# Synthetic Modulation of the Peripheral 2-, 3-, 9- and 12-Oxygenation Pattern of Rotenoids

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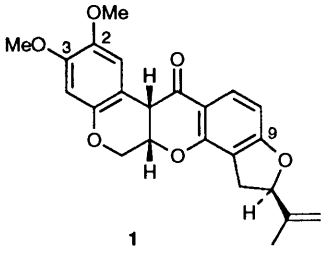
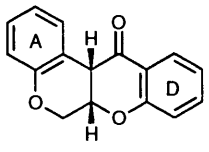
Synthetic modulations of the rotenoid munduserone, in terms of the peripheral oxygenation pattern, have been carried out for structure–activity purposes. Synthesis by propargyl Claisen rearrangement was successful in cases having 2,3-dimethoxylation in ring A (as in natural Leguminous rotenoids), but failed when this electron release was not present. Attempts to catalyse an unsuccessful case led instead to an alkylidenedihydrobenzofuranone. The rotenoid lacking 2,3-dimethoxylation was made by chromanone β-ester synthesis, as was the parent rotenoid of the *Boerhaavia* (monocotyledonous) group.

The rotenoid 12-carbonyl can be removed by reduction and dehydration, and the resulting stilbene, when catalytically hydrogenated, gives the *cis*-B/C-12-deoxy compound. When the reduction is effected by dissolving magnesium in methanol a separable mixture of *cis*- and *trans*-12-deoxyrotenoids is obtained.

Members of the rotenoid group of natural products, among which is rotenone **1**, possess ichthyotoxic properties[1] valued in wildlife conservation, though their insecticidal[2] and anti-feedant[3] properties are best known, and are commercially important. Other useful biological activities such as anti-microbial and antiviral action,[4] and the ability to inhibit microtubule formation from tubulin,[5] are recognised. The insect and fish toxicities depend on inhibition of the NADH–ubiquinone reductase system, part of the electron-transport chain,[6] and can be modelled in terms of a submitochondrial preparation from blowfly flight muscle. A number of natural rotenoids and their readily available chemical modifications have been examined in this type of test[7,8] (as well as in terms of whole insect activity)[9] but the restriction to mainly natural product structures and their close derivatives has limited the development of useful structure–activity relationships.



**1**



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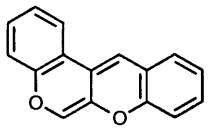

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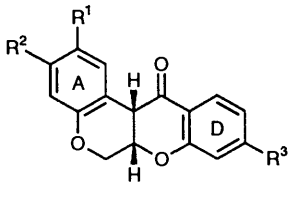
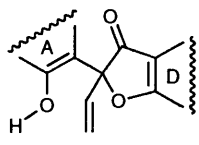


| Ring A | Ring D |
|---|---|
| **4** $R^1 = R^2 = R^3 = OMe$ | |
| **5** $R^1 = R^2 = OMe$, $R^3 = H$ | |
| **6** $R^1 = R^2 = H$, $R^3 = OMe$ | |
| **2** $R^1 = R^2 = R^3 = H$ | |
| **7** $R^1 = R^2 = OMe$, $R^3 = OH$ | |

The essential structural core of the natural rotenoid group is the chromanochromone **2**, (6a*S*,12a*S*)-6a,12a-dihydro-6*H*-rotoxen-12-one, derived from the primitive rotoxene skeleton **3**.[10] The well known Leguminous rotenoids, of which rotenone is a member, possess oxygenation at C-2, -3 and -9 (and sometimes C-11), as well as at the 12-carbonyl, and an objective of this paper was the synthesis of representatives systematically lacking parts of this oxygenation in order to assess its importance for activity. Munduserone **4** was taken as a starting point, and then compounds with ring D, then ring A, then both rings D and A stripped of oxygenation as in structures **5**, **6**, and **2**. A considerable number of synthetic approaches to the natural rotenoids have been made,[11,12] but most have been aimed at the C-2, -3, -9 oxygenation pattern which contains a highly electron-rich ring A. This in itself can lead to certain synthetic limitations, as will be seen.



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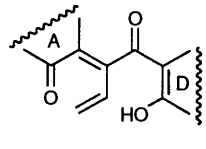

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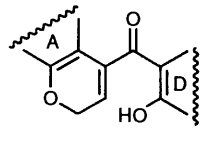

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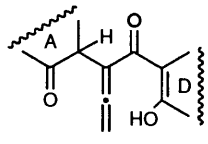
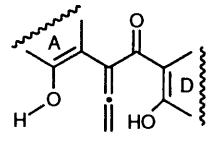


**11**

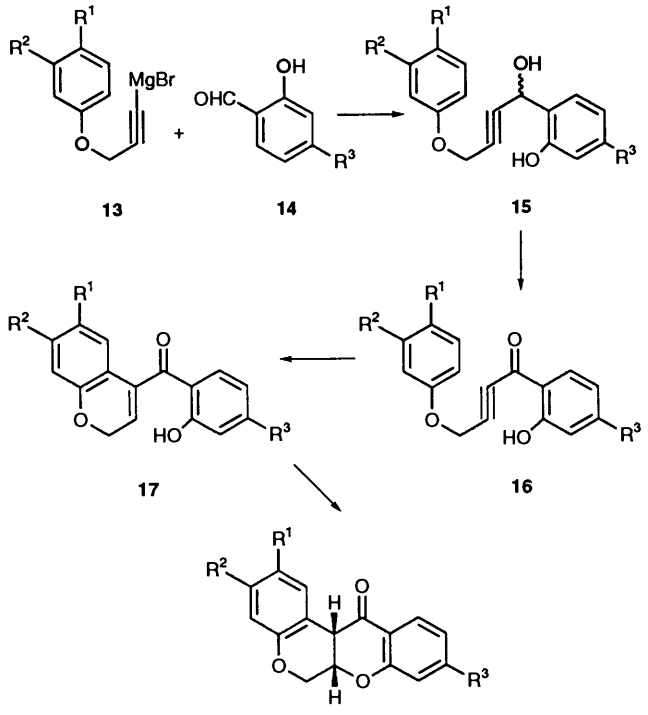


**12**

## Results and Discussion

In earlier work we have developed a synthesis of rotenone and isorotenone in which a dienone **9**, formed thermally from a vinylcumaranone **8**, undergoes electrocyclisation to form a chromene **10**: under basic conditions the latter undergoes intramolecular *O*-Michael addition of the ring D phenolate anion, thus completing the assembly of rings A–D.[13] The overall reaction involves merely heating the vinylcumaranone in pyridine, and the cumaranone is readily made, in turn, by the addition of dimethylsulfoxonium ylide to an isoflavone (synthetic or natural). The need for a suitable isoflavone places restrictions, however, and we decided initially to use Omokawa and Yamashita's approach,[14] which employs starting materials that are potentially easy to vary. This is indicated in generalised form in Scheme 1. The later stages of the sequence must be similar to the vinylcumaranone reaction, and the overall method is a substituted variant of Schmid's acetylene-based chromenylation using the Claisen rearrangement.[15] The reaction involves a [3,3] sigmatropic rearrangement of the aryl propargyl ether **16**, leading to the keto allene **11**: it is thought that this is the

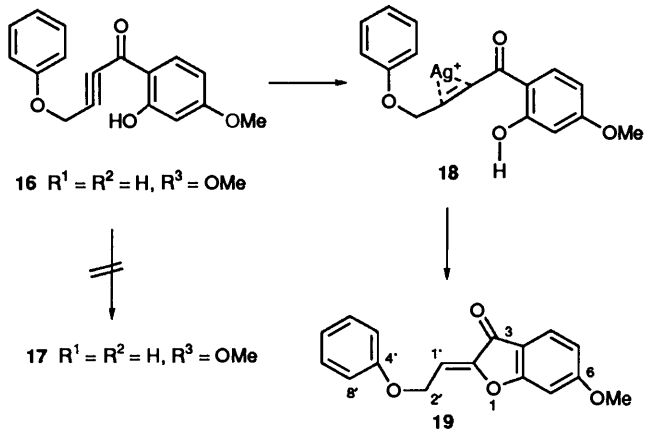
slow, rate-determining step of the mechanism. The ketone then undergoes enolisation to regain aromaticity, forming the phenol allene **12**, which participates in a [1,5] suprafacial shift of hydride to form ketone **9**, setting up the molecule for a further [3,3] electrocyclic process, resulting in the desired chromene intermediate **10** which can be cyclised to the desired rotenoid under mild basic conditions.



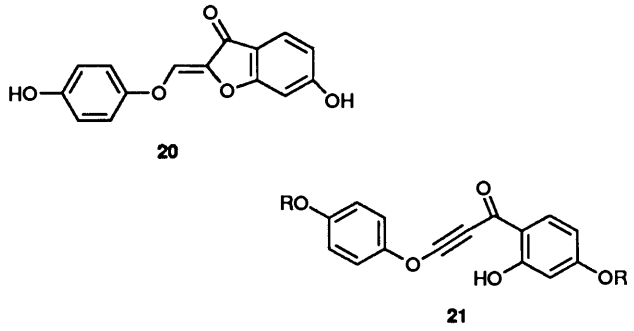

**Scheme 1** Synthesis of rotenoids by propargyl Claisen rearrangement[14]

The procedure[14] was first used to make 9-*O*-demethylmunduserone **7**, a key biosynthetic parent of rotenone required for biosynthetic work, and, by methylation, munduserone **4** itself. Our main departure from Omokawa and Yamashita's method was catalytic hydrogenolysis of benzyl protection used in the D-ring, since aluminium bromide in benzene, as recommended, caused the formation of diphenylmethane which was difficult to remove. Yields for the conversion of reagents **13** + **14** into the alcohol **15**, then ketone **16**, were 33% overall ($R^1 = R^2 = OMe$, $R^3 = OBn$). For the conversion of ketone **16** into the chromene **17**, then into chromanochromone ($R^1 = R^2 = OMe$, $R^3 = OBn$), the overall yield was 21%. Demethylation by hydrogenolysis over a palladium catalyst gave (±)-9-*O*-demethylmunduserone **7**, methylated (70%) to (±)-munduserone **4**. The rotenoid **5**, lacking 9-oxygenation in ring-D, was then made similarly, corresponding overall yields being 29% for the formation of compound **16** ($R^1 = R^2 = OMe$, $R^3 = H$) and 28% for conversion of the latter into the chromanochromone **5** ($R^1 = R^2 = OMe$, $R^3 = H$). In both syntheses rather stern conditions (9–11 h in refluxing *o*-dichlorobenzene, b.p. 179 °C) were required to bring about the Claisen rearrangement. However, when the method was applied to the example **6**, lacking 2,3-methoxylation, although the precursor **16** ($R^1 = R^2 = H$, $R^3 = OMe$) was obtained in 24% yield from phenyl propargyl ether, no Claisen rearrangement took place even after heating of the precursor **16** for several days refluxing in *o*-dichlorobenzene. All of the four examples described by Omokawa and Yamashita give rotenoids having 2,3-dimethoxylation in ring A of the final product and it appears that an electron-rich ring A is necessary to the success of the initial step of the Claisen rearrangement, thus placing limitations on its utility for our purposes.

A number of catalysts[16] have been reported for Cope and Claisen rearrangements but many are 'hard' Lewis acids which would not be compatible with other functionality in our type of precursor. The preferred catalyst for cyclisation of aryl propargyl ethers is a silver(I) salt,[17] and the mechanism of this charge-accelerated Claisen rearrangement has been studied by Schmidt.[18] The silver salt is considered to complex with the p-orbitals of the acetylene which are not involved in the [3,3] sigmatropic shift (see structure **18**). Silver tetrafluoroborate in chloroform at room temperature did indeed result in complete consumption of the starting acetylene **16** ($R^1 = R^2 = H$, $R^3 = OMe$), but the product was not the expected product **17** ($R^1 = R^2 = H$, $R^3 = OMe$), but instead the five-membered ketone **19** (Scheme 2). It had $\nu_{max}$ 1705 $cm^{-1}$, compared with ~1650 $cm^{-1}$ expected for an unstrained α,β-unsaturated six-membered ketone, and a coupling constant of 6.5 Hz between the vinyl and allyl protons. The geometry is proposed to be *Z* on the basis that the compression between the methylene hydrogens and the ring oxygen is much less (2.6 Å) than the compression between the methylene hydrogens and the carbonyl oxygen of the *E*-form (2.1 Å). Such an argument was used by us in connection with the stereochemistry of chalaurenol **20**,[19] a peroxidase enzyme product formed from a chalcone, and confirmed by an X-ray structure determination. Indeed the present work suggests that chalaurenol itself might be synthesized by silver salt-catalysed cyclisation of the precursor **21**, though we have not explored this practically. After this work had been completed, a silver-catalysed cyclisation of a similar type leading to an aurone was noted.[20]

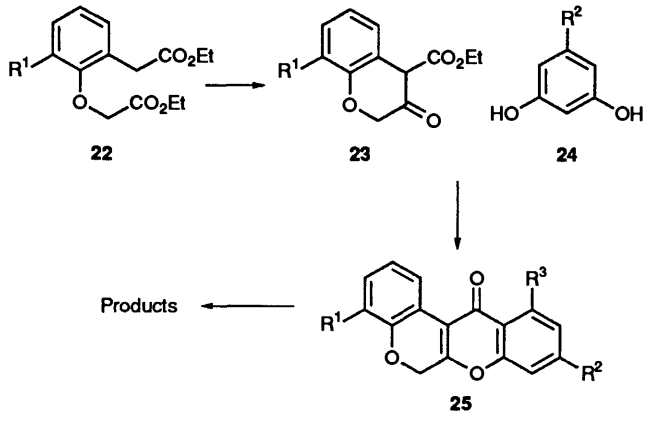



**Scheme 2** Silver tetrafluoroborate-catalysed cyclisation



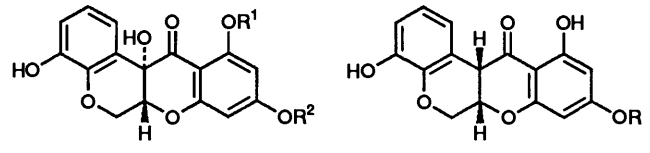

In view of these limitations of the acetylenic ether approach, we turned to methods involving preformed rings A and B.[21,22] The chromanone ester **23** ($R^1 = H$) was prepared (68%) by Dieckmann condensation from diester **22** ($R^1 = H$) and was then condensed with resorcinol **24** ($R^2 = H$) at 150–160 °C under reduced pressure to give the 6a,12a-didehydrorotenoid **25** ($R^1 = R^3 = H$, $R^2 = OH$) (36%) (Scheme 3). This was

methylated ($CH_2N_2$), reduced with diisobutylaluminium hydride (DIBAL) in tetrahydrofuran (THF) at low temperature and epimerised at C-12a to form the required thermodynamically stable *cis*-rotenoid **6** with the 2,3-methoxy groups of ring A stripped away, but that at C-9 in position (the use of DIBAL in this context is discussed elsewhere).[23]




**Scheme 3** Rotenoid synthesis *via* chromanone ester condensation[21,22]

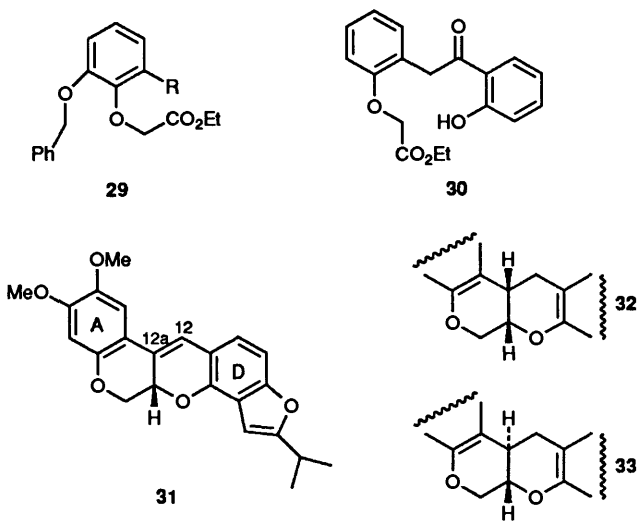
As mentioned above the long known rotenoids from the Papilionatae division of the Leguminosae (Fabaceae) carry oxygenation at C-2, -3 and -9: a further well known sub-group has additional oxygenation at C-11 (*e.g.* toxicarol).[24] More recently, rotenoids have been found in the monocotyledonous families Nyctaginaceae and Iridaceae, far removed from the Leguminosae in classification terms, and these lack the characteristic 2,3-oxygenation of ring A. *Iris spuria*, for example, contains rotenoids lacking ring A oxygenation on C-1 to C-4,[25] and compounds **26** and **27** are found in *Boerhaavia coccinea*.[26] To extend knowledge of the effects of oxygenation patterns in the rotenoid series, we have therefore made compound **28** (R = H), parent of the latter series. We also hoped to make compound **28** (R = Me), though protection difficulties were encountered here.




**26** $R^1 = R^2 = H$
**27** $R^1 = H$, $R^2 = Me$

**28**

2,3-Dihydroxybenzaldehyde was selectively monobenzylated using Kessar's method[27] and the product was then alkylated with ethyl bromoacetate under standard conditions to give ester **29** (R = CHO) in excellent yield. Reduction to the alcohol with sodium borohydride, followed by chain extension (*via* the chloride and nitrile), gave the required diester **22** ($R^1$ = OBn), which was cyclised in poor yield (23%) under Dieckmann conditions to give the β-keto ester **23** ($R^1$ = OBn). The latter was condensed by being heated with phloroglucinol **24** ($R^2$ = OH) under reduced pressure at 150–160 °C. During this process the benzyl protection was unexpectedly lost so the planned selective methylation at the unchelated 9-position could not be attained. However, the required didehydro compound **25** ($R^1 = R^2 = R^3$ = OH) was obtained (21%). This could be reduced at C-6a, -12a by our DIBAL technique[28] and epimerised at C-12a to give the parent rotenoid **28** (R = H) of the two *Boerhaavia* compounds. Whilst the C-1 proton was hidden in a multiplet at δ 6.55–6.66, and its exact position cannot be stated, the general position was consistent with a *cis*-B/C fusion and this was borne out by a 3.8 Hz coupling between the C-6a and -12a protons. The C-8 and C-10 protons show *meta*-coupling, appearing as a pair of doublets (*J* 2.5 Hz), and the proton of the chelated 11-hydroxy group resonated at δ 12.03. The expected mass spectral cleavages were observed.




6a,12a-Dihydrorotoxen-12(6*H*)-one **2**, the rotenoid core bereft of all hydroxylation and methylation, has already been obtained in our earlier work.[10,29] It is easily obtained largely because the parent deoxybenzoin is readily accessible through a symmetrical benzoin condensation using salicyaldehyde methoxymethyl ether.[30] The deoxybenzoin is easily converted into compound **30** and this was cyclised by base to give the 6a,12a-didehydro precursor **25** ($R^1 = R^2 = R^3$ = H) of compound **2**.[30] There are suitable methods for the reduction of this to give compound **2**. This work thus provides the comparative set of four rotenoids, compounds **4**, **5**, **6**, and **2**, for biological evaluation of oxygenation patterns on the rotenoid core.

Finally, in connection with these structural modulations, a suitable method for removal of the 12-carbonyl group, giving the deoxygenated B/C-system in *cis*- and *trans*-fusions, was required. The problem was explored on isorotenone as a model. Reduction of the 12-carbonyl with sodium borohydride gives a 12α-hydroxy compound easily dehydrated to the stilbene **31**.[10] Catalytic hydrogenation of the latter over a palladium on charcoal catalyst gave the *cis*-B/C-deoxyisorotenone **32**, delivery of hydrogen from the catalyst to the less hindered face of the molecule. On the other hand, reduction with magnesium in methanol gave two products separable by HPLC. One of these was again the *cis*-B/C-product **32** having $J_{6a,12a}$ 4.5 Hz; the other was its *trans*-B/C-isomer **33** having $J_{6a,12a}$ 9.5 Hz.

Products from this and the following papers have been assayed for their inhibition of NADH dehydrogenase in a blowfly flight-muscle submitochondrial preparation.[31] For earlier data see Burgos and Redfearn[8] and Horgan *et al.*[7]

## Experimental

$^1$H NMR spectra were recorded using 400 MHz Bruker AM400, 250 MHz Bruker WM250 or AM250, 90 MHz Perkin-Elmer R32, 80 MHz Bruker WP80SY or 60 MHz Varian T60 spectrometers. The operating frequency and solvent are quoted in parentheses before the chemical-shift values (δ relative to internal $SiMe_4$). *J*-Values are given in Hz. $^{13}$C NMR spectra were recorded using either a Bruker AM400 spectrometer operating at 100 MHz or a Bruker WM250 spectrometer

operating at 63 MHz, with broad-band decoupling. Primary, secondary, tertiary and quaternary carbons were assigned by use of a DEPT pulse sequence. NMR Locants throughout refer to the rotenone numbering scheme. Mass spectra were recorded on a VG 70E or an updated AEI MS 902 instrument. UV data were measured in EtOH using a Philips PU8720 spectrometer. IR spectra were measured on a Pye-Unicam SP3-100 or a Perkin-Elmer 983g instrument. M.p.s were determined by use of a Kofler hot-stage microscope.

Analytical TLC was performed on 5 × 2 cm silica gel $HF_{254}$-coated (0.25 mm) plates, inspected under UV light or visualised by conc. sulfuric acid–*p*-anisaldehyde spray. Analytical and semi-preparative high-performance liquid chromatography (HPLC) was performed using Waters equipment (UV and refractive index detection) and RAD PAK (10 cm × 8 mm i.d.) columns of μ-Porosil. Light petroleum refers to the fraction boiling in the range 60–80 °C

*Acetylenic Ketones* **16** ($R^1$ = $R^2$ = H, $R^3$ = OMe), **16** ($R^1$ = $R^2$ = OMe, $R^3$ = H) *and* **16** ($R^1$ = $R^2$ = OMe, $R^3$ = OBn).—Ethylmagnesium bromide was prepared from ethyl bromide (1.6 g, 1.10 $cm^3$, 14.6 mmol) and magnesium (0.34 g, 14.6 mmol) in dry THF (5 $cm^3$). A solution of phenyl propargyl ether[32] (1.93 g, 14.6 mmol) in dry THF (10 $cm^3$) was added and the mixture was stirred (1 h). A solution of 2-hydroxy-4-methoxybenzaldehyde **14** ($R^3$ = OMe) (1.02 g, 6.6 mmol) in dry THF (10 $cm^3$) was then added dropwise and the mixture was stirred overnight. After addition of aq. ammonium chloride, the mixture was extracted with ethyl acetate and the extract was washed successively with saturated aq. sodium hydrogen carbonate and water, and dried ($MgSO_4$). Evaporation gave an oil, which was dissolved in methylene dichloride (300 $cm^3$) and stirred with activated manganese dioxide (30 g) for 1.5 h. Filtration and evaporation, followed by chromatography on dry silica, and elution with light petroleum–ethyl acetate (10:1), gave the *acetylenic ketone* **16** ($R^1$ = $R^2$ = H, $R^3$ = OMe) (0.44 g, 24% overall), m.p. 111–112 °C (from EtOH) (Found: C, 72.2; H, 4.95%; $M^+$, 282.089. $C_{17}H_{14}O_4$ requires C, 72.35; H, 5.00%; M, 282.089); $\lambda_{max}$(EtOH)/nm 202, 217, 303 and 338 (ε 16 600, 16 100, 11 700 and 9100); $\nu_{max}$(KBr)/$cm^{-1}$ 3400mb (OH), 2980w (CH), 2220m (C≡C), 1630s (CO), 1590s and 1490s (aromatics); $\delta_H$(250 MHz; $CDCl_3$) 3.83 (3 H, s, OMe), 4.98 (2 H, s, $CH_2$), 6.38 (2 H, m, 2 × ArH), 7.04 (3 H, m, 3 × ArH), 7.34 (2 H, m, 2 × ArH), 7.63 (1 H, d, *J* 9.6 11-H) and 11.94 (1 H, s, OH); *m/z* (EI, +ve) 282 (56%, $M^+$), 265 (16, $M^+$ − OH), 189 (64, $M^+ - C_6H_5O$), 188 (49, $C_{11}H_8O_3^+$), 161 (72), 151 (100, $C_8H_7O_3^+$), 132 (30) and 94 (47).

The butynone **16**, ($R^1$ = $R_2$ = OMe, $R^3$ = H)[14] was made similarly from 2,4-dimethoxyphenyl propargyl ether (4.20 g, 22 mmol), magnesium (0.53 g, 22 mmol) and salicylaldehyde **14** ($R^3$ = H) (1.22 g, 10 mmol). The alcohol intermediate **15** was oxidised with activated manganese dioxide (40 g) in methylene dichloride (300 $cm^3$). 4-(3,4-Dimethoxyphenoxy)-1-(2-hydroxyphenyl)but-2-yn-1-one **16** ($R^1$ = $R^2$ = OMe, $R^3$ = H) (0.92 g, 29%) had m.p. 87–88 °C (lit.,[14] 89–89.5 °C).

The butynone **16** ($R^1$ = $R^2$ = OMe, $R^3$ = OBn) was similarly made from 3,4-dimethoxyphenyl propargyl ether (4.20 g, 22 mmol), magnesium (0.53 g, 22 mmol) and 4-benzyloxy-2-hydroxybenzaldehyde **14** ($R^3$ = OBn)[33] (2.30 g, 10 mmol). The alcohol intermediate **15** was oxidised with activated manganese dioxide (40 g) in methylene dichloride (300 $cm^3$) to give the butynone **16** ($R^1$ = $R^2$ = OMe, $R^3$ = OBn) (1.40 g, 33%) as a yellow oil after chromatography, which crystallised on storage m.p. 96–97 °C (lit.,[14] 107.5 °C): it was used directly in the thermolysis and was not recrystallised.

*9-Demethoxymunduserone* **5**.—The phenyl phenoxypropynyl ketone **16** ($R^1$ = $R^2$ = OMe, $R^3$ = H) (130 mg, 0.417 mmol) was refluxed in *o*-dichlorobenzene (15 $cm^3$) under nitrogen for 11 h, after which no starting material remained (TLC). The solvent was removed under reduced pressure and the remaining oil was refluxed with saturated ethanolic sodium acetate (15 $cm^3$) for 2.5 h. The product was poured into water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated. Purification of the product by preparative TLC (PLC) developed with light petroleum–ethyl acetate (4:1) (3 runs), gave 9-demethoxymunduserone **5** (36 mg, 28%) as needles from methanol, m.p. 139–140 °C (lit.,[14] 142.5–143.5 °C); $\nu_{max}$(mull)/$cm^{-1}$ 1690s (CO), 1610s and 1510s (aromatics); $\delta_H$(80 MHz; $CDCl_3$) 3.75 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.90 (1 H, d, *J* 4, 12a-H), 4.17 (1 H, d, *J* 12, 6-H[a]), 4.63 (1 H, dd, *J* 12 and 4, 6-H[b]), 4.95 (1 H, m, 6a-H), 6.47 (1 H, s, 4-H), 6.72 (1 H, s, 1-H), 6.96 (1 H, d, *J* 8, 8-H), 7.04 (1 H, d, *J* 8, 10-H), 7.46 (1 H, ddd, *J* 8, 8 and 2, 9-H) and 7.93 (1 H, dd, *J* 8 and 2, 11(H).

*9-Benzyloxy-2,3-dimethoxy-6a,12a-dihydro*[1]*benzopyrano*-[3,4-b][1]*benzopyran*-12(6H)-*one*.—The ketone **16** ($R^1$ = $R^2$ = OMe, $R^3$ = OBn) (1.26 g, 3.01 mmol) and degassed *o*-dichlorobenzene (40 $cm^3$) were heated under argon for 9 h, after which no starting material remained (TLC). After evaporation under reduced pressure, the product was refluxed with saturated ethanolic sodium acetate (40 $cm^3$) for 2.5 h, and was worked up as above. Chromatography on flash silica, with light petroleum–ethyl acetate (50:3), gave the title compound (0.26 g, 21%), m.p. 170–173 °C (from EtOAc–EtOH) (lit.,[14] 178 °C); $\nu_{max}$(KBr)/$cm^{-1}$ 1665s (CO), 1585s and 1515s (aromatics); $\delta_H$(90 MHz; $CDCl_3$) 3.78 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.83 (1 H, d, *J* 4, 12a-H), 4.11 (1 H. d. *J* 12, 6-H[a]), 4.59 (1 H, dd, *J* 12 and 4, 6-H[b]), 4.90 (1 H, m, 6a-H), 5.06 (2 H, s, $PhCH_2O$), 6.50 (1 H, s, 4-H), 6.51 (1 H, d, *J* 2, 8-H), 6.68 (1 H, dd, *J* 8 and 2, 10-H), 6.83 (1 H, s, 1-H), 7.41 (5 H, s, Ph) and 7.82 (1 H, d, *J* 8, 11-H).

(±)-*Munduserone* **4**.—9-Benzyloxy-2,3-dimethoxy-(6a,12a-dihydro[1]benzopyrano[3,4-*b*][1]benzopyran-12(6*H*)-one (25 mg, 0.060 mmol) was hydrogenated in ethyl acetate (5 $cm^3$) over a 10% palladium on carbon catalyst (3 mg) for 3 h. Filtration through Florisil and crystallisation from chloroform–methanol gave (±)-9-*O*-demethylmunduserone (18 mg, 92%) as needles, m.p. 185–186 °C (lit.,[13] 203–204 °C); $\nu_{max}$(KBr)/$cm^{-1}$ 3450s and 3200s (OH), 1670s (CO). 1620s, 1590s and 1515s (aromatics); $\delta_H$(80 MHz; $CDCl_3$) 3.73 (3 H, s, OMe), 3.78 (3 H, s, OMe), 3.83 (1 H, d, *J* 5, 12a–H), 4.15 (1 H, d, *J* 12, 6-H[a]), 4.61 (1 H, dd, *J* 12 and 3, 6-H[b]), 4.91 (1 H, m, 6a-H), 6.45 (2 H, 4- and 8-H), 6.50 (1 H, dd, *J* 8 and 2, 10-H), 6.76 (1 H, s, 1-H), 7.33 (1 H, s, 9-OH) and 7.83 (1 H, d, *J* 8, 11-H).

A solution of 9-*O*-demethylmunduserone (72 mg, 0.22 mmol) in methanol (8 $cm^3$) was treated with diazomethane [from methyl(nitroso)urea (1.0 g) in diethyl ether]. After storage overnight, the solvent was evaporated off and the product was chromatographed over flash silica, with hexane–ethyl acetate (7:3) as eluent, to give (±)-munduserone **4** (53 mg, 70%), m.p. 165–166 °C (from $CHCl_3$–MeOH) (lit.,[13a] 172 °C); $\nu_{max}$(KBr)/$cm^{-1}$ 1680s (CO), 1615s and 1510s (aromatics); $\delta_H$(90 MHz; $CDCl_3$) 3.71 (3 H, s, OMe), 3.75 (6 H, s, 2 × OMe), 3.80 (1 H, d, *J* obscured, 12a-H), 4.11 (1 H, d, *J* 12, 6-H[a]), 4.58 (1 H, dd, *J* 12 and 3, 6-H[b]), 4.90 (1 H, m, 6a-H), 6.39 (1 H, d, *J* 2, 8-H), 6.43 (1 H, s, 4-H), 6.52 (1 H, dd, *J* 9 and 2, 10-H), 6.75 (1 H, s, 1-H) and 7.85 (1 H, d, *J* 9, 11-H).

*Attempted Claisen Rearrangement of the Acetylenic Ketone* **16** $R^1$ = $R^2$ = H, $R^3$ = OMe.—A solution of the title ketone (55 mg, 0.195 mmol) in degassed *o*-dichlorobenzene was refluxed under nitrogen for 4 days, after which time no starting material remained (TLC). The solvent was removed under reduced pressure and the remaining brown oil was refluxed with

saturated ethanolic sodium acetate (25 $cm^3$) for 2.5 h. Work-up as above gave a brown oil. Careful PLC on silica gel, with light petroleum–ethyl acetate (2:1) as eluent, gave no indication of the formation of a rotenoid.

*Treatment of the Acetylenic Ketone* **16** ($R^1 = R^2 = H$, $R^3 = OMe$) *with Silver Tetrafluoroborate.*—A solution of the title ketone (87 mg, 0.309 mmol) in dry chloroform (1 $cm^3$) was stirred under argon with silver tetrafluoroborate (60 mg, 0.308 mmol) at room temperature overnight. The mixture was filtered through a pad of neutral alumina (Brockmann grade 1), eluted with chloroform, and the solvent was removed under reduced pressure to give the *ketone* **19** (52 mg, 60%), m.p. 103–104 °C (Found: C, 72.45; H, 5.2%; $M^+$, 282.081. $C_{17}H_{14}O_4$ requires C, 72.35; H, 5.0%; M, 282.089); $\lambda_{max}$(EtOH)/nm 199, 219, 258, 265 and 303 (ε 23 100, 25 900, 15 700, 17 100 and 21 400); $\nu_{max}$(KBr)/$cm^{-1}$ 1705s (CO), 1670s (C=C), 1600s and 1495s (aromatics): $\delta_H$(400 MHz; $CDCl_3$) 3.92 (3 H, s, OMe), 4.97 (2 H, d, *J* 6.5, $CH_2$), 6.24 (1 H, t, *J* 6.5, =CH), 6.67 (1 H, d, *J* 2.1, 7-H), 6.74 (1 H, dd, *J* 8.5 and 2.1, 5-H), 6.90–7.06 (3 H, m, 3 × ArH), 7.28 (2 H, m, 2 × ArH) and 7.67 (1 H, d, *J* 8.5, 4-H); $\delta_C$(100 MHz; $CDCl_3$) 56.1 (OMe), 62.0 ($CH_2$, C-2′), 96.5 (CH, C-1′), 109.2 (CH, C-7), 112.2 (CH, C-5), 114.8 (CH, C-5′ and 9′), 117.9 (C, C-3a), 121.3 (CH, C-7′), 126.1 (CH, C-4), 129.6 (CH, C-6′ and 8′), 149.6 (C, C-2), 158.1 (C, C-4′), 163.1 (C, C-6), 167.9 (C, C-7a) and 181.8 (C, C-3); *m/z* (EI, +ve) 282 (23%, $M^+$), 189 (100, $M^+ - C_6H_5O$), 161 (18) and 94 (9).

*Rotoxen*-12(6H)-*one* **25** ($R^1 = R^2 = R^3 = H$).—2,2′-Dihydroxydeoxybenzoin (1.14 g, 5.02 mmol), prepared according to the literature,[30] was dissolved in dry ethanol (15 $cm^3$) to which sodium (0.23 g, 10 mg-atoms) had been added. Ethyl bromoacetate (0.85 g, 0.56 $cm^3$, 5.03 mmol) was added and the mixture was refluxed for 3 h. Hot water (15 $cm^3$) was added and the crystals which separated were filtered off, and recrystallised from ethanol to give rotoxen-12(6*H*)-one (310 mg, 25%), m.p. 135 °C (lit.,[30] 135 °C); $\nu_{max}$(mull)/$cm^{-1}$ 1640s (CO), 1610m, 1570m and 1490m (aromatics and C=C); $\delta_H$(80 MHz; $CDCl_3$) 4.91 (2 H, s, $CH_2$), 7.20 (6 H, m, 6 × ArH), 8.16 (1 H, dd, *J* 8 and 2, 11-H) and 8.67 (1 H, dd, *J* 7 and 2, 1-H).

cis-6a,12a-*Dihydrorotoxen*-12(6H)-*one* **2**.—A solution of rotoxen-12(6*H*)-one (1.00 g, 4.00 mmol) in THF (50 $cm^3$) was warmed to 60 °C and a solution of potassium borohydride (0.6 g, 11.1 mmol) in 50% aq. ethanol (10 $cm^3$) was added. The solution was kept at 60 °C (90 min), cooled, washed with saturated brine, dried ($MgSO_4$), and evaporated. The product was chromatographed on silica gel, with diethyl ether–light petroleum (1:3) as eluent, to give the 6a,12a-dihydro-12-hydroxy compound (540 mg, 53%), m.p. 178–180 °C (lit.,[10] 179–180 °C); $\nu_{max}$(mull)/$cm^{-1}$ 3600mbr (OH), 1610m, 1590m and 1490m (aromatics); $\delta_H$(90 MHz; [$^2H_6$]acetone) 3.0 (1 H, br s, OH), 3.58 (1 H, dd, *J* 6 and 4, 12a-H), 4.40 (2 H, q, *J* 12, 6-$H_2$), 4.80 (1 H, m, 6a-H), 5.29 (1 H, d, *J* 4, 12-H) and 7.20 (8 H, m, 8 × ArH).

The 12-hydroxy compound (502 mg, 1.98 mmol) was dissolved in acetone (65 $cm^3$) and chromium trioxide (500 mg, 5 mmol) was added, the mixture being stirred at room temperature for 36 h. The reaction mixture was poured into water and extracted with diethyl ether. After drying ($MgSO_4$), the extracts were evaporated and the residue was crystallised from methanol to give the title compound **2** (300 mg, 63%), m.p. 163–164 °C (lit.,[10] 163 °C) (Found: $M^+$, 252.078. Calc. for $C_{16}H_{12}O_3$: M, 252.079); $\lambda_{max}$(EtOH)/nm 201, 215, 254 and 322 (ε 27 600, 23 700, 8900 and 2890); $\nu_{max}$(KBr)/$cm^{-1}$ 1696s (CO) 1602s and 1582m (aromatics); $\delta_H$ (400 MHz; [$^2H_6$]benzene) 3.34 (1 H, d, *J* 12.3, 6-H$^a$), 3.45 (1 H, d, *J* 3.8, 12a-H), 3.88 (1 H, m, 6a-H), 4.12 (1 H, dd, *J* 12.1 and 3.0, 6-H$^b$), 6.40–7.10 (6 H, m, 6 × ArH), 7.44 (1 H, d, *J* 7.8, 1-H) and 8.10 (1 H, dd, *J* 7.8 and 1.6, 11-H); $\delta_C$(100 MHz; [$^2H_6$]benzene) 45.5 (CH, C-12a), 66.0 ($CH_2$, C-6), 72.0 (CH, C-6a), 114.5 (C, C-12b), 117.4 (CH, C-4), 118.0 (CH, C-8), 119.6 (C, C-11a), 121.6 (CH, C-10), 121.8 (CH, C-2), 127.8 (CH, C-11), 128.0 (CH, C-1), 129.3 (CH, C-3), 136.2 (CH, C-9), 154.1 (C, C-4a), 160.9 (C, C-7a) and 189.8 (C, C-12); *m/z* (EI, + ve) 252 (10%, $M^+$), 250 (5, $M^+ - 2$), 132 (47, $C_9H_8O^+$) and 131 (100, $C_9H_7O^+$).

9-*Hydroxyrotoxen*-12(6H)-*one* **25** ($R^1 = R^3 = H$, $R^2 = OH$).—Ethyl 3-oxochromane-4-carboxylate **23** ($R^1 = H$) (500 mg, 2.27 mmol), prepared according to Verhé and Schamp,[22] and resorcinol **24** ($R^2 = H$) (165 mg, 1.5 mmol) were heated together at 150–160 °C (bath) for 2 h under reduced pressure (10 mmHg). On cooling, diethyl ether (2 $cm^3$) was added and the gum was triturated until it solidified, when it was filtered off, and washed with cold diethyl ether. Crystallisation from ethyl acetate–diethyl ether gave the *title compound* (142 mg, 36%), m.p. 258–259 °C (Found: C, 72.25; H, 3.75%; $M^+$, 266.060. $C_{16}H_{10}O_4$ requires C, 72.2; H, 3.8%; M, 266.058); $\lambda_{max}$(EtOH)/nm 197, 223, 271 and 298 (ε 26 900, 23 000, 27 200 and 14 300); $\nu_{max}$(KBr)/$cm^{-1}$ 3100s br (OH), 1625s (CO), 1580s and 1490s (aromatics); $\delta_H$(400 MHz; [$^2H_6$]acetone) 5.12 (2 H, s, 6-$H_2$), 6.80–7.30 (6 H, m, 5 × ArH and OH), 8.09 (1 H, d, *J* 8.8, 11-H) and 8.78 (1 H, dd, *J* 7.8 and 1.5, 1-H); *m/z* (El, +ve) 266 (100%, $M^+$), 265 (48, $M^+ - H$), 237 (73) and 120 (26).

9-*Methoxyrotoxen*-12(6H)-*one* **25** ($R^1 = R^3 = H$, $R^2 = OMe$).—A solution of the above 9-hydroxy compound (200 mg, 0.752 mmol) in acetone–methanol (25 $cm^3$) was treated with excess of diazomethane in diethyl ether and set aside overnight. The product was evaporated and the residue was crystallised from methanol to give the *title didehydrorotenoid* (138 mg, 66%), m.p. 142–144 °C (Found: C, 72.6; H, 4.15%; $M^+$, 280.074. $C_{17}H_{12}O_4$ requires C, 72.85; H, 4.3%; M, 280.074); $\lambda_{max}$(EtOH)/nm 200, 224, 270 and 293 (ε 24 400, 23 000, 28 900 and 15 300); $\nu_{max}$(KBr)/$cm^{-1}$ 1635s (CO), 1610s and 1495s (aromatics); $\delta_H$(400 MHz; $CDCl_3$) 3.92 (3 H, s, OMe), 5.04 (2 H, s, 6-$H_2$), 6.85 (1 H, d, *J* 2.3, 8-H), 6.96 (1 H, *J* 8.0, 4-H), 7.00 (1 H, dd, *J* 8.9 and 2.3, 10-H), 7.10 (1 H, m, 3-H), 7.22 (1 H, m, 2-H), 8.22 (1 H, d, *J* 8.9, 11-H) and 8.78 (1 H, dd, *J* 7.8 and 1.5, 1-H); *m/z* (EI, +ve) 280 (100%, $M^+$), 279 (29, $M^+ - H$), 251 (39, $M^+ - CHO$) and 134 (13).

(±)-cis-9-*Methoxy*-6a,12a-*dihydrorotoxen*-12(6H)-*one* **6**.—A solution of DIBAL in toluene (1.0 mol $dm^{-3}$; 1.07 $cm^3$, 1.07 mmol) was added to a solution of the above rotenoid **25** ($R^1 = R^3 = H$, $R^2 = OMe$) (120 mg, 0.429 mmol) in dry THF (5 $cm^3$) at −78 °C under nitrogen, and the mixture was stirred at this temperature for 1 h before warming to room temperature, when dry methanol (2 $cm^3$) was added and the mixture was stirred (30 min) and poured into 1 mol $dm^{-3}$ hydrochloric acid and extracted with chloroform. The extracts were washed successively with water and brine, dried ($MgSO_4$), and evaporated. The off-white solid was dissolved in chloroform (5 $cm^3$) acidified with hydrochloric acid (5 drops) and the solution was refluxed (1 h) under nitrogen. After being poured into water the mixture was re-extracted with chloroform and the extracts were washed and dried as before. Evaporation, and crystallisation from chloroform–methanol, gave the *title* cis-*rotenoid* (66 mg, 55%) as needles, m.p. 151–152 °C (Found: C, 72.15; H, 5.0%; $M^+$, 280.074. $C_{17}H_{14}O_4$ requires C, 72.35; H, 5.0%; M, 280.074); $\lambda_{max}$(EtOH)/nm 205, 212, 276 and 316 (ε 26 400, 25 700, 18 500 and 8400); $\nu_{max}$(KBr)/$cm^{-1}$ 1680s (CO), 1605s and 1490m (aromatics); $\delta_H$(400 MHz; $CDCl_3$) 3.79 (3 H, s, OMe), 3.91 (1 H, d, *J* 3.8, 12a-H), 4.25 (1 H, d, *J* 12.1, 6-H$^a$), 4.66 (1 H, dd, *J* 12.1 and 3.1, 6-H$^b$), 4.97 (1 H, m, 6a-H), 6.41 (1 H, d, *J* 2.4, 8-H), 6.56 (1 H, dd, *J* 8.8 and 2.4, 10-H), 6.80–6.96 (2

H, m, 2 × ArH), 7.10–7.30 (2 H, m, 2 × ArH) and 7.87 (1 H, d, *J* 8.8, 11-H); $\delta_C$(100 MHz; $CDCl_3$) 45.5 (CH, C-12a) 55.7 ($CH_3$, OMe), 66.3 ($CH_2$, C-6), 72.4 (CH, C-6a), 100.8 (CH, C-8), 110.7 (CH, C-10), 112.9 (C, C-11a), 114.4 (C, C-12b), 117.1 (CH, C-4), 121.5 (CH, C-2), 128.5 (CH, C-3), 129.0 (CH, C-1), 129.4 (CH, C-11), 153.4 (C, C-4a), 162.7 (C, C-7a), 166.6 (C, C-9) and 188.9 (C, C-12); *m/z* (EI, +ve) 282 (10%, $M^+$), 280 (5, $M^+ - H_2$), 151 (100, $C_8H_7O_3^+$), 132 (64, $C_9H_8O^+$) and 131 (99, $C_9H_7O^+$).

*Benzyloxy Aldehydo Ester* **29** (R = CHO).—3-Benzyloxy-2-hydroxybenzaldehyde[27] (5.00 g, 21.9 mmol), anhydrous potassium carbonate (5.00 g), dry acetone (100 $cm^3$), ethyl bromoacetate (4.02 g, 2.67 $cm^3$, 24.1 mmol) and potassium iodide (50 mg) were refluxed together for 5 h, cooled, and filtered. Evaporation, and crystallisation from methanol, gave the *aldehydo ester* **29** (R = CHO) (6.32 g, 92%), m.p. 55–56 °C (Found: C, 68.6; H, 5.75%; $M^+$, 314.116. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.75%; M, 314.115); $\lambda_{max}$(EtOH)/nm 219 and 259 (ε 26 000, 12 300); $\nu_{max}$(KBr)/$cm^{-1}$ 1750s (CO), 1695s (CO), 1590 m and 1475 m (aromatics); $\delta_H$(400 MHz; $CDCl_3$) 1.23 (3 H, t, *J* 7.0, Me), 4.15 (2 H, q, *J* 7.0, $OCH_2Me$), 4.86 (2 H, s, $OCH_2CO_2Et$), 5.13 (2 H, s, $OCH_2Ph$), 7.00–7.50 (8 H, m, 8 × ArH) and 10.64 (1 H, s, CHO); *m/z* (EI, +ve) 314 (6%, $M^+$), 223 (34, $M^+ - C_7H_7$), 91 (100, $C_7H_7^+$) and 65 (25).

*Ethyl 2-Benzyloxy-6-(cyanomethyl)phenoxyacetate* **29** (R = $CH_2CN$).—A solution of the aldehydo ester **29** (R = CHO) (1.00 g, 3.18 mmol) in ethanol (15 $cm^3$) was stirred with sodium borohydride (30 mg, 0.796 mmol) at 0 °C for 30 min. Work-up, and chromatography on flash silica, with hexane–ethyl acetate (7:3) as eluent, gave the *benzyl alchohol* **29** (R = $CH_2OH$) (941 mg, 94%) as an oil (Found: $M^+$, 316.132. $C_{18}H_{20}O_5$ requires M, 316.131); $\nu_{max}$(film)/$cm^{-1}$ 3440s br (OH), 1735s (CO), 1590m and 1480s (aromatics).

A solution of thionyl dichloride (262 mg, 160 $mm^3$, 2.20 mmol) in dry diethyl ether (5 $cm^3$) was added dropwise to a solution of the above alcohol (630 mg, 1.99 mmol) and pyridine (160 mg, 160 $mm^3$, 2.0 mmol) in dry diethyl ether (10 $cm^3$) over a period of 30 min, the temperature being kept below 5 °C. After the mixture had been kept at 20 °C for 1 h, ice–water was added and the product was extracted with diethyl ether, and worked up to give, after chromatography on flash silica with hexane–ethyl acetate (7:3) as eluent, the chloride **29** (R = $CH_2Cl$) (443 mg, 60%), $\nu_{max}$(film)/$cm^{-1}$ 1755s (ester).

The chloride (5.37 g, 16.07 mmol), potassium iodide (1.33 g, 8 mmol), potassium cyanide (2.09 g, 32.14 mmol), and dry DMF (15 $cm^3$) were stirred together at 60–70 °C under nitrogen for 3 h, cooled, and poured into water. Extraction with diethyl ether, followed by washing (brine), drying ($MgSO_4$), and evaporation gave an oil, which was chromatographed on silica gel with hexane–ethyl acetate (4:1) as eluent to give the *title cyanide* **29** (R = $CH_2CN$) (1.57 g, 31%) as a pale yellow oil (Found: C, 70.2; H, 6.05; N, 4.1%; $M^+$, 325.131. $C_{19}H_{19}NO_4$ requires C, 70.15; H, 5.9; N, 4.3%; M, 325.131); $\nu_{max}$(film)/$cm^{-1}$ 2250w (CN), 1750s (CO), 1590m and 1475s (aromatics); $\delta_H$ (400 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.1, Me), 4.00 (2 H, s, $CH_2CN$), 4.14 (2 H, q, *J* 7.1, $OCH_2Me$), 4.79 (2 H, s, $OCH_2CO_2Et$), 5.10 (2 H, s, $OCH_2Ph$), 6.96 (1 H, dd, *J* 7.1 and 2.7, 5-H), 7.01–7.08 (2 H, m, 3- and 4-H) and 7.32–7.45 (5 H, m, 5 × ArH); *m/z* (EI, +ve) 325 (6%, $M^+$) 160 (3), 91 (100, $C_7H_7^+$) and 65 (11).

*The Diester* **22** ($R^1$ = $OCH_2Ph$).—The cyanide **29** (R = $CH_2CN$) (42 mg, 0.135 mmol) was refluxed with 30% aq. sodium hydroxide (2 $cm^3$) and 100 vol. hydrogen peroxide (1 $cm^3$) for 30 min. The solution was cooled, acidified with hydrochloric acid (10%), and extracted with diethyl ether. The extracts were dried ($MgSO_4$) and evaporated to give the crude diacid (43 mg), which was refluxed overnight under nitrogen with dry ethanol (3 $cm^3$) containing 5 drops of conc. sulfuric acid. After concentration, water was added and the product was extracted into diethyl ether. The extracts were washed successively with aq. sodium hydrogen carbonate and water, and dried ($MgSO_4$). Evaporation, and chromatography on dry silica with hexane–ethyl acetate (4:1) as eluent, gave the *title diester* (38 mg, 76%) (Found: C, 67.5; H, 6.6%; $M^+$, 372.157. $C_{21}H_{24}O_6$ requires C, 67.75; H, 6.5%; M, 372.157); $\nu_{max}$(film)/$cm^{-1}$ 1760s (ester), 1730s (ester), 1585m and 1475s (aromatics); $\delta_H$ (400 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.1, Me), 1.25 (3 H, t, *J* 7.1, Me), 3.81 (2 H, s, $ArCH_2CO_2Et$), 4.13 (2 H, q, *J* 7.1, $OCH_2Me$), 4.14 (2 H, q, *J* 7.1, $OCH_2Me$), 4.68 (2 H, s, $OCH_2CO_2Et$), 5.08 (2 H, s, $OCH_2Ph$), 6.83 (1 H, dd, *J* 7.5 and 1.5, ArH *p*- to BnO), 6.90 (1 H, dd, *J* 8.3 and 1.5 ArH *o*- to BnO), 6.99 (1 H, dd *J* 8.3 and 7.5, ArH *m*- to BnO) 7.30–7.45 (5 H, m, $OCH_2Ph$); *m/z* (EI, +ve) 372 (15%, $M^+$), 207 (7), 149 (18), 91 (100, $C_7H_7^+$) and 65 (14).

*Ethyl 8-Benzyloxy-3-oxochromane-4-carboxylate* **23** ($R^1$ = $OCH_2Ph$).—A solution of diester **22** ($R^1$ = $OCH_2Ph$) (725 mg, 1.95 mmol) in dry toluene (5 $cm^3$) was added dropwise over a period of 1.5 h to a solution of sodium (58 mg, 2.54 mg-atom) in a mixture of dry toluene (3 $cm^3$) and ethanol (10 $mm^3$) under reflux. After being refluxed (2 h), the product was decomposed with cold 10% acetic acid (5 $cm^3$) and extracted with diethyl ether. The extracts were washed successively with water and brine, dried ($MgSO_4$), and evaporated, and the product was chromatographed on flash silica gel with hexane–ethyl acetate (9:1) as eluent to give the *title chroman-3-one* (147 mg, 23%) as an oil which eventually crystallised, m.p. 75–76 °C (Found: C, 69.75; H, 5.65%; $M^+$, 326.113. $C_{19}H_{18}O_5$ requires C, 69.95; H, 5.55%; M, 326.115); $\lambda_{max}$(EtOH)/nm 216 and 293 (ε 42 000 and 6300); $\nu_{max}$(KBr)/$cm^{-1}$ 3500–2500s br (OH), 1650s (CO), 1600s, 1580s and 1480s (aromatics); $\delta_H$(250 MHz; $CDCl_3$) 1.42 (3 H, t, *J* 7.0, Me), 1.61 (1 H, br s, OH), 4.41 (2 H, q, *J* 7.0, $OCH_2Me$), 4.69 (2 H, s, $OCH_2$), 5.15 (2 H, s, $OCH_2Ph$), 6.75 (1 H, dd, *J* 8.1 and 1.4, 7-H), 6.86 (1 H, dd, *J* 8.1 and 8.1, 6-H), 7.25–7.50 (6 H, m, 6 × ArH); *m/z* (EI, +ve) 326 (4%, $M^+$), 280 (19, $M^+$ – EtOH), 151 (7), 91 (100, $C_7H_7^+$) and 65 (11).

4,9,11-*Trihydroxyrotoxen*-12(6H)-*one* **25** ($R^1 = R^2 = R^3$ = OH).—The chroman-3-one **23** ($R^1$ = $OCH_2Ph$) (115 mg, 0.353 mmol) and phloroglucinol dihydrate **24** ($R^2$ = OH) (45 mg, 0.278 mmol) were stirred and heated together (4 h) under reduced pressure (22 mmHg) at 150–160 °C, and were then cooled, and triturated with ice-cold diethyl ether. The solid was filtered off, and washed with cold diethyl ether to leave the *title compound* **25** ($R^1 = R^2 = R^3$ = OH) (17 mg, 21%), m.p. > 300 °C (Found: C, 64.55; H, 3.75%; $M^+$, 298.047. $C_{16}H_{10}O_6$ requires C, 64.45, H, 3.9%; M, 298.048); $\lambda_{max}$(EtOH)/nm 202, 218 and 271 (ε 11 500, 9600 and 13 900); $\nu_{max}$(KBr)/$cm^{-1}$ 3340s br (OH), 1650s (CO), 1585m and 1480s (aromatics); $\delta_H$(80 MHz; [$^2H_6$]acetone) 5.22 (2 H, s, 6-$H_2$), 6.42 (1 H, d, *J* 2.2, 8-H), 6.55 (1 H, d, *J* 2.2, 10-H), 6.90–7.20 (2 H, m, 2- and 3-H), 8.24 (1 H, dd, *J* 6.6 and 3.0, 1-H) and 13.08 (1 H, s, 11-OH); *m/z* (EI, +ve) 298 (100, $M^+$), 269 (22, $M^+$ – CHO) and 242 (25, $M^+ - C_2O_2$).

(±)-cis-4,9,11-*Trihydroxy*-6a,12a-*dihydrorotoxen*-12(6H)-*one* **28** (R = H).—A solution of 4,9,11-Trihydroxyrotoxen-12(6H)-one **25** ($R^1 = R^2 = R^3$ = OH) (13 mg, 0.44 mmol) in dry THF (0.5 $cm^3$) was treated dropwise at −78 °C with DIBAL in toluene (1.0 mol $dm^{-3}$; 150 $mm^3$, 0.15 mmol) under nitrogen. After being stirred (1 h), the mixture was worked up as described for the rotenoid **6** above. Purification by PLC on silica gel, and elution with methanol–chloroform (1:19), gave the *title rotenoid* **28** (R = H) (5 mg, 38%), m.p. 232–234 °C

(Found: $M^+$, 300.063. $C_{16}H_{12}O_6$ requires M, 300.063); $\nu_{max}$(KBr)/cm$^{-1}$ 3400s br (OH) and 1640 (chelated CO); $\delta_H$(400 MHz; [$^2H_6$]acetone) 3.88 (1 H, d, *J* 3.8, 12a-H), 4.24 (1 H, d, *J* 12.3, 6-H$^a$), 4.55 (1 H, dd, *J* 12.3 and 2.7, 6-H$^b$), 5.00 (1 H, m, 6a-H), 5.77 (1 H, d, *J* 2.5, 8-H), 5.79 (1 H, d, *J* 2.5, 10-H), 6.55–6.66 (3 H, m, 3 × ArH), 7.60 (1 H, br s, OH), 9.70 (1 H, br s, OH) and 12.03 (1 H, s, chelated 11-OH); *m/z* (EI, +ve) 300 (30%, $M^+$), 298 (14, $M^+ - H_2$), 153 (100, $C_7H_5O_4^+$), 148 (42, $C_9H_8O_2^+$) and 147 (30, $C_9H_7O_2^+$).

(±)-cis *and* trans-12-*Deoxo*-12,12-*dihydroisorotenones* **32** and **33**.—(Experiments by Dr G. Proudfoot). The stilbene **31**[10] (100 mg), magnesium (5 g) and dry methanol (30 cm$^3$) were heated under reflux for 4 h, when the product was poured through Celite and the filtrate was concentrated. The product was treated with hydrochloric acid and extracted into diethyl ether. The extracts were washed, dried ($MgSO_4$), and evaporated, and the residue was purified by HPLC on μ-Porasil, with chloroform–diethyl ether–hexane (1:2:2) as eluent. The faster eluting component proved to be the trans-*isomer* **33** of 12-*deoxo*-12,12-*dihydroisorotenone* (22 mg), which gave needles from methanol, m.p. 167 °C (Found: $M^+$, 380.163. $C_{23}H_{24}O_5$ requires M, 380.162); $\delta_H$(250 MHz; $CDCl_3$) 1.34 (6 H, d, *J* 7, 7′-$Me_2$), 2.85 (1 H, dd, *J* 12 and 15, 12-H$^a$), 3.06 (1 H, m, *J* 7, 6′-H), 3.21 (1 H, m, $J_{12a,6a}$ 9.5, 12a-H), 3.38 (1 H, dd, *J* 5 and 15, 12-H$^b$), 3.85 (3 H, s, OMe), 3.89 (3 H, s, OMe), 4.13 (1 H, m, 6-H$^b$, 4.22 (1 H, m, $J_{6a,12a}$ 9.5, 6a-H), 4.61 (1 H, dd, *J* 9 and 3.5, 6-H$^a$), 6.43 (1 H, s, 4-H), 6.46 (1 H, s, 4′-H), 6.77 (1 H, s, 1-H) and 7.02 (2 H, ABq, 10- and 11-H); *m/z* (EI, +ve) 380 (10%, $M^+$), 180 (19), 179 (100) and 151 (15).

The cis-*isomer* **32** (18 mg), the slower running component, formed needles from methanol, m.p. 146–147 °C (Found: $M^+$, 380.162); $\delta_H$(250 MHz; $CDCl_3$) 1.31 (6 H, d, *J* 7, 7′-$Me_2$), 3.05 (1 H, m, *J* 7, 6′-H), 3.17 (2 H, m, 12-$H_2$), 3.34 (1 H, m, $J_{12a,6a}$ 4.5, 12a–H), 3.80 (3 H, s, OMe), 3.81 (3 H, s, OMe), 4.30 (2 H, m, 6-$H_2$), 4.78 (1 H, m, $J_{6a,12a}$ 4.5, 6a-H), 6.41 (1 H, s, 4′-H), 6.42 (1 H, s, 4-H), 6.67 (1 H, s, 1-H) and 6.90 (2 H, ABq, 10 and 11-H).

The stilbene **31** (100 mg) was hydrogenated in ethyl acetate over 10% palladium on charcoal catalyst until uptake of hydrogen ceased. The catalyst was removed by filtration through Celite, and the filtrate was evaporated to give a solid, which on recrystallisation from methanol gave the above *cis*-isomer **32** (85 mg, 84%), m.p. 146–147 °C, identical with the specimen above.

## Acknowledgements

We thank Wellcome (Berkhamsted) and the SERC for a CASE award to J. L. J., and Dr Geoffrey Proudfoot for experiments on the 12-deoxo systems.

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*Paper* 0/03036I
*Received* 27*th May* 1993
*Accepted* 18*th June* 1993