Copper-Catalyzed Diastereoselective Arylation of Tryptophan Derivatives: Total Synthesis of (+)-Naseseazines A and B

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Supporting Information 1 (Experimental Procedures):

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I. General Procedures. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N) and methanol (MeOH) were distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. Copper(I) trifluoromethanesulfonate toluene complex [$(CuOTf)_2$•PhMe] was purchased from Sigma-Aldrich (99.9% trace metal basis) or Alfa-Aesar (98%). All reactions were monitored by LCMS on an Agilent 1290 Series LCMS using an Eclipse Plus C18 column (RRHD 1.8 μm, 2.1 x 50 mm, 11,072 plates) and electrospray ionization (ESI), or by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, potassium permanganate ($KMnO_4$), or cerium ammonium molybdate (CAM) staining. Flash column chromatography was performed as described by Still et al.[1] using silica gel (partical size 0.032-0.063). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, $\delta = 7.26$), CD_3OD (^1H, $\delta = 3.31$), or DMSO (^1H, $\delta = 2.50$), and $CDCl_3$ (^{13}C, $\delta = 77.0$), CD_3OD (^{13}C, $\delta = 49.0$), or DMSO (^{13}C, $\delta = 40.0$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode. LRMS were acquired using an Agilent 1290 Series LCMS using an Eclipse Plus C18 column (RRHD 1.8 μm, 2.1 x 50 mm, 11,072 plates) and electrospray ionization (ESI).

II. Preparation of α-Diimine ligands.

α-Diimine ligands were prepared following literature precedent by Bercaw et al.[1] $^{Mes}DAB_{Me}$ (**L7**) and $^{tBu}DAB_{Me}$ (**L6**) were readily prepared on greater than 40 gram scale in comparable yields to those reported in the literature. Ligands were thoroughly dried under high-vacuum (< 1.0 mTorr) at 50 °C for 4 hours and stored in a glovebox under inert atmosphere.

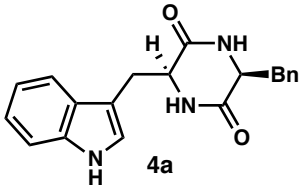
III. Preparation of Diketopiperazine Substrates

The preparation of diketopiperazines **4a-f** have been previously prepared in the literature. Diketopiperazine substrates **4d** and **4e** were prepared according to known literature procedures.[2] Improved yields were obtained for substrates **4a-4c** using an analogous procedure as reported by Movassaghi et al.[3]

General Procedure (I) *for the Synthesis of Diketopiperazine Substrates:*

To a solution of L-tryptophan methyl ester hydrochloride (1.0 equiv) in CH_2Cl_2 (0.1 M) at 0 °C was added Et_3N (4.5 equiv) dropwise. HOBt•H_2O (1.5 equiv) and Boc-amino acid (2.0 equiv) were sequentially added and stirred vigorously. Once homogenous, EDC•HCl (1.5 equiv) was added in a single portion and the solution allowed to warm to 23 °C. The reaction was stirred for 15 hours, at which time it was quenched by the addition of 1N HCl, and the aqueous layer extracted with CH_2Cl_2 (2 x). The combined organics were then washed with saturated aqueous $NaHCO_3$, and the aqueous layer back extracted with CH_2Cl_2 (2 x). The organics were pooled, then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting oil/foam was subsequently dissolved in CH_2Cl_2 (0.2 M), and cooled to 0 °C. TFA (1.5 mL/5 mL CH_2Cl_2) was added dropwise, then the solution was warmed to 23 °C and stirred for 2 h. The mixture was concentrated *in vacuo* and the resulting viscous residue dissolved in methanol (0.25 M), and cooled to 0°C. Ammonium hydroxide (28–30% in H_2O, 1 mL/ 6 mL MeOH) was then added dropwise and the reaction mixture allowed to warm to 23 °C and stirred for 24 h. The resulting suspension was cooled to 0 °C, and the fine white precipitate was filtered and rinsed with cold methanol. The white solid is then crushed and dried under high vacuum (< 1 mTorr) at 50 °C for a minimum of 2 h.

Cyclo-(L)-Trp-(L)-Phe (4a)



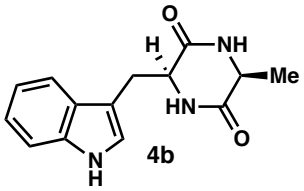
4a

Prepared from L-tryptophan methyl ester hydrochloride following *General Procedure I* on 19.6 mmol scale. The crude reaction mixture was filtered to yield 5.8

[1] Zhong, H. A.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2002**, *124*, 1378.
[2] Cabarallero, E; Avendano, C; Menendez, J. C. *Tetrahedron-Asymmetr.* **1998**, *17*, 3025.
[3] Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 14940.

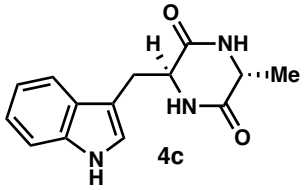
g (89% yield) of **4a** as a white solid. Spectral data matches that reported in the literature.[4]

Cyclo-(L)-Trp-(L)-Ala (4b)



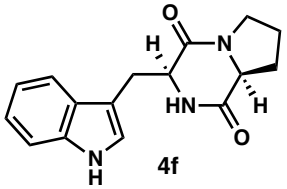
Prepared from L-tryptophan methyl ester hydrochloride following *General Procedure I* on 9.8 mmol scale. The crude reaction mixture was filtered to yield 2.3 g (92% yield) of **4b** as a white solid. Spectral data matches that reported in the literature.[5]

Cyclo-(L)-Trp-(D)-Ala (4c)



Prepared from L-tryptophan methyl ester hydrochloride following *General Procedure I* on 7.9 mmol scale. The crude reaction mixture was filtered to yield 1.8 g (89% yield) of **4c** as a white solid. Spectral data matches that reported in the literature.[4]

Large Scale Preparation of Cyclo-(L)-Trp-(L)-Pro (4f):

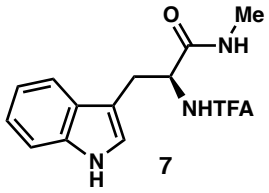


To a solution of L-proline methyl ester hydrochloride (11.0 g, 66.6 mmol, 1.00 equiv) in CH_2Cl_2 (700 mL) at 0 °C was added triethylamine (32.5 mL, 233 mmol, 3.50 equiv) dropwise by addition funnel. *N*-hydroxybenzotriazole monohydrate (15.3, 100 mmol, 1.50 equiv) and Boc-(L)-tryptophan (31.8 g, 100 mmol, 1.50 equiv) were then added successively. After 10 minutes, EDC•HCl (19.2 g, 100 mmol, 1.50 equiv) was added in a single portion and the mixture allowed to warm to 23 °C over 2.0 hours. After 20 hours, the solution was quenched by the addition of 1N HCl (1.0 L), and the aqueous layer extracted with CH_2Cl_2 (2 x 150 mL). The combined organics were then washed with saturated aqueous $NaHCO_3$ (1.0 L), and the aqueous layer back extracted with CH_2Cl_2 (200 mL). The combined organics were then dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The resulting white foam was then dissolved in CH_2Cl_2 (200 mL), and trifluoroacetic acid (60 mL) added dropwise by addition funnel. After 2 h, the solution was concentrated in vacuo and the viscous residue dissolved in methanol (900 mL) and cooled to 0 °C. Ammonium hydroxide (28 to 30% in H_2O, 35.0 mL) was added dropwise by addition funnel. The solution was then stirred for 14 hours, concentrated in vacuo, and redissolved in CH_2Cl_2 (1.0 L). The solution was next washed with H_2O (3 x 500 mL), and the aqueous layer back extracted with CH_2Cl_2 (250 mL). The organic layers were then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in MeOH (200 mL) and the solution cooled to 0 °C. After 20 minutes, the resulting white precipitate was collected. The filtrate was then concentrated to 100 mL and recooled to 0 °C, and a second crop of

[4] Tullberg, M.; Grotli, M.; Luthman, K. *Tetrahedron*. **2006**, *62*, 7484.
[5] Caballero, E.; Avendano, C.; Menendez, J. C. *Tetrahedron-Asymmetr.* **1998**, *9*, 967.

precipitate collected. The process was repeated a third time to collect a third crop of product. The resulting precipitates were combined, powdered, and dried under high vacuum at 50 °C for 12 hours to afford analytically pure cyclo-L-Pro-L-Trp as a white solid (12.4 g, 43.8 mmol, 66% yield). Spectral data matches that reported in the literature.[6]

Preparation of Trifluoroacetyltryptophan methyl carboxamide (7):



7

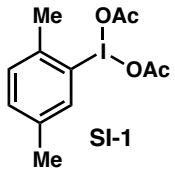
To (L)-Tryptophan methyl ester hydrochloride (5.84 g, 22.9 mmol) was added methylamine (33% solution in EtOH, 50 mL). The mixture was stirred for 48 h at 20 °C, then concentrated *in vacuo*, and the mixture co-evaporated with CH_2Cl_2 (50 mL), then Et_2O (3 x 100 mL), sequentially to afford a white solid. The solid was then suspended in anhydrous CH_2Cl_2 (250 mL), and Et_3N (9.6 mL, 68.7 mmol, 3.0 equiv) was added dropwise by syringe at 20 °C. The resulting mixture was then cooled to 0 °C, and TFAA (3.23 mL, 22.9 mmol, 1.00 equiv) added dropwise by syringe. After 24 hours, the reaction was quenched with 1N HCl (200 mL), extracted with CH_2Cl_2 (200 mL), dried over Na_2SO_4, filtered and concentrated. The residue was then dissolved in EtOAc (250 mL), and filtered through a short plug of silica gel, and the filter cake washed with additional EtOAc (250 mL). The filtrate was then concentrated, and the resulting yellow solid was treated with Et_2O/pentane to afford **7** as a white, amorphous powder (2.97 g, 42% yield). ^{1}H NMR (500 MHz, DMSO-d_6) 10.82 (d, J = 0.9 Hz, 1H), 9.61 (d, J = 8.2 Hz, 1H), 8.21 (q, J = 4.3 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 2.3 Hz, 1H), 7.10 – 7.04 (m, 1H), 6.99 (ddd, J = 7.9, 7.1, 1.0 Hz, 1H), 4.52 (ddd, J = 9.9, 8.5, 4.8 Hz, 1H), 3.20 (dd, J = 14.6, 4.6 Hz, 1H), 3.08 (dd, J = 14.6, 10.0 Hz, 1H), 2.62 (d, J = 4.6 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) 170.3, 156.2 (q, $J_{C\text{-}F}$ = 36.4 Hz), 136.1, 127.1, 123.7, 121.0, 118.4, 118.3, 115.8 (q, $J_{C\text{-}F}$ = 288.2 Hz), 111.4, 109.7, 54.3, 27.2, 25.7; FTIR (NaCl, thin film): 3277, 1700, 1696, 1653, 1636, 1560, 1347, 1185; $[\alpha]_D^{25}$ = +8.53 (c = 0.44, $CHCl_3$); LRMS (EI+) calc'd $[M+H]^+$ 314.1, found 314.1.

[6] Caballero, E.; Avedano, C.; Menendez, J. C. *J. Org. Chem.* **2003**, *68*, 6944.

IV. Preparation of Diaryliodonium Salts

The following diaryliodonium salts were prepared following known procedures: diphenyliodonium tetrafluoroborate,[7] diphenyliodonium hexafluoroarsentate,[8] diphenyliodonium triflate,[9] bis-*p*-tolyliodonium triflate,[9] and bis-*p*-methoxyiodonium triflate.[10] Diphenyliodonium hexafluorophosphate was purchased from Alfa-Aesar. *m*-CPBA (Sigma-Aldrich, <77%) was dried under high vacuum (< 1 mTorr) at 23 °C for 4 hours as reported by Oloffson and coworkers.[11]

Preparation of 2-iodo-*p*-xylene diacetate (SI-1):



SI-1

To a solution of 2-iodo-1,4-dimethylbenzene (11.6 g, 50.0 mmol, 1.00 equiv) in AcOH (1.0 L) at 50 °C was added $NaBO_3$•$4H_2O$ (84.7 mmol, 0.55 mmol, 11.0 equiv) portion wise over 30 minutes. The solution was vigorously stirred at 50 °C for 5 hours, then cooled to ambient temperature and diluted with H_2O (500 mL) and extracted with CH_2Cl_2 (3 x 500 mL). The combined organics were then washed with water (3 x 500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was suspended in a minimum of Et_2O, then triturated with hexanes and the precipitate collected by vacuum filtration. 2-Iodo-*p*-xylene diacetate was obtained as a white, crystalline solid (14.0 g, 40.0 mmol, 80% yield). Spectral data obtained match that previously reported,[12] ^{1}H and ^{13}C NMR data is reported for convenience. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 1.2 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.30 (dd, J = 7.8, 1.2 Hz, 1H), 2.65 (s, 3H), 2.36 (s, 3H), 1.97 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.3, 138.5, 137.3, 137.3, 133.5, 130.4, 126.8, 24.9, 20.6, 20.2.

General Procedure II[7]

To a solution of iodoarene in CH_2Cl_2 (0.25 M) was added *m*CPBA (1.1 equiv), and BF_3•OEt_2 (2.5 equiv). The solution was stirred for 45 minutes, then the solution cooled to 0 °C in a dry ice corresponding aryl boronic acid (1.00 equiv) added a solid in a single portion. The solution was stirred for 15 minutes, then warmed to room temperature and stirring continued for 45 minutes. The solution was then recooled to 0 °C and TfOH (2.00 equiv) added dropwise via syringe. The solution was stirred for 5 minutes at 0 °C, then warmed to room temperature and concentrated under reduced pressure. The resulting solution was then filtered through a plug of silica gel, eluting with 5% MeOH/CH_2Cl_2, the filtrate concentrated, and the residue triturated from Et_2O to afford pure diaryliodonium triflate, typically as a white, crystalline solid.

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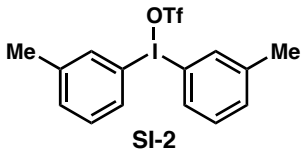
[7] Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602.
[8] Zhu, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 10815.
[9] Bielawski, M.; Zhu; M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610.
[10] Zhu, M,; Jalalian N.; Olofsson, B. *Synlett* **2008**, *4*, 592.
[11] Bielawski, M.; Olofsson, B. *Org. Synth.* **2009**, *86*, 308.
[12] Sharefkin, J. G.; Saltzman, H.; *Anal. Chem.,* **1963***, 35*, 1428.

General Procedure III

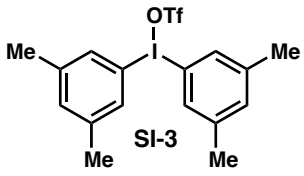
To a solution of aryl boronic acid (1.00 equiv) in CH_2Cl_2 (0.25 M) at 0 °C was added BF_3•OEt_2 (1.1 equiv) dropwise by syringe. The solution was stirred for 15 minutes, then a solution of iodoxylene diacetate (1.00 equiv) in CH_2Cl_2 (0.5 M) added dropwise by cannula transfer over 15 minutes. The solution was slowly warmed to 23 °C over 1 h, then recooled to 0 °C and TfOH (2.00 equiv) added dropwise via syringe. The solution was stirred for 5 minutes at 0 °C, then warmed to room temperature and concentrated under reduced pressure. The resulting solution was then filtered through a plug of silica gel, eluting with 5 % MeOH/CH_2Cl_2, the filtrate concentrated, and the residue triturated from Et_2O to afford pure diaryliodonium triflate salt, typically as a white, crystalline solid.

Di-(3-tolyl)iodonium triflate (SI-2)



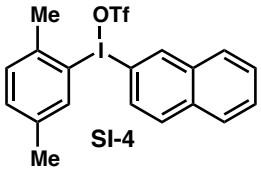
Prepared by *General Procedure II* from 3-methylphenyl boronic acid and 3-methyliodobenzene on 5.00 mmol scale. Trituration from Et_2O afforded **SI-2** as a white, crystalline solid (1.54 g, 3.36 mmol, 67% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10 (td, J = 1.8, 0.9 Hz, 2H), 8.04 (ddt, J = 7.9, 1.8, 0.9 Hz, 2H), 7.48 (ddt, J = 7.7, 1.8, 1.0 Hz, 2H), 7.41 (t, J = 7.8 Hz, 2H), 2.34 (d, J = 0.8 Hz, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 142.3, 135.78, 133.2, 132.7, 131.9, 116.6, 21.2; FTIR (NaCl, thin film): 3744, 3675, 1596, 1259, 1172, 1036, 1026 cm^{-1}; LRMS (EI+) calc'd $[M–OTf]^+$ 309.1, found 309.0.

Di-(3,5-dimethylphenyl)iodonium triflate (SI-3)



Prepared by *General Procedure II* from 3,5-dimethyliodobenzene and 3,5-dimethylphenylboronic acid on 10.0 mmol scale. Trituration from Et_2O afforded **SI-3** as a white, crystalline solid (3.72 g, 7.65 mmol, 77% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (dt, J = 1.5, 0.8 Hz, 4H), 7.30 (tt, J = 1.5, 0.8 Hz, 2H), 2.30 (d, J = 0.9 Hz, 12H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 141.9, 133.9, 132.9, 116.2, 21.1; FTIR (NaCl, thin film): 1599, 1558, 1451, 1381, 1243, 1221, 1171, 1154, 1026 cm^{-1}; LRMS (EI+) calc'd $[M–OTf]^+$ 337.2, found 337.2.

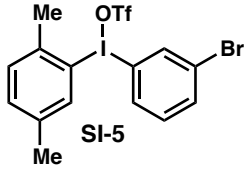
(2-naphthyl)(*p*-xylyl)iodonium triflate (SI-4)



Prepared by *General Procedure III* from 2-naphthyl boronic acid on 5.00 mmol scale. Trituration from Et_2O afforded **SI-4** as a white, crystalline solid (2.15 g, 4.23 mmol, 85% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (d, J = 1.9 Hz, 1H), 8.29 (dd, J = 1.7, 0.9 Hz, 1H), 8.18 (dd, J = 8.8, 1.9 Hz, 1H), 8.10 – 7.99 (m, 4H), 7.73 – 7.66 (m, 2H), 7.43 (d, J = 7.8 Hz, 1H), 7.38 (ddd, J = 7.7, 1.7, 0.8 Hz, 1H), 2.61 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 139.6, 137.9, 137.6, 136.5, 134.4, 133.9, 133.8, 132.00, 131.5, 130.6, 129.4, 128.6, 128.6, 128.4,

121.6, 113.0, 25.0, 20.5; FTIR (NaCl, thin film): 3670, 3588, 1653, 1635, 1490, 1347, 1259, 1172, 1036, 1024 cm^{-1}; LRMS (EI+) calc'd $[M–OTf]^+$ 359.0, found 359.0.

(3-bromophenyl)(*p*-xylyl)iodonium triflate (SI-5)



SI-5

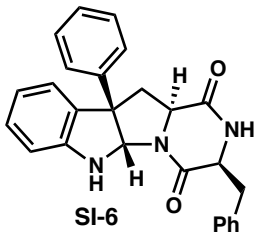
Prepared by *General Procedure III* from 3-bromophenyl boronic acid on 5.00 mmol scale. Trituration from Et_2O afforded **SI-5** as a white, crystalline solid (1.33 g, 2.48 mmol, 50% yield). ^1H NMR (500 MHz, DMSO-d_6) δ 8.53 (dd, J = 1.8, 1.8 Hz, 1H), 8.28 (dd, J = 1.8, 0.9 Hz, 1H), 8.18 (ddd, J = 8.0, 1.8, 0.9 Hz, 1H), 7.85 (ddd, J = 8.1, 1.9, 0.9 Hz, 1H), 7.51 - 7.42 (m, 2H), 7.44 - 7.38 (m, 1H), 2.57 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 139.2, 137.5, 137.1, 136.7, 134.9, 133.9, 133.6, 133.5, 131.1, 123.3, 121.2, 116.1, 24.5, 20.0; FTIR (NaCl, thin film): 3074, 1569, 1554, 1490, 1456, 1275, 1242, 1170, 1025 cm^{-1}; LRMS (EI+) calc'd $[M–OTf]^+$ 388.1, found 388.9.

V. Optimization of Reaction Parameters

Optimization Procedure – In a glovebox, $(CuOTf)_2$•PhMe (20.7 mg, 0.040 mmol), and ligand (0.088 mmol) were dissolved in anhydrous CH_2Cl_2 (4.0 mL). The solution was stirred vigorously for 1.0 h, filtered through a plug of cotton and removed from the glovebox. A portion of the solution (1.00 mL, 0.020 mmol, 20 mol % in Cu) was added to an oven-dried, 1-dram vial containing diketopiperazine (0.100 mmol) and diaryliodonium salt (0.110 mmol). The solution was stirred at 23 °C (care was taken not to exceed 25 °C) for 24 h, then quenched by the addition of concentrated ammonia (28–30% in H_2O, 1.0 mL). After 5 minutes, the mixture was diluted with EtOAc (30 mL) and washed with a mixture water (20 mL) and brine (20 mL). The aqueous layer was then back extracted with EtOAc (2 x 10 mL) and the combined organics dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford a solid residue.

The residue was then dissolved in a standard solution of maleic acid in DMSO-d_6, and the solution analyzed for yield, C3:C2 ratio, and dr. NMR yields were obtained via careful integration against the standard.

Preparation of minor diastereomer SI-6



SI-6

To an oven dried vial was added diketopiperazine **4a** (33 mgs, 0.1 mmol), diaryliodonium hexafluorophosphate (47 mgs, 0.11 mmol) and $(CuOTf)_2$•PhMe (5.2 mgs, 0.01 mmol). The solids were dissolved in 1 mL CH_2Cl_2 and the reaction was allowed to stir for 24 hours, then quenched by the addition of 1 mL NH_4OH. The mixture was diluted with EtOAc and extracted with EtOAc (2 X 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The minor diastereomer was purified from the crude residue by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **SI-6** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) 7.30 – 7.27 (m, 2H), 7.26 – 7.22 (m, 3H), 7.22 – 7.16 (m, 3H), 7.15 – 7.09 (m, 2H), 7.04 (ddd, J = 7.7, 7.7, 1.3 Hz, 1H), 6.88 – 6.83 (m, 1H), 6.67 (ddd, J = 7.5, 7.5, 1.0 Hz, 1H), 6.61 (d, J = 7.8 Hz, 1H), 5.77 (s, 1H), 5.69 (d, J = 9.3 Hz, 1H), 4.40 – 4.32 (m, 1H), 4.16 (ddd, J = 10.5, 3.8, 1.3 Hz, 1H), 3.51 (dd, J = 14.5, 3.8 Hz, 1H), 3.15 (dd, J = 13.7, 7.3 Hz, 1H), 2.69 (ddd, J = 16.6, 14.1, 10.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) 168.8, 166.8, 147.2, 142.3, 135.6, 133.3, 129.2, 128.9, 128.8, 128.6, 127.5, 127.3, 126.5, 124.1, 119.6, 109.6, 85.5, 59.2, 58.6, 56.1, 38.6, 36.2; FTIR (NaCl, thin film): 3306, 3058, 2929, 1674, 1607, 1482, 1447, 1318, 1223, 1071 cm^{-1}; $[\alpha]_D^{25}$ = –329 (c = 0.31, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 410.2, found 410.2.

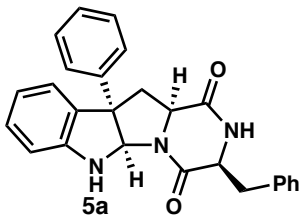
VI. Substrate Scope – Characterization Data

General Procedure IV: Tryptophan Arylation

Catalyst Preparation – In a glovebox, copper(I)trifluoromethanesulfonate toluene complex (0.10 equiv) and alpha-diimine-ligand (0.22 equiv) were dissolved in anhydrous CH_2Cl_2 (0.1 M in Cu). The solution was vigorously stirred for 1.0 hour, and then filtered through a plug of cotton.[13] The solution was then removed from the glovebox for immediate use.

Arylation Reaction – A flame-dried flask containing a magnetic stirbar was charged with tryptophan substrate (0.300 mmol, 1.00 equiv) and diaryliodonium salt (0.330 mmol, 1.1 equiv), then equipped with a rubber septum. To the solids was added the freshly-prepared Cu-catalyst solution prepared above (3.00 mL, 0.030 mmol, 20 mol %) and the solution vigorously stirred at 20 °C. After the time indicated below, the solution was quenched with aqueous ammonia (3.00 mL of a 27-33% solution in H_2O) and stirred for 5 minutes. The reaction was then diluted with EtOAc (30 mL) and washed with a mixture of H_2O (30 mL) and brine (30 mL). The aqueous portion was back extracted with EtOAc (2 x 10 mL) and the combined organics dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to afford pure aryl pyrroloindoline product, typically as either a white, amorphous powder or a white foam.

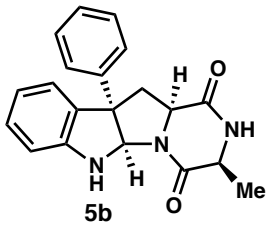
Pyrroloindoline 5a



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and diphenyliodonium triflate. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **5a** as a white solid (104.0 mg, 0.254 mmol, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 6H), 7.28 (ddd, *J* = 5.1, 2.3, 2.3 Hz, 2H), 7.20 (d, *J* = 7.0 Hz, 2H), 7.12 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H), 6.97 – 6.89 (m, 1H), 6.75 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 5.85 (s, 1H), 5.60 (s, 1H), 4.44 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.24 (ddd, *J* = 10.7, 3.7, 1.1 Hz, 1H), 3.61 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.23 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.77 (ddd, *J* = 13.6, 10.2, 2.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 166.8, 147.1, 142.3, 135.6, 133.3, 129.3, 128.9, 128.9, 128.7, 127.6, 127.6, 126.5, 124.2, 119.7, 109.7, 85.5, 59.3, 58.7, 56.2, 38.6, 36.3; FTIR (NaCl, thin film): 3315, 3087, 3052, 3027, 2928, 2849, 1676, 1605, 1498, 1407, 1348, 1306, 1261, 1221 cm^{-1}; $[\alpha]_D^{25}$ = +113 (*c* = 1.8, $CHCl_3$); LRMS (EI+) calc'd $[M+H]^+$ 410.2, found 410.2.

[13] Filtering the catalyst solution was found to improve the overall selectivity, reactivity, and reproducibility of the reaction.

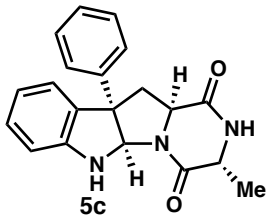
Pyrroloindoline 5b



5b

Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and diphenyliodonium triflate for 24 h. Reaction was run with additional CH_2Cl_2 (3.00 mL) for solubility. The crude residue was purified by silica gel chromatography (20% hexanes : 77.5% ethyl acetate: 2.5% methanol) to afford **5b** as a white solid (66.2 mg, 0.199 mmol, 66% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.32 – 7.26 (m, 1H), 7.09 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 7.5, 7.5 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.82 (d, *J* = 8.3 Hz, 1H), 5.79 (s, 1H), 4.48 (dd, *J* = 8.3, 8.3 Hz, 1H), 4.15 – 4.05 (m, 1H), 3.21 (dd, *J* = 13.8, 7.6 Hz, 1H), 2.84 (dd, *J* = 13.8, 9.3 Hz, 1H), 1.46 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 167.9, 147.2, 142.3, 133.2, 128.9, 128.7, 127.4, 126.5, 124.2, 119.7, 109.8, 85.5, 59.4, 59.0, 51.3, 38.3, 15.7; FTIR (NaCl, thin film): 3255, 2928, 2849, 1669, 1653, 1486, 1419, 1219 cm^{-1}; $[\alpha]_D^{25}$ = +158 (*c* = 0.85, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 334.2, found 334.1.

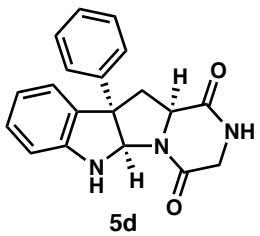
Pyrroloindoline 5c



5c

Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and diphenyliodonium triflate for 24 h. Reaction was run with additional CH_2Cl_2 (3.00 mL) for solubility. The crude residue was purified by silica gel chromatography (77.5% ethyl acetate, 20% hexanes, 2.5% methanol) to afford **5c** as a white solid (49.5 mg, 0.149 mmol, 50% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.31 – 7.26 (m, 1H), 7.09 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 7.01 (d, *J* = 3.8 Hz, 1H), 6.88 (dd, *J* = 7.4, 0.5 Hz, 1H), 6.72 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 5.84 (d, *J* = 3.0 Hz, 1H), 5.54 (d, *J* = 3.0 Hz, 1H), 4.43 (dd, *J* = 10.6, 7.0 Hz, 1H), 4.01 (qd, *J* = 7.2, 4.2 Hz, 1H), 3.29 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.65 (dd, *J* = 13.7, 10.7 Hz, 1H), 1.46 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 167.9, 147.1, 142.2, 133.6, 128.9, 128.7, 127.3, 126.7, 124.0, 119.5, 109.6, 86.0, 58.8, 57.2, 53.6, 39.4, 19.8; FTIR (NaCl, thin film): 3275, 3042, 2913, 1684, 1652, 1437, 1308, 1266, 1221 cm^{-1}; $[\alpha]_D^{25}$ = +119 (*c* = 1.1, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 334.2, found 334.1

Pyrroloindoline 5d



5d

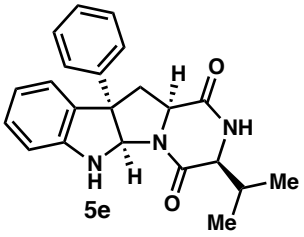
Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and diphenyliodonium triflate for 24 h. Reaction was run with additional CH_2Cl_2 (3.00 mL) for solubility. The crude residue was purified by silica gel chromatography (77.5% ethyl acetate, 20% hexane, 2.5% methanol) to afford **5d** as a white solid (61.5 mg, 0.193 mmol, 64% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 4H), 7.29 – 7.26 (m, 1H), 7.09 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 6.96 – 6.90 (m, 1H), 6.86 (d, *J* = 4.2 Hz, 1H), 6.73 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.81 (s, 1H), 4.43 (dd, *J* = 8.5, 8.5 Hz, 1H), 4.02 (dd, *J* = 17.0, 1.6 Hz,

1H), 3.85 (dd, *J* = 17.0, 4.6 Hz, 1H), 3.23 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.77 (dd, *J* = 13.8, 9.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 165.2, 147.1, 142.3, 133.3, 128.9, 128.7, 127.3, 126.5, 124.2, 119.7, 109.8, 85.4, 59.2, 58.0, 46.7, 38.7; FTIR (NaCl, thin film): 3280, 3047, 2928, 2854, 1674, 1602, 1483, 1441, 1310, 1263, 1219, 1155 cm^{-1}; $[\alpha]_D^{25}$ = +80.2 (*c* = 0.59, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 320.1, found 320.1.

Pyrroloindoline 5e

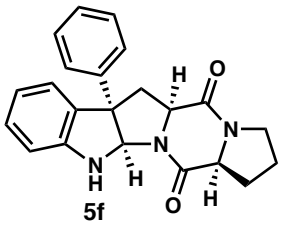
Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and diphenyliodonium triflate for 24 h. The crude residue was purified by silica gel chromatography (20% hexanes, 77.5% ethyl acetate, 2.5% methanol) to afford **5e** as a white solid (55.5 mg, 0b.154 mmol, 51% yield).



5e

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 7.11 – 7.06 (m, 1H), 6.96 – 6.92 (m, 1H), 6.73 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.66 – 6.62 (m, 1H), 5.87 (s, 1H), 5.80 (d, *J* = 2.6 Hz, 1H), 5.44 (d, *J* = 2.4 Hz, 1H), 4.47 – 4.39 (m, 1H), 3.91 – 3.87 (m, 1H), 3.23 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.79 (dd, *J* = 13.7, 9.7 Hz, 1H), 2.60 (heptd, *J* = 7.1, 2.6 Hz, 1H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 166.7, 147.3, 142.4, 133.3, 128.9, 128.6, 127.3, 126.5, 124.3, 119.6, 109.5, 85.5, 60.4, 59.1, 58.2, 38.8, 28.4, 19.3, 16.0; FTIR (NaCl, thin film): 3292, 2964, 1669, 1609, 1483, 1465, 1419, 1347, 1291, 1222 cm^{-1}; $[\alpha]_D^{25}$ = +107 (*c* = 0.52, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 362.2, found 362.2.

Pyrroloindoline 5f

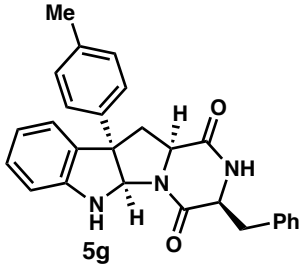


5f

Prepared following *General Procedure IV* using 40 mol % $^{t\text{-}Bu}DAB_{Me}$ and diphenyliodonium hexafluorophosphate for 4 h. The crude residue was purified by silica gel chromatography (77.5% ethyl acetate, 20% hexanes, 2.5% methanol) to afford **5f** as a white solid (76.6 mg, 0.213 mmol, 71% yield).

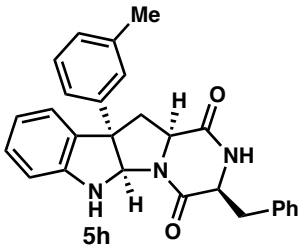
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 - 7.34 (m, 4H), 7.31 - 7.27 (m, 1H), 7.08 (ddd, *J* = 7.9, 7.5, 1.3 Hz, 1H), 6.91 (ddd, *J* = 7.5, 1.3, 0.6 Hz, 1H), 6.73 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.67 - 6.61 (m, 1H), 5.83 (s, 1H), 5.36 (s, 1H), 4.55 - 4.48 (m, 1H), 4.14 (ddd, *J* = 9.1, 7.3, 1.6 Hz, 1H), 3.54 - 3.46 (m, 2H), 3.21 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.81 (dd, *J* = 13.9, 9.8 Hz, 1H), 2.31 (dddd, *J* = 12.8, 7.0, 7.0, 3.4 Hz, 1H), 2.17 (dddd, *J* = 12.9, 10.7, 9.2, 7.2 Hz, 1H), 2.07 - 1.96 (m, 1H), 1.90 (dddd, *J* = 14.9, 6.8, 4.0, 1.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 165.7, 147.0, 142.3, 133.6, 128.8, 128.8, 128.6, 127.3, 126.7, 124.1, 119.7, 109.7, 85.3, 60.5, 60.3, 59.9, 45.2, 38.1, 27.6, 23.2; FTIR (NaCl, thin film): 3330, 2952, 2878, 1665, 1607, 1484, 1467, 1423, 1340, 1313, 1219, 1154, 1068 cm^{-1}; $[\alpha]_D^{25}$ = +108 (*c* = 0.63, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 360.2, found 360.2.

Pyrroloindoline 5g



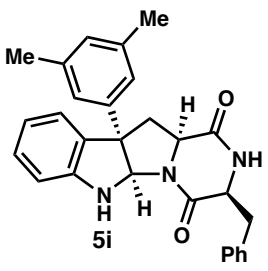
Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and di(*p*-tolyl)iodonium triflate for 32 h. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **5g** as a white solid (98.2 mg, 0.232 mmol, 77% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.28 (ddd, *J* = 4.7, 1.9, 1.9 Hz, 1H), 7.24 – 7.18 (m, 4H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.11 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 6.93 – 6.89 (m, 1H), 6.74 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 5.84 (d, *J* = 2.9 Hz, 1H), 5.56 (s, 1H), 5.43 (d, *J* = 2.8 Hz, 1H), 4.48 – 4.38 (m, 1H), 4.23 (ddd, *J* = 10.8, 3.7, 1.3 Hz, 1H), 3.61 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.21 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.74 (ddd, *J* = 18.4, 14.1, 10.4 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 166.8, 147.1, 139.3, 137.1, 135.6, 133.5, 129.5, 129.3, 128.9, 128.6, 127.6, 126.4, 124.1, 119.7, 109.6, 85.6, 59.0, 58.7, 56.2, 38.7, 36.3, 20.9; FTIR (NaCl, thin film): 3315, 3027, 2923, 2859, 1686, 1602, 1412, 1343, 1308, 1219 cm^{-1}; $[\alpha]_D^{25}$ = +208 (*c* = 0.61, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 424.2, found 424.2.

Pyrroloindoline 5h



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and di(*m*-tolyl)iodonium triflate for 4 h. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **5h** as a white solid (119.0 mg, 0.280 mmol, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.1 Hz, 2H), 7.16 – 7.07 (m, 4H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.74 (dd, *J* = 13.8, 6.3 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 5.87 (d, *J* = 2.9 Hz, 1H), 5.60 (s, 1H), 5.46 (d, *J* = 2.7 Hz, 1H), 4.49 – 4.39 (m, 1H), 4.24 (dd, *J* = 10.8, 2.7 Hz, 1H), 3.61 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.23 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.81 – 2.68 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 166.8, 147.1, 142.2, 138.6, 135.6, 133.4, 129.3, 128.9, 128.7, 128.6, 128.1, 127.6, 127.2, 124.1, 123.6, 119.6, 109.6, 85.5, 59.2, 58.7, 56.2, 38.7, 36.3, 21.6; FTIR (NaCl, thin film): 3385, 3270, 3032, 2918, 2839, 1676, 1602, 1409, 1350, 1313, 1234, 1197 cm^{-1}; $[\alpha]_D^{25}$ = +169 (*c* = 0.81, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 424.2, found 424.2.

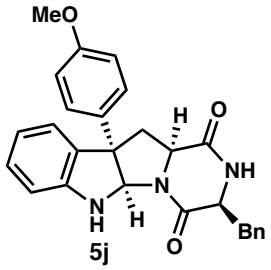
Pyrroloindoline 5i



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and bis(3,5-dimethylphenyl)iodonium triflate for 4 h. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **5i** as a white solid (119.4 mg, 0.273 mmol, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.37 – 7.31

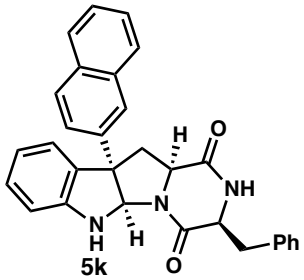
(m, 2H), 7.30 – 7.26 (m, 1H), 7.23 – 7.18 (m, 2H), 7.14 – 7.09 (m, 1H), 6.97 – 6.94 (m, 2H), 6.94 – 6.90 (m, 2H), 6.74 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.71 – 6.65 (m, 1H), 5.88 (d, *J* = 2.9 Hz, 1H), 5.61 (s, 1H), 5.44 (d, *J* = 2.8 Hz, 1H), 4.43 (ddd, *J* = 9.8, 7.1, 1.0 Hz, 1H), 4.24 (ddd, *J* = 10.8, 3.7, 1.4 Hz, 1H), 3.62 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.23 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.77 (dd, *J* = 14.5, 10.8 Hz, 1H), 2.68 (dd, *J* = 13.7, 10.1 Hz, 1H), 2.30 (d, *J* = 0.4 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) 168.9, 166.7, 147.1, 142.1, 138.4, 135.7, 133.5, 129.3, 129.0, 128.9, 128.5, 127.6, 124.4, 124.1, 119.6, 109.6, 85.5, 59.1, 58.7, 56.2, 38.8, 36.3, 21.4; FTIR (NaCl, thin film): 3288, 3051, 2919, 2854, 1684, 1604, 1484, 1455, 1418, 1346, 1312, 1255, 1204, 1156, 1109 cm^{-1}; $[\alpha]_D^{25}$ = +101 (*c* = 2.0, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 438.2, found 438.2.

Pyrroloindoline 5j



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ using di(*p*-methoxyphenyl)iodonium triflate for 42 h. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **5j** as a white solid (88.1 mg, 0.200 mmol, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.36 – 7.30 (m, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.27 – 7.23 (m, 2H), 7.20 (d, *J* = 7.0 Hz, 2H), 7.11 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H), 6.91 (dd, *J* = 7.4, 0.7 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.74 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 5.81 (s, 1H), 5.57 (s, 1H), 4.48 – 4.40 (m, 1H), 4.24 (ddd, *J* = 10.8, 3.7, 1.2 Hz, 1H), 3.79 (s, 3H), 3.61 (dd, *J* = 14.5, 3.5 Hz, 1H), 3.18 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.74 (ddd, *J* = 20.3, 14.1, 10.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) 168.9, 166.8, 158.7, 147.1, 135.6, 134.2, 133.5, 129.3, 128.9, 128.6, 127.7, 127.6, 124.1, 119.7, 114.2, 109.7, 85.7, 58.8, 58.7, 56.2, 55.3, 38.7, 36.3; FTIR (NaCl, thin film): 3309, 3052, 2938, 2839, 1684, 1653, 1609, 1513, 1457, 1419, 1312, 1251, 1183, 1032 cm^{-1}; $[\alpha]_D^{25}$ = +70 (*c* = 0.80, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 440.2, found 440.2.

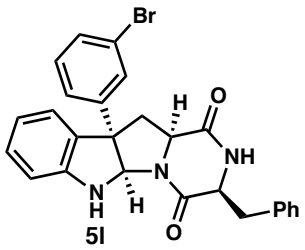
Pyrroloindoline 5k



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and (2-naphthyl)(*p*-xylyl)iodonium triflate for 42 h. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **5k** as a white solid (113.0 mg, 0.246 mmol, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.85 – 7.78 (m, 4H), 7.54 – 7.45 (m, 2H), 7.38 (ddd, *J* = 11.4, 3.9, 3.9 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 7.23 – 7.18 (m, 2H), 7.14 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H), 6.93 (dd, *J* = 7.4, 0.9 Hz, 1H), 6.78 – 6.68 (m, 2H), 5.98 (s, 1H), 5.59 (s, 1H), 5.50 (s, 1H), 4.57 – 4.49 (m, 1H), 4.25 (ddd, *J* = 10.8, 3.7, 1.3 Hz, 1H), 3.62 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.39 (ddd, *J* = 16.0, 8.0, 8.0 Hz, 1H), 2.80 (ddd, *J* = 14.4, 12.1, 10.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 166.7, 147.2, 139.2, 135.6, 133.3, 133.0, 132.4, 129.3, 129.0, 128.9, 128.8, 128.0, 127.6, 127.5, 126.6, 126.4,

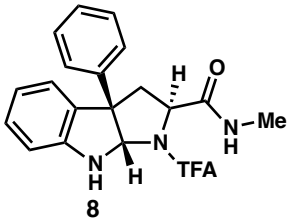
125.5, 124.3, 124.2, 119.7, 109.7, 85.4, 59.5, 58.8, 56.2, 38.5, 36.3; FTIR (NaCl, thin film): 3330, 3052, 2918, 1676, 1605, 1483, 1409, 1343, 1303 cm^{-1}; $[\alpha]_D^{25}$ = +237 (*c* = 0.57, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 460.2, found 460.2.

Pyrroloindoline 5l



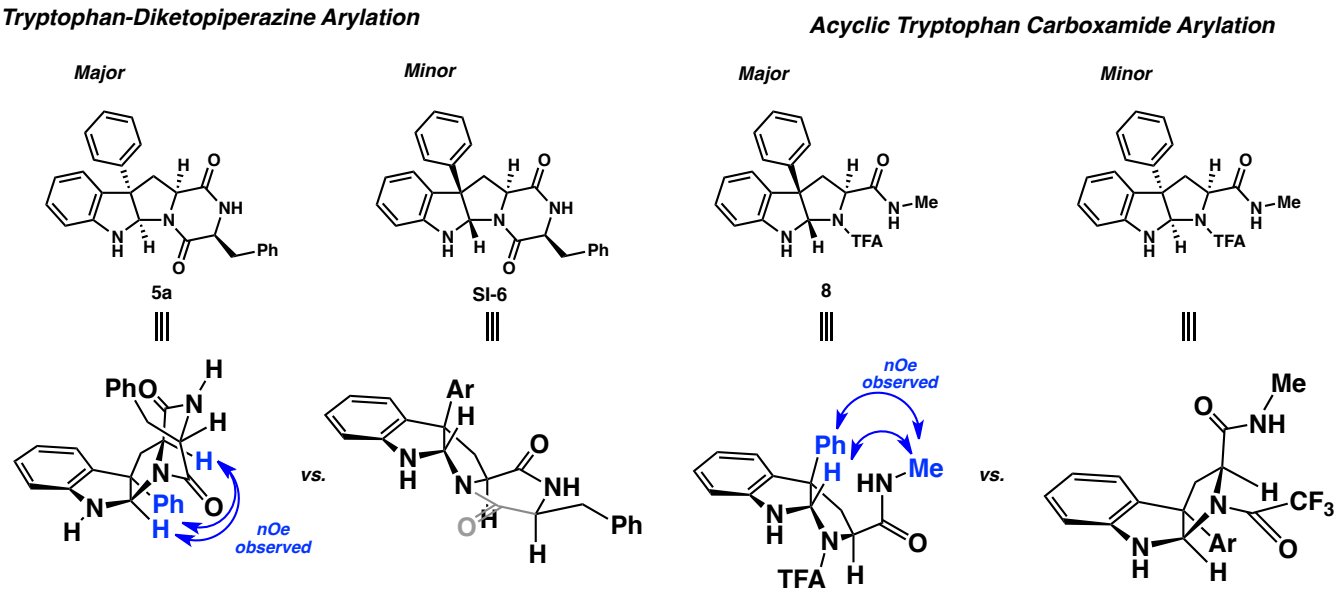
Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and (3-bromophenyl)(*p*-xylyl)iodonium triflate for 42 h. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **5l** as a white solid (79.3 mg, 0.163 mmol, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.48 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.33 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.30 – 7.25 (m, 2H), 7.24 – 7.18 (m, 3H), 7.13 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.76 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 5.79 (d, *J* = 1.3 Hz, 1H), 5.59 (s, 1H), 5.50 (s, 1H), 4.42 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.25 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.60 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.15 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.78 (ddd, *J* = 18.5, 14.2, 10.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) 168.6, 166.9, 147.1, 144.8, 135.5, 132.5, 130.6, 130.4, 129.6, 129.3, 129.0, 128.9, 127.6, 125.3, 124.2, 123.1, 119.9, 109.9, 85.4, 59.1, 58.5, 56.2, 38.5, 36.2; FTIR (NaCl, thin film): 3315, 3057, 2933, 2864, 1679, 1612, 1560, 1482, 1412, 1343, 1313, 1221 cm^{-1}; $[\alpha]_D^{25}$ = +91.4 (*c* = 2.8, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 488.1, found 488.1.

Pyrroloindoline 8



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and diphenyliodonium triflate for 3 h. The crude residue was purified by silica gel chromatography (60% hexanes, 37.5% ethyl acetate, 2.5% methanol) to afford **8** as a white solid (94.6 mg, 0.243 mmol, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.55 (d, *J* = 2.9 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.30 – 7.27 (m, 1H), 7.27 – 7.23 (m, 1H), 7.23 – 7.18 (m, 3H), 6.96 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.17 (d, *J* = 2.8 Hz, 1H), 4.63 (d, *J* = 2.3 Hz, 1H), 4.25 (ddd, *J* = 12.6, 4.2, 4.2 Hz, 1H), 3.24 (dd, *J* = 12.6, 4.1 Hz, 1H), 3.07 (s, 3H), 2.48 (dd, *J* = 12.6, 12.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) 169.0, 156.9 (q, $J_{C\text{-}F}$ = 37.6 Hz), 148.0, 144.9, 130.1, 129.4, 128.9, 127.5, 125.9, 125.3, 120.9, 115.5 (q, $J_{C\text{-}F}$ = 287.7 Hz), 110.3, 83.8, 53.4, 49.1, 35.9, 33.3; FTIR (NaCl, thin film): 3361, 3057, 2937, 1718, 1653, 1608, 1559, 1487, 1469, 1320, 1268, 1216, 1187, 1163, 1058, 1034 cm^{-1}; $[\alpha]_D^{25}$ = +215 (*c* = 1.3, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 390.1, found 390.1.

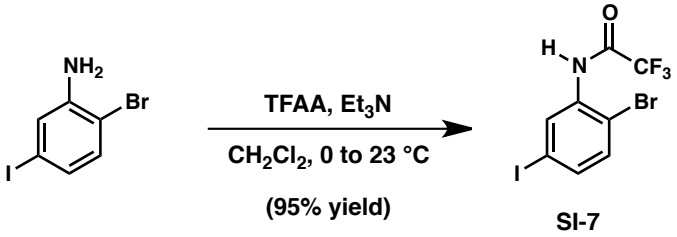
VII. Stereochemical Assignment of Tryptophan Arylation



The stereochemical assignment of the pyrroloindole products was assigned by ^{1}H, ^{13}C, COSY, HSQC, HMBC, and NOESY 2D experiments on L-Trp-L-Phe derived pyrroloindoline **5a** and assigned by spectroscopic analogy for pyrroloindoles **5b-f**. Acyclic tryptophan-derived carboxamide **8** was independently analyzed by ^{1}H, ^{13}C, COSY, HSQC, HMBC, and NOESY 2D experiments and found to arylate from the opposite face of the prochiral indole moiety. Selected NOESY 2D data is included in Supporting Information 2 (Spectral Data).

VIII. Total Synthesis of (+)-Naseseazines A and B

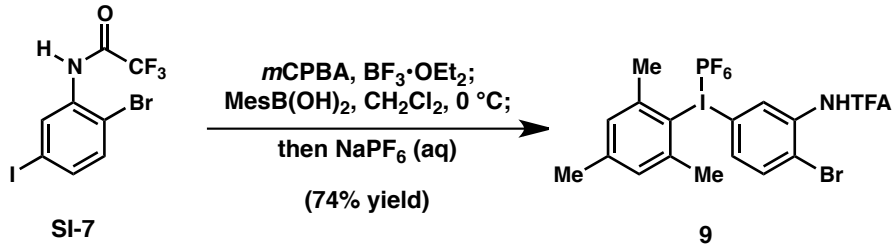
Preparation of *N*-**(2-bromo-5-iodophenyl)-2,2,2-trifluoroacetamide (SI-7)**



SI-7

To a solution of 2-bromo-5-iodoaniline (14.9 g, 50.0 mmol, 1.0 equiv) in CH_2Cl_2 (250 mL) was added Et_3N (10.4 mL, 75.0 mmol, 1.50 equiv). The solution was cooled to 0 °C and trifluoroacetic anhydride (7.8 mL, 55.0 mmol, 1.10 equiv) added dropwise by syringe. The solution was stirred for 30 minutes and slowly warmed to 23 °C and stirring continued for 4 hours. The reaction was then quenched by the addition of 0.5 N HCl (150 mL), and the reaction washed with 0.5 N HCl (2 x 100 mL). The combined organics were then back extracted with Et_2O (100 mL), and the organics dried over Na_2SO_4, filtered, and concentrated in vacuo to afford pure 2-bromo-5-iodotrifluoroacetanilide as a white fluffy solid (18.8 g, 47.7 mmol, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, *J* = 2.0 Hz, 1H), 8.37 (s, 1H), 7.42 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.58 (q, *J* = 38.0 Hz), 136.2, 134.0, 133.7, 130.5, 115.3 (q, *J* = 288.7 Hz), 113.8, 93.0; IR (NaCl, thin film): 3267, 3081, 1709, 1574, 1529, 1459, 1395, 1260, 1186, 1165, 1034 cm^{-1}; LRMS (EI+) calc'd for $[M+H]^+$ 393.9, found 393.9.

Preparation of (3-trifluoroacetamido-4-bromophenyl)(mesityl)iodonium hexafluorophosphate (9)

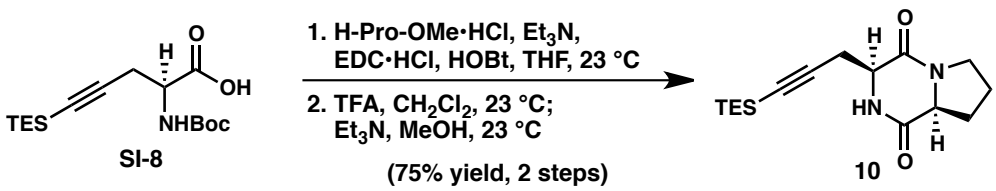


SI-7 **9**

To a solution of 2-bromo-5-iodotrifluoroacetanilide **SI-7** (11.8 g, 30.0 mmol, 1.00 equiv) in CH_2Cl_2 (120 mL) was added *m*CPBA (80%, 7.15 g, 33.0 mmol, 1.10 equiv). The solution was stirred for 5 minutes, then BF_3•OEt_2 (9.26 mL, 75.0 mmol, 2.50 equiv) was added dropwise by syringe to afford a bright orange solution. After 45 minutes, the solution was cooled to 0 °C and 2,4,6-trimethylphenylboronic acid (5.41 g, 33.0 mmol, 1.10 equiv) added in a single portion. The mixture was stirred for an additional 15 minutes, warmed to 23 °C over 15 minutes, then stirred for an additional 20 minutes at room temperature. Saturated aqueous $NaPF_6$ (150 mL) was added to the solution, and the heterogeneous mixture stirred vigorously for 1 h. The solution was diluted with CH_2Cl_2 (100 mL) and H_2O (150 mL), the layers separated, and the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). The

combined organics were then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a thick oil. The oil was co-evaporated once from Et_2O (100 mL), and diluted with Et_2O (500 mL). The clear supernatant was decanted and the residual oil co-evaporated from Et_2O (200 mL), resulting in precipitation. The resulting solid was suspended in Et_2O (500 mL) and cooled in an ice-bath for 20 minutes, then collected by vacuum filtration and dried under high vacuum (<1 mTorr) for 15 h to afford diaryliodonium hexafluorophosphate **10** as an off-white, powdery solid (14.6 g, 22.2 mmol, 74 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.53 (s, 1H), 8.24 (d, J = 1.8 Hz, 1H), 7.91 (dd, J = 8.6, 1.9 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.27 – 7.21 (m, 2H), 2.62 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.9 (q, J = 37.6 Hz), 143.8, 142.1, 136.5 (d, J = 13.8 Hz), 135.7 (d, J = 35.8 Hz), 130.4, 126.0, 123.4, 116.3 (q, J = 288.2 Hz), 113.2 , 26.8, 21.0; FTIR (NaCl, thin film): 3365, 3092, 2926, 1735, 1582, 1523, 1457, 1405, 1267, 1204, 1157, 1031 cm^{-1}; LRMS (EI+) calc'd $[M–PF_6]^+$ 511.9, found 511.9.

Preparation of Diketopiperazine 10



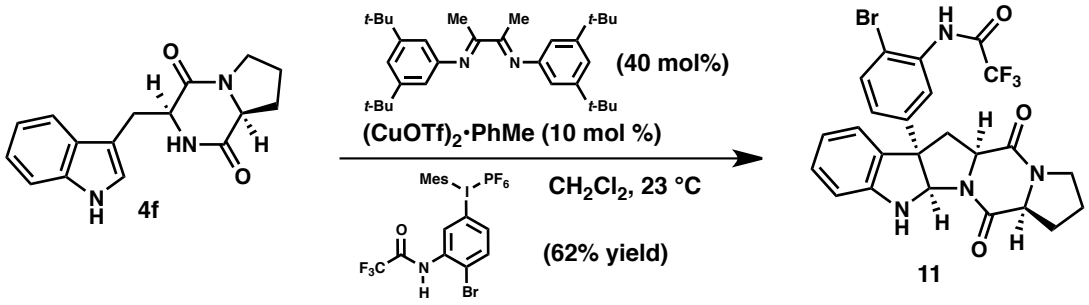
To a solution of freshly prepared acid[14] (**SI-8**) (4.75 g, 14.5 mmol, 1.00 equiv) in THF (0.4 M, 240 mL) at 0 °C was added EDC•HCl (3.34 g, 17.4 mmol, 1.20 equiv), anhydrous HOBt (2.74 g, 20.3 mmol, 1.40 equiv) and Et_3N (4.5 mL, 32 mmol, 2.2 equiv). The mixture was then stirred for 5 minutes, and *L*- proline methyl ester hydrochloride (2.89 g, 17.4 mmol, 1.20 equiv) was added. The reaction was slowly warmed to 23 °C over 2 hours and stirring continued for 20 hours. The reaction was then quenched with 1 N HCl (500 mL) and extracted with EtOAc (3 x 250 mL), then the combined organics washed with saturated aqueous $NaHCO_3$ (500 mL), and aqueous layer back extracted with EtOAc (200 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford crude dipeptide as a viscous oil.

The residue was then dissolved in CH_2Cl_2 (100 mL), and trifluoroacetic acid (30 mL) was added dropwise by addition funnel at room temperature over 10 minutes. Stirring was continued for 20 minutes, then the solution diluted with toluene (100 mL) and the mixture concentrated in vacuo to afford a thick oil. The residue was then redissolved in MeOH (75 mL) and the mixture cooled to 0 °C. Et_3N (55 mL) was then added dropwise the stirring solution over 10 minutes by addition funnel. Upon completion of the addition, the cooling bath was removed and the reaction was warmed to 23 °C over 1 h. After an additional 3 h at room temperature, the solution

[14] Newhouse, T., Lewis, C. A., & Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 6360.

was concentrated, the crude residue dissolved in Et_2O (500 mL), and the solution washed with water (2 x 500 mL). The organic layers were back extracted with Et_2O (250 mL), and the combined organic layers washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford a yellow oil. The residue was purified by silica gel flash chromatography (5% MeOH in EtOAc) to afford diketopiperazine **11** as a white solid (3.32 g, 10.8 mmol, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (s, 1H), 4.17 – 4.10 (m, 2H), 3.65 – 3.57 (m, 1H), 3.53 (ddd, *J* = 12.0, 8.9, 3.2 Hz, 1H), 3.10 (dd, *J* = 17.5, 3.6 Hz, 1H), 2.58 (dd, *J* = 17.5, 10.5 Hz, 1H), 2.43 – 2.32 (m, 1H), 2.14 – 1.97 (m, 2H), 1.97 – 1.83 (m, 1H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 163.9, 101.9, 86.6, 59.3, 53.9, 45.4, 28.4, 22.6, 22.5, 7.4, 4.3; FTIR (NaCl, thin film): 3233, 2954, 2908, 2873, 2176, 1675, 1457, 1417, 1338, 1306, 1018 cm^{-1}; $[\alpha]_D^{25}$ = –108 (*c* = 0.93, $CHCl_3$); HRMS (MM) calc'd for $[M+H]^+$ 307.1836, found 307.1839.

Preparation of Pyrroloindoline 12

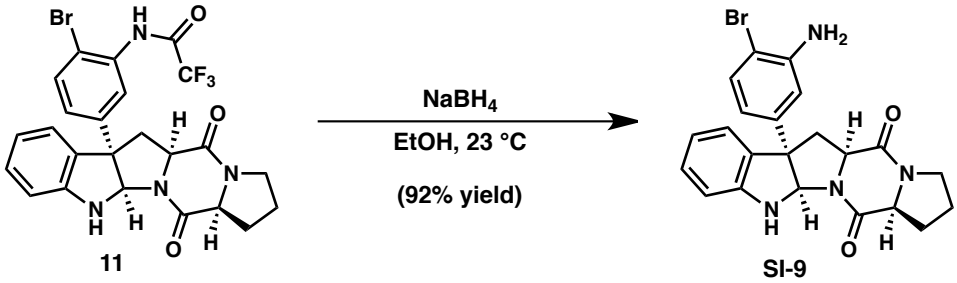


In a glovebox, $Cu(OTf)_2$•PhMe (310 mg, 0.600 mmol) and $^{tBu}DAB_{Me}$ (1.10 g, 2.40 mmol) were added to an oven-dried, 200 mL round-bottomed flask. Anhydrous CH_2Cl_2 (60.0 mL) was then added by syringe, and the resulting deep-purple solution was stirred for 1 h at 25 °C in the glovebox. The solution was then filtered through a tight plug of cotton, and the resulting solution removed from the glovebox.

To a flame-dried, 1-liter round-bottomed flask was charged cyclo-L-Pro-L-Trp **4f** (1.50 g, 5.30 mmol, 1.00 equiv), (4-bromo-3-trifluoroacetamidophenyl)mesityliodonium hexafluorophosphate (4.19 g, 6.36 mmol, 1.20 equiv) in anhydrous CH_2Cl_2 (480 mL). The solution was stirred at 23 °C for 10 minutes, then cooled to 15 °C in a cold water bath. To the flask was then added the freshly prepared catalyst solution of $Cu^I(^{tBu}DAB_{Me})$ (53.0 mL, 1.06 mmol, 0.20 equiv) dropwise over 20 minutes. The deep-purple solution was allowed to warm to 23 °C over 2 hours, then stirred for 20 hours at 23 °C by which time the solution had turned to a deep red. The solution was then quenched by the addition of aqueous ammonium hydroxide (1.8 M, 500 mL). The mixture was transferred to a separatory funnel, vigorously shaken, and the layers partitioned. The aqueous layer was then back extracted with EtOAc (2 x 100 mL), and the combined organic layers dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Repeated silica gel chromatography (5% MeOH, 25% Hexanes, 70% EtOAc) afforded aryl pyrroloindoline **13** as an amorphous white solid (1.79 g, 3.26 mmol, 62% yield).

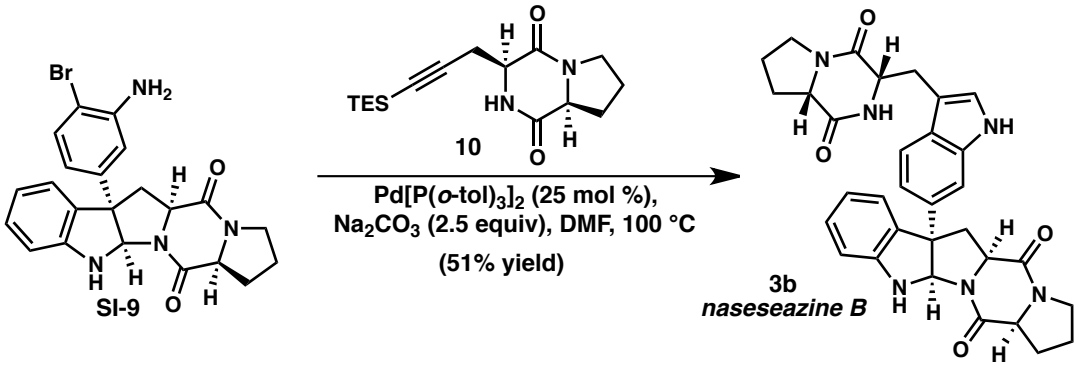
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.42 (d, *J* = 2.3 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.10 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.97 (ddd, *J* = 7.6, 1.2, 0.5 Hz, 1H), 6.76 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.64 (ddd, *J* = 7.8, 0.8, 0.8 Hz, 1H), 5.73 (s, 1H), 4.59 - 4.51 (m, 1H), 4.20 - 4.11 (m, 1H), 3.51 - 3.40 (m, 2H), 3.09 (dd, *J* = 14.0, 7.9 Hz, 1H), 2.96 (dd, *J* = 14.0, 8.9 Hz, 1H), 2.30 (dddd, *J* = 12.9, 7.0, 7.0, 3.5 Hz, 1H), 2.15 (dddd, *J* = 13.0, 10.5, 9.0, 7.2 Hz, 1H), 2.02 - 1.93 (m, 1H), 1.88 (ddddd, *J* = 17.2, 10.5, 8.6, 4.3, 4.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 165.4, 154.8 (q, $J_{C\text{-}F}$ = 38.0 Hz), 147.2, 144.1, 133.5, 132.8, 132.0, 129.0, 125.9, 124.2, 120.0, 119.9, 115.46 (q, $J_{C\text{-}F}$ = 288.7 Hz), 112.8, 110.0, 85.0, 60.5, 60.1, 59.8, 45.2, 38.1, 27.5, 23.3; FTIR (NaCl, thin film): 3270, 1733, 1683, 1586, 1539, 1485, 1467, 1418, 1312, 1245, 1198, 1162 cm^{-1}; $[\alpha]_D^{25}$ = +67.8 (*c* = 1.8, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 549.1, found 549.1.

Preparation of Aniline SI-9:



To a solution of pyrroloindoline **12** (150 mg, 0.273 mmol, 1.00 equiv) in EtOH at 23 °C was added $NaBH_4$ (77.0 mg, 2.02 mmol, 7.4 equiv). The solution was stirred vigorously for 1 h, then cooled to 0 °C and slowly quenched with saturated aqueous ammonium chloride (5 mL). The mixture was then diluted with H_2O (50 mL) and extracted with EtOAc (3 x 25 mL). The combined organics were then dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude residue by flash silica gel chromatography (75% EtOAc, 20% Hexanes, 5% MeOH) afforded bromoaniline **SI-9** as a white, amorphous solid (114 mg, 0.252 mmol, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.3 Hz, 1H), 7.08 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 6.93 - 6.89 (m, 1H), 6.72 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.70 (d, *J* = 2.3 Hz, 1H), 6.65 - 6.58 (m, 2H), 5.76 (d, *J* = 2.8 Hz, 1H), 5.35 (d, *J* = 3.0 Hz, 1H), 4.52 - 4.44 (m, 1H), 4.18 - 4.07 (m, 3H), 3.48 (ddd, *J* = 8.6, 5.2, 5.2 Hz, 2H), 3.11 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.76 (dd, *J* = 13.9, 9.7 Hz, 1H), 2.31 (dddd, *J* = 12.8, 7.0, 7.0, 3.3 Hz, 1H), 2.15 (dddd, *J* = 12.9, 10.6, 9.2, 7.2 Hz, 1H), 2.05 - 1.96 (m, 1H), 1.95 - 1.86 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ167.9, 165.6, 147.1, 144.3, 143.0, 133.1, 132.8, 128.7, 124.1, 119.7, 117.4, 114.0, 109.6, 108.0, 85.1, 60.5, 60.2, 59.5, 45.2, 38.0, 27.6, 23.3; FTIR (NaCl, thin film): 3457, 3341, 3003, 2953, 2881, 1661, 1612, 1572, 1484, 1466, 1422, 1341, 1293, 1252, 1214, 1152 cm^{-1}; $[\alpha]_D^{25}$ = +118 (*c* = 0.80, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 453.1, found 453.1.

Preparation of (+)-Naseseazine B (3b)



In a glovebox, a 1-dram vial was charged with bromoaniline **SI-9** (74.6 mg, 0.165 mmol, 1.00 equiv), alkyne **10** (127 mg, 0.412 mmol, 2.50 equiv), Na_2CO_3 (43.7 mg, 0.412 mmol, 2.50 equiv), and $Pd[P(o\text{-tol})_3]_2$ (29.5 mg, 0.0412 mmol, 25 mol %). DMF (1.70 mL) was then added and the solution stirred vigorously for 3 minutes at 25 °C. The solution was then heated to 100 °C for 1.5 h, cooled, and concentrated under reduced pressure and dried under high vacuum to ensure complete removal of residual DMF. The residue was then dissolved in CH_2Cl_2 (3 mL) and filtered through a plug of silica gel (50 g) to remove residual catalyst and base, then the filter cake rinsed (5% MeOH in CH_2Cl_2, 200 mL). The filtrate was then concentrated, and the crude residue dissolved in 1M methanolic HCl (10 mL), and stirred for 2 h at 23 °C. The solution was then concentrated and the residue was quenched by the addition of methanolic NH_3 (1 N, 5 mL) and reconcentrated. The residue was purified by flash chromatography on silica gel (2 to 7% MeOH in CH_2Cl_2) afforded naseseazine B (**3b)** as a white, powdery solid (47.3 mg, 0.837 mmol, 51% yield). Excess TES-alkyne **10** could be recovered during chromatography.

Spectroscopic and physical data, including ^1H, ^{13}C NMR in CD_3OD, DMSO-*d6,* IR, MS, and $[\alpha]_D^{25}$, obtained for naseseazine B matched that as reported during isolation by Raju et. al[15] and data obtained by Movassaghi and Kim.[2] See below for ^1H and ^{13}C comparison table. The use of natural amino acids in this report to synthesize (+)-naseseazine B is in agreement with Movassaghi and Kim's structural reassignment of the natural product.[2] During the course of this study, we determined that the exact chemical shifts (δ) of naseseazine B observed in CD_3OD had a slight concentration dependence.

^1H NMR (600 MHz, CD_3OD) δ 7.56 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 0.6 Hz, 1H), 7.12 (s, 1H), 7.04 (td, J = 7.6, 1.1 Hz, 1H), 7.00 (dd, J = 8.5, 1.1 Hz, 1H), 6.82 (dd, J = 7.2, 1.0 Hz, 1H), 6.69 – 6.64 (m, 2H), 5.82 (s, 1H), 4.71 – 4.61 (m, 1H), 4.38 (app t, J = 4.4 Hz, 1H), 4.24 (app t, J = 8.1, 1H), 3.96 (dd, J = 9.6, 6.6 Hz, 1H),

[15] Raju, R.; Piggott, A. M.; Conte, M.; Aalbersberg, W. G. L.; Feussner, K.; Capon, R. J. *Org Lett* **2009**, *11*, 3862.

3.51 – 3.36 (m, 3H), 3.30 – 3.27 (m, 2H), 3.26 – 3.21 (m, 2H), 2.57 (dd, J = 13.7, 10.1 Hz, 1H), 2.24 (dddd, J = 10.0, 6.9, 6.9, 3.1 Hz, 1H), 2.13 – 2.03 (m, 1H), 2.00 – 1.93 (m, 2H), 1.93 – 1.84 (m, 1H), 1.72 – 1.60 (m, 1H), 1.49 – 1.40 (m, 1H), 1.01 – 0.92 (m, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 170.8, 170.1, 168.4, 167.3, 149.1, 137.9, 137.0, 136.0, 129.4, 127.7, 126.4, 124.9, 120.5, 119.6, 111.1, 110.4, 109.7, 86.9, 61.8, 61.7, 61.5, 60.0, 57.1, 46.2, 45.9, 39.5, 29.2, 29.0, 28.5, 24.2, 22.6.

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.80 (d, J = 2.4 Hz, 1H), 7.68 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 1.6 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.03 – 6.96 (m, 2H), 6.80 (dd, J = 7.5, 1.2 Hz, 1H), 6.75 (s, 1H), 6.61 (d, J = 6.6, 1 H), 6.58 (dd, J = 6.6, 1H), 5.68 (s, 1H), 4.72 (ddd, J = 9.3, 7.7, 1.3 Hz, 1H), 4.34 (ddd, J = 8.9, 7.4, 1.4 Hz, 1H), 4.29 (app t J = 5.3 Hz, 1H), 4.06 (ddd, J = 9.9, 6.8, 1.4 Hz, 1H), 3.37 – 3.33 (m, 2H), 3.25 (ddd, J = 12.1, 9.0, 3.9 Hz, 1H), 3.22 (dd, J = 14.9, 4.8 Hz, 1H), 3.13 (dd, J = 13.7, 7.4 Hz, 1H), 3.05 (dd, J = 14.9, 5.8 Hz, 1H), 2.37 (dd, J = 13.7, 10.4 Hz, 1H), 2.16 (dddd, J = 12.4, 7.0, 7.0, 3.6 Hz, 1H), 2.03 - 1.91 (m, 2H), 1.90 - 1.78 (m, 2H), 1.69 (dddd, J = 10.7, 8.7, 5.8, 2.5 Hz, 1H), 1.67 - 1.57 (m, 1H), 1.46 - 1.38 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6)[16] δ 169.1, 167.9, 165.9, 165.5, 148.1, 135.9, 135.6, 134.6, 127.9, 126.1, 125.1, 123.4, 119.2, 118.0, 117.9, 109.3, 109.2, 84.9, 60.0, 59.8, 59.5, 58.4, 55.2, 44.6, 38.7, 27.7, 27.1, 25.7, 23.0, 21.9.

IR: 3270, 2943, 2859, 1653, 1559, 1419, 1340 cm^{-1}; $[\alpha]_D^{25}$ = +97 (c = 0.45, MeOH) LRMS (EI+) calc'd for $[M+H]^+$ 565.3, found 565.3.

Table S1. Comparison of ^{1}H NMR data for Natural vs. Synthetic (+)-Naseseazine B

Raju et al. Report,[15] Natural (+)–Naseseazine B ^{1}H NMR, 600 MHz, CD_3OD	This Work, Synthetic (+)–Naseseazine B ^{1}H NMR, 600 MHz, CD_3OD
δ 7.58 (d, J = 8.4 Hz, 1H)	δ 7.56 (d, J = 8.5 Hz, 1H)
7.41 (d, J = 1.4 Hz, 1H)	7.40 (d, J = 0.6 Hz, 1H)
7.12 (s, 1H)	7.12 (s, 1H)
7.06 (td, J =7.6, 1.3 Hz)	7.04 (td, J = 7.6, 1.1 Hz, 1H)
7.03 (dd, J = 8.4, 1.8 Hz, 1H)	7.00 (dd, J = 8.5, 1.1 Hz, 1H)
6.84 (dt, J =7.2, 0.9 Hz, 1H)	6.82 (dt, J = 7.2 Hz, 1.0 Hz, 1H),
6.69 (t, J = 7.6 Hz, 1H)	6.69 – 6.64 (m, 2H)
6.68 (t, J = 7.6 Hz, 1H)	–
5.85 (s, 1H)	5.82 (s, 1H)
4.75 (dd, J = 10.2, 8.7 Hz, 1H)	4.71 – 4.61 (m, 1H)
4.40 (br t, J =4.7 Hz, 1H)	4.38 (app t, J = 4.4, 1H)
4.33 (dd, J = 9.5, 7.1 Hz, 1H)	4.24 (app t, J = 8.1, 1H)
3.99 (ddd, J = 11.4, 6.6 , 1.6 Hz, 1H)	3.96 (dd, J = 9.6, 6.6 Hz, 1H)
3.49 (m, 1H)	3.51 – 3.36 (m, 3H)
3.44 (m, 1H)	–

[16] Movassaghi and Kim report multiple ^{13}C resonances at 120.6 and 61.9 (CD_3OD). See reference (2) of Supporting Information.

3.44 (m, 1H)	–
3.32 (m, 1H)	3.30 – 3.27 (m, 2H)
3.28 (m, 1H)	–
3.27 (m, 1H)	3.26 – 3.21 (m, 2H)
3.24 (m, 1H)	–
2.59 (dd, *J* = 13.8, 10.2 Hz, 1H)	2.57 (dd, *J* = 13.7, 10.1 Hz, 1H)
2.28 (m, 1H)	2.24 (dddd, *J* = 10.0, 6.9, 6.9, 3.1 Hz, 1H)
2.11 (m, 1H)	2.13 – 2.03 (m, 1H)
2.00 (m, 1H)	2.00 – 1.93 (m, 2H)
1.97 (m, 1H)	–
1.95 (m, 1H)	1.93 – 1.84 (m, 1H)
1.67 (m, 1H)	1.72 – 1.60 (m, 1H)
1.44 (m, 1H)	1.49 – 1.40 (m, 1H)
0.92 (m, 1H)	1.01 – 0.92 (m, 1H)

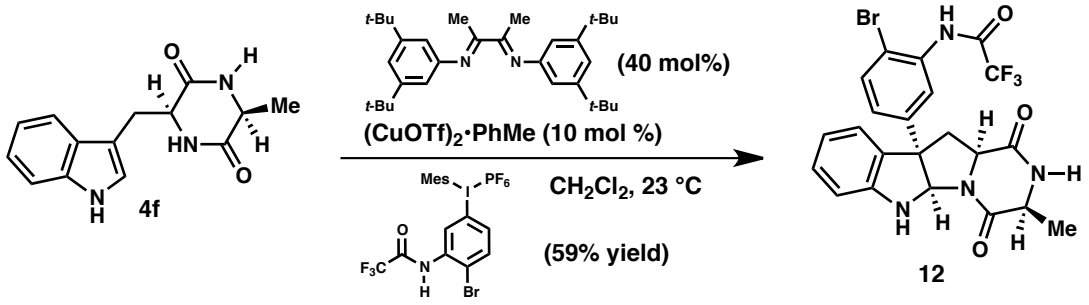
Table S2. Comparison of ^{13}C NMR data for Natural vs. Synthetic (+)-Naseseazine B

Raju et al. Report,[15] Natural (+)–Naseseazine B ^{13}C NMR, 151 MHz, CD_3OD	This Work, Synthetic (+)–Naseseazine B ^{13}C NMR, 126 MHz, CD_3OD	Chemical Shift Difference, Δδ
δ 170.7	δ 170.8	0.1
170.2	170.1	0.1
168.4	168.4	0.0
167.3	167.3	0.0
149.0	149.1	0.1
137.9	137.9	0.0
136.9	137.0	0.1
136.0	136.0	0.0
129.1	129.4	0.3
127.6	127.7	0.1
126.1	126.4	0.3
124.8	124.9	0.1
120.3	120.5	0.2
120.3	–[17]	–
119.4	119.6	0.2
111.0	111.1	0.1
110.3	110.4	0.1
109.5	109.4	0.1
86.8	86.9	0.1
61.8	61.8	0.0
61.7	61.7	0.0
61.3	61.5	0.2
59.9	60.0	0.1
57	57.1	0.1
45.9	46.2	0.3

[17] Raju et. al report two resonances at 120.3. The spectrum acquired in this report (126 MHz) only contains a single visible peak at 120.5 due to overlap.

45.8	45.9	0.1
39.5	39.5	0.0
29.2	29.2	0.0
29.1	29.0	0.1
28.3	28.5	0.2
24.1	24.2	0.1
22.4	22.6	0.2

Preparation of Pyrroloindoline 13

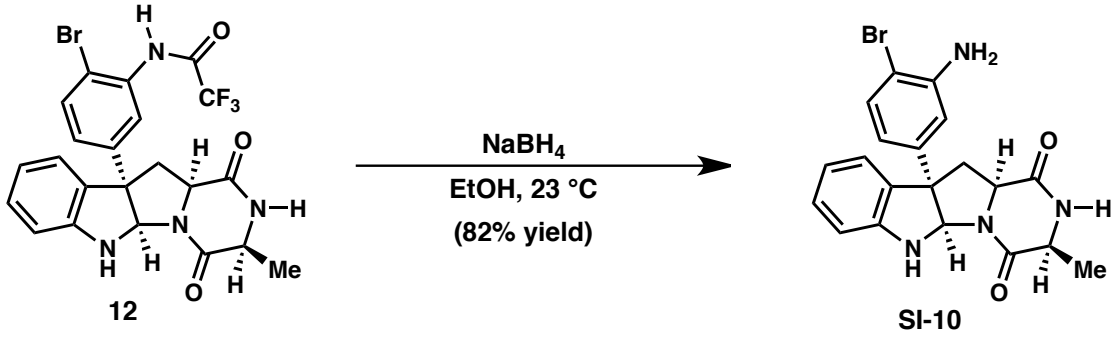


In a glovebox, $Cu(OTf)_2$•PhMe (77.6 mg 0.150 mmol) and $^{t\text{Bu}}DAB_{Me}$ (277 mg, 0.600 mmol, 2.40 mmol) were added to an oven-dried, 50 mL round-bottomed flask. Anhydrous CH_2Cl_2 (27.0 mL) was then added by syringe, and the resulting deep-purple solution was stirred for 1 h at 25 °C in the glovebox. The solution was then filtered through a tight plug of cotton, and the resulting solution removed from the glovebox.

To a flame-dried, 100-mL round-bottomed flask was charged cyclo-L-Ala-L-Trp **4f** (334 mg, 1.30 mmol, 1.00 equiv) and (4-bromo-3-trifluoroacetamidophenyl)mesityliodonium hexafluorophosphate (940 mg, 1.43 mmol, 1.10 equiv)). To the flask was then added the freshly prepared catalyst solution of $Cu^{I}(^{t\text{Bu}}DAB_{Me})$ (26.0 mL, 0.260 mmol, 0.20 equiv) dropwise over 20 minutes. The deep-purple solution was allowed to warm to 23 °C over 2 hours, then stirred for 8 hours at 23 °C. The solution was then quenched by the addition of aqueous ammonium hydroxide (1.8 M, 20 mL). The mixture was then diluted with EtOAc (100 mL), transferred to a separatory funnel, vigorously shaken, and the layers partitioned. The aqueous layer was then back-extracted with EtOAc (2 x 100 mL), and the combined organic layers dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Silica gel flash chromatography (78% EtOAc, 20% hexanes, 2 % MeOH) afforded aryl pyrroloindoline **12** as a white solid (402.0 mg, 0.767 mmol, 59% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.39 (d, J = 2.3 Hz, 1H), 7.53 (d, J = 8.5 Hz, 1H), 7.20 (s, 1H), 7.09 (ddd, J = 7.7, 7.7, 1.0 Hz, 1H), 7.03 (dd, J = 8.5, 2.3 Hz, 1H), 6.95 (d, J = 7.4 Hz, 1H), 6.73 (dd, J = 7.5, 7.5 Hz, 1H), 6.64 (d, J = 7.9 Hz, 1H), 5.73 (s, 1H), 5.68 (br s, 1H), 4.47 (dd, J = 8.3, 8.3 Hz, 1H), 4.10 – 4.03 (m, 1H), 3.09 (dd, J = 13.9, 7.9 Hz, 1H), 2.89 (dd, J = 13.9, 8.9 Hz, 1H), 1.41 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 168.4, 154.8 (q, $J_{C\text{-}F}$ = 38.0 Hz) 147.3, 144.0, 133.4, 132.8, 131.9, 129.0, 125.9, 124.0, 120.0, 119.7, 115.4 (q, $J_{C\text{-}F}$ = 288.6 Hz) 113.0, 110.1, 85.1, 59.3, 58.7,

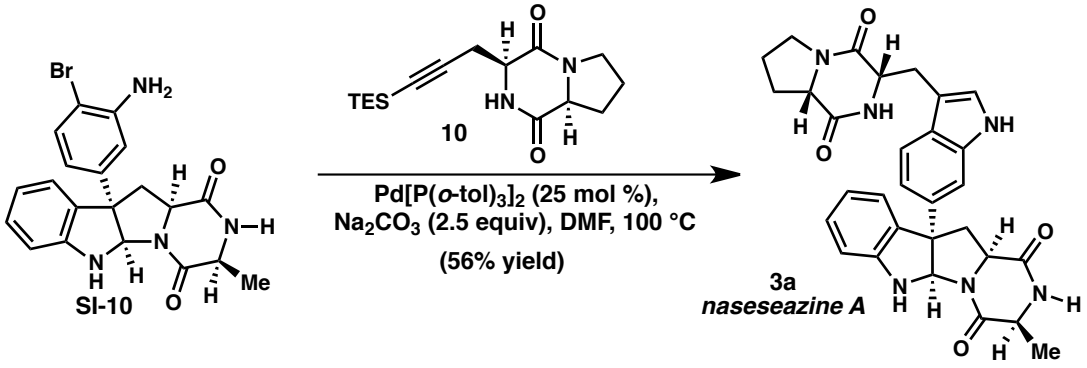
51.2, 38.2, 15.2; FTIR (NaCl, thin film): 3270, 1733, 1683, 1586, 1539, 1485, 1467, 1418, 1312, 1245, 1198, 1162 cm^{-1}; $[\alpha]_D^{25}$ = +84 (*c* = 0.42, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 523.1, found 523.1.

Preparation of Aniline SI-10



To a solution of pyrroloindoline **12** (140 mg, 0.268 mmol, 1.00 equiv) in EtOH (5.4 mL) at 23 °C was added $NaBH_4$ (76.3 mg, 2.00 mmol, 7.5 equiv). The solution was stirred vigorously for 1 h, then cooled to 0 °C and slowly quenched with saturated aqueous ammonium chloride (5 mL). The mixture was then diluted with H_2O (50 mL) and extracted with EtOAc (3 x 45 mL). The combined organics were then dried over sodium sulfate, filtered, and concentrated in vacuo. Purification of the crude residue by flash silica gel chromatography (75% EtOAc, 20% Hexanes, 5% MeOH) afforded bromoaniline **SI-10** as a white, amorphous solid (94.0 mg, 0.220 mmol, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.4 Hz, 1H), 7.04 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 6.91 - 6.85 (m, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.67 (ddd, *J* = 19.2, 7.7, 1.0 Hz, 2H), 6.56 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.72 (s, 1H), 4.56 (ddd, *J* = 10.0, 7.4, 1.6 Hz, 1H), 4.14 (qd, *J* = 6.8, 1.5 Hz, 1H), 3.10 (ddd, *J* = 14.0, 7.5, 1.7 Hz, 1H), 2.52 (dd, *J* = 13.6, 9.9 Hz, 1H), 1.37 (d, *J* = 6.9 Hz, 2H); FTIR (NaCl, thin film): 3345, 2919, 1668, 1605, 1483, 1418, 1300, 1209 cm^{-1}; $[\alpha]_D^{25}$ = +156 (*c* = 0.38, MeOH); LRMS (EI+) calc'd for $[M+H]^+$ 427.1, found 427.1.

Preparation of (+)-Naseseazine A (3a)



In a glovebox, a 1-dram vial was charged with bromoaniline **SI-10** (79.8 mg, 0.187 mmol, 1.00 equiv), alkyne **10** (143 mg, 0.467 mmol, 2.50 equiv), Na_2CO_3 (49.5 mg, 0.467 mmol, 2.50 equiv), and $Pd[P(o\text{-tol})_3]_2$ (33.4

mg, 0.0467 mmol, 25 mol %). DMF (1.90 mL) was then added and the solution stirred vigorously for 3 minutes at 25 °C. The solution was then heated to 100 °C for 1 h, cooled, and concentrated under reduced pressure and dried under high vacuum to ensure complete removal of residual DMF. The residue was then dissolved in CH_2Cl_2 (3 mL) and filtered through a plug of silica gel (50 g) to remove residual catalyst and base, then the filter cake rinsed (6% MeOH in CH_2Cl_2, 260 mL). The filtrate was then concentrated, and the crude residue dissolved in 1M methanolic HCl (12 mL), and stirred for 2 h at 23 °C. The solution was then concentrated and the residue was quenched by the addition of methanolic NH_3 (1 N, 12 mL) and reconcentrated. The residue was purified by flash chromatography on silica gel (2 to 10% MeOH in CH_2Cl_2) afforded (+)-naseseazine A (**3b)** as a white, powdery solid (56.5 mg, 0.105 mmol, 56% yield). Excess TES-alkyne **10** could be recovered during chromatography.

Spectroscopic and physical data, including ^{1}H, ^{13}C NMR in CD_3OD, DMSO-*d6,* IR, MS, and $[\alpha]_D^{25}$, obtained for naseseazine A matched that as reported during isolation by Raju et. al[15] and data obtained by Movassaghi and Kim.[2] See below for ^{1}H and ^{13}C comparison table. The use of natural amino acids in this report to synthesize (+)-naseseazine A is in agreement with Movassaghi and Kim's structural reassignment of the natural product.[2] During the course of this study, we determined that the exact chemical shifts (δ) of naseseazine A observed in CD_3OD had a slight concentration dependence.

^{1}H NMR (600 MHz, CD_3OD) δ 7.55 (d, *J* = 8.4 Hz, 1H), 7.38 (s, 1H), 7.11 (s, 1H), 7.04 (app t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.70 – 6.62 (m, 2H), 5.80 (s, 1H), 4.58 (app t, *J* = 8.6 Hz, 1H), 4.37 (dd, *J* = 4.7, 4.7 Hz, 1H), 4.10 (q, *J* = 6.8 Hz, 1H), 3.95 (dd, *J* = 10.7, 6.5 Hz, 1H), 3.41 (dt, *J* = 11.8, 8.3 Hz, 1H), 3.29 – 3.25 (m, 3H), 3.23 (dd, *J* = 13.2, 7.8 Hz, 2H), 2.58 (dd, *J* = 13.5, 10.0 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.71 – 1.60 (m, 1H), 1.48 – 1.40 (m, 1H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.01 – 0.91 (m, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 172.5, 170.8, 170.7, 167.3, 149.1, 137.9, 137.2, 135.9, 129.4, 127.6, 126.4, 125.0, 120.5, 120.4, 119.6, 111.1, 110.3, 109.7, 87.1, 61.2, 60.3, 60.0, 57.1, 52.2, 45.9, 39.7, 29.2, 29.0, 22.6, 15.3.

^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.80 (s, 1H), 8.18 (s, 1H), 7.68 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.29 (s, 1H), 7.19 (s, 1H), 7.01 – 6.96 (m, 2H), 6.83 (d, *J* = 7.3 Hz, 1H), 6.73 (s, 1H), 6.65 – 6.54 (m, 2H), 5.66 (s, 1H), 4.61 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.28 (dd, *J* = 4.6, 4.6 Hz, 1H), 4.14 (q, *J* = 6.7 Hz, 1H), 4.10 – 4.03 (m, 1H), 3.40 – 3.35 (m, 1H), 3.28 – 3.18 (m, 2H), 3.07 (ddd, *J* = 26.8, 14.2, 6.7 Hz, 2H), 2.42 (dd, *J* = 13.1, 10.3 Hz, 1H), 2.02 – 1.93 (m, 1H), 1.70 (ddd, *J* = 27.0, 9.2, 9.2 Hz, 1H), 1.65 – 1.56 (m, 1H), 1.48 – 1.37 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-*d6*) δ 170.0, 169.1, 168.6, 165.5, 148.1, 135.9, 135.7, 134.4, 127.9, 126.1, 125.0, 123.6, 119.1, 117.9, 117.8, 109.3, 109.2, 109.1, 85.0, 59.3, 58.4, 58.4, 55.2, 50.3, 44.6, 38.8, 27.7, 25.7, 21.9, 14.8.

FTIR: 3306, 2913, 2859, 1668, 1449, 1418, 1343, 1308 cm^{-1}; $[\alpha]_D^{25}$ = +121 (*c* = 0.30, MeOH); LRMS (EI+) calc'd for $[M+H]^+$ 539.2, found 539.2.

Table S3. Comparison of ^{1}H NMR data for Natural vs. Synthetic (+)-Naseseazine A

Raju et al. Report,[15] (+)–Naseseazine A ^{1}H NMR, 600 MHz, CD_3OD	**This Work (+)–Naseseazine A ^{1}H NMR, 600 MHz, CD_3OD**
δ 7.57 (d, *J* = 8.4 Hz, 1H)	δ 7.55 (d, *J* = 8.4 Hz, 1H)
7.40 (s, 1H)	7.38 (s, 1H)
7.11 (s, 1H)	7.11 (s, 1H)
7.05 (t, 7.2 Hz, 1H)	7.04 (app t, *J* = 7.6 Hz, 1H)
7.02 (d, *J* = 8.4 Hz, 1H)	7.00 (d, *J* = 8.4 Hz, 1H)
6.85 (d, *J* = 7.4 Hz, 1H)	6.83 (d, *J* = 7.4 Hz, 1H)
6.69 (d, *J* = 7.6 Hz, 1H)	6.70 – 6.62 (m, 2H)
6.67 (t, *J* = 8.5 Hz, 1H)	–
5.83 (s, 1H)	5.80 (s, 1H)
4.64 (dd, *J* = 8.4, 7.4 Hz, 1H)	4.58 (app t, *J* = 8.6 Hz, 1H)
4.39 (br t, *J* = 4.5 Hz, 1H)	4.37 (dd, *J* = 4.7, 4.7 Hz, 1H)
4.15 (q, *J* = 6.9 Hz, 1H)	4.10 (q, *J* = 6.8 Hz, 1H)
3.97 (dd, *J* = 10.8, 6.6 Hz, 1H)	3.95 (dd, *J* = 10.7, 6.5 Hz, 1H
3.42 (dt, *J* = 11.8, 8.1 Hz, 1H)	3.41 (dt, *J* = 11.8, 8.3 Hz, 1H)
3.30 (m, 1H)	3.29 – 3.25 (m, 3H)
3.29 (m, 1H)	–
3.26 (m, 1H)	–
3.24 (m, 1H)	3.23 (dd, *J* = 13.2, 7.8 Hz, 2H)
2.59 (dd, *J* = 13.7, 10.2 Hz, 1H)	2.58 (dd, *J* = 13.5, 10.0 Hz, 1H)
1.97 (m, 1H)	2.00 – 1.91 (m, 1H)
1.66 (m, 1H)	1.71 – 1.60 (m, 1H)
1.43 (m, 1H)	1.48 – 1.40 (m, 1H)
1.38 (d, *J* = 6.9 Hz, 1H)	1.36 (d, *J* = 6.8 Hz, 3H)
0.93 (m, 1H)	1.01 – 0.91 (m, 1H)

Table S4. Comparison of ^{13}C NMR data for Natural vs. Synthetic (+)-Naseseazine A

Raju et al. Report,[15] (+)–Naseseazine A ^{13}C NMR, 151 MHz, CD_3OD	This Work (+)–Naseseazine A ^{13}C NMR, 126 MHz, CD_3OD	Chemical Shift Difference, Δδ
172.6	172.5	0.1
170.6	170.8	0.2
170.6	170.7	0.1
167.3	167.3	0.0
149.1	149.1	0.0
137.9	137.9	0.0
137.2	137.2	0.0
135.8	135.9	0.1
129.2	129.4	0.2
127.6	127.6	0.0
126.2	126.4	0.2
124.9	125.0	0.1
120.3	120.5	0.2
120.2	120.4	0.2
119.5	119.6	0.1
110.9	111.1	0.2
110.1	110.3	0.2
109.5	109.7	0.2
87.1	87.1	0.0
61.2	61.2	0.0
60.2	60.3	0.1
60.0	60.0	0.0
57.2	57.1	0.1
52.1	52.2	0.1
45.8	45.9	0.1
39.7	39.7	0.0
29.0	29.2	0.2
29.0	29.0	0.0
22.5	22.6	0.1
15.2	15.3	0.1