A General Synthesis of 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octane Lignans Applicable to Unsymmetrically Substituted Compounds

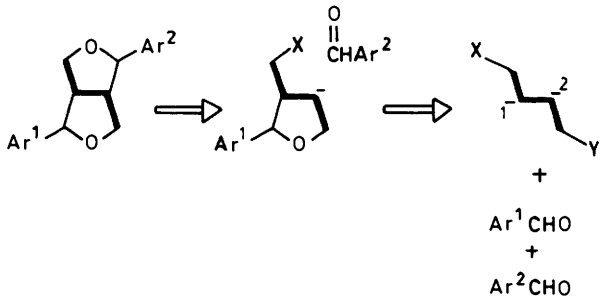
Andrew Pelter,* Robert S. Ward,* Peter Collins, and Revuru Venkateswarlu
Chemistry Department, University College of Swansea, Singleton Park, Swansea SA2 8PP
I. Trevor Kay
I.C.I. Plant Protection Division, Jealott's Hill, Bracknell, Berkshire RG12 6EY

A new synthesis is described of 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes which has been used to prepare unsymmetrically substituted lignans such as methyl piperitol, and affords the first stereoselective synthesis of equatorial–axial isomers such as methyl pluviatilol and methyl xanthoxylol. The method utilises a new four carbon synthon (**6**) which allows regiospecific and stepwise anion production. Two alternative routes are given from the 2,6-diaryl-4,8-dimethoxy-1-methylthio-3,7-dioxabicyclo-[3.3.0]octanes (**14b**) and (**14c**) to the parent lignans. One of these procedures shows that the methylthio group is capable of acting as a highly effective stereocontrol element. The stereochemical consequences of both procedures have been analysed and can be rationalised in terms of equilibration during a Lewis acid catalysed reduction step. Thus, while one route affords selectively methyl pluviatilol (**19**) in high yield, the other route gives a 2:1:1 mixture of methyl piperitol, methyl pluviatilol, and methyl xanthoxylol.

Lignans exhibit a wide range of physiological activity[1-6] and their synthesis is therefore of intense interest.[7] The 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes constitute one of the largest groups of lignans amongst which types (**1**)—(**3**) (Scheme 2) are of particular interest.[8]

We have previously reported several syntheses of symmetrically substituted compounds ($Ar^1 = Ar^2$) of types (**1**)—(**3**).[9,10] These compounds have also been prepared by using 2,5-bis(trimethylsilyloxy)furan[11] and the dianions of *N,N,N,N*-tetra-alkylsuccinamides,[12a] as four-carbon synthons. The latter method, whilst conceptually short and elegant, suffers from the apparent lack of ability of the dianion to condense in a stepwise manner with aldehydes.[12b] It is therefore unsuitable for the preparation of unsymmetrically substituted compounds ($Ar^1 \neq Ar^2$) such as methyl piperitol, methyl pluviatilol, and methyl xanthoxylol. Furthermore, the condensation gives a mixture of diastereoisomers, only one of which gives the required dilactones, and then only as minor products.[12a]

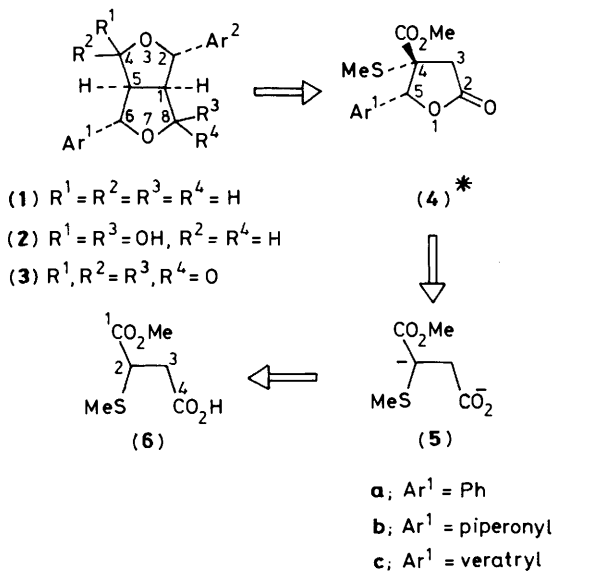
Our own approach to this problem[13] was based upon the retrosynthetic analysis shown in Scheme 1 from which it was



Scheme 1.

clear that we required a four-carbon synthon in which anion formation could be directed first to one and then to the other of the two central carbon atoms. Indeed, it is expected that this approach could be extended to the synthesis of many other of the wide variety of lignan types which contain a central four-carbon unit.

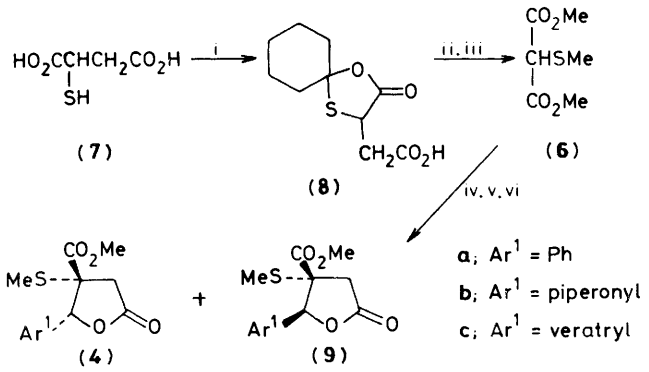
The need for *sequential* addition of the two aldehyde units led us to consider the monolactone (**4**) as the immediate precursor of (**3**) (Scheme 2). Compound (**4**) has the advantage that it would



Scheme 2. * N.m.r. numbering scheme

react with the second aldehyde only at C-3 and that it could be generated from the monoester (**6**) *via* the dianion (**5**) in which carbanion formation has occurred specifically at C-2. The methylthio group in compound (**4**) serves three purposes: (i) it blocks the position α to the methoxycarbonyl group, thus ensuring that anion formation takes place exclusively at C-3; (ii) it directs attack by the derived carbanion in such a way that the second aldehyde has a chance of being introduced *cis* to the methoxycarbonyl group [this latter requirement is important since previous syntheses of lignans involving tandem addition to butenolide,[14] for example, could not be used to prepare compounds of types (**1**)—(**3**) owing to the *trans* disposition of the substituents introduced]; (iii) as will be seen later the methylthio group can serve to direct the stereochemistry of the final products.

The monoester (**6**), b.p. 150—155 °C/0.3 mmHg is selectively and readily produced in 70% overall yield from commercially available mercaptosuccinic acid (**7**) by a process involving nucleophilic attack on the oxathiolone (**8**) by sodium methoxide followed by *in situ* selective methylation with methyl iodide (Scheme 3). Treatment of compound (**6**) with two equivalents of lithium di-isopropylamide (LDA) and an aromatic aldehyde followed by work-up with trifluoroacetic acid gave mixtures of the diastereoisomeric monolactones (**4a—c**) and (**9a—c**) in total isolated yields of 50, 50, and 70% respectively. The ratios of compounds (**4**) : (**9**) were *ca.* 2:1 and the two isomers could be separated by trituration with ether. The ^{1}H n.m.r. spectra of compounds (**4b**) and (**4c**) and (**9b**) and (**9c**) are compared in Table 1 from which it can be seen that the isomeric series can be readily distinguished on the basis of the chemical shifts of the methylthio and methoxycarbonyl groups. Thus in compounds (**4b**) and (**4c**) the methylthio group is shielded by the neighbouring aryl group and appears at δ 1.76—1.79, compared with δ 2.20—2.27 in (**9b**) and (**9c**), whereas the methoxycarbonyl group of (**9b**) and (**9c**) is shielded by the neighbouring aryl group and appears at δ 3.44—3.49, compared with 3.92—3.94 in (**4b**) and (**4c**).

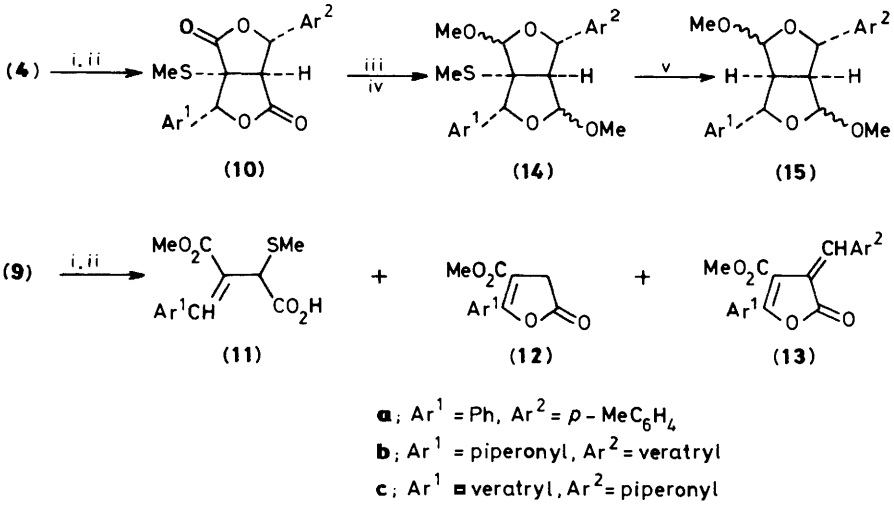


Scheme 3. *Reagents:* i, cyclohexanone, TosOH; ii, NaOMe; iii, MeI; iv, 2 eq. LDA; v, Ar^1CHO; vi, TFA

On treatment with LDA and a second aldehyde, compounds (**4**) and (**9**) behaved differently. Thus, compound (**4b**) reacted with veratraldehyde to give the desired dilactone (**10b**), m.p. 197—199 °C in 58% yield and (**4c**) reacted with piperonal to give the product (**10c**), m.p. 154—155 °C in 49% yield (Scheme 4). However compounds (**9b**) and (**9c**), when treated under the same conditions, gave only low yields of products with the suggested structures (**11b**) and (**12b**), and the uncyclised addition product (**13c**), along with recovered starting materials.

The ^{1}H and ^{13}C n.m.r. spectra of the dilactones (**10b**) and (**10c**) are presented in Tables 2 and 3 along with those of the totally symmetrical dilactones (**17d**) and (**17e**) which are presented for comparison purposes.

Despite many attempts under a wide variety of conditions, we were unable to remove the methylthio grouping from either



Scheme 4. *Reagents:* i, LDA, −78 °C; ii, Ar^2CHO; iii, Bu^i_2AlH; iv, MeOH/HCl (1 drop); v, Raney Ni

Table 1. ^{1}H N.m.r. spectra of monolactones*

Proton	δ/p.p.m. (*J*/Hz) (**4b**)	(**9b**)	(**12b**)	(**4c**)	(**9c**)	(**13c**)†
3-H	2.91d (18)	2.81d (18)		3.00d (18)	2.90d (18)	
	3.38d (18)	3.53d (18)	3.66s	3.49d (18)	3.62d (18)	
5-H	5.85s	5.38s		6.00s	5.54s	
OCH_2O	5.95s	5.94s	6.01s			6.12s
CO_2Me	3.92s	3.44s	3.76s	3.94s	3.49s	3.84s
MeS	1.76s	2.20s		1.79s	2.27s	
Arom	6.7—7.0m	6.7m	6.83d (8) 7.56m	6.9—7.2m	6.8—7.0m	6.9—8.1m
OMe				3.98s	3.94s	3.80s

* All spectra run in $CDCl_3$ solution unless otherwise indicated. † Run in [$^2H_6$]-DMSO.

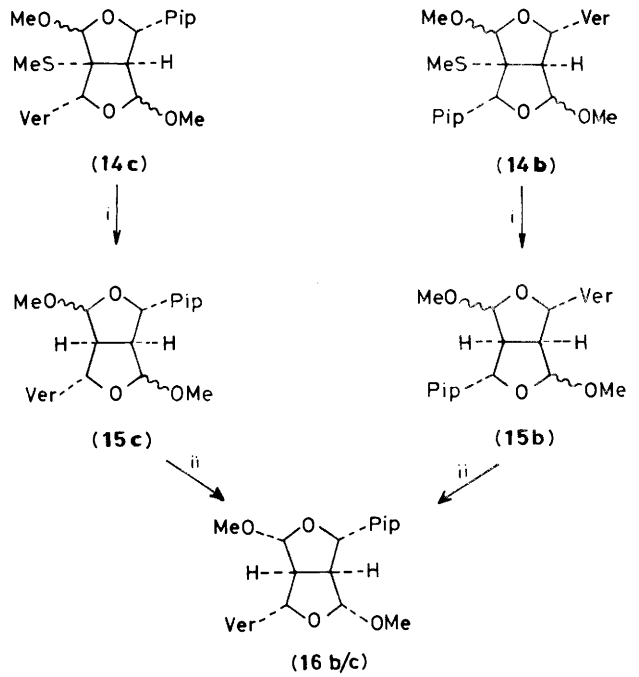
Table 2. ^{1}H N.m.r. spectra of dilactones

	δ/p.p.m. (*J*/Hz)			
Proton	(10b)*	(10c)*	(17d)†	(17e)†
1-H	3.53d (2)	3.48d (2)	3.91br s	4.22br s
5-H	—	—		
2-H	5.83d (2)	5.80d (2)	5.79br s	5.78br s
6-H	5.77s	5.82s		
ArOMe	3.84s	3.86s		3.74s, 3.77s
Arom.	6.7—7.0m	6.7—7.0m	6.7—6.9m	6.8—7.0m
OCH_2O	5.96s	5.97s	5.95s	
SMe	1.82s	1.79s		

* Run in $CDCl_3$. † Run in [$^2H_6$]-DMSO.

compound (**10b**) or (**10c**). However, if the dilactone groups were reduced to hemiacetals and methylated, the desired desulphurisation could be accomplished.

Reduction of compound (**10b**) with di-isobutylaluminium hydride gave the corresponding dilactol (88%), m.p. 197—199 °C which was converted into the dimethyl acetal (**14b**) (92%), m.p. 127—128 °C by treatment with methanolic HCl. The methylthio group was then removed with Raney nickel to give methyl 4,8-dimethoxypiperitol (**15b**) (89%). When compound (**10c**) was carried through the same series of reactions it gave an isomeric compound (**15c**) (79%) (Scheme 5). After



Scheme 5. *Reagents:* i, MeOH/HCl (1 drop)

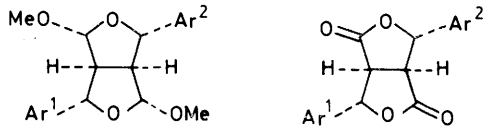
equilibration with methanolic HCl both products (**15b**) and (**15c**) were converted into an identical compound (**16b/c**). Since the stereochemistry at C-2 is known to be equatorial in both series of compounds [(**4b**)→(**16b**) and (**4c**)→(**16c**)] from the structures of the corresponding monolactones (**4b**) and (**4c**), and since these centres do not epimerise under the conditions used it follows that both aryl groups must be equatorial in compound (**16b/c**) and therefore in all of the compounds described so far. This is further demonstrated by the ^{1}H and ^{13}C n.m.r. spectra of the dimethyl acetals (Tables 4 and 5) which show that not only is a common product obtained starting from either compound (**4b**)

Table 3. ^{13}C N.m.r. spectra of dilactones

Carbon	(10b)*	(10c)*	(17d)†	(17e)†
C-1	54.51	54.84	48.2	48.1
C-5	55.87	56.37		
C-2	80.76	80.38	81.9	81.7
C-6	85.38	85.20		
C-4	173.54	173.41	174.9	175.3
C-8				
C-1′-1″	127.69	126.11	131.7	130.5
	129.46	130.87		
C-2′-2″	107.53	105.72	105.6	110.0
	108.15	108.41		
C-3′-3″	148.00	148.08	148.3	146.3
	148.95	148.21		
C-4′-4″	149.42	148.88	148.5	149.4
	149.51	150.20		
C-5′-5″	108.44	110.63	108.6	111.7
	111.16	110.77		
C-6′-6″	117.67	118.86	119.0	118.8
	121.87	120.19		
ArOMe	55.95	55.87		55.6
	56.07	56.07		55.7
OCH_2O	101.66	101.51	101.5	
SMe	13.77	13.19		

* Run in $CDCl_3$. † Run in [$^2H_6$]-DMSO.

or (**4c**), but also that its spectra are simply the summation of those of the symmetrically substituted compounds (**16d**) and (**16e**). This proves beyond doubt the relative stereochemistry of the two aryl groups at C-2 and C-6.



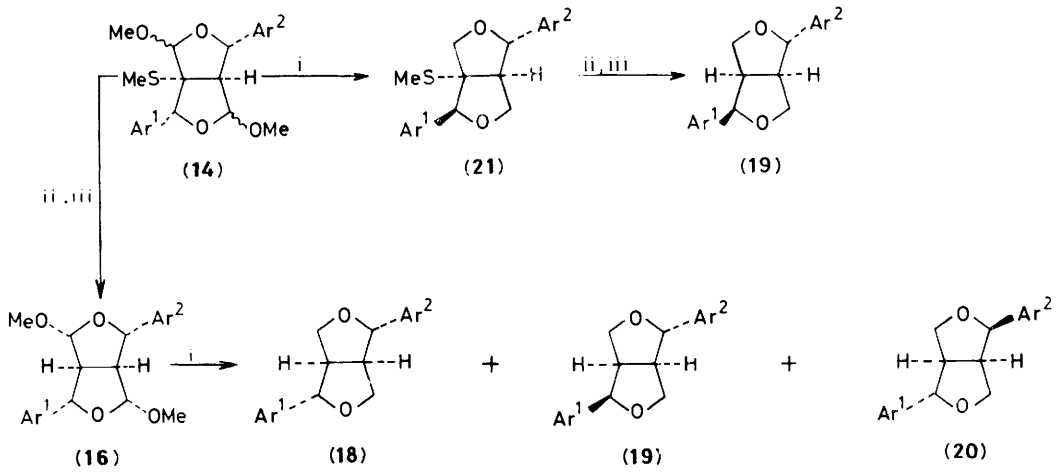
b; Ar^1 = piperonyl, Ar^2 = veratryl
c; Ar^1 = veratryl, Ar^2 = piperonyl
d; Ar^1 = Ar^2 = piperonyl
e; Ar^1 = Ar^2 = veratryl

Having thus obtained methyl 4,8-dimethoxypiperitol (**15b/c**) in two equivalent series of high yielding reactions, it was expected that this could readily be converted into methyl piperitol (**18**) itself, using known methods.[9] However, although this could be achieved in low yield by hydrolysis followed by reduction and cyclisation, the hydrolysis step in particular proved to be irreproducible and invariably gave a mixture of products. An alternative method for removing the two methoxy groups directly and without any ring opening was therefore sought. It was eventually found that treatment with triethylsilane and trifluoroborane–ether cleanly removed both methoxy groups and afforded a mixture of three diastereoisomeric products, namely methyl piperitol (**18c**) (35.4%), methyl pluviatilol (**19c**) (18.4%), and methyl xanthoxylol (**20c**) (17.4%), presumably arising from benzylic equilibration of the product stereoisomers by trifluoroborane (Scheme 6). The yields and relative proportions were determined by h.p.l.c. and the identity of the products was established by comparison with authentic samples. [^{1}H and ^{13}C N.m.r. spectra of compounds (**18c**)—(**21c**) are given in Tables 6 and 7.] The relative proportions reflect the

Table 4. ^{1}H N.m.r. spectra of 4,8-dimethoxy-2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes *

Proton	(14b)	(14c)	(15b)	(15c)	(16b/c)	(16d)	(16e)
1-H	2.93dd (2,8)	2.88dd (2,8)	2.97br t (8)	2.93br t (8)	3.10m	3.06dd (2,6)	3.18dd (2,6)
5-H	—	—	3.22t (5)	3.22m			
2-H	5.06d (8)	5.03d (8)	4.89d (8)	4.86d (8)	4.90m	4.92br d (6)	4.89d (6)
6-H	5.23s	5.23s	5.01d (1)	5.00d (1)			
4-H	5.88s	5.87s	5.29d (5)	5.27d (6)	5.00s	4.98s	5.01s
8-H	4.98d (2)	4.99d (2)	5.60d (5)	5.59d (5)			
ArOMe	3.86s	3.85s	3.85s	3.92s	3.86s		3.87s
	3.88s	3.87s	3.88s	3.94s	3.89s		3.85s
ROMe	3.45s	3.45s	3.34s	3.33s	3.40s	3.39s	3.38s
	3.55s	3.53s	3.49s	3.46s			
Arom.	6.7—7.1m	6.7—7.3m	6.7—7.0m	6.7—7.1m		6.7—7.0m	6.7—7.1m
OCH_2O	5.92s	5.93s	5.90s	5.90s		5.95s	
SMe	1.67s	1.60s					

* All spectra run in $CDCl_3$ solution.



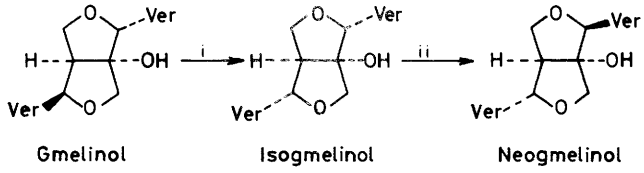
b; Ar^1 = piperonyl, Ar^2 = veratryl

c; Ar^1 = veratryl, Ar^2 = piperonyl

Scheme 6. *Reagents:* i, Et_3SiH/BF_3–Et_2O; ii, Raney Ni; iii, MeOH/HCl (1 drop)

known preference for the diequatorial configuration in such systems.[8] The methyl piperitol was isolated by column chromatography whereas the methyl pluviatilol and methyl xanthoxylol were obtained as an inseparable mixture.

As an alternative to the above procedure, it was decided to remove the methoxy groups *prior* to removal of the methylthio group. Hence, the dimethyl acetal (**14c**) was treated with triethylsilane and trifluoroborane–ether. The two aliphatic methoxy substituents were removed stereoselectively to give the isomer (**21c**) in 89% yield. Two other stereoisomers were obtained in a combined yield of 8%. Subsequent treatment of compound (**21c**) with Raney nickel gave methyl pluviatilol (**19c**) in 75% yield, thus proving the relative stereochemistry of (**21c**). Hence the thiomethyl group in equilibrating conditions is directing the adjacent aryl group *trans* to itself, even though this results in the aryl group taking up a hindered axial position. This is consistent with isomerisations in the gmelinol series.[8] Gmelinol in acidic conditions first proceeds to the diequatorial isogmelinol, but then in yet stronger acid gives neogmelinol, with the aryl group adjacent to the hydroxy group in an axial position (Scheme 7). This seems therefore to be simply a steric effect. In our case the thiomethyl group provides an excellent



Scheme 7. *Reagents:* i, HCO_2H, H_2O; ii, $HClO_4$, AcOH

stereo-steering element, and should be generally useful in variations of our procedure to yield other natural products. In particular, use of compound (**14b**) in the same series of reactions would afford a stereoselective synthesis of methyl xanthoxylol.

Experimental

I.r. and u.v. spectra were recorded on Pye Unicam SP1050 and Perkin-Elmer 402 spectrometers, respectively. ^{1}H and ^{13}C N.m.r. spectra were recorded on Varian HA100 and XL100 instruments using tetramethylsilane as internal standard. Mass spectra were recorded on an A.E.I. MS9 double focussing

Table 5. ^{13}C N.m.r. spectra of 4,8-dimethoxy-2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes *

Carbon	(14b)	(14c)	(15b)	(15c)	(16b/c)	(16d)	(16e)
C-1	66.67	66.85	61.28	61.38	59.22	59.32	
C-5	66.83	66.98	59.39		59.34		
C-2	81.82	81.96	81.27	81.46	85.64	85.64	
C-6	83.22	83.56	81.35	81.35		85.83	
C-4	106.21	106.68	107.88	106.66	107.21	107.21	
C-8	106.77	106.95	108.10	108.26	107.79		107.90
C-1′-1″	131.92	130.88	132.74	134.35	136.10	136.07	
	132.21	133.59	137.74	136.29	134.69	137.74	136.29
C-2′-2″	109.28	108.39	105.18	105.32	107.91	107.84	
	110.68	110.88	107.19	108.26	110.01		110.03
C-3′-3″	147.00	147.70	146.74	148.13	148.13	147.44	
	149.17	148.22	147.78	148.34	149.02		149.04
C-4′-4″	147.08	148.22	149.11	148.25	148.25		
	149.38	148.71	149.41	149.07	149.56		149.58
C-5′-5″	109.40	110.07	109.43	110.07	108.02	108.03	
	111.18	112.35	111.28	110.97	110.97		110.96
C-6′-6″	118.88	119.91	118.92	118.86		120.43	120.43
	121.89	120.99	119.91	119.88	119.44		119.50
ArOMe	55.87	55.81	56.22	56.25	55.81		55.80
	56.27	56.31	56.40	56.34	55.98		56.01
ROMe	55.87	55.81	55.16	55.78	55.05	55.06	
			54.97	55.93	55.95		54.99
OCH_2O	110.90	101.19	100.92	101.14	101.11	101.12	
SMe	13.23	13.28					

Table 6. ^1H N.m.r. spectra of 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes *

Proton	(21c)	(19)/(20)	(18c)
1-H	2.82dd (5,8)	2.90m	3.06m
5-H		3.33m	
2-H	4.45d (8)	4.42d (7)	4.73d (4)
6-H	4.74s	4.85d (5)	
4-H	3.70s	3.33m	3.86m
		3.70m	4.26m
8-H	3.90m	3.70m	
	4.11br d (9)	4.13br d (9)	
ArOMe	3.88s	3.86s	3.87s
	3.92s	3.90s	3.90s
Arom.	6.7—7.2m	6.7—7.2m	6.8—7.0m
OCH_2O	5.93s	5.92s	5.95s
SMe	2.29s		

* All spectra run in $CDCl_3$ solution.

Table 7. ^{13}C N.m.r. spectra of 2,6-diaryl-3,7-dioxabicyclo[3.3.0]-octanes *

Carbon	(21c)	(19/20)	(18c)
C-1	62.44	54.57	54.07
C-5	65.29	50.10	54.26
C-2	88.23	87.64	85.61
C-6	85.40	81.99	85.66
C-4	75.15	70.98	71.61
C-8	69.60	69.68	
C-1′-1″	134.23	135.20	134.94
	129.40	130.98	133.38
C-3′-3″	147.48	147.20	146.87
	148.08	148.00	147.75
C-4′-4″	148.56	148.87	148.43
	148.76		148.99
C-2′-2″	106.53	106.50	106.33
	108.26	108.11	107.99
C-5′-5″	109.34	109.07	109.10
	110.94	111.15	110.93
C-6′-6″	118.29	117.75	118.07
	119.59	119.51	119.15
ArOMe	55.91	55.88	55.84
OCH_2O	101.11	101.00	100.90
SMe	13.06		

instrument at 250 °C and 70 eV. Tetrahydrofuran was distilled over calcium hydride and stored under nitrogen. Toluene was distilled and stored over sodium wire. Dichloromethane was distilled and passed through an alumina column. Raney nickel was prepared according to the method described in the literature (*Org. Synth.*, Coll. Vol. III, p. 181). Ether refers to diethyl ether.

Preparation of 2-Oxo-1-oxa-4-thiaspiro[4.5]*decan-3-ylacetic Acid* (**8**).—Mercaptosuccinic acid (100 g), cyclohexanone (65.5 g), and toluene-*p*-sulphonic acid (10 mg) were added to toluene (500 ml). The solution was refluxed until the correct amount of water (11.8 ml) was collected in a Dean and Stark apparatus. The toluene was removed by evaporation under reduced pressure and saturated $NaHCO_3$ solution (100 ml) was added. The aqueous solution was extracted with chloroform (3 × 50 ml) to remove the excess of cyclohexanone before being acidified with concentrated HCl to pH 1. The acidic solution was then extracted with chloroform, washed with water (100 ml), dried ($MgSO_4$), and evaporated to give an off-white crystalline solid which was recrystallised from ether–light petroleum (b.p. 40—60 °C) to give the pure *product* (**8**) as white crystals (120.5 g, 79.4%), m.p. 112—114 °C; $\nu_{max.}$(Nujol) 1 710, and 1 762 cm^{-1}; $\delta(CDCl_3)$ 1.64 (m, 10 H), 3.02 (m, 2 H), 4.32 (dd, 1 H), and 10.06 (s, 1 H); *m/z* 230 (M^+, 12), 104 (13), 99 (100), and 98 (16) (Found: C, 52.2; H, 6.1; S, 13.9. $C_{10}H_{14}SO_4$ requires C, 51.56; H, 6.02; S, 14.06%).

3-Methoxycarbonyl-3-methylthiopropanoic Acid (**6**).—Sodium (1 g) was dissolved in absolute methanol (100 ml) under nitrogen. The oxathiolone (**8**) (5 g) was added and the reaction mixture left stirring for 1 h. Iodomethane (1.35 ml) was added and the mixture stirred for a further 30 min. Water (200 ml) was added and the mixture extracted with chloroform (3 × 50 ml) to remove the cyclohexanone produced in the reaction. The basic solution was then acidified to pH 1 using concentrated HCl and extracted with chloroform (3 × 50 ml). The extracts were dried

($MgSO_4$) and evaporated to give a light brown oil (4.73 g) which was distilled at 150—155 °C/0.3 mmHg to give the pure *product* (**6**) (3.25 g, 84%); δ($CDCl_3$) 2.17 (s, 3 H), 2.88 (m, 2 H), 3.58 (dd, 1 H), and 3.74 (s, 3 H); $\nu_{max.}$(film) 1 720 cm^{-1} (Found: C, 40.45; H, 5.6. $C_6H_{10}SO_4$ requires C, 40.24; H, 5.98%).

Preparation of the Monolactones (**4a**) *and* (**9a**).—Di-isopropylamine (7.4 g) was dissolved in dry tetrahydrofuran (THF) (100 ml) at 0 °C under nitrogen, n-butyl-lithium (4.8 ml, 33.7 × 10^{-3}M) was added, and the solution was cooled to −78 °C. A solution of the acid (**6**) (6 g) in dry THF (50 ml) was added slowly during 20 min and the mixture stirred for a further 30 min. Benzaldehyde (3.57 g) was added and the mixture stirred for a further 30 min before being quenched with TFA (11.6 ml). The solution was then left to warm to room temperature overnight. Most of the THF was removed under reduced pressure and the residue diluted with aqueous $NaHCO_3$ (100 ml) and extracted with $CHCl_3$ (4 × 100 ml). The extracts were dried and evaporated to give the crude product (7.68 g) which was further purified by column chromatography followed by trituration with light petroleum to afford the crystalline product *methyl 3-methylthio-5-oxo-2-phenyltetrahydrofuran-3-carboxylate* as a mixture of isomers (**4a**) and (**9a**) (3.5 g, 50%), m.p. 72—75 °C (Found: C, 58.5; H, 5.5. $C_{13}H_{14}SO_4$ requires C, 58.65; H, 5.26%); $\nu_{max.}$ 1 782 and 1 712 cm^{-1}.

Preparation of the Monolactones (**4b**) *and* (**9b**).—Di-isopropylamine (7.4 g) was dissolved in dry THF (100 ml) and cooled to −10 °C under nitrogen. Bu^{n}Li (44 ml; 1.6M) was added to the solution and the mixture then stirred for 15 min before the temperature was lowered to −78 °C. To the LDA solution was added the acid (**6**) (6 g) in THF (20 ml) and the mixture stirred for 30 min before piperonal (5.05 g) in THF (20 ml) was added. After 1 h the reaction was quenched with trifluoroacetic acid (11.4 ml) and the mixture allowed to warm to room temperature overnight. Most of the THF was removed under reduced pressure and aqueous $NaHCO_3$ (100 ml) added. The aqueous solution was extracted with chloroform (3 × 100 ml) and the extracts dried ($MgSO_4$), filtered and evaporated to give an orange oil (16.0 g). The oil was triturated with ether which gave a white crystalline solid (12.1 g) which was recrystallised from ethanol to give methyl 3-methylthio-5-oxo-2-piperonyltetrahydrofuran-3-carboxylate, (**4b**) and (**9b**) as a mixture of isomers (10.4 g, 50%). Separation of the isomers by trituration with ether afforded *compound* (**4b**), m.p. 85—87 °C (Found: C, 54.1; H, 4.7. $C_{14}H_{14}SO_6$ requires C, 54.19; H, 4.52%). For ^{1}H n.m.r. spectra see Table 1.

Preparation of Methyl 3-Methylthio-5-oxo-2-veratryltetrahydrofuran-3-carboxylate (**4c**) *and* (**9c**).—To a solution of lithium di-isopropylamide (prepared from 188 ml of 1.55M-Bu^{n}Li and 33.5 g of di-isopropyl amine) in anhydrous THF (450 ml) at −70 °C was added dropwise and with stirring the acid (**6**) (26.9 g) in THF (90 ml). Following the addition, the mixture was kept at −70 °C for 30 min under nitrogen and 3,4-dimethoxybenzaldehyde (25.08 g) in THF (90 ml) was added dropwise. The mixture was kept for a further 1 h at −70 °C when trifluoroacetic acid (51 ml) was added dropwise and the mixture allowed to warm to room temperature. The following day most of the solvent was removed under reduced pressure and the residue was acidified with hydrochloric acid and extracted with dichloromethane (3 × 150 ml). The dried extracts were evaporated and the oily residue triturated with ether (500 ml). The isomer (**4c**) (23 g, 48%) was separated and crystallised from CH_2Cl_2–CCl_4, m.p. 128—130 °C. Following the removal of the isomer (**4c**), the ethereal residue was evaporated and the residue chromatographed on silica using di-isopropyl ether as eluant to give the isomer (**9c**) as a pale yellow gum (12 g, 24%); $\nu_{max.}$(film) 1 785, 1 735 cm^{-1}. For ^{1}H n.m.r. spectra see Table 1.

Preparation of 1-Methylthio-8-phenyl-4-p-tolyl-3,7-dioxabicyclo[3.3.0]*octane-2,6-dione* (**10a**).—Di-isopropylamine (0.92 g) was dissolved in THF (40 ml) under nitrogen at 0 °C. Bu^{n}Li (6 ml; 1.4M soln) was added and the mixture cooled to −78 °C. The monolactones (**4a**) and (**9a**) (2.2 g) in THF (10 ml) were added and the mixture left stirring for 30 min. *p*-Tolualdehyde (0.99 g) was added and the mixture stirred for a further 30 min. Trifluroacetic acid (1.6 ml) was then added and the mixture allowed to warm to room temperature overnight. Most of the THF was removed and the residue diluted with $CHCl_3$ (100 ml). The organic layer was washed with dilute HCl and dried and evaporated to leave an oil which was crystallised from ether to give the crystalline *dilactone* (**10a**) (881 mg, 30%), m.p. 183—185 °C (Found: C, 67.9; H, 4.8. $C_{20}H_{18}SO_4$ requires C, 67.80; H, 5.08%); $\nu_{max.}$ 1 787 and 1 766 cm^{-1}.

Preparation of 1-Methylthio-8-piperonyl-4-veratryl-3,7-dioxabicyclo[3.3.0]*octane-2,6-dione* (**10b**).—Bu^{n}Li (32.26 × 10^{-3}M; 20.8 ml) was added to di-isopropylamine (4.6 ml) at −10 °C under nitrogen; the mixture was stirred for 15 min before the addition of THF (100 ml) and lowering of the temperature to −78 °C. 3,4-Dimethoxybenzaldehyde (10.7 g) dissolved in THF (20 ml) was then added followed by the monolactone [1.5:1 mixture of (**4b**) and (**9b**)] (10 g) dissolved in THF (20 ml) and the mixture was then stirred at −78 °C for 1 h. Trifluoroacetic acid (6.2 ml) was added and the reaction mixture then stirred overnight. Most of the THF was removed and ethyl acetate (100 ml) was added. The solution was washed with dilute HCl and aqueous $NaHCO_3$, dried, and evaporated to give the crude product (20.4 g) which was treated with ether and recrystallised from chloroform–ether to give the crystalline *dilactone* (**10b**) [5.05 g, 58% based on (**4b**)], m.p. 197—198 °C (Found: C, 59.7; H, 4.2. $C_{22}H_{20}SO_8$ requires C, 59.46; H, 4.50%); $\nu_{max.}$(film) 1 782 cm^{-1}.

Acidification of the $NaHCO_3$ extract followed by extraction with dichloromethane yielded a small amount of the acid (**11b**) (0.65 g) derived from the monolactone (**9b**). For n.m.r. spectra see Tables 2 and 3.

Preparation of 1-Methylthio-4-piperonyl-8-veratryl-3,7-dioxabicyclo[3.3.0]*octane-2,6-dione* (**10c**).—Bu^{n}Li (1.6M; 2.5 ml) was added to di-isopropylamine (0.5 ml) under nitrogen at −10 °C during 15 min and the solvent then evaporated to give a white solid. Dry THF (15 ml) was added and the mixture cooled to −78 °C. Piperonal (1.05 g) in THF (20 ml) was cooled to −78 °C and added to the LDA at −78 °C through a double ended needle during 30 min. The mixture was stirred for a further 1 h and then the monolactone (**4c**) (1.04 g) in THF (50 ml), cooled to −78 °C, was added during 15 min. The mixture was stirred for 45 min and then TFA (0.6 ml) added dropwise during 15 min. The mixture was stirred at −78 °C for 1 h and then at room temperature overnight. Water (10 ml) was added and the THF evaporated. The aqueous residue was extracted with ethyl acetate (2 × 25 ml) and the organic extracts washed successively with dilute HCl (2 × 25 ml), aqueous $NaHCO_3$ (2 × 25 ml), and water (2 × 25 ml) before being dried ($MgSO_4$) and then evaporated to give a brown gum (1.9 g). Crystallisation from chloroform–ether yielded the *dilactone* (**10c**) as a white crystalline solid (0.7 g, 49%), m.p. 154—155 °C. For n.m.r. spectra see Tables 2 and 3; $\nu_{max.}$(film) 1 770, 1 465, and 1 160 cm^{-1}; *m/z* 444 (M^+, 26%), 280 (46), 203 (16), 166 (100), 165 (16), 149 (66), and 100 (14) (Found: M^+, 444.0879. $C_{22}H_{20}SO_8$ requires *M*, 444.0879).

Reduction of the Dilactone (**10b**).—The dilactone (2 g) was dissolved in dry THF (100 ml) under nitrogen and the

temperature lowered to −50 °C. DIBAL (45×10^{-3}M; 22.5 ml) was added and the mixture stirred for 4 h. Water (50 ml) and ethyl acetate (50 ml) were added and the mixture allowed to warm to room temperature. More water was then added and the aqueous layer was extracted with ethyl acetate; the organic layer was dried and evaporated to yield a white solid (2.03 g). Recrystallisation from ethyl acetate afforded the dilactol (1.75 g, 88%), m.p. 186—188 °C; $\nu_{max.}$(KBr) 3 320—3 440 cm^{-1}.

Preparation of 2,6-*Dimethoxy*-1-*methylthio*-8-*piperonyl*-4-*veratryl*-3,7-*dioxabicyclo*[3.3.0]*octane* (**14b**).—The dilactol (1 g) was dissolved in methanol (20 ml) and a few drops of concentrated HCl added. The solution was refluxed for 30 min and allowed to cool when crystals separated and were filtered off to give the *dimethyl acetal* (828 mg, 92%), m.p. 127—128 °C (Found: C, 60.6; H, 6.3. $C_{24}H_{28}SO_8$ requires C, 60.50; H, 5.88%). For n.m.r. spectra see Tables 4 and 5.

Reduction of the Dilactone (**10c**).—The dilactone (600 mg) in THF (35 ml) was cooled to −78 °C under nitrogen and DIBAL (1M; 21 ml) added. The reaction mixture was stirred at −40 °C for 3 h and ethyl acetate (30 ml) was then added followed by water (150 ml). The mixture was then allowed to warm to room temperature, water (500 ml) was added, and the mixture stirred overnight. It was then extracted with ethyl acetate (3 × 100 ml), washed with brine (3 × 100 ml), and dried ($MgSO_4$). On evaporation of the solvent a colourless gum (600 mg) was obtained which crystallised from methanol to give the dilactol (**13c**) as a colourless crystalline solid (488 mg, 81%), m.p. 198 °C (Found: C, 58.7; H, 5.1. $C_{22}H_{24}SO_8$ requires C, 58.92; H, 5.36%); $\nu_{max.}$(KBr) 3 200—3 600, 1 250, and 1 035 cm^{-1}.

Preparation of 2,6-*Dimethoxy*-1-*methylthio*-4-*piperonyl*-8-*veratryl*-3,7-*dioxabicyclo*[3.3.0]*octane* (**14c**).—The dilactol (0.36 g) was treated with dry methanol (15 ml). Concentrated HCl (6 drops) was added, and the mixture refluxed for 30 min. On cooling a colourless crystalline *solid* (**14c**) separated out (255 mg, 67%), m.p. 193 °C (Found: C, 60.4; H, 5.8. $C_{24}H_{28}SO_8$ requires C, 60.5; H, 5.88%). For n.m.r. spectra see Tables 4 and 5; *m/z* 476 (M^+, 3%), 397 (4), 191 (4), 165 (11), 160 (100), and 145 (15). Evaporation of the mother-liquor gave a further quantity of (**14c**) as a gum (105 mg; total yield 96%).

Desulphurisation of the Dimethyl Acetal (**14c**).—To compound (**14c**) (442 mg) was added 3 spoonfuls of Raney nickel in ethanol (50 ml) and THF (50 ml). The mixture was refluxed for 10 h and stirred overnight; the Raney nickel was then filtered off. Evaporation of the solvent gave a gum which was purified over a silica column using chloroform as eluant to give the desulphurised *product* (**15c**) as a white crystalline solid (355 mg, 89%), m.p. 193 °C (Found: C, 64.3; H, 6.2. $C_{23}H_{26}O_8$ requires C, 64.18; H, 6.04%). For n.m.r. spectra see Tables 4 and 5; *m/z* 430 (M^+, 2%), 398 (3), 356 (4), 207 (100), 195 (10), 191 (41), 165 (25), 160 (17), 151 (14), 149 (30), and 135 (13).

Equilibration of Compound (**15c**).—The above product (40 mg) was dissolved in dry methanol (4 ml) and 1 drop of concentrated HCl added. The mixture was refluxed for 1 h under nitrogen. The solvent was then evaporated and the residue extracted with dichloromethane (5 ml). The organic layer was washed with aqueous $NaHCO_3$ (2 × 2 ml) and brine (2 × 2 ml), and dried ($MgSO_4$). Removal of the solvents gave the dimethyl acetal (**16c**) as a pale yellow gum (35 mg, 88%). For n.m.r. spectra see Tables 4 and 5.

Desulphurisation of the Dimethyl Acetal (**14b**).—To compound (**14b**) (450 mg) was added 4 spoonfuls of freshly prepared Raney nickel in dry ethanol (60 ml) and THF (60 ml). The mixture was heated under reflux for 24 h under nitrogen, then filtered and evaporated to give a pale yellow gum (415 mg) which, after treatment with dry MeOH and filtration, gave a clear solution. Evaporation gave *compound* (**15b**) as a white crystalline solid (368 mg, 91%), m.p. 130—131 °C after recrystallisation from methanol (Found: C, 64.0; H, 6.0. $C_{23}H_{26}O_8$ requires C, 64.19; H, 6.05%). For n.m.r. spectra see Tables 4 and 5.

Equilibration of Compound (**15b**).—The above product (200 mg) was dissolved in dry methanol (6 ml) and 1 drop of concentrated HCl added. The mixture was refluxed for 1 h under nitrogen, the solvent then evaporated and the residue extracted with chloroform. The chloroform layer was washed with aqueous $NaHCO_3$ (3 × 5 ml) and brine (3 × 5 ml) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the dimethyl acetal (**16b**) as a pale yellow gum (195 mg, 98%). For n.m.r. spectra see Tables 4 and 5.

Demethoxylation of Methyl 4,8-*Dimethoxypiperitol*.—To methyl 4,8-dimethoxypiperitol (**16b/c**) (90 mg) in dichloromethane (3 ml) cooled to −78 °C under nitrogen was added triethylsilane (0.4 ml) and BF_3–ether (0.06 g), and the mixture stirred at −78 °C for 3 h and then at room temperature for 48 h. The reaction was quenched with aqueous $NaHCO_3$ and extracted with dichloromethane (3 × 10 ml). The organic layer was washed with aqueous $NaHCO_3$ (3 × 10 ml) and brine (3 × 10 ml), and dried ($MgSO_4$). Removal of the solvent yielded a residue (68 mg) which was purified by flash chromatography on a column of silica gel eluted with CH_2Cl_2–5% EtOAc. Analysis (by h.p.l.c.) of the fractions so obtained revealed methyl piperitol (**18c**) (22.86 mg, 35.4%) as a pure fraction and a mixture of methyl pluviatilol (**19c**) (11.89 mg, 18.4%), and methyl xanthoxylol (**20c**) (11.24 mg, 17.4%).

Methyl piperitol and methyl pluviatilol were identified by comparison with authentic samples. For ^1H and ^{13}C n.m.r. spectra see Tables 6 and 7.

Demethoxylation of the Dimethyl Acetal (**14c**).—To the acetal (**14c**) (400 mg) in dichloromethane (12 ml) cooled to −78 °C under nitrogen was added triethylsilane (1.4 ml) and BF_3–ether (0.24 g) and the mixture stirred at room temperature for 48 h. The reaction was quenched with aqueous $NaHCO_3$ and extracted with dichloromethane (3 × 10 ml). The organic layer was washed with aqueous $NaHCO_3$ (3 × 10 ml) and brine (3 × 10 ml) and dried ($MgSO_4$). After removal of the solvent it yielded a residue (412 mg) which was purified by flash chromatography on a column of silica gel eluted with light petroleum–ethyl acetate to give methyl thiomethylpluviatilol (**21c**) (0.32 g, 88.5%); *m/z* 416 (M^+, 25%), 250 (18), 203 (36), 173 (10), 166 (17), 151 (15), 150 (25), 149 (28), 135 (22), 131 (10), and 100 (100), and a minor isomer (0.03 g, 7.5%); *m/z* 416 (M^+, 20%), 250 (23), 203 (39), 173 (11), 166 (16), 165 (11), 151 (12), 150 (25), 149 (29), 135 (27), and 100 (100). For n.m.r. spectra of compound (**21c**) see Tables 6 and 7.

Desulphurisation of Methyl Thiomethylpluviatilol (**21c**).—To the thiomethyl compound (100 mg) was added two spoonfuls of Raney nickel in ethanol (30 ml) and THF (30 ml) and the mixture refluxed for 4 h. It was then filtered and evaporated to give methyl pluviatilol (**19c**) (67 mg, 75.3%), identified by comparison with an authentic sample. For n.m.r. spectra see Tables 6 and 7.

Reaction of the Lactone (**9b**) *with Veratraldehyde*.—n-Butyllithium (3.23×10^{-3}M; 2.7 ml) was added to di-isopropylamine (0.46 ml) at −10 °C under nitrogen and stirred for 5 min before THF (20 ml) was added and the temperature lowered to −78 °C. The monolactone (**9b**) (1 g) dissolved in THF (10 ml) was

added and the mixture stirred for 30 min. 3,4-Dimethoxybenzaldehyde (0.54 g) dissolved in THF (10 ml) was added and the mixture stirred for 1 h. Trifluoroacetic acid (0.62 ml) was then added and the mixture allowed to warm to room temperature overnight. The reaction mixture was diluted with chloroform (100 ml) and extracted with dilute HCl and aqueous $NaHCO_3$, dried, and evaporated to give an orange oil (1.45 g) which was purified by chromatography on silica, eluting with diisopropyl ether. This afforded the unsaturated lactone (**12b**) (242 mg), $\nu_{max.}$(film) 1 820 and 1 712 cm^{-1}; $\delta(CDCl_3)$ 3.66 (s, 2 H), 3.76 (s, 3 H), 6.01 (s, 2 H), 6.83 (d, *J* 8 Hz, 1 H), 7.54 (s, 1 H), and 7.58 (dd, *J* 2.8 Hz, 1 H) and veratraldehyde (603 mg). Acidification of the $NaHCO_3$ extracts gave the unsaturated *acid* (**11b**) (112 mg), m.p. 157—160 °C after recrystallisation from ether–light petroleum, $\nu_{max.}$ 2 700 and 1 760—1 700 cm^{-1}; δ(DMSO) 7.67 (s, 1 H), 4.69 (s, 1 H), 3.69 (s, 3 H), 1.91 (s, 3 H), 6.04 (s, 2 H), and 6.8—7.2 (m, 3 H) (Found: C, 52.5; H, 4.5. $C_{14}H_{14}SO_6$ requires C, 54.18; H, 4.55%).

Reaction of the Monolactone (**9c**) *with Piperonal.*—This was carried out exactly as for the reaction of (**4c**) but on three times the scale described above. At the end of the reaction TFA was added and the mixture allowed to warm to room temperature overnight. Water (50 ml) was then added and most of the THF evaporated. The residue was extracted with ethyl acetate (3 × 30 ml), washed with dilute HCl, aqueous $NaHCO_3$, and brine, dried ($MgSO_4$) and evaporated to give a gummy residue (6.4 g) which was purified by chromatography on a silica column eluted with light petroleum followed by mixtures of light petroleum and dichloromethane to give piperonal (1.85 g), recovered monolactone (1.88 g), the dilactone (**10c**) (0.25 g), and the unsaturated *lactone* (**13c**) (0.25 g), m.p. 200 °C, *m/z* 410 (M^+, 34%) and 165 (100); $\nu_{max.}$(KBr) 1 772 and 1 705 cm^{-1}; $\lambda_{max.}(CHCl_3)$ 419 nm (4.57); δ(DMSO) 3.80 (s, 6 H), 3.84 (s, 3 H), 6.12 (s, 2 H), and 6.9—8.1 (m, 7 H) (Found: M^+, 410.1002. $C_{22}H_{18}O_8$ requires *M*, 410.1001).

Acknowledgements

We gratefully acknowledge financial support from the S.E.R.C. and I.C.I. Limited and the receipt of a Royal Society/Nuffield Foundation Commonwealth Bursary.

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Received 9*th July* 1984; *Paper* 4/1168