A regio- and stereo-selective synthesis of 2-hydroxy-3-methylochromycinone in three steps from 2-bromo-5-acetoxy-1,4-naphthoquinone and 1-acetoxy-3,3-dimethyl-5-vinylcyclohexa-1,5-diene †

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2-Hydroxy-3-methylochromycinone **4** has been synthesised using a three stage strategy. The Diels–Alder reaction between 2-bromo-5-acetoxy-1,4-naphthoquinone and 1-acetoxy-3,3-dimethyl-5-vinylcyclohexa-1,5-diene gives a single racemic diastereoisomer of 1-acetoxy-12a-bromo-3,3-dimethyl-7,12-dioxo-3,4,6,6a,7,12,12a,12b-octahydrobenzo[*a*]anthracen-8-yl acetate **5** in 63% yield, which may be epoxidised to give the bis-epoxide 8-acetoxy-12a-bromo-3,3-dimethyl-7,8-dioxo-3,4,4a,5,6,6a,7,12,12a,12b-decahydro-1a*H*-benzo[6,7]oxireno[2′,3′:10,10a]phenanthro[3,4-*b*]-oxiren-12-yl acetate **6** in 82% yield. The bis-epoxide **6** may be converted directly into 2-hydroxy-3-methylochromycinone **4** in 45% yield, or *via* one of two intermediates [*e.g.* 2,5-dihydroxy-3,3-dimethyl-1,7,12-trioxo-1,2,3,4,5,6,7,12-octahydrobenzo[*a*]anthracen-8-yl acetate **8**] in 80–85% yield. The intermediate **8** shows moderate anticancer activity at μM concentrations against lung, breast and central nervous system cancers, while the target compound **4** is only active at 10^{-4} M.

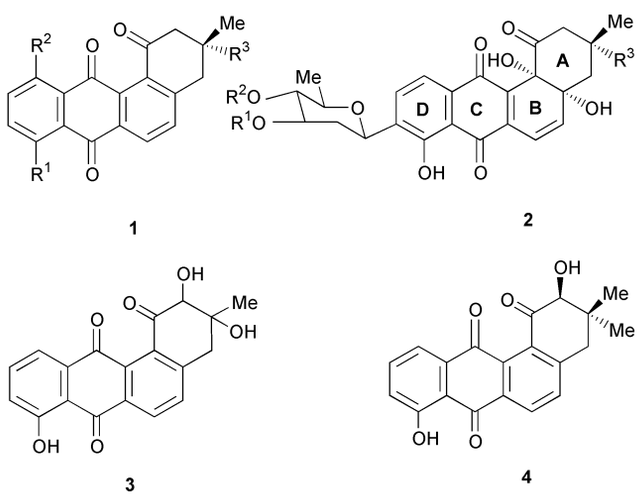
Introduction

We have initiated a programme to synthesise model angucyclinones related to ochromycinone (**1**, $R^1 = OH$, $R^2 = R^3 = H$)[1] and the anticancer active saquayamycins (**2**, R^1, R^2 and R^3 are carbohydrate residues of varying complexity),[2,3] with a view to producing model compounds with significant anticancer activity. We have already made **1** for $R^1 = OH$, $R^2 = H$, $R^3 = Me$; $R^1 = H$, $R^2 = OH$, $R^3 = Me$; and $R^1 = R^2 = OH$, $R^3 = Me$[4,5] using Diels–Alder methodology.[6–8] These quinones and their first-formed Diels–Alder intermediates have shown modest broad-spectrum anticancer activity at μM concentrations in the 60 tumor line test programme of the National Cancer Institute [NCI (Washington, DC)]. To introduce the saquayamycin *cis*-dihydroxy substitution at the A/B ring junction is a more difficult undertaking: to date, we have not achieved this aim.[5]

There is a third type of angucyclinone which is reported to exhibit bio-activity, *viz*., that with a 2-hydroxy group in the A ring: an example is **3** (the stereochemistry of the groups on the A ring is unknown), a metabolite isolated from *Streptomyces phaeochromogenes*.[9] The aim of the work reported in this paper is to synthesise racemic 2-hydroxy-3-methylochromycinone (**4**) and to assess the anticancer activity of this model system. As before,[4,5] we utilise a *gem*-dimethyl substituent at the 3 position in order that a single racemic diastereoisomer may be formed as the final product.

Results and discussion

The strategy of the proposed synthesis is shown in Scheme 1. An *endo* Diels–Alder reaction between 2-bromo-5-acetoxy-1,4-naphthoquinone and 1-acetoxy-3,3-dimethyl-5-vinylcyclohexa-1,5-diene should yield the single racemic diastereoisomer **5**. The polarisation of the diene and dienophile shown in Scheme 1, together with steric interactions, should effect the reaction shown and the 1-acetate substituent on the triene should ensure that the reacting diene is that shown, and not the 1,5-diene of the ring. The second step of the synthesis involves bis-epoxidation to yield **6**, with the stereochemistry of the epoxide rings predicted to be as shown. Ring opening of both epoxides, elimination of two molecules of water and hydrogen bromide, together with hydrolysis of the hemiketal formed at the 1-position should produce the required racemic derivative **4**.



1-Acetoxy-3,3-dimethyl-5-vinylcyclohexa-1,5-diene was made in quantitative yield by enolising 5,5-dimethyl-3-vinylcyclohex-2-en-1-one[4] with lithium diisopropylamide at −78 °C, followed by reaction of the enolate with pyridine and acetic anhydride. The reaction of this triene with 2-bromo-5-acetoxy-1,4-naphthoquinone in toluene at reflux and under

† Electronic supplementary information (ESI) available: further details of the NMR spectra of compounds **5**, **6**, **8** and **9**. See http://www.rsc.org/suppdata/p1/b1/b101756j/

 DOI: 10.1039/b101756j

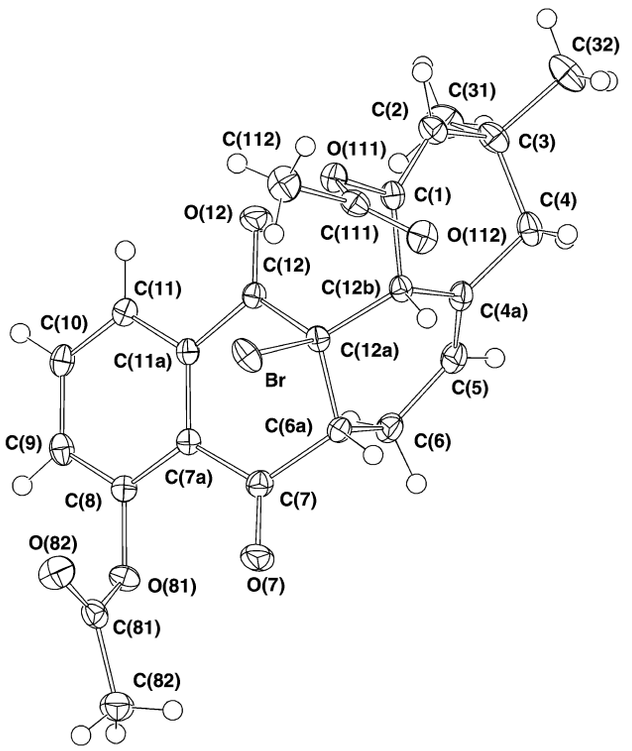
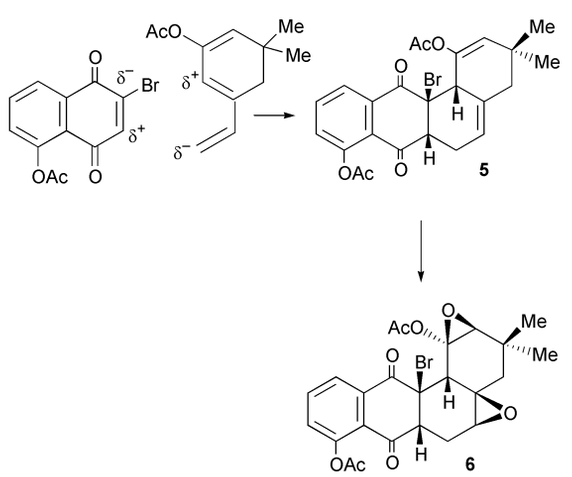


Fig. 1 Projection of the Diels–Alder adduct **5**, showing 50% amplitude displacement ellipsoids for the non-hydrogen atoms, hydrogen atoms having arbitrary radii of 0.1 Å.



Scheme 1

nitrogen for 24 hours gave a 92% yield of the Diels–Alder adduct **5**.

The regiochemistry of **5** was confirmed as follows. Adduct **5** upon treatment with aqueous sodium hydroxide (saturated) in tetrahydrofuran (1 : 4) gave the known 3-methylochromycinone **1** (R^1 = OH, R^2 = H, R^3 = Me)[4] in 20% yield. The regio- and stereo-chemistries of **5** were confirmed by the results of an X-ray study (Fig. 1). One formula unit comprises the asymmetric unit of the structure. In terms of the fused ring system, conformational parameters are shown in Table 1 and are in close agreement with a similar system **7**,[10] after due allowance for the change in the C(1)–C(2) bond order. Perhaps, in consequence of the latter, and further, in conjugation with the introduction of the bromine atom at the bridgehead in **5**, we find the bromine to adjacent hydrogen distances Br · · · H(6a), (12b) 2.91(2), 2.93(2) Å, with concomitant diminution of Br–C(12a)–C(6a), C(12) [104.42 (8), 101.68 (8)°]. Ring C (6a,7,7a,11a,12,12a) in both structures is essentially an 'envelope', with C(12a) at the flap, but there are considerable differences in the torsions, in particular those associated with

Table 1 Torsion angles/° for compounds **5** and **7**[a]

	5	**7**
Ring A		
12b–1–2–3	1.6(2)	59(2)
1–2–3–4	−25.8(1)	−63(1)
2–3–4–4a	51.8(1)	55(2)
3–4–4a–5	123.0(1)	145(1)
4–4–12b–1	30.3(1)	35(2)
4a–12b–1–2	−2.6(2)	−43(2)
5–4a–12b–1	−150.6(1)	163(1)
4–4a–12b–12a	160.4(1)	−152(1)
Ring B		
12b–4a–5–6	−1.0(2)	2(2)
4a–5–6–6a	−8.9(2)	−11(2)
5–6–6a–12a	40.3(1)	42(1)
6–6a–12a–12b	−63.5(1)	−64(1)
6a–12a–12b–4a	51.5(1)	52(1)
12a–12b–4a–5	−20.5(2)	−23(2)
7–6a–12a–12b	175.2(1)	176(1)
6–6a–12a–12	67.2(1)	62(1)
Ring C		
7–6a–12a–12	−54.1(1)	−57(1)
6a–12a–12–11a	34.2(2)	57(1)
12a–12–11a–7a	−5.7(2)	−25(2)
12–11a–7a–7	−3.3(2)	−7(2)
11a–7a–7–6	−17.6(2)	6(2)
7a–7–6a–12a	46.5(2)	26(2)
11a–7a–7–O(7)	166.9(1)	−174(1)
7a–11a–12–O(12)	175.6(1)	160(1)

[a] Values are given for the three fused non-aromatic rings of **5**: carbon atoms being denoted by number only.

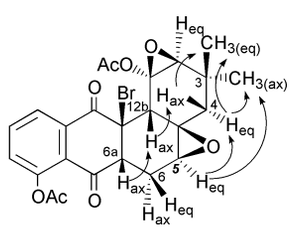
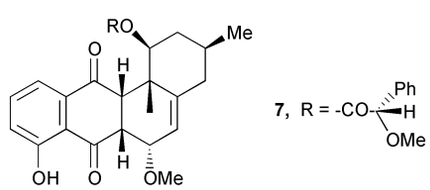


Fig. 2 ROESY NMR data for bis-epoxide **6**.



departures of the 'quinonoid' oxygen atoms from the plane of the aromatic ring.

Treatment of **5** with 2.5 equivalents of dimethyldioxirane in anhydrous acetone at 0 °C for 16 h, gave the racemic bis-epoxide **6** in a purified yield of 82%. We could not obtain a crystal of **6** suitable for X-ray analysis. The bond connectivity of **6** is confirmed by the spectroscopic data summarised in the Experimental and the stereochemistry at the seven chiral centres is confirmed by 2D NMR experiments. Full details of the ^{1}H NMR experiments for **6** are recorded in the electronic supplementary information (ESI), including COSY and ROESY experiments. Relevant ROESY data are summarised in Fig. 2. A 12.6 Hz coupling constant between H6a and $H6_{ax}$ indicates a pseudo *trans*-diaxial relationship, meaning that these two hydrogens are on opposite faces of the molecule. Conversely, $H6_{eq}$ interacts with H6a with a coupling constant

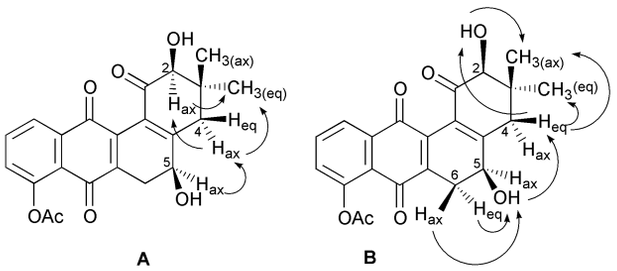


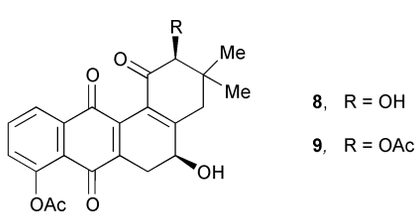
Fig. 3 ROESY NMR data for hydroxyketone (**8**).

of 4.2 Hz meaning these two hydrogens are on the same side of the molecule. The intense 1,3-diaxial interactions between H6a, H12b$_{ax}$ and H4$_{ax}$ indicate that these hydrogens are all on the same face of the molecule. There are cross peaks between H4$_{ax}$ and 3-Me$_{eq}$ and H4$_{eq}$ and 3-Me$_{ax}$, but no cross peaks between H4$_{ax}$ and 3-Me$_{ax}$ or H4$_{eq}$ and 3-Me$_{eq}$, confirming the stereochemical relationship between the 3 and 4 substituents shown in Fig. 2. The cross peaks between H5, 3-Me$_{ax}$ and H4$_{eq}$ and the lack of a cross peak between H5 and H12b show that H5 is equatorial. Finally, an NOE difference experiment allows the assignment of the relative stereochemistry of the 1,2-epoxide ring compared with the rest of the molecule. Irradiation of the H2 signal at 3.35 ppm enhances both of the 3-Me signals by 1.2%. Thus, H2 is equatorial and equidistant from each of the two methyl groups.

Bis-epoxide **6** can be converted to the racemic α-hydroxyketone **4** in two ways. Firstly, treatment of **6** under acid conditions, followed by reaction of the unpurified products under basic conditions gives **4** in a purified yield of 45%.‡ Alternatively, the products of mild acid hydrolysis may be separated and characterised and then converted to **4**: in this case, the overall yield from **6** is about 65%. The structure of **4** is confirmed by spectroscopic data. The infrared spectrum shows three carbonyl vibrations: *viz*., 1693 (α-hydroxycarbonyl), 1666 (quinone carbonyl) and 1633 (*peri*-OH hydrogen bonded quinone carbonyl) cm^{-1}; the mass spectrum shows the characteristic retro Diels–Alder fragmentation [M$^{+\bullet}$ − C$_4$H$_8$O], while the ^{1}H NMR spectrum, in particular, shows the *peri*-OH (12.22 ppm), the two coupled doublets of H5 and H6 [7.58 and 8.36 ppm (7.8 Hz)], and the H10 triplet (7.29 ppm) coupled to the two overlapping doublets of H9 and H11 [7.68 ppm (3.9 Hz)].

An insight into the mechanism of the formation of **4** from **6** is forthcoming when the two major products of the toluene-*p*-sulfonic acid catalysed ring opening of bis-epoxide **6** are isolated and characterised.

Chromatography of this product mixture over silicic acid gave **8** and **9** in yields of 55 and 20% respectively. Mass spectrometric analysis of the residual material identified small amounts of other products corresponding to the further losses of HBr, H$_2$O and (H$_2$O + HBr) from each of **8** and **9**. None of



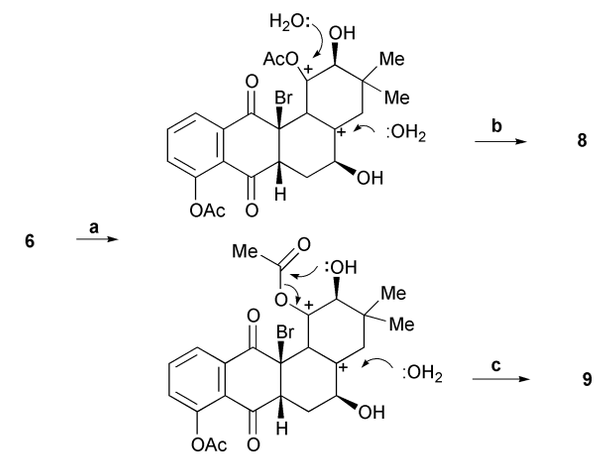
8, R = OH

9, R = OAc

these minor products were further characterised. Either **8** or **9** (or a mixture of both) was treated first under acidic, then basic conditions to give racemic **4** in yields ranging from 80 to 85%. Since we were unable to obtain crystals of either **8** or **9** that were suitable for X-ray analysis, the stereochemistry of each of the racemic diastereoisomers shown was confirmed using 2D NMR experiments. Full results of ROESY and NOESY experiments are given in the ESI, while particularly relevant spatial ROESY data are shown for **8** in Fig. 3.

The ROESY cross peaks between H2$_{ax}$, H4$_{ax}$ and H5$_{ax}$ (4.30, 2.47 and 4.44 ppm) (Fig. 3A) confirm that these H substituents are on the same side of the molecule, while the cross peaks between the 3-methyl (1.26 ppm), H4$_{ax}$ and H2$_{ax}$ assign this methyl group as equatorial. Other interactions are shown in Fig. 3B. The relative stereochemistry of the two hydroxy groups is *syn*, since the 5-OH (5.58) interacts with H4$_{eq}$ (3.07), which additionally interacts with the 2-OH (4.15). Axial H6 is identified by coupling to H5$_{ax}$ with a coupling constant of 15.6 Hz, indicating a large dihedral angle (pseudo *trans*-diaxial). The stereochemistry of the analogous molecule **9** is derived similarly (see ESI).

Mechanistic rationales for the formation of **8** and **9** are summarised in Scheme 2. The protonations of both epoxide



Scheme 2 (a) H$^+$; (b) −(AcOH + H$_2$O + HBr); (c) −(H$_2$O + HBr).

rings in the ring opened carbocation forms are shown together in cartoon form in Scheme 2. Attack of water at both carbocation centres followed by elimination of acetic acid and water yield the α-hydroxyketone **8** as the major product. The formation of the minor product **9** involves an acetyl rearrangement, as shown in Scheme 2.[10] Both **8** and **9** can be converted directly into the required angucyclinone product **4**.

The target compound **4** together with intermediates **8** and **9** have been tested for anticancer activity [by NCI (Washington, DC)] against lung and breast cancer and cancer of the central nervous system. All are active, the least active being **4**, which shows some activity at the 10^{-4} M concentration. In contrast, intermediates **8** and **9** show activity at 10^{-6} M concentrations. Further tests are being carried out with all three compounds.

In conclusion, the target molecule 2-hydroxy-3-methylochromycinone **4** has been synthesised using a three stage synthesis commencing with the Diels–Alder reaction between 2-bromo-5-acetoxy-1,4-naphthoquinone and 1-acetoxy-3,3-dimethyl-5-vinylcyclohexa-1,5-diene. The angucyclinone **4** shows only minor anticancer activity, with the reduced derivatives **8** and **9** showing moderate anticancer activity at μM concentrations. Since the activities of these systems do not match those of the saquayamycins **2**, the dihydroxy substitution at the A/B ring junction must be a key feature in determining the activity of naturally occurring quinones like the saquayamycins.

Experimental

Melting points were determined with a Kofler hot-stage apparatus equipped with a Reichart microscope and are uncorrected. Flash chromatography was performed using Merck 60PF$_{254}$

‡ The reason why acid treatment precedes base treatment, and why base treatment alone must not be used, is because base treatment of **6** opens the A ring to give 2-substituted anthraquinones.[5,9]

silica gel (230–400 mesh). Microanalyses were performed by the University of Otago, Dunedin, New Zealand. Infrared spectra were recorded with an ATI Mattson Genesis FT IR spectrometer (in liquid cells using deuteriochloroform as solvent). Mass measurements were measured for $M^{+\bullet}$ species with a Kratos Concept ISQ mass spectrometer at the University of Tasmania (Dr N. Davies). Ultraviolet spectra were measured in ethanol with a Hewlett Packard 845A Diode Array spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using either Varian Gemini 2000 (300 MHz ^{1}H INOVA) or Varian 600 MHz ^{1}H spectrometers (using deuteriochloroform as solvent unless stated to the contrary). Signals were assigned by interpretation of COSY, HMQC, HMBC and ROESY spectra. Electron impact mass spectra were measured by direct insertion using a Finnigan GCQ ion trap mass spectrometer The molecular ion value and diagnostic fragmentations are recorded.

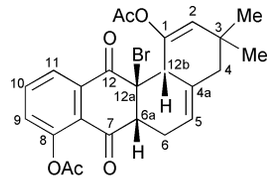
2-Bromo-5-acetoxy-1,4-naphthoquinone was prepared from juglone (5-hydroxy-1,4-naphthoquinone) by a reported procedure.[10] 5,5-Dimethyl-3-vinylcyclohex-2-en-1-one was synthesised by a reported techique.[11]

1-Acetoxy-3,3-dimethyl-5-vinylcyclohexa-1,5-diene

A hexane solution of freshly titrated butyllithium (2.32 M, 3.32 cm^3) was concentrated *in vacuo*, and under nitrogen, the residue dissolved in anhydrous tetrahydrofuran (10 cm^3) and cooled to −78 °C. Diisopropylamine (1.06 cm^3) in anhydrous tetrahydrofuran (10 cm^3) was added and the mixture stirred for 30 min at −78 °C. 5,5-Dimethyl-3-vinylcyclohex-2-en-1-one (1 g) in anhydrous tetrahydrofuran (5 cm^3) was added, the mixture stirred for 45 min at −78 °C, quenched with acetic anhydride (1.22 cm^3), pyridine (0.14 cm^3) and anhydrous tetrahydrofuran (10 cm^3). The mixture was allowed to warm to 20 °C over a period of 45 min, hexane (100 cm^3) and iced water (50 cm^3) were added, the organic layer was washed with aqueous sodium hydrogen carbonate (saturated, 2 × 50 cm^3), water (50 cm^3), dried ($MgSO_4$) and the the solvent removed *in vacuo* to give the crude product (1.22 g, 95% yield), which is best used immediately for the next stage of the synthesis. Distillation gave the pure triene (0.92 g, 75% yield), bp 175–176 °C at 760 mmHg. $M^{+\bullet}$ 192.1150; $C_{12}H_{16}O_2$ requires 192.1150. λ_{max}/nm (log ε/mol^{-1} dm^3 cm^{-1}) 247 (3.63), 277 (3.40). ν_{max} (neat)/cm^{-1} 2958, 1763, 1653, 1605, 1368. ^{1}H NMR (300 MHz) δ 1.08 (6H, s, 2 × Me); 2.15 (3H, s, Me); 2.24 (2H, d, 1.2 Hz, H4); 5.12 (1H, d, 10.8 Hz); 5.23 (1H, d, 1.2 Hz, H6); 5.28 (1H, d, 17.4 Hz); 5.69 (1H, s, H2); 6.41 (1H, dd, 17.4, 10.8 Hz). ^{13}C NMR (75 MHz) δ 20.68 (CH_3); 28.05 (2 × CH_3); 31.99 (C3); 36.3 (CH_2); 113.30; 121.20; 122.73; 136.84 (C5); 137.59; 144.73 (C1); 168.91 (CO). *m*/*z* 193 [(MH^+), 100%], 177 [−(CH_4), 10], 151 [−(C_2H_2O), 22], 135 [−(C_2H_2O + CH_4), 47].

1-Acetoxy-12a-bromo-3,3-dimethyl-7,12-dioxo-3,4,6,6a,7,12,12a,12b-octahydrobenzo[*a*]anthracen-8-yl acetate 5

A mixture of 5-acetoxy-2-bromo-1,4-naphthoquinone (3.08 g) and 1-acetoxy-3,3-dimethyl-5-vinylcyclohexa-1,5-diene (2.0 g) in anhydrous toluene (160 cm^3) was heated at reflux for 24 h under nitrogen. The reaction mixture was cooled to 20 °C and the solvent removed *in vacuo* to afford an orange residue (2.33 g, 92%), which was purified by flash chromatography on silica eluting with dichloromethane–acetone (98 : 2) under nitrogen, followed by crystallisation from propan-2-ol–diethyl ether (1 : 1) (under nitrogen) to give colourless crystals of **5** (1.63 g, 63%) (mp 112 °C with decomposition), which oxidise readily on contact with air. Found: C, 59.0; H, 4.6%; $C_{24}H_{23}O_6Br$ requires C, 59.15; H. 4.75%. λ_{max}/nm (log ε/mol^{-1} dm^3 cm^{-1}) 258 (shoulder, 3.60), 312 (3.37). ν_{max} (Nujol)/cm^{-1} 1773, 1751, 1704, 1589, 1233, 1217, 1180. ^{1}H NMR (600 MHz COSY and GHMBC) δ 1.04 (3H, s, CH_3); 1.12 (3H, s, CH_3); 2.10 (3H, s, 1-acetate); 2.06 (1H, dd, 1.8, 12.9 Hz, H4); 2.30 (1H, ddd, 4.2, 12.0, 12.8 Hz, H6); 2.34 (1H, br d, 12.9 Hz, H4); 2.45 (1H, ddd,



5

4.2, 6.0, 12.8 Hz, H6); 3.62 (1H, dd, 6.0, 12.0 Hz, H6a), 3.97 (1H, br s, H12b); 5.40 (1H, dd, 1.5, 1.8 Hz, H2); 5.54 (1H, td, 2.0, 4.2 Hz, H5); 7.37 (1H, dd, 1.2, 7.8 Hz, H9); 7.75 (1H, t, 7.8 Hz, H10); 8.00 (1H, dd, 1.2, 7.8 Hz, H11). ^{13}C NMR (150 MHz) δ 20.98 (CH_3 acetate); 21.90 (CH_3 acetate); 26.94 (CH_3); 28.13 (C6); 30.14 (CH_3); 32.16 (C3); 45.79 (C12b); 46.74 (C4); 59.3 (C6a); 62.32 (C12a); 119.46 (C5); 122.87 (C7a); 126.02 (C11); 127.10 (C2); 129.10 (C9); 133.64 (C4a); 134.11 (C11a); 135.05 (C10); 143.80 (C1); 149.62 (C8); 169.15 (CO acetate); 170.36 (CO acetate); 187.99 (CO, C12); 193.45 (CO, C7). *m*/*z* 487 (MH^+, 10%); 489 (MH^+, 10); 407 [−(CH_3CO_2H), 22]; 407 [−(HBr), 43]; 387 and 389 [−(CH_3CO_2H + CH_2CO), 53]; 365 [−(HBr + CH_2CO), 86]; 347 [−(HBr + CH_3CO_2H), 100]; 305 [−(CH_3CO_2H + CH_2CO + HBr), 58].

8-Acetoxy-12a-bromo-3,3-dimethyl-7,8-dioxo-3,4,4a,5,6,6a,7,12,12a,12b-decahydro-1a*H*-benzo[6,7]oxireno[2′,3′:10,10a]-phenanthro[3,4-*b*]oxiren-12-yl acetate 6§

A solution of dimethyldioxirane in acetone (81 cm^3, 3.0 mmol) was added to a solution of **5** (586 mg, 1.2 mmol) in acetone (20 cm^3) and allowed to stir at 0 °C for 16 h under nitrogen. The reaction mixture was warmed to 20 °C, dried ($MgSO_4$), and the solvent removed *in vacuo* to give crude **6** (567 mg, 91%), which was crystallised from dichloromethane–diethyl ether (1 : 1) as colourless crystals (512 mg, 82% yield), mp 111 °C with decomposition. The product is unstable and needs to be stored at −20 °C under nitrogen. Found: C, 55.35; H, 4.3%; $C_{24}H_{23}O_8Br$ requires C, 55.5; H, 4.5%. λ_{max}/nm (log ε/mol^{-1} dm^3 cm^{-1}) 267 (shoulder, 3.72), 314 (3.45), 342 (shoulder, 2.87). ν_{max} ($CDCl_3$)/cm^{-1} 1770, 1708, 1594, 1432, 1369, 1263, 1193. ^{1}H NMR (600 MHz) δ 0.71 (1H, d, 13.8 Hz, H4); 1.20 (3H, s, CH_3); 1.25 (3H, s, CH_3); 1.95 (3H, s, 1-acetate); 1.96 (1H, ddd, 1.2, 12.6, 14.0 Hz, H6); 2.27 (1H, d, 13.8 Hz, H4); 2.40 (3H, s, 8-acetate); 2.43 (1H, ddd, 2.4, 4.2, 14.0 Hz, H6); 2.96 (1H, br s, H5); 3.35 (1H, br s, H2); 3.73 (1H, dd, 4.2, 12.6 Hz, H6a); 3.76 (1H, br s, H12b); 7.40 (1H, dd, 1.2, 7.5 Hz, H9); 7.78 (1H, t, 7.5 Hz, H10); 7.96 (1H, dd, 1.2, 7.5 Hz, H11). ^{13}C NMR (150 MHz) δ 20.97 (CH_3, 8-acetate); 22.43 (CH_3); 22.51 (CH_3, 1-acetate); 27.71 (CH_3); 28.05 (C6); 31.40 (C3); 41.44 (C4); 45.83 (C12b); 54.58 (C6a); 56.99 (C4a); 60.68 (C5); 61.21 (C12a); 67.04 (C2); 83.78 (C1); 122.68 (C7a); 125.70 (C11); 130.30 (C9); 134.66 (C11a); 135.23 (C10); 149.57 (C8); 169.13 (CO, 8-acetate); 169.57 (CO, 1-acetate); 189.34 (C12); 192.41 (C7). *m*/*z* 519 (MH^+, 4%); 517 (MH^+, 4); 479 and 477 [−(CH_2CO), 5]; 461 and 459 [−(CH_3CO_2H), 5]; 379 [−(CH_3CO_2H + HBr), 50]; 337 [−(CH_3CO_2H + HBr + CH_2CO), 100]; 319 [−(CH_3CO_2H + HBr + CH_2CO + H_2O), 30].

Mild acid hydrolysis of 6

A mixture of **6** (400 mg), water (5 cm^3), tetrahydrofuran (80 cm^3) and toluene-*p*-sulfonic acid (5 mg) was heated under reflux for 16 h under nitrogen. With the system under nitrogen, the solvent was removed *in vacuo*, dichloromethane (100 cm^3) was added, and the mixture washed with water (50 cm^3), aqueous sodium chloride (saturated, 50 cm^3), dried ($MgSO_4$), and the solvent removed *in vacuo*. The mixture was separated by

§ The numbering used in the NMR data for compound **6** is as indicated in the title. The IUPAC name for compound **6** is 7-acetoxy-11a-bromo-2,2-dimethyl-6,11-dioxo-2,3,4a,5,5a,6,11,11a,11b,11c-decahydro-1a*H*-benzo[6,7]oxireno[2′,3′:10,10a]phenanthro[3,4-*b*]oxiren-11c-yl acetate.

flash chromatography over silica and under nitrogen, eluting with dichloromethane–acetone (9 : 1) to give a major product **7** (130 mg, 43%) and a minor product **8** (90 mg, 27% yield).

2,5-Dihydroxy-3,3-dimethyl-1,7,12-trioxo-1,2,3,4,5,6,7,12-octahydrobenzo[*a*]anthracen-8-yl acetate (8). Crystallised from ethanol as light orange crystals [112 mg, purified yield from **6** 37%], mp 184 °C with decomposition. Product **7** oxidises in air, and should be kept at −20 °C under nitrogen. Found: C, 66.8; H, 5.1%; $C_{22}H_{20}O_7$ requires C, 66.7; H, 5.1%. λ_{max}/nm (log ε/mol^{-1} dm^3 cm^{-1}) 250 (4.31), 284 (shoulder, 4.00), 345 (3.68). ν_{max} (Nujol)/cm^{-1} 3436, 1772, 1769, 1749, 1671, 1656, 1589, 1274, 1184. ^{1}H NMR (600 MHz) δ 0.84 (3H, s, CH_3); 1.26 (3H, s, CH_3); 2.34 (1H, dd, 15.6, 16.8 Hz, H6); 2.43 (3H, s, 8-acetate); 2.47 (1H, d, 20.0 Hz, H4); 3.07 (1H, d, 20.00 Hz, H4); 3.22 (1H, dd, 6.6, 16.8 Hz, H6); 4.15 (1H, br d, 4.2 Hz, 2-OH); 4.30 (1H, d, 4.2 Hz, H2); 4.44 (1H, ddd, 6.0, 6.6, 15.6 Hz, H5); 5.58 (1H, d, 6.0 Hz, 5-OH); 7.37 (1H, dd, 1.2, 7.8 Hz, H9); 7.77 (1H, t, 7.8 Hz, H10); 7.93 (1H, dd, 1.2, 7.8 Hz, H11). ^{13}C NMR (150 MHz) δ 18.34 (CH_3); 20.12 ($COCH_3$); 26.85 (CH_3); 27.76 (C6); 37.85 (C4); 39.00 (C3); 66.62 (C5); 78.91 (C2); 122.23 (C7a); 123.74 (C11); 124.52 (C12b); 128.28 (C9); 133.56 (C11a); 133.76 (C10); 137.44 (C6a); 141.20 (C12a); 148.26 (C8); 165.98 (C4a); 168.21 (CO acetate); 179.86 (C12); 180.67 (C7); 196.03 (C1). *m*/*z* 396 ($M^{+\bullet}$, 2%); 378 [−(H_2O), 9]; 336 [−(H_2O + CH_2CO), 61]; 318 [−(H_2O + CH_2CO + H_2O), 42]; 290 [−(H_2O + CH_2CO + H_2O + CO), 43]; 264 [−(H_2O + CH_2CO + C_4H_8O), 100].

2-Acetoxy-5-hydroxy-3,3-dimethyl-1,7,12-trioxo-1,2,3,4,5, 6, 7,12-octahydrobenzo[*a*]anthracen-8-yl acetate (9). Crystallised from chloroform–diethyl ether (1 : 1) as light orange crystals (74 mg, purified yield from **6** 22%), mp 164–166 °C. Product **8** oxidises in the air and should be stored at −20 °C under nitrogen. Found: C, 65.5; H, 5.1%; $C_{24}H_{22}O_8$ requires C, 65.75; H, 5.1%. λ_{max}/nm (log ε/mol^{-1} dm^3 cm^{-1}) 249 (4.08), 280 (shoulder, 3.81), 345 (3.46). ν_{max} (Nujol)/cm^{-1} 3474, 1770, 1733, 1689, 1650, 1640, 1587, 1243, 1193. ^{1}H NMR (600 MHz) δ 1.01 (3H, s, CH_3, 8-acetate); 2.24 (3H, s, CH_3, 2-acetate); 2.40 (1H, dd, 11.4, 16.8 Hz, H6); 2.43 (3H, s, CH_3, 8-acetate); 2.58 (1H, br d, 20.2 Hz, H4); 2.81 (1H, d, 5.4 Hz, 5-OH); 3.07 (1H, d, 20.2 Hz, H4); 3.23 (1H, dd, 7.0, 16.8 Hz, H6); 4.59 (1H, ddd, 5.4, 7.0, 11.4 Hz, H5); 5.43 (1H, s, H2); 7.27 (1H, dd, 1.2, 7.8 Hz, H9); 7.65 (1H, 7.8 Hz, H10); 7.91 (1H, dd, 1.2, 7.8 Hz, H11). ^{13}C NMR (600 MHz GHMQC) δ 20.70 (CH_3); 20.74 ($COCH_3$); 21.09 ($COCH_3$); 27.48 (CH_3); 28.76 (C6); 38.30 (C4); 39.42 (C3); 68.17 (C5); 80.96 (C2); 122.92 (C7a); 125.28 (C11); 126.79 (C12b); 129.02 (C9); 134.34 (C11a); 134.80 (C10); 138.35 (C6a); 142.74 (C12a); 149.10 (C8); 163.22 (C4a); 169.54 (CO acetate); 170.52 (CO acetate); 180.43 (C12); 181.63 (C7); 190.41 (C1). *m*/*z* 438 ($M^{+\bullet}$, 1%); 396 [−(CH_2CO), 25]; 378 [−($C_2H_4O_2$), 24]; 360 [−($C_2H_4O_2$ + H_2O), 20]; 336 [−($C_2H_4O_2$ + CH_2CO), 100], 318 [−($C_2H_4O_2$ + CH_2CO + H_2O), 62].

2,8-Dihydroxy-3,3-dimethyl-1,7,12-trioxo-1,2,3,4,7,12-hexahydrobenzo[*a*]anthracene 4

From 6. The bis-epoxide **6** (100 mg) was dissolved in acetic acid (glacial, 10 cm^3) containing sulfuric acid (98%, 0.2 cm^3), then stirred for 2 h at 20 °C, cooled to 0 °C, diluted with diethyl ether (100 cm^3), neutralised with aqueous sodium hydroxide (20%, 35 cm^3), the organic layer separated, washed with water (2 × 50 cm^3), then the solvent removed *in vacuo*. Tetrahydrofuran (30 cm^3) was added, followed by aqueous sodium hydroxide (20%, 5 cm^3) and the mixture stirred at 20 °C for 3 h. The mixture was cooled to 0 °C, aqueous hydrogen chloride (10%, 50 cm^3) was added, followed by water (50 cm^3), the extract dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was crystallised from hot ethanol–methanol (1 : 1) as fine orange crystals (38 mg, 45%), mp 172 °C with decomposition. $M^{+\bullet}$ = 336.0991; $C_{20}H_{16}O_5$ requires 336.0997. λ_{max}/nm (log ε/mol^{-1} dm^3 cm^{-1}) 265 (3.96), 400 (3.21). ν_{max} (Nujol)/cm^{-1} 3440, 1693, 1666, 1633, 1589, 1348, 1284. ^{1}H NMR (300 MHz) δ 0.78 (3H, s, CH_3); 1.35 (3H, s, CH_3); 2.95 (1H, d, 17.4 Hz, H4); 3.21 (1H, d, 17.4 Hz, H4); 3.88 (1H, br s, 2-OH); 4.65 (1H, s, H2); 7.29 (1H, t, 3.9 Hz, H10); 7.57 (1H, d, 7.8 Hz, H5); 7.68 (2H, br d, 3.9 Hz, H9, H_{11}); 8.36 (1H, d, 7.8 Hz, H6); 12.22 (1H, s, 8-OH). ^{13}C NMR (75 MHz) δ 18.49 (CH_3); 27.52 (CH_3); 42.38 (C3); 43.34 (C4); 80.89 (C2); 115.04; 119.28; 123.44; 129.88; 132.87; 133.32; 133.56; 134.94; 136.90; 149.36; 163.81 (8-OH); 182.50; 186.91; 198.78. *m*/*z* 336 [($M^{+\bullet}$), 45%]; 318 [−(H_2O), 20]; 290 [−(H_2O + CO), 30]; 264 [−(C_4H_8O), 100]; 236 [−(C_4H_8O + CO), 15].

From 8 and/or 9. The required product **4** can be produced from either **8** or **9** by the same procedure as that used from **6** above. The crude yield from both procedures is greater than 90%, the purified yield (after crystallisation), 80–85%.

X-Ray structure determination¶

A full sphere of 'low temperature' CCD area-detector diffractometer data was measured (Bruker AxS instrument, *T ca.* 153 K; ω-scans, $2\varphi_{max}$ = 75°; monochromatic Mo Kα radiation, λ = 0.71073 Å) yielding 40562 total reflections, merging to 10667 (R_{int} = 0.036) after 'empirical'/multiscan absorption correction (proprietary software), 6875 with $F > 4\sigma(F)$ considered 'observed' and used in the full matrix least squares refinement, refining non-hydrogen atom anisotropic displacement parameters and (x, y, z, U_{iso})$_H$. Conventional residuals R, R_w on |F| at convergence were 0.030, 0.028; neutral atom complex scattering factors were employed within the Xtal 3.7 program system.[12] Pertinent results are given in Fig. 1, Table 1, and the .cif deposition.§ $C_{24}H_{23}BrO_6$, M = 487.4, monoclinic, space group $P2_1/c$ (C^5_{2h}, No. 14), a = 8.8741(4), b = 20.104(1), c = 12.2989(6) Å, β = 101.637(1)°, V = 2149.0 Å^3, Dc (Z = 4) = 1.50$_6$ g cm^{-3}, μ_{Mo} = 19.5 cm^{-1}; specimen: 0.30 × 0.25 × 0.20 mm. T_{min}, T_{max} = 0.71, 0.80.

¶ CCDC reference number 159020. See http://www.rsc.org/suppdata/pl/b1/b101756j/ for crystallographic files in .cif or other electronic format.

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