New Synthetic Methods in Rotenoid Chemistry: [7′-^{13}C]- and [7′-^{14}C]-(−)-Rotenone and (±)-Isorotenone

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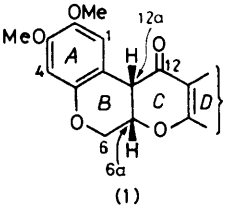
A reconstructive circuit for ^{13}C- and ^{14}C-labelling of the 7′-methylene group of (−)-rotenone is described. It involves blocking the enolisable 12a-site with a trimethylsilyloxy-group, followed by removal and reintroduction of the methylene, and elision of the blocking group: the radiochemical yield is 19%. Consequences of failure to block the 12a-site in reactions with ylides are illustrated by reactions of (−)-isorotenone, (−)-rotenone, and (−)-rotenone 7′-norketone (1f) with dimethyloxosulphonium methylide, which leads to *C-seco*-cyclopropyl ketones.

A new rotenoid synthesis from 2,2′-dihydroxydeoxybenzoins which produces the *B*/*C*-ring system directly at the correct oxidation level is described. This involves blocking of the two unwanted nucleophilic sites by ring formation. The *O*-methylene aldehyde is concealed as an allyl group for introduction purposes, and after removal of the blocking ring, development of the aldehyde, and base-catalysed cyclisation, (±)-isorotenone (used as the model rotenoid) was obtained. Since 2,2′-dihydroxydeoxybenzoins are readily made by degradation of natural rotenoids, the method can be used for reconstructive isotopic labelling at C-6 and C-6a.

THE natural product rotenone (1a) is a powerful inhibitor of mitochondrial electron transport, acting on the oxygen side of $NADH_2$ dehydrogenase flavoprotein,[1] and finds commercial use as an insecticide and piscicide. Earlier work in our laboratory on the biosynthesis of rotenoids by *Amorpha fruticosa* and *Derris elliptica* shows that the tetracyclic *A*/*B*/*C*/*D* system (1) is constructed *via* a chalcone–isoflavone route, leading to 9-demethylmunduserone (1c), which is regarded as the parent of this particular rotenoid group.[2] 8-Prenylation follows, with subsequent modifications of this unit to afford dalpanol (1b), rotenone (1a), and amorphigenin (1e). Unfortunately, study of the latter phase of the biosynthesis is made difficult by poor incorporation of prenyl precursors such as mevalonic acid, dimethylallyl alcohol, isopentenyl alcohol, and 3-hydroxy-3-methylglutaric acid.[2,3]



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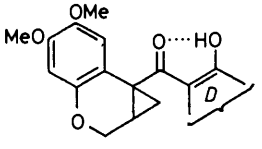

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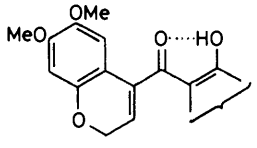

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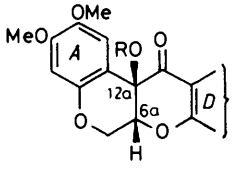
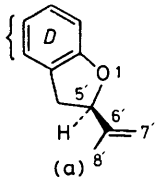


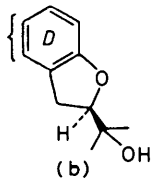
(4) R = H
(5) R = $SiMe_3$

Further progress demands the availability of specifically labelled whole rotenoids, and this paper is concerned particularly with development of a reconstructive synthesis for [7′-^{14}C]- and [7′-^{13}C]-rotenone, and a new synthesis which makes certain labelling at C-6 and C-6a feasible. As will be seen in the following paper,[4] 7′-labelled rotenone can be converted into (*E*)-4′-labelled rotenonic acid (1d), a key precursor used for biosynthetic experimentation in the third paper of this group.[5]

The norketone (1f) is readily available from rotenone by osmium tetraoxide-catalysed cleavage with sodium



(a)



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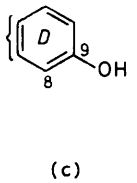

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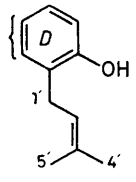

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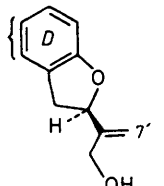

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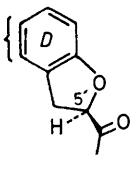
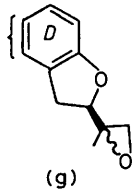


(f)



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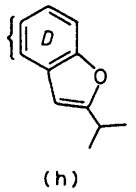
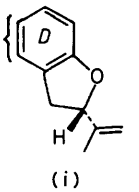


(h)



(i)

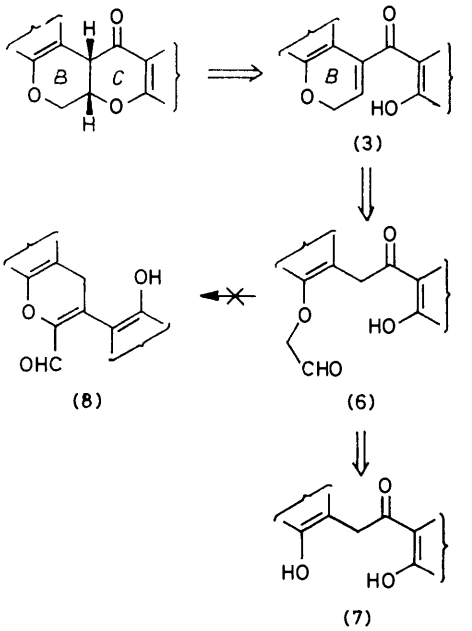
periodate,[6] and direct methylenation to re-form 7′-methylene-labelled rotenone is obviously attractive. However, although such a reaction has been claimed (without report of yield or experimental detail),[7] in our hands treatment with methylenetriphenylphosphorane (1 mol) gave pure (−)-rotenone only in very low yields. Doubtless the basic ylide induces proton transfer from C-12a, wasting labelled ylide, and apart from racemisation by β-elimination, other reactions are initiated: this

is illustrated later by the reaction of the norketone (1f) and other rotenoids with dimethyloxosulphonium methylide. Direct methylenations using methylene di-iodide or dibromide and magnesium amalgam [8] were also unsuccessful, even with highly reactive magnesium prepared by the Rieke method.[9] One way of overcoming the ready 12a-deprotonation would be protection of the 12-carbonyl as a cyclic acetal but such a process is apparently not thermodynamically favoured in the case of rotenone and attempts using ethane-1,2-diol, propane-1,3-diol, or ethane-1,2-dithiol with various acid catalysts were unrewarding. In the light of these experiences the following successful reconstructive synthesis was devised.

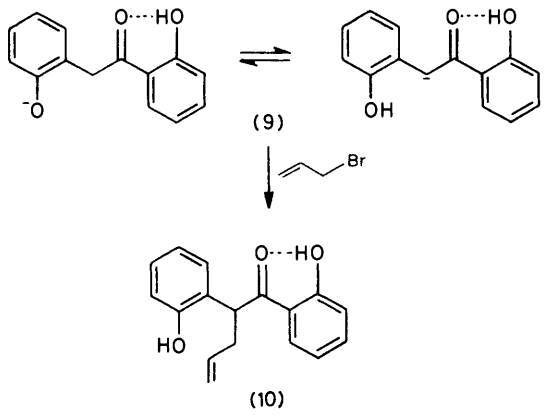
(—)-Rotenone was oxidised by chromium trioxide to 6aβ,12aβ-rotenolone (4a), a reaction which we have shown earlier to proceed with stereochemical retention at these centres.[10] Its trimethylsilyl ether (5a), blocked towards bases causing 12a-enolisation, was oxidised to the norketone (5f), and (5a) was smoothly reconstructed from (5f) by treatment with methylenetriphenylphosphorane without any epimerisation at C-5′. In order to enter the 5′α-series, (5f) was deliberately epimerised at C-5′ by contact with alumina: the resulting mixture (*ca.* 1 : 1) reacted with the Wittig reagent to afford (5a) (5′β-) and (5i) (5′α-), separable by crystallisation and clearly distinguishable from each other by ^{1}H n.m.r. spectroscopy. Protiodesilylation of (5a) using methanolic hydrochloric acid–potassium iodide gave (4a), from which rotenone was stereospecifically regenerated with zinc and acetic acid. The features of this sequence were fully amenable to isotopic labelling work and, using [^{14}C]methyl iodide to form the methylide, the regenerative circuit from natural (—)-rotenone to (—)-[7′-^{14}C]rotenone was effected in 19% radiochemical yield. In other ' cold ' experiments an improved yield of 32% has been attained. (—)-[7′-^{13}C]Rotenone was produced in a similar manner.

Epoxides can be converted into methylene compounds *via* reaction with potassium selenocyanate [11] or other reagents, and with such a sequence in mind, the reaction of the norketone (1f) with dimethyloxosulphonium methylide was examined. A new compound, m.p. 139—140.5 °C, was formed. However it was not the epoxide (1g), spectroscopic data showing that bismethylene addition had occurred to the starting 6′,12-diketone: the 12-carbonyl was retained but now appeared chelated to a proximate phenolic hydroxy-group. In a similar reaction with dimethyloxosulphonium methylide, rotenone (1a) and isorotenone (1h) also gave new chelated ketones, m.p. 133—134 and 116—118 °C, respectively, analytical data for which indicated mono-addition of reagent. The latter was identified as the (±)-cyclopropyl ketone (2h) from ^{1}H n.m.r. data ($CDCl_3$ and C_6D_6; one chelated OH) and ^{13}C n.m.r. information; this has since been confirmed by an *X*-ray single crystal structure determination (direct methods) by Dr. M. J. Begley in our laboratory. The (—)-product from (—)-rotenone is a pair of diastereoisomers epimeric at the cyclopropane position 12a (2a) (two OH in the n.m.r.). Spectra for the compound of m.p. 139—140.5 °C from (1f) show it to have undergone the same *B*/*C* reaction together with the expected epoxide formation at position 6′: it thus has structure (2g). Which diastereoisomers (probably a pair, two OH in the n.m.r.) we are handling is, however, less certain: conditions are basic so even the configuration at position 5′ is not assured, and there are eight possible diasteroisomers. Mechanistically, the formation of (2g) can be readily understood as involving 12a-deprotonation of (1f) followed by ring-*C* opening to the didehydrorotenol-type structure (3); cyclopropanation of (3) then follows the usual course, accompanied by epoxide formation at the 6′-carbonyl. Spectral data for (2h) and (2g) are given in the Experimental section; certain marked deshieldings of cyclopropane protons are readily rationalised as due to carbonyl and aryl long-range effects.

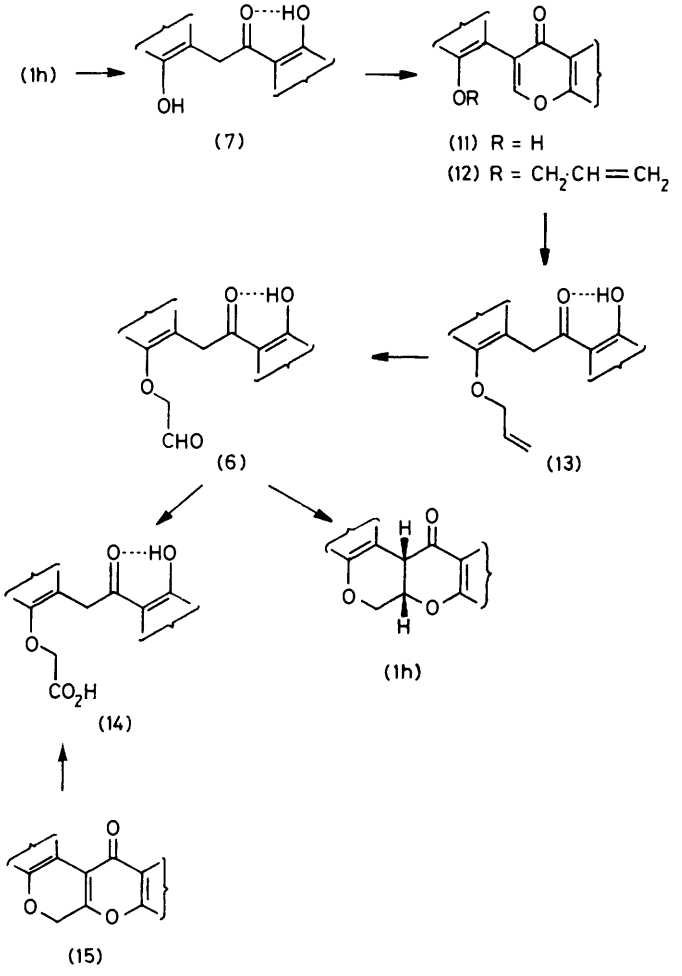
The essence of rotenoid synthesis lies in the construction of the *A*/*B*/*C*/*D* system. All known approaches employ appropriately substituted aromatic rings *A* and *D*, and build in the linking *B*/*C*-system. Most methods approach the target *via* the 6a,12a-didehydro oxidation level [12] and undesirable reduction and oxidation steps follow. Two more recent routes however circumvent this. One is the sulphonium ylide method developed in this laboratory,[13] and the other employs a acetylenic cyclisation approach.[14] We now report a third route starting from 2,2′-dihydroxydeoxybenzoins. Such phenolic ketones are available by the classical Hoesch or other methods. Alternatively they are readily available from a parent natural rotenoid by a simple degradation, thus providing a convenient reconstructive procedure by which isotopes may be introduced at C-6 or C-6a.



SCHEME 1 Rotenoid disconnections



The present approach is based on the disconnections of Scheme 1, and depends on (*a*) the viability of the cyclisation of a *C-seco*-intermediate (3) to the (more stable) *cis-B/C*-fusion (this we have demonstrated earlier [15]), and (*b*) the intramolecular cross-aldol reaction (6) ⟶ (3) which as expected proved to be preferred to the alternative (6) ⟶ (8) pathway. Direct conversion of a 2,2′-dihydroxydeoxybenzoin (7) to the key oxo-aldehyde (6) *via* *O*-alkylation with an α-halogeno-acetaldehyde acetal in the presence of base meets with difficulties since (i) halides such as 2-bromomethyldioxolan are poor electrophiles and this compound (and related acetals) proved resistant to reaction with the potassium salt of phenol (7h) even in acetonitrile containing 18-crown-6, and (ii) the phenolic ketone (9) formed a tautomeric anion which is allylated preferentially at carbon to yield (10).[16] The following procedure of masking two unwanted functionalities by an easily removed isoflavone ring was therefore devised.



SCHEME 2 Synthesis of (±)-isorotenone

Isorotenone (1h) was cleaved with zinc and alkali [15] to produce a suitable deoxybenzoin, isoderritol (7h) (Scheme 2). Simultaneous protection of two nucleophilic sites in (7h) was achieved (81%) by treatment with sodium–ethyl formate to give (11h). The sodium salt of the latter (formed with sodium hydride) was treated with allyl bromide, used as the concealed halogeno-acetaldehyde fragment, to give the *O*-allylisoflavone (12h) (64%). Elision of the protecting isoflavone segment by alkaline hydrolysis gave the *O*-allyl ketone (13h) (53%), which by standard hydroxylation and diol cleavage gave the required aldehyde (6h) as an unstable oil after chromatographic purification. The new aldehyde was characterised and identified by oxidation to isoderrisic acid (14h), identical with an authentic crystalline specimen made by alkaline hydrolysis of 6a,12a-didehydroisorotenone (15h).[16] On refluxing in pyridine the aldehyde (6h) gave (±)-isorotenone (1h) (30%), m.p. and mixed m.p. 165 °C with authentic material; [17] it was also spectroscopically identical.

EXPERIMENTAL

Except where otherwise stated, the following apply. M.p.s were determined on a calibrated Büchi apparatus. Optical rotations were measured using an ETL–NPL Automatic polarimeter, Type 143A. U.v. spectra were measured in ethanol (log ε follows $\lambda_{max.}$ in parentheses). Infra red spectra were recorded in chloroform. ^{1}H N.m.r. spectra were determined at 100 MHz in deuteriochloroform, using tetramethylsilane standard. ^{13}C N.m.r. data were recorded at 25.15 MHz on a JEOL PFT 100 spectrometer (Nicolet 1080 data system). Radioactive samples were counted in dioxan-based NE 250 scintillant, using weighed internal standards for calibration. In chromatographic work, analytical t.l.c. refers to silica gel G in 0.3 mm layers, p.l.c. involves 0.5 and 0.8 mm layers both with HF_{254} indicator: for larger scale work 40 × 40 cm plates were spread with silica HF_{254} (90 g). 'Drying' refers to the use of sodium sulphate; 'evaporation' implies use of reduced pressure.

6a,12a-*Methanorotenol* 6′,7′-*Epoxide* (2g).—Rotenone norketone (1f), m.p. 199—200 °C (lit.,[6] 200—201 °C) was prepared (46%) from rotenone. The diketone (1f) (0.5 g) in tetrahydrofuran (10 cm^3) was added to dimethyloxosulphonium methylide prepared over 15 min from trimethyloxosulphonium iodide (0.45 g), dimethyl sulphoxide (5 cm^3), and sodium hydride (0.085 g; 55% suspension in oil). The mixture was stirred under nitrogen at ambient temperature for 10 min, and at 45—55 °C for 50 min; it was then poured into water. The product was washed with

light petroleum and then extracted with chloroform (3 × 20 cm³). The combined extracts were washed (water), dried, and evaporated. The residue was purified by p.l.c. (chloroform–methanol, 99 : 1); the major and highest R_F band afforded *compound* (2g) (75 mg, 12%), m.p. 139.5—140.5 °C (from methanol), $[\alpha]_D^{25}$ −45° (*c* 1.59, $CHCl_3$) (Found: C, 67.35; H, 5.8%; M^+, 424.155. $C_{24}H_{24}O_7$ requires C, 67.9; H, 5.65%; *M*, 424.155); $\lambda_{max.}$ ($CHCl_3$) 245 (4.20), 295 (4.31), and 319 nm (4.02); $\nu_{max.}$ 2 800br, 1 640, and 1 600 cm⁻¹; δ 12.43 and 12.41 (1 H, s, OH, indicates two diastereoisomers), 7.72 (1 H, d, *J* 8 Hz, 11-H), 6.52 (1 H, s, 1-H), 6.47 (1 H, s, 4-H), 6.27 (1 H, d, *J* 8 Hz, 10-H), 4.84 (1 H, m, 5′-H), 4.29 (2 H, m, 6-H_2), 3.84 and 3.67 (both 3 H, s, OMe), 3.20 (2 H, m, 4′-H_2), 2.79 (2 H, m, 7′-H_2), 1.94 (2 H, br, 6a-H, cyclopropyl-C$H_a$$H_b$), 1.38 (3 H, s, 8′-$H_3$), and 1.30 (1 H, br, cyclopropyl-CH_aH_b).

6a,12a-*Methanorotenol* (2a).—Following the method described above, rotenone (0.5 g) was converted into 6a,12a-*methanorotenol* (2a) (370 mg, 71%), m.p. 133—134 °C (from methanol), $[\alpha]_D^{27}$ −105° (*c* 0.95, $CHCl_3$) (Found: C, 70.35; H, 6.05%; M^+, 408. $C_{24}H_{24}O_6$ requires C, 70.6; H, 5.9%; *M*, 408); $\lambda_{max.}$ ($CHCl_3$) 246 (4.58), 298 (4.32), and 318 nm (4.10); $\nu_{max.}$ 2 800br, 1640, and 1 600 cm⁻¹; δ 12.43 and 12.41 (1 H, s, 8-OH, indicates diastereoisomers), 7.92 (1 H, d, *J* 8 Hz, 11-H), 6.56 (1 H, s, 1-H), 6.55 (1 H, s, 4-H), 6.30 (1 H, d, *J* 8 Hz, 10-H), 5.35 (1 H, t, 5′-H), 5.12 (1 H, s, 7′-H), 4.98 (1 H, s, 7′-H), 4.30 (2 H, 6-H_2), 3.58 and 3.68 (each 3 H, s, OMe), 3.20 (2 H, m, 4′-H_2), 1.95 (2 H, 6a-H, cyclopropyl-C*H*H), 1.79 (3 H, s, 8′-H_3), and 1.34 (1 H, cyclopropyl-CH*H*).

(±)-6a,12a-*Methanoisorotenol* (2h).—Following the method described above, isorotenone (0.5 g) was transformed into *compound* (2h) (370 mg, 71%), m.p. 116—118 °C (from methanol) (Found: C, 70.4; H, 6.2%; M^+, 408.157. $C_{24}H_{24}O_6$ requires C, 70.6; H, 5.9%; *M*, 408.155); $\lambda_{max.}$ ($CHCl_3$) 246 (4.58), 253 (4.56), 263 (4.23), 288 (4.21), and 342 nm (2.64); δ 12.70 (1 H, s, OH), 7.59 (1 H, d, *J* 10 Hz, 11-H), 6.75 (1 H, d, *J* 10 Hz, 10-H), 6.55 (1 H, s, 1-H), 6.30 (1 H, s, 4-H), 6.40 (1 H, s, 4′-H), 4.23 (2 H, 6-H_2), 3.50 and 3.55 (each 3 H, s, OMe), 3.00 (1 H, m, *J* 6 Hz, 6′-H), 1.94 (2 H, 6a-H, cyclopropyl C*H*H), 1.30 (6 H, d, CH*Me*$_2$), and 1.3 (1 H, cyclopropyl-CH*H*). In C_6D_6 the δ 4.30 (6-H_2) signal shifted to δ 3.90, and the broad high field signals resolved into multiplets; the results of irradiation at δ 3.90 allowed the three cyclopropyl protons to be assigned to the signals at δ 1.55 (6a-H), 1.32 (*trans*-methylene-H), 1.95 (*cis*-methylene-H), with J_{gem} 3.5, $J_{vic\text{-}cis}$ 7.0, $J_{vic\text{-}trans}$ 5.5 Hz.

6aβ,12aβ-*Rotenolone Trimethylsilyl Ether*.—(−)-Rotenone was oxidised (dichromate–acetic acid) by the literature method [10] to yield 6aβ,12aβ-rotenolone (4a) (51%), m.p. 86—87 °C (MeOH solvate) (lit.,[10] 88 °C). The ketol (1 g; free from methanol of crystallisation) in dry pyridine (35 cm³) with hexamethyldisilazane (4 cm³) and trimethylsilyl chloride (1 cm³) was stirred overnight at ambient temperature. The solution was diluted with water, and the mixture extracted with chloroform. The extracts were washed with dilute hydrochloric acid and water, dried, and evaporated. The residual gum crystallised from methanol to yield the *trimethylsilyl ether* (5a) (0.76 g, 65%), m.p. 153.5—154 °C, $[\alpha]_D^{25}$ −75° (*c* 1.92, $CHCl_3$) (Found: C, 64.75; H, 6.2%; M^+, 482.173. $C_{26}H_{30}O_7Si$ requires C, 64.85; H, 6.1%; *M*, 482.176); $\lambda_{max.}$ ($CHCl_3$) 247 (4.07), 295 (4.16), and 315 nm (3.94); $\nu_{max.}$ (KBr) 1 680 and 1 609 cm⁻¹; δ 7.9 (1 H, d, *J* 9 Hz, 11-H), 6.64 (1 H, s, 1-H), 6.58 (1 H, d, *J* 9 Hz, 10-H), 6.52 (1 H, s, 4-H), 5.25 (1 H, t, 5′-H), 5.10 and 4.98 (each 1 H, br, s, 7′-H_2), 4.58 (3 H, 6-H_2 and 6a-H), 3.89 and 3.78 (each 3 H, s, OMe), 3.10 (2 H, 4′-H_2), 1.76 (3 H, s, 8′-H_3), and 0.10 (9 H, s, $SiMe_3$).

Trimethylsilyl Ether of 6aβ,12aβ-*Rotenolone* 6′-*Norketone* (5f).—The rotenolone ether (5a) (0.5 g) in dioxan (25 cm³) and water (2.5 cm³) was stirred with osmium tetraoxide (*ca.* 8 mg) for 15 min. Sodium periodate (0.75 g) was added over 1 h, and the mixture set aside with stirring for 36 h. It was then filtered and the precipitate washed with chloroform. The combined filtrate and washings were evaporated to dryness, the residue was dissolved in chloroform, and the solution was washed with aqueous sodium hydrogencarbonate and water, dried, and evaporated. The residual gum was chromatographed on a dry silica G column, packed in nylon tube, using hexane–ether–ethyl acetate–propan-2-ol (12 : 12 : 4 : 1). Material from the major band crystallised from ether–hexane or dry methanol to yield the *diketone* (5f) (170 mg), m.p. 113—114 °C, $[\alpha]_D^{25}$ −38° (*c* 2.2, $CHCl_3$) (Found: C, 61.5; H, 6.0%; M^+, 484.157. $C_{25}H_{28}O_8Si$ requires C, 62.0; H, 5.8%; *M*, 484.155); $\lambda_{max.}$ ($CHCl_3$) 289 (4.27) and 315 nm (3.91); $\nu_{max.}$ (KBr) 1 712, 1 678, and 1 610 cm⁻¹; δ 7.92 (1 H, d, *J* 8 Hz, 11-H), 6.68 (1 H, s, 1-H), 6.61 (1 H, d, *J* 8 Hz, 10-H), 6.52 (1 H, s, 4-H), 5.12 (1 H, 5′-H), 4.61 (3 H, 6-H_2 and 6a-H), 3.90 and 3.80 (each 3 H, s, OMe), 3.18 (2 H, m, 4′-H_2), 2.32 (3 H, s, 8′-H_3), and 0.07 (9 H, s, $SiMe_3$).

6aβ,12aβ-*Rotenolone Trimethylsilyl Ether* (5a) *from Wittig Methylenation*.—(*a*) [^{14}C]Methyltriphenylphosphonium iodide (0.113 g, 0.27 mmol) (from triphenylphosphine and [^{14}C]methyliodide) was dissolved in anhydrous tetrahydrofuran (5 cm³) under nitrogen. The solution was stirred at ambient temperature during the addition of n-butyl-lithium in hexane (0.2 cm³; 1.4M-solution); after 5 min the ketone (5f) (0.143 g, 0.29 mmol) in tetrahydrofuran (4 cm³) was added slowly and the mixture stirred for 1.5 h at ambient temperature. The mixture was diluted with water and extracted with ether (4 × 10 cm³). The extracts were washed, dried, and evaporated. The residue, in hexane–ether–ethyl acetate (3 : 3 : 1) was filtered through a short silica column and then purified by p.l.c. (same solvent system) to yield the title ether (81 mg, 60%). The [^{14}C]-specimen was used without further purification. The specimen from a 'cold' run, m.p. 153 °C, had ^{1}H n.m.r. signals identical with those from an authentic sample.

(*b*) In a different experiment, on the same scale, the ketone (5f) run through an alumina column was employed in the methylenation: the product (35 mg) from p.l.c. was thrice crystallised from methanol to yield the 6aβ,12aβ,5′α-*epimer* (5i) (7.5 mg), m.p. 212—214 °C (Found: M^+, 482.173. $C_{26}H_{30}O_7Si$ requires *M*, 482.176); δ 7.90 (1 H, d, *J* 9 Hz, 11-H), 6.68 (1 H, s, 1-H), 6.58 (1 H, d, *J* 9 Hz, 10-H), 6.52 (1 H, s, 4-H), 5.30 (1 H, 5′-H), 5.08 and 4.95 (each 1 H, br, s, 7′-H_2), 4.58 (3 H, 6-H_2 and 6a-H), 3.87 and 3.78 (each 3 H, s, OMe), 3.10 (2 H, m, 4′-H_2), 1.70 (3 H, s, 8′-H_3), and 0.10 (9 H, s, $SiMe_3$). From the mother liquor was obtained the 6aβ,12aβ,5′β-epimer, (5a) (8.3 mg), m.p. 148—150 °C, with ^{1}H n.m.r. signals identical with those of an authentic specimen (above).

Protiodesilylation of 6aβ,12aβ-[7′-^{14}C]*Rotenolone Trimethylsilyl Ether*.—The silyl ether (5a) (81 mg) was dissolved in methanol (15 cm³) at 40 °C, and potassium iodide (100 mg) and 2M-hydrochloric acid (2 cm³) were added. After 10 min at 40 °C the mixture was poured into water and the product extracted with chloroform. The extracts were

washed with aqueous sodium disulphite and water, dried, and evaporated. The residue crystallised on addition of methanol to yield [7′-^{14}C]rotenolone methanol solvate (4a) (63 mg, 91%), m.p. and mixed m.p. with an authentic sample [10] 86—87 °C. The ^{1}H n.m.r. spectrum of a sample from a 'cold' run was identical with that of authentic material.

[7′-^{14}C]*Rotenone*.—6aβ,12aβ-[7′-^{14}C]Rotenolone (63 mg) in acetic acid (8 cm^3) was added to a suspension of zinc dust (5 g) in acetic acid (30 cm^3). The mixture was refluxed with rapid and efficient stirring under nitrogen. The reaction was monitored by t.l.c. and three portions of zinc dust (2 g) were added at 3 h intervals. After 11.5 h, the mixture was cooled, filtered, and mixed with water (20 cm^3) and chloroform. Solid sodium hydrogencarbonate was added until effervescence ceased. The chloroform layer was separated and the aqueous fraction extracted with the same solvent. The organic extracts were washed, dried, and evaporated. The residue was purified by p.l.c. (chloroform–methanol, 99 : 1) to yield (−)-[7′-^{14}C]rotenone (21 mg, 35%) after recrystallisation from ethanol, m.p. 156—159 °C (lit.,[17] 163 °C), $[\alpha]_D^{22}$ −258° (*c* 0.46, C_6H_6) {lit.,[18] $[\alpha]_D^{20}$ −228° (*c* 2.22, C_6H_6)}. In 'cold' runs on the same scale the product had a ^{1}H n.m.r. spectrum identical with that of an authentic spectrum. In these experiments both the yield of rotenone (maximum attained 60%) and the time required for reduction (minimum 5 h) were variable (surface reaction). A little (2—10%) 12,12a-didehydrodeoxyrotenone [18] was obtained from the p.l.c., identified by comparison with authentic material.

O-*Allylisoderritol Isoflavone* (12h).—(−)-Isorotenone [19] (prepared from natural rotenone by acidic isomerisation), was cleaved by zinc–alkali [19] to isoderritol (7h), m.p. 146 °C (lit.,[20] 150 °C), which was then transformed by standard methods [21] into the corresponding isoflavone (11h), m.p. 181—182 °C (lit.,[21] 182—183 °C). The isoflavone (350 mg, 1.0 mmol) in dry redistilled dimethylformamide (5 cm^3) was treated with sodium hydride (30 mg, 1.25 mmol) with stirring, for 15 min; allyl bromide (0.2 cm^3, 2.47 mmol) was then added. After 2 h at room temperature more sodium hydride (20 mg) and allyl bromide (0.1 cm^3) were added in turn, and the mixture was stirred for 1 h more, then poured into water. An oil separated and solidified; it was collected in ether. The extracts were washed with 2M-sodium hydroxide and water, dried, and evaporated. The residue crystallised from methanol to yield O-*allylisoderritol isoflavone* (12h) (267 mg, 64%), m.p. 145—146 °C (Found: C, 71.3; H, 6.0. $C_{25}H_{24}O_6$ requires C, 71.4; H, 5.7%); $\lambda_{max.}$ 237.5 (4.57), 246 (4.53), and 296 nm (4.99); $\nu_{max.}$ 1 645, 1 614, 1 585, 1 518, and 787 cm^{-1}; δ 1.37 (6 H, d, CH*Me*$_2$), 3.10 (1 H, m, C*H*Me$_2$), 3.79 and 3.83 (both 3 H, s, OMe), 4.40 (2 H, m, O–CH$_2$), 5.12 (2 H, m, C=CH$_2$), 5.82 (1 H, m, C*H*=CH$_2$), 6.53 (1 H, s) and 6.90 (1 H, s) (ring *A** H), 6.61 (1 H, s, ring *E* H), 7.34 (1 H, d, *J* 9 Hz) and 7.98 (1 H, d, *J* 9 Hz) (ring *D* H), and 7.94 (1 H, s, O–CH=C).

O-*Allylisoderritol* (13h).—*O*-Allylisoderritol isoflavone (194 mg, 0.46 mmol) was refluxed in ethanol (25 cm^3) containing water (2.5 cm^3) and sodium hydroxide (1 g) for 25 min. The mixture was diluted with water and acidified, then extracted with ether. The extracts were washed, dried, and evaporated. The residue crystallised from methanol to yield *ketone* (13h) (110 mg, 58%), m.p. 91—92 °C (Found: C, 70.4; H, 6.75. $C_{24}H_{26}O_6$ requires C, 70.25; H, 6.35%); $\lambda_{max.}$ 242 (4.63), 247 (4.57), 261 (4.86), 281.5 (4.36), and 334.5 nm (3.63); $\nu_{max.}$ 1 644, 1 616, 1 599, 1 531, 924, and 779 cm^{-1}, δ 1.32 (6 H, d, CH*Me*$_2$), 3.02 (1 H, m, C*H*Me$_2$), 3.76 and 3.80 (each 3 H, s, OMe), 4.22 (2 H, s, CH$_2$CO), 4.45 (2 H, m, CH$_2$O), 5.19 (2 H, m, C=CH$_2$), 5.88 (1 H, m, CH=C), 6.46 (1 H, s, ring *A* H), 6.46 (1 H, s, ring *E* H), 6.68 (1 H, s, ring *A* H), 6.86 and 7.70 (each 1 H, d, *J* 9 Hz, ring *D* H), and 13.94 (1 H, s, OH).

The Aldehyde (6h).—*O*-Allylisoderritol (100 mg) and osmium tetraoxide (5 mg) were dissolved in dioxan (3 cm^3) and water (1 cm^3) and the mixture was stirred at room temperature for 10 min. Sodium periodate (150 mg) was added and the mixture shaken for 2 h, then poured into brine. The organic products were collected in ether and purified by p.l.c. (chloroform–methanol, 98 : 2). The major band afforded the *aldehyde* (6h) as an unstable gum (31 mg, 31%) (Found: M^+, 412.150. $C_{23}H_{24}O_7$ requires *M*, 412.153); $\lambda_{max.}$ 242 (4.60), 247 (4.54), 260 (4.10), 282 (4.05), and 335 nm (3.62); $\nu_{max.}$ (CCl_4) 1 745, 1 640, 1 617, 1 523, and 943 cm^{-1}; δ 1.29 (6 H, d, CH*Me*$_2$), 2.95 (1 H, m, C*H*Me$_2$), 3.74 and 3.76 (each 3 H, s, OMe), 4.26 (2 H, s, CH$_2$CO), 4.46 (2 H, s, OCH$_2$), 6.36 and 6.71 (each 1 H, s, ring *A* H), 6.48 (1 H, s, ring *E* H), 6.90 and 7.71 (each 1 H, d, *J* 9 Hz, ring *D* H), 9.65 (1 H, s, CHO), and 13.92 (1 H, s, OH).

Isoderrisic Acid (14h).—The aldehyde (6h) (12 mg) was refluxed with fresh silver(I) oxide (300 mg) in dry acetone for 1 h. The mixture was filtered, and the filtrate and washings were evaporated to dryness. The residue crystallised from methanol to yield isoderrisic acid (4.6 mg, 37%), m.p. and mixed m.p. with an authentic specimen [22] 153—154 °C and with an i.r. spectrum identical with that of the authentic spectrum.

(±)-*Isorotenone*.—The aldehyde (6h) (50 mg) was refluxed in dry pyridine (1 cm^3) for 30 min. After dilution of the solution with water, the product was extracted with chloroform. The extracts were washed with 2M-hydrochloric acid and water, dried, and evaporated. The residue was purified by p.l.c. (chloroform–methanol, 99 : 1) and material from the major band was recrystallised from methanol to yield (±)-isorotenone (15 mg, 30%), m.p. and mixed m.p. 164—165 °C. The i.r. spectra of the product and authentic (±)-isorotenone were identical.

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* Rotenoid lettering retained.

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