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The first stereoselective synthesis of orostanal, a novel abeo-sterol inducing apoptosis in leukemia cells

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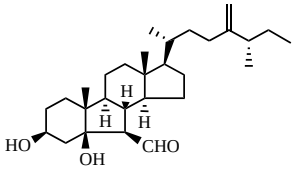
Abstract—An efficient approach to the synthesis of a sterol derivative, orostanal, has been achieved by a series of reactions from methyl hyodeoxycholanate.

Recently a novel sterol named as orostanal which consisted of 6-5-6-5 fused rings was isolated from a Japanese marine sponge of *Stelletta hiwasaensis*.[1] Orostanal induced apoptosis in human acute promyelotic leukemia cells at 10 μg/ml and inhibited 50% cell growth at 1.7 μM. Some well-known natural anticancer drugs, such as etoposide and camptothecin, also induce apoptosis in cancer cells, so that substances which can induce apoptosis may be useful for human cancer chemotherapy.[2]



Orostanal

Although it showed meaningful biological activity, only 3.6 mg of orostanal was obtained from 2.0 kg of *S. hiwasaensis*. Thus, it was desirable to establish an efficient route for the stereoselective synthesis of orostanal.

This was achieved starting from **3** which was prepared from hyodeoxycholic acid methyl ester.[3] Ozonolysis of **3** in a mixed solvent (CH_2Cl_2: MeOH = 4:1) at −78°C afforded **4** which was converted to **5** in the presence of neutral alumina[4] at room temperature in a 80% yield, far superior to the yield obtained by Higuchi et al.[1] The aldehyde **5** was protected as its methyl acetal with NH_4Cl as catalyst[5] to give **6**, the secondary hydroxyl at C-3 of which was then silylated[6] by TBSCl to yield **7**. Next, we planned to reduce the methyl ester moiety on the terminal of the side chain of **7** to -OH by $LiAlH_4$. However, the TBS ether on A ring of **7** was cleaved to the hydroxyl group when the ester group was reduced. Using $LiBH_4$[7] as reductant afforded the desired alcohol **8** which was oxidized[8] to an aldehyde and coupled with boronate (−)-**9** to form **10** under Roush's conditions.[9] Reduction of **10** by diimide,[10] generated in situ, afforded **11** which was subjected to a Swern oxidation[7] to yield the ketone **12** (Scheme 1) Considering that a Wittig reaction of **12** might cause racemization[11] at C-25, we applied the combined reagent $TiCl_4$–Zn–CH_2Br_2 for methylenation of the carbonyl group of **12** according to Lombardo's method.[12] After removal of the protective groups under mild conditions,[13,14] orostanal was obtained as an colorless oil whose spectroscopic data[15] were identical to those reported.[1]

To summarize, orostanal was synthesized for the first time via 12 steps in 18% total yield from **3**. This synthetic route could provide enough orostanal to probe efficiently its mode of action of apoptosis.

Keywords: stereoselective synthesis; sterol; apoptosis.

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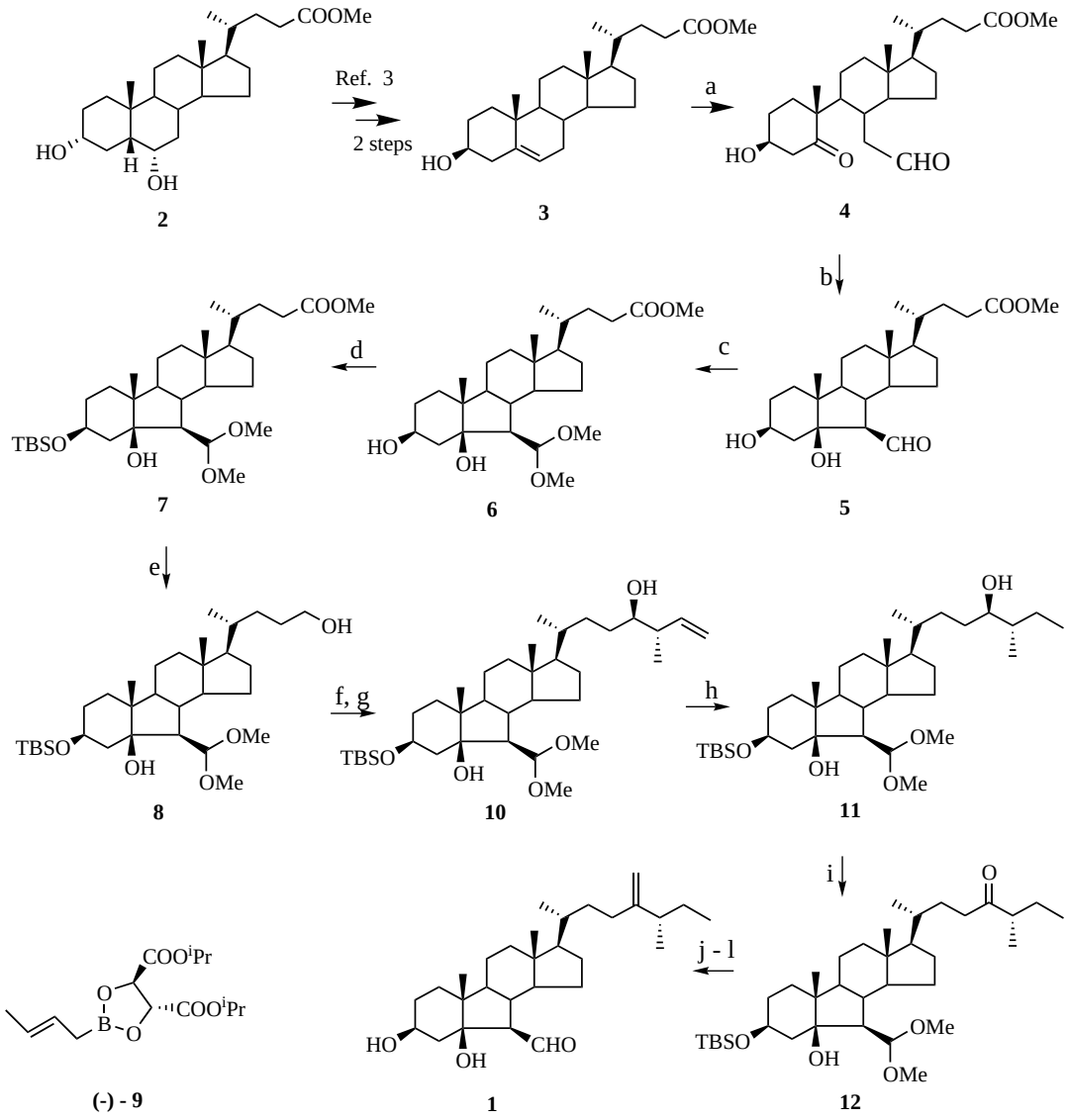

Scheme 1. *Reagents and conditions*: (a) O_3, CH_2Cl_2–MeOH (4:1), −78°C, then Me_2S, 90%; (b) neutral Al_2O_3, benzene, rt, 80%; (c) NH_4Cl, $HC(OMe)_3$, absolute MeOH, 30°C, 83%; (d) TBSCl, imidazole, DMF, rt, 92%; (e) $LiBH_4$, THF, reflux, 85%; (f) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N; (g) (−)-**9**, toluene, 4 Å MS, −78°C, 92% for two steps; (h) H_2NNH_2, H_2O_2, EtOH, 94%; (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, 88%; (j) $TiCl_4$–Zn–CH_2Br_2 (Lombardo's reagent, prepared according to Ref. 12), CH_2Cl_2, 25°C; (k) $LiBF_4$, MeCN/CH_2Cl_2 (2:1), trace of water, 25°C; (l) HF, MeCN, 25°C, 50% for three steps.

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15. Our synthetic orostanal was characterized by ^{1}H, ^{13}C NMR, NOESY and IR spectra. ^{1}H NMR (600 MHz, $CDCl_3$): 0.72 (3H, s, Me-18), 0.83 (3H, t, 7.2, Me-29), 0.93 (3H, s, Me-19), 0.94 (3H, d, 6.6, Me-21), 1.00 (3H, d, 6.6, Me-27), 1.73 (1H, dd, 3.1, 14.9, H-4), 2.24 (1H, dd, 2.8, 9.0, H-7), 4.12 (1H, m, H-3), 4.69 (2H, s, CH_2-28), 9.71 (1H, d, 2.8, H-6); ^{13}C NMR (150 MHz, $CDCl_3$): 11.9 (C-29), 12.5 (C-18), 18.4 (C-19), 18.8 (C-21), 19.8 (C-27), 21.6 (C-11), 24.6 (C-15), 26.8 (C-1), 28.0 (C-2), 28.3 (C-16, 26), 30.4 (C-23), 34.6 (C-22), 35.6 (C-20), 39.8 (C-12), 40.0 (C-8), 41.7 (C-25), 44.3 (C-4), 44.8 (C-13), 45.5 (C-10), 50.6 (C-9), 55.6 (C-17), 56.2 (C-14), 64.0 (C-7), 67.4 (C-3), 84.3 (C-5), 107.2 (C-28), 155.2 (C-24), 204.6 (C-6); IR (film, cm^{-1}): 3443, 2928, 2872, 2734, 1720, 1641, 1459, 1378, 887.