Synthetic approaches to the angucycline antibiotics: the total syntheses of (±)-rubiginone B_1 and B_2, (±)-emycin A, and related analogues

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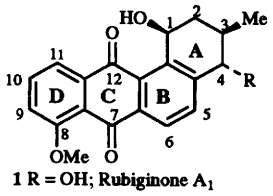
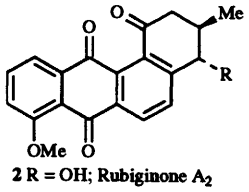
The syntheses of the angucyclinone antibiotics; (±)-rubiginone B_1 **3** and B_2 **4**, (±)-ochromycinone **7**, and (±)-emycin A **12** are reported. The key step for the construction of the benzo[*a*]anthracene nucleus in each of the syntheses was a highly stereoselective, tetra-*O*-acetyl diborate-promoted Diels–Alder cycloaddition of 5-hydroxy-1,4-naphthoquinone **8** and the diene, E-(1*R**,5*R**)-1-acetoxy-3-(2'-methoxyvinyl)-5-methylcyclohex-2-ene **21**. Base-induced aromatisation of the cycloadduct **30** gave the benzo[*a*]anthraquinone, (1*R**,3*R**)-1-acetoxy-8-hydroxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene-7,12-dione **28** which served as an intermediate for the syntheses of the above natural products. The syntheses of (±)-13-norrubiginone B_1 **34** and B_2 **35**, and (±)-1-*epi*-rubiginone B_1 **11** using modifications of the synthetic strategy are also described.

Introduction

The wide range of biological properties associated with the angucycline class of antibiotics has stimulated great interest in these compounds.[1] Among the simpler subclass, the angucyclinones (the group possessing the benzo[*a*]anthracene nucleus but devoid of carbohydrate functionality), are the rubiginone family of antibiotics. The six related factors isolated by Oka and co-workers,[2] rubiginone A_1 **1**, A_2 **2**, B_1 **3**, B_2 **4**, C_1 **5** and C_2 **6** are secondary metabolites produced by a strain



1 R = OH; Rubiginone A_1
3 R = H; Rubiginone B_1
5 R = $OCOPr^i$; Rubiginone C_1

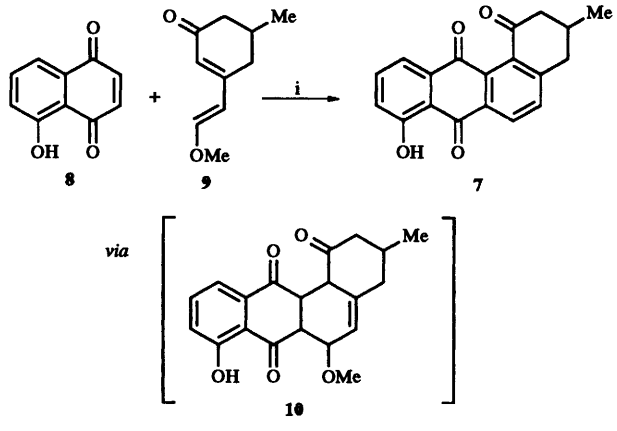


2 R = OH; Rubiginone A_2
4 R = H; Rubiginone B_2
6 R = $OCOPr^i$; Rubiginone C_2

of *Streptomyces griseorubiginosus*. All of these compounds have been shown to potentiate the cytotoxicity of the chemotherapeutic agent vincristine against vincristine resistant P388 leukaemia and human Moser cells *in vitro* and *in vivo*. The most active member of this group is rubiginone B_1 **3**. Its mode of action was studied by Hamagishi and co-workers[3] who found that the effect was synergistic and concluded that **3** and congeners could serve as efflux blockers (like verapamil) in cancer chemotherapy for the treatment of a variety of protein-involved multi-drug resistant tumour cells in combination with cytotoxic agents such as vincristine.

Although there have been a large number of angucyclines and angucyclinones isolated, relatively little has been reported on their syntheses.[4–11] To date the only members of this group to yield to synthesis are ochromycinone **7**,[4,5] X-14881 C[5] and rabelomycin,[6] albeit in racemic forms, and the antipode of the more complex *C*-glycoside urdamycinone B.[7] However, most studies have concentrated on the synthesis of model systems.[8]

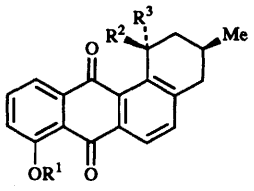
A very elegant Diels–Alder approach to racemic ochromycinone [(±)-**7**] was developed by Guingant *et al.*[4] The power of their strategy was its highly convergent nature with the tetra-*O*-acetyl diborate-promoted reaction of 5-hydroxy-1,4-naphthoquinone **8** and the dienone **9** directly giving the racemic form of the natural product in 75% yield (Scheme 1). Although a



Scheme 1 *Reagents and conditions:* i, $B_2O(OAc)_4$, CH_2Cl_2

beneficial aerial oxidation and aromatisation of the intermediary cycloadduct **10** occurred spontaneously, it limits the versatility of this approach. The inherent stereoselectivity associated with the Diels–Alder reaction and the functionality of such an intermediate could be used to access a much wider range of angucyclines/angucyclinones.

We felt that a simple modification to this approach would not only allow the isolation of such cycloadducts but also the control of regiochemistry and relative stereochemistries. Stereoselective reduction of the carbonyl group of **9** would result in increased reactivity of the diene and the lack of an electron-withdrawing carbonyl group at C-1 of the corresponding cycloadduct would increase its stability. The functionality at C-1 and C-3 of such a cycloadduct would mirror that of a number of angucyclinones including rubiginone B_1 **3**. Furthermore, the introduction of a chiral centre adjacent to the dienyl functionality might control the facial selectivity of the Diels–Alder cycloaddition. This has been shown for a similar diene system by Franck and co-workers[9] who reported that 3-vinylcyclohex-2-enol and its derivatives exhibit good to excellent diastereofacial selectivities in their thermal cycloaddition reactions with *N*-phenylmaleimide. Utilising this approach, we have recently communicated the syntheses of (±)-**3**[10] and its C-1 epimer (±)-**11**[11] as part of a programme aimed at developing a versatile synthetic approach to this group of antibiotics. The key step in their syntheses was a highly regio- and stereo-selective Diels–

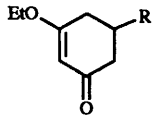


11 R^1 = Me, R^2 = H, R^3 = OH
12 R^1 = H, R^2 = OH, R^3 = H

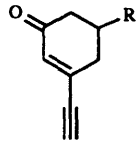
Alder reaction. This paper reports the detailed syntheses of (±)-**3**, (±)-**11**, the natural products (±)-rubiginone B_2 **4**, (±)-emycin A **12** and structurally related analogues as well as an alternative synthesis of (±)-**11**.

Results and discussion

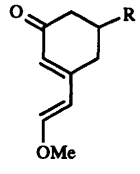
The dienes used in this study were prepared by a modification of an approach communicated by Guingant *et al.*[4] Treatment of the 3-ethoxycyclohexenones **13** and **14** with ethynylmagnesium bromide in THF gave the ynenones **15** and **16** in 89 and 91% yields respectively.† Conjugate addition of methanol promoted by *N*-methylmorpholine in benzene gave the unstable dienones **17** and **9** which were used without purification for the subsequent step. The procedure developed by Heathcock and co-workers[12] for the reduction of 5-methyl-3-vinylcyclohex-2-enone was utilised for the reduction of **17** and **9**. Treatment of **17** in THF at 0 °C with lithium aluminium hydride gave the dienol **18** in 94% crude yield from **15**. Similarly, careful reduction of **9** in THF at −78 °C to room temperature gave the dienol **19** in 93% crude yield from **16**. The stereochemistry of the product and the selectivity of the reduction were difficult to ascertain from the spectral data. The assignment of the *cis* relationship of the 1-hydroxy and 5-methyl groups was made by analogy to Heathcock's work[12] and confirmed later in the synthetic sequence. Acetylation of the dienols **18** and **19** was effected by reaction with acetic anhydride and triethylamine to give the dienes **20** and **21**. All of the dienes (*i.e.* **18** to **21**) proved



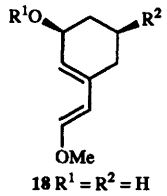
13 R = H
14 R = Me



15 R = H
16 R = Me



17 R = H
9 R = Me



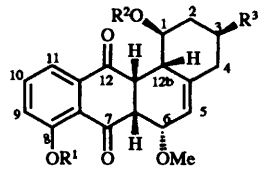
18 R^1 = R^2 = H
19 R^1 = H, R^2 = Me
20 R^1 = Ac, R^2 = H
21 R^1 = Ac, R^2 = Me

extremely labile and were used in their crude form. Aqueous work-up and/or silica gel column chromatography invariably resulted in hydrolysis of the enol ether moieties and, generally, these compounds were used immediately after preparation.

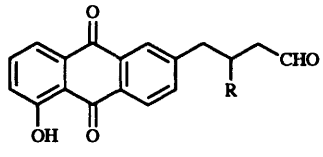
† Severe dermatitis among some workers in our laboratory was directly attributed to the ynenones **15** and **16**.

The tetra-*O*-acetyl diborate promoted cycloadditions of 5-hydroxy-1,4-naphthoquinone **8** and the dienol **18** proceeded rapidly in dichloromethane at 0 °C to give the adduct **22** in 84% yield after recrystallisation from dichloromethane and diethyl ether. Similarly, the dienol **19** gave the cycloadduct **23** in 73% yield after rapid flash column chromatography and crystallisation from diethyl ether and light petroleum. For both reactions, the ^{1}H NMR spectrum of the crude product showed the formation of only one diastereoisomeric cycloadduct.‡ The relative stereochemistry of the products was evident from their ^{1}H NMR spectra. In adduct **23** for instance, the 1-H resonance exists as a doublet of doublets of triplets. Both the $J_{1,12b}$ and $J_{1,2ax}$ coupling constants of 11.5 Hz indicate the *trans* diaxial relationship between 1-H and 2ax-H, and 1-H and 12b-H, respectively. The *cis* relationship of the 1-hydroxyl and the 3-methyl was confirmed by the clearly resolved quartet attributed to 2ax-H at δ 1.11. The coupling constants; $J_{1,2ax}$, $J_{2ax,2eq}$ and $J_{2ax,3}$ each of 11.5 Hz indicated the axial orientations of 1-H, 2ax-H and 3-H. Furthermore, the coupling constants associated with the signals of the protons at the newly created chiral centres were consistent with the product arising from an *endo* transition state.§ The regiochemical assignment of the cycloadduct was made by analogy to the work of Kelly and co-workers[13] who have rigorously studied the Lewis acid-promoted Diels–Alder reactions of the naphthoquinone **8** with a variety of oxygenated dienes. The regiochemical outcome of the cycloadditions in this study was subsequently confirmed later in the synthetic sequences.

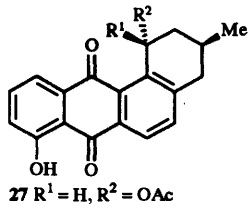
The planned aromatisation of the B-ring of the cycloadducts **22** and **23** proved problematical. Treatment with various acids and bases resulted in fragmentation of the C(1)–C(12b) bond and after aerial oxidation gave the substituted anthraquinones **24** and **25**. For instance, in controlled experiments using triethylamine in dichloromethane the adducts **22** and **23** gave **24** and **25** in yields of 92 and 94%, respectively. The mechanism of



22 R^1 = R^2 = R^3 = H
23 R^1 = R^2 = H, R^3 = Me
26 R^1 = R^2 = Ac, R^3 = Me



24 R = H
25 R = Me



27 R^1 = H, R^2 = OAc
28 R^1 = OAc, R^2 = H

‡ During the course of this work a similar approach to the angucyclines was reported.[8e] The thermally promoted Diels–Alder reaction of 5-acetoxy-6-bromo-1,4-naphthoquinone and 1-*tert*-butyldimethylsiloxy-3-vinylcyclohex-2-ene showed similar diastereofacial selectivity.

§ For example, the coupling constants $J_{6,6a}$, $J_{6a,12a}$ and $J_{12a,12b}$ all of 5.0 Hz for the adduct **22** indicate dihedral angles for H(6)–C–C–H(6a), H(6a)–C–C–H(12a) and H(12a)–C–C–H(12b) of *ca.* 50° (based on the modified Karplus equation,[15] $J = 11 \cos^2 \theta$. This is consistent with the structure of this compound having an *endo* configuration.

this fragmentation process is uncertain and could arise from a β-elimination of methanol followed by a retro-aldol like fragmentation of the C(1)–C(12b) bond and oxidation under either acidic or basic conditions.

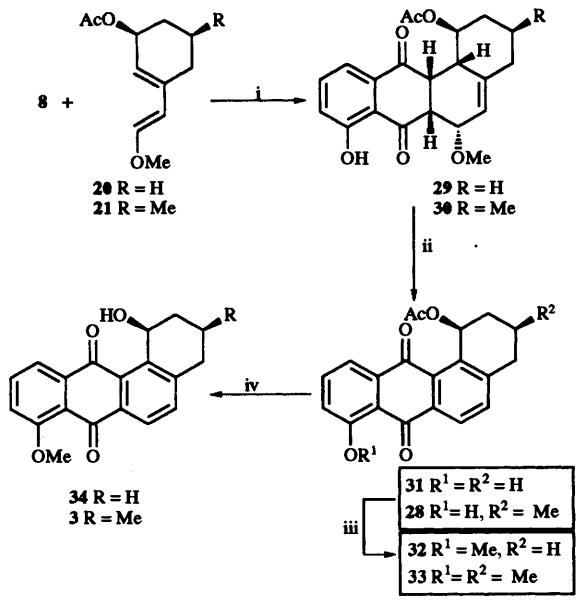
It was envisaged that protection of the C-1 alcohol using an electron-withdrawing protecting group would disfavour the fragmentation process. Acetylation of **23** using acetic anhydride and pyridine gave the diacetate **26** in 91% yield. Unfortunately, attempted aromatisations using triethylamine, DBN and DBU lead to complex mixtures of unidentified products.

The problem was overcome by treatment of **23** with a large excess of tetra-*O*-acetyl diborate in THF. Aromatisation of the B-ring without fragmentation proceeded slowly to give a 5:1 inseparable mixture of the angucyclinones **27** and **28** in 79% yield. Unfortunately, the difficulty associated with the removal of boron species in the work-up procedure complicated this reaction and repetition gave variable yields (51–79%). Both compounds possessed acetate functionality at C-1 and the major diastereoisomer **27** had the 1-acetate and 3-methyl group in a *trans* relationship. It was envisaged that co-ordination of tetra-*O*-acetyl diborate to the 1-hydroxy group of **23** prevented fragmentation of the C(1)–C(12b) bond and facilitated aromatisation. The introduction and epimerisation of the 1-acetate functionality could possibly be occurring by an S_N1-like process with adventitious acetic acid providing the nucleophile. However, the order of events is unknown. The relative stereochemistry at C-1 and C-3 in **27** was assessed on the basis of the ^1H NMR spectrum. The triplet at δ 6.80 attributed to 1-H exhibited coupling constants $J_{1,2ax}$ and $J_{1,2eq}$ of 3.5 Hz indicating a pseudo-axial orientation of the acetoxy group while the highly resolved resonance attributed to 2ax-H showed the coupling constant $J_{2ax,3}$ of 13.0 Hz indicating an equatorial orientation of the 3-methyl group.

The beneficial introduction of acetate functionality would allow selective methylation of the 8-hydroxy group, however, the relative stereochemistry of **27** would eventually lead to the synthesis of the C-1 epimer of rubiginone B_1 [*i.e.* (±)-**11**]. Methylation (MeI–K_2CO_3–acetone in the absence of light) then deacetylation of the 5:1 mixture of **27** and **28** followed by recrystallisation from diethyl ether and dichloromethane gave light-sensitive racemic 1-*epi*-rubiginone B_1 **11** in a 48% yield from the cycloadduct **23**.

Our attention was then turned to the synthesis of rubiginone B_1 **3** (Scheme 2). We felt that selective acetylation of the 1-hydroxyl group of **23** might favour base-promoted aromatisation of the B-ring of the cycloadducts without fragmentation of the C(1)–C(12b) bond. It was proposed that the hydrogen bonding between the 8-phenolic hydrogen and the 7-carbonyl oxygen might facilitate a β-elimination of methanol from the B-ring while the electron-withdrawing acetyl protecting group would disfavour the fragmentation pathway. The desired monoacetylated cycloadducts **29** and **30** were prepared in 73 and 71% yields using the tetra-*O*-acetyl diborate promoted cycloadditions of hydroxynaphthoquinone **8** and the dienes **20** and **21**, respectively (Scheme 2). Once again, both dienes exhibited high diastereofacial selectivities with the ^1H NMR spectra of the crude products each showing the formation of a single diastereoisomeric cycloadduct. As before, the relative stereochemistries of each were apparent from coupling constant information.

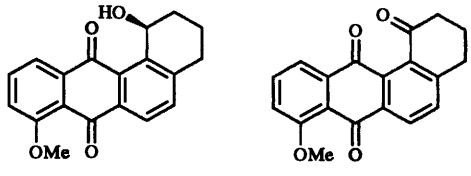
Aromatisation (DBU, CH_2Cl_2, 0 °C, air) of both **29** and **30** proceeded rapidly to give the angucyclinones **31** and **28** in 88 and 86% yields, respectively. The relative stereochemistry at C-1 and C-3 of **28** was once again deduced from the ^1H NMR spectrum. The signal attributed to 1-H resonated as a triplet at δ 6.80 ($J_{1,2ax}$ and $J_{1,2eq}$ 8.0 Hz) indicating a pseudo-equatorial orientation of the acetoxy group. Similarly, the coupling constant $J_{2ax,3}$ of 11.5 Hz indicated an equatorial orientation of the 3-methyl group.



Scheme 2 *Reagents and conditions:* i, $B_2O(OAc)_4$; ii, DBU, CH_2Cl_2, 0 °C, air; iii, Ag_2O, MeI; iv, NaOMe, THF–MeOH

Confirmation of regiochemistry and relative stereochemistry was achieved at this stage of the synthesis. Deacetylation of **28** (NaOMe–MeOH, 78%) gave the natural product emycin A¶ **12**,[1] albeit in racemic form. This compound gave ^1H and ^{13}C NMR, and mass spectra identical with those from an authentic sample.‖ Furthermore, the chromatographic properties were also identical.

Methylations of **31** and **28** were effected (MeI, Ag_2O) in boiling dichloromethane to give the photosensitive methyl ethers **32** and **33** in 89 and 86% yields, respectively. The exclusion of oxygen and light was vital for the success of the reaction and isolation of the products could only be achieved under low light conditions (*i.e.* dark room). Deacetylation of the methyl ethers under an inert atmosphere and light-free conditions using sodium methoxide in methanol gave (±)-13-norrubiginone B_1 **34** (93%) and (±)-rubiginone B_1 **3** (91%). Both synthetic **3** and its analogue **34** were extremely light



34 **35**

sensitive, especially as dichloromethane or chloroform solutions. The structure of synthetic **3** was confirmed by comparison of the spectroscopic data with those reported[2] for the natural **3**. The 300 MHz ^1H and 75 MHz ^{13}C NMR spectra acquired in [$^2H_6$]-DMSO were consistent with those reported for the natural product at 400 and 100 MHz, respectively, in the same solvent system.

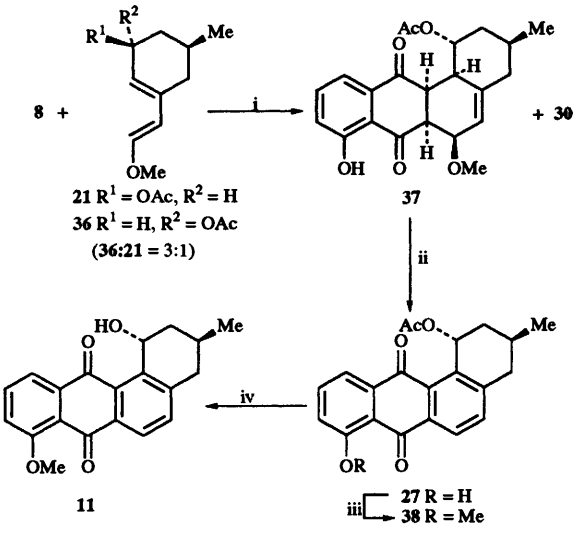
¶ The regiochemistry of the natural products **3** and **12** have been based on UV and NMR spectroscopic studies, and therefore have not been unequivocally established.

‖ The authors thank Dr. J. Rohr, Institut für Organische Chemie der Universitat Göttingen, for the generous gift of a sample of emycin A and related spectral data.

The photosensitivity of angucyclinones **3** and **34** allowed the synthesis of their B_2 congeners. Irradiation of dichloromethane solutions of both with a broad spectrum tungsten filament lamp under an atmosphere of oxygen resulted in a rapid oxidation (*ca.* 15 min) of the 1-hydroxy-group to give (±)-rubiginone B_2 **4** and its 13-nor analogue **35**, both in 96% yield. The reactions were easily monitored with the initial yellow solutions turning an intense red on irradiation. The oxidation was complete when the red colouration had reverted back to yellow. These observations were in accord with those reported by Oka and co-workers[14] for the oxidation of natural rubiginone A_1 **1**.

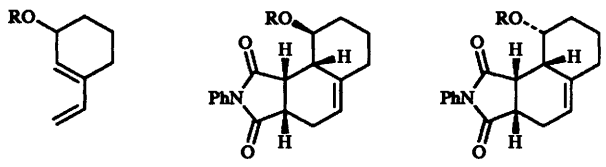
The rate of the photochemical oxidations of angucyclinones in this study appeared to be associated with the functionality at C-8. Angucyclinones containing a 8-methoxy group, such as **3**, **32**, **33** and **34** underwent such oxidations at a much greater rate than their 8-hydroxy analogues. For instance, the oxidation of (±)-emycin A **12** to (±)-ochromycinone **7** required a 17 h reaction time. In the latter case the formation of an intensely red intermediate was not observed. The photochemical behaviour of these compounds is currently under investigation.

The syntheses of the racemic forms of rubiginone B_1 **3** and B_2 **4**, their 13-nor analogues **34** and **35**, emycin A **12**, ochromycinone **7**, and 1-*epi*-rubiginone B_1 **11** had been successfully completed. Unfortunately, the synthesis of the latter was complicated by the work-up procedure in the aromatisation step. It was envisaged that an alternative route to **11** would require the synthesis of a diene with *trans* stereochemistry of the acetoxy and methyl groups already established. This was achieved by lithium aluminium hydride reduction of the dienone **9** at 0 °C in THF followed by acetylation. The ^{1}H NMR spectrum of the product from this reaction proved remarkably similar to that of the previous low temperature reduction. However, using diene prepared in this way, a tetra-*O*-acetyl diborate-promoted cycloaddition with hydroxynaphthoquinone **8** gave a 3:1 mixture of two diastereoisomeric cycloadducts **37** and **30** (Scheme 3). On this basis it was assumed that the



Scheme 3 *Reagents and conditions:* i, $B_2O(OAc)_4$; ii, DBU, CH_2Cl_2, 0 °C, air; iii, Ag_2O, MeI; iv, NaOMe, THF–MeOH

diene was a 3:1 mixture of *trans* and *cis* dienes **36** and **21**. Fractional crystallisation of the mixture of cycloadducts from dichloromethane and diethyl ether gave the *trans* isomer **37** in 56% yield. The stereochemistry of the 1-acetoxy group and 3-methyl groups was evident from the subsequent step. Aromatisation promoted by DBU gave the angucyclinone **27** in 90% yield. Methylation gave the light-sensitive methyl ether **38** (90%) which was deacetylated to give (±)-**11** (89%). The overall



a R = H, **b** R = Me, **c** R = $SiMe_3$

yield of the (±)-1-*epi*-rubiginone B_1 **11** from the dienophile **8** was 40%.

The key reaction in all the syntheses was the cycloaddition of the dienophile **8** with appropriately substituted dienes. In all examples a single diastereoisomeric cycloadduct was formed which could be seen as arising from an *endo* approach of the dienophile to the face of the diene *anti* to the allylic oxygenated substituent (Fig. 1). This is consistent with work by Franck and co-workers[9] who proposed that the reactions of semicyclic dienes such as **39a–c** with *N*-phenylmaleimide in benzene, that the facial selectivity was governed by steric factors involving the size of the allylic oxygenated substituent. They reported that reaction of the diene **39a** in benzene gave a 37:63 mixture of the *anti* and *syn* adducts, **40a** and **41a**, respectively. Increasing the bulk of the allylic substituent to a methoxy group (*i.e.* the diene **39b**) led to a reversal of selectivity favouring the *anti* adduct **40b** over the *syn* adduct **41b** in an 89:11 ratio. Similarly, the trimethylsiloxy diene **39c**, showed a 91:9 *anti* to *syn* ratio. Changing the solvent to one capable of hydrogen bonding (*i.e.* methanol) resulted in a reversal of the selectivity exhibited by the diene **39a** (*anti* to *syn* adducts, 64:36). For this example

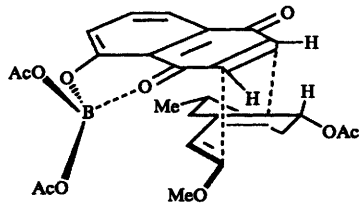


Fig. 1

Franck proposed that the hydroxy group became bulkier due to hydrogen bonding with the solvent and hence increased the steric interactions which destabilised the *syn* transition state. By analogy, the high *anti* selectivity exhibited by the hydroxylated dienes **18** and **19** in dichloromethane probably arises due to interaction of either the Lewis acid promoter or adventitious acetic acid with the allylic hydroxy group.

In summary, this synthetic approach to the angucyclinone antibiotics has resulted in the efficient syntheses of the racemic forms of rubiginone B_1 **3** (48%), rubiginone B_2 **4** (47%), 13-norrubiginone B_1 **34** (53%) and its B_2 congener **35** (51%), emycin A **12** (48%), ochromycinone **7** (46%), and the C-1 epimer **11** (40%). The overall yields (in brackets) are based on the commercially available dienophile 5-hydroxynaphthoquinone **8**. Furthermore, the high diastereoselectivity of the Diels–Alder step in the sequences will enable the stereoselective introduction of functionality into the B-ring of the cycloadducts *via* the C(4a)–C(5) double bond. The excellent facial selectivity exhibited by the dienes **18**, **19**, **20** and **21** will facilitate the asymmetric synthesis of angucyclinone antibiotics. The asymmetric synthesis of these dienes is currently under investigation.

Experimental

Mps were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. Varian Gemini 200 and

VXR300 spectrometers were used to obtain ^1H (200 and 300 MHz) and ^{13}C (50 and 75 MHz) NMR spectra. All spectra were measured on solutions of the compound in deuteriochloroform using the residual chloroform (δ 7.26) as internal reference unless otherwise stated. Chemical shifts are reported as parts per million (ppm) using the δ scale. Coupling constants (J) are reported to ±0.5 Hz. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrophotometer. EI and FAB mass spectra were recorded on a Kratos MSORF mass spectrometer operating with an accelerating voltage of 4 kV and an ionisation energy of 70 eV. For FAB mass spectrometry *m*-nitrobenzyl alcohol was used as the matrix and xenon as the ionising gas. Elemental analyses were carried out by Dr. R. G. Cunninghame and associates at the Campbell Microanalytical Laboratory, University of Otago, Dunedin, New Zealand. Thin layer chromatography (TLC) was performed on Merck silica gel DC Alurolle Kieselgel $60F_{254}$ plates and were visualised under an UV lamp and/or with a spray consisting of 5% (w/v) dodecamolybdophosphoric acid in ethanol with subsequent heating. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). All chromatography solvents were reagent grade. THF was distilled from sodium/potassium–benzophenone ketyl under nitrogen and dichloromethane was distilled from P_2O_5. All other solvents and reagents were purified using the methods outlined in *Purification of Laboratory Chemicals*, 2nd edn., Perrin, Armarego, and Perrin, Pergamon Press.

Preparation of the dienes 18, 19, 20 and 21

3-Ethynylcyclohex-2-enone 15. A solution of 3-ethoxycyclohex-2-enone **13** (15.0 g, 107 mmol) in THF (50 cm^3) was added to a solution of ethynylmagnesium bromide (200 mmol) in THF (400 cm^3) at ambient temperature. The mixture was stirred until the presence of **13** could not be detected (TLC) (18–48 h) after which it was acidified with hydrochloric acid (1 mol dm^{-3}; *ca.* 800 cm^3) and stirred for a further 15 min. The mixture was extracted with dichloromethane (5 × 200 cm^3) and the combined extracts were washed with water (2 × 200 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by silica gel column chromatography [diethyl ether–hexanes (3 : 1) as eluent] gave the title compound **15** (11.4 g, 89%) as a pale oil (Found: C, 79.9; H, 6.6%; *m/z* 120.0575 (M^+). C_8H_8O requires C, 80.0; H, 6.7%; *m/z* 120.0575); ν_{max}(film)/cm^{-1} 3241 (alkynyl CH), 2949 (CH), 2092 (C≡C) and 1673 (C=O); δ_H($CDCl_3$, 200 MHz) 1.97–2.15 and 2.38–2.52 (6 H, m, 4-, 5- and 6-H), 3.57 (1 H, s, ≡CH) and 6.26 br (1 H, t, *J* 2.5 and 2.5, 2-H); *m/z* (EI) 120 (M^+, 77%) and 92 (100%).

(±)-3-Ethynyl-5-methylcyclohex-2-enone 16. Treatment of 3-ethoxy-5-methylcyclohex-2-enone **14** (15.4 g, 108 mmol) in THF (50 cm^3) with ethynylmagnesium bromide (200 mmol) in THF (500 cm^3) using the preceding protocol gave the title compound **16** (12.2 g, 84%) as a viscous pale oil (Found: C, 80.6; H, 7.5. $C_9H_{10}O$ requires C, 80.6; H, 7.5%); ν_{max}(film)/cm^{-1} 3244 (alkynyl CH), 2957, 2928 and 2874 (CH), 2093 (C≡C) and 1658 (C=O); δ_H($CDCl_3$, 300 MHz) 1.07 (3 H, d, *J* 6.5, 5-Me), 2.02–2.34 and 2.43–2.54 (3 H and 2 H, m, 5-H, 4- and 6-H_2), 3.52 (1 H, s, ≡CH) and 6.50 br (1 H, s, 2-H); *m/z* (EI) 134 (M^+, 50%) and 92 (100%).

(±)-(*E*)-3-(2′-Methoxyvinyl)cyclohex-2-enol 18. 4-Methylmorpholine (9.2 cm^3, 83.2 mmol) was added to a solution of the ynenone **15** (10.00 g, 83.2 mmol) and methanol (13.5 cm^3, 333 mmol) in dry benzene (100 cm^3). The solution was stirred at ambient temperature for 20 h after which removal of the solvent under reduced pressure (temp. < 30 °C) gave (*E*)-3-(2′-methoxyvinyl)cyclohex-2-enone **17** as a crude reaction product, ν_{max}(film)/cm^{-1} 1657 (C=O), 1618 and 1580 (C=C); δ_H($CDCl_3$, 200 MHz) *inter alia* 1.86–2.00 and 2.20–2.40 (2 H and 4 H, m, 4-, 5- and 6-H_2), 3.61 (3 H, s, OMe), 5.54 (1 H, d, *J* 13.0, 1′-H), 5.73 br (1 H, s, 2-H) and 6.94 (1 H, d, *J* 13.0, 2′-H).

The crude dienone **17** was carefully added to a suspension of lithium aluminium hydride (3.15 g, 83.2 mmol) in THF (100 cm^3) under nitrogen at 0 °C and the mixture was warmed to room temperature and stirred for a further 30 min. After cooling of the mixture to 0 °C aqueous sodium hydroxide (25% w/v; 5 cm^3) was cautiously added to it over several minutes and stirring continued for a further 15 min. Anhydrous magnesium sulfate was added to the resultant suspension which after 10 min, was filtered through a Celite pad. The insoluble material was washed thoroughly with diethyl ether and the combined organic fractions were evaporated under reduced pressure (temp. < 30 °C) to give the title compound **18** (12.10 g, 94%) as a slightly impure, viscous pale oil (Found: *m/z* 154.0992 (M^+). $C_9H_{14}O_2$ requires *m/z* 154.0994); ν_{max}(film)/cm^{-1} 3374 (OH), 1643 (C=O) and 1619 (C=C); δ_H($CDCl_3$, 200 MHz) *inter alia* 1.50–2.15 (7 H, m, OH, 4-, 5- and 6-H_2), 3.55 (3 H, s, OMe), 4.15–4.29 (1 H, m, 1-H), 5.48 br and 5.50 (2 H, overlapping d and s, *J* 13.0, 1′- and 1-H) and 6.56 (1 H, d, *J* 13.0, 2′-H); *m/z* (EI) 154 (M^+, 87%) and 123 (M^+ − OMe, 100%).

(*E*,1*R,5*R**)-3-(2′-Methoxyvinyl)-5-methylcyclohex-2-enol 19.** 4-Methylmorpholine (8.2 cm^3, 74.5 mmol) was added to a solution of the ynenone **16** (10.00 g, 74.5 mmol) and methanol (12.2 cm^3, 302 mmol) in dry benzene (100 cm^3). The solution was stirred at ambient temperature for 20 h after which it was evaporated under reduced pressure (temp. < 30 °C) to give the (*E*,1*R**,5*R**)-3-(2′-methoxyvinyl)-5-methylcyclohex-2-enone **9** as a crude reaction product, ν_{max}(film)/cm^{-1} 1652 (C=O), 1618 and 1580 (C=C); δ_H($CDCl_3$, 300 MHz) *inter alia* 1.06 (3 H, d, *J* 6.5, 5-Me), 1.90–2.24 and 2.35–2.55 (6 H, m, 5-H, OH, 4- and 6-H_2), 3.67 (3 H, s, OMe), 5.60 (1 H, d, *J* 13.0, 1′-H), 5.78 br (1 H, s, 2-H) and 7.00 (1 H, d, *J* 13.0, 2′-H).

A solution of the crude dienone **9** in THF (20 cm^3) at −78 °C was carefully added to a suspension of lithium aluminium hydride (2.82 g, 74.5 mmol) in THF (100 cm^3) under nitrogen at −78 °C. The mixture was stirred at this temperature for 35 min and then slowly warmed to room temperature over 17 h. After cooling of the mixture to 0 °C aqueous sodium hydroxide (25% w/v; 5 cm^3) was cautiously added to it over several minutes after which stirring was continued for a further 15 min. Anhydrous magnesium sulfate was added to the resultant suspension and after 10 min the mixture was filtered through a Celite pad. The insoluble material was washed thoroughly with diethyl ether after which evaporation of the combined organic fractions under reduced pressure (temp. < 30 °C) gave the title compound **19** (9.36 g, 75%) as a viscous pale oil [Found: *m/z* 168.1157 (M^+). $C_{10}H_{16}O_2$ requires 116.1150]; ν_{max}(film)/cm^{-1} 3355 (OH), 1644 and (C=O) and 1620 (C=C); δ_H($CDCl_3$, 300 MHz) *inter alia* 0.95–1.15 (4 H, m, 6-H and 5-Me), 1.50–1.80 and 1.94–2.55 (2 H and 3 H, m, OH, 5-, 6-H and 4-H_2), 3.56 (3 H, s, OMe), 4.25–4.35 (1 H, m, 1-H), 5.44 br (1 H, s, 2-H), 5.50 (1 H, d, *J* 13.0, 1′-H) and 6.55 (1 H, d, *J* 13.0, 2′-H); *m/z* (EI) 168 (M^+, 22%) and 91 (100%).

(±)-1-Acetoxy-3-(2′-methoxyvinyl)cyclohex-2-ene 20. A solution of the dienol **18** (10.0 g, 65 mmol), triethylamine (18.0 cm^3, 130 mmol) and acetic anhydride (12.3 cm^3, 130 mmol) were stirred at ambient temperature for 4 h after which removal of the triethylamine, acetic anhydride and by-products from the reaction by vacuum distillation gave the title compound **20** (10.94 g) as an unstable brown syrup, ν_{max}(film)/cm^{-1} 1730 (acetate), 1644 and 1620 (C=O, C=C); δ_H($CDCl_3$, 200 MHz) *inter alia* 1.60–2.18 (6 H, m, 4-, 5-, 6-H_2), 2.19 (3 H, s, OAc), 3.56 (3 H, s, OMe), 5.20–5.37 (1 H, m, 2-H), 5.48 (1 H, d, *J* 13.0, 1′-H) and 6.60 (1 H, d, *J* 13.0, 2′-H); *m/z* (EI) 137 (M^+ − AcO, 30%).

(*E*,1*R,5*R**)-1-Acetoxy-3-(2′-methoxyvinyl)-5-methylcyclohex-2-ene 21.** A solution of the dienol **19** (9.36 g, 55.6 mmol), triethylamine (15.5 cm^3, 111 mmol) and acetic anhydride (10.5 cm^3, 111 mmol) were allowed to react using the above procedure and gave the title compound **21** (10.94 g) as an unstable brown syrup, ν_{max}(film)/cm^{-1} 1729 (acetate), 1647 and 1620 (C=C); δ_H($CDCl_3$, 200 MHz) *inter alia* 1.02 (3 H, d, *J* 6.5, 5-Me), 2.04 (3 H, s, OAc), 3.57 (3 H, s, OMe), 5.38 br (1 H, s, 2-H), 5.51 (1 H, d, *J* 13.0, 1′-H) and 6.59 (1 H, d, *J* 13.0, 2′-H); *m*/*z* (EI) 210 (M^+, 100%).

Diels–Alder cycloaddition of the naphthoquinone 8 and the dienes 18, 19, 20 and 21

(a) (1*R,6*R**,6a*S**,12a*S**,12b*R**)-1,8-Dihydroxy-6-methoxy-1,2,3,4,6,6a,12a,12b-octahydrobenzo[*a*]anthracene-7,12-dione 22.** The dienol **18** (0.211g, 1.37 mmol) was added to a solution of tetra-*O*-acetyl diborate (0.314 g, 1.15 mmol) and 5-hydroxy-1,4-naphthoquinone **8** (0.200 g, 1.15 mmol) in dichloromethane (15 cm^3) at 0 °C. The mixture was stirred for 1 min and then poured onto water (20 cm^3). The mixture was extracted with dichloromethane (2 × 20 cm^3) and the combined extracts were washed thoroughly with water, dried ($MgSO_4$), and concentrated under reduced pressure to *ca.* 10 cm^3. The residue was diluted with diethyl ether (100 cm^3) and then slowly concentrated to *ca.* 20 cm^3. Storage provided finely divided crystals which were recrystallised from dichloromethane–diethyl ether to give the title compound **22** (0.317 g, 84%) as pale crystals, mp 162–164 °C (Found: C, 69.5; H, 6.1. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%); ν_{max}(KBr)/cm^{-1} 3469 (OH), 1711 and 1634 (C=O), and 1573; δ_H(300 MHz, $CDCl_3$) 1.24–1.50 (1 H, m, 2-H_{ax}), 1.56 (1 H, tq, *J* 13.0, 13.0, 13.0, 4.0 and 4.0, 3-H_{ax}), 1.75–1.85 (2 H, m, 3-H_{eq} and 1-OH), 2.00–2.17 (2 H, m, 2-H_{eq} and 4-H_{ax}), 2.20–2.28 (1 H, m, 12b-H), 2.31–2.41 (1 H, m, 4-H_{eq}), 3.00 (3 H, s, 6-OMe), 3.16 (1 H, t, *J* 5.0 and 5.0, 6a-H), 3.75 (1 H, t, *J* 5.0 and 5.0, 12a-H), 4.03 br (1 H, t, *J* 5.0 and 5.0, 6-H), 4.88 (1 H, dt, *J* 11.0, 11.0 and 4.0, 1-H), 5.77 (1 H, qn, *J* 5.0, 2.5 and 2.5, 5-H), 7.16 (1 H, dd, *J* 8.0 and 1.0, 9-H), 7.37 (1 H, dd, *J* 8.0 and 1.0, 11-H), 7.58 (1 H, t, *J* 8.0 and 8.0, 10-H) and 12.04 (1 H, s, 8-OH); *m*/*z* 328 (EI) (M^+, 8%) and 296 (M^+ – MeOH, 90%).

(b) (1*R,3*R**,6*R**,6a*S**,12a*S**,12b*R**)-1,8-Dihydroxy-6-methoxy-3-methyl-1,2,3,4,6,6a,12a,12b-octahydrobenzo[*a*]-anthracene-7,12-dione 23.** The dienol **19** (0.232 g, 1.38 mmol) was added to a solution of tetra-*O*-acetyl diborate (0.314 g, 1.15 mmol) and naphthoquinone **8** (0.200 g, 1.15 mmol) in dichloromethane (15 cm^3) at 0 °C and the mixture was stirred for 1 min; it was then poured onto water (20 cm^3). The mixture was extracted with dichloromethane (2 × 20 cm^3) and the combined extracts were washed thoroughly with water, dried ($MgSO_4$), and evaporated. Purification of the residue by flash column chromatography on silica gel [diethyl ether–hexanes (1:4) as eluent], and crystallisation from diethyl ether–light petroleum gave the title compound **23** (0.295 g, 75%) as colourless crystals, mp 134–136 °C (Found: C, 69.9; H, 6.3. $C_{20}H_{22}O_5$ requires C, 70.2; H, 6.5%); ν_{max}(KBr)/cm^{-1} 3512 (OH) and 1709 and 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 1.00 (3 H, d, *J* 6.0, 3-Me), 1.11 (1 H, q, *J* 11.5, 11.5 and 11.5, 2-H_{ax}), 1.71–1.82 (2 H, m, 3- and 4-H_{ax}), 2.00–2.10 (1 H, m, 2-H_{eq}), 2.15–2.23 (1 H, m, 12b-H), 2.25–2.40 (1 H, m, 4-H_{eq}), 3.00 (3 H, s, 6-OMe), 3.16 (1 H, t, *J* 4.5 and 4.5, 6a-H), 3.74 (1 H, t, *J* 5.5 and 5.5, 12a-H), 4.03 br (1 H, t, *J* 4.0 and 4.0, 6-H), 4.90 (1 H, ddt, *J* 11.0, 11.0, 5.0 and 4.5, 1-H), 5.70–5.80 (1 H, m, 5-H), 7.16 (1 H, dd, *J* 7.5 and 1.0, 9-H), 7.36 (1 H, dd, *J* 8.0 and 1.0, 11-H), 7.57 (1 H, t, *J* 8.0 and 8.0, 10-H) and 12.05 (1 H, s, 8-OH); addition of D_2O led to exchange of a signal at δ 1.75 and simplification of the signal at δ 4.90 br (1 H, dt, *J* 11.0, 11.0 and 4.5, 1-H); *m*/*z* (FAB) 343 (MH^+, 5%) and 311 (M^+ – MeOH, 15%).

(c) (1*R,6*R**,6a*S**,12a*S**,12b*R**)-1-Acetoxy-8-hydroxy-6-methoxy-1,2,3,4,6,6a,12a,12b-octahydrobenzo[*a*]anthracene-7,12-dione 29.** Reaction of the diene **20** (0.271 g, 1.38 mmol), tetra-*O*-acetyl diborate (0.314 g, 1.15 mmol), and naphthoquinone **8** (0.200 g, 1.15 mmol) using the procedure outlined in part (b) gave, after purification by silica column chromatography [diethyl ether–hexanes (3:7) as eluent] and crystallisation from diethyl ether–light petroleum, the title compound **29** (0.312 g, 73%) as cream coloured needles, mp 142–144 °C (Found: C, 68.0; H, 5.8. $C_{21}H_{22}O_6$ requires C, 68.1; H, 6.0%); ν_{max}(KBr)/cm^{-1} 1727 (C=O, ester), 1701, 1643 (C=O) and 1602; δ_H(300 MHz, $CDCl_3$) 1.18–1.38 (1 H, m, 2-H_{ax}), 1.65 br (1 H, qt, *J* 12.0, 12.0, 12.0, 5.0 and 5.0, 3-H_{ax}), 1.76–1.86 (1 H, m, 3-H_{eq}), 1.94 (3 H, s, OAc), 2.04–2.19 (1 H, m, 4-H_{ax}), 2.28–2.47 (3 H, m, 2- and 4-H_{eq}, and 12b-H), 3.00 (3 H, s, 6-OMe), 3.19 (1 H, t, *J* 5.0 and 5.0, 6a-H), 3.52 (1 H, t, *J* 5.0 and 5.0, 12a-H), 3.90–4.06 (1 H, m, 6-H), 5.76 (1 H, qn, *J* 5.0, 2.5 and 2.5, 5-H), 5.87 (1 H, dt, *J* 10.5, 10.5 and 4.5, 1-H), 7.14 (1 H, dd, *J* 8.0 and 1.0, 9-H), 7.35 (1 H, dd, *J* 8.0 and 1.0, 11-H), 7.56 (1 H, t, *J* 8.0 and 8.0, 10-H) and 11.98 (1 H, s, 8-OH); *m*/*z* (FAB) 371 (MH^+, 8%), 279 (M^+ – MeOH – AcO, 40%).

(d) (1*R,3*R**,6*R**,6a*S**,12a*S**,12b*R**)-1-Acetoxy-8-hydroxy-6-methoxy-3-methyl-1,2,3,4,6,6a,12a,12b-octahydrobenzo[*a*]anthracene-7,12-dione 30.** Reaction of the diene **21** (0.271 g, 1.38 mmol), tetra-*O*-acetyl diborate (0.314 g, 1.15 mmol) and naphthoquinone **8** (0.200 g, 1.15 mmol) using the procedure outlined in part (b) gave, after purification by silica column chromatography [diethyl ether–hexanes (3:7) as eluent] and crystallisation from diethyl ether–light petroleum, the title compound **30** (0.315 g, 71%) as cream coloured needles, mp 148–150 °C (Found: C, 68.7; H, 6.3. $C_{22}H_{24}O_6$ requires C, 68.7; H, 6.3%); ν_{max}(KBr)/cm^{-1} 1717 and 1644 (C=O); δ_H(300 MHz, $CDCl_3$) 1.00 (3 H, d, *J* 6, 3-Me), 1.05 (1 H, q, *J* 11.5, 11.5 and 11.5, 2-H_{ax}), 1.72–1.93 (2 H, m, 3-H and 4-H_{ax}), 1.94 (3 H, s, OAc), 2.26 (1 H, ddd, *J* 11.5, 4.5 and 4.0, 2-H_{eq}), 2.31–2.42 (2 H, m, 4-H_{eq} and 12b-H), 3.00 (3 H, s, 6-OMe), 3.19 (1 H, t, *J* 5.0 and 5.0, 6a-H), 3.52 (1 H, t, *J* 5.0 and 5.0, 12a-H), 4.04 br (1 H, t, *J* 5.0 and 5.0, 6-H), 5.75 (1 H, qn, *J* 5.0, 2.5 and 2.5, 5-H), 5.91 (1 H, dt, *J* 11.0, 11.0 and 4.5, 1-H), 7.15 (1 H, dd, *J* 8.5 and 1.0, 9-H), 7.35 (1 H, dd, *J* 8.5 and 1.0, 11-H), 7.56 (1 H, t, *J* 8.5 and 8.5, 10-H) and 11.98 (1 H, s, 8-OH).

Fragmentation of the cycloadducts 22 and 23

(a) 4-(5′-Hydroxy-9′,10′-dioxo-9′,10′-dihydroanthracen-2′-yl)-butanal 24. Triethylamine (0.170 cm^3, 1.22 mmol) was added to a solution of the cycloadduct **22** (0.100 g, 0.304 mmol) in dichloromethane (20 cm^3) under an air atmosphere. The mixture was poured into dilute hydrochloric acid (1 mol dm^{-3}; 50 cm^3) and then extracted with dichloromethane (2 × 20 cm^3). The combined extracts were dried ($MgSO_4$), diluted with hexanes (20 cm^3) and then concentrated to *ca.* 5 cm^3. Filtration of the residue gave the title compound **24** (0.082 g, 92%) as yellow crystals, mp 87–89 °C (Found: C, 73.4; H, 4.7. $C_{18}H_{14}O_4$ requires C, 73.5; H, 4.8%); ν_{max}(KBr)/cm^{-1} 1713 (C=O, aldehyde), 1668, 1638 (C=O, quinone) and 1600; δ_H(300 MHz, $CDCl_3$) 1.98–2.12 (2 H, m, 3-H_2), 2.53 (2 H, dt, *J* 7.5, 7.5 and 1.0, 2-H_2), 2.85 (2 H, t, *J* 7.5 and 7.5, 4-H_2), 7.32 (1 H, dd, *J* 8.5 and 1.0, 6′-H), 7.63 (1 H, dd, *J* 8.5 and 2.0, 3′-H), 7.67 (1 H, t, *J* 7.5 and 7.5, 7′-H), 7.83 (1 H, dd, *J* 7.5 and 1.0, 8′-H), 8.11 (1 H, d, *J* 2.0, 1′-H), 8.25 (1 H, d, *J* 8.0, 4′-H), 9.80 (1 H, t, *J* 1.0 and 1.0, 1-H) and 12.65 (1 H, s, 5-OH); *m*/*z* (EI) 294 (M^+, 70%) and 250 (100%).

(b) (±)-4-(5′-Hydroxy-9′,10′-dioxo-9′,10′-dihydroanthracen-2′-yl)-3-methylbutanal 25. Triethylamine (0.163 cm^3, 1.17 mmol) was added to a solution of the cycloadduct **23** (0.100 g, 0.292 mmol) in dichloromethane (20 cm^3) under an aerial atmosphere. Work-up and crystallisation of the product (as for aldehyde **24**) gave the title compound **25** (0.085 g, 94%) as

yellow crystals, mp 93–95 °C (Found: C, 74.1; H, 5.1. $C_{19}H_{16}O_4$ requires C, 74.0; H, 5.2%); ν_{max}(KBr)/cm^{-1} 1716 (C=O, aldehyde), 1668 and 1638 (C=O, quinone) and 1598; δ_H(300 MHz, $CDCl_3$) 1.00 (3 H, d, *J* 6.5, 3-Me), 2.30–2.56 (3 H, m, 3-H and 2-H_2), 2.69 (1 H, dd, *J* 13.5 and 7.5, 4-H), 2.84 (1 H, dd, *J* 13.5 and 6.0, 4-H), 7.31 (1 H, dd, *J* 8.5 and 1.0, 6′-H), 7.62 (1 H, dd, *J* 8.0 and 2.0, 3′-H), 7.67 (1 H, t, *J* 8.0 and 8.0, 7′-H), 7.84 (1 H, dd, *J* 8.0 and 1.0, 8′-H), 8.08 (1 H, d, *J* 2.0, 1′-H), 8.25 (1 H, d, *J* 8.0, 4′-H), 9.76 (1 H, t, *J* 1.5 and 1.5, 1-H) and 12.65 (1 H, s, 5-OH); *m/z* (EI) 308 (M^+, 50%) and 264 (100%).

Acetylation of 23. The cycloadduct **23** (0.100 g, 0.292 mmol) was added to a solution of acetic anhydride (3 cm^3) and pyridine (3 cm^3) and the resultant mixture stirred under a nitrogen atmosphere until the presence of the starting material could not be detected by TLC (*ca.* 3.5 h). The mixture was poured into aqueous hydrochloric acid (*ca.* 50 cm^3) and stirred at ambient temperature for 30 min after which it was extracted with diethyl ether (3 × 20 cm^3). The combined extracts were dried ($MgSO_4$), diluted with hexanes (20 cm^3), and slowly concentrated under reduced pressure to yield a light brown solid. Recrystallisation of this from diethyl ether–light petroleum yielded the (1*R**,3*R**,6*R**,6a*S**,12a*S**,12b*R**)-1,8-diacetoxy-6-methoxy-3-methyl-1,2,3,4,6,6a,12a,12b-*octahydrobenzo*[a]-*anthracene*-7,12-*dione* **26** as clear crystals (0.113 g, 91%), mp 179–181 °C (Found: C, 67.4; H, 6.0. $C_{24}H_{26}O_7$ requires C, 67.6; H, 6.1%); ν_{max}(KBr)/cm^{-1} 1773, 1725 and 1687 (C=O); δ_H(300 MHz, $CDCl_3$) 0.99 (3 H, d, *J* 6.0, 3-Me), 1.04 (1 H, q, *J* 11.5, 11.5 and 11.5, 2-H_{ax}), 1.70–1.94 (2 H, m, 3-H and 4-H_{ax}), 1.95 (3 H, s, 1-OAc), 2.20–2.35 (2 H, m, 12b-H and 2-H_{eq}), 2.36 (1 H, br d, *J* 15.0, 4-H_{eq}), 2.43 (3 H, s, 8-OAc), 2.97 (3 H, s, 6-OMe), 3.11 (1 H, t, *J* 5.0 and 5.0, 6a-H), 3.59 (1 H, t, *J* 5.0 and 5.0, 12a-H), 3.99 (1 H, br t, *J* 4.5 and 4.5, 6-H), 5.73 (1 H, qn, *J* 9.0, 4.5 and 4.5, 6-H), 5.89 (1 H, td, *J* 10.0, 10.0 and 4.5, 1-H), 7.26 (1 H, dd, *J* 8.0 and 1.5, 9-H), 7.67 (1 H, t, *J* 7.5 and 7.5, 10-H) and 7.80 (1 H, dd, *J* 7.5 and 1.0, 11-H); *m/z* (EI) 366 (M^+ − AcOH, 85%) and 323 (100%).

Aromatisation of the adducts 29 and 30.

(a) A mixture of the cycloadduct **29** (0.200 g, 0.595 mmol) and DBU (0.161 g, 1.06 mmol) in dichloromethane (10 cm^3) was stirred at 0 °C under an aerial atmosphere until no starting material was detected by TLC (*ca.* 15 min). The mixture was then poured into hydrochloric acid (0.5 mol dm^{-3}; 30 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to *ca.* 20 cm^3 and then diluted with diethyl ether (100 cm^3). Concentration of the mixture to *ca.* 10 cm^3 followed by storage and filtration gave finely divided yellow crystals of (±)-1-*acetoxy*-8-*hydroxy*-1,2,3,4-*tetrahydrobenzo*[a]*anthracene*-7,12-*dione* **31** (0.159 g, 88%), mp 206–208 °C (Found: C, 71.1; H, 4.6. $C_{20}H_{16}O_5$ requires C, 71.4; H, 4.8%); ν_{max}(KBr)/cm^{-1} 1737 (acetate) and 1666 and 1637 (C=O); δ_H(300 MHz, $CDCl_3$) 1.80–2.00 (3 H, m, 2-H_{ax} and 4-H), 2.02 (3 H, s, OAc), 2.30–2.41 (1 H, m, 2-H_{eq}), 2.85–2.99 (1 H, m, 3-H_{ax}), 3.01–3.13 (1 H, m, 3-H_{eq}), 6.78 (1 H, t, *J* 3.5 and 3.5, 1-H), 7.25 (1 H, dd, *J* 8.0 and 1.0, 9-H), 7.58 (1 H, d, *J* 8.0, 5-H), 7.64 (1 H, t, *J* 8.0 and 8.0, 10-H), 7.75 (1 H, dd, *J* 8.0 and 1.0, 11-H), 8.28 (1 H, d, *J* 8.0, 6-H) and 12.43 (1 H, s, 8-OH); *m/z* (FAB) 337 (MH^+, 5%) and 277 (MH^+ − AcOH, 20%).

(b) (1*R,3*R**)-1-Acetoxy-8-hydroxy-3-methyl-1,2,3,4-tetrahydrobenzo[*a*]anthracene-7,12-dione 28.** Aromatisation of the cycloadduct **30** (0.200 g, 0.523 mmol) using the procedure outlined in part (a) gave the title compound **28** (0.157 g, 86%) as yellow crystals, mp 206–208 °C (Found: C, 71.8; H, 5.4. $C_{21}H_{18}O_5$ requires C, 72.0; H, 5.2%); ν_{max}(KBr)/cm^{-1} 3500 (OH), 1735 (acetate) and 1670 and 1630 (C=O); δ_H(300 MHz, $CDCl_3$) 1.13 (3 H, d, *J* 6.5, 3-Me), 1.45 (1 H, ddd, *J* 13.0, 11.5 and 8.5, 2-H_{ax}), 1.96 (3 H, s, OAc), 1.96–2.10 (1 H, m, 3-H_{ax}), 2.60 (1 H, ddt, *J* 12.5, 5.0, 5.0 and 2.5, 2-H_{eq}), 2.66 (1 H, dd, *J* 17.0 and 10.5, 4-H_{ax}) 2.92 (1 H, ddd, *J* 17.0, 4.5 and 2.0, 4-H_{eq}), 6.80 (1 H, t, *J* 8.0 and 8.0, 1-H), 7.26 (1 H, dd, *J* 8.0 and 2.0, 9-H), 7.53 (1 H, d, *J* 8.0, 5-H), 7.64 (1 H, t, *J* 7.5 and 7.5, 10-H), 7.69 (1 H, dd, *J* 7.5 and 1.5, 11-H), 8.27 (1 H, d, *J* 8.0, 6-H) and 12.41 (1 H, s, 8-OH); *m/z* (FAB) 351 (MH^+, 40%), 307 (M^+ − Ac, 95%) and 291 (MH^+ − AcOH, 100%).

(±)-Emycin A [(1*R,3*R**)-1,8-dihydroxy-3-methyl-1,2,3,4-tetrahydrobenzo[*a*]anthracene-7,12-dione] 12.** Sodium methoxide in methanol (10% w/v; 10 cm^3) was added to a solution of the acetate **28** (0.100 g, 0.286 mmol) in THF (10 cm^3) at ambient temperature under nitrogen and the mixture was stirred for 10 min. Hydrochloric acid (0.5 mol dm^{-3}; 50 cm^3) was added to the mixture which was then extracted with ethyl acetate (4 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated and purification of the product by silica gel column chromatography [diethyl ether–hexanes (1:3) as eluent] followed by crystallisation from diethyl ether–light petroleum gave the title compound **12** (0.069 g, 78%) as yellow crystals, mp 149–151 °C (Found: C, 73.9; H, 5.2. $C_{19}H_{16}O_4$ requires C, 74.0; H, 5.2%); ν_{max}(KBr)/cm^{-1} 3500 br (OH) and 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 1.15 (3 H, d, *J* 7.0, 3-Me), 1.65 (1 H, ddd, *J* 13.0, 12.5 and 9.0, 2-H_{ax}), 1.82–1.97 (1 H, m, 3-H_{ax}), 2.40 (1 H, ddt, *J* 12.5, 7.5, 2.5 and 2.5, 2-H_{eq}), 2.68 (1 H, dd, *J* 17.0 and 10.0, 4-H_{ax}), 2.88 (1 H, dt, *J* 17.0, 3.5 and 3.5, 4-H_{eq}), 4.90 (1 H, d, *J* 5.0, 1-OH), 5.48 br (1 H, dt, *J* 9.0, 8.0 and 5.0, 1-H), 7.29 (1 H, d, *J* 8.5, 9-H), 7.55 (1 H, d, *J* 7.5, 5-H), 7.67 (1 H, t, *J* 8.0 and 8.0, 10-H), 7.80 (1 H, d, *J* 8.0, 11-H), 8.25 (1 H, d, *J* 8.0, 6-H) and 12.50 (1 H, s, 8-OH); δ_C(75 MHz, $CDCl_3$) 21.6 (3-Me), 27.6 (C-3), 40.0 (C-4), 40.6 (C-2), 66.7 (C-1), 120.2 (C-9), 124.1 (C-11), 126.5 (C-5), 133.9 (C-11a), 134.7 (C-12a), 135.6 (C-10), 136.7 (C-6), 143.5 (C-12b), 147.1 (C-4a) and 161.9 (C-8); *m/z* (EI) 308 (M^+, 100%).

Methylation of the phenols 31 and 28

(a) A solution of the phenol **31** (0.100 g, 0.297 mmol) in dichloromethane (1 cm^3) was added to a suspension of silver(I) oxide (0.100 g, 0.431 mmol) in argon-purged iodomethane (10 cm^3) under an argon atmosphere and in the dark. The mixture was heated at reflux until the presence of **31** could not be detected (*ca.* 60 min, TLC). The work-up procedure was carried out in the dark (darkroom). The mixture was filtered through a pad of Celite which was then washed with diethyl ether (20 cm^3). The combined filtrate and washings were evaporated under reduced pressure and the residue was dissolved in dichloromethane (1 cm^3) and the solution diluted with diethyl ether (25 cm^3) and hexanes (5 cm^3). After this it was slowly concentrated to *ca.* 10 cm^3 and stored overnight in the dark under oxygen-free conditions. Filtration gave (±)-1-*acetoxy*-8-*methoxy*-1,2,3,4-*tetrahydrobenzo*[a]*anthracene*-7,12-*dione* **32** (0.093 g, 89%) as yellow crystals, mp 171–173 °C (Found: C, 71.8; H, 5.1. $C_{21}H_{18}O_5$ requires C, 72.0; H, 5.2%); ν_{max}(KBr)/cm^{-1} 1738 (acetate), 1669 (C=O) and 1590; δ_H(300 MHz, $CDCl_3$) 1.78–2.00 (3 H, m, 2-H_{ax} and 3-H_2), 2.04 (3 H, s, OAc), 2.28–2.39 (1 H, m, 2-H_{eq}), 2.81–2.95 (1 H, m, 4-H_{ax}), 3.03 br (1 H, dt, *J* 17.5, 4.5 and 4.5, 4-H_{eq}), 4.03 (3 H, s, OMe), 6.72 (1 H, br t, *J* 3.5 and 3.5, 1-H), 7.28 (1 H, dd, *J* 7.5 and 1.0, 9-H), 7.53 (1 H, d, *J* 8.0, 5-H), 7.68 (1 H, t, *J* 8.0 and 8.0, 10-H), 7.86 (1 H, dd, *J* 7.5 and 1.0, 11-H) and 8.24 (1 H, d, *J* 8.0, 6-H); *m/z* (FAB) 351 (MH^+, 8%) and 307 (M^+ − Ac, 70%).

(b) The phenol **28** (0.100 g, 0.285 mmol) was methylated as in part (a) to give (1R*,3R*)-1-*acetoxy*-8-*methoxy*-3-*methyl*-1,2,3,4-*tetrahydrobenzo*[a]*anthracene*-7,12-*dione* **33** (0.089 g, 86%) as light-sensitive yellow crystals, mp 139–140 °C (Found: C, 72.2; H, 5.6. $C_{22}H_{20}O_5$ requires C, 72.5; H, 5.5%); ν_{max}(KBr)/cm^{-1} 1739 (acetate), 1676 and 1659 (C=O), 1584 and 1570; δ_H(300 MHz, $CDCl_3$) 1.16 (3 H, d, *J* 6.5, 3-Me), 1.48 (1 H, ddd, *J* 13.0, 11.5 and 9.5, 2-H_{ax}), 2.00 (3 H, s, OAc), 2.00–2.12 (1 H, m, 3-H), 2.56–2.74 (2 H, m, 2-H_{eq} and 4-H_{ax}), 2.97 (1 H, ddd,

J 17.0, 5.0 and 2.5, 4-H_{eq}), 4.10 (3 H, s, OMe), 6.81 (1 H, br t, *J* 8.0 and 8.0, 1-H), 7.33 (1 H, dd, *J* 8.5 and 1.0, 9-H), 7.52 (1 H, d, *J* 8.0, 5-H), 7.73 (1 H, t, *J* 8.0 and 8.0, 10-H), 7.81 (1 H, dd, *J* 7.5 and 1.0, 11-H) and 8.25 (1 H, d, *J* 8.0, 6-H); *m/z* (EI) 364 (M^+, 8%) and 321 (M^+ − Ac, 100%).

Deacetylation of compounds 32 and 33

(a) (±)-13-Norrubiginone B_1 [(±)-1-hydroxy-8-methoxy-1,2,3,4-tetrahydrobenzo[*a*]anthracene-7,12-dione] 34. Sodium methoxide in methanol (10% w/v; 10 cm^3) was added to a solution of the acetate **32** (0.100 g, 0.285 mmol) in THF (10 cm^3) at ambient temperature under nitrogen in the dark and the mixture was stirred for 10 min. Hydrochloric acid (0.5 mol dm^{-3}; 50 cm^3) was added to the mixture which was then extracted with ethyl acetate (4 × 20 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated and the residue was purified by silica gel column chromatography [diethyl ether–hexanes (1:3) as eluent] followed by crystallisation from diethyl ether–light petroleum to give the title compound **34** (0.082 g, 93%) as light-sensitive yellow crystals, mp 158–160 °C [Found: C, 74.1; H, 5.2%; *m/z* (EI) 308.1044 (M^+, 100%) $C_{19}H_{16}O_4$ requires C, 74.0; H, 5.2%; *m/z* 308.1049]; ν_{max}(KBr)/cm^{-1} 3460 (OH), 1652 (C=O), 1574, 1571 and 1568; δ_H(300 MHz, $CDCl_3$) 1.65–1.90 (2 H, m, 2-H_{ax} and 3-H_{eq}), 2.13 (1 H, ddq, *J* 13.0, 13.0, 13.0, 5.5 and 3.0, 3-H_{ax}), 2.24–2.35 (1 H, m, 2-H_{eq}), 2.84 (1 H, ddd, *J* 18.0, 12.0 and 6.0, 4-H_{ax}), 3.01 br (1 H, dd, *J* 17.5 and 5.0, 4-H_{eq}), 4.04 (3 H, s, OMe), 4.85 (1 H, dd, *J* 3.5 and 1.5, 1-OH), 5.14 br (1 H, q, *J* 3.5, 3.5 and 3.5, 1-H), 7.30 br (1 H, d, *J* 7.5, 9-H), 7.53 (1 H, d, *J* 8.0, 5-H), 7.70 (1 H, t, *J* 8.0 and 8.0, 10-H), 7.84 (1 H, dd, *J* 7.5 and 1.0, 11-H) and 8.16 (1 H, d, *J* 8.0, 6-H); addition of D_2O led to exchange of the signal at δ 4.85 and simplification of the signal at δ 5.14 (1 H; t, *J* 3.5 and 3.5, 1-H); δ_C(75 MHz, $CDCl_3$) 16.8 (t, C-3), 30.8 and 31.2 (each t, C-2 and C-4), 56.7 (q, OMe), 63.4 (d, C-1), 117.7 (d), 119.9 (d), 120.9 (s), 126.8 (d), 131.9 (s), 135.1 (d), 136.1 (d), 137.3 (s), 140.1 (s), 144.4 (s), 159.8 (s, C-8), 182.5 (s, C-7) and 188.0 (s, C-12); *m/z* (EI) 308 (M^+, 100%).

(b) (±)-Rubiginone B_1 [(1*R,3*R**)-1-hydroxy-8-methoxy-3-methyl-1,2,3,4-tetrahydrobenzo[*a*]anthracene-7,12-dione] 3.** Deacetylation of **33** (0.100 g, 0.274 mmol) using the above procedure gave the title compound (±)-**3** (0.081 g, 91%) as light-sensitive yellow crystals, mp 154–156 °C [Found: C, 74.6; H, 5.7%; *m/z* (EI) 322.1203 (M^+, 100%); $C_{20}H_{18}O_4$ requires C, 74.5; H, 5.6%; *m/z* 322.1205]; ν_{max}(KBr)/cm^{-1} 3460 (OH), 1656 (C=O), 1581 and 1570; δ_H(300 MHz, $CDCl_3$) 1.21 (3 H, d, *J* 6.5, 3-Me), 1.70 (1 H, ddd, *J* 13.0, 11.0 and 9.0, 2-H_{ax}), 1.88–2.03 (1 H, m, 3-H), 2.45 (1 H, ddt, *J* 13.0, 7.5, 2.5 and 2.5, 2-H_{eq}), 2.70 (1 H, dd, *J* 17.0 and 10.5, 4-H_{ax}), 2.90 (1 H, ddd, *J* 17.0, 4.5 and 2.5, 4-H_{eq}), 4.10 (3 H, s, OMe), 5.17 (1 H, d, *J* 4.5, 1-OH), 5.49 (1 H, dt, *J* 8.0, 8.0 and 4.5, 1-H), 7.38 (1 H, dd, *J* 8.0 and 0.5, 9-H), 7.57 (1 H, d, *J* 8.0, 5-H), 7.77 (1 H, t, *J* 8.0 and 8.0, 10-H), 7.96 (1 H, dd, *J* 8.0 and 1.0, 11-H) and 8.23 (1 H, d, *J* 8.0, 6-H); addition of D_2O led to exchange of the signal at δ 5.17 and simplification of the signal at 5.49 br (1 H, t, *J* 8.0 and 8.0, 1-H); δ_C(75 MHz, [$^2H_6$]-DMSO) 21.7 (C-3 Me), 27.0 (C-3), 38.8 (C-4), 40.9 (C-2), 56.4 (OMe), 64.8 (C-1), 118.1 (C-9), 118.9 (C-11), 119.9 (C-7a), 125.2 (C-6), 132.4 (C-12a), 134.1 (C-5), 134.6 (C-6a), 135.4 (C-10), 137.3 (C-11a), 141.7 (C-12b), 144.5 (C-4a), 159.1 (C-8), 181.3 (C-7) and 186.4 (C-12); *m/z* (EI) 322 (M^+, 100%).

Oxidation of compounds 3, 12 and 34

(a) (±)-Rubiginone B_2 [(±)-8-methoxy-3-methyl-1,2,3,4-tetrahydrobenzo[a]anthracene-1,7,12-trione] 4. A solution of (±)-rubiginone B_1 **3** (0.100 g, 0.310 mmol) in dichloromethane (10 cm^3) under an atmosphere of oxygen was irradiated with a broad spectrum tungsten filament lamp (150 W). The solution, initially yellow, immediately turned an intense red and then slowly returned to yellow (15 min). Evaporation of the solution and crystallisation of the residue from diethyl ether–light petroleum gave the title compound **4** (0.097 g, 99%) as yellow crystals, mp 178–180 °C (Found: C, 75.0; H, 5.0. $C_{20}H_{16}O_4$ requires C, 75.0; H, 5.0%); ν_{max}(KBr)/cm^{-1} 1698, 1674 (C=O) and 1585; δ_H(300 MHz, $CDCl_3$) 1.20 (3 H, d, *J* 6.5, 3-Me), 2.38–2.74 and 2.94–3.40 (3 H and 2 H, m, 3-H, 2- and 4-H_2), 4.04 (3 H, s, OMe), 7.29 (1 H, br d, *J* 8.5, 9-H), 7.50 (1 H, d, *J* 8.0, 5-H), 7.70 (1 H, t, *J* 8.0 and 8.0, 10-H), 7.77 (1 H, dd, *J* 8.5 and 1.5, 11-H) and 8.26 (1 H, d, *J* 8.0, 6-H); *m/z* (EI) 320 (M^+, 100%) and 278 (M^+ − CO, 78%).

(b) 13-Norrubiginone B_2 [8-methoxy-1,2,3,4-tetrahydrobenzo-[*a*]anthracene-1,7,12-trione] 35. A solution of (±)-13-norrubiginone B_1 **34** (0.100 g, 0.327 mmol) in dichloromethane (10 cm^3) was oxidised using the procedure in (a) above to give the title compound **35** (0.96 g, 96%) as yellow crystals, mp 178–180 °C (Found: C, 74.5; H, 4.6%; $C_{19}H_{14}O_4$ requires C, 74.5; H, 4.6%); ν_{max}(KBr)/cm^{-1} 1692, 1667 (C=O) and 1589; δ_H(300 MHz, $CDCl_3$) 2.16–2.28 (2 H, m, 3-H_2), 2.85–2.96 (4 H, m, 2- and 4-H_2), 4.04 (3 H, s, OMe), 7.30 (1 H, dd, *J* 8.5 and 1.0, 9-H), 7.52 (1 H, d, *J* 8.5, 5-H), 7.70 (1 H, t, *J* 8.0 and 8.0, 10-H), 7.78 (1 H, dd, *J* 7.5 and 1.5, 11-H) and 8.26 (1 H, d, *J* 8.0, 6-H); *m/z* (EI) 306 (M^+, 80%) and 278 (M^+ − CO, 100%).

(c) (±)-Ochromycinone [(±)-8-hydroxy-3-methyl-1,2,3,4-tetrahydrobenzo[*a*]anthracene-1,7,12-trione] 7. A solution of (±)-emycin A **12** (0.100 g, 0.325 mmol) was photolysed using the procedure outlined in (a) for 17 h after which it was diluted with hexanes (10 cm^3), concentrated under reduced pressure to *ca.* 2 cm^3. After storage, the yellow crystals were filtered off to give the title compound **7** (0.097 g, 97%), mp 164–166 °C (lit.,[5] 168–169 °C); ν_{max}(KBr)/cm^{-1} 1700 and 1634; δ_H(300 MHz, $CDCl_3$) 1.21 (3 H, d, *J* 6.5, 3-Me), 2.39–2.55 (1 H, m, 3-H), 2.58 (1 H, dd, *J* 16.0 and 11.0, 4-H_{ax}), 2.69 (1 H, dd, *J* 17.0 and 11.0, 2-H_{ax}), 2.95–3.08 (2 H, m, 2- and 4-H_{eq}), 7.27 (1 H, dd, *J* 7.5 and 2.5, 9-H), 7.55 (1 H, br d, *J* 8.0, 5-H), 7.63–7.71 (2 H, m, 10- and 11-H), 8.29 (1 H, d, *J* 8.0, 6-H) and 12.30 (1 H, s, 8-OH); *m/z* (EI) 306 (M^+, 80%) and 278 (M^+ − CO, 35%).

Synthesis of (±)-1-*epi*-rubiginone B_1 11 *via* the *trans*-diene 36

(*E*,1*R,5*S**)-1-Acetoxy-3-(2′-methoxyvinyl)-5-methylcyclohex-2-ene 36.** A solution of the crude dieneone **9** (5.0 g, 30 mmol) in THF (20 cm^3) at 0 °C was carefully added to a suspension of lithium aluminium hydride (1.1 g, 30 mmol) in THF (100 cm^3) under nitrogen at 0 °C. The mixture was stirred at this temperature for 30 min after which it was warmed to room temperature over 17 h. After cooling to 0 °C, aqueous sodium hydroxide (25% w/v; 5 cm^3) was cautiously added over several minutes to the mixture whcih was then stirred for a further 15 min. Anhydrous magnesium sulfate was added to the resultant suspension which, after 10 min, was filtered through a Celite pad. The insoluble material was washed thoroughly with diethyl ether and the combined filtrate and washings were evaporated under reduced pressure (temp. < 30 °C). A mixture of the crude product, triethylamine (7.8 cm^3, 56 mmol) and acetic anhydride (5.3 cm^3, 56 mmol) was stirred at ambient temperature for 4 h. Work-up using the procedure described for the preparation of **20** gave a 3:1 mixture of the title compound **36** and **21** (5.4 g) as an unstable brown syrup, ν_{max}(film)/cm^{-1} 1729 (acetate), 1647 and 1620 (C=C); δ_H($CDCl_3$, 200 MHz) *inter alia* 1.02 (3 H, s, 5-Me), 3.57 (3 H, s, OMe), 5.38 (1 H, br s, 2-H), 5.51 (1 H, d, *J* 13.0, 1′-H) and 6.59 (1 H, d, *J* 13.0, 2′-H).

***Trans*-Cycloadduct 37.** Reaction of the dienes **21** and **36** (0.227 g, 1.14 mmol) as prepared above, tetra-*O*-acetyl diborate (0.314 g, 1.15 mmol) and naphthoquinone **8** (0.200 g, 1.15 mmol) using the procedure outlined for the synthesis of the cycloadduct **30**, gave after purification by silica column chromatography [diethyl ether–hexanes (1:4 to 1:1) gradient elution] crys-

tallisation from dichloromethane–diethyl ether, and recrystallisation from diethyl ether–light petroleum, (1R*,3S*,6R*,6aS*,12aS*,12bR*)-1-*acetoxy*-8-*hydroxy*-6-*methoxy*-3-*methyl*-1,2,3,4,6,6a,12a,12b-*octahydrobenzo*[a]*anthracene*-7,12-*dione* **37** (0.248 g, 56%) as cream coloured needles, mp 139–141 °C (Found: C, 69.0; H, 6.3%. $C_{22}H_{24}O_6$ requires C, 68.7; H, 6.3%); ν_{max}(KBr)/cm^{-1} 1722, 1716 and 1647 (C=O); δ_H(300 MHz, $CDCl_3$) 1.23 (3 H, d, *J* 6.5, 3-Me), 1.48–1.60 (1 H, m, 2-H_{ax}), 1.97 (3 H, s, OAc), 2.11–2.24 (3 H, m, 3-H, 2-H_{eq} and 4-H_{ax}), 2.31–2.44 (2 H, m, 2-H_{eq} and 12b-H), 3.00 (3 H, s, 6-OMe), 3.20 (1 H, t, *J* 4.5 and 4.5, 6a-H), 3.52 (1 H, t, *J* 5.0 and 5.0, 12a-H), 4.02–4.07 (1 H, m, 6-H), 5.77 (1 H, qn, *J* 5.0, 2.5 and 2.5, 5-H), 6.10 (1 H, dt, *J* 10.5, 10.5 and 4.5, 1-H), 7.15 (1 H, dd, *J* 8.5 and 1.5, 9-H), 7.36 (1 H, dd, *J* 8.0 and 1.5, 11-H), 7.57 (1 H, t, *J* 7.5 and 7.5, 10-H) and 11.98 (1 H, s, 8-OH); *m*/*z* (EI) 384 (M^+, 0.5%) and 324 (M^+ − AcOH, 100%).

Aromatisation of compound 37. Treatment of a solution of the cycloadduct **37** (0.200 g, 0.520 mmol) in dichloromethane (10 cm^3) with DBU using the procedure described for the preparation of angucyclinone **31** gave, after crystallisation from dichloromethane–diethyl ether, (1R*,3S*)-1-*acetoxy*-8-*hydroxy*-3-*methyl*-1,2,3,4-*tetrahydrobenzo*[a]*anthracene*-7,12-*dione* **27** (0.156 g, 90%) as yellow crystals, mp 190–192 °C (Found: C, 71.8; H, 5.2. $C_{21}H_{18}O_5$ requires C, 72.0; H, 5.2%); ν_{max}(KBr)/cm^{-1} 3400 (OH), 1736 (acetate) and 1671 and 1634 (C=O); δ_H(300 MHz, $CDCl_3$) 1.16 (3 H, d, *J* 6.5, 3-Me), 1.53 (1 H, ddd, *J* 15.0, 13.0 and 3.5, 2-H_{ax}), 2.02 (3 H, s, OAc), 2.02–2.22 (1 H, m, 3-H_{ax}), 2.38 (1 H, dq, *J* 14.5, 2.5, 2.5 and 2.5, 2-H_{eq}), 2.53 (1 H, dd, *J* 18.0 and 12.0, 4-H_{ax}), 3.08 (1 H, ddd, *J* 17.5, 5.0 and 2.0, 4-H_{eq}), 6.80 (1 H, t, *J* 3.0 and 3.0, 1-H), 7.24 (1 H, dd, *J* 7.5 and 2.0, 9-H), 7.57 (1 H, br d, *J* 8.0, 5-H), 7.66 (1 H, t, *J* 8.5 and 8.5, 10-H), 7.76 (1 H, dd, *J* 7.5 and 1.5, 11-H), 8.31 (1 H, d, *J* 8.0, 6-H) and 12.43 (1 H, s, 8-OH).

Methylation of compound 27. The phenol **27** (0.100 g, 0.297 mmol) was methylated using the procedure described for the methylation of **28** to give (1R*,3S*)-1-*acetoxy*-8-*methoxy*-3-*methyl*-1,2,3,4-*tetrahydrobenzo*[a]*anthracene*-7,12-*dione* **38** (0.091 g, 87%) as light-sensitive yellow crystals, mp 204–206 °C (Found: C, 72.4; H, 5.4. $C_{22}H_{20}O_5$ requires C, 72.5; H, 5.5%); ν_{max}(KBr)/cm^{-1} 1729 (acetate), 1669 (C=O) and 1586; δ_H(300 MHz, $CDCl_3$) 1.10 (3 H, d, *J* 6.5, 3-Me), 1.52 (1 H, ddd, *J* 15.0, 13.0 and 4.0, 2-H_{ax}), 2.04 (3 H, s, OAc), 2.05–2.20 (1 H, m, 3-H), 2.33 (1 H, dq, *J* 14.5, 2.5, 2.5 and 2.5, 2-H_{eq}), 2.50 (1 H, dd, *J* 17.5 and 12.0, 4-H_{ax}), 3.05 (1 H, ddd, *J* 17.0, 5.0 and 2.0, 4-H_{eq}), 4.00 (3 H, s, OMe), 6.74 (1 H, t, *J* 3.0 and 3.0, 1-H), 7.28 (1 H, dd, *J* 9.0 and 1.0, 9-H), 7.53 (1 H, d, *J* 8.5, 5-H), 7.68 (1 H, t, *J* 8.0 and 8.0, 10-H), 7.89 (1 H, dd, *J* 8.0 and 1.5, 11-H) and 8.25 (1 H, d, *J* 8.5, 6-H); *m*/*z* (EI) 364 (M^+, 8%) and 321 (M^+ − Ac, 100%).

(±)-1-*epi*-Rubiginone B_1 [(1*R,3*S**)-1-hydroxy-8-methoxy-3-methyl-1,2,3,4-tetrahydrobenzo[*a*]anthracene-7,12-dione] 11.** Treatment of **38** (0.100 g, 0.274 mmol) with sodium methoxide using the procedure outlined for the deacetylation of **32** and crystallisation from dichloromethane–diethyl ether gave the title compound **11** (0.079 g, 89%) as light-sensitive yellow crystals, mp 167–169 °C (Found: C, 74.1; H, 5.6%; *m*/*z* 322.1205 (M^+). $C_{20}H_{18}O_4$ requires C, 74.5; H, 5.6%; *m*/*z* 322.1205); ν_{max}(KBr)/cm^{-1} 3490 (OH), 1662 (C=O), 1583 and 1567; δ_H(300 MHz, $CDCl_3$) 1.12 (3 H, d, *J* 6.0, 3-Me), 1.45 (1 H, ddt, *J* 13.0, 13.0, 4.0 and 2.0, 2-H_{ax}), 2.24 (1 H, dq, *J* 13.0, 2.5, 2.5 and 2.5, 2-H_{eq}), 2.26–2.40 (1 H, m, 3-H_{ax}), 2.44 (1 H, dd, *J* 17.0 and 11.5, 4-H_{ax}), 3.02 br (1 H, ddd, *J* 17.0, 4.0 and 2.0, 4-H_{eq}), 4.04 (3 H, s, OMe), 4.87 (1 H, dd, *J* 4.0 and 2.0, 1-OH), 5.17 (1 H, dt, *J* 4.0, 4.0 and 2.0, 1-H), 7.31 (1 H, dd, *J* 8.0 and 1.0, 9-H), 7.52 (1 H, d, *J* 8.0, 5-H), 7.70 (1 H, t, *J* 8.0 and 8.0, 10-H), 7.82 (1 H, dd, *J* 8.0 and 1.0, 11-H) and 8.16 (1 H, d, *J* 8.0, 6-H); addition of D_2O led to exchange of the signal at δ 4.87 and simplification of the signal at δ 5.17 br (1 H, t, *J* 4.0 and 4.0, 1-H); *m*/*z* (EI) 322 (M^+, 100%).

Synthesis of (±)-1-*epi*-rubiginone B_1 11 *via* the tetra-*O*-acetyl diborate-promoted aromatisation of the cycloadduct 23

Compound 27. Tetra-*O*-acetyl diborate (2.0 g) was added to a solution of the cycloadduct **23** (0.100 g, 0.292 mmol) in dry THF (10 cm^3) and the mixture was stirred at ambient temperature for 17 h. It was then poured into hydrochloric acid (1 mol dm^{-3}; 100 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined organic extracts were vigorously washed with water (3 × 50 cm^3), dried ($MgSO_4$), and evaporated. Purification of the crude product by silica gel column chromatography (diethyl ether–hexanes 1:4 as eluent), and crystallisation from diethyl ether–hexanes gave a 5:1 mixture of (1R*,3S*)-**27** and (1R*,3R*)-1-*acetoxy*-8-*hydroxy*-3-*methyl*-1,2,3,4-*tetrahydrobenzo*[a]*anthracene*-7,12-*dione* **28** (0.081 g, 79%) as yellow crystals, mp 141–143 °C (Found: C, 72.0; H, 5.0. $C_{21}H_{18}O_5$ requires C, 72.0; H, 5.2%); ν_{max}(KBr)/cm^{-1} 1664, 1632 (C=O), 1580 and 1560.

(±)-1-*epi*-Rubiginone B_1 11. A 5:1 mixture of compounds **27** and **28** (0.086 g, 0.250 mmol), iodomethane (0.5 cm^3, 8.0 mmol) and potassium carbonate (1.0 g) in acetone (20 cm^3) under argon in the dark was stirred at ambient temperature for 17 h. The suspension was poured into hydrochloric acid (1 mol dm^{-3}; 50 cm^3) and extracted with ethyl acetate (4 × 10 cm^3). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil which was treated with sodium methoxide in methanol (10% w/v; 20 cm^3) using the procedure outlined for the deacetylation of **32**. Crystallisation and recrystallisation of the crude product from diethyl ether–hexanes gave the title compound **11** (0.067 g, 83%) as yellow crystals, mp 167–169 °C.

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