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AN ENANTIOSELECTIVE SYNTHESIS OF (+)-BOSTRYCIN LEADING TO A REVISION OF THE ABSOLUTE CONFIGURATION OF ITS NATURAL ANTIPODE[1,§]

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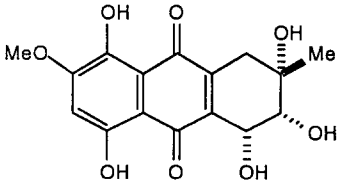
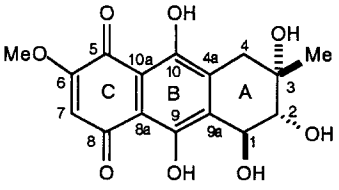
Abstract—An asymmetric Diels—Alder reaction, involving the protected naphthopurpurin **(4)** and the D-glucose-derived diene **(9a)**, is used to assemble compound **(22)**, which is transformed by way of compounds **(26)**, **(27)** and **(28)** into (+)-bostrycin **(3)** An X-ray analysis of compound **(28)** confirms that (+)-bostrycin possesses the stereostructure **(3)** and, therefore, that (-)-bostrycin is its antipode, *i.e* **(2)**. The use of naphthazarin **(14a)** and juglone **(14c)** as dienophiles in the Diels—Alder reaction enables the synthesis of (+)-demethoxybostrycin **(12a)** and (+)-demethoxy-5-deoxybostrycin **(12b)** to be effected.

INTRODUCTION

(-)-Bostrycin, a red pigment isolated from *Bostrychonema alpestre*,[2] *Nigrospora oryzae*,[3] *Arthrinium phaeospermum*,[4] and *Alternaria eichhorniae*,[5] is endowed with antibacterial[2] and herbicidal activity.[5] The structure **(1)**,† originally proposed for the antibiotic,[2] was revised by Kelly and his co-workers[6] to the structure **(2)** on the basis of a synthesis of (+/-)-bostrycin and an X-ray structure analysis of the 2,3-*O*-isopropylidene derivative of (+/-)-bostrycin Subsequently, Kelly's group[7] devised an elegant asymmetric synthesis of (-)-bostrycin and revised the absolute configuration of the antibiotic to the structure **(3)**.



(1)



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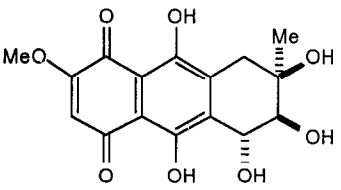


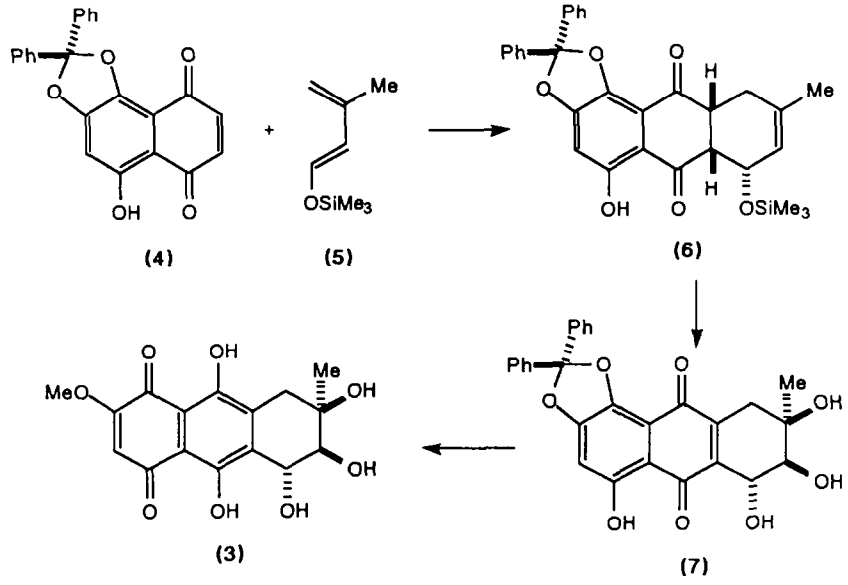
(3)

The synthesis of (+/-)-bostrycin, summarised in Scheme 1, involved[6] a Diels – Alder reaction of the protected naphthopurpurin **(4)** with the diene **(5)** in the presence of tetra-acetyl diborate to

§Dedicated, with appreciation, to David Ollis on the occasion of his sixty-fifth birthday.

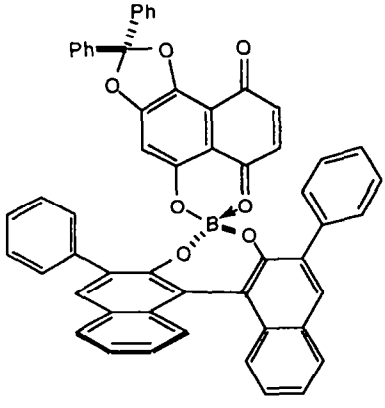
†To facilitate comparisons, bostrycin and its relatives are numbered in this paper in the manner shown in structure **(2)**

afford the (+/-)-cycloadduct (**6**); hydroxylation (OsO_4), dehydrogenation (O_2/NaOH), and mild hydrolysis then gave (+/-)-compound (**7**). Removal of the acetal protecting group (HCl/EtOH) and treatment of the product with diazomethane afforded (+/-)-bostrycin (**3**).



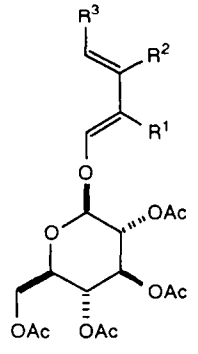
Scheme 1

The key step in the synthesis of (-)-bostrycin (**3**) involved[7] the cycloaddition of compounds (**4**) and (**5**) in the presence of a Lewis acid generated by sequential treatment of (*S*)-3,3'-diphenyl-(1,1'-binaphthalene)-2,2'-diol with borane.tetrahydrofuran (THF) complex and acetic acid. It was postulated that the diene (**5**) underwent *endo*-cycloaddition to the less-hindered 'bottom' face of the presumed complex (**8**) to give the cycloadduct (**6**). Processing of the last-cited compound as in Scheme 1 then led to (-)-bostrycin (**3**).



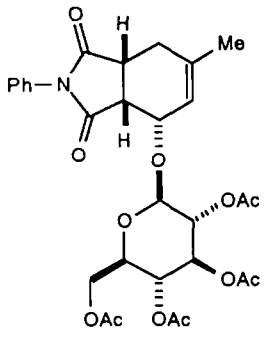
(**8**)

As part of our interest in the asymmetric Diels-Alder reaction, we have developed a range of 1-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyloxy)buta-1,3-dienes of type **(9)** and shown that they display notable diastereofacial reactivities towards cyclic dienophiles.[8,9] For example, the diene **(9a)** reacted with *N*-phenylmaleimide in benzene to give an 88:12 mixture of the cycloadducts **(10)** and **(11)** from which the former material was isolated in 60% yield after crystallisation.[9] Guided by the protocol developed by the Boston College workers, were envisaged that the diene **(9a)** would serve as a precursor of bostrycin **(3)** and bostrycin relatives.



(9)

a; R^1 = H, R^2 = Me, R^3 = H



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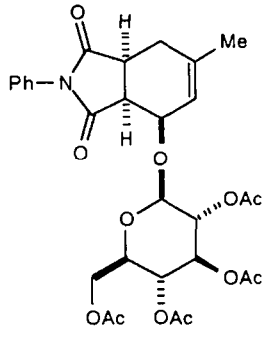


(11)

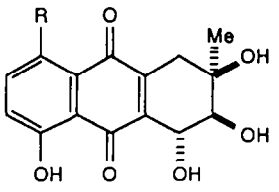
RESULTS AND DISCUSSION

Synthesis of (+)-Demethoxybostrycin

Initially, we decided to embark upon the synthesis of demethoxybostrycin **(12a)**,¶ a compound prepared in racemic form by Krohn and his co-workers[10] [who erroneously[6] assigned it the stereostructure **(13)**]. As well as starting with naphthazarin **(14a)** as the dienophile [which, besides being much more accessible than the protected naphthopurpurin **(4)**, avoids the regiocontrol issue], the synthesis would serve to highlight any problems that might be associated with the use of the D-glucose-based diene **(9a)**.

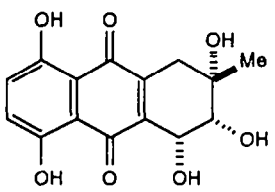
The diene **(9a)** reacted with naphthazarin **(14a)** in boiling benzene to give, after chromatography, an 85:15 mixture of the cycloadducts **(15a)** and **(16a)** in 71% yield; a comparable outcome was observed when the reaction was conducted in THF at room temperature in the presence of zinc chloride. Attempts to separate the components of the mixture by fractional recrystallisation were unsuccessful.

¶ This structure will be used although, as in the case of bostrycin, a tautomeric form is also feasible.



(12)

a; R = OH
b; R = H



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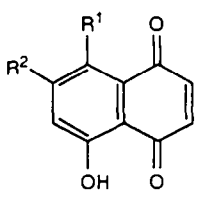
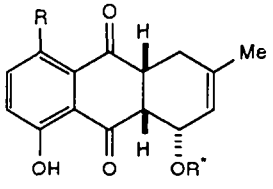


(14)

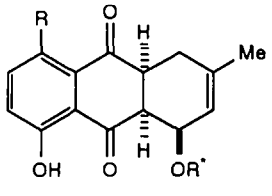
a; R^1 = OH, R^2 = H
b; R^1 = OH, R^2 = OH
c; R^1 = H, R^2 = H

In the presence of potassium chlorate and a catalytic quantity of osmium(VIII) oxide in aqueous THF [conditions that were successfully employed by Krohn's group[10] to effect the *cis*-hydroxylation of the cycloadduct derived from naphthazarin (**14a**) and the diene (**5**)], the 85:15 mixture of compounds (**15a**) and (**16a**) afforded several products. However, following chromatography, a homogeneous red solid was isolated in 26% yield. It was identified as the quinone (**17**) on the basis of its spectroscopic properties. Presumably, compound (**15a**) had reacted to give the diol (**18a**) which had then undergone aerial oxidation to give the quinone (**17**).



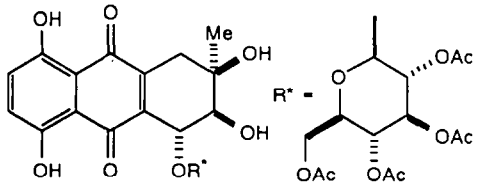
(15)

a; R = OH
b; R = H



(16)

a; R = OH
b; R = H



(17)

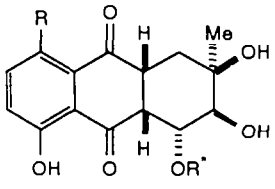
When subjected to the action of 1.5 molar equivalents of osmium(VIII) oxide in carbon tetrachloride followed by saturated aqueous sodium metabisuphite [conditions that were similar to those used by Kelly[6,7] to effect the *cis*-hydroxylation of compound (**6**)], the 85:15 mixture of compounds (**15a**) and (**16a**) was converted into an osmium-containing product. Recrystallisation of the material afforded a homogeneous pale-yellow solid in 63% yield which was identifed as the dimeric derivative (**19a**) on the basis of its analytical and spectroscopic properties. In particular, the FAB mass spectrum featured a molecular ion cluster at *m/z* 1475 – 1483 (the most intense ion appearing at *m/z* 1480). Osmium(VI) complexes analogous to compound (**19a**) have been reported by Griffith and by Skapski;[11] in them, the metal atom has been shown to possess a five-co-ordinate square-pyramidal arrangement.

Treatment of the osmium complex (**19a**) with hydrogen sulphide in chloroform and subjection of the product to the action of acidic 2,2-dimethoxypropane led to the isolation of a pale-

yellow solid in 67% yield, identified as the isopropylidene derivative **(20a)** on the basis of its analytical and spectroscopic properties.

A number of oxidants were examined in the quest to convert compound **(20a)** into the quinone **(21a)**. The best results were achieved by the use of activated manganese dioxide in boiling benzene; after crystallisation, the quinone **(21a)** was isolated as an analytically pure red solid in 68% yield.

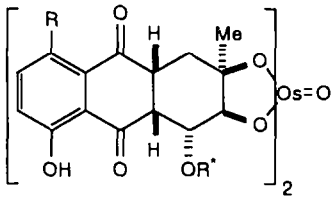
When heated in ethanolic hydrochloric acid, the glycoside **(21a)** was transformed in 75% yield into a dark-red solid which was identified as demethoxybostrycin **(12a)** on the basis of its spectroscopic properties. The glycoside **(17)** was similarly converted into demethoxybostrycin **(12a)** (84% yield) by the action of hot hydrochloric acid. The 300 MHz ^{1}H NMR spectrum of our sample matched that quoted by Krohn[10] for (+/-)-demethoxybostrycin. Surprisingly, however, the optical rotation of the material {$[\alpha]_D$ +230° (Me_2SO)}, although similar in magnitude, was opposite in sign to that reported[7] for (-)-bostrycin† {$[\alpha]_D$ -295° (Me_2SO)}, obtained by total synthesis and isolated from *Bostrychonema alpestre*. Whilst this discrepancy might have been caused by the structural difference between bostrycin and demethoxybostrycin, a more likely explanation appeared to be that the absolute stereochemistry of our synthetic (+)-demethoxybostrycin was opposite to that of (-)-bostrycin.



(18)

a; R = OH

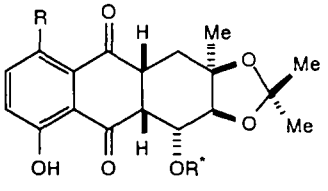
b; R = H



(19)

a; R = OH

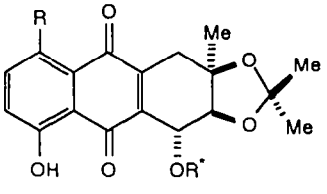
b; R = H



(20)

a; R = OH

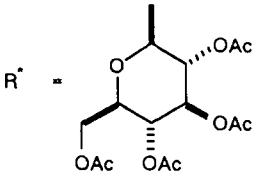
b; R = H



(21)

a; R = OH

b; R = H

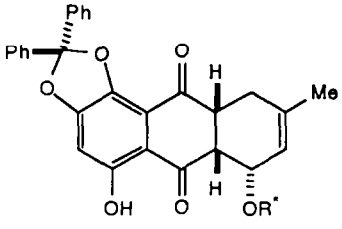


† (+)Bostrycin, isolated from *Alternaria eichhorniae*, was claimed[5] to display $[\alpha]_D$ -81° (Me_2SO).

Synthesis of (+)-Bostrycin

We experienced some difficulty in preparing the protected naphthopurpurin **(4)** by Kelly's method[6] [treatment of naphthopurpurin **(14b)**[12] with Ph_2CCl_2 and $K_2CO_3.1.5H_2O$ in dry MeCN at room temperature]. However, when anhydrous potassium carbonate was used and the mixture was heated at 60 – 70 °C, the desired product **(4)** was obtained in 65% yield after recrystallisation.

The diene **(9a)** reacted with the protected naphthopurpurin **(4)** in boiling benzene to give a 61:12:24:3 mixture of the cycloadducts **(22)**, **(23)**, **(24)** and **(25)**; addition of diethyl ether to the mixture and filtration gave the cycloadduct **(22)** in *ca.* 54% yield in a slightly impure state. When the reaction was conducted in diethyl ether in the presence of tetra-acetyl diborate and the product subjected to chromatography and crystallisation, the pure cycloadduct **(22)** was obtained in 43% yield.



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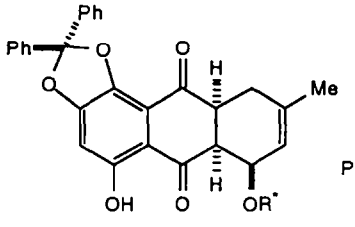

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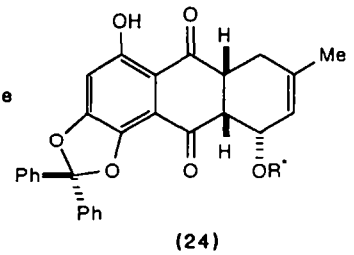

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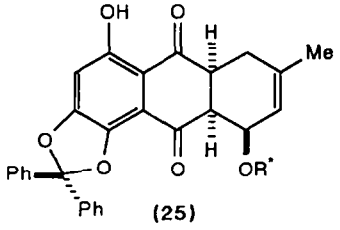
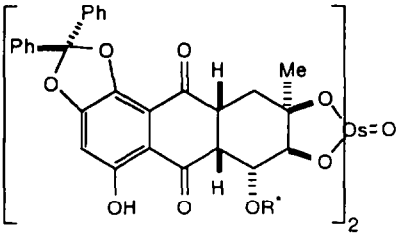
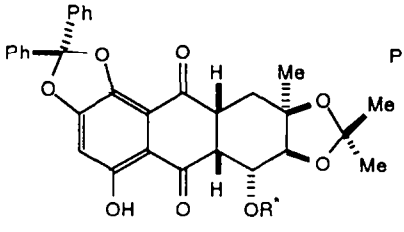


(25)



(26)



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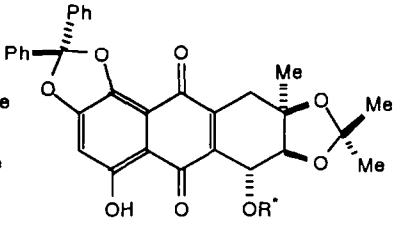
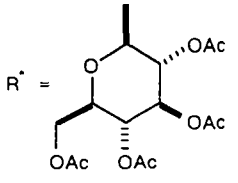


(28)



A complex mixture of products was obtained when compound **(22)** was treated with osmium(VIII) oxide under catalytic conditions ($KClO_3$ as the re-oxidant). However, the use of 1.5 molar equivalents of the oxidant in carbon tetrachloride and a reductive work-up afforded the osmium(VI) derivative **(26)** in 86% yield. As well as being analytically and spectroscopically characterised, the last-cited compound showed a molecular ion cluster at *m/z* 1833 – 1841 (the most intense ion appearing at *m/z* 1838) in its FAB mass spectrum.

Sequential treatment of the osmium complex **(26)** with hydrogen sulphide and acidic 2,2-dimethoxypropane gave the isopropylidene derivative **(27)** (82% yield after recrystallisation) which was transformed into the quinone **(28)** (50% yield after chromatography) by the action of manganese dioxide. Both compounds were analytically and spectroscopically characterised.

Acidic hydrolysis of compound **(28)** and treatment of the product in THF with ethereal diazomethane gave bostrycin **(3)** in *ca.* 61% yield. The IR, UV and 300 MHz ^1H NMR spectra of the material matched those of a sample of natural (-)-bostrycin (NMR spectroscopy revealed small amounts of impurities in both samples). The optical rotation of our material {$[\alpha]_D$ +225° (Me_2SO)} was slightly lower than that of natural (-)-bostrycin {$[\alpha]_D$ -275° (Me_2SO)}. However, this discrepancy is probably not very significant because of the poor transmittance of the deep-red solutions. The CD spectra of synthetic (+)-bostrycin and natural (-)-bostrycin, recorded in acetonitrile at identical concentrations, are shown in Figure 1. As well as leaving no doubt about the enantiomeric relationship of the samples, the spectra suggest that the enantiomeric purity of synthetic (+)-bostrycin at least matches that of natural (-)-bostrycin.

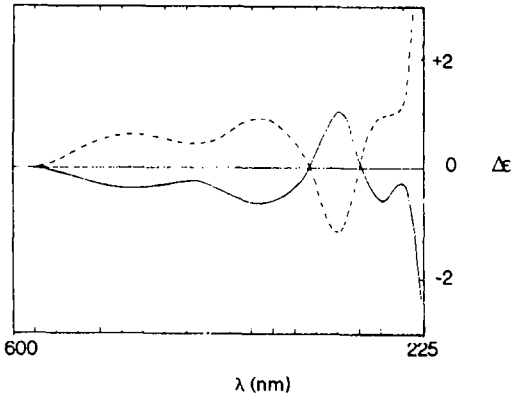


Figure 1. CD Spectra of (+)-bostrycin **(3)** (dashed line) and (-)-bostrycin **(2)** (solid line)

Clearly, our synthesis had led to the enantiomer of (-)-bostrycin and, therefore, either our expectations concerning the diastereofacial reactivity of the diene **(9a)** were not realised or Kelly's assignments were in error. That the latter situation was the case was established by a single

crystal X-ray structure analysis of compound **(28)**. The molecular structure is shown in Figure 2.† In confirming that compound **(28)** possessed the absolute configuration that we had anticipated, the analysis corroborated our structural assignments. Consequently, (-)-bostrycin must possess the absolute configuration **(2)**.

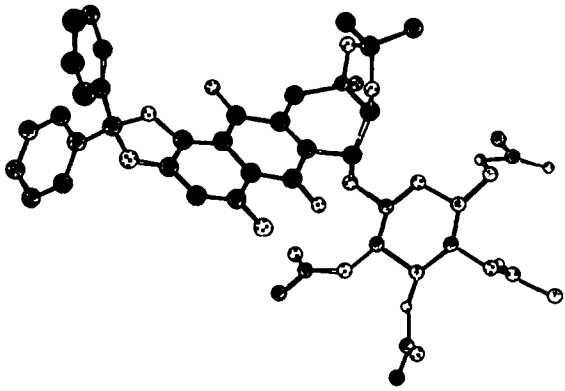
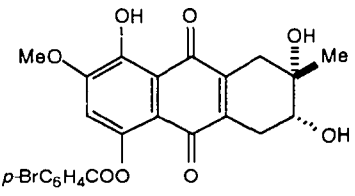


Figure 2. Molecular structure of compound **(28)**

It is worth noting that the original assignment of the stereostructure **(1)** to (-)-bostrycin was based upon an absolute X-ray determination of compound **(29)**,[2] derived from (-)-bostrycin Although, as pointed out by Kelly,[7] the poor discrepancy index (R = 0.138) of the analysis made such an assignment tenuous, the conclusion was in fact correct.

As a consequence of this work, Kelly has re-examined his synthesis. It appears that (*R*)-3,3'-diphenyl-(1,1'-binaphthalene)-2,2'-diol [and not the (*S*)-binaphthol as claimed in the paper[7]] is required[13] to generate (-)-bostrycin **(2)**.



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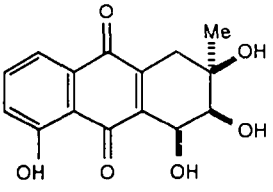


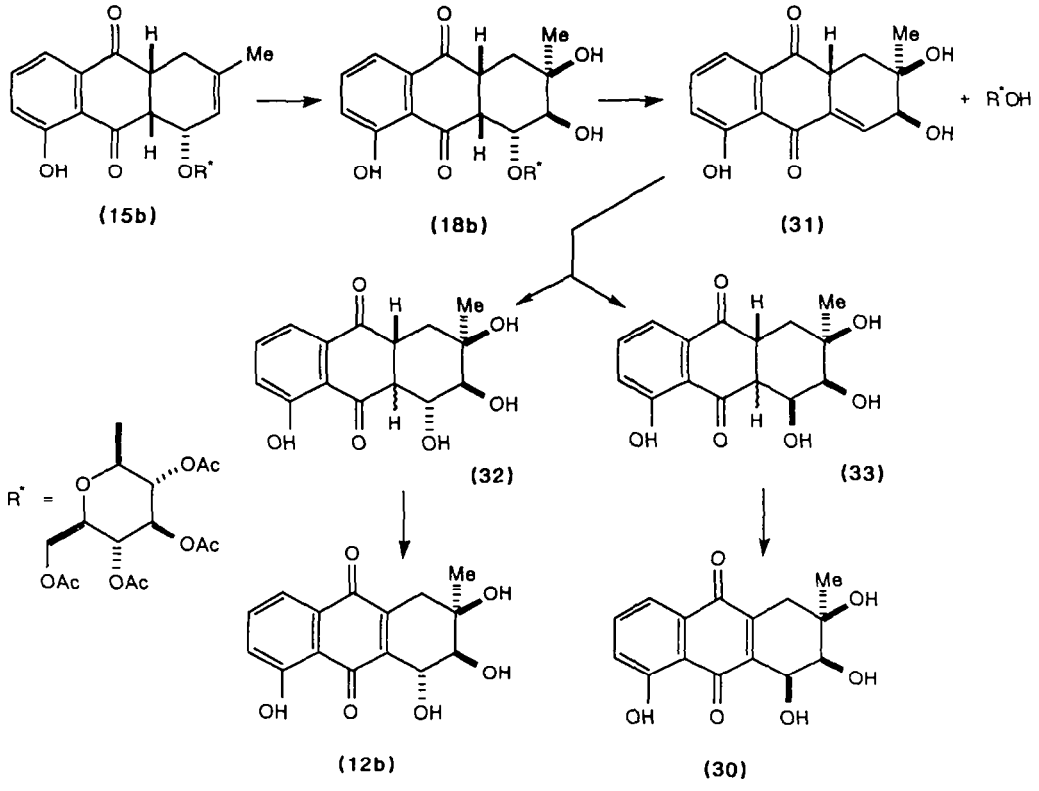
(30)

Synthesis of (+)-Demethoxy-5-deoxybostrycin

The methodology was also applicable to the synthesis of the demethoxydeoxybostrycin **(12b)**. Thus, in diethyl ether, the diene **(9a)** reacted with juglone **(14c)** in the presence of tetra-acetyl diborate to give the cycloadduct **(15b)** (35% yield after chromatography and crystallisation)

†Details of the analysis were presented earlier.[1]

A complex mixture of products resulted when compound **(15b)** was subjected to the usual catalytic hydroxylation conditions. Chromatographic fractionation led to the isolation of a small quantity of a mixture of two compounds, tentatively considered to be the demethoxydeoxybostrycin **(12b)** and its epimer **(30)** on the basis of 300 MHz ^{1}H NMR spectroscopy. Further fractionation by HPLC afforded an almost pure sample of the demethoxydeoxybostrycin **(12b)**.



Scheme 2

The suggested origin of the demethoxydeoxybostrycins **(12b)** and **(30)** is summarised in Scheme 2. Thus, *cis*-hydroxylation of compound **(15b)** would give the diol **(18b)** which may then afford the alkene **(31)** and 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose by a β-elimination reaction. Hydration of the enone moiety of compound **(31)** followed by aerial oxidation of the adducts **(32)** and **(33)** would yield the products **(12b)** and **(30)**.

When subjected to the action of osmium(VIII) oxide in carbon tetrachloride and a reductive work-up, the cycloadduct **(15b)** was converted in 80% yield into the osmium complex **(19b)** which, as well as being analytically and spectroscopically characterised, displayed a molecular ion cluster at *m/z* 1444 – 1452 (the most intense ion appearing at *m/z* 1448) in its FAB mass spectrum.

Under the usual conditions, the osmium complex **(19b)** was transformed *via* the isopropylidene derivative **(20b)** into the quinone **(21b)**. Compound **(20b)** was isolated in 69% yield after recrystallisation; the yield of compound **(21b)** was 47% after chromatography. Both compounds were analytically and spectroscopically characterised.

Acidic hydrolysis of the glycoside **(21b)** gave the demethoxydeoxybostrycin **(12b)** {$[\alpha]_D$ +197° (CH_2Cl_2)} as a yellow solid in 74% yield.

Conformational Considerations

The aforecited synthetic work provided the opportunity of assessing the conformation of the A-ring in a variety of structural situations. The results will now be considered.

In Table 1, the coupling constants of the A-ring-associated hydrogen atoms of the cycloadducts **(15a,b)** and **(22)**, of the osmium complexes **(19a,b)** and **(26)**, and of the isopropylidene derivatives **(20a,b)** and **(27)** are compared. Clearly, there is a consistency within each series. The values [when converted into torsion angles (θ) using the modified Karplus[14] relationship: $J = 11 \cos^2\theta$] imply that the average A-ring conformation is represented by a sofa-like geometry of type **(34)** in the case of the cycloadducts **(15a,b)** and **(22)**, by a flattened chair-like conformation of type **(35)** in the case of compounds **(19a,b)** and **(26)**, and by a boat-like conformation of type **(36)** in the case of compounds **(20a,b)** and **(27)**.

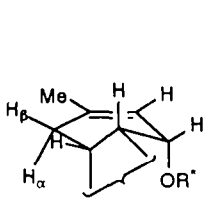
Table 1. Coupling constants (Hz) (measured in $CDCl_3$) of the A-ring-associated hydrogen atoms of compounds **(15a,b)** **(22)**, **(19a,b)**, **(26)**, **(20a,b)** and **(27)**.

Compound	$J_{1,2}$	$J_{4\alpha,4\beta}$	$J_{4\alpha,4a}$	$J_{4\beta,4a}$	$J_{4a,9a}$	$J_{1,9a}$
(15a)		18	<2	7	7	5
(15b)		18	<2	7	7	5
(22)		18	<2	7	7	5
(19a)	<2	15	9	8	10	<1
(19b)	<2	15	8	8	9	1
(26)	<1	15	8	8	9	<2
(20a)	4	14	11	5	11	4
(20b)	4	14	9	7	9	4
(27)	4	14	9	6	9	4

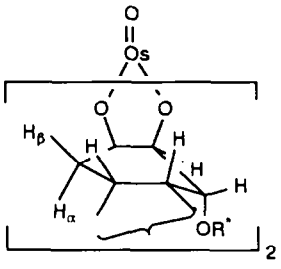
In the case of the isopropylidene bostrycins **(21a,b)** and **(28)**, the vicinal coupling constant between H_1 and H_2 (J 3 Hz) is indicative of a dihedral angle of *ca.* 60°. This angle is consistent with the adoption of a boat-like conformation of type **(37)** by the A-ring in deuteriochloforom solution and matches that observed in the crystal state for compound **(28)** (in which $\theta_{1,2} = 65°$).

An interesting feature of the conformational behaviour is the axial-like disposition of the 1-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyloxy) substituent in conformers of types **(34)** – **(37)**; a similar phenomenon was noted earlier in related compounds.[8] Before, we suggested that this orientation is stabilised by a through-space interaction between an electron pair on the oxygen

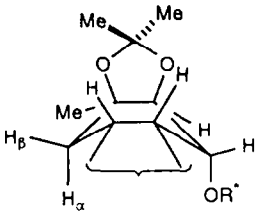
atom and the π^* orbital of the 9-carbonyl group. It is noteworthy, however, that the O(1)....C(9) interatomic distance in compound **(28)** (3.29 Å) is near the sum of the van der Waals radii of the atoms (in related compounds, the comparable interatomic distance is 2.69 – 2.88 Å).



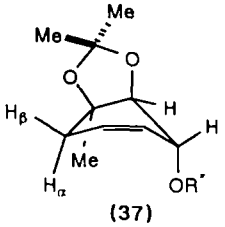
(34)



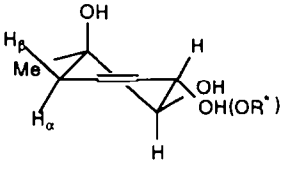
(35)



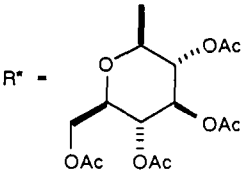
(36)



(37)



(38)



In the case of the bostrycins **(3)**,**(12a,b)** and **(17)**, the vicinal coupling constant between H_1 and H_2 is enlarged to 5 – 7 Hz, consistent with a dihedral angle of *ca.* 40°. Moreover, with compounds **(12b)** and **(17)** (the spectra of which were recorded in $CDCl_3$), a long-range coupling between H_1 and $H_{4\alpha}$ (J 2 Hz) was in evidence. Assuming that $H_{4\alpha}$ is pseudo-axial (it appears at higher field than $H_{4\beta}$) and that a zig-zag pathway is involved in the long-range coupling, a half-chair conformer of type **(38)** is likely for the A-ring in these compounds.

EXPERIMENTAL

Dry solvents, referred to in the ensuing experiments, were prepared as follows: THF was distilled from sodium – benzophenone immediately prior to use; benzene was distilled from sodium wire; carbon tetrachloride was distilled from calcium hydride. Light petroleum refers to that fraction boiling in the range 30 – 40 °C. Ethereal diazomethane was generated from Diazald.[15] Activated manganese dioxide was prepared from manganese(II) sulphate by oxidation with potassium permanganate.[16] Column chromatography was effected under pressure using Sorbicil C60 silica gel. Deactivated silica gel was prepared by adding 1 part of water to 99 parts of silica gel. TLC was performed on Merck plastic plates coated with silica gel ($60F_{254}$); the plates were initially examined under UV light and then developed with iodine vapour. Preparative HPLC was carried out using a column (20 x 0.8 cm^3) of Partisil 10 silica, a LDC Constametric III pump, and a Cecil CE212 variable wavelength detector. Evaporations refer to the removal of solvents at < 40 °C

using a Buchi rotary evaporator. M.p.s with determined by using a Buchi 512 apparatus. Optical rotations were measured at *ca.* 20 °C with either a Thorn Automation Type 243 polarimeter or an Optical Activity 1000 polarimeter. A Jasco J40-CS was employed to measure CD spectra. IR spectra were determined with a Perkin–Elmer 580 and UV spectra with a Unicam SP800. ^{1}H NMR spectra were measured at 300 MHz with a Bruker AC300. Mass spectra were recorded on a Kratos Concept 1S spectrometer.

Reaction of the Diene **(9a)** *with Naphthazarin* **(14a)**

(a) A solution of the diene **(9a)**[9] (0.690 g, 1.67 mmol) and naphthazarin **(14a)** (0.300 g, 1.67 mmol)) in dry benzene (10 cm^3) was heated under reflux in an argon atmosphere for 5 h. Evaporation of the solvent, purification of the mixture by silica-gel column chromatography [light petroleum–Et_2O (2:3) as eluant], and recrystallisation of the product from diethyl ether–light petroleum gave a 85:15 mixture of (1S,4aR,9aR)-1,4,4a,9a-*tetrahydro*-5,8-*dihydroxy*-3-*methyl*-1-(2',3',4',6'-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)*anthracene*-9,10-*dione* **(15a)** and its (1R,4aS,9aS)-*isomer* **(16a)** (0.669 g, 71%) [the ratio was calculated from the integrals of the s at δ 11.32 and 11.98, ascribed to the hydroxy groups of compound **(16a)**, compared with those at δ 11.39 and 11.94, attributed to the hydroxy groups of compound **(15a)**], as a pale-yellow solid; m.p. 82–86 °C; $[\alpha]_D$ +206° (2.3% in CH_2Cl_2); ν_{max}(KBr) 3440br (OH), 1755 (ester CO), and 1640 cm^{-1} (quinone CO); λ_{max}(EtOH) 229 (ε 13,900), 258 (9200), and 395 nm (7200); δ(300 MHz; $CDCl_3$) [for **(15a)**] 1.79, 1.90, 1.98, and 2.10 (each 3 H, s, 4 x $MeCO_2$), 1.82 (3 H, br s, 3-Me), 3.09 (1 H, br d, separation 18 Hz, 4-H_α), 3.25 (1 H, dd, *J* 7 and 5 Hz, 9a-H), 3.38 (1 H, t, separation 7 Hz, 4a-H), 3.59 (1 H, ddd, *J* 9, 5, and 3 Hz, 5'-H), 4.09 (1 H, dd, *J* 12 and 5 Hz, 6'-H), 4.15 (1 H, dd, *J* 12 and 3 Hz, 6'-H), 4.39 (1 H, br t, *J* 5 and 5 Hz, 1-H), 4.41–4.50 (2 H, m, 1'- and 2'-H), 4.85–5.02 (2 H, m, 3'- and 4'-H), 5.65–5.73 (1 H, m, 2-H), 7.15 and 7.25 (each 1 H, d, *J* 8 Hz, 6- and 7-H), and 11.39 and 11.94 (each 1 H, s, 5- and 8-OH) (the signals for 4-H_β were partly obscured by an acetoxy s at δ 2.10); *m/z* (FAB; thioglycerol) 604 (M^+, 8%), 331 (60), and 257 (100) (Found. C, 57.7; H, 5.4. $C_{29}H_{32}O_{14}$ requires C, 57.6; H, 5.35%).

(b) A mixture of the diene **(9a)** (0.654 g, 1.58 mmol), naphthazarin **(14a)** (0.200 g, 1.05 mmol) and freshly fused zinc chloride (0.286 g, 2.10 mmol) in dry THF (10 cm^3) was stirred overnight and then poured into 0.1M hydrochloric acid (100 cm^3). The solution was extracted with dichloromethane and the organic extract dried ($MgSO_4$) and concentrated. Subjection of the residue to silica-gel column chromatography [light petroleum–Et_2O (3:7) as eluant] led to the isolation of a pale-yellow solid (0.432 g, 68%) which comprised an 83:17 mixture of compounds **(15a)** and **(16a)** by 300 MHz ^{1}H NMR spectroscopy.

Preparation of (1R,2S,3R)-1,2,3,4-*Tetrahydro*-2,3,5,8-*tetrahydroxy*-3-*methyl*-1-(2',3',4',6'-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)*anthracene*-9,10-*dione* **(17)**

Potassium chlorate (0.300 g, 2.45 mmol) and a few drops of 2% aqueous osmium(VIII) oxide were added to a stirred solution of the 85:15 mixture of cycloadducts **(15a)** and **(16a)** (0.300 g, 0.50 mmol) in a 5:1 mixture of THF and water (6 cm^3). After 20 h, the mixture was partitioned between water and dichloromethane. Evaporation of the dried ($MgSO_4$) organic phase and

subjection of the residue to silica-gel chromatography [light petroleum – EtOAc (2:3) as eluant] gave the title compound **(17)** (0.082 g, 26%) as a red solid; ν_{max}(KBr) 3450br (OH), 1750 (ester CO), and 1610 cm^{-1} (quinone CO); λ_{max}(EtOH) 218 (ε 31,500), 278 (8200), 428 (2900), 485 (5500), 512 (5900), and 549 nm (3600); δ (300 MHz; $CDCl_3$) 1.46 (3 H, s, 3-Me), 1.87, 2.01, 2.04, and 2.16 (each 3 H, s, 4 x $MeCO_2$), 2.56 (1 H, dd, *J* 19 and 2 Hz, 4-H_β), 3.06 (1 H, d, *J* 19 Hz, 4-H_α), 3.79 (1 H, s, OH), 3.83 (1 H, d, *J* 6 Hz, 2-H), 4.27 (1 H, ddd, *J* 10, 7, and 3 Hz, 5'-H), 4.19 (1 H, dd, *J* 12 and 7 Hz, 6'-H), 4.21 (1 H, br s, OH), 4.35 (1 H, dd, *J* 12 and 3 Hz, 6'-H), 4.74 (1 H, dd, *J* 6 and 2 Hz, 1-H), 4.99 (1 H, dd, *J* 10 and 8 Hz, 2'-H), 5.07 (1 H, t, *J* 10 and 10 Hz, 4'-H), 5.20 (1 H, d, *J* 8 Hz, 1'-H), 5.37 (1 H, t, *J* 10 and 10 Hz, 3'-H), 7.24 (2 H, s, 6- and 7-H), and 12.40 and 12.53 (each 1 H, s, 5- and 8-OH).

Preparation of Oxobis[(1S,2S,3R,4aR,9aR)-1,2,3,4,4a,9a-*hexahydro*-5,8-*dihydroxy*-3-*methyl*-9,10-*dioxo*-1-(2',3',4',6'-t*etra*-O-*acetyl*-β-D-*glucopryanosyloxy)anthracene*-2,3-*diolato*]*osmium* (VI) **(19a)**

The 5:1 mixture of the cycloadducts **(15a)** and **(16a)** (0.600 g, 0.99 mmol) was stirred with a 2% solution of osmium(VIII) oxide in carbon tetrachloride (18.9 cm^3, 1.49 mmol) for 24 h. THF (10 cm^3) and saturated aqueous sodium metasulphite (1 cm^3) were added and the mixture was stirred vigorously for 1 h. The mixture was then partitioned between water and dichloromethane. Evaporation of the dried ($MgSO_4$) organic phase and crystallisation of the dark residue from dichloromethane – diethyl ether gave the *title compound* **(19a)** (0.460 g, 63%) as a pale-yellow solid; m.p. 215 °C (decomp.); $[\alpha]_D$ -70° (0.5% in CH_2Cl_2); ν_{max}(KBr) 3440 (OH), 1755 (ester CO), and 1630 cm^{-1} (quinone CO); δ (300 MHz; $CDCl_3$) 1.43, 1.88, 1.98, and 2.08 (each 3 H, s, 4 x $MeCO_2$), 1.59 (3 H, br s, 3-Me), 2.18 (1 H, d, J 10 Hz, 9a-H), 2.79 (1 H, dd, *J* 15 and 8 Hz, 4-H_α), 2.96 (1 H, dd, *J* 15 and 9 Hz, 4-H_β), 3.43 (1 H, q, separation 9 Hz, 4a-H), 3.57 – 3.67 (1 H, m, 5'-H), 4.15 (2 H, d, separation 4 Hz, 6'-H_2), 4.37 (1 H, br s, 2-H), 4.47 (1 H, d, *J* 8 Hz, 1'-H), 4.67 (1 H, t, *J* 9 and 9 Hz, 2'-H), 4.90 – 5.05 (2 H, m, 3'- and 4'-H), 5.33 (1 H, s, 1-H), 7.18 and 7.31 (each 1 H, d, *J* 10 Hz, 2- and 3-H), and 11.64 and 11.93 (each 1 H, s, 5- and 8-OH); *m/z* (FAB; *m*-nitrobenzyl alcohol) 1480 [M^+, 1.5% (a cluster of ions was observed at 1475, 1476, 1477, 1478, 1479, 1480, 1481, 1482, and 1483 in the ratio of 1:3:5:8:6:10:7:5:2)], 331 (40), and 169 (100) (Found: C, 47.1; H, 4.3; Os, 12.0. $C_{58}H_{64}O_{33}Os$ requires C, 47.05; H, 4.35; Os, 12.85%).

Preparation of (1S,2S,3R,4aR,9aR)-1,2,3,4,4a,9a-*Hexahydro*-2,3-O-i*sopropylidene*-3-*methyl*-9,10-*dioxo*-1-(2',3',4',6'-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy)anthacene*-2,3,5,8-*tetraol* **(20a)**

A solution of the osmium derivative **(19a)** (0.300 g, 0.20 mmol) in chloroform (5 cm^3) was saturated with hydrogen sulphide. Filtration of the mixture through Celite and evaporation of the filtrate left a residue which was stirred with 2,2-dimethoxypropane (5 cm^3) and a trace of *p*-toluenesulphonic acid for 1 h. The mixture was partitioned between water and dichloromethane and the organic phase was dried ($MgSO_4$) and concentrated. Addition of diethyl ether to the residue and reccrystallisation of the insoluble material from dichloromethane – diethyl ether gave the *title compound* **(20a)** (0.185 g, 67%) as a pale-yellow solid; m.p. 199 °C (decomp.); $[\alpha]_D$ +57° (0.2% in CH_2Cl_2); ν_{max}(KBr) 3440br (OH), 1760, 1755, and 1740 (ester CO), and 1620 cm^{-1} (quinone CO); λ_{max}(EtOH) 214 (ε 17,900), 230 (16,900), 258 (9800), and 397 nm (7400); δ (300

MHz; $CDCl_3$) 1.45 and 1.46 (6 and 3 H, each br s, Me_2C and 3-Me), 1.53, 1.94, 2.02, and 2.09 (each 3 H, s, 4 x $MeCO_2$), 2.16 (1 H, dd, *J* 14 and 5 Hz, 4-Hβ), 3.36 (1 H, dt, *J* 11, 11, and 5 Hz, 4a-H), 3.55 (1 H, dd, *J* 11 and 4 Hz, 9a-H), 3.72 (1 H, ddd, *J* 10, 5, and 3 Hz, 5'-H), 4.19 (1 H, dd, *J* 12 and 5 Hz, 6'-H), 4.28 (1 H, dd, *J* 12 and 3 Hz, 6'-H), 4.31 (1 H, d, *J* 4 Hz, 2-H), 4.60 (1 H, d, *J* 8 Hz, 1'-H), 4.76 (1 H, dd, *J* 10 and 8 Hz, 2'-H), 4.78 (1 H, t, *J* 4 and 4 Hz, 1-H), 5.00 (1 H, t, *J* 10 and 10 Hz, 4'-H), 5.14 (1 H, t, *J* 10 and 10 Hz, 3'-H), 7.23 and 7.29 (each 1 H, d, *J* 9 Hz, 2- and 3-H), and 12.47 and 12.52 (each 1 H, s, 5- and 8-OH) (the signals for 4-H_α were partly obscured by an acetoxy s at δ 2.02); *m/z* (FAB; *m*-nitrobenzyl alcohol) 678 (M^+, 30%), 331 (95), and 169 (100) (Found: C, 56.3; H, 5.7. $C_{32}H_{38}O_{16}$ requires C, 56.65; H, 5.65%).

Preparation of (1R,2S,3R)-1,2,3,4-*Tetrahydro*-2,3-O-*isopropylidene*-3-*methyl*-9,10-*dioxo*-1-(2',3',4',6'-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy)anthracene*-2,3,5,8-*tetraol* **(21a)**

A mixture of compound **(20a)** (0.120 g, 0.18 mmol) and activated manganese dioxide (1.00 g) in dry benzene (20 cm^3) was heated under reflux for 1 h. The mixture was filtered through Celite and the residues were washed with dichloromethane. Evaporation of the filtrate and crystallisation of the residue from dichloromethane–diethyl ether–light petroleum gave the *title compound* **(21a)** (0.081 g, 68%) as a red solid; m.p. 186–189 °C; $[\alpha]_D$ +127° (0.1% in CH_2Cl_2); ν_{max}(KBr) 3450br (OH), 1760 (ester CO), and 1615 cm^{-1} (quinone CO); λ_{max}(EtOH) 216 (ε 39,600), 282 (6900), 491sh (5900), 522 (6600), and 562sh nm (3900); δ(300 MHz; $CDCl_3$) 1.01 and 1.35 (each 3 H, s, Me_2C), 1.59 (3 H, s, 3-Me), 1.83, 1.97, 2.02, and 2.15 (each 3 H, s, 4 x $MeCO_2$), 2.21 (1 H, d, *J* 17 Hz, 4-H_α), 3.43 (1 H, d, *J* 17 Hz, 4-H_β), 3.68–3.78 (1 H, m, 5'-H), 4.22 (1 H, dd, *J* 13 and 2 Hz, 6'-H), 4.32 (1 H, dd, *J* 13 and 5 Hz, 6'-H), 4.50 (1 H, d, *J* 8 Hz, 1'-H), 4.51 (1 H, d, *J* 3 Hz, 2-H), 4.91 (1 H, dd, *J* 9 and 8 Hz, 2'-H), 5.02–5.18 (2 H, m, 3'- and 4'-H), 5.56 (1 H, d, *J* 3 Hz, 1-H), 7.23 (2 H, s, 6- and 7-H), and 12.61 and 12.64 (each 1 H, s, 5- and 8-OH); *m/z* (FAB; *m*-nitrobenzyl alcohol) 676 (M^+, 12%), 331 (70), and 271 (100) (Found: C, 57.0; H, 5.6. $C_{32}H_{36}O_{16}$ requires C, 56.8; H, 5.35%).

Preparation of (1R,2S,3R)-1,2,3,4-*Tetrahydro*-1,2,3,5,8-*pentahydroxy*-3-*methylanthracene*-9,10-*dione (Demethoxybostrycin)* **(12a)**

(*a*) The glycoside **(21a)** (0.050 g, 0.074 mol) was heated under reflux in a 1:1 mixture of 1M hydrochloric acid and ethanol (60 cm^3) for 12 h. After having been diluted with water (100 cm^3), the red solution was washed with diethyl ether (2 x 50 cm^3) and then extracted with ethyl acetate (5 x 50 cm^3). Evaporation of the combined dried ($MgSO_4$) extracts gave a dark-red solid which was dissolved in a minimum volume of ethyl acetate; addition of light petroleum induced the precipitation of the title compound **(12a)** (0.017 g, 75%) as a slightly impure dark-red solid; m.p. 175 °C (decomp.){lit.,[10] 200–203 °C (decomp.) [for (+/-)-**(12a)**]}; $[\alpha]_D$ +230° (0.02% in Me_2SO); CD (MeCN) 258 (Δε +1.3), 292 (-1.3), 347 (+1.7), 407 (-0.04), 417 (+0.16), 433 (+0.04), and 480br nm (+0.42); ν_{max}(KBr) 3540 and 3420br (OH), and 1595 cm^{-1} (quinone CO); λ_{max}(EtOH) 216 (ε 32,500), 280 (7800), 482sh (5400), 510 (5900), and 548 nm (3500); δ(300 MHz; CD_3SOCD_3) *inter alia* 1.21 (3 H, s, 3-Me), 2.61 (2 H, s, 4-H_2), 3.47 (1 H, t, separation 4 and 4 Hz, 2-H), 4.55 (1 H, s, 3-OH), 4.67 (1 H, t, separation 5 and 5 Hz, 1-H), 5.00 (1 H, d, *J* 4 Hz, 2-OH), 5.34 (1 H, d, *J* 5 Hz, 1-

OH), 7.37 (2 H, s, 2- and 3-H), and 12.29 and 12.48 (each 1 H, s, 5- and 8-OH) [addition of D_2O caused the s at δ 2.61 to appear as an AB q (*J* 17 Hz, separation of inner lines 8 Hz), the t at δ 4.67 to appear as a d (*J* 5 Hz) at δ 4.63 , and the signals at δ 5.00 and 5.34 to disappear]; *m/z* (CI, NH_3) 324 (MNH_4^+, 10%) and 307 (MH^+, 100%).

(*b*) A mixture of the glycoside **(17)** (0.042 g, 0.066 mmol) and 1M-hydrochloric acid (25 cm^3) was heated under reflux for 1.5 h. The cooled solution was extracted with ethyl acetate (4 x 50 cm^3) and the extracts were dried ($MgSO_4$) and concentrated. Crystallisation of the residue from ethyl acetate – light petroleum gave a red solid (0.017 g, 84%) which was identified as the title compound **(12a)** on the basis of its 300 MHz ^1H NMR spectrum.

Preparation of 5,6-O-*Diphenylmethylidenenaphthopurpurin* **(4)**

Dichlorodiphenylmethane (0.6 cm^3, 3.2 mmol) was added in drops to a stirred mixture of naphthopurpurin **(14b)**[12] (0.670 g, 3.2 mmol) and anhydrous potassium carbonate (1.00 g, 7.2 mmol) in dry acetonitrile (80 cm^3). The mixture was heated at 60 – 70 °C for 4 h, cooled, and poured into water (200 cm^3). Following acidification with 1M hydrochloric acid, the mixture was extracted with dichloromethane. Evaporation of the dried ($MgSO_4$) organic extract, purification of the residue by column chromatography on deactivated silica gel (light petroleum – CH_2Cl_2; gradient elution), and recrystallisation of the product from diethyl ether gave the title compound **(4)** (0.782 g, 65%) as red crystals; m.p. 182 – 184 °C (lit.,[6] 188-189 °C); ν_{max}(KBr) 3420br (OH), 1665 and 1640 (quinone CO), 1605, and 1580 cm^{-1}; λ_{max}(EtOH) 222 (ε 40,400), 263 (9000), 350 (1800), and 474 nm (7300); δ(300 MHz; $CDCl_3$) 6.73 (1 H, s, 7-H), 6.89 (2 H, AB q, *J* 10 Hz, separation of inner lines 22 Hz, 2- and 3-H), 7.39 – 7.41 and 7.56 – 7.59 (6 and 4 H, each m, 2 x Ph), and 13.25 (1 H, s, 8-OH).

Reaction of the Diene **(9a)** *with* 1,2-O-*Diphenylmethylidenenaphthopurpurin* **(4)**

(*a*) A mixture of the diene **(9a)** (0.094 g, 0.23 mmol) and the protected naphthopurpurin **(4)** (0.079 g, 0.21 mmol) in dry benzene (5 cm^3) was heated under reflux. After 3 h, a further portion of the diene **(9a)** (0.040 g, 0.096 mmol) was added and the mixture was heated under reflux for a further 6 h. Evaporation of the solvent left a residue which comprised a 61:12:24:3 mixture of the cycloadducts **(22)**, **(23)**, **(24)**, and **(25)** [the ratio was calculated from the integrals of the s at δ 12.31, 12.32, 13.00, and 13.07, ascribed to the hydroxy groups of compounds **(23)**, **(25)**, **(22)**, and **(24)**]. Addition of diethyl ether to the residue and filtration gave the cycloadduct **(22)** (0.080 g, *ca.* 54%) in a slightly impure state.

(*b*) A mixture of the diene **(9a)** (0.590 g, 1.42 mmol), the protected naphthopurpurin **(4)** (0.350 g, 0.95 mmol), and tetra-acetyl diborate (0.261 g, 0.95 mmol) in diethyl ether (20 cm^3) was stirred for 20 h. The mixture was diluted with diethyl ether and then washed with water. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel column chromatography (light petroleum – Et_2O; gradient elution) gave a pale-yellow foam which, when triturated with diethyl ether, afforded (1S,4aR,9aR)-5,6-O-*diphenylmethylidene*-1,4,4,4a,9a-*tetrahydro*-3-*methyl*-9,10-*dioxo*-1-(2',3',-4',6'-*tetra*-O-acetyl-β-D-*glucopyranosyloxy*)*anthracene*-5,6,8-*triol* **(22)** as an off-white solid. After recrystallisation from diethyl ether, the sample (0.320 g,

43%) showed m.p. 160 °C (decomp.); $[\alpha]_D$ +159° (0.2% in CH_2Cl_2); ν_{max}(KBr) 1755 (ester CO), and 1705 and 1640 cm^{-1} (quinone CO); λ_{max}(EtOH) 237 (ε 8900), 269 (5100), 297sh (2300), and 376nm (4300); δ(300 MHz; $CDCl_3$) 1.67, 1.87, 1.99, and 2.10 (each 3 H, s, 4 x $MeCO_2$), 1.79 (3 H, br s, 3-Me), 3.03 (1 H, br d, separation 18 Hz, 4-H_α), 3.20 (1 H, dd, *J* 7 and 5 Hz, 9a-H), 3.25 (1 H, t, separation 7 Hz, 4a-H), 3.52–3.62 (1 H, m, 5'-H), 4.07 (1 H, dd, *J* 12 and 5 Hz, 6'-H), 4.16 (1 H, dd, *J* 12 and 3 Hz, 6'-H), 4.33–4.47 (3 H, m, 1-, 1'-, and 2'-H), 4.84-5.01 (2 H, m, 3'- and 4'H), 5.59–5.68 (1 H, m, 2-H), 6.62 (1 H, s, 7-H), 7.36–7.41 and 7.54–7.62 (6 and 4-H, each m, 2 x Ph), and 13.00 (1 H, s, 4-OH) (the signals for 4-H_β were partly obscured by an acetoxy s at δ 1.99); *m/z* (FAB; *m*-nitrobenzyl alcohol) 748 (M^+, 40%) and 437 (100) (Found: C, 64.3; H, 5.1. $C_{42}H_{40}O_{15}$ requires C, 64.3; H, 5.15%).

Preparation of Oxobis [(1R,2S,3R,4aR,9aR)-1,2,3,4,4a,9a-*Hexahydro*-5,6,8-*trihydroxy*-3-*methyl*-9,10-*dioxo*-5,6-O-*diphenylmethylidene*-1-(2',3',4',6'-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)-*anthracene*-2,3-*diolato*]*osmium*(VI) **(26)**

A solution of the cycloadduct **(22)** (0.620 g, 0.79 mmol) in dichloromethane (5 cm^3) was stirred with a 2% solution of osmium(VIII) oxide in carbon tetrachloride (15 cm^3, 1.19 mmol). After 22 h, THF (10 cm^3) and saturated aqueous sodium metabisulphite (1 cm^3) were added and the mixture was stirred vigorously for 1 h. The mixture was then partitioned between water and dichloromethane. Evaporation of the dried ($MgSO_4$) organic phase and titruration of the residue with dichloromethane–light petroleum gave the *title compound* **(26)** as a pale-brown solid. After recrystallisation from diethyl ether–light petroleum, the sample (0.629 g, 86%) showed m.p. 167 °C (decomp.); $[\alpha]_D$ +119° (0.1% in CH_2Cl_2); ν_{max}(KBr) 3440br (OH), 1760 (ester CO), and 1700 and 1630 cm^{-1} (quinone CO); λ_{max}(EtOH) 237 (ε 4300), 272 (2600), and 376 nm (2300); δ(300 MHz; $CDCl_3$) 1.29, 1.89, 1.98, and 2.07 (each 3 H, s, 4 x $MeCO_2$), 1.57 (3 H, br s, 3-Me), 2.12 (3 H, br d, *J* 9 Hz, 9a-H), 2.61 (1 H, dd, *J* 15 and 8 Hz, 4-H_α), 3.00 (1 H, dd, *J* 15 and 8 Hz, 4-H_β), 3.30 (1 H, q, separation 9 Hz, 4a-H), 3.50–3.64 (1 H, m, 5'-H), 4.10 (1 H, dd, *J* 12 and 3 Hz, 6'-H), 4.17 (1 H, dd, *J* 12 and 7 Hz, 6'-H), 4.39 (1 H, br s, 2-H), 4.40 (1 H, d, *J* 8 Hz, 1'-H), 4.60–4.72 (1 H, m, 2'-H), 4.90–5.02 (2 H, m, 3'- and 4'-H), 5.22 (1 H, s, 1-H), 6.65 (1 H, s, 7-H), 7.36–7.41 and 7.56–7.62 (6 and 4 H, each m, 2 x Ph), and 12.73 (1 H, s, 8-OH); *m/z* (FAB; *m*-nitrobenzyl alcohol) 1838 [M^+, 2% (a cluster of ions was observed at 1833, 1834, 1835, 1836, 1837, 1838, 1839, 1840 ,and 1841 in the ratio of 1:3:6:8:7:10:8:4:2)] and 169 (100) (Found: C, 55.0; H, 4.1. $C_{84}H_{80}O_{35}Os$ requires C, 54.8; H, 4.4%).

Preparation of (1R,2S,3R,4aR,9aR)-5,6-O-*Diphenylmethylidene*-1,2,3,4,4a,9a-*hexahydro*-2,3-O-*isopropylidene*-3-*methyl*-9,10-*dioxo*-1-(2',3',4',6'-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy*)-*anthracene*-2,3,5,6,8-*pentaol* **(27)**

A solution of the osmium derivative **(26)** (0.350 g, 0.19 mmol) in dichloromethane (5 cm^3) was saturated with hydrogen sulphide. Filtration of the mixture through Celite and evaporation of the filtrate left a residue which was stirred with 2,2-dimethoxypropane (10 cm^3) and a trace of *p*-toluenesulphonic acid for 1 h. The mixture was partitioned between water and dichloromethane and the organic phase was dried ($MgSO_4$) and concentrated. Crystallisation of the residue from

diethyl ether–light petroleum gave the *title compound* **(27)** (0.265 g, 82%) as a pale-orange solid; m.p. 105 °C (decomp.); $[\alpha]_D$ -47° (0.1% in CH_2Cl_2); ν_{max} (KBr) 3450br (OH), 1760 (ester CO), and 1640 (quinone CO); λ_{max}(EtOH) 234 (ε 20,700), 268 (11,600), 293sh (5200), and 378 nm (10,800); δ(300 MHz; $CDCl_3$) 1.43, 1.448, and 1.461 (each 3 H, br s, Me_2C and 3-Me), 1.456, 1.92, 2.01, and 2.09 (each 3 H, s, 4 x $MeCO_2$), 2.18 (1 H, dd, *J* 14 and 9 Hz, 4-H_β), 3.22 (1 H, t, *J* 9, 9, and 6 Hz, 4a-H), 3.50 (1 H, dd, *J* 9 and 4 Hz, 9a-H), 3.68 (1 H, ddd, *J* 9, 5, and 3 Hz, 5'-H), 4.13–4.23 (2 H, m, 6'-H_2), 4.24 (1 H, d, *J* 4 Hz, 2-H), 4.55 (1 H, dd, *J* 8 Hz, 1'-H), 4.67 (1 H, t, separation 9 Hz, 2'-H), 4.68 (1 H, t, *J* 4 and 4 Hz, 1-H), 4.98 (1 H, t, *J* 9 and 9 Hz, 4'-H), 5.07 (1 H, t, *J* 9 and 9 Hz, 3'-H), 6.69 (1 H, s, 7-H), 7.35–7.41 and 7.53–7.59 (6 and 4 H, each m, 2 x Ph), and 13.46 (1 H, s, 8-OH) (the signals for 4-H_α were partly obscured by an acetoxy s at δ 2.09); *m/z* (FAB) 858 (M^+, 80%), 451 (50) and 747 (100) (Found: C, 62.6; H, 5.5. $C_{45}H_{46}O_{17}$ requires C, 62.95; H, 5.40%).

Preparation of (1R,2S,3R)-5,6-O-*Diphenylmethylidene*-1,2,3,4-*tetrahydro*-2,3-O-*isopropylidene*-3-*methyl*-9,10-*dioxo*-1-(2',3',3',4',6'-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy)anthracene*-2,3,5,6,8-*pentaol* **(28)**

A mixture of compound **(27)** (0.120 g, 0.14 mmol) and activated manganese dioxide (1.0 g) in dry benzene (20 cm^3) was heated under reflux for 7 h. The mixture was filtered through Celite and the residues were washed with dichloromethane. Evaporation of the filtrate and purification of the residue by silica-gel column chromatography [light petroleum–Et_2O (2:3) as eluant] gave the starting material **(27)** (0.005 g, 4%) and the *title compound* **(28)** as red crystals. After recrystallisation from diethyl ether–light petroleum, the latter sample (0.060 g, 50%) displayed m.p. 220–223 °C; $[\alpha]_D$ +147° (0.1% in CH_2Cl_2); ν_{max}(KBr) 3440 (OH), 1755 (ester CO), and 1645 cm^{-1} (quinone CO); λ_{max}(EtOH) 225 (ε 56,300), 282 (11,900), and 501 nm (8900); δ(300 MHz; $CDCl_3$) 1.08, 1.34, and 1.55 (each 3 H, s, Me_2C and 3-Me), 1.87, 1.97, 2.02, and 2.14 (each 3 H, s, 4 x $MeCO_2$), 2.13 (1 H, d, *J* 18 Hz, 4-H_α), 3.35 (1 H, d, *J* 18 Hz, 4-H_β), 3.68–3.78 (1 H, m, 5'-H), 4.23 (1 H, dd, *J* 13 and 2 Hz, 6'-H), 4.31 (1 H, dd, *J* 13 and 5 Hz, 6'-H), 4.46 (1 H, d, *J* 3 Hz, 2-H), 4.51 (1 H, d, *J* 8 Hz, 1'-H), 4.91 (1 H, dd, *J* 10 and 8 Hz, 2'-H), 5.06 (1 H, t, *J* 10 and 10 Hz, 4'-H), 5.12 (1 H, t, *J* 10 and 10 Hz, 3'-H), 5.51 (1 H, d, *J* 3 Hz, 1-H), 6.74 (1 H, s, 7-H), 7.37-7.42 and 7.54–7.61 (6 and 4 H, each m, 2 x Ph), and 13.34 (1 H, s, 8-OH); *m/z* (FAB; *m*-nitrobenzyl alcohol) 856 (M^+, 65%), 451 (50), and 77 (100) (Found: C, 63.0; H, 4.9. $C_{45}H_{44}O_{17}$ requires C, 63.1; H, 5.2%).

Preparation of (1R,2S,3R)-1,2,3,4-*Tetrahydro*-1,2,9,10-*tetrahydroxy*-6-*methoxy*-3-*methylanthracene*-5,8-*dione (Bostrycin)* **(3)**

The glycoside **(28)** (0.050 g, 0.06 mmol) was heated under reflux in a 1:1 mixture of 1M hydrochloric acid and ethanol (60 cm^3) for 12 h. After having been diluted with water, the red solution was washed with diethyl ether (2 x 50 cm^3) and then extracted with ethyl acetate (5 x 50 cm^3). Evaporation of the combined dried ($MgSO_4$) extracts gave a residue which was dissolved in THF (20 cm^3); the solution was treated with ethereal diazomethane until no starting material remained (the reaction was monitored by TLC). The residue, obtained after removal of the solvent, was triturated with light petroleum to give the title compound **(3)** (0.012 g, 61%) as a slightly

impure red solid; m.p. 210 °C (decomp.) {lit.,[2] 222 – 224 °C (decomp.) [for **(2)**]; lit.,[6] 218 – 220 °C (decomp.) [for (+/-)-**(3)**]}; $[\alpha]_D$ +225° (0.03% in Me_2SO); CD(MeCN) 243sh ($\Delta\varepsilon$ +1.1), 302 (-1.1), 374br (+0.9), 436br (+0.36), and 494br nm (+0.54); ν_{max}(KBr) 3400 – 3500 (OH) and 1600 cm^{-1} (quinone CO); λ_{max}(EtOH) 226 (absorbance 2.35), 301 (0.74) and 504 nm (0.61); δ(300 MHz; CD_3SOCD_3) 1.22 (3 H, s, 3-Me), 2.70 (2 H, AB q, *J* 18 Hz, separation of inner lines, 4 Hz, 4-H_2), 3.51 (1 H, t, *J* 5 and 5 Hz, 2-H), 3.91 (3 H, s, MeO), 4.53 (1 H, s, 3-OH), 4.74 (1 H, br t, *J* 5 and 5 Hz, 1-H), 4.99 (1 H, d, *J* 5 Hz, 2-OH), 5.29 (1 H, br d, *J* 5 Hz, 1-OH), 6.48 (1 H, s, 7-H), and 12.6 and 13.4 (each 1 H, br s, 9- and 10-H); *m/z* (EI) 336 (M^+, 0.3%), 320 (22). and 336 (100).

Reaction of the Diene **(9a)** *with Juglone* **(14c)**

The diene **(9a)** (0.857 g, 2.07 mmol) was added to a stirred mixture of juglone **(14c)** (0.300 g, 1.72 mmol) and tetra-acetyl diborate (0.857 g, 3.14 mmol) in diethyl ether (20 cm^3). After 15 h, the mixture was partitioned between water and diethyl ether. The organic phase was washed with water, dried ($MgSO_4$) and concentrated. Purification of the residue by silica-gel chromatography [light petroleum – Et_2O (3:7) as eluant] gave a pale-yellow foam which after trituration with diethyl ether and sonication gave (1S,4aR,9aR)-1,4,4a,9a-*tetrahydro*-8-*hydroxy*-3-*methyl*-1-(2',3',4',6'-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxyanthracene*-9,10-*dione* **(15b)** (0.355 g, 35%) as an off-white solid; m.p. 105-110 °C (decomp.); $[\alpha]_D$ +216° (0.3% in CH_2Cl_2); ν_{max}(KBr) 3450br (OH), 1755 (ester CO), and 1710 and 1645 cm^{-1} (quinone CO); λ_{max}(EtOH) 229 (ε 20,200), 262sh (5100), and 346 nm (5100); δ(300 MHz; $CDCl_3$) 1.74, 1.87, 1.97, and 2.10 (each 3 H, s, 4 x $MeCO_2$), 1.82 (3 H, br s, 8-Me), 3.06 (1 H, br d, separation 18 Hz, 4-H_α), 3.31 (1 H, dd, *J* 7 and 5 Hz, 9a-H), 3.34 (1 H, t, separation 7 Hz, 4a-H), 3.57 (1 H, ddd, *J* 9, 6, and 3 Hz, 5'-H), 4.06 (1 H, dd, *J* 13 and 6 Hz, 6'-H), 4.15 (1 H, dd, *J* 13 and 3 Hz, 6'-H), 4.35 – 4.45 (3 H, m, 1-, 1'-, and 2'-H), 4.83 – 5.00 (2 H, m, 3'- and 4'-H), 5.63 – 5.70 (1 H, m, 2-H), 7.18 (1 H, dd, *J* 8 and 1 Hz, 7-H), 7.48 (1 H, dd, *J* 8 and 1 Hz, 5-H), 7.62 (1 H, t, *J* 8 and 8 Hz, 6-H), and 12.08 (1 H, s, 8-OH) (the signals for 4-H_β were partly obscured by an acetoxy s at δ 2.10); *m/z* (FAB) 589 (MH^+, 5%), 331 (70), and 149 (100) (Found: C, 59.1; H, 5.6. $C_{29}H_{32}O_{14}$ requires C, 59.2; H, 5.5%).

Reaction of the Cycloadduct **(15b)** *with Osmium* (VIII) *Oxide and Potassium Chlorate*

A solution of the cycloadduct **(15b)** (0.100 g, 0.17 mmol) and potassium chlorate (0.100 g, mmol) in 20% aqueous THF (5 cm^3) was treated with a catalytic quantity of osmium(VIII) oxide (added as a 2% solution in CCl_4). After having been stirred for 24 h, the mixture was diluted with dichloromethane and washed with saturated aqueous sodium metabisulphite followed by water. Evaporation of the dried ($MgSO_4$) organic phase left a yellow residue which was dissolved in a mixture of ethanol (25 cm^3) and 1M hydrochloric acid (25 cm^3). The mixture was heated under reflux overnight, poured into water and extracted with ethyl acetate. Evaporation of the dried ($MgSO_4$) organic layer and purification of the residue by silica-gel chromatography (EtOAc as eluant) gave a 60:40 mixture of demethoxy-5-deoxybostrycin **(12b)** and demethoxy-5-deoxy-1-*epi* bostrycin **(30)** (0.002 g, 4%) in a slightly impure state; δ(300 MHz; $CDCl_3$) *inter alia* 1.37 and 1.45 (1.2 and 1.8 H, each s, 3-Me), 2.57 and 2.64 [0.6 and 0.4 H, dd (*J* 20 and 2 Hz) and d (*J* 20 Hz), 4-H_β], 3.00 and 3.04 (0.6 and 0.4 H, each dd, *J* 20 Hz, 4-H_α), 3.71 and 3.72 [0.6 and 0.4 H, d (*J* 7

Hz) and d (*J* 3 Hz), 2-H], 4.13 (1 H, br s, OH), 4.93 and 4.97 [0.6 and 0.4 H, br d (separation 7 Hz) and br d (separation 3 Hz), 1-H)], 7.22 – 7.28 (1 H, m, 7-H), 7.57 – 7.63 (2 H, m, 5- and 6-H), and 11.80 and 11.90 (0.6 and 0.4 H, each s, 8-OH).

Subjection of the mixture to semi-preparative HPLC led to the isolation of demethoxy-7-deoxybostrycin **(12b)** in an almost pure state. The ^{1}H NMR spectrum of the sample matched that of the material that was subsequently prepared.

Preparation of Oxobis [(1R,2S,3R,4aR,9aR)-1,2,3,4,4a,9a-*hexahydro*-8-*hydroxy*-3-*methyl*-9,10-*dioxo*-1-(2',3',4',6'-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy)anthacene*-2,3-*diolato*]*osmium* (VI) **(19b)**

A solution of the cycloadduct **(15a)** (0.250 g, 0.425 mmol) in dry carbon tetrachloride (2 cm^3) was stirred with a 2% solution of osmium(VIII) oxide in carbon tetrachloride (8.1 cm^3, 0.64 mmol) for 16 h. THF (10 cm^3) and saturated aqueous sodium metabisulphite (1 cm^3) were added and the mixture was stirred vigorously for 1 h. The mixture was then partitioned between water and dichloromethane. Evaporation of the dried ($MgSO_4$) organic phase left a residue which was dissolved in a minimum volume of dichloromethane; addition of diethyl ether induced the precipitation of the *title compound* **(19b)** (0.252 g, 82%) as a pale-green solid; m.p. 240 °C (decomp.); $[\alpha]_D$ -100° (0.1% in CH_2Cl_2); ν_{max}(KBr) 3440br (OH), 1750 (ester CO), and 1705 and 1630 cm^{-1} (quinone CO); λ_{max}(EtOH) 230 (ε 39,500), 243sh (30,500), 270sh (18,000), and 347 nm (12,300); δ(300 MHz; $CDCl_3$) 1.38, 1.87, 1.98, and 2.08 (each 3 H, s, 4 x $MeCO_2$), 1.59 (3 H, br s 3-Me), 2.28 (1 H, dd, *J* 10 and 1 Hz, 9a-H), 2.70 (1 H, dd, *J* 15 and 8 Hz, 4-H$_\alpha$), 3.07 (1 H, dd, *J* 15 and 8 Hz, 4-H$_\beta$), 3.40 (1 H, q, separation 9 Hz, 4a-H), 3.53 – 3.67 (1 H, m, 5'-H), 4.07 – 4.23 (2 H, m, 6-H$_2$), 4.40 (1 H, br s, 2-H), 4.40 (1 H, *J* 8 Hz, 1'-H), 4.56 – 4.67 (1 H, m, 2'-H), 4.90 – 5.02 (2 H, m, 3'- and 4'-H), 5.28 (1 H, br s, 1-H), 7.21 (1 H, dd, *J* 8 and 1 Hz, 7-H), 7.58 (1 H, dd, *J* 8 and 1 Hz, 5-H), 7.70 (1 H, t, *J* 8 and 8 Hz, 6-H), and 11.65 (1 H, s, 8-OH); *m/z* (FAB; *m*-nitrobenzyl alcohol) 1449 [*M*$^+$, 1% (a cluster of ions was observed at 1444, 1445, 1446, 1447, 1448, 1449, 1450, 1451, and 1452 in the ratio of 2:5:8:10:10:10:8:3:1)], 331 (60), and 169 (100) (Found: C, 47.8; H, 4.5. $C_{58}H_{64}O_{31}Os$ requires C, 48.15; H, 4.45%).

Preparation of (1R,2S,3R,4aR,9aR)-1,2,3,4,4a,9a-*Hexahydro*-2,3-O-*isopropylidene*-3-*methyl*-9,10-*dioxo*-1-(2',3',4',6'-*tetra*-O-*acetyl*-β-D-*glucopyranosyloxy)anthracene*-2,3,8-*triol* **(20b)**

A solution of the osmium derivative **(19b)** (0.350 g, 0.24 mmol) in chloroform (5 cm^3) was saturated with hydrogen sulphide. Filtration of the mixture through Celite and evaporation of the filtrate left a residue which was stirred with 2,2-dimethoxypropane (5 cm^3) and a trace of *p*-toluenesulphonic acid for 1 h. The mixture was partitioned between water and dichloromethane and the organic phase was dried ($MgSO_4$) and concentrated. Crystallisation of the residue from diethyl ether gave the *title compound* **(20b)** (0.220 g, 69%) as a pale-yellow solid; m.p. 162 – 165 °C (decomp.); $[\alpha]_D$ +37° (0.1% in CH_2Cl_2); ν_{max}(KBr) 3450br (OH), 1755 (ester CO), and 1690 and 1640 cm^{-1} (quinone C=O); λ_{max}(EtOH) 231 (ε 22,500), 349 (5000), and 362sh nm (5300); δ(300 MHz; $CDCl_3$) 1.43, 1.45, and 1.46 (each 3 H, s, Me_2C and 3-Me), 1.50, 1.92, 2.01, and 2.04 (each 3 H, s, 4 x $MeCO_2$), 3.32 (1 H, dt, *J* 9, 9, and 7 Hz, 4a-H), 3.60 (1 H, dd, *J* 9 and 4 Hz, 9a-H), 3.69 (1 H, ddd, *J* 10, 5, and 3 Hz, 5'-H), 4.17 (1 H, dd, *J* 12 and 5 Hz, 6'-H), 4.25 (1 H, dd, *J* 12 and 3 Hz,

6'-H), 4.28 (1 H, d, *J* 4 Hz, 2-H), 4.56 (1 H, d, *J* 8 Hz, 1'-H), 4.59 (1 H, t, separation 9 Hz, 2'-H), 4.71 (1 H, t, *J* 4 and 4 Hz, 1-H), 4.97 (1 H, t, *J* 10 and 10 Hz, 4'-H), 5.09 (1 H, *J* 10 and 10 Hz, 3'-H), 7.23 (1 H, dd, *J* 8 and 1 Hz, 7-H), 7.59 (1 H, dd, *J* 8 and 1 Hz, 5-H), 7.67 (1 H, t, *J* 8 and 8 Hz, 6-H), and 12.45 (1 H, s, 8-OH) (the signals for 4-H_2 were partly obscured by an acetoxy s at δ 2.04); *m/z* (FAB; *m*-nitrobenzyl alcohol) 662 (M^-, 100%).

Preparation of (1R,2S,3R)-1,2,3,4-*Tetrahydro*-2,3-O-*isopropylidene*-3-*methyl*-9,10-*dioxo*-1-*(2,3',4',6'-tetra*-O-*acetyl*-β-D-*glucopyranosyloxy)anthracene*-2,3,8-*triol* **(21b)**

A mixture of compound **(20b)** (0.150 g, 0.226 mmol) and activated manganese(IV) oxide (0.50 g) in dry benzene (10 cm^3) was heated under reflux for 23 h. The mixture was filtered through Celite and the residues were washed with dichloromethane. Evaporation of the filtrate and purification of the residue by silica-gel column chromatography (light petroleum – Et_2O; gradient elution) gave the *title compound* **(21b)** (0.070 g, 47%) as yellow crystals. After recrystallisation from dichloromethane – light petroleum, the sample showed m.p. 222 – 224 °C; $[\alpha]_D$ +28° (0.1% in CH_2Cl_2); ν_{max} 1760 (ester CO), and 1670, 1650, and 1625 cm^{-1} (quinone CO); $\lambda_{max.}$ (EtOH) 209 (ε 4000), 270 (1500), and 429 nm (900); δ(300 MHz; $CDCl_3$) 1.07 and 1.34 (each 3 H, s, Me_2C), 1.83, 1.97, 2.02, and 2.15 (each 3 H, s, 4 x $MeCO_2$), 2.18 (1 H, d, *J* 17 Hz, 4-H_α), 3.41 (1 H, d, *J* 17 Hz, 4-H_β), 3.75 (1 H, ddd, *J* 9, 5, and 2 Hz, 5'-H), 4.23 (1 H, dd, *J* 12 and 2 Hz, 6'-H), 4.32 (1 H, dd, *J* 12 and 5 Hz, 6'-H), 4.48 (1 H, d, *J* 3 Hz, 2-H), 4.54 (1 H, d, *J* 8 Hz, 1'-H), 4.91 (1 H, t, separation 9 Hz, 2'-H), 5.07 (1 H, t, *J* 9 and 9 Hz, 4'-H), 5.14 (1 H, t, *J* 9 and 9 Hz, 3'-H), 5.48 (1 H, d, *J* 3 Hz, 1-H), 7.31 (1 H, dd, *J* 8 and 2 Hz, 7-H), 7.61 – 7.78 (2 H, m, 5- and 6-H), and 12.01 (1 H, s, 8-OH); *m/z* (EI) 661 (MH^+ <1%), 645 (M^+-CH_3, 5), and 255 (100) (Found: C, 58.1; H, 5.5. $C_{32}H_{36}O_{15}$ requires C, 58.2; H, 5.5%).

Preparation of (1R,2S,3R)-1,2,3,4-*Tetrahydro*-1,2,3,8-*tetrahydroxy*-3-*methylanthracene*-9,10-*dione (Demethoxy*-5-*deoxybostrycin)* **(12b)**

The glycoside **(21b)** (0.040 g, 0.06 mmol) was heated under reflux in a 2:1 mixture of 1M-hydrochloric acid and ethanol (15 cm^3) for 5 h. Evaporation of the solvent left a residue which (since hydrolysis appeared to be incomplete by ^1H NMR spectroscopy) was dissolved in 1M-hydrochloric acid (10 cm^3) and heated under reflux for a further 2 h. The mixture was diluted with water (100 cm^3) and extracted with ethyl acetate (4 x 50 cm^3). Evaporation of the combined dried ($MgSO_4$) extracts and crystallisation of the residue from dichloromethane – light petroleum gave the *title compound* **(12b)** (0.013 g, 74%) as a yellow solid; m.p. 160 °C (decomp.); $[\alpha]_D$ +197° (0.04% in CH_2Cl_2); ν_{max} (KBr) 3420br (OH), and 1665, 1640, and 1625 cm^{-1} (quinone CO); λ_{max} (EtOH) 210 (ε 34,000), 246 (9800), 271 (11,100), and 419 nm (4100); δ(300 MHz; $CDCl_3$) 1.48 (3 H, s, 3-Me), 2.14 (1 H, br s, OH), 2.59 (1 H, dd, *J* 20 and 2 Hz, 4-H_β), 2.83 (1 H, br s, OH), 3.02 (1 H, d, *J* 20 Hz, 4-H_α), 3.74 (1 H, d, *J* 7 Hz, 2-H), 4.04 (1 H, s, OH), 4.94 (1 H, d, *J* 7 Hz, 1-H), 7.24 – 7.27 (1 H, m, 7-H), 7.58 – 7.63 (2 H, m, 5- and 6-H), and 11.84 (1 H, s, 8-OH); *m/z* (CI, NH_3) 308 (MNH_4^+, 21%), 291 (MH^+, 36), and (339); *m/z* (EI) 290 and 217 (100) (Found: M^+, 209.0795. $C_{15}H_{14}O_6$ requires *M*, 290.0790).

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