Synthesis of Lignans Related to the Podophyllotoxin Series

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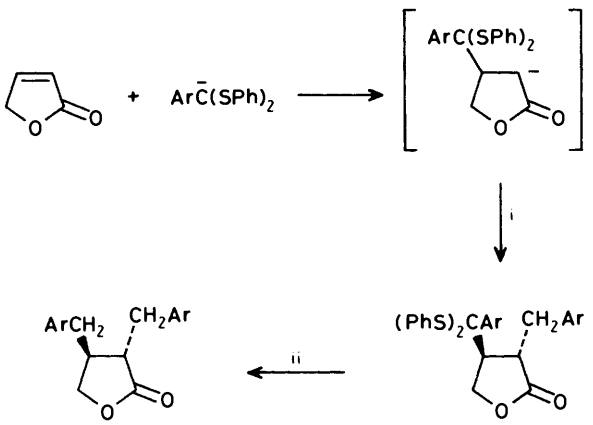
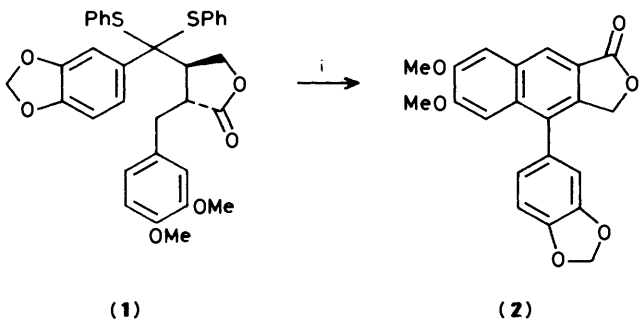
The dibenzyl-γ-butyrolactone derivative (**6**), readily prepared by tandem conjugate addition to but-2-en-4-olide, undergoes cyclisation with trifluoroacetic acid to afford retrochinensin (**10**). After desulphurisation of (**6**) with Raney nickel, cyclisation yields the aryltetralin lactone (**9**). Treatment of (**6**) with concentrated perchloric acid gives a quantitative yield of the rearranged compound (**11**), which after appropriate modification can be cyclised to afford either the retro-dihydroarylnaphthalene lactone (**13**), or the 4-substituteed aryltetralin lactone (**15**). Extension of this approach to a second dibenzylbutyrolactone derivative (**21**) leads to the retro-dihydroarylnaphthalene lactone (**25**), but gives only a low yield of the required podophyllotoxin derivative (**27**).

Conjugate addition reactions provide short efficient routes to several lignan types.[1] Thus, addition of a thioacetal carbanion to but-2-en-4-olide followed by trapping of the resulting enolate anion with a suitable electrophile leads directly to the *trans*-dibenzyl-γ-butyrolactone skeleton. We have used this approach to synthesise the dimethyl ether of enterolactone (Scheme 1).[2]



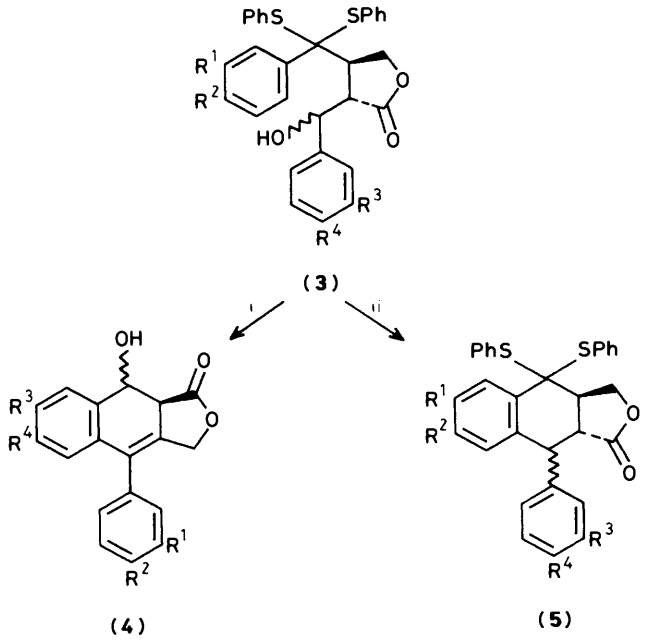
Scheme 1. *Reagents:* i, $ArCH_2Br$; ii, Raney nickel

Other types of lignans can be prepared by cyclisation of the adducts produced by conjugate addition reactions.[3–7] Thus, treatment of adducts such as (**1**) with mercury salts affords arylnaphthalene lactones of type (**2**) (Scheme 2).[2]



Scheme 2. *Reagent:* i, Hg^{2+}

In continuation of this work[8] we chose to study the cyclisation of the benzylic alcohols (**3**) which could in principle cyclise to afford two alternative series of lignan lactones by selective displacement of either an SPh or OH group (Scheme 3).



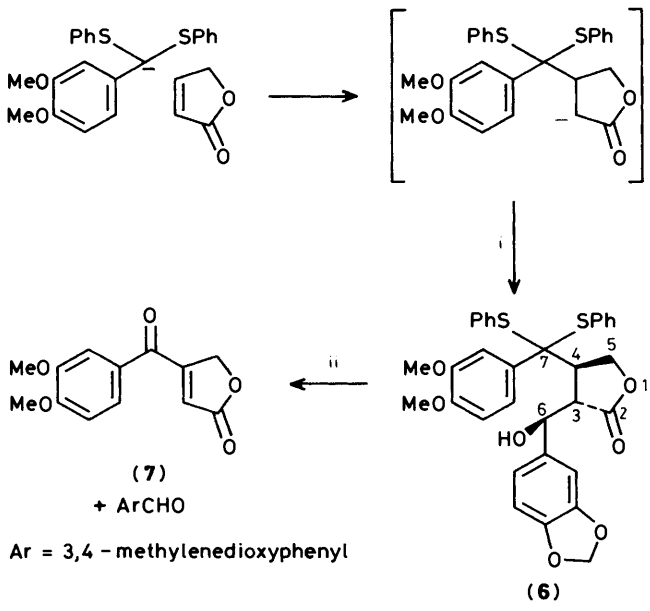
Scheme 3. *Reagents:* i, Hg^{2+} or Me^+; ii, H^+

The benzylic alcohol (**6**) was prepared in quantitative yield by treating the carbanion derived from 3,4-dimethoxybenzaldehyde diphenyl dithioacetal with but-2-en-4-olide, followed by piperonal (Scheme 4). The ^1H n.m.r. spectrum of the product was complex but showed clearly that only one diastereoisomer had been produced. The coupling constant between 3-H and 4-H could not be measured but it was assumed, by analogy with previous work,[2,3] that the addition had taken place in such a way as to give the *trans* configuration of the two benzylic groups on the lactone ring. The coupling constant between 3-H and 6-H (3 Hz) indicated, again by analogy with previous work,[3,9] that the *erythro* isomer (**6**) had been produced.

Treatment of compound (**6**) with an excess of mercury(II) trifluoroacetate failed to give either the desired dihydroarylnaphthalene [*cf.* (**3**) ⟶ (**4**)] or the corresponding fully aromatic

compound. Purification of the crude product by column chromatography yielded only a mixture of piperonal and 3-(3′,4′-dimethoxybenzoyl)but-2-en-4-olide (**7**), presumably formed by way of a retro-aldol reaction followed by dehydrogenation.

Desulphurisation of disulphide (**6**) with Raney nickel gave the benzyl alcohol (**8**) which on treatment with trifluoroacetic acid (TFA) gave the aryltetralin (**9**)[7] (100%). However, treatment of compound (**6**) with TFA gave retrochinensin (**10**) (60%), indicating that under these conditions the SPh group is the preferred leaving group. It should be noted that the cyclisation of dibenzylbutyrolactones such as (**1**) and (**6**) represents a short and efficient synthesis of retro-arylnaphthalene lactones.



Scheme 4. *Reagents:* i, ArCHO; ii, Hg^{2+}. The n.m.r. numbering scheme is displayed

Treatment of compound (**6**) with perchloric acid gave a quantitative yield of two epimeric rearrangement products (**11a**) and (**11b**) (Scheme 5), while treatment with tin(IV) chloride gave a mixture of retrochinensin (**10**), (**11a**), and (**11b**).

The two isomers (**11a**) and (**11b**) 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). Both isomers showed strong absorptions in their i.r. spectra at 1 780 and 1 680 cm^{-1} due to the lactone and ketone groups. Their mass spectra were also almost identical, containing prominent ions at *m/z* 492 (1%, $M^{\cdot+}$), 383 (30%, *M* − SPh), and 165 (100%, $ArCO^+$). Significant differences were however observed in their ^1H n.m.r. spectra (Table 1) where one of the protons of the lactone CH_2 group was moved downfield in isomer (**11a**) due to the influence of the adjacent thiophenyl group. Examination of molecular models and observed differences in the reactivity of the two isomers (see below) indicated that (**11a**) was the C-3, C-6-*erythro* isomer.

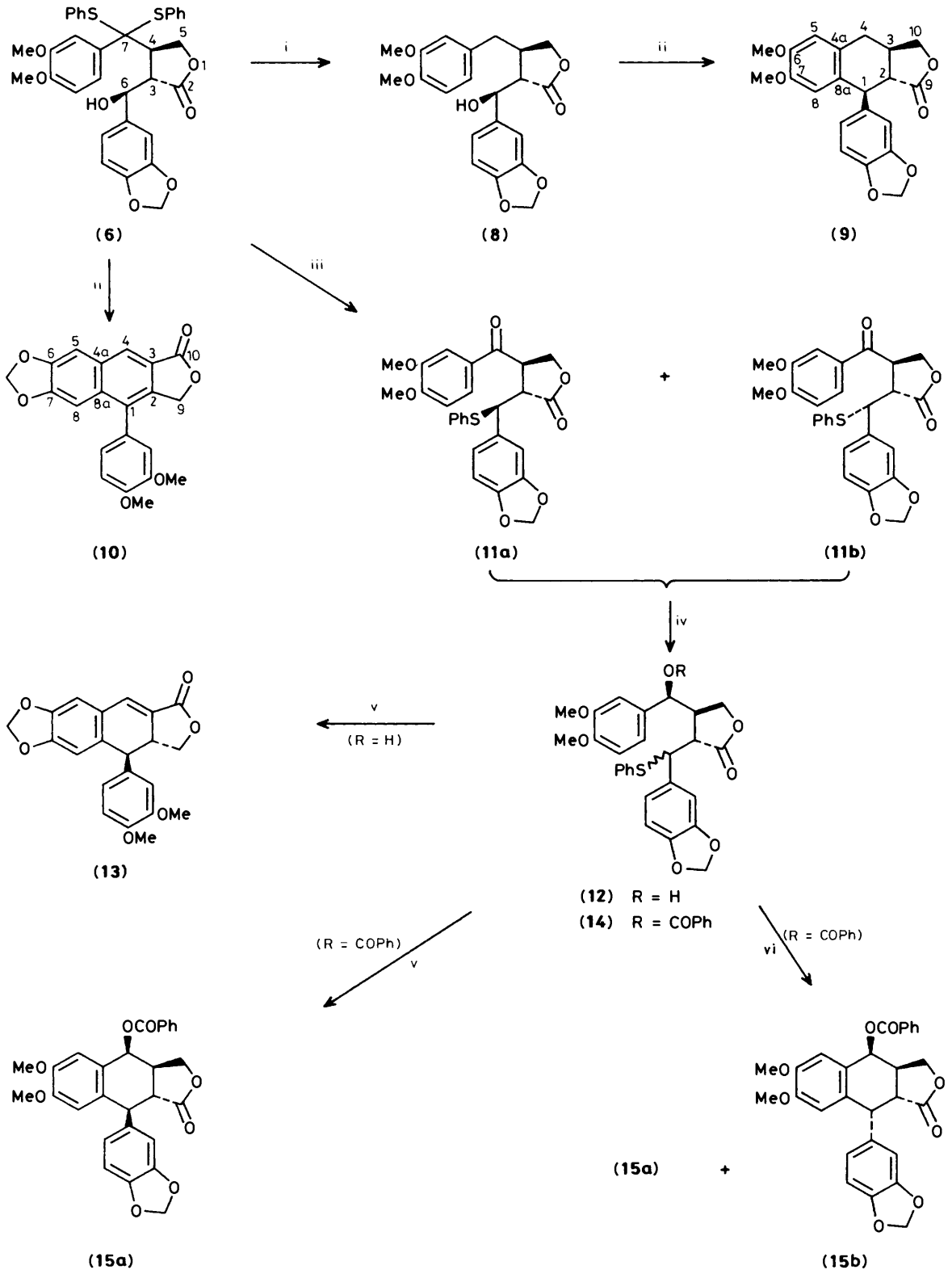
A possible mechanism to account for the formation of epimers (**11a**) and (**11b**) is shown in Scheme 6. In support of this mechanism, attempted cyclisation of the *threo* isomer (**11b**) using TFA resulted in its conversion into a mixture of the *erythro* isomer (**11a**) and the unsaturated lactone (**16**). This

Table 1. ^1H N.m.r. spectra of dibenzylbutyrolactone derivatives[a]

Proton(s)	(6)	(8)	(11a)[b]	(11b)[b]	(16)	(17a)	(17d)
3-H	3.25m	2.30m	3.82dd (3.4, 8.3)	3.88dd (4.5, 8.5)		3.60m	3.25m
4-H	2.95m		4.39q (8.4)	4.54m	5.10m	3.00m	2.95m
5-H_a	4.05dd (8, 10)	3.90dd (3, 9)	4.13t (8.7)		4.35dd (4, 9)	4.25dd (7, 10)	4.20dd (2, 8)
5-H_b	4.60dd (2, 10)	4.30dd (7, 9)	3.99m	4.07t (7.4)	4.65d (9)	4.60dd (3, 10)	4.65m
6-H	5.10d (3)	5.20d (3)	4.92d (3.4)	4.68d (4.5)	7.70d (2)	6.10d (6)	
7-H		2.60dd (3, 6) 2.75m					
OH	3.10m	3.25m					
OMe	3.70s 3.80s	3.70s 3.80s	3.97s 3.99s	3.91s 3.98s	3.85s 3.95s	3.70s 3.80s	3.70s 3.80s 3.15s
OCH_2O	5.90s	5.90s	5.94m	5.85 5.87s	5.90s	5.90s	5.95s
ArH	6.5—7.3m	6.3—6.8m	6.7—7.5m	6.5—7.5m	6.7—7.6m	6.5—6.8m	6.4—7.4m

Proton(s)	(18)	(19)	(12)	(21)	(22)	(23)	(24)	(26)
3-H	3.20d (4)	3.55m	3.30t (5)	3.15m 3.35m	3.9—4.2m	3.30m	3.30t (4)	3.10m
4-H		4.10m	2.70m	2.90m		2.80m	3.10m	
5-H_a 5-H_b	4.40s	4.50m	4.15d (6)	4.20m 4.5—4.8m	4.50m	4.20m	4.1—4.6m	3.90m
6-H	4.90d (4)	5.35m	4.50d (4)	4.90d (5) 5.15d (3)	4.70d (4) 4.90d (3)	4.60d (4) 4.85d (3)	4.65d (4) 4.80d (3)	4.60d (3)
7-H			4.70d (5)			4.70d (6)	6.00m	6.15d (7)
OH		2.70m	2.50m	2.8—3.4m		2.3br		
OMe	3.65s 3.75s 3.35s	3.80s 3.90s	3.80s 3.90s	3.70s 3.80s	3.60s 3.75s	3.85s 3.87s	3.86s 3.88s	3.80s 3.85s 3.25s
OCH_2O	5.82s 5.88s	5.72s 5.78s	5.90s	5.90s	6.00s	6.00m	6.02m	5.90s
ArH	6.1—7.2m	6.5—7.3m	6.5—7.3m	6.3—7.4m	6.5—7.4m	6.5—7.4m	6.5—8.2m	6.5—8.1m

[a] All spectra recorded in $CDCl_3$ solution at 100 MHz unless otherwise indicated. Numbering schemes used are those shown in the Schemes. *J*-Values (Hz) are in parentheses. [b] 360 MHz spectra.



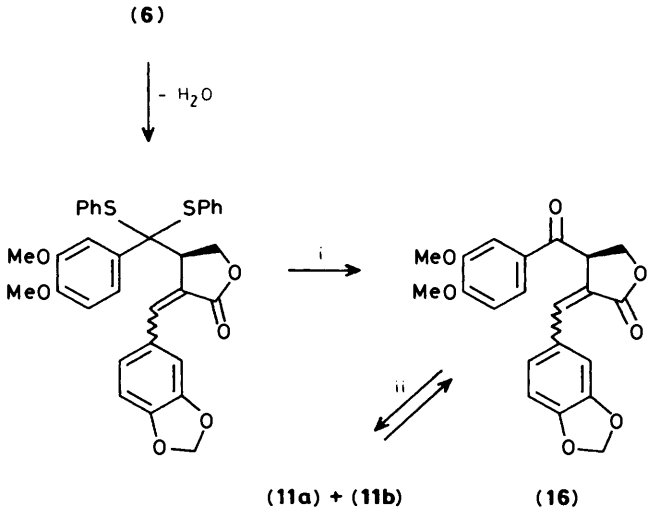
Scheme 5. *Reagents:* i, Raney nickel; ii, TFA; iii, $HClO_4$; iv, $NaBH_4$; v, FSO_3Me; vi, $Me_3O^+ BF_4^-$. The n.m.r. numbering schemes are displayed

suggests that the two isomers can be interconverted under acidic conditions by an elimination/addition mechanism involving the unsaturated lactone (**16**), and furthermore that the *anti* conformation required for elimination is less favourable in the case of the *erythro* isomer (**11a**). This was confirmed by an examination of molecular models and therefore lends support to the relative configurations assigned to compounds (**11a**) and (**11b**).

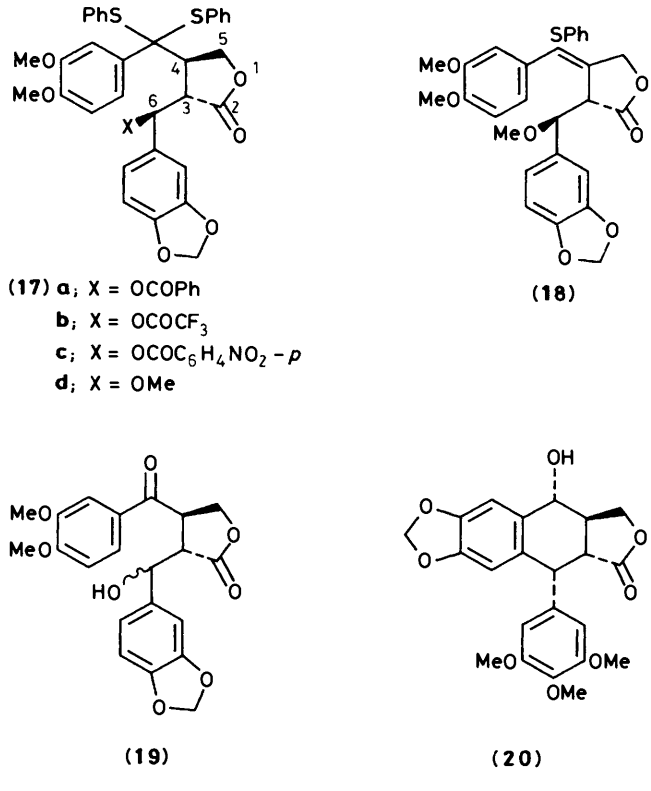
Table 2. ^{13}C N.m.r. spectra of dibenzylbutyrolactone derivatives[a]

Carbon	(6)	(17a)	(17d)	(8)	(11a)	(11b)	(12)[b]	(14)[b]	(22)[b]	(23)[b]	(24)[b]
2	178.07	174.81	176.34	178.51	175.27	174.99	177.22	176.36	175.10	177.54	176.32
3	51.58	49.10	50.88	52.81	48.78	50.17	48.10	48.81	50.02	47.80	48.74
4	45.77	46.38	44.78	36.43	43.87	45.03	44.77	43.01	45.14	44.80	43.16
5	69.88	68.51	68.86	72.88	68.82	68.48	69.87	69.61	68.50	69.87	69.14
6	73.67	75.25	82.63	71.66	51.61	53.59	53.97	54.41	54.08	54.52	55.04
7	73.06	73.21	72.69	39.37	195.08	194.51	74.60	76.70	193.82	74.19	76.27
1′, 1″	133.15, 134.59	130.48, 132.67	130.91, 132.88	130.47, 135.14	133.02, 133.79	133.10, 133.97	133.80, 131.30	134.00, 130.90	132.62, 134.77	134.15, 135.29	134.06, 134.18
2′, 2″	106.45, 107.97	106.77, 108.29	106.33, 107.79	105.78, 107.85	109.13, 108.32	108.11, 108.38	107.08, 108.50	107.90, 108.10	108.20, 105.05	105.92, 105.54	106.21, 105.36
3′, 3″	147.10, 147.10	147.93, 148.02	146.88, 147.53	146.85, 147.72	147.49, 147.97	147.10, 147.95	149.00, 148.70	149.30, 149.10	148.80, 153.24	148.81, 152.91	148.13, 153.31
4′, 4″	148.51, 148.86	148.73, 149.13	148.02, 148.40	147.81, 147.92	147.54, 154.46	149.61, 154.40	147.80, 147.00	147.40, 147.20	152.93, 137.50	147.13, 137.18	147.78, 137.69
5′, 5″	110.57, 112.62	110.77, 112.76	110.28, 112.12	111.12, 111.55	110.30, 110.68	110.24, 110.50	108.80, 111.10	111.30, 109.20	108.20, 153.24	107.85, 152.91	108.14, 153.31
6′, 6″	119.21, 120.99	120.05, 120.99	119.41, 120.67	118.27, 120.67	122.36, 123.35	121.45, 123.14	117.90, 121.80	118.00, 121.40	124.87, 105.05	118.82, 105.54	119.55, 105.36
OCH_2O	100.99	101.29	100.58	101.20	101.19	101.19	101.25	101.37	102.30	101.28	101.54
OMe	55.61, 55.81	55.64, 55.87	55.17, 55.37	55.58, 55.78	56.04, 56.19	56.09, 56.24	55.75, 55.92	55.72, 55.84	55.92, 60.78	56.03, 60.68	56.09, 60.73
PhCO		164.78	57.06					165.32			165.21

[a] All spectra recorded in $CDCl_3$ solution. Numbering schemes used are those shown in the Schemes. [b] Signals for major isomer only listed.

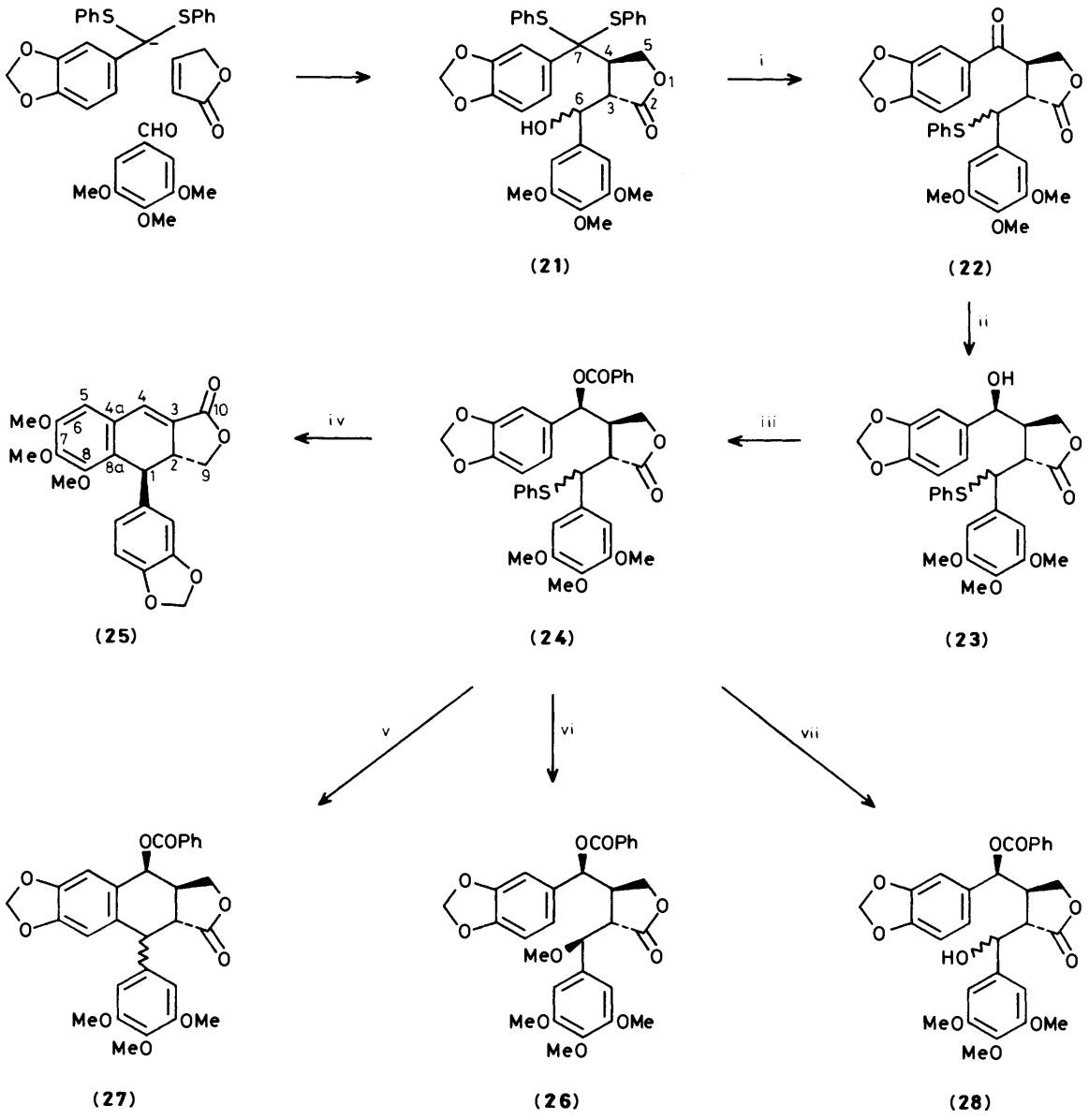


Scheme 6. *Reagents:* i, H_3O^+; ii, PhSH



Since all of the cyclisation reactions carried out on compound (**6**) were apparently initiated by displacement of the thiophenyl group, a series of derivatives (**17a**—**c**) was prepared in the hope of improving the lability of the benzylic oxygen substituent relative to the thiophenyl group. However, treatment of compounds (**17a**—**c**) with perchloric acid resulted only in high yields of the ketones (**11a**) and (**11b**). Several other acidic reagents were tried but they also failed to bring about the desired ring closure, producing only mixtures of the starting material, retrochinensin (**10**), and (**11a**), and (**11b**). Similarly, reaction of the methyl ether (**17d**) with perchloric acid gave only (**11a**) and (**11b**), while treatment of (**17d**) with TFA gave retrochinensin (**10**)[10] (55%). Treatment of (**17d**) with an excess of mercury(II) trifluoroacetate gave an elimination product (**18**) as the major product, although in low yield, with no evidence for any cyclised material.

Since compounds (**11a**) and (**11b**) were obtained in quantitative yield from the dithioacetal (**6**), their cyclisation by displacement of the SPh group was of interest. However, despite several attempts, direct cyclisation under acid conditions could not be achieved. Similarly, treatment of (**11b**) with mercury(II) trifluoroacetate also failed to bring about cyclisation, producing instead a mixture of products from which one compound, identified as (**19**), could be isolated in low yield. It was assumed that the inability to bring about cyclisation of (**11a**) and (**11b**) was due to the presence of the deactivating carbonyl group, and the ketone was therefore reduced to the corresponding alcohol



Scheme 7. *Reagents:* i, $HClO_4$; ii, $NaBH_4$; iii, BuLi, then PhCOCl; iv, $Me_3O^+ BF_4^-$; v, FSO_3Me; vi, $Me_3O^+ BF_4^-$, K_2CO_3; vii, Hg^{2+}

(**12**). H.p.l.c. and ^1H n.m.r. spectroscopy showed that the reduction was stereospecific producing only the C-4, C-7-*erythro* isomer. Treatment of this compound with methylating agents such as methyl fluorosulphonate surprisingly afforded the dihydroarylnaphthalene lactone (**13**), which on dehydrogenation by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) gave retrochinensin (**10**), thus confirming that cyclisation had proceeded by displacement of the OH group. However, after benzoylating to give ester (**14**), treatment with methyl fluorosulphonate in the presence of anhydrous potassium carbonate gave compound (**15a**) (29%) along with a small amount of (**13**) while treatment with trimethyloxonium tetrafluoroborate again in the presence of anhydrous potassium carbonate gave almost equal amounts of (**15a**) and a second compound, tentatively identified as the C-1 epimer (**15b**). This result was encouraging for two reasons, firstly because it fulfilled our original objective of achieving cyclisation to give the two alternative lactone series (**13**) and (**15**), and secondly because it showed that direct cyclisation could yield compounds with the relative configurations at C-1, C-2, and C-3 as found in podophyllotoxin, (**20**), and its derivatives.[11,12]

We therefore turned our attention to the synthesis of compounds containing the piperonyl and trimethoxyphenyl groups present in the podophyllotoxin series. The required conjugate addition product (**21**) was prepared in almost quantitative yield as a 65:35 mixture of C-3, C-6-*erythro* and *threo* isomers. Treatment of compound (**21**) with perchloric acid gave the *erythro* and *threo* isomers of the ketone (**22**), which by reduction was converted into the alcohol (**23**) (Scheme 7). H.p.l.c. analysis showed (**23**) to be a mixture of only two isomers, indicating once again that the sodium tetrahydroborate reduction had occurred in a stereospecific manner. The configuration at C-7 could not be determined due to the complexity of the ^1H n.m.r. spectrum, but was assumed to be the same as in compound (**12**) prepared analogously. Benzoylation gave compound (**24**), which on treatment with trimethyloxonium tetrafluoroborate gave the retro-dihydroarylnaphthalene lactone (**25**) in 52% yield. When the same reaction was repeated in the

presence of anhydrous potassium carbonate the major product (87%) was the methyl ether (**26**). When methyl fluorosulphonate was used, again in the presence of anhydrous potassium carbonate, the ether (**26**) was again produced (28%) along with a low yield (9%) of one of the isomers of the desired aryltetralin (**27**). However, the configuration at C-1 of (**27**) could not be assigned due to the complexity of the ^{1}H n.m.r. spectrum. Treatment of the sulphide (**24**) with an excess of mercury(II) trifluoroacetate gave a mixture of products from which only one major component (**28**) could be isolated, in 51% yield.

The formation of the uncyclised products (**26**) and (**28**) and the retro-dihydroarylnaphthalene lactone (**25**) in preference to the desired aryltetralin lactone (**27**) may be due to the poor stabilisation afforded to an adjacent carbocation by the 3,4,5-trimethoxyphenyl group, resulting from the geometric disposition of the 4-methoxy group,[13,14] as compared with the stabilisation afforded by 3,4-dimethoxy- or 3,4-methylenedioxyphenyl groupings.

Although the route described afforded access to a wide range of lignan lactones, the lack of control over the direction of cyclisation and the low yield of the podophyllotoxin derivative (**27**) clearly imposed limits on the overall usefulness of this approach. We therefore decided to investigate an alternative route, still involving conjugate addition as the key step, and which, it was hoped, would overcome these problems. This approach is described in the following paper.

Experimental *

I.r. and u.v. spectra were recorded on Pye Unicam SP1050 and Perkin-Elmer 402 spectrometers, respectively. ^{1}H 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 ^{1}H 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-focusing 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 LDC CI-10 integrator using a Hypersil 5μ column.

Reactions carried out under nitrogen refer to 'white spot' nitrogen used directly from the cylinder. Tetrahydrofuran (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 benzene 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 was prepared according to the method described in the literature.[15] But-2-en-4-olide was prepared as described.[16]

Preparation of 3,4-*Dimethoxybenzaldehyde Diphenyl Dithioacetal* [1-*Bis*(*phenylthio*)*methyl*-3,4-*dimethoxybenzene*].—3,4-Dimethoxybenzaldehyde (16.6 g) was dissolved in AnalaR $CHCl_3$ (120 ml) and the solution was cooled to 0 °C. Thiophenol (20.5 ml, 2 mol equiv.) was then added and dry HCl gas was bubbled through the cooled reaction mixture for *ca.* 1 h. After being stirred for a further 1 h, the solution was treated with 4M NaOH and extracted with $CHCl_3$. The extract was dried ($MgSO_4$), filtered, and evaporated to give a white gum, which was crystallised by addition of EtOH to give the diphenyl dithioacetal as a white solid (25.33 g, 69%), m.p. 67 °C; δ_H(100 MHz; $CDCl_3$) 3.80 (3 H, s, OMe), 3.85 (3 H, s, OMe), 5.40 (1 H, s, ArC*H*), and 6.40—7.40 (13 H, m, ArH).

Preparation of 3-[3″,4″-*Dimethoxy*-α,α-*bis*(*phenylthio*)*benzyl*](α-*hydroxy*-3′,4′-*methylenedioxybenzyl*)-γ-*butyrolactone* (**6**).—The diphenyl dithioacetal (13.72 g, 37.3 mmol) was dissolved in dry THF (170 ml) under argon and the solution was cooled to −78 °C. BuLi (27.25 ml of 1.37M, 37.3 mmol, 1 mol equiv.) was added to the cooled solution which was then stirred for a further 30 min at −78 °C. After this time but-2-en-4-olide (3.5 ml, 49.8 mmol, 1.33 mol equiv.) was added to the orange solution. The resulting clear solution was stirred at −78 °C for a further 90 min and then a solution of piperonal (5.61 g, 37.3 mmol) in dry THF (20 ml) added. After being stirred at −78 °C for another 2 h the solution was quenched with water, allowed to warm to room temperature, and extracted with ethyl acetate. The extract was dried over $MgSO_4$, filtered, and evaporated to give compound (**6**) (22 g, 98%) as a yellow gum, $\nu_{max.}$(KBr) 3 520 (OH) and 1 775 cm^{-1} (γ-lactone); $\lambda_{max.}$($CHCl_3$) 250 and 286 nm. For ^{1}H and ^{13}C n.m.r. spectra see Tables 1 and 2; *m/z* 235 [4%, M^+ − ArC(SPh)$_2$], 234 (5), 233 (6), 216 (5), and 149 (100).

Preparation of 3-(3′,4′-*Dimethoxybenzoyl*)*but*-2-*en*-4-*olide* (**7**).—The dibenzylbutyrolactone (**6**) (0.23 g, 0.4 mmol) was dissolved in dry THF (15 ml), and the solution was treated with mercury(II) trifluoroacetate (0.66 g, 1.5 mmol) and stirred at room temperature for 48 h. After this time the solvent was removed under reduced pressure, water was added, and the solution was extracted into ethyl acetate. The extracts were repeatedly washed with water, aqueous Na_2CO_3, and water again, and then dried ($MgSO_4$). Filtration and evaporation of the organic extract gave a brown gum (0.49 g). Purification of the product by column chromatography on silica yielded piperonal (26 mg) and 3-(3′,4′-dimethoxybenzoyl)but-2-en-4-olide (**7**) (28 mg, 30%), δ_H(100 MHz; $CDCl_3$)† 3.90 (3 H, s, OMe), 3.95 (3 H, s, OMe), 5.15 (2 H, d, *J* 2 Hz, 5-H$_2$), and 6.40—7.50 (4 H, m, 3-H and ArH); *m/z* 248.0686 (M^+, 100%), 218 (23), 202 (11), 192 (11), 167 (15), 165 (61), and 149 (51).

Preparation of Retrochinensin (**10**).—The dibenzylbutyrolactone derivative (**6**) (0.62 g, 1.0 mmol) was dissolved in TFA (6 ml) and the deep red reaction mixture was refluxed for 2 h, then allowed to cool, and was quenched with saturated aq. $NaHCO_3$. The solution was then extracted with CH_2Cl_2 and the extract was dried ($MgSO_4$), filtered, and evaporated to give a brown gum (0.62 g). Treatment with $CHCl_3$–light petroleum (b.p. 60—80 °C) gave *retrochinensin* (**10**) (0.233 g, 62%), m.p. 228—230 °C (lit.,[10] 234 °C) as a yellow solid (Found: C, 69.1; H, 4.5. Calc. for $C_{21}H_{16}O_6$: C, 69.23; H, 4.39%); $\nu_{max.}$(KBr) 1 765 cm^{-1} (γ-lactone); $\lambda_{max.}$($CHCl_3$) 258 nm. For ^{1}H and ^{13}C n.m.r. data see Tables 3 and 4; *m/z* 364 (100%, M^+).

Attempted Cyclisation of the Dibenzylbutyrolactone (**6**) *with* $SnCl_4$.—To a stirred soluton of the dibenzylbutyrolactone (**6**) (0.60 g, 1.0 mmol) in dry CH_2Cl_2 (25 ml) maintained under nitrogen was added $SnCl_4$ (0.12 ml, 1.0 mmol). The resulting deep red solution was stirred at room temperature for 1 h, poured into saturated aq. $NaHCO_3$, and thoroughly extracted

* Note that the systematic nomenclature used here does not necesssarily coincide with the numbering schemes shown in the Schemes, and used for the n.m.r. data (Tables 1—4).

† See Scheme 4 for numbering.

with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), filtered, and evaporated to provide a yellow gum (0.414 g). Examination of the crude product by ^1H n.m.r. spectroscopy showed it to be a mixture of retrochinensin (**10**) and the rearrangement products (**11a**) and (**11b**) (see below for spectral data).

Preparation of C-3, C-6-erythro (**11a**) *and* threo (**11b**) *Isomers of 3-(3″,4″-Dimethoxybenzoyl)-2-(3′,4′-methylenedioxy-α-phenylthiobenzyl)butyrolactone*.—The dibenzylbutyrolactone derivative (**6**) (0.22 g, 0.4 mmol) was dissolved in AnalaR EtOAc (20 ml) to which was added conc. $HClO_4$ (3 drops). The resulting mixture was stirred for 24 h at room temperature, after which time water was added. The solution was extracted with EtOAc and the extracts were combined, dried ($MgSO_4$), and evaporated to give a *ca.* 1:1 (h.p.l.c.) mixture of *ketones* (**11a**) and (**11b**) (180 mg, ~100%). The isomers were separated by repeat injection h.p.l.c. and were characterised as follows. The mixture of (**11a**) and (**11b**) had m.p. 124—128 °C (Found: C, 66.1; H, 4.5. $C_{27}H_{24}O_7S$ requires C, 65.85; H, 4.88%); $\nu_{max.}$(KBr) (of mixture) 1 780 (γ-lactone) and 1 680 cm^{-1} (ketone); $\lambda_{max.}$($CHCl_3$) (of mixture) 282 nm. For ^1H and ^{13}C n.m.r. data see Tables 1 and 2; *m/z* 492 (1%, M^+), 383 (30 M^+ − SPh), and 165 (100).

General Procedure for the Preparation of the Benzoyl (**17a**) *Trifluoroacetyl* (**17b**), *and* p-*Nitrobenzoyl* (**17c**) *Derivatives of Dibenzylbutyrolactone* (**6**).—The dibenzylbutyrolactone derivative (**6**) (200 mg, 0.33 mmol) was dissolved in dry THF (5 ml) under argon and the solution was cooled to −78 °C. Then a solution of BuLi in hexane (1.1 mol equiv.) was added and the resulting orange solution was stirred for 15 min at −78 °C, after which time either benzoyl chloride, trifluoroacetic anhydride, or *p*-nitrobenzoyl chloride (1.5 mol equiv.) was added. The solution was then allowed to warm to room temperature, when it was quenched with saturated aq. $NaHCO_3$ and then extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated.

(*a*) The benzoyl derivative (**17**) was isolated as a brown gum (99%), $\nu_{max.}$(KBr) 1 785 (γ-lactone) and 1 730 cm^{-1} (benzoyl ester). For ^1H and ^{13}C n.m.r. spectra see Tables 1 and 2; $\lambda_{max.}$($CHCl_3$) 246 and 286 nm.

(*b*) The trifluoroacetyl derivative (**17b**) was produced as a brown gum (96%), $\nu_{max.}$(KBr) 1 785—1 800 cm^{-1} (γ-lactone and CF_3CO_2); $\lambda_{max.}$($CHCl_3$) 252 and 284 nm; δ_H(60 MHz; $CDCl_3$)* 3.00 (1 H, m, 4-H), 3.60 (1 H, m, 3-H), 3.75 (3 H, s, OMe), 3.85 (3 H, s, OMe), 4.00 (1 H, m, 5-H_a), 4.70 (1 H, dd, *J* 2 and 9 Hz, 5-H_b), 5.90 (2 H, s, OCH_2O), 6.05 (1 H, d, *J* 4 Hz, 6-H), and 6.40—7.50 (16 H, m, ArH).

(*c*) The *p*-nitrobenzoyl derivative (**17c**) was recovered in the form of a brown gum (98%), δ_H(60 MHz; $CDCl_3$)* 2.95 (1 H, m, 4-H), 3.65 (1 H, m, 3-H), 3.80 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.90 (1 H, m, 5-H_a), 4.55 (1 H, dd, *J* 2 and 10 Hz, 5-H_b), 5.90 (2 H, s, OCH_2O), 6.05 (1 H, d, *J* 5 Hz, 6-H), and 6.50—8.40 (20 H, m, ArH).

Attempted Cyclisations of the Ester Derivatives (**17a**), (**17b**), and (**17c**).—(a) *Use of* $HClO_4$. The benzoyl derivative (**17a**) (686 mg, 1.0 mmol) was dissolved in AnalaR EtOAc (15 ml) and conc. $HClO_4$ (3 drops) was added. The reaction mixture was then stirred for 24 h after which time it was quenched with aq. $NaHCO_3$. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated to give a brown gum, which was purified by chromatography on silica (CH_2Cl_2–EtOAc gradient elution) to give the rearrangement products (**11a**) and (**11b**) in quantitative yield.

(b) *Use of* BF_3·Et_2O. The benzoyl derivative (**17a**) (115 mg, 0.16 mmol) was dissolved in dry CH_2Cl_2 (10 ml) under nitrogen and freshly distilled BF_3·Et_2O (0.02 ml, 0.16 mmol) was added dropwise. After the reaction mixture had been stirred at room temperature for 30 min, saturated aq. $NaHCO_3$ was added. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated to give a brown gum (88 mg), which was shown to be a mixture of retrochinensin (**10**) and the rearrangement products (**11a**) and (**11b**) by ^1H n.m.r. spectroscopy.

(c) *Use of TFAA*/$HClO_4$. The trifluoroacetyl derivative (**17b**) (168 mg, 0.24 mmol) was dissolved in a mixture of dry THF (8 ml) and trifluoroacetic anhydride (TFAA) (15 ml) under nitrogen. To this was added conc. $HClO_4$ (2 drops) and the resulting solution was stirred at room temperature for 24 h. After this time the reaction mixture was concentrated to give a brown gum (410 mg). Analysis of the crude reaction mixture by ^1H n.m.r. spectroscopy showed it to contain polymerised THF and the rearrangement products (**11a**) and (**11b**).

(d) *Use of TFAA*/CF_3SO_3H. The trifluoroacetyl derivative (**17b**) (206 mg, 0.30 mmol) was dissolved in a mixture of TFAA (15 ml) and AnalaR EtOAc (5 ml) under argon. Trifluoromethanesulphonic acid (2 drops) was then slowly added and the reaction mixture was stirred at room temperature for 40 h. T.l.c. analysis of the reaction mixture, however, showed only the presence of starting material even when the reaction mixture was refluxed for 8 h.

Preparation of the Methyl Ether (**17d**).—The dibenzylbutyrolactone derivative (**6**) (400 mg, 0.66 mmol) was dissolved in dry THF (30 ml) under nitrogen and the solution was cooled to −78 °C. BuLi (0.55 ml of 1.26M, 0.69 mmol) was added and the resulting orange solution stirred for 15 min at −78 °C. After this time FSO_3Me (0.054 ml, 1 mol equiv.) was added dropwise *via* a 25 μl h.p.l.c. syringe. The reaction vessel was then removed from the cooling bath and allowed to warm to room temperature during 2.5 h. Water was then added and the solution was extracted with EtOAc. The extracts were dried ($MgSO_4$), filtered, and evaporated to give a yellow gum (460 mg), which was shown to contain the desired methyl ether (**17d**) and polymerised THF by ^1H n.m.r. spectroscopy. Subsequent purification by flash chromatography on silica yielded the methyl ether (**17d**) as a white gum (367 mg, 90%), $\nu_{max.}$(KBr) 1 775 cm^{-1} (γ-lactone); $\lambda_{max.}$($CHCl_3$) 250 and 285 nm. For ^1H and ^{13}C n.m.r. spectra see Tables 1 and 2; *m/z* 507 (1%, M^+ − SPh), 472 (14), 367 (14), 364 (14), 364 (12), and 165 (100).

Attempted Cyclisation Reactions of 3-[3″,4″-Dimethoxy-α,α-bis(phenylthio)benzyl]-2-(α-methoxy-3′,4′-methylenedioxybenzyl)-γ-butyrolactone (**17d**).—(a) *Treatment of* (**17d**) *with* $Hg(OCOCF_3)_2$. Compound (**17d**) (200 mg, 0.32 mmol) was dissolved in a mixture of dry THF (15 ml) and dry glyme ($MeOCH_2CH_2OMe$) (10 ml) under nitrogen. To this solution was added a solution of $Hg(CO_2CF_3)_2$ (1.25 g, 2.9 mmol, 9 mol equiv.) in dry THF. The resulting mixture was stirred at room temperature for 72 h after which time the reaction was quenched with water and EtOAc was added. The organic extracts were dried ($MgSO_4$) and evaporated to give an orange gum (386 mg), which was shown to contain 5 discernible compounds by t.l.c. (CH_2Cl_2–EtOAc, 95:5). Separation of the crude product by column chromatography on silica (CH_2Cl_2–EtOAc, 95:5) yielded one major product, R_F 0.56, which was 3-(3″,4″-dimethoxy-α-phenylthiobenzylidene)-2-(α-methoxy-3′,4′-methylenedioxybenzyl)-γ-butyrolactone (**18**) (42 mg, 21%), $\nu_{max.}$(KBr) 1 785 cm^{-1} (γ-lactone). For ^1H n.m.r. data see Table 1; *m/z* 474 (1%, M^+ − MeOH), 321 (9), and 165 (100).

* See structure (**17**) for numbering scheme.

Table 3. ^{1}H N.m.r. spectra of arylnaphthalene derivatives[a]

Proton(s)	(9)	(10)	(13)	(15a)[b]	(25)	(27)
1-H	4.5m		3.85m	4.12d (11, 3)	3.80m	4.2—4.6m
2-H	2.4—2.8m		3.60ddd (3, 8, 16)	3.18dd (11.3, 14.3)	3.40ddd (3, 9, 16)	3.1—3.3m
3-H				2.92m (3, 14.3, 7, 11)		
4-H	2.9br d (6)	8.30s	7.45d (3)	6.38d (3)	7.25d (3)	6.00br s
5-H	6.30s	7.14s	6.30s	6.40s	6.70s	6.5—8.2m
8-H	6.60s	7.36s	6.90s	6.97s		
9-H		5.20s	4.45t (8), 3.85m		4.25t (9), 3.80m	
10-H_2	3.75—4.15m			4.03dd (8.8, 11), 4.50dd (8.8, 7)		4.2—4.6m
OMe	3.60s, 3.85s	3.88s, 3.98s	3.95s	3.65s, 3.85s	3.20s, 3.75s, 3.85s	3.84s, 3.86s
OCH_2O	5.90s	6.10s	6.00s	5.93s	5.90s	6.00br s

[a] All spectra recorded in $CDCl_3$ solution at 100 MHz unless otherwise indicated. Numbering schemes used are those shown in the Schemes. [b] 360 MHz spectra.

Table 4. ^{13}C N.m.r. spectra of arylnaphthalene derivatives[a]

Carbon	(9)	(15a)	(13)	(25)	(10)
1	48.91	45.74	50.53	47.78	133.00
2	45.79	43.57	40.87	43.70	131.31
3	40.04	42.70	127.08	124.00	124.55
4	32.57	68.64	132.32	138.65	138.43
5	108.06	108.25	108.74	108.18	102.11
6	147.84	150.11	149.53	145.19	150.54
7	147.75	148.13	149.53	152.78	149.47
8	111.50	112.63	110.88	152.83	111.79
8a	131.32	133.62	131.73	129.16	128.60
4a	126.90	126.11	125.89	125.42	129.02
9	175.62	174.93	71.93	72.30	69.53
10	71.04	67.16	169.64	169.52	171.54
1′	136.99	136.66	134.77	132.14	133.46
2′	113.00	112.93	112.35	107.42	112.40
3′	147.75	147.92	146.82	147.88	149.16
4′	146.65	146.70	146.82	146.07	148.42
5′	109.25	109.30	109.26	109.60	105.23
6′	123.00	123.03	121.68	119.91	121.68
OCH_2O	100.98	101.07	101.67	101.00	101.89
OMe	55.89	55.86, 56.00	56.05, 55.89	56.10, 59.95, 60.71	56.7
PhCO		166.14			

[a] All spectra recorded in $CDCl_3$ solution. Numbering schemes used are those in the Schemes.

(b) *Treatment of compound* (**6**) *with* FSO_3Me. Compound (**6**) (250 mg, 0.42 mmol) was dissolved in dry THF (15 ml) under nitrogen and the solution was cooled to −78 °C. BuLi (0.33 ml of 1.38M, 0.46 mmol) was added and the resulting orange solution was stirred for 15 min at −78 °C, when FSO_3Me (0.17 ml, 2.1 mmol) was added. The reaction vessel was immediately taken out of the cooling bath and allowed to warm to room temperature during 2.5 h. The reaction mixture was then quenched with water and extracted with CH_2Cl_2. The organic layer was subsequently dried ($MgSO_4$), filtered, and evaporated to leave a yellow gum (180 mg). Analysis of the crude product by t.l.c. (CH_2Cl_2–EtOAc, 9:1) showed it to contain two close running spots on t.l.c. Subsequent separation by column chromatography on silica gave the olefin (**18**) (45 mg, 20%) as one fraction (R_F 0.61) which had been previously synthesised (see above), and a mixture (85 mg) containing more of the olefin and another component (R_F 0.58) as a second fraction.

Preparation of C-3, C-6-erythro-3-(3″,4″-*Dimethoxybenzyl*)-3-(α-*hydroxy*-3′,4′-*methylenedioxybenzyl*)*butyrolactone* (**8**).—Two spoonfuls (a large excess) of Raney nickel were added to a solution of the dibenzylbutyrolactone derivative (**6**) (0.70 g, 1.16 mmol) in dry ethanol (100 ml). The suspension was refluxed under nitrogen for 5 h, after which the reaction mixture was allowed to cool and was then filtered through Celite, and the filter washed with dry ethanol. The resulting filtrate was concentrated on a rotary evaporator and allowed to crystallise in an ice-bath. The desulphurised adduct (**8**) was isolated as a white solid (0.235 g, 51%), m.p. 156—158 °C (lit.,[7] 158—159 °C); $\nu_{max.}$(KBr) 3 520 (OH) and 1 770 cm^{-1} (γ-lactone). See Tables 1 and 2 for ^{1}H and ^{13}C n.m.r. data; *m/z* 368 (1%, $M^+ - H_2O$), 236 (20), and 151 (100).

Preparation of 3-*Hydroxymethyl*-6,7-*dimethoxy*-1-(3′,4′-*methylenedioxyphenyl*)-1,2,3,4-*tetrahydro*-2-*naphthoic Acid* γ-*Lactone* (**9**).—Compound (**8**) (43 mg, 0.11 mmol) was dissolved in dry CH_2Cl_2 (10 ml) under nitrogen at room temperature. To this clear solution was added a solution of TFA (0.3 ml, 0.33 mmol) in dry CH_2Cl_2 (15 ml). The resulting solution was stirred at room temperature for 1 h, after which time it was washed with water, dried ($MgSO_4$), filtered, and evaporated to give the aryltetralin (**9**) as a white solid (41 mg, 100%), m.p. 216—218 °C (lit.,[7] 223—224 °C) (Found: C, 68.7; H, 5.1. Calc for $C_{21}H_{20}O_6$: C, 68.48; H, 5.43%); $\nu_{max.}$(KBr) 1 775 cm^{-1} (γ-lactone). See Tables 3 and 4 for ^{1}H and ^{13}C n.m.r. data; *m/z* 368 (100%, M^+).

Attempted Cyclisation of Compound (**11b**) *with TFA*.—Compound (**11b**) (150 mg, 0.30 mmol) was dissolved in dry CH_2Cl_2 (25 ml) under nitrogen at room temperature. To this solution was added TFA (20 ml) during 5 days, in 1 ml aliquots. After this time the reaction mixture was washed with water, dried ($MgSO_4$), filtered, and evaporated to give a yellow gum (130 mg). Purification of the crude product by column chromatography on silica produced two fractions, the first of which (76 mg, 51%) was shown to be the isomer (**11a**). The second fraction was (E)-3-(3″,4″-*dimethoxybenzyl*)-2-*methylenedioxybenzylidene*)*butyrolactone* (**6**), which was obtained as a yellow solid (40 mg, 34%), m.p. 188—190 °C (Found: C, 66.0; H, 4.6. $C_{21}H_{18}O_7$ requires C, 65.97; H, 4.71%); $\nu_{max.}$(KBr) 1 745 cm^{-1} (γ-lactone); $\lambda_{max.}$(MeOH) 235 nm. For ^{1}H n.m.r. data see Table 1; *m/z* 382 (6%, M^+) and 165 (100).

Attempted Cyclisation of Compound (**11b**) *with Mercury*(II) *Trifluoroacetate*.—Compound (**11b**) (195 mg, 0.40 mmol) was dissolved in dry THF (10 ml) under nitrogen. A solution of

$Hg(OCOCF_3)_2$ (1.69 g, 4.0 mmol) in dry THF (15 ml) was added to the solution, which was then stirred at room temperature for 24 h. Water was then added and the solution was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), filtered, and evaporated to give a brown gum (225 mg). Purification by column chromatography on silica (CH_2Cl_2–EtOAc, 9:1) gave one major fraction (70 mg) having R_F 0.23 (CH_2Cl_2–EtOAc, 9:1). Recrystallisation from methanol gave a white solid, which was shown to be the benzylic alcohol (**9**) (30 mg, 19%), $\nu_{max.}$(KBr) 3 250 (OH), 1 770 (γ-lactone), and 1 680 cm^{-1} (ketone). For the ^1H n.m.r. spectrum see Table 1; *m/z* 400.1151 (4%, M^+), 350 (127), and 165 (100).

Preparation of 3-(α-*Hydroxy*-3″,4″-*dimethoxybenzyl*)-2-(3,4-*methylenedioxy*-α-*phenylthiobenzyl*)-γ-*butyrolactone* (**12**) .—A mixture (2 g, 4.0 mmol) of compounds (**11a**) and (**11b**) was suspended in dry MeOH (120 ml). The suspension was cooled to 0 °C and $NaBH_4$ (500 mg, 13.2 mmol) was slowly added to the stirred suspension. The reaction mixture was stirred at 0 °C for 4 h after which time it was carefully acidified with 0.3M HCl and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), filtered, and evaporated to give the alcohol (**12**) as a yellow gum (1.91 g, 95%), which was shown by h.p.l.c. to be a 50:50 mixture of the epimeric alcohols (**12**) (isomeric at C-6) (Found: C, 65.5; H, 5.2. $C_{27}H_{26}O_7S$ requires C, 65.59; H, 5.26%); $\nu_{max.}$(KBr) 3 510 (OH) and 1 770 cm^{-1} (γ-lactone); $\lambda_{max.}$(MeOH) 230 and 280 nm. For ^1H and ^{13}C n.m.r. data see Tables 1 and 2.

Attempted Cyclisation of Compound (**16**) *with TFA*.—Compound (**12**) (120 mg, 0.24 mmol) was dissolved in dry CH_2Cl_2 (20 ml) under nitrogen at room temperature. To this solution was added TFA (1.5 ml, 12 mmol) and the resulting mixture was stirred for 3 h, when water was added. The solution was extracted with CH_2Cl_2 and the extracts were dried ($MgSO_4$), filtered, and evaporated to give a brown gum (133 mg). Examination of the crude product by t.l.c. (CH_2Cl_2–EtOAc, 9:1) showed it to be a mixture of at least 5 compounds. Further reactions on compound (**12**) using high concentrations of TFA and heat gave similar results.

Preparation of 4-(3′,4′-*Dimethoxyphenyl*)-3-*hydroxymethyl*-6,7-*methylenedioxy*-3,4-*dihydro*-2-*naphthoic Acid* γ-*Lactone* (**13**).—Compound (**12**) (300 mg, 0.61 mmol) was dissolved in dry CH_2Cl_2 (10 ml) under argon and freshly distilled FSO_3Me (0.25 ml, 3.1 mmol) was added. The resulting deep red solution was stirred at room temperature for 18 h after which time water was added and the solution was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), filtered, and evaporated to give a clear gum (260 mg). Purification by column chromatography on silica (CH_2Cl_2–EtOAc, 9:1) gave a white solid (110 mg, 50%), which was shown to be the *dihydroarylnaphthalene* (**13**), m.p. 186—190 °C (Found: C, 68.6; H, 4.9. $C_{21}H_{18}O_6$ requires C, 68.85; H, 4.92%); $\nu_{max.}$(KBr) 1 760 cm^{-1} (γ-lactone); $\lambda_{max.}$(MeOH) 240 nm. See Tables 3 and 4 for ^1H and ^{13}C n.m.r. data; *m/z* 366 (100%, M^+), 336 (20), 335 (48), and 291 (65).

Oxidation of Compound (**13**) *with DDQ*.—Compound (**13**) (110 mg, 0.30 mmol) was dissolved in a mixture of dry benzene (30 ml) and AnalaR $CHCl_3$ (5 ml). To this solution was added DDQ (340 mg, 1.5 mmol) and the resulting suspension was refluxed under argon for 48 h. After this time the reaction mixture was allowed to cool to room temperature and saturated aq. Na_2CO_3 was added. The solution was extracted with EtOAc, and the combined extracts were dried ($MgSO_4$), filtered, and evaporated to give a brown solid (108 mg, ~100%), which was identified as retrochinensin (**10**) by ^1H n.m.r. spectroscopy.

Preparation of 3-(α-*Benzoyloxy*-3″,4″-*dimethoxybenzyl*)-2-(3′,4′-*methylenedioxy*-α-*phenylthiobenzyl*)-γ-*butyrolactone* (**14**).—Compound (**12**) (1.5 g, 3.0 mmol) was dissolved in dry THF (30 ml) under argon the solution was cooled to −78 °C. BuLi (1.3 ml of 2.5M, 3.3 mmol) was added and the resulting deep orange solution was quenched at −78 °C with benzoyl chloride (0.4 ml) and subsequently allowed to warm to room temperature during 2 h. After this time saturated aq. $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), filtered, and evaporated to give a yellow gum (1.7 g). Purification by column chromatography on silica gave one main fraction (a yellow gum) which was shown (h.p.l.c.) to be a mixture of the epimeric benzoates (**14**) (isomeric at C-6) (1.56 g, 86%), $\nu_{max.}$(Nujol) 1 775 (γ-lactone) and 1 730 cm^{-1} ($PhCO_2$); δ_H(60 MHz; $CDCl_3$)* 3.3 (2 H, m, 3- and 4-H), 3.8 (6 H, s, 2 × OMe), 4.3 (2 H, m, 5-H_2), 4.7 (1 H, m, 6-H), 5.9 (2 H, s, OCH_2O), 6.0 (1 H, d, *J* 4 Hz, 7-H), and 6.6—8.1 (16 H, m, ArH). See Table 2 for ^{13}C n.m.r. data.

Preparation of 4-*Benzoyloxy*-3-*hydroxymethyl*-1-(3′,4′-*methylenedioxyphenyl*)-6,7-*dimethoxy*-1,2,3,4-*tetrahydroxy*-2-*naphthoic Acid* γ-*Lactone* (**15a**).—Compounds (**14**) (300 mg, 0.5 mmol) were dissolved in dry CH_2Cl_2 (10 ml) under nitrogen. An excess of anhydrous K_2CO_3 was added followed by FSO_3Me (0.2 ml, 2.5 mmol). The resulting orange solution was stirred for 20 h at room temperature after which time water was added and the solution was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), filtered, and evaporated to give a gum (275 mg), which showed three spots on t.l.c. (CH_2Cl_2–EtOAc, 9:1) at R_F values of 0.80, 0.75, and 0.69. Separation by column chromatography on silica gave three fractions. The first fraction (50 mg) (R_F 0.80) was an unidentifiable mixture. The fraction at R_F 0.69 (15 mg) was shown to be the dihydroarylnaphthalene (**13**) whilst the fraction at R_F 0.75 gave the *title compound* (**15a**) (70 mg, 29%) as a white solid, m.p. 178—180 °C (Found: C, 69.1; H, 5.0. $C_{28}H_{24}O_8$ requires C, 68.85; H, 4.92%); $\nu_{max.}$ 1 785 (γ-lactone) and 1 720 cm^{-1} ($PhCO_2$). See Tables 3 and 4 for ^1H and ^{13}C n.m.r. data; *m/z* 488.1471 (20%, M^+) and 367 (100, M^+ − SPh).

Cyclisation of Compound (**14**) *using* Me_3OBF_4.—Lactones (**14**) (750 mg, 1.25 mmol) were dissolved in dry CH_2Cl_2 (15 ml) under argon, and several spatulas of anhydrous K_2CO_3, followed by Me_3OBF_4 (0.93 g, 6.3 mmol), were added. The resulting black solution was stirred at room temperature for 24 h after which time water and CH_2Cl_2 were added. The CH_2Cl_2 layer was then separated, dried ($MgSO_4$), filtered, and evaporated to yield a grey gum. Part of the crude product was purified by repeat injection h.p.l.c. (eluant: 0.3% MeOH in CH_2Cl_2), when one major fraction was isolated (130 mg, 65%—extrapolated yield) and was shown to consist of two inseparable peaks of equal area. The peak at shorter retention time was unequivocally shown to be compound (**15a**) by h.p.l.c. comparison with an authentic sample. The ^1H n.m.r. spectrum of the mixture was similar to that of (**15a**) but most peaks were doubled up thus indicating the presence of another isomer. (**15b**). The two additional MeO peaks had shifts of δ_H 3.48 and δ 3.88 whilst the extra –OCH_2O– peak was at δ_H 5.90.

Preparation of 3,4-*Methylenedioxybenzaldehyde Diphenyl Dithioacetal* [1-*Bis*(*phenylthiomethyl*)-3,4-*methylenedioxybenzene*].—Piperonal (15 g, 0.1 mmol) was dissolved in AnalaR $CHCl_3$ (75 ml) and the solution was cooled to 0 °C. Dry PhSH (22 g, 0.2 mmol) was added and dry HCl gas was passed through the mixture for 1 h. The reaction mixture was left to stand for 1 h at 0 °C, and then 4M NaOH was added and the mixture was

* See Scheme 5 for numbering scheme.

extracted with $CHCl_3$. The extract was dried ($MgSO_4$), filtered, and evaporated to give the diphenyl dithioacetal as a white solid (34 g, 97%), m.p. 46—47 °C; δ_H (60 MHz; $CDCl_3$) 5.3 (1 H, s, ArC*H*), 5.7 (2 H, s, OCH_2O), and 6.5—7.5 (13 H, m, aromatics).

Preparation of 2-(α-*Hydroxy*-3′,4′,5′-*trimethoxybenzyl*)-3-[3″,4″-*methylenedioxy*-α,α-*bis*(*phenylthio*)*benzyl*]-γ-*butyrolactone* (**21**).—3,4-Methylenedioxybenzaldehyde diphenyl dithioacetal (15 g, 44 mmol) was dissolved in dry THF (200 ml) under argon and the solution was cooled to −78 °C. BuLi (24.75 ml of 1.98M, 49 mmol) was then added and the resulting yellow solution was stirred for 90 min at −78 °C. But-2-en-4-olide (4.30 g, 51 mmol) was then added to the reaction mixture, which was stirred for a further 90 min at −78 °C, after which time a solution of 3,4,5-trimethoxybenzaldehyde (9.61 g, 49 mmol) in dry THF (30 ml) was added. The reaction mixture was stirred at −78 °C for 2 h and quenched with water. The mixture was allowed to warm to room temperature and was then extracted with EtOAc. The extracts were dried ($MgSO_4$), filtered, and evaporated to give a yellow gum (31.8 g). Part of the crude product (20 g) was purified by column chromatography on silica to yield the *title dibenzylbutyrolactone* (**21**) as a white gum (16.5 g, 97%) (Found: C, 64.4; H, 5.4. $C_{34}H_{32}O_8S_2$ requires C, 64.56; H, 5.06%); $\nu_{max.}$(KBr) 3 500 (OH) and 1 780 cm^{-1} (γ-lactone). For ^1H n.m.r. data see Table 1.

Preparation of 3-(3″,4″-*Methylenedioxybenzoyl*)-2-(3′,4′,5′-*trimethoxy*-α-*phenylthiobenzyl*)-γ-*butyrolactone* (**22**).—Compound (**21**) (10 g, 16 mmol) was dissolved in AnalaR EtOAc (100 ml) to which was added conc. $HClO_4$ (15 drops). The reaction mixture was stirred for 19 h at room temperature, after which time water was added. The solution was extracted with EtOAc and the extracts were dried ($MgSO_4$), filtered, and evaporated to give a mixture of the C-3, C-6-*erythro*- and *threo*-isomers of the *ketone* (**22**) in the form of a brown solid (7.0 g, 85%), m.p. 148 °C (Found: C, 64.35; H, 5.1. $C_{28}H_{26}O_8S$ requires C, 64.37; H, 4.98%); $\nu_{max.}$(KBr) 1 780 (γ-lactone) and 1 680 cm^{-1} (ketone). For ^1H and ^{13}C n.m.r. data see Tables 1 and 2; *m/z* 413 (17%, M^+ − SPh), 412 (15), and 149 (100).

Preparation of 3-(α-*Hydroxy*-3″,4″-*methylenedioxybenzyl*)-2-(3′,4′,5′-*trimethoxy*-α-*phenylthiobenzyl*)-γ-*butyrolactone* (**23**).—The ketone (**22**) (6.8 g, 13 mmol) was suspended in dry MeOH (150 ml) and the mixture was cooled to 0 °C and treated slowly with $NaBH_4$ (1.48 g, 39 mmol). The resulting reaction mixture was stirred at 0 °C for 4 h after which it was acidified and extracted with EtOAc. The extracts were dried ($MgSO_4$), filtered, and evaporated to give a white gum (6.1 g). The crude product was purified by column chromatography on silica to give a mixture of the C-3, C-6-*erythro*- and *threo*-isomers of the alcohol (**23**) as a clear gum (3.77 g, 55%), $\nu_{max.}$(KBr) 3 500 (OH) and 1 770 cm^{-1} (γ-lactone). For ^1H and ^{13}C n.m.r. spectra see Tables 1 and 2; *m/z* 506 (0.4%, $M^+ - H_2O$), 415 (23, M^+ − SPh), 414 (100, M^+ − PhSH), and 383 (30).

Preparation of 3-(α-*Benzoyloxy*-3″,4″-*methylenedioxybenzyl*)-2-(3′,4′,5′-*trimethoxy*-α-*phenylthiobenzyl*)-γ-*butyrolactone* (**24**).—The alcohol (**23**) (3.43 g, 6.5 mmol) was dissolved in dry THF (40 ml) under argon and the solution was cooled to −78 °C. To this cooled solution was added BuLi (7.5 mmol) and the resulting yellow solution was stirred at −78 °C for 30 min. After this time benzoyl chloride (0.88 ml, 6.3 mmol) was added and the reaction mixture was allowed to warm to room temperature; 3 h after the addition of benzoyl chloride, the reaction mixture was quenched with saturated aq. $NaHCO_3$ and extracted with EtOAc. The extract was dried ($MgSO_4$), filtered, and evaporated to give a brown gum (4.4 g). The crude product was purified by column chromatography on silica to give the *erythro* and *threo* isomer is (isomeric at C-6) of the benzoate (**24**) as a white gum (3.35 g, 82%), $\nu_{max.}$(KBr) 1 780 (γ-lactone) and 1 730 cm^{-1} (benzoyl carbonyl). For ^1H and ^{13}C n.m.r. data see Tables 1 and 2; *m/z* 518.1577 (0.4%, M^+ − PhSH), 396 (3), 368 (8), 263 (19), and 255 (10).

Preparation of 3-*Hydroxymethyl*-5,6,7-*trimethoxy*-4-(3′,4′-*methylenedioxyphenyl*)-3,4-*dihydro*-2-*naphthoic Acid* γ-*Lactone* (**25**).—The benzoate derivative (**24**) (400 mg, 0.64 mmol) was dissolved in dry CH_2Cl_2 under argon and Me_3OBF_4 (471 mg, 3.2 mmol) was added. The resulting red solution was stirred for 17 h after which time water was added and the reaction mixture was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), filtered, and evaporated to give a grey solid. Purification of the crude products by column chromatography on silica yielded the *title compound* (**25**) (135 mg, 52%) as a white solid, m.p. 170—172 °C (Found: C, 66.6; H, 5.3. $C_{22}H_{20}O_7$ requires C, 66.66; H, 5.05%); $\nu_{max.}$(KBr) 1 770 cm^{-1} (γ-lactone). See Tables 3 and 4 for ^1H and ^{13}C n.m.r. data; *m/z* 396 (100%, M^+).

Attempted Cyclisation of the Sulphide (**24**) *with* Me_3OBF_4 *in the Presence of* K_2CO_3.—Ester (**24**) (150 mg, 0.24 mmol) was dissolved in dry CH_2Cl_2 (10 ml) under argon and several spatulas of anhydrous K_2CO_3 were added. Me_3OBF_4 (106 mg, 0.72 mmol) was then added to the suspension which was stirred for 19 h. After this time water was added and the solution was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), filtered, and evaporated to give the methyl ether (**26**) as a white solid (114 mg, 87%), $\nu_{max.}$(KBr) 1 785 (γ-lactone) and 1 730 cm^{-1} ($PhCO_2$). For ^1H n.m.r. data see Table 1; *m/z* 550.1889 (4%, M^+) and 211 (100).

Preparation of 4-*Benzoyloxy*-3-*hydroxymethyl*-6,7-*methylenedioxy*-1-(3′,4′,5′-*trimethoxyphenyl*)-1,2,3,4-*tetrahydro*-2-*naphthoic Acid* γ-*Lactone* (**27**).—The sulphide (**24**) (400 mg, 0.64 mmol) was added to a suspension of anhydrous K_2CO_3 (two spatulas) in dry CH_2Cl_2 (15 ml) under argon. To this suspension was then added freshly distilled FSO_3Me (0.26 ml, 3.2 mmol, 5 mol equiv.). The resulting orange solution was stirred for 18 h, when water was added and the reaction mixture was extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), filtered and evaporated to give a brown gum (340 mg). Column chromatography on silica yielded two fractions, with R_F values of 0.64 and 0.49 on t.l.c. (CH_2Cl_2–EtOAc, 9:1). The fraction at R_F 0.49 (97 mg, 28%) was shown to be the previously synthesised methyl ether (**26**) by ^1H n.m.r. spectroscopy. The fraction at R_F 0.64 (30 mg, 9%) was the title compound (**27**), $\nu_{max.}$(KBr) 1 780 (γ-lactone) and 1 730 cm^{-1} (benzoyl carbonyl). For ^1H n.m.r. data see Table 3; *m/z* 518.1577 (0.8%, M^+), 397 (5, M^+ − OCOPh), 263 (13), and 105 (100).

Attempted Cyclisation of the Sulphide (**24**) *with* $Hg(OCOCF_3)_2$.—The sulphide (**24**) (300 mg, 0.48 mmol) was dissolved in dry THF (5 ml) under nitrogen, and a solution of $Hg(OCOCF_3)_2$ (1.02 g, 2.4 mmol) in dry THF (10 ml) was added. The resulting orange solution was stirred at room temperature for 15 h after which time it was colourless. Saturated aq. $NaHCO_3$ was then added and the solution was extracted with EtOAc. The extracts were dried ($MgSO_4$), filtered, and evaporated to give a white gum (340 mg), which gave two spots on t.l.c. (CH_2Cl_2–EtOAc, 9:1) at R_F values 0.90 and 0.48. The two products were separated by column chromatography on silica to give $(PhS)_2$ (75 mg) as the higher fraction. The lower fraction at R_F 0.48 (133 mg) showed as a very broad peak by h.p.l.c. and was consequently dissolved in $CHCl_3$ and extracted with dil. HCl. Evaporation gave 3-(α-benzoyloxy-3″,4″-methylenedioxybenzyl)-2-α-hydroxy-3′,4′,5′,-trimethoxybenzyl)-γ-butyrolactone (**28**) as a white solid (130

mg, 51%), m.p. 272—276 °C; $\nu_{max.}$($CHCl_3$) 3 550 (OH), 1 785 (γ-lactone), and 1 740 cm^{-1} (benzoyl carbonyl); δ_H(60 MHz; $CDCl_3$)* 2.9—3.4 (2 H, m, 3- and 4-H), 3.8 (6 H, s, 2 × OMe), 3.85 (3 H, s, OMe), 4.1 (2 H, d, *J* 6 Hz, 5-H_2), 4.9 (1 H, m, 6-H), 5.9 (3 H, br s, 7-H and OCH_2O), and 6.5—8.1 (10 H, m, ArH); *m/z* 396 (1%, $M^+ - H_2O -$ OCOPh), 340 (14), 218 (24), 196 (18), and 105 (100).

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* N.m.r. numbering scheme is given in Scheme 7.

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