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A new synthesis of potent antitumor saponin OSW-1 via Wittig rearrangement

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Abstract

OSW-1 and its analogues in which thiophene ring was introduced at the side chain were synthesized employing Wittig rearrangement of 17*E*(20)-ethylidene-16α-(4′-methyl-2′-thienyl)methyloxy steroid. The synthesis required nine steps from the known 17*E*(20)-ethylidene-16α-hydroxy steroid in 15.6% overall yield.

Keywords: OSW-1; Analogues; Thiophene; Wittig rearrangement

OSW-1 (**1**), an acylated cholestane diglycoside, has been isolated from the bulbs of *Ornithogalum saundersiae* (Liliaceae) by Sashida, Mimaki and co-workers in 1992 (Fig. 1).[1] OSW-1 exhibited extremely potent cytotoxic activity against various human malignant tumor cells. Its cytotoxic activities are from 10- to 100-fold more potent than some well-known anticancer agents in clinical use, such as mitomycin C, adriamycin, cisplatin, camptothecin, and taxol.[2] While OSW-1 is exceptionally cytotoxic against various tumor cells, it showed little toxicity to normal human cells. Much attention has been paid on the synthesis of OSW-1 because of its extraordinary potent activity.[3,4] A number of OSW saponin analogues with modified disaccharides,[5] side chains,[3d,6] and steroidal nuclei[7] have been obtained by means of chemical synthesis for SAR (structure–activity relationship) studies.

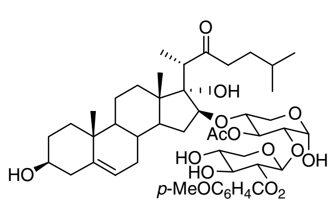

Fig. 1. Structure of OSW-1 (**1**).

Fuchs et al. proposed that the active intermediate might be an 22-oxocarbenium ion, which could be generated from 22-carbonyl and 16α-hydroxy moieties.[4b] Yu et al. have recently reported that both 22-methylene and 23-heteroatom (O, S, NH) analogues of OSW-1 were found to be as potent as the parent natural products against the growth of tumor cells.[6b–d] The precise mechanism by which OSW-1 exerts its effect remains unclear. For further study of a structure–activity relationship OSW-1 analogues having heterocyclic ring, such as thiophene and thiazole, at the side chain were designed. As part of our continuing work on the synthesis of naturally occurring compounds employing furan and related compounds as versatile synthons, we have succeeded in the synthesis of biologically active steroids with highly oxygenated side chains.[8] In this regard, we intended to synthesize an extremely potent antitumor saponin OSW-1 and its analogues by means of the Wittig rearrangement[9,10] of allyl thiophenemethyl ether for the construction of (20*S*)-22-hydroxy steroidal side chain. Here we wish to report the synthesis of OSW-1 and its analogues having thiophene ring at the side chain.

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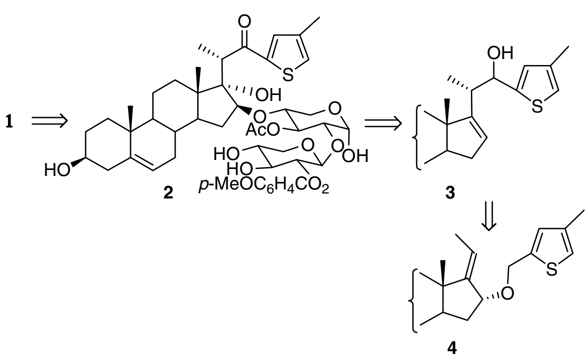
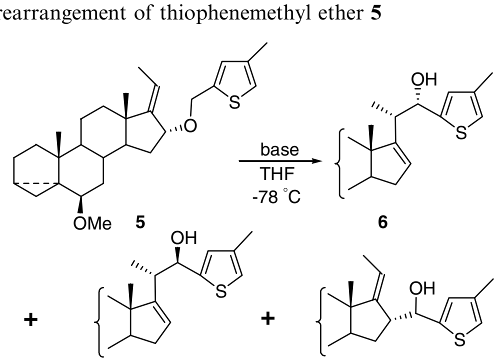
The key feature of our synthesis is based on stereoselective conversion of 22-hydroxy-22-(4′-methylthienyl) steroid **3** into OSW-1 thiophene analogue **2** by introduction of trans-diol functionality at the C-16 and -17 positions and glycosylation of aglycone with disaccharide (Scheme 1). Reductive desulfurization of thiophene analogue **2** would afford OSW-1 (**1**). (20*S*)-22-Hydroxy steroid **3** could be prepared by Wittig rearrangement of 17*E*(20)-ethylidene-16α-(4′-methyl-2′-thienyl)methyloxy steroid **4**.

We first investigated the Wittig rearrangement of allyl thiophenemethyl ether (Table 1). Model compound **5** was prepared by etherification of the known 16α-allylic alcohol[11] with 4-methyl-2-thiophenemethyl bromide[12] in 95% yield. Treatment of **5** with *n*-BuLi (10 equiv) in THF at −78 °C followed by warming to 0 °C gave [2,3]-rearranged products **6** and **7** and [1,2]-rearranged product **8** in a ratio of 23:23:54, respectively, in 97% total yield (entry 1), whereas reaction of **5** with *s*-BuLi (3 equiv) in THF at −78 °C produced **6**–**8** in a ratio of 19:34:47 in moderate yield (62%) (entry 2). *t*-BuLi was found to be the base of choice for the [2,3]-rearrangement (entry 3). The inconsistent diastereoselectivity observed at the C-22 position would not be rationally explained.



Scheme 1. Synthetic strategy for OSW-1 and its analogue.

Table 1
Witting rearrangement of thiophenemethyl ether **5**



Entry	Base[a]	Yield[c] (%)	Ratio of **6**/**7**/**8**
1	*n*-BuLi[b]	97	23:23:54
2	*s*-BuLi	62	19:34:47
3	*t*-BuLi	90	40:18:42

[a] *n*-BuLi (10 equiv), *s*-BuLi (3 equiv), and *t*-BuLi (5 equiv) were employed.
[b] *T* (°C): −78 to 0.
[c] Total yield of **6**–**8**.

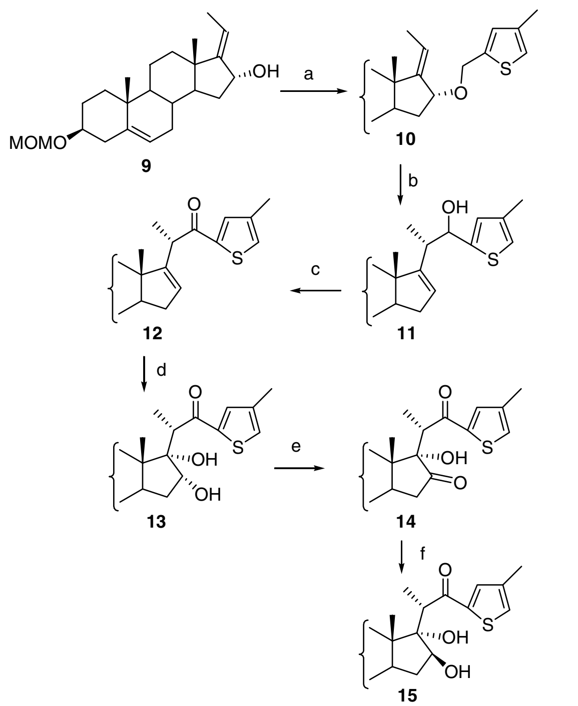
The absolute configuration at the C-22 position in 22-hydroxy steroids **6** and **7** was determined by the modified Mosher's method[13] and is shown in Figure 2.

We then embarked on the synthesis of OSW-1 and its thiophene analogues employing the Wittig rearrangement of thiophenemethyl ether (Scheme 2). Requisite thiophenemethyl ether **10** was prepared by etherification of the known allylic alcohol[14] **9** with 4-methyl-2-thiophenemethyl bromide[12] in the presence of 18-crown-6 in 92% yield. Treatment of **10** with *t*-BuLi (5 equiv) in THF at −78 °C gave [2,3]-rearranged product **11** (22α- and 22-β alcohols in a ratio of 78:22) in 59% yield. Oxidation of **11** with Dess–Martin periodinane[15] in CH_2Cl_2 afforded ketone **12** quantitatively. Attempts to convert **12** into trans-diol **15** via 16α,17α-epoxide were unsuccessful because stereoselective ring-opening reaction of the epoxide did not occur. Dihydroxylation of **12** with OsO_4 in the presence of pyridine gave cis-diol **13**, which was subjected to Swern oxidation[16] to furnish diketone **14** in 85% yield (two steps). Reduction of **14** with $NaBH_4$ in MeOH–CH_2Cl_2 (1:1, v/v) at −15 °C occurred chemoselectively to afford the desired trans-diol **15** in 82% yield. Pleasingly, intramolecular hemiacetalization of **15** did not proceed in our synthesis, while protection of carbonyl moiety at C-22 position was required at an early stage in most syntheses of OSW-1.[3,4]

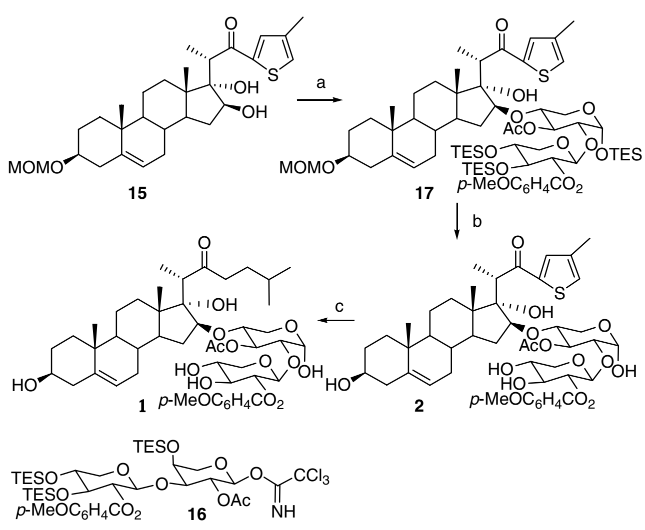
Glycosylation of steroid aglycone **15** with disaccharide imidate **16**, prepared from D-xylose and L-arabinose by the reported method,[3a] in the presence of TMSOTf provided β-glycoside **17** in 72% yield (Scheme 3). All the protecting groups, one MOM and three TES, were removed by treatment of **17** with TMSBr[17] to give OSW-1 thiophene analogue **2** in 73% yield. Finally, thiophene ring in **2** was reductively desulfurized with W-2 Raney Ni[18] under an atmosphere of hydrogen, furnishing OSW-1 (**1**) in 79% yield. The physical data of synthetic OSW-1 (**1**) are identical with those reported by Sashida.[1]

In conclusion, we have succeeded in a new approach to the synthesis of OSW-1 and its thiophene analogues using (20*S*)-22-hydroxy steroid with thiophene ring at the side chain, which was obtained by Wittig rearrangement of thiophenemethyl ether. Since OSW-1 analogue with thiophene **2** is similar to the above mentioned 23-heteroatom (O, S, NH) analogues of OSW-1 regarding the reactivity of carbonyl group at the C-22 position, thiophene analogue

Fig. 2. $\Delta\delta_{R-S}$ Values obtained for the MTPA esters of (22*S*)-alcohol **6** and (22*R*)-alcohol **7**.



Scheme 2. Reagents and conditions: (a) NaH (3 equiv), 18-crown-6 (3 equiv), 4-methyl-2-thiophenemethyl bromide (2 equiv), benzene, 70 °C, 12 h, 92%; (b) *t*-BuLi (5 equiv), THF, −78 °C, 30 min, 59% (α/β = 78:22); (c) Dess–Martin periodinane (1.3 equiv), CH_2Cl_2, rt, 1 h, 99%; (d) OsO_4, pyridine, CH_2Cl_2, −78 °C, 12 h, 99%; (e) oxalyl chloride (3 equiv), DMSO (6 equiv), CH_2Cl_2, −78 °C, 4 h, then Et_3N (12 equiv), −78 °C→rt, 86%; (f) $NaBH_4$ (5.5 equiv), MeOH–CH_2Cl_2 (1/1), −15 °C, 4 h, 82%.



Scheme 3. Reagents and conditions: (a) **16** (1.5 equiv), TMSOTf (0.2 equiv), MS4A, CH_2Cl_2, −78 °C, 1.5 h, 72%; (b) TMSBr (3.9 equiv), CH_2Cl_2, 0 °C, 1 h, 73%; (c) H_2, W-2 Raney Ni, MeOH, rt, 3 h, 79%.

2 could be expected to show potent antitumor activity. Currently, synthesis of OSW-1 analogues modified at the side chain with other heterocycles, such as thiazole, and investigation of its SAR are in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.087.

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