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A highly efficient synthesis of 22-deoxy-OSW-1 by utilizing the intact skeleton of diosgenin

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Abstract—**22-Deoxy-OSW-1** (**1**), an analogue of **OSW-1** with the potent anticancer activity, was synthesized by utilizing the intact skeleton of diosgenin in 11 steps in 13.7% overall yield. This synthesis demonstrated an effective and reasonable synthetic strategy for bioactive steroids with side chains.

OSW-1 and its analogues were isolated from *Ornithogalum saundersiae* bulbs.[1] They are members of the cholestane glycoside family characterized by the attachment of a disaccharide to the C-16 position of the steroid aglycone. Their IC_{50} values against human leukemia HL-60 cells range from 0.1 to 0.3 nM.[2] **OSW-1**, the main constituent of the bulbs, exhibits extraordinary cytostatic activities against various human malignant tumor cells. Its anticancer activities are 10–100 times more potent than some of the well-known anticancer agents currently in clinical use, such as mitomycin C, adriamycin, cisplatin, camptothecin, and taxol, but its toxicity to normal human pulmonary cells is significantly lower (IC_{50} 1500 nM). Recently, Yu and co-worker synthesized some **OSW-1** analogues for exploring the structure–activity relationship (SAR) of **OSW-1** and found that **22-deoxy-OSW-1** (**1**) (Fig. 1), with the 22-one (of **OSW-1**) being saturated into a CH_2, was slightly more potent than **OSW-1** against the tested three cancer cell lines [including AGS (stomach cancer cells) IC_{50} 1.38 μM, 7404 (liver carcinoma cells) IC_{50} 0.063 μM, and MCF-7 (breast cancer cells) 0.060 μM].[3]

The routine synthesis for **OSW-1** and analogues start from epiandrosterone.[3,4] It was prepared through the degradation of diosgenin, a procedure including thermal fragmentation in 200 °C acetic acid, chromic oxide induced oxidation, elimination, oximation and rearrangement reaction.[5] In connect with our project on the study of rational utilization of resource compounds,[6] we wish to explore a new synthesis of **22-deoxy-OSW-1** (**1**) directly from diosgenin rather than its degraded product—epiandrosterone. Different from routine synthesis of **22-deoxy-OSW-1**, the basic skeleton, 27-carbon atoms and functional groups of starting material diosgenin were fully expressed in the structure of **22-deoxy-OSW-1** in our new synthetic strategy (Scheme 1).

Comparing **22-deoxy-OSW-1** with the E/F ring-opened reduction product of diosgenin, one notices that they both have related side chains and the same disposal of the C-16 hydroxyl and the 21-methyl groups. Using the E/F ring-opened reduction product of diosgenin directly to synthesize the aglycone of **22-deoxy-OSW-1** (**1**), one only needs to move a hydroxyl group at C-26 to C-17 (Scheme 1). Obviously, it is a highly reasonable synthetic strategy according to atom economy.[7]

According to our synthetic strategy shown in Scheme 2, diosgenin (**2**) was reacted with benzyl bromide in the presence of NaH to protect the C3-OH of diosgenin in 98% yield. On treatment of **3** with Zn–Hg and hydrochloric acid in refluxing ethanol according to the literature[8] afforded the E/F ring-opening reduction product, 16β,26-dihydroxyl cholesterol **4** in 84.7% yield. Removal of the C26-OH of synthetic intermediate **4** was achieved via reduction of its tosylate **5** with $LiAlH_4$ in 73% overall yield in two steps. Subsequent oxidation of the C16-OH with Jones reagent provided the C16-ketone product **7** in excellent yield (91%). An attempt to introduce

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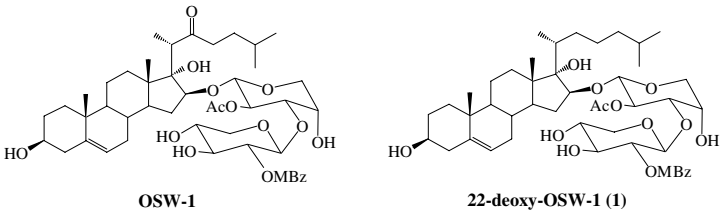
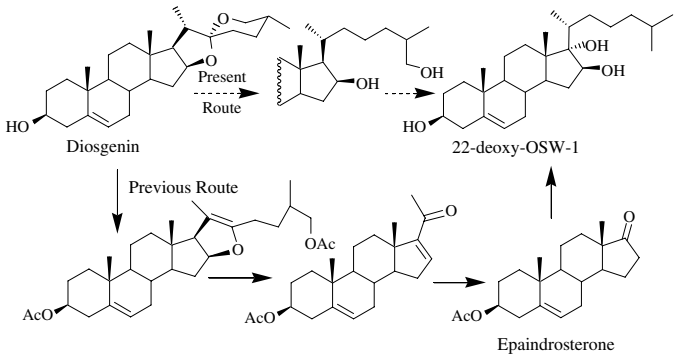
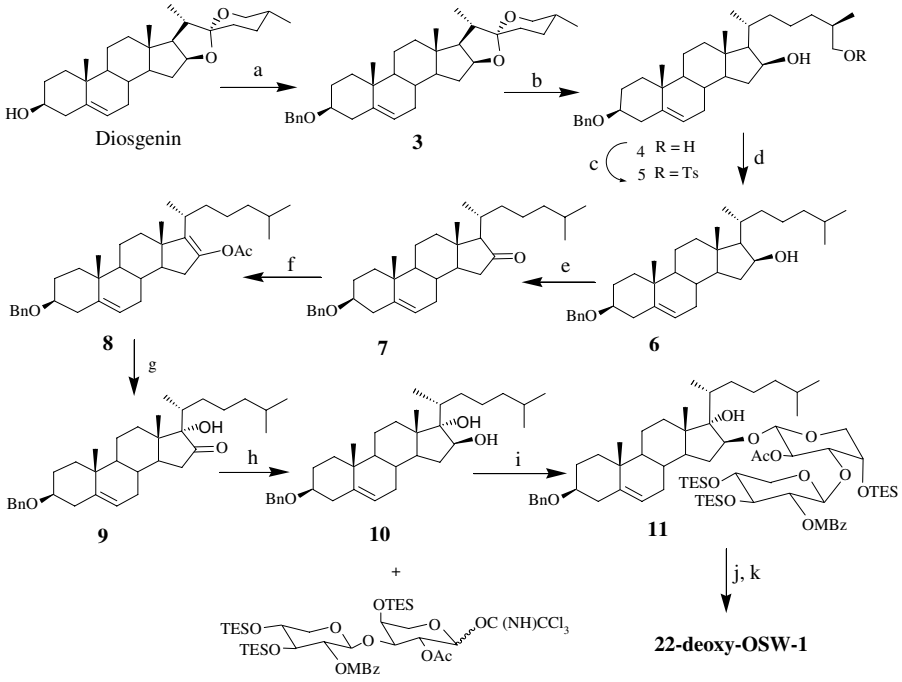


Figure 1. The structures of **OSW-1** and **22-deoxy-OSW-1**.



Scheme 1.



Scheme 2. Reagents and conditions: (a) BnBr, NaH, THF/DMF (1:2), 90 °C, 98%; (b) Zn, HCl, EtOH, reflux, 84.7%; (c) TsCl, pyridine, 0 °C to rt; (d) $LiAlH_4$, THF, rt, 73% (two steps); (e) Jones oxidation, 91%; (f) Ac_2O, $HClO_4$ (0.01 equiv), CCl_4, 86%; (g) (i) *t*-BuOK, THF, 0 °C; (ii) Davis reagent, −78 °C, 75%; (h) $LiAlH_4$, THF, −78 °C, 90%; (i) TMSOTf (0.1 equiv), −20 °C, CH_2Cl_2, 59%; (j) W-2 Raney Ni, anhydrous EtOH, rt, 93%; (k) AcOH–THF–H_2O (V/V, 8:8:1), 45 °C, 77%.

C17α-hydroxyl group in **7** through air oxidation in the presence of potassium *tert*-butoxide was unsuccessful. In order to functionalize C17, the 16-oxycholesterol **7** was converted to the corresponding enol acetate **8** with treatment of acetic anhydride and $HClO_4$ (0.01 equiv) as the catalyst.[9] Generation of the enolate from **8** by potassium ethoxide or potassium *tert*-butoxide[10] followed by in situ oxidation by Davis reagent stereoselectively gave 17α-hydroxy-16-oxocholesterol **9** in 75% yield. Stereoselective reduction of **9** by $LiAlH_4$ at −78 °C provided the requisite 16β,17α-dihydroxyl cholesterol **10** in 90% yield.[11] Thus, the protected aglycone of **22-deoxy-OSW-1** was synthesized with eight operations in 32.1% overall yield. The glycosylation of aglycone **10** with disaccharide trichloroacetimidate **12**[12] provided the corresponding protected **22-deoxy-OSW-1**

11 in 59% yield. Removal of all of the protecting groups by sequential treatment of compound **11** with W-2 Raney nickel at room temperature (for the deprotection of the benzyl groups) and AcOH–THF–H_2O (V/V, 8:8:1) at 45 °C (for the removal of the silyl groups) afforded the desired **22-deoxy-OSW-1** (**1**) in 77% yield. Its spectral data[13] were identical with that reported in the literature.[3]

In conclusion, the highly potent anticancer agent **22-deoxy-OSW-1** was successfully synthesized by utilizing the intact skeleton of diosgenin in 11 steps in 13.7% overall yield. This new synthetic strategy resulted in a remarkable improvement of synthetic efficiency, and more importantly, it enhanced the utilization efficiency of the resource compound diosgenin, decreased the production of chemical wastes without using some highly toxic reagents such as OsO_4 in the synthesis of **22-deoxy-OSW-1** compared with known procedures.[3]

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12. Disaccharide trichloroacetimidate **12** was synthesized according to the methods reported in Ref. 4.
13. Analytical data for our synthesized **22-deoxy-OSW-1** (**1**): $[\alpha]_D^{25}$ −18.6 (*c* 0.40, CH_3OH, lit.[3] −17.2 (*c* 0.40, CH_3OH)); ^1H NMR (300 MHz, C_5D_5N): δ 8.27 (d, $J = 9.0$ Hz, 2H), 7.02 (d, $J = 9.0$ Hz, 2H), 6.17 (br s, 1H), 5.85 (t, $'J = 7.5$ Hz, 1H), 5.65 (t-like, $J = 8.4$, 7.8 Hz, 1H), 5.32 (br d, $J = 4.5$ Hz, 1H), 5.08 (d, $J = 8.0$ Hz, 1H), 4.73 (d, $J = 7.2$ Hz, 1H), 4.59 (br s, 2H), 4.48 (s, 1H), 4.33–4.15 (6H, m), 3.68 (s, 3H), 2.53 (br d, $J = 6.8$ Hz, 2H), 1.85 (s, 3H), 1.28 (d, $J = 6.6$ Hz, 3H), 1.22 (s, 3H), 0.93 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (75 MHz, C_5D_5N): δ 169.35, 165.69, 164.00, 142.11, 132.56, 121.40, 114.23, 103.67, 102.60, 88.13, 86.99, 80.85, 76.31, 75.26, 71.95, 71.49, 70.96, 68.67, 67.10, 55.65, 50.64, 49.56, 49.06, 47.27, 43.67, 40.66, 37.98, 37.08, 35.83, 34.29, 33.42, 32.42, 30.83, 29.40, 28.43, 25.83, 23.24, 23.00, 21.20, 19.76, 17.89, 14.49, 13.36; HRMS (MALDI) calcd for $C_{47}H_{70}O_{14}Na$ $[M+Na]^+$: 881.46480; found: 881.46578.