Convenient synthetic route to antimicrobial benzo[c]pyranquinones

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A general synthetic strategy has been developed for the synthesis of racemic 3,4-dihydro-3-methyl-1H-benzo[c]pyran-5,8-dione 25, trans-1(R,3R)-5,8-dihydroxy-1,3-dimethyl-4-oxo-1H-benzo[c]pyran 39, rel-(1R,3R,R)-3,4-dihydro-1,3-dimethyl-4-hydroxy-1H-benzo[c]pyran-5,8-dione 41 and the rel-(4S)-dias-stereoisomer 42.

We recently briefly reported on the synthesis and biological activity of some benzopyran systems. In the present paper we describe fully the synthetic routes to these molecules and demonstrate how this methodology has been used in the synthesis of additional highly active benzo[c]pyranquinones.

For many years the biological potential of the naphtho[2,3-c]pyran-5,10-quinones as antineoplastic antibiotics has been recognized and their synthesis has been successfully undertaken by several groups. Compounds belonging to these systems include eleutherin 1, isoeleutherin 2, 57 nanaomycin A 3, nanaomycin D 4, fusarubin 5 and marticin 6. An interesting variant of these systems is hongconin 7, used as a remedy for angina pectoris, and which was recently synthesized as its racemate.

Moore described the naphthopyranquinone systems as 'bioreductive alkylating agents'. Basing much of his proposed mechanism for the biological activity of these systems on work done by Sartorelli and co-workers, he suggested that the introduced pyranquinone, viz. 8, undergoes an in vivo reduction to the quinol 9, which could ring-open by way of cleavage of the pyran C-1-O bond followed by cleavage of the C-4-O bond. The resultant highly active bisquinone-methine system 10 would then react with the nucleophilic centres, e.g. nitrogen, found in tumours and microbial agents to form products 11, as depicted in Scheme 1. It has also been proposed that once the natural structure of the tumour or alien DNA has been modified in this way, its template function will become inhibited.

It appeared to us that the most important structural feature for biological activity in these systems is the
aryl-[2,3-c]pyranquinone nucleus and that the 4-hydroxy group would certainly increase the activity, according to Scheme 1. Consequently, our initial aim was the synthesis of racemic 3,4-dihydro-3-methyl-1/H-benzo[c]pyran-5,8-dione 25 in order to study the importance of the position of the oxygen in the pyran ring for antimicrobial activity.

Thus, Claisen rearrangement of ester 12 gave the expected quinol 13 as a result of an ortho migration of the allyl group to the sterically disfavoured position. However, subjection of ether 14 to similar Claisen conditions yielded phenol 16 as the sole product. The structure of 16 is based on the 'H NMR spectrum, which showed the 3- and 6-H signals as singlets at δ 6.75 and 7.40, respectively. This finding further demonstrated that when hydrogen bonding between the ester carbonyl group and the hydroxyl group on C-2 was absent, migration of the allyl group was to the less-crowded alternative ortho position at C-4. Furthermore, when ester 15 was pyrolysed, quinol 17 was the sole product isolated, indicating that the allyl group at the C-5 ether position had migrated to the disfavoured position at C-6. In order to account for this apparent anomaly it is proposed that the initial step in the rearrangement is prior migration of the allyl group from the C-2-O to C-3, thereby allowing hydrogen bonding to be re-established as before, and thus dictating the migration route of the allyl group from the C-5-O to C-6.

Chemical verification for the assignment of structure 17 was considered necessary since the single resonance in the 'H NMR spectrum at δ 6.85 was in our view not conclusive evidence to discount the alternative isomer 18. Thus methylation of quinol 17 with methyl iodide and potassium carbonate in boiling acetone yielded ether 19, which upon reduction with lithium aluminium hydride afforded the alcohol 21. This underwent smooth, anaerobic base-catalysed cyclization to the benzo[pyran 23. During cyclization of the alcohol 21, the propenyl group on C-3 underwent conjugation leading to product 23, as was evident from the 'H NMR spectrum in which the 3'-CH, appeared as a doublet at δ 6.75 and 7.40, respectively. This finding further demonstrated that when hydrogen bonding between the ester carbonyl group and the hydroxyl group on C-2 was absent, migration of the allyl group was to the less-crowded alternative ortho position at C-4. Furthermore, when ester 15 was pyrolysed, quinol 17 was the sole product isolated, indicating that the allyl group at the C-5 ether position had migrated to the disfavoured position at C-6. In order to account for this apparent anomaly it is proposed that the initial step in the rearrangement is prior migration of the allyl group from the C-2-O to C-3, thereby allowing hydrogen bonding to be re-established as before, and thus dictating the migration route of the allyl group from the C-5-O to C-6.

Our attention was then focused on the synthesis of the hydroxy benzo[pyranquinones 41 and 42 since these molecules resemble models for the aphid pigments and consequent degradative compounds, the benzo[pyran nucleus being included in these systems. Consequently, 2-acetyloxy-4,5-dihydroxybenzene was monoallylated to produce the 5-allyloxy-2-hydroxyacetophenone 20, which when subjected to Claisen rearrangement at
215 °C resulted in the formation of two products. The minor product (8%), which was eluted first from the column, was assigned the structure 29, in which the allyl group at the C-4 position has migrated to the less sterically crowded C-5 position. This is supported by the 1H NMR spectrum, which shows the aromatic protons as a doublet of quartets at δ 4.54 and 6.5 Hz), a doublet of doublets at δ 6.78 and 6.98 (J 2 Hz, which confirmed that the C-5 alcohol function is thus pseudo-equatorial. Confirmation of the stereochemistry between the 3-H and 4-H of the minor isomeric pyran ring was evident from the 1H NMR spectrum, in which the three pyran protons appeared as a doublet of doublets at δ 6.08 (J 2 and 6.5 Hz), a doublet of doublets at δ 4.54 (J 2 Hz, and a quartet at δ 5.10 (J 6.7 Hz), assigned to the 3-H, 4-H and 1-H protons, respectively. The relative stereochemistry between the 3-H and 4-H pyran ring protons was established as axial and pseudo-equatorial, by virtue of the common coupling constant of 2 Hz, which confirmed that the C-4 alcohol function for the major isomer 36 is pseudo-axial. The corresponding coupling constant between the 3-H and 4-H of the minor isomeric alcohol 37 is 7 Hz, confirming the fact that the 4-H is pseudo-axial and that the C-4 alcohol function is thus pseudo-equatorial.

In a similar way, treatment of 34 with 4 mol equiv. of cerium(IV) ammonium nitrate in aqueous acetone produced the 4-hydroxyquinone derivatives 41 and 42 in yields of 66% and 15%, respectively. The infrared spectrum of the major isomeric alcohol 36 showed a sharp absorption at 3480 cm⁻¹, which confirmed the presence of the alcohol group, while the molecular ion at m/z 238.1184 in the mass spectrum gave support for the molecular formula of the pyran 36. Confirmation of the stereochemistry about the pyran ring was evident from the 1H NMR spectrum, in which the three pyran protons appeared as a doublet of doublets at δ 6.08 (J 2 and 6.5 Hz), a doublet of doublets at δ 4.54 (J 2 Hz, and a quartet at δ 5.10 (J 6.7 Hz), assigned to the 3-H, 4-H and 1-H protons, respectively. The relative stereochemistry between the 3-H and 4-H pyran ring protons was established as axial and pseudo-equatorial, by virtue of the common coupling constant of 2 Hz, which confirmed that the C-4 alcohol function for the major isomer 36 is pseudo-axial. The corresponding coupling constant between the 3-H and 4-H of the minor isomeric alcohol 37 is 7 Hz, confirming the fact that the 4-H is pseudo-axial and that the C-4 alcohol function is thus pseudo-equatorial.
cm<sup>-1</sup> which confirmed the presence of the alcohol and quinone groups, respectively. The <sup>1</sup>H NMR spectrum displayed a close similarity to that of the pyran 36 while the <sup>1</sup>H NMR spectra of pyranquinone 42 and pyran 37 had confirmatory similarities, thereby establishing the assigned relative stereochemistries of the protons at C-1, C-3 and C-4 of the pyran ring. Attempts at oxidizing the pyranquinone 41 to the ketoquinone 40 using pyridinium dichromate failed in our hands, with the starting two hydroxyl groups was evident from the <sup>1</sup>H NMR spectrum which confirmed the presence of the alcohol and quinone groups, respectively. The <sup>1</sup>H NMR spectrum of pyranquinone 42 and pyran 37 had confirmatory similarities, thereby establishing the assigned relative stereochemistries of the protons at C-1, C-3 and C-4 of the pyran ring. Attempts at oxidizing the pyranquinone 41 to the ketoquinone 40 using pyridinium dichromate failed in our hands, with the starting two hydroxyl groups evident from the <sup>1</sup>H NMR spectrum.

An alternative route investigated for the synthesis of quinol 39 proved to be successful and involved the initial oxidation of the C-4 hydroxy pyran 36 to the C-4 keto pyran 38 with pyridinium dichromate in dichloromethane in fair yield. The absence of bands in the 3400 cm<sup>-1</sup> region and the appearance of a strong band at 1690 cm<sup>-1</sup> in the infrared spectrum confirmed the desired oxidation had occurred. Finally, oxidative demethylation<sup>14</sup> of keto pyran 38 afforded the pyranquinol 39 in a yield of 62%. Assignment of the structure 39 to the product is based on a strong band at 3370, a weaker band at 1700 and a strong band at 1650 cm<sup>-1</sup> in the infrared spectrum, while the molecular ion at m/z 208.0742 in the mass spectrum supported the molecular formula of C<sub>8</sub>H<sub>5</sub>O<sub>4</sub> for pyran 39. Confirmation of the two hydroxyl groups was evident from the <sup>1</sup>H NMR spectrum, in which the C-8 hydroxyl group appeared as a D<sub>2</sub>O-exchangeable single peak at δ 4.90, while the hydrogen-bonded C-5 hydroxyl group appeared downfield as a sharp D<sub>2</sub>O-exchangeable peak at δ 11.32.

The reluctance of quinol 39 to undergo oxidation to the corresponding quinone 40 under the conditions used is a result of the strong H-bonding stabilization between the C-5 hydroxyl and C-4 carbonyl groups, since oxidative demethylation of pyran 35, in which the C-4 carbonyl is absent, afforded quinone 43 in a yield of 90%. Thus, a general strategy has been developed for the synthesis of benzof]<sup>1</sup>pyran ring systems which are considered to be appropriate for microbiological testing. Very encouraging results have been obtained thus far in the development of benzo[c]pyran ring systems.

**Experimental**

<sup>1</sup>H NMR spectra were recorded in deuteriochloroform on a Varian EM-360 spectrometer unless otherwise stated. Coupling constants (J) are given in Hz. IR spectra were measured as Nujol mulls or neat on a Pye-Unicam SP-300 spectrophotometer. Melting points are uncorrected and were determined on a Fischer-Johns apparatus. Column chromatography was carried out on dry columns using silica gel (70—230 mesh). Hexane had a b.p. range of 70—75 °C. The phrase ‘residue obtained upon work-up’ refers to the material remaining when the organic layer was separated, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure.

**Prop-2'-enyl 3,6-dihydroxy-2-prop-2'-enylbenzoate 13.** The ester 12<sup>4</sup> (650 mg, 2.8 mmol) was pyrolysed at 210 °C under nitrogen for 5 h. The tarry product was chromatographed using ethyl acetate–hexane (1:9) as eluent to yield the *Claisen product 13* (453 mg, 69%) as a light brown oil; <sup>1</sup>H NMR (film) 3440, 1670 and 1470 cm<sup>-1</sup>; δ<sub>H</sub> 3.75(2H, dt, J 6 and 2, 1'-CH<sub>2</sub>), 4.85(2H, dt, J 6 and 2, CO<sub>2</sub>CH<sub>3</sub>), 4.87(1H, s, D<sub>2</sub>O exchangeable, 3'-OH), 5.10—5.65(4H, m, 3'-CH<sub>2</sub> and CO<sub>2</sub>CH<sub>2</sub>CH=CH<sub>2</sub>), 6.56—6.65(2H, m, 2'-CH and CO<sub>2</sub>CH<sub>2</sub>CH=CH<sub>2</sub>), 6.80(1H, d, J 9, 5-H), 7.30(1H, d, J 9, 4-H) and 10.45(1H, s, D<sub>2</sub>O exchangeable, 6-OH) (Found: C, 66.5; H, 6.2%; M<sup>+</sup>, 234. Calc. for C<sub>11</sub>H<sub>10</sub>O<sub>5</sub>; C, 66.7; H, 6.0%; M<sup>+</sup>, 234).

**Prop-2'-enyl 2-methoxy-5-prop-2'-enylbenzoate 14.** The ester 12<sup>4</sup> (1.2 g, 5.1 mmol) was pyrolysed in dry acetone (60 cm<sup>3</sup>) containing iodomethane (7.2 g, 51 mmol) and potassium carbonate (2.15 g, 15.6 mmol) was vigorously stirred under reflux for 24 h. The cooled reaction mixture was filtered and the filtrate stripped of solvent to leave an oily residue which was chromatographed using ethyl acetate–hexane (3:7) as eluent to afford the *methoxy ether 14* (775 mg, 61%) as an oil; <sup>1</sup>H NMR (film) 1730 and 1505 cm<sup>-1</sup>; δ<sub>H</sub> 3.85(3H, s, OCH<sub>3</sub>), 4.50(2H, dt, J 6 and 2, 5-OCH<sub>2</sub>CH=CH<sub>2</sub>), 4.83(2H, dt, J 6 and 2, CO<sub>2</sub>CH<sub>3</sub>), 5.15—5.68(4H, m, 2 χ OCH<sub>2</sub>CH=CH<sub>2</sub>), 5.70—6.60(2H, m, 2 χ OCH<sub>2</sub>CH=CH<sub>2</sub>), 6.87(1H, d, J 9, 3-H), 7.10(1H, dd, J 9 and 3, 4-H) and 7.37(1H, d, J 3, 6-H) (Found: C, 67.5; H, 6.3%; M<sup>+</sup>, 248.1073. Calc. for C<sub>11</sub>H<sub>11</sub>O<sub>4</sub>; C, 67.7; H, 6.45%; M<sup>+</sup>, 248.1049).

**Prop-2'-enyl 5-hydroxy-2-methoxy-4-prop-2'-enylbenzoate 15.** Ester 14 (775 mg, 3.1 mmol) was pyrolysed as above for 12 and the tarry residue was chromatographed using ethyl acetate–hexane (1:9) as eluent to afford the *methoxy ether 15* (1.2 g, 52%) as white crystals, m.p. 36—37 °C (from hexane); <sup>1</sup>H NMR (film) 4.78(1H, s, D<sub>2</sub>O exchangeable, 3'-OH), 5.10—5.68(4H, m, 2 χ OCH<sub>2</sub>CH=CH<sub>2</sub>), 6.80(1H, s, D<sub>2</sub>O exchangeable, 5'-OH), 6.73(1H, s, 3-H) and 7.40(1H, s, 6-H) (Found: C, 67.4; H, 6.25%; M<sup>+</sup>, 248. Calc. for C<sub>11</sub>H<sub>11</sub>O<sub>4</sub>; C, 67.7; H, 6.45%; M<sup>+</sup>, 248).
potassium carbonate (6.5 g, 47.1 mmol) and iodo-
methane (6.7 g, 47.2 mmol) in acetone (60 cm³) was
vigorously stirred and heated under reflux for 24 h. The
cooled solution was filtered and the filtrate was stripped of
solvent to yield an oil which was chromatographed using
ethyl acetate–hexane (1:9) as eluent to afford the
**dimethyl ether** (19) (1.39 g, 96%) as an oil; v
_\text{var. (film)}_ 1720 cm⁻¹; δ_6 3.35 and 3.45(each 2H, each dt, J 6 and 2,
5- and 2-CH,CH=CH₂), 3.75 and 3.85(each 3H, s, 2 ×
OCH₃), 4.85(2H, d, J 6, 2, CO₂CH₂CH=CH₂), 5.00—
5.65(H, m, 3 × CH₂CH=CH₂), 5.75—6.50(3H, m, 3 ×
CH₂CH=CH₂) and 6.80(1H, s, 4-H) (Found: C, 72.6; H,
7.6%; M⁺, 208).

(E)-3-Dihydro-5,8-dimethoxy-3-methyl-7-prop-2'-eny-
-lH-benzo[c]pyran 23. Alcohol 21 (207 mg, 0.83
mmol) in dry dimethylformamide (15 cm³) was treated
with potassium tert-butoxide (561 mg, 5 mmol) under
nitrogen and the mixture was stirred and heated at 60 °C
(oil bath) for 15 min. After quenching the reaction with
water (50 cm³), the aqueous solution was extracted with
ether. The residue obtained upon work-up was chromato-
graphed with ethyl acetate–hexane (1:9) as eluent to
afford the **pyran** 23 (178 mg, 86%) as white needles,
m.p. 55—56 °C (from hexane); v_\text{var. (film)}_, 1223 and 1135 cm⁻¹;
δ_6 1.35(3H, d, J 6, 3-CH₃), 1.92(3H, d, J 6, 3'-CH₃),
2.35(1H, dd, J 17 and 10, pseudo-axial 4-H), 2.80(1H,
dd, J 17 and 4, pseudo-equatorial 4-H), 3.62 and
3.85(each 3H, s, 2 × OCH₃), 3.40—3.90(1H, m, 3-H
partially obscured by OCH₃ signals), 4.65(1H, d, J 15,
pseudo-axial 1-H), 5.05(1H, d, J 15, pseudo-equatorial
1-H), 6.10(1H, dq, J 16 and 6, 2'-H), 6.40(1H, dq, J 16
and 2, 1'-H) and 6.84(1H, s, 6-H) (Found: C, 72.6; H,
7.9%; M⁺, 248. Calc. for C₄H₁₀O₂: C, 72.6; H, 8.1%; M,
248).

Prop-2-eny 3,6-dimethoxy-2-prop-2'-enylbenzoate 20.
Quinol 13 (622 mg, 2.7 mmol) was methylated as for
compound 19. The residue obtained upon work-up was
chromatographed using ethyl acetate–hexane (1:4) as
eluent, to give **product** 20 (672 mg, 95%) as an oil;
v_\text{var. (film)}_, 1735 cm⁻¹; δ_6 3.35(2H, d, J 6 and 2, CH₂=
CH₂), 3.75(6H, s, 2 × OCH₃), 4.83(2H, d, J 6 and 2,
CH₂CH=CH₂), 5.07—5.40(4H, m, 2 × CH₂CH=CH₂),
5.80—6.10(2H, m, 2 × CH₂CH=CH₂), 6.70(1H, d,
J 9, 5-H) and 6.90(1H, d, J 9, 4-H) (Found: C, 68.6; H,
6.9%; M⁺, 262. Calc. for C₁₉H₂₃O₇: C, 68.7; H, 6.9%; M,
262).

3,6-Dimethoxy-1-hydroxymethyl-2-prop-2'-enylben-
zoene 22. Ester 20 (925 mg, 3.34 mmol) in dry ether (20
cm³) was added dropwise to a stirred suspension of
lithium aluminium hydride (673 mg, 17.7 mmol) in dry
ether (50 cm³) over a 5-min period and the mixture was
stirred for 30 min at room temperature. Reduction was
halted by the slow addition of a saturated solution of
ammonium chloride (2 cm³). Dichloromethane (60 cm³)
and magnesium sulphate (5 g) were added and the mixture
was filtered. The residue obtained by removal of the
solvent from the filtrate was chromatographed using
ethyl acetate–hexane (1:4) as eluent and gave the
**product** 22 (660 mg, 90%) as white crystals, m.p. 46—
47 °C (from hexane); v_\text{var. (film)}_, 3365 cm⁻¹; δ_6 3.55(2H, d, J 6
and 2, CH₂CH=CH₂), 3.75 and 3.80(each 3H, each 2 ×
OCH₃), 4.70(1H, s, D,O exchangeable, OH), 4.73(2H, s,
ArCH=OH), 4.94—5.10(2H, m, CH₂CH=CH₂), 5.65—
6.40(1H, m, CH₂CH=CH₂), 6.71 and 6.77(each 1H, d, J 9,
3- and 4-H) (Found: C, 69.1; H, 7.4%; M⁺, 208. Calc. for
C₁₉H₂₃O₇: C, 69.2; H, 7.7%; M, 208).

3,4-Dihydro-5,8-dimethoxy-3-methyl-1H-benzo[c]-
pyran 24. Potassium tert-butoxide (602 mg, 5.28
mmol) was added at once to a stirred solution of the alcohol 22
(270 mg, 1.30 mmol) in dry dimethylformamide (20
cm³). The resultant mixture was stirred under nitrogen at
60 °C (oil bath) for 15 min, after which it was quenched by
the addition of water (60 cm³). The product was
extracted into ether and the residue obtained upon work-
up was chromatographed using ethyl acetate–hexane
(1:9) as eluent to afford the **pyran** 24 (220 mg, 82%) as
white crystals, m.p. 74—75 °C (from dichloromethane–
hexane); v_\text{var. (film)}_, 1735 cm⁻¹; δ_6 1.35(3H, d, J 6, 3-
CH₃), 2.35(1H, dd, J 17 and 10, pseudo-axial 4-H),
2.85(1H, dd, J 17 and 4, pseudo-equatorial 4-H), 3.75
and 3.78(each 3H, each 2 × OCH₃), 3.39—4.00(1H,
m, partially obscured by OCH₃ signals, 3-H), 4.56(1H,
d, J 15, pseudo-axial 1-H), 4.95(1H, d, J 15, pseudo-
equatorial 1-H), 6.60 and 6.65(each 1H, d, J 9, 6-
and 7-H) (Found: C, 69.2; H, 7.6%; M⁺, 208. Calc. for
C₁₉H₂₃O₇: C, 69.2; H, 7.7%; M, 208).

3,4-Dihydro-3-methyl-1H-benzo[c]pyran-5,8-
dione 25. To a stirred mixture of pyran 24 (59 mg, 0.3
mmol) and silver(ll) oxide (176 mg, 2.5 mmol) in
dioxan (10 cm³) was added nitric acid (0.4 cm³ of a 6 mol
dm⁻³ solution) over a period of 5 min. Stirring was
continued for a further 10 min after which the reaction
was quenched by the addition of a dichloromethane–
water (26:6) mixture. The residue obtained upon work-up was chromatographed using ethyl acetate–hexane (3:7) as eluent to afford the quinone 25 (35 mg, 70%) as a yellow oil, Rf 0.40 (from dichloromethane–hexane). ν<sub>max</sub> (film) 1660 cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz) 1.35 (3H, d, J = 6.0 Hz, 3-CH<sub>3</sub>), 2.08 (1H, ddd, J = 10.5, 3.5, and 2.5 Hz, pseudo-axial 4-H), 2.60 (1H, d, J = 10.5 Hz, pseudo-equatorial 4-H), 3.35—3.85 (1H, m, 3-H), 4.35—4.45 (1H, d, J = 9.5 Hz, pseudo-axial 1-H), 4.75 (1H, dd, J = 9.5 and 3.5 Hz, pseudo-equatorial 1-H) and 6.75 (2H, s, 5- and 6-H) (Found: C, 67.3; H, 5.3%; M<sup>+</sup>, 232). The residue obtained after work-up was chromatographed using ethyl acetate–hexane (3:7) as eluent to give the minor product 22 (40 mg, 61%) as a red oil, v<sub>max</sub> (film) 1690 cm<sup>-1</sup>; δ<sub>H</sub> (200 MHz) 1.12 (3H, d, J = 6.8 Hz, 6, 3-CH<sub>3</sub>), 2.53 (3H, s, CH<sub>3</sub>CO), 3.30 (2H, dt, J = 10.5 and 1.5 Hz, CH<sub>2</sub>), 3.80—4.25 (1H, m, 3-H), 5.10 (1H, q, J = 6.5 Hz, 2-CH<sub>2</sub>CO), 3.50—4.00 (4H, m, 2 × CH<sub>2</sub>CH=CH<sub>2</sub>), 5.00—5.60 (4H, m, 2 × CH<sub>2</sub>CH=CH<sub>2</sub>) and 6.74 (2H, s, 5- and 6-H) (Found: C, 70.5; H, 8.0%; M<sup>+</sup>, 222). Calc. for C<sub>12</sub>H<sub>10</sub>O<sub>2</sub>; C, 70.3; H, 8.1%; M<sup>+</sup>, 222.

2-Acetyl-3-prop-2'-enyl-1,4-dimethoxybenzene 31. Quinol 30 (6.00 g, 31.3 mmol) was dissolved in dry acetonitrile (150 cm<sup>3</sup>) containing iodomethane (17.5g, 125 mmol) and potassium carbonate (17.25 g, 125 mmol) and the resulting mixture was stirred under reflux in a nitrogen atmosphere for 18 h. The cooled reaction mixture was filtered and the filtrate was evaporated to an oil which was chromatographed using ethyl acetate–hexane (1:4) as eluent to afford the product 31 (6.89 g, 100%) as an oil, ν<sub>max</sub> (film) 1690 cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz) 1.35 (3H, d, J = 6.9 Hz, 6, 3-CH<sub>3</sub>), 2.53 (3H, s, CH<sub>3</sub>CO), 3.30 (2H, dt, J = 10.5 and 1.5 Hz, CH<sub>2</sub>), 3.80—4.25 (1H, m, 3-H), 5.20—5.60 (4H, m, 2 × CH<sub>2</sub>CH=CH<sub>2</sub>), 5.00—5.60 (4H, m, 2 × CH<sub>2</sub>CH=CH<sub>2</sub>) and 6.74 (2H, s, 5- and 6-H) (Found: C, 71.1; H, 7.3%; M<sup>+</sup>, 220. Calc. for C<sub>17</sub>H<sub>12</sub>O<sub>2</sub>; C, 70.9; H, 7.3%; M<sup>+</sup>, 220).

1,4-Dimethoxy-2-(1'-hydroxyethyl)-3-prop-2'-enylbenzene 33. The ketone 31 (2.23 g, 10.1 mmol) in dry ether (50 cm<sup>3</sup>) was added dropwise to a stirred slurry of lithium aluminium hydride (76.0 mg, 2 mmol) in dry ether (60 cm<sup>3</sup>) over a period of 5 min. After all the starting material had been consumed (5 h), saturated aqueous ammonium chloride (1 cm<sup>3</sup>) was added to quench the reaction. Dichloromethane (100 cm<sup>3</sup>) was added and the residue obtained upon work-up was chromatographed using ethyl acetate–hexane (3:7) as eluent to afford the product 33 (2.15 g, 96%) as an oil, ν<sub>max</sub> (film) 3550 cm<sup>-1</sup>; δ<sub>H</sub> (200 MHz) 1.35 (3H, d, J = 6.9 Hz, 6, 3-CH<sub>3</sub>), 2.45 (2H, dt, J = 6.0 and 2.0 Hz, 2-CH<sub>2</sub>CH=CH<sub>2</sub>), 3.76 and 3.86 (each 3H, each s, 2 χ OCH<sub>3</sub>), 4.90 (1H, dm, J = 16, trans-CH<sub>2</sub>CH=CH<sub>2</sub>), 4.95 (1H, dm, J = 9, cis-CH<sub>2</sub>CH=CH<sub>2</sub>), 5.65—6.15 (1H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 6.70 (1H, d, J = 9, 5-H) and 6.83 (1H, d, J = 9, 4-H) (Found: C, 71.1; H, 7.3%; M<sup>+</sup>, 220. Calc. for C<sub>17</sub>H<sub>12</sub>O<sub>2</sub>; C, 70.9; H, 7.3%; M<sup>+</sup>, 220).

2-Acetyl-5-prop-2'-enyl-1,4-dihydroquinone 29 and 2-acetyl-5-prop-2'-enyl-1,4-dihydroxquinone 30. The allyloxyacetophenone 28 (7.33 g, 38.3 mmol) was pyrolyzed under nitrogen at 215 °C (oil bath) for 1.5 h. The hard, tarry product was chromatographed using ethyl acetate–hexane (3:7) as eluent to afford the minor product 29 (620 mg, 8%) as olive-green plates, m.p. 100—102°C (from ethanol). ν<sub>max</sub> (film) 3350 cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz) 2.53 (3H, s, COCH<sub>3</sub>), 3.30 (2H, dt, J = 6.0 and 2.0 Hz, 2-CH<sub>2</sub>CH=CH<sub>2</sub>), 5.00—5.10 (2H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.25 (1H, s, D<sub>O</sub> exchangeable, 3-OH), 5.72—6.22 (1H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 6.80 (1H, s, 5-H), 7.17 (1H, s, 2-H), 11.87 (1H, s, D<sub>O</sub> exchangeable, 6-OH) (Found: C, 68.6; H, 6.4%; M<sup>+</sup>, 192. Calc. for C<sub>11</sub>H<sub>8</sub>O<sub>2</sub>; C, 68.75; H, 6.25%; M<sup>+</sup>, 192).

Later runs yielded the major product 30 (6.16 g, 84%) as tan crystals, m.p. 104—105 °C (lit.,<sup>17</sup> m.p. 103—104 °C); ν<sub>max</sub> (film) 3420, 3270, 1660 and 1610 cm<sup>-1</sup>; δ<sub>H</sub> 2.60 (3H, s, COCH<sub>3</sub>), 3.56 (2H, dt, J = 6.0 and 2.0 Hz, 2-CH<sub>2</sub>CH=CH<sub>2</sub>), 4.70 (1H, s, D<sub>O</sub> exchangeable, 3-OH), 5.07 (1H, dm, J = 17, trans-CH<sub>2</sub>CH=CH<sub>2</sub>), 5.23 (1H, dm, J = 9, cis-CH<sub>2</sub>CH=CH<sub>2</sub>), 5.80—6.30 (1H, m, CH<sub>2</sub>CH=CH<sub>2</sub>), 6.78 (1H, d, J = 9, 5-H), 6.98 (1H, d, J = 9, 4-H) and 10.30 (1H, s, D<sub>O</sub> exchangeable, 6-OH) (Found: C, 68.7; H, 6.1%; M<sup>+</sup>, 192. Calc. for C<sub>17</sub>H<sub>12</sub>O<sub>2</sub>; C, 68.75; H, 6.25%; M<sup>+</sup>, 192).
trans-3,4-Dihydro-1,3-dimethyl-1H-benzoc[pyran-5,8-di one 43. Pyran 35 (200 mg, 0.90 mmol) in a solution of acetonitrile–water (9:1) (10 cm³) was treated over a period of 5 min with cerium(IV) ammonium nitrate (997 mg, 1.82 mmol) dissolved in water (1 cm³). Stirring was continued for an additional 15 min, after which water (100 cm³) was added and the resulting mixture was extracted with dichloromethane. The residue obtained upon work-up was chromatographed using ethyl acetate–hexane (15:85) as eluent to afford the product 43 (156 mg, 90%) as an orange crystals, m.p. 102–104 °C (from hexane) (lit. 15; m.p. 102.5–105.5 °C).

(E)-2-Acetyl-1,4-dimethoxy-3-prop-1′-estrylbenzene 32. Ketone 31 (600 mg, 2.73 mmol) was dissolved in freshly distilled tetrahydrofuran (20 cm³) and the system was flushed with nitrogen for 5 min. Potassium tert-butoxide (1.28 g, 9.2 mmol) was added at once to the flask and stirring was continued for 2 h at 60 °C (oil bath). Aqueous ammonium chloride (5 cm³) was added and the resulting mixture was quenched by the addition of saturated ammonium bicarbonate (5 cm³) followed by water (100 cm³). The residue obtained upon work-up was chromatographed using ethyl acetate–hexane (1:4) over 5 min with cerium(IV) ammonium nitrate (1.04 g, 1.9 mmol) in ethanol (10 cm³). Stirring was continued for an additional 15 min, after which water (100 cm³) was added and the residue obtained was extracted with dichloromethane. The residue obtained upon work-up was chromatographed using ethyl acetate–hexane (15:85) as eluent to afford the product 41 (415 mg, 66%) as yellow solid, m.p. 98.5–99.5 °C (from hexane); νmax 3480–3100 cm⁻¹ (br); δ max (200 MHz) 1.38(3H, d, J 6.2, 3′-CH₃), 2.24(1H, d, J 6.2, 3′-CH₂), 4.02(1H, d, J 5.9, 1′-CH), 4.54 (1H, d, J 7.8, 3′-CH), 5.00(1H, q, J 6.5, 2′-CH), 6.43(1H, d, J 7.4, 2-CH) and 6.80(2H, s, 4- and 5-H) (Found: C, 63.6; H, 6.1% M, 222). Calcul. for C₁₅H₁₂O₂: C, 63.5; H, 6.1%; M, 222. Calc. for C₁₅H₁₂O₂: C, 63.5; H, 6.1%; M, 222.

(E)-1,4-Dimethoxy-2-(1′-hydroxyethyl)-3-prop-1′-estrylbenzene 34. To a slurry of lithium aluminium hydride (490 mg, 12.9 mmol) in dry ether (10 cm³) was added a solution of ketone 32 (570 mg, 2.59 mmol) in dry ether (20 cm³) over 3 min, followed by stirring of the reaction mixture for an additional 20 min. The reaction was quenched by the addition of saturated ammonium chloride and then diluted with the addition of dichloromethane (80 cm³). The residue obtained upon work-up was chromatographed using ethyl acetate–hexane (1:4) to afford the product 34 (560 mg, 97%) as a white crystalline solid, m.p. 83.5–84.5 °C (from hexane); νmax 3520 cm⁻¹; δmax (film) 1698 cm⁻¹; δ max (200 MHz) 1.37(3H, d, J 6.3, 3′-CH₃), 2.42(3H, s, COCH₃), 3.77 and 3.80 (each 3H, each s, 2 x OCH₃), 6.00(1H, dd, J 16 and 6, 2′-CH), 6.45(1H, d, J 16, 1′-CH) and 6.80(2H, s, 4- and 5-H) (Found: C, 71.5; H, 7.2%; M⁺, 220). Calc. for C₁₅H₁₂O₂: C, 70.9; H, 7.3%; M⁺, 220.

(E)-3,4-Dihydro-5,8-dimethoxy-1,3-dimethyl-4-oxo-1H-benzo[ç]pyran 36. To a solution of alcohol 34 (105 mg, 0.47 mmol) in acetonitrile (10 cm³) and water (10 cm³) over 5 min. Stirring was continued for an additional 20 min and then the reaction mixture was extracted with dichloromethane. The residue obtained upon work-up was chromatographed using ethyl acetate–hexane (1:4) as eluent to afford the product 36 (25 mg, 21%) as an oil; νmax (film) 3480–3100 cm⁻¹ (br); δ max (200 MHz) 1.37(3H, d, J 6.3, 3′-CH₃), 1.55(3H, d, J 6.7, 1′-CH), 3.74 and 3.84 (each 3H, s, OCH₃), 3.96(3H, m, 3-H and pseudo-equatorial 4-OH), 1.85(3H, d, J 7.4, 2′-CH), 4.54(1H, q, J 6.5, 2′-CH) and 6.74(2H, s, 4- and 5-H) (Found: C, 63.5; H, 6.05%; M⁺, 220. Calc. for C₁₅H₁₃O₃: C, 65.5; H, 7.6%; M⁺, 220.)

trans-5,8-Dimethoxy-1,3-dimethyl-4-oxo-1H-benzo[c] pyran 38. To a solution of pyran 36 (426 mg, 1.79 mmol) in dry dichloromethane (20 cm³) under an atmosp-
phore of nitrogen was added pyridinium dichromate (10 g, 26.9 mmol) and the reaction mixture was stirred for 12 h. After filtration the solvent was removed from the filtrate to leave a residue that was chromatographed using ethyl acetate–hexane (1:4) to elute the ketone 38 (126 mg, 30%) as a white solid, m.p. 82—84 °C from hexane; νmax 1690 cm⁻¹, δ(200 MHz) 1.43(3H, d, J 6.6, 3-CH3), 1.90(3H, s, D 9.1, 7-CH3), 6.74(1H, d, J 6.6, 3-H), and 6.79(1H, d, J 6.6, 1-H) and 6.97(1H, d, J 9.1, 7-H) (Found: C, 66.0; H, 6.8%; M+, 208.0742. Calc. for C11H9O2: C, 66.1; H, 6.8%; M, 208.0736).

Further elution afforded the starting material 36 (250 mg, 59%).

trans-(1R,3R)-5,8-Dihydroxy-1,3-dimethyl-4-oxo-1H-benzo(c)pyran 39. To a stirred mixture of pyran 38 (120 mg, 0.51 mmol) in dioxane (5 cm³) containing silver(II) oxide (253 mg, 2.04 mmol) was added nitric acid (2.5 cm³ of a 6 mol dm⁻³ solution) dropwise until all the silver(II) oxide had dissolved. The reaction mixture was stirred for an additional 10 min, after which water (60 cm³) was added and the solution extracted with dichloromethane. The residue obtained upon work-up was chromatographed using ethyl acetate-hexane (1:4) as eluent to afford the product 39 (66 mg, 62%) as white crystals, m.p. 94—95 °C (from hexane); νmax, 3370, 1700 and 1650 cm⁻¹; δ(200 MHz) 1.43(3H, d, J 6.6, 3-CH3), 1.51(3H, d, J 6.7, 1-CH3), 4.57(1H, q, J 6.6, 3-H), 4.90(1H, br s, D2O exchangeable, 8-CH3), 5.23(1H, q, J 6.7, 1-H), 6.67(1H, d, J 8.8, 6-H), 6.87(1H, d, J 8.8, 7-H) and 11.32(1H, s, D2O exchangeable, 5-CH3) (Found: C, 63.3; H, 5.8%; M, 208.0742. Calc. for C11H9O3: C, 63.5; H, 5.8%; M, 208.0736).

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References
2 Full details of the biological activity of these compounds will be published elsewhere.