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# Synthesis of 5(6)-dihydro-OSW-1 by using the intact skeleton of tigogenin

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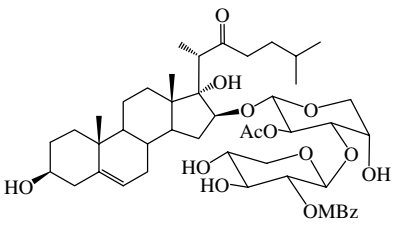
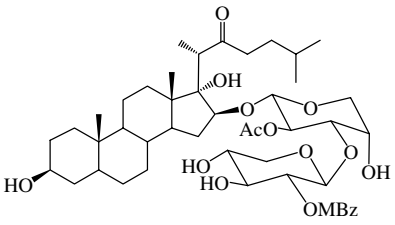
**Abstract**—5(6)-Dihydro-OSW-1 (**1**), an analogue of OSW-1 with the potent anticancer activity, was synthesized by utilizing the intact skeleton of tigogenin in 13 steps in 9.0% overall yield. This synthesis demonstrated an effective and reasonable synthetic strategy for bioactive steroids with side chains as compared with their routine synthesis.


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 nM 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-workers reported that 5(6)-dihydro-OSW-1 (**1**) (Fig. 1) with simplified and easy prepared structure was slightly more potent than OSW-1 against the tested three cancer cell lines [including AGS (stomach cancer cells) $IC_{50}$ 0.71 μM, 7404 (liver carcinoma cells) $IC_{50}$ 0.025 μM, and MCF-7 (breast cancer cells) 0.029 μM].[3]

The routine synthesis for OSW-1 and its analogues is starting from dehydroepiandrosterone.[3,4] It was prepared through the degradation of diosgenin, the procedure including thermal fragmentation in acetic acid at 200 °C, chromic oxide induced oxidation, elimination, oximation, and rearrangement.[5] As one part of our projects on the study of rational utilization of resource compounds,[6] we wish exploring a new synthesis of 5(6)-dihydro-OSW-1 (**1**) directly from tigogenin rather than the degradated product of diosgenin, epiandrosterone. Different from the reported synthesis of 5(6)-dihydro-OSW-1, the basic skeleton, 27-carbon atoms and functional groups of starting material tigogenin were fully, rationally utilized in our new synthetic strategy of 5(6)-dihydro-OSW-1 aglycon (Scheme 1).




**OSW-1**




**5,6-dihydro-OSW-1(1)**

**Figure 1.** The structures of OSW-1 and 5(6)-dihydro-OSW-1.

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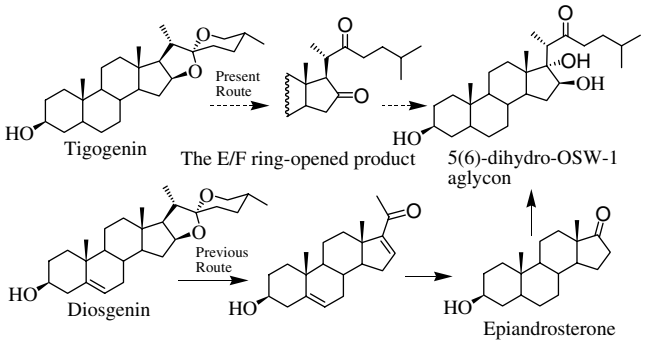
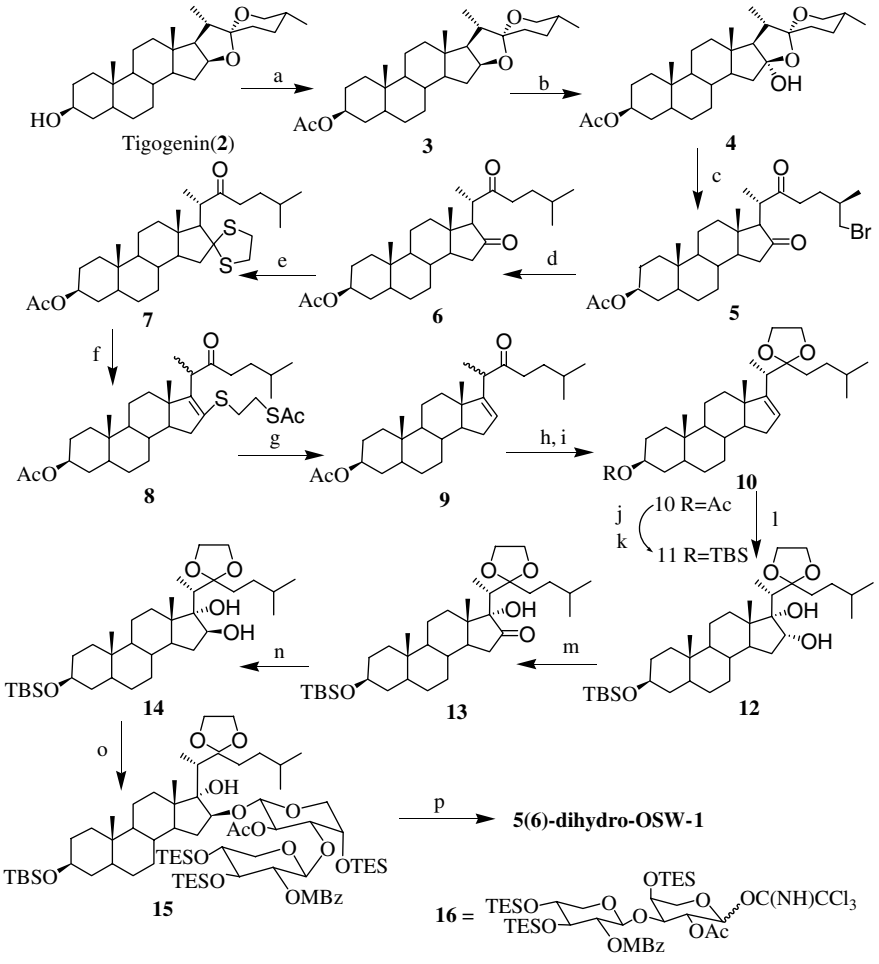



**Scheme 1.**

Comparing the structure of 5(6)-dihydro-OSW-1 with the E/F ring-opened product of tigogenin, it is easy to find that both have similar side chains and the same disposal of the C-16 hydroxyl and the 21-methyl groups. To synthesize the aglycon of 5(6)-dihydro-OSW-1 (**1**) starting from the E/F ring-opened product of tigogenin directly, one only needs to introduce a hydroxyl group at C-17 in the latter (Scheme 1). Obviously, it is a reasonable synthetic strategy according to the principle of atom economy in the organic synthesis.[7]

According to our synthetic plan shown in Scheme 2, tigogenin (**2**), an abundant and cheap steroidal sapogenin isolated from industrial waste, was readily acetylated with $Ac_2O$ in the presence of pyridine to afford the C-3 acetate of tigogenin in 99% yield. Tigogenin acetate **3** underwent regioselective oxone® oxidation of C-16 to produce **4** in 90% yield.[6d,e] The reaction of **4** with HOAc/HBr in $CH_2Cl_2$ afforded the E/F ring-opened brominated product **5** in 89% yield.[8] The reduction of **5** with Zn and $NH_4Cl$ in refluxing ethanol gave the key intermediate **6** in 93% yield.

Subsequently, **6** underwent regioselectively thioketalization to afford C-16 mono-thioketal **7**.[9] 16-Thioketal **7** reacted with $Ac_2O$ in the presence of 70% $HClO_4$ to produce 16(17)-alkene **8** through a thioketal-opening-acetylization (TOA reaction).[6d,e] Desulfurization of **8** with W-2 Raney nickel at room temperature afforded compound **9**. Unlike their 5(6)-dehydro analogues, compound **8** and **9** were sensitive to the epimerization at




**Scheme 2.** Reagents and conditions: (a) $Ac_2O$, Py, 45 °C, 99%; (b) oxone®, $NaHCO_3$, buffer, $H_2O$/acetone, 90%; (c) HBr/HOAc (30%), $CH_2Cl_2$, rt, 89%; (d) Zn, $NH_4Cl$, EtOH, 93%; (e) $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, $CH_2Cl_2$, 99%; (f) $Ac_2O$, $HClO_4$ (0.01 equiv), $CH_2Cl_2$, 65%; (g) W-2 Raney Ni, EtOH, rt, 99%; (h) $HOCH_2CH_2OH$, $HC(OEt)_3$, $BF_3OEt_2$, $CH_2Cl_2$, 81%; (i) recrystalize, 67%; (j) $K_2CO_3$, MeOH; (k) TBSCl, imid., DMAP, $CH_2Cl_2$, 99% for two steps; (l) $OsO_4$, Py, ether, −78 °C to rt, 10 h, then $H_2S$ bubbled through, 58%; (m) Swern oxidation, 88%; (n) LAH, THF, −78 °C, 70%; (o) 4 Å MS, **16**, then TMSOTf (0.05 equiv), −20 °C, $CH_2Cl_2$, 80%; (p) AcOH/ $H_2O$ (v/v, 3:1), 70 °C, 60%.

C20,[6d] so we got a mixture of 21α-methyl and 21β-methyl steroids. The mixture appears a single point on thin layer chromatography and is inseparable. The C-22 carbonyl group of **9** was protected by ethylene glycol ketal[6d,10] to give 20-epimers. Fortunately, the two isomers of **10** could be separated by simple recrystallization. We performed similar transformations according to the literature,[3,6d] that is, conversion of 3-OAc in **10** to 3-OTBS in **11**, dihydroxylation of the 16,17-alkene function in **11** with $OsO_4$, Swern oxidation of the 16α-OH group in **12**, and stereoselective reduction of the 16-keto group in **13** to the 16β-OH group in **14**. Thus, the protected aglycone of 5(6)-dihydro-OSW-1 was synthesized with 13 steps in 9.0% overall yield. The glycosylation of aglycone **13** with disaccharide trichloroacetimidate **16**[11] in the presence of TMSOTf provided the corresponding protected 5(6)-dihydro-OSW-1 **15** in 80% yield. Removal of all of the protecting groups in AcOH/$H_2O$ (v/v = 3:1) at 70 °C afforded the desired 5(6)-dihydro-OSW-1 (**1**) in 60.2% yield. Its spectral data are identical with that of reported in the literature.[3,12]

## References and notes


1. Kubo, S.; Mimaki, Y.; Terao, M.; Sashida, Y.; Nikaida, T.; Ohmato, T. *Phytochemistry* **1992**, *31*, 3969.
2. Mimaki, Y.; Kuroda, M.; Kameyama, A.; Sashida, Y.; Hirano, T.; Oka, K.; Maekawa, R.; Wada, T.; Sugita, K.; Beutler, A. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 633.
3. Deng, L.; Wu, H.; Yu, B.; Jiang, M.; Wu, J. *Chin. J. Chem.* **2004**, *22*, 994.
4. (a) Guo, C.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 1099; (b) Deng, S.; Yu, B.; Hui, Y. *J. Org. Chem.* **1999**, *64*, 202; (c) Morzychi, J. W.; Gryszkiewicz, A.; Jastrzebska, I. *Tetrahedron Lett.* **2000**, *41*, 3751; (d) Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2001**, *123*, 3369; (e) Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2002**, *124*, 6576.
5. (a) Marker, R. E. *J. Am. Chem. Soc.* **1940**, *62*, 3350; (b) Rosenkranz, G.; Mancera, O.; Sondheimer, F.; Djerassi, C. *J. Org. Chem.* **1956**, *21*, 520.
6. (a) Tian, W. S. *Acta Chim. Sinica* **1992**, *50*, 72; (b) Tian, W. S.; Guan, H. P.; Pan, X. F. *Chin. Chem. Lett.* **1994**, *5*, 1013; (c) Tian, W. S.; Guan, H. P.; Pan, X. F. *Chin. J. Chem.* **2003**, *21*, 793; (d) Xu, Q. H.; Peng, X. W.; Tian, W. S. *Tetrahedron Lett.* **2003**, *44*, 9375; (e) Tian, W. S.; Xu, Q. H.; Chen, L.; Zhao, C. F. *Sci. China, Ser. B: Chem.* **2004**, *47*, 142; (f) Qin, H. J.; Tian, W. S.; Lin, C. W. *Tetrahedron Lett.* **2006**, *47*, 3217.
7. Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.
8. Tian, W. S.; Wang, J.; Xu, Q. H.; Lin, J. R. China Patent 200610029252.2, 2006.
9. Arthur, F. K.; Michael, L. M.; Leslie, G. P. *J. Org. Chem.* **1985**, *50*, 2359.
10. (a) Guo, C. X.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 1099; (b) Deng, S. J.; Yu, B.; Lou, Y.; Hui, Y. Z. *J. Org. Chem.* **1999**, *64*, 202.
11. Disaccharide trichloroacetimidate **16** was synthesized according to the methods reported in Ref. 4.
12. Analytical data for our synthesized 5(6)-dihydro-OSW-1 (**1**): $[\alpha]_D^{25}$ −18.3 (*c* 0.38, $CH_3OH$, lit.[3] −12.6 (*c* 0.8, $CH_3OH$)); $^1H$ NMR (500 MHz, $C_5D_5N$): $\delta$ 8.40 (d, $J = 8.6$ Hz, 2H), 7.16 (d, $J = 8.6$ Hz, 2H), 5.76 (t, $J = 8.2$ Hz, 1H), 5.63 (t, 1H), 5.20 (d, $J = 7.6$ Hz, 1H), 4.87 (s, 1H), 4.67 (d, $J = 6.0$ Hz, 1H), 4.47 (br s, 1H), 4.32–4.22 (m, 6H), 3.83 (s, 3H), 3.25 (q, $J = 7.6$ Hz, 1H), 2.12 (s, 3H), 1.35 (d, $J = 7.2$ Hz, 3H), 1.05 (s, 3H), 0.96 (d, $J = 7.2$ Hz, 3H), 0.94 (d, $J = 7.2$ Hz, 3H), 0.91 (s, 3H). $^{13}C$ NMR (125 MHz, $C_5D_5N$): $\delta$ 219.05, 169.38, 165.55, 164.01, 132.54, 114.37, 114.24, 103.79, 100.95, 88.51, 85.78, 81.10, 76.46, 75.25, 72.18, 70.83, 70.76, 67.16, 55.61, 54.31, 48.27, 47.00, 46.45, 45.29, 39.44, 39.38, 37.57, 35.90, 35.64, 33.07, 32.81, 32.61, 29.22, 27.84, 22.93, 22.59, 21.01, 14.03, 12.61, 11.95; MS (ESI): 897 ($M+Na^+$), 874 ($M^+$).