Asymmetric Total Synthesis of Pseurotin A

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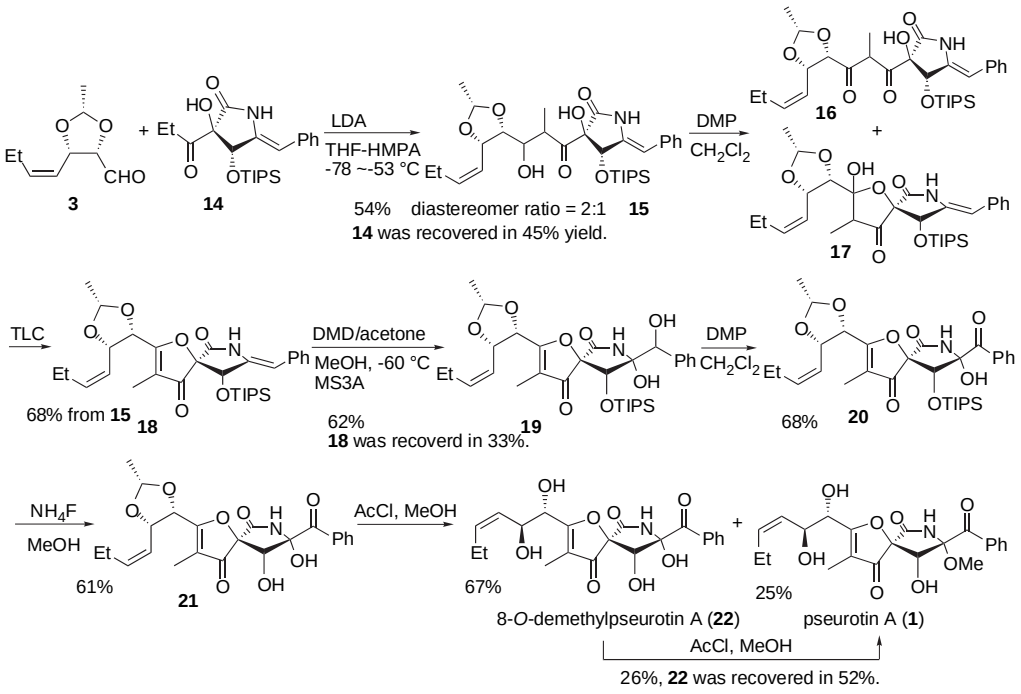

Experimental Section

General Procedures. All reactions were carried out under argon and monitored by thin-layer chromatography using Merck 60 F254 precoated silica gel plates (0.25 mm thickness). Specific optical rotations were measured using a JASCO P-1020 polarimeter. FTIR spectra were recorded on a Horiba FT-720 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AM400 (400 MHz) instrument. High-resolution mass spectral analyses (HRMS) were carried out using JEOL JMS-SX 102A. Preparative thin layer chromatography was performed using Merk Silica Gel 60 F254 and Wakogel B-5F purchased from Wako Pure Chemical Industries, Tokyo, Japan. Flash chromatography was performed using silica gel Merck Art 7734 and silica gel 60N of Kanto Chemical Co. Int., Tokyo, Japan. Ethyl ketone **14** was prepared by our reported method (Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi, S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, H.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 12078).

Procedures

(3*S*, 4*S*)-(*Z*)-5-Benzylidene-3-[3-((2*S*,4*S*,5*S*)-(*Z*)-5-but-1-enyl-2-methyl-[1,3]dioxolan-4-yl)-3-hydroxy-2-methylpropionyl]-3-hydroxy-4-triisopropylsiloxypyrrolidin-2-one (**15**)

To a THF solution (2.0 mL) of diisopropylamine (0.23 mL, 1.62 mmol) and HMPA (0.31 mL, 1.80 mmol) was added a hexane solution of BuLi (1.43 N, 1.0 mL, 1.51 mmol) at 0 °C and the reaction mixture was stirred for 10 minutes. To the reaction mixture was added a THF solution (1.6 mL) of ketone **14** (150 mg, 0.36 mmol) at –78 °C and the reaction mixture was stirred for 1 h. Aldehyde **3** (171 mg, 1.00 mmol, *E*/*Z*=1/4) was added to the reaction mixture at –78 °C and then the reaction temperature was raised to –53 °C over 1 h. The reaction was quenched by the addition of sat. $NaHCO_3$, and the organic materials were extracted with ethyl acetate 3 times and the combined organic extracts were washed with brine 3 times, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* after filtration. Purification by column chromatography (ethyl acetate:hexane=1:20) gave 113 mg (54%) of aldols **15** along with the recovery of the ketone **14** (67 mg, 45%). A mixture of diastereomers was employed in the next experiment, but careful TLC separated the major isomer, which shows the following spectral data.

Major isomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.5 Hz), 1.04 – 1.25 (21H, m), 1.30 (3H, d, *J* = 6.6 Hz), 1.38 (3H, t, *J* = 4.8 Hz), 1.89 – 2.12 (2H, m), 3.17 (1H, dq, *J*d = 9.2 Hz, *J*q = 6.6 Hz), 3.57 (1H, t, *J* = 9.4 Hz), 3.69 (1H, d, *J* = 7.7 Hz), 4.71 (1H, t, *J* = 7.9 Hz), 4.78 (1H, s), 4.98 (1H, q, *J* = 4.8 Hz), 5.17 (1H, d, *J* = 1.9 Hz), 5.52 – 5.62 (1H, m), 5.67 (1H, dt, *J*d = 11.4 Hz, *J*t = 7.3 Hz), 5.98 (1H, d, *J* = 1.5 Hz), 7.21 – 7.42 (5H, m), 7.98 (1H, bs);

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4, 14.1, 14.4, 17.8, 17.9, 19.0, 21.3, 46.7, 72.0, 75.5, 77.9, 89.5, 100.5, 103.5, 123.8, 127.2, 127.3, 129.1, 135.0, 135.9, 137.4, 168.3, 207.1;

IR (neat): 3255, 2945, 2870, 1740, 1693, 1452, 1186, 1142, 816, 685 cm^{-1};

HRMS (FAB): calcd for $C_{32}H_{49}NO_7Si$ 587.3278, found 587.3234.

(5*S*,9*S*)-(*Z*)-8-Benzylidene-2-((2*S*,4*S*,5*S*)-(*Z*)-5-but-1-enyl-2-methyl-[1,3]dioxolan-4-yl)-3-methyl-9-triisopropylsiloxy-1-oxa-7-aza-spiro[4.4]non-2-ene-4,6-dione (**18**)

To a CH_2Cl_2 solution (1.8 mL) of a mixture of diastereomers of aldol **15** (108 mg, 0.184 mmol) was added Dess-Martin periodinane (234 mg, 0.550 mmol) at 0 °C and the reaction mixture was stirred for 5 minutes at 0 °C, then for 1 h at room temperature. The reaction was quenched by the addition of sat. $NaHCO_3$, and the organic materials were extracted with ethyl acetate 3 times and the combined organic extracts were washed with brine 3 times, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* after filtration. By purification with thin-layer chromatography (Ethyl acetate:hexane=1:3), followed by the successive another purification with TLC (Ethyl acetate:chloroform=1:8), gave 71.3 mg (68%) of azaspiro[4.4]nonenedione **18** and 17.8 mg (17%) of side-chain *E*-isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, *J* = 7.5 Hz), 1.01 - 1.19 (21H, m), 1.49 (3H, d, *J* = 4.8 Hz), 1.59 (3H, s), 2.00 - 2.24 (2H, m), 5.03 (1H, d, *J* = 2.9 Hz), 5.05 (1H, s), 5.23 (1H, q, *J* = 4.8 Hz), 5.45 (1H, d, *J* = 2.0 Hz), 5.73 (1H, dt, *J*d = 18.4 Hz, *J*t = 7.4 Hz), 5.81 - 5.86 (1H, m), 5.89 (1H, d, *J* = 1.5 Hz), 7.19 - 7.28 (3H, m), 7.35 (2H, t, *J* = 7.6 Hz), 7.75 (1H, bs);
^{1}H NMR (400 MHz, C_6D_6): δ 0.72 (3H, t, *J* = 7.5 Hz), 1.10 - 1.18 (21H, m), 1.49 (3H, s), 1.52 (3H, d, *J* = 4.8 Hz), 1.65 - 1.90 (2H, m), 4.63 (1H, d, *J* = 7.3 Hz), 4.76 (1H, dt, *J*d = 0.7 Hz. *J*t = 8.6 Hz), 5.09 (1H, q, *J* = 4.8 Hz). 5.41 (1H, d, *J* = 2.0 Hz), 5.61 (1H, dt, *J*d = 18.4 Hz, *J*t = 7.3 Hz), 5.98 (1H, d, *J* = 1.9 Hz), 6.31 – 6.39 (1H, m), 6.92 - 7.10 (5H, m), 7.44 (1H, bs);
^{13}C NMR (100 MHz, $CDCl_3$): δ 5.4, 12.8, 14.3, 18.0, 18.1, 19.4, 21.2, 72.7, 75.1, 75.9, 92.6, 102.9, 103.9, 113.2, 122.4, 126.8, 127.6, 127.7, 129.0, 134.7, 135.2, 138.7, 164.7, 182.7, 195.6 ;
^{13}C NMR (100 MHz, C_6D_6): δ 6.2, 13.8, 15.0, 18.9, 19.0, 20.4, 22.0, 73.8, 76.1, 77.0, 93.6, 103.6, 104.2, 113.9, 124.3, 127.3, 128.5, 129.8, 136.0, 136.2, 138.2, 138.6, 165.4, 183.3, 195.9 ;
IR (neat): 3276, 2943, 2868, 1741, 1709, 1637, 1450, 1190, 1144, 683 cm^{-1};
HRMS (FAB): calcd for $[C_{32}H_{45}NO_6Si+H]^+$ 568.3094, found 568.3065;
$[\alpha]_D^{23}$ +207° (*c* 0.22, $CHCl_3$).

(5*S*,8*S*,9*R*)-2-((2*S*,4*S*,5*S*)-(*Z*)-5-But-1-enyl-2-methyl-[1,3]dioxolan-4-yl)-8-hydroxy-8-(hydroxyphenylmethyl)-3-methyl-9-triisopropylsiloxy-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (**19**)

To a MeOH solution (2.8 mL) of azaspiro[4.4]nonenedione **18** (35 mg, 0.0617mmol) was added MS4A (9.8 mg) and an acetone solution of dimethyl dioxirane (0.11 N, 5.6 ml, 0.617 mmol) at -60 °C and the reaction mixture was stirred for 10.5 h. The reaction was quenched by the addition of sat. $Na_2S_2O_3$, and the organic materials were extracted with ethyl acetate three times and the combined organic extracts were washed with brine 3 times, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* after filtration. Purification by thin-layer chromatography (ethyl acetate:hexane=1:2) gave 22.8 mg (62%) of diol **19** with the recovery of **18** (11.7 mg, 33%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, *J* = 7.5 Hz), 1.00 – 1.15 (21H, m), 1.50 (3H, d, *J* = 4.7 Hz), 1.59 (3H, s), 2.00 – 2.23 (2H, m), 4.92 (1H, s), 5.00 – 5.10 (2H, m), 5.25 (1H, q, *J* = 4.7 Hz), 5.39 (1H, s), 5.70 – 5.96 (2H, m), 5.85 (1H, s), 6.01 (1H, bs), 7.32 – 7.43 (3H, m), 7.45 (2H, d, *J* = 7.3 Hz);
^{13}C NMR (100 MHz, $CDCl_3$): δ 5.4, 12.7, 14.3, 18.0, 19.4, 21.1, 29.7, 71.6, 71.8, 72.8, 76.0, 86.6, 95.1, 103.1, 113.5, 122.2, 127.0, 128.6, 128.7, 138.4, 139.0, 164.0, 185.6, 199.9;
IR (neat): 3346, 2927, 2868, 1738, 1693, 1624, 1464, 1146, 810, 579 cm^{-1};
HRMS (FAB): calcd for $[C_{32}H_{47}NO_8Si - H]^-$ 600.7951, found 600.3015;
$[\alpha]_D^{17}$ +55° (*c* 0.83, $CHCl_3$).

(5*S*,8*S*,9*R*)-8-Benzoyl-2-((2*S*,4*S*,5*S*)-(*Z*)-5-but-1-enyl-2-methyl-[1,3]dioxolan-4-yl)-8-hydroxy-3-methyl-9-triisopropylsiloxy-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (**20**)

To a CH_2Cl_2 solution (1.1 mL) of diol **19** (38.2 mg, 0.0636 mmol) was added Dess-Martin

periodinane (DMP, 35.3 mg, 0.0831 mmol) at room temperature. After stirring the reaction mixture for 2.5 h at that temperature, the reaction was quenched by the addition of sat. $NaHCO_3$ and ethyl acetate. Separated organic phase was washed with sat. $NaHCO_3$ three times and dried over anhydrous Na_2SO_4, and concentrated *in vacuo* after filtration. Purification by thin-layer chromatography (Et_2O:benzene=1:3) gave 25.9 mg (68%) of benzoyl product **20**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 – 1.14 (24H, m), 1.47 (3H, d, *J* = 4.8 Hz), 1.63 (3H, s), 2.03 – 2.24 (2H, m), 5.01 – 5.10 (2H, m), 5.24 (1H, q, *J* = 4.8 Hz), 5.51 (1H, s), 5.76 (1H, dt, *J*d = 11.0, *J*t = 7.4 Hz), 5.81 – 5.90 (1H, m), 6.45 (1H, s), 6.69 (1H, bs), 7.48 (2H, t, *J* = 7.6 Hz), 7.60 (1H, t, *J* = 7.4 HZ), 8.31 (2H, d, J = 7.*2* Hz);
^{13}C NMR (100 MHz, $CDCl_3$): δ 5.4, 12.3, 14.3, 17.9, 19.3, 21.3, 22.5, 72.5, 72.9, 76.1, 88.3, 94.0, 103.2, 113.4, 122.2, 128.8, 130.7, 133.1, 134.0, 138.9, 163.7, 186.4, 191.9, 199.9;
IR (neat): 3338, 2927, 2868, 1736, 1689, 1624, 1464, 1146, 810, 683 cm^{-1};
HRMS (FAB): calcd for $[C_{32}H_{45}NO_8Si+H]^+$ 600.2999, found 600.3035;
$[\alpha]_D^{23}$ +58° (*c* 0.42, $CHCl_3$).

(5*S*,8*S*,9*R*)-8-Benzoyl-2-((2*S*,4*S*,5*S*)-(*Z*)-5-but-1-enyl-2-methyl-[1,3]dioxolan-4-yl)-8,9-dihydroxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (**21**)
To a MeOH solution (1.4 mL) of **20** (20.1 mg, 0.0336 mmol) was added NH_4F (21.0 mg, 0.557 mmol) at room temperature. After stirring the reaction mixture for 2.5 h, the volatile organic materials were removed under reduced pressure, purification by thin-layer chromatography (Ethyl acetate:hexane=1:1) gave 9.1 mg (60%) of diol **21**.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98, (3H, t, *J* = 7.5 Hz), 1.51 (3H, d, *J* = 4.8 Hz), 1.76 (3H, s), 1.98 – 2.24 (2H, m), 4.86 (1H, s), 5.00 (1H, d, *J* = 7.7 Hz), 5.07 (1H, t, *J* = 8.6 Hz), 5.19 (1H, q, *J* = 4.8 Hz), 5.45 – 5.54 (1H, m), 5.72 (1H, dt, *J*d = 10.9 Hz, *J*t = 7.6 Hz), 6.42 (1H, bs), 7.48 (2H, t, *J* = 7.7 Hz), 7.61 (1H, t, *J* = 7.4 Hz), 7.61 (2H, d, *J* = 7.7 Hz), 8.25 (1H, bs);
^{13}C NMR (100 MHz, $CDCl_3$): δ 5.5, 14.1, 19.1, 21.3, 72.4, 75.1, 87.7, 93.1, 103.0, 113.4, 122.2, 128.8, 130.6, 133.0, 134.3, 138.9, 163.4, 187.3, 192.1, 200.3;
IR (neat): 3300, 2931, 1738, 1734, 1687, 1684, 1620, 1616, 1244, 1146, 899, 665 cm^{-1};
HRMS (FAB): calcd for $C_{23}H_{26}NO_8$ 444.1658, found 444.1649;
$[\alpha]_D^{17}$ +69° (*c* 0.61, MeOH).

Pseurotin A (**1**) and 8-*O*-demethylpseurotin A (**22**)
To a MeOH solution (0.41 mL) of **21** (3.3 mg, 0.00745 mmol) was added the acetyl chloride (28.4 mL, 0.399 mmol) at room temperature. After stirring the reaction mixture for 11 h at that temperature, the volatile organic materials were removed under reduced pressure, purification by thin-layer chromatography (Et_2O) gave 0.8 mg (25%) of pseurotin A (**1**) and 2.2 mg (67%) of 8-*O*-demethylpseurotin A (**22**).

Convertion of 8-*O*-demethylpseurotin A (**22**) to pseurotin A (**1**)

To a MeOH solution (0.6 mL) of 8-*O*-demethylpseurotin A (**22**) (2.7 mg, 0.00647 mmol) was added the acetyl chloride (42.6 mL, 0.599 mmol) at room temperature. After stirring the reaction mixture for 6 h at that temperature, the volatile organic materials were removed under reduced pressure, purification by thin-layer chromatography (Et_2O) gave 0.7 mg (25%) of pseurotin A (**1**) and 1.4 mg (52%) of 8-*O*-demethylpseurotin A (**22**).

Pseurotin A (**1**)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (3H, t, *J* = 7.5 Hz), 1.65 (3H, s), 2.02 – 2.16 (2H, m), 3.33 (3H, s), 4.51 - 4.68 (4H, m), 5.31 (1H, m), 5.62 (1H, dt, *J*d = 11.3 Hz, *J*t = 14.9 Hz), 7.43 (2H, t, *J* = 5.0 Hz), 7.57 (1H, t, *J* = 4.1 Hz), 8.22 (2H, d, *J* = 7.2 Hz);

^{13}C NMR (100 MHz, $CDCl_3$): δ 5.9, 14.5, 21.9, 52.3, 69.7, 72.9, 75.4, 91.4, 92.7, 129.2, 129.3, 131.3, 134.8, 135.9;

IR (neat): 3353, 2923, 2852, 1735, 1704, 1685, 1621, 1261, 1101, 800, 698 cm_{-1};

HRMS (FAB): calcd for $C_{22}H_{26}NO_8$ 432.1658, found 432.1691;

$[\alpha]_D^{31}$ -4.8° (*c* 0.15, MeOH).

8-*O*-demethylpseurotin A (**22**)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, *J* = 7.6 Hz), 1.69 (3H, s), 1.99 – 2.21 (2H, m), 3.04 (1H, bs), 3.43 (1H, bs), 4.64 (2H, bs), 4.77 (1H, bs), 4.89 (1H, bs), 5.17 – 5.22 (1H, m), 5.58 (1H, dt, *J*t = 7.5 Hz, *J*d = 10.6 Hz), 6.71 (1H, s), 7.48 (2H, t, *J* = 7.6 Hz), 7.62 (1H, d, *J* = 7.6 Hz), 8.08 (1H, bs), 8.34 (2H, d, *J* = 7.5 Hz);

^{13}C NMR (100 MHz, $CDCl_3$): δ 6.2, 14.0, 21.4, 70.8, 71.6, 71.7, 89.1, 94.8, 113.0, 126.2, 128.6, 131.4, 133.1, 134.5, 136.6, 164.8, 188.9, 193.8, 198.8;

IR (neat): 3305, 2923, 2852, 1731, 1695, 1625, 1446, 1257, 1186, 1062 cm^{-1};

$[\alpha]_D^{32}$ –30° (*c* 0.25, MeOH).