Expedient Synthesis of Potent Cannabinoid Receptor Agonist (–)-CP55,940

Noriaki Itagaki, Tsutomu Sugahara, and Yoshiharu Iwabuchi[†]

Graduate School of Pharmaceutical Sciences, Tohoku University

Aobayama, Sendai 980-8578, Japan

Fax: +81-22-795-6845

E-mail: iwabuchi@mail.pharm.tohoku.ac.jp

Supporting Information

Table of Contents

1. General	S-2
2. Experimental Procedures	
(1) Preparation of chiral building block [(+)- 5]	S-2
(2) Preparation of the amino acid catalyst	S-4
(3) Preparation of the aromatic component of CP 55,940	S-5
(4) Synthesis of CP 55,940 (3)	S-8
3. References	S-13
4. NMR spectra	S-14

1. General.

IBX¹ was prepared according to the literature procedures. Other chemicals and solvents were purchased from commercial suppliers or purified by standard techniques. All reactions were stirred magnetically, under an argon atmosphere, unless otherwise noted, and monitored with analytical TLC (Merck Kieselgel 60 F₂₅₄). Column chromatography was carried out with silica gel 60 particle size 0.063-0.210 mm. Melting points were taken with Yazawa BY-2 and are uncorrected. NMR spectra were measured in JEOL JNM-AL400 (400 MHz) or JEOL ECA600 (600 MHz). Chemical shifts were reported in the δ scale relative to tetramethylsilane (TMS) as 0.00 ppm for ¹H (CDCl₃) and residual CHCl₃ (7.26 ppm for ¹H and 77.00 ppm for ¹³C), as internal reference. The infrared (IR) spectra were recorded on JASCO IR-700 or JASCO FT/IR-410. Mass spectra were measured on JEOL JMS-DX303 (for low resolution MS) and JMS-AX500 or JMS-700 (for high resolution MS) instruments. The specific rotations were measured on JASCO DIP-370. Elemental analyses utilized Yanaco CHN CORDER MT-6.

2. Experimental procedures.

(1) Preparation of chiral building block [(+)-5]

(1R,5S,8S)-8-hydroxybicyclo[3.3.1]nonan-2-one [(+)-2]: A solution of ketoaldehyde **1** (100mg, 0.648 mmol) in MeCN (2.6 ml) was added dropwisely to a stirred solution of (2*R*,4*R*)-4-TBDPSOxy-D-proline (60 mg, 0.16 mmol) in MeCN (2.6 ml) at room temperature. The reaction mixture was stirred for 23 h at room temperature. Then, the mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography [hexane-AcOEt (4:1 v/v)] to afford hydroxyketone (+)-**2** (68 mg, 68 %) as colorless needles. An aliquot sample was recrystallized from diisopropyl ether-hexane. mp 131-133 °C; $[\alpha]_D^{31} = +2.00^\circ$ (c 0.8, CHCl₃). [lit.² $[\alpha]_D^{20} = +3.6^\circ$ (c 0.65, CHCl₃)]; IR (CHCl₃ solution): 3520, 1700 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 3.78 (m, 1H), 2.79 (br. s, 1H), 2.66 (s, 1H), 2.54 (m, 1H), 2.37 (m, 1H), 2.18-2.05 (m, 3H), 1.97 (m, 1H) 1.69 (m, 4H), 1.38 (m, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 216.3, 71.6, 51.6, 39.0, 31.0, 30.7, 29.7, 26.7, 24.9; MS *m/z* : 154 (M⁺), 70 (100%); HRMS Calcd. C₉H₁₄O₂: 154.0993. Found: 154.0983; *Anal.* Calcd. for C₉H₁₄O₂: C, 70.10;

H, 9.15. Found: C, 70.05; H, 9.13.

(1*R*,5*S*,8*S*)-8-methoxymethoxybicyclo[3.3.1]nonan-2-one [(-)-4]: MOMCl (0.22 ml, 2.90 mmol) and diisopropylethylamine (0.62 ml, 3.56 mmol) was added to a stirred solution of alcohol (+)-**2** (250 mg, 1.62 mmol, >99% ee) at room temperature and the mixture was stirred for 18 h at the same temperature. Then, the reaction mixture was diluted with Et₂O and washed with H₂O. The aqueous layer was extracted with Et₂O and the combined organic extract was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (17:3 v/v)] to afford ether (-)-**4** (323 mg, 100 %) as a colorless oil.

$[\alpha]_D^{29} = -0.60^\circ$ (c 1.06, CHCl₃); IR (neat): 1702 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 4.76 (dd, 1H, *J* = 7.1, 1.5 Hz), 4.61 (dd, 1H, *J* = 6.8, 1.5 Hz), 3.85 (m, 1H), 3.37 (d, 3H, *J* = 1.5 Hz), 2.88 (br.s, 1H), 2.56-2.41 (m, 2H), 2.09-1.68 (m, 9H); ¹³C-NMR (100 MHz, CDCl₃) δ 211.6, 94.0, 74.9, 55.3, 50.4, 40.2, 32.4, 30.3, 29.7, 28.3, 25.9; MS *m/z* : 198 (M⁺), 45 (100%); HRMS Calcd. C₁₁H₁₈O₃: 198.1255. Found: 198.1239; *Anal.* Calcd. for C₁₁H₁₈O₃: C, 66.64; H, 9.15. Found: C, 66.59; H, 8.96.

(1*R*,5*R*,8*S*)-8-methoxymethoxybicyclo[3.3.1]non-3-en-2-one [(+)-5]: IBX (3.33 g, 11.9 mmol) was added to a solution of ketone (-)-**4** (590 mg, 2.98 mmol) in toluene-DMSO (29.7 ml, 2:1 v/v) at room temperature. The mixture was heated to 55-75 °C and stirred for 11 h. After cooling, the reaction mixture was diluted with Et₂O, filtered through a Celite pad, and the organic solution was washed with saturated aqueous NaHCO₃ and H₂O. The aqueous layer was extracted with Et₂O and the combined organic extract was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (4:1 v/v)] to afford enone (+)-**5** (470 mg, 80 %) as a colorless oil.

$[\alpha]_D^{28} = +18.4^\circ$ (c 0.95, CHCl₃); IR (neat): 1671 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 6.90 (dd, 1H, *J* = 9.0, 6.8 Hz), 6.20 (d, 1H, *J* = 9.8 Hz), 4.82 (d, 1H, *J* = 6.8 Hz), 4.64 (d, 1H, *J* = 6.8 Hz), 3.76 (m, 1H), 3.40 (s, 3H), 2.83 (br.s, 1H), 2.57 (br.s, 1H), 2.32 (d, 1H, *J* = 10.5 Hz), 1.91 (m, 1H), 1.80-1.62 (m, 4H); ¹³C-NMR (100

MHz, CDCl₃) δ 199.3, 151.2, 132.3, 94.1, 73.7, 55.5, 47.1, 33.3, 29.9, 25.7, 25.0; MS m/z : 196 (M⁺), 45 (100%); HRMS Calcd. C₁₁H₁₆O₃: 196.1099. Found: 196.1075; Anal. Calcd. for C₁₁H₁₆O₃: C, 67.32; H, 8.22. Found: C, 67.03; H, 7.96. The enantiomeric purity of (+)-**5** was determined to be >99% ee by chiral HPLC analysis using DAICEL CHIRALCEL OD. The conditions used for the analysis of **5** and the retention time were as follows; Solvent: *i*-PrOH-hexane (3:97). Flow rate: 0.5 ml/min. Retention time: (1*S*,5*S*,8*R*)-**5**; 20.0 min, (1*R*,5*R*,8*S*)-**5**; 22.1 min

(2) Preparation of the amino acid catalyst

The catalyst **14** was synthesized as shown in the following scheme.

(2*R*,4*R*)-4-(*tert*-butyldiphenylsiloxy)pyrrolidine-1,2-dicarboxylic acid dibenzyl ester [(+)-16**]**: TBDPSCI (1.54 ml, 5.92 mmol) and imidazole (804 mg, 11.8 mmol) were added to a solution of alcohol **15** (1.75 g, 34.8 mmol) in DMF (5.0 ml) at room temperature. The reaction mixture was stirred for 24 h at the same temperature. Then, the reaction mixture was diluted with Et₂O and the organic solution was washed with H₂O. The aqueous layer was extracted with Et₂O and the combined organic solution was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (97:3 v/v)] to afford silyl ether (+)-**16** (2.852 g, 98 %) as a colorless oil.

$[\alpha]_D^{28} = +26.5^\circ$ (*c* 0.84, CHCl₃); IR (neat): 1798, 1747 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 7.62-7.23 (m, 20H), 5.19-4.97 (m, total 4H_{rotamer}), 4.50 (dd, 0.5H_{rotamer}, *J* = 8.8, 3.4 Hz), 4.40 (dd, 0.5H_{rotamer}, *J* = 8.8, 3.9 Hz), 4.32 (m, 1H), 3.57 (d, 1H, *J* =

4.4 Hz), 3.49 (m, 1H), 2.28-2.12 (m, 2H), 1.03 and 1.02 (each s, total 9H_{rotamer}); ¹³C-NMR (100 MHz, CDCl₃) (rotamer) δ 171.5, 171.2, 154.7, 154.2, 136.5, 136.3, 135.6, 135.5, 135.4, 133.2, 133.1, 133.0, 129.8, 129.7, 128.39, 128.37, 128.3, 128.2, 128.1, 128.0, 127.9, 127.80, 127.76, 127.72, 127.7, 127.68, 127.64, 127.6, 71.6, 70.7, 67.03, 66.95, 66.9, 66.8, 58.02, 57.77, 54.9, 54.4, 39.3, 38.4, 26.7, 19.0; MS *m/z* : 536 (M⁺-C₄H₉), 91 (100%). HRMS Calcd. C₃₂H₃₀NO₅Si (M⁺-C₄H₉) : 536.1891. Found : 536.1899; *Anal.* Calcd. for C₃₆H₃₉NO₅Si: C, 72.82; H, 6.62; N, 2.36. Found: C, 72.75; H, 6.51; N, 2.40.

(2*R*,4*R*)-4-(*tert*-butyldiphenylsilyloxy)-D-proline [(+)-14]: 10% (w/w) Pd/C (255 mg) was added to a solution of ester-carbamate (+)-**16** (2.550 g, 4.29 mmol) in MeOH (23.3 ml) and the mixture was stirred under atmospheric pressure of H₂ for 48 h at room temperature. Then, the reaction mixture was filtered through a Celite pad, and concentrated under reduced pressure to afford amino acid (+)-**14** (1.583 g, 100 %) as a colorless solid.

mp 137-138.5 °C; $[\alpha]_D^{27} = +3.85^\circ$ (c 0.7, CH₃OH); IR (nujol): 3404, 1714 cm⁻¹. ¹H-NMR (400 MHz, CD₃OD) δ 7.67-7.63 (m, 4H), 7.48-7.39 (m, 6H), 4.50 (br.s, 1H), 4.24 (m, 1H), 3.34 (d, 1H, *J* = 12.2 Hz), 3.18 (q, 1H, *J* = 12.2, 3.7 Hz), 2.39 (m, 1H), 2.29 (m, 1H), 1.05 (s, 9H); ¹³C-NMR (100 MHz, CD₃OD) δ 172.7, 136.93, 136.87, 134.1, 133.9, 131.29, 131.27, 129.1, 129.0, 72.9, 60.4, 54.9, 39.4, 27.2, 19.8; MS *m/z* : 312 (M⁺-C₄H₉), 234 (100%). HRMS Calcd. C₁₇H₁₈NO₃Si (M⁺-C₄H₉) : 312.1055. Found : 312.1022.

(3) Preparation of the aromatic component of CP 55,940

Trifluoromethanesulfonic acid 4-(1,1-dimethylheptyl)-2,6-dimethoxyphenyl ester: 2,4,6-Collidine (17.3 ml, 130 mmol) and trifluoromethanesulfonic anhydride (6.48 ml, 38.5 mmol) were added to a stirred solution of 4-(1,1-dimethylheptyl)-2,6-dimethoxyphenol (9.00 g, 32.1 mmol) in CH₂Cl₂ (160 ml) at 0 °C and stirring was continued for 24 h at the same temperature. Then, the mixture was diluted with Et₂O and washed with H₂O. The aqueous layer was extracted with Et₂O and the combined organic extract was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (19:1 v/v)] to afford

triflate (10.55 g, 80 %) as colorless needles.

mp 34-35 °C; IR (neat): 1603, 1415, 1203 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.55 (s, 2H), 3.87 (s, 6H), 1.56 (m, 2H), 1.28 (s, 6H), 1.28-1.18 (m, 6H), 1.06 (m, 2H), 0.85 (t, 3H, $J = 6.8$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 151.6, 151.1, 125.7, 118.6 (q, $J = 318$ Hz), 102.7, 56.1, 44.5, 38.5, 31.7, 30.0, 29.0, 24.6, 22.7, 14.1; MS m/z : 412 (M^+), 279 (100%); HRMS Calcd. $\text{C}_{18}\text{H}_{27}\text{F}_3\text{O}_5\text{S}$: 412.1530. Found: 412.1528; Anal. Calcd. for $\text{C}_{18}\text{H}_{27}\text{F}_3\text{O}_5\text{S}$: C, 52.41; H, 6.60. Found: C, 52.34; H, 6.51.

1-(1,1-Dimethylheptyl)-3,5-dimethoxybenzene (8): Et_3N^4 (8.7 ml, 62.4 mmol) and 10 % (w/w) Pd/C (10.0 g) were added to a solution of trifluoromethanesulfonic acid 4-(1,1-dimethylheptyl)-2,6-dimethoxyphenyl ester (10.30 g, 24.97 mmol) in MeOH (190 ml) at room temperature and the mixture was stirred under atmospheric pressure of H_2 for 8 days at the same temperature. Then, the reaction mixture was filtered through a Celite pad eluting with MeOH, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (19:1 v/v)] to afford *t*-alkyldimethoxybenzene **8** (5.385 g, 82 %) as a colorless oil.

IR (neat): 1602 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.40 (d, 2H, $J = 2.2$ Hz), 6.22 (t, 1H, $J = 2.2$ Hz), 3.71 (s, 6H), 1.48 (m, 2H), 1.18 (s, 6H), 1.20-1.07 (m, 6H), 0.98 (m, 2H), 0.77 (t, 3H, $J = 7.1$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 160.3, 152.4, 104.6, 96.5, 55.1, 44.5, 38.0, 31.8, 30.0, 28.9, 24.6, 22.7, 14.1; MS m/z : 264 (M^+), 180 (100%); HRMS Calcd. $\text{C}_{17}\text{H}_{28}\text{O}_2$: 264.2088. Found: 264.2095.

3-(1,1-Dimethylheptyl)-5-methoxyphenol: 1-Propanethiol (19.8 ml, 219 mmol) was added to a suspension of NaH (60 %) (3.60 g, 90.0 mmol) in DMF (400 ml) at room temperature and the mixture was stirred for 30 min at the same temperature. Then, to the mixture was added a solution of *t*-alkyldimethoxybenzene **8** (4.971 g, 18.8 mmol) in DMF (100 ml) and the reaction mixture was stirred for 20 h at 120 °C. After cooling to room temperature, 10 %aqueous HCl was added to this and the mixture was extracted with Et_2O and washed with H_2O . The aqueous layer was extracted with Et_2O and the combined organic extract was washed with brine, dried over MgSO_4 , and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (19:1 v/v)] to afford phenol (3.196 g, 68 %) as a colorless oil.

IR (neat): 3378, 1594 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.47 (t, 1H, $J = 1.8$ Hz), 6.40 (t, 1H, $J = 1.8$ Hz), 6.23 (t, 1H, $J = 2.2$ Hz), 4.89 (br.s, 1H), 3.77 (s, 3H), 1.53 (m, 2H), 1.23 (s, 6H), 1.25-1.16 (m, 6H), 1.04 (m, 2H), 0.84 (t, 3H, $J = 7.0$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 160.3, 156.2, 152.9, 105.7, 105.0, 97.9, 55.2, 44.5, 37.8, 31.8, 30.0, 28.9, 24.7, 22.7, 14.1; MS m/z : 264 (M^+), 166 (100%); HRMS Calcd. $\text{C}_{16}\text{H}_{26}\text{O}_2$: 250.1931. Found: 250.1944.

Trifluoromethanesulfonic acid 3-(1,1-dimethylheptyl)-5-methoxyphenyl ester: 2,4,6-Collidine (6.86 ml, 51.6 mmol) and trifluoromethanesulfonic anhydride (2.58 ml, 15.3 mmol) were added to a stirred solution of 3-(1,1-dimethylheptyl)-5-methoxyphenol (3.196 g, 12.76 mmol) in CH_2Cl_2 (64 ml) at 0 °C and stirring was continued for 24 h at the same temperature. Then, the mixture was diluted with Et_2O and washed with H_2O . The aqueous layer was extracted with Et_2O and the combined organic extract was washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (19:1 v/v)] to afford triflate (4.569 g, 87 %) as colorless oil.

IR (neat): 1618, 1582, 1422, 1210 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.88 (s, 1H), 6.81 (s, 1H), 6.62 (s, 1H), 3.80 (s, 3H), 1.57 (m, 2H), 1.27 (s, 6H), 1.28-1.17 (m, 6H), 1.03 (m, 2H), 0.84 (t, 3H, $J = 6.7$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 160.3, 153.6, 150.1, 118.7 (q, $J = 318$ Hz), 112.6, 111.2, 103.5, 55.5, 44.4, 38.2, 31.7, 29.9, 28.7, 24.6, 22.7, 14.0; MS m/z : 382 (M^+), 297 (100%); HRMS Calcd. $\text{C}_{17}\text{H}_{25}\text{F}_3\text{O}_4\text{S}$: 382.1424. Found: 382.1427.

1-(1,1-Dimethylheptyl)-3-methoxybenzene: Et_3N^4 (2.91 ml, 20.9 mmol) and 10 % (w/w) Pd/C (3.2 g) were added to a solution of trifluoromethanesulfonic acid 3-(1,1-dimethylheptyl)-5-methoxyphenyl ester (3.196 g, 8.36 mmol) in MeOH (50 ml) at room temperature and the mixture was stirred under atmospheric pressure of H_2 for 5 days at the same temperature. Then, the reaction mixture was filtered through a Celite pad, and concentrated under

reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (19:1 v/v)] to afford *t*-alkylmethoxybenzene (1.97 g, quant.) as a colorless oil.

IR (neat): 1579 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.21 (m, 1H), 6.90 (m, 2H), 6.70 (m, 1H), 3.78 (d, 3H, $J = 3.2$ Hz), 1.58 (m, 2H), 1.28 (s, 6H), 1.28-1.16 (m, 6H), 1.07 (br.s, 2H), 0.84 (m, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 159.2, 151.5, 128.7, 118.3, 112.5, 109.6, 55.0, 44.6, 37.8, 31.8, 30.1, 29.0, 24.7, 22.7, 14.1; MS m/z : 234 (M^+), 149 (100%); HRMS Calcd. $\text{C}_{16}\text{H}_{26}\text{O}$: 234.1982. Found: 234.1969.

1-Bromo-4-(1,1-dimethylheptyl)-2-methoxybenzene (9): Br_2 (0.65 ml, 12.7 mmol) in AcOH (10 ml) was added dropwisely to a stirred solution of 1-(1,1-dimethylheptyl)-3-methoxybenzene (1.489 g, 6.35 mmol) in AcOH (30 ml) at room temperature. The mixture was stirred for 4 h at the same temperature. Then, the reaction mixture was quenched with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with Et_2O and washed with H_2O . The aqueous layer was extracted with Et_2O and the combined organic extract was washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. The residue was chromatographed using [hexane-AcOEt (99:1 v/v)] to afford bromobenzene **9** (1.74 g, 87 %) and 1-bromo-2-(1,1-dimethylheptyl)-4-methoxybenzene (153 mg, 7.7 %) and 1,5-dibromo-2-(1,1-dimethylheptyl)-4-methoxybenzene (123 mg, 4.9 %) as inseparable mixture.

IR (neat): 1571 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.41 (d, 1H, $J = 8.3$ Hz), 6.85 (d, 1H, $J = 2.2$ Hz), 6.79 (dd, 1H, $J = 8.3, 2.0$ Hz), 3.88 (s, 3H), 1.57 (m, 2H), 1.27 (s, 6H), 1.27-1.17 (m, 6H), 1.05 (m, 2H), 0.84 (t, 3H, $J = 7.0$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 155.3, 150.8, 132.4, 119.5, 110.0, 108.3, 56.1, 44.5, 37.9, 31.8, 30.0, 29.0, 24.6, 22.7, 14.1; MS m/z : 314 (M^+ , ^{81}Br), 312 (M^+ , ^{79}Br), 227 (100%); HRMS Calcd. $\text{C}_{16}\text{H}_{25}^{79}\text{BrO}$: 312.1088. Found: 312.1077; Calcd. $\text{C}_{16}\text{H}_{25}^{81}\text{BrO}$: 314.1068. Found: 314.1056.

(4) Synthesis of CP 55,940 (**3**)

(1*R*,4*R*,5*R*,8*S*)-4-[4-(1,1-Dimethylheptyl)-2-methoxyphenyl]-8-methoxymethoxybicyclo[3.3.1]nonan-2-one [(+)-10**]:** An apparatus

containing a mixture of Mg (120 mg, 4.94 mmol) and a small amount of I_2 was flame-dried from bottom to top. After cooling, to the mixture was added a solution of bromobenzene **9** (1.38 g, 4.40 mmol) in THF (2.5 ml) and the mixture was stirred for 80 min at refluxing temperature to generate the corresponding Grignard reagent. After cooling, hexamethylphosphoric triamide (0.67 ml, 3.46 mmol) was added to this at 0 °C and the whole mixture was added to $CuBr \cdot Me_2S$ (72 mg, 0.35 mmol) in another flask at 0 °C. The mixture was stirred for 25 min at the same temperature. Then, to the stirred mixture was added dropwisely a solution of bicyclononenone (+)-**5** (340 mg, 1.73 mmol) in THF (5.5 ml) at -78 °C and stirring was continued for 2 h at the same temperature. After the reaction mixture was quenched with saturated aqueous NH_4Cl , the mixture was filtered through a Celite pad, extracted with Et_2O and washed with H_2O . The aqueous layer was extracted with Et_2O and the combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (19:1 v/v)] to afford silyl enol ether as a colorless oil. To a solution of silyl enol ether in THF (5.0 ml) was added 1.0 M TBAF in THF (3.46 ml, 3.46 mmol) at room temperature and the mixture was stirred for 30 min at the same temperature. Then, the solvent was removed under reduced pressure, Et_2O was added to this residue, and the organic solution was washed with H_2O . The aqueous layer was extracted with Et_2O and the combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (9:1 v/v)] to afford ketone (+)-**10** (638 mg, 85 %) as a colorless oil.

$[\alpha]_D^{33} = +16.7^\circ$ (c 0.8, $CHCl_3$); IR (neat): 1701, 1608, 1570 cm^{-1} ; 1H -NMR (600 MHz, $CDCl_3$) δ 6.94 (d, 1H, $J = 5.5$ Hz), 6.84 (d, 1H, $J = 6.4$ Hz), 6.80 (s, 1H), 4.82 (d, 1H, $J = 4.6$ Hz), 4.66 (d, 1H, $J = 4.6$ Hz), 3.86 (m, 1H), 3.81 (s, 3H), 3.58 (m, 1H), 3.40 (d, 3H, $J = 0.9$ Hz), 2.88 (br.s, 1H), 2.75 (m, 2H), 2.15-2.06 (m, 3H), 1.98 (br.s, 1H), 1.81 (m, 2H), 1.57-1.50 (m, 3H), 1.26 (s, 6H), 1.26-1.17 (m, 6H), 1.06 (m, 2H), 0.84 (t, 3H, $J = 4.4$ Hz); ^{13}C -NMR (150 MHz, $CDCl_3$) δ 213.0, 156.1, 149.6, 131.7, 127.3, 118.0, 108.4, 94.4, 76.9, 55.6, 55.2, 49.7, 45.3, 44.6, 39.0, 37.8, 32.1, 31.8, 31.1, 30.1, 29.2, 28.2, 27.9, 24.7, 22.7, 14.1; MS m/z : 430 (M^+), 398 (100%); HRMS Calcd. $C_{27}H_{42}O_4$: 430.3081. Found: 430.3099.; *Anal.* Calcd.

for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.27; H, 9.68.

(7*R*,8*R*)-7-[4-(1,1-Dimethylheptyl)-2-methoxyphenyl]-8-(2-[1,3]dioxolan-2-ylethyl)-1,4-dioxaspiro[4.5]decane [(-)-11]: Ethyleneglycol (0.195 ml, 3.49 mmol) and *p*-toluenesulfonic acid (13.2 mg, 0.69 mmol) were added to a solution of bicycloketone (+)-**10** (300 mg, 0.697 mmol) in xylene (34.8 ml) at room temperature and the mixture was stirred for 1 h at refluxing temperature. After cooling to room temperature, the mixture was quenched with saturated aqueous NH_4Cl , extracted with Et_2O and washed with H_2O . The aqueous layer was extracted with Et_2O and the combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (9:1 v/v)] to afford diketal (-)-**11** (291 mg, 88 %) as a colorless oil.

$[\alpha]_D^{31} = -13.9^\circ$ (*c* 0.6, $CHCl_3$); IR (neat): 1608, 1570 cm^{-1} ; 1H -NMR (600 MHz, $CDCl_3$) δ 7.01 (br, 1H), 6.83 (br.s, 1H), 6.76 (s, 1H), 4.61 (t, 1H, $J = 3.0$ Hz), 3.95-3.71 (m, 8H), 3.77 (s, 3H), 3.15 (br.s, 1H), 1.90-1.17 (m, 24H), 1.04 (m, 3H), 0.83 (t, 3H, $J = 4.6$ Hz); ^{13}C -NMR (150 MHz, $CDCl_3$) δ 157.1, 148.7, 129.7, 126.1, 118.3, 109.2, 108.8, 105.2, 64.8, 64.7, 64.4, 64.2, 55.5, 44.8, 42.4, 41.4, 37.7, 37.2, 35.0, 31.8, 31.2, 30.1, 29.3, 29.0, 27.5, 24.7, 22.7, 14.2; MS m/z : 474 (M^+), 331 (100%); HRMS Calcd. $C_{29}H_{46}O_5$: 474.3343. Found: 474.3336.

3-((7*R*,8*R*)-7-[4-(1,1-Dimethylheptyl)-2-methoxyphenyl]-1,4-dioxaspiro[4.5]dec-8-yl)propan-1-ol [(-)-12]: 2,6-Lutidine (0.26 ml, 2.23 mmol) and TESOTf (0.336 ml, 1.49 mmol) were added to a stirred solution of diketal (-)-**11** (160 mg, 0.371 mmol) in CH_2Cl_2 (3.7 ml) at 0 °C and stirring was continued for 30 min at the same temperature. After H_2O was added, the mixture was further stirred for 30 min at 0 °C. Then, the mixture was extracted with Et_2O and washed with H_2O . The aqueous layer was extracted with Et_2O and the combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Next, $NaBH_4$ (14 mg, 0.37 mmol) was added to a solution of this crude product in MeOH (4.5 ml) at 0 °C and the mixture was stirred for 10 min at the same temperature. After the solvent was removed under reduced pressure, AcOEt was added to this residue, and the

organic solution was washed with H₂O. The aqueous layer was extracted with AcOEt and the combined organic solution was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (4:1 v/v)] to afford alcohol (–)-**12** (110 mg, 75 %) as a colorless oil.

$[\alpha]_D^{30} = -10.2^\circ$ (c 0.38, CHCl₃); IR (neat): 3416, 1607, 1569 cm⁻¹; ¹H-NMR (600 MHz, CDCl₃) δ 7.00 (br.s, 1H), 6.84 (br.s, 1H), 6.77 (s, 1H), 3.97-3.88 (m, 4H), 3.78 (s, 3H), 3.42 (m, 2H), 3.17 (br.s, 1H), 1.92-1.17 (m, 24H), 1.04 (m, 2H), 0.95 (m, 1H), 0.83 (t, 3H, *J* = 4.8 Hz); ¹³C-NMR (150 MHz, CDCl₃) δ 157.0, 148.8, 130.0, 126.0, 118.3, 109.2, 108.8, 64.3, 64.2, 63.1, 55.6, 44.7, 42.4, 41.2, 37.7, 37.2, 35.0, 31.8, 30.0, 29.8, 29.3, 29.0, 24.7, 22.7, 14.1; MS *m/z* : 432 (M⁺), 331 (100%); HRMS Calcd. C₂₇H₄₄O₄: 432.3237. Found: 432.3246.

(3*R*,4*R*)-3-[4-(1,1-Dimethylheptyl)-2-methoxyphenyl]-4-(3-hydroxypropyl)

cyclohexanone: 10% Aqueous HCl (10 ml) was added to a solution of ketal (–)-**12** (150 mg, 0.347 mmol) in THF (3 ml) at 0 °C and the mixture was stirred for 32 h at the same temperature. After neutralization with 15% aqueous NaOH, the mixture was extracted with AcOEt and washed with H₂O. The aqueous layer was extracted with AcOEt and the combined organic solution was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (4:1-3:1 v/v)] to afford ketoalcohol (114 mg, 85 %) as a colorless oil.

$[\alpha]_D^{30} = -47.5^\circ$ (c 2.05, CHCl₃); IR (neat): 3436, 1706, 1607, 1571 cm⁻¹; ¹H-NMR (600 MHz, CDCl₃) δ 7.03 (d, 1H, *J* = 5.5 Hz), 6.87 (d, 1H, *J* = 5.5 Hz), 6.80 (s, 1H), 3.79 (s, 3H), 3.46 (m, 2H), 3.12 (m, 1H), 2.63 (t, 1H, *J* = 8.9 Hz), 2.43 (m, 3H), 2.21 (m, 1H), 2.11 (m, 1H), 1.87 (br.s, 1H), 1.62-1.18 (m, 18H), 1.05 (m, 3H), 0.84 (t, 3H, *J* = 4.6 Hz); ¹³C-NMR (150 MHz, CDCl₃) δ 212.0, 156.9, 149.7, 128.3, 127.3, 118.4, 108.9, 63.0, 55.3, 47.6, 44.7, 43.5, 41.1, 39.6, 37.8, 31.8, 31.1, 30.00, 29.98, 29.0, 24.7, 22.7, 14.1; MS *m/z* : 388 (M⁺), 303 (100%); HRMS Calcd. C₂₅H₄₀O₃: 388.2975. Found: 388.2961.

(1*R*,3*R*,4*R*)-3-[4-(1,1-Dimethylheptyl)-2-methoxyphenyl]-4-(3-

hydroxypropyl)cyclohexanol [(–)-13**]:** LiAlH₄ (25.4 mg, 0.669 mmol) was

added to a solution of (3*R*,4*R*)-3-[4-(1,1-dimethylheptyl)-2-methoxyphenyl]-4-(3-hydroxypropyl)cyclohexanone (105 mg, 0.270 mmol) in Et₂O-THF (5.0ml, 3:2 v/v) at -78 °C and the mixture was stirred for 3h at the same temperature. After warming to room temperature, the mixture was quenched with H₂O and 3*N* aq.NaOH and stirring was continued for 30 min at the same temperature. The mixture was extracted with AcOEt and washed with H₂O. The aqueous layer was extracted with AcOEt and the combined organic solution was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (4:1-3:1 v/v)] to afford diol (-)-**13** (89 mg, 84 %, equatorial alcohol) and its epimer (13 mg, 12 %, axial alcohol) as a colorless oil respectively.

$[\alpha]_D^{30} = -33.6^\circ$ (c 0.42, CHCl₃); IR (neat): 3350, 1610, 1569 cm⁻¹; ¹H-NMR (600 MHz, CDCl₃) δ 7.03 (d, 1H, *J* = 5.0 Hz), 6.86 (d, 1H, *J* = 4.6 Hz), 6.79 (s, 1H), 3.79 (s, 3H), 3.70 (m, 1H), 3.43 (m, 2H), 2.87 (br.s, 1H), 2.05 (m, 1H), 1.97 (m, 2H), 1.60-1.02 (m, 25H), 0.90 (m, 1H), 0.84 (t, 3H, *J* = 4.6 Hz); ¹³C-NMR (150 MHz, CDCl₃) δ 156.8, 148.8, 129.9, 126.1, 118.3, 108.7, 70.9, 63.2, 55.5, 44.6, 43.6, 40.6, 38.5, 37.6, 35.5, 31.6, 30.1, 29.9, 29.7, 28.90, 28.88, 24.6, 22.5, 14.0; MS *m/z* : 390 (M⁺), 390 (100%); HRMS Calcd. C₂₅H₄₂O₃: 390.3132. Found: 390.3137.

CP 55,940 [(-)-3]: 1.6 M *n*-BuLi in hexane (1.25 ml, 2.0 mmol) was added dropwisely to a solution of 1-PrSH (0.300 ml, 3.31 mmol) in hexamethylphosphoric triamide (3.0 ml) at 0 °C and the mixture was stirred for 10 min at the same temperature. The mixture was further stirred for 10 min at room temperature. Then, the whole mixture was added to aryl methyl ether (-)-**13** (12 mg, 0.031 mmol) in another flask at room temperature. The reaction mixture was heated to 100-120 °C and stirred for 5 h at the same temperature. After cooling, the mixture was quenched with saturated aqueous NH₄Cl, extracted with AcOEt and washed with H₂O. The aqueous layer was extracted with AcOEt several times and the combined organic extract was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane-AcOEt (3:2-1:1 v/v)] to afford CP 55,940 [(-)-**3**] (10.4 mg, 90 %) as a white solid.

mp 65-68 °C; $[\alpha]_D^{29} = -28.2^\circ$ (c 0.15, CHCl_3) [an authentic sample purchased from TOCRIS Co., Ltd. $\text{C}_{24}\text{H}_{40}\text{O}_3 \cdot 1/2\text{H}_2\text{O}$: $[\alpha]_D^{33} = -27.7^\circ$ (c 0.20, CHCl_3)]; IR (neat): 3338, 1578 cm^{-1} ; ^1H -NMR (600 MHz, CD_3OD) δ 7.01 (br.s, 1H), 6.74 (br.s, 1H), 3.62 (br.s, 1H), 3.33 (m, 2H), 2.89 (br.s, 1H), 2.01 (m, 3H), 1.55 (m, 3H), 1.40-0.90 (m, 21H), 0.85 (t, 3H, $J = 4.8$ Hz); ^{13}C -NMR (150 MHz, CD_3OD) δ 155.4, 149.4, 129.5, 127.4, 118.4, 114.0, 71.7, 63.6, 45.7, 44.7, 42.4, 39.7, 38.2, 36.4, 32.9, 31.3, 31.1, 30.9, 30.6, 29.5, 25.8, 23.6, 14.4; MS m/z : 376 (M^+), 273 (100%); HRMS Calcd. $\text{C}_{24}\text{H}_{40}\text{O}_3$: 376.2975. Found: 376.2971. These spectral data were identical with those of a commercially available CP 55,940 from TOCRIS Co., Ltd.

3. References

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S-19