Synthesis of Lignan Lactones by Conjugate Addition of Thioacetal Carbanions to Butenolide

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The conjugate addition of carbanions derived from arylbis(phenylthio)methanes to butenolide followed by trapping of the enolate anion so generated by a benzyl halide affords adducts (8) containing the basic lignan skeleton. Desulphurisation of these adducts by Raney nickel affords a short efficient synthesis of *trans*-dibenzylbutyrolactones and this route has been used to prepare enterolactone (9c) and an anti-tumour lignan (9b), derived from *Bursera schlechtendalii*. Treatment of the adducts (8) with heavy-metal salts induces cyclisation leading to arylnaphthalene lactones, including retrojusticidin B (13).

Lignan lactones such as (1)—(6) are known to exhibit a wide range of biological activity,[1-10] and have attracted great interest on account of their anti-tumour properties.[3-8] Furthermore, the recent observation of cyclic excretion of lignan lactones, in particular enterolactone, by human beings, particularly during the luteal phase of the menstrual cycle and in early pregnancy, is very striking.[11-14] The biological significance of these compounds remains to be established but their resemblance to anti-tumour agents suggsets a relationship to the control of cell growth.

We have previously reported the synthesis and reactions of a series of dilactones of type (1),[15] and in this paper report a short efficient synthesis of *trans*-dibenzylbutyrolactones,[16] and a novel mercury-mediated synthesis of certain arylnaphthalene lactones.[17]

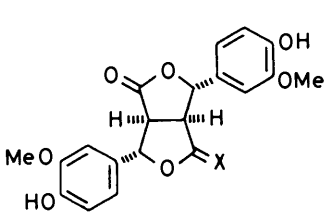
In common with other groups [18-21] we were attracted by the possibility of generating the basic lignan skeleton by a tandem addition, as shown in Scheme 1.

We chose to utilise the arylbis(phenylthio)methanes (7; R = Ph), readily prepared from the corresponding aromatic aldehydes, because we proposed to displace the phenylthio group by heavy metals (see later). The *trans*-adducts (8) were obtained in 65—70% yield and on treatment with Raney nickel in refluxing ethanol gave the *trans*-dibenzylbutyrolactones (9) in quantitative yield (Scheme 2). Thus the di-*O*-methyl enterolactone (9a) was obtained in 68% overall yield and was converted into enterolactone (9c) [22-25] in 80% yield by demethylation with boron tribromide. This therefore constitutes a short, efficient total synthesis of enterolactone. Both of the previously reported syntheses of this compound involve multistep procedures, one of which proceeds in 35% yield from a fairly advanced precursor,[26] whilst no yields are given in the other case.[27] Another recently reported synthesis proceeds in 35% overall yield.[28]

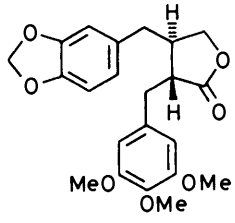
Similarly the methylenedioxy-analogue (9b) was prepared in 67% overall yield by tandem addition followed by Raney-nickel reduction. This compound is a natural product which has been isolated from *Bursera schlechtendalii* and has been reported to exhibit anti-tumour activity.[3]

The ^1H and ^{13}C n.m.r. spectra of compounds (8a), (8b), (9a), and (9b) are listed in Table 1 and the ^{13}C n.m.r. spectra of compounds (9a) and (9b) are listed in Table 2. They confirm the *trans*-stereochemistry of the two benzyl substituents and also, by comparison with known compounds (9d), (9e), and (9f),[29,30] confirm the overall gross structure assigned to these compounds.

The bis(phenylthio) derivatives (8) were also considered as possible precursors for lignan lactones of the aryltetralin and aryldihydronaphthalene series. The reaction of *gem*-diarylthio compounds with a heavy-metal salt or an alkylating agent can provide access to stabilised cations or their equivalents under



(1) X = O
(2) X = H_2



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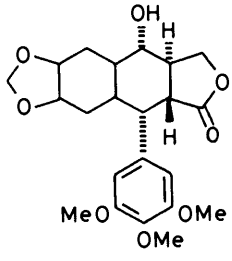

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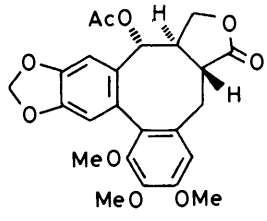

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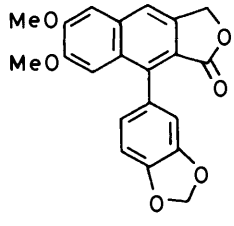
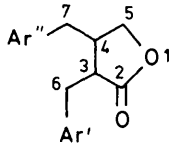


(6)

non-acidic conditions. On the other hand, benzylic alcohols readily yield cations under mild acidic conditions. It is therefore conceivable in a molecule such as (10), containing both groups, that ring closure could be carried out in a controlled fashion to give access to two groups of lignan lactones (Scheme 3).[18,19]

In order to test the feasibility of the heavy-metal-initiated ring closure without possible complications owing to the presence of a benzylic alcohol group, we initiated a study of the thioacetal adducts (8a) and (8b), prepared above. Thus, we hoped that treatment of adduct (8b) with a heavy-metal salt would yield a stabilised cation which could undergo

Table 1. ^{1}H N.m.r. spectra (360 MHz) [a]



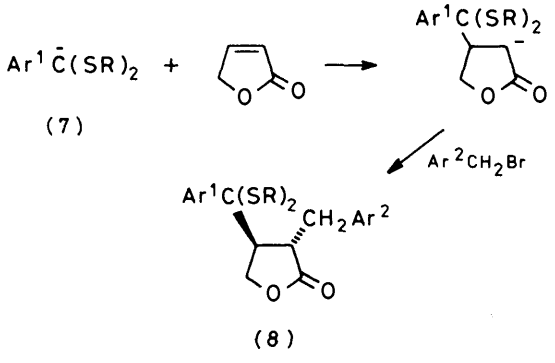
	(8a)	(8b)	(9a)	(9b)
5a-H	4.42dd (3, 10) [b]	4.42dd (3, 10)	4.10dd (7, 9)	4.09dd (7, 9)
5b-H	3.55dd (8, 10)	3.54dd (8, 10)	3.85dd (8, 9)	3.8m
6a-H	3.11dd (5, 14)	3.05dd (5, 14)	3.05dd (5, 14)	2.95dd (5, 14)
6b-H	2.81dd (6, 14)	2.79dd (6, 14)	2.90dd (7, 14)	2.86dd (7, 14)
3-H	3.34dt (3, 5)	3.25dt (3, 5)		
4-H	2.95dt (8, 3)	2.85dt (8, 3)	2.49m (2 H)	2.46m (2 H)
7a-H			2.61m (2 H)	2.55m (2 H)
7b-H				
OMe	3.72s	3.75s	3.75s	3.81s
OMe	3.73s	3.85s	3.77s	3.84s
OCH_2O		5.95 AB		5.90 AB
Arom	6.5—7.4m	6.5—7.4m	6.5—7.3m	6.4—7.3m

[a] All spectra run in $CDCl_3$. [b] Coupling constants (Hz) in parentheses.

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

	(9a)	(9b)	(9d) [b]	(9e) [b]	(9f) [b]
C-2 [c]	178.41	178.62	178.6	178.2	177.9
C-3	46.30	46.52	46.5	46.3	46.1
C-4	41.25	41.09	40.9	41.2	41.0
C-5	71.13	71.16	71.3	71.0	70.7
C-6	35.09	35.64	34.5	34.6	34.4
C-7	38.51	38.29	38.3	38.1	37.9
1'1''	139.57	131.65	129.5	131.1	131.2
	139.32	130.20	129.4	129.5	131.0
2'2''	114.86	108.78	111.3	110.9	109.0
	114.49	108.26	110.8	109.2	108.4
3'3''	159.85	149.09	146.5	147.5	147.4
	159.85	148.00	146.4	146.4	147.4
4'4''	112.35	147.90	144.3	146.1	146.0
	111.88	146.35	144.2	144.2	145.8
5'5''	129.69	112.29	114.3	114.3	107.8
	129.63	111.23	113.9	107.2	107.8
6'6''	121.58	121.39	121.9	122.0	121.8
	120.90	121.56	121.2	121.0	121.1
OCH_2O		101.05		100.8	100.6
OMe	55.09	55.83	55.7	55.7	

[a] All spectra run in $CDCl_3$. [b] Taken from refs. 29, 30. [c] See Table 1 for numbering scheme.

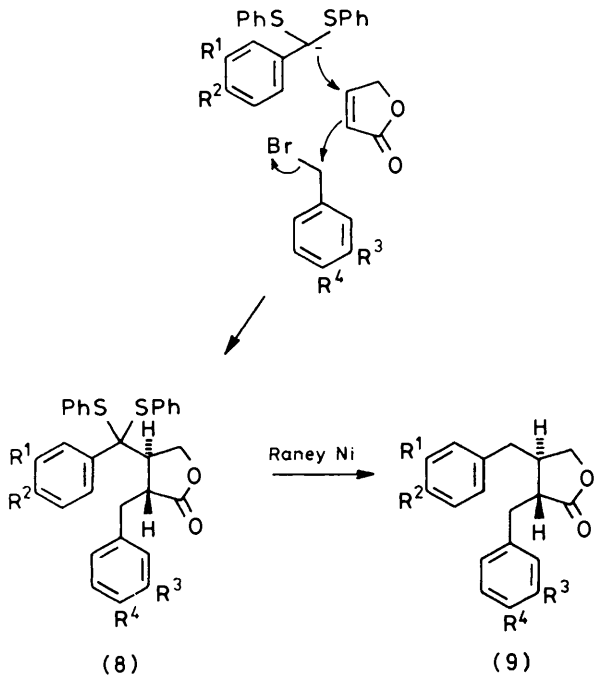


Scheme 1

cyclisation to compound (11) followed by heavy-metal-assisted elimination to give the naphthalene derivative (12) (Scheme 4). From (12), by hydrogenation it should be possible to obtain the tetrahydronaphthalene lignan lactones in a stereocontrolled fashion, or naphthalene lignans by dehydrogenation. In the event, it was found that, with all the reagents tried [$Hg(O_2CCF_3)_2$, $HgCl_2$, and $CuCl_2$] under a variety of conditions, the only cyclised product obtained was the arylnaphthalene (13). Accepting this we found that optimum conditions for the cyclisation of the butyrolactone (8b) involved using an excess of $Hg(O_2CCF_3)_2$ and passing a stream of oxygen through the reaction mixture to give retrojusticidin B (13) in 59% yield. When shorter reaction times were used two acyclic lactones (14) and (15) were also isolated, each in 16% yield, along with diphenyl disulphide.

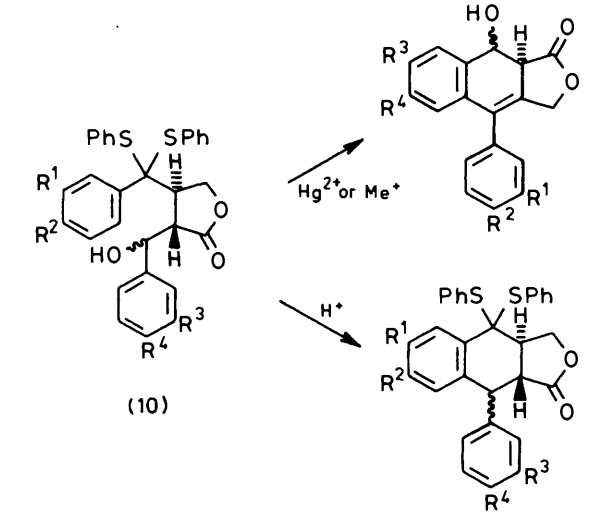
Treatment of (8a) under similar conditions gave two arylnaphthalene lactones (16) and (17) in 20 and 34% yield (Scheme 5). Compound (16) was completely characterised, but (17) was not obtained pure and its structure is based on u.v., ^{1}H n.m.r., and mass spectral data.

Thus, although the cyclisation process could not be stopped at the desired dihydronaphthalene stage, it provides a short, efficient synthesis of the arylnaphthalene lignans and shows

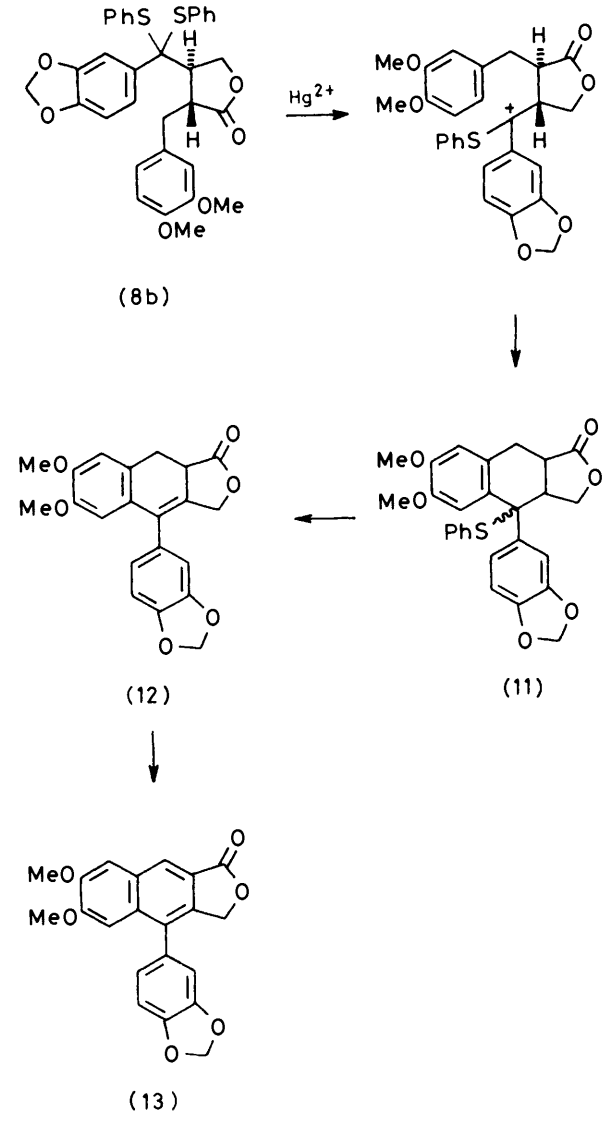


Scheme 2

a; $R^1 = R^3 = OMe$, $R^2 = R^4 = H$
b; $R^1R^2 = OCH_2O$, $R^3 = R^4 = OMe$
c; $R^1 = R^3 = OH$, $R^2 = R^4 = H$
d; $R^1 = R^3 = OMe$, $R^2 = R^4 = OH$
e; $R^1 = OMe$, $R^2 = OH$, $R^3R^4 = OCH_2O$
f; $R^1R^2 = OCH_2O$, $R^3R^4 = OCH_2O$



Scheme 3



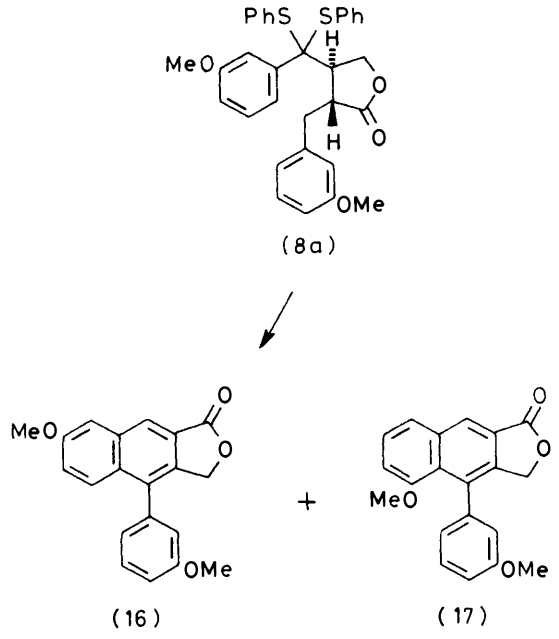
Scheme 4

that the concept of metal-mediated cyclisation in non-acidic conditions is viable.

Experimental

I.r. and u.v. spectra were recorded on Pye Unicam SP1050 and Perkin-Elmer 402 spectrometers, respectively. ^1H and ^{13}C N.m.r. spectra were recorded on Varian HA 100 and XL 100 instruments using tetramethylsilane as internal standard. Mass spectra were obtained on an A.E.I. MS9 double focusing instrument at 250 °C and 70 eV.

3-(3-Methoxybenzyl)-4-[3-methoxy-α,α-bis(phenylthio)-benzyl]butyrolactone (8a).—To a stirred solution of 3-methoxybenzaldehyde bis(phenylthio) acetal (3.4 g) in dry THF (20 ml) maintained under nitrogen at −78 °C, was added a solution of n-butyl-lithium (8.8 ml; 1.14M) in hexane. The resulting solution was stirred for 2½ h and a solution of



Scheme 5

butenolide (0.84 g) in dry THF (2 ml) added. The reaction mixture was again stirred for 2½ h at −78 °C and then treated dropwise with a solution of 3-methoxybenzyl bromide (2.01 g) and HMPA (1.8 ml) in dry THF (5 ml). The reaction mixture was allowed to slowly warm to room temperature overnight and then quenched with water. The mixture was thoroughly extracted with ethyl acetate and the extracts washed with water. Evaporation of the solvent left an orange gum (5.0 g) which was purified by flash chromatography with CH_2Cl_2 on silica gel to give the product as a gum (3.2 g, 60%); R_F 0.55 (hexane–EtOAc, 7 : 3); $\nu_{max.}$ 1 780 cm^{-1}; $\lambda_{max.}$($CHCl_3$) 260sh (3.81) and 275 nm (3.85); *m/e* 433 (*M* − SPh, 7%), 432(7), 325(19), 324(13), 323(13), 311(15), 229(11), 171(21), 121(100), and 110(56) (Found: *M* − SPh, 433.1470. $C_{26}H_{25}SO_4$ requires *M* − Sph, 433.1474); ^1H and ^{13}C n.m.r., see Tables 1 and 2.

3-(3,4-*Dimethoxybenzyl*)-4-[3,4-*methylenedioxy*-α,α-*bis*-(*phenylthio*)*benzyl*]*butyrolactone* (8b).—Prepared in the same manner as above, the product was obtained as an *amorphous powder* (1.9 g, 76%) after flash chromatography; m.p. 75—85 °C (indefinite); R_F 0.25 (hexane–EtOAc, 7 : 3); $\nu_{max.}$ 1 770 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 257 (2.68) and 285 nm (3.41); *m/e* 477 (*M* − SPh, 1%), 369(11), 247(22), 218(14), 151(100), 135(78), and 110(35) (Found: *M* − SPh, 477.1369. $C_{29}H_{25}SO_6$ requires *M* − SPh, 477.1372); ^1H and ^{13}C n.m.r., see Tables 1 and 2.

3,4-*Bis*(3-*methoxybenzyl*)*butyrolactone* (9a).—The conjugate addition product (8a) (90 mg) was dissolved in absolute ethanol (25 ml) and refluxed with Raney nickel (900 mg) for 4 h. Filtration of the crude desulphurised product through silica gel gave the product as a *gum* in quantitative yield; $\nu_{max.}$ 1 780 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 275 (3.49) and 282 nm (3.47); *m/e* 326 (12%, $M^{+\cdot}$), 296(7), 205(7), 193(15), 178(7), 149(29), 148(8), 147(16), 122(100), and 121(52) (Found: $M^{+\cdot}$ 326.1518. $C_{20}H_{22}O_4$ requires $M^{+\cdot}$ 326.1518); ^1H and ^{13}C n.m.r., see Tables 1 and 2.

3-(3,4-*Dimethoxybenzyl*)-4-(3,4-*methylenedioxybenzyl*)-*butyrolactone* (9b).—Prepared using the same method as above, this compound was obtained in quantitative yield; $\nu_{max.}$ 1 775 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 246 (3.66) and 285 nm (3.73); *m/e* 370 (39%, $M^{+\cdot}$), 208(5), 162(3), 161(3), 151(100), and 135(23) (Found: $M^{+\cdot}$ 370.1418. $C_{21}H_{22}O_6$ requires $M^{+\cdot}$ 370.1416); ^1H and ^{13}C n.m.r., see Tables 1 and 2.

3,4-*Bis*(3-*hydroxybenzyl*)*butyrolactone* (9c).—The di-*O*-methyl ether (9a) (100 mg) in dry CH_2Cl_2 was treated with boron tribromide (250 mg) at 0 °C and the mixture stirred for 4 h. It was then allowed to warm to room temperature overnight and shaken with water and extracted with ether. The crude product obtained on evaporation (77 mg, 76%) was purified by flash chromatography with benzene–ethyl acetate (9 : 1) on silica gel to give the pure product which had physical data identical with those reported for enterolactone;[12,14,23] $\nu_{max.}$ 3 540 and 1 775 cm^{-1}; $\lambda_{max.}$ (EtOH) 227 (4.66) and 281 nm (4.64); *m/e* 298 (12%, $M^{+\cdot}$), 191(16), 145(11), 134(13), 133(22), 108(100), and 107(64); δ_H 2.4—2.7 (m 3-, 4-, 7-H), 2.8—3.0 (m, 6-H), 3.8—4.1 (m, 5-H), and 6.5—7.2 (m, arom) (Found: $M^{+\cdot}$ 298.1203. $C_{18}H_{18}O_4$ requires $M^{+\cdot}$ 298.1205).

Reaction of the Lactone (8b) *with Mercury*(II) *Trifluoroacetate.*—(*a*) The conjugate addition product (8b), (100 mg) dissolved in dry THF (7 ml) was treated with $Hg(O_2CCF_3)_2$ (150 mg) and the mixture stirred at room temperature for 2 h. The THF was removed under reduced pressure, water was added and the mixture extracted into ethyl acetate. The ethyl acetate extracts were repeatedly washed with water, aqueous Na_2CO_3 and water, and dried ($MgSO_4$). Filtration and evaporation of the ethyl acetate gave a brown gum which showed four spots on t.l.c. Purification by preparative t.l.c., eluting with hexane–ethyl acetate (65 : 35) gave (i) diphenyl disulphide (12 mg); (ii) retrojusticidin B (13) (8 mg, 8%), for physical data see below; (iii) 3-(3,4-dimethoxybenzyl)-4-(3,4-methylenedioxy-α-phenylthiobenzyl)furan-2(5*H*)-one (14) (12 mg, 16%), $\nu_{max.}$ 1 765 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 260 (3.76) and 285 nm (3.83); *m/e* 476 (5%, $M^{+\cdot}$), 369(12), 368(44), 367(21), 366(32), 364(17), 245(14), 128(14), 201(52), 151(81), 138(53), 135(58), 110(100), and 109(40); δ ($CDCl_3$) 3.13 (d, 15), 3.43 (d, 15), 3.78 (s, 3 H), 3.85 (s, 3 H), 4.65 (d, 18), 5.05 (d, 18), 5.29 (s, 1 H), 5.96 (s, 2 H), and 6.6—7.0 (m, 6 H) (Found: $M^{+\cdot}$ 476.1295. $C_{27}H_{24}SO_6$ requires $M^{+\cdot}$ 476.1290); (iv) 3-(3,4-dimethoxybenzyl)-4-(3,4-methylenedioxybenzoyl)butyrolactone (15) (10 mg, 16%), *m/e* 384 (39% $M^{+\cdot}$), 208(60), 151(100), and 149(56); δ ($CDCl_3$) 3.00 (d, 3), 3.06 (s, 1 H), 3.75 (s, 3 H), 3.82 (s, 3 H), 3.4—4.5 (m, 4 H), 6.05 (s, 2 H), and 6.6—7.3 (m, 6 H).

(*b*) The conjugate addition product (8b) (150 mg) dissolved in dry THF (10 ml) was treated with $Hg(O_2CCF_3)_2$ (1 g) and stirred at room temperature while oxygen was bubbled through the reaction mixture for 72 h. After work-up as described above the product was purified by flash chromatography on silica gel, eluted with hexane–ethyl acetate (7 : 3), to give retrojusticidin B (13) (55 mg, 59%), m.p. 218—220 °C; $\nu_{max.}$ 1 763 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 267 (4.08) and 318 nm (3.76); *m/e* 364 (100%, $M^{+\cdot}$), 335(40), 202(11), 167(10), 151(21), 149(22), 122(17), 110(32), and 109(22); δ ($CDCl_3$) 3.86 (s, 3 H), 4.05 (s, 3 H), 5.22 (s, 2 H), 6.08 (m, 2 H), 6.7—7.3 (m, 5 H), and 8.30 (s, 1 H) (Found: C, 69.2; H, 4.62%; $M^{+\cdot}$ 364.0946. $C_{21}H_{16}O_6$ requires C, 69.2; H, 4.39%; $M^{+\cdot}$ 364.0946).

Reaction of the Lactone (8a) *with Mercury*(II) *Trifluoroacetate.*—The conjugate addition product (8a) (240 mg) dissolved in dry THF (15 ml) was treated with $Hg(O_2CCF_3)_2$ (1.6 g) and stirred at room temperature for 72 h. Work-up in the usual way gave a brown gum (300 mg) which showed two fluorescent spots on t.l.c. Purification by column chromatography on silica gel, eluted with hexane–ethyl acetate (7 : 3), gave: (i) 7-methoxy-4-(3-methoxyphenyl)naphtho[2,3-*c*]furan-

1(3*H*)-one (16) (12 mg, 20%), $\nu_{max.}$ 1 762 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 293 (3.38), 348 (2.93), and 361 nm (2.89); *m/e* 320 (100%, $M^{+\cdot}$), 291(40), 189(10), and 149(26) (Found: $M^{+\cdot}$ 320.1047. $C_{20}H_{16}O_4$ requires $M^{+\cdot}$ 320.1049); δ ($CDCl_3$) 3.85 (s, 3 H), 3.97 (s, 3 H), 5.25 (s, 2 H), 6.9—7.8 (m, 7 H), and 8.40 (s, 1 H); and (ii) the 5-methoxy-analogue (17) (48 mg, 34%), $\nu_{max.}$ 1 765 cm^{-1}; $\lambda_{max.}$ ($CHCl_3$) 283 (4.42) and 370 nm (3.74); *m/e* 320 (100%, $M^{+\cdot}$), 291(36), 205(16), 202(25), 200(19), 1 678(16), 135(53), and 121-(18) (Found: $M^{+\cdot}$ 320.1048. $C_{20}H_{16}O_4$ requires $M^{+\cdot}$ 320.1049); δ ($CDCl_3$) 3.87 (s, 3 H), 3.99 (s, 3 H), 5.24 (s, 2 H), 6.7—8.0 (m, 7 H), and 8.37 (s, 1 H).

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