Supporting Information
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Synthesis of an Advanced Intermediate toward the hNK-1 Antagonist with the Cyclopentane Core

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Table 1 Asymmetric Hydrolysis of Dimethoxyacetate i

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enzyme</th>
<th>Time</th>
<th>ee (%)</th>
<th>Yield (%)</th>
<th>Conversion (%)</th>
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<td>98</td>
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<td>2</td>
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<td>7</td>
<td>PLE</td>
<td>65 h</td>
<td>45</td>
<td>n.d.</td>
<td>65</td>
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</table>

b Determined by HPLC using Chiralcel OD-H (hexane–i-PrOH = 9:1) after conversion of the product to the corresponding benzoate.

b Isolated yield.

c Determined by ¹H NMR analysis.

d Not determined.

e The S-isomer was obtained.
General.

Infrared (IR) spectra are reported in wave numbers (cm$^{-1}$). The $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were measured in CDCl$_3$ or CD$_3$OD using SiMe$_4$ ($\delta = 0$ ppm) and the center line of CDCl$_3$ triplet ($\delta = 77.1$ ppm) as internal standards, respectively. Signal patterns are indicated as br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants ($J$) are given in hertz (Hz). The following solvents were distilled before use: THF (from Na/benzophenone), Et$_2$O (from Na/benzophenone), and CH$_2$Cl$_2$ (from CaH$_2$). Chromatographic purification was carried out by using silica gel (silica gel 60 from Merck; spherical silica gel 60 N from Kanto, Japan).

(1$R$,4S)-4-Hydroxycyclopent-2-enyl Methoxyacetate ((1$R$)-4).

A solution of the optically active monoacetate (1$R$)-7 (ref. 1) (878 mg, 6.18 mmol), TBSCl (1.12 g, 7.42 mmol), and imidazole (670 mg, 9.84 mmol) in DMF (7 mL) was stirred at room temperature for 2 h, cooled to 0 °C, and diluted with saturated NaHCO$_3$ with vigorous stirring. The mixture was extracted with hexane/Et$_2$O (1 : 1) four times, and the combined extracts were dried over MgSO$_4$ and concentrated to afford the silyl ether 8, which was used for the next reaction without further purification. The $^1$H NMR spectrum of the crude product was identical with that reported (ref. 2).

A mixture of the above silyl ether and LiOH·H$_2$O (1.30 g, 30.9 mmol) in THF (6 mL), MeOH (2 mL), and H$_2$O (2 mL) was stirred at room temperature for 40 min and diluted with saturated NH$_4$Cl with vigorous stirring. The mixture was extracted with EtOAc four times. The combined extracts were dried over MgSO$_4$ and concentrated to leave alcohol 9, which was used for the next reaction without further purification. The $^1$H NMR spectrum of

the crude product was identical with that reported (ref. 3).

To an ice-cold solution of the above alcohol and pyridine (1.50 mL, 18.5 mmol) in CH$_2$Cl$_2$ (12 mL) was added MeOCH$_2$COCl (0.85 mL, 9.27 mmol). The resulting mixture was stirred at room temperature for 1 h, cooled to 0 °C, and diluted with saturated NaHCO$_3$ with vigorous stirring. The organic and aqueous layers were separated and the aqueous layer was extracted with EtOAc three times. The combined extracts were dried over MgSO$_4$ and concentrated to leave the TBS ether of (1R)-4, which was used for the next reaction without further purification.

To a solution of the above ester in THF (7 mL) was added a solution of TBAF (18.5 mL, 1.0 M in THF, 18.5 mmol). The solution was stirred at room temperature for 90 min, cooled to 0 °C, and diluted with saturated NH$_4$Cl with vigorous stirring. The mixture was extracted with EtOAc four times. The combined extracts were dried over MgSO$_4$ and concentrated to afford an residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to give (1R)-4 (776 mg, 73% overall yield, 91% ee by HPLC analysis of the derived benzoate with a chiral stationary phase column (Chiralcel OD-H)): $[\alpha]_D^{24} +62$ (c 0.286, CHCl$_3$).

![Chemical Reaction](image1)

**1S,2R)-2-(4-Fluorophenyl)-3-cyclopenten-1-ol (5).**

To an ice-cold solution of $p$-fluoriodobenzene (2.03 mL, 17.6 mmol) in Et$_2$O (15 mL) was added $n$-BuLi (8.82 mL, 2.0 M in hexane, 17.6 mmol) dropwise. After 30 min at 0 °C, a solution of ZnBr$_2$ (40 mL, 0.45 M in THF, 17.6 mmol), CuCl (130 mg, 1.31 mmol), and a solution of (1R)-4 (91% ee, 760 mg, 4.41 mmol) in THF (5 mL) were added to it, each after 10 min interval. The mixture was stirred at room temperature for 11 h and then diluted with saturated NH$_4$Cl with vigorous stirring. The mixture was extracted with EtOAc four times, and the organic layers were dried over MgSO$_4$ and concentrated to afford a residual oil, which was a mixture of alcohol 5 and its methoxycetate in 10:1 by $^1$H NMR spectroscopy. The residue was treated with LiOH·H$_2$O (925 mg, 22.0 mmol) in THF/MeOH/H$_2$O (10 mL, 3:1:1) at room temperature to hydrolyze the ester. After 1 h, the mixture was diluted with

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saturated NH$_4$Cl and the resulting mixture was extracted with EtOAc four times. The combined layers were dried over MgSO$_4$ and concentrated to afford a residue, which was purified by chromatography on silica gel (hexane/EtOAc = 9:1 to 4:1) to give 5 (664 mg, 84%): $[\alpha]_{D}^{26}$ +177 (c 0.60, CHCl$_3$); IR (neat) 3338, 1605, 1507, 829 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.82 (d, $J$ = 4 Hz, 1 H), 2.37 (dm, $J$ = 17 Hz, 1 H), 2.80 (ddm, $J$ = 17, 6.5 Hz, 1 H), 3.75 (br s, 1 H), 4.16–4.30 (m, 1 H), 5.76 (dq, $J$ = 6, 2 Hz, 1 H), 5.90 (dq, $J$ = 6, 2 Hz 1 H), 6.98 (t, $J$ = 8 Hz, 2 H), 7.14 (dd, $J$ = 8 Hz, 2 H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 41.2, 59.7, 80.8, 115.2 (d, $J$ = 2 Hz), 128.7 (d, $J$ = 8 Hz), 129.7, 132.1, 138.3 (d, $J$ = 3 Hz), 161.7 (d, $J$ = 243 Hz). The spectral data were identical with those reported previously (ref 4).

![Chemical structure](image)

(1S,2R,3S,4R)-2-(4-Fluorophenyl)-3,4-epoxycyclopentan-1-ol (6a).

To an ice-cold mixture of alcohol 5 (664 mg, 3.73 mmol) and NaHCO$_3$ (1.25g, 14.9 mmol) in CH$_2$Cl$_2$ (35 mL) was added m-CPBA (1.67 g, 77% purity, 7.45 mmol) in portions. The mixture was vigorously stirred with slow warming to room temperature. After 6 h of stirring, Me$_2$S (0.44 mL, 6.00 mmol) was added to the mixture. After 10 min at room temperature, the mixture was diluted with saturated NaHCO$_3$ and CH$_2$Cl$_2$. The layers were separated, and the aqeous layer was extracted with EtOAc three times. The combined organic layers were dried over MgSO$_4$ and concentrated to afford a mixture of epoxide 6a and the diastereoisomer 10 in 80 : 20 by $^1$H NMR spectroscopy. The mixture was subjected to chromatography on silica gel (hexane/EtOAc = 4:1) to isolate epoxide 6 (519 mg, 72%): $[\alpha]_{D}^{25}$ +82 (c 1.66, CHCl$_3$); IR (neat) 3406, 1607, 1511, 831 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 2.13–2.24 (m, 2 H), 2.61 (d, $J$ = 12 Hz, 1 H), 3.44 (s, 1 H), 3.74 (br s, 1 H), 3.89 (br s, 1 H), 3.88–3.95 (m, 1 H), 7.02 (tm, $J$ = 8.5 Hz, 2 H), 7.07–7.16 (m, 2 H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 36.0, 54.2, 58.4, 60.5, 77.1, 115.8 (d, $J$ = 21 Hz), 128.9 (d, $J$ = 8 Hz), 134.3 (d, $J$ = 3 Hz), 161.8 (d, $J$ = 244 Hz).

**Diastereoisomer 10:** $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.73 (d, $J$ = 4 Hz, 1 H), 1.82 (ddd, $J$ = 14, 11, 1 Hz, 1 H), 2.68 (dd, $J$ = 14, 7.5 Hz, 1 H), 2.96 (d, $J$ = 7.5 Hz, 1 H), 3.53 (br s, 1 H), 3.64 (br s, 1 H), 3.85–4.01 (m, 1 H), 7.04 (t, $J$ = 8.5 Hz, 2 H), 7.36–7.46 (m, 2 H).

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(1S,2S,3S,4R)-1-(tert-Butyldimethylsilyloxy)-2-(4-fluorophenyl)-3,4-epoxycyclopentane (6b).

To an ice-cold solution of epoxide 6a (82.3 mg, 0.42 mmol) and imidazole (115 mg, 1.69 mmol) in DMF (0.5 mL) was added TBSCl (130 mg, 0.86 mmol). The solution was stirred at room temperature for 3 h and diluted with saturated NaHCO₃ with vigorous stirring. The resulting mixture was extracted with hexane/Et₂O (1:1) four times. The combined extracts were dried over MgSO₄ and concentrated to give the residue, which was purified by chromatography on silica gel (hexane/EtOAc = 20:1) to afford 6b (109 mg, 83%): [α]D²⁷ +61 (c 0.79, CHCl₃); IR (neat) 1607, 1511, 1083, 836 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ –0.04 (s, 3 H), –0.03 (s, 3 H), 0.85 (s, 9 H), 2.04 (dd, J = 15, 2 Hz, 1 H), 2.28 (ddd, J = 15, 8, 1.5 Hz, 1 H), 3.22 (s, 1 H), 3.46 (d, J = 2 Hz, 1 H), 3.69 (s, 1 H), 4.19 (d, J = 8 Hz, 1 H), 6.97–7.13 (m, 4 H); ¹³C NMR (CDCl₃, 75 MHz) δ –4.7, –4.5, 18.1, 25.9, 38.0, 55.9, 58.7, 61.6, 80.7, 115.7 (d, J = 21 Hz), 129.0 (d, J = 8 Hz), 136.4 (d, J = 3 Hz), 161.8 (d, J = 244 Hz).

(1R,2S,3S)-3-(tert-Butyldimethylsilyloxy)-2-(4-fluorophenyl)cyclopentan-1-ol (11).

To a solution of epoxide 6b (108 mg, 0.35 mmol) in THF (5 mL) was added LiEt₃BH (1.40 mL, 1.01 M in THF, 1.41 mmol). After 1 h at room temperature, saturated NH₄Cl was added to the solution with vigorous stirring. The resulting mixture was stirred for 10 min and extracted with EtOAc four times. The combined layers were dried over MgSO₄ and concentrated to give a residual oil, which was subjected to chromatography on silica gel (hexane/EtOAc = 4:1) to afford 11 (99 mg, 91%): [α]D²⁸ +13.2 (c 0.60, CHCl₃); IR (neat) 3317, 1604, 1511, 837 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ –0.20 (s, 3 H), –0.12 (s, 3 H), 0.79 (s, 9 H), 1.78–2.20 (m, 5 H), 2.90 (t, J = 7 Hz, 1 H), 4.07 (q, J = 6 Hz, 1 H), 4.23 (quint., J = 6 Hz, 1 H), 7.01 (t, J = 8.5 Hz, 2 H), 7.17 (dd, J = 8.5, 5 Hz, 2 H); ¹³C NMR (CDCl₃, 75 MHz) δ –5.0, –4.9, 18.0, 25.7, 31.8, 32.4, 62.4, 77.0, 79.1, 115.3 (d, J = 21 Hz), 129.2 (d, J = 8 Hz), 136.6 (d, J = 3 Hz), 161.8 (d, J = 243 Hz).
(1S,2S,3S)-3-(tert-Butyldimethylsilyloxy)-2-(4-fluorophenyl)cyclopentyl 3,5-Dinitrobenzoate (12).

To an ice-cold solution of 11 (42.2 mg, 0.136 mmol), PPh₃ (71 mg, 0.27 mmol), and 3,5-dinitrobenzoic acid (58 mg, 0.27 mmol) in THF (1 mL) was added DIAD (0.054 mL, 0.27 mmol) and the solution was stirred for 3 h, during which time temperature was raised slowly to room temperature. After the reaction, saturated NaHCO₃ was added to the solution and the resulting mixture was extracted with hexane four times. The combined layers were dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc = 20:1 to 4:1) to afford 12 (59 mg, 86%): \([\alpha]_D^{26} +142 \ (c 1.03, \text{CHCl}_3)\); IR (neat) 1732, 1166, 838 cm⁻¹; \(^1\)H NMR (CDCl₃, 300 MHz) \(\delta\) –0.13 (s, 3 H), –0.02 (s, 3 H), 0.79 (s, 9 H), 1.69–1.85 (m, 1 H), 1.97 (ddt, \(J = 14, 3, 8\) Hz, 1 H), 2.20–2.35 (m, 1 H), 2.45–2.62 (m, 1 H), 3.31 (t, \(J = 7\) Hz, 1 H), 4.64 (q, \(J = 7\) Hz, 1 H), 5.61 (dt, \(J = 7, 4\) Hz, 1 H), 6.99 (t, \(J = 9\) Hz, 2 H), 7.21–7.29 (m, 2 H), 8.88 (d, \(J = 2\) Hz, 2 H), 9.17 (t, \(J = 2\) Hz, 1 H); \(^{13}\)C NMR (CDCl₃, 75 MHz) \(\delta\) –4.8, –4.5, 0.08, 18.0, 25.7, 30.3, 33.0, 57.7, 78.8, 115.2 (d, \(J = 21\) Hz), 122.3, 129.2, 130.8 (d, \(J = 8\) Hz), 133.2 (d, \(J = 3\) Hz), 134.0, 148.6, 161.7, 161.9 (d, \(J = 244\) Hz).

(1R,2S,3S)-3-(tert-Butyldimethylsilyloxy)-2-(4-fluorophenyl)cyclopentanamine (3).

A solution of 12 (194 mg, 0.384 mmol) and Et₃N (0.27 mL, 1.92 mmol) in MeOH (3 mL) was stirred at room temperature for 10 h and diluted with saturated NaHCO₃. The resulting mixture was extracted with EtOAc four times. The combined layers were dried over MgSO₄ and concentrated to give an oil, which was passed through a short silica gel column (hexane/EtOAc = 4:1) to furnish semi-purified alcohol 13: \(^1\)H NMR (300 MHz, CDCl₃) (characteristic signals) \(\delta\) –0.26 (s, 3 H), –0.18 (s, 3 H), 0.68 (s, 9 H), 1.47–1.79 (m, 2 H), 2.08–2.23 (m, 2 H), 2.81–2.89 (m, 1 H), 4.14–4.19 (m, 1 H), 4.42–4.56 (m, 1 H), 6.92
To an ice-cold solution of 13, PPh$_3$ (210 mg, 0.801 mmol), and phthalimide (118 mg, 0.80 mmol) in THF (3 mL) was added DIAD (0.15 mL, 0.76 mmol). The solution was stirred at room temperature for 10 h, and diluted with saturated NaHCO$_3$. The products were extracted four times with hexane. The combined layers were dried over MgSO$_4$ and concentrated to give an oil, which was passed through a short column of silica gel (hexane/EtOAc = 20:1 to 9:1) to afford the corresponding imide 14: $^1$H NMR (300 MHz, CDCl$_3$) (characteristic signals) δ –0.38 (s, 3 H), –0.19 (s, 3 H), 0.79 (s, 9 H), 1.91–2.20 (m, 3 H), 2.38–2.46 (m, 1 H), 3.78–3.87 (m, 1 H), 3.95–4.03 (m, 1 H), 4.71–4.82 (m, 1 H), 6.91 (t, J = 8 Hz, 2 H), 7.17–7.24 (m, 2 H), 7.59–7.69 (m, 2 H), 7.71–7.79 (m, 2 H).

A solution of the above imide in ethanolamine (5 mL) was stirred at 90 °C for 10 h, cooled to room temperature, and diluted with Et$_2$O and saturated NaHCO$_3$. The resulting mixture was extracted with Et$_2$O four times. The combined organic layers were dried over MgSO$_4$ and concentrated to afford a residual oil, which was purified by chromatography on silica gel (CH$_2$Cl$_2$ to THF/CH$_2$Cl$_2$/28% aqueous NH$_3$ = 1:1:0.01) to afford amine 3 (52 mg, 44% from 12): [α]$_D$$^26$ +7.6 (c 0.93, CHCl$_3$); IR (neat) 3276, 3176, 1510, 837 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ –0.30 (s, 3 H), –0.21 (s, 3 H), 0.74 (s, 9 H), 1.46–1.89 (m, 4 H), 1.93–2.18 (m, 2 H), 2.51 (dd, J = 10, 8.5, 1 H), 3.25 (q, J = 8 Hz, 1 H), 4.01 (q, J = 7 Hz, 1 H), 6.99 (t, J = 9 Hz, 2 H), 7.10–7.20 (m, 2 H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ –5.03, –4.98, 18.0, 25.7, 32.3, 32.6, 57.0, 64.1, 79.6, 115.3 (d, J = 21 Hz), 129.4 (d, J = 8 Hz), 137.0 (d, J = 3 Hz), 161.8 (d, J = 242 Hz).

(1S,2S,3S)-3-(tert-Butyldimethylsilyloxy)-2-(4-fluorophenyl)cyclopentanamine (18).

To an ice-cold solution of 11 (73 mg, 0.24 mmol), PPh$_3$ (127 mg, 0.48 mmol), and phthalimide (73 mg, 0.50 mmol) in THF (2 mL) was added DIAD (0.09 mL, 0.46 mmol). The solution was stirred at room temperature for 2 h and diluted with saturated NaHCO$_3$. The resulting mixture was extracted with hexane four times. The combined extracts were dried over MgSO$_4$ and concentrated to leave an oil, which was purified by chromatography on silica gel (hexane/EtOAc = 20:1 to 4:1) to give the corresponding imide 17: $^1$H NMR (300 MHz, CDCl$_3$) (characteristic signals) δ –0.50 (s, 3 H), 0.03 (s, 3 H), 0.77 (s, 9
H), 1.63–1.77 (m, 1 H), 2.21–2.47 (m, 3 H), 3.35 (t, $J = 7$ Hz, 1 H), 4.96–5.07 (m, 1 H),
6.77 (t, $J = 8$ Hz, 2 H), 7.02–7.12 (m, 2 H), 7.58–7.69 (m, 4 H).

A solution of the above imide in ethanolamine (2 mL) was heated to 90 °C for 12 h, cooled to room temperature, and diluted with saturated NaHCO₃. After extraction with Et₂O four times, the combined organic layers were dried over MgSO₄ and concentrated to afford a residual oil, which was purified by chromatography on silica gel (CH₂Cl₂ to THF/CH₂Cl₂/28% aqueous NH₃ = 1:1:0.01) to afford 18 (49 mg, 67% from 11): $[\alpha]_D^{25} + 82$
(c 0.84, CHCl₃); IR (neat) 3371, 1511, 837 cm⁻¹; $^1$H NMR (CDCl₃, 300 MHz) δ −0.15 (s, 3 H), −0.06 (s, 3 H), 0.76 (s, 9 H), 1.19 (br s, 2 H), 1.38–1.53 (m, 1 H), 1.55–1.75 (m, 1 H), 2.11–2.34 (m, 2 H), 2.98 (t, $J = 7$ Hz, 1 H), 3.55 (q, $J = 5$ Hz, 1 H), 4.55 (q, $J = 7$ Hz, 1 H), 7.00 (t, $J = 8$ Hz, 2 H), 7.14–7.24 (m, 2 H); $^{13}$C NMR (CDCl₃, 75 MHz) δ −4.8, −4.5, 18.0, 25.8, 32.6, 33.1, 54.2, 59.1, 77.2, 114.9 (d, $J = 21$ Hz), 130.6 (d, $J = 7$ Hz), 135.2 (d, $J = 3$ Hz), 161.7 (d, $J = 243$ Hz).