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SYNTHESIS OF A 2,3-DIMETHOXYROTENONOID

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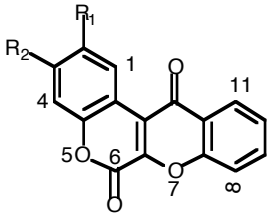
Abstract - Photo-Fries rearrangement of the *o*- fluoro ester of 3-hydroxy-6, 7-dimethoxycoumarin yielded the corresponding 3-hydroxy-4-(2-fluorobenzoyl)-coumarin which, in the presence of potassium carbonate, cyclised to the 2,3-dimethoxyrotenonoid. (1)-Benzofuran-(2, 3-*c*)–(6*H*, 12*H*)-(1)–benzoxepin-6-ones underwent oxidation to the corresponding β -rotenonoids reluctantly.

INTRODUCTION

Rotenoids are well known and very potent naturally occurring insecticides, piscicides and antifeedants,[1] showing a wide range of biological properties including antibacterial and antiviral activity.[2] They occur most frequently in members of the Leguminosae family. 6-Oxorotenoids, also referred to as rotenonoids, have the general structure (**1a**), and have been found co-occurring with rotenoids in plants.[3-6]



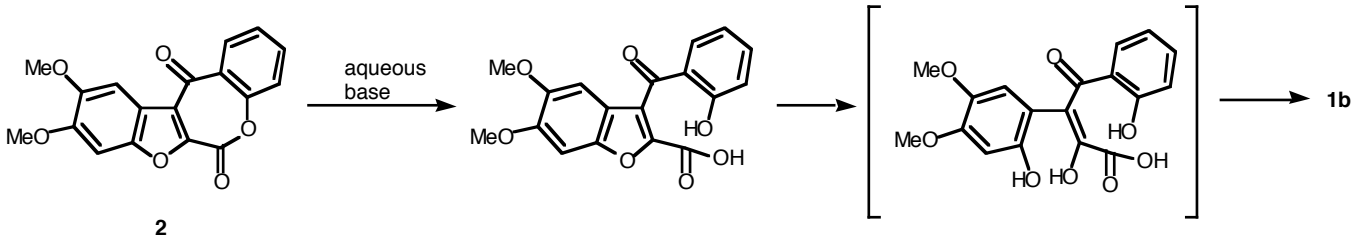
1a $R_1 = R_2 = H$
1b $R_1 = R_2 = OMe$

Oberholzer *et al.*[4] suggested that the association of rotenoids with rotenonoids in the same plant, may be indicative of a biogenetic pathway from rotenoids to rotenonoids. Their similarity in structure could also indicate similar biological activity. Not a great deal is known about rotenonoids, however, as synthesis of these compounds is quite difficult.

Synthesis of rotenonoids has primarily been by initial synthesis of rotenoids and subsequent oxidation using either nitrosyl chloride, chromic acid or *via* Kornblum oxidation.[7] This is a rather inefficient route to rotenonoids, however, since rotenoids are themselves quite difficult to synthesize and most of the

pathways reported are long and low yielding.[8] We set out to develop an efficient synthetic pathway to rotenonoids (this would allow for detailed study of their biological activity), and approached the synthesis from the following two standpoints.

i) Rearrangement of β-rotenonoids (**2**) to rotenonoids under basic conditions is well known (Scheme 1).[9] The β-rotenonoids seemed amenable to synthesis, and with successful synthesis of these, we could claim synthesis of rotenonoids.

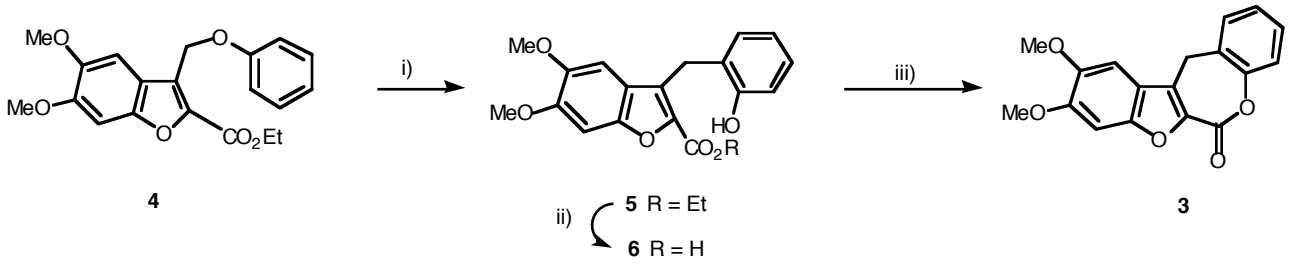


Scheme 1

ii) Benzoates of 3-hydroxy-6, 7-dimethoxycoumarin (**9**)[10] are known to undergo photo-Fries rearrangement to the corresponding 3-hydroxy-4-benzoylcoumarins.[11] Appropriately substituted 3-hydroxy-4-benzoylcoumarins should cyclize readily to rotenonoids.

RESULTS AND DISCUSSION

In earlier work, we had developed a relatively efficient synthesis of (1)-benzofuran-(2,3-*c*)–(6*H*, 12*H*-(1)–benzoxepin-6-ones e.g. **3**, by the pathway outlined in Scheme 2.[12] We synthesized compound (**3**) with the hope of oxidizing it to the desired β-rotenonoid (**2**).

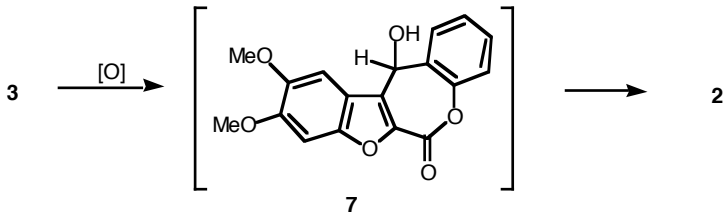


Reagents: i) TFA ii) NaOH, aq. EtOH iii) thionyl chloride, pyridine

Scheme 2

Since the only available position for oxidation in **2** is a methylene group which is both allylic and benzylic, we anticipated success, though we approached it with some reserve since the difficulty with which 3-benzylbenzofurans are oxidized to 3-aroylbenzofurans has been reported.[13]

The ether (**4**) was readily prepared in 91% yield from phenol and ethyl 3-bromomethylbenzofuran-2-carboxylate,[14] in the presence of potassium carbonate and dry acetone. Rearrangement of the ether in trifluoroacetic acid (TFA) produced the ester (**5**), which was then hydrolysed to the acid (**6**). Subsequent cyclization using thionyl chloride/pyridine yielded the lactone (**3**) in about 40% overall yield from the ether (**4**).

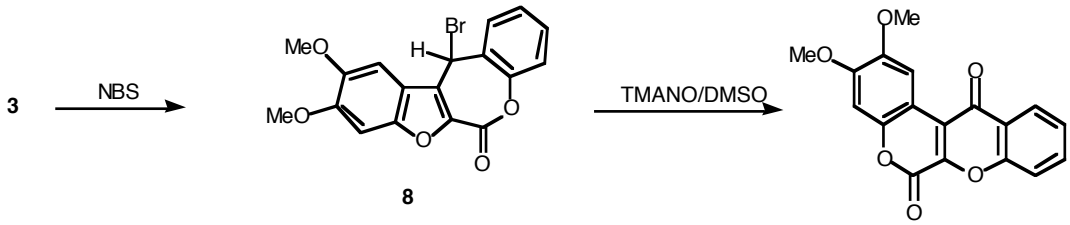


Scheme 3

The lactone (**3**), however, proved very resistant to oxidation. Many different reagents – SeO_2, DDQ, benzeneseleninic anhydride, *tert*-BuOOH and NBS/DMSO, were tried, all without success. When *tert*-butyl hydroperoxide was used in conjunction with chromium trioxide or with pyridinium dichromate, we saw evidence of a very small yield of the intermediate hydroxylated lactone (**7**) (Scheme 3), which proved to be unstable.

Biotransformation reactions using *Fusarium oxysporum,* subculture of *Curvularia protuberata, Mortierella isabellina, Cunninghamella echinulata* var. *elegans,* all fungi known to carry out allylic oxidations[15] were also attempted, but these proved unsuccessful.

Still in anticipation of the β-rotenonoid, we went on to pursue another route. Trimethylamine-*N*-oxide (TMANO) is known to convert alkyl halides to the corresponding aldehyde or ketone.[16] Compound (**3**) was thus converted to the allyl bromide (**8**) by treatment with *N*-bromosuccinimide (NBS). Reaction of **8** with TMANO in DMSO produced, after work-up, not the β-rotenonoid as we had anticipated, but the rotenonoid (**1b**) in 7% yield from lactone (**3**) (Scheme 4).

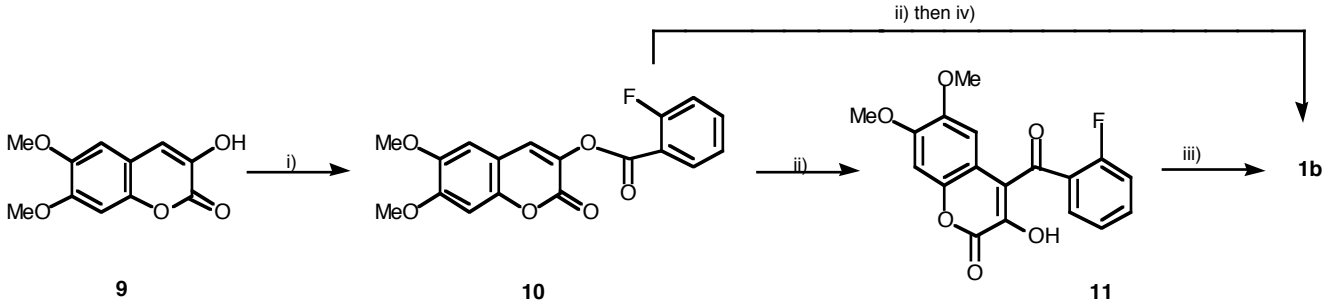


Scheme 4

This observation suggested that we had achieved allylic oxidation of **8** to **2**, and that rearrangement of the β-rotenonoid had also occurred under these conditions. The reaction, however, went very poorly. It is

clear that compounds of type (**3**) undergo oxidation to the corresponding β-rotenonoids reluctantly, if at all. ^{1}H-NMR data of the reaction product showed the characteristic downfield singlet (δ 8.9) which corresponds to the proton at C-1 in rotenonoids, and IR absorptions at 1741 and 1640 cm^{-1}, which are also markers for the rotenonoid system.[4-6, 17]

We next turned to synthesis of the title compound *via* photo-Fries rearrangement of the *o*-fluorobenzoate of 3-hydroxycoumarin (**9**), and subsequent cyclization. This proved to be a much more facile pathway.



Reagents: i) *o*-fluorobenzoyl chloride, pyridine ii) benzene:ethanol, light iii) K_2CO_3, toluene iv) K_2CO_3, MeI, acetone

Scheme 5

The fluoroester (**10**) was prepared in 80% yield by condensation of **9** with *o*-fluorobenzoyl chloride. Irradiation of a 0.2% solution of **10** in benzene:ethanol (1:1), by sunlight, for 8 h, produced the compound (**11**) which when treated with potassium carbonate in refluxing acetone, was quickly converted to **1b** (79%). The compound obtained from TMANO reaction of **8** is identical in all respects (MP, IR, NMR, MS) to the product (**1b**) obtained from the pathway in Scheme 5. With our improved synthesis of compound (**9**),[10] this route signifies an efficient and general pathway to rotenonoids.

EXPERIMENTAL

General

All mp are uncorrected. IR spectra were obtained on a Perkin Elmer 735B model or a Perkin Elmer 1600 FT-IR spectrophotometer and are for KBr discs. NMR spectra (Bruker 200 MHz spectrometer) were determined in $CDCl_3$ solution and the resonances are reported in δ units downfield from TMS; *J* values are given in Hz. Elemental analyses were carried out by MEDAC Ltd., Egham, Surrey, UK.

5,6-Dimethoxy-2-carboethoxy-3-phenoxymethylbenzofuran (4)

To a solution of phenol (0.285 g, 3.03 mmol) in acetone (38 mL) was added, with stirring, potassium carbonate (1.630 g, 11.8 mmol) followed by 3-bromomethyl-2-carboethoxy-5,6-dimethoxybenzo-furan (0.869 g, 2.87 mmol).[14] The reaction mixture was then heated at reflux for 2 h, filtered and the filter cake

washed with hot acetone. The filtrate was concentrated *in vacuo* and the crude product recrystallised from methanol to produce **4** as fluffy white needles (0.934 g, 91%), mp 123 - 125°C; ν_{max} /cm^{-1} 1704, 1593; δ_H 1.42 (3H, t, *J* 7, -O-CH_2-C<u>H</u>$_3$), 3.80 (6H, s, 2 x OCH_3), 4.42 (2H, q, *J* 7, -O-C<u>H</u>$_2$-CH_3), 5.60 (2H, s, -CH_2-OPh), 7.00 (4H, m), 7.35 (3H, m); δ_c 14.3, 56.1, 61.3, 61.8, 94.8, 102.5, 114.5, 119.2, 121.2, 129.5, 139.8, 147.3, 150, 151.2, 158.2. Anal. Calcd for $C_{20}H_{20}O_5$: C, 67.39; H, 5.66. Found: C, 67.00; H, 5.58.

5,6-Dimethoxy-2-carboethoxy-3-(2'-hydroxyphenylmethyl)benzofuran (5)

Compound (**4**) (3.0 g, 9.22 mmol) was dissolved in trifluoroacetic acid (TFA) (50 mL) with stirring. The reaction mixture was then heated at reflux for 6 h. TFA was removed *in vacuo* and the crude product was dissolved in chloroform and washed to neutral with water. The chloroform solution was then dried (Na_2SO_4), concentrated *in vacuo* and chromatographed (SiO_2, hexane-EtOAc 5:2) to yield **5** as a pale yellow powder (1.4 g, 46%), mp 163-165°C (MeOH/hexane); ν_{max} /cm^{-1} 1699, 1657, 3373; δ_H 1.50 (3H, t, *J* 7, -O-CH_2-C<u>H</u>$_3$), 3.90 (6H, s, 2 x OMe), 4.40 (2H, s, CH_2-Ar), 4.50 (2H, q, *J* 7, -O-C<u>H</u>$_2$-CH_3), 6.80 (2H, m) 6.95 (1H, s, 6-H), 7.10 (2H, m), 7.40 (1H, d, *J* 8.5, 6´-H), 7.62 (1H, br s, OH); δ_c 14.2, 25.7, 56.13, 61.8, 94.9, 101.6, 116.7, 119.9, 120.1, 123.7, 128.3, 129.2, 130.6, 139.0, 147.2, 150.0, 151.4, 154.7, 162.0. Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.39; H, 5.66. Found: C, 67.38; H, 5.63.

5,6-Dimethoxy-3-(2'-hydroxyphenylmethyl)benzofuran-2-carboxylic acid (6)

3M NaOH (9.5 mL, 28.5 mmol) was added to a mixture of compound (**5**) (1.302 g, 4.0 mmol) in methanol (40 mL) and the mixture was heated at reflux for 3 h. The mixture was then concentrated *in vacuo* and the resulting solid was diluted with the minimum volume of water and acidified with concentrated HCl. The mixture was cooled and the resultant white precipitate was collected by filtration and washed to neutral with cold water. The product was dried in an oven at 80°C to give **6** as a white powder (1.15 g, 96%), mp 223-225°C (EtOH); ν_{max} /cm^{-1} 1670, 1580, 3503, 3435; δ_H 3.80 (3H, s, OMe), 3.90 (3H, s, OMe), 4.42 (2H, s, CH_2-Ar), 6.70 - 6.90 (2H, m), 7.00 - 7.28 (3H, m), 7.40 (1H, s, 4-H); δ_c 24.5, 55.9, 94.5, 101.9, 115.1, 115.5, 119.4, 120.1, 124.6, 127.4, 128.6, 130.1, 146.6, 149.6, 150.8, 154.8, 162.7.

2,3-Dimethoxy-(1)-benzofuran-(2, 3-*c*)-(6*H*, 12*H*)-(1)-benzoxepin-6-one (3)

To a solution of the carboxylic acid (**6**) (1.01 g, 3.41 mmol) in pyridine (30 mL) was added thionyl chloride (0.5 mL, 6.85 mmol) and the reaction mixture left to stand for 2 h. The mixture was then poured into crushed ice/water (200 mL). The brown precipitate formed was collected by filtration and

recrystallised from chloroform/methanol, to produce **3** as fluffy brown crystals (0.873 g, 92%), mp 206-208°C; ν_{max} /cm^{-1} 1733, 1624, 1572; δ_H 3.90 (3H, s, OMe), 3.95 (3H, s, OMe), 4.12 (2H, s, CH_2-Ar), 6.95 (1H, s, 1- or 4-H), 7.00 (1H, s, 1- or 4-H), 7.05-7.35 (4H, m); δ_c 27.3, 56.3, 56.4, 95.2, 100.5, 122.4, 126.0, 128.5, 129.4, 147.9, 151.5, 152.0. Anal. Calcd for $C_{18}H_{14}O_5$: C, 69.66; H, 4.49. Found: C, 69.18; H, 4.49.

6,7-Dimethoxycoumarin-3-(2'-fluoro)benzoate (10).

3-Hydroxy-6, 7-dimethoxycoumarin (2.5 g, 11.3 mmol) was dissolved in pyridine (45 mL) and 2-fluorobenzoyl chloride (1.35 mL, 11.3 mmol) was added with cooling. The reaction mixture was stirred at rt for 24 h then poured onto crushed ice (~250 g) with stirring. The resultant brown precipitate was collected by suction filtration and recrystallised to give **10** as light brown crystals (3.11 g, 80%), mp (MeOH) 218-220°C; ν_{max} /cm^{-1} 1723, 1760; δ_H 3.92 and 3.97 (each 3H, s, OMe), 6.88 and 6.93 (each 1H, s, 5- and 8-H), 7.20-7.35 (2H, m), 7.57 – 7.70 (2H, m), 8.10-8.20 (1H, m, 6´-H); δ_c 55.93, 56.1, 99.8, 108.6, 117.0, 117.5, 124.6, 132.4, 133.1, 136.2, 136.4, 146.4, 147.6, 152.2, 159.1, 164.3. Anal. Calcd. for $C_{18}H_{13}O_6F$. H_2O : C, 59.67 ; H, 4.14. Found: C, 59.79; H, 3.78.

2,3-Dimethoxyrotenonoid (1b)

a) From (1)-Benzofuran-(2, 3-*c*)-(6*H*, 12*H*-1)-benzoxepin-6-one (3). To a mixture of compound (**3**) (0.25 g, 0.89 mmol) in CCl_4 (17 mL), *N*-bromosuccinimide (0.23 g, 1.29 mmol) was added with stirring. The reaction was enclosed in a dark box and illuminated with a 100 watt bulb for 8 h. (This allowed gentle reflux.) The reaction mixture was then filtered and the filtrate concentrated *in vacuo* to produce **8** as a brown solid (0.16 g) which was used in the next reaction without further purification.

Trimethylamine-*N*-oxide (0.18 g, 2.40 mmol) dissolved in DMSO (12 mL), was added to the above solid with stirring. The reaction mixture was left to stir at rt for 4 h and then poured into a 50% saline solution and left to stand for 24 h. The aqueous mixture was extracted with chloroform, the organic extract dried (Na_2SO_4), and the solution concentrated *in vacuo*. The crude product was recrystallised from chloroform/ethanol to yield **1b** as bright yellow needles (20 mg, 7% from lactone (**3**)), mp 312-313°C; ν_{max} /cm^{-1} 1741, 1640, 1612, 1516; δ_H 3.90 and 4.05 (each 3H, s, OCH_3), 6.90 (1H, s, 4-H), 7.53 (1H, td, *J* 7, 2, 9-H), 7.70-7.90 (2H, m, 8-H, 10-H), 8.33 (1H, dd, *J* 9, 2, 11-H), 8.97 (1H, s, 1-H); δ_c 56.3, 56.2, 99.3, 107.3, 107.5, 111.7, 118.5, 125.7, 125.8, 135.2, 145.2, 148.2, 154.3, 155.6, 165.7; *m/z* (relative intensity) 324 (100), 309 (36). HRMS calcd for $C_{18}H_{12}O_6$: 324.0634. Found: 324.0660. Anal. Calcd for $C_{18}H_{12}O_6$: C, 66.65; H, 3.73. Found: C, 66.92; H, 3.86.

b) From 6,7-dimethoxycoumarin-3-(2'-fluoro)benzoate (10). A solution of the ester (**10**) (600 mg, 1.74 mmol) in benzene:ethanol (1:1, 300 mL) was irradiated by sunlight for 8 h, in an atmosphere of nitrogen. The solvent was evaporated *in vacuo* and the residue purified by chromatography (SiO_2, acetone: hexane-2:3). The major product was **11** - a bright yellow powder (240 mg) which proved difficult to characterise. Treatment of **11** (160 mg, 0.47 mmol) in acetone (12 mL) with K_2CO_3(160 mg, 1.16 mmol), MeI (0.10 mL, 1.61 mmol) - in an effort to get a more stable and more readily characterised product, yielded **1b**. Compound (**11**) was therefore subjected to cyclization using potassium carbonate.
To a solution of the above solid (0.20 g) in toluene (8 mL) was added potassium carbonate (0.16 g, 1.16 mmol), and the mixture was heated at reflux for 45 min. The mixture was cooled, filtered and the filter cake washed with ethyl acetate (15 mL). The combined organic solution was concentrated *in vacuo* and the crude solid purified by chromatography (SiO_2, $CHCl_3$) to yield **1b** as a bright yellow powder (148 mg, 79% (32% from ester **10**)).

ACKNOWLEDGEMENTS

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