare than **3**. Attempted synthesis of **4** by condensation of diethyl malonate and cyclohexane-1,2-dione mediated by base (NaOMe, MeOH) or Lewis acids was unsuccessful, perhaps unsurprisingly in view of the likely predominance of the enol tautomer of the dione. In a second approach, we hoped to use allylic oxidation to introduce the ketone functionality in **4**. Treatment of cyclohexanone with dimethyl malonate under standard Knoevenagel conditions afforded the known[10] exocyclic olefin **5**. However, attempted allylic oxidation of **5** under various conditions (*e.g.* SeO_2 or CrO_3) failed to effect the desired transformation, probably because the alkene is highly electron deficient.



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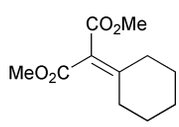

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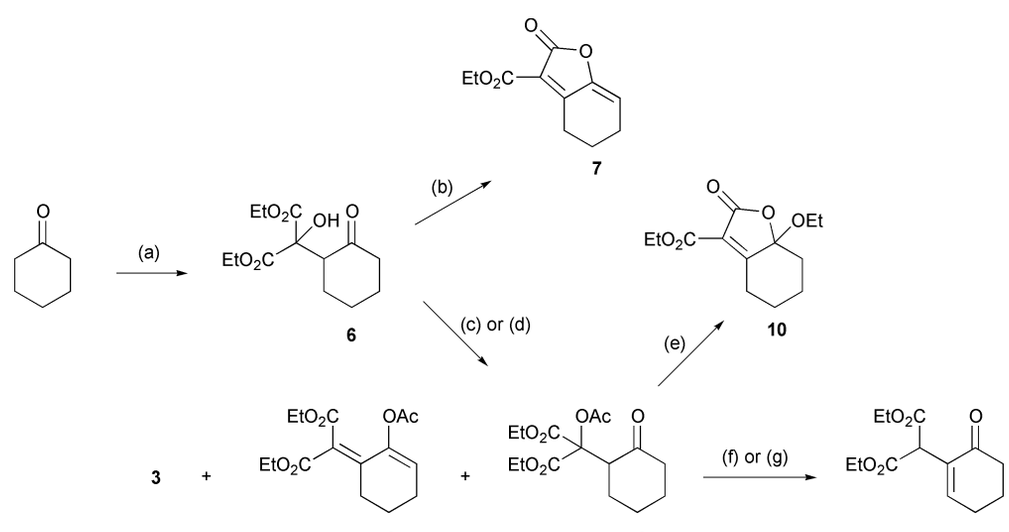
In view of these unsuccessful studies, we successfully reversed the roles of the two components, making the malonate portion the electrophile, and the cyclohexanone the nucleophile. Hence, treatment of the lithium enolate of cyclohexanone with diethyl oxomalonate generated the tertiary alcohol **6** in good yield (Scheme 2). It was now hoped that we could effect elimination of this alcohol to create the exocyclic olefin **4**. Several conditions were tried, without success: thionyl chloride,[11] Burgess' reagent[12] and boron tribromide[13] failed to react with the tertiary alcohol. We were also unable to form a mesylate§ from **6**. Reaction did occur with phosphorus tribromide, but the major product was lactone **7** (Scheme 2), presumably derived from elimination of the tertiary alcohol and subsequent lactonisation of the enol form of the ketone. Exposure of tertiary alcohols to Swern conditions ($(COCl)_2$–DMSO) has been reported to effect elimination,[14] but treatment of **6** in this way furnished only the corresponding methylthiomethyl ether. Following these unsuccessful efforts to effect elimination of alcohol **6**, attempts to convert it to the corresponding acetate leaving group yielded more interesting and encouraging results. Treatment with acetic anhydride and triethylamine in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) provided acetate **9** (19%) along with enol acetate **8** (20%) and—encouragingly—the desired enone **3** (8%), presumed generated from **9** *via* base-mediated elimination followed by alkene isomerisation.

As a viable route for the synthesis of **3**, this reaction was clearly unsatisfactory, as it was low yielding and gave rise to several unwanted by-products. Since **3** appeared to arise from acetate **9**, we attempted to find conditions for the clean formation of the latter, and were pleased to find that the use of catalytic trimethylsilyl trifluoromethanesulfonate in acetic anhydride as recently reported by Procopiou and co-workers[15] provided acetate **9** in a very rapid and clean reaction, with none of the by-products observed under the base-mediated conditions (Scheme 2). With a clean synthesis of acetate **9** in hand, we next examined the elimination step. Reaction of **9** with NaH in DMF afforded a moderate yield (43%) of a product which was isomeric with the desired alkenes **3** and **4** but which did not display the expected ^1H and ^{13}C NMR characteristics. Most notably, it lacked the ketone carbon in the ^{13}C NMR spectrum, and the ^1H NMR spectrum indicated the presence of only one ethyl ester. This compound was tentatively assigned the structure **10** which is believed to arise from elimination to give the exocyclic alkene **4** followed by rearrangement to the more stable pseudoester. There is precedent for this rearrangement

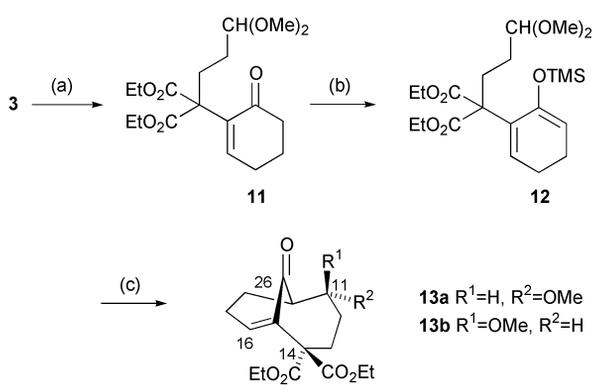
§ The IUPAC name for mesylate is methanesulfonate.



Scheme 2 *Reagents and conditions*: (a) (i) LDA, THF, −78 °C, 1 h, (ii) diethyl oxomalonate, −78 to 0 °C, 12 h, 80%. (b) 1 eq. PBr_3, PhH, reflux, 83%. (c) 1.5 eq. Ac_2O, 10 mol% DMAP, 10 eq. Et_3N, 24 h, (**9**) 19%, (**8**) 20% and (**3**) 8%. (d) 1.5 eq. Ac_2O, 2 mol% TMSOTf, 0 °C, 20 min, (**9**) 80%. (e) NaH, DMF, 43%. (f) 2 eq. DBU, toluene, 0 °C, 32%. (g) 2 eq. Dabco™, toluene, reflux, 90 min, 75%.

in acyclic 4-oxo-2-alkan-2-ylidenemalonates.[16] Fortunately, however, amine bases did yield the desired elimination products. Treatment of **9** with 2 eq. DBU in toluene at 0 °C led to formation of endocyclic olefin **3**, albeit in low yield (32%). We attributed the low yield to base-induced polymerisation side-reactions. This route gave us rapid access to our required ketone **3** in just 3 steps, from cyclohexanone. However, it was still rather inefficient at the elimination stage, and upon scaling up to gram quantities of material, yields were found to drop even further. In an effort to reduce polymerisation and other side-reactions, we performed the reaction at lower temperatures and higher dilutions. Adding the base at −20 °C caused complete cessation of reaction, and no improvement in yield was seen under higher dilution conditions. We then turned to alternative strong bases to effect the reaction. Neither LDA (2 eq.) nor sodium *tert*-butoxide (2 eq.) caused any reaction to occur, and treatment of **9** with two equivalents of triethylamine in toluene at reflux gave only a 16% yield of **3**. Eventually, 1,4-diazabicyclo[2.2.2]octane (Dabco™) in toluene at reflux was found to effect the required conversion in high and reproducible yields. It is assumed that the increase in yield relative to the DBU conditions is due to the lower basicity of Dabco™ which reduces polymerisation side-reactions that may be a problem with the stronger base. It is possible, however, that Dabco™ promotes alternative mechanistic pathways by acting as a nucleophilic catalyst. While it is assumed that the formation of **3** from **9** proceeds *via* the exocyclic isomer **4**, performing the reaction in an NMR tube in d_6-toluene at 100 °C, recording spectra at 5 minute intervals, displayed no detectable intermediates, suggesting that isomerisation of **4** is rapid.

Now that we had access to large quantities of ketone **3** *via* a simple three-step route from cyclohexanone, we were in a position to investigate its use as a bis-nucleophile. A range of carbon–carbon bond-forming reactions were considered for the cyclisation, and of these, the Mukaiyama directed aldol reaction was thought to be a particularly good option.[17] The intramolecular Mukaiyama aldol reaction has frequently been employed as a versatile tool for the synthesis of medium rings.[18] Unlike the base-catalysed crossed-aldol reaction, it allows control over which component is the nucleophile—the silyl enol ether—and which is the electrophile: an aldehyde or acetal. With this in mind, we proceeded to pursue a Mukaiyama aldol cyclisation approach to the core bicycle of CP-225,917. In order to introduce the acetal we required, ketone **3** was alkylated with commercially available 3-bromopropionaldehyde dimethyl acetal (Scheme 3), corresponding to the bis-electrophile unit



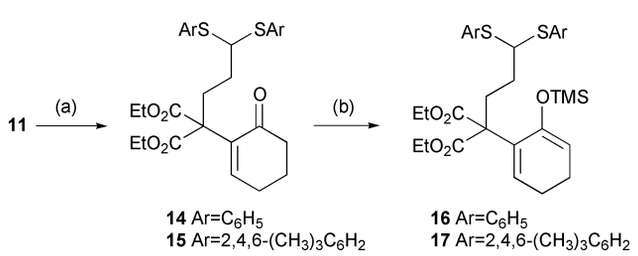
Scheme 3 *Reagents and conditions*: (a) (i) 1.05 eq. NaH, DMF, 0 °C, 1 h (ii) Bu_4NI, 3-bromopropionaldehyde dimethylacetal, 60 °C, 21 h, 68%. (b) (i) LDA, THF, −78 °C, 10 min (ii) 1.8 eq. TMSCl, −78 °C, 4 h, 92%. (c) $TiCl_4$, CH_2Cl_2, −78 °C to RT, 15 h, **13a**: 12%, **13b**: 40%.

envisaged in our retrosynthesis (Scheme 1). The anion of **3** was pre-formed by treatment with an equimolar amount of sodium hydride in DMF and then alkylated with 3-bromopropionaldehyde dimethyl acetal in the presence of catalytic tetrabutylammonium iodide, providing acetal **11** in 68% yield. Formation of the silyloxydiene **12** was achieved by trapping the kinetic lithium enolate of **11** with trimethylsilyl chloride. In the key cyclisation reaction, treatment of **12** with titanium tetrachloride in dichloromethane generated the model [4.3.1]-bicycle **13** as a mixture of diastereomers, which could be separated by flash chromatography to give **13a** (12%) and **13b** (40%).

Assignment of the bicyclic structure shown to be ketone **13** was initially made by spectroscopic analysis. The upfield shift observed for the vinylic proton at C16 (natural product numbering) in the ^{1}H NMR spectrum (*ca.* 6.4 ppm in **13** compared to 6.95 ppm in **11**) suggests that the enone is not able to adopt planarity in the cyclised product and supports formation of the anti-Bredt system. ^{1}H-COSY, HMQC and HMBC data confirmed the connectivity. Additionally, the carbonyl stretching frequencies in the IR spectrum of **13a** (1708 cm^{-1}) and **13b** (1715 cm^{-1}) were similar to that reported (1710 cm^{-1}) for bicyclo[4.3.1]dec-1(9)-en-10-one itself.[19] In our preliminary communication of this work,[8] we proposed a tentative assignment of relative stereochemistry at the methoxy-bearing C11-stereocentre based on NOE and molecular mechanics studies. However, we subsequently obtained an X-ray crystal structure[20] of the minor isomer **13a** which showed our initial tentative assignment to be incorrect and allowed unambiguous assignment of the stereochemistry as depicted in Scheme 3, as well as structural confirmation.

Whilst the yield obtained in the initial small-scale Mukaiyama aldol cyclisations of **12** was good, it proved difficult to attain consistently high yields in repeat runs of the experiment, particularly on larger scales. In the pursuit of higher reproducibility, we examined alternative Lewis acids. Boron trifluoride–diethyl ether gave a similar overall yield (20% **13a** and 28% **13b**), whilst none of the cyclised product could be observed when trimethylsilyltrifluoromethanesulfonate or $TiCl(O^iPr)_3$ was used. Use of scandium triflate¶ in THF–water[21] afforded only the hydrolysed ketone **11**, whilst the same Lewis acid in dichloromethane at −78 °C gave only a 23% yield of aldol products **13** (**13a** : **13b** approx 1 : 4). The best reproducibility on a larger scale was found using zinc(II) chloride and 4 Å molecular sieves[22] in dichloromethane at room temperature, which gave a higher yield of aldol products (40–62%) with a 40 : 60 diastereoisomeric ratio of **13a** : **13b** along with 10–34% of starting ketone **11**.

The C11-methoxy-substituent in **13** did not appear amenable to further synthetic manipulation towards the required anhydride unit. Indeed, preliminary attempts at its selective cleavage using trimethylsilyl iodide[18d] resulted in the opening of the bicyclic ring system by retro-aldol reaction. We were attracted to the possibility of employing a dithioacetal in the ring closure step, since the resulting thioether in the cyclisation product could be converted to an alkene by oxidation and sulfoxide *syn*-elimination, or transformed into a ketone by a Pummerer-type process. The required dithioacetal **14** was prepared by treatment of dimethoxyacetal **11** with (phenylthio)trimethylsilane in the presence of TMSOTf (Scheme 4).



Scheme 4 *Reagents and conditions*: (a) for **14**: Me_3SiSPh, TMSOTf, CH_2Cl_2, 98%. For **15**: $Me_3SiS(2,4,6\text{-}(CH_3)_3C_6H_2)$, TMSOTf, CH_2Cl_2, 64%. (b) TMSOTf, Et_3N, CH_2Cl_2, 88%.

¶ The IUPAC name for triflate is trifluoromethanesulfonate.

Unfortunately, the derived silyl enol ether **16** did not undergo cyclisation on exposure to a range of Lewis acids ($Hg(OTf)_2$), $ZnCl_2$, $TiCl_4$, or $SnCl_4$). Heathcock and co-workers have reported that the mesityl-dithioacetal counterparts are more reactive in intermolecular reactions with silyl enol ethers.[23] However, attempted cyclisation of **17** proved similarly unsuccessful (using TMSOTf, $ZnCl_2$, $ZnBr_2$, $TiCl_4$, $SnCl_4$, $Ag(OTf)_2$, $Hg(OTf)_2$, $HgCl_2$, or $Me_2(MeS)SBF_4$). At this time, therefore, it seems likely that the most fruitful approach for progressing the total synthesis will involve the conventional acetal-mediated cyclisation, using an acetal that leads to a more readily deprotected C11-ether (*e.g.* benzyl).

Conclusions

The work reported here is an important first step in the development of a synthetic approach to the CP-compounds **1** and **2**. The bis-electrophile approach using the Mukaiyama aldol reaction as the key cyclisation step has allowed a highly concise synthesis of model bicycle **13** which incorporates several of the key features of the natural product. It is noteworthy that the anti-Bredt bicyclic system can be prepared using straightforward chemistry, and the diester **3** can be envisaged as a versatile precursor to a variety of analogues. The model compound **13** has a *gem*-diester group which could be converted to the lactone acetal unit of the natural product, as well as having the C26-bridgehead ketone in the correct oxidation state. Further manipulations, as well as the asymmetric synthesis of analogues of the key bis-nucleophile **3** bearing sidechain functionality, are under exploration and will be reported in due course.

Experimental

Unless otherwise indicated, ^1H and ^{13}C spectra were recorded in $CDCl_3$ on Bruker DRX 500 MHz, AM 400 MHz or WM 250 MHz NMR spectrometers, using residual protic solvent ($CHCl_3$, $\delta_H = 7.26$ ppm) or $CDCl_3$ ($\delta_C = 77.0$ ppm, t) as internal reference. Coupling constants are measured in Hertz. The multiplicities in ^{13}C spectra were determined by DEPT experiments. Infra-red spectra were run on a Perkin-Elmer 1605 FT-IR machine from 4000–600 cm^{-1}. Mass spectra were recorded under conditions stated for that particular compound using a VG-7070B, VG Micromass 70E, VG Biotech Quatro II, VG ZAB-E, VG Autospec or Micromass LCT (Electrospray) instrument. Microanalyses were performed at the University of Nottingham. Column chromatography was performed on Merck Kiesegel 60 (230–400 mesh). Diethyl ether and tetrahydrofuran solvents were distilled from sodium–benzophenone ketyl, dichloromethane from calcium hydride and dimethylformamide from anhydrous magnesium sulfate. Petrol refers to petroleum ether of boiling range 40–60 °C which was distilled prior to use. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kiesegel 60 F254) and visualised by ultra-violet light and/or acidic ceric ammonium molybdate, or 2,4-dinitrophenylhydrazine as appropriate.

Dimethyl 2-cyclohexylidenemalonate 5[10a]

A solution of titanium tetrachloride in dichloromethane (1 M, 20 ml, 20 mmol) was added dropwise over 1 h to dry tetrahydrofuran (400 ml) and stirred under nitrogen at 0 °C. Subsequently, cyclohexanone (1.04 ml, 10 mmol) and dimethyl malonate (0.57 ml, 10 mmol) were added rapidly, followed by a solution of pyridine (3.3 ml, 40 mmol) in tetrahydrofuran (10 ml), which was added dropwise over 1 h. The mixture was allowed to warm to room temperature, and was stirred for 135 hours. It was then quenched with water (400 ml) and extracted with diethyl ether (3 × 200 ml). The combined organic extracts were washed with brine (100 ml), saturated aqueous sodium bicarbonate (50 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Chomatography (5% EtOAc–petrol) gave the *diester* **5** (700 mg, 33%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) 3.75 (6H, s, 2 × O*Me*), 2.50 (4H, t, *J* 6.1, C(2)H_2 and C(6)H_2), 1.71–1.65 (4H, m, C(3)H_2 and C(5)H_2), 1.62–1.57 (2H, m, C(4)H_2); δ_C (100 MHz, $CDCl_3$) 166.1, 162.3, 121.1, 52.0, 32.7, 28.1, 25.9.

Diethyl 2-hydroxy-2-(2-oxocyclohexyl)malonate 6

A solution of *n*-butyllithium (2.3 M, 4.35 ml, 10 mmol) was added dropwise to an ice-cool solution of diisopropylamine (1.4 ml, 10 mmol) in tetrahydrofuran (25 ml) under nitrogen. The mixture was stirred at 0 °C for 30 min before being cooled to −78 °C. Cyclohexanone (1.04 ml, 10 mmol) was added dropwise and the solution stirred for 45 minutes. Diethyl oxomalonate (1.52 ml, 10 mmol) was added and the mixture stirred for 15 hours, before being quenched with saturated aqueous ammonium chloride (30 ml), extracted with ethyl acetate (6 × 10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the crude residue gave the *alcohol* **6** (2.19 g, 80%) as a yellow oil (Found: C, 57.14; H, 7.69; $C_{13}H_{20}O_6$ requires C, 57.30; H, 7.43%); bp 149–151 °C (1.5 mmHg); ν_{max}(film)/cm^{-1} 3497, 1738 (br); δ_H (270 MHz, $CDCl_3$) 4.26–4.12 (4H, m, 2 × CH_2O), 3.87 (1H, br s, O*H*), 3.45 (1H, dd, *J* 5, 12, C(1′)*H*CO), 2.38–2.21 (2H, m, C(3′)H_2CO), 2.05–1.55 (6H, m), 1.22 (6H, m, 2 × Me); δ_C (67.5 MHz, $CDCl_3$) 208.9 (s), 169.8 (s), 169.0 (s), 78.9 (s), 62.5 (t), 62.5 (t), 55.3 (d), 41.8 (t), 27.5 (t), 26.8 (t), 24.5 (t), 14.0 (q), 13.8 (q); *m*/*z* (FAB) 295 (MNa^+, 85%), 273 (100, MH^+), 199 (40, $M^+ - CO_2Et$).

Ethyl 2-oxo-2,4,5,6-tetrahydrobenzofuran-3-carboxylate 7

Phosphorus tribromide (44 µl, 0.48 mmol) was added dropwise to a stirred solution of the alcohol **6** (64 mg, 0.24 mmol) in benzene (0.5 ml). The solution was heated to reflux for 7 hours, then cooled and diluted with diethyl ether (15 ml) and water (5 ml). The layers were separated, and the organic phase washed with 5 M sodium bicarbonate (10 ml) and water (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield the *benzofuran* **7** (41 mg, 83%) as an oil; ν_{max}(film)/cm^{-1} 1778, 1710, 1653, 1590; δ_H (400 MHz, $CDCl_3$) 6.17 (1H, t, *J* 5, *H*C(7)=), 4.34 (2H, q, *J* 7.1, CH_2O), 3.08 (2H, t, *J* 7, C(6)H_2), 2.47 (2H, dd, *J* 6, 11, C(4)H_2), 1.94–1.64 (2H, m, C(5)H_2), 1.36 (3H, t, *J* 7.1, Me); *m*/*z* (EI) 208 (M^+, 100%), 163 (83, $M^+ - EtO$), 135 (20, $M^+ - EtO_2C$) (Found M^+, 208.0737. $C_{11}H_{12}O_4$ requires *M*, 208.0736).

Reaction of alcohol 6 with acetic anhydride–4-(dimethylamino)-pyridine

4-(Dimethylamino)pyridine (5 mg, 37 µmol) was rapidly added to a stirred solution of alcohol **6** (100 mg, 0.37 mmol) in triethylamine (500 µl), followed by acetic anhydride (52 µl, 0.55 mmol). The solution was stirred for 24 hours, diluted with methanol (5 ml), stirred for 10 minutes and then concentrated *in vacuo*. The residue was dissolved in diethyl ether (10 ml), washed successively with 2 M hydrochloric acid (5 ml), saturated aqueous sodium bicarbonate (2 × 5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (20% EtOAc–petrol) gave acetate **9** (22 mg, 19%), alkene **3** (7 mg, 8%) and diethyl 2-(2-acetoxycyclohex-2-enylidene)malonate, **8** (22 mg, 20%), as a colourless oil; **8** showed the following data: ν_{max}(film)/cm^{-1} 1767, 1719, 1630, 1597; δ_H (250 MHz, $CDCl_3$) 5.91 (1H, t, *J* 4.5, *H*C(3′)=), 4.27 (2H, q, *J* 7.1, CH_2O), 4.19 (2H, q, *J* 7.1, CH_2O), 3.01–2.95 (2H, m, C(4′)H_2), 2.40–2.33 (2H, m, C(6′)H_2), 2.10 (3H, s, *Ac*O), 1.80 (2H, q, *J* 6, C(5′)H_2); δ_C (67.5 MHz, $CDCl_3$) 168.7, 166.4, 164.1, 145.5, 143.2, 129.6, 120.0, 61.3, 61.0, 27.7, 24.8, 21.5, 20.8, 14.0, 13.9; *m*/*z* (EI) 296 (M^+, 16 %), 253 (4, $M^+ - MeCO$), 223 (7, $M^+ - CO_2Et$) (Found M^+, 296.1250. $C_{15}H_{20}O_6$ requires *M*, 296.1260).

Diethyl 2-acetoxy-2-(2-oxocyclohexyl)malonate 9

Trimethylsilyl trifluoromethanesulfonate (2 μl, 5 mmol) was added rapidly with stirring to an ice-cold solution of alcohol **6** (28 g, 0.1 mol) in acetic anhydride (20 ml) under nitrogen. The solution was stirred vigorously for 20 minutes and then diluted with dichloromethane (20 ml). After a further 15 minutes the mixture was quenched with saturated aqueous sodium bicarbonate (200 ml) and extracted with dichloromethane (4 × 100 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (100 ml) and brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Azeotroping with toluene (2 × 50 ml) and recrystallisation from pentane gave the *acetate* **9** (25 g, 80%) as white crystals; mp 45–47 °C (pentane) (Found C, 57.25; H, 7.05; $C_{15}H_{22}O_7$ requires C, 57.32; H, 7.05%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1747 br, 1719; δ_H (400 MHz, $CDCl_3$) 4.29–4.21 (4H, m, 2 × CH_2O), 3.25 (1H, dd, *J* 12.8, 5.3, C(1′)*H*CO), 2.42–2.33 (2H, m, C(3′)H_2CO), 2.13 (3H, s, AcO), 2.12–1.95 (4H, m), 1.68–1.58 (2H, m), 1.28 (3H, t, *J* 7.1, Me), 1.27 (3H, t, *J* 7.0, Me); δ_C (100 MHz, $CDCl_3$) 206.7 (s), 169.2 (s), 166.5 (s), 166.1 (s), 81.3 (s), 62.2 (t), 62.0 (t), 56.5 (d), 42.3 (t), 29.0 (t), 27.2 (t), 25.1 (t), 20.7 (t), 13.8 (q); *m*/*z* (EI) 314 (M^+, 2%), 272 (6, $M^+ - CH_2CO$), 254 (7, $M^+ - AcO$).

Diethyl 2-(6-oxocyclohex-1-enyl)malonate 3

A solution of acetate **9** (1.0 g, 3.2 mmol) and 1,4-diazabicyclo[2.2.2]octane (720 mg, 6.4 mmol) in dry toluene (10 ml) was heated to reflux under nitrogen for 90 minutes. The solution was diluted with diethyl ether (100 ml) and washed successively with saturated aqueous ammonium chloride (100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (20% EtOAc–petrol) gave the *alkene* **3** (612 mg, 75%) as a colourless oil (Found: C, 61.63; H, 7.24; $C_{13}H_{18}O_5$ requires C, 61.41; H, 7.13%); ν_{max}(film)/cm^{-1} 1732, 1682, 1641 w; δ_H (250 MHz, $CDCl_3$) 7.02 (1H, t, *J* 4.1, *H*C(2′)=), 4.69 (1H, d, *J* 1, *H*C(2)($CO_2Et)_2$), 4.20 (2H, q, *J* 7.1, CH_2O), 4.18 (2H, q, *J* 7.1, CH_2O), 2.51–2.43 (4H, m, C(5′)H_2, C(3′)H_2), 2.08–2.00 (2H, m, C(4′)H_2), 1.25 (6H, t, *J* 7.1, 2 × Me); δ_C (100 MHz, $CDCl_3$) 196.4 (s), 167.7 (s), 148.4 (d), 132.6 (s), 61.4 (t), 50.4 (d), 37.5 (t), 25.8 (t), 22.2 (t), 13.7 (q); *m*/*z* (FAB) 277 (MNa^+, 54%), 255 (100, MH^+), 209 (17, $M^+ - EtO$).

Ethyl 7a-ethoxy-2-oxo-2,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate 10

Sodium hydride (60% in mineral oil, 26 mg, 0.64 mmol) was washed with hexane and suspended in dimethylformamide (1 ml). The suspension was cooled to 0 °C and a solution of acetate **9** (100 mg, 0.32 mmol) in dimethylformamide (1 ml) was added rapidly *via* cannula. The solution was stirred for 15 minutes and quenched with saturated aqeuous ammonium chloride (10 ml) and extracted with diethyl ether (3 × 10 ml). The combined organic extracts were washed with water (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (15% EtOAc–petrol) gave the *lactone* **10** (35 mg, 43%) as a colourless oil (Found: C, 61.11; H, 7.20; $C_{13}H_{18}O_5$ requires C, 61.41; H, 7.13%); ν_{max}(film)/cm^{-1} 1789, 1716, 1672, 1444, 1295; δ_H (400 MHz, $CDCl_3$), 4.34 (2H, q, *J* 7.1, CH_2O), 3.53–3.45 (2H, m, CH_2O), 3.27–3.19 (1H, m), 2.54 (1H, dd, *J* 2, 13), 2.25 (1H, td, *J* 5.8, 13), 2.12–2.07 (1H, m), 1.78–1.67 (2H, m), 1.62–1.39 (2H, m), 1.36 (3H, t, *J* 7.1), 1.19 (3H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 176.2 (s, C=O), 165.6 (s, C=O), 160.9 (s, C=C), 118.6 (s, C3), 105.0 (s, C7a), 61.4 (t), 58.9 (t), 38.1 (t), 27.4 (t), 27.1 (t), 21.7 (t), 15.1 (q), 14.1 (q); *m*/*z* (EI) 254 (M^+, 4%), 209 (5, $M^+ - EtO$), 181 (100, $M^+ - CO_2Et$), 163 (22) (Found M^+, 254.1164. $C_{13}H_{18}O_5$ requires *M*, 254.1154).

Diethyl 2-(3,3-dimethoxypropyl)-2-(6-oxocyclohex-1-enyl)-malonate 11

Sodium hydride (60%, 120 mg, 3 mmol) was washed with hexane and suspended in dimethylformamide (5 ml). A solution of diester **3** (743 mg, 2.9 mmol) in dimethylformamide (5 ml) was added dropwise *via* cannula and the solution stirred for 1 hour. Tetrabutylammonium iodide (35 mg, 0.09 mmol) was added, followed by 3-bromopropionaldehyde dimethyl acetal (460 μl, 3 mmol). The solution was warmed to 60 °C overnight, cooled and diluted with ethyl acetate (100 ml), washed with water (2 × 20 ml) and brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (20% EtOAc–petrol) gave starting material **3** (200 mg, 27%) and the acetal **11** (720 mg, 68%) as a colourless oil; ν_{max}(film)/cm^{-1} 1725, 1679; δ_H (400 MHz, $CDCl_3$) 6.95 (1H, t, *J* 4, *H*C=), 4.33 (1H, t, *J* 6, *H*C($OMe)_2$), 4.20–4.14 (4H, m, 2 × CH_2O), 3.28 (6H, s, 2 × MeO), 2.46–2.43 (4H, m), 2.15–2.10 (2H, m), 2.02–1.97 (2H, m), 1.64–1.58 (2H, m), 1.23 (6H, t, *J* 7.1, 2 × Me); δ_C (100 MHz, $CDCl_3$) 197.2 (s), 170.1 (s), 147.0 (d), 137.2 (s), 104.4 (d), 61.5 (t), 59.6 (s), 52.6 (q), 38.6 (t), 29.1 (t), 28.5 (t), 26.2 (t), 22.3 (t), 13.9 (q); *m*/*z* (EI) 324 (M^+ − MeOH, 5%), 251 (16, M^+ − MeOH − CO_2Et) (Found M^+ − MeO, 325.1630. $C_{17}H_{25}O_6$ requires *M* − MeO, 325.1651).

Preparation of enol silane 12

A solution of *n*-butyllithium (2.5 M, 800 μl, 2 mmol) was added dropwise to a stirred, ice-cold solution of diisopropylamine (280 μl, 2 mmol) in tetrahydrofuran (10 ml). The solution was stirred for 30 minutes and then added *via* cannula to a stirred solution of **11** (390 mg, 1.1 mmol) in tetrahydrofuran (15 ml) at −78 °C. Trimethylsilyl chloride (255 ml, 2 mmol) was added and stirring continued for 4 hours. The solution was diluted with ethyl acetate (50 ml) and washed with 5% aqueous ammonium hydroxide solution (2 × 10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give **12** (430 mg, 92%) as a yellow oil. The crude silyloxydiene was used without further purification and showed the following data: ν_{max}(film)/cm^{-1} 1730; δ_H (400 MHz, $CDCl_3$) 5.70 (1H, br s, *H*C=), 4.78 (1H, br s, *H*C=), 4.32 (1H, t, *J* 6, *H*C($OMe)_2$), 4.19–4.09 (4H, m, 2 × CH_2O), 3.26 (6H, s, 2 × MeO), 2.11–2.01 (6H, m), 1.73–1.68 (2H, m), 1.22 (6H, t, *J* 7.1, 2 × Me), 0.15 (9H, s, Me_3Si); δ_C (100 MHz, $CDCl_3$) 170.6 (s), 147.9 (s), 133.3 (s), 126.6 (d), 104.6 (d), 100.5 (d), 61.0 (t), 60.6 (s), 52.2 (q), 29.2 (t), 28.2 (t), 23.1 (t), 21.3 (t), 13.9 (q), −0.2 (q); *m*/*z* (EI) 428 (M^+, 13%), 413 (13, M^+ − Me), 396 (7, M^+ − MeOH), 355 (37, M^+ − TMS) (Found M^+, 428.2246. $C_{21}H_{36}O_7Si$ requires *M*, 428.2230).

Diethyl 5-methoxy-10-oxobicyclo[4.3.1]dec-1(9)-ene-2,2-dicarboxylate 13

A solution of titanium(IV) chloride in dichloromethane (1 M, 240 μl, 0.24 mmol) was added dropwise to a stirred solution of **12** (100 mg, 0.23 mmol) in dichloromethane (2 ml) under nitrogen at −78 °C. The mixture was stirred at −78 °C for 2 hours and then allowed to warm to room temperature over 12 hours, quenched with saturated aqueous sodium bicarbonate at 0 °C, and extracted with diethyl ether (3 × 10 ml). The combined ether extracts were washed with water (10 ml), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography (20% EtOAc–petroleum ether) yielded **13a** (9 mg, 12%) and **13b** (30 mg, 40%) as oils. Data for **13a** (less polar; R_f 0.28, 25% EtOAc–petrol) (Found: C, 63.07; H, 7.45; $C_{17}H_{24}O_6$ requires C, 62.95; H, 7.46%) ν_{max}(film)/cm^{-1} 1736, 1708, 1451, 1245, 1088; δ_H (400 MHz, $CDCl_3$) 6.46 (1H, dd, *J* 4.3, 7.8, *H*C=), 4.31–4.20 (4H, m, 2 × CH_2O), 3.29 (s, 2H, MeO), 3.28–3.15 (2H, m, C*H*CO and C*H*OMe), 2.36–2.21 (2H, m, CH_2), 2.09–1.94 (1H, m), 1.87–1.56 (5H, m), 1.28 (6H, t, *J* 7.1, 2 × Me); δ_C (100 MHz, $CDCl_3$) 204.1, 169.3, 169.2, 137.6, 135.4, 82.2, 61.8, 61.8, 59.1, 56.6, 50.6, 30.7, 27.7, 22.3, 19.4, 14.0, 13.9; *m*/*z* (EI) 324 (M^+, 0.14 %), 279 (1, M^+ − EtO), 251 (5, M^+ − CO_2Et) (Found M^+, 324.1554. $C_{17}H_{24}O_6$ requires *M*, 324.1573). A sample of **13a** was further purified by Kugelrohr distillation; this sample

crystallised on standing, allowing structure determination by X-ray crystallography.†‖

Data for **13b** (more polar R_f 0.22, 25% EtOAc–petrol): ν_{max}(film)/cm^{-1} 1731, 1715, 1449, 1243, 1201; δ_H (500 MHz, $CDCl_3$) 6.34 (1H, dd, *J* 4.2 and 7.7, *H*C=), 4.28–4.19 (4H, m, 2 × CH_2O), 3.30 (3H, s, CH_3O), 3.15 (1H, m, C*H*OMe), 2.96 (1H, m—resolution enhanced to ddd, *J* 2.6, 5.2, 8.3, C*H*CO), 2.33–1.90 (6H, m, 3 × CH_2), 1.85 (1H, m), 1.36–1.21 (7H, m); δ_C (67.5 MHz, $CDCl_3$) 202.8 (s), 169.6 (s), 169.2 (s), 138.2 (s), 133.4 (d), 81.0 (d), 61.8 (t), 57.3 (t), 56.3 (q), 51.8 (d), 27.4 (t), 24.9 (t), 24.5 (t), 21.7 (t), 14.0 (q); *m*/*z* (FAB) 347 (MNa^+, 36%), 324 (18, MH^+), 293 (10, M^+ − OMe), 279 (15, M^+ − EtO) (Found MH^+, 325.1640. $C_{17}H_{25}O_6$ requires *MH*, 325.1651).

Cyclisation of 12 using $ZnCl_2$. A suspension of silyl enol ether **12** (23.8 mmol) and activated 4 Å molecular sieves (3.5 g) in dichloromethane (25 ml) was added *via* cannula to a suspension of 4 Å molecular sieves (3.5 g) and a solution of $ZnCl_2$ (1 M in Et_2O, 25 ml). The reaction mixture was stirred for 7 h at room temperature, and then filtered on Celite. The filtrate was diluted with dichloromethane and washed with saturated aqueous $NaHCO_3$. The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (20 to 50% EtOAc–petrol) gave **13a** (1.62 g, 21%) and **13b** (2.38 g, 31%) as oils. Ketone **11** (1.79 g, 16%) was also recovered.

Diethyl 2-[3,3-bis(phenylsulfanyl)propyl]-2-(6-oxocyclohex-1-enyl)malonate 14

To a solution of (phenylthio)trimethylsilane[24] (0.72 g, 3.23 mmol) and acetal **11** (576 mg, 1.61 mmol) in CH_2Cl_2 (10 ml) at −78 °C under nitrogen was added dropwise TMSOTf (50 µl, 0.276 mmol). The reaction was then allowed to warm to room temperature overnight. Solid $NaHCO_3$ (*ca.* 5 g) was then added and the mixture stirred for a further 2 hours before addition of water (20 ml). The organic layer was then extracted with ether (3 × 30 ml), the combined organic layers dried ($MgSO_4$) and the solvent removed to produce a pale yellow oil. Chromatography (50% ether–petrol; R_f = 0.22) produced the *thioacetal* **14** (0.775 g, 98%) as a colourless oil; ν_{max}(film)/cm^{-1} 1729, 1679; δ_H (250 MHz, $CDCl_3$) 7.46–7.41 (4H, m, Ar–H), 7.33–7.22 (6H, m, Ar–H), 6.90 (1H, t, *J* 4.3, *H*C=), 4.35 (1H, t, *J* 6.6, C*H*(SPh)$_2$), 4.14 (4H, q, *J* 7.1, CH_2O), 2.45–2.33 (6H, m), 1.94–1.81 (4H, m), 1.20 (6H, t, *J* 7.0, CH_3); δ_C (62.5 MHz, $CDCl_3$) 197.0 (s), 169.7 (s), 147.1 (d), 136.8 (s), 134.2 (s), 132.4 (d), 128.8 (d), 127.5 (d), 61.5 (t), 59.6 (s), 58.0 (d), 38.5 (t), 31.6 (t), 26.0 (t), 22.1 (t), 13.9 (q); *m*/*z* (CI) 513 (MH^+) (Found MH^+, 513.1763. $C_{28}H_{33}O_5S_2$ requires 513.1769).

Silyl enol ether 16

To a solution of thioacetal **14** (301 mg, 0.611 mmol) and triethylamine (1.28 ml, 9.16 mmol) in CH_2Cl_2 (5 ml) at −78°C was added dropwise TMSOTf (1.58 ml, 8.73 mmol). The reaction was then allowed to stir at −78°C for 1 h before being allowed to warm to 0 °C and stirred for a further hour. After this time an excess of solid $NaHCO_3$ was added to the flask and the solvent removed under reduced pressure. The remaining residue was then stirred vigorously with *n*-pentane for 20 min and the resulting slurry passed through a 5 cm Celite plug with further washing with *n*-pentane. The solvent was then removed under reduced pressure to produce the *silyl enol ether* **16** (302 mg, 88%) as a colourless oil, which was used crude in attempted cyclisations; ν_{max}(film)/cm^{-1} 1729 (CO_2Et); δ_H (250 MHz, $CDCl_3$) 7.47–7.42 (4H, m, ArH), 7.32–7.20 (6H, m, ArH), 5.74–5.68 (1H, m, 2″-H), 4.81–4.77 (1H, m, 5″-H), 4.39 (1H, t, *J* 6.7, C*H*(SPh)$_2$), 4.25–4.09 (4H, m, 2 × CH_2O), 2.44–2.37 (2H, m), 2.13–1.96 (6H, m), 1.27–1.17 (6H, m, CH_3), 0.20 (9-H, s, Si(CH_3)$_3$); δ_C (62.5 MHz, $CDCl_3$) 170.3 (s), 147.6 (s), 134.5 (s), 133.0 (s), 132.3 (d), 128.6 (d), 127.3 (d), 126.7 (d), 100.4 (d), 61.0 (t), 60.7 (s), 59.3 (d), 31.9 (t), 29.5 (t), 23.0 (t), 21.2 (t), 13.9 (q), 1.0 (q); *m*/*z* (EI) 584 (M^+) (Found M^+, 584.2078. $C_{31}H_{40}O_5S_2Si$ requires 584.2078).

Diethyl 2-[3,3-bis(mesitylsulfanyl)propyl]-2-(6-oxocyclohex-1-enyl)malonate 15

To a solution of (mesitylthio)trimethylsilane[23] (1.31 g, 5.85 mmol) and acetal **11** (1.045 g, 2.93 mmol) in CH_2Cl_2 (20 ml) at −78 °C under N_2 was added dropwise TMSOTf (1.36 ml, 7.51 mmol). The reaction was stirred for 30 min before addition of a concentrated aqueous solution of $NaHCO_3$ and subsequent warming of the reaction to room temperature. The organic layer was then extracted with ether (3 × 30 ml), the combined organic layers dried ($MgSO_4$) and the solvent removed to produce a pale yellow oil. Purification was achieved by recrystallisation (ether) to produce the *thioacetal* **15** (1.12 g, 64%) as colourless rectangular prismatic crystals, mp 95–97 °C; ν_{max}(film)/cm^{-1} 1731, 1681; δ_H (250 MHz, $CDCl_3$) 6.92 (1H, t, *J* 4.3, *H*C=), 6.88–6.86 (4H, m, Ar–H), 4.11 (4H, q, *J* 7.1, CH_2O), 3.80 (1H, t, *J* 6.7, C*H*(SAr)$_2$), 2.36 (12H, s, *o*-Ar–CH_3), 2.41–2.26 (6H, m), 2.23 (6H, s, *p*-Ar–CH_3), 1.98–1.85 (2H, m), 1.79–1.70 (2H, m), 1.18 (6H, t, *J* 7.0, CH_3); δ_C (62.5 MHz, $CDCl_3$) 196.8 (s), 169.6 (s), 147.0 (d), 143.0 (s), 138.3 (s), 136.8 (s), 129.3 (s), 128.9 (d), 61.3 (t), 59.5 (s), 58.8 (d), 38.3 (t), 32.6 (t), 31.3 (t), 26.0 (t), 22.1 (t), 21.7 (q), 20.8 (q), 13.8 (q); *m*/*z* (CI) 614 (MNH_4^+) (Found [MH^+ − ArSH] 445.2049. $C_{25}H_{33}O_5S$ requires 445.2038).

Silyl enol ether 17

To a solution of thioacetal **14** (1.02 g, 1.66 mmol) in CH_2Cl_2 (100 ml) was added Et_3N (1.4 ml, 10 mmol) followed by TMSOTf (1.65 ml, 9.12 mmol). The reaction was then allowed to stir at −78 °C for 20 h before addition of saturated aqueous $NaHCO_3$ solution and warming of the reaction to room temperature. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 ml) and the combined organic extracts washed with brine (70 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography (50% ether–petrol + 3% Et_3N, R_f = 0.63) provided the *silyl enol ether* **17** (0.97 g, 88%) as a colourless oil, which was used crude in attempted cyclisations; ν_{max}(film)/cm^{-1} 1742, 1731; δ_H (250 MHz, $CDCl_3$) 6.87 (4H, br s, Ar–H), 5.69–5.65 (1H, m, 2″-H), 4.72–4.69 (1H, m, 5″-H), 4.15–4.02 (4H, m, CH_2O), 3.82 (1H, t, *J* 7.0, C*H*(SAr)$_2$), 2.36 (12H, s, *o*-Ar–CH_3), 2.35–2.26 (2H, m), 2.23 (6H, s, *p*-Ar–CH_3), 2.09–2.04 (4H, m), 1.94–1.84 (2H, m), 1.17 (6H, t, *J* 7.2, CH_3), 0.13 (9H, s, Si(CH_3)$_3$; δ_C (62.5 MHz, $CDCl_3$) 170.4 (s), 147.7 (s), 143.1 (s), 138.2 (s), 133.1 (s), 129.5 (s), 128.9 (d), 126.5 (d), 100.3 (d), 61.0 (d), 60.6 (s), 59.4 (d), 32.8 (t), 32.0 (t), 23.1 (t), 21.8 (q), 21.2 (t), 20.9 (q) 13.8 (q), −0.2 (q); *m*/*z* (CI) 669 (MH^+) (Found MH^+ − ArSH, 517.2408. $C_{28}H_{41}O_5SSi$ requires 517.2444).

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