

Supporting Information for

Discovery of ABBV/GLPG-3221, a Potent Corrector of CFTR for the Treatment of Cystic Fibrosis

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The synthesis of compound **19** is shown in Scheme S1 and the subsequent experimentals.

The synthesis of compounds **5-7** is shown in Scheme S2 and the subsequent experimentals.

The synthesis of compounds **8** and **10** is shown in Scheme S3 and the subsequent experimentals.

The synthesis of compound **9** is shown in Scheme S4 and the subsequent experimentals.

The synthesis of compound **11** is shown in Scheme S5 and the subsequent experimentals.

The synthesis of compounds **12** and **13** is shown in Scheme S6 and the subsequent experimentals.

The synthesis of compound **14** is shown in Scheme S7 and the subsequent experimentals.

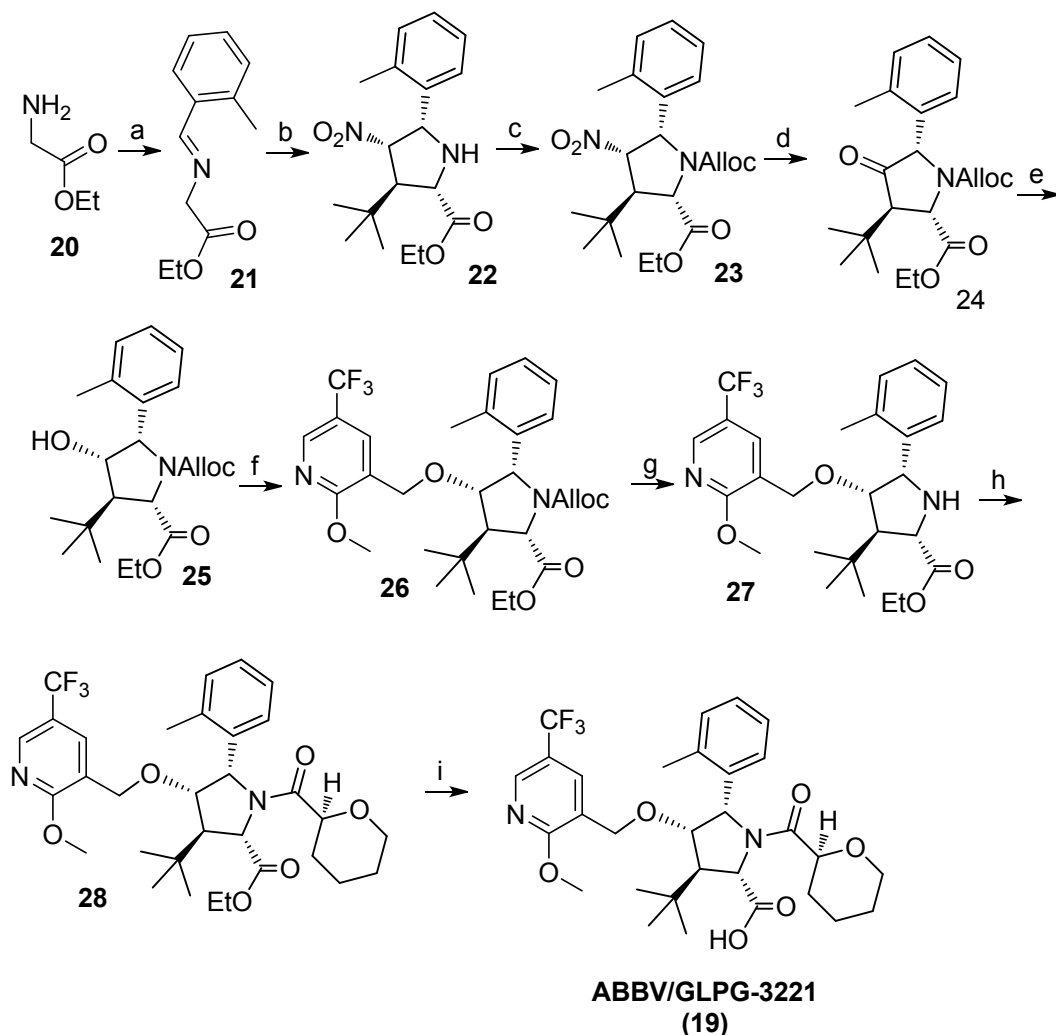
The synthesis of compound **15** is shown in Scheme S8 and the subsequent experimentals.

The synthesis of compound **16** is shown in Scheme S9 and the subsequent experimentals.

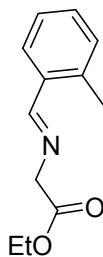
The synthesis of compound **17** is shown in Scheme S10 and the subsequent experimentals.

The synthesis of compound **18** is shown in Scheme S11 and the subsequent experimentals.

Scheme S1. Discovery Synthesis of ABBV/GLPG-3221 (19)^a

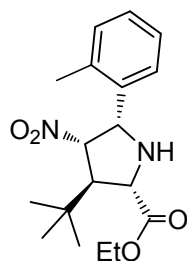


^aReagents and conditions: (a) MgSO₄, TEA, 2-methylbenzaldehyde, DCM; (b) (2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron, Cu(OTf)₂, KOtBu, (*E*)-3,3-dimethyl-1-nitrobut-1-ene, THF; (c) allyl chloroformate, toluene; (d) PDC, 6N HCl, Zn dust, (e) NaBH₄, EtOH; (f) KOtBu, 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine, DMF; (g) 1,3-Dimethylbarbituric acid, Pd(PPh₃)₄, EtOAc/DCM; (h) Tetrahydropyran-2-carboxylic acid, oxalyl chloride, DMF, DCM; (i) LiOH, MeOH/THF.



(*E*)-ethyl 2-((2-methylbenzylidene)amino)acetate (21)

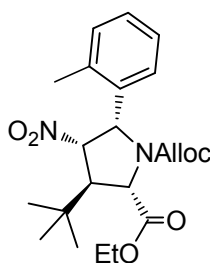
Ethyl 2-aminoacetate hydrochloride (3.97 g, 28.5 mmol) and magnesium sulfate (3.43 g, 28.5 mmol) were stirred in dichloromethane (43.1 mL) at ambient temperature, and triethylamine (3.97 mL, 28.5 mmol) was added. The mixture was stirred for 5 minutes and 2-methylbenzaldehyde (2.97 mL, 25.9 mmol) was added dropwise. The mixture was stirred at ambient temperature for 16 hours. The solid material was filtered through a disposable plastic frit and washed with dichloromethane. The organic layer was washed with 30 mL of water, dried over sodium sulfate, filtered, and concentrated to provide (*E*)-ethyl 2-((2-methylbenzylidene)amino)acetate as a thick oil (5.3 g, 100 % yield). ¹H NMR (500 MHz, CDCl₃) δ ppm 8.63 (d, J = 1.4 Hz, 1H), 7.96 (dd, J = 7.7, 1.4 Hz, 1H), 7.35 (td, J = 7.5, 1.5 Hz, 1H), 7.32 - 7.25 (m, 1H), 7.25 - 7.18 (m, 1H), 4.45 (d, J = 1.4 Hz, 2H), 4.28 (q, J = 7.2 Hz, 2H), 2.55 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). MS (ESI+) *m/z* 206 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-4-nitro-5-(*o*-tolyl)pyrrolidine-2-carboxylate (22)

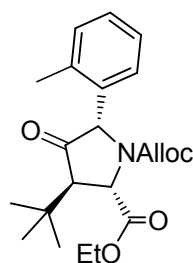
(2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron (0.222 g, 0.294 mmol) and copper (I) triflate dimer, benzene complex (0.064 g, 0.127 mmol) were dissolved in tetrahydrofuran (51.7 mL) that had been sparged with a stream of nitrogen for 4 hours. The resulting mixture was stirred for 1.5 hours at ambient temperature, and (*E*)-ethyl 2-((2-methylbenzylidene)amino)acetate (5.31 g, 25.9 mmol) was added after cooling to <5 °C in an ice-water bath. Potassium 2-methylpropan-2-olate (0.203 mL, 0.203 mmol) was added dropwise, followed by addition of (*E*)-3,3-dimethyl-1-nitrobut-1-ene (3.51 g, 27.2 mmol) neat over 25 minutes, maintaining an internal temperature <10 °C. After the addition was complete, the reaction was stirred for 90 minutes at the same temperature. The reaction mixture was diluted with methyl *tert*-butyl ether (100 mL) and stirred with 50 mL of saturated aqueous ammonium chloride at ambient temperature for 15 minutes. The organic layer was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, and filtered. The filtrate was

concentrated and was diluted with 80 mL of heptanes and the solvent was reduced in volume until a solid precipitated out. The mixture was cooled in an ice bath to <5 °C for 15 minutes, and the resulting material was filtered, washed with 20 mL of heptanes, and dried to constant weight in a vacuum oven to provide (2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-4-nitro-5-(*o*-tolyl)pyrrolidine-2-carboxylate (4.85 g, 14.50 mmol, 56 % yield). ¹H NMR (501 MHz, CDCl₃) δ ppm 7.34 - 7.27 (m, 1H), 7.27 - 7.16 (m, 3H), 5.18 (dd, J = 6.1, 2.6 Hz, 1H), 4.55 (dd, J = 10.1, 5.9 Hz, 1H), 4.35 (qd, J = 7.2, 1.2 Hz, 2H), 3.81 (t, J = 7.1 Hz, 1H), 3.31 (s, 1H), 3.07 (dd, J = 7.3, 2.6 Hz, 1H), 2.41 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.08 (s, 9H). MS (APCI+) *m/z* 335 (M+H)⁺



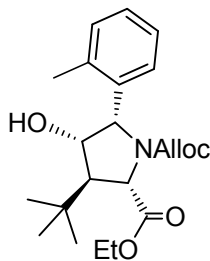
(2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-4-nitro-5-(*o*-tolyl)pyrrolidine-1,2-dicarboxylate (23)

To a mixture of Compound **22** (946 mg, 2.83 mmol) in toluene (3 mL) and saturated aqueous NaHCO₃ (3mL) was added allyl carbonochloridate (360 μL, 3.39 mmol) dropwise at room temperature. The mixture was stirred at room temperature overnight. The reaction was poured into water (50 mL) and extracted with dichloromethane (50 mL). The organic layer was washed with brine and concentrated *in vacuo*. Purification by silica gel chromatography, eluting with ethyl acetate in heptane, provided the title compound, 1.22 g (quantitative yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.79 (dd, J = 7.8, 1.9 Hz, 1H), 7.24 - 7.04 (m, 3H), 5.69 (ddt, J = 17.4, 10.5, 5.1 Hz, 1H), 5.60 (d, J = 8.9 Hz, 1H), 5.55 (dd, J = 8.9, 3.1 Hz, 1H), 5.07 - 4.96 (m, 2H), 4.56 (d, J = 3.9 Hz, 1H), 4.42 (dtd, J = 5.2, 1.7, 0.7 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.08 (t, J = 3.5 Hz, 1H), 2.36 (s, 3H), 1.29 (td, J = 7.1, 0.7 Hz, 3H), 1.03 (d, J = 0.8 Hz, 9H); MS (ESI+) *m/z* 419.0 (M+H)⁺.



(2S,3R,5S)-1-allyl 2-ethyl 3-(*tert*-butyl)-4-oxo-5-(*o*-tolyl)pyrrolidine-1,2-dicarboxylate (24)

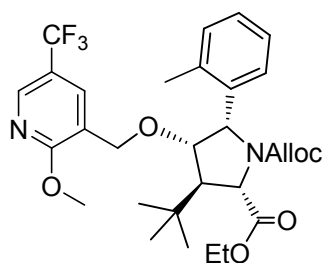
Pyridinium dichromate (2.74 g, 7.29 mmol) was dissolved in 6N aqueous HCl (64.0 mL) and cooled in an ice bath. Zinc dust (5.24 g, 80 mmol) was added in portions, then the flask was removed from the ice bath, and the reaction mixture was stirred at room temperature for 75 minutes (until zinc had dissolved and bubbling had stopped). The blue solution was transferred via cannula over about 20 minutes to a refluxing solution of Compound **23** (1.22 g, 2.92 mmol) in ethanol (32 mL). The reaction mixture was refluxed overnight. The reaction mixture was cooled to room temperature, and extracted three times with dichloromethane. The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The resulting material was taken up in 5.5 mL of ethanol and treated with a solution (prepared at 0°C) of 1.85 mL acetyl chloride in 9 mL ethanol. The reaction mixture was refluxed for 1 hour. After this time, the mixture was concentrated *in vacuo*, and the residue was purified by silica gel chromatography, eluting with 0 to 40% ethyl acetate-heptanes to provide the title compound, 0.693 g, (61% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.68 - 7.61 (m, 1H), 7.21 - 7.06 (m, 3H), 5.70 (m, 1H), 5.23 (s, 1H), 5.08 - 4.97 (m, 2H), 4.63 (d, J = 5.1 Hz, 1H), 4.46 (m, 2H), 4.28 - 4.18 (m, 2H), 2.64 (dd, J = 5.3, 1.0 Hz, 1H), 2.38 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H); MS (ESI⁺) *m/z* 388.0 (M+H)⁺.



(2S,3R,4S,5S)-1-allyl 2-ethyl 3-(*tert*-butyl)-4-hydroxy-5-(*o*-tolyl)pyrrolidine-1,2-dicarboxylate (25)

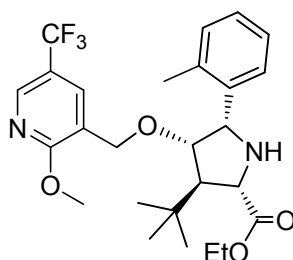
A solution of Compound **24** (0.693 g, 1.789 mmol) in ethanol (8.9 mL) was cooled to -10° and then treated with one portion of sodium borohydride (0.081 g, 2.146 mmol). The reaction stirred

at -10 °C to -5 °C for 90 minutes, and it was quenched carefully with 0.6 mL acetone. The mixture was concentrated *in vacuo*, and the resulting material was taken up in 10 mL ethyl acetate and stirred vigorously with 10 mL of saturated aqueous NaHCO₃ solution for 30 minutes. The mixture was transferred to a separatory funnel, the phases were separated, and the aqueous layer was extracted twice more with ethyl acetate (10 mL each). The combined organics were dried over Na₂SO₄, filtered, and concentrated *in vacuo*, and the crude product was purified by silica gel chromatography, eluting with 5 to 40 % ethyl acetate-heptanes to provide the title compound, 0.280 g (40% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.85 (m, 1H), 7.11 - 7.01 (m, 3H), 5.73 - 5.61 (m, 1H), 5.08 (d, J = 6.6 Hz, 1H), 4.99 (m, 2H), 4.45 - 4.33 (m, 3H), 4.30 (m, 1H), 4.22 - 4.12 (m, 2H), 3.82 (m, 1H), 2.29 (s, 3H), 2.28 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 0.99 (s, 9H); MS (ESI⁺) *m/z* 390.1 (M+H).



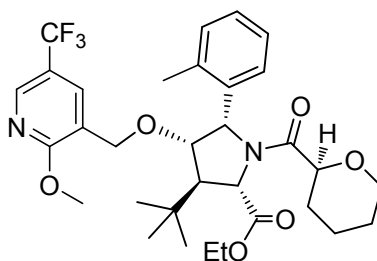
(2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-5-(*o*-tolyl)pyrrolidine-1,2-dicarboxylate (26)

Compound **25** (0.280 g, 0.719 mmol), dried azeotropically with toluene, was dissolved in dimethylformamide (7.2 mL), and the solution was cooled to 0 °C. Potassium 2-methylpropan-2-olate solution (1M in tetrahydrofuran) (0.79 mL, 0.79 mmol) was added dropwise, followed by dropwise addition of 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine (0.233 g, 0.863 mmol). The reaction mixture stirred at 0 °C for 45 minutes, the mixture was poured into 30 mL of saturated aqueous NH₄Cl solution and extracted three times with methyl *tert*-butyl ether (3 x 30 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated *in vacuo*, and the crude product was purified by silica gel chromatography, eluting with 0 to 30% methyl *tert*-butyl ether-heptanes to provide the title compound, 0.224 g (54% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.28 (m, 1H), 7.85 (tt, J = 4.6, 3.0 Hz, 0H), 7.18 - 7.13 (m, 1H), 7.04 - 6.96 (m, 3H), 5.69 (ddt, J = 16.3, 10.5, 5.1 Hz, 1H), 5.19 (d, J = 5.8 Hz, 1H), 5.06 - 4.95 (m, 2H), 4.48 (d, J = 2.3 Hz, 1H), 4.40 (dq, J = 5.1, 1.5 Hz, 2H), 4.34 - 4.22 (m, 2H), 4.11 (q, J=7.0 Hz, 2H), 3.86 (s, 3H), 3.83 (dt, J = 13.7, 1.1 Hz, 1H), 2.86 - 2.79 (m, 1H), 2.51 (m, 1H), 2.31 (s, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.03 (s, 9H); MS (ESI⁺) *m/z* 578.9 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-5-(*o*-tolyl)pyrrolidine-2-carboxylate (27)

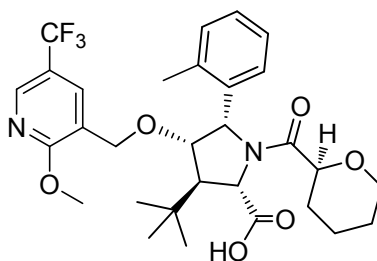
Compound **26** (0.224 g, 0.387 mmol) was dissolved in ethyl acetate (2 mL) and dichloromethane (2 mL), and the solution was treated with 1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (0.121 g, 0.774 mmol) and tetrakis(triphenylphosphine)palladium (4.5 mg, 3.87 μ mol). The reaction stirred at room temperature overnight. After this time, the reaction mixture was diluted with methyl *tert*-butyl ether (20 mL) and stirred with 20 mL of 10% aqueous Na₂CO₃ solution for 15 minutes. The phases were then separated, and the organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Silica gel chromatography, eluting with 0 to 30% methyl *tert*-butyl ether-heptanes, provided the title compound, 0.176 g (92 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.30 (s, 1H), 7.66 - 7.50 (m, 1H), 7.35 (d, *J* = 2.4 Hz, 1H), 7.05 (m, 3H), 4.34 - 4.10 (m, 5H), 4.10 - 3.99 (m, 1H), 3.86 (s, 3H), 3.79 (d, *J* = 13.9 Hz, 1H), 3.63 (s, 1H), 2.38 (dd, *J* = 6.5, 1.7 Hz, 1H), 2.32 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.99 (s, 9H); MS (APCI⁺) *m/z* 495.6 (M+H)⁺.



Ethyl (2*S*,3*R*,4*S*,5*S*)-3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-1-((*S*)-tetrahydro-2*H*-pyran-2-carbonyl)-5-(*o*-tolyl)pyrrolidine-2-carboxylate (28)

Tetrahydropyran-2-carboxylic acid (64.1 mg, 0.493 mmol) was dissolved in dichloromethane (2 mL). Oxalyl chloride (2M in dichloromethane, 300 μ L, 0.60 mmol) was added followed by dimethylformamide (25 μ L). The reaction was stirred at ambient temperature for 3 hours, at which point it was concentrated, redissolved in dichloromethane (1 mL), and concentrated again. The residue was taken up in dichloromethane (3 x 1 mL) and added to a solution of Compound **27** (116 mg, 0.235 mmol) and triethylamine (130 μ L, 0.933 mmol) in dichloromethane (3 mL). The reaction was stirred at ambient

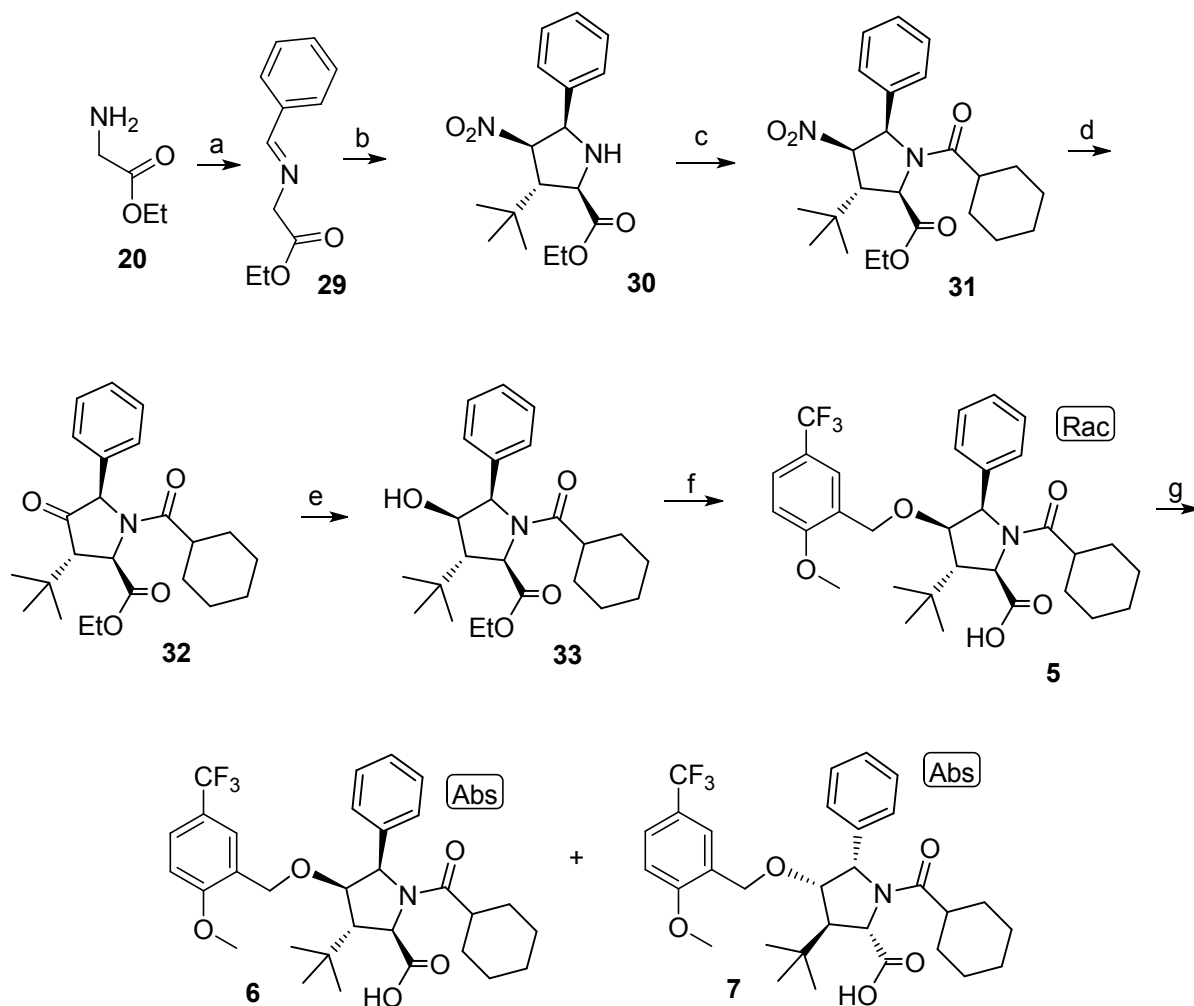
temperature for 17 hours. After this time, the mixture was diluted with dichloromethane (100 mL) and washed twice with saturated NaHCO₃, and once with brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by reverse-phase preparative HPLC on a Phenomenex® Luna® C8(2) 5 μm 100Å AXIA™ column (30 mm × 75 mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50 mL/minute (0-0.5 minutes 10% A, 0.5-7.0 minutes linear gradient 10-95% A, 7.0-10.0 minutes 95% A, 10.0-12.0 minutes linear gradient 95-10% A). The title compound was the second eluting diastereomer and was isolated as the TFA salt (43.1 mg, 26%). ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.28 (s, 1H), 8.01 – 7.91 (m, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.13 – 6.91 (m, 3H), 5.56 (s, 1H), 4.68 (s, 1H), 4.33 – 4.21 (m, 3H), 4.09 (qd, *J* = 7.1, 2.8 Hz, 2H), 3.86 (s, 3H), 3.82 (d, *J* = 13.9 Hz, 1H), 3.75 (d, *J* = 11.4 Hz, 1H), 2.90 (s, 1H), 2.42 (t, *J* = 1.3 Hz, 1H), 2.34 (s, 3H), 1.77 – 1.22 (m, 6H), 1.14 (t, *J* = 7.0 Hz, 3H), 1.02 (s, 9H); MS (ESI+) *m/z* 607 (M+H)⁺.



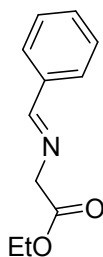
(2*S*,3*R*,4*S*,5*S*)-3-*tert*-Butyl-4-{{2-methoxy-5-(trifluoromethyl)pyridin-3-yl}methoxy}-5-(2-methylphenyl)-1-[(2*S*)-oxane-2-carbonyl]pyrrolidine-2-carboxylic acid (19, ABBV-3221)

Compound **28** (40.7 mg, 0.056 mmol) was dissolved in methanol (1 mL), and tetrahydrofuran (1 mL). Aqueous LiOH (1 M, 0.5 mL, 0.5 mmol) was added and the reaction was heated to 50 °C for 16 hours. The reaction was quenched by the addition of 1M aqueous HCl (0.5 mL), concentrated and purified by reverse-phase preparative HPLC on a Phenomenex® Luna® C8(2) 5 μm 100Å AXIA™ column (30 mm × 75 mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50 mL/minute (0-0.5 minutes 10% A, 0.5-7.0 minutes linear gradient 10-95% A, 7.0-10.0 minutes 95% A, 10.0-12.0 minutes linear gradient 95-10% A) to provide the title compound (27.0 mg, 69%) as the TFA salt. ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.31 - 8.24 (m, 1H), 8.08 - 7.99 (m, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.11 - 6.98 (m, 3H), 5.56 (s, 1H), 4.64 (s, 1H), 4.32 - 4.24 (m, 2H), 3.91 - 3.82 (m, 5H), 3.76 (d, *J* = 11.3 Hz, 2H), 2.50 (s, 1H), 2.33 (s, 3H), 1.74 - 1.23 (m, 6H), 1.02 (s, 9H); MS (ESI+) *m/z* 579.3 (M+H)⁺.

Scheme S2. Discovery Synthesis of Compounds 5-7^a

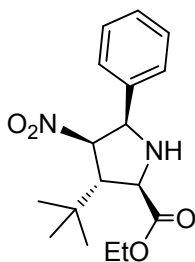


^aReagents and conditions: (a) MgSO₄, TEA, 2-methylbenzaldehyde, DCM; (b) Ag(OAc)₂, *(E)*-3,3-dimethyl-1-nitrobut-1-ene, TEA, 3 Å molecular sieves, toluene; (c) cyclohexanecarbonyl chloride, TEA, DCM; (d) PDC, 6N HCl, Zn dust, (e) NaBH₄, MeOH; (f) NaH, 2-(bromomethyl)-1-methoxy-4-(trifluoromethyl)benzene, DMF; LiOH, MeOH; (g) chiral preparative SFC.



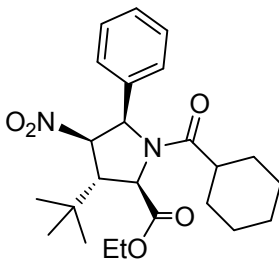
(*E*)-ethyl 2-(benzylideneamino)acetate (29)

To a mixture of glycine ethyl ester hydrochloride (7.23 g, 51.8 mmol) and magnesium sulfate (7.09 g, 58.9 mmol) in dichloromethane (80 mL) was added triethylamine (7.22 mL, 51.8 mmol). The mixture was stirred at ambient temperature for 20 minutes, and benzaldehyde (4.79 mL, 47.1 mmol) was added dropwise. The mixture was stirred overnight. The reaction mixture was filtered and the solid was washed with dichloromethane (20 mL x 2). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to yield (*E*)-ethyl 2-(benzylideneamino)acetate 8.2 g, (91 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.30 (s, 1H), 7.83 - 7.71 (m, 2H), 7.48 - 7.37 (m, 2H), 4.40 (d, J = 1.4 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); MS (ESI+) *m/z* 292.1 (M+H)⁺.



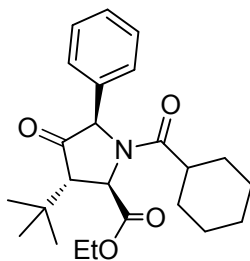
***rac*-(2*R*,3*R*,4*R*,5*R*)-ethyl 3-(*tert*-butyl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (30)**

To a solution of Compound **29** (1.0 g, 5.23 mmol) and (*E*)-3, 3-dimethyl-1-nitrobut-1-ene (0.810 g, 6.28 mmol) in toluene (30 mL) cooled in an ice-bath was added silver acetate (1.309 g, 7.84 mmol) and 3Å molecular sieves. Triethylamine (1.458 mL, 10.46 mmol) was added slowly to the well stirred reaction mixture. After stirring at 0 °C for 10 minutes, the reaction mixture was allowed to warm to ambient temperature and was stirred for another 4 hours. Saturated aqueous ammonium chloride was added, the precipitate was filtered off and the residue was extracted with ether. The combined organic fractions were dried over MgSO₄, filtered, concentrated, and purified by chromatography on 40 g silica gel cartridge, eluting with ethyl acetate in heptane, 0-40% gradient to provide the title compound (1.6 g, 95 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.39 - 7.26 (m, 5H), 5.12 (dd, J = 6.0, 2.5 Hz, 1H), 4.44 (d, J = 5.7 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.81 (d, J = 7.1 Hz, 1H), 3.30 (s, 1H), 2.95 (dd, J = 7.1, 2.5 Hz, 1H), 1.34 (t, J = 7.2 Hz, 3H), 1.06 (s, 9H); MS(ESI+) *m/z* 321 (M+H)⁺.



***rac*-(2*R*,3*S*,4*R*,5*R*)-ethyl 3-(*tert*-butyl)-1-(cyclohexanecarbonyl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (31)**

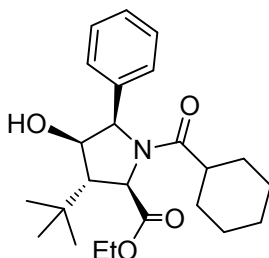
A solution of Compound 30 (5.0 g, 15.61 mmol) and triethylamine (3.27 mL, 23.41 mmol) in dichloromethane (40 mL) cooling in an ice-bath was treated with cyclohexanecarbonyl chloride (2.71 mL, 20.29 mmol). The mixture was stirred at 0 °C for 30 minutes and was allowed to warm to room temperature. Dichloromethane (20 mL) was added. The mixture was washed with saturated aqueous NaHCO₃ and brine, and dried over MgSO₄, filtered and concentrated. Purification via chromatography on an 80 g silica gel cartridge eluting with ethyl acetate in heptanes at 0-40 % gradient provided the title compound 6.2 g (92 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.64 (d, J = 7.1 Hz, 2H), 7.42 - 7.31 (m, 3H), 5.43 (d, J = 9.1 Hz, 1H), 5.34 (dd, J = 9.0, 4.4 Hz, 1H), 4.79 (d, J = 4.6 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.12 (t, J = 4.7 Hz, 1H), 2.03 (dd, J = 13.3, 10.0 Hz, 1H), 1.85 - 1.65 (m, 2H), 1.61 (d, J = 13.1 Hz, 1H), 1.54 - 1.38 (m, 4H), 1.35 (d, J = 7.2 Hz, 3H), 1.27 (d, J = 13.7 Hz, 1H), 1.15 (d, J = 14.5 Hz, 1H), 1.04 (s, 9H), 0.56 (q, J = 13.2 Hz, 1H); MS (ESI+) *m/z* 431 (M+H).



***rac*-(2*R*,3*S*,5*R*)-methyl 3-(*tert*-butyl)-1-(cyclohexanecarbonyl)-4-oxo-5-phenylpyrrolidine-2-carboxylate (32)**

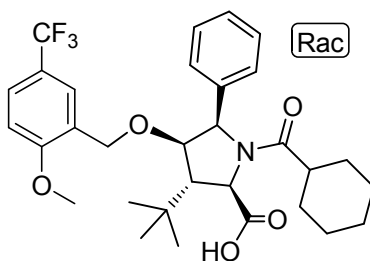
Potassium dichromate (5.11 g, 17.37 mmol) was dissolved in 6 M aqueous HCl acid (60 mL) and zinc (6 g, 92 mmol) was added under N₂ atmosphere. Complete dissolution of the zinc provided a clear light blue solution. The formed chromium(II) chloride was transferred to a refluxing solution of Compound 31 (1.1 g, 2.55 mmol) in ethanol (60 mL) under N₂. The reaction mixture was refluxed for 16 hours. LC/MS indicated conversion was complete and two products were formed, one was desired product and another was hydrolyzed acid. The mixture was cooled to ambient temperature and extracted with ethyl acetate (60 mL x 3). The organics were washed with saturated aqueous NaHCO₃ solution and brine, dried over MgSO₄, filtered, and concentrated. The residue was dissolved in ethanol (5 mL), cooled in an ice-bath, and acetyl chloride (1 mL) in ethanol (2 mL) was slowly added. The mixture was stirred at 60 °C for 2 hours and LC/MS indicated all acid was converted to the ester. The solvent was reduced in volume and the crude material was purified via chromatography on a 80 g silica gel cartridge, eluting with ethyl acetate in heptanes using a 0-40% gradient to provide the title compound (860 mg, 86% yield). ¹H NMR

(400 MHz, CDCl₃) δ ppm 7.68 (dd, $J = 7.3, 1.7$ Hz, 2H), 7.45 – 7.38 (m, 2H), 7.37 – 7.31 (m, 1H), 4.90 (s, 1H), 4.84 (d, $J = 5.0$ Hz, 1H), 4.28 (q, $J = 7.2$ Hz, 2H), 2.54 (dd, $J = 5.0, 1.0$ Hz, 1H), 2.08 (tt, $J = 11.4, 3.3$ Hz, 1H), 1.70 (t, $J = 14.9$ Hz, 2H), 1.54 – 1.48 (m, 2H), 1.47 – 1.37 (m, 2H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.10 (s, 9H), 0.92 – 0.82 (m, 4H); MS (ESI+) m/z 400.1 (M+H).



***rac*-(2*R*,3*S*,4*R*,5*R*)-ethyl 3-(*tert*-butyl)-1-(cyclohexanecarbonyl)-4-hydroxy-5-phenylpyrrolidine-2-carboxylate (33)**

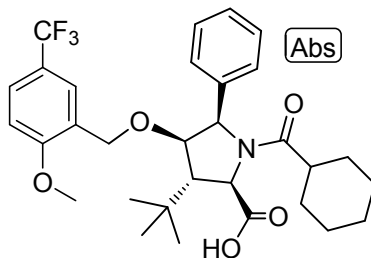
A solution of Compound **32** (200 mg, 0.501 mmol) in methanol (10 mL) was cooled in an ice-bath and was treated with sodium borohydride (37.9 mg, 1.001 mmol). The mixture was stirred at 0 °C for 30 minutes, and was allowed to warm to ambient temperature. The solvent was removed and dichloromethane (20 mL) was added. The mixture was washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄, filtered, and concentrated to provide title compound, 196 mg (98 % yield) which used in next step without further purification. LC/MS (APCI+) m/z 402 (M+H)⁺.



***rac*-(2*R*,3*S*,4*R*,5*R*)-3-*tert*-butyl-1-(cyclohexanecarbonyl)-4-{[2-methoxy-5-(trifluoromethyl)phenyl]methoxy}-5-phenylpyrrolidine-2-carboxylic acid (5)**

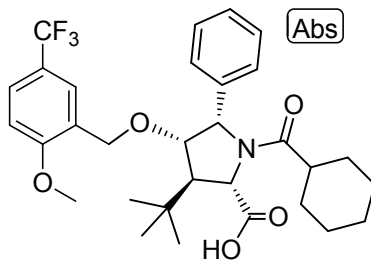
To 2-(bromomethyl)-1-methoxy-4-(trifluoromethyl)benzene (40 mg, 0.149 mmol) and Compound **33** (49.7 mg, 0.124 mmol) in dimethylformamide (1.0 mL) in an ice-bath was added sodium hydride (7.43 mg, 0.186 mmol) portionwise. The mixture was warmed to 60 °C and stirred for 3 hours. Ethyl acetate and water were added. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was dissolved in methanol (2 mL) and 6M aqueous LiOH (0.5 mL) and stirred at 50 °C overnight. The mixture was adjusted

to pH 1~2 by adding 2M aqueous HCl. The reaction mixture was extracted with ethyl acetate. The organic layers were combined, dried over sodium sulfate, and concentrated. The residue was purified via chromatography, eluting with ethyl acetate/methanol (9:1) in heptanes using a 0-40% gradient to provide the title compound, 22 mg (35% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.42 - 7.37 (m, 1H), 7.33 (qd, J = 7.7, 6.7, 3.8 Hz, 3H), 7.25 - 7.20 (m, 2H), 6.81 - 6.75 (m, 2H), 5.17 (d, J = 6.6 Hz, 1H), 4.66 (d, J = 3.7 Hz, 1H), 4.56 (d, J = 13.3 Hz, 1H), 4.22 - 4.11 (m, 2H), 3.77 (s, 3H), 3.15 (t, J = 3.5 Hz, 1H), 2.35 - 2.23 (m, 1H), 1.77 (d, J = 7.1 Hz, 1H), 1.68 (d, J = 13.2 Hz, 2H), 1.55 - 1.41 (m, 2H), 1.40 - 1.20 (m, 2H), 1.14 (t, J = 10.5 Hz, 2H), 1.02 (s, 9H), 0.73 (t, J = 12.8 Hz, 1H); MS (ESI-) *m/z* 560.3 (M-H)⁻.



(2R,3S,4R,5R)-3-tert-butyl-1-(cyclohexanecarbonyl)-4-([2-methoxy-5-(trifluoromethyl)phenyl]methoxy)-5-phenylpyrrolidine-2-carboxylic acid (6)

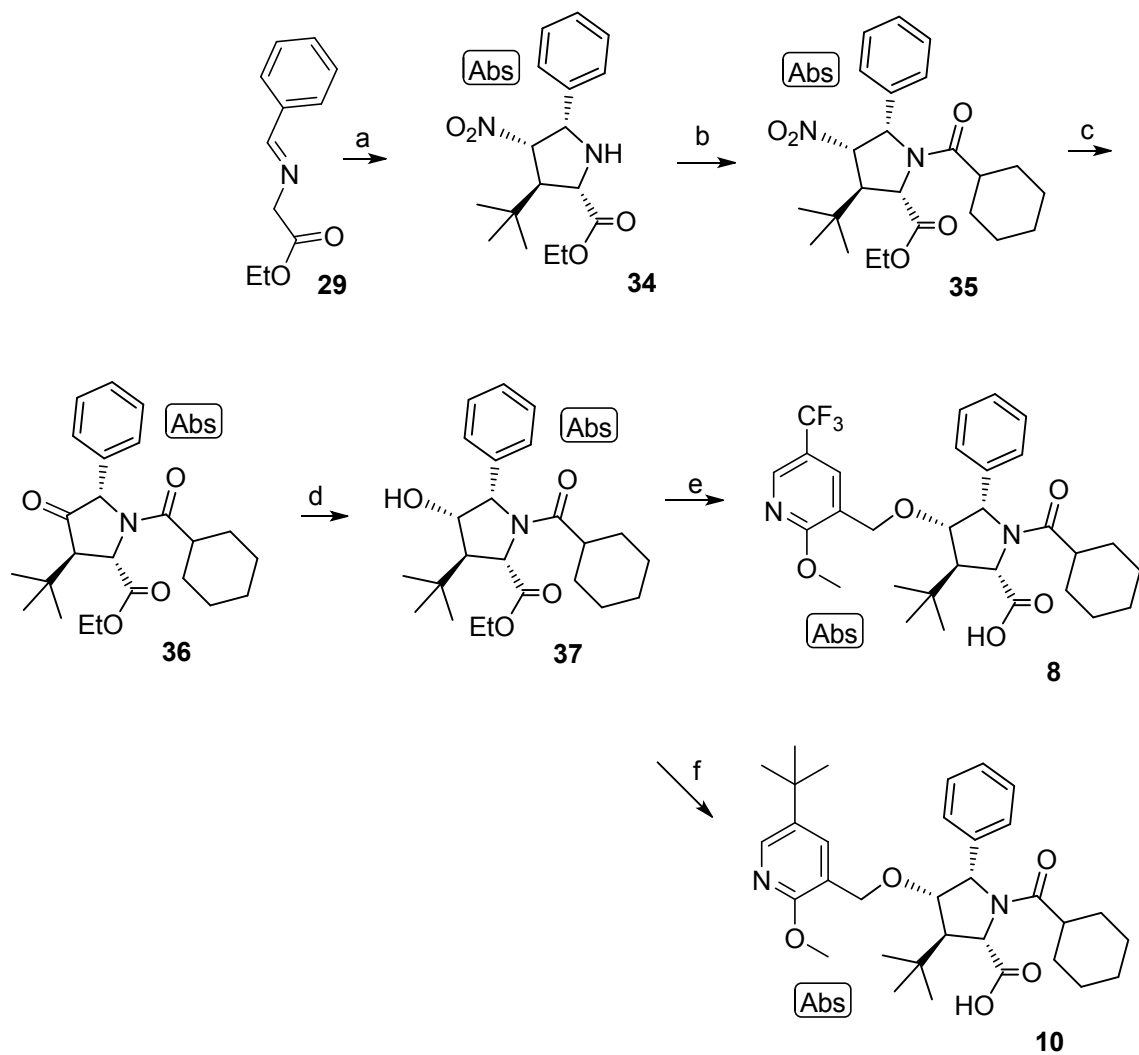
Racemic compound **5** (6.55 g) was separated by chiral preparative SFC using a CHIRALPAK OZ-H, column size 30 x 250 mm, 5 micron, serial Number: OZH0SANG001-101201, using a concentration of 65 mg/mL in methanol with 2-propanol cosolvent (30%) at a flow rate of 56 g/min CO₂ to provide 2.10 g of the title compound. R_T (chiral SFC) = 7.9 min; ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 7.66 (d, J = 7.4 Hz, 2H), 7.44 (dd, J = 8.8, 2.4 Hz, 1H), 7.19 (dt, J = 26.6, 7.3 Hz, 3H), 7.07 - 6.89 (m, 2H), 5.21 (d, J = 6.4 Hz, 1H), 4.49 (d, J = 3.4 Hz, 1H), 4.32 (d, J = 13.2 Hz, 1H), 4.25 (dd, J = 6.5, 2.7 Hz, 1H), 3.98 (d, J = 13.2 Hz, 1H), 3.77 (s, 3H), 2.51 (s, 1H), 2.24 (s, 1H), 1.65 (d, J = 9.8 Hz, 2H), 1.48 (s, 2H), 1.36 - 1.03 (m, 5H), 0.99 (s, 9H), 0.65-0.80 (m, 1H); MS (ESI+) *m/z* 562.3 (M+H)⁺.



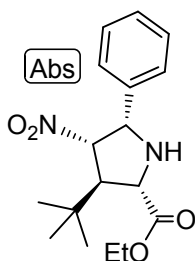
(2*S*,3*R*,4*S*,5*S*)-3-*tert*-butyl-1-(cyclohexanecarbonyl)-4-{[2-methoxy-5-(trifluoromethyl)phenyl]methoxy}-5-phenylpyrrolidine-2-carboxylic acid (7)

Racemic compound **5** (6.55 g) was separated by chiral preparative SFC chromatography using a CHIRALPAK OZ-H, column size 30 x 250 mm, 5 micron, serial Number: OZH0SANG001-101201, using a concentration of 65 mg/mL in methanol with 2-propanol cosolvent (30%) at a flow rate of 56 g/min CO₂ and UV monitoring at 220 nm to provide 1.92 g of (2*S*,3*R*,4*S*,5*S*)-3-(*tert*-butyl)-1-(cyclohexanecarbonyl)-4-((2-methoxy-5-(trifluoromethyl)benzyl)oxy)-5-phenylpyrrolidine-2-carboxylic acid. The absolute structure of the title compound was determined by X-ray crystallography. R_T (chiral SFC) = 6.0 min; ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 7.66 (d, *J* = 7.4 Hz, 2H), 7.44 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.19 (dt, *J* = 26.6, 7.3 Hz, 3H), 7.07 – 6.89 (m, 2H), 5.21 (d, *J* = 6.4 Hz, 1H), 4.49 (d, *J* = 3.4 Hz, 1H), 4.32 (d, *J* = 13.2 Hz, 1H), 4.25 (dd, *J* = 6.5, 2.7 Hz, 1H), 3.98 (d, *J* = 13.2 Hz, 1H), 3.77 (s, 3H), 2.51 (s, 1H), 2.24 (s, 1H), 1.65 (d, *J* = 9.8 Hz, 2H), 1.48 (s, 2H), 1.36 – 1.03 (m, 5H), 0.99 (s, 9H), 0.60-0.81 (m, 1H); MS (ESI+) *m/z* 562.3 (M+H)⁺; [α]^{24.8} = +83.9 ° (*c* = 0.85, methanol)⁺.

Scheme S3. Discovery Synthesis of Compounds 8 and 10^a

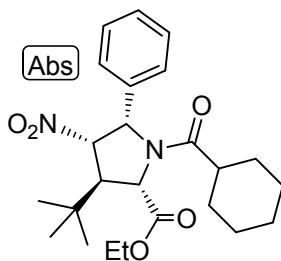


^aReagents and conditions: (a) (2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron, Cu(OTf)₂, KO^{*t*}Bu, (*E*)-3,3-dimethyl-1-nitrobut-1-ene, THF; (b) cyclohexanecarbonyl chloride, TEA, DCM; (c) PDC, 6N HCl, Zn dust, (d) NaBH₄, EtOH; (e) 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine, KO^{*t*}Bu, DMF; LiOH, MeOH; (f) 3-(bromomethyl)-5-(*tert*-butyl)-2-methoxypyridine, KO^{*t*}Bu, DMF; LiOH, MeOH.



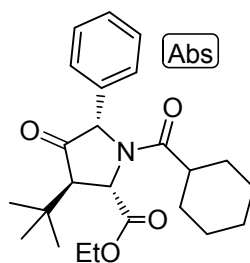
(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (34)

(2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron (2.98 g, 3.96 mmol) and copper (I) triflate dimer, benzene complex (0.859 g, 1.707 mmol; 90% technical grade, Aldrich) were dissolved in tetrahydrofuran (697 mL) that had been sparged with a nitrogen stream for 2 hours. The resulting mixture was stirred for 90 minutes at ambient temperature, at which point the flask was cooled to an internal temperature below 5 °C. (*E*)-Ethyl 2-(benzylideneamino)acetate (73.3 g, 383 mmol) was added in one portion via syringe. Potassium 2-methylpropan-2-olate (2.73 mL, 2.73 mmol, 1M solution in tetrahydrofuran) was added dropwise, followed by addition of (*E*)-3,3-dimethyl-1-nitrobut-1-ene (45 g, 348 mmol) neat over 25 minutes via syringe, maintaining an internal temperature <10 °C. After the addition was complete, the reaction was stirred for an additional 5 minutes at the same temperature, at which point LC-MS showed complete conversion of the starting nitroalkene. The reaction mixture was diluted with 300 mL of methyl *tert*-butyl ether and stirred with 300 mL of saturated aqueous ammonium chloride at ambient temperature for 15 minutes. The layers were separated, and the organic layer was washed with saturated aqueous ammonium chloride and brine and dried over sodium sulfate. After filtration, the organic extracts were concentrated *in vacuo* to provide a crude residue (140 g), which was precipitated from 800 mL of heptanes. The resulting material was removed via filtration using a fritted funnel, washed with 200 mL of cold heptanes, and dried to constant weight in a vacuum oven to provide 72.5 g (65 %) of the title compound. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.37 – 7.18 (m, 5H), 5.13 (dd, *J* = 6.0, 2.5 Hz, 1H), 4.45 (dd, *J* = 12.4, 6.0 Hz, 1H), 4.32 (qd, *J* = 7.2, 1.2 Hz, 2H), 3.82 (dd, *J* = 9.7, 7.1 Hz, 1H), 3.30 (dd, *J* = 12.3, 9.8 Hz, 1H), 2.96 (dd, *J* = 7.2, 2.5 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H); MS (ESI+) *m/z* 321.1 (M+H)⁺; [α]^{24.8} = +16.1 ° (*c* = 1, methanol).



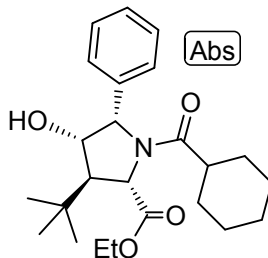
(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-1-(cyclohexanecarbonyl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (35)

To a cooled (ice bath) mixture of compound **34** (2.0g, 6.24 mmol) and triethylamine (2.61 mL, 18.73 mmol) in dichloromethane (20 mL) was added cyclohexanecarbonyl chloride (1.002 mL, 7.49 mmol) dropwise. The mixture was stirred in the ice-bath for 10 minutes and allowed to warm to room temperature. Dichloromethane (10 mL) was added. The mixture was washed with brine, dried over MgSO₄, filtered, and concentrated to provide the title compound (2.45 g, 91%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.73 - 7.61 (m, 2H), 7.38 (q, J = 8.2, 7.4 Hz, 3H), 5.46 (d, J = 9.0 Hz, 1H), 5.37 (dd, J = 8.9, 4.5 Hz, 1H), 4.82 (d, J = 4.7 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 3.15 (d, J = 4.6 Hz, 1H), 2.06 (ddt, J = 11.5, 7.0, 3.5 Hz, 1H), 1.68 (dd, J = 33.2, 12.5 Hz, 2H), 1.55 - 1.41 (m, 4H), 1.38 (t, J = 7.1 Hz, 3H), 1.34 - 1.13 (m, 3H), 1.07 (s, 9H), 0.59 (d, J = 12.6 Hz, 1H); MS (ESI+) *m/z* 431 (M+H)⁺.



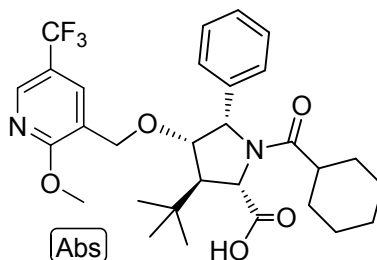
(2S,3R,5S)-ethyl 3-(*tert*-butyl)-1-(cyclohexanecarbonyl)-4-oxo-5-phenylpyrrolidine-2-carboxylate
(36)

To potassium dichromate (4.65 g, 15.79 mmol) in 6 M aqueous HCl (60 mL), zinc (5.3 g, 81 mmol) was added under N₂ atmosphere. Complete dissolution of zinc provided a clear light blue solution. The formed chromium(II) chloride was transferred to the refluxing solution of compound **35** (1g, 2.323mmol) in ethanol (60 mL). The reaction mixture was refluxed overnight. The mixture was cooled and concentrated to half of its volume and extracted with dichloromethane (30 mL x 3). The combined organic phase was washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was dissolved in ethanol (2 mL) and added to a prepared solution of acetyl chloride (1 mL) in ethanol (4mL) cooling in an ice-bath. The mixture was heated to 60 °C for 2 hours, concentrated, and dissolved in ethyl acetate (50 mL) and saturated aqueous NaHCO₃ (30 mL). The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated to provide a residue which purified via chromatography on a 40 g silica gel cartridge, eluting with ethyl acetate in heptanes at 0-30% gradient to provide the title compound (688 mg, 74.1 % yield).



(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-1-(cyclohexanecarbonyl)-4-hydroxy-5-phenylpyrrolidine-2-carboxylate (37)

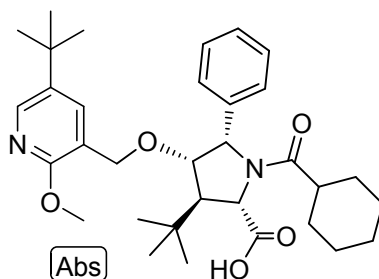
Compound **36** (730 mg, 1.827 mmol) in ethanol (10 mL) cooled in an ice-bath was added sodium borohydride (138 mg, 3.65 mmol) portionwise. The mixture was stirred in ice-bath for 30 minutes and was allowed to warm to room temperature. LC/MS indicated the reaction was finished and showed two product peaks at ratio about 3 to 1, with the title compound as the major isomer. Saturated NH₄Cl (2 mL) was added, and the mixture was concentrated, dissolved in dichloromethane (30 mL), washed with brine, dried over MgSO₄, filtered, and concentrated. Purification via chromatography on a 40 g silica gel cartridge eluting with ethyl acetate/methanol (9:1) in heptanes at 0-40% gradient provided the title compound (480 mg, 65.4 % yield). LC/MS (APCI+) *m/z* 402 (M+H)⁺



(2*S*,3*R*,4*S*,5*S*)-3-*tert*-butyl-1-(cyclohexanecarbonyl)-4-{[2-methoxy-5-(trifluoromethyl)pyridin-3-yl]methoxy}-5-phenylpyrrolidine-2-carboxylic acid (8)

To compound **37** and 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine (121 mg, 0.448 mmol) in dimethylformamide (2 mL) cooled in an ice-bath, potassium 2-methylpropan-2-olate (62.9 mg, 0.560 mmol, 0.56 mL, 1.0 M in tetrahydrofuran) was added dropwise. The mixture was stirred in the ice-bath for 20 minutes, and allowed to warm to room temperature. Methanol (1.5 mL) and 6M aqueous LiOH (0.5mL) was added. The mixture was stirred at 50 °C overnight, and adjusted to pH 1~2 by adding 2M aqueous HCl. The solvent was removed and dichloromethane was (1 mL) added. The reaction mixture was filtered through a syringe filter and the filtrate was purified via chromatography, eluting with methanol in dichloromethane at 0-20% gradient to provide title compound, 130 mg (61.9 % yield). ¹H

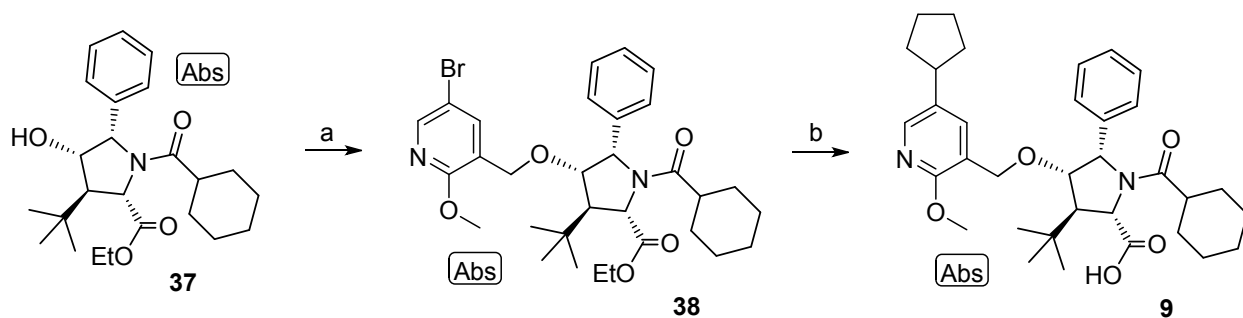
NMR (400 MHz, DMSO-*d*₆) δ ppm 8.29 (td, *J* = 1.9, 0.8 Hz, 1H), 7.66 (d, *J* = 7.3 Hz, 2H), 7.28 – 7.08 (m, 4H), 5.23 (d, *J* = 6.3 Hz, 1H), 4.51 (d, *J* = 3.1 Hz, 1H), 4.38 – 4.24 (m, 2H), 3.95 (d, *J* = 13.9 Hz, 1H), 3.89 (s, 3H), 2.51 (s, 1H), 2.23 (s, 1H), 1.65 (d, *J* = 9.5 Hz, 2H), 1.49 (s, 2H), 1.17 (d, *J* = 73.3 Hz, 6H), 1.01 (s, 9H); MS (ESI+) *m/z* 561.3 (M-H)⁻.



(2*S*,3*R*,4*S*,5*S*)-3-*tert*-butyl-4-[(5-*tert*-butyl-2-methoxypyridin-3-yl)methoxy]-1-(cyclohexanecarbonyl)-5-phenylpyrrolidine-2-carboxylic acid (10)

The title compound was prepared according to the procedure described for compound **8**, substituting 3-(bromomethyl)-5-(*tert*-butyl)-2-methoxypyridine for 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.94 (d, *J* = 3.5 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.30 – 7.10 (m, 4H), 5.21 (d, *J* = 6.4 Hz, 1H), 4.47 (d, *J* = 3.5 Hz, 1H), 4.23 (dd, *J* = 11.2, 5.5 Hz, 2H), 3.91 (d, *J* = 13.0 Hz, 1H), 3.77 (s, 3H), 2.5 (m, 1H), 2.24 (s, 1H), 1.65 (d, *J* = 9.8 Hz, 2H), 1.49 (s, 2H), 1.25 (d, *J* = 10.0 Hz, 2H), 1.21 (s, 9H), 1.08 (td, *J* = 10.1, 9.5, 4.0 Hz, 3H), 0.99 (s, 9H), 0.87 – 0.82 (m, 1H); MS (ESI-) *m/z* 549.3 (M-H)⁻.

Scheme S4. Discovery Synthesis of Compound 9^a



^aReagents and conditions: (a) 5-bromo-3-(bromomethyl)-2-methoxypyridine; (e) PEPPSI-IPentCl, Cyclopentylzinc bromide; LiOH, THF/MeOH.

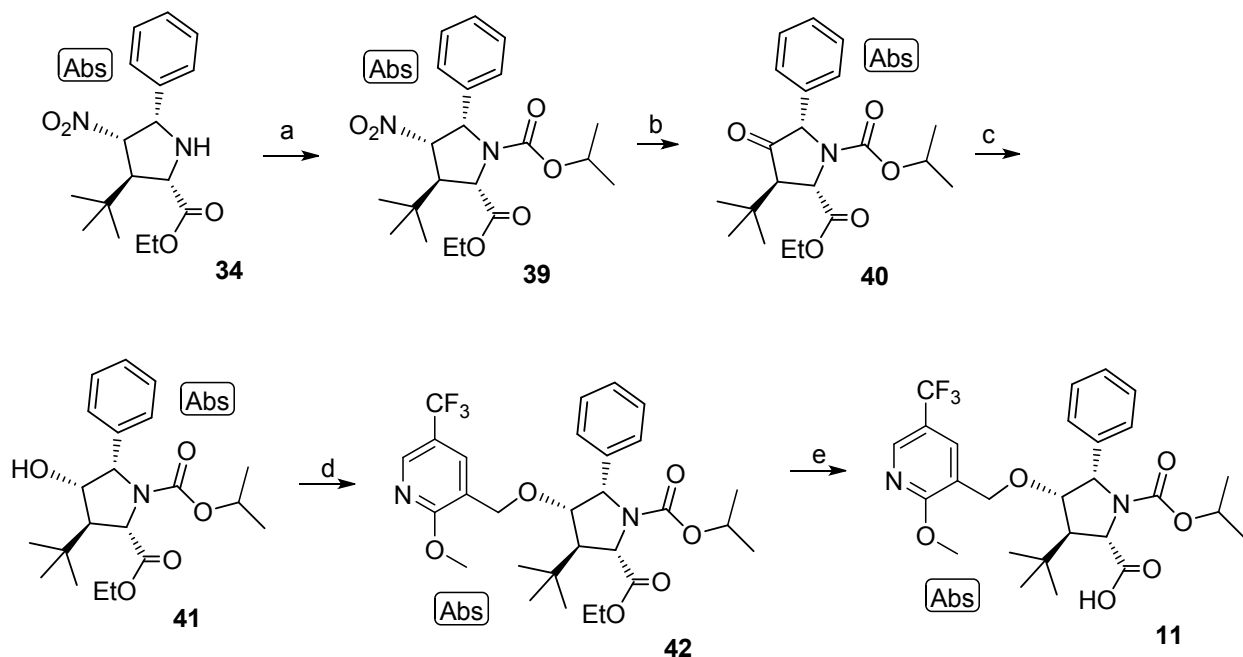
(2*S*,3*R*,4*S*,5*S*)-ethyl 4-((5-bromo-2-methoxypyridin-3-yl)methoxy)-3-(*tert*-butyl)-1-(cyclohexanecarbonyl)-5-phenylpyrrolidine-2-carboxylate (38)

The title compound was prepared according to the procedure described for compound **8**, substituting 5-bromo-3-(bromomethyl)-2-methoxypyridine for 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine. LC/MS (APCI+) m/z 603.0 (M+H)⁺.

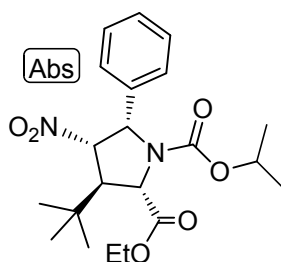
(2*S*,3*R*,4*S*,5*S*)-3-*tert*-butyl-1-(cyclohexanecarbonyl)-4-[(5-cyclopentyl-2-methoxypyridin-3-yl)methoxy]-5-phenylpyrrolidine-2-carboxylic acid (9)

In a 4 mL vial, compound **38** (50.0 mg, 0.083 mmol, 1.0 eq) and dichloro[4,5-dichloro-1,3-bis(2,6-Di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) (PEPPSI-IPentCl, 7.15 mg, 0.0083 mmol, 0.1 eq) were dissolved in tetrahydrofuran (1.0 mL), flushed with nitrogen, and stirred at room temperature. Cyclopentylzinc bromide (0.5 M, 498 μ L, 0.25 mmol, 3.0 eq) was added and reaction was stirred at room temperature for 30 minutes. The solvent was removed under a stream of nitrogen, and the crude material was reconstituted in 3:2 tetrahydrofuran/methanol (1.0 mL). LiOH monohydrate (34 mg, 0.83 mmol, 10 eq) in H₂O (300 μ L) was added and reaction was stirred overnight at 45 °C. The solvent was removed under a stream of nitrogen. The residue was acidified with 1 M aqueous HCl and extracted with dichloromethane (3 x 2 mL). The solvent was removed and the crude material was reconstituted in acetonitrile. The reaction was loaded directly into an injection loop and purified using prep LC method TFA8 to provide the title compound (36.0 mg, 64.0% yield). ¹H NMR (400 MHz, 120 °C, DMSO-*d*₆:D₂O = 9:1 (v/v)) δ ppm 7.78 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 7.3 Hz, 2H), 7.28 – 7.13 (m, 3H), 6.90 (d, J = 2.4 Hz, 1H), 5.19 (d, J = 6.3 Hz, 1H), 4.49 (d, J = 3.3 Hz, 1H), 4.25 – 4.16 (m, 2H), 3.90 (d, J = 13.0 Hz, 1H), 3.76 (s, 3H), 2.88 – 2.74 (m, 1H), 2.50 – 2.46 (m, 1H), 2.29 – 2.13 (m, 1H), 1.95 – 1.87 (m, 2H), 1.81 – 1.70 (m, 2H), 1.68 – 1.59 (m, 4H), 1.50 – 1.45 (m, 2H), 1.46 – 1.30 (m, 2H), 1.27 – 1.03 (m, 5H), 0.98 (s, 9H), 0.81 – 0.56 (m, 1H); MS (APCI+) m/z 563.1 (M+H)⁺.

Scheme S5. Discovery Synthesis of Compound 11^a



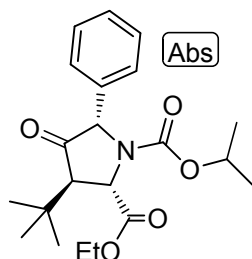
^aReagents and conditions: (a) isopropyl chloroformate, TEA, DCM; (b) PDC, 6N HCl, Zn dust, (c) NaBH₄, EtOH; (d) 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine, KOtBu, DMF; (e) LiOH (aq), MeOH.



(2*S*,3*R*,4*S*,5*S*)-2-ethyl 1-isopropyl 3-(*tert*-butyl)-4-nitro-5-phenylpyrrolidine-1,2-dicarboxylate (39)

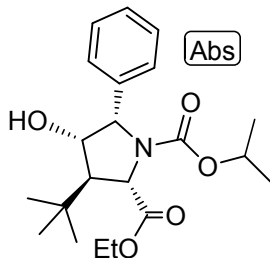
To a solution of compound **34** (2.193 g, 6.84 mmol) in dichloromethane (20 mL) and triethylamine (4 mL, 28.7 mmol) was added a 1M solution of isopropyl chloroformate (15 mL, 15.00 mmol) in toluene dropwise via addition funnel over about 3 minutes. After 30 minutes, additional 1M isopropyl chloroformate (6 mL) was added and after another 30 minutes additional 1M isopropyl chloroformate (6 mL) was added. The reaction mixture was stirred at room temperature for 3 hours more. The reaction mixture was diluted with dichloromethane (200 mL) and a small amount of ethanol and washed with saturated aqueous sodium bicarbonate (50 mL), dried over sodium sulfate, filtered, and concentrated. The crude material was purified using a 40 g silica gel cartridge with a gradient of 5-100% ethyl acetate/heptanes over 30 minutes to provide (2*S*,3*R*,4*S*,5*S*)-2-ethyl 1-isopropyl 3-(*tert*-butyl)-4-nitro-5-phenylpyrrolidine-1,2-

dicarboxylate (2.790 g, 6.88 mmol, 100 % yield). ^1H NMR (400 MHz, 120°C , $\text{DMSO-}d_6$) δ ppm 7.56 - 7.46 (m, 2H), 7.30 - 7.15 (m, 3H), 5.61 (dd, $J = 8.8, 3.3$ Hz, 1H), 5.43 (d, $J = 8.8$ Hz, 1H), 5.33 (dd, $J = 6.6, 3.2$ Hz, 0H), 4.67 (pd, $J = 6.1, 0.7$ Hz, 1H), 4.50 (d, $J = 3.8$ Hz, 1H), 4.25 (qd, $J = 7.1, 0.6$ Hz, 2H), 2.98 (t, $J = 3.6$ Hz, 1H), 1.29 (td, $J = 7.0, 0.7$ Hz, 3H), 1.06 (d, $J = 6.2$ Hz, 3H), 1.03 - 0.98 (m, 9H), 0.92 (d, $J = 6.2$ Hz, 3H); MS (APCI+) m/z 407 (M+H) $^+$.



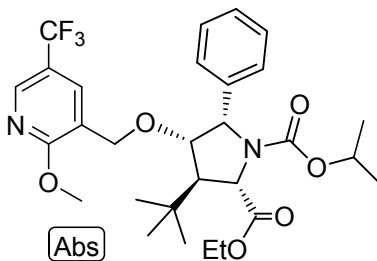
(2S,3R,5S)-2-ethyl 1-isopropyl 3-(tert-butyl)-4-oxo-5-phenylpyrrolidine-1,2-dicarboxylate (40)

Compound **39** (2.366 g, 5.82 mmol) was dissolved in ethanol (75 mL) and the solution was heated to 71°C . A separate solution of CrCl_2 was prepared by dissolving pyridinium dichromate (5.82 g, 19.79 mmol) in hydrochloric acid (6M, 75 mL) and adding Zn (10.47 g, 160 mmol) in portions while cooling in an ice bath. The suspension was stirred until all almost all of the Zn dissolved, leaving a brilliant blue solution. The CrCl_2 solution was transferred via cannula over 15 minutes to the solution of starting material (cooled to 65°C during the addition) and heating was continued at 80°C for 16 hours. The mixture was cooled to room temperature, reduced in volume *in vacuo*, diluted with water, and extracted with 3 x 200 mL of dichloromethane. The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was loaded onto a 80 g silica gel column and eluted with 0-100% ethyl acetate/heptanes over 40 minutes to provide (2S,3R,5S)-2-ethyl 1-isopropyl 3-(tert-butyl)-4-oxo-5-phenylpyrrolidine-1,2-dicarboxylate (0.793 g, 2.112 mmol, 36.3 % yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.48 - 7.40 (m, 2H), 7.33 - 7.27 (m, 2H), 7.26 - 7.19 (m, 1H), 4.91 (s, 1H), 4.77 - 4.69 (m, 1H), 4.62 (d, $J = 4.4$ Hz, 1H), 4.19 (qd, $J = 7.1, 1.4$ Hz, 2H), 2.56 (dd, $J = 4.5, 0.9$ Hz, 1H), 1.22 (t, $J = 7.1$ Hz, 3H), 1.11 (d, $J = 6.2$ Hz, 3H), 1.05 (s, 9H), 0.98 (d, $J = 6.2$ Hz, 3H); MS (APCI+) m/z 376 (M+H) $^+$.



(2*S*,3*R*,4*S*,5*S*)-2-ethyl 1-isopropyl 3-(*tert*-butyl)-4-hydroxy-5-phenylpyrrolidine-1,2-dicarboxylate (41)

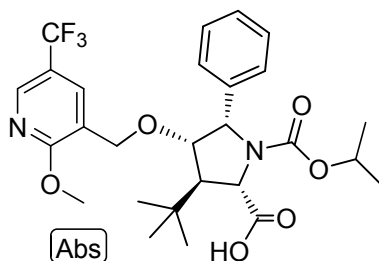
Compound **40** (0.611 g, 1.627 mmol) was dissolved in ethanol (8.14 mL) and sodium borohydride (0.123 g, 3.25 mmol) was added in one portion after cooling the reaction to < 5 °C in an ice-water bath. The reaction was stirred at the same temperature for 30 minutes, concentrated, and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organics were concentrated and purified using a 40 g silica gel cartridge and eluting with 0-100% ethyl acetate/heptanes over 40 minutes on to provide (2*S*,3*R*,4*S*,5*S*)-2-ethyl 1-isopropyl 3-(*tert*-butyl)-4-hydroxy-5-phenylpyrrolidine-1,2-dicarboxylate (0.506 g, 1.340 mmol, 82 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.50 (dd, *J*=8.1,1.5 Hz, 2H), 7.19-7.27 (m, 2H), 7.09-7.19 (m, 1H), 4.82 (d, *J*=6.7 Hz, 1H), 4.62 (pd, *J*=6.2,1.1 Hz, 1H), 4.27-4.35 (m, 1H), 4.22 (dd, *J*=4.8,1.2 Hz, 1H), 4.10-4.19 (m, 2H), 3.84 (d, *J*=7.4 Hz, 1H), 2.21-2.28 (m, 1H), 1.24 (td, *J*=7.1,1.0 Hz, 3H), 1.04 (dd, *J*=6.3,1.2 Hz, 3H), 0.98 (d, *J*=1.1 Hz, 9H), 0.90 (d, *J*=6.2 Hz, 3H); MS (APCI+) *m/z* 378 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-2-ethyl 1-isopropyl 3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-5-phenylpyrrolidine-1,2-dicarboxylate (42)

Compound **41** (37 mg, 0.098 mmol) and 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine (47.6 mg, 0.176 mmol) were dissolved in dry dimethylformamide (0.5 mL). After cooling in an ice bath, potassium 2-methylpropan-2-olate (0.157 mL, 0.157 mmol) solution was added dropwise over 2 minutes. LC/MS showed desired product. The mixture was acidified with 1M aqueous HCl (10 drops) and warmed to room temperature. The mixture was concentrated and loaded onto a 12 g silica gel column and eluted with 5-100% ethyl acetate/heptanes over 20 minutes to provide (2*S*,3*R*,4*S*,5*S*)-2-ethyl 1-isopropyl 3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-5-phenylpyrrolidine-

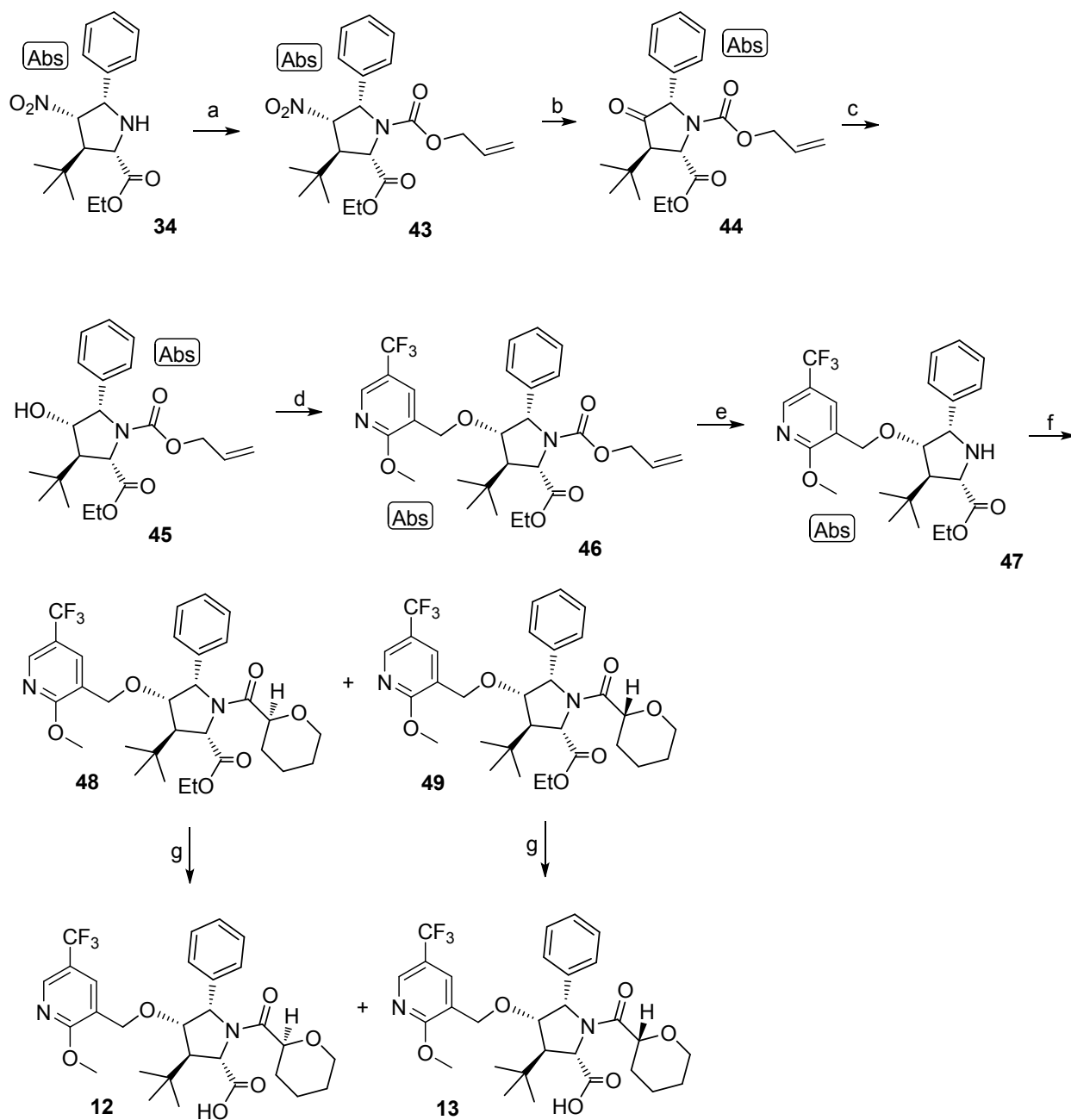
1,2-dicarboxylate (52 mg, 0.092 mmol, 94 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.28 (s, 1H), 7.58 - 7.53 (m, 2H), 7.22 (d, J = 2.3 Hz, 1H), 7.17 (dd, J = 8.2, 6.6 Hz, 2H), 7.13 - 7.07 (m, 1H), 5.02 (d, J = 6.1 Hz, 1H), 4.64 (pd, J = 6.2, 0.9 Hz, 1H), 4.37 (d, J = 3.1 Hz, 1H), 4.30 - 4.24 (m, 2H), 4.16 - 4.03 (m, 2H), 3.87 (d, J = 0.9 Hz, 3H), 2.87 - 2.81 (m, 2H), 1.15 (td, J = 7.1, 0.9 Hz, 3H), 1.05 (d, J = 6.2 Hz, 3H), 1.01 (d, J = 0.9 Hz, 9H), 0.90 (d, J = 6.2 Hz, 3H); MS (APCI+) *m/z* 567 (M+H)⁺.



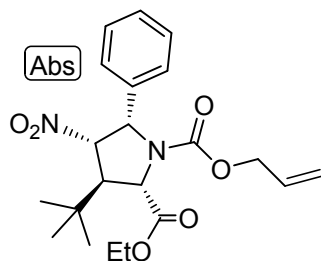
(2*S*,3*R*,4*S*,5*S*)-3-*tert*-butyl-4-[(2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy]-5-phenyl-1-[(propan-2-yl)oxy]carbonylpyrrolidine-2-carboxylic acid (11)

Compound **42** (52 mg, 0.092 mmol) was dissolved in methanol (0.5 mL) and a 2M aqueous solution of lithium hydroxide (0.459 mL, 0.918 mmol) was added. The reaction was warmed at 45 °C overnight, acidified with 2M aqueous HCl (0.460 mL), and concentrated. The residue was loaded onto a 12 g silica gel column and eluted with 5-100% ethyl acetate/ethanol/heptanes over 20 minutes to provide (2*S*,3*R*,4*S*,5*S*)-3-(*tert*-butyl)-1-(isopropoxycarbonyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-5-phenylpyrrolidine-2-carboxylic acid (22 mg, 0.041 mmol, 44.5 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.68 - 7.62 (m, 2H), 7.20 - 7.16 (m, 2H), 7.16 - 7.12 (m, 2H), 7.13 - 7.05 (m, 1H), 5.00 (d, J = 6.5 Hz, 1H), 4.63 (p, J = 6.2 Hz, 1H), 4.30 (d, J = 14.0 Hz, 1H), 4.26 (d, J = 3.1 Hz, 1H), 4.21 (dd, J = 6.5, 2.5 Hz, 1H), 3.93 (d, J = 13.9 Hz, 1H), 3.88 (s, 3H), 2.55 (t, J = 2.8 Hz, 1H), 1.06 (d, J = 6.2 Hz, 3H), 1.00 (s, 9H), 0.89 (d, J = 6.2 Hz, 3H); MS (APCI+) *m/z* 539.2 (M+H)⁺.

Scheme S6. Discovery Synthesis of Compounds 12 and 13^a

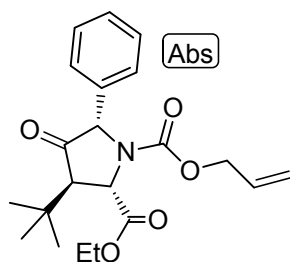


^aReagents and conditions: (a) allyl chloroformate, TEA, DCM; (b) PDC, 6N HCl, Zn dust, (c) NaBH₄, EtOH; (d) 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine, KO^tBu, DMF; (e) 1,3-Dimethylbarbituric acid, Pd(PPh₃)₄, EtOAc/DCM; (f) Tetrahydropyran-2-carboxylic acid, oxalyl chloride, DMF, DCM; (g) LiOH (aq), MeOH.



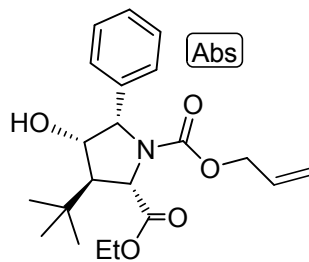
(2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-4-nitro-5-phenylpyrrolidine-1,2-dicarboxylate (43)

To compound **34** (1.0 g, 3.12 mmol) in toluene (3 mL) and saturated NaHCO₃ (3.00 mL) was added allyl chloroformate (0.332 mL, 3.12 mmol) dropwise at ambient temperature, and the mixture was stirred for 30 minutes. LC/MS indicated the conversion was finished. Dichloromethane (20 mL) and water (10 mL) were added and the organic layer washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified via silica gel chromatography, eluting with ethyl acetate in heptane at 0-40% gradient to provide the title compound (1.0 g, 95 % yield). ¹H NMR (501 MHz, CDCl₃) δ ppm 7.58 - 7.51 (m, 2H), 7.37 - 7.26 (m, 3H), 5.61 (s, 2H), 5.43 (d, J = 8.7 Hz, 1H), 5.30 (dd, J = 8.7, 2.6 Hz, 1H), 5.00 (s, 1H), 4.70 (s, 1H), 4.56 (s, 2H), 4.39 (qd, J = 7.1, 1.8 Hz, 2H), 3.11 (t, J = 2.9 Hz, 1H), 1.40 (t, J = 7.1 Hz, 3H), 1.10 (s, 9H); MS (ESI+) *m/z* 405 (M+H)⁺.



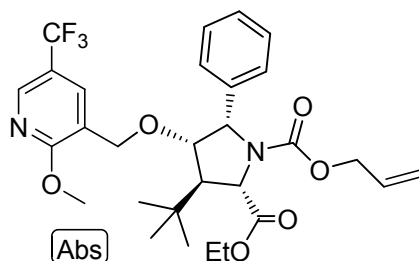
(2*S*,3*R*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-4-oxo-5-phenylpyrrolidine-1,2-dicarboxylate (44)

Compound **44** was prepared according to the procedure described to prepare compound **24** from compound **23**. LC/MS (ESI+) = 374.45 (M+H)⁺.



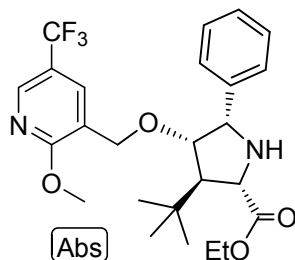
(2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-4-hydroxy-5-phenylpyrrolidine-1,2-dicarboxylate (45)

To compound **44** (560 mg, 1.5 mmol) in ethanol (4 mL) cooling in an ice-bath was added sodium borohydride (113 mg, 3.00 mmol) portionwise. The mixture was stirred in the ice-bath for 30 minutes, and allowed to warm to ambient temperature. LC/MS showed two product peaks, in a ratio of about 6 to 1. The solvent was removed, dichloromethane (20 mL) was added and the organics were washed with brine. The organics were dried over MgSO₄, filtered, and concentrated. Purification via chromatography, eluting with ethyl acetate/methanol (9:1) in heptanes at 0-40% gradient provided title compound as the second eluent (340 mg, 60 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.64 – 7.56 (m, 2H), 7.43 – 7.36 (m, 2H), 7.33 – 7.28 (m, 1H), 5.55 (s, 1H), 5.04 (s, 1H), 4.97 – 4.70 (m, 1H), 4.64 – 4.38 (m, 3H), 4.35 – 4.31 (m, 1H), 4.27 (ddd, *J* = 10.8, 7.0, 3.4 Hz, 2H), 2.41 – 2.32 (m, 1H), 1.47 (d, *J* = 5.0 Hz, 1H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.07 (s, 9H); LC/MS (ESI+) *m/z* 376.5 (M+H)⁺. Also obtained was the other diastereomer (*2S,3R,4R,5S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-4-hydroxy-5-phenylpyrrolidine-1,2-dicarboxylate as the first eluting isomer (56 mg, 10 % yield).



(*2S,3R,4S,5S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-5-phenylpyrrolidine-1,2-dicarboxylate (46**)**

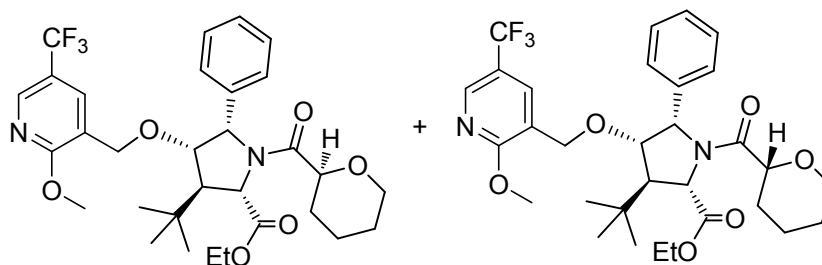
To compound **45** (340 mg, 0.906 mmol) and 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine (293 mg, 1.087 mmol) in dimethylformamide (2 mL) in an ice-bath was added potassium 2-methylpropan-2-olate (152 mg, 1.358 mmol, 1.6 mL, 1.0 M in tetrahydrofuran) dropwise. The mixture was stirred in ice-bath for 20 minutes, and allowed to warm to room temperature. Saturated aqueous NH₄Cl (2 mL) was added, and dichloromethane (20 mL) was added. The mixture was washed with brine, dried over MgSO₄, filtered, and concentrated. Purification of the residue via chromatography, eluting with ethyl acetate/methanol (9:1) in heptanes at 0-40% gradient provided the title compound (380 mg, 71 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.29 (t, *J* = 1.5 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.26 – 7.15 (m, 3H), 7.13 – 7.05 (m, 1H), 5.73 – 5.66 (m, 1H), 5.08 (d, *J* = 6.1 Hz, 1H), 5.04 (dq, *J* = 3.2, 1.8 Hz, 1H), 5.01 (t, *J* = 1.7 Hz, 1H), 4.41 (ddd, *J* = 5.1, 3.6, 2.3 Hz, 3H), 4.30 – 4.25 (m, 2H), 4.10 (qd, *J* = 7.1, 2.3 Hz, 2H), 3.87 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.01 (s, 9H); MS (ESI+) *m/z* 565 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-5-phenylpyrrolidine-2-carboxylate (47)

To compound **46** (320 mg, 0.567 mmol) in a mixture of acetonitrile and water (3.3 mL, 10:1) was added diethylamine (0.117 mL, 1.134 mmol) and tetrakis(triphenylphosphine) palladium(0) (14.41 mg, 0.012 mmol). The mixture was stirred at ambient temperature overnight.

Dichloromethane (10 mL) and water (10 mL) were added. The organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated. Purification via chromatography, eluting with ethyl acetate/methanol (10:1) in heptanes at 0-50% gradient provided the title compound (260 mg, 95 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.24 (dt, *J* = 1.9, 0.9 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 4.33 (dt, *J* = 14.0, 0.9 Hz, 1H), 4.25 (qd, *J* = 7.2, 0.8 Hz, 2H), 4.17 (d, *J* = 4.1 Hz, 1H), 3.94 (dd, *J* = 4.2, 1.4 Hz, 1H), 3.93 – 3.88 (m, 4H), 3.74 (d, *J* = 6.2 Hz, 1H), 2.85 (s, 1H), 2.43 (dd, *J* = 6.3, 1.3 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H); MS (ESI+) *m/z* 563 (M+H)⁺.



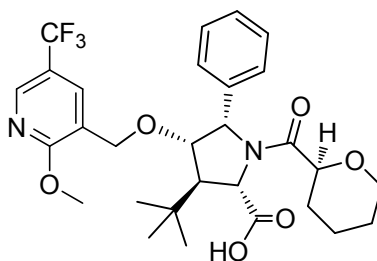
(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-5-phenyl-1-((*S*)-tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate (48)

and

(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-5-phenyl-1-((*R*)-tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate (49)

To tetrahydro-2H-pyran-2-carboxylic acid (65.0 mg, 0.499 mmol) in dichloromethane (6 mL) and a drop of dimethylformamide was added oxalyl dichloride (127 mg, 1.0 mmol, 0.5 mL, 2M in dichloromethane). The mixture was stirred for 30 minutes and the solvent was removed under pressure and fresh

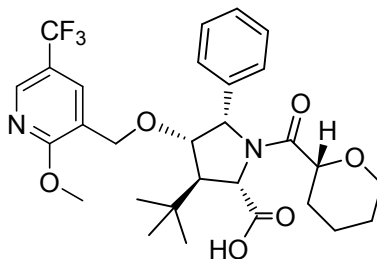
dichloromethane was added and removed again. The residue was dissolved in dichloromethane (1 mL) and was added dropwise to the solution of compound **47** (120 mg, 0.250 mmol) and triethylamine (0.139 mL, 1.0 mmol) in dichloromethane (6 mL) cooled with an ice-bath. The mixture was stirred in an ice-bath for 30 minutes and was warmed to room temperature. LC/MS indicated the reaction was finished and showed two diastereoisomers peaks at a ratio of about 1:1. Saturated aqueous NH₄Cl (2 mL) and dichloromethane (10 mL) were added. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. Purification via chromatography on a 24 g silica gel cartridge, eluting with ethyl acetate in heptanes at 0-40% gradient provided compound **48** as the first eluting isomer (55 mg, 37 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.29 - 8.16 (m, 1H), 7.75 - 7.61 (m, 2H), 7.40 - 7.24 (m, 3H), 7.12 (d, J = 2.3 Hz, 1H), 5.52 (d, J = 6.1 Hz, 1H), 4.74 (d, J = 3.1 Hz, 1H), 4.32 (d, J = 14.1 Hz, 1H), 4.21 (qq, J = 7.1, 3.7 Hz, 2H), 4.15 - 4.06 (m, 1H), 3.91 (s, 3H), 3.85 (dd, J = 13.7, 4.5 Hz, 2H), 3.38 (dd, J = 10.3, 2.7 Hz, 1H), 2.95 (td, J = 11.5, 2.5 Hz, 1H), 2.51 (t, J = 2.7 Hz, 1H), 1.77 - 1.29 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H), 1.07 (s, 9H); MS (ESI+) *m/z* 593.1(M+H)⁺. Compound **49** was obtained as the second eluting isomer (52 mg, 35% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.22 (tt, J = 2.5, 1.2 Hz, 1H), 7.72 - 7.61 (m, 1H), 7.52 - 7.48 (m, 1H), 7.36 - 7.31 (m, 1H), 7.30 - 7.23 (m, 2H), 7.19 - 7.13 (m, 1H), 5.24 (d, J = 5.6 Hz, 1H), 5.19 (d, J = 1.5 Hz, 1H), 4.34 (dd, J = 24.7, 14.0 Hz, 1H), 4.28 - 4.12 (m, 3H), 4.11 - 3.94 (m, 3H), 3.91 (d, J = 7.2 Hz, 3H), 3.83 - 3.73 (m, 1H), 3.47 (td, J = 11.1, 2.6 Hz, 1H), 2.70 (s, 1H), 1.99 - 1.60 (m, 4H), 1.56 - 1.48 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H), 1.08 (d, J = 13.1 Hz, 9H); MS (ESI+) *m/z* 593.2 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-5-phenyl-1-((*S*)-tetrahydro-2*H*-pyran-2-carboxyl)pyrrolidine-2-carboxylic acid (12**)**

The mixture of Compound **48** (50 mg, 0.084 mmol) in methanol (1.5 mL) and 6M aqueous LiOH (0.5 mL) was stirred at 45 °C for overnight. The mixture was adjusted to pH to 1~2 by adding 2M aqueous HCl. The reaction mixture was concentrated, taken up in dichloromethane, and filtered through a syringe filter. The filtrate was purified via chromatography on a 4 g silica gel cartridge, eluting with methanol in dichloromethane at 0-20% gradient to provide the title compound (30 mg, 63.0 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.37 - 8.29 (m, 1H), 7.66 (d, *J* = 7.4 Hz, 2H), 7.21 (d, *J* = 7.5 Hz, 3H), 7.16 (d, *J*

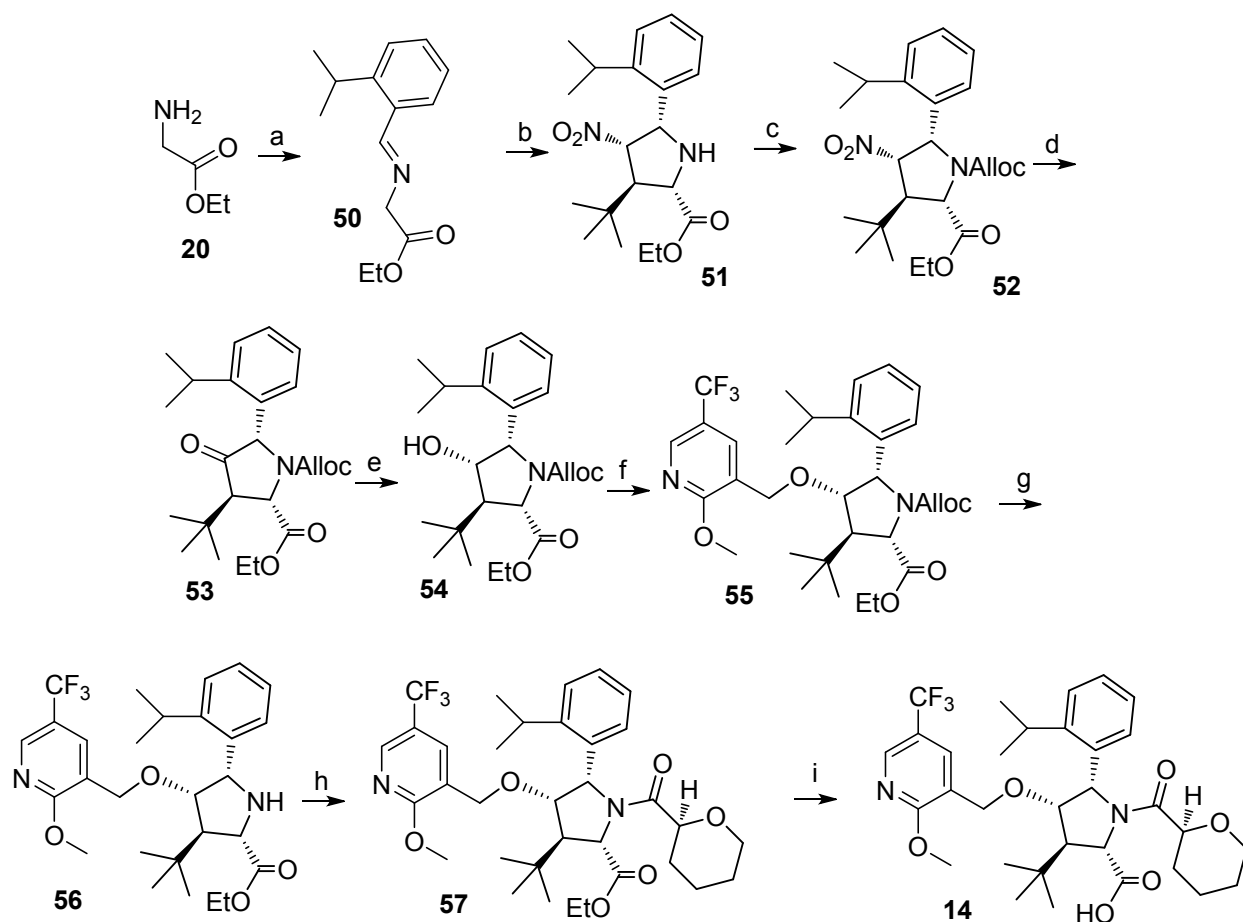
= 7.5 Hz, 1H), 5.42 (s, 1H), 4.55 (s, 1H), 4.33 – 4.25 (m, 2H), 3.91 (d, $J = 13.9$ Hz, 1H), 3.88 (s, 3H), 3.79 (d, $J = 11.3$ Hz, 1H), 3.51 (s, 1H), 2.84 (s, 2H), 1.72 – 1.26 (m, 6H), 1.00 (s, 9H); MS (ESI+) m/z 565.1 (M+H)⁺.



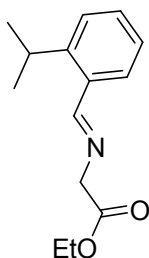
(2*S*,3*R*,4*S*,5*S*)-3-*tert*-butyl-4-{{2-methoxy-5-(trifluoromethyl)pyridin-3-yl}methoxy}-1-[(2*R*)-oxane-2-carbonyl]-5-phenylpyrrolidine-2-carboxylic acid (13)

The title compound was prepared from compound **49** according to the procedure described to convert compound **48** to compound **12**. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.28 (s, 1H), 7.55 (s, 2H), 7.26 7.13 (m, 3H), 7.10 (d, $J = 6.9$ Hz, 1H), 5.19 (d, $J = 6.2$ Hz, 1H), 4.81 (s, 1H), 4.36 4.20 (m, 2H), 3.88 (s, 4H), 3.79 (d, $J = 12.0$ Hz, 1H), 2.58 (s, 1H), 1.82 1.27 (m, 7H), 1.01 (d, $J = 3.6$ Hz, 9H); MS (ESI+) m/z 565.1 (M+H)⁺.

Scheme S7. Discovery Synthesis of Compound 14^a



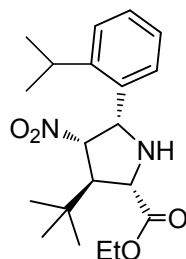
^aReagents and conditions: (a) MgSO_4 , TEA, 2-methylbenzaldehyde, DCM; (b) (2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron, $\text{Cu}(\text{OTf})_2$, KOtBu , (*E*)-3,3-dimethyl-1-nitrobut-1-ene, THF; (c) allyl chloroformate, toluene; (d) PDC, 6N HCl, Zn dust, (e) NaBH_4 , EtOH; (f) KOtBu , 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine, DMF; (g) 1,3-Dimethylbarbituric acid, $\text{Pd}(\text{PPh}_3)_4$, EtOAc/DCM; (h) Tetrahydropyran-2-carboxylic acid, oxalyl chloride, DMF, DCM; (i) LiOH, MeOH/THF.



(*E*)-ethyl 2-((2-isopropylbenzylidene)amino)acetate (50)

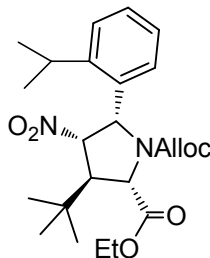
Ethyl 2-aminoacetate hydrochloride (5.02 g, 36.0 mmol) and magnesium sulfate (5.20 g, 43.2 mmol) were suspended in dichloromethane (45 mL) and treated with triethylamine (9.9 mL, 71.0 mmol). The mixture was stirred for 20 minutes and was treated dropwise with 2-isopropylbenzaldehyde (5 g, 33.7 mmol). The

reaction mixture stirred at room temperature for 3 days. The mixture was filtered (fritted glass funnel), and the filter pad was washed with copious amount of CH₂Cl₂. The filtrates were washed twice with water and once with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield the title compound, 7.066 g (90 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.73 (m, 1H), 7.94 (dd, J = 7.9, 1.5 Hz, 1H), 7.42 (m, 1H), 7.35 (dd, J = 7.9, 1.4 Hz, 1H), 7.24 (m, 1H), 4.44 (d, J = 1.4 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.53 (hept, J = 6.8 Hz, 1H), 1.34 - 1.29 (m, 9H). MS (ESI⁺) *m/z* 234.1 (M+H)⁺.



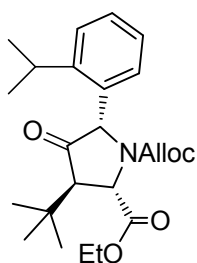
(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-isopropylphenyl)-4-nitropyrrolidine-2-carboxylate (51)

Tetrahydrofuran (30 mL) was sparged with nitrogen for 75 minutes, then it was treated with copper(I) triflate dimer, benzene complex (0.033 g, 0.065 mmol) and (2-(bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron (0.098 g, 0.129 mmol). The mixture was stirred at room temperature for 1 hour. The mixture was cooled to < 5 °C and treated dropwise with a solution of compound **50** (4.15 g, 17.80 mmol) in 8 mL tetrahydrofuran, followed by dropwise addition of potassium 2-methylpropan-2-olate (1M in tetrahydrofuran; 0.1 mL, 0.100 mmol), keeping the temperature < 5 °C. Neat (*E*)-3,3-dimethyl-1-nitrobut-1-ene (2.09 g, 16.18 mmol) was then added dropwise over about 10 minutes to keep the temperature < 10 °C. After completion of the addition, the reaction continued to stir in the ice bath for 25 minutes. The reaction mixture was then quenched with 25 mL of saturated aqueous NH₄Cl solution and warmed up to room temperature. The mixture was diluted with methyl *tert*-butyl ether and washed twice with saturated aqueous NH₄Cl solution and once with brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Silica gel chromatography, eluting with 10 to 50% ethyl acetate-heptanes, afforded the title compound, 1.902 g, (32% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.42 - 7.34 (m, 1H), 7.30 - 7.17 (m, 2H), 7.08 (ddd, J = 7.5, 6.9, 1.7 Hz, 1H), 5.08 (dd, J = 6.9, 3.6 Hz, 1H), 4.77 (d, J = 6.9 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.77 (d, J = 7.6 Hz, 1H), 3.25 (br s, 1H), 3.21 - 3.06 (m, 2H), 1.33 - 1.14 (m, 9H), 0.98 (s, 9H). MS (ESI⁺) *m/z* 363.1 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-5-(2-isopropylphenyl)-4-nitropyrrolidine-1,2-dicarboxylate (52)

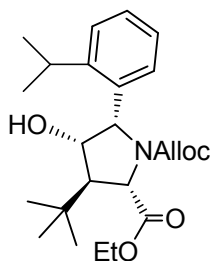
Compound **51** (12.3 g, 33.9 mmol) was dissolved in toluene (120 mL) and saturated aqueous sodium bicarbonate (120 mL) was added. Allyl chloroformate (3.98 mL, 37.3 mmol) was added, and the reaction mixture was stirred at ambient temperature for 20 minutes, at which point LC/MS indicated complete conversion of the starting material. The reaction was diluted with methyl *tert*-butyl ether (70 mL) and the layers were separated. The organic layer was washed with 1M aqueous HCl (2 x 30 mL), 1M aqueous NaOH (2 x 30 mL) and brine (30 mL). The organic layer was dried over sodium sulfate, filtered, concentrated, and purified via flash chromatography, eluting with 0:100 to 30:70 methyl *tert*-butyl ether:heptanes over 30 minutes on a 330 g silica gel column to provide 12.3 g of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 7.86 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.32 – 7.14 (m, 2H), 7.05 (ddd, *J* = 8.4, 6.5, 2.1 Hz, 1H), 5.72 (d, *J* = 9.0 Hz, 1H), 5.65 (ddd, *J* = 17.2, 10.7, 5.3 Hz, 1H), 5.53 (dd, *J* = 8.9, 3.6 Hz, 1H), 5.08 – 4.93 (m, 2H), 4.55 (d, *J* = 4.3 Hz, 1H), 4.41 (d, *J* = 5.2 Hz, 2H), 4.27 (qd, *J* = 7.0, 0.9 Hz, 2H), 3.24 (p, *J* = 6.7 Hz, 1H), 3.14 – 3.05 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.19 (d, *J* = 6.7 Hz, 3H), 1.03 (s, 9H); MS (ESI+) *m/z* 447.3 (M+H)⁺.



(2*S*,3*R*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-5-(2-isopropylphenyl)-4-oxopyrrolidine-1,2-dicarboxylate (53)

Compound **52** (11.2 g, 25.08 mmol) was dissolved in ethanol (226 mL) and the solution was heated to 75 °C. A separate solution of CrCl₂ was prepared by dissolving pyridinium dichromate (23.59 g, 62.7 mmol) in aqueous hydrochloric acid, (6M, 452 mL) and adding Zn (44.3 g, 667 mmol) in portions while cooling in an ice bath, maintaining an internal temperature below 35 °C.

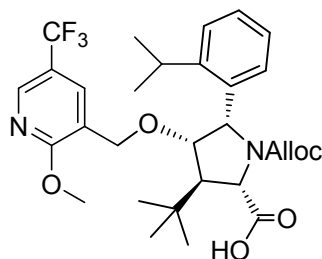
The resulting suspension was stirred at ambient temperature for 30 minutes after removing the flask from the ice bath, leaving a blue solution of CrCl₂, which was added via cannula over 20 minutes to the reaction flask containing the solution of the starting material in ethanol at 75 °C. Heating was continued at 85 °C for 36 hours. The flask was cooled to ambient temperature, and the organic material was extracted with dichloromethane (3 x 200 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated. The material was redissolved in an anhydrous solution of HCl in ethanol that was prepared by the addition of acetyl chloride (8.9 mL, 125 mmol) to 100 mL of ethanol via syringe while cooling in an ice-water bath. The resulting solution was heated to 45 °C for 1 hour, at which point complete re-esterification had occurred. The reaction mixture was concentrated and the crude material was partitioned between saturated aqueous sodium bicarbonate and methyl *tert*-butyl ether (300 mL each). The organic extracts were dried over sodium sulfate, filtered, and concentrated to provide (2*S*,3*R*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-5-(2-isopropylphenyl)-4-oxopyrrolidine-1,2-dicarboxylate (10 g) as an inseparable mixture with unreacted oxime. The mixture was used in the next step without additional purification



(2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-4-hydroxy-5-(2-isopropylphenyl)pyrrolidine-1,2-dicarboxylate (54)

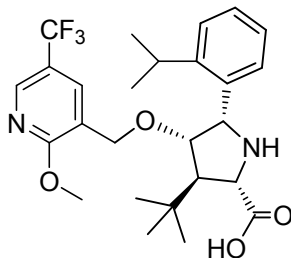
Compound **53** (10 g, 24.07 mmol) was dissolved in 100 mL of ethanol and sodium borohydride (0.910 g, 24.07 mmol) was added in one portion after cooling to -5 °C. The reaction was complete in 10 minutes at this temperature, as indicated by LC/MS. Acetone (10 mL) was added to quench the excess borohydride, and the reaction mixture was stirred at the same temperature for 15 minutes. The flask was warmed to ambient temperature, concentrated *in vacuo*, and partitioned between methyl *tert*-butyl ether and saturated sodium bicarbonate (100 mL each). The organic extracts were concentrated *in vacuo* to provide crude material, which was purified via flash chromatography, eluting with 0:100 to 30:70 methyl *tert*-butyl ether:heptanes over 40 minutes on a 220 g silica gel column to provide 5.5 g (41 %) of the desired diastereomer (2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-4-hydroxy-5-(2-isopropylphenyl)pyrrolidine-1,2-

dicarboxylate as an inseparable mixture with the oxime from the previous step. $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$, $120\text{ }^\circ\text{C}$) δ ppm 7.90 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.20 (ddd, $J = 7.7, 4.4, 1.5$ Hz, 1H), 7.13 (tdd, $J = 7.6, 2.8, 1.5$ Hz, 1H), 7.05 (ddd, $J = 8.9, 7.2, 1.5$ Hz, 1H), 5.70 – 5.59 (m, 1H), 5.22 (d, $J = 6.6$ Hz, 1H), 5.04 – 4.84 (m, 2H), 4.35 (m, 3H), 4.30 (d, $J = 4.6$ Hz, 1H), 4.24 – 4.14 (m, 2H), 3.75 (br s, 1H), 3.19 (dt, $J = 13.6, 6.9$ Hz, 1H), 2.37 – 2.25 (m, 1H), 1.26 (d, $J = 5.7$ Hz, 3H), 1.24 (t, $J = 4$ Hz, 3H), 1.20 (d, $J = 5.7$ Hz, 3H), 1.00 (s, 9H); MS (ESI+) m/z 418.1 (M+H) $^+$.



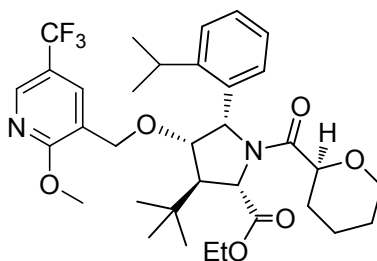
(2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-5-(2-isopropylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)pyrrolidine-1,2-dicarboxylate (55)

Compound **54** (1.75 g, 3.14 mmol) was dissolved in 1.2 mL of dry dimethylformamide. After cooling to $0\text{ }^\circ\text{C}$ in an ice bath, potassium *tert*-butoxide (1M in tetrahydrofuran, 4.6 mL, 4.6 mmol) solution was added dropwise, followed immediately by addition of 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine (1.36 g, 5.0 mmol) dropwise via syringe. LC/MS after 10 minutes showed complete conversion of the starting alcohol. The reaction was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with methyl *tert*-butyl ether (3 x 20 mL). The combined organic extracts were concentrated *in vacuo* and purified via flash chromatography, eluting on a 120 g silica gel column with 0:100 to 20:80 methyl *tert*-butyl ether:heptanes over 20 minutes to provide 955 mg (50 %) of the title compound. $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$, $120\text{ }^\circ\text{C}$) δ ppm 8.33 – 8.21 (m, 1H), 7.92 (dd, $J = 7.9, 1.4$ Hz, 1H), 7.17 (dt, $J = 5.7, 1.5$ Hz, 2H), 7.10 (td, $J = 7.5, 1.4$ Hz, 1H), 7.01 – 6.93 (m, 1H), 5.66 (ddt, $J = 16.2, 10.4, 5.1$ Hz, 1H), 5.33 (d, $J = 5.7$ Hz, 1H), 5.04 – 4.87 (m, 2H), 4.50 (d, $J = 2.2$ Hz, 1H), 4.39 (d, $J = 5.2$ Hz, 2H), 4.29 – 4.22 (m, 2H), 4.13 (qd, $J = 7.1, 1.2$ Hz, 2H), 3.86 (s, 3H), 3.78 (d, $J = 13.8$ Hz, 1H), 3.24 (p, $J = 6.8$ Hz, 1H), 2.52 (t, $J = 1.6$ Hz, 1H), 1.23 (d, $J = 6.7$ Hz, 3H), 1.19 (d, $J = 7.0$ Hz, 3H), 1.15 (t, $J = 8$ Hz, 3H), 1.05 (s, 9H); MS (ESI+) m/z 607.0 (M+H) $^+$.



(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-isopropylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)pyrrolidine-2-carboxylate (56)

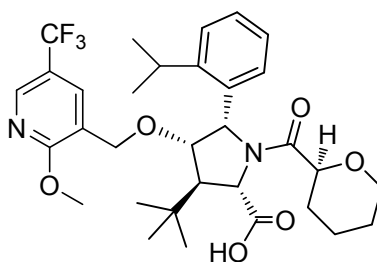
Compound **55** (850 mg, 1.401 mmol) and 1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (438 mg, 2.80 mmol) were dissolved in 14 mL of a 1:1 mixture of dichloromethane and ethyl acetate that had been degassed for 5 minutes. Palladium tetrakis(triphenylphosphine)palladium (16.19 mg, 0.014 mmol) was added, and the reaction mixture was stirred at ambient temperature for 15 minutes, at which point the reaction was complete as indicated by LC/MS. The reaction mixture was diluted with methyl *tert*-butyl ether (50 mL) and stirred with 10 mL of 10% aqueous sodium carbonate solution for 10 minutes. The organic layer was washed with brine and concentrated *in vacuo* to provide crude material. The crude material was purified via flash chromatography, eluting with 0:100 to 30:70 methyl *tert*-butyl ether:heptanes over 20 minutes on a 40 g silica gel column to provide 623 mg (85 %) of (2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-isopropylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)pyrrolidine-2-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.34 – 8.26 (m, 1H), 7.63 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.22 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.14 (td, *J* = 7.5, 1.4 Hz, 1H), 7.02 (td, *J* = 7.6, 1.4 Hz, 1H), 4.42 (d, *J* = 4.5 Hz, 1H), 4.22 (d, *J* = 13.6 Hz, 1H), 4.15 (q, *J* = 8 Hz, 2H), 3.96 (dd, *J* = 4.6, 1.8 Hz, 1H), 3.85 (s, 3H), 3.77 (d, *J* = 13.7 Hz, 1H), 3.65 (d, *J* = 6.5 Hz, 1H), 3.24 (p, *J* = 6.8 Hz, 1H), 2.42 (dd, *J* = 6.5, 1.8 Hz, 1H), 1.22 (t, *J* = 8 Hz, 3H), 1.21 (br s, 3H), 1.19 (br s, 3H) 1.00 (s, 9H); MS (ESI+) *m/z* 523.1 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-isopropylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-1-((*S*)-tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate (57)

Compound **56** (370 mg, 0.71 mmol) was dissolved in dichloromethane (7.1 mL) and triethylamine (0.30 mL, 2.1 mmol) was added. After cooling in an ice bath to <10 °C, a solution of freshly-prepared

tetrahydro-2H-pyran-2-carbonyl chloride (158 mg, 1.062 mmol) was added dropwise, and the reaction was complete as soon as the addition was done, as indicated by LC/MS. The reaction mixture was diluted with methyl *tert*-butyl ether (10 mL) and 1M aqueous HCl (10 mL) was added. The layers were separated, and the organic layer was washed with 1M aqueous HCl (2 x 5 mL) and brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a crude residue. The crude material was purified via flash chromatography, eluting with 0:100 to 20:80 methyl *tert*-butyl ether:heptanes over 5 minutes then isocratic 20:80 methyl *tert*-butyl ether:heptanes for 40 minutes on an 80 g silica gel column to provide Compound **57** (144 mg) as the first-eluting diastereomer and (2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-isopropylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-1-((*R*)-tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate (120 mg, 27 %) as the second-eluting diastereomer. Compound **57**: ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.33 – 8.19 (m, 1H), 8.00 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.15 (s, 2H), 7.03 (d, *J* = 7.9 Hz, 1H), 5.61 (d, *J* = 0.8 Hz, 1H), 4.74 (d, *J* = 1.8 Hz, 1H), 4.29 (d, *J* = 13.8 Hz, 1H), 4.24 (d, *J* = 5.7 Hz, 1H), 4.09 (qd, *J* = 7.1, 2.9 Hz, 2H), 3.86 (s, 3H), 3.80 (d, *J* = 13.9 Hz, 1H), 3.73 (s, 1H), 3.24 (p, *J* = 6.8 Hz, 1H), 3.18 – 2.93 (m, 1H), 2.45 (d, *J* = 1.7 Hz, 2H), 1.74 – 1.61 (m, 1H), 1.54 (t, *J* = 10.7 Hz, 2H), 1.37 (s, 3H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 9H); MS (ESI+) *m/z* 635.1 (M+H)⁺.

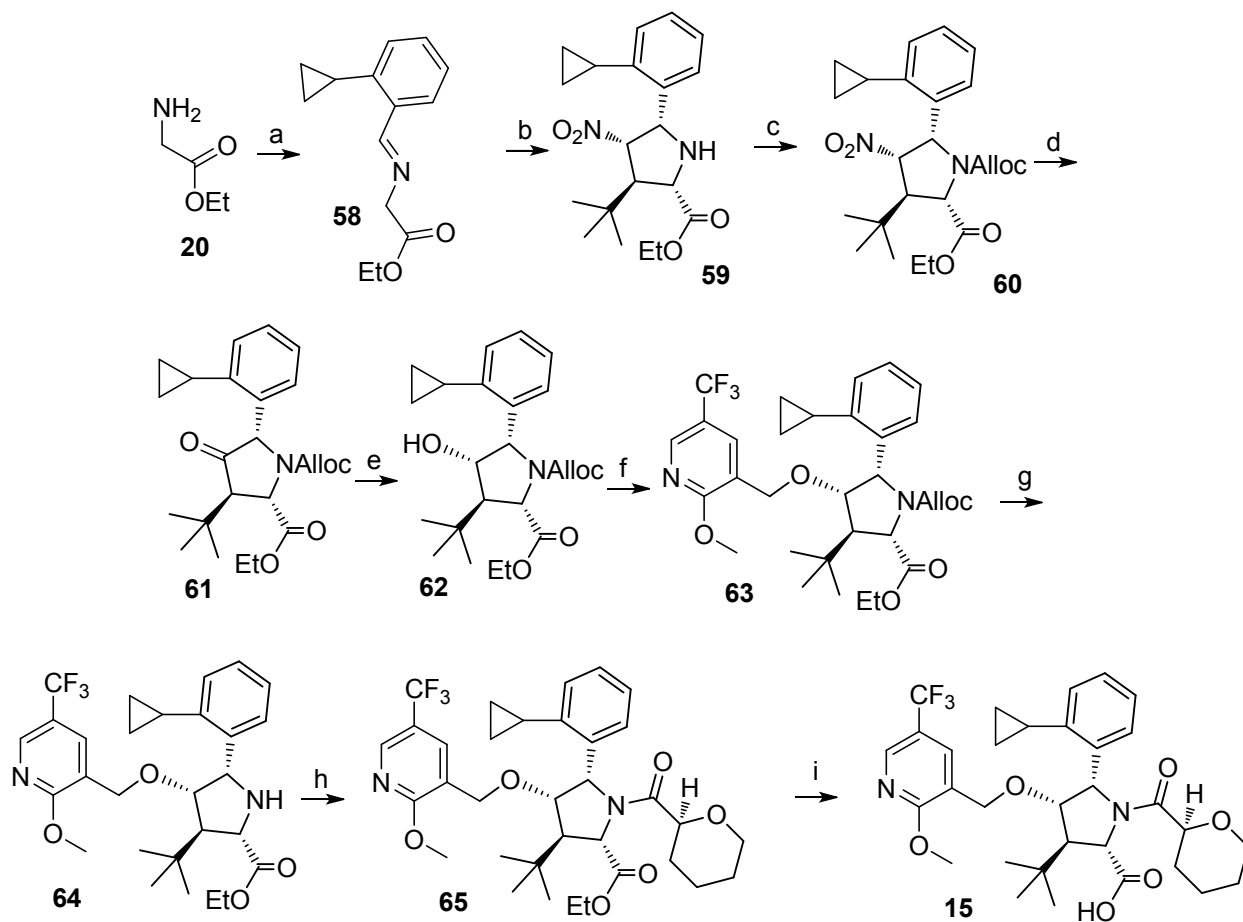


(2*S*,3*R*,4*S*,5*S*)-3-*tert*-butyl-4-{2-methoxy-5-(trifluoromethyl)pyridin-3-yl}methoxy-1-[(2*S*)-oxane-2-carbonyl]-5-[2-(propan-2-yl)phenyl]pyrrolidine-2-carboxylic acid (14**)**

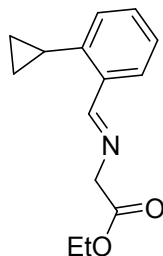
Compound **57** (140 mg, 0.22 mmol) was dissolved in a mixture of 0.9 mL of tetrahydrofuran, 0.9 mL of water, and 0.45 mL of methanol. Lithium hydroxide hydrate (93 mg, 2.21 mmol) was added, and the reaction mixture was heated to 50 °C for 16 hours. The reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), acidified with 1M aqueous HCl to pH = 3, and extracted with 3 x 5 mL dichloromethane. The organic extracts were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide Compound **14**. X-ray confirmation of the absolute stereochemistry confirmed the identity of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.33 – 8.18 (m, 1H), 8.06 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.32 – 6.93 (m, 4H), 5.63 (s, 1H), 4.71 (d, *J* = 1.7 Hz, 1H), 4.33 (d, *J* = 14.0 Hz, 1H), 4.24 (d, *J* = 5.8 Hz, 1H), 3.87 (s, 3H), 3.84 (d, *J* = 8.0 Hz, 1H), 3.75 (d, *J* = 11.2 Hz,

1H), 3.24 (p, $J = 6.8$ Hz, 1H), 3.20-2.80 (br s, 2H), 2.52 (d, $J = 1.7$ Hz, 1H), 1.73 – 1.22 (m, 6H), 1.30 (d, $J = 6.7$ Hz, 3H), 1.13 (d, $J = 6.7$ Hz, 3H), 1.04 (s, 9H); MS (ESI+) m/z 605.3 (M-H)⁻.

Scheme S8. Discovery Synthesis of Compound 15^a

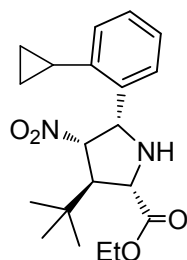


^aReagents and conditions: (a) MgSO_4 , TEA, 2-methylbenzaldehyde, DCM; (b) (2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron, $\text{Cu}(\text{OTf})_2$, KOtBu , (*E*)-3,3-dimethyl-1-nitrobut-1-ene, THF; (c) allyl chloroformate, toluene; (d) PDC, 6N HCl, Zn dust; (e) NaBH_4 , EtOH; (f) KOtBu , 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine, DMF; (g) 1,3-Dimethylbarbituric acid, $\text{Pd}(\text{PPh}_3)_4$, EtOAc/DCM; (h) Tetrahydropyran-2-carboxylic acid, oxalyl chloride, DMF, DCM; (i) LiOH, MeOH/THF.



(*E*)-ethyl 2-((2-cyclopropylbenzylidene)amino)acetate (58**)**

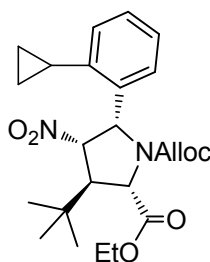
Ethyl 2-aminoacetate hydrochloride (4.50 g, 32.2 mmol) and magnesium sulfate (6.21 g, 51.6 mmol) were suspended in dichloromethane (43.0 mL) and the suspension was treated with triethylamine (4.49 mL, 32.2 mmol). After 1 hour, 2-cyclopropylbenzaldehyde (3.77 g, 25.8 mmol) in 5 mL of dichloromethane was added and the reaction was stirred at room temperature for 16 hours. The solid material was removed via filtration and the filtrate was washed with water and brine, dried over sodium sulfate, filtered, and concentrated to provide (*E*)-ethyl 2-((2-cyclopropylbenzylidene)amino)acetate (5.68 g, 24.56 mmol, 95 % yield), which was used in the next step without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.92 (d, *J* = 1.5 Hz, 1H), 7.81 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.35 (td, *J* = 7.6, 1.5 Hz, 1H), 7.22 (td, *J* = 7.6, 1.2 Hz, 1H), 7.05 (dd, *J* = 7.8, 1.2 Hz, 1H), 4.45 (d, *J* = 1.3 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.33 (tt, *J* = 8.5, 5.3 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.03 – 0.90 (m, 2H), 0.75 – 0.63 (m, 2H). MS (ESI⁺) *m/z* 232.1 (M+H)⁺.



(*2S,3R,4S,5S*)-ethyl 3-(*tert*-butyl)-5-(2-cyclopropylphenyl)-4-nitropyrrolidine-2-carboxylate (59**)**

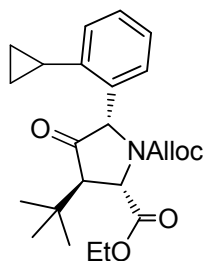
(2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron (0.241 g, 0.319 mmol) and copper (I) triflate dimer, benzene complex (0.062 g, 0.123 mmol) were dissolved in tetrahydrofuran (63.0 mL) that had been sparged with an nitrogen stream for 2 hours. The resulting mixture was stirred for 1.5 hours at room temperature, and (*E*)-ethyl 2-((2-cyclopropylbenzylidene)amino)acetate, (**58**, 5.68 g, 24.56 mmol) in tetrahydrofuran (8 mL) was added after cooling to <5 °C in an ice-water bath. Potassium 2-methylpropan-2-olate (0.246 mL, 0.246 mmol) was added drop wise, followed by addition of (*E*)-3,3-dimethyl-1-nitrobut-1-ene (3.17 g, 24.56 mmol) neat over 25 minutes, maintaining an internal temperature <10 °C. After the addition was complete, the reaction was stirred for 15 minutes at the same temperature, diluted with methyl *tert*-butyl

ether (100 mL) and stirred with 75 mL of saturated ammonium chloride at room temperature for 15 minutes. The organic layer was separated, washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated and purified by flash chromatography (0 to 30 % ethyl acetate in heptane) to provide (2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-cyclopropylphenyl)-4-nitropyrrolidine-2-carboxylate (6.85 g, 19.00 mmol, 77 % yield). ee > 97%. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 7.34 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.15 (dtd, *J* = 25.3, 7.5, 1.6 Hz, 2H), 7.07 – 7.01 (m, 1H), 5.31 (dd, *J* = 6.7, 3.1 Hz, 1H), 4.92 (dd, *J* = 8.4, 6.6 Hz, 1H), 4.27 – 4.12 (m, 2H), 3.75 (t, *J* = 7.7 Hz, 1H), 3.51 (t, *J* = 8.1 Hz, 1H), 3.04 (dd, *J* = 7.6, 3.1 Hz, 1H), 2.06 (tt, *J* = 8.5, 5.4 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.95 (s, 9H), 1.00 – 0.78 (m, 2H), 0.81 – 0.68 (m, 1H), 0.64 – 0.55 (m, 1H). MS (ESI⁺) *m/z* 361.2 (M+H)⁺.



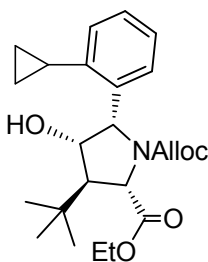
1-allyl 2-ethyl (2*S*,3*R*,4*S*,5*S*)-3-(*tert*-butyl)-5-(2-cyclopropylphenyl)-4-nitropyrrolidine-1,2-dicarboxylate (60)

Compound **59** (2.00 g, 5.55 mmol) was dissolved in toluene (10 mL) and saturated aqueous NaHCO₃ (10 mL) was added followed by allyl chloroformate (0.708 mL, 6.66 mmol). The reaction was stirred at ambient temperature for 17 hours, at which point it was complete. The reaction was diluted with dichloromethane (50 mL) and washed with 1M aqueous HCl (2 x 50 mL) and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated to provide the crude product. The residue was purified by silica gel chromatography (5% ethyl acetate in dichloromethane) to provide the title compound (1.76 g, 71%). ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 7.78 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.17 - 7.04 (m, 2H), 7.01 - 6.95 (m, 1H), 6.00 (d, *J* = 8.6 Hz, 1H), 5.67 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.56 (dd, *J* = 8.6, 2.5 Hz, 1H), 5.05 - 4.89 (m, 2H), 4.60 (d, *J* = 3.4 Hz, 1H), 4.41 (dq, *J* = 5.2, 1.5 Hz, 2H), 4.27 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.05 (ddd, *J* = 3.3, 2.5, 0.7 Hz, 1H), 2.06 (tt, *J* = 8.5, 5.4 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.04 (s, 9H), 1.02 - 0.88 (m, 2H), 0.85 - 0.75 (m, 1H), 0.54 (dtd, *J* = 7.9, 5.1, 2.9 Hz, 1H); MS (ESI⁺) *m/z* 445 (M+H)⁺.



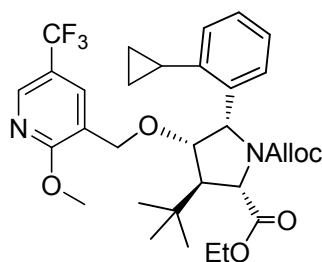
**1-allyl 2-ethyl (2*S*,3*R*,5*S*)-3-(*tert*-butyl)-5-(2-cyclopropylphenyl)-4-oxopyrrolidine-1,2-dicarboxylate
(61)**

Compound **60** (1.79 g, 3.93 mmol) was dissolved in 44 mL of ethanol and the solution was heated to 75 °C. A separate solution of CrCl₂ was prepared by dissolving pyridinium dichromate (4.066 g, 10.81 mmol) in 88 mL of 6M aqueous HCl and adding Zn (7.904 g, 119 mmol) in portions while cooling in an ice bath. The suspension was stirred until all Zn dissolved, leaving a brilliant blue solution. The CrCl₂ solution was transferred via cannula over 15 minutes to the solution of starting material and heating was continued for 16 hours. The temperature was maintained between 70 °C and 75 °C during the addition, and was maintained between 75 °C and 80 °C overnight (total 16 hours). The reaction mixture was cooled to room temperature, diluted with water and extracted with dichloromethane (3 x 200 mL). The combined extracts were washed with brine, and dried over sodium sulfate, filtered, and concentrated. The crude residue was dissolved ethanol (6 mL). A separate solution of HCl/ethanol was prepared by addition of 1 mL of acetyl chloride to 4 mL of ethanol at 0 °C, and poured into the reaction flask and the mixture was heated to 45 °C for 1 hour. The reaction mixture was concentrated *in vacuo* and loaded onto a 40 g silica gel column and was eluted with 5% ethyl acetate in dichloromethane over to provide the title compound (518.9 mg, 32%). ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 7.69 (dd, *J* = 7.1, 2.0 Hz, 1H), 7.19 - 7.05 (m, 3H), 5.74 - 5.63 (m, 2H), 5.07 - 4.94 (m, 2H), 4.65 (d, *J* = 5.0 Hz, 1H), 4.45 (dd, *J* = 5.3, 1.8 Hz, 2H), 4.28 - 4.18 (m, 2H), 2.63 (dd, *J* = 5.0, 0.9 Hz, 1H), 2.13 (tt, *J* = 8.5, 5.4 Hz, 1H), 1.26 (td, *J* = 7.1, 0.8 Hz, 3H), 1.07 (d, *J* = 0.8 Hz, 9H), 0.95 - 0.83 (m, 2H), 0.83 - 0.72 (m, 1H), 0.52 (dddd, *J* = 7.8, 6.6, 3.9, 1.5 Hz, 1H); MS (ESI+) *m/z* 414 (M+H)⁺.



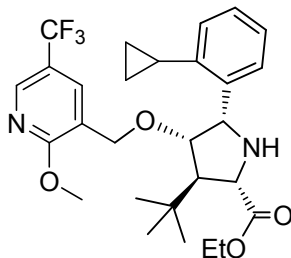
1-allyl 2-ethyl (2*S*,3*R*,4*S*,5*S*)-3-(*tert*-butyl)-5-(2-cyclopropylphenyl)-4-hydroxypyrrolidine-1,2-dicarboxylate (62)

Compound **61** (504.6 mg, 1.220 mmol) was dissolved in ethanol (5 mL), and the reaction was cooled to 0 °C. Sodium borohydride (75.0 mg, 1.982 mmol) was added and the reaction was stirred at 0 °C for 1 hour, and warmed to ambient temperature for another 1 hour. The solvent was removed *in vacuo* and the residue was extracted with ethyl acetate (50 mL), washed with saturated aqueous NaHCO₃ (50 mL) and brine (50 mL), dried over Na₂SO₄, filtered, and concentrated to provide crude product, which was purified by silica gel chromatography (5% ethyl acetate in dichloromethane) to provide the title compound (280 mg, 55%). ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 7.89 - 7.83 (m, 1H), 7.10 - 7.04 (m, 2H), 7.01 - 6.95 (m, 1H), 5.72 - 5.60 (m, 1H), 5.51 (d, J = 6.2 Hz, 1H), 5.03 - 4.91 (m, 2H), 4.45 (td, J = 5.6, 2.9 Hz, 1H), 4.36 (td, J = 3.5, 2.1 Hz, 3H), 4.18 (q, J = 7.1 Hz, 2H), 3.71 (s, 1H), 2.31 (t, J = 3.4 Hz, 1H), 1.97 (tt, J = 7.9, 5.4 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.01 (s, 9H), 0.88 (tt, J = 12.7, 8.9, 5.6 Hz, 2H), 0.73 (dtd, J = 9.4, 5.4, 3.6 Hz, 1H), 0.61 - 0.49 (m, 1H); MS (ESI+) *m/z* 416 (M+H)⁺.



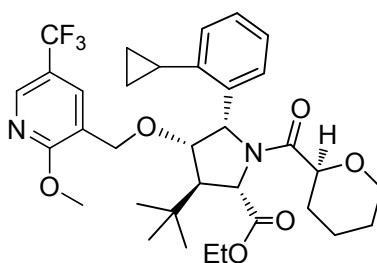
1-allyl 2-ethyl (2S,3R,4S,5S)-3-(tert-butyl)-5-(2-cyclopropylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)pyrrolidine-1,2-dicarboxylate (63)

Compound **62** (275.0 mg, 0.662 mmol) and 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine (312.1 mg, 1.156 mmol) were dissolved in dimethylformamide (2.6 mL). The reaction was cooled to 0 °C, and potassium *tert*-butoxide (1M in tetrahydrofuran, 0.80 mL, 0.80 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for 1 hour. The reaction mixture was poured into saturated aqueous NH₄Cl (35 mL), extracted with methyl *tert*-butyl ether (3 x 35 mL), and purified by silica gel chromatography (5% ethyl acetate in dichloromethane) to provide the title compound (350.8 mg, 88%). ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.33 - 8.25 (m, 1H), 7.88 (dd, J = 7.3, 2.1 Hz, 1H), 7.20 - 7.15 (m, 1H), 7.02 (ddd, J = 7.0, 4.5, 1.9 Hz, 2H), 6.94 (dd, J = 6.9, 2.1 Hz, 1H), 5.73 - 5.58 (m, 2H), 5.05 - 4.90 (m, 2H), 4.52 (d, J = 2.0 Hz, 1H), 4.41 - 4.37 (m, 2H), 4.37 - 4.33 (m, 1H), 4.27 (d, J = 13.8 Hz, 1H), 4.11 (dtd, J = 8.0, 6.9, 1.2 Hz, 2H), 3.87 - 3.79 (m, 4H), 2.52 (t, J = 1.3 Hz, 1H), 1.99 (td, J = 8.4, 4.2 Hz, 1H), 1.15 (td, J = 7.1, 0.7 Hz, 3H), 1.05 (s, 9H), 0.96 - 0.83 (m, 2H), 0.59 (dd, J = 5.2, 2.6 Hz, 2H); MS (ESI+) *m/z* 605 (M+H)⁺.



ethyl (2*S*,3*R*,4*S*,5*S*)-3-(*tert*-butyl)-5-(2-cyclopropylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)pyrrolidine-2-carboxylate (64)

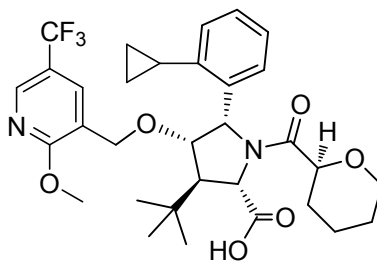
Compound **63** (350 mg, 0.579 mmol) was dissolved in ethyl acetate (2.5 mL) and dichloromethane (2.5 mL) and treated with 1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (183.2 mg, 1.173 mmol) and tetrakis(triphenylphosphine)palladium (7.2 mg, 6.23 μ mol). The reaction mixture was stirred at ambient temperature. After 1 hour, the reaction mixture was diluted with methyl *tert*-butyl ether (50 mL) and stirred with 15 mL of 10% aqueous Na₂CO₃ (50 mL) solution for 30 minutes. The phases were separated, and the organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with 5% to 10% ethyl acetate in dichloromethane to provide the title compound (220.4 mg, 73%). ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.29 (s, 1H), 7.59 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.12 - 7.00 (m, 2H), 6.95 (dd, *J* = 7.2, 1.7 Hz, 1H), 4.65 (d, *J* = 4.4 Hz, 1H), 4.23 (d, *J* = 13.8 Hz, 1H), 4.19 - 4.08 (m, 3H), 3.85 (s, 3H), 3.80 (d, *J* = 13.8 Hz, 1H), 3.66 (d, *J* = 6.4 Hz, 1H), 2.40 (dd, *J* = 6.3, 1.6 Hz, 1H), 1.99 (tt, *J* = 8.5, 5.5 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.01 (s, 10H), 0.90 (dq, *J* = 8.3, 2.1 Hz, 2H), 0.68 - 0.55 (m, 2H); MS (ESI+) *m/z* 521 (M+H)⁺.



ethyl (2*S*,3*R*,4*S*,5*S*)-3-(*tert*-butyl)-5-(2-cyclopropylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-1-((*S*)-tetrahydro-2*H*-pyran-2-carbonyl)pyrrolidine-2-carboxylate (65)

Tetrahydropyran-2-carboxylic acid (53.7 mg, 0.413 mmol) was dissolved in dichloromethane (2 mL). Oxalyl chloride (2M in dichloromethane, 250 μ L, 0.50 mmol) was added followed by dimethylformamide (25 μ L). The reaction was stirred at room temperature for 3 hours, at which point it was concentrated, redissolved in dichloromethane (1 mL), and concentrated again. The residue was taken up in

dichloromethane (3 x 1 mL) and was added to a solution of Compound **64** (90.4 mg, 0.174 mmol) and triethylamine (100 μ L, 0.717 mmol) in dichloromethane (3 mL). The reaction was stirred at ambient temperature for 17 hours. After this time, the mixture was diluted with dichloromethane (100 mL) and washed twice with saturated aqueous NaHCO₃ and once with brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by reverse-phase preparative HPLC on a Phenomenex® Luna® C8(2) 5 μ m 100Å AXIA™ column (30 mm \times 75 mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50 mL/minute (0-0.5 minutes 10% A, 0.5-7.0 minutes linear gradient 10-95% A, 7.0-10.0 minutes 95% A, 10.0-12.0 minutes linear gradient 95-10% A). The title compound was the second eluting diastereomer and was isolated as the TFA salt (43.7 mg, 34%). ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.27 (s, 1H), 7.96 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.16 (d, *J* = 2.5 Hz, 1H), 7.06 (t, *J* = 9.6 Hz, 2H), 6.95 (d, *J* = 7.1 Hz, 1H), 5.90 (s, 1H), 4.72 (s, 1H), 4.36 (d, *J* = 5.6 Hz, 1H), 4.28 (d, *J* = 13.9 Hz, 1H), 4.08 (qd, *J* = 7.1, 3.0 Hz, 2H), 3.89 - 3.80 (m, 5H), 3.75 (d, *J* = 11.4 Hz, 1H), 3.45 (s, 1H), 2.44 (d, *J* = 1.8 Hz, 1H), 2.06 - 1.94 (m, 1H), 1.72 - 1.26 (m, 6H), 1.13 (t, *J* = 7.1 Hz, 3H), 1.04 (s, 9H), 0.99 - 0.84 (m, 2H), 0.80 - 0.67 (m, 1H), 0.57 - 0.46 (m, 1H); MS (ESI+) *m/z* 633 (M+H)⁺.

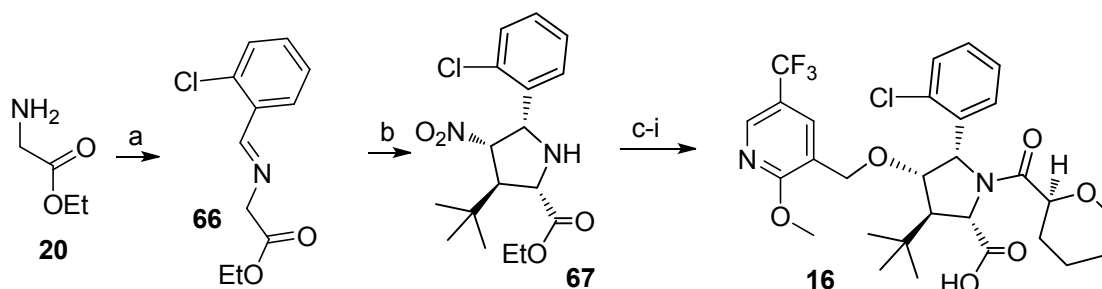


(2*S*,3*R*,4*S*,5*S*)-3-*tert*-butyl-5-(2-cyclopropylphenyl)-4-[[2-methoxy-5-(trifluoromethyl)pyridin-3-yl]methoxy]-1-[(2*S*)-oxane-2-carbonyl]pyrrolidine-2-carboxylic acid (15**)**

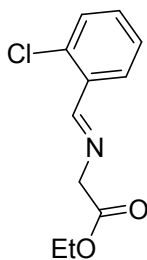
Compound **65** (40.7 mg, 0.055 mmol) was dissolved in methanol (1 mL), and tetrahydrofuran (1 mL). Aqueous LiOH (1 M, 0.5 mL, 0.5 mmol) was added and the reaction was heated to 50 °C for 16 hours. The reaction mixture was quenched by the addition of 1M aqueous HCl (0.5 mL), concentrated and purified by reverse-phase preparative HPLC on a Phenomenex® Luna® C8(2) 5 μ m 100Å AXIA™ column (30 mm \times 75 mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50 mL/minute (0-0.5 minutes 10% A, 0.5-7.0 minutes linear gradient 10-95% A, 7.0-10.0 minutes 95% A, 10.0-12.0 minutes linear gradient 95-10% A) to provide the title compound (27.3 mg, 70%) as the TFA salt. ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.27 (d, *J* = 2.4 Hz, 1H), 8.02 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.13 (s, 1H), 7.11 - 6.99 (m, 2H), 6.94 (dd, *J* = 7.3, 1.7 Hz, 1H), 5.90 (s, 1H), 4.69 (s, 1H), 4.35 (d, *J* = 5.8 Hz, 1H), 4.31 (d, *J* = 14.0 Hz, 1H), 3.95 - 3.84 (m, 5H), 3.76 (d, *J* =

11.5 Hz, 1H), 3.47 (s, 1H), 2.50 (d, $J = 1.8$ Hz, 1H), 2.07 - 1.94 (m, 1H), 1.71 - 1.25 (m, 6H), 1.04 (s, 9H), 0.98 - 0.84 (m, 2H), 0.78 - 0.65 (m, 1H), 0.49 (dtd, $J = 9.1, 5.3, 3.0$ Hz, 1H); MS (ESI+) m/z 605.1 (M+H)⁺.

Scheme S9. Discovery Synthesis of Compound 16^a



^aReagents and conditions: (a) MgSO₄, TEA, 2-methylbenzaldehyde, DCM; (b) (2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron, Cu(OTf)₂, KOtBu, (*E*)-3,3-dimethyl-1-nitrobut-1-ene, THF; (c) allyl chloroformate, toluene; (d) PDC, 6N HCl, Zn dust, (e) NaBH₄, EtOH; (f) KOtBu, 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine, DMF; (g) 1,3-Dimethylbarbituric acid, Pd(PPh₃)₄, EtOAc/DCM; (h) Tetrahydropyran-2-carboxylic acid, oxalyl chloride, DMF, DCM; (i) LiOH, MeOH/THF.

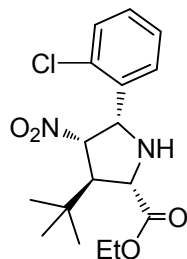


(*E*)-ethyl 2-((2-chlorobenzylidene)amino)acetate (66)

A mixture of ethyl 2-aminoacetate hydrochloride (1.85 g, 13.25 mmol) and magnesium sulfate (3.19 g, 26.5 mmol) in dichloromethane (22.09 mL) (anhydrous) was treated with triethylamine (1.847 mL, 13.25 mmol), stirred for 30 minutes, and treated with the 2-chlorobenzaldehyde (1.86 g, 13.25 mmol) as a solution in 3 mL of dichloromethane. The reaction was stirred at ambient temperature overnight. The solid material was filtered and the filtrate was concentrated.

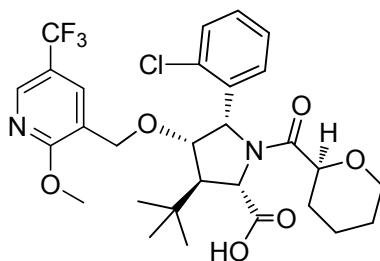
Toluene (5 mL) was added, the mixture was filtered again and concentrated, giving (*E*)-ethyl 2-((2-chlorobenzylidene)amino)acetate (2.76 g, 12.23 mmol, 92 % yield) which was used directly in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.77 (d, $J = 1.5$ Hz, 1H), 8.19 - 8.04 (m,

1H), 7.45 - 7.39 (m, 2H), 7.34 (ddd, J = 8.3, 6.0, 2.6 Hz, 1H), 4.48 (d, J = 1.5 Hz, 2H), 4.28 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H).



(2S,3R,4S,5S)-ethyl 3-(*tert*-butyl)-5-(2-chlorophenyl)-4-nitropyrrolidine-2-carboxylate (67)

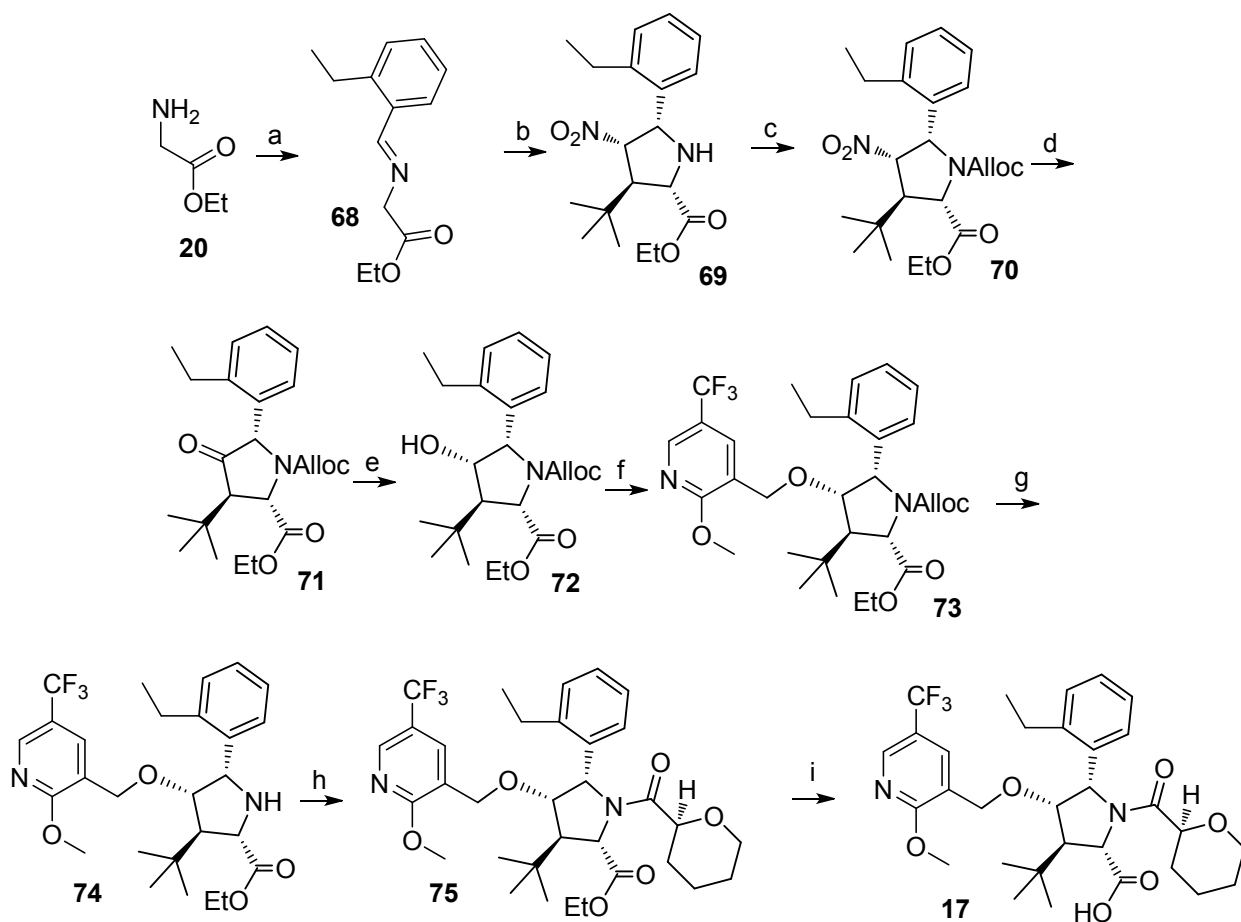
(2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron (0.175 g, 0.232 mmol) and copper (I) triflate dimer, benzene complex (0.047 g, 0.093 mmol) were dissolved in tetrahydrofuran (19.36 mL mL) that had been sparged with an N₂ stream for 1 hour. The resulting mixture was stirred for 1 hour at ambient temperature (continue nitrogen sparge), and (*E*)-ethyl 2-((2-chlorobenzylidene)amino)acetate (**66**, 2.75 g, 12.19 mmol) was added as a solution in 2 mL of tetrahydrofuran and the resulting solution was cooled to <5 °C in an ice-water bath. Potassium 2-methylpropan-2-olate in tetrahydrofuran (0.209 mL, 0.209 mmol) was added dropwise, followed by addition of neat (*E*)-3,3-dimethyl-1-nitrobut-1-ene (1.5 g, 11.61 mmol) over 20 minutes, maintaining a temperature less than 7 °C. The reaction mixture was stirred for 1 hour at 0 °C and quenched with 60 mL of saturated aqueous ammonium chloride and 100 mL of ethyl acetate and warmed to ambient temperature. The organic layer was separated and washed with saturated aqueous ammonium chloride (2 x 50 mL) and brine and filtered through a pad of silica gel. The organic layer was concentrated. Heptane (70 mL) was added, and the resulting precipitate was filtered. The filtrate was purified by chromatography using a 40 g silica gel cartridge eluting with a gradient of 0-60% heptanes/ethyl acetate over a period of 20 minutes to provide additional product (2S,3R,4S,5S)-ethyl 3-(*tert*-butyl)-5-(2-chlorophenyl)-4-nitropyrrolidine-2-carboxylate (2.85 g, 8.03 mmol, 69.2 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.56 - 7.48 (m, 1H), 7.45 - 7.38 (m, 1H), 7.35 - 7.24 (m, 2H), 5.25 (dd, J = 6.7, 3.0 Hz, 1H), 4.71 (t, J = 7.0 Hz, 1H), 4.15-4.24 (m, 2H), 3.78 (t, J = 7.3 Hz, 1H), 3.68 (t, J = 7.3 Hz, 1H), 3.07 (dd, J = 7.4, 3.0 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H); MS (APCI+) *m/z* 355 (M+H)⁺.



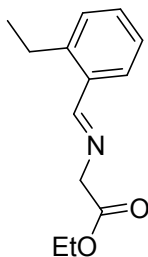
(2*S*,3*R*,4*S*,5*S*)-3-*tert*-butyl-5-(2-chlorophenyl)-4-[[2-methoxy-5-(trifluoromethyl)pyridin-3-yl]methoxy}-1-[(2*S*)-oxane-2-carbonyl]pyrrolidine-2-carboxylic acid (16**)**

The title compound was prepared using the procedures described for compound **15** substituting compound **67** for compound **59**. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.31 (s, 1H), 8.28 (s, 1H), 7.27 (s, 1H), 7.17 (s, 2H), 7.09 (d, *J* = 2.2 Hz, 1H), 5.80 (s, 1H), 4.63 - 4.54 (m, 1H), 4.37 (d, *J* = 14.0 Hz, 1H), 4.32 (d, *J* = 6.3 Hz, 1H), 4.00 (d, *J* = 14.0 Hz, 1H), 3.88 (s, 3H), 3.80 (d, *J* = 11.2 Hz, 1H), 3.25 (bs, 2H), 2.58 (s, 1H), 1.70 (s, 1H), 1.54 (s, 2H), 1.37 (bs, 3H), 1.01 (s, 9H); MS (ESI+) *m/z* 599 (M+H)⁺.

Scheme S10. Discovery Synthesis of Compound 17^a

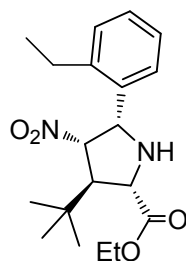


^aReagents and conditions: (a) MgSO₄, TEA, 2-methylbenzaldehyde, DCM; (b) (2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron, Cu(OTf)₂, KOtBu, (*E*)-3,3-dimethyl-1-nitrobut-1-ene, THF; (c) allyl chloroformate, toluene; (d) PDC, 6N HCl, Zn dust, (e) NaBH₄, EtOH; (f) KOtBu, 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine, DMF; (g) 1,3-Dimethylbarbituric acid, Pd(PPh₃)₄, EtOAc/DCM; (h) Tetrahydropyran-2-carboxylic acid, oxalyl chloride, DMF, DCM; (i) LiOH, MeOH/THF.



(*E*)-ethyl 2-((2-ethylbenzylidene)amino)acetate (68)

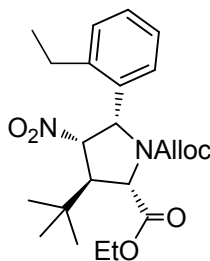
A mixture of ethyl 2-aminoacetate hydrochloride (1.85 g, 13.25 mmol) and magnesium sulfate (3.19 g, 26.5 mmol) in dichloromethane (22 mL) (anhydrous) was treated with triethylamine (1.847 mL, 13.25 mmol), stirred for 10 minutes and treated with 2-ethylbenzaldehyde (1.78 g, 13.25 mmol) as a solution in 1 mL of dichloromethane. The flask was capped and stirred at ambient temperature overnight. The solid material was filtered, the filtrate was washed with water, and the organic layer was dried with Na₂SO₄ and filtered again. The filtrate was concentrated, giving (*E*)-ethyl 2-((2-ethylbenzylidene)amino)acetate (2.65 g, 12.09 mmol, 91 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.63 (s, 1H), 7.96 (dd, J = 7.8, 1.5 Hz, 1H), 7.37 (td, J = 7.5, 1.5 Hz, 1H), 7.26 (d, J = 6.1 Hz, 1H), 7.25 - 7.19 (m, 1H), 4.43 (d, J = 1.4 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 2.89 (q, J = 7.5 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.6 Hz, 3H).



(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-nitropyrrolidine-2-carboxylate (69)

(2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron (0.182 g, 0.242 mmol) and copper (I) triflate dimer, benzene complex (0.049 g, 0.097 mmol) were dissolved in tetrahydrofuran (18 mL) that had been sparged with an N₂ stream for 1 hour. The resulting mixture was stirred for 1 hour at ambient temperature (continued nitrogen sparge), and (*E*)-ethyl 2-((2-ethylbenzylidene)amino)acetate (**68**, 2.65 g, 12.09 mmol) in 1 mL

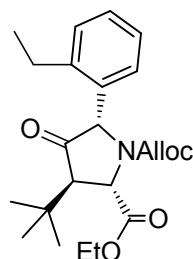
tetrahydrofuran was added. The resulting solution was cooled to $< 5\text{ }^{\circ}\text{C}$ in an ice-water bath. Potassium 2-methylpropan-2-olate in tetrahydrofuran (0.218 mL, 0.218 mmol) was added dropwise, followed by addition of (*E*)-3,3-dimethyl-1-nitrobut-1-ene (1.561 g, 12.09 mmol) in 1 mL tetrahydrofuran over 2 minutes, maintaining a temperature less than $7\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for 1.5 hours at $0\text{ }^{\circ}\text{C}$. The mixture was quenched with 20 mL of saturated aqueous ammonium chloride and 50 mL of ethyl acetate and warmed to ambient temperature. The organic layer was separated and washed with saturated aqueous ammonium chloride (2 x 50 mL) and brine and filtered through a pad of silica gel. The filtrate was concentrated. The crude material was purified by chromatography using a 40 g silica gel cartridge eluting with a gradient of 0-60% heptanes/ethyl acetate over a period of 20 minutes. The crude material was triturated with heptane and the precipitate was filtered to provide (2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-nitropyrrolidine-2-carboxylate (2.11 g, 6.06 mmol, 50.1 % yield). ^1H NMR (501 MHz, $\text{DMSO-}d_6$) δ ppm 7.40 - 7.29 (m, 1H), 7.25 - 7.15 (m, 2H), 7.11 (td, $J = 7.4, 1.8$ Hz, 1H), 5.17 (dd, $J = 7.0, 3.5$ Hz, 1H), 4.64 (t, $J = 7.4$ Hz, 1H), 4.19 (qd, $J = 7.1, 3.8$ Hz, 2H), 3.72 (t, $J = 7.6$ Hz, 1H), 3.47 (t, $J = 7.5$ Hz, 1H), 3.07 (dd, $J = 7.9, 3.5$ Hz, 1H), 2.72 (dt, $J = 15.0, 7.5$ Hz, 1H), 2.63 (dt, $J = 15.0, 7.5$ Hz, 1H), 1.22 (dt, $J = 16.4, 7.3$ Hz, 6H), 0.93 (s, 9H); MS (APCI+) m/z 349 (M+H) $^+$.



(2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-nitropyrrolidine-1,2-dicarboxylate (70)

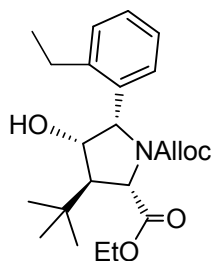
To compound **69** (1.43 g, 4.10 mmol) in toluene (4.77 mL) and saturated aqueous NaHCO_3 (4.77 mL) was added allyl carbonochloridate (0.463 mL, 4.23 mmol) dropwise at ambient temperature. The mixture was stirred at ambient temperature for 16 hours. Ethyl acetate (30 mL) and water (25 mL) were added and the organic layer was washed with brine and concentrated. The resulting material was purified on a 24 g silica gel cartridge eluting with a gradient of 0-65% ethyl acetate/heptanes over a period of 20 minutes to provide (2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-nitropyrrolidine-1,2-dicarboxylate (1.64 g, 3.79 mmol, 92 % yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ ppm 7.83 (d, $J = 7.7$ Hz, 1H), 7.19 - 7.13 (m, 1H), 7.13 - 7.05 (m, 2H), 5.72 (bs, 1H), 5.66 (dd, $J = 8.8, 2.9$ Hz, 1H), 5.58 (d, $J = 8.8$ Hz, 1H), 4.97 (d, 2H), 4.53 (d, $J = 3.8$ Hz, 1H), 4.42 (s, 2H), 4.24 (q, $J = 7.1$ Hz, 2H), 3.03 (d, $J =$

3.5 Hz, 1H), 2.84 (dq, $J = 14.8, 7.4$ Hz, 1H), 2.58 (dq, $J = 15.1, 7.6$ Hz, 1H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.18 (t, $J = 7.5$ Hz, 3H), 1.00 (s, 9H); MS (APCI+) m/z 433 (M+H)⁺.



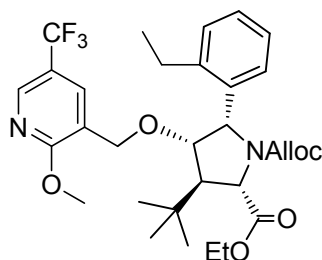
(2*S*,3*R*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-oxopyrrolidine-1,2-dicarboxylate (71)

To potassium dichromate (6.02 g, 20.48 mmol) in 6N aqueous HCl (93 mL) was added zinc (6.84 g, 105 mmol) portionwise under N₂ atmosphere at room temperature. After the almost complete dissolution of zinc (~2 hours) provided a clear light blue solution, the formed chromium(II) chloride was transferred via cannula to the refluxing solution of compound **70** (1.64 g, 3.79 mmol) in ethanol (79 mL) under N₂. The reaction mixture was refluxed at 86 °C internally for 20 hours, cooled, and concentrated. The mixture was extracted with dichloromethane three times. The organic phase was washed with saturated aqueous NaHCO₃ solution and brine, dried over MgSO₄, filtered, and concentrated. The residue (1.65 g) was subjected to re-esterification. Acetyl chloride (2 mL, 28.13 mmol) was added slowly to an ice-cooled flask containing ethanol (6 mL). After the addition was complete, the reaction was stirred at room temperature for 5 minutes before pouring the resulting HCl/ethanol solution into a separate flask containing the crude ester/acid mixture. The mixture was heated to 65 °C for an additional hour, at which point nearly complete conversion was noted. The mixture was cooled to room temperature and concentrated. The crude material was purified on a 24 g cartridge eluting with a gradient of 0-70% ethyl acetate/heptanes over a period of 20 minutes to provide (2*S*,3*R*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-oxopyrrolidine-1,2-dicarboxylate (0.802 g, 1.998 mmol, 52.7 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.77 (d, $J = 7.6$ Hz, 1H), 7.25 - 7.05 (m, 3H), 5.69 (d, $J = 101.2$ Hz, 1H), 5.26 (s, 1H), 4.90 (d, 1H), 4.73 - 4.29 (m, 4H), 4.20 (qd, $J = 7.1, 1.6$ Hz, 2H), 2.73 (tt, $J = 14.5, 7.1$ Hz, 3H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.16 (t, $J = 7.5$ Hz, 3H), 1.03 (s, 9H); MS (APCI+) m/z 402 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-hydroxypyrrolidine-1,2-dicarboxylate (72)

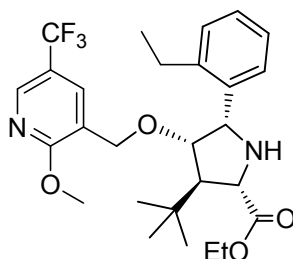
Compound **71** (0.8 g, 1.993 mmol) was dissolved in ethanol (9.96 mL) and sodium borohydride (0.151 g, 3.99 mmol) was added after cooling the reaction to <-10 °C in an ice/acetone bath. The ice bath was removed and the mixture was allowed to warm to room temperature over 20 minutes. The reaction mixture was concentrated and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organics were concentrated and purified using a 40 g silica gel cartridge and eluting with 0-2% methanol/dichloromethane over a period of 20 minutes to provide (2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-hydroxypyrrolidine-1,2-dicarboxylate, 2173 (601 mg, 1.489 mmol, 74.7 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.92 (s, 1H), 7.13 - 7.02 (m, 3H), 5.67 (d, J = 107.5 Hz, 1H), 5.23 (m, 1H), 5.07 (d, J = 6.6 Hz, 1H), 4.85 (m, 1H), 4.61 (s, 1H), 4.47 - 4.27 (m, 3H), 4.24 (d, J = 4.9 Hz, 1H), 4.14 (qd, J = 7.1, 1.9 Hz, 2H), 2.69 (dq, J = 14.4, 7.2 Hz, 1H), 2.54 (dd, J = 14.7, 7.5 Hz, 1H), 2.23 (s, 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.4 Hz, 3H), 0.95 (s, 9H); MS (APCI+) *m/z* 404 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)pyrrolidine-1,2-dicarboxylate (73)

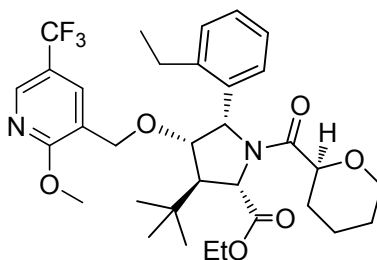
Compound **72** (400 mg, 0.991 mmol) and 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine (428 mg, 1.586 mmol) were dissolved in dry dimethylformamide (5 mL). After cooling in an ice bath, potassium 2-methylpropan-2-olate (1.437 mL, 1.437 mmol) solution was added dropwise over 4 minutes. After 60 minutes, the reaction was acidified with 1M aqueous HCl (1.2 mL) and warmed to room temperature. The reaction mixture was diluted with water (20 mL) and extracted with dichloromethane. The organic extracts were loaded onto a 24 g silica gel column and eluted with a gradient of 0-80% ethyl acetate/heptanes over 20 minutes to provide (2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)pyrrolidine-1,2-dicarboxylate (421 mg, 0.710 mmol, 71.7 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.33 (dd, J = 2.5, 1.2 Hz, 1H), 7.91 (s, 1H), 7.15 - 6.93 (m, 4H), 5.66 (d, J = 128.9 Hz, 1H), 5.18 (d, J = 5.4 Hz, 3H), 5.00 - 4.53 (m, 1H), 4.47 (d, J = 1.8 Hz, 2H), 4.31 (s, 2H), 4.28 (d, J = 14.6 Hz, 2H), 4.06 (qt, J = 7.1, 3.6 Hz, 2H), 3.82 (d, J =

14.6 Hz, 4H), 2.73 (dq, J = 14.9, 7.4 Hz, 1H), 2.54 (dt, J = 14.7, 7.5 Hz, 1H), 1.14 (t, J = 7.6 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H), 1.00 (s, 9H); MS (APCI+) m/z 593 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)pyrrolidine-2-carboxylate (74)

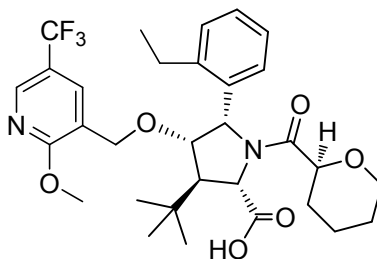
To a solution of compound **73** (420 mg, 0.709 mmol) in acetonitrile/water (1.24 mL, 10:1) was added tetrakis(triphenylphosphine)palladium(0) (18.02 mg, 0.016 mmol) and diethylamine (0.147 mL, 1.417 mmol). The mixture was stirred at room temperature overnight. Dichloromethane and water were added, and the organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The crude material was purified by chromatography, eluting on 12 g silica gel cartridge with a gradient of 0-70% ethyl acetate/heptanes over 20 minutes to provide (2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)pyrrolidine-2-carboxylate (321 mg, 0.631 mmol, 89 % yield). ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.41 - 8.30 (s, 1H), 7.67 - 7.55 (d, 1H), 7.27 (d, J = 2.5 Hz, 1H), 7.19 - 7.09 (m, 2H), 7.05 (ddd, J = 8.5, 5.7, 3.0 Hz, 1H), 4.25 (d, J = 4.5 Hz, 1H), 4.22 (d, J = 13.8 Hz, 2H), 4.17 - 4.07 (m, 2H), 3.96 (dd, J = 4.5, 1.6 Hz, 1H), 3.83 (s, 3H), 3.72 (d, J = 13.9 Hz, 1H), 3.59 (t, J = 7.1 Hz, 1H), 3.12 (t, J = 7.8 Hz, 1H), 2.68 (dq, J = 15.0, 7.5 Hz, 1H), 2.59 (dq, J = 14.9, 7.5 Hz, 1H), 2.34 (dd, J = 6.8, 1.5 Hz, 1H), 1.22 - 1.17 (t, 3H), 1.17 - 1.13 (t, 3H), 0.95 (s, 9H); MS (APCI+) m/z 509 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-1-((*S*)-tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate (75)

To a solution of compound **74** (320 mg, 0.629 mmol) in dichloromethane (2.5 mL) at 0°C was added triethylamine (0.395 mL, 2.83 mmol) followed by tetrahydro-2H-pyran-2-carbonyl chloride (159 mg,

1.070 mmol) as a solution in 2 mL dichloromethane. After stirring for 15 minutes, the reaction was quenched with 5 mL of saturated aqueous sodium bicarbonate. The crude material was chromatographed three times using a 24 g silica gel cartridge (3 times with a gradient of 0-80% ethyl acetate/heptanes over a period of 20 minutes to provide (2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-1-((*S*)-tetrahydro-2*H*-pyran-2-carbonyl)pyrrolidine-2-carboxylate (166 mg, 0.267 mmol, 42.5 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.27 (d, *J* = 2.4 Hz, 1H), 8.02 - 7.94 (d, 1H), 7.20 (s, 1H), 7.13 (s, 2H), 7.04 (d, *J* = 7.5 Hz, 1H), 5.56 (s, 1H), 4.69 (s, 1H), 4.32 - 4.20 (m, 2H), 4.09 (qd, *J* = 7.0, 3.0 Hz, 2H), 3.85 (s, 3H), 3.80 (d, *J* = 13.8 Hz, 1H), 3.72 (d, *J* = 11.4 Hz, 1H), 3.41 (bs, 2H), 2.75 (dt, *J* = 15.1, 7.6 Hz, 1H), 2.66 (dd, *J* = 14.9, 7.4 Hz, 1H), 2.42 (d, *J* = 1.8 Hz, 1H), 1.65 (d, *J* = 12.9 Hz, 1H), 1.52 (d, *J* = 11.9 Hz, 2H), 1.34 (s, 3H), 1.22 (t, *J* = 7.5 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.03 (s, 9H); MS (APCI+) *m/z* 621 (M+H)⁺. Also obtained was (2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-ethylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-1-((*R*)-tetrahydro-2*H*-pyran-2-carbonyl)pyrrolidine-2-carboxylate (168 mg, 0.271 mmol, 43.0 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.27 (s, 1H), 7.78 (s, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.09 - 7.03 (m, 2H), 6.97 (d, *J* = 8.3 Hz, 1H), 5.31 (d, *J* = 5.6 Hz, 1H), 4.94 (s, 1H), 4.29 - 4.20 (m, 2H), 4.13 (qd, *J* = 7.1, 2.2 Hz, 2H), 3.91 (bs, 2H), 3.85 (s, 3H), 3.83 - 3.76 (m, 1H), 3.26 (bs, 1H), 2.75 (dq, *J* = 14.9, 7.6 Hz, 1H), 2.63 (dt, *J* = 14.8, 7.5 Hz, 1H), 2.57 (d, *J* = 2.4 Hz, 1H), 1.77 (s, 1H), 1.51 (s, 2H), 1.41 (s, 3H), 1.22 (t, *J* = 7.5 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.03 (s, 9H); MS (APCI+) *m/z* 621 (M+H)⁺.

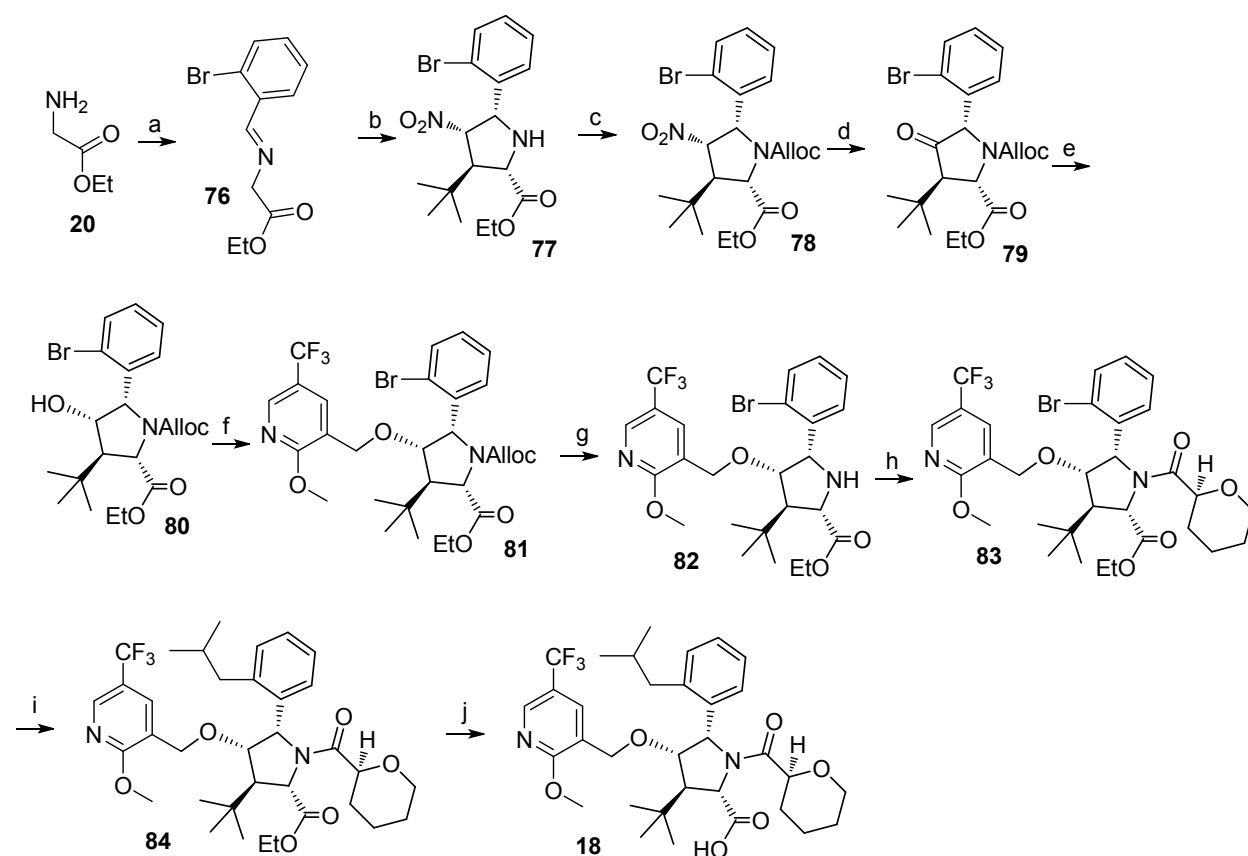


(2*S*,3*R*,4*S*,5*S*)-3-*tert*-butyl-5-(2-ethylphenyl)-4-[[2-methoxy-5-(trifluoromethyl)pyridin-3-yl]methoxy]-1-[(2*S*)-oxane-2-carbonyl]pyrrolidine-2-carboxylic acid (17)

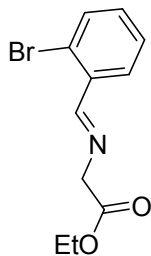
To a solution of compound **75** (156 mg, 0.251 mmol) in tetrahydrofuran (0.760 mL), methanol (0.760 mL), and water (0.760 mL) was added lithium hydroxide, H₂O (73.8 mg, 1.759 mmol). The reaction mixture was heated at 45°C for 16 hours. LC/MS showed desired product and the solvent was removed under a stream of nitrogen. Water (0.5 mL) was added to the crude material. The mixture was acidified with 1M aqueous HCl (1.53 mL) to pH~6, extracted once with heptanes (discarded), and once with dichloromethane. The solvent was evaporated *in vacuo*. The resulted crude material was chromatographed using a 4 g silica gel cartridge with a gradient of 0-10% methanol/dichloromethane over

a period of 10 minutes to provide (2*S*,3*R*,4*S*,5*S*)-3-(*tert*-butyl)-5-(2-ethylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-1-((*S*)-tetrahydro-2*H*-pyran-2-carbonyl)pyrrolidine-2-carboxylic acid (87 mg, 0.147 mmol, 58.4 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.26 (s, 1H), 8.05 (d, *J* = 7.3 Hz, 1H), 7.16 (s, 1H), 7.10 (s, 2H), 7.03 (m, 1H), 5.56 (s, 1H), 4.65 (s, 1H), 4.28 (d, *J* = 14.0 Hz, 1H), 4.23 (d, *J* = 5.8 Hz, 1H), 3.86 (d, 4H), 3.73 (d, *J* = 11.5 Hz, 1H), 3.42 (bs, 2H), 2.79 - 2.69 (m, 1H), 2.64 (dq, *J* = 15.0, 7.6 Hz, 1H), 2.48 (m, 1H), 1.71 - 1.60 (m, 1H), 1.52 (m, 2H), 1.34 (m, 3H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.02 (s, 9H); MS (APCI+) *m/z* 593 (M+H)⁺.

Scheme S11. Discovery Synthesis of Compound 18^a

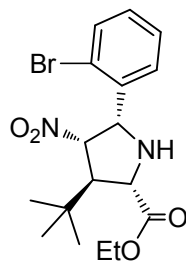


^aReagents and conditions: (a) MgSO₄, TEA, 2-methylbenzaldehyde, DCM; (b) (2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron, Cu(OTf)₂, KOtBu, (*E*)-3,3-dimethyl-1-nitrobut-1-ene, THF; (c) allyl chloroformate, toluene; (d) PDC, 6*N* HCl, Zn dust, (e) NaBH₄, EtOH; (f) KOtBu, 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine, DMF; (g) 1,3-Dimethylbarbituric acid, Pd(PPh₃)₄, EtOAc/DCM; (h) Tetrahydropyran-2-carboxylic acid, oxalyl chloride, DMF, DCM; (i) isobutylboronic acid, K₂CO₃, Pd(dppf)Cl₂; (j) LiOH, MeOH/THF.



(*E*)-ethyl 2-((2-bromobenzylidene)amino)acetate (76)

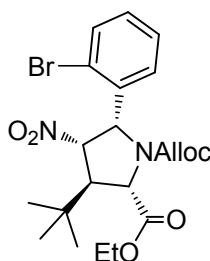
Ethyl 2-aminoacetate hydrochloride (2.63 g, 18.85 mmol) and magnesium sulfate (2.269 g, 18.85 mmol) were stirred in dichloromethane (28.6 mL) at ambient temperature, and triethylamine (2.63 mL, 18.85 mmol) was added. The mixture was stirred for 5 minutes, 2-bromobenzaldehyde (2.0 mL, 17.13 mmol) was added dropwise, and the mixture was stirred at ambient temperature for 16 hours. The solid material was filtered through a disposable plastic frit and washed with dichloromethane. The organic layer was washed with 30 mL of water then dried over sodium sulfate, filtered, and concentrated to provide (*E*)-ethyl 2-((2-bromobenzylidene)amino)acetate (4.6 g, 17.03 mmol, 99 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.70 (d, *J* = 1.6 Hz, 1H), 8.12 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.38 (tt, *J* = 7.6, 1.1 Hz, 1H), 7.35 - 7.27 (m, 1H), 4.48 (d, *J* = 1.4 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); MS (ESI+) *m/z* 270 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-ethyl 5-(2-bromophenyl)-3-(*tert*-butyl)-4-nitropyrrolidine-2-carboxylate (77)

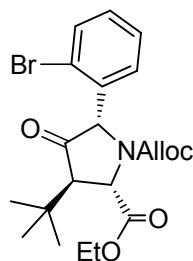
(2-(Bis(3,5-bis(trifluoromethyl)phenyl)phosphino)-3-((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)cyclopenta-2,4-dien-1-yl)(cyclopenta-2,4-dien-1-yl)iron (0.147 g, 0.195 mmol) and copper (I) triflate dimer, benzene complex (0.042 g, 0.084 mmol) were dissolved in tetrahydrofuran (34.3 mL) that had been sparged with stream of nitrogen for 1 hour. The resulting mixture was stirred for 1.5 hours at ambient temperature, and (*E*)-ethyl 2-((2-bromobenzylidene)amino)acetate (**76**, 4.63 g, 17.14 mmol) was added after cooling to <5 °C in an ice-water bath. Potassium 2-methylpropan-2-olate (0.134 mL, 0.134 mmol) was added dropwise, followed by addition of (*E*)-3,3-dimethyl-1-nitrobut-1-ene (2.324 g, 18.00 mmol) neat over 25 minutes, maintaining an internal temperature <10 °C. After the addition was complete and stirred for 90 minutes, LC-MS showed complete conversion. The mixture was diluted with methyl *tert*-butyl ether (150 mL) and stirred with 50 mL of saturated aqueous ammonium chloride at ambient temperature for 15

minutes. The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated, and precipitated from 50 mL of heptane. The mixture was cooled in an ice bath to <5 °C for 15 minutes, and the resulting material was filtered and washed with 20 mL of heptanes to provide (2*S*,3*R*,4*S*,5*S*)-ethyl 5-(2-bromophenyl)-3-(*tert*-butyl)-4-nitropyrrolidine-2-carboxylate (4.303 g, 10.78 mmol, 62.9 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.58 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.41 - 7.29 (m, 2H), 7.24 - 7.14 (m, 1H), 5.43 (dd, *J* = 5.9, 2.3 Hz, 1H), 4.70 (dd, *J* = 10.7, 5.9 Hz, 1H), 4.33 (qd, *J* = 7.1, 1.2 Hz, 2H), 3.82 (t, *J* = 7.5 Hz, 1H), 3.22 (t, *J* = 9.8 Hz, 1H), 3.03 (dd, *J* = 7.0, 2.3 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 9H); MS (APCI+) *m/z* 399 (M+H)⁺.



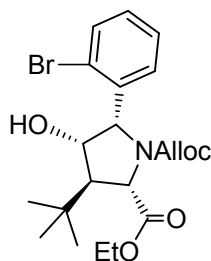
(2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 5-(2-bromophenyl)-3-(*tert*-butyl)-4-nitropyrrolidine-1,2-dicarboxylate (78)

Compound **77** (957 mg, 2.397 mmol) in toluene (10 mL) and saturated aqueous NaHCO₃ (10 mL) was added allyl carbonochloridate (0.3 mL, 2.82 mmol) dropwise at ambient temperature. The mixture was stirred at ambient temperature overnight. The reaction was poured into water (50 mL) and extracted with dichloromethane (3 x 50 mL). The organic layer was washed with brine and concentrated and purified by silica gel chromatography using a 40 g cartridge and eluting with 0->5% ethyl acetate in dichloromethane to provide (2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 5-(2-bromophenyl)-3-(*tert*-butyl)-4-nitropyrrolidine-1,2-dicarboxylate (1.16 g, 2.400 mmol, 100 % yield). ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 7.78 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.24 - 7.04 (m, 2H), 6.99 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.00 (d, *J* = 8.6 Hz, 1H), 5.67 (ddt, *J* = 17.2, 10.5, 5.2 Hz, 1H), 5.56 (dd, *J* = 8.6, 2.5 Hz, 1H), 5.05 - 4.92 (m, 2H), 4.60 (d, *J* = 3.4 Hz, 1H), 4.41 (dq, *J* = 4.8, 1.5 Hz, 2H), 4.31 - 4.21 (m, 2H), 3.06 (t, *J* = 3.0 Hz, 1H), 2.06 (tt, *J* = 8.4, 5.4 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.04 (s, 9H), 1.02 - 0.89 (m, 2H), 0.80 (dtd, *J* = 9.4, 5.2, 3.4 Hz, 1H), 0.59 - 0.48 (m, 1H).; MS (APCI+) *m/z* 483/485 (M+H)⁺ Br doublet.



(2*S*,3*R*,5*S*)-1-allyl 2-ethyl 5-(2-bromophenyl)-3-(*tert*-butyl)-4-oxopyrrolidine-1,2-dicarboxylate (79)

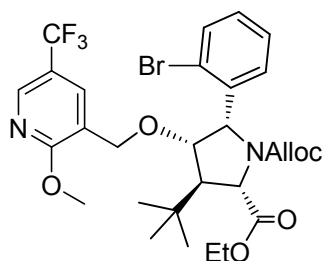
To a solution of potassium dichromate (3.72 g, 12.65 mmol) in 6 N aqueous HCl (50 mL) was added zinc (4.41 g, 67.5 mmol) under N₂ atmosphere. After the almost complete dissolution of zinc yielded a clear bright blue solution, the formed chromium(II) chloride was transferred to the refluxing solution of compound **78** (1.14 g, 2.359 mmol) in ethanol (25 mL) under N₂ using an addition funnel (internal temp 78°C). The reaction mixture was refluxed at 85 °C overnight and cooled and diluted with 300 mL of dichloromethane. The organic phase was separated, dried over sodium sulfate, filtered and concentrated. The crude material was then taken up in anhydrous ethanol and treated with a solution of HCl in ethanol (prepared by adding 2.0 mL of acetyl chloride to an ice bath cooled solution of 6 mL of ethanol), and heated at 65°C for one hour. The ethanol was removed and the crude material was diluted with 300 mL of methyl *tert*-butyl ether, washed with 50 mL each of saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate. After filtration, the solvent was removed *in vacuo* to provide (2*S*,3*R*,5*S*)-1-allyl 2-ethyl 5-(2-bromophenyl)-3-(*tert*-butyl)-4-oxopyrrolidine-1,2-dicarboxylate (1.067 g, 2.359 mmol, 100 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.81 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.33 (td, *J* = 7.6, 1.3 Hz, 1H), 7.19 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H), 5.71 (ddt, *J* = 16.9, 11.0, 5.2 Hz, 1H), 5.45 (s, 1H), 5.10 - 4.99 (m, 2H), 4.64 (dd, *J* = 4.6, 0.6 Hz, 1H), 4.46 (dtd, *J* = 5.2, 1.5, 0.7 Hz, 2H), 4.29 - 4.16 (m, 2H), 2.63 (dd, *J* = 4.6, 0.9 Hz, 1H), 1.30 - 1.22 (m, 3H), 1.06 (s, 9H); MS (APCI+) *m/z* 452 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 5-(2-bromophenyl)-3-(*tert*-butyl)-4-hydroxypyrrrolidine-1,2-dicarboxylate (80)

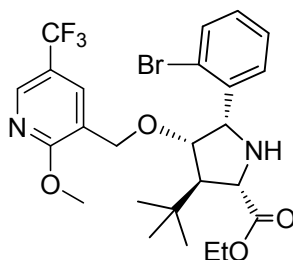
Compound **79** (850 mg, 1.879 mmol) was dissolved in ethanol (10 mL) and cooled in an ice/acetone bath. Sodium tetrahydroborate (85 mg, 2.255 mmol) was added in small portions over 30 minutes. The

reaction mixture was concentrated *in vacuo* (no heat) and 10 mL of saturated aqueous sodium bicarbonate and 15 mL of ethyl acetate were added. The reaction mixture was stirred at room temperature for 30 minutes. The organics were diluted with 50 mL more ethyl acetate, separated, washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude residue was loaded onto a 24 g silica gel column and eluted with 5-100% ethyl acetate/heptanes to provide a 0.584 g of a mixture of diastereomers. The crude material was rechromatographed using a 24 g silica gel cartridge with a gradient of 5-30% ethyl acetate/heptanes over 20 minutes to provide (2*S*,3*R*,4*S*,5*S*)-1-allyl 2-ethyl 5-(2-bromophenyl)-3-(*tert*-butyl)-4-hydroxypyrrolidine-1,2-dicarboxylate (0.465 g, 1.023 mmol, 54.5 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.93 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.47 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.09 (td, *J* = 7.7, 1.7 Hz, 1H), 5.69 (ddt, *J* = 17.7, 10.1, 5.0 Hz, 1H), 5.20 (d, *J* = 6.0 Hz, 1H), 5.05 – 4.94 (m, 2H), 4.51 – 4.42 (m, 2H), 4.41 – 4.33 (m, 3H), 4.20 (d, *J* = 7.0 Hz, 2H), 2.29 (t, *J* = 2.8 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 9H); MS (APCI+) *m/z* 454 (M+H)⁺.



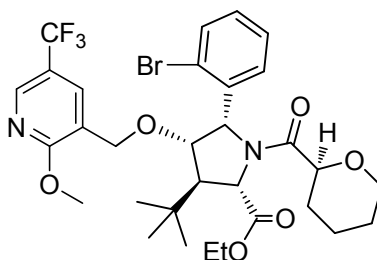
1-allyl 2-ethyl (2*S*,3*R*,4*S*,5*S*)-5-(2-bromophenyl)-3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)pyrrolidine-1,2-dicarboxylate (81**)**

Compound **80** (6.92 g, 15.23 mmol) and 3-(bromomethyl)-2-methoxy-5-(trifluoromethyl)pyridine (5.16 g, 19.11 mmol) were dissolved in dimethylformamide (61 mL). The reaction was cooled to 0 °C, and potassium *tert*-butoxide (1M in tetrahydrofuran, 19.0 mL, 19.0 mmol) was added dropwise. The reaction was stirred at ambient temperature for 1 hour. The reaction was poured into saturated aqueous NH₄Cl (50 mL), diluted with water (100 mL) and extracted with methyl *tert*-butyl ether (3 x 100 mL). The combined organics were washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel chromatography (0% to 5% ethyl acetate in dichloromethane) to provide the title compound (9.80 mg, 52%). ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.34 - 8.25 (m, 1H), 7.96 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.22 (td, *J* = 7.6, 1.3 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.08 (td, *J* = 7.6, 1.8 Hz, 1H), 5.72 (ddt, *J* = 17.5, 10.0, 5.0 Hz, 1H), 5.33 (d, *J* = 5.6 Hz, 1H), 5.09 - 4.99 (m, 2H), 4.54 (d, *J* = 2.0 Hz, 1H), 4.47 - 4.37 (m, 4H), 4.34 (dd, *J* = 13.6, 0.9 Hz, 1H), 4.12 (qd, *J* = 7.1, 1.2 Hz, 2H), 3.88 (s, 3H), 2.52 (t, *J* = 1.5 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 9H); MS (ESI+) *m/z* 643 & 645 (M+H)⁺.



ethyl (2*S*,3*R*,4*S*,5*S*)-5-(2-bromophenyl)-3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)pyrrolidine-2-carboxylate (82**)**

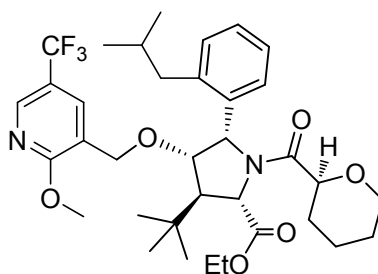
Compound **81** (4.925 mg, 7.65 mmol) was dissolved in ethyl acetate (15 mL) and dichloromethane (15 mL) and treated with 1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (2.39 g, 15.31 mmol) and tetrakis(triphenylphosphine)palladium (94.5 mg, 0.082 mmol). The reaction mixture was stirred at ambient temperature. After 1 hour, the reaction mixture was diluted with methyl *tert*-butyl ether (100 mL) and stirred with 10% aqueous Na₂CO₃ (100 mL) solution for 30 minutes. The phases were then separated, and the organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated to provide the title compound (4.28 g, 100%). ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.35 (dd, *J* = 2.5, 1.2 Hz, 1H), 7.75 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.48 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.26 (td, *J* = 7.5, 1.3 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.12 (td, *J* = 7.6, 1.8 Hz, 1H), 5.61 - 5.43 (m, 1H), 5.07 - 4.92 (m, 1H), 4.35 (t, *J* = 5.5 Hz, 1H), 4.28 (d, *J* = 14.1 Hz, 1H), 4.18 - 4.04 (m, 2H), 3.89 - 3.78 (m, 4H), 3.65 (t, *J* = 6.2 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.95 (s, 9H); MS (ESI+) *m/z* 559 & 561 (M+H)⁺.



ethyl (2*S*,3*R*,4*S*,5*S*)-5-(2-bromophenyl)-3-(*tert*-butyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-1-((*S*)-tetrahydro-2H-pyran-2-carbonyl)pyrrolidine-2-carboxylate (83**)**

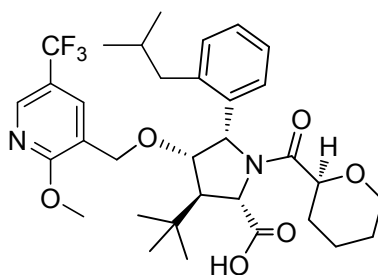
(*S*)-Tetrahydro-2H-pyran-2-carboxylic acid (1.21 g, 9.30 mmol) was dissolved in dichloromethane (40 mL). Oxalyl chloride (2M in dichloromethane, 4.65 mL, 9.30 mmol) was added followed by dimethylformamide (50 μL). The reaction was stirred at ambient temperature for 3 hours. The reaction was chilled to 0 °C and Compound **82** (4.28 g, 7.65 mmol) and triethylamine (4 mL, 28.7 mmol) dissolved in dichloromethane (20 mL) were added. The reaction was allowed to warm to ambient temperature and was stirred at ambient temperature for 17 hours. The mixture was diluted with

dichloromethane (100 mL) and washed twice with saturated aqueous NaHCO₃ and once with brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel chromatography, eluting with 5% ethyl acetate in dichloromethane to provide the title compound (3.33 g, 65%). ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.29 (d, J = 1.7 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.24 (s, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.11 (s, 1H), 5.77 (s, 1H), 4.73 (s, 1H), 4.38 (d, J = 6.0 Hz, 1H), 4.32 (d, J = 13.7 Hz, 1H), 4.09 (qd, J = 7.1, 2.2 Hz, 2H), 3.98 - 3.90 (m, 1H), 3.87 (s, 3H), 3.83 - 3.73 (m, 1H), 3.51 - 3.20 (m, 2H), 2.45 - 2.38 (m, 1H), 1.68 (s, 1H), 1.45 (d, J = 54.8 Hz, 5H), 1.14 (t, J = 7.1 Hz, 3H), 1.02 (s, 9H); MS (ESI+) *m/z* 671 & 673 (M+H)⁺.



(2*S*,3*R*,4*S*,5*S*)-ethyl 3-(*tert*-butyl)-5-(2-isobutylphenyl)-4-((2-methoxy-5-(trifluoromethyl)pyridin-3-yl)methoxy)-1-((*S*)-tetrahydro-2*H*-pyran-2-carbonyl)pyrrolidine-2-carboxylate (84)

Compound **83** (178C, 174 mg, 0.259 mmol), isobutylboronic acid (52.8 mg, 0.518 mmol) and potassium carbonate (107 mg, 0.777 mmol) were suspended in toluene (2.5 mL). The reaction was purged with nitrogen for 2 minutes, and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (10.58 mg, 0.013 mmol) was added. The reaction was capped and heated at 110 °C for 4 hours. The solvent was reduced under a stream of nitrogen and the crude material was purified using a 10 g silica gel cartridge with a gradient of 5-100% ethyl acetate/heptanes over 20 minutes to give the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.28 (s, 1H), 8.00 (dd, J = 7.7, 1.4 Hz, 1H), 7.22 (s, 1H), 7.13 - 6.97 (m, 3H), 5.48 (s, 1H), 4.71 (s, 1H), 4.40 - 4.28 (m, 1H), 4.25 (d, J = 13.8 Hz, 1H), 4.21 (d, J = 5.6 Hz, 1H), 4.08 (qd, J = 7.1, 3.3 Hz, 2H), 3.94 (d, J = 13.6 Hz, 1H), 3.87 (s, 1H), 3.84 (s, 3H), 3.78 (d, J = 13.8 Hz, 1H), 3.73 (d, J = 12.9 Hz, 2H), 2.55 (d, J = 7.0 Hz, 1H), 2.43 (d, J = 1.8 Hz, 1H), 1.94 (td, J = 15.7, 14.3, 5.8 Hz, 1H), 1.66 (s, 1H), 1.52 (d, J = 12.1 Hz, 1H), 1.36 (s, 3H), 1.14 (t, J = 7.1 Hz, 3H), 1.02 (d, J = 2.0 Hz, 9H), 0.93 (t, J = 6.4 Hz, 6H); MS (APCI+) *m/z* 649 (M+H)⁺.



(2S,3R,4S,5S)-3-tert-butyl-4-{[2-methoxy-5-(trifluoromethyl)pyridin-3-yl]methoxy}-5-[2-(2-methylpropyl)phenyl]-1-[(2S)-oxane-2-carbonyl]pyrrolidine-2-carboxylic acid (18)

Compound **84** (160 mg, 0.247 mmol) was dissolved in methanol (822 μ l) and tetrahydrofuran (822 μ l). A solution of lithium hydroxide (56 mg, 2.338 mmol) in water (822 μ l) was added. The reaction was heated at 45 °C for 16 hours. The solvent was reduced in volume, and acidified with 1M aqueous HCl to pH ~3. The reaction was extracted with dichloromethane. The solvent was removed and the crude material was purified by reverse-phase preparative HPLC on a Phenomenex® Luna® C8(2) 5 μ m 100Å AXIA™ column (30 mm \times 150 mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used, at a flow rate of 50 mL/minute (0-0.5 minutes 10% A, 0.5-7.0 minutes linear gradient 10-95% A, 7.0-10.0 minutes 95% A, 10.0-12.0 minutes linear gradient 95-10% A) to give the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.27 (dq, *J* = 2.0, 1.0 Hz, 1H), 8.06 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.06 (q, *J* = 8.8, 7.1 Hz, 3H), 5.50 (s, 1H), 4.67 (d, *J* = 1.7 Hz, 1H), 4.29 (d, *J* = 13.9 Hz, 1H), 4.21 (d, *J* = 5.7 Hz, 1H), 4.07 - 3.97 (m, 1H), 3.86 (s, 3H), 3.84 - 3.79 (m, 1H), 3.78 - 3.70 (m, 1H), 3.18 (d, *J* = 6.3 Hz, 1H), 2.53 (dd, *J* = 7.1, 4.0 Hz, 2H), 2.49 (d, *J* = 1.7 Hz, 1H), 1.91 (dd, *J* = 13.3, 6.8 Hz, 1H), 1.69 - 1.61 (m, 1H), 1.54 (q, *J* = 11.5 Hz, 1H), 1.35 (d, *J* = 11.8 Hz, 3H), 1.03 (s, 9H), 1.00 (d, *J* = 3.3 Hz, 1H), 0.92 (t, *J* = 6.8 Hz, 6H); MS (ESI+) *m/z* 621.3 (M+H)⁺.

Table 1. LRMS Table for compounds 5-19 and HPLC purity

Compound	Molecular Formula	Mass Found	Mass Required	HPLC Purity
5	C ₃₁ H ₃₈ F ₃ NO ₅	MS (ESI-) <i>m/z</i> 560.3 (M-H) ⁻	560.3 (M-H) ⁻	97.0%
6	C ₃₁ H ₃₈ F ₃ NO ₅	MS (ESI+) <i>m/z</i> 562.3 (M+H) ⁺	562.3 (M+H) ⁺	96.7%
7	C ₃₁ H ₃₈ F ₃ NO ₅	MS (ESI+) <i>m/z</i> 562.3 (M+H) ⁺	562.3 (M+H) ⁺	97.1%
8	C ₃₀ H ₃₇ F ₃ N ₂ O ₅	MS (ESI-) <i>m/z</i> 561.3 (M-H) ⁻	561.3 (M-H) ⁻	98.1%
9	C ₃₄ H ₄₆ N ₂ O ₅	MS (APCI+) <i>m/z</i> 563.1 (M+H) ⁺	563.3 (M+H) ⁺	97.3%
10	C ₃₃ H ₄₆ N ₂ O ₅	MS (ESI-) <i>m/z</i> 549.3 (M-H) ⁻	549.3 (M+H) ⁺	96.9%
11	C ₂₇ H ₃₃ F ₃ N ₂ O ₆	MS (APCI+) <i>m/z</i> 539.2 (M+H) ⁺	539.2 (M+H) ⁺	98.2%
12	C ₂₉ H ₃₅ F ₃ N ₂ O ₆	MS (ESI+) <i>m/z</i> 565.1 (M+H) ⁺	565.2 (M+H) ⁺	97.3%
13	C ₂₉ H ₃₅ F ₃ N ₂ O ₆	MS (ESI+) <i>m/z</i> 565.1 (M+H) ⁺	565.2 (M+H) ⁺	98.5%
14	C ₃₂ H ₄₁ F ₃ N ₂ O ₆	MS (ESI+) <i>m/z</i> 605.3 (M+H) ⁻	605.3 (M+H) ⁻	97.9%
15	C ₃₂ H ₃₉ F ₃ N ₂ O ₆	MS (ESI+) <i>m/z</i> 605.1 (M+H) ⁺	605.2 (M+H) ⁺	98.4%

16	C ₂₉ H ₃₄ ClF ₃ N ₂ O ₆	MS (ESI+) <i>m/z</i> 599.2 (M+H) ⁺	599.2 (M+H) ⁺	96.3%
17	C ₃₁ H ₃₉ F ₃ N ₂ O ₆	MS (APCI+) <i>m/z</i> 593.4 (M+H) ⁺	593.3 (M+H) ⁺	97.6%
18	C ₃₃ H ₄₃ F ₃ N ₂ O ₆	MS (ESI+) <i>m/z</i> 621.3 (M+H) ⁺	621.3 (M+H) ⁺	97.0%
19	C ₃₀ H ₃₇ F ₃ N ₂ O ₆	MS (ESI+) <i>m/z</i> 579.3 (M+H) ⁺	579.3 (M+H) ⁺	98.7%

Biology

Determination of Biological Activity

Cellular Assays

Cell Surface Expression-Horse Radish Peroxidase (CSE-HRP) Assay:

A cellular assay for measuring the F508del CFTR cell surface expression after correction with test compounds either without or with a co-corrector (2 μM of 3-[(2*R*,4*R*)-4-({[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropyl]carbonyl}amino)-7-methoxy-3,4-dihydro-2*H*-chromen-2-yl]benzoic acid, **1**), was developed in human lung derived epithelial cell line (CFBE41o-).¹ This was achieved by expressing the F508del CFTR mutation along with a horseradish peroxidase (HRP) in the fourth exofacial loop and then measuring the HRP activity using luminescence readout from these cells, CFBE41o-F508del CFTR-HRP, that were incubated overnight with the test corrector compounds.² Briefly, for this primary assay, the CFBE41o-F508del CFTR-HRP cells were plated in 384-well plates at 4,000 cells/well along with 0.5 μg/mL doxycycline to induce the F508del CFTR-HRP expression and further incubated at 37 °C, 5% CO₂ for 72 hours. The test compounds were then added at the required concentrations and further incubated for 18-24 hours at 33 °C. The highest concentration tested was 20 μM with an 8-point concentration response curve using a 3-fold dilution. Three replicate plates were run to determine one EC₅₀. All plates contained negative controls (dimethyl sulfoxide, DMSO) and positive controls (3 μM of 3-[(2*R*,4*R*)-4-({[1-(2,2-difluoro-1,3-

benzodioxol-5-yl)cyclopropyl]carbonyl} amino)-7-methoxy-3,4-dihydro-2*H*-chromen-2-yl]benzoic acid) (Compound **1**) as well as on-plate concentration response of the positive control. Post incubation, the plates were washed 5× times with Dulbecco's phosphate buffered saline (DPBS), followed by the addition of the HRP substrate, luminol (50 µL), and measuring the HRP activity using luminescence readout on EnVision® Multilabel Plate Reader. The raw counts from the experiment are analyzed using Accelrys® Assay Explorer v3.3.

The % activity measured at each of the 8 test concentrations of the test compound was normalized to the on-plate positive control using the following formula:

$$\% \text{ activity} = [(\text{test compound response} - \text{DMSO response}) / (\text{positive control response} - \text{DMSO response})] * 100$$

The maximum % activity achieved for the test compound at any tested concentration is presented in Tables along with the EC₅₀ calculated using the general sigmoidal curve with variable Hill slope equation.

Trans-epithelial Current Clamp on Human Bronchial Epithelial Cells Conductance Assay:

A cell based assay using the primary human bronchial epithelial cells (hBE) was used as a secondary assay to test novel F508del CFTR correctors for their activity on primary hBE cells with F508del/F508del CFTR mutation. Primary human bronchial epithelial (hBE) cells from F508del/F508del CFTR patients were expanded from 1×10⁶ to 250×10⁶ cells.³ For this purpose, cells isolated from CF patients with the homozygous mutation were seeded onto 24 well Corning (Cat # 3378) filter plates that were coated with 3T3 conditioned media and grown at an air-liquid interface for 35 days using an Ultrosor® G supplemented differentiation media. Apical surface mucus was removed 72 hours before the experiment by incubating the apical surface of the cells

for 30 minutes with 3 mM dithiothreitol (DTT) prepared in the differentiation media, followed by aspiration of the mucus along with the media. The apical surface is washed again with phosphate buffered saline (PBS) incubated for 30 minutes followed with aspiration. The cells were then incubated with the desired dose of the corrector compounds 18-24 hours at 37 °C, 5% CO₂. The corrector compounds were prepared as 10 mM stocks and the desired concentrations were prepared in differentiation media and were always applied on the basolateral side of the epithelial cells.

On the day of measuring the corrector activity on the TECC, the cells were switched into a bicarbonate and serum free F-12 Coon's medium and allowed to equilibrate for 90 minutes in a CO₂ free incubator. At the time of measurement, the apical and basolateral sides of the filter were bathed with the F-12 Coon's modification media (with 20 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), pH 7.4 (using 1 M tris(hydroxymethyl)aminomethane (Tris))), and the measurements were made at 36.5 °C. Current responses before and after the sequential addition of benzamil (apical 6 μM addition; for inhibiting epithelial ENaC channel), forskolin (apical and basolateral 10 μM addition; for activating the CFTR channel), control potentiator (*N*-(3-carbamoyl-5,5,7,7-tetramethyl-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-2-yl)-1*H*-pyrazole-5-carboxamide; apical and basolateral 0.75 μM addition; for potentiating the CFTR channel) and bumetanide (basolateral 20 μM addition; for inhibiting the Na:2Cl:K co-transporter, an indirect measure of inhibiting the Cl⁻ secretion driven by CFTR channel) were measured. The assay uses a TECC-24 (Trans epithelial Current Clamp for 24 wells) instrument that measures the functionality of the mutated channel by measuring the equivalent CFTR current (I_{EQ}) generated by the polarized primary epithelial cells. The instrument works by measuring the transepithelial potential difference (V_T) and transepithelial conductance (G_T)

under current clamp conditions using a custom designed multi-channel current clamp and electrode manifold. Each measured V_T values are corrected for the electrode offset potential, and each measured G_T values are corrected for the combined solution series and empty filter resistances. The corrected V_T and G_T values were then used to calculate the equivalent current, I_{EQ} using Ohm's law ($I_{EQ} = V_T \cdot G_T$). In addition to calculating the I_{EQ} , the area under the curve (AUC) for the time period between the forskolin peak I_{EQ} response and at the time of bumetanide addition was also calculated using a one-third trapezoid method. The assay was run in a 24-well format and all 24-wells were measured at the same time point giving a higher throughput for this assay.

All plates contained negative controls (dimethyl sulfoxide, DMSO) which coupled with the control potentiator (0.75 μ M of *N*-(3-carbamoyl-5,5,7,7-tetramethyl-4,7-dihydro-5*H*-thieno[2,3-*c*]pyran-2-yl)-1*H*-pyrazole-5-carboxamide, GLPG1837) sets the null response and positive controls (0.15 μ M of 4-[(2*R*,4*R*)-4-[[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropanecarbonyl]amino]-7-(difluoromethoxy)chroman-2-yl]benzoic acid ABBV-2222) coupled with the control potentiator sets the 100% response to measure the correction of the mutated CFTR channel. The specificity of the Forskolin-activated current is via CFTR activation, as demonstrated by inhibition with CFTR Inh172. The maximum percent activity (E_{max}) is reported relative to the positive control value.

The % activity measured at each of the 6 test concentrations of the test compound was normalized to the on-plate positive control using the following formula: % activity = [(test compound response – DMSO response) / (positive control response – DMSO response)]*100. The I_{EQ} and AUC at different test concentrations were fit and an EC_{50} was calculated using the general sigmoidal curve with variable Hill slope equation included in the Prism v5 software.

CYP3A4 Induction:

Cryopreserved primary human hepatocytes were thawed and cultured overnight prior to treatment. Cultured hepatocytes were treated with either test compounds (10 μ M), vehicle control (0.1% v/v DMSO), or prototypical inducer of CYP3A4 (rifampin 10 μ M) for 48 hours, with culture medium being refreshed every 24 hours. Following the 48 hour treatment, CYP3A4 mRNA levels measured in compound treated hepatocytes were expressed as a percentage of the response of positive control (Rifampin 10 μ M). In test compound treated hepatocytes, CYP3A4 mRNA level increase by less than 20% of the response of positive control (Rifampin) is considered low risk for CYP3A4 induction.

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