Rotenoid Synthesis by Wadsworth–Emmons Coupling and Mukaiyama Cyclisation: Application to 5-Thiorotenoids

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A new synthesis of general applicability to rotenoid structures is described, though its specific objectives were 5-thiorotenoids. The synthons carrying the A/B- and the B/C-ring components are coupled by Wadsworth–Emmons synthesis and the ring B chromene is formed by Mukaiyama directed aldol cyclisation: Michael addition completes the formation of the rotenoid at its correct oxidation state and in its stable *cis*-form. Examples with, and without 2,3-dimethoxylation in ring A are described.

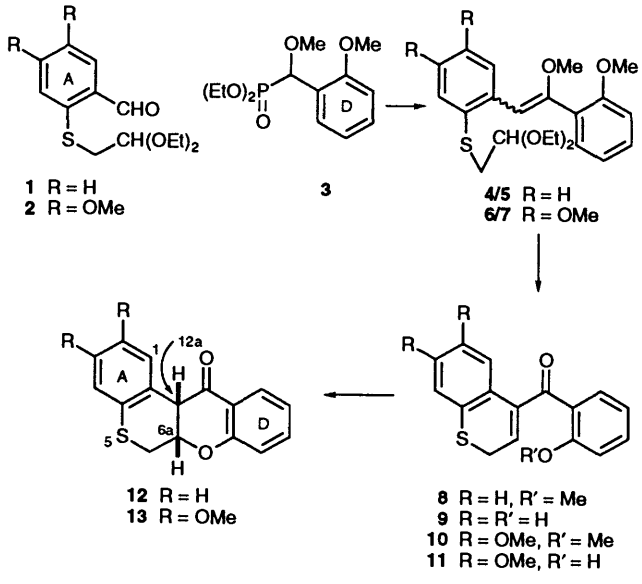
As will be apparent from the preceding paper,[1] some of the existing rotenoid syntheses have limitations in terms of their ability to accommodate different substitution patterns, and in terms of yield. Our aim in that paper was to prepare suitable rotenoids in order to examine the significance of oxygen substitution on the rotenoid core in disrupting the electron-transport chain of the blowfly flight muscle, as assessed by a submitochondrial particle test. Thio-Claisen rearrangements[2] are still less easy to perform than those of the oxygen type, and in this paper, in order to provide 5-thiorotenoid modulations, we have developed a new rotenoid synthesis capable of handling considerable structural variety.[3] The synthesis employs Wadsworth–Emmons coupling, and cyclisation by intramolecular Mukaiyama-type reaction.[4,5] Unlike many rotenoid syntheses the final rotenoid emerges at the correct oxidation level, thereby avoiding the extra steps necessary when a 6a,12a-didehydrorotenoid is the cyclisation product.

Results and Discussion

Our first requirement was for the sulfur-containing aldehydo acetal **1**. To this end *o*-bromothiophenol was alkylated[6] with bromoacetaldehyde diethyl acetal to form compound **14**, and the intention was to effect formylation with *N*,*N*-dimethylformamide (DMF)[7] after halogen–lithium exchange. However, a number of attempts failed, including trapping of the intermediate aryl anion with methyl iodide at low temperature, because of rapid intramolecular proton abstraction with elimination of ethoxide anion, forming the vinyl sulfide **15**. A different route was more successful. 2-Thiosalicylic acid was reduced with lithium aluminium hydride in diethyl ether[8] to form the benzylic alcohol (91%), which was treated with one mole equivalent of sodium hydride in DMF and then alkylated with bromoacetaldehyde diethyl acetal. This procedure was very selective for the more acidic thiol group, and gave the acetal **16** in good yield (82%). The alcohol was now oxidised under Swern conditions[9] to give the desired aldehyde **1** in 95% yield.

The phosphonate reagent **3** carrying the D-ring was made from salicylaldehyde methyl ether which was converted (80%) into its acetal **17** by treatment with triethyl orthoformate in the presence of toluene-*p*-sulfonic acid (PTSA). Treatment with triethyl phosphite[10] in the presence of boron trifluoride–diethyl ether then gave the phosphonate **3** in 99% yield.

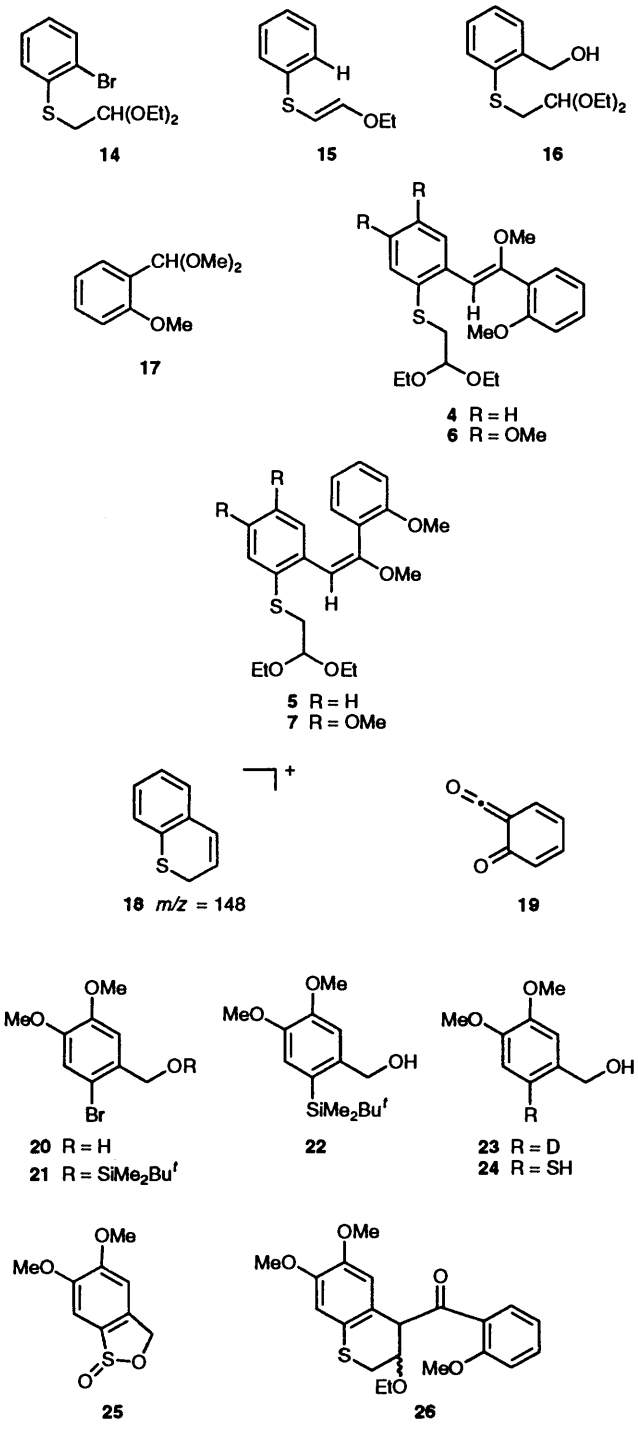
The phosphonate **3** was converted into its anion by treatment with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) and was then treated with the aldehyde **1**. Monitoring showed no reaction at room temperature, but on refluxing for several hours a slow reaction was noted. The solvent was therefore changed to the higher boiling 1,2-dimethoxyethane (DME). Refluxing in this solvent for 24 h effected complete reaction and on work-up a mixture (1:2) of the (*Z*)- and (*E*)-enol ethers, **4** and **5** respectively, was isolated in 50% yield. The two isomers were separated by HPLC and their geometries were assigned by NOE difference spectra. The aryl methoxy groups in isomers **4** and **5** appeared at lower field (δ 3.86 and 3.89, respectively) than did the enol ether methyl groups (δ 3.60 and 3.52 respectively). The (*Z*)-form **4** showed an NOE enhancement between the aromatic methoxy methyl and the olefinic 7-H but no enhancement as between this proton and the enolic methoxy methyl. The (*E*)-form **5** showed an NOE between 7-H and the enolic methoxy methyl, but not between the aromatic methoxy methyl and this proton. For quantitation purposes the ratio of the integrals for the vinyl protons was used [the (*Z*)-proton resonates at δ 6.23, the (*E*)- at δ 6.27].



Scheme 1 The general rotenoid synthesis, as applied to 5-thiorotenoids

The stereochemistry of the enol ether component is not important for the Mukaiyama reaction, and a mixture of unseparated geometrical isomers **4**/**5** was therefore used, the enol ethers being added to titanium tetrachloride in methylene dichloride at −78 °C. The intermediate β-ethyl ether was not isolated, but elimination was carried out directly by heating with methanolic hydrochloric acid to give the thiochromene **8** in 52% overall yield. Demethylation[11] of the methyl ether with boron tribromide in methylene dichloride at −78 °C gave the desired phenol **9** (58%), showing the expected chelated hydroxy group at δ 12.05 in the NMR spectrum. Cyclisation of ring C

was effected by refluxing with saturated aq. sodium acetate in ethanol to give the new thiorotenoid **12**, m.p. 128–129 °C (Scheme 1). In the mass spectrum it showed a retro-Diels–Alder cleavage[12] giving species **18** and **19** and the carbonyl stretching in the IR spectrum was at 1695 cm^{-1} as expected. ^1H and ^{13}C NMR spectra were fully assigned with the aid of COSY and hetero-COSY spectra, along with specific decoupling experiments. A coupling constant of 4 Hz between the protons at C-6a and C-12a demonstrated the thermodynamically stable *cis*-fusion, just as in the case of its oxygen analogue.



For comparison of its biological activities with those of its oxygen analogue, the 2,3-dimethoxy-5-thiorotenoid **13** was also required. The aldehyde **2** was therefore needed and our starting point was 3,4-dimethoxybenzaldehyde, which was brominated (74%) and then reduced in effectively quantitative yield to give the alcohol **20**. The alcohol function was protected (95%) (silyl ether **21**) by using *tert*-butyldimethylsilyl (TBDMS) chloride and imidazole in THF. As a preliminary, a test was made to see if halogen–lithium exchange occurred satisfactorily on treatment with butyllithium in THF, but it was found that, after quenching with water, migration of the TBDMS grouping onto the aromatic ring had occurred, giving the alcohol **22**. It was therefore decided to dispense with protection and to use 2 mol equiv. of butyllithium. We were encouraged when bromo alcohol **20** was quenched with D_2O to give the ring-deuteriated product **23**, though the anion failed to react with elemental sulfur. The experiment was therefore repeated, with quenching with sulfur dioxide at −78 °C, when the crystalline γ-sultine **25**[13] was obtained in 73% yield. Reduction of the latter with lithium aluminium hydride in THF at 0 °C then gave the thiol **24** (93%). The thiol was selectively alkylated at the thiol group by using bromoacetaldehyde diethyl acetal and sodium hydride in DMF to give the 4,5-dimethoxy analogue of compound **16** (81%). As before, this was oxidised (59%) to the aldehyde **2** under Swern conditions.

Under conditions similar to those mentioned above, a Wadsworth–Emmons reaction was carried out between substrates **2** and **3**. Reflux for several hours was required to complete the reaction, and a mixture of the two geometrical isomers **6** and **7** was obtained in 64% yield. The isomers could be separated by HPLC and the *Z*- and *E*-geometries were again assigned by using NOE difference spectroscopy. Mukaiyama reactions under the usual conditions, with 1 mol equiv. of titanium tetrachloride, produced a mixture of the β-ethyl ether **26** and the thiochromene **10** (45%). As it was suspected that the *ortho* methoxy groups on ring A might be acting as a bidentate ligand and to be complexing with the Lewis acid, the amount of titanium tetrachloride was increased to 2 mol equiv. Although the reaction products **10** and **26** could be separated, this was not done (for yield purposes) and the mixture was treated with acidic methanol to complete elimination and to give the thiochromene **10** in 53% overall yield.

Since direction of attack is affected by the neighbouring carbonyl group, it is possible selectively to demethylate the 2'-methoxy group in the presence of other methoxy groups. Thus one mole equivalent of boron tribromide at −78 °C gave the alcohol **11**, which was not isolated but was refluxed with sodium acetate to give the desired 2,3-dimethoxylated thiorotenoid **13** as yellow needles in 27% overall yield. It showed the expected Diels–Alder fragmentation and had ν_{max} 1687 cm^{-1}. As expected it belongs to the stable *cis*-series ($J_{6a,12a}$ 4.1 Hz) with the C-1 proton resonating at δ 6.62. ^1H and ^{13}C NMR assignments were aided by proton–proton connectivity (COSY) and ^1H–^{13}C connectivity (hetero-COSY) experiments.

This new and flexible synthetic approach to 5-thiorotenoids should be of general applicability to the synthesis of rotenoids, both synthetic and natural. In 5-oxorotenoids, when ring A is heavily oxygenated, the nucleophilicity of the phenolate anion which is to be reacted with bromoacetaldehyde diethyl acetal is diminished and this might cause difficulty in some situations. If necessary it can be overcome by alkylation with the more reactive allyl bromide, followed by standard degradation to form the two-carbon aldehyde fragment.[14]

Experimental

For general experimental conditions see preceding paper.

Diethyl Acetal **14**.—2-Bromothiophenol (8.00 g, 5.09 cm^3, 42 mmol) was added dropwise to a stirred suspension of sodium hydride (1.04 g, 43 mmol; from 60% suspension in mineral oil) in dry DMF (200 cm^3) under nitrogen. The mixture was stirred

(1 h) at room temperature, when bromoacetaldehyde diethyl acetal (8.47 g, 6.47 cm^3, 43 mmol) was added, and the mixture was stirred overnight. Water was added and the product was recovered by extraction with diethyl ether. The extracts were washed, dried ($MgSO_4$), and evaporated to give the *diethyl acetal* **14** (11.94 g, 84%). A portion was purified by bulb-to-bulb distillation (110 °C, 1 mmHg) (Found: M^+, 304.013. $C_{12}H_{17}BrO_2S$ requires M, 304.013); δ_H(400 MHz; $CDCl_3$) 1.21 (6 H, t, *J* 7, 2 × Me), 3.38 (2 H, d, *J* 5, SCH_2), 3.62 (4 H, m, 2 × OCH_2), 4.66 [1 H, t, *J* 5, C*H*$(OEt)_2$], 6.98 (1 H, m, 4-H), 7.17 (1 H, m, 5-H), 7.35 (1 H, dd, *J* 8 and 1.5, 6-H) and 7.50 (1 H, dd, *J* 8 and 1.5, 3-H); *m/z* (EI, +ve) 306 (2%, M^+), 304 (2.5, M^+), 261 (4, $M^+ - C_2H_5O$), 260 (3, $M^+ - C_2H_5OH$), 259 (4, $M^+ - C_2H_5O$), 258 (4, $M^+ - C_2H_5OH$), 180 (3, $M^+ - C_2H_5BrO$) and 103 [100, $^+CH(OC_2H_5)_2$].

Vinyl Ether **15**.—Butyllithium in hexane (1.6 mol dm^{-3}; 0.95 cm^3, 1.52 mmol) was added dropwise under nitrogen to a solution of the diethyl acetal **14** (0.5 g, 1.52 mmol) in dry THF (10 cm^3) at −78 °C, the mixture then being stirred at that temperature for another 30 min. Methyl iodide (0.216 g, 95 mm^3, 1.52 mmol) was added and the mixture was stirred at −78 °C for 30 min, then was allowed to warm to room temperature and was stirred for a further 1 h. Water was added, and the mixture was worked up with diethyl ether in the usual way to give the *vinyl ether* **15** (249 mg, 91%) (Found: M^+, 180.060. $C_{10}H_{12}OS$ requires M, 180.061); δ_H(60 MHz; $CDCl_3$) 1.31 (3 H, t, *J* 7, Me), 3.92 (2 H, q, *J* 7, OCH_2), 5.44 (1 H, d, *J* 12, SCH=), 6.82 (1 H, d, *J* 12, OCH=) and 7.00–7.50 (5 H, m, Ph); *m/z* (EI, +ve) 180 (100%, M^+) and 123 (63, $M^+ - C_3H_5O$).

Thio Hydroxy Acetal **16**.—A solution of 2-thiosalicylic acid (21. 8 g, 142 mmol) in dry diethyl ether (1 dm^3) was added dropwise to a suspension of lithium aluminium hydride (10 g) in diethyl ether (120 cm^3) at 0 °C under nitrogen. After being stirred (1.5 h) the mixture was decomposed with water, then with 10% sulfuric acid. The organic layer was washed successively with aq. sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated to give a red oil. Hexane was added and the resulting solid was filtered off, washed with hexane, and dried over P_2O_5 *in vacuo* to give *o*-mercaptobenzyl alcohol (18.0 g, 91%) as a yellow solid, m.p. 30–31 °C (lit.,[8] 31–32 °C); ν_{max}(mull)/cm^{-1} 3260s br (OH), 2520m (SH), 1580m and 1560m (aromatics); δ_H(60 MHz; $CDCl_3$) 3.40 (1 H, br s, OH), 2.70 (2 H, s, CH_2) and 7.0–7.4 (4 H, 4 × ArH).

A solution of the mercaptobenzyl alcohol (18 g, 129 mmol) in dry DMF (30 cm^3) was added to a stirred suspension of sodium hydride (3.10 g, 129 mmol; from 60% dispersion) in dry DMF (400 cm^3) under nitrogen. After 45 min, bromoacetaldehyde diethyl acetal (25.4 g, 19.4 cm^3, 129 mmol) was added dropwise and the solution was kept overnight, after which it was poured into water and worked up by extraction with diethyl ether. The extract was washed (water then brine) and evaporated, and then taken up in hexane, again washed (water then brine), dried ($MgSO_4$), and evaporated to give the *acetal* **16** (27.18 g, 82%) (Found: M^+, 256.112. $C_{13}H_{20}O_3S$ requires M, 256.113); ν_{max}(film)/cm^{-1} 3440s br (OH) and 1590m (aromatic); δ_H(250 MHz; $CDCl_3$) 1.18 (6 H, t, *J* 7, 2 × Me), 3.11 (2 H, d, *J* 6, SCH_2), 3.30–3.75 (5 H, m, OH and 2 × OCH_2), 4.58 (1 H, t, *J* 6, CH), 4.79 (2 H, d, *J* 7, CH_2OH), 7.20–7.33 (2 H, m, 2 × ArH), 7.35–7.42 (1 H, m, ArH) and 7.45–7.53 (1 H, m, ArH); *m/z* (EI, +ve) 256 (3%, M^+), 136 (18, $C_8H_8S^+$), 135 (25, $C_8H_7S^+$), 103 [100, $CH(OC_2H_5)_2^+$], 77 (17, $C_6H_5^+$), 75 (51, $C_3H_7O_2^+$) and 59 (12, $C_3H_7O^+$).

Aldehydo Acetal **1**.—Oxalyl dichloride (3.0 cm^3, 33 mmol) was added to cooled, dry methylene dichloride (75 cm^3) under nitrogen. Dimethyl sulfoxide (DMSO) (5.1 cm^3, 66 mmol) as a solution in methylene dichloride (15 cm^3) was added to the former, stirred solution at −60 °C. The mixture was stirred for a further 2 min, when a solution of the hydroxy acetal **16** (7.94 g, 31 mmol) in methylene dichloride (30 cm^3) was added over a period of 3 min, the mixture being stirred for another 15 min. Triethylamine (21 cm^3, 150 mmol) was then added and the solution was stirred at −60 °C for 5 min and was then allowed to attain room temperature. Water was added, and the organic phase was separated, the aqueous phase being further extracted with methylene dichloride. The organic phases were united, washed (brine), dried ($MgSO_4$), and evaporated to give *aldehyde* **1** (7.94 g, 95%) (Found: M^+, 254.100. $C_{13}H_{18}O_3S$ requires M 254.098); ν_{max}(film)/cm^{-1} 1690s (CO) and 1590s (aromatic); δ_H(60 MHz; $CDCl_3$) 1.17 (6 H, t, *J* 7, 2 × Me), 3.19 (2 H, d, *J* 6, SCH_2), 3.30–4.00 (4 H, m, 2 × OCH_2), 4.58 [1 H, t, *J* 6, C*H*$(OEt)_2$], 7.00–7.59 (3 H, m, 3 × ArH), 7.61 (1 H, dd, *J* 6, 1, 6-H) and 10.50 (1 H, s, CHO); *m/z* (EI, +ve) 254 (1%, M^+), 137 (37, $C_7H_5OS^+$), 136 (12, $C_7H_4OS^+$), 103 [100, $^+CH(OC_2H_5)_2$] and 75 (66, $C_3H_7O_2^+$).

The Diethyl Phosphonate **3**.—*o*-Anisaldehyde dimethyl acetal was prepared (80%) by a literature method[15] from anisaldehyde and triethyl orthoformate. A mixture of the acetal (12 g, 66 mmol) and triethyl phosphite (10.96 g, 11.3 cm^3, 66 mmol) in dry methylene dichloride (120 cm^3) was treated with boron trifluoride–diethyl ether (9.84 g, 7.94 cm^3, 69.3 mmol), added dropwise under nitrogen at −20 °C. The mixture was allowed to attain room temperature and was stirred overnight, after which water was added. The organic layer was separated, dried ($MgSO_4$), and evaporated. The oil was dissolved in chloroform and chromatographed on silica gel, with ethyl acetate–chloroform (1:4) as eluent, to give the *diethyl phosphonate* **3** (18.83 g, 99%) as a pale oil (Found: M^+, 288.114. $C_{13}H_{21}O_5P$ requires M, 288.113); ν_{max}(film)/cm^{-1} 1605m (aromatic), 1250s (PO) and 1030s (POEt); δ_H(60 MHz; $CDCl_3$) 1.23 (6 H, dt, *J* 6 and 6, 2 × Me), 3.30 (3 H, s, OMe), 3.78 (3 H, s, OMe), 4.00 (4 H, m, 2 × OCH_2), 5.01 (1 H, d, *J* 14, CH) and 6.48–7.44 (4 H, m, 4 × ArH); *m/z* (EI, +ve) 288 (1%, M^+), 151 (100, $C_9H_{11}O_2^+$), 91 (6, $C_7H_7^+$) and 45 (39, $C_2H_5O^+$).

The (Z)- *and* (E)-*Enol Ethers* **4** *and* **5**.—Diisopropylamine (1.75 g, 2.43 cm^3, 17.4 mmol) was added to dry DME (2 cm^3) at −70 °C under nitrogen, followed by butyllithium (1.15 mol dm^{-3} in hexane; 15.1 cm^3, 17.4 mmol) added dropwise. The mixture was allowed to warm to room temperature and was then again cooled to −70 °C, when a solution of the diethyl phosphonate **3** (5.00 g, 17.4 mmol) in DME (50 cm^3) was added dropwise and the mixture was stirred at −70 °C for 20 min. A solution of the aldehyde **1** (4.41 g, 17.4 mmol) in DME (30 cm^3) was added dropwise and the mixture was stirred at −70 °C for 10 min and was then allowed to attain room temperature. The mixture was finally heated under reflux in nitrogen for 24 h, poured into water, and extracted with diethyl ether. The extracts were washed with water, dried ($MgSO_4$), and evaporated. The resulting oil was chromatographed on dry column silica, with hexane–ethyl acetate (9:1) as eluent, to give a mixture of (*Z*)- and (*E*)-enol ethers **4**/**5** (3.40 g, 50%). This was separated by preparative HPLC on silica, with hexane–ethyl acetate (4:1) as eluent. The (*Z*)-*enol ether* **4** (t_R 8 min 25 s) was an oil (Found: M^+, 388.168. $C_{22}H_{28}O_5S$ requires M, 388.171); λ_{max}(EtOH)/nm 212, 258 and 280 (ε 12 900, 7430 and 7920); ν_{max}(film)/cm^{-1} 1630s (C=C), 1590s and 1580s (aromatics); δ_H(250 MHz; $CDCl_3$) 1.21 (6 H, t, *J* 7, 2 × Me), 3.16 (2 H, d, *J* 6, SCH_2), 3.60 (3 H, s, vinyl OMe), 3.62 (4 H, m, 2 × OCH_2), 3.86 (3 H, s, Ar-O*Me*), 4.70 [1 H, t, *J* 6, C*H*$(OEt)_2$], 6.23 (1 H, s, vinyl) and 6.60–7.60 (8 H, m, 8 × ArH); *m/z* (EI, +ve) 388 (9%, M^+) and 103 [100, $^+CH(OC_2H_5)_2$]. The (E)-*enol ether* **5** (t_R 9 min 15 s)

also was an oil. (Found: M^+, 388.170); λ_{max}(EtOH)/nm 212, 266 and 290 (ε 15 000, 10 400 and 11 900); ν_{max}(film)/cm^{-1} 1635s (C=C), 1600s and 1575s (aromatics); δ_H(250 MHz; $CDCl_3$) 1.16 (6 H, t, *J* 7, 2 × Me), 3.07 (2 H, d, *J* 6, SCH_2), 3.52 (3 H, s, vinyl OMe), 3.53 (4 H, m, 2 × OCH_2), 3.89 (3 H, s, Ar-O*Me*), 4.58 [1 H, t, *J* 6, C*H*$(OEt)_2$], 6.27 (1 H, s, vinyl), 6.90–7.50 (7 H, m, 7 × ArH) and 8.14 (1 H, dd, *J* 8 and 1, 5-H); *m/z* (EI, +ve) 388 (12%, M^+) and 103 [100, $^+CH(OC_2H_5)_2$].

4-(o-*Methoxybenzoyl*)-2H-*thiochromene* **8**.—A solution of the mixed enol ethers **4**/**5** (3.16 g, 8.12 mmol) in dry methylene dichloride (40 cm^3) was added to a solution of titanium tetrachloride (8.9 mmol) in methylene dichloride (40 cm^3) at −78 °C under nitrogen and the mixture was stirred at that temperature for 30 min. Saturated brine was added to quench the reaction and the organic layer was separated, and washed successively with aq. sodium hydrogen carbonate, water, and brine, dried ($MgSO_4$), and evaporated to give an oil. The latter was dissolved in methanol (20 cm^3) containing 10 drops of conc. hydrochloric acid and the solution was heated under reflux for 2 h. The product was poured into water and extracted with chloroform. After being washed and dried as before, the extract was evaporated and was then chromatographed on dry silica, with hexane–ethyl acetate (9:1) as eluent, to give the *title thiochromene* **8** (1.19 g, 52%) as an oil (Found: M^+, 282.070. $C_{17}H_{14}O_2S$ requires M, 282.071); λ_{max}(EtOH)/nm 199 and 240 (ε 29 800 and 18 900); ν_{max}(film)/cm^{-1} 1660s (CO) and 1600s (aromatic); δ_H(250 MHz; $CDCl_3$) 3.40 (2 H, d, *J* 6, SCH_2), 3.60 (3 H, s, OMe), 6.54 (1 H, d, *J* 6, CH_2CH) and 6.80–7.70 (8 H, 8 × ArH); δ_C(100 MHz; $CDCl_3$)* 25.1 (CH_2, C-6), 55.4 (CH_3, OMe), 111.7 (CH, C-8), 120.6 (CH, C-10), 125.5 (CH, C-2), 127.1 (CH, C-3), 127.5 (CH, C-11), 128.1 (CH, C-4), 128.6 (C, C-11a), 129.8 (CH, C-1), 130.5 (CH, C-9), 131.6 (C, C-4a), 133.1 (CH, C-6a), 133.7 (C, C-12b), 142.4 (C, C-12a), 158.2 (C, C-7a) and 195.9 (C, C-12); *m/z* (EI, +ve) 282 (41%, M^+), 147 (67, $C_9H_7S^+$) and 135 (100, $C_8H_7O_2^+$).

4-(o-*Hydroxybenzoyl*)-2H-*thiochromene* **9**.—A solution of boron tribromide in methylene dichloride (1.0 mol dm^{-3}; 0.85 cm^3) was added dropwise to a solution of the methoxy compound **8** (217 mg, 0.77 mmol) in dry methylene dichloride (5 cm^3) at −78 °C under nitrogen. After being stirred at −78 °C (5 min) the reaction mixture was evaporated to dryness under reduced pressure at 20 °C. Methanol (5 cm^3) and water (5 cm^3) were added and the mixture was heated under reflux for 2 h. The product was extracted with chloroform and the extracts were washed successively with aq. sodium hydrogen carbonate, water, and brine, and were then dried ($MgSO_4$) and evaporated. Chromatography on flash silica [hexane–ethyl acetate (9:1) as eluent] gave 4-(o-*hydroxybenzoyl*)-2H-*thiochromene* **9** (119 mg, 58%) (Found: M^+, 268.056. $C_{16}H_{12}O_2S$ requires M, 268.056); ν_{max}(film)/cm^{-1} 3060s br (chelated OH) and 1630s br (chelated CO); δ_H(250 MHz; $CDCl_3$) 3.55 (2 H, d, *J* 6, SCH_2), 6.27 (1 H, t, *J* 6, CH_2CH), 6.70–7.60 (8 H, m, ArH) and 12.05 (1 H, s, chelated OH); δ_C(100 MHz; $CDCl_3$)* 24.5 (CH_2, C-6), 118.3 (CH, C-8), 118.9 (CH, C-10), 119.2 (C, C-11a), 125.2 (CH, C-2), 126.0 (CH, C-3), 126.7 (CH, C-4), 128.0 (CH, C-1), 128.8 (CH, C-11), 130.8 (C, C-4a), 132.7 (C, C-12b), 133.3 (CH, C-9), 136.9 (CH, C-6a), 139.5 (C, C-12a), 163.3 (C, C-7a) and 202.3 (C, C-12); *m/z* (EI, +ve) 268 (49%, M^+), 267 (11, $M^+ - H$), 266 (39, $M^+ - H_2$), 237 (100), 147 (65, $C_9H_7S^+$) and 121 (76, $C_7H_5O_2^+$).

6a,12a-*Dihydro*-5-*thiorotoxen*-12(6H)-*one* **12**.—The thiochromene **9** (above) (83 mg, 0.31 mmol) was dissolved in a saturated solution of sodium acetate in ethanol (10 cm^3) and the solution was refluxed for 4 h. The mixture was poured into water and the product was extracted with ethyl acetate. After washing, drying ($MgSO_4$), and evaporation, the resulting oil was chromatographed on flash silica, with hexane–ethyl acetate (10:1) as eluent to give the title 5-*thiorotenoid* **12** (65 mg, 78%), m.p. 128–129 °C (from $CHCl_3$–MeOH) (Found: C, 71.6; H, 4.5%; M^+, 268.057. $C_{16}H_{12}O_2S$ requires C, 71.6; H, 4.5%; M, 268.056); λ_{max}(EtOH)/nm 213, 253 and 322 (ε 35 600, 19 500 and 2900); ν_{max}(mull)/cm^{-1} 1695 (CO) and 1610s (aromatic); δ_H(250 MHz; $CDCl_3$) 3.28 (1 H, ddd, *J* 13, 4 and 1, 6-H[a]), 3.41 (1 H, dd, *J* 13 and 7, 6-H[b]), 3.99 (1 H, d, *J* 4, 12a-H), 5.23 (1 H, m, 6a-H), 6.90–7.20 (6 H, m, 6 × ArH), 7.43–7.52 (1 H, m, ArH) and 7.93 (1 H, dd, *J* 8 and 2, 11-H); δ_C(100 MHz; $CDCl_3$) 28.5 (CH, C-12a), 49.7 (CH_2, C-6), 73.6 (CH, C-6a), 118.1 (CH, C-8), 119.6 (C, C-11a), 122.0 (CH, C-10), 124.9 (CH, C-2), 126.5 (C, C-4a), 126.8 (CH, C-3), 127.8 (CH, C-4), 128.1 (CH, C-1), 130.9 (CH, C-11), 131.7 (C, C-12b), 136.6 (CH, C-9), 160.0 (C, C-7a) and 191.2 (C, C-12); *m/z* (EI, +ve) 268 (26%, M^+), 148 (61, $C_9H_8S^+$), 147 (100, $C_9H_7S^+$) and 121 (10, $C_7H_5O_2^+$).

2-*Bromo*-4,5-*dimethoxybenzyl Alcohol* **20**.—A solution of 3,4-dimethoxybenzaldehyde (50 g, 300 mmol) in glacial acetic acid (120 cm^3) was treated with a solution of bromine (15 cm^3, 46.5 g, 300 mmol) in glacial acetic acid (20 cm^3). Work-up and crystallisation from aq. methanol, gave 2-bromo-4,5-dimethoxybenzaldehyde (54.82 g, 74%), m.p. 148.5 °C (lit.,[16] 149 °C).

Sodium borohydride (700 mg, 18.4 mmol) was added portionwise to a stirred suspension of 2-bromo-4,5-dimethoxybenzaldehyde (4.52 g, 18.4 mmol) in methanol (1000 cm^3), cooled in ice. When effervescence ceased, the mixture was poured into water, extracted with chloroform, and worked up to give the title alcohol **20** (4.59 g, 100%), m.p. 97–98 °C (lit.,[16] 88–91 °C); ν_{max}(mull)/cm^{-1} 3500s (OH), 1610s and 1510s (aromatics); δ_H(250 MHz; $CDCl_3$) 1.97 (1 H, t, *J* 6, OH), 3.88 (3 H, s, OMe), 3.89 (3 H, s, OMe), 4.69 (2 H, d, *J* 6, CH_2OH), 7.01 (1 H, s, 6-H) and 7.02 (1 H, s, 3-H).

tert-*Butyldimethylsilyl Ether of* 2-*Bromo*-4,5-*dimethoxybenzyl Alcohol, Compound* **21**.—The alcohol **20** (680 mg, 2.75 mmol) imidazole (0.56 g, 8.25 mmol), *tert*-butyldimethylsilyl chloride (0.50 g, 3.30 mmol) and dry DMF (2 cm^3) were stirred overnight at room temperature under nitrogen. The product was poured into water, extracted with hexane, and worked up to give the *silyl ether* **21** (943 mg, 95%) as an oil. A sample was prepared for analysis by bulb-to-bulb distillation (200 °C/1 mmHg) (Found: M^+, 362.069. $C_{15}H_{25}BrO_3Si$ requires M, 362.074); δ_H(250 MHz; $CDCl_3$) 0.17 (6 H, s, $SiMe_2$), 1.01 (9 H, s, CMe_3), 3.90 (3 H, s, OMe), 3.92 (3 H, s, OMe), 4.71 (2 H, s, CH_2), 7.02 (1 H, s, 6-H) and 7.17 (1 H, s, 3-H); *m/z* (EI, +ve) 362 (1%, M^+), 305 (44, $M^+ - C_4H_9$) and 229 (100, $C_9H_{10}BrO_2^+$).

2-(tert-*Butyldimethylsilyl*)-4,5-*dimethoxybenzyl Alcohol* **22**.—Butyllithium (1.6 mol dm^{-3} in hexane; 1.33 cm^3, 2.12 mmol) was added to a solution of the *tert*-butyldimethylsilyl ether **21** (697 mg, 1.93 mmol) in dry THF (10 cm^3) at −78 °C under nitrogen. The mixture was allowed to warm to room temperature and was stirred for 30 min, when it was poured into water and extracted with diethyl ether. The extract was washed, dried ($MgSO_4$), and evaporated, and was then chromatographed on dry silica and eluted with hexane–ethyl acetate (2:1) to give the C-*silyl alcohol* **22** (448 mg, 82%) (Found: M^+, 282.164. $C_{15}H_{26}O_3Si$ requires M, 282.165); ν_{max}(film)/cm^{-1} 3500s br (OH), 1600s, 1570m and 1510s (aromatics); δ_H(250 MHz; $CDCl_3$) 0.36 (6 H, s, $SiMe_2$), 0.88 (9 H, s, CMe_3), 3.88 (3 H, s, OMe), 3.91 (3 H, s, OMe), 4.68 (2 H, CH_2), 6.95 (1 H, s, ArH) and 7.08 (1 H, s, ArH); *m/z* (EI,

* Locants refer to rotenoid numbering (see structures **12**, **13**).

+ve) 282 (4%, M^+), 225 (100, $M^+ - C_4H_9$) and 207 (47, $C_{11}H_{15}O_2Si^+$).

2-Deuterio-4,5-dimethoxybenzyl Alcohol **23**.—A solution of 2-bromo-4,5-dimethoxybenzyl alcohol **20** (234 mg, 0.947 mmol) in dry THF (10 cm^3) was treated under nitrogen with butyllithium (1.6 mol dm^{-3} in hexane; 1.48 cm^3, 2.37 mmol) at −78 °C. After being stirred (15 min) the mixture was allowed to warm to room temperature and D_2O (0.5 cm^3, 25 mmol) was added. The product was poured into water and extracted with diethyl ether. Work-up gave an oil, which was chromatographed on flash column silica, with ethyl acetate–hexane (2:1) as eluent, to give 2-deuterio-4,5-dimethoxybenzyl alcohol **23** (160 mg, 100%); ν_{max}(film)/cm^{-1} 3410s br (OH), 1605s and 1505s (aromatic); δ_H(250 MHz; $CDCl_3$) 1.68 (1 H, s, OH), 3.89 (3 H, s, OMe), 3.90 (3 H, s, OMe), 4.63 (2 H, s, CH_2) and 6.80–7.00 (2 H, m, 2 × ArH); *m/z* (EI, +ve) 169 (100%, M^+) and 152 (27, $M^+ - OH$).

5,6-Dimethoxy-3H-benz[2,1]oxathiole S-Oxide **25**.—A solution of 2-bromo-4,5-dimethoxybenzyl alcohol **20** (24.7 g, 100 mmol) in dry THF (500 cm^3) was cooled to −78 °C under nitrogen and butyllithium (1.1 mol dm^{-3} in hexane; 200 cm^3, 220 mmol) was added dropwise. After being stirred (15 min), the mixture was allowed to warm to 0 °C, stirred for 15 min, and then cooled to −78 °C again. Excess of sulfur dioxide was bubbled through the mixture, which was then allowed to attain room temperature. The solvent was evaporated off and water (50 cm^3) and conc. hydrochloric acid (50 cm^3) were added, the mixture being stirred for 10 min and then extracted with methylene dichloride. Washing (aq. sodium hydrogen carbonate), drying ($MgSO_4$), and evaporation of the extracts gave the *title γ-sultine* **25** (15.65 g, 73%), m.p. 161 °C, as needles from ethanol (Found: C, 50.5; H, 4.8%; M^+, 214.030. $C_9H_{10}O_4S$ requires C, 50.45; 4.7%; M, 214.030); ν_{max}(KBr)/cm^{-1} 1605m, 1590m (aromatic) and 1050s (SO); δ_H(250 MHz; $CDCl_3$) 3.95 (6 H, s, 2 × OMe), 5.49 (1 H, d, *J* 13, CH^a), 5.94 (1 H, d, *J* 13, CH^b), 6.90 (1 H, s, 4-H) and 7.18 (1 H, s, 7-H); *m/z* (EI, +ve) 214 (76%, M^+) and 166 (100, $M^+ - SO$).

2-Mercapto-4,5-dimethoxybenzyl Alcohol **24**.—A solution of lithium aluminium hydride in THF (1.0 mol dm^{-3}; 50 cm^3, 50 mmol) was added dropwise to a solution of the γ-sultine **25** (5.00 g, 23.4 mmol) in THF (100 cm^3) at 0 °C under nitrogen and the mixture was then stirred for 1 h at room temperature. The reaction mixture was worked up in the usual way with 10% sulfuric acid, after removal of THF by evaporation under reduced pressure, and the product was extracted into methylene dichloride. The extracts were extracted into 2 mol dm^{-3} aq. sodium hydroxide, acidified with dil. hydrochloric acid, and re-extracted into methylene dichloride. Washing (water then brine), drying ($MgSo_4$), and evaporation then gave *2-mercapto-4,5-dimethoxybenzyl alcohol* **24** (4.68 g, 93%), m.p. 98 °C (Found: C, 54.3; H, 6.2%; M^+, 200.049. $C_9H_{12}O_3S$ requires C, 54.0; H, 6.0%; M, 200.051); ν_{max}(mull)/cm^{-1} 3200m br (OH), 2560w (SH), 1600m and 1505m (aromatic); δ_H(250 MHz; $CDCl_3$) 1.96 (1 H, t, *J* 6, OH), 3.51 (1 H, s, SH), 3.87 (6 H, s, 2 × OMe), 4.71 (2 H, d, *J* 6, CH_2), 6.90 (1 H, s, ArH) and 6.92 (1 H, s, ArH); *m/z* (EI, +ve), 200 (19%, M^+) and 182 (100, $M^+ - H_2O$).

Dimethoxy Acetal **2**.—A solution of 2-mercapto-4,5-dimethoxybenzyl alcohol **24** (3.96 g, 19.8 mmol) in dry DMF (10 cm^3) was added dropwise to sodium hydride (475 mg, 19.8 mmol, from washed 60% mineral oil suspension) in dry DMF (100 cm^3) under nitrogen, and was stirred for 30 min. Bromoacetaldehyde diethyl acetal (3.90 g, 2.98 cm^3, 19.8 mmol) was added dropwise, and the mixture was stirred overnight and then poured into water and extracted with diethyl ether. Work-up gave the *alcohol precursor to compound* **2** as an oil (5.04 g, 81%). A portion was prepared for analysis by chromatography on flash column silica, with hexane–ethyl acetate (7:3) as eluent (Found: M^+, 316.134. $C_{15}H_{24}O_5S$ requires M, 316.134); ν_{max}(film)/cm^{-1} 3460s br (OH), 1600s and 1500s (aromatic); δ_H(250 MHz; $CDCl_3$) 1.16 (6 H, t, *J* 7, 2 × Me), 3.02 (2 H, d, *J* 6, SCH_2), 3.30–3.60 (4 H, m, 2 × OCH_2Me), 3.89 (3 H, s, OMe), 3.90 (3 H, s, OMe), 4.52 [1 H, t, *J* 6, $CH(OEt)_2$], 4.76 (2 H, d, *J* 6, CH_2OH), 6.93 (1 H, s, ArH) and 7.06 (1 H, s, ArH); *m/z* (EI, +ve) 316 (10%, M^+), 103 [100, $CH(OEt)_2^+$] and 75 (53, $C_3H_7O_2^+$).

A solution of oxalyl dichloride (2.04 g, 1.40 cm^3, 16.1 mmol) in methylene dichloride (40 cm^3) was cooled to −78 °C under nitrogen, and a solution of DMSO (2.52 g, 2.29 cm^3, 32.2 mmol) in methylene dichloride (8 cm^3) was added dropwise, and the mixture was then stirred for 10 min at this temperature. A solution of the above alcohol (4.60 g, 14.6 mmol) in dry methylene dichloride (15 cm^3) was added dropwise and the mixture was stirred at −78 °C for 20 min. Triethylamine (7.37 g, 10.1 cm^3, 73 mmol) was then added, and the mixture was stirred for a further 20 min at −78 °C, and was then allowed to attain room temperature. Water was added and the reaction product was recovered by extraction with methylene dichloride. The extracts were washed successively with dil. hydrochloric acid, aqueous sodium hydrogen carbonate, water and brine, dried ($MgSO_4$), and evaporated. The oily product was chromatographed on dry column silica and eluted with hexane–ethyl acetate (5:1) to give the *4,5-dimethoxy acetal* **2** (2.97 g, 59%) (Found: C, 57.4; H, 7.4%; M^+, 314.119. $C_{15}H_{22}O_5S$ requires C, 57.3; H, 7.1%; M, 314.119); ν_{max}(film)/cm^{-1} 1680s (CO), 1590s and 1505s (aromatics); δ_H(400 MHz; $CDCl_3$) 1.15 (6 H, t, *J* 7, 2 × Me), 3.05 (2 H, d, *J* 5, SCH_2), 3.40–3.70 (4 H, m, 2 × OCH_2), 3.90 (3 H, s, OMe), 3.94 (3 H, s, OMe), 4.57 [1 H, t, *J* 5, $CH(OEt)_2$], 7.07 (1 H, s, 6-H), 7.37 (1 H, s, 3-H) and 10.50 (1 H, s, CHO); *m/z* (EI, +ve) 314 (6%, M^+), 197 (26, $C_9H_9O_3S^+$), 103 [100, $CH(OC_2H_5)_2^+$] and 75 (61, $C_3H_7O_2^+$).

Enol Ether Acetals **6** *and* **7**.—Diisopropylamine (901 mm^3, 650 mg, 6.44 mmol) was added to DME (3 cm^3) at −78 °C under nitrogen, followed by butyllithium (1.15 mol dm^{-3} in hexane; 5.6 cm^3, 6.44 mmol), added dropwise, and the mixture was stirred at −78 °C for 20 min. A solution of the diethyl phosphonate **3** (1.86 g, 6.44 mmol) in DME (20 cm^3) was added and the mixture was stirred at −78 °C for 20 min. A solution of the dimethoxy acetal **2** (2.02 g, 6.44 mmol) in DME (12 cm^3) was added dropwise and the mixture was stirred at −78 °C for 10 min and was then allowed to attain room temperature, finally being refluxed under nitrogen for 7 h. The product was poured into water, extracted with diethyl ether, and worked up in the usual way. Chromatography on dry column silica, and elution with hexane–ethyl acetate (4:1), gave a *Z*/*E* mixture of enol ethers **6** and **7** (1.84 g, 64%). A portion (50 mg) of the mixture was separated by preparative HPLC on μ-Porosil, and elution with hexane–ethyl acetate (9:1) at a flow rate of 9 cm^3 min^{-1}.

The first eluted (t_R 60 min) was the *(Z)-enol ether* **6** (Found: C, 64.1; H, 7.5%; M^+, 448.195. $C_{24}H_{32}O_6S$ requires C, 64.25; H, 7.2%; M, 448.192); λ_{max}(EtOH)/nm 202, 258 and 285 (ε 28 300, 10 600 and 11 200); δ_H(400 MHz; [$^2H_6$]acetone) 1.16 (6 H, t, *J* 7, 2 × Me), 3.05 (2 H, d, *J* 6, SCH_2), 3.21 (3 H, s, 12-OMe), 3.40–4.00 (4 H, m, 2 × OCH_2), 3.67 (3 H, s, 2-OMe), 3.74 (3 H, s, 3-OMe), 3.80 (3 H, s, 7a-OMe), 4.63 [1 H, t, *J* 6, $CH(OEt)_2$], 6.26 (1 H, s, 1-H), 6.36 (1 H, s, 12a-H), 6.90–7.40 (4 H, m, 4 × ArH) and 7.01 (1 H, s, 4-H); *m/z* (EI, +ve) 448 (18%, M^+), 135 (67, $C_5H_{11}O_2S^+$), 103 [100, $^+CH(OC_2H_5)_2$] and 75 (42, $C_3H_7O_2^+$).

The (E)-*enol ether* **7** had t_R 72 min. (Found: M^+, 448.191);

δ_H(400 MHz; [$^2H_6$]acetone)* 1.07 (6 H, t, *J* 7, 2 × Me), 2.94 (2 H, d, *J* 6, SCH_2), 3.40–3.70 (4 H, m, OCH_2), 3.52 (3 H, s, 12-OMe), 3.83 (3 H, s, 3-OMe), 3.85 (3 H, s, 2-OMe), 3.90 (3 H, s, 7a-OMe), 4.51 [1 H, t, *J* 6, C*H*$(OEt)_2$], 6.41 (1 H, s, 12a-H), 7.00–7.20 (2 H, m, 2 × ArH), 7.12 (1 H, s, 4-H), 7.35–7.45 (2 H, m, 2 × ArH) and 7.91 (1 H, s, 1-H); *m/z* (EI, +ve) 448 (9%, M^+), 135 (9, $C_5H_{11}O_2S^+$), 103 [100, $CH(OC_2H_5)_2^+$] and 75 (52, $C_3H_7O_2^+$).

6,7-*Dimethoxy*-4-(o-*methoxybenzoyl*)-2H-*thiochromene* **10**.—A solution of the *Z*/*E* mixture of enol ethers **6** and **7** (1.15 g, 2.57 mmol) in methylene dichloride (10 cm^3) was added dropwise to a solution of titanium tetrachloride (5.14 mmol) in methylene dichloride (15 cm^3) at −78 °C, under nitrogen. The red solution was stirred at −78 °C for 30 min, when the cooling bath was removed and saturated brine (10 cm^3) was added. The product was isolated by extraction with methylene dichloride and the extracts were washed successively with aq. sodium hydrogen carbonate, water and brine, dried ($MgSO_4$), and evaporated to give an oil, which was dissolved in methanol (10 cm^3)–conc. hydrochloric acid (10 drops), and the solution was heated under reflux for 2 h, when it was allowed to cool and was poured into water and extracted with chloroform. The extracts were washed and worked up as above to give an oil, which was chromatographed on dry silica and eluted with hexane–ethyl acetate (7:3), to afford 6,7-*dimethoxy*-4-(o-*methoxybenzoyl*)-2H-*thiochromene* **10** (469 mg, 53%) as an oil (Found: M^+, 342.093. $C_{19}H_{18}O_4S$ requires M, 342.093); λ_{max}(EtOH)/nm 204 and 237 (ε 27 100 and 20 900); ν_{max}(mull)/cm^{-1} 1645s (CO), 1600 (C=C) and 1505 (aromatic); δ_H(400 MHz; $CDCl_3$)* 3.38 (2 H, d, *J* 6, SCH_2), 3.63 (6 H, s, 2 × OMe), 3.87 (3 H, s, OMe), 6.50 (1 H, t, *J* 6, CH_2CH), 6.80–7.10 (2 H, m, 2 × ArH), 6.87 (1 H, s, 4-H), 6.96 (1 H, s, 1-H) and 7.30–7.60 (2 H, m, 2 × ArH); δ_C(100 MHz; $CDCl_3$)* 25.2 (CH_2, C-6), 55.3 (CH_3, OMe), 55.5 (CH_3, OMe), 55.7 (CH_3, OMe), 110 (CH, C-8), 110.6 (CH, C-4), 111.5 (CH, C-1), 120.3 (CH, C-10), 124.3 (C, C-11a), 124.6 (C, C-4a), 128.4 (CH, C-11), 128.8 (C, C-12b), 130.0 (CH, C-9), 132.7 (CH, C-6a), 141.4 (C, C-2), 146.5 (C, C-3), 148.6 (C, C-12), 157.9 (C-7a) and 196.0 (C, C-12); *m/z* (EI, +ve) 342 (49%, M^+), 207 (74, $C_{11}H_{11}O_2S^+$), 135 (60, $C_8H_7O_2^+$) and 75 (100).

2,3-*Dimethoxy*-6a,12a-*dihydro*-5-*thio*-6H-*rotoxen*-12-*one* **13**.—A solution of boron tribromide in methylene dichloride (1.0 mol dm^{-3}; 1.40 cm^3, 1.40 mmol) was added dropwise to a solution of 4-(*o*-methoxybenzoyl)-6,7-dimethoxy-2*H*-thiochromene **10** (435 mg, 1.27 mmol) in dry methylene dichloride (10 cm^3) under nitrogen at −78 °C and the mixture was stirred for 5 min; the reaction mixture was then allowed to warm to room temperature. The mixture containing the phenol **11** was evaporated to dryness, methanol (10 cm^3) and water (10 cm^3) were added, and the mixture was heated under reflux for 1 h, then was cooled and extracted with chloroform. The extracts were washed successively with aq. sodium hydrogen carbonate, water and brine, dried ($MgSO_4$), and evaporated. Saturated ethanolic sodium acetate (20 cm^3) was added and the mixture was heated under reflux (3 h), poured into water, and extracted with chloroform. Washing, drying, and evaporation of the extracts gave a yellow gum, which was chromatographed on flash column silica and eluted with hexane–ethyl acetate (4:1) to give the 2,3-*dimethoxy*-6a,12a-*dihydro*-5-*thio*-6H-*rotoxen*-12-*one* **13** (112 mg, 27%) as yellow needles, m.p. 164–165 °C (from $CHCl_3$–MeOH) (Found: C, 66.0; H, 4.95%; M^+, 328.076. $C_{18}H_{16}O_4S$ requires C, 65.85; H, 4.9%; M, 328.077); λ_{max}(EtOH)/nm 217, 253 and 303 (ε 51 200, 21 900 and 5300); ν_{max}(KBr)/cm^{-1} 1687s (CO), 1607s and 1517s (aromatics); δ_H(400 MHz; $CDCl_3$) 3.32 (1 H, ddd, *J* 13.1, 3.1 and 0.6, 6-H^a), 3.38 (1 H, dd, *J* 13.1 and 7.1, 6-H^b), 3.78 (3 H, s, OMe), 3.82 (3 H, s, OMe), 3.91 (1 H, d, *J* 4.1, 12a-H), 5.19 (1 H, m, *J* 7.1, 3.1, 4.1 and 1.0, 6a-H), 6.62 (1 H, s, 1-H), 6.69 (1 H, s, 4-H), 6.98 (1 H, d, *J* 8.4, 8-H), 7.03 (1 H, ddd, *J* 7.8, 7.6 and 0.5, 10-H), 7.48 (1 H, ddd, *J* 8.4, 7.6 and 0.8, 9-H) and 7.92 (1 H, dd, *J* 7.8 and 1.8, 11-H); δ_C(100 MHz, $CDCl_3$) 28.6 (CH_2, C-6), 49.0 (CH, C-12a), 55.9 (CH_3, OMe), 56.0 (CH_3, OMe), 73.3 (CH, C-6a), 109.4 (CH, C-4), 113.5 (CH, C-1), 117.9 (CH, C-8), 118.0 (C, C-11a), 119.4 (C, C-4a), 121.8 (CH, C-10), 122.4, (C, C-12b), 127.6 (CH, C-11), 136.4 (CH, C-9), 146.7 (C, C-2), 148.8 (C, C-3), 160 (C, C-7a) and 191.4 (C, C-12); *m/z* (EI, +ve) 328 (55%, M^+), 208 (100, $C_{11}H_{12}O_2S^+$) and 207 (42, $C_{11}H_{11}O_2S^+$).

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References

1 L. Crombie and J. L. Josephs, *J. Chem. Soc., Perkin Trans. 1*, 1993, preceding paper.
2 H. Kwart and T. J. George, *J. Chem. Soc., Chem. Commun.*, 1970, 433.
3 For preliminary information see L. Crombie, J. L. Josephs, J. Larkin and J. B. Weston, *J. Chem. Soc., Chem. Commun.*, 1991, 972.
4 T. Mukaiyama, *Org. React.*, 1982, **28**, 238.
5 For examples see: A. Alexakis, M. J. Chapelaine, G. H. Posner and A. W. Runquist, *Tetrahedron Lett.*, 1978, 4205; J. H. Hutchinson, G. Pattenden and P. L. Myers, *Tetrahedron Lett.*, 1987, 1313; G. S. Cockerill, P. Kocienski and R. Treadgold, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2093, 2101.
6 J. E. Banfield, W. Davis, B. C. Ennis, S. Middleton and Q. N. Porter, *J. Chem. Soc.*, 1956, 2603.
7 E. A. Evans, *J. Chem. Soc.*, 1956, 4691.
8 G. W. Stacy, F. W. Villaescusa and T. E. Wollner, *J. Org. Chem.*, 1965, **30**, 4074.
9 A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
10 E. Schaumann and F.-F. Grabley, *Justus Liebigs Ann. Chem.*, 1977, 88; D. Burkhouse and H. Zimmer, *Synthesis*, 1984, 330.
11 W. Schäfer and B. Franck, *Chem. Ber.*, 1966, **99**, 160; J. F. W. McOmie, M. L. Watts and D. E. West, *Tetrahedron*, 1968, **24**, 2289.
12 R. I. Reed and J. M. Wilson, *J. Chem. Soc.*, 1963, 5949.
13 T. Durst, J. L. Charlton and D. B. Mount, *Can. J. Chem.*, 1986, **64**, 246.
14 D. Carson, M. W. Cass, L. Crombie, I. Holden and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1982, 773.
15 J. Klein and E. D. Bergmann, *J. Am. Chem. Soc.*, 1957, **79**, 3452.
16 R. Pschorr, *Justus Liebigs Ann. Chem.*, 1912, **391**, 23.

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