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Synthesis of Gymnasterone B, an antitumor steroid from *Gymnascella dankaliensis*

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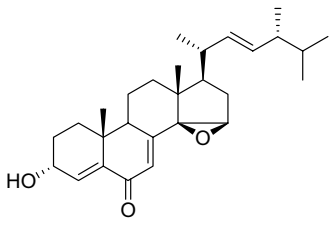
Abstract—A stereoselective approach toward a marine natural product, Gymnasterone B, has been achieved via a series reaction from cholic acid.

Marine natural products have been a prolific source of useful leads in the development of pharmaceutical agents for the treatment of diverse diseases like cancers, cardiovascular diseases, central nervous system (CNS) diseases and so on.[1] Since late 1990s, numerous novel cytotoxic compounds have been isolated and identified from *Gymnascella dankaliensis*, a specific strain from the sponge *Halichondria japonica*. These include, but are not limited to Gymnastatins A–K,[2] Gymnasterones A and B,[3] and Gymnasterol.[4] Among them, Gymnasterone B exhibited a significant cytotoxicity against cultured P388 cells.[3] Besides its meaningful biological activity, Gymnasterone B is also a representative of the structurally novel ergostanoids whose 14,15-epoxide are rarely found in natural products (Fig. 1).



Gymnasterone B

Figure 1.

Although Gymnasterone B has a potential for both biological and chemical study, its natural paucity impedes further advances, since only 8 mg of Gymnasterone B was obtained from 60 L of MeOH extract from the mycelium of the cultured fungal strain. Therefore, it is desirable to explore and establish an efficient route for the regioselective and stereoselective synthesis of Gymnasterone B. Herein, we wish to report the first synthesis of Gymnasterone B from cholic acid.

According to the method reported by Fisher,[5] cholic acid was converted to compound **1** in four steps. Further protection of the free 3-hydroxyl with TBDPSCl afforded **2** in high yield. With **2** in hand, we investigated the method to introduce the Δ^{14} moiety into the substrate. Employing the combination of photolysis/ene reaction reported by Fuchs in the total synthesis of Cephalostatin 1,[6] we were fortunate to obtain the desired intermediate **3** in moderate yield. Barton decarboxylation of **3** followed by a phenylselenyl bromide/hydrogen peroxide mediated oxidative dehydrogenation[7] furnished **4**, which was an important precursor to construct the side chain of Gymnasterone B. Inspired by Zhou's stereoselective synthesis of 25-methylbrassinolide,[7] we prepared (22*S*,23*R*)-**5a**[8] by selective dihydroxylation of the more flexible and less hindered Δ^{14} function of **4**. The stereochemistries of **5a** and **5b** were easily assigned as the 22*S*,23*R*- and 22*R*,23*S*-configurations based on ^{1}H NMR vicinal coupling constants $J(20, 22) = 3.5$ Hz (**5a**) and $J(22, 23) = 3.5$ Hz (**5b**). Conversion of **5a** according to acetonide **6** following similar procedure employed in the Brassinolide synthesis[7] delivered **7**. As is quite in line with our expectation, selective

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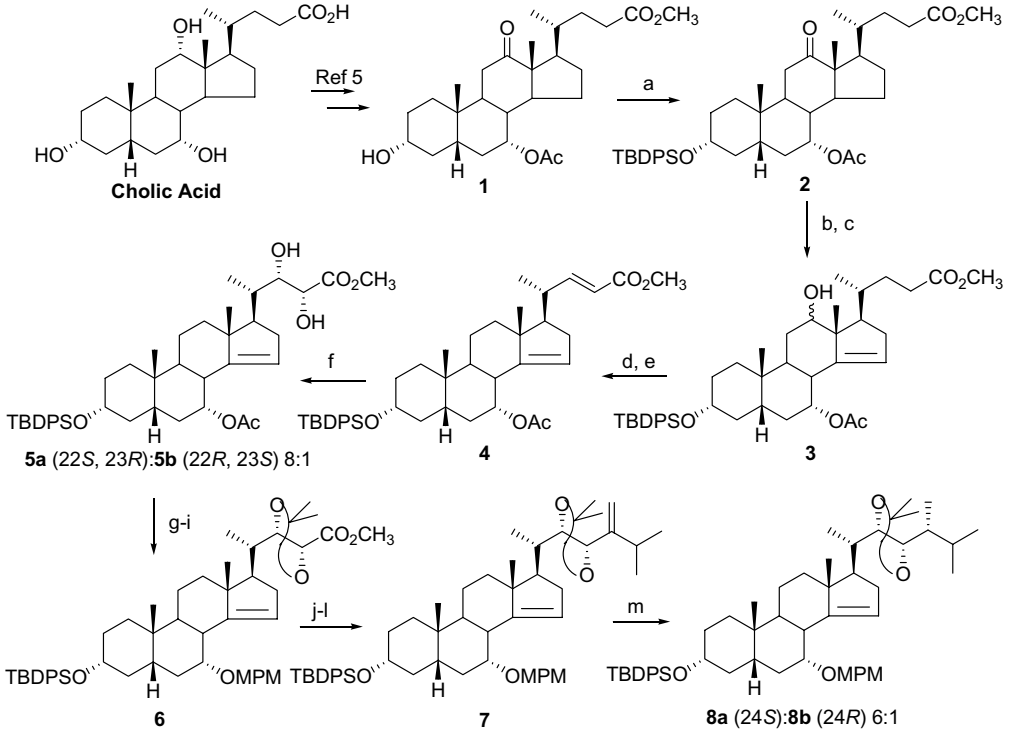
diimide reduction[9] of the less hindered $\Delta^{24(25)}$-olefin provided the desired (22*S*,23*R*,24*S*)-**8a** along with unwanted (22*S*,23*R*,24*R*)-**8b** in a ratio of 6:1. The C_{24} configurations in compound **8a** and **8b**[10] were identified according to the ^{1}H NMR vicinal coupling constants $J(23,\ 24) = 0$ Hz (**8a**) and $J(23,\ 24) = 4.0$ Hz (**8b**) (Scheme 1).

After the stereochemistry of the side chain was secured, we next began investigations of means to establish the 14β,15β-epoxide. So far, not many methods except for m-cpba oxidation have been reported in stereoselectively generating the *cis*-14,15-epoxide.[11] However, treatment of **8a** with m-cpba gave two products, which could be carefully detected on the TLC plate ($R_f = 0.31$, $R_f = 0.32$, respectively; eluent: EtOAc/hexanes = 3:2). ^{1}H NMR data showed that the amounts of the α-epoxide and β-epoxide were almost identical. Further efforts to separate the two isomers were also fruitless. Noticing that the $\Delta^{14(15)}$–C_8–C_7–OH constitutes a homoallylic alcohol unit, we explored the Sharpless epoxidation[12] to establish the desired 14β,15β-epoxide. However, we were disappointed to find the epoxidation of **9** was unsuccessful by using either D or L-tartrate ligand since **9** was recovered quantitatively. Reversion of the 7α-OH to 7β-OH via a Mitsunobu reaction[13] afforded **10**, which underwent the Sharpless epoxidation smoothly, delivering the desired **11**[14] as the only product, whose 14β,15β-epoxide was confirmed by the NOEs from 15-H to 7-H. It is worth noticing that employment of different chiral ligands in the epoxidation of **10** gave the same result, with a slight difference in the reaction time. Further study revealed that the tartrate ligand was not necessary for this highly stereoselective transformation (Scheme 2).

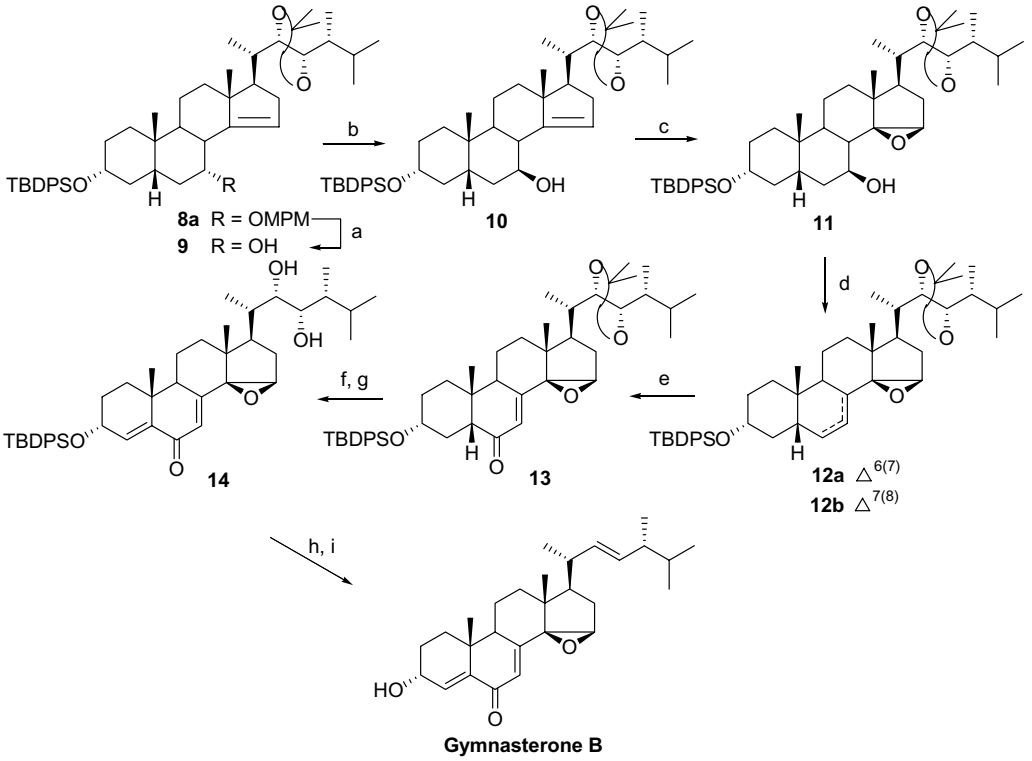
Therefore, we surmised that the successful conversion of the Δ^{14}-ene to 14β,15β-epoxide was due to the space proximity of the 7β-OH and Δ^{14}-ene function. Instead of being assisted by the chiral ligands, the stereospecific epoxidation of **10** was secured by the 7β-OH function.[15]

The modification of **11** toward the target proceeded without difficulties. On treatment of $SOCl_2$ and pyridine, **11** was converted into an inseparable mixture of **12a** and **12b**, which was subjected to SeO_2 mediated allylic oxidation without further purification to give the α,β-unsaturated ketone **13** in 57% yield (two steps overall) after flash chromatographic isolation. Other polar impurities were not identified. Introduction of $\Delta^{4(5)}$ to **13** was effected by IBX oxidation[16] to afford **14**, which was hydrolyzed in mild acid and underwent a Corey olefination[17] to deliver a TBDPS protected Gymnasterone B. After removal of the protective group in mild conditions, Gymnasterone B was achieved as an off-white amorphous solid whose spectroscopic data were identical to those reported.[3]

In summary, Gymnasterone B was synthesized for the first time from cholic acid. This synthetic route could offer enough Gymnasterone B for biological studies. It



Scheme 1. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 0 °C to rt, 96%; (b) *hv*, dioxane; (c) $BF_3{\cdot}OEt_2$, benzene, 25 °C, 54% in two steps; (d) (1) DBU, CS_2, CH_3I, DMF, 0 °C to rt, 100%; (2) Bu_3SnH, AIBN, toluene, 120 °C, 86%; (e) (1) LDA, PhSeBr, THF, −78 °C, 4 h; (2) 30% H_2O_2, MeOH, rt, 2 h, 86% in two steps; (f) OsO_4, $K_3Fe(CN)_6$, *t*-BuOH/H_2O (1:1), rt, 20 h, 73%; (g) 2,2′-dimethoxypropane, PTSA, CH_2Cl_2, 0 °C to rt, 96%; (h) 5% NaOH (aq), MeOH, 0 °C, 1 h, 84%; (i) NaH, MPMCl, DMF, 0 °C to rt, 95%; (j) *i*-PrMgI, −78 °C to 0 °C, 36 h; (k) Dess–Martin agent, $NaHCO_3$ (aq), CH_2Cl_2, rt, 2 h, 90% in two steps; (l) $TiCl_4$–Zn–CH_2Br_2, CH_2Cl_2, 25 °C, 82%; (m) NH_2OH, EtOAc, rt, 84%.



Scheme 2. Reagents and conditions: (a) CAN, CH_3CN/H_2O, v:v, 4:1, 0 °C, 30 min, 98%; (b) (1) DIAD, HCO_2H, Ph_3P; (2) $NaBH_4$, MeOH, 92% in two steps; (c) *t*-BuOOH, $Ti(iPrO)_4$, *t*-BuOH/H_2O 1:1, rt, 20 h, 87%; (d) $SOCl_2$, pyridine, THF, 0 °C to rt; (e) SeO_2, CH_3CN, rt, 36 h, 57% in two steps; (f) IBX, DMSO, 85 °C, 20 h, 83%; (g) AcCl/MeOH, 0 °C, 6 h, 95%; (h) thiocarbonyldiimidazole, CH_2Cl_2, then $P(OMe)_3$, 77%; (i) TBAF, THF, rt, 100%.

could also provide a method to establish the skeletons of other novel ergostanoids such as Gymnastatins and Gymnasterol.

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8. Compound **5a** as an amorphous solid: $[\alpha]_D^{25}$ −4.87 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, $J = 6.5$ Hz, 3H, 21-H), 1.10 (s, 3H), 1.12 (s, 3H), 2.01 (s, 3H), 3.38–3.42 (m, 1H, 3-H), 3.64 (s, 3H), 3.80 (d, $J = 3.5$ Hz, 22-H), 4.61 (s, 1H, 7-H), 4.91 (s, 23-H), 5.40 (s, 1H), 7.20–7.26 (m, 6H), 7.71–7.77 (m, 4H). Compound **5b** as an amorphous solid: $[\alpha]_D^{25}$ +10.42 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, $J = 7.2$ Hz, 3H, 21-H), 1.05 (s, 3-H), 1.11 (s, 3H), 2.01 (s, 3H), 3.35–3.40 (m, 1H, 3-H), 3.66 (s, 3H), 3.85 (d, $J = 3.5$ Hz, 1H, 22-H), 4.57 (s, 1H, 7-H), 4.90 (d, $J = 3.5$ Hz, 1H, 23-H), 5.40 (s, 1H, 15-H), 7.19–7.27 (m, 6H), 7.72–7.77 (m, 4H).
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10. Compound **8a** as an amorphous solid: $[\alpha]_D^{25}$ −6.54 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, $J = 7.2$ Hz, 3H), 1.21 (s, 3H), 1.37 (s, 3H), 1.38–1.48 (d × 3, 9H), 2.01 (s, 3H), 3.20–3.31 (m, 1H, 3-H), 3.48 (s, 3H), 3.78 (s, 1H, 23-H), 3.96 (d, $J = 4.0$ Hz, 22-H), 4.20 (s, 1H, 7-H), 4.40–4.43 (m, 2H), 5.44 (s, 15-H), 6.80 (d, $J = 8.2$ Hz, 2H), 7.20–7.30 (m, 8H), 7.71–7.78 (m, 4H). Compound **8b** as an amorphous solid: $[\alpha]_D^{25}$ 2.41 (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, $J = 6.8$ Hz, 3H), 1.20 (s, 3H), 1.31 (s, 3H), 1.35–1.47 (d × 3, 9H), 2.00 (s, 3H), 3.25–3.30 (m, 1H, 3-H), 3.44 (s, 3H), 3.78 (d, $J = 3.8$ Hz, 1H, 23-H), 3.92 (d, $J = 4.0$ Hz, 1H, 22-H), 4.19 (s, 1H, 7-H), 4.40–4.43 (m, 2H), 5.50 (s, 1H, 15-H), 6.81 (d, $J = 8.4$ Hz, 2H), 7.20–7.30 (m, 8H), 7.70–7.76 (m, 4H).

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14. Compound **11** as amorphous solid: $[\alpha]_D^{25}$ −15.34 (*c* 0.75, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.65 (d, $J = 6.8$ Hz, 3H), 0.80 (s, 3H), 1.20 (s, 3H), 1.22–1.30 (d × 3, 9H), 1.32 (s, 3H), 1.65 (s, 3H), 2.85 (m, 1H, 17-H), 3.20–3.26 (m, 1H, 3-H), 3.50 (t, $J = 11.0$ Hz, 1H, 7α-H), 3.63 (s, 1H, 15-H), 3.78 (s, 1H, 23-H), 3.80 (d, $J = 4.2$ Hz, 22-H), 7.20–7.23 (m, 6H), 7.68–7.76 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.21, 136.12, 133.90, 130.25, 128.71, 89.63, 81.02, 75.04, 73.42, 71.20, 69.87, 54.06, 52.24, 45.81, 44.37, 39.72, 36.31, 35.55, 34.57, 33.82, 33.70, 31.51, 29.30, 28.27, 27.26, 26.41, 22.54, 21.50, 21.36, 20.90, 19.27, 15.78, 14.02, 11.90, 10.45.
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