

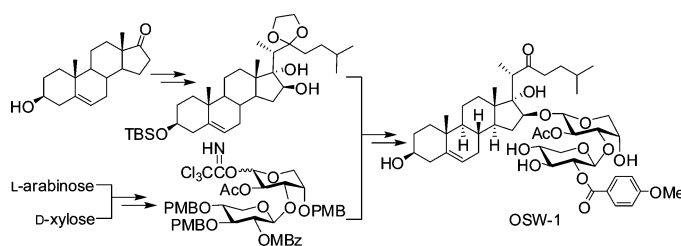
A Total Synthesis of OSW-1

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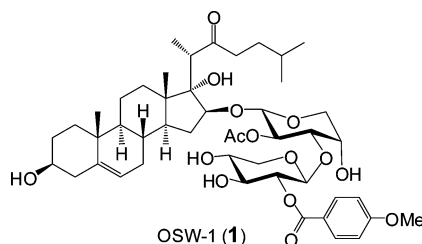
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A new and practical method was developed to synthesize OSW-1, a natural saponin with potent antitumor activities, from (+)-dehydroisoandrosterone, L-arabinose, and D-xylose on gram scale. The synthesis was achieved in 10 linear steps with an overall yield of 6.4% starting from (+)-dehydroisoandrosterone.

Introduction

OSW-1 (**1**) is a steroidal saponin isolated from *Ornithogalum saundersid*,¹ which belongs to a group of cholestane glycosides. The structure of OSW-1 is rather unique in that its disaccharide moiety linked to the steroidal aglycon O-16 position contains a *p*-methoxybenzoyl group. OSW-1 has exhibited exceptionally potent cytotoxicity,^{2,3} with IC₅₀ between 0.1 and 0.7 nM, to a variety of malignant tumor cells, including leukemia, mastocarcinoma, lung adenocarcinoma, pulmonary large cell carcinoma, and pulmonary squamous cell carcinoma. Therefore, OSW-1 is a promising lead compound for development of novel antitumor drugs.^{4,5}



Owing to its interesting structure and highly potent anticancer activity, OSW-1 has been an attractive synthetic target for organic chemists. For example, Yu^{6,7} and Jin^{8,9} groups have

independently developed total syntheses of OSW-1, while other groups have reported the synthesis of OSW-1 aglycon and other partial structures,^{10–13} as well as OSW-1 analogues.^{14–30}

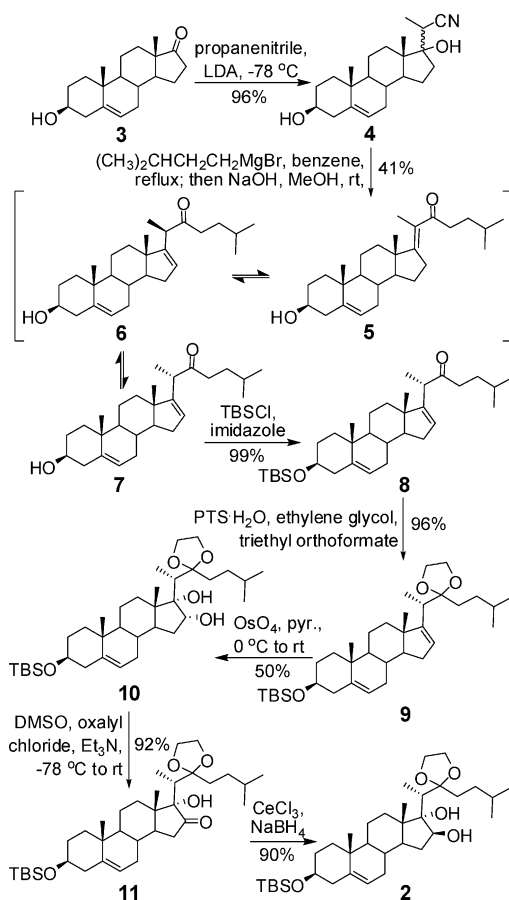
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SCHEME 1



Structure–activity relationship studies on OSW-1 analogues have revealed new compounds that have potent antitumor activity.^{7,19,21} In this paper, we have described a new, efficient, and practical synthesis of OSW-1, which can be performed on gram scales.

Results and Discussion

Synthesis of the Aglycon. Our overall synthetic design for OSW-1 was to first prepare the aglycon and the disaccharide moiety, which have different properties, separately and then couple them together to obtain the synthetic target. Scheme 1 has outlined the preparation of the aglycon, using commercially available (+)-dehydroisoandrosterone **3** as the starting material. In this synthesis, a key step was to introduce a side chain to the C-17, as described by Yu^{6,7} and Jin.^{8,9} For this purpose, we first added propanenitrile to **3** at $-78\text{ }^{\circ}\text{C}$ by an aldol condensation reaction catalyzed by LDA to obtain an epimeric mixture

4 in an excellent yield upon recrystallization. As both isomers could be used in the next step, we did not try to separate them further. However, we discovered that, when the reaction was quenched at room temperature, instead of $-78\text{ }^{\circ}\text{C}$, the yield of **4** was poor, while the starting material was recovered, suggesting that the retro-aldol condensation reaction was prominent at higher temperature. Further elongation of the side chain by refluxing **4** with a Grignard reagent in benzene proceeded smoothly, but the addition reaction was accompanied by β -elimination to give **5** as well as a small amount of **6** and **7** as an inseparable mixture. We have also tested some other reaction conditions, e.g., using THF or diethyl ether as the reaction solvent, but the reaction in benzene gave the best results. According to the literature,³¹ **5**, **6**, and **7** would reach an equilibrium under basic conditions to give the thermodynamically more stable **7** as the major product. Therefore, we treated the mixture of **5**, **6**, and **7** with NaOH in MeOH. The NMR spectrum of the newly formed mixture revealed 4:3:5 ratios of **5**, **6**, and **7**. Although these three compounds were inseparable on TLC or by silica gel column chromatography, fortunately, the desired product **7** could be separated from the other two isomers by recrystallization from hexane. Moreover, after **7** was collected, the mother liquid could be concentrated, and the residue was treated with NaOH again to yield another crop of **7** upon recrystallization from hexane. This procedure was repeated another time to finally obtain **7** in a good yield (73%). The stereochemistry of epimers **6** and **7** was determined through analysis of their ^1H NMR spectra. According to the literature,³¹ the proton NMR signal of 21-CH₃ in **6** appears downfield (δ 1.25) compared to that of 21-CH₃ in **7** (δ 1.15). The configuration of **7** was further confirmed by comparing the physical data of its subsequent products with those of the same structures reported in the literature. For example, after selective protection of 3-OH in **7** by *tert*-butyldimethylsilyl (TBS) via reacting with TBS chloride and imidazole in DMF and then protection of the C-22 carbonyl group by ethylene glycol to form a ketal, the product **9** gave ^1H and ^{13}C NMR spectra identical with that reported by Yu et al.⁶ Both reactions were very clean and gave excellent yields. Eventually, the key intermediate **9** was obtained from **3** in only 4 separate steps, in contrast to 7 to 9 steps described in the literature.⁶ In addition, the reactions were very reliable and the reaction products were easily purified through recrystallization, facilitating large-scale synthesis.

Compound **9** was transformed into **2** in 3 steps as described in the literature.^{6,10} First, **9** was regioselectively dihydroxylated to afford 16 α ,17 α -diol **10** in a moderate yield with the recovery of some starting material and the observation of some polar byproducts which might be derived from excessive oxidation. The inversion of C-16 stereochemistry was conveniently realized after regioselective Swern oxidation of 16-OH with DMSO and oxalyl chloride and then reduction of the resultant ketone **11** by NaBH₄ in the presence of CeCl₃ to give **2** exclusively. Consequently, **2** was obtained from (+)-dehydroisoandrosterone in 7 steps and an overall yield of 15%.

Synthesis of the Disaccharide Moiety. Monosaccharides as glycosyl acceptors and donors employed in this synthesis were prepared from L-arabinose and D-xylose, respectively (Scheme 2). After **12** was obtained from L-arabinose as reported,³² it was regioselectively *p*-methoxybenzylated with the assist of dibutyltin complex to afford **13**, which was directly subjected to

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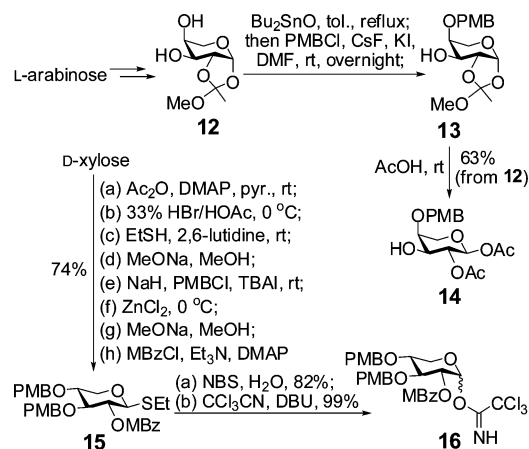
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SCHEME 2

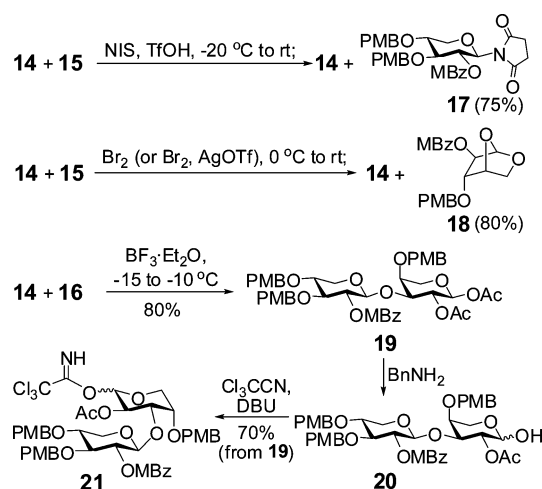


acetolysis to give the desired glycosyl acceptor **14**. In contrast to galactose derivatives in which 3-OH is usually more reactive than 4-OH, in **12**, 4-OH was more reactive than 3-OH, probably because, as a pentose, arabinose has a less hindered 4-OH. Compound **14** had an acetyl group attached to its 2-OH, while its 4-OH and 1-OH groups were protected by a *p*-methoxybenzyl (PMB) group and an acetyl group, respectively. It was expected that its anomeric acetyl group could be selectively removed, after the desired disaccharide was constructed, to subsequently convert the disaccharide into a glycosyl donor used for glycosylation of the aglycon. Eventually, **14** was synthesized from L-arabinose on multigram scales in an overall yield of 56%.

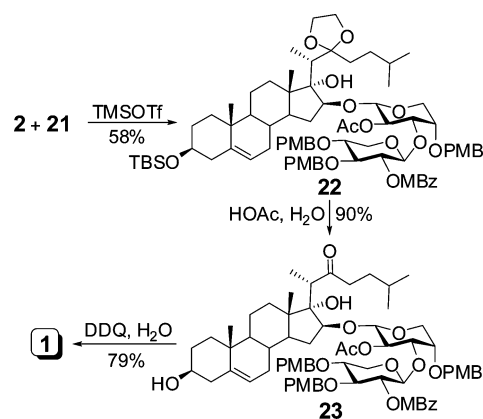
Monosaccharide donors **15** and **16** were prepared according to Jin's method⁹ with modified workup procedures. In brief, D-xylose was transformed into **15** through a series of reactions without isolation of the reaction intermediates, and only **15** was finally purified by column chromatography to get an overall yield of 74% on a multigram scale. Thereafter, **15** was converted to Schmidt donor **16** following oxidative deprotection of the anomeric center with *N*-bromosuccinimide (NBS) and H₂O and then trichloroacetimidation of the resultant hemiacetal. The α - and β -anomers of **16** were separable and both isomers were individually characterized, but their mixture was employed in subsequent glycosylation.

We first tried the glycosylation of **14** using **15** as glycosyl donor and *N*-iodosuccinimide (NIS) and triflic acid (TfOH) as promoter. Instead of the desired disaccharide, the reaction gave **17** as the major product with complete recovery of **14**. This result indicated that **15** was activated by NIS/TfOH, but the resultant reactive intermediate reacted with the byproduct of NIS, rather than **14**, suggesting that the former might be more nucleophilic than the latter. To avoid this problem, we then used bromine as promoter in the presence, as well as in the absence, of silver triflate (AgOTf). This reaction also failed to yield the desired disaccharide; instead, **18** was obtained as the major product. These results suggest that **14** is a particularly poor glycosyl acceptor, which is consistent with the relative reactivity shown by the two hydroxyl groups in **12**. Fortunately, the glycosylation of **14** with **16** as glycosyl donor went well to give **19** in a good yield and stereoselectivity, and the reaction was also proved to be very reliable. Finally, **19** was converted to glycosyl donor **21** as an α - and β -anomeric mixture upon selective removal of the anomeric acetyl group and then trichloroacetimidation of the resultant hemiacetal **20**.

SCHEME 3



SCHEME 4



Synthesis of OSW-1. With both the aglycon **2** and the disaccharide donor **21** in hand, the final assembly of OSW-1 was straightforward (Scheme 4). The glycosylation of **2** by **21** was achieved with trimethylsilyl triflate (TMSOTf) as promoter to produce the protected OSW-1 **22**. Global deprotection of **22** was accomplished in two separate steps. First, the TBS and ketal groups at O-3 and C-22 positions of the aglycon, respectively, were removed under mild acidic conditions. Next, the PMB groups on the disaccharide moiety of **23** were removed by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation to afford the synthetic target OSW-1 (**1**). The physical data of our final product were identical with the reported data of OSW-1.^{1,6,9}

In summary, OSW-1 was synthesized from (+)-dehydroisoandrosterone **3** in 10 linear steps and an overall yield of 6.4%, with new and efficient procedures developed to prepare the aglycon as well as the monosaccharide and disaccharide building blocks. This synthesis is highlighted by the reliability of all involved transformations and the simple workup procedures. For example, in the preparation of the aglycon and the monosaccharide building blocks, most intermediates were either purified through recrystallization or directly used in subsequent reactions without purification, which enabled large-scale synthesis. Consequently, OSW-1 was obtained in gram scale. This new synthetic strategy is currently employed to prepare various derivatives of OSW-1 for studies of its structure–activity relationships and for exploration of novel anticancer therapeutics.

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Experimental Section

Compound 4.³¹ To the solution of (+)-dehydroisoandrosterone (3, 3.06 g, 10.6 mmol) and propanenitrile (5 mL, 70 mmol) in 200 mL of THF was added LDA in THF (20 mL, 40 mmol) at -78°C . After the reaction mixture was stirred for another 30 min, it was diluted with diethyl ether and then quenched with saturated aq NH_4Cl solution at -78°C . The organic layer was separated and dried over anhydrous Na_2SO_4 . After filtration and removal of the solvent, the residue was recrystallized from diethyl ether and hexane to give **4** (3.5 g, 96%) as colorless crystals. ^1H NMR (CDCl_3 , 400 MHz): δ 5.33 (br, 1H), 4.58–4.46 (m, 1H), 2.84–2.70 (q, $J = 6.8$ Hz, 1H), 2.32–2.20 (m, 2H), 2.04–1.83 (m, 6H), 1.76–1.40 (m, 12H), 1.35 (d, $J = 6.8$ Hz, 3H), 1.18–1.10 (m, 1H), 1.04 (s, 3H), 0.94 (s, 3H). HR ESI MS: calcd for $\text{C}_{22}\text{H}_{33}\text{NO}_2$ 343.2511, found 343.2507 (M^+).

Compound 7.³¹ To the solution of **4** (2.78 g, 8.1 mmol) in 200 mL of benzene was added freshly prepared 3-methylbutylmagnesium bromide in benzene (80 mL, 64 mmol). The reaction mixture was refluxed overnight. TLC indicated the complete consumption of starting materials. Then, the organic solvent was removed under reduced pressure, and 200 mL of aq HCl solution (1 N) was added. After the mixture was stirred at rt overnight, it was extracted with diethyl ether. The combined organic layer was dried with anhydrous Na_2SO_4 and condensed. The residue was purified with a silica gel column briefly to afford an inseparable mixture of **5**, **6**, and **7** (1.78 g, 55%). To a solution of 2.98 g of the mixture of **5**, **6**, and **7** in 40 mL of MeOH and 12 mL of H_2O was added 6 g of NaOH. After the mixture was refluxed for 4 h, MeOH was removed under reduced pressure. The remaining mixture was extracted with diethyl ether. The combined organic layer was dried with anhydrous Na_2SO_4 and condensed. The residue was then dissolved in 100 mL of hot hexane for recrystallization to obtain 1.10 g of the desired product **7**. The mother liquid was condensed and the residue was dissolved in MeOH and H_2O and treated with NaOH again. Following the same workup and recrystallization protocol, another crop of pure **7** was obtained. After repeating this procedure one more time, a total of 2.20 g of **7** was obtained (73%). $[\alpha]^{20}_{\text{D}} + 11.0$ (c 1.0, CH_2Cl_2). ^1H NMR (CDCl_3 , 400 MHz): δ 5.37 (s, 2H), 3.35 (m, 1H), 3.20 (q, $J = 6.8$ Hz, 1H), 2.53–2.45 (m, 1H), 2.39–2.20 (m, 3H), 2.18–1.80 (m, 7H), 1.70–1.24 (m, 13H), 1.15 (d, $J = 6.8$ Hz, 3H), 1.14–0.96 (m, 4H), 0.90–0.80 (m, 7H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 154.5, 141.3, 125.4, 121.6, 71.8, 57.3, 50.8, 47.5, 45.9, 42.5, 38.5, 37.4, 36.9, 34.9, 33.3, 31.8, 31.7, 31.5, 30.8, 27.8, 22.7, 22.5, 21.0, 19.5, 17.1, 16.5. EI MS: calcd for $\text{C}_{27}\text{H}_{42}\text{O}_2$ 398.3, found 399.5 ($\text{M} + \text{H}^+$).

Compound 8.⁶ To the solution of **7** (1.03 g, 2.58 mmol) and imidazole (0.45 g, 7.76 mmol) in 20 mL of CH_2Cl_2 was added TBSCl (0.58 g, 3.87 mmol) at rt. After the reaction mixture was stirred for 2 h, aq HCl solution (1 N) was added to quench the reaction, and the reaction mixture was extracted with diethyl ether. The combined organic layer was washed with saturated NaHCO_3 , dried over anhydrous Na_2SO_4 , and then condensed. The residue was purified by column chromatography to give **8** (1.37 g, 99%) as a white solid. $[\alpha]^{20}_{\text{D}} + 18.6$ (c 1.0, CH_2Cl_2). ^1H NMR (CDCl_3 , 200 MHz): δ 5.34 (br, 2H), 3.55–3.40 (m, 1H), 3.18 (q, $J = 6.8$ Hz, 1H), 2.58–1.80 (m, 7H), 1.80–1.40 (m, 17H), 1.15 (d, $J = 6.8$ Hz, 3H), 1.09 (s, 6H). ^{13}C NMR (CDCl_3 , 50 MHz): δ 211.6, 154.4, 141.9, 125.2, 120.9, 72.6, 57.2, 50.8, 47.4, 45.7, 42.9, 38.3, 37.4, 36.9, 34.7, 33.1, 32.1, 31.6, 31.3, 30.7, 27.7, 25.0, 25.7, 22.6, 22.3, 20.8, 19.4, 18.3, 16.9, 16.3, 4.5. EI MS: calcd for $\text{C}_{33}\text{H}_{56}\text{O}_2\text{Si}$ 512.4, found 513.7 ($\text{M} + \text{H}^+$).

Compound 9.⁶ To the solution of **8** (1.39 g, 2.71 mmol), ethylene glycol (0.5 mL, 8.94 mmol), and triethyl orthoformate (0.5 mL, 3.00 mmol) in 20 mL of benzene was added $\text{PTS} \cdot \text{H}_2\text{O}$ (20 mg, 0.10 mmol). The mixture was stirred at rt for 2 days and then quenched with saturated aq NaHCO_3 solution. The mixture was then extracted with Et_2O . After the organic layer was dried over anhydrous Na_2SO_4 and condensed, the product was purified by

column chromatography to give **9** (1.46 g, 96%) as a white solid. $[\alpha]^{25}_{\text{D}} + 38.4$ (c 1.0, CH_2Cl_2). ^1H NMR (CDCl_3 , 200 MHz): δ 5.66 (br, 1H), 5.35 (br, 1H), 3.96 (s, 4H), 3.60–3.40 (m, 1H), 2.44 (q, $J = 7.0$ Hz, 1H), 2.32–2.18 (m, 3H), 2.18–1.90 (m, 2H), 1.90–1.38 (m, 21H), 1.38–1.10 (m, 6H), 1.10–0.92 (m, 9H), 0.92–0.76 (m, 11H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 156.6, 141.1, 124.0, 121.6, 113.9, 71.7, 65.9, 65.3, 57.3, 47.5, 42.4, 39.2, 37.2, 36.8, 34.9, 34.0, 32.5, 31.7, 31.4, 30.7, 28.4, 22.7, 20.9, 19.4, 17.4, 15.7, -4.5 . EI MS: calcd for $\text{C}_{35}\text{H}_{60}\text{O}_3\text{Si}$ 556.4, found 557.6 ($\text{M} + \text{H}^+$).

Compound 10.⁶ To the solution of **9** (0.40 g, 0.71 mmol) in 10 mL of diethyl ether and 0.5 mL of pyridine was added OsO_4 (0.35 g, 1.38 mmol) at -60°C . Then, the reaction mixture was warmed to rt and stirred for 3 h. The reaction was quenched with saturated aq NaHSO_3 solution and the suspension was stirred overnight. The mixture was extracted with ethyl acetate, and the combined organic layer was dried over anhydrous Na_2SO_4 . After concentration, the residue was purified by column chromatography to give **10** (0.21 g, 50%) as a white solid. $[\alpha]^{25}_{\text{D}}$ 56.67 (c 0.99 CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ 5.30 (1H, d, $J = 4.2$ Hz), 4.28 (1H, m), 3.97 (4H, m), 3.47 (1H, m), 1.12 (3H, d, $J = 7.0$ Hz), 0.98 (3H, s), 0.88 (9H, s), 0.77 (3H, s), 0.04 (6H, s). ^{13}C NMR (CDCl_3 , 75 MHz): δ 141.5, 120.9, 115.7, 82.4, 75.9, 72.6, 65.8, 64.4, 49.9, 49.6, 48.0, 45.3, 42.8, 37.2, 36.5, 33.3, 32.8, 32.1, 31.8, 31.3, 29.7, 28.1, 25.9, 22.7, 20.4, 19.4, 18.2, 14.3, 13.1, -4.6 . EI MS: calcd for $\text{C}_{35}\text{H}_{62}\text{O}_5\text{Si}$ 590.4, found 591.5 ($\text{M} + \text{H}^+$).

Compound 11.⁶ After the solution of oxalyl chloride (0.11 mL) and DMSO (0.18 mL) in 2 mL of CH_2Cl_2 was stirred at -50°C for 15 min, a solution of **10** (0.26 g, 0.44 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was stirred at -50°C for another 15 min, and then 1.0 mL of triethylamine was added. After the reaction mixture was warmed to rt slowly, the product was extracted with CH_2Cl_2 , dried with anhydrous Na_2SO_4 , and condensed. The residue was purified by column chromatography to give **11** (0.24 g, 92%) as a white solid. $[\alpha]^{25}_{\text{D}} - 150$ (c 1.13, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz): δ 5.30 (1H, d, $J = 5.2$ Hz), 4.05–3.90 (4H, m), 3.47 (1H, m), 2.72 (1H, q, $J = 7.4$ Hz), 1.02 (3H, s), 1.01 (3H, d, $J = 7.4$ Hz), 0.87 (9H, s), 0.05 (6H, s). ^{13}C NMR (CDCl_3 , 75 MHz): δ 215.5, 141.6, 120.7, 115.4, 85.4, 72.5, 63.4, 63.3, 49.5, 46.9, 45.4, 42.7, 41.2, 37.2, 37.1, 36.7, 32.7, 32.2, 32.0, 30.8, 30.2, 28.3, 25.9, 22.7, 22.4, 20.1, 19.4, 18.2, 15.0, 14.3, -4.6 . EI MS: calcd for $\text{C}_{35}\text{H}_{60}\text{O}_5\text{Si}$ 588.4, found 589.7 ($\text{M} + \text{H}^+$).

Compound 2.⁸ To a solution of **11** (0.40 g, 0.07 mmol) in 50 mL of THF was added 0.80 g of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ and 0.40 g of NaBH_4 at 0°C . The reaction mixture was stirred at 0°C for 4 h and then extracted with CH_2Cl_2 . The organic layer was dried and concentrated, and the residue was purified by column chromatography to provide **2** (0.36 g, 90%) as a white solid. $[\alpha]^{25}_{\text{D}} - 36$ (c 1.0, CHCl_3). ^1H NMR (CDCl_3 , 400 MHz): δ 5.30 (d, 1 H, $J = 4.2$ Hz, H-6), 4.05 (m, 1 H), 3.94–4.07 (m, 4 H), 3.48 (m, 1 H), 2.59 (q, 1 H, $J = 7.5$ Hz), 1.18 (s, 3 H), 1.02 (d, 3 H, $J = 7.5$ Hz), 0.90 (s, 3 H), 0.87 (s, 9 H), 0.89, 0.87 (2d, 6 H, $J = 6.5$ Hz), 0.02 (s, 6 H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 141.6, 121.3, 116.7, 92.5, 87.0, 81.8, 72.8, 64.3, 63.0, 49.8, 48.1, 48.0, 43.0, 37.5, 36.7, 36.1, 34.1, 33.3, 33.0, 32.9, 32.3, 32.1, 28.5, 26.1, 22.9, 22.5, 20.9, 19.6, 18.4, 112.7, 12.2, -4.4 . HR FAB MS: calcd for $\text{C}_{35}\text{H}_{61}\text{O}_5\text{Si}$ ($\text{M} - \text{H}^+$) 589.4288, found 589.4250.

Compound 14. A mixture of **12** (5.55 g, 26.9 mmol) and Bu_2SnO (6.72 g, 27 mmol) in 100 mL of toluene was refluxed with azeotropic removal of H_2O for 2 h. The reaction mixture was concentrated under reduced pressure. To the residue were added DMF (50 mL), CsF (7.6 g, 50 mmol), KI (6 g, 40 mmol), and *p*-methoxybenzyl chloride (4.38 mL, 32 mmol) at 0°C . The mixture was stirred at rt overnight and then diluted with CH_2Cl_2 . The organic phase was washed with brine, dried over Na_2SO_4 , and concentrated to obtain **13**. The crude product **13** was dissolved in 50 mL of AcOH, stirred at rt for 1 h, and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and washed with brine, dried over Na_2SO_4 , and concentrated. Flash column chromatography of the product gave **14** as colorless syrup (6.0 g,

63%). $[\alpha]^{25}_D +51.2$ (c 1.0, CHCl_3). ^1H NMR (CDCl_3 , 400 MHz): δ 7.26 (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.8$ Hz, 2H), 5.58 (d, $J = 6.4$ Hz, 1H), 5.10 (t, $J = 6.4$ Hz, 1H), 4.66 (d, $J = 11.2$ Hz, 1H), 4.48 (d, $J = 11.2$ Hz, 1H), 4.08 (dd, $J = 13.2, 3.2$ Hz, 1H), 3.80 (s, 3H), 3.75 (br, 2H), 3.52 (d, $J = 13.2$ Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 170.4, 169.7, 159.8, 129.8, 129.4, 114.2, 92.2, 74.1, 71.5, 71.4, 70.7, 62.4, 55.5, 21.2, 21.1. ESI MS: calcd for $\text{C}_{17}\text{H}_{22}\text{O}_8$ 354.1, found 377.0 ($\text{M} + \text{Na}^+$). HR EI MS: calcd for $\text{C}_{17}\text{H}_{22}\text{O}_8$ 354.1315, found 354.1324 (M^+).

Disaccharide 19. After a mixture of **16** (13.4 g, 20 mmol), **14** (3.55 g, 10 mmol), and 4 Å MS (5.0 g) in dry CH_2Cl_2 (50 mL) was stirred at rt for 3 h and then cooled to -15°C , $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2 mmol, 10%) was added. The reaction mixture was stirred at -15 to -10°C for another 2 h, and the ^1H NMR spectrum of the mixture showed the completion of reaction. Et_3N (1.0 mL) was added to quench the reaction, and the mixture was filtered off to remove molecular sieves. The filtrate was combined and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to afford **19** (6.9 g, 80%) as a white foamy solid. $[\alpha]^{25}_D +6.6$ (c 1.0, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ 7.92 (d, $J = 9.0$ Hz, 2H), 7.26 (d, $J = 8.5$ Hz, 2H), 7.24 (d, $J = 9.0$ Hz, 2H), 7.09 (d, $J = 9.0$ Hz, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 6.86 (d, $J = 9.0$ Hz, 2H), 6.84 (d, $J = 8.5$ Hz, 2H), 6.67 (d, $J = 8.5$ Hz, 2H), 5.53 (d, $J = 5.5$ Hz, 1H), 5.20 (t, $J = 7.5$ Hz, 1H), 5.17 (t, $J = 7.5$ Hz, 1H), 4.70 (d, $J = 6.0$ Hz, 1H), 4.66 (d, $J = 11.5$ Hz, 2H), 4.63 (d, $J = 11.5$ Hz, 1H), 4.62 (d, $J = 11.5$ Hz, 1H), 4.58 (d, $J = 11.5$ Hz, 1H), 4.53 (d, $J = 11.5$ Hz, 1H), 3.98 (dd, $J = 7.0, 4.5$ Hz, 1H), 3.92 (dd, $J = 7.5, 6.0$ Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H), 3.50 (dd, $J = 12.5, 2.5$ Hz, 1H), 3.27–3.39 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 169.9, 169.2, 164.9, 163.7, 159.6, 159.4, 159.3, 132.1, 130.5, 130.3, 129.9, 129.8, 122.5, 114.1, 113.9, 113.8, 102.0, 95.0, 92.2, 79.2, 76.8, 73.9, 72.8, 72.0, 71.8, 69.9, 63.1, 55.6, 55.5, 55.3, 21.0, 20.8. ESI MS: calcd for $\text{C}_{46}\text{H}_{52}\text{O}_{16}$ 860.3, found 883.3 ($\text{M} + \text{Na}^+$), 899.3 ($\text{M} + \text{K}^+$). HR EI MS: calcd for $\text{C}_{46}\text{H}_{52}\text{O}_{16}$ 860.3255, found 860.3267 (M^+).

Protected OSW-1 (22). To a solution of compound **19** (3.45 g, 4.0 mmol) in THF (40 mL) was added benzylamine (4 mL). After the reaction mixture was stirred at rt overnight, it was diluted with CH_2Cl_2 . The organic layer was sequentially washed with aq HCl solution (1 N) and H_2O and then dried over Na_2SO_4 . The solvent was removed under reduced pressure, and the product was purified by silica gel column chromatography to give an α - and β -anomeric mixture of **20** as colorless syrup. To a solution of **20** in dry CH_2Cl_2 (20 mL) was added trichloroacetonitrile (1.0 mL) and DBU (2 drops), and the mixture was stirred at rt overnight before the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on a Et_3N deactivated silica gel column to afford **21** (2.87 g), which was directly applied to the next step of synthesis. A solution of **21** (1.5 g, 1.6 mmol), **2** (0.69 g, 1.1 mmol), and 4 Å MS (1.0 g) in dry CH_2Cl_2 (10 mL) was stirred at rt for 3 h. After the mixture was cooled to -20°C , TMSOTf (10.6 μL , 0.055 mmol) was added. The reaction mixture was stirred at -15 to -10°C for 4 h and then quenched with Et_3N (0.3 mL). After the reaction solution was filtered off to remove molecular sieves and the filtrate was condensed under reduced pressure, the residue was purified by flash column chromatography on a Et_3N deactivated silica gel column to afford **22** (0.58 g, 58%) as a white foamy solid, with the recovery of some **2** (0.25 g). **22**: $[\alpha]^{25}_D -19.2$ (c 1.0, CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): δ 7.96 (d, $J = 9.2$ Hz, 2H), 7.26 (d, $J = 8.8$ Hz, 2H), 7.25 (d, $J = 8.8$ Hz, 2H), 7.16 (d, $J = 8.8$ Hz, 2H), 6.81 (d, $J = 9.2$ Hz, 2H), 6.80 (d, $J = 8.0$ Hz, 2H), 6.79 (d, $J = 8.8$ Hz, 2H), 6.73 (d, $J = 8.0$ Hz, 2H), 5.25 (br, 2H), 5.09 (br, 1H), 5.02 (br, 1H), 4.76 (d, $J = 11.2$ Hz, 1H), 4.11 (m, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 3.07 (q, $J = 7.2$ Hz, 1H), 2.64 (q, $J = 7.6$ Hz, 1H),

1.98 (s, 3H), 1.14 (d, $J = 7.6$ Hz, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.85 (s, 3H), 0.67 (d, $J = 6.8$ Hz, 3H), 0.57 (d, $J = 5.6$ Hz, 3H), 0.05 (s, 6H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 169.2, 165.2, 164.1, 163.7, 159.3, 159.1, 141.2, 132.3, 130.6, 130.4, 130.3, 129.8, 129.5, 128.8, 122.3, 121.6, 116.6, 113.9, 113.8, 113.7, 101.2, 92.1, 87.4, 72.9, 71.6, 71.3, 64.6, 62.8, 55.6, 55.5, 55.3, 49.9, 48.3, 48.2, 46.1, 43.0, 37.5, 36.6, 35.4, 33.7, 32.6, 32.5, 32.3, 31.9, 31.8, 29.9, 28.4, 26.2, 22.9, 22.7, 22.1, 21.2, 20.9, 19.6, 18.5, 12.7, -4.3 . ESI MS: calcd for $\text{C}_{79}\text{H}_{110}\text{O}_{19}\text{Si}$ 1390.7, found 1429.2 ($\text{M} + \text{K}^+$).

Partially Protected OSW-1 (23). After a solution of **22** (0.55 g, 0.39 mmol) in a mixture of AcOH and H_2O (1:5, 5 mL) was stirred at 70°C for 2 h, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography to give **23** (0.44 g, 90%) as a white solid. $[\alpha]^{25}_D -22.8$ (c 1.0, CHCl_3). ^1H NMR (CDCl_3 , 400 MHz): δ 7.97 (d, $J = 9.2$ Hz, 2H), 7.24 (d, $J = 8.8$ Hz, 2H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.16 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 8.4$ Hz, 2H), 6.82 (d, $J = 8.4$ Hz, 2H), 6.69 (d, $J = 8.8$ Hz, 2H), 5.30 (br, 1H), 5.18 (t, $J = 4.8$ Hz, 1H), 4.79 (br, 2H), 4.67 (d, $J = 11.2$ Hz, 1H), 4.63 (d, $J = 12.4$ Hz, 1H), 4.58 (d, $J = 11.2$ Hz, 1H), 4.53 (d, $J = 11.6$ Hz, 1H), 4.52 (d, $J = 11.2$ Hz, 1H), 4.49 (d, $J = 11.2$ Hz, 1H), 4.29 (br, 1H), 4.21 (d, $J = 4.0$ Hz, 1H), 3.94 (dd, $J = 11.2, 7.6$ Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.72 (s, 3H), 3.59 (q, $J = 4.0$ Hz, 1H), 3.52 (m, 1H), 3.42 (m, 2H), 3.03 (q, $J = 7.2$ Hz, 1H), 1.89 (s, 3H), 1.13 (d, $J = 7.6$ Hz, 3H), 0.95 (s, 3H), 0.79 (s, 3H), 0.74 (d, $J = 6.8$ Hz, 3H), 0.73 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 169.1, 164.9, 163.7, 159.4, 159.2, 159.1, 140.5, 139.6, 132.1, 130.6, 130.3, 130.2, 129.6, 129.4, 129.1, 122.4, 121.8, 113.9, 113.8, 113.7, 113.6, 100.3, 85.8, 72.0, 71.9, 71.4, 55.6, 55.4, 55.2, 49.6, 48.1, 46.1, 46.0, 42.4, 39.1, 37.3, 36.5, 32.3, 32.2, 31.9, 31.8, 31.7, 27.5, 22.6, 22.3, 20.9, 20.7, 19.5, 13.7, 11.9. ESI MS: calcd for $\text{C}_{71}\text{H}_{92}\text{O}_{18}$ 1232.6, found 1255.2 ($\text{M} + \text{Na}^+$), 1271.2 ($\text{M} + \text{K}^+$).

OSW-1 (1).^{1,6,9} To a mixture of **23** (0.68 g, 0.5 mmol) in CH_2Cl_2 and H_2O (10:1, 50 mL) was added DDQ (0.40 g, 1.8 mmol) at rt. The reaction mixture was stirred at rt overnight and then concentrated in vacuum. The residue was purified by column chromatography to give **1** (0.32 g, 79%) as a white solid. $[\alpha]^{25}_D -40$ (c 0.3, CH_3OH) [lit.¹ -43 (c 0.25, CH_3OH)]. ^1H NMR ($\text{C}_5\text{D}_5\text{N}$, 500 MHz): δ 8.31 (d, 2 H, $J = 8.8$ Hz), 7.07 (d, 2 H, $J = 8.8$ Hz), 5.67 (dd, 1 H, $J = 9.1, 7.8$ Hz), 5.55 (d, 1 H, $J = 7.9, 6.3$ Hz), 5.37 (d, 1 H, $J = 3.9$ Hz), 5.11 (d, 1 H, $J = 7.6$ Hz), 4.79 (s, 1 H), 4.57 (d, 1 H, $J = 6.0$ Hz), 4.39 (br s, 1 H), 4.31 (dd, 1 H, $J = 5.2, 11.1$ Hz), 4.26–4.20 (m, 2 H), 4.20–4.12 (m, 3 H), 3.81 (br s, 1 H), 3.73 (s, 3 H), 3.18 (q, $J = 7.4$ Hz, 1 H), 1.96 (s, 3 H), 1.27 (d, 3 H, $J = 7.5$ Hz), 1.06 (s, 3 H), 0.98 (s, 3 H), 0.87 (d, 3 H, $J = 6.4$ Hz), 0.84 (d, 3 H, $J = 6.4$ Hz). ^1H NMR (CD_3OD , 500 MHz): δ 8.04 (d, $J = 6.8$ Hz, 2 H), 7.02 (d, $J = 6.8$ Hz, 2 H), 5.33 (d, $J = 4.0$ Hz, 1 H), 4.93 (t, $J = 6.0$ Hz, 1 H), 4.86 (m, 1 H), 4.66 (d, $J = 5.6$ Hz, 1 H), 4.14 (d, $J = 4.8$ Hz, 1 H), 3.96 (m, 2 H), 3.87 (s, 3 H), 3.82 (dd, $J = 10.0, 3.6$ Hz, 1 H), 3.76 (m, 2 H), 3.62 (m, 4 H), 3.47 (dd, $J = 9.6, 1.6$ Hz, 1 H), 2.92 (q, $J = 5.6$ Hz, 1 H), 2.47 (m, 1 H), 2.14–2.25 (m, 4 H), 1.70 (s, 3 H), 1.11 (d, $J = 6.0$ Hz, 3 H), 1.02 (s, 3 H), 0.82 (m, 9 H). HR FAB MS: calcd for $\text{C}_{47}\text{H}_{68}\text{NaO}_{15}$ 895.4456, found 895.4459 ($\text{M} + \text{Na}^+$).

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Supporting Information Available: Experimental procedures to prepare **15**, **16**, and **18**, as well as the NMR spectra of **1**, **2**, **7**, **10**, **14**, **16** α , **16** β , **19**, **22**, and **23**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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