Studies on the Synthesis of Aphidicolin. The Diels–Alder Route to Spirocyclic Intermediates

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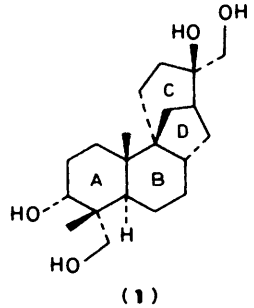
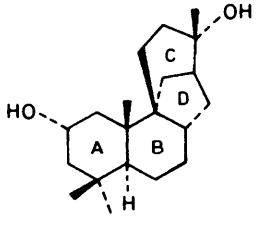
The isopropylidene cyclohexylidenemalonates (**6**; $R^1 = R^2 = H$; R^1, $R^2 = OCH_2CH_2O$; and R^1, $R^2 = SCH_2CH_2S$) undergo cycloaddition with butadiene, 2-trimethylsilyloxybuta-1,3-diene, and 3-trimethylsilyloxypenta-2,4-diene to give the corresponding spirocyclic adducts (**7**; $R^1 = R^2 = H$), (**11**; R^1, $R^2 = OCH_2CH_2O$; R^1, $R^2 = SCH_2CH_2S$), and (**23**; R^1, $R^2 = OCH_2CH_2O$; R^1, $R^2 = SCH_2CH_2S$). The trimethylsilylenol ether (**11**; R^1, $R^2 = SCH_2CH_2S$) was converted *via* compounds (**12**), (**14**), (**15**), (**16**), and (**17**) to the toluene-*p*-sulphonate (**18**) which undergoes base-catalysed intramolecular enolate alkylation to give the bicyclo[3.2.1]octanones (**19**) and (**20**) which serve as models for aphidicolin (**1**) and stemodine (**2**) synthesis. The adduct (**23**; R^1, $R^2 = SCH_2CH_2S$) was converted *via* the trione (**25**) into the ester (**27**) whose enol ether derivative (**28**) is a promising precursor to the key aphidicolin intermediate (**4**).

Aphidicolin (**1**) is an unusual tetracyclic diterpenoid containing a bicyclo[3.2.1]octane skeleton. It was isolated by Hesp and co-workers in 1972,[1] and has aroused great interest as an inhibitor of animal DNA polymerase α,[2] and as a potential anticancer compound.[3] Stemodine (**2**),[4] stemodinone, maritimol, and stemodinol possess a diastereoisomeric bicyclo[3.2.1]octane system to that present in aphidicolin. Six successful syntheses of aphidicolin (**1**) have been reported,[5–10] and two of the stemodine (**2**) syntheses are based on those previously developed for aphidicolin.[11,12] A third synthesis of stemodinone diterpenoids, based on much earlier investigations,[13] has been reported.[14] Maritimol has also been prepared by a biomimetic type route;[15] biosynthetic investigations have confirmed the origin of the carbon skeleton and some details of the formation of the bicyclo[3.2.1]octane systems.[16] Various approaches to the aphidicolin and stemodine skeletons have been reported.[17]

The logical target for aphidicolin synthesis is the ketone (**3**), a degradation product of aphidicolin, which has been converted into (**1**) by a two-step procedure.[1,7] Our own synthetic strategy,



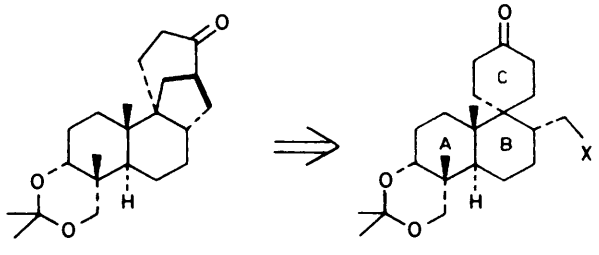
(**1**)



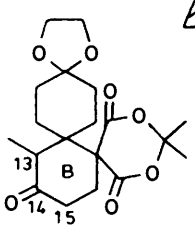
(**2**)

which was being developed concurrently with the published syntheses, was to prepare a suitable spirocyclic ketone (**4**) which, it was expected, would undergo an intramolecular enolate alkylation to form the required tricyclic ketone (**3**). This strategy had the advantage that the alternative alkylation product would provide an entry to the stemodane skeleton, as has been shown by Corey,[7,11] and subsequently by us in model studies. Here we describe the synthesis of these compounds and a precursor to the spirocyclic ketone (**4**).

Our approach to the ketone (**4**) envisaged construction of

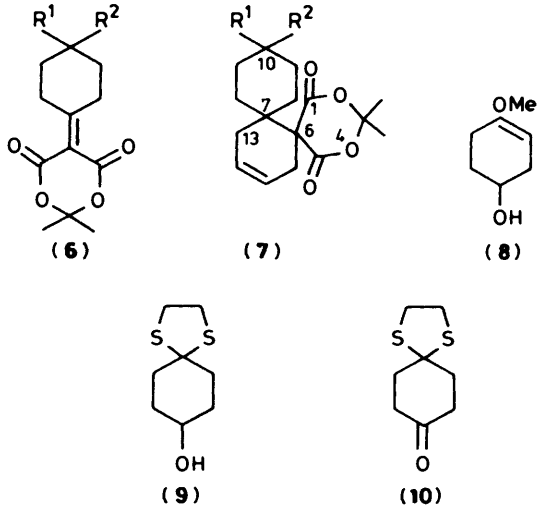


(**3**) (**4**)



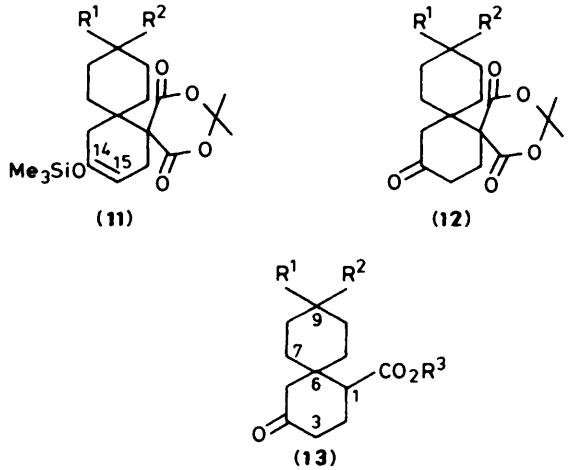
(**5**)

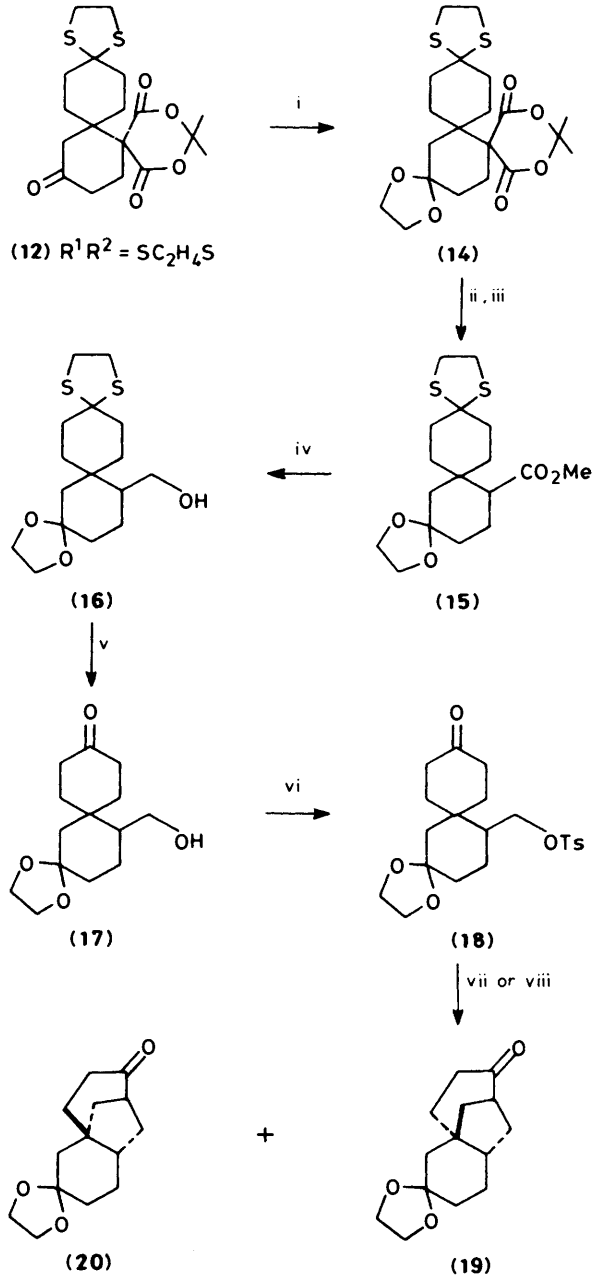
ring B of the B–C ring skeleton (**5**) by a cycloaddition route,[18] followed by formation of ring A by a Robinson annelation sequence and subsequent standard elaboration of the enone. Isopropylidene alkylidenemalonates have been shown by Dauben[19] to be reactive dienophiles in cycloaddition reactions leading to heavily substituted cyclohexene derivatives, and it occured to us that the use of the corresponding cyclohexylidene compounds (**6**) could afford a convenient synthesis of spirocyclic compounds related to compound (**5**). The model isopropylidene cyclohexylidenemalonate (**6**; $R^1 = R^2 = H$)[20] was prepared by an improved method involving the condensation of cyclohexanone with isopropylidene malonate (Meldrum's acid)[21] in pyridine in the presence of 4Å molecular sieves. The use of titanium tetrachloride in an attempt to catalyse this condensation was unsuccessful.[22] The model dienophile (**6**; $R^1 = R^2 = H$) reacted with butadiene (150 °C, 18 h) to give the spirocyclic adduct (**7**; $R^1 = R^2 = H$) in 16% yield. Although the yield of this adduct was not promising, the dienophiles (**6**; R^1, $R^2 = OC_2H_4O$ or SC_2H_4S) were prepared with the intention of preparing spirocycles containing a masked carbonyl group in the potential ring C of aphidicolin. The



ethylene acetal (**6**; R^1, R^2 = OC_2H_4O) was prepared by the condensation of cyclohexane-1,4-dione monoethylene acetal[23] with Meldrum's acid, while the thioacetal (**6**; R^1, R^2 = SC_2H_4S) was initially obtained by transacetalisation of the oxygen acetal with ethanedithiol in the presence of hydrogen chloride. More recently, an improved preparation of the thioacetal (**6**; R^1, R^2 = SC_2H_4S) was achieved by the direct condensation of Meldrum's acid with cyclohexanedione monoethylene thioacetal (**10**) which was obtained by pyridinium dichromate oxidation of the alcohol (**9**).[24] This alcohol was prepared by transthioacetalisation of the enol ether (**8**) which is readily available by Birch reduction of *p*-methoxyphenol. The reaction of the dienophiles (**6**; R^1, R^2 = OC_2H_4O or SC_2H_4S) with butadiene was unsuccessful and led only to decomposition products. Such decomposition may resemble that occurring in the pyrolytic formation of methyleneketenes from alkylidene malonates.[25]

Since the required target molecule (**5**) contained a carbonyl group at C-14, an attractive possibility was to utilise a 2-oxy-substituted butadiene in the cycloaddition, since this would be both more reactive towards the dienophiles (**6**) and would lead to an adduct (**11**) containing a masked carbonyl group at C-14. Both the acetal (**6**; R^1, R^2 = OC_2H_4O) and the thioacetal (**6**; R^1, R^2 = SC_2H_4S) reacted with 2-trimethylsilyloxybuta-1,3-diene[26] in refluxing benzene to give the corresponding crystalline spirocyclic adducts (**11**) in 90% yield. After the completion of this phase of our work Jung reported similar



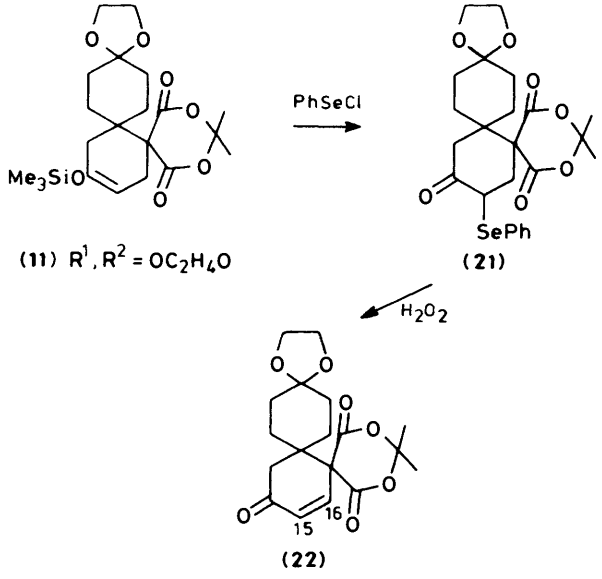


Scheme 1. *Reagents:* i, $HO(CH_2)_2OH$–pyridinium toluene-*p*-sulphonate; ii, NaOMe–MeOH–C_6H_6, reflux, 4 h (81%); iii, pyridine, reflux. 0.5 h (61%); iv, $LiAlH_3OEt$–ether, room temp., 4 h (86%); v, $HgCl_2$–$CaCO_3$–MeOH–H_2O (4:1), 4.5 h, reflux (68%); vi, TsCl–4-dimethylaminopyridine–pyridine, room temp., 24 h (81%); vii, NaOMe–MeOH, 4.5 days, (70% conversion); viii $LiN(Bu^t)_2$, 2-methyltetrahydrofuran, −120 °C to room temp. (34%).

regioselective cycloadditions of the diene to methyl acrylate and other related dienophiles.[27] Hydrolysis[28] of the silylated enol ethers (**11**; R^1, R^2 = OC_2H_4O or SC_2H_4S) gave the ketones (**12**). These compounds served as models for examining the construction of the BCD skeleton of compound (**1**) (Scheme 1). Attempted cleavage of the cyclic malonate ester group in (**12**) with methanolic sodium methoxide[19] to give a half ester sodium salt which could be decarboxylated to yield the keto ester (**13**) was a capricious reaction complicated by competing cycloreversion to (**6**). This was overcome by protecting the

ketone (**12**; R^1, R^2 = SC_2H_4S) as the corresponding acetal (**14**) which was then cleaved and decarboxylated to give the methyl ester (**15**). The methyl ester was reduced to the corresponding alcohol (**16**), the thioacetal protecting group was cleaved, and the alcohol was converted into the toluene-*p*-sulphonate (**18**). Treatment of the keto sulphonate (**18**) with methanolic sodium methoxide furnished a single ketone product which, by analogy with Corey's observations,[7] was assigned the structure (**19**) corresponding to the aphidicolin BCD skeleton. On the other hand, the keto sulphonate (**18**) reacted with lithium di-t-butylamide[29] in 2-methyltetrahydrofuran to give a major ketone product, assigned structure (**20**) by analogy with Corey's results,[11] and a minor product (**19**). Following on these model cyclisation studies, we investigated routes to a suitable aphidicolin precursor (**4**).

One possible method of formation of (**5**) would be by methylation at C-13 of compounds (**12**) or at C-5 or compounds (**13**). The selectivity of alkylation at C-13 or C-5 respectively could be made favourable by blocking C-15 or C-3. One such blocking approach is illustrated in Scheme 2, in

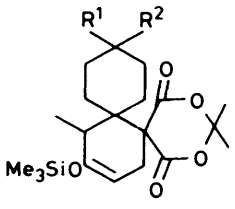


(**11**) R^1, R^2 = OC_2H_4O (**21**) (**22**)

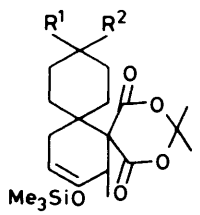
Scheme 2.

which a C(15—C(16) double bond was introduced [compound (**22**)] *via* the selenide (**21**), but alkylation studies of this have not been pursued.

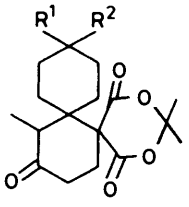
An alternative to the above described strategy was to introduce the required methyl group at C-13 in compound (**5**) by utilising an appropriately substituted diene such as 3-trimethylsilyloxypenta-2,4-diene. However, it was expected that this diene would experience opposing directive influences in the regioselectivity of a cycloaddition reaction with dienophiles such as (**6**). The methyl substituent would be expected to favour 'ortho' selectivity,[19] whereas the silyloxy substituent would favour 'para' selectivity.[27] Despite this uncertainty the experiment was carried out. 3-Trimethylsilyloxypenta-2,4-diene was prepared from ethyl vinyl ketone according to the general procedure reported by House.[30] Almost simultaneously with our preliminary report of this diene,[18] Danishefsky described its preparation and use in a different context.[31] The acetal dienophile (**6**; R^1, R^2 = OC_2H_4O) reacted with 3-trimethylsilyloxypenta-2,4-diene in refluxing toluene for 20 h to give a crystalline mixture of adducts (**23**) and (**24**; R^1, R^2 = OC_2H_4O) in 13% yield. Hydrolysis[28] of the enol ethers gave



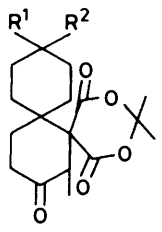
(**23**)



(**24**)



(**25**)

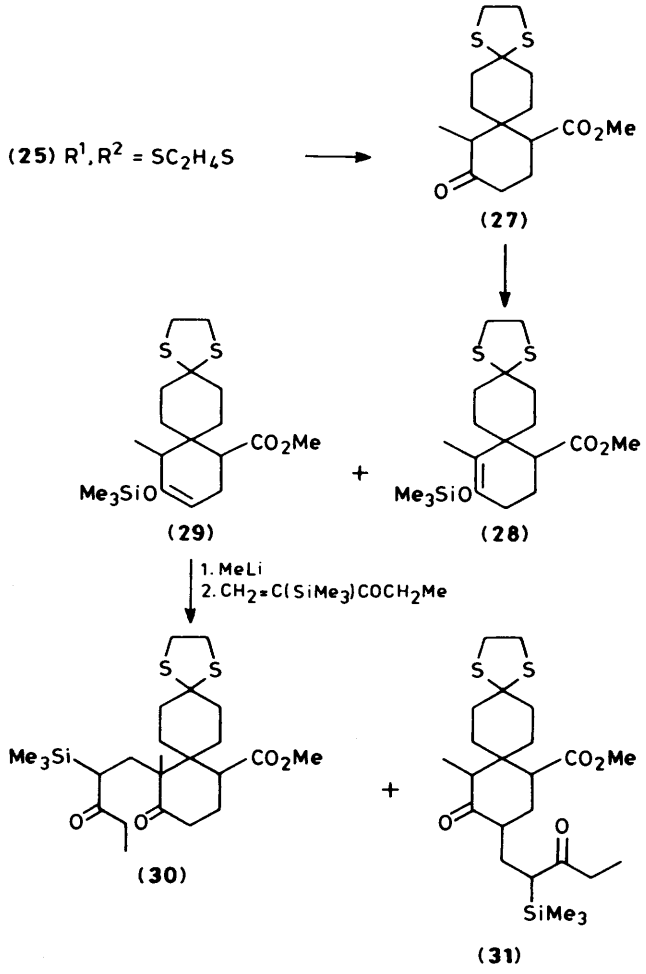


(**26**)

a mixture of the corresponding regioisomeric ketones (**25**) and (**26**), but neither these nor the precursor enol ethers could be easily separated by routine chromatographic methods. However, the reaction of the thioacetal dienophile (**6**; R^1, R^2 = SC_2H_4S) with 3-trimethylsilyloxypenta-2,4-diene in refluxing chloroform for 4 days gave a mixture of the regioisomeric adducts (**23**; R^1, R^2 = SC_2H_4S) and (**24**; R^1, R^2 = SC_2H_4S) in 74% yield. These could not be separated but the corresponding ketones, (**25**; R^1, R^2 = SC_2H_4S) and (**26**; R^1, R^2 = SC_2H_4S) obtained by hydrolysis of the adducts, could be separated by short column chromatography.[32] The first eluted, less polar ketone (**25**), m.p. 168—170 °C, was obtained in 44% yield, and the more polar ketone (**26**), m.p. 174—176 °C, was obtained in 29% yield from the dienophile (**6**; R^1, R^2 = SC_2H_4S). The assignment of structure to these ketones could not be achieved by various chemical methods, but the question was finally resolved by *X*-ray crystallographic methods. Large monoclinic crystals of the ketone (**25**; R^1, R^2 = SC_2H_4S) were obtained by diffusion of cyclohexane into a chloroform solution of the compound. The space group was $P2_1/C$, with cell dimensions a = 9.498(3), b = 21.076(6), c = 9.621(2) Å, β = 95.75(3)°, V = 1 916.2 Å^3, D_x = 1.380 g cm^{-3}, Z = 4, μ = 26.18 cm^{-1}. The structure was refined to an R of 0.082 for 2 039 unique reflexions.[33]

The proportion of the isomers (**25**) to (**26**) indicates that the effect of the oxygen substituent on the regioselectivity of the cycloaddition of 3-trimethylsilyloxypenta-1,3-diene is favoured over that of the methyl substituent by a factor of 2:1. This observation is to be contrasted with a recent observation by Danishefsky in which only one regioisomer was obtained using the above diene in a related cycloaddition.[34]

With the ketone (**25**) in hand strenuous efforts were made to prepare the enone (ring A of aphidicolin) by a Robinson annelation sequence.[35] However, all attempts at base-catalysed reactions with ethyl vinyl ketone or a synthetically equivalent reagent were uniformly unsuccessful. Similarly, acid-catalysed Robinson annelations[36] were also unsuccessful. It would appear that under forcing conditions either the isopropylidene malonate or the thioacetal groups are unstable. The former problem was circumvented by conversion of compound (**25**; R^1, R^2 = SC_2H_4S) into the keto ester (**27**) (mixture of isomers) by the previously described method. Neither base- nor acid-catalysed annelation reactions of compound (**27**) could be effected. However, a preliminary study has indicated that (**27**) can be converted into a 1:2 mixture of the regioisomeric silyl enol ethers (**28**) and (**29**). Treatment with methyl-lithium at



−78 °C is assumed to generate the corresponding lithium enolates which then react with α-trimethylsilylethyl vinyl ketone according to the general procedure formulated by Stork and Ganem[37] to give a Michael addition product tentatively formulated as a mixture of compounds (**30**) and (**31**). With these preliminary results in hand there is promise that the intermediate (**4**) could be obtained by carrying out the sequence on a regioisomerically pure enol ether (**28**); this remains to be verified.

Experimental

I.r. spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer in 0.1 mm solution cells. ^{1}H N.m.r. spectra were recorded on Perkin-Elmer R-12B, Hitachi–Perkin-Elmer R-24A, Varian CFT-20, HA-100, EM-390 and Bruker WM-250 spectrometers using either $SiMe_4$ or $CHCl_3$ as an internal standard. Mass spectra were determined using A.E.I. MS12, MS30, and MS902 instruments. Analytical t.l.c. was carried out on Merck pre-coated 0.25 mm thick plates of silica gel 60 GF_{254}. Preparative layer chromatography was carried out on 20 cm × 20 cm silica gel to 60 PF_{254} coated to a thickness of 1 mm. Melting points were determined on either a Büchi apparatus or on a Kofler hot-stage apparatus. Microanalyses were carried out by Mr. D. Flory and staff in the University Chemical Laboratory.

Isopropylidene Cyclohexylidenemalonate (**6**; $R^1 = R^2 =$ H).—A solution of isopropylidene malonate (1.44 g, 1 mmol)[21] and cyclohexanone (1 g, 1 mmol) in dry, degassed pyridine was stirred under argon at room temperature over 4A molecular sieves for 24 h. The solution was filtered, the molecular sieves were washed with chloroform (5 × 5 ml), and the combined organic fractions were evaporated. The resulting residue was dissolved in chloroform (40 ml), and the organic solution was washed with cold, saturated NaCl solution, dried (Na_2SO_4), treated with activated charcoal, and then filtered through Kieselguhr filter aid. Evaporation of the solvent gave a light yellow oil which solidified (1.67 g). Recrystallisation from aqueous acetone gave the *malonate* (**6**; $R^1 = R^2 =$ H) (1.1 g, 50%) as rods, m.p. 85.5—87 °C (lit.,[20] 86—87 °C); δ($CDCl_3$) 1.7 (12 H, s), and 2.91 (4 H, m); $\nu_{max.}$ ($CHCl_3$) 1 720s and 1 600s cm^{-1}; $\lambda_{max.}$(EtOH) 245 nm (ε 9 000).

3,3-*Dimethyl*-2,4-*dioxadispiro*[5.0.5.4]*hexadec*-14-*ene*-1,5-*dione* (**7**; $R^1 = R^2 =$ H).—The malonate (**6**; $R^1 = R^2 =$ H) (0.12 g, 0.54 mmol) was heated in a sealed tube in a solution of benzene (3 ml) saturated with butadiene and containing hydroquinone (3 mg) at 150 °C for 18 h. Evaporation of the solvent gave an orange oil which was purified by layer chromatography in ether–light petroleum (b.p. 30—40 °C) (75:25) to give the *dispiro-compound* (**7**; $R^1 = R^2 =$ H) (25 mg, 16%) as an oil; δ($CDCl_3$) 1.7 (3 H, s), 1.65 (3 H, s) 1.0—3.15 (14 H, m), and 5.4—5.7 (2 H, m); $\nu_{max.}$($CHCl_3$) 1 730s and 1 665m cm^{-1}; *m/z* 278 (M^+, 3.5%), 220 (100), 202 (98), 174 (76), and 148 (77).

Isopropylidene 1,4-*Dioxaspiro*[4.5]*decan*-8-*ylidenemalonate* (**6**; R^1, $R^2 = OC_2H_4O$).—A solution of 1,4-dioxaspiro[4.5]-decan-8-one[23a] (0.5 g, 3.2 mmol) and isopropylidene malonate (0.46 g, 3.2 mmol) in dry degassed pyridine (1.5 ml) was stirred at room temperature under argon in the presence of 4A molecular sieves for 24 h. The solution was filtered, the sieves were washed with chloroform (5 × 5 ml), and the combined filtrate and washings were evaporated. The resulting red solid was dissolved in chloroform, and the solution was washed with cold saturated aqueous NaCl solution, dried (Na_2SO_4) treated with activated charcoal, filtered through Kieselguhr filter aid, and evaporated. This gave a pale yellow crystaline solid which was recrystallised from chloroform–hexane to yield the ethylene acetal (**6**; R^1, $R^2 = OC_2H_4O$) (0.54 g, 59%) as needles, m.p. 155—157 °C; δ($CDCl_3$) 1.73 (6 H, s), 1.95 (4 H, t, *J* 8 Hz), 3.15 (4 H, t, *J* 8 Hz), and 3.95 (4 H, s); $\nu_{max.}$($CHCl_3$) 1 725s and 1 600s cm^{-1}; *m/z* 282 (M^+ 7.5%), and 224 (100); $\lambda_{max.}$(EtOH) 238 nm (ε 9 150) (Found: C, 59.6; H, 6.45. $C_{14}H_{18}O_6$ requires C, 59.6; H, 6.4%).

1,4-*Dithiaspiro*[4.5]*decan*-8-*one* (**10**).—The alcohol (**9**)[24] (15 g, 0.079 mol) in DMF (100 ml) was added to a solution of pyridinium dichromate (68 g, 0.195 mol) in DMF (150 ml) at 0 °C and the mixture was stirred at 0 °C (12 h). The mixture was then poured into ice–water (200 ml) and the aqueous solution was extracted with ether (8 × 200 ml). The combined organic phases were washed with saturated aqueous NaCl solution and dried (Na_2SO_4). Evaporation of the ether gave a brown oil which was purified by flash chromatography[38] [ethyl acetate–light petroleum (b.p. 60—80 °C), 1:1] then Kugelrohr distillation to give the ketone (**10**) (9.9 g, 67%) as a colourless liquid, b.p. 100—102 °C/0.1 mmHg (lit.,[39] 102 °C/0.13 mmHg). This procedure is superior to those previously reported.[24,39]

Isopropylidene 1,4-*Dithiaspiro*[4.5]*decan*-8-*ylidenemalonate*.—(**6**; R^1, $R^2 = SC_2H_4S$). The ethylene acetal (**6**; R^1, $R^2 = OC_2H_4O$) (0.3 g, 1.1 mmol), and ethane-1,2-dithiol (0.1 g, 1.1 mmol) were stirred in dry hydrogen chloride–saturated chloroform (4 ml) at room temperature for 3 h while hydrogen

chloride was passed slowly through the reaction mixture. The reaction mixture was poured onto ice, and the organic phase was diluted with chloroform (20 ml). The organic layer was separated and the aqueous layer was extracted with chloroform (20 ml). The chloroform extracts were washed with cold 10% NaOH solution (20 ml), and cold saturated aqueous NaCl (2 × 20 ml), and then they were combined, and dried (Na_2SO_4). Evaporation of the solvent gave a white solid which was recrystallised from chloroform–hexane to give the *thioacetal* (**6**; R^1, R^2 = SC_2H_4S) (0.26 g, 82%) as plates, m.p. 147—149 °C; δ($CDCl_3$) 1.75 (6 H, s), 2.4 (4 H, t, *J* 8 Hz), 3.22 (4 H, t, *J*, 8 Hz), and 3.39 (4 H, s); $\nu_{max.}$($CHCl_3$) 1 725s and 1 600s cm^{-1}; *m/z* 314 (M^+, 33%) and 118 (100); $\lambda_{max.}$(EtOH) 230 nm (ε 17 300), and 252sh (13 700) (Found: C, 53.2; H, 5.95. $C_{14}H_{18}O_4S_2$ requires C, 53.5; H, 5.7%). This compound is prepared in 86% yield directly from the ketone (**10**).[24]

10,10-*Ethylenedioxy*-3,3-*dimethyl*-14-*trimethylsilyloxy*-2,4-*dioxadispiro*[5.0.5.4]*hexadec*-14-*ene*-1,5-*dione* (**11**; R^1, R^2 = OC_2H_4O).—A solution of the ethylene acetal (**6**; R^1, R^2 = OC_2H_4O) (3.62 g, 13 mmol), 2-trimethylsilyloxybutadiene[26] (4.06 g, 26 mmol), and hydroquinone (5 mg) in benzene (50 ml) was heated under reflux in an argon atmosphere for 22 h. Evaporation of the solvent and recrystallisation of the resulting solid from light petroleum (b.p. 100—120 °C) gave the *spirocyclic adduct* (**11**; R^1, R^2 = OC_2H_4O) (5.3 g, 97%) as needles, m.p. 162—164 °C; δ($CDCl_3$) 0.15 (9 H, s), 1.6 and 1.65 (14 H, 2 br s), 2.2 (2 H, m), 2.6 (2 H, m) 3.9 (4 H, s), and 4.8 (1 H, m) $\nu_{max.}$($CHCl_3$) 1 770m, 1 730s, 1 680m, and 1 620m cm^{-1}; *m/z* 424 (M^+, 30%), 366 (41), and 99 (100) (Found: C, 59.5; H, 7.5. $C_{21}H_{32}O_7Si$ requires C, 59.4; H, 7.6%).

10,10-*Ethylenedithio*-3,3-*dimethyl*-14-*trimethylsilyloxy*-2,4-*dioxadispiro*[5.0.5.4]*hexadec*-14-*ene*-1,5-*dione* (**11**; R^1, R^2 = SC_2H_4S).—The cycloaddition of the thioacetal (**6**; R^1, R^2 = SC_2H_4S) (4.6 g, 14.7 mmol) to 2-trimethylsilyloxybuta-1,3-diene (4.5 g, 30 mmol) as described above for the ethylene acetal gave, after recrystallisation from light petroleum (b.p. 100—120 °C), the *spirocyclic adduct* (**11**; R^1, R^2 = SC_2H_4S) (6.01 g, 90%) as needles, m.p. 168—170 °C; δ($CDCl_3$) 0.22 (9 H, s) 1.6—2.35 (16 H, m, including 2 × s at 1.63 and 1.72), 2.63 (2 H, m), 3.22 (4 H, s), and 4.81 (1 H, m); $\nu_{max.}$ ($CHCl_3$) 1 770s, 1 730s, and 1 685m cm^{-1}; *m/z* 456 (M^+, 37%), 398 (43) and 110 (100) (Found: C, 55.3; H, 7.0, $C_{21}H_{32}O_5S_2Si$ requires C, 55.3; H, 7.0%).

10,10-*Ethylenedioxy*-3,3-*dimethyl*-2,4-*dioxadispiro*[5.0.5.4]-*hexadecane*-1,5,14-*trione* (**12**; R^1, R^2 = OC_2H_4O).—The trimethylsilyl enol ether (**11**; R^1, R^2 = OC_2H_4O) (0.5 g, 1.18 mmol) was stirred with acetic acid (16 ml) in THF (8 ml) and water (5.5 ml) at room temperature for 5 h.[28] Ice was added, and the mixture was neutralised ($NaHCO_3$) and extracted with ethyl acetate (2 × 100 ml). The organic layers were washed with saturated aqueous $NaHCO_3$ (100 ml), saturated aqueous NaCl (100 ml), and then were combined and dried (Na_2SO_4). Evaporation of the solvent gave a solid which was recrystallised from benzene–light petroleum (b.p. 60—80 °C) to give the ketone (**12**; R^1, R^2 = OC_2H_4O) as needles, m.p. 195—197 °C; δ($CDCl_3$) 1.4—1.92 (14 H, m, including 2 × s at 1.7, 1.77), 2.4 (2 H, t, *J* 7.5 Hz), 2.74 (2 H, t, *J* 7.5 Hz) 2.78 (2 H, s), and 3.88 (4 H, s); $\nu_{max.}$($CHCl_3$) 1 765m, 1 730s, and 1 710s cm^{-1}; *m/z* 352 (M^+, 7%), 294 (7), and 99 (100) (Found: C, 61.1; H, 6.85. $C_{18}H_{24}O_7$ requires C, 61.4; H, 6.8%).

10,10-*Ethylenedithio*-3,3-*dimethyl*-2,4-*dioxadispiro*[5.0.5.4]-*hexadecane*-1,5,14-*trione* (**12**; R^1, R^2 = SC_2H_4S).—The trimethylsilylenol ether (**11**; R^1, R^2 = SC_2H_4S) (1.97 g, 4.32 mmol) was hydrolysed in a mixture of glacial acetic acid (16 ml), THF (10 ml), and water (6 ml) at room temperature for 5 h. Ice was added, and the mixture was neutralised with solid $NaHCO_3$. The aqueous mixture was extracted with ethyl acetate (3 × 50 ml) and the combined organic layers were washed with cold saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution (50 ml) and dried (Na_2SO_4). Evaporation of the solvent and recrystallisation of the residue gave the *ketone* (**12**; R^1, R^2 = SC_2H_4S) (1.28 g, 70%) as colourless plates (m.p. 215—216 °C); δ($CDCl_3$) 1.40—2.55 (16 H, m, including 2 × s at 1.72 and 1.80), 2.6—2.86 (4 H, m), and 3.29 (4 H, s); $\nu_{max.}$($CHCl_3$) 1 770m, 1 730s, and 1 720s cm^{-1}; *m/z* 384 (M^+, 100%) and 326 (90) (Found: C, 56.0; H, 6.0. $C_{18}H_{24}O_5S_2$ requires C, 56.3; H, 6.2%).

Methyl 9,9-*Ethylenedioxy*-4-*oxospiro*[5.5]*undecane*-1-*carboxylate* (**13**; R^1, R^2 = OC_2H_4O, R^3 = Me).—The enol ether (**11**; R^1, R^2 = OC_2H_4O) (0.3 g, 0.71 mmol) was stirred in 0.5M-sodium methoxide in methanol (4 ml) at room temperature for 8 h under nitrogen. Evaporation of the solvent gave a buff-coloured solid which was heated in an oil bath at 160—170 °C for 4 h under a stream of dry nitrogen. After the evolution of CO_2 had ceased (monitored using barium hydroxide solution), cold saturated NH_4Cl solution (5 ml) was added and the aqueous solution was extracted with chloroform (2 × 20 ml). The organic extracts were washed with cold saturated aqueous NaCl (5 ml) and dried (Na_2SO_4). Evaporation of the solvent gave an oil which was purified by p.l.c. on Merck 2 mm alumina plates in methanol–benzene (5:95) to give the *keto ester* (**13**; R^1, R^2 = OC_2H_4O, R^3 = Me) (0.127 g, 64%) as an oil; δ($CDCl_3$), 1.2—2.4 (13 H, m, including s at 1.52), 2.7 (2 H, m), 3.7 (3 H, s), and 3.9 (4 H, s); $\nu_{max.}$($CHCl_3$) 1 720 s and 1 705 s cm^{-1}; *m/z* 282 (M^+, 37%), 251 (32), and 99 (100) (Found: C, 63.9; H, 7.8. $C_{15}H_{22}O_5$ requires C, 63.8; H, 7.8%).

9,9-*Ethylenedithio*-4-*oxospiro*[5.5]*undecane*-1-*carboxylic Acid* (**13**; R^1, R^2 = SC_2H_4S, R^3 = H).—The keto diester (**12**; R^1, R^2 = SC_2H_4S) (0.1 g, 0.26 mmol) was hydrolysed in refluxing water–acetone until no starting material remained (36 h). The solution was evaporated to dryness and the residue was heated in refluxing pyridine (10 ml) (0.5 h) and the pyridine was then removed under reduced pressure. Preparative t.l.c. on silica developed in chloroform–light petroleum (b.p. 60—80 °C)–methanol (3:7:1.4) gave the *carboxylic acid* (**13**; R^1, R^2 = SC_2H_4S, R^3 = H) (0.042 g, 54%) as a viscous oil; $\nu_{max.}$($CHCl_3$) 3 500—2 500s and 1 710s cm^{-1}; *m/z* 300 (M^+, 20%) and 131 (100) (Found: M^+, 300.0867. $C_{14}H_{20}O_3S_2$ requires *M*, 300.0854).

14,14-*Ethylenedioxy*-10,10-*ethylenedithio*-3,3-*dimethyl*-2,4-*dioxadispiro*[5.0.5.4]*hexadecane*-1,5-*dione* (**14**).—The ketone (**12**; R^1, R^2 = SC_2H_4S) (1.4 g, 3.64 mmol), ethylene glycol (0.452 g, 7.28 mmol) and a catalytic amount of pyridinium-toluene-*p*-sulphonate[40] (0.091 g, 0.364 mmol) in dry benzene (40 ml) were heated under reflux (4 h) in a flask fitted with a Dean-Stark trap containing 4A molecular sieves. The solvent was evaporated, and the residue was taken up in chloroform and washed with saturated aqueous $NaHCO_3$ (10 ml). After drying (Na_2SO_4) the organic solvent was evaporated to give a residue which was recrystallised from chloroform–light petroleum (b.p. 60—80 °C) to yield the *ethylene acetal* (**14**) (1.27 g, 81%) as colourless plates, m.p. 221 °C (decomp.); δ($CDCl_3$) 1.68 (3 H, s), 1.78 (3 H, s), 1.8—2.4 (14 H, m), 3.28 (4 H, s), and 3.96 (4 H, s); $\nu_{max.}$($CHCl_3$) 1 770m and 1 735s cm^{-1}; *m/z* 428 (M^+, 100%) and 370 (38) (Found: C, 55.8; H, 6.6. $C_{20}H_{28}O_6S_2$ requires C, 56.1; H, 6.5%).

Methyl 4,4-*Ethylenedioxy*-9,9-*ethylenedithiospiro*[5.5]*undecane*-1-*carboxylate* (**15**).—The malonate ester (**14**) (0.4 g, 0.23

mmol) was added to a methanolic solution (20 ml) containing sodium methoxide [from Na (0.03 g)]. The methanol was removed under reduced pressure and the residue was heated in refluxing pyridine (20 ml) for 0.5 h. The pyridine was removed under reduced pressure, and the resulting residue was treated with saturated aqueous NH_4Cl (10 ml) and ether (30 ml). The organic layer was separated, the aqueous layer was extracted with ethyl acetate (3 × 30 ml), and the combined organic layers were dried (Na_2SO_4) and evaporated. The resulting solid was purified on a silica preparative t.l.c. plate (developed in ethyl acetate–hexane) to give the *mono-ester* (**15**) (0.2 g, 61%) as a colourless solid, m.p. 89—90 °C; δ($CDCl_3$) 1.26—2.5 (15 H, m), 3.26 (4 H, s), 3.67 (3 H, s), and 3.93 (4 H, s); $\nu_{max.}$($CHCl_3$) 1 725s cm^{-1}; *m/z* 358 (M^+, 100%), 257 (100), and 227 (90) (Found: C, 57.0; H, 7.3%; M^+, 358.1288. $C_{17}H_{26}O_4S_2$ requires C, 57.0; H, 7.3%; *M*, 358.1276).

4,4-*Ethylenedioxy*-9,9-*ethylenedithiospiro*[5.5]*undecan*-1-*ylmethanol* (**16**).—Absolute ethanol (0.02 ml) was added rapidly to a stirred solution of $LiAlH_4$ (0.11 g) in ether (5 ml). A portion of the resulting solution of $LiAlH_3OEt$ (1.5 ml) was added dropwise to a solution of the ester (**15**) (0.24 g, 0.67 mmol) in ether (5 ml), and the reaction mixture was stirred at room temperature (4 h). The solution was carefully quenched with a solution of Rochelle's salt (5 ml; sodium potassium tartrate) and the solvent was removed under reduced pressure. The resulting residue was purified by preparative t.l.c. on alumina developed in ethyl acetate–light petroleum (b.p. 60—80 °C) (1:1) to give the *alcohol* (**16**) (0.19 g, 86%) as an oil; δ($CDCl_3$) 1.1—2.35 (16 H, m, including 1.95, 1 H, s), 3.23 (4 H, s), 3.4—3.8 (2 H, m), and 3.83 (4 H, s); $\nu_{max.}$($CDCl_3$) 3 620m and 3 470m cm^{-1}; *m/z* 330 (M^+ 100%), 257 (50), and 131 (60) (Found: M^+ 330.1332. $C_{16}H_{26}O_3S_2$ requires *M*, 330.1323).

4,4-*Ethylenedioxy*-1-*hydroxymethylspiro*[5.5]*undecan*-9-*one*.—A solution of the thioacetal (**16**) (0.19 g, 0.58 mmol) in aqueous methanol [7 ml; methanol (4): water (1)] was added to an efficiently stirred suspension of $HgCl_2$ (0.34 g) and $CaCO_3$ (0.12 g) in the same solvent (10 ml), and the mixture was heated under reflux (4.5 h). The cooled reaction mixture was filtered through Celite, and the filter cake was washed with chloroform (40 ml). The filtrate and washings were combined and the organic layer was separated. The aqueous layer was extracted with chloroform (3 × 20 ml). The combined organic layers were washed with aqueous ammonium acetate solution, water, and saturated aqueous NaCl (each 10 ml), and the organic layer was dried ($NaSO_4$). The solvent was removed, and the residue was chromatographed (ethyl acetate, R_F 0.27) on silica t.l.c. The *ketone* (**17**) was obtained (0.1 g, 68%) as an oil; δ($CDCl_3$) 1.33—2.53 (16 H, m), 3.4—3.9 (2 H, m), and 3.96 (4 H, s); $\nu_{max.}$($CHCl_3$) 3 615m and 3 470m cm^{-1}; *m/z* 254 (M^+, 8%), 181 (45), and 99 (100) (Found: M^+ 254.1514. $C_{14}H_{22}O_4$ requires *M*, 254.1518).

4,4-*Ethylenedioxy*-1-p-*tolylsulphonyloxymethylspiro*[5.5]*undecan*-9-*one* (**18**).—Toluene-*p*-sulphonyl chloride (135 mg, 0.71 mmol) was added to a solution of the alcohol (**17**) (90 mg, 0.35 mmol) and a catalytic quantity of 4-dimethylaminopyridine (4.3 mg, 0.035 mmol) in dry pyridine (5 ml). The mixture was stirred at room temperature (24 h), quenched with ice–water (5 ml), and was then extracted with ether (3 × 20 ml). The organic layers were washed with cold dilute aqueous HCl, then saturated aqueous $NaHCO_3$, and then dried (Na_2SO_4). Removal of the solvent gave a residue which was chromatographed on silica t.l.c. (R_F 0.18, developed in ethyl acetate–light petroleum (b.p. 60—80 °C) (1:1) to give the toluene-*p*-sulphonate (**18**) (117 mg, 81%) as an oil; δ($CDCl_3$) 1.2—2.5 (15 H, m), 2.46 (3 H, s), 3.95 (4 H, s), 3.8—4.4 (2 H, m), 7.3 (2 H, d, *J* 9 Hz), and 7.76 (2 H, d, *J* 9 Hz); $\nu_{max.}$($CHCl_3$) 1 710s and 1 600s cm^{-1}; *m/z* 408 (M^+, 5%) and 253 (100) (Found: M^+ 408.1606. $C_{21}H_{28}O_6S$ requires *M*, 408.1607).

Cyclisation of the Toluene-p-*sulphonate* (**18**).—(*a*) *With sodium methoxide*.—The sulphonate (**18**) (19.7 mg, 0.048 mmol) in dry methanol (1 ml) was added to a stirred solution of sodium methoxide [from Na, (13.3 mg, 0.579 mol)] in methanol (10 ml) maintained at 0 °C under nitrogen. The solution was allowed to warm to room temperature and was then stirred for 4.5 days. Water (5 ml) was added and the mixture was extracted with ether (3 × 10 ml). The combined organic extracts were washed with saturated aqueous NaCl and then dried (Na_2SO_4). Evaporation of the solvent gave a residue which was purified on silica preparative t.l.c., developed in ethyl acetate–light petroleum (b.p. 60—80 °C) (1:1). There was obtained starting material (**18**) (4 mg) and a single product (R_F 0.24), presumed by analogy with the results of Corey [7] to be the *ketone* (**19**) (6.3 mg, 70% conversion); δ($CDCl_3$) 1.22—2.74 (16 H, m) and 3.92 (4 H, s); $\nu_{max.}$($CDCl_3$) 1 710 cm^{-1} (Found: M^+ 236.1411. $C_{14}H_{20}O_3$ requires *M*, 236.1412).

(*b*) *With lithium di-t-butylamide*. n-Butyl-lithium solution (1.6M; 0.043 ml, 0.069 mmol) in hexane was added at room temperature under nitrogen to a stirred solution containing di-t-butylamine [29] (9.7 mg, 0.069 mmol) in 2-methyltetrahydrofuran (0.5 ml). Stirring was continued for 0.3 h, and the resulting solution was cooled to −120 °C, and the toluene-*p*-sulphonate (**18**) (25.6 mg, 0.063 mmol) in 2-methyltetrahydrofuran (0.5 ml) was added slowly by syringe. The bath temperature was maintained at −120 °C for 1 h, then it was raised slowly to room temperature. After a total reaction time of 28 h the reaction mixture was quenched with water (5 ml), and extracted with ether (3 × 20 ml). The combined organic extracts were washed with 2M-HCl, water, and saturated aqueous NaCl (10 ml each), and dried (Na_2SO_4). Evaporation of the solvent and preparative silica t.l.c. of the residue in ethyl acetate–light petroleum (b.p. 60—80 °C) (1:1) gave a minor product, identical to the ketone (**19**) (1.39 mg, 9.4%) and a major product (3.72 mg, 24.5%) (R_F 0.22) presumed by analogy with Corey's results [11,29] to be the *ketone* (**20**); δ($CDCl_3$) 1.24—2.74 (16 H, m) and 3.92 (4 H, s); $\nu_{max.}$($CDCl_3$) 1 705s cm^{-1} (Found: M^+ 236.1421. $C_{14}H_{20}O_3$ requires *M*, 236.1412).

10,10-*Ethylenedioxy*-3,3-*dimethyl*-15-*phenylseleno*-2,4-*dioxadispiro*[5.0.5.4]*hexadecane*-1,5,14-*trione* (**21**).—A solution of benzeneselenenyl chloride in hexane [10 ml; prepared from diphenyl diselenide (0.37 g, 1.18 mmol) and chlorine gas] was added to a solution of the silyl enol ether (**11**; R^1, R^2 = OC_2H_4O) (1 g, 2.36 mmol). The reaction mixture was stirred at room temperature, and the colour changed from deep red to pale orange. The solvent was evaporated and the residue was chromatographed on a silica column which was eluted with ethyl acetate–light petroleum, (b.p. 60—80 °C) (1:1) to give the *selenide* (**21**) (0.81 g, 68%) which was recrystallised from chloroform–light petroleum (b.p. 60—80 °C) as colourless crystals, m.p. 168—169 °C; δ($CDCl_3$) 1.7—3.25 (18 H, m, including 2 × s at 2.05 and 2.15), 3.85 (4 H, br s), 4.63 (1 H, dd, *J* 4.7 Hz), and 6.5—6.8 (5 H, m); $\nu_{max.}$($CDCl_3$) 1 770s, 1 740s, 1 720s, and 1 580w cm^{-1}; *m/z* 508 and 506 (M^+).

10,10-*Ethylenedioxy*-3,3-*dimethyl*-2,4-*dioxadispiro*[5.0.5.4]-*hexadec*-15-*ene*-1,5,14-*trione* (**22**).—The seleno ketone (**21**) (0.12 g, 0.235 mmol) was dissolved in CH_2Cl_2 (5 ml) containing pyridine (0.04 ml, 0.47 mmol), and was cooled in an ice bath with stirring. Hydrogen peroxide (34%; 0.05 ml) in water (1 ml) was cautiously added to the well-stirred solution at such a rate as to maintain the temperature between 30—35 °C. After being stirred vigorously for a further 15 min, the reaction mixture was shaken with dichloromethane (5 ml) and saturated aqueous

$NaHCO_3$ solution (5 ml). The aqueous layer was separated and re-extracted with dichloromethane (2 × 5 ml). The combined organic layers were washed with cold dilute HCl, then saturated aqueous NaCl, and dried (Na_2SO_4). Removal of the solvent gave the *enone* (**22**) (0.08 g, 94%) which was recrystallised from ethyl acetate to give a colourless solid, m.p. 205 °C (decomp); δ($CDCl_3$) 1.5—2.0 (14 H, m), 2.8 (2 H, br s), 3.83 (4 H, s), 6.15 (1 H, d, *J* 10 Hz), and 6.46 (d, *J* 10 Hz); $\nu_{max.}$($CHCl_3$) 1 780s, 1 740s, and 1 690s cm^{-1}; *m/z* 292 ($M^+ - Me_2CO$, 2%) and 99 (100). (Found: $M^+ - Me_2CO$, 292.0945. $C_{15}H_{16}O_6$ requires $M - Me_2CO$ 292.0947).

3-*Trimethylsilyloxypenta*-2,4-*diene*.—A mixture containing ethyl vinyl ketone (20 g, 0.24 mol), trimethylchlorosilane (30.5 g, 0.28 mol), and triethylamine (57 g, 0.56 mol) in DMF (120 ml) was heated under reflux in a nitrogen atmosphere for 60 h. The cooled reaction mixture was diluted with pentane (200 ml) and washed with cold saturated aqueous $NaHCO_3$ solution (2 × 200 ml) followed by successive portions (100 ml) of cold 1.5M-HCl, cold saturated $NaHCO_3$, and cold saturated NaCl. After drying (Na_2SO_4), the pentane solution was distilled through a Vigreux column first at atmospheric pressure and then under water pump vacuum, to give 3-*trimethylsilyloxypenta*-2,4-*diene* (20 g, 54%) as a colourless oil, b.p. 46—48 °C/20 mmHg (*cf.*[31] b.p. 82—85 °C/75 mmHg); δ($CDCl_3$) 0.32 (9 H, s), 1.75 (3 H, d, *J* 7 Hz), 4.78—5.46 (3 H, m), and 6.3 (1 H, dd, J_{trans} 18 Hz, J_{cis} 12 Hz); $\nu_{max.}$($CHCl_3$) 1 645m and 1 600s cm^{-1}; *m/z* 156 (M^+, 16%), 141 (16), 127 (26), 85 (8), and 75 (100).

10,10-*Ethylenedioxy*-3,3,13-*trimethyl*-14-*trimethylsilyloxy*-2,4-*dioxadispiro*[5.0.5.4]*hexadec*-14-*ene*-1,5-*dione* (**23**; R^1, R^2 = OC_2H_4O) *and* 10,10-*Ethylenedioxy*-3,3,16-*trimethyl*-15-*trimethylsilyloxy*-2,4-*dioxadispiro*[5.0.5.4]*hexadec*-14-*ene*-1,5-*dione* (**24**; R^1, R^2 = OC_2H_4O).—A solution of the ethylene acetal dienophile (**6**; R^1, R^2 = OC_2H_4O) (1 g, 3.55 mmol), 3-trimethylsilyloxypenta-2,4-diene (1 g, 6.4 mmol), and hydroquinone (5 mg) in dry toluene was heated in an atmosphere of nitrogen under reflux for 20 h. Evaporation of the solvent gave a brown oil which upon trituration with light petroleum (b.p. 100—120 °C) gave a solid, which was recrystallised from cyclohexane to give a mixture of the *adducts* (**23**; R^1, R^2 = OC_2H_4O) and (**24**; R^1, R^2 = OC_2H_4O) as needles m.p. 135—139 °C; δ($CDCl_3$) 0.2 (9 H, s), 1.0—2.1 (17 H, m), 2.3 (2 H, m), 3.12 (1 H, m), 3.9 (4 H, 3 overlapping s), and 5.58 (1 H, m); $\nu_{max.}$($CHCl_3$) 1 760m, 1 730s, and 1 665w cm^{-1}; *m/z* 438 (M^+, 17%), 380 (28), and 183 (100) (Found: C, 60.3; H. 7.6; $C_{22}H_{34}O_7Si$ requires C, 60.3; H, 7.8%).

10,10-*Ethylenedioxy*-3,3,13-*trimethyl*-2,4-*dioxadispiro*-[5.0.5.4]*hexadecane*-1,5,14-*trione* (**25**; R^1, R^2 = OC_2H_4O) *and* 10,10-*Ethylenedioxy*-3,3,16-*trimethyl*-2,4-*dioxadispiro*[5.0.5.4]-*hexadecane*-1,5,15-*trione* (**26**; R^1, R^2 = OC_2H_4O).—The mixture of enol ethers (**23**; R^1, R^2 = OC_2H_4O) and (**24**; R^1, R^2 = OC_2H_4O) (0.04 g, 0.90 mmol) was hydrolysed in glacial acetic acid (2.2 ml), THF (1 ml), and water (0.7 ml) at room temperature for 5 h. The reaction mixture was worked up as for the preparation of the ketone (**12**) to give a solid which was recrystallised from methanol to give a mixture of the ketones (**25**; R^1, R^2 = OC_2H_4O) and (**26**; R^1, R^2 = OC_2H_4O) (0.025 g, 76%) as rosettes, m.p. 215—218 °C; δ($CDCl_3$) 1.3—2.2 (17 H, m, including 3 × s at 1.08, 1.7, and 1.75) 2.4 (4 H, m), 3.11 (1 H, q, *J* 7 Hz), and 3.95 (4 H, s); $\nu_{max.}$($CHCl_3$) 1 760m and 1 730s cm^{-1}; *m/z* 366 (M^+, 26%), 308 (50), 181 (100), and 99 (75). (Found: M^+ 366.1679. $C_{19}H_{26}O_7$ requires *M*, 366.4 128).

10,10-*Ethylenedithio*-3,3,13-*trimethyl*-2,4-*dioxadispiro*-[5.0.5.4]*hexadecane*-1,5,14-*trione* (**25**; R^1, R^2 = SC_2H_4S) *and* 10,10-*Ethylenedithio*-3,3,16-*trimethyl*-2,4-*dioxadispiro*[5.0.5.4]-*hexadecane*-1,5,15-*trione* (**26**; R^1, R^2 = SC_2H_4S).—The thioacetal dienophile (**6**; R^1, R^2 = SC_2H_4S (1 g, 3.18 mmol), 3-trimethylsilyloxypenta-2,4-diene (1 g, 6.4 mmol) and hydroquinone (5 mg) were heated in refluxing chloroform for 4.5 days. The solvent was evaporated and the resulting oil was stirred in THF (9 ml) containing glacial acetic acid (16 ml) and water (5.5 ml) at room temperature for 5 h. Ice was added, and the mixture was neutralised with solid $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (2 × 100 ml), and the separate organic extracts were washed with cold saturated aqueous $NaHCO_3$ (100 ml), and saturated aqueous NaCl (100 ml). The combined organic layers were dried (Na_2SO_4) and evaporated to give a solid (1.3 g). This was chromatographed on a short fat column of silica gel[32] (200 g). Elution of the column with chloroform–light petroleum (b.p. 60—80 °C)–methanol (15:85:7) (1 l) gave a colourless oil, R_F 0.5 (silica gel–chloroform–light petroleum–methanol 3:7:1.4) which was recrystallised from chloroform–hexane to give the ketone (**25**; R^1, R^2 = SC_2H_4S) (0.57 g, 44%) as large colourless prisms, m.p. 168—170 °C; δ($CDCl_3$) 1.23 (3 H, d, *J* 7 Hz), 1.68 (3 H, s), 1.82 (3 H, s), 1.9—2.1 (8 H, m), 2.5 (2 H, t, *J* 8 Hz), 2.79 (2 H, t, *J* 7 Hz), 3.02 (1 H, q, *J* 7 Hz), and 3.28 (4 H, s); $\nu_{max.}$($CHCl_3$) 1 765m, 1 730s, and 1 705s cm^{-1}; *m/z* 398 (M^+, 14%), 340 (21) and 131 (100) (Found: C, 57.3; H, 6.5. $C_{19}H_{26}O_5S_2$ requires C, 57.4; H, 6.6%). Further elution of the column with the above solvent gave a solid, R_F 0.45 (silica gel–chloroform–light petroleum–methanol (3:7:1.4), which was recrystallised from chloroform–hexane to give the ketone (**26**; R^1, R^2 = SC_2H_4S) (0.38 g, 29%) as colourless prisms, m.p. 174—176 °C; δ($CDCl_3$) 1.08 (3 H, d, *J* 7 Hz), 1.2—3.6 (18 H, m, including 2 × s at 1.69 and 1.77), 3.14 (1 H, m), and 3.3 (4 H, s); $\nu_{max.}$($CHCl_3$) 1 700m, 1 735s, and 1 710s cm^{-1}; *m/z* 398 (M^+, 14%), and 340 (25) (Found: C, 57.05; H, 6.8. $C_{19}H_{26}O_5S_2$ requires C, 57.3; H, 6.5%).

Methyl 9,9-*Ethylenedithio*-5-*methyl*-4-*oxodispiro*[5.5]-*undecane*-1-*carboxylate* (**27**).—The ketone (**25**; R^1, R^2 = SC_2H_4S) (0.25 g, 0.63 mmol) was stirred at room temperature under nitrogen for 20 min in 0.16M-sodium methoxide in methanol (4 ml). After evaporation of the solvent the resulting solid was heated in refluxing pyridine (15 ml) for 0.5 h under a stream of nitrogen. The pyridine was evaporated and reaction mixture was worked up as for the preparation of the keto ester (**13**) to give an oil which was purified by layer chromatography in acetone–light petroleum (b.p. 60—80 °C) (20:80). This yielded a solid, R_F 0.56 [silica gel–chloroform–light petroleum–methanol (3:7:1.4)] which was recrystallised from chloroform–light petroleum (b.p. 60—80 °C) to give the *keto ester* (**27**) (0.11 g, 51%), as small prisms, m.p. 120—122 °C; δ($CDCl_3$) 1.06 (3 H, d, *J* 6 Hz), 1.46—3.16 (14 H, m), 3.25 (4 H, s), and 3.68 (3 H, s); $\nu_{max.}$($CHCl_3$) 1 725s and 1 710s cm^{-1}; *m/z* 328 (M^+, 16%), 296 (11), and 131 (100) (Found: C, 58.3; H, 7.3. $C_{16}H_{24}O_3S_2$ requires C, 58.5; H, 7.3%).

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