Studies of a novel biomimetic radical spirocyclisation

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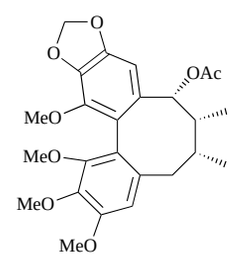
1 PERKIN

The mechanism of the radical spirocyclisation 7→9 has been investigated. It has been shown by isotopic labelling that the biaryl ether oxygen does not emerge as the carbonyl group oxygen in the product, nor does the latter arise by hydrolysis of an intermediate *e.g.* 33 by added water. The mechanism of Scheme 1 path *a* is proposed, involving oxygen transfer from an aromatic nitro group to carbon in a cyclohexadienyl radical. Radical decarboxylation of the biarylamine derivative 29 does not lead to spirodienone 9 but diverts instead to the azathiaacetal 30.

The lignans are a diverse group of natural products, almost entirely of plant origin, which comprise a number of well defined subgroups including the dibenzocyclooctadienes, *e.g.* (−)-kadsurin **1**.[1] In a previous paper[2] we drew attention to the novel structural features of a number of these *o*,*o*-bridged biaryls, exemplified by interiorin A **2**[3] and kadsulignan C **3**.[4] These compounds contain a spirodienone subunit with a dihydrofuran ring plausibly derived from a phenolic *O*-methyl group. In that paper we presented a biosynthetic hypothesis based on oxidation of a precursor **4** by a cytochrome P_{450} to an aryloxymethyl radical **5** which undergoes spirocyclisation to the relatively stable cyclohexadienyl radical **6** before further oxidation to the *p*- or *o*-cyclohexadienone systems observed in the metabolites **2** and **3** respectively.



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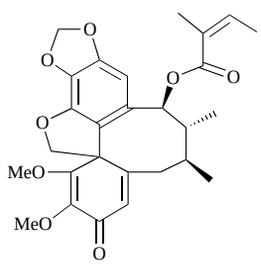

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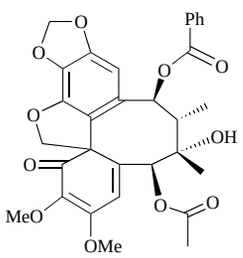

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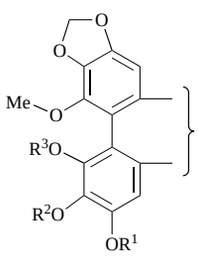

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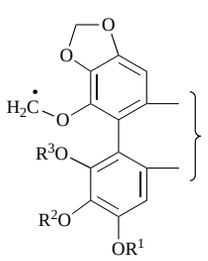

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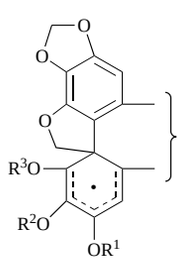

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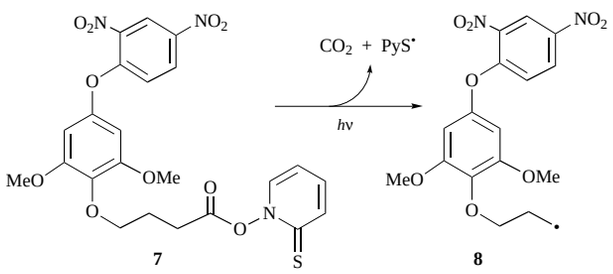
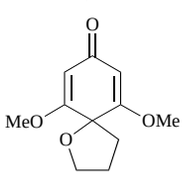
In support of this suggestion we presented[2] a chemical model for radical spirocyclisation, in which the thiohydroxamate ester **7** was heated under reflux in benzene with irradiation from a tungsten lamp, to induce homolytic fragmentation to the methylene radical **8**, followed by further reactions to yield eventually the heterocyclic spirodienone **9** (49%). Since no oxidising reagents are present an intramolecular redox process is implied.



7 **8**



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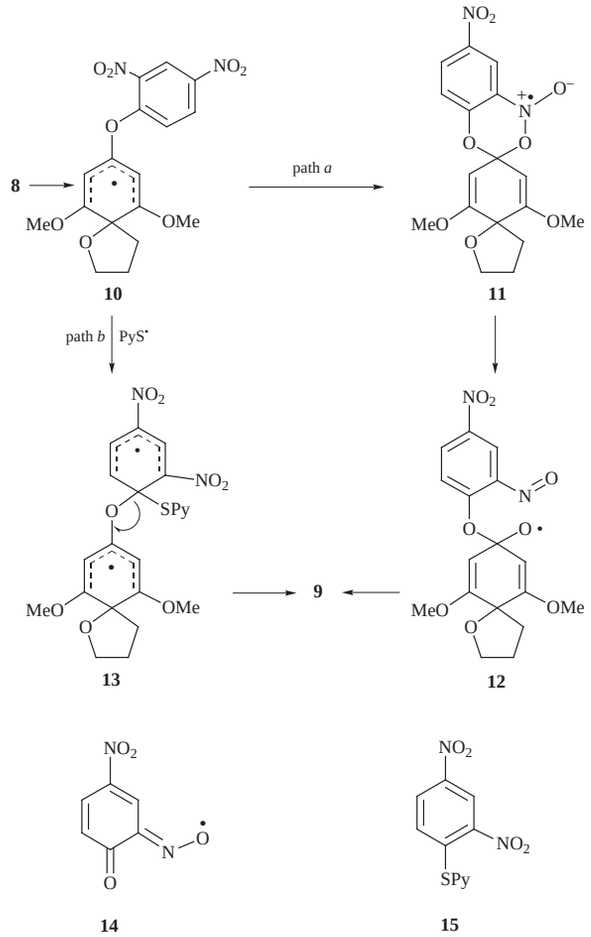
In devising this reaction sequence we conceived that oxygen transfer from a nitro group to a carbon radical centre would be involved. However more than one mechanistic pathway might be followed, and we thought it necessary to investigate the possible routes before we embarked upon further synthetic developments. In this paper we present evidence supporting the role of a nitro group as oxidant, and include some observations on the scope of the process. A preliminary account of this work has appeared.[5]

Our initial views on the mechanism centred on the two mechanisms which appeared most likely. These are shown in Scheme 1. Initial N–O homolysis and decarboxylation[6] must afford the primary radical **8**, which can cyclise to the spirocyclohexadienyl radical **10**. Trapping (6-*endo*-*trig*) of the carbon radical by oxygen of the *ortho*-nitro group (path *a*) would lead to the nitrogen centred radical **11** which is set up to undergo N–O α-scission followed by fragmentation of the intermediate oxygen radical **12**, providing the product spirodienone **9** and the relatively stable radical **14**. In other work a similar iminoxyl radical has been studied by ESR.[7] Alternatively (path *b*) the intermediate species **10** could react with a pyridine thiyl radical, still within a solvent cage, to form the diradical **13** which could undergo fast α-cleavage to form the observed dienone **9** and 2,4-dinitro-

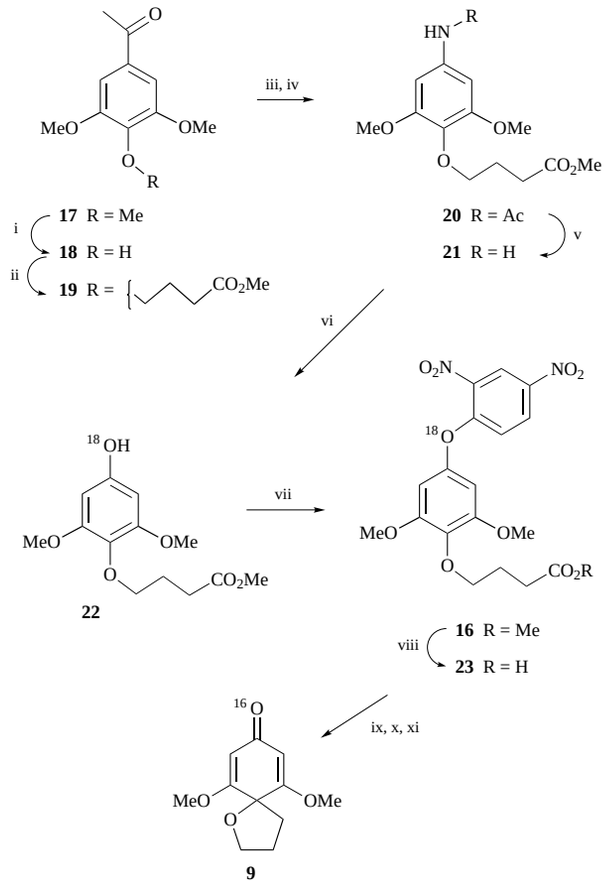


Scheme 1

1-(pyridine-2-thio)benzene **15**. Examination of the reaction products suggested that path *b* was not operating, since we could establish, with the aid of an authentic sample, that the free aryl thioether **15** was not present among the products. However apart from the dienone **9** and a minor by-product (*ca.* 5%)[2] we could find no other identifiable material, the mass balance being made up with dark polymeric material of low solubility whose ^{13}C NMR indicated aromatic and nitro-aromatic carbons and which offered no clues to the mechanism.

Thus we felt it necessary to seek a clear distinction between these two pathways, or variants of them, which would provide direct evidence that the carbonyl oxygen of the final product **9** did not derive from the ether oxygen of the biaryl ether **7** (and originally from a phenolic oxygen) but from the *ortho*-nitro group. To this end we synthesised the ^{18}O-labelled biaryl ether **16** as shown in Scheme 2.

3,4,5-Trimethoxyacetophenone **17** was reacted with aluminium chloride to form the *p*-demethylated ketone **18** (60%), which was then *O*-alkylated with methyl 4-bromobutanoate to afford the ester **19** (60%). The corresponding oxime was then generated and rearranged under standard Beckmann conditions to give the amide **20** (45%). Selective amide cleavage was effected with dry acidic methanol to produce the amine **21** (85%), which was then diazotized using 10% ^{18}O-water, forming the ^{18}O-labelled phenol **22** (50%) with incorporation of the label clearly shown by mass spectrometry. Formation of the biaryl ether **16** (44%) was effected using Sanger's reagent, and the ester was hydrolysed to the acid **23** (50%) in aq. hydrochloric acid. The acid **23** was then converted into the corresponding thiohydroxamate ester which was irradiated *in situ* in refluxing benzene with a 200 W tungsten lamp, to yield the spirodienone **9**. The MS of this sample of spirodienone **9** showed complete loss of ^{18}O label, within experimental limits. Thus we conclude that the carbonyl oxygen of spirodienone **9** is not derived from

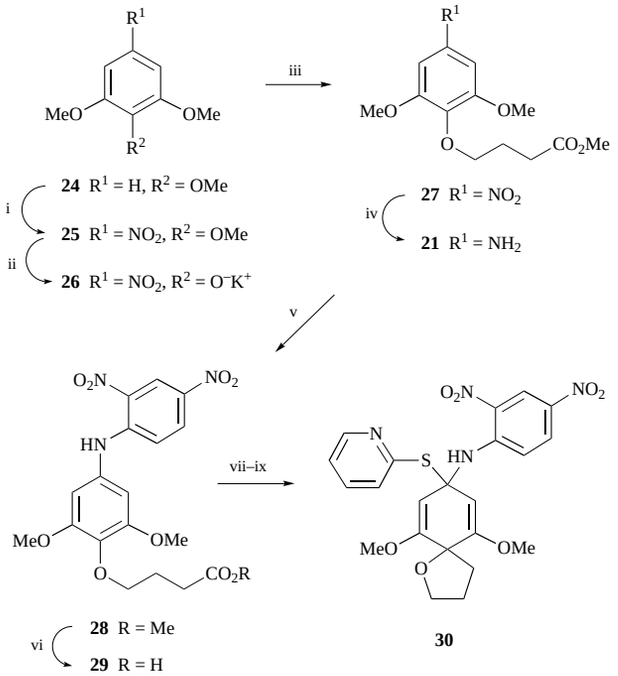


Scheme 2 *Reagents:* i, $AlCl_3$, benzene, reflux; ii, methyl 4-bromobutanoate, K_2CO_3, 18-crown-6, butanone, reflux; iii, $NH_2OH{\cdot}HCl$, EtOH; iv, $SOCl_2$, Et_2O, room temp.; v, MeOH, H_2SO_4; vi, $NaNO_2$, $H_2{}^{18}O$, H_2SO_4; vii, NaH, DMF, 2,4-dinitrofluorobenzene, room temp.; viii, aq. HCl, Me_2CO; ix, $(COCl)_2$, benzene; x, 2-mercaptopyridine *N*-oxide Na salt, benzene; xi, *hv*, benzene, reflux

the biaryl ether oxygen, and that path *b*, Scheme 1, is untenable.

This result suggested that it might be possible to extend the synthetic scope of this radical spirocyclisation by replacing the biaryl ether oxygen with a different linking atom, *e.g.* nitrogen. To test this possibility we undertook the synthesis of the biarylamine analogue of acid **23**, by the route shown in Scheme 3. 5-Nitro-1,2,3-trimethoxybenzene **25**, from mild nitration of pyrogallol trimethyl ether, was heated at reflux in concentrated aq. potassium hydroxide to form the potassium salt **26** (50%). *O*-Alkylation with methyl 4-bromobutanoate then formed the ester **27** (68%), and then the nitro group was smoothly reduced by catalytic hydrogenation, yielding the amine **21** (64%) by a more expeditious route than that in Scheme 2. Reaction of this amine with Sanger's reagent gave the dinitrobiarylamine **28** (80%), and the sequence was completed by ester hydrolysis to afford the acid **29** (65%).

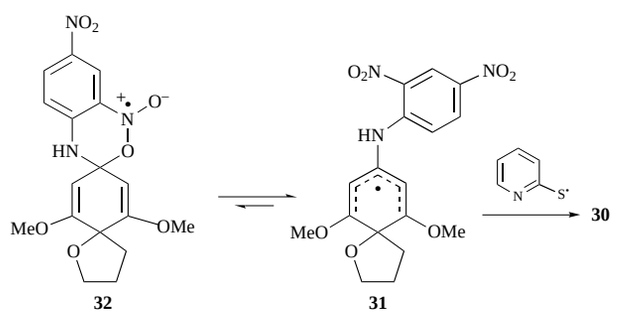
The acid **29** was then transformed into the corresponding thiohydroxamate and this product was subjected to the conditions for radical decarboxylation, as in the above example. No sign of the spirodienone **9** was observed by NMR, IR, or TLC in the total crude reaction product. Instead chromatography afforded a new product (72%), with molecular formula $C_{22}H_{22}N_4O_7S$ (by FAB MS) to which was assigned the azathioketal structure **30**. The subunits of **30** were readily recognised from their NMR spectral patterns, as observed in other compounds in this series. No evidence for the presence of two diastereomers was seen in the NMR spectra. Although diastereomers are likely to be present they are geometrically very similar, and the tetrahydrofuran ring is inflexibly isolated from the aryl rings, so that it is not surprising that the NMR



Scheme 3 *Reagents:* i, HNO_3, AcOH, 0 °C; ii, aq. KOH, reflux; iii, methyl 4-bromobutanoate, 18-crown-6, butanone, reflux; iv, H_2, Pd/C; v, 2,4-dinitrofluorobenzene, K_2CO_3, MeCN; vi, aq. MeOH, K_2CO_3; vii, $(COCl)_2$, benzene; viii, 2-mercaptopyridine *N*-oxide Na salt, benzene; ix, *hν*, benzene, reflux

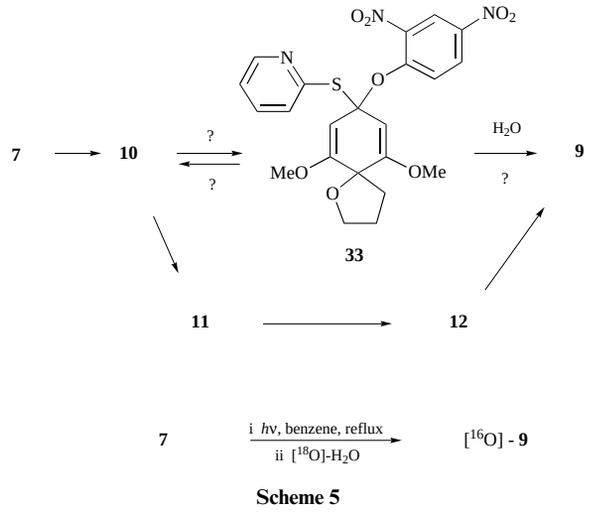
differences were not detectable in the spectra (^{1}H at 250 MHz, ^{13}C at 100.6 MHz).

The mechanism of formation of the unexpected product is rationalised in Scheme 4, and implicates a cyclohexadienyl



Scheme 4

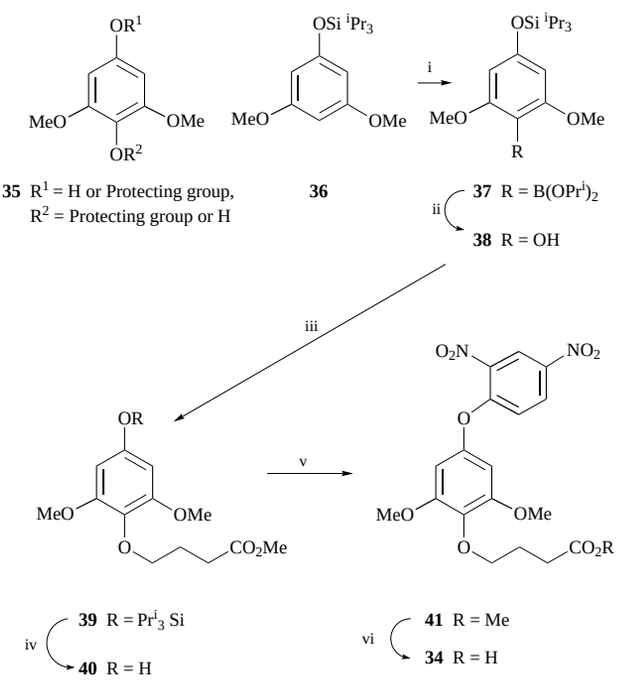
radical **31** (analogous to intermediate **10**, Scheme 1). This nitrogen stabilised radical is presumed to be now more stable[8] than both the oxygen stabilised radical **10** and the cyclized product **32**, and predominates in any equilibrium with **32**, eventually being quenched by the pyridine thiyl radical to form **30**. This result provoked the idea that the analogue **33**, Scheme 5, of the ketal **30** might in fact be the initial product from the radical decarboxylation of thiohydroxamate **7**, and that the spirodienone **9** is formed only after hydrolysis of ketal **33** by water in the product isolation. This possibility was eliminated by repeating the preparation of spirodienone **9** but using 10% [^{18}O]-water for the work-up (Scheme 5), when no incorporation of [^{18}O] into the product was observed (MS). In fact direct evaporation of the reaction mixture before work up gave only a mixture of dipyridyl disulfide, spirodienone **9**, and a black polymer of low solubility the NMR of which showed only aromatic carbons. Thus we consider that the **7**→**10**→**11**→**12**→**9** route remains the most likely pathway for the spirodienone formation, on the present information. Direct evidence of oxygen transfer from the nitro group to the carbon radical centre remains desirable, in our view, but requires the



Scheme 5

development of suitable methodology for the synthesis of [^{18}O]-labelled arylnitro groups.

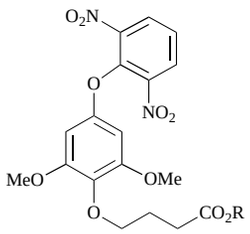
In order to carry out the experiments in Scheme 5 we required a further supply of the carboxylic acid precursor **34** of the thiohydroxamate **7**. The key for access to compounds of this type is a convenient method of preparation of selectively *O*-protected 2,6-dimethoxyquinols **35**. In our first route[2] we employed Baeyer–Villiger oxidation of a derivative of syringaldehyde to generate such a compound. However this reaction proved difficult to reproduce satisfactorily, and yields were variable, so a more reliable sequence was sought. Several alternative routes were investigated and the most expeditious of these is shown in Scheme 6. 3,5-Dimethoxy-1-triisopropylsilyloxy-



Scheme 6 *Reagents:* i, *n*-BuLi, THF, $(Pr^iO)_3B$, room temp; ii, aq. NaOH, H_2O_2; iii, methyl 4-bromobutanoate, KI, K_2CO_3, 18-crown-6, MeCN, reflux; iv, TBAF, THF; v, see ref. 2; vi, see ref. 2

benzene **36** could be selectively deprotonated with *n*-butyllithium, and the resulting anion trapped with triisopropyl borate. The arylboronic ester **37** was then oxidised to the quinol **38** with alkaline peroxide (52% yield from **36**). Insertion of the butanoate residue to form **39** (77%), and desilylation (60%) gave the phenol **40**, linking with our previous work,[2] and this product was taken forward to the desired ester **41** and acid **34** as before.[2]

We used these approaches to explore the consequences of some variations in reactant structure on the radical spirocyclisation. Thus acid **42**; R = H was prepared, containing the 2,6-



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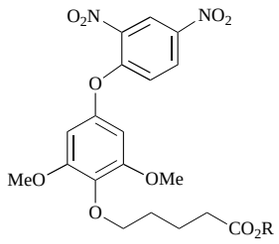

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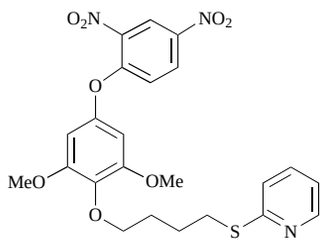

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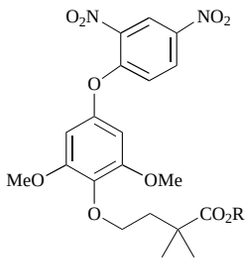

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dinitrophenyl oxygen donor. This compound also afforded the spirodienone **9** but in no greater yield than with the 2,4-dinitrophenyl substituent. The acid **43**; R = H with an extra methylene in the acid side chain underwent radical decarboxylation without spirocyclisation, to our disappointment; the major product appeared to be the thioether **44** although it was not fully purified. The branched chain acid **45**; R = H was also prepared and decarboxylated, but gave only a complex mixture containing no detectable quantity of a spirodienone.

We consider that evidence adduced above points to the conclusion that the carbonyl oxygen in the bicyclospirodienone **9** is derived from the *ortho*-nitro group, as in Scheme 1 path *a*. Limited precedent for nitro-group oxidation of carbon radicals was found in the literature. Thus aromatic nitro groups were postulated by Jackson and Waters[9] to be oxygen donors in the oxidation of benzyl radicals to benzaldehyde, although the nitroso intermediates were not isolated. Hey, Perkins and coworkers[10] explained the role of added nitrobenzene on homolytic aromatic phenylation in terms of reduction of nitrobenzene to nitrosobenzene by phenylcyclohexadienyl radicals; the relatively stable diphenylnitroxide was then formed, the concentration of which determined the product ratios. Gill and Williams[11] also proposed the formation of a nitro group oxygen–cyclohexadienyl radical carbon bond in the intermediate they put forward in their interpretation of the catalytic role of nitrobenzene in the thermal decomposition of benzoyl peroxide in benzene. Given that the mechanism in Scheme 1 path *a* is correct, it should now be possible to invent new intramolecular reactions which will take advantage of this process.

Experimental

For experimental generalisations, see ref. 2.

Methyl 4-(4-acetyl-2,6-dimethoxyphenoxy)butanoate 19
4-Hydroxy-3,5-dimethoxyacetophenone[12] (3.0 g, 15.3 mmol), potassium carbonate (4.23 g, 30.6 mmol) and methyl 4-bromobutanoate (3.05 g, 15.9 mmol) were heated at reflux in dry butanone (100 ml) for 48 h under nitrogen. 18-Crown-6 (808 mg, 3.0 mmol) was then added and reflux was continued for 1 h more. The cooled mixture was evaporated and the residue was partitioned between ether and water. The organic phase was washed with aq. sodium hydroxide (2 M) and brine, dried and evaporated. The residue crystallised on standing to yield the *title ester* **19** (2.70 g, 60%), mp 52–52 °C (Found: *m*/*z* 296.128. $C_{15}H_{22}O_6$ requires M^+ 296.129); ν_{max}film/cm^{-1} 1725, 1674 and 1585; δ_H 2.05 (2H, tt, *J* 6.1, 7.2, 3-CH_2), 2.58 (3H, s, COMe), 2.60 (2H, t, *J* 7.2, 2-CH_2), 3.68 (3H, s, CO_2Me), 3.89 (6H, s, ArOMe), 4.08 (2H, t, *J* 6.1, 4-CH_2), 7.26 (2H, s, ArH); on treatment with hydroxylamine hydrochloride and sodium acetate in aq. ethanol under standard conditions this ketone formed the corresponding *oxime*, mp 81–83 °C (Found: C, 57.78; H, 7.23; H, 4.56%; *m*/*z* 311.134. $C_{15}H_{21}NO_6$ requires C, 57.85; H, 6.80; N, 4.50%; M^+ 311.135); δ_H 2.04 (2H, tt, *J* 6.1, 7.4, 3-CH_2), 2.27 (3H, s, Me), 2.63 (2H, t, *J* 7.4, 2-CH_2), 3.68 (3H, s, CO_2Me), 3.90 (6H, s, ArOMe), 4.02 (2H, t, *J* 6.1, 4-CH_2), 6.83 (2H, s, ArH).

Methyl 4-(4-acetylamino-2,6-dimethoxyphenoxy)butanoate 20
Thionyl chloride (2.4 ml) in ether (40 ml) was gradually added to a solution of the above oxime (2.40 g, 7.7 mmol) in ether (40 ml) and the mixture was stirred under nitrogen for 1 h. Water (80 ml) was added to the reaction mixture which was then stirred vigorously for 1.5 h. The organic phase was separated, and the aqueous layer was extracted with dichloromethane. The combined organic phases were washed, dried and evaporated to yield the *amide* **20** as a red–brown gum (1.81 g, 75%) (Found: C, 57.73; H, 6.72%; *m*/*z* 311.137. $C_{15}H_{21}NO_6$ requires C, 57.87; H, 6.78%; M^+ 311.137); ν_{max}film/cm^{-1} 1731, 1674, 1610 and 1602; δ_H 1.91 (2H, tt, *J* 6.1, 7.2, 3-CH_2), 2.13 (3H, s, NHCOMe), 2.51 (2H, t, 7.2, 2-CH_2), 3.58 (3H, s, CO_2Me), 3.63 (6H, s, ArOMe), 3.85 (2H, t, *J* 6.1, 4-CH_2), 6.78 (2H, s, ArH) and 8.67 (1H, s, NH).

Methyl 4-(4-amino-2,6-dimethoxyphenoxy)butanoate 21
The amide **20** (1.81 g, 5.81 mmol), methanol (45 ml) and sulfuric acid (3.6 ml) were heated together at reflux for 48 h. The cooled reaction mixture was neutralised (aq. sodium hydroxide), diluted with water, and extracted with dichloromethane. The extracts were washed, dried and evaporated to give the *amine* **21** as a brown crystalline solid (1.22 g, 78%), mp 77–79 °C (Found: *m*/*z* 296.126. $C_{13}H_{19}NO_5$ requires M^+ 296.126); ν_{max}KBr/cm^{-1} 3381 and 1740; δ_H 2.00 (2H, tt, *J* 6.1, 7.4, 3-CH_2), 2.61 (2H, t, *J* 7.4, 2-CH_2), 3.67 (3H, s, CO_2Me), 3.78 (6H, s, ArOMe), 3.89 (2H, t, *J* 6.1, 4-CH_2), 5.91 (2H, s, ArH); δ_C 25.3 (CH_2), 30.5 (CH_2), 51.3 (CH_3), 55.7 (CH_3), 72.5 (CH_2), 92.7 (CH), 129.6 (C), 142.8 (C), 153.9 (C) and 174.2(C).

Methyl 4-(2,6-dimethoxy-4-[^{18}O]hydroxyphenoxy)butanoate 22
Sodium nitrite (0.21 g, 3.04 mmol) in [^{18}O]-labelled water (1.5 ml; 10 atom%) was added dropwise to a solution of methyl 4-(4-amino-2,6-dimethoxyphenoxy)butanoate (0.82 g, 3.04 mmol) in [^{18}O]-labelled water (3.5 ml; 10 atom%) and sulfuric acid (0.41 ml), maintaining the temperature between 0–5 °C. The reaction mixture was stirred at this temperature for 1 h, when sulfuric acid (0.8 ml) was added and the mixture was heated to reflux for 5 min. The cooled solution was diluted with water and extracted with ether. The extracts were washed, dried and evaporated to yield an acid residue which was treated with ethereal diazomethane to provide the *title ester* **22** as a gum (0.39 g, 50%) (Found: *m*/*z* 272. $C_{13}H_{18}{}^{18}O^{16}O_5$ requires M^+ 272), with NMR and IR spectra closely similar to those of an unlabelled specimen.[2]

Methyl [2,6-dimethoxy-4-(2,4-dinitro[^{18}O]phenoxy)phenoxy]-butanoate 16
Sodium hydride (60% in mineral oil, 52 mg, 1.29 mmol) was washed with light petroleum and suspended in DMF (10 ml). Methyl 4-(2,6-dimethoxy-4-[^{18}O]hydroxyphenoxy)butanoate (320 mg, 1.18 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 introduced. The reaction

mixture was stirred for 3 h when it was diluted with ether, washed, dried and concentrated. The residue was chromatographed (light petroleum–ethyl acetate, 2:1) to give the *title aryl ether* **16** as a yellow solid (227 mg, 44%) (Found: *m/z* 438. $C_{19}H_{20}N_2{}^{18}O^{16}O_9$ requires M^+ 438), with NMR spectra closely similar to those of an unlabelled sample.[2]

4-[2,6-Dimethoxy-4-(2,4-dinitro[^{18}O]phenoxy)phenoxy]butanoic acid 23

A solution of the above ester **16** (227 mg, 0.67 mmol) in acetone (5 ml) and hydrochloric acid (2 M, 5 ml) was heated at reflux for 8 h. The cooled reaction mixture was extracted with ether; the combined ether extracts were then extracted with sat. aq. sodium hydrogen carbonate. The alkaline aqueous extracts were acidified to liberate the organic acid which was collected in ether. Drying and evaporation of the ethereal solution afforded the *title acid* **23** as a yellow solid (105 mg, 50%), mp 167–168 °C (Found: *m/z* 338. $C_{18}H_{18}N_2{}^{18}O^{16}O_9$ requires $M - C_4H_6O_2{}^+$ 338), with NMR spectra closely similar to those of an unlabelled sample.[2]

Radical decarboxylation of 4-[2,6-dimethoxy-4-(2,4-dinitro[^{18}O]-phenoxy)phenoxy]butanoic acid 23

The title acid (100 mg, 0.23 mmol) was stirred under nitrogen with oxalyl chloride (100 mg, 0.23 mmol) and DMF (0.05 ml) in dichloromethane (5 ml) for 2 h. The solution was evaporated, the residue redissolved in benzene (5 ml) and evaporated again. The residue was added to a dried (Dean and Stark) suspension of 2-mercaptopyridine *N*-oxide sodium salt (42 mg, 0.28 mmol) and DMAP (8 mg) in benzene (80 ml) and the mixture was heated at reflux for 30.5 h in the dark. At this point the reaction mixture was irradiated with a 200 W tungsten lamp, and reflux was continued, for 1 h. The cooled mixture was washed, dried and evaporated, and the residue was chromatographed (light petroleum–ethyl acetate, 1:5) to yield 6,10-dimethoxy-1-oxospiro[4,5]deca-6,9-dien-8-one **9** (16 mg, 40%) as a colourless, amorphous solid (Found: *m/z* 210. $C_{11}H_{14}{}^{16}O_4$ requires M^+ 210), with IR and NMR spectra closely similar to those of an authentic sample.[2] No ^{18}O could be detected by mass spectrometry.

Potassium 2,6-dimethoxy-4-nitrophenoxide 26

A mixture of 5-nitro-1,2,3-trimethoxybenzene[13] (1.00 g, 4.69 mmol) and potassium hydroxide (1.00 g, 25 mmol) in water (30 ml) was heated at reflux for 48 h. The solution crystallised on cooling. The product was filtered off, washed with ethanol and chloroform, and dried to yield the *title salt* **26** as red plates (0.55 g, 50%) (Found: *m/z* 237.005. $C_8H_8NO_5K$ requires M^+ 237.003); δ_H 3.67 (6H, s, ArOMe), 8.27 (2H, ArH); δ_C 55.4 (CH_3), 103.7 (CH), 124.0 (C), 149.0 (C) and 165.5 (C).

Methyl 4-(2,6-dimethoxy-4-nitrophenoxy)butanoate 27

A solution of the potassium salt **26** (1.00 g, 4.21 mmol), methyl 4-bromobutanoate (0.84 g, 4.6 mmol) and 18-crown-6 (222 mg) in butanone (30 ml) was heated at reflux for 48 h after which it was concentrated by evaporation. The residue was diluted with water and extracted with ether. The organic extracts were washed with aq. sodium hydroxide and brine, dried and evaporated. The residue was chromatographed (light petroleum–ethyl acetate 3:1) to afford the *title ester* **27** as a yellow amorphous solid (0.72 g, 68%) (Found: C, 52.12; H, 5.74%; *m/z* 299.100. $C_{13}H_{17}NO_7$ requires C, 52.17; H, 5.73%; M^+ 299.100); δ_H 2.06 (2H, tt, *J* 5.9, 7.6, 3-CH_2), 2.62 (2H, t, *J* 7.6, 2-CH_2), 3.69 (3H, s, CO_2Me), 3.92 (6H, s, ArOMe), 4.11 (2H, t, *J* 5.9, 4-CH_2), 7.51 (2H, s, ArH); δ_H 25.3 (CH_2), 30.1 (CH_2), 51.5 (CH_3), 56.3 (CH_3), 72.1 (CH_2), 101.1 (CH), 143.2 (C), 143.9 (C), 153.0 (C) and 173.8 (C).

Methyl 4-[2,6-dimethoxy-4-(2,4-dinitrophenylamino)phenoxy]-butanoate 28

Methyl 4-(2,6-dimethoxy-4-nitrophenoxy)butanoate (1.25 g, 4.18 mmol) in methanol (30 ml) was hydrogenated at ambient temperature and pressure over 10% palladium-on-carbon catalyst (10 mg), until hydrogen uptake ceased. The reaction mixture was filtered and evaporated to give methyl 4-(4-amino-2,6-dimethoxyphenoxy)butanoate **21** as a brown crystalline solid (0.79 g, 64%), mp 73–74 °C, spectroscopically indistinguishable from the sample described above. This amine (0.48 g, 1.78 mmol), 2,4-dinitrofluorobenzene (0.33 g, 1.78 mmol) and potassium carbonate (0.49 g, 3.5 mmol) were stirred together in acetonitrile (30 ml) for 24 h. The reaction mixture was diluted with ether, washed, dried and evaporated. The residue was chromatographed (light petroleum–ethyl acetate, 3:1) to afford the *title diarylamine* **28** as an orange amorphous solid (0.62 g, 80%) (Found: *m/z* 435.128. $C_{19}H_{21}N_3O_9$ requires M^+ 435.127); ν_{max}KBr/cm^{-1} 3327 and 1731; δ_H 1.99 (2H, tt, *J* 6.2, 7.1, 3-CH_2), 2.57 (2H, t, 7.1, 2-CH_2), 3.63 (3H, s, CO_2Me), 3.76 (6H, s, ArOMe), 3.97 (2H, t, *J* 6.2, 4-CH_2), 6.43 (2H, s, 3′-H, 5′-H), 7.07 (1H, d, *J* 9.5, 6″-H), 8.10 (1H, dd, *J* 2.6, 9.5, 5″-H), 9.09 (1H, d, *J* 2.6, 3″-H), 9.79 (1H, br s, NH); δ_C 25.4 (CH_2), 30.4 (CH_2), 51.6 (CH_3), 55.9 (CH_3), 72.4 (CH_2), 103.3 (CH), 116.4 (CH), 124.0 (CH), 129.9 (CH), 131.1 (C), 132.2 (C), 137.2 (C), 137.3 (C), 147.5 (C), 154.6 (C) and 175.3 (C).

4-[2,6-Dimethoxy-4-(2,4-dinitrophenylamino)phenoxy]butanoic acid 29

A solution of the above ester **28** (100 mg, 0.22 mmol) and potassium carbonate (353 mg, 0.25 mmol) in methanol (10 ml) and water (5 ml) was heated to reflux for 48 h. The cooled solution was extracted with ether, and the bulked organic phases were then extracted with aq. sodium hydrogen carbonate. Acidification of the aq. alkaline extracts afforded the crude acid which was collected in ether. The ether solution was washed, dried and evaporated to give the *title acid* **29** as an orange–red crystalline solid (65 mg, 65%), mp 135–136 °C (Found: C, 51.36; H, 4.13%; *m/z* 421.112. $C_{18}H_{19}N_3O_6$ requires C, 51.29; H, 4.13%; M^+ 421.112); δ_H 2.07 (2H, tt, *J* 6.1, 7.2, 3-CH_2), 2.72 (2H, t, 7.2, 2-CH_2), 3.48 (6H, s, ArOMe), 4.06 (2H, t, *J* 6.1, 4-CH_2), 6.51 (2H, s, 3′-H, 5′-H), 7.14 (1H, d, *J* 9.2, 6″-H), 8.15 (1H, dd, *J* 2.2, 9.2, 5″-H), 9.14 (1H, d, *J* 2.2, 3″-H).

Radical decarboxylation of 4-[2,6-dimethoxy-4-(2,4-dinitro-phenylamino)phenoxy]butanoic acid 29

The title acid (100 mg, 0.28 mmol) was stirred under nitrogen with oxalyl chloride (100 mg, 0.23 mmol) and DMF (0.05 ml) in dichloromethane (5 ml) for 2 h. The solution was evaporated, redissolved in benzene (5 ml) and evaporated again. The residue was added to a dried (Dean and Stark) suspension of 2-mercaptopyridine *N*-oxide sodium salt (42 mg, 0.28 mmol) and DMAP (4.7 mg) in benzene (80 ml) and the mixture was heated at reflux for 30.5 h in the dark. At this point the reaction mixture was irradiated with a 200 W tungsten lamp, and reflux was continued for 1 h. The cooled mixture was washed, dried and evaporated, and the residue was chromatographed (light petroleum–ethyl acetate, 1:5) to yield the *azathiaketal* **30** as a brown gum (75 mg, 72%) [Found: (FAB MS) *m/z* 487, 409, 349. $C_{22}H_{22}N_4O_7S$ requires $(M + H)^+$ 487, $(M + H - C_5H_4N)^+$ 409, $(M + H - C_5H_4NS - C_2H_4)^+$ 349]; δ_H 2.15–2.35 (4H, m, 3-CH_2, 4-CH_2), 3.69 (6H, s, ArOMe), 4.13 (2H, t, *J* 6.3, 2-CH_2), 6.50 (2H, s, 7-H, 9-H), 7.09 (1H, d, *J* 8.7, 6′-H), 7.02–7.06 (1H, m, 5″-H), 7.17 (1H, d, *J* 2.6, 7.6, 3″-H), 7.59–7.61 (1H, m, 4″-H), 8.30 (1H, dd, *J* 2.5, 8.7, 5′-H), 8.46 (1H, d, *J* 4.7, 6″-H), 8.88 (1H, d, *J* 2.5, 3′-H); δ_C (2 quaternary C and 1 CH signals not observed) 27.8 (CH_2), 35.8 (CH_2), 56.0 (CH_3), 71.9 (CH_2), 103.2 (CH), 116.3 (CH), 119.4 (CH), 121.7 (CH), 124.2 (C), 129.8 (CH), 132.1 (C), 136.1 (C), 137.2 (C), 137.3 (CH), 149.3 (CH), 158.6 (C).

3,5-Dimethoxy-1-triisopropylsiloxybenzene 36

3,5-Dimethoxyphenol (3.5 g, 22.5 mmol), triisopropylsilyl

chloride (7.5 ml, 34.3 mmol) and imidazole (3.15 g, 46.5 mmol) in DMF (100 ml) was stirred at ambient temperature under nitrogen for 20 h. The mixture was diluted with aq. sodium hydroxide (10%) and extracted with hexane. The combined organic extracts were washed with dil. hydrochloric acid (0.5 M) and water, dried and evaporated. The residue was distilled to provide the *title silyl ether* **36** as a pale yellow oil (6.72 g, 95%), bp 180 °C/3.5 mmHg, lit.,[14] bp 145 °C/0.06 mmHg (Found: C, 65.68; H, 10.07; *m/z* 310.197. Calculated for $C_{17}H_{30}SiO_3$: C, 65.76; H, 9.74; M^+ 310.196); δ_H 1.11 (18H, d, *J* 7.2, SiCH*Me*), 1.21–1.30 (3H, m, C*H*Me_2), 3.75 (6H, s, OMe), 6.07 (2H, d, *J* 2.15, 2-H, 6-H) and 6.09 (1H, t, *J* 2.15, 4-H); δ_C 12.6 (CH), 17.9 (CH_3), 55.1 (CH_3), 93.3 (CH), 98.6 (CH), 157.0 (C) and 161.2 (C).

3,5-Dimethoxy-4-hydroxy-1-triisopropylsiloxybenzene 38

n-Butyllithium (1.6 M, 2.2 ml, 3.52 mmol) was added dropwise to a stirred solution of 3,5-dimethoxy-1-triisopropylsiloxybenzene (1.00 g, 3.21 mmol) in THF (10 ml) at room temperature under nitrogen. After 1 h triisopropyl borate (1.5 ml, 3.52 mmol) was added dropwise and the mixture was stirred for 15 min. when it was diluted with methanol and evaporated. The residue was dissolved in THF (30 ml) and the solution was added to aq. sodium hydroxide (3 M, 15 ml) and hydrogen peroxide (30%, 23 ml). The reaction mixture was stirred at room temperature for 30 min, then diluted with water and extracted with ether. The extracts were washed with saturated aq. sodium dithionite and water, dried and evaporated. The residue was chromatographed (light petroleum–ether, 4:1) to afford the *title phenol* **38** as a yellow oil (0.46 g, 52%) (Found: C, 62.58; H, 9.82; *m/z* 326.190. $C_{17}H_{30}SiO_4$ requires C, 62.54; H, 9.57; M^+ 326.191); ν_{max}film/cm^{-1} 3461 and 1510; δ_H 1.10 (18H, d, *J* 7.2, SiCH*Me*), 1.20–1.30 (3H, m, C*H*Me), 3.83 (6H, s, OMe), 6.15 (2H, s, ArH); δ_C 12.5 (CH), 17.7 (CH_3), 56.1 (CH_3), 97.2 (CH), 129.1 (C), 147.0 (C) and 148.9 (C).

Methyl 4-(2,6-dimethoxy-4-triisopropylsiloxyphenoxy)butanoate 39

A mixture of the phenol **38** (1.00 g, 3.06 mmol), methyl 4-bromobutanoate (0.62 g, 3.4 mmol), potassium carbonate (0.84 g, 6.12 mmol), potassium iodide (0.44 g, 2.75 mmol) and 18-crown-6 (140 mg, 0.61 mmol) was heated to reflux in acetonitrile (20 ml) for 14 h. The solution was cooled, filtered and evaporated. The residue was partitioned between water and ether. The organic phase was washed with aq. sodium hydroxide (2 M) and brine, dried and evaporated. The product was chromatographed (light petroleum–ethyl acetate, 3:1) to yield the *title ester* **39** as a yellow oil (1.05 g, 77%) (Found: C, 61.90; H, 8.55; *m/z* 426.244. $C_{22}H_{38}SiO_6$ requires C, 61.94; H, 8.98; M^+ 426.244); ν_{max}film/cm^{-1} 1738 and 1590; δ_H 1.10 (18H, d, *J* 6.7, SiCH*Me*), 1.18–1.21 (3H, m, C*H*Me), 2.01 (2H, tt, *J* 6.1, 7.1, 3-CH_2), 2.62 (2H, t, *J* 7.1, 2-CH_2), 3.68 (3H, s, CO_2Me), 3.77 (6H, s, OMe), 3.92 (2H, t, *J* 6.1, 4-CH_2), 6.10 (2H, s, ArH); δ_C 12.6 (CH), 17.8 (CH_3), 25.3 (CH_2), 30.4 (CH_2), 51.3 (CH_3), 55.8 (CH_3), 72.2 (CH_2), 97.3 (CH), 122.3 (C), 152.3 (C), 153.5 (C) and 174.8 (C).

Methyl 4-(2,6-dimethoxy-4-hydroxyphenoxy)butanoate 40

To a solution of the above ester **39** (1.00 g, 2.34 mmol) in THF (20 ml) at 0 °C was added TBAF (1 M in THF, 2.33 ml, 2.34 mmol) and the reaction mixture was stirred for 30 min, when it was poured into water and extracted with ethyl acetate. The extracts were washed, dried and evaporated, and the residue was chromatographed (light petroleum–ethyl acetate, 2:1) to yield the *title phenolic ester* **40** as orange crystals (0.43 g, 60%), mp 69–70 °C (Found: C, 58.00; H, 6.91; *m/z* 270.111. $C_{13}H_{18}O_6$ requires C, 57.77; H, 6.71; M^+ 270.110). This product had IR and NMR spectra closely similar to those of a non-crystalline sample prepared previously by a different route.[2]

Formation of the bicyclospirodienone 9 from radical decarboxylation of 4-[2,6-dimethoxy-4-(2,6-dinitrophenoxy)phenoxy]-butanoic acid

Methyl 4-(2,6-dimethoxy-4-hydroxyphenoxy)butanoate **40** (0.45 g, 1.7 mmol) was dissolved in dry DMF (50 ml) and sodium hydride (oil free, 79 mg, 2 mmol) was added. The mixture was stirred for 1 h and 2,6-dinitrochlorobenzene was then added; stirring was continued for 10 h more. Water (100 ml) was added, and the solution was extracted with ether (3 × 100 ml). The combined extracts were washed, dried and evaporated to yield *methyl* 4-[2,6-*dimethoxy*-4-(2,6-*dinitrophenoxy*)*phenoxy*]-*butanoate* **42**; R = Me in essentially quantitative yield (Found: *m/z* 436.112. $C_{19}H_{20}O_{10}N_2$ requires M^+ 436.110); δ_H 2.11 (2H, m, 3-CH_2), 2.70 (2H, t, *J* 7.0, 2-CH_2), 3.65 (3H, s, CO_2CH_3), 3.83 (6H, s, ArOMe), 4.02 (2H, t, *J* 6.6, 4-CH_2), 6.17 (2H, s, ArH), 7.62 (1H, t, *J* 8.2, 4′-H), 8.24 (2H, d, *J* 8.2, 3′-H, 5′-H); δ_C 25.4 (CH_2), 30.5 (CH_2), 51.5 (CH_3), 56.2 (CH_3), 72.3 (CH_2), 93.6 (CH), 125.3 (CH), 129.3 (CH), 141.8 (C), 144.8 (C), 153.0 (C), 154.1 (C), 174.1 (C).

Hydrolysis of this ester (0.7 g) in acetone (10 ml) and hydrochloric acid (2 M, 10 ml) at reflux for 3 h afforded the *title acid* **42**; R = H, (0.55 g, 86%) as a gum (Found: *m/z* 422.096. $C_{18}H_{18}O_{10}N_2$ requires M^+ 422.096); δ_H 1.92 (2H, m, 3-CH_2), 2.59 (2H, m, 2-CH_2), 3.65 (6H, s, ArOMe), 3.86 (2H, m, 4-CH_2), 6.02 (2H, s, ArH), 7.45 (1H, t, *J* 8.4, 4′-H), 8.07 (2H, d, *J* 8.4, 3′-H, 5′-H); δ_C 24.8 (CH_2), 28.9 (CH_2), 55.9 (CH_3), 71.9 (CH_2), 93.3 (CH), 125.4 (CH), 129.3 (CH), 141.40 (C), 144.5 (C), 153.0 (C), 153.8 (C), 179.2 (C).

Radical decarboxylation of this acid (0.55 g, 1.3 mmol) under the conditions reported above gave the bicyclospirodienone **9** (43%), spectroscopically identical to the previously isolated samples.

Methyl 5-[2,6-dimethoxy-4-(2,4-dinitrophenoxy)phenoxy]-pentanoate 43

Methyl 5-(2,6-dimethoxy-4-hydroxyphenoxy)pentanoate[15] (1.0 g, 3.5 mmol) was dissolved in THF (50 ml), and sodium hydride (oil free, 0.168 g, 7 mmol) was added. The mixture was stirred for 30 min, when 2,4-dinitrofluorobenzene (0.744 g, 4 mmol) was introduced. The reaction mixture was stirred at ambient temperature for a further 16 h when water (50 ml) was added, and the solution was extracted with dichloromethane (3 × 75 ml). The combined extracts were washed, dried and evaporated. The residue was chromatographed (light petroleum–ethyl acetate, 3:1) to afford the *title ester* **43**; R = Me as a yellow crystalline solid, mp 90.5–92 °C (Found: *m/z* 450.127. $C_{20}H_{22}O_{10}N_2$ requires M^+ 450.125); ν_{max}KBr/cm^{-1} 1736, 1607, 1579, 1541, 1500; δ_H 1.80 (4H, m, 3-CH_2, 4-CH_2), 2.38 (2H, t, *J* 7.0, 2-CH_2), 3.64 (3H, s, CO_2Me), 3.78 (6H, s, OMe), 3.94 (2H, t, *J* 6.3, 5-CH_2), 6.34 (2H, s, ArH), 7.05 (1H, d, *J* 9.2, 6′-H), 8.29 (1H, dd, *J* 9.2, 2.7, 5′-H), 8.79 (1H, d, *J* 2.7, 3′-H); δ_C 21.4 (CH_2), 29.4 (CH_2), 33.6 (CH_2), 51.5 (CH_3), 56.2 (CH_3), 72.8 (CH_2), 98.1 (CH), 118.0 (CH), 122.0 (CH), 128.8 (CH), 135.4 (C), 139.0 (C), 141.1 (C), 149.1 (C), 154.6 (C), 156.4 (C) and 174.1 (C).

Hydrolysis of this ester (1.04 g) in acetone (60 ml) and hydrochloric acid (2 M, 60 ml) at reflux for 4 h afforded 5-[2,6-*dimethoxy*-4-(2,4-*dinitrophenoxy*)*phenoxy*]*pentanoic acid* **44**; R = H, (0.55 g, 55%) (Found: *m/z* 436.110. $C_{19}H_{20}O_{10}N_2$ requires M^+ 436.112); δ_H 1.80–1.96 (4H, m, 3-CH_2, 4-CH_2), 2.52 (2H, t, *J* 7.1, 2-CH_2), 3.86 (6H, s, OMe), 4.03 (2H, t, *J* 6.3, 5-CH_2), 6.42 (2H, s, ArH), 7.12 (1H, d, *J* 9.3, 6′-H), 8.37 (1H, dd, *J* 9.3, 2.8, 6′-H), 8.87 (1H, d, *J* 2.8, 3′-H); δ_C (2 quaternary C unobserved) 21.2 (CH_2), 29.2 (CH_2), 33.5 (CH_2), 56.2 (CH_3), 72.8 (CH_2), 98.1 (CH), 118.0 (CH), 122.0 (CH), 128.8 (CH), 141.2 (C), 149.1 (C), 154.6 (C), 156.4 (C) and 179.2 (C).

Ethyl 4-[2,6-dimethoxy-4-(2,4-dinitrophenoxy)phenoxy]-2,2-dimethylbutanoate 45

Sodium hydride (60% dispersion, 57 mg, 1.48 mmol) was

washed with light petroleum and suspended in DMF (10 ml). 2,6-Dimethoxy-4-(2,4-dinitrophenoxy)phenol (0.5 g, 1.48 mmol)[15] was added and the mixture was stirred at room temperature under nitrogen for 1 h. Ethyl 4-bromo-2,2-dimethylbutanoate (0.39 g, 1.77 mmol) was added, and the reaction mixture was heated at reflux for 48 h. The cooled product was diluted with ether, washed, dried and evaporated. The residue was chromatographed (light petroleum–ethyl acetate, 3:1) to afford the *title ether* **45**; R = Et as a brownish gum (240 mg, 33%); (Found: *m*/*z* 433.124. $C_{22}H_{26}N_2O_{10}$ requires (M − $C_2H_5O)^+$ 433.125); δ_H 1.26 (3H, t, *J* 7.2, CH_2CH_3), 1.29 (6H, s, Me), 2.09 (2H, t, *J* 6.6, 3-CH_2), 3.75 (6H, s, OMe), 4.04 (2H, t, *J* 6.6, 4-CH_2), 4.16 (2H, q, *J* 7.2, OCH_2), 6.19 (2H, s, 3′-H, 5′-H), 6.88 (1H, d, *J* 9.2, 6″-H), 8.25 (1H, dd, *J* 2.8, 9.2, 5″-H), 8.85 (1H, d, *J* 2.8, 3″-H); δ_C 25.4 (CH_3), 38.9 (CH_2), 40.5 (C), 56.1 (CH_3), 60.2 (CH_2), 65.1 (CH_2), 92.0 (CH), 116.7 (CH), 121.9 (CH), 124.0 (CH), 128.7 (C), 138.0 (C), 140.6 (C), 152.7 (C), 157.1 (C), 158.0 (C) and 177.2 (C).

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References

1 Y.-P. Chen, R. Liu, H.-Y. Hsu, S. Yamamura, Y. Shizuri and Y. Hirata, *Bull. Chem. Soc. Japan*, 1977, **50**, 1824; N. Ookawa, T. Ikeya, H. Taguchi and I. Yosioka, *Chem. Pharm. Bull.*, 1981, **29**, 123.
2 S. P. Green and D. A. Whiting, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 193.
3 L. Shide, D. Zhikuei, R. Mayer, G. Rucker, G. Will, A. Kirfel and R. Langen, *Planta Medica*, 1988, **54**, 440; Z.-H. Ding and S.-D. Luo, *Huaxue Xuebao*, 1990, **48**, 1075 (*Chem. Abstr.*, 1991, **114**, 182 040r).
4 J.-S. Liu, M.-F. Huang and H.-X. Zhou, *Can. J. Chem.*, 1991, **69**, 1403; J.-S. Liu and M.-F. Huang, *Phytochemistry*, 1992, **31**, 957; J.-S. Liu, H.-X. Zhou and L. Li, *Phytochemistry*, 1992, **31**, 1379.
5 U. P. Topiwala and D. A. Whiting, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 2443.
6 *Inter alia*: D. H. R. Barton, H. Togo and S. Z. Zard, *Tetrahedron*, 1985, **41**, 5507; D. H. R. Barton, D. Crich and W. B. Motherwell, *Tetrahedron*, 1985, **41**, 3901; D. H. R. Barton, D. Crich and G. Kretzschmar, *J. Chem. Soc.*, *Perkin Trans. 1*, 1986, 39; D. H. R. Barton, D. Bridon, I. Fernandez-Picot and S. Z. Zard, *Tetrahedron*, 1987, **43**, 2733; D. H. R. Barton, Y. Hervé, P. Potier and J. Thierry, *Tetrahedron*, 1988, **44**, 5479.
7 J. R. Thomas, *J. Am. Chem. Soc.*, 1964, **86**, 1446; W. M. Fox and W. A. Waters, *J. Chem. Soc.*, 1965, 4628.
8 See for example, J. Sinnreich and D. Elad, *Tetrahedron*, 1968, **24**, 4509; D. Elad and R. D. Youssefyeh, *Chem. Commun.*, 1965, 4509; D. Elad, G. Friedman and R. D. Youssefyeh, *J. Chem. Soc.* (*C*), 1968, 870.
9 R. A. Jackson and W. A. Waters, *J. Chem. Soc.*, 1960, 1653.
10 G. B. Chalfont, D. H. Hey, K. S. Y. Liang and M. J. Perkins, *J. Chem. Soc.*, *Chem. Commun.*, 1967, 367; *J. Chem. Soc.* (*B*), 1971, 233, and refs. cited therein.
11 G. B. Gill and G. H. Williams, *J. Chem. Soc.* (*B*), 1966, 880.
12 K. Kurosaw, A. Hashiba and H. Takahashi, *Bull. Chem. Soc. Japan*, 1978, **51**, 3612.
13 R. F. Collins and M. Davis, *J. Chem. Soc.*, 1961, 1863.
14 J. J. Landi and K. Ramig, *Syn. Comm.*, 1991, **21**, 167.
15 Preparation of these starting materials will be discussed in a paper in preparation, dealing with other solutions to the problem of regiospecific synthesis of aryl alkyl ethers of substituted hydroquinones.

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