**Structure Reassignment and Synthesis of Jenamidines A₁/A₂. Synthesis of (+)-
NP25302, and Formal Synthesis of SB-311009 Analogues**

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9110.

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General Procedures. All reactions were performed under nitrogen atmosphere. All commercially available reagents were used without further purification unless otherwise noted. Dichloromethane was distilled from CaH₂ under nitrogen. Ether and tetrahydrofuran were freshly distilled from benzophenone ketyl radical under nitrogen prior to use. Flash chromatography was performed with silica gel (40-63 μ m). Optical rotations were measured on a precision automated polarimeter. NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in δ and coupling constants (J values) in Hz. IR spectra were recorded on an FT-IR spectrometer and are reported in cm⁻¹. The Wittig reactions of **76** were carried out in a sealed vessel in a CEM Discover microwave oven with automatic temperature and pressure display.

5a,6,8,9-Tetrahydro-5H-pyrido[2,1-b]quinazoline-7,11-dione (6). A solution of 2,3-dihydro-4-pyridinone (**4**)⁴ (100 mg, 1.09 mmol), isatoic anhydride (**5**, 178 mg, 1.09 mmol), and triethylamine (0.17 mL, 1.20 mmol) in 10 mL of dry THF was stirred in a sealed tube under N₂ for 8 h in an 80 °C oil bath. The mixture was cooled and concentrated to yield a mixture of recovered **4**, anthranilic acid, the desired product **6**, and the decomposition product **7**. Flash chromatography on silica gel (95:5 CH₂Cl₂/MeOH) yielded 150 mg of a mixture of **6** and **7** followed by 65 mg of **4** (65%). The mixture of **6** and **7** was diluted with CHCl₃ and filtered. The filtrate was concentrated and the resulting oil was then taken up in minimal CH₂Cl₂. The solution was filtered and added dropwise to a solution of hexanes. The milky suspension was filtered and the precipitate was collected to give 67 mg of 90% pure **6** (29% yield, 65% based on recovered SM). Quinazoline **6** was unstable at room temperature and decomposed to form **7** over time.

Data for **6**: mp 122-123 °C; ¹H NMR (CD₃OD) 7.71 (d, 1, J = 8.0), 7.25 (dd, 1, J = 8.0, 7.7), 6.73 (dd, 1, J = 8.0, 7.7), 6.65 (d, 1, J = 8.0), 5.12 (dd, 1, J = 3.7, 9.2), 4.51 (ddd, 1, J = 4.3, 6.1, 13.4), 3.29 (ddd, 1, J = 4.3, 10.4, 13.4), 2.86 (dd, 1, J = 9.2, 15.3), 2.64 (dd, 1, J = 3.7, 15.3), 2.52 (ddd, 1, J = 6.1, 10.4, 15.9), 2.42 (ddd, 1, J = 4.3, 4.3,

15.9); ¹H NMR (CDCl₃) 7.91 (d, 1, *J* = 7.9), 7.31 (dd, 1, *J* = 7.9, 7.3), 6.86 (dd, 1, *J* = 7.9, 7.3), 6.67 (d, 1, 7.9), 5.17 (ddd, 1, *J* = 1.8, 3.8, 9.2), 4.96 (br s, 1, NH), 4.73 (ddd, 1, *J* = 4.0, 6.1, 13.7), 3.24 (ddd, 1, *J* = 4.0, 10.7, 13.7), 2.92 (dd, 1, *J* = 9.2, 14.8), 2.72 (dd, 1, *J* = 3.8, 14.8), 2.62 (ddd, 1, *J* = 6.1, 10.7, 16.2), 2.49 (ddd, 1, *J* = 4.0, 4.0, 16.2); ¹³C NMR (CD₃OD) 207.8, 165.4, 148.5, 135.2, 129.1, 119.5, 115.7, 115.2, 67.6, 47.8, 40.9, 39.7; ¹³C NMR (CDCl₃) 205.7, 163.2, 145.5, 134.0, 128.5, 119.5, 114.7, 114.6, 66.5, 47.7, 40.2, 38.9; IR (KBr) 3303, 1720, 1640.

3-(3-Oxobutyl)-4(3*H*)-quinazolone (7). Complete conversion to **7** was easily achieved by washing a solution of 10 mg of **6** in CH₂Cl₂ three times with 5% aqueous HCl. The organic fraction was dried over magnesium sulfate and concentrated to give 8 mg of **7**: ¹H NMR (CDCl₃) 8.28 (d, 1, *J* = 6.7), 8.27 (s, 1), 7.76 (dd, 1, *J* = 7.9, 7.4), 7.71 (d, 1, *J* = 7.9), 7.50 (dd, 1, *J* = 7.4, 6.7), 4.22 (t, 2, *J* = 6.1), 3.07 (t, 2, *J* = 6.1), 2.16 (s, 3); ¹³C NMR 206.2, 161.2, 148.0, 147.5, 134.2, 127.4, 127.1, 126.3, 121.9, 42.2, 41.4, 30.0; IR (neat) 1714, 1672. The ¹H NMR spectral data are identical to those previously reported.⁶

1,3-Bis[[trifluoromethyl)sulfonyl]oxy]-6,7-dihydro-5*H*-pyrrolizine (16). Keto amide **15**¹¹ (100 mg, 0.71 mmol) in 1 mL of dry CH₂Cl₂ was added to NaH (63 mg, 1.56 mmol) in 1 mL of dry CH₂Cl₂ at 0 °C under N₂. The mixture was stirred for 10 min and Tf₂O (0.24 mL, 1.42 mmol) was added dropwise. The mixture was stirred for 1 h at 0 °C, quenched with 2 mL of saturated NH₄Cl solution, diluted with CH₂Cl₂, and stirred for 30 min at 25 °C. The organic layer was separated, washed with H₂O and brine, dried over MgSO₄, and concentrated to yield 260 mg (91%) of 90% pure bistriflate **16**. Flash chromatography on silica gel (97:2:1 hexanes/EtOAc/pyridine) gave 50 mg (17%) of pure unstable bistriflate **16**: ¹H NMR (CDCl₃) 5.93 (s, 1), 4.02 (t, 2, *J* = 7.0), 2.95 (t, 2, *J* = 7.3), 2.56 (tt, 2, *J* = 7.0, 7.3).

***N*-Cyano-*N'*-methoxy-*N'*-methylprolinamide (18).** *N*-Methylmorpholine (5.1 mL, 46.5 mmol) in 20 mL of dry CH₂Cl₂ and then ethyl chloroformate (8.6 mL, 90

mmol) in 20 mL of dry CH₂Cl₂ were added to *N*-Boc-proline (10 g, 46.5 mmol) in 60 mL of dry CH₂Cl₂ at -15 °C under N₂ and the mixture was stirred for 15 min.

N-Methylmorpholine (10.0 mL, 90.3 mmol) and *N,O*-dimethylhydroxylamine were added portionwise and the mixture was stirred for 1 h at -15 °C and at 25 °C for 15h. The mixture was diluted with H₂O and extracted with EtOAc. The combined organic extracts were washed successively with 10% sodium bicarbonate solution, brine, 5% HCl solution, and brine, dried over MgSO₄, and concentrated. Flash chromatography on silica gel (1:1 EtOAc/CH₂Cl₂) afforded 9.3 g (78%) of the *N*-Boc Weinreb amide as a 1:1 mixture of rotamers: ¹H NMR (CDCl₃) 4.68-4.74 (m, 1 × 0.5), 4.57-4.62 (m, 1 × 0.5), 3.79 (s, 3 × 0.5), 3.72 (s, 3 × 0.5), 3.35-3.65 (m, 2), 3.20 (s, 3), 1.80-2.25 (m, 4), 1.46 (s, 9 × 0.5), 1.42 (s, 9 × 0.5).

The *N*-Boc Weinreb amide (316 mg, 1.2 mmol) was stirred in 4 mL of 1:1 TFA/CH₂Cl₂ solution for 18 h and concentrated. A solution of the resulting oil in 4 mL of EtOH was added to a solution of sodium bicarbonate (500 mg, 6.0 mmol) and cyanogen bromide (140 mg, 1.32 mmol) in 9 mL of EtOH. The mixture was stirred for 2 h at 25 °C, treated with 2 mL of H₂O, stirred for 15 min, and extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄ and concentrated. Flash chromatography on silica gel (98:2 CH₂Cl₂/MeOH) gave 185 mg (84%) of cyanamide **18**: ¹H NMR (CDCl₃) 4.57 (dd, 1, *J* = 3.7, 8.5), 3.74 (s, 3), 3.62-3.70 (m, 1), 3.45-3.55 (m, 1), 3.23 (s, 3), 2.20-2.28 (m, 1), 1.90-2.10 (m, 3).

Addition of *tert*-Butyl Acetate to **18.** *tert*-Butyl acetate (0.18 mL, 1.3 mmol) was added to a freshly prepared solution of LDA (1.3 mmol in 4 mL THF) at -78 °C under N₂ and the mixture was stirred for 15 min. Weinreb amide cyanamide **18** (215 mg, 1.17 mmol) was added in 2 mL of dry THF. The mixture was stirred for 2 h at -78 °C, quenched with 5% HCl solution, and extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄ and concentrated. Flash chromatography on silica gel (98:2 CH₂Cl₂/MeOH) gave 90 mg (30%) of **24**, followed by 50 mg (21%) of **23**,

and 75 mg (32%) of **22**. A solution of urea **23** in CDCl₃ containing several drops of TFA completely isomerized to **22** in 2 h.

Data for *tert*-butyl 1-(2,5,6,7-tetrahydro-3-oxo-3*H*-pyrrolo[1,2-*c*]imidazole)acetate (**22**): ¹H NMR (CDCl₃) 9.30 (br s, 1, NH), 3.66 (t, 2, *J* = 6.7), 3.27 (s, 2), 2.66 (t, 2, *J* = 7.3), 2.40 (tt, 2, *J* = 6.7, 7.3), 1.45 (s, 9); ¹³C NMR (CDCl₃) 169.0, 151.1, 124.6, 105.4, 81.5, 41.8, 32.2, 28.3, 27.9 (3 C), 22.0.

Data for *tert*-butyl (2*Z*)-(2,5,6,7-tetrahydro-3-oxo-3*H*-pyrrolo[1,2-*c*]imidazol-1-ylidene)acetate (**23**): ¹H NMR (CDCl₃) 8.70 (br s, 1, NH), 5.19 (s, 1), 4.87 (dd, 1, *J* = 7.3, 7.3), 3.59 (ddd, 1, *J* = 8.0, 8.0, 11.0), 3.24-3.34 (m, 1), 2.58-2.66 (m, 1), 2.00-2.10 (m, 2), 1.40-1.52 (m, 1), 1.46 (s, 9); ¹³C NMR (CDCl₃) 166.5, 161.8, 155.1, 91.8, 79.5, 64.6, 44.8, 30.1, 28.3 (3 C), 26.4; HRMS (DCI/NH₃) calcd for C₁₂H₁₉N₂O₃ (MH⁺) 239.1396, found 239.1402.

Data for *tert*-butyl 2-(1-carbamoyl-pyrrolidine)-3-hydroxypropenoate (**24**): ¹H NMR (CDCl₃) 8.95 (br s, 1, OH or NH₂), 4.87 (s, 1), 4.33 (dd, 1, *J* = 7.9, 7.9), 3.59 (ddd, 1, *J* = 7.9, 7.9, 11.0), 3.15-3.22 (m, 1), 1.95-2.20 (m, 3), 1.55-1.65 (m, 1), 1.48 (s, 9).

***tert*-Butyl 3-Amino-5,6,7,7a-tetrahydro-1-oxo-1*H*-pyrrolizine-2-carboxylate (**26**)**. *tert*-Butyl acetate (1.5 mL, 11.1 mmol) was added dropwise over a period of 10 min to a freshly prepared solution of LDA (10 mmol in 27 mL THF) at -45 °C under N₂. The solution was stirred for 15 min and treated with methyl (*S*)-1-cyano-2-pyrrolidinecarboxylate (**25**)¹⁹ (680 mg, 4.4 mmol) in 5 mL of dry THF. The mixture was stirred for 1 h at -45 °C, treated dropwise with LHMDS (5 mL, 1.0 M in THF) and allowed to warm to 25 °C. The mixture was stirred for 2 h at 25 °C, quenched with H₂O, and extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄ and concentrated. Flash chromatography on silica gel (95:5 CH₂Cl₂/MeOH) gave 250 mg (24%) of byproduct **28** followed by 280 mg (27%) of pure **26**.

Data for **26**: mp 200-203 °C; [α]_D²² -66.9 (*c* 1.2, MeOH); UV (MeOH) λ_{max} nm (log ε) 211(4.17), 241 (4.21), 264 (4.11); ¹H NMR (CDCl₃) 8.00 (br, 1, NH), 5.42 (br, 1,

NH), 3.87 (dd, 1, $J = 6.7, 9.8$), 3.34-3.42 (m, 1), 3.20-3.28 (m, 1), 2.06-2.26 (m, 3), 1.54-1.60 (m, 1), 1.55 (s, 9); ^{13}C NMR (CDCl_3) 193.1, 174.0, 164.9, 90.5, 79.9, 69.7, 46.6, 28.5 (3 C), 27.6, 26.7; IR (KBr) 3475, 3077, 1714, 1638; HRMS (DEI) calcd for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_3$ (M^+) 238.1317, found 238.1315.

Data for **28**: ^1H NMR (CDCl_3) 9.95 (br s, 1, NH), 4.34 (s, 1), 3.98 (dd, 1, $J = 8.6, 8.6$), 3.31-3.38 (m, 1), 3.21 (ddd, 1, $J = 7.9, 7.9, 10.4$), 1.98-2.26 (m, 3), 1.64-1.75 (m, 1), 1.47 (s, 9); ^{13}C NMR (CDCl_3) 173.4, 169.4, 160.9, 79.1, 72.6, 63.6, 49.9, 28.4 (3 C), 27.3, 27.1. A 1D NOESY experiment showed an NOE from the alkene hydrogen (δ 4.34) to the *tert*-butyl hydrogens (δ 1.47) and the methylene group adjacent to the ring fusion nitrogen (δ 3.21 and δ 3.31-3.38) establishing that the stereochemistry is *E* as drawn.

3-(2-Methyl-2*E*-butenoylamino)-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one

(31). 2-Methyl-2*E*-butenoyl chloride (27 mg, 0.23 mmol) was treated with **26** (25 mg, 0.10 mmol) and NaH (10 mg, 0.25 mmol) and hydrolyzed and decarboxylated with 9:1 $\text{CH}_2\text{Cl}_2/\text{TFA}$ as described below for the preparation of **39d** to give 15 mg (69%) of **31** after flash chromatography on silica gel (98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$): $[\alpha]_D^{22}$ 1.3 (c 0.7, MeOH); ^1H NMR (CD_3OD) 6.60 (q, 1, $J = 6.7$), 5.65 (s, 1), 3.95 (dd, 1, $J = 8.2, 8.2$), 3.42-3.50 (m, 1), 3.22 (ddd, 1, $J = 7.3, 7.3, 11.0$), 2.06-2.22 (m, 3), 1.88 (s, 3), 1.87 (d, 3, $J = 6.7$), 1.50-1.60 (m, 1); ^{13}C NMR (CD_3OD) 204.5, 173.7, 169.9, 136.3, 133.2, (93.6, 93.5), 70.7, 28.8, (27.5, 27.4), 14.4, 12.3 (one C is obscured by the CD_3OD peak between 49-50).

Jenamidines A₁/A₂ 4'-Acetate (39a). (*S*)-4-Acetoxy-2-methylpent-2*E*-enoyl chloride (**38a**, 80 mg, 0.44 mmol) (prepared as described for **39d** using AcCl instead of methoxyacetyl chloride) was treated with **26** (36 mg, 0.15 mmol) and NaH (14 mg, 0.33 mmol) and hydrolyzed and decarboxylated with 9:1 $\text{CH}_2\text{Cl}_2/\text{TFA}$ as described below for the preparation of **39d** to give 37 mg (84%) of **39a** as a 1:1 mixture of diastereomers upon flash chromatography (95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$): $[\alpha]_D^{22}$ -27.5 (c 0.8, MeOH); ^1H NMR

(CD₃OD) 6.28-6.38 (m, 1), 5.59-5.68 (m, 1), 5.62 (s, 1), 3.94 (dd, 1, $J = 8.5, 7.9$), 3.39-3.46 (m, 1), 3.16-3.24 (m, 1), 2.06-2.20 (m, 3), 2.03 (s, 3×0.5), 2.02 (s, 3×0.5), 1.95 (s, 3×0.5), 1.94 (s, 3×0.5), 1.48-1.57 (m, 1), 1.35 (d, $3 \times 0.5, J = 6.7$), 1.34 (d, $3 \times 0.5, J = 6.7$); ¹³C NMR (CD₃OD) 204.6, 173.5, 172.0, (169.5, 169.4), (138.74, 139.69), 133.7, 93.9, 70.8, (68.9, 68.8), 28.8, 27.5, 21.0, 19.7, 13.2, one C is obscured by the CD₃OD peak between 49-50; HRMS (MeOH/NBA) calcd for C₁₅H₂₁N₂O₄ (MH⁺) 293.1501, found 293.1504.

Triisopropylsilylation of Hydrocupreine. Triisopropylsilyl chloride (4.28 g, 22.2 mmol) was added to a solution of hydrocupreine³⁶ (3.45 g, 11.1 mmol) and imidazole (1.51 g, 22.2 mmol) in 21 mL of DMF and the resulting solution was stirred overnight at room temperature and then poured into ethyl acetate (115 mL). The organic solution was washed with water (3×100 mL), dried over Na₂SO₄, and concentrated to give the crude TIPS silyl ether as a yellow oil. Flash chromatography on silica gel (CHCl₃ 200 mL, then 9:1:0.1 CHCl₃/MeOH/ NH₄OH) afforded 4.94 g (95%) of TIPS-DHQ: $[\alpha]_D^{22} -8.1$ (c 1.0, CHCl₃); ¹H NMR (CDCl₃) 8.63 (d, 1, $J = 4.3$), 7.64 (d, 1, $J = 9.1$), 7.63 (d, 1, $J = 4.3$), 7.35 (d, 1, $J = 2.4$), 6.97 (dd, 1, $J = 2.4, 9.1$), 6.41 (br s, 1, OH), 6.23 (br s, 1), 4.42-4.52 (m, 1), 3.37 (dd, 1, $J = 12.0, 12.0$), 3.24 (dd, 1, $J = 9.7, 13.4$), 2.98-3.08 (m, 1), 2.63 (br d, 1, $J = 13.4$), 2.09-2.15 (m, 1), 2.01-2.06 (m, 1), 1.94 (br s, 1), 1.68-1.78 (m, 2), 1.27-1.34 (m, 3), 1.08-1.14 (m, 21), 0.77 (t, 3, $J = 7.3$); ¹³C NMR (CDCl₃) 153.9, 147.4, 144.6, 143.1, 130.6, 125.2, 124.1, 118.9, 110.3, 66.6, 59.9, 56.6, 43.8, 35.4, 27.0, 24.9, 24.4, 17.91 (3 C), 17.87 (3 C), 12.6 (3 C), 11.4; IR (neat) 3226, 2936, 2861, 1619, 1502, 1456, 1237, 1259.

DHQ-PYR-OH (60). Potassium hydroxide (600 mg, 10.6 mmol) was added to a solution of the TIPS ether (611 mg, 1.33 mmol) and 4,6-dichloro-2,5-diphenylpyrimidine (400 mg, 1.33 mmol) in 27 mL of dry toluene. The mixture was heated in a 90 °C oil bath. The temperature of the oil bath was slowly raised to 115 °C and the mixture was stirred for 1 h at this temperature. The mixture was cooled, diluted with H₂O, and

extracted with EtOAc. The combined organic fractions were dried over MgSO₄ and concentrated to give 990 mg of 80% pure TIPS-DHQ-PYR that was used without further purification.

HF (48-51% aqueous solution, 3 mL) was added dropwise to a solution of the above TIPS-DHQ-PYR in 33 mL of CH₃CN. The mixture was stirred for 30 min, carefully quenched with a saturated sodium bicarbonate solution and extracted with EtOAc. The combined organic fractions were dried over MgSO₄ and concentrated. Flash chromatography on silica gel (95:5 CH₂Cl₂/MeOH) gave 400 mg (52% from the TIPS ether) of **60**: $[\alpha]_D^{22} +259.4$ (c 1.0, CHCl₃); ¹H NMR (CDCl₃) 8.68 (br s, 1), 8.61 (d, 1, *J* = 4.6), 7.97 (d, 1, *J* = 9.1), 7.87 (br d, 2, *J* = 7.3), 7.60 (dd, 2, *J* = 7.3, 7.3) 7.48-7.56 (m, 3), 7.27 (dd, 1, *J* = 2.1, 9.1), 7.24-7.27 (m, 1), 7.18 (d, 1, *J* = 4.6), 6.95-7.01 (m, 3), 3.05-3.16 (m, 3), 2.67-2.74 (m, 1), 2.31 (d, 1, *J* = 12.8), 1.76-1.81 (m, 1), 1.63 (br s, 1), 1.43-1.52 (m, 2), 1.08-1.21 (m, 3), 0.83 (br s, 1), 0.71 (t, 3, *J* = 7.0) (the OH was not observed); ¹³C NMR (CDCl₃) 165.9, 162.7, 159.7, 157.0, 146.3, 143.8, 143.6, 135.1, 132.2, 131.2, 130.9, 129.9 (2 C), 128.63 (2 C), 128.60, 128.3 (2 C), 128.1 (2 C), 127.2, 123.0, 118.5, 117.1, 107.5, 76.2, 58.4, 58.2, 43.4, 36.7, 27.2, 26.5, 24.8, 20.3, 11.8; IR (neat) 3580, 3055, 2955, 2868, 1619, 1571, 1517, 1408, 1376, 1241, 999, 851, 756, 700; HRMS (CI) Calcd for C₃₅H₃₄ClN₄O₂ (MH⁺) 577.2370, found 577.2357.

Ethyl 2-Methyl-2-nitro-5-oxohexanoate (52). DABCO (48 mg, 0.41 mmol) was added to a solution of ethyl 2-nitropropionate (**51**, 600 mg, 4.08 mmol) in 6 mL of dry CH₂Cl₂ and the mixture was stirred for 10 min. Methyl vinyl ketone (**50**, 0.85 mL, 10.2 mmol) was then added dropwise and the resulting solution was stirred for 5 h at 25 °C, passed through a short pad of silica gel with Et₂O to remove the catalyst and concentrated to give 866 mg (98%) of pure (±)-**52**, whose data matched those previously reported.^{31,34}

A solution of catalyst **60** (240 mg, 0.40 mmol) and ethyl 2-nitropropionate (600 mg, 4.08 mmol) in 8 mL of dry CH₂Cl₂ was kept at -20 °C for 2 h and methyl vinyl ketone (0.85 mL, 10.2 mmol) was then added dropwise. The resulting solution was kept

at -20 °C for 3 d, passed through a short pad of silica gel with Et₂O to remove the catalyst and concentrated to give 890 mg (100%) of pure (+)-**52**: $[\alpha]_D^{22} +3.3$ (*c* 1.0, MeOH).

Removal of catalyst **60** was critical for the success of the one-pot reduction using H₂ and Pd at neutral and then acidic pH.

Ethyl α ,2-Dimethyl- α -nitro-1,3-dioxolane-2-butanoate. A solution of (+)-**52** (20 mg, 0.09 mmol), ethylene glycol (0.1 ml) and TsOH (5 mg) in 2 mL of benzene was stirred at reflux for 4 h as described by Feringa.³⁴ The mixture was cooled, diluted with saturated sodium bicarbonate solution and extracted with EtOAc. The combined organic extracts were dried over MgSO₄ and concentrated to give 22 mg (94%) of pure dioxolane: $[\alpha]_D^{22} -4.7$ (*c* 1.0, MeOH); ¹H NMR (CDCl₃) 4.27 (q, 2, *J* = 7.3), 3.90-4.00 (m, 4), 2.36 (ddd, 1, *J* = 13.1, 13.1, 4.2), 2.25 (ddd, 1, *J* = 13.1, 13.1, 4.2), 1.77 (s, 3), 1.69 (ddd, 1, *J* = 13.1, 13.1, 4.2), 1.60 (ddd, 1, *J* = 13.1, 13.1, 4.2), 1.33 (s, 3), 1.29 (t, 3, *J* = 7.3); ¹³C NMR (CDCl₃) 167.3, 108.9, 92.3, 64.7 (2 C), 62.8, 33.0, 30.9, 23.9, 21.4, 13.8.

The enantiomer excess was determined to be 90% (95:5) by HPLC analysis [Daicel chiralcel OJ, hexanes/IPA, 90:10, 1.00 ml/min, λ 220 nm, *t* (major) = 11.3 min, *t* (minor) = 12.6 min].³⁴ A similar analysis performed with Michael adduct (-)-**52**, formed using catalyst **59**,³⁵ showed a 90:10 mixture of enantiomers (80% ee): *t* (major) = 12.6 min, *t* (minor) = 11.3 min].

Reduction of **52 over Pd at 1 atm of H₂.** A solution of **52** (866 mg, 3.99 mmol) in 20 mL of EtOH containing 10% Pd on activated carbon (430 mg, 0.41 mmol) and Na₂SO₄ (600 mg, 4.22 mmol) was stirred under 1 atm of H₂ at 25 °C for 12 h. The mixture was filtered through Celite and concentrated to give 735 mg (99%) of ethyl 2,5-dimethyl-1-pyrroline-5-carboxylate 1-oxide (**55**): ¹H NMR (CDCl₃) 4.15-4.31 (m, 2), 2.75-2.86 (m, 1), 2.64-2.73 (m, 1), 2.41-2.49 (m, 1), 2.10 (s, 3), 1.98-2.08 (m, 1), 1.71 (s, 3), 1.29 (t, 3, *J* = 7.0); ¹³C NMR (CDCl₃) 170.4, 145.2, 78.6, 62.0, 30.4, 30.3, 20.9, 13.9, 13.0.

Ethyl 2,5-Dimethyl-1-hydroxy-2-pyrrolidinecarboxylate (53). Nitrone **55** (735 mg, 3.97 mmol) was stirred with PtO₂ (92 mg, 0.40 mmol) in 20 mL of EtOH under 1 atm of H₂ at 25 °C for 8 h. The mixture was filtered through Celite and concentrated to give 750 mg (100%) of hydroxylamine **53** containing 5% of the diastereomer **54** that was used without purification. An analytical sample of **53** was prepared by flash chromatography on silica gel (75:25 hexanes/EtOAc): ¹H NMR (CDCl₃) 5.08 (br s, 1, OH), 4.15-4.23 (m, 2), 3.04-3.12 (m, 1), 2.08-2.16 (m, 1), 1.85-1.95 (m, 1), 1.72-1.80 (m, 1), 1.30-1.40 (m, 1) 1.35 (s, 3), 1.28 (t, 3, *J* = 7.0), 1.22 (d, 3, *J* = 6.1); ¹³C NMR (CDCl₃) 175.5, 69.6, 60.8, 58.2, 31.2, 26.0, 19.0, 16.6, 14.2; IR (neat) 3446, 1731; HRMS (NH₃/CI) Calcd for C₉H₁₈NO₃ (MH⁺) 188.1287, found 188.1283.

Ethyl *trans*-2,5-Dimethyl-2-pyrrolidinecarboxylate (49). Zn dust (1.28 g, 19.5 mmol) and Cu(OAc)₂ (71 mg, 0.39 mmol) were stirred for 15 min at 25 °C in 4 mL of HOAc and then treated with a solution of hydroxylamine **53** (730 mg, 3.9 mmol) in 2 mL of EtOH and 4 mL of HOAc. The mixture was stirred for 2.5 h at 70 °C and then cooled to rt. EDTA (4 g) was added and the solution was adjusted to pH 10 with 2 M NaOH and extracted with EtOAc. The combined organic extracts were dried over MgSO₄ and concentrated to give 422 mg (63%) of pure **49**: ¹H NMR (CDCl₃) 4.18 (q, 2, *J* = 7.0), 3.27 (ddd, 1, *J* = 6.1, 6.1, 9.2), 2.32 (br s, 1, NH), 2.22-2.31 (m, 1), 1.88-1.96 (m, 1), 1.66-1.75 (m, 1), 1.38 (s, 3), 1.28 (t, 3, *J* = 7.0), 1.18-1.28 (m, 1), 1.19 (d, 3, *J* = 6.1); ¹³C NMR (CDCl₃) 177.6, 65.8, 61.1, 54.5, 38.5, 34.6, 26.6, 20.9, 14.1; IR (neat) 3345, 1727; HRMS (EI) Calcd for C₉H₁₆NO₂ (M-H⁺) 170.1181, found 170.1181.

(*S*)-Mosher Amide of (-)-49 (63). The Mosher acid chloride was prepared analogously (see preparation of **64**) from (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (32 mg, 0.14 mmol), DMF (10 μL, 0.14 mmol) and oxalyl chloride (60 μL, 0.66 mmol). The acid chloride was stirred with (-)-**49**•HCl (20 mg, 0.12 mmol, prepared with catalyst **60**) and diisopropylethylamine (42 μL, 0.24 mmol) in 1 mL of dry CH₂Cl₂ for 1 h at 25 °C. The mixture was concentrated, taken up in a saturated ammonium chloride

solution, and extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄ and concentrated. Flash chromatography on silica gel (80:20 hexanes/EtOAc) gave 35 mg (76%) of Mosher amide **63**: [α]_D²² -98 (*c* 1.0, MeOH); ¹H NMR (CDCl₃) 7.50-7.54 (m, 2), 7.37-7.41 (m, 3), 4.16-4.27 (m, 2), 3.73 (s, 3), 3.25-3.31 (m, 1), 2.16 (ddd, 1, *J* = 12.8, 12.8, 6.1), 1.70-1.76 (m, 1), 1.67 (s, 3), 1.56-1.64 (m, 1), 1.26-1.35 (m, 1), 1.28 (t, 3, *J* = 7.0), 1.24 (d, 3, *J* = 6.7); ¹³C NMR (CDCl₃) 173.6, 165.0, 134.5, 129.2, 128.1 (2 C), 126.5 (2 C), 123.7 (q, *J* = 291), 84.4 (q, *J* = 23), 68.4, 61.3, 56.2, 55.1, 34.9, 32.1, 20.3, 19.8, 14.1; IR (neat) 1749, 1643; HRMS (ES) Calcd for C₁₉H₂₅NO₄F₃ (MH⁺) 388.1736, found 388.1731.

(R)-Mosher Amide of (-)-49 (64). Oxalyl chloride (60 μ L, 0.66 mmol) was added to a solution of (*R*)- α -methoxy- α -(trifluoromethyl)phenylacetic acid (32 mg, 0.14 mmol) and DMF (10 μ L, 0.14 mmol) in 1 mL of hexane and the mixture was stirred for 1 h at 25 °C, filtered, and concentrated. The resulting acid chloride was stirred with (-)-49•HCl (20 mg, 0.12 mmol, prepared with catalyst **60**) and diisopropylethylamine (42 μ L, 0.24 mmol) in 1 mL of dry CH₂Cl₂ for 1 h at 25 °C. The mixture was concentrated, taken up in a saturated ammonium chloride solution, and extracted with CH₂Cl₂. The combined organic extracts were dried over MgSO₄ and concentrated. Flash chromatography on silica gel (80:20 hexanes/EtOAc) gave 34 mg (74%) of Mosher amide **64**: [α]_D²² +70 (*c* 1.0, MeOH); ¹H NMR (CDCl₃) 7.59-7.62 (m, 2), 7.36-7.40 (m, 3), 4.53-4.60 (m, 1), 4.17-4.27 (m, 2), 3.67 (s, 3), 2.04-2.20 (m, 2), 1.78-1.82 (m, 1), 1.63 (s, 3), 1.57-1.63 (m, 1), 1.31 (t, 3, *J* = 7.0), 0.21 (d, 3, *J* = 6.1); ¹³C NMR (CDCl₃) 173.5, 163.8, 133.5, 129.4, 128.1 (2 C), 127.2 (2 C), 123.7 (q, *J* = 290), 84.5 (q, *J* = 24), 68.1, 61.2, 54.8, 54.7, 34.5, 32.8, 20.7, 19.0, 14.1; IR (neat) 1731, 1641; HRMS (ES) Calcd for C₁₉H₂₅NO₄F₃ (MH⁺) 388.1736, found 388.1732.

Oxidation of 26 with Two Equivalents of Lead Tetraacetate at Reflux to Give *tert*-Butyl (4 β ,7 $\alpha\beta$)-4,7 α -Diacetoxy-3-amino-5,6,7,7 α -tetrahydro-1-oxo-1H-pyrrolizine-2-carboxylate (65). Lead tetraacetate (257 mg, 0.58 mmol) was added to a

solution of **26** (70 mg, 0.29 mmol) in 9 mL of dry benzene. The mixture was stirred under N₂ at reflux for 20 h, filtered, and washed with saturated sodium bicarbonate solution. The organic layer was dried over MgSO₄ and concentrated to give 45 mg of crude diacetate **65**. Flash chromatography on silica gel (97:3 CH₂Cl₂/MeOH) gave 40 mg (39%) of pure **65**: UV (MeOH) λ_{max} nm (log ϵ) 207 (3.98), 239 (4.16), 268 (4.08); ¹H NMR (CDCl₃) 8.28 (br s, 1, NH), 7.95 (br s, 1, NH), 6.04 (dd, 1, *J* = 6.1, 6.7, H-4), 2.55-2.65 (m, 2, H-5), 2.34 (dd, 1, *J* = 6.1, 13.5, H-6 α), 2.14 (s, 3), 2.08 (s, 3), 1.74 (ddd, 1, *J* = 12.8, 12.8, 9.2, H-6 β), 1.54 (s, 9); ¹³C NMR (CDCl₃) 185.0, 173.2, 171.3, 168.2, 165.2, 97.6, 88.2, 84.2, 80.4, 32.2, 31.9, 28.4 (3 C), 21.3, 21.0; IR (neat) 1759, 1730, 1656, 1625; HRMS (ES) Calcd for C₁₆H₂₃N₂O₇ (MH⁺) 355.1505, found 355.1517.

An NOE was observed between H₄ at δ 6.04 and one or both H₅'s at δ 2.55-2.65, H₆ at δ 1.74 and the acetate at δ 2.14.

Oxidation of (7aS)-tert-Butyl 3-Amino-5,6,7,7a-tetrahydro-1-oxo-1H-pyrrolizine-2-carboxylate (26) with One Equivalent of Lead Tetraacetate at 25 °C.

Lead tetraacetate (110 mg, 0.25 mmol) was added to a solution of **26** (50 mg, 0.20 mmol) in 6 mL of dry benzene. The mixture was stirred under N₂ at 25 °C for 20 h, filtered, and washed with saturated sodium bicarbonate solution. The organic layer was dried over MgSO₄ and concentrated to give 30 mg of a mixture of **26**, **66**, and **67**. Flash chromatography on silica gel (39:1 CH₂Cl₂/MeOH) gave 12 mg of 90% pure **66**, followed by 4 mg of pure **66**, 1 mg of a 2:1 mixture of **66** and **68**, 3 mg of pure **68** and 6 mg of recovered **26**.

Data for *tert*-butyl 3-amino-5,6,7,7a-tetrahydro-7a-methoxy-1-oxo-1H-pyrrolizine-2-carboxylate (**68**): UV (MeOH) λ_{max} nm (log ϵ) 211 (3.73), 239 (3.83), 270 (3.60); ¹H NMR (CDCl₃) 8.35 (br s, 1, NH), 5.48 (br s, 1, NH), 3.42-3.50 (m, 1), 3.27-3.35 (m, 1), 3.21 (s, 3), 2.30-2.42 (m, 1), 2.06-2.16 (m, 2), 1.60-1.70 (m, 1), 1.55 (s, 9); ¹³C NMR (CDCl₃) 80.5, 51.4, 46.2, 32.2, 28.5 (3 C), 26.1, five quaternary carbons were

not observed; IR (neat) 1712, 1650, 1616; HRMS (ES) Calcd for C₁₃H₂₁N₂O₄ (MH⁺) 269.1501, found 269.1508.

Data for *tert*-butyl (4 β ,7 α)-4-acetoxy-3-amino-5,6,7,7 α -tetrahydro-1-oxo-1*H*-pyrrolizine-2-carboxylate (**66**): UV (MeOH) λ_{max} nm (log ϵ) 204 (3.51), 239 (3.63), 260 (3.57); ¹H NMR (CDCl₃) 8.05 (br s, 1, NH), 7.72 (br s, 1, NH), 5.95 (dd, 1, *J* = 5.5, 5.5, H-4), 4.05 (dd, 1, *J* = 8.0, 9.1, H-7 α), 2.50-2.58 (m, 1, H-5), 2.25-2.40 (m, 2, H-5, H-6), 2.16 (s, 3), 1.65-1.75 (m, 1, H-6), 1.55 (s, 9); ¹³C NMR (CDCl₃) 83.6, 68.4, 33.6, 28.5 (3 C), 26.0, 21.4, six quaternary carbons were not observed; IR (neat) 1726, 1652, 1620; HRMS (ES) Calcd for C₁₄H₂₁N₂O₅ (MH⁺) 297.1450, found 297.1454.

An NOE was observed between H₄ at δ 5.95 and H₅ at δ 2.55. Another NOE was observed between H_{7 α} at δ 4.05 and H₆ and/or H₅ at δ 2.3, and lastly, an NOE was observed between H₆ at δ 1.7 and H₆ and/or H₅ at 2.3 and H₅ at 2.55.

Oxidation of 26 with One Equivalent of Lead Tetraacetate at Reflux. Lead tetraacetate (180 mg, 0.40 mmol) was added to a solution of **26** (100 mg, 0.40 mmol) in 12 mL of dry benzene. The mixture was stirred under N₂ at reflux for 1.5 h, filtered, and washed with saturated sodium bicarbonate solution. The organic layer was dried over MgSO₄ and concentrated to give 50 mg of a 3:3:2 mixture of **26**, **67**, and **66**, and a trace of diacetate **65**.

(S)-Proline-*N*-carboxyanhydride (76) was prepared as previously described.⁴⁹ Triphosgene (62 mg, 0.21) in 2 mL of dry THF was added over a 5-10 min period to a solution of proline (**75**, 60 mg, 0.52 mmol) in 2 mL of dry THF at 15 °C. The mixture was submerged in a 40-45 °C oil bath and stirred until the solution was homogenous (60-90 min). The solution was then concentrated to an oil with careful exclusion of air to eliminate any excess HCl present. The oil was dissolved in 2 mL of dry THF and cooled to 0 °C. Triethylamine (72 μ L, 0.52 mmol) was added dropwise over a period of 10 min and the mixture was stirred for 30 min. The mixture was filtered with careful exclusion of air to give proline-NCA in a solution of THF that was used immediately.

Methyl (2*E*)-[(7*aS*)-Tetrahydro-3-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-1-ylidene]-acetate (78). A solution of **76** in 2 mL of THF (prepared from 0.52 mmol of proline) was added to methyl (triphenylphosphoranylidene)acetate (**77**, 87 mg, 0.26 mmol) in 1 mL of dry toluene under N₂ in a microwave tube. The mixture was heated at 150 °C at 75 psi for 15 min in a microwave. After cooling, the mixture was concentrated to give crude **78** as a 9:1 mixture of the *E* and *Z* products. Flash chromatography on silica gel (98:2 CH₂Cl₂/MeOH) gave 18 mg (35%) of pure **78**: $[\alpha]_D^{22}$ -207 (*c* 1.0, MeOH); UV (MeOH) $\lambda_{\max}$ nm (log ϵ) 212 (4.01), 238 (4.13); ¹H NMR (CDCl₃) 5.66 (d, 1, *J* = 1.8), 4.92 (ddd, 1, *J* = 7.3, 7.3, 1.8), 3.73 (s, 3), 3.69 (ddd, 1, *J* = 8.0, 8.0, 11.6), 3.27-3.34 (m, 1), 2.58-2.67 (m, 1), 2.02-2.18 (m, 2), 1.55-1.68 (m, 1); ¹³C NMR 166.6, 165.6, 156.6, 95.3, 64.2, 51.4, 45.9, 30.2, 26.2; IR (neat) 1804, 1716, 1667; HRMS (ES) Calcd for C₉H₁₂NO₄ (MH⁺) 198.0766, found 198.0767.

ppm (f1)

10.0

5.0

0.0

ppm (t1)

200

150

100

50

0

166.499

161.811

155.075

91.780

79.454

77.318

77.000

76.682

64.616

44.774

30.074

28.317

26.445

ppm (t1)

10.0

5.0

0.0

28

ppm (f1)

10.0

5.0

0.0

ppm (f1)

200
150
100
50
0

31

204.512

173.709

169.945

136.290

133.163

93.568

70.669

49.638

49.427

49.212

48.998

48.788

48.574

48.359

28.844

27.502

27.401

14.446

12.343

ppm (f1)

10.0

5.0

0.0

34

ppm (f1)

10.0

5.0

0.0

ppm (f1)

10.0

5.0

0.0

ppm (f1)

10.0

5.0

0.0

ppm (τ¹)

10.0

5.0

0.0

ppm (t1)

10.0

5.0

0.0

ppm (f1)

39d in CD₃OD

204.647

173.354

171.375

171.359

169.371

169.317

138.039

137.994

134.199

134.175

93.896

70.742

70.472

69.418

69.316

59.526

49.640

49.428

49.285

49.213

49.000

48.788

48.575

48.361

28.792

27.474

19.775

13.292

13.264

ppm (f1)

10.0

5.0

0.0

ppm (f1)

200
150
100
50
0

197.506

178.502

72.115

49.640

49.427

49.213

49.000

48.788

48.574

48.361

47.656

29.319

28.206

ppm (t1)

200

150

100

50

0

TIPS-DHQ

153.908

147.392

144.593

143.122

130.643

125.240

124.071

118.854

110.250

77.319

77.000

76.681

66.618

59.877

56.647

43.759

35.443

26.981

24.868

24.421

17.917

17.870

12.592

11.366

10.0

5.0

0.0

ppm (t_1)

10.0

5.0

0.0

200
150
100
50
0

175.522

77.318

77.000

76.682

69.628

60.833

58.185

31.155

25.996

18.953

16.616

14.174

200
150
100
50
0

177.606

77.318

77.000

76.682

65.780

61.078

54.505

38.481

34.611

26.646

20.870

14.105

10.0

5.0

0.0

200
150
100
50
0

172.875

114.466

77.319

77.000

76.683

68.025

61.819

58.311

37.149

31.959

22.963

19.471

14.036

203.118

177.067

172.592

165.975

114.671

114.587

89.653

82.153

81.522

77.318

77.000

76.682

73.368

67.400

59.804

58.880

45.300

37.224

35.768

31.798

31.592

28.143

27.856

23.669

21.896

19.452

19.413

200
150
100
50
0

195.805

170.621

166.152

90.675

79.921

77.318

77.000

76.682

75.291

53.862

35.324

29.210

28.526

24.442

17.250

200
150
100
50
0

167.281

164.193

158.211

117.587

93.509

77.318

77.000

76.682

74.750

54.757

35.412

28.188

27.793

24.625

20.447

17.437

63 (S-Mosher amide)

63 (S-Mosher amide)

200
150
100
50
0

173.600

164.998

134.471

129.232

128.099

126.453

125.100

122.205

77.318

77.000

76.682

68.395

61.262

56.237

55.148

34.926

32.117

20.257

19.770

14.104

64 (*R*-Mosher amide)

64 (*R*-Mosher amide)

200
150
100
50
0

173.476

163.839

133.547

129.372

128.148

127.244

125.102

122.213

77.318

77.000

76.682

68.074

61.199

54.815

54.697

34.486

32.750

20.710

19.009

14.085

10.0

5.0

0.0

200
150
100
50
0

184.982

173.176

171.282

168.247

165.201

97.613

88.185

84.202

80.430

77.318

77.000

76.682

32.162

31.868

28.427

21.262

20.972

10.0

5.0

0.0

ppm (t_1)

10.0

5.0

0.0

200
150
100
50
0

166.557
165.640
156.643

95.270

77.318
77.000
76.682
64.186

51.417
45.914

30.216
26.233

ppm (t1)

10.0

5.0

0.0