Supplemental methods

1. Synthesis of ent-VP1-001

ent-Steroid 2

ent-Testosterone (1) was prepared as described previously (Covey, D.F., Polish J. Chem., 2006, 80, 511-522; see also references therein). To a solution of ent-testosterone (1, 3.8 g, 13.2 mmol) in acetic anhydride (80 mL) was added NaI (7.92 g, 52 mmol) and trimethylsilyl chloride (5.8 mL, 52 mmol) at 0 °C under N₂. After addition, the reaction was allowed to warm to room temperature for 2 h. The reaction was added to Et₃N (40 mL) in diethyl ether (100 mL). The ether solution was washed with brine (50 mL x 4), aqueous NaHCO₃ (50 mL x 2) and dried over Na₂SO₄. After filtration, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel eluted with 25% EtOAc in hexanes) to give ent-steroid 2 (3.05 g, 70%): ¹H NMR (400 MHz, CDCl₃) δ 5.33-5.32 (m, 1H), 4.60 (t, J = 8.3 Hz, 1H), 3.52-3.47 (m, 1H), 2.30-0.90 (m), 2.02 (s, 3H), 1.00 (s, 3H), 0.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.2, 140.9, 121.1, 82.7, 71.5, 51.0, 50.0, 42.3, 42.2, 37.2, 36.7, 36.5, 31.6, 31.5, 31.4, 27.4, 23.5, 21.1, 20.5, 19.3, 11.8.

ent-Steroid 3

ent-Steroid 2 (3.05 g, 4.04 mmol) was dissolved in CH₂Cl₂ (50 mL) and cooled to 0 °C. (i-Pr)₂EtN (3.0 mL) and ClCH₂OMe (1.35 ml, 18.0 mmol) were added and the reaction was stirred at room temperature for 16 h. The reaction was made basic by adding aqueous NaHCO₃ solution and the product was extracted into CH₂Cl₂. The combined
extracts were washed with brine, dried over Na₂SO₄, filtered and solvent removed to give a viscous liquid which was purified by flash column chromatography (silica gel eluted with 10% EtOAc in hexanes) to give *ent*-steroid 3 as a colorless liquid (2.65 g, 77%): ¹H NMR (400 MHz, CDCl₃) δ 5.33-5.32 (m, 1H), 4.65 (s, 2H), 4.59 (t, J = 8.2 Hz, 1H), 3.39-3.35 (m, 1H), 3.34 (s, 3H), 2.35-0.89 (m), 2.01 (s, 3H), 0.99 (s, 3H), 0.78 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 140.7, 121.2, 94.6, 82.6, 76.7, 55.0, 50.9, 50.0, 42.3, 39.4, 37.1, 36.7, 31.6, 31.4, 28.8, 27.4, 23.5, 21.0, 20.4, 19.3, 11.8.

*ent*-Steroid 4

To a solution of *ent*-steroid 3 (2.65 g, 7.05 mmol) in methanol (60 mL) was added K₂CO₃ (4.0 g) at room temperature. The mixture was refluxed for 16 h. Methanol was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel eluted with 25% EtOAc in hexanes) to give *ent*-steroid 4 (2.31 g, 99%): ¹H NMR (400 MHz, CDCl₃) δ 5.32-5.30 (m, 1H), 4.64 (s, 2H), 3.61 (t, J = 8.6 Hz, 1H), 3.40-3.34 (m, 1H), 3.33 (s, 3H), 2.31-0.87 (m), 0.95 (s, 3H), 0.72 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 140.7, 121.3, 94.5, 81.6, 76.7, 55.0, 51.2, 50.2, 42.6, 39.4, 37.2, 36.7, 36.5, 31.8, 31.4, 30.3, 28.8, 23.3, 20.5, 19.3, 10.9.

*ent*-Steroid 5

To a solution of *ent*-steroid 4 (1.5 g, 4.54 mmol) in CH₂Cl₂ (60 mL) was added Dess–Martin periodinane (2.5 g, 6 mmol) at room temperature. After 1 h, water (50 mL) was
added, the product was extracted into CH$_2$Cl$_2$ (150 mL x 3) and the combined extracts
were washed with brine (50 mL x 2). The organic layer was dried over Na$_2$SO$_4$, filtered,
and the solvents removed. The residue was purified by flash column chromatography (silica gel eluted with 10% EtOAc in hexanes) to give ent-steroid 5 (1.5 g, 100%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.39-5.38 (m, 1H), 4.68 (s, 2H), 3.45-3.38 (m, 1H), 3.37 (s, 3H), 2.49-0.98 (m), 1.03 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 221.0, 140.9, 120.9, 94.7, 76.7, 55.1, 51.7, 50.2, 47.5, 39.5, 37.1, 36.8, 35.8, 31.4, 31.3, 30.8, 28.8, 21.8, 20.3, 19.3, 13.5.

ent-Steroid 6

A solution of freshly prepared sodium ethoxide (sodium 0.4 g, 15 mmol dissolved in ethanol 15 mL) was added dropwise slowly to a solution of ent-steroid 5 (1.5 g, 4.54 mmol) and triethyl phosphonoacetate (3.44 g, 15 mmol) in anhydrous ethanol (25 mL) under N$_2$ while stirring at 35-40 °C. After addition, the reaction was refluxed for 16 h. After cooling to room temperature, the ethanol was removed and the residue was dissolved in ether which was washed with water, dried over Na$_2$SO$_4$ and filtered. Solvent was removed and the residue was purified by flash column chromatography (silica gel eluted with 10% EtOAc in hexanes) to give ent-steroid 6 (1.68 g, 87%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.52 (s, 1H), 5.35-5.34 (m, 1H), 4.66 (s, 2H), 4.15-4.09 (m, 2H), 3.43-3.33 (m, 1H), 3.35 (s, 3H), 2.84-2.79 (m, 2H), 2.36-0.93 (m), 1.01 (s, 3H), 0.82 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 176.1, 167.3, 140.7, 121.3, 108.6, 94.6,
The reaction sequence reported below that converts ent-steroid 6 into ent-steroid 16 (ent-VP1-001) is based on that reported previously for the preparation of the natural stereoisomer of ent-steroid 16 (Wicha, J.; Bal, K. J. C. S. Perkin I, 1978, 1282-1288).

**Unpurified ent-Steroid 7**

To a solution of ent-steroid 6 (1.4 g, 3.48 mmol) in EtOAc (150 mL) was added PtO₂ (15 mg) at room temperature. Hydrogenation was carried out under 20 psi for 6 h. Solvent was removed and the residue was purified by flash column chromatography (silica gel eluted with 10% EtOAc in hexanes) to give unpurified ent-steroid 7 (1.4 g, 100%): ¹H NMR δ 4.63-4.60 (m, 1H), 4.08-4.03 (m, 2H), 3.48-3.32 (m, 1H), 3.31 (s, 3H), 2.34-0.57 (m), 0.76 (s, 3H), 0.54 (s, 3H); ¹³C NMR δ 176.1, 140.7, 121.3, 94.4, 76.2, 60.0, 55.3, 55.0, 54.5, 46.9, 44.9, 42.1, 37.4, 37.0, 35.6, 35.5, 35.3, 35.2, 32.1, 28.7, 28.1, 24.4, 20.9, 14.2, 12.5.

Unpurified ent-steroid 7 contains minor amounts of the ent-steroid in which the Δ⁵ double bond has been hydrogenated. This saturated ent-steroid could not be removed easily by chromatography on silica gel. To separate the two compounds chromatographically, ent-steroid 7 was converted first into ent-steroid 8 and then into
ent-steroid 9 which is easily purified. ent-Steroid 9 was then converted back via ent-
steroid 8 into ent-steroid 7 and then subsequently into ent-steroid 10.

**Unpurified ent-Steroid 8**

Acetyl chloride (2 mL) was slowly added to unpurified hydrogenation product ent-steroid
7 (1.4 g, 3.48 mmol) in ethanol (30 mL) at room temperature. After 2 h, water was
added and the product was extracted into CH₂Cl₂ (100 mL x 2). The combined extracts
were dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure.
The residue was purified by flash column chromatography (silica gel eluted with 25%
EtOAc in hexanes) to give unpurified ent-steroid 8 (1.2 g): ¹H NMR (400 MHz, CDCl₃) δ
5.35-5.34 (m, 1H), 4.13-4.07 (m, 2H), 3.55-3.47 (m, 1H), 2.38-0.81 (m), 1.10 (s, 3H),
0.61 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 173.9, 140.8, 121.5, 71.6, 60.1, 55.5, 50.3,
46.8, 42.2, 41.9, 37.3, 37.2, 36.5, 35.2, 31.9, 31.8, 31.6, 28.1, 24.5, 20.8, 19.4, 14.2,
12.4.

**ent-Steroid 9**

To a solution of unpurified ent-steroid 8 (1.2 g, 3.33 mmol) in diethyl ether (100 mL) and
acetic acid (5 mL) was slowly added Br₂ in HOAc (3 mL) until a brown color persisted.
After 5 min, aqueous Na₂S₂O₃ was added and the reaction became colorless. EtOAc
(100 mL) was added and the EtOAc solution was washed with aqueous NaHCO₃ (50
mL x 2), brine (50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent
was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel eluted with 20% EtOAc in hexanes) to give ent-steroid 9 (1.41 g, 81%): $^1$H NMR (400 MHz, CDCl$_3$) δ 4.82-4.81 (m, 1H), 4.44-4.37 (m, 1H), 4.12-4.06 (m, 2H), 2.72-1.08 (m), 1.43 (s, 3H), 0.62 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.8, 89.6, 68.9, 60.1, 56.0, 54.0, 47.6, 46.6, 45.6, 42.2, 42.0, 37.2, 37.0, 36.7, 35.2, 30.9, 30.1, 28.0, 24.2, 21.0, 20.3, 14.2, 12.7.

Purified ent-Steroid 8

Zinc dust (6.0 g) was added to a solution of ent-steroid 9 (1.4 g, 2.7 mmol) in HOAc (20 mL) and EtOAc (30 mL) at room temperature. After 16 h, the mixture was filtered through Celite and washed with EtOAc (200 mL). Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel eluted with 25% EtOAc in hexanes) to give purified ent-steroid 8 (925 mg, 95%): $^1$H NMR (400 MHz, CDCl$_3$) δ 5.26-5.25 (m, 1H), 4.06-4.01 (m, 2H), 3.85 (s, br, 1H), 3.47-3.40 (m, 1H), 2.31-0.73 (m), 0.93 (s, 3H), 0.54 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.8, 140.7, 121.1, 71.2, 60.0, 55.4, 50.1, 46.6, 41.9, 41.7, 37.1, 37.0, 36.3, 35.0, 31.7, 31.7, 31.2, 27.9, 24.3, 20.6, 19.2, 14.0, 12.2.

Purified ent-Steroid 7

Purified ent-steroid 8 (925 mg, 2.57 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL) and cooled to 0 °C. (i-Pr)$_2$EtN (1.3 mL, 7.5 mmol) and ClCH$_2$OMe (0.45 ml, 6.0 mmol) were added
and the reaction was stirred at room temperature for 16 h. The reaction mixture was made basic by adding aqueous saturated NaHCO₃ solution and the product extracted into CH₂Cl₂. The combined extracts were washed with brine, dried over anhydrous Na₂SO₄ and solvent removed to give a viscous liquid which was purified by flash column chromatography (silica gel eluted with 20% EtOAc in hexanes) to give purified ent-steroid 7 as a colorless liquid (1.02 g, 98%): \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 5.34-5.33 (m, 1H), 4.67 (s, 2H), 4.12 (q, \(J = 7.0\) Hz, 2H), 3.42-3.36 (m, 1H), 3.35 (s, 3H), 2.37-0.80 (m), 1.00 (s, 3H), 0.60 (s, 3H); \(^{13}\)C NMR (CDCl₃) \(\delta\) 173.8, 140.7, 121.5, 94.6, 76.8, 60.0, 55.5, 55.1, 50.3, 46.7, 41.9, 39.5, 37.2, 37.1, 36.7, 35.2, 31.9, 31.8, 28.9, 28.1, 24.5, 20.7, 19.3, 14.2, 12.3.

**ent-Steroid 10**

To a solution of ent-steroid 7 (500 mg, 1.25 mmol) in THF (20 mL) was added LDA (1.25 mL, 2.0 M, 2.5 mmol) and HMPA (0.5 mL) at -78 °C. After 1 h, 2-(3-iodopropyl)-2-methyl-1,3-dioxolane (960 mg, 3.75 mmol) was added. After addition, the mixture was warmed to room temperature for 16 h. Aqueous NH₄Cl was added and the product was extracted into EtOAc (100 mL x 2), dried over Na₂SO₄ and filtered. Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel eluted with 20% EtOAc in hexanes) to give ent-steroid 10 (594 mg, 90%): \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 5.34-5.33 (m, 1H), 4.67 (s, 2H), 4.14-4.08 (m, 2H), 3.94-3.86 (m, 4H), 3.42-3.38 (m, 1H), 3.36 (s, 3H), 2.32-0.90 (m), 0.99 (s, 3H), 0.70 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 176.1, 140.7, 121.5, 109.9, 94.7, 76.9, 64.6,
To a solution of ent-steroid 10 (594 mg, 1.12 mmol) in diethyl ether (20 mL) was added LiAlH₄ (2.0 M in THF, 4.0 mL, 8.0 mmol) at room temperature. After 2 h, water (0.32 mL), 10% aqueous NaOH (0.64 mL) and water (0.96 mL) were slowly added sequentially. After stirring for 30 min, the mixture was filtered through Celite and washed with CH₂Cl₂ (100 mL). Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel eluted with 25% EtOAc in hexanes) to give ent-steroid 11 (530 mg, 97%): ¹H NMR (400 MHz, CDCl₃) δ 5.31-5.30 (m, 1H), 4.63 (s, 2H), 3.92-3.85 (m, 4H), 3.70-3.33 (m, 3H), 3.31 (s, 3H), 2.32-0.76 (m), 0.96 (s, 3H), 0.65 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 140.5, 121.5, 110.0, 94.5, 77.3, 64.4, 62.3, 56.5, 55.0, 50.1, 50.0, 42.2, 41.9, 39.4, 39.3, 39.0, 37.1, 36.6, 31.7, 29.3, 28.8, 27.5, 24.0, 23.6, 20.9, 20.5, 19.2, 12.0.

ent-Steroid 12

To a solution of ent-steroid 11 (530 mg, 1.08 mmol) in CH₂Cl₂ (15 mL) was added mesyl chloride (2 mmol, 0.15 mL) and Et₃N (0.42 mL, 3 mmol) at 0 °C. After 1 h, aqueous NH₄Cl was added and the product was extracted into CH₂Cl₂ (100 mL x 2). The combined extracts were dried over anhydrous Na₂SO₄, filtered and the solvents
removed under reduced pressure. The residue was purified by flash column chromatography (silica gel eluted with 10% EtOAc in hexanes) to give ent-steroid 12 (625 mg, 99%): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.34-5.33 (m, 1H), 4.67 (s, 2H), 4.37-4.08 (m, 3H), 3.95-3.88 (m, 4H), 3.43-3.38 (m, 1H), 3.35 (s, 3H), 2.99 (s, 3H), 2.35-0.79 (m, 30H), 0.99 (s, 3H), 0.69 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 190.7, 121.5, 109.8, 94.6, 76.8, 70.0, 64.5, 56.4, 55.1, 49.9, 42.1, 39.7, 39.5, 39.3, 39.0, 37.2, 37.1, 36.6, 31.8, 31.7, 29.4, 28.8, 27.4, 24.0, 23.7, 21.0, 20.1, 19.3, 12.2.

**ent-Steroid 13**

To a solution of ent-steroid 12 (625 mg, 1.08 mmol) in diethyl ether (30 mL) was added LiAlH\(_4\) (2.0 M in THF, 4.0 mL, 8.0 mmol) at room temperature. After 2 h, water (0.32 mL), 10% aqueous NaOH (0.64 mL) and water (0.96 mL) were slowly added sequentially. After stirring for 30 min, the mixture was filtered through Celite and washed with CH\(_2\)Cl\(_2\) (100 mL). Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel eluted with 10% EtOAc in hexanes) to give ent-steroid 13 (510 mg, 99%): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.32-5.31 (m, 1H), 4.65 (s, 2H), 3.90-3.37 (m, 4H), 3.40-3.36 (m, 1H), 3.33 (s, 3H), 2.33-0.86 (m, 0.98 (s, 3H), 0.64 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 140.6, 121.6, 110.1, 94.6, 76.7, 64.5, 64.4, 56.6, 56.0, 55.0, 50.0, 42.2, 39.7, 39.6, 39.5, 37.1, 36.6, 36.0, 35.6, 31.8, 31.7, 28.8, 28.1, 24.2, 23.6, 20.9, 20.5, 19.3, 18.6, 11.7.

**ent-Steroid 14**
To a solution of ent-steroid 13 (270 mg, 0.57 mmol) in acetone (30 mL) was added p-toluenesulfonic acid (100 mg) at room temperature. The reaction was stirred at room temperature for 2 h. Acetone was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel eluted with 15% EtOAc in hexanes) to give ent-steroid 14 (235 mg, 96%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.29-5.27 (m, 1H), 4.62 (s, 2H), 3.37-3.33 (m, 1H), 3.37-3.33 (m, 1H), 3.30 (s, 3H), 2.35-0.83 (m), 2.07 (s, 3H), 0.95 (s, 3H), 0.62 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 208.9, 140.5, 121.5, 94.5, 76.8, 56.4, 55.7, 55.0, 50.0, 44.0, 42.2, 39.6, 39.4, 37.1, 36.5, 35.5, 35.3, 31.7, 31.7, 29.7, 28.8, 28.0, 24.1, 20.9, 20.2, 19.2, 18.4, 11.7.

**ent-Steroid 15**

To a solution of ent-steroid 14 (235 mg, 0.55 mmol) in THF (20 mL) was added 6 N HCl (10 mL) at room temperature. After 2 h, the product was extracted into CH$_2$Cl$_2$ (100 mL x 2) and the combined extracts were washed with aqueous NaHCO$_3$ (50 ml x 2), dried over Na$_2$SO$_4$ and filtered. Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel eluted with 25% EtOAc in hexanes) to give ent-steroid 15 (208 mg, 98%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.35-5.34 (m, 1H), 3.55-3.48 (m, 1H), 2.39-0.89 (m), 2.13 (s, 3H), 1.01 (s, 3H), 0.68 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 309.4, 140.8, 121.6, 71.7, 56.7, 55.8, 50.1, 44.2, 42.3, 42.2, 39.7, 37.2, 36.5, 35.6, 35.4, 31.9(2C), 31.6, 29.8, 28.2, 24.2, 21.0, 20.4, 19.4, 18.6, 11.8.
### ent-Steroid 16 (ent-VP1-001)

To a solution of ent-steroid 15 (208 mg, 0.54 mmol) in benzene (6 mL) and diethyl ether (10 mL) was added methyl lithium (1.6 M in diethyl ether, 2 mL, 3.2 mmol) at 0 °C. After 1 h, aqueous NH₄Cl was added and the product was extracted into EtOAc (100 mL x 2), dried over Na₂SO₄ and filtered. Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel eluted with 25% EtOAc in hexanes) to give ent-steroid 16 (ent-VP1-001) (147 mg, 68%): mp 181-183 °C; [α]_D²⁰ +38.3 (c = 0.06, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.36-5.35 (m, 1H), 3.56-3.50 (m, 1H), 2.31-0.93 (m), 0.95 (s, 3H), 0.69 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 140.8, 121.7, 71.8, 71.1, 56.7, 56.1, 50.1, 44.4, 42.3, 42.2, 39.8, 37.2, 36.5, 36.4, 35.7, 31.9(2C), 31.6, 29.3, 29.2, 28.2, 24.2, 21.1, 20.7, 19.4, 18.7, 11.8.