Total synthesis of enantiopure 1,3-dimethylpyranonaphthoquinones including ventiloquinones E, G, L and eleutherin

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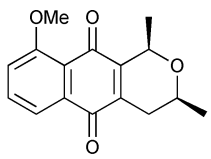
A new synthetic approach to enantiopure pyranonaphthoquinones is described. (*S*)-Mellein **10**, prepared in 6 steps from (*S*)-propylene oxide **16**, is converted stereospecifically to the (1*R*,3*S*)-dimethylpyran **15**. The pyran **15** is then converted to the benzoquinone **14**, which undergoes regiospecific Diels–Alder reactions with a variety of oxygenated butadienes to give pyranonaphthoquinones including ventiloquinones E, G, L, eleutherin and *ent*-deoxyquinone A.

Introduction

Pyranonaphthoquinones are widespread in nature having been isolated from plant, insect, bacterial and fungal sources.[1] Members of this family of compounds display a range of biological activities[2] and have also been proposed to act as bioreductive alkylating agents.[3] This has stimulated considerable effort towards their total synthesis.[4] One of the simplest members of this group is eleutherin **1**, a topoisomerase II inhibitor[5] first isolated from the bulbs of *Eleutherine bulbosa* (Iradaceae).[6] Eleutherin **1** has been the subject of total synthesis a number of times, but only in racemic form.[4]



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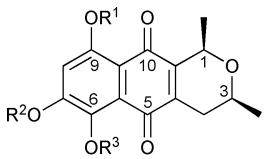

2 $R^1 = R^2 = R^3 = Me$
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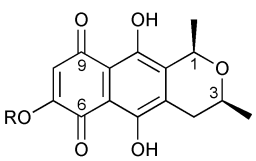

6 R = H
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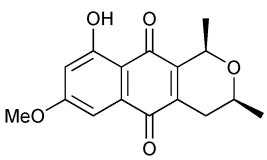

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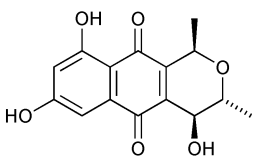

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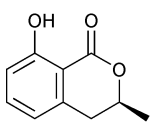
Numerous other 1,3-dimethylpyranoquinones possessing a variety of oxygenation patterns in the quinone moiety are known as natural products.[1] Examples include the ventiloquinone family of which there are 15 members. Amongst this group are ventiloquinones E **2** and G **6** isolated from the plant *Ventilago maderaspatana*[7] and ventiloquinone L **8** from *V. goughii*.[8] A number of racemic syntheses of members of the ventiloquinone group have been reported.[4,9] A rare example of the total synthesis of 1,3-dimethylpyranoquinones in enantiopure form has been reported by Giles[10] and involved the synthesis of all 8 stereoisomers of quinone A **9**, a natural derivative of the aphid insect pigments.[11] Herein we wish to report full details[12] of our approach to pyranoquinones that makes available enantiopure ventiloquinones E **2**, G **6**, L **8**, eleutherin **1** and related pyranoquinones.

Results and discussion

We have previously reported the synthesis of both enantiomers of the natural product mellein **10** beginning from the appropriate stereoisomer of propylene oxide.[13] We have since used (*S*)-mellein **10** as an intermediate in the first total synthesis of the fungal pigment (1*R*,3*S*)-thysanone **11**[14] and felt that this methodology could be extended to the synthesis of 1,3-dimethylpyranonaphthoquinones in enantiopure form.



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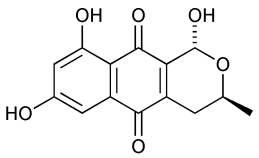

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Our planned approach to pyranonaphthoquinones is shown retrosynthetically in Scheme 1. Thus, quinones of the type **12** with variously substituted aromatic rings may be formed by Diels–Alder cycloaddition between appropriately oxygenated butadienes **13** and the benzoquinone **14**, which itself may be available from the dimethylpyran **15**. The key dimethylpyran **15** should be available from (*S*)-mellein **10** by use of the method by Kraus *et al.*,[15] which involves introduction of the alkyl group at C-1 followed by stereospecific reduction with hydride. In order to pursue this method, quantities of (*S*)-mellein **10** were firstly prepared from ethyl (*S*)-lactate **17** *via* (*S*)-propylene oxide **16** according to the method we have described earlier.[13] The spectroscopic data, including specific rotation, for (*S*)-mellein

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† In memoriam of Dr Melvyn Gill, under whose guidance this work was undertaken.

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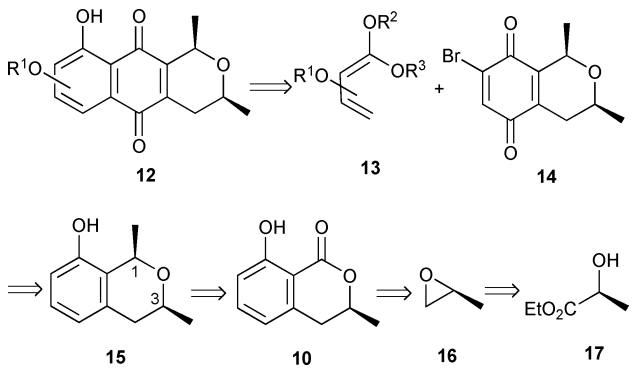
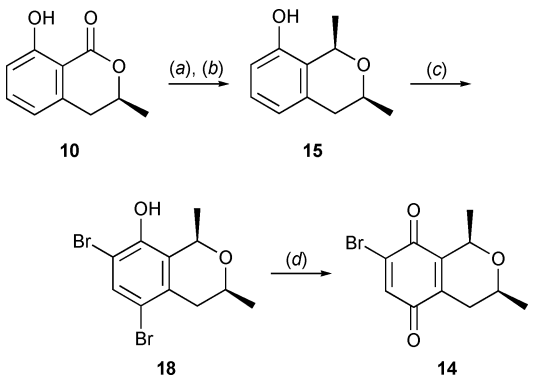


Scheme 1

obtained in this way were consistent with those described in the literature.[13,16]

The lactone **10** was treated with methyllithium in tetrahydrofuran at −78 °C according to the method of Kraus *et al*.[15] The intermediate addition product was isolated and exposed immediately to trifluoroacetic acid and triethylsilane in dichloromethane at −80 °C (Scheme 2). The required 1,3-dimethylpyran **15** was isolated in yields as high as 83%, over 2 steps, after hydrolysis of a silylated derivative. However, inconsistent yields were obtained using this method. Reproducible results were obtained by treatment of the lactone **10** with methyl magnesium bromide in ether at 0 °C followed by reduction with trifluoroacetic acid and triethylsilane as before.[15] Thus, the ether **15** was isolated as colourless plates with $[\alpha]_D^{26}$ +206 in 92% yield from **10**.



Scheme 2 *Reagents and conditions*: (*a*) MeLi, THF, −80 °C, 3 h; *or* MeMgBr, ether, 0 °C → rt, 1 h; (*b*) Et_3SiH, CF_3CO_2H, CH_2Cl_2, −80 °C → rt, 2 h; (*c*) NBS (2 eq.), DMF, rt, 18 h; (*d*) CAN, MeCN, H_2O, rt, 20 min.

The 1,3-diequatorial disposition of the methyl groups in the pyran **15** was established by analysis of the chemical shifts of the 1-H and 3-H methine protons. Previous studies[17] have ascertained that there are significant differences in the ^{1}H NMR spectra of *cis*-1,3-dimethyl (diequatorial) *versus trans*-1,3-dimethyl (axial/equatorial) 3,4-dihydropyrans. It is consistently observed that 1-H and 3-H are deshielded for *trans*-isomers relative to their *cis* counterpart. Particularly diagnostic is the signal associated with 3-H that, although pseudo axial in both *cis*- and *trans*-isomers, resonates at $<\delta$ 3.75 for *cis*-isomers and $>\delta$ 3.95 for *trans*-isomers. For benzopyran **15** the 1-H (δ 5.07) and 3-H (δ 3.71) signals in the ^{1}H NMR spectrum are consistent with a *cis*-1,3-dimethyl arrangement. Thus, we can confidently assign the stereochemistry at C-1 as (*R*) since we know the stereochemistry at C-3 is (*S*) since it originates from (*S*)-propylene oxide **16**.

Bromination of the benzopyran **15** with *N*-bromosuccinimide (2 equivalents) in *N*,*N*-dimethylformamide gave, upon crystallization of the crude material, (1*R*,3*S*)-dibromobenzopyran **18** for the first time as fine colourless needles in 82% yield and with $[\alpha]_D^{22}$ +155. The incorporation of two bromine atoms into the molecule was confirmed by the presence of a proton singlet (δ 7.55) in the ^{1}H NMR spectrum and in the mass spectrum, a molecular ion measured at *m*/*z* 334.9291 for the pseudomolecular ion {[M + H]$^+$, $^{79}Br_2$}. Oxidation was effected by adding an aqueous solution of cerium(IV) ammonium nitrate to the dibromobenzopyran **18** in acetonitrile to give the (1*R*,3*S*)-benzoquinone **14** as a yellow solid in 86% yield. The benzoquinone **14** has the potential to act as a versatile dienophile in Diels–Alder reactions. This ability is demonstrated by the successful reaction of benzoquinone **14** with a range of oxygenated butadienes as summarised in Scheme 3.

Firstly, the (1*R*,3*S*)-benzoquinone **14** was exposed to 1-methoxy-1-trimethylsiloxybuta-1,3-diene **22** in benzene at room temperature. After filtration through silica, chromatographic purification gave a single product as yellow needles. This pigment exhibited a strong positive optical rotation measurement, $[\alpha]_D^{21}$ +190, and a high resolution mass measurement on the pseudomolecular ion {[M − H]$^-$} led to the molecular formula $C_{15}H_{14}O_4$. Signals in the ^{1}H NMR spectrum include a sharp singlet at δ 12.01 due to a chelated hydroxyl proton, a set of 3 contiguous aromatic protons at δ 7.63 (dd, *J* 7.6 and 1.5 Hz), 7.60 (dd, *J* 8.0 and 7.6 Hz) and 7.24 (dd, *J* 8.0 and 1.5 Hz) and a set of signals with chemical shifts and coupling constants[17] consistent with the presence of a 1,3-diequatorial substituted pyran ring (Experimental). These data were consistent with the structure **19**, however, the naphthoquinone **19** was obtained in a moderate 10% yield. Treatment of the benzoquinone **14** with 1-methoxy-1,3-cyclohexadiene **23** in benzene, followed by pyrolysis, proceeded only slightly more readily to give eleutherin **1** as yellow needles (mp 140–145 °C) in 13% yield. The EI mass spectrum for this product exhibited a molecular ion at *m*/*z* 272 consistent with the formula $C_{16}H_{16}O_4$, whilst the ^{1}H NMR spectrum includes 3 aromatic proton signals and a methoxy signal (Table 1). All other spectroscopic data for the synthetic material **1** (Experimental) is in complete accord with the assigned structure.

The spectroscopic data for synthetic eleutherin **1** also agrees closely with those reported for the natural product (Table 1)[17] as well as those recorded using an authentic sample of eleutherin **1**. Significantly, the optical rotation measurement of synthetic eleutherin **1** {$[\alpha]_D^{22}$ +291} agrees well with that recorded for natural eleutherin **1** {$[\alpha]_D^{15}$ +346} from *Eleutherine bulbosa*.[6] This agreement is consistent with the absolute configuration of the synthetic compound **1** being (1*R*,3*S*) as expected from its synthesis from ethyl (*S*)-lactate **17**. The absolute configuration of eleutherin **1** is known to be (1*R*,3*S*) by the chemical degradation of the natural product and comparison with 3-hydroxybutyric acid.[18] Many racemic, but not enantiopure, syntheses of eleutherin **1** have been reported,[4] this is the first synthesis of enantiomerically pure eleutherin **1**.

The bromoquinone **14** was then reacted with 1-methoxy-3-trimethylsiloxybuta-1,3-diene **24** in dry benzene at 60 °C for 24 hours. Preparative thin layer chromatography gave a single bright yellow compound that was purified by gel filtration. The

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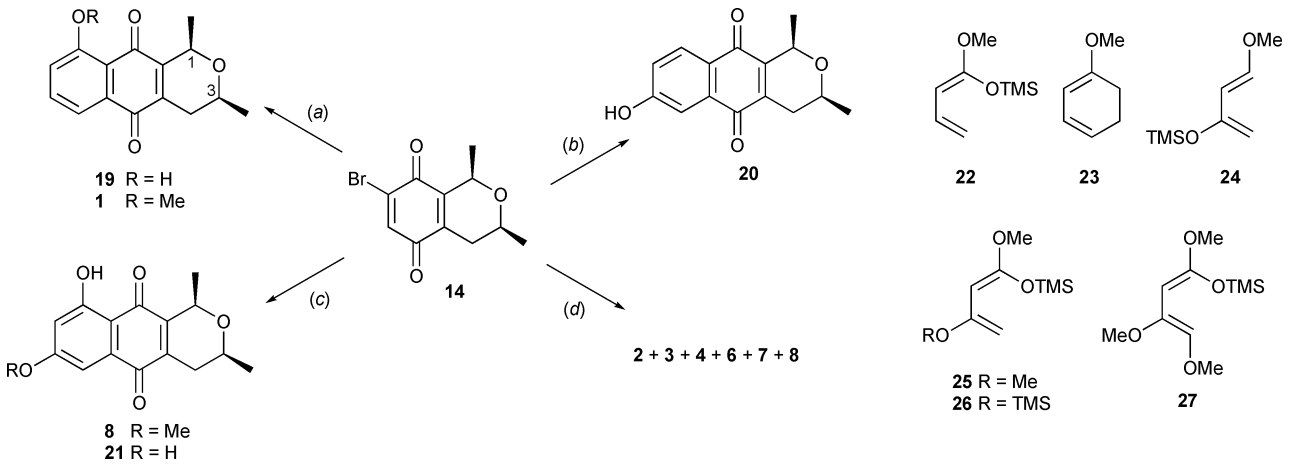


Scheme 3 *Reagents and conditions*: (*a*) **22**, benzene, rt, 3.5 h (for **19**); (i) **23**, benzene, 80 °C, 1 h; (ii) CH_2Cl_2, NEt_3, rt, 18 h; (iii) 150 °C, 30 min (for **1**); (*b*) **24**, benzene, 60 °C, 24 h; (*c*) **25**, benzene, 60 °C, 100 min (for **8**); **26**, benzene, rt, 18 h (for **21**); (*d*) **27**, benzene, rt, 18 h.

Table 1 ^{1}H NMR data [δ, multiplicity and coupling constants (Hz)] for synthetic and naturally occurring eleutherin **1** and ventiloquinone L **8** in $CDCl_3$

Proton(s)	Synthetic eleutherin **1**[a]	Natural eleutherin **1**[b]	Synthetic ventiloquinone L **8**[a]	Natural ventiloquinone L **8**[b]
1-H	4.85 (m)	4.85 (m)	4.82 (ddq, *J* 3.9, 2.6, 6.6)	4.81 (ddq, *J* 3.9, 2.6, 6.6)
3-H	3.58 (m)	3.58 (m)	3.57 (ddq, *J* 10.2, 2.6, 6.4)	3.57 (ddq, *J* 10.2, 2.6, 6.6)
4-H_{ax}	2.20 (ddd, *J* 18.3, 10.3, 3.7)	2.19 (ddd, *J* 18, 10, 4)	2.22 (ddd, *J* 18.6, 10.2, 3.9)	2.22 (ddd, *J* 18.0, 10.2, 3.9)
4-H_{eq}	2.75 (dt, *J* 18.3, 2.7)	2.75 (dt, *J* 18, 2.5)	2.73 (dt, *J* 18.6, 2.6)	2.73 (dt, *J* 18.0, 2.6)
6-H	7.73 (d, *J* 7.8)	7.72 (m)	7.15 (d, *J* 2.4)	7.15 (d, *J* 2.6)
7-H	7.64 (dd, *J* 8.5, 7.8)	7.63 (m)	—	—
8-H	7.27 (d, *J* 8.5)	7.27 (m)	6.61 (d, *J* 2.4)	6.61 (d, *J* 2.6)
1-Me	1.53 (d, *J* 6.6)	1.53 (d, *J* 6.5)	1.57 (d, *J* 6.6)	1.57 (d, *J* 6.6)
3-Me	1.36 (d, *J* 6.3)	1.36 (d, *J* 6)	1.36 (d, *J* 6.4)	1.35 (d, *J* 6.6)
7-OMe	—	—	3.89 (s)	3.88 (s)
9-OH	—	—	12.25 (s)	12.22 (s)
9-OMe	3.99 (s)	3.99 (s)	—	—

[a] Synthetic eleutherin **1** and ventiloquinone L **8** recorded at 400 MHz. [b] Natural eleutherin **1**[17] and ventiloquinone L **8**[8] recorded at 300 MHz and 360 MHz, respectively.

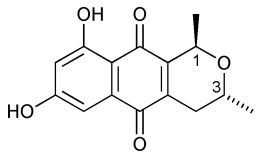
product (1*R*,3*S*)-7-hydroxynaphthoquinone **20** was isolated as a yellow solid with $[\alpha]_D^{15}$ +290 in 49% yield. The ^{1}H NMR spectrum of **20** includes three aromatic proton signals at δ 7.98 (d, *J* 8.4 Hz), δ 7.50 (d, *J* 2.6 Hz) and δ 7.14 (dd, *J* 8.4 and 2.6 Hz), consistent with the substitution pattern in **20**.

The next diene to be pursued, 1,3-dimethoxy-1-trimethylsiloxybuta-1,3-diene **25**, was introduced to a solution of the bromoquinone **14** in dry benzene and heated at 60 °C for 100 minutes. A small amount of silica was added to the solution to ensure complete aromatization. After chromatographic purification the product was isolated as orange needles in 41% yield with $[\alpha]_D^{26}$ +420. The EI mass spectrum for the product exhibited a molecular ion at *m*/*z* 288, a high resolution mass measurement of which gave the molecular formula $C_{16}H_{16}O_5$. The pigment was identified as (1*R*,3*S*)-ventiloquinone L **8** by inspection of the spectroscopic data (Table 1 and Experimental). Comparison of the spectroscopic data for synthetic ventiloquinone L **8** with the corresponding data recorded for naturally occurring ventiloquinone L **8** (Table 1 and $[\alpha]_D^{30}$ +387)[8] establishes the identity of the synthetic and natural materials. Although racemic ventiloquinone L **8** has been synthesized previously,[9a,19] this is the first synthesis in enantiopure form and establishes unequivocally for the first time the (1*R*,3*S*) absolute stereochemistry of the natural product **8**.

To the bromoquinone **14** dissolved in benzene was added 1-methoxy-1,3-bis(trimethylsiloxy)buta-1,3-diene **26**. After stirring overnight, silica was added and the suspension was purified to give a single product as yellow needles. A high resolution mass measurement on the molecular ion at *m*/*z* 274 led to the formula $C_{15}H_{14}O_5$. The ^{1}H NMR indicated the presence of a chelated hydroxy proton (δ 12.19) as well as a free phenolic proton (δ 7.09), a pair of *meta*-coupled aromatic protons (δ 7.15 and 6.62, *J* 1.8 Hz) and a set of signals consistent with the presence of an intact 1,3-dimethyl substituted pyran ring. Combining all of the spectroscopic data leads to the new structure (1*R*,3*S*)-7,9-dihydroxynaphthoquinone **21**, which was isolated in 24% yield. This pigment **21** is not itself found in nature but its C-3 epimer (1*R*,3*R*)-deoxyquinone A **28** is known as a degradation product of deoxyprotoaphin **29**.[20]

Epimerisation of the C-1 methyl group in quinone **21** was achieved using boron tribromide[7] and gave the *trans*-pyran **30** as an orange solid with $[\alpha]_D^{18}$ −210, albeit in low (11%) yield. Full details of the optical rotation measurement of the (1*R*,3*R*)-compound **28** have not been reported, it has been noted however that the 7,9-dimethyl ether of **28** is dextrorotatory.[19] As noted earlier, Giles has prepared all 8 stereoisomers of quinone A **9**, also using lactate from the chiral pool as a source of asymmetry.[10] The method

described here provides a distinctly different approach for the construction of the pyran ring in quinones such as **21**.



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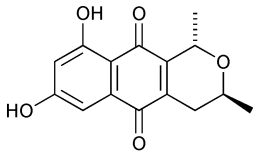

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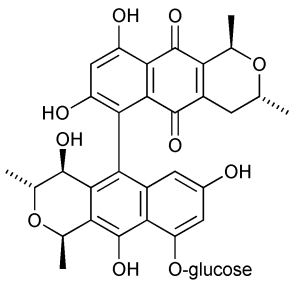

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The next diene to be combined with the bromoquinone **14** was the more highly oxygenated butadiene **27** (Scheme 3). Thus, to the bromoquinone **14** in benzene was added 1,3,4-trimethoxy-1-trimethylsiloxybuta-1,3-diene **27** and after stirring at room temperature overnight silica was added and the dark orange suspension was filtered through a short silica pad and an orange band was collected. Chromatographic analysis revealed the presence in this mixture of at least 6 pigments that were separated and each purified by extensive chromatography. The first compound was obtained only in trace amounts and was identified as ventiloquinone L **8**. The pigment was found to be chromatographically, physically and spectroscopically indistinguishable from the sample described earlier.

The next two quinone products, **6** and **7**, were identified as naphthazarin derivatives from the UV–vis spectra that exhibited long wavelength absorption at 519 and 553 nm and 502 and 535 nm, respectively.[21] The ^{1}H NMR data from quinone **6** reveal the presence of an isolated quinonoid proton, one non-chelated and two chelated hydroxy protons and a set of methyl, methylene and methine protons consistent with the dimethylpyran ring system (Experimental). That the quinone **6** exists predominantly in the tautomeric form shown follows from the characteristic shift of the quinone proton (δ 6.35).[22] The quinone **6** proved identical in all respects, including the sign of the specific rotation, with ventiloquinone G **6** isolated from *Ventilago maderaspatana*.[7] The second red quinone was identified as the 7-*O*-methyl ether **7** of ventiloquinone G **6** from the spectroscopic data, principally by comparison of the ^{1}H NMR spectrum of the entirely synthetic material with that of the naturally derived material.[7]

The remaining three orange/yellow quinones were identified as ventiloquinone E **2** and its isomeric 7- and 9-desmethyl ethers **3** and **4**, respectively, from the ^{1}H NMR data (Experimental). Ventiloquinone E **2** occurs along with several other quinones in the root bark of *Ventilago maderaspatana*.[7] Comparison of the ^{1}H NMR spectra of the synthetic and natural products established the identity of the two. The 7- and 9-desmethyl derivatives **3** and **4**, respectively, of ventiloquinone E **2**, are not themselves natural products but their structural isomer, 6-hydroxy-7-methoxyeleutherin **5**, is a constituent of *Karwinskia humboldtiana*.[23] The fact that the ^{1}H NMR data for the dimethyl ethers **3** and **4** are distinctly different from the spectrum of the isomer **5**,[23] excludes **5** from the possible products from the reaction of diene **27** and reduced the structural possibilities of the final two yellow quinones to **3** and **4**. The isomers **3** and **4** could be differentiated by the observation that the ^{1}H NMR spectrum of **3** contains two methoxy singlets and a non-chelated hydroxy resonance (δ 6.68), while the spectrum of **4** exhibits two methoxy singlets and one strongly chelated phenolic hydroxy resonance (δ 13.04). This reaction provides three natural products, the ventiloquinones E **2**, G **6** and L **8**, in one pot, albeit in low yield. This is the first report of the enantiopure synthesis of these natural products.

Conclusions

The chemistry described here demonstrates a versatile new route to enantiopure 1,3-dimethylpyranonaphthoquinones. The synthetic method has led to the first total synthesis of a variety of pyranonaphthoquinones including ventiloquinones E **2**, G **6**, L **8** and eleutherin **1** unequivocally establishing the absolute stereochemistry of these natural products. The method contains further versatility when it is recognized that the C-3 alkyl group is dependent on the choice of chiral oxirane starting material and the C-1 substituent derives from the choice of organometallic reagent, providing the ability to incorporate numerous different functional groups at C-1 and C-3. The realization of this potential will be reported in due course.

Experimental

Melting points were determined on a hot-stage apparatus and are uncorrected. Infrared (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 ethanol or methanol 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. Chemical shifts are relative to tetramethylsilane with *J* values given in Hz. Mass spectra were recorded on a Shimadzu GCMS-QP505A spectrometer at 70 eV [probe; electron ionisation (EI)] and a Micromass QUATTRO II [electrospray ionisation (ESI)]. Specific rotations were measured using a JASCO DIP-1000 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Thin-layer chromatography (TLC) and preparative TLC (PLC) were performed on Merck pre-coated 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 ultraviolet (UV) light (254 or 366 nm).

(1*R*,3*S*)-8-Hydroxy-1,3-dimethyl-3,4-dihydro-1*H*-2-benzopyran **15**

To a solution of (*S*)-mellein **10** (502 mg, 2.8 mmol) in anhydrous ether (15 mL) at 0 °C was added methylmagnesium bromide (2 M in ether, 5 mL, 10 mmol) dropwise over 5 min. The mixture was stirred for 30 min at 0 °C, then for a further 60 min at

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room temperature. The reaction was quenched with sat. aq. ammonium chloride and the mixture was extracted with ether (3 × 30 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a colourless solid that was dissolved in dichloromethane (10 mL) and cooled to −80 °C. Trifluoroacetic acid (0.65 mL, 8.4 mmol) and then triethylsilane (1.4 mL, 8.8 mmol) were added dropwise and the resulting solution was stirred for 30 min followed by warming to room temperature over 90 min. The solution was concentrated under reduced pressure, then treated overnight in a mixture of tetrahydrofuran (5 mL), acetic acid (10 mL) and water (5 mL). The solution was neutralized with sat. aq. sodium bicarbonate and extracted with ether (3 × 30 mL). The combined ethereal extracts were washed with sat. aq. sodium bicarbonate (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (dichloromethane then ether) gave (1*R*,3*S*)-dimethylpyran **15** (464 mg, 92%), as colourless plates, mp 166–169 °C (ether–hexanes) (subl., morphological changes at 110 °C) (lit.[15b] mp [(±)-form] 111–112 °C, ether–hexanes); $[\alpha]_D^{26}$ +206 (*c* 0.100, $CHCl_3$); found: C, 74.0; H, 7.8%; $[M + Na]^+$, 201.0893. $C_{11}H_{14}O_2$ requires: C, 74.1; H, 7.9%; $[M + Na]^+$, 201.0891; ν_{max} (KBr) 3248, 2970, 2935 and 2851 cm^{-1}; δ_H(400 MHz) 1.35 (3H, d, *J* 6.0, 3-Me), 1.61 (3H, d, *J* 6.3, 1-Me), 2.59 (1H, dd, *J* 15.6 and 2.0, 4-H_{ax}), 2.71 (1H, dd, *J* 15.6 and 10.6, 4-H_{eq}), 3.71 (1H, ddq, *J* 10.6, 2.0 and 6.0, 3-H), 5.07 (1H, br q, *J* 6.3, 1-H), 5.12 (1H, br s, 8-OH), 6.57 (1H, d, *J* 8.0, 7/5-H), 6.68 (1H, d, *J* 7.7, 5/7-H) and 7.02 (1H, t, *J* 7.8, 6-H). δ_C(100 MHz) 21.47, 21.53, 37.2, 69.7, 70.8, 113.2, 121.0, 126.1, 126.8, 136.8 and 152.1; *m*/*z* (EI) 178 {$[M]^+$, 4}, 163 (100), 145 (26) and 91 (20).

(1*R*,3*S*)-5,7-Dibromo-8-hydroxy-1,3-dimethyl-3,4-dihydro-1*H*-2-benzopyran 18

To a solution of (1*R*,3*S*)-benzopyran **15** (144 mg, 0.81 mmol) in dimethylformamide (10 mL) was added *N*-bromosuccinimide (288 mg, 1.62 mmol). The solution was stirred at room temperature in the dark for 18 h. After dilution with water (50 mL), the solution was extracted with dichloromethane (3 × 20 mL) and the combined organic extracts were washed with water (4 × 20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Crystallization from dichloromethane–hexanes gave (1*R*,3*S*)-dibromobenzopyran **18** (223 mg, 82%) as colourless needles, mp 153–155 °C; $[\alpha]_D^{22}$ +155 (*c* 1.00, $CHCl_3$); found: C, 39.3; H, 3.6%; {$[M + H]^+$, $^{79}Br_2$}, 334.9291; {$[M]^+$, $^{79}Br_2$}, 333.9193. $C_{11}H_{12}O_2Br_2$ requires: C, 39.3; H, 3.6%; {$[M + H]^+$, $^{79}Br_2$}, 334.9283; {$[M]^+$, $^{79}Br_2$}, 333.9205; ν_{max} (KBr) 3409, 3078, 2977, 2928 and 2843 cm^{-1}; δ_H(400 MHz) 1.37 (3H, d, *J* 6.3, 3-Me), 1.57 (3H, d, *J* 6.3, 1-Me), 2.43 (1H, ddd, *J* 16.6, 10.7 and 1.5, 4-H_{ax}), 2.72 (1H, br d, *J* 16.6, 4-H_{eq}), 3.61 (1H, ddq, *J* 10.7, 2.3 and 6.3, 3-H), 4.98 (1H, br q, *J* 6.3, 1-H), 5.60 (1H, s, 8-OH) and 7.55 (1H, s, 6-H); δ_C(100 MHz) 21.0, 21.4, 37.6, 69.3, 71.1, 108.5, 115.1, 129.7, 131.8, 135.9 and 147.7; *m*/*z* (EI) 336 {$[M]^+$, 21}, 323 (51), 321 (100), 319 (50), 292 (36), 224 (24), 222 (24), 132 (34), 131 (26) and 77 (31).

(1*R*,3*S*)-7-Bromo-1,3-dimethyl-3,4-dihydro-1*H*-2-benzopyran-5,8-dione 14

A solution of cerium(IV) ammonium nitrate (268 mg, 0.49 mmol) in water (7 mL) was added dropwise to (1*R*,3*S*)-dibromobenzopyran **18** (53 mg, 0.16 mmol) in acetonitrile (7 mL). After stirring for 20 min the solution was poured into water (20 mL) and extracted with chloroform (3 × 20 mL). The combined organic extracts were washed with water (3 × 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resultant oil was purified by gel filtration (Sephadex LH20, methanol–dichloromethane, 1 : 1) to give (1*R*,3*S*)-benzoquinone **14** (37 mg, 86%), as a yellow solid, which was used immediately and without further purification; δ_H(400 MHz) 1.33 (3H, d, *J* 6.1, 3-Me), 1.49 (3H, d, *J* 6.6, 1-Me), 2.16 (1H, ddd, *J* 18.8, 10.0 and 4.2, 4-H_{ax}), 2.60 (1H, dt, *J* 18.8 and 2.6, 4-H_{eq}), 3.55 (1H, ddq, *J* 10.0, 2.6 and 6.1, 3-H), 4.70 (1H, ddq, *J* 4.2, 2.6 and 6.6, 1-H) and 7.25 (1H, s, 6-H).

(1*R*,3*S*)-9-Hydroxy-1,3-dimethyl-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 19

A solution of 1-methoxy-1-trimethylsiloxybuta-1,3-diene **22** (42 mg, 0.24 mmol) in benzene (2 mL) was added dropwise to a solution of the (1*R*,3*S*)-benzoquinone **14** (22 mg, 0.081 mmol) in benzene (2 mL). The reaction was stirred at room temperature for 3.5 h, silica gel (1.0 g) was added and the solvent was evaporated at reduced pressure. Column chromatography (dichloromethane–1% formic acid) and gel filtration (Sephadex LH20, methanol–dichloromethane, 1 : 1) gave (1*R*,3*S*)-naphthoquinone **19** as yellow microneedles (2 mg, 10%), mp 83–86 °C (MeOH); $[\alpha]_D^{21}$ +190 (*c* 0.030, $CHCl_3$); CD $\lambda_{extrema}$(MeOH) 256 ($\Delta\varepsilon$ +0.55), 283 (+3.03), 340 (+1.17), 437 (−0.59) and 482 nm (−0.15); found: $[M - H]^-$, 257.0818. $C_{15}H_{14}O_4$ requires: $[M - H]^-$, 257.0814; λ_{max}(MeOH) 212 (log ε 4.25), 246 (3.72), 273 (3.76) and 417 nm (3.27); δ_H(400 MHz) 1.37 (3H, d, *J* 6.3, 3-Me), 1.58 (3H, d, *J* 6.6, 1-Me), 2.24 (1H, ddd, *J* 18.8, 10.0 and 3.9, 4-H_{ax}), 2.74 (1H, dt, *J* 18.8 and 2.5, 4-H_{eq}), 3.59 (1H, ddq, *J* 10.0, 2.5 and 6.3, 3-H), 4.85 (1H, ddq, *J* 3.9, 2.5 and 6.6, 1-H), 7.24 (1H, dd, *J* 8.0 and 1.5, 8-H), 7.60 (1H, dd, *J* 8.0 and 7.6, 7-H), 7.63 (1H, dd, *J* 7.6 and 1.5, 6-H) and 12.01 (1H, s, 9-OH); *m*/*z* (EI) 258 {$[M]^+$, 7}, 115 (26), 92 (28), 77 (24), 71 (24), 69 (40), 67 (27), 65 (34), 64 (24), 63 (52), 57 (99), 56 (33), 55 (100), 53 (30) and 51 (38); *m*/*z* (ESI–) 257.0 $[M - H]^-$.

(1*R*,3*S*)-9-Methoxy-1,3-dimethyl-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (eleutherin) 1

To a solution of (1*R*,3*S*)-benzoquinone **14** (55 mg, 0.20 mmol) in benzene (1 mL) was added 1-methoxy-1,3-cyclohexadiene **23** (69 mg, 0.63 mmol) and the mixture was heated at reflux for 1 h. After removal of the solvent under reduced pressure, the residual oil was dissolved in dichloromethane (2 mL), triethylamine (0.2 mL) was added and the mixture stirred at room temperature overnight. The solution was washed with 1 M HCl (2 × 1 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude adduct was heated at 150 °C for 30 min and, after cooling, the residual oil was purified by preparative thin layer chromatography (dichloromethane–ethyl acetate 95 : 5) followed by gel filtration (Sephadex LH20, methanol–dichloromethane, 1 : 1) and crystallization from methanol to give eleutherin **1** as yellow needles (7 mg, 13%), mp 140–145 °C (lit.[6] mp 175 °C); $[\alpha]_D^{22}$ +291 (*c* 0.10, $CHCl_3$) {lit.[6] $[\alpha]_D^{15}$ +346 (*c* 1.01, $CHCl_3$)}; ν_{max} (KBr) 3055, 2985, 1699, 1660 and 1587 cm^{-1}; λ_{max}(MeOH) 245 (log ε 4.18), 272 (3.94), 348 (3.47) and 391 nm (3.45); δ_H(400 MHz) 1.36 (3H, d, *J*

6.3, 3-Me), 1.53 (3H, d, *J* 6.6, 1-Me), 2.20 (1H, ddd, *J* 18.3, 10.3 and 3.7, 4-H_{ax}), 2.75 (1H, dt, *J* 18.3 and 2.7, 4-H_{eq}), 3.58 (1H, m, 3-H), 3.99 (3H, s, 9-OMe), 4.85 (1H, m, 1-H), 7.27 (1H, d, *J* 8.5, 8-H), 7.64 (1H, dd, *J* 8.5 and 7.8, 7-H) and 7.73 (1H, d, *J* 7.8, 6-H); δ_C(100 MHz) 20.8, 21.2, 29.9, 56.5, 68.7, 70.3, 117.7, 119.0, 120.3, 134.0, 134.6, 139.9, 148.7, 159.4, 183.8 and 184.1; *m*/*z* (EI) 272 {[M]$^+$, 17}, 257 (30), 76 (25), 45 (35), 44 (21), 43 (100) and 41 (22).

(1*R*,3*S*)-7-Hydroxy-1,3-dimethyl-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 20

To a solution of (1*R*,3*S*)-benzoquinone **14** (32 mg, 0.12 mmol) in dry benzene (2 mL) was added 1-methoxy-3-trimethylsiloxybuta-1,3-diene **24** (41 mg, 0.24 mmol). The mixture was stirred at 60 °C for 24 h, concentrated and purified by preparative thin layer chromatography (toluene–ethyl formate–formic acid, 50 : 49 : 1) followed by gel filtration (Sephadex LH20, methanol–dichloromethane, 1 : 1) to give (1*R*,3*S*)-7-hydroxynaphthoquinone **20** (15 mg, 49%), isolated as a yellow solid, mp 228 °C (dec.) (MeOH); $[\alpha]_D^{15}$ +290 (*c* 0.050, EtOH); CD $\lambda_{extrema}$(MeOH) 270 ($\Delta\varepsilon$ +0.25), 285 (+7.36), 375 (+0.51), 428 (−0.68) and 482 nm (+0.02); found: [M − H]$^-$, 257.0812. $C_{15}H_{14}O_4$ requires: [M − H]$^-$, 257.0814; λ_{max}(MeOH) 208 (log ε 4.20), 266 (4.16) and 395 nm (3.05); δ_H(400 MHz) 1.37 (3H, d, *J* 6.2, 3-Me), 1.55 (3H, d, *J* 6.6, 1-Me), 2.25 (1H, ddd, *J* 18.4, 10.2 and 3.9, 4-H_{ax}), 2.75 (1H, dt, *J* 18.4 and 2.6, 4-H_{eq}), 3.60 (1H, ddq, *J* 10.2, 2.6 and 6.2, 3-H), 4.85 (1H, ddq, *J* 3.9, 2.6 and 6.6, 1-H), 6.09 (1H, s, 7-OH), 7.14 (1H, dd, *J* 8.4 and 2.6, 8-H), 7.50 (1H, d, *J* 2.6, 6-H) and 7.98 (1H, d, *J* 8.4, 9-H); δ_C(100 MHz) 20.9, 21.2, 30.3, 68.8, 70.2, 112.4, 120.9, 125.8, 129.3, 133.7, 142.0, 147.2, 161.0, 183.1 and 184.4; *m*/*z* (EI) 258 {[M]$^+$, 65}, 243 (52), 229 (29), 225 (35), 215 (26), 213 (27), 197 (42), 187 (23), 185 (20), 157 (33), 141 (20), 131 (23), 129 (21), 128 (43), 127 (25), 121 (40), 120 (27), 115 (48), 93 (23), 92 (64), 77 (33), 69 (22), 66 (21), 65 (61), 64 (37), 63 (100), 62 (24), 57 (33), 55 (46), 53 (39) and 51 (46); *m*/*z* (ESI–) 257.1 [M − H]$^-$.

(1*R*,3*S*)-9-Hydroxy-7-methoxy-1,3-dimethyl-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (ventiloquinone L) 8

To a solution of (1*R*,3*S*)-benzoquinone **14** (37 mg, 0.14 mmol) in benzene (2 mL) was added 1,3-dimethoxy-1-trimethylsiloxybuta-1,3-diene **25** (83 mg, 0.41 mmol) in benzene (2 mL). The mixture was stirred at 60 °C for 100 min, then silica gel (0.5 g) was added and the suspension was stirred for a further 2.5 h at room temperature. The mixture was filtered and the filter cake was washed with ethyl acetate (20 mL). The filtrate was concentrated under reduced pressure and the residual oil was purified by column chromatography (dichloromethane–1% formic acid) followed by gel filtration (Sephadex LH20, methanol–dichloromethane, 1 : 1) to give (1*R*,3*S*)-ventiloquinone L **8** (16 mg, 41%) as orange needles, mp 116–118 °C from methanol–dichloromethane (lit.[8] mp 126 °C, benzene–hexane); $[\alpha]_D^{26}$ +420 (*c* 0.009, $CHCl_3$) {lit.[8] $[\alpha]_D^{30}$ +387.1 (*c* 0.01, $CHCl_3$)}; CD $\lambda_{extrema}$(MeOH) 268 ($\Delta\varepsilon$ +0.21), 296 (+5.26), 409 (−0.09) and 451 nm (+0.47); found: [M]$^+$, 288.0997. $C_{16}H_{16}O_5$ requires: [M]$^+$, 288.0998; λ_{max}(MeOH) 220 (log ε 4.46), 270 (4.09), 290 sh (3.93) and 423 nm (3.51); δ_H(400 MHz) 1.36 (3H, d, *J* 6.4, 3-Me), 1.57 (3H, d, *J* 6.6, 1-Me), 2.22 (1H, ddd, *J* 18.6, 10.2 and 3.9, 4-H_{ax}), 2.73 (1H, dt, *J* 18.6 and 2.6, 4-H_{eq}), 3.57 (1H, ddq, *J* 10.2, 2.6 and 6.4, 3-H), 3.89 (3H, s, 7-OMe), 4.82 (1H, ddq, *J* 3.9, 2.6 and 6.6, 1-H), 6.61 and 7.15 (each 1H, d, *J* 2.4, 6-H and 8-H) and 12.25 (1H, s, 9-OH); δ_C(100 MHz) 21.19, 21.20, 30.6, 56.0, 68.6, 69.8, 106.2, 107.6, 109.6, 133.3, 143.2, 146.7, 164.3, 165.8, 183.1 and 187.5; *m*/*z* (EI) 288 {[M]$^+$, 100}, 273 (55), 259 (30), 255 (20), 244 (20) and 69 (29).

(1*R*,3*S*)-7,9-Dihydroxy-1,3-dimethyl-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (3-*epi*-4-deoxyquinone A) 21

To a solution of (1*R*,3*S*)-benzoquinone **14** (140 mg, 0.52 mmol) in benzene (5 mL) was added 1-methoxy-1,3-bis(trimethylsiloxy)buta-1,3-diene **26** (900 mg, 3.46 mmol) in benzene (3 mL) and the reaction mixture was stirred at room temperature overnight. Silica (1.0 g) was added and the suspension was stirred for 18 h. The suspension was concentrated under reduced pressure and column chromatography (ethyl acetate then ethyl acetate–1% formic acid) gave a yellow band that was collected and concentrated under reduced pressure. The residual oil was dissolved in dichloromethane (20 mL) and washed sequentially with sodium bicarbonate (3 × 20 mL) and 3.0 M sodium hydroxide (3 × 20 mL). The combined basic extracts were acidified with conc. hydrochloric acid and extracted with dichloromethane (3 × 20 mL). Drying ($MgSO_4$) and concentration of the solution gave an oil that was purified by column chromatography (light petroleum → ethyl acetate) to give 3-*epi*-4-deoxyquinone A **21** as yellow needles (34 mg, 24%), mp 127–129 °C (dichloromethane–light petroleum); $[\alpha]_D^{23}$ +526 (*c* 0.050, $CHCl_3$); CD $\lambda_{extrema}$(MeOH) 240 ($\Delta\varepsilon$ +1.98), 262 (+0.38), 297 (+5.46), 410 (−0.26) and 452 nm (+0.57); found: [M]$^+$, 274.0834. $C_{15}H_{14}O_5$ requires: [M]$^+$, 274.0841; ν_{max} (KBr) 3414, 2978, 2936, 2901, 2873, 2855, 1637 and 1609 cm^{-1}; λ_{max}($CHCl_3$) 270 (log ε 4.16), 288 (3.97) and 433 nm (3.57); δ_H(400 MHz) 1.37 (3H, d, *J* 6.1, 3-Me), 1.58 (3H, d, *J* 6.6, 1-Me), 2.24 (1H, ddd, *J* 18.6, 10.0 and 3.9, 4-H_{ax}), 2.72 (1H, dt, *J* 18.6 and 2.5, 4-H_{eq}), 3.60 (1H, ddq, *J* 10.0, 2.5 and 6.1, 3-H), 4.84 (1H, ddq, *J* 3.9, 2.5 and 6.6, 1-H), 7.09 (1H, br s, 7-OH), 6.62 and 7.15 (each 1H, d, *J* 1.8, 6-H and 8-H) and 12.19 (1H, s, 9-OH); δ_C(100 MHz) 21.1, 21.2, 30.5, 68.7, 69.9, 108.3, 108.6, 109.7, 133.5, 142.9, 147.1, 162.7, 164.3, 183.5 and 187.3; *m*/*z* (EI) 274 {[M]$^+$, 100}, 259 (59), 245 (38), 241 (24), 231 (26), 230 (30), 229 (21), 213 (22), 137 (21), 69 (43) and 51 (28).

(1*S*,3*S*)-7,9-Dihydroxy-1,3-dimethyl-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (*ent*-deoxyquinone A) 30

(1*R*,3*S*)-Pyranonaphthoquinone **21** (7 mg, 0.03 mmol) in dichloromethane (10 mL) was cooled to −78 °C. To this solution was added boron tribromide (1.2 M in dichloromethane, 0.5 mL) over 2 min. The mixture was allowed to stir for 5 min at −78 °C, then was warmed to 0 °C and stirred for a further 5 min. The reaction was quenched by the addition of sat. aq. sodium bicarbonate (10 mL) and extracted with chloroform (3 × 20 mL). The combined organic extracts were washed with brine (1 × 20 mL), dried ($MgSO_4$) and concentrated at reduced pressure. The orange residue was purified by preparative thin layer chromatography (75 : 24 : 1 toluene–ethyl formate–formic acid) to give two fractions. The most mobile fraction was identified as unreacted (1*R*,3*S*)-pyranoquinone **21** (0.6 mg, 9%). The less mobile fraction was identified as *ent*-deoxyquinone A **30** (0.8 mg,

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11%), isolated as an orange solid, mp 147–149 °C (acetone); $[\alpha]_D^{18}$ −210 (*c* 0.0028, EtOH); CD $\lambda_{extrema}$(MeOH) 226 (Δε +2.15), 247 (−0.94), 256 (−0.66), 265 (−0.93), 268 (−0.77), 276 (−1.15), 311 (+0.16), 355 (−0.35), 406 (−0.20) and 445 nm (−0.34); found: $[M]^+$, 274.0848. $C_{15}H_{14}O_5$ requires: $[M]^+$, 274.0841; λ_{max}(MeOH) 219 (log ε 4.21), 231 sh (3.94), 273 (3.87), 290 (3.80) and 441 nm (4.3); δ_H(400 MHz) 1.35 (3H, d, *J* 6.4, 3-Me), 1.56 (3H, d, *J* 6.8, 1-Me), 2.22 (1H, ddd, *J* 19.3, 10.0 and 2.0, 4-H_{ax}), 2.72 (1H, dd, *J* 19.3 and 3.4, 4-H_{eq}), 3.99 (1H, ddq, *J* 10.0, 3.4 and 6.4, 3-H), 5.00 (1H, dq, *J* 2.0 and 6.8, 1-H), 6.03 (1H, br s, 7-OH), 6.61 and 7.10 (each 1H, d, *J* 2.4, 6-H and 8-H) and 12.22 (1H, s, 9-OH); δ_C(100 MHz) 19.8, 21.5, 29.9, 62.4, 67.0, 108.1, 108.3, 109.7, 133.7, 141.9, 146.8, 162.3, 164.3, 183.2 and 186.8; *m*/*z* (EI) 274 {$[M]^+$, 28}, 259 (26), 137 (22), 108 (30), 91 (29), 83 (21), 81 (25), 79 (24), 77 (38), 71 (32), 69 (100), 67 (30), 65 (37), 63 (31), 57 (81), 55 (86), 53 (43), 52 (24), 51 (64) and 50 (24); *m*/*z* (ESI–) 274.1 $[M]^-$ and 273.1 $[M-H]^-$.

Diels–Alder reaction of (1*R*,3*S*)-benzoquinone 14 with diene 27

To a solution of (1*R*,3*S*)-benzoquinone **14** (140 mg, 0.52 mmol) in benzene (5 mL) was added 1,3,4-trimethoxy-1-trimethylsiloxybuta-1,3-diene **27** (840 mg, 3.62 mmol) in benzene (2 mL). The reaction was stirred at room temperature overnight then silica gel (0.5 g) was added and the suspension was stirred for 70 min, filtered through a silica pad (ethyl acetate–1% formic acid) and the orange band was collected and concentrated under reduced pressure. The resulting oil was purified by repeated column chromatography (toluene–ethyl formate–formic acid, 50 : 49 : 1, light petroleum–ethyl acetate and ethyl acetate–1% formic acid) and gel filtration (Sephadex LH20, 100% methanol or methanol–dichloromethane, 1 : 1) to give a total of six compounds with differing spectroscopic data, listed below in order of decreasing mobility when subjected to thin layer chromatography (toluene–ethyl formate–formic acid, 50 : 49 : 1).

Ventiloquinone L **8** (trace), the spectroscopic data for this compound matched both those recorded for the independently synthesized material described earlier and data reported for the natural product;[8] (1*R*,3*S*)-9-desmethyl ventiloquinone E **4**, an orange solid (0.5 mg, 0.3%), mp 180 °C (dec.) (MeOH); $[\alpha]_D^{22}$ +270 (*c* 0.025, $CHCl_3$); CD $\lambda_{extrema}$(MeOH) 232 (Δε −0.31), 256 (+1.36), 277 (+0.62), 296 (+1.38), 417 (−0.12) and 449 nm (+0.01); found: $[M]^+$, 318.1105. $C_{17}H_{18}O_6$ requires: $[M]^+$, 318.1103; λ_{max}(MeOH) 223 (log ε 4.32), 275 (3.90) and 442 nm (3.41); δ_H(400 MHz) 1.36 (3H, d, *J* 6.3, 3-Me), 1.57 (3H, d, *J* 6.6, 1-Me), 2.20 (1H, ddd, *J* 18.8, 10.3 and 3.6, 4-H_{ax}), 2.79 (1H, ddd, *J* 18.8, 2.7 and 2.4, 4-H_{eq}), 3.56 (1H, ddq, *J* 10.3, 2.4 and 6.3, 3-H), 3.87 and 3.94 (each 3H, s, 6- and 7-OMe), 4.82 (1H, ddq, *J* 3.6, 2.7 and 6.6, 1-H), 6.65 (1H, s, 8-H) and 13.04 (1H, s, 9-OH); *m*/*z* (EI) 318 {$[M]^+$, 33}, 303 (37), 273 (23), 260 (22), 259 (27), 257 (26), 245 (28), 241 (24), 217 (23), 115 (37), 95 (21), 91 (27), 77 (37), 69 (100), 67 (25), 66 (33), 65 (47), 63 (31), 59 (51), 55 (37), 53 (71) and 51 (32); *m*/*z* (ESI–) 317.1 $[M-H]^-$; (1*R*,3*S*)-ventiloquinone G **6**, a red solid (1.2 mg, 0.8%), mp 220 °C (dec.) (MeOH) (lit.[7] mp 183 °C, methanol–light petroleum); $[\alpha]_D^{28}$ +115 (*c* 0.0075, methanol) {lit.[7] $[\alpha]_D^{18}$ +720 (*c* 0.10, MeOH)}; CD $\lambda_{extrema}$(MeOH) 273 (Δε +0.23), 311 (−0.10), 358 (+0.12) and 388 nm (−0.01); found: $[M-H]^-$, 289.0725. $C_{15}H_{14}O_6$ requires: $[M-H]^-$, 289.0712; λ_{max}(MeOH) 206 (log ε 3.79), 243 (3.55), 308 (3.04), 490 sh (2.97), 519 (3.09), 553 (3.05) and 590 sh nm (2.65); δ_H(400 MHz) 1.40 (3H, d, *J* 6.4, 3-Me), 1.64 (3H, d, *J* 6.3, 1-Me), 2.42 (1H, ddd, *J* 17.6, 10.5 and 2.7, 4-H_{ax}), 2.88 (1H, dt, *J* 17.6 and 2.2, 4-H_{eq}), 3.63 (1H, ddq, *J* 10.5, 2.2 and 6.4, 3-H), 5.04 (1H, tq, *J* 2.5 and 6.3, 1-H), 6.35 (1H, s, 8-H), 7.35 (1H, br s, 7-OH), 11.96 and 13.48 (each 1H, s, 5- and 10-OH); *m*/*z* (ESI–) 289.1 $[M-H]^-$; (1*R*,3*S*)-7-desmethyl ventiloquinone E **3**, which was isolated as an orange solid (0.4 mg, 0.2%); $[\alpha]_D^{23}$ +370 (*c* 0.020, MeOH); λ_{max}(MeOH) 220 (log ε 4.29), 267 (4.00), 292 sh (3.89) and 454 nm (3.29); δ_H(400 MHz) 1.35 (3H, d, *J* 6.1, 3-Me), 1.52 (3H, d, *J* 6.6, 1-Me), 2.13 (1H, ddd, *J* 18.1, 10.2 and 3.6, 4-H_{ax}), 2.75 (1H, dt, *J* 18.1 and 2.4, 4-H_{eq}), 3.55 (1H, ddq, *J* 10.2, 2.4 and 6.1, 3-H), 3.90 and 3.93 (each 3H, s, 6- and 9-OMe), 4.82 (1H, tq, *J* 3.6 and 6.6, 1-H), 6.68 (1H, br s, 7-OH) and 6.88 (1H, s, 8-H); δ_C(100 MHz) 20.7, 21.3, 29.7, 56.6, 62.1, 68.8, 70.1, 104.3, 113.7, 125.1, 139.9, 140.5, 148.0, 155.9, 158.0, 182.5 and 183.7; (1*R*,3*S*)-ventiloquinone G 7-*O*-methyl ether **7** (0.5 mg, 0.3%), a red pigment with mp 225 °C (dec.) (MeOH); $[\alpha]_D^{22}$ +271 (*c* 0.025, $CHCl_3$); CD $\lambda_{extrema}$(MeOH) 225 (Δε +2.36), 248 (+0.49), 261 (+0.64), 304 (−1.47), 387 (+0.81) and 454 nm (−0.02); found: $[M]^+$, 304.0955. $C_{16}H_{16}O_6$ requires: $[M]^+$, 304.0947; λ_{max}(MeOH) 227 (log ε 4.23), 302 (3.59), 502 (3.50), 535 (3.42) and 570 sh nm (3.09); δ_H(400 MHz) 1.39 (3H, d, *J* 6.1, 3-Me), 1.64 (3H, d, *J* 6.3, 1-Me), 2.40 (1H, ddd, *J* 17.6, 10.3 and 2.5, 4-H_{ax}), 2.88 (1H, dt, *J* 17.6 and 2.2, 4-H_{eq}), 3.62 (1H, ddq, *J* 10.3, 2.2 and 6.1, 3-H), 3.94 (3H, s, 7-OMe), 5.01 (1H, tq, *J* 2.5 and 6.3, 1-H), 6.21 (1H, s, 8-H), 12.76 and 13.36 (each 1H, s, 5- and 10-OH); *m*/*z* (EI) 304 {$[M]^+$, 7}, 71 (28), 69 (61), 67 (30), 59 (25), 57 (95), 56 (29), 55 (100) and 51 (24); *m*/*z* (ESI–) 303.1 $[M-H]^-$; and the yellow trimethyl ether (1*R*,3*S*)-ventiloquinone E **2** (trace); δ_H(300 MHz) 1.34 (3H, d, *J* 6.1, 3-Me), 1.50 (3H, d, *J* 6.6, 1-Me), 2.11 (1H, ddd, *J* 18.3, 10.3 and 3.7, 4-H_{ax}), 2.78 (1H, dt, *J* 18.3 and 2.4, 4-H_{eq}), (~3.6 signal obscured), 3.87 (3H, s, 7-OMe), 3.97 (6H, s, 6- and 9-OMe), 4.80 (1H, ddq, *J* 3.7, 2.4 and 6.6, 1-H) and 6.72 (1H, s, 8-H).

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