The Synthesis of Lignans and Related Structures using Quinodimethanes and Isobenzofurans: Approaches to the Podophyllins

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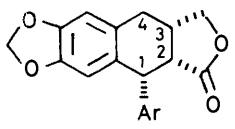
Novel routes to 1-aryl-5,6-dialkoxy-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxides (**13**) and to the corresponding benzo[*c*]furan (**8**) have been developed; these species yield quinodimethanes (**12**) *via* thermal extrusion of SO_2 and isobenzofurans (**5c**) in an acid-catalysed process, respectively, which then react with various dienophiles to provide structural analogues of the aryltetralin and arylnaphthalene lignans.

In a recent comprehensive review,[1] Ward described many of the methods which have been used to synthesise lignans. We now report two new routes which allow ready access to the aryltetralin lignans, *e.g.* 4-deoxyisopicrophyllotoxin (**1**)[2] and phyltetralin (**2**),[3] and to the arylnaphthalene lignans, *e.g.* justicidin E (**3**) and taiwanin C (**4**).[4]

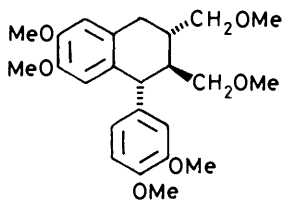
Initially, we chose a route which proceeds *via* the isobenzofurans (**5**). There are many reports in the literature concerning isobenzofurans,[5] but prior to the commencement of our work they had not been used for the construction of lignans. However, their potential utility in natural product synthesis had been demonstrated by, *inter alia*, Kende *et al.*[6] in their synthesis of 7-deoxydaunomycinone from the isobenzofuran (**5a**), and by Contreras *et al.*[7] in their synthesis of polysubstituted naphthalenes from the isobenzofuran (**5b**).

In our route the bromoacetal (**6b**) was prepared from bromopiperonal (**6a**)[8] using methanol and one of several acid catalysts, and then treated with n-butyl-lithium and 3,4,5-trimethoxybenzaldehyde to produce the expected hydroxyacetal (**7a**). However, all attempts to obtain an analytical sample failed owing to the ready conversion of compound (**7a**) into the 1,3-dihydrobenzo[*c*]furan (**8**). In consequence, treatment of the crude acetal–dihydrofuran mixture with a solution of *N*-phenylmaleimide in benzene containing a small amount of toluene-*p*-sulphonic acid, provided good yields of the crystalline cycloadduct (**9a**), presumably *via* compound (**5c**). Compounds of this type have been converted into arylnaphthalene lignans [*e.g.* (**9b**) into (**3**) and (**4**)[4]], but our desire to use this route, and in particular the first-formed cycloadducts (**10**), for syntheses of aryltetralin lignans was frustrated by the extreme lability of these compounds. If the acid-catalysed reaction was carried out at −10 °C, the adduct with *N*-phenylmaleimide (**10**; X = NPh) could be isolated; this was sufficiently stable towards aromatisation for an n.m.r. spectrum to be obtained (δ 3.4—3.8, m, for 2-H and 3-H; and δ 5.2, d, *J* 13 Hz for 4-H). However, at about this time, Rodrigo and co-workers published their first paper concerning an approach to aryltetralin lignans *via* the cycloadduct (**11**),[9] and in consequence we turned our attention to alternative methods for the construction of these lignans.

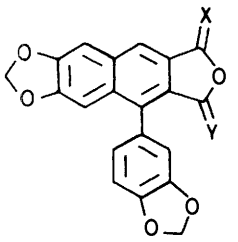
Conceptually, the simplest approach to these structures would involve the use of a quinodimethane (**12**), and there are a number of methods available for the synthesis of such compounds. These include thermolysis of benzocyclobutenes,[10] of isochromanones,[11] or of oxathiins;[12] but we chose to investigate the thermolysis of 1-aryl-5,6-dialkoxy-1,3-dihydrobenzo[c]thiophene 2,2-dioxides (**13**). The pioneering work of Cava,[13] and Jensen and Coleman,[14] demonstrated that a thermal chelotropic elimination of SO_2 from such sulphones produced quinodimethanes, which could be trapped by simple dienophiles. More recently Oppolzer[15] and Nicolaou[16] have prepared estrogens through the intermediacy of sulphones such as (**14**), and an intramolecular cycloaddition between the derived quinodimethane and the ethenyl appendage.



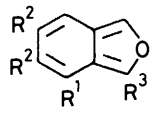
(**1**)



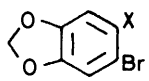
(**2**)



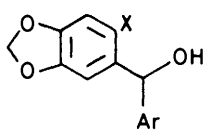
(**3**) X = H_2, Y = O
(**4**) X = O, Y = H_2



(**5**) **a**; R^1 = OMe, R^2 = R^3 = H
b; R^1 = H, R^2 = OMe, R^3 = OEt
c; R^1 = H, R^2, R^2 = −OCH_2O−, R^3 = Ar



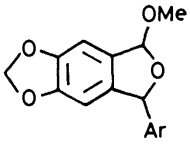
(**6**) **a**; X = CHO
b; X = $CH(OMe)_2$
c; X = CH_2OH



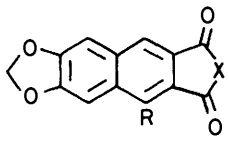
(**7**) **a**; X = $CH(OMe)_2$
b; X = CH_2OH

Ar = 3,4,5-Trimethoxyphenyl

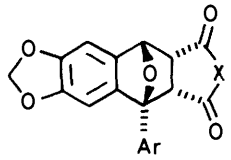
Initially we prepared the sulphone (**13a**) from bromopiperonyl alcohol (**6c**) which, upon reaction with n-butyl-lithium (2 equiv.) and 3,4,5-trimethoxybenzaldehyde, yielded the diol (**7b**). Several methods were tried in the hope of preparing the corresponding dibromide, but the water sensitivity of this compound precluded the isolation of useful amounts. In consequence, a 'one-pot' sequence to the thiophthalan (**15**) was developed. Treatment of the diol (**7b**) with methanesulphonyl chloride (2 equiv.) and triethylamine (2.2 equiv.) in CH_2Cl_2 at 0 °C, followed by removal of the solvent and the addition of an excess of sodium sulphide in dimethyl sulphoxide (DMSO), provided the desired thiophthalan (**15**) after acidification. It was necessary to purify this product by flash chromatography prior to oxidation, and yields of the thiophthalan were only modest (typically 50—60% on the



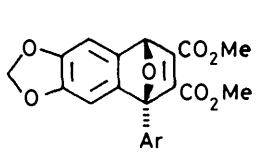
(8)



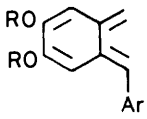
(9) a; X = NPh, R = Ar
b; X = O, R = 3,4-methylenedioxyphenyl



(10)



(11)



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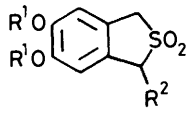
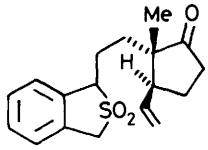
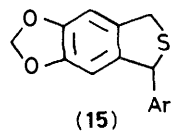


(13) a; R^1,R^1 = $-CH_2-$, R^2 = Ar
b; R = Me, R^2 = 3,4-dimethoxyphenyl
c; R^1,R^1 = $-CH_2-$, R^2 = 3,4-methylenedioxyphenyl

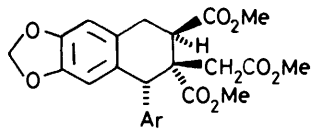
Ar = 3,4,5-Trimethoxyphenyl



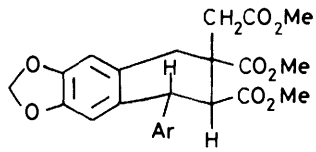
(14)



(15)



(16a)



(16b)

Ar = 3,4,5-Trimethoxyphenyl

multigramme scale). The oxidation with peracetic acid, however, gave almost quantitative yields of the sulphone (**13a**).

After the problems with the route to the sulphones,* it was gratifying to find that the chelotropic elimination of SO_2 and subsequent cycloaddition reactions with dienophiles provided excellent yields of products with a high degree of regio- and stereo-selectivity. The reactions were carried out in di-n-butyl phthalate at around 200—210 °C, with a three-fold excess of dienophile, and were complete after 3—4 h. Purification was effected by flash chromatography of the whole reaction mixture, and, even on the multigramme scale, the solvent and excess of dienophile were easily separated from the products by gradient elution. The results of typical experiments carried out with the sulphone (**13a**; R^1,R^1 = methylenedioxy, R^2 = 3,4,5-trimethoxyphenyl) are given in Table 1.

As noted in our preliminary communication,[17] the regioselectivity observed in each case is in accord with predictions based on a consideration of frontier orbitals,[18] and is consistent with the exclusive participation of (*E*)-dienes of the general form (**12**). The corresponding (*Z*)-dienes are known[13] to undergo intramolecular cycloaddition, but such cycloadducts were never observed.

Entries F, G, and J (Table 1) deserve some additional comment. With bromomaleic anhydride we were not able to isolate any cycloadduct containing bromine, and it seems that the initially formed cycloadduct loses HBr at elevated temperature, a dihydronaphthalene and fully aromatised product (naphthalene proton at δ 8.30) being obtained. The olefinic product lacked a 1-H proton (normally between δ 4.0 and 4.5), and possessed a complex ABX pattern for its 4-H protons. Although we have made no attempt to optimise the ratio of arylnaphthalene to aryldihydronaphthalene, this route is attractive for the construction of arylnaphthalene lignans such as (**3**) and (**4**). An even better route utilises the cycloaddition of acetylenedicarboxylate (entry H), and this yields a suitably functionalised arylnaphthalene directly.

The cycloaddition with (*E*)-dimethyl 3-methoxycarbonylpent-2-enedioate (entry G) produced two products in good yield. The major product was assigned structure (**16a**) following an *X*-ray crystallographic study, and it showed a singlet for the 1-H proton in the ^1H n.m.r. spectrum; the minor product has been assigned structure (**16b**) ($J_{1,2}$ 12 Hz, showing a diaxial relationship of 1-H and 2-H, and J_{gem} 17 Hz for 4-H, no 3-H proton signal). The regioselectivity is not unexpected since C-3 of the triester would be expected to be less electrophilic than C-2.

Our only failure to obtain a cycloaddition product was with carboxymethylmaleic anhydride (entry J), and we propose the mechanism shown in the Figure to explain the formation of the observed acyclic product.

To demonstrate the synthetic utility of the cycloaddition method, we first prepared phyltetralin (**2**) from the cycloadduct (**17a**), by reduction with $LaAlH_4$ to produce the diol (**17b**),

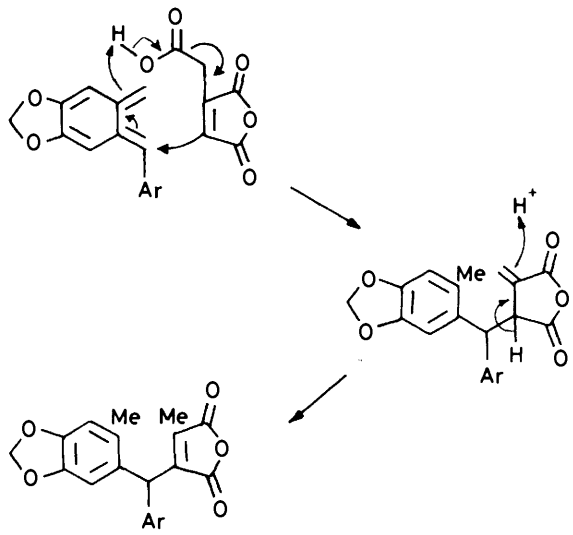
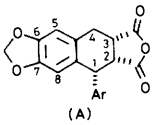
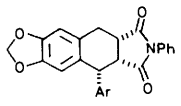
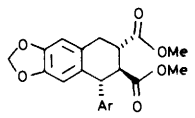
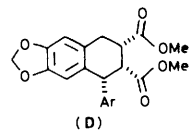
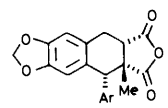
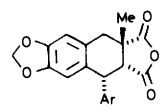
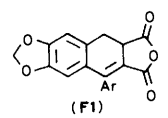
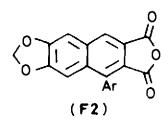
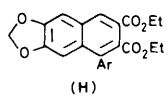
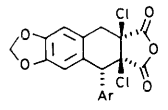
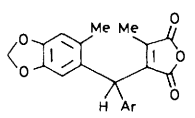


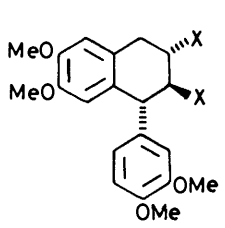
Figure.

* We have now shown that the sulphone may be obtained more easily using P_2S_5 in benzene (1 h at 80 °C) to form the thiophthalan, with immediate oxidation after filtration. Experiments by A. A. Usmani.

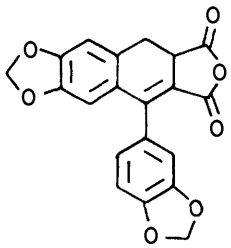
Table 1. Typical cycloaddition reactions of the sulphone (**13c**)

Entry	Dienophile	Cycloadduct *	Product yield (%)
A	Maleic anhydride	 (A)	72
B	*N*-Phenylmaleimide	 (B)	85
C	(*E*)-Dimethyl butenedioate	 (C)	90
D	(*Z*)-Dimethyl butenedioate	 (D)	90
E	Methylmaleic anhydride	 (E1)  (E2)	90 [(**E1**):(**E2**) = 7:3]
F	Bromomaleic anhydride	 (F1)  (F2)	92 [(**F1**):(**F2**) = 3:2]
G	(*E*)-Dimethyl 3-methoxycarbonylpent-2-enedioate	(16a) and (16b)	85 [(**16a**):(**16b**) = 3:1]
H	Diethyl acetylenedicarboxylate	 (H)	56
I	Dichloromaleic anhydride	 (I)	46
J	Carboxymethylmaleic anhydride	 (J)	21

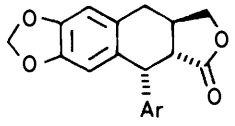
* Ar = 3,4,5-Trimethoxyphenyl



(17) a; X = CO_2Me
b; X = CH_2OH



(18)



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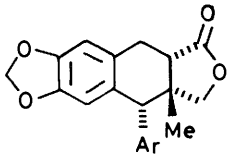
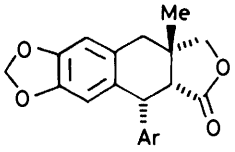


(20a)



(20b)

Ar = 3,4,5-Trimethoxyphenyl

which was then methylated (MeI–NaH–DMSO). The compound possessed identical chromatographic and spectroscopic characteristics with those of an authentic sample.

Secondly, we prepared the sulphone (**13c**) and treated this with 2-bromomaleic anhydride to produce two cycloadducts (**9b**) and (**18**) in the ratio *ca.* 5:3 and a combined yield of around 80%. Since compound (**18**) can be aromatised to yield (**9b**), and the latter has been converted into both justicidin E (**3**) and taiwanin C (**4**),[4] this constitutes a formal total synthesis of these arylnaphthalene lignans. It also compares very favourably with the other syntheses by virtue of its brevity.

Finally, since our major intention was (and remains) the synthesis of novel analogues of the cytotoxic lignan deoxypodophyllotoxin (**19**),[2] we investigated the selective reduction of several anhydride cycloadducts. Reduction of the crude cycloadduct mixture (**E1**)/(**E2**) (see Table 1) with sodium borohydride yielded the lactone (**20a**) as the major product, and its isomer (**20b**) as the minor product (ratio 4:1), with only traces of other products. Such regioselectivity with reduction primarily or exclusively at the most sterically hindered carbonyl, has many parallels in the literature.[19]

Alternatively, reduction of a maleic anhydride adduct (entry A, Table 1) with K-selectride in tetrahydrofuran (THF), then work-up using alkaline H_2O_2, and subsequent treatment with 6M-HCl to effect lactonisation of the resultant hydroxy acid, yielded isodeoxypicrophyllotoxin (**1**) (57% yield after chromatography).

We have utilised the routes described in this paper to produce a large number of analogues of deoxypodophyllotoxin (**19**), and the biological profiles of these compounds will be described elsewhere.

Experimental

I.r. spectra were recorded with a Perkin-Elmer 157 double beam grating spectrophotometer (liquid films for oils and Nujol mulls for solids); ^{1}H n.m.r. spectra * were recorded with a Varian T-60 (60 MHz), Varian HA 100 (100 MHz), or Perkin-Elmer R34 (220 MHz) instrument (tetramethylsilane as internal standard); and mass spectra were recorded on an A.E.I. MS 12 spectrometer. Flash chromatography was performed using Woelm silica gel (*ca.* 200—450 mesh). Organic solvents were distilled from calcium hydride when required anhydrous. Light petroleum, b.p. 40—60 °C, was employed. Ether refers to diethyl ether.

6-Bromo-3,4-methylenedioxybenzaldehyde (*6-Bromopiperonal*) (**6a**).—To a solution of piperonal (20 g) in glacial acetic acid (40 ml) was added a solution of bromine (8 ml) in glacial acetic acid (25 ml). The mixture was left at room temperature overnight, then poured into water (1 500 ml), and the precipitated product was then filtered off at the pump. The precipitate was thoroughly washed with aqueous sodium thiosulphate, once (rapidly) with ice-cold diethyl ether, and finally recrystallised from methanol. The yield of white needles was 18 g (59%); m.p. 128 °C (lit., 129 °C); $\nu_{max.}$ 1 700 cm^{-1} (C=O); δ($CDCl_3$) 6.1 (2 H, s, OCH_2O), 7.05 (1 H, s, 5-H), 7.37 (1 H, s, 2-H), and 10.2 (1 H, s, CHO).

6-Bromo-3,4-methylenedioxybenzaldehyde Dimethyl Acetal (*6-Bromopiperonal Dimethyl Acetal*) (**6b**).—A mixture of 6-bromopiperonal (11.45 g, 50 mmol), methanol (60 ml), trimethyl orthoformate (5.83 g, 55 mmol), and an acid catalyst (NH_4Cl, 0.27 g; or toluene-*p*-sulphonic acid, 0.95 g; or Dowex 50W-X8 standard H^+ resin, 1 g) was heated under reflux for 7—10 h. After this time, the catalyst was removed by filtration, and all volatiles were then removed under reduced pressure. Purification of the crude acetal was then effected by flash chromatography (light petroleum–ether 9:1) to yield a colourless oil. Yields 79% (NH_4Cl), 53% (toluene-*p*-sulphonic acid), and 25% (Dowex); δ($CDCl_3$) 3.4 (6 H, s, OMe), 5.47 (1 H, s, acetal H), 5.97 (2 H, s, OCH_2O), 7.0 (1 H, s, 5-H), and 7.1 (1 H, s, 2-H); *m/z* (%) 276 (M^+ for ^{81}Br, 2), 274 (M^+ for ^{79}Br, 3), 268 (17), 241 (98), and 239 (100).

[*Hydroxy*(3,4,5-*trimethoxyphenyl*)*methyl*]-3,4-*methylenedioxybenzaldehyde Dimethyl Acetal* (**7a**).—To a stirred solution of 6-bromopiperonal dimethyl acetal (5.5 g, 20 mmol) in dry THF (50 ml) kept at −78 °C under nitrogen, was added n-butyllithium (12.5 ml of 1.6M, 20 mmol). The mixture was then stirred at −78 °C for 30 min to 1 h before the addition of 3,4,5-trimethoxybenzaldehyde (3.92 g, 20 mmol) in THF (20 ml). Stirring was continued for a further 3 h while the temperature was allowed to rise to room temperature. Water (5 ml) was then added, and the THF was removed under reduced pressure, further water was added, and the product was extracted into dichloromethane. A yellow oil was obtained, but this defied attempts to purify it, and this crude product was used for further reactions. δ($CDCl_3$) 3.4, 3.5, and 3.6 [3 × s for acetal OCH_3 of (**7a**) and single OCH_3 of (**8**) in admixture], 3.87 (9 H, s, 3 × OCH_3 of trimethoxyphenyl), 5.9—6.2 (3 H, m, OCH_2O and acetal CHO), and 6.5—6.9 (4 H, m, aromatic H's); *m/z* 392 [M^+ for (**7a**)].

6,7-*Methylenedioxy*-N-*phenyl*-1-(3,4,5-*trimethoxyphenyl*)-*naphthalene*-2,3-*dicarboximide* (**9a**).—To a solution of the crude hydroxyacetal (**7a**) (5 g) in dry benzene (50 ml) kept at −10 °C was added toluene-*p*-sulphonic acid (0.2 g), and the mixture was stirred at this temperature until t.l.c. analysis (light petroleum–EtOAc, 1:4) showed complete conversion of the starting acetal into a faster running component [presumably (**8**)] after 10—15

* Primed and double primed numbers are used for the n.m.r. assignments of substituents on attached phenyl groups where these occur.

min. *N*-Phenylmaleimide (excess) was then added and the mixture stirred for 1—2 h at room temperature until the formation of a red precipitate appeared to be complete. The solid was filtered off, and washed liberally with ice-cold isopropyl alcohol. Recrystallisation from THF afforded a white solid (3.9 g), m.p. 278 °C, $\nu_{max.}$(Nujol) 1 770 and 1 715 (C=O of cyclic imide), 1 580, 1 510, 1 410, 1 370, 1 250, 1 130, and 1 040 cm^{-1}; δ(CD_2Cl_2) 3.8 (6 H, s, 3′- and 5′-OCH_3), 3.87 (3 H, s, 4′-OCH_3), 6.1 (2 H, s, OCH_2O), 6.55 (2 H, s, 2′- and 6′-H), 7.1 (1 H, s, 8-H), 7.33 (1 H, s, 5-H), 7.4 (5 H, m, phenyl), and 8.2 (1 H, s, 4-H); *m/z* (%) 483.1321 (M^+, 100) (Calc. for $C_{28}H_{21}NO_7$: 483.1312).

6,7-*Methylenedioxy*-4-(3,4,5-*trimethoxyphenyl*)-N-*phenyl*-1,4-*epoxy*-1,2,3,4-*tetrahydronaphthalene*-2,3-*dicarboximide* (**10**; X = NPh).—To a solution of the crude hydroxyacetal (2 g) in dry toluene (20 ml) held at −10 °C was added toluene-*p*-sulphonic acid (50 mg) and the mixture was stirred for 15 min at this temperature to maximise the formation of compound (**8**) (*vide supra*). At this point, an excess of *N*-phenylmaleimide was added and the mixture was stirred at 0 °C for 1—2 h, until the formation of a white precipitate was judged to be complete. This solid was filtered off, washed well with light petroleum and dried quickly *in vacuo*. An n.m.r. spectrum was then obtained immediately; δ($CDCl_3$) 3.4—3.8 (2 H, m, 2- and 3-H), 3.83 (6 H, s, 3′- and 5′-OCH_3), 3.9 (3 H, s, 4′-OCH_3), 5.2 (1 H, d, *J* 13 Hz, 4-H), 6.0 (2 H, s, OCH_2O), 6.6 (3 H, m, 2′-, 6′-, and 8-H), and 7.4 (6 H, m, 5-H and phenyl). Attempts to recrystallise the product from a variety of solvent systems led to aromatisation and obtention of compound (**9a**).

6-*Bromo*-3,4-*methylenedioxybenzyl Alcohol* (**6c**).—6-Bromopiperonal (**6a**) (6.5 g, 28.38 mmol) was dissolved in THF (100 ml) at room temperature, and sodium borohydride (2.0 g, 52.5 mmol) was added in portions while the mixture was vigorously stirred. Stirring was continued for 1—2 h, and the mixture was then poured into a mixture of ice cold water–2M HCl (1:1). The product was then extracted into dichloromethane, and the organic extract was dried and concentrated to *ca.* 50 ml volume. Light petroleum was added, and the product precipitated as white crystals (5.2 g, 79%), m.p. 91 °C; $\nu_{max.}$($CHCl_3$) 3 650 (OH), 2 400, 1 510, 1 480, 1 240, 1 110, 0 140, 985, and 870 cm^{-1}; δ($CDCl_3$) 2.46 (1 H, s, OH), 4.6 (2 H, s, CH_2OH), 5.95 (2 H, s, OCH_2O), 6.95 (1 H, s, 5-H), and 7.0 (1 H, s, 2-H); *m/z* (%) 232 (M^+ for ^{81}Br, 70), 230 (M^+ for ^{79}Br, 80), 151 (85), 135 (5), and 93 (100).

[*Hydroxy*(3,4,5-*trimethoxyphenyl*)*methyl*]-3,4-*methylenedioxybenzyl Alcohol* (**7b**).—6-Bromopiperonyl alcohol (**6c**) (4.62 g, 20 mmol) was dissolved in anhydrous THF (100 ml), and the solution was cooled to −78 °C under nitrogen prior to the addition of n-butyl-lithium (25 ml of a 1.6M solution, 40 mmol). The solution was then stirred at −78 °C for 1 h, freshly recrystallised (from ether) 3,4,5-trimethoxybenzaldehyde (3.92 g, 20 mmol) dissolved in THF (20 ml) was added, and the mixture was then allowed to warm to room temperature. Water (1 ml) was added, and the THF was removed on the rotary evaporator. A further aliquot (1 ml) of water was added, and the products were extracted into dichloromethane. The organic extract was dried and then concentrated to yield a yellow viscous oil. A little benzene was added until a homogeneous solution was obtained, and then light petroleum was added slowly with stirring. A white precipitate was deposited, and this could be recrystallised from a benzene–light petroleum system (5.8 g, 83%); m.p. 141 °C; $\nu_{max.}$(Nujol) 3 600—3 100 (OH); δ($CDCl_3$) 3.2—3.4 (1 H, br s, OH), 3.75 (6 H, s, 3′- and 5′-OCH_3), 3.8 (3 H, s, 4′-OCH_3), 3.9—4.1 (1 H, br s, OH), 4.5 (2 H, q, *J* 11 Hz, CH_2OH), 5.88 (1 H, s, CHAr·OH), 5.9 (2 H, s, OCH_2O), 6.55 (2 H, s, 2′- and 6′-H), 6.65 (1 H, s, 5-H), and 6.8 (1 H, s, 2-H); *m/z* (%) 348.1207 (M^+, 18) (Calc. for $C_{18}H_{20}O_7$: 348.1209).

5,6-*Methylenedioxy*-1-(3,4,5-*trimethoxyphenyl*)-1,3-*dihydrobenzo*[c]*thiophene* (**15**).—The diol (**7b**) (2.0 g, 5.75 mmol) was dissolved in dichloromethane (50 ml) and placed in a flask under nitrogen. The solution was cooled to 0 °C and triethylamine (1.7 ml, 12 mmol) and methanesulphonyl chloride (1.2 ml, 15 mmol) were added successively. After being stirred for 1 h at 0 °C, the solvent was removed under reduced pressure, and a mixture of hydrated sodium sulphide ($Na_2S·9H_2O$) (3 g) in DMSO (50 ml) was added. The mixture was then stirred at room temperature overnight, poured into ice-cold water, and the product extracted into dichloromethane (100 ml). The extract was dried and concentrated to *ca.* 15 ml, a few drops of concentrated HCl added, and the yellowish brown solution was then stirred at room temperature for 3 h. Water was added, and the dichloromethane layer was separated, dried, and concentrated. Flash chromatography using light petroleum–ethyl acetate (4:1) as eluant provided essentially pure thiophthalan (**15**) (*ca.* 1 g, *ca.* 50%). This was exceedingly sensitive to oxidation, and was usually used without delay. Spectral data for the yellow crystals were: δ($CDCl_3$) 3.83 (9 H, s, 3 × OCH_3), 4.3 (2 H, dd, *J* 3 Hz, CH_2S), 5.6 (1 H, t, *J* 3 Hz, CHS), 5.95 (2 H, s, OCH_2O), 6.4 (1 H, s, 7-H), 6.5 (2 H, s, 2′- and 6′-H), and 6.7 (1 H, s, 4-H); *m/z* (%) 346 (M^+, 100), 345 (27), 344 (27), 331 (19), 329 (27), 315 (50), 314 (12), 313 (31), 282 (50), 181 (27), 179 (38), 119 (58), and 105 (69).

5,6-*Methylenedioxy*-1-(3,4,5-*trimethoxyphenyl*)-1,3-*dihydrobenzo*[c]*thiophene* 2,2-*Dioxide* (**13a**).—The thiophthalan (**15**) was dissolved in dichloromethane and treated at 0 °C with 40% peracetic acid (2 equiv.). The solution was stirred at room temperature overnight, then water was added, and the product was extracted into dichloromethane. The total organic extract was dried, concentrated, and the product precipitated by the addition of ether to a concentrated solution. Yields were in the range 80—*ca.* 100%, m.p. 197 °C; $\nu_{max.}$ 2 960—2 880, 2 850, 1 590, 1 500, 1 485, 1 465, 1 425, 1 370, 1 335, 1 310, 1 260, 1 200, 1 120, 1 035, 1 000, 940, 860, and 820 cm^{-1}: δ($CDCl_3$) 3.83 (6 H, s, 3′- and 5′-OCH_3), 3.87 (3 H, s, 4′-OCH_3), 4.33 (2 H, s, CH_2SO_2), 5.3 (1 H, s, $CHSO_2$), 6.0 (2 H, s, OCH_2O), 6.47 (2 H, s, 2′- and 6′-H), 6.6 (1 H, s, 7-H), and 6.8 (1 H, s, 4-H); *m/z* (%) 378.0764 (M^+, 5), 283.0970 ($C_{17}H_{15}O_4$, 100) ($C_{18}H_{18}O_7S$ requires 378.0773).

Cycloaddition Reactions: Extrusion of SO_2.—The sulphone (1 equiv.), the dienophile (4 equiv.), and di-n-butyl phthalate (2 ml per mmol of sulphone) were placed in a round-bottomed flask fitted with a reflux condenser, and kept under argon. The reaction mixture was heated at 200—210 °C for 1—3 h, then cooled and loaded onto a silica column for flash chromatography. These reactions have been carried out routinely on amounts of sulphone ranging from 0.5—5 g.

Typical Cycloadducts (*Table 1*) (^1H *N.m.r. Data in Table 2*).—A. 6,7-*Methylenedioxy*-1-(3,4,5-*trimethoxyphenyl*)-1,2,3,4-*tetrahydro*-2,3-*naphthoic anhydride* (**A**). This *adduct* was formed after 2 h at 210 °C in 86% yield after chromatography (light petroleum–ether, 1:1); m.p. 185 °C (from $CHCl_3$–ether); $\nu_{max.}$ 3 000, 2 880, 2 850, 1 860, and 1 785 (C=O), 1 600, 1 465, 1 370, 1 335, 1 270, 1 130, 1 040, 1 005, 970, 905, and 870 cm^{-1}; *m/z* (%) 412.1163 (M^+, 100%) (Calc. for $C_{22}H_{20}O_8$: 412.1158) (Found: C, 64.2; H, 5.1. $C_{22}H_{20}O_8$ requires C, 64.06; H, 4.891%).

B. 6,7-*Methylenedioxy*-N-*phenyl*-1-(3,4,5-*trimethoxyphenyl*)-1,2,3,4-*tetrahydronaphthalene*-2,3-*dicarboximide* (**B**). This adduct was formed after 2 h at 210 °C; 85% yield after chromatography (light petroleum–ether, 1:1); m.p. 215 °C

Table 2. ^{1}H N.m.r. spectral data for cycloadducts (**A**)—(**I**) (see Table 1)*

Cyclo-adduct	1-H	2-H	3-H	4-H$_\alpha$	4-H$_\beta$	5-H	8-H	2'-H	6'-H	Methylene-dioxy H	4'-OCH$_3$	3'- and 5'-OCH$_3$	Other
(**A**)	4.3 (d, 5.5)	3.7 (dd, 5.5, 9.3)	3.6 (m)	3.09 (dd)	3.27 (dd) ($J_{3,4\alpha}$ 8.5, $J_{3,4\beta}$ 4.2, $J_{4\alpha,4\beta}$ 16.85)	6.75 (s)	6.62 (s)	6.5 (s)		5.91 (s)	3.85 (s)	3.8 (s)	
(**B**)	4.5 (d, 5)		3.2—3.6 (m)			6.8 (s)	6.67 (s)	6.43 (s)		5.95 (s)	3.82 (s)	3.66 (s)	6.8—7.4 (m, NPh)
(**C**)	4.13 (d, 10.5)		3.02—3.25 (m)			6.6 (s)	6.26 (s)	6.31 (s)		5.88 (m)	3.85 (s)	3.8 (s)	3.5 (s, 2-CO_2Me) 3.5 (s, 3-CO_2Me)
(**D**)	4.63 (d, 4.6)	3.43 (dd, 4.6, 6.8)	2.9—3.25 (m)			6.63 (s)	6.43 (s)	6.24 (s)		5.88 (m)	3.8 (s)	3.74 (s)	3.63 (s, 2-CO_2Me) 3.86 (s, 3-CO_2Me)
(**E1**)	3.9 (s)		3.18 (dd)	3.10 (dd)	3.40 (dd) ($J_{3,4\alpha}$ 9.8, $J_{3,4\beta}$ 3.2, $J_{4\alpha,4\beta}$ 15.9)	6.75 (s)	6.58 (s)	6.32 (s)		5.9 (s)	3.8 (s)	3.75 (s)	1.42 (s, 2-CH_3)
(**E2**)	4.15 (d, 4)	3.25 (d, 4)	2.6—3.04 (dd, $J_{4\alpha,4\beta}$ 15)			6.70 (s)	6.54 (s)	6.75 (s)		5.9 (s)	3.86 (s)	3.82 (s)	1.56 (s, 3-CH_3
(**F1**)			4.95 (m)	3.8—4.2 (m)		6.75 (s)	6.59 (s)	6.32 (s)		5.95 (s)		3.8—4.2 (s + m)	
(**F2**)				8.3 (s)		7.38 (s)	7.20 (s)	6.56 (s)		6.15 (s)	3.96 (s)	3.84 (s)	
(**G1**)	4.66 (s)		3.34 (s)	2.5—2.9 (dd, $J_{4\alpha,4\beta}$ 14)		6.66 (s)	6.34 (s)	6.28 (s)		5.9 (s)	3.86 (s)	3.78 (s)	3.5 (s, CH_2CO_2); 3.54, 3.66, and 3.68 (each s, 3 × CO_2CH_3)
(**G2**)	4.19 (d, 12)	3.1 (d, 12)		2.42—3.4 (dd, $J_{4\alpha,4\beta}$ 17)		6.54 (s)	6.26 (s)	6.26 (s)		5.84 (s)	3.78 (s)	3.74 (s)	3.2—3.38 (dd, CH_2CO_2); 3.44, 3.58 and 3.64 (each s, 3 × CO_2CH_3)
(**H**)	Not visible			8.32 (s)		7.15 (s)	6.88 (s)	6.58 (s)		6.0 (s)	3.9 (s)	3.8 (s)	1.05 and 1.4 (2 t, 7, 2 × CH_3); 4.0—4.6 (2 q, 7, 2 × CH_2)
(**I**)	4.65 (s)			3.4—4.06 (dd, 16)		6.76 (s)	6.55 (s)	6.4 (s)		5.98 (s)	3.88 (s)	3.8 (s)	

* The multiplicity and J values (in Hz) are given in parentheses. The data for the cycloadduct (**J**) are given in the Experimental section.

(white needles from benzene–light petroleum); $\nu_{max.}$ 3 060—2 880, 2 850, 1 785, and 1 715 (C=O), 1 600, 1 505, 1 490, 1 465, 1 425, 1 390, 1 335, 1 245, 1 130, 1 040, 1 010, 930, 880, 850, 810, 760, 730, and 695 cm^{-1}; *m/z* (%) 487.1637 (M^+, 100%) (Calc. for $C_{28}H_{25}NO_7$: 487.1631).

C. *Dimethyl* 6,7-*methylenedioxy*-r-1-(3,4,5-*trimethoxyphenyl*)-1,2,3,4-*tetrahydronaphthalene*-t-2,c-3-*dicarboxylate* (**C**). This compound was formed after 2.5 h at 210 °C; 98% yield after chromatography (light petroleum–ether, 4:1); m.p. 193 °C (from CH_2Cl_2–petroleum or from propan-2-ol–EtOH); $\nu_{max.}$ 3 060—2 880, 2 840, 1 740 (C=O), 1 595, 1 510, 1 490, 1 465, 1 435, 1 330, 1 230, 1 200, 1 170, 1 130, 1 040, 1 005, and 940 cm^{-1}; *m/z* (%) 458 (M^+, 70), 399 (9), 339 (100), 283 (15).

D. *Dimethyl* 6,7-*methylenedioxy*-r-1-(3,4,5-*trimethoxyphenyl*)-1,2,3,4-*tetrahydronaphthalene*-c-2,c-3-*dicarboxylate* (**D**). This compound was formed after 1 h at 210 °C; 90% after chromatography (light petroleum–EtOAc 4:1) with traces (6%) of the *t*-2,*t*-3-dicarboxylate isomer; m.p. 178 °C (from CH_2Cl_2–light petroleum); $\nu_{max.}$ 3 020—2 840, 1 740 (C=O), 1 595, 1 510, 1 490, 1 470, 1 380, 1 345, 1 230, 1 130, 1 040, 1 010, 940, 910, 870, 845, and 810 cm^{-1}; *m/z* (%) 458.1573 (M^+, 67) (Calc. for $C_{24}H_{26}O_9$: 458.1576).

E. 2-*Methyl*-6,7-*methylenedioxy*-1-(3,4,5-*trimethoxyphenyl*)-1,2,3,4-*tetrahydro*-2,3-*naphthoic anhydride* (**E1**). This *compound* was formed after 2 h at 205—210 °C in 90% total yield [including the adduct (**E2**), *vide infra*] after chromatography (light petroleum–ether, 1:1); m.p. 153 °C (from light petroleum–ether); $\nu_{max.}$ (solution in CH_2Cl_2) 2 900, 1 850, and 1 785 (C=O), 1 590, 1 505, 1 485, 1 460, 1 330, 1 230, 1 125, 1 040, 1 005, 960, 940, and 865 cm^{-1}; *m/z* (%) 426.1305 (M^+, 100) (Calc. for $C_{23}H_{22}O_8$: 426.1308) (Found: C, 65.0; H, 5.2. $C_{23}H_{22}O_8$ requires C, 64.77; H, 5.20%).

3-Methyl-6,7-methylenedioxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-2,3-naphthoic anhydride (**E2**). This compound was formed with (**E1**) in a ratio of 7:4 [(**E1**):(**E2**)], but could not be completely separated from it; the ^{1}H n.m.r. data in Table 2 were obtained by difference treatment.

F. 6,7-*Methylenedioxy*-1-(3,4,5-*trimethoxyphenyl*)-3,4-*dihydro*-2,3-*naphthoic anhydride* (**F1**). This compound was formed after 2 h at 205 °C; 55% yield after chromatography (ether–light petroleum, 2:1, R_F 0.32); m.p. of yellow crystals 198—200 °C (from ether–light petroleum); $\nu_{max.}$ (solution in CH_2Cl_2) 2 940—2 840, 1 850 and 1 775 (C=O), 1 590, 1 505, 1 485, 1 460, 1 325, 1 225, 1 130, 1 040, 940, 900, and 800 cm^{-1}; *m/z* (%) 410.1001 (M^+, 25) (Calc. for $C_{22}H_{18}O_8$: 410.0996).

6,7-*Methylenedioxy*-1-(3,4,5-*trimethoxyphenyl*)*naphthoic anhydride* (**F2**). This compound was formed with (**F1**); 36% yield after chromatography (ether–light petroleum 2:1, R_F 0.17); m.p.

of yellow crystals 275—277 °C (from CH_2Cl_2–light petroleum); $\nu_{max.}$(CH_2Cl_2) 2 950, 1 855 and 1 775 (C=O), 1 620, 1 510, 1 490, 1 470, 1 325, 1 225, 1 115, 1 040, 940, and 900 cm^{-1}; *m/z* (%) 408.0847 (M^+, 100) (Calc. for $C_{22}H_{16}O_8$: 408.0838).

G. *Dimethyl 2- and 3-methoxycarbonylmethyl-6,7-methylenedioxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate* (**16a**) *and* (**16b**). These compounds were formed after 2 h at 205 °C; (**16a**) (63%) and (**16b**) (21%) after chromatography (ether–light petroleum 4:1); R_F 0.2 and 0.28 respectively.

(**16a**), m.p. 165 °C (from ether); $\nu_{max.}$(CH_2Cl_2) 1 735 (C=O), 1 590, 1 505, 1 490, 1 460, 1 225, 1 125, 1 040, and 940 cm^{-1}; *m/z* (%) 530.1780 (M^+, 29) (Calc. for $C_{27}H_{30}O_{11}$: 530.1779).

(**16b**), m.p. 190 °C (from ether–light petroleum); $\nu_{max.}$(Nujol) 1 735 (C=O), 1 585, 1 240, 1 210, 1 160, 1 120, 1 025, 990, 910, and 860 cm^{-1}; *m/z* (%) 530.1786 (M^+, 100) (Calc. for $C_{27}H_{30}O_{11}$: 530.1779).

H. *Diethyl 1-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxynaphthalene-2,3-dicarboxylate* (**H**). This compound was formed after 2 h at 205 °C in 56% yield after chromatography; m.p. (from ether–light petroleum); $\nu_{max.}$(CH_2Cl_2) 1 720 (C=O), 1 580, 1 460, 1 235, 1 125, 1 040, and 945 cm^{-1} (Found: C, 64.8; H, 5.4. $C_{26}H_{26}O_6$ requires C, 64.71; H, 5.43%).

I. *2,3-Dichloro-6,7-methylenedioxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-2,3-naphthoic anhydride* (**I**). This compound was formed after 2 h at 205 °C in a yield of 46% after chromatography, as white crystals (ether–light petroleum), m.p. 196 °C; $\nu_{max.}$(CH_2Cl_2) 3 000—2 820, 1 875 and 1 810 (anhydride carbonyl), 1 595, 1 505, 1 485, 1 465, 1 420, 1 335, 1 240, 1 130, 1 040, 1 000, and 935 cm^{-1} (Found: C, 55.1; H, 3.9. $C_{22}H_{18}Cl_2O_8$ requires C, 54.996; H, 3.78%).

J. *1-(2-Methyl-4,5-methylenedioxyphenyl)-1-(3,4,5-trimethoxyphenyl)but-cis-2-ene-2,3-dicarboxylic anhydride* (**J**). This compound was formed after 3 h at 205 °C in 21% yield after chromatography; yellow crystals from ether, m.p. 160—162 °C; $\nu_{max.}$(CH_2Cl_2) 3 060—2 820, 1 835 and 1 770 (anhydride carbonyl), 1 590, 1 500, 1 480, 1 460, 1 420, 1 330, 1 240, 1 130, 1 040, 1 005, and 940 cm^{-1} (Found: C, 64.2: H, 5.6. $C_{23}H_{22}O_8$ requires C, 64.77; H, 5.20%); δ ($CDCl_3$; 60 MHz) 1.65 (3 H, s, 3-methyl), 2.2 (3 H, s, 2″-methyl), 3.75 (6 H, s, 3′- and 5′-OCH_3), 3.80 (3 H, s, 4′-OCH_3), 5.4 (1 H, s, 1-H), 5.9 (2 H, s, methylenedioxy), 6.3 (2 H, s, 2′- and 6′-H), 6.4 (1 H, s, 6″-H), and 6.7 (1 H, s, 3″-H).

Dimethyl 6,7-Dimethoxy-r-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-t-2,c-3-dicarboxylate (**17a**).—The sulphone (**13b**) [prepared by a simple adaption of the route to (**13a**)] (0.4 g, 1.09 mmol) and dimethyl fumarate (0.634 g, 4.4 mmol) were dispersed in di-n-butyl phthalate (2 ml), and the mixture was heated at 210 °C under argon for 3 h. After being cooled to a room temperature, the mixture was chromatographed using light petroleum–ethyl acetate (4:1) as eluant, to afford two products: the desired *t*-2,*c*-3-diester (**17a**) (0.33 g, 68%), and the *c*-2,*t*-3 diester (0.083 g, 17%) in the ratio *ca.* 4:1. The major product crystallised as white needles from CH_2Cl_2–light petroleum, m.p. 127 °C; $\nu_{max.}$ 3 070, 3 010, 2 980—2 900, 2 840, 1 740 (C=O), 1 610, 1 595, 1 520, 1 470, 1 440, 1 360, 1 240, 1 175, 1 155, 1 120, 1 030, 1 000, 910, 870, and 810 cm^{-1}; δ($CDCl_3$) 3.0—3.3 (12 line multiplet, 4 H, 2- and 3-H, 4-H_α and 4-H_β), 3.47 (3 H, s, ester OCH_3 at C-2), 3.58 (3 H, s, ester OCH_3 at C-3), 3.7 (3 H, s, 3′-OCH_3), 3.8 (3 H, s, 4′-OCH_3), 3.86 and 3.88 (6 H, 2 s, 6- and 7-OCH_3), 4.17 (1 H, d, *J* 11 Hz, 1-H), 6.24 (1 H, s, 8-H), and 6.57—6.8 (4 H, m, 5-H, 2′-, 5′-, and 6′-H); *m/z* (%) 444.1782 (M^+, 100) (Calc. for $C_{24}H_{28}O_8$: 444.1784).

r-1-(3,4-*Dimethoxyphenyl*)-t-2,c-3-*bis*(*hydroxymethyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydronaphthalene* (**17b**).—To a stirred suspension of $LiAlH_4$ (1 g) in dry THF (15 ml) was added dropwise a solution of the diester (**17a**) (0.22 g, 0.6 mmol) in the same solvent (25 ml). The mixture was stirred under reflux for 3 h, then treated with a few drops of 2M-NaOH, and the resultant granular precipitate was filtered off and discarded. The filtrate was concentrated to yield a white solid (0.178 g, 92%), giving white needles from light petroleum–ethyl acetate, m.p. 150—152 °C (lit. value,[3] m.p. 156 °C); $\nu_{max.}$ 3 690, 3 620, 3 060, 3 000—2 880, 1 515, 1 425, 1 260, 1 030, 900, 800, and 625br cm^{-1}; δ($CDCl_3$) 1.72—1.9 (1 H, m, 2-H), 1.95—2.15 (1 H, m, 3-H), 2.7—3.2 (4 H, m, 4-H and 2 × OH), 3.46 (2 H, dd, CH_2O at C-2), 3.59 (3 H, s, 4′-OCH_3), 3.68 (2 H, dd, CH_2O at C-3), 3.8, 3.82, and 3.88 (10 H, 3 s, 3′-, 6- and 7-OCH_3 and 1-H), 6.23 (1 H, s, 8-H), and 6.6—6.85 (4 H, m, 5-, 2′-, 5′-, and 6′-H); *m/z* (%) 388.1879 (M^+, 100) (Calc. for $C_{22}H_{28}O_6$: 388.1885).

(±)-*Phyltetralin* (**2**).—To a flask containing sodium hydride (50%, 0.048 g, 1 mmol) twice washed with light petroleum, and kept under nitrogen, was added a solution of the diol (**17b**) (0.1 g, 0.258 mmol) in dry DMSO (10 ml). To this was then added methyl iodide (0.5 ml), and the mixture was stirred at 60 °C for 5 h. Aqueous work-up and ether extraction afforded an oil, which after column chromatography (light petroleum–ethyl acetate, 1:1 as eluant) yielded a colourless oil which crystallised on standing. The product was recrystallised from light petroleum–ether to yield a white crystalline solid (86 mg, 81%), m.p. 94 °C (lit. value,[3] m.p. 97—98 °C), which co-chromatographed with an authentic sample of phyltetralin in three solvent systems: light petroleum–ethyl acetate (1:1); ether–CCl_4 (9:1); and benzene–ethyl acetate (9:1). In addition, the spectral data given below were identical with those obtained from an authentic sample: $\nu_{max.}$ 1 610, 1 595, 1 515, 1 465, 1 235, 1 220, 1 110, 1 030, 910, 810, and 650; δ($CDCl_3$) 1.6—2.0 (1 H, m, 2-H), 2.0—2.3 (1 H, m, 3-H), 2.85 (2 H, d, 4-H), 3.1 and 3.35 (2 H, dd and m, CH_2O at C-3), 3.46 (2 H, br d, CH_2O at C-2), 3.25 and 3.34 (2 × s, 6 H, CH_2OCH_3), 3.57 (3 H, s, 7-OCH_3), 3.8, 3.82, and 3.87 (9 H, 3 × s, other aryl OCH_3), 4.0 (1 H, d, *J* 10 Hz, 1-H), 6.24 (1 H, s, 8-H), and 6.6—6.88 (4 H, m, 5-, 2′-, 5′-, and 6′-H).

5,6-*Methylenedioxy-1-(3,4-methylenedioxyphenyl)-1,3-dihydrobenzo*[c]*thiophene* 2,2-*Dioxide* (**13c**).—This compound was prepared in an exactly analogous fashion to that described for the sulphone (**13a**). After recrystallisation from ether, yellow crystals were obtained, m.p. 165 °C; $\nu_{max.}$(CH_2Cl_2) 2 900, 1 505, 1 480, 1 320, 1 240, 1 130, 1 040, 940, and 910 cm^{-1}; δ ($CDCl_3$; 60 MHz) 4.3 (2 H, s, CH_2SO_2), 5.3 (1 H, s, $CHSO_2$), 5.98 (4 H, s, 2 × methylenedioxy H), 6.5 (1 H, s, 7-H), 6.6 (1 H, s, 4-H), 6.8 (3 H, s, 2′-, 5′-, and 6′-H).

Products from the Cycloaddition between Compound (**13c**) *and 2-Bromomaleic Anhydride: 6,7-Methylenedioxy-1-(3,4-methylenedioxyphenyl)naphthalene-2,3-dicarboxylic Anhydride* (**9b**) *and 6,7-Methylenedioxy-1-(3,4-methylenedioxyphenyl)-3,4-dihydronaphthalene-2,3-dicarboxylic Anhydride* (**18**).—The minor *product* (**18**) was obtained as yellow crystals (from ether) (isolated yield 32%), m.p. 218 °C; $\nu_{max.}$(CH_2Cl_2) 1 855, 1 775 (anhydride C=O), 1 505, 1 490, 1 230, 1 040, 940, and 900 cm^{-1}; δ ($CDCl_3$; 100 MHz) 3.85 (2 H, d, 4-H), 4.95 (1 H, t, *J* 5 Hz, 3-H), 5.92 (4 H, split s, 2 × methylenedioxy H), 6.54—6.58 (2 H, 2 × s, 5′- and 6′-H), 6.72 (1 H, s, 2′-H), 6.74 (1 H, s, 8-H), and 6.76 (1 H, s, 5-H) (Found: C, 65.6; H, 3.4. $C_{20}H_{12}O_7$ requires C, 65.92; H, 3.32%).

The major *product* (**9b**) was obtained in an isolated yield of 51% as yellow crystals from dichloromethane–light petroleum, m.p. 226—228 °C; $\nu_{max.}$(CH_2Cl_2) 1 840 and 1 780 (anhydride C=O), 1 505, 1 470, 1 240, 1 220, 1 040, 955, and 675 cm^{-1}; δ (CD_2Cl_2; 100 MHz) 6.10 and 6.16 (2 × 2 H, 2 × s, 2 × methylenedioxy H), 6.8—7.06 (3 H, m, 2′-, 5′-, and 6′-H), 7.22 (1 H, s, 8-H), 7.40 (1 H, s, 5-H), and 8.30 (1 H, s, 4-H) (Found: C, 66.2; H, 2.9. $C_{20}H_{10}O_7$ requires C, 66.29; H, 2.78%).

Regioselective Reduction of a Mixture of 2-Methyl- and 3-Methyl-6,7-methylenedioxy-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylic Anhydrides to produce the Lactones (**20a**) *and* (**20b**).—The cycloadducts produced from the cycloaddition between the sulphone (**13a**) and 2-methylmaleic anhydride (entry E, Table 1) (0.8 g, 1.9 mmol) was stirred in isopropyl alcohol (200 ml) at room temperature, and treated with $NaBH_4$ (0.15 g, 3.9 mmol) to produce a clear solution. This was stirred overnight at room temperature, and then for a further 2 days; the solvent was removed under reduced pressure, and HCl (2M; 2—3 ml) was then added to the residue to produce a yellow solution. Upon addition of more HCl (20 ml; 2M), a sticky yellow solid was obtained, and hydrolysis was completed by gentle heating on a steam-bath for about 5 min. The product was finally extracted into dichloromethane. T.l.c. analysis using ether–light petroleum (9:1) as eluant indicated the presence of two products (plus traces of other products) at R_F 0.5 and 0.4. Flash chromatography using ether–CCl_4 (4:1) as eluant led to the obtention of the two products in pure form. t-9a-*Methyl*-6,7-*methylenedioxy*-r-9-(3,4,5-*trimethoxyphenyl*)-3a,4,8a,9-*tetrahydronaphtho*[2,3-c]*furan*-1(3H)-*one* (**20a**)* (0.3 g, 29%), R_F 0.3 (ether–CCl_4, 4:1 as eluant) (recrystallised from ether–light petroleum); $\nu_{max.}$(CH_2Cl_2) 2 820—3 000, 1 770 (lactone C=O), 1 590, 1 505, 1 485, 1 460, 1 420, 1 330, 1 240, 1 130, 1 040, and 940 cm^{-1}; δ ($CDCl_3$; 220 MHz) 1.3 (3 H, s, methyl), 2.75 (1 H, m, 3-H), 3.0—3.2 (2 H, m, 2 × 4-H), 3.75 (1 H, s, 1-H), 3.85 (6 H, s, 3′- and 5′-OCH_3), 3.92 (3 H, s, 4′-OCH_3), 4.0—4.2 (2 H, dd, $J_{11\alpha,11\beta}$ 9 Hz, 11_α- and 11_β-H), 5.95 (2 H, s, methylenedioxy H), 6.35 (2 H, s, 6′- and 2′-H), 6.5 (1 H, s, 8-H), and 6.8 (1 H, s, 5-H); on expansion 4_α-, 4_β-, and 3-H showed an ABX pattern of 12 lines with $J_{4\alpha,4\beta}$ 17 Hz, $J_{4\alpha,3}$ 3 Hz, and $J_{4\beta,3}$ 9 Hz (Found: C, 67.0; H, 6.0. $C_{23}H_{24}O_7$ requires C, 66.97; H, 5.87%).

The t-3a-*methyl isomer* (**20b**)* (yield 0.52, 7%), had R_F 0.32 (ether–CCl_4 4:1 as eluant); small colourless crystals from ether–light petroleum, m.p. 195 °C; $\nu_{max.}$(CH_2Cl_2) 2 840—2 950, 1 770 (lactone C=O), 1 590, 1 505, 1 485, 1 460, 1 330, 1 240, 1 130, and 1 040 cm^{-1}; δ ($CDCl_3$; 220 MHz) 1.32 (3 H, s, methyl), 2.6—2.9 (2 H, dd, 4_α- and 4_β-H), 2.8 (1 H, d, 2-H), 3.7—4.1 (2 H, dd, 11_α- and 11_β-H), 3.8 (6 H, s, 3′- and 5′-OCH_3), 3.9 (3 H, s, 4′-OCH_3), 4.4 (1 H, d, 1-H), 6.0 (2 H, s, methylenedioxy H), 6.65 (2 H, s, 2′- and 6′-H), 6.7 (1 H, s, 8-H), and 6.8 (1 H, s, 5-H); on careful analysis the coupling constants were identified: $J_{4\alpha,4\beta}$ 17 Hz, $J_{11\alpha,11\beta}$ 8.8 Hz, and $J_{1,2}$ 4 Hz (Found: C, 66.85; H, 6.00. $C_{23}H_{24}O_7$ requires C, 66.97; H, 5.87%).

Reduction of the Cycloadduct obtained from Maleic Anhydride and the Sulphone (**13a**): *Formation of 4-Deoxyisopicrophyllotoxin* (**1**).—The maleic anhydride cycloadduct (see entry A in Table 1) (1.01 g, 2.6 mmol) was dissolved in dry THF (70 ml) and treated with K-selectride (1M solution THF; 3.9 ml) at −78 °C under nitrogen. The reaction mixture was stirred at −78 °C for 5 h, then treated with water (2 ml), and allowed to warm to room temperature. It was then oxidised with a mixture of NaOH (2M; 0.03 mol, 15 ml) and H_2O_2 solution (8 ml, 30%) at room temperature with continuous stirring for 16 h. The mixture was then acidified with HCl (6M; 8 ml), and again stirring was continued for about 3 h. The organic layer was then separated, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and treated with toluene-*p*-sulphonic acid (few crystals). After standing overnight at room temperature, the solution was concentrated and the product isolated by flash chromatography using ether–light petroleum (4:1) as eluant, giving white crystals (0.5 g, 57%); m.p. 207 °C (lit.,[20] 204 °C); $\nu_{max.}$(CH_2Cl_2) 2 800—3 000, 1 765 (lactone C=O), 1 590, 1 500, 1 480, 1 460, 1 380, 1 240, 1 120, 1 040, and 1 000 cm^{-1}; δ ($CDCl_3$; 100 MHz) 2.70—2.95 (2 H, m, 2- and 3-H), 3.15 (2 H, m, 4_α- and 4_β-H), 3.50 (1 H, m, 11_β-H), 3.76 (6 H, s, 3′- and 5′-OCH_3), 3.82 (3 H, s, 4′-OCH_3), 4.40 (2 H, m, 1- and 11_α-H), 5.94 (2 H, s, methylenedioxy H), 6.52 (2 H, s, 2′- and 6′-H), 6.65 (1 H, s, 8-H), and 6.74 (1 H, s, 5-H) (Found: C, 66.25: H, 5.6. $C_{22}H_{22}O_7$ requires C, 66.31; H, 5.57%).

* The numbering scheme corresponding to the starting dicarboxylic acids, rather than that used for the systematic names, is employed in the n.m.r. assignments of the lactones (**20a**) and (**20b**), for ease of comparison with compounds described earlier.

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