A Short Versatile Synthesis of Aryltetralin Lignans including Deoxyisopodophyllotoxin and Epi-isopodophyllotoxin

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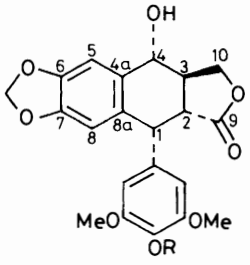
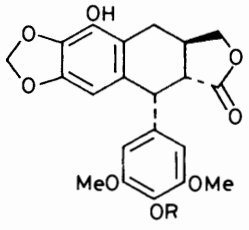
Cyclisation of tandem conjugate addition products (**10**), (**15**), and (**20**), prepared by reaction of anions derived from benzyl phenyl and benzyl t-butyl sulphides with but-2-en-4-olide, affords a series of aryltetralin lignans belonging to either the 'normal' or the 'retro' lactone series. Desulphurisation of compound (**15**) followed by cyclisation, or desulphurisation of the cyclised product (**22b**), affords deoxyisopodophyllotoxin (**5**), while treatment of compound (**22b**) with mercury(II) trifluoroacetate yields epi-isopodophyllotoxin (**6**).

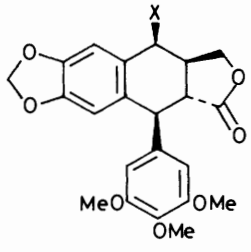
Lignans display a wide range of physiological activities.[1] Many for example have been shown to be of interest as cytotoxic agents. Podophyllotoxin (**1**), its demethyl derivative (**2**), and α- and β-peltatin, (**3**) and (**4**), show powerful and specific cytotoxic activity,[2,3] and the podophyllotoxin-based compounds etoposide (VP-16) and teniposide (VM-26) are in clinical use against small cell lung cancer and testicular cancer.[4,5] In addition, extracts containing compounds (**1**)—(**4**) have been widely used for the treatment of genital warts.[6,7] In continuation of our earlier studies on the synthesis of lignan lactones *via* conjugate addition reactions,[8,9] we have now prepared a number of aryltetralin lactones, of both the 'normal' and 'retro' series, including deoxyisopodophyllotoxin (**5**) and epi-isopodophyllotoxin (**6**).[10]



(**1**) R = Me
(**2**) R = H

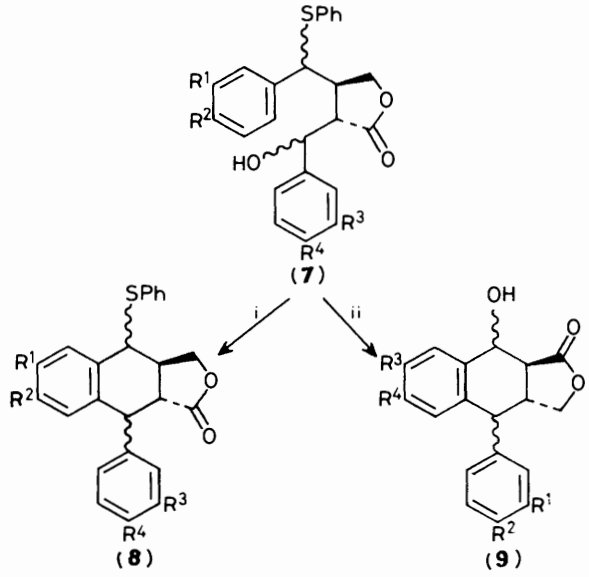


(**3**) R = H
(**4**) R = Me



(**5**) X = H
(**6**) X = OH

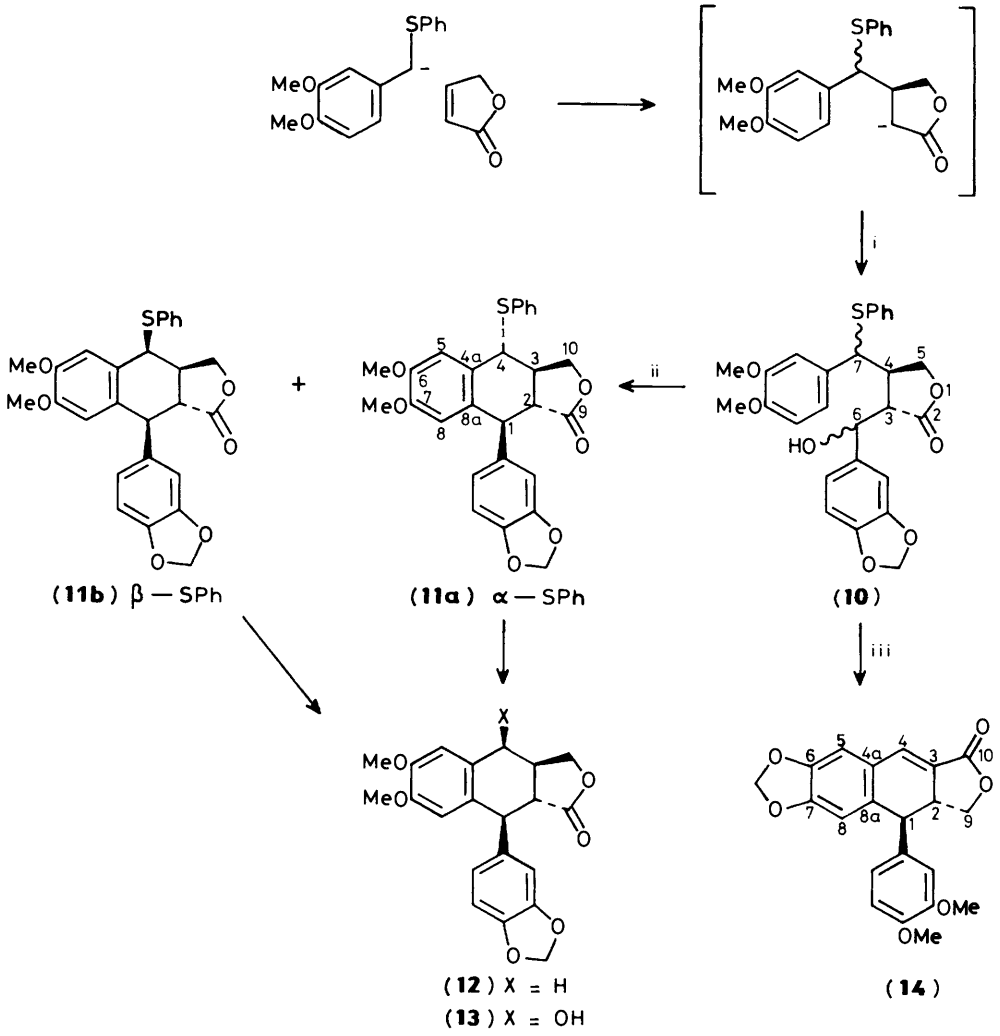
The preceding paper[9] described the results of several cyclisation reactions of bis(phenylthio)dibenzyl-γ-butyrolactone derivatives. In almost every case, attempted cyclisation resulted in preferential attack on, and subsequent cleavage of, the carbon–sulphur bonds of the bis(phenylthio) group. In an effort to reduce the ease with which the phenylthio group was lost we decided to prepare the corresponding adducts containing only one phenylthio group. Thus, treatment of the monophenylthio derivative (**7**) under either acid or alkylating conditions should yield the phenylthio-substituted aryltetralin lactone (**8**) or the 'retro' lactone (**9**) respectively (Scheme 1).



Scheme 1. *Reagents:* i, H^+; ii, Me^+

The monophenylthio adducts (**10**) were obtained in quantitative yield by treating the carbanion derived from 3,4-dimethoxybenzyl phenyl sulphide with but-2-en-4-olide, followed by piperonal (Scheme 2). Analysis of the product by n.m.r. spectroscopy and h.p.l.c. indicated that the four stereoisomers corresponding to the *erythro* and *threo* isomers at C-6 and C-7 had been produced in approximately equal proportions.

Treatment of the dibenzylbutyrolactones (**10**) with excess of trifluoroacetic acid (TFA) yielded the epimeric aryltetralins (**11a**) and (**11b**) (61 and 16% respectively) which could be separated by repeat injection h.p.l.c. and were identified on the basis of their i.r., mass, and n.m.r. spectra (Tables 1 and 2). In the i.r. spectra both isomers showed an absorption at 1 780 cm^{-1} due to the lactone group, and the mass spectra of the two isomers were also very similar, both showing a molecular ion at *m/z* 476 and a large M − SPh ion at *m/z* 367 (100%). Analysis of the 360 MHz ^1H n.m.r. spectra of both isomers (Table 1),



Scheme 2. *reagents:* i, ArCHO; ii, TFA; iii, Me_3O^+ BF_4^-. N.m.r. numbering schemes are shown

including a 2D scalar correlation (COSY) experiment on (**11a**) in C_6D_6 (Figure 1), enabled their relative configurations to be established. Thus the 11 Hz coupling between 3-H and 4-H and also between 1-H and 2-H in (**11a**) indicates that these pairs of protons have an axial–axial configuration. In contrast the same coupling constants in isomer (**11b**) are 3.7 and 10.5 Hz, indicating that in this case 3-H and 4-H have an axial–equatorial relationship. The large coupling constant (14 Hz) between 2-H and 3-H in both isomers indicates that these protons are *trans* and diaxial to one another and confirms that the dibenzylbutyrolactone (**10**) has the *trans* configuration. Further confirmation of the relationship between (**11a**) and (**11b**) was provided by Raney nickel reduction which gave the same product (**12**)[11] in each case, confirming that they are indeed isomeric only at C-4. Treatment of (**11a**) with mercury(II) oxide and boron trifluoride–diethyl ether, followed by aqueous work-up, gave the benzylic alcohol (**13**), whose structure was assigned on the basis of the similarity of its ^1H n.m.r. spectrum to that of epi-isopodophyllotoxin (**6**).[12]

Treatment of the dibenzylbutyrolactone (**10**) with an excess of trimethyloxonium tetrafluoroborate gave the 'retro' dehydroaryltetralin lactone (**14**)[9] (40%), by selective attack on sulphur, followed by dehydration. Thus, our initial objective (Scheme 1) had been achieved since cyclisation of compound (**10**) could be induced by selective displacement of either the benzylic alcohol or the benzylic phenylthio group, leading to products (**11**) and (**14**) respectively. This therefore constitutes a very versatile route to these compounds and indeed provides an extremely short synthesis of lignans belonging to either the normal or the retro-lactone series. We therefore turned our attention to the use of this methodology for the synthesis of compounds belonging to the clinically important podophyllotoxin series.

The required conjugate addition product (**15**) was obtained in 40% yield as a mixture of four stereoisomers, corresponding to *erythro* and *threo* isomers at C-6 and C-7. Desulphurisation of compound (**15**) with Raney nickel gave a mixture of the *erythro* and *threo* benzyl alcohols (**16**)[13] (60% yield, 1:1) which on treatment with TFA gave deoxyisopodophyllotoxin (**5**)[14] (100%), identified by comparison with an authentic sample.* However, when compound (**15**) was treated directly with TFA using the same conditions as employed in the successful cyclisation of compound (**10**) only unchanged starting material was recovered. A series of reactions was therefore carried out using steadily increasing concentrations of TFA. The reactions were closely monitored by t.l.c. and quenched after disappearance of the starting material. Purification by column chromatography of the mixture obtained using *ca.* 50% TFA in

* Sample provided by Prof. E. Brown, University of Le Mans.

Table 1. ^{1}H N.m.r. spectra of 'normal' aryltetralin lactones[a]

Proton(s)	(11a)[b,c]	(11b)[b]	(12)	(13)	(5)
1-H	3.84d (11)[d]	4.03d (10.5)	4.4—4.6m	3.90d (12)	3.95m
2-H	2.16dd (11, 14)	3.26dd (10.5, 13.7)	2.4—2.8m	3.20dd (12, 14)	2.60m
3-H	2.43ddt (14, 7, 11)	3.03m		2.60m	
4-H	3.99d (11)	4.72d (3.7)	2.8—3.0br d (6)	4.75d (3)	3.00d (6)
5-H	7.72s	6.60s	6.60s	6.76s	6.60s
8-H	6.44s	6.30s	6.30s	6.40s	6.35s
10-H_2	3.42dd (11, 9) 4.24dd (7, 9)	4.26m	3.95—4.15m	4.35m	3.95m 4.50m
OMe	3.26s 3.62s	3.60s 3.70s	3.60s 3.85s	3.60s 3.80s	3.82s 3.85s
OCH_2O	5.40s 5.44s	5.90s	5.90s	5.90s	5.89s
OH				4.40 br	

Proton(s)	(6)	(19)	(22a)[b]	(22b)[b]
1-H	4.00d (11)	4.00m	3.96d (10.5)	4.08d (11)
2-H	3.28dd (12, 15)	2.70m	3.00dd (10.5, 14)	2.68dd (11, 13)
3-H	2.6—2.8m		2.92m (14, 6.5, 10, 4)	2.62m (13, 6, 10.5, 11)
4-H	4.92d (3)	4.50m	4.06d (4)	3.90d (11)
5-H	6.76s	7.60s	6.75s	7.44s
8-H	6.40s	6.40s	6.30s	6.30s
10-H_2	4.36dd (4, 10) 4.54dd (2, 10)	3.80m 4.50m	4.36dd (8.5, 6.5) 4.44dd (8.5, 10)	4.04dd (8.5, 10.5) 4.70dd (8.5, 6)
OMe	3.82s 3.86s	3.84s 3.90s	3.82s 3.85s	3.82s 3.86s
OCH_2O	5.93s	6.00s	5.88s 5.92s	5.88s 5.92s
OH	1.80s			

[a] All spectra recorded in $CDCl_3$ solution at 100 MHz unless otherwise indicated. N.m.r. numbering schemes are shown in the structures and schemes. [b] 360 MHz spectra. [c] Run in C_6D_6. [d] *J*-Values/Hz in parentheses.

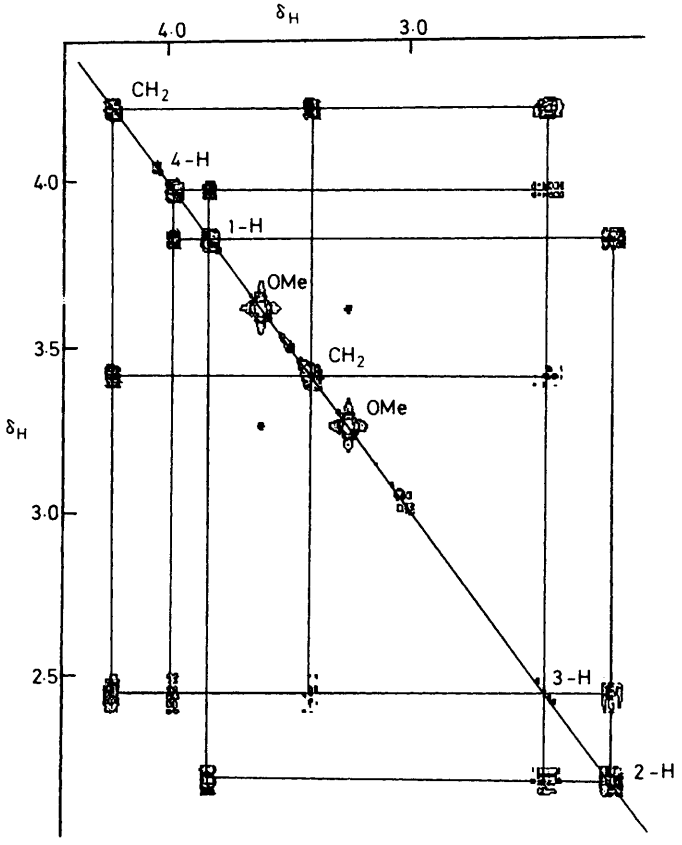


Figure 1. 2D COSY ^{1}H n.m.r. spectrum of compound (**11a**) in C_6D_6. See Scheme 2 for n.m.r. numbering scheme

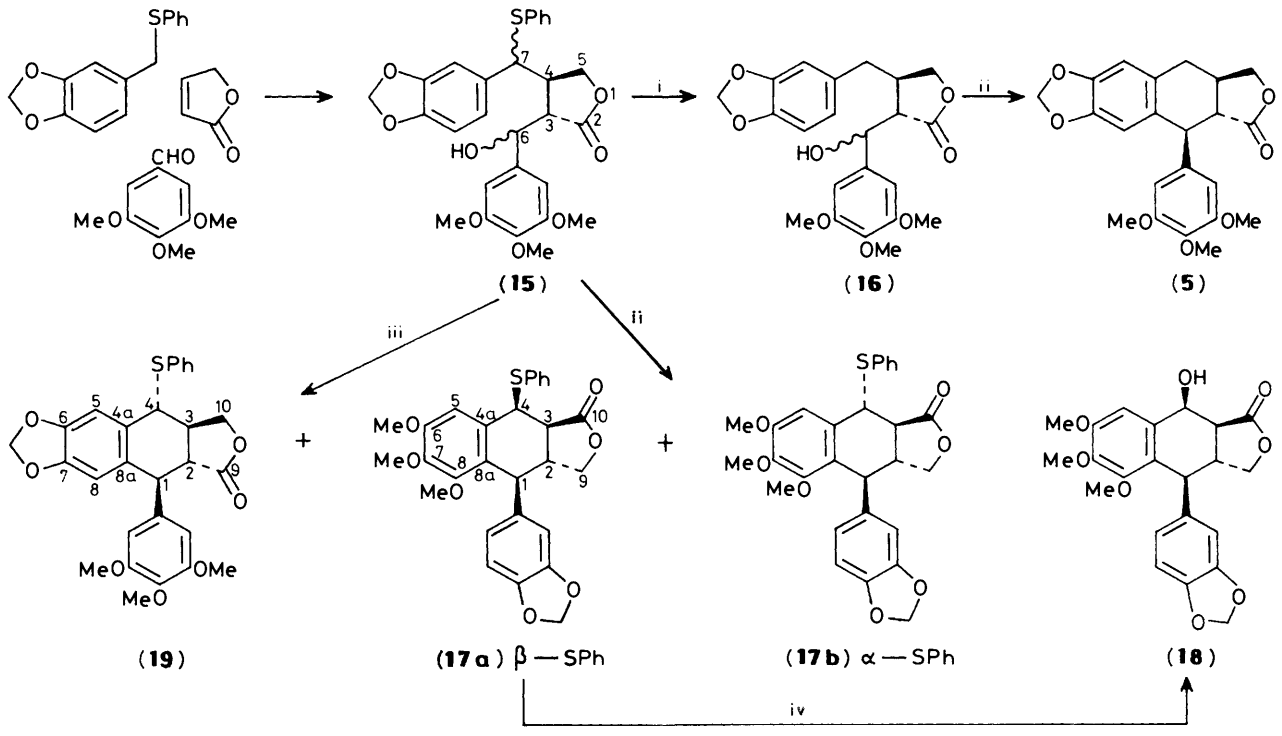
Table 2. ^{13}C N.m.r. spectra of 'normal' aryltetralin lactones ($CDCl_3$)[a]

Carbon	(11a)	(11b)	(12)	(13)	(22a)
1	48.23	45.62	48.91	45.89	43.81
2	45.35	44.49	45.79	44.90	43.69
3	46.13	43.14	40.04	41.18	42.99
4	51.26	48.72	32.57	66.49	46.02
5	108.93	109.33	108.06	108.12	108.08
6	147.63	147.85	147.84	149.57	147.28
7	147.54	146.60	147.75	148.12	146.96
8	111.12	112.40	111.50	112.15	109.53
8a	132.51	131.90	121.32	132.30	132.27
4a	128.63	127.61	126.90	130.23	131.83
10	70.08	68.82	71.04	67.40	69.37
1′	136.12	136.99	136.99	136.56	136.97
2′	112.63	112.54	113.00	112.81	106.48
3′	148.10	149.15	147.75	147.82	153.17
4′	146.33	147.85	146.45	146.57	139.28
5′	107.91	108.14	109.25	109.25	153.17
6′	122.80	123.06	123.00	123.05	106.48
OCH_2O	100.83	100.02	100.98	101.02	101.31
OMe	55.68 55.84	55.84	55.89	55.87 56.01	56.18 60.79
CO		175.47	175.62	176.22	175.56
SPh	174.21 129.04 128.02	135.21 131.18 129.48 127.51			
SBu^t					31.76 45.07

[a] N.m.r. numbering schemes are shown in Schemes 2 and 4.

CH_2Cl_2 yielded two products which were identified on the basis of their mass and n.m.r. spectra as the 'retro' lactones (**17a**) and (**17b**) (58 and 8% respectively; Scheme 3).

The most striking feature of the ^{1}H n.m.r. spectra (Table 3) of



Scheme 3. *Reagent:* i, Raney nickel; ii, TFA; iii, $HClO_4$; iv, Hg^{2+}. N.m.r. numbering schemes are shown

compounds (**17a**) and (**17b**) was the appearance of one methoxy group resonance at δ_H *ca.* 3.15 which is characteristic of a methoxy group at C-8 in such compounds.[13,15] It is assumed that compounds (**17a**) and (**17b**) are produced by cyclisation with displacement of the phenylthio group followed by dehydration and attack by thiophenol. The difference in the mode of cyclisation of the dibenzylbutyrolactones (**10**) and (**15**) can be attributed to the poor stabilisation afforded to an adjacent carbocation by the 3,4,5-trimethoxyphenyl group,[9,16-17] as compared with the stabilisation afforded by 3,4-dimethoxy- or 3,4-methylenedioxy-phenyl groups. Treatment of compound (**17a**) with mercury(II) trifluoroacetate followed by aqueous work-up afforded a 62% yield of the benzylic alcohol (**18**).

Treatment of compound (**15**) with perchloric acid produced, in addition to compounds (**17a**) and (**17b**), a low yield (21%) of the desired aryltetralin lactone (**19**), which did not contain a peak at δ_H *ca.* 3.15 in the ^1H n.m.r. spectrum. The mass spectrum of compound (**19**) showed a molecular ion at *m/z* 506 and a prominent fragment ion at *m/z* 397 (100%) corresponding to *M* − SPh. The ^1H n.m.r. spectrum confirmed the orientation of the lactone group and, by comparison with other compounds (see later), can be assigned the configuration shown.

In an attempt to reduce further the leaving-group ability of the sulphide group we decided to replace the SPh group by an SBu^t group. The dibenzyl-γ-butyrolactone (**20**) was therefore prepared in the usual way and, on treatment with TFA, gave two products which were identified as the 'retro' lactone (**21**) (46%) and the desired aryltetralin lactone as the 4β epimer (**22a**) (18%) (Scheme 4). Following our previous observation that perchloric acid enhanced the production of compound (**19**) from (**15**), treatment of compound (**20**) with perchloric acid instead of TFA gave the 'retro' lactone (**21**) (43%) and the desired isomeric lactone (**22b**) (47%). It is particularly interesting to note that under these conditions the desired cyclisation occurs in improved yield, and also the lactone is produced only as the C-4α epimer (**22b**). The two C-4 epimers can be easily distinguished on the basis of their ^1H n.m.r. spectra (*cf.* Tables 1 and 3). Thus compounds having the sulphide group at C-4α show 5-H at much lower field [δ 7.72 in (**11a**), 7.45 in (**17b**), 7.60 in (**19**), and 7.44 in (**22b**)] than in their C-4β epimers. This effect is presumably due to the proximity of the SR group to 5-H in the α isomers (see Figure 2).

Desulphurisation of compound (**22b**) with Raney nickel gave a quantitative yield of deoxyisopodophyllotoxin (**5**), identical with the sample prepared by cyclisation of compound (**16**), while treatment of compound (**22b**) with mercury(II) trifluoroacetate gave a 60% yield of epi-isopodophyllotoxin (**6**), identified by comparison of its spectral data with those published in the literature.[12,18]

Experimental

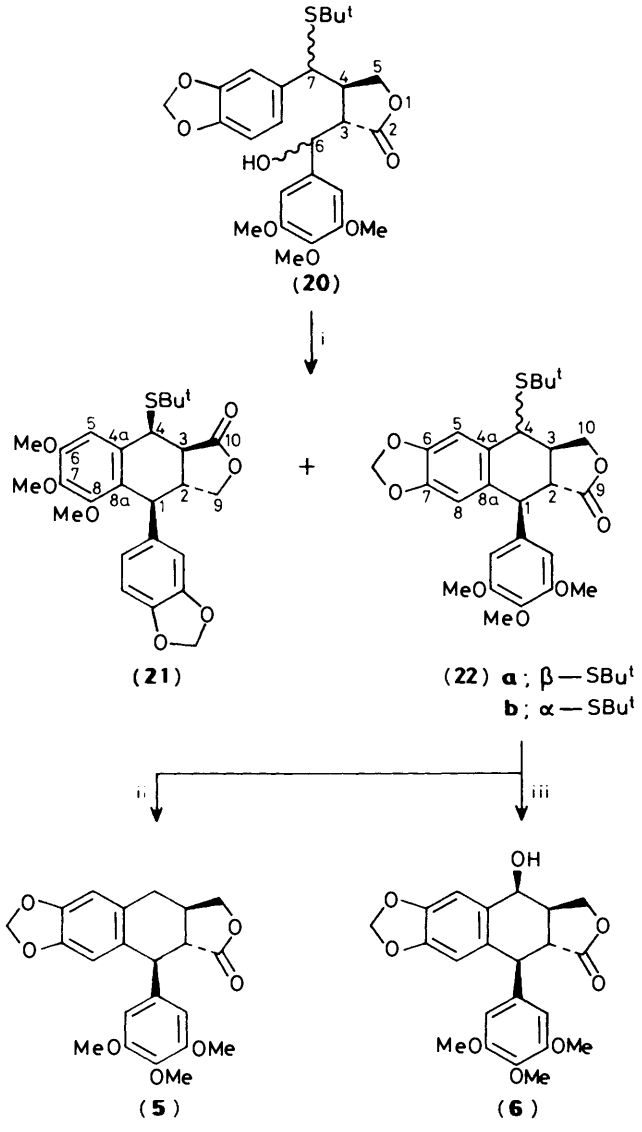
I.r. and u.v. spectra were recorded on Pye Unicam SP1050 and Perkin-Elmer 402 spectrometers, respectively. ^1H N.m.r. spectra were recorded on an Hitachi Perkin-Elmer R24B spectrometer at 60 MHz and either a Varian HA-100 or a Varian XL-100 instrument at 100 MHz. High-field ^1H n.m.r. spectra were recorded on a Bruker WH-360 spectrometer at 360 MHz. ^{13}C N.m.r. spectra were obtained from the Varian XL-100 spectrometer. Mass spectra were recorded on an AEI MS-9 double-focussing instrument operating at 250 °C and 70 eV. M.p.s were recorded on a Gallenkamp Hot Stage instrument and are uncorrected. T.l.c. was carried out on Chemlab Polygram silica gel UV_{254} fluorescent plates. Column chromatography was performed with silica gel (Merck, Kieselgel 60, 230—400 mesh). Analytical h.p.l.c. was carried out on an LDC gradient elution instrument linked to an LCD CI-10 integrator using a Hypersil 5μ column. Preparative h.p.l.c. separations were performed on a Jones Chromatography repeat injection instrument in conjunction with an Altex 110 pump and a Cecil CE-212 u.v. detector.

Reactions carried out under nitrogen refer to 'white spot' nitrogen used directly from the cylinder. Tetrahydrofuran

Table 3. ^{1}H N.m.r. spectra of 'retro' aryltetralin lactones[a]

Proton(s)	(14)	(17a)	(17b)[b]	(18)	(21)
1-H	3.85m	3.94d(10.7)[c]	3.74d (10.5)	3.80m	3.9—4.1m
2-H	3.60ddd (3, 8, 16)	3.01ddt (7.0, 14.1, 10.7)	2.41ddt (6.4, 14.0, 10.4)	3.10m	2.6—2.9m
3-H		2.83dd (3.7, 14.1)	2.32dd (11.0, 14.0)	2.50dd (3, 14)	
4-H	7.45d (3)	4.59d (3.7)	4.47d (11.0)	5.10d (3)	4.30m
5-H	6.90s	6.22s	7.45s	6.70s	6.70s
8-H	6.30s				
9-H_2	3.85m, 4.45t (8)	4.05dd (10.7, 8.5), 4.39dd (7.0, 8.5)	3.88dd (10.4, 8.7), 4.08dd (6.4, 8.7)	4.1—4.3m	3.9—4.1m, 4.30m
OMe	3.95br s	3.72s, 3.66s, 3.17s	3.90s, 3.76s, 3.15s	3.85s, 3.75s, 3.20s	3.80s, 3.70s, 3.10s
OCH_2O	6.00br s	5.93s	5.90s	5.90s	5.90s
OH				2.60br s	

[a] All spectra recorded in $CDCl_3$ solution at 100 MHz unless otherwise indicated. N.m.r. numbering schemes are shown in Schemes 2—4. [b] 360 MHz spectra. [c] Figures in parentheses are the coupling constants.



Scheme 4. *Reagents:* i, H^+; ii, Raney nickel; iii, $Hg(OCOCF_3)_2$. N.m.r. numbering schemes are shown

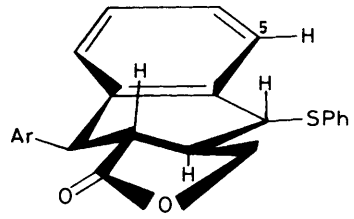


Figure 2.

(THF) was dried by passage down a dry alumina column, then stirring with calcium hydride overnight at room temperature. It was kept over calcium hydride under argon and distilled when needed. Dichloromethane was purified by passage through an alumina column and distillation over calcium hydride. Dry toluene was prepared by distillation from sodium and stored over sodium wire. Ethanol or methanol was purified by refluxing over magnesium turnings and iodine followed by distillation. Raney nickel[19] and but-2-en-4-olide[20] were prepared according to the methods described in the literature.

Preparation of 3,4-*Dimethoxybenzyl Phenyl Sulphide.*—A solution of 3,4-dimethoxybenzyl alcohol (33.5 g, 0.20 mol) in dry toluene (250 ml) was chilled in an ice-bath and saturated with dry HCl gas. The resulting red mixture was then kept at −5 °C overnight. An equal volume of ice–water was then added, the toluene layer was separated, and the aqueous layer was extracted with toluene. The organic layers were combined, dried ($MgSO_4$), and concentrated to give a brown gum. The gum was repeatedly extracted with dry, boiling light petroleum (b.p. 60—80 °C) and the extract was evaporated to give 3,4-dimethoxybenzyl chloride (31.9 g, 86%), $\nu_{max.}$(film) 820 cm^{-1} (C–Cl); δ_H(60 MHz; $CDCl_3$) 3.80 (6 H, s, 2 × OMe), 4.50 (2 H, s, ArCH_2), and 6.80 (3 H, m).

Sodium (3.09 g, 134 mmol) was added to dry MeOH (50 ml) and after dissolution PhSH (13.8 ml, 135 mmol) was added and the mixture was stirred at room temperature for 30 min. After this time 3,4-dimethoxybenzyl chloride (25 g, 0.23 mmol) was added dropwise whereupon a white precipitate (NaCl) appeared. The suspension was stirred at room temperature for 2 h after which time water was added and the solution was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$) and evaporated to give 3,4-*dimethoxybenzyl phenyl sulphide* as a white solid (32 g, 92%), m.p. 74—76 °C; δ_H (60 MHz; $CDCl_3$) 3.8

(6 H, d, 2 × OMe), 4.0 (2 H, s, ArCH_2), 6.7 (3 H, ArH), and 7.2 (5 H, br s, PhS); *m/z* 260 (M^+, 6%) and 151 (M − SPh, 100%) (Found: C, 69.3; H, 6.4. $C_{15}H_{16}O_2S$ requires C, 69.20; H, 6.19%).

Preparation of 3-(3″,4″-*Dimethoxy*-α-*phenylthiobenzyl*)-2-(α-*hydroxy*-3′,4′-*methylenedioxybenzyl*)-γ-*butyrolactone* (**10**).—3,4-Dimethoxybenzyl phenyl sulphide (1.25 g, 4.8 mmol) was dissolved in dry THF (20 ml) under argon and the solution was cooled to −78 °C. BuLi (1.92 ml of 2.5M, 4.8 mmol) was added and the resulting orange solution was stirred at −78 °C for 3 h after which time but-2-en-4-olide (0.5 g, 6.0 mmol) was added. The resulting clear solution was stirred for 40 min at −78 °C, when a solution of piperonal (0.72 g, 4.8 mmol) in dry THF was added. The solution was then stirred at −78 °C for 90 min before being quenched with water. After the mixture had warmed to room temperature, it was extracted with EtOAc and the extracts were dried ($MgSO_4$) and evaporated to give a green gum (2.50 g). The crude product was purified by column chromatography (eluant EtOAc–CH_2Cl_2, 1:9) to give the *dibenzyl*-γ-*butyrolactone derivative* (**10**) as a green gum (2.38 g, ~100%). H.p.l.c. of the pure product showed 4 peaks of roughly equal areas, corresponding to the *erythro* and *threo* isomers at the C-6 and C-7 positions (Found: C, 65.6; H, 5.25. $C_{27}H_{26}O_7S$ requires C, 65.59; H, 5.26%); $\nu_{max.}$(KBr) 3 500 (OH) and 1 770 cm^{-1} (γ-lactone); $\lambda_{max.}$(MeOH) 224 and 240 nm; δ_H(60 MHz; $CDCl_3$)* 2.8—3.1 (2 H, m, 3-H and 4-H), 3.7—3.9 (6 H, m, 2 × OMe), 4.2—5.3 (4 H, m, 5-H_2 and 6- and 7-H), 5.9 (2 H, br s, OCH_2O), and 6.3—7.2 (11 H, m, ArH).

Preparation of the 4α-(**11a**) *and* 4β-(**11b**) *Isomers of* 3-*Hydroxymethyl*-6,7-*dimethoxy*-1-(3′,4′-*methylenedioxyphenyl*)-4-*phenylthio*-1,2,3,4-*tetrahydro*-2-*naphthoic Acid* γ-*Lactone*.—Compound (**10**) (750 mg, 1.5 mmol) was dissolved in dry CH_2Cl_2 (25 ml) under argon and TFA (0.55 ml) was added dropwise. After the mixture had been stirred for 3.5 h further TFA (0.55 ml) was added. The resulting red solution was stirred for a further 22 h, when water was added followed by CH_2Cl_2. The CH_2Cl_2 layer was separated, dried ($MgSO_4$), filtered, and evaporated to yield a yellow solid (640 mg). H.p.l.c. of the crude product revealed the presence of two main peaks. The crude product (190 mg) was purified by repeat injection h.p.l.c. (silica column, eluant 0.1% MeOH in CH_2Cl_2) to give the *major isomer* (**11a**) as a white solid (115 mg, 61%), m.p. 190—192 °C (Found: C, 68.3; H, 4.8. $C_{27}H_{24}O_6S$ requires C, 68.07; H, 5.04%); $\nu_{max.}$(KBr) 1 780 cm^{-1} (γ-lactone); $\lambda_{max.}$(MeOH) 217, 242, and 286 nm; *m/z* 476 (M^+, 1%) and 367 (M^+ − PhS, 68). The minor isomer (**11b**) was obtained as a white gum (30 mg), 16%), $\nu_{max.}$(KBr) 1 785 cm^{-1} (γ-lactone); $\lambda_{max.}$ (MeOH) 213, 240, and 284 nm; *m/z* 476 (M^+, 1%) and 367 (M^+ − PhS, 75). See Tables 1 and 2 for ^1H and ^{13}C n.m.r. data.

Synthesis of Lactone (**12**) *by Reduction of Sulphides* (**11**).—Compounds (**11**) (85 mg, 0.18 mmol) were dissolved in dry EtOH (15 ml) to which was added two spoonfuls (*i.e.* an excess) of freshly prepared Raney nickel. The suspension was refluxed for 18 h after which time the cooled reaction mixture was filtered through Celite and the filtrate was concentrated. The residue was taken up in CH_2Cl_2, and the extract was washed with water, dried ($MgSO_4$), filtered, and evaporated. The crude product was then purified by column chromatography to yield the previously synthesised aryltetralin lactone (**12**) as a white solid (65 mg).[9,11] See Tables 1 and 2 for ^1H and ^{13}C n.m.r. spectra.

* The numbering Scheme used is that shown in Scheme 2.

Table 4. ^{13}C N.m.r. spectra of 'retro' aryltetralin lactones ($CDCl_3$)[a]

Carbon	(17a)	(17b)	(18)	(21)	(14)
1	46.41	48.16	47.28	54.95	50.53
2	46.11	46.23	46.24	44.02	40.87
3	43.90	43.60	41.23	41.15	127.08
4	49.48	48.91	65.38	46.88	132.32
5	197.27	196.71	197.25	197.15	198.74
6	152.57	152.81	152.19	152.95	149.53
7	142.18	141.56	142.97	131.64	149.53
8	152.34	151.46	152.36	152.25	110.88
8a	124.26	126.42	125.75	124.60	131.73
4a	139.88	139.35	139.53	140.05	125.89
9	71.77	69.96	71.90	71.80	71.93
1′	134.41	134.32	133.14	137.01	134.77
2′	197.82	108.37	108.33	147.38	112.35
3′	145.97	146.06	146.00	145.88	146.82
4′	147.82	147.93	147.87	147.76	146.82
5′	108.29	108.78	109.11	108.23	109.26
6′	119.79	119.32	119.74	119.79	121.68
OCH_2O	100.93	100.99	100.94	100.87	101.67
OMe	55.66 59.39 60.37	55.98 59.58 60.68	56.02 59.52 60.48	55.71 59.37 60.36	56.05 55.99
CO	173.67	174.10	175.33	173.74	169.64
SPh	134.76 129.11 128.37 134.56	134.08 128.92 128.28 132.54			
SBu^t				32.26 45.54	

[a] N.m.r. numbering schemes are shown in Schemes 2—4.

Cyclisation of Sulphide (**10**) *with Trimethyloxonium Tetrafluoroborate to give Compound* (**14**).—Compound (**10**) (200 mg, 0.40 mmol) was dissolved in dry CH_2Cl_2 (10 ml) under argon and Me_3O^+ BF_4^- (300 mg, 2.0 mmol) was added. The mixture was stirred for 18 h at room temperature, after which time water was added to the resulting black solution followed by CH_2Cl_2. The CH_2Cl_2 layer was separated, dried ($MgSO_4$), filtered, and evaporated to yield a white gum (160 mg), which was purified by column chromatography (eluant CH_2Cl_2–EtOAc, 9:1) to give the previously synthesised 'retro' dihydroaryltetralin (**14**)[9] as a white solid (60 mg, 40%). See Tables 3 and 4 for ^1H and ^{13}C n.m.r. spectra.

Preparation of 4-*Hydroxy*-3-*hydroxymethyl*-6,7-*dimethoxy*-1-(3′,4′-*methylenedioxyphenyl*)-1,2,3,4-*tetrahydro*-2-*naphthoic Acid* γ-*Lactone* (**13**).—Compound (**11a**) (9.4 g, 20 mmol) was dissolved in 15% aqueous THF (250 ml) to which was added HgO (12.83 g, 60 mmol) and BF_3·Et_2O (16.8 ml, 60 mmol). The suspension was stirred at room temperature for 72 h after which time EtOAc was added. The solution was washed with saturated aq. Na_2CO_3 and the organic phase was dried ($MgSO_4$), filtered, and evaporated to give a brown solid (6.8 g). The crude product was recrystallised several times from MeOH to precipitate out $(SPh)_2$. The remaining mother liquor was purified by column chromatography on silica (eluant EtOAc), when compound (**13**) (R_F 0.13; CH_2Cl_2–EtOAc, 9:1) was collected as a white gum (1.39 g, 19%), $\nu_{max.}$(KBr) 3 500 (OH) and 1 780 cm^{-1} (γ-lactone). For ^1H and ^{13}C n.m.r. data see Tables 1 and 2; *m/z* 384.1209 (M^+, 100%) and 366 (M^+ − H_2O, 22).

Preparation of 3,4-*Methylenedioxybenzyl Phenyl Sulphide*.—3,4-Methylenedioxybenzyl alcohol (26 g, 0.17 mmol) was dissolved in a mixture of dry toluene (350 ml) and AnalaR $CHCl_3$ (25 ml) and the solution was cooled to 0 °C, saturated

with dry HCl gas, and left overnight at −5 °C. After this time an equal volume of ice–water was added, the toluene layer was separated, and the aqueous layer was extracted with toluene. The organic layers were combined, dried ($MgSO_4$), and concentrated to give a brown gum. The gum was repeatedly extracted with dry, warm light petroleum (b.p. 60—80 °C) and the extract was evaporated to give 3,4-methylenedioxybenzyl chloride (27.7 g, 95%), δ_H (60 MHz; $CDCl_3$) 4.4 (2 H, s, CH_2Cl), 5.8 (2 H, s, OCH_2O), and 6.7 (3 H, m, ArH).

Sodium (2.1 g, 91 mmol) was dissolved in absolute MeOH (40 ml) and PhSH (9.38 g, 85 mmol) was added. The solution was stirred at room temperature for 30 min and then 3,4-methylenedioxybenzyl chloride (15.6 g, 91 mmol) was added dropwise, when a white precipitate of NaCl appeared. The resulting suspension was stirred at room temperature for a further 2 h, when water was added and the solution was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), filtered, and evaporated to give, after recrystallisation from MeOH, 3,4-*methylenedioxybenzyl phenyl sulphide* as a white solid (12.8 g, 58%), m.p. 40—41 °C; δ_H (60 MHz; $CDCl_3$) 3.95 (2 H, s, $ArCH_2$), 5.8 (2 H, s, OCH_2O), 6.7 (3 H, m, ArH), and 7.2 (5 H, br s, PhS); *m/z* 244 (M^+, 9%) and 135 (M − SPh, 100) (Found: C, 68.7; H, 5.0. $C_{14}H_{12}O_2S$ requires C, 68.80; H, 4.95%).

Preparation of 2-(α-*Hydroxy*-3′,4′,5′-*trimethoxybenzyl*)-3-(3″,4″-*methylenedioxy*-α-*phenylthiobenzyl*)-γ-*butyrolactone* (**15**).—3,4-Methylenedioxybenzyl phenyl sulphide (12.52 g, 51 mmol) was dissolved in dry THF (130 ml) under argon, the solution was cooled to −78 °C, and BuLi (1.1 mol equiv.) was added. A yellow precipitate appeared which remained even after addition of a further quantity (100 ml) of dry THF. After the reaction mixture had been stirred for 1.5 h at −78 °C, but-2-en-4-olide (5.39 g, 64 mmol) was added, and the precipitate promptly dissolved. The reaction mixture was stirred for a further hour at −78 °C, when a solution of 3,4,5-trimethoxybenzaldehyde (10.07 g, 51 mmol) in THF was added, and the resulting solution was stirred at −78 °C for 2 h before addition of water. The reaction mixture was allowed to warm to room temperature and was then extracted with EtOAc. The extracts were dried ($MgSO_4$), filtered, and evaporated to yield a yellow gum (27 g). Purification of the crude product by column chromatography on silica (eluant CH_2Cl_2–EtOAc, 9:1) gave the desired *dibenzylbutyrolactone* (**15**) (shown by h.p.l.c. to be 4 isomers in *ca.* equal proportions) as a yellow gum (13.6 g, 51%) (Found: C, 64.5; H, 5.5. $C_{28}H_{28}O_8S$ requires C, 64.12; H, 5.34%); $\nu_{max.}$(Nujol) 3 500 (OH) and 1 770 cm^{-1} (γ-lactone). The ^1H and ^{13}C n.m.r. spectra of the mixture of isomers were very complex although the presence of the piperonyl, trimethoxyphenyl, and lactone rings was apparent from the spectra.

Preparation of the 1α-(**17a**) *and* 1β-(**17b**) *Isomers of* 3-*Hydroxymethyl*-5,6,7-*trimethoxy*-4-(3′,4′-*methylenedioxyphenyl*)-1-*phenylthio*-1,2,3,4-*tetrahydro*-2-*naphthoic Acid* γ-*Lactone*.—Compound (**15**) (0.8 g, 1.5 mmol) was dissolved in dry CH_2Cl_2 (10 ml), and TFA (10 ml) was added. The resulting red solution was stirred at room temperature for 1 h, when a further quantity (8 ml) of TFA was added. Additional TFA (4 ml) was added 3 h later and the reaction mixture was stirred for a further 1 h before being washed with water (3 × 30 ml). The organic phase was then dried ($MgSO_4$), filtered, and evaporated to yield a yellow solid (720 mg). Subsequent purification of the crude product by column chromatography on silica (eluant CH_2Cl_2–EtOAc, 95:5) gave the 1α-phenylthio-substituted aryltetralin (**17a**) as a yellow gum (450 mg, 58%), $\nu_{max.}$(KBr) 1 790 cm^{-1} (γ-lactone); *m/z* 396.1194 (M^+ − PhSH, 28%); and the 1β-phenylthio-substituted aryltetralin (**17b**) as a white solid (60 mg, 8%), m.p. 152—156 °C (Found: C, 66.4; H, 5.15. $C_{28}H_{26}O_7S$ requires C, 66.40; H, 5.14%). See Tables 3 and 4 for ^1H and ^{13}C n.m.r. data.

Preparation of 1-*Hydroxy*-3-*hydroxymethyl*-5,6,7-*trimethoxy*-4-(3′,4′-*methylenedioxyphenyl*)-1,2,3,4-*tetrahydro*-2-*naphthoic Acid* γ-*Lactone* (**18**).—Compound (**17a**) (90 mg, 0.23 mmol) was dissolved in dry THF (10 ml) under argon and a solution of $Hg(O_2CCF_3)_2$ (168 mg, 0.4 mmol) in dry THF (5 ml) was added. The reaction mixture was stirred for 3 h at room temperature, after which water (10 ml) was added. After the mixture had been stirred for a further 30 min, aq. $NaHCO_3$ was added and the solution was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), filtered, and evaporated to give a white solid (130 mg). The crude product was separated by column chromatography on silica (eluant CH_2Cl_2–EtOAc, 95:5) and $(SPh)_2$ (25 mg) was isolated together with *compound* (**18**) (46 mg, 62%), m.p. 178—180 °C (Found: C, 63.8; H, 5.6. $C_{22}H_{22}O_8$ requires C, 63.77; H, 5.31%); $\nu_{max.}$(KBr) 3 500 (OH) and 1 780 cm^{-1} (γ-lactone); $\lambda_{max.}$(MeOH) 225 and 286 nm; *m/z* 414.1315 (M^+, 100%) and 396 (11.3). For ^1H and ^{13}C n.m.r. data see Tables 3 and 4.

Cyclisation of Sulphide (**15**) *with Perchloric Acid*.—Compound (**15**) (200 mg, 0.38 mmol) was dissolved in AnalaR EtOAc (10 ml), $HClO_4$ (4 drops) was added, and the solution was stirred for 2 h, when a precipitate appeared. The suspension was stirred for a further 4 h at room temperature, after which time the precipitate was filtered off. Examination of the filtrate after washing with water, drying ($MgSO_4$), and evaporation showed it to contain the aryltetralin (**17a**) (135 mg, 70%). The precipitate collected was dissolved in CH_2Cl_2 and the solution was washed with water, dried ($MgSO_4$), filtered and evaporated to yield 3-hydroxymethyl-6,7-methylenedioxy-4-phenylthio-1-(3′,4′,5′-trimethoxyphenyl)-1,2,3,4-tetrahydro-2-naphthoic acid γ-lactone (**19**) (40 mg, 21%), m.p. 262—266 °C; $\nu_{max.}$(KBr) 1 790 cm^{-1} (γ-lactone); $\lambda_{max.}$(MeOH) 222 and 293 nm. For ^1H n.m.r. data see Table 1; *m/z* 506 (M^+, 18.8%) and 397 (M^+ − SPh, 100).

Preparation of 2-(α-*Hydroxy*-3′,4′,5′-*trimethoxybenzyl*)-3-(3″,4″-*methylenedioxybenzyl*)-γ-*butyrolactone* (**16**).—Compound (**15**) (700 mg, 1.3 mmol) was dissolved in warm, dry EtOH (25 ml) to which was added two spoonfuls (an excess) of Raney nickel. The suspension was refluxed for 6 h after which time the cooled reaction mixture was filtered through Celite which was then washed with dry EtOH. The filtrate was concentrated, the residue was taken into CH_2Cl_2, and the extract was washed with water, dried ($MgSO_4$), filtered, and concentrated to give a white gum (450 mg), which was purified by column chromatography on silica (eluant CH_2Cl_2–EtOAc, 9:1) to give a mixture of the *erythro*- and *threo*-isomers (1:1) of the desulphurised adduct (**16**)[13] as a clear gum (375 mg, 60%), δ_H(60 MHz; $CDCl_3$) 2.20—2.70 (4 H, m, 3- and 4-H and 7-H_2), 6.80 (9 H, s, 3 × OMe), 4.40 (1 H, m, 5-H_a), 4.80 (1 H, m, 5-H_b), 5.20 (1 H, m, 6-H), 5.85 (2 H, s, OCH_2O), and 6.20—6.70 (5 H, m, ArH); *m/z* 416 (M^+, 0.5%), 220 (16), 196 (44), 181 (17), and 135 (100).

Preparation of Deoxyisopodophyllotoxin (**5**).—Compound (**16**) (100 mg, 0.24 mmol) was dissolved in TFA (10 ml) under argon and the solution was stirred for 2.5 h at room temperature. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), filtered, and evaporated to give a white solid (95 mg, 100%), which was shown to be identical (h.p.l.c. ^1H n.m.r.) with an authentic sample of deoxyisopodophyllotoxin (**5**), m.p. 258—260 °C (lit.,[14] 256—258 °C) (Found C, 66.4; H, 5.4. Calc. for $C_{22}H_{22}O_7$: C, 66.33; H, 5.53%); *m/z* 398 (M^+, 100%), 383 (17), 196 (10), and 135 (37). For ^1H n.m.r. data see Table 1.

Preparation of 3,4-*Methylenedioxybenzyl t-Butyl Sulphide.*—Sodium (1.63 g, 70 mmol) was dissolved in dry MeOH (30 ml) and Bu^{t}SH (7.95 ml, 70 mmol) was added dropwise. The solution was stirred for 75 min, when 3,4-methylenedioxybenzyl chloride (10 g, 60 mmol) was added dropwise. A white precipitate appeared and the resulting suspension was stirred at room temperature for 1 h. After this time water and CH_2Cl_2 were added and the organic phase was dried ($MgSO_4$), filtered, and evaporated to yield the *title sulphide* (11.5 g, 76%), m.p. 30—34 °C (from MeOH); δ_H(60 MHz; $CDCl_3$) 1.3 (9 H, s, Me_3C), 3.6 (2 H, s, ArCH_2), 5.8 (2 H, s, OCH_2O), and 6.7 (3 H, m, ArH) (Found: C, 64.1; H, 7.3. $C_{12}H_{16}O_2S$ requires C, 64.25; H, 7.19%); *m/z* 224 (M^+, 25%) and 135 (M − SPh, 100).

Preparation of 2-(α-*Hydroxy*-3′,4′,5′-*trimethoxybenzyl*)-3-(3″,4″-*methylenedioxy*-α-*t*-*butylthiobenzyl*)-γ-*butyrolactone* (**20**).—3,4-Methylenedioxybenzyl t-butyl sulphide (4 g, 18 mmol) was dissolved in dry THF (80 ml) under argon and the solution was cooled to −78 °C. To this cooled solution was added BuLi (20 mmol) and the yellow reaction mixture was stirred at −78 °C for 2.5 h. But-2-en-4-olide (1.8 g, 21 mmol) was added, and the reaction mixture became colourless and was stirred for a further 30 min at −78 °C, after which time a solution of 3,4,5-trimethoxybenzaldehyde (3.50 g, 18 mmol) in dry THF (15 ml) was added. Finally, after the reaction mixture had been stirred at −78 °C for a further 2 h it was quenched with water, allowed to warm to room temperature, and extracted with CH_2Cl_2. The extracts were combined, dried ($MgSO_4$), filtered, and evaporated to give an orange gum (8 g). Purification of the crude product by column chromatography on silica (eluant CH_2Cl_2–EtOAc, 9:1) produced the desired *dibenzylbutyrolactone* (**20**) (shown to be 4 isomers in the proportions 5:4:4:1 by h.p.l.c.) as a gum (4.4 g, 49%) (Found: C, 62.0; H, 6.6. $C_{26}H_{32}O_8S$ requires C, 61.90; H, 6.35%); $\nu_{max.}$(KBr) 3 500 (OH) and 1 775 cm^{-1} (γ-lactone); $\lambda_{max.}$(MeOH) 230 and 294 nm; δ_H(60 MHz; $CDCl_3$) 1.1 (9 H, s, Me_3C), 2.8 (1 H, m, 4-H), 2.9 (1 H, m, OH), 3.5 (1 H, m, 3-H), 3.85 (9 H, s, OMe), 4.1—4.4 (3 H, m, 7-H and 5-H_2), 5.2 (1 H, m, 6-H), 5.9 (1 H, s, OCH_2O), and 6.3—6.8 (5 H, m, ArH); *m/z* 504 (M^+, 0.8%), 308 (16.2), and 219 (100).

Reaction of Compound (**20**) *with TFA.*—Compound (**20**) (350 mg, 0.7 mmol) was dissolved in TFA (10 ml) and the resulting red solution was stirred at room temperature for 6 h. After this time, CH_2Cl_2 and water were added, and the organic layer was separated, dried ($MgSO_4$), filtered, and evaporated to yield a brown gum (350 mg). The crude product was separated by column chromatography on silica (eluant CH_2Cl_2–EtOAc, 95:5) to yield 3-*hydroxymethyl*-5,6,7-*trimethoxy*-4-(3′,4′-*methylenedioxyphenyl*-1-*t*-*butylthio*-1,2,3,4-*tetrahydro*-2-*naphthoic acid* γ-*lactone* (**21**) (160 mg, 47%), m.p. 148—152 °C (Found: C, 64.0; H, 6.0. $C_{26}H_{20}O_7S$ requires C, 64.20; H, 6.17%); $\nu_{max.}$(KBr) 1 795 cm^{-1} (γ-lactone). See Tables 3 and 4 for ^{1}H and ^{13}C n.m.r. data; *m/z* 486 (M^+, 10%) and 397 (M^+ − PhS, 100); and 3-*hydroxymethyl*-6,7-*methylenedioxy*-4β-*t*-*butylthio*-1-(3′,4′,5′-*trimethoxyphenyl*)-1,2,3,4-*tetrahydro*-2-*naphthoic acid* γ-*lactone* (**22a**) (60 mg, 18%), m.p. 202—205 °C (Found: C, 64.4; H, 6.4. $C_{26}H_{30}O_7S$ requires C, 64.20; H, 6.17%); $\nu_{max.}$(KBr) 1 790 cm^{-1} (γ-lactone). See Tables 1 and 2 for ^{1}H and ^{13}C n.m.r. data; *m/z* 486 (M^+, 75%) and 397 (M^+ − PhS, 100).

Preparation of 3-*Hydroxymethyl*-6,7-*methylenedioxy*-4α-*t*-*butylthio*-1-(3′,4′,5′-*trimethoxyphenyl*)-1,2,3,4-*tetrahydro*-2-*naphthoic Acid* γ-*Lactone* (**22b**).—Compound (**20**) (300 mg, 0.6 mmol) was dissolved in AnalaR EtOAc (10 ml), conc. $HClO_4$ (5 drops) was added, and the resulting mixture was stirred for 20 h at room temperature, after which time the solid which had precipitated was filtered off. The filtrate was washed with water, dried ($MgSO_4$), filtered, and evaporated to leave a brown gum (124 mg, 43%), which was shown by spectroscopic data and h.p.l.c. to be mainly the 'retro' cyclised aryltetralin (**21**) which had been previously synthesised (see above for spectral data). The white precipitate recovered from the reaction mixture was taken up in CH_2Cl_2 and the solution was washed with water. The organic layer was subsequently dried ($MgSO_4$) and evaporated to yield *compound* (**22b**) as a white solid (135 mg, 47%), m.p. 276—280 °C (Found: C, 64.4; H, 6.1%); $\nu_{max.}$(KBr) 1 790 cm^{-1} (γ-lactone); $\lambda_{max.}$(MeOH) 216 and 294 nm. See Table 1 for ^{1}H n.m.r. data; *m/z* 486 (M^+, 66.4%) and 397 (M^+ − PhS, 100).

Reduction of Compound (**22b**) *with Raney Nickel.*—Compound (**22b**) (280 mg, 0.6 mmol) was suspended in dry EtOH (150 ml) and two spoonfuls (large excess) of freshly prepared Raney nickel were added. The resulting suspension was refluxed for 24 h after which time the cooled reaction mixture was filtered through Celite. The filtrate was evaporated, the residue was taken up in CH_2Cl_2, and the solution was washed several times with water, dried ($MgSO_4$), filtered, and evaporated to yield deoxyisopodophyllotoxin (**5**) as a white solid (230 mg, ~100%), identical with the sample prepared from compound (**16**) (see above).

Preparation of Epi-isopodophyllotoxin (**6**).—Compound (**22b**) (150 mg, 0.3 mmol) was suspended in dry THF (30 ml) under nitrogen. To this suspension was added a solution of $Hg(O_2CCF_3)_2$ (263 mg, 0.6 mmol, 2 mol equiv.) in dry THF (10 ml). The suspension was stirred at room temperature for 30 min to give a clear solution. The mixture was stirred for a further 4 h, water (10 ml) was added, and the mixture was stirred for a further 1 h, when 1M aq. $NaHCO_3$ was added together with CH_2Cl_2. The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated to give a white solid (130 mg), which was recrystallised from MeOH–$CHCl_3$ to yield epi-isopodophyllotoxin (**6**) (77 mg, 60%), m.p. 256—259 °C (lit.,[12] 258—260 °C); $\nu_{max.}$(KBr) 3 500 (OH) and 1 765 cm^{-1} (γ-lactone). For ^{1}H n.m.r. data see Table 1; *m/z* 414 (M^+, 100%) and 396 (M^+ − H_2O, 21).

Acknowledgements

We gratefully acknowledge financial support from the S.E.R.C. and I.C.I. Ltd. We also thank Mr. H. R. Kipps (I.C.I. Plant Protection) and Dr. I. Sadler (Edinburgh University) for help in obtaining and interpreting the high-field ^{1}H n.m.r. spectra.

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Received 20*th July* 1987; *Paper* 7/1306