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Graphical Abstract

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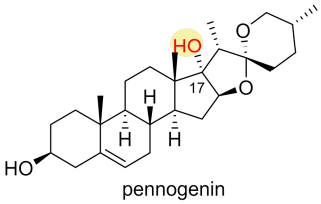

pennogenin

1.

An Improved Synthesis of Pennogenin

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Keywords:

Pennogenin; chonglou; diosgenin; diboration/oxidation; C17α-OH steroid

ABSTRACT:

An improved synthesis of pennogenin, a bioactive component of Chinese herb "Chonglou" (*Paris*), is described. A ring-switching process opened the ring E of diosgenin and allowed the use of a hydroxyl-directed diboration/oxidation to introduce C17α-OH, hence eliminating the use of OsO_4. This strategy might be rendered to synthesize similar steroids with C17α-OH.

1. Introduction

Recently, steroidal natural products with a C17α-OH, due to their interesting structures and diverse bioactivities, have drawn much attention from organic chemists.[1-10] The presence of the C17α-OH was reported to be crucial to their bioactivities.[11,12] Our group has long been attracted by these compounds and completed the syntheses of cephalostatin 1 (**1**)[3] and the aglycone of OSW-1 (**2**)[13] (Figure 1). Meanwhile, we also explored the synthesis of pennogenin (**3**), a less complex but potentially more useful natural steroid with C17α-OH.

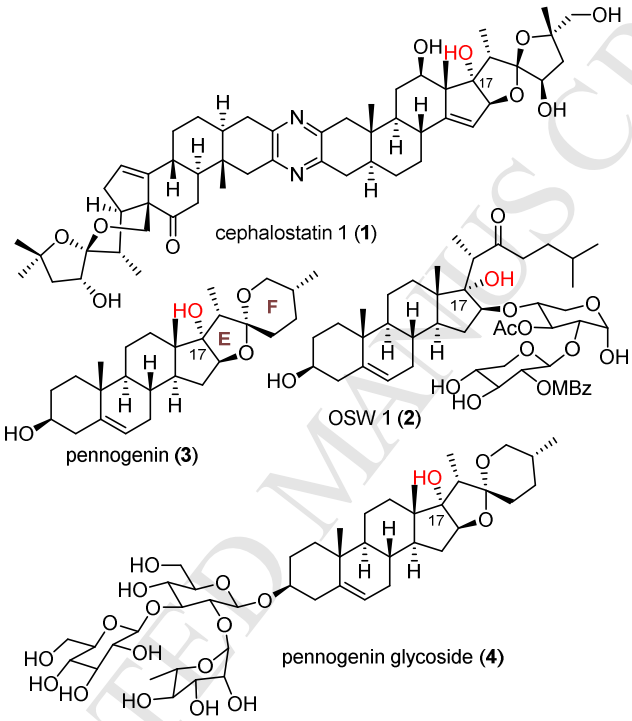
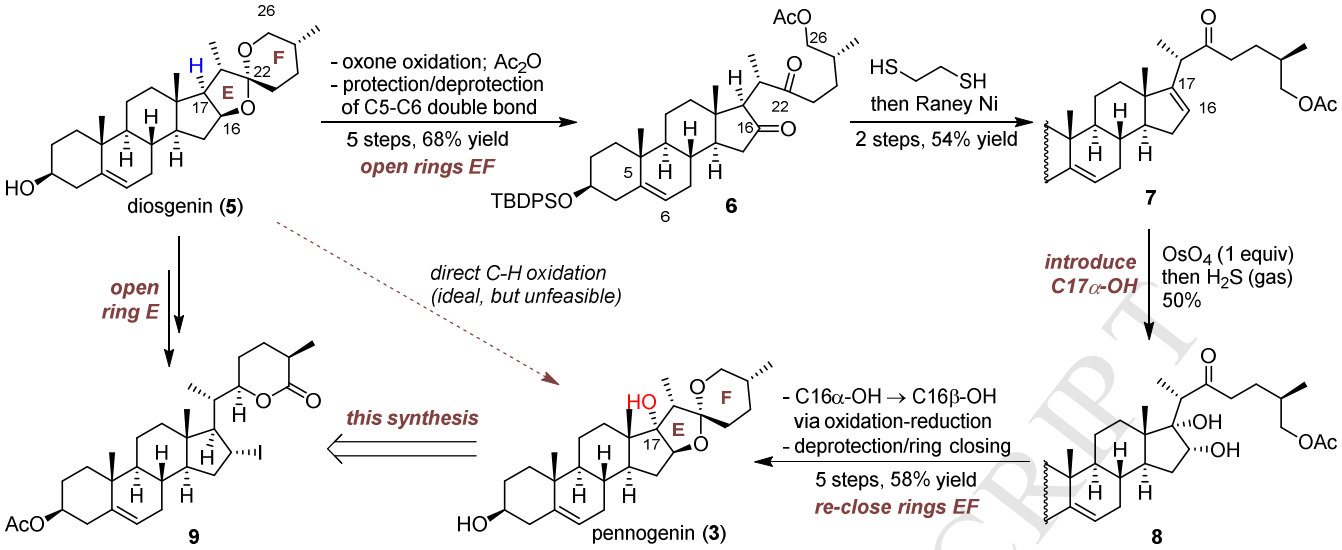


Figure 1. Selected Examples of Natural Steroids with C17α-OH

Pennogenin (**3**) and its glycosides exist widely in plants used in traditional Chinese herbal medicine, and possess a variety of biological activities, such as antibiotic and antitumor activities, and are widely used as haemostatic agents. For example, pennogenin glycoside **4** was isolated from Chinese herb *Rhizoma Paridis* (Chonglou), and exhibits potent antitumor activity with the IC_{50} values ranging from 0.5 to 5.1 μg/mL against human promyelocytic leukemia HL-60 cells.[14] Natural **3** and its glycosides are not easy to harvest from natural resources, because they are mixed with many other highly polar steroidal saponins and **3** itself could not survive the acidic hydrolysis that isolation of steroidal sapogenins routinely requires. As the demand of pennogenin and the related drugs was increasing and the plant resource decreasing, further development of some Chinese traditional medicines encountered the supply problem of **3** and its glycosides. Chemical synthesis of **3** might be a practical solution to this problem.

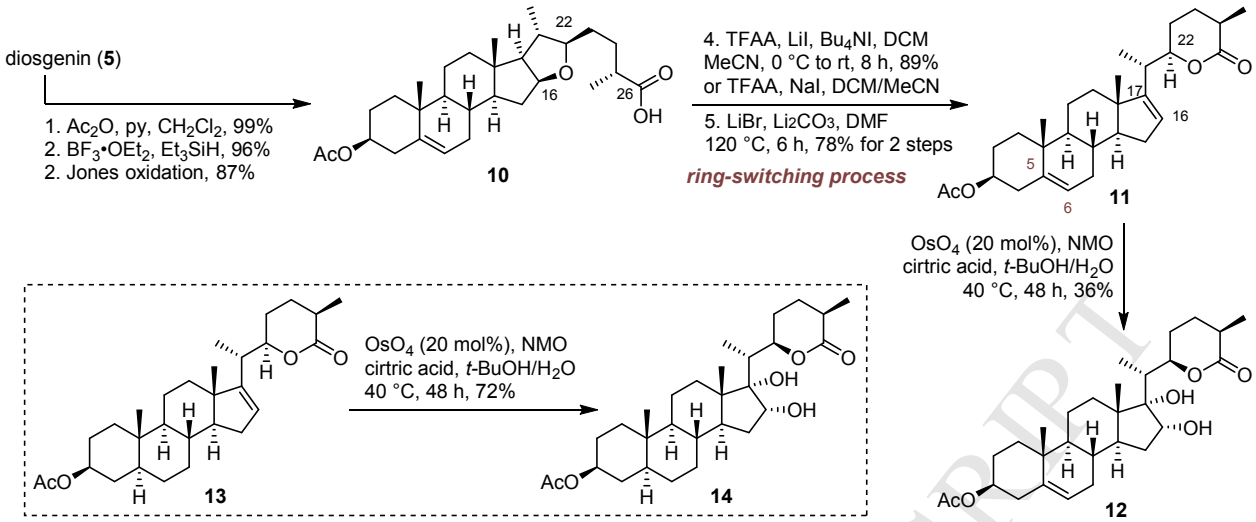


Scheme 1. Our Previous Synthesis of Pennogenin and Brief Plan for an Improved Synthesis

In 2004, we completed our first synthesis of pennogenin from diosgenin (**5**), a cheap and readily available steroidal sapogenin widely used in steroidal industry (Scheme 1).[15] Compared with diosgenin, pennogenin has an extra C17α-OH. To introduce this C17α-OH, one ideal method might be through direct C17-H oxidation, which, although reported occasionally[16-18], was not yet synthetically usable. We thus adopted a less direct approach, namely, to open spirokeal rings EF and introduce the C17α-OH and re-close the rings. As outlined briefly in Scheme 1, this synthesis was accomplished in 13 steps with an overall yield of 10%, with serveral problems remained. The C16-H oxidation with potassium peroxymonosulfate (oxone) took days to complete, the C5-C6 double bonds needed protection, the dihydroxylation of C16-C17 double bond required stoichiometric amount of OsO_4, and the environmentally unfriendly ethanedithiol and hydrogen sulfide were used. Aiming to minimize/exclude the use of OsO_4 and other unfavorable reagents, our second synthesis started a decade later based on intermediate **9**, which was prepared via a new ring-opening process we recently developed[19-21]. Herein, we would like to report this improved synthesis.

2. Results and discussion

As shown in Scheme 2, the synthesis began with opening the ring E of diosgenin (**5**) to make C17 modifiable. The C3-OH of diosgenin was acetylated, the ring F was opened reductively, and the resultant C26-OH was oxidized with Jones reagent to provide furostan-26-acid **10** in 83% yield. Using trifluoroacetic anhydride as an activation agent and lithium iodide as a nucleophile in DCM/MeCN provided lactone **9**, which, upon treating with lithium bromide and lithium carbonate in DMF at 120 °C, underwent bromination-elimination to provide **11** in 78% yield from acid **10**.

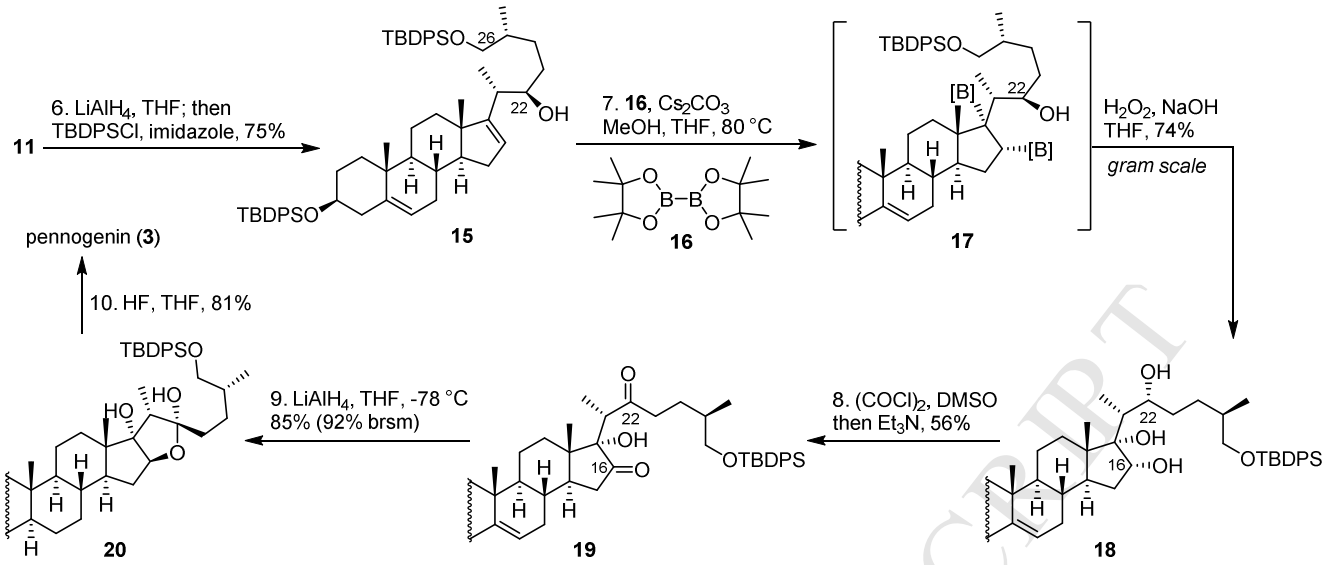


Scheme 2. Open the Ring E of Diosgenin and Oxidize with OsO_4.

With alkene **11** in hand, we first tried to run dihydroxylation of C16-C17 double bond with less OsO_4. Previously, we have performed the dihydroxylation of **13** with a catalytic amount of OsO_4 in the presence citric acid[22,23] at 40 °C to deliver diol **14** in 72% yield, which allowed us to synthesize the aglycon of aspafilioside E, 5α,6-dihydropennogein.[20] However, on **11** the selectivity issue (C16-C17 vesus C5-C6) emerged. The same procedure provided the desired **12** in 36% yield, along with comparable amount of over-oxidation product. It should be noted that oxidation with stoichiometric amount of OsO_4 at low temperature also did not show the same selectivity as in our fisrt synthesis. Such selectivity was not good enough to guarantee an efficient synthesis of pennogenin.

Further optimization was focused on excluding the use of toxic OsO_4 and improving the selectivity of oxidation. One option was to use the C22-OH as a directing group. Since opening the lactone ring of **11** through methanolysis was reversible and might cause epimerization at C25,[19,21] we decided to reduce it to a diol. Lactone **11** was therefore treated with $LiAlH_4$, and the resulting C3-OH and C26-OH were selectively protected as TBDPS ethers, leaving the C22-OH exposed for further use (Scheme 3).

Selective oxidation of double bonds directed by an adjacent hydroxyl group have been extensively investigated. The epoxidation of **15** with $VO(acac)_2$/t-BuOOH system could deliver the desired 16α,17α-epoxide in 66% yield (structure not showed). Since the 16α,17α-epoxides undergo Wagner-Meerwein rearrangement easily under most acidic medium systems that could promote an intramolecular endo-type or intermolecular *O*-epoxide-opening process, this compound was useless for our synthesis.



Scheme 3. Completion of the Synthesis of Pennogenin

We then looked for other OH-directing reactions. Recently, Morken and co-workers developed an alkoxide-catalyzed directed diboration of alkenyl alcohols, which could be used as a dihydroxylation method.[24-26] The diboration reportedly benefited from substrate directiong effects and we therefore assumed it could react with the C16-C17 double bond of **15** in the presence of the C5-C6 double bond. Indeed, homoallylic alcohol **15** was heated with $B_2(pin)_2$ (**16**) and Cs_2CO_3 in MeOH/THF for 6 h, and the resulting diboration product **17** underwent an oxidative workup (NaOH, H_2O_2) to give triol **18** in 74% yield on gram scale.

Having installed the C17α-OH, we then moved to rebuild the spiroketal rings, and the method in our first synthesis was adopted. Swern oxidation of triol **18** (large access of reagents) gave diketone **19** in moderate yield. Selective reduction of the C16-ketone with $LiAlH_4$ at -78 °C delivered hemiketal **20** in excellent yield (85%, 92% based on recovery of starting material). Treating **20** with aqueous HF solution removed the TBDPS ethers that protected the C3-OH and C26-OH, and promoted the formation of spiroketal, providing pennogenin (**3**) in 81% yield. This route delivered pennogenin from diosgenin in ten steps with an overall yield of 15%. The NMR data of synthetic **3** matched those reported.

3. Conclusion

In summary, we developed an improved synthesis of pennogenin using a ring-switching process to open the ring E and a hydroxyl-directed diboration/oxidation process to introduce 16α,17α-diol selectively. Although using nine steps to install a C17α-OH appears far from ideal, this synthesis provides an example of hydroxyl-directed stereoselective diboration/oxidation in the context of complex natural product synthesis, which excludes the use of highly toxic OsO_4 and might be applicable to the synthesis of similar steroids with C17α-OH, such as OSW-1.

4. Experimental Section

General Information: All reactions sensitive to air or moisture were performed in flame-dried round bottom flasks with rubber septum under a positive pressure of argon or nitrogen atmosphere, unless otherwise noted. Air and moisture-sensitive liquids and solutions were transferred via syringe and stainless steel cannula. The solvents and reagents, when needed, was purified according to the standard procedures described in *Purification of Laboratory Chemicals* (2009). Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates using UV light as visualizing agent and an ethanolic solution of phosphomolybic acid, and heat as developing agents. NMR spectra were recorded on Bruker DRX-400 instrument and calibrated using residual undeuterated solvent as an internal reference [^{1}H NMR: $CHCl_3$ (7.26); ^{13}C NMR: $CDCl_3$ (77.16)]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br = broad.

*4.1.1 Lactone **11***

Under a positive pressure of nitrogen, to a solution of **10** (3.32 g, 7.0 mmol) and sodium iodide (3.15 g, 21 mmol) in CH_2Cl_2/MeCN (40 mL/10 mL) was added $(CF_3CO)_2O$ (TFAA, 2.0 mL, 13 mmol) at 0 °C. The resulting mixture was vigorously stirred at ambient temperature for 12 h, quenched with saturated aqueous $NaHCO_3$ and saturated aqueous Na_2SO_3, diluted with water, and extracted with CH_2Cl_2 (80 + 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and used in the next step without purification.

Under nitrogen, to a solution of the crude in DMF (40 mL) were added lithium carbonate (1.66 g, 20.6 mmol) and lithium bromide (1.47 g, 13.6 mmol). The mixture was stirred at 120 °C for 6 h and concentrated under reduced pressure to remove the solvent. The residue was diluted with water and extracted with EtOAc (120 + 80 mL); the combined oganic layers were washed with brine, dried over sodium sulfate, filtered, concentrated in vacuo, and purified through silica gel chromatography (PE/EA: 7/1) to give **11** (2.48 g, 78%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (s, 1H), 5.39 (d, *J* = 4.6 Hz, 1H), 4.65 – 4.55 (m, 1H), 4.42 – 4.33 (m, 1H), 2.66 – 2.54 (m, 1H), 2.53 – 2.43 (m, 1H), 2.03 (s, 3H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.05 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.55, 170.69, 155.80, 140.04, 124.31, 122.58, 80.61, 74.03, 57.45, 50.69, 47.14, 38.26, 37.05, 36.94, 36.47, 34.83, 33.21, 31.66, 31.41, 30.60, 27.88, 25.75, 22.93, 21.59, 20.82, 19.38, 16.60, 16.47, 16.44; HRMS-MALDI (*m/z*): $[M+Na]^+$ calcd for $C_{29}H_{42}O_4$: 477.2975, found: 477.2977.

*4.1.2 Diol **12***

To a solution of cirtric acid (1.26 g, 6.5 mmol) and **11** (910 mg, 2.0 mmol) in *t*-BuOH/water (20 mL/10 mL) were added OsO_4 (4.0 mL, 0.10 M in *t*-BuOH, 4.0 mmol) and NMO (1.25 mL, 4.0 M solution, 6.0 mmol). The mixture was stirred at 40 °C for 48 h, quenched with saturated aqueous Na_2SO_3, and extracted with $CHCl_3$ (30 + 15 mL). The combined organic layers were washed with brine, dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified through flash column chromatography on silica gel (PE/EA: 2/1 to 1/1) to give the starting material **11** (112 mg) and **12** (311 mg, 36% based on recovery of **11**) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (d, *J* = 4.2 Hz, 1H), 4.64 – 4.57 (m, 2H), 4.32 (d, *J* = 7.2 Hz, 1H), 2.87 (brs, 1H), 2.68 – 2.56 (m, 1H), 2.14 (dd, *J* = 12.8, 6.3 Hz, 1H), 2.03 (s, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.03 (dd, *J* = 10.9, 3.9 Hz, 3H), 0.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.74, 170.69, 139.76, 122.43, 82.86, 79.95, 76.11, 74.01, 49.46, 48.89, 48.81, 43.54, 38.19, 36.98, 36.62, 35.96, 33.28, 32.94, 31.91, 31.78, 27.84, 25.92, 23.91, 21.58, 20.51, 19.40, 16.34, 14.62, 10.49. ESI-MS (*m/z*): 511.2, $[M+Na]^+$.

*4.1.3 Di-TBDPS-protected triol **15***

To a solution of lactone **11** (1.20 g, 2.6 mmol) in dry THF (50 mL) was added $LiAlH_4$ (400 mg, 10.5 mmol) at 0 °C under argon. The mixture was stirred for several hours, and quenched by adding water (0.40 mL), 10% aqueous NaOH solution (0.80 mL), and water (1.2 mL) sequentially. The mixture was filtered and washed with dry THF. The filtrate was concentrated to dryness and dissolved in dry DCM (40 mL). To the solution were added imidazole (760 mg, 11.1 mmol) and TBDPSCl (1.8 mL, 6.9 mmol). The mixture was stirred at ambient temperature for several hours, quenched with a saturated aqueous solution of $NaHCO_3$, and extracted with DCM (30 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography on silica gel (PE/EA: 120/1 to 50/1) provided **15** (1.78 g, 75%) as a white foam. $[\alpha]_D^{22}$ −37.0 (*c* 0.6, $CHCl_3$); IR (KBr): 3070, 2930, 2856, 1471, 1461, 1427, 1111, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 8H), 7.44 – 7.34 (m, 12H), 5.47 (s, 1H), 5.17 – 5.12 (m, 1H), 3.55 (m, *J* = 9.8, 6.9 Hz, 3H), 3.47 (dd, *J* = 9.8, 6.4 Hz, 1H), 1.07 (s, 9H), 1.06 (s, 9H), 1.03 (s, 3H), 0.95 (dd, *J* = 6.8, 4.8 Hz, 6H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 141.7, 135.9, 135.9, 135.8, 134.9, 134.9, 134.2, 134.2, 129.6, 129.6, 127.7, 127.6, 127.6, 123.2, 121.0, 110.1, 74.0, 73.3, 69.2, 57.6, 50.75, 47.3, 42.6, 40.2, 37.3, 36.9, 36.1, 34.8, 32.0, 31.7, 31.4, 31.1, 30.7, 29.3, 27.15, 27.0, 20.8, 19.5, 19.5, 19.3, 18.1, 17.0, 16.3; HRMS-ESI (*m/z*): $[M-H]^-$ calcd for $C_{59}H_{80}O_3Si_2$: 891.5562, found: 891.5553.

*4.1.4 Triol **18***

To a suspension of **15** (1.70 g, 1.9 mmol) and Cs_2CO_3 (360 mg, 1.1 mmol) were added bis(pinacolato)diboron (**16**, 2.18 g, 8.6 mmol) and MeOH (1.80 mL) at ambient temperature under argon.

The vessel was sealed and placed in an oil bath at 80 °C for 6 h. The reaction was allow to cool to 0 °C. To the mixture was added an aqueous solution of NaOH (1.9 g, 47 mmol), and added dropwise 30% aqueous soltuion of H_2O_2 (2.0 mL). After the diboration product disappeared on TLC, the reaction was cautiously quenched with saturated aquous $Na_2S_2O_3$ solution, diluted with water, and extracted with ethyl acetate (40 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude by flash column chromatography on silica gel (PE/EA: 12/1 to 10/1) provided triol **18** (1.31 g, 74%) as a white foam. $[\alpha]_D^{29}$ −22.4 (*c* 0.6, $CHCl_3$); IR (KBr): 3392, 2931, 2897, 2857, 1472, 1462, 1387, 1111, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 8H), 7.45 – 7.32 (m, 12H), 5.12 (s, 1H), 4.25 (d, *J* = 7.3 Hz, 1H), 3.70 (t, *J* = 7.2 Hz, 1H), 3.58 – 3.43 (m, 3H), 3.23 (s, 1H), 1.05 (d, *J* = 2.0 Hz, 18H), 0.97 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 135.9, 135.9, 135.7, 135.7, 134.9, 134.9, 133.9, 129.8, 129.6, 129.6, 127.8, 127.6, 127.6, 121.1, 82.8, 76.2, 73.8, 73.3, 69.0, 49.4, 48.7, 44.6, 42.6, 37.2, 36.5, 35.5, 34.0, 33.3, 32.7, 31.9, 31.9, 31.8, 28.2, 27.1, 27.0, 20.6, 19.5, 19.4, 19.3, 16.9, 14.1, 13.2. HRMS-ESI (*m/z*): **[**M+H]$^+$ calcd for $C_{59}H_{82}O_5Si_2$: 926.5774, found: 927.5746.

*4.1.5 Swern oxidation led to diketone **19***

To a solution of oxalyl chloride (0.087 mL, 1.0 mmol) in dry DCM (4.0 mL) was slowly added dry DMSO (0.144 mL, 2.0 mmol) at -78 °C under argon. After the evolution of gas ceased (*ca.* 30 min), a solution of alcohol **18** (92.0 mg, 0.10 mmol) in dry DCM (4 mL) was slowly added to the resulting cold solution. After 35 min, Et_3N (0.21 mL, 1.5 mmol) was added and the reaction was left to reach ambient temperature. After 2 h, the reaction was quenched by addition of water. The organic layer was separated and the aqueous phase was extracted with DCM (15 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude by flash column chromatography on silica gel (PE/EA: 40/1 to 10/1) provided ketone **19** (52 mg, 56%) as a white foam. $[\alpha]_D^{29}$ −75.9 (*c* 0.5, $CHCl_3$); IR (KBr): 3374, 3070, 2932, 2857, 1742, 1696, 1471, 1461, 1427, 1379, 1110, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.62 (m, 8H), 7.39 (m, *J* = 16.9, 9.6, 4.8 Hz, 12H), 5.55 (s, 1H), 5.11 (d, *J* = 4.7 Hz, 1H), 3.61 – 3.43 (m, 4H), 1.09 (d, *J* = 7.2 Hz, 3H), 1.06 (s, 9H), 1.05 (s, 9H), 1.01 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.5, 217.5, 141.5, 135.9, 135.8, 134.9, 134.9, 134.1, 134.0, 129.6, 129.6, 129.6, 127.7, 127.6, 127.6, 120.6, 85.9, 73.2, 68.7, 49.3, 45.3, 45.2, 43.0, 42.5, 41.2, 37.0, 36.7, 35.5, 35.3, 31.9, 31.2, 30.2, 27.2, 27.0, 26.7, 20.2, 19.6, 19.5, 19.3, 17.0, 13.9, 11.8. HRMS-ESI (*m/z*): [M+H]$^+$ calcd for $C_{59}H_{78}O_5Si_2$: 923.5461, found: 923.5430.

*4.1.6 Hemiketal **20***

To a solution of diketone **19** (26 mg, 0.028 mmol) in dry THF (4 mL) was added $LiAlH_4$ (22 mg, 0.58 mmol) at -78 °C under argon. The reaction was stirred for 2 h, quenched by addition of EtOAc, and diluted with EtOAc (30 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude by flash column chromatography on silica gel (PE/EA: 10/1 to 8/1) provided **20** (22 mg, 85%, 92% brsm) as a white foam and the starting material **19** (2.0 mg). $[\alpha]_D^{29}$ −40.3 (*c* 0.7, $CHCl_3$); IR (KBr): 2960, 2924, 2854, 1749, 1734, 1457, 1261, 1020, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.61 (m, 8H), 7.40 (m, *J* = 14.7, 7.6 Hz, 12H), 5.11 (s, 1H), 4.14 (m, *J* = 14.5, 7.1 Hz, 1H), 3.60 – 3.41 (m, 3H), 1.06 (s, 9H), 1.05 (s, 9H), 1.01 (s, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 135.9, 135.9, 135.8, 134.9, 134.9, 134.1, 129.7, 129.6, 129.6, 127.7, 127.6, 127.6, 120.9, 111.57, 90.8, 73.3, 68.8, 52.8, 49.7, 44.2, 42.7, 42.6, 37.3, 36.7, 36.0, 35.2, 32.1, 32.0, 31.8, 31.6, 31.3, 27.2, 27.0, 26.8, 20.7, 19.6, 19.4, 19.3, 17.1, 17.0, 8.6; HRMS-ESI (*m/z*): $[M+H]^+$ calcd for $C_{59}H_{80}O_5Si_2$: 925.5617, found: 925.5601.

*4.1.7 Pennogenin (**3**)*

To a solution of hemiketal **20** (18 mg, 0.019 mmol) in THF (3.0 mL) was added 30% aqueous HF solution (0.50 mL) at ambient temperature. After TLC showed the completion of the reaction, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude by flash column chromatography on silica gel (PE/EA: 8/1 to 3/1) provided pennogenin **3** (6.0 mg, 81%) as a white solid. mp 236 °C; $[\alpha]_D^{20}$ −111 (*c* 0.234, $CHCl_3$); IR (KBr): 3533, 3489, 1059, 977 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.34 (d, *J* = 5.0 Hz, 1H), 3.97 (t, *J* = 7.8 Hz, 1H), 3.53 – 3.46 (m, 2H), 3.37 (t, *J* = 10.8 Hz, 1H), 1.02 (s, 3H), 0.90 (d, *J* = 7.2 Hz, 3H), 0.81 (s, 3H), 0.79 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 121.3, 110.1, 90.9, 90.1, 71.7, 66.8, 52.8, 49.6, 44.6, 43.7, 42.2, 37.2, 36.6, 32.0, 31.6, 31.6, 31.5, 31.2, 30.7, 30.0, 28.1, 20.6, 19.4, 17.1, 17.0, 8.1; HRMS-MALDI (*m/z*): $[M+Na]^+$ calcd for $C_{27}H_{42}O_4$: 453.2976, found: 453.2975.

Acknowledgments

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