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The first stereoselective synthesis of orostanal isolated from a marine sponge *Stelletta hiwasaensis*

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Abstract—The synthesis of orostanal, containing novel 6-5-6-5 fused rings and exhibiting meaningful bioactivity against HL-60 cells, has been achieved via 12 steps in 18% total yield from a readily accessible intermediate **7**. The key steps for the synthesis entailed an alumina-mediated intramolecular aldol cyclization and asymmetric crotylation to construct the chirality of carbon-25.

1. Introduction

Structurally, 6-5-6-5 fused rings sterols are uncommon in nature. In 1998, several sterols exhibiting a novel skeleton of 6-5-6-5 fused rings were isolated by Lin[1] et al. from the leaves of *Taiwania cryptomerioides*, which were named as taiwaniasterols A–D (**1**–**4**). Although no evidence for their bioactivities was reported and the biogenesis of these sterols awaited further investigation, it was the first time that the novel structure from nature has been reported. After that, Higuchi and his coworkers reported another example of this novel skeleton.[2] While searching for biologically active substances from marine invertebrates, they obtained a 5(6→7) *abeo*-sterol named as orostanal (**5**) from a Japanese marine sponge, *Stelletta hiwasaensis*. The structural determination of orostanal was made based on the ^{1}H, ^{13}C NMR, $^{1}H-^{1}H$ COSY, TOCSY and HSQC spectra besides the IR and HR-EI MS spectra. The relative stereochemistry except C-25 was assigned on the basis of the NOESY correlations, and the stereochemistry of C-25 was elucidated by comparison of the ^{1}H NMR data with those of (25*S*)- and (25*R*)- 24(28)-dehydroaplysterols. The absolute configuration of **5** was determined by comparison of the CD spectrum with that of a synthetic analogue prepared from cholesterol (Fig. 1).

Orostanal can induce apoptosis in HL-60 cells at 10 μg/ml, and inhibit 50% cell growth at 1.7 μM. Apoptosis is the term used by biologists to describe cell suicide. Thus, those compounds which could induce apoptosis of cancer cells may be useful for human cancer chemotherapy. Meanwhile, the supply of orostanal from

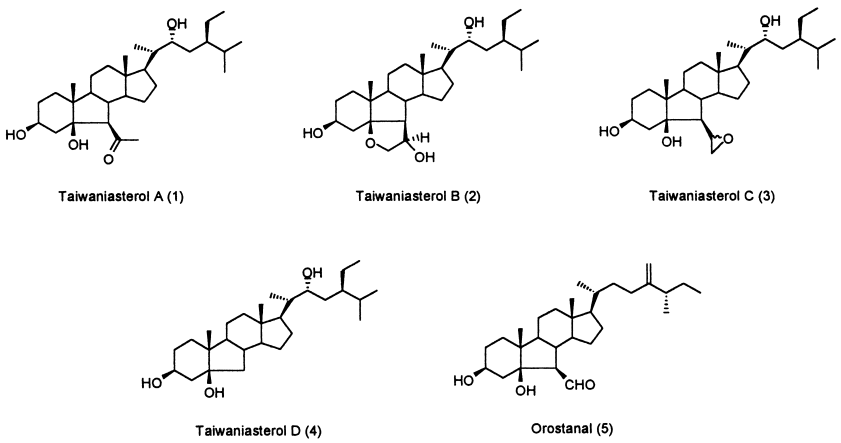

Figure 1.

Keywords: stereoselective; orostanal; apoptosis.

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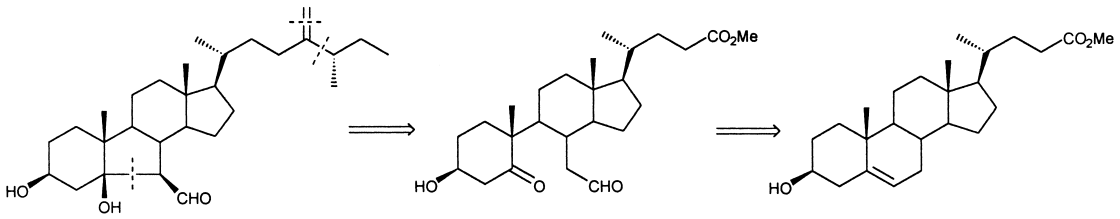
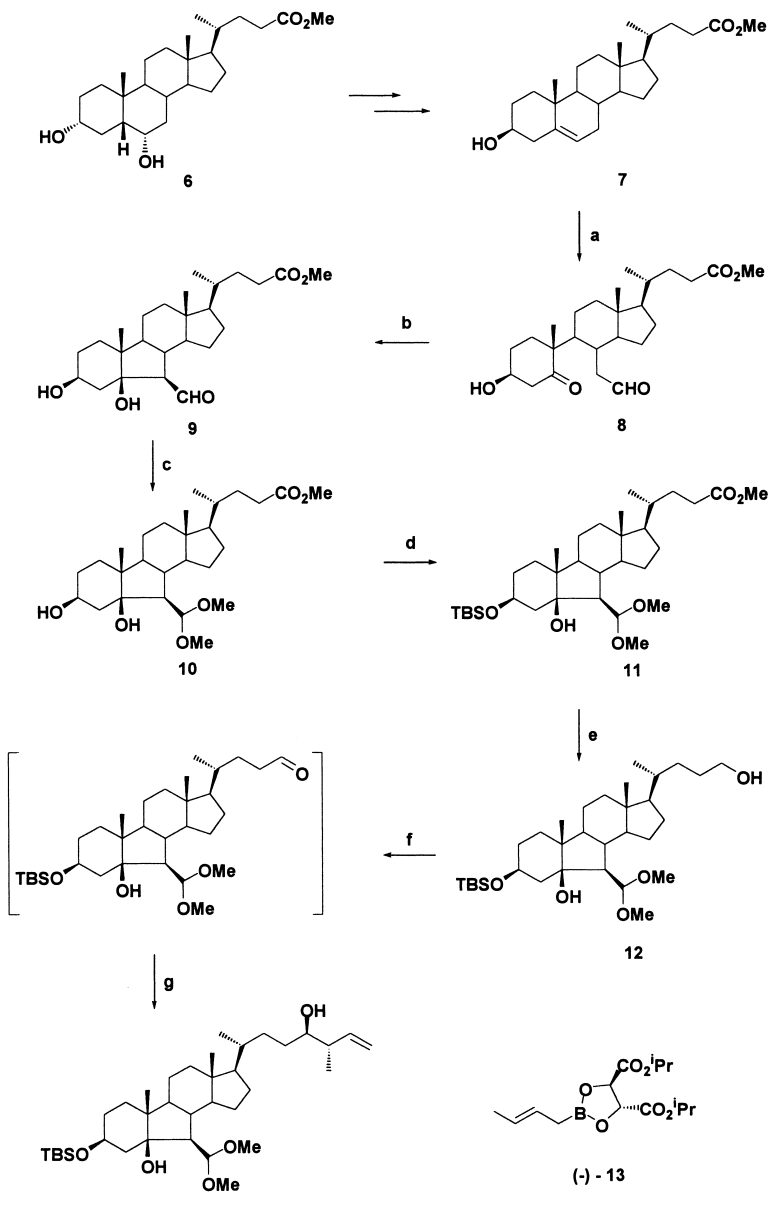


Scheme 1.

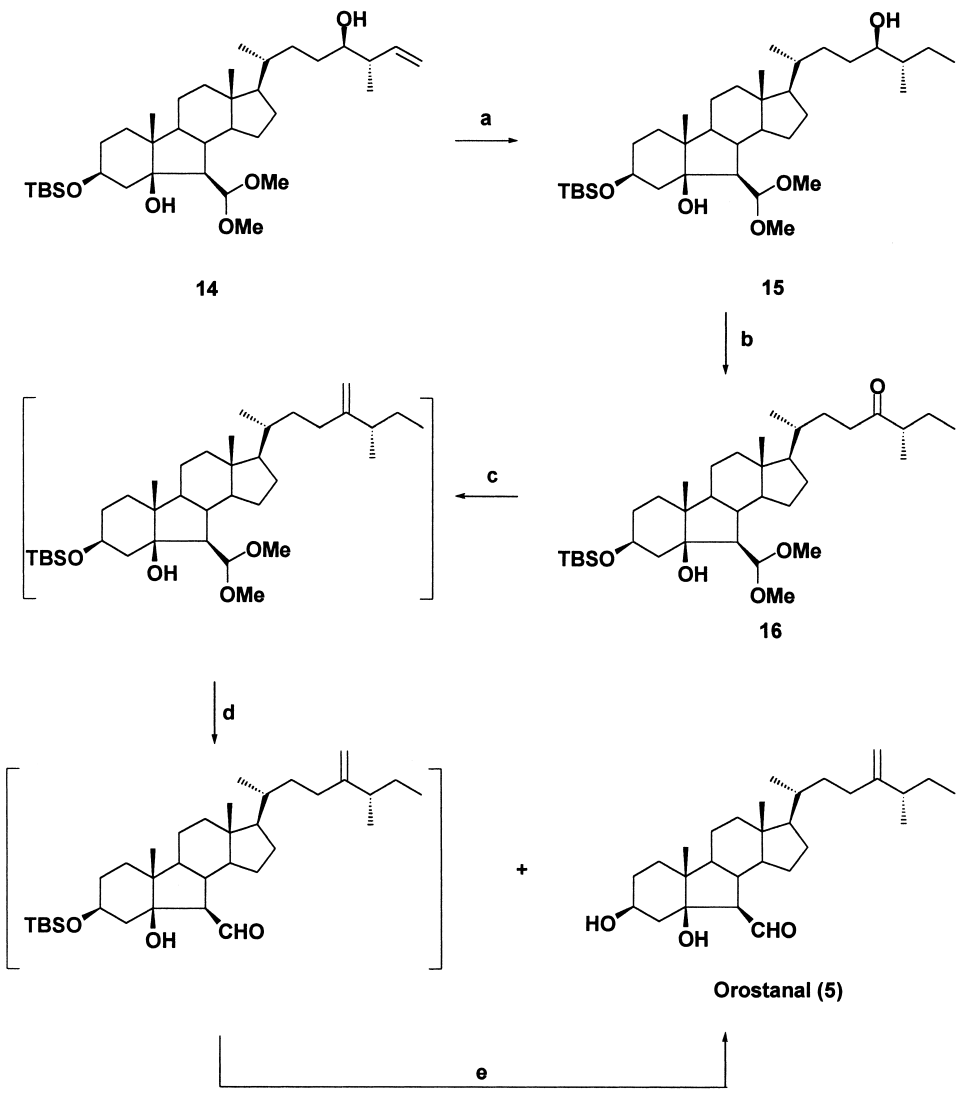
the natural source is very limited (only 3.6 mg could be isolated from 2.0 kg of *S. hiwasaensis*), although further studies on the mechanism of apoptosis caused by it on HL-60 cells and on bioactivities for other cells are very necessary.

2. Results and discussion

Considering its novel structure and scarcity, we conducted the stereoselective synthesis of orostanal. Herein we would like to describe the full details.[3]



Scheme 2. *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) (−)-**13**, toluene, 4 Å MS, −78°C, 92% for two steps.



Scheme 3. *Reagents and conditions*: (a) H_2NNH_2, H_2O_2, EtOH, 94%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then Et_3N, 88%; (c) $TiCl_4$–Zn–CH_2Br_2 (Lombardo's reagent, prepared according to Ref. 14), CH_2Cl_2, 25°C; (d) $LiBF_4$, MeCN/CH_2Cl_2 (2:1), trace of water, 25°C; (e) HF, MeCN, 25°C, 50% for three steps.

The retro-synthetic analysis was shown in Scheme 1.

The double bond on the side chain of orostanal could be obtained from a hydroxyl of C-24 via oxidation and then methylenation. The stereochemistry of C-25 was facile to be realized by reaction of the corresponding aldehyde with Roush's reagent (−)-**13**. The β-hydroxyl aldehyde structure of ring B could be transformed from an intramolecular aldol reaction of a product of ozonolysis.

Our synthetic route started with compound **7** which was prepared from hyodeoxycholic acid methyl ester **6** in two steps.[4] Due to the low solubility of **7** in CH_2Cl_2, ozonolysis of **7** was executed in a mixture of CH_2Cl_2 and MeOH (CH_2Cl_2/MeOH=4:1) at −78°C. After bubbling O_2 to expel the excess O_3 and adding Me_2S to reduce the produced H_2O_2, we obtained **8** which was subjected to neutral alumina[5] to realize the intramolecular aldol condensation affording compound **9**. Ocassionally, we found that compound **8** was unstable and could lead to intramolecular aldol self-condensation slowly to give **9** during its storage. The relative stereochemistry of **9** was confirmed by ^1H–^1H NOESY spectrum (600 MHz). Aldehyde **9** was then protected as the dimethyl acetal by treatment with trimethyl orthoformate in absolute methanol promoted by NH_4Cl,[6] although this reaction catalyzed by $CeCl_3$[7] proved sluggish and that catalyzed by TsOH[8] turned to form complex products. Protecting the hydroxyl at carbon-3 with *tert*-butyldimethylsilyl chloride in the presence of imidazole gave compound **11**. To our surprise, reduction of the ester group on the side chain with $LiAlH_4$ brought about the removal of TBS group simultaneously. However, $LiBH_4$[9] proved to be a superior reducing agent to $LiAlH_4$ and afforded the desired alcohol **12**. Swern oxidation[10] of **12** gave an aldehyde smoothly which was immediately coupled with boronate (−)-**13** at −78°C in toluene in the presence 4 Å MS according to Roush's procedure (Scheme 2).[11]

Saturation of the double bond of **14** with diimide,[12] generated in situ, followed by oxidation yielded the ketone **16**. Because some examples that a direct Wittig reaction caused racemization of adjacent stereogenic centers had been reported,[13] Lombardo's reagent ($TiCl_4$–Zn–CH_2Br_2)[14] was applied for methylenation of the carbonyl

group of **16**, which was followed by deprotection with $LiBF_4$[15] and HF[16] to afford our target molecule (Scheme 3).

In summary, orostanal has been synthesized via alumina-mediated intramolecular aldol cyclization to construct stereogenic center on ring B and Roush's reaction to introduce the chirality of carbon-25 on the side chain. This ensures the facile supply of orostanal to finish its detailed bioactive assay.

3. Experimental

3.1. General methods

All melting points are uncorrected. IR spectra were recorded with FT-IR apparatus. ^1H and ^{13}C NMR spectra were recorded at 300 or 600 MHz in $CDCl_3$. Chemical shifts are reported in ppm relative to TMS as internal standard. Mass spectra were recorded by EI or ESI methods. Flash column chromatography was carried out with silica gel (300–400 mesh).

3.1.1. Methyl 3β-hydroxyl-5,6-dioxo-5,6-secocholanate (8) and methyl 6β-formyl-3β,5β-dihydroxyl-B-norcholanate (9). A flow of O_3 in O_2 was bubbled through a solution of **7** (99 mg, 0.26 mmol) in a mixture of CH_2Cl_2 (16 ml) and MeOH (4 ml) at −78°C for 50 min until the solution turned pale blue. The mixture was purged with O_2 for 1.5 h, and then Me_2S (2 ml) was added. The mixture was allowed to warm to room temperature and was stirred overnight. After removing the solvents and dimethylsulfide, the residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was separated and dried. The solvent was removed in vacuo, and the residue was chromatographed on silica gel to afford the pure **8** (96 mg, 90%) as a colorless oil which was immediately used for the next reaction. A small portion of it was characterized: IR (film) 3462, 1742, 1720, 1701; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.62 (s, 1H), 4.48 (m, 1H), 3.67 (s, 3H), 3.10 (dd, J=13.8, 3.9 Hz, 1H), 0.98 (s, 3H), 0.92 (d, J=6.3 Hz, 3H), 0.68 (s, 3H).

Neutral Al_2O_3 (3.8 g, unactivated) was added to the solution of **8** (380 mg, 0.9 mmol) in benzene (20 ml). The solution was stirred at room temperature for 3.5 h, Al_2O_3 was filtered and then washed with large quantities of $CHCl_3$ until TLC showed no product remained on Al_2O_3. After evaporation of the solvent and chromatography (CAUTION: the product is unstable on silica and should be purified as soon as possible). Compound **9** (303 mg, 80%) was obtained as a colorless solid: mp 95–96°C; $[\alpha]_D^{20}$=+34.6 ($CHCl_3$, c=1.0); IR (KBr) 3496, 3541, 2831, 2735, 1726 (shoulder); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.70 (d, J=3.0 Hz, 1H), 4.13 (m, 1H), 3.66 (s, 3H), 3.57 (s, 1H), 2.50 (d, J=5.1 Hz, 1H), 0.93 (s, 3H), 0.92 (d, J=6.3 Hz, 3H), 0.72 (s, 3H); MS (EI) m/z (rel. intensity) 403 (M^+-OH, 10), 375 (55), 360 (57), 250 (65), 55 (100); Anal: C, 71.66; H, 9.44; Calcd for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59.

3.1.2. Methyl 3β,5β-dihydroxyl-6β-dimethoxylmethyl-B-norcholanate (10). NH_4Cl (35 mg, 0.65 mmol) and **9** (120 mg, 0.29 mmol) were added to a flame-dried flask under Ar. Then absolute methyl alcohol (4 ml) and trimethyl orthoformate (0.32 ml, 2.86 mmol) were added and the mixture was stirred at 30°C for 10.5 h. After the solvent was evaporated in vacuo, the residue was partitioned between $CHCl_3$ and water. Organic layer was seperated and concentrated. The residue was purified by chromatography (CAUTION: the product should be eluted quickly from silica) to give **10** (111 mg, 83%) as a colorless oil: $[\alpha]_D^{20}$=+41.5 ($CHCl_3$, c=1.05); IR (film) 3474, 1741; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.28 (d, J=4.5 Hz, 1H), 4.00 (s, 1H), 3.91 (br., 2H), 3.67 (s, 3H), 3.45 (s, 3H), 3.44 (s, 3H), 0.93 (d, J=6.3 Hz, 3H), 0.90 (s, 3H), 0.68 (s, 3H); MS (ESI) m/z 489.3208, calcd for $C_{27}H_{46}O_6Na$ ($M+Na^+$) 489.3192.

3.1.3. Methyl 3β-*tert*-butyldimethylsilyloxyl-5β-hydroxyl-6β-dimethoxylmethyl-B-norcholanate (11). To a solution of **10** (693 mg, 1.49 mmol) in anhydrous DMF (6 ml) was added imidazole (907 mg, 13.32 mmol) and TBSCl (669 mg, 4.44 mmol) in turn. After the mixture was stirred at room temperature overnight, the solution was diluted with EtOAc. The organic layer was washed with water and then with brine and dried (Na_2SO_4). The crude product obtained after evaporation of the solvent was purified by flash chromatography to give **11** (792 mg, 92%) as a colorless solid: mp 71–72°C; $[\alpha]_D^{20}$=+9.3 ($CHCl_3$, c=1.30); IR (KBr) 3495, 1745; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.42 (d, J=4.5 Hz, 1H), 4.05 (m, 1H), 3.66 (s, 3H), 3.56 (s, 1H), 3.44 (s, 3H), 3.40 (s, 3H), 0.92 (d, J=6.0 Hz, 3H), 0.90 (s, 9H), 0.84 (s, 3H), 0.69 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); MS (ESI) m/z 603.4042, calcd for $C_{33}H_{60}O_6SiNa$ ($M+Na^+$) 603.4057.

3.1.4. β-*tert*-Butyldimethylsilyloxyl-5β,24-dihydroxyl-6β-dimethoxylmethyl-B-norcholestane (12). A solution of $LiBH_4$ in THF (7.67 ml, ca. 1 M) was added to **11** (890 mg, 1.53 mmol) in THF (12 ml). The mixture was refluxed overnight under Ar. After the mixture was cooled to room temperature, methyl alcohol was added dropwise slowly to quench the reaction. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and treated with 2N NaOH solution for 20 min. The product was extracted into CH_2Cl_2, and the combined extracts were dried (Na_2SO_4). Removal of the solvent left a residue which was fractionated by flash chromatography to afford **12** (720 mg, 85%) as a colorless solid: mp 127–128°C; $[\alpha]_D^{20}$=+20.6 ($CHCl_3$, c=0.70); IR (KBr) 3489, 1064; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.42 (d, J=4.8 Hz, 1H), 4.05 (m, 1H), 3.62 (m, 2H), 3.57 (s, 1H), 3.45 (s, 3H), 3.40 (s, 3H), 0.93 (d, J=6.6 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 3H), 0.69 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); MS (ESI) m/z 575.4128, calcd for $C_{32}H_{60}O_5SiNa$ ($M+Na^+$) 575.4108.

3.1.5. Δ^{26}-3β-*tert*-Butyldimethylsilyloxyl-5β,24*R*-dihydroxyl-6β-dimethoxylmethyl-25*S*-methyl-B-norcholestene (14). To a solution of $(COCl)_2$ (0.11 ml, 1.24 mmol) in CH_2Cl_2 (3 ml) stirred at −78°C was added DMSO(0.18 ml, 2.48 mmol) in CH_2Cl_2(1 ml). The mixture was stirred at −78°C for 10 min. A solution of **12** (343 mg, 0.62 mmol) in CH_2Cl_2 (1.2 ml) was added and the stirring was continued at −78°C for 50 min. After triethylamine (1 ml) was added, the mixture was stirred for 10 min and then diluted with CH_2Cl_2 (10 ml). The solution was washed

with water and brine. Drying (Na_2SO_4) and evaporation of the solvent gave the aldehyde (341 mg, >99%) as colorless needles which was used without further purification for the next step. A solution of (*E*)-ctotylboronate **13** in toluene (1.8 ml, ca. 1 M, crude reagent) was added at −78°C dropwise to the solution of aldehyde (341 mg, 0.62 mmol) in toluene (10 ml) treated with powdered 4 Å MS (260 mg). The reaction mixture was stirred over −78°C for 1.5 h and then treated with 2 ml of 2N NaOH solution to hydrolyze boronate. The two-phase mixture was warmed to room temperature and stirred for 10 min before being filtered through a pad of Celite. The aqueous layer was extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4, evaporated and chromatograghed through silica gel to provide **14** (346 mg, 92% for two steps) as a colorless oil: $[\alpha]_D^{20}$=+31.2 ($CHCl_3$, *c*=0.90); IR (film) 3504, 1648, 1074; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70–5.82 (m, 1H), 5.13 (s, 1H), 5.07–5.10 (m, 1H), 4.42 (d, *J*=4.5 Hz, 1H), 4.04–4.06 (m, 1H), 3.56 (s, 1H), 3.44 (s, 3H), 3.39 (s, 3H), 1.03 (d, *J*=6.9 Hz, 3H), 0.92 (d, *J*=6.6 Hz, 3H), 0.90 (s, 9H), 0.87 (s, 3H), 0.69 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H); MS (ESI) *m/z* 629.4578, calcd for $C_{36}H_{66}O_5SiNa$ (M+Na^+) 629.4577.

3.1.6. 3β-*tert*-Butyldimethylsilyloxyl-5β,24*R*-dihydroxyl-6β-dimethoxylmethyl-25*S*-methyl-B-norcholestane (15). A cooled (0°C) solution of **14** (313 mg, 0.52 mmol) and 85% hydrazine (760 mg, 12.9 mmol) in 10 ml of ethyl alcohol was treated dropwise with 0.6 ml of 30% hydrogen peroxide. After stirring at room temperature overnight, the solvent was evaporated and the residue was partitioned between CH_2Cl_2 and brine. After drying (Na_2SO_4) and flash chromatography, **15** (296 mg, 94%) was obtained as a colorless oil: $[\alpha]_D^{20}$=+27.4 ($CHCl_3$, *c*=1.75); IR (film) 3508, 1074; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.42 (d, *J*=4.8 Hz, 1H), 4.05 (m, 1H), 3.56 (s, 1H), 3.44 (s, 3H), 3.40 (s, 3H), 0.92 (d, *J*=6.6 Hz, 3H), 0.90 (s, 9H), 0.87 (d, *J*=6.6 Hz, 3H), 0.86 (s, 3H), 0.69 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); MS (ESI) *m/z* 631.4753, calcd for $C_{36}H_{68}O_5$-SiNa (M+Na^+) 631.4734.

3.1.7. 3β-*tert*-Butyldimethylsilyloxyl-5β-hydroxyl-6β-dimethoxylmethyl-25*S*-methyl-B-norcholestane-24-one (16). To a solution of oxalyl chloride (65 μl, 0.74 mmol) in CH_2Cl_2 (1.5 ml) at −78°C was added dropwise a solution of DMSO (105 μl, 1.49 mmol) in CH_2Cl_2 (0.5 ml). The resulting solution was stirred for 5 min. A solution of alcohol **15** (181 mg, 0.30 mmol) in CH_2Cl_2 (0.6 ml) was added. After the solution had been stirred at −78°C for 40 min, Et_3N (0.5 ml) was added and stirring was continued at −78°C for 50 min. The solution was allowed to warm to room temperature and stirred for 20 min. After 10 ml of CH_2Cl_2 was added, the solution was washed with water and brine and dried (Na_2SO_4). Evaporation of the solvent gave a yellow residue which was chromatographed on silica gel to provide **16** (158 mg, 88%) as a colorless oil: $[\alpha]_D^{20}$=+43.7 ($CHCl_3$, *c*=0.35); IR (film) 3503, 1716, 1074; ^{1}H NMR (CDCl3, 300 MHz) δ 4.41 (d, *J*=4.2 Hz, 1H), 4.04 (m, 1H), 3.55 (s, 1H), 3.44 (s, 3H), 3.39 (s, 3H), 2.38–2.50 (m, 3H), 1.05 (d, *J*=6.6 Hz, 3H), 0.90 (d, *J*=6.0 Hz, 3H), 0.90 (s, 9H), 0.86 (s, 3H), 0.68 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); MS (ESI) *m/z* 629.4564, calcd for $C_{36}H_{66}O_5SiNa$ (M+Na^+) 629.4577.

3.2. Orostanal (5)

A dry THF solution of Lombardo's reagent (2.0 ml, ca. 0.60 mmol) was added to ketone **16** (73 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (5 ml) at 25°C. After being stirred for 50 min, the resulting mixture was quenched by $NaHCO_3$ solution. Filtering through a pad of Celite, washing with CH_2Cl_2 and evaporating the solvent gave a colorless solid which was dissolved in CH_3CN (5 ml) and CH_2Cl_2 (2.5 ml). $LiBF_4$ (11.5 mg, 0.15 mmol) was added to the above solution. After two drops of water were added, the resulting mixture turned clear, which was stirred at 25°C for 1.5 h. Evaporating the solvent afforded a residue which was subjected to flash chromatography with Et_2O/hexane as the eluent affording 8.8 mg of a colorless solid and 16.5 mg of orostanal as a colorless oil. The solid was then dissolved in CH_2Cl_2 (0.5 ml) and CH_3CN (1 ml), and the 40% solution of HF (50 μl) was added. After being stirred at room temperature for 40 min, the reaction mixture was directly subjected to chromatography to provide 7.0 mg of orostanal. Combination of two portions of product gave 23.5 mg of orostanal (50% for 3 steps) as a colorless oil: $[\alpha]_D^{20}$=+46.1 ($CHCl_3$, *c*=0.40), {lit.[2] $[\alpha]_D$=+50.6 ($CHCl_3$, *c*=0.30)}; IR (film) 3443, 1720, 1641; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.71 (d, *J*=2.8 Hz, 1H), 4.69 (s, 2H), 4.12 (m, 1H), 2.24 (dd, *J*=9.0, 2.8 Hz, 1H), 1.00 (d, *J*=6.6 Hz, 3H), 0.94 (d, *J*=7.5 Hz, 3H), 0.93 (s, 3H), 0.83 (t, *J*=7.2 Hz, 3H), 0.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): 11.9, 12.5, 18.4, 18.8, 19.8, 21.6, 24.6, 26.8, 28.0, 28.3, 30.4, 34.6, 39.8, 40.0, 41.7, 44.3, 44.8, 45.5, 50.6, 55.6, 56.2, 64.0, 67.4, 84.3, 107.2, 155.2, 204.6.

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