Investigations towards the synthesis of xylindein, a blue-green pigment from the fungus *Chlorociboria aeruginosa*

Christopher D. Donner [a,b,∗], Anthony N. Cuzzupe [a], Cheryl L. Falzon [a], Melvyn Gill [a,†]

[a] *School of Chemistry, The University of Melbourne, Victoria 3010, Australia*
[b] *Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Victoria 3010, Australia*

ABSTRACT

An approach towards the synthesis of the fungal pigment xylindein **1** is described. Synthesis of the pyranonaphthoquinone corresponding to one half of the xylindein framework is achieved over 11 steps from 1,2-epoxypentane, utilizing multiple Diels–Alder cycloaddition processes. Methods for self-coupling of dihydroxynaphthoquinones to give extended quinones are explored.

Crown Copyright © 2012 Published by Elsevier Ltd. All rights reserved.

1. Introduction

The green colour of wood infected with the fungus *Chlorociboria aeruginosa* is due to the presence of the extended quinone xylindein **1**, a novel pigment with a long and interesting history. A process for artificially colouring wood with *C. aeruginosa* was patented and oak stained in this way was used for making 'Tunbridge ware', a special kind of marquetry. Over one hundred years ago Liebermann obtained the pigment in crystalline form for the first time by extraction of infected wood with aqueous phenol and crystallization from the same solvent.[1] However, structural studies of xylindein **1** were severely hampered by its extremely low solubility in all common organic solvents. In the 1920s Kogl made the first advances in the structure elucidation of xylindein by establishing the presence of two acidic hydroxy groups, two lactone rings, and an extended quinone system.[2,3] The complete structure of xylindein **1** was elucidated, independently, by Todd and co-workers[4,5] and by Edwards and Kale.[6] The methods relied on derivatization of the natural material and degradative studies, the details of which have been succinctly documented by Thomson.[7]
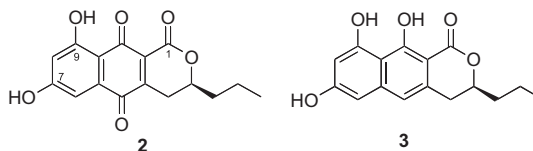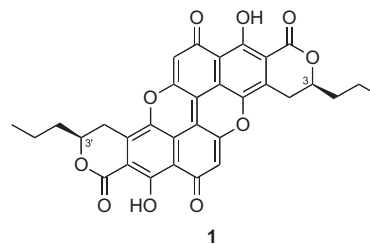

More recently, Saikawa and co-workers[8] have established the (3*S*,3′*S*) absolute configuration of xylindein **1** using natural material extracted from fruiting bodies of *C. aeruginosa*, *Chlorociboria aeruginascens* and *Chlorociboria omnivirens*. X-ray crystallographic analysis of the natural product confirmed that the structure **1** is indeed the tautomeric form of natural xylindein, whilst derivatization of **1** as a bis *para*-bromobenzyl derivative gave material suitable for X-ray crystallographic heavy atom analysis.

∗ Corresponding author. Tel.: +61 3 8344 2411; fax: +61 3 9347 8189; e-mail address: cdonner@unimelb.edu.au (C.D. Donner).
† Deceased.

It has been postulated that synthetically xylindein **1** could be formed by dimerization of lactone **2**, a process that would involve no change in oxidation level but rather is formally a dehydration.[9] Giles and co-workers have prepared the 7,9-dideoxy analogue of **2** in racemic form.[9,10] Unfortunately, attempts to apply their strategy to the more highly oxygenated system **2** were unsuccessful.[10] We have previously prepared (±)-naphthopyranone **3**, the 5-deoxo analogue of **2**, in four steps from 1,2-epoxypentane.[11] However, attempted oxidative phenolic coupling of **3** towards xylindein met with little success.

Based on our previous work[12] we doubted that the lactone **2** would itself be synthetically useful due to the unfavourable reactivity induced by the juxtaposition of the lactone and the quinone carbonyl groups. However, the 1-deoxo analogue of **2** may be a more viable substrate for extended quinone formation. This proposal is based on the work of Blackburn and co-workers who were able to convert the aphid insect pigment derivative 'quinone A' **4** directly to the extended quinone xylaphin **5** under anaerobic, buffered aqueous conditions (Scheme 1).[13] The product **5** so formed contains the same extended quinone chromophore that occurs in xylindein **1**. Herein we report our preparation of the 1-deoxo analogue of **2** as a potential precursor for the synthesis of xylindein **1**.
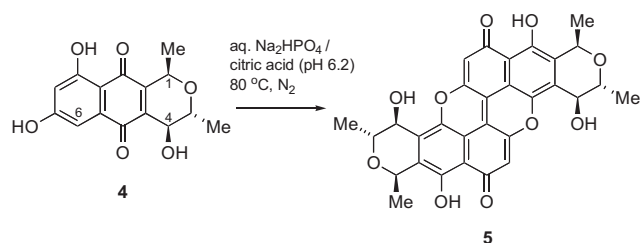
**Scheme 1.** Conversion of 'quinone A' **4** to xylaphin **5**.[13]

2. Results and discussion

Our proposed approach to the synthesis of xylindein **1** is shown retrosynthetically in Scheme 2. According to our plans phenolic coupling of the pyranonaphthoquinone **6** followed by oxidation at the benzylic position in both of the pyran rings would lead to xylindein **1**. The naphthoquinone **6** should, in turn, be available by Diels–Alder cycloaddition between an appropriate butadiene and the benzoquinone **7**. The bromoquinone **7** may be prepared from the benzopyranone **8**, which itself should be accessible via Diels–Alder reaction of the acetylene **9** with 1-methoxy-1,3-cyclohexadiene. The octynoate ester **9** should be available from 1,2-epoxypentane **10**.
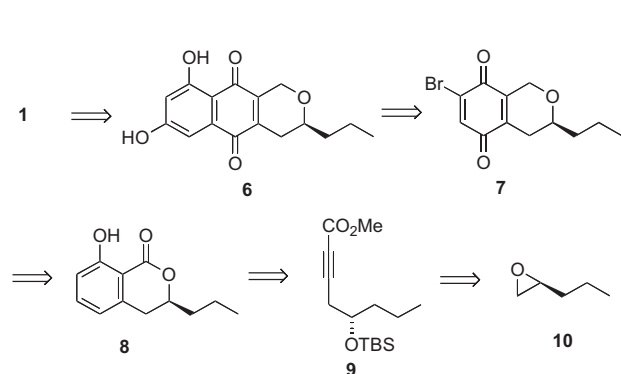

Scheme 2. Retrosynthesis of xylindein **1**.

In order to firstly establish the viability of our proposed approach, our study began with (±)-1,2-epoxypentane **10** (Scheme 3) that was treated with the ethylene diamine complex of lithium acetylide to form the acetylenic alcohol **11**. Treatment of the alcohol **11** with TBSCl in DMF gave the silyl ether **12** in 94% yield. Carbomethoxylation of the alkyne **12** was achieved by lithiation with *n*-butyllithium at −78 °C followed by addition of methyl chloroformate to give the acetylenic ester (±)-**9** in 89% yield. Diels–Alder cycloaddition between the octynoate ester **9** and 1-methoxy-1,3-cyclohexadiene in a sealed tube at 185 °C for 72 h gave exclusively the benzoate **13**, after loss of ethylene. Exposure of the benzoate **13** to *para*-toluenesulfonic acid (*p*-TsOH) in CH$_2$Cl$_2$ effected both removal of the silyl protecting group and subsequent lactonization to give the benzopyranone **14** in 91% yield, the spectroscopic data (Experimental section) being in complete accord with the structure **14**.
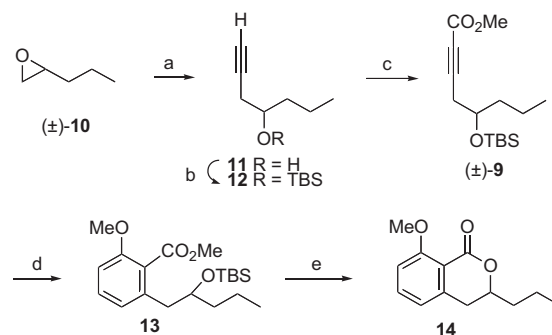
Scheme 3. Reagents and conditions: (a) LiC≡CH/H$_2$N(CH$_2$)$_2$NH$_2$ complex, DMSO, 0 °C to rt, overnight (50%); (b) TBSCl, imidazole, DMF, overnight (94%); (c) (i) ^{n}BuLi, THF, −78 °C, 30 min; (ii) ClCO$_2$Me, −78 °C to rt, 2 h (89%); (d) 1-methoxy-1,3-cyclohexadiene, dichloromaleic anhydride, N-phenyl-β-naphthylamine, sealed tube, 185 °C, 72 h (84%); (e) *p*-TsOH·H$_2$O, CH$_2$Cl$_2$, 72 h (91%).
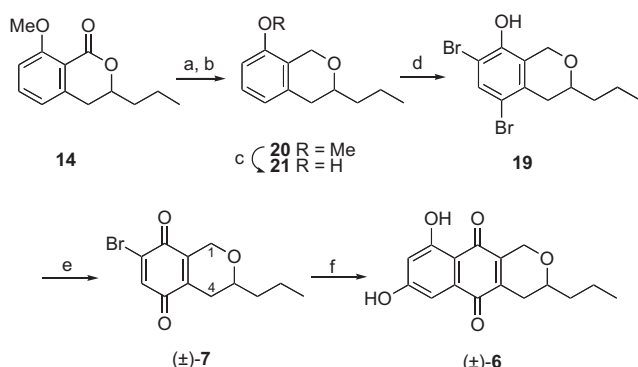
We next explored two routes to convert the benzopyranone **14** to the bromobenzoquinone (±)-**7**. The incorporation of a halogen at C7 in benzoquinone **7** is required to ensure the subsequent Diels–Alder process occurs in a highly regioselective manner,[14,15] whilst ensuing loss of HBr ensures complete aromatization. In the first approach towards **7**, outlined in Scheme 4, the hindered methyl ether in **14** was cleaved by treatment with BCl$_3$ in CH$_2$Cl$_2$ to give the phenol (±)-**8** in 94% yield. Treatment of the benzopyranone **8** with 2 equiv of NBS in DMF gave the dibromophenol **15** in 94% yield. It was necessary to reduce the lactone at this stage as such a structural feature is incompatible with a neighbouring quinone moiety.[12] This firstly required methylation of phenol **15**, effected using dimethyl sulfate in acetone at reflux, to give the ether **16** in near quantitative yield.
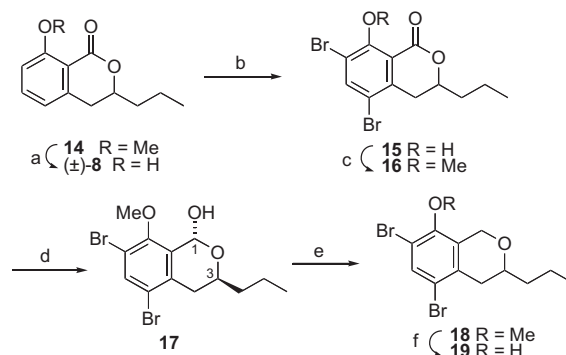
Scheme 4. Reagents and conditions: (a) BCl$_3$, CH$_2$Cl$_2$, 0 °C to rt, 12 h (94%); (b) NBS, DMF, 18 h (94%); (c) Me$_2$SO$_4$, K$_2$CO$_3$, acetone, reflux, 45 min (98%); (d) DIBAL-H, toluene, −70 °C, 45 min (94%); (e) Et$_3$SiH, TFA, CH$_2$Cl$_2$, 0 °C to rt, 45 min (98%); (f) (PhCH$_2$Se)$_2$, NaBH$_4$, DMF, reflux, 1.5 h (82%).

Reduction of the lactone carbonyl group in **16** to afford the benzopyran **18** was achieved over two steps. Firstly, treatment of **16** with DIBAL-H in toluene at −70 °C gave the lactol **17** in 94% yield as a single diastereomer. The ^{1}H NMR spectrum of **17** contains a methoxy resonance at δ 3.94, an aromatic resonance at δ 7.74 and double doublets centred at δ 2.36 and 2.74 from the C4 methylene protons. The relative configuration of the lactol **17** is clearly (1R*,3S*) as evidenced by the chemical shifts of both the acetal proton (δ 6.17) and C3 methine proton (δ 4.28) in the ^{1}H NMR spectrum, which are consistent with the C1 hydroxy group being in an axial orientation[12] as would be favoured by the anomeric effect.[16] Reduction of the lactol **17** to the benzopyran **18** was achieved by exposure of the lactol to triethylsilane in the presence of TFA. Direct oxidation of the benzopyran **18** to the benzoquinone **7** was unsuccessful, thus it was necessary to cleave the aromatic methyl ether. As we have found with related benzopyrans,[12] O-demethylation of these systems is best achieved using the benzylselenolate ion in hot DMF.[17] Thus, treatment of the ether **18** with a mixture of dibenzyldiselenide and sodium borohydride gave the phenol **19** in 82% yield.

An alternate and potentially more direct route to the phenol **19** from benzopyranone **14** was also explored in which the lactone carbonyl group was reduced prior to bromination. In this approach (Scheme 5) the lactone in **14** was firstly reduced by treatment with DIBAL-H at −70 °C. The intermediate lactol was not isolated but was instead further reduced by using Et$_3$SiH/TFA to give the benzopyran **20**, the physical and spectroscopic data of which was fully consistent with the assigned structure. All attempts to brominate the methyl ether **20** to form the dibromoether **18** led only to the formation of mixtures of products. Therefore, the methyl ether **20** was first demethylated by using a mixture of dibenzyldiselenide and sodium borohydride to give the phenol **21** in 70% yield. The phenol **21** could then be smoothly brominated on treatment with NBS in DMF to afford the dibromophenol **19** as the sole product, in 82% yield. The spectroscopic data for the phenol **19** obtained in this way proved to be identical to those of the material prepared earlier. This second approach to the phenol **19** (Scheme 5) proceeds in 51% yield over four steps from **14**. In comparison, the previous approach (Scheme 4) gave the phenol **19** in 65% yield over six steps from the same methyl ether **14**.
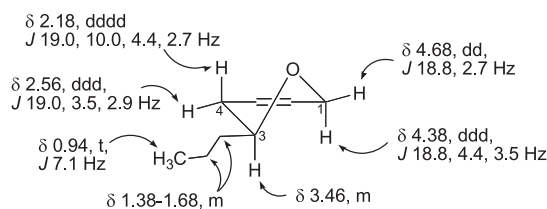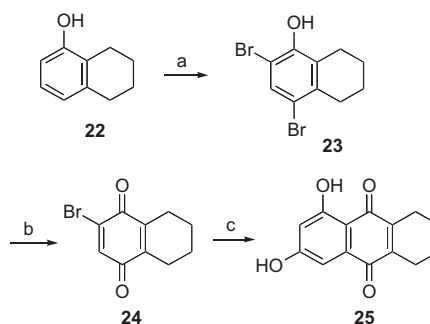
Fig. 1. Preferred half chair conformation in the dihydropyran ring of the pyranobenzoquinone (±)-**7**.

and δ 2.56, ddd) due to geminal, vicinal and homoallylic coupling consistent with the dihydropyran ring in **7** adopting a half chair conformation with the C3 propyl group in a *pseudo*-equatorial orientation.

In order to assemble the tricyclic system present in the naphthopyranone **6** the benzoquinone **7** was subjected to Diels−Alder cycloaddition with 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene.[18] After chromatographic purification and crystallization the naphthoquinone (±)-**6** was obtained as orange needles in 43% yield. The ^{1}H NMR spectrum of **6**, which includes two *meta*-coupled (J 2.5 Hz) aromatic proton signals (δ 6.51 and 6.97) and signals from chelated (δ 12.02) and free (δ 10.36, broad) aromatic hydroxy protons, along with all the other spectroscopic data (see Experimental section) are in full accord with the assigned structure. With the crucial dihydroxynaphthoquinone **6** in hand its possible conversion to xylindein **1** could now be investigated.

The self-coupling ability of dihydroxynaphthoquinones to give extended quinones has been demonstrated for the conversion of 'quinone A' **4** to the extended quinone xylaphin **5** by heating under anaerobic conditions in a buffered (pH 6.2) aqueous solution (Scheme 1).[13] Additionally, when 'quinone A' **4** was treated with an aqueous buffer of boric acid and sodium hydroxide (pH 9.0) the reaction stopped at the level of the C6/C6′ dimer of **4**, that was subsequently transformed to xylaphin **5** on treatment with acid.[13]

In order to assess the applicability of these self-coupling procedures to the synthesis of xylindein **1** the simpler model dihydroxynaphthoquinone system **25** was prepared as outlined in Scheme 6. Thus, 5,6,7,8-tetrahydro-1-naphthol **22** was brominated using 2 equiv of NBS in DMF to afford the dibromophenol **23** in 96% yield. The bromophenol **23** was oxidized by using CAN in aqueous acetonitrile to give the bromobenzoquinone **24** and subsequent Diels−Alder cycloaddition between the benzoquinone **24** and 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene gave the dihydroxynaphthoquinone **25** in 83% yield.

Scheme 5. Reagents and conditions: (a) DIBAL-H, toluene, −70 °C, 1 h; (b) Et$_3$SiH, TFA, CH$_2$Cl$_2$, 0 °C, 1 h (89%, two steps); (c) (PhCH$_2$Se)$_2$, NaBH$_4$, DMF, reflux, 2 h (70%); (d) NBS, DMF, 18 h (82%); (e) CAN, MeCN, THF, H$_2$O, 30 min (91%); (f) 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene, benzene, reflux, 1.5 h (43%).

Scheme 6. Reagents and conditions: (a) NBS, DMF, 18 h (96%); (b) CAN, MeCN, H$_2$O, 30 min (87%); (c) 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene, benzene, 4 h (83%).

Subsequent conversion of the phenol **19** to the benzoquinone (±)-**7** was achieved by addition of an aqueous solution of CAN to the phenol **19** in acetonitrile (Scheme 5). The benzoquinone **7** was obtained as a yellow oil with absorption maxima at 205 and 273 nm in the electronic spectrum, consistent with a benzoquinone chromophore.[7] The ^{1}H NMR spectrum of (±)-**7**, summarized in Fig. 1, shows a complex coupling pattern for the C4 methylene protons (δ 2.18, dddd

When the dihydroxynaphthoquinone **25** was exposed to a buffered aqueous solution (pH 6) containing disodium hydrogen phosphate and citric acid according to Blackburn's method[13] no coupled products were observed and the substrate was recovered unchanged. When the model quinone **25** was exposed to boric acid and sodium hydroxide[13] in aqueous THF at 80 °C a blue precipitate, indicative of

an extended quinone chromophore, was formed in trace quantities. Isolation of this material, however, proved fruitless. Nonetheless, similar alkaline conditions were then applied to the functionalized naphthoquinone **6** in an attempt to construct the complete carbon framework of xylindein **1**. Similarly, this resulted in the formation of trace quantities of a blue precipitate and, although the electronic spectrum of this material indicated the presence of an extended quinone chromophore, inadequate quantities could be obtained for complete structural assignment. The precise conditions required for the transformation of dihydroxynaphthoquinones, such as **4**, **6** and **25**, to their respective extended quinone dimers appear to be extremely substrate specific. As was originally noted during the formation of xylaphin **5**, the most minor changes in the structure of the substrate (e.g., inversion of the stereochemistry of the C4 hydroxy group in **4**) reduce the efficiency of the reaction, presumably due to subtle differences in oxidation–reduction potential.[13]

3. Summary and conclusions

In summary, the pyranonaphthoquinone (±)-**6**, an anticipated precursor to xylindein **1**, has been prepared over 11 steps from propyl oxirane (±)-**10**. Preliminary attempts to couple the naphthoquinone **6** in order to form the complete carbon skeleton of xylindein **1**, using conditions applied in the preparation of the related extended quinone xylaphin **5**,[13] have met with limited success. As such, the more readily accessible[11,19] naphthopyranone precursors, such as **3**, are being considered as potentially more robust substrates for biaryl coupling. Work in this area towards the first total synthesis the unusual extended quinone pigment xylindein **1** will be reported in due course.

4. Experimental section

4.1. General

All reactions requiring anhydrous conditions were performed in oven- or flame-dried glassware under an atmosphere of dry nitrogen. ^{1}H and ^{13}C NMR spectra were recorded on Varian Unity Plus 400, Varian Unity INOVA 400 or Varian Unity 300 spectrometers for solutions in deuteriochloroform with residual chloroform (δ 7.26 for ^{1}H and δ 77.0 for ^{13}C) as internal reference, unless indicated otherwise. ^{1}H NMR data are reported as follows: chemical shift (δ) [relative integral, multiplicity, coupling constant(s) J (Hz), assignment]. Chemical shifts are given relative to tetramethylsilane with multiplicities indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or br (broad) in the usual fashion. Electronic spectra were recorded on a Varian SuperScan-3 or Shimadzu UV-2401PC spectrometer using the solvent specified in a 10 mm quartz cell. Infra-red spectra were obtained as KBr discs for solids and between NaCl plates for liquids by using Perkin–Elmer 983G grating or 1600 series Fourier transform spectrophotometers. Electron impact (EI) mass spectra were obtained using a V. G. Micromass 7070F or Shimadzu GC–MS-QP505A spectrometer. The mass of each ion is given followed by its relative abundance. Only ions of relative intensity greater than 50% of the base peak are reported, unless they are of particular significance. Electrospray ionization (ESI) mass spectra were obtained using a Micromass QUATTRO II spectrometer. Flash column chromatography was performed over Merck Kieselgel 60 silica gel. Thin-layer chromatography was performed using pre-coated sheets (0.25 mm, Kieselgel 60 GF$_{254}$). Gel permeation chromatography was carried out using columns of Sephadex LH-20 (Pharmacia) suspended in and eluted with the solvent specified. Ether refers to diethyl ether, while light petroleum refers to the hydrocarbon fraction boiling in the range 40–60 °C. Brine refers to a saturated aqueous solution of sodium chloride. Melting points were determined on a Kofler hot-stage and are uncorrected.

Microanalyses were carried out by Chemical and MicroAnalytical Services Pty. Ltd., Geelong, Victoria, Australia.

4.2. Experimental procedures

4.2.1. (±)-1-Heptyn-4-ol (**11**). To a suspension of lithium acetylide–ethylene diamine complex (7.50 g, 81.5 mmol) in dimethyl sulfoxide (100 mL) cooled to 0 °C under nitrogen was added dropwise (±)-1,2-epoxypentane **10** (4.70 g, 54.6 mmol). After complete addition the suspension was allowed to warm slowly to room temperature and the mixture was stirred overnight. The reaction mixture was poured onto ice (200 mL) and the product was extracted into ether (4×150 mL). The combined extracts were washed sequentially with brine (6×150 mL) and water (3×150 mL) and dried (MgSO$_4$). Removal of the solvent under reduced pressure followed by distillation of the residue yielded the alcohol **11** (3.05 g, 50%) as a colourless liquid, bp 66–67 °C/16 mmHg (lit.[20] 58–59 °C/11 mmHg); ν_{max} 3373br, 3308, 2960, 2119, 1466, 1426, 1124, 1075, 1045, 1018 cm^{-1}; δ_H (300 MHz) 0.93 (3H, t, J 7.1 Hz, H$_3$7), 1.32–1.56 (4H, m, H$_2$5 and H$_2$6), 1.96 (1H, br s, OH), 2.05 (1H, t, J 2.7 Hz, H1), 2.30 (1H, ddd, J 16.7, 6.7 and 2.7 Hz, H$_A$3), 2.43 (1H, ddd, J 16.7, 4.8 and 2.7 Hz, H$_B$3), 3.72–3.80 (1H, m, H4); δ_C (75 MHz) 13.9, 18.8, 27.3, 38.3, 69.6, 70.7, 80.9. The spectral data (^{1}H and ^{13}C NMR) was identical to that reported.[21]

4.2.2. (±)-4-tert-Butyldimethylsilyloxyhept-1-yne (**12**). A solution of (±)-1-heptyn-4-ol **11** (3.0 g, 26.7 mmol), imidazole (3.60 g, 52.9 mmol) and tert-butylchlorodimethylsilane (4.03 g, 26.7 mmol) in N,N-dimethylformamide (25 mL) was stirred overnight. The mixture was diluted with water (20 mL) and the product was extracted into ether (3×20 mL) and the combined organic extracts were washed sequentially with brine (6×20 mL) and water (3×20 mL) and dried (MgSO$_4$). After removal of the solvent under reduced pressure Kugelrohr distillation of the residue yielded the title compound **12** (5.70 g, 94%) as a colourless liquid, bp 75–78 °C/20 mmHg; ν_{max} 3309, 2954, 2121, 1469, 1460, 1254, 1109, 836, 774 cm^{-1}; δ_H (400 MHz) 0.06 and 0.08 (each 3H, s, SiMe), 0.89 (9H, s, SiCMe$_3$), 0.91 (3H, t, J 7.4 Hz, H$_3$7), 1.28–1.62 (4H, m, H$_2$5 and H$_2$6), 1.97 (1H, t, J 2.7 Hz, H1), 2.30–2.32 (2H, m, H$_2$3), 3.76–3.82 (1H, m, H4); δ_C (100 MHz) −4.7 and −4.5 (each SiMe), 14.2, 18.1 (SiCMe$_3$), 18.4, 25.8 (SiCMe$_3$), 27.4, 38.9, 69.7, 70.7, 81.8. m/z (ESI) 227 ([M+H]$^+$); m/z (EI) 169 ([M−C$_4$H$_9$]$^+$, 49%), 86 (56), 84 (100). The spectral data (^{1}H and ^{13}C NMR) was identical to that reported.[21]

4.2.3. (±)-Methyl 5-tert-butyldimethylsilyloxyoct-2-ynoate (**9**). To a stirred solution of the (±)-silyl ether **12** (4.00 g, 17.7 mmol) in THF (60 mL) at −78 °C was added n-butyllithium (8.50 mL, 2.5 M in hexane, 21.2 mmol). After 30 min methyl chloroformate (1.64 mL, 21.2 mmol) was added dropwise and the mixture was allowed to warm to room temperature. After 2 h the reaction mixture was diluted with water (40 mL) and extracted with ether (3×50 mL). The combined extracts were washed with brine (3×30 mL), dried (MgSO$_4$) and concentrated under reduced pressure. Kugelrohr distillation yielded the title compound **9** (4.45 g, 89%) as a colourless liquid, bp 95–98 °C/0.3 mmHg; ν_{max} 2954, 2239, 1716, 1250, 1073, 836, 775 cm^{-1}; δ_H (400 MHz) 0.06 and 0.08 (each 3H, s, SiMe), 0.88 (9H, s, SiCMe$_3$), 0.91 (3H, t, J 7.5 Hz, H$_3$8), 1.27–1.59 (4H, m, H$_2$6 and H$_2$7), 2.44–2.46 (2H, m, H$_2$4), 3.75 (3H, s, CO$_2$Me), 3.84–3.87 (1H, m, H5); δ_C (100 MHz) −4.7 and −4.6 (each SiMe), 14.1 (C8), 18.0 (SiCMe$_3$), 18.3 (C7), 25.8 (SiCMe$_3$), 27.6 (C4), 39.2 (C6), 52.6 (CO$_2$Me), 70.1 (C5), 74.1 (C2), 87.2 (C3), 154.1 (CO$_2$Me); m/z (EI) 284 (M$^+$, 2%), 227 ([M−C$_4$H$_9$]$^+$, 8%), 97 (58), 85 (72), 83 (77), 81 (50), 71 (88), 69 (100), 67 (51).

4.2.4. (±)-Methyl 2-(2-tert-butyldimethylsilyloxypentyl)-6-methoxybenzoate (**13**). A mixture of the (±)-octynoate **9** (4.00 g,

14.1 mmol), 1-methoxy-1,3-cyclohexadiene (a commercial sample of the 1,3- and the 1,4-dienes in a 65:35 ratio, 3.33 mL, 28.1 mmol), dichloromaleic anhydride (10.0 mg, 59.9 μmol) and N-phenyl-β-naphthylamine (20.0 mg, 91.2 μmol) was heated in a sealed tube, with stirring, at 185 °C for 72 h. Flash column chromatography using a graded solvent system (light petroleum/ether) gave the *title compound* **13** (4.35 g, 84%) as a viscous colourless oil; R_f (light petroleum/ether 2:1) 0.55; ν_{max} 2951, 1727, 1468, 1267, 1073 cm^{-1}; δ_H (400 MHz) −0.25 and −0.08 (each 3H, s, SiMe), 0.83 (9H, s, SiCMe$_3$), 0.87 (3H, t, J 7.1 Hz, H5′), 1.27−1.41 (4H, m, H23′ and H24′), 2.64 (1H, dd, J 13.5 and 7.7 Hz, H$_A$1′), 2.72 (1H, dd, J 13.5 and 5.5 Hz, H$_B$1′), 3.81 (3H, s, CO$_2$Me), 3.82−3.85 (1H, m, H2′), 3.90 (3H, s, OMe), 6.77 (1H, d, J 8.2 Hz, H5), 6.85 (1H, d, J 7.6 Hz, H3), 7.22−7.26 (1H, m, H4); δ_C (100 MHz) −5.0 and −4.9 (each SiMe), 14.2, 18.0 (SiCMe$_3$), 18.5, 25.9 (SiCMe_3), 39.7, 41.4, 52.1 (CO$_2$$Me$), 55.9 (OMe), 72.7 (C2′), 108.7, 123.8, 124.0, 129.8, 138.0, 156.3, 168.8 (C O$_2$Me); m/z (EI) 309 ([M−C$_4$H$_9$]$^+$, 87%), 277 (71), 73 (100).

4.2.5. (±)-8-Methoxy-3-propyl-3,4-dihydro-1H-2-benzopyran-1-one (14).

A solution of the (±)-benzoate **13** (2.40 g, 6.55 mmol) in dichloromethane (40 mL) containing *para*-toluenesulfonic acid monohydrate (100 mg, 52.6 μmol) was stirred at room temperature for 72 h. After removal of the solvent under reduced pressure the residue was purified by flash column chromatography (ether) to give the *title compound* **14** (1.31 g, 91%) as a colourless oil; R_f (ether) 0.37; ν_{max} 2953, 1720, 1473, 1232, 1086, 1057 cm^{-1}; δ_H (400 MHz) 0.94 (3H, t, J 7.3 Hz, H3′), 1.44−1.86 (4H, m, H21′ and H22′), 2.82 (1H, dd, J 16.0 and 3.3 Hz, H$_{eq}$4), 2.90 (1H, dd, J 16.0 and 10.8 Hz, H$_{ax}$4), 3.93 (3H, s, OMe), 4.35−4.41 (1H, m, H3), 6.79 (1H, d, J 7.5 Hz, H5), 6.90 (1H, d, J 8.6 Hz, H7), 7.41−7.45 (1H, m, H6); δ_C (100 MHz) 13.8 (C3′), 18.2 (C2′), 34.4 (C4), 36.7 (C1′), 56.1 (OMe), 77.5 (C3), 110.7 (C7), 113.9 (C8a), 119.2 (C5), 134.3 (C6), 142.0 (C4a), 161.0 (C8), 162.8 (C1); m/z (EI) 220 (M$^+$, 47%), 149 (100), 148 (66), 91 (82), 90 (52), 77 (54). The spectral data (^{1}H NMR) was identical to that reported.[22]

4.2.6. (±)-8-Hydroxy-3-propyl-3,4-dihydro-1H-2-benzopyran-1-one (8).

To the (±)-methyl ether **14** (350 mg, 1.59 mmol) in dichloromethane (30 mL) at 0 °C was added boron trichloride (1 M in dichloromethane, 2.00 mL, 2.00 mmol) and the solution was allowed to warm slowly to room temperature and stirred for a further 12 h. Water (30 mL) was added and stirring was continued for 10 min followed by extraction with dichloromethane (3×10 mL). The combined extracts were dried (MgSO$_4$), concentrated under reduced pressure and purified by flash column chromatography (ether) to give the *title compound* **8** (308 mg, 94%) as a colourless oil; R_f (ether) 0.70; ν_{max} 3109br, 2957, 1678, 1616, 1460, 1229, 1207, 1108 cm^{-1}; δ_H (400 MHz) 0.98 (3H, t, J 7.3 Hz, H3′), 1.46−1.92 (4H, m, H21′ and H22′), 2.91−2.94 (2H, m, H24), 4.56−4.61 (1H, m, H3), 6.69 (1H, d, J 7.3 Hz, H5), 6.88 (1H, d, J 8.4 Hz, H7), 7.38−7.42 (1H, m, H6), 11.03 (1H, s, OH); δ_C (100 MHz) 13.8 (C3′), 18.1 (C2′), 32.9 (C4), 36.8 (C1′), 79.4 (C3), 108.5 (C), 116.1 (CH), 117.9 (CH), 136.0 (CH), 139.5 (C), 162.1 (C), 170.0 (C1); m/z (EI) 206 (M$^+$, 100%), 135 (52), 134 (65); HRMS (ESI): [M+Na]$^+$, found 229.0837. C$_{12}$H$_{14}$NaO$_3$ requires 229.0835.

4.2.7. (±)-5,7-Dibromo-8-hydroxy-3-propyl-3,4-dihydro-1H-2-benzopyran-1-one (15).

To a solution of the (±)-phenol **8** (260 mg, 1.26 mmol) in dimethylformamide (10 mL) was added a solution of N-bromosuccinimide (460 mg, 2.58 mmol) in dimethylformamide (2 mL) dropwise. The reaction mixture was stirred at room temperature, in the dark, for 18 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$_4$). After removal of the solvent under reduced pressure the residue was purified by flash column chromatography (dichloromethane) to give the *title*

compound **15** (432 mg, 94%) as a colourless oil; R_f (dichloromethane) 0.73; ν_{max} 3434br, 2933, 1684, 1420, 1202 cm^{-1}; δ_H (400 MHz) 0.99 (3H, t, J 7.3 Hz, H33′), 1.47−1.95 (4H, m, H21′ and H22′), 2.79 (1H, dd, J 17.1 and 11.8 Hz, H$_{ax}$4), 3.14 (1H, dd, J 17.1 and 3.4 Hz, H$_{eq}$4), 4.55−4.62 (1H, m, H3), 7.91 (1H, s, H6), 11.88 (1H, s, OH); δ_C (100 MHz) 13.7 (C3′), 18.0 (C2′), 33.0 (C4), 36.7 (C1′), 79.1 (C3), 110.4 (C), 110.5 (C), 111.2 (C), 137.9 (C), 141.7 (CH), 158.3 (C), 169.0 (C1); m/z (EI) 366 (M$^+$, ^{81}Br$_2$, 18%), 364 (M$^+$, ^{81}Br^{79}Br, 34%), 362 (M$^+$, ^{79}Br$_2$, 19%), 149 (67), 85 (56), 71 (100), 69 (82); HRMS (ESI): [M−H]$^-$, found 360.9085. C$_{12}$H$_{11}^{79}$Br$_2$O$_3$ requires 360.9080.

4.2.8. (±)-5,7-Dibromo-8-methoxy-3-propyl-3,4-dihydro-1H-2-benzopyran-1-one (16).

To the (±)-dibromophenol **15** (385 mg, 1.06 mmol) in acetone (20 mL) were added potassium carbonate (750 mg, 5.43 mmol) and dimethyl sulfate (0.250 mL, 2.64 mmol) and the reaction mixture was heated at reflux for 45 min. After cooling to room temperature water (15 mL) was added and the product was extracted into chloroform (3×10 mL) and the combined extracts were dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (dichloromethane) to give the *title compound* **16** (390 mg, 98%) as a colourless oil; R_f (dichloromethane) 0.60; ν_{max} 2956, 1726, 1453, 1413, 1266, 1217, 1101 cm^{-1}; δ_H (400 MHz) 0.98 (3H, t, J 7.3 Hz, H33′), 1.46−1.91 (4H, m, H21′ and H22′), 2.75 (1H, dd, J 16.9 and 11.4 Hz, H$_{ax}$4), 3.10 (1H, dd, J 16.9 and 2.9 Hz, H$_{eq}$4), 3.98 (3H, s, OMe), 4.37−4.43 (1H, m, H3), 7.97 (1H, s, H6); δ_C (100 MHz) 13.8 (C3′), 18.1 (C2′), 34.5 (C4), 36.6 (C1′), 62.3 (OMe), 77.3 (C3), 117.1 (C), 118.7 (C), 121.8 (C), 140.2 (C), 140.5 (CH), 158.4 (C), 160.9 (C1); m/z (EI) 380 (M$^+$, ^{81}Br$_2$, 9%), 378 (M$^+$, ^{81}Br^{79}Br, 17%), 376 (M$^+$, ^{79}Br$_2$, 7%), 85 (53), 74 (74), 71 (81), 69 (100), 60 (75); HRMS (ESI): [M+Na]$^+$, found 398.9218. C$_{13}$H$_{14}$Br$_2$NaO$_3$ requires 398.9202.

4.2.9. (±)-5,7-Dibromo-1-hydroxy-8-methoxy-3-propyl-3,4-dihydro-1H-2-benzopyran (17).

To the (±)-lactone **16** (350 mg, 0.926 mmol) in toluene (40 mL) at −70 °C was added diisobutylaluminium hydride (1.5 M in toluene, 0.85 mL, 1.28 mmol) dropwise. The reaction mixture was maintained at −70 °C for 45 min and then allowed to warm to room temperature (30 min). The solution was then poured into saturated potassium sodium tartrate (40 mL) and stirred vigorously for 1 h. Extraction with chloroform (3×10 mL), drying (MgSO$_4$) of the combined organic extracts, concentration under reduced pressure and crystallization from ethyl acetate/hexane gave the *title compound* **17** (330 mg, 94%) as colourless needles, mp 129−132 °C; ν_{max} 3410br, 2952, 1452, 1089, 984 cm^{-1}; δ_H (400 MHz) 0.99 (3H, t, J 7.3 Hz, H33′), 1.44−1.75 (4H, m, H21′ and H22′), 2.36 (1H, dd, J 17.4 and 11.6 Hz, H$_{ax}$4), 2.74 (1H, dd, J 17.4 and 3.4 Hz, H$_{eq}$4), 2.95 (1H, d, J 3.7 Hz, OH), 3.94 (3H, s, OMe), 4.24−4.31 (1H, m, H3), 6.17 (1H, d, J 3.7 Hz, H1), 7.74 (1H, s, H6); m/z (EI) 382 (M$^+$, ^{81}Br$_2$, 30%), 380 (M$^+$, ^{81}Br^{79}Br, 60%), 378 (M$^+$, ^{79}Br$_2$, 31%), 308 (100), 306 (60), 290 (53); HRMS (ESI): [M+Na]$^+$, found 400.9375. C$_{13}$H$_{16}^{79}$Br$_2$NaO$_3$ requires 400.9358.

4.2.10. (±)-5,7-Dibromo-8-methoxy-3-propyl-3,4-dihydro-1H-2-benzopyran (18).

To the (±)-lactol **17** (300 mg, 0.789 mmol) in dichloromethane (50 mL) at 0 °C was added trifluoroacetic acid (0.180 mL, 2.34 mmol) and the solution was stirred for 15 min. Triethylsilane (0.380 mL, 2.38 mmol) was added and the solution was allowed to warm slowly to room temperature then stirred for a further 45 min. Water (20 mL) was added and the product was extracted into chloroform (3×10 mL) and the combined extracts were dried (MgSO$_4$) and concentrated under reduced pressure. Flash column chromatography (dichloromethane) and crystallization from ether/hexane gave the *title compound* **18** (280 mg, 98%) as colourless needles, mp 112−116 °C; R_f (dichloromethane) 0.65; ν_{max} 2951, 1448, 1174, 1096 cm^{-1}; δ_H (400 MHz) 0.98 (3H, t, J 7.2 Hz, H33′), 1.44−1.74 (4H, m, H21′ and H22′), 2.42 (1H, dd, J 17.2 and

10.7 Hz, $H_{ax}4$), 2.70 (1H, dd, J 17.2 and 3.4 Hz, $H_{eq}4$), 3.52–3.59 (1H, m, H3), 3.80 (3H, s, OMe), 4.65 (1H, d, J 16.0 Hz, $H_{ax}1$), 4.99 (1H, d, J 16.0 Hz, $H_{eq}1$), 7.64 (1H, s, H6); δ_C (100 MHz) 14.1 (C3'), 18.6 (C2'), 34.7 (C4), 37.9 (C1'), 60.4 (OMe), 64.8 (C1), 74.3 (C3), 114.3 (C), 119.9 (C), 132.6 (C), 133.7 (CH), 134.6 (C), 152.1 (C); m/z (EI) 366 (M^+, $^{81}Br_2$, 8%), 364 (M^+, $^{81}Br^{79}Br$, 15%), 362 (M^+, $^{79}Br_2$, 13%), 292 (100), 290 (61), 281 (51), 279 (54), 75 (56), 71 (64).

4.2.11. (±)-5,7-Dibromo-8-hydroxy-3-propyl-3,4-dihydro-1H-2-benzopyran (19); prepared by demethylation of (±)-methyl ether (18).

To a solution of dibenzyldiselenide (150 mg, 0.44 mmol) in dimethylformamide (8 mL) was added sodium borohydride (115 mg, 3.04 mmol). After stirring for 15 min the (±)-methyl ether **18** (230 mg, 0.632 mmol) in dimethylformamide (2 mL) was added and the solution was heated under reflux for 1.5 h. After cooling to room temperature the solution was diluted with water (5 mL), acidified (dil aq H_2SO_4) and extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed sequentially with brine (3×15 mL) and water (3×15 mL) and dried (MgSO₄). Concentration under reduced pressure followed by flash column chromatography (dichloromethane/light petroleum) and crystallization from dichloromethane/hexane gave the *title compound* **19** (180 mg, 82%) as colourless needles, mp 99–100 °C; R_f (dichloromethane/light petroleum 1:1) 0.35; ν_{max} 3379br, 3066, 1437, 1202, 1173 cm⁻¹; δ_H (400 MHz) 0.98 (3H, t, J 7.2 Hz, H_33'), 1.43–1.74 (4H, m, H_21' and H_22'), 2.42 (1H, dd, J 17.1 and 10.5 Hz, $H_{ax}4$), 2.71 (1H, dd, J 17.1 and 3.2 Hz, $H_{eq}4$), 3.52–3.59 (1H, m, H3), 4.59 (1H, d, J 16.1 Hz, $H_{ax}1$), 4.95 (1H, d, J 16.1 Hz, $H_{eq}1$), 5.49 (1H, s, OH), 7.54 (1H, s, H6); δ_C (100 MHz) 14.1 (C3'), 18.7 (C2'), 34.7 (C4), 37.8 (C1'), 64.7 (C1), 74.1 (C3), 107.3 (C), 115.2 (C), 125.4 (C), 131.7 (CH), 134.7 (C), 147.1 (C); m/z (EI) 352 (M^+, $^{81}Br_2$, 9%), 350 (M^+, $^{81}Br^{79}Br$, 19%), 348 (M^+, $^{79}Br_2$, 11%), 280 (52), 278 (100), 276 (50); HRMS (ESI): $[M+Na]^+$, found 370.9263. $C_{12}H_{14}^{79}Br_2NaO_2$ requires 370.9253.

4.2.12. (±)-8-Methoxy-3-propyl-3,4-dihydro-1H-2-benzopyran (20).

To the (±)-lactone **14** (350 mg, 1.59 mmol) in toluene (35 mL) at −70 °C, under nitrogen, was added diisobutylaluminium hydride (1.5 M in toluene, 1.50 mL, 2.25 mmol). The reaction mixture was maintained at −70 °C for 1 h and then allowed to warm slowly to room temperature (approx. 1 h). The mixture was poured into a saturated aqueous solution of potassium sodium tartrate (40 mL) and stirred vigorously (1 h). The product was extracted into chloroform (4×15 mL) and the combined organic extracts were dried (MgSO₄). Concentration under reduced pressure gave an oil, which was dissolved in dichloromethane (25 mL) and cooled to 0 °C. Trifluoroacetic acid (0.380 mL, 4.96 mmol) was added and the solution was stirred for 10 min. Triethylsilane (0.760 mL, 4.76 mmol) was added and the solution was stirred at 0 °C for 1 h. Water (20 mL) was added and the product was extracted into dichloromethane (3×10 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. Flash column chromatography (dichloromethane) gave the *title compound* **20** (292 mg, 89%) as colourless needles, mp 40–41 °C (hexane); [Found: C, 75.59; H, 8.89. $C_{13}H_{18}O_2$ requires C, 75.69; H 8.80%]; R_f (dichloromethane) 0.60; ν_{max} 2949, 1584, 1469, 1257, 1085, 1056, 767 cm⁻¹; δ_H (400 MHz) 0.97 (3H, t, J 7.2 Hz, H_33'), 1.43–1.72 (4H, m, H_21' and H_22'), 2.67–2.68 (2H, m, H_24), 3.57–3.63 (1H, m, H3), 3.80 (3H, s, OMe), 4.62 (1H, d, J 15.9 Hz, $H_{ax}1$), 4.94 (1H, d, J 15.9 Hz, $H_{eq}1$), 6.67 (1H, d, J 8.3 Hz, H5), 6.71 (1H, d, J 7.6 Hz, H7), 7.11–7.15 (1H, m, H6); δ_C (100 MHz) 14.1 (C3'), 18.7 (C2'), 33.9 (C4), 38.0 (C1'), 55.0 (OMe), 64.6 (C1), 73.9 (C3), 107.0 (CH), 120.8 (CH), 123.6 (C), 126.7 (CH), 135.0 (C), 155.3 (C); m/z (EI) 206 (M^+, 23%), 134 (100). The spectral data (¹H NMR) was identical to that reported.[22]

4.2.13. (±)-8-Hydroxy-3-propyl-3,4-dihydro-1H-2-benzopyran (21).

To a solution of dibenzyldiselenide (224 mg, 0.658 mmol) in dimethylformamide (12 mL) was added sodium borohydride (190 mg, 5.02 mmol). After stirring for 20 min the (±)-methyl ether **20** (170 mg, 0.824 mmol) in dimethylformamide (2 mL) was added and the solution was heated under reflux for 2 h. After cooling to room temperature the solution was diluted with water (20 mL), acidified (dil aq H_2SO_4) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were washed sequentially with brine (3×30 mL) and water (3×30 mL) and dried (MgSO₄). Concentration under reduced pressure followed by flash column chromatography using a graded solvent system (dichloromethane/ethyl acetate) and crystallization from dichloromethane/hexane gave the *title compound* **21** (110 mg, 70%) as colourless plates, mp 119–122 °C; R_f (dichloromethane/ethyl acetate 1:1) 0.60; ν_{max} 3240br, 2957, 1589, 1467, 1276, 1043, 776 cm⁻¹; δ_H (400 MHz) 0.96 (3H, t, J 7.2 Hz, H_33'), 1.40–1.74 (4H, m, H_21' and H_22'), 2.68–2.70 (2H, m, H_24), 3.62–3.68 (1H, m, H3), 4.69 (1H, d, J 15.6 Hz, $H_{ax}1$), 5.00 (1H, d, J 15.6 Hz, $H_{eq}1$), 5.29 (1H, br s, OH), 6.55 (1H, d, J 7.9 Hz, H5), 6.69 (1H, d, J 7.6 Hz, H7), 7.00–7.04 (1H, m, H6); δ_C (100 MHz) 14.1 (C3'), 18.7 (C2'), 33.9 (C4), 37.9 (C1'), 64.4 (C1), 74.3 (C3), 112.1 (CH), 121.0 (CH), 122.0 (C), 126.9 (CH), 135.5 (C), 151.4 (C); m/z (EI) 192 (M^+, 0.6%), 40 (100); HRMS (ESI): $[M−H]^-$, found 191.1078. $C_{12}H_{15}O_2$ requires 191.1078.

4.2.14. (±)-5,7-Dibromo-8-hydroxy-3-propyl-3,4-dihydro-1H-2-benzopyran (19); prepared by bromination of (±)-phenol (21).

To a solution of the (±)-phenol **21** (36.0 mg, 0.187 mmol) in dimethylformamide (2 mL) was added a solution of N-bromosuccinimide (68.0 mg, 0.382 mmol) in dimethylformamide (0.5 mL) dropwise. The reaction mixture was stirred at room temperature, in the dark, for 18 h, diluted with water (5 mL), extracted with ethyl acetate (3×5 mL) and the combined extracts were washed with water (4×10 mL) and dried (MgSO₄). After removal of the solvent under reduced pressure the residue was purified by flash column chromatography (dichloromethane/light petroleum) to give the *title compound* **19** (54.0 mg, 82%) as colourless needles, mp 99–100 °C, from dichloromethane/hexane. All physical and spectroscopic data were identical to the data obtained for the same product prepared from (±)-ether **18**, as described above.

4.2.15. (±)-7-Bromo-3-propyl-3,4-dihydro-1H-2-benzopyran-5,8-dione (7).

To a solution of the (±)-phenol **19** (155 mg, 0.443 mmol) in acetonitrile (10 mL) and THF (0.30 mL) was added a solution of cerium (IV) ammonium nitrate (728 mg, 1.33 mmol in water; 1.5 mL). The solution was stirred at room temperature for 30 min, diluted with water (15 mL) and extracted with chloroform (3×5 mL). The combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The residual oil in dichloromethane/ethyl acetate (95:5) was filtered through a short column (0.5 cm) of silica and the filtrate was concentrated to give the *title compound* **7** (115 mg, 91%) as a yellow oil; ν_{max} 2955, 2929, 1663, 1654, 1587, 735 cm⁻¹; δ_H (400 MHz) 0.94 (3H, t, J 7.1 Hz, H_33'), 1.38–1.68 (4H, m, H_21' and H_22'), 2.18 (1H, dddd, J 19.0, 10.0, 4.4 and 2.7 Hz, $H_{ax}4$), 2.56 (1H, ddd, J 19.0, 3.5 and 2.9 Hz, $H_{eq}4$), 3.43–3.49 (1H, m, H3), 4.38 (1H, ddd, J 18.8, 4.4 and 3.5 Hz, $H_{ax}1$), 4.68 (1H, dd, J 18.8 and 2.7 Hz, $H_{eq}1$), 7.24 (1H, s, H6); δ_C (100 MHz) 14.0 (C3'), 18.4 (C2'), 27.5 (C4), 37.4 (C1'), 63.3 (C1), 73.0 (C3), 136.9 (C), 137.8 (CH), 140.4 (C), 140.5 (C), 177.9 (C), 183.5 (C); λ_{max} (EtOH) 205 (log ε 4.24), 273 nm (4.02); m/z (EI) 286 (M^+, ^{81}Br, 20%), 284 (M^+, ^{79}Br, 15%), 279 (56), 216 (71), 214 (84), 77 (54), 71 (100).

4.2.16. (±)-3,4-Dihydro-7,9-dihydroxy-3-propyl-1H-naphtho[2,3-c]pyran-5,10-dione (6).

To the (±)-benzoquinone **7** (115 mg, 0.403 mmol) in benzene (2 mL) was added 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (210 mg, 0.806 mmol) in

benzene (1 mL). The mixture was stirred at room temperature for 1 h then heated at reflux for 1.5 h. After cooling to room temperature silica (200 mg) was added and the solution was stirred for a further 15 min. After removal of the solvent under reduced pressure the residue was filtered slowly through a short column of silica (dichloromethane/ethyl acetate 2:1+1% formic acid). The yellow fractions were combined, concentrated, further chromatographed (Sephadex LH-20, dichloromethane/methanol 1:1) and crystallized from acetone/chloroform to give the *title compound* **6** (50.0 mg, 43%) as orange needles, mp 180–182 °C (dec); ν_{max} 3413br, 1637, 1614, 1321, 1153 cm^{-1}; δ_H (400 MHz, acetone-d_6) 0.94 (3H, t, J 7.2 Hz, H$_3$3'), 1.40–1.61 (4H, m, H$_2$1' and H$_2$2'), 2.07–2.16 (1H, m, H$_{ax}$4), 2.58 (1H, ddd, J 18.8, 3.2 and 2.9 Hz, H$_{eq}$4), 3.48–3.55 (1H, m, H3), 4.38 (1H, ddd, J 18.5, 3.7 and 3.2 Hz, H$_{ax}$1), 4.68 (1H, dd, J 18.5 and 2.6 Hz, H$_{eq}$1), 6.51 (1H, d, J 2.5 Hz, H8), 6.97 (1H, d, J 2.5 Hz, H6), 10.36 (1H, br s, 7-OH), 12.02 (1H, s, 9-OH); δ_C (100 MHz, acetone-d_6) 14.2 (C3'), 19.2 (C2'), 28.6 (C4), 38.3 (C1'), 63.3 (C1), 73.6 (C3), 108.0 (C8), 109.0 (C6), 109.2 (C9a), 134.7 (C5a), 142.9 (C4a/10a), 143.5 (C4a/10a), 165.0 (C9), 165.6 (C7), 183.2 (C5), 187.5 (C10); λ_{max} (EtOH) 219 (log ε 4.43), 271 (4.09), 289 (3.98), 440 nm (3.45); (EtOH+1 drop 1 M aq NaOH) 208 (log ε 4.79), 232 (4.29), 295 (4.07), 530 nm (3.37); m/z (EI) 288 (M$^+$, 68%), 216 (100); HRMS (ESI): [M−H]$^-$, found 287.0926. C$_{16}$H$_{15}$O$_5$ requires 287.0925.

4.2.17. 2,4-Dibromo-5,6,7,8-tetrahydro-1-naphthol (*23*).
To a solution of 5,6,7,8-tetrahydro-1-naphthol **22** (100 mg, 0.675 mmol) in dimethylformamide (3 mL) was added a solution of *N*-bromosuccinimide (246 mg, 1.38 mmol) in dimethylformamide (1 mL). The solution was stirred at room temperature, in the dark, for 18 h, diluted with water (20 mL), extracted with ethyl acetate (3×10 mL) and the combined organic extracts were washed with water (4×15 mL) and dried (MgSO$_4$). Removal of the solvent under reduced pressure and crystallization from hexane gave the *title compound* **23** (197 mg, 96%) as colourless needles, mp 54–55 °C; ν_{max} 3398br, 2934, 1425, 1301, 1221, 689 cm^{-1}; δ_H (400 MHz) 1.73–1.80 (4H, m, H$_2$6 and H$_2$7), 2.64–2.72 (4H, m, H$_2$5 and H$_2$8), 5.48 (1H, s, OH), 7.50 (1H, s, H3); δ_C (100 MHz) 21.9 (CH$_2$), 22.5 (CH$_2$), 24.5 (CH$_2$), 30.3 (CH$_2$), 106.8 (C), 115.9 (C), 127.5 (C), 130.9 (CH), 137.5 (C), 149.1 (C); m/z (EI) 308 (M$^+$, ^{81}Br$_2$, 22%), 306 (M$^+$, ^{81}Br^{79}Br, 46%), 304 (M$^+$, ^{79}Br$_2$, 26%), 146 (70), 84 (54), 57 (92), 55 (100), 51 (61); HRMS (ESI): [M−H]$^-$, found 302.9029. C$_{10}$H$_9^{79}$Br$_2$O requires 302.9026.

4.2.18. 2-Bromo-5,6,7,8-tetrahydro-1,4-naphthoquinone (*24*).
To the dibromophenol **23** (175 mg, 0.572 mmol) in acetonitrile (25 mL) was added a solution of cerium (IV) ammonium nitrate (817 mg, 1.49 mmol in water; 2 mL). The mixture was stirred at room temperature for 30 min, diluted with water (20 mL), extracted with chloroform (3×10 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 and the filtrate was concentrated to give the *title compound* **24** (120 mg, 87%) as a yellow oil; ν_{max} 3015, 1662, 1647, 1213, 753 cm^{-1}; δ_H (400 MHz) 1.68–1.72 (4H, m, H$_2$6 and H$_2$7), 2.41–2.50 (4H, m, H$_2$5 and H$_2$8), 7.20 (1H, s, H3); δ_C (100 MHz) 20.7 (CH$_2$), 21.1 (CH$_2$), 22.6 (CH$_2$), 23.5 (CH$_2$), 137.1 (C), 137.8 (CH), 142.2 (C), 142.9 (C), 179.6 (C), 184.9 (C); λ_{max} (EtOH) 203 (log ε 4.39), 275 nm (4.42); m/z (EI)

242 (M$^+$, ^{81}Br, 58%), 240 (M$^+$, ^{79}Br, 44), 161 (100), 105 (53), 79 (71), 77 (73).

4.2.19. 1,3-Dihydroxy-5,6,7,8-tetrahydro-9,10-anthraquinone (*25*).
To the benzoquinone **24** (120 mg, 0.498 mmol) in benzene (2 mL) was added 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (250 mg, 0.960 mmol). The solution was stirred at room temperature for 4 h and then heated at reflux for 1 h. After cooling to room temperature, silica (0.5 g) 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, further chromatographed (Sephadex LH-20, dichloromethane/methanol 1:1) and crystallized from acetone/chloroform to give the *title compound* **25** (100 mg, 83%) as orange needles, mp 188–191 °C (dec); ν_{max} 3407br, 1630, 1609, 1316, 1156 cm^{-1}; δ_H (400 MHz, d_6-acetone) 1.69–1.72 (4H, m, H$_2$6 and H$_2$7), 2.45–2.51 (4H, m, H$_2$5 and H$_2$8), 6.52 (1H, d, J 2.4 Hz, H2), 6.98 (1H, d, J 2.4 Hz, H4), 9.81 (1H, br s, 3-OH), 12.31 (1H, s, 1-OH); δ_C (100 MHz, acetone-d_6) 21.6 (C6 and 7), 23.1 (C5/8), 23.7 (C5/8), 107.8 (C2/4), 108.3 (C2/4), 109.6 (C9a), 134.9 (C4a), 145.3 (C8a/10a), 145.6 (C8a/10a), 164.9 (C1/3), 165.0 (C1/3), 184.2 (C10), 189.2 (C9); λ_{max} (EtOH) 219 (log ε 4.44), 271 (4.12), 291 (4.05), 426 nm (3.50); (EtOH+1 drop 1 M aq NaOH) 207 (log ε 4.73), 231 (4.35), 250 (4.08), 295 (4.18), 518 nm (3.48); m/z (EI) 244 (M$^+$, 22%), 86 (70), 84 (79), 71 (100), 70 (58), 69 (99).

Supplementary data

^{1}H NMR and ^{13}C NMR spectra for compounds **6–9**, **11–21** and **23–25**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.02.009.

References and notes

1. Liebermann, C. *Ber. Dtsch. Chem. Ges.* **1874**, *7*, 1102–1103.
2. Kogl, F.; von Tauffenbach, G. *Liebigs Ann. Chem.* **1925**, *445*, 170–180.
3. Kogl, F.; Erxleben, H. *Liebigs Ann. Chem.* **1930**, *484*, 65–84.
4. Blackburn, G. M.; Neilson, A. H.; Todd, A. R. *Proc. Chem. Soc.* **1962**, 327–328.
5. Blackburn, G. M.; Ekong, D. E. U.; Neilson, A. H.; Todd, L. *Chimia* **1965**, *19*, 208–212.
6. Edwards, R. L.; Kale, N. *Tetrahedron* **1965**, *21*, 2095–2107.
7. Thomson, R. H. *Naturally Occurring Quinones*, 2nd ed.; Academic: London, 1971.
8. Saikawa, Y.; Watanabe, T.; Hashimoto, K.; Nakata, M. *Phytochemistry* **2000**, *55*, 237–240.
9. Giles, R. G. F.; Reuben, M. K.; Roos, G. H. P. S. *Afr. J. Chem.* **1979**, *32*, 127–129.
10. Giles, R. G. F.; Green, I. R.; Hugo, V. I. S. *Afr. J. Chem.* **1990**, *43*, 28–33.
11. Donner, C. D.; Gill, M.; Tewierik, L. M. *Molecules* **2004**, *9*, 498–512.
12. Donner, C. D.; Gill, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 938–948.
13. Blackburn, G. M.; Cameron, D. W.; Chan, H. W.-S. *J. Chem. Soc. C* **1966**, 1836–1842.
14. Banville, J.; Brassard, P. *J. Org. Chem.* **1976**, *41*, 3018–3020.
15. Roberge, G.; Brassard, P. *J. Org. Chem.* **1981**, *46*, 4161–4166.
16. Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: New York, NY, 1983.
17. Ahmad, R.; Saá, J. M.; Cava, M. P. *J. Org. Chem.* **1977**, *42*, 1228–1230.
18. Yamamoto, K.; Suzuki, S.; Tsuji, J. *Chem. Lett.* **1978**, 649–652.
19. Tan, N. P. H.; Donner, C. D. *Tetrahedron* **2009**, *65*, 4007–4012.
20. Henbest, H. B.; Jones, E. R. H.; Walls, I. M. S. *J. Chem. Soc.* **1949**, 2696–2700.
21. Schwartz, B. D.; Hayes, P. Y.; Kitching, W.; De Voss, J. J. *J. Org. Chem.* **2005**, *70*, 3054–3065.
22. Giles, R. G. F.; Green, I. R.; Pestana, J. A. X. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2389–2395.