Synthesis of the *C*-Glycoside Fragment of Nogalamycin and some Nogalamycin Precursors

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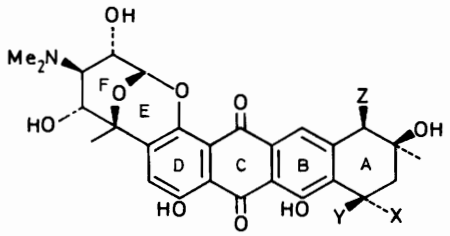
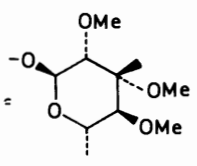
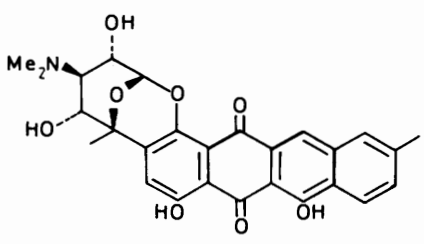
A short, stereoselective method for generation of the fused *C*-glycoside unit of the anticancer agent nogalamycin is described; in particular, synthesis of the D,E,F ring system. The method utilises a total synthesis of the glycosidic unit from an aryl furyl alcohol. Initial studies are described for the preparation of highly substituted phthalides, useful for the further annulation of the D,E,F ring system to the rest of the nogalamycin skeleton.

Nogalamycin (1) and its congeners are anthracycline antibiotics possessing reduced cardiotoxicity compared with daunomycin and related compounds.[1] In particular, the derivative 7-con-*O*-methylnogarol (**2**) has been reported to exhibit more promising anticancer activity than the parent compound.[1,2] A novel part of the structure of these compounds is the condensed *C*-glycoside unit involving rings D, E, and F. Herein we describe a route to these systems and some initial studies on further adumbration into the nogarol system (**2**). Since our studies commenced, Terashima and co-workers have reported on a multistage approach leading to the inactive derivative (+)-nogarene (**3**).[3] The approach taken in our work



(1) X =  , Y = H, Z = CO_2Me

(2) X = Z = H, Y = OMe



(3)

was to develop a flexible method suitable for the construction of the *C*-glycoside part of the natural product and for the preparation of a wide range of analogues.[4]

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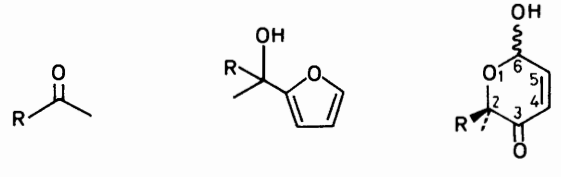
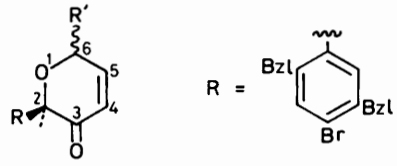
Reaction of 2,5-dibenzyloxy-4-bromoacetophenone (**4**) with 2-furyl-lithium produced the alcohol (**5**), which was directly oxidised with 3-chloroperbenzoic acid to yield the diastereoisomeric pyranuloses (**6**). Methylation of the alcohols (**6**) with methyl iodide–silver oxide in acetone afforded the corresponding methyl acetals. The major isomer (**7**), isolated in 65% yield, was assigned as that with the methoxy and aryl substituents *trans*-oriented with respect to the pyranulose ring whilst, in the minor isomer (**8**), isolated in 10% yield, these substituents were *cis*-oriented. Shielding by the aromatic ring causes the anomeric proton to resonate at δ 4.90 for the *trans*-isomer (**7**) as compared with the chemical shift of δ 5.25 observed for the anomeric proton in the minor, *cis*-isomer (**8**). This effect was useful in structural elucidation as the pyranulose rings in compounds (**7**) and (**8**) are conformationally mobile and it is difficult to make assignments based on ring proton coupling constants.[5]



(4) (5) (6)

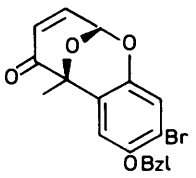


(7) R′ = ----OMe
(8) R′ = ▬OMe

R =

Bzl = $PhCH_2$

Treatment of either the methyl acetals (**7**) and (**8**) or the pyranulose mixture (**6**) with two equivalents of trimethylsilyl bromide,[6] or iodide,[7] in acetonitrile produced the cyclic pyranulose (**9**) in high yield. The chemistry of the enone (**9**) was briefly explored. With alkaline t-butyl hydroperoxide[8] a single αβ-epoxy ketone was produced. Since the least hindered face of the enone was that *syn* to the oxygen bridge this epoxide was assigned the *syn*-configuration (**10**) indicated. Further proof for this assignment came from its chemical behaviour; no reaction occurred with either dimethylamine (sealed tube; 60 °C) or sodium azide in dimethylformamide (DMF), indicating steric encumbrance towards axial opening of the epoxide bond by the aromatic ring. Reduction of the ketone with sodium boro-



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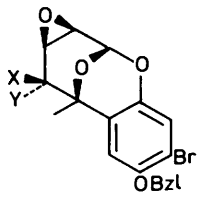
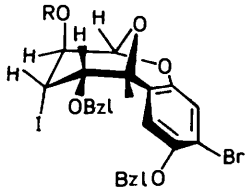


(10) XY = O
(11) X = H, Y = OH
(12) X = H, Y = OBzl

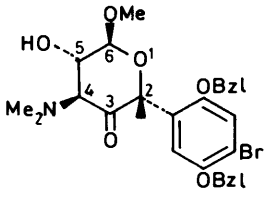


(13) R = H
(14) R = Ac

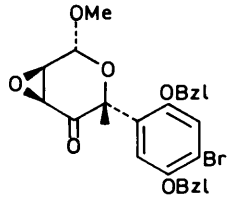
hydride gave the alcohol (**11**) and this readily formed a benzyl ether (**12**). Reaction with hydrogen iodide[5] opened up the epoxide to give a single iodohydrin (**13**) which formed the corresponding acetate (**14**) with acetic anhydride and pyridine. High-field ^{1}H n.m.r. analysis of compound (**14**) showed coupling constants (Table 1) consistent with 2-H, 3-H, and 4-H equatorial and 5-H axial. The zero coupling constant between 3-H and 4-H reflects slight flattening of the pyran ring so as to move C-4 away from the aromatic ring, as would be expected to take place if the large iodine atom were substituted axially at C-4. Confirmation that the iodo and acetate groups were *trans*-diaxial came from the ready reformation of the epoxide (**12**) on treatment of (**14**) with sodium ethoxide. Thus, as a consequence of the steric shielding of the lower face of the enone system (**9**) the epoxides (**10**), (**11**), and (**12**) have the wrong configuration required to give the appopriate ring F substituent pattern of nogalamycin. This problem can be avoided by breaking the fixed relationship between rings D and F and attention was therefore directed to the acetals (**7**) and (**8**). Epoxidation of the major, *trans*-acetal (**7**) with alkaline t-butyl hydroperoxide gave a single epoxide (**15**), whilst the *cis*-acetal (**8**) reacted to give the isomeric epoxide (**16**). The epoxide (**15**) was readily identified as it gave a single amino alcohol (**17**) with dimethylamine; similar treatment of the isomeric epoxide (**16**) gave a mixture of products. The relative stereochemistry of the amino alcohol (**17**) was determined by its 400 MHz ^{1}H n.m.r. spectrum. In this 4-H appeared as a doublet (*J* 11 Hz), indicating a diequatorial arrangement of the substituent groups at C-4 and C-5, amine attack occurring at C-4. The amino alcohol was unstable to heat or base and attempted reduction with either sodium borohydride or sodium bis(methoxyethoxy)aluminium hydride gave dehydration to the αβ-unsaturated ketone (**18**) before reduction; storage at room temperature gradually formed substantial amounts of the acetophenone (**4**). In order to avoid these side reactions the epoxide (**15**) was reduced with sodium borohydride before opening of the epoxide ring, the reduction giving the epoxy alcohol (**19**) in good yield; subsequent reaction with dimethylamine, at 90 °C, gave the required dimethylamino diol (**20**). The opening of the epoxide, by attack away from the anomeric position, is well precedented.[9] Treatment of the amino sugar (**20**) with trimethylsilyl iodide in acetonitrile caused

Table 1. Coupling constants (Hz) for compounds (**14**) in $CDCl_3$

	3-H	4-H	5-H
2-H	1.5	1.0	1.0
3-H		0	0
4-H			5.5



(17)



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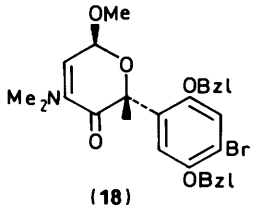

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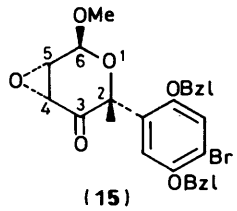

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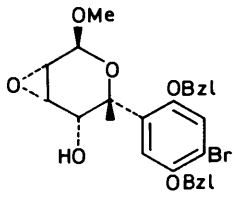

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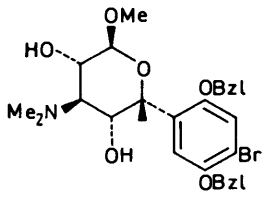

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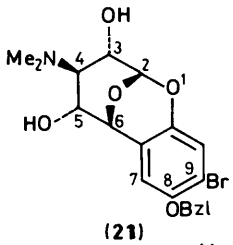

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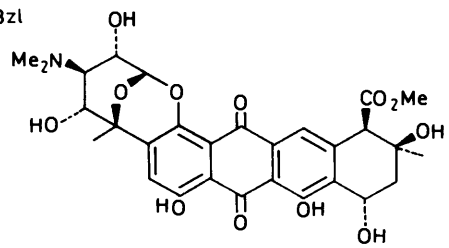


(22)

selective debenzylation and cyclisation, with loss of methanol, to give the desired benzo-fused 2,9-dioxabicyclo[3.3.1]nonane (**21**). The n.m.r. data for this sugar, and the precursor (**20**), compare well with the reported values for the nogalamycin aglycone derivative nogalarol (**22**), as indicated in Table 2.

The successful synthesis of the *C*-glycoside unit prompted a search to incorporate this structure, or its precursors, into a

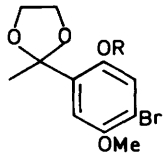
Table 2. ^{1}H Chemical shifts and J values for compounds (**20**), (**21**), and (**22**)[a]

	(**20**)	(**21**)	(**22**) (Nogalarol)
2-H	4.05 ($J_{2,3}$ 7.0)	5.47 (3.6)	5.87 (3.3)
3-H	3.60 ($J_{3,4}$ 10.5)	3.98 (10.2)	4.16 (10.5)
4-H	2.87 ($J_{4,5}$ 10.5)	2.15 (10.2)	2.86 (10.5)
5-H	3.59	3.47	3.66

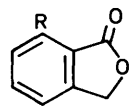
[a] See formula (**21**) for numbering.

material suitable for generating the anthracyclinone skeleton; this requires methods for fusing ring C to the D, E, F structure; see structure (**2**). The aryne–phthalide route was studied.[10] For simpler systems this reaction worked, for example the acetal (**23**) reacted with phthalide (**25**) to give a 41% yield of the quinizarin (**27**). Previous work had shown that precursors, such as (**23**), gave 1:1 mixtures of anthraquinones when treated with 7-substituted phthalides.[10] Attempts to control regioselectively the cyclisation reaction, by using the 2-methoxymethoxy derivative (**24**), in place of the dimethoxy-substituted benzene (**23**), and the phthalide (**26**) failed to give any regioselection, a 1:1 mixture of the quinizarins (**28**) and (**29**) being obtained, albeit in good yield (60%). With more highly substituted derivatives of the bromobenzene ring yields of the aryne condensation reaction decreased and this route was abandoned in favour of studies employing Michael addition methodology, such as that developed by ourselves,[11] Hauser,[12] and others.[13] This uses the conjugate addition of phthalides to enones. For example, it was found that the sulphonyl-substituted phthalide (**30**) reacted in a regiospecific manner with cyclohexenone, with lithium t-butoxide as base, to give the substituted naphthalene (**31**) in 59% yield. In order to apply this methodology to a synthesis of 7-con-*O*-methylnogarol a route to highly substituted phthalides of the type (**32**) or their precursors was required.

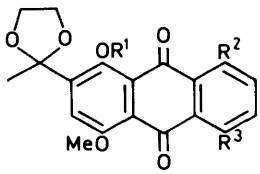
Grignard reaction of the bromobenzene (**23**) with methyl *N*,*N*-diethylcarbamate produced the diethylamide (**33**), some of which was converted into the model methoxyethyl derivative (**34**) (see Experimental section). The diethylamide unit was used as a masked carboxyl function that helps to direct *ortho*-lithiation,[14] thus helping to avoid lithiation at the alternative aromatic ring site. Evidence for such selective lithiation in these derivatives was obtained by deuterium incorporation experiments; treatment of the amide (**34**) with s-butyl-lithium at −78 °C, followed by quenching with deuterium oxide, afforded the derivative (**35**) with >95% deuterium in position 3. Introduction of a formyl group into this position was more difficult, a maximum of 40% of the aldehyde (**36**) being achieved with methyl formate, the major side product being recovered starting material; extended reaction times or use of an excess of methyl formate did not increase the yield of aldehyde. Molecular models indicate the position *ortho* to the amide group is extremely hindered, owing to a steric clash between the 5-methoxy group and the 4-(1-methoxyethyl) substituent. Some further evidence for this steric encumbrance was obtained by treating the lithium anion with trimethylsilyl cyanide; a low yield of the silylated derivative (**37**) was isolated but none of the products expected from attack at the nitrile group. Surprisingly, methyl iodide reacted efficiently to give the methyl derivative (**38**) in 92% yield. The steric encumbrance in both this material (**38**) and the derivatives (**36**) and (**37**) was reflected in their ^{1}H n.m.r. properties. Each exhibited two sets of proton resonances, assigned to different rotamers involving the amide and methoxyethyl substituents. In the methyl series separation of both rotamers was possible by t.l.c.; however, the separated



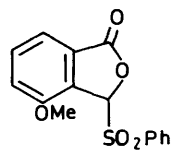
(**23**) R = Me
(**24**) R = CH_2OMe



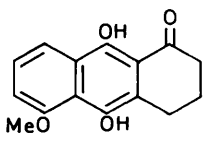
(**25**) R = H
(**26**) R = OMe



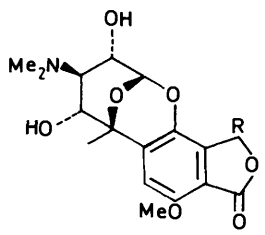
(**27**) R^1 = Me, R^2 = R^3 = H
(**28**) R^1 = CH_2OMe, R^2 = H, R^3 = OMe
(**29**) R^1 = CH_2OMe, R^2 = OMe, R^3 = H



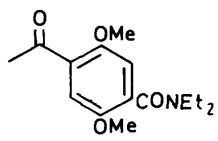
(**30**)



(**31**)



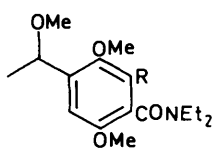
(**32**) R = H, SO_2Ph, or CN



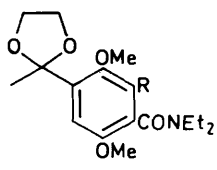
(**33**)

isomers rapidly (30 min) re-equilibrated at ambient temperature to re-form the starting material.

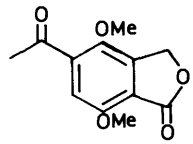
The acetal (**39**) behaved in a similar manner to the ether (**34**), methylation with methyl iodide giving the methyl derivative (**40**) in good yield. Reaction with paraformaldehyde also proceeded, although the product was not isolated directly but



(**34**) R = H
(**35**) R = D
(**36**) R = CHO
(**37**) R = $SiMe_3$
(**38**) R = Me



(**39**) R = H
(**40**) R = Me



(**41**)

instead treated with potassium hydroxide, followed by hydrochloric acid, to give the phthalide (**41**) in moderate (48%) yield.

The above results detail a method for generating the desired *C*-glycoside unit of nogalamycin and a means for generating highly substituted phthalides of synthetic utility for preparing aromatic systems. Further work is required to apply this methodology to a synthesis of the target substances such as (**2**).

Experimental

General Techniques.—M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 1420 Ratio Recording Spectrophotometer. ^{1}H N.m.r. spectra were recorded on a Perkin-Elmer R32 (90 MHz), a Jeol FX 90Q (90 MHz), or a Bruker AM250 (250 MHz) spectrometer and are quoted in p.p.m. relative to tetramethylsilane (TMS) (internal reference) for solutions in deuteriochloroform. Mass spectra were obtained with a Kratos MS 25 instrument. Accurate mass determinations were obtained with an AEI-Kratos MS9/50 machine. Microanalytical determinations were performed by the University of Leeds, School of Chemistry, Microanalytical Department. T.l.c. was carried out on glass plates precoated with Merck Kieselgel 60 GF_{254}. Chromatography was carried out on columns of either Kieselgel 60G (Merck) or MN-Kieselgel 60 (Camlab) and columns were generally packed and run under pressure. Solvents used for chromatography were distilled before use and solvent ratios are described in ratios of volumes before mixing. Light petroleum refers to that fraction with boiling range 60—80 °C and ether refers to diethyl ether throughout. Extracts of organic compounds, unless otherwise stated, were dried over anhydrous sodium sulphate. Solvents were dried using the methods given by Perrin.[15]

4-*Bromo*-2,5-*dimethoxyacetophenone.*—A solution of 2-bromo-1,4-dimethoxybenzene (25.9 g, 0.12 mol) in nitrobenzene (50 ml) and acetyl chloride (13 ml) was stirred at room temperature under dry N_2 whilst a mixture of aluminium chloride (24 g, 0.18 mol) in nitrobenzene (150 ml) was slowly added. After the addition the mixture was stirred for 2 h before being poured onto ice–conc. HCl (100 ml). The nitrobenzene layer was separated and the aqueous phase was extracted with methylene dichloride (3 × 100 ml). The combined organic layers were dried ($MgSO_4$) and the organic solvents were removed by distillation under reduced pressure. The solid residue was dissolved in methylene dichloride (100 ml) and washed successively with 2M sodium hydroxide (3 × 50 ml) and water (50 ml) before the solution was dried and evaporated. The residue was recrystallised from methanol to give the *title compound* (28.2 g, 92%), m.p. 101 °C; $\nu_{max.}$(Nujol) 1 665, 1 600, 1 495, 1 215, 885, and 845 cm^{-1}; δ 2.65 (3 H, s, Me), 3.80 (3 H, s, OMe), 3.90 (3 H, s, OMe), 7.25 (1 H, s, aromatic H), and 7.40 (1 H, s, aromatic H) (Found: C, 46.6; H, 4.2; Br, 30.8. $C_{10}H_{11}BrO_3$ requires C, 46.4; H, 4.3; Br, 30.8%).

2,5-*Dibenzyloxy*-4-*bromoacetophenone* (**4**).—A solution of 4-bromo-2,5-dimethoxyacetophenone (2.0 g, 7.7 mmol) in dry methylene dichloride (30 ml) was cooled to −70 °C under dry N_2. Boron tribromide (2.0 ml, 20.9 mmol) was added and the mixture was stirred at −70 °C for 30 min before being allowed to warm to room temperature, and was then poured into a mixture of ice–conc. hydrochloric acid (50 ml). The two-phase mixture was then filtered through Celite and the yellow organic phase was separated. The aqueous phase was extracted with methylene dichloride (3 × 50 ml) and the extracts were combined, dried ($MgSO_4$), and evaporated to leave 4-bromo-2,5-dihydroxyacetophenone as a yellow solid (1.6 g, 90%), m.p. 152 °C (lit.,[16] 148—149 °C).

The solid was dissolved in acetone (7 ml) to which were added potassium carbonate (0.5 g) and a solution of benzyl bromide (2.85 g, 1.2 mol equiv.) in acetone (4 ml) and the mixture was stirred overnight at room temperature, then filtered, and the solution was evaporated to dryness to produce a solid which, after recrystallisation from ethanol, gave the *title compound* (2.02 g, 71%), m.p. 107—108 °C; $\nu_{max.}$(Nujol) 1 660, 1 595, 1 485, 1 390, 1 375, 740, and 695 cm^{-1}; δ 2.60 (3 H, s, Me), 5.10 (2 H, s, PhCH_2), 5.15 (2 H, s, PhCH_2), 7.35 (1 H, s, aryl H), and 7.40 (11 H, m, aryl H) (Found: C, 64.4; H, 4.4; Br, 19.5. $C_{22}H_{19}BrO_3$ requires C, 64.4; H, 4.4; Br, 19.5%).

2-(2,5-*Dibenzyloxy*-4-*bromophenyl*)-6-*hydroxy*-2-*methyl*-6H-*pyran*-3(2H)-*one* (**6**).—A solution of the acetophenone (**4**) (1.64 g, 4 mmol) in THF (25 ml) was added dropwise to a solution, at 0 °C, of furan (0.27 g, 4 mmol) in THF (25 ml), which had been stirred for 30 min with a solution of butyl-lithium (1.1 mol equiv.) in hexane (1.2M solution). The reaction mixture was stirred for a further 1 h at 0 °C before being quenched with saturated aqueous ammonium chloride and the THF layer was separated. The aqueous layer was extracted with methylene dichloride (2 × 50 ml) and the combined organic phases were dried and evaporated. The crude mixture of products was filtered through silica, with ethyl acetate–light petroleum (1:6) as solvent, to give the unstable furfuryl alcohol (**5**) as an oil. The product (1.53 g, 3.2 mmol) was dissolved in methylene dichloride (20 ml) and treated with 85% 3-chloroperbenzoic acid (0.71 g, 1.1 mol equiv.) overnight at room temperature. The solution was washed successively with 10% w/v aqueous sodium thiosulphate, followed by saturated aqueous sodium hydrogen carbonate, and the organic phase was separated. The aqueous layer was extracted with more CH_2Cl_2 and the combined organic extracts were dried and evaporated to give a yellow oil. The oil was chromatographed through silica gel with ethyl acetate–light petroleum (1:4) as solvent to afford the *title compound* (1.15 g, 58% overall), $\nu_{max.}$($CHCl_3$) 3 380, 2 980, 2 920, 2 870, 1 685, 1 600, 1 570, 1 475, and 1 420 cm^{-1}; ^{1}H n.m.r. indicated the product to be a 5:1 mixture of two anomers, the major one showing δ 1.70 (3 H, s, Me), 4.86 and 5.86 (2 H, ABq, *J* 14 Hz, benzylic H), 5.04 (2 H, s, OCH_2Ph), 5.87 (1 H, dd, *J* 10.2 and 1.2 Hz, 6-H), 6.40 (1 H, dd, *J* 10.2 and 3.0 Hz, 5-H), 6.93 (1 H, s, aryl H), 7.13 (1 H, s, aryl H), and 7.25—7.50 (10 H, m, 2 × Ph). The minor isomer showed 1.72 (3 H, s, Me), 5.36 (1 H, dd, *J* 2.5 and 1.4 Hz), 5.87 (1 H, dd, *J* 10.2 and 1.4 Hz), 6.49 (1 H, dd, *J* 10.2 and 2.5 Hz, 5-H), 6.90 (1 H, s, aryl H), 7.10 (1 H, s, aryl H), and 7.25—7.50 (10 H, m, 2 × Ph) (Other protons hidden under major peaks.) (Found: C, 63.3; H, 4.5; Br, 16.1. $C_{26}H_{23}BrO_5$ requires C, 63.1; H, 4.7; Br, 16.1%).

2-(2,5-*Dibenzyloxy*-4-*bromophenyl*)-6-*methoxy*-2-*methyl*-6H-*pyran*-3(2H)-*ones* (**7**) *and* (**8**).—Silver(I) oxide was prepared from silver(I) nitrate (1.87 g, 11 mmol) and added, portionwise, to a stirred solution of the pyranone (**6**) (0.5 g, 1.0 mmol) and methyl iodide (1.0 ml, 16 mmol) in dry acetone (20 ml) under dry nitrogen. After addition of the oxide, the mixture was stirred for a further 16 h, decolouring charcoal (0.2 g) was added, and the mixture was heated to reflux for 5 min before being cooled and filtered through Celite. The clear, colourless solution was evaporated and the crude product was chromatographed through silica gel, with ethyl acetate–light petroleum (1:6) as eluant, to give, initially, the *trans*-ethyl ether (**7**) (0.33 g, 65%), followed by the *cis*-isomer (**8**) (0.05 g, 10%).

The trans-*isomer* (**7**) showed m.p. 123—126 °C; $\nu_{max.}$(Nujol) 1 695, 1 210, 1 045, and 965 cm^{-1}; δ 1.77 (3 H, s, Me), 3.42 (3 H, s, OMe), 4.82 and 4.96 (2 H, ABq, *J* 11 Hz, OCH_2Ph), 5.00 (1 H, br d, *J* 3.2 Hz, 6-H), 5.11 (2 H, s, OCH_2Ph), 5.81 (1 H, dd, *J*

10.4 and 1.0 Hz, 4-H), 6.44 (1 H, dd, *J* 10.4 and 3.2 Hz, 5-H), 7.04 (1 H, s, aryl H), 7.18 (1 H, s, aryl H), 7.32 (5 H, m, Ph), and 7.2—7.6 (5 H, m, Ph) (Found: C, 63.7; H, 5.1; Br, 15.5. $C_{27}H_{25}BrO_5$ requires C, 63.7; H, 5.0; Br, 15.7%).

The cis-*isomer* (**8**) showed m.p. 132—134 °C; $\nu_{max.}$ 1 695, 1 490, 1 200, and 1 040 cm^{-1}; δ 1.68 (3 H, s, Me), 3.22 (3 H, s, OMe), 4.81 and 4.97 (2 H, AB q, *J* 11 Hz, OCH_2Ph), 5.09 (2 H, s, OCH_2Ph), 5.33 (1 H, m, 6-H of pyranone ring), 5.85 (1 H, dd, *J* 10.5 and 1.4 Hz, 4-H), 6.52 (1 H, dd, *J* 10.5 and 1.8 Hz, 5-H), 7.04 (1 H, s, aryl H), 7.15 (1 H, s, aryl H), and 7.2—7.6 (10 H, m, 2 × Ph) (Found: C, 63.6; H, 5.1; Br, 15.5%).

8-*Benzyloxy*-9-*bromo*-6-*methyl*-2,6-*epoxy*-6H-1-*benzoxec*-3-*en*-5(2H)-*one* (**9**).—To the acetal (**7**) (1.00 g, 2.0 mmol) were added acetonitrile (12 ml) and sodium bromide (0.23 g, 1.1 mol equiv.) and the solution was stirred at room temperature whilst trimethylsilyl chloride (0.24 g, 1.1 mol equiv.) was added. The solution was stirred overnight under dry nitrogen before being quenched with saturated aqueous sodium hydrogen carbonate followed by sufficient 10% w/v aqueous sodium thiosulphate to remove the iodine colour. The mixture was extracted with methylene dichloride and the extract was dried and evaporated to produce a gum, which was purified by chromatography through silica gel, with ethyl acetate–light petroleum (1:9) as eluant, to afford the *title compound* (433 mg, 56%) as a solid; $\nu_{max.}(CHCl_3)$ 1 700, 1 605, 1 480, 1 190, 985, and 700 cm^{-1}; δ 1.70 (3 H, s, Me), 5.10 (2 H, s, $ArCH_2O$), 5.95 (1 H, d, *J* 3 Hz, 2-H), 6.20 (1 H, d, *J* 10 Hz, 4-H), 6.70 (1 H, s, aryl H), 6.85 (1 H, dd, *J* 10 and 3 Hz, 3-H), 7.20 (1 H, s, aryl H), and 7.45 (5 H, br s, Ph) (Found: C, 59.3; H, 4.1; Br, 20.3; M^+, 386.015 18 and 388.014 18. $C_{19}H_{15}BrO_4$ requires C, 59.0; H, 3.9; Br, 20.6%; *M*, 386.015 42 and 388.013 45 respectively).

Use of sodium iodide (1.1 mol equiv.) in place of sodium bromide afforded the title compound (65%) together with a new minor product (22%) identified as the corresponding *saturated ketone*, isolated as a viscous oil; $\nu_{max.}(CHCl_3)$ 1 725, 1 485, 1 395, 1 175, and 985 cm^{-1}; δ 1.55 (3 H, s, Me), 1.90—2.80 (4 H, m, CH_2CH_2), 5.00 (2 H, s, OCH_2Ph), 5.85 (1 H, m, 2-H), 6.75 (1 H, s, aryl H), 7.10 (1 H, s, aryl H), and 7.1—7.5 (5 H, m, Ph) (Found: C, 58.9; H, 4.6; Br, 20.4. $C_{19}H_{17}BrO_4$ requires C, 58.6; H, 4.4; Br, 20.5%).

The enone (**9**) was also produced, in similar yield, from the isomeric acetal (**8**) and from the hemiacetal (**6**).

Epoxidation of the Enone (**9**).—To a solution of the enone (0.81 g, 2.1 mmol) in methanol (20 ml) at 0 °C were added t-butyl hydroperoxide (0.20 g, 2.2 mmol) and Triton B (0.1 ml) and the solution was stirred under N_2 whilst being allowed to warm to ambient temperature during 2 h. The reaction mixture was quenched with saturated brine, the bulk of the methanol removed under reduced pressure, and the residue extracted with methylene dichloride. The extract was dried and the solvent removed to leave the crude epoxide (**10**), which was immediately purified by chromatography through silica, with ethyl acetate–light petroleum (1:6) as eluant, to produce crystals of the *epoxide* (**10**) (0.531 g, 63%), m.p. 150—152 °C; $\nu_{max.}$(Nujol) 1 720, 1 605, 1 265, 1 190, 1 030, and 735 cm^{-1}; $\delta(CDCl_3)$ 1.65 (3 H, s, Me), 3.23 (1 H, d, *J* 3 Hz, 4-H), 3.58 (1 H, dd, *J* 3.5 and 2.5 Hz, 3-H), 5.04 (2 H, s, OCH_2Ph), 5.89 (1 H, br s, 2-H), 6.58 (1 H, s, aryl H), 7.18 (1 H, s, aryl H), and 7.3—7.5 (5 H, m, Ph) (Found: M^+, 402.010 57 and 404.008 74. $C_{19}H_{15}BrO_5$ requires *M*, 402.010 33 and 404.008 36).

Reduction of the Epoxide (**10**).—A solution of the epoxide (0.480 g, 1.2 mmol) in propan-2-ol (5 ml) was stirred under N_2 at room temperature with sodium borohydride (60 mg, 1.5 mmol). After 14 h the mixture was quenched with saturated brine, the organic solvent was removed under reduced pressure, and the residue was extracted with methylene dichloride. This extract was dried (Na_2SO_4) and evaporated to give the crude product. Chromatography through silica gel, with ethyl acetate–light petroleum (1:6) as eluant, afforded needles of the *alcohol* (**11**) (381 mg, 79%), δ 1.50 (3 H, s, Me), 2.35 (1 H, br d, *J* 8 Hz, exch. with D_2O, OH), 2.95 (1 H, d, *J* 4 Hz), 3.15 (1 H, d, *J* 4 Hz), 3.80 (1 H, br d, *J* 8 Hz, 5-H), 5.05 (2 H, s, OCH_2Ph), 5.55 (1 H, s, 2-H), 6.75 (1 H, s, aryl H), 7.20 (1 H, s, aryl H), and 7.40 (5 H, br s, Ph) (Found: C, 56.0; H, 4.2; Br, 19.3. $C_{19}H_{17}BrO_5$ requires C, 56.3; H, 4.2; Br, 19.7%).

Benzylation of the Alcohol (**11**).—A solution of the alcohol (340 mg, 0.84 mmol) in THF (5 ml), under N_2, was stirred with sodium hydride (50% oil dispersion; 1.1 mol equiv.) for 15 min before benzyl bromide (170 mg, 1.0 mmol) was added and the mixture was heated to reflux for 2 h. The mixture was quenched with saturated aqueous NH_4Cl extracted with methylene dichloride, and the extract was dried. The crude product was purified by chromatography through silica, with ethyl acetate–light petroleum (1:12) as eluant to afford the *benzyl ether* (**12**) (328 mg, 79%), m.p. 120—124 °C; $\nu_{max.}$(Nujol) 1 260, 1 195, and 815 cm^{-1}; δ 1.5 (3 H, s, Me), 3.15 (2 H, m, 3- and 4-H), 3.60 (1 H, s, 5-H), 4.55 (1 H, d, *J* 11 Hz, ROC*H*HPh), 4.85 (1 H, d, *J* 11 Hz, ROCH*H*Ph), 4.90 (2 H, s, $ArOCH_2Ph$), 5.60 (1 H, s, 2-H), 6.85 (2 H, s, aryl H), 7.1—7.3 (5 H, m, Ph), and 7.35 (5 H, s, Ph) (Found: C, 63.0; H, 4.2; Br, 16.0. $C_{26}H_{23}BrO_5$ requires C, 63.0; H, 4.7; Br, 16.2%).

Reactions of the Epoxide (**12**).—A solution of the epoxide (294 mg, 0.6 mmol) in dry acetone (40 ml) containing hydriodic acid (54% w/v; 2.5 ml) was heated to reflux for 4 h before being quenched with 10% w/v aqueous sodium thiosulphate (40 ml) followed by saturated aqueous sodium hydrogen carbonate (40 ml). The mixture was evaporated to remove the acetone and then extracted with methylene dichloride (3 × 20 ml). The combined extracts were dried and evaporated, and the residue was chromatographed on silica gel with ethyl acetate–light petroleum (1:2) as eluant to give the *iodohydrin* (**13**) (173 mg, 47%); $\nu_{max.}(CHCl_3)$ 3 460, 1 605, 1 480, 1 400, 1 180, 1 015, and 695 cm^{-1}; δ 1.54 (3 H, s, Me), 3.11 (1 H, d, *J* 3 Hz, 4-H), 4.34 (1 H, d, *J* 11 Hz, ROC*H*HPh), 4.50 (2 H, m, 3- and 5-H), 4.74 (1 H, d, *J* 11 Hz, ROCH*H*Ph), 4.95 (2 H, s, $ArOCH_2Ph$), 5.48 (1 H, br s, 2-H), 6.69 (1 H, s, aryl H), 7.05 (1 H, s, aryl H), and 7.36 (10 H, m, 2 × Ph) (Found: C, 49.9; H, 4.1; Br, 12.7; I, 20.1. $C_{26}H_{24}BrIO_5$ requires C, 50.1; H, 3.9; Br, 12.8; I, 20.3%).

A sample of the iodohydrin was acetylated with pyridine–acetic anhydride (1:1) at room temperature overnight. After removal of the solvent under reduced pressure the residue was purified by preparative layer chromatography p.l.c.), ethyl acetate–light petroleum (1:6) as developer, to give the *acetate* (**14**); δ 1.60 (3 H, s, Me), 2.14 (3 H, s, acetate Me), 2.93 (1 H, dd, *J* 1.0 and 5.5 Hz, 4-H), 4.33 (1 H, d, *J* 11 Hz, ROC*H*HPh), 4.46 (1 H, d, t, *J* 1.0, 5.5 Hz, 5-H), 4.69 (1 H, d, *J* 11 Hz, ROCH*H*Ph), 4.97 (1 H, d, *J* 12 Hz, ArOCH*H*Ph), 5.01 (1 H, d, *J* 12 Hz, ArOCH*H*Ph), 5.44 (1 H, t, *J* 1.5 Hz, 3-H), 5.49 (1 H, dt, *J* 1.5 and 1.0 Hz, 2-H), 7.11 (1 H, s, aryl H), 7.18 (1 H, s, aryl H), and 7.3—7.5 (10 H, m, 2 × Ph) (Found: M^+, 663.995 78 and 665.993 98. $C_{28}H_{26}BrIO_6$ requires *M*, 663.995 98 and 665.994 01).

Treatment of a sample (50 mg) of the iodohydrin (**13**) with sodium ethoxide (2 mol equiv.) in ethanol, at room temperature, rapidly re-formed the epoxide (**12**), as ascertained by following the reaction by t.l.c. A sample of the isolated epoxide (p.l.c.) showed m.p. and mixed m.p. 120—124 °C with an authentic sample.

Treatment of a sample of the epoxide (**12**) with dimethylamine gave no reaction at room temperature or in a sealed tube at 100 °C for 6 h.

Epoxidation of the Enones (**7**) *and* (**8**).—A solution of the enone (1.0 mol equiv.) in benzene (10 ml $mmol^{-1}$) at 0 °C was stirred with t-butyl hydroperoxide (1.1 mol equiv.) and Triton B (0.5 mol equiv.) under N_2 and the solution was allowed to come to room temperature during 2 h before being quenched with saturated brine. The layers were separated, the aqueous phase re-extracted with methylene dichloride, and the organic layers were combined, dried, and evaporated under reduced pressure. The crude product was purified by column chromatography through silica gel with ethyl acetate–light petroleum (1:5) as eluant.

The *trans*-acetal (**7**) afforded, in quantitative yield, the *epoxide* (**15**), m.p. 133—134 °C; $\nu_{max.}(CHCl_3)$ 1 730, 1 490, 1 375, and 1 020 cm^{-1}; δ 1.63 (3 H, s, Me), 3.49 (3 H, s, MeO), 3.3—3.6 (2 H, m, 4- and 5-H), 4.98 (2 H, s, OCH_2Ph), 5.07 (1 H, br s, 6-H), 5.12 (2 H, s, OCH_2Ph), 7.11 (1 H, s, aryl H), 7.17 (1 H, s, aryl H), and 7.2—7.7 (10 H, m, 2 × Ph) (Found: C, 61.9; H, 5.0; Br, 15.4. $C_{27}H_{25}BrO_6$ requires C, 61.7; H, 4.8; Br, 15.2%).

The *cis*-acetal (**8**) afforded, in 94% yield, the epoxide (**16**), m.p. 109 °C; $\nu_{max.}(CHCl_3)$ 1 725, 1 600, 1 375, and 940 cm^{-1}; δ 1.60 (3 H, s, Me), 2.65 (1 H, d, *J* 4 Hz, 4-H), 2.80 (3 H, s, MeO), 3.15 (1 H, dd, *J* 2 and 4 Hz, 5-H), 4.85 (2 H, br s, OCH_2Ph), 4.90 (1 H, br s, 6-H), 5.10 (2 H, s, OCH_2Ph), 7.05 (2 H, s, aryl H), and 7.2—7.4 (10 H, m, 2 × Ph).

r-2-(2,5-*Dibenzyloxy*-4-*bromophenyl*)-t-4-*dimethylamino*-c-5-*hydroxy*-5-6-*methoxy*-2-*methyl*-5,6-*dihydro*-4H-*pyran*-3(2H)-*one* (**17**).—The epoxide (**15**) (0.26 g, 0.5 mmol) was suspended in dimethylamine (20 ml) and kept in a sealed tube at room temperature overnight. The solid gradually dissolved. The tube was opened and the contents were evaporated to produce, as an amorphous solid, the title amine (0.28 g, 100%); $\nu_{max.}(CHCl_3)$ 1 725, 1 470, 1 350, and 1 010 cm^{-1}; δ 1.44 (3 H, s, Me), 2.38 (6 H, s, Me_2N), 3.39 (1 H, d, *J* 11 Hz, 4-H), 3.50 (3 H, s, OMe), 3.76 (1 H, dd, *J* 7 and 11 Hz, 5-H), 4.60 (1 H, d, *J* 7 Hz, 6-H), 4.92 (1 H, d, *J* 12 Hz, OCH*H*Ph), 4.98 (1 H, d, *J* 12 Hz, OC*H*HPh), 5.09 (1 H, d, *J* 12 Hz, OC*H*HPh), 5.13 (1 H, d, *J* 12 Hz, OCH*H*Ph), 7.13 (1 H, s, aryl H), 7.18 (1 H, s, aryl H), and 7.3—7.5 (10 H, m, 2 × Ph).

The material was unstable and, on attempted chromatography or base treatment, it rapidly dehydrated to form the enamine (**18**). The latter, formed quantitatively from the alcohol (**17**) by treatment with catalytic quantities of sodium borohydride in methanol, was also unstable to chromatography. The crude product showed δ 1.75 (3 H, s, Me), 2.45 (6 H, s, NMe_2), 3.40 (3 H, s, MeO), 4.95 (2 H, s, OCH_2Ph), 5.10 (2 H, s, OCH_2Ph), 5.15 (1 H, d, *J* 3 Hz, 5- or 6-H), 5.25 (1 H, d, *J* 3 Hz, 6- or 5-H), 7.15 (1 H, s, aryl H), 7.20 (1 H, s, aryl H), and 7.3 (10 H, m, 2 × Ph).

On storage for three weeks at 20—25 °C the amino alcohol decomposed, the major product, isolated by p.l.c., being the acetophenone (**4**), m.p. and mixed m.p. 107—108 °C.

r-2-(2,5-*Dibenzyloxy*-4-*bromophenyl*)-c-4,5-*epoxy*-c-3-*hydroxy*-t-6-*methoxy*-2-*methyl*-3,4,5,6-*tetrahydro*-2H-*pyran* (**19**).—The ketone (**15**) (1.50 g, 2.0 mmol) was dissolved in propan-2-ol (10 ml) and sodium borohydride (100 mg, 2.8 mmol) was added. The mixture was stirred overnight under N_2 and then quenched with saturated brine. The mixture was evaporated under reduced pressure to remove the organic solvent and then extracted with methylene dichloride and the combined organic extracts were dried and evaporated to give the crude alcohol. Recrystallisation from ethanol gave the *title alcohol* (1.45 g, 96%), m.p. 159—160 °C; $\nu_{max.}(CHCl_3)$ 3 550, 1 485, 1 375, 1 090, and 850 cm^{-1}; δ 1.55 (3 H, s, Me), 3.30 (1 H, m, 4- or 5-H), 3.45 (3 H, s, OMe), 3.55 (1 H, m, 5- or 4-H), 4.60 (1 H, d, *J* 7 Hz, 3-H), 5.00 (1 H, d, *J* 4 Hz, 6-H), 5.05 (2 H, s, OCH_2Ph), 5.08 (2 H, s, OCH_2Ph), 7.15 (1 H, s, aryl H), 7.25 (1 H, s, aryl H), 7.3—7.4 (10 H, m, 2 × Ph) (Found: C, 61.6; H, 5.0; Br, 15.0. $C_{27}H_{27}BrO_6$ requires C, 61.5; H, 5.1; Br, 15.1%).

r-2-(2,5-*Dibenzyloxy*-4-*bromophenyl*)-t-4-*dimethylamino*-c-3,c-5-*dihydroxy*-t-6-*methoxy*-2-*methyl*-3,4,5,6-*tetrahydro*-2H-*pyran* (**20**).—The epoxide (**19**) (294 mg, 0.56 mmol) was dissolved in dimethylamine (20 ml) in a steel bomb and the vessel was kept at 90 °C overnight. After cooling, the contents were evaporated and the residue was chromatographed on silica; elution with ethyl acetate containing a trace (0.1% v/v) of triethylamine gave the *title amine* (1.79 mg, 56%), m.p. 138—140 °C; $\nu_{max.}(CHCl_3)$ 3 430, 1 625, 1 490, 1 455, and 840 cm^{-1}; δ 1.76 (3 H, s, Me), 2.41 (6 H, s, NMe_2), 2.87 (1 H, t, *J* 10 Hz, 4-H), 3.28 (3 H, s, OMe), 3.58 (1 H, d, *J* 10 Hz, 3-H), 3.59 (1 H, dd, *J* 7.5 and 10 Hz, 5-H), 4.05 (1 H, d, *J* 7.5 Hz, 6-H), 4.95 (1 H, d, *J* 12 Hz, OCH*H*Ph), 5.05 (1 H, d, *J* 12 Hz, OCH*H*Ph), 5.08 (1 H, d, *J* 12 Hz, OCH*H*Ph), 5.10 (1 H, d, *J* 12 Hz, OC*H*HPh), 7.25 (1 H, s, aryl H), 7.3—7.6 (10 H, m, 2 × Ph) and 7.84 (1 H, s, aryl H) (Found: C, 61.0; H, 6.1; N, 2.6; Br, 13.9. $C_{29}H_{34}BrNO_6$ requires C, 60.9; H, 6.0; N, 2.5; Br, 13.9%).

8-*Benzyloxy*-9-*bromo*-2,6-*epoxy*-4-*dimethylamino*-3,5-*dihydroxy*-6-*methyl*-3,4,5,6-*tetrahydro*-2H-1-*benzoxecane* (**21**).—The acetal (**20**) (103 mg, 0.18 mmol) was dissolved in acetonitrile (6 ml) containing sodium iodide (60 mg, 0.4 mmol) and the suspension was stirred under N_2 whilst trimethylsilyl chloride (42 mg, 1.2 mol equiv.) was added. The mixture was heated to reflux for 6 h, cooled, quenched with saturated aqueous sodium hydrogen carbonate and then treated with 10% w/v aqueous sodium thiosulphate. The mixture was extracted with methylene dichloride, and the combined extracts were dried and evaporated to give the crude product. Chromatography through silica gel, with ethanol–ethyl acetate (1:9) containing a few drops of triethylamine as eluant, gave the *title oxecane* (39 mg, 48%); $\nu_{max.}$ 3 340, 1 660, 1 605, 1 485, 1 400, 1 200, 1 050, and 870 cm^{-1}; δ 1.61 (3 H, s, Me), 2.15 (1 H, t, *J* 10.2 Hz, 4-H), 2.45 (6 H, s, NMe_2), 3.47 (1 H, d, *J* 10.2 Hz, 5-H), 3.98 (1 H, dd, *J* 10.2 and 3.6 Hz, 3-H), 5.09 (2 H, s, OCH_2Ph), 5.47 (1 H, d, *J* 3.6 Hz, 2-H), 6.71 (1 H, s, aryl H), 7.14 (1 H, s, aryl H), and 7.2—7.5 (5 H, m, Ph) (Found: M^+, 449.084 01. $C_{21}H_{24}BrNO_5$ requires *M*, 449.083 82).

2-(4-*Bromo*-2,5-*dimethoxyphenyl*)-2-*methyl*-1,3-*dioxolane* (**23**).—A solution of 4-Bromo-2,5-dimethoxyacetophenone (5.20 g, 20 mmol) in benzene (200 ml) and ethane-1,2-diol (1.85 g, 1.5 mol equiv.) containing toluene-4-sulphonic acid monohydrate (0.5 g) was heated to reflux in a Dean–Stark apparatus for 6 h, with removal of the water formed at regular intervals. The cooled solution was neutralised with saturated aqueous sodium hydrogen carbonate, the benzene layer was separated, and the aqueous layer was further extracted with methylene dichloride. The combined organic phases were dried and evaporated to give the crude acetal. Chromatography of this through silica gel, ethyl acetate–light petroleum (1:4) as eluant, gave the *title product* as a gum (4.93 g, 81%); $\nu_{max.}$ 1 490, 1 380, and 1 035 cm^{-1}; δ 1.75 (3 H, s, Me), 3.90 (6 H, s, 2 × MeO), 3.84—4.2 (4 H, m, CH_2CH_2), and 7.20 2 H, s, aryl H) (Found: C, 47.7; H, 5.0; Br, 26.3. $C_{12}H_{15}BrO_4$ requires C, 47.5; H, 5.0; Br, 26.3%).

2-(4-*Bromo*-5-*methoxy*-2-*methoxymethoxyphenyl*)-2-*methyl*-1,3-*dioxolane* (**24**).—To a stirred solution of the acetophenone (**4**) (2.6 g, 10 mmol) in methylene dichloride (30 ml) at −70 °C under dry N_2 was slowly added a solution of boron trichloride (1.3 g, 1.1 mol equiv.) in the same solvent (20 ml). The mixture was stirred for a further 15 min before being allowed to attain ambient temperature during 2 h. The mixture was then poured into ice–conc. hydrochloric acid, the organic layer was

separated, and the aqueous phase was extracted with chloroform. The combined extracts were dried and evaporated to give *2-acetyl-5-bromo-4-methoxyphenol.* Recrystallisation from ethanol gave pale yellow needles (1.35 g, 55%), m.p. 119 °C; $\nu_{max.}$(Nujol) 1 640, 1 605, 1 210, 880, and 810 cm^{-1}; δ 2.60 (3 H, s, Me), 3.90 (3 H, s, MeO), 7.15 (1 H, s, aryl H), 7.25 (1 H, s, aryl H), and 11.00 (1 H, s, exch., OH) (Found: C, 44.2; H, 3.7; Br, 32.7. $C_9H_9BrO_3$ requires C, 44.1; H, 3.7; Br, 32.6%).

The hydroxyacetophenone (1.22 g, 10 mmol) was converted into its corresponding ethylene acetal using the method described above. The product *phenol* (1.06 g, 74%) showed m.p. 167 °C; δ 1.70 (3 H, s, Me), 3.85 (3 H, s, OMe), 3.75—3.95 and 4.00—4.20 (4 H, m, CH_2CH_2), 6.85 (1 H, s, aryl H), 7.10 (1 H, s, aryl H), and 7.80 (1 H, s, exch., OH).

The phenol (0.7 g, 2.2 mmol) was dissolved in tetrahydrofuran (THF) (15 ml) under N_2 and was treated with sodium hydride (50% oil dispersion; 300 mg, 3 mol equiv.); the mixture was stirred for 15 min, chloromethyl methyl ether (0.3 ml, 2 mol equiv.) was added, and the mixture was stirred for a further 16 h before being quenched with saturated aqueous ammonium chloride (30 ml) and extracted with methylene dichloride (3 × 10 ml). The combined extracts were dried, concentrated, and chromatographed through silica gel, eluting with ethyl acetate–light petroleum (1:6) to give the *title ether* (0.53 g, 72%) as a mobile oil; $\nu_{max.}$($CHCl_3$) 1 590, 1 380, 1 155, 1 075, and 1 045 cm^{-1}; δ 1.75 (3 H, s, Me), 3.50 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.8—4.1 (4 H, m, CH_2CH_2), 5.10 (2 H, s, OCH_2O), 7.10 (1 H, s, aryl H), and 7.35 (1 H, s, aryl H) (Found: C, 47.0; H, 5.1. $C_{13}H_{17}BrO_5$ requires C, 46.9; H, 5.1%).

Synthesis of Anthraquinones.—The following general method was used on reactions of between 1—5 mmol scale. A solution of a phthalide (1.1 mol equiv.) in dry THF (3 ml $mmol^{-1}$) at −70 °C was treated with freshly prepared lithium di-isopropylamide. The yellow solution was stirred at −70 °C for 15 min before being warmed to −40 °C and treated, dropwise, with a solution of the aryl bromide (1.0 mol equiv.) in THF (3 ml $mmol^{-1}$). The ensuing dark red solution was stirred at −40 °C for 15 min before being allowed to slowly warm to room temperature. After 1 h, air was allowed into the reaction vessel and the mixture was stirred overnight before being quenched with saturated aqueous ammonium chloride and extraction with methylene dichloride. The combined extracts were dried and evaporated before chromatography through silica gel. The following quinones were thus obtained.

1,4-*Dimethoxy*-2-(2-*methyl*-1,3-*dioxalan*-2-*yl*)*anthraquinone* (**27**). Elution with ethyl acetate–light petroleum (2:3) gave the *product* (41%), m.p. 167 °C; $\nu_{max.}$($CHCl_3$) 1 670, 1 595, 1 360, 1 335, 1 230, and 1 040 cm^{-1}; δ 1.83 (3 H, s, Me), 3.95 (3 H, s, OMe), 4.03 (3 H, s, OMe), 3.9—4.3 (4 H, m, CH_2CH_2), 7.62 (1 H, s, 3-H), 7.7—7.9 (2 H, m, 6- and 7-H), and 8.2—8.5 (2 H, m, 5- and 8-H) (Found: C, 67.5; H, 5.1. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%).

Anthraquinones (**28**) *and* (**29**). The mixture could not be separated by chromatography through silica; the mixture was obtained in 60% yield. One of the isomers crystallised out from acetone. This product showed m.p. (from EtOH) 154—156 °C; $\nu_{max.}$($CHCl_3$) 1 645, 1 590, 1 460, and 1 015 cm^{-1}; δ 1.75 (3 H, s, Me), 3.92 (3 H, s, OMe), 3.84 (3 H, s, OMe), 3.95 (3 H, s, OMe), 3.9—4.2 (4 H, m, CH_2CH_2), 4.97 and 5.27 (2 H, ABq, *J* 7 Hz, OCH_2O), 7.09 (1 H, dd, *J* 1.3 and 8 Hz, 6- or 7-H), 7.23 (1 H, s, 3-H), 7.41 (1 H, t, *J* 8 Hz, 7- or 6-H), 7.71 (1 H, dd, *J* 1.3 and 8 Hz, 5- or 8-H) (Found: M^+, 414.136 58. $C_{22}H_{22}O_8$ requires *M*, 414.131 46).

4-*Methoxy*-3-*phenylsulphonylphthalide* (**30**).—A solution of *N,N*-diethyl-3-methoxybenzamide (3.87 g, 19 mmol) in dry ether (50 ml) at −78 °C was stirred and treated with tetramethylethylenediamine (1.9 g, 19 mmol) and then s-butyllithium (22 ml; 0.91M in hexane) for 1 h before addition of DMF (4.0 ml, 1.2 mol equiv.) and the solution was stirred for a further 1 h at −78 °C before the temperature was allowed to rise to ambient and the mixture quenched with saturated aqueous ammonium chloride. The layers were separated and the organic layer was washed with water (50 ml), dried, and the solvent was evaporated off. The residue was chromatographed through silica gel, with ethyl acetate as eluant, to give *N,N*-diethyl-2-formyl-3-methoxybenzamide (3.07 g, 70%).

The amide (3.00 g) was immediately hydrolysed with aqueous 2M potassium hydroxide at room temperature overnight; the reaction mixture was acidified with conc. hydrochloric acid and then extracted with ether (3 × 50 ml). The extracts were dried and evaporated to yield 2-formyl-3-methoxybenzoic acid (2.18 g, 95%), m.p. 153—156 °C.

The acid (0.73 g, 4 mmol) was treated with thiophenol (0.52 g, 1.2 mol equiv.) and toluene-4-sulphonic acid (50 mg) in benzene (30 ml) at reflux, under N_2 and using a Dean–Stark apparatus to remove water as it formed. The cooled benzene solution was washed with saturated aqueous sodium hydrogen carbonate (2 × 30 ml), then dried, and the solvent was removed to give a crystalline solid, identified as 4-*methoxy*-3-*phenylthiophthalide* (the sulphide corresponding to the title compound) (0.95 g, 85%), m.p. 84—86 °C; δ 4.01 (3 H, s, MeO), 6.66 (1 H, s, 3-H), and 7.03—7.60 (8 H, m, aromatic H) (Found: C, 66.1; H, 4.4. $C_{15}H_{12}O_3S$ requires C, 66.2; H, 4.4%).

To a solution of the sulphide (0.90 g, 3.3 mmol) in methylene dichloride (25 ml) at 0 °C was added a solution of 3-chloroperbenzoic acid (1.65 g, 2.4 mol equiv.). The solution was stirred at 0 °C for 20 min and then at room temperature for 30 min before addition of a further portion of the peracid (0.25 g), and the mixture was stirred for a further 1 h. The reaction mixture was worked up by quenching with saturated aqueous sodium hydrogen carbonate, then dried, and removal of the solvent gave the *title sulphone* as a crystalline solid (0.94 g, 90%), m.p. 185—187 °C; δ 3.90 (3 H, s, MeO), 6.56 (1 H, s, 3-H), and 7.23—7.88 (8 H, m, aromatic H) (Found: C, 59.3; H, 4.0. $C_{15}H_{12}O_5S$ requires C, 59.2; H, 3.9%).

9,10-*Dihydroxy*-5-*methoxy*-3,4-*dihydroanthracen*-1(2H)-*one* (**31**).—A solution of t-butyl alcohol (34.1 μl, 0.3 mmol) in THF (3 ml) was cooled under nitrogen to −30 °C and butyl-lithium (0.32 ml of 0.95M solution in hexane; 0.3 mmol) was added. To this stirred solution was added the substituted phthalide (**30**) (0.10 g, 0.3 mmol). After a few minutes neat cyclohex-2-enone (35 μl, 0.3 mmol) was added and the solution was allowed to warm to ambient temperature before being heated to reflux for 30 min. The reaction mixture was quenched with 1M HCl (10 ml) and extracted with ether (3 × 10 ml); the extract was dried and the solvent was removed under reduced pressure. The residues were chromatographed through silica gel to produce the *title compound* (57 mg, 67%), m.p. (from methylene dichloride–light petroleum–ethanol) 147—148 °C; δ 1.95—2.23 (2 H, m, CH_2), 2.65—2.79 (2 H, m, CH_2), 3.00 (2 H, t, *J* 6.2 Hz, CH_2), 4.06 (3 H, s, OMe), 6.97 (1 H, dd, *J* 1.0 and 7.9 Hz, ArH), 7.33 (1 H, t, *J* 8.1 Hz, ArH), 8.04 (1 H, dd, *J* 1.1 and 8.4 Hz, ArH), 9.04 (1 H, s, OH), and 13.44 (1 H, s, OH) (Found: C, 69.7; H, 5.5. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.5%).

4-*Acetyl*-N,N-*diethyl*-2,5-*dimethoxybenzamide.* (**33**).—Magnesium turnings (4.69 g, 0.2 mol) were suspended in dry THF (100 ml) under N_2. A small crystal of iodine and ethylene dibromide (0.8 ml) were added and the mixture was heated to reflux before addition of the bromide (**23**) (27.8 g, 92 mmol) and more ethylene dibromide (7.2 ml) in THF (20 ml), addition being regulated to maintain a gentle reflux. After 1 h a solution of methyl *N,N*-diethylcarbamate (16.86 g, 130 mmol) in THF

(10 ml) was added and the mixture was heated to reflux for 20 h under N_2 before being cooled, slowly quenched with 1M hydrochloric acid (50 ml), filtered, and extracted with ether (3 × 50 ml). The extract was dried, the solvent was removed, and the residue was chromatographed through silica gel, with ethyl acetate–light petroleum–acetic acid (70:30:1) as eluant. The major fraction (15.82 g, 63%), isolated as an oil, corresponded to the *title amide*, δ 1.10 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.28 (3 H, t, *J* 7 Hz, *Me*CH_2), 2.66 (3 H, s, MeCO), 3.20 (2 H, q, *J* 7 Hz, MeCH_2), 3.62 (2 H, q, *J* 7 Hz, MeCH_2), 3.85 (3 H, s, MeO), 3.94 (3 H, s, MeO), 6.95 (1 H, s, aromatic H), and 7.38 (1 H, s, aromatic H) (Found: C, 64.6; H, 7.7; N, 5.0. $C_{15}H_{21}NO_4$ requires C, 64.5; H, 7.6; N, 5.0%).

N,N-*Diethyl*-4-(1-*methoxyethyl*)-2,5-*dimethoxybenzamide* (**34**).—A solution of the acetophenone (**33**) (4.71 g, 17 mmol) in ethanol (50 ml) at 0 °C was treated with sodium borohydride (0.95 g, 25 mmol) in one portion and the mixture was stirred at room temperature for 2 h before the addition of a few drops of acetic acid to destroy the excess of the reductant. To the product mixture was added brine (50 ml) and the whole was extracted with ethyl acetate (2 × 40 ml); the extract was washed with more brine before being dried and evaporated. The product was chromatographed through silica gel, with ethyl acetate as eluant, to give the product *N*,*N*-diethyl-4-(1-hydroxyethyl)-2,5-dimethoxybenzamide (4.59 g, 97%) as an oil, δ 1.04 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.24 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.41 (3 H, d, *J* 6 Hz, *Me*CH), 3.18 (2 H, q, *J* 7 Hz, MeCH_2), 3.58 (2 H, q, *J* 7 Hz, MeCH_2), 3.78 (3 H, s, MeO), 3.80 (3 H, s, MeO), 5.16 (1 H, q, *J* 6 Hz, MeC*H*), 6.68 (1 H, s, aromatic H), and 7.00 (1 H, s, aromatic H).

A solution of the alcohol (2.94 g, 10 mmol) in THF (50 ml) was treated with sodium hydride (light petroleum washed; 0.38 g, 15 mmol) at reflux for 1.5 h before cooling to room temperature and addition of dimethyl sulphate (1.98 ml, 2 mol equiv.), and the mixture was then stirred at room temperature overnight before addition of methanol (5 ml). After removal of the bulk of the solvent the product was partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate. The aqueous phase was re-extracted with ethyl acetate and the organic extracts were dried and evaporated to dryness. The crude product was chromatographed through silica gel, with ethyl acetate–light petroleum (1:1) as eluant, to give the *title product* (2.49 g, 81%), δ 1.05 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.24 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.35 (3 H, d, *J* 6.5 Hz, *Me*CH), 3.21 (2 H, q, *J* 7 Hz, MeCH_2), 3.28 (3 H, s, MeO), 3.59 (2 H, q, *J* 7 Hz, MeCH_2), 3.80 (6 H, s, 2 × MeO), 4.74 (1 H, q, *J* 6.5 Hz, MeC*H*), 6.73 (1 H, s, aromatic H), and 6.98 (1 H, s, aromatic H) (Found: C, 65.0; H, 8.6; N, 4.6. $C_{16}H_{25}NO_4$ requires C, 65.1; H, 8.5; N, 4.7%).

N,N-*Diethyl*-2,6-*dimethoxy*-4-(2-*methyl*-1,3-*dioxolan*-2-*yl*)-*benzamide* (**39**).—This was prepared from the acetal (**23**) in a similar manner to the ketone (**33**) except that, during work-up, the reaction was quenched with aqueous ammonium chloride. The product was chromatographed through silica gel, with ethyl acetate–light petroleum (3:7) as eluant, to give the *title compound* (65%), m.p. 81—83 °C; δ 1.05 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.25 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.76 (3 H, s, Me), 3.18 (2 H, q, *J* 7 Hz, MeCH_2), 3.59 (2 H, q, *J* 7 Hz, MeCH_2), 3.7—4.2 (4 H, m, OCH_2CH_2O), 3.81 (3 H, s, MeO), 3.85 (3 H, s, MeO), 6.82 (1 H, s, aromatic H), and 7.15 (1 H, s, aromatic H) (Found: C, 63.2; H, 7.8; N, 4.2. $C_{17}H_{25}NO_5$ requires C, 63.1; H, 7.8; N, 4.3%).

2-*Deuterio*-N,N-*diethyl*-3,6-*dimethoxy*-4-(1-*methoxyethyl*)-*benzamide* (**35**).—The amide (**34**) (0.1 g, 0.3 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (0.2 ml, 1.2 mmol) were dissolved in dry ether (5 ml) at −78 °C under N_2 and the solution was treated with s-butyl-lithium (0.82 ml, 0.6 mmol) at −78 °C for 1 h. [$^2H_2$]Water (0.1 ml, 5 mmol) was added and the reaction mixture was allowed to warm to room temperature being quenched with saturated aqueous NH_4Cl (60 ml) and extracted with ether. The extract was dried, the solvent was removed, and the residue was chromatographed through silica gel, with ethyl acetate–light petroleum (1:1) as eluant, to afford the title compound (69 mg, 69%). ^1H N.m.r. spectroscopy showed loss of an aromatic proton signal: δ 1.08 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.26 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.38 (3 H, d, *J* 6.5 Hz, *Me*CH), 3.23 (2 H, q, *J* 7 Hz, MeCH_2), 3.31 (3 H, s, MeO), 3.61 (2 H, q, *J* 7 Hz, MeCH_2), 3.83 (6 H, s, 2 × MeO), 4.77 (1 H, q, *J* 65 Hz, MeC*H*), and 7.04 (1 H, s, ArH); *m*/*z* 296 (36%), 281 (20), 265 (10), 224 (100), 192 (40), and 75 (23).

N,N-*Diethyl*-2-*formyl*-3,6-*dimethoxy*-4-(1-*methoxyethyl*)-*benzamide* (**36**).—A solution of the amide (**34**) (0.10 g, 0.3 mmol) and TMEDA (0.2 ml, 1.4 mmol) in dry ether (5 ml) at −78 °C under N_2 was treated with s-butyl-lithium (0.82 ml; equiv. to 0.6 mmol) and stirred for 1 h at −78 °C before addition of methyl formate (0.1 ml, 1.5 mmol); the mixture was warmed to 0 °C before being quenched with saturated aqueous NH_4Cl (10 ml) and extracted with ether. The extract was dried, concentrated to small bulk, and chromatographed through silica gel, with ethyl acetate–light petroleum–acetic acid (79:20:1) as eluant. Initial fractions yielded recovered starting amide (39 mg, 39%) followed by the *title compound* (44 mg, 40%), m.p. 92—103 °C. The ^1H n.m.r. spectrum showed this to be a mixture of rotamers (*ca.* 1:1) as follows, δ 1.02 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.31 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.40 (3 H, d, *J* 7 Hz, *Me*CH), 3.09 (2 H, q, *J* 7 Hz, MeCH_2), 3.22 and 3.31 (3 H, s, MeO rotamers), 3.54 and 3.68 (2 H, q, *J* 7 Hz, MeCH_2, rotamers), 3.83 (3 H, s, MeO), 3.84 (3 H, s, MeO), 4.70 (1 H, m, MeC*H*), 7.23 (1 H, s, aromatic H), and 10.29 (1 H, s, CHO) (Found: C, 63.0; H, 7.6; N, 4.2. $C_{17}H_{25}NO_5$ requires C, 63.1; H, 7.8; N, 4.3%).

N,N-*Diethyl*-3,6-*dimethoxy*-4-(1-*methoxyethyl*)-2-*trimethylsilylbenzamide* (**37**).—A solution of the amide (**34**) (0.14 g, 0.5 mmol) and TMEDA (0.18 ml, 1.25 mmol) in THF at −78 °3, under N_2 was treated with s-butyl-lithium (in hexane; 0.85 ml, 0.6 mmol), the solution was stirred for 1 h, and then trimethylsilyl cyanide (0.08 ml, 0.6 mmol) was added. The reaction mixture was slowly warmed to 0 °C (1 h), then quenched with saturated aqueous NH_4Cl and extracted with ether. The dried extract was evaporated to give an oil, which was chromatographed through silica gel, ethyl acetate–light petroleum (1:1) as eluant. Elution afforded the title compound as a rotameric mixture (0.15 g, 86%); *m*/*z* 367 (7%), 352 (100), 336 (26), and 295 (14).

N,N-*Diethyl*-3,6-*dimethoxy*-4-(1-*methoxyethyl*)-2-*methylamide* (**38**).—A solution of the amide (**34**) (0.1 g, 0.3 mmol) and TMEDA (0.11 ml, 0.7 mmol) in THF (5 ml) at −78 °C under N_2 was treated with s-butyl-lithium (in hexane; 0.45 ml, 0.33 mmol) and the solution was stirred for 15 min before addition of methyl iodide (0.11 ml, 1.5 mmol). The solution was allowed to warm slowly to room temperature before being quenched with saturated aqueous NH_4Cl (10 ml) and extracted with ethyl acetate. The extracts were dried and evaporated, the residue was chromatographed through silica gel, with ethyl acetate–light petroleum–acetic acid (70:20:1) as eluant, to give the title compound as an inseparable mixture of rotamers (95 mg, 91%); *m*/*z* 309 (21%), 294 (27), and 237 (100). For this mixture separation was observed on t.l.c. but, within 1 h at room temperature, the individual entities had re-equilibrated to the rotameric mixture, either upon the t.l.c. plate or after extraction from it.

N,N-*Diethyl*-3,6-*dimethoxy*-2-*methyl*-4-(2-*methyl*-1,3-*dioxolan*-2-*yl*)*benzamide* (**40**).—A solution of TMEDA (0.55 ml, 3.6 mmol) in ether (10 ml) was cooled to −90 °C before being treated with s-butyl-lithium (in hexane; 2.2 ml, 1.8 mmol) followed, after 5 min, by the dropwise addition of a solution of the amide (**39**) (0.5 g, 1.5 mmol) in ether (10 ml). After this addition the solution was stirred for a further 15 min at between −90 and −70 °C, when methyl iodide (0.57 ml, 9 mmol) was added. The reaction mixture was allowed to warm to −30 °C before being quenched with saturated aqueous NH_4Cl (30 ml) and extracted with ether. The extract was dried and evaporated and the residue was crystallised from ethyl acetate–toluene–light petroleum to give the title amide (0.47 g, 92%), m.p. 109—111 °C; δ 1.03 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.25 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.76 (3 H, s, OCMe), 2.18 (3 H, s, Ar*Me*), 3.12 (2 H, q, *J* 7 Hz, MeC*H*$_2$), 3.48 (2 H, q, *J* 7 Hz, MeC*H*$_2$), 3.68—4.16 (4 H, m, OCH_2CH_2O), 3.74 (3 H, s, OMe), 3.77 (3 H, s, OMe), and 6.91 (1 H, s, ArH); *m*/*z* 337 (45%), 322 (100), 265 (68), 221 (23), 193 (40), and 87 (32).

5-*Acetyl*-4,7-*dimethoxyphthalide* (**41**).—To a solution of TMEDA (0.7 ml, 4.5 mmol) in ether (10 ml) at −90 °C was added s-butyl-lithium (in hexane; 2.8 ml, 2.25 mmol) followed, after 10 min, by the dropwise addition for a solution of the amide (**39**) (0.5 g, 1.5 mmol) in ether (10 ml), the temperature being maintained at −90 °C. After 25 min paraformaldehyde (0.46 g, 15 mmol) was added as a solid and the mixture was allowed to warm slowly to 10 °C. The reaction mixture was filtered, the solids were washed with a little ether, and the combined filtrate and washings were quenched with saturated aqueous NH_4Cl, dried, and evaporated, and the residue was filtered through silica gel, with ethyl acetate–acetic acid (98:2) as eluant. The major fraction was dissolved in 1:1 aqueous dioxane (10 ml) containing potassium hydroxide (0.28 g; 0.5M solution) and the solution was stirred at room temperature for 18 h before being acidified with conc. HCl and stirred for a further 1 h. Brine (10 ml) was added before extraction with ethyl acetate. The extract was dried and evaporated, and the residue was crystallized from methylene dichloride–toluene to give the title phthalide (0.17 g, 48%), m.p. 155—156 °C; δ 2.70 (3 H, z, MeCO), 3.98 (3 H, s, OMe), 3.99 (3 H, s, OMe), 5.44 (2 H, s, CH_2), and 7.20 (1 H, s, ArH); *m*/*z* 236 (100%), 221 (61), 207 (32), 190 (28), and 162 (18) (Found: C, 61.0; H, 5.2. $C_{12}H_{12}O_5$ requires C, 61.0; H, 5.1%).

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