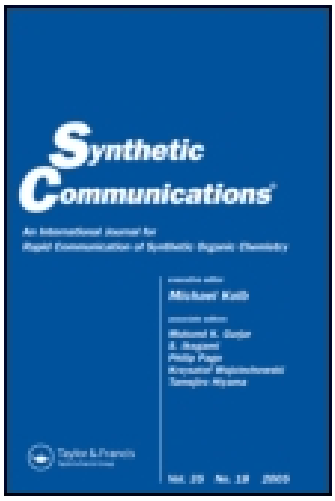

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Young S. Rho [a], Siho Park [a], Wan-Joong Kim [a], Gyuil Kim [a], Dong Jin Yoo [b], Heun-Soo Kang [c] & Soon-Ryang Chung [d]

[a] Department of Chemistry, Chonbuk National University, Chonju, 561-756, Korea

[b] Department of Chemistry, Seonam University, Namwon, 590-711, Korea

[c] Metabolic Engineering Laboratories Co., Ltd., 28 Yongon-Dong, Chongno-Gu, Seoul, 110-799, Korea

[d] Department of Chemistry, Woosuk University, Wanju, 565-701, Korea

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SYNTHESIS OF NEW ANTHRACYCLINE DERIVATIVES CONTAINING PYRUVIC, ASPARTIC, OR *N*-ACETYLASPARTIC ACID MOLECULE

Young S. Rho,[1,*] Siho Park,[1] Wan-Joong Kim,[1] Gyuil Kim,[1] Dong Jin Yoo,[2] Heun-Soo Kang,[3] and Soon-Ryang Chung[4]

[1]Department of Chemistry, Chonbuk National University, Chonju 561-756, Korea
[2]Department of Chemistry, Seonam University, Namwon 590-711, Korea
[3]Metabolic Engineering Laboratories Co., Ltd., 28 Yongon-Dong, Chongno-Gu, Seoul 110-799, Korea
[4]Department of Chemistry, Woosuk University, Wanju 565-701, Korea

ABSTRACT

The new anthracycline analogues (**2–10**) as potential anticancer agents were synthesized from daunomycin (**1a**) and doxorubicin (**1b**). Compounds **2**, **6**, and **7** were prepared by the nucleophilic displacement type esterification of a 14-bromodaunomycin (**1c**) with a sodium pyruvate, aspartate, and

*Corresponding author. Fax: +82-63-270-3408; E-mail: ysrho@moak.chonbuk.ac.kr

N-acetylaspartic acid, respectively. Whereas compounds (**3**, **8**) and (**4**, **9**) were prepared by the reaction of daunomycin (**1a**) or doxorubicin (**1b**) with one equivalent of the corresponding acids in the presence of EDCI/PP, compounds (**5**, **10**) were obtained from **1b** by reaction with two equivalents of the corresponding acids in the same manner.

The anticancer antibiotics daunomycin (**1a**) and doxorubicin (**1b**) (Figure 1) are the most representative examples of the anthracycline series developed as antitumor agents and widely used intercalating drugs for the treatment of several types of human cancers. Particularly, doxorubicin (**1b**) is of growing current interest because of its powerful activity against major solid tumors.[1] Doxorubicin (**1b**) having broader activity spectrum and less toxicity than daunomycin (**1a**) is currently the most active and widely used agent in anticancer drugs against breast, bladder, lung, thyroid, ovary, osteogenic, sarcoma, wilm's tumor, neuroblastoma, Hodgkin's disease, lymphomas, leukemia cancer, etc.[2] In biological and clinical studies, **1a** has been also known to restrict the virus multiplication because of its strong activity against solid and ascite tumors. However, their uses for cancer chemotherapy have severely still lots of limitation by cytotoxicity and other undesirable side effects.[3] Moreover, the clinical utility of **1a** is frequently restricted by the appearance of the cardiotoxicity originated in the damage of normal cell by oxygen radical.[4–7] For this reason, numerous synthetic efforts have been devoted to overcome these disadvantages culminating in the development of daunomycin (**1a**) or doxorubicin (**1b**) derivatives.[8–11]

Anthracyclines containing a pyruvic or aspartic acid residue are expected to be good potential delivery drugs as well as give a protection role of oxidative tissue damage depending on radical.[12] Recently, there

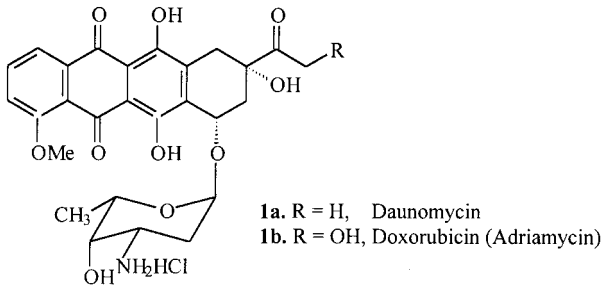


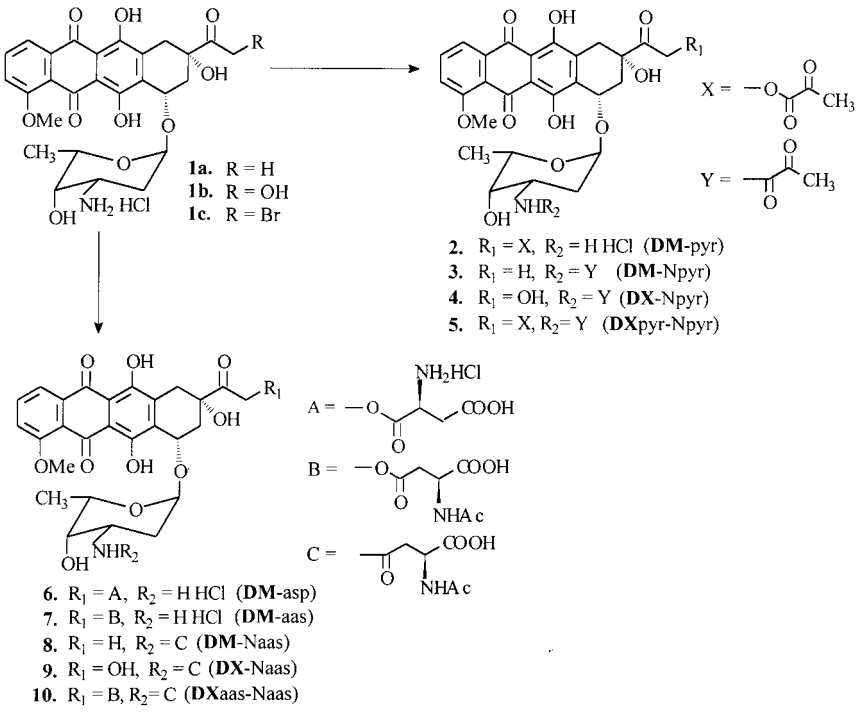
Figure 1. Structures of two clinically used daunomycin (**1a**) and doxorubicin (**1b**).

were many reported examples of coupling **1a** or **1b** with some amino acids as well as blending **1a** or **1b** with some acids.[8] For example, DA-125 including an β-alanine developed by Dong-A Pharmaceutical Co., Ltd. (KR) was prepared by nucleophilic substitution with a *N*-Boc-β-alanine sodium salt and a C-14 bromodaunomycin. The DA-125 prodrug was found to have higher anticancer activity and less cardiotoxicity than **1a** and **1b**.[9] In this report, we describe the synthesis of some new anthracycline analogues by coupling **1a** (or **1b**) with pyruvic, aspartic acid, or *N*-acetylaspartic acid expecting to obtain compounds with less toxicity than anything else previously developed.

In the precedent publications, we frequently used Michael-type condensation[13–16] or Friedel-Crafts acylation[17,18] for the total synthesis of anthracyclinone derivatives. Here, we report the successful preparation of a new aglycon containing an ester linkage at C-14 through a nucleophilic displacement esterification method.[18] In connection with recent studies towards the development of a new 7-deoxyidarubicinone derivative through functionalization of the C-14 site in the aglycon, we wished to prepare some new anthracycline analogues starting directly from commercially available anticancer glycosides such as daunomycin (DM, **1a**) or doxorubicin (DX, **1b**). Several new anthracycline derivatives were synthesized using two esterification methods (Scheme 1). All compounds **2–10** were obtained through acylation of the C-14 hydroxyl group in the aglycon and/or the amine group at C-3′ in the glycon moiety with aspartic, pyruvic, or *N*-acetylaspartic acid. Clearly different reaction patterns were observed for the individual carboxylic acids.

DM-pyr (**2**) and DM-asp (**6**) were prepared by the nucleophilic displacement type esterification of 14-bromo DM (**1c**) with the corresponding acid sodium salts. The synthesis of 14-bromo DM (**1c**) was accomplished by the known procedure:[19,20] **1c** was synthesized in best yield when a minimum quantity of co-solvent (methanol/1,4-dioxane, v/v = 1 : 2) was used which diminished the formation of side product from dimethylketalization of ketone at C-13. The rate of bromination depended on the reaction temperature and time. The optimal conditions are bromination at 30°C for 40 min. After esterification of 14-bromo DM (**1c**) with 12 equivalents of pyruvic acid sodium salt,[18] product separation by column chromatography on silica gel ($CH_2Cl_2/CH_3OH/HCO_2H/H_2O = 88/15/2/1$) followed by the treatment with etheral HCl afforded DM-pyr (**2**, 59%) as a red solid.

All our attempts to prepare DM-asp (**6**) through nucleophilic displacement type esterification of 14-bromo DM (**1c**) with the sodium or potassium salts of aspartic acid in various solvents were not successful. Only the aglycon was obtained.[21–23] Protection of the amino group in sodium aspartic acid with di-*tert*-butyldicarbonate and reaction of the *N*-BOC-aspartic acid sodium salt with **1c** gave daunomycin-14-(*N*-Boc)-aspartate



Scheme 1. Synthesis of new anthracycline analogues **2–10**.

in relatively low yield (<50%). After removing the BOC group with CF_3CO_2H at −20°C and treatment with methanolic HCl,[24] DM-asp (**6**) (total 34%) was obtained as a red solid. Prolonged reaction times in the CF_3CO_2H deprotecting of the BOC group led to the cleavage of the glycosidic bond. Therefore, evaporation of reaction solvent within 20 min is necessary to avoid hydrolysis of the amino sugar moiety. The reaction of **1a** or **1b** with aspartic acid or its acid sodium salt furnished only compound **6**.

Many attempts to prepare DM-Npyr (**3**) and DX-Npyr (**4**) through direct coupling of the NH_2·HCl group in daunomycin (**1a**) or doxorubicin (**1b**) with pyruvic acid using DCC/DMAP[25] failed. Reactants and reduced DCU (dicyclohexylurea) were observed as main products. Eventually, DM-Npyr (**3**) and DX-Npyr (**4**) were synthesized by coupling of the NH_2·HCl group in **1a** and **1b** with pyruvic acid using using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and 4-pyrrolidinopyridine (PP) as catalysts.[26,27] However, for the reaction

of **1b** competition between the hydroxyl at C-14 and the amino group was observed. Both products DX-Npyr **4** and DXpyr-Npyr **5** formed, the product ratio depended on the amounts of pyruvic acid and EDCI used in the reaction.

All coupling reactions of **1a** or **1b** with *N*-acetyl-L-aspartic acid were very easily accomplished. DM-aas (**7**) was prepared from **1c** by reaction with *N*-acetyl-L-aspartic acid in triethylamine without using any coupling reagent. However, DM-Naas (**8**), DX-Naas (**9**), and DXaas-Naas (**10**) were synthesized using EDCI as coupling reagent. In all these cases, only one isomer was obtained pure as Kovach's results.[28] The reaction of *N*-acetyl-L-aspartic acid with the corresponding aglycon furnished β-aspartic acid esters (**7**, **8**, **9**, and **10**) rather than α-aspartic acid esters because the L-aspartic acid has bulky *N*-acetyl group on the α-amine moiety. Synthesis of DX-Naas (**9**) and DXaas-Naas (**10**) was carried out as follow: *N*-Acetyl-L-aspartic acid (1.2 eq.) and EDCI (2.0 eq.) was dissolved in dry DMF and the mixture was stirred at 0°C for 30 min; to the reaction mixture was added DX (**1b**) and catalytic amounts of PP, and the resulting solution was stirred at room temperature for 5 h to give DX-Naas (**9**). DXaas-Naas (**10**) was prepared using 2.2 equivalent of the corresponding acid and EDCI (2.5 eq.) in the same manner.

The cytotoxic activities of anthracycline derivatives **2–10** against two kinds of human tumor cells (SNU-16 and MCF-7) and their adriamycin-resistant cell lines are shown in Table 1. It showed that compounds **2** and **7** exhibited cytotoxicity activity equivalent to adriamycin against SNU-16 and MCF7 cell lines, but compound **6** was much lower cytotoxic than free drug against SNU-16 and MCF7 cell lines. In addition, the others (**3–5** and **7–10**) exhibited very low antitumor activity compared with the reference. These results indicate that acylation of C-14 OH (**2**, **7**) maintains the activity inherent in the parent anthracycline antibiotics, whereas amidation of 3′-NH_2 (**3–5** and **8–10**) causes a decrease in the antibiotic activity.

In conclusion, we have synthesized the new anthracycline analogues expected to exhibit biologically activity and low cardiotoxicity[29] as potential anticancer agents through the esterification reactions. Further detailed biological tests of the title glycosides in vitro will be reported elsewhere sooner or later.

EXPERIMENTAL SECTION

All reactions were carried out under argon atmosphere in dried glassware. Solvents were carefully dried and distilled as reported.[30] Bulk grade hexane was distilled prior to use. Merck pre-coated silica gel plates (Art.5554) with fluorescent indicator were used as analytical TLC. Flash

Table 1. The Cytotoxic Activity of the Novel Anthracycline Derivatives (**2–10**) was Tested "In Vitro" in Comparison with Adriamycin on Cultured SNU-16 and MCF-7 Cells

	IC_{50}[c] (μM)			
Agents	SNU-16[a]	SNU-16/Adr	MCF7[b]	MCF7/Adr
Adriamycin	0.16	0.35 (2.19[d])	0.29	0.43 (1.48)
2	0.14	0.38 (2.71)	0.26	0.49 (1.88)
3	28.21	20.55	17.63	19.29
4	25.12	24.28	21.78	20.47
5	32.87	37.96	30.26	20.58
6	21.20	28.35 (1.34)	1.33	3.56 (2.67)
7	0.23	0.78 (3.39)	0.35	0.52 (1.48)
8	34.84	38.15	18.96	22.24
9	30.98	40.63	16.25	20.33
10	37.29	42.54	22.36	30.15

[a]Human stomach adenocarcinoma.
[b]Human breast adenocarcinoma.
[c]Concentration inhibiting colony growth by 50%.
[d]Relative resistance (IC_{50} of resistant cell lines/IC_{50} of parental cell lines).

column chromatography was 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 spectra were recorded on a Nicolet 5-DXB series FT-IR spectrophotometer. Mass spectra were obtained on a JEOL JMS HX-110/110A Tandem mass spectrometer (FAB^{+}, ESI). UV–VIS absorption spectra were recorded on a Hitachi-556 spectrophotometer. Optical rotatory dispersions (ORD) 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 are uncorrected.

14-Bromodaunomycin Hydrochloride (1c)

Trimethylorthoformate (0.20 mL, 1.83 mmol) was added to a solution of daunomycin hydrochloride (**1a**, 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, 0.68 mL, 0.43 mmol) solution, and the mixture was then stirred for 40 min at 30°C. The resulting mixture was poured into dry ether (200 mL), the solid residue was filtered with off and washed with ether (50 mL × 3). The solid was recrystallized from acetone/ether (v/v = 1 : 1, 10 mL), filtered off, washed with ether, and dried over P_2O_5 to give 14-bromo DM (**1c**, 0.19 g, 84%) as a red solid: m.p. 176–177°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.00 (s, 1H, PhOH), 13.30 (s, 1H, PhOH), 7.99 (bs, 2H, NH_2), 7.91 (m, 2H, ArH), 7.89 (m, 1H, ArH), 5.55 (m, 1H, $C_{4'}H$), 5.28 (m, 1H, $C_{7eq}H$), 4.49 (m, 1H, $C_{1'}H$), 4.21 (q, 1H, J = 6.68 Hz, $C_{5'}H$), 4.00 (s, 2H, $C_{14}H$), 3.97 (s, 3H, C_4OCH_3), 3.78 (bs, 1H, $C_{4'}OH$), 3.60 (m, 1H, $C_{3'}H$), 3.05 (d, 1H, J = 18.10 Hz, $C_{10eq}H$), 2.92 (d, 1H, J = 18.10 Hz, $C_{10ax}H$), 2.44 (d, 1H, J = 14.21 Hz, $C_{8eq}H$), 2.07 (dd, 1H, J = 14.21, 5.43 Hz, $C_{8ax}H$), 1.88 (dd, 1H, J = 12.70, 9.00 Hz, $C_{2'eq}H$), 1.85 (d, 1H, J = 12.70 Hz, $C_{2'ax}H$), 1.65 (d, 3H, J = 6.68 Hz, $C_{5'}CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 187.51, 186.11, 169.25, 161.20, 161.01, 160.12, 137.98, 135.80, 134.93, 132.21, 122.01, 120.10, 119.01, 109.90, 105.23, 98.54, 84.56, 73.47, 69.37, 68.01, 55.94, 54.11, 38.42, 37.04, 34.12, 21.20,16.72.

Daunomycin-14-pyruvate Hydrochloride (2)

14-Bromodaunomycin hydrochloride (**1c**, 0.50 g, 0.78 mmol) and pyruvic acid sodium salt (1.03 g, 9.33 mmol) in acetone (800 mL) were refluxed for 15 h. After completing the reaction by monitored on TLC, the solvent was evaporated. To the residue dissolved in dry THF (250 mL) was added etheral HCl, and the mixture was stirred at −20°C for 2 h. The organic solvent was concentrated by a rotary evaporator and purified by column chromatography on silica gel ($CH_2Cl_2/CH_3OH/HCO_2H/H_2O$ = 88 : 15 : 2 :1) to give daunomycin-14-pyruvate hydrochloride (**2**, 0.30 g, 59%) as a red powder: m.p. 178–180°C; $[\alpha]_D^{20}$ + 224.94° (c 0.004, CH_3OH); IR (KBr) 3445, 2939, 1732, 1615, 1584, 1406, 1289, 1215, 1116, 984 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.99 (s, 1H, PhOH), 13.29 (s, 1H, PhOH), 8.26 (bs, 2H, NH_2), 7.91 (m, 2H, ArH), 7.66 (m, 1H, ArH), 5.86 (d, 1H, J = 8.79 Hz, $C_{4'}H$), 5.46 (d, 1H, J = 3.91 Hz, $C_{7eq}H$), 5.31 (d, 1H, J = 18.07 Hz, $C_{14}H$), 5.22 (m, 1H, $C_{1'}H$), 5.12 (d, 1H, J = 18.07 Hz, $C_{14}H$), 4.96 (s, 1H, C_9OH), 4.23 (q, 1H, J = 6.84 Hz, $C_{5'}H$), 3.99 (s, 3H, C_4OCH_3), 3.58 (s, 1H, $C_{4'}OH$), 3.33 (m, 1H, $C_{3'}H$), 3.05 (d, 1H, J = 19.53 Hz, $C_{10eq}H$), 2.80 (d, 1H, J = 19.53 Hz, $C_{10ax}H$), 2.14 (d, 1H, J = 14.65 Hz, $C_{8eq}H$), 2.09 (s, 3H, $C_{17}CH_3$), 2.02 (dd, 1H, J = 14.65, 3.91 Hz, $C_{8ax}H$), 1.88 (dd, 1H, J = 12.70, 9.00 Hz, $C_{2'eq}H$), 1.67 (d, 1H, J = 12.70, $C_{2'ax}H$), 1.37 (d, 3H, J = 6.84 Hz, $C_{5'}CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 209.86, 187.53, 185.99, 160.96, 160.73, 160.06, 159.89, 138.38, 135.67, 134.93, 132.86, 122.11, 119.55, 118.45, 109.86, 105.07, 98.23, 79.08,

73.46, 69.41, 67.46, 66.04, 56.54, 53.57, 41.08, 37.28, 37.05, 34.81, 23.11, 20.67; UV (CH_3OH) λ (log ε) 204 (0.59), 234 (0.77), 251 (0.55); Mass (FAB^+, Na) m/z 637 $(M\text{-}HCl + Na)^+$.

Daunomycin-3′-*N*-pyruviccarboamide (3)

The mixture of pyruvic acid (0.10 mL, 1.49 mmol) and EDCI (0.48 g, 2.48 mmol) in dry DMF (500 mL) was stirred on an ice bath for 30 min and allowed to reach room temperature. To the stirred solution was added daunomycin hydrochloride (**1a**, 0.70 g, 1.24 mmol) and catalytic amounts of 4-pyrrolidinopyridine, and the mixture was then stirred for 12 h. The resulting mixture was dissolved with CH_2Cl_2 (300 mL), washed with water (200 mL × 2) and brine (200 mL × 2), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/hexane/CH_3OH = 12 : 6 : 1) to give daunomycin-3′-*N*-pyruviccarboamide (**3**, 0.45 g, 61%) as a red powder: m.p. 167-169°C; $[\alpha]_D^{20} + 74.98^\circ$ (c 0.004, CH_3OH); IR (KBr) 3445, 2939, 1713, 1627, 1578, 1418, 1289, 1209, 1123, 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 13.93 (s, 1H, PhOH), 13.19 (s, 1H, PhOH), 7.89 (d, 1H, J = 7.81 Hz, ArH), 7.75 (dd, 1H, J = 8.30, 7.81 Hz, ArH), 7.34 (d, 1H, J = 8.30 Hz, ArH), 6.04 (d, 1H, J = 8.30 Hz, $C_{4'}H$), 5.45 (d, 1H, J = 3.91 Hz, $C_{7eq}H$), 5.17 (m, 1H, $C_{1'}H$), 4.46 (s, 1H, C_9OH), 4.20 (q, 1H, J = 6.84 Hz, $C_{5'}H$), 4.02 (s, 3H, C_4OCH_3), 3.64 (s, 1H, $C_{4'}OH$), 3.39 (m, 1H, $C_{3'}H$), 3.16 (d, 1H, J = 19.04 Hz, $C_{10eq}H$), 2.83 (d, 1H, J = 19.04 Hz, $C_{10ax}H$), 2.41 (s, 3H, $C_{14}CH_3$), 2.27 (d, 1H, J = 14.65 Hz, $C_{8eq}H$), 2.06 (dd, 1H, J = 14.65, 3.91 Hz, $C_{8ax}H$), 1.93 (s, 3H, sugar-NPyCH_3), 1.83 (dd, 1H, J = 13.18, 4.46 Hz, $C_{2'eq}H$), 1.74 (dd, 1H, J = 13.18, 4.39 Hz, $C_{2'ax}H$), 1.28 (d, 3H, J = 6.84 Hz, $C_{5'}CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.92, 186.66, 186.26, 172.38, 169.33, 160.75, 156.22, 155.59, 135.52, 135.31, 134.33, 133.88, 120.68, 119.66, 118.25, 111.27, 111.08, 100.58, 76.60, 69.94, 69.53, 67.09, 56.61, 45.44, 35.10, 33.42, 29.94, 24.98, 23.41, 16.84; UV (CH_3OH) λ (log ε) 204 (0.41), 233 (0.59), 251 (0.42); Mass (FAB^+, Na) m/z 621 $(M + Na)^+$.

Doxorubicin-3′-*N*-pyruviccarboamide (4)

The mixture of pyruvic acid (0.09 mL, 1.29 mmol) and EDCI (0.48 g, 2.07 mmol) in dry DMF (500 mL) was stirred on an ice bath for 30 min and allowed to reach room temperature. To the stirred solution was added doxorubicin hydrochloride (**1b**, 0.60 g, 1.04 mmol) and catalytic amounts

of 4-pyrrolidinopyridine, and the mixture was then stirred for 13 h. The resulting mixture was dissolved with CH_2Cl_2 (300 mL), washed with water (200 mL × 2) and brine (200 mL × 2), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/hexane/$CH_3OH = 8:8:1$) to give doxorubicin-3′-*N*-pyruviccarboamide (**4**, 0.38 g, 60%) as a red powder: m.p. 175–176°C; $[\alpha]_D^{20} + 49.99^\circ$ (c 0.004, CH_3OH); IR (KBr) 3445, 2939, 1732, 1627, 1578, 1418, 1289, 1215, 1116, 1018, 990 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 13.98 (s, 1H, PhOH), 13.26 (s, 1H, PhOH), 8.05 (d, 1H, $J = 7.81$ Hz, ArH), 7.79 (dd, 1H, $J = 8.30$, 7.81 Hz, ArH), 7.39 (d, 1H, $J = 8.30$ Hz, ArH), 5.82 (d, 1H, $J = 8.30$ Hz, $C_{4'}H$), 5.49 (d, 1H, $J = 3.91$ Hz, $C_{7eq}H$), 5.29 (m, 1H, $C_{1'}H$), 4.75 (s, 2H, $C_{14}H$), 4.53 (s, 1H, C_9OH), 4.17 (q, 1H, $J = 6.84$ Hz, $C_{5'}H$), 4.09 (s, 3H, C_4OCH_3), 3.64 (s, 1H, $C_{4'}OH$), 3.33 (d, 1H, $J = 18.55$ Hz, $C_{10eq}H$), 3.04 (d, 1H, $J = 18.55$ Hz, $C_{10ax}H$), 2.92 (m, 1H, $C_{3'}H$), 2.34 (d, 1H, $J = 14.65$ Hz, $C_{8eq}H$), 2.17 (dd, 1H, $J = 14.65$, 3.91 Hz, $C_{8ax}H$), 1.95 (s, 3H, sugar-NPyCH_3), 1.77 (dd, 1H, $J = 13.67$, 4.88 Hz, $C_{2'eq}H$), 1.72 (dd, 1H, $J = 13.67$, 4.40 Hz, $C_{2'ax}H$), 1.29 (s, 3H, $J = 6.84$ Hz, $C_{5'}CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.76, 190.82, 186.94, 186.52, 160.91, 159.70, 156.07, 155.56, 154.96, 135.68, 135.41, 133.47, 133.44, 120.78, 119.79, 118.36, 111.53, 111.34, 100.83, 79.67, 77.20, 69.79, 67.53, 67.36, 56.69, 47.49, 35.45, 30.25, 26.91, 16.83; UV (CH_3OH) λ (log ε) 204 (0.45), 234 (0.56), 251 (0.41); Mass (FAB^+, Na) m/z 637 $(M + Na)^+$.

Doxorubicin-14,3′-*N*-dipyruvate (5)

The mixture of pyruvic acid (0.16 mL, 2.30 mmol) and EDCI (0.50 g, 2.59 mmol) in dry DMF (500 mL) was stirred on an ice bath for 30 min and allowed to reach room temperature. To the stirred solution was added doxorubicin hydrochloride (**1b**, 0.60 g, 1.03 mmol) and catalytic amounts of 4-pyrrolidinopyridine, and the mixture was then stirred for 12 h. The resulting mixture was extracted with CH_2Cl_2 (300 mL), washed with water (200 mL × 2) and brine (200 mL × 2), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/hexane/$CH_3OH = 8:2:1$) to give doxorubicin-14,3′-*N*-dipyruvate (**5**, 0.40 g, 57%) as a red powder: m.p. 136–138°C; $[\alpha]_D^{20} + 166.63^\circ$ (c 0.004, CH_2Cl_2); IR (KBr) 3432, 2927, 2953, 1738, 1621, 1375, 1246, 1129, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 13.99 (s, 1H, PhOH), 13.27 (s, 1H, PhOH), 8.03 (d, 1H, $J = 7.81$ Hz, ArH), 7.79 (dd, 1H, $J = 8.30$, 7.81 Hz, ArH), 7.40 (d, 1H, $J = 8.30$ Hz,

ArH), 5.80 (d, 1H, $J = 8.30$ Hz, $C_{4'}H$), 5.51 (d, 1H, $J = 3.40$ Hz, $C_{7eq}H$), 5.48 (d, 1H, $J = 18.07$ Hz, $C_{14}H$), 5.33 (d, 1H, $J = 18.07$ Hz, $C_{14}H$), 5.29 (m, 1H, $C_{1'}H$), 4.82 (s, 1H, C_9OH), 4.30 (q, 1H, $J = 6.34$ Hz, $C_{5'}H$), 4.09 (s, 3H, C_4OCH_3), 3.65 (s, 1H, $C_{4'}OH$), 3.49 (m, 1H, $C_{3'}H$), 3.34 (d, 1H, $J = 19.53$ Hz, $C_{10eq}H$), 2.93 (d, 1H, $J = 19.53$ Hz, $C_{10ax}H$), 2.56 (s, 3H, $C_{17}CH_3$), 2.45 (d, 1H, $J = 14.65$ Hz, $C_{8eq}H$), 2.02 (dd, 1H, $J = 14.65$, 3.40 Hz, $C_{8ax}H$), 1.95 (s, 3H, sugar-NPyCH_3), 1.43–1.74 (m, 2H, $C_{2'}H$), 1.32 (d, 3H, $J = 6.34$ Hz, $C_{5'}CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.23, 196.52, 191.80, 187.12, 187.11, 163.44, 160.29, 159.95, 150.85, 150.84, 140.32, 132.97, 131.25, 131.23, 125.33, 125.31, 125.25, 122.10, 117.50, 92.11, 83.83, 78.37, 68.65, 63.54, 57.20, 49.62, 45.29, 41.10, 35.67, 26.55, 17.68, 16.02, 14.91; UV (CH_2Cl_2) λ (log ε) 235 (2.31), 251 (1.42), 482 (0.69); Mass (FAB$^+$, Na) m/z 707 $(M + Na)^+$.

Daunomycin-14-aspartate Dihydrochloride (6)

Di-*tert*-butyldicarbonate (0.84 g, 3.85 mmol) and dioxane (10 mL) was added to aspartic acid sodium salt (0.50 g, 3.22 mmol) in H_2O (20 mL), and the mixture was stirred for 10 min. Et_3N (0.90 mL, 6.45 mmol) and dioxane (10 mL) was slowly added to the reaction mixture, and the resulting mixture was then stirred overnight. The organic solvent was removed, and the resulting mixture was recrystallized from acetone to yield *N*-BOC-aspartic acid sodium salt (54%, m.p. 240°C) as a white powder. 14-Bromodaunomycin hydrochloride (**1c**, 0.10 g, 0.16 mmol) and *N*-BOC-aspartic acid sodium salt (0.24 g, 0.92 mmol) in acetone (350 mL) was vigorously stirred at reflux for 60 h. After the reaction mixture was cooled to room temperature, the precipitate was filtered and the organic solvent was evaporated. After the combined products was dissolved in CF_3CO_2H (10 mL) at −20°C, the resulting mixture was stirred for 20 min, and then the solvent was evaporated under reduce pressure. After the residue was purified by column chromatography on silica gel ($CH_2Cl_2/CH_3OH/HCO_2H/H_2O = 88:20:2:1$), the isolated product was dissolved in HCl/CH_3OH (10 mL) at 0°C and allowed to reach room temperature for 1 h. The organic solvent was concentrated by a rotary evaporator to give **6** (0.04 g, 34%) as a red solid: m.p. 209–211°C; $[\alpha]_D^{20} - 125.01°$ (c 0.004, 0.2 N HCl solution); IR (KBr) 3432, 2939, 1732, 1615, 1387, 1283, 1215, 1116, 990 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.01 (s, 1H, PhOH), 13.95 (s, 1H, PhOH), 8.01 (bs, 2H, NH_2), 7.90 (m, 2H, ArH), 7.64 (t, 1H, $J = 7.89$ Hz, ArH), 5.63 (m, 1H, $C_{4'}H$), 5.05 (m, 1H, $C_{7eq}H$), 4.82(m, 1H, $C_{1'}H$), 4.60 (t, 1H, $J = 5.41$ Hz, $C_{16}H$), 4.05 (q, 1H, $J = 6.80$ Hz, $C_{5'}H$), 4.02 (s, 2H, $C_{14}H$), 3.98 (s, 3H, C_4OCH_3), 3.80 (d, 2H, $J = 5.92$ Hz, $C_{17}H$), 3.68 (bs, 1H, $C_{4'}OH$), 3.28 (m, 1H, $C_{3'}H$),

2.85 (d, 1H, $J = 18.36$ Hz, $C_{10eq}H$), 2.58 (d, 1H, $J = 18.36$ Hz, $C_{10ax}H$), 2.47 (d, 1H, $J = 14.56$ Hz, $C_{8eq}H$), 2.27 (dd, 1H, $J = 14.56$, 4.40 Hz, $C_{8ax}H$), 2.06 (dd, 1H, $J = 12.05$, 7.98 Hz, $C_{2'eq}H$), 1.95 (d, 1H, $J = 12.05$ Hz, $C_{2'ax}H$), 1.26 (d, 3H, $J = 6.80$ Hz, $C_{5'}CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 210.01, 188.12, 186.12, 178.96, 167.78, 160.89, 160.12, 139.05, 135.98, 135.00, 132.92, 122.32, 120.01, 118.56, 110.10, 105.45, 98.52, 79.09, 73.51, 69.49, 67.86, 56.52, 53.69, 37.52, 37.15, 34.98, 20.78; UV (0.2 N HCl solution) λ (log ε) 233 (0.67), 253 (0.44), 481 (0.20); Mass (FAB^+, Na) m/z 682 $(M\text{-}2\,HCl + Na)^+$.

Daunomycin-14-(*N*-acetyl)aspartate Hydrochloride (7)

14-bromodaunomycin hydrochloride (**1c**, 0.30 g, 0.47 mmol) and *N*-acetyl-L-aspartic acid (0.10 g, 0.57 mmol) was dissolved in acetone (300 mL). To the mixture was added triethyl amine (0.08 mL, 0.57 mmol), and the mixture was then stirred at room temperature for 8 h. After removing the solvent by a rotary evaporator, an etheral HCl in dry THF (200 mL) was added to the reaction mixture. The resulting mixture was stirred at −20°C for 2 h, and the solvent was then removed under reduced pressure. Purification of the residue by column chromatography ($CH_2Cl_2/CH_3OH/HCO_2H/H_2O = 88:15:2:1$) gave pure daunomycin-14-(*N*-acetyl)aspartate hydrochloride (**7**, 0.21 g, 61%) as a red powder: m.p. 155–157°C; $[\alpha]_D^{20} - 41.66°$ (c 0.004, CH_3OH); IR (KBr) 3420, 2939, 1738, 1621, 1578, 1412, 1289, 1215, 1116, 1012, 984 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.98 (s, 1H, PhOH), 13.22 (s, 1H, PhOH), 8.34 (s, 1H, C_{17}NHAc), 8.25 (d, 1H, $J = 7.81$ Hz, ArH), 7.87 (dd, 1H, $J = 8.30$, 7.81 Hz, ArH), 7.67 (d, 1H, $J = 8.30$ Hz, ArH), 7.60 (m, 1H, $C_{3'}$NH), 5.73 (m, 1H, $C_{4'}H$), 5.71 (s, 1H, C_9OH), 5.28 (d, 1H, $J = 18.06$ Hz, $C_{14}H$), 5.17 (m, 1H, $C_{7eq}H$), 5.10 (d, 1H, $J = 18.07$ Hz, $C_{14}H$), 4.91 (m, 1H, $C_{1'}H$), 4.32 (dd, 1H, $J = 6.84$, 7.81 Hz, $C_{17}H$), 4.20 (q, 1H, $J = 6.34$ Hz, $C_{5'}H$), 3.96 (s, 3H, C_4OCH_3), 3.70 (m, 1H, $C_{4'}$OH), 3.34 (m, 1H, $C_{3'}H$), 3.02 (d, 1H, $J = 17.58$ Hz, $C_{10eq}H$), 2.80 (d, 1H, $J = 17.58$ Hz, $C_{10ax}H$), 2.75 (dd, 1H, $J = 16.40$, 6.84 Hz, $C_{16}H$), 2.60 (dd, 1H, $J = 16.40$, 7.81 Hz, $C_{16}H$), 2.24 (d, 1H, $J = 12.70$ Hz, $C_{8eq}H$), 2.04 (dd, 1H, $J = 12.70$, 4.34 Hz, $C_{8ax}H$), 1.80 (s, 3H, C_{17}NH**Ac**), 1.63–1.87 (m, 2H, $C_{2'}H$), 1.12 (d, 3H, $J = 6.34$ Hz, $C_{5'}CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 211.56, 189.93, 189.08, 178.27, 173.21, 171.60, 163.23, 154.01, 149.93, 141.30, 135.74, 132.20, 128.46, 123.52, 120.70, 120.38, 119.66, 110.64, 110.11, 96.68, 70.74, 65.36, 55.45, 54.10, 52.16, 49.19, 46.49, 32.01, 30.03, 28.42, 22.74, 16.86, 12.12; UV (CH_3OH) λ (log ε) 233 (0.76), 253 (0.58), 482 (0.28); Mass (FAB^+, Na) m/z 724 $(M\text{-}HCl + Na)^+$.

Daunomycin-3′-*N*-(*N*-acetyl)asparticcarboamide (8)

The mixture of *N*-acetyl-L-aspartic acid (0.15 g, 0.86 mmol) and EDCI (0.27 g, 1.41 mmol) in dry DMF (250 mL) was stirred on an ice bath for 30 min and allowed to room temperature. To the stirred solution was added daunomycin hydrochloride (**1a**, 0.40 g, 0.71 mmol) and catalytic amounts of 4-pyrrolidinopyridine, and the mixture was then stirred for 4 h. The resulting mixture was extracted with 5% CH_3OH in $CHCl_3$ (200 mL), washed with water (100 mL × 2) and brine (100 mL × 2), dried over $MgSO_4$, and the solvent was then removed under reduced pressure. The residue was purified by column chromatography ($CH_2Cl_2/CH_3OH/HCO_2H/H_2O$ = 88 : 15 : 2 : 1) to give daunomycin-3′-(*N*-acetyl)asparticcarboamide (**8**, 0.36 g, 74%) as a red powder: m.p. 149–151°C; $[\alpha]_D^{20} + 149.97^\circ$ (c 0.004, CH_3OH); IR (KBr) 3420, 2927, 1713, 1652, 1578, 1418, 1289, 1209, 1129, 987 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 13.93 (s, 1H, PhOH), 13.18 (s, 1H, PhOH), 8.10 (d, 1H, J = 7.81 Hz, ArH), 7.80 (dd, 1H, J = 8.30, 7.81 Hz, ArH), 7.55 (bs, 1H, sugar-N**H**Ac), 7.32 (d, 1H, J = 8.30 Hz, ArH), 5.47 (m, 1H, $C_{4'}H$), 5.19 (d, 1H, J = 3.42 Hz, $C_{7eq}H$), 4.85 (m, 1H, $C_{1'}H$), 4.47 (dd, 1H, J = 5.86, 7.81 Hz, sugar-aspC**H**CO_2H), 4.17 (q, 1H, J = 6.84 Hz, $C_{5'}H$), 3.93 (s, 3H, C_4OCH_3), 3.59 (m, 1H, $C_{4'}OH$), 3.37 (m, 1H, $C_{3'}H$), 3.03 (d, 1H, J = 18.06 Hz, $C_{10eq}H$), 2.85 (d, 1H, J = 18.06 Hz, $C_{10ax}H$), 2.57 (d, 2H, J = 5.86 Hz, sugar-aspCH_2), 2.39 (d, 1H, J = 12.14 Hz, $C_{8eq}H$), 2.28 (dd, 1H, J = 12.14, 3.42 Hz, $C_{8ax}H$), 2.17 (d, 1H, J = 14.16 Hz, $C_{2'eq}H$), 2.06 (dd, 1H, J = 14.16, 5.86 Hz, $C_{2'ax}H$), 1.79 (s, 3H, sugar-aspNH**Ac**), 1.12 (d, 3H, J = 6.84 Hz, $C_{5'}CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 211.44, 186.05, 185.97, 175.86, 175.55, 171.56, 169.10, 160.44, 151.30, 150.39, 148.88, 141.25, 135.35, 119.42, 118.57, 110.50, 110.37, 100.18, 89.59, 80.06, 77.78, 75.09, 74.37, 71.17, 67.85, 66.62, 56.47, 49.44, 47.19, 36.12, 24.09, 22.48, 16.98; UV (CH_3OH) λ (log ε) 203 (0.70), 234 (0.91), 251 (0.66); Mass (FAB^+, Na) m/z 708 $(M + Na)^+$.

Doxorubicin-3′-*N*-(*N*-acetyl)asparticcarboamide (9)

The mixture of *N*-acetyl-L-aspartic acid (0.11 g, 0.63 mmol) and EDCI (0.20 g, 1.05 mmol) in dry DMF (200 mL) was stirred on an ice bath for 30 min and allowed to reach room temperature. To the stirred solution was added doxorubicin hydrochloride (**1b**, 0.30 g, 0.52 mmol) and catalytic amounts of 4-pyrrolidinopyridine, and the mixture was then stirred for 5 h. The resulting mixture was extracted with 5% CH_3OH in $CHCl_3$ (200 mL), washed with water (100 mL × 2) and brine (100 mL × 2), dried over $MgSO_4$, and the solvent was then removed under reduced pressure.

The residue was purified by column chromatography ($CH_2Cl_2/CH_3OH/HCO_2H/H_2O = 88:15:2:1$) to give **9** (0.26 g, 71%) as a red powder: m.p. 163–165°C; $[\alpha]_D^{20}$ +83.32° (c 0.004, H_2O); IR (KBr) 3445, 2939, 1726, 1627, 1560, 1412, 1283, 1215, 1123, 984 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 13.96 (s, 1H, PhOH), 13.95 (s, 1H, PhOH), 8.42 (bs, 1H, $C_{3'}NH$), 8.16 (d, 1H, $J = 7.81$ Hz, ArH), 7.83 (dd, 1H, $J = 8.30$, 7.81 Hz, ArH), 7.59 (d, 1H, $J = 7.81$ Hz, sugar-aspNH), 7.38 (d, 1H, $J = 8.30$ Hz, ArH), 5.76 (m, 1H, $C_{4'}H$), 5.71 (s, 1H, C_9OH), 5.33 (d, 1H, $J = 18.07$ Hz, $C_{14}H$), 5.26 (m, 1H, $C_{7eq'}H$), 5.18 (d, 1H, $J = 18.07$ Hz, $C_{14}H$), 4.89 (m, 1H, $C_{1'}H$), 4.49 (dd, 1H, $J = 5.86$, 7.81 Hz, sugar-asp$CHCO_2H$), 4.21 (q, $J = 6.84$ Hz, 1H, $C_{5'}H$), 3.95 (s, 3H, C_4OCH_3), 3.37 (s, 1H, $C_{4'}OH$), 3.03 (d, 1H, $J = 18.06$ Hz, $C_{10eq}H$), 2.73–2.87 (m, 2H, $C_{3'}$&$C_{10ax}H$), 2.67 (dd, 1H, $J = 16.40$, 5.86 Hz, sugar-aspCH_2), 2.59 (dd, 1H, $J = 16.40$, 7.81 Hz, sugar-aspCH_2), 2.39 (d, 1H, $J = 12.14$ Hz, $C_{8eq}H$), 2.31 (dd, 1H, $J = 12.14$, 3.91 Hz, $C_{8ax}H$), 2.02 (m, 2H, $C_{2'}H$), 1.80 (s, 3H, sugar-aspNH**Ac**), 1.13 (d, 3H, $J = 6.84$ Hz, $C_{5'}CH_3$); ^{13}H NMR (100 MHz, DMSO-d_6) δ 207.27, 186.09, 186.02, 172.69, 171.89, 171.53, 171.02, 170.60, 170.54, 169.61, 169.13, 169.05, 168.55, 160.48, 155.83, 154.27, 135.15, 134.33, 119.69, 110.56, 110.41, 75.10, 75.08, 56.52, 54.91, 48.67, 48.55, 36.11, 22.57, 22.46, 22.39, 22.29, 16.97; UV (H_2O) λ (log ε) 202 (1.93), 251 (1.05), 480 (0.45); Mass (FAB^+, Na) m/z 724 $(M + Na)^+$.

Doxorubicin-14,3′-*N*-di(*N*-acetyl)aspartate (10)

The mixture of *N*-acetyl-L-aspartic acid (0.20 g, 1.14 mmol) and EDCI (0.25 g, 1.30 mmol) in dry DMF (200 mL) was stirred on an ice bath for 30 min and allowed to reach room temperature. To the stirred solution was added doxorubicin hydrochloride (**1b**, 0.30 g, 0.52 mmol) and catalytic amounts of 4-pyrrolidinopyridine, and the mixture was then stirred for 10 h. The resulting mixture was extracted with 5% CH_3OH in $CHCl_3$ (200 mL), washed with water (100 mL × 2) and brine (100 mL × 2), dried over $MgSO_4$, and the solvent was then removed under reduced pressure. The residue was purified by column chromatography on silica gel ($CH_2Cl_2/CH_3OH/HCO_2H/H_2O = 88:15:2:1$) to give **10** (0.30 g, 67%) as a red solid: m.p. 110–112°C; $[\alpha]_D^{20}$ +249.95° (c 0.004, H_2O); IR (KBr) 3383, 3087, 2939, 1732, 1627, 1547, 1412, 1283, 1215, 1024, 984 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 14.00 (s, 1H, PhOH), 13.20 (s, 1H, PhOH), 8.36 (s, 1H, $C_{3'}NH$), 8.24 (s, 1H, $C_{17}NHAc$), 8.13 (d, 1H, $J = 7.81$ Hz, ArH), 7.88 (dd, 1H, $J = 8.30$, 7.81 Hz, ArH), 7.62 (d, 1H, $J = 7.32$ Hz, sugar-aspNH), 7.37 (d, 1H, $J = 8.30$ Hz, ArH), 5.63 (m, 1H, $C_{4'}H$), 5.30 (d, 1H, $J = 18.07$ Hz, $C_{14}H$), 5.19 (d, 1H, $J = 3.91$ Hz, $C_{7eq}H$), 5.16 (d, 1H,

$J = 18.07$ Hz, $C_{14}H$), 4.91 (m, 1H, $C_{1'}H$), 4.69 (dd, 1H, $J = 6.84$, 7.81 Hz, $C_{17}H$), 4.45 (dd, 1H, $J = 5.86$, 7.81 Hz, sugar-asp$CHCO_2H$), 4.17 (q, 1H, $J = 6.35$ Hz, $C_{5'}H$), 3.96 (s, 3H, C_4OCH_3), 3.49 (s, 1H, $C_{4'}OH$), 3.31 (m, 1H, $C_{3'}H$), 3.04 (d, 1H, $J = 18.55$ Hz, $C_{10eq}H$), 2.85 (d, 1H, $J = 18.55$ Hz, $C_{10ax}H$), 2.78 (dd, 1H, $J = 16.38$, 6.84 Hz, $C_{16}CH_2$), 2.70 (dd, 1H, $J = 16.40$, 5.86 Hz, sugar-aspCH_2), 2.63 (dd, 1H, $J = 16.38$, 7.81 Hz, $C_{16}CH_2$), 2.55 (dd, 1H, $J = 16.40$, 7.81 Hz, sugar-aspCH_2), 2.36 (d, 1H, $J = 12.14$ Hz, $C_{8eq}H$), 2.29 (dd, 1H, $J = 12.14$, 3.91 Hz, $C_{8ax}H$), 1.96 (m, 2H, $C_{2'}H$), 1.82 (s, 3H, $C_{17}NH$**Ac**), 1.78 (s, 3H, aspNH**Ac**), 1.11 (d, 3H, $J = 6.35$ Hz, $C_{5'}CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 212.27, 187.23, 173.08, 172.35, 171.71, 169.72, 169.05, 168.98, 168.09, 163.79, 145.32, 144.56, 134.52, 131.34, 124.99, 118.83, 109.54, 106.63, 101.85, 100.30, 99.65, 83.82, 78.21, 67.83, 66.62, 57.62, 56.54, 53.67, 49.57, 45.09, 40.51, 36.61, 36.44, 28.66, 22.49, 22.34, 19.03, 16.95; UV (H_2O) λ (log ε) 233 (0.59), 253 (0.42), 480 (0.19); Mass (FAB^+, Na) m/z 881 $(M + Na)^+$.

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