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Semisynthesis of Azedarachol from Pregnanetriol, a Degradative Product of Tigogenin

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We report the first semisynthesis of the natural insect antifeedant azedarachol. The synthesis features the employment of pregnanetriol, a degradative product of the resource natural product tigogenin, as the starting material, the symbiotic reaction involving the mutually-promoting elimination of toluene-sulfonate and deprotection of acetonide, and the controllable reactions between the C16-OH and the C20-OH in pregnane-16,20-diols.

Keywords azedarachol, pregnanetriol, natural products, symbiotic reaction, synthesis

Introduction

Tigogenin (**1**, Figure 1) is easily available from the waste water collected from the industrial production of sisal fiber, which constitutes an important resource natural product. Using it in the syntheses of steroidal drugs and bioactive natural steroids not only provides resource chemical for steroidal industry, but also diminishes the environmental pollution in sisal industry.[1] For this purpose, our group has studied in detail the reactions of tigogenin and their application in organic synthesis.[2] Herein, we report the first semisynthesis of azedarachol (**3**), a natural insect antifeedant, from pregnanetriol (**2**), a degradative product which could be easily prepared from tigogenin in 10 kg scale.

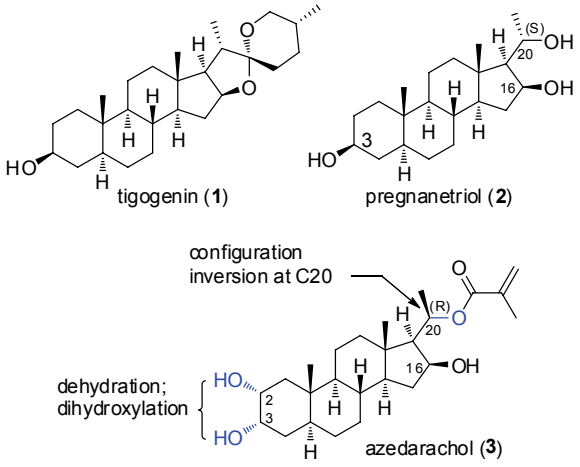

Figure 1 Structures of tigogenin (**1**), pregnanetriol (**2**), and azedarachol (**3**).

Azedarachol was isolated by Nakatani and coworkers in 0.003% yield from the root bark of *Melia azedarach* L. in 1984.[3] It showed antifeedant activity against the larvae of *Ajrotis sejetum* Denis, a Japanese insect pest, with the leaf disk choice test (500 ppm). Its remarkable antifeedant activity and structural similarity with **2** attracted us to pursue its synthesis from **2**.

Experimental

Pregnane-3*S*,16*S*,20*S*-triol acetonide To a solution of triol **2** (1.01 g, 3.0 mmol) in acetone/ dichloromethane (15 mL/30 mL) was added TsOH (60 mg). The mixture was stirred at ambient temperature for 6 h and quenched with saturated aqueous solution of $NaHCO_3$ (10 mL) and concentrated. The residue was stirred in water (30 mL), filtrated, and concentrated to afford the title compound (1.11 g, 98%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.82 (s, 3H, 19-H), 0.87 (s, 3H, 18-H), 1.19 (d, J=6.3 Hz, 3H, 21-H), 1.33 (s, 6H, $C(CH_3)_2$), 3.54—3.64 (m, 1H, 3-H), 3.84 (dq, J=10.2, 6.3 Hz, 1H, 20-H), 4.10—4.18 (m, 1H, 16-H).

Pregnane-16*S*,20*S*-acetonide-3β-toluenesulfonate (4) To a solution of triol acetonide (24.4 g, 65 mmol) and DMAP (790 mg, 6.5 mmol) in dry pyridine (200 mL) was added TsCl (24.7 g, 130 mmol) in two portions at ambient temperature. The reaction was stirred for 24 h, quenched with MeOH (2.6 mL), and poured into an ice water (3 L). The solid was collected by filtration and dissolved with ethyl acetate (700 mL), washed successively with 1.2 mol/L HCl and saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The crude was recrystallized from ethyl acetate to give **4** (25.8 g, 75%) as a white solid. ^{1}H NMR (300 MHz,

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$CDCl_3$): 0.79 (s, 3H,19-H), 0.85 (s, 3H, 18-H), 1.18 (d, J=6.3 Hz, 3H, 21-H), 1.32 (s, 6H, $C(CH_3)_2$), 2.44 (s, 3H, $PhCH_3$), 3.83 (dq, J=10.2, 6.3 Hz, 1H, 20-H), 4.09−4.16 (m, 1H, 16-H), 4.36−4.47 (m, 1H, 3-H), 7.33 (d, J=8.4 Hz, 2H), 7.79 (d, J=8.4 Hz, 2H).

Pregnane-2,3-en-16*S*,20*S*-diol (5) A suspension of **4** (1.142 g, 2.15 mmol) and LiBr (1.14 g, 11 mmol) in dry *N*,*N*-dimethylformamide (DMF, 20 mL) was stirred at 140 ℃ for 4 h. The solution was cooled and diluted with ethyl acetate (100 mL), washed with saturated solution of $CuSO_4$ and brine, dried over Na_2SO_4, filtered, and concentrated. Purification of the residue on silica gel afforded diol **5** (602 mg, 87%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.76 (s, 3H, 19-H), 0.87 (s, 3H, 18-H), 1.30 (d, J=6.3 Hz, 3H, 21-H), 2.08 (d, J=5.4 Hz, 1H, 20-OH), 2.61 (d, J=3.3 Hz, 1H, 16-OH), 4.07−4.18 (m, 1H, 20-H), 4.44−4.52 (m, 1H, 16-H), 5.52−5.64 (m, 2H, 2-H+3-H).

Pregnane-2,3-en-16*S*-ol-20*S*-mesylate (6) To a solution of diol **5** (318 mg, 1 mmol), DMAP (14 mg) and Et_3N (0.36 mL, 2.6 mmol) was added MsCl (0.10 mL, 1.3 mmol) under ice/acetone bath (−15 ℃). The mixture was warmed to ambient temperature and stirred for 12 h, then diluted with EtOAc (100 mL), washed with 1 mol/L HCl, saturated solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography on silica gel provided **6** (287 mg, 72%) as a white solid. Trace byproduct was isolated. m.p. 117 ℃ (dec.); $[\alpha]_D^{22}$ +64.9 (c 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.76 (s, 3H, 19-H), 0.89 (s, 3H, 18-H), 1.54 (d, J=6.3 Hz, 3H, 21-H), 2.94 (d, J=3.9 Hz, 1H, 16-OH), 3.06 (s, 3H, OSO_2CH_3), 4.31−4.39 (m, 1H, 16-H), 5.30 (dq, J=10.2, 6.3 Hz, 1H, 20-H), 5.53−5.64 (m, 2H, 2-H+3-H); IR (KBr) v: 3020, 2941, 2852, 1327, 1174, 977, 928, 906, 889 cm^{-1}; ESI-MS m/z (%): 414.3 (M+ NH_4^+, 63), 415.2 (M+1+ NH_4^+, 14). Anal. calcd for $C_{22}H_{36}O_4S$: C 66.63, H 9.15; found C 66.50, H 8.94.

Pregnane-2,3-en-20*S*-ol-16*S*-pivalate (7) A solution of diol **5** (1.59 g, 5 mmol), DMAP (122 mg, 1 mmol) and Et_3N (1.7 mL, 12 mmol) in dry DCM (50 mL) was treated with PivCl (0.75 mL, 6 mmol) at 0 ℃ and the mixture was stirred at ambient temperature for 12 h before 1 mol/L HCl solution (20 mL) was added. The mixture was extracted with DCM for three times; the combined extracts were washed with saturated solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. Purification of the crude by column chromatography on silica gel gave **7** (1.55 g, 77%) as a white solid and 20-pivalate (233 mg, 11%) as a white solid. m.p. 114−116 ℃; $[\alpha]_D^{26}$ +70.0 (c 0.72, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.76 (s, 3H, 19-H), 0.85 (s, 3H, 18-H), 1.22 (s, 9H, $C(CH_3)_3$), 1.26 (d, J=6.3 Hz, 3H, 21-H), 3.90−3.97 (m, 1H, 20-H), 5.28−5.35 (m, 1H, 16-H), 5.54−5.63 (m, 2H, 2-H+3-H); IR (KBr) v: 3310, 3019, 2968, 2932, 1725, 1290, 1164 cm^{-1}; EI-MS m/z (%): 402 (M^+, 0.18), 300 (M^+–PivOH, 4.0), 256 (100). Anal. calcd for $C_{26}H_{42}O_3$: C 77.56, H 10.51; found C 77.23, H 10.14. For 20-pivalate: m.p. 182−184 ℃; $[\alpha]_D^{26}$ +31.1 (c 0.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.76 (s, 3H, 19-H), 0.91 (s, 3H, 18-H), 1.19 (s, 9H, $C(CH_3)_3$), 1.31 (d, J=6.0 Hz, 3H, 21-H), 4.18−4.25 (m, 1H, 16-H), 5.23−5.34 (m, 1H, 20-H), 5.53−5.63 (m, 2H, 2-H+3-H); IR (KBr) v: 3512, 3019, 2975, 2917, 1707, 1296, 1180 cm^{-1}; EI-MS m/z (%): 300 (M^+–PivOH, 29.7), 285 (M^+–PivOH–CH_3, 8.6), 246 (100); Anal. calcd for $C_{26}H_{42}O_3$: C 77.56, H 10.51; found C 77.53, H 10.60.

Pregnane-2,3-en-20-oxo-16*S*-pivalate (9) A solution of **7** (201 mg, 0.5 mmol) in acetone was added Jones reagents at 0 ℃ until the red color retained. The mixture was stirred for 1.5 h at ambient temperature, filtered with celite, and concentrated in vacuo. The residue was dissolved in ethyl acetate (30 mL), washed with saturated solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography on silica gel afforded **9** (165 mg, 82%) as a white solid and enone (18 mg, 12%) as a white solid. m.p. 48−50 ℃; $[\alpha]_D^{17}$ +73.0 (c 1.39, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.77 (s, 3H, 19-H), 1.08 (s, 3H, 19-H), 1.16 (s, 9H, $C(CH_3)_3$), 2.06 (s, 3H, 21-H), 2.36 (d, J=7.2 Hz, 1H, 17-H), 5.47−5.59 (m, 3H, 2-H+3-H+16-H); IR (KBr) v: 3020, 2971, 2913, 1730, 1716, 1286, 1154 cm^{-1}; EI-MS m/z (%): 400 (M^+, 0.64), 385 (M^+–CH_3, 0.82), 298 (M^+–PivOH, 32.3), 283 (298–CH_3, 8.5), 57 (100); HRFT-MS: $[M+N]^+$ calcd for $C_{26}H_{40}O_3$ 423.28697, found 423.2889. For enone: m.p. 144−145 ℃; $[\alpha]_D^{26}$ +114.1 (c 0.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.78 (s, 3H, 19-H), 0.90 (s, 3H, 18-H), 2.26 (s, 3H, 21-H), 5.53−5.63 (m, 2H, 2-H+3-H), 6.70 (dd, J=3.3, 1.8 Hz, 1H, 16-H); IR (KBr) v: 3028, 2937, 2923, 1662, 1583, 1373, 1230, 665 cm^{-1}; EI-MS m/z (%): 299 (M^++1, 20.4), 298 (M^+, 80.5), 283 (M^+–CH_3, 38.0), 255 (M^+–$COCH_3$, 75.9), 43 (100). Anal. calcd for $C_{21}H_{30}O$: C 84.51, H 10.13; found C 84.16, H 9.90.

Pregnane-2,3-ene-20*R*-ol-16*S*-pivalate (10) A solution of ketone **9** (300 mg, 0.75 mmol) and $CeCl_3$ (235 mg, 0.94 mmol) in anhydrous THF (12 mL) and absolute MeOH (1 mL) was cooled to −78 ℃ then added a solution of $NaBH_4$ (57 mg, 1.5 mmol) in absolute MeOH (1 mL). The reaction was stirred for 2 h and added acetone (1 mL) and warmed to room temperature and then added 1 mol/L HCl (20 mL). The mixture was extracted with ethyl acetate for three times; the combined organic layers were washed with saturated solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude on silica gel gave **10** (201 mg, 67%) and **7** (84 mg, 28%). m.p. 221−222 ℃; $[\alpha]_D^{20}$ +100.6 (c 0.44, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.77 (s, 3H, 19-H), 0.99 (s, 3H, 18-H), 1.17 (d, J=6.0 Hz, 3H, 21-H), 1.18 (s, 9H, $C(CH_3)_3$), 4.15 (dq, J=9.9, 6.0 Hz, 1H, 20-H), 5.06 (ddd, J=7.8, 7.8, 3.6 Hz, 1H, 16-H), 5.54−5.64 (m, 2H, 2-H+3-H); IR (KBr) v: 3570, 3531, 3015, 2970, 2930, 2911, 1711, 1480, 1294, 1184, 1176,

1166, 661 cm^{-1}; EI-MS *m/z* (%): 402 (M^+), 348 (M^+–C_4H_6), 300 (M^+–PivOH, 47.7), 285 (M^+– PivOH–CH_3, 100). Anal. calcd for $C_{26}H_{42}O_3$: C 77.56, H 10.51; found C 77.40, H 10.39.

Pregnane-2,3-ene-16*S*,20*R*-diol (11) To a solution of **10** (1.61 g, 4.0 mmol) in dry THF (40 mL) was added $LiAlH_4$ (228 mg, 6 mmol) at ambient temperature. The reaction was stirred for 12 h and quenched with 1.2 mol/L HCl (50 mL). The mixture was diluted with DCM (50 mL), separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified on silica gel to afford diol **11** (1.26 g, 99%) as white solid. m.p. 181－183 ℃; $[\alpha]_D^{25}$ ＋64.1 (*c* 0.59, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 0.76 (s, 3H, 19-H), 1.02 (s, 3H, 18-H), 1.35 (d, *J*＝6.3 Hz, 3H, 21-H), 4.22 (dq, *J*＝9.0, 6.3 Hz, 1H, 20-H), 4.31 (ddd, *J*＝7.5, 7.5, 4.5 Hz, 1H, 16-H), 5.51－5.63 (m, 2H, 2-H ＋3-H); IR (KBr) *v*: 3429, 3361, 3254, 3023, 2968, 1377, 1089, 1066, 1030 cm^{-1}; EI-MS *m/z* (%): 300 (M^+ －18, 26.5), 285 (M^+–H_2O–15, 11.3), 246 (100, M^+ –H_2O–C_4H_6); HRFT-MS: $[M + Na]^+$ calcd for $C_{21}H_{34}O_2$: 341.2451; found 341.2469.

Pregnane-2,3-ene-20*R*-ol-16*S*-OTBS (12) To a solution of diol **11** (1.99 g, 6.25 mmol), DMAP (152 mg) and Et_3N (2.1 mL, 15 mmol) in DCM was added TBSCl (1.32 g, 8.75 mmol). The reaction was stirred at ambient temperature for 36 h and quenched with water and diluted with DCM (50 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the crude product afforded **12** (2.65 g, 99%) as white solid. m.p. 192－194 ℃; $[\alpha]_D^{25}$ ＋60.8 (*c* 0.84, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ: 0.037, 0.043 (2s, 6H, $Si(CH_3)_2$), 0.77 (s, 3H, 19-H), 0.88 (s, 9H, $C(CH_3)_3$), 1.04 (s, 3H, 18-H), 1.26 (d, *J*＝6.3 Hz, 3H, 21-H), 4.15－4.31 (m, 2H, 16-H＋20-H), 5.53－5.64 (m, 2H, 2-H＋3-H); IR (KBr) *v*: 3563, 2960, 2930, 2854, 1253, 1061, 839, 778 cm^{-1}; EI-MS *m/z* (%): 375 (M^+–Bu-*t*, 11.5), 283 (M^+＋1–TBSOH–H_2O, 100). Anal. calcd for $C_{27}H_{48}O_2Si$: C 74.94, H 11.18; found C 74.87, H 11.26.

Pregnane-2*α*,3*α*-acetonide-16*S*-OTBS-20*R*-methacrylate (15) To a solution of NMO (270 mg, 2.0 mmol) and OsO_4 (28 mg) in THF/water (5 mL/0.5 mL) was added **12** (216 mg, 0.5 mmol) at 0 ℃. The reaction was stirred for another 3.5 h and quenched with semi-saturated solution of Na_2SO_3. After 20 min, the mixture was extracted with EtOAc (60 mL) for three times, and the combined organic layers were washed sequentially with 1 mol/L HCl, saturated solution of $NaHCO_3$ and brine. Concentration under reduced pressure afforded **13** which was used without purification. The crude was dissolved in acetone (6 mL) and treated with PPTS (13 mg) at ambient temperature for 23 h. Concentration in vacuo gave acetonide **14**. Crude **14** was dissolved with dry DCM (5 mL), treated with DMAP (12 mg), Et_3N (0.21 mL, 1.5 mmol) and methacryloyl chloride (98 μL, 1 mmol) at 0 ℃. The reaction was stirred at ambient temperature for 10 h and quenched with 1.2 mol/L HCl (4 mL). The mixture was diluted with EtOAc (100 mL), washed with saturated solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel afforded **15** (185 mg, 64% from **12**) as white solid. m.p. 194－195 ℃; $[\alpha]_D^{20}$ ＋48.3 (*c* 0.405, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 0.03 (s, 6H, $Si(CH_3)_2$), 0.70 (s, 3H, 19-H), 0.85 (s, 3H, 18-H), 0.89 (s, 9H, $C(CH_3)_3$), 1.26 (d, *J*＝5.7 Hz, 3H, 21-H), 1.33, 1.49 (2s, 6H, $O_2C(CH_3)_2$),1.94 (s, 3H, C＝CCH_3), 4.06－4.20 (m, 2H, 2-H＋3-H), 4.30 (ddd, *J*＝7.5, 7.5, 1.2 Hz, 1H, 16-H), 5.34 (dq, *J*＝10.8, 5.7 Hz, 1H, 20-H), 5.54 (t, *J*＝1.5 Hz, 1H, H_a), 6.07 (brs, 1H, H_b); IR (KBr) *v*: 2928, 1716, 1215, 1058 cm^{-1}; EI-MS *m/z* (%): 559 (M^+ –CH_3, 1.10), 299 (357–CH_3COCH_3, 39.5), 143 (100). Anal. calcd for $C_{34}H_{58}O_5Si$: C 71.03, H 10.17; found C 71.39, H 10.03.

Azedarachol (3) A solution of **15** (58 mg, 0.1 mmol) in acetonitrile (5 mL) was treated with 40% HF (2.5 mL) at ambient temperature for 5 h and quenched with $NaHCO_3$. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified on silca gel to give azedarachol (33 mg, 78%) as white solid. m.p. 218－220 ℃ (lit. 231－232 ℃, MeOH); $[\alpha]_D^{27}$ ＋18.4 (*c* 0.10, $CHCl_3$, lit.＋20.0, $CHCl_3$); ^1H NMR (300 MHz, CD_3OD) δ: 0.82, 0.84 (2s, 6H, 18-H＋19-H), 1.33 (d, *J*＝6.0 Hz, 3H, 21-H), 1.92 (s, 3H, C＝CCH_3), 3.66 (dt, *J*＝11.4, 3.9 Hz, 1H, 2-H), 3.87 (brs, 1H, 3-H), 4.29 (ddd, *J*＝7.8, 7.8, 4.8 Hz, 1H, 16-H), 5.33 (dq, *J*＝11.1, 6.0 Hz, 1H, 20-H), 5.62 (t, *J*＝1.5 Hz, 1H, H_a), 6.07 (brs, 1H, H_b); ^1H NMR (300 MHz, $CDCl_3$) δ: 0.80 (s, 3H, 19-H), 0.86 (s, 3H, 18-H), 1.37 (d, *J*＝6.0 Hz, 3H, 21-H), 1.95 (s, 3H, C＝CCH_3), 3.73－3.79 (m, 1H, 2-H), 3.97 (brs, 1H, 3-H), 4.31－4.38 (m, 1H, 16-H), 5.35 (dq, *J*＝10.5, 6.0 Hz, 1H, 20-H), 5.56 (t, *J*＝1.5 Hz, 1H, H_a), 6.09 (brs, 1H, H_b); IR (KBr) *v*: 3562, 3426, 2927, 2852, 1703, 1186, 1033 2927, 2852, 1703, 1186, 1033 cm^{-1}; EI-MS *m/z* (%): 334 (M^+–$C_3H_5CO_2H$, 13.0), 316 (334–H_2O, 41.1), 69 (100).

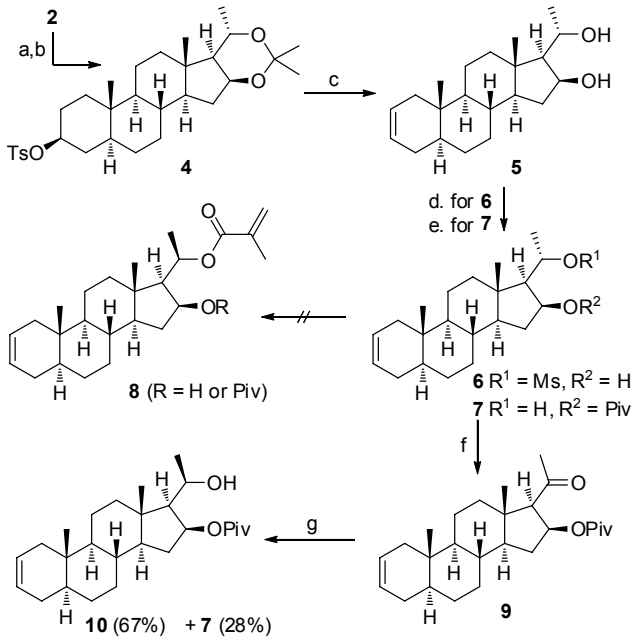
Results and Discussion

Depicted briefly in Figure 1 is our synthetic plan of azedarachol (**3**). We envisioned that its 2,3-*cis*-vicinal diol be introduced through a dehydration of C3-OH in **2** and a substrate-controlled dihydroxylation of the resulting C2－C3 double bond, and its 20*R*-methyacrylate be installed through configurational inversion of C20*S*-OH. We decided to perform the dehydration of C3-OH and to keep the resulting C2－C3 double bond as precursor for vicinal diol before C20*R*-OH is installed. The main challenge is how to selectively manipulate the secondary OHs in **2**.

The 16,20-diol unit in **2** was protected as the acetonide (TsOH, acetone/dichloromethane) and the

C3-OH was transformed into the toluene sulfonate (TsCl, pyridine, r.t., 24 h), providing **4** in 73% yield (Scheme 1). The bromination-elimination[4] of **4** proceeded smoothly in the presence of 5 equiv of lithium bromide in DMF at 140 ℃ for 4 h, and the deprotection of the acetonide was realized in the same flask when the generated acid was not neutralized with lithium carbonate, affording diol **5** directly in high yield. Being triggered and promoted by the acid, the cleavage of the acetonide also consumed the acid (TsOH or HBr), thereby acting as a base to facilitate the elimination step. Both reactions proceeded in one flask and got benefits from each other, hence being considered a symbiotic reaction.[2a]

Scheme 1



Conditions and reagents: (a) TsOH, acetone/CH_2Cl_2 (1/1), r.t., 6 h, 97%; (b) TsCl, DMAP, pyridine, r.t., 24 h, 75%; (c) LiBr, DMF, 140 ℃, 4 h, 87%; (d) MsCl, DMAP, Et_3N, CH_2Cl_2, −15 ℃ to r.t., 12 h, 72%; (e) PivCl, Et_3N, DMAP, CH_2Cl_2, 0 ℃ to r.t., 12 h, 77% for **7**, 11% for C20-OPiv; (f) CrO_3, H_2SO_4, acetone, 0 ℃, 1.5 h, 82%; (g) $CeCl_3$, $NaBH_4$, MeOH/THF, −78 ℃, 2 h, 67% for **10**, 28% for **7**, 82% for **10** after one cycle.

To inverse the configuration at C20, we needed to differentiate the hydroxyl groups in **5**. Interestingly, the mesylation of **5** (MsCl, Et_3N, DCM) gave only **6**, the reaction with TBDPSCl or TBSCl exhibited poor selectivities (C20/C16: 1/1.5—2), and the esterification of **5** with PivCl gave **7** as the major product (C20/C16: 1/7). Such selectivities, we assumed, were caused by the higher reactivity and steric hinderance of the C20*S*-OH than that of the C16*S*-OH. Therefore, MsCl reacted with the C20*S*-OH faster, while TBDPSCl and TBSCl, being sterically sensitive, reacted with both hydroxyl groups at similar rates, therefore exhibiting poor selectivities. Although PivCl was also sterically demanding, its ester could undergo transesterification between the more reactive C20*S*-OH and the less hindered C20*S*-OH, the more stable product **7** was therefore obtained. In this way, both hydroxyl groups could be protected selectively.

However, neither the Mitsunobu reaction of **7** nor the substitution of **6** with cesium methacrylate succeeded in introducing the desired C20*R*-methacrylate **8**. We resorted to an oxidation/reduction procedure. Jones oxidation of **7** afforded in 82% yield the ketone **9**, which was apt to undergo *β*-elimination under Swern oxidation conditions and during storage, hence was used immediately.

Several groups have reported the selective reduction of C20-ketone to C20*R*-OH, with $NaBH_4$ and $LiAlH_4$,[5] in substrates with *α*/*β*-ester at C16, however, these conditions did not succeed in our case, giving nonselective products (20*R*/20*S*: 1/1–2 by NMR). We reasoned that a chelation between the C20-ketone and the C16*β*-OPiv would change the conformation of the ketone and therefore reverse the selectivity of the reduction, as depicted in Figure 2. Indeed, after much attempts and optimization,[6] upon reducing **9** with $NaBH_4$ in the presence of anhydrous $CeCl_3$ in MeOH/THF at low temperature, the desired **10** with C20*R*-OH was obtained in 67% yield and its epimer **7** in 28% yield. Compound **7** was recycled and used again to improve the yield of **10** to 82% after one cycle.

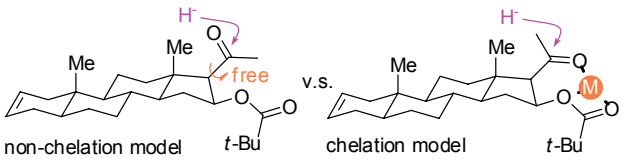


Figure 2 Change the conformation of C20-ketone of **9** during reduction through chelation.

To avoid the possible trouble in selective deprotection, we should not retain the pivalate in **10** anymore. As depicted in Scheme 2, $LiAlH_4$ reduction of **10** removed its pivalate to give diol **11**. Considering the difficulty in achieving the selective methacrylation of **11** and the incompatibility of the terminal double bond in the forthcoming dihydroxylation step, we decided to delay the formation of the C20*R*-methacrylate and to protect the C16*S*-OH as the TBS ether, a protecting group which could be painlessly removed at the last step. Selective protection of **11** with TBSCl was achieved by running the reaction in dichloromethane to afford **12** as the sole product, whereas the reaction in DMF only gave a 2/1 selectivity. It should be noted that under the same conditions such selectivity was not achieved in diol **5**, the 20-epimer of **11**.

With **12** in hand, we performed the dihydroxylation[7] of its C2–C3 double bond to yield the 2*α*,3*α*-vicinal diol **13** whose newly generated hydroxyl groups were protected as acetonide to give **14**. Then the methacrylate unit was introduced by treating **14** with methacrylic

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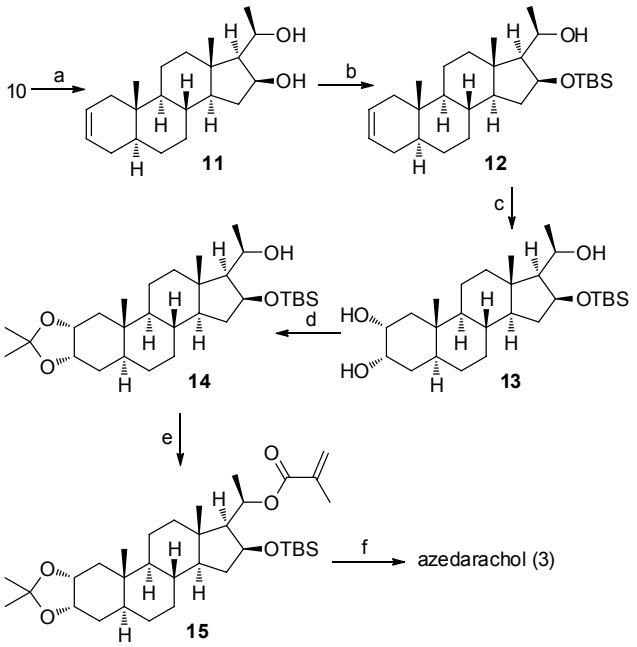
Scheme 2



Conditions and reagents: (a) $LiAlH_4$, THF, r.t., 12 h, 99%; (b) TBSCl, Et_3N, DMAP, CH_2Cl_2, r.t., 36 h, 99%; (c) OsO_4, NMO, THF, 0 ºC, 4 h; (d) PPTS, acetone, r.t., 23 h; (e) methacrylic chloride, Et_3N, DMAP, CH_2Cl_2, 0 ºC to r.t., 10 h, 65% from **12**; (f) 40% HF, MeCN, r.t., 5 h, 78%.

chloride to give **15** in an overall yield of 65% from **12**. One-pot removal of the acetonide and the TBS ether in **15** with 40% aqueous HF solution in acetonitrile afforded azedarachol **3** in good yield. The physical and spectroscopic data of the synthetic **3** matched those of the natural product. Since the methacrylate in **3** underwent transesterification from the C20*R*-OH to the C16*S*-OH easily in both basic and acidic medium, **3** should be handled and stored carefully.

Conclusions

In conclusion, we have accomplished the first semisynthesis of azedarachol **3**, an insect antifeedant, in 12 steps from triol **2** with an overall yield of 16%. Key transformations include differentiating the C20*R*/*S*-OHs and the C16*S*-OH flexibly with protecting groups, inversing the C20 configuration through an oxidation/reduction process, and introducing the 2,3-*cis*-vicinal diol through a substrate-controlled dihydroxylation. The practice of the symbiotic process, *i.e.* a reaction system where two or more reactions live in and benefit from each other, is also notable. Currently, using steroidal sapogenins and their degradative products in the syntheses of more natural products are ongoing in our group.

References

[1] For more examples of ultilizing industrial waste materials in organic synthesis, see: (a) Stingl, K.; Martens, J. *Liebigs Ann. Chem*. **1994**, 243; (b) von Keyserlingk, N. G.; Martens, J.; Ostendorf, D.; Saak, W.; Weidenbruch, M. *J. Chem. Soc*., *Perkin Trans. 1* **2001**, 706; (c) Stingl, K.; Martens, J. *Liebigs Ann. Chem*. **1994**, 479; (d) Wilken, J.; Thorey, C.; Groger, H.; Haase, D.; Saak, W.; Pohl, S.; Muzart, J.; Martens, J. *Liebigs Annalen-Recueil* **1997**, 2133; and references therein.

[2] (a) Tian, W.-S.; Shi, Y. *Prog. Chem.* **2010**, *22*, 538; (b) Tian, W.-S. *CN1146457* (*A*), **1996** [*Chem. Abstr*. **1998**, *128*, 167599]; (c) Tian, W.-S. *Chin. J. Org. Chem*. **2000**, *18*, 11 (in Chinese); (d) Tian, W.-S.; Liu, S.-S.; Qiu, B.-K.; Wu, X.-J. *CN1475494A*, **2004** [*Chem. Abstr.* **2004**, *142*, 374022]; (e) Gui, J.-H.; Wang, D.-H.; Tian, W.-S. *Angew. Chem*., *Int. Ed*. **2011**, *50*, 7093; (f) Shi, Y.; Jia, L.-Q.; Xiao, Q.; Lan, Q.; Tang, X.-H.; Wang, D.-H.; Li, M.; Ji, Y.; Zhou, T.; Tian, W.-S. *Chem.-Asian J*. **2011**, *6*, 786; (g) Wang, S.-S.; Shi, Y.; Tian, W.-S. *Org. Lett*. **2014**, *16*, 2177.

[3] Nakatani, M.; Takao, H.; Miura, I.; Hase, T. *Phytochemistry* **1985**, *24*, 1945.

[4] (a) Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *J. Am. Chem. Soc*. **1986**, *108*, 7055; (b) Comin, M. J.; Elhalem, E.; Rodriguez, J. B. *Tetrahedron* **2004**, *60*, 11851; (c) Ramírez, J. A.; Gros, E. G.; Galagovsky, L. R. *Tetrahedron* **2000**, *56*, 6171; (d) Takatsuto, S.; Ikekawa, N. *J. Chem. Soc*., *Perkin Trans. 1* **1986**, 2269; (e) Cong, R.; Zhang, Y.; Tian, W. *Tetrahedron Lett*. **2010**, *51*, 3890.

[5] (a) Miki, T.; Morita, K.; Noguchi, S.; Kishi, T.; Hiraga, K.; Nawa, H. *Chem. Pharm. Bull*. **1963**, *11*, 95; (b) Vitali, R.; Gardi, R. *Steroids* **1966**, *8*, 537; (c) Kirk, D. N.; Sae Melo, M. L. *J. Chem. Soc*., *Perkin Trans. 1* **1982**, 723; (d) Löken, B.; Kaufmann, S.; Rosenkranz, G.; Sondheimer, F. *J. Am. Chem. Soc*. **1956**, *78*, 1738.

[6] Reducing reagents we screened include: DIBAL-H in combine with $MgBr_2$ and $Ti(OiPr)_4$, $NaBH_4$ in combine with ZnI_2, $MgBr_2$, $TiCl_4$, and $CeCl_3$, and so on.

[7] (a) Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J. Org. Chem*. **1993**, *58*, 844; (b) Pataki, J.; Rosenkranz, G.; Djerassi, C. *J. Am. Chem. Soc.* **1951**, *73*, 5375; (c) Thompson, M. J.; Mandava, N. B.; Meudt, W. J.; Lusby, W. R.; Spaulding, D. W. *Steroids* **1981**, *38*, 567; (d) Slates, H. L.; Wendler, N. L. *J. Am. Chem. Soc.* **1956**, *78*, 3749; (e) Rosado-Abón, A.; de Dios-Bravo, G.; Rodríguez-Sotres, R.; Iglesias-Arteaga, M. A. *Steroids* **2012**, *77*, 461.

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