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A new strategy for synthesizing the steroids with side chains from steroidal sapogenins: synthesis of the aglycone of OSW-1 by using the intact skeleton of diosgenin

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Abstract—The protected aglycone of saponin OSW-1, a new antitumor natural product, was synthesized in 13 linear steps in 9.5% overall yield by utilizing the intact skeleton of diosgenin. This strategy demonstrated a higher efficiency than the routine synthesis of steroids with side chains.

OSW-1 (**1**) and its analogues (**2**–**5**) 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, whereas compounds **4** and **5** have another glycosyl sugar connected at the C-3 position of the steroid (Fig. 1). Their IC_{50} values against human leukemia HL-60 cells range from 0.1 nM to 0.3 nM.[2] OSW-1 (**1**), the main constituent of the bulbs, exhibits extraordinary cytostatic activities against various human malignant tumor cells. Its anticancer activities are 10- to 100-fold 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).

OSW-1 (**1**) has been a very attractive synthetic target owing to its highly potent anticancer activities, novel structure and low content in natural plants.[1] Fuchs first reported the synthesis of the protected aglycone of OSW-1 starting from epiandrosterone,[3] which was prepared through the degradation of diosgenin (**6**) even though it is commercially available. The overall yield of epiandrosterone from **6** ranged from 25 to 50% (Scheme 1).[4,5] In 1999, Hui's group reported the total synthesis of OSW-1 by using a similar approach.[6] Recently, Jin and his co-workers presented a somewhat different approach to the synthesis of OSW-1 employing a stereoselective 1,4-addition of α-alkoxy vinyl cuprate to a steroid $\Delta^{17(20)}$-en-16-one,[7] in which epiandrosterone was still used as the starting material. In contract to the synthetic strategies mentioned above, we planned to synthesize the aglycone of OSW-1 and analogues with related side chains from the intact sapogenin skeletons rather than from their degradation products.

It is well known that side chain-containing natural steroids, such as vitamin D, brassinolide and cephalo-

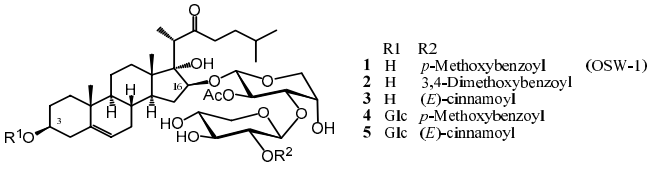
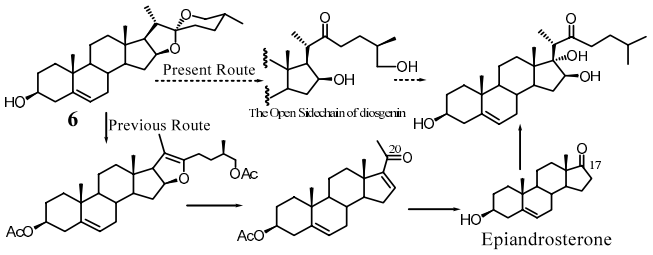


Figure 1. The structures of OSW-1 and its analogues.



Scheme 1.

Keywords: OSW-1; antitumor; aglycone; diosgenin; steroids.
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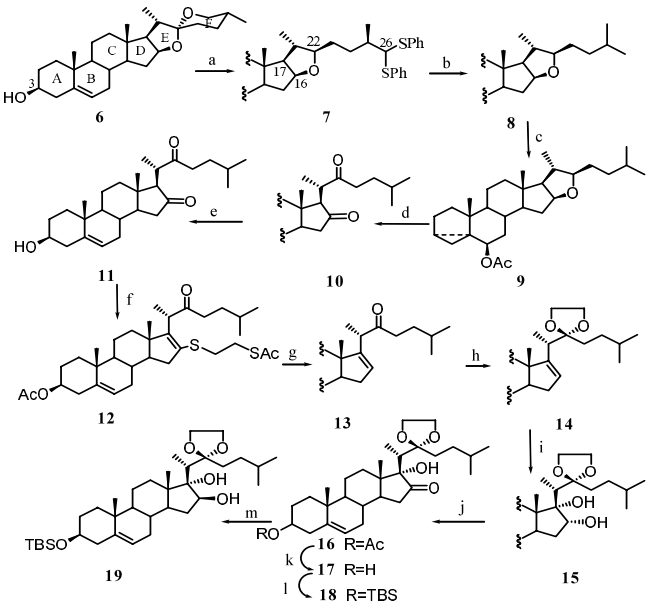


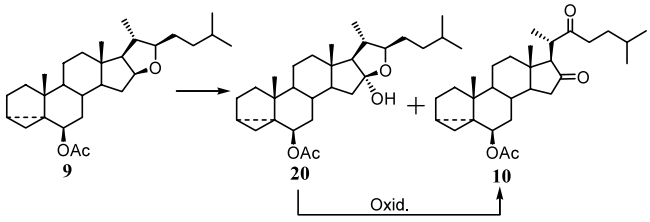
Scheme 2. *Reagents and conditions*: (a) PhSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 88.3%; (b) W-2 Raney Ni, anhydrous EtOH, reflux, 93.1%; (c) i. TsCl, Py, rt, ii. KOAc, acetone/H_2O, reflux, iii. Ac_2O, Py, DMAP, rt, 75.2%; (d) Oxone®, $NaHCO_3$, buffer, CH_2Cl_2/acetone, 80% after four-time oxidation; (e) TsOH, dioxane/H_2O, reflux, 0.5 h, 97%; (f) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, HOAc, 2.5 h, then Ac_2O, 20 min, 63.5%; (g) W-2 Raney Ni, anhydrous EtOH, rt, 0.5 h, 90%; (h) $HOCH_2CH_2OH$, $HC(OEt)_3$, TsOH, rt, 6.5 h, 85%; (i) OsO_4, Py, ether, −78°C ~ rt, 4 h, then H_2S bubbled through, 57.1%; (j) Swern oxidation, 87%; (k) K_2CO_3, MeOH, 100%; (l) TBSCl, imidazole, DMF, 87%; (m) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF, 94%.

statins and other marine steroids, are usually synthesized from steroid 17-ketones, or 20-ketones or 22-aldehydes.[8,9] There have been only a few reports on their synthesis by exploiting the intact skeletons of steroidal sapogenins.[10] Comparing OSW-1 with the E/F ring-opened form 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 open side chain of diosgenin directly to synthesize OSW-1, one only needs to move a hydroxyl group at C-26 to C-17 (Scheme 1). Obviously, it is a more reasonable synthetic strategy according to atom economy.[11] We present herein for the first time a successful synthesis of the aglycone of OSW-1 using the intact skeleton of diosgenin (Scheme 2).

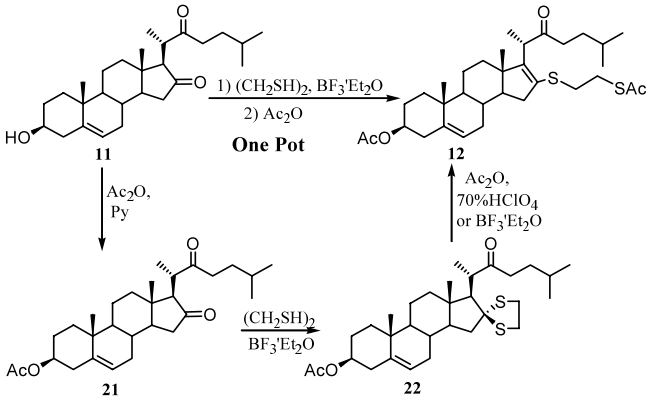
The opening of the E/F rings was the first key step for utilizing the intact skeleton of sapogenins to synthesize the aglycone of OSW-1. Diosgenin (**6**), an abundant and cheap plant-derived steroidal sapogenin, readily reacted with thiols or dithiols in the presence of a Lewis acid such as $BF_3{\cdot}Et_2O$ to afford directly the 26-thioacetal **7**.[12,13] Attempts to open the E/F rings by thioketalization of the C-22 spiroketal were unsuccessful due to intramolecular redox reaction between the C-22 and the C-26 functional groups.[12–14] Lewis acid catalyzed acetylation at the C-16 and C-26 hydroxyl groups failed in our previous exploration.[15] The 26-thioacetal **7** underwent reductive desulfurization catalyzed by W-2 Raney nickel[14b] to realize the needed conversion at C-26. For further modification of the E ring, the $\Delta^{5(6)}$-double bond and C-3 hydroxyl group in the A/B rings of **8** were protected via a classical carbocation rearrangement.[16] The oxidation of the A/B rings protected compound **9** by dimethyldioxirane which was generated in situ from Oxone® and acetone in a buffer of 4×10^{-4} mol/l aqueous ethylenediaminetetraacetic acid disodium salt (EDTADS)[17,18] directly resulted in the formation of the expected E-ring opened compound **10** (32%) and C-16 hydroxylation product **20** (61%). The latter could be transformed to compound **10** by further oxidation (Scheme 3).

After deprotection of the double bond, compound **11** was obtained, which had the same side chain and A/B rings as OSW-1. However, low conversion of **11** hampered the application of the similar strategy of constructing the 16,17-alkene from the 16-keto with PhSH in the presence of $BF_3{\cdot}Et_2O$.[19] Fortunately, **11** or its acetate **21** underwent 16-thioketalization with ethanedithiol regioselectively leaving the C-22 carbonyl group intact.[14b] The thioketal-opening-acetylization (TOA reaction) took place when the 16-thioketal was treated with Ac_2O in the presence of 70% $HClO_4$ or $BF_3{\cdot}Et_2O$ to produce the 16,17-alkene **12**. We also found that **11** could be converted to **12** in one-pot with $BF_3{\cdot}Et_2O$ catalyzing the acetylization, thioketalization and TOA reaction (Scheme 4).[19] The conversion from **11** to **12** is another key step in our route.[20]

Desulfurization of **12** with W-2 Raney nickel at room temperature produced compound **13**, which is a known intermediate in the synthetic strategies of Fuchs and



Scheme 3.



Scheme 4.

Hui.[3,6] We performed the further transformations according to the literature,[3,6] that is, ethylene glycol ketal protection of the 22-ketone **13**, dihydroxylation of the 16,17-alkene function in **14** with OsO_4, Swern oxidation of the 16α-OH group in **15**, conversion of 3-OAc in **16** to 3-OTBS in **18**, and stereoselective reduction of the 16-keto group in **18** to the 16β-OH group in **19**. Therefore, we completed the synthesis of the protected aglycone of saponin OSW-1 (compound **19**), which displayed identical spectral data with those reported.[21] Further optimization and synthesis of the disaccharide moiety of OSW-1 are currently in progress in our laboratory.

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20. *Syntheses of compound **12** from **11** in one-pot*: To the solution of **11** (2.08 g, 5.0 mmol) in 35 ml of HOAc, were added $HSCH_2CH_2SH$ (1.06 ml, 12.6 mmol) and $BF_3{\cdot}Et_2O$ (1.30 ml, 10.3 mmol) dropwise. The mixture was stirred at room temperature for 2.5 h and 20 ml of Ac_2O was added. The resultant mixture was stirred for an additional 20 min. The reaction was quenched with aqueous saturated $NaHCO_3$ solution, and then solid $NaHCO_3$ was added until no alveoli bubbled up. The mixture was extracted with EtOAc (50 ml×3). The combined organic layer was washed with aqueous saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography over silica gel (petroleum ether:ethyl acetate = 40:1) to afford **12** (1.830 g, 63.5%) as a yellowish oil.
*The spectra of compound **12***: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.40 (1H, d, J = 3.9 Hz, 6-H), 4.64–4.58 (1H, m, 3-H), 3.68 (1H, q, J = 6.8 Hz, 20-H), 3.00–2.95 and 2.84–2.78 (4H, m, SCH_2CH_2S), 2.35 (3H, s, SAc), 2.04 (3H, s, OAc), 1.22 (3H, d, J = 7.2 Hz, 21-Me), 1.05 (3H, s, 19-Me), 0.98 (3H, s, 18-Me), 0.87 (6H, d, J = 5.7 Hz, 26,27-Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.0, 195.1, 170.5, 153.4, 139.9, 131.0, 122.1, 73.8, 56.5, 50.1, 48.9, 46.8, 38.6, 38.0, 36.7, 36.7, 35.1, 34.4, 33.0, 31.3, 30.6, 30.1, 29.8, 27.6, 22.4, 22.4, 21.4, 20.4, 19.2, 17.1, 14.3; MS (EI) m/z (intensity): 574 (M^+, 1.2), 475 (M^+–99, 100); IR (KBr): 1734, 1713, 1696 cm^{-1}.
21. The spectral data of our synthesized compound **19**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.29 (1H, d, J = 4.8 Hz, 6-H), 4.10–3.96 (6H, m, OCH_2CH_2O, 16-OH, 17-OH), 3.89–3.87 (1H, m, 16-H), 3.47–3.39 (1H, m, 3-H), 2.59 (1H, q, J = 7.2 Hz, 20-H), 1.18 (3H, d, J = 7.2 Hz, 21-Me), 0.99 (3H, s, 19-Me), 0.89 (18H, brs, 18,26,27-Me and t-Bu), 0.05 (6H, s, Me-Si); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4, 121.1, 116.5, 86.8, 81.5, 72.5, 64.0, 62.8, 49.6, 47.8, 47.8, 42.7, 37.2, 36.5, 35.8, 33.9, 33.1, 32.7, 32.7, 32.0, 31.9, 31.8, 28.3, 25.9, 22.7, 22.2, 20.6, 19.4, 18.2, 12.5, 11.9, –4.6; MS (EI) m/z (intensity): 575 (M^+–15, 0.9), 533 (M^+–57, 6.8), 485 (18.9); IR (KBr): 3545, 3472, 1076 cm^{-1}.