Pigments of fungi. Part 68.[1] Synthesis and absolute configuration of thysanone[2]

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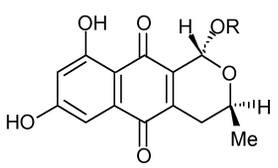
The (1*R*,3*S*)-absolute stereochemistry of thysanone **1**, a fungal benzoisochromanquinone with potent human rhinovirus 3C-protease inhibitory activity, is established for the first time by total synthesis of the natural product from ethyl (*S*)-lactate and CD comparison with authentic material.

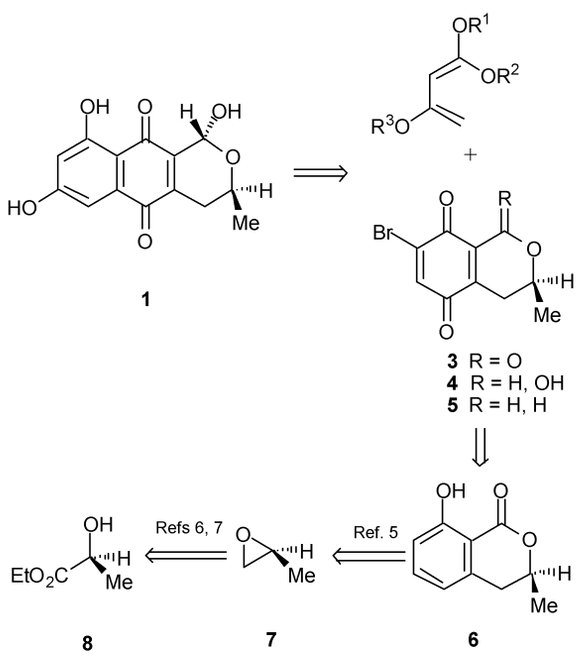
Thysanone **1** is a yellow, crystalline benzoisochromanquinone that was isolated from solid-state fermentations of the fungus *Thysanophora penicilloides* by chemists at Merck Sharp & Dohme during a screening programme aimed at the eventual control, or cure, of the common cold.[3] Thysanone **1** shows potent activity (IC_{50}: 13 μg ml^{-1}) against human rhinovirus (HRV) 3C-protease, one of a family of picornaviruses that are responsible, *inter alia*, for afflictions such as polio, hepatitis A and foot-and-mouth disease.[4] The structure **1** (*or its enantiomer*) for thysanone was reported by Singh *et al.* from the spectroscopic data and a single crystal X-ray analysis of the methyl acetal derivative **2**.[3] With the exception of our preliminary communication,[2] there has been no subsequent discussion in the literature of either the absolute configuration or the synthesis of thysanone. We report here full details of the total synthesis of (1*R*,3*S*)-thysanone **1**, beginning from ethyl (*S*)-lactate **8**. Direct spectroscopic and CD comparison of the synthetic and the natural materials and their respective methyl acetals establishes unequivocally the (1*R*,3*S*)-absolute configuration **1** for natural thysanone.



1 R = H
2 R = Me

Results and discussion

We recently reported the synthesis of both of the enantiomers of the natural product 8-hydroxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran-1-one (mellein) **6** beginning from the appropriate stereoisomer of propylene oxide **7**.[5] Our concept for the extension of this chemistry from (*S*)-mellein **6** to (1*R*,3*S*)-thysanone **1** *via* a bromobenzoquinone such as **3**, **4** or **5** is shown retrosynthetically in Scheme 1. Our first task was therefore to prepare workable quantities of (*S*)-mellein **6**. Although both the (*R*)- and (*S*)-enantiomers of propylene oxide are available commercially they are both very expensive commodities and a more economic alternative was to prepare (*S*)-propylene oxide **7**, $[\alpha]_D$ −18.7 (*c* 0.24, CCl_4) in 38% yield over three steps from readily available, and cheap, ethyl (*S*)-lactate **8**.[6,7] Subsequently, (*S*)-propylene oxide **7** was transformed into (*S*)-mellein **6**, $[\alpha]_D$ +101 (*c* 0.67, $CHCl_3$) over 6 steps and in 22% overall yield by the method that we have described earlier.[5]



Scheme 1 Retrosynthesis of (1*S*,3*R*)-thysanone from ethyl (*S*)-lactate *via* (*S*)-propylene oxide.

Our first synthetic approach to (1*R*,3*S*)-thysanone **1** involved the labile benzoquinone lactone **3** (Scheme 2) as an intermediate. To synthesise the quinone **3**, (*S*)-mellein **6** was first treated with bromine in dichloromethane at room temperature to afford (*S*)-5-bromomellein **9**, mp 96–97 °C (86% yield). The ^{1}H NMR spectrum of bromomellein **9** contains a pair of *ortho*-coupled aromatic proton doublets (*J* 9.0 Hz) consistent with the presence of a single bromine atom. The location of the bromine atom at C5 rather than C7 in **9** is evident from the effect of the halogen atom on the chemical shift of the signals from the C4 methylene protons. Thus, in the ^{1}H NMR spectrum of (*S*)-mellein **6** the C4 protons appear as a tight, two proton multiplet at δ 3.00. In contrast, the signals from these protons in the spectrum of **9** appear as a well resolved pair of double doublets centred at δ 2.80 (*J* 17.0 and 11.7 Hz) and 3.19 (*J* 17.0 and 3.3 Hz).

Extended exposure of mellein **6** or its 5-bromo derivative **9** to bromine in dichloromethane did not lead to any 5,7-dibromomellein **10**. However, when either **6** or **9** was treated, individually, with *N*-bromosuccinimide, the new dibromo derivative **10** was obtained in both cases in near quantitative yield. The

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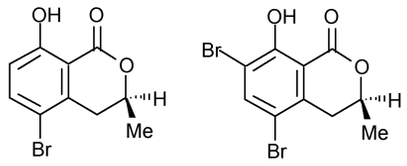
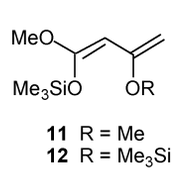
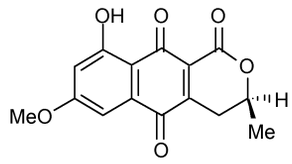


9 **10**



11 R = Me
12 R = Me_3Si



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molecular formula $C_{10}H_8Br_2O_3$ for **10** was established by combustion analysis and the presence in the mass spectrum of a molecular ion cluster at *m*/*z* 334/336/338 with the isotope pattern of an ion containing two bromine atoms. The ^{1}H NMR spectrum of (*S*)-5,7-dibromomellein **10** contains only one aromatic proton signal (δ 7.92), together with signals from a chelated hydroxy proton (δ 11.88), a *C*-methyl group (δ 1.58, *J* 6.4 Hz) and an ABX couplet with components centred at δ_A 2.78 (dd, *J* 17.1 and 11.7 Hz), δ_B 3.18 (dd, *J* 17.1 and 3.2 Hz) and δ_X 4.73 (m).

In our first attempt to oxidize 5,7-dibromomellein **10** to the corresponding quinone **3** an aqueous solution of cerium(IV) ammonium nitrate was added to **10** in acetonitrile at room temperature. The solution, which darkened rapidly, subsequently assumed a deep orange colour that quickly faded in colour and finally lead to a complex mixture of products. When the reaction time was restricted to two minutes and the temperature reduced to 0 °C the quinone **3** was obtained as a yellow oil that was, nevertheless, still difficult to purify further. The ^{1}H NMR spectrum of **3** includes a singlet at δ 7.42, consistent with the presence of a quinonoid methine proton, an ABX couplet with components centred at δ 2.52 (dd, *J* 19.1 and 11.6 Hz), δ 3.02 (dd, *J* 19.1 and 3.1 Hz) and δ 4.60 (m) arising from the C4 methylene group and C3 methine proton, respectively. The C3 methine signal is also coupled to the protons of the C3 methyl group that appears at δ 1.53 (d, *J* 6.3 Hz). The ^{13}C NMR spectrum of **3** includes three carbonyl carbon signals (δ 158.6, 173.8 and 182.7) consistent with the proposed structure. Despite the inherent instability of the quinone **3** its potential as a dienophile in cycloaddition reactions was explored by its exposure, without further purification, to 1,3-dimethoxy-1-trimethylsilyloxybutadiene **11** prepared according to Brassard's method.[8]

The presence of strategically placed halogen substituents in benzo- and naphthoquinone dienophiles has been used extensively to control the regiochemical outcome of their Diels–Alder reactions with oxygenated butadienes.[8–10] On that basis a successful cycloaddition between the diene **11** and the benzoquinone **3** should lead predominantly to the naphthoquinone **13** after aromatisation of the initial cycloadduct(s). The oxygenation pattern in the naphthoquinone **13**, albeit at a different oxygenation level, accords with that in thysanone **1**. Unfortunately, when the diene **11** and the benzoquinone **3** were brought together in dichloromethane at −30 °C a mixture of two isomeric products was obtained, neither of which corresponded to the desired quinone **13**. The products proved inseparable by chromatography but a ratio of 4 : 1 for the two constituents of the mixture could be determined by integration of selected signals in the ^{1}H NMR spectrum. The signals due to the major component, to which we assign the structure **14** (Fig. 1), include a methyl proton doublet (*J* 6.3 Hz) at δ 1.46,

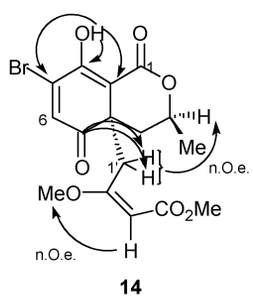

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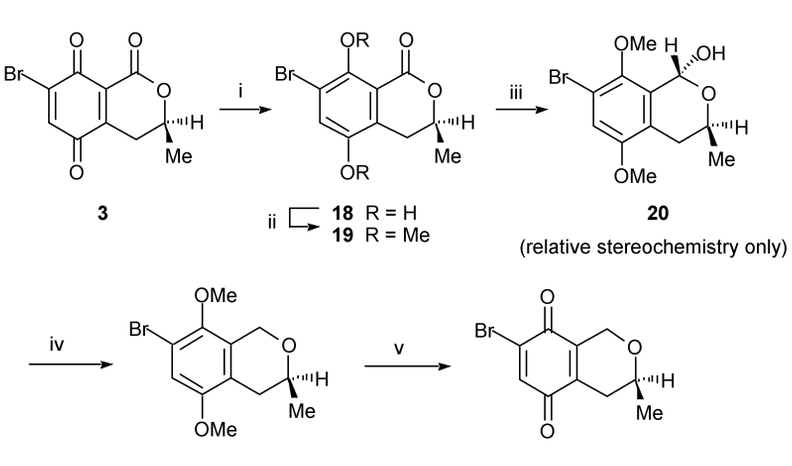
Fig. 1 Selected HMBC and NOE correlations in the adduct **14**.

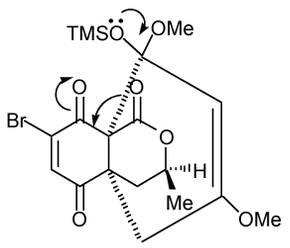
methylene proton resonances at δ 1.69 (dd, *J* 14.6 and 12.2 Hz) and 2.31 (dd, *J* 14.6 and 2.6 Hz), a methine proton multiplet at δ 5.03 and a chelated hydroxy proton singlet at δ 13.65 but it did not contain the necessary pair of *meta*-coupled aromatic signals expected for **13**. Instead, signals characteristic of an olefinic proton (δ 5.13), two methoxy groups (δ 3.52 and 3.63) and a pair of diastereotopic methylene protons (δ 2.50 and 4.05, each d, *J* 12.4 Hz) were observed. The ^{13}C NMR spectrum of the major product **14** contains sixteen discrete signals including three carbonyl resonances (δ 167.4, 169.8 and 196.9) and a mass spectrum that leads to the molecular formula $C_{16}H_{18}BrO_7$ (*m*/*z* 401/403). The formation of Michael adducts such as **14** is not uncommon in such systems, especially when the quinonoid dienophile is extremely electrophilic.[8] In the present case Michael attack at C4a in **3** by **11** would lead to **14** or an alternative tautomer. Both tautomers are consistent with the ^{1}H and



3 **18** R = H, **19** R = Me, **20** (relative stereochemistry only), **21**, **5**

Scheme 2 Synthesis of (±)-pyranobenzoquinone **5** *via* the (1*R**,3*S**)-lactol **20**. *Reagents and conditions*: i, $Na_2S_2O_4$; ii, Me_2SO_4, K_2CO_3, acetone, reflux; iii, DIBAL-H, toluene, −60 °C to rt; iv, $NaBH_4$, CF_3CO_2H, 30 °C or Et_3SiH, CF_3CO_2H, −70 °C to rt; v, CAN, MeCN, H_2O, rt.

^{13}C NMR data but the identity of the major product, including the double bond geometry and the relative stereochemistry, as **14** was deduced from the results of HMBC, HMQC and NOE experiments that are summarised in Fig. 1. The adduct **14** might arise by direct Michael addition of the diene **11** to the benzoquinone **3** or, alternatively, by way of the Diels–Alder cycloadduct **15** followed by a retro-Claisen reaction.[11] The latter mechanism would help to explain the (*E*)-geometry in the 2′,3′-double bond in **14**.



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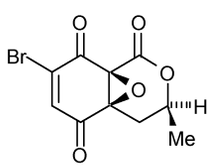

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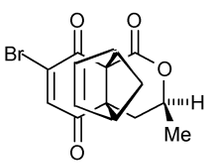

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The electrophilicity of the C4a–C8a double bond in the quinone **3** obviously stems from its position between the lactone and quinonoid carbonyl groups and, as a result, it is much more dienophilic than the C6–C7 double bond. Consequently, we briefly investigated the prospect of temporarily masking the C4a–C8a bond prior to exploiting the bromoquinone system. Two approaches were explored, neither of them successful. Firstly, we tried to generate the C4a–C8a epoxide **16** by treating the benzoquinone **3** with *m*-chloroperoxybenzoic acid. Unfortunately, all attempts to purify the unstable epoxide **16** led to extensive decomposition and afforded only an unworkably low yield of **16**. Next, we treated **3** with cyclopentadiene[12] and, while the quinone **3** was clearly being consumed (as monitored by TLC) all attempts to isolate the adduct **17** were unsuccessful.

Having failed to engage the quinone **3** in a Diels–Alder reaction we next explored the temporary masking of the lactone carbonyl group by reduction to the corresponding lactol **4**, or better still, the pyran **5** levels. There is ample precedent that, once removed, oxygenation in the form of a hydroxy or a carbonyl group could be re-introduced at C1 later in the sequence without difficulty.[13,14] Accordingly, two separate routes to the pyranobenzoquinone **5** were explored.

Synthesis of the (±)-pyranobenzoquinone 5 *via* the bromolactol 20

Our first attempt to reduce the lactone carbonyl group in the unstable (±)-benzoquinone **3** by using diisobutylaluminium hydride was not successful. Consequently, the quinone **3** was first converted to the quinol dimethyl ether **19** (63% yield over two steps), mp 146–147 °C, as shown in Scheme 2. The formula $C_{12}H_{13}BrO_4$ for the new benzoisocoumarin **19** was established by a combination of combustion analysis and mass spectrometry and is supported by the ^{1}H and ^{13}C NMR data (Experimental). The (±)-leucomethyl ether **19** was reduced to the lactol **20**, mp 138–139 °C, in 94% yield with diisobutylaluminium hydride at low temperature. The infra-red spectrum of **20** showed hydroxy absorption at 3328 cm^{-1} but no absorption due to a carbonyl group. The electrospray mass spectrum of **20** contains an ion cluster at *m*/*z* 285/287 corresponding to $[C_{12}H_{15}BrO_4 - H_2O]^+$. The relative stereochemistry at C1 and C3 in the lactol **20** was evident from the ^{1}H NMR spectrum, which consisted of a single set of resonances that includes a new one proton singlet at δ 6.15 due to H1. The configuration at C1 in **20** is controlled by the anomeric effect,[15] and the ^{1}H NMR data that support this will be discussed in more detail in due course.

The (±)-lactol **20** was not purified further but rather was reduced by using either sodium borohydride (70% yield) or triethylsilane (83%) in the presence of trifluoroacetic acid at low temperature to give the benzopyran **21**. The ^{1}H NMR spectrum of the new benzopyran **21** contains geminally coupled doublets (*J* 15.9 Hz) with components centred at δ 4.69 and 4.97 due to the protons of the new C1 methylene group. The rest of the ^{1}H NMR spectrum is in full accord with the structure **21**.

Finally, oxidative demethylation of the benzopyran **21** by using cerium(IV) ammonium nitrate in aqueous acetonitrile gave the (±)-pyranobenzoquinone **5** in 79% yield. The quinone **5** showed carbonyl absorptions at 1659, 1647 and 1583 cm^{-1} in the infra-red spectrum and the ^{1}H and ^{13}C NMR spectra, both of which will be discussed in more detail later, are in complete accord with the quinone structure **5**.

Synthesis of the (*S*)-pyranobenzoquinone 5 *via* the dibromolactol 23

During the development of the chemistry described above we recognised an alternative and potentially more efficient approach to the quinone **5** commencing from (*S*)-5,7-dibromomellein **10** that would avoid the troublesome intermediate **3**.

Thus, methylation of the phenolic hydroxy group in (*S*)-5,7-dibromomellein **10** with dimethyl sulfate (Scheme 3) gave the methyl ether **22**, $[a]_D$ +147 (*c* 1.17, $CHCl_3$), in 98% yield as colourless needles, mp 87–90 °C. The molecular formula $C_{11}H_{10}Br_2O_3$ of the ether **22** followed from combustion analysis and electrospray mass spectrometry, which shows a *pseudo*-molecular ion cluster at *m*/*z* 349/351/353. Importantly, in the ^{1}H NMR spectrum of **22** a three proton singlet at δ 3.97 appears due to the new C8 methoxy group. All other signals are in accord with the structure **22** (Experimental).

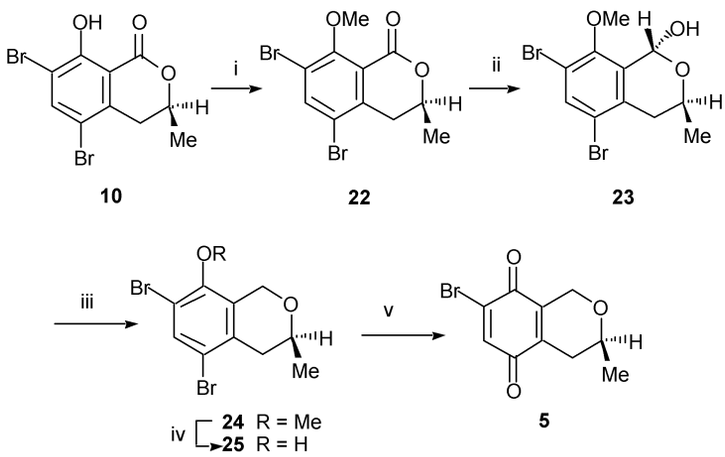
The methyl ether **22** was reduced in 95% yield to the (1*R*,3*S*)-lactol **23** with diisobutylaluminium hydride at −70 °C. The lactol **23** was isolated as a colourless, crystalline solid, mp 156–159 °C, $[a]_D$ +8.24 (*c* 1.00, $CHCl_3$). The combination of combustion analysis and mass spectrometry confirmed the molecular formula $C_{11}H_{12}Br_2O_3$. In the ^{1}H NMR spectrum of **23** there is a three proton singlet at δ 3.94 that was assigned to the aromatic methoxy group, an aromatic proton singlet at δ 7.75 and a methine proton signal that appears as a doublet (*J* 3.6 Hz) at δ 6.16. The multiplicity of the signal from H1 is due to coupling with the C1 hydroxy proton, which itself resonates as a broad doublet at δ 2.96. The ^{1}H and ^{13}C NMR spectra of the lactol **23** consist of only one set of resonances, consistent with the presence of a single diastereoisomer.

The (1*R*,3*S*)-absolute stereochemistry of the lactol **23** was established as follows. In the ^{1}H NMR spectrum of **23** the benzylic methylene protons at C4 resonate at δ 2.35 and 2.76 as double doublets with coupling constants (Table 1) that are characteristic of a *trans*-diaxial relationship between H3 and the axial proton at C4 in the half-chair conformation shown in Fig. 2a. This conformation is supported by NOE correlations (Fig. 2) between the C3 methyl group, H3 and both of the C4 protons and between H3 and $H_{eq}4$. Significantly, there is no NOE between H3 and H1 in **23**, as would be expected to be the case in these systems when H1 and H3 are *trans* disposed (see Fig. 2b discussed below). These results place the C1 hydroxy group in **23** in an axial configuration, favoured by the anomeric effect,[15] and defines the stereochemistry of **23** as (1*R*,3*S*).

Importantly, when a solution of the (1*R*,3*S*)-lactol **23** in deuteriochloroform was monitored by ^{1}H NMR spectroscopy over five days, new signals gradually developed due to formation of the epimeric lactol **26**. These new signals include a three proton doublet (*J* 6.1 Hz) at δ 1.50, methoxy and aromatic

Table 1 ^{1}H NMR data (400 MHz; $CDCl_3$) from the protons of the pyran ring in the lactols **23**, **26**, **20** and **1**

	Chemical shift (δ), multiplicity and coupling constant (J/Hz)			
Nucleus	**23**	**26**	**20**	**1**
H1	6.16, d, 3.6	6.25, s	6.15, s	6.05, s
H3	4.43, m	4.67, m	4.38, m	4.36, m
3-Me	1.40, d, 6.1	1.50, d, 6.1	1.38, d, 6.3	1.40, d, 6.4
$H_{ax}4$	2.35, dd, 17.4 and 11.4	2.41, dd, 17.3 and 11.7	2.25, dd, 17.5 and 11.6	2.24, dd, 19.6 and 11.1
$H_{eq}4$	2.76, dd, 17.4 and 3.3	2.83, dd, 17.3 and 3.7	2.73, dd, 17.5 and 3.4	2.75, dd, 19.6 and 3.2



10 22 23 5

Scheme 3 Synthesis of (*S*)-pyranobenzoquinone **5** *via* the (1*R*,3*S*)-lactol **23**. *Reagents and conditions*: i, Me_2SO_4, K_2CO_3, acetone, reflux; ii, DIBAL-H, toluene, −70 °C; iii, $NaBH_4$, TFA, THF, 30 °C, 1 h or Et_3SiH, CF_3CO_2H, 0 °C to rt; iv, $(PhCH_2Se)_2$, $NaBH_4$, DMF, reflux, 1 h; v, CAN, MeCN, H_2O, rt, 0.5 h.

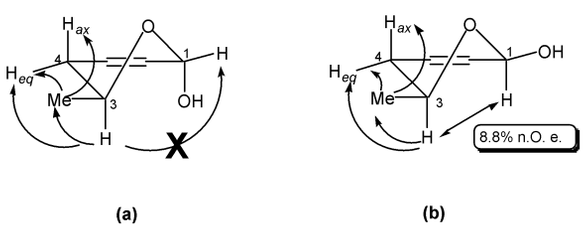
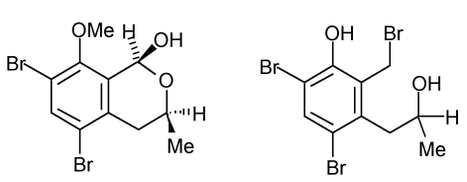


Fig. 2 Nuclear Overhauser enhancement in the ^{1}H NMR spectra of (a) the (1*R**,3*S**)-lactols **20**, **23** and **1**, and (b) the (1*S**,3*S**)-lactol **26**.

singlets at δ 3.84 and δ 7.71, respectively, a methine proton multiplet at δ 4.67 and signals from the C4 methylene protons at δ 2.41 and 2.83. NOE experiments with the lactol **26** (Fig. 2b) show strong correlation between H1 and H3 thus confirming their *cis*-1,3-diaxial relationship. Epimerisation of the (1*R*,3*S*)-lactol **23** presumably takes place *via* the corresponding aldehyde catalysed by traces of deuterium chloride in the solvent. The (1*S*,3*S*)-lactol **26**, in which both the C1 hydroxy and C3 methyl groups are in an equatorial configuration should be favoured thermodynamically.



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Reduction of the (1*R*,3*S*)-lactol **23** to the (*S*)-benzopyran **24** was achieved by using either sodium borohydride (92% yield) or triethylsilane (98%) in the presence of trifluoroacetic acid. The resulting pyran **24**, $[\alpha]_D$ +85.8 (*c* 1.00, $CHCl_3$), was obtained as colourless needles, $C_{11}H_{12}Br_2O_2$, mp 73–75 °C. In the ^{1}H NMR spectrum of **24** the methylene protons at C1 appear as doublets (J 16.3 Hz) at δ 4.66 and 4.97 while the C4 methylene protons give rise to signals at δ 2.44 and 2.71 forming part of an ABX system with the C3 methine proton (δ 3.70).

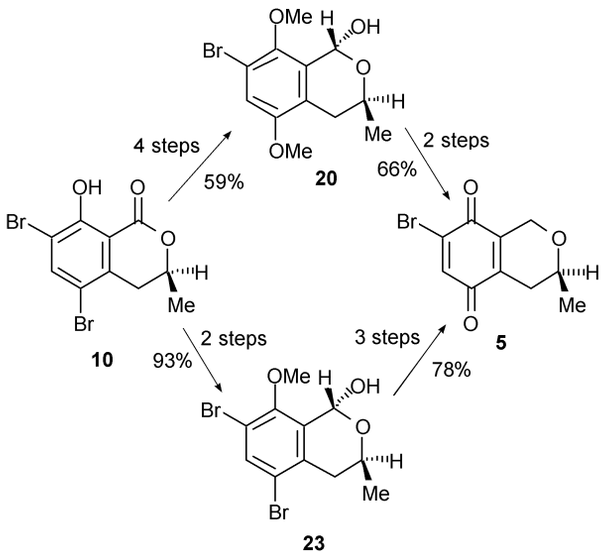
Conversion of the (*S*)-pyran **24** to the desired chiral pyranobenzoquinone **5** first required cleavage of the phenolic methyl ether. To this end, treatment of the ether **24** with a mixture of dibenzyl diselenide and sodium borohydride in dimethylformamide at reflux gave the free (*S*)-phenol **25** in 86% yield. Spectroscopic data (Experimental) are fully consistent with the formula shown.

Other attempts to cleave the aromatic methyl ether group in **24** using reagents such as aluminium chloride,[16] hydrobromic acid in acetic acid[17] and iodotrimethylsilane[18] were unsuccessful. On the other hand, boron tribromide[19] cleaved the pyran ring in **24** and, if used in excess, led to the benzylic bromide **27**.

Oxidation of the (*S*)-phenol **25** with cerium(IV) ammonium nitrate in aqueous acetonitrile gave the new (*S*)-pyranobenzoquinone **5** as yellow crystals, mp 100–103 °C, $[\alpha]_D$ +195 (*c* 0.64, $CHCl_3$) in 93% yield. The structure was unequivocally established, as shown, from the spectroscopic data. Thus, the electronic spectrum shows absorption maxima at 212 and 273 nm, consistent with a benzoquinone chromophore[20] and, in the infra-red spectrum strong absorptions occur at 1658, 1647 and 1590 cm^{-1}. In turn, the ^{1}H NMR spectrum of **5** contains a singlet at δ 7.26 due to the quinonoid methine proton, a doublet (J 6.3 Hz) at δ 1.34 due to the C3 methyl group, which is itself coupled to H3 (δ 3.63). The C4 methylene protons resonate at δ 2.20 (dddd, J 19.2, 10.0, 4.3, 2.7 Hz) and 2.58 (ddd, J 19.2, 3.4, 2.9 Hz) as the AB component of an ABX pattern with H3 while the new C1 methylene protons resonate as geminally coupled doublets (J 18.7 Hz) at δ 4.41 ($H_{ax}1$) and 4.71 ($H_{eq}1$). The C1 methylene protons are also coupled allylically with the protons at C4.

This approach to the (*S*)-pyranobenzoquinone **5**, *via* the (1*R*,3*S*)-lactol **23**, gives this pivotal intermediate in 73% yield over five steps from the mellein derivative **10**. This may be favourably compared with the earlier approach *via* the (1*R**,3*S**)-lactol **20** that gave the same pyranobenzoquinone,

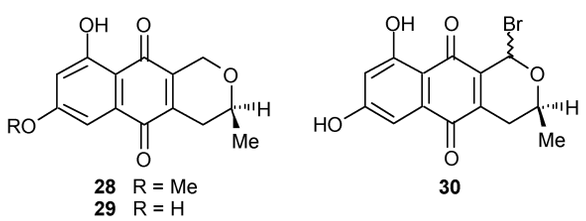
albeit in isochiral form, in 38% yield over six steps from (±)-5,7-dibromomellein **10**. The comparison is summarised diagrammatically in Scheme 4.



Scheme 4 Alternate routes from 5,7-dibromomellein **10** to the novel pyranobenzoquinone **5**.

Diels–Alder cycloaddition reactions involving the pyranobenzoquinone 5

Diels–Alder cycloaddition between the (±)-pyranobenzoquinone **5** and 1,3-dimethoxy-1-trimethylsilyloxybutadiene **11** in toluene at reflux gave a single orange crystalline compound **28**, mp 161–162 °C, in 42% yield. The mass spectrum of this compound exhibits a molecular ion at *m*/*z* 274 which, together with combustion analysis data, led to the molecular formula $C_{15}H_{14}O_5$. The electronic spectrum contains absorption maxima at 218, 268, 285 and 429 nm, indicating a naphthoquinone (rather than a benzoquinone) chromophore.[20] The ^{1}H NMR spectrum of **28** includes a signal at δ 12.13 due to a chelated phenolic hydroxy proton, *meta*-coupled aromatic doublets (J 2.4 Hz) centred at δ 6.62 and 7.19 and a three proton singlet at δ 3.90, fully consistent with the presence of the appended A ring in **28**.



Significantly, the pyranonaphthoquinone **28** contains the complete carbon skeleton of thysanone **1**. The requirement for synthesis of thysanone itself was thence to cleave the 7-*O*-methyl ether and hydroxylate the pyran ring. Surprisingly, all attempts to cleave the C7 methyl ether in **28** were unsuccessful and to circumvent this unexpected stumbling block we turned to 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene **12** as the diene component in a cycloaddition reaction with **5**.

The diene **12** was prepared in 46% yield in two steps from methyl acetoacetate according to the method of Yamamoto.[21] Diels–Alder reaction between the diene **12** and the (*S*)-pyranobenzoquinone **5** was achieved by heating the components together in toluene at reflux. Aromatization of the cycloadduct(s) with silica gel and chromatography gave the (*S*)-pyranonaphthoquinone **29** in 73% yield as yellow crystals, mp 171–173 °C, $[a]_D$ +160 (*c* 0.28, MeOH). The new quinone **29** exhibits spectroscopic properties in full accord with the assigned structure. Thus, the mass spectrum contains a molecular ion at *m*/*z* 260, which by high resolution mass measurement led to the molecular formula $C_{14}H_{12}O_5$. The electronic spectrum contains absorptions at 219, 270, 290 and 429 nm, consistent with a naphthoquinone chromophore,[20] whilst the ^{13}C NMR spectrum contains fourteen signals that include two quinonoid carbonyl carbon resonances (δ 183.2 and 187.6). The ^{1}H NMR spectrum of **29**, which is summarised diagrammatically in Fig. 3 confirms the composition of the peripheral A and C rings

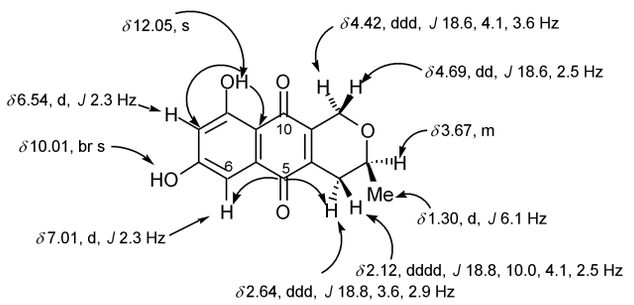


Fig. 3 ^{1}H NMR data (400 MHz, d_6-acetone) and selected INEPT correlations for the pyanonaphthoquinone **29**.

in the quinone and their relative orientation was established from the results of 1D-INEPT NMR experiments (Fig. 3). Most importantly, they reveal long range ^{1}H–^{13}C correlation between (i) the C5 carbonyl carbon (δ 183.2) and both H6 (δ 7.01) and $H_{eq}4$ (δ 2.64) and (ii) the C9 hydroxy proton (δ 12.05) and with both C8 (δ 108.1) and C9a (δ 109.3). This pattern is consistent only with the structure **29** and firmly establishes that the cycloaddition between the diene **12** and the bromobenzoquinone **5** had proceeded with the expected regiochemical control.

Conversion of the (3*S*)-pyranonaphthoquinone **29** to (1*R*,3*S*)-thysanone **1** required stereospecific hydroxylation at C1. Accordingly, irradiation of a mixture of the quinone **29** and bromine in carbon tetrachloride gave the benzylic bromide **30** that was not isolated but instead was treated, *in situ*, with aqueous tetrahydrofuran. Chromatographic purification gave thysanone **1**, $C_{14}H_{12}O_6$, mp 197–198 °C (decomp.), in 85% yield over the two steps. The ^{1}H NMR spectrum of **1** (Table 2) contains a one proton signal at δ 12.23 consistent with a chelated phenolic hydroxy group and *meta*-coupled (J 2.4 Hz) aromatic proton signals at δ 6.57 and 7.02. These data are in full accord with the structure of the A ring, while at higher field the spectrum contains signals from the acetal methine proton (δ 5.90), the *C*-methyl group (δ 1.28), and an ABX pattern due to $H_2$4 and H3, confirming the composition of the C ring. The ^{13}C NMR spectrum of **1** consists of a single set of fourteen signals including signals from two carbonyl carbon (δ 184.4 and 187.4), an acetal carbon (δ 86.6), methyl (δ 21.3), methylene (δ 30.0) and a methine carbon (δ 62.1), all in accord with the assigned structure.

The relative stereochemistry of the newly formed C1 lactol chiral centre in **1** was established by comparison of the chemical shifts of H1 and H3 in the ^{1}H NMR spectrum of **1** with those of their counterparts in the (1*R*,3*S*)-lactols **20** and **23** and the (1*S*,3*S*)-lactol **26** (Table 2). The data in Table 2 show a far closer correlation between the chemical shift and coupling constants for protons in the lactol rings **20**, **23** and **1** than is the case with the lactol **26**. This suggests a configuration in **1** in which H1 and H3 are mutually *trans* disposed. This is supported by the fact that, whereas the (1*S*,3*S*)-lactol **26** shows a strong (8.8%) NOE between H1 and H3 (Fig. 2) there is no corresponding NOE between these protons in the spectra of the lactols **1**, **20** and **23** (Fig. 2). Thysanone **1**, as prepared above, must therefore have the (1*R*,3*S*)-absolute configuration by virtue of its derivation from ethyl (*S*)-lactate **8**

Table 2 ^{1}H and ^{13}C NMR data (d_6-acetone) for natural[3] and synthetic thysanone **1**

Position	Thysanone from *T. penicilloides*[3]		Synthetic (1*R*,3*S*)-thysanone **1**	
	δ_H[a] (multiplicity) and coupling constants (*J*/Hz)	δ_C[a]	δ_H[b] (multiplicity) and coupling constants (*J*/Hz)	δ_C[b]
1	5.84 (s)	86.5	5.90 (s)	86.6
3	4.21 (m)	62.0	4.30 (m)	62.1
4_{ax}	2.05 (dd, 19.4, 11.0)	29.9	2.10 (dd, 19.4, 11.3)	30.0
4_{eq}	2.62 (dd, 19.4, 3.5)		2.65 (dd, 19.4, 3.5)	
4a	—	144.0	—	144.1
5	—	184.2	—	184.4
5a	—	134.6	—	134.7
6	6.97 (d, 2.3)	108.7	7.02 (d, 2.4)	108.8
7	—	165.2	—	165.5
8	6.53 (d, 2.3)	108.4	6.57 (d, 2.4)	108.4
9	—	165.1	—	165.2
9a	—	109.5	—	109.5
10	—	187.3	—	187.4
10a	—	142.0	—	142.2
3-Me	1.25 (d, 6.3)	21.4	1.28 (d, 6.2)	21.3
9-OH	12.19 (s)	—	12.23 (s)	—

[a] Lit.[3] field strength not specified. [b] 400 MHz for ^{1}H and 100 MHz for ^{13}C.

A comparison of the ^{1}H and ^{13}C NMR data recorded for synthetic (1*R*,3*S*)-thysanone **1** with the data reported for the natural product[3] is made in Table 2. From this comparison it is clear that both the natural and synthetic quinones possess the same constitution, substitution pattern and, in the lactol ring, the same relative configuration. We have also prepared the methyl acetal **2**, $C_{15}H_{14}O_6$, of synthetic thysanone **1**, and the spectroscopic data for the synthetic material (Experimental) are in close agreement with the data reported for the methyl acetal of natural thysanone.[3]

The absolute configuration of natural thysanone

Thysanone from *Thysanophora penicilloides* is reported to be dextrorotatory {$[\alpha]_D$ +29 (*c* 1.62, MeOH)}[3] but the specific rotation of the corresponding methyl acetal was not reported. The specific rotation of synthetic (1*R*,3*S*)-thysanone **1** (and its acetal **2**) gave widely fluctuating, unreliable readings at concentrations close to that quoted for thysanone in the literature.[3] However, at higher dilution both synthetic compounds were consistently laevorotatory at the sodium D-line, thereby suggesting, if anything, that they were enantiomeric with the natural system.[2] However, we were sufficiently sceptical of this conclusion that we sought samples of natural thysanone and its methyl acetal in order to make a direct comparison with synthetic materials. These were kindly provided by Dr S. B. Singh of Merck Sharp & Dohme. In our hands, the specific rotation of both natural thysanone and its methyl acetal were variable at the concentration quoted in the literature but, at higher dilution, were consistently laevorotatory consistent with the synthetic and natural quinones having the same absolute configuration.

In order to resolve this apparent quandary the circular dichroism (CD) spectra of synthetic (1*R*,3*S*)-thysanone **1** and its methyl acetal **2** and those of their natural counterparts were recorded. The CD spectra of (1*R*,3*S*)-thysanone **1** and natural thysanone are shown together in Fig. 4. Both show negative Cotton effects close to 300 nm and positive Cotton effects close to 260 nm. The near superimposability of these curves (rather than a mirror image relationship) establishes beyond any doubt that thysanone, as it occurs in *Thysanophora penicilloides*, has the (1*R*,3*S*)-absolute configuration shown in structure **1**. Similarly, the synthetic (1*R*,3*S*)-acetal **2** and its naturally derived counterpart show closely matched CD spectra (Fig. 5).

Summary

The work described above constitutes the first and, to date, the only total synthesis of (1*R*,3*S*)-thysanone **1**. Direct comparison of the synthetic and natural materials establishes unequivocally the structure and absolute stereochemistry of the natural product. The synthetic method uses cheap, readily available starting materials and is applicable, in principle, to the synthesis of a wide range of analogous pyranonaphthoquinones with the potential for improved biological profiles.

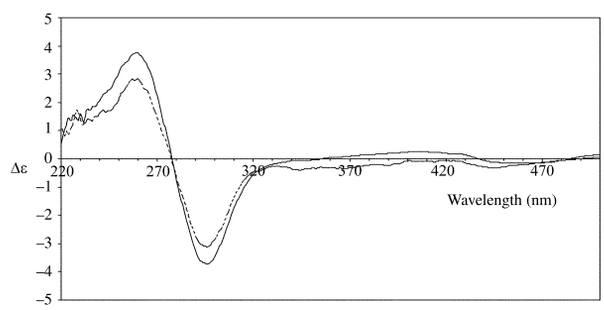


Fig. 4 Circular dichroism spectra (MeOH) of natural thysanone (—) and synthetic (1*R*,3*S*)-thysanone **1** (- - -).

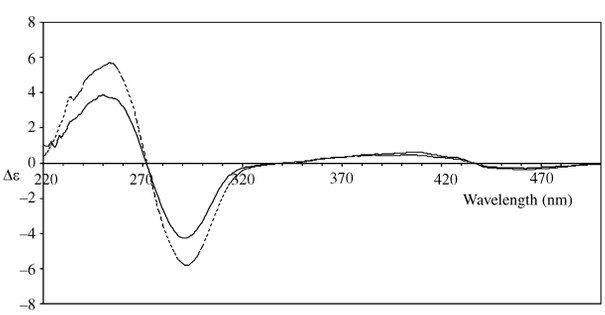


Fig. 5 Circular dichroism spectra (MeOH) of naturally derived thysanone methyl acetal (—) and synthetic (1*R*,3*S*)-thysanone methyl acetal **2** (- - -).

Experimental

General and materials

Melting points were determined on a hot-stage apparatus and are uncorrected. IR spectra were recorded using a Perkin-Elmer 983 G spectrophotometer for samples as potassium bromide discs. Electronic spectra were recorded on a Shimadzu UV-2401PC spectrophotometer using either ethanolic or methanolic solutions in a 10 mm quartz cell. NMR spectra were recorded with JEOL JNM-GX-400 and Varian Unity 400

spectrometers (^{1}H at 400 MHz and ^{13}C at 100 MHz) for solutions in $CDCl_3$ unless stated otherwise. Mass spectra were recorded on a Shimadzu GCMS-QP505A spectrometer at 70 eV (probe; EI) and a Micromass QUATTRO II (ESI). Specific rotations were measured using a JASCO DIP-1000 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. CD spectra were obtained using an AVIV 62DS spectrometer for solutions in methanol.

Materials

Thin layer chromatography (TLC) and preparative TLC (PLC) were performed on Merck precoated silica gel 60 F_{254} and Merck Kieselgel 60 GF_{254} (20 g silica gel spread on 20 × 20 cm glass plates), respectively. Visualisation was under UV light (254 or 366 nm). Gel permeation chromatography employed a column (40 × 3.5 cm) of Sephadex LH-20 suspended in and eluted with methanol–dichloromethane.

(*S*)-(+)-5-Bromomellein [(*S*)-(+)-5-bromo-8-hydroxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran-1-one] 9. To a solution of (*S*)-(+)-mellein **6** $[a]_D$ +101 (*c* 0.67, $CHCl_3$) {lit.[22] $[a]_D$ +102 (*c* 1.07, $CHCl_3$), $[a]_D$ +88 (*c* 1.03, MeOH)} (230 mg, 1.29 mmol; prepared by the methods described previously)[5] in dichloromethane (12 ml) was added bromine (248 mg, 1.55 mmol) in dichloromethane (3 ml). The solution was stirred for 30 min at room temperature and washed sequentially with dilute sodium thiosulfate (10 ml) and water (2 × 10 ml) then dried ($MgSO_4$). Removal of the solvent under reduced pressure followed by flash vacuum pad chromatography (dichloromethane–light petroleum 1 : 1, R_F 0.50) and crystallisation from dichloromethane–hexane gave *(S)-(+)-5-bromomellein* **9** (285 mg, 86%) as colourless prisms, mp 96–97 °C [(±)-form, mp 97–99 °C]; $[a]_D$ +116 (*c* 1.02, $CHCl_3$) (Found: C, 46.8; H, 3.5. $C_{10}H_9BrO_3$ requires C, 46.7; H, 3.5%). ν_{max} 3333br, 2979, 1676, 1453, 1210, 737 cm^{-1} [(±)-form, 3319br, 2978, 1663, 1452, 1221, 1207 cm^{-1}]. δ_H (400 MHz) 1.57 (3H, d, *J* 6.4 Hz, 3-Me), 2.80 (1H, dd, *J* 17.0 and 11.7 Hz, $H_{ax}4$), 3.19 (1H, dd, *J* 17.0 and 3.3 Hz, $H_{eq}4$), 4.71 (1H, m, H3), 6.84 (1H, d, *J* 9.0 Hz, H7), 7.62 (1H, d, *J* 9.0 Hz, H6), 11.19 (1H, s, OH). δ_C (100 MHz) 20.6 (3-Me), 34.8 (C4), 75.4 (C3), 109.6, 111.0, 117.9, 138.3, 139.4 and 161.5 (all Ar), 169.3 (C1). Mass spectrum (EI) *m*/*z* 258 [M$^+$, ^{81}Br (45%)], 256 [M$^+$, ^{79}Br (37%)], 238 (22), 171 (37), 170 (56), 169 (40), 168 (55), 167 (27), 154 (20), 153 (21), 149 (25), 135 (35), 134 (49), 131 (22), 129 (23), 128 (35), 127 (34), 125 (20), 123 (21), 115 (21), 111 (30), 109 (26), 105 (34), 104 (20), 103 (21), 98 (21), 97 (50), 96 (23), 95 (43), 91 (35), 85 (49), 84 (46), 83 (72), 82 (37), 81 (60), 79 (36), 78 (23), 77 (53), 73 (20), 71 (70), 70 (49), 69 (100), 68 (24), 67 (54), 65 (21), 63 (24).

(*S*)-(+)-5,7-Dibromomellein [(*S*)-(+)-5,7-dibromo-8-hydroxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran-1-one] 10. *Method 1.* To a solution of (*S*)-(+)-5-bromomellein **9** (240 mg, 0.93 mmol) in dimethylformamide (10 ml) was added dropwise a solution of *N*-bromosuccinimide (174 mg, 0.98 mmol) in dimethylformamide (2 ml). The reaction mixture was stirred at room temperature, in the dark, for 14 h, diluted with water (20 ml), extracted with chloroform (3 × 10 ml) and the combined extracts were washed with water (5 × 10 ml) and dried ($MgSO_4$). Removal of solvent under reduced pressure followed by flash vacuum pad chromatography of the residue (dichloromethane, R_F 0.70) and crystallisation from dichloromethane–hexane gave *(S)-(+)-5,7-dibromomellein* **10** (305 mg, 97%) as colourless prisms, mp 144–145 °C [(±)-form, mp 170–172 °C]; $[a]_D$ +80.4 (*c* 1.01, $CHCl_3$) (Found: C, 35.7; H, 2.4. $C_{10}H_8Br_2O_3$ requires C, 35.8; H, 2.4%). ν_{max} 3433br, 2977, 1683, 1414, 1198 cm^{-1} [(±)-form, 3430br, 3059, 2980, 1665, 1418, 1205 cm^{-1}]. δ_H (400 MHz) 1.58 (3H, d, *J* 6.4 Hz, 3-Me), 2.78 (1H, dd, *J* 17.1 and 11.7 Hz, $H_{ax}4$), 3.18 (1H, dd, *J* 17.1 and 3.2 Hz, $H_{eq}4$), 4.73 (1H, m, H3), 7.92 (1H, s, H6), 11.88 (1H, s, OH). δ_C (100 MHz) 20.7 (3-Me), 34.7 (C4), 75.8 (C3), 110.3, 110.6, 111.2, 137.7, 141.8 and 158.4 (all Ar), 169.0 (C1). Mass spectrum (EI) *m*/*z* 338 [M$^+$, $^{81}Br_2$ (50%)], 336 [M$^+$, ^{81}Br/^{79}Br (100%)], 334 [M$^+$, $^{79}Br_2$ (52%)], 320 (28), 318 (55), 316 (27), 307 (25), 292 (24), 211 (21), 102 (29), 84 (24), 77 (23), 76 (21), 75 (33).

Method 2. To a solution of (*S*)-(+)-mellein **6** (55.5 mg, 0.31 mmol) in dimethylformamide (2 ml) was slowly added a solution of *N*-bromosuccinimide (114 mg, 0.64 mmol) in dimethylformamide (0.5 ml). The reaction mixture was stirred at room temperature, in the dark, for 16 h, diluted with water (10 ml), extracted with chloroform (3 × 8 ml) and the combined extracts were washed with water (3 × 10 ml) and dried ($MgSO_4$). After removal of the solvent under reduced pressure the residue was purified by flash vacuum pad chromatography (dichloromethane, R_F 0.70) to give (*S*)-(+)-5,7-dibromomellein **10** (94.7 mg, 91%), identical in all respects to the product described above.

(±)-7-Bromo-3-methyl-3,4-dihydro-1*H*-2-benzopyran-1,5,8-trione 3. To (±)-5,7-dibromomellein **10** (50 mg, 0.15 mmol) in acetonitrile (5 ml) at 0 °C was added a solution of cerium(IV) ammonium nitrate (245 mg, 0.45 mmol) in water (0.8 ml). The reaction mixture was stirred for 2 min, diluted with chloroform (5 ml) and water (5 ml) and extracted with chloroform (3 × 5 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the (±)-benzoquinone **3** (40 mg, 99%) as a yellow oil, which was not purified further. ν_{max} 2979, 1727, 1657, 1588, 1252, 758 cm^{-1}. δ_H (400 MHz) 1.53 (3H, d, *J* 6.3 Hz, 3-Me), 2.52 (1H, dd, *J* 19.1 and 11.6 Hz, $H_{ax}4$), 3.02 (1H, dd, *J* 19.1 and 3.1 Hz, $H_{eq}4$), 4.60 (1H, m, H3), 7.42 (1H, s, H6). δ_C (100 MHz) 20.5 (3-Me), 28.6 (C4), 73.9 (C3), 126.4, 137.2, 139.6, 149.6, 158.6, 173.8, 182.7.

1,3-Dimethoxy-1-trimethylsilyloxybuta-1,3-diene 11. A mixture of methyl acetoacetate (5.86 g, 0.05 mol), trimethyl orthoformate (5.36 g, 0.05 mol) and sulfuric acid (3 drops) was stirred at room temperature for 24 h. Quinoline (4 drops) was added and the solution was distilled under reduced pressure to give methyl (*E*)-3-methoxybut-2-enoate (5.84 g, 89%) as a colourless liquid, bp 108–110 °C/115 mmHg (lit.[8] 175–177 °C). ν_{max} 2946, 2841, 1708, 1623, 1437, 1391, 1277, 1192, 1140, 1050 cm^{-1}. δ_H (300 MHz) 2.26 (3H, s, $H_3$4), 3.60 and 3.64 (each 3H, s, 1,3-OMe), 5.00 (1H, s, H2). δ_C (75 MHz) 18.8 (C4), 50.6 and 55.3 (each OMe), 90.4 (C2), 168.2, 173.2.

To a solution of LDA [prepared from diisopropylamine (4.5 g, 44 mmol) in tetrahydrofuran (40 ml) and *n*-butyllithium (29.5 ml, 1.5 M in hexane, 44 mmol) at 0 °C, then cooled to −78 °C] was added methyl (*E*)-3-methoxybut-2-enoate (5.5 g, 42 mmol) over 30 min. After a further 45 min chlorotrimethylsilane (5.5 g, 50.7 mmol) in tetrahydrofuran (8 ml) was added at −78 °C and the solution was allowed to warm to room temperature (1.5 h), filtered and the filtrate was concentrated under reduced pressure. The residual oil was diluted with pentane (70 ml), filtered through Celite®, concentrated and distilled to give the diene **11** (6.46 g, 76%), bp 48–50 °C/0.6 mmHg (lit.[8] 54 °C/0.5 mmHg). ν_{max} 1656, 1626, 1266, 1251, 1199, 1168, 1095, 846 cm^{-1}. δ_H (300 MHz) 0.25 (9H, s, $SiMe_3$), 3.55 and 3.56 (each 3H, s, 1,3-OMe), 3.97 (1H, br s, H_a4), 4.02 (1H, br s, H_b4), 4.33 (1H, br s, H2).

Reaction of the benzoquinone 3 with 1,3-dimethoxy-1-trimethylsilyloxybuta-1,3-diene 11. To the (±)-benzoquinone **3** (40 mg, 0.15 mmol) in dichloromethane (2 ml) at −30 °C was added 1,3-dimethoxy-1-trimethylsilyloxybuta-1,3-diene **11** (30 mg, 0.15 mmol) in dichloromethane (1 ml). The mixture was stirred at −30 °C for 15 min then allowed to warm to room temperature (30 min). Concentration under reduced pressure, slow filtration through a short column of silica (ethyl acetate) followed by preparative thin-layer chromatography (50 : 49 : 1 toluene–ethyl formate–formic acid, R_F 0.65) gave a 4 : 1 mixture

of the Michael adduct **14** and a minor isomer (20 mg, 34%) as a pale yellow oil (Found: $[M + H]^+$, 401.0224, $C_{16}H_{18}{}^{79}BrO_7$ requires $[M + H]^+$, 401.0236). ν_{max} 3015, 1700, 1674, 1625, 1285, 1214, 1142, 770 cm^{-1}. δ_H (400 MHz) (major isomer only) 1.46 (3H, d, *J* 6.3 Hz, 3-Me), 1.69 (1H, dd, *J* 14.6 and 12.2 Hz, $H_{ax}4$), 2.31 (1H, dd, *J* 14.6 and 2.6 Hz, $H_{eq}4$), 2.50 (1H, d, *J* 12.4 Hz, H_a1'), 3.52 (3H, s, OMe), 3.63 (3H, s, CO_2Me), 4.05 (1H, d, *J* 12.4 Hz, H_b1'), 5.03 (1H, m, H3), 5.13 (1H, s, H3′), 6.78 (1H, s, H6), 13.65 (1H, s, OH). δ_C (100 MHz) (major isomer) 21.7 (3-Me), 35.0 (C4), 41.7 (C1′), 49.0 (C4a), 51.4 (CO_2*Me*), 55.6 (OMe), 73.6 (C3), 94.6 (C3′), 100.4 (C8a), 136.0 (C6), 136.1 (C7), 159.8 (C8), 167.4 (C4′), 168.3 (C2′), 169.8 (C1), 196.9 (C5).

(±)-7-Bromo-5-methoxymellein 8-*O*-methyl ether [(±)-7-bromo-5,8-dimethoxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran-1-one] 19. To the crude (±)-benzoquinone **3** (40 mg, 0.15 mmol) in tetrahydrofuran (5 ml) under nitrogen was added sodium dithionite (200 mg) and water (2 ml). The mixture was stirred vigorously for 30 min after which time a further aliquot of sodium dithionite (100 mg) was added and stirring was continued for 30 min. The mixture was diluted with water (10 ml), extracted with chloroform (3 × 10 ml) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in acetone (8 ml) containing dimethyl sulfate (0.08 ml) in the presence of anhydrous potassium carbonate (400 mg) and the mixture was heated at reflux for 1.5 h. The mixture was cooled, diluted with water (10 ml), extracted with chloroform (3 × 10 ml) and the combined organic extracts were concentrated to approximately 5 ml. To this solution was added water (1 ml) and ammonium hydroxide (0.3 ml) and the emulsion was stirred vigorously for 1 h. Addition of water (10 ml), extraction with chloroform (3 × 10 ml), washing of the combined extracts with water (5 × 10 ml), drying ($MgSO_4$) and concentration under reduced pressure gave an oil that was purified by flash vacuum pad chromatography (dichloromethane–ethyl acetate 98 : 2, R_F 0.30) and crystallised from ethyl acetate to give the *(±)-dimethoxyisocoumarin* **19** (28 mg, 63%) as colourless rhomboids, mp 146–147 °C (Found: C, 47.8; H, 4.4. $C_{12}H_{13}BrO_4$ requires C, 47.9; H, 4.4%). ν_{max} 2974, 2929, 1722, 1471, 1423, 1261, 1216, 1206, 1124, 1061, 969 cm^{-1}. δ_H (400 MHz) 1.48 (3H, d, *J* 6.3 Hz, 3-Me), 2.52 (1H, dd, *J* 17.0 and 11.6 Hz, $H_{ax}4$), 3.09 (1H, dd, *J* 17.0 and 2.9 Hz, $H_{eq}4$), 3.83 and 3.91 (each 3H, s, OMe), 4.50 (1H, m, H3), 7.24 (1H, s, H6). δ_C (100 MHz) 20.7 (3-Me), 29.2 (C 4), 56.1 and 62.0 (each OMe), 74.2 (C3), 117.6, 119.5, 120.4, 129.3, 151.6 and 151.9 (all Ar), 161.5 (C1). Mass spectrum (ESI) *m*/*z* 303 $\{[M + H]^+, {}^{81}Br\}$, 301 $\{[M + H]^+, {}^{79}Br\}$.

(1*R,3*S**)-(±)-7-Bromo-1-hydroxy-5,8-dimethoxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran 20.** To the (±)-lactone **19** (110 mg, 0.37 mmol) in toluene (18 ml) at −60 °C under nitrogen was added diisobutylaluminium hydride (1.5 M in toluene, 0.32 ml, 0.48 mmol). The reaction mixture was maintained at −60 °C for 45 min and allowed to warm slowly to room temperature (approx. 45 min) and stirred for a further 30 min. The solution was poured into a saturated aqueous solution of potassium sodium tartrate (50 ml) and stirred vigorously (30 min). The product was extracted into chloroform (4 × 15 ml) and the combined extracts were dried ($MgSO_4$). Concentration under reduced pressure gave the (±)-lactol **20** (104 mg, 94%), mp 138–139 °C, which was not purified further. ν_{max} 3328br, 2960, 2941, 1474, 1237, 1041, 994 cm^{-1}. δ_H (400 MHz) 1.38 (3H, d, *J* 6.3 Hz, 3-Me), 2.25 (1H, dd, *J* 17.5 and 11.6 Hz, $H_{ax}4$), 2.73 (1H, dd, *J* 17.5 and 3.4 Hz, $H_{eq}4$), 3.79 and 3.90 (each 3H, s, OMe), 4.38 (1H, m, H3), 6.15 (1H, s, H1), 6.96 (1H, s, H6). Mass spectrum (ESI) *m*/*z* 287 $\{[M - OH]^+, {}^{81}Br\}$, 285 $\{[M - OH]^+, {}^{79}Br\}$.

(1*R,3*S**)-(±)-7-Bromo-5,8-dimethoxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran 21.** *Method 1.* To the (±)-lactol **20** (68 mg, 0.224 mmol) and sodium borohydride (85 mg, 2.25 mmol) in tetrahydrofuran (4 ml) under nitrogen was slowly added trifluoroacetic acid (0.5 ml). The mixture was stirred at 30 °C for 1 h, diluted with water (10 ml) and stirred for 10 min. The product was extracted into chloroform (3 × 5 ml) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (ether–light petroleum 1 : 2, R_F 0.51) gave the (±)-benzopyran **21** (45 mg, 70%) as a colourless oil. ν_{max} 3012, 2968, 2932, 1470, 1229, 1213, 755 cm^{-1}. δ_H (400 MHz) 1.36 (3H, d, *J* 6.3 Hz, 3-Me), 2.31 (1H, dd, *J* 17.1 and 10.6 Hz, $H_{ax}4$), 2.69 (1H, dd, *J* 17.1 and 3.3 Hz, $H_{eq}4$), 3.69 (1H, m, H3), 3.75 and 3.78 (each 3H, s, OMe), 4.69 (1H, d, *J* 15.9 Hz, $H_{ax}1$), 4.97 (1H, d, *J* 15.9 Hz, $H_{eq}1$), 6.86 (1H, s, H6). δ_C (100 MHz) 21.6 (3-Me), 30.1 (C4), 55.7 and 60.5 (each OMe), 64.7 (C1), 70.2 (C3), 112.1, 113.3, 123.4, 130.6, 146.4 and 153.6 (all Ar).

Method 2. To the (±)-lactol **20** (32 mg, 0.106 mmol) in dichloromethane (6 ml) at −70 °C was added trifluoroacetic acid (24 µl, 0.31 mmol) and the solution was stirred for 15 min. Triethylsilane (49 µl, 0.31 mmol) was added and after 15 min at −70 °C the solution was allowed to warm to room temperature and stirred for a further 30 min. Water (10 ml) was added and the product was extracted into chloroform (3 × 8 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the (±)-benzopyran **21** (26 mg, 83%) identical to the product described above.

(±)-7-Bromo-3-methyl-3,4-dihydro-1*H*-2-benzopyran-5,8-dione 5. To a solution of the (±)-benzopyran **21** (27 mg, 0.094 mmol) in acetonitrile (5 ml) was added dropwise a solution of cerium(IV) ammonium nitrate (154 mg, 0.28 mmol) in water (1 ml). The mixture was stirred at room temperature for 30 min, diluted with water (10 ml), extracted with chloroform (3 × 5 ml) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil in dichloromethane was filtered through a short column (0.5 cm) of silica gel and the filtrate was concentrated to give the (±)-pyranobenzoquinone **5** (19 mg, 79%) as a yellow oil. ν_{max} 2979, 1659, 1647, 1583, 1135 cm^{-1}. λ_{max} (EtOH) 212 (log ε 4.30), 273 nm (3.94). δ_H (400 MHz) 1.34 (3H, d, *J* 6.3 Hz, 3-Me), 2.20 (1H, dddd, *J* 19.2, 10.0, 4.3 and 2.7 Hz, $H_{ax}4$), 2.58 (1H, ddd, *J* 19.2, 3.4 and 2.9 Hz, $H_{eq}4$), 3.63 (1H, m, H 3), 4.41 (1H, ddd, *J* 18.7, 4.3 and 3.4 Hz, $H_{ax}1$), 4.71 (1H, dd, *J* 18.7 and 2.7 Hz, $H_{eq}1$), 7.26 (1H, s, H 6). δ_C (100 MHz) 21.1 (3-Me), 29.1 (C4), 63.3 (C1), 69.4 (C3), 137.0, 137.8 (C6), 140.28, 140.29, 177.9 (C5), 183.5 (C8). Mass spectrum (EI) *m*/*z* 258 $\{[M]^+, {}^{81}Br$ (23%)$\}$, 256 $[M]^+, {}^{79}Br$ (19), 243 (24), 241 (28), 216 (31), 215 (20), 214 (62), 212 (39), 186 (21), 177 (21), 134 (20), 105 (59), 86 (53), 84 (100), 77 (55).

(*S*)-(+)-5,7-Dibromomellein 8-*O*-methyl ether [(*S*)-(+)-5,7-dibromo-8-methoxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran-1-one] 22. To a solution of (*S*)-(+)-5,7-dibromomellein **10** (67 mg, 0.20 mmol) in acetone (8 ml) were added potassium carbonate (200 mg) and dimethyl sulfate (0.1 ml) and the mixture was heated at reflux for 45 min. After cooling to room temperature, water (10 ml) was added and the product was extracted into chloroform (3 × 5 ml) and the combined extracts were dried ($MgSO_4$) and evaporated. Chromatography (dichloromethane, R_F 0.40) and crystallisation from ethyl acetate–hexane yielded the *(S)-(+)-methyl ether* **22** (68 mg, 98%) as colourless needles, mp 87–90 °C [(±)-form, mp 87–88 °C]; $[a]_D$ +147 (*c* 1.17, $CHCl_3$) (Found: C, 37.6; H, 2.9. $C_{11}H_{10}Br_2O_3$ requires C, 37.7; H, 2.9%). ν_{max} 2943, 1717, 1459, 1413, 1272, 1221, 1113 cm^{-1} [(±)-form, 2932, 1722, 1452, 1414, 1268, 1221, 1210 cm^{-1}]. δ_H (400 MHz) 1.52 (3H, d, *J* 6.4 Hz, 3-Me), 2.73 (1H, dd, *J* 17.0 and 11.6 Hz, $H_{ax}4$), 3.12 (1H, dd, *J* 17.0 and 2.7 Hz, $H_{eq}4$), 3.97 (3H, s, OMe), 4.54 (1H, m, H3), 7.97 (1H, s, H6). δ_C (100 MHz) 20.5 (3-Me), 36.1 (C4), 62.3 (OMe), 73.8 (C3), 117.1, 118.8, 121.5, 140.1, 140.5 and 158.4

(all Ar), 160.8 (C1). Mass spectrum (ESI) *m/z* 353 {[M + H]$^+$, $^{81}Br_2$}, 351 {[M + H]$^+$, ^{81}Br/^{79}Br}, 349 {[M + H]$^+$, $^{79}Br_2$}.

(1*R*,3*S*)-(+)-5,7-Dibromo-1-hydroxy-8-methoxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran 23. To the (*S*)-(+)-lactone **22** (230 mg, 0.657 mmol) in toluene (20 ml) at −70 °C was slowly added diisobutylaluminium hydride (1.5 M in toluene, 0.57 ml, 0.85 mmol). The mixture was maintained at −70 °C for 1 h and allowed to warm to room temperature (30 min). The solution was poured into saturated potassium sodium tartrate (30 ml) and stirred vigorously for 30 min. Extraction with chloroform (3 × 15 ml), drying ($MgSO_4$) of the combined organic extracts, concentration under reduced pressure and crystallisation of the residue from ethyl acetate–hexane gave the *(1R,3S)-(+)-lactol* **23** (220 mg, 95%) as colourless needles, mp 156–159 °C [(±)-form, mp 161–163 °C]; $[\alpha]_D$ +8.24 (*c* 1.00, $CHCl_3$) (Found: C, 37.4; H, 3.4. $C_{11}H_{12}Br_2O_3$ requires C, 37.5; H, 3.4%). ν_{max} 3324br, 2961, 1453, 1172, 1041, 991 cm^{-1} [(±-form, 3363br, 2923, 1453, 1416, 1166, 1067, 1027 cm^{-1}]. δ_H (400 MHz) 1.40 (3H, d, *J* 6.1 Hz, 3-Me), 2.35 (1H, dd, *J* 17.4 and 11.4 Hz, $H_{ax}4$), 2.76 (1H, dd, *J* 17.4 and 3.3 Hz, $H_{eq}4$), 2.96 (1H, br d, *J* 3.6 Hz, OH), 3.94 (3H, s, OMe), 4.43 (1H, m, H3), 6.16 (1H, d, *J* 3.6 Hz, H1), 7.75 (1H, s, H6). δ_C (100 MHz) 21.1 (3-Me), 35.9 (C4), 61.8, 62.4, 88.5 (C1), 115.1, 119.4, 132.1, 135.1, 135.9 and 154.2 (all Ar). Mass spectrum (EI) *m/z* 354 {[M]$^+$, $^{81}Br_2$ (14%)}, 352 {[M]$^+$, ^{81}Br/^{79}Br (31)}, 350 {[M]$^+$, $^{79}Br_2$ (19)}, 335 (22), 310 (43), 308 (36), 293 (20), 292 (39), 290 (31), 86 (55), 84 (100), 77 (25), 71 (21).

(1*S*,3*S*)-5,7-Dibromo-1-hydroxy-8-methoxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran 26. A solution of the (1*R*,3*S*)-(+)-lactol **23** in $CDCl_3$ was maintained at 20 °C for 5 days after which time the ^{1}H NMR spectrum revealed the presence of residual lactol **23** (30%) and the *title compound* **26** (70%). δ_H (400 MHz) (epimer **26** only) 1.50 (3H, d, *J* 6.1 Hz, 3-Me), 2.41 (1H, dd, *J* 17.3 and 11.7 Hz, $H_{ax}4$), 2.83 (1H, dd, *J* 17.3 and 3.7 Hz, $H_{eq}4$), 3.84 (3H, s, OMe), 4.67 (1H, m, H3), 6.25 (1H, s, H1), 7.71 (1H, s, H6).

(*S*)-(+)-5,7-Dibromo-8-methoxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran 24. *Method 1.* To a stirred solution of the (1*R*,3*S*)-(+)-lactol **23** (216 mg, 0.614 mmol) and sodium borohydride (232 mg, 6.1 mmol) in tetrahydrofuran (10 ml) was added trifluoroacetic acid (1.5 ml) and the mixture was heated at 30 °C for 1 h. Dilution with water (10 ml), extraction with chloroform (3 × 10 ml), drying ($MgSO_4$) of the combined organic extracts and concentration under reduced pressure gave an oil that was further purified by flash vacuum pad chromatography (ether–light petroleum 1 : 2, R_F 0.60). Crystallisation from ether–hexane gave the *title compound* **24** (190 mg, 92%) as colourless needles, mp 73–75 °C [(±)-form, mp 74–75 °C]; $[\alpha]_D$ +85.8 (*c* 1.00, $CHCl_3$) (Found: C, 39.4; H, 3.6. $C_{11}H_{12}O_2Br_2$ requires C, 39.3; H, 3.6%). ν_{max} 2962, 2926, 1449, 1418, 1115, 1036 cm^{-1} [(±)-form, 2959, 2918, 1447, 1035 cm^{-1}]. δ_H (400 MHz) 1.38 (3H, d, *J* 6.1 Hz, 3-Me), 2.44 (1H, dd, *J* 17.2 and 10.6 Hz, $H_{ax}4$), 2.71 (1H, dd, *J* 17.2 and 3.3 Hz, $H_{eq}4$), 3.70 (1H, m, H3), 3.79 (3H, s, OMe), 4.66 (1H, d, *J* 16.3 Hz, $H_{ax}1$), 4.97 (1H, d, *J* 16.3 Hz, $H_{eq}1$), 7.63 (1H, s, H 6). δ_C (100 MHz) 21.4 (3-Me), 36.3 (C4), 60.4 (OMe), 64.7 (C1), 70.6 (C3), 114.4, 119.8, 132.3, 133.8, 134.5 and 152.1 (all Ar). Mass spectrum (EI) *m/z* 306 {[M − CH_3OH]$^+$, $^{81}Br_2$ (72%)}, 304 {[M − CH_3OH]$^+$, ^{81}Br/^{79}Br (100)}, 302 {[M − CH_3OH]$^+$, $^{79}Br_2$ (44)}, 291 (54), 289 (100), 287 (51), 277 (23), 276 (23), 263 (29), 251 (73), 250 (30), 248 (47), 246 (24), 169 (30), 167 (24), 116 (28), 115 (22), 103 (26), 102 (27), 89 (23), 88 (21), 86 (23), 84 (21), 77 (31), 75 (64), 74 (42), 63 (26), 62 (21).

Method 2. To a solution of the (1*R*,3*S*)-(+)-lactol **23** (216 mg, 0.614 mmol) in dichloromethane (30 ml) at 0 °C was added trifluoroacetic acid (141 µl, 1.84 mmol) and the solution was stirred for 15 min. Triethylsilane (294 µl, 1.84 mmol) was added and the mixture was allowed to warm slowly to room temperature (1 h), stirred for a further 45 min and water (20 ml) was added. The product was extracted into chloroform (3 × 15 ml) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash vacuum pad chromatography (ether–light petroleum 1 : 2, R_F 0.60) of the residue gave the *(S)-(+)-pyran* **24** (202 mg, 98%) identical in all respects to the product described above.

(*S*)-(+)-5,7-Dibromo-8-hydroxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran 25. To a solution of dibenzyl diselenide (47 mg, 0.138 mmol) in dimethylformamide (2 ml) was added sodium borohydride (40 mg, 1.06 mmol). After 15 min a solution of the (*S*)-(+)-methyl ether **24** (67 mg, 0.199 mmol) in dimethylformamide (0.5 ml) was added and the mixture was heated under reflux for 1.5 h. After cooling to room temperature the mixture was diluted with water (15 ml), acidified with dil. H_2SO_4 and the product was extracted into ethyl acetate (3 × 10 ml). The combined organic extracts were washed sequentially with brine (3 × 10 ml) and water (3 × 20 ml) and dried ($MgSO_4$). Concentration under reduced pressure followed by flash vacuum pad chromatography (dichloromethane, R_F 0.40) and crystallisation from dichloromethane gave the *(S)-(+)-phenol* **25** (55 mg, 86%) as colourless needles, mp 139–141 °C [(±)-form, mp 140–141 °C]; $[\alpha]_D$ +101 (*c* 1.00, $CHCl_3$) (Found: M$^+$, 319.9040, $C_{10}H_{10}{}^{79}Br_2O_2$ requires M$^+$, 319.9049). ν_{max} 3409br, 1435, 1425, 1139, 1111, 1087, 1050 cm^{-1} [(±)-form, 3397br, 1437, 1140, 1111, 1083, 1048 cm^{-1}]. δ_H (400 MHz) 1.38 (3H, d, *J* 6.3 Hz, 3-Me), 2.41 (1H, dd, *J* 17.2 and 10.6 Hz, $H_{ax}4$), 2.72 (1H, dd, *J* 17.2 and 2.0 Hz, $H_{eq}4$), 3.71 (1H, m, H3), 4.62 (1H, d, *J* 16.0 Hz, $H_{ax}1$), 4.94 (1H, d, *J* 16.0 Hz, $H_{eq}1$), 5.50 (1H, br s, OH), 7.54 (1H, s, H6). δ_C (100 MHz) 21.4 (3-Me), 36.2 (C4), 64.6 (C1), 70.4 (C3), 107.4, 115.1, 125.1, 131.7, 134.5 and 147.1 (all Ar). Mass spectrum (EI) *m/z* 324 {[M]$^+$, $^{81}Br_2$ (11%)}, 322 {[M]$^+$, ^{81}Br/^{79}Br (25%)}, 320 {[M]$^+$, $^{79}Br_2$ (13%)}, 280 (65), 278 (100), 276 (55), 91 (31), 90 (24), 89 (25).

(±)-4,6-Dibromo-2-bromomethyl-3-(2-hydroxypropyl)-1-hydroxybenzene 27 from reaction of (±)-5,7-dibromo-8-methoxy-3-methyl-3,4-dihydro-1*H*-2-benzopyran 24 with boron tribromide. To the (±)-pyran **24** (43 mg, 0.128 mmol) in dichloromethane (3 ml) at 0 °C was added boron tribromide (96 mg, 0.383 mmol) in dichloromethane (0.5 ml). The reaction mixture was allowed to warm slowly to room temperature and stirred overnight. Dilution with water (10 ml) and extraction with dichloromethane (3 × 5 ml), drying ($MgSO_4$) of the combined organic phases and concentration under reduced pressure gave the (±)-benzylic bromide **27** (51.5 mg, 100%) as an oil that was not purified further. ν_{max} 3493, 1434, 1303, 1262, 1209, 1145, 738 cm^{-1}. δ_H (400 MHz) 1.85 (3H, d, *J* 6.7 Hz, $H_3$3′), 3.31 (1H, dd, *J* 15.0 and 5.4 Hz, H_a1′), 3.40 (1H, dd, *J* 15.0 and 9.0 Hz, H_b1′), 4.55 (1H, m, H2′), 4.80 (1H, d, *J* 10.5 Hz, CH_aBr), 4.86 (1H, d, *J* 10.5 Hz, CH_bBr), 5.85 (1H, br s, OH), 7.68 (1H, s, H5). δ_C (100 MHz) 25.9, 26.4, 42.7, 48.4, 109.7, 116.1, 126.3, 135.2, 138.0, 150.3. Mass spectrum (EI) *m/z* 388 {[M − H_2O]$^+$, $^{81}Br_3$ (13%)}, 386 {[M − H_2O]$^+$, $^{81}Br_2$/^{79}Br (19%)}, 384 {[M − H_2O]$^+$, ^{81}Br/$^{79}Br_2$ (11%)}, 382 {[M − H_2O]$^+$, $^{79}Br_3$ (4%)}, 307 (36), 306 (20), 305 (7), 304 (26), 303 (40), 279 (33), 226 (54), 225 (31), 224 (54), 223 (21), 146 (20), 145 (97), 144 (35), 117 (23), 116 (26), 115 (39), 91 (22), 90 (36), 82 (96), 81 (43), 80 (100), 79 (40), 75 (34), 74 (21), 72 (31), 63 (35).

(*S*)-(+)-7-Bromo-3-methyl-3,4-dihydro-1*H*-2-benzopyran-5,8-dione 5. To a solution of the (*S*)-(+)-phenol **25** (55 mg, 0.171 mmol) in acetonitrile (7 ml) was added a solution of cerium(IV) ammonium nitrate [280 mg, 0.511 mmol in water (1.3 ml)]. The solution was stirred at room temperature for 30 min, diluted with brine (10 ml) and extracted with chloroform

(3 × 6 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil in dichloromethane was filtered through a short column (0.5 cm) of silica gel and the filtrate was concentrated to give the (*S*)-(+)-pyranobenzoquinone **5** (41 mg, 93%) as a yellow crystalline solid, mp 100–103 °C; $[\alpha]_D$ +195 (*c* 0.64, $CHCl_3$). ν_{max} 1658, 1647, 1590, 1225 cm^{-1}. All other spectroscopic data were identical to those of the (±)-benzoquinone **5** obtained by oxidation of (±)-dimethoxypyran **21**.

(±)-3,4-Dihydro-9-hydroxy-7-methoxy-3-methyl-1*H*-naphtho-[2,3-*c*]pyran-5,10-dione 28. To the (±)-pyranobenzoquinone **5** (9 mg, 0.035 mmol) in toluene (1 ml) was added a solution of 1,3-dimethoxy-1-trimethylsilyloxybuta-1,3-diene **11** (18 mg, 0.089 mmol) in toluene (0.5 ml) and the mixture was heated under reflux for 15 h. After cooling, the solution was concentrated under reduced pressure and filtered slowly through a short column of silica (dichloromethane–ethyl acetate 2 : 1 + 1% formic acid). The yellow fractions were combined, concentrated, further chromatographed (50 : 49 : 1 toluene–ethyl formate–formic acid, R_F 0.85) and crystallised from dichloromethane–hexane to give the *(±)-pyranonaphthoquinone* **28** (4 mg, 42%) as yellow plates, mp 161–162 °C (Found: C, 65.7; H, 5.1. $C_{15}H_{14}O_5$ requires C, 65.7; H, 5.1%). ν_{max} 3439br, 2981, 1658, 1641, 1613, 1311, 1199, 1160 cm^{-1}. λ_{max} (EtOH) 204 (log ε 4.49), 218 (4.40), 268 (3.98), 285sh (3.78), 429 nm (3.46); (EtOH + 1 drop 1 M aq. NaOH) 209 (log ε 4.96), 231 (4.32), 285 (3.88), 527 nm (3.35). δ_H (400 MHz) 1.38 (3H, d, *J* 6.1 Hz, 3-Me), 2.28 (1H, dddd, *J* 19.0, 9.7, 4.2 and 2.6 Hz, $H_{ax}4$), 2.72 (1H, ddd, *J* 19.0, 3.5 and 2.9 Hz, $H_{eq}4$), 3.67 (1H, m, H3), 3.90 (3H, s, OMe), 4.51 (1H, ddd, *J* 18.8, 4.2 and 3.5 Hz, $H_{ax}1$), 4.84 (1H, dd, *J* 18.8 and 2.6 Hz, $H_{eq}1$), 6.62 (1H, d, *J* 2.4 Hz, H8), 7.19 (1H, d, *J* 2.4 Hz, H6), 12.13 (1H, s, OH). δ_C (100 MHz) 21.2 (3-Me), 29.5 (C4), 56.0 (OMe), 63.0 (C1), 69.6 (C3), 106.0, 108.1, 109.1, 133.4 (C5a), 142.3, 142.8, 164.3, 166.0, 182.9 (C5), 186.7 (C10). Mass spectrum (EI) *m/z* 274 (M^+, 100%), 245 (31), 231 (25), 230 (26), 202 (27), 201 (28), 108 (22), 72 (24), 71 (30).

1-Methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene12. To a solution of LDA [prepared from diisopropylamine (9.15 g, 90 mmol) in tetrahydrofuran (100 ml) and *n*-butyllithium (60.0 ml, 1.5 M in hexane, 90 mmol) at 0 °C, then cooled to −78 °C] was added methyl acetoacetate (10 g, 86 mmol) dropwise over 1 h. After a further 45 min chlorotrimethylsilane (11.2 g, 103 mmol) was added at −78 °C and the solution was allowed to warm to room temperature (2 h), filtered through Celite® and concentrated under reduced pressure. The residual oil was diluted with dry pentane (10 ml), filtered through Celite®, and the filtrate was concentrated and the residual oil distilled to give methyl (*E*)-3-trimethylsilyloxybut-2-enoate (9.69 g, 60%) as a colourless liquid, bp 70–72 °C/8 mmHg (lit.[23] 59–61 °C/2.0 mmHg). ν_{max} 2951, 1711, 1618, 1136, 1037, 846 cm^{-1}. δ_H (300 MHz) 0.26 (9H, s, $SiMe_3$), 2.26 (3H, s, $H_3$4), 3.65 (3H, s, OMe), 5.12 (1H, s, H2). δ_C (75 MHz) 0.16, 20.7, 50.6, 99.3, 168.3, 169.9.

To a solution of LDA (22.4 mmol, prepared as described above) was added a solution of methyl (*E*)-3-trimethylsilyloxybut-2-enoate (4.0 g, 21.4 mmol) in tetrahydrofuran (4 ml) over 15 min. After a further 45 min chlorotrimethylsilane (2.78 g, 25.6 mmol) was added at −78 °C and the solution was allowed to warm to room temperature (2 h) and concentrated under reduced pressure. The residual oil was diluted with pentane (40 ml), filtered through Celite®, concentrated and distilled (Kügelrohr) to give the diene **12** (4.28 g, 77%), bp 55–60 °C/0.5 mmHg (lit.[21] 56–58 °C/2.0 mmHg). ν_{max} 2956, 1647, 1250, 1018, 844 cm^{-1}. δ_H (300 MHz) 0.21 and 0.24 (each 9H, s, $SiMe_3$), 3.55 (3H, s, OMe), 3.94 (1H, d, *J* 1.5 Hz, H_a4), 4.14 (1H, d, *J* 1.5 Hz, H_b4), 4.47 (1H, s, H2). δ_C (75 MHz) 0.20, 0.44, 54.9, 77.5, 89.2, 153.3, 158.6.

(*S*)-(+)-3,4-Dihydro-7,9-dihydroxy-3-methyl-1*H*-naphtho-[2,3-*c*]pyran-5,10-dione 29. To the (*S*)-(+)-pyranobenzoquinone **5** (42 mg, 0.163 mmol) in toluene (1.5 ml) was added 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene **12** (106 mg, 0.407 mmol) in toluene (0.5 ml). The mixture was heated at reflux for 3 h and allowed to cool to room temperature. Silica (200 mg) was added and the solution was stirred for a further 30 min. After removal of the solvent under reduced pressure the residue was filtered slowly through a short column of silica (dichloromethane–ethyl acetate 1 : 1 + 1% formic acid). The yellow fractions were combined, concentrated, filtered through Sephadex LH-20 with dichloromethane–methanol 1 : 1 as eluant and crystallised from chloroform to give the *(S)-(+)-pyranonaphthoquinone* **29** (31 mg, 73%) as yellow needles, mp 171–173 °C (decomp.) [(±)-form, mp 179–183 °C (decomp.)]; $[\alpha]_D$ +160 (*c* 0.28, MeOH). ν_{max} 3421br, 1639, 1614, 1319, 1167, 1153 cm^{-1} [(±)-form, 3414br, 1638, 1613, 1318, 1167, 1153 cm^{-1}]. λ_{max} (EtOH) 219 (log ε 4.33), 270 (4.02), 290 (3.92), 429 nm (3.39); (EtOH + 1 drop 1 M aq. NaOH) 208 (log ε 4.76), 232 (4.20), 294 (3.99), 395 (2.37), 530 nm (3.25). δ_H (400 MHz, d_6-acetone) 1.30 (3H, d, *J* 6.1 Hz, 3-Me), 2.12 (1H, dddd, *J* 18.8, 10.0, 4.1 and 2.5 Hz, $H_{ax}4$), 2.64 (1H, ddd, *J* 18.8, 3.6 and 2.9 Hz, $H_{eq}4$), 3.67 (1H, m, H3), 4.42 (1H, ddd, *J* 18.6, 4.1 and 3.6 Hz, $H_{ax}1$), 4.69 (1H, dd, *J* 18.6 and 2.5 Hz, $H_{eq}1$), 6.54 (1H, d, *J* 2.3 Hz, H8), 7.01 (1H, d, *J* 2.3 Hz, H6), 10.01 (1H, br s, 7-OH), 12.05 (1H, s, 9-OH). δ_C (100 MHz, d_6-acetone) 21.4 (3-Me), 30.1 (C4), 63.3 (C1), 70.0 (C3), 108.1 (C8), 108.9 (C6), 109.3 (C9a), 134.8 (C5a), 142.8 (C4a/10a), 143.4 (C4a/10a), 165.1 (C9), 165.4 (C7), 183.2 (C5), 187.6 (C10). Mass spectrum (EI) *m/z* 260 (M^+, 28%), 86 (33), 84 (54), 71 (100), 70 (26), 69 (56).

(1*R*,3*S*)-(−)-Thysanone 1. To the (*S*)-(+)-pyranonaphthoquinone **29** (15 mg, 0.057 mmol) in carbon tetrachloride (14 ml) was added bromine (9.2 mg, 0.056 mmol) in carbon tetrachloride (1.1 ml) and the solution was irradiated with a 375 W tungsten lamp for 30 min. After removal of solvent under reduced pressure the resultant yellow oil was dissolved in tetrahydrofuran (6 ml) and water (2 ml) and stirred at room temperature for 1 h. Dilution with water (10 ml) followed by extraction with chloroform (3 × 5 ml), drying ($MgSO_4$) of the combined organic extracts and concentration under reduced pressure gave a yellow solid that was purified by preparative thin-layer chromatography (50 : 49 : 1 toluene–ethyl formate–formic acid, R_F 0.40) and crystallised from methanol to give *(1R,3S)-(−)-thysanone* **1** (8.3 mg, 85%) as yellow needles, mp 197–198 °C (decomp.) [lit.[3] mp 205–206 °C (decomp.)]. $[\alpha]_D$ −29.7 (*c* 0.002, MeOH) {lit.[3] $[\alpha]_D$ +29 (*c* 1.62, MeOH)}. CD 257 (Δε +2.8), 296 (−3.1), 417 (−0.1), 445 nm (−0.3) (Found: M^+, 276.0625, $C_{14}H_{12}O_6$ requires M^+, 276.0634). ν_{max} 3411br, 2924, 1647, 1610, 1390, 1323, 1274, 1155, 1075 cm^{-1} [(±)-form, 3409br, 2925, 1647, 1611, 1390, 1322, 1276, 1172, 1076 cm^{-1}]. λ_{max} (MeOH) 219 (log ε 4.33), 263 (4.04), 288sh (3.94), 421 nm (3.38). δ_H (400 MHz, d_6-acetone) see Table 2. δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.4 Hz, 3-Me), 2.24 (1H, dd, *J* 19.6 and 11.1 Hz, $H_{ax}4$), 2.75 (1H, dd, *J* 19.6 and 3.2 Hz, $H_{eq}4$), 4.36 (1H, m, H3), 6.05 (1H, s, H1), 6.63 (1H, d, *J* 2.5 Hz, H8), 7.11 (1H, d, *J* 2.5 Hz, H6), 12.10 (1H, s, 9-OH). δ_C (100 MHz, d_6-acetone) see Table 2. Mass spectrum (EI) *m/z* 276 (M^+, 13%), 260 (37), 259 (26), 258 (100), 257 (24), 256 (21), 243 (22), 232 (24), 231 (20), 230 (25), 229 (24), 215 (22), 204 (20), 137 (26), 128 (30), 115 (21), 83 (24), 81 (24), 79 (20), 77 (31), 73 (28), 71 (43), 70 (25), 69 (83), 67 (27), 65 (24), 64 (34), 63 (25), 60 (35), 57 (63), 56 (24), 55 (70), 53 (27), 51 (37).

(1*R*,3*S*)-(−)-Thysanone methyl acetal 2. To (1*R*,3*S*)-(−)-thysanone **1** (8.2 mg, 0.028 mmol) in methanol (6 ml) was added a trace of concentrated sulfuric acid and the mixture was stirred at room temperature for 16 h. Water (15 ml) was added and the product was extracted into chloroform (3 × 5 ml) and the

combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The resultant yellow solid was purified by preparative thin-layer chromatography (50 : 49 : 1 toluene–ethyl formate–formic acid, R_F 0.60) and crystallised from methanol to give *(1R,3S)-(−)-thysanone methyl acetal* **2** (4.7 mg, 55%) as yellow needles, mp 202–205 °C (decomp.) [lit.[3] mp 212–215 °C (decomp.)]. $[\alpha]_D$ −93.6 (*c* 0.002, MeOH). CD 253 (Δε +5.7), 292 (−5.8), 406 (+0.6), 462 nm (−0.4) (Found: M^+, 290.0795, $C_{15}H_{14}O_6$ requires M^+, 290.0790). ν_{max} 3425br, 2923, 1647, 1614, 1393, 1324, 1275, 1176, 1093, 1050 cm^{-1}. λ_{max} (MeOH) 219 (log ε 4.31), 267 (3.92), 288sh (3.79), 435 nm (3.30). δ_H (400 MHz, d_6-acetone) 1.33 (3H, d, *J* 6.1 Hz, 3-Me), 2.14 (1H, dd, *J* 19.4 and 11.0 Hz, $H_{ax}4$), 2.69 (1H, dd, *J* 19.4 and 3.5 Hz, $H_{eq}4$), 3.49 (3H, s, 1-OMe), 4.14 (1H, m, H3), 5.43 (1H, s, H1), 6.61 (1H, d, *J* 2.2 Hz, H8), 7.07 (1H, d, *J* 2.2 Hz, H6), 12.21 (1H, s, 9-OH). Mass spectrum (EI) *m*/*z* 290 (M^+, 27%), 260 (50), 259 (100), 231 (40), 216 (27), 111 (22), 109 (24), 97 (32), 95 (35), 85 (24), 83 (38), 81 (41), 79 (21), 77 (23), 71 (60), 70 (30), 69 (89), 67 (39), 57 (86), 56 (33), 55 (93), 53 (21), 51 (22).

Thysanone 1 from *Thysanophora penicilloides*. A sample of thysanone isolated from *Thysanophora penicilloides* was generously supplied by Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065, USA. In our hands, the following spectroscopic data were recorded: $[\alpha]_D$ −49.6 (*c* 0.002, MeOH). CD 259 (Δε +3.8), 296 (−3.7), 407 (+0.3), 453 nm (−0.1). δ_H (400 MHz, d_6-acetone) 1.29 (3H, d, *J* 6.3 Hz, 3-Me), 2.10 (1H, dd, *J* 19.3 and 11.4 Hz, $H_{ax}4$), 2.68 (1H, dd, *J* 19.3 and 3.4 Hz, $H_{eq}4$), 4.32 (1H, m, H3), 5.91 (1H, s, H1), 6.61 (1H, d, *J* 2.5 Hz, H8), 7.07 (1H, d, *J* 2.5 Hz, H6), 12.26 (1H, s, 9-OH) [lit.[3] δ_H (d_6-acetone) see Table 1].

The methyl acetal of natural thysanone. A sample of thysanone methyl acetal was kindly supplied by Merck Sharp & Dohme Laboratories. In our hands the following spectroscopic data were obtained: $[\alpha]_D$ −57.8 (*c* 0.002, MeOH). CD 250 (Δε +,3.9), 291 (−4.3), 403 (+0.5), 462 nm (−0.3). δ_H (400 MHz, d_6-acetone) 1.33 (3H, d, *J* 6.4 Hz, 3-Me), 2.14 (1H, dd, *J* 19.5 and 11.0 Hz, $H_{ax}4$), 2.69 (1H, dd, *J* 19.5 and 3.4 Hz, $H_{eq}4$), 3.49 (3H, s, 1-OMe), 4.14 (1H, m, H3), 5.43 (1H, s, H1), 6.61 (1H, d, *J* 2.4 Hz, H8), 7.07 (1H, d, *J* 2.4 Hz, H6), 12.21 (1H, s, 9-OH).

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