

SUPPORTING INFORMATION

Formal Total Synthesis of (–)-Haouamine A

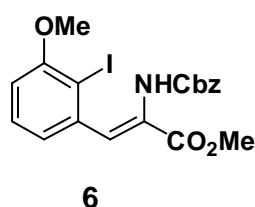
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General: All reactions were carried out in flame-dried glassware under Ar. The solvents were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et₂O (Mg-anthracene), DME (Na), CH₂Cl₂, MeCN, Et₃N, EtOAc, pyridine (CaH₂), EtOH, MeOH (Mg), DMF (Desmodur®, dibutyltin dilaurate), CHCl₃ (P₄O₁₀), 1,4-dioxane, hexanes, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230-400 mesh) or CombiFlash Companion (Teledyne Isco). NMR: Spectra were recorded on Bruker DPX 300, AV 400, or DMX 600 spectrometers in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale (CDCl₃: $\delta_C \equiv 77.0$ ppm; residual CHCl₃ in CDCl₃: $\delta_H \equiv 7.26$ ppm; CD₂Cl₂: $\delta_C \equiv 54.0$ ppm; residual CH₂Cl₂ in CD₂Cl₂: $\delta_H \equiv 5.32$ ppm). ¹¹B NMR chemical shifts are given relative to external BF₃·Et₂O ($\equiv 0$ ppm). IR: Nicolet Magna IR-750 or Perkin-Elmer spectrometer, wavenumbers ($\tilde{\nu}$) in cm⁻¹. MS (EI): Finnigan MAT 8200 (70 eV), Finnigan MAT 8400, ESI-MS: Bruker ESQ 3000, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). Melting points: Büchi melting point apparatus B-540 (corrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. Unless stated otherwise, all commercially available compounds (Fluka, Lancaster, Aldrich) were used as received.

Z-2-Methyl-(benzyloxycarbonylamino)-3-(2-iodo-3-methoxy-phenyl)acrylate (6): DBU



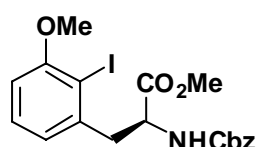
(2.54 mL, 16.7 mmol) was added to a solution of phosphonate **5** (5.56 g, 16.8 mmol)¹ in CH₂Cl₂ (25 mL) and the resulting solution was stirred at ambient temperature for 15 min before aldehyde **4** (4.00 g, 15.3 mmol)² was introduced in several portions to the chilled (0°C) mixture. The resulting solution was stirred at room temperature for 45 min before the

¹ a) U. Schmidt, A. Lieberknecht, J. Wild, *Synthesis* **1984**, 53; b) E. Teoh, E. M. Campi, W. R. Jackson, A. J. Robinson, *New J. Chem.* **2003**, 27, 387.

² L. F. Tietze, S. G. Stewart, M. E. Polomska, A. Modi, A. Zeeck, *Chem. Eur. J.* **2004**, 10, 5233.

reaction was diluted with EtOAc (50 mL) and quenched with HCl (2 M, 20 mL). A standard extractive work up followed by flash chromatography (SiO₂, EtOAc/hexanes, 1:4) gave product **6** as a pale yellow syrup which solidified upon standing (6.00 g, 86%). m.p. 88-89°C; ¹H NMR (400 MHz, CDCl₃, 25°C): δ = 7.35-7.28 (m, 5H), 7.26-7.23 (m, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.38 (s, 1H), 5.03 (s, 2H), 3.88 (s, 3H), 3.84 (s, 3H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ = 165.2, 158.4, 153.3, 140.0, 135.8, 132.8, 129.0, 128.4, 128.2, 128.1, 125.9, 121.4, 110.4, 92.3, 67.4, 56.4, 52.8; IR (KBr): $\tilde{\nu}$ = 3271, 3063, 3028, 3005, 2952, 2838, 1729, 1692, 1646, 1559, 1508, 1465, 1272, 1257, 1075, 770, 738, 695; MS (EI): *m/z* (%): 467 (<1) [*M*⁺], 376 (3), 340 (43), 300 (2), 265 (3), 236 (6), 205 (16), 173 (12), 130 (3), 91 (100); HRMS (ESI⁺): *m/z*: calcd for C₁₉H₁₈INO₅+Na: 490.0122 [*M*⁺+Na]; found: 490.0118 [*M*⁺+Na]; elemental analysis calcd (%) for C₁₉H₁₈INO₅ (467.3): C 48.84, H 3.88, N 3.00; found: C 48.79, H 3.83, N 2.97.

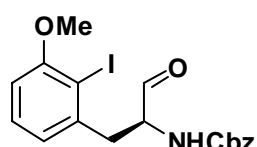
(S)-Methyl-2-(benzyloxycarbonylamino)-3-(2-iodo-3-methoxyphenyl)propanoate (8):



8

Alkene **6** (17.1 g, 36.5 mmol) was added to a solution of complex **7** (200 mg, 0.28 mmol) in EtOAc (150 mL) and the resulting orange-red mixture was stirred for 24 h under an atmosphere of H₂ (20 bar) in an autoclave. For work up, the solvent was evaporated and the residue purified by flash chromatography (SiO₂, EtOAc/hexanes, 1:2) to give product **8** as a colorless syrup, which slowly solidified upon standing (16.6 g, 97%); ee = 99% [Chiralpak AD-RH, 150 mm, MeCN/H₂O, 0.5 mL/min, 35°C, retention times: 21.3 min (major); 25.0 (minor)]. m.p. 81-82°C; [α]_D²⁰ = -5.0° (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 25°C): δ = 7.36-7.26 (m, 5H), 7.19 (t, *J* = 7.9 Hz, 1H), 6.79 (d, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 5.35 (d, *J* = 8.2 Hz, 1H), 5.06 (s, 2H), 4.73 (q, *J* = 8.2 Hz, 1H), 3.86 (s, 3H), 3.71 (d, 3H), 3.37 (dd, *J* = 13.9, 6.0 Hz, 1H), 3.21 (dd, *J* = 13.9, 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ = 172.0, 158.2, 155.5, 141.0, 136.2, 129.0, 128.4, 128.0, 128.0, 122.7, 109.4, 93.5, 66.8, 56.4, 54.1, 52.4, 43.0; IR (film): $\tilde{\nu}$ = 3339, 3064, 3006, 2951, 2838, 1722, 1567, 1520, 1465, 1264, 1214, 1075, 1015, 776, 739, 698; MS (EI): *m/z* (%): 469 (3) [*M*⁺], 410 (2), 366 (7), 342 (32), 318 (6), 298 (9), 247 (16), 207 (9), 191 (34), 148 (6), 91 (100); HRMS (ESI⁺): *m/z*: calcd for C₁₉H₂₀INO₅+Na: 492.0278 [*M*⁺+Na]; found: 492.0277 [*M*⁺+Na]; elemental analysis calcd (%) for C₁₉H₂₀INO₅ (469.3): C 48.63, H 4.30, N 2.98; found: C 48.71, H 4.26, N 2.95.

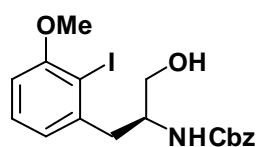
(S)-Benzyl-1-(2-iodo-3-methoxyphenyl)-3-oxopropan-2-yl-carbamate (8a):



8a

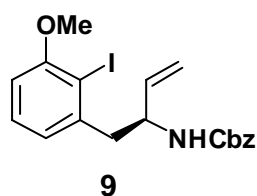
Dibal-H (21 mL, 1.0 M in hexanes, 21 mmol) was added via syringe pump over a period of 2.5 h to a solution of ester **8** (4.80 g, 10.2 mmol) in toluene (50 mL) at -78°C and the resulting mixture was stirred at that temperature for 15 min once the addition was complete. The reaction was quenched upon slow addition of EtOAc (20 mL) via syringe pump (ca. 30 min) before it was allowed to reach ambient temperature. For work up, the mixture was diluted with EtOAc (150 mL) and sat. aq. Na/K-tartrate (ROCHELLE's salt, 20 mL) and

stirred until a clean separation of the phases was reached. The aqueous layer was extracted with EtOAc (2 x 30 mL), the combined organic phases were dried over Na₂SO₄ and evaporated, and the residue was purified by flash chromatography to give the title aldehyde (4.48 g, 90%) which contained traces of the corresponding alcohol. Analytically pure samples of the aldehyde were obtained by recrystallization from EtOAc. m.p. 136-137°C; $[\alpha]_D^{20} = -32.7^\circ$ (c = 0.7, CHCl₃); ¹H NMR (400 MHz, CDCl₃, 25°C): δ = 9.68 (s, 1H), 7.38-7.30 (m, 5H), 7.19 (t, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 5.39 (d, *J* = 6.3 Hz, 1H), 5.08 (s, 2H), 4.53 (q, *J* = 6.8 Hz, 1H), 3.87 (s, 3H), 3.41 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.23 (dd, *J* = 14.0, 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ = 198.4, 158.4, 155.9, 140.8, 136.1, 129.2, 128.5, 128.2, 128.1, 123.1, 109.4, 93.4, 67.1, 60.4, 56.5, 40.3; IR (KBr): $\tilde{\nu} = 3314, 3060, 2965, 2940, 2894, 2838, 2750, 1729, 1673, 1533, 1464, 1276, 1265, 737, 696$; MS (EI): *m/z* (%): 439 (2) [*M*⁺], 410 (16), 366 (19), 320 (5), 312 (3), 247 (8), 91 (100); HRMS (ESI⁺): *m/z*: calcd for C₁₈H₁₈INO₄+Na: 462.0173 [*M*⁺+Na]; found: 462.0173 [*M*⁺+Na]; elemental analysis calcd (%) for C₁₈H₁₈INO₄ (439.2): C 49.22, H 4.13, N 3.19; found: C 49.30, H 4.21, N 3.08.



The alcohol by-product formed in the Dibal-H reduction step analyzed as follows: m.p. 91-92°C; $[\alpha]_D^{20} = -47.0^\circ$ (c = 1.2, CH₂Cl₂); ¹H NMR (300 MHz, CD₃CN, 70°C): δ = 7.37-7.27 (m, 5H), 7.23 (dd, *J* = 7.9, 7.8 Hz, 1H), 6.92 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.79 (dd, *J* = 8.2, 1.4 Hz, 1H), 5.44 (s, 1H), 5.02-4.90 (m, 2H), 4.08-3.96 (m, 1H), 3.85 (s, 3H), 3.68-3.54 (m, 2H), 3.09 (dd, *J* = 13.9, 5.2 Hz, 1H), 2.92 (dd, *J* = 13.9, 9.3 Hz, 1H), 2.87 (m, 1H); ¹³C NMR (75 MHz, CD₃CN, 70°C): δ = 159.6, 157.2, 144.7, 138.6, 130.1, 129.5, 128.8, 128.6, 124.4, 110.7, 94.1, 66.9, 65.2, 57.5, 54.8, 43.5; IR (KBr): $\tilde{\nu} = 3332, 3064, 3032, 2935, 2874, 1696, 1540, 1464, 1425, 1262, 1078, 1054, 1013$; MS (EI): *m/z* (%): 441 (<1) [*M*⁺], 410 (4) [*M*⁺-CH₃O], 366 (8), 314 (14), 270 (8), 247 (10), 206 (6), 194 (25), 150 (23), 121 (4), 91 (100); HRMS (ESI⁺): *m/z*: calcd for C₁₈H₂₀INO₄+Na: 464.0329 [*M*⁺+Na]; found: 464.0333 [*M*⁺+Na]; elemental analysis calcd (%) for C₁₈H₂₀INO₄ (441.3): C 48.99, H 4.57, N 3.17; found: C 48.71, H 4.54, N 3.08.

(S)-Benzyl-1-(2-iodo-3-methoxyphenyl)-but-3-en-2-yl-carbamate (9): Aldehyde **8a** (379

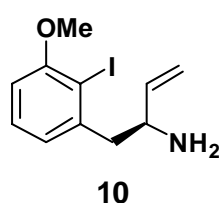


mg, 0.863 mmol) was added in one portion to a solution of Ph₃P=CH₂ (700 mg, 2.53 mmol)³ in toluene (60 mL) at 0°C and the resulting mixture stirred at that temperature for 1 h. Quenching of the reaction with EtOAc (100 mL) and H₂O (30 mL) followed by a standard extractive work up and purification of the crude product by flash chromatography (SiO₂, EtOAc/hexanes, 1:4) gave alkene **9** as a colorless solid (315 mg, 84%). m.p. 87-88°C; $[\alpha]_D^{20} = -16.7^\circ$ (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CD₃CN, 25°C): δ = 7.36-7.24 (m, 5H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.88 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.78 (dd, *J* = 8.2,

³ R. Köster, D. Simic, M. A. Grassberger, *Liebigs Ann.* **1970**, 739, 211.

1.1 Hz, 1H), 5.87 (ddd, $J = 17.1, 10.4, 5.7$ Hz, 1H), 5.76 (d, $J = 7.6$ Hz, 1H), 5.18 (dt, $J = 17.2, 1.5$ Hz, 1H), 5.09 (dt, $J = 10.4, 1.4$ Hz, 1H), 4.95 (m, 2H), 4.50 (m, 1H), 3.83 (s, 3H), 3.07 (dd, $J = 13.8, 5.2$ Hz, 1H), 2.89 (dd, $J = 13.6, 9.8$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN , 25°C): $\delta = 159.1, 156.5, 143.7, 139.5, 138.3, 129.8, 129.3, 128.6, 128.3, 124.3, 115.0, 110.2, 93.5, 66.5, 57.1, 54.3, 46.4$; IR (KBr): $\tilde{\nu} = 3308, 3073, 2964, 2836, 1697, 1643, 1550, 1465, 1265, 990, 919, 777, 755, 696$; MS (EI): m/z (%): 346 (1) [$M^+ - \text{C}_7\text{H}_7$], 310 (2) [$M^+ - \text{I}$], 266 (10), 247 (9), 190 (12), 146 (19), 91 (100); HRMS (ESI+): m/z : calcd for $\text{C}_{19}\text{H}_{21}\text{INO}_3$: 438.0561 [$M^+ + \text{H}$]; found: 438.0561 [$M^+ + \text{H}$]; elemental analysis calcd (%) for $\text{C}_{19}\text{H}_{20}\text{INO}_3$ (437.3): C 52.19, H 4.61, N 3.20; found: C 52.02, H 4.61, N 3.15.

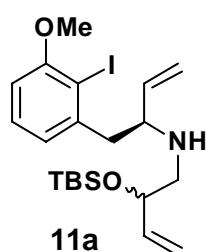
(S)-1-(2-Iodo-3-methoxyphenyl)-but-3-enyl-2-amine (10): A solution of HBr in HOAc (2.4



mL, 33% w/w) was added to a solution of carbamate **9** (2.74 g, 6.27 mmol) in CH_2Cl_2 (15 mL) at 0°C and the resulting mixture was stirred for 3 h at ambient temperature before it was poured, with vigorous stirring, into ice water (100 mL). The aqueous phase was extracted with Et_2O (50 mL), the organic layer was washed with water, and the combined aqueous phases

were carefully neutralized with aq. sat. NaHCO_3 , causing a vigorous evolution of gas. The product was extracted with CH_2Cl_2 (3 x 30 mL), the combined organic layers were washed with brine (20 mL), dried over Na_2SO_2 and evaporated to give amine **10** as a pale brown oil which was immediately used in the next step without further purification (1.79 g, 94%). ^1H NMR (400 MHz, CDCl_3 , 25°C): $\delta = 7.21$ (t, $J = 7.8$ Hz, 1H), 6.84 (dd, $J = 7.5, 1.1$ Hz, 1H), 6.68 (dd, $J = 8.1, 1.0$, 1H), 5.93 (ddd, $J = 17.0, 10.3, 6.3$ Hz, 1H), 5.16 (dt, $J = 17.2, 1.2$ Hz, 1H), 5.05 (dt, $J = 10.3, 1.2$ Hz, 1H), 3.87 (s, 3H), 3.73 (m, 1H), 3.02 (dd, $J = 13.3, 5.6$ Hz, 1H), 2.83 (dd, $J = 13.3, 8.3$ Hz, 1H), 1.80 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3 , 25°C): $\delta = 158.2, 143.4, 141.5, 128.7, 123.4, 114.0, 108.9, 93.4, 56.5, 53.9, 48.7$; IR (film): $\tilde{\nu} = 3367, 3072, 3003, 2937, 2835, 1641, 1566, 1464, 1425, 1295, 1263, 1069, 1012, 994, 919, 776$; MS (EI): m/z (%): 304 (<1) [M^+], 247 (2), 176 (13), 105 (3), 90 (3), 77 (4), 56 (100); HRMS (ESI+): m/z : calcd for $\text{C}_{11}\text{H}_{15}\text{INO}$: 304.0193 [$M^+ + \text{H}$]; found: 304.0195 [$M^+ + \text{H}$].

(S)-2-(tert-Butyldimethylsilyloxy)-N-(1-(2-iodo-3-methoxy-phenyl)-but-3-en-2-yl)-but-3-

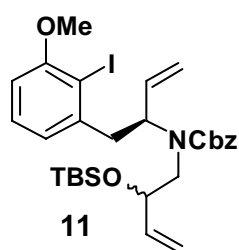


en-1-amine (11a): A mixture containing paraformaldehyde (92 mg, 3.1 mmol) and amine **10** (930 mg, 3.07 mmol) in toluene (15 mL) was stirred in a closed vessel at 90°C until a clear solution had formed (ca. 20 min). After reaching ambient temperature, boronate **19** (1.37 g, 4.60 mmol) was introduced and the mixture again stirred at 90°C in the sealed vessel for 1 h.

The mixture was then diluted with EtOAc (50 mL), the organic phase was successively washed with water and brine (20 mL each), dried over Na_2SO_4 and evaporated. Flash chromatography (SiO_2 , EtOAc/hexanes, 1:10) of the residue furnished the title compound as a colorless oil (1.03 g, 69%). ^1H NMR (400 MHz, CDCl_3 , 25°C , 3:1 mixture of diastereomers): $\delta = 7.18$ (t, $J = 7.7$ Hz, 1H), 7.18 (t, $J = 7.7$ Hz, 1H), 6.86-6.80 (m, 2H), 6.68-6.65 (m, 2H), 5.82-5.66 (m, 4H), 5.20-5.00 (m, 8H), 4.23-4.16 (m, 2H), 3.87 (s, 6H), 3.48-

3.39 (m, 2H), 3.00-2.89 (m, 4H), 2.71 (dd, $J = 11.7, 6.2$ Hz, 1H), 2.64 (dd, $J = 11.9, 4.3$ Hz, 1H), 2.51 (dd, $J = 11.7, 4.8$ Hz, 1H), 2.47 (dd, $J = 11.9, 7.9$ Hz, 1H), 1.62 (s, 2H), 0.83 (s, 9H), 0.83 (s, 9H), 0.01 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3 , 25°C , 3:1 mixture of diastereomers): $\delta = 158.3, 158.2, 143.5, 143.2, 140.4, 140.4, 140.0, 139.9, 128.7, 128.6, 123.7, 123.6, 116.4, 116.1, 115.1, 115.0, 108.9, 108.8, 95.6, 93.4, 73.6, 73.1, 61.4, 61.4, 56.5, 54.0, 53.8, 47.2, 47.1, 25.9, 25.9, 18.1, -4.2, -4.3, -4.7, -4.9$; IR (film): $\tilde{\nu} = 3320, 3075, 3004, 2954, 2928, 2893, 2855, 1642, 1567, 1464, 1262, 1077, 993, 922, 836, 777$; MS (EI): m/z (%): 487 (2) [M^+], 472 (3), 430 (9), 360 (3), 316 (100), 287 (3), 261 (11), 240 (87), 211 (7), 189 (28), 160 (59); HRMS (ESI+): m/z : calcd for $\text{C}_{21}\text{H}_{35}\text{INO}_2\text{Si}$: 488.1476 [$M^+ + \text{H}$]; found: 488.1474 [$M^+ + \text{H}$]; elemental analysis calcd (%) for $\text{C}_{21}\text{H}_{34}\text{INO}_2\text{Si}$ (487.5): C 51.74, H 7.03, N 2.87; found: C 51.80, H 7.08, N 2.77.

(S)-Benzyl-2-(tert-butyldimethylsilyloxy)but-3-enyl-(1-(2-iodo-3-methoxyphenyl)but-3-en-2-yl)carbamate (11):



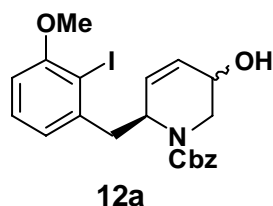
K_2CO_3 (1.21 g, 8.73 mmol) and $\text{BnOC}(\text{O})\text{Cl}$ (0.70 mL, 4.92 mmol) were successively added to a vigorously stirred solution of amine **11a** (2.13 g, 4.37 mmol) in $\text{EtOAc}/\text{H}_2\text{O}$ (1:1, 20 mL) at 0°C . The mixture was then stirred at ambient temperature for 30 min before the reaction was quenched with aq. KH_2PO_4 (1 M). A standard extractive work up followed by purification of the crude product by flash

chromatography (SiO_2 , $\text{EtOAc}/\text{hexanes}$, 1:4) afforded product **11** as a colorless oil (2.54 g, 94%). ^1H NMR (300 MHz, $[\text{D}_6]-\text{DMSO}$, 100°C , 3:1 mixture of diastereomers): $\delta = 7.39-7.30$ (m, 10H), 7.19 (t, $J = 7.7$ Hz, 1H), 7.18 (t, $J = 7.7$ Hz, 1H), 6.86-6.81 (m, 2H), 6.75-6.70 (m, 2H), 6.14 (ddd, $J = 10.7, 6.5, 4.0$ Hz, 2H), 5.72-5.63 (m, 2H), 5.18-4.98 (m, 12H), 4.54-4.44 (m, 2H), 4.38-4.22 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.30-3.08 (m, 6H), 2.98-2.90 (m, 2H), 0.85 (s, 18H), 0.01 (s, 3H), -0.01 (s, 3H), -0.02 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (75 MHz, $[\text{D}_6]-\text{DMSO}$, 100°C , 3:1 mixture of diastereomers): $\delta = 157.6, 154.7, 154.6, 142.0, 138.7, 136.9, 136.5, 136.1, 136.1, 128.2, 128.2, 127.6, 127.6, 127.2, 127.1, 127.1, 127.1, 122.6, 122.5, 115.4, 115.2, 114.6, 114.3, 109.4, 92.8, 92.8, 71.3, 71.1, 65.8, 65.7, 60.5, 60.4, 56.1, 52.7, 42.4, 42.3, 25.1, 17.1, -5.2, -5.2, -5.3, -5.4$; IR (film): $\tilde{\nu} = 3073, 3032, 2955, 2929, 2894, 2856, 1700, 1642, 1587, 1567, 1497, 1465, 1426, 1410, 1362, 1296, 1263, 1072, 993, 925, 837, 776, 698$; MS (EI): m/z (%): 621 (1) [M^+], 564 (14), 450 (5), 374 (24), 358 (6), 330 (30), 323 (18), 247 (2), 232 (14), 171 (6), 160 (26), 91 (100); HRMS (ESI+): m/z : calcd for $\text{C}_{29}\text{H}_{40}\text{INO}_4\text{Si} + \text{Na}$: 644.1664 [$M^+ + \text{Na}$]; found: 644.1658 [$M^+ + \text{Na}$]; elemental analysis calcd (%) for $\text{C}_{29}\text{H}_{40}\text{INO}_4\text{Si}$ (621.6): C 56.03, H 6.49, N 2.25; found: C 56.11, H 6.42, N 2.27.

(S)-Benzyl-5-hydroxy-2-(2-iodo-3-methoxybenzyl)-5,6-dihydro-pyridine-1(2H)-carboxylate (12a): A solution of diene **11** (2.31 g, 3.72 mmol) and the second generation Grubbs catalyst $(\text{Cy}_3\text{P})(\text{SIMes})\text{Cl}_2\text{Ru}=\text{CHPh}$ (157 mg, 0.185 mmol)⁴ in toluene (150 mL) was stirred for 6 h at 80°C . For work up, the solvent was evaporated and the residue dissolved in

⁴ M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953.

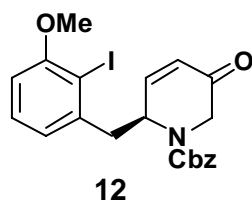
EtOAc and passed through a short silica column which was rinsed with EtOAc/hexane (1:4). The filtrate was evaporated and the residue dissolved in THF (10 mL) before a solution of



TBAF (4.09 mL, 1.0 M in THF, 4.09 mmol) was introduced. After stirring for 2 h, all volatile materials were evaporated and the crude product purified by flash chromatography (SiO₂, EtOAc/hexanes, 1:2→1:1) to give the title alcohol as a colorless foam (1.59 g, 89%). An aliquot was re-chromatographed to give analytically pure samples of both isomers, which analyzed as follows: **Major diastereomer:**

$[\alpha]_D^{20} = +40.1^\circ$ (c = 1.0, CH₂Cl₂); ¹H NMR (300 MHz, CD₃CN, 70°C): δ = 7.38-7.24 (m, 5H), 7.20 (m, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.76 (dd, J = 8.2, 1.3 Hz, 1H), 5.94 (ddt, J = 10.1, 5.2, 1.4 Hz, 1H), 5.84 (dd, J = 10.1, 4.0 Hz, 1H), 5.00 (d, J = 12.5 Hz, 1H), 4.88 (m, 1H), 4.70 (s, 1H), 4.20 (d, J = 14.2 Hz, 1H), 4.00 (m, 1H), 3.83 (s, 3H), 3.22 (dd, J = 14.2, 2.7 Hz, 1H), 3.11 (dd, J = 13.5, 5.5 Hz, 1H), 2.99 (dd, J = 13.5, 8.6 Hz, 1H), 2.50 (s, 1H); ¹³C NMR (75 MHz, CD₃CN, 70°C): δ = 159.6, 156.7, 144.2, 131.9, 130.0, 129.4, 128.8, 128.2, 124.5, 110.7, 94.1, 67.7, 63.4, 57.4, 53.3, 46.0, 43.6; IR (film): $\tilde{\nu}$ = 3399, 3034, 2924, 1697, 1566, 1465, 1428, 1263, 1221, 1123, 1069, 744, 698; MS (EI): m/z (%): 352 (5) [M⁺-I], 308 (6) [M⁺-I-CO₂], 247 (9), 232 (49), 188 (42), 91 (100); HRMS (ESI+): m/z: calcd for C₂₁H₂₂INO₄+Na: 502.0486 [M⁺+Na]; found: 502.0490 [M⁺+Na]. **Minor diastereomer:** $[\alpha]_D^{20} = -19.7^\circ$ (c = 1.4, CH₂Cl₂); ¹H NMR (300 MHz, CD₃CN, 70°C): δ = 7.36-7.29 (m, 3H), 7.20 (m, 3H), 6.83 (d, J = 7.5 Hz, 1H), 6.77 (dd, J = 8.2, 1.3 Hz, 1H), 5.82-5.78 (m, 1H), 5.70 (ddd, J = 10.3, 3.6, 1.8 Hz, 1H), 4.97 (d, J = 12.1 Hz, 1H), 4.68 (m, 1H), 4.25 (dd, J = 12.4, 6.0 Hz, 1H), 4.15 (m, 1H), 3.83 (s, 3H), 3.14 (dd, J = 13.5, 5.5 Hz, 1H), 3.04 (dd, J = 13.5, 8.6 Hz, 2H), 2.78 (dd, J = 12.5, 9.6 Hz, 1H), 2.01 (s, 1H); ¹³C NMR (75 MHz, CD₃CN, 70°C): δ = 159.6, 156.0, 144.4, 132.9, 130.0, 129.5, 128.9, 128.8, 124.5, 110.8, 94.0, 67.8, 64.3, 57.5, 53.5, 45.1, 44.4; IR (film): $\tilde{\nu}$ = 3387, 2924, 2852, 1696, 1465, 1427, 1265, 1071; MS (EI): m/z (%): 352 (5) [M⁺-I], 308 (6) [M⁺-I-CO₂], 247 (9), 232 (50), 188 (42), 91 (100); HRMS (ESI+): m/z: calcd for C₂₁H₂₂INO₄+Na: 502.0486 [M⁺+Na]; found: 502.0485 [M⁺+Na].

(S)-Benzyl-2-(2-iodo-3-methoxybenzyl)-5-oxo-5,6-dihydro-pyridine-1(2H)-carboxylate



(12): NaHCO₃ (1.49 g, 17.73 mmol) and DESS-MARTIN periodinane (1.65 g, 3.90 mmol)⁵ were successively added to a solution of alcohol **12a** (1.70 g, 2.80 mmol) in CH₂Cl₂ (40 mL) and the resulting mixture was stirred for 4 h. The reaction was quenched with aq. sat. Na₂S₂O₃ (20 mL) and stirring was continued for another 10 min before the mixture was diluted with EtOAc (100 mL). The organic layer was washed with

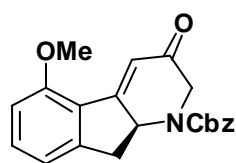
aq. sat. NaHCO₃ and brine (2 x 30 mL each) before it was dried over Na₂SO₄ and evaporated. Flash chromatography of the residue (SiO₂, EtOAc/hexanes, 1:4) afforded ketone **12** as a

⁵ a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155; b) R. K. Boeckman, P. Shao, J. J. Mullins, *Org. Synth.* **2000**, *77*, 141.

colorless solid (1.44 g, 85%). m.p. 131-132°C; $[\alpha]_D^{20} = -21.5^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (300 MHz, CD_3CN , 70°C): $\delta = 7.37$ -7.30 (m, 3H), 7.25-7.18 (m, 3H), 7.08 (dd, $J = 10.4$, 5.1 Hz, 1H), 6.85 (dd, $J = 7.6$, 1.3 Hz, 1H), 6.79 (dd, $J = 8.2$, 1.3 Hz, 1H), 6.08 (dd, $J = 10.4$, 1.6 Hz, 1H), 5.22 (m, 1H), 5.00 (d, $J = 12.4$ Hz, 1H), 4.79 (s, 1H), 4.51 (d, $J = 18.4$ Hz, 1H), 3.88 (d, $J = 18.5$ Hz, 1H), 3.84 (s, 3H), 3.30 (dd, $J = 13.7$, 5.3 Hz, 1H), 3.15 (dd, $J = 13.7$, 8.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3CN , 70°C): $\delta = 193.6$, 159.8, 155.7, 151.1, 143.1, 137.8, 130.3, 129.5, 129.0, 129.0, 127.8, 124.4, 111.1, 94.0, 68.3, 57.5, 53.7, 50.0, 43.1; IR (KBr): $\tilde{\nu} = 3062$, 3039, 3006, 2963, 2937, 2837, 1696, 1630, 1586, 1566, 1468, 1432, 1266, 1217, 773, 747, 698; MS (EI): m/z (%): 477 (<1) [M^+], 350 (3) [$M^+ - \text{I}$], 329 (2), 306 (21), 247 (12), 186 (15), 91 (100); HRMS (ESI+): m/z : calcd for $\text{C}_{21}\text{H}_{20}\text{INO}_4 + \text{Na}$: 500.0329 [$M^+ + \text{Na}$]; found: 500.0328 [$M^+ + \text{Na}$]; elemental analysis calcd (%) for $\text{C}_{21}\text{H}_{20}\text{INO}_4$ (477.3): C 52.84, H 4.22, N 2.93; found: C 52.72, H 4.20, N 2.83.

(S)-Benzyl-5-methoxy-3-oxo-2,3,9a-tetrahydro-1H-indeno[2,1-b]pyridine-1-

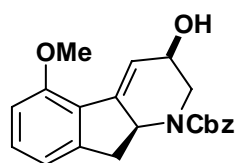
carboxylate (13): A mixture comprising enone **12** (280 mg, 0.587 mmol), Ph_3P (31 mg, 0.12 mmol), $\text{Pd}(\text{OAc})_2$ (26 mg, 0.12 mmol) and Ag_2CO_3 (162 mg, 0.587 mmol) in MeCN (10 mL) was stirred in a sealed flask for 20 min at 65°C. The resulting dark mixture was filtered through a short pad of Celite[®], which was carefully rinsed with EtOAc, the combined filtrates were evaporated and the residue purified by flash chromatography (SiO_2 , EtOAc/hexanes, 1:4) to give product **13** as pale brown solid (155 mg, 75%).



13

m.p. 139-140°C (dec); $[\alpha]_D^{20} = +50.8^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (400 MHz, CD_2Cl_2 , 25°C): $\delta = 7.43$ -7.33 (m, 6H), 6.96 (d, $J = 7.5$ Hz, 1H), 6.82 (d, $J = 8.3$ Hz, 1H), 6.77 (d, $J = 2.5$ Hz, 1H), 5.20 (s, 2H), 4.62 (m, 1H), 4.44 (d, $J = 18.4$ Hz, 1H), 3.92 (s, 3H), 3.87 (dd, $J = 18.4$, 1.4 Hz, 1H), 3.84 (dd, $J = 16.0$, 7.6 Hz, 1H), 3.21 (dd, $J = 16.1$, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2 , 25°C): $\delta = 193.5$, 162.7, 158.8, 156.9, 148.3, 137.1, 134.3, 129.1, 128.7, 128.5, 124.2, 119.7, 117.9, 109.8, 67.9, 58.7, 56.0, 53.0, 39.9; IR (KBr): $\tilde{\nu} = 1710$, 1654, 1625, 1602, 1590, 1492, 1408, 1312, 1286, 1082, 780, 750; MS (EI): m/z (%): 349 (7) [M^+], 258 (9), 214 (7), 186 (100), 171 (5), 143 (8), 115 (11), 91 (33); HRMS (ESI+): m/z : calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_4 + \text{Na}$: 372.1206 [$M^+ + \text{Na}$]; found: 372.1210 [$M^+ + \text{Na}$]; elemental analysis calcd (%) for $\text{C}_{21}\text{H}_{19}\text{NO}_4$ (349.4): C 72.19, H 5.48, N 4.01; found: C 72.25, H 5.42, N 3.94.

Compound 14. Crystals suitable for X-ray structure determination were grown from toluene/pentane. ^1H NMR (400 MHz, CD_2Cl_2): $\delta = 1.83$ (br s, 1H), 2.81 (dd, $J = 15.2$, 8.6 Hz, 1H), 3.10-3.30 (m, 1H), 3.53 (dd, $J = 15.0$, 7.5 Hz, 1H), 4.18 (dd, $J = 11.8$, 4.1 Hz, 1H), 4.40-4.50 (m, 1H), 4.62 (tt, $J = 8.1$, 2.9 Hz, 1H), 5.21 (m, 2H), 6.18 (t, $J = 2.6$ Hz, 1H), 7.24-7.44 (m, 9H);

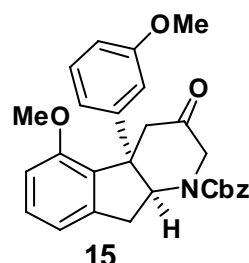


14

^{13}C NMR (100 MHz, CD_2Cl_2 , 25°C): $\delta = 38.0$, 48.7, 57.9, 65.6, 67.5, 115.8, 120.7, 122.1, 125.5, 127.2, 128.1, 128.2, 128.6, 129.0, 136.4, 137.5,

142.2, 142.3, 156.3; IR (film): $\tilde{\nu}$ = 3417, 2953, 1701, 1416, 1352, 1233, 1114, 1071, 837, 754, 698; MS (EI): m/z (%): 321 (6) $[M]^+$, 260 (5), 230 (7), 186 (4), 158 (100), 129 (27), 91 (67); HRMS (ESI+): m/z : calcd for $C_{20}H_{19}NNaO_3$ $[M+Na]^+$: 344.1257; found: 344.1259.

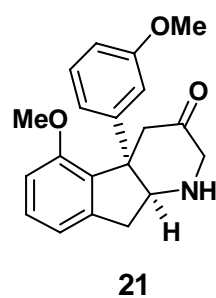
(4a*S*,9a*S*)-Benzyl-5-methoxy-4a-(3-methoxyphenyl)-3-oxo-2,3,4,4a,9,9a-hexahydro-1*H*-indeno[2,1-*b*]pyridine-1-carboxylate (15): A solution of freshly prepared 3-methoxyphenyl-



magnesium bromide (1 M in THF, 0.21 mL, 0.21 mmol) was added to a suspension of purified CuI (20 mg, 0.11 mmol)⁶ in THF (1.0 mL) at -78°C and the resulting mixture allowed to slowly warm to 0°C over the course of 1 h. After stirring for 45 min at 0°C , a solution of enone **13** (25 mg, 0.07 mmol) in THF (0.5 mL) was introduced and stirring continued for 5 min before the reaction was quenched with a mixture (9:1, 4 mL) of aq. sat. NH_4Cl and aq. NH_4OH at ambient temperature. A standard

extractive work up followed by purification of the crude product by flash chromatography (SiO_2 , EtOAc/hexanes, 1:4) gave product **15** as a colorless foam (20 mg, 61%). m.p. $43\text{--}45^\circ\text{C}$; $[\alpha]_D^{20} = -33.0^\circ$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (300 MHz, CD_3CN , 70°C): $\delta = 7.39\text{--}7.29$ (m, 6H), 7.22 (t, $J = 8.1$ Hz, 1H), 6.92 (m, 1H), 6.84 (d, $J = 8.5$ Hz, 1H), 6.81 (ddd, $J = 8.2, 2.5, 0.9$ Hz, 1H), 6.67 (ddd, $J = 7.8, 1.9, 0.9$ Hz, 1H), 6.62 (m, 1H), 5.19 (m, 2H), 5.08 (m, 1H), 4.40 (dd, $J = 19.3, 1.1$ Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.51–3.41 (m, 1H), 3.40 (d, $J = 2.5$ Hz, 2H), 3.10 (d, $J = 19.3$ Hz, 1H), 2.94 (d, $J = 17.7$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3CN , 70°C): $\delta = 208.5, 161.3, 158.0, 156.4, 147.7, 145.2, 138.2, 132.3, 131.7, 130.8, 129.6, 129.1, 128.8, 119.4, 113.6, 112.9, 111.5, 68.5, 65.6, 58.2, 56.2, 56.1, 51.0, 46.2, 38.5$; IR (film): $\tilde{\nu} = 3064, 3031, 2938, 2836, 1735, 1701, 1591, 1480, 1423, 1267, 1191, 1080, 772, 737, 699$; MS (EI): m/z (%): 457 (39) $[M]^+$, 366 (29), 348 (28), 338 (15), 322 (36), 304 (7), 294 (26), 265 (41), 214 (8), 121 (10), 91 (100); HRMS (ESI+): m/z : calcd for $\text{C}_{28}\text{H}_{27}\text{NO}_5 + \text{Na}$: 480.1781 $[M^+ + \text{Na}]$; found: 480.1786 $[M^+ + \text{Na}]$; elemental analysis calcd (%) for $\text{C}_{28}\text{H}_{27}\text{NO}_5$ (457.5): C 73.51, H 5.95, N 3.06; found: C 73.38, H 6.08, N 3.02.

(4a*S*,9a*S*)-5-Methoxy-4a-(3-methoxyphenyl)-4,4a,9,9a-tetrahydro-1*H*-indeno[2,1-*b*]pyridin-3(2*H*)-one (21): Palladium on charcoal (30 mg, 10% w/w) was added to a solution of



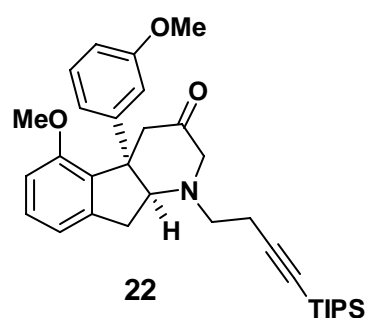
compound **15** (104 mg, 0.227 mmol) in MeOH (2 mL) and the resulting suspension stirred for 20 min under an atmosphere of H_2 (1 atm). The catalyst was then filtered off through a short pad of Celite[®], the filtrate was evaporated and the residue purified by flash chromatography to give product **21** as a pale yellow oil (70 mg, 94%). ^1H NMR (400 MHz, CD_3CN , 25°C): $\delta = 7.28$ (t, $J = 7.8$ Hz, 1H), 7.16 (t, $J = 8.1$ Hz, 1H), 6.92 (dd, $J = 7.5, 0.8$ Hz, 1H), 6.80 (d, $J = 8.1$ Hz, 1H), 6.74 (ddd, $J = 8.2, 2.5, 0.8$ Hz, 1H), 6.54 (ddd, $J = 7.8, 1.8, 0.9$ Hz, 1H), 6.52 (m, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 3.51 (dd, J

⁶ *Organometallics in Synthesis – A Manual* (M. Schlosser, Ed.), 2nd Ed., John Wiley & Sons Ltd., Chichester, 2002, p. 669.

= 7.8, 1.3 Hz, 1H), 3.43 (d, $J = 14.8$ Hz, 1H), 3.44-3.38 (m, 1H), 3.19 (d, $J = 14.9$ Hz, 1H), 3.16 (d, $J = 2.3$ Hz, 2H), 2.81 (d, $J = 17.1$ Hz, 1H), 2.44 (s, 1H); ^{13}C NMR (100 MHz, CD_3CN , 25°C): $\delta = 215.4, 160.6, 157.5, 149.6, 145.1, 134.9, 130.5, 130.4, 119.0, 117.7, 113.1, 111.5, 110.4, 67.9, 58.2, 55.7, 55.6, 54.4, 47.0, 39.6$; IR (film): $\tilde{\nu} = 3329, 3000, 2937, 2836, 1721, 1600, 1479, 1434, 1290, 1264, 1085, 1050, 772, 700$; MS (EI): m/z (%): 323 (100) [M^+], 295 (21), 266 (72), 252 (44), 235 (26), 174 (36), 165 (9), 145 (13), 121 (14), 115 (10); HRMS (ESI+): m/z : calcd for $\text{C}_{20}\text{H}_{21}\text{NO}_3 + \text{Na}$: 346.1414 [$M^+ + \text{Na}$]; found: 346.1418 [$M^+ + \text{Na}$].

(4a*S*,9a*S*)-5-Methoxy-4a-(3-methoxyphenyl)-1-(4-(tri-*iso*-propylsilyl)but-3-ynyl)-

4,4a,9,9a-tetrahydro-1*H*-indeno[2,1-*b*]pyridin-3(2*H*)-one (22): A mixture containing amine



21 (87 mg, 0.27 mmol), KHCO_3 (81 mg, 0.81 mmol) and 1-iodo-4-(tri-*iso*-propyl)silyl-3-butyne (272 mg, 0.81 mmol)⁷ in MeCN (2 mL) was stirred in a sealed flask at 90°C for 72 h. After reaching ambient temperature, the mixture was diluted with water (1 mL) and extracted with EtOAc (3 x 5 mL), the combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 , and evaporated. Purification of the residue by

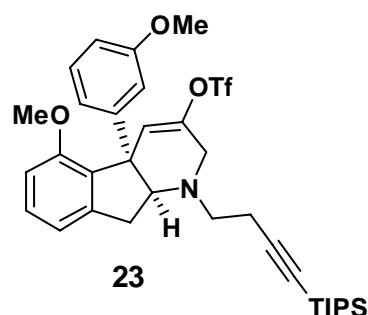
flash chromatography (SiO_2 , EtOAc/hexanes, 1:8) furnished product **22** as a colorless oil (101 mg (0.19 mmol, 70%). $[\alpha]_D^{20} = +9.2^\circ$ ($c = 0.6$, CH_2Cl_2); ^1H NMR (400 MHz, CD_2Cl_2 , 25°C): $\delta = 7.26$ (t, $J = 7.7$ Hz, 1H), 7.20 (t, $J = 8.1$ Hz, 1H), 6.89 (m, 1H), 6.76-6.70 (m, 3H), 6.63 (t, $J = 2.1$ Hz, 1H), 3.86 (t, $J = 5.3$ Hz, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 3.58 (d, $J = 13.8$ Hz, 1H), 3.28 (d, $J = 13.8$ Hz, 1H), 3.17 (d, $J = 5.3$ Hz, 2H), 3.10 (d, $J = 18.3$ Hz, 1H), 2.88 (d, $J = 18.7$ Hz, 1H), 2.81 (t, $J = 7.0$ Hz, 2H), 2.46 (t, $J = 6.9$ Hz, 2H), 1.07 (m, 21H); ^{13}C NMR (100 MHz, CD_2Cl_2 , 25°C): $\delta = 211.4, 160.3, 157.1, 149.4, 144.4, 133.6, 130.3, 129.8, 118.8, 117.2, 113.0, 111.2, 110.2, 107.6, 81.7, 71.6, 57.4, 57.2, 55.8, 55.6, 53.2, 45.4, 32.8, 19.9, 19.0, 12.0$; IR (film): $\tilde{\nu} = 2941, 2864, 2171, 1729, 1591, 1480, 1464, 1265, 1084, 883, 773, 677$; MS (EI): m/z (%): 531 (<1) [M^+], 488 (1), 336 (100), 289 (9), 279 (9), 121 (7); HRMS (ESI+): m/z : calcd for $\text{C}_{33}\text{H}_{45}\text{NO}_3\text{Si} + \text{Na}$: 554.3061 [$M^+ + \text{Na}$]; found: 554.3056 [$M^+ + \text{Na}$]; elemental analysis calcd (%) for $\text{C}_{33}\text{H}_{45}\text{NO}_3\text{Si}$ (531.8): C 74.53, H 8.53, N 2.63; found: C 74.38, H 8.41, N 2.51.

(4a*S*,9a*S*)-5-Methoxy-4a-(3-methoxyphenyl)-1-(4-(tri-*iso*-propylsilyl)but-3-ynyl)-

2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-*b*]pyridin-3-yl-trifluoromethanesulfonate (23): A solution of ketone **22** (100 mg, 0.19 mmol) in THF (2 mL) was added to a solution of KHMDS (30 mg, 0.15 mmol) in THF (5 mL) at -78°C . The resulting mixture was stirred for 15 min at that temperature and for additional 15 min at 0°C before solid 2-[*N,N*-bis(trifluoromethanesulfonyl)amino]pyridine (68 mg, 0.19 mmol) was introduced and stirring continued for another 10 min at 0°C . Quenching of the reaction with aq. sat. NH_4Cl followed by a standard extractive work up and flash chromatography (SiO_2 , EtOAc/hexanes, 1:4) of the

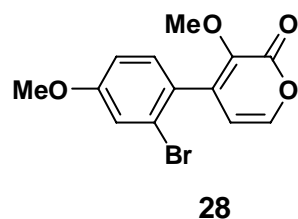
⁷ J. Chan, T. F. Jamison, *J. Am. Chem. Soc.* **2003**, *125*, 11514.

crude material delivered triflate **23** as a colorless oil (84 mg, 67%) and a second fraction containing unreacted **22** (22 mg, 22%). $[\alpha]_D^{20} = +18.6^\circ$ ($c = 0.6$, CH_2Cl_2); $^1\text{H NMR}$ (400 MHz, CD_2Cl_2 , 25°C): $\delta = 7.26$ (dd, $J = 7.7, 7.6$ Hz, 1H), 7.17 (dd, $J = 8.8, 7.7$ Hz, 1H), 6.89 (dd, $J = 7.5, 0.5$ Hz, 1H), 6.78 - 6.71 (m, 4H), 6.13 (m, 1H), 3.74 (s, 3H), 3.72 (t, $J = 8.4$ Hz, 1H), 3.55 (s, 3H), 3.51 (d, $J = 1.4$ Hz, 2H), 3.03 (dd, $J = 15.7, 8.8$ Hz, 1H), 2.94 (dd, $J = 15.8, 7.9$ Hz, 1H), 2.86 - 2.78 (m, 1H), 2.76 - 2.68 (m, 1H), 2.31 (ddd, $J = 7.7, 6.8, 2.1$ Hz, 2H), 1.03 (m, 21H); $^{13}\text{C NMR}$ (150 MHz, CD_2Cl_2 , 25°C): $\delta = 159.9, 156.8, 147.6,$



$146.5, 143.3, 131.4, 130.2, 129.2, 120.5, 119.6, 119.1$ (q, $J_{\text{C,F}} = 321$ Hz), $118.3, 113.4, 112.0, 110.3, 107.3, 81.9, 71.8, 57.1, 55.6, 55.0, 48.1, 29.2, 20.2, 18.9, 11.8$; IR (film): $\tilde{\nu} = 3068, 2942, 2865, 2172, 1686, 1600, 1481, 1465, 1422, 1265, 1247, 1213, 1143, 883, 678$; MS (EI): m/z (%): 663 (<1) [M^+], 620 (3), 530 (2), 468 (100), 307 (5), 265 (35), 250 (5), 238 (8), 196 (3); HRMS (ESI+): m/z : calcd for $\text{C}_{34}\text{H}_{44}\text{F}_3\text{NO}_5\text{SSi}+\text{Na}$: 686.2554 [$M^++\text{Na}$]; found: 686.2552 [$M^++\text{Na}$]; elemental analysis calcd (%) for $\text{C}_{34}\text{H}_{44}\text{F}_3\text{NO}_5\text{SSi}$ (663.9): C 61.51, H 6.68, N 2.11; found: C 61.38, H 6.62, N 2.04 .

4-(2-Bromo-4-methoxyphenyl)-3-methoxy-2H-pyran-2-one (28): A suspension of stannane

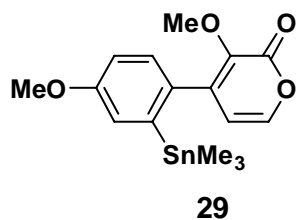


27 (220 mg, 0.76 mmol),⁸ 3-bromo-4-iodoanisole (238 mg, 0.76 mmol), CuI (13 mg, 68 μmol), CsF (210 mg, 1.38 mmol) and Pd(PPh₃)₄ (40 mg, 35 μmol) in DMF (1 mL) was stirred at 40°C for 3 h. Quenching of the reaction with water followed by a standard extractive work up and flash chromatography of the crude product (SiO₂, EtOAc/hexanes, 1:8 \rightarrow 1:4) gave compound **28** as a pale yellow solid (125 mg, 53%). m.p. 84 - 86°C ; $^1\text{H NMR}$ (400 MHz, CDCl_3 , 25°C): $\delta = 7.28$ (d, $J = 5.3$ Hz, 1H), 7.21 (d, $J = 2.5$ Hz, 1H), 7.17 (d, $J = 8.6$ Hz, 1H), 6.92 (dd, $J = 8.6, 2.5$ Hz, 1H), 6.12 (d, $J = 5.3$ Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3 , 25°C): $\delta = 160.4, 159.9, 144.3, 142.3, 139.1, 130.9, 127.3, 122.1, 118.3, 113.6, 109.7, 59.9, 55.6$; IR (film): $\tilde{\nu} = 3106, 2941, 2838, 1717, 1635, 1601, 1496, 1437, 1326, 1290, 1231, 1032, 1020, 851, 791$; MS (EI): m/z (%): 310 (97) [M^+], 282 (12), 267 (31), 253 (12), 239 (32), 231 (100) [$M^+-\text{Br}$], 211 (42), 203 (29), 132 (84); HRMS (ESI+): m/z : calcd for $\text{C}_{13}\text{H}_{11}\text{BrO}_4+\text{Na}$: 332.9733 [$M^++\text{Na}$]; found: 332.9735 [$M^++\text{Na}$]; elemental analysis calcd (%) for $\text{C}_{13}\text{H}_{11}\text{BrO}_4$ (311.1): C 50.18, H 3.56; found: C 50.30, H 3.48.

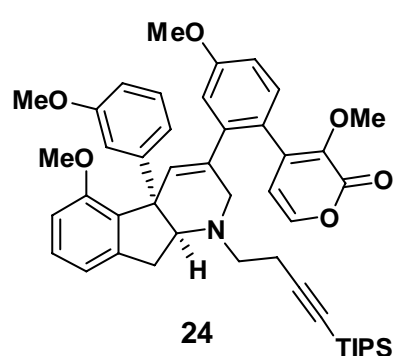
3-Methoxy-4-(4-methoxy-2-(trimethylstannyl)phenyl)-2H-pyran-2-one (29): A solution of bromide **28** (300 mg, 0.96 mmol), Me₃SnSnMe₃ (0.20 mL, 1.0 mmol) and Pd(PPh₃)₄ (33 mg, 29 μmol) in toluene (4 mL) was stirred in a sealed flask at 120°C until GC-MS showed complete consumption of the starting material. For work up, the mixture was filtered through a pad of Celite[®], the filtrate was evaporated and the residue purified by flash chromatography

⁸ P. S. Baran, N. Z. Burns, *J. Am. Chem. Soc.* **2006**, 128, 3908.

(SiO₂, CombiFlash[®]) to give product **29** as a pale yellow oil (117 mg, 31%). ¹H NMR (300 MHz, CD₂Cl₂, 25°C): δ = 7.31 (d, *J* = 5.2 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 2.7 Hz, 1H), 6.91 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.14 (d, *J* = 5.3 Hz, 1H), 3.84 (s, 3H), 3.64 (s, 3H), 0.19 (s, 9H); ¹³C NMR (75 MHz, CD₂Cl₂, 25°C): δ = 160.3, 159.6, 145.6, 144.9, 143.3, 141.9, 134.4, 130.0, 123.1, 113.6, 110.6, 60.0, 55.8, -7.4; IR (film): $\tilde{\nu}$ = 2977, 2936, 2836, 1721, 1633, 1586, 1565, 1284, 1230, 792, 772, 529; MS (EI): *m/z* (%): 396 (2) [*M*⁺], 381 (100) [*M*⁺-CH₃], 377 (43), 338 (18), 308 (8), 251 (8); HRMS (ESI⁺): *m/z*: calcd for C₁₆H₂₀O₄Sn+Na: 419.0275 [*M*⁺+Na]; found: 419.0278 [*M*⁺+Na].



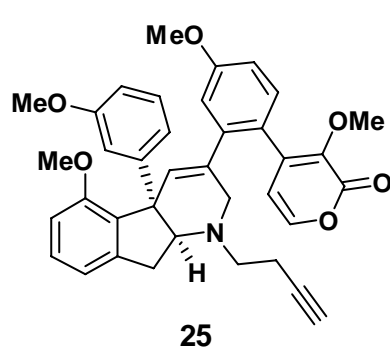
Pyrone 24: A Schlenk flask was charged with commercial tetra-*n*-butylammonium diphenylphosphinate (85 mg, 0.19 mmol), which was melted and allowed to re-cool to ambient temperature under high vacuum (10⁻⁴ Torr) twice. Thereafter, Pd(PPh₃)₄ (7 mg, 6 μmol) and copper thiophene-2-carboxylate (35 mg, 0.19 mmol)⁹ were introduced and the mixture was suspended in DMF (0.5 mL) before a degassed solution of triflate **23** (82 mg, 0.12 mmol) in DMF (0.5 mL) was added, followed by slow addition of a degassed solution of stannane **29** (49 mg, 0.12 mmol) in DMF (0.5 mL) over a period of 15 min. Once the addition was complete, stirring was continued for another 15 min before the reaction was quenched with water (2 mL), diluted with EtOAc (10 mL) and filtered through a short pad of Celite[®]. The filtrate was washed with water and brine (5 mL each) before the organic layer was dried over Na₂SO₄ and evaporated. Purification of the residue by preparative TLC (SiO₂, EtOAc/hexanes, 1:2) gave product **24** as a colorless foam (60 mg, 65%, 86% based on recovered starting material) and a second fraction containing unreacted triflate **23** (21 mg). m.p. 70-75°C; [α]_D²⁰ = -51.2° (c = 1.1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃, 25°C): δ = 7.24 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.12 (t, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 2.6 Hz, 1H), 6.86 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.82 (d, *J* = 7.4 Hz, 1H), 6.76-6.68 (m, 3H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.54 (d, *J* = 5.2 Hz, 1H), 5.77 (s, 1H), 5.60 (d, *J* = 5.2 Hz, 1H), 3.87 (s, 3H), 3.76 (m, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.64 (d, *J* = 15.5 Hz, 1H), 3.43 (s, 3H), 3.38 (dd, *J* = 15.0, 1.9 Hz, 1H), 2.98-2.71 (m, 4H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.03 (m, 21H); ¹³C NMR (100 MHz, CDCl₃, 25°C): δ = 159.9, 159.7, 159.0, 155.9, 148.8, 143.9, 142.5, 141.3, 141.2, 140.8, 133.6, 131.3, 131.3, 129.9, 129.2, 128.3, 125.5, 119.4, 117.6, 114.1, 113.5, 112.6, 110.2, 109.7, 108.9, 107.1, 81.2, 70.3, 59.2, 56.7, 55.4, 55.1, 55.0, 54.8, 49.8, 28.0, 19.7, 18.6, 11.3; IR (KBr): $\tilde{\nu}$ = 2942, 2864, 2836, 2170, 1718, 1603, 1480, 1464, 1384, 1289, 1264, 883, 678; MS (EI): *m/z* (%): 745 (2) [*M*⁺], 714 (4),



⁹ G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1996**, *118*, 2748.

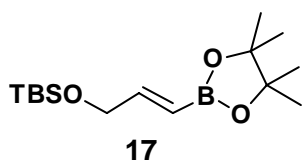
550 (100); HRMS (ESI+): m/z : calcd for $C_{46}H_{55}NO_6Si+Na$: 768.3691 [M^++Na]; found: 768.3690 [M^++Na].

Alkyne 25: Commercial tetra-*n*-butylammonium fluoride hydrate (12 mg, 46 μ mol) was added to a solution of compound **24** (23 mg, 31 μ mol) in THF (1.0 mL) at 0°C and the resulting mixture allowed to stir at ambient temperature for 20 min. The reaction was quenched with aq. sat. NH_4Cl (2 mL) and extracted with EtOAc (3x 5 mL), the combined organic layers were washed with water and brine (5 mL each) before they were dried over Na_2SO_4 and evaporated. Purification of the residue by flash chromatography (SiO_2 , EtOAc/hexanes, 1:2) afforded product **25** as a colorless foam (12 mg, 68%). m.p. 70-75°C;



$[\alpha]_D^{20} = -75.2^\circ$ ($c = 1.2$, CH_2Cl_2); 1H NMR (600 MHz, $CDCl_3$, 25°C): $\delta = 7.24$ (t, $J = 8.1$ Hz, 1H), 7.20 (d, $J = 8.5$ Hz, 1H), 7.13 (t, $J = 8.2$ Hz, 1H), 7.00 (d, $J = 2.6$ Hz, 1H), 6.87 (dd, $J = 8.5, 2.6$ Hz, 1H), 6.83 (d, $J = 7.5$ Hz, 1H), 6.77-6.74 (m, 2H), 6.71-6.69 (m, 1H), 6.66 (d, $J = 8.2$ Hz, 1H), 6.54 (d, $J = 5.2$ Hz, 1H), 5.79 (m, 1H), 5.61 (d, $J = 5.2$ Hz, 1H), 3.88 (s, 3H), 3.74 (m, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 3.64 (m, 1H), 3.44 (s, 3H), 3.36 (dd, $J = 16.9, 2.1$ Hz, 1H), 2.94 (dd, $J = 15.5, 9.3$ Hz, 1H), 2.83 (dd, $J = 15.5, 8.2$ Hz, 1H), 2.80-2.72 (m, 2H), 2.30-2.26 (m, 2H), 1.89 (t, $J = 2.7$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, 25°C): $\delta = 159.9, 159.7, 159.0, 155.9, 148.7, 144.0, 142.5, 141.2, 141.2, 140.8, 133.5, 131.4, 131.1, 129.9, 129.2, 128.3, 125.4, 119.4, 117.5, 114.1, 113.5, 112.5, 110.2, 109.7, 108.9, 82.6, 70.3, 69.1, 59.2, 56.7, 55.4, 55.1, 54.8, 54.2, 49.7, 28.0, 18.1$; IR (film): $\tilde{\nu} = 3284, 2937, 2835, 1712, 1634, 1602, 1479, 1320, 1289, 1264, 1210, 778$; MS (EI): m/z (%): 589 (11) [M^+], 558 (25), 550 (100), 252 (13), 53 (2); HRMS (ESI+): m/z : calcd for $C_{37}H_{35}NO_6+Na$: 612.2357 [M^++Na]; found: 612.2350 [M^++Na]; elemental analysis calcd (%) for $C_{37}H_{35}NO_6$ (589.7): C 75.36, H 5.98, N 2.38; found: C 75.30, H 6.07, N 2.33.

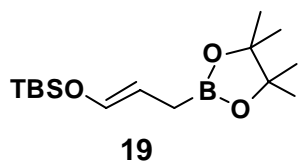
Vinylboronate 17. Pinacolborane (1.50 mL, 10.4 mmol) was added at 0°C to a solution of 3-(*tert*-butyldimethylsilyloxy)-1-propyne **16** (2.00 mL, 9.86 mmol) in CH_2Cl_2 (8 mL). After stirring for 5 min, the resulting mixture was transferred via canula to a cooled (0°C) suspension of $Cp_2ZrH(Cl)$ (136 mg, 0.493 mmol) in CH_2Cl_2 (4 mL) and the resulting mixture stirred at ambient temperature for 24 h. The reaction was quenched



by slow addition of H_2O (foaming!) and diluted with Et_2O (100 mL). A standard extractive work up followed by flash chromatography gave vinylboronate **17** as a colorless oil (2.06 g, 70%). The compound is prone to undergo slow hydrolysis but can be stored under inert atmosphere at -20°C for extended periods of time. 1H NMR (400 MHz, $CDCl_3$): $\delta = 0.04$ (s, 6H), 0.90 (s, 9H), 1.25 (s, 12H), 4.23 (dd, $J = 3.5, 2.1$ Hz, 2H), 5.74 (dt, $J = 17.9, 2.1$ Hz, 1H), 6.65 (dt, $J = 17.9, 3.5$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = -5.4, 18.4, 24.7, 25.9, 64.5, 83.1, 152.1$; ^{11}B NMR (128 MHz, $CDCl_3$): $\delta = 30.8$ ppm; IR (film): $\tilde{\nu} = 2979, 2930, 2896,$

2857, 1645, 1472, 1340, 1320, 1257, 1146, 1109, 974, 838, 777; MS (EI): m/z (%): 298 (1) $[M]^+$, 283 (7), 241 (42), 199 (1), 183 (2), 159 (4), 141 (100), 117 (5), 101 (28), 83 (39).

(E)-tert-Butyldimethyl-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-enyloxy)-



silane (19). Hydrogen gas was bubbled through a solution of [(cod)Ir(Ph₂PMe)₂]PF₆ (**18**) (100 mg, 0.118 mmol) in THF (40 mL) until the solution was colorless. The mixture was then purged with argon for 20 sec to remove residual hydrogen before a solution of

compound **17** (3.00 g, 10.1 mmol) in THF (5 mL) was introduced. The flask was sealed and the mixture stirred for 4 h before the solvent was evaporated and the residue triturated with hexane (3 x 10 mL). The combined hexane fractions were evaporated and the residue purified by Kugelrohr distillation (0.01 mbar, 125-150°C) to give product **19** as a colorless oil (2.40 g, 80%). ¹H NMR (400 MHz, CDCl₃): δ = 0.10 (s, 6H), 0.89 (s, 9H), 1.23 (s, 12H), 1.45 (d, *J* = 7.6 Hz, 2H), 5.01 (dt, *J* = 11.9, 7.6 Hz, 1H), 6.20 (dt, *J* = 11.9, 1.5 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ = -5.2, 18.3, 24.8, 25.7, 83.1, 106.3, 140.1; ¹¹B NMR (128 MHz, CDCl₃): δ = 34.0; IR (film): $\tilde{\nu}$ = 3035, 2978, 2887, 2858, 1660, 1472, 1362, 1325, 1254, 1132, 968, 839, 782, 672; MS (EI): m/z (%): 298 (6) $[M]^+$, 283 (5), 241 (35), 240 (11), 199 (2), 183 (6), 157 (2), 141 (100), 127 (3), 99 (32), 83 (38), 73 (34). These data correspond to those reported in the literature except that the ¹³C NMR signal at δ = 18.3 is missing in ref 10.

Crystallographic Summary

Crystal data for compound 14: C₂₁H₂₁N O₄, *M* = 351.39, colorless block, 0.30 x 0.30 x 0.30 mm³, orthorhombic, space group *P*2₁2₁2₁, (No. 19), *a* = 5.11170(10), *b* = 9.8304(2), *c* = 34.9917(8) Å, *V* = 1758.33(6) Å³, *Z* = 4, *D*_c = 1.327 g · cm⁻³, Cu-Kα radiation, λ = 1.54178 Å, *T* = 100 K, 2θ_{max} = 68.79°, 34417 reflections collected, 3215 unique (*R*_{int} = 0.051). Final GooF = 1.162, *R*1 = 0.034, *wR*2 = 0.079, 3189 reflections with *I* > 2σ(*I*), refinement on *F*², 237 parameters, multi-scan absorption correction applied, μ = 0.749 mm⁻¹; residual electron density = ± 0.2 eÅ⁻³. Absolute structure parameter = 0.2(2).¹¹

¹⁰ Y. Yamamoto, T. Miyairi, T. Ohmura, N. Miyaura, *J. Org. Chem.* **1999**, *64*, 296.

¹¹ H. D. Flack, *Acta Crystallogr., Sect. A*, **1983**, *39*, 876.