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A useful strategy for synthesis of the disaccharide of OSW-1†

Bin Wang,‡*[a] Yan Zhang‡[a] and Xiangyan He *[b]

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A flexible, efficient, and practical synthesis route was developed to synthesize an OSW-1 disaccharide. The synthesis took 13 steps from L-arabinose and D-xylose derivatives, and the overall yield was 7.2%. The region preferentially protects various D-xylose hydroxides because the TBS group selectively reacts with this hydroxide at low concentrations due to greater activity at the C-4 hydroxyl of D-xylose. Then, high efficiency selectively protects C-2 hydroxyl and C-3 hydroxyl of D-xylose, respectively. The first high yield of glycosylation on an OSW-1 synthesis disaccharide was achieved by taking sulfide donor **4** with β-PMP anomeric L-arabinose acceptor **12**. The cytotoxicity reveals that the analogy has a high IC50 for a variety of cell types. This approach should provide a versatile way to modify OSW-1's disaccharide.

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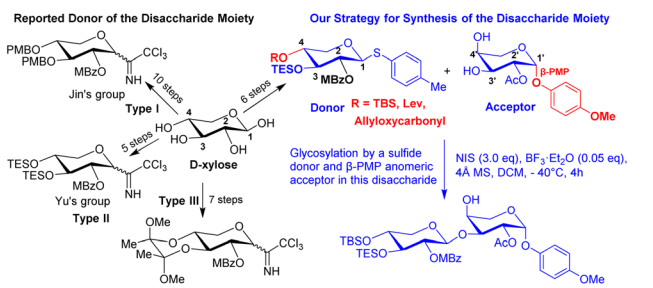
Introduction

A natural saponin, OSW-1, was isolated from the bulbs of *Ornithogalum saudersiae* by Sashida *et al.* in 1992.[1] Pharmacological studies showed that OSW-1 exhibits exceptionally potent antitumor activities in nanomolar concentration (IC50 0.1–0.7 nM).[2a] It is more potent than those used in clinical treatment as anticancer agents such as mictomycincadeiamycin and Taxol.[2] Therefore, the higher potential anticancer activity and structure of OSW-1 has always attracted chemists and biologists.[3]

The structure of OSW-1 can be separated into two parts: aglycon and disaccharide moieties. Fuchs *et al.* reported the first synthesis of the aglycone portion of OSW-1 in 1998.[3a] Yu *et al.* reported the first complete synthesis of OSW-1 in 1999.[3b] Jin *et al.* published another complete synthesis of OSW-1 in 2001.[3c] Even though many synthetic methods for the preparation of disaccharides have been published to date,[3–6] Yu's method appears to be the most straightforward and practical. However, they used hydrogenation to remove the benzyl group. Three major types of donors have been reported (Scheme 1), Jin's group reported 10 steps from D-xylose to generate the type I donor.[3c,d] Yu's group reported the shortest synthesis from D-xylose to generate the type II donor,[3b,f,6e,13a] but they had to use hydrogenation to remove the benzyl group. Seven steps from D-xylose to generate type III donor by using 2,3-butanedione to selective protection of the 3,4-diol moiety of D-xylose,[6b] but this donor does not very commonly apply in total synthesis OSW-1 or analogies. Though these three types of donors use different protection groups, there is the same concept of using the same group to protect the 3,4-diol moiety of D-xylose. The structure–activity relationship studies of OSW-1 found that the disaccharide moiety, particularly the C-2 position of 4-methoxybenzoyl (MBz) and C-2′ position of groups acetyl (Ac) at the disaccharide unit, play a critical role. Recently, a lot of studies on site-selective functionalization of carbohydrates have been reported.[7] Sakurai group reported the synthesis of OSW-1 derivatives *via* site-selective acylation on the xylose moiety, and they discovered an effective approach was to insert fluorescence or a biotin moiety on the xylose portion with no activity loss.[8] Therefore, developing a route to simplify the selective modification of xylose and provide a flexible intermediate compound for OSW-1 or analogies modification at the end of the synthesis is extremely important.

In this report, we describe a flexible, efficient, and practical synthesis of the disaccharide moiety, with a focus on shortening the xylose donor synthesis route and selectively introducing different groups at C-2 hydroxyl, C-3 hydroxyl and C-4 hydroxyl on the xylose donor. We specifically report the acceptable yield



Scheme 1 Synthetic plan for the disaccharide moiety.

[a]*Department of Pharmacy, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang Uygur Autonomous Region, China. E-mail: binw4870@gmail.com*
[b]*Scientific Research and Education Centre, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang Uygur Autonomous Region, China. E-mail: xiangyan.he9@gmail.com*

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‡ Equal contribution as first-author.

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of glycosylation in this disaccharide utilizing a sulfide donor. Meanwhile, the presence of β-PMP in the anomeric position of arabinose caused C-3′ hydroxyl to be more active than C-4′ hydroxyl, which improved the yield of glycosylation (Scheme 1).

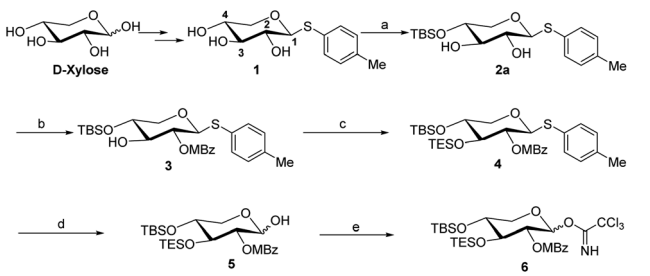
Result and discussion

The synthesis of the xylose moiety was outlined in Scheme 2 utilizing xylose as a starting material, and compound **1** was synthesized as described in the literature.[3c,d]

The crucial step was regioselective introducing the TBS protect group to the C-4 hydroxy position. After optimization of the reaction conditions (Table S1†), we found that a low concentration of **1** was prepared initially in dry dichloromethane, followed by slowly adding TBSCl at room temperature to afford regioselective **2a** in a yield of 85%. However, we noticed that when TBSOTf replaced TBSCl or increased the concentration of compound **1**, the yield of **2a** was decreased, and in the meantime, we acquired a by-product that was both C-4 and C-2 hydroxyl position protected. Encouraging by successfully synthesized compound **2a**, we plan to introduce another different group at the 4-hydroxyl position of xylose, after scanning several conditions (Table 1). Compound **1** could regio-selectively react with ally chloroformate using *N*,*N*-diisopropylethylamine (DIPEA) as a base to afford **2b** in 70%. Meanwhile, treating compound **1** with levulinic acid and *N*,*N*′-diisopropylcarbodiimide to afford compound **2c**, even though the yield was moderate (57%). This result successfully supplied an extra protection group in the xylose moiety.

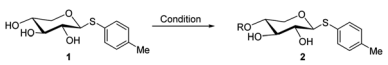
With compound **2a** in hand, we have tried to finish the rest of the xylose part. The C-2 hydroxyl site was selectively acetylated using *p*-methoxybeznoyl chloride to yield **3** (Scheme 2). While compound **2a** is reacted with ally chloroformate using triethylamine (Et_3N) as a base, it produced the high-yield product **3a**, which provides more options for disaccharide modification, as shown in ref. 9. The TES protection of the C-3 hydroxy position by TESOTf in dimethylformamide (DMF) went off without a hitch. We tried a variety of different conditions (Table S2†), such as using a different solvent (*e.g.*, dichloromethane or tetrahydrofuran) or replacing TESOTf with TESCl as the reagent, but only the reaction employing TESOTf in DMF with DMAP yielded the best results. Finally, hemiacetal **5** was obtained by deprotecting S-Tol of glycoside **4** in the presence of *N*-bromosuccinimide, followed by trichloroacetimidation with trichloroacetonitrile under normal conditions to generate. After five steps from compound **1**, the target Schmidt donor **6** was produced with a total yield of 39%.

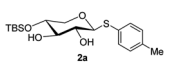
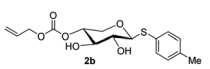
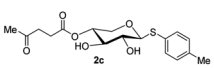
The acceptor synthesis is depicted in Scheme 3. β-PMP-glycoside **8** was made from tetra-acetyl-L-arabinose **7** utilizing BF_3Et_2O as a promoter, and the acetyl group was deprotected with sodium methoxide to afford **9**. Protection of the *cis*-3′,4′-diol **9** with 2,2-dimethoxypropane resulted in **10**, while protection of the C-2′ hydroxy group with acetyl anhydride resulted in **11**. The 3′,4′-acetonide was deprotected by 70% acetic acid/H_2O, yielding diol **12**. We attempted to protect position C-4′hydroxy with TESCl reagent, but C-3′ hydroxyl protected as the major product, and only 19% of the desired compound **13**. This result is different from the α-anomeric position which only protected C-4′ hydroxyl with TESCl reagent.[3c,d] The C-4′ hydroxyl selectivity has been observed in the previous attempts to synthesize OSW-1 analogues,[6] including a detailed analysis by Pakulski and co-workers. They concluded this unusual C-4′ hydroxyl selectivity to a novel equatorial C-4′ hydroxyl of arabinose with the $^1C_4$ conformation constrained by the intramolecular hydrogen bonding between C-3′ hydroxyl and the *cis*-anomeric oxygen atom of arabinoside. We assume that the presence of β-PMP in the anomeric position causes C-3′ hydroxyl more active than C-4′



Scheme 2 Reaction condition: (a) TBSCl (1.1 eq.), imidazole, DCM (c = 0.02), rt, 85% yield; (b) MBzCl, DMAP, Et_3N, DCM, room temperature, 2 h, 81% yield; (c) TESOTf, DMAP, Et_3N, DMF, room temperature, 2 h, 79% yield; (d) NBS, acetone/aq. $NaHCO_3$ (5 : 1), 30 min, rt, 86% yield; (e) Cl_3CCN, DBU, DCM, overnight, room temperature, 87% yield.

Table 1 Regioselectivity introducing the protecting group to the C-4 OH position



Entry	Condition	Result
1	TBSCI (1.1 eq.), imidazole DCM (c = 0.02), rt	
2	Allyl chloroformate (1.1 eq.), DIPEA (c = 0.02), 0 °C	
3	Levulinic acid (1.1 eq.), DIC, Et_3N DCM (c = 0.02), rt	

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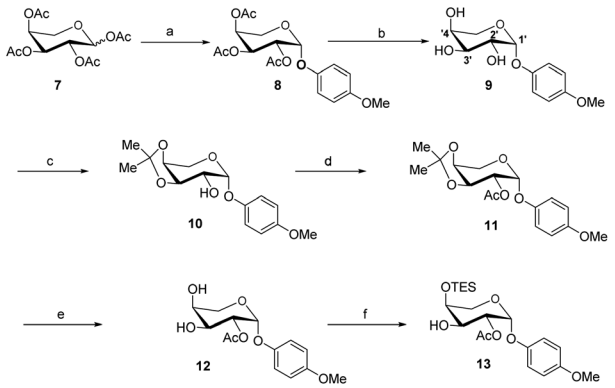
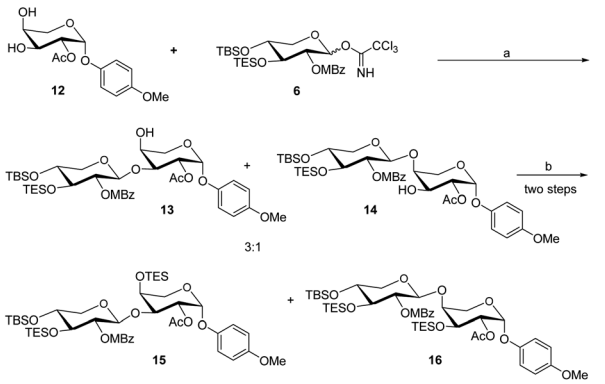


Scheme 3 Reaction condition: (a) PMP-OH, $BF_3 \cdot Et_2O$, DCM, 0–25 °C. 3 days, 57% yield; (b) MeONa, MeOH, 95% yield; (c) CAS, 2,2-dimethoxypropane, DMF, 50 °C, 90% yield; (d) Ac_2O, pyridine, 94% yield; (e) 70% AcOH, 86% yield; (f) TESCl, Et_3N, DCM, −50 °C, 25% yield.

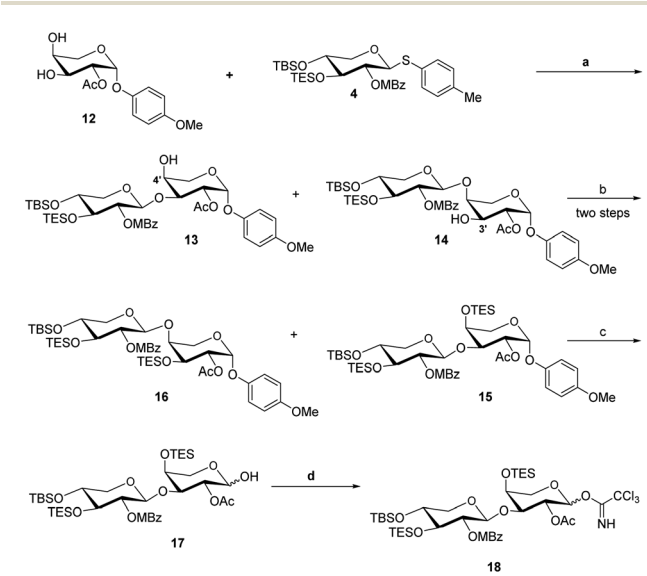
hydroxyl, which is consistent with Pakulski's report.[6c,d] The structure of compound **13** was confirmed by 2D NMR after being treated with chloroacetyl chloride (as shown in ESI†). With compounds **6** and **13** in hand, we focused on glycosylation. After optimization of the reaction conditions (Table S3†), we found that the glycosylation of **13** with **6** as glycosyl donor and 0.1 eq. $BF_3 \cdot Et_2O$ as a promoter, the reaction gave **15** with a yield of 78%. This result confirmed that glycosylation occurred in the presence of $BF_3 \cdot Et_2O$, but the yield of compound **13** is insufficient. Meanwhile, we realized that utilizing **12** as the acceptor directly should be the better option. After five processes, the necessary acceptor **12** was prepared with a total yield of 40%.

In the presence of $BF_3 \cdot Et_2O$, glycosylation of **12** with **6** as the glycosyl donor resulted in an inseparable mixture of disaccharides **13** and **14** (Scheme 4). The protection of the mixture compound with TESCl using Et_3N as the base. The disaccharide **15** (72% yield) and **16** (20% yield) were obtained by chromatographic separation of the combination using DCM with hexane as elution.

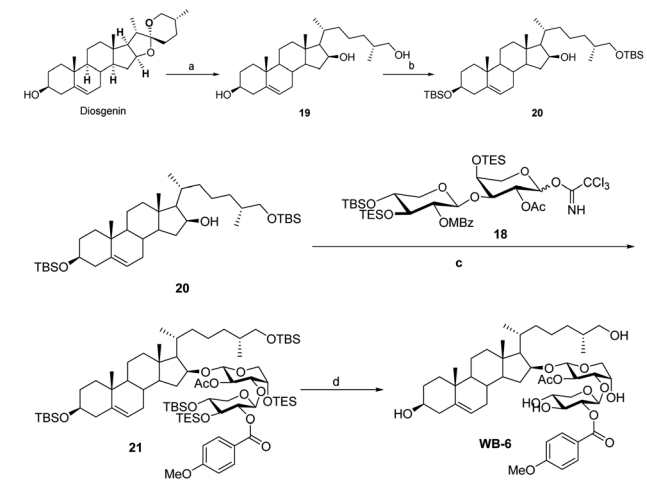
Even though we were able to properly produce disaccharide **15**, this synthesis method is not very efficient. In 2008, Guo *et al.*, attempted to glycosylate this disaccharide by a sulfide donor with α-acetyl anomeric acceptor, but were unsuccessful, despite employing *N*-iodosuccinimide (NIS) and triflic acid as promoters or bromine as a promoter with silver triflate.[10] In 2019, Yu's group achieved the glycosylation of this disaccharide by a sulfide donor with a β-benzyl anomeric acceptor, but only 23% yield of the desired product. We thus decided to undertake the direct glycosylation of sulfide donor and β-PMP anomeric acceptor in one-pot reaction. After optimization of the glycosylation of this disaccharide by a sulfide donor with β-PMP anomeric acceptor (Table S4†), we found that utilizing NIS and $BF_3 \cdot Et_2O$ as promoters, the glycosylation of **12** with **4** was successfully generated a mixture of the target **13** and by-product



Scheme 4 Reaction condition: (a) $BF_3 \cdot Et_2O$ (0.1 eq.), 4 Å MS, DCM, −60 °C, 1.5 h; (b) TESOTf, Et_3N, room temperature, DCM, 2 h.



Scheme 5 Reaction condition: (a) NIS (3.0 eq.), $BF_3 \cdot Et_2O$ (0.05 eq.), 4 Å MS, DCM, −40 °C, 4 h; (b) TESOTf, Et_3N, room temperature, DCM, 2 h; (c) CAN, CH_3CN/H_2O (4 : 1), −10 °C, 10 min, 75% yield; (d) Cl_3CCN, DBU, DCM, overnight, room temperature, 88% yield.



Scheme 6 Reaction condition: a, diosgenin (1 g), Zn (150 eq.), conc. HCl (75 mL), EtOH (150 mL), reflux, 66% yield; (b) TBSCl, DBU, THF, rt 16 h, 92% yield; (c) TMSOTf, 4 Å MS, DCM, −40 °C, 3 h, 68% yield; (d) Pd $(MeCN)Cl_2$, acetone/H_2O,overnight, room temperature, 82% yield.

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Table 2 Cell cytotoxicity of **WB-06** and Taxol

	IC_{50} (nM)						
	HCT-50	HeLa	MDA-MB-231	MCF-7	SKOV-3	HMC-3M	MCF-10A
WB-06	95.6	18.6	20.5	16.3	22.1	65.1	56.3
Taxol	57.8	2.1	5.5	12.1	9.8	—	—

14, then TES protection to generate **15** in 68% (Scheme 5). Furthermore, we confirmed β-PMP anomeric enhanced 3′-hydroxyl activity by using compound **13** as an accepter to glycosylate with donor **4** using NIS and BF_3Et_2O as promoters generated compound **15** in a 65% yield, as shown in ref. 11. Finally, hemiacetal **17** was obtained by deprotecting PMP of glycoside **15** in the presence of CAN, followed by trichloroacetimidation with trichloroacetonitrile under normal conditions to generate **18**.

Sapogenin **20** was synthesized from diosgenin using a process described in the literature (Scheme 6).[12] The OSW-1 analogy was synthesized with both aglycon **20** and the disaccharide donor **18** readily hand. Under typical conditions, compound **20** reacted with disaccharide donor **18** to produce **21**. The OSW-1 analogue **WB-6** was produced by the deprotection of **21** with Pd $(MeCN)Cl_2$. The physical characteristics of **WB-6** are the same as those reported.[12b]

Antitumor activities *in vitro*

The synthetic OSW-1 analogue **WB-06** was screened against HCT-8, HeLa, MDA-MB-231, MCF7, Skov-3. HMC-3, MCF-10A cell lines by alamarBlue cytotoxicity assay. Taxol was used as a positive control; all the experiments were repeated three times. The HCT-8, HeLa, MDA-MB-231, and MCF7 cell line was selected for comparison with the literature-reported OSW-1 or OSW-1 analogy cytotoxicity data.[12c,13] All of the other cell lines were screened for the first time. The results presented in Table 2 illustrate the concentrations required for 50% cell death (IC50 values) when compared to the vehicle-treated negative control. The IC50 value for **WB-6** range from 18.6 nM to 110.6 nM less active to Taxol. In particular, the IC50 value for HeLa, MDA-MB-231, and MCF7 cells is comparable to the literature-reported value. **WB-6** also showed valuable benefits to Skov-3 cell lines. Unfortunately, no selectivity between tumor and non-tumor cell lines (HMC-3 and MCF-10A) was observed for **WB-6**.

The *in vitro* cytotoxicity against HCT-8 (colon carcinoma cell line), HeLa (cervical cancer cell line), MDA-MB-231 (Human Breast cancer cell line), MCF7 (breast cancer cell line), Skov-3 (ovarian cancer cell line), HMC-3 (human microglia cell line), MCF-10A (non-tumorigenic epithelial cell line) cell lines were evaluated by the standard MTT assay.

Conclusions

Finally, we have developed a flexible synthesis strategy for OSW-1 disaccharide, which was synthesized in 13 steps with an overall yield of 7.2% from xylose derivate **1** and arabinose derivate **7**. A new and effective process for preparing disaccharide building blocks has been created. Donor **4** was achieved by protecting the C-2, C-3, and C-4 hydroxyl positions independently, allowing for easy modification. The xylose donor moiety is useful for studying the structure–activity relationship of OSW-1 and discovering new anticancer treatments. Specifically, the first high yield of glycosylation on an OSW-1 synthesis disaccharide was achieved by sulfide donor **4** with β-PMP anomeric L-arabinose acceptor **12**. The cell analysis shows that analogy has higher anti-tumor potential. This strategy should provide a versatile way to modify OSW-1's disaccharide. Further application of this disaccharide to generate OSW-1 and analogies is in progress in our laboratory.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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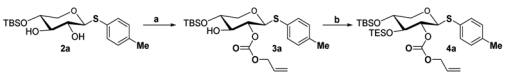
9 While compound **3a** is reacted with ally chloroformate using triethylamine (Et_3N) as a base, it produces the high yield product **4a**, which provides more options for disaccharide modification.



Scheme 7. Reaction condition: (a) allyl chloroformate, Et_3N, DMF, room temperature, 2 h. (b) TESOTf, DMAP, Et_3N, DMF, room temperature, 2 h.

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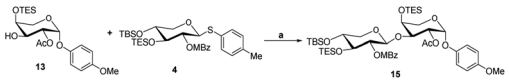
11 Compound **13** as an accepter to glycosylate with donor **4** using *N*-iodosuccinimide (NIS) and BF_3Et_2O as promoters generated compound **15**.



Scheme 5. Reaction condition: (a) $BF_3 \cdot Et_2O$ (0.05 eq.), 4 Å MS, DCM, −40 °C.

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