Total Synthesis of (+)-Hatomarubigin B

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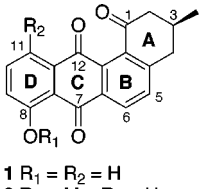
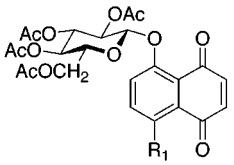
The first total synthesis of (+)-hatomarubigin **3** is described. The tetra-*O*-acetyl diborate promoted Diels−Alder reaction of 5-hydroxy-8-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-1,4-naphthoquinone **8** and (*E*, 1*R**,5*R**)-3-(2′-methoxyvinyl)cyclohex-2-enol (±)-**7** gave a mixture of four cycloadducts from which (1*S*,3*S*,6*S*,6a*R*,12a*R*,12b*S*)-1,8-dihydroxy-6-dimethoxy-1-hydroxy-3-methyl-11-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-1,2,3,4,6,6a,12a,12b-octahydrobenz[*a*]anthracene-7,12-dione **12** was isolated in 51% yield. Selective methylation and acetylation of **12** gave (1*S*,3*S*,6*S*,6a*R*,12a*R*,12b*S*)-1-acetoxy-6,8-dimethoxy-3-methyl-11-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyloxy)-1,2,3,4,6,6a,12a,12b-octahydrobenz[*a*]anthracene-7,12-dione **10a**. Sequential aromatization, photooxidation and hydrolysis of the glucosyl unit gave (+)-**3** (98% ee) in an 8% overall yield from **8**.

Introduction

The angucycline antibiotics have attracted much interest in the past decade because of their wide ranging biological properties and structural diversity.[1] Much progress has been made toward strategies for their preparation with the total syntheses of the natural products (+)-ochromycinone **1**,[2,3] (+)-emycin A,[2] (+)-rubiginone B_2 **2**,[3] (+)-urdamycinone B,[4] SF2315A,[4] and aquayamycin[5] having been accomplished. In our continuing efforts to develop asymmetric syntheses of the angucyclines our attention turned to the those members which possess the naphthazarin motif in the CD ring system (i.e., those with hydroxyl or protected hydroxyl functionality at both C-8 and C-11 of the benz[*a*]anthraquinone core). This substitution pattern is only exhibited by the hatomarubigin and landomycin subgroups. Of the latter, landomycin A has attracted much attention due to its potential as an antitumor agent.[6]



1 $R_1 = R_2 = H$
2 $R_1 = Me$, $R_2 = H$
3 $R_1 = Me$, $R_2 = OH$



4 $R_1 = H$
8 $R_1 = OH$

The most general strategy employed for the construction of angucyclinones has been the Diels−Alder reaction between suitably functionalized vinylcyclohexenes and naphthoquinones. An asymmetric synthesis of (+)-urdamycinone B was achieved by Sulikowski et al. using a diene synthesized from (−)-quinic acid.[4] We have reported the syntheses of (+)-emycin A and (+)-ochromycinone **1** using a chiral Lewis acid to promote a cycloaddition that resulted in a kinetic resolution of the racemic diene partner.[2] The latter approach has been further developed by Carreño et al. who synthesized (+)-**1** and (+)-rubiginone B_2 **2**, both in 80% ee, using the cycloaddition of an enantiomerically pure sulfinylquinone dienophile as the source of asymmetry to affect a kinetic resolution of a racemic diene.[3]

The success of the latter work has prompted us to develop asymmetric syntheses of the angucyclines possessing the naphthazarin motif in the CD ring system using a chiral dienophile. Our initial aim was to synthesize (+)-hatomarubigin B **3**, a compound which has been shown to potentiate the activity of colchicine against KB-(CH^R) cancer cell lines.[7] Work directed at the synthesis of enantiopure anthraquinones by Stoodley and coworkers has demonstrated the use of a tetra-*O*-acetyl-*β*-D-glucopyranosyl residue as a chiral auxiliary attached to the dienophile in Diels−Alder reactions of naphthoquinones with achiral dienes.[8] In the thermal cycloaddition of quinone **4** with cyclopentadiene only one of the two possible endo stereoisomers, adduct **5**, was formed, and this was isolated in high yield. We have previously shown that the semicyclic dienes (±)-**6** and

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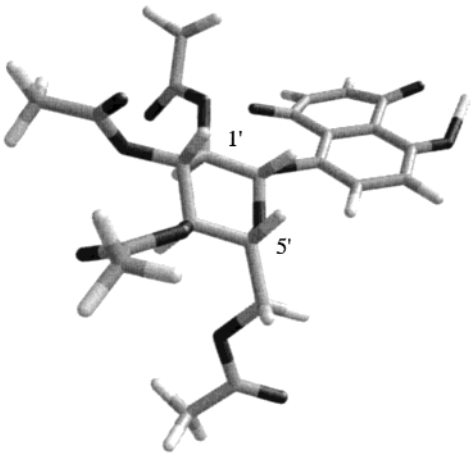
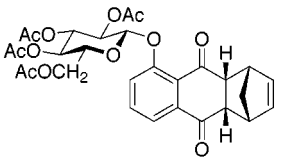


Figure 1. Conformation of dienophile **8**.

(±)-**7** react with 5-hydroxynaphthoquinone, in the presence of Lewis acids, to give single diastereoisomeric cycloadducts.[9] The outcome of these reactions was explained by way of a model where the favored approach of the dienophile is endo and anti to the face of the diene bearing the allylic substituent. Based on the arguments above we envisaged that a Lewis acid promoted cycloaddition of naphthazarin glycoside **8** and (±)-**6** should result in an effective kinetic resolution of the diene partner, and further manipulation of the resulting cycloadduct would give (+)-hatomarubigin B **3** in enantiomerically enriched form.

Results and Discussion

Glucoside **8** was prepared from the silver(I) oxide-promoted reaction of naphthazarin and tetra-*O*-acetyl-α-D-glucopyranosyl bromide in acetonitrile in 29% yield. The starting material, naphthazarin (35%), was also recovered, and traces of a diglucosidic product were detected. The NOESY spectrum of **8** exhibited, in addition to the cross-peaks expected between the axial protons of the sugar residue, strong enhancements between the anomeric proton and H-5′ to H-7 of the naphthoquinone unit. This can be explained by the adoption of a solution conformation similar to that depicted in Figure 1. This is similar to the observed NOE enhancements reported by Stoodley et al. in their study of the solution conformation of glucoside **4**.[8] From an X-ray crystallographic study they also found that **4** adopted a similar conformation in the solid state which appeared to be stabilized by both the exo-anomeric effect and also a nonbonding interaction between the C-4 carbonyl oxygen and the carbonyl carbon of the C-2′ acetoxyl group on the sugar residue. The result of such an orientation of the sugar residue is facial blocking of the top face of quinones **4** and **8** by the O-2′ acetyl group.



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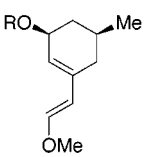

(±)-**6** R = Ac
(±)-**7** R = H

The tetra-*O*-acetyl diborate promoted Diels−Alder reaction of **8** and (±)-**6** gave an 18:1:0.4:0.1 mixture of four cycloaddition products based on integration of the downfield hydrogen-bonded phenolic protons singlets in the ^{1}H NMR spectrum (Scheme 1). The structure of the major product was assigned as **9a** while the minor adducts were tentatively assigned the structures **9b**, **9c**, and **9d**. The structure of **9a** was deduced from the analysis of coupling constant data from the ^{1}H NMR spectrum ($J_{1,12b}$ 9.5 Hz, $J_{1,2ax}$ 11.5 Hz, and $J_{2ax,3}$ 12.0 Hz) which indicates axial orientations of H-1, -3, and -12b. This is consistent with an endo approach of the dienophile−Lewis acid complex anti to the face of the diene bearing the allylic substituent. The configurations of the newly formed chiral centers were assigned on the basis of Stoodley's model of facial blocking.[8] Unfortunately, no coupling constant data could be gained from the ^{1}H NMR spectrum of the mixture to confirm the structures of the three minor adducts. However, it is likely that **9b** is formed by reaction of the diene in an endo approach to the more hindered face of **8**. In an earlier study,[10] the reaction of naphthazarin acetate and diene **6** gave small amounts of 1,3-trans substituted tetracycles. These were believed to arise from minor impurities in the diene where the acetoxyl and methyl groups of the cyclohexene ring are trans related to each other. Cycloadducts **9c** and **9d** are believed to be formed from this impurity.

All attempts at isolation of the major adduct **9a** were unsuccessful, and the mixture of diastereoisomers was used in subsequent steps. Methylation of the 8-hydroxyl group of **9** was achieved by reaction with silver(I) oxide in refluxing iodomethane to give methyl ether **10** as a diastereoisomeric mixture in 90% yield (Scheme 2). Aromatization of the B ring of **10** was effected by treatment with DBU in refluxing THF under an atmosphere of air to give a photounstable intermediate which was immediately photo-oxidized in methanol under an atmosphere of oxygen by irradiation with a tungsten lamp to give ketone **11** in a 39% yield from **10**. The low overall yield for the process was attributed to further oxidation of the D ring of the benz[*a*]anthraquinone resulting in the formation of very polar products. From the NMR data for the isolated product it appeared that only a single diastereoisomer had been formed. However, on the basis that a mixture of cycloadducts **9** was used in the sequence, it was very likely that the C-3 epimer of **11**, with identical NMR properties, was also present to some degree.

Removal of the glucosidic chiral auxiliary of **11** by acid hydrolysis gave (+)-hatomarubigin B **3** in 84% yield after crystallization from pentane and chloroform. The high-resolution mass spectrum supported the molecular formula $C_{20}H_{16}O_5$ and the ^{1}H and ^{13}C NMR data were identical to those reported for the natural product. The optical rotation {$[\alpha]_D$ +105 ($CHCl_3$); lit.[7] $[\alpha]_D$ +146 ($CHCl_3$)} indicated that we had synthesized the natural product with 72% optical purity. This value compares well to the ee of 78% measured from the ^{1}H NMR spectrum of a mixture of (+)-**3** and the chiral solvating agent, (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol.[11] The ee

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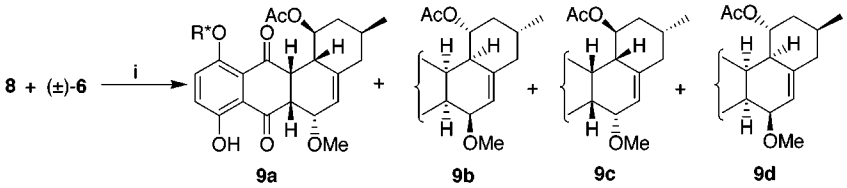
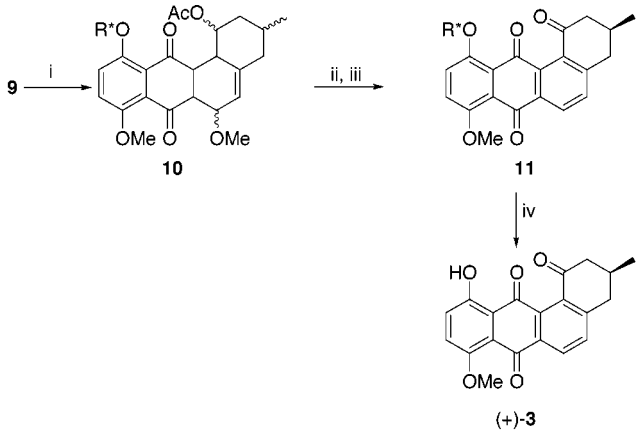
Scheme 1[a]



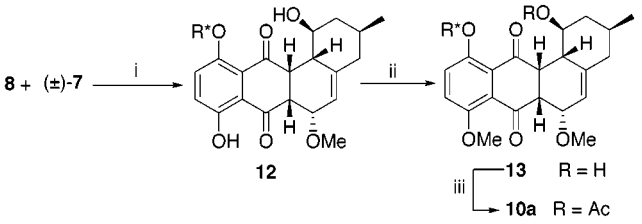
[a] Reagents and conditions: i, $B_2O(OAc)_4$, CH_2Cl_2; R* = 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl.

Scheme 2[a]



[a] Reagents and conditions: i, MeI, Ag_2O; ii, DBU, THF; iii, *hν*, MeOH iv, H^+, H_2O−EtOH. R* = tetra-*O*-acetyl-*β*-D-glucopyranosyl.

Scheme 3[a]



[a] Reagents and conditions: i, $B_2O(OAc)_4$, CH_2Cl_2; ii, Ag_2O, MeI; iii, Ac_2O, Py R* = tetra-*O*-acetyl-*β*-D-glucopyranosyl.

was assessed from the integrals of the signals associated with the C-8 methoxyl protons. The ^{1}H NMR spectrum of a 1:6 mixture of racemic **3** prepared in an earlier study[10] and the chiral solvating agent showed two clearly resolved singlets of equal intensity for these protons.

The overall yield of (+)-**3** for the five-step sequence from the dienophile **8** was 22%. We felt that a simple modification to the synthetic strategy might allow separation of the diastereomeric cycloadducts which could then be transformed into enantiomerically pure (+)-hatomarubigin **3**. To this end the tetra-*O*-acetyl diborate promoted Diels−Alder reaction of dienol (±)-**7** and **8** gave a mixture of four cycloadducts in a ratio of 6:1:0.5:0.2. The major adduct **12** was isolated in 51% yield after column chromatography and crystallization from diethyl ether and hexanes (Scheme 3). Methylation of the C-8 hydroxyl group gave methyl ether **13** (75%) which on treatment with acetic anhydride and pyridine furnished acetate **10a** in quantitative yield, this time as a single stereoisomer **10a**. Aromatization and photooxidation of **10a** as previously described gave isomerically pure ketone **11** (31%) which on acid hydrolysis of **11** yielded the target compound (+)-**3** with specific rotation, $[\alpha]_D$ +142 ($CHCl_3$){lit.[7] $[\alpha]_D$ +146 ($CHCl_3$)}. The ee of (+)-**3** was judged to be 98% on the basis of NMR experiments using the chiral solvating agent.

The assignment of absolute stereochemistry of the hatomarubigins was made by analogy to their related congeners, the rubiginones, whose configurations were deduced by NMR methods.[12] In the current work, single crystals of glucoside **11** were obtained by slow crystallization from pentane and chloroform. The solution of the single crystal X-ray crystal data unambiguously confirmed the structure and the assignment of the 3*S* absolute configuration of **11** on the basis of the known configuration of the tetra-*O*-acetyl-*β*-D-glucopyranosyl unit.[13] The absolute stereochemistry of (+)-hatomarubigin B **3** is therefore established. It is worthy of note that, in the solid state, the glucose residue adopts a similar conformation to that proposed for dienophile **8**.

In summary, (+)-hatomarubigin B **3** (78% ee) has been synthesized from the naphthazarin glucoside **8** and diene (±)-**6** in five steps in an overall yield of 22%. The crucial step involved a Lewis acid catalyzed Diels−Alder reaction of **8** and (±)-**6** that resulted in an effective kinetic resolution of the diene partner. An analogous sequence involving **8** and dienol **7** allowed purification of the resulting cycloadduct **12**, modification of which gave (+)-**3** in 8% yield from **8** but with an ee of 98%. Hatomarubigin (+)-**3** was unambiguously assigned the 3*S* configuration based upon a single-crystal X-ray study of glucoside **11**.

Experimental Section

Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. ^{1}H (300 and 500 MHz) and ^{13}C (75 and 125 MHz) NMR spectra were measured on solutions of the compound in deuteriochloroform using the residual chloroform (δ_H 7.26 and δ_C 77.08 ppm) 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. For FAB mass spectra, *m*-nitrobenzyl alcohol was used as the matrix and xenon as the ionizing gas. Elemental analyses were carried out by Dr. R. G. Cunninghame and associates at the Campbell Microanalytical Laboratory, University of Otago, Dunedin, New

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(13) *Crystal data* for **11**·$(H_2O)_{0.25}$·$C_{34}H_{34.5}O_{14.25}$, pale yellow plate, 0.04 × 0.20 × 0.62 mm, M = 671.12, tetragonal, I4, a = 29.556(6), c = 7.4883(17) Å, U = 6541(2) Å^3, Z = 8, μ = 0.11 mm^{-1}. 42275 Reflections were collected at 168 K on a Bruker SMART diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71013 Å). The structure was solved by direct methods (SHELXS-97) and refined against all F^2 data (SHELXL-97) to $R1$ = 0.0511 [for 3844 $F > 4\sigma(F)$]; $wR2$ = 0.1252 and goodness of fit = 0.941 for all 6177 independent F^2; 442 parameters; hydrogen atoms inserted at calculated positions; absolute structure known due to the presence of the tetra-*O*-acetyl-*β*-D-glucopyranosyl residue]. Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and the deposition number CCDC 161596.

Zealand. Thin-layer chromatography (TLC) was preformed on Merck silica gel DC Alurolle Kieselgel 60F_{254} plates and were visualized under an UV lamp and/or with a spray consisting of 2.5% w/v anisaldehyde and sulfuric 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.

5-Hydroxy-8-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1,4-naphthoquinone 8. A cooled (0 °C) mixture of 5,8-dihydoxy-1,4-naphthoquinone (0.250 g, 1.32 mmol), tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0.650 g, 1.58 mmol), and freshly prepared silver(I) oxide (0.305 g, 1.32 mmol) in acetonitrile (10 mL) was sonicated for 90 min. The mixture was absorbed onto silica gel (1 g) and purified by silica gel column chromatography (1:1 hexanes−CH_2Cl_2 to 9:1 CH_2Cl_2−diethyl ether, gradient elution) to return starting material (0.087 g, 35%). A second fraction (R_f 0.4) eluted which gave, after crystallization from CH_2Cl_2 and diethyl ether, the title compound **8** (0.198 g, 29%) as orange needles. mp 138−145 °C decomp; ν_{max}(KBr)/cm^{-1} 3420, 1753, 1640; $[\alpha]^{20}_D$ −19 (1.0, $CHCl_3$); ^{1}H NMR δ ($CDCl_3$, 500 MHz) 2.06, 2.06, 2.09, 2.17 (each 3H, 4 × s), 3.77−3.83 (1H, m), 4.18 (1H, dd, *J* 12.5 and 2.5 Hz), 4.27 (1H, dd, *J* 12.5 and 5.0 Hz), 5.01 (1H, d, *J* 8.0 Hz), 5.17 (1H, t, *J* 9.5 Hz), 5.32 (1H, t, *J* 9.5 Hz), 5.40 (1H, dd, *J* 10.0 and 8.0 Hz), 6.83 (1H, d, *J* 10.5 Hz), 6.90 (1H, d, *J* 10.5 Hz), 7.24 (1H, d, *J* 10.0 Hz), 7.54 (1H, d, *J* 9.0 Hz), 12.43 (1H, s); ^{13}C NMR δ ($CDCl_3$, 75 MHz) 20.7, 20.7, 20.8, 21.0, 61.9, 68.4, 70.8, 72.2, 72.5, 100.5, 114.6, 120.3, 125.8, 131.1, 136.7, 141.1, 149.3, 158.7, 169.4 169.7, 170.2, 170.4, 182.7, 190.3; *m*/*z* (FAB) 521 (MH^+, 5%), 331 ($MH^+-C_{10}H_6O_4$, 100%). Anal. Calcd for $C_{24}H_{24}O_{13}$: C, 55.4; H, 4.7. Found: C, 55.3; H, 4.7%.

(1*S*,3*S*,6*S*,6a*R*,12a*R*,12b*S*)-1,8-Dihydroxy-6-methoxy-3-methyl-11-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1,2,3,4,6,6a,12a,12b-octahydrobenz[*a*]anthracene-7,12-dione 12. A cooled (0 °C) solution of diene (±)-**7**[9c] (0.605 g, 3.60 mmol) in CH_2Cl_2 (5 mL) was added to a mixture of **8** (0.470 g, 0.90 mmol) and tetra-*O*-acetyl diborate (0.200 g, 0.73 mmol) in CH_2Cl_2 (10 mL) at 0 °C, and the resulting mixture was stirred for 10 min. The reaction mixture was diluted with CH_2Cl_2, washed with 0.2 M hydrochloric acid, brine, and water, and dried over $MgSO_4$. Removal of the solvent and purification of the residue by silica gel column chromatography (CH_2Cl_2−diethyl ether 19:1 to 9:1, gradient elution) and crystallization of the fraction (R_f 0.1, CH_2Cl_2−diethyl ether 9:1) from diethyl ether and hexanes gave the title compound **12** (0.316 g, 51%) as colorless needles. mp 204−206 °C; ν_{max}(KBr)/cm^{-1} 3499, 1754, 1716, 1643. $[\alpha]^{22}_D$ +90 (0.1, $CHCl_3$); ^{1}H NMR δ ($CDCl_3$, 500 MHz) 0.98 (3H, d, *J* 6.0 Hz), 1.12 (1H, q, *J* 11.5 Hz), 1.65−1.80 (2H, m), 2.01, 2.02, 2.04, 2.13 (each 3H, 4 × s), 2.00−2.20 (2H, m), 2.32 (1H, br d, *J* 11.0 Hz), 2.72 (1H, d, *J* 5.0 Hz), 3.05 (3H, s), 3.12 (1H, dd, *J* 6 and 4.5 Hz), 3.70 (1H, ddd, *J* 10.0, 5.0 and 2.5 Hz), 3.77 (1H, t, *J* 5.5 Hz), 4.04−4.10 (2H, m′), 4.25 (1H, dd, *J* 12 and 5 Hz), 4.82 (1H, dddd *J* 11.0, 10.5, 5.5 and 4.5 Hz), 4.89 (1H, d, *J* 7.5 Hz), 5.11 (1H, dd, *J* 9.0 and 7.5 Hz), 5.16 (1H, t, *J* 9.5 Hz), 5.29 (1H, t, *J* 9 Hz), 5.72 (1H, dt, *J* 5.5 and 2.0 Hz), 7.03 (1H, d, *J* 9.0 Hz), 7.34 (1H, d, *J* 9.0 Hz), 12.13 (1H, s); ^{13}C NMR δ ($CDCl_3$, 75 MHz) 20.7, 20.7, 20.8, 21.0, 22.1, 29.5, 42.7, 44.7, 44.7, 45.9, 54.1, 56.4, 61.8, 68.2, 68.7, 72.1, 72.2, 72.2, 73.9, 100.8, 117.7, 119.1, 121.8, 129.9, 130.6, 142.1, 145.3, 158.1, 169.4, 170.4, 170.5, 170.6, 194.0, 204.8; *m*/*z* (FAB) 688 (M^+, 5%), 358 ($MH^+ - C_{14}H_{18}O_9$, 15%), 331 ($C_{14}H_{19}O_9^+$, 100%). Anal. Calcd for $C_{34}H_{40}O_{15}$: C, 59.3; H, 5.9. Found: C, 59.3; H, 6.0%.

(1*S*,3*S*,6*S*,6a*R*,12a*R*,12b*S*)-6,8-Dimethoxy-1-hydroxy-3-methyl-11-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1,2,3,4,6,6a,12a,12b-octahydrobenz[*a*]anthracene-7,12-dione 13. A mixture of **12** (0.340 g, 0.50 mmol), silver(I) oxide (0.115 g, 0.50 mmol), and iodomethane (10 mL) under nitrogen was heated at refluxed for 3 h. The mixture was filtered through a Celite pad, and the pad was washed with CH_2Cl_2. The filtrate was evaporated and the product crystallized from a mixture of CH_2Cl_2 and hexanes to give the title compound **13** (0.271 g, 75%) as colorless needles. mp 195−196 °C d.; ν_{max}(KBr)/cm^{-1} 3526, 1757, 1744, 1690; $[\alpha]^{19}_D$ +134 (0.23, $CHCl_3$); ^{1}H NMR δ ($CDCl_3$, 300 MHz) 1.00 (3H, d, *J* 6 Hz), 1.13 (1H, q, *J* 12.0 Hz), 1.65−1.76 (2H, m), 2.02, 2.05, 2.06, 2.18 (each 3H, 4 × s), 2.00−2.12 (2H, m), 2.32 (1H, br d, *J* 10.0 Hz), 3.05 (3H, s), 3.08 (1H, dd, *J* 6.0 and 4.5 Hz), 3.70 (1H, ddd, *J* 9.5, 4.5 and 2.5 Hz), 3.81 (1H, t, *J* 6.0 Hz), 3.94 (3H, s), 4.08−4.12 (2H, m), 4.24 (1H, dd, *J* 12.5 and 4.5 Hz), 4.79 (1H, td, *J* 11.0 and 4.5 Hz), 4.85 (1H, d, *J* 7.0 Hz), 5.14−5.21 (2H, m), 5.26 (1H, t, *J* 9.0 Hz), 5.73 (1H, dt, *J* 5.0 and 2.0 Hz), 7.06 (1H, d, *J* 9.5 Hz), 7.35 (1H, d, *J* 9.5 Hz); ^{13}C NMR δ ($CDCl_3$, 75 MHz) 20.7, 20.7, 20.8, 21.0, 22.1, 29.6, 42.8, 44.8, 44.9, 45.6, 54.0, 56.6, 56.8, 61.8, 68.2, 68.9, 71.9, 72.1, 72.3, 74.4, 100.8, 115.7, 118.2, 124.3, 128.3, 133.2, 141.4, 145.9, 156.2, 169.4, 170.3, 170.5, 170.6, 194.9, 196.0; ES−HRMS calcd for $C_{35}H_{42}O_{15}$ (MNa^+): 725.2421, found: 725.2457 (MNa^+).

(1*S*,3*S*,6*S*,6a*R*,12a*R*,12b*S*)-1-Acetoxy-6,8-dimethoxy-3-methyl-11-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyloxy)-1,2,3,4,6,6a,12a,12b-octahydrobenz[*a*]anthracene-7,12-dione 10a A mixture of **13** (0.170 g, 0.24 mmol), pyridine (2 mL), acetic anhydride (2 mL), and CH_2Cl_2 (0.5 mL) was stirred at room temperature for 16 h. The mixture was diluted with CH_2Cl_2 and washed with brine, water, saturated aqueous sodium bicarbonate, and water, and dried over $MgSO_4$. The organic phase was concentrated and then filtered through a pad of silica gel (CH_2Cl_2−diethyl ether, 9:1 as eluent). The filtrate was concentrated, and crystallization of the residue from diethyl ether, CH_2Cl_2 and hexanes gave the title compound **10a** (0.182 g, 100%) as a white powder. m.p 117−118 °C. $[\alpha]^{20}_D$ +96 (1.0, $CHCl_3$); ^{1}H NMR δ ($CDCl_3$, 500 MHz) inter alia 1.00 (3H, d, *J* 6.0 Hz), 1.17 (1H, q, *J* 12.0 Hz), 1.70−1.86 (2H, m), 1.97, 2.02, 2.03, 2.04, 2.25 (each 3H, 5 × s), 2.10−2.22 (2H, m), 2.36 (1H, br d, *J* 11.0 Hz), 3.02 (3H, s), 3.12 (1H, t, *J* 5.5 Hz), 3.42 (1H, dd, *J* 4.5 and 5.5 Hz), 3.69 (1H, ddd, *J* 10.0, 4.5, and 2.5 Hz), 3.93 (3H, s), 4.01 (1H, br t, *J* 5.0 Hz), 4.13 (1H, dd, *J* 12.5 and 2.5 Hz), 4.23 (1H, dd, *J* 12.5 and 4.5 Hz), 4.96 (1H, d, *J* 7.5 Hz), 5.16 (1H, dd, *J* 9.0 and 10.0 Hz), 5.25 (1H, dd, *J* 7.5 and 9.0 Hz), 5.35 (1H, t, *J* 9.0 Hz), 5.64−5.66 (1H, m), 5.67 (1H, ddd, *J* 11.0, 9.5, and 5.5 Hz), 7.08 (1H, d, *J* 9.5 Hz), 7.42 (1H, d, *J* 9.5 Hz); ^{13}C NMR δ ($CDCl_3$, 125 MHz) inter alia 20.7, 20.8, 20.8, 21.1, 21.6, 21.9, 28.7, 40.2, 42.4, 42.5, 45.8, 54.5, 56.6, 57.1, 61.8, 68.9, 71.0, 71.4, 72.4, 72.7, 73.6, 100.5, 116.1, 118.3, 124.4, 132.2, 132.3, 139.7, 145.7, 156.8, 169.6, 170.3, 170.3, 170.4, 170.7, 192.8, 195.7.ES−HRMS calcd for $C_{37}H_{44}O_{16}$ (MK^+): 783.2266, found: 783.2261.

(3*S*)-8-Methoxy-3-methyl-11-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-2,3,4-trihydrobenz[*a*]anthracene-1,7,12-trione 11. A solution of methyl ether **10** (0.180 g, 0.24 mmol) and DBU (0.500 mL, 3.2 mmol) in THF (10 mL) under oxygen was heated at reflux for 1.5 h. After cooling, the solution was diluted with CH_2Cl_2 and washed with 0.5 M hydrochloric acid. The organic phase was concentrated and the residue purified by rapid filtration through of silica gel (5 mL). The silica pad was washed with CH_2Cl_2−diethyl ether (17:3), and the solvent was removed. A solution of the residue in methanol (20 mL) under an atmosphere of oxygen was irradiated with light from a 60 W broad-band tungsten filament bulb. After 15 min, the solution was cooled then irradiated for a further 15 min. The solvent was removed and the residue purified by silica gel column chromatography (9:1 to 4:1 CH_2Cl_2−diethyl ether, gradient elution) to give the title compound **11** (0.090 g, 39%; R_f 0.1, CH_2Cl_2−diethyl ether, 9:1) as light yellow crystals from diethyl ether and hexanes. mp 205 °C. $[\alpha]^{22}_D$ −77 (0.25, $CHCl_3$). ν_{max}(KBr)/cm^{-1} 1757, 1702, 1677; ^{1}H NMR δ ($CDCl_3$, 500 MHz) 1.18 (3H, d, *J* 6.5 Hz), 2.03, 2.04, 2.05, 2.21, (each 3H, 4 × s), 2.40−2.52 (1H, m), 2.49 (1H, dd, *J* 15.5 and 11.5 Hz), 2.68 (1H, dd, *J* 17.0 and 10.0 Hz), 2.88 (1H, ddd, *J* 15.0, 3.5, and 2.0 Hz), 3.01 (1H, ddd, *J* 17.0, 4.0, and 2.0 Hz), 3.79 (1H, ddd, *J* 10.0, 4.5, and 2.5 Hz), 4.13 (1H, dd, *J* 12.5 and 2.5 Hz), 4.25 (1H, dd, *J* 12.0 and 4.5 Hz), 5.20 (1H, dd, *J* 9.0 and 10.0 Hz), 5.33 (1H, dd, *J* 7.5 and 8.0 Hz), 5.35 (1H, dd, *J* 1.0 and 7.5 Hz), 5.43 (1H, ddd, *J* 9.0, 8.0, and 1.5 Hz), 7.16 (1H, d, *J* 9.5 Hz), 7.44 (1H, d, *J* 8.0 Hz), 7.52 (1H, d, *J* 9.0 Hz), 8.13 (1H, d, *J* 8.0 Hz); ^{13}C NMR δ ($CDCl_3$, 125 MHz) 20.7, 20.8, 20.8, 21.0, 21.4, 30.8, 38.4, 47.2, 56.8, 61.8, 68.7, 71.3, 71.8, 72.9, 100.9, 117.2, 121.8, 129.3, 129.5, 131.9, 132.3, 133.9, 134.2, 138.2, 147.0, 149.3, 156.6, 169.6, 170.2, 170.3, 170.6, 181.8, 185.1, 196.9; ES−HRMS calcd for

$C_{34}H_{34}O_{14}$ [MNa^+]: 689.1846, found 689.1845. Anal. Calcd for $C_{34}H_{34}O_{14}$·0.25H_2O: C, 60.8; H, 5.2. Found: C, 60.5; H, 5.1%. (The X-ray crystal structure shows the incorporation of 0.25 H_2O molecules per molecule of **11**).

[3*S*]-11-Hydroxy-8-methoxy-3-methyl-2,3,4-trihydrobenz[*a*]anthracene-1,7,12-trione (+)-3 (Hatomarubigin B, 98% ee). A sample of **12** (0.050 g, 0.075 mmol) was hydrolyzed in a manner similar to that described previously for the synthesis of **3** (78% ee) to give, after crystallization from CH_2Cl_2 and hexanes, (+)-hatomarubigin B **3** (0.017 g, 68%, 98% ee) as dark red needles. mp 262−264 °C [lit.[7] 254−256 °C]; $[\alpha]^{24}_D$ +142 (0.05, $CHCl_3$) [lit.[7] $[\alpha]^{22}_D$ +146 (0.1, $CHCl_3$)].

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Supporting Information Available: X-ray crystallographic data for **11**. Experimental procedures for **9a**−**d**, **10a**−**d**, **11**, and (+)-**3** (78% ee). ^{1}H NMR spectra for compounds **8**, **10a**, **11**, **12**, **13**, and **3**. Accurate mass measurements for **13** and **3**. This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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