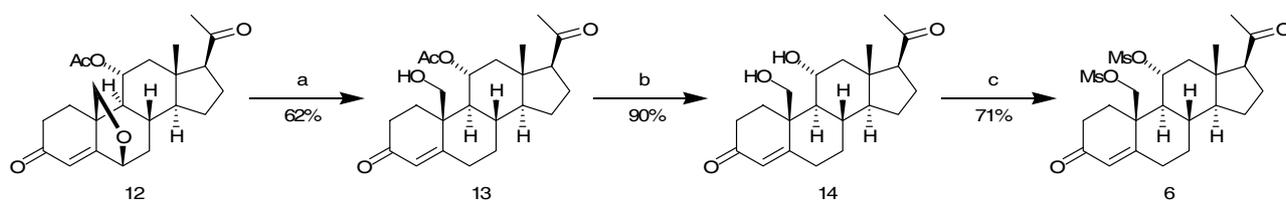


## **Synthesis of 6,19-cyclopregnanes. Constrained analogues of steroid hormones**

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**Electronic Supplementary Information**



**Scheme 3.** Synthesis of mesylate **6**. Reagents and conditions: a) i. Zn, AcOH, *i*-PrOH, 3 h, 70 °C; ii. dil HCl, MeOH, CH<sub>2</sub>Cl<sub>2</sub>; b) KOH, MeOH, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C; c) MsCl, py, 0 °C.

## Experimental

Zinc powder was activated by stirring with 1N HCl for 15 min; it was then washed successively with water (until neutral), ethanol and diethyl ether and dried at 110 °C for 2 h. 11 $\alpha$ -Acetyloxy-6,19-epoxyprogesterone (**12**) was obtained from 11 $\alpha$ -hydroxyprogesterone (Steraloids Inc.) following essentially the procedure described by Wettstein *et al.*,<sup>16</sup> but using iodobenzene diacetate (DIB) instead of lead tetraacetate for functionalization of C-19.<sup>17</sup>

### 19-Hydroxy-11 $\alpha$ -acetyloxyprogesterone-4-ene-3,20-dione **13**

To a solution of compound **12** (0.745 g, 1.93 mmol) in a mixture of isopropanol (41.2 cm<sup>3</sup>) and acetic acid (3.98 cm<sup>3</sup>), activated zinc powder (1.10 g) was added. The reaction mixture was stirred for 4 h at 75 °C, filtered and concentrated to a third of its volume. Water was added to the residue and then extracted with dichloromethane. The solid obtained after evaporation of the solvent, was dissolved in dichloromethane (20.3 cm<sup>3</sup>) and methanol (62.7 cm<sup>3</sup>). Water (4.6 cm<sup>3</sup>) and conc. HCl (9.9 cm<sup>3</sup>) were added and the mixture was vigorously stirred for 1 h at room temperature. The reaction mixture was neutralized with 10% aqueous sodium hydroxide and concentrated to a third of its volume. Water was added to the residue and then extracted with dichloromethane. The organic layer was washed with water, dried with sodium sulfate and the solvent evaporated; flash chromatography (ethyl acetate/hexane 6:4) afforded compound **13** (0.461 g, 62 %) as a white solid: mp 165-166 °C (from hexane-ethyl acetate); (Found C 71.1, H 8.3, C<sub>23</sub>H<sub>32</sub>O<sub>5</sub> requires C 71.1, H 8.3);  $\nu_{\max}$ (KBr)/cm<sup>-1</sup> 4442, 2933, 2877, 1726, 1700, 1654, 1363, 1242, 1026;  $\delta_{\text{H}}$ (500.13 MHz;

CDCl<sub>3</sub>; Me<sub>4</sub>Si) 5.88 (1 H, s, 4-H), 5.37 (1 H, dt, *J* 10.7 and 5.2, 11-H), 3.95 (2 H, s, 19-H), 2.04 (3 H, s, 11-OAc), 2.09 (3 H, s, 21-H), 0.73 (3 H, s, 18-H);  $\delta_C$ (125.77 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 208.0 (C-20), 198.0 (C-3), 170.0 (11-OCOCH<sub>3</sub>), 166.4 (C-5), 127.0 (C-4), 71.5 (C-11), 65.5 (C-19), 63.0 (C-17), 55.6 (C-14 or C-9), 55.3 (C-9 or C-14), 45.7 (C-12), 44.7 (C-10), 43.8 (C-13), 35.6 (C-8), 34.7 (C-1), 34.3 (C-2), 33.3 (C-6), 31.8 (C-7), 31.3 (C-21), 24.2 (C-15), 23.0 (C-16), 21.9 (11-OCOCH<sub>3</sub>), 14.2 (C-18); *m/z* (EI) 388 (M<sup>+</sup>, 1), 328 (11), 298 (67), 213 (20), 161(25), 43 (100).

### **11,19-Di(methanesulfonyloxy)pregn-4-ene-3,20-dione 6**

To a solution of compound **13** (0.100 g, 0.257 mmol) in methanol (5.2 cm<sup>3</sup>) and dichloromethane (0.25 cm<sup>3</sup>), was added a solution of KOH (0.028g, 0.516 mmol) in methanol (0.190 cm<sup>3</sup>). The mixture was stirred at room temperature for 30 min, neutralized with 1N HCl and concentrated to a third of its volume. Water was added to the residue and then extracted with dichloromethane. The organic layer was washed with water, dried with sodium sulfate and the solvent evaporated to give the 11,19-diol **14** (0.080 g, 90 %):  $\delta_H$ (500.13 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 5.83 (1 H, s, 4-H), 4.20 (1 H, m, 11-H), 4.10 (1 H, d, *J* 10.6, 19a-H), 3.90 (1 H, d, *J* 10.6, 19b-H), 2.13 (3 H, s, 21-H), 0.74 (3 H, s, 18-H). Methanesulfonyl chloride (0.278 g, 2.45 mmol) was added to a stirred solution of the 11,19-diol (0.080 g, 0.23 mmol) in dry pyridine (3.0 cm<sup>3</sup>) at 0 °C under nitrogen. After 3 hours, the reaction mixture was acidified with 1N HCl, and extracted with dichloromethane. The organic layer was washed with 5% aqueous NaHCO<sub>3</sub> and water, dried with sodium sulfate, and the solvent was evaporated. The resulting solid was purified by flash chromatography (ethyl acetate/hexane 6:4) to give mesylate **8** (0.82 g, 71 %) as an amorphous solid; (Found C 55.1, H 6.8, C<sub>23</sub>H<sub>34</sub>O<sub>8</sub>S<sub>2</sub> requires C 55.0, H 6.8);  $\nu_{max}$  (KBr)/(cm<sup>-1</sup>) 2943, 1699, 1670, 1338, 1170, 925;  $\delta_H$ (500.13 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 5.95 (1 H, s, 4-H), 5.25 (1 H, m, 11-H), 4.65 (1 H, d, *J* 10.2, 19a-H), 4.53 (1 H, d, *J* 10.2, 19b-H), 3.10 (3 H, s, 11-OMs), 3.00 (3 H, s, 19-OMs), 2.13 (3 H, s, 21-H), 0.80 (3 H, s, 18-H);  $\delta_C$ (125.77 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 208.0 (C-20), 198.2 (C-3), 162.8 (C-5), 127.8 (C-4), 79.6 (C-11), 69.0 (C-19), 62.5 (C-17), 55.6 (C-14), 55.0 (C-9), 46.6 (C-12), 43.6 (C-13), 42.9 (C-10), 40.6 (11-

OMs), 37.5 (19-OMs), 35.5 (C-8), 34.6 (C-2), 33.6 (C-6), 32.3 (C-1), 31.7 (C-7), 31.1 (C-21), 24.0 (C-15), 23.2 (C-16), 14.0 (C-18);  $m/z$  (EI) 502 ( $M^+$ , 10), 407 (12), 312 (10), 269 (2), 241 (5), 43 (100).