Aryloxymethyl Radical Cyclizations Mimicking Biological C–C Bond Formation to Methoxy Groups

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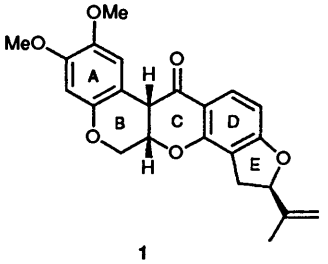
Attention is drawn to a small group of diverse natural products whose biosynthesis is unusual in involving formation of *O*-heterocyclic rings by C–C bond formation to aromatic methoxy groups, in net oxidative and non-oxidative processes. It is shown that aryloxymethyl radicals, generated by decarboxylation of thiohydroxamate esters of aryloxyacetic acids, undergo addition to both electron rich and electron poor double bonds, cyclizing in 5-*exo*, 6-*endo* and 6-*exo* fashions, and also substitute regioselectivity into pyridinium nuclei, thus mimicking the biochemical processes, as well as forming a useful new synthetic approach to *O*-heterocycles. Biosynthetic mechanisms are briefly discussed.

The study of biogenetic processes sometimes reveals unusual reactions for which laboratory parallels are rare, and which naturally provoke mechanistic speculation. Such a reaction was discovered in the extensive investigations into the biogenesis of rotenone **1** and its congeners in leguminous plants,[1] which highlighted a remarkable enzyme-mediated process (Scheme 1)



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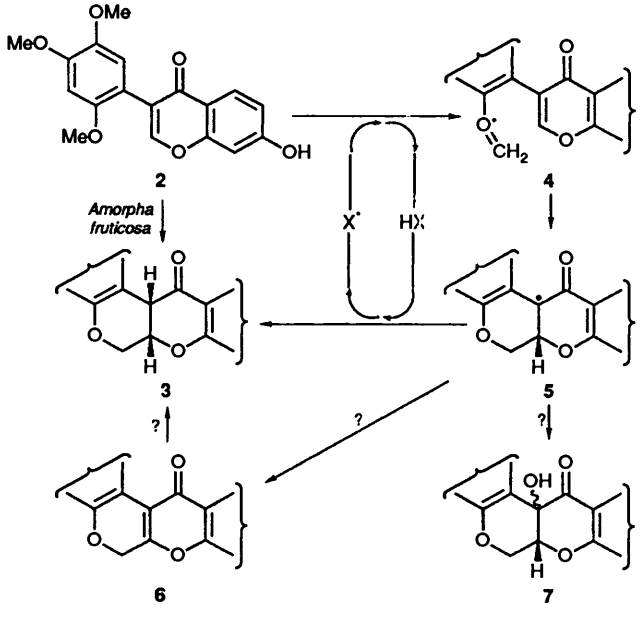
in which an *O*-methyl group of a precursor isoflavone **2** becomes the ring-B methylene of the rotenoid **3** by addition to a double bond in a net non-oxidative fashion. The favoured mechanism, on current information, requires abstraction of hydrogen to form an intermediate cation or radical **4** whose cyclization is followed by hydrogen return to C-12a. However the possibility cannot be rigorously excluded that intermediate **5** loses hydrogen to give a 6a,12a-didehydro species **6** reduced *in situ* to **3**, although there is no evidence supporting this idea. Intermediate **5** might also be oxygenated to afford rotenolones **7**. The biosynthetic picture is complicated by the facts that while structural types **6**, **7** are often extracted from natural sources, they can be formed readily by aerial oxidation of the parent rotenoid **3**, *e.g.* during chromatography, and their status as true natural products is unclear as yet.

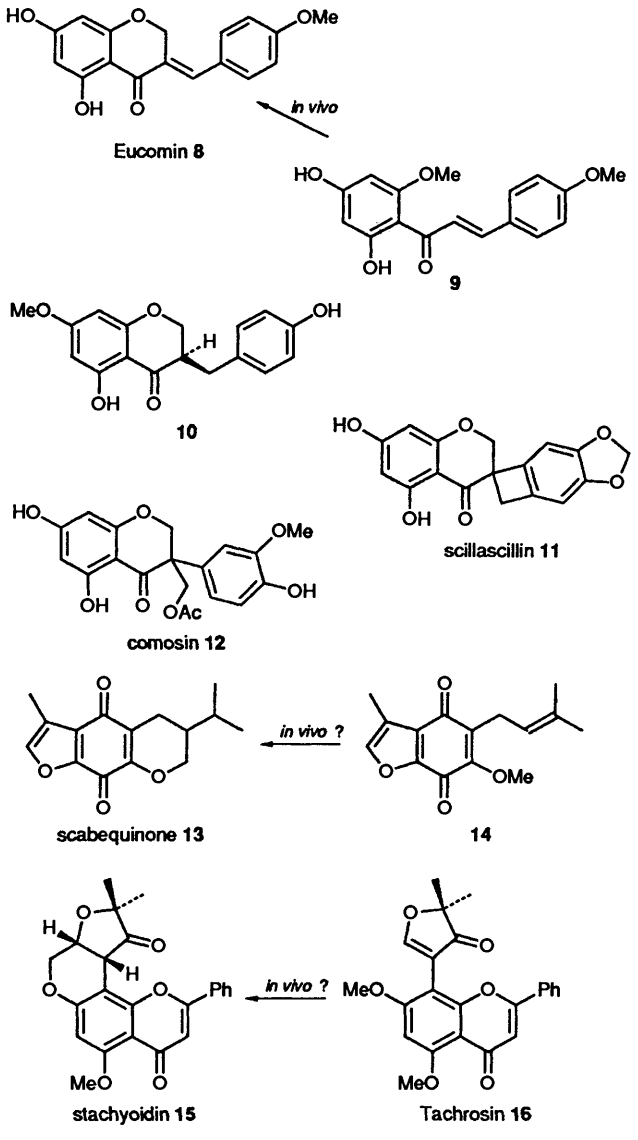


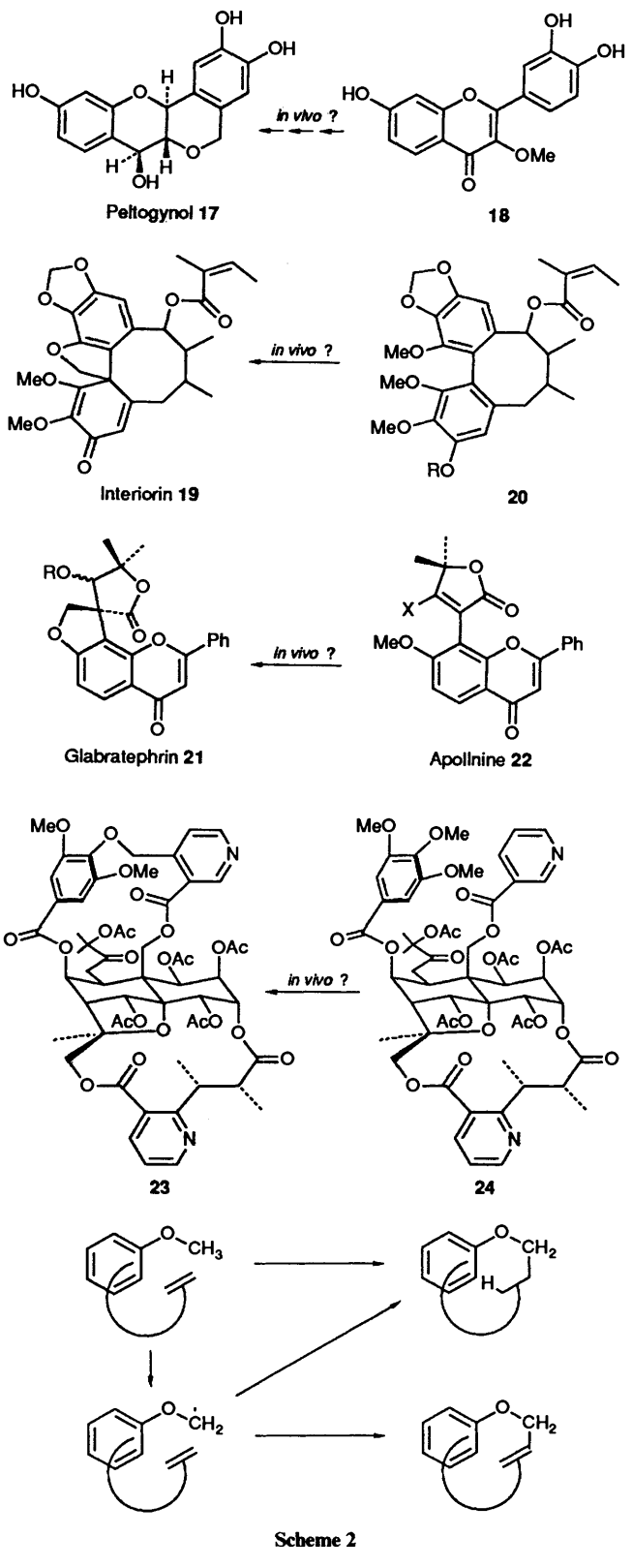
Scheme 1

A similar sequence has been supported experimentally for the biosynthesis of eucomin **8**, from the chalcone **9**[2] in *Eucomis bicolor*. We have noted a number of other examples in the literature where circumstantial evidence (*e.g.* cooccurrence of metabolites) suggests that related processes operate. Thus the 3-benzylchromanone **10** and a range of closely similar homoisoflavonoids, from *e.g. Muscari* species[3] are also likely to be formed from 2′-methoxychalcones. This group includes structural variants such as those of scillascillin[3a,4] **11** and comosin[5] **12**. Other examples involving formation of a six-membered ring are scabequinone **13**, which may be formed from the methoxybenzoquinone **14** with which it co-occurs in *Cyperus* species[6] and stachyoidin **15** whose precursor might well be tachrosin **16** in *Tephrosia polystachyoides*[7] and peltogynol **17** potentially derivable from a 3-methoxyflavone[8] **18**.

Cyclization to five-membered rings is represented by the product–precursor pairs interiorin **19** and the bridged biaryl **20**,[9] and glabratephrin **21** and apollinine **22** (X = H), or a relative **22** (X = OR), again from *Tephrosia* species.[10] The formation of the methylenedioxy function is a well known related reaction.[11] Macrocyclization features in the striking example of cathedulins E3 and E4 **23** and the metabolite **24** (cathedulin K12).[12] Other examples may well be extant but not known to us.

These diverse natural products contain a structural moiety which appears to be derived by addition of an aromatic methoxy group to a double bond as generalized in Scheme 2; hydrogen abstraction by an unknown co-factor to a carbon radical or cation must precede cyclization. A new ring results, five- or six-membered or larger, and the overall reaction may involve no net change in oxidation level as for example in the biosynthesis of **1**, **10**, **13**, **15** and **21**. Alternatively, the cyclization is at face value oxidative as in the case of **8**, **17**, **19** and **23**. *A priori* we inclined towards a radical mechanism although we noted that the intermediate aryloxymethyl radicals would have to be able to add to both electron-rich and electron-poor double





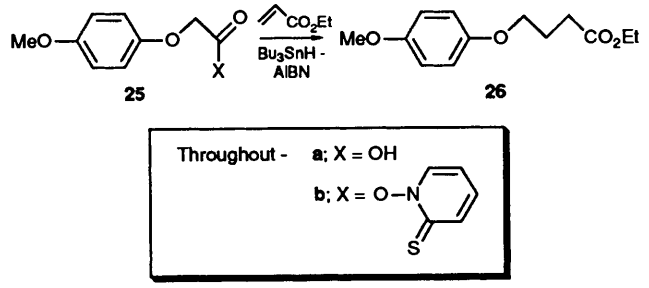
Scheme 2

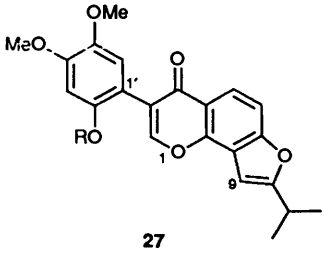
bonds, while 5-*exo*, 6-*exo*, 6-*endo*, and other modes would be involved. Thus, we sought to test the viability of radical processes *in vivo* by examination of the cyclization of aryloxymethyl radicals formed *in vitro*, and perhaps follow on to develop a biomimetic new synthetic method.

In this paper, we address this problem, and we report the fate of aryloxymethyl radicals **4**, showing that they can cyclize *via* various pathways in a biomimetic fashion. For our purpose we chose to employ the decarboxylation strategy of Barton and coworkers[13] to generate the desired radicals. This method requires the formation of a thiohydroxamate ester, *e.g.* **25b**, from reaction of an aryloxyethanoyl chloride with sodium pyridine-2-thiolate *N*-oxide, followed by photolysis in the presence of a suitable hydrogen donor.

As a first test we looked at a simple intermolecular case, and fragmented ester **25b** using the above conditions and tributyltin hydride–azoisobutyronitrile in the presence of methyl acrylate; we were pleased to find a modest yield of the desired ester **26**, the product of addition of *p*-methoxyphenoxymethyl radicals to acceptor, and quenching by hydrogen abstraction. The yield was not optimized but we moved on immediately to investigate an intramolecular case designed to parallel the biosynthesis of rotenoids.

We chose to work for convenience in isorotenone series as represented by the isoflavone **27**; this group contains the benzofuran rather than the benzodihydrofuran ring E of rotenone. Isoderritol isoflavone **27** (R = H) was prepared by literature methods[14] and was converted into the corresponding aryloxy acetic acid. The thioxopyridyl ester **28** was prepared *in situ*[13] and irradiated (tungsten lamp) in refluxing tetrahydrofuran (THF) solution (0.022 mol dm^{-3}) with 2-methylpropane-2-thiol (0.033 mol dm^{-3}) to afford a mixture containing one major product. This proved to be dehydroisorotenone[15] **29**





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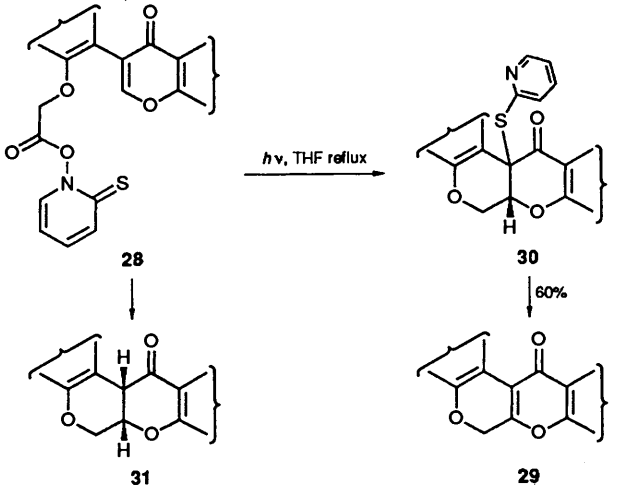
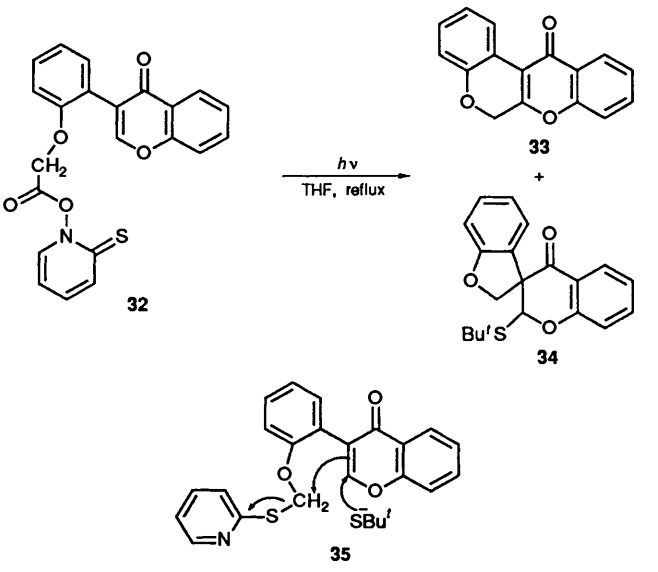
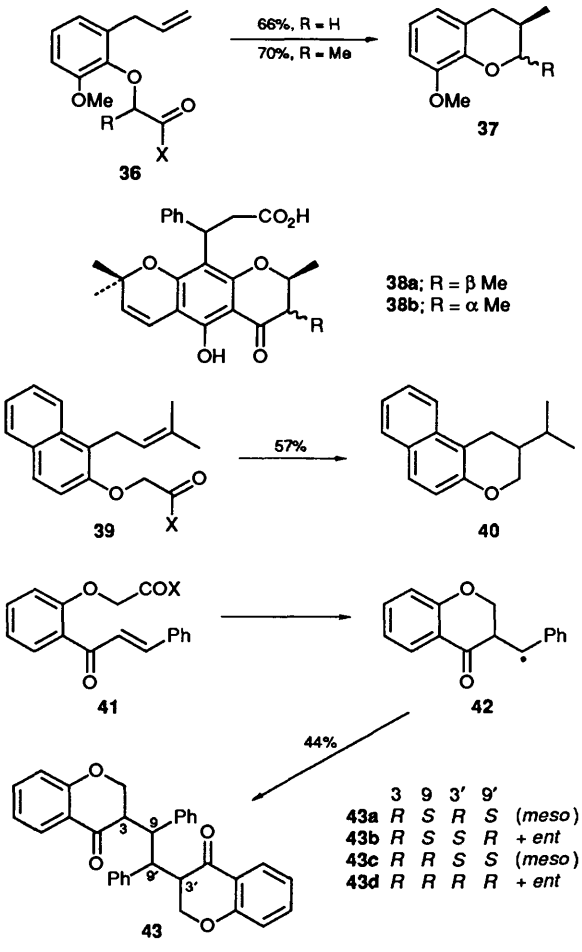


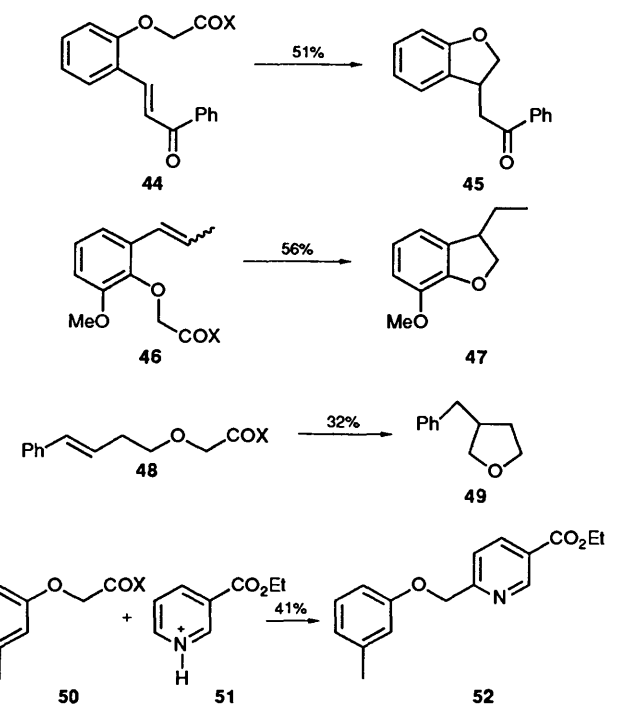


identified by comparison with authentic material; in further experiments the yield was raised to 60%. A trace of isorotenone **31** was also detected with **29**:**31** *ca.* 11:2. Under our experimental conditions it appears that the initially formed radical cyclizes *cf.* **4**→**5** and abstracts a pyridylthio moiety to form **30** which undergoes thermal elimination to the major product **29**; a minor pathway can involve hydrogen abstraction from thiol to yield isorotenone **31**. It is clear from this experiment that radicals of type **4** do undergo the desired 6-*endo* cyclization to form the rotenoid ring-B. The synthetic isoflavone hydroxamate **32** was also investigated; it decomposed on irradiating a refluxing THF solution (0.011 mol dm^{-3}) with 2-methylpropane-2-thiol (0.016 mol dm^{-3}) to produce two major compounds, 6a,12a-didehydrorotoxen-12-one[16] **33** (25%), and the thioacetal **34** (11%). The best explanation for this observation may be that the initial oxymethyl radical cyclized inefficiently (perhaps unaided by ring A methoxyls) and was also trapped to yield the sulfide **35**. The latter then reacted with the thiol *via* polar conjugate addition with subsequent anionic displacement of 2-mercaptopyridine, as shown in cipher **35**.

We then investigated systems set up to form a 3-alkylchroman ring system, paralleling the proposed biosynthesis of this substructure of scabequinone, *i.e.* **36** (R = H) and **39**. This required radical additon to an unactivated alkene rather than an enone as in the previous case. 2-Allyl-5-methoxyphenol was prepared by the Claisen rearrangement of 2-allyloxyanisole,[17] and converted into the aryloxyacetate **36** (R = H, X = OEt) by reaction with ethyl bromoacetate–potassium carbonate–sodium iodide. The corresponding acid, acid chloride, and thiohydroxamate ester, **36b** (R = H) were prepared conventionally. 1-Dimethylallyl-2-naphthol was synthesized by alkylation of 2-naphthol with isoprene and trimethylsilyl chloride,[18] and similarly converted *via* **39a** into **39b**. Photolysis (tungsten lamp) of **36b** and **39b** in refluxing benzene with 2-methylpropane-2-thiol gave the desired products **37** (R = H) (66%) and **40** (57%) from non-oxidative 6-*exo* cyclization. Much lower yields of **40** were found in photolysis at room temperature, when 1-dimethylallyl-2-naphthyl methyl ether became a significant product (from hydrogen abstraction before cyclization); a similar temperature effect was observed in other radical reactions reported in this paper. Cyclization of **36b** (R = Me) was also readily effected (70%) giving the expected *cis*/*trans* mixture (1:1) of stereoisomers **37** (R = Me). *cis*- and *trans*-2,3-Dimethylchromans are known in Nature, *e.g.* chapelieric acid **38a** and isochapelieric acid **38b**.[19]

We then extended this study to include an analogue of the homoisoflavanoid systems **8**/**10**. The aryloxyacetic acid **41** derived from 2'-hydroxychalcone was decarboxylated as before, but in the absence of an H donor. We hoped to observe trapping of the product radical **42** with 2-pyridinethiyl, with subsequent thermal elimination to a 3-benzylidenechroman like eucomin **8**. However, under a range of conditions, the major product proved to be the dimers **43**, best overall yield observed, 44%. Again the desired 6-*exo* radical cyclization has taken place, but dimerization of the stabilized radicals **42** and 2-pyridinethiyl appears to be preferred to cross coupling under our conditions. The stereochemistry of dimer **43** deserves comment. The structure was demonstrated by MS (M^+, 474.183, $C_{32}H_{26}O_4$), and the ^1H and ^{13}C NMR spectra which show signals indicating a product with distinguishable half-units. At first sight this suggested a non-symmetric structure, but an alternative explanation might be that the material, although unresolvable into two components by HPLC, is in fact an unseparated mixture of two symmetrical stereoisomers. The two *meso* forms **43a**, **c** and the two racemates **43b**, **d** with a two-fold axis are possible. It seems to us most likely that the dimerization would lead to symmetrical products, and a pair with the same relative 3, 9 and 3', 9' stereochemistry would be probable, *i.e.* **43a**, **b** or





43c, **d**. Further stereochemical investigations appeared to us not to be germane to the present studies.

Next we demonstrated that 5-*exo* ring closures were feasible in three simple cases. The acid **44a** was readily prepared from 2-hydroxychalcone; photolysis of the hydroxamate **44b** smoothly provided the saturated ketone **45** (51%). (*E*/*Z*)-1-Propenyl-5-methoxyphenol (prepared by base catalysed isomerization of the allyl isomer[20]) was used to form acid **46a**, decarboxylative cyclization of which afforded the dihydrobenzofuran **47**. At this stage an example **48** was chosen to test the viability of employing alkyloxy- (rather than aryloxy-) acetic acid derivatives. Radical closure was again observed, although γ-hydrogen abstraction looked a possible competing pathway. Only 32% of 3-benzyltetrahydrofuran[21] was obtained, but this, in part, resulted from the difficulties of isolating and purifying the small quantities of volatile product.

Finally, we examined a model for the radical substitution into the pyridine nucleus of a nicotinoate ester which appears to occur in the biogenesis of the bis-macrocyclic alkaloids cathedulins E3 and E4, constituents of *Catha edulus* (Khat). An intermolecular case was the most straightforward to set up, and also was considered a stringent test in terms of entropy of activation. Guided by the observation that pyridinium camphor sulfonates are good substrates for radical substitution,[22] we photolysed a mixture of the hydroxamate **50b** with the camphorsulfonate of ethyl nicotinoate **51**; we were able to isolate the 6-alkylated pyridine product **52** in 41% yield, without optimization. Further, no isomers of **52** could be discovered in the reaction mixture. This suggests that this biogenetic proposal is reasonable, and that macrocyclization using these methods could be incorporated into biomimetic syntheses of cathedulin derivatives.

Thus, in conclusion, we have observed that aryloxymethyl radicals can be generated, and that they do add intramolecularly to both electron-rich and electron-poor double bonds in a net non-oxidative manner, mimicking the biological process. A biological radical process is thus at least chemically sensible. A new synthetic approach to *O*-heterocycles also emerges from this work.

The question of oxidative/non-oxidative radical processes deserves attention. In this work, non-oxidative cyclizations have been realized using a suitable hydrogen donor: an oxidative case (formation of **29**) was only achievable by trapping product radical with a thiyl radical, and subsequent elimination. In the possible biochemical mechanisms, oxidative radical cyclization may readily be conceived through the action of P-450 enzymes. These are well known to generate carbon radicals, and in special cases, cyclization may intervene before radical quenching; the latter could proceed, *e.g.* by one electron oxidation to a carbocation, with proton loss to afford a product double bond as in the case in eucomin **8**. Hydroxylation of a product radical could be postulated, *e.g.* the rotenolones **7** might arise this way. A biological non-oxidative cyclization would be more unusual; a mechanism similar to that of B12 catalysed reactions would be required, and it might be that a related Co-protein system is involved in such cases. However, it must be said that the *in vivo* 'non-oxidative' examples might involve oxidative cyclization followed by reduction, and this cannot be rigorously excluded on current information.

Thus, the formation of dehydrorotenoids in this chemistry may have biosynthetic significance if it proves that these products, which have been isolated from natural sources, are formed in enzyme-mediated reactions and are not artefacts; their present status is equivocal. It would then be necessary to test whether they were in fact biosynthetic intermediates (*i.e.*, **5**→**6**→**3**). Further biosynthetic experimentation in these areas is clearly important, and could lead to isolation, purification, and mechanistic study of the enzymes responsible for this unusual biochemistry.

Experimental

For experimental generalizations, see *J. Chem. Soc., Perkin Trans. 1*, 1991, 1901.

Formation of Ethyl Aryloxyacetates.—The following general method was used: the appropriate phenol (x mmol) in dry acetone (0.7–1.5 mol dm^{-3}), potassium iodide (1.0–1.2 x mmol), and potassium carbonate (1.0–1.2 x mmol) were refluxed together, with TLC monitoring, until reaction was complete (16–48 h). The cooled solution was diluted with water and extracted with ethyl acetate. The organic extracts were washed with dil aq. sodium hydroxide, water and brine, dried and evaporated. The product esters were purified on silica columns, with ethyl acetate–hexane elution. Using these methods the following aryloxyacetates were prepared.

(i) *Ethyl (2-cinnamoylphenoxy)acetate* **41** (X = OEt) (76%), m.p. 57 °C from hexane (Found: C, 73.4; H, 6.0%; M^+, 310.117. $C_{19}H_{18}O_4$ requires C, 73.53; H, 5.85%; *M*, 310.120); ν_{max}/cm^{-1} 1750, 1650, 1590 and 1570; λ_{max}/nm 306 (4.17); δ_H(80 MHz) 1.24 (3 H, t, *J* 7, CH_2*Me*), 4.24 (2 H, q, *J* 7, CH_2Me), 4.71 (2 H, s, OCH_2) and 6.83–7.74 (11 H, ArH, CH=CH).

(ii) *Ethyl (6-allyl-2-methoxyphenoxy)acetate* **36** (R = H, X = OEt) (90%) as an oil (Found; M^+, 250.115. $C_{14}H_{18}O_4$ requires M 250.120); ν_{max}/cm^{-1} 1735, 1639, 1599 and 1586; δ_H(80 MHz) 1.29 (3 H, t, *J* 7.1, CH_2*Me*), 3.47–3.65 (2 H, m, ArCH_2C), 3.80 (3 H, s, OMe), 4.25 (2 H, q, CH_2Me), 4.59 (2 H, s, ArO CH_2C), 4.93–5.12 (2 H, m, CH=CH_2), 5.72–6.25 (ArC*H*=CH_2) and 6.72–7.21 (3 H, m, ArH).

(iii) *Ethyl* 1-(3,3-*dimethylallyl*)-2-*naphthyloxyacetate* **39** (X = OEt) (81%) as an oil (Found: M^+, 298.153. $C_{19}H_{22}O_3$ requires *M*, 298.157); ν_{max}/cm^{-1} 1740, 1673 and 1596; δ_H(80 MHz) 1.29 (3 H, t, *J* 7.2, CH_2*Me*), 1.68 and 1.89 (each 3 H, s, Me), 3.88 (2 H, d, *J* 6.0, CH_2CH=C), 4.27 (2 H, q, *J* 7.2, CH_2Me), 4.72 (2 H, s, $ArOCH_2$), 5.24–5.26 (1 H, m, C*H*=C) and 7.08–8.02 (6 H, m, ArH).

(iv) *Ethyl* 2-(6-*allyl*-2-*methoxyphenoxy*)*propanoate* **36** (R = Me, X = OEt) (44%) as an oil (Found: M^+, 264.136. $C_{15}H_{20}O_4$ requires *M*, 264.136); ν_{max}/cm^{-1} 1750, 1640 and 1590; δ_H(90 MHz) 1.25 (3 H, t, *J* 7.0, CH_2*Me*), 1.53 (3 H, d, *J* 7.0, OCH*Me*), 3.40–3.56 (2 H, m, ArCH_2), 3.77 (3 H, s, OMe), 4.19 (2 H, q, *J* 7.0, CH_2Me), 4.78 (1 H, q, *J* 7.0, OC*H*Me), 4.95–5.14 (2 H, m, CH=CH_2), 5.74–6.20 (1 H, m, C*H*=CH_2) and 6.67–7.05 (3 H, m, ArH).

(v) *Ethyl (6-allyl-2-methoxyphenoxy)acetate* **46** (X = OEt) (67%, as a 6:1 *trans*:*cis* mixture) (Found: C, 67.0; H, 7.35 %; M^+, 250.115. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25%; *M*, 250.120); ν_{max}/cm^{-1} 1762, 1655, 1598 and 1577; δ_H(250 MHz) (*trans* isomer) 1.32 (3 H, t, *J* 7.2, CH_2CH_3), 1.89 (3 H, dd, *J* 1.7, 7.1, =$CHCH_3$), 3.81 (3 H, s, OMe), 4.28 (2 H, q, *J* 7.2, CH_2CH_3), 4.58 (2 H, s, OCH_2), 6.24 (1 H, dq, *J* 7.1, 15.9, CH=C*H*) and 6.87–7.08 (4 H, m, ArH, CH=C); (*cis* isomer) 1.30 (3 H, t, *J* 7.2, CH_2CH_3), 1.82 (3 H, dd, *J* 1.7, 7.1, =$CHCH_3$), 3.83 (3 H, s, OMe), 4.25 (2 H, q, *J* 7.2, CH_2CH_3), 4.56 (2 H, s, OCH_2), 5.85 (1 H, dq, *J* 7.1, 11.6, CH=C*H*) and 6.87–7.08 (4 H, m, ArH, CH=C).

O-Ethoxycarbonylmethyl Isoderritol Isoflavone.—Isoderritol isoflavone[14] **27** (R = H) (163 mg) and ethyl bromoacetate (79 mg) in acetone (10 cm^3) over potassium carbonate (89 mg) were refluxed for 15 h under nitrogen. Filtration and evaporation of acetone gave the *title compound* **27** (R = CH_2CO_2Et) (103 mg, 52%) as needles from methanol m.p. 95 °C (Found: C, 66.5; H, 5.7%; M^+, 466.164. $C_{26}H_{26}O_8$ requires C, 66.95; H, 5.62%; *M*, 466.163); ν_{max}/cm^{-1} 1710, 1639, 1619 and 1589; δ_H(90 MHz) 1.22 (3 H, t, *J* 5, Me), 1.41 (6 H, d, *J* 7, $CHMe_2$), 3.91 (6 H, s, 2 × OMe), 4.20 (2 H, q, *J* 5, CH_2Me), 4.57 (2 H, s, OCH_2), 6.68 (1 H, s, 9-H), 6.75 (1 H, s, 5′-H), 7.09 (1 H, s, 2′-H), 7.45 (1 H, d, *J* 10, 5-H), 7.50 (1 H, s, 2-H) and 8.12 (1 H, d, *J* 10, 6-H).

Ethyl (4-Phenylbut-3-enyl)oxyacetate.—(*E*)-4-Phenylbut-3-en-1-ol[23] (1.2 g) (prepared from 4-phenylbut-3-enoic acid[24]) was added to a stirred suspension of sodium hydride (290 mg) in dry benzene (50 cm^3). After 30 min, ethyl bromoacetate (2.02 g) was added, and the mixture was stirred at ambient temperature for 20 h. It was then diluted with water and the organic products were collected in ethyl acetate. Evaporation of the dried extracts and chromatography (silica, hexane–ethyl acetate) afforded the title compound **48** (X = OEt) (800 mg, 42%), as a *cis*/*trans* mixture; ν_{max}/cm^{-1} 1752, 1636, 1599 and 1577. The crude ester was hydrolysed (below) without further purification.

Formation of Aryloxyacetic Acids.—The following general method was used: the appropriate ethyl ester (x mmol) was dissolved in ethanol–water (9:1) (0.05–0.5 mol dm^{-3}, according to solubility and scale) with potassium hydroxide (2x mmol) and set aside at room temperature with TLC monitoring until reaction was complete (40 min–16 h). The mixture was acidified with dil. hydrochloric acid and extracted with ethyl acetate; the organic extracts were then extracted with aq. sodium hydrogen carbonate. The aqueous layers were acidified, and extracted with ethyl acetate. The organic extracts were washed with water and brine, dried and evaporated. The product acids were purified on silica columns, with ethyl acetate–hexane elution.

Using these methods the following aryloxyacetic acids were prepared.

(i) *(2-Cinnamoylphenoxy)acetic acid* **41** (X = OH) (48%), m.p. 106–107 °C from ethyl acetate–hexane (Found: C, 72.3; H, 5.1%; M^+, 282. $C_{17}H_{14}O_4$ requires C, 72.32; H, 5.00%; *M* 282); ν_{max}/cm^{-1} 3600–2500, 1750, 1660, 1605 and 1580; λ_{max}/nm 311 (4.38); δ_C([$^2H_4$]methanol) 66.15 (CH_2), 113.37 (CH), 122.54 (CH), 128.12 (CH), 129.37 (CH), 129.86 (CH), 130.51 (C), 131.37 (CH), 134.24 (CH), 136.41 (C), 144.87 (CH), 157.87 (C), 171.62 (C) and 194.70 (C).

(ii) *6-Allyl-2-methoxyphenoxy)acetic acid* (**36**; R = H, X = OH) (82%), m.p. 52–54 °C from hexane (Found: C, 64.7; H, 6.5. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%); ν_{max}/cm^{-1} 3600–2400, 1725, 1635 and 1600; δ_H(80 MHz) 3.51 (2 H, d, *J* 6.5, ArCH_2C), 3.85 (3 H, s, OMe), 4.61 (2 H, s, ArOCH_2C), 4.93–5.13 (2 H, m, CH=CH_2), 5.83–6.25 (1 H, m, ArC*H*=CH_2) and 6.71–7.12 (3 H, m, ArH).

(iii) 1-(3,3-*Dimethylallyl*)-2-*naphthyloxyacetic acid* **39** (X = OH) (21%), m.p. 104–107 °C from hexane (Found: M^+, 270.126. $C_{17}H_{18}O_3$ requires *M*, 270.126); ν_{max}/cm^{-1} 3441, 1750, 1626 and 1598; δ_H(80 MHz) 1.69 and 1.89 (each 3 H, s, Me), 3.86 (2 H, d, *J* 6.8, CH_2CH=C), 4.77 (2 H, s, $ArOCH_2$), 5.21–5.23 (1 H, m, C*H*=C) and 7.10–8.02 (6 H, m, ArH).

(iv) 2-(6-*Allyl*-2-*methoxyphenoxy*)*propanoic acid* **36** (R = Me, X = OH) (60%) as an oil (Found: M^+, 236.102. $C_{13}H_{16}O_4$ requires *M*, 236.105); ν_{max}/cm^{-1} 3650–2300, 1725, 1640 and 1590; δ_H(80 MHz) 1.58 (3 H, d, *J* 7.0, OCH*Me*), 3.43 (2 H, d, *J* 7.0, $ArCH_2$), 3.78 (3 H, s, OMe), 4.70 (1 H, q, *J* 7.0, OC*H*Me), 4.90–5.15 (2 H, m, CH=CH_2), 5.73–6.28 (1 H, m, C*H*=CH_2) and 6.73–7.10 (3 H, m, ArH).

(v) *Ethyl (6-allyl-2-methoxyphenoxy)acetic acid* **46** (X = OH) (72%, as a 6:1 *trans*:*cis* mixture) (Found: C, 65.4; H. 6.6%; M^+, 222.089. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%; *M*, 222.089); ν_{max}/cm^{-1} 3600–2600, 1736, 1599 and 1577; δ_H(250 MHz) (*trans* isomer), 1.87 (3 H, dd, *J* 1.7, 7.1, =$CHCH_3$), 3.92 (3 H, s, OMe), 4.56 (2 H, s, OCH_2), 6.18–6.27 (1 H, m, CH=C*H*), 6.52–7.05 (4 H, m, ArH, CH=C) and 10.06 (OH); (*cis* isomer) 1.78 (3 H, dd, *J* 1.7, 7.1, =$CHCH_3$), 3.80 (3 H, s, OMe), 4.53 (2 H, s, OCH_2), 5.82–5.91 (1 H, m, CH=C*H*), 6.52–7.05 (4 H, m, ArH, C*H*=C) and 10.06 (OH).

(vi) (E)-(4-*Phenylbut*-3-*enyloxy*)*acetic acid* **48** (X = OH) (81%) as an oil (Found: M^+, 206.094 $C_{12}H_{12}O_3$ requires *M*, 206.094); δ_H(80 MHz) 2.55 (2 H, dt, *J* 6, 6, =$CHCH_2$), 3.70 (2 H, t, *J* 6.6, CCH_2O), 4.16 (2 H, s, OCH_2CO_2), 6.00–6.69 (2 H, m, CH=CH), 7.31 (5 H, s, PhH) and 9.68 (1 H, s, OH).

O-Carboxymethyl Isoderritol Isoflavone.—The above ester **27**

(R = CH_2CO_2Et) (580 mg) was refluxed in 90% aq. ethanol (20 cm^3) containing potassium hydroxide (140 mg) for 30 min. Ethanol was then evaporated off and the residue was acidified and extracted with ether. The extracts, on drying and evaporation, afforded the *title compound* **27** (X = OH) (300 mg, 55%) as needles from methanol, m.p. 146–150 °C (Found: C, 65.8; H, 5.1%; M^+, 438.132. $C_{24}H_{22}O_8$ requires C, 65.75; H, 5.06%; *M*, 438.131); ν_{max}/cm^{-1} 1735, 1629, 1610, 1600 and 1580; δ_H(90 MHz) 1.41 (6 H, d, *J* 7, $CHMe_2$), 3.85 and 3.89 (each 3 H, s, OMe), 4.72 (2 H, s, OCH_2), 6.59 (1 H, s, 9-H), 6.75 (1 H, s, 5′-H), 6.82 (1 H, s, 2′-H), 7.52 (1 H, d, *J* 10, 5-H), 8.15 (1 H, s, 2-H) and 8.19 (1 H, d, *J* 10, 6-H).

o-(2-*Benzoylvinyl*)*phenoxyacetic Acid*.—2-Formylphenoxyacetic acid (250 mg) and benzoylmethylene(triphenyl)phosphorane (1.05 g) in dry THF were refluxed under nitrogen for 24 h. The mixture was evaporated and the residue was dissolved in chloroform. The organic solution was extracted with aq. sodium hydrogen carbonate. The extracts were acidified and extracted with chloroform. The dried extracts were evaporated and the residue was chromatographed on silica (hexane–ethyl acetate, 2:1) to yield the *title acid* **44** (X = OH) (300 mg, 76%), m.p. 126–127 °C from hexane (Found: M^+, 282.088 $C_{17}H_{14}O_4$ requires *M*, 282.089); ν_{max}/cm^{-1} 3600–2300, 1735, 1650, 1590 and 1570; δ_H(90 MHz) 4.79 (2 H, s, OCH_2) and 6.80–8.29 (12 H); δ_C(22.5 MHz) 38.36 (CH_2), 111.87 (CH), 122.22 (CH), 128.88 (CH), 129.21 (CH), 129.69 (CH), 133.79 (CH), 138.31 (C), 156.78 (C) and 201.34 (C): other signals not reliably observed above background.

Radical Decarboxylation/Cyclizations: General Methods.—The appropriate acid (0.5 mmol) was stirred under nitrogen with oxalyl chloride (0.25 cm^3) and dry DMF (0.05 cm^3) in dry benzene (4 cm^3) for 2 h. After evaporation of the solvent the residue was redissolved in benzene, and the solvent was evaporated again, to yield the corresponding acid chloride. This acid chloride in benzene (5 cm^3) was added to a dried (Dean and Stark) refluxing suspension of sodium pyridine-2-thiolate *N*-oxide (90 mg, 0.6 mmol) in benzene (80 cm^3) containing 4-dimethylaminopyridine (DMAP) (10 mg), in the dark (foil wrapped). After 30 min 2-methylpropane-2-thiol (68 mg, 0.75 mmol) was added, and the refluxing mixture was exposed to radiation from a 200 W tungsten lamp for 1 h. After cooling, water was added and the mixture was extracted with ethyl acetate. The dried extracts were evaporated to provide the crude product which was purified by column chromatography on silica (hexane–ethyl acetate elution). In this way the following compounds were synthesized.

(i) 8-*Methoxy*-3-*methylchroman* **37** (R = H) (66%) as an oil (Found: M^+, 178.098. $C_{11}H_{14}O_2$ requires *M*, 178.099); δ_H(80 MHz) 1.00 (3 H, d, *J* 6.4, Me), 2.05–2.93 (3 H, m, $ArCH_2CH$), 3.86 (3 H, s, OMe), 3.61–4.40 (2 H, m, OCH_2CH) and 6.57–6.90 (3 H, ArH); δ_C(22.5 MHz) 16.92 (CH_3), 26.87 (CH_2), 33.11 (CH_2), 55.73 (CH_3), 72.08 (CH_2), 109.01 (CH), 110.46 (C), 114.92 (C), 119.62 (CH), 121.66 (CH) and 133.14 (C).

(ii) 2,3-*Dihydro*-3-*isopropylnaphtho*[2,1-b]*pyran* **40** (57%) as an oil (Found: M^+, 226.136. $C_{16}H_{18}O$ requires *M*, 226.136); δ_H(400 MHz) 1.00 and 1.01 (each 3 H, d, *J* 5.8, 2 × Me), 1.52–1.69 (2 H, m, $ArCH_2CHCH$), 2.76 (1 H, dd, *J* 5.5, 16.3, ArCHa), 3.08 (1 H, ddd, *J* 1.6, 5.5, 16.3, ArCHb), 3.76 (1 H, dd, *J* 10.3, OCHa), 4.29–4.34 (1 H, m, OCHb), 6.98 (1 H, d, *J* 8.9, ArH), 7.27 (1 H, dd, *J* 7.1, 7.1, ArH), 7.42 (1 H, dd, *J* 7.1, 7.1, ArH), 7.53 (1 H, d, *J* 8.9, ArH), 7.69 (1 H, d, *J* 8.4, ArH) and 7.77 (1 H, d, *J* 8, 4, ArH); λ_{max}/nm 267 (3.48), 277 (3.52), 288 (3.38), 322 (3.18) and 335 (3.21).

(iii) 8-*Methoxy*-2,3-*dimethylchroman* **37** (R = Me) (70%) m.p. 76–77 °C from pentane (Found: M^+, 192.119. $C_{12}H_{16}O_2$ requires *M*, 192.115); δ_H(400 MHz) 1.04 (3 H, d, *J* 6.8, 3-Me), 1.45 (3 H, d, *J* 6.2, 2-Me), 1.77–1.88 (1 H, m, 3-H), 2.48 (1 H, dd, *J* 10.4, 16.4, 4-Ha), 2.77 (1 H, dd, *J* 5.2, 16.4, 4-Hb), 3.82–3.90 (4 H, 2-H, OMe), 6.65 (1 H, d, *J* 7.4, ArH), 6.70 (1 H, d, *J* 7.4, ArH) and 6.78 (1 H, t, *J* 7.4, ArH); δ_C(100.6 MHz) 18.01 (CH_3), 19.61 (CH_3), 32.99 (CH), 33.44 (CH_2), 56.12 (CH_3), 78.04 (CH), 109.92 (CH), 119.73 (CH), 121.57 (CH), 123.15 (C), 144.30 (C) and 148.41 (C).

(iv) 3-*Ethyl*-7-*methoxy*-2,3-*dihydrobenzo*[b]*furan* **47** (56%) as an oil (Found: M^+, 178.099. $C_{11}H_{14}O_2$ requires *M*, 178.099); δ_H(250 MHz) 0.96 (3 H, t, *J* 7.4, Me), 1.56–1.86 (2 H, m, CH_2Me), 3.40–3.51 (1 H, m, 3-H), 3.86 (3 H, s, OMe), 4.29 (1 H, dd, *J* 4.7, 8.9, 2-Ha), 4.69 (1 H, dd, *J* 8.9, 8.9, 2-Hb) and 6.73–6.85 (3 H, m, ArH); δ_C(22.5 MHz) 11.43 (CH_3), 27.73 (CH_2), 44.20 (CH), 56.23 (CH_3), 77.30 (CH_2), 111.81 (CH), 116.85 (CH), 121.07 (CH), 132.39 (C), 144.91 (C) and 147.07 (C).

(v) 3-(*Benzoylmethyl*)-2,3-*dihydrobenzo*[b]*furan* **45** (51%), m.p. 98–100 °C (from hexane) (Found: M^+, 238.100. $C_{16}H_{14}O_2$ requires *M*, 238.099); ν_{max}/cm^{-1} 3450, 1680 and 1600; δ_H(400 MHz) 3.21 (1 H, dd, *J* 9.5, 18.1, COC*H*aHb), 3.47 (1 H, dd, *J* 4.5, 18.1, COCHa*H*b), 3.97–4.04 (1 H, m, 3-H), 4.14 (1 H, dd, *J* 6.2, 9.2, 2-Ha), 4.82 (1 H, dd, *J* 9.2, 9.2, 2-Hb), 6.76 (1 H, d, *J* 8.0, ArH), 6.81 (1 H, d, *J* 7.9, ArH), 7.14 (1 H, t, *J* 7.9, ArH), 7.41 (2 H, d, *J* 7.9, ArH), 7.52 (1 H, m, ArH) and 7.90 (2 H, d, *J* 7.13, ArH); δ_C(100.6 MHz) 30.01 (CH_2), 37.73 (CH), 44.84 (CH_2), 110.03 (CH), 120.81 (CH), 124.62 (CH), 128.33 (CH), 128.86 (CH), 129.02 (CH), 130.03 (C), 133.74 (CH), 136.83 (C), 160.23 (C) and 195.58 (C).

(vi) 3-*Benzyltetrahydrofuran* **49** (32%) (Found: M^+, 162.103. $C_{11}H_{14}O$ requires *M*, 162.104); δ_C(100.6 MHz) 32.45 (CH_2), 39.61 (CH_2), 41.25 (CH), 68.18 (CH_2), 73.30 (CH_2), 126.36 (CH), 128.72 (CH), 128.97 (CH) and 141.10 (C).

Radical Cyclization of Thiohydroxamate **28** *to Isorotenone and Dehydroisorotenone*.—The acid **27** (R = CO_2H) (83 mg) in benzene (1 cm^3) was treated with oxalyl chloride (0.1 cm^3) and DMF (0.05 cm^3) at room temperature for 3 h, when the mixture was evaporated to dryness. The residue was re-evaporated from benzene (1 cm^3) to yield the crude acid chloride. This product in benzene (0.5 cm^3) was added to a refluxing suspension of sodio-2-mercaptopyridine *N*-oxide (34 mg) in benzene (3.8 cm^3) containing DMAP (3 mg), and the mixture was refluxed for 30 min in the dark. After evaporation (dark) the residue was dissolved in THF (7.6 cm^3) with 2-methylpropane-2-thiol (26 mg), and the mixture was irradiated for 30 min at room temperature with a tungsten lamp (200 W). Water was then added and the mixture was extracted with ether. The extracts were washed with dil. hydrochloric acid and aq. sodium hydrogen carbonate, dried and evaporated. The residue was chromatographed on silica (chloroform) to yield dehydroisorotenone **29** (36 mg, 49%), m.p. 190 °C (lit.,[15] m.p. 191 °C) (Found: C, 70.5; H, 5.1%; M^+, 392.130. $C_{23}H_{20}O_6$ requires C, 70.40: H, 5.14%; *M*, 392.126), with a ^1H NMR spectrum indistinguishable from that of an authentic sample. A trace of isorotenone (*ca.* 2 mg) was also eluted, with a ^1H NMR spectrum superimposable on that of an authentic specimen.

Formation of 6a,12a-*Dehydrorotoxen*-12-*one*.—2′-Hydroxyisoflavone[25] (200 mg), potassium carbonate (140 mg), sodium iodide (150 mg), and ethyl bromoacetate (170 mg), were refluxed together in dry acetone (5 cm^3) under nitrogen for 16 h. The mixture was diluted with water and extracted with ether. The organic extracts were washed with aq. sodium hydroxide, dried and evaporated. The residue was taken up in ethanol (18 cm^3) with potassium hydroxide (90 mg) in water (2 cm^3), and the solution was stirred for 14 h at ambient temperature, when it was concentrated, acidified, and extracted with ethyl acetate. The extracts yielded the crude aryloxyacetic acid (160 mg, 64%) as a gum, δ_H 4.14 (2 H, s, OCH_2), which was decarboxylated by

the general procedure given above to afford two products; (a) 6a,12a-*dehydrorotoxen*-12-*one* **33** (33 mg, 25%), m.p. 132–133 °C (from methanol) (lit.,[16] m.p. 135 °C) (Found: M^+, 250.063. $C_{16}H_{10}O_3$ requires *M*, 250.063); ν_{max}/cm^{-1} 1642, 1626, 1600 and 1567; δ_H(80 MHz) 5.06 (2 H, s, $ArOCH_2$), 6.91–7.70 (6 H, m, ArH), 8.32 (1 H, dd, *J* 1.9, 8.2, 1-H) and 8.79 (1 H, dd, *J* 1.9, 7.4, 11-H); δ_C(22.5 MHz) 64.89 (CH_2), 116.41 (CH), 118.04 (CH), 122.86 (CH), 125.79 (CH), 126.81 (CH), 127.73 (CH), 128.14 (CH) and 133.75 (CH) (quaternary carbons unobserved): and (b) the *spirochromanone* **34** (20 mg, 11%), m.p. 190–191 °C (from methanol) (Found: M^+, 340.113. $C_{20}H_{20}O_3S$ requires *M*, 340.113); ν_{max}/cm^{-1} 1685, 1599 and 1583; δ_H(80 MHz) 1.39 (9 H, s, CMe_3), 4.69 (1 H, d, *J* 9, C*H*aHb), 5.13 (1 H, d, *J* 9, CHa*H*b), 5.64 (1 H, s, SC*H*) and 6.70–8.10 (8 H, m, ArH).

Methyl 4-(3-*Methoxyphenoxy*)*butanoate* **26**.—3-Methoxyphenoxyacetic acid[26] (180 mg), oxalyl chloride (0.5 cm^3), dry DMF (0.05 cm^3) and dry benzene (5 cm^3) were stirred together under nitrogen for 2 h. After evaporation the residue was dissolved in benzene (5 cm^3) and the solvent evaporated again. The residue in benzene (5 cm^3) was added to a dry refluxing suspension of sodium pyridine-2-thiolate *N*-oxide (180 mg) in benzene (10 ml) in the dark. After 1 h, tributyl tinhydride (870 mg) and AIBN (10 mg) in methyl acrylate (5 cm^3) were added dropwise over 30 min, and the mixture was refluxed for 16 h. Tetrachloromethane (10 cm^3) was added and heating was continued for 1 h. After cooling, the solvent was evaporated and the residue was stirred vigorously overnight with sat. aq. potassium fluoride (20 cm^3) and a saturated solution of iodine in dichloromethane (30). The white precipitate was filtered off and washed with dichloromethane. The combined organic phases were washed with aq. sodium thiosulfate, water and brine, dried and evaporated. The residue was separated on a silica column (hexane, ethyl acetate) to yield the *title compound* (20 mg) (Found: M^+, 224.106 $C_{12}H_{16}O_4$ requires *M*, 224.105); δ_H(80 MHz) 1.92–2.63 (4 H, m, $CH_2CH_2CO_2Me$), 3.69 and 3.78 (each 3 H, s, ArOMe, CO_2Me), 3.99 (2 H, t, *J* 9, $ArOCH_2$) and 6.44–7.51 (4 H, m, ArH) and 2-*methoxyphenoxy*(2-*pyridylthio*)*methane* (3 mg) (Found: M^+, 247. $C_{13}H_{13}NO_2S$ requires *M*, 247); δ_H(80 MHz) 3.76 (3 H, s, ArOMe), 5.88 (2 H, s, OCH_2S), 6.96–7.64 (4 H, m, ArH), 6.53–6.64 (2 H) and 8.45–8.55 (2 H, pyr H).

Formation of α,α′-*Bis*(4-*oxochroman*-3-*yl*)-α,α′-*bibenzyl*.—(2-Cinnamoylphenoxy)acetic acid (208 mg) was converted into the corresponding hydroxamate by the general method above; the crude product was refluxed in THF for 1 h with irradiation from a 200 W tungsten lamp. After cooling the mixture was diluted with water and extracted with ethyl acetate. The dried extracts were evaporated and the residue purified on silica (hexane-ethyl acetate) to yield the *title compound* **43** (77 mg, 44%), m.p. 229–231 °C (from hexane) (Found: M^+, 474 183 $C_{32}H_{26}O_4$ requires *M*, 474.183); λ_{max}/nm 213 (4.11), 251 (3.71) and 322 (3.47); δ_H(400 MHz) 2.96 (1 H, ddd, *J* 4.3, 5.9, 10), 3.10 (1 H, ddd, *J* 4.3, 5.9, 10), 3.98 (1 H, dd, *J* 9.4, 11.7), 4.10 (1 H, dd, *J* 5.9, 9.2), 4.40 (1 H, dd, *J* 5.9, 9.2), 4.48 (1 H, dd, *J* 9.4, 11.7), 4.62 (1 H, dd, *J* 4.3, 11.7), 4.65 (1 H, dd, *J* 4.3, 11.7), 6.87–7.12 (14 H) and 7.40–7.45 (2 H) (ArH), 7.76 (1 H, dd, *J* 1.7, 7.8) and 7.88 (1 H, dd, *J* 1.7, 7.8) (ArH); δ_C(41.87 MHz) (CH), 43.07 (CH), 48.02 (CH), 49.48 (CH), 68.34 (CH_2), 69.06 (CH_2), 117.64 (CH), 117.73 (CH), 121.03 (CH), 121.37 (CH), 121.50 (CH), 126.79 (CH), 127.00 (CH), 127.66 (CH), 127.91 (CH), 128.01 (CH), 129.84 (CH), 135.90 (CH), 135.96 (CH), 137.67 (C), 139.29 (C), 161.16 (C), 161.39 (C), 193.22 (C) and 193.57 (C).

Ethyl 6-(3-*Methylphenoxymethyl*)*nicotinoate*.—*tert*-Butyldimethylsilyl(*m*-tolyloxy)acetate (420 mg) was stirred with oxalyl chloride (0.7 cm^3) and DMF (50 mm^3) in dry benzene (5 cm^3) under nitrogen for 2 h. After evaporation the residue was redissolved in dry benzene (4 cm^3) and evaporated again to yield the crude acid chloride. This product in dichloromethane (5 cm^3) was added to a suspension of sodium pyridine-2-thiolate *N*-oxide (90 mg), and DMAP (10 mg) in dichloromethane (20 cm^3), in the dark. Ethyl nicotinoate (1.04 g) and camphorsulfonic acid (1.59 g) were mixed in dichloromethane (5 cm^3) until homogeneous, and then added to the reaction mixture (dark). After 30 min the mixture was irradiated (150 W lamp) for 1 h. The cooled product was diluted with ethyl acetate, washed with aq. sodium hydrogen carbonate and brine, dried and evaporated. The residue was purified by column chromatography (alumina, hexane, ethyl acetate) and PLC, to yield the *title compound* **52** (167 mg, 41%), m.p. 69–71 °C (from hexane) (Found: M^+, 271.121. $C_{16}H_{17}NO_3$ requires *M*, 271.121); ν_{max}/cm^{-1} 1719, 1602 and 1590; λ_{max}/nm 222 (4.08) and 267 (3.56); δ_H(80 MHz) 1.41 (3 H, t, *J* 7.2, CH_2Me), 2.32 (3 H, s, ArMe), 4.42 (2 H, q, *J* 7.2, CH_2Me), 5.25 (2 H, s, $ArOCH_2$), 6.74–6.82 (3 H, m, ArH), 7.07–7.18 (1 H, m, ArH), 7.56–7.65 (1 H, m, pyr 5-H), 8.24–8.37 (1 H, m, pyr 4-H) and 9.16–9.19 (1 H, m, pyr 2-H); δ_C(2.5 MHz) 14.57 (CH_3), 21.77 (CH_3), 61.64 (CH_2), 70.69 (CH_2), 112.03 (CH), 116.09 (CH), 120.80 (CH), 122.59 (CH), 129.63 (CH), 138.08 (CH), 140.03 (C), 150.71 (CH) and 162.30 (C); other quaternary carbons not reliably observed above background.

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