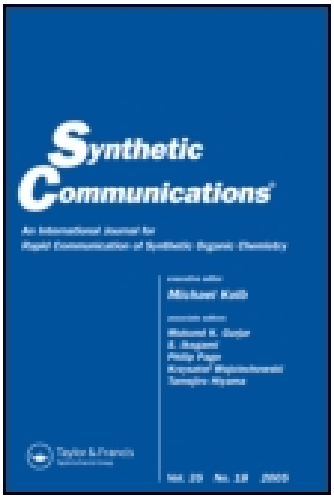

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New Strategy for Synthesis of the Disaccharide Moiety of the Highly Potent Anticancer Natural Product OSW-1

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NEW STRATEGY FOR SYNTHESIS OF THE DISACCHARIDE MOIETY OF THE HIGHLY POTENT ANTICANCER NATURAL PRODUCT OSW-1

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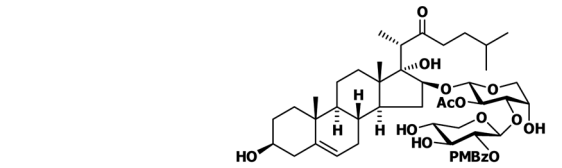
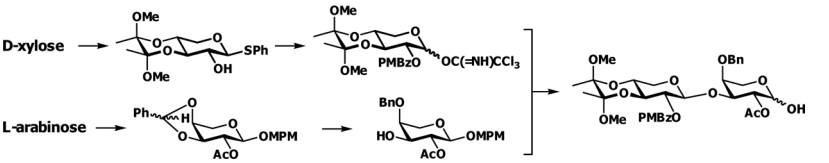
GRAPHICAL ABSTRACT





Abstract *The facile synthesis of a partially protected OSW-1 disaccharide moiety, having a 2-O-p-methoxybenzoyl-*β*-*D*-xylopyranosyl-(1 → 3)-2-O-acetyl-*L*-arabinopyranoside structure, was elaborated by glycosylation in a* β*-stereoselective fashion. The xylopyranose donors were synthesized by a short synthetic approach via convenient selective 1,2-diacetal protection of 3,4-*trans*-diequatorial hydroxyl group. Regioselective ring opening of 1,2-diacetal-protected substrates efficiently led to the arabinopyranose acceptor with a free 3-hydroxyl group. Glycosylation of the xylopyranose donor with the arabinopyranose acceptor provided the* β*-disaccharide.*

Keywords Anticancer; disaccharide; OSW-1; selective ring opening; synthesis

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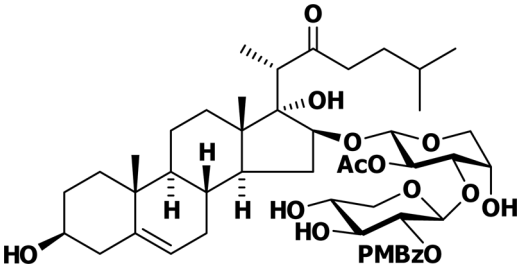


Figure 1. Structure of OSW-1 (**1**).

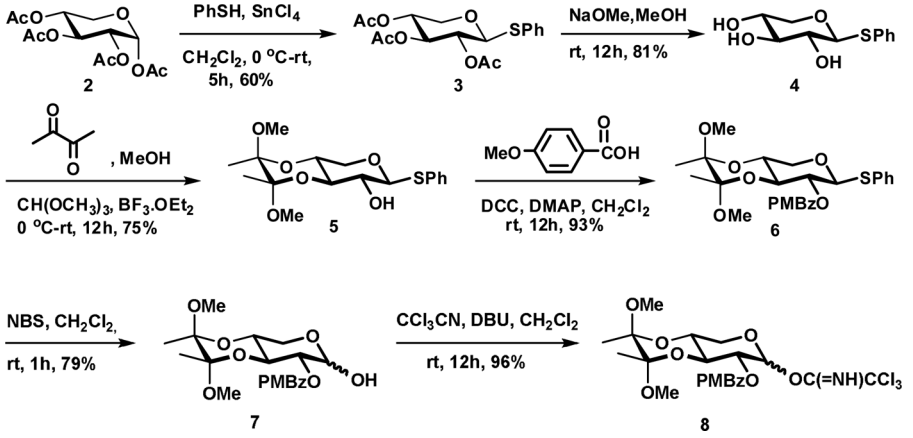
INTRODUCTION

OSW-1 (**1**) (Fig. 1), a highly potent anticancer natural product, is a member of the cholestane glycoside. It exhibited exceptionally potent cytostatic activities against various human malignant tumor cells. The anticancer activities of this compound are found to be between 10 to 100 times more potent than some well-known anticancer agents in clinical use, such as mitomycin C, adriamycin, cisplatin, camptothecin, and even taxol. In addition, it has demonstrated significantly lower toxicity (IC_{50} 1500 nM) to normal human pulmonary cells.[1,2] The structural novelty of OSW-1 is characterized by the attachment of a disaccharide to the C-16 position of the steroid aglycone.[3] Because of the extraordinary antitumor activities, OSW-1 is an attractive synthetic target. The synthesis of the aglycone part was reported in 1998 by Guo and Fuchs.[4] In 1999, the disaccharide moiety of OSW-1 was synthesized by Deng et al.[5] as part of the first total synthesis of OSW-1. Later in 2001, Jin and Yu[6] reported the synthesis of this disaccharide moiety by using a slightly different approach. Because the disaccharide part of the OSW-1 molecule is important for biological activity, modification of this carbohydrate backbone was biologically evaluated by Suhr and Thiem in 2004.[7] As part of our research on steroidal synthesis and the regioselectivity of ketal ring opening in carbohydrate molecules, our interest focused on alternative pathways and glycosylation directed toward the disaccharide moiety.

The use of 1,2-diacetals as protecting groups for *trans*-1,2-diols has been shown to be a particularly useful method for the efficient construction of complex, biologically significant oligosaccharides.[8] The high selectivity for *trans*-1,2-diols, in the presence of other polyols, rapidly leads to protected monosaccharides amenable for further synthetic manipulation. In this article we describe the high-yielding, selective protection of phenylthioxyloside **4** with butane-2,3-dione, affording the corresponding butane-2,3-diacetal (BDA) intermediate **5**, which could be further manipulated in the expedient synthesis of the disaccharide moiety **18** of OSW-1 (**1**).

RESULTS AND DISCUSSION

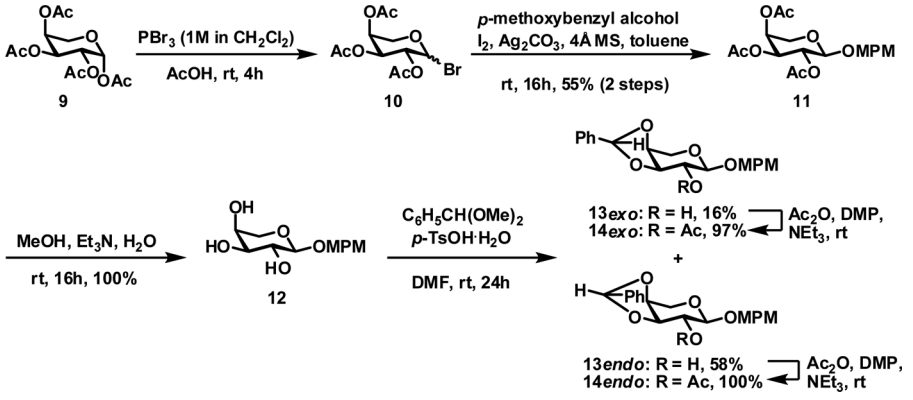
The synthesis of the disaccharide **18** was carried out in a straightforward manner. Phenylthioxyloside **4**, prepared from tetraacetyl-D-xylose **2** (Scheme 1),[6,14] was reacted with butane-2,3-dione and $BF_3 \cdot OEt_2$ to selectively protect the vicinal



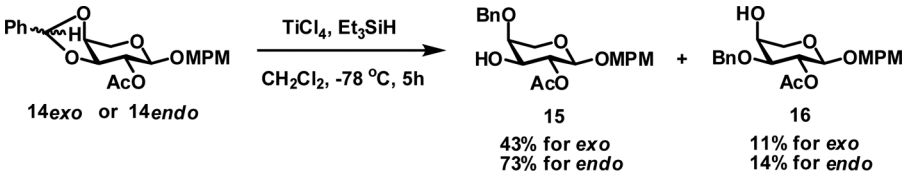
Scheme 1. Synthesis of trichloroacetimidate **8**.

diequatorial alcohols, giving BDA-protected **5** in good yield. The *p*-methoxy benzoyl group was then introduced by treatment of **5** with *p*-methoxybenzoic acid, *N*,*N*′-dicyclohexylcarbodiimide (DCC), and 4-dimethylaminopyridine (DMAP) in dichloromethane (DCM) affording **6** in 93% yield. The phenylthiol in **6** was removed by treatment with *N*-bromosuccinimide (NBS) to furnish lactol **7**, which was subsequently converted to the corresponding trichloroacetimidate **8** in 96% yield.[9]

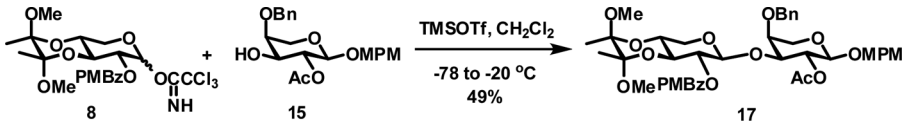
Meanwhile, the arabinoside acceptor **15** was prepared by selective ring opening of the corresponding 3,4-benzylidene ketal **14,** which was readily prepared from tetraacetyl L-arabinose **9**[10] in five steps in 41% yield (Scheme 2). The *p*-methoxybenzyl α-L-arabinopyranoside **12** was prepared from **9** according to the standard method.[10] The 3,4-diol of **12** was selectively protected as benzylidene acetal to give **13** in 74% yield, which were subsequently acetylated to yield *exo*-**14** and *endo*-**14**, respectively. The *endo*-configuration of the benzylidene ring of **13***endo* was confirmed on the basis of ^{1}H and ^{13}C NMR spectroscopic data; the benzylidene proton resonated at δ 5.94 ppm and the signal of the acetalic carbon atom appeared at 104.5 ppm, whereas



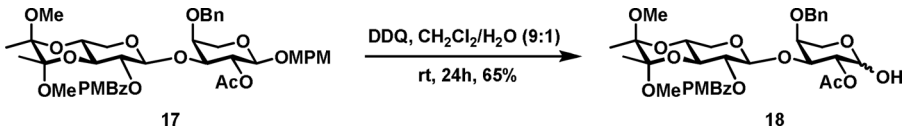
Scheme 2. Synthesis of *exo*-and *endo*-3,4-*O*-benzylidene-β-L-arabinopyranosides.



Scheme 3. Reductive ring opening of benzylidene acetals **14**.



Scheme 4. Glycosylation of BDA-protected xylopyranoside donor **8** with arabinopyranoside acceptor **15**.



Scheme 5. Synthesis of disaccharide of OSW-1.

the benzylidene proton of the *exo*-isomer **13** was found at δ 6.19 ppm and the signal of the acetalic carbon atom appeared at 103.3 ppm. These values are in good agreement with the corresponding data reported in the literature.[11]

By using the method discovered by others[12,13] and recently by our group,[11] *exo*-benzylidene acetal of **14***exo* was selectively cleaved using $TiCl_4/Et_3SiH$ in CH_2Cl_2 at $-78\,^{\circ}C$ to give 4-benzyl ether **15** in 43% yield and 3-benzyl ether **16** in 11% yield, whereas the *endo*- isomer**14** provided ether **15** in 73% and isomeric ether **16** in 14% yields (Scheme 3).

The synthesis of disaccharide **17** was finally achieved by glycosylation of xylosyl trichloroacetimidate **8** and the arabinosyl acceptor **15** in the presence of TMSOTf, furnishing the disaccharide moiety **17** in moderate yield (Scheme 4).

Selective removal of the anomeric *p*-methoxybenzyl group from the disaccharide **17** with DDQ led to the corresponding hydroxyl compound **18** in 65% yield as a mixture of α-and β-anomer (ratio = 2:3) (Scheme 5), ready for coupling with OSW-1 aglycone.

CONCLUSION

We report a facile synthesis of the partially protected disaccharide, a moiety of OSW-1 by glycosylation of xylopyranoside donor with arabinopyranoside acceptor. The xylopyranoside donor was prepared via selective 1,2-diacetal protection of 3,4-*trans*-diequatorial hydroxyl groups using butane-2,3-dione/$BF_3 \cdot OEt_2$ in methanol

to give the BDA-protected xylopyranoside whereas the arabinopyranoside acceptor with a free 3-hydroxyl group was prepared by regioselective reductive ring opening of benzylidene acetal using $TiCl_4$ and Et_3SiH. This procedure offers a new approach for the construction of complex, biologically significant oligosaccharides by using the 1,2-diacetal as a highly effective protecting groups for *trans*-vicinal diols and selective monobenzylation of the *cis*-vicinal diols by reductive ring opening of benzylidene acetal.

EXPERIMENTAL

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Gemini 300 spectrophotometer. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in $CDCl_3$ unless otherwise stated. The peak due to residual $CHCl_3$ (7.26 ppm for ^{1}H and 77.2 ppm for ^{13}C) was used as the internal reference. Coupling constants (*J*) are given in Hz, and multiplicity is defined as follows: br = broad, s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplet, t = triplet, q = quartet, m = multiplet. Infrared (IR) spectra were recorded in cm^{-1} on a Perkin-Elmer 2000 Fourier transform infrared spectrophotometer at the Chemistry Department, Faculty of Science, Kasetsart University. Samples were analyzed as KBr disks. Optical rotations were measured on a JASCO P-2000 polarimeter. Mass spectra were obtained on an Agilent Technology 1100 series LL/MSD Trap. Melting points (mp) were determined on a Fisher John apparatus and MEL-TEMP capillary melting-point apparatus and are uncorrected. All chemicals and solvents were purified by general methods before being used.

General Procedure for the Synthesis of 4-Methoxybenzyl 2-*O*-Acetyl-4-*O*-benzyl-3-*O*-[2-*O*-(4-methoxybenzoyl)-3,4-*O*-(2′,3′-dimethoxybutan-2′,3′-diyl)-β-D-xylopyranosyl]-β-L-arabinopyranoside (17)

A solution of **15** (163 mg, 0.40 mmol), **8** (514 mg, 0.95 mmol), and activated 4 Å MS (1.65 g) in dry dichloromethane (24.8 mL) was stirred for 1 h at room temperature. The reaction mixture was cooled to −78 °C for 30 min followed by the dropwise addition of a 0.1 M solution of TMSOTf in dry CH_2Cl_2 (0.07 mL, 0.007 mmol). Stirring was continued and the reaction mixture was allowed to warm to −20 °C for 2 h. Then the reaction mixture was quenched with triethylamine and filtered through celite, and the solvents were evaporated. Purification by flash column chromatography (EtOAc/hexane, 3:7) gave the title compound.

Compound 17

Yield: (152 mg, 49%), white solid; mp 85–86 °C; $[\alpha]_D^{25}$ + 45.0, (c = 0.23, $CHCl_3$); IR (neat, cm^{-1}) ν_{max} 1745, 1726, 1606, 1513, 1456, 1371, 1256, 1168, 1138, 1111, 1098, 1048; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 [d, *J* = 9.0 Hz, 2H, Ar(H)], 7.40–7.38 [m, 2H, Ar(H)], 7.34–7.30 [m, 2H, Ar(H)], 7.28–7.23 [m, 1H, Ar(H)], 7.02 [d, *J* = 8.6 Hz, 2H,

Ar(H)], 6.90 [d, $J = 9.0$ Hz, 2H, Ar(H)], 6.76 [d, $J = 8.7$ Hz, 2H, Ar(H)], 5.22 (dd, $J = 7.3$, 9.6 Hz, 1H, H-2′), 5.14 (dd, $J = 6.0$, 7.5 Hz, 1H, H-2), 4.82 (d, $J = 12.3$ Hz, 1H, $OC\underline{H}_2ArOCH_3$), 4.67 (d, $J = 12.2$ Hz, 1H, $OC\underline{H}_2ArOCH_3$), 4.67 (d, $J = 7.3$ Hz, 1H, H-1′), 4.50 (d, $J = 12.2$ Hz, 1H, $OC\underline{H}_2Ar$), 4.37 (d, $J = 12.2$ Hz, 1H, $OC\underline{H}_2Ar$), 4.25 (d, $J = 6.0$ Hz, 1H, H-1), 3.96–3.85 (m, 4H, H-3′, H-4′, H-5, H-5′), 3.83 (s, 3H, $ArOC\underline{H}_3$), 3.81–3.75 (m, 2H, H-3, H-4), 3.76 (s, 3H, $ArOC\underline{H}_3$), 3.46–3.40 (m, 1H, H-5′), 3.35 (dd, $J = 1.8$, 12.1 Hz, 1H, H-5), 3.27 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 1.67 (s, 3H, $OCOC\underline{H}_3$), 1.28 (s, 3H, $CC\underline{H}_3$), 1.22 (s, 3H, $CC\underline{H}_3$);^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0 ($O\underline{C}OCH_3$), 164.3 ($O\underline{C}OArOCH_3$), 163.3 (C-Ar), 159.0 (C-Ar), 138.5 (C-Ar), 131.7 × 2 (CH-Ar), 129.3 × 2 (CH-Ar), 129.3 (C-Ar), 128.1 × 2 (CH-Ar), 128.0 × 2 (CH-Ar), 127.4 (CH-Ar), 122.6 (C-Ar), 113.6 × 2 (CH-Ar), 113.5 × 2 (CH-Ar), 102.9 (C-1′), 99.7, 99.5 ($\underline{C}CH_3$), 98.4 (C-1), 77.6 (C-4), 73.6 (C-3), 71.9 ($O\underline{C}H_2ArOCH_3$), 70.1 (C-2′), 70.7 (C-3′), 70.5 (C-2), 68.5 ($O\underline{C}H_2Ar$), 65.7 (C-4′), 63.9 (C-5), 62.7 (C-5′), 55.4 ($OCOArO\underline{C}H_3$), 55.2 ($ArO\underline{C}H_3$), 47.9, 47.6 ($O\underline{C}H_3$), 20.5 ($OCO\underline{C}H_3$), 17.6, 17.5 ($C\underline{C}H_3$); HRMS (ESI) m/z: $C_{41}H_{50}O_{15}Na$ $[M + Na]^+$ calcd. 805.3042; found: 805.3066.

General Procedure for the Synthesis of 2-*O*-Acetyl-4-*O*-benzyl-3-*O*-[2-*O*-(4-methoxy benzoyl)-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-β-D-xylopyranosyl]-α/β-L-arabino Pyranoside (18)

DDQ (7 mg, 0.029 mmol) was added in one portion to a solution of **17** (10.0 mg, 0.013 mmol) in CH_2Cl_2 (0.54 mL) and water (0.06 mL). After the reaction mixture was stirred at room temperature for 24 h, the mixture was quenched by addition of saturated aq. $Na_2S_2O_3$ solution and $NaHCO_3$. The reaction mixture was then extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane, 1:1) to give the title compound.

Compound 18

Yield: 5.5 mg (65%) as a white solid; mp 129–130 °C; $[\alpha]_D^{25} - 0.25$, (c = 0.11, CH_2Cl_2); IR (KBr, cm^{-1}) ν_{max} 3421, 1742, 1724, 1605, 1513, 1456, 1371, 1257, 1168, 1138, 1110, 1095, 1048; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, $J = 8.9$ Hz, 2H, Ar(H)-α,β), 7.41–7.27 (m, 5H, Ar(H)-α,β), 6.92 (d, $J = 9.0$ Hz, 2H, Ar(H)-α), 6.91 (d, $J = 9.0$ Hz, 2H, Ar(H)-β), 5.28 (brd, $J = 3.1$ Hz, 1H, H-1β), 5.24 (dd, $J = 7.4$, 9.7 Hz, 1H, H-2′β), 5.21 (dd, $J = 6.9$, 9.6 Hz, 1H, H-2′α), 5.07 (dd, $J = 3.1$, 9.3 Hz, 1H, H-2β), 4.97 (dd, $J = 5.6$, 7.9 Hz, 1H, H-2α), 4.85 (d, $J = 12.2$ Hz, 1H, $OC\underline{H}_2Ar$-β), 4.80 (d, $J = 11.9$ Hz, 1H, $OC\underline{H}_2Ar$-α), 4.73 (d, $J = 7.0$ Hz, 1H, H-1′α), 4.72 (d, $J = 7.4$ Hz, 1H, H-1′β), 4.68 (d, $J = 12.2$ Hz, 1H, $OC\underline{H}_2Ar$-β), 4.66 (d, $J = 12.0$ Hz, 1H, $OC\underline{H}_2Ar$-α), 4.49 (d, $J = 5.6$ Hz, 1H, H-1α), 4.12 (dd, $J = 3.0$, 9.2 Hz, 1H, H-3β), 3.97 (dd, $J = 5.0$, 12.6 Hz, 1H, H-5α), 3.96–3.86 (m, 8H, H-3α, H-3′β, H-4β, H-4′α, H-4′β, H-5β, H-5′α, H-5′β), 3.86 (s, 3H, $ArOC\underline{H}_3$-α), 3.85 (s, 3H, $ArOC\underline{H}_3$-β), 3.84– 3.81 (m, 1H, H-4α), 3.67 (dd, $J = 3.7$, 11.9 Hz, 1H, H-5β), 3.49 (dd, $J = 2.6$, 12.3 Hz, 1H, H-5α), 3.49–3.46 (m, 2H, H-5′α,β), 3.44 (dd, $J = 3.0$, 7.4 Hz, 1H, H-3′α), 3.28 (s, 3H, OCH_3-β), 3.26 (s, 3H, OCH_3-α), 3.22 (s, 3H, OCH_3-α), 3.21 (s, 3H, OCH_3-β), 1.75 (s, 3H, $OCOC\underline{H}_3$-α), 1.68 (s, 3H,

OCOC$\underline{H}_3$-β), 1.29 (s, 3H, CC$\underline{H}_3$-β), 1.28 (s, 3H, CC$\underline{H}_3$-α), 1.24 (s, 3H, CC$\underline{H}_3$-α,β); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (O$\underline{C}$OCH$_3$-α), 169.9 (O$\underline{C}$OCH$_3$-β), 164.4 (O$\underline{C}$OArOCH$_3$-β), 163.5 (O$\underline{C}$OArOCH$_3$-α), 163.4 (C-Ar), 138.6 (C-Ar), 138.2 (C-Ar), 131.8 × 2 (CH-Ar-α), 131.7 × 2 (CH-Ar-β), 128.3 × 2 (CH-Ar-α), 128.2 × 2 (CH-Ar-β), 128.1 × 2 (CH-Ar-β), 128.0 × 2 (CH-Ar-α), 127.6 (CH-Ar-α), 127.5 (CH-Ar-β), 122.4, 122.2 (C-Ar-α,β), 113.7 × 2 (CH-Ar-α,β), 103.4 (C-1′β), 103.0 (C-1′α), 99.8, 99.6 ($\underline{C}$CH$_3$-α,β), 95.2 (C-1α), 91.0 (C-1β), 75.1, 74.9 (C-3α,β, C-3′α,β), 72.6, 71.6, 71.2 (C-4α,β, C-4′α,β), 70.7, 70.5, 70.4 (C-2α,β, C-2′α,β), 65.8 (O$\underline{C}$H$_2$Ar-β), 65.6 (O$\underline{C}$H$_2$Ar-α), 63.9, 61.8 (C-5α,β, C-5′α,β), 55.4 (OCOArO$\underline{C}$H$_3$-α,β), 48.0, 47.7 (O$\underline{C}$H$_3$-α,β), 20.5 (OCO$\underline{C}$H$_3$-α), 20.4 (OCO$\underline{C}$H$_3$-β), 17.6, 17.5 (C$\underline{C}$H$_3$-α,β); HRMS (ESI) m/z: $C_{33}H_{42}O_{14}Na$ $[M + Na]^+$ calcd. 685.2467; found: 685.2478.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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