Supporting Information

Discovery of Potent Formyl Peptide Receptor 2 (FPR2) Selective Agonist for the Treatment of Heart Failure

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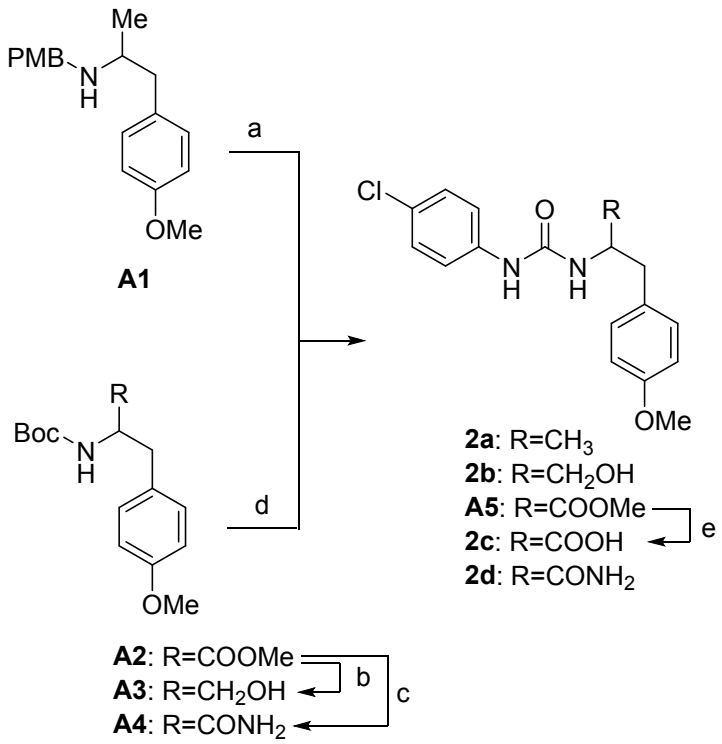
1. Synthesis

Melting points were measured on an OptiMelt automated meltiong point system MPA100 without correction. Infrared spectra (IR) were recorded with a Perkin Elmer Spectrum 100 spectrometer. Measurements of mass spectra (MS) and high resolution MS (HRMS) were performed with a JEOL JMS SX-102A or a JEOL JMS-T100LP mass spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured with a JEOL JMN-EX400 (400 MHz) or a JEOL JMN-ECA-400 (400 MHz) spectrometer. The chemical shifts are expressed in parts per million (δ value) downfield from tetramethylsilane, using tetramethylsilane ($\delta = 0$) and/or residual solvents such as chloroform (δ = 7.26) as an internal standard. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br; broad peak. Specific optical rotations were measured on a JASCO P-1000 polarimeter. Purity data were collected by an Agilent 1100 HPLC with Agilent G1315B diode array detector. The column was used was a RP-AQUA (50 mm × 2.1 mm i.d., 2.6 μm, ChromaNik Technologies Inc., Japan) with a temperature of 45 °C and a flow rate of 0.5 mL/min. Mobile phase A and B were a mixture of 0.05% formic acid in water, and 0.05% formic acid in MeCN, respectively. The ratio of mobile phase was increased lineally from 5% to 95% over 5 min, 95% over the next 3 min. Column chromatography was carried out with silica gel [silica gel 60 (Kanto)] as an absorbent. Merck precoated thin layer chromatography (TLC) plates (silica gel 60 F_{254}, 0.25 mm, Art 5715) were used for the TLC analysis.

a. Synthesis of Acyclic Urea Derivatives 3

Scheme A[a].



All compounds are racemate

[a]Reagents and conditions: (a) (1) **A1** 10% Pd−C, AcOH-MeOH; (2) 4-chlorophenyl isocyanate, THF, 46% (two steps for **2a**); (b) **A2**, $LiAlH_4$, THF, 39%; (c) **A2**, 7 mol/L NH_3 in MeOH, 100%; (d) (1) **A2**, **A3** or **A4**, 4 mol/L HCl in AcOEt; (2) 4-chlorophenyl isocyanate, THF, 73% (two steps for **A5**), 73% (two steps for **2b**), 72% (two steps for **2d**); (e) **A5**, 1 mol/L NaOH, THF−MeOH, 96% (for **2c**).

1-(4-Chlorophenyl)-3-[1-(4-methoxyphenyl)propan-2-yl]urea (2a). A suspension of **A1**[1] (300 mg, 1.05 mmol), 10% Pd−C (30.0 mg), acetic acid (2 mL), and MeOH (2 mL) was stirred at 60 °C for 5 h under H_2 atmosphere (balloon). After the insoluble materials were filtered off, the filtrate was concentrated in vacuo. To a solution of the residue in THF (2 mL), was added a solution of 4-chlorophenyl isocyanate (154 mg, 1.00 mmol) in THF (1 mL), the whole mixture was stirred at room temperature for 10 min, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 4:1) of the residue gave **2a** (147 mg, 44%) as a white powder. Mp: 168−169 °C. ^{1}H NMR (DMSO−d_6) δ: 1.03 (d, J = 6.7 Hz, 3H), 2.59 (dd, J = 13.3, 7.3 Hz, 1H), 2.71 (dd, J = 13.3, 6.1 Hz, 1H), 3.72 (s, 3H), 3.81−3.88 (m, 1H), 6.03 (d, J = 7.9 Hz, 1H), 6.84−6.88 (m, 2H), 7.10−7.14 (m, 2H), 7.22−7.26 (m, 2H), 7.37−7.41 (m, 2H), 8.47 (s, 1H). MS (ESI$^+$) *m/z*: 319 (M^+ + H). HRMS (ESI$^+$) for $C_{17}H_{20}ClN_2O_2$ (M^+ + H): calcd, 319.12133; found, 319.12113. IR (ATR) cm^{-1}: 3314, 1634. HPLC purity: 99.5%.

tert-Butyl (1-Hydroxy-3-(4-methoxyphenyl)propan-2-yl)carbamate (A3). A solution of **A2**[2] (309 mg, 1.00 mmol) in THF (7 mL) was added dropwise to a suspension of $LiAlH_4$ (114 mg, 3.00 mmol) in THF (7 mL), and the whole mixture was stirred at room temperature for 10 min. After quenching the reaction by adding water and 2 mol/L aqueous NaOH solution, the insoluble materials were filtered off and then concentrated in vacuo. Flash chromatography (hexane/AcOEt

=4:1) of the residue gave **A3** (110 mg, 39%) as a white solid. ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 9H), 2.78 (d, J = 6.7 Hz, 2H), 3.50−3.58 (m, 1H), 3.62−3.70 (m, 1H), 3.79, (s + br, 4H), 4.70 (br, 1H), 6.84 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H).

1-(4-Chlorophenyl)-3-[1-hydroxy-3-(4-methoxyphenyl)propan-2-yl]urea (2b). A suspension of **A3** (108 mg, 0.384 mmol) in 4 mol/L HCl dioxane solution (1.5 mL) was stirred at room temperature for 1 h and then the resulting precipitates were collected by filtration. To a mixture of the collected precipitate in THF (2 mL), was added triethylamine (77.0 mg, 0.761 mmol) and 4-chlorophenyl isocyanate (58.0 mg, 0.378 mmol), the whole mixture was stirred at room temperature for 30 min and then concentrated in vacuo. After dilution of the residue with AcOEt, the whole mixture was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 1:1) of the residue gave **2b** (93.0 mg, 73%) as a white powder. Mp: 168−169 ℃. ^{1}H NMR (DMSO−d_6) δ: 2.62 (dd, J = 13.3, 7.3 Hz, 1H), 2.76 (dd, J = 13.9, 6.7 Hz, 1H), 3.29−3.39 (m, 2H), 3.71 (s, 3H), 3.73−3.78 (m, 1H), 4.86 (t, J = 5.4 Hz, 1H), 6.08 (d, J = 8.5 Hz, 1H), 6.83−6.87 (m, 2H), 7.12−7.16 (m, 2H), 7.22−7.26 (m, 2H), 7.36−7.40 (m, 2H), 8.62 (s, 1H). MS (ESI$^+$) *m/z*: 335 (M^+ + H). HRMS (ESI$^+$) for $C_{17}H_{20}ClN_2O_3$ (M^+ + H): calcd, 335.11624; found, 335.11584. IR (ATR) cm^{-1}: 3412, 3338, 1621. HPLC purity: 99.8%.

Methyl 2-[3-(4-Chlorophenyl)ureido]-3-(4-methoxyphenyl)propanoate (A5). To a solution of **A2** (1.00 g, 3.23 mmol) in AcOEt (3.2 mL), 4 mol/L HCl AcOEt solution (3.2 mL, 12.8 mmol) was added, and the whole mixture was stirred at room temperature for 4.5 h. The resulting mixture was adjusted to pH 9 by addition of saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with AcOEt. The extract was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. To a solution of the residue in THF (8 mL), 4-chlorophenyl isocyanate (0.41 mL, 3.23 mmol) was added; the whole mixture was stirred at room temperature for 50 min and then concentrated in vacuo. Trituration of the residue with diisopropyl ether gave **A5** (1.14 g, 97%) as a white solid.

^{1}H NMR (DMSO−d_6) δ: 2.90 (dd, J = 13.9, 7.3 Hz, 1H), 2.97 (dd, J = 13.9, 5.5 Hz, 1H), 3.63 (s, 3H), 3.71 (s, 3H), 4.41−4.49 (m, 1H), 6.44 (d, J = 7.9 Hz, 1H), 6.85 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 9.1 Hz, 2H), 7.37 (d, J = 9.1 Hz, 2H), 8.81 (s, 1H).

2-[3-(4-Chlorophenyl)ureido]-3-(4-methoxyphenyl)propanoic Acid (2c).

To a solution of **A5** (1.30 g, 3.58 mmol) in MeOH (3.6 mL) and THF (3.6 mL), 2 mol/L aqueous NaOH solution (3.60 mL, 7.20 mmol) was added, the whole mixture was stirred at room temperature for 20 h. After addition of water, the resulting mixture was washed with AcOEt and adjusted to acidic by addition of citric acid aqueous solution, and then extracted with AcOEt. The extract was washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo to give **2c** (1,19 g, 96%) as a white powder. Mp: 171−173 ℃. ^{1}H NMR (DMSO−d_6) δ: 2.89 (dd, J = 13.9, 7.3 Hz, 1H), 3.01 (dd, J = 13.9, 4.8 Hz, 1H), 3.72 (s, 3H), 4.37−4.42 (m, 1H), 6.32 (d, J = 8.5 Hz, 1H), 6.84−6.88 (m, 2H), 7.10−7.13 (m, 2H), 7.23−7.27 (m, 2H), 7.36−7.40 (m, 2H), 8.83 (s, 1H), 12.8 (s, 1H). MS (ESI$^+$) *m/z*: 349 (M^+ + H). HRMS (ESI$^+$) for $C_{17}H_{18}ClN_2O_4$

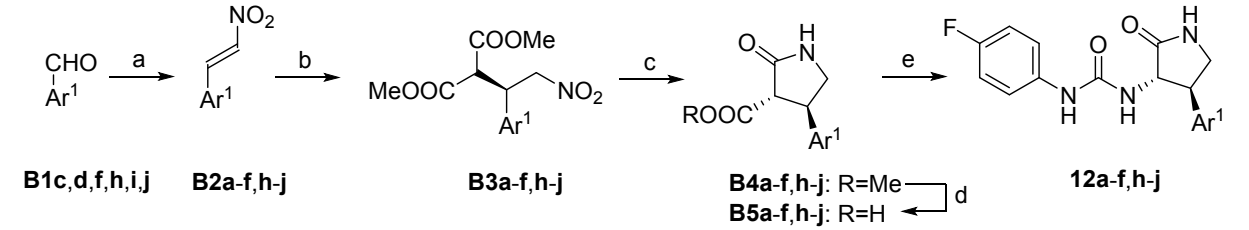
(M^+ + H): calcd, 349.09551; found, 349.09558. IR (ATR) cm^{-1}: 3378, 1717, 1646. HPLC purity: 99.9%.

tert-Butyl [1-Amino-3-(4-methoxyphenyl)-1-oxopropan-2-yl]carbamate (A4). A mixture of **A2** (1.43 g, 4.63 mmol) and 7 mol/L ammonia MeOH solution (15 mL) was stirred at room temperature for 4 days. The resulting mixture was concentrated in vacuo to give **A4** (1.36 g, 100%) as a white solid. Compound **A4** used for next step without further purification. ^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 9H), 2.95−3.08 (m, 2H), 3.79 (s, 3H), 4.30 (br, 1H), 5.03 (br, 1H), 5.32 (br, 1H), 5.72 (br, 1H), 6.85 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H).

2-[3-(4-Chlorophenyl)ureido]-3-(4-methoxyphenyl)propanamide (2d). To a mixture of **A4** (200 mg, 0.679 mmol) and AcOEt (2.6 mL), 4 mol/L HCl AcOEt solution (1.3 mL) was added, and the whole mixture was stirred at room temperature for 5 h, and then concentrated in vacuo. To a solution of the residue in THF (5 mL), triethylamine (206 mg, 2.04 mmol) and 4-chlorophenyl isocyanate (104 mg, 0.677 mmol) were added, and the whole mixture was stirred at room temperature for 30 min, and then concentrated in vacuo. After quenching the reaction by adding water, the resulting mixture was extracted with AcOEt. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (AcOEt) of the residue gave **2d** (170 mg, 72%) as a white powder. Mp: 201−204 °C. ^{1}H NMR (DMSO−d_6) δ: 2.77 (dd, J = 13.9, 7.9 Hz, 1H), 2.94 (dd, J = 13.9, 5.4 Hz, 1H), 3.71 (s, 3H), 4.35−4.40 (m, 1H), 6.27 (d, J = 8.5 Hz, 1H), 6.81−6.85 (m, 2H), 7.09−7.13 (m, 3H), 7.22−7.26 (m, 2H), 7.35−7.39 (m, 2H), 7.56 (s, 1H), 8.82 (s, 1H). MS (ESI^+) *m/z*: 348 (M^+ + H). HRMS (ESI^+) for $C_{17}H_{19}ClN_3O_3$ (M^+ + H): calcd, 348.11149; found, 348.11181. IR (ATR) cm^{-1}: 3432, 3286, 1670, 1654. HPLC purity: 99.8%.

b. Synthesis of Ar^1-substitued Pyrrolidinone Urea Derivatives 12

Scheme B[a]



a: Ar^1= 2-F-4-OMe-Ph
b: Ar^1= 3-F-4-OMe-Ph
c: Ar^1=2-Cl-4-OMe-Ph
d: Ar^1=2-Me-4-OMe-Ph
e: Ar^1=2-F-4-Cl-Ph
f: Ar^1=2,5-diF-4-OMe-Ph
h: Ar^1=3-F-5-OMe-2-pyridyl
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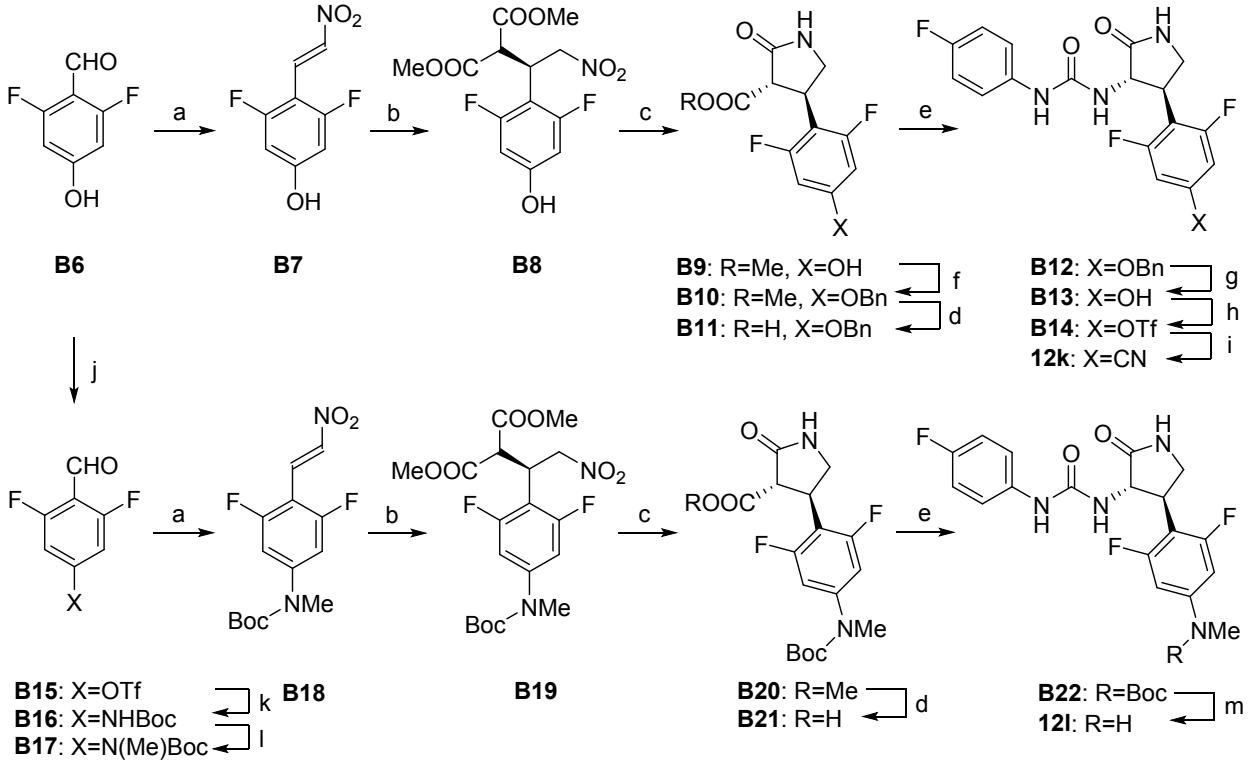
j: Ar^1=2,6-diF-4-Et-Ph



[a]Reagents and conditions: (a) 2-Hydroxyethylammonium formate, $MeNO_2$, 94% (for **B2c**), 79% (for **B2d**), 87% (for **B2f**), 63% (for **B2h**), 94% (for **B2i**), 71% (for **B2j**), 91% (for **B7**), 86% (for **B18**); (b) dimethyl malonate, Ni(II)-bis[(*S*,*S*)-*N*,*N*'-dibenzylcyclohexane-1,2-diamine]bromide (3 mol%), toluene, 72% (for **B3a**), 76% (for **B3b**), 98% (for **B3c**), 93% (for **B3d**), 93% (for **B3e**), 98% (for **B3f**), 89% (for **B3h**), 92% (for **B3i**), 99% (for **B3j**), 96% (for **B8**), 96% (for **B19**); (c) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, 75% (for **B4a**), 93% (for **B4b**), 74% (for **B4c**), 83% (for **B4d**), 100% (for **B4e**), 100% (for **B4f**), 85% (for **B4h**), 100% (for **B4i**), 100% (for **B4j**), 70% (for **B9**), 86% (for **B20**); (d) 1mol /L NaOH aq., MeOH, 61% (for **B5a**), 67% (for **B5b**), 76% (for **B5c**), 100% (for **B5d**), 50% (for **B5e**), 80% (for **B5f**), 100% (for **B5h**), 83% (for **B5i**), 81% (for **B5j**), 80% (for

B11), 95% (for **B21**); (e) DPPA, Et_3N, toluene then 4-fluoroaniline, 45% (for **12a**), 45% (for **12b**), 50% (for **12c**), 24% (for **12d**), 42% (for **12e**), 80% (for **12f**), 38% (for **12h**), 16% (for **12i**), 60% (for **12j**), 80% (for **B12**), 80% (for **B22**); (f) BnBr, K_2CO_3, DMF, 97% (for **B10**); (g) H_2, 10%Pd−C, EtOH, 98% (for **B13**); (h) Tf_2O, pyridine, CH_2Cl_2, 78% (for **B14**); (i) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 89% (for **12k**); (j) Tf_2O, pyridine, CH_2Cl_2, 80% (for **B15**); (k) $BocNH_2$, $Pd_2(dba)_3$, Xanthophos, Cs_2CO_3, toluene, 42% (for **B16**); (l) MeI, NaH, DMF, 64% (for **B17**); (m) TFA, 47% (for **12l**).

(*E*)-2-Chloro-4-methoxy-1-(2-nitrovinyl)benzene (B2c). Nitromethane (314 μL, 5.86 mmol) was added to a mixture of **B1c** (1.00g, 5.86 mmol) and 2-hydroxyethylammonium formate[3] (3.10g, 29.3 mmol), the whole mixture was stirred at room temperature for 6 h. After addition of water (10 mL), and then resulting precipitates were collected by filtration. The filtered precipitates were washed with water and dried in vacuo to give **B2c** (1.18g, 94%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ: 3.87 (s, 3H), 6.87 (dd, J = 8.5, 2.4 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 13.3 Hz, 1H), 8.38 (d, J = 13.9 Hz, 1H). MS (FI$^+$) *m/z*: 213 (M$^+$). HRMS (FI$^+$) for $C_9H_8ClNO_3$ (M$^+$): calcd, 213.01927; found, 213.01895. IR (ATR) cm^{-1}: 1625, 1594.

(*E*)-4-Methoxy-2-methyl-1-(2-nitrovinyl)benzene (B2d). The compound **B2d** (2.03 g, 79%) was prepared from **B1d** (2.00 g, 13.3 mmol) by the same method as that used for **B2c**. Yellow solid. ^{1}H NMR ($CDCl_3$) δ: 2.47 (s, 3H), 3.85 (s, 3H), 6.77−6.80 (m, 2H), 7.46−7.52 (m, 2H), 8.27 (d, J = 13.3 Hz, 1H). MS (EI$^+$) *m/z*: 193 (M$^+$). IR (ATR) cm^{-1}:1594.

(*E*)-2,5-Difluoro-4-methoxy-(2-nitrovinyl)benzene (B2f). The compound **B2f** (1.20 g, 87%) was prepared from **B1f** (1.10 g, 6.39 mmol) by the same method as that used for **B2c**. Brown solid. ^{1}H NMR ($CDCl_3$) δ: 3.95 (s, 3H), 6.79 (dd, J = 11.0, 6.7 Hz, 1H), 7.21 (dd, J = 11.0, 6.7 Hz, 1H), 7.61 (d, J = 13.4 Hz, 1H), 7.98 (d, J = 14.1 Hz, 1H). MS (EI$^+$) *m/z*: 215 (M$^+$). HRMS (EI$^+$) for $C_9H_7F_2NO_3$ (M$^+$): calcd, 215.03940; found, 215.03948. IR (ATR) cm^{-1}: 1629, 1495.

(*E*)-3-Fluoro-5-methoxy-2-(2-nitrovinyl)pyridine (B2h). The compound **B2h** (460 mg, 63%) was prepared from **B1h**[4] (570 mg, 3.67 mmol) by the same method as that used for **B2c**. Yellow oil. ^{1}H NMR ($CDCl_3$) δ: 3.93 (s, 3H), 6.98 (dd, J = 11.0, 2.4 Hz, 1H), 7.93 (d, J = 13.4 Hz, 1H), 8.13 (d, J = 12.8, 1.2 Hz, 1H), 8.23 (dd, J = 2.4, 1.2 Hz, 1H). MS (ESI$^+$) *m/z*: 199 (M$^+$ + H). HRMS (ESI$^+$) for $C_8H_8FN_2O_3$ (M$^+$ + H): calcd, 199.05190; found, 199.05111. IR (ATR) cm^{-1}: 1640, 1597, 1516.

(*E*)-4-Ethoxy-2.6-difluoro-(2-nitrovinyl)benzene (B2i). The compound **B2i** (725 mg, 94%) was prepared from **B1i**[5] (626 mg, 3.36 mmol) by the same method as that used for **B2c**. Pale brown solid. ^{1}H NMR ($CDCl_3$) δ: 1.45 (t, J = 7.3 Hz, 3H), 4.07 (q, J = 7.3 Hz, 2H), 6.54 (d, J = 10.4 Hz, 2H), 7.76 (d, J = 14.1 Hz, 1H), 8.11 (d, J = 13.4 Hz, 1H). MS (ESI$^+$) *m/z*: 230 (M$^+$ + H). HRMS (ESI$^+$) for $C_{10}H_{10}F_2NO_3$ (M$^+$ + H): calcd, 230.06287; found, 230.06346. IR (ATR) cm^{-1}: 1629, 1317, 1152.

(*E*)-4-Ethyl-2.6-difluoro-(2-nitrovinyl)benzene (B2j). The compound **B2j** (890 mg, 71%) was prepared from **B1j**[5] (1000 mg, 5.87 mmol) by the same method as that used for **B2c**. Yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.26 (t, J = 7.3 Hz, 3H), 2.69 (q, J = 7.3 Hz, 2H), 6.86 (d, J = 9.8 Hz, 2H),

7.82 (d, J = 13.4 Hz, 1H), 8.13 (d, J = 14.1 Hz, 1H). MS (EI$^+$) *m/z*: 213 (M$^+$). HRMS (EI$^+$) for $C_{10}H_9F_2NO_2$ (M$^+$): calcd, 213.06013; found, 213.06038. IR (ATR) cm^{-1}: 1631, 1521, 1343.

Dimethyl (*R*)-[1-(2-Fluoro-4-methoxyphenyl)-2-nitroethyl]malonate (B3a). To a solution of **B2a**[6] (960 mg, 4.87 mmol) in toluene (10 mL) was added dimethyl malonate (0.668 mL, 5.84 mmol) and nickel(II)-bis[(*S*,*S*)-*N*,*N*'-dibenzylcyclohexan-1,2-diamine]bromide (118 mg, 0.147 mmol), and the whole mixture was stirred at room temperature for 51 h and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 9:1 → AcOEt) of the residue gave **B3a** (1150 mg, 72%). ^{1}H NMR ($CDCl_3$) δ: 3.57 (s, 3H), 3.77 (s, 6H), 3.96 (d, J = 9.7 Hz, 1H), 4.33−4.39 (m, 1H), 4.89 (d, J = 6.7 Hz, 2H), 6.59−6.64 (m, 2H), 7.11 (t, J = 9.1 Hz, 1H). MS (FD$^+$) *m/z*: 329 (M$^+$). HRMS (FD$^+$) for $C_{14}H_{16}FNO_7$ (M$^+$): calcd, 329.09108; found, 329.09128. IR (ATR) cm^{-1}: 1729, 1552.

Dimethyl (*R*)-[1-(3-Fluoro-4-methoxyphenyl)-2-nitroethyl]malonate (B3b). The compound **B3b** (885 mg, 76%) was prepared from **B2b**[7] (700 mg, 3.55 mmol) by the same method as that used for **B3a**. ^{1}H NMR ($CDCl_3$) δ: 3.61 (s, 3H), 3.77 (s, 3H), 3.81 (d, J = 9.1 Hz, 1H), 3.86 (s, 3H), 4.14−4.20 (m, 1H), 4.79−4.91 (m, 2H), 6.87−6.99 (m, 3H). MS (FI$^+$) *m/z*: 329 (M$^+$). HRMS (FI$^+$) for $C_{14}H_{16}FNO_7$ (M$^+$): calcd, 329.09108; found, 329.09133. IR (ATR) cm^{-1}: 1732, 1555.

Dimethyl (*R*)-[1-(2-Chloro-4-methoxyphenyl)-2-nitroethyl]malonate (B3c). The compound **B3c** (1.60 g, 98%) was prepared from **B2c** (1.00 g, 4.68 mmol) by the same method as that used for **B3a**. Pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 3.64 (s, 3H), 3.74 (s, 3H), 3.78 (s, 3H), 4.08 (d, J = 8.6 Hz, 1H), 4.67 (dt, J = 8.6, 4.3 Hz, 1H), 4.92 (dd, J = 13.4, 4.3 Hz, 1H), 5.07 (dd, J = 13.4, 8.6 Hz, 1H), 6.77 (dd, J = 8.6, 3.1 Hz, 1H), 6.94 (d, J = 3.1 Hz, 1H), 7.14 (d, J = 8.6 Hz, 1H). MS (FI$^+$) *m/z*: 345 (M$^+$). HRMS (FI$^+$) for $C_{14}H_{16}ClNO_7$ (M$^+$): calcd, 345.06153; found, 345.06198. IR (ATR) cm^{-1}: 1733, 1553.

Dimethyl (*R*)-[1-(4-Methoxy-2-methylphenyl)-2-nitroethyl]malonate (B3d). The compound **B3d** (1.05 g, 93%) was prepared from **B2d** (600 mg, 3.11 mmol) by the same method as that used for **B3a**. Yellow oil. ^{1}H NMR ($CDCl_3$) δ: 2.38 (s, 3H), 3.54 (s, 3H), 3.739 (s, 3H), 3.744 (s, 3H), 3.78 (d, J = 9.1 Hz, 1H), 4.48 (dt, J = 9.1, 5.5 Hz, 1H), 4.79 (dd, J = 13.3, 9.1 Hz,1H), 4.85 (dd, J = 12.7, 5.5 Hz, 1H), 6.67 (s, 1H), 6.69 (d, J = 9.2 Hz, 1H), 7.02 (d, J = 9.2 Hz, 1H). MS (FI$^+$) *m/z*: 325 (M$^+$). HRMS (FI$^+$) for $C_{15}H_{19}NO_7$ (M$^+$): calcd, 325.11615; found, 325.11654. IR (ATR) cm^{-1}: 1733, 1553.

Dimethyl (*R*)-[1-(4-Chloro-2-fluorophenyl)-2-nitroethyl]malonate (B3e). The compound **B3e** (767 mg, 93%) was prepared from **B2e**[8] (500 mg, 2.48 mmol) by the same method as that used for **B3a**. White solid. ^{1}H NMR ($CDCl_3$) δ: 3.60 (s, 3H), 3.78 (s, 3H), 3.96 (d, J = 9.7 Hz, 1H), 4.39−4.45 (m, 1H), 4.91 (d, J = 7.3 Hz, 2H), 7.10−7.13 (m, 2H), 7.19 (t, J = 8.5 Hz, 1H). MS (FI$^+$) *m/z*: 333 (M$^+$). HRMS (FI$^+$) for $C_{13}H_{13}ClFNO_6$ (M$^+$): calcd, 333.04154; found, 333.04186. IR (ATR) cm^{-1}: 1752, 1727, 1551.

Dimethyl (*R*)-[1-(2,5-Difluoro-4-methoxyphenyl)-2-nitroethyl]malonate (B3f). The compound **B3f** (1.74 g, 98%) was prepared from **B2f** (1.10 g, 5.11 mmol) by the same method as that used for **B3a**. ^{1}H NMR ($CDCl_3$) δ: 3.61 (s, 3H), 3.78 (s, 3H), 3.86 (s, 3H), 3.92 (d, J = 9.8

Hz, 1H), 4.34 (dt, J = 8.6, 5.5 Hz, 1H), 4.87 (d, J = 8.6 Hz, 1H), 4.88 (d, J = 5.5 Hz, 1H), 6.69 (dd, J = 11.6, 6.7 Hz, 1H), 6.96 (dd, J = 11.0, 7.3 Hz, 1H). MS (FI^+) *m/z*: 347 (M^+). HRMS (FI^+) for $C_{14}H_{15}F_2NO_7$ (M^+): calcd, 347.08166; found, 347.08201. IR (ATR) cm^{-1}: 1734, 1555.

Dimethyl (*R*)-[1-(3-Fluoro-5-methoxypyridin-2-yl)-2-nitroethyl]malonate (B3h). The compound **B3h** (670 mg, 89%) was prepared from **B2h** (450 mg, 2.27 mmol) by the same method as that used for **B3a**. ^1H NMR ($CDCl_3$) δ: 3.66 (s, 3H), 3.76 (s, 3H), 3.84 (s, 3H), 3.98 (d, J = 7.9 Hz, 1H), 4.65 (dt, J = 9.8, 4.3 Hz, 1H), 4.89 (dd, J = 14.1, 4.3 Hz, 1H), 5.09 (dd, J = 14.1, 9.8 Hz, 1H), 6.94 (dd, J = 11.0, 2.4 Hz 1H), 8.05 (d, J = 2.4 Hz, 1H). MS (ESI^+) *m/z*: 331 (M^+ + H). HRMS (ESI^+) for $C_{13}H_{16}FN_2O_7$ (M^+ + H): calcd, 331.09415; found, 331.09438. IR (ATR) cm^{-1}: 1734, 1553.

Dimethyl (*R*)-[1-(4-Ethoxy-2,6-difluorophenyl)-2-nitroethyl]malonate (B3i). The compound **B3i** (1040 mg, 92%) was prepared from **B2i** (720 mg, 3.14 mmol) by the same method as that used for **B3a**. White solid. ^1H NMR ($CDCl_3$) δ: 1.40 (t, J = 7.3 Hz, 3H), 3.57 (s, 3H), 3.80 (s, 3H), 3.92 (d, J = 10.4 Hz, 1H), 3.96 (q, J = 7.3 Hz, 2H), 4.66 (dt, J = 10.4, 4.9 Hz, 1H), 4.81 (dd, J = 12.8, 9.8 Hz, 1H), 4.91 (dd, J = 12.8, 4.9 Hz, 1H), 6.39−6.45 (m, 2H). MS (EI^+) *m/z*: 361 (M^+). HRMS (EI^+) for $C_{15}H_{17}F_2NO_7$ (M^+): calcd, 361.09731; found, 361.09763. IR (ATR) cm^{-1}: 1729, 1552.

Dimethyl (*R*)-[1-(4-Ethyl-2,6-difluorophenyl)-2-nitroethyl]malonate (B3j). The compound **B3j** (1.42 g, 99%) was prepared from **B2j** (880 mg, 4.13 mmol) by the same method as that used for **B3a**. ^1H NMR ($CDCl_3$) δ: 1.20 (t, J = 7.3 Hz, 3H), 2.60 (q, J = 7.3 Hz, 2H), 3.55 (s, 3H), 3.80 (s, 3H), 3.95 (d, J = 10.4 Hz, 1H), 4.72 (dt, J = 10.4, 4.9 Hz, 1H), 4.84 (dd, J = 13,4, 9.8 Hz, 1H), 4.93 (dd, J = 13.4, 4.9 Hz, 1H), 6.70−6.75 (m, 2H). MS (ESI^+) *m/z*: 346 (M^+ + H). HRMS (ESI^+) for $C_{15}H_{18}F_2NO_6$ (M^+ + H): calcd, 346.11022; found, 346.11023. IR (ATR) cm^{-1}: 1731, 1552.

Methyl (3*S*,4*R*)-4-(2-Fluoro-4-methoxyphenyl)-2-oxopyrrolidine-3-carboxylate (B4a). To a mixture of **B3a** (1100 mg, 3.34 mmol) and nickel(II) chloride hexahydrate (794 mg, 3.34 mmol) in MeOH (33 mL) was added portionwise $NaBH_4$ (760 mg, 20.0 mmol) under ice cooling, and the whole mixture was stirred at room temperature for 1 h. After addition of saturated aqueous NH_4Cl solution to the reaction mixture, the whole mixture was extracted with AcOEt. The extract was washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography ($CHCl_3$/MeOH = 98:2 → 80:20) of the residue gave **B4a** (666 mg, 75%). ^1H NMR ($CDCl_3$) δ: 3.44 (t, J = 8.6 Hz, 1H), 3.66 (d, J = 10.4 Hz, 1H), 3.75−3.80 (m, 7H), 4.22 (q, J = 8.6 Hz, 1H), 5.92 (br s, 1H), 6.62−6.69 (m, 2H), 7.15 (t, J = 8.6 Hz, 1H). MS (EI^+) *m/z*: 267 (M^+). HRMS (EI^+) for $C_{13}H_{14}FNO_4$ (M^+): calcd, 267.09069; found, 267.09077. IR (ATR) cm^{-1}: 3244, 1737, 1697.

Methyl (3*S*,4*R*)-4-(3-Fluoro-4-methoxyphenyl)-2-oxopyrrolidine-3-carboxylate (B4b). The compound **B4b** (660 mg, 93%) was prepared from **B3b** (870 mg, 2.64 mmol) by the same method as that used for **B4a**. White solid. ^1H NMR ($CDCl_3$) δ: 3.38 (t, J = 8.6 Hz, 1H), 3.50 (d, J = 9.8 Hz, 1H), 3.76−3.81 (m, 4H), 3.88 (s, 3H), 4.06 (q, J = 8.6 Hz, 1H), 5.94 (br s, 1H), 6.90−7.01 (m, 3H). MS (FI^+) *m/z*: 267 (M^+).

Methyl (3*S*,4*R*)-4-(2-Chloro-4-methoxyphenyl)-2-oxopyrrolidine-3-carboxylate (B4c). The compound **B4c** (970 mg, 74%) was prepared from **B3c** (1.60 g, 4.62 mmol) by the same method as that used for **B4a**. White solid. ^{1}H NMR ($CDCl_3$) δ: 3.67 (d, J = 8.6 Hz, 1H), 3.78−3.80 (m, 7H), 3.89 (t, J = 8.6 Hz, 1H), 4.47 (q, J = 8.6 Hz, 1H), 5.70 (br, 1H), 6.82 (dd, J = 8.6, 2.4 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 7.21 (d, J = 8.6 Hz, 1H). MS (FD$^+$) *m/z*: 283 (M$^+$). HRMS (FD$^+$) for $C_{13}H_{14}ClNO_4$ (M$^+$): calcd, 283.06114; found, 283.06159.

Methyl (3*S*,4*R*)-4-(4-Methoxy-2-methylphenyl)-2-oxopyrrolidine-3-carboxylate (B4d). The compound **B4d** (689 mg, 83%) was prepared from **B3d** (1.02 g, 3.11 mmol) by the same method as that used for **B4a**. White solid. ^{1}H NMR ($CDCl_3$) δ: 2.34 (s, 3H), 3.29 (dd, J = 9.7, 7.9 Hz, 1H), 3.56 (d, J = 9.2 Hz, 1H), 3.75 (s, 3H), 3.76 (s, 3H), 3.75−3.79 (m, 1H), 4.29 (q, J = 7.9 Hz, 1H), 6.00 (br s, 1H), 6.71 (d, J = 3.0 Hz, 1H), 6.74 (dd, J = 8.5, 3.0 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H). MS (ESI$^+$) *m/z*: 264 (M$^+$ + H). HRMS (ESI$^+$) for $C_{14}H_{18}NO_4$ (M$^+$ + H): calcd, 264.12358; found, 264.12302. IR (ATR) cm^{-1}: 3239, 1736, 1698.

Methyl (3*S*,4*R*)-4-(4-Chloro-2-fluorophenyl)-2-oxopyrrolidine-3-carboxylate (B4e). The compound **B4e** (673 mg, 100%) was prepared from **B3e** (750 mg, 2.24 mmol) by the same method as that used for **B4a**. White solid. ^{1}H NMR ($CDCl_3$) δ: 3.44 (t, J = 9.1 Hz, 1H), 3.68 (d, J = 9.7 Hz, 1H), 3.79 (s, 3H), 3.83 (t, J = 9.7 Hz, 1H), 4.26 (q, J = 9.7 Hz, 1H), 6.57 (br s, 1H), 7.10−7.16 (m, 2H), 7.20 (d, J = 7.9 Hz, 1H). MS (ESI$^+$) *m/z*: 272 (M$^+$ + H). HRMS (ESI$^+$) for $C_{12}H_{12}ClFNO_3$ (M$^+$ + H): calcd, 272.04897; found, 272.04971.

Methyl (3*S*,4*R*)-4-(2,5-Difluoro-4-methoxyphenyl)-2-oxopyrrolidine-3-carboxylate (B4f). The compound **B4f** (1.38 g, 96%) was prepared from **B3f** (1.74 g, 5.01 mmol) by the same method as that used for **B4a**. White solid. ^{1}H NMR ($CDCl_3$) δ: 3.42 (t, J = 8.6 Hz, 1H), 3.62 (d, J = 9.8 Hz, 1H), 3.75−3.81 (m, 1H), 3.79 (s, 3H), 3.87 (s, 3H), 4.20 (q, J = 8.6 Hz, 1H), 6.14 (br s, 1H), 6.71 (dd, J = 11.0, 7.3 Hz, 1H), 6.98 (dd, J = 11.0, 7.3 Hz, 1H). MS (EI$^+$) *m/z*: 285 (M$^+$). HRMS (EI$^+$) for $C_{13}H_{13}F_2NO_4$ (M$^+$): calcd, 285.08126; found, 285.08169. IR (ATR) cm^{-1}: 3225, 1736, 1698.

Methyl (3*S*,4*R*)-4-(3-Fluoro-5-methoxypyridin-2-yl)-2-oxopyrrolidine-3-carboxylate (B4h). The compound **B4h** (450 mg, 85%) was prepared from **B3h** (650 mg, 1.97 mmol) by the same method as that used for **B4a**. ^{1}H NMR ($CDCl_3$) δ: 3.53 (t, J = 9.2 Hz, 1H), 3.76−3.82 (m, 4H), 3.86 (s, 3H), 4.04 (d, J = 9.2 Hz, 1H), 4.52 (q, J = 8.6 Hz, 1H), 5.72 (br, 1H), 6.94 (dd, J = 11.0, 2.4 Hz, 1H) 8.11 (d, J = 2.4 Hz, 1H). MS (ESI$^+$) *m/z*: 269 (M$^+$ + H). HRMS (ESI$^+$) for $C_{12}H_{14}FN_2O_4$ (M$^+$ + H): calcd, 269.09376; found, 269.09317. IR (ATR) cm^{-1}: 3245, 1736, 1697.

Methyl (3*S*,4*R*)-4-(4-Ethoxy-2.6-difluorophenyl)-2-oxopyrrolidine-3-carboxylate (B4i). The compound **B4i** (837 mg, quant.) was prepared from **B3i** (925 mg, 2.56 mmol) by the same method as that used for **B4a**. Pale yellow solid. ^{1}H NMR ($CDCl_3$) δ: 1.40 (t, J = 7.3 Hz, 3H), 3.51 (t, J = 9.2 Hz, 1H), 3.67 (t, J = 9.2 Hz, 1H), 3.78 (s, 3H), 3.79 (d, J = 11.0 Hz, 1H), 3.98 (q, J = 7.3 Hz, 2H), 4.46 (q, J = 9.2 Hz, 1H), 6.33 (br, 1H), 6.42−6.48 (m, 2H).

Methyl (3*S*,4*R*)-4-(4-Ethyl-2.6-difluorophenyl)-2-oxopyrrolidine-3-carboxylate (B4j). The compound **B4j** (940 mg, 82%) was prepared from **B3j** (1.40 g, 4.05 mmol) by the same method as that used for **B4a**. White solid. ^{1}H NMR ($CDCl_3$) δ: 1.22 (t, J = 8.0 Hz, 3H), 2.62 (q, J = 8.0 Hz,

2H), 3.53 (t, J = 9.2 Hz, 1H), 3.68 (t, J = 9.2 Hz, 1H), 3.78 (s, 3H), 3.83 (d, J = 9.8 Hz, 1H), 4.52 (q, J = 9.2 Hz, 1H), 6.03 (br s, 1H), 6.75 (d, J = 9.2 Hz, 2H). MS (ESI$^+$) *m/z*: 284 (M^+ + H). HRMS (ESI$^+$) for $C_{14}H_{16}F_2NO_3$ (M^+ + H): calcd, 284.10982; found, 284.10944. IR (ATR) cm^{-1}: 3141, 1743, 1702.

(3*S*,4*R*)-4-(2-Fluoro-4-methoxyphenyl)-2-oxopyrrolidine-3-carboxylic Acid (B5a). To a solution of **B4a** (4.14 g, 15.5 mmol) in MeOH (31 mL) was added 2 mol/L aqueous NaOH solution (15.5 mL, 31.0 mmol), and the whole mixture was stirred at 60 °C for 3 h. After addition of 1 mol/L HCl (40 mL) to the reaction mixture, the whole mixture was extracted with AcOEt (3 × 150 mL). The combined extracts was washed with brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Trituration of the residue with diisopropyl ether gave **B5a** (3.76 g, 96%) as a white solid. ^{1}H NMR (DMSO−d_6) δ: 3.18 (t, J = 9.1 Hz, 1H), 3.48 (d, J = 11.0 Hz, 1H), 3.55 (t, J = 9.2 Hz, 1H), 3.74 (s, 3H), 4.00 (q, J = 9.2 Hz, 1H), 6.76 (dd, J = 8.6, 3.1 Hz, 1H), 6.81 (dd, J = 12.8, 3.1 Hz, 1H), 7.37 (t, J = 8.6 Hz, 1H), 8.10 (s, 1H), 12.7 (br, 1H). MS (ESI$^-$) *m/z*: 252 (M^+ - H). HRMS (ESI$^-$) for $C_{12}H_{11}FNO_4$ (M^+ − H): calcd, 252.06721; found, 252.06751. IR (ATR) cm^{-1}: 3276, 1760, 1731, 1648, 1628.

(3*S*,4*R*)-4-(3-Fluoro-4-methoxyphenyl)-2-oxopyrrolidine-3-carboxylic Acid (B5b). The compound **B5b** (420 mg, 67%) was prepared from **B4b** (660 mg, 2.47 mmol) by the same method as that used for **B5a**. ^{1}H NMR (DMSO−d_6) δ: 3.16 (t, J = 9.7 Hz, 1H), 3.47 (d, J = 10.9 Hz, 1H), 3.54 (t, J = 8.5 Hz, 1H), 3.76−7.84 (m, 4H), 7.06−7.12 (m, 2H), 7.23−7.29 (m, 1H), 8.05 (s, 1H), 12.7 (br s, 1H). MS (ESI$^-$) *m/z*: 252 (M^+ - H). HRMS (ESI$^-$) for $C_{12}H_{11}FNO_4$ (M^+ − H): calcd, 252.06721; found, 252.06713. IR (ATR) cm^{-1}: 3336, 1737, 1653.

(3*S*,4*R*)-4-(2-Chloro-4-methoxyphenyl)-2-oxopyrrolidine-3-carboxylic Acid (B5c). The compound **B5c** (687 mg, 76%) was prepared from **B4c** (950 mg, 3.35 mmol) by the same method as that used for **B5a**. White solid. ^{1}H NMR (DMSO−d_6) δ: 3.11 (t, J = 9.2 Hz, 1H), 3.56−3.61 (m, 2H), 3.75 (s, 3H), 4.20 (q, J = 8.6 Hz, 1H), 6.93 (dd, J = 8.6, 2.4 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 8.10 (s, 1H), 12.7 (br, 1H). MS (ESI$^-$) *m/z*: 268 (M^+ - H). HRMS (ESI$^-$) for $C_{12}H_{11}ClNO_4$ (M^+ − H): calcd, 268.03766; found, 268.03818. IR (ATR) cm^{-1}: 3265, 1690.

(3*S*,4*R*)-4-(4-Methoxy-2-methylphenyl)-2-oxopyrrolidine-3-carboxylic Acid (B5d). The compound **B5d** (689 mg, quant.) was prepared from **B4d** (682 mg, 2.59 mmol) by the same method as that used for **B5a**. White olid. ^{1}H NMR (DMSO−d_6) δ: 2.28 (s, 3H), 3.08 (t, J = 9.1 Hz, 1H), 3.44 (d, J = 10.3 Hz, 1H), 3.55 (t, J = 9.1 Hz, 1H), 3.70 (s, 3H), 4.01 (q, J = 9.1 Hz, 1H), 6.73−6.76 (m, 2H), 7.33 (d, J = 7.9 Hz, 1H), 8.04 (s, 1H), 12.6 (br, 1H). MS (ESI$^+$) *m/z*: 250 (M^+ + H). HRMS (ESI$^+$) for $C_{13}H_{16}NO_4$ (M^+ + H): calcd, 250.10793; found, 250.10712. IR (ATR) cm^{-1}: 3278, 1746, 1705, 1656.

(3*S*,4*R*)-4-(4-Chloro-2-fluorophenyl)-2-oxopyrrolidine-3-carboxylic Acid (B5e). The compound **B5e** (303 mg, 50%) was prepared from **B4e** (640 mg, 2.35 mmol) by the same method as that used for **B5a**. White solid. ^{1}H NMR (DMSO−d_6) δ: 3.21 (t, J = 9.2 Hz, 1H), 3.53 (d, J = 10.4 Hz, 1H), 3.59 (t, J = 9.2 Hz, 1H), 4.06 (q, J = 8.6 Hz, 1H), 7.29 (dd, J = 11.0, 2.4 Hz, 1H),

7.43 (dd, J = 11.0, 2.4 Hz, 1H), 7.53 (t, J = 8.6 Hz, 1H), 8.14 (s, 1H), 12.8 (br, 1H). MS (ESI$^-$) *m/z*: 256 (M^+ - H). HRMS (ESI$^-$) for $C_{11}H_8ClFNO_3$ (M^+ − H): calcd, 256.01767; found, 256.01705. IR (ATR) cm^{-1}: 3296, 1753, 1666.

(3*S*,4*R*)-4-(2,5-Difluoro-4-methoxyphenyl)-2-oxopyrrolidine-3-carboxylic Acid (B5f). The compound **B5f** (1.04 g, 80%) was prepared from **B4f** (1.38 g, 4.83 mmol) by the same method as that used for **B5a**. White solid. ^{1}H NMR (DMSO−d_6) δ: 3.18 (t, J = 9.2 Hz, 1H), 3.48−3.56 (m, 2H), 3.82 (s, 3H), 4.02 (q, J = 9.2 Hz, 1H), 7.10 (dd, J = 12.2, 7.3 Hz, 1H), 7.44 (dd, J = 12.2, 7.3 Hz, 1H), 8.11 (s, 1H), 12.7 (br, 1H). MS (ESI$^+$) *m/z*: 272 (M^+ + H). HRMS (ESI$^+$) for $C_{12}H_{12}F_2NO_4$ (M^+ + H): calcd, 272.07344; found, 272.07377. IR (ATR) cm^{-1}: 3240, 1734, 1656.

(3*S*,4*R*)-4-(3-Fluoro-5-methoxypyridin-2-yl)-2-oxopyrrolidine-3-carboxylic Acid (B5h). The compound **B5h** (417 mg, 100%) was prepared from **B4h** (440 mg, 1.64 mmol) by the same method as that used for **B5a**. Brown solid. ^{1}H NMR (DMSO−d_6) δ: 3.28 (t, J = 9.2 Hz, 1H), 3.62 (t, J = 9.2 Hz, 1H), 3.64 (d, J = 9.2 Hz, 1H), 3.83 (s, 3H), 4.21 (q, J = 9.2 Hz, 1H), 7.44 (dd, J = 11.6, 2.4 Hz, 1H), 8.06 (s, 1H), 8.17 (d, J = 1.8 Hz, 1H), 12.7 (br, 1H). MS (ESI$^-$) *m/z*: 253 (M^+ - H). HRMS (ESI$^-$) for $C_{11}H_{10}FN_2O_4$ (M^+ - H): calcd, 253.06246; found, 253.06204. IR (ATR) cm^{-1}: 3255, 1725, 1649.

(3*S*,4*R*)-4-(4-Ethoxy-2,6-difluorophenyl)-2-oxopyrrolidine-3-carboxylic Acid (B5i). The compound **B5i** (603 mg, 83%) was prepared from **B4i** (837 mg, 2.56 mmol) by the same method as that used for **B5a**. White solid. ^{1}H NMR (DMSO−d_6) δ: 1.29 (t, J = 6.7 Hz, 3H), 3.24 (t, J = 9.2 Hz, 1H), 3.42 (d, J = 9.8 Hz, 1H), 3.56 (t, J = 9.2 Hz, 1H), 4.03 (q, J = 6.7 Hz, 2H), 4.14 (q, J = 9.2 Hz, 1H), 6.74 (d, J = 10.4 Hz, 2H), 8.19 (s, 1H), 12.8 (br, 1H). MS (ESI$^+$) *m/z*: 286 (M^+ + H). HRMS (ESI$^+$) for $C_{13}H_{14}F_2NO_4$ (M^+ + H): calcd, 286.08909; found, 286.09000. IR (ATR) cm^{-1}: 3586, 1727, 1638.

(3*S*,4*R*)-4-(4-Ethyl-2,6-difluorophenyl)-2-oxopyrrolidine-3-carboxylic Acid (B5j). The compound **B5j** (720 mg, 81%) was prepared from **B4j** (940 mg, 3.31 mmol) by the same method as that used for **B5a**. White solid. ^{1}H NMR (DMSO−d_6) δ: 1.15 (t, J = 7.3 Hz, 3H), 2.59 (q, J = 7.3 Hz, 2H), 3.27 (t, J = 9.2 Hz, 1H), 3.46 (d, J = 10.4 Hz, 1H), 3.58 (t, J = 9.2 Hz, 1H), 4.20 (q, J = 9.2 Hz, 1H), 6.99 (d, J = 9.8 Hz, 2H), 8.22 (s, 1H), 12.8 (br, 1H). MS (ESI$^+$) *m/z*: 270 (M^+ + H). HRMS (ESI$^+$) for $C_{13}H_{14}F_2NO_3$ (M^+ + H): calcd, 270.09417; found, 270.09393. IR (ATR) cm^{-1}: 3303, 1756, 1669, 1638.

1-[(3*S*,4*R*)-4-(2-fluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)urea (12a). To a mixture of **B5a** (3.70 g, 14.6 mmol), toluene (73 mL) and MeCN (4.0 mL) was added triethylamine (2,23 mL, 16.1 mmol) and diphenyphosphoryl azide (3.60 mL, 16.1 mmol), and the whole mixture was stirred at room temperature for 3 h and then 90 °C for 20 min. To the reaction mixture was added 4-fluoroaniline (2.80 mL, 29.2 mmol), and the whole mixture was stirred at 90 °C for 3 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. To the residue was added 1 mol/L HCl, and the whole mixture was extracted with AcOEt. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 1:1 → AcOEt → AcOEt/MeOH

= 95:5) of the residue gave **12a** (2.35 g, 45%) as a white amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.17 (t, J = 9.8 Hz, 1H), 3.45 (t, J = 9.2 Hz, 1H), 3.68 (q, J = 9.8 Hz, 1H), 3.73 (s, 3H), 4.57 (dd, J = 11.0, 8.6 Hz, 1H), 6.41 (d, J = 8.6 Hz, 1H), 6.74−6.80 (m, 2H), 7.00−7.05 (m, 2H), 7.32−7.37 (m, 2H), 7.45 (t, J = 9.2 Hz, 1H), 7.95 (s, 1H), 8.59 (s, 1H). MS (ESI$^+$) *m/z*: 362 (M$^+$ + H). HRMS (ESI$^+$) for $C_{18}H_{18}F_2N_3O_3$ (M$^+$ + H): calcd, 362.13162; found, 362.13222. IR (ATR) cm^{-1}: 3315, 1708, 1628. $[\alpha]^{28}_D$ −100 (*c* 0.099, EtOH). HPLC purity 99.7%.

1-[(3*S*,4*R*)-4-(3-fluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)urea (12b). The compound **12b** (192 mg, 45%) was prepared from **B5b** (300 mg, 1.18 mmol) by the same method as that used for **12a**. Pale brown amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.14−3.21 (m, 1H), 3.44−3.52 (m, 2H), 3.80 (s, 3H), 4.49 (t, J = 9.1 Hz, 1H), 6.43 (d, J = 9.1 Hz, 1H), 7.01−7.15 (m, 4H), 7.32 (dd, J = 13.3, 2.4 Hz, 1H), 7.34−7.39 (m, 2H), 7.93 (s, 1H), 8.59 (s, 1H). MS (ESI$^+$) *m/z*: 362 (M$^+$ + H). HRMS (ESI$^+$) for $C_{18}H_{18}F_2N_3O_3$ (M$^+$ + H): calcd, 362.13162; found, 362.13176. IR (ATR) cm^{-1}: 3299, 1667. $[\alpha]^{28}_D$ −128 (*c* 0.102, EtOH). HPLC purity 95.6%.

1-[(3*S*,4*R*)-4-(2-chloro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)urea (12c). The compound **12c** (280 mg, 50%) was prepared from **B5c** (400 mg, 1.48 mmol) by the same method as that used for **12a**. White amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.08 (t, J = 9.7 Hz, 1H), 3.49−3.54 (m, 1H), 3.75 (s, 3H), 3.92 (q, J = 9.7 Hz, 1H) 4.67 (dd, J = 11.5, 9.1 Hz, 1H), 6.43 (d, J = 8.5 Hz, 1H), 6.94 (dd, J = 8.5, 2.4 Hz, 1H), 7.01−7.07 (m, 3H), 7.33−7.39 (m, 2H), 7.60 (d, J = 8.5 Hz, 1H), 7.95 (s, 1H), 8.58 (s, 1H). MS (ESI$^+$) *m/z*: 378 (M$^+$ + H). HRMS (ESI$^+$) for $C_{18}H_{18}ClFN_3O_3$ (M$^+$ + H): calcd, 378.10207; found, 378.10192. IR (ATR) cm^{-1}: 3295, 1708, 1656. $[\alpha]^{26}_D$ −87.4 (*c* 0.219, EtOH). HPLC purity 99.2%.

1-(4-Fluorophenyl)-3-[(3*S*,4*R*)-4-(4-methoxy-2-methylphenyl)-2-oxopyrrolidin-3-yl]urea (12d). The compound **12d** (140 mg, 24%) was prepared from **B5d** (400 mg, 1.60 mmol) by the same method as that used for **12a**. White amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 2.28 (s, 3H), 3.06 (t, J = 9.7 Hz, 1H), 3.44−3.49 (m, 1H), 3.70 (s, 3H), 3.75 (q, J = 9.7 Hz, 1H), 4.52 (dd, J = 11.5, 9.1 Hz, 1H), 6.37 (d, J = 9.1 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 8.5, 3.0 Hz, 1H), 7.00−7.06 (m, 2H), 7.32−7.38 (m, 2H), 7.42 (d, J = 9.1 Hz, 1H), 7.90 (s, 1H), 8.52 (s, 1H). MS (ESI$^+$) *m/z*: 358 (M$^+$ + H). HRMS (ESI$^+$) for $C_{19}H_{21}FN_3O_3$ (M$^+$ + H): calcd, 358.15669; found, 358.15698. IR (ATR) cm^{-1}: 3302, 1707, 1664. $[\alpha]^{23}_D$ −187 (*c* 0.353, EtOH). HPLC purity 98.1%.

1-[(3*S*,4*R*)-4-(4-Chloro-2-fluorophenyl)-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)urea (12e). The compound **12e** (165 mg, 42%) was prepared from **B5e** (280 mg, 1.08 mmol) by the same method as that used for **12a**. White powder. Mp: 195-201℃. ^{1}H NMR (DMSO−d_6) δ: 3.21 (t, J = 9.8 Hz, 1H), 3.48 (t, J = 9.2 Hz, 1H), 3.77 (q, J = 9.8 Hz, 1H), 4.59 (dd, J = 11.0, 9.2 Hz, 1H), 6.44 (d, J = 8.6 Hz, 1H), 6.99−7.05 (m, 2H), 7.28 (dd, J = 8.6, 2.4 Hz, 1H), 7.31−7.35 (m, 2H), 7.39 (dd, J = 11.0, 2.4 Hz, 1H), 7.62 (t, J = 8.6 Hz, 1H), 8.00 (s, 1H), 8.63 (s, 1H). MS (ESI$^+$) *m/z*: 366 (M$^+$ + H). HRMS (ESI$^+$) for $C_{17}H_{15}ClF_2N_3O_2$ (M$^+$ + H): calcd, 366.08209; found, 366.08186. IR (ATR) cm^{-1}: 3290, 1705, 1642. $[\alpha]^{26}_D$ −138 (*c* 0.203, EtOH).. HPLC purity 95.2%.

1-[(3*S*,4*R*)-4-(2,5-Difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)urea (12f). The compound **12f** (150 mg, 31%) was prepared from **B5f** (350 mg, 1.29 mmol) by the same method as that used for **12a**. White amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.20 (t, J = 9.7 Hz,

1H), 3.45 (t, J = 9.1 Hz, 1H), 3.73 (q, J = 9.7 Hz, 1H), 3.82 (s, 3H), 4.54 (dd, J = 11.5, 9.1 Hz, 1H), 6.43 (d, J = 8.5 Hz, 1H), 7.01−7.11 (m, 3H), 7.32−7.38 (m, 2H), 7.53 (dd, J = 12.1, 7.3 Hz, 1H), 7.97 (s, 1H), 8.63 (s, 1H). MS (ESI$^+$) *m/z*: 380 (M^+ + H). HRMS (ESI$^+$) for $C_{18}H_{17}F_3N_3O_3$ (M^+ + H): calcd, 380.12220; found, 380.12219. IR (ATR) cm^{-1}: 3299, 1709, 1663. $[\alpha]^{28}_D$ −123 (*c* 0.100, EtOH). HPLC purity 99.8%.

1-[(3*S*,4*R*)-4-(3-fluoro-5-methoxypyridin-2-yl)-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)urea (12h). The compound **12h** (220 mg, 38%) was prepared from **B5h** (420 mg, 1.65 mmol) by the same method as that used for **12a**. Pale brown amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.40 (t, J = 9.7 Hz, 1H), 3.44−3.51 (m, 1H), 3.84 (s, 3H), 3.98 (q, J = 9.7 Hz, 1H), 4.53 (dd, J = 10.3, 8.5 Hz, 1H), 6.47 (d, J = 7.9 Hz, 1H), 7.00−7.06 (m, 2H), 7.31−7.36 (m, 2H), 7.40 (dd, J = 11.6, 2.4 Hz, 1H), 7.96 (s, 1H), 8.21 (d, J = 2.4 Hz, 1H),8.62 (s, 1H). MS (ESI$^+$) *m/z*: 363 (M^+ + H). HRMS (ESI$^+$) for $C_{17}H_{17}F_2N_4O_3$ (M^+ + H): calcd, 363.12687; found, 363.12667. IR (ATR) cm^{-1}: 3297, 1706, 1658. $[\alpha]^{28}_D$ −142 (*c* 0.100, EtOH). HPLC purity 98.4%.

1-[(3*S*,4*R*)-4-(4-Ethoxy-2,6-difluorophenyl)-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)urea (12i). The compound **12i** (31.0 mg, 16%) was prepared from **B5i** (137 mg, 0.479 mmol) by the same method as that used for **12a**. White amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 1.30 (t, J = 7.3 Hz, 3H), 3.30 (t, J = 9.7 Hz, 1H), 3.45 (t, J = 9.7 Hz, 1H), 3.80 (q, J = 9.7 Hz, 1H), 4.03 (q, J = 7.3 Hz, 2H), 4.57 (dd, J = 10.9, 8.5 Hz, 1H), 6.57 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 10.9 Hz, 2H), 6.99−7.06 (m, 2H), 7.32−7.37 (m, 2H), 8.05 (s, 1H), 8.77 (s, 1H). MS (ESI$^+$) *m/z*: 394 (M^+ + H). HRMS (ESI$^+$) for $C_{19}H_{19}F_3N_3O_3$ (M^+ + H): calcd, 394.13785; found, 394.13725. IR (ATR) cm^{-1}: 3297, 1638. $[\alpha]^{26}_D$ -149 (*c* 0.133, EtOH). HPLC purity 99.4%.

1-[(3*S*,4*R*)-4-(4-Ethyl-2,6-difluorophenyl)-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)urea (12j). The compound **12j** (226 mg, 60%) was prepared from **B5j** (270 mg, 1.00 mmol) by the same method as that used for **12a**. White amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 1.16 (t, J = 7.3 Hz, 3H), 2.59 (q, J = 7.3 Hz, 2H), 3.33 (t, J = 9.7 Hz, 1H), 3.47 (t, J = 9.1 Hz, 1H), 3.87 (q, J = 9.7 Hz, 1H), 4.60 (dd, J = 10.9, 8.5 Hz, 1H), 6.49 (d, J = 8.5 Hz, 1H), 6.97 (d, J = 9.7 Hz, 2H), 7.00−7.06 (m, 2H), 7.31−7.36 (m, 2H), 8.08 (s, 1H), 8.68 (s, 1H). MS (ESI$^+$) *m/z*: 378 (M^+ + H). HRMS (ESI$^+$) for $C_{19}H_{19}F_3N_3O_2$ (M^+ + H): calcd, 378.14294; found, 378.14316. IR (ATR) cm^{-1}: 3299, 1658. $[\alpha]^{28}_D$ −147 (*c* 0.101, EtOH). HPLC purity 97.2%.

(*E*)-3,5-Difluoro-4-(2-nitrovinyl)phenol (B7). Ammonium acetate (11.6 g, 0.150 mol) and nitrometane (33.5 mL, 0.626 mol) were added to a solution of **B6** (19.8 g, 0.125 mol) in acetic acid (125 mL), and the whole mixture was stirred at 100 °C for 7h, and then concentrated in vacuo. After addition of water to the residue, the resulting precipitates were collected by filtration. The filtered precipitates were wshed with water and dried in vacuo to gave **B7** (22.9 g, 91%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ: 6.49−6.54 (m, 2H), 7.76 (d, J = 14.1 Hz, 1H), 8.10 (d, J = 14.1 Hz, 1H). MS (FI$^+$) *m/z*: 201 (M^+). HRMS (FI$^+$) for $C_8H_5F_2NO_3$ (M^+): calcd, 201.02375; found, 201.02333. IR (ATR) cm^{-1}: 3345, 1619, 1457.

Dimethyl (*R*)-[1-(2,6-difluoro-4-hydroxyphenyl)-2-nitroethyl]malonate (B8). The compound **B8** (350 mg, 96%) was prepared from **B7** (220 mg, 1.09 mmol) by same method as that used for

B3a. Brown oil. ^{1}H NMR ($CDCl_3$) δ: 3.58 (s, 3H), 3.80 (s, 3H), 3.92 (d, J = 10.4 Hz, 1H), 4.66 (dt, J = 10.4, 4.9 Hz, 1H), 4.80 (dd, J = 12.8, 10.4 Hz, 1H), 4.91 (dd, J = 12.8, 4.9 Hz, 1H), 5.79 (br s, 1H), 6.35−6.40 (m, 2H). MS (FI$^+$) *m/z*: 333 (M$^+$). HRMS (FI$^+$) for $C_{13}H_{13}F_2NO_7$ (M$^+$): calcd, 333.06601; found, 333.06600. IR (ATR) cm^{-1}: 3419, 1735, 1638, 1556.

Methyl (3*S*,4*R*)-4-(2.6-Difluoro-4-hydroxyphenyl)-2-oxopyrrolidine-3-carboxylate (B9). The compound **B9** (200 mg, 70%) was prepared from **B8** (350 mg, 1.05 mmol) by the same method as that used for **B4a**. White solid. ^{1}H NMR (DMSO−d_6) δ: 3.25 (t, J = 9.2 Hz, 1H), 3.53 (d, J = 10.4 Hz, 1H), 3.56 (d, J = 9.8 Hz, 1H), 3.63 (s, 3H), 4.12 (q, J = 9.2 Hz, 1H), 6.43−6.49 (m, 2H), 8.27 (s, 1H), 10.4 (br, 1H). MS (ESI$^+$) *m/z*: 272 (M$^+$ + H). HRMS (ESI$^+$) for $C_{12}H_{12}F_2NO_4$ (M$^+$ + H): calcd, 272.07344; found, 272.07306. IR (ATR) cm^{-1}: 3285, 1748, 1698, 1668, 1637.

Methyl (3*S*,4*R*)-4-(4-Benzloxy-2.6-difluorophenyl)-2-oxopyrrolidine-3-carboxylate (B10). Benzyl bromide (0.23 mL, 1.94 mmol) and K_2CO_3 (268 mg, 1.94 mmol) were added to a solution of **B9** (500 mg, 1.84 mmol) in DMF (3.6 mL), and the whole mixture was stirred at room temperature for 25 h. After addition of saturated aqueous NH_4Cl solution (10 mL) to the reaction mixture, the whole mixture was extracted with AcOEt (30 mL). The extract was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 80:20 → AcOEt) of the residue gave **B10** (643 mg, 97%) as a white amorphous solid. ^{1}H NMR ($CDCl_3$) δ: 3.50 (t, J = 9.1 Hz, 1H), 3.66 (t, J = 9.1 Hz, 1H), 3.74−3.84 (m, 4H), 4.46 (q, J = 9.1 Hz, 1H), 5.02 (s, 2H), 5.89 (br s, 1H), 6.54 (d, J = 10.3 Hz, 2H), 7.33−7.45 (m, 5H). MS (ESI$^+$) *m/z*: 362 (M$^+$ + H). HRMS (ESI$^+$) for $C_{19}H_{18}F_2NO_4$ (M$^+$ + H): calcd, 362.12039; found, 362.12109. IR (ATR) cm^{-1}: 3232, 1739, 1703, 1637.

(3*S*,4*R*)-4-(4-Benzloxy-2.6-difluorophenyl)-2-oxopyrrolidine-3-carboxylic Acid (B11). The compound **B11** (490 mg, 80%) was prepared from **B10** (640 mg, 1.77 mmol) by the same method as that used for **B5a**. White solid. ^{1}H NMR (DMSO−d_6) δ: 3.25 (t, J = 9.1 Hz, 1H), 3.43 (d, J = 10.3 Hz, 1H), 3.56 (t, J = 9.1 Hz, 1H), 4.15 (q, J = 9.1 Hz, 1H), 5.11 (s, 2H), 6.85 (d, J = 10.9 Hz, 2H), 7.32−7.44 (m, 5H), 8.18 (s, 1H), 12.8 (br, 1H). MS (ESI$^-$) *m/z*: 346 (M$^+$ - H). HRMS (ESI$^-$) for $C_{18}H_{14}F_2NO_4$ (M$^+$ - H): calcd, 346.08909; found, 346.08902. IR (ATR) cm^{-1}: 3303, 1760, 1660, 1638.

1-[(3*S*,4*R*)-4-(4-Benzyloxy-2,6-difluorophenyl)-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)urea (B12). The compound **B12** (490 mg, 80%) was prepared from **B11** (470 mg, 1.35 mmol) by the same method as that used for **12a**. White amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.26-3.31 (m, 1H), 3.44 (t, J = 8.6 Hz, 1H), 3.79 (q, J = 9.8 Hz, 1H), 4.56 (dd, J = 11.0, 8.6 Hz, 1H), 5.10 (s, 2H), 6.46 (d, J = 8.6 Hz, 1H), 6.82 (d, J = 10.4 Hz, 2H), 6.99−7.05 (m, 2H), 7.30−7.44 (m, 7H), 8.05 (s, 1H), 8.66 (s, 1H). MS (ESI$^+$) *m/z*: 456 (M$^+$ + H). HRMS (ESI$^+$) for $C_{24}H_{21}F_3N_3O_3$ (M$^+$ + H): calcd, 456.15350; found, 456.15260. IR (ATR) cm^{-1}: 3300, 1666, 1638.

1-[(3*S*,4*R*)-4-(2,6-Difluoro-4-hydroxyphenyl)-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)urea (B13). A suspension of **B12** (490 mg, 1.07 mmol) and 10% Pd−C (wetted with ca. 55% water, 49.0 mg) in EtOH (10 mL) was stirred at room temperature for 4 h under H_2 atmosphere. After the insoluble materials were filtered off, the filttrare was concentrated in vacuo. Flash

chromatography (hexane/AcOEt = 4:1 → AcOEt) of the residue gave **B13** (383 mg, 98%) as a white solid. ^{1}H NMR (DMSO−d_6) δ: 3.28 (t, J = 9.7 Hz, 1H), 3.43 (t, J = 9.7 Hz, 1H), 3.76 (q, J = 9.7 Hz, 1H), 4.54 (dd, J = 10.9, 8.5 Hz, 1H), 6.43−6.46 (m, 3H), 7.01−7.06 (m, 2H), 7.32−7.37 (m, 2H), 8.03 (s, 1H), 8.66 (s, 1H), 10.4 (br, 1H). MS (ESI$^+$) *m/z*: 366 (M^+ + H). HRMS (ESI$^+$) for $C_{17}H_{15}F_3N_3O_3$ (M^+ + H): calcd, 366.10655; found, 366.10620. IR (ATR) cm^{-1}: 3280, 1667, 1638. $[\alpha]^{28}_D$ −150 (*c* 0.101, EtOH). HPLC purity 96.5%.

3,5-Difluoro-4-[(3S,4R)-4-[3-(4-fluorophenyl)ureido]-5-oxopyrrolidin-3-yl]phenyl Tirifluoromethanesulfonate (B14). Trifluoromethanesulfonic anhydride (0.246 mL, 1.50 mmol) was added to a solution of **B13** (365 mg, 1.00 mmol) and pyridine (0.404 mL, 5.00 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C, and the whole mixture was stirred at room temperature for 3 h. After addition of water (10 mL) to the reaction mixture, the whole mixture was extracted with AcOEt (30 mL). The extract was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 9:1 → AcOEt) of the residue gave **B14** (388 mg, 78%) as a brown amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.36 (t, J = 9.8 Hz, 1H), 3.52 (t, J = 9.2 Hz, 1H), 3.93 (q, J = 9.2 Hz, 1H), 4.55 (dd, J = 10.4, 7.9 Hz, 1H), 6.50 (d, J = 7.3 Hz, 1H), 6.98−7.04 (m, 2H), 7.27−7.33 (m, 2H), 7.58 (d, J = 8.6 Hz, 2H), 8.13 (s, 1H), 8.74 (s, 1H). MS (ESI$^+$) *m/z*: 498 (M^+ + H). HRMS (ESI$^+$) for $C_{18}H_{14}F_6N_3O_5S$ (M^+ + H): calcd, 498.05583; found, 498.05655. IR (ATR) cm^{-1}: 3334, 1692, 1627.

1-[(3*S*,4*R*)-4-(4-Cyano-2,6-difluorophenyl)-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)urea (12k).

Zinc cyanide (53.0 mg, 0.451 mmol) and trtrakis(triphenylphosphine)palladium(0) (18.0 mg, 0.0156 mmol) were added to a solution of **B14** (150 mg, 0.302 mmol) in DMF (3.0 mL), and the whole mixture was stirred at 80 °C for 5 h. After the insoluble materials were filtered off, the filtrate was concentrated in vacuo. Flash chromatography (hexane/AcOEt = 4:1 → AcOEt) of the residue gave **12k** (100 mg, 89%). ^{1}H NMR (DMSO−d_6) δ: 3.37 (t, J = 9.7 Hz, 1H), 3.53 (t, J = 9.7 Hz, 1H), 3.97 (q, J = 10.3 Hz, 1H), 4.59 (dd, J = 10.3, 7.9 Hz, 1H), 6.53 (d, J = 7.9 Hz, 1H), 6.99−7.06 (m, 2H), 7.28−7.34 (m, 2H), 7.82 (d, J = 8.5 Hz, 2H), 8.19 (s, 1H), 8.77 (s, 1H). MS (ESI$^+$) *m/z*: 375 (M^+ + H). HRMS (ESI$^+$) for $C_{18}H_{14}F_3N_4O_2$ (M^+ + H): calcd, 375.10688; found, 375.10648. IR (ATR) cm^{-1}: 3321, 1672. $[\alpha]^{28}_D$ −146 (*c* 0.099, EtOH). HPLC purity 100%.

3,5-Difluoro-4-formylphenyl Trifluoromethanesulfonate (B15). Trifluoromethansulfonic anhydride (2.02 g, 7.17 mmol) and pyridine (772 mg, 9.76 mmol) were added to a solution of **B6** (1.03 g, 6.51 mmol) in CH_2Cl_2 (30 mL), and the whole mixture was stirred at room temperature for 3 h. After addition of water to the reaction mixture, the whole mixture was extracted with AcOEt. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 4:1) of the residue gave **B15** (1.50 g, 79%). ^{1}H NMR ($CDCl_3$) δ: 6.99−7.04 (m, 2H), 10.3 (s, 1H).

tert-Butyl *N*-(3,5-Difluoro-4-formylphenyl)carbamate (B16). A mixture of **B15** (637 mg, 2.20 mmol), tert-butyl carbamate (379 mg, 3.24 mmol), tris(dibenzylideneacetone)dipalladium(0) (101 mg, 0.110 mg), 4,5-bis(diphenylphosphine)-9,9-dimethylxanthene (127 mg, 0.219 mmol), Cs_2CO_3

(1080 mg, 3.31 mmol) and toluene (10 mL) was stirred at 100 °C for 7 h. After addition of water to the reaction mixture, the whole mixture was extracted with AcOEt. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 4:1) of the residue gave **B16** (240 mg, 42%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ: 1.53 (s, 9H), 6.77 (br s, 1H), 7.07 (d, J = 11.0 Hz, 2H), 10.2 (s, 1H). MS (ESI$^+$) *m/z*: 258 (M^+ + H). HRMS (ESI$^+$) for $C_{12}H_{14}F_2NO_3$ (M^+ + H): calcd, 258.09417; found, 258.09397.

tert-Butyl *N*-(3,5-Difluoro-4-formylphenyl)-*N*-methylcarbamate (B17). Iodomethane (0.11 mL, 1.72 mmol) was added to a mixture of **B16** (220 mg, 0.855 mmol), NaH (60% dispersion in paraffin liquid, 51.0 mg, 1.28 mmol) and DMF (4.0 mL) at 0 °C, and then the whole mixture was stirred at room temperature for 3 h. After quenching the reaction by adding saturated aqueous NH_4Cl solution, the whole mixture was extracted with AcOEt. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 4:1) of the residue gave **B17** (150 mg, 64%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.53 (s, 9H), 3.32 (s, 3H), 7.05 (d, J = 11.0 Hz, 2H), 10.3 (s, 1H).

tert-Butyl (*E*)-*N*-[3,5-Difluoro-4-(2-nitrovinyl)phenyl]-*N*-methylcarbamate (B18). The compound **B18** (145 mg, 86%) was prepared from **B17** (145 mg, 0.535 mmol) by same method as that used for **B2c**. Pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.53 (s, 9H), 3.31 (s, 3H), 7.09 (d, J = 11.6 Hz, 2H), 7.81 (d, J = 14.1 Hz, 1H), 8.11 (d, J = 14.1 Hz, 1H). MS (EI$^+$) *m/z*: 314 (M^+). HRMS (EI$^+$) for $C_{14}H_{16}F_2N_2O_4$ (M^+): calcd, 314.10781; found, 314.10738.

(*R*)-2-[1-[4-[*N*-(tert-Butoxycarbonyl)-*N*-methylamino]-2,6-difluorophenyl]-2-nitroethyl]malonate (B19). The compound **B19** (145 mg, 73%) was prepared from **B18** (140 mg, 0.445 mmol) by same method as that used for **B3a**. ^{1}H NMR ($CDCl_3$) δ: 1.48 (9H, s,), 3.23 (s, 3H), 3.58 (s, 3H), 3.80 (s, 3H), 3.94 (d, J = 10.4 Hz, 1H), 4.68−4.73 (m, 1H), 4.83 (dd, J = 12.8, 9.8 Hz, 1H), 4.93 (dd, J = 13.4, 4.9 Hz, 1H), 6.92 (d, J = 10.4 Hz, 2H).

Methyl (3*S*,4*R*)-4-[4-[*N*-(tert-Butoxycarbonyl)-*N*-methylamino]-2,6-difluorophenyl]-2-oxopyrrolidine-3-carboxylate (B20). The compound **B20** (90.0 mg, 75%) was prepared from **B19** (140 mg, 0.314 mmol) by the same method as that used for **B4a**. Colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 3.25 (s, 3H), 3.53 (t, J = 8.9 Hz, 1H), 3.67−3,72 (m, 1H), 3.79 (s, 3H), 3.82 (d, J = 9.8 Hz, 1H), 4.52 (q, J = 9.4 Hz, 1H), 5.99 (br s, 1H), 6.92 (d, J = 10.4 Hz, 2H).

(3*S*,4*R*)-4-[4-[*N*-(tert-Butoxycarbonyl)-*N*-methylamino]-2,6-difluorophenyl]-2-oxopyrrolidine-3-carboxylic Acid (B21). The compound **B21** (82.0 mg, 95%) was prepared from **B20** (90.0 mg, 0.234 mmol) by the same method as that used for **B5a**. White solid. ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 3.25 (s, 3H), 3.58 (t, J = 9.2 Hz, 1H), 3.70 (t, J = 9.2 Hz, 1H), 3.84 (d, J = 11.0 Hz, 1H), 4.34 (q, J = 9.2 Hz, 1H), 6.16 (br s, 1H), 6.94 (d, J = 10.4 Hz, 2H). MS (ESI$^+$) *m/z*: 371 (M^+ + H). HRMS (ESI$^+$) for $C_{17}H_{21}F_2N_2O_5$ (M^+ + H): calcd, 371.14185; found, 371.14141.

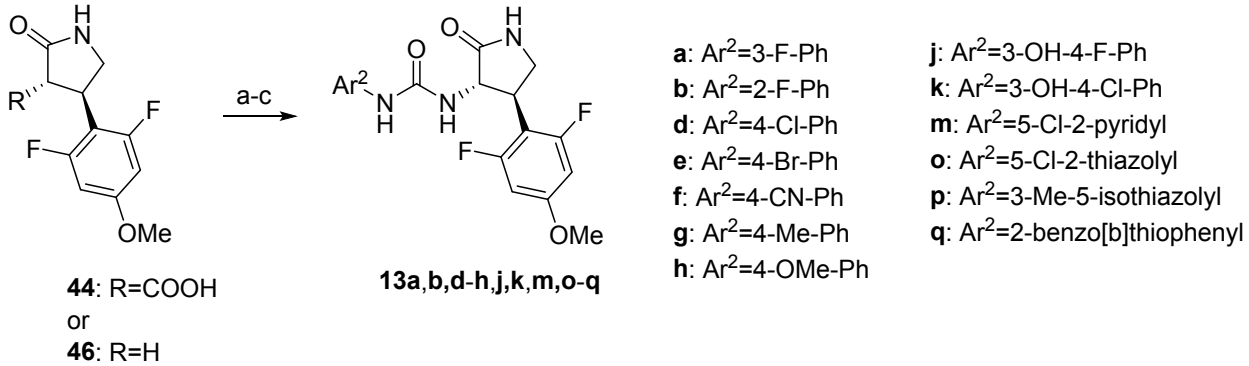
1-[(3*S*,4*R*)-4-[4-[*N*-(tert-Butoxycarbonyl)-*N*-methylamino]-2,6-difluorophenyl]-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)ure (B22). The compound **B22** (80.0 mg, 77%) was prepared from **B21** (80.0 mg, 0.216 mmol) by the same method as that used for **12a**. ^{1}H NMR

($CDCl_3$) δ: 1.49 (s, 9H), 3.25 (s, 3H), 3.59−3.71 (m, 2H), 4.19−4.26 (m, 1H), 4.54−4.58 (m, 1H), 5.76 (br s, 1H), 6.03 (br s, 1H), 6.82 (t, J = 8.6 Hz, 2H), 6.92 (d, J = 10.4 Hz, 2H), 7.13−7.17 (m, 2H), 7.29 (br s, 1H).

1-[(3*S*,4*R*)-4-(2,6-Difluoro-4-(methylamino)phenyl)-2-oxopyrrolidin-3-yl]-3-(4-fluorophenyl)urea (12l). A mixture of **B22** (80.0 mg, 0.167 mmol) and trifluoroacetic acid (1.0 mL) was stirred at 60 °C for 1 h and then concentrated in vacuo. After addition of saturated aqueous $NaHCO_3$ solution to the residue, the whole mixture was extracted with AcOEt. The extract was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. Flash chromatography (AcOEt) of the residue gave **12l** (30.0 mg, 47%) as a white amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 2.64 (d, J = 4.8 Hz, 3H), 3.26 (t, J = 9.7 Hz, 1H), 3.39 (t, J = 9.7 Hz, 1H), 3.68 (q, J = 10.3 Hz, 1H), 4.53 (dd, J = 10.9, 8.5 Hz, 1H), 6.17 (d, J = 12.1 Hz, 2H), 6.22 (d, J = 4.8 Hz, 1H), 6.41 (d, J = 8.5 Hz, 1H), 6.99−7.06 (m, 2H), 7.32−7.38 (m, 2H), 7.99 (s, 1H), 8.62 (s, 1H). MS (ESI$^+$) *m/z*: 379 (M^+ + H). HRMS (ESI$^+$) for $C_{18}H_{18}F_3N_4O_2$ (M^+ + H): calcd, 379.13818; found, 379.13909. IR (ATR) cm^{-1}: 3344, 1646. $[\alpha]^{24}_D$ −188 (*c* 0.143, EtOH). HPLC purity 99.6%.

c. Synthesis of Ar^2-substituted Pyrrolidione Urea Derivatives 13.

Scheme C.



[a]Reagents and coditions: (a) **44**, DPPA, Et_3N, toluene then Ar_2-NH_2, 38% (for **13b**), 59% (for **13d**), 67% (for **13e**), 45% (for **13f**), 59% (for **13h**), 63% (for **13j**), 70% (for **13k**), 16% (for **13m**), 11% (for **13o**), 7% (for **13p**), 28% (for **13q**); (b) **46**, 3-fluorophenyl isocyanate, THF, 83% (for **13a**); (c) **46**, *p*-toluic acid, DPPA, Et_3N, toluene, 90% (for **13g**).

1-[(3*S*,4*R*)-4-(2,6-Difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl]-3-(3-fluorophenyl)urea (13a). A mixture of **46** (40.0 mg, 0.165 mmol) and 3-fluorophenyl isocyanate (20.0 μL, 0.175 mmol) in THF (1.7 mL) was stirred at room temperature for 30 min, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 3:1 → AcOEt) of the residue gave **13a** (52 mg, 83%) as a white amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.32 (t, J = 9.7 Hz, 1H), 3.46 (t, J = 9.7 Hz, 1H), 3.76 (s, 3H), 3.82 (q, J = 10.3 Hz, 1H), 4.58 (dd, J = 10.9, 8.5 Hz, 1H), 6.58 (d, J = 8.5 Hz, 1H), 6.69 (dt, J = 7.9, 2.4 Hz, 1H), 6.75 (d, J = 10.9 Hz, 2H), 7.00−7.03 (m,

1H), 7.21 (q, J = 8.5 Hz, 1H), 7.36 (dt, J = 12.7, 2.4 Hz, 1H), 8.08 (s, 1H), 8.92 (s, 1H). MS (ESI$^+$) *m/z*: 380 (M$^+$ + H). HRMS (ESI$^+$) for $C_{18}H_{17}F_3N_3O_3$ (M$^+$ + H): calcd, 380.12220; found, 380.12168. IR (ATR) cm^{-1}: 3315, 1665, 1638. $[\alpha]^{27}_D$ −152 (*c* 0.103, EtOH). HPLC purity 99.8%.

1-[(3*S*,4*R*)-4-(2,6-Difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl]-3-(2-fluorophenyl)urea (13b). To a suspension of **44** (80.0 mg, 0.295 mmol), triethylamine (50.0 μL, 0.359 mmol) and molecular sieves 4A (powder, 160 mg) in toluene (5.5 mL) and MeCN (1.9 mL) was added diphenylphosphoryl azide (70.0 μL, 0.312 mmol), and the mixture was stirred at 80 °C for 1 h. After cooling to room temperature, 2-fluoroaniline (56.5 μL, 0.590 mmol) was added, and the mixture was stirred at 100 °C for 3 h, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 3:1 → AcOEt → AcOEt/MeOH = 5:1) of the residue gave **13b** (43.2 mg, 38%) as a white amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.33 (t, J = 9.1 Hz, 1H), 3.48 (t, J = 8.5 Hz, 1H), 3.73 (q, J = 9.1 Hz, 1H), 3.77 (s, 3H), 4.59 (dd, J = 10.9, 8.5 Hz, 1H), 6.76 (d, J = 10.9 Hz, 2H), 6.89−6.95 (m, 2H), 7.02−7.06 (m, 1H), 7.16 (ddd, J = 9.7, 8.5, 1.8 Hz, 1H), 7.97 (dt, J = 8.5, 1.8 Hz, 1H), 8.13 (s, 1H), 8.42 (d, J = 2.4 Hz, 1H). MS (ESI$^+$) *m/z*: 380 (M$^+$ + H). HRMS (ESI$^+$) for $C_{18}H_{17}F_3N_3O_3$ (M$^+$ + H): calcd, 380.12220; found, 380.12166. IR (ATR) cm^{-1}: 3320, 1670, 1638. $[\alpha]^{27}_D$ −152 (*c* 0.105, EtOH). HPLC purity 95.4%.

1-(4-Chlorophenyl)-3-[(3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl)urea (13d). Compound **13d** (86.0 mg, 59%) was prepared from **44** (100 mg, 0.369 mmol) and 4-chloroaniline (102 mg, 0.738 mmol) by the same method as that used for **13b**. White amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.31 (t, J = 9.7 Hz, 1H), 3.46 (t, J = 9.7 Hz, 1H), 3.76 (s, 3H), 3.81 (q, J = 8.5 Hz, 1H), 4.58 (dd, J = 10.9, 8.5 Hz, 1H), 6.53 (d, J = 8.5 Hz, 1H), 6.75 (d, J = 10.9 Hz, 2H), 7.21−7.25 (m, 2H), 7.35−7.39 (m, 2H), 8.08 (s, 1H), 8.80 (s, 1H). MS (ESI$^+$) *m/z*: 396 (M$^+$ + H). HRMS (ESI$^+$) for $C_{18}H_{17}ClF_2N_3O_3$ (M$^+$ + H): calcd, 396.09265; found, 396.09307. IR (ATR) cm^{-1}: 3316, 1662, 1638. $[\alpha]^{27}_D$ −195 (*c* 0.104, EtOH). HPLC purity 98.7%.

1-(4-Bromophenyl)-3-[(3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl)urea (13e). Compound **13e** (553 mg, 67%) was prepared from **44** (510 mg, 1.88 mmol) and 4-bromoaniline (647 mg, 3.76 mmol) by the same method as that used for **13b**. White amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.31 (t, J = 9.7 Hz, 1H), 3.46 (t, J = 9.1 Hz, 1H), 3.76 (s, 3H), 3.81 (q, J = 10.3 Hz, 1H), 4.58 (dd, J = 10.9, 8.5 Hz, 1H), 6.54 (d, J = 8.5 Hz, 1H), 6.75 (d, J = 10.9 Hz, 2H), 7.30−7.37 (m, 4H), 8.08 (s, 1H), 8.82 (s, 1H). MS (ESI$^+$) *m/z*: 440 (M$^+$ + H). HRMS (ESI$^+$) for $C_{18}H_{17}BrF_2N_3O_3$ (M$^+$ + H): calcd, 440.04214; found, 440.04166. IR (ATR) cm^{-1}: 3282, 1667, 1637. $[\alpha]^{25}_D$ −97.9 (*c* 0.104, EtOH). HPLC purity 98.3%.

1-(4-Cyanophenyl)-3-[(3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl)urea (13f). Compound **13f** (64.0 mg, 45%) was prepared from **44** (100 mg, 0.369 mmol) and 4-aminobenzonitrile (87.0 mg, 0.738 mmol) by the same method as that used for **13b**. White amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.32 (t, J = 9.7 Hz, 1H), 3.47 (t, J = 8.5 Hz, 1H), 3.76 (s, 3H), 3.84 (q, J = 9.7 Hz, 1H), 4.59 (dd, J = 10.9, 8.5 Hz, 1H), 6.74−6.78 (m, 3H), 7.51−7.54 (m, 2H), 7.62−7.66 (m, 2H), 8.10 (s, 1H), 9.27 (s, 1H). MS (ESI$^+$) *m/z*: 387 (M$^+$ + H). HRMS (ESI$^+$) for $C_{19}H_{17}F_2N_4O_3$ (M$^+$ + H): calcd, 387.12687; found, 387.12722. IR (ATR) cm^{-1}: 3329, 2223, 1683, 1637. $[\alpha]^{26}_D$ −163 (*c* 0.103, EtOH). HPLC purity 99.8%.

1-[(3*S*,4*R*)-4-(2,6-Difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl)-3-(4-methylphenyl)urea (13g). To a suspension of *p*-toluic acid (35.1 mg, 0.258 mmol), triethylamine (34.0μL, 0.246 mmol) and molecular sieves 4A (powder, 180 mg) in toluene (5.5 mL) was added diphenylphosphoryl azide (55.0 μL, 0.246 mmol), and the mixture was stirred at room temperature for 1 h, 80 °C for 40 min, and then 100 °C for 3 h. After addition of **46** (38.0 mg, 0.156 mmol), the mixture was stirred at 100 °C for 35 min, and then concentrated in vacuo. Flash chromatography (hexane/AcOEt = 3:1 → AcOEt) of the residue gave **13g** (52.9 mg, 90%) as a white amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 2.19 (s, 3H), 3.31 (t, J = 9.1 Hz, 1H), 3.45 (t, J = 9.1 Hz, 1H), 3.75−3.82 (m, 4H), 4.57 (dd, J = 10.9, 8.5 Hz, 1H), 6.41 (d, J = 8.5 Hz, 1H), 6.74 (d, J = 10.3 Hz, 2H), 6.99 (d, J = 7.9 Hz, 2H), 7.19−7.23 (m, 2H), 8.06 (s, 1H), 8.51 (s, 1H). MS (ESI$^+$) *m/z*: 376 (M$^+$ + H). HRMS (ESI$^+$) for $C_{19}H_{20}F_2N_3O_3$ (M$^+$ + H): calcd, 376.14727; found, 376.14758. IR (ATR) cm^{-1}: 3311, 1637. $[\alpha]^{27}_D$ −144 (*c* 0.103, EtOH). HPLC purity 97.1%.

1-[(3*S*,4*R*)-4-(2,6-Difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl)-3-(4-methoxyphenyl)urea (13h). Compound **13h** (68.4 mg, 59%) was prepared from **44** (80.0 mg, 0.295 mmol) and *p*-anisidine (73.0 mg, 0.593 mmol) by the same method as that used for **13b**. White amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.30 (t, J = 9.7 Hz, 1H), 3.45 (t, J = 9.1 Hz, 1H), 3.67 (s, 3H), 3.72−3.82 (m, 4H), 4.57 (dd, J = 10.9, 8.5 Hz, 1H), 6.36 (d, J = 8.5 Hz, 1H), 6.74 (d, J = 10.9 Hz, 2H), 6.78 (d, J = 9.1 Hz, 2H), 7.23 (d, J = 9.1 Hz, 2H), 8.05 (s, 1H), 8.42 (s, 1H). MS (ESI$^+$) *m/z*: 392 (M$^+$ + H). HRMS (ESI$^+$) for $C_{19}H_{20}F_2N_3O_4$ (M$^+$ + H): calcd, 392.14219; found, 392.14277. IR (ATR) cm^{-1}: 3311, 1707, 1637. $[\alpha]^{28}_D$ −168 (*c* 0.290, EtOH). HPLC purity 99.2%.

1-[(3*S*,4*R*)-4-(2,6-Difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl]-3-(4-fluoro-3-hydroxyphenyl)urea (13j). Compound **13j** (110 mg, 63%) was prepared from **44** (150 mg, 0.446 mmol) and 5-amino-2-fluorophenol (113 mg, 0.889 mmol) by the same method as that used for **13b**. Pale brown amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.30 (d, J = 9.7 Hz, 1H), 3.45 (t, J = 9.1 Hz, 1H), 3.74−3.82 (m, 4H), 4.57 (dd, J = 10.9, 7.9 Hz, 1H), 6.39 (d, J = 8.5 Hz, 1H), 6.60−6.64 (m, 1H), 6.74 (d, J = 10.9 Hz, 2H), 6.92 (dd, J = 10.9, 8.5 Hz, 1H), 7.14 (dd, J = 8.5, 2.4 Hz, 1H), 8.06 (s, 1H), 8.56 (s, 1H), 9.65 (s, 1H). MS (ESI$^+$) *m/z*: 396 (M$^+$ + H). HRMS (ESI$^+$) for $C_{18}H_{17}F_3N_3O_4$ (M$^+$ + H): calcd, 396.11712; found, 396.11802. IR (ATR) cm^{-1}: 3301, 1637. $[\alpha]^{26}_D$ −184 (*c* 0.253, EtOH). HPLC purity 98.4%.

1-(4-Chloro-3-hydroxyphenyl)-3-[(3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl]urea (13k). Compound **13k** (170 mg, 70%) was prepared from **44** (198 mg, 0.589 mmol) and 5-amino-2-chlorophenol (169 mg, 1.18 mmol) by the same method as that used for **13b**. White amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.31 (t, J = 9.7 Hz, 1H), 3.45 (t, J = 9.1 Hz, 1H), 3.75−3.82 (m, 4H), 4.58 (dd, J = 10.9, 8.5 Hz, 1H), 6.43 (d, J = 8.5 Hz, 1H), 6.68 (dd, J = 9.1, 2.4 Hz, 1H), 6.74 (d, J = 10.9 Hz, 2H), 7.09 (d, J = 8.5 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H), 8.68 (s, 1H), 9.96 (s, 1H). MS (ESI$^+$) *m/z*: 412 (M$^+$ + H). HRMS (ESI$^+$) for $C_{18}H_{17}ClF_2N_3O_4$ (M$^+$ + H): calcd, 412.08756; found, 412.08844. IR (ATR) cm^{-1}: 3299, 1638. $[\alpha]^{26}_D$ −124 (*c* 0.178, EtOH). HPLC purity 99.9%.

1-(5-Chloropyridin-2-yl)-3-[(3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl]urea (13m). Compound **13m** (18.7 mg, 16%) was prepared from **44** (80.0 mg, 0.295 mmol)

and 2-amino-5-chloropyridine (75.8 mg, 0.590 mmol) by the same method as that used for **13b**. White amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.33 (t, J = 9.7 Hz, 1H), 3.49 (t, J = 9.1 Hz, 1H), 3.76 (s, 3H), 3.83 (q, J = 9.7 Hz, 1H), 4.60 (dd, J = 10.9, 7.9 Hz, 1H), 6.75 (d, J = 10.3 Hz, 2H), 7.50 (d, J = 9.1 Hz, 1H), 7.72−7.83 (br m, 2H), 8.13 (s, 1H), 8.21 (d, J = 2.4 Hz, 1H), 9.36 (s, 1H). MS (ESI$^+$) *m/z*: 397 (M$^+$ + H). HRMS (ESI$^+$) for $C_{17}H_{16}ClF_2N_4O_3$ (M$^+$ + H): calcd, 397.08790; found, 397.08756. IR (ATR) cm^{-1}: 3219, 1679, 1637. $[\alpha]^{27}_D$ −180 (*c* 0.105, EtOH). HPLC purity 98.3%.

1-(5-Chlorothiazol-2-yl)-3-[(3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl]urea (13o). Compound **13o** (13.4 mg, 11%) was prepared from **44** (80.0 mg, 0.295 mmol) and 2-amino-5-chlorothiazole hydrochloride (101 mg, 0.590 mmol) by the same method as that used for **13b**. White powder. Mp: 186−190 ℃. ^{1}H NMR (DMSO−d_6) δ: 3.32 (t, J = 9.7 Hz, 1H), 3.47 (t, J = 9.7 Hz, 1H), 3.77 (s, 3H), 3.89 (q, J = 10.9 Hz, 1H), 4.56 (dd, J = 10.9, 8.5 Hz, 1H), 6.76 (d, J = 10.9 Hz, 2H), 6.94 (d, J = 8.5 Hz, 1H), 7.32 (s, 1H), 8.12 (s, 1H), 11.0 (s, 1H). MS (ESI$^+$) *m/z*: 403 (M$^+$ + H). HRMS (ESI$^+$) for $C_{15}H_{14}ClF_2N_4O_3S$ (M$^+$ + H): calcd, 403.04432; found, 403.04390. IR (ATR) cm^{-1}: 3268, 1705, 1688, 1638. $[\alpha]^{27}_D$ −87.5 (*c* 0.102, EtOH). HPLC purity 99.5%.

1-[(3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl]-3-(3-methylisothiazol-5-yl)urea (13p). Compound **13p** (7.30 mg, 7.5%) was prepared from **44** (80.0 mg, 0.295 mmol) and 5-amino-3-methylisothiazole (33.7 mg, 0.295 mmol) by the same method as that used for **13b**. Pale yellow amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 2.23 (s, 3H), 3.32 (t, J = 9.1 Hz, 1H), 3.47 (t, J = 9.1 Hz, 1H), 3.76 (s, 3H), 3.89 (q, J = 10.3 Hz, 1H), 4.56 (dd, J = 10.9, 8.5 Hz, 1H), 6.48 (s, 1H), 6.76 (d, J = 10.3 Hz, 2H), 7.10 (d, J = 8.5 Hz, 1H), 8.11 (s, 1H), 10.5 (s, 1H). MS (ESI$^+$) *m/z*: 383 (M$^+$ + H). HRMS (ESI$^+$) for $C_{16}H_{17}F_2N_4O_3S$ (M$^+$ + H): calcd, 383.09894; found, 383.09885. IR (ATR) cm^{-1}: 3265, 1680, 1638. $[\alpha]^{27}_D$ −182 (*c* 0.217, EtOH). HPLC purity 99.4%.

1-(Benzo[b]thiophen-2-yl)-3-[(3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl]urea (13q). Compound **13q** (35.3 mg, 28%) was prepared from **44** (80.0 mg, 0.295 mmol) and 2-aminobenzo[b]thiophene (88.0 mg, 0.590 mmol) by the same method as that used for **13b**. Pale brown amorphous solid. ^{1}H NMR (DMSO−d_6) δ: 3.33 (t, J = 10.3 Hz, 1H), 3.47 (t, J = 9.1 Hz, 1H), 3.76 (s, 3H), 3.88 (q, J = 10.3 Hz, 1H), 4.60 (dd, J = 10.9, 8.5 Hz, 1H), 6.67 (s, 1H), 6.76 (d, J = 10.9 Hz, 2H), 6.88 (d, J = 7.9 Hz, 1H), 7.08−7.12 (m, 1H), 7.20−7.24 (m, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 8.10 (s, 1H), 10.1 (s, 1H). MS (ESI$^+$) *m/z*: 418 (M$^+$ + H). HRMS (ESI$^+$) for $C_{20}H_{18}F_2N_3O_3S$ (M$^+$ + H): calcd, 418.10369; found, 418.10312. IR (ATR) cm^{-1}: 3280, 1671, 1637. $[\alpha]^{27}_D$ −74.4 (*c* 0.100, EtOH). HPLC purity 95.4%.

References

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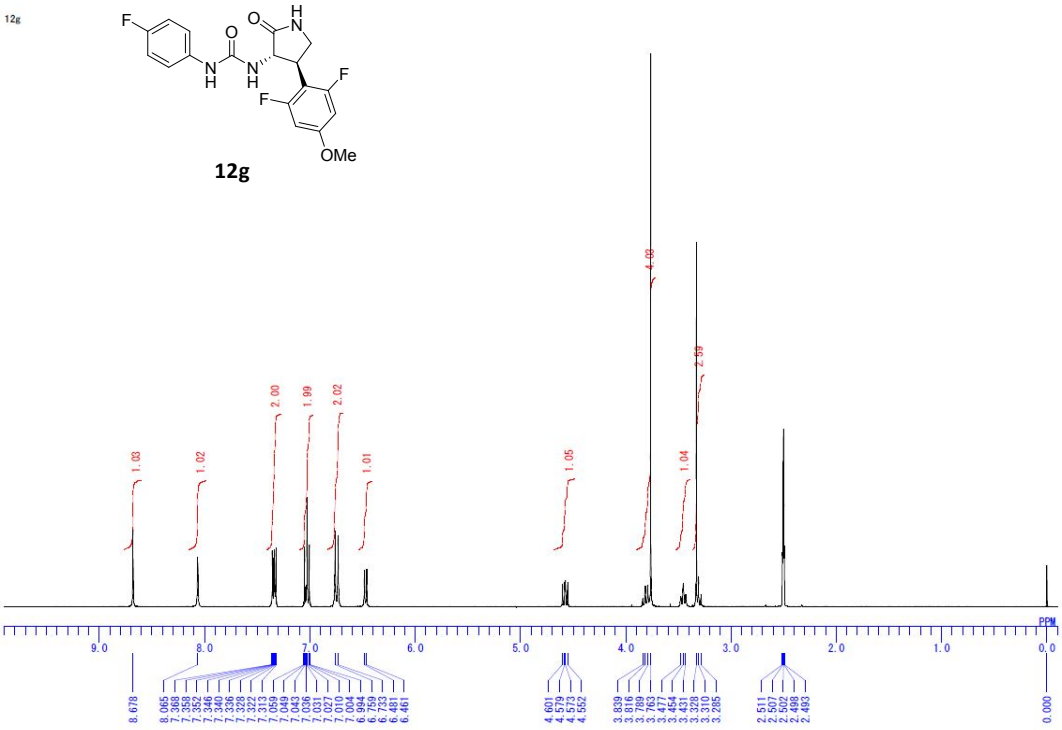
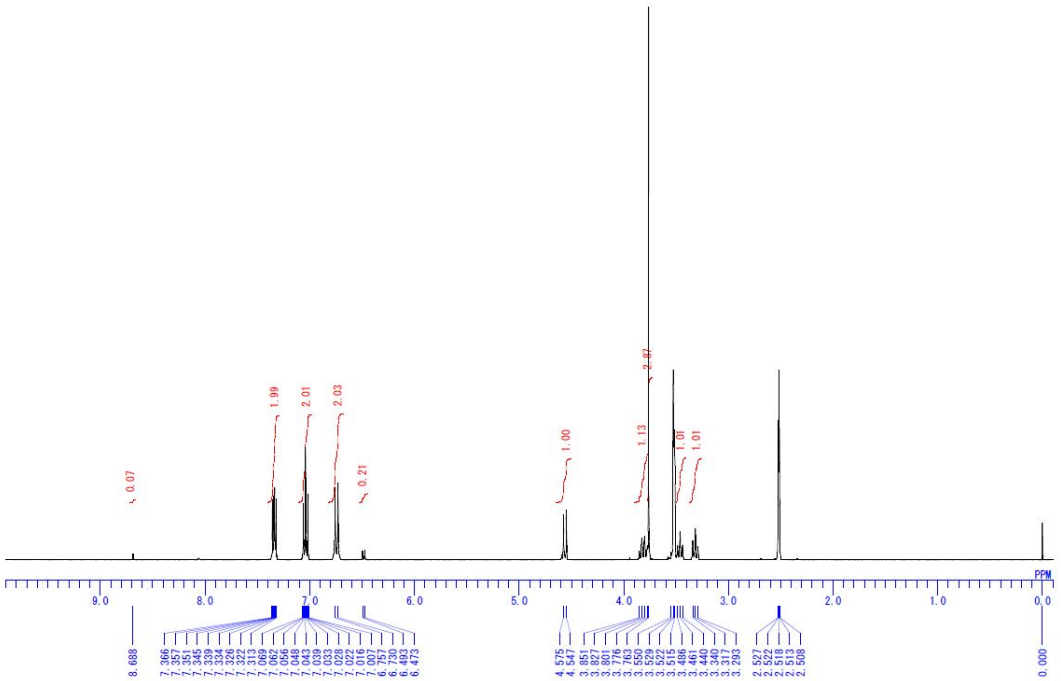
^{1}H NMR Spectrum

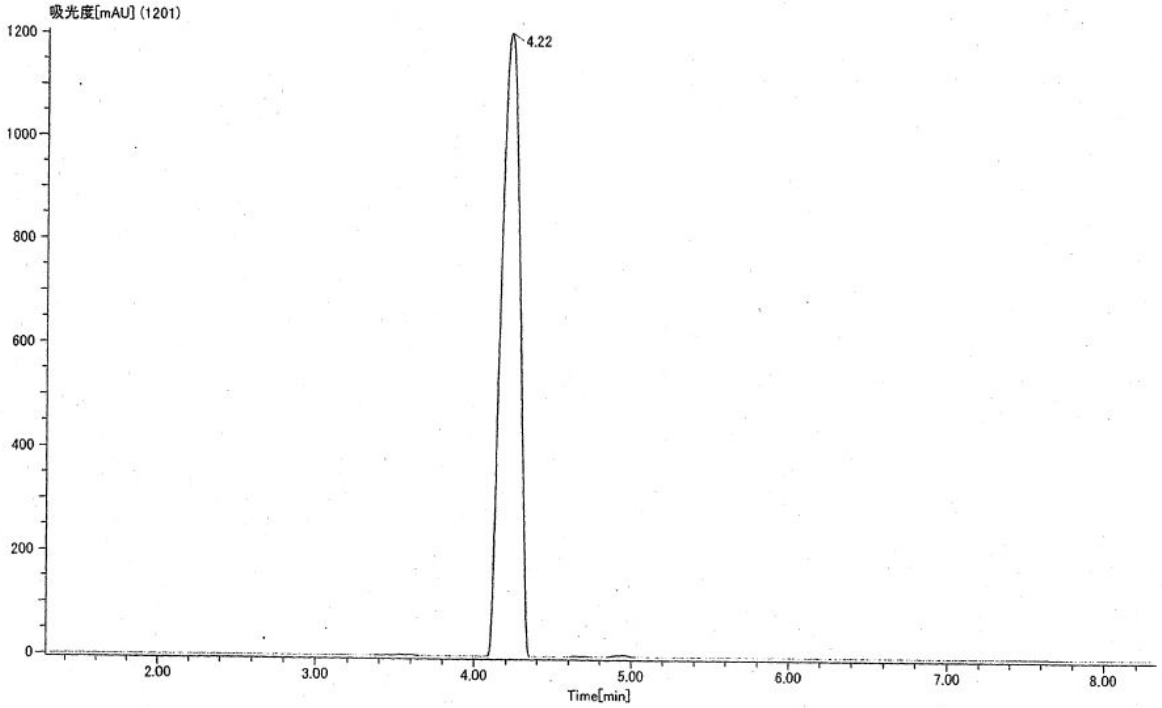


12g (D2O exchange)



HPLC Chromatogram

Purity: 99.4%



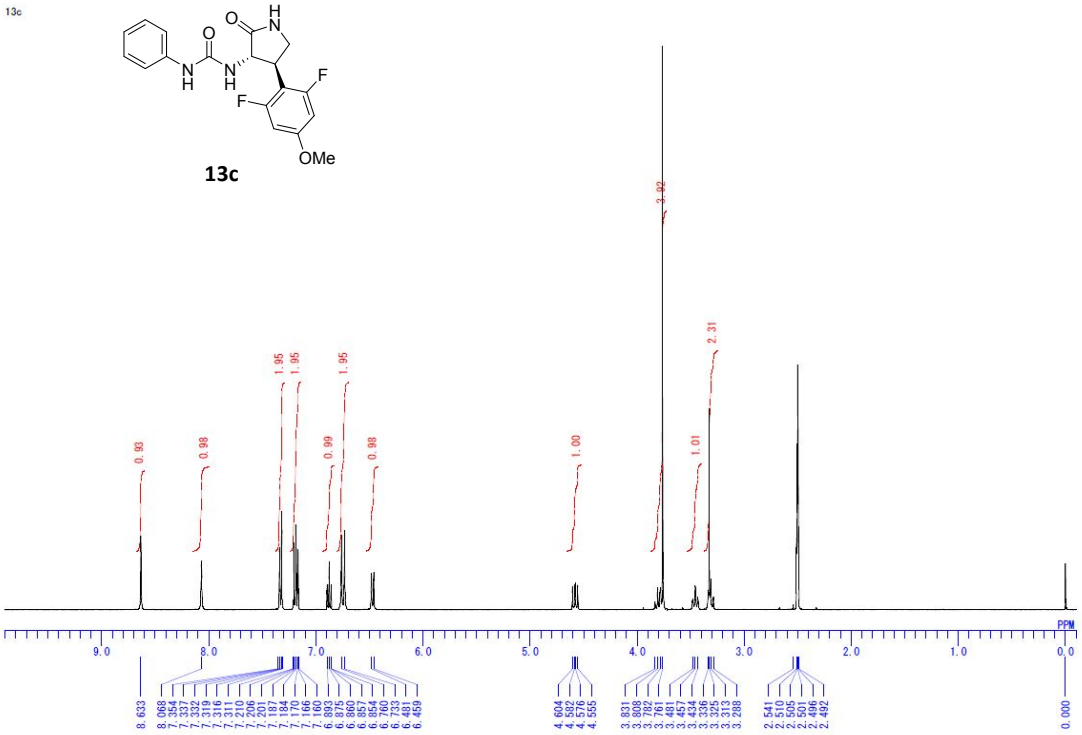
測定データ名: 163-9-P119
試料名(分子量): 163-9-P119(mw=379)
イオン化モード: 1:デュアルESI+
波長範囲: 231[nm]
実験日時: 2013/05/27 9:29:10

装置構成: JMS-T100LP

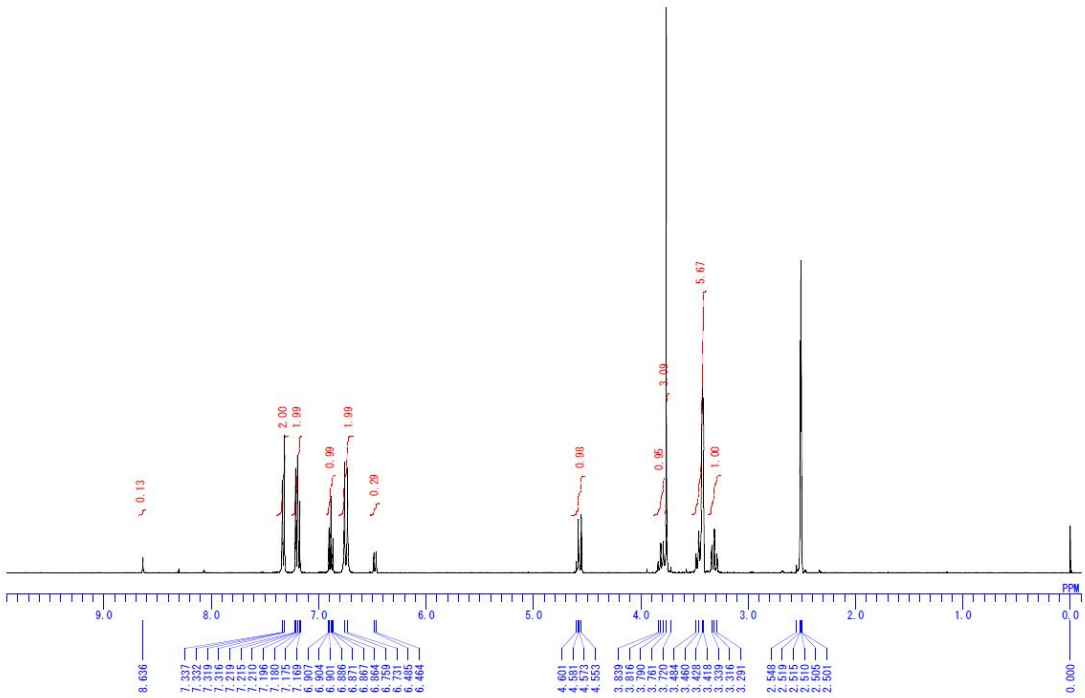
波長: 200..500[nm]

ピーク番号	Time [min]	タイプ	面積 [Intens.*sec]	面積 [% Max.]	面積 [% of Total]	高さ	説明	開始点 時間[min]	終了点 時間[min]
1	3.56	BB	21.77	0.22	0.22	2.37		3.28	3.78
2	4.22	BB	9811.55	100.00	99.38	1201.05		4.04	4.40
3	4.94	BB	28.92	0.29	0.29	3.42		4.54	5.08
4	7.56	BB	10.64	0.11	0.11	0.48		6.62	8.27

^{1}H NMR Spectrum

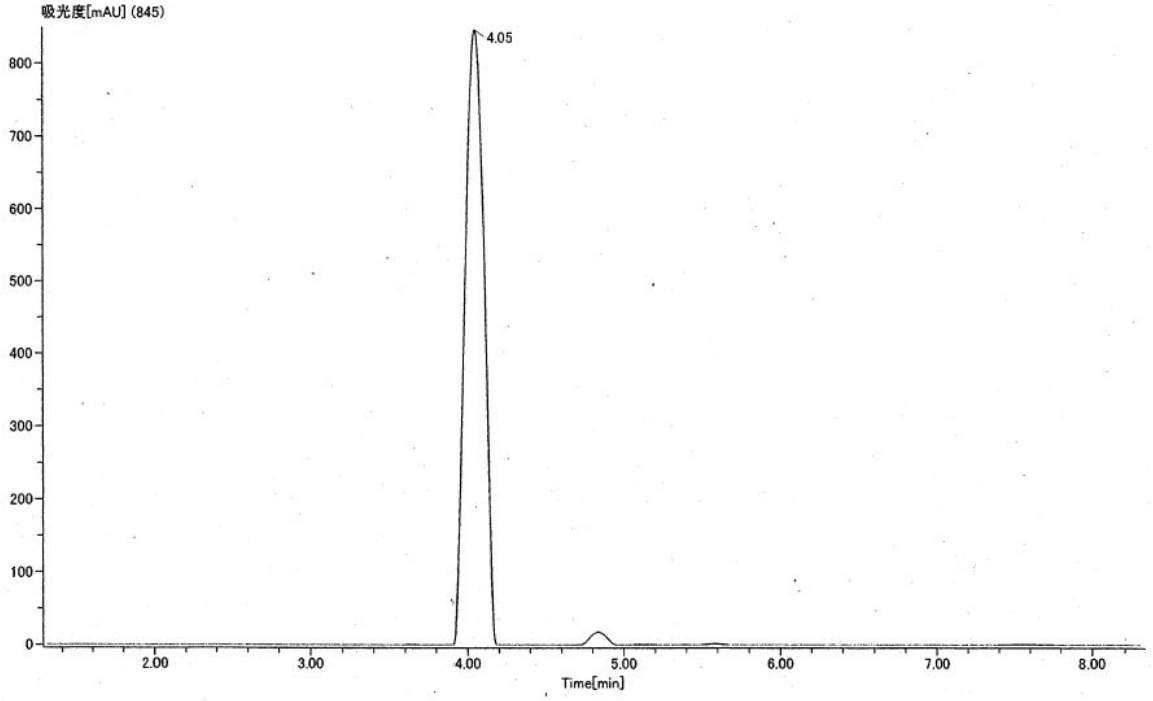


13c (D2O exchange)



HPLC Chromatogram

Purity: 98.1%



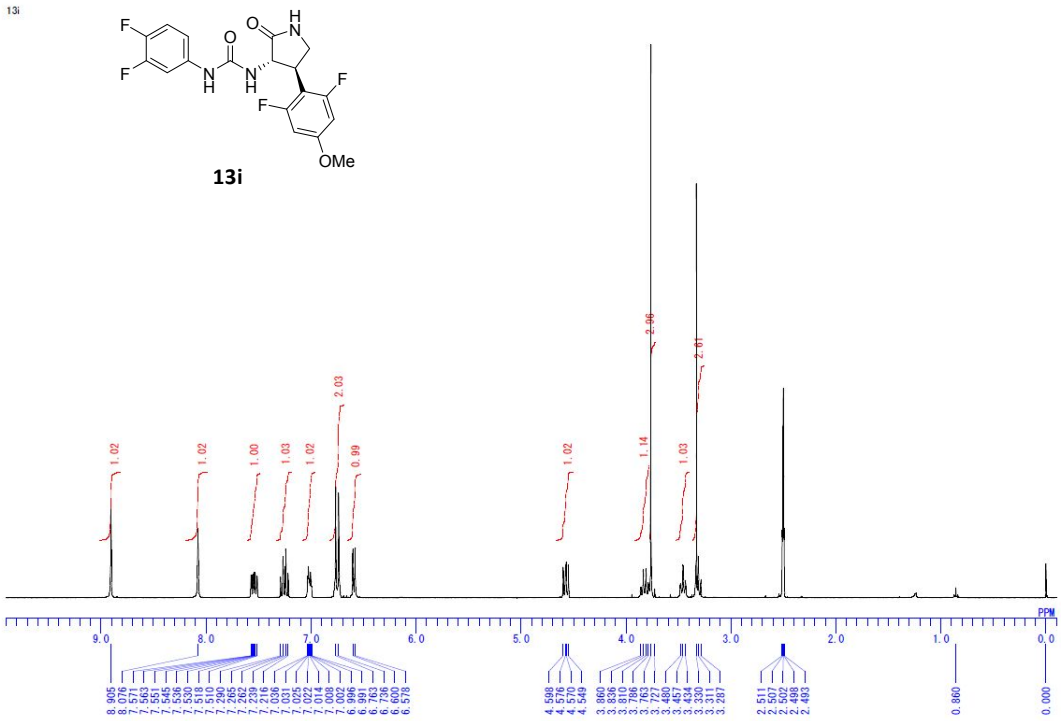
測定データ名: 172-1-P062
試料名(分子量): 172-1-P062(mw=361)
イオン化モード: 1:デュアルESI+
波長範囲: 230[nm]
実験日時: 2013/06/17 13:51:18

装置構成: JMS-T100LP

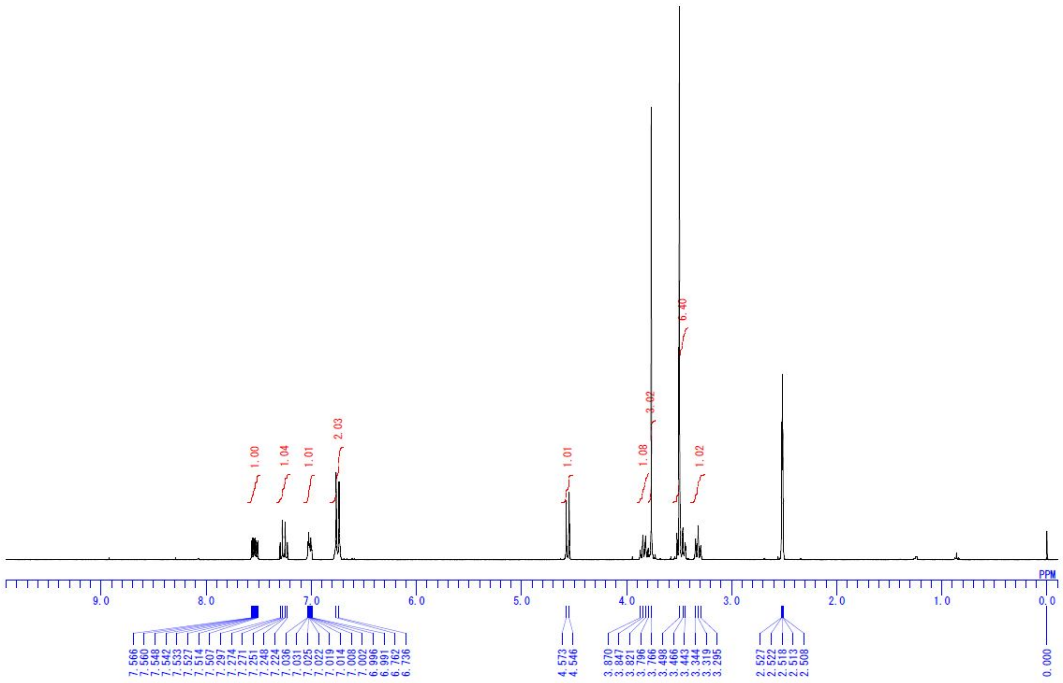
波長: 200..500[nm]

ピーク番号	Time [min]	タイプ	面積 [Intens.*sec]	面積 [% Max.]	面積 [% of Total]	高さ	説明	開始点 時間[min]	終了点 時間[min]
1	4.05	BB	7146.29	100.00	98.08	845.01		3.86	4.24
2	4.83	BB	125.71	1.76	1.73	17.70		4.65	4.96
3	5.57	BB	14.17	0.20	0.19	1.43		5.00	6.04

^{1}H NMR Spectrum

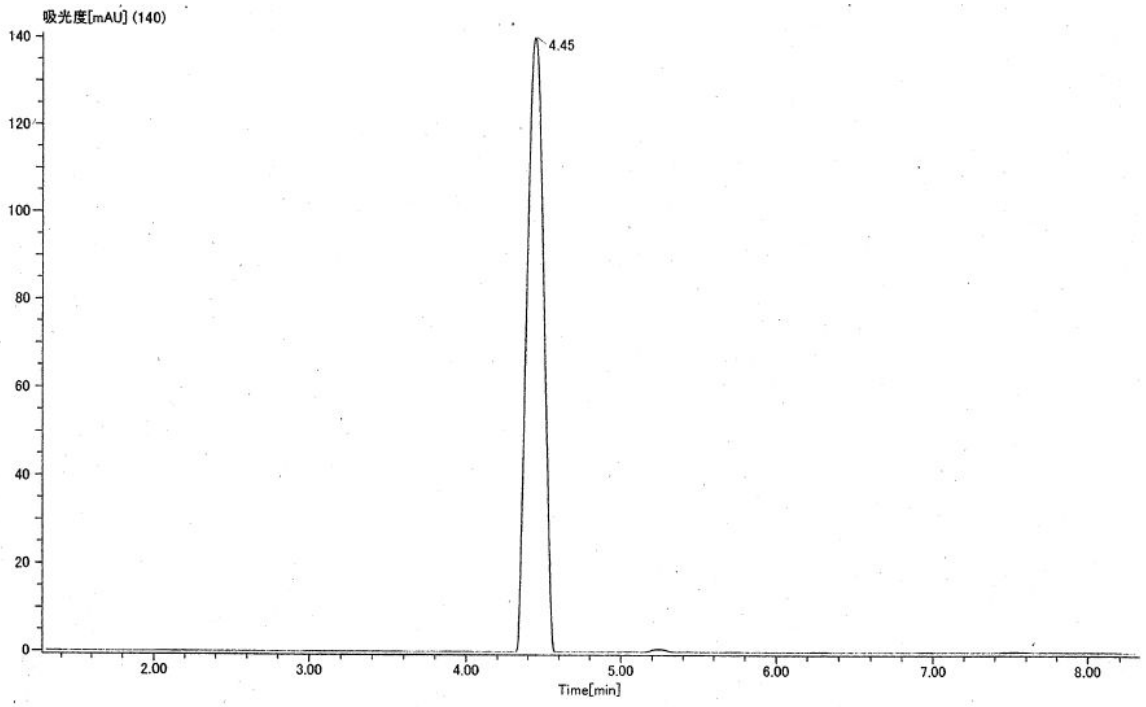


13i (D2O exchange)



HPLC Chromatogram

Purity: 99.5%



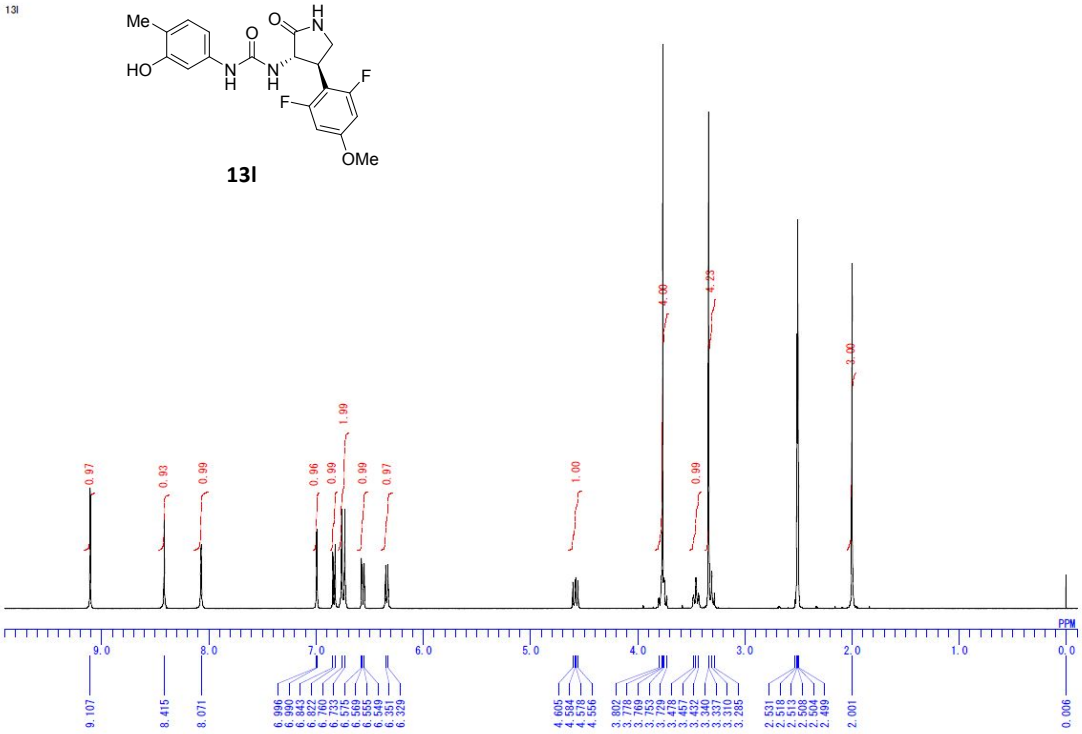
測定データ名: 172-1-P149
試料名(分子量): 172-1-P149(mw=397)
イオン化モード: 1:デュアルESI+
波長範囲: 272[nm]
実験日時: 2013/08/22 14:40:34

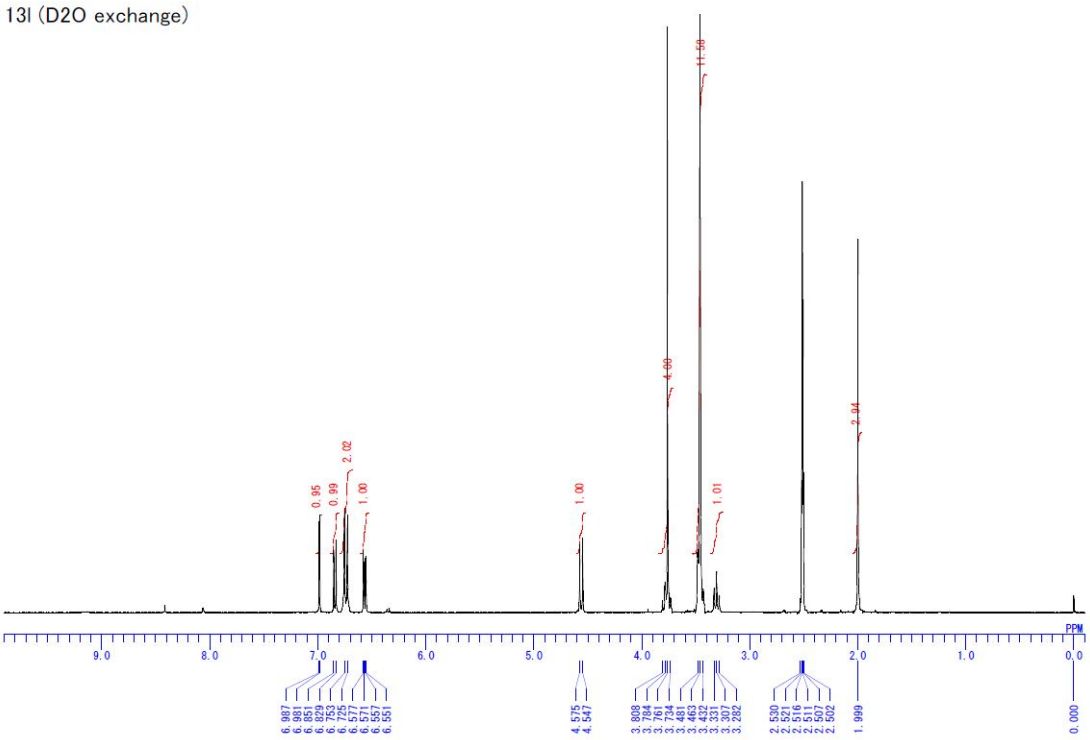
装置構成: JMS-T100LP

波長: 200..500[nm]

ピーク番号	Time [min]	タイプ	面積 [Intens.*sec]	面積 [% Max.]	面積 [% of Total]	高さ	説明	開始点時間[min]	終了点時間[min]
1	4.45	BB	1043.33	100.00	99.45	140.14		4.27	4.63
2	5.24	BB	4.37	0.42	0.42	0.67		5.09	5.37
3	7.53	BB	1.45	0.14	0.14	0.16		7.29	8.06

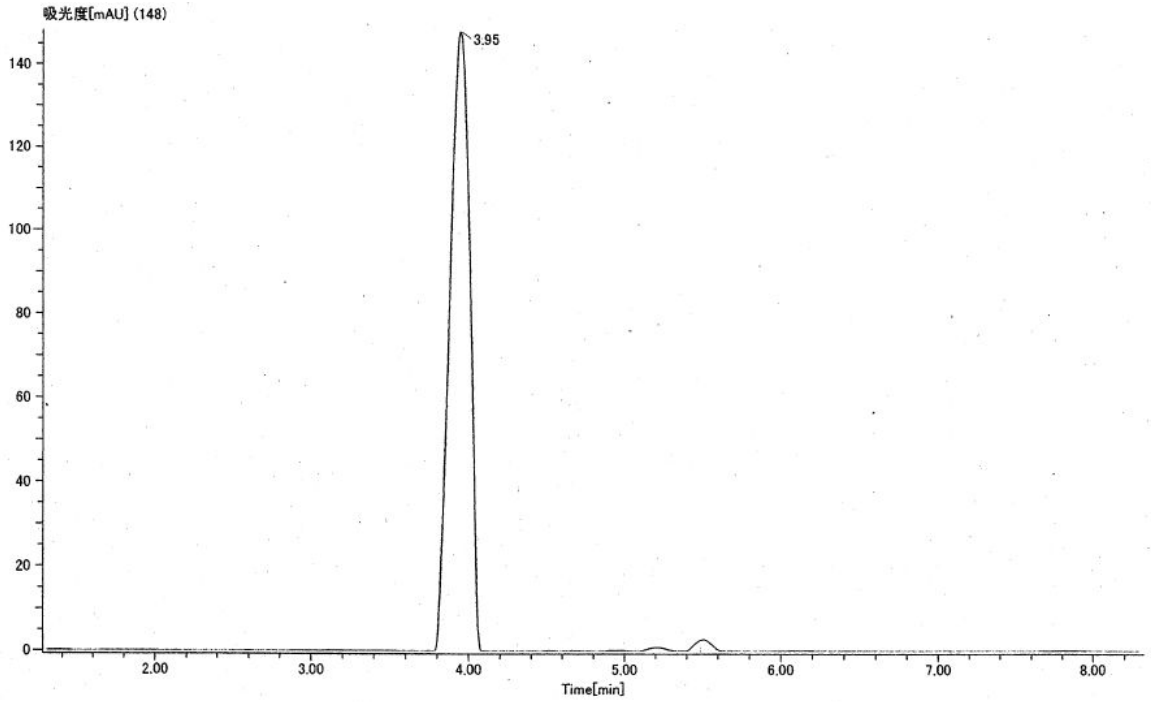
^{1}H NMR Spectrum





HPLC Chromatogram

Purity: 97.9%



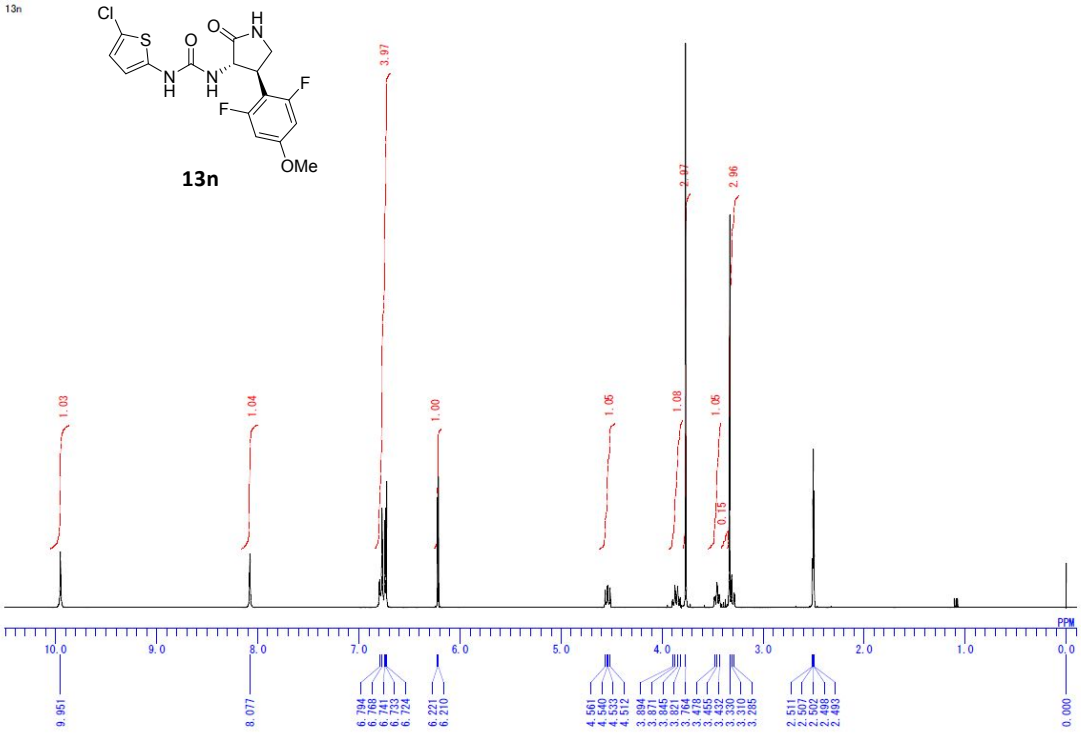
測定データ名: 148-10-1731
試料名(分子量): 148-10-1731(mw=391)
イオン化モード: 1:デュアルESI+
波長範囲: 283[nm]
実験日時: 2014/05/08 9:28:28

装置構成: JMS-T100LP

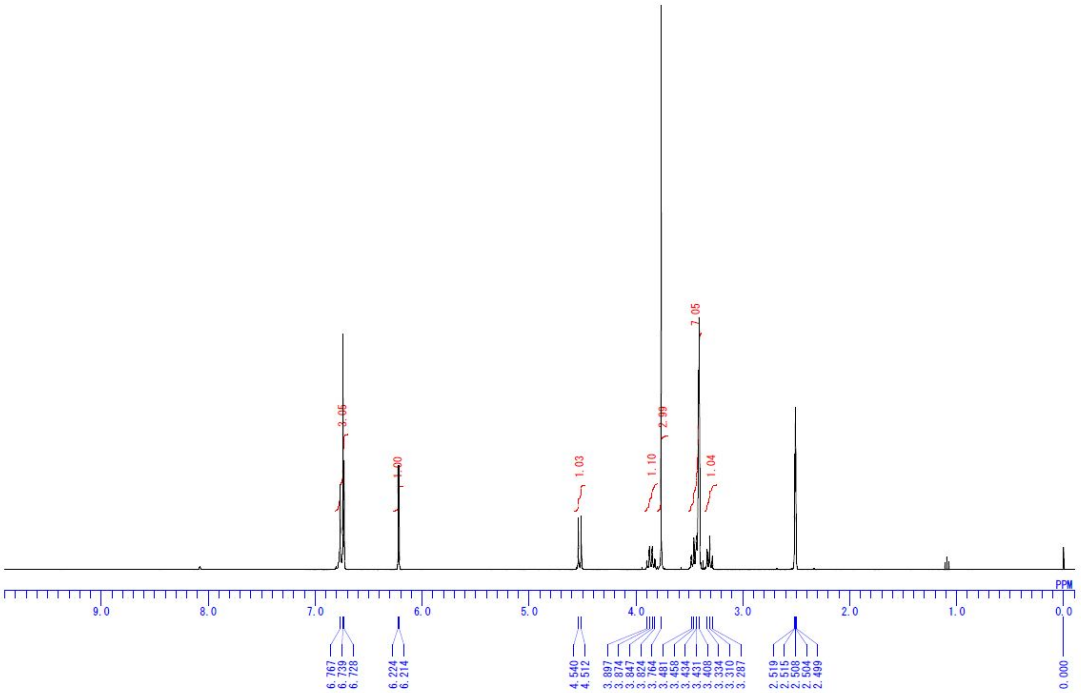
波長: 200..500[nm]

ピーク番号	Time [min]	タイプ	面積 [Intens.*sec]	面積 [% Max.]	面積 [% of Total]	高さ	説明	開始点 時間[min]	終了点 時間[min]
1	3.95	BB	1302.64	100.00	97.93	147.56		3.70	4.20
2	4.51	BB	0.56	0.04	0.04	0.07		4.35	4.79
3	4.93	BB	0.94	0.07	0.07	0.15		4.83	5.05
4	5.21	BB	6.42	0.49	0.48	0.85		5.08	5.34
5	5.51	BB	19.66	1.51	1.48	2.68		5.37	5.68

^{1}H NMR Spectrum

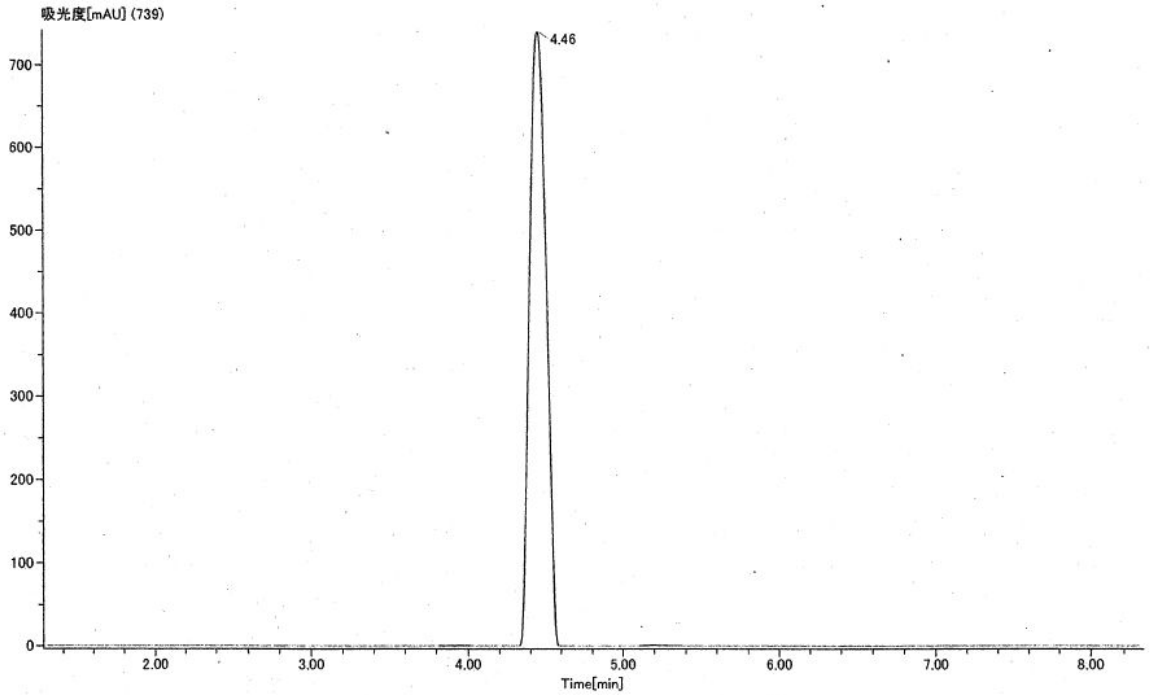


13n (D2O exchange)



HPLC Chromatogram

Purity: 99.8%



測定データ名: 172-1-P064
試料名(分子量): 172-1-P064(mw=401)
イオン化モード: 1:デュアルESI+
波長範囲: 274[nm]
実験日時: 2013/07/08 14:56:59

装置構成: JMS-T100LP

波長: 200..500[nm]

ピーク番号	Time [min]	タイプ	面積 [Intens.*sec]	面積 [% Max.]	面積 [% of Total]	高さ	説明	開始点 時間[min]	終了点 時間[min]
1	3.92	BB	3.47	0.06	0.06	0.44		3.44	4.18
2	4.46	BB	5543.14	100.00	99.78	738.94		4.28	4.66
3	5.19	BB	8.49	0.15	0.15	0.92		4.96	5.50