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Mercury(II) mediated cyclisation of *R*-1-(1′-hydroxyethyl)-2-(1″-propenyl)-3-alkoxy-4-methoxybenzenes to chiral isochromanes

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Abstract—A protocol has been established for the transformation of chiral *ortho* 1-hydroxyethyl propenyl benzenes under both anaerobic and oxidative mercury(II) mediated conditions to produce chiral isochromanes. Further transformations of the former products yielded chiral isochromanquinones, while the latter afforded the corresponding chiral 4-hydroxyisochromanquinones.

1. Introduction

Many naturally occurring quinones possessing either the naphthopyran or the isochromane nucleus demonstrate a wide spectrum of biological activity.[1–3] This has in major part been attributed to the positions of (a) the pyran ring oxygen atom (O-2), (b) the presence of a good leaving group at C-4 of the pyran ring.[4] Indeed we[5] and others[6,7] have had some success employing aspects of these ideas towards the synthesis of compounds containing these key features. Two substantive reviews on the isolation and structural determination of naphthopyranquinones[8] as well as their general syntheses[9] have recently appeared. Typical examples of these quinones include eleutherin **1**,[10] nanomycin D **2**,[11] erythrostominone **3**,[12] and granaticin **4**[13] (Fig. 1).

The pyran ring of these molecules generally contains either two, e.g., **1** and **3** or three, e.g., **2** and **4** stereogenic centres that have to be assembled in a stereocontrolled fashion. In this regard considerable efforts have been made in developing protocols for the synthesis of some enantiomerically pure naphthopyranquinones.[2,14–16]

As part of an ongoing research programme directed towards the synthesis of the chiral isochromanquinone nucleus, we have utilized Corey-Bakshi-Shibata asymmetric reductions of carbonyl precursors to provide what will ultimately be the stereogenic methyl substituent present at C-1 of the target compounds (Fig. 1). This has been described in previous reports from these laboratories.[17,18]

This paper describes the details of mercury(II) mediated cyclisations of these chiral benzylic alcohol precursors into chiral isochromanes and eventually into the corresponding quinones.

2. Results and discussions

2.1. Synthesis of racemic isochromanquinones

In order to validate the sequence of transformations envisaged for the synthesis of the required isochromanes in a racemic manner, the racemic alcohols **6a–c**[18] were treated, under established conditions,[19b] with 4 molar equivalents of potassium *t*-butoxide in DMF at 80 °C for 45 min to afford the corresponding *trans*-1,3-dimethylisochromanes **7a–c** in good yields. In all three products 3-H appeared as a multiplet at δ 4.00–3.98 which demonstrated that the relative stereochemistry of the methyl groups at C-1 and C-3 was *trans*.[19a]

The benzyl group was removed from isochromane **7c** by catalytic hydrogenolysis to afford the corresponding phenol **8** in 96% yield while boron tribromide at −78 °C was used to remove the isopropyl group in **7b** to produce the same racemic phenol **8** but in a reduced yield of 75%. Finally, phenol **8** was oxidized with Fremy's salt[20] to the bright yellow racemic *trans*-1,3-dimethylisochromanquinone **9** in 61% yield (Scheme 1).

Keywords: Isochromanes; Mercury(II) acetate; Quinones; Oxidative cyclisation.
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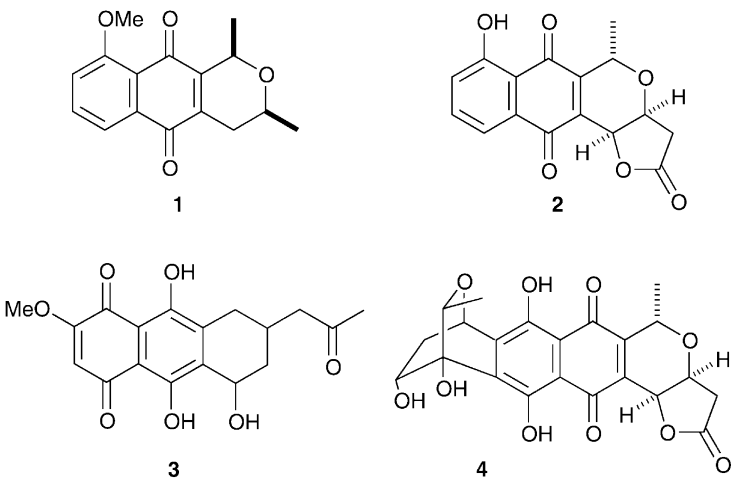
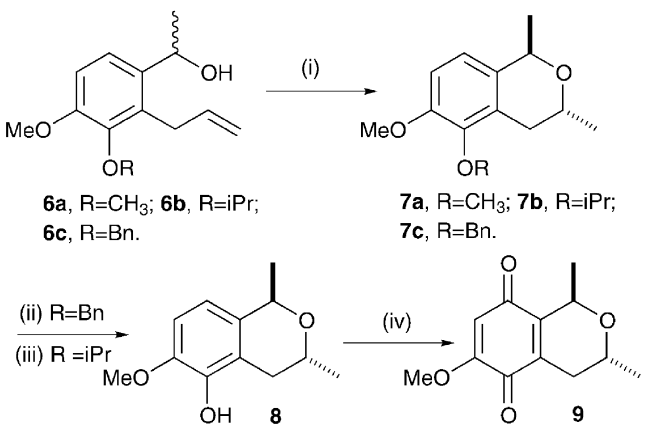


Figure 1.



Scheme 1. (i) KOBu^t, DMF, 80 °C, **7a**, 96%; **7b**, 90%; **7c**, 77%; (ii) H_2, 5% Pd/C, EtOAc, 96%; (iii) BBr_3/CH_2Cl_2, −78 °C, 75%; (iv) $K(SO_3)_2NO$, MeOH/phosphate buffer, 25 °C, 61%.

2.2. Synthesis of chiral isochromanes

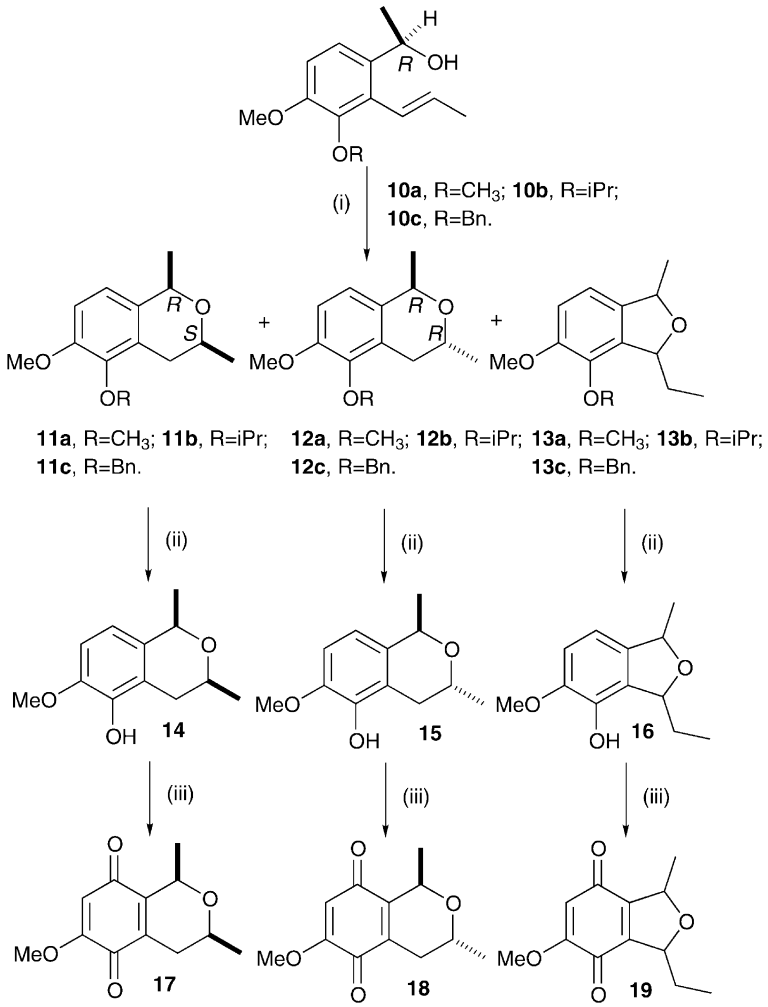
In turning our attention towards the transformation of the chiral alcohols **10a–c**[18] into the corresponding chiral isochromanes, either mercury(II) acetate[21] or potassium *t*-butoxide[19b] could be used since the former method affords both the *cis*- and *trans*-1,3-dimethylisochromanes non-diastereoselectively,[22,23] while the latter method was developed to provide a completely diastereoselective route to solely the *trans* compounds for the purposes of natural product synthesis.[24] In the present context the former method was chosen since it thus offered the potential for the additional *cis*-diastereoisomer to be produced. Furthermore, it is known that prolonged treatment by butoxide leads to some isomerisation of the *trans* isomer into its *cis* isomer.[19b] Since the precise mechanism of this latter isomerisation is not fully understood, its use would raise the unlikely possibility of racemisation of an asymmetric carbon.

Thus the *R*-alcohols **10**[18] (75% ee) in a THF–H_2O (1:1) solution were treated with mercury(II) acetate followed by aqueous sodium hydroxide and later by sodium borohydride to afford the separable diastereoisomeric mixtures of the pyrans **11** (1*R*, 3*S*) and **12** (1*R*, 3*R*) in a ratio of 1:1 and average yields of 60% together with trace quantities (~4%) of the benzofurans **13** as determined by ^{1}H NMR spectroscopy and GCMS as shown in Scheme 2.

Since the absolute configuration of the starting alcohol is known to be (*R*), assignment of the absolute configurations for pyrans **11** and **12** is based on the chemical shift for 3-H in the ^{1}H NMR spectra. For *cis*-pyran **11**, 3-H appeared as a multiplet at δ 3.71–3.75, while in *trans*-pyran **12** the same proton appeared as a multiplet at δ 3.98–4.00 similar to our earlier findings.[25] Benzofurans **13** could not be obtained pure enough at this stage for a complete structural assignment, since the R_f was similar to pyran **12**. However, the corresponding quinone **19** was isolated in pure form (vide infra).

Catalytic hydrogenolysis of the pyran mixture of **11c**, **12c** and **13c** afforded the corresponding phenolic mixture of **14**, **15** and **16** in 97% crude yield in the ratio of 47:47:6 by GCMS. Owing to the chemically sensitive nature of phenols, the mixture was not separated but immediately oxidized using Fremy's salt[20] to afford a mixture of the quinones **17**, **18**, and **19** in a crude yield of 70%.

Good separation was effected using radial chromatography to afford initially the benzofuranquinone **19** (6%) which apart from a molecular ion of *m*/*z* 222 in the mass spectrum had a strong C=O absorption at 1665 cm^{-1} in the infrared spectrum. The ^{1}H NMR spectrum showed, inter alia, a 3-proton triplet at δ 0.99 (J=7.2 Hz) coupled to a 2-proton multiplet at δ 1.71 (COSY) for the C-1 ethyl group; a 3-proton doublet at δ 1.47 (J=6.2 Hz) assigned to the C-3 methyl group; a 2-proton multiplet at δ 5.26 for 1- and 3-H which were confirmed by COSY cross peaks to both the 1-CH_3 and the CH_2 of the ethyl side chain at C-1. The next quinone to elute (26%) was assigned the absolute configuration of structure **17**, while the last to elute (28%) was assigned the absolute configuration of structure **18**. Assignment of the absolute configurations to these quinones is based on ^{1}H NMR data. For quinone **17**, the signal for 3-H appeared as a multiplet at δ 3.53 thus placing the C-1 and C-3 methyl groups *cis* to each other and di-equatorial; the signal for the 4-Ha appeared as a ddd at δ 2.13 with ^2J=18.4 to 4-H_e, ^3J=10.0 to 3-H_a and ^5J=4.0 to 1-H_a; the signal due



Scheme 2. (i) $Hg(OAc)_2$, NaOH, $NaBH_4$, THF/H_2O; for **11a** and **12a** 64%; for **11b** and **12b** 55%; for **11c** and **12c** 62%; trace quantities (~4%) of **11c**, **11b** and **11c** in each rxtn; (ii) BBr_3/CH_2Cl_2, −78 °C; or for **11c**–**13c** (R=Bn) (ii) H_2, 5% Pd/C, EtOAc, H^+, each 97%; (iii) $K(SO_3)_2NO$, MeOH/phosphate buffer, 25 °C; **14**→ **17**, 56%; **15**→ **18**, 59%; **16**→ **19**, 94%.

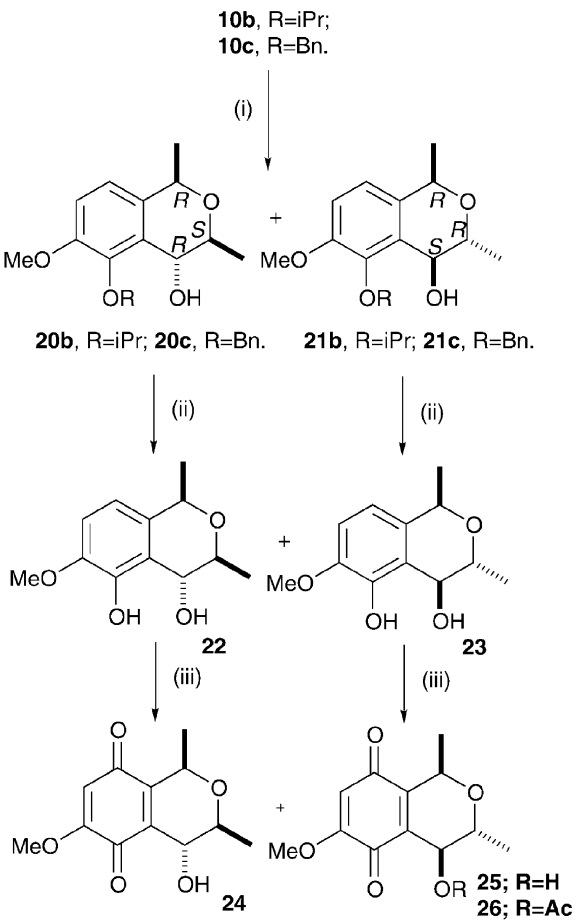
to 4-H_e appeared as a ddd at δ 2.61 with ^2J=18.4 to 4-H_a, ^3J=3.6 to 3-H_a and ^5J=1.0 to 1-H_a. Finally, the signal assigned to 1-H_a appeared as a ddq at δ 4.69 with ^3J=6.6 Hz and ^5J of 4.0 and 1.0 Hz. Assignment of the absolute stereochemistry for quinone **18** was based inter alia on the position of 3-H_a, which appeared as a multiplet at δ 3.92. Upon addition of 10 mol% of the lanthanide shift reagent, Eu(hfc)$_3$, all the signals experienced a strong deshielding effect, the most dramatic being 7-H from δ 5.83 to separate into two peaks at δ 7.04 and 6.99, which were used to determine the de values for **18** and **17** as 75%.

2.3. Synthesis of chiral 4-hydroxyisochromanes

Earlier, de Koning et al.[26] reported on an oxidative mercury(II) mediated ring closure procedure of *ortho* allyl hydroxymethyl benzene systems based on the work of Hill and Whitesides[27] during which the formed radical intermediate trapped oxygen specifically at the benzylic position. It was surmised that under similar conditions it might be possible to prepare chiral-4-hydroxy-1,3-dimethylisochromanes.

Initial attempts based upon the above protocol using chiral alcohol **10c** afforded only one product viz. **21c** (Scheme 3), but in a yield of 7% after 4 h, together with starting material. Increasing the reaction time to 12 h again afforded the hydroxypyran **21c** in 7% yield together with a new compound (11%) to which the dimeric structure **27** has been assigned (Fig. 2). Its HRMS indicated the molecular formula $C_{38}H_{42}O_6$. Four doublets in the ^{1}H NMR spectrum characterized the dimeric nature of the product viz., δ 1.28 and 1.35 (J=6.2 Hz) for the C-3 and C-3′ methyl groups and δ 1.50 and 1.55 (J=6.6 Hz) for the C-1 and C-1′ methyl groups. It is of interest to note that 3-H and 3′-H appear as two separate signals one at δ 3.98 and the other at δ 4.28 (dq, J=6.6 and 6.2 Hz for both), which would support the fact that the two methyl groups at C-1 and C-3 are *trans* to each other. The larger coupling of 6.6 Hz between 3-H and 4-H would suggest that these protons are *trans* and that the C-4, C-4′ bond is thus pseudoequatorial in both pyran rings. COSY spectroscopy supported the assigned structure as the 2-proton multiplet at δ 2.87 assigned to 4- and 4′-H showed two clear cross-peaks to the signals of 3- and 3′-H which in turn had cross-peaks to the C-3 and C-3′ methyl groups.

By employing a modification to the earlier method of cyclisation,[26,27] as outlined in Section 3, oxidative cyclisation



Scheme 3. (i) $Hg(OAc)_2$, NaOH, $NaBH_4$, O_2, DMF, R=iPr 50%; R=Bn, 75%; (ii) for **20c** and **21c** H_2, 5% Pd/C, EtOAc, H^+, 96%; (iii) $K(SO_3)_2NO$, MeOH/phosphate buffer, 25 °C, **25**, 35%, **24**, decomposed.

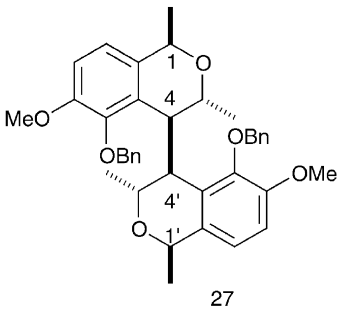


Figure 2.

was successfully effected on alcohol **10b** to afford **20b** and **21b** in 50% yield as a 1:1 mixture by GCMS while alcohol **10c** was oxidatively cyclised into a 1:1 mixture of **20c** and **21c** in an improved yield of 75% (Scheme 3). Isochromanes **20b** and **21b** proved extremely difficult to separate with only **20b** obtained pure; **21b** always had a trace (~5%) of **20b** present thus precluding optical measurements. Assignment of the absolute configurations for pyran **20b**, the 1*R*, 3*S*, 4*R* isomer, is based on the following ^{1}H NMR spectral data; a well-defined dq at δ 3.60 for 3-H clearly established the 1,3-diequatorial orientations of the two methyl groups from its chemical shift. The ^3J coupling constant of 6.2 Hz for the quartet corresponded to the coupling with the C-3 methyl group while a ^3J of 8.0 Hz to 4-H supported an approximately *trans* diaxial relationship between 3-H and 4-H and consequently the 4-OH is pseudoequatorial. Unfortunately, the signals due to 1-H, 4-H and the methine proton of the isopropyl group all overlapped at δ 4.70. On the other hand, compound **21b** exhibited a dq at δ 3.96 assigned to 3-H in the ^{1}H NMR spectrum. In this instance the chemical shift was consistent with a *trans* arrangement of the methyl substituents, while ^3J for the doublet was 6.6 Hz also demonstrating a *trans* diaxial relationship between 3-H and 4-H and thus supporting the orientation of 4-OH as pseudoequatorial. As further support for the assignment, the signal due to 4-OH appeared as a doublet at δ 4.10 (J=3.0 Hz) while 4-H appeared as a dd at δ 4.58 (J=6.6 and 3.0 Hz) and collapsed to a doublet (J=6.6 Hz) after D_2O washing.

Similarly pyrans **20c** and **21c** proved equally difficult to separate with only **20c** being obtained in pure form. Assignments were made using the same arguments as above. Pd/C catalyzed debenzylation of the pyran mixture of **20c** and **21c** yielded the expected mixture of the corresponding phenols **22** and **23**. Since these had the potential for instability,[14] they were immediately oxidized with Fremy's salt to afford a quinone mixture of **24** and **25** (60%) from which only one optically enriched diastereoisomer **25** was isolated (35%), the other undergoing decomposition.

Assignment of the configurations at the pyran ring carbons of **25** is based inter alia on the following signals in the ^{1}H NMR spectrum; a dq at δ 3.82 assigned to 3-H_a with ^3J to the C-3 methyl of 6.2 Hz and *trans* coupling of 7.8 Hz to 4-H_a; a D_2O exchangeable doublet at δ 3.42 (J=2.6 Hz) for 4-OH_e and a ddd at δ 4.34 assigned to 4-H_a with ^3J of 7.8 Hz to 3-H_a, ^3J of 2.6 to the 4-OH_e and ^5J of 1.0 Hz to 1-H_e. After a D_2O wash this signal collapsed to the expected dd (J=7.8 and 1.0 Hz). Since addition of the lanthanide shift reagent proved inconclusive to determine the de value for **25**, it was converted into the corresponding C-4 acetate **26** in pyridine and acetic anhydride. Addition of 10% $Eu(hfc)_3$ successfully caused the signal of the acetate group at δ 2.08 to become deshielded and split into two distinct signals at δ 2.86 and 2.79 which allowed the de to be determined as 70% (c=0.45; $CDCl_3$).

In conclusion, a method has been developed for the synthesis of chiral isochromanequinones in which a methoxy group is at position 6 for improved biological activity.[5] By a slight modification during the oxidative cyclisation step, a C-4 hydroxy group has been introduced stereoselectively to afford the corresponding 4-hydroxy isochromanequinones. Methods of improving the yields and ee's are currently under investigation.

3. Experimental

3.1. General

^{1}H- and ^{13}C spectra were recorded on a Varian 200 MHz spectrometer at 20 °C in deuterochloroform and J values are given in Hz. Assignments with the same superscript may be interchanged. Infrared spectra were measured as nujol mulls on a Perkin Elmer FT-IR 1000 PC spectrometer. Mass

spectra were recorded on a Finnigan Matt GCQ spectrometer or a VG 70E MS spectrometer. Melting points are uncorrected and were measured on a Fischer–John melting point apparatus. Elemental analysis was performed on a Carlo Erba 1500 NA analyser. Optical rotations were measured on a Perkin Elmer-Polarimeter 141, at 20 °C using the sodium D line. Preparative column chromatography was carried out on dry-packed columns using Silica Gel 60 (particle size 0.063–0.02 nm). The term 'residue obtained upon work-up' refers to the drying of the extract over magnesium sulfate, filtration and evaporation of the solvent.

3.1.1. General methodology for the base-induced cyclisation of racemic alcohols 6a, 6b and 6c. To a rapidly stirred solution of the alcohol **6** (2 mmol) in dimethylformamide (50 ml) under nitrogen at an oil bath temperature of 80 °C was added in one batch potassium *t*-butoxide (8 mmol) and the resulting mixture was stirred for 45 min. Water (200 ml) and ether (100 ml) were added to the cooled reaction mixture, which was exhaustively extracted with ether. The residue obtained upon work-up was purified by column chromatography using EtOAc/hexane (1:9) as the eluent to yield the racemic isochromanes as follows.

3.1.2. (±) *trans* 3,4-Dihydro-5,6-dimethoxy-1,3-dimethylbenzo[*c*]pyran 7a. Colourless oil (96%); δ_H 1.33 (3H, d, J=6.2 Hz, 3-CH_3), 1.49 (3H, d, J=6.6 Hz, 1-CH_3), 2.42 (1H, dd, J=16.8, 9.9 Hz, 4-Ha), 2.91 (1H, dd, J=16.8, 3.6 Hz, 4-He), 3.81 and 3.95 (each 3H, s, OCH_3), 4.00 (1H, m, 3-H), 5.00 (1H, q, J=6.6 Hz, 1-H), 6.75 (1H, d, J=8.4 Hz, 7-H), and 6.78 (1H, d, J=8.4 Hz, 8-H); δ_C 21.6 (3-CH_3), 22.4 (1-CH_3), 30.4 (C-4), 55.9 and 60.2 (OCH_3), 63.5 (C-3), 70.3 (C-1), 110.4 (C-7), 120.7 (C-8), 127.8 (C-8a)[a], 132.4 (C-4a)[a], 146.2 (C-5)[6], and 150.6 (C-6)[b]; MS (E1): *m*/*z* (%): 222 (M^+, 20), 207 (100), 189 (11), 176 (16). Calcd for $C_{13}H_{18}O_3$: C, 70.2; H, 8.2%; M 222. Found: C, 70.1; H, 8.2%.

3.1.3. (±) *trans* 3,4-Dihydro-5-isopropyloxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 7b. Colourless oil (90%); δ_H 1.25 [6H, d, J=6.2 Hz, CH(CH_3)$_2$], 1.29 (3H, d, J=6.2 Hz, 3-CH_3), 1.48 (3H, d, J=6.6 Hz, 1-CH_3), 2.42 (1H, dd, J=16.4, 9.4 Hz, 4-H_a), 2.91 (1H, dd, J=16.4, 3.4 Hz, 4-H_e), 3.81 (3H, s, OCH_3), 3.98 (1H, m, 3-H), 4.49 [1H, septet, J=6.2 Hz, C*H*(CH_3)$_2$], 5.00 (1H, q, J=6.6 Hz, 1-H), 6.72 (1H, d, J=8.4 Hz, 7-H), and 6.76 (1H, d, J=8.4 Hz, 8-H); δ_C 21.5 (3-C), 22.5 (1-C), 22.8 [×2, CH(*C*H_3)$_2$], 31.4 (C-4), 55.9 (OCH_3), 63.8 (C-3), 70.2 (C-1), 74.4 [*C*H(CH$_3$)$_2$] 110.4 (C-7), 120.1 (C-8), 128.5 (C-8a)[a], 132.4 (C-4a)[a], 144.1 (C-6)[b], and 150.8 (C-5)[b]; MS (EI): *m*/*z* (%): 250 (M^+, 19), 235 (29), 193 (100), 143 (13). Calcd for $C_{15}H_{22}O_3$: C, 71.95; H, 8.9%, M 250. Found: C, 72.1; H, 8.6%.

3.1.4. *trans* 3,4-Dihydro-5-benzoloxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 7c. White needles (77%), mp 85–87 °C (from hexane–ethyl acetate); δ_H 1.26 (3H, d, J=6.2 Hz, 3-CH_3), 1.48 (3H, d, J=6.6 Hz, 1-CH_3), 2.31 (1H, dd, J=16.8, 9.6 Hz, 4-H_a), 2.82 (1H, d, J=16.8, 3.4 Hz, 4-H_e), 3.87 (3H, s, OCH_3), 3.98 (1H, m, 3-H), 4.97 (1H, q, J=6.6 Hz, 1-H), 4.99 (2H, s, O*C*H_2Ph), 6.76 (1H, d, J=8.8 Hz, 7-H), 6.82 (1H, d, J=8.8 Hz, 8-H), and 7.38 (5H, m, aryl); δ_C 21.4 (3-CH_3), 22.5 (1-CH_3), 30.8 (C-4), 56.0 (OCH_3), 63.6 (C-3), 70.2 (C-1), 74.3 (O*C*H_2Ph), 110.5 (C-7), 120.8 (C-8), 127.9 (Ph), 128.0 (×2, Ph), 128.2 (×2, Ph), 128.4 (Ph), 132.4 (C-4a)[a], 138.0 (C-8a)[a], 145.0 (C-5)[b], and 150.7 (C-6)[b]; MS (EI): *m*/*z* (%): 298 (M^+, 31), 283 (73), 254 (46), 207 (14), 177 (20), 163 (53), 135 (17), 91 (100). Calcd for $C_{19}H_{22}O_3$: C, 76.5; H, 7.45%, M 298. Found: C, 76.4; H, 7.3%.

3.1.5. (±) *trans* 3,4-Dihydro-5-hydroxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 8. *Method A*. Pyran **7c** (123 mg; 0.41 mmol) in ethyl acetate (15 ml) containing 5% Pd on charcoal (15 mg) and 1 drop 10 M hydrochloric acid was hydrogenated. The residue obtained upon work-up was flash chromatographed using EtOAc/hexane (1:4) to yield the phenol **8** as a red oil (82 mg; 96%). ν_{max} 3472 cm^{-1} (bs, OH); δ_H 1.33 (3H, d, J=6.2 Hz, 3-CH_3), 1.49 (3H, d, J=6.6 Hz, 1-CH_3), 2.42 (1H, dd, J=16.8, 8.0 Hz, 4-H_a), 2.85 (1H, dd, J=16.8, 3.6 Hz, 4-H_e), 3.87 (3H, s, OCH_3), 4.12 (1H, m, 3-H), 4.99 (1H, q, J=6.6 Hz, 1-H), 5.69 (1H, bs, D_2O exchangeable, 5-OH), 6.54 (1H, d, J=8.4 Hz, 7-H), and 6.73 (1H, d, J=8.4 Hz, 8-H); δ_C 21.7 (3-CH_3), 22.6 (1-CH_3), 30.2 (C-4), 56.3 (OCH_3), 63.4 (C-3), 70.6 (C-1), 108.6 (C-7), 116.3 (C-8), 120.1 (C-4a)[a], 133.1 (C-8a)[a], 143.3 (C-5)[b], and 144.4 (C-6)[b]; MS (EI): *m*/*z* (%): 208 (M^+, 22), 193 (100), 161 (11), 143 (25), 133 (20). Calcd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.6%; M 208. Found: C, 69.3; H, 7.4%.

Method B. Pyran **7b** (250 mg; 1 mmol) in dichloromethane (25 ml) at −78 °C under nitrogen was treated with boron tribromide (2.5 mmol) and allowed to stir for 1 h. The excess of reagent was destroyed with water (1 ml) and the residue obtained upon work-up was flash chromatographed as in Method A to yield phenol **8** as a red oil (158 mg; 75%) having identical spectral properties as measured earlier.

3.1.6. (±) *trans* 6-Methoxy-1,3-dimethylbenzo[*c*]pyran-5,8-dione 9. To 4.7 ml of an aqueous buffered solution (79 ml of 0.2 M sodium hydrogen phosphate and 171 ml of 0.2 M sodium dihydrogen phosphate) containing Fremy's salt (200 mg; 0.56 mmol)[20] was added in one batch a solution of phenol **8** (58 mg; 0.28 mmol) in methyl alcohol (0.4 ml). After stirring for 1 h, water (10 ml) was added and the reaction mixture extracted with dichloromethane. The residue obtained upon work-up was chromatographed using EtOAc/hexane (1:4) as eluent to yield the quinone **9** (38 mg; 61%), mp 134–136 °C (from hexane–ethyl acetate). Lit. mp 137–138 °C.[5]

3.1.7. (1*R*, 3*S*)-3,4-Dihydro-5,6-dimethoxy-1,3-dimethylbenzo[*c*]pyran 11a, (1*R*, 3*R*)-3,4-dihydro-5,6-dimethoxy-1,3-dimethylbenzo[*c*]pyran 12a and 6,7-dimethoxybenzofurans 13a. A solution of *R*-alcohol **10a**[18] (520 mg; 2.34 mmol) in tetrahydrofuran (17 ml) and water (17 ml) was treated with mercury(II) acetate (746 mg; 2.34 mmol) and stirred at 25 °C for 1 h. Aqueous sodium hydroxide (17 ml of a 3 M solution) was added and stirring was continued for a further 1 h. A further portion of aqueous sodium hydroxide (17 ml of a 3 M solution) and sodium borohydride (1.95 g; 51.5 mmol) were added and stirring continued for a further 1 h. The reaction mixture was exhaustively extracted with ethyl acetate and the residue chromatographed using EtOAc/hexane (1:4) as eluent to afford a (1:1) mixture of pyrans **11a** and **12a** together with

the benzofurans **13a** (332 mg; 64%) in a ratio of (48:48:4) by GC–MS. PLC purification of 50 mg of this sample using EtOAc/hexane (1:9) as eluent afforded the benzofurans **13a** (1.6 mg) followed by the *cis* dimethylpyran **11a** (21 mg) as an oil. δ_H 1.39 (3H, d, J=6.2 Hz, 3-CH_3), 1.52 (3H, d, J=6.6 Hz, 1-CH_3), 2.51 (1H, dd, J=17.0, 10.6 Hz, 4-H_a), 2.88 (1H, dd, J=17.0, 3.4 Hz, 4-H_e), 3.75 (1H, m, H-3a), 3.81 and 3.85 (each 3H, s, OCH_3), 4.91 (1H, q, J=6.6 Hz, 1-H), 6.76 (1H, d, J=8.4 Hz, 7-H), and 6.83 (1H, d, J=8.4 Hz, 8-H); δ_C 21.6 (3-CH_3), 22.4 (1-CH_3), 30.5 (C-4), 55.9 and 60.2 $(OCH)_3$, 63.5 (C-3), 70.3 (C-1), 110.4 (C-7), 120.7 (C-8), 127.8 (C-4a)[a], 132.4 (C-8a)[a], 146.2 (C-6)[b], 150.6 (C-5)[b]; MS (EI): *m/z* (%): 222 (M^+, 20), 207 (100), 189 (11), 176 (16). Calcd for $C_{13}H_{18}O_3$: C, 70.2; H, 8.2%; M 222. Found C, 70.1; H, 8.2%.

The next fraction to elute was the *trans* dimethylpyran **12a** (20 mg) as an oil with NMR spectral properties identical to the racemic pyran **7a**.

3.1.8. (1*R*, 3*S*)-3,4-Dihydro-5-isopropoxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 11b, (1*R*, 3*R*)-3,4-dihydro-5-isopropoxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 12b and the benzofurans 13b. Using an analogues synthetic protocol described for pyrans **11a** and **12a** the *R*-isopropoxy alcohol **10b**[18] (404 mg; 1.62 mmol, 75% ee) afforded a residue, which was chromatographed to yield a mixture of the pyrans **11b** and **12b** and the furans **13b** (220 mg; 55%) in the ratio of (47:47:6) by GC–MS. PLC of a 50 mg portion using EtOAc/hexane (1:9) afforded the benzofurans **13b** (2.5 mg) followed by the *cis* dimethylpyran **11b** (22 mg) as an oil. δ_H 1.26 [6H, d, J=6.2 Hz, $CH(CH_3)_2$], 1.34 (3H, d, J=6.2 Hz, 3-CH_3), 1.47 (3H, d, J=6.6 Hz, 1-CH_3), 2.40 (1H, dd, J=16.4, 9.8 Hz, 4-Ha), 2.89 (1H, dd, J=16.4, 3.2 Hz, 4-He), 3.71 (1H, m, 3-Ha), 3.81 (3H, s, OCH_3), 4.47 [1H, septet, J=6.2 Hz, $CH(CH_3)_2$], 4.77 (1H, q, J=6.2 Hz, 1-H), 6.73 (1H, d, J=8.4 Hz, 7-H), and 6.75 (1H, d, J=8.4 Hz, H-8); δ_C 21.5 (3-CH_3), 22.5 (1-CH_3), 22.7 (×2) [$CH(CH_3)_2$], 31.4 (C-4), 55.9 (CH_3), 66.3 (C-3), 70.2 (C-1), 74.4 [$CH(CH_3)_2$], 110.7 (C-7), 120.1 (C-8), 128.5 (C-4a)[a], 132.4 (C-8a)[a], 144.1 (C-6)[b] and 150.8 (C-5)[b]. MS (EI): *m/z* (%): 250 (M^+, 19), 235 (29), 193 (100), 143 (13). Calcd for $C_{15}H_{22}O_{33}$: C, 71.95; H, 8.9%; M 235. Found: C, 72.2; 8.4%. Further elution afforded the *trans* dimethylpyran **12b** (23 mg) as an oil with NMR spectra identical to the racemic pyran **7b**.

3.1.9. (1*R*, 3*S*)-5-Benzyloxy-3,4-dihydro-6-methoxy-1,3-dimethylbenzo[*c*]pyran 11c, (1*R*, 3*R*)-5-benzyloxy-3,4-dihydro-6-methoxy-1,3-dimethylbenzo[*c*]pyran 12c and the benzofurans 13c. Applying the same synthetic protocol as described above the *R*-benzyloxy alcohol **10c**[18] (375 mg; 1.26 mmol) afforded a residue, which was chromatographed using EtOAc/hexane (1:4) as eluent to produce a mixture of the pyrans **11c** and **12c** and furans **13c** (233 mg; 62%) in the ratio of (47:47:6) by GC–MS. PLC of a 50 mg portion using EtOAc/hexane (1:9) as eluent afforded the benzofurans **13c** (2.7 mg) followed by the *cis* dimethylpyran **11c** (20 mg) as an oil. δ_H 1.32 (3H, d, J=6.2 Hz, 3-CH_3), 1.46 (3H, d, J=6.2 Hz, 1-CH_3), 2.30 (1H, dd, J=16.8, 11.0 Hz, 4-H_a), 2.85 (1H, dd, J=16.8, 3.2 Hz, 4-H_e), 3.75 (1H, m, H-3_a), 3.87 (3H, s, OCH_3), 4.78 (1H, q, J=6.2 Hz, 1-H), 4.99 (2H, s, CH_2Ph), 6.78 (1H, d, J=8.8 Hz, H-7), 6.80 (1H, d, J=8.8 Hz, H-8), and 7.38 (5H, m, Ph); δ_C 21.3 (3-CH_3), 22.5 (1-CH_3), 30.8 (C-4), 56.0 (OCH_3), 63.6 (C-3), 70.2 (C-1), 74.3 (OCH_2Ph), 110.7 (C-7), 120.8 (C-8), 127.9 (aryl), 128.2 (×2, aryl), 128.3 (×2, aryl), 128.4 (aryl), 134.4 (C-4a)[a], 138.0 (C-8a)[a], 145.0 (C-5)[b], and 150.7 (C-6)[b]; MS (EI): *m/z* (%): 298 (M^+, 31), 283 (73), 254 (46), 207 (14), 177 (20), 163 (53), 135 (17), 91 (100). Calcd for $C_{19}H_{22}O_3$: C, 76.5; H, 7.45%; M 298. Found C, 76.6; H, 7.5%. Further elution afforded the *trans* dimethyl pyran **12c** (22 mg) as an oil with NMR spectral data similar to the racemic *trans* pyran **7c**.

3.1.10. (1*R*, 3*S*)-3,4-Dihydro-5-hydroxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 14, (1*R*, 3*R*)-3,4-dihydro-5-hydroxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 15 and the benzofurans 16. An isomeric mixture of the pyrans **11c**, **12c** and **13c** (988 mg; 3.32 mmol) in ethyl acetate (40 ml) containing palladium on charcoal (5%, 100 mg) and two drops of concentrated aqueous hydrogen chloride was hydrogenated for 15 h, filtered and removal of the solvent gave a mixture (670 mg; 97%) of phenols **14**, **15** and **16** in the ratio of 47:47:6 by GC–MS, as a red oil. ν_{max} 3500–3000 cm^{-1}; δ_H 1.30–1.54 (12H, 4×d, J=6.6, 6.2 Hz, 1- and 3-CH_3), 2.40 (2H, overlapping dd, J=17.0, 10.0 Hz, 4-H_a), 2.82 (2H, overlapping dd, J=17.0, 3.8 Hz, 4-H_e), 3.86 and 3.87 (each 3H, s, OCH_3), 3.90 and 4.12 (2H, m, 3-H of *cis* and *trans* isomers), 4.80 and 5.00 (2H, each q, J=7.6 Hz, 1-H), 5.78 (2H, bs, D_2O exchangeable, 5-OH), 6.65 (4H, overlapping pairs of d's, J=8.4 Hz, 7- and 8-H).

3.1.11. 1-Ethyl-6-methoxy-3-methylbenzo[*c*]furan-4,7-dione 19, (1*R*, 3*S*)-6-methoxy-1,3-dimethylbenzo[*c*]-pyran-5,8-dione 17 and (1*R*, 3*R*)-6-methoxy-1,3-dimethylbenzo[*c*]pyran-5,8-dione 18. To a buffered aqueous solution of 78.8 ml 0.2 M disodium hydrogen phosphate and 171.2 ml 0.2 M sodium dihydrogen phosphate (12 ml) containing Fremy's salt (773 mg; 1.44 mmol) was added a mixture of the phenols **14**, **15** and **16** (150 mg; 0.72 mmol) in methanol (1.0 ml) with rapid stirring which was continued for 1 h. Extraction of the reaction mixture with dichloromethane afforded a residue (112 mg; 70%) that was separated by radial chromatography using EtOAc/hexane (1:9) as eluent to give the furandione **19** (9 mg; 6%) as a bright yellow oil. ν_{max} 1665 cm^{-1}; δ_H 0.93 (3H, t, J=7.2 Hz, 2′-CH_3), 1.47 (3H, d, J=6.2 Hz, 1-CH_3), 1.71 (2H, m, 1′-CH_2), 3.83 (3H, s, OCH_3), 5.26 (2H, m, 1- and 3-H), 5.84 (1H, s, 5-H). δ_C 9.2 (2′-CH_3), 21.0 (1-CH_3), 27.4 (1′-CH_2), 56.8 (OCH_3), 79.8 (C-3), 83.8 (C-1), 107.6 (C-5), 142.6 (C-3a)[a], 148.3 (C-7a)[a], 159.7 (C-6), 178.7 (C=O), and 183.9 (C=O); MS (EI): *m/z* (%): 222 (M^+, 22), 193 (100), 165 (26). Calcd for $C_{12}H_{14}O_4$: C, 64.8; H, 6.4%; M 222. Found: C, 64.7; H, 6.5%.

The next product to elute was the benzopyrandione **17** (42 mg; 26%) as bright yellow crystals, mp 100–103 °C (from hexane–ethyl acetate). ν_{max} 1680 and 1666 cm^{-1}; δ_H 1.33 (3H, d, J=6.2 Hz, 3-CH_3), 1.48 (3H, d, J=6.6 Hz, 1-CH_3), 2.13 (1H, ddd, J=18.4, 10.0, 4.0 Hz, 4-H_a), 2.61 (1H, ddd, J=18.4, 3.6, 1.0 Hz, 4-H_e), 3.53 (1H, m, 3-H_a), 3.80 (3H, s, OCH_3), 4.69 (1H, ddq, J=1.0, 4.0, 6.6 Hz, 1-H), 5.83 (1H, s, 7-H); δ_C 21.1 (3-CH_3), 21.3 (1-CH_3), 29.9 (C-4), 56.3 (OCH_3), 68.8 (C-3), 69.9 (C-1), 107.8 (C-7), 138.3 (C-8a)[a], 144.8 (C-4a)[a], 158.3 (C-6), 181.3 (C=O),

and 186.5 (C=O); MS (EI): *m/z* (%): 222 (M^+, 28), 207 (100), 193 (28), 179 (37), 165 (28), 151 (26), 119 (13), 91 (14); $[\alpha]_D$=+97° (*c*=0.545, CH_2Cl_2); de 75% [Eu(hfc)$_3$]. Calcd for $C_{12}H_{14}O_4$: C, 64.8; H, 6.4%; M 222. Found: C, 64.6; H, 6.5%. The last product to elute was the benzopyrandione **18** (44 mg; 28%) as bright yellow crystals, mp 104–106 °C (from hexane–ethyl acetate). ν_{max} 1680 and 1665 cm^{-1}; δ_H 1.31 (3H, d, 6.2, 3-CH_3), 1.46 (3H, d, *J*=7.0 Hz, 1-CH_3), 2.12 (1H, ddd, *J*=19.0, 10.0, 2.2 Hz, 4-Ha), 2.60 (1H, dd, *J*=19.0, 3.2 Hz, 4-H_e), 3.81 (3H, s, OCH_3), 3.95 (1H, m, 3-H_a), 4.85 (1H, dq, *J*=2.2, 7.0 Hz, 1-H), and 5.85 (1H, s, 7-H); δ_C 19.9 (3-CH_3), 21.5 (1-CH_3), 29.3 (C-4), 56.3 (OCH_3), 62.7 (C-3), 67.2 (C-1), 107.4 (C-7), 137.4 (C-8a)[a], 144.7 (C-4a)[a], 158.5 (C-6), 181.4 (C=O), and 186.0 (C=O); MS (EI): *m/z* (%): 222 (M^+, 28), 207 (100), 193 (28), 179 (37), 165 (28), 151 (26), 119 (13), 91 (14); $[\alpha]_D$=−14 °C (*c*=0.720, CH_2Cl_2); de 75% [Eu(hfc)$_3$]. Calcd for $C_{12}H_{14}O_4$: C, 64.8; H, 6.4%; M 222. Found: C, 64.9; H, 6.4%.

3.1.12. (3*S*, 4*R*)-5-Benzyloxy-3,4-dihydro-4-hydroxy-6-methoxy-1,3-di-methylbenzo[*c*]pyran 20c and dimer 27. Treatment of (*R*)-alcohol **10c** (280 mg; 0.94 mmol) in tetrahydrofuran (25 ml) with mercury(II) acetate (400 mg; 1.25 mmol) at 25 °C with stirring for 2 h followed by the addition of sodium bromide (129 mg, 1.25 mmol) in hot methanol (10 ml) and stirring for another 2 h produced a residue upon removal of the solvents on a rotary evaporator at 40 °C. The residue was taken up in dimethylformamide (25 ml) and then added dropwise to a slurry of sodium borohydride (71 mg; 1.88 mmol) in dimethylformamide (12 ml) into which oxygen had previously been bubbled for 30 min. The resulting mixture was stirred at 25 °C with the passage of oxygen for 12 h. Removal of the solvents at 50 °C under reduced pressure afforded a greasy semi-solid material which was mixed with water (40 ml) and extracted with dichloromethane and the residue was chromatographed using ethyl acetate/hexane (3:7) as eluent to yield the dimer **27** (60 mg; 11%) as off-white crystals, mp 172–174 °C (from ethyl acetate–hexane); δ_H 1.28 (3H, d, *J*=6.2 Hz, 3-CH_3), 1.35 (3H, d, *J*=6.2 Hz, 3′-CH_3), 1.50 (3H, d, *J*=6.6 Hz, 1-CH_3), 1.51 (3H, d, *J*=6.6 Hz, 1′-CH_3), 2.87 (2H, m, 4- and 4′-H), 3.90 (6H, s, OCH_3), 3.98 (1H, dq, *J*=6.6, 6.2 Hz, 3-H), 4.28 (1H, dq, *J*=6.6, 6.2 Hz, 3′-H), 4.76 and 4.89 (2H, each a doublet, *J*=11.0 Hz; CH_2Ph), 4.90 (2H, m, 1- and 1′-H), 5.34 and 5.44 (2H, each doublet, *J*=11.0 Hz, CH_2Ph), 6.80 (4H, m, 7-, 8-, 7′ and 8′-H), 7.40 (10H, m, aryl); δ_C 21.7, 22.0, 22.3, 23.8, 55.9, 60.0, 67.1, 69.6, 73.2, 73.5, 75.8, 76.1, 76.4, 77.3, 110.0, 110.4, 120.5, 121.2, 128.8 (×2), 128.9 (×2), 129.0 (×4), 129.1 (×4), 129.8 (×2), 131.8 (×2), 136.9, 137.1, 150.7 and 151.0; HRMS calcd for $C_{38}H_{42}O_6$: 594.29813, C, 76.7; H, 7.1%; Found: 594.29788; C, 76.7; H, 7.3%). Further elution afforded the desired isochromanol **20c** (20 mg; 7%) as an oil. See spectral details vide infra.

3.1.13. (3*S*, 4*R*)-3,4-Dihydro-4-hydroxy-5-isopropoxy-6-methoxy-1,3-dimethylbenzo[*c*]pyran 20b and the (1*R*, 3*R*, 4*S*) diastereomer 21b. *R*-isopropoxy alcohol **10b** (250 mg; 1.0 mmol) was dissolved in tetrahydrofuran (30 ml) at 25 °C and water (30 ml) was added with vigorous stirring. Mercury(II) acetate (320 mg; 1.0 mmol) was added and the resulting mixture was stirred for 1 h after which aqueous sodium hydroxide (7.2 ml of 3 M solution; 21.6 mmol) was added and stirring continued for a further 1 h to then be followed by the addition of sodium bromide (103 mg; 1.0 mmol). After an additional 1 h stirring, oxygen was bubbled through for 1 h and then sodium borohydride (719 mg; 19.0 mmol) and additional aqueous sodium hydroxide (7.2 ml of a 3 M solution; 21.6 mmol) were added and oxygen was rapidly passed through this solution at 25 °C for 4 h after which period the solution was no longer gray. The residue obtained from extraction of the aqueous phase with ethyl acetate was purified by chromatography using ethyl acetate/hexane (15:85) to afford a pale yellow oily mixture of the isochromanes **20b** and **21b** (133 mg; 50%) in a ratio of 1:1 by GC–MS. A small amount of the mixture (40 mg) was subjected to PLC using ethyl acetate/hexane (1:9) as eluent to yield the pure benzopyranol **20b** (16 mg as an oil. ν_{max} 3506 cm^{-1}; δ_H 1.24 (3H, d, *J*=6.2 Hz, 3-CH_3), 1.43 (3H, d, *J*=5.8 Hz, 1-CH_3), 1.48 [6H, d, *J*=6.6 Hz, CH(CH_3)$_2$], 3.16 (1H, s, D_2O exchangeable, 4-OH), 3.60 (1H, dq, *J*=8.0, 6.2 Hz, 3-H_a), 3.84 (3H, s, OCH_3), 4.60–4.80 [3H, m, 1-, 4-, and C*H*(CH$_3$)$_2$], 6.80 (1H, d, *J*=7.8 Hz, 7-H) and 6.83 (1H, d, *J*=7.8 Hz, 8-H); δ_C 19.1 (3-CH_3), 21.7 (1-CH_3), 22.5 (CH_3 of isopropoxy), 23.2 (CH_3 of isopropyl), 55.9 (OMe), 70.7 (C-3)[a], 72.9 (CH of isopropyl)[a], 75.2 (C-1)[a], 75.7 (C-4)[a], 112.0 (C-7), 119.5 (C-8), 131.8 (C-4a)[b], 133.5 (C-8a)[b], 144.7 (C-5)[c] and 150.9 (C-6)[c]; MS (EI): *m/z* (%) 266 (9), 249 (11), 222 (64), 191 (100), 180 (60), 163 (22) and 133 (27); $[\alpha]_D$=+30.5° (*c*=1.11, CH_2Cl_2); de not possible due to inconclusive results with Eu(hfc)$_3$. Calcd for $C_{15}H_{22}O_4$: C, 67.6; H, 8.3%; M^+ 266. Found: C, 67.6; H, 8.3%.

The next band contained isochromane **21b** (18 mg) contaminated with a trace (5%) of pyran **20b** (by GC–MS) as an oil. ν_{max} 3510 cm^{-1}; δ_H 1.22 (3H, d, *J*=6.0 Hz, 3-CH_3), 1.34 [3H, d, *J*=6.6 Hz, CH(CH_3)$_2$], 1.42 (3H, d, *J*=6.2 Hz, 1-CH_3), 1.53 [3H, d, *J*=6.6 Hz, CH(CH_3)$_2$], 3.83 (3H, s, OCH_3), 3.96 (dq, *J*=6.0, 6.6 Hz, 3-H_a), 4.10 (1H, d, *J*=3.0 Hz, D_2O exchangeable, 4-OH), 4.58 (1H, dd, *J*=6.6, 3.0 Hz, 4-H_a), 4.69 [1H, m, C*H*(CH$_3$)$_2$], 4.89 (1H, q, *J*=6.2 Hz, 1-H), 6.72 (1H, d, *J*=8.2 Hz, 7-H), and 6.84 (1H, d, *J*=8.2 Hz, 8-H); δ_C 17.8 (3-CH_3), 21.9 (1-CH_3), 22.4 (CH_3 of isopropyl), 23.2 (CH_3 of isopropyl), 55.0 (OCH_3), 68.7 (C-3)[a], 69.2 (CH of isopropyl)[a], 69.4 (C-1)[a], 75.4 (C-4)[a], 112.4 (C-7), 120.2 (C-8), 130.3 (C-4a)[b], 132.6 (C-8a)[b], 145.2 (C-5)[c] and 150.8 (C-6)[c].

3.1.14. (1*R*, 3*S*, 4*R*)-5-Benzyloxy-3,4-dihydro-4-hydroxy-6-methoxy-1,3-di-methylbenzo[*c*]pyran 20c and its (1*R*, 3*R*, 4*S*) diastereomer 21c. By an analogues protocol describe vide infra *R*-alcohol **10c** (793 mg; 2.66 mmol) afforded a pale yellow oily mixture of the two diastereoisomers **20c** and **21c** (626 mg; 75%) in a 1:1 ratio by GC–MS. A small amount of the mixture (36 mg) was subjected to PLC and eluted with ethyl acetate/hexane (1:9) to provide benzopyranol **20c** (14 mg) as an oil. ν_{max} 3539 cm^{-1}; δ_H 1.42 (3H, d, *J*=5.8 Hz, 3-CH_3), 1.49 (3H, d, *J*=6.6 Hz, 1-CH_3), 3.59 (1H, d, *J*=8.8, 5.8 Hz, 3-Ha), 3.90 (3H, s, OCH_3), 4.14 (1H, *J*=1.6 Hz, D_2O exchangeable, 4-OH), 4.46 (1H, dd, *J*=8.8, 1.6 Hz, 4-H_a), 4.75 (1H, q, *J*=6.6 Hz, 1-H), 4.98 (1H, d, *J*=10.6 Hz, CH_2Ph), 5.24 (1H, d, *J*=10.6 Hz, CH_2Ph), 6.84 (1H, d, *J*=8.1 Hz, 7-H), 6.90 (1H, d, 8.1, 8-H), and 7.40 (5H, m, Ph); δ_C 19.2

(3-CH_3), 21.5 (1-CH_3), 56.0 (CH_3O), 70.0 (C-4)[a], 72.8 (C-1)[a], 75.2 (C-3)[a], 75.4 (CH_2Ph)[a], 112.1 (C-7), 120.0 (C-8), 128.1 (aryl), 128.6 (×2, aryl), 128.7 (×2, aryl), 131.5 (aryl), 133.7 (C-4a)[b], 137.0 (C-8a)[b], 145.9 (C-5)[c] and 150.9 (C-6)[c]; MS (EI): *m/z* (%): 314 (M^+, 2), 206 (44), 191 (100), 179 (28), 164 (31), 149 (13) and 91 (27); $[\alpha]_D$=+27.0° (*c*=0.690, CH_2Cl_2). Calcd for $C_{19}H_{22}O_4$: C, 72.6; H, 7.1%, M 314. Found: C, 72.4; H, 7.15%.

The next band provided mainly benzopyranol **21c** (19 mg) contaminated with ~5% of **20c** by GC–MS as an oil. ν_{max} 3539 cm^{-1}, 1.34 (3H, d, *J*=6.6 Hz, 3-CH_3), 1.46 (3H, d, *J*=6.6 Hz, 1-CH_3), 2.02 (1H, d, *J*=8.2 Hz, D_2O exchangeable, 4-OH), 3.90 (3H, s, OCH_3), 3.90 (1H, m, 3-H), 4.50 (1H, bd, *J*=8.0 Hz, 4-H), 5.04 (1H, q, *J*=6.6 Hz, 1-H), 5.07 (1H, d, *J*=10.6 Hz, CH_2Ph), 5.20 (1H, d, *J*=10.6 Hz, CH_2Ph), 6.78 (1H, d, *J*=8.0 Hz, 7-H), 6.89 (1H, d, *J*=8.0 Hz, 8-H), 7.39 (3H, m, 3′-, 4′- and 5′-H of aryl ring), and 7.44 (2H, m, 2′- and 6′-H of aryl ring); δ_C 17.0 (3-CH_3), 21.4 (1-CH_3), 56.2 (CH_3O), 63.5 (C-4)[a], 66.7 (C-1)[a], 70.9 (C-3)[a], 75.5 (CH_2Ph), 113.5 (C-7), 121.1 (C-8), 128.2 (aryl), 128.5 (×4, aryl), 131.6 (aryl), 131.9 (C-4a)[b], 137.8 (C-8a)[b], 146.0 (C-5)[c] and 151.1 (C-6)[c]; HRMS calcd for $C_{19}H_{22}O_4$: 314.1518. Found: 314.1518.

3.1.15. (1*R*, 3*R*, 4*S*)-3,4-Dihydro-4-hydroxy-6-methoxy-1,3-dimethyl-5,8-dioxybenzo[*c*]pyran 25. A mixture of hydroxypyrans **20c** and **21c** (150 mg; 0.48 mmol) in ethyl acetate (25 ml) containing palladium on C (21 mg of a 10% mixture) and one drop of concentrated aqueous hydrogen chloride was hydrogenated at 1 atm. for 15 h. The filtered solution afforded a residue on evaporation of the solvent and this was dissolved in methyl alcohol (3 ml) and added to 10 ml of the buffered solution (described earlier) containing Fremy's salt (0.99 g; 1.84 mmol). The residue obtained on work up (68 mg) was chromatographed to yield the isochromane quinone **25** (40 mg; 35%) as a bright yellow oil. ν_{max} (film) 3494 and 1672 cm^{-1}; δ_H 1.36 (3H, d, *J*=6.2 Hz, 3-CH_3), 1.52 (3H, d, *J*=7.0 Hz, 1-CH_3), 3.42 (1H, d, *J*=2.6 Hz, D_2O exchangeable, 4-OH), 3.82 (3H, s, OCH_3), 3.82 (1H, m, 3-H_a), 4.34 (1H, ddd, *J*=7.2, 2.6, 1.0 Hz, 4-H_a), 4.77 (1H, dq, *J*=7.0, 1.0 Hz, 1-H), 5.88 (1H, s, 7-H); δ_C 18.5 (3-CH_3), 19.2 (1-CH_3), 56.5 (CH_3O), 67.1 (C-3)[a], 67.2 (C-1)[a], 67.6 (C-4)[a] 107.8 (C-7), 137.1 (C-4a)[b], 146.1 (C-8a)[b], 158.8 (C-6), 183.0 (C=O) and 185.8 (C=O); MS (EI): *m/z* (%): 239 (M^++1, 1), 194 (81), 166 (100), 151 (84), 123 (13), 109 (15), 69 (12); $[\alpha]_D$=−69° (*c*=1.28, CH_2Cl_2). Calcd for $C_{12}H_{14}O_5$: C, 60.5; H, 5.9%, M 238. Found: C, 60.6; H, 5.8%.

3.1.16. (1*R*, 3*R*, 4*S*)-4-Acetoxy-3,4-dihydro-6-methoxy-1,3-dimethyl-5,8-dioxy-benzo[*c*]pyran 26. Pyranquinone **25** (12 mg; 0.05 mmol) was stirred in a mixture of pyridine (0.3 ml) and acetic anhydride (0.5 ml) for 2 h and then hydrolysed with water (20 ml). Extraction with ethyl acetate afforded a residue, which was chromatographed using ethyl acetate/hexane (3:7) as eluent to provide the acetate **26** (8 mg; 57%) as a yellow oil. ν_{max} (film) 1728 and 1675 cm^{-1}; δ_H 1.24 (3H, d, *J*=6.6 Hz, 3-CH_3), 1.54 (3H, d, *J*=6.8 Hz, 1-CH_3), 2.08 (3H s, $COCH_3$), 3.82 (3H, s, OCH_3), 4.04 (1H, dq, *J*=5.6, 6.6 Hz, 3-Ha), 4.76 (1H, dq, *J*=6.8, 1.8 Hz, 1-H_e), 5.61 (1H, dd, *J*=5.6, 1.8 Hz, 4-H_a), 5.90 (1H, s, 7-H); δ_C 17.0 (3-CH_3), 19.5 (1-CH_3), 20.9 (CH_3CO), 56.3 (CH_3O), 65.4 (C-1)[a], 65.5 (C-3)[a], 67.9 (C-4)[a], 107.6 (C-7), 133.7 (C-4a)[b], 147.6 (C-8a)[b], 158.6 (C-6), 170.0 ($COCH_3$), 179.6 (C=O) and 185.4 (C=O). HRMS calcd for $C_{14}H_{16}O_6$: 280.09469. Found: 280.09504; de 70% [Eu(hfc)$_3$].

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