New carbon radical chemistry as a model for the biogenesis of the interiorin/kadsulignan type of dibenzocyclooctadiene lignan

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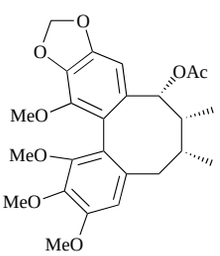
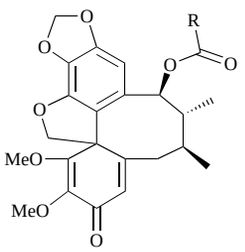
Novel intramolecular radical spirocyclisation reactions in aromatic nuclei, 48→49, 40→22 and 34→32, are presented, which mimic a key step in the proposed biosynthesis of the interiorins 2a–d, the kadsulignans 3a,b and relatives.

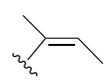
The natural dibenzocyclooctadienes[1] are an important subgroup of the lignan family, containing significant biologically active compounds such as steganone. (−)-Kadsurin **1**[2] provides



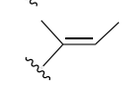
1 (–)-Kadsurin



2a (Interiorin A); R =

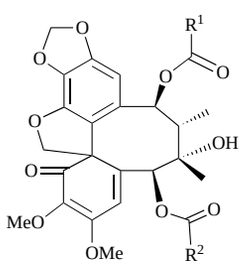


2b (Interiorin B); R =



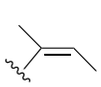
2c (Interiorin C); R = Me

2d (Interiorin D); R = Ph



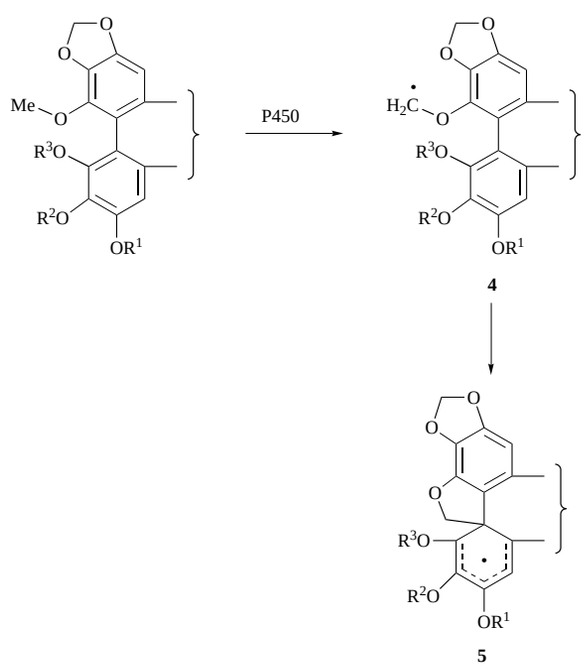
3a (Kadsulignan C); R^1 = Ph, R^2 = Me

3b (Kadsulignan D); $R^1 = R^2$ =



a typical example, in which the two cinnamate derived units have linked first to generate a 2,3-dibenzylbutane, followed by phenolic coupling to form the biaryl link. We were intrigued by a novel structural feature of certain compounds of this type, first observed in the interiorins A–D **2a**–**d**,[3] and subsequently in kadsulignans C–J,[4] *e.g.* **3a**,**b** and the heteroclitins D–F.[5] These lignans display an unusual spirodienone subunit which appears to have its biosynthetic origin in an *O*-methyl group, and we have drawn attention to a number of other secondary metabolites whose biosynthesis involves C–C bond formation, apparently through radical processes.[6] In these cases we have postulated that a carbon radical is generated through hydrogen abstraction, most probably by cytochrome P450 operating in its normal C–H hydroxylation mode. However, rather than the common rapid oxygenation of the C-radical by 'hydroxyl rebound', radical reactions such as cyclisation, substitution, or rearrangement intervene, followed either by a final oxidative step or by recovery of hydrogen, perhaps from protein thiol functions. We envisage that this relatively rare situation arises only in secondary metabolism, with monooxygenases less efficient than those in primary metabolism which have been the focus of most study. In support of this contention, we have reported a number of biomimetic transformations—cyclisation of aryloxymethylene radicals, pyridine alkylation, ring expansion and aromatisation *etc*.—using unambiguous radical processes.[6]

In the lignan examples in focus here both '*para*' and '*ortho*'† dienone substructures are observed. A reasonable biosynthetic pathway‡ could begin with formation of an aryloxymethylene radical **4**, effected by cytochrome P450,[8] followed by (5-*exo*-*trig*) cyclisation onto the second aryl ring (Scheme 1a) to yield



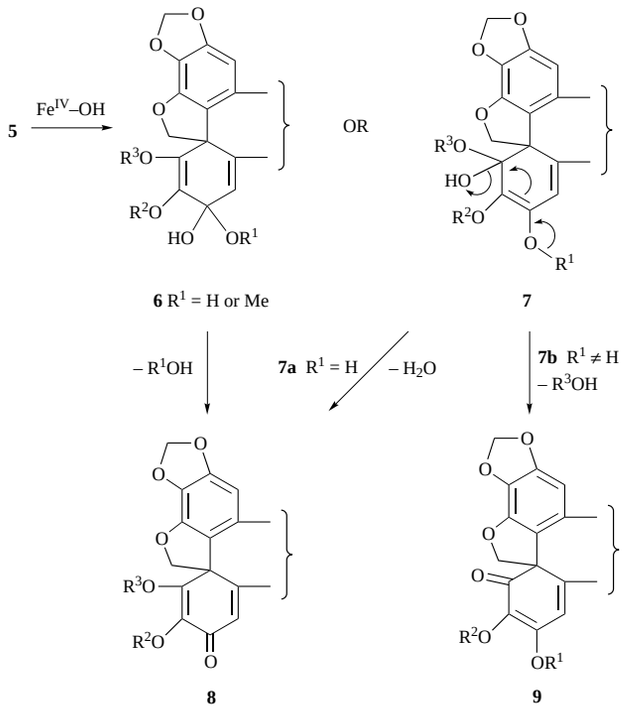
4

5

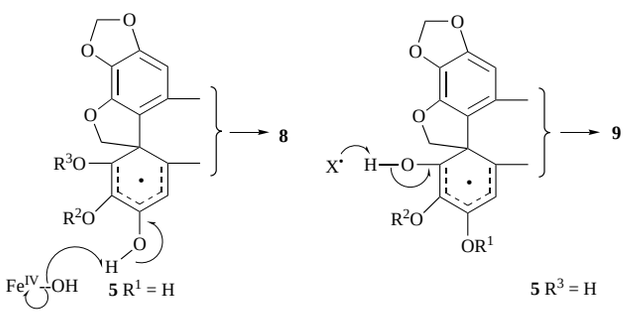
Scheme 1a

a resonance- and oxygen-stabilised radical **5**. Two different pathways through to the spirodienones may then be envisaged, as shown in Schemes 1b and 1c.

† For substructures of this type, '*para*' and '*ortho*' refer to the position of the ketone group with respect to the spiro carbon centre.
‡ See ref. 7 for a preliminary communication.



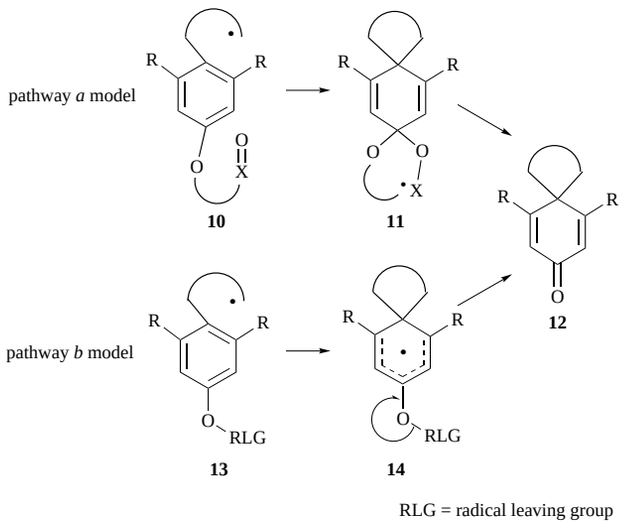
Scheme 1b Pathway a



Scheme 1c Pathway b

In Scheme 1b it is proposed that the intermediate cyclohexadienyl radical **5** is hydroxylated by the accepted 'oxygen rebound' mechanism, at either of two sites, followed by loss of water from the resulting hydrate (R′ = H) or hemiacetal (R′ = Me) (**6** or **7**), either directly or by a vinylogous path as illustrated, leading to the '*para*' or '*ortho*' spirodienone compounds **8** and **9**. An alternative course to the natural product structure is displayed in Scheme 1c. In this route the abstraction of a hydrogen atom from the cyclohexadienyl radical **5** is envisaged, through the agency of an Fe^{IV}–OH species or another radical equivalent species, yielding **8** and **9** directly. The major difference between these two schemes is that in the former pathway (Scheme 1b) complete or partial exchange of oxygen with external oxygen from cytochrome P450 is implied, while in the latter (Scheme 1c) all the oxygen atoms of the precursor **4** are retained in the final products. We set out to devise simple models for both of these possibilities to see what could be learned about the thermodynamic and kinetic viability of such radical processes from *in vitro* studies.

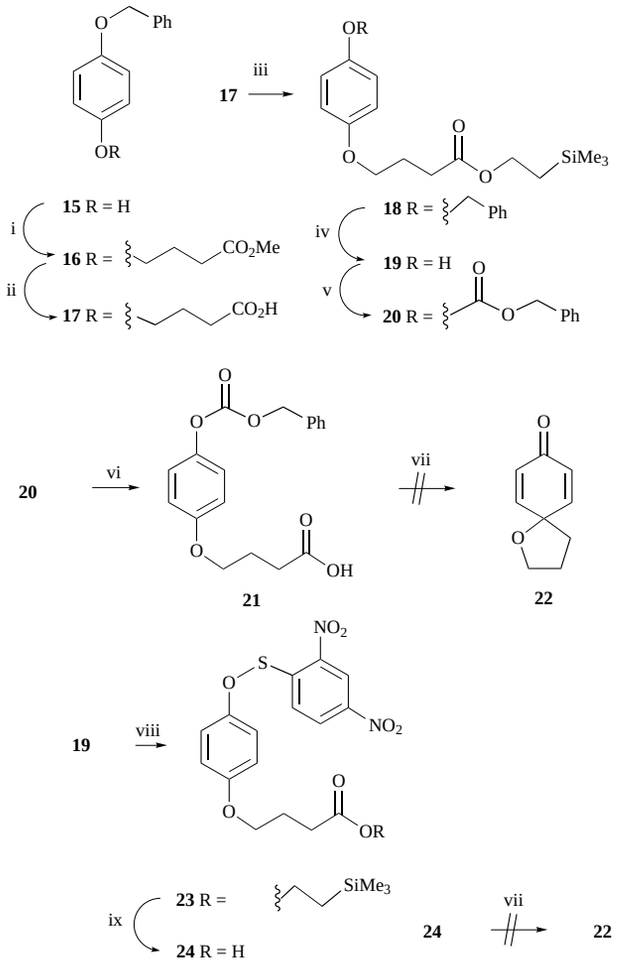
Scheme 2 shows in concept the proposed studies. We envisaged the generation of a carbon radical at the terminus of a short tether to an aromatic nucleus, as in *e.g.* **10**, so as to permit 5-*exo*-*trig* cyclisation to a spiro-linked cyclohexadienyl radical. It was essential to this study that a non-oxidative method of forming the initial radical be employed, to avoid the oxidation of any intermediate carbon radicals to carbocations, opening up new mechanistic possibilities and preventing tests of a pure radical route. We thus chose to form the starting carbon radicals by photolysis of thiohydroxamate esters under neutral



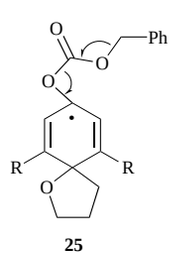
Scheme 2

conditions,[9] as used in earlier biomimetic studies of radicals. For the pathway *a* model, Scheme 2, we proposed to parallel active site hydroxylation by means of intramolecular oxygen transfer (**10**→**11**→**12**) from a suitable oxygen function. As a pathway *b* model we intended to mimic (rather loosely) protein cavity abstraction of hydrogen by a fragmentation sequence, **13**→**14**→**12**, where RLG represents a good radical leaving group.

We embarked on the synthesis of a set of substrates for investigating this projected radical chemistry, and the first results we obtained related to the path *b* model and are exhibited in Scheme 3. 4-Benzyloxyphenol **15** was reacted with methyl 4-bromobutanoate to provide the ester **16**; ester hydrolysis to the free acid **17** was followed by re-esterification with 2-trimethylsilylethanol to yield ester **18**. This acid protecting function was selected to allow flexibility in functional group manipulation later in the sequence. Catalytic debenzylation of **18** then afforded phenol **19** to which a variety of potential 'radical leaving groups' could be added. Thus for example the benzyloxycarbonyl derivative **20** was prepared, and the silyl ethyl ester group deprotected using TBAF to form the desired acid **21**. This acid was subjected to Barton radical decarboxylation in the hope of observing the spirodienone **22** among the products; however a complex mixture resulted in which no trace of the dienone **22** could be observed by NMR spectroscopy. Later in this work a sample of **22** became available and we could confirm that a few percent yield of that compound would have been detected. Similarly we prepared the sulfenate ester **23** of phenol **19**, selectively cleaved the trimethylsilylethyl ester function, and subjected the product acid **24** to Barton decarboxylation. Again no trace of spirodienone **22** was detected by NMR spectroscopy in the products. In the light of subsequent results it may be that the required cyclohexadienyl radical **25** (R = H) is insufficiently stabilised to be formed in significant amounts, and its propensity to fragmentation remains untested. Alongside the work just described we were also pushing forward a biaryl model system as summarised in Scheme 4. To synthesise the necessary test reactant, we generated the aryl tributylstannane **27** from the corresponding bromide **26** by way of the intermediate lithiated species. The stannane **27** was then coupled with the aryl iodide **28**, readily prepared from 2-iodophenol, using tris(dibenzylideneacetone) dipalladium catalyst with triphenylarsine as a ligand (the presence of triphenylarsine was essential to a good yield).[10] The biaryl product **29** was then debenzylated using hydrogenolysis over palladium–carbon catalyst to provide the free phenol **30**. We reacted the sodium salt of this phenol with 2,4-dinitrophenylsulfenyl chloride, looking to form the sulfenate **31**. A clean reaction ensued and the product had ^{1}H and ^{13}C NMR spectra concordant with



Scheme 3 *Reagents and conditions*: i, $Br(CH_2)_3CO_2Me$, K_2CO_3; ii, aq. MeOH, K_2CO_3; iii, (a) $(COCl)_2$, (b) $Me_3Si(CH_2)_2OH$; iv, H_2, Pd/C; v, $PhCH_2COCl$, pyridine, CH_2Cl_2; vi, TBAF; vii, (a) $(COCl)_2$, (b) Na salt of 2-mercaptopyridine-*N*-oxide, (c) *hv*, 200 W tungsten lamp; viii, 2,4-dinitrophenylsulfenyl chloride, $AgOCOCF_3$, THF, pyridine; ix, H_3O^+, acetone



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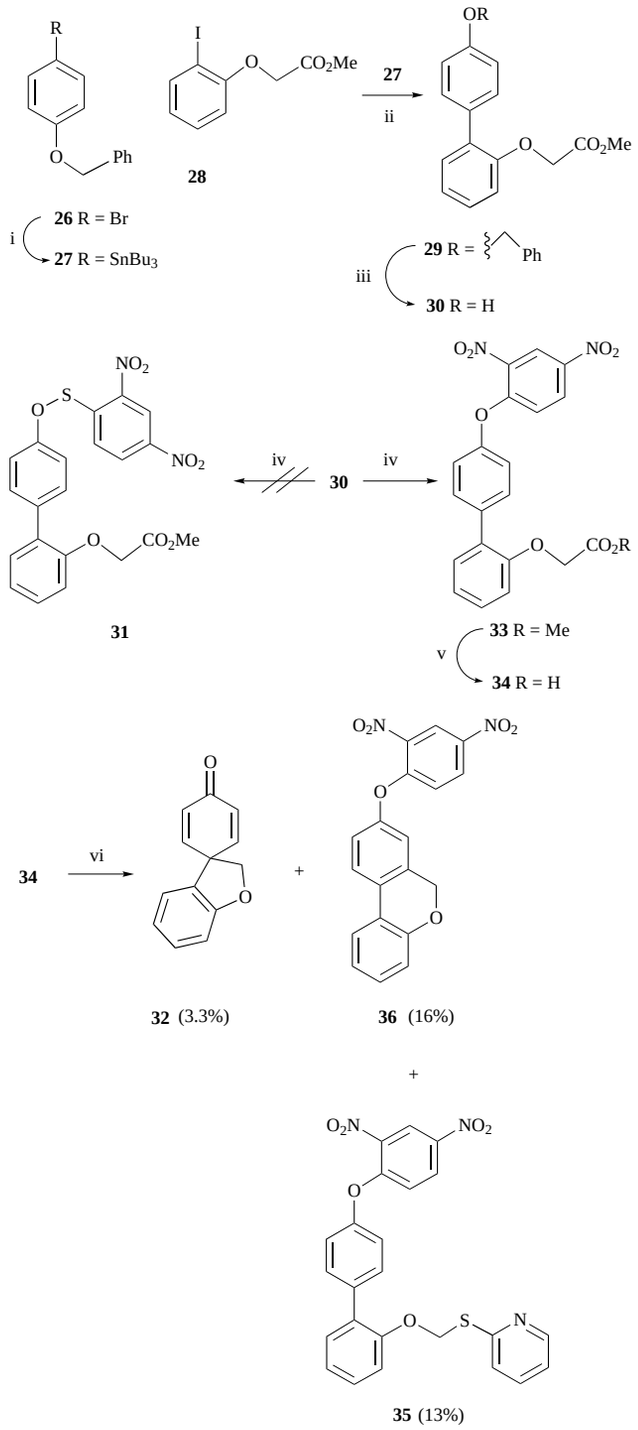
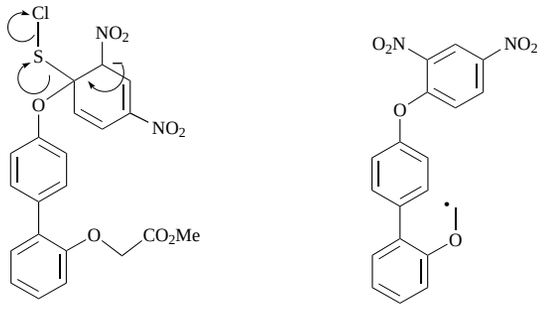


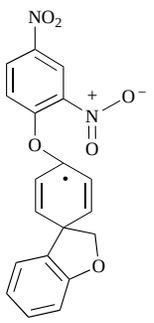
Scheme 4 *Reagents and conditions*: i, (a) Bu^{t}Li, −78 °C, (b) Bu_3SnCl, −78 °C; ii, dba_3Pd_2, Ph_3As, THF, reflux, 48 h; iii, H_2, Pd/C; iv, (a) NaH, THF, (b) 2,4-dinitrosulfenyl chloride, THF, 30 min, RT; v, H_3O^+, acetone; vi, (a) $(COCl)_2$, (b) Na salt of 2-mercaptopyridine-*N*-oxide, (c) *hv*, 200 W tungsten lamp

structure **31**. Hydrolysis to the corresponding acid was straightforward, and the acid was subjected to radical decarboxylation as above. The NMR spectrum of the reaction product mixture indicated the presence of a cyclohexadienone product and separation afforded the hoped-for spirodienone **32**, albeit in only 3.3% yield, with NMR, IR and MS data in complete accord with the structure. However the elation induced by this first sign that we were on the right track turned to initial puzzlement when the MS measurements were returned on the product formed from phenol **30** on reaction with 2,4-dinitrophenylsulfenyl chloride. The mass of the molecular ion pointed to the structure **33** rather than **31**, and this conclusion was rapidly confirmed by unambiguous synthesis of biaryl ether **33** from reaction of phenol **30** with Sanger's reagent. Thus reaction with the arylsulfenyl chloride had proceeded through nucleophilic attack on carbon rather than sulfur to form intermediate **37a** which presumably collapsed with loss of sulfur and chloride ion. This contrasted with the successful formation of sulfenate **23**; however the latter was formed in a reaction of the phenol in THF–pyridine with 2,4-dinitrophenylsulfenyl chloride and silver trifluoroacetate,[11] while in the formation of **33** sodium phenolate and 2,4-dinitrophenylsulfenyl chloride in THF was used.[12] The coordination of silver(I) to the reagent presumably leads to a harder sulfur centre which is then preferentially attacked by phenolic oxygen.

The other products formed alongside spirodienone **32** were assigned as the arylchromane **36** and the monothioacetal **35**, and it was now apparent to us that the Barton decarboxylation had proceeded as expected to form the aryloxy radical **37b** which had reacted in three ways. A minor proportion had cyclised to the cyclohexadienyl radical **37c**, followed by *intra-*



37a **37b**



37c

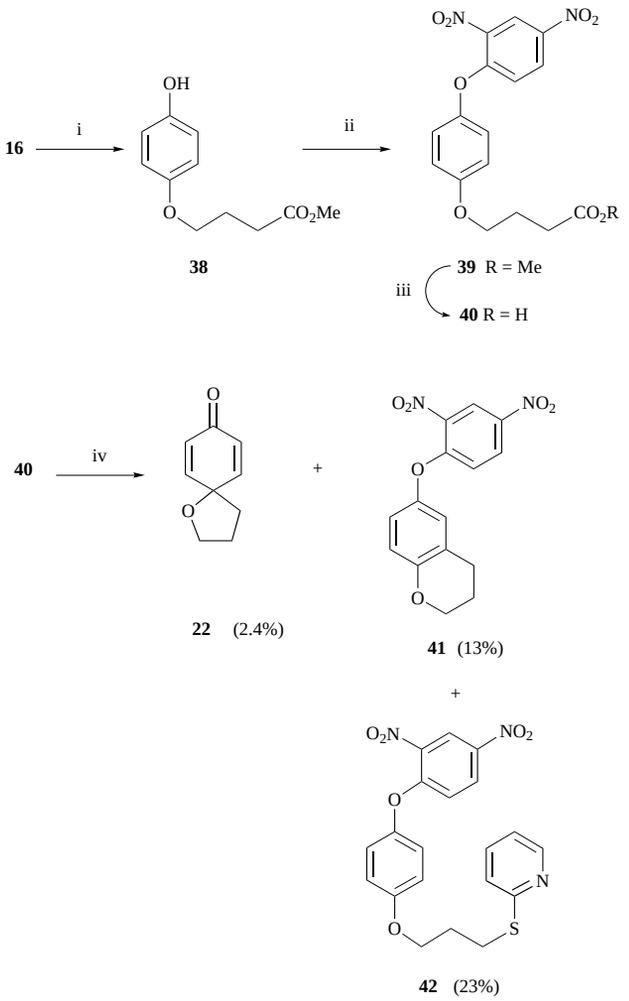
molecular oxygenation by the ortho-*nitro group*, *i.e.* we had uncovered a suitable model for the proposed path a, anticipating our further plans. There is literature precedent for the oxidation of carbon radicals by nitrobenzene,[13] although the reaction has not to our knowledge been used preparatively. We suppose that the aryl chromane product **36** was formed by 6-*exo*-cyclisation of radical **37b**, rather than a 1,2 shift in intermediate **37c**, while thioacetal **35** was produced by trapping of **37b** with the pyridinesulfanyl radical.

The chemistry of Scheme 3 was then diverted to test the possibility of nitro group oxygenation in a very simple monoaryl system. Thus, as shown in Scheme 5, the *O*-benzylhydroquinol derivative **16** was debenzylated by hydrogenolysis and the product **38** was allowed to react with Sanger's reagent in DMF to generate the dinitroaryl ether **39**. Hydrolysis of the ester function delivered the acid **40** which on decarboxylation gave a trace of the bicyclic spirodienone **22**, together with the chromane **41** and the pyridine sulfide **42**. Thus the course of the reaction was closely parallel to that shown in Scheme 4. Although the yield of spirodienone was very small, we were now in a position to plan a more significant model reaction. Obviously the spirocyclisation in Scheme 5 could be favoured by blocking the aromatic substitution pathway, and selecting substituents for this purpose which would stabilise the cyclohexadienyl radical (*c.f.* **25**, R = OMe) should be beneficial. Thus we set out on the sequence displayed in Scheme 6. Syringaldehyde **43** was reacted with methyl 4-bromobutanoate to give the ester **44**. Oxidation with MCPBA afforded the formate **45**,§ and selective ester cleavage yielded the phenol **46**.

The dinitrophenyl ether **47** was readily formed and the derived acid **48** was subjected to radical decarboxylation under the standard conditions employed throughout. We were then very pleased to find that the dimethoxyspirodienone **49** was the major product (49%). A minor quantity of the sulfide **50** was formed, and the remainder of the material was polymeric in character.

These novel reactions indicate that, in a suitable substrate, a viable radical pathway exists for ipso addition (5-*exo*) of a carbon radical to an aromatic unit, and that intramolecular oxygenation can be engineered in such a way as to lead to a *para*-spirodienone. In the natural product examples both electronic and stereochemical factors are more favourable than in the models discussed here, and, taken with our earlier work, we consider that a circumstantial but strong case for a radical process *in vivo* is established. A similar process could lead to *ortho*-spirodienone systems as found in the kadsulignans. Biological studies of the cytochromes involved in this type of biosynthetic process would be rewarding.

The detailed mechanism of the key cyclisation/intramolecular oxygenation step has been investigated further, and will be discussed in a later paper.



38 **39** R = Me **40** R = H **22** (2.4%) **41** (13%) **42** (23%)

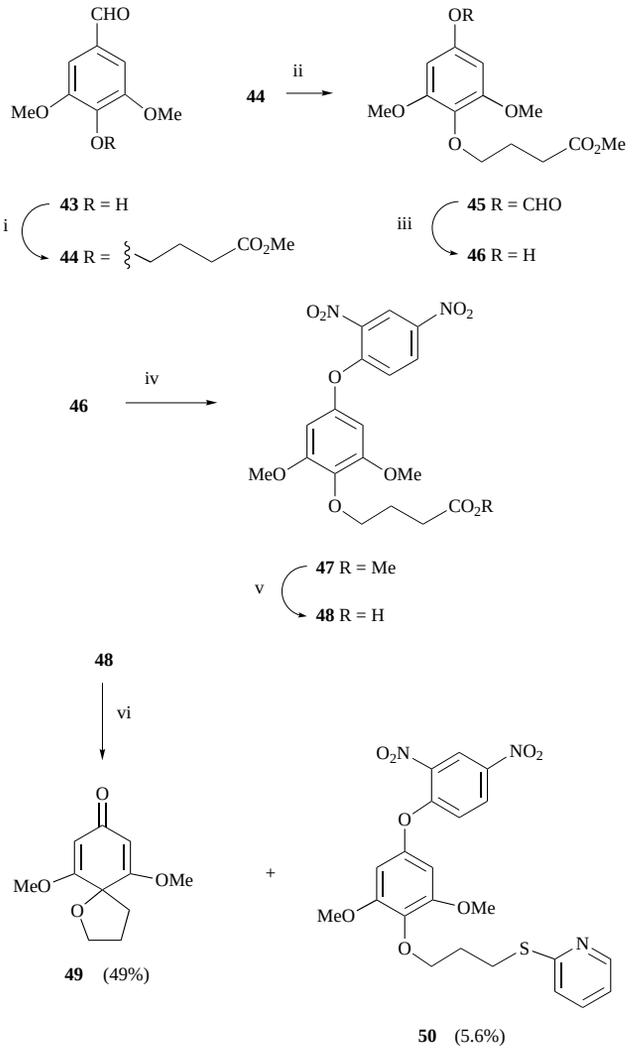
Scheme 5 *Reagents and conditions*: i, H_2, Pd/C, ii, (a) NaH, DMF, (b) 2,4-dinitrofluorobenzene, DMF, RT; iii, H_3O^+, acetone; iv, (a) $(COCl)_2$, (b) Na salt of 2-mercaptopyridine-*N*-oxide, (c) *hv*, 200 W tungsten lamp

Experimental

General details

Unless otherwise stated the following apply. Melting points were recorded using a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured in deuteriochloroform at either 250 or 400 MHz (proton) and either 67.8 or 100.6 MHz (carbon) using an internal $SiMe_4$ standard; multiplicities in ^{13}C NMR were obtained using a DEPT sequence. Observed splittings, *J*, are given in Hz. Mass spectra were obtained using electron impact or chemical ionisation methods. Infrared spectra were collected from thin films (oils) or potassium bromide discs (solids). All solvents were dried by standard methods before use; 'light petroleum' was the fraction bp 40–60 °C; 'ether' means diethyl ether. Temperatures are recorded in °C. 'Evaporation' refers to evaporation under reduced pressure; 'washed' indicates the use of water and aq.

§ It should be noted that the Baeyer–Villiger reaction with MCPBA proved in later work to be a very capricious reaction and alternative routes to the acid **48** had to be devised.



Scheme 6 *Reagents and conditions*: i, $Br(CH_2)_3CO_2Me$, K_2CO_3, 18-crown-6, butanone, reflux, 48 h; ii, MCPBA, RT, 48 h; iii, MeOH, Me_2NH, 1 min; iv, (a) NaH, DMF, (b) 2,4-dinitrofluorobenzene, DMF, RT; v, H_3O^+, acetone; vi, (a) $(COCl)_2$, (b) Na salt of 2-mercaptopyridine-*N*-oxide, (c) *hv*, 200 W tungsten lamp

sodium hydrogen carbonate as appropriate; 'dried' implies the use of magnesium sulfate. 'Chromatography' means column chromatography using silica gel 60; eluting solvents are listed, and gradient elution was employed with mixed solvents.

Methyl 4-(4-benzyloxyphenoxy)butanoate 16

4-Benzyloxyphenol (3.23 g, 16.2 mmol),[14] potassium carbonate (4.46 g) and methyl 4-bromobutanoate (3.22 g, 17.8 mmol) were refluxed together overnight in acetone (50 ml). 18-Crown-6 (500 mg, 1.9 mmol) was then added, and the reflux was maintained for 4 h more. The reaction mixture was then cooled and evaporated, and the residue was partitioned between water and ether. The organic phase was washed with aq. sodium hydroxide and brine, dried, and evaporated. The residue was crystallised from ether–light petroleum to afford *methyl* 4-(4-*benzyloxyphenoxy*)*butanoate* **16** (4.19 g, 81%) as cream flakes, mp 88–89 °C (Found: C, 72.21; H, 6.98%; *m*/*z*, 300.136. $C_{18}H_{20}O_4$ requires C, 71.98; H, 6.71%; M^+, 300.136); ν_{max}(KBr)/cm^{-1} 1746, 1511; δ_H 2.08 (2H, tt, *J* 7.3, 6.1, 3-CH_2), 2.52 (2H, t, *J* 7.3, 2-CH_2), 3.68 (3H, s, OMe), 3.94 (2H, t, *J* 6.1, 4-CH_2), 5.01 (2H, s, OCH_2Ph), 6.81 and 6.89 (each 2H, d, *J* 9.2, ArH), 7.31–7.43 (5H, m, PhH); δ_C 24.5 (CH_2), 30.4 (CH_2), 51.4 (CH_3), 67.0 (CH_2), 70.4 (CH_2), 115.2 (CH), 115.6 (CH), 127.3 (CH), 127.7 (CH), 128.4 (CH), 137.1 (C), 152.8 (C), 153.0 (C) and 173.5 (C).

4-(4-Benzyloxyphenoxy)butanoic acid 17

A mixture of methyl 4-(4-benzyloxyphenoxy)butanoate (122 mg, 0.41 mmol) and potassium carbonate (200 mg, 1.46 mmol) in methanol (10 ml) and water (5 ml) was refluxed overnight. The reaction mixture was washed with ether and the aqueous phase was acidified and extracted with ether. The organic extracts were dried and evaporated to yield the *title acid* **17** as white flakes (106 mg, 91%), mp 131–133 °C (from ether–light petroleum) (Found: C, 71.39; H, 6.57%; *m*/*z*, 286.118. $C_{17}H_{18}O_4$ requires C, 71.30, H, 6.34%; M^+, 286.121); ν_{max}(KBr)/cm^{-1} 1713, 1591, 1511; δ_H 2.09 (2H, tt, *J* 7.3, 6.0, 3-CH_2), 2.58 (2H, t, *J* 7.3, 2-CH_2), 3.96 (2H, t, *J* 6.0, 4-CH_2), 5.01 (2H, s, OCH_2Ph), 6.81 and 6.90 (each 2H, d, *J* 9.3, 2′-H, 3′-H, 5′-H, 6′-H) and 7.31–7.44 (5H, m, PhH); δ_C 24.4 (CH_2), 30.6 (CH_2), 67.0 (CH_2), 70.6 (CH_2), 115.4 (CH), 115.8 (CH), 127.4 (CH), 127.9 (CH), 128.5 (CH), 137.2 (C), 153.0 (C), 153.0 (C) and 179.5 (C).

2-Trimethylsilylethyl 4-(4-benzyloxyphenoxy)butanoate 18

4-(4-Benzyloxyphenoxy)butanoic acid (1.81 g, 6.33 mmol) and oxalyl chloride (1.33 g, 10.5 mmol) were stirred together in methylene chloride (40 ml) with DMF (0.05 ml) for 3 h at ambient temperature. The mixture was evaporated, and the residue was dissolved in benzene (10 ml). This solution was evaporated and mixed with 2-trimethylsilylethanol (746 mg, 6.33 mmol) in pyridine (15 ml). The resulting solution was stirred for 3 h when it was diluted with ether and washed with dil. hydrochloric acid, aq. sodium hydrogen carbonate and brine. Evaporation afforded the *title ester* **18** as white flakes (2.07 g, 85%), mp 47–48 °C (from ether–light petroleum) (Found: *m*/*z*, 386.192. $C_{22}H_{30}O_4Si$ requires M^+, 386.191); ν_{max}(KBr)/cm^{-1} 1738, 1607, 1592, 1514; δ_H 0.04 (9H, s, $SiMe_3$), 0.98 (2H, t, *J* 8.3, $SiCH_2$), 2.07 (2H, tt, *J* 7.3, 6.1, 3-CH_2), 2.49 (2H, t, *J* 7.3, 2-CH_2), 3.95 (2H, t, *J* 6.1, 4-CH_2), 4.17 (2H, t, *J* 8.3, OCH_2), 5.01 (2H, s, CH_2Ph), 6.81 and 6.89 (each 2H, d, *J* 9.3, 2′-H, 3′-H, 5′-H, 6′-H) and 7.31–7.44 (5H, m, PhH); δ_C −1.6 (CH_3), 17.2 (CH_2), 24.6 (CH_2), 30.8 (CH_2), 62.5 (CH_2), 67.2 (CH_2), 70.5 (CH_2), 115.3 (CH), 115.6 (CH), 127.3 (CH), 127.7 (CH), 128.4 (CH), 137.2 (CH), 152.8 (CH), 153.1 (C) and 173.2 (C).

2-Trimethylsilylethyl 4-(4-hydroxyphenoxy)butanoate 19

2-Trimethylsilylethyl 4-(4-benzyloxyphenoxy)butanoate (990 mg, 2.56 mmol) was hydrogenated in ethanol (50 ml) at atmospheric pressure over 5% palladium–carbon catalyst (100 mg) until no more hydrogen was absorbed. Evaporation of the filtered reaction mixture provided the *title phenol* **19** as an oil (754 mg, 99%) (Found: *m*/*z*, 296.144. $C_{15}H_{24}O_4Si$ requires M^+, 296.144); ν_{max}(film)/cm^{-1} 3419, 1738, 1512; δ_H 0.05 (9H, s, $SiMe_3$), 0.99 (2H, t, *J* 8.4, $SiCH_2$), 2.08 (2H, tt, *J* 7.3, 6.1, 3-CH_2), 2.50 (2H, t, *J* 7.3, 2-CH_2), 3.94 (2H, t, *J* 6.1, 4-CH_2), 4.19 (2H, t, *J* 8.4, OCH_2) and 6.76 (4H, br s, 2′-H, 3′-H, 5′-H, 6′-H); δ_C −1.7 (CH_3), 17.1 (CH_2), 24.6 (CH_2), 31.0 (CH_2), 62.9 (CH_2), 67.2 (CH_2), 115.5 (CH), 115.9 (CH), 150.0 (C), 152.4 (C) and 174.1 (C).

2-Trimethylsilylethyl 4-[4-(benzyloxycarboxy)phenoxy]-butanoate 20

Benzyl chloroformate (138 mg, 0.84 mmol) was added to a solution of 2-trimethylsilylethyl 4-(4-hydroxyphenoxy)butanoate (240 mg, 0.84 mmol) and pyridine (1 ml) in methylene chloride (5 ml) at 0 °C. After 10 min the mixture was allowed to warm to room temperature and allowed to stand for 2 h before it was diluted with methylene chloride and washed with dil. hydrochloric acid, aq. sodium hydroxide and brine. Evaporation and chromatography of the residue provided the *title compound* **20** as a white powder (157 mg, 46%) (Found: *m*/*z*, 430.184. $C_{23}H_{30}O_6Si$ requires M^+, 430.181); ν_{max}(film)/cm^{-1} 1763, 1732, 1599, 1508; δ_H 0.04 (9H, s, $SiMe_3$), 0.98 (2H, t, *J* 8.4, $SiCH_2$), 2.08 (2H, tt, *J* 7.3, 6.1, 3-CH_2), 2.48 (2H, t, *J* 7.3,

2-CH_2), 3.97 (2H, t, *J* 6.1, 4-CH_2), 4.18 (2H, t, *J* 8.4, OCH_2), 5.24 (2H, s, OCH_2Ph), 6.85 and 7.07 (each 2H, d, *J* 9.1, 2′-H, 3′-H, 5′-H, 6′-H) and 7.34–7.45 (5H, m, PhH); δ_C −1.6 (CH_3), 17.3 (CH_2), 24.5 (CH_2), 30.8 (CH_2), 62.6 (CH_2), 67.0 (CH_2), 70.2 (CH_2), 114.9 (CH), 121.8 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 134.8 (C), 144.7 (C), 154.0 (C), 156.6 (C) and 173.2 (C).

4-[4-(Benzyloxycarboxy)phenoxy]butanoic acid 21

Tetra-*n*-butylammonium fluoride (1.44 ml, 1 M in THF, 1.44 mmol) was added to 2-trimethylsilylethyl 4-[4-(benzyloxycarboxy)phenoxy]butanoate (155 mg, 0.36 mmol) in DMF (5 ml) at room temperature. After 1 h the reaction was diluted with ether and washed with water. The acid product was then extracted into aq. sodium hydrogen carbonate whence it was recovered through acidification and extraction into ether. The dried ether layers on evaporation gave the *title acid* **21** as a white amorphous solid (20 mg, 17%) (Found: *m*/*z*, 330.112. $C_{18}H_{18}O_6$ requires M^+, 330.110); ν_{max}(KBr)/cm^{-1} 1759, 1712, 1507; δ_H 2.08 (2H, tt, *J* 7.3, 6.1, 3-CH_2), 2.56 (2H, t, *J* 7.3, 2-CH_2), 3.97 (2H, t, *J* 6.1, 4-CH_2), 5.22 (2H, s, OCH_2Ph), 6.86 and 7.06 (each 2H, d, *J* 9.2, 2′-H, 3′-H, 5′-H, 6′-H) and 7.34–7.46 (5H, m, PhH); δ_C 24.3 (CH_2), 30.4 (CH_2), 66.9 (CH_2), 70.3 (CH_2), 115.0 (CH), 121.9 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 135.0 (C), 144.9 (C), 154.1 (C), 156.5 (C) and 178.9 (C).

2-Trimethylsilylethyl 4-[4-(2,4-dinitrophenylsulfanyloxy)-phenoxy]butanoate 23

A mixture of 2-trimethylsilylethyl 4-(4-hydroxyphenoxy)-butanoate (240 mg, 0.81 mmol), 2,4-dinitrobenzenesulfenyl chloride (190 mg, 0.81 mmol), silver trifluoroacetate (179 mg, 0.81 mmol) and pyridine (0.1 ml) with THF (5 ml) was stirred under nitrogen in the dark for 30 min. The reaction mixture was diluted with ether, washed, dried, and evaporated. The residue was crystallised from ether–light petroleum to afford the *title compound* **23** as yellow crystals (171 mg, 43%), mp 80–81 °C, which were stored in the dark (Found: *m*/*z*, 494.112. $C_{21}H_{26}O_8N_2SSi$ requires M^+, 494.118); ν_{max}(KBr)/cm^{-1} 1721, 1599, 1522, 1503; δ_H 0.04 (9H, s, $SiMe_3$), 0.98 (2H, t, *J* 8.4, CH_2Si), 2.09 (2H, tt, *J* 7.2, 6.1, 3-CH_2), 2.48 (2H, t, *J* 7.2, 2-CH_2), 3.97 (2H, t, *J* 6.1, 4-CH_2), 4.18 (2H, t, *J* 8.4, CO_2CH_2), 6.83 and 7.11 (each 2H, d, *J* 9.1, 2′-H, 3′-H, 5′-H, 6′-H), 7.89 (1H, d, *J* 9.1, 6″-H), 8.45 (1H, dd, *J* 9.1, 2.3, 5″-H) and 9.14 (1H, d, *J* 2.3, 3″-H); δ_C −1.5 (CH_3), 17.3 (CH_2), 24.5 (CH_2), 30.8 (CH_2), 62.7 (CH_2), 67.3 (CH_2), 115.5 (CH), 117.2 (CH), 120.9 (CH), 124.0 (CH), 128.1 (CH), 139.5 (C), 145.0 (C), 151.4 (C), 153.5 (C), 155.4 (C) and 173.2 (C).

4-[4-(2,4-Dinitrophenylsulfanyloxy)phenoxy]butanoic acid 24

A solution of 2-trimethylsilylethyl 4-[4-(2,4-dinitrophenylsulfanyloxy)phenoxy]butanoate (125 mg, 0.25 mmol), in acetone (20 ml) and dil. sulfuric acid (2 M, 10 ml) was refluxed in the dark for 3 h. The cooled mixture was extracted with ethyl acetate, and the extracts were washed with water, dried and evaporated to provide the *title acid* **24** as a yellow solid (37 mg, 37%) which was not further purified and was stored in the dark; ν_{max}(KBr)/cm^{-1} 3441, 1702, 1594, 1499; δ_H 2.08 (2H, tt, *J* 7.2, 6.1, 3-CH_2), 2.56 (2H, t, *J* 7.2, 2-CH_2), 3.96 (2H, t, *J* 6.1, 4-CH_2), 6.81 and 7.10 (each 2H, d, *J* 9.1, 2′-H, 3′-H, 5′-H, 6′-H), 7.86 (1H, d, *J* 9.1, 6″-H), 8.43 (1H, dd, *J* 9.1, 2.3, 5″-H) and 9.13 (1H, d, *J* 2.3, 3″-H); δ_C 24.3 (CH_2), 30.4 (CH_2), 67.0 (CH_2), 115.5 (CH), 117.3 (CH), 120.9 (CH), 124.0 (CH), 128.2 (CH), 139.5 (C), 145.0 (C), 151.5 (C), 153.5 (C), 155.4 (C) and 178.9 (C).

4-Benzyloxyphenyl(tri-*n*-butyl)tin 27

4-(Benzyloxy)bromobenzene[15] (7.37 g, 28.1 mmol) was dissolved in dry THF (200 ml). The solution was cooled to −78 °C and treated with *tert*-butyllithium (37 ml, 1.7 M, 63 mmol). After 5 h at −78 °C tri-*n*-butyltin chloride (9.19 g, 28.1 mmol) was added, and after 1 h more the reaction was quenched with saturated aq. ammonium chloride. The organic phase was dried and evaporated, and residual starting materials were removed by distillation at 200 °C/1 mmHg. The residue was purified by chromatography (light petroleum) to afford 4-*benzyloxyphenyl*(*tri*-n-*butyl*)*tin* **27** as a colourless oil (5.02 g, 38%) [Found: *m*/*z*, 417.120. $C_{25}H_{38}OSn$ requires $(M - Bu)^+$, 417.124]; δ_H [0.9 (9H, t, *J* 7.3) and 1.0–1.6 (18H, m), (Bu^n)$_3$], 5.07 (2H, s, OCH_2), 6.98 (2H, d, *J* 8.5, ArH) and 7.33–7.48 (7H, m, ArH); δ_C 9.5 (CH_2), 13.2 (CH_3), 26.9 (CH_2), 28.6 (CH_2), 69.6 (CH_2), 114.7 (CH), 127.0 (CH), 127.3 (CH), 128.1 (CH), 132.3 (C), 136.7 (C), 137.0 (CH) and 158.9 (C).

Methyl (2-iodophenoxy)acetate 28

Sodium hydride (60% dispersion, 800 mg, 20 mmol) was washed with light petroleum, and covered with THF (150 ml). 2-Iodophenol (4.00 g) was carefully added, and the resulting mixture was heated to reflux under nitrogen. After 10 min methyl bromoacetate (2.78 g, 18 mmol) was added, and the mixture was refluxed for 1 h more. The reaction mixture was diluted with ether and was washed successively with water, aq. sodium hydroxide, and brine, when it was evaporated. The residual oil crystallised on standing to provide the *methyl* (2-*iodophenoxy*)*acetate* **28** as pale yellow needles (4.56 g, 86%), mp 39–41 °C (Found: *m*/*z*, 291.964. $C_9H_9IO_3$ requires M^+, 291.960); ν_{max}(film)/cm^{-1} 1760, 1582; δ_H 3.81 (3H, s, OMe), 4.71 (2H, s, OCH_2), 6.71–6.80 (2H, m, 4-H, 6-H), 7.28 (1H, ddd, *J* 8.0, 7.8, 1.6, 5-H) and 7.80 (1H, dd, *J* 7.7, 1.6, 3-H); δ_C 52.3 (CH_3), 66.2 (CH_2), 86.4 (C), 112.3 (CH), 123.6 (CH), 129.4 (CH), 139.7 (CH), 156.5 (C) and 168.7 (C).

Methyl (4′-benzyloxybiphenyl-2-yloxy)acetate 29

Methyl (2-iodophenoxy)acetate (1.13 g, 3.87 mmol) was dissolved in dry THF (25 ml) and the solution was treated with triphenylarsine (245 mg, 0.80 mmol) and tris(dibenzylideneacetone)dipalladium (91 mg, 0.10 mmol) at ambient temperature under nitrogen. After 10 min 4-benzyloxyphenyl-(tri-*n*-butyl)tin (2.20 g, 4.64 mmol) was added, and the resulting mixture was heated to reflux. After 24 h, more triphenylarsine (87 mg) and tris(dibenzylideneacetone)dipalladium (32 mg) were added, and reflux was maintained for a further 24 h. The reaction mixture was evaporated and the residue was chromatographed (light petroleum–ethyl acetate) to yield the *title biaryl* **29** as a white crystalline solid (950 mg, 70%), mp 139–140 °C (from ether–light petroleum) (Found: C, 75.68; H, 5.88%; *m*/*z*, 348.137. $C_{22}H_{20}O_4$ requires C, 75.84; H, 5.79%; M^+, 348.136); ν_{max}(KBr)/cm^{-1} 1741, 1608; δ_H 3.77 (3H, s, OMe), 4.60 (2H, s, OCH_2), 5.10 (2H, s, OCH_2Ph), 6.85 (1H, dd, *J* 8.2, 0.8, 3-H), 7.02–7.10 (3H, m, 5-H, 3′-H, 5′-H), 7.26 (1H, ddd, *J* 8.0, 7.7, 1.8, 4-H), 7.32–7.48 (6H, m, PhH, 6-H) and 7.55 (2H, d, *J* 8.9, 2′-H, 6′-H); δ_C 52.1 (CH_3), 65.6 (CH_2), 69.9 (CH_2), 112.6 (CH), 114.3 (CH), 122.1 (CH), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 130.6 (C), 130.7 (CH), 130.8 (C), 131.0 (C), 137.0 (C), 154.6 (C), 158.0 (CH) and 169.5 (C).

Methyl (4′-hydroxybiphenyl-2-yloxy)acetate 30

Methyl (4′-benzyloxybiphenyl-2-yloxy)acetate (930 mg, 2.67 mmol) was dissolved in ethyl acetate (35 ml), and hydrogenated over 5% palladium on carbon (300 mg) at atmospheric pressure until hydrogen uptake ceased. The mixture was filtered through Celite and evaporated to provide the *title phenolic ester* **30** as a white crystalline solid (632 mg, 92%), mp 98–99 °C (from ether–light petroleum) (Found: C, 69.78; H, 5.53%; *m*/*z*, 258.089. $C_{15}H_{14}O_4$ requires C, 69.76; H, 5.46%; M^+, 258.089); ν_{max}(KBr)/cm^{-1} 3401, 1737; δ_H 3.75 (3H, s, OMe), 4.58 (2H, s, OCH_2), 6.32 (1H, br s, OH), 6.82–6.86 (3H, m, 3-H, 3′-H, 5′-H), 7.04 (1H, ddd, *J* 7.4, 6.8, 0.6, 5-H), 7.23 (1H, ddd, *J* 7.4, 6.8, 1.6, 4-H),

7.29 (1H, dd, *J* 7.4, 1.6, 6-H) and 7.45 (2H, d, *J* 8.5, 2′-H, 6′-H); δ_C 52.3 (CH_3), 65.8 (CH_2), 112.8 (CH), 115.0 (CH), 122.2 (CH), 128.0 (CH), 130.2 (C), 130.8 (CH), 131.0 (CH), 131.0 (C), 154.5 (C), 154.9 (C) and 170.0 (C).

Methyl [4′-(2,4-dinitrophenoxy)biphenyl-2-yloxy]acetate 33

Method a. Sodium hydride (60% dispersion, 54 mg, 1.35 mmol) was washed with light petroleum and suspended in THF (5 ml). Methyl (4′-hydroxybiphenyl-2-yloxy)acetate (304 mg, 1.18 mmol) was added and the mixture was stirred at ambient temperature for 30 min when 2,4-dinitrobenzenesulfenyl chloride (276 mg, 1.36 mmol) in THF (10 ml) was added. After stirring the reaction mixture for 30 min it was diluted with ether and was washed with dilute hydrochloric acid and brine, dried and evaporated. The residue was chromatographed (light petroleum–ethyl acetate, gradient elution) to yield the *title dinitrophenyl ether* **33** as a yellow crystalline solid (448 mg, 90%), mp 139–149 °C (from methylene chloride–light petroleum) (Found: C, 59.23; H, 3.63; N, 6.31%; *m/z*, 424.092. $C_{21}H_{16}N_2O_8$ requires C, 59.44; H, 3.80; N, 6.60%; M^+, 424.092); ν_{max}(KBr)/cm^{-1} 1752, 1615, 1603, 1536, 1511; λ_{max}(EtOH)/nm 250 (ε/dm^3 mol^{-1} cm^{-1} 21 700), 287 (15 200); δ_H 3.80 (3H, s, OMe), 4.67 (2H, s, OCH_2), 6.88 (1H, d, *J* 8.2, 3-H), 7.08–7.21 (4H, m, 5-H, 3′-H, 5′-H, 6″-H), 7.30–7.39 (2H, m, 4-H, 6-H), 7.73 (2H, d, *J* 8.7, 2′-H, 6′-H), 8.34 (1H, dd, *J* 9.3, 2.7, 5″-H) and 8.86 (1H, d, *J* 2.7, 3″-H); δ_C 52.2 (CH_3), 65.3 (CH_2), 112.2 (CH), 118.6 (CH), 120.0 (CH), 122.1 (CH), 122.2 (CH), 128.8 (CH), 129.1 (CH), 129.5 (C), 131.1 (CH), 131.9 (CH), 136.5 (C), 139.4 (C), 141.3 (C), 152.5 (C), 154.5 (C), 156.2 (C) and 169.2 (C).

Method b. A closely similar experiment was undertaken using 2,4-dinitrofluorobenzene instead of 2,4-dinitrobenzenesulfenyl chloride. After parallel product isolation, the same dinitrophenyl ether was obtained (46%), spectroscopically indistinguishable from the above sample.

[4′-(2,4-Dinitrophenoxy)biphenyl-2-yloxy]acetic acid 34

A solution of methyl [4′-(2,4-dinitrophenoxy)biphenyl-2-yloxy]acetate (161 mg, 0.38 mmol) in acetone and hydrochloric acid (2 M, 8 ml) was heated under reflux for 24 h, when the cooled mixture was extracted with ether. The organic phases were washed and dried and evaporated to give the *title acid* **34** as a yellow solid (122 mg, 78%), mp 193–195 °C (from ether–light petroleum) (Found: *m/z*, 410.074. $C_{20}H_{14}N_2O_8$ requires M^+, 410.075); ν_{max}(KBr)/cm^{-1} 3432, 1734, 1608, 1530, 1510; δ_H 4.70 (2H, s, OCH_2), 6.93 (1H, d, *J* 7.9, 3-H), 7.12–7.23 (4H, m, 5-H, 3′-H, 5′-H, 6″-H), 7.33–7.40 (2H, m, 4-H, 6-H), 7.69 (2H, d, *J* 8.9, 2′-H, 6′-H), 8.35 (1H, dd, *J* 9.1, 2.6, 5″-H) and 8.87 (1H, d, *J* 2.6, 3″-H); δ_C 65.4 (CH_2), 113.2 (CH), 120.1 (CH), 120.6 (CH), 122.4 (CH), 122.5 (CH), 129.8 (CH), 130.0 (CH), 130.1 (C), 131.6 (CH), 132.6 (CH), 137.5 (C), 140.7 (C), 142.6 (C), 153.8 (C), 155.8 (C), 156.5 (C) and 170.4 (C).

Radical decarboxylation of [4′-(2,4-dinitrophenoxy)biphenyl-2-yloxy]acetic acid

[4′-(2,4-Dinitrophenoxy)biphenyl-2-yloxy]acetic acid (122 mg, 0.3 mmol) was stirred under nitrogen with oxalyl chloride (0.25 ml) and dry DMF (0.05 ml) in methylene chloride (5 ml) for 2 h. After evaporation the residue was dissolved in benzene (5 ml), and the solution was evaporated. The crude acid chloride in benzene (5 ml) was added to a dried (Dean and Stark) refluxing suspension of 2-mercaptopyridine-*N*-oxide sodium salt (50 mg, 0.36 mmol) and 4-dimethylaminopyridine (DMAP) (6 mg) in benzene (50 ml), in foil-covered apparatus to exclude light. After 30 min the foil was removed and the bright yellow mixture was irradiated with a 200 W tungsten lamp. Reflux was maintained for 1 h when the mixture was cooled, washed, dried, and evaporated. The residue was chromatographed (light petroleum–ethyl acetate) to yield; (i) *spiro*[4-*oxo*-2,3-*dihydrobenzofuran*-3,1′-*cyclohexa*-2′,5′-*diene*] **32** as an oil, further purified by HPLC (1.8 mg, 3.3%) (Found: *m/z*, 198.066. $C_{13}H_{10}O_2$ requires M^+, 198.068): ν_{max}(film)/cm^{-1} 1665, 1596, 1540; δ_H 4.57 (2H, s, OCH_2), 6.34 (2H, d, *J* 10.1, 3′-H, 5′-H), 6.91–6.98 (3H, m, ArH), 6.99 (2H, d, *J* 10.1, 2′-H, 6′-H) and 7.25–7.29 (1H, m, ArH); (ii) 8-(2,4-*dinitrophenoxy*)-6H-*benzo*[c]*chromene* **36** as a brownish gum (16 mg, 16%) (Found: *m/z*, 364.072. $C_{19}H_{12}N_2O_6$ requires M^+, 364.070); ν_{max}(film)/cm^{-1} 1607, 1535; δ_H 5.11 (2H, s, 6-H_2), 6.97 (1H, d, *J* 2.5, 7-H), 7.02 (1H, d, *J* 8.2, 4-H), 7.10 (1H, dd, *J* 7.9, 7.5, 2-H), 7.12 (1H, d, *J* 9.2, 6′-H), 7.15 (1H, dd, *J* 8.8, 2.5, 9-H), 7.28 (1H, ddd, *J* 8.2, 7.5, 1.3, 3-H), 7.72 (1H, dd, *J* 7.9, 1.3, 1-H), 7.79 (1H, d, *J* 8.8, 10-H), 8.34 (1H, dd, *J* 9.2, 2.7, 5′-H) and 8.86 (1H, d, *J* 2.7, 3′-H); δ_C 67.9 (CH_2), 116.8 (CH), 117.6 (CH), 118.7 (CH), 120.4 (CH), 121.8 (C), 122.1 (CH), 122.5 (CH), 123.3 (CH), 124.4 (CH), 128.4 (C), 128.8 (CH), 130.1 (CH), 134.1 (C), 141.6 (C), 153.0 (C), 154.5 (C) and 155.9 (C); (iii) 2-(2-*pyridylsulfanylmethoxy*)-4′-(2,4-*dinitrophenoxy*)*biphenyl* **35** as a dark orange amorphous solid (19 mg, 13%) (Found: *m/z*, 475. $C_{24}H_{17}N_3O_6S$ requires M^+, 475); δ_H 5.87 (2H, s, OCH_2S), 7.01 (2H, d, *J* 7.6, 3′-H, 5′-H), 7.07–7.11 (1H, m, 5‴-H), 7.09 (1H, d, *J* 9.3, 6″-H), 7.13–7.17 (3H, m, 3-H, 5-H, 3‴-H), 7.33–7.38 (2H, m, 4-H, 6-H), 7.50 (2H, d, *J* 7.6, 2′-H, 6′-H), 7.49–7.53 (1H, m, 4‴-H), 8.32 (1H, dd, *J* 9.3, 2.7, 5″-H), 8.46 (1H, m, 6‴-H) and 8.86 (1H, d, *J* 2.7, 3″-H).

Methyl 4-(4-hydroxyphenoxy)butanoate 38

Methyl 4-(4-benzyloxyphenoxy)butanoate (740 mg, 2.47 mmol) was hydrogenated at atmospheric pressure in ethyl acetate (30 ml) over 5% palladium–carbon catalyst (300 mg) until hydrogen uptake ceased. The mixture was filtered and evaporated to provide the *title phenol* **38** (509 mg, 95%) as white crystals, mp 94–95 °C (from ether–light petroleum) (Found: C, 63.03; H, 6.74%; *m/z*, 210.084. $C_{11}H_{14}O_4$ requires C, 62.83; H, 6.72%; M^+, 210.089); ν_{max}(KBr)/cm^{-1} 3423, 3375, 1741, 1606, 1515; δ_H 2.08 (2H, tt, *J* 7.3, 6.1, 3-CH_2), 2.53 (2H, t, *J* 7.3, 2-CH_2), 3.70 (3H, s, OMe), 3.93 (2H, t, *J* 6.1, 4-CH_2) and 6.75 (4H, br s, ArH); δ_C 24.6 (CH_2), 30.6 (CH_2), 51.8 (CH_3), 67.3 (CH_2), 115.5 (CH), 116.0 (CH), 149.7 (C), 152.7 (C) and 174.2 (C).

Methyl 4-[4-(2,4-dinitrophenoxy)phenoxy]butanoate 39

Sodium hydride (60% dispersion, 84 mg, 2.1 mmol) was washed with light petroleum and suspended in DMF (5 ml). Methyl 4-(4-hydroxyphenoxy)butanoate (400 mg, 1.9 mmol) was added followed after 10 min stirring at ambient temperature by 2,4-dinitrofluorobenzene (354 mg, 1.9 mmol) in DMF (5 ml). After stirring the mixture for 30 min it was diluted with ether, washed, dried and evaporated. The residue was chromatographed (ethyl acetate–light petroleum) to yield the *title compound* **39** as a yellow crystalline solid (623 mg, 87%), mp 79–81 °C from ether–light petroleum (Found: *m/z*, 376.094. $C_{17}H_{16}N_2O_8$ requires M^+, 376.091); ν_{max}(KBr)/cm^{-1} 1741, 1613, 1533, 1506; δ_H 2.15 (2H, tt, *J* 7.3, 6.1, 3-CH_2), 2.56 (2H, t, *J* 7.3, 2-CH_2), 3.71 (3H, s, OMe), 4.05 (2H, t, *J* 6.1, 4-CH_2), 6.97 and 7.07 (each 2H, d, *J* 8.9, 2′-H, 3′-H, 5′-H, 6′-H), 7.01 (1H, d, *J* 9.1, 6″-H), 8.29 (1H, dd, *J* 9.1, 2.7, 5″-H) and 8.82 (1H, d, *J* 2.7, 3″-H); δ_C 24.4 (CH_2), 30.2 (CH_2), 51.5 (CH_3), 67.1 (CH_2), 116.0 (CH), 117.6 (CH), 121.6 (CH), 121.9 (CH), 128.7 (CH), 138.8 (C), 140.8 (C), 146.4 (C), 156.8 (C), 157.0 (C) and 173.4 (C).

4-[4-(2,4-Dinitrophenoxy)phenoxy]butanoic acid 40

The above ester (616 mg, 1.64 mmol) in acetone (10 ml) and hydrochloric acid (8 ml, 2 M) was refluxed overnight. The cooled reaction mixture was extracted with ether, and the extracts were washed with aq. sodium hydrogen carbonate. Acidification of the washings afforded the *title acid* **40** (398 mg, 67%) as a yellow solid, mp 154–155 °C (Found: *m/z*, 362.076. $C_{16}H_{14}N_2O_8$ requires M^+, 362.075); ν_{max}(KBr)/cm^{-1} 3441, 1722, 1616, 1532; δ_H 2.16 (2H, tt, *J* 7.3, 6.1, 3-CH_2), 2.63 (2H, t, *J* 7.3, 2-CH_2), 4.06 (2H, t, *J* 6.1, 4-CH_2), 6.97 and 7.07 (each 2H, d, *J* 9.2, 2′-H, 3′-H, 5′-H, 6′-H), 6.99 (1H, d, *J* 9.1,

6″-H), 8.29 (1H, dd, *J* 9.1, 2.7, 5″-H) and 8.82 (1H, d, *J* 2.7, 3″-H); δ_C([$^2H_6$]acetone) 25.3 (CH_2), 30.4 (CH_2), 68.1 (CH_2), 117.0 (CH), 119.0 (CH), 122.5 (CH), 122.7 (CH), 129.9 (CH), 140.2 (C), 142.2 (C), 147.9 (C), 157.3 (C), 158.1 (C) and 174.3 (C).

Radical decarboxylation of 4-[4-(2,4-dinitrophenoxy)phenoxy]-butanoic acid

Decarboxylation of the title acid (397 mg, 1.09 mmol) by the method described above but using 2-mercaptopyridine-*N*-oxide sodium salt (200 mg, 1.35 mmol) and DMAP (22 mg) in benzene (200 ml) gave after chromatography; (i) a sample judged from NMR spectral data to be 1-oxaspiro[4.5]deca-6,9-dien-8-one **22** (4 mg, 2.4%); δ_H 2.07–2.13 (4H, m, 3-CH_2, 4-CH_2), 4.08 (2H, t, *J* 6.4, 2-CH_2), 6.13 (2H, d, *J* 10.1, 7-H, 9-H) and 6.81 (2H, d, *J* 10.1, 6-H, 10-H); (ii) 6-(2,4-*dinitrophenoxy*)*chromane* **41** as a brownish oil (46 mg, 13%) (Found: M^+, 316.070. $C_{15}H_{12}N_2O_6$ requires M^+, 316.070); δ_H 1.96 (2H, tt, *J* 6.5, 5.2, 3-CH_2), 2.73 (2H, t, *J* 6.5, 4-CH_2), 4.15 (2H, t, *J* 5.2, 2-CH_2), 6.76–6.78 (3H, m, 5-H, 7-H, 8-H), 6.96 (1H, d, *J* 9.3, 6′-H), 8.21 (1H, dd, *J* 9.3, 2.8, 5′-H) and 8.74 (1H, d, *J* 2.8, 3′-H); δ_C 21.8 (CH_2), 25.0 (CH_2), 66.6 (CH_2), 117.8 (CH), 118.5 (CH), 119.6 (CH), 121.6 (CH), 122.0 (CH), 124.3 (C), 128.7 (CH), 139.0 (C), 140.9 (C), 146.0 (C), 153.3 (C) and 158.1 (C); (iii) di(2-pyridyl) disulfide (53 mg, 44%), identified by comparison with an authentic specimen; (iv) 4-[3-(2-*pyridylsulfanyl*)*propoxy*]-1-(2,4-*dinitrophenoxy*)*benzene* **42** as an amorphous solid (110 mg, 23%) (Found: *m*/*z*, 427.087. $C_{20}H_{17}N_3O_6S$ requires M^+, 427.084); δ_H 2.16 (2H, tt, *J* 6.9, 6.1, 2″-CH_2), 3.31 (2H, t, *J* 6.9, 3″-CH_2), 4.05 (2H, t, *J* 6.1, 1″-CH_2), 6.88–6.93 (2H, m, 6′-H, 5‴-H), 6.90 and 6.98 (each 2H, d, *J* 9.0, 2-H, 3-H, 5-H, 6-H), 7.12 (1H, d, *J* 8.0, 3‴-H), 7.39–7.44 (1H, m, 4‴-H), 8.20 (1H, dd, *J* 9.3, 2.7, 5′-H), 8.34 (1H, d, *J* 4.4, 6‴-H) and 8.74 (1H, d, *J* 2.7, 3′-H); δ_C 26.5 (CH_2), 29.0 (CH_2), 68.8 (CH_2), 116.2 (CH), 117.6 (CH), 119.4 (CH), 121.7 (CH), 122.0 (CH), 122.4 (CH), 128.7 (CH), 136.1 (CH), 139.0 (C), 141.0 (C), 146.6 (C), 149.3 (CH), 156.9 (C), 157.2 (C) and 158.6 (C).

Methyl 4-(2,6-dimethoxy-4-formylphenoxy)butanoate 44

A mixture of syringaldehyde (3 g, 16.5 mmol), potassium carbonate (4.55 g, 33.0 mmol) and methyl 4-bromobutanoate (3.28 g, 18.2 mmol) in dry butanone (100 ml) was refluxed for 48 h under nitrogen. 18-Crown-6 (870 mg, 3.3 mmol) was then added, and reflux was continued for 1 h more. The mixture was then evaporated, and the residue was partitioned between ether and water. The organic phase was washed with aq. sodium hydroxide and brine, dried, and evaporated. The residue was chromatographed (ethyl acetate–light petroleum) to afford the *title ether* **44** as an orange gum (2.75 g, 59%) (Found: *m*/*z*, 282.109. $C_{14}H_{18}O_6$ requires M^+, 282.110); ν_{max}(film)/cm^{-1} 1732, 1693, 1589; δ_H 2.01 (2H, tt, *J* 6.7, 5.8, 3-CH_2), 2.64 (2H, t, *J* 6.7, 2-CH_2), 3.71 (3H, s, CO_2Me), 3.95 (6H, s, 2 × OMe), 4.12 (2H, t, *J* 5.8, 4-CH_2), 7.14 (2H, s, 3′-H, 5′-H) and 9.85 (1H, s, CHO).

Methyl 4-[2,6-dimethoxy-4-(formyloxy)phenoxy]butanoate 45

Methyl 4-(2,6-dimethoxy-4-formylphenoxy)butanoate (2.75 g, 9.74 mmol) and *m*-chloroperbenzoic acid (5.09 g, 29.4 mmol) were dissolved in methylene chloride (50 ml), and the solution was stirred at room temperature for 48 h. Aqueous sodium dithionite was added, and the mixture was stirred vigorously for 30 min. The organic phase was washed, dried and evaporated. The residue was chromatographed to yield the *title ester* **45** as a gum (2.30 g, 79%) (Found: *m*/*z*, 298.108. $C_{14}H_{18}O_7$ requires M^+, 298.105); ν_{max}(film)/cm^{-1} 1732, 1615, 1589; δ_H 2.04 (2H, tt, *J* 7.3, 6.1, 3-CH_2), 2.63 (2H, t, *J* 7.3, 2-CH_2), 3.69 (3H, s, CO_2Me), 3.82 (6H, s, 2 × OMe), 3.98 (2H, t, *J* 6.1, 4-CH_2), 6.36 (2H, s, 3′-H, 5′-H) and 8.29 (1H, s, ArOCHO).

Methyl 4-(2,6-dimethoxy-4-hydroxyphenoxy)butanoate 46

Methyl 4-[2,6-dimethoxy-4-(formyloxy)phenoxy]butanoate (2.30 g, 8.5 mmol) was dissolved in methanol, (50 ml) and diethylamine (1.11 g, 17 mmol) was added. The resulting solution was immediately evaporated and the residue was chromatographed (ethyl acetate–light petroleum) to afford the *title phenol* **46** (1.00 g, 48%) (Found: C, 57.77; H, 6.71%; *m*/*z*, 270.111. $C_{13}H_{18}O_6$ requires C, 57.64; H, 6.86%; M^+, 270.110); ν_{max}(film)/cm^{-1} 3316, 1731, 1599; δ_H 2.01 (2H, tt, *J* 7.4, 6.1, 3-CH_2), 2.62 (2H, t, *J* 7.4, 2-CH_2), 3.69 (3H, s, CO_2Me), 3.73 (6H, s, 2 × OMe), 3.92 (2H, t, *J* 6.1, 4-CH_2), 5.80 (1H, br s, OH) and 6.06 (2H, s, 3′-H, 5′-H).

Methyl 4-[2,6-dimethoxy-4-(2,4-dinitrophenoxy)phenoxy]-butanoate 47

Sodium hydride (60% dispersion in oil, 52 mg, 1.29 mmol) was washed with light petroleum and then suspended in DMF (5 ml). Methyl 4-(2,6-dimethoxy-4-hydroxyphenoxy)butanoate (316 mg, 1.17 mmol) was added and the mixture was stirred under nitrogen for 10 min, when 2,4-dinitrofluorobenzene (218 mg, 1.17 mmol) in DMF (1 ml) was added. The reaction mixture was stirred for 1 h more, then diluted with ether, washed, dried and evaporated. The residue was chromatographed (ethyl acetate–light petroleum) to give the *title aryl ether* **47** as a viscous yellow oil (417 mg, 88%) [Found: *m*/*z*, 437. $C_{19}H_{20}N_2O_{10}$ requires $(M + H)^+$, 437]; ν_{max}(film)/cm^{-1} 1734, 1608, 1537, 1500; δ_H 2.01 (2H, tt, *J* 7.3, 6.1, 3-CH_2), 2.60 (2H, t, *J* 7.3, 2-CH_2), 3.66 (3H, s, CO_2Me), 3.78 (6H, s, 2 × OMe), 3.98 (2H, t, *J* 6.1, 4-CH_2), 6.36 (2H, s, 3′-H, 5′-H), 7.06 (1H, d, *J* 9.3, 6″-H), 8.30 (1H, dd, *J* 9.3, 2.7, 5″-H) and 8.77 (1H, d, *J* 2.7, 3″-H); δ_C 25.0 (CH_2), 30.0 (CH_2), 51.2 (CH_3), 55.9 (CH_3), 72.0 (CH_2), 97.8 (CH), 117.9 (CH), 121.7 (CH), 128.7 (CH), 134.9 (C), 138.6 (C), 140.8 (C), 148.9 (C), 154.3 (C), 156.2 (C) and 173.7 (C).

4-[2,6-Dimethoxy-4-(2,4-dinitrophenoxy)phenoxy]butanoic acid 48

A solution of methyl 4-[2,6-dimethoxy-4-(2,4-dinitrophenoxy)phenoxy]butanoate (410 mg, 0.94 mmol) in acetone (5 ml) and dil. hydrochloric acid (2 M, 5 ml) was refluxed overnight. The cooled mixture was extracted with ether, and the combined organic phases were extracted with aq. sodium hydrogen carbonate. Acidification liberated the free acid which was collected in ether. The ether solution was washed with water, dried, and evaporated to yield the *title acid* **48** as a yellow crystalline solid (275 mg, 69%), mp 166–167 °C [Found: C, 51.05; H, 4.23; N, 6.51%; *m*/*z*, 336.058. $C_{18}H_{18}N_2O_{10}$ requires C, 51.17; H, 4.30; N, 6.64%; $(M - PrCO_2)^+$, 336.059]; ν_{max}(KBr)/cm^{-1} 3429, 1703, 1610, 1584, 1538, 1501; δ_H 2.06 (2H, tt, *J* 7.2, 5.9, 3-CH_2), 2.72 (2H, t, *J* 7.2, 2-CH_2), 3.81 (6H, s, 2 × OMe), 4.03 (2H, t, *J* 5.9, 4-CH_2), 6.38 (2H, s, 3′-H, 5′-H), 7.08 (1H, d, *J* 9.3, 6″-H), 8.33 (1H, dd, *J* 9.3, 2.7, 5″-H) and 8.83 (1H, d, *J* 2.7, 3″-H); δ_C 25.0 (CH_2), 30.3 (CH_2), 56.2 (CH_3), 72.1 (CH_2), 98.1 (CH), 118.0 (CH), 122.1 (CH), 128.9 (CH), 134.9 (C), 138.6 (C), 140.8 (C), 149.3 (C), 154.6 (C), 156.4 (C) and 179.4 (C).

Radical decarboxylation of 4-[2,6-dimethoxy-4-(2,4-dinitrophenoxy)phenoxy]butanoic acid

4-[2,6-Dimethoxy-4-(2,4-dinitrophenoxy)phenoxy]butanoic acid (246 mg, 0.58 mmol) was stirred under nitrogen with oxalyl chloride (0.25 ml) and dry DMF (0.05 ml) in methylene chloride (5 ml) for 2 h. After evaporation the residue was dissolved in benzene (5 ml), and the solution was evaporated. The crude acid chloride in benzene (5 ml) was added to a dried (Dean and Stark) refluxing suspension of 2-mercaptopyridine-*N*-oxide sodium salt (104 mg, 0.70 mmol) and DMAP (12 mg) in benzene (90 ml), in foil-covered apparatus to exclude light. After 30 min the foil was removed and the bright yellow mixture was irradiated with a 200 W tungsten lamp. Reflux was maintained for 1 h when the mixture was cooled, washed, dried, and evaporated. The residue was chromatographed (light petroleum–ethyl acetate) to yield; (i) 6,10-*dimethoxy*-1-*oxaspiro*[4.5]*deca*-6,9-

dien-8-*one* **49** as an amorphous solid (60 mg, 49%) (Found: *m*/*z*, 210.090. $C_{11}H_{14}O_4$ requires M^+, 210.089); ν_{max}(film)/cm^{-1} 1657, 1596, 1532, 1499; δ_H 2.17–2.26 (4H, m, 3-CH_2, 4-CH_2), 3.75 (6H, s, 2 × OMe), 4.17 (2H, t, *J* 6.3, 2-CH_2) and 5.40 (2H, s, 7-H, 9-H); δ_C 27.6 (CH_2), 36.1 (CH_2), 56.0 (CH_3), 72.1 (CH_2), 79.6 (C), 99.7 (CH), 173.0 (C) and 187.5 (C); (ii) 4-[3-(2-*pyridylsulfanyl*)*propoxy*]-1-(2,4-*dinitrophenoxy*)-3,5-*dimethoxybenzene* **50** as a brownish amorphous solid (16 mg, 5.6%) [Found: *m*/*z*, 488.108. $C_{22}H_{21}O_8N_3S$ requires $(M + H)^+$, 488.112]; δ_H 2.17 (2H, dd, *J* 6.9, 5.9, 2″-CH_2), 3.49 (2H, d, *J* 6.9, 3″-CH_2), 3.82 (6H, s, 2 × OMe), 4.14 (2H, d, *J* 5.9, 1″-CH_2), 6.38 (2H, s, 2-H, 6-H), 7.02–7.06 (1H, m, 5‴-H), 7.09 (1H, d, *J* 9.3, 6′-H), 7.25 (1H, d, *J* 8.0, 3‴-H), 7.53–7.58 (1H, m, 4‴-H), 8.34 (1H, dd, *J* 9.3, 2.7, 5′-H), 8.46 (1H, d, *J* 4.7, 6‴-H) and 8.85 (1H, d, *J* 3.7, 3′-H).

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