Synthetic Studies on Electron Transport Inhibitors. Part 2. Approaches to the Synthesis of Myxalamide D

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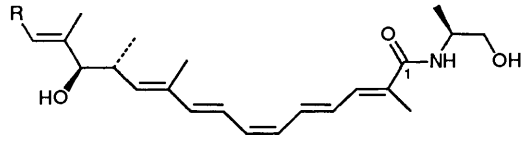
In a synthetic approach to ethyl myxalate-D **5** (X = OEt) the butendial monoacetals **12** and **15** were transformed by a Wadsworth–Emmons reaction and controlled hydrolysis into the (*E,E*)-aldehydo-ester (**17**); a *Z*-selective reaction with Bestmann's ylide **18** afforded ethyl (2*E*,4*E*,6*Z*)-8,8-diethoxy-2-methylocta-2,4,6-trienoate **21** and hence the corresponding aldehyde **22**. Reaction of aldehyde **22** with lithiated (+)-(4*R*,5*R*,2*E*,6*E*)-sulphone **24** afforded the coupled benzoyloxy sulphone **25**. Reductive elimination from **25** with sodium amalgam–methanol gave only the vinyl sulphone **27**; the use of sodium naphthalenide provided the required pentaene ester **30** but with loss of stereochemical integrity.

The myxalamides **1**–**4** are a group of antibiotics originally discovered in the gliding bacterium *Myxococcus xanthus* Mk 12,[1] and later identified in *Stigmatella aurantica* Sg a15.[2] Myxalamide B, the major metabolite, is a very effective electron transport inhibitor, blocking NADH oxidation at Complex I in mitochondria.[1a] It thus belongs to a group of actual and potential insecticides acting at the same biological site. As part of a general programme on the synthesis of electron transport inhibitors, we have investigated a synthetic route to the simplest member of the myxalamide group, myxalamide D.

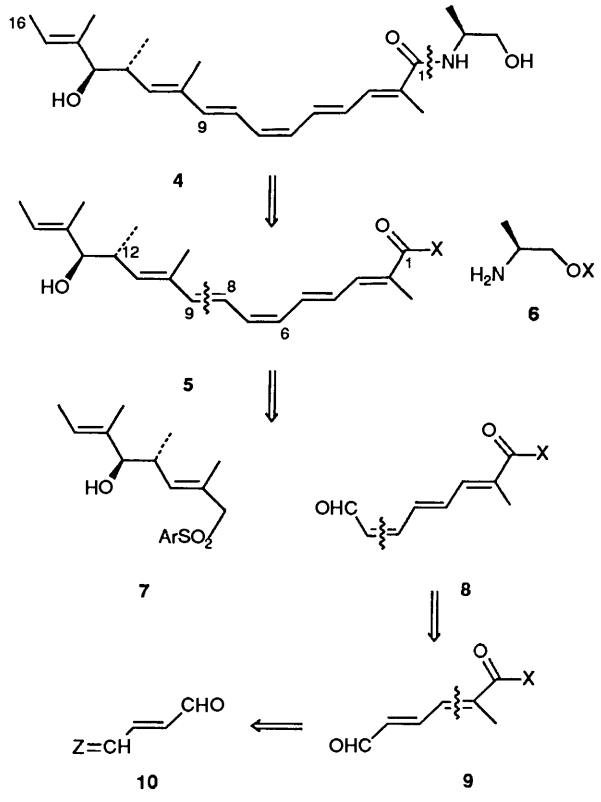


1; R = *S*-Bu^i
2; R = Pr^i
3; R = Et
4; R = Me

An approach was required that was flexible enough to lead to both the target and to structural variants. The plan adopted was based on the disconnections of Scheme 1. The amide link was to be formed late in the synthesis, both to avoid problems which might arise from the presence of the amide proton and to allow a range of amine partners to be employed. Thus ethyl myxalate-D **5** (X = OEt) became the immediate target. This contains the (*E,E,Z,E,E*)-pentaene ester system, known in natural myxalamides to isomerise readily to the all-*E* structure. Further, it was chosen to disconnect the C(8)=C(9) double bond, separating the chiral centres at C-12 and C-13 from the *Z* double bond. Synthesis using Julia olefination of the (2*Z*)-trienal **8** by the sulphone **7** then appeared a reasonable strategy.

In part 1[3] it was shown that the suphone **7** could be synthesised from tiglic aldehyde in seven steps with 84% e.e. and that further improvements in optical purity were possible. In this paper attention is turned to the aldehydo ester **8** containing an (*E,E,Z*)-triene moiety, and to the coupling of the units **7** and **8**. It transpired that the aldehyde **8** could be satisfactorily synthesised with control of geometry and that the desired sulphone olefination could be achieved by a new modification of the Julia method to yield the pentaene ester **30** as required, but without stereochemical specificity.

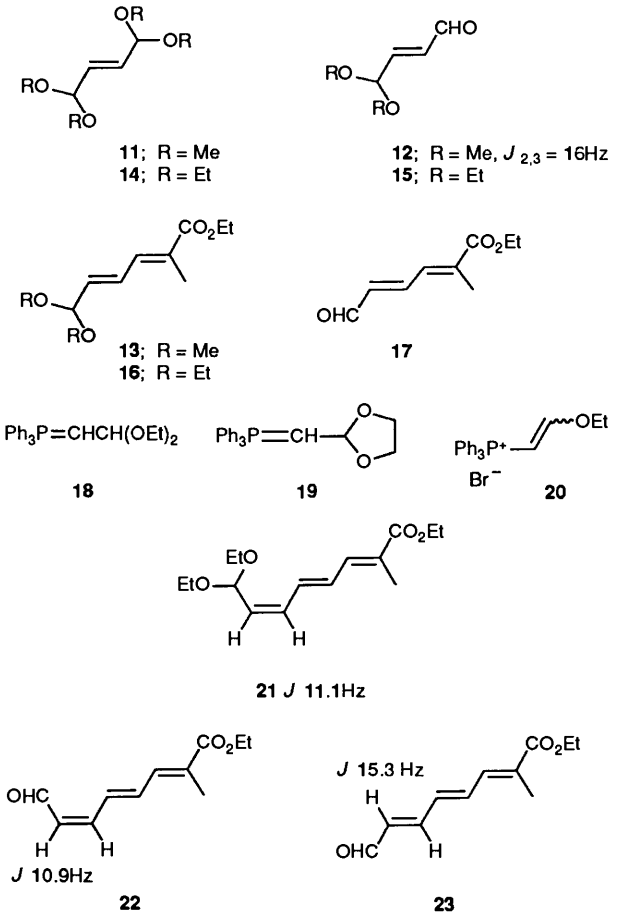
The route to the synthon **8** rested on the disconnections to **9** and **10** in Scheme 1, which require a suitably protected



Scheme 1

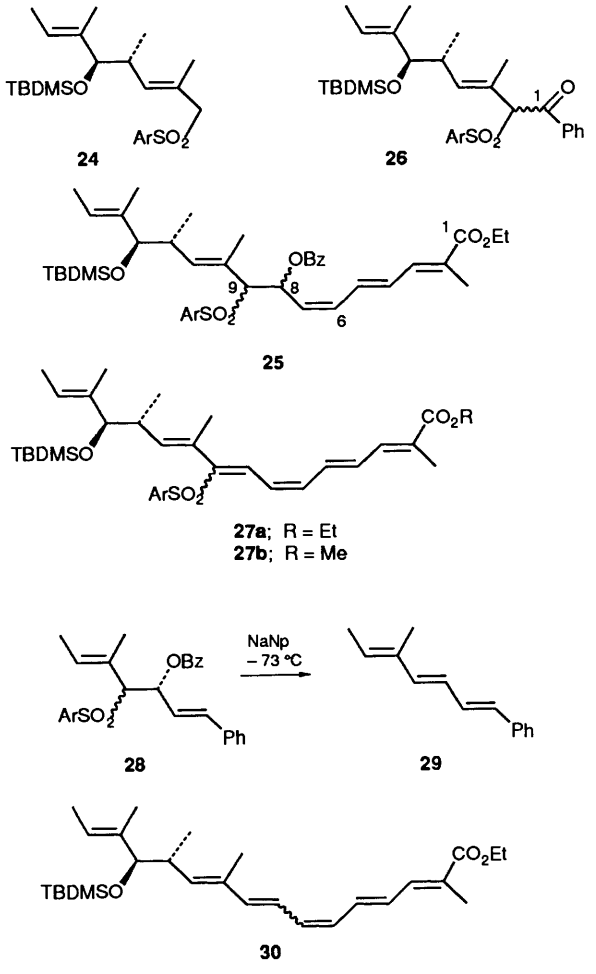
butenedial as starting material. Thus, furan in methanol was treated with bromine to afford the (*E*)-bis acetal **11** (69%).[4] Brief hydrolysis with Amberlyst-15[5] provided the (*E*)-aldehyde **12**, and a Wadsworth–Emmons reaction with triethyl 2-phosphonopropanoate gave the (*E,E*)-ester **13** (85%), but contaminated with some methyl ester. Redistillation of the aldehyde **12** to remove traces of methanol immediately before use gave the pure ester **13**, albeit in only 37% yield. However this preparation was carried out only once. The corresponding reaction with diethoxybutenal **15**, prepared from bisacetal **14** gave the (*E,E*)-ester **16** (74%). Both acetals were smoothly hydrolysed (Amberlyst-15) to the (*E,E*)-aldehydo ester **17**.

To set up the required *Z*-double bond we utilised Bestmann's ylide **18**.[6] This can be prepared from formylmethylene-(triphenyl)phosphorane and has been shown to afford high *Z*:*E* ratios in reactions with saturated and aromatic aldehydes. The



method has been used effectively in natural product synthesis to generate *Z* olefinic linkages.[7] It is curious that the closely related ylide **19** provides *E*-geometry preferentially.[8] Formylmethylene(triphenyl)phosphorane was treated with bromoethane to give the phosphonium bromide **20** in excellent yield. Using commercial phosphorane, (*E*) **20** was formed exclusively but with material made by literature methods[6] *E*:*Z* product ratios 1:2–1:3 were observed. Bestmann and co-workers[6] reported *E*:*Z* = 1:4. Traces of methylphosphonium bromide in commercial phosphorane are a likely cause of the difference.[9] The phosphonium salt **20** was then treated with sodium ethoxide to yield the ylide **18**. It proved essential to prepare the sodium ethoxide freshly, rigorously free of sodium hydroxide. When the aldehyde **17** was treated with 4 equiv. of the ylide **18**, the desired acetal **21** was obtained. In preliminary experiments it was found that chromatographic purification of the acetal was attended by significant loss of material; however a pure specimen (37%) was obtained, showing exclusively 6*Z* geometry **21** as judged by ^{1}H NMR spectroscopy. It was found expedient to hydrolyse the crude acetal (Amberlyst) to yield an (85:15) mixture of the (*E*,*E*,*Z*)- and (*E*,*E*,*E*)-aldehydes **22** and **23** respectively; these were readily separated by chromatography to give the desired *E*,*E*,*Z*-form in a satisfactory overall 70% yield from **17**. Isomers **22** and **23** were readily distinguished by ^{1}H NMR spectroscopy. The all-*E* form probably arises during acid hydrolysis; an authentic specimen was also obtained by reaction of aldehyde **17** with formylmethylene(triphenyl)phosphorane.

With the synthesis of the 'right hand' portion of the target **5** completed, attention was turned to the coupling between the *O*-protected form **24** of the hydroxy sulphone **7**, with the aldehyde **22**. After some preliminary experimentation it was found that deprotonation of the sulphone **24** with butyllithium at −73 °C generated the desired carbanion, which was then allowed to react with the aldehyde **22** at −73 °C for 45 min. Quenching with benzoyl chloride provided two products; the major (48%) proved to be the benzoylated sulphone **26**, as a mixture of 1*R*,1*S* stereoisomers. This product originated from unchanged carbanion. The other product in low but welcome yield (20%, unoptimised) proved to be the required coupled product **25** as the expected mixture of C-8, C-9 diastereoisomers. Quenching the reaction mixture with acetic anhydride proved unsatisfactory.



Reductive elimination from the benzoyloxy sulphone **25** was then investigated, first using the literature reagent,[10] sodium amalgam in methanol–tetrahydrofuran at −23 °C. TLC analysis showed the formation of two more conjugated products (blue fluorescence under 366 nm radiation), but these turned out to be the 8*E*,8*Z* stereoisomers of the vinyl sulphone **27**, resulting from sodium methoxide catalysed elimination of benzoic acid from **25**, rather than reductive elimination. Some transesterification also occurred giving **27** (R = Et) and **27** (R = Me) (7:3). However, the 6-*Z* geometry was retained, as evinced by the ^{1}H NMR spectrum: the benzoyloxy sulphone must also have the 6*Z* double bond, although in this case the 6,7 protons are obscured in the NMR. We thus explored the application of an electron transfer reducing system which could be used under neutral conditions at low temperature. Sodium naphthalenide, although it has not to our knowledge been used before in Julia olefin synthesis, appeared to suit our purpose. In a model system the benzoyloxy sulphone **28** (prepared from cinnamaldehyde, see Experimental section) was titrated with sodium naphthalenide at −73 °C, until a green colour persisted and starting material was nearly all consumed. Product isolation gave the aryltriene **29**. Although the yield was poor

(27%) it was markedly better than with sodium amalgam. Thus encouraged, we similarly titrated the benzoyloxy sulphone **25** with sodium naphthalenide. The products were isolated by chromatography with maximum protection from light. Two fluorescent products were obtained (38% yield at 60% conversion, not optimised). Spectroscopic examination of the mixture of these two labile compounds demonstrated that the desired reductive elimination had been induced but that stereomutation had also occurred, affording **30** with the desired gross structure but stereochemically inhomogeneous. It is likely that loss of *Z* geometry, adjacent to the reacting sites, has taken place, possibly catalysed by electron transfer processes. Although Julia olefination usually gives *E* products exclusively, the method has not, to our knowledge, been employed before in the synthesis of pentaenes or related stereolabile conjugated systems. However a case of stereomutation has been reported, in Vitamin D4 synthesis.[11] The future work requires an alternative approach offering more control over the elusive *E,E,Z,E,E* pentaene system.

Experimental

For experimental generalisations see ref. 3.

(2E)-1,1,4,4-*Tetramethoxybut*-2-*ene* **11**.*—Bromine (21.1 g) in dry methanol (60 ml) was added dropwise over 30 min to a stirred solution of furan (8.8 g) in methanol (60 ml) under nitrogen at −55 °C. The solution was maintained at −10 °C for 2.5 h, when anhydrous sodium carbonate (20 g) was added in portions. The mixture was stirred for 18 h at room temperature, filtered and evaporated. Distillation of the residue gave the bis-acetal **11** (15.76 g, 69%), b.p. 66–74 °C/1 mmHg) (lit.,[4] b.p. 85–90 °C/15 mmHg) (Found: *m/z* 176.1. Calc. for $C_8H_{16}O_4$: *M*, 176.2); δ_H 5.83 (2 H, m), 4.84 (2 H, m) and 3.31 (12 H, s).

(2E)-4,4-*Dimethoxybut*-2-*enal* **12**.—Amberlyst-15 (1.97 g) was added to the bis-acetal **11** (8.66 g) in acetone (195 ml) and water (3 ml). The mixture was stirred at room temperature for 10 min and filtered. The filtrate was evaporated and the residue was distilled to yield the aldehyde **12** (4.75 g, 74%), b.p. 76–82 °C/14 mmHg (lit.,[12] b.p. 72–80 °C/11 mmHg); 2835, 2720 and 1695; δ_H 9.58 (1 H, d, *J* 7, CHO), 6.62 (1 H, dd, *J* 16, 3.5, 3-H), 6.29 (1 H, dd, *J* 16, 7, 2-H), 5.01 (1 H, d, *J* 3.5, 4-H) and 3.32 (6 H, s, 2 × OMe).

(2E)-1,1,4,4-*Tetraethoxybut*-2-*ene* **14** *and* (2E)-4,4-*Diethoxybut*-2-*enal* **15**.—Furan (8.8 g) was treated with bromine (21.1 g) and ethanol (170 ml) as in the preparation of compound **11**. Isolation of the products as before gave a yellow liquid which on careful distillation yielded the aldehyde **15** (4.50 g, 22%), b.p. 88–92 °C/10 mmHg (lit.,[13] b.p. 56–58 °C/0.8 mmHg); ν_{max}/cm^{-1} 2730 and 1690; δ_H 9.63 (1 H, *J* 7, CHO), 6.71 (1 H, dd, *J* 15.5, 3.8, 3-H), 6.33 (1 H, ddd, *J* 15.5, 7.0, 1, 2-H), 5.16 (1 H, dd, *J* 3.8, 1, 4-H), 3.70 (2 H, dq, *J* 10, 7, 2 × OCH*H*), 3.53 (2 H, dq, *J* 10.7, 2 × OC*H*H) and 1.23 (6 H, t, *J* 7, 2 × Me); followed by the *bis-acetal* **14** (3.39 g, 11%), b.p. 126–130 °C/18 mmHg; (Found: *m/z* 187.135. $C_{12}H_{24}O_4$ requires M − OEt 187.133); δ_H 5.84 (2 H, m, 2-H, 3-H), 4.93 (2 H, m, 1-H, 4-H), 3.65 (4 H, dq, *J* 9.6, 7, 4 × OC*H*H), 3.51 (4 H, dq, *J* 9.6, 7, 4 × OCH*H*) and 1.23 (12 H, t, *J* 7, 4 × Me).

(2E,4E)-*Ethyl* 6,6-*Dimethoxy*-2-*methylhexa*-2,4-*dienoate* **13**.—Triethyl 2-phosphonopropanoate (9.0 g) was added dropwise with stirring over 10 min to sodium hydride (1.15 g) in tetrahydrofuran (THF) (50 ml) at 0 °C. After being stirred for 10 min at 0 °C and for 15 min at room temperature, the mixture was cooled to 0 °C and the aldehyde (4.70 g) in THF (10 ml) was added over 10 min. The reaction mixture was set aside at room temperature for 17 h and then was diluted with water (60 ml). The mixture was extracted with ether. The washed, dried extracts were evaporated and the residual oil was chromatographed on neutral alumina (ether–hexane, 1:18–1:15) to give the *title ester* **13** as an oil (2.90 g, 37%), b.p. (oven temp.) 153–155 °C/1.5 mmHg (Found: *m/z* 214.119. $C_{11}H_{18}O_4$ requires *M*, 214.121); ν_{max}/cm^{-1} 2830, 1705, 1640, 1615, 980 and 750; δ_H 7.15 (1 H, d, *J* 11.5, 3-H), 6.67 (1 H, ddd, *J* 15.3, 11.5, 1, 4-H), 5.93 (1 H, dd, *J* 15.3, 4.4, 5-H), 4.92 (1 H, dd, *J* 4.4, 1, 6-H), 4.20 (2 H, q, *J* 7.2, OCH_2Me), 3.34 (6 H, s, 2 × OMe), 1.98 (3 H, d, *J* 1, 2-Me) and 1.29 (3 H, t, *J* 7.2, Me).

Ethyl (2E,4E)-6,6-*Diethoxy*-2-*methylhexa*-2,4-*dienoate* **16**.—The aldehyde **15** (3.03 g) was treated with triethyl 2-phosphonopropanoate (4.7 g) and sodium hydride (0.58 g) as described in the preceding experiment. Chromatography on neutral alumina (dry column) (ether–hexane, 1:20–1:14) gave the *title ester* **16** as an oil (3.44 g, 74%), b.p. (oven) 118–121 °C/0.1 mmHg (Found: *m/z* 242.152. $C_{13}H_{22}O_4$ requires *M*, 242.152); ν_{max}/cm^{-1} 1705, 1645, 1615, 980 and 755; δ_H 7.18 (1 H, d, *J* 11.5, 3-H), 6.67 (1 H, ddd, *J* 15.3, 11.5, 1, 4-H), 6.01 (1 H, dd, *J* 15.3, 4.8, 5-H), 5.04 (1 H, d, *J* 4.8, 6-H), 4.22 (2 H, q, *J* 7.1, CO_2CH_2Me), 3.67 (2 H, dq, *J* 9.4, 7.1, 2 × OC*H*HMe), 3.53 (2 H, dq, *J* 9.4, 7.1, 2 × OCH*H*Me), 1.97 (3 H, d, *J* 1, 2-Me), 1.31 (3 H, t, *J* 7.1, Me) and 1.24 (6 H, t, *J* 7.1, 2 × Me).

Ethyl (2E,4E)-2-*Methyl*-6-*oxohexa*-2,4-*dienoate* **17**.—The acetal **13** (2.79 g) in acetone (50 ml) and water (1 ml) was treated in the dark with Amberlyst-15 (0.53 g) at room temperature with stirring for 1 h. The mixture was filtered and the filtrate was evaporated. The residue was taken up in ether, dried and the solvent was evaporated. The residual oil was chromatographed on neutral alumina (dry column) using ether–hexane (1:14, 1:8, 1:4) to yield the *aldehyde* **17** (1.64 g, 75%) as a solid, m.p. 35–37 °C (Found: *m/z* 168.078; C, 64.25; H, 7.2%. $C_9H_{12}O_3$ requires *M*, 168.079; C, 64.27; H, 7.19%); λ_{max}(EtOH)/nm 281 (4.43); ν_{max}/cm^{-1} 2730, 1700, 1675, 1630, 1590, 1110 and 975; δ_H 9.71 (1 H, d, *J* 7.9, CHO). 7.66–7.24 (2 H, m, 3-H, 4-H), 6.38 (1 H, dd, *J* 13.2, 7.9, 5-H), 4.27 (2 H, q, *J* 7.0, OCH_2), 2.13 (3 H, s, 2-Me) and 1.34 (3 H, t, *J* 7.0, Me); δ_C 192.6d, 166.5s, 144.4d, 136.6s, 135.6d, 133.7d, 60.7t, 13.7q and 12.9q.

2-*Ethoxyvinyl*(*triphenyl*)*phosphonium Bromide*.—Formylmethylene(triphenyl)phosohorane (5.26 g) was refluxed with bromoethane (25 ml) for 48–64 h. Evaporation and drying *in vacuo* gave the phosphonium bromide **20** (6.95 g, 97%), *E*:*Z* = 1:2–1:3, m.p. 134–139 °C (lit.,[6] m.p. 136–137 °C); δ_H(*E* isomer) 8.1–7.3 (15 H, ArH), 6.68 (2 H, m, 2 × CH), 4.52 (2 H, q, *J* 7.0) and 1.40 (3 H, t, *J* 7.0) (OEt); δ_H(*Z* isomer) 8.29 (1 H, dd, *J* 32.6, 7.0, CHOEt), 7.95–7.35 (15 H, ArH), 5.70 (1 H, dd, *J* 16.4, 7.0, CHP), 4.19 (2 H, q, *J* 7.1) and 0.96 (3 H, t, *J* 7.1) (OEt). Using commercial starting ylide **18** (Aldrich) pure *E* isomer was formed.

Ethyl (2E,4E,6Z)-8,8-*Diethoxy*-2-*methylocta*-2,4,6-*trienoate* **21**.—2-Ethoxyvinyl(triphenyl)phosphonium bromide (1.04 g, 2.52 mmol) was added to a stirred mixture of sodium ethoxide (220 mg, 3.23 mmol) and THF (20 ml) at 0 °C under nitrogen; stirring was continued at 0 °C for 5 min and at room temperature for 55 min. The mixture was cooled to 0 °C and the aldehyde **17** (101 mg, 0.60 mmol) in THF (4 ml) was added dropwise over 5 min. The reaction mixture was stirred at 0 °C in

* Synthesis of the *Z*-isomer has been reported;[4b] however the b.p. of the '*Z*' material is identical with that of the *E*-isomer,[4a] and the ^1H NMR data are very close to those in the present work. Thus doubt must remain as to the authenticity of the '*Z*' form.

the dark for 15 min and at room temperature for 3 h. The mixture was filtered through a Florisil pad (10 cm) washing with ether and dichloromethane. Evaporation of the solvents gave an oil, which was chromatographed on silica gel 60 using ether–hexane (1:5) to give the *acetal ester* **21** (60 mg, 37%) as a pale yellow oil (Found: *m/z* 268.166; $C_{15}H_{24}O_4$ requires *M*, 268.167); λ_{max}(EtOH)/nm 298 (4.63); ν_{max}/cm^{-1} 1675, 1605, 1100 and 990; δ_H(assignments confirmed by COSY) 7.25 (1 H, d, *J* 11.7, 3-H), 6.91 (1 H, dd, *J* 14.7, 11.7. 5-H), 6.54 (1 H, dd, *J* 14.7, 11.7, 4-H), 6.29 (1 H, dd, *J* 11.7, 11.1, 6-H), 5.62 (1 H, dd, *J* 11.1, 6.3, 7-H), 5.36 (1 H, dd, *J* 6.3, 1.2, 8-H), 4.22 (2 H, q, *J* 7.1, CO_2CH_2Me), 3.66 (2 H, dq, *J* 9.4, 7, 2 × OC*H*HMe), 3.53 (2 H, dq, *J* 9.4, 7, 2 × OCH*H*Me), 1.98 (3 H, d, *J* 1.1, 2-Me), 1.32 (3 H, *J* 7.1, $CO_2CH_2CH_3$) and 1.23 (6 H, t, *J* 7, 2 × OCH_2CH_3); δ_C 168.3s, 137.6d (C-3), 133.7d (C-5), 131.6d (C-6), 131.3d (C-7), 130.2d (C-4), 128.6s, 97.7d, 60.7t, 2 × 15.3q, 14.3q and 12.8q.

Ethyl (2E,4E,6Z)-2-*Methyl*-8-*oxoocta*-2,4,6-*trienoate* **22**.—The unpurified oil, obtained as above from the aldehyde **17** (168.4 mg, 1.00 mmol), in acetone (6 ml) and water (0.9 ml) was treated with Amberlyst-15 (70 mg) at room temperature in the dark with stirring for 35 min. Filtration and evaporation gave an oil which was dissolved in ether and dried. Evaporation of the solvent and chromatography of the residue on silica gel 60 (ether–hexane, 1:5) gave the (6Z)-*aldehyde* **22** (130 mg, 70%) as pale yellow needles, m.p. 53–56 °C (Found: *m/z* 194.095; C, 67.45; H, 7.1%. $C_{11}H_{14}O_3$ requires *M*, 194.094; C, 68.02; H, 7.26%); λ_{max}(EtOH)/nm 318 (4.64); ν_{max}/cm^{-1} 2740, 1685, 1660, 1605, 1105, 1005 and 955; δ_H(assignments confirmed by COSY) 10.22 (1 H, d, *J* 7.6, CHO), 7.46 (1 H, dd, *J* 14.5, 12, 5-H), 7.30 (1 H, d, *J* 11.8, 3-H), 7.04 (1 H, dd, *J* 12, 10.9, 6-H), 6.86 (1 H, dd, *J* 14.5, 11.8, 4-H), 5.99 (1 H, dd, *J* 10.9, 7.6, 7-H), 4.25 (2 H, q, *J* 7.1, OCH_2Me), 2.04 (3 H, d, *J* 1.1, 2-Me) and 1.33 (3 H, t, *J* 7.1, OCH_2CH_3); δ_C 190.0d (C-8), 167.7s, 145.6d (C-6), 136.6d, 136.0, 132.7s, 131.2d (C-5), 128.7d (C-7), 61.0t, 14.2q and 13.2q ppm. The 6*E*-isomer (5 mg) was also obtained (see below).

Ethyl (2E,4E,6E)-2-*Methyl*-8-*oxoocta*-2,4,6-*trienoate* **23**.—Formylmethylene(triphenyl)phosphorane (206.1 mg) and the aldehyde **17** (112.6 mg) were refluxed together in benzene (20 ml) for 24 h. Evaporation of the solvent gave a residue which was extracted with ether. The extracts were evaporated and the residue was chromatographed on silica gel 60 using ether–hexane, (1:6–1:4), to afford the title *aldehyde* **23** (40 mg, 31%) as yellow crystals, m.p. 40–43 °C (Found: *m/z* 194.095); λ_{max}(EtOH)/nm 318 (4.7); ν_{max}/cm^{-1} 2730, 1700, 1675, 1620, 1605, 1095, 990 and 915; δ_H(assignments confirmed by COSY) 9.63 (1 H, d, *J* 7.9, CHO), 7.27 (1 H, d, *J* 11.7, 3-H), 7.22 (1 H, dd, *J* 15.3, 11.3, 6-H), 6.97 (1 H, dd, *J* 14.8, 11.7, 4-H), 6.73 (1 H, dd, *J* 14.8, 11.3, 5-H), 6.26 (1 H, dd, *J* 15.3, 7.9, 7-H), 4.25 (2 H, q, *J* 7.1, OCH_2Me), 2.05 (3 H, d, *J* 1.4, 2-Me) and 1.33 (3 H, t, *J* 7.1, OCH_2CH_3); δ_C 193.3d (C-8), 167.7s, 150.4d (C-6), 136.6d, 136.0d, 135.4d (C-5), 133.2d (C-7), 132.8s, 61.1t, 14.3q and 13.2q.

3-*Benzoyloxy*-5-*methyl*-1-*phenyl*-4-p-*tolylsulphonylhepta*-1E,5E-*diene* **28**.—Butyllithium (1.6 mol dm^{-3} in hexane; 3.0 ml) was added dropwise to (*E*)-2-methyl-1-*p*-tolylsulphonylbut-2-ene[3] (0.82 g) in THF (10 ml) at −73 °C under nitrogen. The yellow solution was stirred for 20 min when cinnamaldehyde (0.52 g) in THF (3 ml) was added dropwise during 5 min; the colour faded in this time. After 35 min at −73 °C benzoyl chloride (1.1 g) was added; the mixture was kept at −73 °C for 3 h, when it was allowed to warm to room temperature over 1 h. Water (10 ml) was added and the mixture was extracted with ether. The washed, dried, extracts were evaporated to yield an oil which slowly crystallised (2.94 g). Chromatography on silica gel 60 using ether–hexane (1:20, 1:10, 1:2) gave the *title sulphone* **28** (1.33 g, 79%) as a solid mixture of diastereoisomers (Found: *m/z* 338.134. $C_{28}H_{28}O_4S$ requires $M - C_7H_5O_2$, 338.134). The major diastereoisomer was obtained as white needles from chloroform–hexane, m.p. 150–153 °C (Found: C, 73.15; H, 6.1. $C_{28}H_{28}O_4S$ requires C, 73.02; H, 6.13%); δ_H 8.2–7.0 (14 H, m, ArH), 6.77 (1 H, d, *J* 15.1, 1-H), 6.5–5.9 (2 H, m, 2-H, 3-H), 5.85–5.35 (1 H, m, 6-H), 4.19 (1 H, d, *J* 9.4, 4-H), 2.22 (3 H, s, ArMe), 1.76 (3 H, s, 5-Me) and 1.59 (3 H, d, *J* 6.8, 6-Me).

(1E,3E,5E)-5-*Methyl*-1-*phenylhepta*-1,3,5-*triene* **29**.—Sodium naphthalenide (0.5 mol dm^3 in THF) was added dropwise to a stirred solution of the benzyloxy sulphones **28** (228.2 mg) in THF (25 ml) at −73 °C under nitrogen. Each drop gave a deep red colouration which was allowed to fade before continuing. Addition was completed when a green colour persisted and TLC indicated almost all the starting material had been consumed. The mixture was quenched with water, allowed to warm, and diluted with pentane. The aqueous phase was extracted with dichloromethane. Combined organic phases were washed, dried and evaporated. The residue was chromatographed on silica gel 60 using hexane and ether–hexane (1:2, 2:3) to afford the *title triene* **29** (25 mg, 25%) as a white semi-solid [Found: *m/z*(CI) 185. $C_{14}H_{16}$ requires *M* + H, 185); λ_{max}($CHCl_3$)/nm 311sh, 323 (4.26) and 338 (4.13); ν_{max}/cm^{-1} 3030, 1595, 1590, 1490 and 990; δ_H 7.55–7.2 (5 H, m, ArH), 6.88 (1 H, dd, *J* 15.6, 9.1, 2/3-H), 6.57 (1 H, d, *J* 15.6, 1/4-H), 6.43 (1 H, d, *J* 15.2, 4/1-H), 6.34 (1 H, dd, *J* 15.2, 9.1, 3/2-H), 5.69 (1 H, q, *J* 7.5, 6-H), 1.83 (3 H, br s, 5-Me) and 1.80 (3 H, d, *J* 7.5, 6-Me).

Ethyl (12R,13R,2E,4E,6Z,10E,14E)-8-*Benzoyloxy*-13-(tert-*butyldimethylsilyloxy*)-2,10,12,14-*tetramethyl*-9-p-*tolylsulphonylhexadeca*-2,4,6,10,14-*pentaenoate* **26**.—Butyllithium (1.4 mol dm^3 in hexane; 0.49 ml) was added dropwise to the sulphone **24** (129.6 mg) in THF (5 ml) at −73 °C under nitrogen. The resulting deep orange solution was stirred for 10 min at −73 °C when the aldehyde **22** (58.7 mg) in THF (2 ml) was added dropwise over 5 min. The mixture was stirred at −73 °C for 40 min after which benzoyl chloride (97 mg) was added, and stirring was continued at −73 °C for 2.3 h in the dark. The mixture was then allowed to warm to room temperature and quenched with water (5 ml). The organic layer was washed with water, dried and evaporated. The residual oil (280 mg) was chromatographed on silica gel 60 using ether–hexane (1:10, 1:5) to yield first (5R,6R,3E,7E)-6-(tert-*butyldimethylsilyloxy*)-3,5,7-*trimethyl*-1-*phenyl*-2-p-*tolylsulphonylnona*-3,7-*dien*-1-*one* **26** (77.1 mg, 48%) as a pale yellow oil and a mixture of epimers at C-2 (Found: *m/z* 483; $C_{31}H_{44}O_4SSi$ requires *M* − Bu, 483); λ_{max}/nm 233 (4.23) and 250infl; δ_H 7.95–7.0 (9 H, m, ArH), 5.53 (s, 2-H, minor isomer), 5.50 (s, 2-H, major), 3.63 (1 H, m, 6-H), 2.75–2.15 (1 H, m, 5-H), 2.41 (3 H, s, ArMe), 1.96 (d, *J* 1.4, 3-Me, major), 1.66 (d, *J* 1.3, 3-Me, minor), 1.45–1.2 (6 H, m, 7-Me, 8-Me), 1.0–0.65 (3 H, m, 5-Me), 0.76 (s, Bu^t, minor), 0.66 (s, Bu^t, major), 0.00 (s, SiMe), −0.12 (s, SiMe), −0.23 (s, SiMe) and −0.26 (s, SiMe). The next product eluted was the *title compound* **25** (42.7 mg, 20%) as a colourless oil and a mixture of diastereoisomers: λ_{max}/nm 228 (4.22), 287infl, 301 (4.44) and 314infl; ν_{max}/cm^{-1} 1720, 1695, 1605, 1320, 1305, 1290, 1145 and 1105; δ_H 8.05 and 7.87 (2 H, 2 × d, *J* 7.0, *o*-ArH), 7.75–6.1 (12 H, m, ArH and 3, 4, 5, 6, 7-H), 5.8–5.05 (3 H, m, 8, 11, 15-H), 4.26 (2 H, q, *J* 7.1, OCH_2Me), 4.15 and 3.76 (1 H, d, *J* 4.7 and 9.4, 9-H), 3.72 and 3.67 (1 H, d, *J* 4.9 and 4.7, 13-HO, 2.65–2.3 (1 H, m, 12-H), 2.42 (3 H, s, ArMe), 2.26 (3 H, s, 2-Me), 1.98 (3 H, s, 14-Me), 1.96 (3 H, d, *J* 10.1, 15-Me), 1.61 (3 H, d, *J* 0.9, 10-Me), 1.38 and 1.37 (3 H, t, *J* 7.1, OCH_2CH_3), 0.90 and 0.83 (9 H, 2 × s, Bu^t), 0.56 and 0.54 (3 H, d, *J* 7.0 and 6.9, 12-Me) and 0.01–0.02, −0.06 and −0.10 (6 H, 4 × s, 2 × SiMe). Molecular ions could not be observed in the mass spectra under EI or CI conditions.

Treatment of the Benzyloxy Sulphones **25** *with Sodium Amalgam in Methanol.*—Sodium amalgam (5%; 106 mg) was added to a stirred solution of the benzyloxy sulphones **25** (7.5 mg) in THF (0.6 ml) and methanol (0.2 ml) at −23 °C under nitrogen, and the mixture was stirred in the dark for 4.5 h. After dilution with pentane the mixture was filtered, and the filtrate was washed, dried and evaporated to yield a yellow oil (5.5 mg). Chromatography of this on silica gel 60 using ether–hexane (1:25, 1:8) gave a mixture of ethyl and methyl (2*E*,4*E*,6*Z*, 8*E*/*Z*,10*E*,14*E*) 13-(*tert*-butyldimethylsilyloxy-2,10,12,14-tetramethyl-9-*p*-tolysulphonylhexadeca-2,4,6,8,10,14-hexaenoate **27** (1.2 mg, 20%); TLC showed two spots fluorescing blue under UV light (366 nm), R_f (SiO_2, ether–hexane 2:3) 0.41, 0.36 (Found: *m*/*z* 597, 583, 555 and 541. $C_{35}H_{52}O_5SSi$ requires *M* − Me, 597, M − Bu^t 555; $C_{34}H_{50}O_5SSi$ requires *M* − Me 583, *M* − Bu^t 541); λ_{max}($CDCl_3$)/nm 3341infl, 349 (4.69), 365 (4.63); δ_H 7.7 (2 H, m, ArH), 7.5–7.2 (m, ArH, 8-H, 3-H major isomer), 7.15 (1 H, dd, *J* 11, 14, 5-H), 6.90 (d, *J* 12, 3-H minor isomer), 6.67 (1 H, dd, *J* 12, 14, 4-H), 6.49 (dd, *J* 11, 11, 6/7-H minor), 6.41 (dd, *J* 11, 11, 6/7-H major), 6.13 (dd, *J* 11, 11, 7/6-H major), 5.4–5.2 (1 H, m, 15-H), 5.06 (d, *J* 9.5, 11-H minor), 4.86 (d, *J* 9.5, 11-H major), 4.25 (q, *J* 7.1, OCH_2Me major), 4.21 (q, *J* 7.1, OCH_2Me minor), 3.80 (s, OMe, major), 3.76 (s, OMe, minor), 3.65 (d, *J* 4.9, 13-H major), 3.62 (d, *J* 6.7, 13-H minor), 2.41 (3 H, s, ArMe), 2.6–2.2 (1 H, m, 12-H), 2.01 (3 H, s, 2-Me), 1.83 (d, *J* 1, 10-Me minor), 1.72 (d, *J* 1.4, 10-Me major), 1.53 (3 H, d, *J* 11.2, 15-Me), 1.48 (3 H, s, 14-Me), 1.36 (t, *J* 7.1, OCH_2CH_3), 0.86 (s, Bu^t, minor), 0.79 (s, Bu^t, major), 0.66 (d, *J* 6.9, 12-Me major), 0.63 (d, *J* 6.9, 12-Me minor), −0.01 and −0.08 (2 × s, 2 × SiMe minor) and −0.08 and −0.12 (2 × s, 2 × SiMe major).

Ethyl 13-(tert-*Butyldimethylsilyloxy*)-2,10,12,14-*tetramethylhexadeca*-2,4,6,8,10,14-*hexaenoate* **30**.—Sodium naphthalenide solution (0.5 mol dm^3 in THF) was added dropwise to a stirred solution of the benzyloxy sulphones **25** (35.6 mg) in THF (3 ml) at −73° under nitrogen in the dark. Each drop gave a deep blue–purple colour which faded rapidly. When the purple colour persisted addition was stopped and the mixture was stirred for 20 min, when water was added and the mixture was allowed to warm to room temperature. The product was diluted with pentane (5 ml) and the aqueous phase was extracted with ether. The combined organic phases were washed, dried and evaporated. The residue was chromatographed on silica gel 60 using hexane then ether–hexane (1:25, 1:20, 1:2) to yield the title ester **30** (5 mg, 23%; 38% at 60% conversion) as a mixture of isomers; TLC showed two spots which fluoresced blue under UV light (366 nm), R_f (ether–hexane 1:6) 0.44 and 0.36; λ_{max}(EtOH)/nm 309i, 323, 339 and 357; λ_{max}($CDCl_3$)/cm^{-1} 314i, 328, 344 and 362; δ_H 7.35–6.00 (7 H, m, 3, 4, 5, 6, 7, 8, 9-H_7), 5.4–5.25 (2 H, m, 15-H, 11-H), 4.22 (2 H, OCH_2Me), 3.66 (d, *J* 8, 13-H major isomer), 3.65 (d, *J* 8, 13-H minor), 2.65 (m, 12-H), 1.83 (d, *J* 1, C=CMe major), 1.79 (d, *J* 1, C=CMe minor), 1.76 (s, C=CMe major), 1.74 (s, C=CMe minor), 1.6–1.5 (6 H, m, C=CMe and 14-Me), 0.94 (3 H, t, *J* 7.4, OCH_2CH_3), 0.81 (s, Bu^t, major), 0.80 (s, Bu^t, minor), 0.78 (d, *J* 6.9, 12-Me major), 0.77 (d, *J* 6.9, 12-Me minor), −0.05 and −0.07 (each 3 H, s, SiMe). Starting material (14.4 mg, 40%) was eluted next.

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