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Angucycline C5 Glycosides: Regio- and Stereocontrolled Synthesis and Cytotoxicity

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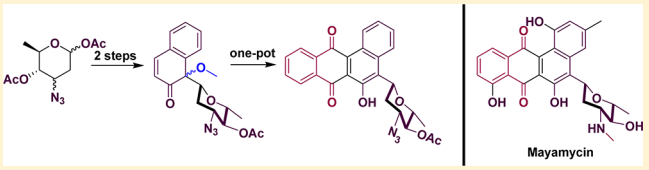
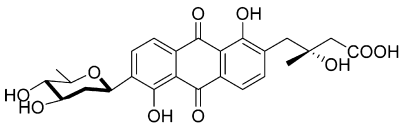
Supporting Information

ABSTRACT: This study discloses a general and convergent route for the regio- and stereospecific construction of the C5 glycosyl angucycline framework of mayamycin. *C*-Glycosidation, dearomatization, and Hauser annulation are the key steps. The synthetic analogues show cytotoxicity against different human cancer cell lines with IC_{50} values between 16.4 and 1.2 μM.

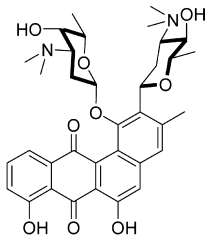


INTRODUCTION

Aryl *C*-glycosides consist of a carbohydrate unit and an arene nucleus. The carbohydrate unit is conjugated to the arene via a C−C bond at the anomeric position.[1] The C−C linkage imparts the glycosides greater in vivo stability toward acidic and enzymatic cleavages compared with the corresponding *O*-glycosides and thus allows a longer intracellular lifetime for trafficking to the nucleus to form complexes with DNA.[2] Consequently, aryl *C*-glycosides are considered superior analogues of the corresponding more commonly encountered *O*-glycosides.[3] Furthermore, aryl *C*-glycosides have received significant attention because of their prevalence in the structures of natural products with important biological properties. Among the aryl *C*-glycosides, quinone-containing glycosides are well-known DNA intercalators. They exhibit a wide range of biological activities,[4] which include antibacterial, anticancer, and antiviral activities; activities against multidrug-resistant (MDR) bacteria; and inhibition of carbohydrate-processing enzymes. The structures of select *C*-glycosidic quinonoids (**1** and **2**)[4] are displayed in Figure 1. Herein we report a facile route for the regio- and stereocontrolled synthesis of angucycline C5-glycosides related to mayamycin (**3**)[5] and their anticancer activities.



Vineomycinone B2 (**1**)



Benzanthrin A (**2**)

Figure 1. Structures of selected aryl *C*-glycoside natural products.

Mayamycin (**3**) was isolated in 2010 by Schneemann et al. from the cultures of marine *Streptomyces* sp. strain HB202.[5] It was found to exhibit potent cytotoxic activities against eight human cancer cell lines and showed activity against several bacteria, including antibiotic-resistant strains. The most striking structural feature of the angucycline is the unusual site of the carbohydrate residue, which prompted us to undertake the total synthesis of mayamycin.

There are several strategies[6] in the literature for the synthesis of aryl *C*-glycosides. Most of them involve formation of anomeric C−C bonds as the key step because the sugar units are readily accessible from commercially available carbohydrates. This tactic works well for low-molecular-weight aglycones such as naphthols and phenols. With higher-molecular-weight aglycones (e.g., anthracenes and benz[*a*]-anthracenes), the low yield and poor regioselectivity[7a] are major problems. In other instances, a large excess of a glycoside donor[6i] is employed to secure optimum yields. Direct *C*-glycosylation of the angucycline or anthracycline core is more challenging, since the strong electron-withdrawing nature of the quinone motifs makes the adjacent rings highly electron-deficient. The strong intramolecular hydrogen bonding between the phenolic OH and the carbonyl group of the quinone obstructs the initial *O*-glycosylation.[6h] To overcome these difficulties, reductive methylation of the quinone functionality is required prior to the glycosylation step to fulfill the electron demand of the fused rings. In the first synthetic study of mayamycin (**3**),[7b] the failed glycosylation (i.e., Scheme 1) prevented its total synthesis.

RESULTS AND DISCUSSION

With these problems in mind, we envisaged a strategy based on the combination of early-stage glycosylation, oxidative dearomatization (**4** → **5**), and late-stage Hauser annulation[7c,d](**5** →

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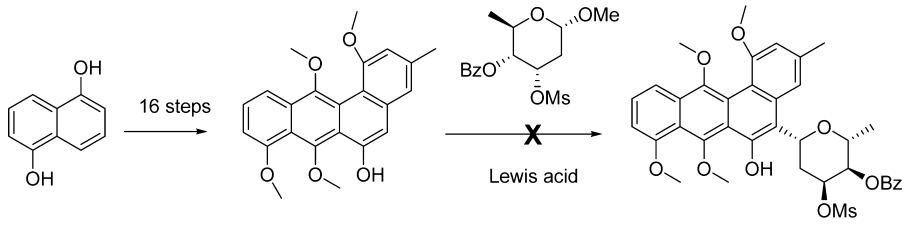
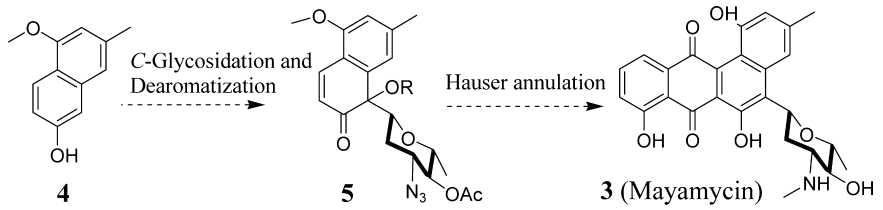
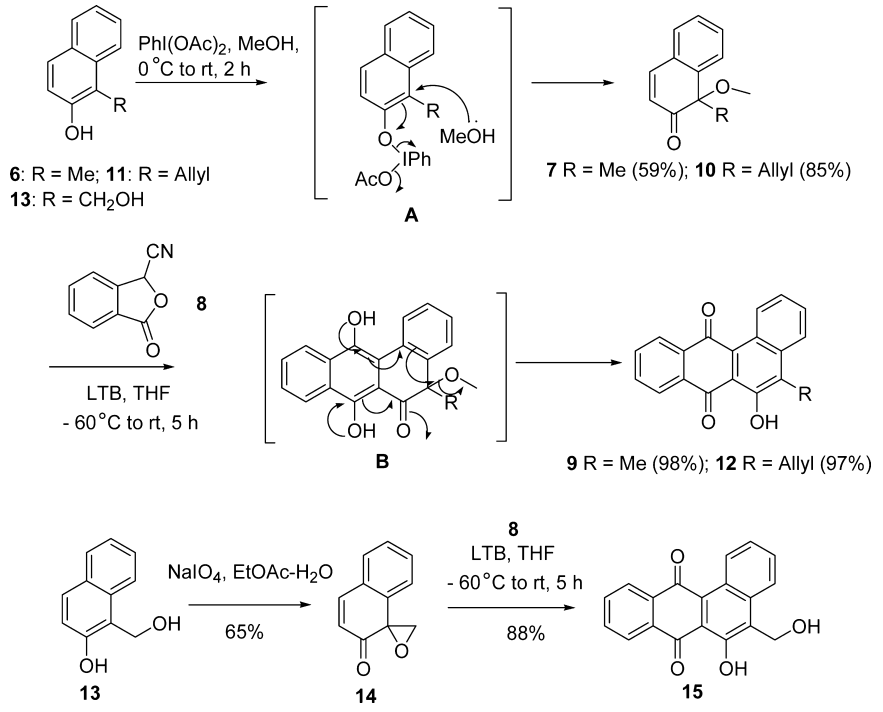
Scheme 1. Zhang's Synthetic Study[7b] of Mayamycin



Scheme 2. Proposed Route to Mayamycin



Scheme 3. Dearomatization of 2-Naphthols and Subsequent Annulation Studies



3) for the synthesis of mayamycin-like molecules (Scheme 2). To test the feasibility of the analysis (Scheme 2), we carried out model studies with naphthol **6**.[7e] Upon treatment with $PhI(OAc)_2$ (PIDA) in methanol, dearomatizaion of **6** took place with regiospecific nucleophilic attack by methanol at C1 to provide naphthalenone **7** (via intermediate A) as the sole product (Scheme 3). Hauser annulation of **7** with 3-cyanophthalide (**8**) in the presence of lithium *tert*-butoxide (LTB) afforded benz[*a*]anthracenedione **9** in 98% yield. The initial Hauser product B loses a molecule of methanol to form benz[*a*]anthracenedione **9** (Scheme 3). The sequence for **6** → **9** was then shown to be general for few more naphthols. Naphthalenone **10** was similarly prepared from 1-allyl-2-naphthol (**11**)[8a] by treatment with PIDA in methanol and then submitted to annulation with **8** to furnish **12** in 97% yield. Oxidation of 1-hydroxymethyl-2-naphthol (**13**) with sodium periodate provided spiro[napthalene-1(2*H*),2′-oxiran]-2-one (**14**)[8b] in 65% yield, which upon Hauser annulation with **8** furnished 5-hydroxymethyl angucycline **15** in 88% yield.

For an entry into C5-glycosidic angucyclines, tri-*O*-methyl- and tri-*O*-benzyl-2-deoxy-D-glucoses **16a** and **16b**, respectively, were synthesized from glycal **17** using literature procedures.[9a] Glycosylations[9b] of 2-naphthol (**18**) with **16a** and **16b** in the presence of TMSOTf (Scheme 4) furnished the corresponding naphthyl *C*-glycosides **19a** and **19b**[9c] in both regio- and stereoselective manners. The carbohydrate residue was incorporated regioselectively at C1 of **18** rather than at C3. The stereochemistry at the anomeric position was assigned as β on the basis of the large coupling constants of the anomeric proton (for **19a**, J = 12.0, 2.0 Hz) as well as its high chemical shift (for **19a**, δ = 5.47 ppm).[10] The *C*-glycosylation reaction involves initial formation of an *O*-glycosidic linkage with the

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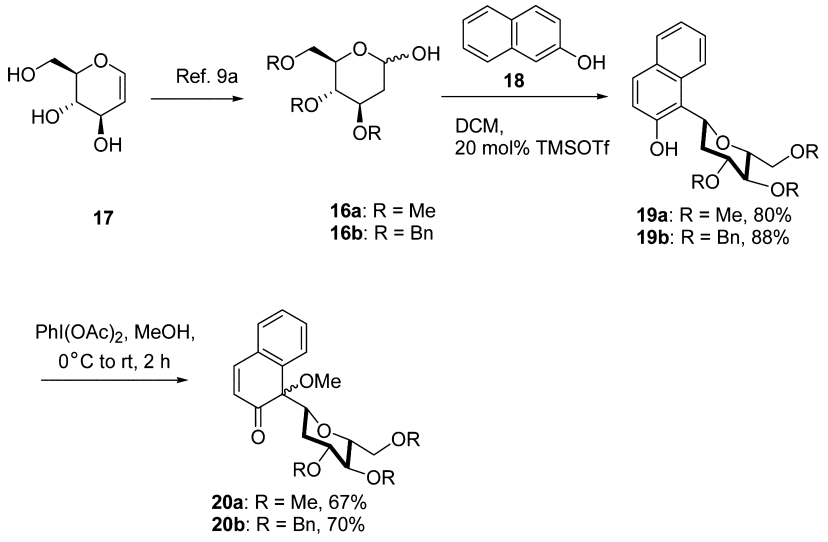
Scheme 4. Synthesis of 1-Glycosyl-2-Naphthalenones



naphthol followed by Fries-like O to C rearrangement. In the presence of excess Lewis acid, the *O*-glycoside rearranges to thermodynamically favorable *β*-*C*-glycosides.[6i] While there may be concomitant formation of a certain amount of the *α*-*C*-glycoside at low temperature, upon warming to room temperature it rearranges to the more stable *β*-*C*-glycoside via a quinone methide[6h] intermediate to avoid the 1,3-diaxial interaction. PIDA-mediated oxidative dearomatization of *C*-naphthyl glycosides **19a** and **19b** (Scheme 4) provided the desired 2-glycosyl bicyclic acceptors **20a** and **20b** as an inseparable mixture of two diastereomers in good yields. Since the C1 stereochemistry of the naphthalenones is of no consequence, we subjected this mixture of acceptors to annulation with **8**. To our delight, the expected angucyclines **21a** and **21b** were obtained in 82% and 93% yield, respectively. The structure of **21a** was confirmed by NOESY experiments (see the Supporting Information). The correlation between the anomeric proton and the C4 hydrogen confirmed the presence of the *C*-glycosidic linkage,[5] and the chemical shift of the anomeric proton (δ = 5.68 ppm) established the equatorial orientation of the aryl moiety in the *C*-glycoside (Figure 2).

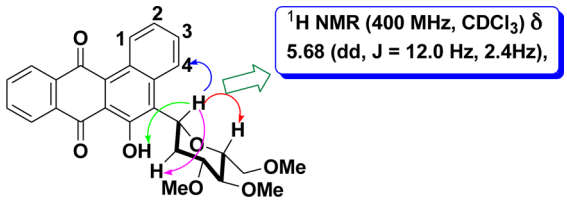


Figure 2. NOESY correlation of the anomeric proton of **21a**.

Since the C8 methoxy group is a common structural feature of natural angucyclines[4] and also of mayamycin (**3**), we chose 7-methoxy-3-cyanophthalide (**22**) as the Hauser donor and condensed it with the acceptors **20a** and **20b**. In both the cases, the *C*-glycosyl angucyclines (**23a** and **23b**, respectively) were expectedly obtained in good yields. The occurrence of chlorine at C9 and methoxy at C8 in BE-23254[11] and related chlorinated angucyclines prompted us to explore reactivity of 6-chloro-substituted phthalide **24**.[11] Annulation of **24** with the Michael acceptors **20a** and **20b** in the presence of LTB in THF furnished the correspondiing chlorinated angucyclines **25a** and **25b** in good yields (Scheme 5).

Following our success in constructing the C5-glycosyl angucycline core, we focused on the glycosylation of azidosugar **26** en route to the *N*-demethylangolosamine moiety[6i] in mayamycin. To this end, commercially available glycal **17** was converted into azidosugar **26** by literature sequences[6i] as a mixture of diastereomers. Treatment of the **26** mixture with naphthol **18** in the presence of $SnCl_4$[7a] produced a C3′-epimeric mixture of *C*-glycosides, from which the major and required isomer **27a** was isolated in 60% yield by column chromatography (Scheme 6). PIDA-mediated dearomatization of **27a** provided the acceptor **28** in 88% yield as a mixture of two diastereomers. Hauser annulation of **28** with cyanophthalide **8** in the presence of LTB furnished *C*-glycosyl angucycline **29** in 71% yield along with the deacetylated product **30** in 10% yield. Extension of the protocol to the C3′ epimer **27b** furnished dearomatized product **31** and C3-epimeric angucycline **32** in very good yields (Scheme 7). In this case of annulation, the prolonged reaction time resulted in the complete deacetylation of the initial Hauser product, and **32** was obtained as the sole product.

Since an axial orientation of 2-oxygenated carbohydrate residues in natural angucycline is very rare, we synthesized **33** to determine the consequence of the stereochemistry on cytotoxicity. The required tetra-*O*-benzyl mannosyl naphthol **34**[12] was prepared according literature sequences. Oxidative dearomatization of **34** with PIDA/MeOH afforded glycosyl acceptor **35** in 74% yield (Scheme 8). Anionic annulation of **8** with **35** in the presence of LTB followed by aq. NH_4Cl workup provided *C*-mannosyl angucycline **33** in 76% yield. The stereochemistry of **33** at the anomeric position was assigned as *α* on the basis of the ^{1}H NMR chemical shift of the anomeric proton, which appeared at 5.54 ppm as a singlet. In the NOESY experiments with **33** (see the Supporting Information), there was no correlation between the anomeric proton and the C4 hydrogen, confirming the presence of the *α*-*C*-glycosidic linkage.

The cytotoxicity[2] of the synthetic compounds was investigated by MTT assay[13] against human colon adenocarcinoma grade II cells (HT29), human osteosarcoma cells (MG63), and human cervical cancer cells (HeLa). The IC_{50}

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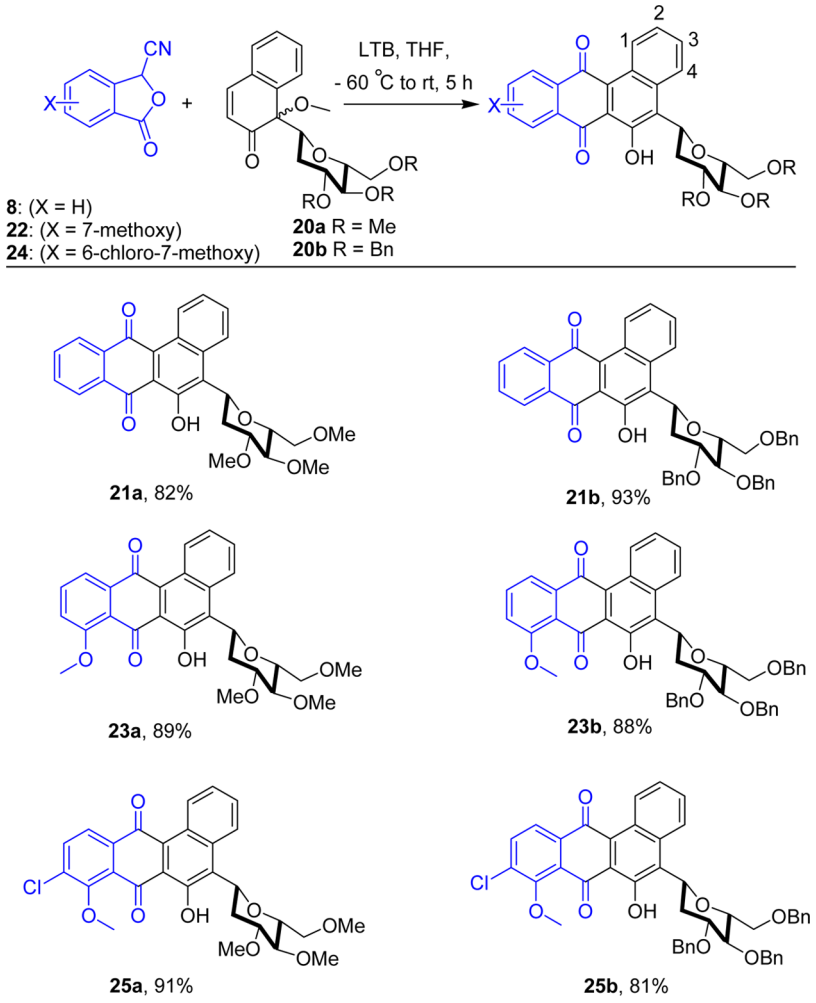
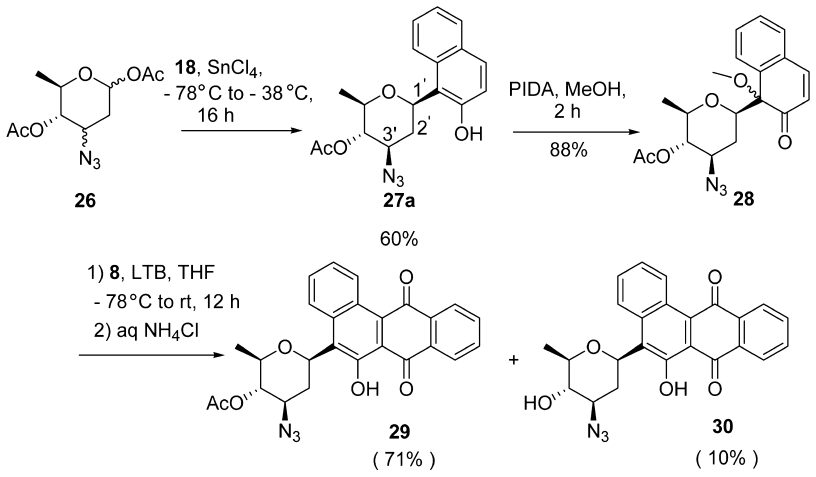
Scheme 5. Mayamycin-like *C*-Glycosyl Angucyclines



Scheme 6. Synthesis of Azidoglycosidic Mayamycin Models



values (Table 1) indicated that compound **15** is the most cytotoxic among the C5-alkylated angucyclines. The IC_{50} values for **29**, **30**, and **32** indicate beneficial effects of the azidosugar residues on the cytotoxicity. The IC_{50} values of these azidoglycosidic angucyclines are comparable to that for the standard doxorubicin. Substituents such as Cl and OMe do not have a pronounced effect on the cytotoxicity (Table 1). It is noteworthy that the simple 5-hydroxymethyl angucycline **15** was found to be 4-fold more active than doxorubicin against the HT29 cell line.

For furtherance of the methodology and to compare the cytotoxicities of the protected angucyclines with the aza-angucyclines in a meaningful way, selective debenzylation of the angucycline **23b** was investigated (Scheme 9). In the presence

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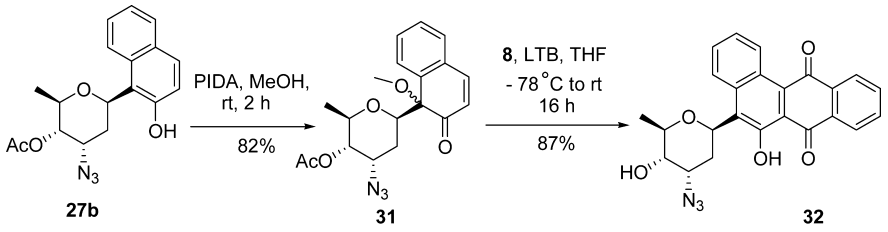
Scheme 7. Synthesis of the Epimeric Azidoglycosidic Angucycline



Scheme 8. Synthesis of *C*-Mannosyl Angucycline

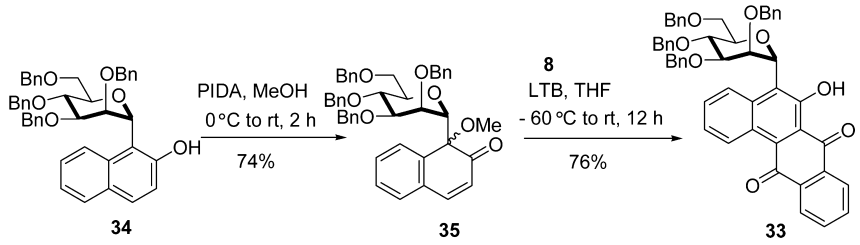
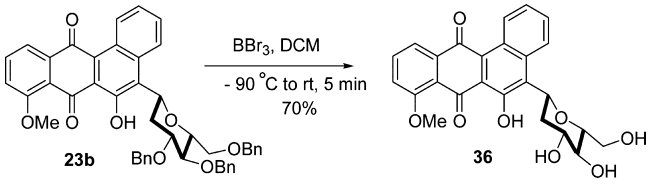


Table 1. IC_{50} Values (μM) against Human Cancer Cell Lines by MTT Assay

entry	compound[a]	HT29	HeLa	MG63
1	**9**	>17.4	16.4	>17.4
2	**12**	>15.9	>15.9	>15.9
3	**15**	1.2	1.4	3.3
4	**21a**	>10.8	>10.8	>10.8
5	**21b**	>7.2	5.0	>7.2
6	**23a**	>10.1	5.5	>10.1
7	**23b**	>6.5	5.0	>6.5
8	**25a**	>9.4	>9.4	>9.4
9	**25b**	>6.6	>6.6	>6.6
10	**29**	10.6	8.2	5.3
11	**30**	>11.6	8.6	4.4
12	**32**	4.8	5.4	3.8
13	**33**	>6.2	>6.2	>6.2
14	doxorubicin[14]	5.3	1.7	14.9

[a]For compounds **12**, **21a**, **23a**, **25a**, and **33**, precipitation occurred at higher concentrations.

Scheme 9. Selective Debenzylation of Angucycline



of BBr_3 at low temperature, debenzylation occurred smoothly to furnish angucycline **36** in 70% yield. It is noteworthy that under these conditions both the methyl ether and the pyran ring remained intact. Angucycline **36** was only sparingly soluble in DMSO-d_6 and could be characterized only by NMR spectroscopy. Unfortunately, the MTT assay of **36** could not be done because of its poor solubility and rapid precipitation during the course of the study.

CONCLUSION

A robust regio- and stereocontrolled route for the synthesis of the mayamycin scaffold has been developed. The key features of the route are (i) synthesis of *C*-glycosyl-2(1*H*)-naphthalenones by oxidative dearomatization and (ii) their regiospecific Hauser annulation. This aglycone elaboration strategy is step-economical because it does not require the protection–deprotection steps for the quinone functionality. Most of the synthetic compounds displayed potent anticancer activities at low micromolar concentration against three different human cancer cell lines by MTT assay. The application of this methodology to the total synthesis of mayamycin is underway.

EXPERIMENTAL SECTION

General Methods. All commercial reagents were used without further purification. Melting points are uncorrected. Mass spectra were recorded on an MS-TOF mass spectrometer. 2D $^1H-^1H$ NOESY experiments were carried out for the structure determination of selected compounds. Diastereomeric excesses were determined using Chiralpak IA or IC columns with isopropyl alcohol/hexane as the mobile phase.

General Procedure for PIDA-Mediated Dearomatization of 1-Substituted-2-Naphthols. To a stirred solution of the naphthol (1 mmol) in 5 mL of dry methanol at −0 °C under an inert atmosphere was added PIDA (1.2 mmol), and the reaction mixture was stirred at −0 °C for 20 min and then for ∼3 h at room temperature until the starting materials disappeared. After 3 h, the methanol was evaporated, and the crude product was subjected to column chromatography to obtain the pure product.

General Procedure for Hauser Annulation. A solution of 3-cyanophthalide (1 mmol) in dry THF (5 mL) was added to a suspension of LTB (3.6 mmol) in dry THF (5 mL) at −60 °C under an inert atmosphere. The resulting solution was stirred at −60 °C for 30 min, after which a solution of the Michael acceptor (1.2 mmol) in dry THF (5 mL) was added. The reaction mixture was then stirred for another 30 min at −60 °C and then for 6–8 h at room temperature. The reaction was then quenched with saturated ammonium chloride solution (10 mL), and THF was removed under reduced pressure. The residue was then extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with brine (3 × $^1/_3$ vol.), dried (Na_2SO_4), and concentrated to provide the crude product, which was then purified by column chromatography using ethyl acetate/hexanes as the eluent to obtain the pure compound.

*1-Methoxy-1-methyl-1H-napthalen-2-one (**7**).* The general procedure for dearomatization of naphthols was followed using 1-methyl-2-naphthol (**6**) (100 mg, 0.63 mmol) and PIDA (216 mg, 0.67) in methanol (4 mL).The crude product was purified by column chromatography on silica gel (eluting with 15% EtOAc/hexanes as

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the eluent) to afford **7** as a yellow semisolid (70 mg, 59%). IR (KBr, cm^{-1}) 2928, 1674, 1616, 1237, 1104, 1077, 1029, 828, 759; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 1H), 7.44−7.37 (m, 2H), 7.31−7.30 (m, 2H), 6.15 (d, J = 8.0 Hz, 1H), 3.0 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 222.0 (C═O), 145.0 (CH), 143.5 (C), 130.5 (CH), 129.6 (CH), 128.1 (CH and C), 126.2 (CH), 125.2 (CH), 82.6 (C), 53.8 (OMe), 30.9 (CH_3); HRMS (TOF MS ES+) found $[M + Na]^+$ 211.0731, calcd $C_{12}H_{12}O_2{}^{23}Na$ 211.0735.

*6-Hydroxy-5-methylbenz[a]anthracene-7,12-dione (**9**).* The general procedure for the Hauser annulation was followed using 3-cyanophthalide **8** (46 mg, 0.29 mmol), Michael acceptor **7** (66 mg, 0.87 mmol), and LTB (71 mg, 0.87 mmol). The crude product was purified by column chromatography on silica gel (using 25% EtOAc/hexanes as the eluent) to afford **9** as a red solid (82 mg, 98%). Mp 175−178 °C; IR (KBr, cm^{-1}) 1653, 1636, 1588, 1439, 1294, 1192, 1007, 747; ^1H NMR (400 MHz, $CDCl_3$) δ 12.84 (s, 1H), 9.40 (d, J = 8.8 Hz, 1H), 8.20 (d, J = 7.6 Hz, 2H), 7.87 (d, J = 8.4 Hz, 1H), 7.80−7.71 (m, 2H), 7.51 (t, J = 8 Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3 (C═O), 185.1 (C═O), 154.4 (C), 137.8 (C), 134.9(C), 134.8 (CH), 133.3 (CH), 131.8 (C), 129.1 (CH), 128.9 (CH), 128.8 (C), 127.3 (CH and C), 127.1 (CH), 126.3 (CH), 125.8 (C), 123.3 (CH), 118.2 (C), 11.5 (CH_3); HRMS (TOF MS ES+) found $[M + H]^+$ 289.0883, calcd $C_{19}H_{13}O_3$ 289.0865.

*1-Allyl-1-methoxy-1H-napthalen-2-one (**10**).* The general procedure for dearomatization of naphthols was followed using 1-allyl-2-naphthol (**11**) (220 mg, 1.2 mmol) and PIDA (410 mg, 1.32) in methanol (10 mL). The crude product was purified by column chromatography on silica gel (using 10% EtOAc/hexanes as the eluent) to afford **10** as a yellow semisolid (220 mg, 85%). IR (KBr, cm^{-1}) 1673, 1290, 1203, 1110, 1087, 990, 921, 820, 760; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 1H), 7.48−7.44 (m, 1H), 7.39−7.32 (m, 3H), 6.16 (d, J = 9.6 Hz, 1H), 5.55−5.44 (m, 1H), 4.93 (d, J = 10 Hz, 1H), 4.83 (d, J = 17.2 Hz, 1H), 3.05 (s, 3H), 2.65−2.60 (m, 1H), 2.55−2.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4 (C═O), 145.0 (CH), 141.7 (C), 131.4 (C), 130.5 (CH), 130.0 (CH), 129.4 (CH), 128.2 (CH), 126.9 (CH), 125.9 (CH), 119.1 (CH_2), 85.1 (C), 53.5 (OMe), 48.7 (CH_2); HRMS (TOF MS ES+) found $[M + Na]^+$ 237.0888, calcd $C_{14}H_{14}O_2{}^{23}Na$ 237.0891.

*5-Allyl-6-hydroxybenz[a]anthracene-7,12-dione (**12**).* The general procedure for the Hauser annulation was followed using 3-cyanophthalide **8** (64 mg, 0.4 mmol), Michael acceptor **10** (102 mg, 0.48 mmol), and LTB (98 mg, 1.2 mmol). The crude product was purified by column chromatography on silica gel (using 20% EtOAc/hexanes as the eluent) to afford **12** as a red solid (122 mg, 97%). Mp 182−186 °C; IR (KBr, cm^{-1}) 1635, 1591, 1442, 1372, 1337, 1293, 1240, 1116, 1017, 755; ^1H NMR (400 MHz, $CDCl_3$) δ 12.92 (s, 1H), 9.45 (d, J = 8.8 Hz, 1H), 8.23 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.82−7.73 (m, 2H), 7.57−7.48 (m, 2H), 6.10−6.03 (m, 1H), 5.09−5.0 (m, 2H), 3.95 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6 (C═O), 185.6 (C═O), 154.7 (C), 137.8 (C), 135.3 (CH), 135.2 (CH), 135.1 (C), 133.7 (CH), 132.1 (C), 130.1 (C), 129.7 (CH), 129.3 (CH), 128.6 (C), 127.6 (CH), 127.4 (CH), 126.6 (CH), 126.3 (C), 123.8 (CH), 118.8 (CH), 116.3 (CH_2), 29.6 (CH_2); HRMS (TOF MS ES+) found $[M + H]^+$ 315.1023, calcd $C_{21}H_{15}O_3$ 315.1021.

*6-Hydroxy-5-hydroxymethylbenz[a]anthracene-7,12-dione (**15**).* The general procedure for the Hauser annulation was followed using 3-cyanophthalide **8** (50 mg, 0.32 mmol), Michael acceptor **14** (67 mg, 0.39 mmol), and LTB (78 mg, 0.96 mmol). The crude product was purified by column chromatography on silica gel (using 30% EtOAc/hexanes as the eluent) to afford **15** as a red solid (86 mg, 88%). Mp 180−184 °C; IR (KBr, cm^{-1}) 1633, 1442, 1378, 1337, 1246, 1217, 1118, 1045, 1008, 862, 758; ^1H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, J = 8.8 Hz, 1H), 8.15−8.1 (m, 3H), 7.94−7.86 (m, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 5.22 (s, 1H), 4.94 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.1 (C═O), 190.0 (C═O), 158.8 (C), 142.6 (CH), 140.5 (CH), 139.5 (C), 139.1 (C), 136.6 (CH), 134.8(CH), 134.5 (CH), 134.3 (CH), 133.3 (CH), 132.3 (CH), 131.9 (C), 131.2 (C), 130.3 (C), 129.36 (C), 123.8 (C), 57.6 (CH_2); HRMS (TOF MS ES+) found $[M + Na]^+$ 327.0642, calcd $C_{19}H_{12}O_4{}^{23}Na$ 327.0633.

*1-(4,5-Dimethoxy-6-methoxymethyltetrahydropyran-2-yl)-naphthalen-2-ol (**19a**).* To a stirred solution of glycosyl donor **16a** (22 mg, 0.1 mmol), 2-naphthol (**18**) (28 mg, 0.2 mmol), and silver perchlorate (10 mg, 0.05 mmol) in dry CH_3CN (4 mL) was added trimethylsilyl trifluoromethanesulfonate (3.8 μL, 0.05 mmol) dropwise at 0 °C under an argon atmosphere. The reaction mixture was stirred at rt for 1 h and then cooled 0 °C. The reaction was quenched with triethylamine, and the mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel (using 10% EtOAc/hexanes as the eluent) to afford **19a** as a yellow semisolid (27 mg, 80%). $[\alpha]_D^{35}$ = +168.0 (c 0.5, $CHCl_3$); IR (KBr, cm^{-1}) 2927, 2828, 1621, 1599, 1466, 1405, 1115, 1108, 1078, 947, 817, 746; ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1 H), 7.77 (d, J = 8.4 Hz, 1H), 7.70−7.65 (m, 2H), 7.48−7.44 (m, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 5.47 (dd, J = 12, 2 Hz, 1H), 3.75−3.66 (m, 2H), 3.62 (s, 3H), 3.58−3.49 (m, 2H), 3.45 (s, 3H), 3.44 (s, 3H), 3.43−3.40 (m, 1H), 2.46−2.41 (m, 1H), 1.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0 (C), 130.8 (C), 129.9 (CH), 129.1 (CH), 128.8 (C), 126.9 (CH), 123.0 (CH), 120.7 (CH), 120.3 (CH), 115.3 (C), 82.0 (CH-anomeric), 79.2, 79.1, 75.7, 70.9 (CH_2), 61.0, 59.5, 57.0, 35.5 (CH_2). HRMS (TOF MS ES+) found $[M + Na]^+$ 355.1522, calcd $C_{19}H_{24}O_5{}^{23}Na$ 355.1521.

*1-(4,5-Dimethoxy-6-methoxymethyltetrahydropyran-2-yl)-1-methoxy-1H-naphthalen-2-one (**20a**).* The general procedure for dearomatization of naphthols was followed using *C*-glycosyl naphthol **19a** (217 mg, 0.65 mmol) and PIDA (230 mg, 0.72 mmol) in methanol (8 mL). The crude product was purified by column chromatography on silica gel (using 25% EtOAc/hexanes as the eluent) to afford **20a** as a yellow semisolid (242 mg, 67%) as a mixture of two diastereomers. IR (KBr, cm^{-1}) 2931, 2829, 1670, 1445, 1378, 1189, 1111, 978, 762; ^1H NMR (400 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.63 (d, J = 7.6 Hz), 7.47−7.28 (m), 6.18 (d, J = 10.8 Hz), 6.15 (d, J = 10.0 Hz), 3.53−3.33 (m), 3.21−3.0 (m), 2.85−2.22 (m), 2.41−2.22 (m); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two diastereomers) δ 202.4 (C═O), 200.3 (C═O), 145.3, 140.2, 133.5, 132.9, 129.9, 129.7, 129.2, 129.0, 128.7, 128.1, 126.7, 126.3, 85.4, 85.0, 83.2, 82.7, 82.5, 80.0, 79.8, 79.7, 77.9, 71.8 (CH_2), 71.4 (CH_2), 60.5, 59.5, 57.2, 56.9, 53.7, 53.6, 29.9 (CH_2), 29.3 (CH_2); HRMS (TOF MS ES+) found $[M + Na]^+$ 385.1609, calcd $C_{20}H_{26}O_6{}^{23}Na$ 385.1627.

*5-(4,5-Dimethoxy-6-methoxymethyltetrahydropyran-2-yl)-6-hydroxybenz[a]anthracene-7,12-dione (**21a**).* The general procedure for the Hauser annulation was followed using 3-cyanophthalide **8** (46 mg, 0.29 mmol), Michael acceptor **20a** (115 mg, 0.32 mmol), and LTB (71 mg, 0.87 mmol). The crude product was purified by column chromatography on silica gel (using 30% EtOAc/hexanes as the eluent) to afford **21a** as a red solid (110 mg, 82%). The $[\alpha]$ value could not be determined because the solution was opaque[15] even at c 0.001. Mp 162−168 °C; IR (KBr, cm^{-1}) 2927, 1658, 1635, 1590, 1444, 1337, 1309, 1113, 1078, 1023, 759; ^1H NMR (400 MHz, $CDCl_3$) δ 13.16 (s, 1H), 9.41 (d, J = 8.4 Hz, 1H), 8.79 (d, J = 9.2 Hz, 1H), 8.27 (d, J = 7.6 Hz, 2H), 7.85−7.76 (m, 2H), 7.58−7.50 (m, 2H), 5.68 (dd, J = 12.0 Hz, 2.4 Hz, 1H), 3.80−3.41 (m, 14H), 2.36−2.31 (m, 1H), 2.20−2.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6 (C═O), 185.7 (C═O), 153.8 (C), 137.6 (C), 135.34 (C), 135.31 (CH), 133.8 (CH), 132.1(C), 130.3 (C), 129.6 (CH), 129.3 (C), 129.1 (CH), 127.5 (C), 127.4 (CH), 126.8 (C), 126.7 (CH), 126.1 (C), 118.5 (C), 83.0 (CH-anomeric), 80.2, 80.0, 72.2, 71.7, 61.0, 59.7, 57.2, 35.4 (CH_2); HRMS (TOF MS ES+) found $[M + Na]^+$ 485.1573, calcd $C_{27}H_{26}O_7{}^{23}Na$ 485.1576.

*5-(4,5-Dimethoxy-6-methoxymethyltetrahydropyran-2-yl)-6-hydroxy-8-methoxybenz[a]anthracene-7,12-dione (**23a**).* The general procedure for the Hauser annulation was followed using 7-methoxy-3-cyanophthalide (**22**) (50 mg, 0.27 mmol), Michael acceptor **20a** (110 mg, 0.30 mmol), and LTB (90 mg, 1.1 mmol). The crude product was purified by column chromatography on silica gel (using 30% EtOAc/hexanes as the eluent) to afford **23a** as a red solid (118 mg, 89%). The $[\alpha]$ value could not be determined because the solution was opaque[15] even at c 0.001. Mp 167−170 °C; IR (KBr, cm^{-1}) 2929, 1634, 1585,

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1445, 1380, 1333, 1280, 1224, 1185, 1113, 1033, 952, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.24 (s, 1H), 9.25 (d, J = 8.8 Hz, 1H), 8.77 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.55−7.46 (m, 2H), 7.30−7.26 (m, 1H), 5.67 (dd, J = 12.0, 2.4 Hz, 1H), 4.05 (s, 3H), 3.79−3.40 (m, 14H), 2.34−2.29 (m, 1H), 2.18−2.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1 (C═O), 185.9 (C═O), 160.3 (C), 153.6 (C), 137.5 (C), 136.9 (C), 136.4 (CH), 129.0 (C), 128.8 (C), 128.2 (CH), 128.0 (CH), 126.4 (CH), 125.2 (CH), 125.1 (CH), 120.0 (CH), 119.9 (C), 119.5 (C), 117.5 (CH), 82.9 (CH-anomeric), 80.2, 79.9, 72.2 (CH_2), 71.6, 60.9, 59.7, 57.1, 56.9, 35.4 (CH_2); HRMS (TOF MS ES+) found $[M + Na]^+$ 515.1680, calcd $C_{28}H_{28}O_8{}^{23}Na$ 515.1682.

*9-Chloro-5-(4,5-dimethoxy-6-methoxymethyltetrahydropyran-2-yl)-6-hydroxy-8-methoxybenz[a]anthracene-7,12-dione (**25a**).* The general procedure for the Hauser annulation was followed using 6-chloro-7-methoxy-3-cyanophthalide **24** (28 mg, 0.125 mmol), Michael acceptor **20a** (50 mg, 0.137 mmol), and LTB (41 mg, 0.5 mmol). The crude product was purified by column chromatography on silica gel (using 30% EtOAc/hexanes as the eluent) to afford **25a** as a red solid (60 mg, 91%). The $[\alpha]$ value could not be determined because the solution was opaque[15] even at c 0.001. Mp 164−167 °C; IR (KBr, cm^{-1}) 2932, 1637, 1443, 1405, 1337, 1309, 1223, 1184, 1113, 1082, 1019, 771; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.97 (s, 1H), 9.25 (dd, J = 8.7, 1.5 Hz, 1H), 8.81−8.73 (m, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H), 7.59−7.45 (m, 2H), 5.66 (dd, J = 12.0, 2.4 Hz, 1H), 4.03 (s, 3H), 3.77 (dd, J = 10.9, 4.5 Hz, 1H), 3.72−3.37 (m, 13H), 2.32 (ddd, J = 13.1, 5.3, 2.4 Hz, 1H), 2.20−2.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4 (C═O), 184.7 (C═O), 156.3 (C), 153.4 (C), 137.2 (C), 136.8 (C), 136.5 (CH), 135.5 (C), 129.9 (C), 129.5 (C), 129.3 (CH), 128.8 (CH), 127.5 (CH), 126.2 (C), 126.1 (C), 126.0 (CH), 124.3 (CH), 119.2 (C), 82.9 (CH-anomeric), 80.1, 80.0, 72.2 (CH_2), 71.7, 62.0, 60.9, 59.7, 57.2, 35.4 (CH_2); HRMS (TOF MS ES+) found $[M + Na]^+$ 549.1288, calcd $C_{28}H_{27}O_8Cl^{23}Na$ 549.1292.

*1-(4,5-Dibenzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)-naphthalen-2-ol (**19b**).* To a stirred solution of glycosyl donor **16b** (217 mg, 0.5 mmol), 2-naphthol **18** (1.0 mmol), and silver perchlorate (21 mg, 0.1 mmol) in dry CH_3CN (8 mL) was added trimethylsilyl trifluoromethanesulfonate (19 μL, 0.1 mmol) dropwise at 0 °C under argon. The reaction mixture was stirred at 25 °C for 1 h and then cooled to 0 °C. The reaction was quenched with triethylamine, and the mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel (using 20% EtOAc/hexanes as the eluent) to afford **19b**[9c] as a yellow semisolid (246 mg, 88%). $[\alpha]_D^{35}$ = +80.7 (c 0.1, $CHCl_3$); IR (KBr, cm^{-1}) 3029, 2920, 2863, 1621, 1599, 1453, 1359, 1224, 1097, 1028, 741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.77 (d, J = 8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.39−7.24 (m, 17H), 5.48 (dd, J = 10, 1.6 Hz, 1H), 4.97 (d, J = 10.8 Hz, 1H), 4.72−4.63 (m, 3H), 4.58 (d, J = 10.8 Hz, 1H), 4.50 (d, J = 12 Hz, 1H), 3.91−3.83 (m, 3H), 3.74 (dd, J = 10.4 Hz, J = 2 Hz, 1H), 3.66 (dd, J = 9.2, 2.4 Hz, 1H), 2.49 (dd, J = 14, 2 Hz, 1H), 2.02−1.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.1 (C), 138.5 (C), 138.4 (C), 138.9 (C), 130.8 (CH), 129.8 (CH), 129.1, 128.8, 128.5, 128.2, 128.0, 127.9, 127.8, 126.8, 123.0 (CH), 120.7 (CH), 120.4 (CH), 115.2 (C), 80.4 (CH-anomeric), 79.05, 77.9, 75.7, 75.4 (CH_2), 73.5 (CH_2), 71.4 (CH_2), 68.1 (CH_2), 36.2 (CH_2); HRMS (TOF MS ES+) found $[M + Na]^+$ 583.2457, calcd $C_{37}H_{36}O_5{}^{23}Na$ 583.2460.

*1-(4,5-Dibenzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)-1-methoxy-1H-naphthalen-2-one (**20b**).* The general procedure for dearomatization of naphthols was followed using C-glycosyl naphthol **19b**[9c] (170 mg, 0.33 mmol) and PIDA (115 mg, 0.37) in methanol (7 mL). The crude product was purified by column chromatography on silica gel (using 20% EtOAc/hexanes as the eluent) to afford **20b** as a yellow semisolid (128 mg, 70%) as a mixture of two diastereomers. IR (KBr, cm^{-1}) 2927, 1611, 1548, 1315, 1220, 1100, 1025, 751; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.57 (d, J = 7.5 Hz), 7.43 (d, J = 7.7 Hz), 7.38−6.96 (m), 6.23−5.98 (m), 4.75 (d, J = 11.2 Hz), 4.71 (d, J = 10.5 Hz), 4.62 (t, J = 12.6 Hz), 4.52 (d, J = 11.5 Hz), 4.45 (dt, J = 10.2, 5.1 Hz), 4.36 (d, J = 12.1 Hz), 4.27 (d, J = 12.0 Hz), 4.21 (d, J = 3.2 Hz), 3.67−3.36 (m), 3.25−3.14 (m), 2.98 (s, 3H), 2.40 (dd, J = 12.2, 4.7 Hz), 2.27 (dd, J = 12.9, 4.9 Hz), 1.33 (qd, J = 11.8, 5.0 Hz), 1.17 (dd, J = 8.6, 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of two diastereomers) δ 202.5 (C═O), 200.3 (C═O), 145.3 (CH), 140.0 (C), 138.8 (C), 138.5 (C), 138.4 (C), 138.36 (C), 137.4 (C), 133.4 (C), 132.8 (C), 129.8, 129.6, 129.2, 129.0, 128.9, 128.6, 128.55, 128.4, 128.3, 128.26, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.48, 127.4, 127.3, 127.25, 126.6, 126.2, 85.2, 84.8, 83.5, 83.2, 80.9, 80.8, 79.9, 79.8, 78.0, 76.7, 75.0 (CH_2), 74.93 (CH_2), 73.4 (CH_2), 73.3 (CH_2), 71.6 (CH_2), 71.2 (CH_2), 69.6 (CH_2), 69.2 (CH_2), 53.6 (OMe), 53.5 (OMe), 30.5 (CH_2), 29.9 (CH_2); HRMS (TOF MS ES+) found $[M + Na]^+$ 613.2563, calcd $C_{38}H_{38}O_6{}^{23}Na$ 613.2566.

*5-(4,5-Dibenzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)-6-hydroxybenz[a]anthracene-7,12-dione (**21b**).* The general procedure for the Hauser annulation was followed using 3-cyanophthalide **8** (15 mg, 0.1 mmol), Michael acceptor **20b** (60 mg, 0.11 mmol), and LTB (27 mg, 0.3 mmol). The crude product was purified by column chromatography on silica gel (using 20% EtOAc/hexanes as the eluent) to afford **21b** as a red solid (61 mg, 93%). The $[\alpha]$ value could not be determined because the solution was opaque[15] even at c 0.001. Mp 165−169 °C; IR (KBr, cm^{-1}) 2863, 1723, 1658, 1635, 1451, 1361, 1337, 1294, 1099, 1024, 755, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.07 (s, 1H), 9.33 (d, J = 8.9 Hz, 1H), 8.81 (d, J = 8.9 Hz, 1H), 8.18 (d, J = 7.7 Hz, 2H), 7.81−7.61 (m, 2H), 7.43 (t, J = 7.8 Hz, 1H), 7.38−7.07 (m, 16H), 5.65 (d, J = 11.1 Hz, 1H), 4.96 (d, J = 10.9 Hz, 1H), 4.71−4.54 (m, 4H), 4.47 (d, J = 12.3 Hz, 1H), 3.95−3.84 (m, 3H), 3.72 (d, J = 10.8 Hz, 1H), 3.62 (d, J = 7.5 Hz, 1H), 2.35 (d, J = 13.1 Hz, 1H), 2.24 (q, J = 12.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6 (C═O), 185.7 (C═O), 153.7 (C), 138.8 (C), 138.6 (C), 137.5 (C), 135.3 (CH), 133.8 (CH), 132.1, 130.3, 129.6, 129.3, 129.1, 128.5, 128.3, 127.9, 127.8, 127.6, 127.5, 126.8, 126.7, 126.3, 118.4, 81.6 (CH-anomeric), 79.9, 78.4, 75.5 (CH_2), 73.4 (CH_2), 71.8 (CH_2), 71.6, 69.4 (CH_2), 36.1 (CH_2); HRMS (TOF MS ES+) found $[M + Na]^+$ 713.2518, calcd $C_{45}H_{38}O_7{}^{23}Na$ 713.2515.

*5-(4,5-Dibenzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)-6-hydroxy-8-methoxybenz[a]anthracene-7,12-dione (**23b**).* The general procedure for the Hauser annulation was followed using 7-methoxy-3-cyanophthalide **22** (65 mg, 0.34 mmol), Michael acceptor **20b** (210 mg, 0.38 mmol), and LTB (83 mg, 1.02 mmol). The crude product was purified by column chromatography on silica gel (using 25% EtOAc/hexanes as the eluent) to afford **23b** as a red solid (204 mg, 88%). The $[\alpha]$ value could not be determined because the solution was opaque[15] even at c 0.001. Mp 167−172 °C; IR (KBr, cm^{-1}) 2863, 1634, 1585, 1448, 1334, 1224, 1185, 1098, 1031, 739, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.16 (s, 1H), 9.21 (d, J = 8.9 Hz, 1H), 8.81 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.43 (dd, J = 13.8, 6.4 Hz, 1H), 7.45−7.29 (m, 17H), 5.66 (dd, J = 11.9, 2.6 Hz, 1H), 4.96 (d, J = 10.8 Hz, 1H), 4.74−4.54 (m, 4H), 4.47 (d, J = 12.2 Hz, 1H), 4.02 (s, 3H), 4.00−3.94 (m, 3H), 3.72 (dd, J = 11.1, 1.9 Hz, 1H), 3.62 (s, 1H), 2.34 (d, J = 13.0 Hz, 1H), 2.23 (d, J = 11.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0 (C═O), 185.8 (C═O), 160.2 (C), 153.5 (C), 138.8 (CH), 138.6 (C), 137.4 (C), 136.8 (C), 136.3 (CH), 129.7, 129.4, 128.9, 128.7, 128.5, 128.5, 128.4, 128.2, 127.8, 127.77, 127.7, 127.5, 127.4, 127.1, 126.1, 126.0, 120.0, 119.4, 117.4, 81.5 (CH-anomeric), 79.8, 78.4, 75.3 (CH_2), 73.3 (CH_2), 71.7 (CH_2), 71.6, 69.5 (CH_2), 56.6 (OMe), 36.3 (CH_2); HRMS (TOF MS ES+) found $[M + Na]^+$ 743.2619, calcd $C_{46}H_{40}O_8{}^{23}Na$ 743.2621.

*5-(4,5-Dibenzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)-9-chloro-6-hydroxy-8-methoxybenz[a]anthracene-7,12-dione (**25b**).* The general procedure for the Hauser annulation was followed using 6-chloro-7-methoxy-3-cyanophthalide **24** (47 mg, 0.21 mmol), Michael acceptor **20b** (125 mg, 0.23 mmol), and LTB (51 mg, 0.63 mmol). The crude product was purified by column chromatography on silica gel (using 30% EtOAc/hexanes as the eluent) to afford **25b** as a red solid (122 mg, 81%). The $[\alpha]$ value could not be determined because the solution was opaque[15] even at c 0.001. Mp 162−165 °C; IR (KBr, cm^{-1}) 2861, 1632, 1563, 1444, 1361, 1307, 1274, 1141, 1086, 1016, 772, 735, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.98 (s, 1H), 9.29 (d, J = 8.8 Hz, 1H), 8.90 (d, J = 8.8 Hz, 1H), 8.02 (d, J = 8 Hz,

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1H), 7.83 (d, J = 8.4 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.43−7.31 (m, 16 H), 5.74 (d, J = 11.2 Hz, 1H), 5.04 (d, J = 10.8 Hz, 1H), 4.77−4.64 (m, 4H), 4.55 (d, J = 12.4 Hz, 1H), 4.06 (s, 3H), 4.01−3.95 (m, 3H), 3.80 (d, J = 10.4 Hz, 1H), 3.70 (d, J = 4.8 Hz, 1H), 2.44−2.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2 (C═O), 184.5 (C═O), 156.1 (C), 153.1 (C), 138.63 (C), 138.6 (C), 138.4 (C), 137.0 (C), 136.5 (C), 136.3 (CH), 128.0, 127.6, 127.58, 127.3, 127.25, 126.0 (C), 125.96 (C), 125.9 (CH), 124.1 (CH), 118.9 (C), 81.3, 79.7, 78.1, 76.7, 75.2 (CH_2), 73.1 (CH_2), 71.5 (CH_2), 71.4, 69.2 (CH_2), 61.8 (OMe), 35.8 (CH_2); HRMS (TOF MS ES+) found $[M + Na]^+$ 777.2229, calcd $C_{46}H_{39}O_8Cl^{23}Na$ 777.2231.

*4-Azido-6-(2-hydroxynapthalen-1-yl)-2-methyltetrahydropyran-3-yl Acetate (**27a** and **27b**).* To a stirred solution of 2-naphthol **18** (325 mg, 2.26 mmol), hexopyranoside **26** (995 mg, 3.87 mmol), and 4 Å molecular sieves in DCM (100 mL) was added tin(IV) chloride (1 M solution in DCM, 12.8 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 10 min, and then the temperature was gradually increased to −35 °C and maintained overnight. The reaction was quenched with saturated sodium sulfate, and the mixture was extracted with methylene chloride. The organic phase was dried, concentrated, and purified by flash column chromatography (using 20% EtOAc/hexanes as the eluent) to obtain **27a** (460 mg, 60%) as yellow semisolid and **27b** (230 mg, 30%) as white solid.

Data for **27a**: $[\alpha]_D^{35}$ = +45.8 (c 0.5, $CHCl_3$); IR (KBr, cm^{-1}) 3448, 2098, 1702, 1654, 1561, 1459, 1226; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 5.52 (d, J = 11.6 Hz, 1H), 4.91 (dd, J = 9.6, 9.6 Hz, 1H), 3.85−3.74 (m, 2H), 2.45 (dd, J = 14.0, 3.2 Hz, 1H), 2.20 (s, 3H), 2.15−2.03 (m, 1H), 1.37 (d, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (C═O of acetate), 153.8 (C), 130.7 (C), 130.4 (CH), 129.3 (CH), 128.9 (C), 127.2 (CH), 123.3 (CH), 120.5 (CH), 120.1 (CH), 114.0 (C), 76.6, 76.3, 75.1, 61.1, 36.1 (CH_2), 21.0 (CH_3 of acetate), 18.1 (CH_3); HRMS (TOF MS ES+) found $[M + Na]^+$ 364.1269, calcd $C_{18}H_{19}N_3O_4{}^{23}Na$ 364.1273.

Data for **27b**: $[\alpha]_D^{35}$ = +93.8; mp 85−89 °C; IR (KBr, cm^{-1}) 2925, 2115, 1739, 1654, 1622, 1459, 1375, 1296, 1223, 1077, 1050; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.79−7.66 (m, 3H), 7.50 (t, J = 8.2 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 5.76 (dd, J = 7.2, 6.6 Hz, 1H), 4.92 (dd, J = 10.0, 3.2 Hz, 1H), 4.31−4.24 (m, 2H), 2.21−2.10 (m, 5H), 1.38 (d, J = 6.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.2 (C═O of acetate), 153.9 (C), 130.9 (C), 130.2 (CH), 129.1 (CH), 128.9 (C), 127.2 (CH), 124.3 (CH), 120.8 (CH), 120.0 (CH), 114.2 (C), 74.7, 73.2, 72.1, 58.5, 35.8 (CH_2), 20.9 (CH_3 of acetate), 18.3 (CH_3); HRMS (TOF MS ES+) found $[M + Na]^+$ 364.1269, calcd $C_{18}H_{19}N_3O_4{}^{23}Na$ 364.1273.

*4-Azido-6-(1-methoxy-2-oxo-1,2-dihydronapthalen-1-yl)-2-methyltetrahydropyran-3-yl Acetate (**28**).* The general procedure for dearomatization of naphthols was followed using *C*-glycosyl naphthol **27a** (260 mg, 0.76 mmol) and PIDA (322 mg, 1.3) in methanol (5 mL). The crude product was purified by column chromatography on silica gel (using 20% EtOAc/hexanes as the eluent) to afford **28** as a light-yellow semisolid (249 mg, 88%) as a mixture of two diastereomers. IR ($CHCl_3$, cm^{-1}) 2099, 1744, 1671, 1373, 1226, 1046; ^{1}H NMR (200 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.55 (d, J = 7.8 Hz), 7.48−7.15 (m), 6.10 (dd, J = 9.8, 1.8 Hz), 4.43−4.23 (m), 3.65−3.55 (m), 3.48−3.27 (m), 3.21−3.06 (m), 3.01 (s), 2.98 (s), 2.10−2.03 (m), 1.99 (s), 1.54−1.31 (m), 0.98 (d, J = 6.1 Hz), 0.89 (d, J = 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, mixture of two diastereomers) δ 201.9 (C═O), 199.9 (C═O), 169.9 (C═O of acetate), 145.6 (CH), 145.3 (CH), 139.3 (C), 137.1 (C), 133.3 (C), 132.7 (C), 129.4 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.1 (CH), 126.3 (CH), 126.1 (CH), 85.2, 84.7, 82.8, 82.4, 74.9, 74.7, 61.6, 61.2, 53.8, 53.6, 30.4 (CH_2), 29.7 (CH_2), 20.9 (CH_3 of acetate), 20.8 (CH_3 of acetate), 17.5 (CH_3), 17.4 (CH_3). HRMS (TOF MS ES+) found $[M + Na]^+$ 394.1358, calcd $C_{19}H_{21}N_3O_5{}^{23}Na$ 394.1379.

*5-(4-Azido-5-acetoxy-6-methyltetrahydropyran-2-yl)-6-hydroxybenz[a]anthracene-7,12-dione (**29**) and 5-(4-Azido-5-hydroxy-6-methyltetrahydropyran-2-yl)-6-hydroxybenz[a]anthracene-7,12-dione (**30**).* The general procedure for the Hauser annulation was followed using 3-cyanophthalide **8** (78 mg, 0.49 mmol), Michael acceptor **28** (200 mg, 0.54 mmol), and LTB (126 mg, 1.56 mmol). The crude product was purified by column chromatography on silica gel (using 20% EtOAc/hexanes as the eluent) to afford **29** as a red solid (165 mg, 71%) along with the deacetylated product **30** (23 mg, 10%) as a red solid.

Data for **29**: The $[\alpha]$ value could not be determined because the solution was opaque[15] even at c 0.001. Mp 180−185 °C decomp.; IR (KBr, cm^{-1}) 2098, 1737, 1658, 1633, 1443, 1377, 1337, 1293, 1229, 1043. ^{1}H NMR (200 MHz, $CDCl_3$) δ 13.16 (s, 1H), 9.51−9.20 (m, 1H), 8.79−8.53 (m, 1H), 8.20 (dd, J = 7.1, 1.9 Hz, 2H), 7.80−7.72 (m, 2H), 7.63−7.37 (m, 2H), 5.74 (dd, J = 10.5, 3.7 Hz, 1H), 5.00 (t, J = 9.6 Hz, 1H), 4.01−3.53 (m, 2H), 2.40−2.17 (m,5H), 1.33 (d, J = 6.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 190.5 (C═O), 185.4 (C═O), 170.5 (C═O of acetate), 153.8 (C), 137.2 (C), 135.3 (C), 135.1 (CH), 133.8 (CH), 131.9 (C), 130.5 (C), 129.7 (CH), 129.3 (CH), 128.1 (C), 127.5 (CH), 127.49 (CH), 126.36 (CH), 125.4 (CH), 118.4 (C), 75.8, 75.7, 71.9, 62.0, 35.5 (CH_2), 21.2 (CH_3 of acetate), 18.1 (CH_3); HRMS (TOF MS ES+) found $[M + Na]^+$ 494.1325, calcd $C_{26}H_{21}N_3O_6{}^{23}Na$ 494.1328.

Data for **30**: the $[\alpha]$ value could not be determined because the solution was opaque[15] even at c 0.001; mp 188−192 °C (decomp); IR (KBr, cm^{-1}) 2099, 1654, 1636, 1510, 1376, 1338, 1293, 1232, 1059; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.19 (s, 1H), 9.43−9.41 (m, 1H), 8.71−8.69 (m, 1H), 8.27−8.25 (m, 2H), 7.85−7.76 (m, 2H), 7.60−7.51 (m, 2H), 5.77 (dd, J = 11.6, 3.2 Hz, 1H), 3.84−3.77 (m, 1H), 3.67−3.63 (m, 1H), 3.48 (t, J = 9.2 Hz, 1H), 2.41−2.28 (m, 3H), 1.49 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5 (C═O), 185.5 (C═O), 153.9 (C), 137.3 (C), 135.3 (C), 135.2 (CH), 133.8 (CH), 132.0 (C), 130.4 (C), 129.5 (CH), 129.3 (CH), 128.6 (C), 127.5 (CH), 127.4 (CH), 126.7 (CH), 125.4 (CH), 118.5, 77.43, 76.2, 71.9, 64.8, 35.3 (CH_2), 18.5 (CH_3); HRMS (TOF MS ES+) found $[M + Na]^+$ 452.1220, calcd $C_{24}H_{19}N_3O_5{}^{23}Na$ 452.1222.

*4-Azido-6-(1-methoxy-2-oxo-1,2-dihydronapthalen-1-yl)-2-methyltetrahydropyran-3-yl Acetate (**31**).* The general procedure for dearomatization of naphthols was followed using *C*-glycosyl naphthol **27b** (100 mg, 0.29 mmol) and PIDA (120 mg, 0.37) in methanol (7 mL). The crude product was purified by column chromatography on silica gel (using 20% EtOAc/hexanes as the eluent) to afford **31** as a yellow semisolid (88 mg, 82%) as a mixture of two diastereomers. IR ($CHCl_3$, cm^{-1}) 2933, 2112, 1741, 1655, 1561, 1458, 1372, 1227, 1108, 1050, 759; ^{1}H NMR (200 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.54 (dd, J = 8.8, 1.6 Hz), 7.43−7.25 (m), 6.12 (d, J = 9.8 Hz), 6.08 (d, J = 10.0 Hz), 4.42 (dd, J = 9.8, 3.4 Hz), 4.32 (dd, J = 9.8, 3.4 Hz), 4.09−4.04 (m), 3.88−3.75 (m), 3.65−3.55 (m), 3.02 (s), 2.01 (s), 1.98−1.74 (m), 0.95 (d, J = 6.4 Hz), 0.92 (d, J = 6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$, mixture of two diastereomers) δ 201.8 (C═O), 200.3 (C═O), 170.1 (C═O of acetate), 170.0 (C═O of acetate), 145.3 (CH), 144.9 (CH), 140.1 (C), 137.8 (C), 133.1 (C), 132.9 (C), 129.8 (C), 129.78 (CH), 129.3 (CH), 129.0 (CH), 128.8(CH), 128.76 (C), 128.68 (CH), 127.8 (CH), 126.6 (CH), 126.3 (CH), 85.5, 85.4, 79.7, 78.8, 74.6, 74.4, 70.5, 70.4, 58.3, 58.2, 53.8, 53.76, 29.9 (CH_2), 29.1 (CH_2), 20.7 (two acetate CH_3), 17.7 (CH_3), 17.6 (CH_3); HRMS (TOF MS ES+) found $[M + Na]^+$ 394.1355, calcd $C_{19}H_{21}N_3O_5{}^{23}Na$ 394.1379.

*5-(4-Azido-5-hydroxy-6-methyltetrahydropyran-2-yl)-6-hydroxybenz[a]anthracene-7,12-dione (**32**).* The general procedure for the Hauser annulation was followed using 3-cyanophthalide **8** (66 mg, 0.42 mmol), Michael acceptor **31** (170 mg, 0.46 mmol), and LTB (110 mg, 1.35 mmol). The crude product was purified by column chromatography on silica gel (using 20% EtOAc/hexanes as the eluent) to afford **32** as a red solid (172 mg, 87%). The $[\alpha]$ value could not be determined because the solution was opaque[15] even at c 0.001. Mp 188−192 °C (decomp); IR (KBr, cm^{-1}) 2118, 1751, 1654, 1636, 1560, 1542, 1458, 1339, 1058, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.18 (s, 1H), 9.46−9.44 (m, 1H), 8.76−8.73 (m, 1H), 8.31−8.26 (m, 2H), 7.88−7.79 (m, 2H), 7.60−7.53 (m, 2H), 6.01 (dd, J = 11.6, 2.0 Hz, 1H), 4.31 (dd, J = 6.4, 3.2 Hz, 1H), 3.87−3.93 (m, 1H), 3.74−3.68 (m, 1H), 2.65−2.58 (m, 1H), 2.23−2.18 (m, 1H), 2.08 (d, J = 9.2

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Hz, 1H), 1.44 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5 (C═O), 185.7 (C═O), 154.1 (C), 137.6 (C), 135.3 (CH), 135.28 (CH), 133.9 (C), 132.1 (C), 130.4 (C), 129.4 (two CH), 129.0 (C), 127.5 (CH), 127.4 (CH), 126.74 (C), 126.7 (CH), 125.4 (CH), 118.6 (C), 74.2, 73.4, 68.5, 61.9, 34.8, 18.5; HRMS (TOF MS ES+) found $[M + Na]^+$ 452.1216, calcd $C_{24}H_{19}N_3O_5{}^{23}Na$ 452.1222.

*1-(3,4,5-Tribenzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)-2-naphthol (**34**).*[12a] To a solution of diphenyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannosyl phosphate (250 mg, 0.32 mmol) in DCM (10.0 mL) at 0 °C was added 2-naphthol (70 mg, 0.49 mmol) followed by TMSOTf (70 μL, 0.38 mmol). The reaction mixture was allowed to warm to ambient temperature over 1 h. After 1 h, the reaction was quenched by the addition of Et_3N (100 μL), and the solvent was removed in vacuo. Purification by flash chromatography (using 20% EtOAc/hexanes as the eluent) afforded **34** as a yellow oil (140 mg, 65%). The NMR data of the compound were in good agreement with the previously reported[12b] values. $[\alpha]_D^{35}$ = +51.8 (c 0.5, $CHCl_3$) {lit. $[\alpha]_D^{24}$ = +49.1 (c 0.46, $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.39−7.21 (m, 18H), 7.15 (d, J = 8.8 Hz, 1H), 7.09−6.96 (m, 5H), 5.40 (s, 1H), 4.95 (d, J = 10.8 Hz, 1H), 4.71−4.65 (m, 3H), 4.59 (d, J = 8.8 Hz, 1H), 4.54 (d, J = 12.0, 1H), 4.35 (d, J = 9.0, 1H), 4.27−4.17 (m, 2H), 4.34−4.32 (m, 1H), 3.89−3.65 (m, 4H).

*1-(3,4,5-Tribenzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)-1-methoxy-1H-naphthalen-2-one (**35**).* The general procedure for dearomatization of naphthols was followed using *C*-glycosyl naphthol **34**[12] (235 mg, 0.36 mmol) and PIDA (145 mg, 0.45) in methanol (6 mL). The crude product was purified by column chromatography on silica gel (using 20% EtOAc/hexanes as the eluent) to afford **35** as a yellow semisolid (238 mg, 67%) as a mixture of two diastereomers. IR ($CHCl_3$, cm^{-1}) 2930, 1625, 1525, 1318, 1244, 1126, 1031, 768; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of two diastereomers) δ 7.50 (d, J = 7.6 Hz), 7.24−6.94 (m), 5.83 (d, J = 10.0 Hz), 4.94 (d, J = 10.4 Hz), 4.79−4.41 (m), 4.23 (d, J = 10.4 Hz), 4.10−3.89 (m), 3.72−3.38 (m), 3.22 (s), 3.09 (s); ^{13}C NMR (50 MHz, $CDCl_3$, mixture of two diastereomers) δ 199.9 (C═O), 144.0 (CH), 139.9 (C), 139.2 (C), 139.1 (C), 138.6 (C), 138.3 (C), 138.1 (C), 133.5 (CH), 129.3 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.3 (CH), 127.0 (CH), 103.8 (CH), 88.4 (CH), 85.7 (CH), 85.5 (CH), 81.3 (CH), 78.7 (CH), 77.9 (CH), 75.2 (CH), 75.0 (CH), 74.7 (CH_2), 74.0 (CH_2), 73.8 (CH_2), 73.5 (CH_2), 73.1 (CH_2), 72.1 (CH), 71.0 (CH_2), 69.9 (CH_2), 69.6 (CH_2), 53.9 (OMe), 53.7 (OMe); HRMS (TOF MS ES+) found $[M + Na]^+$ 719.2980, calcd $C_{45}H_{44}O_7{}^{23}Na$ 719.2985.

*6-Hydroxy-5-(3,4,5-tribenzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)benz[a]anthracene-7,12-dione (**33**).* The general procedure for the Hauser annulation was followed using 3-cyanophthalide **8** (27 mg, 0.17 mmol), Michael acceptor **35** (120 mg, 0.17 mmol), and LTB (50 mg, 0.51 mmol). The crude product was purified by column chromatography on silica gel (using 20% EtOAc/hexanes as the eluent) to afford **33** as a red solid (102 mg, 76%). The $[\alpha]$ value could not be determined because the solution was opaque[15] even at c 0.001. Mp 170−174 °C; IR (KBr, cm^{-1}) 2924, 1874, 1720, 1655, 1583, 1458, 1089, 1022, 734, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.01 (s, 1H), 9.37 (d, J = 9.2 Hz, 1H), 9.23 (d, J = 9.2 Hz, 1H), 8.29 (t, J = 7.6 Hz, 2H), 7.88−7.79 (m, 2H), 7.50 (t, J = 7.2 Hz, 1H), 7.43 (d, J = 7.2 Hz, 2H), 7.37−7.28 (m, 14H), 6.83−6.82 (m, 3H), 6.56−6.54 (m, 2H), 5.54 (s, 1H), 5.01 (d, J = 10.8 Hz, 1H), 4.83 (s, 2H), 4.72−4.68 (m, 2H), 4.60 (d, J = 12.4 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.30−4.24 (m, 2H), 4.00 (d, J = 11.6 Hz, 1H), 3.98−3.90 (m, 2H), 3.81 (d, J = 10.4 Hz, 1H), 3.68−3.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6 (C═O), 185.8 (C═O), 153.5 (CH), 139.1 (C), 138.9 (C), 138.8 (C), 138.7 (C), 137.7 (C), 135.5 (C), 135.3 (CH), 133.7 (CH), 132.2 (C), 129.9 (C), 129.5 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.59 (CH), 128.55 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.79 (CH), 127.7 (CH), 127.6 (CH), 127.59 (CH), 127.55 (CH), 127.2 (CH), 126.9 (CH), 126.6 (CH), 117.7 (CH), 84.8 (CH-anomeric), 80.5, 77.4, 75.5 (CH_2), 75.3, 74.9 (CH_2), 73.5 (CH_2), 72.7 (CH_2), 69.6 (CH_2); HRMS (TOF MS ES+) found $[M + Na]^+$ 819.2931, calcd $C_{52}H_{44}O_8{}^{23}Na$ 819.2934.

*5-(4,5-Dihydroxy-6-hydroxymethyltetrahydropyran-2-yl)-6-hydroxy-8-methoxybenzo[a]anthracene-7,12-dione (**36**).* To a stirred solution of **23b** (30 mg, 0.046 mmol) in dry DCM (5 mL) at −90 °C was added BBr_3 (0.83 mL, 0.83 mmol, 1 M in DCM), and the mixture was stirred for 5 min at −90 °C. After 5 min, MeOH (1 mL) and saturated $NaHCO_3$ (1 mL) were added. The cooling bath was then removed, and the reaction mixture was allowed to attain room temperature. The organic layer was separated, and the aqueous layer was extracted with DCM (5 mL × 2). The combined organic layers were washed with water H_2O (5 mL) and brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by washing with 50% ethyl acetate/petroleum ether to obtain **36** as a red solid (14 mg, 75%). The $[\alpha]$ value could not be determined because of the poor solubility of **36**. ^{1}H NMR (400 MHz, DMSO-d_6, sparingly soluble) δ 13.35 (s, 1H), 9.21 (d, J = 8.4 Hz, 1H), 8.79 (d, J = 8.8 Hz, 1H), 7.29 (t, J = 8.4 Hz, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.68−7.55 (m, 3H), 5.56 (dd, J = 9.6, 2.4 Hz, 1H), 5.06 (d, J = 5.2 Hz, 1H), 5.01 (d, J = 5.2 Hz, 1H), 4.53 (t, J = 5.6 Hz, 1H), 4.02 (s, 1H), 3.63−3.57 (m, 3H), 2.15−1.90 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, sparingly soluble) δ 189.2 (C═O), 185.9 (C═O), 159.9, 152.5, 136.7, 136.6, 135.7, 129.0, 128.9, 128.5, 128.1, 126.7, 125.8, 124.8, 119.4, 119.1, 118.6, 118.1, 82.3 (CH-anomeric), 72.4, 71.7, 70.8, 61.4, 56.6, 38.5 (CH_2).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR of all new compounds, HPLC chromatograms, and a typical MTT assay procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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