The synthesis of 1,8-dihydroxynaphthalene-derived natural products: palmarumycin CP_1, palmarumycin CP_2, palmarumycin C_{11}, CJ-12,371, deoxypreussomerin A and novel analogues

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Received (in Glasgow) 22nd January 1999, Accepted 9th February 1999

Total syntheses of the title fungal metabolites are described *via* a route which utilises initial acetalisation with 1,8-dihydroxynaphthalene followed by elaboration of the ring A functionality. Novel analogues are also reported. Structural clarification is provided for palmarumycin C_{11}, bipendensin and Sch 53,823.

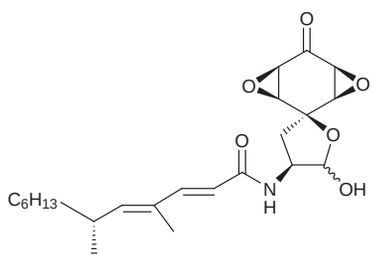
The isolation of MK3018 **1** in 1989[1] and bipendensin **2** in 1990[2] introduced a new family of bioactive natural products based on a 1,8-dihydroxynaphthalene derived spiroacetal unit linked to a second, oxidised naphthalene moiety. Subsequently, a number of related compounds have been isolated, some of which are illustrated in Fig. 1.[3–5] These compounds exhibit an elaborate range of hydroxylation/unsaturation patterns and include bis-epoxides such as **13**–**16**. The preussomerins (*e.g.* **17**–**20**), first described in 1990,[6] are a closely related, though structurally more complex, group of fungal metabolites in which both naphthalene rings are more highly oxygenated.

The compounds illustrated in Fig. 1 are of obvious interest from a structural viewpoint, but they also have a range of potentially useful biological properties. Thus, the palmarumycins, the largest group with *ca.* twenty members, isolated from the endophytic fungus *Coniothyrium palmarum* and a related *Coniothyrium* species, were shown to possess antibacterial, antifungal and herbicidal activity.[3a,b] CJ-12,371 **11** and CJ-12,372 **12** are closely related structurally and are DNA gyrase inhibitors.[4] The Schering-Plough compounds **2** and **4** are phospholipase D inhibitors,[3c] and diepoxin ζ **15**[3b] exhibits antibiotic, antifungal and antitumour activities. The preussomerins (*e.g.* **17**–**20**),[6] isolated from the coprophilous fungus *Preussia isomera* and the endophytic fungus *Harmonema dematioides*, act as novel inhibitors of *ras* farnesyltransferase, and thus are of interest in terms of their potential in cancer chemotherapy.[7]

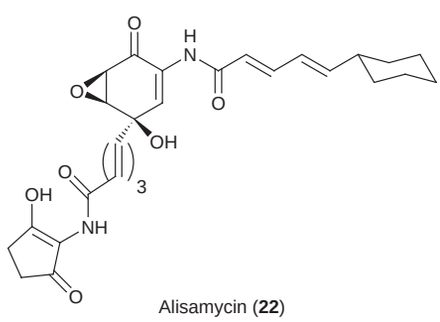
We became interested in these dihydroxynaphthalene natural products as part of our ongoing programme to prepare novel epoxycyclohexanone antibiotics (*e.g.* aranorosin **21**[8]) and *ras* farnesyltransferase inhibitors (*e.g.* alisamycin **22**[9] and manumycin A **23**[10]) for biological screening.

When we commenced our research in the dihydroxynaphthalene natural product area, there were no publications on any aspect of their synthesis. In view of our experience with the application of electrochemical and chemical oxidative cyclisation procedures to natural product synthesis,[8] we initially investigated the use of these methods for the construction of the key dihydroxynaphthalene unit.[11] During the course of this study, however, Krohn *et al.*[12] reported the isolation of *Coniothyrium* metabolite **24** and its silver oxide mediated cyclisation to generate the non-natural spirocyclic 1,8-dihydroxynaphthalene acetal **25** in a putative biomimetic procedure [Scheme 1(a)]. Subsequently, Wipf *et al.* utilised a similar route, with bis-(acetoxy)iodobenzene as the oxidant, to prepare palmarumycin CP_1 **5** and deoxypreussomerin A **3** [Scheme 1(b)].[13]

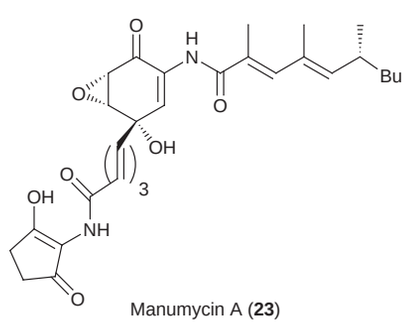
We therefore turned our attention to a route in which the dihydroxynaphthalene derived spiroacetal unit is introduced at the start of the synthetic route.[14] This paper describes full details of this research, including the syntheses of palmarumycin CP_1 **5**, palmarumycin CP_2 **6** and CJ-12,371 **11** reported in the preliminary communication,[14] and additionally includes the extension of the synthetic route to prepare palmarumycin C_{11} **2** and palmarumycin C_2/deoxypreussomerin A **3**. Barrett *et al.* recently reported[15] the total syntheses of palmarumycin CP_1 and CP_2, and CJ-12,371 using similar methodology.



Aranorosin (**21**)



Alisamycin (**22**)



Manumycin A (**23**)

Results and discussion

In view of the paucity of information concerning 1,8-dihydroxy-

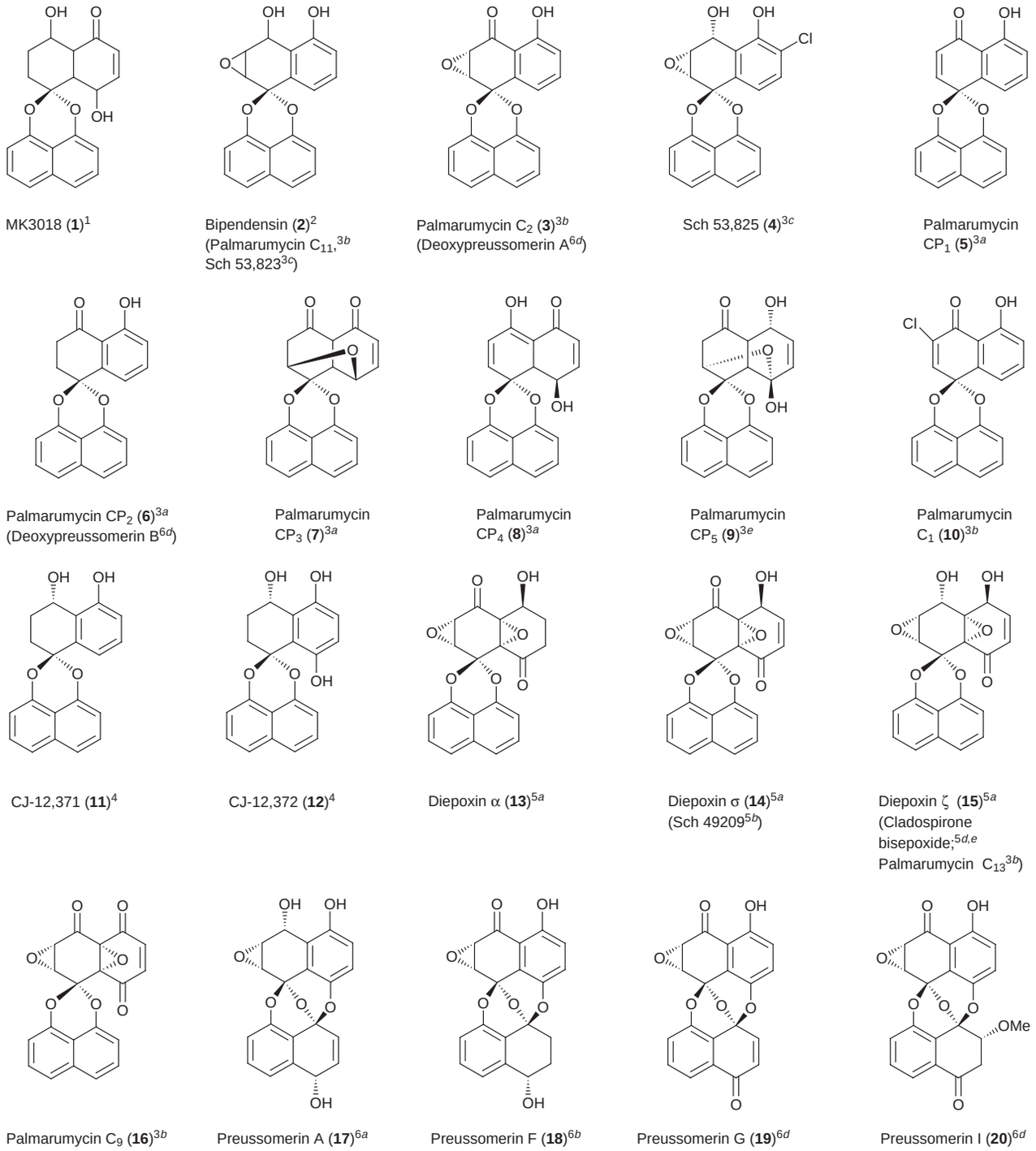
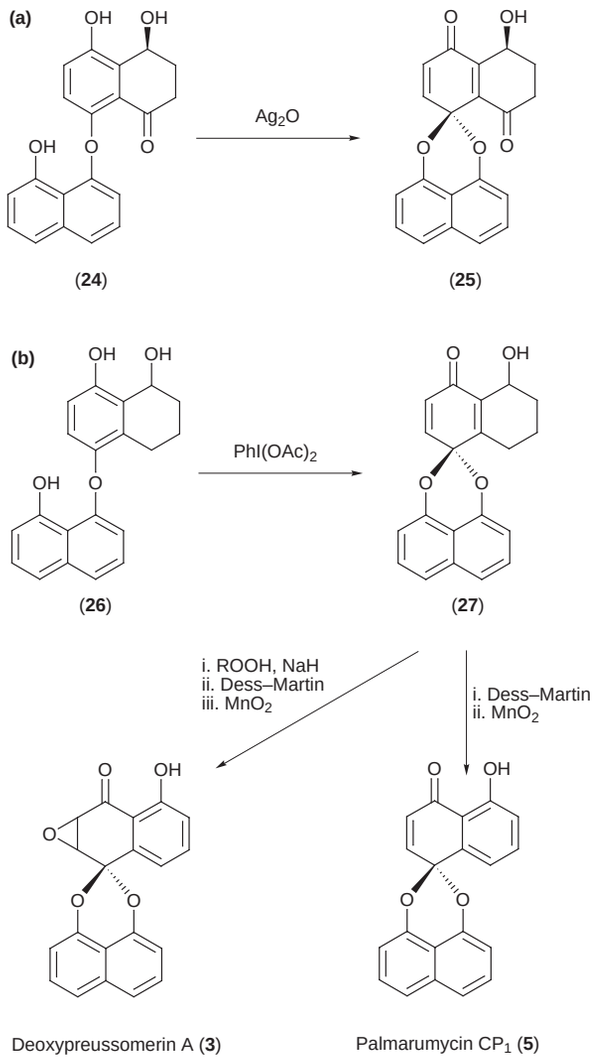


Fig. 1 Structures of compounds **1**–**20**.

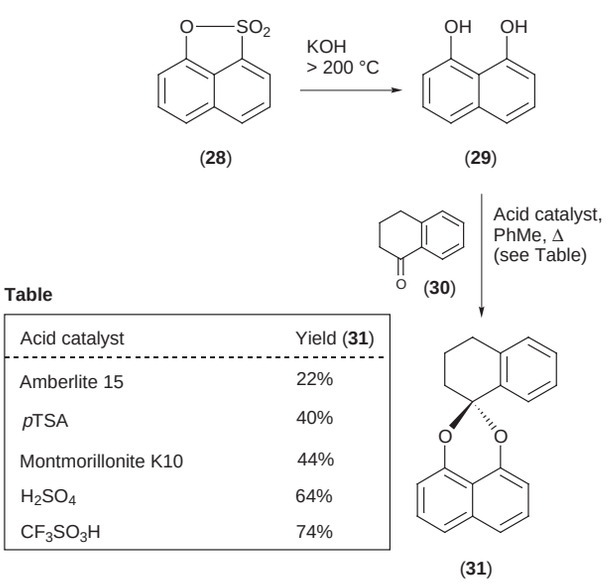
naphthalene derived acetals in the synthetic literature[16] we first carried out the model studies shown in Scheme 2.[14]

There are numerous procedures for the conversion of commercially available 1,8-naphthosultone **28** into diol **29** in the recent literature but, in our hands, the most efficient procedure is that described by Erdmann in 1888[17] which allows multigram quantities to be prepared in good yield (86% on a 10 g scale). The reaction between diol **29** and tetralone (3,4-dihydronaphthalen-1(2*H*)-one) **30** to give spiroacetal **31** proved to be surprisingly difficult and forcing conditions were required (see Table in Scheme 2). The optimum procedure required treatment with 0.2 equivalents of triflic or concentrated sulfuric acid in refluxing toluene until the reaction was complete (*ca.* 3 days). The ^{13}C-NMR spectrum of **31** showed the characteristic acetal carbon at 100.5 ppm. This study established for the first time that 1,8-dihydroxynaphthalene-derived acetals can be prepared by ketone acetalisation.

We were then in a position to utilise this method to prepare natural products (Scheme 3). Commercially available 5-methoxytetralone **32** was converted into spiroacetal **33** in good yield using the conditions described above. Benzylic oxidation was achieved using excess pyridinium dichromate and *tert*-butyl hydroperoxide (*t*BHP)[18a] giving **34** in 64% yield (93% based on recovered starting material). Related oxidative procedures (*e.g.* pyridinium chlorochromate,[18b] benzeneseleninic anhydride,[18c] potassium persulfate[18d]) were also attempted but without success. Direct dehydrogenation of **34** to **35** was achieved in 64% yield by treatment with benzeneseleninic anhydride[19] in the presence of sodium bicarbonate (to prevent acetal hydrolysis). The same transformation could also be accomplished *via* the



Scheme 1



Table

Acid catalyst	Yield (**31**)
Amberlite 15	22%
*p*TSA	40%
Montmorillonite K10	44%
H_2SO_4	64%
CF_3SO_3H	74%

Scheme 2

more traditional α-carbonyl selenation–oxidative elimination sequence (33% yield over 2 steps). Demethylation of **34** and **35** was accomplished using boron tribromide to produce palmarumycin CP_2 **6** and CP_1 **5**, respectively. In the latter case vinyl bromide **36** was obtained as a byproduct: this is the bromo analogue of palmarumycin C_1 **10**. The authenticity of **5** and **6** was confirmed by comparison of their NMR data with those reported [*e.g.* CP_1: δ_H ($CDCl_3$) 6.37 (1 H, d, *J* 10.5 Hz, H-3), 7.03 (1 H, d, *J* 10.5 Hz, H-2); lit.,[3a] δ_H ($CDCl_3$) 6.36 (1 H, d, *J* 10.6 Hz, H-3), 7.02 (1 H, d, *J* 10.4 Hz, H-2). CP_2: δ_H ($CDCl_3$) 2.50 (2 H, t, *J* 6.5 Hz, CH_2-2), 2.85 (2 H, t, *J* 6.5 Hz, CH_2-3); lit.,[3a] δ_H ($CDCl_3$) 2.49 (2 H, t, *J* 6.5 Hz, CH_2-2), 2.85 (2 H, t, *J* 6.5 Hz, CH_2-3)].

We next investigated reductive processes to access CJ-12,371 **11** (Scheme 4). Sodium borohydride reduction of **34** proceeded quantitatively but attempted demethylation of alcohol **37** using boron tribromide resulted in ring A aromatisation and acetal cleavage to give **38a**. The use of sodium ethanethiolate did give a low yield of **11** but the cleavage product **38b** was obtained in a similar amount. (±)-CJ-12,371 **11** was eventually obtained in quantitative yield by reduction of palmarumycin CP_2 **6** with sodium borohydride [δ_C (DMSO-d_6) 60.9 (C-4), 100.0 (C-1). Lit.,[4] δ_C (DMSO-d_6) 61.0 (C-4), 100.0 (C-1)].

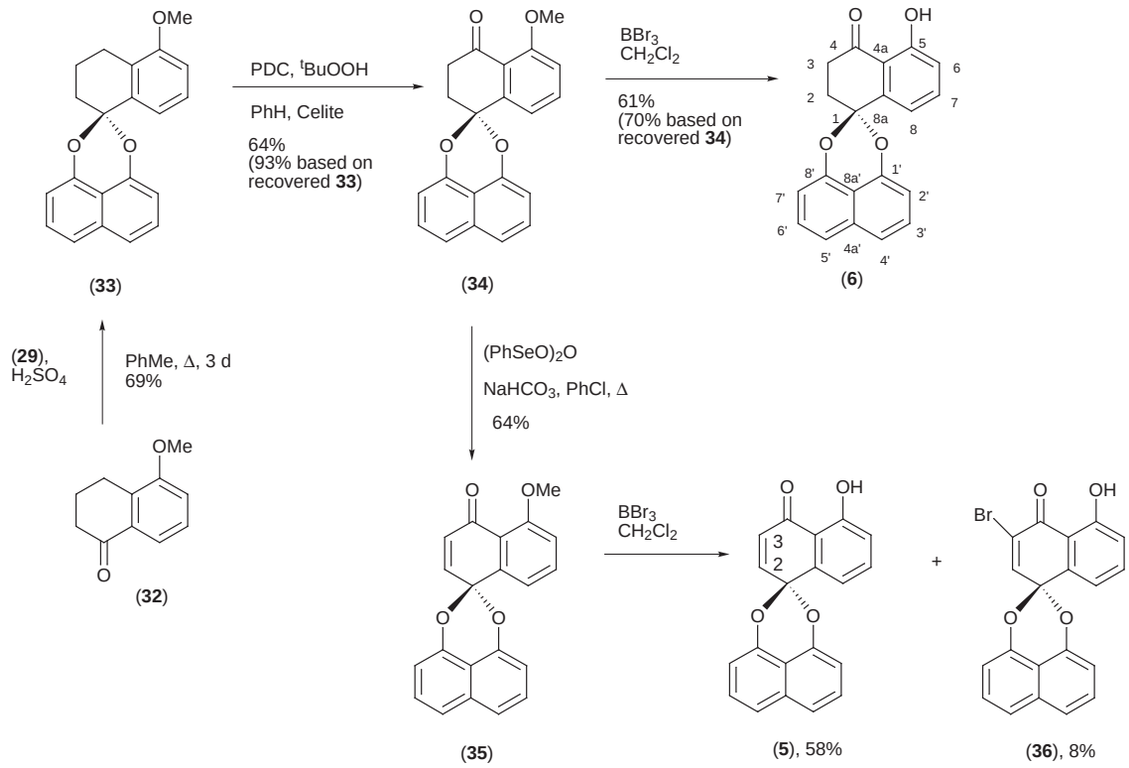
We were also able to utilise palmarumycin CP_1 **5** to prepare deoxypreussomerin A **3** and palmarumycin C_{11} *syn*-**2** (Scheme 5). Epoxidation of enone **5** was unsuccessful using H_2O_2–NaOH in aqueous methanol. However, we were pleased to find that epoxidation could be achieved using *t*BHP and 1,5,7-triazabicyclo[4.4.0]dec-5-ene[20] to give deoxypreussomerin A (palmarumycin C_2) **3** in 53% yield. This is the first report of the successful epoxidation of the palmarumycin nucleus. The authenticity of deoxypreussomerin A **3** was established by full characterisation and comparison of spectroscopic data with those published [*e.g.* δ_C ($CDCl_3$) 196.5 (C-4), 53.2 (C-2,3); lit.,[3b] δ_C ($CDCl_3$) 196.5 (C-4), 53.2 (C-2,3)].

Reduction of deoxypreussomerin A **3** was achieved using sodium borohydride to give a single diastereomeric product. The borohydride reduction of a keto epoxide such as **3** would be expected[9] to give a predominance of the *syn*-hydroxy epoxide. Indeed, the product displayed NMR data entirely consistent with palmarumycin C_{11} *syn*-**2** [δ_H ($CDCl_3$) 3.87 (1 H, d, *J* 4.4 Hz, H-2), 3.74 (1 H, dd, *J* 4.4, 2.5 Hz, H-3); δ_C ($CDCl_3$) 66.6 (C-4); lit.,[3b] δ_H ($CDCl_3$) 3.87 (1 H, d, *J* 4.4 Hz, H-2), 3.74 (1 H, dd *J* 4.4, 2.7 Hz, H-3); lit.,[3b] δ_C ($CDCl_3$) 66.7 (C-4)]. The *syn*-hydroxy-epoxide stereochemistry of palmarumycin C_{11} was tentatively proposed by Krohn *et al.*[3b] and our synthesis adds further support to this assignment.

Connolly *et al.*[2] and Chu *et al.*[3c] have also reported the isolation of **2** from natural sources, but at first sight it would appear that the NMR data for these compounds are different to each other and different to those reported for palmarumycin C_{11} (*syn*-**2**).[3b] Professor Connolly kindly provided copies of the original NMR spectra (recorded in $CDCl_3$–DMSO-d_6) and it is clear that, if these are referenced to take the mixed solvent system into account, the data correspond well to those reported by Chu *et al.*[3c] (in DMSO-d_6). This NMR comparison confirms that bipendensin and Sch 53,823 possess the same relative stereochemistry, although the specific rotation of bipendensin was not reported and so they may be enantiomeric. It is also clear that they differ from palmarumycin C_{11}: the ^{13}C-NMR signal for C-4 is particularly diagnostic [lit.,[3c] δ_C (DMSO-d_6) for Sch 53,823, 58.5 ppm; *syn*-**2** δ_C (DMSO-d_6) 65.0].

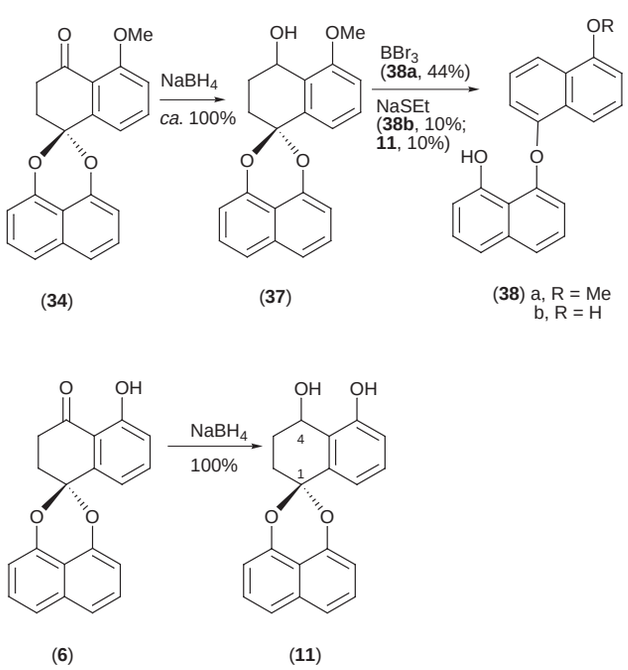
If the arguments concerning the likely *syn*-stereoselectivity of the reduction of **3** to give **2** are correct, then bipendensin and Sch 53,823 must have the *anti*-hydroxy-epoxide structure. We were concerned, however, that the hydride reduction of **3** could only be achieved using borohydride, and thus the assignment was based on a single piece of evidence. We also debated whether the presence of the unprotected phenolic group in **3** might influence the stereoselectivity of the reduction reaction. We therefore prepared the corresponding methyl ether **39** and investigated its reduction reactions to obtain additional information (Scheme 6).

Epoxidation of enone **35** proceeded smoothly to give ketone **39**. Reduction of epoxy ketone **39** with Super-Hydride® ($LiEt_3BH$) gave two inseparable products (99%, **40**:**41** = 3.6:1).



Scheme 3

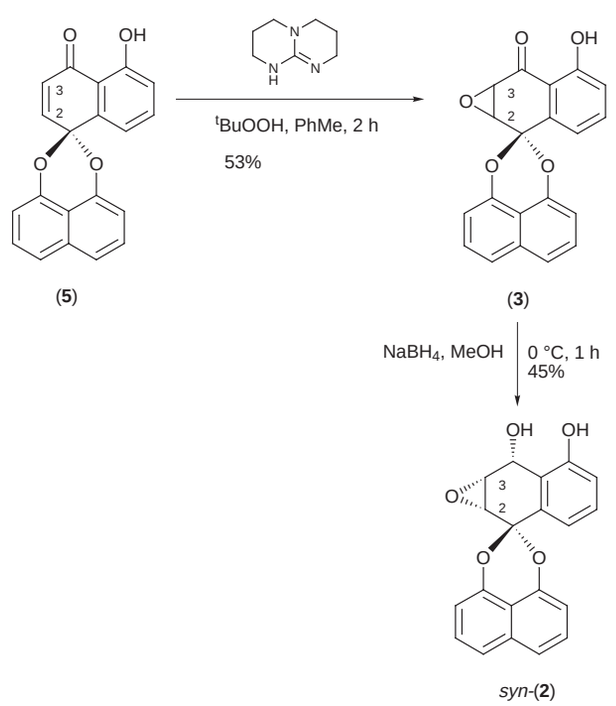
The predominant product **40** would be expected [10] to be the *syn*-hydroxy-epoxide on steric grounds. In addition, DIBAL-H would be expected [21] to reduce epoxy ketone **39** to give a predominance of the *anti*-hydroxy-epoxide **41**, and the major product formed from this reaction (84%, *ca.* 95:5) corresponded to the minor isomer from the Super-Hydride® reaction (attempts to demethylate **41** were unsuccessful). The ^{13}C-NMR data for **40** and **41** were also consistent [δ_C ($CDCl_3$) **40**, 64.2 ppm (C-4); δ_C ($CDCl_3$) **41**, 61.3 ppm (C-4)].



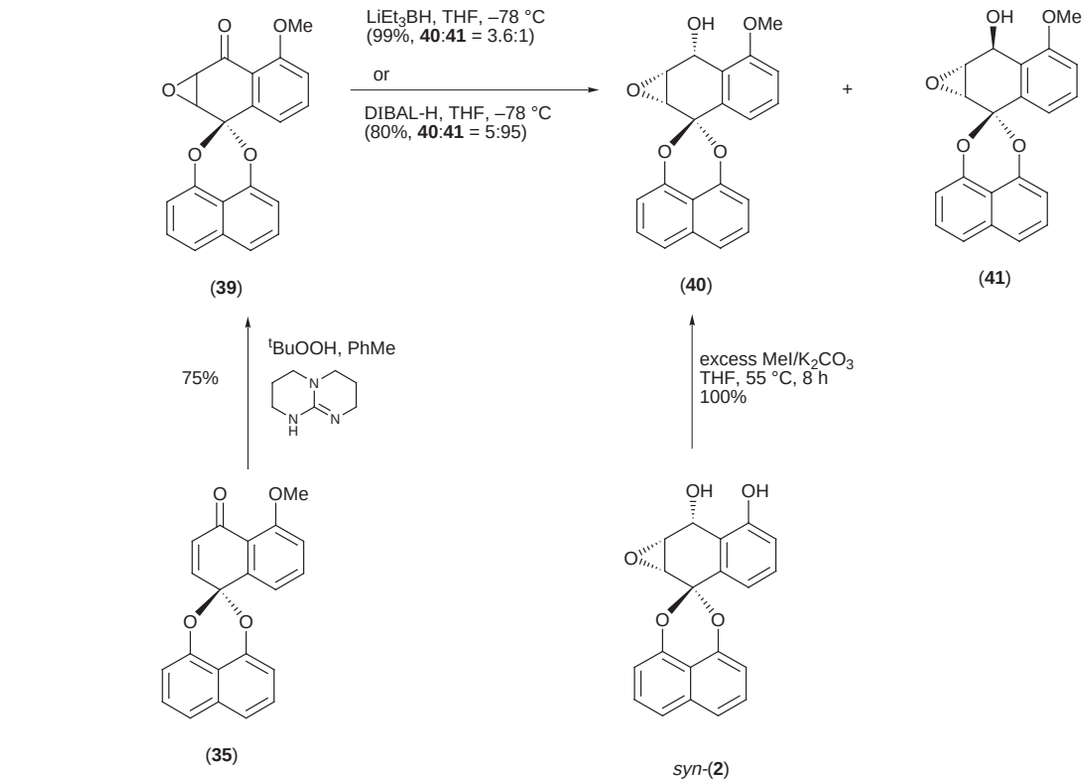
Scheme 4

Finally, *syn*-**2**, produced by direct reduction of deoxypreussomerin A **3**, was methylated in quantitative yield to produce **40**. All of these results give added support to the natural product structures proposed above. It should be noted, however, that Chu *et al.* carried out NOESY studies on a derivative of Sch 53,825 **4**, a co-metabolite of Sch 53,823 **2**, which appeared to confirm a *syn*-hydroxy-epoxide arrangement for **4**. Further studies are therefore needed to completely resolve this structural uncertainty.

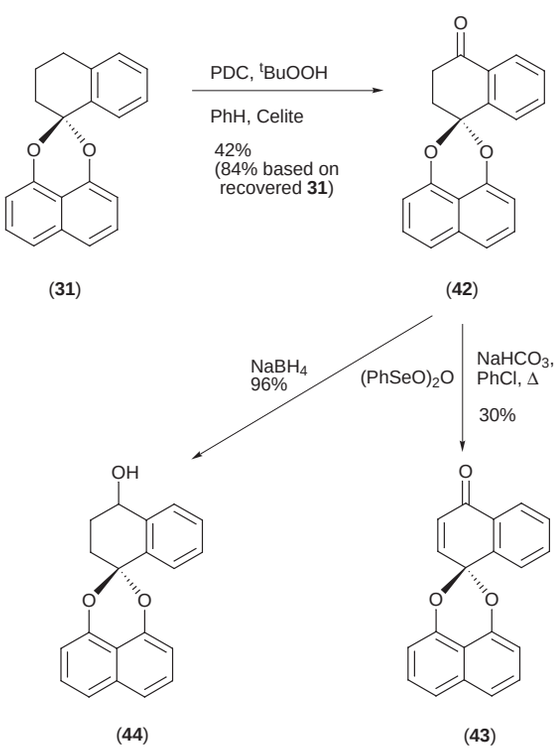
The chemistry described above is extremely straightforward and can be used for the preparation of a range of novel analogues simply by variation of the ketone starting material. Thus, using similar methodology, tetralone **31** was converted into the deoxy-ring B palmarumycin analogues **42**–**44** (Scheme 7).



Scheme 5



Scheme 6



Scheme 7

We are currently developing asymmetric reduction and epoxidation procedures for use in this programme and utilising these with the methodology described above to prepare the other natural products shown in Fig. 1 in enantiomerically pure form.

Experimental

NMR spectra were recorded on JEOL GX-270 or Bruker AMX 500 instruments. Tetramethylsilane (TMS) or $CDCl_3$–$CHCl_3$ was used as the internal standard and *J* values are in Hz. Carbon spectra were verified using DEPT experiments. Melting points were recorded on an Electrothermal IA9100 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer; deposited samples were prepared by dissolving solids in a small volume of $CHCl_3$ and forming a thin film on a NaCl plate by allowing the solvent to evaporate. Ultraviolet (UV) spectra were recorded on a Hewlett Packard 8453 instrument. Low resolution electron impact (EI) mass spectra were recorded on a Kratos MS 25 spectrometer. Chemical ionisation (CI) and high resolution mass spectra were recorded on a Micromass Autospec spectrometer. Elemental analyses were carried out at the University of Newcastle. Chromatography is medium pressure flash column chromatography and was performed using ICN silica gel (32–63) or Matrex silica gel 60 (70–200) using the eluant specified. Preparative TLC was carried out using pre-prepared plates (Merck silica gel 60 F-254, 5715). PE is petroleum ether (bp 40–60 °C), DCM is dichloromethane, EtOAc is ethyl acetate, ether is diethyl ether, THF is tetrahydrofuran and DMF is dimethylformamide. Where necessary, ether and THF were distilled from sodium–benzophenone ketyl, and DCM from calcium hydride, immediately before use. Except where specified, all reagents were purchased from commercial sources and were used without further purification. RT is room temperature. The numbering system used is shown on structure **6** in Scheme 3.

1,8-Dihydroxynaphthalene (29)

Commercially available 1,8-naphthosultone (**28**) (10 g, 0.048 mol) and KOH (41 g, 0.73 mol) were heated together in a stainless steel beaker at 300 °C with a Bunsen burner, and the temperature was kept at 300 °C (internal temperature) for 30 min until the mixture became a homogeneous black liquid. It was then cooled down to RT and hydrochloric acid (conc. HCl–H_2O, 1 : 2) added with stirring until neutral pH was obtained. Water (*ca.* 400 mL) was added followed by EtOAc (200 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*.

The dark oily residue was purified by chromatography (EtOAc–PE, 1:9) to obtain 1,8-dihydroxynaphthalene **29** (6.7 g, 86%) as a white solid, mp 141–142 °C (lit.,[17] mp 141–142 °C); R_f 0.63 (EtOAc–PE, 1:1); ν_{max} (deposited)/cm^{-1} 3153, 1612, 1408, 1282, 1032 and 814; δ_H (500 MHz; $CDCl_3$) 7.92 (2 H, br s, 2-OH), 7.36 (2 H, dd, *J* 0.8 and 8.4, H-4, H-5), 7.28 (2 H, br t_{app}, *J ca.* 8.0, H-3, H-6), 6.80 (2 H, dd, *J* 0.8 and 7.5, H-2, H-7); δ_C (125 MHz; $CDCl_3$) 152.5 (C-1, C-8), 137.0 (C-4a), 126.7 (C-3, C-6), 120.5 (C-4, C-5), 114.5 (C-8a), 109.3 (C-2, C-7).

1,2,3,4-Tetrahydrospiro[naphthalene-1,2′-naphtho[1,8-*de*][1,3]-dioxine] (31)

A mixture of diol **29** (150 mg, 0.936 mmol), commercially available 1-tetralone (**30**) (125 μL, 137 mg, 0.94 mmol) and degassed toluene (20 mL) was heated under Dean–Stark conditions for *ca.* 15 min until a small amount of solvent (*ca.* 5 mL) had been collected. The mixture was cooled to 60 °C and triflic acid (28 mg, 0.187 mmol) added. The mixture was heated under Dean–Stark conditions and monitored by TLC until completion (3 d). Triethylamine (a few drops) was then added to the cooled mixture. Evaporation of the solvent and purification by column chromatography (EtOAc–PE, 2:98) gave the *title compound* **31** (200 mg, 74%) as a white solid which was recrystallised from methanol to afford colourless crystals, mp 140–141 °C; R_f 0.39 (EtOAc–PE, 2:98); ν_{max} (deposited)/cm^{-1} 3058, 2957, 1633, 1606, 1585, 1411, 1381, 1272, 1126, 1066, 910, 822 and 756; δ_H (500 MHz; $CDCl_3$) 7.89 (1 H, dd, *J* 2.4 and 6.8, H-8), 7.51 (2 H, d, *J* 8.4, H-4′, H-5′), 7.45 (2 H, dd, *J* 7.4 and 8.4, H-3′, H-6′), 7.35–7.40 (2 H, m, H-6, H-7), 7.25 (1 H, dt, *J* 2.4 and 7.5, H-5), 6.95 (2 H, d, *J* 7.4, H-2′, H-7′), 2.94 (2 H, t, *J* 6.3, CH_2-2), 2.20 (2 H, m, CH_2-4), 1.95–1.98 (2 H, m, CH_2-3); δ_C (125 MHz; $CDCl_3$) 148.2 (C-1′, C-8′), 137.9, 135.2, 134.1, 129.4, 128.6, 127.5, 127.3 (C-3′, C-6′), 126.6, 120.2 (C-4′, C-5′), 113.6 (C-8a′), 109.2 (C-2′, C-7′), 100.5 (C-1), 30.9 (C-2), 29.3 (C-4), 19.6 (C-3); *m/z* (CI) 289 (MH^+, 100%) [HRMS (CI): calcd. for $C_{20}H_{17}O_2$, 289.12285. Found: MH^+, 289.12302 (0.6 ppm error)].

5-Methoxy-1,2,3,4-tetrahydrospiro[naphthalene-1,2′-naphtho-[1,8-*de*][1,3]dioxine] (33)

This compound was prepared as described for **31** using commercially available 5-methoxy-1-tetralone (**32**) (1.70 g, 9.65 mmol) and 4 drops of concentrated H_2SO_4 as the catalyst. After 3 d reflux, and purification by column chromatography (hexane–EtOAc, 10:1) the product was recrystallised from EtOAc–hexane to give the *title compound* **33** (2.1 g, 69%) as grey micro-needles, mp 149–150 °C (Found: C, 79.07; H, 5.75. $C_{21}H_{18}O_3$ requires C, 79.21; H, 5.70%); R_f 0.36 (EtOAc–PE, 1:9); ν_{max} (deposited)/cm^{-1} 2939, 1606, 1471, 1412, 1379, 1329, 1273, 1261 and 1063; δ_H (500 MHz; $CDCl_3$) 7.51 (1 H, dd, *J* 0.8 and 8.0, H-8), 7.50 (2 H, dd, *J* 0.8 and 8.4, H-4′, H-5′), 7.44 (2 H, dd, *J* 7.4 and 8.4, H-3′, H-6′), 7.35 (1 H, t, *J* 8.0, H-7), 6.94 (2 H, dd, *J* 0.8 and 7.4, H-2′, H-7′), 6.93 (1 H, dd, *J* 0.8 and 8.0, H-6), 3.89 (3 H, s, OMe), 2.82 (2 H, t, *J* 6.4, CH_2-2), 2.16–2.13 (2 H, m, CH_2-4), 1.96–1.92 (2 H, m, CH_2-3); δ_C (125 MHz; $CDCl_3$) 156.6 (C-5), 148.2 (C-1′, C-8′), 136.2 (C-8a), 134.1 (C-4a′), 127.4 (C-4a), 127.3 (C-3′, C-6′), 127.0 (C-7), 120.1 (C-4′, C-5′), 119.1 (C-6), 113.6 (C-8a′), 110.3 (C-8), 109.2 (C-2′, C-7′), 100.5 (C-1), 55.5 (OMe), 30.3 (C-2), 23.0 (C-4), 18.7 (C-3); *m/z* (CI) 319 (MH^+, 100%) [HRMS (CI): calcd. for $C_{21}H_{19}O_3$, 319.13342. Found: MH^+, 319.13330 (1.2 ppm error)].

2,3-Dihydro-5-methoxyspiro[naphthalene-1(4*H*),2′-naphtho-[1,8-*de*][1,3]dioxin]-4-one (34)

To a stirred solution of **33** (260 mg, 0.82 mmol) and Celite (1.5 g) in benzene (10 mL) at 10 °C was added pyridinium dichromate (0.77 g, 2.05 mmol) followed by the slow (5 min) addition of a 5.0–6.0 M solution of *t*BHP in decane (0.45 mL). After 15 min at 10 °C, the mixture was stirred at RT overnight. TLC showed clean but incomplete conversion. The mixture was filtered though Celite and quenched with a saturated solution of sodium sulfite. Extraction with EtOAc, drying ($MgSO_4$) and evaporation of the solvent gave *ca.* 0.5 g of an orange oil which was purified by column chromatography (PE–EtOAc, 6:4) to yield 80 mg of starting material **33**, followed by the *title compound* **34** (175 mg, 64%, 93% based on recovered starting material) as a pale yellow solid, mp 126–128 °C (Found: C, 75.73; H, 4.78. $C_{21}H_{16}O_3$ requires C, 75.89; H, 4.85%); R_f 0.32 (EtOAc–PE, 4:6); ν_{max} (deposited)/cm^{-1} 3059, 2966, 2939, 2839, 1687, 1608, 1595, 1473, 1452, 1412, 1379, 1323, 1273, 1250, 1209, 1192 and 1060; δ_H (270 MHz; $CDCl_3$) 7.61 (1 H, t, *J* 8.0, H-7), 7.55 (1 H, dd, *J* 1.4 and 8.0, H-8), 7.50 (2 H, dd, *J* 1.0 and 8.5, H-4′, H-5′), 7.43 (2 H, br t_{app}, *J ca.* 8.0, H-3′, H-6′), 7.10 (1 H, dd, *J* 1.4 and 8.0, H-6), 6.95 (2 H, dd, *J* 1.0 and 7.4, H-2′, H-7′), 3.96 (3 H, s, OMe), 2.76 (2 H, t, *J* 6.8, CH_2-3), 2.46 (2 H, t, *J* 6.8, CH_2-2); δ_C (67.5 MHz; $CDCl_3$) 195.2 (C-4), 159.4 (C-5), 147.4 (C-1′, C-8′), 142.6 (C-8a), 134.7 (C-7), 134.0 (C-4a′), 127.4 (C-3′, C-6′), 120.8 (C-4a), 120.6 (C-4′, C-5′), 117.6 (C-8), 113.4 (C-6), 113.3 (C-8a′), 109.2 (C-2′, C-7′), 98.7 (C-1), 56.2 (OMe), 35.2 (C-3), 29.2 (C-2); *m/z* (CI) 333 (MH^+, 100%) [HRMS (CI): calcd. for $C_{21}H_{17}O_4$, 333.1127. Found: MH^+, 333.11198 (2.1 ppm error)].

5-Methoxyspiro[naphthalene-1(4*H*),2′-naphtho[1,8-*de*][1,3]-dioxin]-4-one (35)

Spiroacetal **34** (100 mg, 0.301 mmol) in chlorobenzene (2 mL) was added under nitrogen to a solution of benzeneseleninic anhydride (163 mg, 0.453 mmol) and $NaHCO_3$ (126 mg, 1.500 mmol) in chlorobenzene (4 mL) at RT. The mixture was stirred at reflux for 8 h. Evaporation of the solvent followed by column chromatography (PE–EtOAc, 6:4) afforded the *title compound* **35** (64 mg, 64%) as a yellow oil that crystallised on standing to give a yellow solid, mp 203–204 °C (Found: C, 76.45; H, 4.29. $C_{21}H_{14}O_3$ requires C, 76.36; H, 4.27%); R_f 0.34 (EtOAc–PE, 4:6); ν_{max} (deposited)/cm^{-1} 3057, 2939, 2839, 1673, 1642, 1607, 1595, 1473, 1455, 1412, 1378, 1328, 1272, 1257, 1117, 1086, 1060, 1042, 1003, 940, 821, 794, 757 and 732; δ_H (500 MHz; $CDCl_3$) 7.70 (1 H, br t_{app}, *J ca.* 8.0, H-7), 7.60 (1 H, d, *J* 7.8, H-8), 7.57 (2 H, d, *J* 8.4, H-4′, H-5′), 7.47 (2 H, br t_{app}, *J ca.* 8.0, H-3′, H-6′), 7.18 (1 H, d, *J* 8.4, H-6), 6.98 (2 H, d, *J* 7.5, H-2′, H-7′), 6.86 (1 H, d, *J* 10.5, H-2), 6.30 (1 H, d, *J* 10.5, H-3), 4.02 (3 H, s, OMe); δ_C (67.5 MHz; $CDCl_3$) 182.9 (C-4), 159.8 (C-5), 147.3 (C-1′, C-8′), 141.0 (C-8a), 135.1 (C-2), 134.9 (C-7), 134.1 (C-4a′), 132.1 (C-3), 127.5 (C-3′, C-6′), 121.1 (C-4′, C-5′), 120.1 (C-8), 118.9 (C-4a), 113.7 (C-6), 113.0 (C-8a′), 109.8 (C-2′, C-7′), 93.3 (C-1), 56.4 (OMe); *m/z* (CI) 331 (MH^+, 100%) [HRMS (CI): calcd. for $C_{21}H_{15}O_4$, 331.09703. Found: MH^+, 331.09678 (0.8 ppm error)].

Palmarumycin CP_2 (2,3-dihydro-5-hydroxyspiro[naphthalene-1-(4*H*),2′-naphtho[1,8-*de*][1,3]dioxin]-4-one) (6)

A solution of methyl ether **34** (30 mg, 0.09 mmol) in dry DCM (5 mL) under nitrogen was cooled to −78 °C and a 1.0 M solution of BBr_3 in DCM (60 μL, 0.06 mmol) was slowly added over 5 min. The mixture was stirred for 15 min at −78 °C and then 1 h at RT. The reaction was quenched by addition of 5% NaOH (1 mL) and then brine and EtOAc were added and the two layers were separated. The aqueous phase was extracted three times with EtOAc, and the combined organic layers were dried ($MgSO_4$). Evaporation of the solvents followed by column chromatography (hexane–EtOAc, 6:4) gave unreacted starting material **34** (4 mg), followed by palmarumycin CP_2 (**6**) (17.5 mg, 61%; 70% based on recovered starting material) as a colourless oil which solidified on standing to give a white solid which was recrystallised from DCM–PE to give white needles, mp 170 °C (decomp.) [lit.,[3a] mp 170 °C (decomp.)]; R_f 0.64 (EtOAc–PE, 4:6), 0.57 (DCM); λ_{max}(DCM)/nm 256 (ε/dm^3 mol^{-1} cm^{-1} 8974), 300 (9484), 314 (9572) and 328 (9817); ν_{max} (deposited)/

cm^{-1} 3057, 1643, 1608, 1585, 1455, 1411, 1378, 1348, 1330, 1271, 1116 and 1106; δ_H (500 MHz; $CDCl_3$) 12.45 (1 H, br s, Ar-OH), 7.63 (1 H, br t_{app}, *J ca.* 8.0, H-7), 7.54 (2 H, dd, *J* 0.8 and 8.4, H-4′, H-5′), 7.47 (2 H, dd, *J* 7.5 and 8.4, H-3′, H-6′), 7.46 (1 H, dd, *J* 1.1 and 7.6, H-8), 7.11 (1 H, dd, *J* 1.1 and 8.5, H-6), 6.98 (2 H, dd, *J* 0.8 and 7.5, H-2′, H-7′), 2.85 (2 H, t, *J* 6.5, CH_2-3), 2.50 (2 H, t, *J* 6.5, CH_2-2); δ_C (125 MHz; $CDCl_3$) 203.2 (C-4), 162.4 (C-5), 147.4 (C-1′, C-8′), 140.9 (C-8a), 137.2 (C-7), 134.2 (C-4a′), 127.5 (C-3′, C-6′), 120.9 (C-4′, C-5′), 119.6 (C-8), 116.7 (C-6), 115.4 (C-4a), 113.3 (C-8a′), 109.4 (C-2′, C-7′), 98.4 (C-1), 34.1 (C-3), 29.4 (C-2); *m*/*z* (CI) 319 (MH^+, 100%) [HRMS (CI): calcd. for $C_{20}H_{15}O_4$, 319.09703. Found: MH^+, 319.09723 (0.6 ppm error)].

Palmarumycin CP_1 (5-hydroxyspiro[naphthalene-1(4*H*),2′-naphtho[1,8-*de*][1,3]dioxin]-4-one) (5) and 3-bromo-5-hydroxyspiro[naphthalene-1(4*H*),2′-naphtho[1,8-*de*][1,3]dioxin]-4-one (36)

This reaction was carried out as described for the preparation of compound **6**. Starting with **35** (40 mg, 0.12 mmol) the reaction gave a mixture of two products which were separated by preparative TLC (DCM). The more polar fraction afforded palmarumycin CP_1 (**5**) (22 mg, 58%) as a yellow solid, mp 170 °C (decomp.) [lit.,[3a] mp 170 °C (decomp.)]; R_f 0.63 (EtOAc–PE, 4:6), 0.60 (DCM); λ_{max}(DCM)/nm 288 (ε/dm^3 mol^{-1} cm^{-1} 8452), 296 (8770), 312 (5902), 330 (5781) and 362 (4742); ν_{max} (deposited)/cm^{-1} 3059, 1662, 1608, 1456, 1412, 1378, 1346, 1268, 1239, 1114, 1075 and 944; δ_H (500 MHz; $CDCl_3$) 12.17 (1 H, br s, Ar-OH), 7.67 (1 H, br t_{app}, *J ca.* 8.0, H-7), 7.59 (2 H, dd, *J* 0.5 and 8.4, H-4′, H-5′), 7.48 (2 H, br t_{app}, *J ca.* 8.0, H-3′, H-6′), 7.47 (1 H, br d, *J* 7.5, H-8), 7.15 (1 H, dd, *J* 0.9 and 8.4, H-6), 7.03 (1 H, d, *J* 10.5, H-2), 6.99 (2 H, dd, *J* 0.5 and 7.6, H-2′, H-7′), 6.37 (1 H, d, *J* 10.5, H-3); δ_C (125 MHz; $CDCl_3$) 188.7 (C-4), 161.8 (C-5), 147.2 (C-1′, C-8′), 139.7 (C-2), 138.8 (C-8a), 136.6 (C-7), 134.1 (C-4a′), 129.7 (C-3), 127.6 (C-3′, C-6′), 121.3 (C-4′, C-5′), 119.7 (C-8), 119.3 (C-6), 113.8 (C-4a), 113.0 (C-8a′), 109.9 (C-2′, C-7′), 92.8 (C-1); *m*/*z* (EI) 316 (M^+, 100%), 288 ($M^+ - CO$, 20) and 287 ($M^+ - CHO$, 25) [HRMS (EI): calcd. for $C_{20}H_{12}O_4$, 316.07356. Found: M^+, 316.07390 (1.1 ppm error)].

The less polar fraction afforded the *bromide* **36** (4 mg, 8%) as a yellow powder, mp 179–180 °C (decomp.); R_f 0.80 (DCM); λ_{max}(DCM)/nm 258 (ε/dm^3 mol^{-1} cm^{-1} 4498), 286 sh (5730), 299 (6194), 314 (4416), 328 (3459) and 370 (3184); ν_{max} (deposited)/cm^{-1} 3059, 2924, 2850, 1651, 1609, 1584, 1455, 1411, 1379, 1347, 1271, 1228, 1169, 1068, 941 and 898; δ_H (500 MHz; $CDCl_3$) 11.90 (1 H, br s, Ar-OH), 7.70 (1 H, br t_{app}, *J ca.* 8.0, H-7), 7.62 (2 H, dd, *J* 1.0 and 8.4, H-4′, H-5′), 7.51 (2 H, dd, *J* 7.6 and 8.4, H-3′, H-6′), 7.47 (1 H, dd, *J* 1.0 and 7.6, H-8), 7.44 (1 H, s, H-2), 7.19 (1 H, dd, *J* 1.0 and 8.4, H-6), 7.01 (2 H, br d, *J* 7.6, H-2′, H-7′); δ_C (125 MHz; $CDCl_3$) 181.9 (C-4), 162.1 (C-5), 146.7 (C-1′, C-8′), 140.0 (C-2), 138.5 (C-8a), 137.2 (C-7), 134.2 (C-4a′), 127.7 (C-3′, C-6′), 127.1 (C-3), 121.7 (C-4′, C-5′), 120.0 (C-8), 119.7 (C-6), 112.8 (C-4a), 112.7 (C-8a′), 110.1 (C-2′, C-7′), 93.8 (C-1); *m*/*z* (CI) 397, 395 (MH^+, 100%) [HRMS (CI): calcd. for $C_{20}H_{13}O_4{}^{79}Br$ 394.99189. Found: MH^+, 394.99277 (2.2 ppm error)].

5-Methoxy-1,2,3,4-tetrahydrospiro[naphthalene-1,2′-naphtho-[1,8-*de*][1,3]dioxin]-4-ol (37)

Ketone **34** (50 mg, 0.15 mmol) was dissolved in methanol (2 mL) by gently warming the solution with an air gun. Sodium borohydride (3 mg, 0.08 mmol) was added to the gold yellow solution which turned pale yellow after 10 min. TLC showed a clean and complete conversion. EtOAc and water were added, the two layers were separated and the organic phase washed with water and brine, and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* yielded a colourless oil. Column chromatography (DCM–EtOAc, 8:2) afforded the *title compound* **37** (50 mg, 100%) as a white solid, mp >260 °C (decomp.); R_f 0.63 (DCM–EtOAc, 4:1); ν_{max} (deposited)/cm^{-1} 3573, 3444, 3057, 2956, 2937, 2839, 1607, 1594, 1411, 1380, 1328, 1272, 1061, 958, 820, 756 and 733; δ_H (500 MHz; $CDCl_3$) 7.56 (1 H, br d, *J* 7.8, H-8), 7.52 (2 H, dd, *J* 0.9 and 8.4, H-4′, H-5′), 7.46 (2 H, br t_{app}, *J ca.* 8.0, H-3′, H-6′), 7.44 (1 H, dd, *J* 7.8 and 8.2, H-7), 7.02 (1 H, br d, *J* 8.2, H-6), 6.98 (1 H, br d, *J* 7.4, H-2′ or H-7′), 6.92 (1 H, br d, *J* 7.4, H-2′ or H-7′), 5.20 (1 H, t, *J* 4.4, H-4), 3.96 (3 H, s, OMe), 3.10 (1 H, br s, OH), 2.36 (1 H, ddd, *J* 2.4, 11.3 and 13.9, H-2), 2.28–2.23 (1 H, m, H-2), 2.23–2.16 (1 H, m, H-3), 2.08–2.04 (1 H, m, H-3); δ_C (125 MHz; $CDCl_3$) 157.0 (C-5), 148.1 (C-1′ or C-8′), 147.8 (C-1′ or C-8′), 136.1 (C-8a), 134.1 (C-4a′), 129.3 (C-7), 127.8 (C-4a), 127.3 (C-3′ or C-6′), 127.2 (C-3′ or C-6′), 120.3 (C-4′ or C-5′), 120.2 (C-4′ or C-5′), 119.3 (C-8), 113.5 (C-8a′), 111.2 (C-6), 109.3 (C-2′ or C-7′), 109.1 (C-2′ or C-7′), 99.9 (C-1), 62.6 (C-4), 55.7 (OMe), 26.3 (C-3), 25.8 (C-2); *m*/*z* (EI) 334 (M^+, 20%), 316 (100) [HRMS (EI): calcd. for $C_{21}H_{18}O_4$, 334.12051. Found: M^+, 334.12030 (0.6 ppm error)].

CJ-12,371 (4,5-dihydroxy-1,2,3,4-tetrahydrospiro[naphthalene-1(4*H*),2′-naphtho[1,8-*de*][1,3]dioxine]) (11)

Palmarumycin CP_2 (**6**) (9 mg, 0.03 mmol) was dissolved in methanol (2 mL) by gently warming the solution with an air gun. Sodium borohydride (1 mg, 0.026 mmol) was added and after 10 min TLC showed a clean and complete conversion. EtOAc and water were added, the two layers were separated and the organic phase washed with water and brine, and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* yielded a colourless oil. Purification though a microcolumn (EtOAc) afforded the *title compound* (**11**) (9 mg, 100%) as a white solid, mp >260 °C (decomp.) [lit.,[4] mp >260 °C (decomp.)]; R_f 0.31 (PE–EtOAc, 6:4); ν_{max} (deposited)/cm^{-1} 3299, 3059, 3017, 2927, 2855, 1633, 1607, 1463, 1411, 1380, 1326, 1272, 1216, 1112, 1067, 1051, 1023, 957, 821, 794 and 756; δ_H (500 MHz; DMSO-d_6) 9.67 (1 H, br s, Ar-OH), 7.57 (1 H, br d, *J* 8.4, H-4′), 7.57 (1 H, br d, *J* 8.4, H-5′), 7.49 (1 H, br t_{app}, *J ca.* 8.0, H-3′), 7.47 (1 H, br t_{app}, *J ca.* 8.0, H-6′), 7.24 (1 H, dt, *J* 0.7 and 7.9, H-7), 7.16 (1 H, br d, *J* 7.9, H-8), 6.99 (1 H, br d, *J* 7.4, H-2′), 6.93 (1 H, br d, *J* 7.9, H-6), 6.92 (1 H, br d, *J* 7.4, H-7′), 5.12 (1 H, br d, *J* 4.5, 4-OH), 4.98 (1 H, br q, *J* 4.0, H-4), 2.26–2.21 (1 H, m, H-2), 2.01–1.95 (2 H, m, H-2, H-3), 1.84–1.79 (1 H, m, H-3); δ_C (125 MHz; DMSO-d_6) 155.4 (C-5), 147.8 (C-8′), 147.5 (C-1′), 135.5 (C-8a), 133.7 (C-4a′), 128.5 (C-7), 127.7 (C-3′, C-6′), 126.4 (C-4a), 120.2 (C-4′, C-5′), 117.4 (C-8), 116.1 (C-6), 113.0 (C-8a′), 109.14 (C-2′), 109.12 (C-7′), 100.0 (C-1), 60.9 (C-4), 27.7 (C-3), 25.3 (C-2); *m*/*z* (EI) 320 (M^+, 5%), 302 (100) [HRMS (EI): calcd. for $C_{20}H_{16}O_4$, 320.10486. Found: M^+, 320.10509 (0.7 ppm error)].

Palmarumycin C_2 (2,3-epoxy-2,3-dihydro-5-hydroxyspiro-[naphthalene-1(4*H*),2′-naphtho[1,8-*de*][1,3]dioxin]-4-one) (deoxypreussomerin A, 3)

A solution of enone **5** (90 mg, 0.28 mmol) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (21 mg, 0.15 mmol) in toluene (2 mL) under nitrogen was cooled to 0 °C. *t*BHP in toluene (2.65 M, 0.53 mL, 1.4 mmol) was slowly added over 5 min and the mixture was left under stirring for 2 h at RT. The reaction was quenched by addition of a saturated solution of Na_2SO_3 (1 mL), and then EtOAc (15 mL) and brine (5 mL) were added, and the two layers were separated. The aqueous phase was extracted twice with EtOAc, and the organic layers were combined and dried ($MgSO_4$). Evaporation of the solvents followed by column chromatography (DCM) and then preparative TLC (DCM) gave palmarumycin C_2 (**3**) (50 mg, 53%) as a pale yellow solid, mp 225–228 °C (decomp.) [lit.,[3b] mp 228 °C (decomp.)]; R_f 0.60 (DCM); λ_{max} ($CHCl_3$)/nm 283 (ε/dm^3 mol^{-1} cm^{-1} 14265), 300 (13529), 314 (12206) and 329 (12647); ν_{max} (deposited)/cm^{-1} 1654, 1608, 1456, 1412, 1379, 1268, 1239, 1180, 1113, 1065,

1030, 970, 920, 878, 820, 808, 756, 737, 657 and 611; δ_H (270 MHz; $CDCl_3$) 11.36 (1 H, br s, Ar-OH), 7.66 (1 H, br t_{app}, *J ca.* 8.0, H-7), 7.61 (1 H, dd, *J* 1.0 and 8.5, H-4′), 7.58 (1 H, dd, *J* 1.0 and 8.5, H-5′), 7.54 (1 H, br t_{app}, *J ca.* 8.0, H-3′), 7.46 (1 H, br t_{app}, *J ca.* 8.0, H-6′), 7.45 (1 H, dd, *J* 1.0 and 7.8, H-8), 7.20 (1 H, dd, *J* 1.0 and 7.5, H-2′), 7.15 (1 H, dd, *J* 1.0 and 8.5, H-6), 6.93 (1 H, dd, *J* 1.0 and 7.5, H-7′), 4.10 (1 H, d, *J* 4.1, H-3), 3.69 (1 H, d, *J* 4.1, H-2); δ_C (67.5 MHz; $CDCl_3$) 196.5 (C-4), 161.8 (C-5), 146.9 (C-8′), 146.6 (C-1′), 137.6 (C-7), 136.8 (C-8a), 134.1 (C-4a′), 127.7 (C-3′), 127.6 (C-6′), 121.4 (C-4′), 121.3 (C-5′), 120.0 (C-6), 119.0 (C-8), 112.7 (C-8a′), 112.2 (C-4a), 110.1 (C-2′), 109.3 (C-7′), 95.9 (C-1) and 53.2 (C-3 and C-2); *m*/*z* (CI) 350 (MNH_4^+, 100%), 333 (MH^+, 80) [HRMS (CI): calcd. for $C_{20}H_{16}NO_5$, 350.10285. Found: MNH_4^+, 350.10264 (0.6 ppm error)].

Palmarumycin C_{11} (2,3-epoxy-4,5-dihydroxy-1,2,3,4-tetrahydrospiro[naphthalene-1,2′-naphtho[1,8-*de*][1,3]dioxine]) (*syn*-2)

Sodium borohydride (9 mg, 0.24 mmol) was added to a solution of palmarumycin C_2 (**3**) (41 mg, 0.12 mmol) in methanol (2 mL) at 0 °C under nitrogen. The reaction was complete after 1 h (TLC). EtOAc and water were added, the two layers were separated and the organic phase washed with water and brine, and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* yielded a colourless oil which was further purified by column chromatography (DCM–MeOH, 8:2) to afford the *title compound* ***syn*-2** (18 mg, 45%) as a colourless oil which crystallised on standing as a white solid, mp 237–238 °C (decomp.) [lit.,[3b] mp 237–238 °C (decomp.)]; R_f 0.68 (DCM–MeOH, 8:2); λ_{max} (DCM)/nm 289 (ε/dm^3 mol^{-1} cm^{-1} 4235), 301 (4076), 314 (3025) and 329 (2173); ν_{max} (deposited)/cm^{-1} 3334, 3058, 2925, 2854, 1635, 1608, 1487, 1466, 1412, 1379, 1265, 1111, 1029, 968, 870, 820, 795, 756 and 737; δ_H (270 MHz; $CDCl_3$) 8.28 (1 H, br s, Ar-OH), 7.57 (1 H, dd, *J* 1.0 and 8.5, H-4′), 7.55 (1 H, dd, *J* 1.0 and 8.5, H-5′), 7.51 (1 H, br t_{app}, *J ca.* 8.0, H-3′), 7.44 (1 H, br t_{app}, *J ca.* 8.0, H-6′), 7.41 (1 H, dd, *J* 2.4 and 8.0, H-8), 7.37 (1 H, br t_{app}, *J ca.* 8.0, H-7), 7.14 (1 H, dd, *J* 1.0 and 7.5, H-2′), 7.04 (1 H, dd, *J* 2.4 and 6.7, H-6), 6.92 (1 H, dd, *J* 1.0 and 7.5, H-7′), 5.44 (1 H, d, *J* 2.5, H-4), 3.87 (1 H, d, *J* 4.4, H-2), 3.74 (1 H, dd, *J* 2.5 and 4.4, H-3) and 3.17 (1 H, br s, C4-OH); δ_C (67.5 MHz; $CDCl_3$) 156.5 (C-5), 147.3 (C-8′), 147.2 (C-1′), 134.1 (C-4a′), 132.0 (C-8a), 130.6 (C-7), 127.7 (C-3′), 127.4 (C-6′), 121.1 (C-4′), 121.0 (C-5′), 119.3 (C-8), 118.9 (C-6), 118.5 (C-4a), 112.8 (C-8a′), 109.9 (C-2′), 109.1 (C-7′), 96.7 (C-1), 66.6 (C-4), 53.2 (C-2) and 52.8 (C-3); *m*/*z* (CI) 352 (MNH_4^+, 30%), 335 (MH^+, 40), 334 (M^+, 65) [HRMS (CI): calcd. for $C_{20}H_{18}NO_5$, 352.11850. Found: MNH_4^+, 352.11895 (1.3 ppm error)].

5-*O*-Methyl-palmarumycin C_2 (2,3-epoxy-2,3-dihydro-5-methoxyspiro[naphthalene-1(4*H*),2′-naphtho[1,8-*de*][1,3]dioxin-4-one]) (39)

A solution of enone **35** (371 mg, 1.12 mmol) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (90 mg, 0.65 mmol) in toluene (10 mL) under nitrogen was cooled to 0 °C. *t*BHP in toluene (2.65 M, 2.21 mL, 5.86 mmol) was slowly added over 15 min and the mixture was left under N_2 stirring for 14 h at RT. The reaction was quenched by addition of saturated Na_2SO_3 (1 mL). EtOAc (30 mL) and brine (5 mL) were added, the two layers were separated, the aqueous layer extracted twice with EtOAc, and the organic layers combined and dried ($MgSO_4$). Evaporation of the solvents gave the crude product as a yellow solid which was purified by column chromatography (EtOAc–PE, 4:6) to give the *title compound* (**39**) (290 mg, 75%) as a white solid, mp 219 °C (decomp.); R_f 0.30 (EtOAc–PE, 4:6); ν_{max} (deposited)/cm^{-1} 1695, 1595, 1474, 1457, 1437, 1413, 1380, 1317, 1271, 1123, 1060, 905, 820, 801, 757 and 732; δ_H (270 MHz; $CDCl_3$) 7.62 (1H, br t_{app}, *J ca.* 8.0, H-7), 7.58 (1 H, dd, *J* 1.0 and 8.5, H-4′), 7.54 (1 H, dd, *J* 1.0 and 8.5, H-5′), 7.53 (1 H, br t_{app}, *J ca.* 8.0, H-3′), 7.49 (1 H, dd, *J* 1.0 and 8.0, H-8), 7.43 (1 H, br t_{app}, *J ca.* 7.5, H-6′), 7.19 (1 H, dd, *J* 1.0 and 7.0, H-2′), 7.13 (1 H, dd, *J* 1.0 and 8.5, H-6), 6.88 (1 H, dd, *J* 1.0 and 7.5, H-7′), 4.08 (1 H, d, *J* 4.5, H-3), 3.96 (3 H, s, OMe), 3.72 (1 H, d, *J* 4.5, H-2); δ_C (67.5 MHz; $CDCl_3$) 191.7 (C-4), 158.9 (C-5), 147.0 (C-1′ or C-8′), 146.6 (C-1′ or C-8′), 138.0 (C-8a), 134.9 (C-7), 134.1 (C-4a′), 127.6 (C-3′ and C-6′), 121.2 (C-4′ or C-5′), 121.1 (C-4′ or C-5′), 118.7 (C-8), 117.6 (C-4a), 113.9 (C-6), 112.6 (C-8a′), 109.8 (C-2′ or C-7′), 109.2 (C-2′ or C-7′), 96.9 (C-1), 56.3 (OMe), 54.0 (C-3), 52.9 (C-2); *m*/*z* (CI) 347 (MH^+, 100%) [HRMS (CI): calcd. for $C_{21}H_{15}O_5$, 347.09195. Found: MH^+, 347.09215 (0.6 ppm error)].

5-*O*-Methyl-palmarumycin C_{11} (2,3-epoxy-4-hydroxy-5-methoxy-1,2,3,4-tetrahydrospiro[naphthalene-1,2′-naphtho-[1,8-*de*][1,3]dioxine]) (40)

Potassium carbonate (20 mg, 0.15 mmol) and methyl iodide (filtered through alumina, 0.2 mL, 3.2 mmol) were added to a solution of palmarumycin C_{11} (*syn*-**2**) (8 mg, 0.024 mmol) in THF (2 mL) and the mixture was stirred at 55 °C under nitrogen. After 8 h at 55 °C the reaction was complete according to TLC. Purification by microcolumn chromatography (EtOAc) followed by preparative TLC (DCM) gave the *title compound* (**40**) (6 mg, 72%) as a white solid, mp 211–212 °C (decomp.); R_f 0.16 (DCM); ν_{max} (deposited)/cm^{-1} 3527, 1634, 1607, 1412, 1379, 1328, 1271, 1125, 1131, 1065, 957, 820, 793, 756; δ_H (500 MHz; $CDCl_3$) 7.56 (1 H, dd, *J* 1.0 and 8.0, H-4′), 7.54 (1 H, dd, *J* 1.0 and 8.0, H-5′), 7.53 (1 H, dd, *J* 1.0 and 8.0, H-8), 7.50 (1 H, br t_{app}, *J ca.* 8.0, H-3′), 7.45 (1 H, br t_{app}, *J ca.* 8.0, H-6′), 7.42 (1 H, br t_{app}, *J ca.* 8.0, H-7), 7.15 (1 H, dd, *J* 1.0 and 7.5, H-2′), 7.06 (1 H, dd, *J* 1.0 and 8.0, H-6), 6.89 (1 H, dd, *J* 1.0 and 7.5, H-7′), 5.48 (1 H, d, *J* 3.0, H-4), 4.51 (1 H, br s, OH), 3.99 (3 H, s, OMe), 3.77 (1 H, d, *J* 4.5, H-2), 3.75 (1 H, dd, *J* 3.0 and 4.5, H-3); δ_C (67.5 MHz; $CDCl_3$) 157.4 (C-5), 147.5 (C-8′ or C1′), 147.3 (C-8′ or C1′), 134.1 (C-4a′), 132.9 (C-8a), 129.6 (C-7), 127.7 (C-3′ or C-6′), 127.4 (C-3′ or C-6′), 123.3 (C-4a), 120.9 (C-4′ or C-5′ and C-8), 120.4 (C-5′ or C-4′), 113.0 (C-8a′), 112.2 (C-6), 110.1 (C-2′ or C-7′), 108.9 (C-2′ or C-7′), 97.1 (C-1), 64.2 (C-4), 56.0 (OMe), 54.1 (C-2), 51.3 (C-3); *m*/*z* (CI) 366 (MNH_4^+, 35%) and 348 (MH^+, 100) [HRMS (CI): calcd. for $C_{21}H_{20}NO_5$, 366.13415. Found: MNH_4^+, 366.13425 (0.3 ppm error)].

Reduction of 5-*O*-methyl-palmarumycin C_2 (39)

(a) A solution of epoxyketone **39** (28 mg, 0.08 mmol) in THF (2 mL) under nitrogen was cooled down to −78 °C and Super-Hydride® in THF (1 M, 0.20 mL, 0.2 mmol) was added. TLC after 1 h at −78 °C showed a clean and complete conversion. The reaction was quenched with saturated NH_4Cl solution (0.1 mL) and allowed to warm to RT. The reaction mixture was diluted with DCM (5 mL), dried ($MgSO_4$) and the solvent evaporated to give a colourless oil which was purified by preparative TLC (DCM) to give a mixture of alcohols **40** and **41** (28 mg, 99%; **40**:**41** = 3.6:1 by NMR spectroscopy) as a white solid, with data as expected from the individual components.

(b) A solution of epoxyketone **39** (36 mg, 0.10 mmol) in 2 mL THF under nitrogen was cooled down to −78 °C and DIBALH in hexane (1 M, 0.25 mL, 0.25 mmol) was added. TLC after 1 h at −78 °C showed a clean and complete conversion. The reaction was quenched with saturated NH_4Cl solution (0.1 mL), allowed to warm to RT, diluted with DCM (5 mL) and dried ($MgSO_4$). Evaporation of the solvents followed by column chromatography (EtOAc–PE, 4:6) gave *5-O-methylbipendensin* (**41**) (29 mg, 80%; **41**:**40** >95:5 by NMR spectroscopy) as a white solid, mp 240 °C (decomp.); R_f 0.19 (EtOAc–PE, 4:6); ν_{max} (deposited)/cm^{-1} 3527, 3054, 1605, 1474, 1444, 1412, 1378, 1325, 1265, 1113, 1067, 963, 895, 737; δ_H (500 MHz; $CDCl_3$) 7.57 (1 H, dd, *J* 1.0 and 8.5, H-4′), 7.54

(1 H, dd, *J* 1.0 and 8.5, H-5′), 7.51 (1 H, br t_{app}, *J ca.* 8.0, H-3′), 7.50 (1 H, dd, *J* 1.0 and 8.5, H-8), 7.45 (1 H, br t_{app}, *J ca.* 8.0, H-6′), 7.43 (1 H, br t_{app}, *J ca.* 8.0, H-7), 7.15 (1 H, dd, *J* 1.0 and 7.5, H-2′), 7.04 (1 H, dd, *J* 1.0 and 8.0, H-6), 6.93 (1 H, dd, *J* 1.0 and 7.5, H-7′), 5.61 (1 H, br d, *J* 2.5, H-4), 3.95 (3 H, s, OMe), 3.77 (1 H, dd, *J* 1.0 and 4.0, H-2), 3.67 (1 H, dd, *J* 2.5 and 4.0, H-3), 2.10 (1 H, br s, OH); δ_C (67.5 MHz; $CDCl_3$) 157.3 (C-5), 147.3 (C-8′ or C1′), 147.3 (C-8′ or C-1′), 134.1 (C-4a′), 132.2 (C-8a), 130.3 (C-7), 127.7 (C-3′ or C-6′), 127.4 (C-3′ or C-6′), 123.3 (C-4a), 120.9 (C-4′ or C5′), 120.9 (C-4′ or C-5′), 119.3 (C-8), 112.9 (C-8a′), 112.0 (C-6), 109.9 (C-2′ or C-7′), 109.1 (C-2′ or C-7′), 97.8 (C-1), 61.3 (C-4), 55.9 (OMe), 52.8 (C-2), 50.6 (C-3); *m/z* (CI) 366 (MNH_4^+, 3%) and 348 (M^+, 100) [HRMS (CI): calcd. for $C_{21}H_{20}NO_5$, 366.13415. Found: MNH_4^+, 366.13423 (0.6 ppm error)].

2,3-Dihydrospiro[naphthalene-1(4*H*),2′-naphtho[1,8-*de*][1,3]-dioxin]-4-one (42)

To a stirred solution of spiroacetal **31** (500 mg, 1.73 mmol) and Celite (3 g) in benzene (20 mL) at 10 °C was added pyridinium dichromate (1.63 g, 4.33 mmol) followed by the slow (5 min) addition of a 5.0–6.0 M solution of *t*BHP in decane (0.87 mL). After 15 min at 10 °C, the mixture was stirred at RT overnight. TLC showed clean but incomplete conversion. The mixture was filtered though Celite and quenched with a saturated solution of sodium sulfite. Extraction with EtOAc, drying ($MgSO_4$) and evaporation of the solvent afforded an orange oil which was chromatographed (EtOAc–PE, 2:98) to yield recovered starting material **31** (250 mg) followed by the *title compound* **42** (220 mg, 42%, 84% based on recovered starting material), as an orange oil that crystallised on standing to give a yellow solid, mp 110–112 °C; R_f 0.53 (EtOAc–PE, 1:4); ν_{max} (deposited)/cm^{-1} 3060, 2962, 2937, 1693, 1606, 1412, 1381, 1273 and 1076; δ_H (500 MHz; $CDCl_3$) 8.15 (1 H, dd, *J* 1.4 and 7.8, H-5), 7.99 (1 H, dd, *J* 1.3 and 7.8, H-8), 7.74 (1 H, d br t_{app}, *J* 1.4 and *ca.* 8.0, H-7), 7.61 (1 H, d br t_{app}, *J* 1.3 and *ca.* 8.0, H-6), 7.54 (2 H, br d, *J* 8.0, H-4′, H-5′), 7.47 (2 H, br t_{app}, *J ca.* 8.0, H-3′, H-6′), 6.99 (2 H, br d, *J* 7.6, H-2′, H-7′), 2.83 (2 H, t, *J* 6.6, H-3), 2.54 (2 H, t, *J* 6.6, H-2); δ_C (125 MHz; $CDCl_3$) 196.2 (C-4), 147.5 (C-1′, C-8′), 140.4 (C-8a), 134.3, 134.2, 131.5, 130.1, 127.5 (C-3′, C-6′), 127.0, 126.1, 120.8 (C-4′, C-5′), 113.4 (C-8a′), 109.4 (C-2′, C-7′), 98.7 (C-1), 34.2 (C-3), 29.7 (C-2); *m/z* (CI) 303 (MH^+, 100%), 285 (M − 18, 9) [HRMS (CI): calcd. for $C_{20}H_{15}O_3$, 303.10212. Found: MH^+, 303.10097 (3.8 ppm error)].

Spiro[naphthalene-1(4*H*),2′-naphtho[1,8-*de*][1,3]dioxin]-4-one (43)

Spiroacetal **42** (30 mg, 0.10 mmol) in 0.5 mL of chlorobenzene was added under nitrogen to a solution of benzeneseleninic anhydride (54 mg, 0.15 mmol) and $NaHCO_3$ (41 mg, 0.49 mmol) in 0.5 mL chlorobenzene at RT. The mixture was stirred at reflux overnight. Evaporation of the solvent followed by column chromatography (PE–EtOAc, 95:5) of the crude material afforded the *title compound* **43** (9 mg, 30%) as a yellow solid, mp 177–179 °C; R_f 0.39 (EtOAc–PE, 1:9); ν_{max} (deposited)/cm^{-1} 3060, 2927, 1675, 1606, 1595, 1412, 1379, 1269 and 1070; δ_H (500 MHz; $CDCl_3$) 8.19 (1 H, t_{app} d, *J* 1.0 and 7.9, H-5), 7.99 (1 H, t_{app} d, *J* 1.0 and 7.8, H-8), 7.78 (1 H, d br t_{app}, *J* 1.0 and *ca.* 8.0, H-7), 7.65 (1 H, d br t_{app}, *J* 1.0 and *ca.* 8.0, H-6), 7.59 (2 H, d, *J* 8.4, H-4′, H-5′), 7.49 (2 H, dd, *J* 7.6 and 8.4, H-3′, H-6′), 7.03 (1 H, d, *J* 10.5, H-2), 6.99 (2 H, d, *J* 7.6, H-2′, H-7′), 6.40 (1 H, d, *J* 10.5, H-3); δ_C (125 MHz; $CDCl_3$) 183.3 (C-4), 147.3 (C-1′, C-8′), 138.5 (C-8a), 138.4 (C-2), 134.1 (C-4a′), 133.8 (C-5), 130.3 (C-3), 130.2 (C-7), 129.9 (C-4a), 127.8, 127.6 (C-3′, C-6′), 126.3, 121.2 (C-4′, C-5′), 113.1 (C-8a′), 109.8 (C-2′, C-7′), 92.9 (C-1); *m/z* (CI) 318 (MNH_4^+, 35%), 301 (MH^+, 100) [HRMS (CI): calcd. for $C_{20}H_{13}O_3$, 301.08647. Found: MH^+, 301.08637 (0.3 ppm error)].

1,2,3,4-Tetrahydrospiro[naphthalene-1,2′-naphtho[1,8-*de*][1,3]-dioxin]-4-ol (44)

Ketone **42** (32 mg, 0.105 mmol) was dissolved in methanol (2 mL) by gently warming the solution with an air gun. Sodium borohydride (2 mg, 0.053 mmol) was added to the gold yellow solution which turned pale yellow after 10 min. TLC showed a clean and complete conversion. EtOAc and water were added, the two layers were separated and the organic phase washed with water and brine, and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* yielded a colourless oil which was further purified by short column chromatography (hexane–EtOAc, 6:4) to give the *title compound* **44** (31 mg, 96%) as a colourless oil which crystallised, after two days standing, as a white solid, mp 156–158 °C; R_f 0.27 (EtOAc–PE, 3:7); ν_{max} (deposited)/cm^{-1} 3342, 3059, 2952, 2933, 1606, 1411, 1380, 1273, 1127, 1067, 1025, 919, 821 and 756; δ_H (500 MHz; $CDCl_3$) 7.89 (1 H, dd, *J* 1.0 and 7.5, H-8), 7.60 (1 H, br d, *J* 7.5, H-5), 7.52 (2 H, dd, *J* 1.0 and 8.5, H-4′, H-5′), 7.52–7.46 (2 H, hidden, H-6, H-7), 7.45 (1 H, dd, *J* 7.5 and 8.5, H-3′ or H-6′), 7.44 (1 H, dd, *J* 7.5 and 8.5, H-3′ or H-6′), 6.95 (1 H, dd, *J* 1.0 and 7.5, H-2′ or H-7′), 6.93 (1 H, dd, *J* 1.0 and 7.5, H-2′ or H-7′), 4.90 (1 H, dd, *J* 4.5 and 6.0, H-4), 2.43 (1 H, ddd, *J* 3.0, 9.5 and 13.5, H-2a), 2.27–2.21 (1 H, m, H-3a), 2.14 (1 H, ddd, *J* 3.0, 9.5 and 13.5, H-2b), 2.04–1.97 (1 H, m, H-3b), 2.00 (1 H, br s, OH); δ_C (125 MHz; $CDCl_3$) 148.08 (C-1′), 147.98 (C-8′), 139.49, 134.82 (C-4a or C-8a), 134.18 (C-4a or C-8a), 130.14, 128.69, 127.72, 127.45 (C-3′), 127.39 (C-6′), 127.37 (C-4a), 120.42 (C-4′), 120.41 (C-5′), 113.57 (C-8a′), 109.36 (C-2′), 109.31 (C-7′), 99.97 (C-1), 67.81 (C-4), 28.85 (C-3), 27.10 (C-2); *m/z* (EI) 304 (M^+, 15%), 286 (100) [HRMS (EI): calcd. for $C_{20}H_{16}O_3$, 304.10994. Found: M^+, 304.10956 (1.2 ppm error)].

Acknowledgements

We are grateful to Yorkshire Cancer Research for studentship and postdoctoral support (J. P. R. and C. S.), to A. R. C. (France) for postdoctoral funding (M.-L. A.), and to Dr I. Kapfer-Eyer for preliminary studies. We also thank Professor J. D. Connolly (University of Glasgow) for providing copies of the NMR spectra for bipendensin.[2]

This paper is dedicated to the memory of Professor Ralph Raphael FRS: An inspirational scientist and a good friend.

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Paper 9/01076I