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3,6-DIMETHOXYBENZOCYCLOBUTENONE: A REAGENT FOR QUINONE SYNTHESIS

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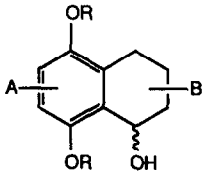
Abstract: 3,6-Dimethoxybenzocyclobutenone **4** is prepared in four efficient steps from 2,5-dimethoxybenzoic acid **8**. The derived benzocyclobutenol **13** undergoes electrocyclic ring opening at 110 - 115 °C to give the hydroxy-*o*-quinone dimethide **21**, which reacts with dienophiles to give 5,8-dimethoxy-1,2,3,4-tetrahydro-1-naphthol derivatives stereoselectively. Since the ketone **4** can be functionalised at C-5 using electrophiles and at C-2 *via* homolytic bromination, the ring opening and cycloaddition sequence offers a flexible route to linear fused hydroquinone and quinone derivatives. In model studies, the benzocyclobutenol derivative **48** underwent thermal electrocyclic ring opening and intramolecular cycloaddition to give **49**, while the analogous reaction with **52** failed due to adverse steric effects during the cycloaddition step. In photochemical experiments, attempts to generate the silyl ether **57** by *in situ* silylation of the dienol **55** and to prepare the benzocyclobutenol **62** *via* irradiation of the *o*-phthalaldehyde monoacetal **60** were unsuccessful.

Because of their widespread natural occurrence and biological activity, quinone and hydroquinone derivatives are important targets for organic synthesis. Linear fused systems of the form **1** have received particular attention in recent years due to the inclusion of this part-structure in the aglycones of the anthracycline anticancer agents, *e.g.* daunomycinone **2** and adriamycinone **3**,[1] and our interest in this general area prompted us to seek an intermediate capable of serving as the common



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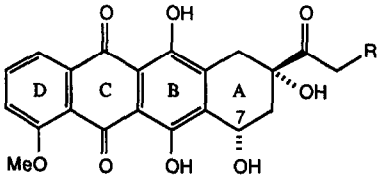
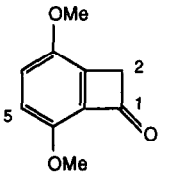


2 R = H
3 R = OH



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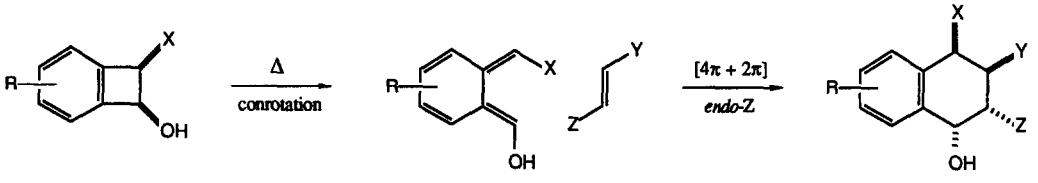


5 **6** **7**

Scheme 1

precursor of a variety of unsymmetrical quinone derivatives. We considered that 3,6-dimethoxybenzocyclobutenone **4** might be especially useful in such a role because of its *peri*-oxygenation pattern, which matches that found in many natural products derived from polyketide biosynthesis,[2] including the anthracyclinones **2** and **3**.

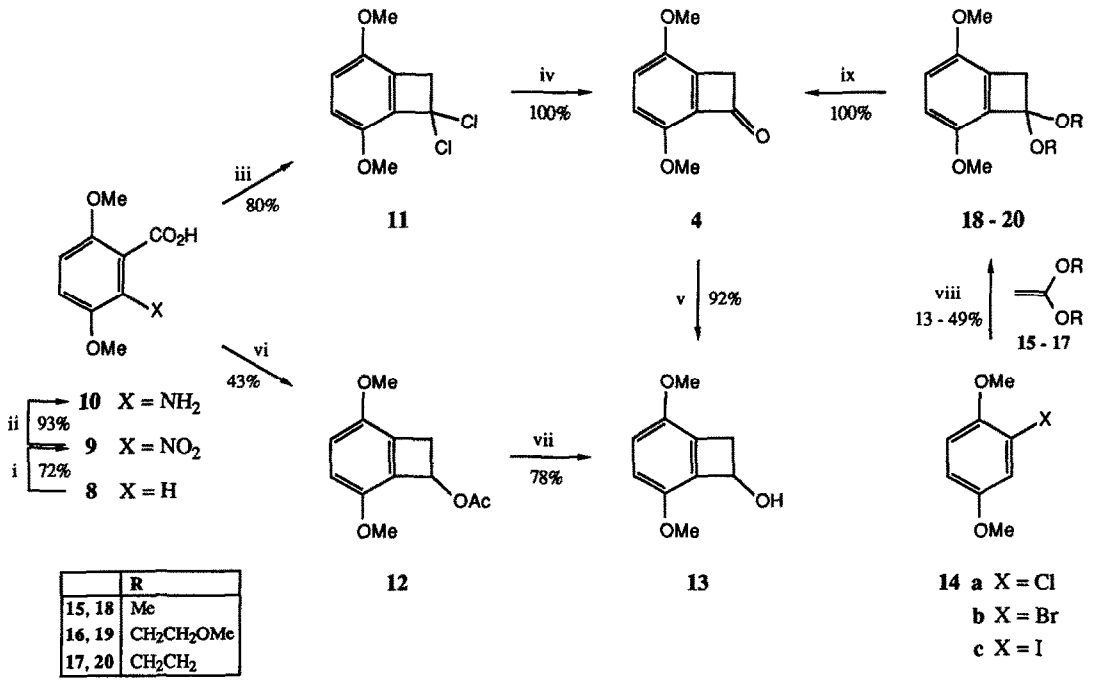
Since they first became widely available some thirty years ago, benzocyclobutenes have been the subject of various theoretical and synthetic studies,[3] and benzocyclobutenols **5** have emerged as particularly significant because their thermal electrocyclic ring-opening reactions proceed stereoselectively under mild conditions (80 - 140 °C) to give the corresponding (*E*)-hydroxy-*o*-quinone dimethides **6**, which can function as electron-rich dienes in [4π + 2π] cycloadditions (Scheme 1).[4]

Since the major products **7** of these reactions derive from *endo*-addition of the dienophile to the diene,[5,6] the combination of selective electrocyclic and cycloaddition processes offers a stereocontrolled route to hydroxytetralins and their homologues. To exploit the benzocyclobutenone **4** in quinone synthesis,[7] nucleophilic addition to C-1 should provide a series of 3,6-dimethoxybenzocyclobutenols for use as in Scheme 1, and this series might be extended through prior functionalisation of C-2 or C-5 using radical or electrophilic reagents respectively, or *via* annulation of the aromatic ring using electrophilic substitution or oxidative demethylation - Diels-Alder cycloaddition methods. In the context of anthracycline synthesis,[8] the sequence in Scheme 1 might be used to construct the A-ring of aglycone precursors complete with the desired 7-hydroxyl function, the introduction of which can otherwise be problematic.[9] With these principles in mind we examined some of the chemistry of 3,6-dimethoxybenzocyclobutenone **4** and related systems, and herein describe in detail some of our findings.[10]

3,6-Dimethoxybenzocyclobutenone **4** was first described by McOmie and coworkers in 1980.[11] Their procedure involved the [2 + 2] cycloaddition of 3,6-dimethoxybenzyne, generated *via* diazotisation of 2-amino-3,6-dimethoxybenzoic acid **10**, to 1,1-dichloroethylene, followed by silver-assisted hydrolysis of the resulting dichloride **11** (26% over two steps). We found the first of these steps troublesome, but the alternative conditions used by Dürr and coworkers in an analogous sequence[12] proved both consistent and effective (80% over two steps), making the ketone **4** available from 2,5-dimethoxybenzoic acid **8** in four steps as shown in Scheme 2. Trapping the aryne with vinyl acetate gave the adduct **12** in modest yield, and 3,6-dimethoxybenzocyclobutenol **13** could be obtained *via* hydrolysis of the acetate **12** or, more efficiently, borohydride reduction of the ketone **4**.

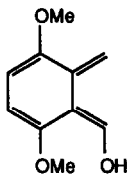
Arynes generated by dehydrohalogenation of haloarenes can be trapped with ketene acetals to give benzocyclobutenone acetals,[13] but we found this method limited as a source of the ketone **4** (Scheme 2). On a 10 millimole scale the 1-halo-2,5-dimethoxybenzenes **14** reacted with sodamide and the keten acetals **15** - **17** to give the corresponding benzocyclobutenone acetals **18** - **20** in modest yields, but larger scale runs were inefficient (see Table 1, experimental section). The useful ethylene acetal **20** was thus more efficiently obtained (86% yield) from the ketone **4** and ethylene glycol.

Heating the benzocyclobutenol **13** with dienophiles at 110 - 115 °C gave the desired cycloadducts, identified by comparing their ^{1}H n.m.r. spectra with those of analogues from benzocyclobutenol,[5] and the major product in each case was that expected from *endo*-addition of the dienophile to the *o*-quinone dimethide **21**. With monosubstituted dienophiles the reactions gave single regioisomers but proceeded with varying stereoselectivity. Thus acrylonitrile gave the *endo*-adduct **22**



	R
15, 18	Me
16, 19	CH_2CH_2OMe
17, 20	CH_2CH_2

Scheme 2 *Reagents:* i, conc. HNO_3; ii, H_2, 10% Pd-C; iii, isoamyl nitrite, HCl, then 1,1-dichloroethylene, propylene oxide; iv, dil. H_2SO_4, MeOH; v, $NaBH_4$, EtOH; vi, isoamyl nitrite, HCl, then vinyl acetate, propylene oxide; vii, Amberlyst® 15, MeOH; viii, $NaNH_2$, tetrahydrofuran; ix, dilute H_2SO_4, tetrahydrofuran.



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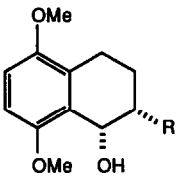
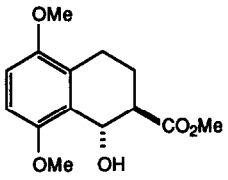


22 R = CN
23 R = CO_2Me



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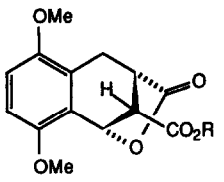
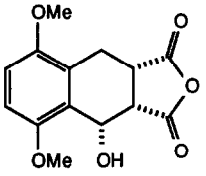


25 R = H
27 R = Me



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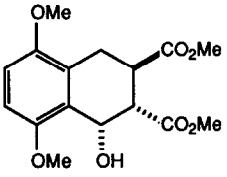

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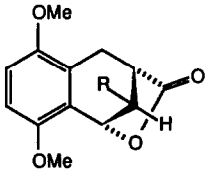
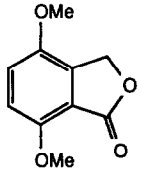


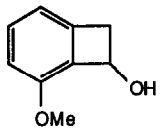
29 R = CO_2Me



30

(80%) as the sole isolated product, whereas methyl acrylate gave the *endo*- and *exo*-isomers **23** and **24** (ratio *ca.* 5:1, total 83%). The reaction of **13** with maleic anhydride furnished the acid lactone **25** (92%), formed *via* lactonisation of the initially-formed *endo*-cycloadduct **26**. Characterisation of **25** [as the methyl ester **27**] confirmed the all-*cis* stereochemistry of the original cycloadduct. Dimethyl fumarate gave a mixture containing mainly the *endo*-cycloadduct **28** (46%), and a minor product assigned the structure **29** (4%), most likely formed *via* the initial *exo*-cycloaddition of the dienophile to **21**, followed by lactonisation. Small amounts of the phthalide **30** were formed in several of the above reactions, indicating the susceptibility of the diene **21** to aerial oxidation. This was confirmed by aeration of a toluene solution of the alcohol **13** under reflux in the absence of a dienophile, which gave the phthalide **30** in 36% yield.[14]

Unless they are generated in the presence of effective trapping agents, hydroxy-*o*-quinone dimethides tend to rearrange *via* hydrogen shifts into *o*-alkyl aromatic carbonyl compounds. A particularly relevant example of this was described by Kametani *et al.*, whose attempts to trap the hydroxy-*o*-quinone dimethide derived from the benzocyclobutenol **31** using an unactivated dienophile gave the aldehyde **32**.[15] By contrast, none of the aldehyde **33** was detected in the reactions of **13** with dienophiles, so the long reaction times (96 h) compared to those of unsubstituted benzocyclobutenol (5 h)[5] would appear to reflect the retarding effect of the 6-methoxy substituent on the electrocyclic process leading to **21**, rather than on its cycloadditions. The successful trapping of *o*-quinone dimethides derived from the ethers **34** and **35**, reported by Franck *et al.*,[16] suggests that protection of the hydroxyl group of the alcohol **13** *via* silylation would provide substrates suitable for use at higher temperatures with less reactive dienophiles.



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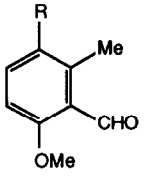
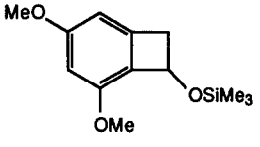


32 R = H
33 R = OMe



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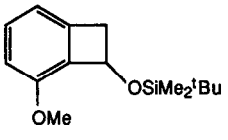
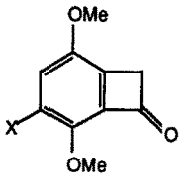


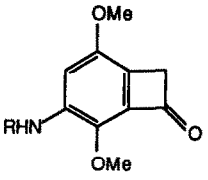
35

The aromatic ring of the ketone **4** reacted selectively with various electrophiles to give 5-substituted analogues. Thus nitration, bromination, and iodination gave good yields of **36**, **37**, and **38** respectively, while catalytic hydrogenation of the nitro compound **36** gave the amine **39**, which was characterised as the amide **40**. These structures were confirmed by converting **36** into the known nitrotoluene **41** ($J_{3,6}$ = 0 Hz), and by preparing the iodide **38** from the amine **39** *via* diazotisation. The benzocyclobutenone **4** could also be functionalised at C-2 using *N*-bromosuccinimide, which gave the monobromide **42** in 82% yield. Electrophilic benzoylation of the aromatic ring of the ketone **4** gave the 5-benzoyl derivative **43** in poor yield, with tin(IV) chloride proving the most effective catalyst of those tested. In contrast, initiating Johnson's

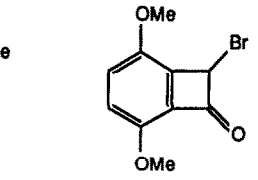
annulation sequence[17] by treatment of the ketone **4** with 3-bromophthalide and tin(IV) chloride gave the desired 5-(3'-phthalido)benzocyclobutenone **44** in 87% yield. However, all attempts to effect the reduction of **44** to the acid **45** were unsuccessful due to the incompatibility of the ketone carbonyl function with the various reducing agents used.



36 X = NO_2
37 X = Br
38 X = I



39 R = H
40 R = COMe



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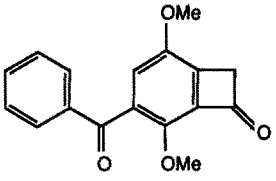
42



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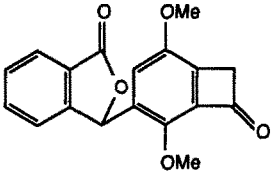

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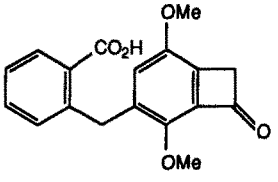
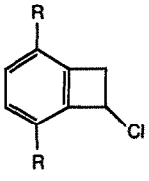
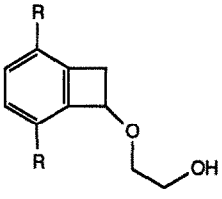


45

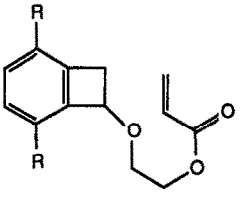
With the aim of using benzocyclobutenols to construct chiral α-tetralones,[18] we envisaged that the sequential attachment of benzocyclobutenyl and dienophilic residues to a chiral glycol might provide a substrate capable of thermally-induced intramolecular cycloaddition, and that under the influence of the topology of the glycol moiety, chirality could be induced in the newly forming ring system. To establish the feasibility of such a process,[19] 1-chlorobenzocyclobutene **46** was converted ($AgBF_4$/ethylene glycol) into the 2-hydroxyethyl ether **47**, which on acryloylation furnished the ester **48**. Although as a neat oil **48** readily polymerised on standing, in solution at 100 - 110 °C it was transformed into the *cis*-fused tricycle **49** ($J_{1,2}$ = 3 Hz) in 51% yield. This was encouraging, since it was anticipated that the use of a less flexible (*e.g.* bicyclic) glycol would render the intramolecular cycloaddition entropically more favourable. The sequence was repeated using the chloride **50** to prepare the acrylate **52**, but thermolysis of the latter gave the aldehyde **33** rather than the desired product **53**, indicating that *peri* interactions within the developing *o*-quinone dimethide are in this instance prohibitive.



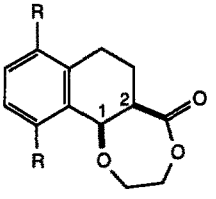
46 R = H
50 R = OMe



47 R = H
51 R = OMe



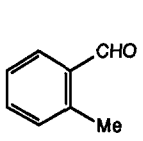
48 R = H
52 R = OMe



49 R = H
53 R = OMe

We briefly investigated the possibility of using photoenolisation[6,20] as a source of benzocyclobutenes. Irradiation of 2-methylbenzaldehyde **54** induces a 1,5-hydrogen shift which leads to the formation of the 'photoenol' **55**, which in thermal equilibrium with benzocyclobutenol **56**.[21] Since photoenols generated from aliphatic α,β-unsaturated ketones can be trapped by *in situ* silylation,[22] we reasoned that photolysis of **54** in the presence of a silylating agent might furnish the ether **57**. However, irradiation of the aldehyde **54** in the presence of *O,N*-bis(trimethylsilyl)acetamide led to its consumption without the detectable formation of the silyl ether **57**.[23] A second model was based on the relative stability of the acetal **58** towards thermal electrocyclic ring opening.[24] The formation of the derived *o*-quinone dimethide **59** requires an electron donor [oxygen] atom to undergo 'inward' conrotation [*i.e.* adopt the (*Z*)-configuration] during the electrocyclic process. Since this is electronically disfavoured,[24,25] it might be anticipated that irradiating a monoacetal of *o*-phthalaldehyde[26] such

as **60** would generate, *via* the 1,4-biradical **61**, an equilibrating mixture of **62** and **63** in which the former would accumulate due to its thermal stability. The photochemistry of the aldehyde **60** was therefore studied, but irradiation failed to produce any of the alcohol **62**, an authentic sample of which had been prepared *via* the benzocyclobutenones **64** and **65**. Given the sensitivity of the photoenolisation process to conformational effects,[6,20] the photochemical properties of other *o*-phthalaldehyde monoacetals require investigation before the behaviour of **60** can be properly explained.



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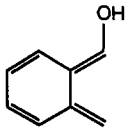

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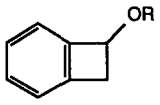
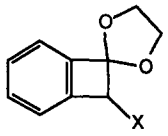
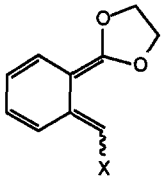


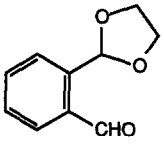
56 R = H
57 R = $SiMe_3$



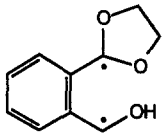
58 R = H
62 R = OH



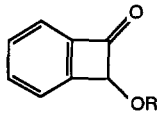
59 R = H
63 R = OH



60



61



64 R = COMe
65 R = H

EXPERIMENTAL

M.p.s are uncorrected. Unless otherwise stated, i.r. spectra were of liquid paraffin mulls on sodium chloride plates, recorded on Perkin-Elmer 297 or 1710FT spectrometers. N.m.r. spectra were measured for solutions in deuteriochloroform unless otherwise indicated, with tetramethylsilane as the internal standard, on Varian EM 360 (^{1}H at 60 MHz), Varian CFT-20 (^{1}H at 80 MHz, ^{13}C at 20 MHz), Perkin-Elmer R32 (^{1}H at 90 MHz), or Bruker AC300 (^{1}H at 300 MHz) instruments. Mass spectra were measured on a Kratos MS30 instrument with a 70 eV electron impact source, and the peak abundances are quoted as a percentage of the base peak. H.p.l.c. was carried out on a Waters 6000 Series system.

Starting materials and solvents were routinely purified by conventional techniques.[27] Distillation of liquid products was performed using a Kugelröhr bulb-to-bulb apparatus, and the temperatures quoted are those of the oven. Organic solutions were dried using anhydrous magnesium sulphate and concentrated by rotary evaporation. Analytical thin layer chromatography (t.l.c.) was carried out on Camlab Polygram SIL G/UV_{254} silica gel or ALOX N/UV_{254} plates. Preparative (column) chromatography was carried out using 60H silica gel (Merck 7736 and hand-bellows pressure, or Merck 9385 and the flash technique[28]), or using Camag 100 - 250 mesh alumina. Compositions of solvent mixtures are quoted as ratios of volume. 'Petroleum' refers to light petroleum, b.p. 40 - 60 °C, unless otherwise stated. 'Ether' refers to diethyl ether.

2,5-Dimethoxybenzoic acid **8**. - Although commercially available (Lancaster Synthesis 3234), oxidation of the corresponding aldehyde is more economical. To a mechanically stirred suspension of 2,5-dimethoxybenzaldehyde (24.9 g, 0.15 mol) in water (400 ml) at 80 °C was added dropwise a solution of potassium permanganate (33.75 g, 0.21 mol) in water (675 ml). After the addition was complete, the mixture was stirred for a further 1 h at 80 °C and then made alkaline by the addition of 10% aqueous potassium hydroxide. The mixture was then filtered while hot, and the residue washed with hot water (3 x 50 ml). The filtrate and washings were combined, cooled, and acidified with concentrated hydrochloric acid. The solid (19.2 g, 70%) was collected on a filter and crystallised from ethyl acetate - petroleum, affording the pure title compound **8** as colourless crystals, m.p. 74 - 75 °C (lit.[29] 78 - 79.5 °C). When the filtrate after acidification was extracted with dichloromethane, evaporation of the extract yielded a further portion (4.2 g, 15%) of the desired product.

3,6-Dimethoxy-2-nitrobenzoic acid **9**.[30] - With continuous stirring and cooling to 0 - 2 °C, finely powdered 2,5-dimethoxybenzoic acid **8** (5.0 g, 27.5 mmol) was added in portions over 30 min to concentrated nitric acid (d 1.42; 20 ml). After the addition the mixture was kept stirring at 0 - 2 °C for a further 3 h, and then poured into ice-water (250 ml). The yellow precipitate was filtered off, washed with cold water, and then crystallised from hot water (*ca.* 300 ml), ethyl acetate - petroleum (b.p. 60 - 80 °C), and again water, giving the title compound **9** (4.5 g, 72%) as yellow needles, m.p. 190 - 192 °C (lit.[30] 194 °C); δ (60 MHz, d_6-DMSO) 3.83 (3 H, s, OMe), 3.87 (3 H, s, OMe), 6.8 (2 H, s, 4-H, 5-H), and 12 - 14 (1 H, br. s, OH).

2-Amino-3,6-dimethoxybenzoic acid **10**. - 3,6-Dimethoxy-2-nitrobenzoic acid **9** (25.2 g, 0.11 mol) and 10% Pd-C (2 g) in ethanol (500 ml) was hydrogenated (50 atm. H_2) for 6 h. The catalyst was removed by filtration and the solvent evaporated under reduced pressure to give the crude aminoacid, which was freed from traces of the 4-amino isomer by chromatography over silica gel. Elution with ether gave the title compound **10** (20.4 g, 93%), m.p. 96 - 97 °C (toluene - petroleum) (lit.[30] 97 °C); ν_{max} 3470, 3350, and 1690 cm^{-1}.

1,1-Dichloro-3,6-dimethoxybenzocyclobutene **11**. - **CAUTION** - DIAZONIUM SALTS ARE POTENTIALLY EXPLOSIVE. READ THE INFORMATION IN REFERENCE 31. USE A SAFETY SCREEN, PLASTIC BÜCHNER FUNNEL, AND PLASTIC SPATULA. In our hands the published method[11] gave yields of up to 15%; the following procedure was adapted from that described by Dürr *et al.*:[12] To a stirred slurry of 2-amino-3,6-dimethoxybenzoic acid **10** (1.97 g, 10 mmol) in absolute ethanol (20 ml) at 4 °C was added dropwise concentrated hydrochloric acid (1.0 ml), followed by isoamyl nitrite (97%; 2.5 ml, 18 mmol). The dark solution was stirred for 10 min in an ice bath, and then cold dry ether (20 ml) was added and the mixture stirred for a further 5 min. The brown crystals of the benzenediazonium-2-carboxylate hydrochloride were collected on a plastic Büchner funnel and washed with cold dry ether (10 ml), using minimal suction for draining so as to prevent complete drying. The salt, still moist with solvent, was immediately transferred to a flask and mixed with 1,2-dichloroethane (20 ml), propylene oxide (2 ml), and 1,1-dichloroethylene (7 ml). The mixture was then heated under reflux for 5 h, further portions of propylene oxide (1 ml) and 1,1-dichloroethylene (3 ml) were added, and the heating was continued overnight. The reaction mixture was then cooled and filtered, and the residue on evaporation of the filtrate was distilled (102 - 104 °C; 0.1 mmHg) to give the *title compound* **11** (1.87 g, 80%) as a pale yellow oil which later solidified. The analytical sample had m.p. 49 - 50 °C (petroleum) (Found: C, 51.4; H, 4.2. $C_{10}H_{10}Cl_2O_2$ requires C, 51.5; H, 4.3%); ν_{max} 1585 (w) and 1260 cm^{-1}; δ (60 MHz) 3.77 (3 H, s, OMe), 4.03 (3 H, s, OMe), 4.13 (2 H, s, 2-H_2), and 6.77 (2 H, br. s, 4-H, 5-H); M^+, 236 ($^{37}Cl_2$), 234 (^{37}Cl, ^{35}Cl), and 232 ($^{35}Cl_2$). Repeating the above procedure on a 60 mmol scale gave **11** in 72% yield.

3,6-Dimethoxybenzocyclobuten-1(2H)-one **4**. - 1,1-Dichloro-3,6-dimethoxybenzocyclobutene **11** (400 mg, 1.72 mmol) in a mixture of 3% sulphuric acid (3 ml) and methanol (3 ml) was heated under reflux for 24 h and then cooled. The methanol was evaporated under reduced pressure and the residue extracted with ether (3 x 20 ml). The extract was washed with saturated aqueous sodium hydrogen carbonate and water, dried, and evaporated, giving the title compound **4** (306 mg, 100%), m.p. 107 - 108 °C (petroleum) (lit.[11] 107 - 108 °C); δ (60 MHz) 3.90 (3 H, s, OMe), 4.05 (2 H, s, 2-H_2), 4.09 (3 H, s, OMe), 6.75 (1 H, d, *J* 9 Hz, 5-H), and 7.00 (1 H, d, *J* 9 Hz, 4-H).

1-Acetoxy-3,6-dimethoxybenzocyclobutene **12**. - This was prepared *via* the method used for 1,1-dichloro-3,6-dimethoxybenzocyclobutene **11**. The benzenediazonium-2-carboxylate hydrochloride [from 2-amino-3,6-dimethoxybenzoic acid **10** (3.94 g, 20 mmol)], still moist with solvent, was mixed with 1,2-dichloroethane (40 ml), propylene oxide (3 ml), and vinyl acetate (15 ml). The mixture was heated under reflux for 5 h, a further portion of propylene oxide (3 ml) was added, and the reflux was continued overnight. The reaction mixture was cooled and filtered, and the residue on evaporation of the filtrate was passed through a short column of silica gel using dichloromethane, giving the *title compound* **12** (43%), which formed colourless crystals, m.p. 55 °C (petroleum) (Found: C, 64.8; H, 6.3. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%); ν_{max} 1720 cm^{-1}; δ (60 MHz) 2.13 (3 H, s, COMe), 3.20 (1 H, dd, *J* 2, 14 Hz, 2-H *cis* to OAc), 3.77 (3 H, s, OMe), 3.77 (1 H, dd, *J* 5, 14 Hz, 2-H *trans* to OAc), 3.80 (3 H, s, OMe), 6.06 (1 H, dd, *J* 2, 5 Hz, 1-H), and 6.73 (2 H, s, 4-H, 5-H); M^+, 222.

3,6-Dimethoxybenzocyclobuten-1-ol **13**. - (i) A solution of 3,6-dimethoxybenzocyclobutenone **4** (356 mg, 2.0 mmol) in ethanol (20 ml) was added dropwise to a stirred suspension of sodium borohydride (760 mg, 20 mmol) in ethanol (10 ml) at room temperature. The reaction mixture was stirred for a further 4 h, and then added to concentrated hydrochloric acid (10 ml) and diluted with water (50 ml). The product was extracted with dichloromethane (3 x 20 ml) and the extract washed with water (2 x 20 ml) and dried. The residue on evaporation was crystallised from ether - petroleum, giving the *title compound* **13** (332 mg, 92%) as colourless crystals, m.p. 85 - 86 °C (Found: C, 66.8; H, 6.7. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.7%); ν_{max} 3410 and 1580 cm^{-1}; δ (60 MHz) 2.85 (1 H, s, OH), 3.03 (1 H, dd, *J* 2, 14 Hz, 2-H *cis* to OH), 3.65 (1 H, dd, *J* 5, 14 Hz, 2-H *trans* to OH), 3.78 (3 H, s, OMe), 3.88 (3 H, s, OMe), 5.27 (1 H, dd, *J* 2, 5 Hz, 1-H), and 6.90 (2 H, s, 4-H, 5-H); M^+, 180.

(ii) A solution of 1-acetoxy-3,6-dimethoxybenzocyclobutene **12** (1.11 g, 5.0 mmol) in methanol (25 ml) was stirred with Amberlyst® 15 ion exchange resin (2.25 g) at room temperature overnight. The mixture was then filtered, the filtrate was evaporated, and the residue was chromatographed, eluting with ether - petroleum, to obtain the alcohol **13** (0.7 g, 78%).

2-Chloro-1,4-dimethoxybenzene **14a**. - A stirred mixture of 2-chlorohydroquinone (36.1 g, 0.25 mol), anhydrous potassium carbonate (107.5 g, 0.78 mol), and dimethyl sulphate (75 ml, 0.79 mol) in dry acetone (900 ml) was heated under reflux for 5 h, cooled, treated with 2M ammonium hydroxide (350 ml), and stirred at room temperature for 0.5 h. After evaporating the acetone, the residue was extracted with ether and the extract washed with M hydrochloric acid, water, and brine, and dried. Evaporation of the ether and distillation of the residue (128 - 130 °C, 18 mmHg) (lit.[32] 123 - 124 °C, 15 mmHg) gave the title compound **14a** (41.1 g, 95%) as a colourless oil, δ (60 MHz) 3.73 (3 H, s, OMe), 3.83 (3 H, s, OMe), 6.8 (2 H, m, 5-H, 6-H), and 6.9 (1 H, m, 3-H).

2-Bromo-1,4-dimethoxybenzene **14b**. - This was prepared using the method described by Swenton *et al.*[33]

2-Iodo-1,4-dimethoxybenzene **14c**. - A stirred mixture of 1,4-dimethoxybenzene (4.60 g, 33.3 mmol), periodic acid dihydrate (98%; 1.55 g, 6.7 mmol), and iodine (3.38 g, 13.3 mmol) in the solvent [methanol : water : sulphuric acid (100:20:3), 80 ml][34] was heated to 50 - 55 °C for 1.5 h, after which most of the iodine colour had disappeared. The mixture was then cooled and filtered, and the filtrate extracted with ether. The extract was washed with water and saturated aqueous sodium hydrogen carbonate, dried, evaporated, and the residue distilled (130 - 132 °C, 18 mmHg) (lit.[35] 157 °C, 10 mmHg) to give the title compound **14c** (6.40 g, 73%) as a pink oil, δ (60 MHz) 3.73 (3 H, s, OMe), 3.79 (3 H, s, OMe), 6.8 (2 H, m, 5-H, 6-H), and 7.36 (1 H, d, *J* 2 Hz, 3-H).

1,1,3,6-Tetramethoxybenzocyclobutene **18**. - The following method was based on that used by Stevens and Bisacchi.[13] A mixture of the 2-halo-1,4-dimethoxybenzene **14** (10 mmol), 1,1-dimethoxyethylene **15**[36] (2.5 ml), and sodamide (0.8 g, 20 mmol) in tetrahydrofuran (30 ml) under nitrogen was heated under reflux and the reaction monitored by t.l.c. until the haloarene was no longer detectable. The mixture was then cooled, treated with water, and extracted with ether. The extract was washed with water, dried, evaporated, and the residue distilled (103 - 105 °C, 0.01 mmHg) to obtain the *title compound* **18** as a colourless oil [δ (60 MHz) 3.38 (2 H, s, 2-H_2), 3.50 (3 H, s, OMe), 3.80 (3 H, s, OMe), and 6.70 (2 H, s, 4-H, 5-H)]. Proportionately less solvent was used on the larger scale runs (150 mmol using 100 ml THF), the results of which are shown in Table 1. The acetal **18** was hydrolysed by stirring in tetrahydrofuran - 3% sulphuric acid (4:1) at room temperature for 3 h. Evaporation of the tetrahydrofuran, extraction of the residue with dichloromethane, and evaporation of the extract gave 3,6-dimethoxybenzocyclobutenone **4** (100%).

1,1-Bis(2'-methoxyethoxy)-3,6-dimethoxybenzocyclobutene **19**. - The procedure used was the same as for 1,1,3,6-tetramethoxybenzocyclobutene **18**, but using the ketene acetal **16**[37] (see Table 1). Distillation (160 °C, 0.3 mmHg) gave the *acetal* **19** as a colourless oil.

3,6-Dimethoxybenzocyclobuten-1(2H)-one ethylene acetal **20**. - The procedure used was the same as for 1,1,3,6-tetramethoxybenzocyclobutene **18**, but using the ketene acetal **17**[38] (see Table 1). Distillation (140 °C, 0.2 mmHg) gave the *acetal* **20** as a colourless oil which solidified on standing. The product was identical (t.l.c., n.m.r., m.p.) to that obtained by acetalisation of 3,6-dimethoxybenzocyclobutenone **4** using ethylene glycol (*vide infra*).

TABLE 1 Reactions of haloarenes **14** with sodium amide and ketene acetals.

Haloarene	Scale (mmol)	Ketene acetal	Time (h)	Product	Yield (%)
14a	10	**15**	28	**18**	48
14a	20	**15**	24	**18**	35
14a	50	**15**	24	**18**	31
14a	100	**15**	24	**18**	21
14a	150	**15**	24	**18**	13
14b	10	**15**	22	**18**	47
14c	10	**15**	168[a]	**18**	49
14a	10	**16**	48	**19**	37[b]
14a	100	**16**	48	**19**	21[b]
14a	150	**16**	48	**19**	18[b]
14a	10	**17**	48	**20**	27

a The product **18** was isolated by chromatography over alumina, eluting with ether - petroleum (1:4). Iodoarene **14c** (7%) was also recovered.
b Isolated yield of the ketone **4** after hydrolysis of the acetal **19**.

3,6-Dimethoxybenzocyclobuten-1(2H)-one ethylene acetal **20** *(from the ketone* **4***).* - A mixture of the benzocyclobutenone **4** (0.89 g, 5.0 mmol), ethylene glycol (5 ml), *p*-toluenesulphonic acid (30 mg), and benzene (65 ml) was heated under reflux in a Dean and Stark apparatus for 18 h. The mixture was then cooled, washed with saturated aqueous sodium hydrogen carbonate, water, and brine, and dried. The residue on evaporation was chromatographed, eluting with ether - petroleum (2:3), to obtain the *title compound* **20** (0.95 g, 86%) as a colourless solid. The analytical sample, obtained by distillation (130 - 132 °C, 0.1 mmHg), had m.p. 51 °C (Found: C, 64.8; H, 6.3. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%); δ (60 MHz) 3.50 (2 H, s, 2-H_2), 3.75 (3 H, s, OMe), 3.80 (3 H, s, OMe), 4.07 (4 H, narrow m, 4'-H_2, 5'-H_2), and 6.65 (2 H, ABq, *J* 9 Hz, 4-H, 5-H); M^+, 222.

cis-*1,2,3,4-Tetrahydro-1-hydroxy-5,8-dimethoxy-2-naphthalenecarbonitrile* **22**. - 3,6-Dimethoxybenzocyclobutenol **13** (180 mg, 1.0 mmol) and acrylonitrile (530 mg, 10 mmol) in dry toluene (20 ml) were heated under reflux for 96 h. The mixture was then cooled and the solvent removed under reduced pressure. Chromatography of the residue, eluting with ether - petroleum (3:2), gave the *title compound* **22** (186 mg, 80%), m.p. 143 - 145 °C (ethyl acetate - petroleum) (Found: C, 67.1; H, 6.55; N, 6.1. $C_{13}H_{15}NO_3$ requires C, 66.9; H, 6.5; N, 6.0%); ν_{max} 3500, 2235, and 1595 cm^{-1}; δ_H (90 MHz) 2.0 - 3.2 (4 H, m, 2-H, 3-H, 4-H_2), 3.1 (1 H, br. s, exchanges with D_2O, OH), 3.75 (3 H, s, OMe), 3.81 (3 H, s, OMe), 5.17 (1 H, d, *J* 4 Hz, 1-H), and 6.71 (2 H, s, Ar-H); δ_C 20.43 (t, 3-C), 22.14 (t, 4-C), 32.62 (d, 2-C), 55.53 (q, 2 x OMe), 61.67 (d, 1-C), 107.79 (d, 6-C or 7-C), 109.42 (d, 6-C or 7-C), 120.25 (s, CN), 125.03 (s, 4a-C or 8a-C), 125.37 (s, 4a-C or 8a-C), 150.93 (s, 5-C or 8-C), and 151.24 (s, 5-C or 8-C); M^+, 233.

Methyl cis-*1,2,3,4-tetrahydro-1-hydroxy-5,8-dimethoxy-2-naphthalenecarboxylate* **23** *and methyl* trans-*1,2,3,4-tetrahydro-1-hydroxy-5,8-dimethoxy-2-naphthalenecarboxylate* **24**. - A solution of 3,6-dimethoxybenzocyclobutenol **13** (180 mg, 1.0 mmol) and methyl acrylate (860 mg, 10 mmol) in dry toluene (20 ml) was heated under reflux for 96 h. The mixture was then cooled and the solvent removed under reduced pressure. Chromatography of the residue, eluting with ether - petroleum (3:2), gave the endo *cycloadduct* **23** (186 mg, 70%), m.p. 111 - 113 °C (ethyl acetate - petroleum) (Found: C, 63.1; H, 6.8. $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.8%); ν_{max} 3510, 1705, and 1590 cm^{-1}; δ (60 MHz) 1.9 - 3.3 (5 H, m, 2-H, 3-H, 4-H_2, OH), 3.80 (6 H, s, 2 x OMe), 3.85 (3 H, s, OMe), 5.37 (1 H, d, *J* 3 Hz, 1-H), and 6.72 (2 H, s, 6-H, 7-H); M^+, 266. Another fraction from the column afforded the exo *cycloadduct* **24** (35 mg, 13%), m.p. 91 - 92 °C (ether - petroleum); ν_{max} 3530, 1725, and 1600 cm^{-1}; δ (60 MHz) 1.8 - 3.3 (6 H, m, 2-H, 3-H_2, 4-H_2, OH), 3.77 (6 H, s, 2 x OMe), 3.85 (3 H, s, OMe), 5.35 (1 H, d, *J* 7 Hz, 1-H), and 6.72 (2 H, s, 6-H, 7-H).

1,3,4,5-Tetrahydro-6,9-dimethoxy-3-oxo-1,4-methano-2-benzoxepin-10-carboxylic acid **25**. - A solution of 3,6-dimethoxybenzocyclobutenol **13** (180 mg, 1.0 mmol) and maleic anhydride (103 mg, 1.05 mmol) in dry toluene (20 ml) was heated under reflux for 112 h. The mixture was then cooled and concentrated to one-half of the initial volume to give the *acid lactone* **25** (256 mg, 92%) as a colourless solid, m.p. 214 - 217 °C (dec.). Methylation of the solid as a suspension in

ether - tetrahydrofuran using ethereal diazomethane gave the *methyl ester* **27** (268 mg, 100%), m.p. 164 - 167 °C (ethyl acetate - petroleum) (Found: C, 61.7; H, 5.2. $C_{15}H_{16}O_6$ requires C, 61.6; H, 5.5%); ν_{max} 1780, 1725, and 1260 cm^{-1}; δ_H (90 MHz) 3.0 - 3.15 (3 H, m, 2-H, 4-H_2), 3.38 (1 H, ddd, *J* 1.5, 3, 5 Hz, 3-H), 3.75 (3 H, s, OMe), 3.79 (6 H, s, 2 x OMe), 6.12 (1 H, d, *J* 1.5 Hz, 1-H), and 6.77 (2 H, s, 6-H, 7-H); δ_C 26.83 (t, 4-C), 39.60 (d, 2-C or 3-C), 50.01 (d, 2-C or 3-C), 52.49 (q, OMe), 55.45 (q, OMe), 56.10 (q, OMe), 73.09 (d, 1-C), 109.71 (d, 6-C or 7-C), 111.44 (d, 6-C or 7-C), 122.66 (s, 4a-C or 8a-C), 125.35 (s, 4a-C or 8a-C), 149.60 (s, 5-C or 8-C), 151.60 (s, 5-C or 8-C), 170.78 (s, C=O), and 176.87 (s, C=O); M^+, 292.

Dimethyl 1,2,3,4-tetrahydro-1-hydroxy-5,8-dimethoxy-2,3-naphthalenedicarboxylate **28** *and methyl 1,3,4,5-tetrahydro-6,9-dimethoxy-3-oxo-1,4-methano-2-benzoxepin-10-carboxylate* **29**. - A solution of the benzocyclobutenol **13** (180 mg, 1.0 mmol) and dimethyl fumarate (158.5 mg, 1.1 mmol) in dry toluene (20 ml) was heated under reflux for 96 h. The mixture was then cooled and the solvent removed under reduced pressure. Chromatography of the residue, eluting with ether - petroleum (3:2), gave the *title compound* **28** (148 mg, 46%), m.p. 152 - 154 °C (ethyl acetate - petroleum) (Found: C, 59.3; H, 6.1. $C_{16}H_{20}O_7$ requires C, 59.25; H, 6.2%); ν_{max} 3500, 1740, and 1600 cm^{-1}; δ_H (90 MHz) 2.25 - 2.65 (2 H, m, 4-H, OH), 2.94 (1 H, dd, *J* 4, 12 Hz, 2-H), 3.1 - 3.45 (2 H, m, 3-H, 4-H), 3.76 (9 H, s, 3 x OMe), 3.82 (3 H, s, OMe), 5.40 (1 H, d, *J* 4 Hz, 1-H), and 6.73 (2 H, s, 6-H, 7-H); δ_C 27.06 (t, 4-C), 35.87 (d, 3-C), 47.22 (d, 2-C), 51.72 (q, 2 x OMe), 55.47 (q, 2 x OMe), 62.72 (d, 1-C), 107.82 (d, 6-C or 7-C), 109.35 (d, 6-C or 7-C), 124.21 (s, 4a-C or 8a-C), 125.94 (s, 4a-C or 8a-C), 150.73 (s, 5-C or 8-C), 151.09 (s, 5-C or 8-C), 172.44 (s, C=O), and 175.76 (s, C=O); M^+, 324. Another fraction from the column afforded a colourless compound assigned as the *lactone ester* **29** (12 mg, 4%), m.p. 117 °C (ethyl acetate - petroleum) (Found: C, 61.4; H, 5.5. $C_{15}H_{16}O_6$ requires C, 61.6; H, 5.5%); ν_{max} 1775, 1735, and 1260 cm^{-1}; δ (60 MHz) 2.95 - 3.5 (4 H, m, 2-H, 3-H, 4-H_2), 3.54 (3 H, s, OMe), 3.75 (3 H, s, OMe), 3.80 (3 H, s, OMe), 6.04 (1 H, d, *J* 5.5 Hz, 1-H), and 6.72 (2 H, s, 6-H, 7-H); M^+, 292.

4,7-Dimethoxyphthalide **30**. - 3,6-Dimethoxybenzocyclobutenol **13** (90 mg, 0.5 mmol) was heated under reflux in toluene (10 ml) with a gentle stream of air bubbling through the solution. After 96 h the mixture was cooled, the solvent was evaporated under reduced pressure, and the residue was chromatographed using ether - petroleum (3:2). The solid (35 mg, 36%) thus obtained gave 4,7-dimethoxyphthalide **30** as colourless crystals, m.p. 164 - 165 °C (water) (lit.[39] 169 °C); ν_{max} 1745 cm^{-1}; δ (60 MHz) 3.87 (3 H, s, OMe), 3.93 (3 H, s, OMe), 5.17 (2 H, s, CH_2), 6.87 (1 H, d, *J* 9 Hz, 6-H), and 7.05 (1 H, d, *J* 9 Hz, 5-H).

3,6-Dimethoxy-5-nitrobenzocyclobuten-1(2H)-one **36**. - To a stirred solution of 3,6-dimethoxybenzocyclobutenone **4** (178 mg, 1.0 mmol) in acetic anhydride (1 ml) at 0 °C was added a solution of fuming nitric acid (0.07 ml) in acetic anhydride (0.5 ml), and the mixture was stirred at 0 °C for 3 h. It was then poured into ice-water and the crude product (174 mg, 78%) was collected on a filter and dried. Crystallisation from ethanol gave *3,6-dimethoxy-5-nitrobenzocyclobuten-1(2H)-one* **36** (143 mg, 64%), m. p. 142 - 145 °C (Found: C, 54.0; H, 4.3; N, 6.45. $C_{10}H_9NO_5$ requires C, 53.8; H, 4.1; N, 6.3%); ν_{max} 1765 cm^{-1}; δ (60 MHz) 3.95 (3 H, s, OMe), 4.03 (2 H, s, 2-H_2), 4.27 (3 H, s, OMe), and 7.63 (1 H, s, 4-H); M^+, 223.

5-Bromo-3,6-dimethoxybenzocyclobuten-1(2H)-one **37**. - A stirred solution of 3,6-dimethoxybenzocyclobutenone **4** (178 mg, 1.0 mmol) and iodine (1 mg) in acetic acid - water (95:5, 2 ml) in an ice bath was treated dropwise with a solution of bromine (168 mg, 1.05 mmol) in acetic acid (0.5 ml). The mixture was then allowed to reach room temperature, stirred for 18 h, and poured into water. The solid was collected, dried, and crystallised to obtain the colourless *title compound* **37** (200 mg, 78%), m.p. 109 - 110 °C (ethanol) (Found: C, 46.8; H, 3.6. $C_{10}H_9BrO_3$ requires C, 46.7; H, 3.5%); ν_{max} 1760 cm^{-1}; δ (60 MHz) 3.88 (3 H, s, OMe), 3.98 (2 H, s, 2-H_2), 4.20 (3 H, s, OMe), and 7.23 (1 H, s, 4-H); M^+, 258, 256.

5-Iodo-3,6-dimethoxybenzocyclobuten-1(2H)-one **38**. - (i) A stirred mixture of 3,6-dimethoxybenzocyclobutenone **4** (178 mg, 1.0 mmol), periodic acid dihydrate (98%; 46.5 mg, 0.2 mmol), and iodine (102 mg, 0.4 mmol) in the solvent [methanol : water : sulphuric acid (100:20:3), 2 ml][34] was heated to 60 - 75 °C for 2.5 h, after which most of the iodine colour had disappeared. The mixture was then cooled, treated with water (4 ml), and extracted with dichloromethane. The extract was washed with water, saturated aqueous sodium hydrogen sulphite, and again water, dried, and evaporated. The residue was crystallised from ethanol - water to obtain the colourless *title compound* **38** (210 mg, 69%), m.p. 110 - 112 °C

(ethanol) (Found: C, 39.6; H, 3.1. $C_{10}H_9IO_3$ requires C, 39.5; H, 3.0%); ν_{max} (FT, CH_2Cl_2) 1771, 1481, 1239, and 1049 cm^{-1}; δ (60 MHz) 3.85 (3 H, s, OMe), 3.97 (2 H, s, 2-H_2), 4.18 (3 H, s, OMe), and 7.40 (1 H, s, 4-H); M^+, 304.

(ii) The amine **39** (13 mg, 0.067 mmol) in 2M sulphuric acid (1 ml) was diazotised at 0 - 5 °C in the usual way with sodium nitrite (98%; 5 mg, 0.071 mmol) in water (0.25 ml). After 0.5 h, a solution of potassium iodide (83 mg, 0.5 mmol) in water (0.5 ml) was added. After allowing the mixture to reach room temperature, extraction and evaporation gave the iodide **38** (5 mg, 24%), which was identical (FT i.r., t.l.c.) with the material prepared by iodination of 3,6-dimethoxybenzocyclobutenone **4**, as described above.

5-Amino-3,6-dimethoxybenzocyclobuten-1(2H)-one **39**. - The nitro compound **36** (100 mg, 0.45 mmol) in ethanol (50 ml) was hydrogenated in the presence of platinum(IV) oxide (10 mg) at atmospheric pressure for 4 h. The catalyst was removed by filtration, the filtrate was evaporated, and the residue was crystallised from ether - petroleum to give the *title compound* **39** (70 mg, 81%), m.p. 130 - 131 °C; ν_{max} 3465, 3370, 1745, and 1625 (w) cm^{-1}; δ (90 MHz) 3.70 (2 H, br. s, NH_2), 3.82 (3 H, s, OMe), 3.95 (2 H, s, 2-H_2), 4.13 (3 H, s, OMe), and 6.43 (1 H, s, 4-H); M^+, 193. The N-*acetyl derivative* **40** had m.p. 195 - 197 °C (ethanol) (Found: C, 61.5; H, 5.6; N, 6.0. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.6; N, 6.0%).

2,5-dimethoxy-4-nitrotoluene **41**. - A mixture of the benzocyclobutenone **36** (112 mg, 0.5 mmol), ethanol (2 ml), water (6 ml), and 2M sodium hydroxide (2 ml) was heated under reflux for 10 min, allowed to cool, stirred at room temperature for 4 h, acidified with 2M sulphuric acid (4 ml), and diluted with water (5 ml). The solid was collected, washed with water, and dried *in vacuo*. It was then mixed with quinoline (2 ml) and copper bronze (300 mg) and heated to 240 °C for 1 h. The mixture was then diluted with dichloromethane (15 ml), filtered through silica gel, and the filtrate washed with 6M hydrochloric acid (4 x 15 ml) and brine (15 ml). The residue on evaporation was purified by medium pressure chromatography, eluting with dichloromethane - petroleum (3:2), which gave the title compound **41** (13 mg, 15%) as yellow plates, m.p. 113 - 115 °C (ethanol); δ (60 MHz) 2.27 (3 H, s, Me), 3.85 (3 H, s, OMe), 3.93 (3 H, s, OMe), 6.88 (1 H, s, 6-H), and 7.38 (1 H, s, 3-H). Material prepared[40] by nitration of 2,5-dimethoxytoluene has m.p. 117 - 118 °C (ethanol).

2-Bromo-3,6-dimethoxybenzocyclobuten-1(2H)-one **42**. - A mixture of 3,6-dimethoxybenzocyclobutenone **4** (178 mg, 1.0 mmol), *N*-bromosuccinimide (186 mg, 1.03 mmol), and 2,2'-azobis(2-methylpropionitrile) (20 mg) in carbon tetrachloride (20 ml) was heated under reflux for 3 h, cooled, and filtered. The filtrate was evaporated and the residue purified by chromatography, eluting with ether - petroleum (1:4), to obtain the *title compound* **42** (210 mg, 82%) as a colourless solid, m.p. 99 - 101 °C (petroleum) (Found: C, 46.9; H, 3.7. $C_{10}H_9BrO_3$ requires C, 46.7; H, 3.5%); ν_{max} 1770 cm^{-1}; δ (60 MHz) 4.00 (3 H, s, OMe), 4.07 (3 H, s, OMe), 5.90 (1 H, s, 2-H), 6.85 (1 H, d, *J* 9 Hz, 5-H), and 7.00 (1 H, d, *J* 9 Hz, 4-H); M^+, 258, 256.

5-Benzoyl-3,6-dimethoxybenzocyclobuten-1(2H)-one **43**. - A mixture of 3,6-dimethoxybenzocyclobutenone **4** (178 mg, 1.0 mmol), benzoyl chloride (0.7 ml, 6.0 mmol), and tin(IV) chloride (1.46 ml, 12 mmol) in 1,2-dichloroethane (15 ml) was heated under reflux (oil bath temperature 100 °C) for 4 days. It was then cooled, diluted with water, and extracted with dichloromethane. The extract was washed with water and saturated aq. sodium hydrogen carbonate, and dried. The residue on evaporation was purified by flash chromatography, eluting with ether - petroleum (3:7), giving the *title compound* **43** (76 mg, 27%), m.p. 128 - 129 °C (ether) (Found: C, 72.3; H, 5.0. $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.0%); ν_{max} 1765 and 1655 cm^{-1}; δ (60 MHz) 4.00 (3 H, s, OMe), 4.10 (3 H, s, OMe), 4.17 (2 H, s, 2-H_2), and 7.4 - 8.1 (6 H, m, ArH); M^+, 282.

3,6-Dimethoxy-5-(3'-phthalido)benzocyclobutenone **44**. - Tin(IV) chloride (1.8 g, 6.9 mmol) was added to a solution of 3,6-dimethoxybenzocyclobutenone **4** (178 mg, 1.0 mmol) and 3-bromophthalide[41] (639 mg, 3.0 mmol) in chloroform (5 ml) at room temperature. The reaction mixture was heated under reflux until the starting material was no longer detected by t.l.c. (4 days). The mixture was then cooled, treated with water and hydrochloric acid, and extracted with dichloromethane. The extract was washed with water, dried, and the residue on evaporation crystallised from ethanol, giving the *title compound* **44** (269 mg, 87%), m.p. 222 - 224 °C (Found: C, 69.5; H, 4.35. $C_{18}H_{14}O_5$ requires C, 69.7; H, 4.55%); ν_{max} 1750, 1680, 1280, 1240, 1205, 1040, 1020, and 930 cm^{-1}; δ (60 MHz) 3.85 (3 H, s, OMe), 4.05 (2 H, s, 2-H_2), 4.25 (3 H, s, OMe), 6.78 (2 H, br. s, 4-H, 3'-H), and 7.65 (4 H, m, ArH); M^+, 310.

1-Chlorobenzocyclobutene **46**.[42] - A stirred solution of benzocyclobutenol **56** (120 mg, 1.0 mmol) [prepared from benzocyclobutenone[12] by reduction with sodium borohydride in ethanol using the same procedure as for 3,6-dimethoxybenzocyclobuten-1-ol **13**, above] in ether (2.5 ml) containing pyridine (80 mg, 1.0 mmol) at -10 °C was treated dropwise with a solution of thionyl chloride (60 mg, 0.5 mmol) in ether (0.5 ml). When the addition was complete, the ether was removed under reduced pressure (bath ≤ 20 °C), the residue treated with thionyl chloride (0.8 g), and the mixture heated under reflux for 1 h. It was then cooled in an ice bath, diluted with ether, and treated dropwise with water to destroy the excess of thionyl chloride. The mixture was then extracted with ether, and the extract washed with water, dried, and evaporated. The residue was purified by filtration through a pad of activated charcoal and anhydrous magnesium sulphate, eluting with dichloromethane. Evaporation of the eluate gave the title compound **46** as a colourless oil (133 mg, 96%); δ (60 MHz) 3.30 (1 H, dd, *J* 2, 14 Hz, 2-H *cis* to Cl), 3.77 (1 H, dd, *J* 4, 14 Hz, 2-H *trans* to Cl), 5.28 (1 H, dd, *J* 2, 4 Hz, 1-H), and 7.2 (4 H, m, ArH).

1-(2'-Hydroxyethoxy)benzocyclobutene **47**. - A stirred mixture of 1-chlorobenzocyclobutene **46** (664 mg, 4.8 mmol), silver(I) tetrafluoroborate (1.0 g, 5.1 mmol), and ethylene glycol (5 ml) was heated to *ca.* 50 °C for 3 h. After cooling, the mixture was diluted with ether (50 ml) and water (25 ml), filtered through Celite, and transferred to a separating funnel. The separated ether layer was washed with water (3 x 25 ml) and brine (25 ml), dried, and evaporated. Chromatography of the residue, eluting with ether - petroleum (1:1), gave the *title compound* **47** (490 mg, 62%) as a colourless oil, b.p. 64 - 66 °C (0.01 mmHg) (Found: C, 73.0; H, 7.7. $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.4%); ν_{max} (neat) 3370 cm^{-1}; δ (60 MHz) 2.83 (1 H, s, OH), 3.10 (1 H, dd, *J* 2, 14 Hz, 2-H *cis* to OR), 3.45 (1 H, dd, *J* 4, 14 Hz, 2-H *trans* to OR), 3.71 (4 H, s, 1'-H_2, 2'-H_2), 5.03 (1 H, dd, *J* 2, 4 Hz, 1-H), and 7.2 (4 H, m, ArH); M^+, 164.

2'-(Benzocyclobuten-1"-yloxy)ethyl propenoate **48**. - Propenoyl chloride (362 mg, 4.0 mmol) was added dropwise to a stirred solution of the alcohol **47** (328 mg, 2.0 mmol), triethylamine (404 mg, 4.0 mmol), and 4-dimethylaminopyridine (34 mg, 0.28 mmol) in dichloromethane (2 ml) at 0 °C. The mixture was stirred for a further 75 min at 0 °C, treated with water, and extracted with dichloromethane. The extract was washed with water, dried, and evaporated to give the *title compound* **48** as a colourless oil (274 mg, 63%), which showed a marked tendency to polymerise on standing at room temperature; ν_{max} (neat) 1715, 1400, and 1190 cm^{-1}; δ (60 MHz) 3.10 (1 H, dd, *J* 2, 14 Hz, 2"-H *cis* to OR), 3.48 (1 H, dd, *J* 4, 14 Hz, 2"-H *trans* to OR), 3.7 - 4.0 (2 H, m, 2'-H_2), 4.25 - 4.5 (2 H, m, 1'-H_2), 5.10 (1 H, dd, *J* 2, 4 Hz, 1"-H), 5.6 - 6.7 (3 H, m, 2-H, 3-H_2), and 7.23 (4 H, s, ArH).

The Lactone **49**. - The acrylate ester **48** (30 mg) in deuteriochloroform (0.5 ml) was heated to 100 - 110 °C in a sealed n.m.r. tube for 20 h, and the mixture then removed from the tube and evaporated. The residue was treated with ether and the solution filtered through a small column of silica gel to give on evaporation a white solid (26 mg). This was purified by medium pressure chromatography, eluting with ether - petroleum (3:7), to obtain the pure *lactone* **49** (15.3 mg, 51%), m.p. 261 - 264 °C (dichloromethane - petroleum) (M^+, 218.0935; $C_{13}H_{14}O_3$ requires 218.0943) (Found: C, 71.0; H, 6.3. $C_{13}H_{14}O_3$ requires C, 71.5; H, 6.5%); ν_{max} 1710 and 1295 cm^{-1}; δ (300 MHz) 2.11 - 2.21 (1 H, m), 2.27 - 2.42 (1 H, m), 2.69 - 2.84 (2 H, m), 3.03 (1 H, ddd, *J* 3.0, 6.6, 17.3 Hz, 4-H), 3.62 (1 H, narrow m, 2'-H), 3.82 (2 H, br. m, 1'-H, $CO_2CH_2C\underline{H}_2O$), 4.65 (1 H, dd, *J* 4.4, 12.1 Hz, $CO_2C\underline{H}_2CH_2O$), 4.81 (1 H, d, *J* 3.0 Hz, 1-H), and 7.1 - 7.3 (4 H, m, ArH); m/z 219 (M + 1, 26%), 218 (M^+, 26), 217 (55), 216 (43), 202 (32), 201 (13), 175 (20), 172 (10), 158 (20), 157 (61), 156 (28), 155 (72), 131 (56), 130 (90), 129 (100), 128 (82), 127 (31), 117 (14), 116 (14), 115 (53), 99 (68), and 91 (34).

1-Chloro-3,6-dimethoxybenzocyclobutene **50**. - The procedure was the same as for 1-chlorobenzocyclobutene **46**. Medium pressure chromatography, eluting with ether - petroleum (3:7) gave the *title compound* **50** (80%), b.p. 84 - 86 °C (0.01 mmHg); m.p. 37 - 39 °C; δ (60 MHz) 3.40 (1 H, dd, *J* 2, 14 Hz, 2-H *cis* to Cl), 3.73 (3 H, s, OMe), 3.83 (1 H, dd, *J* 4, 14 Hz, 2-H *trans* to Cl), 3.86 (3 H, s, OMe), 5.34 (1 H, dd, *J* 2, 4 Hz, 1-H), and 6.65 (2 H, br. s, 4-H, 5-H); M^+, 200, 198.

1-(2'-Hydroxyethoxy)-3,6-dimethoxybenzocyclobutene **51**. - The procedure was the same as for 1-(2'-hydroxyethoxy)dimethoxybenzocyclobutene **47**, using the chloro compound **50** (370 mg, 1.86 mmol). Medium pressure chromatography, eluting with ether, gave the *title compound* **51** (246 mg, 59%), m.p. 36 - 38 °C (ether - petroleum)

(Found: C, 64.1; H, 7.2. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.2%); ν_{max} 3300, 3200, and 1255 cm^{-1}; δ (60 MHz) 2.55 (1 H, br. s, exchanges with D_2O, OH), 3.20 (1 H, dd, *J* 2, 14 Hz, 2-H *cis* to OR), 3.50 (1 H, dd, *J* 4, 14 Hz, 2-H *trans* to OR), 3.73 (4 H, s, 1'-H_2, 2'-H_2), 3.79 (3 H, s, OMe), 3.83 (3 H, s, OMe), 5.10 (1 H, dd, *J* 2, 4 Hz, 1-H), and 6.69 (2 H, br. s, 4-H, 5-H); M^+, 224.

2'-(3",6"-Dimethoxybenzocyclobuten-1"-yloxy)ethyl propenoate **52**. - This was prepared as for the analogue **48**, using 1-(2'-hydroxyethoxy)-3,6-dimethoxybenzocyclobutene **51** (402 mg, 1.79 mmol). Medium pressure chromatography, eluting with ether - petroleum (3:7), gave the *title compound* **52** as a colourless oil (368 mg, 74%); ν_{max} (neat) 1720, 1630 (w), 1615 (w), 1590 (w), 1490, 1260, 1190, and 800 cm^{-1}; δ (60 MHz) 3.20 (1 H, dd, *J* 2, 14 Hz, 2"-H *cis* to OR), 3.56 (1 H, dd, *J* 4, 14 Hz, 2"-H *trans* to OR), 3.7 - 4.0 (2 H, m, 2'-H_2), 3.80 (3 H, s, OMe), 3.87 (3 H, s, OMe), 4.25 - 4.5 (2 H, m, 1'-H_2), 5.14 (1 H, dd, *J* 2, 4 Hz, 1"-H), 5.7 - 6.6 (3 H, m, 2-H, 3-H_2), and 6.72 (2 H, s, 4"-H, 5"-H); M^+, 278.

Attempted Intramolecular Cycloaddition of the Acrylate **52**. - The ester **52** (36 mg, 0.13 mmol) in deuteriochloroform (0.5 ml) in a sealed n.m.r. tube and a second portion of **52** (144 mg, 0.52 mmol) in deuteriochloroform (2 ml) in a screw-capped sealed tube were thermolysed at 100 - 110 °C for 10 days and then at 135 - 140 °C for 4 days, monitoring the smaller sample by ^1H n.m.r. and the larger sample by t.l.c. The starting material was then no longer detectable, t.l.c. indicating that several products had been formed. Medium pressure chromatography of the combined products gave one identifiable product, *3,6-dimethoxy-2-methylbenzaldehyde* **33** (18 mg, 15%), m.p. 60 - 62 °C (ethanol - petroleum, b.p. 60 - 80 °C) (Found: C, 66.85; H, 6.8. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.7%); ν_{max} (FT, neat) 1679, 1598, 1479, 1443, 1410, 1371, 1298, 1268, 1191, 1117, 1082, 1022, and 803 cm^{-1}; δ (60 MHz) 2.45 (3 H, s, 2-Me), 3.79 (3 H, s, OMe), 3.85 (3 H, s, OMe), 6.75 (1 H, d, *J* 9 Hz, 5-H), 7.00 (1 H, d, *J* 9 Hz, 4-H), and 10.62 (1 H, s, CHO).

1-(Trimethylsilyloxy)benzocyclobutene **57**. - A mixture of benzocyclobutenol **56** (120 mg, 1.0 mmol) and *O,N*-bis(trimethylsilyl)acetamide (0.25 ml, 1.0 mmol) in acetonitrile (5 ml) was stirred at room temperature for 1.3 h. Evaporation and chromatography of the residue, eluting with ether - petroleum (1:19) gave the trimethylsilyl ether **57** (180 mg, 94%) as a colourless oil; δ (60 MHz) 0.2 (9 H, s, Me_3), 3.07 (1 H, dd, *J* 2, 14 Hz, 2-H *cis* to OR), 3.53 (1 H, dd, *J* 4, 14 Hz, 2-H *trans* to OR), 5.27 (1 H, dd, *J* 2, 4 Hz, 1-H), and 7.19 (4 H, s, ArH).

Irradiation of 2-Methylbenzaldehyde with O,N-bis(trimethylsilyl)acetamide. - 2-Methylbenzaldehyde **54** (480 mg, 4 mmol) and *O,N*-bis(trimethylsilyl)acetamide (5 ml, 20 mmol) in dry acetonitrile (20 ml) was irradiated under nitrogen in a quartz apparatus using a 125 W medium pressure mercury lamp for 16 h. The starting material was consumed, but none of the desired silylether was detectable among the products using ^1H n.m.r. spectroscopy. The result was the same using acetone as solvent, benzophenone (18 mg) as a sensitiser, a pyrex vessel, or a 400 W lamp. Irradiation of **54** in the presence of maleic anhydride under the same conditions as above led to the consumption of the aldehyde and the formation of the expected cycloadduct[21] within 8 h.

2-(1',3'-Dioxolan-2'-yl)benzaldehyde **60**. - This was prepared by a published route.[43] It is advantageous to purify **60** and intermediate acetals *via* chromatography rather than distillation.[44] The aldehyde **60**, which can also be prepared directly from *o*-phthalaldehyde,[45] had δ (60 MHz) 4.1 (4 H, s, 4'-H_2, 5'-H_2), 6.37 (1 H, s, 2'-H), 7.3 - 8.0 (4 H, m, ArH), and 10.4 (1 H, s, CHO).

Irradiation of 2-(1',3'-Dioxolan-2'-yl)benzaldehyde **60**. - A nitrogen-purged solution of the aldehyde **60** (304 mg, 1.7 mmol) in chloroform (10 ml) was irradiated in a pyrex vessel using a Rayonet reactor equipped with sixteen 75 W medium pressure mercury lamps. T.l.c. and ^1H n.m.r. analysis after several hours indicated that a mixture products was forming, but none corresponded to the desired benzocyclobutenol **62**.

2-Hydroxybenzocyclobuten-1(2H)-one ethylene acetal **62**. - A mixture of the ketol **65** (100 mg, 0.75 mmol), Amberlyst® 15 ion-exchange resin (0.2 g), benzene (25 ml), and ethylene glycol (1 ml) was heated under reflux in a Dean and Stark apparatus for 4 h, cooled, diluted with ether (25 ml), and filtered. The filtrate was washed with water (3 x 25 ml) and brine (25 ml), dried, and evaporated, and the residue dried *in vacuo* to give the *title compound* **62** (82 mg, 62%) as a

colourless solid, m.p. 116 - 117 °C (ethyl acetate - petroleum) (Found: C, 67.5; H, 5.8. $C_{10}H_{10}O_3$ requires C, 67.4; H, 5.7%); ν_{max} 3425, 1345, 1270, 1190, 1160, 1100, 1040, 1000, 950, and 760 cm^{-1}; δ (60 MHz) 2.82 (1 H, d, *J* 11 Hz, exchanges with D_2O, OH), 4.15 (4 H, br. s, 4'-H, 5'-H), 5.15 (1 H, d, *J* 11 Hz, 2-H), and 7.4 (4 H, br. s, ArH); M^+, 178.

2-Acetoxybenzocyclobuten-1(2H)-one **64**. - To a stirred suspension of pyridinium chlorochromate (4.5 g, 21 mmol) in dichloromethane (30 ml) at room temperature was added a solution of *cis*-1-hydroxy-2-acetoxybenzocyclobutene (2.474 g, 13.9 mmol) (prepared[46] from 1,2-diiodobenzocyclobutene[47]) in dichloromethane (30 ml) in one portion. After 16 h the reaction mixture was worked up in the usual manner[48] using ether to isolate the organic products. The residue on evaporation of the ether was chromatographed over neutral alumina, eluting with dichloromethane, to obtain the *title compound* **64** (1.17 g, 48%) as an oil, b.p. *ca.* 100 °C (1 mmHg) (Found: C, 68.2; H, 4.7. $C_{10}H_8O_3$ requires C, 68.2; H, 4.6%); ν_{max} (neat) 1780, 1750, 1590, and 1225 cm^{-1}; δ (60 MHz) 2.15 (3 H, s, Me), 6.50 (1 H, s, 2-H), and 7.5 - 7.8 (4 H, m, ArH).

2-Hydroxybenzocyclobuten-1(2H)-one **65**. - A mixture of the ketoester **64** (0.88 g, 5 mmol), methanol (50 ml), and Amberlite® IR-120H ion-exchange resin (well washed with methanol; 5 g) was stirred at room temperature for 24 h. The solution was then filtered and evaporated, and the residue chromatographed, eluting with ethyl acetate - petroleum (1:9 to 1:4), to obtain the title compound **65** (342 mg, 51%) as an oil which slowly crystallised on drying *in vacuo*. A sublimed sample (bath 70 - 80 °C, ca. 1 mmHg) had m.p. 54 - 56 °C (lit.[49] 57 - 58.5 °C); ν_{max} 3370, 1760, and 1580 cm^{-1}; δ (60 MHz) 4.34 (1 H, br. s, exchanges in D_2O, OH), 5.80 (1 H, s, 2-H), and 7.4 - 7.9 (4 H, m, ArH).

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REFERENCES

1 For a review of anthracycline chemistry, see F. Arcamone, 'Doxorubicin,' Academic Press, New York, 1981. For more recent synthetic aspects, see the 'Symposium in Print' (ed. T.R. Kelly), *Tetrahedron*, 1984, **40**, 4537 - 4793.

2 For a discussion of quinone biosynthesis, see R.H. Thomson, 'Naturally Occurring Quinones,' 2nd Edition, Academic Press, London, 1971; 3rd Edition, Chapman and Hall, London, 1987.

3 Reviews: I.L. Klundt, *Chem. Rev.*, 1970, **70**, 471; A.H. Schmidt and W. Ried, *Synthesis*, 1978, 869; R.P. Thummel, *Acc. Chem. Res.*, 1980, **13**, 70.

4 For reviews of the chemistry of *o*-quinone dimethides, see W. Oppolzer, *Synthesis*, 1978, 793; J.L. Charlton and M.M. Alauddin, *Tetrahedron*, 1987, **43**, 2873. See also S. Inaba, R.M. Wehmeyer, M.W. Forkner, and R.D. Rieke, *J. Org. Chem.*, 1988, **53**, 339, and references cited therein.

5 B.J. Arnold, P.G. Sammes, and T.W. Wallace, *J. Chem. Soc., Perkin Trans. 1*, 1974, 409.

6 P.G. Sammes, *Tetrahedron*, 1976, **32**, 405.

7 For other approaches to quinones from benzocyclobutenones, see D.R. Arnold, E. Hedaya, V.Y. Merritt, L.A. Karnischky, and M.E. Kent, *Tetrahedron Lett.*, 1972, 3917; M.E. Jung and J.A. Lowe, *J. Org. Chem.*, 1977, **42**, 2371; L.S. Liebeskind, S. Iyer, and C.F. Jewell, *ibid.*, 1986, **51**, 3065; S.T. Perri, L.D. Foland, O.H.W. Decker, and H.W. Moore, *ibid.*, 1986, **51**, 3067.

8 Benzocyclobutenes have been used to construct ring C of anthracyclinones: J.S. Swenton, D.K. Anderson, D.K. Jackson, and L. Narasimhan, *J. Org. Chem.*, 1981, **46**, 4825; M.J. Broadhurst, C.H. Hassall, and G.J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2239; M.J. Broadhurst, C.H. Hassall, and G.J. Thomas, *ibid.*, 1982, 2249; D.K. Anderson, C.E. Coburn, A.P. Haag, and J.S. Swenton, *Tetrahedron*, 1984, **40**, 4633. Ring A of a 7-deoxyanthracyclinone has been constructed using an anthra[*b*]cyclobutene: T. Watabe, Y. Takahashi, and M. Oda, *Tetrahedron Lett.*, 1983, **24**, 5623.

9 For pertinent discussions, see D. Dominguez, R.J. Ardecky, and M.P. Cava, *J. Am. Chem. Soc.*, 1983, **105**, 1608; R. Rodrigo, *Tetrahedron*, 1988, **44**, 2093, and references cited therein.

10 Preliminary communication: M.Azadi-Ardakani and T.W. Wallace, *Tetrahedron Lett.*, 1983, **24**, 1829.
11 O. Abou-Teim, R.B. Jansen, J.F.W. McOmie, and D.H. Perry, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1841.
12 H. Dürr, H. Nickels, L.A. Pacala, and M. Jones, *J. Org. Chem.*, 1980, **45**, 973.
13 R.V. Stevens and G.S. Bisacchi, *J. Org. Chem.*, 1982, **47**, 2393.
14 For an alternative route to phthalides from benzocyclobutenones, see K. Kobayashi, M. Itoh, and H. Suginome, *Tetrahedron Lett.*, 1987, **28**, 3369.
15 T. Kametani, T. Honda, H. Matsumoto, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1383.
16 R.W. Franck, T.V. John, K. Olejniczak, and J.F. Blount, *J. Am. Chem. Soc.*, 1982, **104**, 1106; R.W. Franck, V. Bhat, and C.S. Subramaniam, *ibid.*, 1986, **108**, 2455.
17 K.S. Kim, M.W. Spatz, and F. Johnson, *Tetrahedron Lett.*, 1979, 331.
18 Chiral induction in intermolecular cycloadditions of *o*-quinone dimethides is discussed by Charlton and Alauddin [reference 4].
19 For the formation of a seven-membered ring in an analogous system, see R.L. Funk and K.P.C. Vollhardt, *J. Am. Chem. Soc.*, 1976, **98**, 6755.
20 For other discussions of the mechanism of photoenolisation, see R. Haag, J. Wirz, and P.J. Wagner, *Helv. Chim. Acta*, 1977, **60**, 2595; P.K. Das, M.V. Encinas, R.D. Small, and J.C. Scaiano, *J. Am. Chem. Soc.*, 1979, **101**, 6965; J.C. Scaiano, *Acc. Chem. Res.*, 1982, **15**, 252; C.V. Kumar, S.K. Chattopadhyay, and P.K. Das, *J. Am. Chem. Soc.*, 1983, **105**, 5143.
21 B.J. Arnold, P.G. Sammes, and T.W. Wallace, *J. Chem. Soc., Perkin Trans. 1*, 1974, 401.
22 R. Ricard, P. Sauvage, C.S.K. Wan, A.C. Weedon, and D.F. Wong, *J. Org. Chem.*, 1986, **51**, 62; C.S.K. Wan, A.C. Weedon, and D.F. Wong, *ibid.*, 1986, **51**, 3335.
23 For an attempt to prepare the silyl ether **57** *via* a thermally-induced ring closure, see C. Shih and J.S. Swenton, *J. Org. Chem.*, 1982, **47**, 2668.
24 B.J. Arnold, P.G. Sammes, and T.W. Wallace, *J. Chem. Soc., Perkin Trans. 1*, 1974, 415. For an important discussion, see also R.J. Moss, R.O. White, and B. Rickborn, *J. Org. Chem.*, 1985, **50**, 5132.
25 For examples and discussions, see reference 6 and the following: C.W. Jefford, A.F. Boschung, and C.G. Rimbault, *Tetrahedron Lett.*, 1974, 3387; M.J. Curry and I.D.R. Stevens, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1391; S. Ingham, R.W. Turner, and T.W. Wallace, *J. Chem. Soc., Chem. Commun.*, 1985, 1664; N.G. Rondan and K.N. Houk, *J. Am. Chem. Soc.*, 1985, **107**, 2099; W.R. Dolbier, H. Koroniak, D.J. Burton, P.L. Heinze, A.R. Bailey, G.S. Shaw, and S.W. Hansen, *ibid.*, 1987, **109**, 219; K. Rudolf, D.C. Spellmeyer, and K. Houk, *J. Org. Chem.*, 1987, **52**, 3708.
26 For details of the photochemistry of *o*-phthalaldehyde itself, see J.C. Scaiano, M.V. Encinas, and M.V. George, *J. Chem. Soc., Perkin Trans. 2*, 1980, 724, and references cited therein.
27 D.D. Perrin, W.L.F. Armarego, and D.R. Perrin, 'Purification of Laboratory Chemicals,' 2nd Edition, Pergamon, Oxford, 1980.
28 W.C. Still, M. Khan, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
29 F.J. Villani and J. Lang, *J. Am. Chem. Soc.*, 1950, **72**, 2301.
30 P.K. Banerjee and D.N. Chaudhury, *J. Indian Chem. Soc.*, 1959, **36**, 257.
31 F.M. Logullo, A.H. Seitz, and L. Friedman, *Org. Synth.*, 1973, **CV 5**, 54.
32 O. Süs, *Justus Liebigs Ann. Chem.*, 1947, **557**, 237.
33 J.S. Swenton, D.K. Jackson, M.J. Manning, and P.W. Raynolds, *J. Am. Chem. Soc.*, 1978, **100**, 6182.
34 H. Suzuki, K. Nakamura, and R. Goto, *Bull. Chem. Soc. Jpn.*, 1966, **39**, 128.
35 H. Kauffmann and I. Fritz, *Chem. Ber.*, 1908, **41**, 4413.
36 E.J. Corey, J.D. Bass, R. LeMahieu, and R.B. Mitra, *J. Am. Chem. Soc.*, 1964, **86**, 5570.
37 W.C. Kuryla and J.E. Hyre, *Org. Synth.*, 1973, **CV 5**, 684.
38 S.M. McElvain and M.J. Curry, *J. Am. Chem. Soc.*, 1948, **70**, 3781.
39 H. Inouye, *Pharmaceutical Bulletin*, 1954, **2**, 359.
40 P. Mamalis, J. Green, S. Marcinkiewicz, and D. McHale, *J. Chem. Soc.*, 1959, 3350.
41 Y. Hirshberg, D. Lavie, and E.D. Bergmann, *J. Chem. Soc.*, 1951, 1030.
42 B.J. Arnold, Ph. D. Thesis, University of London, 1973. For an alternative procedure, see W.A. Bubb and S. Sternhell, *Aust. J. Chem.*, 1976, **29**, 1685.
43 J. Finkelstein, K.G. Holden, and C.D. Perchonock, *Tetrahedron Lett.*, 1978, 1629. For an alternative route to this compound, see J. Cano, F. Font, M.A. Galan, and A. Vergili, *Afinidad*, 1978, **35**, 123 (*Chem. Abs.*, 1978, **89**, 214576).
44 C.D. Perchonock, personal communication. See also H.D. Perlmutter, R.A. Lalancette, A. Robertiello, and D.V. Bowen, *Tetrahedron Lett.*, 1980, **21**, 817.
45 D.H.R. Barton, P.D. Magnus, and J.I. Okogun, unpublished work.
46 H. Nozaki, R. Noyori, and N. Kozaki, *Tetrahedron*, 1964, **20**, 64
47 F.R. Jensen and W.E. Coleman, *J. Org. Chem.*, 1958, **23**, 869.
48 E.J. Corey and J.W. Suggs, *Tetrahedron Lett.*, 1975, 2647.
49 L.A. Carpino and J.-H. Tsao, *J. Org. Chem.*, 1979, **44**, 2387.