Synthesis of Marine Toxins. A Biomimetic Approach to the Novel Spirobenzoquinonefuran Stypoldione

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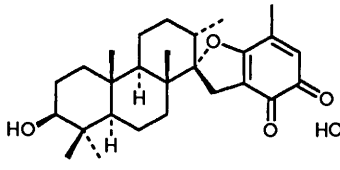
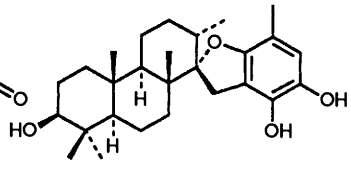
A synthesis of the spirobenzoquinonefuran unit, *i.e.* (**10**), present in stypoldione, a novel marine toxin found in the brown alga *Stypopodium zonale* which shows pronounced narcotic and hyperactive effects upon reef-dwelling fish, is described. The synthesis uses a strategy, *viz* (**17**) ⟶ (**18**) ⟶ (**19**) ⟶ (**11**) ⟶ (**10**), which has close similarities to the probable biogenesis of this portion of the natural product (Scheme 1). The advanced precursors (**30**) and (**36**) for projected syntheses of deoxystypoldione (**33**) and stypodiol (**3**) respectively were also prepared, but neither substrate underwent polyene cyclization to the required pentacyclic molecules.

Brown algae of the family Dictyotaceae are a rich source of structurally novel secondary metabolites, many of which display diverse and useful biological properties.[1] The *o*-quinone stypoldione (**1**), which incorporates an unusual spirobenzofuranyl unit, together with its quinol relative stypotriol (**2**) are two members of a rare class of marine toxins produced by the brown alga *Stypopodium zonale*.[2] The two metabolites co-occur with the benzofuranyl phenol (**3**), the known benzopyran taondiol (**4**),[3] and also the geranyl–geranyl-substituted quinone (**5**) and quinol (**6**).

Stypoldione (**1**) and stypotriol (**2**) show pronounced narcotic and hyperactive effects upon reef-dwelling fish.[4] Stypoldione has also been found to show antitumoural properties and to inhibit cell division in the fertilized sea urchin egg assay.[5] It



(1)



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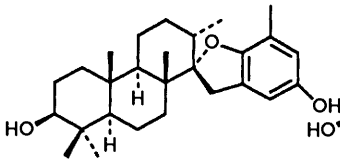

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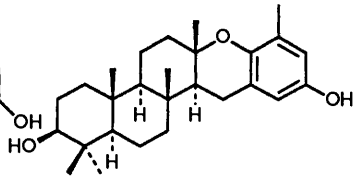

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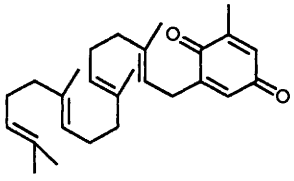

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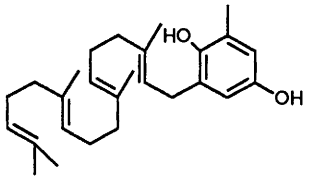
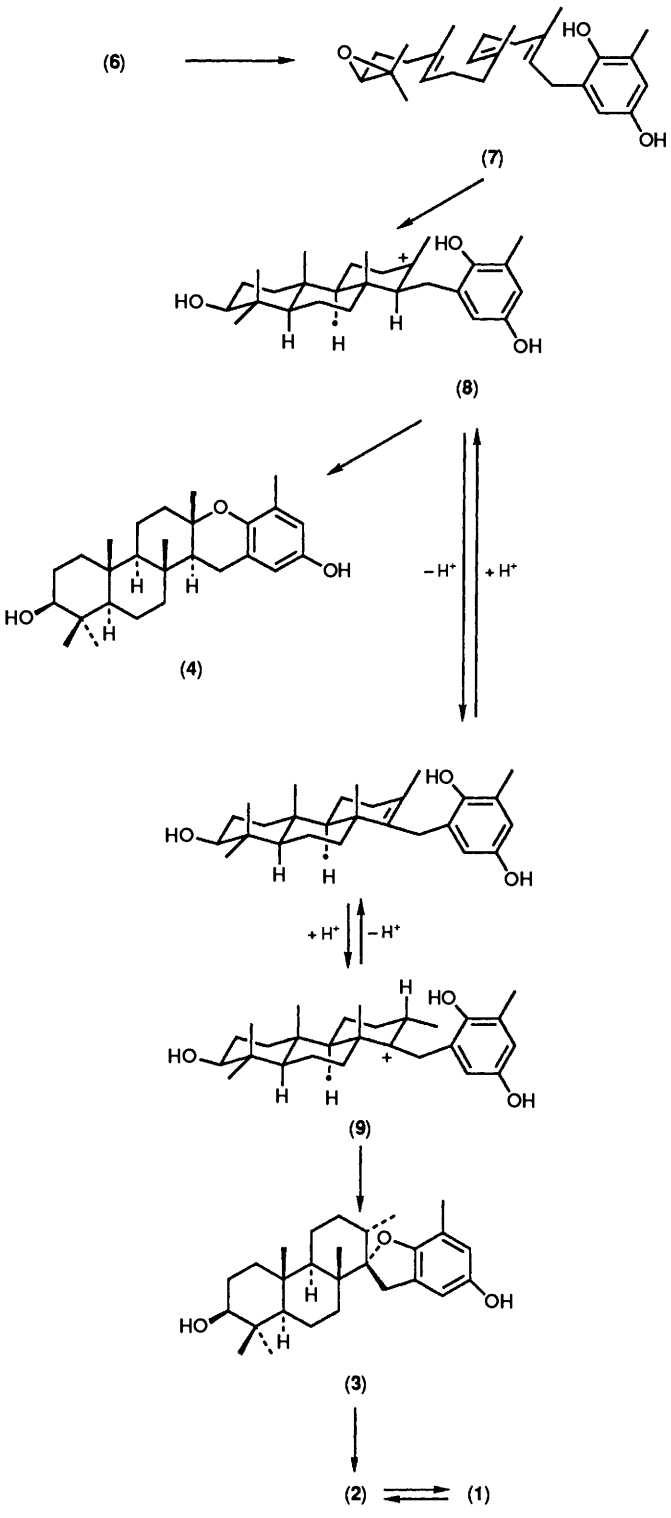


(6)

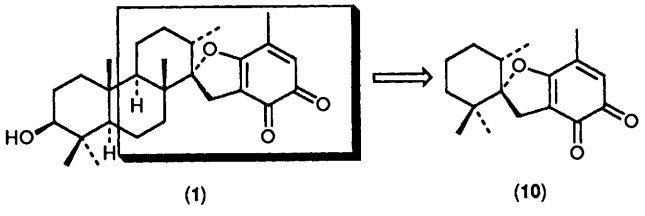
seems likely that the metabolites (**1**)–(**4**) have a common biosynthetic origin with the carbocation (**8**) derived from polyene cyclization of the quinol (**7**) as a central intermediate. Thus, cyclization from cation (**8**) would access the benzopyran taondiol (**4**) whilst rearrangement of ion (**8**) to the carbonium ion (**9**) would allow cyclization to the novel spirobenzofuranyl metabolite stypodiol (**3**), sequential oxidation of which then provides stypotriol (**2**) and stypoldione (**1**) (Scheme 1).[6,7] The novel structures shown by the new metabolites from *S. zonale*, together with their unusual mode of biological activity, combine to make them desirable targets for total synthesis and for structure–activity studies.[8] In this paper we describe a synthesis of the spirobenzoquinonefuran unit, *i.e.* (**10**), present in stypoldione (**1**) using a strategy which has close similarities to the probable biosynthesis of this portion of the natural product.[9] We also summarize the outcome of our efforts towards a biomimetic total synthesis of stypoldione.

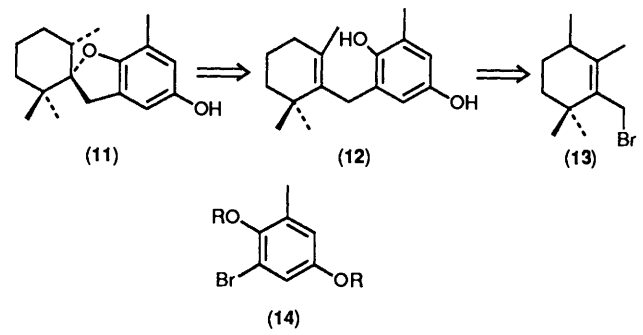
Our strategy for the synthesis of the spirobenzofuranyl unit, *viz* (**11**), in stypoldione (**1**) is summarized in Scheme 2, and was based on regio- and stereo-selective electrophilic cyclization of the quinol-alkene (**12**) derived from cyclogeranyl bromide (**13**) and the aryl bromide (**14**). Thus, conversion of 2-bromo-6-methylhydroquinone (**15**)[10] into the corresponding bis(methoxymethyl) (MOM) derivative (**14**; R = MOM) followed by treatment with n-butyl-lithium at − 40 °C first led to the lithio derivative (**16**). After conversion of compound (**16**) into the corresponding organocuprate reagent, by use of copper(I) iodide, reaction with β-cyclogeranyl bromide (**13**)[11] then led to the coupled product (**17**) in 64% yield.

Epoxidation of the cyclohexene (**17**) with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane at 25 °C next produced the epoxide (**18**), which on treatment with excess of aluminium hydride[12] resulted in regioselective reduction with simultaneous cleavage of the MOM protecting groups, leading to the crystalline alcohol (**19**). Attempts to reduce the same epoxide (**18**) with lithium aluminium hydride or lithium triethylborohydride were unsuccessful and only starting material was recovered. The regiospecific nature of the reduction of compound (**18**) in the presence of aluminium hydride followed from ^{1}H NMR data [δ 0.98 (d, *J* 7, CH*Me*)], and can be rationalized on the basis of nucleophilic hydride attack from the least hindered side of the epoxide. The simultaneous cleavage of the MOM protecting groups in compound (**18**) during reduction is un-

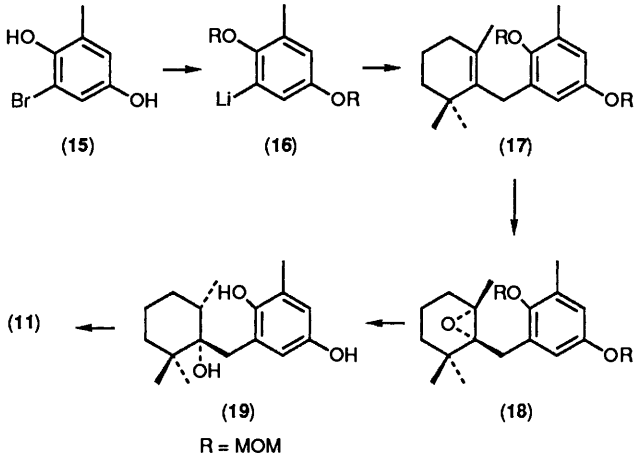


Scheme 1.





Scheme 2.

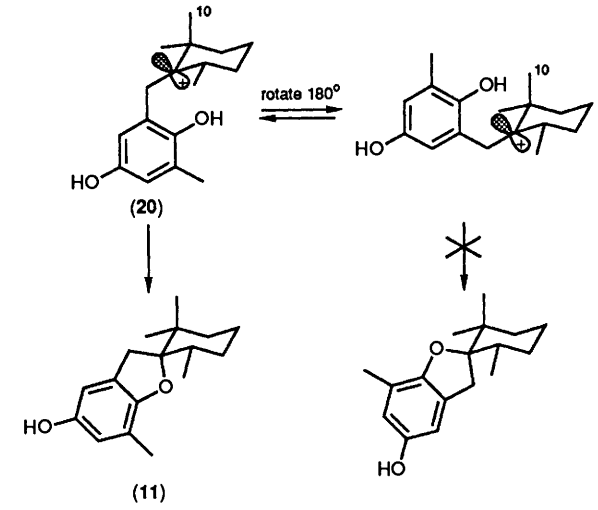


usual, and occurs only after the epoxide ring opening and only over the long reaction period (2–3 weeks).

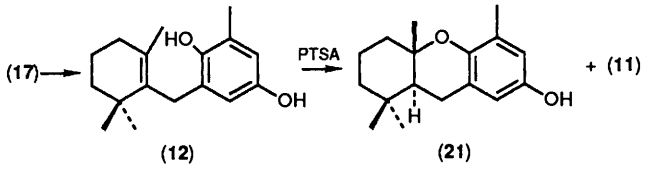
Exposure of the quinol tertiary alcohol (**19**) to catalytic toluene-*p*-sulphonic acid (PTSA) resulted in smooth cyclization to produce solely the spirodihydrofuran (**11**) in an excellent 90% yield. The relative stereochemistry of the adjacent chiral centres in the spiro dihydrofuran (**11**) was established as shown in the formula through an X-ray crystal structure determination on the corresponding 4-nitrobenzoate derivative. Interactive graphical work[13] gave credence to the suppostion that the axial–equatorial orientation of the furyl oxygen and secondary methyl groups in the spirodihydrofuran product (**11**) results from preferential nucleophilic attack by phenolic oxygen onto the intermediate carbonium (**20**) along a reaction co-ordinate which avoids the axial-Me at C-10 (see Scheme 3).

Not unexpectedly, when the MOM protecting groups in the cyclohexene (**17**) were removed and the resulting quinol (**12**) was treated with catalytic PTSA, the major product isolated was the benzopyran (**21**)[14] contaminated by approximately 7% of the aforementioned spirobenzofuran (**11**). The benzopyran (**21**) was easily characterized following interpretation of its spectroscopic data, and comparison of these data with those recorded for natural taondiol (**4**) and its isomers.

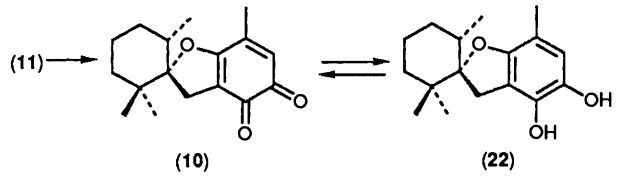
The synthesis of the spirobenzoquinonefuran unit (**10**) in stypoldione (**1**) was finally completed by treatment of the spirobenzofuran (**11**) with Fremy's salt (potassium nitrosodisulphonate)[15] which gave the *o*-quinone (**10**) as a deep red solid, m.p. 111–113 °C. Reduction of the *o*-benzoquinone (**10**) with sodium dithionite in aqueous ethanol then led to the corresponding catechol (**22**), a cream solid, which was immediately and quantitatively oxidized back to the quinone (**10**) on exposure to air.



Scheme 3.



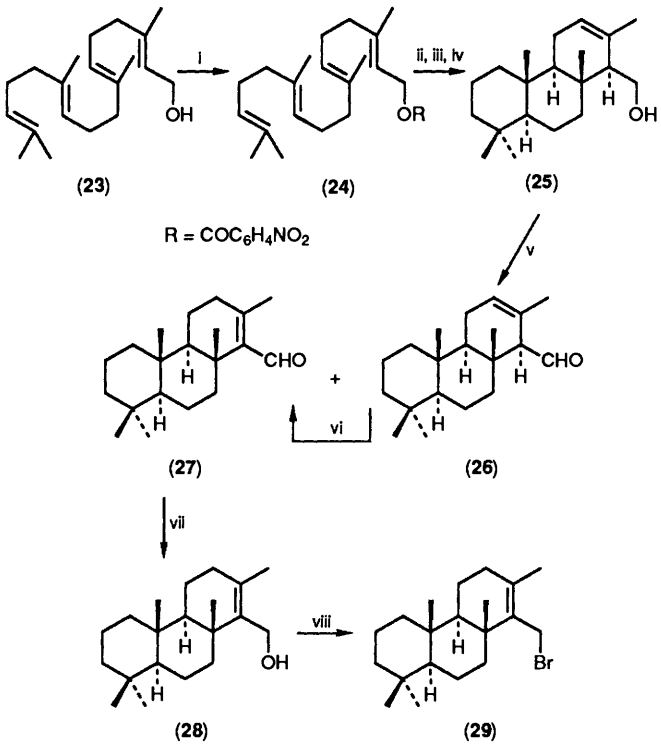
Both the spirobenzoquinonefuran (**10**) and the catechol (**22**) showed NMR spectroscopic data which were superposable on



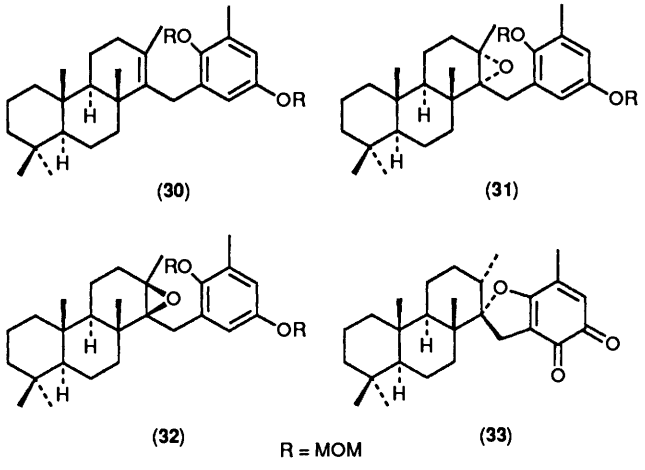
all the signals associated with the CDE ring portions of the corresponding natural products stypoldione (**1**) and stypotriol (**2**) respectively. In addition, both stypoldione and the analogue (**10**) showed a similar growth inhibition of mouse P388 leukaemia cells *in vitro*, with 96% inhibition at 1×10^{-4}M and 17% inhibition at 1×10^{-6}M.*

In an extension to this work and with a view to the elaboration of deoxystypoldione (**33**) we also synthesized the advanced precursor (**30**) from a coupling reaction between the aryl-lithium (**16**) and the tricyclic allylic bromide (**29**). The allylic bromide (**29**) was easily produced, starting from geranylgeraniol (**23**), as outlined in Scheme 4.[16] Epoxidation of alkene (**30**) with MCPBA, unlike that of the analogue (**17**), was not selective however, and led to an inseparable 2:1 mixture of α- (**31**) and β-epoxide (**32**); this approach to spiro compound (**33**) was therefore abandoned.

As a corollary, we also synthesized the quinol (**6**),[2] the quinone (**5**),[2] and the epoxy diterpene substituted quinol derivative (**36**) as a possible direct precursor to stypodiol (**3**) by polyene cyclization (Scheme 5).† Using a range of conditions, particularly recommended procedures based on picric acid, tin(IV) chloride, boron trifluoride, trifluoroacetic acid, and titanium tetrachloride,[16] we were unable to effect cyclization of



Scheme 4. *Reagents and conditions:* (i) p-$O_2NC_6H_4COCl$, pyridine, room temp., 18 h, 75%; (ii) $Hg(OSO_2CF_3)_2 \cdot Me_2NPh$, $MeNO_2$, −20 °C, 2 h; (iii) aq., NaCl, −20 °C to room temp., 16 h; (iv) $NaBH_4$, NaOH, aq. EtOH, room temp., 30 min, 6–10%; (v) PCC, NaOAc, CH_2Cl_2, room temp., 2.5 h, 75%; (vi) KOH, hexanes–MeOH, 0 °C, 4 h, 56%; (vii) $NaBH_4$, hexanes–MeOH, 0 °C, 50 min, 86%; (viii) $(CCl_2Br)_2$, PPh_3, Et_2O, 0 °C, 1.5 h, 95%.



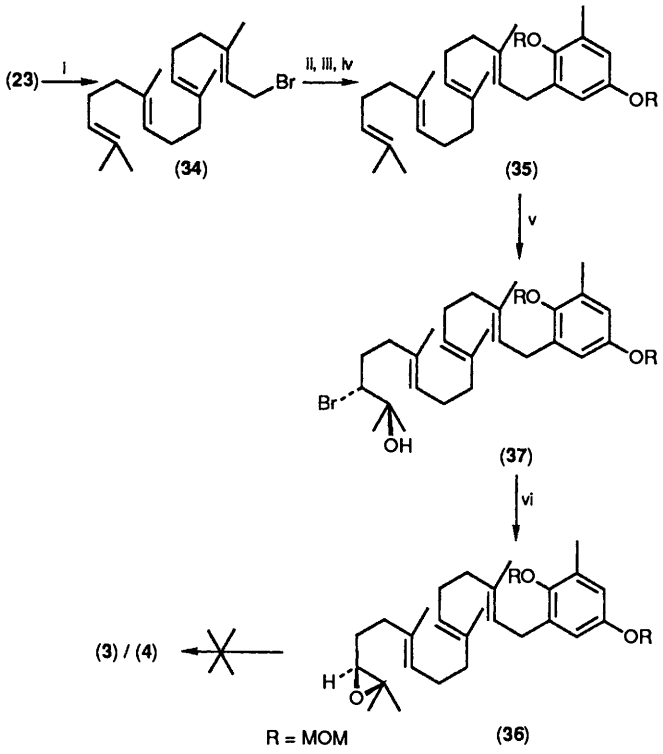
compound (**36**) to either stypodiol (**3**) or to taondiol (**4**); instead complex, inseparable mixtures resulted.

Experimental

General Details.—M.p.s were determined on a Köfler hot-stage apparatus and are uncorrected. UV spectra were recorded on a Philips PU8700 spectrophotometer as solutions in the solvent stated. IR spectra were obtained using a Philips PU9706 or Pye Unicam SP3-100 spectrometer, as liquid films on sodium chloride windows or as solutions in chloroform. ^{1}H NMR spectra were recorded on either a Perkin-Elmer R32 (90 MHz), a Bruker WM250 (250 MHz), or a Bruker AM400 (400 MHz)

* We thank Dr. E. B. Rapson (Wellcome Research Laboratories, Beckenham) for this information.

† For biogenetic-type syntheses pertinent to this work see the reported syntheses of taondiol (**4**) (ref. 10) and its methyl ether (ref. 7).



Scheme 5. *Reagents and conditions:* (i) PBr_3, THF, −10 °C, 15 min, 93%; (ii) (**14**), BuLi, THF, −40 °C, 30 min; (iii) CuI, 30 min; (iv) (**34**), hexanes, 40 °C to room temp., 2 h, 58%; (v) NBS, aq. DME, room temp., 4 h, 49%; (vi) K_2CO_3, MeOH, room temp., 16 h, 97%.

spectrometer; the spectra were recorded for dilute solutions in deuteriochloroform unless stated otherwise. The chemical shifts are recorded relative to internal tetramethylsilane, and the multiplicity of a signal is a singlet unless otherwise stated. ^{13}C NMR spectra were recorded on either a Bruker WM250 at 62.9 MHz or a Bruker AM400 at 100.6 MHz. The spectra were recorded for dilute solutions in deuteriochloroform unless stated otherwise. The chemical shifts are reported relative to internal tetramethylsilane in a broad-band-decoupled mode, and the multiplicities were obtained using a DEPT sequence.

Mass spectra were recorded on an AEI MS-902 or VG MM-7070F instrument. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser.

Column chromatography was carried out using Merck silica gel 60; the solvents light petroleum (b.p. range 40–60 °C) and ethyl acetate were redistilled before use. All reactions were monitored by TLC on Merck silica gel 60 F_{254} precoated glass plates which were visualized with UV light, then acidic vanillin solution, basic potassium permanganate solution, or with acidic 2,4-dinitrophenylhydrazine solution.

Routinely, dry organic solvents were stored under nitrogen. Benzene, and hexanes, were dried over sodium wire. Other organic solvents were distilled from the following drying agents: diethyl ether (lithium aluminium hydride); tetrahydrofuran (THF) (sodium benzophenone ketyl); methanol (magnesium methoxide); dichloromethane (phosphorus pentaoxide); pyridine (calcium hydride); nitromethane (calcium hydride); dimethylformamide (DMF) (calcium hydride at reduced pressure). Organic extracts were dried over magnesium sulphate and concentrated under aspirator pressure on a Büchi rotary evaporator.

2-*Bromo*-6-*methylbenzene*-1,4-*diol* (**15**).—The hydroquinone was prepared by the procedure of Kumanireng *et al.*[10] and showed m.p. 117–118 °C (from EtOH) (lit.,[17] 112 °C); λ_{max}(EtOH) 294 nm (3 060); ν_{max}($CHCl_3$) 3 590, 3 530, 3 320, and 1 590 cm^{-1}; δ_H 2.25 (Ar*Me*), 5.62 (br, OH), 6.69 (d, *J* 4 Hz, ArH), 6.91 (d, *J* 4 Hz, ArH), and 7.35 (br, OH); *m*/*z* 204 (99%, M^+, $C_7H_7{}^{81}BrO_2$), 202 (100, M^+, $C_7H_7{}^{79}BrO_2$), 123 (30, $C_7H_7O_2$, *M* − Br), 94 (22), 66 (13), 65 (12), and 53 (14).

1-*Bromo*-2,5-*bis*(*methoxymethoxy*)-3-*methylbenzene* (**14**; R = MOM).—A solution of butyl-lithium (12.9 ml) in hexanes (1.6M; 20.7 mmol) was added dropwise during 15 min to a stirred solution of 2-bromo-6-methylbenzene-1,4-diol (**15**) (2.0 g, 9.85 mmol) in dry THF (20 ml) under nitrogen at 0 °C. After 15 min, a precooled solution of methoxymethyl chloride (1.74 g, 21.6 mmol) in dry THF (10 ml) was added dropwise during 10 min, and the solution was then warmed to room temperature and stirred for 2 h. Evaporation of the solvents left an oil, which was dissolved in water (30 ml) and then extracted with diethyl ether (3 × 30 ml). The combined extracts were washed successively with dil. sodium hydroxide (30 ml; 2%), water (30 ml), and brine (30 ml), and then dried and evaporated. The oily residue was purified by chromatography on silica gel with 20% diethyl ether in light petroleum as eluant, followed by distillation to give the bis(methoxymethyl) ether (2.31 g, 81%) as a room temperature melting solid, b.p. 110–112 °C at 0.2 mmHg; λ_{max}(EtOH) 282 nm (1 890); ν_{max}(film) 2 940, 2 830, and 1 600 cm^{-1}; δ_H 2.36 (Ar*Me*), 3.51 (OMe), 3.62 (OMe), 5.1 (OCH_2O), 5.16 (OCH_2O), 6.91 (d, *J* 4 Hz, ArH), and 7.2 (d, *J* 4 Hz, ArH); *m*/*z* 292 (14%, M^+, $C_{11}H_{15}{}^{81}BrO_4$), 290 (11, M^+, $C_{11}H_{15}{}^{79}BrO_4$), 262 (6, $C_{10}H_{13}{}^{81}BrO_5$, *M* − CH_2O), 260 (7, $C_{10}H_{13}{}^{79}BrO_3$, *M* − CH_2O), 232 (3, $C_9H_{11}{}^{81}BrO_2$, *M* − $C_2H_4O_2$), 230 (3, $C_9H_{11}{}^{79}BrO_2$, *M* − $C_2H_4O_2$), 211 (7, $C_{11}H_{15}O_4$, *M* − Br), 77 (6, C_6H_5), and 45 (100, C_2H_5O).

2-(*Bromomethyl*)-1,3,3-*trimethylcyclohexene* (**13**).—The allylic bromide was prepared by the procedure of Andrews *et al.*[11] and showed b.p. 160 °C (oven temp.) at 10 mmHg (lit.,[18] b.p. 52 °C at 0.1 mmHg); ν_{max}(film) 2 920, 2 860, 1 630, 1 475, 1 370, 1 210, 1 195, 780, and 750 cm^{-1}; δ_H 1.13 (CMe_2), 1.9–1.4 (m, 4 H), 1.77 (=CMe), 2.06 (t, *J* 7 Hz, CH_2C=), and 4.14 (CH_2Br); *m*/*z* 136 (39%, $C_{10}H_{16}$, *M* − HBr), 121 (100), 107 (16), 105 (21), 93 (39), 91 (18), and 79 (25).

2,5-*Bis*(*methoxymethoxy*)-1-*methyl*-3-(2,6,6,-*trimethylcyclohex*-1-*enylmethyl*)*benzene* (**17**).—A solution of butyl-lithium (8.9 ml) in hexanes (1.5M; 13.7 mmol) was added dropwise during 10 min to a stirred solution of the bis(methoxymethyl) ether (**14**; R = MOM) (3.20 g, 11.0 mmol) in dry THF (75 ml) under nitrogen maintained at −40 °C. The mixture was stirred for 30 min and then copper(I) iodide powder (1.05 g, 5.50 mmol) was added in one portion. After a further 30 min a solution of the allylic bromide (**13**) (2.38 g, 11.0 mmol) in dry hexanes (15 ml) was added dropwise during 15 min and the mixture was stirred at −40 °C for 30 min. The solution was allowed to warm to room temperature during 2 h, and was then evaporated to dryness under reduced pressure. The brown oily residue was extracted with diethyl ether (3 × 50 ml) and the combined extracts were then washed successively with dilute ammonia (50 ml; 2M), water (2 × 50 ml), and brine (50 ml). Evaporation of the dried extracts left an oil, which was purified by chromatography on silica gel with 5% diethyl ether in light petroleum as eluant to give the *couple product* (2.45 g, 64%) as an oil, λ_{max}(hexane) 278 nm (1 690); ν_{max}(film) 2 930, 1 595, 1 475, 1 160, 1 040, and 985 cm^{-1}; δ_H 0.92 (CMe_2), 1.55–1.4 (m, 4 H), 1.51 (=CMe), 1.75–1.55 (m, 2 H), 2.04 (d, *J* 6 Hz, C*H*HAr), 2.06, (d, *J* 6 Hz, CH*H*Ar), 2.28 (Ar*Me*), 3.44 (OMe), 3.63 (OMe), 4.96 (OCH_2O), 6.62 (d, *J* 3 Hz, ArH), and 6.7 (d, *J* 3 Hz, ArH); δ_C 17.1 (q), 19.6 (t), 20.5 (q), 28.3 (t), 28.5 (q), 32.7 (t), 35.0 (s), 39.8 (t), 55.7 (q), 57.2 (q), 95.0 (t), 99.3 (t), 115.0 (d), 115.7 (d), 130.4 (s),

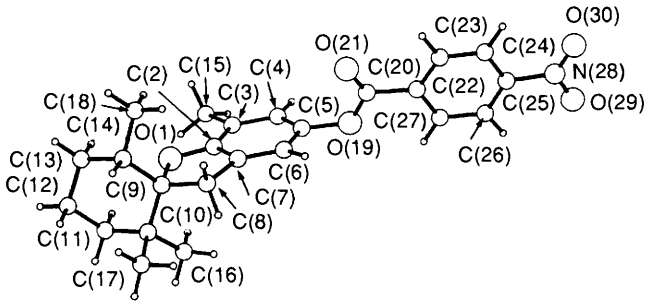


Figure. Crystal structure of the *p*-nitrobenzoate derivative of compound (**11**).

131.5 (s), 134.3 (s), 135.6 (s), 149.2 (s), and 153.5 (s) (Found: M^+, 348.2280; C, 72.3; H, 9.3%. $C_{21}H_{32}O_4$ requires *M*, 348.2300; C, 72.4; H, 9.3%).

1-{[(1R*,2S*)-1,2-*Epoxy*-2,6,6-*trimethylcyclohexyl*]*methyl*}-2,5-*bis*(*methoxymethoxy*)-3-*methylbenzene* (**18**).—MCPBA (1.48 g, 8.57 mmol) was added in one portion to a stirred solution of the cyclohexane (**17**) (2.30 g, 6.59 mmol) in dichloromethane (150 ml) under nitrogen at room temperature, and the mixture was then stirred for 16 h at room temperature. Solid calcium hydroxide and anhydrous sodium sulphate were added, and the mixture was then stirred for 15 min before being filtered. Evaporation of the filtrate left an oil, which was purified by chromatography on silica gel with 20% diethyl ether in light petroleum as eluant to give the *epoxide* (**18**) (2.19 g, 91%) as an oil, λ_{max}(hexane) 278 nm (1 750); ν_{max}(film) 2 940, 1 605, 1 595, 1 480, and 1 100 cm^{-1}; δ_H 0.86 (C*Me*Me), 1.05 (CMe*Me*), 1.18–1.1 (m, 2 H), 1.3 (CH_2C*Me*), 1.5–1.25 (m, 2 H), 2.05–1.75 (m, 2 H), 2.26 (Ar*Me*), 2.63 (d, *J* 17.5 Hz, C*H*HAr), 3.47 (OMe), 3.54 (d, *J* 17.5 Hz, CH*H*Ar), 3.61 (OMe), 4.88 (d, *J* 6 Hz, OC*H*HO), 4.93 (d, *J* 6 Hz, OCH*H*O), 5.11 (OCH_2O), 6.71 (d, *J* 3 Hz, ArH), and 6.88 (d, *J* 3 Hz, ArH); δ_C 17.2 (q), 17.4 (t), 22.0 (q), 25.8 (q), 27.0 (q), 31.2 (t), 31.9 (t), 34.5 (s), 37.6 (t), 55.6 (q), 57.3 (q), 64.4 (s), 68.8 (s), 95.0 (t), 99.5 (t), 115.3 (d), 116.7 (d), 131.8 (s), 133.3 (s), 148.9 (s), and 153.2 (s) (Found: M^+, 364.2251; C, 69.1; H, 8.9%. $C_{21}H_{32}O_5$ requires *M*, 364.2250; C, 69.2; H, 8.85%).

2-{[(1S*,6S*)-1-*Hydroxy*-2,2,6-*trimethylcyclohexyl*]*methyl*}-6-*methylbenzene*-1,4-*diol* (**19**).—A solution of the epoxide (**18**) was added dropwise during 15 min to a stirred solution of aluminium hydride (42 mmol) [prepared from aluminium chloride (1.39 g, 10.4 mmol) and lithium aluminium hydride (1.46 g, 38.5 mmol)] in dry diethyl ether (150 ml) under nitrogen maintained at 0 °C. After 18 days, water (50 ml) was added dropwise to the cooled mixture, and the ether phase was then separated. The aqueous phase was extracted with dichloromethane (2 × 50 ml) and the combined organic phases were then dried and evaporated to leave an off-white solid. Purification by chromatography on silica gel with 30% diethyl ether in light petroleum as eluant gave the *tertiary alcohol* (**19**) (0.70 g, 79%) as a white solid, m.p. 164.5–166 °C (from diethyl ether–light petroleum); λ_{max}(EtOH) 295 nm (3 390); ν_{max}($CHCl_3$) 3 590, 3 280, and 1 605 cm^{-1}; δ_H 0.76 (C*Me*Me), 0.98 (d, *J* 7 Hz, CH*Me*), 1.13 (CMe*Me*), 1.6–0.8 (m, 7 H), 2.2 (Ar*Me*), 2.3 (br, OH), 2.7 (d, *J* 15 Hz, C*H*HAr), 3.06 (d, *J* 15 Hz, CH*H*Ar), 4.35 (br, ArOH), 6.45 (d, *J* 3 Hz, ArH), 6.5 (d, *J* 3 Hz, ArH), and 8.78 (br, ArOH); δ_C 16.5 (q), 16.6 (q), 21.1 (t), 23.4 (q), 25.5 (q), 31.5 (t), 36.7 (d), 38.6 (t), 39.1 (s), 39.7 (t), 81.3 (s), 116.1 (d), 116.4 (d), 126.7 (s), 127.3 (s), 147.9 (s), and 148.1 (s) (Found: M^+, 278.1873; C, 73.0; H, 9.55%. $C_{17}H_{26}O_3$ requires *M*, 278.1881; C, 73.3; H, 9.4%).

(1′S*,6′S*)-2′,2′,6′,7-*tetramethylspiro*[*benzofuran*-2(3H),1′-*cyclohexane*]-5-*ol* (**11**).—A solution of the tertiary alcohol (**19**) (206 mg, 0.74 mmol) in chloroform (50 ml) was heated under reflux in the presence of PTSA monohydrate (10 mg) for 7 days. The cooled mixture was washed successively with saturated aq. sodium hydrogen carbonate (40 ml) and then with brine (40 ml). Evaporation of the dried organic phase left an off-white semi-solid, which was purified by chromatography on silica gel with 30% diethyl ether in light petroleum as eluant to give the *spirobenzofuran* (**11**) (173 mg, 90%) as an amorphous semi-solid, λ_{max}(EtOH) 305 nm (4 100); ν_{max}($CHCl_3$) 3 590, 3 530, 3 450, and 1 605 cm^{-1}; δ_H 0.7 (d, *J* 6.5 Hz, CH*Me*), 0.8 (C*Me*Me), 0.95 (CMe*Me*), 1.9–1.1 (m, 7 H), 2.11 (Ar*Me*), 2.77 (d, *J* 16.5 Hz, C*H*HAr), 3.13 (d, *J* 16.5 Hz, CH*H*Ar), 5.76 (ArOH), 6.4 (br, ArH), and 6.44 (br, ArH); δ_C 15.2 (q), 15.7 (q), 21.6 (t), 22.3 (q), 24.9 (q), 30.9 (t), 35.6 (t), 36.5 (t), 37.1 (d), 38.1 (s), 93.2 (s), 108.2 (d), 115.6 (d) 118.5 (s), 127.2 (s), 148.3 (s), and 153.9 (s) (Found: M^+, 260, 1795. $C_{17}H_{24}O_2$ requires *M*, 260.1775).

(1′S*,6′S*)-5-(4-*Nitrobenzoyloxy*)-2′,2′,6′,7-*tetramethylspiro*[*benzofuran*-2(3H),1′-*cyclohexane*].—A solution of the phenol (**11**) (7.7 mg, 0.03 mmol), 4-nitrobenzoic acid (5.4 mg, 0.032 mmol), *N*,*N*′-dicyclohexylcarbodi-imide (6.7 mg, 0.032 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (1.0 mg) in dry dichloromethane (2.0 ml) was stirred under nitrogen at room temperature for 12 h. The mixture was washed successively with water (3 × 5 ml), dil. acetic acid (4.5 ml), and water (3 × 5 ml), then dried and evaporated to leave a pale yellow solid. Purification by PLC on silica gel with 10% diethyl ether in light petroleum as eluant gave the crystalline 4-nitrobenzoate derivative (3.7 mg, 30%) as pale yellow prisms, m.p. 123–125 °C (from EtOAc); λ_{max}(EtOH) 256 nm (12 300); ν_{max}($CHCl_3$) 1 735 cm^{-1}; δ_H 0.7 (d, *J* 5.5 Hz, CH*Me*), 0.84 (C*Me*Me), 0.99 (CMe*Me*), 1.8–1.2 (m, 7 H), 2.21 (Ar*Me*), 2.87 (d, *J* 16 Hz, C*H*HAr), 3.27 (d, *J* 16 Hz, CH*H*Ar), 6.74 (br, 2 × ArH), and 8.34 (br, 4 × ArH); *m*/*z* 409 (10%, M^+, $C_{24}H_{27}NO_5$), 150 (9, $C_7H_4NO_3$), 123 (33), 97 (37), 85 (44), 83 (37), 71 (64), 69 (49), and 57 (100).

Crystallographic Analysis of the p-*Nitrobenzoate Derivative of the Phenol* (**11**).—*Crystal data.* $C_{24}H_{27}NO_3$, *M* = 409.46, monoclinic, *a* = 19.079(3), *b* = 8.140(2), *c* = 14.181(4) Å, β = 91.55(2)°, *V* = 2 201.38 Å^3, *Z* = 4, D_c = 1.24 g cm^{-3}, *F*(000) = 872, space group $P2_1/c$, Cu-K_α radiation λ = 1.541 78 Å, μ(Cu-K_α) = 7.12 cm^{-1}.

A crystal of approximate dimensions 1.0 × 0.4 × 0.05 mm was mounted on an Enraf-Nonius CAD4 diffractometer and 25 reflections were used to determine accurate lattice parameters. Intensity data were collected using an ω/θ scan for 1° < θ < 60°. A total of 3 257 independent reflections was measured of which 1 215 had $I > 3\sigma(I)$ and were considered observed and used in the subsequent refinement. The data were corrected for Lorentz and polarization factors but no absorption corrections were made. Crystallographic calculations were performed using the CRYSTALS system of programs. The structure was solved by direct methods using the MULTAN program. Least-squares refinement including anisotropic thermal parameters for non-hydrogen atoms and incorporating hydrogen atoms in calculated positions without refinement, terminated at *R* 0.0631 (R_w 0.0805). A final difference map showed no features in excess of 0.3 eÅ^{-3}.

The refined fractional atomic co-ordinates are shown in the Table and the resulting molecular structure is illustrated in the Figure. The resulting geometric data are unexceptional.†

† *Supplementary data* (see section 5.6.3 of Instructions for Authors, in the January issue). Observed and calculated structure factors, thermal parameters, bond lengths, bond angles, and calculated hydrogen atom co-ordinates have been deposited at the Cambridge Crystallographic Data Centre.

Table 1. Fractional atomic co-ordinates for the *p*-nitrobenzoate derivative of the phenol (**11**), with standard deviations in parentheses.

Atom	*x*	*y*	*z*
O(1)	0.336 6(3)	0.064 3(6)	0.513 5(3)
C(2)	0.284 0(4)	0.069(1)	0.446 7(5)
C(3)	0.278 7(4)	−0.046(1)	0.374 1(5)
C(4)	0.223 4(5)	−0.022(1)	0.308 7(5)
C(5)	0.178 7(4)	0.106(1)	0.319 4(5)
C(6)	0.183 3(4)	0.219(1)	0.393 1(6)
C(7)	0.238 2(4)	0.195 5(9)	0.457 3(5)
C(8)	0.259 5(4)	0.295(1)	0.542 5(6)
C(9)	0.327 5(4)	0.211 0(9)	0.577 6(6)
C(10)	0.393 0(4)	0.317(1)	0.568 5(5)
C(11)	0.458 7(5)	0.223(1)	0.600 8(7)
C(12)	0.453 9(5)	0.148(1)	0.694 9(7)
C(13)	0.389 6(5)	0.043(1)	0.703 4(5)
C(14)	0.322 4(5)	0.135(1)	0.675 2(6)
C(15)	0.330 3(5)	−0.181(1)	0.365 6(6)
C(16)	0.401 8(5)	0.363(1)	0.466 0(6)
C(17)	0.385 0(6)	0.479(1)	0.627 0(7)
C(18)	0.260 8(5)	0.019(1)	0.683 6(6)
O(19)	0.127 9(3)	0.134 2(8)	0.242 1(4)
C(20)	0.064 1(5)	0.102(1)	0.262 9(6)
O(21)	0.044 4(3)	0.053 9(9)	0.336 6(5)
C(22)	0.014 0(5)	0.135(1)	0.180 2(6)
C(23)	0.034 9(4)	0.202(1)	0.097 0(6)
C(24)	−0.014 1(5)	0.231(1)	0.024 8(5)
C(25)	−0.081 6(5)	0.195(1)	0.039 6(6)
C(26)	−0.104 0(4)	0.133(1)	0.123 3(7)
C(27)	−0.055 3(5)	0.105(1)	0.191 9(5)
N(28)	−0.134 4(5)	0.217(1)	−0.038 8(7)
O(29)	−0.115 4(5)	0.278(2)	−0.109 1(7)
O(30)	−0.193 1(4)	0.185(1)	−0.026 6(6)

6-[2,6,6-*Trimethylcyclohex*-1-*enyl*)*methyl*]-2-*methylbenzene*-1,4-*diol* (**12**).—A solution of the bis(methoxymethyl) ether (**17**) (259 mg, 0.74 mmol) in methanol (3.0 ml) was added to a stirred solution of methanolic hydrochloric acid (50 ml; 1.0M) under nitrogen at room temperature, and the mixture was then stirred for 3 h. Saturated aq. sodium hydrogen carbonate was added dropwise, and the mixture was then extracted with diethyl ether (3 × 50 ml). The combined extracts were washed successively with saturated aq. sodium hydrogen carbonate (50 ml) and then with brine (50 ml), dried, and evaporated. The residue was purified by chromatography on silica gel with 30% diethyl ether in light petroleum as eluant to give the *hydroquinone* (**12**) (192 mg, 99%) as a white solid, m.p. 47.5–49 °C (from light petroleum); λ_{max}(EtOH) 290 nm (3 120); ν_{max}($CHCl_3$) 3 580, 3 360, 1 650, and 1 505 cm^{-1}; δ_H 0.93 (CMe_2), 1.8–1.2 (m, 4 H), 1.55 (=CMe), 2.2–1.9 (m, 2 H), 2.17 (Ar*Me*), 3.34 (CH_2Ar), 4.9 (br, 2 × OH), and 6.23 (br, 2 × ArH) (Found: M^+, 260.1792. $C_{17}H_{14}O_2$ requires *M*, 260.1775).

Acid-catalysed Cyclization of 6-[2,6,6-*Trimethylcyclohex*-1-*enyl*)*methyl*]-2-*methylbenzene*-1,4-*diol* (**12**).—A solution of the hydroquinone (**12**) (192 mg, 0.74 mmol) in chloroform (25 ml) was heated under reflux in the presence of PTSA monohydrate (10 mg) for 7 days. The cooled mixture was washed with saturated aq. sodium hydrogen carbonate (30 ml), dried, and evaporated to leave a brown oil. Purification by chromatography on silica gel with 25% diethyl ether in light petroleum as eluant gave a 13:1 mixture of the benzopyran (**21**) and the spirobenzofuran (**11**) as an off-white semi-solid (185 mg, 95%). The binary mixture was separated by HPLC on μ-Porasil with 7.5% ethyl acetate in light petroleum as eluant to give: (i) the benzopyran (**21**) (eluted first) as a semi-solid, λ_{max}(EtOH) 299.5 nm (3 100); ν_{max}($CHCl_3$) 3 580, 3 300, 1 605, 1 165, 945, and 860 cm^{-1}; δ_H 0.62 (C*Me*Me), 0.93 (CMe*Me*), 1.14 (CH_2C*Me*), 2.1–1.1 (m, 7 H), 2.1 (Ar*Me*), 2.66 (d, *J* 17.5 Hz, C*H*HAr), 2.96 (dd, *J* 17.5 and 8 Hz, CH*H*Ar), 4.32 (br, OH), 6.38 (d, *J* 2.5 Hz, ArH), and 6.44 (d, *J* 2.5 Hz, ArH) (Found: M^+, 260.1759. Calc. for $C_{17}H_{24}O_2$: *M*, 260.1775), and (ii) the spirobenzofuran (**11**) (eluted second) as a semi-solid, which was identical with the compound described earlier.

(1′S*,6′S*)-2′,2′,6′,7-*Tetramethylspiro*[*benzofuran*-2(3H),1′-*cyclohexane*]-4,5-*dione* (**10**).—A solution of potassium nitrosodisulphonate (462 mg, 1.72 mmol) in water (20 ml) containing aq. potassium dihydrogen orthophosphate (7.5 ml; 0.17M) was added in one portion to a stirred solution of the spirobenzofuran (**11**) (172 mg, 0.66 mmol) in acetone (13 ml). The solution was stirred for 10 min and then diluted with water (13 ml) and left at room temperature for 2 h. The dark red solution was extracted with chloroform (3 × 20 ml) and the combined extracts were evaporated under reduced pressure to leave a dark red solid, which was purified by chromatography on silica gel with 30% diethyl ether in light petroleum as eluant to give the *o-quinone* (139 mg, 77%) as a deep red solid, m.p. 111–113 °C (from light petroleum); λ_{max}(EtOH) 272 (4 980) and 471 nm (1 140); ν_{max}($CHCl_3$) 1 675, 1 650, 1 625, and 1 590 cm^{-1}; δ_H 0.79 (dd, *J* 6.5 and 3 Hz, CH*Me*), 0.81 (d, *J* 3 Hz, C*Me*Me), 0.95 (d, *J* 3 Hz, CMe*Me*), 1.7–1.2 (m, 6 H), 1.9–1.75 (m, 1 H), 2.12 (q, *J* 2 Hz, =CMe), 2.64 (dd, *J* 16 and 3 Hz, C*H*H), 2.92 (dd, *J* 16 and 3 Hz, CH*H*), and 6.13 (d, *J* 2 Hz, =CH); δ_C 15.4 (q), 16.7 (q), 21.1 (t), 22.0 (q), 24.5 (q), 30.5 (t), 30.9 (t), 36.0 (t), 36.9 (d), 38.2 (s), 102.5 (s), 114.6 (s), 128.6 (d), 143.2 (s), 170.3 (s), 174.4 (s), and 182.8 (s) (Found: M^+, 274.1551; C, 74.0; H, 8.1%. $C_{17}H_{22}O_3$ requires *M*, 274.1569; C, 74.4; H, 8.1%).

(1′S*,6′S*)-2′,2′,6′,7-*Tetramethylspiro*[*benzofuran*-2(3H),1′-*cyclohexane*]-4,5-*diol* (**22**).—A solution of sodium dithionite (225 mg, 1.29 mmol) in water (40 ml) was added in one portion to a stirred solution of the *o*-quinone (**10**) (54 mg, 0.20 mmol) in ethanol (20 ml). The red colour of the quinone was discharged immediately, and, after 1 min, dil. hydrochloric acid (50 ml; 5%) was added. The opaque mixture was extracted with diethyl ether (3 × 50 ml) and the combined extracts were then washed with saturated aq. sodium hydrogen carbonate (2 × 50 ml). Evaporation of the dried extracts left the *catechol* (**22**) (53 mg, 97%) as an air-sensitive, cream coloured solid, m.p. 142.5–144.5 °C (from Et_2O) (with partial decomp.); λ_{max}(EtOH) 295 nm (3 580); ν_{max}($CHCl_3$) 3 530, 3 300, 1 630, and 920 cm^{-1}; δ_H([$^2H_5$]pyridine) 0.85 (d, *J* 5 Hz, CH*Me*), 0.91 (C*Me*Me), 0.92 (CMe*Me*), 1.8–1.1 (m, 6 H), 1.94–1.88 (m, 1 H), 2.27 (Ar*Me*), 3.11 (d, *J* 16 Hz, C*H*HAr), 3.44 (d, *J* 16 Hz, CH*H*Ar), 6.94 (ArH), and 10.6 (br, 2 × OH); δ_C([$^2H_5$]pyridine) 15.0 (q), 16.1 (q), 21.8 (t), 22.3 (q), 25.1 (q), 31.2 (t), 33.9 (t), 36.7 (t), 37.3 (d), 38.4 (s), 93.7 (s), 104.7 (s), 114.2 (s), 116.9 (d), 139.7 (s), 141.6 (s), and 153.8 (s) (Found: M^+, 276.1720, $C_{17}H_{24}O_3$ requires *M*, 276.1720).

The catechol underwent oxidation back to the *o*-quinone (**10**) in quantitative yield, as the solid or in solution, immediately on exposure to air. A slightly modified procedure for the reduction of the quinone (**10**), again using sodium dithionite, led to the diacetate corresponding to the quinol (**22**). Thus, a solution of the *o*-quinone (**10**) (54 mg, 0.20 mmol) in diethyl ether (30 ml) was shaken with a solution of sodium dithionite (250 mg, 1.4 mmol) in water (30 ml) until the solution became colourless. The ethereal layer was separated and the aqueous layer was then extracted with diethyl ether (2 × 10 ml). The combined organic mother liquor and extracts were washed successively wth dil. hydrochloric acid (40 ml; 5%), saturated aq. sodium hydrogen carbonate (40 ml), and brine (40 ml), and were then dried and evaporated to leave the *catechol* (46 mg, 84%), which was immediately dissolved in dry pyridine (10 ml) and the solution was stirred with acetic anhydride (10 ml) under

nitrogen at room temperature for 24 h. The mixture was poured into water (50 ml) and then extracted with diethyl ether (2 × 50 ml). The combined extracts were washed successively with dil. hydrochloric acid (2 × 50 ml; 5%), saturated aq. sodium hydrogen carbonate (2 × 50 ml), and brine (50 ml), and were then dried and evaporated to leave an off-white solid. Purification by chromatography on silica gel with 20% diethyl ether in light petroleum as eluant gave the *diacetate* (26 mg, 43%) as a white solid, m.p. 96–98 °C; λ_{max}(EtOH) 287 nm (2 480); ν_{max}($CHCl_3$) 1 760 and 1 610 cm^{-1}; δ_H 0.74 (d, *J* 6.5 Hz, CH*Me*), 0.83 (C*Me*Me), 0.96 (CMe*Me*), 1.3–1.1 (m, 2 H), 1.85–1.35 (m, 5 H), 2.15 (Ar*Me*), 2.25 (Ac), 2.2 (Ac), 2.74 (d, *J* 16.5 Hz, C*H*HAr), 3.09 (d, *J* 16.5 Hz, CH*H*Ar), and 6.68 (ArH); δ_C 14.9 (q), 15.6 (q), 20.5 (q), 20.5 (q), 21.5 (t), 22.7 (q), 24.9 (q), 30.8 (t), 33.5 (t), 36.4 (t), 37.2 (d), 38.2 (s), 95.5 (s), 116.0 (s), 120.6 (s), 122.8 (d), 134.5 (s), 136.1 (s), 157.7 (s), 167.4 (s), and 169.0 (s) (Found: M^+, 360.1918. $C_{21}H_{28}O_5$ requires *M*, 360.1937).

(E,E,E)-3,7,11,15-*Tetramethylhexadeca*-2,6,10,14-*tetraenyl* 4-*Nitrobenzoate* (**24**).—A solution of (*E,E,E*)-geranylgeraniol (**23**)[19] (5.00 g, 17.2 mmol) and 4-nitrobenzoyl chloride (3.83 g, 20.6 mmol) in dry pyridine (75 ml) was stirred under nitrogen at room temperature for 18 h. The solution was concentrated under reduced pressure and the brown oily residue was poured into water (100 ml) and then extracted with diethyl ether (2 × 100 ml). The combined extracts were washed successively with dil. hydrochloric acid (2 × 100 ml; 1M), saturated aq. sodium hydrogen carbonate (3 × 100 ml), and brine (100 ml) and were then dried and evaporated. The oily residue was purified by chromatography on silica gel with 5% ethyl acetate in light petroleum as eluant to give the ester (**24**) (5.66 g, 75%) as a pale yellow, room-temperature melting, solid; λ_{max}(EtOH) 260 nm (13.490); ν_{max}(film) 2 930, 1 735, 1 605, 1 520, 1 280, and 720 cm^{-1}; δ_H 1.58 (d, *J* 6 Hz, =CMe), 1.6 (=CMe), 1.61 (=CMe), 1.68 (=C*Me*Me), 1.79 (=CMe*Me*), 2.2–1.85 (m, 12 H, 3 × CH_2CH_2), 4.89 (d, *J* 7 Hz, CH_2O), 5.15–5.05 (m, 3 H, 3 × =CH), 5.47 (t, *J* 7 Hz, =C*H*CH_2O), 8.21 (d, *J* 9 Hz, 2 × ArH), and 8.28 (d, *J* 9 Hz, 2 × ArH); *m/z* 439 (2%, M^+, $C_{27}H_{37}NO_4$), 27 (3, $C_{20}H_{32}$, *M* − $C_7H_5NO_4$), 167 (9, $C_7H_5NO_4$), 150 (18, $C_7H_4NO_3$), 136 (28), 93 (44), 81 (87), and 69 (100, C_5H_9).

(±)-(1α,4,4aα,4b,5,6,7,8,8aα,9,10,10a-*Dodecahydro*-2,4bβ,8,8,10aβ-*pentamethylphenanthren*-1-*yl*)*methanol* (**25**).—The tricyclic alcohol was prepared from the nitrobenzoate (**24**) by the procedure of Nishizawa *et al.*[20] and showed: δ_H 0.86 (2 × Me), 0.89 (Me), 0.91 (Me), 1.95 (=CMe), 2.2–1.0 (m, 16 H, methylene envelope and OH), 3.84 (m, C*H*$_2$OH), and 5.58 (br, =CH); δ_C 15.8 (q), 15.8 (q), 18.5 (t), 18.8 (t), 21.7 (q), 21.8 (q), 22.6 (t), 33.1 (s), 33.4 (q), 36.2 (s), 37.2 (s), 39.9 (t), 41.5 (t), 41.9 (t), 54.8 (d), 56.2 (d), 57.9 (d), 60.8 (t), 123.8 (d), and 132.7 (s).

(±)-(3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-*Dodecahydro*-2,4bβ,8,8,10aβ-*pentamethylphenanthren*-1-*yl*)*methanal* (**27**).—A solution of the alcohol (**25**) (346 mg, 1.19 mmol) in dry dichloromethane (4.0 ml) was added in one portion to a stirred suspension of pyridinium chlorochromate (PCC) (392 mg, 1.82 mmol) and powdered sodium acetate (30 mg) in dry dichloromethane (8.09 ml) under nitrogen at room temperature, and the mixture was then stirred for 2.5 h. The mixture was treated with Celite (0.5 g), diluted with diethyl ether (35 ml) and then filtered through Celite; the filter was copiously rinsed with diethyl ether. Evaporation of the dried filtrate and washings left an orange oil, which was purified by chromatography on silica gel with 10% ethyl acetate in light petroleum as eluant to give a 1:5 mixture of α,β- and β,γ-unsaturated aldehydes (**27**) and (**26**) (257 mg, 75%) as an oil, ν_{max}(film) 1 715 and 1 665 cm^{-1}.

This mixture was isomerized directly. A solution of the aldehydes (213 mg, 0.74 mmol) in methanol (6.0 ml)–hexanes (5.0 ml) was stirred with potassium hydroxide (41 mg, 0.74 mmol) under nitrogen at 0 °C for 4 h. The mixture was diluted with water (20 ml) and extracted with hexanes (2 × 20 ml) and ethyl acetate (25 ml). Evaporation of the dried extracts left a solid, which was then purified by chromatography upon silica gel with 5% ethyl acetate in light petroleum as eluant to give the recovered β,γ-unsaturated aldehyde (**26**) (45 mg) as needles, followed by the required α,β-*unsaturated aldehyde* (**27**) (119 mg, 56%; 71% based on consumed starting material) as a powder, m.p. 131–135 °C; λ_{max}(EtOH) 241 nm (1 520); ν_{max}($CHCl_3$) 2 910, 2 850, 1 660, and 1 605 cm^{-1}; δ_H 0.82 (Me), 0.84 (Me), 0.86 (Me), 1.19 (Me), 1.75–0.8 (m, 13 H, methylene envelope), 2.02 (=CMe), 2.3–2.15 (m, CHC*H*$_2$), 2.64 (dt, *J* 13 and 6.5 Hz, 1 H), and 10.03 (CHO) (Found: M^+, 288.2440. $C_{20}H_{32}O$ requires *M*, 288.2453).

(±)-3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-*Dodecahydro*-2,4bβ,8,8,10aβ-*pentamethylphenanthren*-1-*yl*)*methanol* (**28**).—A solution of sodium borohydride (17 mg, 0.45 mmol) in methanol (0.5 ml) was added dropwise to a stirred solution of the aldehyde (**27**) (100 mg, 0.35 mmol) in hexanes (5.0 ml)–methanol (5.0 ml) under nitrogen at 0 °C, and the mixture was then stirred at 0 °C for 50 min. Dil. hydrochloric acid (2 ml; 1M) was added and the mixture was poured into water (25 ml) and then extracted with dichloromethane (3 × 15 ml). Evaporation of the dried extracts left an oil, which was purified by chromatography on silica gel with 10% ethyl acetate in cyclohexane as eluant to give the *allylic alcohol* (**28**) (87 mg, 86%) as a solid, m.p. 101–103 °C; ν_{max}($CHCl_3$) 3 660, 3 590, 3 430, 2 910, 2 850, 1 595, and 1 005 cm^{-1}; δ_H 0.92 (Me), 0.84 (Me), 0.84 (Me), 0.96 (Me), 1.71 (=CMe), 1.8–0.9 (m, 15 H, methylene envelope and OH), 2.1–1.95 (m, =CCH_2), 4.04 (d, *J* 11 Hz, C*H*HOH), and 4.18 (d, *J* 11 Hz, CH*H*OH) (Found: M^+, 290.2617. $C_{20}H_{34}O$ requires *M*, 290.2610).

(±)-1-*Bromomethyl*-3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-*dodecahydro*-2,4bβ,8,8,10aβ-*pentamethylphenanthrene* (**29**).—A solution of 1,2-dibromotetrachloroethane (86 mg, 0.26 mmol) in dry diethyl ether (2.0 ml) was added dropwise during 2 min to a stirred solution of the alcohol (**28**) (68 mg, 0.23 mmol) in dry diethyl ether (10 ml) under nitrogen at 0 °C, and the mixture was then stirred at 0 °C for 1.5 h. The mixture was filtered and the filtrate was evaporated to leave a solid, which was then diluted with dry hexanes (4 ml) and refrigerated overnight. Evaporation of the filtered, dried solution gave the allylic bromide (**29**) (77 mg, 95%) as needles, ν_{max}($CHCl_3$) 2 900, 2 860, 1 600, 1 450, and 1 375 cm^{-1}; δ_H 0.84 (Me), 0.86 (Me), 1.0 (Me), 1.71 (=CMe), 1.88–0.9 (m, 14 H, methylene envelope), 2.23–1.9 (m, =CCH_2), 3.97 (d, *J* 11 Hz, C*H*HBr), and 4.15 (d, *J* 11 Hz, CH*H*Br).

(±)-1-[2,5-*Bis*(*methoxymethoxy*)-3-*methylbenzyl*]-3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-*dodecahydro*-2,4bβ,8,8,10aβ-*pentamethylphenanthrene* (**30**).—A solution of butyl-lithium (0.24 ml) in hexanes (1.6M; 0.39 mmol) was added dropwise to a stirred solution of 1-bromo-2,5-bis(methoxymethoxy)-3-methylbenzene (**14**; R = MOM) (86 mg, 0.30 mmol) in dry THF (5.0 ml) under nitrogen maintained at −50 °C. The mixture was stirred for 30 min and then copper(I) iodide powder (33 mg, 0.17 mmol) was added in one portion. After a further 30 min, a solution of the allylic bromide (**29**) (77 mg, 0.22 mmol) in dry hexanes (2.5 ml) was added dropwise during 2 min and then the mixture was stirred at −40 °C for an additional 30 min. The mixture was allowed to warm to room temperature during 2 h, and was then evaporated to dryness under reduced pressure. The residue was diluted with water (20 ml) and extracted with diethyl ether (3 × 20 ml). The combined extracts were evaporated to leave a brown oil, which was purified by chroma-

tography on silica gel with 5% diethyl ether in cyclohexane as eluant to give the coupled product (**30**) (58 mg, 40%) as an oil, δ_H 0.77 (Me), 0.79 (Me), 0.85 (Me), 1.0 (Me), 1.48 (=CMe), 1.8–0.7 (m, 14 H, methylene envelope), 2.11 (m, $=CCH_2$), 3.32 (d, *J* 18 Hz, C*H*HAr), 3.46 (d, *J* 18 Hz, CH*H*Ar), 3.48 (OMe), 4.93 (d, *J* 6 Hz, OC*H*HO), 4.97 (d, *J* 6 Hz, OCH*H*O), 5.10 (OCH_2O), 6.62 (d, *J* 3 Hz, ArH), and 6.7 (d, *J* 3 Hz, ArH); *m/z* 484 (100%, M^+, $C_{31}H_{48}O_4$), 452 (6, $C_{30}H_{44}O_3$, *M* − MeOH), 439 (9, $C_{29}H_{43}O_3$, *M* − $MeOCH_2$), 4.23 (23, $C_{29}H_{43}O_2$, *M* − $MeOCH_2O$), 407 (8, $C_{28}H_{39}O_2$, *M* − $MeOCH_2$ − MeOH), 303 (10), 259 (24, $C_{19}H_{31}$), 233 (34), 215 (28), 181 (61), 163 (33), 137 (37, $C_{10}H_{17}$), 121 (38), 95 (42), and 69 (45, C_5H_9).

(±)-1-[2,5-*Bis*(*methoxymethoxy*)-3-*methylbenzyl*]-1α,2α-*epoxy*-(**31**) *and* (±)-1-[2,5-*Bis*(*methoxymethoxy*)-3-*methylbenzyl*]-1β,2β-*epoxy*-1,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-*tetradecahydro*-2,4bβ,8,8,10aβ-*pentamethylphenanthrene* (**32**).—MCPBA (17.5 mg, 0.10 mmol) was added in one portion to a stirred solution of the olefin (**30**) (38.0 mg, 0.078 mmol) in dichloromethane (5.5 ml) under nitrogen at room temperature and the solution was stirred for 16 h. Solid calcium hydroxide and anhydrous sodium sulphate were added, and the mixture was stirred for 15 min and then filtered. Evaporation of the filtrate left an oil, which was purified by chromatography on silica gel with 10% diethyl ether in light petroleum as eluant to give a 2:1 mixture of the α- and β-epoxide (27.6 mg, 71%) as a semi-solid, δ_H (i) major isomer, 0.74 (Me), 0.75 (Me), 0.77 (Me), 1.1 (Me), 1.22 (OCMe), 1.95–0.9 (m, 16 H, methylene envelope), 2.27 (Ar*Me*), 2.43 (d, *J* 18 Hz, C*H*HAr), 3.64 (d, *J* 18 Hz, CH*H*Ar), 3.5 (OMe), 3.61 (OMe), 4.87 (d, *J* 6 Hz, OC*H*HO), 4.93 (d, *J* 6 Hz, OCH*H*O), 5.12 (d, *J* 7 Hz, OC*H*HO), 5.15 (d, *J* 7 Hz, OCH*H*O), 6.69 (d, *J* 3 Hz, ArH), and 6.9 (d, *J* 3 Hz, ArH); and (ii) minor isomer, 0.77 (Me), 0.78 (Me), 0.83 (Me), 0.99 (Me), 1.22 (OCMe), 1.95–0.9 (m, 16 H, methylene envelope), 2.25 (Ar*Me*), 2.83 (d, *J* 17 Hz, C*H*HAr), 3.32 (d, *J* 17 Hz, CH*H*Ar), 3.48 (OMe), 3.60 (Me), 4.87 (d, *J* 6 Hz, OC*H*HO), 4.9 (d, *J* 6 Hz, OCH*H*O), 5.11 (OCH_2O), 6.71 (d, *J* 3 Hz, ArH), and 6.92 (d, *J* 3 Hz, ArH).

2-*Methyl*-6-[(E,E,E)-3,7,11,15-*tetramethylhexadeca*-2,6,10,14-*tetraenyl*]*benzene*-1,4-*diol* (**6**).—Hydrogen chloride gas was slowly bubbled through a stirred solution of the bis(methoxymethoxy) ether (**35**) (see below) (692 mg, 1.43 mmol) in dry diethyl ether (25 ml) containing dry THF (2.5 ml) and dry methanol (2.5 ml) at room temperature for 18 min (TLC monitoring). The mixture was diluted with ether (20 ml) and then neutralized with saturated aq. sodium hydrogen carbonate (100 ml). The ether extracts were washed successively with saturated aq. sodium hydrogen carbonate (2 × 25 ml), water (50 ml), and brine (50 ml), and evaporation of the dried extracts left a straw-coloured oil. Purification by PLC on silica gel with 50% diethyl ether in light petroleum as eluant gave the hydroquinone (**6**) (445 mg, 78%) as an oil, λ_{max}(EtOH) 291 nm (3 115); ν_{max}(film) 3 380, 2 920, 1 605, 1 195, and 860 cm^{-1}; δ_H 1.59 (3 × =CMe), 1.68 (=C*Me*Me), 1.76 (=CMe*Me*), 2.2–1.9 (m, 12 H, 3 × CH_2CH_2), 2.16 (Ar*Me*), 3.27 (d, *J* 7 Hz, CH_2Ar), 4.86 (OH), 5.15–5.05 (m, 3 × =CH), 5.14 (OH), 5.27 (t, *J* 7 Hz, =C*H*CH_2Ar), 6.44 (d, *J* 3 Hz, ArH), and 6.48 (d, *J* 4 Hz, ArH); δ_C 16.1 (3 × q), 16.2 (q), 17.7 (q), 25.7 (q), 26.3 (t), 26.6 (t), 26.8 (t), 30.3 (t), 39.7 (3 × t), 114.1 (d), 115.5 (d), 121.5 (d), 123.6 (d), 124.1 (d), 124.2 (d), 125.8 (s), 127.6 (s), 131.3 (s), 135.0 (s), 135.6 (s), 138.8 (s), 146.5 (s), and 148.7 (s); *m/z* 396 (23%, M^+, $C_{27}H_{40}O_2$), 137 (33), 86 (26), 84 (39), 81 (34), 69 (100, C_5H_9), and 55 (26). Both the UV and IR absorption data were consistent with those published for natural (**6**).[2]

2-*Methyl*-6-[(E,E,E)-3,7,11,15-*tetramethylhexadeca*-2,6,10,14-*tetraenyl*]*cyclohexa*-2,5-*diene*-1,4-*dione* (**5**).—Air was continuously bubbled through a stirred solution of the hydroquinone (**6**) (88 mg, 0.22 mmol) in dichloromethane (10 ml, periodically replenished) at room temperature for 24 h. Evaporation of the dried solution left an orange oil, which was purified by chromatography on silica gel with 50% diethyl ether in light petroleum as eluant to give the benzoquinone (14 mg, 16%) as a yellow oil, λ_{max}(EtOH) 250 nm; ν_{max}($CHCl_3$) 1 650, 1 630, 1 610, 1 430, 1 375, 1 190, and 910 cm^{-1}; δ_H 1.6 (3 × =CMe), 1.63 (=C*Me*Me), 1.68 (=CMe*Me*), 2.06 (d, *J* 1 Hz, =CMe), 2.15–1.9 (m, 12 H, 3 × CH_2CH_2), 3.13 (d, *J* 17 Hz, CH_2Ar), 5.14–5.0 (m, 3 H, 3 × =CH), 5.15 (t, *J* 7 Hz, =C*H*CH_2Ar), 6.47 (d, *J* 2 Hz, =CH), and 6.55 (d, *J* 2 Hz, =CH); δ_C 16.0 (q), 16.0 (q), 16.1 (q), 16.2 (q), 17.7 (q), 25.7 (q), 26.5 (q), 26.7 (t), 26.8 (t), 27.6 (t), 39.7 (t), 39.7 (t), 39.7 (t), 119.0 (d), 123.8 (d), 124.2 (d), 124.4 (d), 131.2 (d), 132.3 (d), 133.2 (d), 134.9 (s), 135.5 (s), 139.9 (s), 145.9 (s), 148.5 (s), and 188.0 (3 × s); *m/z* 394 (5%, M^+, $C_{27}H_{38}O_2$), 175 (41), 81 (77, C_6H_9), and 69 (100, C_5H_9). Both the UV and IR absorption data were consistent with those published for natural (**5**).[2]

2,5-*Bis*(*methoxymethoxy*)-1-*methyl*-3-[(E,E,E)-3,7,11,15-*tetramethylhexadeca*-2,6,10,14-*tetraenyl*]*benzene* (**35**).—A solution of butyl-lithium (8.1 ml) in hexanes (1.6M; 13.0 mmol) was added dropwise during 10 min to a stirred solution of 1-bromo-2,5-bis(methoxymethoxy)-3-methylbenzene (**14**) (3.00 g, 10.3 mmol) in dry THF (50 ml) under nitrogen at −40 °C. The mixture was stirred for 30 min, and then copper(I) iodide powder (0.98 g, 5.15 mmol) was added in one portion. After a further 30 min, a solution of (*E,E,E*)-geranylgeranyl bromide (**34**)[21] (3.04 g, 8.60 mmol) in hexanes (10 ml) was added dropwise during 10 min, and the mixture was stirred at −40 °C for a further 30 min. The solution was allowed to warm to room temperature during 2 h, and was then evaporated to dryness under reduced pressure. The residue was extracted with diethyl ether (3 × 50 ml), and the combined extracts were then washed successively with dil. ammonia (50 ml; 2M), water (2 × 50 ml), and brine (50 ml). Evaporation of the dried extract left an oil, which was purified by chromatography on silica gel with 5% and then 10% diethyl ether in light petroleum as eluant to give the coupled product (**35**) (2.40 g, 58%) as a pale straw-coloured oil, λ_{max}(EtOH) 278 nm (1 830); ν_{max}(film) 2 920, 1 595, 1 155, 1 040, and 985 cm^{-1}; δ_H 1.6 (3 × Me), 1.68 (d, *J* 1 Hz, =C*Me*Me), 1.71 (d, *J* 1 Hz, =CMe*Me*), 2.2–1.9 (m, 12 H, 3 × CH_2CH_2), 2.28 (Ar*Me*), 3.36 (d, *J* 7 Hz, CH_2Ar), 3.46 (OMe), 3.6 (OMe), 4.91 (OCH_2O), 5.1 (OCH_2O), 5.15–5.0 (m, 3 × =CH), 5.3 (td, *J* 7 and 1 Hz, =C*H*CH_2Ar), 6.68 (d, *J* 3 Hz, ArH), and 6.72 (d, *J* 3 Hz, ArH); δ_C 16.0 (q), 16.0 (q), 16.2 (q), 17.2 (q), 17.6 (q), 25.7 (q), 26.7 (t), 26.7 (t), 26.8 (t), 28.7 (t), 39.7 (3 × t), 55.8 (q), 57.2 (q), 94.7 (t), 99.6 (t), 115.4 (d), 116.0 (d), 122.6 (d), 124.2 (d), 124.3 (d), 124.4 (d), 131.1 (s), 132.0 (s), 134.8 (s), 135.0 (s), 135.8 (s), 136.4 (s), 149 (s), 149.1 (s), and 153.5 (s); *m/z* 484 (10%, M^+, $C_{31}H_{48}O_4$), 81 (15), 69 (50, C_5H_9), and 45 (100, C_2H_5O).

(E,E,E)-16-[2,5-*Bis*(*methoxymethoxy*)-3-*methylphenyl*]-3R*-*bromo*-2,6,10,14-*tetramethylhexadeca*-6,10,14-*trien*-2-*ol* (**37**).—*N*-Bromosuccinimide (NBS) (2.63 g, 14.8 mmol) was added, in one portion, to a stirred solution of the tetraene (**35**) (4.79 g, 9.88 mmol) in aqueous 1,2-dimethoxyethane (DME) (44 ml; DME:water 9:1) at room temperature, and the mixture was then stirred for 4 h, poured into water (100 ml), and extracted with light petroleum (2 × 100 ml). The combined extracts were washed successively with water (100 ml) and brine (100 ml), then dried and evaporated to leave a yellow oil. Purification by chromatography on silica gel with 10–50% diethyl ether in light petroleum as eluant gave the bromohydrin (**37**) (2.82 g, 49%) as a pale straw-coloured oil, λ_{max}(EtOH) 280 nm (1 870); ν_{max}($CHCl_3$) 3 470, 1 595, 1 040, and 985 cm^{-1}; δ_H 1.32 (C*Me*Me), 1.34 (CMe*Me*), 1.59 (=CMe), 1.6 (d, *J* 1 Hz, =CMe),

1.71 (=CMe), 2.4–1.3 (m, 12 H, 3 × CH_2CH_2), 2.28 (Ar*Me*), 3.35 (d, *J* 7 Hz, CH_2Ar), 3.47 (OMe), 3.6 (OMe), 3.95 (br, OH), 3.97 (dd, *J* 11 and 2 Hz, CHBr), 4.91 (OCH_2O), 5.1 (OCH_2O), 5.4–5.15 (m, 3 H, 3 × =CH), 6.68 (d, *J* 3 Hz, ArH), and 6.72 (d, *J* 3 Hz, ArH); δ_C 15.5 (q), 15.7 (q), 15.9 (q), 16.9 (q), 25.9 (q), 26.2 (q), 26.3 (t), 26.3 (t), 28.4 (t), 31.7 (t), 37.8 (t), 39.3 (t), 39.4 (t), 55.4 (t), 56.8 (q), 69.5 (d), 72.0 (s), 94.3 (t), 99.2 (t), 115.0 (d), 115.7 (d), 122.4 (d), 124.0 (d), 125.6 (d), 131.6 (s), 132.6 (s), 134.3 (s), 135.3 (s), 135.9 (s), 148.7 (s), and 153.2 (s); *m/z* 582 (6%, M^+, $C_{31}H_{49}{}^{81}BrO_5$), 580 (6, M^+, $C_{31}H_{49}{}^{79}BrO_5$), 500 (3, $C_{31}H_{48}O_5$, M − HBr), 137 (26), 135 (25), 109 (20), 107 (20), 95 (29), 81 (100), 69 (59), and 55 (44).

(E,E,E)-1-[2,5-*Bis*(*methoxymethoxy*)-3-*methylphenyl*]-14S*,15-*epoxy*-3,7,11,15-*tetramethylhexadeca*-2,6,10-*triene* (**36**).—A solution of the bromohydrin (**37**) (2.02 g, 3.47 mmol) in dry methanol (40 ml) was stirred with anhydrous potassium carbonate powder (3.47 g, 25 mmol) under nitrogen at room temperature for 16 h. The mixture was poured into water (50 ml) and extracted with light petroleum (4 × 50 ml). The combined extracts were washed successively with water (50 ml) and brine (50 ml), then dried and evaporated to leave a straw-coloured oil. Purification by chromatography upon silica gel with 50% diethyl ether in light petroleum as eluant gave the epoxide (**36**) (1.68 g, 97%) as a pale straw-coloured oil, λ_{max}(EtOH) 279 nm (1 680); ν_{max}(film) 2 905, 1 590, 1 155, 1 030, and 975 cm^{-1}; δ_H 1.26 (C*Me*Me), 1.3 (CMe*Me*), 1.58 (d, *J* 0.5 Hz, =CMe), 1.61 (d, *J* 1 Hz, =CMe), 1.7 (d, *J* 1 Hz, =CMe), 2.25–1.5 (m, 12 H, 3 × CH_2CH_2), 2.28 (Ar*Me*), 2.7 (t, *J* 6 Hz, OCH), 3.35 (d, *J* 7 Hz, CH_2Ar), 3.47 (OMe), 3.6 (OMe), 4.91 (OCH_2O), 5.1 (OCH_2O), 5.2–5.05 (m, 2 H, 2 × =CH), 5.29 (t, *J* 7 Hz, =C*H*CH_2Ar), 6.68 (d, *J* 3 Hz, ArH), and 6.72 (d, *J* 3 Hz, ArH); δ_C 16.0 (q), 16.0 (q), 16.2 (q), 17.2 (q), 18.8 (q), 24.9 (q), 26.6 (t), 26.6 (t), 27.5 (t), 28.6 (t), 36.3 (t), 39.6 (t), 39.7 (t), 55.9 (q), 57.3 (q), 58.3 (s), 64.1 (d), 94.7 (t), 99.6 (t), 115.4 (d), 116.0 (d), 122.6 (d), 124.2 (d), 124.9 (d), 132.1 (s), 133.9 (s), 134.9 (s), 135.8 (s), 136.5 (s), 149 (s), and 153.5 (s); *m/z* 500 (22%, M^+, $C_{31}H_{48}O_5$), 189 (41), 181 (39), 137 (38), 135 (38), 95 (32), 86 (36), 84 (59), 81 (100), 71 (52), and 69 (49).

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