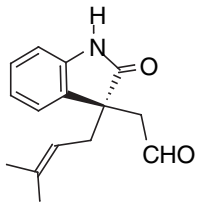
Supporting Information

Total Synthesis of Spirotryprostatin B *via* Asymmetric Nitroolefination

Trusar D. Bagul, Gingipalli Lakshmaiah, Takeo Kawabata and Kaoru Fuji*

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan

fuji@scl.kyoto-u.ac.jp

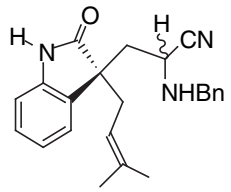


7

To a solution of ammonium acetate (42.5 g, 551 mmole) in 350 mL of methanol:water (4:3) at room temperature was added 20% aq. solution of titanium (III) chloride (42.5 mL, 8.5 g, 55.1 mmol), followed by a solution of nitroolefin **6** (3.0 g, 11.0 mmole) in methanol (30 mL). After 3 h, the mixture was extracted with ether (3 x 100 mL) and the combined etheral portion was successively washed with saturated aq. $NaHCO_3$ solution, brine, dried over Na_2SO_4 and concentrated. Silica gel chromatographic purification (40% ethyl acetate/hexane) afforded the aldehyde **7** (1.48 g, 55%) as a yellow viscous oil**.**

$[\alpha]^{19}_{D}$ = -2.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) : δ 9.51 (t, *J* = 1.7 Hz, 1 H), 8.36 (s,1 H), 7.20 (dt, *J* = 7.5, 1.2 Hz, 1 H), 7.14 (d, *J* = 7.5 Hz, 1 H), 7.0 (dt, J = 7.5, 1.0 Hz, 1 H), 6.90 (d, *J* = 7.5 Hz, 1 H), 4.97-4.90 (m, 1 H), 3.02 (d, *J* = 1.7 Hz, 2 H), 2.56-2.43 (m, 2 H), 1.61 (s, 3 H), 1.50 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz) : δ 198.5, 181.1, 140.6, 136.1,

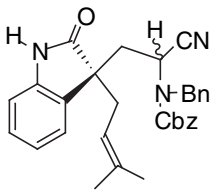
131.1, 127.8, 122.9, 121.9, 116.3, 109.8, 49.5, 48.8, 36.0, 25.7, 17.9. IR ($CHCl_3$): 3259, 2730, 1711, 1619, 1471 cm^{-1}. MS (*m/z*): 243 (M^+), 176, 146, 117. HRMS : calcd for $C_{15}H_{17}O_2N$ 243.1259, found 243.1253.



8 (1:1 mixture)

A solution of **7** (1.40 g, 5.76 mmol) in dichloromethane (25 mL) containing 4A° molecular sieves (0.8 g) was treated with benzylamine (0.65g, 6.05 mmole) and stirred at room temperature for 1.5 h under nitrogen. Trimethylsilyl cyanide (0.68 g, 6.91 mmole) was added and stirring continued for 1.5 h. The mixture was filtered, concentrated and chromatographed (SiO_2, 20% ethyl acetate/hexane) to give **8** (1.88 g, 91%) as a pale yellow oil.

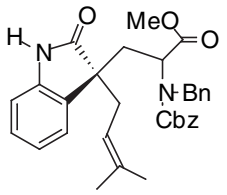
^1H NMR ($CDCl_3$, 400 MHz) : δ 9.09, 8.96 (two br s, 1 H); 7.35-6.85 (m, 9 H); 4.97-4.85 (m, 1 H); 3.68, 3.48 (two ABq, $\Delta\nu_{AB}$=104.8, J_{AB} =12.8 Hz, $\Delta\nu_{AB}$= 151.3 Hz, J_{AB} =12.9 Hz , 2 H), 3.49, 3.13 (t and dd, J = 7.5 Hz, J = 11.9, 3.6 Hz, 1 H); 2.60-2.30 (m, 4 H); 1.61, 1.58 (two s, 3 H), 1.49 (s, 3 H). IR ($CHCl_3$): 3305, 3025, 2913, 1708, 1620 cm^{-1}. MS (*m/z*): 359 (M^+), 332, 290, 263, 199, 173, 91. HRMS: calcd $C_{23}H_{25}ON_3$: 359.1998. Found: 359.1987.



9 (1:1 mixture)

To a stirring mixture of **8** (1.7 g, 4.73 mmole) and NEt_3 (1.14 g, 11.36 mmole) in dichloromethane (30 mL) at 0 °C was added dropwise benzyl chloroformate (0.97g, 5.68 mmole) and stirred overnight at room temperature. The mixture was diluted with 30 mL of dichloromethane and washed succesively with saturated aq. $NaHCO_3$ solution, water and brine. Drying over Na_2SO_4, concentration and chromatographic purification (SiO_2, 20% ethyl acetate/hexane) yielded the **9** (1.12 g, 48 %) as yellow viscous oil along with the recovery of **8** (0.84 g, 50%).

^{1}H NMR ($CDCl_3$, 400 MHz) : δ 9.47, 9.28 (two br s, 1 H); 7.85-7.05 (m, 14 H); 5.28-5.05 (m, 3 H), 4.86, 4.80 (two t, *J* = 6.5, 7.6 Hz, 1 H), 4.14-3.94 (m, 2 H), 3.01-2.61 (m, 3 H), 2.52-2.42 (m, 1 H),1.63, 1.56, 1.50,1.48 (four s, 6 H). IR ($CHCl_3$): 3244, 3032, 2976, 1732, 1586, 1521, 1222 cm^{-1}. MS (*m/z*) : 493 (M^+), 358, 317, 290, 91. HRMS: calcd for $C_{31}H_{31}O_3N_3$: 493.2365. Found: 493.2359.

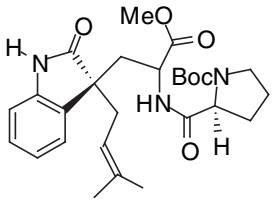


10

A 30 ml of methanolic solution of **9** (1.7 g, 3.44 mmole) was treated with anhydrous K_2CO_3 (1.18 g, 8.62 mmole) and stirred for 6 h. After the removal of K_2CO_3 by filtration, the

resultant solution was acidified with 6.0 mL of aq. 1 M HCL solution and stirred for 30 min. The solution was basified with saturated aq. $NaHCO_3$ solution and taken up in dichloromethane (50 mL) and the aqueous portion extracted in dichloromethane. The combined portions were dried over Na_2SO_4 and concentrated. Chromatographic purification (25% ethyl acetate/hexane) afforded the **10** (1.57 g, 87%) as yellow viscous oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.50, 10.37 (two br s,1 H); 7.90 (two d, *J* = 7.6, 7.8 Hz, 1 H); 7.45-7.10 (m, 11 H), 7.02 (t, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 6.3 Hz, 1 H), 5.24, 5.23 (2 s, 2 H), 5.20, 5.10, 4.10, 3.96 (four d, *J* = 14.8 Hz, 2H), 4.85, 4.74 (two t, *J* = 7.6, 7.3 Hz,1 H), 3.95, 3.91 (t and dd, *J* = 7.3 Hz, *J* = 8.5, 5.0 Hz,, 1 H) 3.72, 3.62 (two s, 3 H), {3.06 (dd, *J* = 6.8, 7.5 Hz), 2.94 (dd, *J* = 7.5, 13.3 Hz), 2.81-2.56 (m), 2.45 (dd, *J* = 8.5, 13.6 Hz), 2.26 (dd, *J* = 7.3, 13.6 H z), total 4 H}, 1.57, 1.48, 1.45 (three s, 6 H). IR ($CHCl_3$): 3231, 3030, 1734, 1674, 1447, 1219 cm^{-1}. MS (*m/z*) : 526 (M^+), 391, 350, 323, 291, 91. HRMS: Exact mass calcd for $C_{32}H_{34}O_5N_2$: 526.2468. Found: 526.2474.



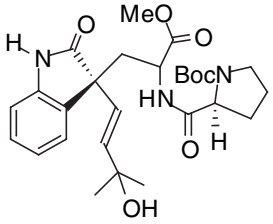
11

Amino ester **10** (0.55 g, 1.0 mmole) was dissolved in a solution of 5% formic acid in methanol (20 mL) and treated with Pd black (0.44 g) in small portions. The resulting suspension stirred for 25 min at room temperature under argon, monitoring the disappearance of **10** periodically by TLC. The catalyst was filtered off, washed repeatedly with methanol and the combined methanolic portions were concentrated under *vacuo*. The crude residue was

taken up in dichloromethane (40 mL) and basified with saturated aq. $NaHCO_3$ solution, the aqueous layer was separated and extracted with dichloromethane (2 x 20mL). The combined dichloromethane portions were washed with brine, dried over Na_2SO_4 and concentrated to give crude free amino ester (0.31g).

To the stirring mixture of L-proline (0.24 g, 1.14 mmole) and 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride (0.24 g, 1.24 mmole) in 25 mL of dichloromethane, at rtoom temperature was added crude free amino ester (0.31 g) in 2.5 ml of dichloromethane and stirred overnight. The reaction mixture was diluted with dichloromethane (25 ml) and washed with water and brine, dried over Na_2SO_4 and concentrated. Chromatographic purification (SiO_2, 40% ethyl acetate/hexane) afforded the **11** (0.36 g, 69 %) as a pale yellow viscous oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.24, 7.96 (two br s, 1 H); 7.24-6.98 (m, 3 H), 6.85, 6.74 (two d, J = 7.2, 7.2 Hz, 1 H), 5.90 (d, J = 9.2 Hz, 1/2 H), 4.91-4.80 (m, 1 H), 4.50-4.06 (m, 2 H), 3.63, 3.45 (two s, 3 H), 3.52-3.20 (m, 2 H), 2.55-1.75 (m, 8 H), 1.58, 1.56 (two s, 3 H), 1.53, 1.48 (two s, 9 H), 1.51, 1.45 (two s, 3 H). IR ($CHCl_3$): 3298, 2977, 1706, 1621, 1473, 1398 cm^{-1}. MS (*m/z*) : 499 (M^+), 399, 331, 186, 146, 114,70. HRMS: Exact mass calcd for $C_{27}H_{37}O_6N_3$: 499.2682. Found: 499.2700.



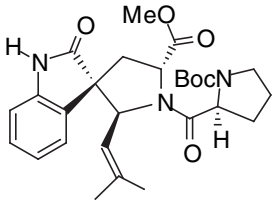
12

A solution of **11** (0.75 g, 1.50 mmole) in dichloromethane (30 mL) was treated with *m*-chloroperbenzoic acid (0.38 g, 1.8 mmole) in dichloromethane (10 mL) at 0 °C and stirred

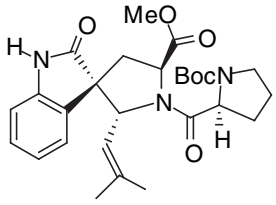
for 6 h. The mixture was treated with 10% aq. sodium sulfite solution and saturated aq. $NaHCO_3$ solution. The aqueous layer separated and extracted with dichloromethane. The combined dichloromethane portions were dried over Na_2SO_4 and concentrated to afford the crude epoxide (0.77 g), which was used without purification for further synthetic transformation.

A methanolic solution (40 mL) of diphenyl diselenide (0.28 g, 0.9 mmole) was treated with $NaBH_4$ (0.072 g, 1.89 mmole) in small portions. A solution of the crude epoxide (0.77 g) in methanol (5 mL) was added and the resultant mixture refluxed for 10 h. The soultion was cooled to 0 °C and diluted with THF (30 mL) and then aq. 30% H_2O_2 solution (2.05 mL, 18 mmol) was added dropwise. After 6 h, the slurry was diluted with water (50 mL) and extracted with ether (3 x 80 mL). The combined etheral portion washed several times with aq. sodium carbonate, dried over Na_2SO_4 and concentrated. Chromatographic purification (SiO_2, 60% ethyl acetate/hexane) afforded allyl alcohol **12** (0.65 g, 85%) as foaming white solid (m.p. 109 °C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.15 (m, 2 H); 7.15-7.12 (m, 1 H); 6.93, 6.78 (two d, *J* = 7.8, 7.8 Hz, 1 H); 5.80, 5.78, 5.65 (three d, *J* = 15.9, 11.6, 15.9 Hz, 2 H), 4.24-4.13 (m, 2 H), 3.64, 3.53 (two s, 3 H), 3.50-3.30 (m, 2 H), 2.60-2.40 (m, 3 H), 2.14-1.98 (m, 1 H), 1.95-1.72 (m, 2 H); 1.52, 1.49, 1.26, 1.23, 1.22 (five s,15 H). IR ($CHCl_3$): 3309, 2977, 1707, 1405 cm^{-1}. Ms *m/z* : 515 (M+), 497, 397, 283, 246, 155,114, 70. HRMS: Exact mass calcd for $C_{27}H_{37}O_7N_3$: 515.2632. Found: 515.2601.



13

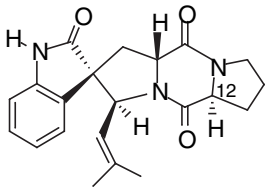


14

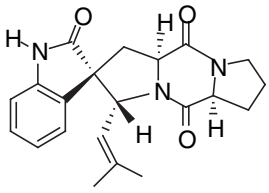
To a solution of **12** (0.5 g, 0.97 mmole) was added *p*-toluenesulfonic acid (18.4 mg, 0.097 mmole, 10 mol%) and the mixture heated under reflux for 20 min till the 50% conversion, monitored periodically by TLC. Mixture was concentrated and the residue purified (SiO_2, 40% EtOAc/hexane) to afford the two diastereomeric spiropyrrolidines **13** (116 mg, 24%) and **14** (111 mg, 23%) along with the recovery of alcohol **12** (244 mg, 49%).

13 : IR ($CHCl_3$): 3253, 3012, 2978, 1717, 1618, 1473, 1405 cm^{-1}. MS (*m/z*) : 497(M+), 424, 397, 355, 300, 252, 155, 114, 70. HRMS: Exact mass calcd for $C_{27}H_{37}O_6N_3$:497.2526. Found:497.2520.

14 : ^1H NMR ($CDCl_3$, 400 MHz): δ 9.08, 8.86, 8.80, 8.55 (four br s,1 H), 7.34 (d, *J* = 7.3 Hz, 1 H), 7.28-7.18 (m, 1 H), 7.06 (t, *J* = 7.8 Hz, 1 H); 6.87 (d, *J* = 7.8 Hz, 1 H), 5.30 (br d, J = 9.7 Hz, 1 H), 5.12 (dd, *J* = 7.5, 9.9 Hz, 1 H); 4.90, 4.87 and 4.81 (three d, *J* = 9.4 Hz, 1 H), 4.77, 4.74 (two dd, *J* = 3.4, 8.2 Hz, 1 H), 3.76, 3.74 (two s, 3 H), 3.63-3.58 (m, 1 H), 3.39-3.33 (m, 1 H), 2.55 (dd, *J* = 7.5, 12.8 Hz, 1 H), 2.25 (dd, *J* = 10.2, 9.9 Hz, 1 H), 2.10-1.75 (m, 4 H), 1.83, 1.63, 1.43, 1.18(four s,15 H). IR ($CHCl_3$): 3259, 2976, 1716, 1621, 1473 cm^{-1}. MS (*m/z*) : 497 (M+), 424, 397, 300, 155, 114, 70. HRMS: Exact mass calcd for $C_{27}H_{37}O_6N_3$: 497.2526. Found: 497.2508.



15



16

A solution of **13** (30 mg, 0.06 mmole) in dichloromethane (5 mL), at 0 °C, was treated with 0.3 mL of 4M HCl solution in dioxan (0.12 mmole) and the mixture was stirred for 0.5 h. Concentration of the reaction mixture gave the crude hydrochloride salt which was taken

up in dichloromethane (5 mL) and treated with NEt_3 (30.3 mg, 0.3 mmol). After stirring for 4 h at room temperature, the mixture was concentrated and purified by PTLC (SiO_2, 40% acetone/hexane) to afford **15** (19.96 mg, 91%) as pale yellow gum.

(3*S*, 9*R*, 12*S*, 18*S*)-Dihydrospirotryprostatin B (15) : $[\alpha]^{19}_D$ = -172 (*c* 0.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) **:** δ 8.53 (s, 1 H), 7.21 (t, *J* = 7.8 Hz, 1 H), 7.11 (d, *J* = 7.5 Hz, 1 H), 6.96 (t, *J* = 7.5 Hz, 1 H), 6.87 (d, *J* = 7.8 Hz, 1 H), 5.41 (d, *J* = 9.2 Hz, 1 H), 5.16 (dt, *J* = 9.2, 1.2 Hz, 1 H), 4.73 (dt, *J* = 1.5, 9.0 Hz, 1 H), 4.28 (ddd, *J* = 1.5, 5.8, 11.8 Hz, 1 H), 3.98-3.90 (m, 1 H), 3.46-3.38 (m, 1 H), 2.66-2.54 (m, 2 H), 2.50-2.43 (m, 1 H), 2.10-1.82 (m, 3 H), 1.60 (s, 3 H), 1.24 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz) **:** δ 180.92, 165.01, 163.52, 140.87, 138.93, 128.45, 128.39, 125.47, 121.91, 118.48, 109.81, 62.58, 60.63, 59.15, 55.06, 44.86, 39.10, 29.88, 25.63, 21.80, 18.12. IR ($CHCl_3$): 3245, 3010, 1653, 1457 cm^{-1}. MS (*m/z*): 365 (M^+), 309, 256, 220, 192, 95. HRMS: Exact mass calcd for $C_{21}H_{23}N_3O_3$: 365.1739. Found: 365.1741.

(3*S*, 9*S*, 12*S*, 18*R*)-Dihydrospirotryprostatin B (16) : $[\alpha]^{19}_D$ = +36 (*c* 0.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz) **:** δ 8.18 (s, 1 H), 7.24 (d, *J* = 7.5 Hz, 1 H), 7.22 (t, *J* =7.5 Hz, 1 H), 7.06 (t, *J* = 7.5 Hz, 1 H), 6.82 (d, *J* = 7.5 Hz, 1 H) , 5.26 (dd, *J* = 6.5, 10.7 Hz, 1 H), 5.18 (dt, *J* = 9.2, 1.2 Hz, 1 H), 4.89 (d, *J* = 9.2 Hz, 1 H), 4.30 (t, *J* = 7.9 Hz, 1 H), 3.66-3.54 (m, 2 H), 2.59 (dd, *J* = 6.5, 13.3 Hz, 1 H), 2.49 (dd, *J* = 10.7, 13.3 Hz, 1 H), 2.31-2.20 (m, 2 H), 2.10-1.90 (m, 2 H), 1.58 (d, *J*=1.2 Hz, 3 H) 1.20 (d, *J*=1.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz) **:** δ 178.88, 166.07, 165.68, 141.09, 137.13, 128.74, 128.64, 122.82, 122.73, 119.09, 109.77, 63.46, 60.48, 56.83, 45.50, 36.95, 27.48, 25.89, 23.43, 18.03. IR ($CHCl_3$): 3234, 3011, 1713, 1662, 1620, 1559, 1541, 1473 cm^{-1}. MS (*m/z*): 365 (M^+), 310, 220, 192, 184, 95. HRMS: Exact mass calcd for $C_{21}H_{23}N_3O_3$: 365.1739. Found: 365.1721.

Hemiaminal 17: a known compound. NMR data were reported in reference 4d. $[\alpha]_D^{19}$ = -89 (*c* 0.4, $CHCl_3$). IR ($CHCl_3$): 3213, 3011, 2927, 1683, 1622, 1473, 1419 cm^{-1}. MS (*m/z*) : 381 (M+), 363, 270, 145, 70. HRMS: Exact mass calcd for $C_{21}H_{23}N_3O_4$: 381.1689. Found: 381.1704.