Synthesis of Albidin (6-Methoxy-3-methylisobenzofuran-4,5-dione) and (±)-Curvulol [(±)-1,3-Dihydro-6-methoxy-3-methylisobenzofuran-4,5-diol]

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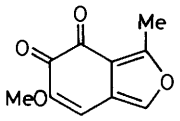
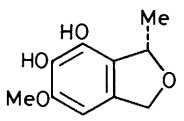
The title compounds have been synthesised by a sequence involving as the key step the cyclization of the radical derived from the reaction of tributylstannane with 3,4-diacetoxy-2-bromo-5-methoxybenzyl vinyl ether.

Grove and Hitchcock recently established that the red pigment albidin, isolated from *Penicillium albidum* Sopp, is 6-methoxy-3-methylisobenzofuran-4,5-dione (**1**).[1] The isolation of this material, which has strong antibiotic and fungistatic activity, was first reported in 1947,[2] and the name albidin was assigned after the reclassification of its source.[3] The structural determination of (**1**) rests primarily on single crystal *X*-ray crystallography, and (**1**) is clearly related to (−)-curvulol [(*S*)-1,3-dihydro-6-methoxy-3-methylisobenzofuran-4,5-diol] (**2**), a



(**1**)

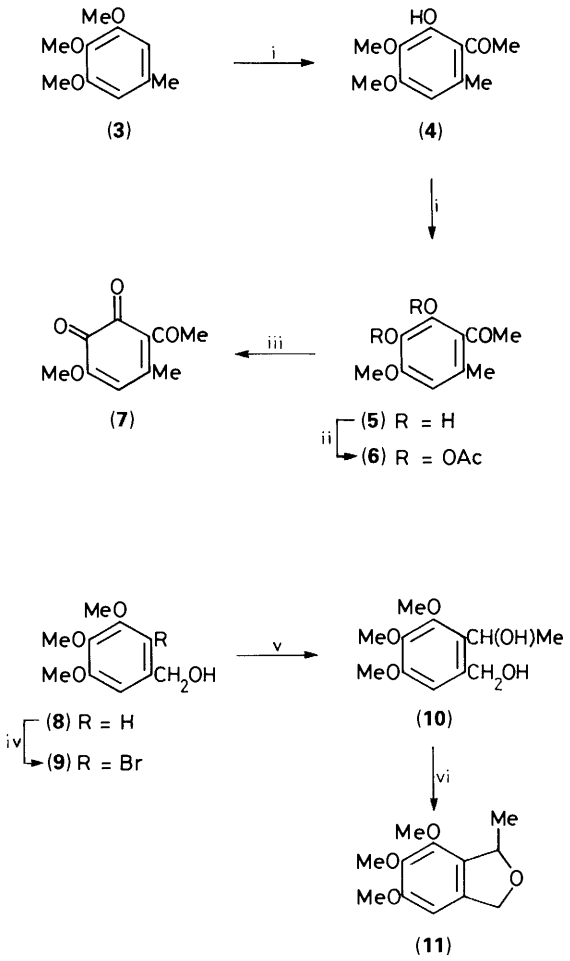


(**2**)

metabolic product of the fungus *Clavularia siddiqui*.[4] As part of our continuing interest in the synthesis of novel substituted isobenzofurans,[5,6] we have carried out a synthesis of (**1**) proceeding *via* (±)-curvulol.

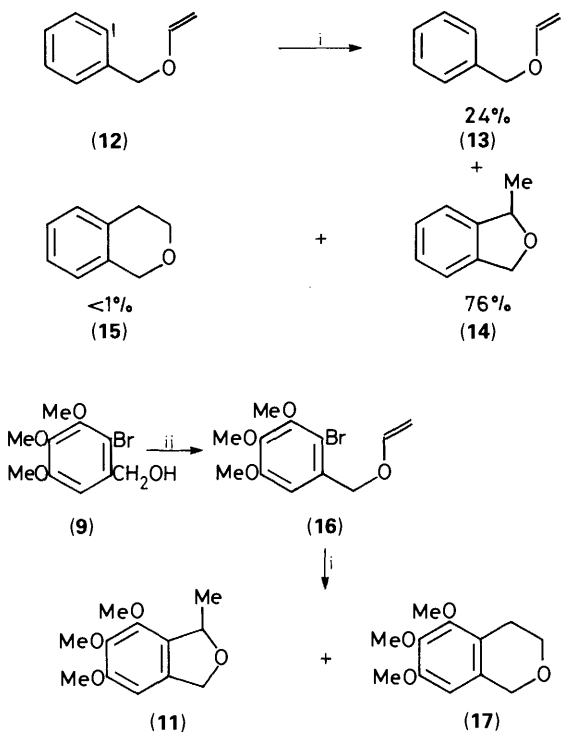
The results of some preliminary experiments are summarised in Scheme 1. 3,4,5-Trimethoxytoluene (**3**), readily prepared from gallic acid,[7] was acetylated by a modification of the method of Baker and Raistrick,[8] using acetyl chloride and aluminium chloride in dichloromethane (instead of ether) to afford the *o*-hydroxyacetophenone (**4**). Use of an excess of aluminium chloride and longer reaction times gave, in addition to (**4**), the catechol (**5**). The site of the second demethylation was established chemically by oxidation of (**5**) to the *o*-quinone (**7**), and spectroscopically by a nuclear Overhauser effect experiment. Thus, irradiation of the aryl methyl resonance of (**5**) gave a 15% enhancement of the aryl proton signal, while irradiation of the methoxy signal resulted in an 18% enhancement of the aryl proton signal. A number of attempts were made to construct the phthalan (1,3-dihydroisobenzofuran) ring system using the acetate (**6**), as well as other derivatives of (**5**), by sequences involving reduction of the ketonic carbonyl group, protection of the resulting alcohol, benzylic bromination, liberation of the alcohol followed by cyclization. These attempts were uniformly unsuccessful, and will not be detailed here. The substituted phthalan ring system of curvulol could however be prepared by starting with 2-bromo-3,4,5-trimethoxybenzyl alcohol (**9**). Metal-halogen exchange with butyl-lithium, followed by quenching with acetaldehyde, gave the diol (**10**). Attempts to dehydrate (**10**) under a variety of conditions led to decomposition, although the action of toluene-*p*-sulphonic acid in benzene under reflux did give 1,3-dihydro-1-methyl-5,6,7-trimethoxyisobenzofuran [(±)-di-*O*-methylcurvulol] (**11**) in modest yield.

In view of these preliminary results, we felt that it would be necessary to adopt a mild method to construct the highly



Scheme 1. *Reagents:* i, AcCl, $AlCl_3$, CH_2Cl_2; ii, Ac_2O; iii, *o*-chloranil; iv, Br_2; v, BuLi, CH_3CHO; vi, TsOH

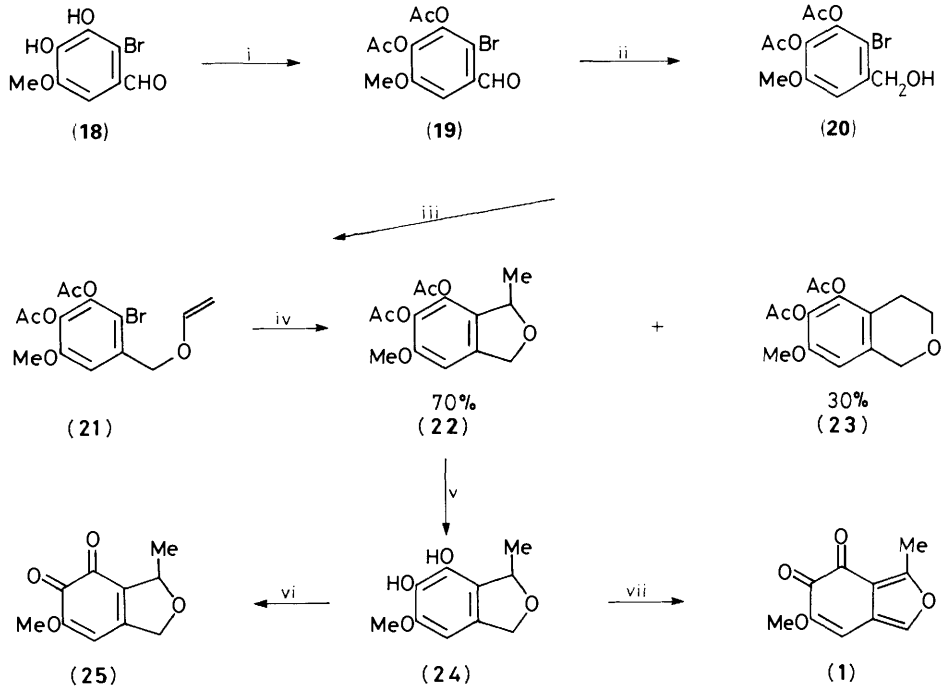
oxygenated phthalan ring system of curvulol. In 1975, Beckwith and Gara reported that treatment of *o*-iodobenzyl vinyl ether (**12**) with tributylstannane in benzene under reflux afforded benzyl vinyl ether (**13**) (24%) and 2-methylphthalan (**14**) (76%).[9] None of the 6-membered ether (**15**) was detected (Scheme 2). Such free radical cyclizations have recently assumed considerable importance in synthesis[10–12] and seemed to be ideally suited to our needs. Accordingly, as a model reaction, 2-bromo-3,4,5-trimethoxybenzyl alcohol (**9**) was converted into the vinyl ether (**16**), which was submitted to the free radical cyclization, using a low concentration of stannane to minimise the likelihood of reductive debromination. This afforded in good yield the



Scheme 2. *Reagents:* i, Bu_3SnH, PhH, AIBN; ii, CH_2=CHOEt, $Hg(OAc)_2$

dominantly in the desired 5-*exo* mode,[13] and that unlike the observation with (**12**), uncyclized material was not present.

In view of this encouraging result, a sequence was designed which would allow liberation of the *o*-dihydroxy system of curvulol at a suitable stage of the synthesis (Scheme 3). Thus the bromoaldehyde (**18**), readily available from vanillin,[14] was acetylated, reduced, and the resulting benzyl alcohol (**20**) converted into the vinyl ether (**21**). Radical cyclization afforded in good yield the two ethers (**22**) and (**23**) in a ratio of 70:30, with no detectable uncyclized material. Thus in the cyclization of the aryl radicals derived from (**16**) and (**21**), a significant proportion of 6-*endo* ring closure, leading to the benzopyrans (**17**) and (**23**), is observed, whereas this mode of reaction is not detected with the radical derived from (**12**). These results may be the consequence of steric factors, since the presence of three contiguous substituents adjoining the aryl radical centre in our systems undoubtedly gives rise to steric compression. This would lead to a more congested transition state for 5-*exo* ring closure than for 6-*endo* ring closure, and the normal balance of stereo-electronic factors[13] which favour the former reaction pathway is upset, leading to an increased proportion of 6-membered ether. It is also possible that the radical centre is stabilised by the presence of the oxygen-substituents so that the formation of the thermodynamic product (6-*endo*) is enhanced relative to the kinetic product (5-*exo*).* It should be noted that this effect appears to be operating only in our highly substituted compounds (**16**) and (**21**), since the presence of a single methoxy group adjacent to the radical centre still results in 5-*endo* ring closure in related systems.[15]



Scheme 3. *Reagents:* i, Ac_2O; ii, $NaBH_4$; ii, CH_2=CHOEt, $Hg(OAc)_2$; iv, Bu_3SnH, PhH, AIBN; v, OH^-, H^+; vi, *o*-chloranil; vii, DDQ, dioxane, 100 °C

desired phthalan (**11**), together with the benzopyran (**17**), in a ratio of 80:20 by g.c. analysis. The product was contaminated by two unidentified tin-containing by-products, which could not be removed by chromatography or distillation because of the non-polar nature of (**11**) and (**17**). However, this experiment clearly showed that the radical cyclization occurred pre-

The ethers (**22**) and (**23**) could be separated by careful radial chromatography, and the ^1H n.m.r. spectrum of (**22**) showed the long range coupling features characteristic of 1-substituted phthalans.[16] Hydrolysis of (**22**) afforded (±)-curvulol (**24**). Although an authentic sample of natural (−)-curvulol could not be obtained, the spectroscopic properties of our material were very similar to those reported for the natural product.[4] Treatment of (**24**) with *o*-chloranil† in ether gave the unstable *o*-quinone (**25**), while heating (**24**) with 2 equiv. of DDQ in

* We thank a referee for this suggestion.

† Tetrachloro-1,2-benzoquinone.

dioxane effected double dehydrogenation to afford albidin (**1**), identical in all respects with an authentic sample.

Experimental

General Directions.—M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed by Canadian Microanalytical Service, Vancouver. N.m.r. spectra were measured at 60 MHz (^{1}H) on a Hitachi-Perkin-Elmer R-24B, at 80 MHz (^{1}H) and 20.1 MHz (^{13}C) on a Bruker WP-80, and at 300 MHz (^{1}H) and 75.5 MHz (^{13}C) on a Bruker AM-300 spectrometer. Unless otherwise stated, n.m.r. spectra were recorded for deuteriochloroform solutions with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Hewlett-Packard 5986 instrument. All molecular ions and peaks with intensities 10% and greater have been recorded. Infrared spectra were measured on either liquid films or KBr discs with a Perkin-Elmer 283 spectrometer. All organic extracts were dried over anhydrous magnesium sulphate and the solvents were removed under reduced pressure. Light petroleum was a fraction b.p. *ca.* 65—75 °C and Silica Gel 60 was used for flash chromatography. Radial chromatography was performed on a Harrison Research Chromatotron with plates coated with Merck Kieselgel 60 PF_{254}.

1-(2-*Hydroxy*-3,4-*dimethoxy*-6-*methylphenyl*)*ethanone* (**4**).—To an ice-cold solution of 1,2,3-trimethoxy-5-methylbenzene (**3**) (1.0 g, 5.5 mmol) in dry CH_2Cl_2 (10 ml) was added $AlCl_3$ (1.2 g, 9.0 mmol) and AcCl (0.7 g, 8.9 mmol) and the reaction mixture was then refluxed for 48 h. After cooling, the reaction mixture was carefully acidified with dilute HCl and extracted with CH_2Cl_2. The combined organic layers were extracted with 10% NaOH and the alkaline layers combined and acidified with conc. HCl. The acidified aqueous layer was extracted with CH_2Cl_2 and the combined organic layers dried and evaporated. Recrystallisation from light petroleum gave the *hydroxy ketone* (**4**) as pale yellow rhombic crystals (0.77 g, 67%), m.p. 77—8 °C (lit.,[8] 92 °C); δ_H(60 MHz) 2.48 and 2.57 (each 3 H, s, 1 × $COCH_3$ and 1 × $ArCH_3$), 3.80 and 3.86 (each 3 H, s, 2 × OCH_3), 6.24 (1 H, s, ArH), and 11.62 (1 H, s, ArOH); δ_C(75.5 MHz) 24.4 ($COCH_3$), 33.0 ($ArCH_3$), 55.9 and 60.7 (2 × OCH_3), 107.0 (ArH), 117.2, 134.5, 136.0, 155.9, 156.7 (5 × Ar), and 204.4 (CO); *m/z* 210 (M^+, 44%), 196 (11), 195 (100), 180 (14), 149 (11), 134 (13), and 43 (21); $\nu_{max.}$(KBr) 3 420 and 1 586 cm^{-1}.

1-(2,3-*Dihydroxy*-4-*methoxy*-6-*methylphenyl*)*ethanone* (**5**).—To an ice-cold solution of th 1,2,3-trimethoxy-5-methylbenzene (**3**) (5.0 g, 27 mmol) in dry CH_2Cl_2 (63 ml) was added $AlCl_3$ (5.5 g, 41 mmol) and AcCl (3.2 g, 41 mmol) and the reaction mixture was then refluxed for 36 h. On cooling the reaction mixture was carefully acidified with dilute HCl and extracted with CH_2Cl_2. The combined organic layers were extracted with 10% NaOH and the alkaline layers combined and acidified with conc. HCl. The acidified aqueous layer was extracted with CH_2Cl_2 and the combined organic layers dried and evaporated. Flash chromatography (EtOAc–light petroleum) of the mixture, followed by recrystallisation (CH_2Cl_2–light petroleum) afforded the *hydroxy ketone* (**4**) (2.0 g, 35%) and the *dihydroxy ketone* (**5**) (2.4 g, 45%), m.p. 132 °C (Found: C, 61.1; H, 6.2. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.2%); δ_H(300 MHz) 2.56 (3 H, d, *J* 0.5 Hz, $ArCH_3$), 2.64 (3 H, s, $ArCOCH_3$), 3.94 (3 H, s, OCH_3), 5.54 (1 H, b, 3-OH), 6.32 (1 H, s, ArH), and 13.22 (1 H, s, 2-OH); δ_C(75.5 MHz) 24.8 ($COCH_3$), 33.1 ($ArCH_3$), 56.0 (OCH_3), 107.0 (ArH), 115.6, 131.5, 132.0, 150.2, and 151.6 (5 × Ar), and 204.9 (ArCO); *m/z* 196 (M^+, 33%), 182 (11), and 181 (100); $\nu_{max.}$(KBr) 3 360, 1 602, and 1 582 cm^{-1}.

1-(2,3-*Diacetoxy*-4-*methoxy*-6-*methylphenyl*)*ethanone* (**6**).—A solution of the dihydroxy ketone (**5**) (1.00 g, 5.1 mmol), Et_3N (4.96 g, 49 mmol), Ac_2O (1.09 g, 10 mmol) and 4-dimethylamidopyridine (DMAP) (10 mg, 0.8 mmol) in CH_2Cl_2 (90 ml) under N_2, was stirred at room temperature for 90 min. The solution was diluted with CH_2Cl_2, washed with saturated Na_2CO_3 solution, H_2O, dried and evaporated. Recrystallisation from CH_2Cl_2–light petroleum afforded the *diacetoxy ketone* (**6**) as colourless spars (1.16 g, 82%), m.p. 114 °C (Found: C, 60.0; H, 5.7. $C_{14}H_{16}O_6$ requires C, 60.0; H, 5.75%); δ_H(60 MHz) 2.25 (6 H, s, $COCH_3$), 2.31 and 2.40 (each 3 H, s, 1 × $ArCOCH_3$ and 1 × $ArCH_3$), 3.80 (3 H, s, OCH_3), and 6.64 (1 H, s, ArH); δ_C(75.5 MHz) 20.2, 20.3, and 20.5 ($COCH_3$), 31.8 ($ArCH_3$) 56.2 (OCH_3), 112.1 (ArH), 127.8, 130.0, 134.2, 140.6, and 152.6 (5 × Ar), 167.7 and 167.8 (2 × $COCH_3$), and 201.1 (ArCO); *m/z* 280 (M^+, 2%), 197 (11), 196 (94), 182 (10), and 181 (100); $\nu_{max.}$(KBr) 1 765 cm^{-1}.

3-*Acetyl*-6-*methoxy*-4-*methyl*-o-*benzoquinone* (**7**).—To a stirred suspension of the dihydroxy ketone (**5**) (510 mg, 2.60 mmol) in dry ether (15 ml) was added a solution of *o*-chloranil (650 mg, 2.64 mmol) in dry ether (8 ml) and the reaction mixture was cooled to −20 °C. After 10 min the product was collected by filtration and dried under vacuum to give purple lustrous needles (474 mg, 94%), m.p. 92—95 °C (Found: C, 61.3; H, 5.2. $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.2%); δ_H(300 MHz) 2.27 and 2.44 (each 3 H, s, $COCH_3$ and $ArCH_3$), 3.85 (3 H, s, OCH_3), and 5.88 (1 H, s, ArH); δ_C(75.5 MHz) 22.7 ($COCH_3$), 33.0 ($ArCH_3$), 56.2 (OCH_3), 112.7 (ArH), 132.2, 153.4, and 156.4 (3 × Ar), 174.1 and 176.2 (2 × CO), and 199.3 (ArCO); *m/z* 196 [$(M + 2)^+$, 55%], 194 (M^+, 18%), 192 (28), 181 (100), 176 (12), 166 (16), 153 (11), 152 (80), 151 (56), 149 (18), 148 (23), 137 (35), 136 (11), 135 (12), 123 (26), 121 (14), 109 (17), 108 (10), 107 (10), 93 (10), 80 (12), 79 (12), 67 (12), 65 (16), 53 (20), 51 (12), and 43 (68); $\nu_{max.}$(KBr) 1 663 and 1 630 cm^{-1}.

(±)-1-*Methyl*-5,6,7-*trimethoxy*-1,3-*dihydroisobenzofuran* (**11**).—To a stirred solution of the bromobenzyl alcohol (**9**)[17] (1.00 g, 3.61 mmol) in dry tetrahydrofuran (THF) (10 ml) cooled to −78 °C under argon was added dropwise BuLi (1.6M hexane solution; 7.9 ml, 12.6 mmol) over 5 min. After 15 min the reaction mixture temperature was allowed to rise to −20 °C and stirring continued for 60 min. Freshly dried and distilled CH_3CHO (278 mg, 6.3 mmol) was added dropwise, during which the white precipitate dissolved. The reaction mixture was allowed to reach room temperature overnight, diluted with H_2O, extracted with CH_2Cl_2, and the combined organic extracts washed with H_2O, dried and evaporated. Radial chromatography (70% EtOAc–CH_2Cl_2) gave (in order of elution) *benzyl alcohol* (**8**) (166 mg, 23%) and *diol* (**10**) (546 mg, 62%); δ_H(300 MHz) 1.55 (3 H, d, *J* 6.7 Hz, CH_3), 296 (2 H, br, 2 × OH), 3.84, 3.86, and 3.94 (each 3 H, s, 3 × OCH_3), 4.50 and 4.80 (2 H, ABq, *J* 12.2 Hz, $ArCH_2$), 5.24 (1 H, q, *J* 6.7 Hz, Ar*CH*), and 6.69 (1 H, s, Ar*H*); δ_C(75.5 MHz) 24.8 (CH_3), 55.9, 60.7, and 61.3 (3 × OCH_3), 63.6 ($ArCH_2$), 65.9 (ArCH), 109.2 (ArH), 128.9, 133.5, 141.6, 151.6, and 152.2 (5 × Ar); *m/z* 242 (M^+, 8%), 224 (21), 210 (13), 209 (100), and 166 (12); $\nu_{max.}$(Film) 3 400 cm^{-1}.

A solution of the foregoing diol (**10**) (328 mg, 1.36 mmol) and toluene-*p*-sulphonic acid (TsOH) (10 mg) in dry C_6H_6 (70 ml) under N_2 was refluxed in a Dean–Stark apparatus for 2 h. After cooling, anhydrous K_2CO_3 (0.3 g) was added and the reaction mixture filtered through Celite, followed by silica, eluting with light petroleum. Evaporation gave a yellow oil which on distillation afforded the ether (**11**) as a colourless oil (122 mg, 40%), b.p. 125 °C (bath)/0.1 mm (Found: C, 63.9; H, 7.1. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.2%); δ_H(300 MHz) 1.50 (3 H, d, *J* 6.3 Hz, CH_3), 3.85 and 3.92 (6 H and 3 H, s, 2 × OCH_3 and

OCH_3), 4.96 and 5.09 (2 H, ddABq, $J_{3\text{-}cis,4}$ 0.8 Hz, $J_{3\text{-}trans,4}$ 0.9 Hz, $J_{1,3cis}$ 1.6 Hz, $J_{1,3trans}$ 2.8 Hz, $J_{3,3gem}$ 11.9 Hz, $ArCH_2$), 5.40 (1 H, ddq, $J_{1,4}$ < 1.0 Hz, $J_{1,3cis}$ 1.6 Hz, $J_{1,3trans}$ 2.8 Hz, *J* 6.3 Hz, ArCH), and 6.51 (1 H, s, ArH); δ_C(75.5 MHz) 21.4 (CH_3), 56.2, 60.6, and 60.9 (3 × OCH_3), 72.6 ($ArCH_2$), 79.8 (ArCH), 99.7 (ArH), 127.7, 134.6, 141.0, 148.1, and 154.1 (5 × Ar); *m/z* 224 (M^+, 19%), 210 (13), 209 (100), 181 (10), and 166 (11).

2-*Bromo*-3,4,5-*trimethoxybenzyl Vinyl Ether* (**16**).—A solution of the bromobenzyl alcohol (**9**) (2.00 g, 7.22 mmol), $Hg(OAc)_2$ (90 mg, 0.3 mmol) in ethyl vinyl ether (11.4 g, 0.16 mol) was refluxed for 2 days under N_2. On cooling the reaction mixture was diluted with Et_2O, washed with saturated $NaHCO_3$, then H_2O, dried and evaporated. Flash chromatography (EtOAc–light petroleum) of the crude product gave the *vinyl ether* (**16**) as a colourless oil (1.17 g, 54%), b.p. 170—175 °C (bath)/0.1 mm (Found: C, 47.55; H, 4.95. $C_{12}H_{15}BrO_4$ requires C, 47.5; H, 5.0%); δ_H(300 MHz) 3.88, 3.88, 3.90 (each 3 H, s, 3 × OCH_3), 4.14 (1 H, dd, J_{BX} 6.8 Hz, J_{AB} 2.3 Hz, H_B of ABX), 4.35 (1 H, dd, J_{AX} 14.3 Hz, J_{AB} 2.3 Hz, H_A of ABX), 4.79 (2 H, s, $ArCH_2$), 6.58 (1 H, dd, J_{AX} 14.3 Hz, J_{BX} 6.8 Hz, H_X of ABX), 6.86 (1 H, s, ArH); δ_C(75.5 MHz) 56.2, 61.0, and 61.1 (3 × OCH_3), 69.5 (Ar CH_2), 87.9 ($CHCH_2$), 107.6 ($CHCH_2$), 108.4, 131.7, 142.5, and 150.8 (4 × Ar), 151.3 (ArH), and 152.9 (Ar); *m/z* 304 (M^+, 4%), 302 (M^+, 4%), 262 (11), 261 (100), 260 (11), 259 (98), and 165 (10). Further elution gave unchanged benzyl alcohol (**9**) (0.77 g, 39%).

Radical Cyclisation of Vinyl Ether (**16**).—A solution of the vinyl ether (**16**) (226 mg, 0.75 mmol), Bu_3SnH (435 mg, 1.50 mmol) and 2,2′-azobisisobutyronitrile (AIBN) (10 mg) in dry C_6H_6 (75 ml) was refluxed under N_2 for 4 h. The reaction mixture was evaporated *in vacuo* and flash chromatography of the crude product gave an oil which was distilled (125—150 °C/0.1 mm) to give a colourless oil (171 mg). G.c.m.s. showed this to be a mixture of four components in a ratio of 10:3:7:2.5 in order of elution. Component 1 was identified as (±)-1-*methyl*-5,6,7-*trimethoxy*-1,3-*dihydroisobenzofuran* (**11**) (see above) on the basis of the ^1H n.m.r. spectrum of the mixture, which showed a doublet at δ 1.50, *J* 6 Hz, due to the methyl group and the mass spectrum: *m/z* 224 (M^+, 21%), 210 (13), 209 (100), and 181 (10). Components 2 and 3 were unidentified tin-containing compounds based on the isotope patterns in the mass spectrum. Component 4 was identified as 5,6,7-*trimethoxy*-3,4-*dihydro*-1H-2-*benzopyran* (**17**) on the basis of the mass spectrum: *m/z* 224 (M^+, 100%), 223 (21), 196 (11), 194 (26), 193 (30), 181 (11), 179 (37), 151 (17), and 91 (10).

3,4-*Diacetoxy*-2-*bromo*-5-*methoxybenzaldehyde* (**19**).—A solution of the dihydroxy benzaldehyde (**18**) (5.00 g, 20.2 mmol), Et_3N (4.50 g, 44.6 mmol), Ac_2O (4.50 g, 44.1 mmol) and DMAP (10 mg, 0.8 mmol) in CH_2Cl_2 (75 ml) under N_2, was stirred at room temperature for 90 min. The reaction mixture was washed with saturated Na_2CO_3 solution, then H_2O, dried and evaporated. Recrystallisation from CH_2Cl_2–light petroleum gave the *aldehyde* (**19**) as colourless spars (5.42 g, 81%), m.p. 125 °C (Found: C, 43.7; H, 3.4. $C_{12}H_{11}BrO_6$ requires C, 43.5; H, 3.35%); δ_H(60 MHz) 2.27 and 2.35 (each 3 H, s, 2 × $COCH_3$), 3.83 (3 H, s, OCH_3), 7.35 (1 H, s, ArH), 10.19 (1 H, s, CHO); δ_C(20 MHz) 20.2 (2 × $COCH_3$), 56.7 (OCH_3), 109.8 (ArH), 113.9, 131.6, 138.7, 142.5, and 152.3 (5 × Ar), 167.0 and 167.3 (2 × CO), and 190.4 (CHO); *m/z* 332 (M^+, 3%), 330 (M^+, 3%), 290 (15), 288 (15), 248 (74), 247 (21), 246 (80), 245 (15), and 43 (100); $\nu_{max.}$(KBr) 1 781, 1 769, and 1 688 cm^{-1}.

3,4-*Diacetoxy*-2-*bromo*-5-*methoxybenzyl Alcohol* (**20**).—To a stirred suspension of the benzaldehyde (**19**) (693 mg, 2.09 mmol) in MeOH (15 ml) under N_2 at 0 °C was added $NaBH_4$ (40 mg, 1.06 mmol). After 30 min the reaction mixture was diluted with H_2O, acidified with 1M H_2SO_4, extracted with CH_2Cl_2, and the combined organic extracts dried and evaporated. Recrystallisation from light petroleum–CH_2Cl_2 afforded the *alcohol* (**20**) as colourless needles (677 mg, 97%), m.p. 138 °C (Found: C, 43.0; H, 4.0. $C_{12}H_{13}BrO_6$ requires C, 43.3; H, 3.9%); δ_H(60 MHz) 2.23 and 2.27 (each 3 H, s, 2 × $COCH_3$), 2.4—2.7 (1 H, br, OH), 3.70 (3 H, s, OCH_3), 4.50 (2 H, s, $ArCH_2$), and 6.95 (1 H, s, ArH); δ_C(20 MHz) 20.3 and 20.4 (2 × $COCH_3$), 56.4 (OCH_3), 64.5 ($ArCH_2$), 106.7 (Ar), 109.3 (ArH), 132.3, 139.1, 141.5, and 151.8 (4 × Ar), 167.8 and 168.0 (2 × *C*O); *m/z* 334 (M^+, 4%), 332 (M^+, 4%), 292 (21), 290 (20), 250 (100), 249 (12), 248 (99), 169 (23), 140 (14), 109 (14), and 43 (85); $\nu_{max.}$(KBr) 3 480, 1 775, and 1 710 cm^{-1}.

3,4-*Diacetoxy*-2-*bromo*-5-*methoxybenzyl Vinyl Ether* (**21**).—A solution of the bromobenzyl alcohol (**20**) (1.93 g, 5.80 mmol), $Hg(OAc)_2$ (200 mg, 0.63 mmol), ethyl vinyl ether (11.4 g, 158 mol) in dry CH_2Cl_2 (10 ml) was refluxed for 16 h under N_2. On cooling the reaction mixture was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$, then H_2O, dried and evaporated. Flash chromatography (EtOAc–light petroleum) of the crude product afforded the *vinyl ether* (**22**) as a colourless oil that crystallised (1.10 g, 53%), m.p. 71—72 °C (Found: C, 46.7; H, 4.3. $C_{14}H_{15}BrO_6$ requires C, 46.8; H, 4.2%); δ_H(300 MHz) 2.30 and 2.36 (each 3 H, s, 2 × $COCH_3$), 3.85 (3 H, s, OCH_3), 4.16 (1 H, dd, J_{BX} 6.8 Hz, J_{AB} 2.4 Hz, H_B of ABX), 4.36 (1 H, dd, J_{AX} 14.3 Hz, J_{AB} 2.4 Hz, H_A of ABX), 4.81 (2 H, s, $ArCH_2$), 6.57 (1 H, dd, J_{AX} 14.3 Hz, J_{BX} 6.8 Hz, H_X of ABX), and 7.07 (1 H, s, ArH); δ_C(75.5 MHz) 20.2 and 20.4 (2 × $COCH_3$), 56.4 (OCH_3), 69.0 ($ArCH_2$), 88.3 ($CHCH_2$), 106.8 (Ar), 109.3 ($CHCH_2$), 132.4, 135.0, and 141.5 (Ar), 151.1 (ArH), 151.6 (Ar), 167.3 and 167.6 (2 × CO); *m/z* 360 (M^+, 1%), 358 (M^+, 1%), 275 (38), 273 (40), 233 (92), 231 (100), and 43 (42); $\nu_{max.}$(KBr) 1 778 cm^{-1}. Further elution gave the unreacted bromobenzyl alcohol (**20**) (0.83 g, 43%).

Radical Cyclisation of the Vinyl Ether (**21**).—A solution of the vinyl ether (**21**) (1.01 g, 2.82 mmol), Bu_3SnH (1.64 g, 5.64 mmol) and AIBN (10 mg) in dry C_6H_6 (260 ml) was refluxed under N_2 for 30 min. The reaction mixture was evaporated *in vacuo* and flash chromatography (30% EtOAc–light petroleum) of the crude product gave a colourless oil that slowly crystallised (688 mg, 87%). G.c.–m.s. and ^1H n.m.r. indicated the product to be a mixture of (**22**) and (**23**) in a ratio of 70:30 respectively. Radial chromatography (EtOAc–light petroleum) of the mixture (688 mg) using two Chromatotrons in series, with fractions being analysed by h.p.l.c., achieved partial separation. Early fractions afforded (±)-6,7-*diacetoxy*-5-*methoxy*-1-*methyl*-1,3-*dihydroisobenzofuran* (**22**) (410 mg) which crystallised from CH_2Cl_2–light petroleum as colourless needles, m.p. 114—115 °C (Found: C, 59.8; H, 5.7. $C_{14}H_{16}O_6$ requires C, 60.0; H, 5.75%); δ_H(300 MHz) 1.41 (3 H, d, *J* 6.3 Hz, CH_3), 2.29 and 2.29 (each 3 H, s, 2 × $COCH_3$), 3.81 (3 H, s, OCH_3), 5.00 and 5.11 (2 H, ddABq, $J_{3cis,4}$ 0.9 Hz, $J_{3trans,4}$ 1.0 Hz, $J_{1,3cis}$ 1.9 Hz, $J_{1,3trans}$ 2.6 Hz, $J_{3,3gem}$ 12.2 Hz, $ArCH_2$), 5.29 (1 H, ddq, $J_{1,4}$ < 1 Hz, $J_{1,3trans}$ 2.6 Hz, *J* 6.3 Hz, ArCH), and 6.72 (1 H, s, ArH); δ_C(75.5 MHz) 20.3 and 20.7 (2 × $COCH_3$ and CH_3), 56.4 (OCH_3), 72.7 ($ArCH_2$), 79.4 (ArCH), 102.6 (ArH), 127.6, 131.2, 137.6, 138.1, and 152.3 (5 × Ar), 167.6 and 168.0 (2 × CO); *m/z* 280 (M^+, 1%), 221 (10), 196 (11), 182 (10), 181 (100), 178 (22), and 43 (18); $\nu_{max.}$(KBr) 1 774 cm^{-1}.

Later fractions afforded 7,8-*diacetoxy*-6-*methoxy*-3,4-*dihydro*-1H-*benzo*-2-*pyran* (**23**) (173 mg) which crystallised from CH_2Cl_2–light petroleum as colourless needles, m.p. 114—116 °C (Found: C, 60.0; H, 5.7. $C_{14}H_{16}O_6$ requires C, 60.0; H, 5.75%); δ_H(300 MHz) 2.30 and 2.31 (each 3 H, s, 2 × $COCH_3$), 2.57 (2 H, t, *J* 5.7 Hz, $ArCH_2CH_2$), 3.79 (3 H, s, OCH_3), 3.92

(2 H, t, *J* 5.7 Hz, CH_2CH_2O), 4.72 (2 H, d, *J* 0.8 Hz, $ArCH_2O$), and 6.51 (1 H, s, ArH); δ_C(75.5 MHz), 20.3 (2 × $COCH_3$), 22.5 ($ArCH_2CH_2$), 56.2 (OCH_3), 64.6 and 67.5 (CH_2CH_2O and $ArCH_2$), 105.8 (ArH), 119.1, 130.5, 133.5, 141.5, 150.3 (5 × Ar), 168.0 and 168.1 (2 × CO); *m/z* 280 (M^+, 3%), 238 (25), 197 (10), 196 (100), 195 (16), 168 (13), 167 (11), 166 (39), and 43 (22); $\nu_{max.}$(KBr) 1 765 cm^{-1}.

(±)-1,3-*Dihydro*-6-*methoxy*-3-*methylisobenzofuran*-4,5-*diol* [(±)-*Curvulol*] (**24**).—A solution of (**22**) (111 mg, 0.40 mmol) in 1% KOH–MeOH (w/v) (10 ml) was stirred under N_2 for 10 min. The reaction mixture was diluted with H_2O, acidified with 2M HCl, extracted with CH_2Cl_2, dried and evaporated to give pale pink crystals (74 mg, 95%), m.p. 195—197 °C (softened at 180 °C) (lit.,[4] 204 °C for optically active material) (Found: C, 60.6, H, 6.2. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.2%); δ_H(300 MHz; [$^2H_6$]DMSO) 1.35 (3 H, d, *J* 6.2 Hz, CH_3), 3.74 (3 H, s, OCH_3), 4.79 and 4.92 (2 H, ddABq, $J_{1cis,7}$ 0.8 Hz, $J_{1trans,7}$ 0.9 Hz, $J_{1,3cis}$ 1.4 Hz, $J_{1,3trans}$ 2.8 Hz, $J_{3,3gem}$ 11.6 Hz, $ArCH_2$), 5.21 (1 H, ddq, $J_{1,4}$ <1 Hz, $J_{1,3cis}$ 1.4 Hz, $J_{1,3trans}$ 2.8 Hz, *J* 6.2 Hz, ArCH), and 6.37 (1 H, s, ArH); δ_C(75.5 MHz; [$^2H_6$]DMSO) 21.0 (CH_3), 56.0 (OCH_3), 71.8 ($ArCH_2$), 78.6 (ArCH), 95.7 (ArH), 122.4, 129.0, 132.8, 140.2, and 148.6 (5 × Ar); δ_H(300 MHz; [$^2H_5$]pyridine) 1.83 (3 H, d, *J* 6.2 Hz, CH_3), 3.75 (3 H, s, OCH_3), 5.15 (2 H, m, $ArCH_2$), 5.80 (1 H, m, ArCH), and 6.45 (1 H, s, ArH); δ_C(75.5 MHz, [$^2H_5$]pyridine) 21.9 (CH_3), 56.4 (OCH_3), 73.1 ($ArCH_2$), 80.3 (ArCH), 96.0 (ArH), 124.0, 130.0, 134.9, 142.5, and 149.8 (5 × Ar); *m/z* 196 (M^+, 23%), 181 (100), and 153 (15); $\nu_{max.}$(KBr) 3 420, 3 400, 3 200, 1 633, and 1 608 cm^{-1}.

(±)-6-*Methoxy*-3-*methyl*-1,3-*dihydroisobenzofuran*-4,5-*dione* (**25**).—To a stirred suspension of (±)-curvulol (**24**) (136 mg, 0.69 mmol) in dry ether (2 ml) was added a solution of *o*-chloranil (171 mg, 0.69 mmol) in dry ether (4 ml) and the reaction mixture was cooled to −20 °C. After 10 min the product was collected by filtration and dried under vacuum to give the *quinone* as a black crystalline solid (82 mg, 61%), m.p. 108—110 °C. This material was unstable in solution, and satisfactory microanalytical data could not be obtained; δ_H(300 MHz) 1.44 (3 H, d, *J* 6.3 Hz, CH_3), 3.82 (3 H, s, OCH_3), 4.82 and 4.92 (2 H, ddABq, $J_{1,7}$ <1 Hz, $J_{1,3cis}$ 3.7 Hz, $J_{1,3trans}$ 5.2 Hz, $J_{3,3gem}$ 17.8 Hz, $ArCH_2$), 5.20 (1 H, ddq, $J_{1,3cis}$ 3.7 Hz, $J_{1,3trans}$ 5.2 Hz, *J* 6.3 Hz, ArCH), and 5.90 (1 H, s, ArH); δ_C(75.5 MHz) 20.7 (CH_3), 56.4 (OCH_3), 74.3 ($ArCH_2$), 80.7 (ArCH), 101.2 (ArH), 131.4, 153.5, and 154.9 (3 × Ar), 172.7 and 176.7 (2 × CO); *m/z* 196 [($M + 2^+$), 12%], 194 (M^+, 30%), 192 (14), 181 (54), 166 (31), 153 (14), 151 (95), 150 (100), 149 (16), 137 (13), 124 (53), 123 (44), 122 (18), 121 (52), 108 (28), 107 (12), 95 (28), 94 (14), 93 (11), 83 (26), 80 (12), 79 (23), 77 (19), 69 (32), 68 (10), 67 (23), 66 (18), 65 (40), 63 (14), 55 (18), 53 (13), 52 (17), 51 (43), 44 (12), 43 (52), and 41(18); $\nu_{max.}$(KBr) 1 709, 1 659, 1 630, and 1 576 cm^{-1}.

6-*Methoxy*-3-*methylisobenzofuran*-4,5-*dione* (*Albidin*) (**1**).—A solution of (±)-curvulol (**24**) (93 mg, 0.48 mmol), and DDQ (227 mg, 1.00 mmol) in dry dioxane (5 ml) was refluxed for 1.5 h under N_2. The solvent was removed under reduced pressure and the residue subjected to radial chromatography (10% MeOH–$CHCl_3$) to afford *albidin* (**1**) as red crystals of indefinite m.p. (28 mg, 30%); δ_H(300 MHz) 2.65 (3 H, s, CH_3), 3.80 (3 H, s, OCH_3), 6.50 (1 H, s, CH), and 7.33 (1 H, s, CH); δ_C(75.5 MHz) 14.4 (CH_3), 55.9 (OCH_3), 105.4 (ArH), 116.2, 119.4, 138.2, 152.3, and 165.5 (Ar), and 174.3 and 178.2 (CO); *m/z* 192 (M^+, 100%), 164 (16), 149 (41), 135 (39), 121 (46), 93 (14), 84 (17), 79 (24), 65 (40), 64 (11), 63 (13), 51 (10), 44 (17), and 43 (16); $\nu_{max.}$(KBr) 3 115, 3 085, 1 695, 1 665, 1 645, 1 618, 1 592, 1 552, 1 059, 912, 872, and 808 cm^{-1}.

These spectra are identical with those reported.[1] In addition the ^1H n.m.r., i.r., and mass spectra of an authentic sample of natural albidin, measured on our instruments, were identical with those of the synthetic material. The R_F values of synthetic and natural material, measured in 3 different solvent systems, were also identical.

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