Retinoids and Related Compounds. Part 14.[1] A Novel Synthesis of Conjugated 4-Alkylidenebutenolides and Their Spectral Characterization

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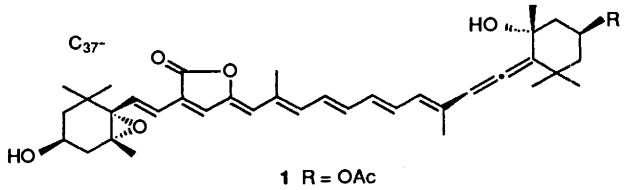
A novel synthesis (the sulfone method) of carotenoidal alkylidenebutenolides is described together with spectral characterization of the latter.

C_{37}-Skeletal nor-carotenoids, peridinin **1**,[2] peridininol **2**,[3] anhydroperidinin,[4] pyrrhoxanthin **3**[3] and pyrrhoxanthinol **4**[3] and C_{40}-carotenoid, uriolide **5**[5] are classified as butenolide carotenoids[6] because of the presence of a 4-alkylidenebutenolide system **6** in the main polyene chain. The principal



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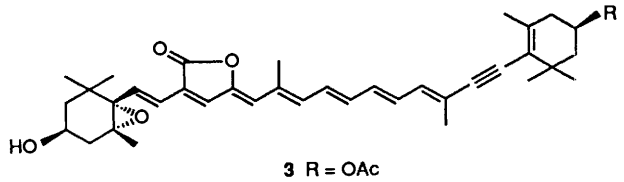
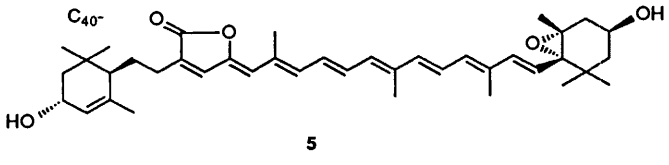
2 R = OH



3 R = OAc
4 R = OH



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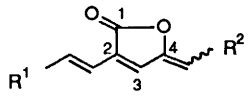
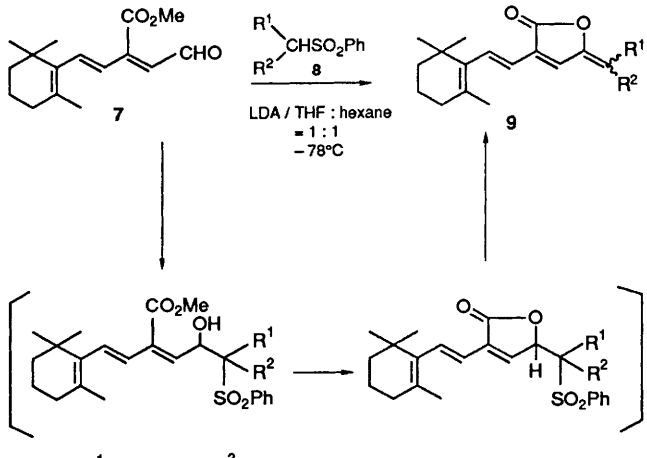


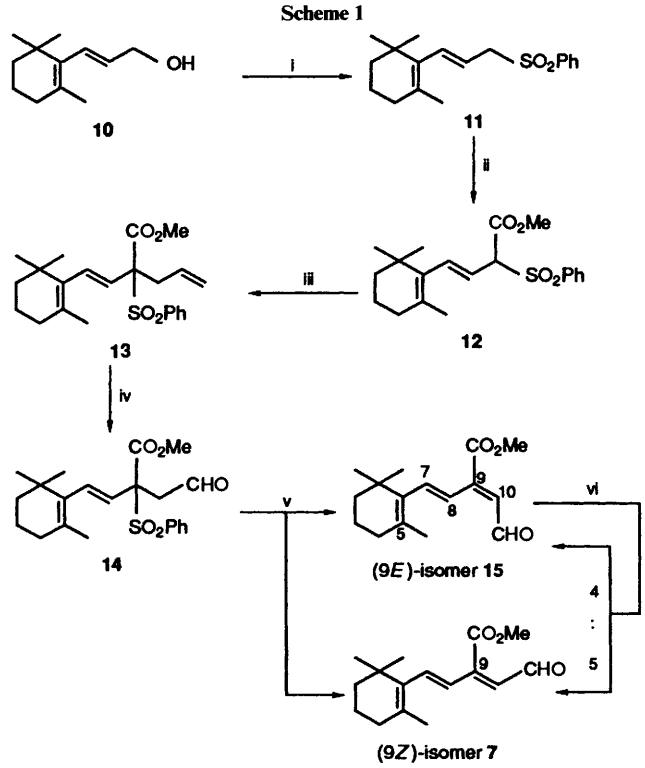
6

R^1, R^2 : polyene chains

carotenoid of the planktonic algae causing 'red tide', peridinin, functions as an auxiliary light-harvesting pigment for photosynthesis.[7] Two Wittig procedures[8,9] directed towards the synthesis of carotenoidal alkylidenebutenolides were less than useful for the preparation of compounds containing a conjugated polyene chain because of the drastic reaction conditions employed. A new method[6,10] (sulfone method, Scheme 1) was then developed to prepare the 4-alkylidenebutenolides **6** displaying extended conjugation at the C-2 position. By use of the sulfone method, the first total synthesis[10] of compounds **1** and **3** was achieved followed by the synthesis of optically active **1**.[6] Here, we describe the details of the sulfone method which is the reaction of the conjugated formyl ester **7** (Scheme 2) with various allylic sulfones **8a–f** (Table 1) in the presence of lithium



Scheme 1

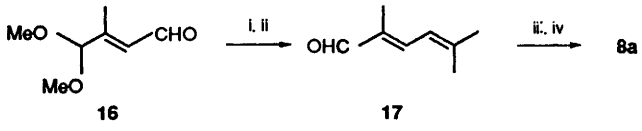


Scheme 2 *Reagents and conditions:* i, $PhSO_2Na{\cdot}2H_2O$, propan-2-ol, AcOH, 61%; ii, BuLi, $ClCO_2Me$, THF, 96%; iii, NaH, $BrCH_2CH{=}CH_2$, DMF, quant.; iv, OsO_4–$NaIO_4$, dioxane–H_2O, 56%; v, Al_2O_3, Et_2O–hexane, 69%; vi, I_2, hexane, 83%.

diisopropylamide (LDA) at −78 °C to give conjugated alkylidenebutenolides **9a–f** in moderate yields as a mixture (*ca.* 1:1) of *Z* and *E* isomers about the ylidene double bond.

Synthesis of the Conjugated Formyl Ester **7**.—Reaction of the allylic alcohol **10**[11] (Scheme 2) prepared by Huisman's procedure, with sodium benzenesulfinate ($PhSO_2Na$) in a mixture of acetic acid and propan-2-ol under reflux for 16 h gave the sulfone **11** (61%); this was treated with methyl chlorocarbonate in the presence of butyllithium (BuLi) as a base to provide the methoxycarbonylated sulfone **12** (96%) and the recovered sulfone **11**. Treatment of **12** with allyl bromide using NaH afforded **13** in quantitative yield and this was oxidized with sodium periodate and a catalytic amount of osmium tetroxide in a mixture of water and dioxane to afford the formyl sulfone **14** (56%). Treatment of **14**[9] with Al_2O_3 resulted in the formation of a mixture of the conjugated formyl esters **7** and **15** (69%) which could be cleanly separated by low-pressure liquid chromatography. The ratio of **15** to **7** was *ca.* 4:5. In the faster eluted isomer **15**, the 9*E*-configuration† was assigned to the newly formed trisubstituted 9,10-double bond. A comparison of the ^1H NMR data of **15** with those of the other isomer **7** shows that the 8-H signal (δ 6.65) of **15** is deshielded by the anisotropic effect of the aldehyde group and that the 10-H signal (δ 6.64) appears at lower field owing to the anisotropic effect of the ester group. Treatment of **15** with I_2 as a catalyst in hexane gave a mixture of **15** and **7** (ratio **15**:**7** = *ca.* 4:5).

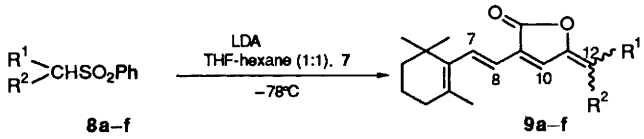
Synthesis of Various Allylic Sulfones **8a–f**.—The six sulfones shown in Table 1 were used in the condensation with the preceding formyl ester **7**. The diene sulfone **8a** was prepared from the known acetal aldehyde **16**[12] in the process shown in Scheme 3. A Wittig reaction of **16** with isopropylphosphonium

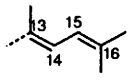
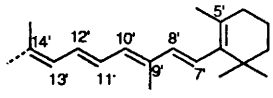
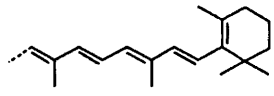
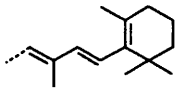
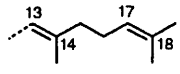
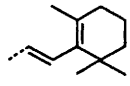


Scheme 3 *Reagents and conditions:* i, BuLi, isopropylphosphonium bromide, Et_2O; ii, 15% H_2SO_4, acetone, 76%; iii, LAH, Et_2O; iv, $PhSO_2Na{\cdot}2H_2O$, AcOH, propan-2-ol, 48%.

bromide[13] in the presence of BuLi, followed by deprotection, gave the dienal **17** (76%) which, on reduction with $LiAlH_4$

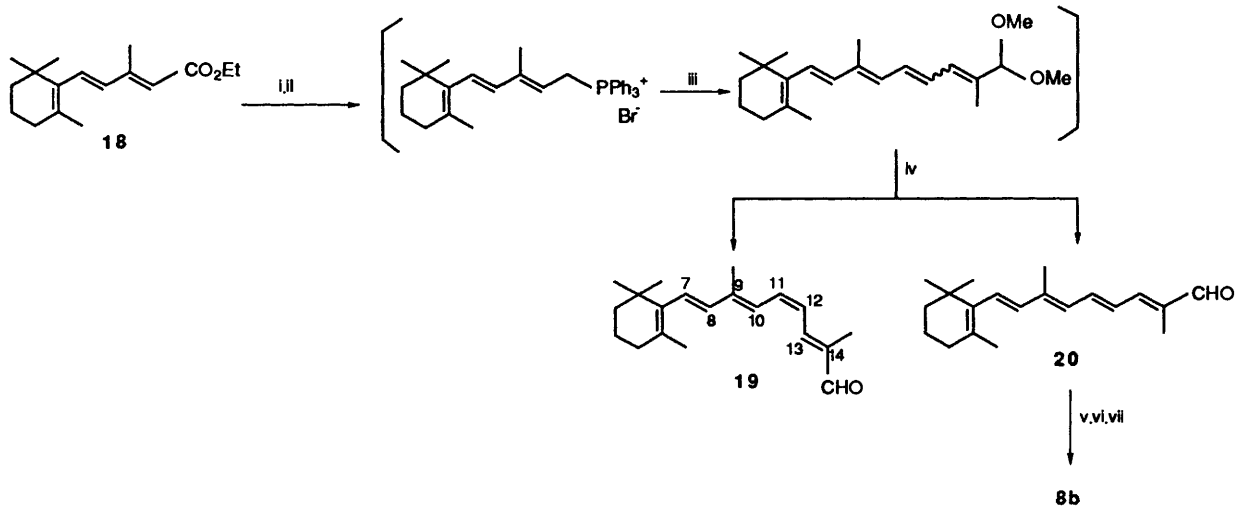
Table 1 Conjugated alkylidenebutenolide synthesis



Entry	Sulfones (**8a–f**) and products (**9a–f**)	Total yield of *E* and *Z* (%)
1	**a**; R^1 = H, R^2 = 	56
2	**b**; R^1 = H, R^2 = 	46
3	**c**; R^1 = H, R^2 = 	46
4	**d**; R^1 = H, R^2 = 	33
5	**e**; R^1 = H, R^2 = 	32
6	**f**; R^1 = Me, R^2 = 	49[a]

[a] Addition of HMPA

† We have employed the numbering system used in the retinoids and carotenoids.



Scheme 4 *Reagents and conditions:* i, LAH, Et_2O; ii, $Ph_3P{\cdot}HBr$, MeOH; iii, NaOEt, **16**; iv, 20% H_2SO_4, acetone, 24%; v, $NaBH_4$, MeOH; vi, Ac_2O, pyridine; vii, $PhSO_2Na{\cdot}2H_2O$, propan-2-ol–H_2O, 55%

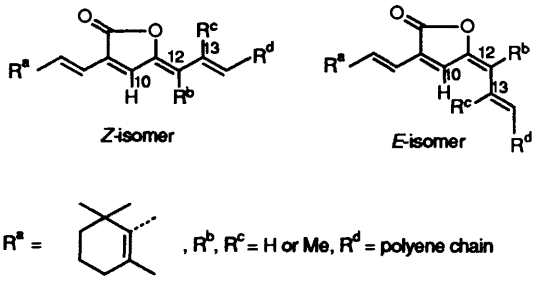
Table 2 UV–VIS absorption maxima for conjugated alkylidenebutenolides

Compound	λ_{max}(EtOH)/nm (ε)	
	Z-Isomer	*E*-Isomer
9a	414 (57 000)	419 (57 000)
	237 (9 000)	238 (9 000)
9b	469 (69 000)	471 (74 000)
	293 (12 000)	290 (13 000)
9c	470 (74 000)	467 (60 000)
	296 (14 000)	304 (16 000)
9d	423 (57 000)	424 (48 000)
	245 (12 000)	311 (11 000)
		252 (13 000)
9e	372 (43 000)	380 (39 000)
	269 (15 000)	268 (8 000)
9f	396 (40 000)	388 (34 000)
	272 (6 000)	288 (9 000)

Table 3 Characteristic ^{1}H NMR data for conjugated alkylidenebutenolides

Compound	^{1}H NMR δ(CDCl$_3$, 200 MHz)					
	Z-Isomer			*E*-Isomer		
	10-H	12-H	13-H	10-H	12-H	13-H
9a	7.02	5.72		7.43	6.39	
9b*	7.04	5.71		7.39	6.34	
9c	7.05	6.13	6.72	7.42	6.39	6.58
9d	7.05	6.11	6.64	7.42	6.33	6.59
9e	7.05	5.96	6.46	7.40	6.44	6.14
9f	7.35		6.91	7.41		6.47

(* 500 MHz)



(LAH), was converted into the corresponding allylic alcohol; sulfonylation of this afforded the sulfone **8a** (48%). The pentaene sulfone **8b** was prepared from the known 13-desmethyl-14-methyl-retinal **20**[14] (Scheme 4): this was derived in four steps from ethyl β-ionylidene acetate **18**[15] by conversion of the latter into its corresponding alcohol, the phosphonium salt of which was treated with **16** in a Wittig condensation and the product deprotected. Reduction of the aldehyde group in **20** with $NaBH_4$ followed by acetylation gave the allylic acetate which, without purification, was refluxed with $PhSO_2Na$ in a mixture of water and propan-2-ol overnight to afford the pentaene sulfone **8b** (55% from **20**). The structure of **8b** was confirmed on the basis of UV and ^{1}H NMR data compared with those[16] of the all-*E*-retinyl sulfone **8c**. The sulfones **8c**,[16] **8d**,[17] **8e**[18] and **8f**[19] were prepared according to the literature.

Synthesis of 4-Alkylidenebutenolides.—As a preliminary to the total synthesis of **1**, optimization of the reaction conditions (base, solvent, molar ratio of reactants, reaction temperature and reaction time) between **7** and the allylic sulfone **8a** was explored. The resulting conjugated alkylidenebutenolide **9a** has the in-chain methyl group and the enolic oxygen atom in the lactone ring in a 1,3-relationship and thus is a simple model for **1**. In consequence, a general synthesis [LDA, tetrahydrofuran (THF)–hexane = 1:1, −78 °C] of conjugated alkylidenebutenolide synthesis (see Experimental section) was established. Results given in Table 1 indicate that the yields were reasonable. In this reaction, **7** readily undergoes nucleophilic addition of the carbanion of the allylic sulfone to give the hydroxy ester in which cyclization and elimination of the sulfone group took place successively in one pot to afford the expected products (Scheme 1). In the reaction of the β-ionyl sulfone **8f** with **7**, the yield of the corresponding alkylidenebutenolide **9f** was 37%, which was improved to 49% by using BuLi as a base in THF containing hexamethylphosphoric triamide (HMPA).

However, the reaction of **7** with the sulfone **11** gave only a low yield of product. The *E* and *Z* alkylidenebutenolide isomers (see Table 1) obtained in a ratio of *ca.* 1:1 were cleanly separated by preparative TLC. Thus, the sulfone method is useful in the preparation of unstable alkylidenebutenolides possessing a long polyene chain. The alkylidenebutenolides prepared were identified on the basis of their spectral data (IR, UV–VIS, ^{1}H NMR and mass spectra). Alkylidenebutenolides showed strong, distinctive bands in the IR region at 1740–1760 cm^{-1}, indicating the presence of α,β-unsaturated γ-lactone. Their UV–VIS light absorption data are summarized in Table 2. Although the *E* and *Z* isomers show similar absorption maxima for the alkylidene portion of the molecule, the molar extinction coefficient of the *Z*-isomer is larger than that of the *E* except for **9b**; this suggests that the conjugated polyene chain in the former is more planar than that in the latter. The stereochemistry of the newly formed alkylidene double bond was determined on the basis of the empirical rule[6] that in compounds of this type, the ^{1}H NMR signal for 10-H in the 11*Z* isomer was observed at δ 7.00–7.20, whereas the corresponding signal for the 11*E* isomer was downfield (< δ 7.40). One exception to this rule was, however, observed: δ 7.35 of 10-H in **9f**. In the *Z* isomer of **9f**, an NOE (nuclear Overhauser effect) was observed between 12(9′)-CH_3 and 10-H (24%). Thus, the downfield shift (δ 7.35) of 10-H in **9f** is attributable to steric crowding[20] with the 12(9′)-CH_3. This suggests that the above empirical rule has to be carefully applied when 10-H is sterically hindered. In addition, chemical shifts of the olefinic hydrogen or the methyl proton at C-13 in the *Z* isomer were found more downfield than those of the corresponding signals in the *E* isomer owing to the effect of the enolic oxygen of a butenolide ring. In the *E* isomer, the olefinic hydrogen or the methyl proton at C-12 was found more downfield than that of the *Z* isomer.

Photoisomerization of Conjugated Alkylidenebutenolides.—As a model of compound **1**, which acts as a light-harvesting pigment for photosynthesis in the sea, the photochemical behaviour of compound **9a** in several solvents was investigated using HPLC (high-performance liquid chromatography) analysis. Irradiation of both isomers of **9a** with a daylight fluorescent lamp at room temperature for 30 min provided a photosteady-state mixture of isomers the ratio of which depended on the properties of the solvent employed. In a nonpolar solvent (hexane or benzene), the 11*Z* isomer predominated.

Experimental

M.p.s are uncorrected. UV–VIS spectra were recorded in ethanolic solution on a Shimadzu UV-200 or UV-200S or UV-160 instrument and IR spectra on a Shimadzu IR-27G spectrometer in a chloroform solution. ^{1}H NMR spectra at 60, 200 or 500 MHz were measured on a JEOL JNM-PMX 60, or a Varian XL-200 or a Varian VXR-500 superconduction FT-NMR spectrometer, respectively, in deuteriochloroform solutions using tetramethylsilane as an internal reference. Mass spectra were determined on a Hitachi M-80 double focusing

GC mass spectrometer. Column Chromatography (CC) was performed on silica gel (Merck Art. 7734) in the case of using an open column and (Merck Art. 7739) in the case of using a short column under reduced pressure. Low-pressure column chromatography was conducted on a Yamazen Low Pressure Liquid Chromatography System using a Lobar Column (Merck LiChroprep Si60). Preparative TLC was performed on silica gel plates (Merck silica gel $60F_{254}$ precoated plates, 0.25 or 0.5 mm thickness). Analytical HPLC was carried out on a Shimadzu LC-5A instrument with a Shimadzu photodiodearray spectrophotometer detector SPD-M6A using a column, LiChrosorb Si-60 (5 μm), 0.4 × 30 cm. Preparative HPLC was conducted on a Shimadzu LC-6A instrument with a Shimadzu UV–VIS detector, SPD-6AV, using a column LiChrosorb Si-60 (5 μm), 0.75 × 30 cm.

Unless otherwise stated, solvent extracts were dried over anhydrous sodium sulfate and all operations were carried out under nitrogen or argon. The filtrate was concentrated under reduced pressure at < 30 °C using a rotary evaporator. Ether refers to diethyl ether and hexane to *n*-hexane.

(E)-[3-(2,6,6-*Trimethylcyclohex*-1-*enyl*)*allyl*]*sulfonylbenzene* **11**.—A mixture of the allylic alcohol **10**[11] (8.67 g, 48 mmol) and $PhSO_2Na{\cdot}2H_2O$ (9.70 g, 49 mmol) in propan-2-ol (9.6 cm^3) and glacial acetic acid (14.3 cm^3) was stirred at room temperature for 15 min and then refluxed for 16 h. The reaction mixture was diluted with ethyl acetate and washed successively with saturated aqueous $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The residue was purified by CC (ether–hexane, 3:17) to afford the sulfone **11** (8.88 g, 61%) as colourless plates, m.p. 80.5–81.5 °C; ν_{max}/cm^{-1} 1310 and 1140 (SO_2); δ_H(200 MHz) 7.93–7.87 (2 H, m, ArH), 7.69–7.49 (3 H, m, ArH), 5.99 (1 H, br d, $J_{7,8}$ 16, 7-H), 5.32 (1 H, dt, $J_{7,8}$ 16, $J_{8,9}$ 7.5, 8-H), 3.91 (2 H, dd, $J_{8,9}$ 7.5, $J_{9.5\text{-Me}}$ 1, 9-H_2), 1.58 (3 H, d, $J_{9.5\text{-Me}}$ 1, 5-Me) and 0.84 (6 H, s, gem-Me) (Found: *m*/*z* 304.150. $C_{18}H_{24}O_2S$ requires *M*, 304.150) (Found: C, 70.6; H, 7.9; S, 10.6. $C_{18}H_{24}O_2S$ requires C, 71.0; H, 7.95; S, 10.5%).

Methyl (E)-2-*Phenylsulfonyl*-4-(2,6,6-*trimethylcyclohex*-1-*enyl*)*but*-3-*enoate* **12**.—A hexane solution of BuLi (10%, w/v; 28 cm^3, 44 mmol) was added to a stirred solution of the sulfone **11** (6.1 g, 20 mmol) in dry THF (15 cm^3) at −78 °C. The mixture was stirred at −78 °C for an additional 30 min after which methyl chloroformate (1.85 cm^3, 24 mmol) was added to it and stirring continued at −78 °C for 20 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl to the mixture which was then extracted with ether. The extracts were washed with brine, dried and evaporated under reduced pressure to give an oil which was purified by CC (ether–hexane, 3:17). This provided the sulfonyl ester **12** (5.42 g, 75%) as colourless plates (m.p. 70–70.5 °C) together with recovered starting material (1.37 g, 22%); ν_{max}/cm^{-1} 1745 (CO_2Me) and 1330 and 1150 (SO_2); δ_H(200 MHz) 7.93–7.87 (2 H, m, ArH), 7.72–7.52 (3 H, m, ArH), 6.19 (1 H, br d, $J_{7,8}$ 16, 7-H), 5.50 (1 H, dd, $J_{7,8}$ 16, $J_{8,9}$ 10, 8-H), 4.61 (1 H, d, $J_{8,9}$ 10, 9-H), 3.75 (3 H, s, CO_2Me), 1.64 (3 H, s, 5-Me) and 0.93 (6 H, s, gem-Me) (Found: *m*/*z* 221.152. $C_{14}H_{21}O_2$ requires *M* − SO_2Ph, 221.154) (Found: C, 66.1; H, 7.2; S, 8.9. $C_{20}H_{26}O_4S$ requires C, 66.3; H, 7.2; S, 8.8%).

Methyl (E)-2-*Phenylsulfonyl*-2-[2-(2,6,6-*trimethylcyclohex*-1-*enyl*)*vinyl*]*pent*-4-*enoate* **13**.—A suspension of NaH (60% oil dispersion; 0.67 g) in dry dimethylformamide (DMF) (34 cm^3) was added to a stirred solution of the ester **12** (4.31 g, 12 mmol) in dry DMF (17 cm^3) at 0 °C. The mixture was stirred at room temperature for 40 min after which allyl bromide (1.14 cm^3, 13 mmol) was added to it at 0 °C; the reaction mixture was then stirred at 0 °C for 10 min and at room temperature for 20 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with ether. The extracts were washed with brine, dried and evaporated under reduced pressure to give an oil which was purified by CC (ether–hexane, 3:17). This afforded the ester **13** (4.82 g, quant.) as colourless solid, ν_{max}/cm^{-1} 1735 (CO_2Me) and 1305 and 1140 (SO_2); δ_H(200 MHz) 7.87–7.80 (2 H, m, ArH), 7.71–7.48 (3 H, m, ArH), 6.37 (1 H, br d, $J_{7,8}$ 17, 7-H), 5.75 (1 H, d, $J_{7,8}$ 17, 8-H), 5.63 (1 H, ddt, *J* 17, 10 and 7, 11-H), 5.20–5.07 (2 H, m, 12-H), 3.70 (3 H, s, CO_2Me), 3.14 and 3.00 (each 1 H, each dd, *J* 14, 7, 10-H_2), 1.69 (3 H, d, *J* 1, 5-Me) and 1.00 and 0.98 (each 3 H, each s, gem-Me) (Found: *m*/*z* 261.185. $C_{17}H_{25}O_2$ requires *M* − SO_2Ph, 261.185).

Methyl (E)-2-*Formylmethyl*-2-*phenylsulfonyl*-4-(2,6,6-*trimethylcyclohex*-1-*enyl*)*but*-3-*enoate* **14**.—Osmium tetroxide (catalytic amounts) was added to a solution of the ester **13** (1.49 g, 3.7 mmol) in dioxane (15 cm^3) and water (5 cm^3) at room temperature and the mixture was stirred at room temperature for 5 min. Sodium metaperiodate (1.79 g, 8.4 mmol) was then added in small portions to the mixture over 30 min at room temperature after which it was stirred at room temperature for 3 h. After completion of the reaction, the mixture was extracted with ether and the extract washed with brine, dried and evaporated under reduced pressure to give an oil. This was quickly purified by CC (ether–hexane, 2:1) to provide the aldehyde **14** (0.84 g, 56%) as a pale yellow oil; ν_{max}/cm^{-1} 1729 (CO_2Me, CHO) and 1315, 1302 and 1141 (SO_2); δ_H(200 MHz) 9.68 (1 H, br s, CHO), 7.85–7.51 (5 H, m, ArH), 6.21 (1 H, br d, $J_{7,8}$ 17, 7-H), 5.87 (1 H, d, $J_{7,8}$ 17, 8-H), 3.73 (3 H, s, CO_2Me), 3.57 and 3.41 (each 1 H, each br d, *J* 18, 10-H_2), 1.65 (3 H, s, 5-Me) and 0.97 and 0.94 (each 3 H, each s, gem-Me) (Found: *m*/*z* 263.165. $C_{16}H_{23}O_3$ requires *M* − SO_2Ph, 263.165).

Methyl (E/Z,E)-4-*Oxo*-2-[(2,6,6-*trimethylcyclohex*-1-*enyl*)-*vinyl*]*but*-3-*enoate* **15**, **7**.—Aluminium oxide for CC (Merck Art. 1064, 10 g) was added to a solution of the aldehyde **14** (1.06 g, 2.6 mmol) in ether and hexane (appropriate quantities) and the mixture was stirred at room temperature. Upon disappearance of the TLC spot of the starting material, aluminium oxide was filtered off. Evaporation of the filtrate gave a yellow oil which was purified by short CC (ether–hexane, 1:9) followed by low-pressure column chromatography (ether–hexane, 1:9) to provide the formyl ester **15** (216 mg, 31%) as a yellow solid and **7** (260 mg, 38%) as a yellow oil. Compound **15**: λ_{max}/nm 337 (ε 4000) and 275 (ε 7000); ν_{max}/cm^{-1} 1725 (CO_2Me), 1670 (CHO) and 1590 (C=C); δ_H(200 MHz) 10.06 (1 H, d, $J_{10.CHO}$ 7.5, CHO), 6.65 (2 H, s, 7- and 8-H), 6.64 (1 H, d, $J_{10.CHO}$ 7.5, 10-H), 3.87 (3 H, s, CO_2Me), 1.79 (3 H, s, 5-Me) and 1.07 (6 H, s, gem-Me) (Found: *m*/*z* 262.157; $C_{16}H_{22}O_3$ requires *M*, 262.157). Compound **7**: λ_{max}(EtOH)/nm 335 (ε 10 000) and 267 (ε 9000); ν_{max}/cm^{-1} 1730 (CO_2Me), 1672 (CHO) and 1581 (C=C); δ_H(200 MHz) 9.78 (1 H, d, $J_{10.CHO}$ 7.5, CHO), 6.71 (1 H, br d, $J_{7,8}$ 16, 7-H), 6.23 (1 H, d, $J_{7,8}$ 16, 8-H), 6.08 (1 H, d, $J_{10.CHO}$ 7.5, 10-H), 3.95 (3 H, s, CO_2Me), 1.76 (3 H, d, *J* 1, 5-Me) and 1.05 (6 H, s, gem-Me) (Found: *m*/*z* 262.152. $C_{16}H_{22}O_3$ requires *M*, 262.157).

Isomerization of the Formyl Ester **15**.—A solution of iodine in hexane (0.01%, w/v; 150 cm^3) was added to a stirred solution of the formyl ester **15** (600 mg, 2.29 mmol) in hexane (150 cm^3) and the mixture was stirred at room temperature for 30 min. It was then washed with aqueous sodium thiosulfate and brine, dried and evaporated under reduced pressure to give an oil. This was purified by short CC (ether–hexane, 1:9) followed by low-pressure column chromatography (ether–hexane, 1:9) to provide **15** [220 mg, 37% (recovered)] and **7** (276 mg, 46%).

(E)-2,5-*Dimethylhexa*-2,4-*dienal* **17**.—A hexane solution of BuLi (10%, w/v; 1.02 cm^3, 2.4 mmol) was added to a stirred suspension of isopropylphosphonium bromide (756 mg, 2.0 mmol) in dry ether (6 cm^3) at 0 °C. The mixture was stirred at room temperature for 30 min after which a solution of the formyl acetal **16**[12] (170 mg, 1.2 mmol) in dry ether (6 cm^3) was added to it at 0 °C. Upon completion of the addition the mixture was stirred at room temperature for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with ether. The extracts were washed with brine, dried and evaporated to give an oil which was then dissolved in acetone (8 cm^3) containing 15% H_2SO_4 (0.3 cm^3) at 0 °C. The mixture was stirred at 0 °C for 15 min with UV monitoring. Upon appearance of an absorption maximum at 288 nm, the mixture was extracted with ether and the extracts were washed with brine, dried and evaporated to give an oil. This was purified by CC (ether–hexane, 1:9) to afford the diene aldehyde **17** (111 mg, 76% from **16**) as a pale yellow oil; λ_{max}/nm 288; ν_{max}/cm^{-1} 1668 (CHO) and 1625 (C=C); δ_H(60 MHz) 9.36 (1 H, s, CHO), 7.04 (1 H, d, $J_{3,4}$ 12, 3-H), 6.26 (1 H, br d, $J_{3,4}$ 12, 4-H), 1.94 (6 H, s, gem-Me) and 1.83 (3 H, s, 2-Me); *m*/*z* 125 (M^+ + H).

(E)-(2,5-*Dimethylhexa*-2,4-*dienyl*)*sulfonylbenzene* **8a**.—A solution of the aldehyde **17** (2.1 g, 17 mmol) in dry ether (37 cm^3) was added dropwise to a stirred suspension of LAH (0.65 g, 17 mmol) in dry ether (37 cm^3) at 0 °C and the mixture was stirred at room temperature for 5 min. The excess of LAH was destroyed by the addition of moist ether and water. The mixture was extracted with ether and the extracts were washed with brine, dried and evaporated to give an oil which was dissolved in propan-2-ol (4.5 cm^3) and glacial acetic acid (6.7 cm^3). To this solution, was added $PhSO_2Na{\cdot}2H_2O$ (4.5 g, 23 mmol) and the mixture was refluxed overnight. The reaction mixture was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ and brine. Evaporation of the dried extracts under reduced pressure provided a residue which was purified by CC (ether–hexane, 3:17) to give the sulfone **8a** (2.06 g, 48%) as colourless plates (m.p. 71–71.5 °C); λ_{max}/nm 252; ν_{max}/cm^{-1} 1554 (C=C) and 1301, 1142 and 1116 (SO_2); δ_H(200 MHz) 7.90–7.84 (2 H, m, ArH), 7.68–7.49 (3 H, m, ArH), 4.90 and 4.75 (each 1 H, each d, $J_{3,4}$ 11.5, 3-and 4-H), 3.79 (2 H, s, 1-H_2) and 1.83, 1.78 and 1.52 (each 3 H, each s, 2-, 5- and 5-Me) (Found: *m*/*z* 250.102. $C_{14}H_{18}O_2S$ requires *M*, 250.103) (Found: C, 66.9; H, 7.2; S, 13.0. $C_{14}H_{18}O_2S$ requires C, 67.2; H, 7.25; S, 12.8%).

(E,E/Z,E,E)-2,7-*Dimethyl*-9-(2,6,6-*trimethylcyclohex*-1-*enyl*)-*nona*-2,4,6,8-*tetraenal* (13-*Desmethyl*-14-*methylretinal*) **19**, **20**.—A solution of ethyl β-ionylideneacetate **18**[15] (2.80 g, 11 mmol) in dry ether (30 cm^3) was added dropwise to a stirred suspension of LAH (0.81 g, 21 mmol) in dry ether (50 cm^3) at 0 °C and the mixture was stirred at room temperature for 15 min. The excess of LAH was destroyed by the addition of moist ether and water and the mixture was extracted with ether. The extracts were washed with brine, dried and evaporated to give an oil which was dissolved in methanol (81 cm^3). To this solution, was added $Ph_3P{\cdot}HBr$ (3.68 g, 11 mmol) and the mixture was stirred at room temperature for 17 h. Evaporation of methanol gave a crude phosphonium salt which was washed with ether and dissolved in dry CH_2Cl_2 (40 cm^3). To this solution, were added the aldehyde **16** (1.39 g, 10 mmol) and a solution of NaOEt (0.88 g, 13 mmol) in ethanol (6 cm^3) at 0 °C. After the addition was complete, the mixture was stirred at 0 °C for 1 h, poured into chilled water and extracted with CH_2Cl_2. The organic extract was washed with brine, dried and evaporated to give an oil which was dissolved in acetone (50 cm^3). 20% H_2SO_4 (1.3 cm^3) was added to the solution at 0 °C and the mixture was stirred at 0 °C for 1 h. Upon appearance of an absorption maximum at 380 nm, the mixture was extracted with ether and the extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated to give an oil. This was purified by short CC (ether–hexane, 3:17) followed by low-pressure column chromatography (ether–hexane, 1:9–3:17) to provide the 11*Z* isomer **19** (0.30 g, 10% from **18**) and the all-*E* one **20** (0.39 g, 14% from **18**) as a yellow oil. Compound **19**: λ_{max}/nm 375 and 249; ν_{max}/cm^{-1} 1663 (CHO) and 1604 and 1578 (C=C); δ_H(200 MHz) 9.53 (1 H, s, CHO), 7.42 (1 H, br d, $J_{12,13}$ 11.5, 13-H), 6.84 (1 H, t, $J_{10,11,12}$ 11.5, 11-H), 6.64 (1 H, br d, $J_{10,11}$ 11.5, 10-H), 6.44 (1 H, t, $J_{11,12,13}$ 11.5, 12-H), 6.40 (1 H, br d, $J_{7,8}$ 16, 7-H), 6.24 (1 H, d, $J_{7,8}$ 16, 8-H), 2.03 (3 H, s, 9-Me), 1.89 (3 H, s, 14-Me), 1.75 (3 H, s, 5-Me) and 1.05 (6 H, s, gem-Me) (Found: *m*/*z*, 284.213. $C_{20}H_{28}O$ requires *M*, 284.214). Compound **20**: λ_{max}/nm 378; ν_{max}/cm^{-1} 1658 (CHO) and 1613 and 1572 (C=C); δ_H(200 MHz) 9.46 (1 H, s, CHO), 7.06 (1 H, dd, $J_{11,12}$ 15, $J_{10,11}$ 12, 11-H), 6.96 (1 H, br d, $J_{12,13}$ 11.5, 13-H), 6.66 (1 H, dd, $J_{11,12}$ 15, $J_{12,13}$ 11.5, 12-H), 6.37 (1 H, br d, $J_{7,8}$ 15.5, 7-H), 6.23 (1 H, br d, $J_{10,11}$ 12, 10-H), 6.17 (1 H, d, $J_{7,8}$ 15.5, 8-H), 2.03 (3 H, s, 9-Me), 1.88 (3 H, s, 14-Me), 1.73 (3 H, d, *J* 1, 5-Me) and 1.04 (6 H, s, gem-Me) (Found: *m*/*z* 284.212. $C_{20}H_{28}O$ requires *M*, 284.214).

(E,E,E,E)-[2,7-*Dimethyl*-9-(2,6,6-*trimethylcyclohex*-1-*enyl*)-*nona*-2,4,6,8-*tetraenyl*]*sulfonylbenzene* **8b**.—$NaBH_4$ (20 mg, 0.53 mmol) was added to a solution of the aldehyde **20** (150 mg, 0.40 mmol) in methanol (3 cm^3) at 0 °C. The mixture was stirred at 0 °C for 10 min, poured into chilled water and extracted with ether. The extracts were washed with brine, dried and evaporated to give an oil which was dissolved in pyridine (2 cm^3) and acetic anhydride (0.2 cm^3, 1.6 mmol). The mixture was stirred at room temperature for 16 h, poured into chilled water, and extracted with ether. The extracts were washed successively with aqueous 5% HCl, saturated aqueous $NaHCO_3$ and brine, dried and evaporated to give an oil. This was dissolved in propan-2-ol (2 cm^3) and water (1 cm^3) and to this solution was added $PhSO_2Na{\cdot}2H_2O$ (162 mg). The mixture was refluxed overnight, poured into chilled water and extracted with ether. The extract was washed with brine, dried and evaporated to give an oil which was purified by a combination of short CC (ether–hexane, 1:1) and preparative TLC (ether–hexane, 1:1) to afford the pale yellow sulfone **8b** (120 mg, 55% from **20**) and recovered acetate (18 mg); λ_{max}/nm 341 and 330sh; ν_{max}/cm^{-1} 1308, 1300 and 1144 (SO_2); δ_H(500 MHz) 7.84 (2 H, d-like, *J* 8, *o*-ArH), 7.63 (1 H, tt, *J* 8, 1.5, *p*-ArH), 7.53 (2 H, t-like, *J* 8, *m*-ArH), 6.42 (1 H, dd, $J_{11,12}$ 14.5, $J_{10,11}$ 11.5, 11-H), 6.31 (1 H, dd, $J_{11,12}$ 14.5, $J_{12,13}$ 11, 12-H), 6.18 (1 H, br d, $J_{7,8}$ 16, 7-H), 6.08 (1 H, d, $J_{7,8}$ 16, 8-H), 6.06 (1 H, br d, $J_{10,11}$ 11.5, 10-H), 5.76 (1 H, br d, $J_{12,13}$ 11, 13-H), 3.80 (2 H, s, 15-H_2), 1.89 (3 H, s, 9-Me), 1.85 (3 H, s, 14-Me), 1.69 (3 H, s, 5-Me) and 1.01 (6 H, s, gem-Me) (Found: *m*/*z*, 410.227. $C_{26}H_{34}O_2S$ requires *M*, 410.228).

Preparation of the Alkylidenebutenolide **9**; *General Procedure for the Conjugated Alkylidenebutenolide Synthesis*.—(Z/E,E,E)-5-(2,5-*Dimethylhexa*-2,4-*dienylidene*)-3-[2-(2,6,6-*trimethylcyclohex*-1-*enyl*)*vinyl*]*furan*-2(5H)-*one* **9a**. A solution of BuLi (1.59 mol dm^{-3} in hexane; 0.36 cm^3, 0.57 mmol) was added to a stirred solution of diisopropylamine (58 mg, 0.57 mmol) in dry THF (1.5 cm^3) and hexane (1.5 cm^3) at −78 °C and the mixture was stirred for a further 30 min. To this LDA solution was added a solution of the sulfone **8a** (143 mg, 0.57 mmol) in a mixture of dry THF and hexane (1:1; 4 cm^3). Upon completion of the addition, the mixture was stirred for 30 min, after which a solution of the formyl ester **7** (100 mg, 0.38 mmol) in dry THF (2 cm^3) and hexane (2 cm^3) was added dropwise at −78 °C. The reaction mixture was then stirred at −78 °C for 10 min before

being allowed to warm to room temperature over *ca.* 20 min with stirring. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ether. The extracts were washed with brine, dried and evaporated to give an oil which was purified by short CC (ether–hexane, 1:9) under reduced pressure to afford **9a** (72 mg, 56%). Isomers ($Z:E$ = *ca.* 1:1) were separated by preparative TLC (benzene–hexane, 2:3) to give each pure specimen. The 11*Z*-isomer of **9a**, m.p. 127–130 °C; λ_{max}/nm (see Table 2); ν_{max}/cm^{-1} 1741 (C=O) and 1612 (C=C); δ_H(200 MHz; see Table 3) 7.25 (1 H, br d, $J_{7,8}$ 16, 7-H), 6.55 (1 H, br d, $J_{14,15}$ 12, 14-H), 6.22 (1 H, br d, $J_{14,15}$ 12, 15-H), 6.20 (1 H, d, $J_{7,8}$ 16, 8-H), 2.20 (3 H, s, 13-Me), 1.91 and 1.86 (each 3 H, each s, 16-gem-Me), 1.76 (3 H, s, 5-Me) and 1.06 (6 H, s, 1-gem-Me) (Found: *m/z* 338.224. $C_{23}H_{30}O_2$ requires *M*, 338.224). The 11*E*-isomer of **9a**, m.p. 123–126 °C; λ_{max}/nm (see Table 2); ν_{max}/cm^{-1} 1744 (C=O) and 1608 (C=C); δ_H(200 MHz; see Table 3) 7.37 (1 H, br d, $J_{7,8}$ 16, 7-H), 6.55 (1 H, br d, $J_{14,15}$ 12, 14-H), 6.24 (1 H, d, $J_{7,8}$ 16, 8-H), 6.22 (1 H, br d, $J_{14,15}$ 12, 15-H), 2.07 (3 H, s, 13-Me), 1.92 and 1.87 (each 3 H, each s, 16-gem-Me), 1.77 (3 H, s, 5-Me) and 1.07 (6 H, s, 1-gem-Me) (Found: *m/z* 338.224. $C_{23}H_{30}O_2$ requires *M*, 338.224).

(Z/E,E,E,E,E,E)-5-[2,7-*Dimethyl*-9-(2,6,6-*trimethylcyclohex*-1-*enyl*)*nona*-2,4,6,8-*tetraenylidene*]-3-[2-(2,6,6-*trimethylcyclohex*-1-*enyl*)*vinyl*]*furan*-2(5H)-*one* **9b**. 11*Z*-Isomer: λ_{max}/nm (see Table 2); ν_{max}/cm^{-1} 1744 (C=O), 1619, 1600 (split) and 1520 (C=C); δ_H(500 MHz; see Table 3) 7.27 (1 H, d, $J_{7,8}$ 16.5, 7-H), 6.79 (1 H, dd, $J_{11',12'}$ 13.5, $J_{10',11'}$ 12, 11'-H), 6.63 (1 H, dd, $J_{11',12'}$ 13.5, $J_{12',13'}$ 12, 12'-H), 6.52 (1 H, d, $J_{12',13'}$ 12, 13'-H), 6.27 (1 H, d, $J_{7',8'}$ 16, 7'-H), 6.22 (1 H, d, $J_{7,8}$ 16.5, 8-H), 6.22 (1 H, d, $J_{10',11'}$ 12, 10'-H), 6.17 (1 H, d, $J_{7',8'}$ 16, 8'-H), 2.24 (3 H, s, 14'-Me), 1.99 (3 H, s, 9'-Me), 1.78 and 1.74 (each 3 H, each s, 5- and 5'-Me) and 1.08 and 1.05 (each 6 H, each s, gem-Me) (Found: *m/z* 498.349. $C_{35}H_{46}O_2$ requires *M*, 498.350). 11*E*-Isomer: λ_{max}/nm (see Table 2); ν_{max}/cm^{-1} 1746 (C=O) and 1602 and 1520 (C=C); δ_H(500 MHz; see Table 3) 7.34 (1 H, d, $J_{7,8}$ 16.5, 7-H), 6.77 (1 H, dd, $J_{11',12'}$ 13.5, $J_{10',11'}$ 11.5, 11'-H), 6.59 (1 H, dd, $J_{11',12'}$ 13.5, $J_{12',13'}$ 11.5, 12'-H), 6.46 (1 H, d, $J_{12',13'}$ 11.5, 13'-H), 6.24 (1 H, d, $J_{7',8'}$ 16.5, 7'-H), 6.22 (1 H, d, $J_{7,8}$ 16.5, 8-H), 6.17 (1 H, d, $J_{10',11'}$ 11.5, 10'-H), 6.12 (1 H, d, $J_{7',8'}$ 16.5, 8'-H), 2.09 (3 H, s, 14'-Me), 1.96 (3 H, s, 9'-Me), 1.75 and 1.70 (each 3 H, each s, 5- and 5'-Me) and 1.05 and 1.01 (each 6 H, each s, gem-Me) (Found: *m/z* 498.350. $C_{35}H_{46}O_2$ requires *M*, 498.350).

(Z/E,E,E,E,E,E)-5-[3,7-*Dimethyl*-9-(2,6,6-*trimethylcyclohex*-1-*enyl*)*nona*-2,4,6,8-*tetraenylidene*]-3-[2-(2,6,6-*trimethylcyclohex*-1-*enyl*)*vinyl*]*furan*-2(5H)-*one* **9c**. 11*Z*-Isomer: λ_{max}/nm (see Table 2); ν_{max}/cm^{-1} 1743 (C=O) and 1618 and 1520 (C=C); δ_H(200 MHz; see Table 3) 7.32 (1 H br d, $J_{7,8}$ 16, 7-H), 6.82 (1 H, dd, $J_{11',12'}$ 15, $J_{10',11'}$ 11, 11'-H), 6.45 (1 H, d, $J_{11',12'}$ 15, 12'-H), 6.28 (1 H, br d, $J_{7',8'}$ 16, 7'-H), 6.24 (1 H, d, $J_{7,8}$ 16, 8-H), 6.20 (1 H, d, $J_{10',11'}$ 11, 10'-H), 6.17 (1 H, d, $J_{7',8'}$ 16, 8'-H), 2.03 and 2.00 (each 3 H, each s, 9'- and 13'-Me), 1.77 and 1.73 (each 3 H, each s, 5- and 5'-Me) and 1.07 and 1.04 (each 6 H, each s, gem-Me) (Found: *m/z* 498.350. $C_{35}H_{46}O_2$ requires *M*, 498.350). 11*E*-Isomer: λ_{max}/nm (see Table 2); ν_{max}/cm^{-1} 1747 (C=O) and 1606 and 1526 (C=C); δ_H(200 MHz; see Table 3) 7.36 (1 H, br d, $J_{7,8}$ 16.5, 7-H), 6.79 (1 H, dd, $J_{11',12'}$ 15, $J_{10',11'}$ 11.5, 11'-H), 6.40 (1 H, d, $J_{11',12'}$ 15, 12'-H), 6.25 (2 H, d, $J_{7',8'}$ 16.5, 7'- and 8-H), 6.16 (1 H, d, $J_{10',11'}$ 11.5, 10'-H), 6.14 (1 H, d, $J_{7',8'}$ 16.5, 8'-H), 2.02 and 2.00 (each 3 H, each s, 9'- and 13'-Me), 1.78 and 1.73 (each 3 H, each s, 5- and 5'-Me) and 1.08 and 1.04 (each 6 H, each s, gem-Me) (Found: *m/z* 498.348. $C_{35}H_{46}O_2$ requires *M*, 498.349).

(Z/E,E,E,E)-5-[3-*Methyl*-5-(2,6,6-*trimethylcyclohex*-1-*enyl*)-*penta*-2,4-*dienylidene*]-3-[2-(2,6,6-*trimethylcyclohex*-1-*enyl*)-*vinyl*]*furan*-2(5H)-*one* **9d**. 11*Z*-Isomer: λ_{max}/nm (see Table 2); ν_{max}/cm^{-1} 1742 (C=O) and 1577 (C=C); δ_H(200 MHz; see Table 3) 7.31 (1 H, br d, $J_{7,8}$ 16.5, 7-H), 6.38 (1 H, br d, $J_{7',8'}$ 16.5, 7'-H), 6.25 (1 H, d, $J_{7',8'}$ 16.5, 8'-H), 6.22 (1 H, d, $J_{7,8}$ 16.5, 8-H), 2.01 (3 H, d, *J* 1, 9'-Me), 1.77 and 1.74 (each 3 H, each s, 5- and 5'-Me), 1.07 and 1.05 (each 6 H, each s, gem-Me) (Found: *m/z* 432.302. $C_{30}H_{40}O_2$ requires *M*, 432.303). 11*E*-Isomer: λ_{max}/nm (see Table 2); ν_{max}/cm^{-1} 1745 (C=O) and 1602 and 1580 (C=C); δ_H(200 MHz; see Table 3) 7.35 (1 H, br d, $J_{7,8}$ 16.5, 7-H), 6.35 (1 H, br d, $J_{7',8'}$ 16.5, 7'-H), 6.24 (1 H, d, $J_{7,8}$ 16.5, 8-H), 6.20 (1 H, d, $J_{7',8'}$ 16.5, 8'-H), 2.00 (3 H, d, *J* 1, 9'-Me), 1.77 and 1.74 (each 3 H, each s, 5- and 5'-Me) and 1.07 and 1.05 (each 6 H, each s, gem-Me) (Found: *m/z* 432.303. $C_{30}H_{40}O_2$ requires *M*, 432.303).

(Z/E,E,E)-5-(3,7-*Dimethylocta*-2,6-*dienylidene*)-3-[2-(2,6,6-*trimethylcyclohex*-1-*enyl*)*vinyl*]*furan*-2(5H)-*one* **9e**. 11*Z*-Isomer: λ_{max}/nm (see Table 2); ν_{max}/cm^{-1} 1744 (C=O) and 1630 (C=C); δ_H(200 MHz; see Table 3) 7.29 (1 H, br d, $J_{7,8}$ 16.5, 7-H), 6.20 (1 H, d, $J_{7,8}$ 16.5, 8-H), 5.09 (1 H, m, 17-H), 1.87 (3 H, d, *J* 1, 14-Me), 1.76 (3 H, s, 5-Me), 1.69 and 1.62 (each 3 H, each s, 18-gem-Me) and 1.07 (6 H, s, 1-gem-Me) (Found: *m/z* 366.253. $C_{25}H_{34}O_2$ requires *M*, 366.256). 11*E*-Isomer: λ_{max}/nm (see Table 2); ν_{max}/cm^{-1} 1749 (C=O) and 1627 (C=C); δ_H(200 MHz; see Table 3) 7.35 (1 H, br d, $J_{7,8}$ 16.5, 7-H), 6.23 (1 H, d, $J_{7,8}$ 16.5, 8-H), 5.09 (1 H, m, 17-H), 1.85 (3 H, d, *J* 1, 14-Me), 1.76 (3 H, s, 5-Me), 1.69 and 1.62 (each 3 H, each s, 18-gem-Me) and 1.07 (6 H, s, 1-gem-Me) (Found: *m/z* 366.254. $C_{25}H_{34}O_2$ requires *M*, 366.256).

(Z/E,E,E)-5-[1-*Methyl*-3-(2,6,6-*trimethylcyclohex*-1-*enyl*)-*allylidene*]-3-[2-(2,6,6-*trimethylcyclohex*-1-*enyl*)*vinyl*]*furan*-2(5H)-*one* **9f**. A solution of BuLi (10%, w/v, in hexane; 0.51 cm^3, 1.21 mmol) was added to a stirred solution of the sulfone **8f** (386 mg, 1.21 mmol) in dry THF (2 cm^3) at −78 °C. The mixture was stirred at −78 °C for 30 min after which a solution of **7** (212 mg, 0.808 mmol) in dry THF (4 cm^3) was added at −78 °C. The mixture was stirred at −78 °C for 20 min and then the reaction was quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with ether and the extracts were washed with brine, dried and evaporated under reduced pressure to give an oil which was purified by CC (ether–hexane, 1:9) and preparative TLC (benzene–hexane, 2:3) to provide the 11*Z*-isomer of **9f** (47 mg, 14%) and the 11*E*-isomer of **9f** (54 mg, 17%) (total yield, 31%), as yellow oil. 11*Z*-Isomer: λ_{max}/nm (see Table 2); ν_{max}/cm^{-1} 1746 (C=O) and 1613 and 1598 (C=C); δ_H(200 MHz; see Table 3) 7.32 (1 H, br d, $J_{7,8}$ 17, 7-H), 6.38 (1 H, br d, $J_{7',8'}$ 16, 7'-H), 6.23 (1 H, d, $J_{7,8}$ 17, 8-H), 2.06 (6 H, s, 5- and 5'-Me), 1.76 (3 H, s, 9'-Me) and 1.07 and 1.06 (each 6 H, each s, gem-Me); irradiation at δ 1.76 (9'-Me) induced NOEs at δ 7.35 (24%, 10-H) and 6.38 (22%, 7'-H) (Found: *m/z* 406.286. $C_{28}H_{38}O_2$ requires *M*, 406.287). 11*E*-Isomer: λ_{max}/nm (see Table 2); ν_{max}/cm^{-1} 1749 (C=O) and 1616 (C=C); δ_H(200 MHz; see Table 3) 7.32 (1 H, br d, $J_{7,8}$ 17, 7-H), 6.47 (2 H, s, 7'- and 8'-H), 6.21 (1 H, d, $J_{7,8}$ 17, 8-H), 2.16 (3 H, s, 9'-Me), 1.76 and 1.75 (each 3 H, each s, 5- and 5'-Me) and 1.07 and 1.05 (each 6 H, each s, gem-Me); irradiation at δ 2.16 (9'-Me) induced an NOE at δ 6.47 (21%, 7'-H) (Found: *m/z* 406.288. $C_{28}H_{38}O_2$ requires *M*, 406.287).

Photoisomerization of **9a**.—The solution of the *Z*- or *E*-isomer (1 mg) of **9a** in an appropriate solvent (*ca.* 1 cm^3) was stirred in a flask whilst being irradiated with a desk fluorescent lamp (30 W). Isomerization was followed by an analytical HPLC procedure (mobile phase, benzene–hexane, 1:1, detection, 350 nm). The ratios ($Z:E$) of isomers after 60 min of irradiation are as follows: acetonitrile (64:36), methanol (68:32), THF (69 ~ 71:31 ~ 29), benzene (82 ~ 84:18 ~ 16) and hexane (85 ~ 90:15 ~ 10).

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