Convenient Syntheses of the Naturally Occurring Benzo[*b*]xanthen-12-one Bikaverin. *X*-Ray Crystallographic Confirmation of the Product Regiochemistry

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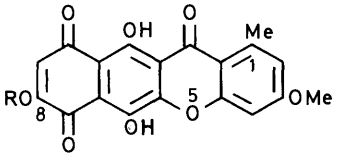
The synthesis of bikaverin (6,11-dihydroxy-3,8-dimethoxy-1-methylbenzo[*b*]xanthene-7,10,12-trione) (**1**) by two related routes is reported. Key steps include the formation of 1,2,4,5,8-pentamethoxynaphthalene (**4**) in good yield and its regiospecific acylation at C-6 with 2-benzyloxy-4-methoxy-6-methylbenzoic acid. Different methods are used to convert the derived orsellinylnaphthalene into 2,3-dihydro-5,8-dihydroxy-6,6'-dimethoxy-4'-methylnaphthalene-2-spiro-2'-2'*H*-benzofuran-1,3',4-trione (**23**) and the corresponding 5,6,6',8-tetramethoxy analogue (**25**). Pyrolysis of these spiro compounds gives high yields of bikaverin from (**23**) and 6,11-dihydroxy-3,7,8,10-tetramethoxy-1-methylbenzo[*b*]xanthen-12-one (**27**) from (**25**). Compound (**27**) is readily converted into bikaverin.

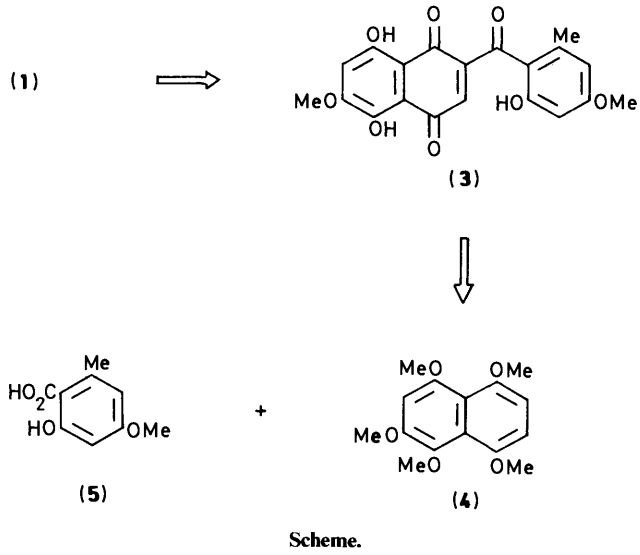
Bikaverin (**1**) is a wine-red pigment isolated from several species of the fungal genera *Fusarium*, *Gibberella*, and *Mycogone*. It has been shown to possess a number of interesting biological properties which include vacuolation,[1] anti-protozoal,[2] and antitumour[3] activities. It was identified simultaneously by Cornforth[4] and Kjaer,[5] the latter also isolating norbikaverin (**2**), the 8-*O*-demethyl derivative of bikaverin. The structure of bikaverin was confirmed by *X*-ray studies.[6] Three syntheses have been reported,[7–9] but these suffer to some extent from either the number of steps or the yields from readily available starting materials. Hauser has just described a more efficient route.[10] We report here two convenient, closely related syntheses, which compare very well with the literature methods.



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

Results and Discussion

Retrosynthetic analysis of structure (**1**) suggested cleavage of the O-5 naphthyl bond to afford the acylnapthopurpurin derivative (**3**), which might itself be obtained by regiospecific acylation of 1,2,4,5,8-pentamethoxynaphthalene (**4**) with the 4-*O*-methyl ether (**5**) of orsellinic acid (Scheme). Acylation of the naphthalene at C-6 might be anticipated on the grounds first that monoacetylation of the corresponding 2,4,5,8-tetramethoxynaphthalene (**6**) (numbering for comparison) affords the 6-acetyl (minor) (**7**) and 1-acetyl (major) (**8**) products;[11] blocking of C-1 in (**4**) by methoxy might then direct

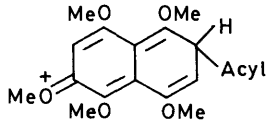


Scheme.

electrophilic attack solely to C-6 provided the additional methoxy did not reduce the selectivity. Secondly, this selectivity would be favoured by a σ-complex of the form (**10**).

A convenient synthesis of the pentamethoxynaphthalene (**4**) was therefore considered. The use of naphthazarin derivatives as starting materials was unattractive since, with the exception of Brassard's assembly of the 2,3-dihalogeno

(**6**) $R^1 = R^2 = H$
(**7**) $R^1 = Ac$, $R^2 = H$
(**8**) $R^1 = H$, $R^2 = Ac$
(**9**) $R^1 = Ac$, $R^2 = OMe$



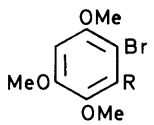
(**10**)

* For synthesis.
† For crystallography.

derivatives,[12] such compounds are formed in yields that are mediocre at best.

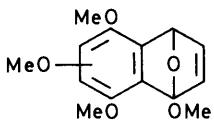
The first route attempted to naphthalene (**4**) involved 1-bromo-2,4,5-trimethoxybenzene (**11**)[13] which is readily available from vanillin in good yield.[14] This was converted into the corresponding trimethoxybenzyne with sodamide,[15] and reacted *in situ* with commercially available 2-methoxyfuran to afford the regioisomeric epoxynaphthalenes (**13**). Purification by silica gel chromatography gave the corresponding naphthols (**14**), which yielded pentamethoxynaphthalene (**4**) on methylation. The overall yield from the bromobenzene (**11**) was modest (30%).

A much higher yield was obtained when the same benzyne was generated by the general method of Hart[16] from the dibromobenzene (**12**)[17] using butyl-lithium. *In situ* reaction as before with 2-methoxyfuran, followed by the earlier procedure, afforded the naphthalene (**4**) in good overall yield (73%) from the dibromobenzene (**12**). This yield was achieved when 0.9 mol equiv. of butyl-lithium was used relative to the dibromo derivative (**12**). With an equimolar quantity of base, the product (**4**) was contaminated by a butyltetramethoxynaphthalene, assigned one * of the structures (**15**) on the basis of its ^{1}H n.m.r. and mass spectra. This product can be rationalised by attack on one of the adducts (**13**) by the butyl carbanion, which would lead to epoxide ring opening to afford intermediate (**16**), and this could protonate oxygen and dehydrate to yield the observed product (**15**). Addition of butyl-lithium to 1,4-dihydronaphthalene 1,4-oxide has previously been observed.[18] With equimolar amounts of base and (**12**), the yield of by-product (**15**) increased as the reaction was scaled up. The unwanted (**15**) was not observed when the base was limited.

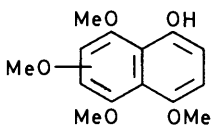


(**11**) R = H

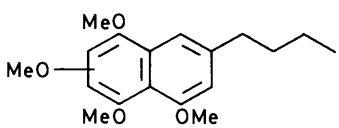
(**12**) R = Br



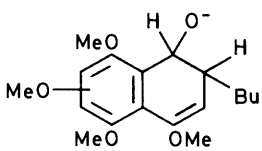
(**13**)



(**14**)



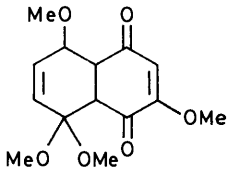
(**15**)



(**16**)

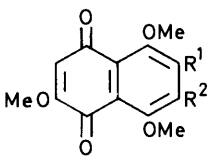
Other routes to (**4**), including manipulation of the Diels–Alder adduct (**17**)[19] between 1,1,4-trimethoxybuta-1,3-diene and 2-methoxy-1,4-benzoquinone, and also of 2-methoxynaphthazarin,[20] were not as satisfactory in our hands.

The regiospecific acylation of the naphthalene (**4**) was then



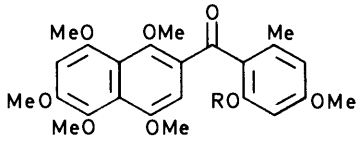
(**17**)

investigated. A single product (83%) was obtained with premixed acetic acid and trifluoroacetic anhydride (TFAA). This was identified as the 6-acetylnaphthalene (**9**) since its oxidation with silver(II) oxide afforded the 6-acetyl-1,4-naphthoquinone (**18**), oxidation having taken place in the more electron-rich ring as anticipated. This was established by comparison of the product with authentic samples of both (**18**) and (**19**).[21]



(**18**) R^1 = Ac, R^2 = H

(**19**) R^1 = H, R^2 = Ac



(**20**) R = $CH_2C_6H_5$

(**21**) R = H

Having shown that regiospecific acetylation of the naphthalene (**4**) occurred in the desired sense, the related reaction with the alternative mixed anhydride obtained from 2-*O*-benzyl-4-*O*-methylorsellinic acid[22] and TFAA was examined. Once again, a single regioisomer (**20**) was obtained (51%). The regiochemistry was confirmed by an *X*-ray crystallographic study of compound (**28**). Acylnaphthalene (**20**) was oxidised with silver(II) oxide to afford the acylnaphthopurpurin (**22**); the assignment was supported by the quinonoid proton appearing at δ 5.92 in its ^{1}H n.m.r. spectrum, this being shielded by the adjacent methoxy substituent.

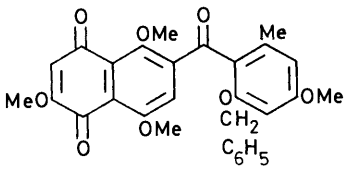
Treatment of the quinone (**22**) with an excess of boron trichloride (7.5 mol equiv.) afforded the two closely related products (**23**) (51%) and (**24**) (14%). Their mass spectral molecular ions indicated a difference of 14 mass units, and the ^{1}H n.m.r. spectra showed two methoxy groups for the former and one for the latter. A characteristic feature of each was the prominent AB quartet, centred at δ ~3.35, assigned to the methylene protons adjacent to the spiro carbon. Thus, boron trichloride had effected the desired deprotection to yield compound (**3**) and its *O*-demethyl analogue, each of which closed spontaneously in a 5-*exo-trig* mode rather than the desired 6-*endo-trig* alternative. Related reactions have previously been observed[23] in an attempt to synthesize bikaverin which failed in the case of the appropriate precursor.

Reactions were carried out on a small scale to optimise the yield of compound (**23**) by reducing the relative amount of boron trichloride used. With 7 mol equiv. the yield of the desired compound (**23**) was increased to 65%, with 13% of product (**24**) obtained. With 6 mol equiv., none of the compound (**24**) was observed, but the yield of the spiro compound (**23**) was reduced to 40%, and a new compound lacking the benzyl and one methyl substituent was obtained. It was not further identified. Lesser amounts of boron trichloride afforded only the latter compound.

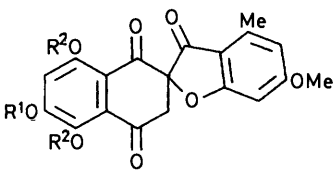
The spiro compound (**23**) was heated at 200 °C in nitrobenzene whereupon bikaverin (**1**) was obtained in 74% yield. Our synthetic sample was shown to be identical with a sample of the natural product.

An alternative route from the naphthalene (**20**) to bikaverin

* The ^{1}H n.m.r. spectrum suggested that the product (**15**) was a single regioisomer. If so, this would suggest preferential attack on one of the isomers (**13**) by butyl. This was not further investigated.



(22)

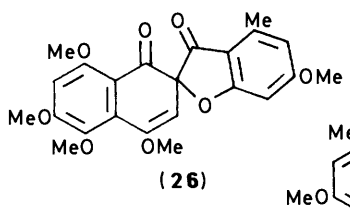


(23) R^1 = Me, R^2 = H
(24) R^1 = R^2 = H
(25) R^1 = R^2 = Me

was investigated in the hope of further improving the overall yield. It was felt in particular that the yield (74%) of the pyrolytic isomerisation of spiro compound (**23**) to give bikaverin might well be improved by methylation of the two phenolic hydroxy groups to protect the hydroquinone in the vigorous thermal isomerisation. However, direct methylation of (**23**) to afford (**25**) was not successful.

The synthesis of compound (**25**) was achieved as follows. The naphthalene (**20**) was hydrogenolysed to afford the naphthoylphenol (**21**) (80%). Oxidation of this product with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.5 mol equiv.) afforded a new spiro compound, the enol ether (**26**), in 61% yield. This was hydrolysed to the desired tetramethyl ether trione (**25**) in high yield (94%) with aqueous trifluoroacetic acid (TFA). This brown spiro compound (**25**) was then heated under reduced pressure at 200 °C and subsequently sublimed to afford the isomeric red hydroquinone (**27**) in 93% yield, thereby justifying the selection of the tetramethyl ether (**25**) as the spiro compound of choice for pyrolytic isomerisation. The ^{1}H n.m.r. spectrum of compound (**27**) confirmed this assignment; in particular two low-field singlets at δ 9.70 and 15.17 represented the phenolic hydroxy groups, the former being hydrogen-bonded to the *peri*-methoxy and the latter to the carbonyl function. In addition, the aromatic methyl signal at δ 2.36 in compound (**25**) was deshielded at δ 2.79 in the planar hydroquinone, a change also observed for the conversion of spiro compound (**23**) into the planar tetracycle (**1**).

The hydroquinone (**27**) was oxidised in high yield (93%) to the corresponding quinone (**29**), a compound previously synthesized by Barton and converted in very good yield (80%) into bikaverin.[7] Quinone (**29**) has also been prepared by Kjaer



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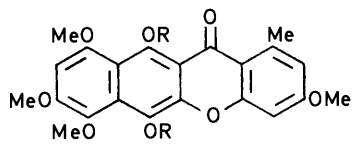
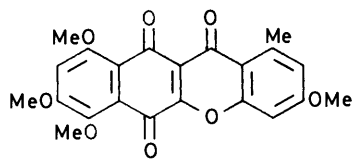


(27) R = H
(28) R = Me



(29)

from natural bikaverin by methylation.[5] Our synthetic (**29**) was identical with the naturally derived material kindly provided by Professor Kjaer.

In order to avoid any doubt whatsoever as to the regiochemistry of our synthetic samples (**20**)—(**29**) and (**1**), a crystal structure determination was carried out on the hexamethyl ether (**28**), obtained by dimethylation of the hydroquinone (**27**). This verified the assignment of compound (**28**), with methoxy at C-8 of the ring system [see structure (**1**)]. This therefore confirmed the regiochemistry of the acylation product (**20**) as well as the migrating atom (oxygen) in the thermal rearrangements of (**23**) and (**25**) to (**1**) and (**27**) respectively.

The conversion of the readily available dibromobenzene (**12**) into bikaverin *via* either the five-step sequence (**12**) ⟶ (**4**) ⟶ (**20**) ⟶ (**22**) ⟶ (**23**) ⟶ (**1**) or the alternative eight-step procedure [*via* the phenol (**21**)] was achieved in an overall yield of *ca.* 12% in each case. In addition, the syntheses described here would readily lend themselves to the assembly of analogues with different substitution patterns.

Crystal Structure of the Hexamethyl Ether (**28**).—The results of the single-crystal *X*-ray structure determination are consistent with the stoicheiometry and connectivity given above for (**28**), establishing the fused ring system substitution array definitively (Figures, Tables 1, 2, and 3). The structure is

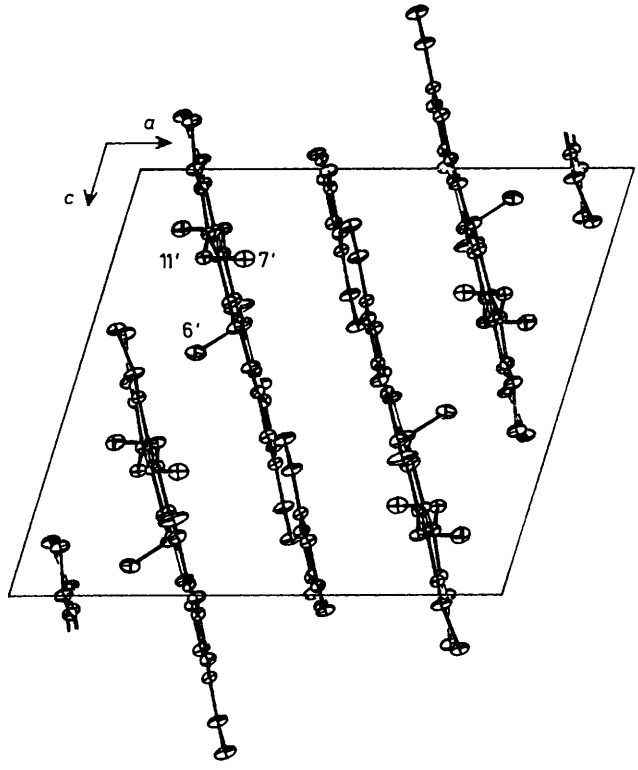


Figure 1. Unit-cell contents, projected down *b*, showing the parallel planar stacking; 20% thermal ellipsoids are shown for the non-hydrogen atoms

agreeably precise, with low thermal motion, establishing all hydrogen-atom positions by refinement; C–H distances lie between 0.90(4)—1.09(4) Å. A number of features of interest may be noted:

(1) In the fused ring system, significant variations in bond order are observed, many C–C bonds deviating non-trivially in length from the aromatic norm (~ 1.40 Å). C(1)–C(2), C(3)–C(4),

Table 1. Fractional atom co-ordinates for compound (**28**)

Atom	*x*	*y*	*z*
C(1)	0.396 3(3)	0.008 2(4)	0.543 6(3)
C(1′)	0.383 0(3)	−0.118 8(4)	0.504 7(3)
C(2)	0.445 2(3)	0.027 8(4)	0.649 5(3)
C(3)	0.458 7(3)	0.143 5(4)	0.691 1(3)
O(3)	0.503 6(2)	0.169 6(3)	0.794 6(2)
C(3′)	0.538 3(4)	0.073 1(4)	0.866 8(4)
C(4)	0.425 2(3)	0.239 5(4)	0.626 1(3)
C(4a)	0.377 6(3)	0.219 9(4)	0.521 5(3)
O(5)	0.347 0(2)	0.322 5(2)	0.463 7(2)
C(5a)	0.294 1(3)	0.315 7(4)	0.358 5(3)
C(6)	0.264 2(3)	0.424 0(4)	0.311 3(3)
O(6)	0.292 4(2)	0.525 2(2)	0.371 7(2)
C(6′)	0.227 7(4)	0.557 5(4)	0.430 2(4)
C(6a)	0.210 9(3)	0.430 0(4)	0.202 8(3)
C(7)	0.178 1(3)	0.540 4(4)	0.150 3(3)
O(7)	0.184 6(2)	0.645 7(3)	0.206 4(2)
C(7′)	0.266 9(4)	0.717 8(4)	0.209 5(4)
C(8)	0.135 1(3)	0.542 2(4)	0.043 0(3)
O(8)	0.110 9(2)	0.652 0(3)	−0.001 8(2)
C(8′)	0.073 4(4)	0.658 8(5)	−0.114 5(6)
C(9)	0.114 5(3)	0.436 8(4)	−0.015 8(3)
C(10)	0.138 9(3)	0.328 8(4)	0.032 7(3)
O(10)	0.115 7(2)	0.224 6(3)	−0.022 1(2)
C(10′)	0.051 0(4)	0.228 4(4)	−0.126 7(4)
C(10a)	0.189 7(3)	0.320 2(4)	0.144 2(3)
C(11)	0.221 3(3)	0.211 4(4)	0.196 6(3)
O(11)	0.206 1(2)	0.106 9(2)	0.140 1(2)
C(11′)	0.120 5(4)	0.044 6(4)	0.139 3(4)
C(11a)	0.272 7(3)	0.206 7(3)	0.304 0(3)
C(12)	0.305 7(3)	0.094 1(4)	0.363 1(3)
O(12)	0.286 9(3)	−0.002 9(3)	0.321 9(3)
C(12a)	0.360 1(3)	0.107 0(4)	0.476 0(3)

C(4)–C(4a), C(5a)–C(6), C(7)–C(8), C(9)–C(10) are all appreciably shorter, while C(6)–C(6a), C(6a)–C(7), C(10)–C(10a), C(10a)–C(11) are appreciably longer.

(2) In spite of the non-aromatic ring within the fused system, the four fused rings are effectively planar. For the ring atoms, χ^2 is 963; atom deviations are (atoms 1 ⟶ 12a in order): −0.02, −0.02, 0.01, 0.02, 0.05, 0.01, −0.02, −0.04, −0.08, 0.04, 0.07, 0.01, −0.03, −0.01, −0.01, −0.01, 0.00, −0.01 Å. Methoxy O,C(H_3) deviations are: −0.07, 1.28, (3); 0.04, −1.24, (6); −0.29, 0.89, (7); 0.07, 0.30, (8); −0.02, −0.27, (10); 0.08, −1.15, (11); deviations of (C1′), O(12) are −0.02, −0.07 Å.

(3) Planarity of the system is reflected in the crystal packing (Figure 1), showing an array of planes parallel to *b*. Overlap between molecules at $(x, \frac{1}{2} - y, \frac{1}{2} + z)$ (Figure 2, Table 3) and $(\bar{x}, 1 - y, \bar{z})$ at <3.6 Å suggests significant charge-transfer interaction.

(4) Methoxy substituent disposition is interesting, if predictable, three groups adopting their normal in-plane disposition, with asymmetry in the exocyclic angles at the point of attachment (the larger angle being enclosed by the methyl group) and with the angle at the oxygen enlarged relative to those substituents which lie out of plane. Methyl hydrogens lie astride the adjacent ring hydrogen. The groups at C(7) and C(11) have substituents to either side precluding an in-plane disposition with symmetrical exocyclic angles at the point of attachment. The substituent at C(6) is also out of plane, for more subtle reasons probably associated with hindrance in the proximity of O(5), by virtue of the charge-transfer interaction of Figure 2(b), and also the closer disposition of O(6) to O(5) [2.594(4) Å], *cf.* (*e.g.*) C(7) [2.907(5) Å]. A number of other exocyclic asymmetries may arise from close substituent O ··· O contacts.

Table 2. Molecular skeletal geometry

(*a*) Bond distances (Å)

Bond	Distance	Bond	Distance
C(1)–C(12a)	1.425(6)	C(6)–C(6a)	1.415(5)
C(1)–C(1′)	1.510(6)	C(6a)–C(10a)	1.441(6)
C(1)–C(2)	1.386(6)	C(6a)–C(7)	1.432(6)
C(2)–C(3)	1.403(6)	C(7)–C(8)	1.370(6)
C(3)–C(4)	1.375(6)	C(7)–O(7)	1.385(5)
C(3)–O(3)	1.361(5)	O(7)–C(7′)	1.427(6)
O(3)–C(3′)	1.434(5)	C(8)–C(9)	1.400(6)
C(4)–C(4a)	1.367(6)	C(8)–O(8)	1.370(5)
C(12a)–C(4a)	1.396(6)	O(8)–C(8′)	1.429(5)
C(12a)–C(12)	1.473(6)	C(9)–C(10)	1.369(6)
C(4a)–O(5)	1.382(5)	C(10)–C(10a)	1.443(5)
O(5)–C(5a)	1.376(5)	C(10)–O(10)	1.366(5)
C(5a)–C(11a)	1.409(6)	O(10)–C(10′)	1.421(5)
C(5a)–C(6)	1.378(6)	C(10a)–C(11)	1.413(6)
C(6)–O(6)	1.380(5)	C(11)–C(11a)	1.395(5)
O(6)–C(6′)	1.423(7)	C(11)–O(11)	1.375(5)
		O(11)–C(11′)	1.416(6)
		C(11a)–C(12)	1.490(6)
		C(12)–O(12)	1.213(5)

(*b*) Angles (degrees)

C(1′)–C(1)–C(2)	118.0(4)	C(6a)–C(7)–C(8)	119.8(4)
C(1′)–C(1)–C(12a)	122.5(4)	C(6a)–C(7)–O(7)	121.4(3)
C(2)–C(1)–C(12a)	119.5(4)	C(8)–C(7)–O(7)	118.7(4)
C(1)–C(2)–C(3)	120.9(4)	C(7)–O(7)–C(7′)	115.2(4)
C(2)–C(3)–O(3)	124.3(4)	C(7)–C(8)–C(9)	121.3(4)
C(2)–C(3)–C(4)	120.0(4)	C(7)–C(8)–O(8)	116.1(4)
O(3)–C(3)–C(4)	115.8(4)	C(9)–C(8)–O(8)	122.6(4)
C(3)–O(3)–C(3′)	118.4(3)	C(8)–O(8)–C(8′)	117.9(3)
C(3)–C(4)–C(4a)	119.0(4)	C(8)–C(9)–C(10)	120.6(4)
C(1)–C(12a)–C(4a)	116.9(4)	C(9)–C(10)–C(10a)	121.3(4)
C(1)–C(12a)–C(12)	123.1(4)	C(9)–C(10)–O(10)	121.6(4)
C(4a)–C(12a)–C(12)	120.1(4)	C(10a)–C(10)–O(10)	117.1(4)
C(4)–C(4a)–C(12a)	123.7(4)	C(10)–O(10)–C(10′)	118.5(3)
C(4)–C(4a)–O(5)	114.1(4)	C(10)–C(10a)–C(6a)	117.0(4)
C(12a)–C(4a)–O(5)	122.2(3)	C(10)–C(10a)–C(11)	123.5(4)
C(4a)–O(5)–C(5a)	120.2(3)	C(6a)–C(10a)–C(11)	119.4(3)
O(5)–C(5a)–C(11a)	122.5(4)	C(10a)–C(11a)–C(11a)	122.0(4)
O(5)–C(5a)–C(6)	114.5(4)	C(10a)–C(11)–O(11)	119.8(3)
C(6)–C(5a)–C(11a)	123.0(3)	C(11a)–C(11)–O(11)	118.1(4)
C(5a)–C(6)–C(6a)	120.3(4)	C(11)–O(11)–C(11′)	115.2(4)
C(5a)–C(6)–O(6)	117.8(3)	C(11)–C(11a)–C(5a)	117.2(4)
C(6a)–C(6)–O(6)	121.7(4)	C(11)–C(11a)–C(12)	123.9(4)
C(6)–O(6)–C(6′)	113.3(3)	C(5a)–C(11a)–C(12)	118.9(3)
C(6)–C(6a)–C(10a)	118.0(4)	C(11a)–C(12)–C(12a)	116.0(4)
C(6)–C(6a)–C(7)	122.3(4)	C(11a)–C(12)–O(12)	122.3(4)
C(10a)–C(6a)–C(7)	119.7(3)	C(12a)–C(12)–O(12)	121.6(4)

Table 3. Non-hydrogen atom intermolecular contacts (<3.63 Å). (Methyl groups are excluded)

Atom 1	Atom 2	Distance (Å)	Atom 1	Atom 2	Distance (Å)
Atom 2 at $(x, \frac{1}{2} - y, \frac{1}{2} + z)$					
C(5a)	O(3)	3.370(6)	C(10)	C(12a)	3.557(4)
C(11)	C(4)	3.381(7)	C(4a)	C(10a)	3.570(7)
C(5a)	O(10)	3.419(6)	O(11)	O(5)	3.600(5)
O(5)	O(10)	3.436(5)	C(12a)	C(9)	3.607(7)
C(4a)	C(10)	3.530(7)	O(3)	O(5)	3.613(5)
C(4)	C(10a)	3.537(7)	C(12)	C(9)	3.587(7)
Atom 2 at $(\bar{x}, 1 - y, \bar{z})$					
O(8)	C(9)	3.472(6)	C(1)	C(1)	3.510(7)
O(8)	C(10)	3.509(6)	C(8)	C(9)	3.518(7)

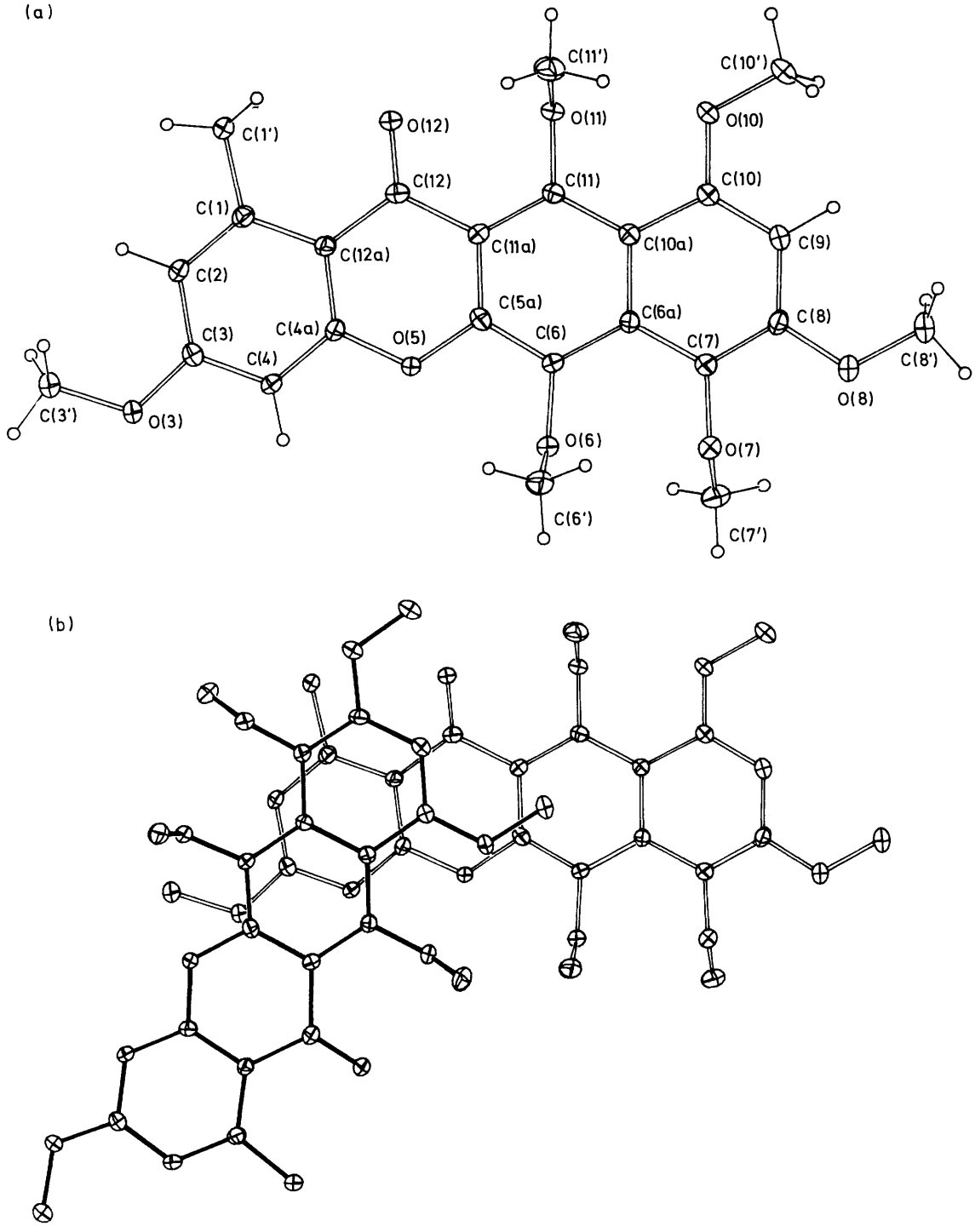


Figure 2. (*a*) A single molecule projected perpendicular to the aromatic plane. Atom labelling is given. Hydrogen atoms have arbitrary radii of 0.1 Å. (*b*) Overlap with the molecule at $(x, \frac{1}{2} - y, \frac{1}{2} + z)$

Experimental

^1H (200 MHz) and ^{13}C(50 MHz) n.m.r. spectra were measured on a VARIAN VXR spectrometer, in [^2H]chloroform with tetramethylsilane as internal reference; 90 MHz ^1H n.m.r. spectra were recorded on a Bruker WH-90 instrument. I.r. spectra were measured for Nujol mulls. Preparative layer chromatography (p.l.c.) was performed on glass plates coated with Merck Kieselgel 60 F_{254}, while column chromatography refers to dry-packed columns using the same gel (70—230 mesh). Light petroleum refers to the fraction of b.p. 60—80 °C, and ether to diethyl ether. The phrase 'residue obtained upon work-up' refers to the residue when the organic layer was separated, dried ($MgSO_4$), and the solvent evaporated under reduced pressure.

1,2,4,5,8-*Pentamethoxynaphthalene* (**4**).—2,3-Dibromo-1,4,5-trimethoxybenzene (**12**) (10.00 g, 30.7 mmol) and 2-methoxyfuran (3.67 g, 33.8 mmol) were stirred in dry tetrahydrofuran

(100 ml) at −78 °C under nitrogen. Butyl-lithium (1.16M; 23.73 ml, 27.5 mmol) was added dropwise during 15 min and the solution was stirred for another 10 min. The reaction mixture was allowed to warm to room temperature, and was added to water (200 ml). The organic material was then extracted with ether (4 × 100 ml). The residue obtained upon work-up was flash-chromatographed (40% ethyl acetate–light petroleum) to afford a light brown oil. This was immediately dissolved in dry acetone (200 ml) to which anhydrous potassium carbonate (42.1 g, 305 mmol) and dimethyl sulphate (29.0 ml, 38.5 g, 306 mmol) were added and the mixture was stirred and heated under reflux for 16 h. The cooled reaction mixture was filtered and evaporated. The residue was dissolved in ether (200 ml) and the solution was washed successively with aqueous ammonia (25%) (4 × 100 ml), water (150 ml), dil. hydrochloric acid (100 ml), and finally water (150 ml). The residue obtained upon work-up was chromatographed (20% ethyl acetate–light petroleum) to afford, first, starting material (0.99 g, 10%) followed by the *title product* (**4**) (5.63 g, 66%, or 73% based on unrecovered starting material) as white needles, m.p. 105—106 °C (from light petroleum) (Found: C, 64.6; H, 6.8. $C_{15}H_{18}O_5$ requires C, 64.75; H, 6.45%); $\nu_{max.}$ 1 601 (C=C) cm^{-1}; δ_H 3.81, 3.88, 3.90, 3.92, and 3.98 (each 3 H, s, OMe), 6.65 (1 H, d, *J* 10 Hz, 6-H), 6.75 (1 H, s, 3-H), and 6.80 (1 H, d, *J* 10 Hz, 7-H); δ_C 57.30, 57.35, 57.61, 57.80, and 61.88 (5 × OMe), 99.20 (C-3), 105.20 (C-6), 108.97 (C-7), 115.54 (C-4a),[a] 124.19 (C-8a)[a], 138.13 (C-2)[b], 149.99 (C-1)[b], 150.13 (C-4)[b], 151.48 (C-5)[b], and 153.85 (C-8)[b] (assignments with the same superscript may be interchanged); 278 (M^+, 100%), 263 (58), and 249 (18). With 1 mol equiv. of butyl-lithium the product (**15**) 6 (or 7)-butyl-1,2,4,8-(or 6)-tetramethoxynaphthalene, was also formed; δ_H 0.95 (3 H, t, *J* 7.2 Hz, CMe), 1.3—1.5 (2 H, m, CH_2Me), 1.6—1.8 (2 H, m, CH_2Et), 2.71 (2 H, t, *J* 7.7 Hz, ArCH_2), 3.84 and 3.96 (each 3 H, s, OMe), 3.98 (6 H, s, OMe), 6.64 (1 H, s, 2- or 3-H), 6.73 (1 H, d, *J* 2 Hz, 7-H), and 7.58 (1 H, d, *J* 2 Hz, 5-H); *m/z* 304 (M^+, 100%), 289 (63), and 261 (44).

2-*Acetyl*-1,4,5,6,8-*pentamethoxynaphthalene* (**9**).—Acetic acid (220 mg, 3.7 mmol) premixed with TFAA (770 mg, 3.7 mmol) was rapidly added to a solution of compound (**4**) (113 mg, 0.41 mmol) in dry methylene dichloride (5 ml). The mixture was stirred at room temperature for 21 h. The reaction was quenched by successive additions of an excess of methanol and saturated aqueous sodium hydrogen carbonate. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate–light petroleum) to afford the *title product* (**9**) (108 mg, 83%) as pale yellow flakes, m.p. 108—109 °C (from CH_2Cl_2–light petroleum) (Found: C, 63.45; H, 6.2. $C_{17}H_{20}O_6$ requires C, 63.75; H, 6.25%); $\nu_{max.}$ 1 679 (C=O) and 1 594 cm^{-1} (C=C); δ_H 2.72 (3 H, s, COMe), 3.76, 3.78, 3.94, 3.98, and 4.00 (each 3 H, s, OMe), 6.75 (1 H, s, 7-H), and 7.07 (1 H, s, 3-H); δ_C 31.03 (CO*Me*), 56.32, 56.41, 56.61, 61.48, and 63.29 (5 × OMe), 97.61 (C-7), 105.31 (C-3), 116.15 (C-8a)[a], 126.00 (C-4a)[a], 126.34 (C-2), 137.82 (C-6)[b], 151.52 (C-5)[b], 152.05 (C-8)[b], 152.52 (C-1)[b], 153.91 (C-4)[b], 199.67 (C=O); *m/z* 320 (M^+, 100%), 305 (60), 290 (10), 277 (20), 273 (17), 247 (10), and 43 (20).

6-*Acetyl*-2,5,8-*trimethoxy*-1,4-*naphthoquinone* (**18**).—The naphthalene (**9**) (67.5 mg, 0.21 mmol), silver(II) oxide (107 mg, 0.84 mmol), and dioxane (5 ml) were stirred together at room temperature. Nitric acid (6M; 0.8 ml) was added immediately and the reaction mixture was stirred for 4 min; then a mixture of methylene dichloride (20 ml) and water (5 ml) was added, and the organic layer was washed with more water. The residue obtained upon work-up was chromatographed (50% ethyl acetate–light petroleum) to give the quinone (**18**) (57 mg, 93%), m.p. 187—188.5 °C (from MeOH) (lit.,[21] 169—170 °C), otherwise identical with an authentic sample. The m.p. was undepressed on admixture with an authentic sample kindly provided by Professor Fariña. The literature[21] value is a typographical error, and should read 187—188 °C. This has kindly been confirmed by Professor Fariña.

2-(2-*Benzyloxy*-4-*methoxy*-6-*methylbenzoyl*)-1,4,5,6,8-*pentamethoxynaphthalene* (**20**).—2-Benzyloxy-4-methoxy-6-methylbenzoic acid (0.83 g, 3.05 mmol) premixed with TFAA (0.64 g, 3.05 mmol) in dry methylene dichloride (5 ml) was rapidly added to a solution of the naphthalene (**4**) (0.85 g, 3.05 mmol) in dry methylene dichloride (20 ml). The mixture was stirred at room temperature for 90 h with addition of further aliquots of the mixed anhydride at 6 and 48 h. The reaction was quenched by the successive additions of an excess of methanol and saturated aqueous sodium hydrogen carbonate. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was chromatographed (20% ethyl acetate–light petroleum) to afford the *title product* (**20**) (0.83 g, 51%) as pale yellow needles, m.p. 152.5—153 °C (from MeOH) (Found: C, 69.9; H, 5.95. $C_{31}H_{32}O_8$ requires C, 69.9; H, 6.0%); $\nu_{max.}$ 1 631 (C=O) and 1 600 cm^{-1} (C=C); δ_H (90 MHz) 2.36 (3 H, s, Ar*Me*), 3.32, 3.82, 3.88, and 3.98 (each 3 H, s, OMe), 3.80 (6 H, s, OMe), 4.82 (2 H, s, ArCH_2O), 6.32 (1 H, d, *J* 2.2 Hz, 3′-H), 6.40 (1 H, d, *J* 2.2 Hz, 5′-H), 6.68 (1 H, s, 7-H), and 6.75—7.12 (6 H, m, Ph and 3-H); *m/z* 532 (M^+, 100%), 517 (13), 410 (20), 395 (25), 366 (12), and 91 (37).

6-(2-*Benzyloxy*-4-*methoxy*-6-*methylbenzoyl*)2,5,8-*trimethoxy*-1,4-*naphthoquinone* (**22**).—The naphthalene (**20**) (200 mg, 0.38 mmol), silver(II) oxide (280 mg, 2.26 mmol), and dioxane (10 ml) were stirred together at room temperature. Nitric acid (6M; 1.15 ml) was added immediately and the reaction mixture was stirred for 15 min. A mixture of methylene dichloride (30 ml) and water (10 ml) was added and the organic layer was separated and washed with more water. The residue obtained upon work-up was chromatographed (eluant 50% ethyl acetate–light petroleum) to afford the *title quinone* (**22**) (132 mg, 70%) as yellow diamonds, m.p. 210—212 °C (from MeOH) (Found: C, 68.8; H, 5.1. $C_{29}H_{26}O_8$ requires C, 69.3; H, 5.2%); $\nu_{max.}$ 1 669, 1 641, and 1 627 (C=O), and 1 602 cm^{-1} (C=C); δ_H 2.46 (3 H, s, Ar*Me*), 3.32 and 3.71 (each 3 H, s, OMe), 3.81 (6 H, s, OMe), 4.69 (2 H, s, ArCH_2O), 5.92 (1 H, s, 3-H), 6.32 (1 H, d, *J* 2.2 Hz, 3′-H), 6.43 (1 H, d, *J* 2.2 Hz, 5′-H), and 6.74—7.18 (6 H, m, Ph and 7-H); δ_C 21.10 (C*Me*), 55.37, 56.30, 56.48, 62.58 (4 × OMe), 70.58 (CH_2), 97.49 (C-3), 108.50, 109.67, and 118.51 (Ar*C*H), 121.83 (C-4a)[a], 125.12 (C-8a)[a], 127.66—128.37 (6 × PhC), 135.03 (C-2)[b], 141.70 (C-6)[b], 146.00 (*C*Me)[b], 150.97, 156.31, 159.64, 159.77, and 162.39 (*C*OMe and *C*OCH_2Ar), 178.49 (C-4), 184.15 (C-1), and 194.97 (ketone C=O); *m/z* 502 (M^+, 40%), 471 (36), 439 (15), 411 (95), 380 (17), 327 (21), 165 (22), 91 (100), and 65 (17).

2,3-*Dihydro*-5,8-*dihydroxy*-6,6′-*dimethoxy*-4′-*methylnaphthalene*-2-*spiro*-2′-2′H-*benzofuran*-1,3′,4-*trione* (**23**) *and* 2,3-*Dihydro*-5,6,8-*trihydroxy*-6′-*methoxy*-4′-*methylnaphthalene*-2-*spiro*-2′-2′H-*benzofuran*-1,3′,4-*trione* (**24**).—(*a*) A solution of the quinone (**22**) (237 mg, 0.47 mmol) in dry methylene dichloride (30 ml) was treated at 0 °C with boron trichloride (415 mg, 3.53 mmol) in the same solvent. After 3 h, the solution was allowed to warm to room temperature and then hydrolysed with an excess of water. The organic material was extracted into methylene dichloride. The residue obtained upon work-up was chromatographed (eluant toluene) using deactivated silica, to yield the *product* (**23**) as dark red needles (92 mg, 51%), m.p. > 300 °C (from CH_2Cl_2–MeOH) (Found: C, 61.9; H, 4.3%; M^+, 384.0867. $C_{20}H_{16}O_8$ requires C, 62.5; H, 4.18%; *M*, 384.0845); $\nu_{max.}$ 3 097 (OH), 1 702 and 1 650 (C=O), and 1 623 cm^{-1} (C=C); δ 2.45 (3 H,

d, *J* 0.6 Hz, Ar*Me*), 3.20 and 3.55 (each 1 H, d, *J* 17.5 Hz, CH_2), 3.93 and 4.00 (each 3 H, s, OMe), 6.47 (1 H, dd, *J* 1.95 and 0.6 Hz, 5′-H), 6.54 (1 H, d, *J* 1.95 Hz, 7′-H), 6.69 (1 H, s, 7-H), and 11.94 and 12.08 (each 1 H, s, OH); *m/z* 384 (M^+, 63%), 383 (27), 382 (100), 368 (28), 367 (82), 366 (15), 339 (29), 311 (13), and 165 (29). This was followed by *product* (**24**) as dark red needles (24 mg, 14%), m.p. >300 °C (from CH_2Cl_2–MeOH) (Found: C, 61.0; H, 3.7%; M^+, 370.0664. $C_{19}H_{14}O_8$ requires C, 61.6; H, 3.8%; *M*, 370.0688); $\nu_{max.}$ 3 369 (OH), 1 700 and 1 695 (C=O), and 1 616 cm^{-1} (C=C); δ 2.45 (3 H, d, *J* 0.7 Hz, Ar*Me*), 3.16 and 3.52 (each 1 H, d, *J* 16.7 Hz, CH_2), 3.90 (3 H, s, OMe), 6.46 (1 H, dd, *J* 2 and 0.7 Hz, 5′-H), 6.54 (1 H, d, *J* 2 Hz, 7′-H), 6.84 (1 H, s, 7-H) 11.73 (1 H, s, OH), and 11.77br (1 H, s, OH); *m/z* 370 (M^+, 100%), 368 (45), 353 (62), 324 (12), 233 (16), 191 (24), 177 (19), 165 (37), and 138 (25).

(*b*) Treatment of the quinone (**22**) (30 mg, 0.06 mmol) as above with boron trichloride (49 mg, 0.42 mmol) afforded the spiro compound (**23**) (15 mg, 65%) and product (**24**) (3 mg, 13%).

6,11-*Dihydroxy*-3,8-*dimethoxy*-1-*methylbenzo*[b]*xanthene*-7,10,12-*trione* (**1**) (*Bikaverin*).—The spiro compound (**23**) (56 mg, 0.15 mmol) was heated in nitrobenzene (10 ml) at 200 °C for 2 h. After distillation to remove the bulk of the nitrobenzene, the crude product was dissolved in methylene dichloride and the solution was washed successively with water and dil. aqueous potassium hydroxide, the product forming a blue colouration in the aqueous basic solution. The aqueous layer was washed with more methylene dichloride, the two layers were separated, the aqueous layer was acidified with dil. hydrochloric acid, and the product was re-extracted into methylene dichloride. The residue obtained upon work-up was chromatographed [Sephadex LH-20; eluant methanol–methylene dichloride (1:9), containing 5 drops of 5M hydrochloric acid in 100 ml of eluant] to yield the product (**1**) (41 mg, 74%) as dark red needles, m.p. >300 °C (from CH_2Cl_2–MeOH) (Found: C, 62.9; H, 3.95. Calc. for $C_{10}H_{14}O_8$: C, 62.8; H, 3.7%); $\nu_{max.}$ 1 665 and 1 643 (C=O) and 1 614 and 1 589 cm^{-1} (C=C); δ 2.79 (3 H, d, *J* 0.7 Hz, Ar*Me*), 3.86 and 3.89 (each 3 H, s, OMe), 6.27 (1 H, s, 9-H), 6.80 (1 H, dq, *J* 2.5 and 0.7 Hz, 2-H), 6.92 (1 H, d, *J* 2.5 Hz, 4-H), 12.71 (1 H, br s, OH), and 14.25 (1 H, s, OH); *m/z* 382 (M^+, 100%), 367 (51), and 339 (25). This synthetic material was identical with a natural sample.

2-(2-*Hydroxy*-4-*methoxy*-6-*methylbenzoyl*)-1,4,5,6,8-*pentamethoxynaphthalene* (**21**).—A solution of the naphthalene (**20**) (559 mg, 0.105 mmol) in ethyl acetate (200 ml) was stirred together with 10% Pd–C (0.5 g) and a drop of conc. hydrochloric acid at room temperature under hydrogen for 1 h. After filtration of the solution and evaporation of the solvent under reduced pressure, the residue was chromatographed (eluant 40% ethyl acetate–light petroleum) to yield the *product* (**21**) (372 mg, 80%) as yellow diamond clusters, m.p. 164—165 °C (from Pr^{i}OH) (Found: C, 65.0; H, 5.8. $C_{24}H_{26}O_8$ requires C, 65.0; H, 5.8%); $\nu_{max.}$ 3 380 (OH) and 1 620 cm^{-1} (C=O); δ 1.85 (3 H, s, ArMe), 3.66, 3.76, 3.78, 3.88, 3.90, and 3.95 (each 3 H, s, OMe), 6.18 (1 H, d, *J* 2.6 Hz, 3′-H), 6.36 (1 H, d, *J* 2.6 Hz, 5′-H), 6.60 (1 H, s, 7-H), 6.74 (1 H, s, 3-H), and 12.97 (1 H, s, OH); δ_C 23.06 (Ar*Me*), 55.35, 56.90 (×2), 57.16, 61.87, and 63.75 (6 × OMe), 98.42 (C-7), 98.76 (C-3′), 104.80 (C-5′), 111.44 (C-3), 115.29 (C-8a)[a], 117.07 (C-1′), 124.73 (C-4a)[a], 130.72 (C-2), 138.08 (C-6), 143.29 (C-6′), 146.97 (C-5)[b], 151.16 (C-8)[b]. 152.54 (C-1), 153.74 (C-4), 164.70 (C-4′), 166.41 (C-2′), and 200.46 (C=O); *m/z* 442 (M^+, 40%), 411 (100), 382 (13), and 165 (22).

4,5,6,6′,8-*Pentamethoxy*-4′-*methyl*-2H-*naphthalene*-2-*spiro*-2′-2′H-*benzofuran*-1,3′-*dione* (**26**).—DDQ (287 mg, 1.26 mmol) was added to a solution of the naphthol (**21**) (372 mg, 0.84 mmol) in dry benzene (30 ml). The mixture was stirred at room temperature (23 °C) for 68 h and the solvent was evaporated off under reduced pressure. The residue obtained was chromatographed (eluant 50% ethyl acetate–light petroleum) to afford the *product* (**26**) (219 mg, 61%) as white grains, m.p. 195—196 °C (from MeOH) (Found: C, 64.5; H, 5.05. $C_{23}H_{22}O_8$ requires C, 64.8; H, 5.15%); $\nu_{max.}$ 1 710 and 1 676 cm^{-1} (C=O); δ 2.39 (3 H, br s, ArMe), 3.75, 3.78, 3.83, 3.85, and 3.93 (each 3 H, s, OMe), 5.00 (1 H, s, 3-H), 6.35 (1 H, br d, *J* 2.2 Hz, 5′-H), 6.53 (1 H, d, *J* 2.2 Hz, 7′-H), and 6.43 (1 H, s, 7-H); *m/z* 426 (M^+, 62%), 411 (100), 383 (31), 368 (29), 367 (21), 353 (17), 351 (11), 247 (11), 120 (12), and 77 (19).

2,3-*Dihydro*-5,6,6′,8-*tetramethoxy*-4′-*methylnaphthalene*-2-*spiro*-2′-2′H-*benzofuran*-1,3′,4-*trione* (**25**).—The enol ether (**26**) (80 mg, 0.19 mmol) was shaken in methylene dichloride (20 ml) with TFA (1.0 ml) in water (20 ml) for 5 min. After removal of the aqueous layer, the organic phase was washed with saturated aqueous sodium hydrogen carbonate. The residue obtained upon work-up was chromatographed (eluant 70% ethyl acetate–light petroleum) to afford the *product* (**25**) (73 mg, 94%) as light brown needles, m.p. darkens 191 °C, melts 214—217 °C (from Pr^{i}OH) (Found: C, 64.05; H, 4.95. $C_{22}H_{20}O_8$ requires C, 64.1; H, 4.85%); $\nu_{max.}$ 1 707 and 1 677 (C=O), and 1 624 cm^{-1} (C=C); δ 2.36 (3 H, d, *J* 0.5 Hz, Ar*Me*), 3.19 and 3.46 (each 1 H, d, *J* 15 Hz, CH_2), 3.81, 3.85, 3.90, and 3.94 (each 3 H, s, OMe), 6.35 (1 H, dq, *J* 2 and 0.5 Hz, 5′-H), 6.46 (1 H, d, *J* 2 Hz, 7′-H), and 6.68 (1 H, s, 7-H); *m/z* 412 (M^+, 100%), 397 (56), 233 (9), 193 (23), 165 (18), 134 (13), and 77 (15).

6,11-*Dihydroxy*-3,7,8,10-*tetramethoxy*-1-*methylbenzo*[b]-*xanthen*-12-*one* (**27**).—The spirotrione (**25**) (55 mg, 0.13 mmol) was heated for 1 h at 200 °C/5 mmHg, and then sublimed at a pressure of 0.06 mmHg for 6 h. The product was dissolved in methylene dichloride and chromatographed (eluant 40% ethyl acetate–light petroleum) to yield the *hydroquinone* (**27**) as red needles (51 mg, 93%), m.p. 235—236 °C (from CH_2Cl_2–light petroleum) (Found: C, 63.9; H, 4.85. $C_{22}H_{20}O_8$ requires C, 64.1; H, 4.85%); $\nu_{max.}$ 3 261 (OH) and 1 679 cm^{-1} (C=O); δ 2.86 (3 H, d, *J* 0.5 Hz, Ar*Me*), 3.88, 3.99, 4.00, and 4.03 (each 3 H, s, OMe), 6.53 (1 H, s, 9-H), 6.62 (1 H, dq, *J* 2.7 and 0.5 Hz, 2-H), 6.83 (1 H, d, *J* 2.7 Hz, 4-H), 9.70 (1 H, s, 6-OH), and 15.17 (1 H, s, 11-OH); *m/z* 412 (M^+, 45%) and 397 (100).

3,7,8,10-*Tetramethoxy*-1-*methylbenzo*[b]*xanthene*-6,11,12-*trione* (**29**).—The hydroquinone (**27**) (10.0 mg, 0.024 mmol), silver(I) oxide (6 mg, 0.024 mmol), and chloroform (3 ml) were stirred together at room temperature for 4 h. The mixture was filtered and the solvent was evaporated off under reduced pressure. The residue obtained was chromatographed (CH_2Cl_2–MeOH) (9.5:0.5) to afford the quinone (**29**) (9.3 mg, 93%) as orange needles, m.p. 264 °C (from $CHCl_3$–ether) (lit.,[5,7] 262—263 °C, undepressed on admixture with authentic, naturally derived material). Its ^1H n.m.r., i.r., and mass spectra, and t.l.c. behaviour were identical with those reported by Kjaer and Kjaer.[5]

3,6,7,8,10,11-*Hexamethoxy*-1-*methylbenzo*[b]*xanthen*-12-*one* (**28**).—The hydroquinone (**27**) (112 mg, 0.27 mmol) was dissolved in dry acetone (100 ml). Dry potassium carbonate (374 mg, 2.7 mmol) and dimethyl sulphate (0.26 ml, 0.35 g, 2.7 mmol) were added, and the mixture was stirred under reflux for 16 h. The cooled reaction mixture was filtered and evaporated. The residue was dissolved in ether and washed successively with 25% aqueous ammonia, water, dil. hydrochloric acid, and finally water. The organic layer was dried and evaporated. The residue obtained upon work-up was chromatographed (50% ethyl

acetate–light petroleum) to afford the *product* (**28**) (99 mg, 83%), as yellow needles, m.p. 204—205 °C (from Pr^{i}OH) (Found: C, 65.5; H, 5.25. $C_{24}H_{24}O_8$ requires C, 65.45; H, 5.45%); $\nu_{max.}$ 1 652 cm^{-1} (C=O); δ 2.86 (3 H, d, *J* 0.5 Hz, Ar*Me*), 3.88, 3.90, 3.99, and 4.03 (each 3 H, s, OMe), 4.01 (6 H, s, OMe), 6.64 (1 H, dq, *J* 2.0 and 0.5 Hz, 2-H), 6.67 (1 H, s, 9-H), and 6.80 (1 H, d, *J* 2.0 Hz, 4-H); *m/z* 440 (M^+, 100%), 425 (96), and 393 (15).

Structure Determination of Compound (**28**).—A unique data set was measured to $2\theta_{max.} = 55°$ using a Syntex $P2_1$ four-circle diffractometer in conventional $2\theta/\theta$ scan mode (monochromatic Mo-K_α radiation, λ 0.7106$_9$ Å; $T \sim 295$ K). 4 694 Independent reflections were obtained, 1 844 with $I > 3\sigma(I)$ being considered 'observed' and used in the full matrix least-squares refinement without absorption correction after solution of the structure by direct methods. Hydrogen atoms (x, y, z) were refined; anisotropic thermal parameters were refined for C and O, and U_{iso} estimated for H. Residuals on $|F|$ at convergence were conventional R 0.050, R' 0.051. Neutral atom complex scattering factors were employed;[24] computation used the XTAL 83 program system[25] implemented by S. R. Hall on a Perkin-Elmer 3240 computer. Pertinent results are presented in the Figures and Tables using quasi-conventional skeletal numbering.*

Crystal data. $C_{24}H_{24}O_8$, $M = 440.4$, Monoclinic, space group $P2_1/c$ (C_{2h}^5 No. 14), $a = 14.415(6)$, $b = 11.243(7)$, $c = 13.205(5)$ Å, $\beta = 107.10(3)°$, $V = 2\,045(2)$ Å^3; D_c ($Z = 4$) = 1.43 g cm^{-3}; $F(000) = 928$; μ(Mo-K_α) = 1.2 cm^{-1}.

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* *Supplementary data* (see section 5.6.3 of Instructions for Authors, in the January issue). Tables of thermal parameters, C–H bond lengths, some non-bonded distances, atomic co-ordinates, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.

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