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Convenient Syntheses of Daunomycinone-7-D-Glucuronides and Doxorubicinone-7-D-Glucuronides

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ABSTRACT

The first synthesis of new doxorubicin and daunomycin analogs containing glucuronic acid moieties instead of daunosamine are described. The desired products, daunomycinone-7-D-glucuronide (DM7G, **10**) and doxorubicinone-7-D-glucuronide (DX7G, **11**) were conveniently prepared through the glycosylation at 7-hydroxyl group of daunomycinone (**4**) or 14-acetoxydoxorubicinone (**6**) with glucuronic acid derivative **7** by the Koenigs-Knorr procedure followed by alkaline deacetylation using aqueous LiOH solution and amberlite cation exchange material. The anomeric configuration and conformation of all products were fully

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characterized by assignment of ^{1}H NMR chemical shifts and H-H coupling constants based on reported literatures.

Key Words: Anthracycline; Daunomycinone; Doxorubicinone; Glucuronic acid; Glycosylation.

INTRODUCTION

Anthracyclines are among the most widely used anticancer agents. Notwithstanding the large efforts to develop new drugs with a better pharmaceutical profile, doxorubicin (DX, **1**), daunorubicin (DM, **2**), and idarubicin (IDA, **3**) are still the most used in clinical practice. Used as single agents or in combination therapy, they are the components of adjuvant, curative, as well as palliative treatments. Their clinical use is, however, limited by undesirable side effects such as drug-cumulative cardiotoxicity and myelosuppression, as well as the appearance of multidrug resistance (MDR) in tumor cells.[1] To circumvent these drawbacks, many chemical and biosynthetic modifications have been undertaken.[2,3]

Many efforts have been made to modify the anthracyclines and to develop analogs with high activity and low toxicity. Recently, the synthesis of anthracycline analogs in which glucuronides are attached to the C-3′ amino group of doxorubicin (and/or daunomycin) have been reported.[4b] The studies comparing antitumor activities of these derivatives and corresponding anthracycline have been also reported.[4a,c] However, the synthesis of daunomycinone-7-D-glucuronide and doxorubicinone-7-D-glucuronide as potential prodrugs has not been reported, and therefore the chemical and biological properties remain unknown. In previous papers, we have been reported the synthesis of novel fucosyl anthracycline analogs containing various amino acids at the C-14 position and a fluorine at the C-9 or C-10 position as well

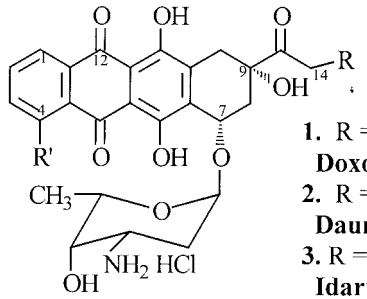

Figure 1. Chemical structures of anthracyclines.

as idarubicinone derivatives.[5] In more recent papers, we have also reported the successful synthesis of idarubicinone-7-β-D-glucurnonide.[5c] Related to these reports, we will report the synthesis of daunomycin or doxorubicin analogs having glucuronic acid instead of daunosamine as a glycone at the C-7 position. Additionally, we also wish to report the assignment of the anomeric configuration of the glucuronic acid moiety.

RESULTS AND DISCUSSION

In this study we endeavored to prepare some DM7G (**10**) or DX7G (**11**) from commercially available daunomycin (**2**). For the coupling reaction, we used daunomycinone (**4**), 14-acetyldoxorubicinone (**6**), and methyl 2,3,4-tri-O-acetyl-D-glucopyranosyuronate bromide (**7**) as starting materials as shown in (Fig. 2). First, compound **4** was readily obtained in 98% from **2** by treating with 0.2 N HCl solution by the known procedure.[6] The synthesis of **6** was accomplished by bromination of **4** with 30% bromine/chloroform in methanol/dioxane followed by the nucleophilic displacement type esterification of 14-bromodaunomycinone (**5**) with sodium acetate in acetone.[7] Glucopyranosyl bromide **7** was prepared from available D-glucuronolactone by the known procedure.[8] The target materials (**10** and **11**) were obtained from coupling of **4** or **6** with a suitably protected glucopyranosyl bromide **7** by modified Koenigs-Knorr glycosylation using mercury (II) bromide[9e] followed by alkaline deacetylation using aqueous LiOH solution.

The coupling reactions were attempted under several conditions in the presence of various catalysts as shown in Table 1. The stereochemical outcome of glycosidation was influenced by the kinds of catalysts and reaction conditions: thus, coupling **4** with glycosyl bromide **7** using AgOTf[9a] or Ag_2CO_3[9b] afforded a mixture of **8a** (DM7αGa) and **8b** (DM7βGa) with an 1 : 1 ratio, whereas using $HgBr_2$[9e] and $CdCO_3$[9d] led to a different ratio of isomers of 3–7 (**8a**/**8b**). Interestingly, the reaction of idarubicinone (no -OMe group at C4 position) with glycosyl bromide **7** using $ZnBr_2$[9c] or $HgBr_2$ afforded the desired products in $\geq$ 53% and $\leq$ 6% yield,[5c] respectively, whereas coupling **4** with $ZnBr_2$ produced only β-anomer (30%) in accordance with the neighboring group participation of Koenigs-Knorr reaction,[10] and the reaction of **4** with $HgBr_2$ gave the best yield of the α- and β-anomers ($\alpha : \beta = 3 : 7$, 74%). Results of the coupling of **4** with glycosyl bromide **7** in various reaction conditions are summarized in Table 1. The thin-layer chromatography (TLC) spots were $R_f = 0.5$ (β-anomer) and 0.7 (α-anomer) in 10% acetone/dichloromethane as an eluent. The tendency of the coupling of **6** with glycosyl bromide **7** for synthesis of **9a** (DX7αGa)/**9b**(DX7βGa) was generally similar to that of the corresponding reaction for

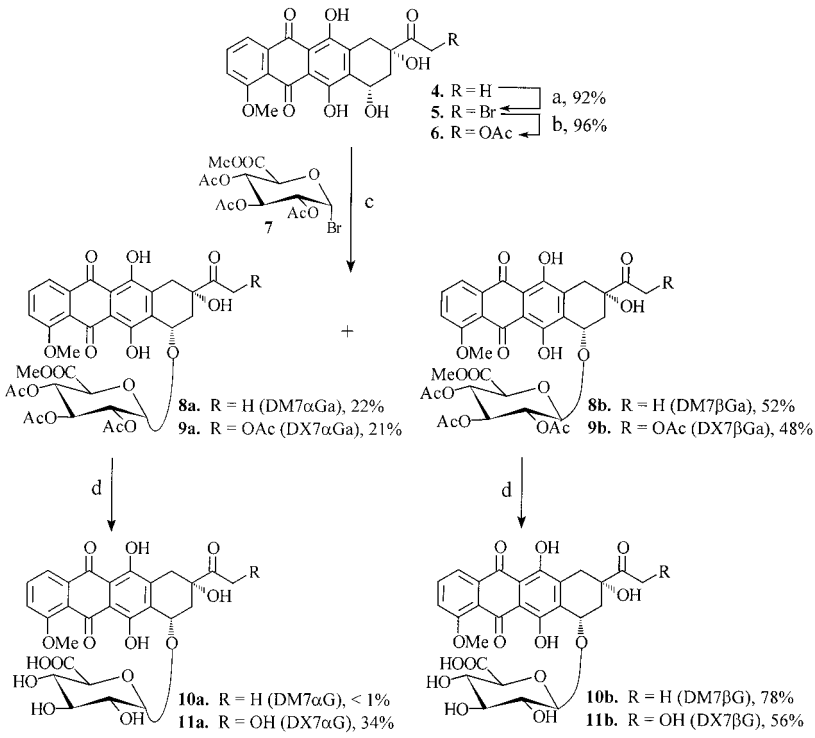

Figure 2. (a) i) Trimethylorthoformate, MeOH/1,4-dioxane, rt, 20 min, ii) $Br_2/CHCl_3$, 30°C, 6 h. (b) NaOAc/acetone, reflux, 6 h. (c) $HgBr_2$, yellow HgO, 3 Å molecular sieves/CH_2Cl_2, reflux, 36 h. (d) 0.1 N LiOH, MeOH/H_2O/THF (5/2/1, v/v), 0°C, 2 h, amberite cation resin..

synthesis of **8a**/**8b**. Therefore, we could isolate two stereochemical compounds for each reaction through a careful flash column chromatography using silica gel in the same eluent.

The assignment of anomeric configuration of DM7Ga (**8**) and DX7Ga (**9**) was fully characterized based on ^{1}H NMR data (chemical shifts and H-H coupling constants) between the 1′-H and 2′-H protons on the glucuronic acid moiety. The coupling constants for the 1′-H and 2′-H protons for various types of drug-glucuronide conjugates have been reported.[11] For α-anomers, coupling constants of $J_{1'2'} = 2-5$ Hz were observed, while $J_{1'2'} = 6-10$ Hz were characteristic for the β-anomer.[9c,11] Additionally, the axial anomeric proton (1′-C) of the β-anomer always resonates at a higher field than the equatorial proton of the corresponding α-anomer.[11a] Hence,

Table 1. Ratios and overall yields of **8a**/**8b** in various reaction conditions.

Reagent	Equiv.	Solvent	Temp.	Ratio[a]	Yield (%)[b]
AgOTf	1.1	CH_2Cl_2	rt	$\alpha/\beta = 1:1$	46
$HgBr_2$	1.1	CH_2Cl_2	reflux	$\alpha/\beta = 3:7$	74
$ZnBr_2$	1.1	CH_2Cl_2	rt	only β	30
Ag_2CO_3	1.1	Benzene	reflux	$\alpha/\beta = 1:1$	49
$CdCO_3$	1.1	Benzene	reflux	$\alpha/\beta = 3:7$	58

[a]Ratio was determined by ^{1}H NMR spectroscopy.
[b]Total isolated yields.

the primary objective of this study was to identify unambiguously the anomeric 1′-H proton and the neighboring 2′-H proton, and to compare their chemical shifts and coupling constants (Table 2). The 4.5–5.3 ppm region of 1D proton NMR spectra, which included the 4′-H, 2′-H, and 3′-H signals, was carefully analyzed. For α-anomer (DM7αGa, **8a**) the 2′-H was assigned to the double-doublet at 4.52 ppm. The observed coupling constants of 3.4 and 6.8 Hz clearly suggest one axial-equatorial interaction (1′-H, 2′-H) and one axial-axial interaction (2′-H, 3′-H). For comparison, in the β-anomer (DM7βGa, **8b**), the 2′-H signal appears as a double-doublet (4.97 ppm, $J = 7.3$, 9.3 Hz), indicating the axial-axial interactions for both 1′-H and 3′-H protons on the sugar ring. The smaller coupling constant of the 2′-H signal in the α-anomer **8a** was assigned to the 1′-H and 2′-H interaction corresponding to the 1′-H doublet at 5.95 ppm, which has a measured coupling constant of 4.9 Hz. It should be noted that the chemical shift of the 1′-H signal in the α-isomer **8a** appears in a lower field than in β-isomer **8b** (5.15 ppm, $J = 7.8$ Hz). In addition, the cross-peaks in the α-isomer of a COSY experiment clearly connect the doublet at 5.95 ppm with the double-doublet at 4.52 ppm. For the β-isomer, the cross-peaks clearly connect the doublet at 5.15 ppm with the doublet-doublet at 4.97 ppm. For DX7Ga (**9a** and **9b**), the anomeric configurations of the glucuronic acid moiety have the same tendency of the spectral data of DM7Ga (**8a** and **8b**) as shown in Table 2.

Deprotection of the carbohydrate moieties of all compounds **8a**,**b** and **9a**,**b** was carried out using 0.1 N LiOH solution in MeOH/THF/H_2O (5/2/1, v/v). After the reaction was completed, the resulting solution was neutralized with ion exchange resin and then the polar compound was purified with reversed-phase C_{18} column chromatography.[4c] Deprotection of **8a** gave mainly hydrolyzed aglycone and glycone, and therefore the desired product, DM7αG (**10a**), was obtained only in small amounts ($<1\%$), whereas deprotection of **8b** and **9a** yielded DM7βG (**10b**) in 78% and DX7αG (**11a**) in 34%, respectively. Additionally, the deprotection of **9b** was more reactive

Table 2. ^{1}H NMR chemical shifts (δ, ppm) and coupling constants (J, Hz) for sugar moieties of DM7Ga (**8**) and DX7Ga (**9**) in $CDCl_3$.[a]

Multiplicity	H-1′ d ($J_{1'2'}$)	H-2′ dd ($J_{1'2'}$, $J_{2'3'}$)	H-3′ t ($J_{2'3'}$, $J_{3'4'}$)	H-4′ dd ($J_{3'4'}$, $J_{4'5'}$)	H-5′ d ($J_{4'5'}$)
8a (DM7αGa)	5.95 (4.9)	4.52 (3.4, 6.8)	5.23 (7.3)	5.17 (d, 7.8)	4.31 (7.8)
8b (DM7βGa)	5.15 (7.8)	4.97 (7.3, 9.3)	5.31 (9.3)	5.24 (9.3, 9.8)	4.16 (9.8)
9a (DX7αGa)	6.31 (3.4)	4.92 (2.9, 9.3)	5.34 (m)	5.21 (m)	4.33 (9.7)
9b (DX7βGa)	5.14 (7.8)	4.95 (7.8, 9.3)	5.30 (9.3)	5.23 (9.3, 9.8)	4.17 (9.8)

[a]Measured at 400 MHz ^{1}H NMR (JEOL JNM EX-400 spectrometer).

than **8b**, but DX7βG (**11b**) was less obtained than **10b**. Although additional attempts for deprotection of **8a** with various bases (0.1 N NaOH, NaOMe, Et_3N, guanidine, etc.) in several reaction conditions were tried, small amounts of product **11a** was always produced in an impure state and the aglycone and glycone moieties were mainly recovered. Actually, **8a** had a less stable structure than **8b**, **9a**, and **9b**; even if waiting for the deacetylation process in room temperature, **8a** was quickly destroyed to daunomycinone (**4**) and glucuronic acid moiety. Moreover, unpurified **8a** of the crude reaction mixture state was converted for 24 h into about 50% of starting materials, **4**, and glycone moiety. Although completely purified, **8a** was somewhat stable in the freezing state, and in the course of the deprotecting process, **8a** was completely converted into starting material, independent of its purity or the variety of reaction conditions. On the other hand, in the case of the other α-anomer, (the tendency of **9a** is not) in accordance with that of **8a**, low yields of α-anomers appeared indicating that α-anomers were less stable than β-anomers. In contrast, β-anomers (**8b** and **9b**) did not have the same tendency; deacetylation of β-anomers progressed well, and therefore side products from β-anomers were also not much more than those of α-anomer. The β-Anomer of DM was clearly known to be more getting than DX due to the base lability of DX.[4c] In addition, the product ratio of α/β-anomer during coupling of DM or DX was almost similar, but the reaction time of DM was much shorter than DX, and therefore the reactivity of the coupling reaction for doxorubicinone seemed to decrease in comparison with daunomycinone.

The solubility of **8**, **9**, **10**, and **11** was significantly different between α- and β-anomer: while α-isomers were soluble in ethylacetate and dichloromethane, β-anomers were found to be poorly soluble in ethylacetate and slightly soluble in dichloromethane. Therefore, pure β-anomers crystallized well using the solvents after charring out column chromatography of the reaction mixture.

In conclusion, pharmaceutically important daunomycinone-7-D-glucuronide (DM7G, **10**) and doxorubicinone-7-D-glucuronide (DX7G, **11**) were prepared from glycosylation of **7** with **4** and **6**, respectively. Detailed NMR analyses unambiguously proved the anomeric configuration of the new compounds.

EXPERIMENTAL SECTION

All reactions were carried out under argon atmosphere in dried glassware. All solvents were carefully dried and distilled as reported.[12] Bulk grade hexane was distilled prior to use. Merck precoated silica gel plates

(Art. 5554) with fluorescent indicator were used as analytical TLC. Gravity column chromatography and flash column chromatography were carried out on silica gel (230–400 mesh from Merck). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM EX-400 spectrometer. Chemical shifts were internally referenced to TMS for ^{1}H or to solvent signals for ^{13}C. Infrared (IR) spectra were recorded on a Nicolet 5-DXB series Fourier-transform infrared (FT-IR) spectrophotometer. Mass spectra were obtained on a JEOL JMS HX-110/110A Tandem mass spectrometer (FAB^{+}, ESI). Ultraviolet-(UV-VIS) absorption spectra were recorded on a Hitachi-556 spectrophotometer. Optical rotations were determined using the Rudolph AUTOPOL IV apparatus with a 0-100-1.5 polarimeter sample tube. Melting points were obtained on a Büchi 510 melting point apparatus and were uncorrected.

Daunomycinone (4). Daunomycin hydrochloride, **2** (1.00 g, 1.77 mmol) was dissolved in 100 mL of 0.2 N HCl solution, and the resulting mixture was heated for 3.5 h at 90–95°C. After completion of the reaction, the mixture cooled and the solid residue was filtered off and washed with water (pH 7). The solid was recrystallized from acetone/ether, filtered off, washed with ether, and dried under reduced pressure to give daunomycinone, **4** (0.69 g, 98%) as a red powder. Melting point (Mp) 213–214°C $[\alpha]_D^{20} + 193.1^{\circ}$ (c 0.1, dioxane); IR (KBr) 3443, 2361, 1710, 1617, 1579, 1421, 1286, 1211, 1123, 1085, 1036, 990, 796, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.92 (s, 1 H, PhOH), 13.23 (s, 1 H, PhOH), 8.01 (d, 1 H, $J = 7.8$ Hz, ArH), 7.78 (dd, 1 H, $J = 7.8$, 8.3 Hz, ArH), 7.39 (d, 1 H, $J = 8.3$ Hz, ArH), 5.32 (d, 1 H, $J = 3.4$ Hz, $C_{7eq}H$), 4.11 (s, 3 H, C_4OCH_3), 3.15 (d, 1 H, $J = 18.5$ Hz, $C_{10eq}H$), 2.90 (d, 1 H, $J = 18.5$ Hz, $C_{10ax}H$), 2.45 (s, 3 H, $C_{14}CH_3$), 2.35 (d, 1 H, $J = 14.5$ Hz, $C_{8eq}H$), 2.15 (dd, 1 H, $J = 3.4$, 14.5 Hz, $C_{8ax}H$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.91, 185.86, 185.73, 160.56, 155.69, 154.62, 137.04, 135.94, 134.22, 133; UV (CH_3OH) λ_{max} (log ε) 202 (0.34), 258 (0.11), 267 (0.11).

Daunomycinone-14-bromide (5). Trimethylorthoformate (0.20 mL, 1.83 mmol) was added to a solution of daunomycin hydrochloride, **2** (0.20 g, 0.35 mmol) dissolved in methanol/1,4-dioxane (v/v = 1 : 2, 12 mL). The reaction mixture was stirred at room temperature for 20 min. To the mixture was added a $Br_2/CHCl_3$ (w/v = 1 : 9, 2.24 mL, 1.42 mmol) solution, and the mixture was then stirred for 6 h at 30°C. The mixture was concentrate in vacuo to give red residue **5** (0.15 g, 92%). Mp 198–200°C; $[\alpha]_D^{20} + 158.2^{\circ}$ (c 0.1, dioxane); IR (KBr) 3427, 2949, 1730, 1618, 1579, 1419, 1379, 1288, 1264, 1208, 1089, 1014, 991, 787 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.87 (s, 1 H, PhOH), 13.13 (s, 1 H, PhOH), 7.83 (m, 1 H, ArH), 7.57 (m, 1 H, ArH), 5.46 (s, 1 H, C_9OH), 5.07 (d, 1 H, $J = 17.7$ Hz, $C_{14}H$), 5.01 (d, 1 H, $J = 3.4$ Hz, $C_{7eq}H$), 4.96 (d, 1 H, $J = 17.7$ Hz, $C_{14}H$), 3.95 (s, 3 H, C_4OCH_3), 3.04 (d, 1 H, $J = 18.9$ Hz, $C_{10eq}H$), 2.78 (d, 1 H, $J = 18.9$ Hz,

$C_{10ax}H$), 2.26 (d, 1 H, $J = 14.0$ Hz, $C_{8eq}H$), 1.94 (dd, 1 H, $J = 3.4$, 14.0 Hz, $C_{8ax}H$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 205.69, 186.19, 186.08, 160.68, 155.64, 154.62, 136.87, 136.06, 134.47, 132.88, 119.77, 119.55, 118.85, 110.62, 110.39, 76.81, 60.27, 56.48, 47.91, 36.09, 32.58; UV (CH_2Cl_2) λ_{max} (log ε) 234 (0.26), 253 (0.14), 288 (0.05); Mass (FAB^+, Na) m/z 863 $(M + Na)^+$.

Doxorubicinone-14-acetate (6). A solution of 14-bromodaunomycinone, **5** (0.05 g, 0.11 mmol) and sodium acetate (0.03 g, 0.21 mmol) in acetone (50 mL) was refluxed for 6 h. Upon completion of the reaction the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (100 mL), washed with water (2 × 100 mL) and brine (2 × 100 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/Hexane/CH_3OH, 10 : 4 : 1) to give doxorubicinone-14-acetate, **6** (46.0 mg, 96%) as a pale red powder. Mp 242–243°C $[\alpha]_D^{20} + 192.9°$ (c 0.1, dioxane); IR (KBr) 3846, 3744, 3620, 2763, 2362, 1741, 1707, 1694, 1645, 1549, 1532, 1517, 1232, 677 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 13.86 (s, 1 H, PhOH), 13.32 (s, 1 H, PhOH), 7.93 (d, 1 H, $J = 7.8$ Hz, ArH), 7.73 (dd, 1 H, $J = 7.8$, 8.3 Hz, ArH), 7.35 (d, 1 H, $J = 8.3$ Hz, ArH), 5.60 (s, 1 H, C_9OH), 5.26 (d, 1 H, $J = 17.1$ Hz, $C_{14}H$), 5.12 (d, 1 H, $J = 17.1$ Hz, $C_{14}H$), 4.84 (d, 1 H, $J = 3.4$ Hz, $C_{7eq}H$), 4.05 (s, 3 H, C_4OCH_3), 3.44 (s, 1 H, C_7OH), 3.21 (d, 1 H, $J = 18.5$ Hz, $C_{10eq}H$), 2.97 (d, 1 H, $J = 18.5$ Hz, $C_{10ax}H$), 2.41 (d, 1 H, $J = 14.5$ Hz, $C_{8eq}H$), 2.91 (dd, 1 H, $J = 3.4$, 14.5 Hz, $C_{8ax}H$), 2.15 (s, 3 H, $C_{14}OAc$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 204.57, 186.60, 186.39, 170.15, 160.68, 156.43, 155.02, 136.07, 135.32, 119.31, 118.22, 111.04, 110.95, 75.34, 70.29, 64.57, 57.28, 56.45, 56.41, 37.02, 31.97, 29.05, 20.35; UV (CH_2Cl_2) λ_{max} (log ε) 234 (0.15), 253 (0.09), 288 (0.04); Mass (FAB^+, Na) m/z 863 $(M + Na)^+$.

Daunomycinone-7-methyl(tri-*O*-acetyl ester)-α-D-glucuronide (DM7αGa, 8a) and daunomycinone-7-methyl(tri-*O*-acetyl ester)-β-D-glucuronide (DM7βGa, 8b). A mixture of daunomycinone, **4** (0.30 g, 0.75 mmol), yellow HgO (0.90 g, 4.14 mmol), $HgBr_2$ (0.43 g, 1.13 mmol), and powdered molecular sieves 3 Å (1.0 g, activated at 350°C under a stream of N_2) in dry CH_2Cl_2 (50 mL) was stirred for 30 min at room temperature. After glucopyranosyl bromide **7** (0.43 g, 1.13 mmol) in dry CH_2Cl_2 (5.0 mL) was added, the mixture was refluxed for 17 h in a dark place. In TLC (CH_2Cl_2/acetone = 10 : 1), the mixture showed spots at R_f 0.7 (**8a**, minor), 0.6 (**8b**, major), and 0.3 (daunomycinone, slight) along with several minor spots. The mixture was filtered through a celite bed, the bed being washed repeatedly with CH_2Cl_2. The filtrate and washings combined were washed with aqueous 30% KI, saturated aqueous $NaHCO_3$, and water, then dried ($MgSO_4$) and concentrated. The residue was purified by

column chromatography on silica gel (CH_2Cl_2/acetone = 10 : 1) to give DM7αGa, **8a** (0.12 g, 22%) and DM7βGa, **8b** (0.28 g, 52%) as a red powder. DM7αGa (**8a**): Mp 115–117°C; $[\alpha]_D^{20} + 72.01°$ (c 0.1, CH_2Cl_2); IR (KBr) 3450, 2990, 2900, 1765, 1711, 1610, 1550, 1455, 1431, 1268, 1250, 1190, 1130, 1010, 850, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 14.04 (s, 1 H, PhOH), 13.24 (s, 1 H, PhOH), 8.02 (d, 1 H, $J = 7.8$ Hz, ArH), 7.79 (dd, 1 H, $J = 7.8$, 8.3 Hz, ArH), 7.40 (d, 1 H, $J = 8.3$ Hz, ArH), 5.95 (d, 1 H, $J = 4.9$ Hz, $C_{1'}H$), 5.54 (s, 1 H, $C_{7eq}H$), 5.23 (t, 1 H, $J = 7.3$, $C_{3'}H$), 5.17 (d, 1 H, $J = 7.8$, $C_{4'}H$), 4.81 (s, 1 H, C_9OH), 4.52 (dd, 1 H, $J = 3.4$, 6.8 Hz, $C_{2'}H$), 4.31 (d, 1 H, $J = 7.8$ Hz, $C_{5'}H$), 4.08 (s, 3 H, C_4OCH_3), 3.79 (s, 3 H, $COOCH_3$), 3.17 (d, 1 H, $J = 18.6$ Hz, $C_{10eq}H$), 3.05 (d, 1 H, $J = 18.6$ Hz, $C_{10ax}H$), 2.56 (d, 1 H, $J = 15.1$ Hz, $C_{8eq}H$), 2.40 (s, 3 H, $C_{14}CH_3$), 2.38 (s, 3 H, sugar OAc), 2.12 (s, 3 H, sugar OAc), 2.10 (s, 3 H, sugar OAc), 2.00 (dd, 1 H, $J = 4.4$, 15.1 Hz, $C_{8ax}H$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.52, 187.14, 186.88, 169.32, 168.77, 168.68, 161.02, 155.80, 155.47, 135.68, 135.45, 135.30, 133.24, 123.78, 122.95, 120.91, 119.77, 118.45, 111.54, 111.48, 96.38, 73.37, 71.87, 70.73, 70.29, 69.04, 68.05, 63.99, 56.66, 52.81, 34.14, 29.95, 24.71, 20.72; UV (CH_2Cl_2) λ_{max} (log ε) 235 (2.50), 250 (1.54), 482 (1.01); Mass (FAB^+, Na) m/z 736.8 $(M + Na)^+$. DM7βGa (**8b**): Mp 215–220°C $[\alpha]_D^{20} + 162.29°$ (c 0.1, CH_2Cl_2); IR (KBr) 3500, 3010, 2980, 2950, 1791, 1749, 1651, 1590, 1475, 1405, 1363, 1265, 1190, 1110, 1050, 991, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 14.03 (s, 1 H, PhOH), 13.22 (s, 1 H, PhOH), 8.26 (d, 1 H, $J = 7.3$ Hz, ArH) 7.89 (dd, 1 H, $J = 7.3$, 8.3 Hz, ArH), 7.63 (d, 1 H, $J = 8.3$ Hz, ArH), 5.40 (s, 1 H, $C_{7eq}H$), 5.31 (t, 1 H, $J = 9.3$ Hz, $C_{3'}H$), 5.24 (dd, 1 H, $J = 9.3$, 9.8 Hz, $C_{4'}H$), 5.15 (d, 1 H, $J = 7.8$ Hz, $C_{1'}H$), 4.97 (dd, 1 H, $J = 7.3$, 9.3 Hz, $C_{2'}H$), 4.19 (s, C_9-OH), 4.16 (d, 1 H, $J = 9.8$ Hz, $C_{5'}H$), 4.10 (s, 3 H, C_4OCH_3), 3.79 (s, 3 H, CO_2CH_3), 3.22 (d, 1 H, $J = 19.1$ Hz, $C_{10eq}H$), 2.99 (d, 1 H, $J = 19.1$ Hz, $C_{10ax}H$), 2.61 (d, 1 H, $J = 14.7$ Hz, $C_{8eq}H$), 2.45 (s, 3 H, $C_{14}CH_3$), 2.17 (s, 6 H, sugar OAc), 2.09 (dd, 1 H, $J = 4.9$, 14.5 Hz, $C_{8ax}H$), 2.05 (s, 3 H, sugar OAc); ^{13}C NMR (400 MHz, $CDCl_3$) δ 213.57, 187.56, 187.16, 170.30, 169.78, 167.46, 161.54, 156.54, 156.26, 136.40, 136.20, 136.00, 132.95, 121.35, 120.29, 118.88, 111.95, 111.75, 101.60, 72.83, 72.04, 71.44, 70.35, 69.90, 58.87, 57.12, 53.33, 35.57, 33.86, 25.44, 21.04, 20.95, 20.88, 18.83; UV (CH_2Cl_2) λ_{max} (log ε) 233 (1.78), 252 (1.01), 483 (0.48); Mass (FAB^+, Na) m/z 736.8 $(M + Na)^+$.

14-Acetoxydoxorubicinone-7-methyl(tri-*O*-acetyl ester)-α-D-glucuronide (DX7αGa, 9a) and 14-acetoxydoxorubicinone-7-methyl(tri-*O*-acetyl ester)-β-D-glucuronide ((DX7βGa, 9b). A mixture of 14-acetoxydoxorubicinone, **6** (0.25 g, 0.55 mmol), yellow HgO (0.65 g, 3.01 mmol), $HgBr_2$ (0.22 g, 0.60 mmol), and powdered molecular sieves 3 Å (1.5 g, activated at 350°C

under a stream N_2) in dry CH_2Cl_2 (60 mL) was stirred for 30 min at room temperature. After glucopyranosyl bromide **7** (0.33 g, 0.82 mmol) in dry CH_2Cl_2 (5.5 mL) was added, the mixture was refluxed for 36 h in a dark place. In TLC (CH_2Cl_2/acetone = 10 : 1), the mixture showed spots at R_f 0.6 (**9a**, minor), 0.5 (**9b**, major), and 0.2 (14-acetoxydoxorubicinone, slight) along with several minor spots. The mixture was filtered through a celite bed, the bed being washed repeatedly with CH_2Cl_2. The filtrate and washings combined were washed with aqueous 30% KI, saturated aqueous $NaHCO_3$, and water, then dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (CH_2Cl_2/acetone = 10 : 1) to give DX7αGa, **9a** (0.09 g, 21%) and DX7βGa, **9b** (0.20 g, 48%) as a red powder. DX7αGa (**9a**): Mp 118–120°C; $[\alpha]_D^{20}$ +98.12° (c 0.1, CH_2Cl_2); IR (KBr) 3054, 2986, 2685, 2305, 1754, 1606, 1550, 1422, 1259, 896, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 13.95 (s, 1 H, PhOH), 13.20 (s, 1 H, PhOH), 8.03 (d, 1 H, J = 7.8 Hz, ArH), 7.79 (dd, 1 H, J = 7.8, 8.3 Hz, ArH), 7.40 (d, 1 H, J = 8.3 Hz, ArH), 6.31 (d, 1 H, J = 3.4 Hz, $C_{1'}H$), 5.56 (s, 1 H, C_9OH), 5.36 (d, 1 H, J = 18.6 Hz, $C_{14}H$), 5.34 (m, 1 H, $C_{3'}H$), 5.21 (m, 1 H, $C_{4'}H$), 5.15 (d, 1 H, J = 18.6 Hz, $C_{14}H$), 4.92 (dd, 1 H, J = 2.9, 9.8 Hz, $C_{2'}H$), 4.71 (s, 1 H, $C_{7eq}H$), 4.33 (d, 1 H, J = 9.7 Hz, $C_{5'}H$), 4.09 (s, 3 H, C_4OCH_3), 3.75 (s, 3 H, $COOCH_3$), 3.28 (d, 1 H, J = 18.6 Hz, $C_{10eq}H$), 2.97 (d, 1 H, J = 18.6 Hz, $C_{10ax}H$), 2.49 (d, 1 H, J = 15.1 Hz, $C_{8eq}H$), 2.23 (dd, 1 H, J = 15.1, 4.4 Hz, $C_{8ax}H$), 2.21 (s, 3 H, $C_{14}OAc$), 2.09 (s, 3 H, sugar OAc), 2.06 (s, 3 H, sugar OAc), 2.03 (s, 3 H, sugar OAc); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.62, 187.60, 187.04, 170.80, 169.94, 169.70, 169.67, 167.17, 161.50, 156.54, 155.88, 136.29, 135.97, 135.50, 134.10, 122.12, 120.29, 118.86, 112.04, 111.96, 111.69, 73.34, 73.08, 71.35, 71.08, 69.89, 69.52, 68.93, 68.71, 66.53, 62.74, 35.89, 33.99, 22.16, 21.04, 20.86; UV (CH_2Cl_2) λ_{max} (log ε) 237 (2.20), 255 (1.61), 481 (0.75); Mass (FAB^+, Na) m/z 794.8 $(M + Na)^+$. DX7βGa (**9b**): Mp 210–213°C $[\alpha]_D^{20}$ +158.98° (c 0.1, CH_2Cl_2); IR (KBr) 3536, 2957, 1755, 1618, 1581, 1440, 1375, 1225, 1043, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 14.04 (s, 1 H, PhOH), 13.16 (s, 1 H, PhOH), 8.02 (d, 1 H, J = 7.8 Hz, ArH), 7.79 (dd, 1 H, J = 7.8, 8.3 Hz, ArH), 7.40 (d, 1 H, J = 8.3 Hz, ArH), 5.39 (s, 1 H, C_9OH), 5.37 (d, 1 H, J = 18.6 Hz, $C_{14}H$), 5.30 (t, 1 H, J = 9.3 Hz, $C_{3'}H$), 5.23 (dd, 1 H, J = 9.8, 9.3 Hz, $C_{4'}H$), 5.20 (d, 1 H, J = 18.6 Hz, $C_{14}H$), 5.14 (d, 1 H, J = 7.8 Hz, $C_{1'}H$), 4.95 (dd, 1 H, J = 9.3, 7.8 Hz, $C_{2'}H$), 4.72 (s, 1 H, $C_{7eq}H$), 4.17 (d, 1 H, J = 9.8 Hz, $C_{5'}H$), 4.09 (s, 3 H, C_4OCH_3), 3.80 (s, 3 H, $COOCH_3$), 3.24 (d, 1 H, J = 19.0 Hz, $C_{10eq}H$), 2.98 (d, 1 H, J = 19.0 Hz, $C_{10ax}H$), 2.26 (d, 1 H, J = 14.0 Hz, $C_{8eq}H$), 2.20 (s, 3 H, $C_{14}OAc$), 2.09 (dd, 1 H, J = 14.0, 3.4 Hz, $C_{8ax}H$), 2.05 (s, 3 H, sugar OAc), 2.00 (s, 3 H, sugar OAc), 1.84 (s, 3 H, sugar OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.57, 187.09, 186.64, 170.35, 169.92, 169.52, 169.46, 167.04, 161.08, 155.97,

155.67, 135.90, 135.44, 135.30, 132.14, 120.73, 119.89, 118.53, 111.55, 111.36, 101.21, 77.24, 76.62, 72.38, 71.51, 70.96, 69.96, 69.42, 66.43, 56.73, 53.06, 35.27, 33.61, 20.59, 20.53, 20.52; UV (CH_2Cl_2) λ_{max} (log ε) 236 (3.15), 251 (2.52), 483 (1.38); Mass (FAB^+, Na) m/z 794.8 $(M + Na)^+$.

Daunomycinone-7-*a*-D-glucuronide (DM7αG, 10a). DM7αGa, **8a** (0.18 g, 0.25 mmol) was dissolved in 18 mL of MeOH/H_2O/THF (5/2/1, v/v) and 15.1 mL (6.0 equiv) of 0.1 N LiOH/H_2O solution was added at 0°C. The resulting deep blue solution was stirred at 0°C under argon atmosphere. Progress of the deprotection was monitored on reversed-phase TLC (SiO_2-C_{18}, MeCN/H_2O, 1/2). After 2 h of deprotection, the reaction mixture was diluted with 15 mL of H_2O and neutralized by adding ca. 0.50 g of amberlite cation exchange material (H^+ form); 2 mL of THF was added to homogenize the suspension. The amberlite resin was removed by filtration. The MeOH and THF suspended in the water layer were removed by evaporation, and red aqueous product solution was transferred to a reversed phase column packed with RP-C_{18} material and eluted with MeCN/H_2O (1 : 3) to purification. The solvents were removed under reduced pressure to give DM7αG, **10a** (1.4 mg, 0.98%) as a red solid. Mp 156–157°C; IR (KBr) 3286, 2922, 2890, 1726, 1614, 1396, 1263, 1217, 1053, 905, 748 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.78 (bs, 1 H, ArH), 7.51 (m, 2 H, ArH), 5.46 (d, 1 H, J = 4.2 Hz, $C_{1'}H$), 5.39 (s, 1 H, $C_{7eq}H$), 4.05 (d, 1 H, J = 10.2 Hz, $C_{5'}H$), 3.97 (s, 3 H, C_4OMe), 3.75 (m, 2 H, $C_{3'}H$, $C_{4'}H$), 3.52 (m, 1 H, $C_{2'}H$), 2.95 (d, 1 H, J = 18.1 Hz, $C_{10eq}H$), 2.71 (d, 1 H, J = 14.2, $C_{8eq}H$), 2.60 (d, 1 H, J = 18.1 Hz, $C_{10ax}H$), 2.43 (s, 1 H, $C_{14}CH_3$), 2.04 (d, 1 H, J = 14.2 Hz, $C_{8ax}H$); Mass (FAB^+, Na) m/z 596.7 $(M + Na)^+$.

Daunomycinone-7-β-D-glucuronide (DM7βG, 10b). Following the above procedure described for **10a**, reaction of DM7βGa, **8b** (0.09 g, 0.13 mmol) with 0.1 N LiOH (7.6 mL, 0.76 mmol) in 12 mL of MeOH/H_2O/THF (5/2/1, v/v) yielded 56.4 mg (78%) of solid **10b**. Mp 166–168°C; $[\alpha]_D^{20}$ +79.87° (c 0.1, H_2O + MeOH); IR (KBr) 3480, 3210, 2910, 2880, 1715, 1698, 1392, 1248, 1229, 1190, 1045, 1011, 991, 898, 798, 772 cm^{-1}; ^1H NMR (400 MHz, Methanol-d_4) δ 7.38 (bs, 1 H, ArH), 7.09 (m, 2 H, ArH), 5.21(s, 1 H, $C_{7eq}H$), 4.80 (d, 1 H, J = 7.2 Hz, $C_{1'}H$), 3.67 (d, 1 H, J = 9.3 Hz, $C_{5'}H$), 3.64 (s, 3 H, C_4OMe), 3.41 (m, 2 H, $C_{3'}H$, $C_{4'}H$), 3.20 (dd, 1 H, J = 7.8, 8.3 Hz, $C_{2'}H$), 2.64 (d, 1 H, J = 17.6 Hz, $C_{10eq}H$), 2.47 (d, 1 H, J = 14.7, $C_{8eq}H$), 2.27 (bs, 4 H, $C_{10ax}H$, $C_{14}CH_3$), 1.77 (d, 1 H, J = 15.1 Hz, $C_{8ax}H$); ^{13}C NMR (400 MHz, Methanol-d_4) δ 212.98, 186.63, 186.34, 173.03, 160.94, 155.94, 155.62, 135.75, 135.57, 135.08, 132.21, 120.35, 119.61, 118.43, 111.36, 111.26, 104.27, 77.61, 76.18, 75.29, 74.31, 73.38, 60.41, 56.62, 34.00, 32.53, 24.80; UV (H_2O) λ_{max} (log ε) 230 (2.40), 251 (1.53), 479 (0.79); Mass (FAB^+, Na) m/z 596.7 $(M + Na)^+$.

Doxorubicinone-7-α-D-glucuronide (DX7αG, 11a). Following the above procedure described for **10a**, reaction of DM7βGa, **9a** (0.11 g, 0.14 mmol) with 0.1 N LiOH (10.0 mL, 0.10 mmol) in 16 mL of MeOH/H_2O/THF (5/2/1, v/v) yielded 28.6 mg (34%) of solid **11a**. Mp 184–187°C; $[\alpha]_D^{20} + 53.29°$ (c 0.1, H_2O + MeOH); IR (KBr) 3427, 2922, 2861, 1957, 1741, 1625, 1516, 1430, 1376, 1249, 11044, 897, 767, 720, 602 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.55 (t, 1 H, $J = 8.0$ Hz, ArH), 7.37 (bs, 1 H, ArH), 7.27 (d, 1 H, $J = 7.7$, ArH), 5.79 (d, 1 H, $J = 4.8$ Hz, $C_{1'}H$), 5.09 (s, 1 H, $C_{7eq}H$), 4.91 (m, 2 H, $C_{14}H$), 3.78 (s, 3 H, C_4OMe), 3.69 (d, 1 H, $J = 9.6$ Hz, $C_{5'}H$), 3.43 (m, 2 H, $C_{3'}H$, $C_{2'}H$), 3.18 (dd, 1 H, $J = 9.6$, 8.8 Hz $C_{4'}H$), 2.77 (d, 1 H, $J = 18.0$ Hz, $C_{10eq}H$), 2.52 (d, 1 H, $J = 15.2$, $C_{8eq}H$), 2.40 (d, 1 H, $J = 18.0$ Hz, $C_{10ax}H$), 2.01 (d, 1 H, $J = 15.2$ Hz, $C_{8ax}H$; ^{13}C NMR (400 MHz, D_2O) δ 210.06, 187.90, 186.81, 172.10, 166.51, 163.48, 161.20, 160.30, 139.90, 138.78, 131.20, 130.86, 126.56, 121.79, 120.87, 120.65, 118.95, 101.10, 77.16, 73.98, 72.87, 72.68, 71.23, 65.43, 63.18, 56.81, 31.29, 30.26; UV (H_2O) λ_{max} (log ε) 238 (1.97), 249 (1.13), 477 (0.45); Mass (FAB^+, Na) m/z 612.9 $(M + Na)^+$.

Doxorubicinone-7-β-D-glucuronide (DX7βG, 11b). Following the above procedure described for **10a**, reaction of DM7βGa, **9b** (0.12 g, 0.16 mmol) with 0.1 N LiOH (10.9 mL, 1.09 mmol) in 18 mL of MeOH/H_2O/THF (5/2/1,v/v) yielded 51.4 mg (56%) of solid **11b**. Mp 170–172°C (decomp); $[\alpha]_D^{20}$ +96.56° (c 0.1, H_2O + MeOH); IR (KBr) 3400, 2919, 2843, 1960, 1733, 1617, 1584, 1413, 1281, 1235, 1061, 797 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 7.45 (bs, 1 H, ArH), 7.18 (bs, 2 H, ArH), 4.77 (d, 1 H, $J = 7.6$ Hz, $C_{1'}H$), 4.67 (m, 3 H, $C_{7eq}H$, $C_{14}H$), 3.69 (s, 3 H, C_4OMe), 3.66 (d, 1 H, $J = 8.8$ Hz, $C_{5'}H$), 3.41 (m, 2 H, $C_{3'}H$, $C_{2'}H$), 3.19 (dd, 1 H, $J = 8.4$, 8.0 Hz $C_{4'}H$), 2.75 (d, 1 H, $J = 18.4$ Hz, $C_{10eq}H$), 2.54 (d, 1 H, $J = 15.6$, $C_{8eq}H$), 2.31 (d, 1 H, $J = 18.4$ Hz, $C_{10ax}H$), 1.82 (dd, 1 H, $J = 14.0$, 4.0 Hz, $C_{8ax}H$; ^{13}C NMR (400 MHz, D_2O) δ 210.21, 188.24, 187.16, 173.24, 162.36, 159.12, 159.07, 136.18, 134.87, 133.68, 133.17, 123.36, 121.68, 120.99, 120.87, 119.16, 103.36, 78.13, 76.87, 75.96, 73.98, 70.30, 64.17, 63.90, 61.76, 56.17, 32.98, 32.76; UV (H_2O) λ_{max} (log ε) 241 (2.21), 251 (1.40), 479 (0.56); Mass (FAB^+, Na) m/z 612.9 $(M + Na)^+$.

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