5-Thiorotenoids: A New Synthesis of General Applicability to Rotenoids

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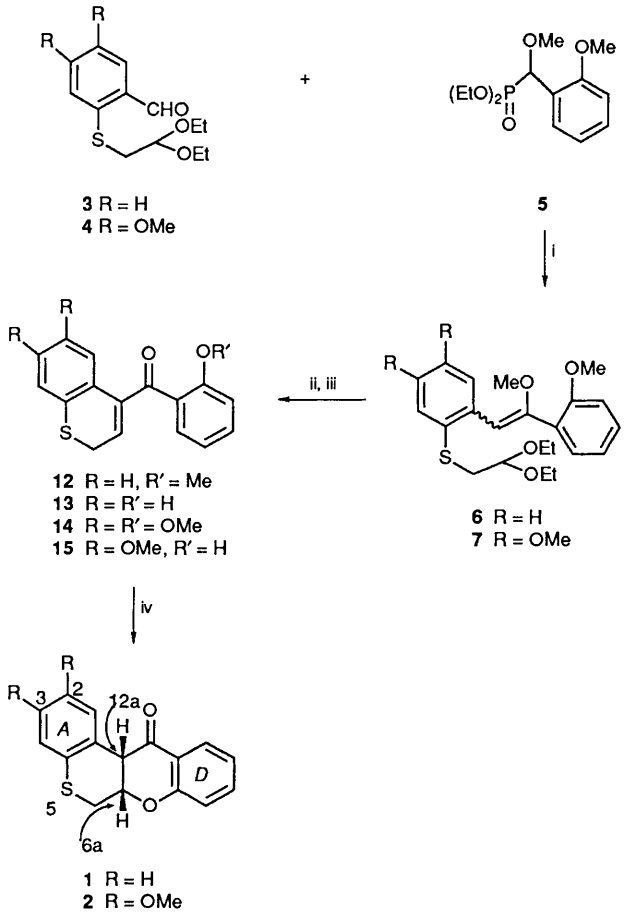
A new synthesis of general utility for rotenoid structures is reported and applied to the specific case of 5-thiorotenoids.

Rotenone and rotenoids have a number of important biological activities such as insecticidal[1] and antifeedant[2] activity, as well as piscicidal[3] activity much valued in wild-life conservation. The rotenone-sensitive NADH (reduced nicotinamide adenine dinucleotide)–ubiquinone reductase system from mitochondria has been much studied,[4] and the compound inhibits the formation of microtubules from tubulin.[5] The relationship between structural modulations and activity is thus of interest and we were concerned specifically with the replacement of the 5-oxygen atom of the rotenoid core by sulphur. During this work a new synthetic approach was developed which, whilst directed specifically to the 5-thio derivative **1**, is flexible and of general applicability in the rotenoid series. Two key steps are the union of **3** and **5** by Wadsworth–Emmons reaction to form **6**[6,7] and cyclisation of the latter by a Mukaiyama-type reaction:[8] unlike a number of earlier rotenoid syntheses, the final rotenoid is produced directly at the correct 6a,12a-oxidation state.

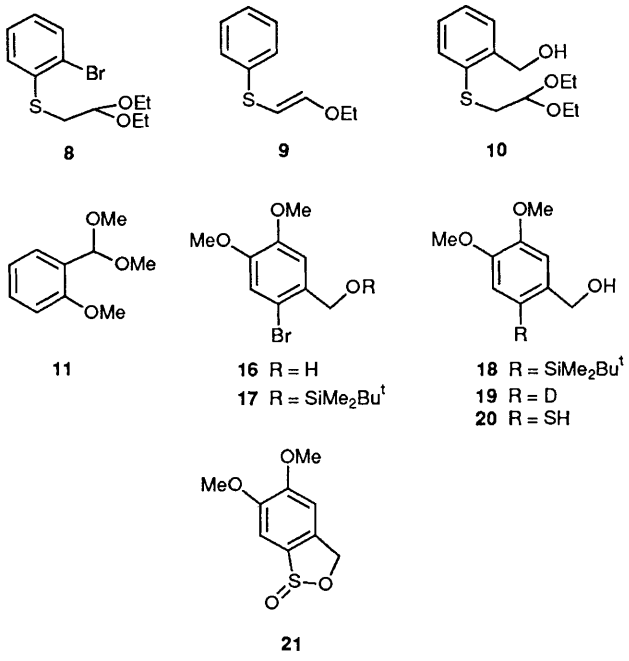
It was initially intended to work from **8**, forming the anion by halogen–lithium exchange and quenching it by a formylating agent. However, attempts to trap this anion led only to **9**, the product of intramolecular proton abstraction and ethoxide elimination. The desired **3** was therefore made from thiosalicylic acid by reduction with lithium aluminium hydride (LAH) (91%), selective alkylation using bromacetaldehyde diethyl acetal (1 mol in the presence of 1 mol sodium hydride in dimethylformamide) to give **10** (82%), which was oxidised to **3** (95%) under Swern conditions.[9] Phosphonate **5** was formed (99%) by condensing the acetal **11** with triethyl phosphite in the presence of boron trifluoride–diethyl ether at −20 °C.[6]

Formation of the anion from **5** (lithium diisopropylamide) followed by slow condensation with **3** in refluxing dimethoxyethane (24 h) gave **6** in 50% yield as a mixture of (*Z*)- and (*E*)-isomers (1:2). These can be separated by HPLC and identified stereochemically through NOE (nuclear Overhauser effect) difference spectroscopy [the vinyl proton for the (*Z*)-isomer resonates at δ 6.23, and for the (*E*)- at δ 6.27]. For Mukaiyama ring closure the stereochemistry of the enol ether is not important[10] and the isomer mixture was treated with titanium tetrachloride in dichloromethane at −78 °C[11] to give, after refluxing with methanolic hydrochloric acid, the thiochromen **12** (52%). The characteristic 6 Hz coupling between the vinyl and allylic protons of ring-*B*, ν_{max} 1660 cm^{-1}, and expected mass spectral cleavages confirm the structure. Treatment of **12** with boron tribromide[12] at −78 °C gave the phenol **13** (58%, δ 12.05, ν_{max} 1630 cm^{-1}) which was cyclised (78%) to give the 5-thiorotenoid core **1** by refluxing ethanolic sodium acetate (see Scheme 1). The new rotenoid, m.p. 128–129 °C, had M^+ 268.0573 ($C_{16}H_{12}O_2S$ requires M_r 268.0557) with the expected fragmentation pattern and ν_{max} 1695 cm^{-1}. Both ^1H† and ^{13}C NMR spectra were fully assigned with the aid of 2D spectra (COSY and heteroCOSY): the 4 Hz coupling of the 6a,12a-protons (analogous to the 5-O case) confirms that the molecule is formed in the thermodynamically favoured *cis-B/C* fusion.

† δ_H (250 MHz, $CDCl_3$): 3.28 (1H, ddd, *J* 13, 4, 1 Hz, 6-Ha), 3.41 (1H, dd, *J* 13, 7 Hz, 6-Hb); 3.99 (1H, d, *J* 4 Hz, 12a-H), 5.23 (1H, m, 6a-H), 6.90–7.20 (6H, m, aromatics), 7.43–7.52 (1H, m, aromatic), 7.93 (1H, dd, *J* 8, 2 Hz, 11-H).



Scheme 1 *Conditions and reagents*: i, Wadsworth–Emmons; ii, $TiCl_4$, −78 °C; iii, BBr_3, −78 °C, iv, NaOAc



Natural rotenoids lacking 2,3-oxygenation in ring-*A* have been recently discovered in the Nyctaginaceae and Iridaceae families,[13–16] but the well known Leguminosae group have 2,3-oxygenation as dimethoxy or methylenedioxy.[17] We have therefore modified the approach to make the 5-thio-2,3-dimethoxy core **2**. For this, a new synthon **4** is required. Bromination of 3,4-dimethoxy-benzaldehyde gave the 6-bromo-derivative (74%), reduced in almost theoretical yield to alcohol **16** which was protected as its *tert*-butyldimethylsilyl derivative **17** (95%). However, the anion formed by treatment with 1 equiv. of n-butyllithium at −78 °C could not be trapped with an electrophile as silyl migration occurred and the product after work-up was **18** (82%). The unprotected alcohol **16** was therefore treated with n-butyllithium (2 equiv.) and formed **19** on quenching with D_2O, indicating the required anion availability. The anion was unreactive towards sulphur but with SO_2 formed a crystalline γ-sultine[18] **21** (73%), reduced by LAH to the thiol **20** (93%). Employment of selective alkylation with bromacetaldehyde diethyl acetal (81%) followed by Swern oxidation (59%) gave the desired synthon **4**.

Wadsworth–Emmons reaction between **4** and **5** gave the enol ether **7** as a (*Z*)–(*E*) mixture (64%), used as such in the Mukaiyama stage (though the individual isomers were separated and identified). Treatment with titanium tetrachloride (2 equiv.), followed by work-up as above gave the chromen **14** (53%). Taking advantage of the complexing ability of the adjacent carbonyl, selective monodemethylation was carried out using boron tribromide (1 equiv.) at −78 °C to give **15**, cyclised by sodium acetate to the desired 2,3-dimethoxy-5-thiorotenoid **2** (27% over two stages).‡ The thiorotenoid crystallised as yellow needles, m.p. 164–165 °C and was fully characterised analytically and spectroscopically.

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‡ δ_H (400 MHz, $CDCl_3$): 3.32 (1H, ddd, *J* 13.1, 3.1, 0.6 Hz, 6-Ha), 3.38 (1H, dd, *J* 13.1, 7.1 Hz, 6-Hb), 3.78 (3H, s, OMe), 3.82 (3H, s, OMe), 3.91 (1H, d, *J* 4.1 Hz, 12a-H), 5.19 (1H, m, *J* 7.1, 3.1, 4.1, 1.0 Hz, 6a-H), 6.62 (1H, s, 1-H), 6.69 (1H, s, 4-H), 6.98 (1H, d, *J* 8.4 Hz, 8-H), 7.03 (1H, ddd, *J* 7.8, 7.6, 0.5 Hz, 10-H), 7.48 (1H, ddd, *J* 8.4, 7.6, 0.8 Hz, 9-Hz), 7.92 (1H, dd, *J* 7.8, 1.8 Hz, 11-H).