# Diastereoselective synthesis of the indeno-tetrahydropyridine core bearing a diaryl-substituted stereogenic quaternary carbon center of haouamine B

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#### **General Procedures.**

<sup>1</sup>H NMR spectra were recorded in chloroform-d, dimethyl sulfoxide-d<sub>6</sub>, or acetonitrile-d<sub>3</sub> on JEOL model JNM-LA 400 (400 MHz) or Bruker AVANCE 600 (600 MHz) spectrometers. <sup>13</sup>C NMR spectra were measured in chloroform-d, dimethyl sulfoxide-d<sub>6</sub>, or acetonitrile-d<sub>3</sub> on JEOL model JNM-LA 400 (100 MHz) or Bruker AVANCE 600 (150 MHz) spectrometers. Chemical shifts were reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard (CDCl<sub>3</sub>: 7.26 ppm for <sup>1</sup>H NMR, 77.0 ppm for <sup>13</sup>C NMR; (CD<sub>3</sub>)<sub>2</sub>SO: 2.49 ppm for <sup>1</sup>H NMR, 39.5 ppm for <sup>13</sup>C NMR; CD<sub>3</sub>CN: 1.93 ppm for <sup>1</sup>H NMR, 118.2 ppm for <sup>13</sup>C NMR). Abbreviations for signal coupling are as follows: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m =multiplet, br = broad. Coupling constants (J values) are given in hertz (Hz). Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. Low- and high- (CI and FAB) resolution mass spectra were determined on JEOL model JMS-AX 500 and JMS-700T spectrometers. Melting points (mp) are uncorrected and were recorded on a Yanagimoto micro melting point apparatus. Elemental analyses were performed with a FISONS EA1108 elemental analyzer by the staff at our Analytical Division. Analytical thin-layer chromatography (TLC) was carried out by precoated silica gel (Merck TLC plates silica gel 60 F<sub>254</sub>). Column chromatography was performed with Merck silica gel 60 (70-230 mesh). All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Yields refer to chromatographically and

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spectroscopically homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Tetrahydrofuran (THF) was distilled over sodium metal/benzophenone ketyl. Methanol (MeOH) was distilled over magnesium. Dichloromethane ( $CH_2Cl_2$ ), triethylamine ( $Et_3N$ ), and toluene were distilled over calcium hydride. 1,4-Dioxane was distilled over sodium metal.

#### **Experimental Procedures.**

Iodide 10. To 400 mL of tetrahydrofuran were successively added phenyllithium (83.3 mL, 188 mmol, 2.26 M in dibutyl ether) and methoxypyridine  $9^6$  (25.0 g, 94.2 mmol) dissolved in 360 mL of tetrahydrofuran at -78 °C under a nitrogen atmosphere, and the mixture was then stirred at 0 °C for 1 h. After the solution was cooled to -78 °C, iodine (29.9 g, 235 mmol) in 180 mL of tetrahydrofuran was added to the solution and the resulting mixture was stirred at the same temperature for 1.5 h. A saturated aqueous solution of sodium thiosulfate was added to the solution, and the aqueous layer was extracted with ethyl acetate three times. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl sulfate = 97:3 to 90:10) on 500 g of silica gel to afford crude iodide 10, which was recrystallized from methanol to provide iodide 10 (26.9 g, 72.9% yield) as a white solid:  $R_f = 0.33$  (hexane/diethyl ether = 80:20); mp 57–58 °C (from methanol);  $\delta_H$ (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 8.85 (1 H, s), 8.43 (1 H, s), 3.99 (3 H, s), 1.45 (3 H, sep, J 7.5), 1.10 (18 H, d, J 7.6);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>; CDCl<sub>3</sub>) 171.7, 160.5, 156.7, 126.0, 87.2, 61.3, 18.9, 11.8; IR (neat)  $v_{max}/cm^{-1}$  2943, 2864, 1543, 1458, 1411, 1387, 1254, 1142, 1063, 996, 881, 811, 735, 675, 642; FAB-MS m/z 392.2 [(M + H)<sup>+</sup>, 100%], 348.2 [(M - C<sub>3</sub>H<sub>7</sub>)<sup>+</sup>, 20], 278.1 (7), 264.1 (8), 248.1 (5), 136.1 (5); FAB-HRMS calcd for  $C_{15}H_{27}NOSiI [(M + H)^+]$  392.0907, found 392.0905; FAB-HRMS calcd for  $C_{12}H_{19}NOSiI$  [(M -  $C_{3}H_{7}$ )<sup>+</sup>] 348.0281, found 348.0286. Found: C, 46.0; H, 6.7; N, 3.6. C<sub>13</sub>H<sub>26</sub>NOSiI requires C, 46.0; H, 6.7; N, 3.6%.

Methoxypyridine 11. To a solution of iodide 10 (25.0 g, 63.9 mmol) in 320 mL of dimethoxyethane were successively added tetrakis(triphenylphosphine)palladium(0) (2.22 g, 1.92

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mmol), 3-methoxyphenylboronic acid (7) (9.71 g, 63.9 mmol), and a 2 M aqueous solution of sodium carbonate (125 mL, 250 mmol), and the mixture was stirred under reflux for 22 h. After the solution was cooled to room temperature, water was added to the solution and the aqueous layer was extracted with ethyl acetate three times. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purifed by column chromatoraphy (hexane/ethyl acetate = 95:5 to 80:20) on 200 g of silica gel to yield a mixture of methoxypyridine 11 and byproducts (9.54 g) and pure methoxypyridine 11 (16.7 g, 70.4% yield). The mixture (9.54 g) was further subjected to column chromatography (hexane/ethyl acetate = 95:5 to 80:20) on 150 g of silica gel to furnish additional methoxypyridine **11** (6.48 g, 27.3% yield, total 97.7% yield) as a brownish oil:  $R_f = 0.48$  (hexane/ethyl acetate = 70:30);  $\delta_H$  (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 8.48 (1 H, s), 8.44 (1 H, s), 7.36 (1 H, t, J 7.9), 7.05 (1 H, d, J 7.6), 7.01 (1 H, dd, J 2.4, 1.5), 6.93 (1 H, dd, J 8.0, 2.4), 3.85 (3 H, s), 3.38 (3 H, s), 1.47 (3 H, sep, J 7.5), 1.12 (18 H, d, J 7.3);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>; CDCl<sub>3</sub>) 169.7, 159.8, 156.2, 153.6, 138.3, 129.7, 127.4, 122.0, 121.5, 114.7, 113.0, 60.1, 55.3, 18.9, 11.7; IR (neat)  $v_{max}/cm^{-1}$  2943, 2889, 2864, 1600, 1579, 1546, 1461, 1393, 1319, 1285, 1239, 1216, 1038, 1011, 882, 806, 792, 701, 675, 641; FAB-MS m/z 372.8  $[(M + H)^+, 100\%]$ , 328.7 (12), 244.5 (12), 228.5 (10); FAB-HRMS calcd for C<sub>22</sub>H<sub>34</sub>NO<sub>2</sub>Si [(M + H)^+, 100\%] H)<sup>+</sup>] 372.2359, found 372.2369.

**Dihydropyridone 12.** To a solution of methoxypyridine **11** (856 mg, 2.30 mmol) in 23 mL of tetrahydrofuran was added dropwise phenyl chloroformate (0.29 mL, 2.30 mmol) at -78 °C under a nitrogen atmosphere, and the mixture was stirred at the same temperature for 20 min. To the solution was added dropwise 3,5-dimethoxybenzylzinc chloride (**8**) (6.0 mL, 2.99 mmol, 0.5 M in tetrahydrofuran), and the mixture was stirred at -78 °C for 30 min. After a 10% aqueous solution of hydrochloric acid (23 mL) was added to the solution, the solution was allowed to warm to room temperature and the mixture was stirred for 17 h. The reaction mixture was extracted with ether three times. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/ethyl acetate = 90:10) on 50 g of silica gel to give a diastereomeric mixture of dihydropyridone **12** (1.14 g, 78.8%

yield) as a pale yellow oil:  $R_f = 0.24$  (hexane/ethyl acetate = 80:20);  $\delta_H$  (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 7.96 (1 H, br s), 7.46–7.00 (5 H, m), 6.95–6.72 (4 H, m), 6.37 (3 H, br s), 5.15 (1 H, br s), 3.74 (9 H, br s), 3.63 (1 H, s), 3.28–3.10 (1 H, m), 2.97–2.83 (1 H, m), 1.38 (3 H, sep, *J* 7.4), 1.08 (9 H, d, *J* 7.3), 1.04 (9 H, d, *J* 7.3);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>; CDCl<sub>3</sub>) 196.3, 161.0, 159.8, 152.0, 150.2, 146.4, 145.2, 138.4, 137.8, 129.7, 129.4, 126.2, 121.1, 119.0, 113.2, 112.7, 112.3, 107.5, 99.3, 59.0, 58.2, 55.2, 55.1, 54.1, 52.7, 38.1, 37.4, 18.73, 18.69, 11.1; IR (neat)  $v_{max}$ /cm<sup>-1</sup> 3059, 2942, 2864, 1736, 1656, 1596, 1575, 1492, 1462, 1430, 1382, 1325, 1295, 1246, 1199, 1149, 1068, 1054, 1006, 920, 882, 835, 736, 693, 639; FAB-MS *m*/*z* 630.5 [(M + H)<sup>+</sup>, 5%], 586.4 (20), 434.3 (100), 372.3 (10), 314.3 (10); FAB-HRMS calcd for C<sub>37</sub>H<sub>48</sub>NO<sub>6</sub>Si [(M + H)<sup>+</sup>] 630.3251, found 630.3234.

Vinylogous Amide 13. To a solution of dihydropyridone 12 (3.47 g, 5.51 mmol) in 180 mL of methanol was added portionwise sodium methoxide (2.98 g, 55.1 mmol) under a nitrogen atmosphere, and the solution was stirred under reflux for 1.5 h. After the solution was cooled to room temperature, oxalic acid (24.8 g, 274 mmol) was added to the solution and the solution was further stirred at room temperature for 42 h. A saturated aqueous solution of sodium bicarbonate was added to the reaction mixture, and the resulting mixture was extracted with dichloromethane three times. The organic layer was dried over potassium carbonate and concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane/methanol = 97:3) on 100 g of silica gel to afford a *trans:cis* = 83:17 mixture of vinylogous amide **13** (1.72 g, 88.4%) yield) based on the <sup>1</sup>H NMR as a pale yellow syrup:  $R_f = 0.24$  (dichloromethane/methanol = 95:5);  $\delta_{\rm H}$  (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 7.26 (0.83 H, t, J 7.9), 7.24 (0.17 H, t, J 7.9), 7.17 (0.17 H, t, J 7.0), 7.09 (0.83 H, t, J 7.1), 6.88 (0.17 H, d, J 7.7), 6.86–6.78 (2.83 H, m), 6.34 (1 H, t, J 2.2), 6.27 (1.66 H, d, J 2.2), 6.26 (0.34 H, d, J 2.2), 5.19–5.15 (0.17 H, d, J 7.0), 5.16 (0.83 H, d, J 7.3), 5.08 (0.83 H, br s), 5.02 (0.17 H, br s), 4.12 (0.17 H, dt, J 10.3, 5.1), 3.89 (0.83 H, tdd, J 10.0, 4.5, 1.5), 3.79 (2.49 H, s), 3.78 (0.51 H, s), 3.77 (4.98 H, s), 3.76 (1.02 H, s), 3.45 (0.83 H, d, J 10.0), 3.41 (0.17 H, d, J 5.4), 2.75 (0.17 H, dd, J 12.7, 4.6), 2.73 (0.83 H, dd, J 13.5, 4.5), 2.65 (0.83 H, dd, J 13.7, 10.2), 2.34 (0.17 H, dd, J 13.9, 10.5); δ<sub>c</sub> (100 MHz; CDCl<sub>3</sub>; CDCl<sub>3</sub>) 192.7 (minor), 192.2 (major), 161.3 (major), 159.9 (major), 159.7 (minor), 150.9 (minor), 149.6 (major), 139.5 (major), 139.3 (major),

139.0 (minor), 136.5 (minor), 129.7 (major), 129.5 (minor), 121.8 (minor), 121.1 (major), 115.3 (minor), 114.9 (major), 112.55 (minor), 112.49 (major), 107.2 (major), 107.1 (minor), 99.8 (major), 98.9 (minor), 98.7 (major), 59.2 (major), 57.5 (minor), 57.3 (major), 55.9 (minor), 55.3 (major), 55.20 (major), 55.18 (minor), 39.7 (major), 37.4 (minor); IR (neat)  $v_{max}$ /cm<sup>-1</sup> 3254, 3047, 3005, 2941, 2837, 1579, 1489, 1461, 1430, 1401, 1345, 1322, 1286, 1259, 1233, 1202, 1147, 1051, 833, 776, 732, 699; FAB-MS *m*/*z* 354.6 [(M + H)<sup>+</sup>, 95%], 266.5 (43), 202.4 (100), 154.2 (30), 136.2 (30); FAB-HRMS calcd for C<sub>21</sub>H<sub>24</sub>NO<sub>4</sub> [(M + H)<sup>+</sup>] 354.1706, found 354.1717.



Iodide 17. To a solution of vinylogous amide 13 (trans:cis = 83:17, 700 mg, 1.98 mmol) in 10 mL of dichloromethane were successively added potassium carbonate (821 mg, 5.94 mmol) and iodine (503 mg, 3.96 mmol) at room temperature under a nitrogen atmosphere, and the solution was stirred at the same temperature for 3 h. A saturated aqueous solution of sodium thiosulfate was added to the solution, and the mixture was extracted with dichloromethane three times. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to provide a *trans:cis* = 85:15 mixture of iodide 17 (926 mg, 97.5% yield) based on the <sup>1</sup>H NMR as a white crystal:  $R_f = 0.50$  (dichloromethane/methanol = 95:5); mp = 155–159 °C;  $\delta_H$  (400 MHz; DMSO-d<sub>6</sub>; (CD<sub>3</sub>)<sub>2</sub>SO) 8.15 (0.15 H, br d, J 4.6), 8.04 (0.85 H, d, J 6.8), 7.87 (0.85 H, d, J 6.6), 7.75 (0.15 H, d, J 6.8), 7.25 (0.85 H, t, J 7.9), 7.21 (0.15 H, t, J 7.8), 6.87 (0.85 H, dd, J 8.2, 2.3), 6.81 (0.15 H, dd, J 8.3, 2.2), 6.74 (1 H, d, J 7.3), 6.68 (1 H, d, J 1.2), 6.35 (1.3 H, s), 6.31 (1.7 H, s), 5.74 (0.15 H, s), 4.36 (0.85 H, q, J 6.4), 4.18-4.09 (0.15 H, m), 3.72 (3 H, s), 3.71 (0.9 H, s), 3.69 (5.1 H, s), 3.56 (0.15 H, d, J 5.4), 3.49 (0.85 H, d, J 4.6), 2.78 (0.15 H, dd, J 13.7, 8.8), 2.72 (0.15 H, dd, J 14.3, 6.2), 2.64 (0.85 H, dd, J 14.0, 6.0), 2.42 (0.85 H, dd, J 13.8, 8.4);  $\delta_{C}$  (100 MHz; DMSO-d<sub>6</sub>; (CD<sub>3</sub>)<sub>2</sub>SO) 185.3 (major), 184.3 (minor), 160.4 (major), 159.2 (minor), 159.1 (major), 157.2 (major), 155.4 (minor), 140.3 (minor), 139.4 (minor), 139.2 (major), 136.5 (major), 129.39 (major), 129.36 (minor),

121.1 (major), 120.0 (minor), 115.1 (major), 113.8 (minor), 112.2 (major), 112.0 (minor), 107.3 (minor), 106.9 (major), 98.7 (major), 98.4 (minor), 57.6 (minor), 56.9 (major), 55.04 (minor), 55.02 (major), 54.92 (minor), 54.87 (major), 53.6 (minor), 53.5 (major), 37.8 (minor), 35.9 (major); IR (neat)  $v_{max}$ /cm<sup>-1</sup> 3237, 3000, 2935, 2836, 1596, 1554, 1489, 1463, 1430, 1331, 1254, 1204, 1151, 1055, 835, 765, 690; FAB-MS *m*/*z* 480.6 [(M + H)<sup>+</sup>, 27%], 354.6 (40), 328.4 (21), 266.5 (100), 202.4 (40), 154.2 (88), 136.2 (80); FAB-HRMS calcd for C<sub>21</sub>H<sub>23</sub>NO<sub>4</sub>I [(M + H)<sup>+</sup>] 480.0672, found 480.0688. Found: C, 52.55; H, 4.6; N, 2.9. C<sub>21</sub>H<sub>22</sub>NO<sub>4</sub>I requires C, 52.6; H, 4.6; N, 2.9%.



**17** (1.95 Dihydropyridone 14. To a solution of iodide g, 4.07 mmol) and 4-(N,N-dimethylamino)pyridine (49.7 mg, 0.407 mmol) in 40 mL of dichloromethane were consecutively added dropwise triethylamine (5.6 mL, 40.7 mmol) and benzyl chloroformate (1.40 mL, 9.76 mmol) under a nitrogen atmosphere at room temperature, and the solution was stirred at the same temperature for 30 min. Water was added to the solution, and the aqueous layer was extracted with dichloromethane three times. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate = 90:10 to 80:20) on 100 g of silica gel to yield dihydropyridone 14 (2.36 g, 94.5% yield) as a pale yellow syrup:  $R_f = 0.39$  (hexane/ethyl acetate = 70:30);  $\delta_{\rm H}$  (600 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 8.40 (0.6 H, br s), 8.25 (0.4 H, br s), 7.43–7.25 (5 H, m), 7.14 (1 H, t, J 8.0), 6.76 (1 H, dd, J 8.2, 2.3), 6.64 (1 H, d, J 7.8), 6.61 (1 H, d, J 2.3), 6.45–6.11 (2 H, br), 6.35 (1 H, s), 5.34–4.85 (2.88 H, br), 4.69 (0.12 H, d, J 5.9), 3.89 (1 H, br s), 3.73 (6 H, br s), 3.69  $(2.55 \text{ H}, \text{ s}), 3.67 (0.45 \text{ H}, \text{ s}), 3.05-2.97 (1 \text{ H}, \text{ br}), 2.84 (1 \text{ H}, \text{dd}, J 9.8, 3.0); \delta_{C} (150 \text{ MHz}; \text{CDCl}_3;$ CDCl<sub>3</sub>) 187.3, 161.1, 159.9, 152.3–150.5 (br), 146.5 (br), 145.8 (br), 137.8, 137.2, 134.5, 129.9, 128.9, 128.8, 128.6, 128.5, 128.3, 127.6, 126.9, 118.9, 113.2, 112.7, 107.3, 99.5, 75.1 (br), 69.6, 65.3, 60.0 (br), 59.4 (br), 55.3, 55.2, 55.1, 53.4, 51.2, 50.8, 38.0–36.8 (br); IR (neat)  $v_{\text{max}}/\text{cm}^{-1}$  3064, 3033, 3000, 2958, 2937, 2837, 1727, 1670, 1594, 1579, 1489, 1456, 1430, 1391, 1324, 1280, 1233,

1205, 1190, 1150, 1051, 912, 835, 754, 734, 695; FAB-MS *m*/*z* 614.8 [(M + H)<sup>+</sup>, 10%], 462.6 (5), 418.6 (15), 328.4 (10), 266.5 (7), 254.5 (15), 152.3 (18), 91.1 (100); FAB-HRMS calcd for  $C_{29}H_{29}NO_6I$  [(M + H)<sup>+</sup>] 614.1039, found 614.1025.



**Dihydropyridone 18.** To a solution of iodide **14** (277 mg, 0.452 mmol), 3-methoxyphenylboronic acid (7) (82.4 mg, 0.542 mmol), tris(dibenzylideneacetone)dipalladium(0) (20.7 mg, 22.6 µmol), and 2-(di-t-butylphosphino)biphenyl (27.0 mg, 90.4 µmol) in 3.6 mL of tetrahydrofuran and 0.9 mL of water was added barium hydroxide monohydrate (257 mg, 1.36 mmol) under a nitrogen atmosphere at room temperature, and the solution was stirred at the same temperature for 2 h. A saturated aqueous solution of ammonium chloride was added to the solution, and the aqueous layer was extracted with ethyl acetate three tomes. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/ethyl acetate = 85:15) on 10 g of silica gel to furnish dihydropyridone 18 (242 mg, 90.1% yield) as a pale yellow syrup:  $R_f = 0.15$  (hexane/ethyl acetate = 80:20);  $\delta_{\rm H}$  (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 8.09 (0.6 H, br s), 7.89 (0.4 H, br s), 7.42–7.27 (5 H, m), 7.26 (1 H, t, J 7.8), 7.16 (1 H, t, J 7.8), 6.95 (2 H, br s), 6.84 (1 H, dd, J 8.4, 1.8), 6.80–6.71 (3 H, m), 6.41 (0.8 H, br s), 6.35 (1 H, s), 6.29 (1.2 H, br s), 5.38–4.85 (2.9 H, m), 4.70–4.66 (0.1 H, m), 3.80 (3 H, s), 3.73 (7 H, br s), 3.68 (3 H, s), 3.20–3.02 (0.9 H, m), 2.94 (0.9 H, dd, J 12.2, 10.0), 2.84 (0.1 H, dd, J 13.1, 9.9), 2.79 (0.1 H, dd, J 13.7, 3.4);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>; CDCl<sub>3</sub>) 191.4, 161.1, 159.9, 159.5, 152.9 (br), 152.4 (br), 139.1 (br), 138.3, 138.0, 135.5, 134.9, 129.9, 129.3, 128.83, 128.78, 128.75, 128.6, 128.5, 128.4, 128.2, 127.6, 127.0, 120.9, 119.1, 118.9 (br), 114.4 (br), 113.1, 112.7 (br), 107.5, 99.5, 69.6, 69.3, 65.3, 59.6 (br), 58.8 (br), 55.33, 55.29, 55.25, 55.1, 52.4 (br), 52.0 (br), 37.8 (br), 37.4 (br); IR (neat)  $v_{\text{max}}$ /cm<sup>-1</sup> 3067, 3033, 3000, 2938, 2836, 1723, 1665, 1595, 1489, 1455, 1429, 1390, 1343, 1283, 1260, 1234, 1205, 1149, 1050, 957, 918, 833, 776, 755, 734, 693; FAB-MS m/z 594.9 [(M + H)<sup>+</sup>, 4%], 460.7 (3), 307.5 (22), 289.5 (15), 154.3 (100), 136.2 (80); FAB-HRMS calcd for C<sub>36</sub>H<sub>35</sub>NO<sub>7</sub> [(M + H)<sup>+</sup>] 594.2492, found 594.2496.



Iodide 5. To a solution of dihydropyridone 18 (36.7 mg, 61.8  $\mu$ mol) in 0.6 mL of dichloromethane were sequentially added N-iodosuccinimide (15.3 mg, 68.0 µmol) and hydroxytosyloxyiodobenzene (2.4 mg, 6.18  $\mu$ mol) at room temperature under a nitrogen atmosphere, and the solution was stirred at the same temperature for 13 h. A saturated aqueous solution of sodium sulfite was added to the solution, and the mixture was extracted with dichloromethane three times. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/ethyl acetate = 90:10 to 80:20) on 3 g of silica gel to afford iodide 5 (37.1 mg, 83.5% yield) as a white syrup:  $R_f = 0.24$  (hexane/ethyl acetate = 70:30);  $\delta_H$  (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 8.08 (0.6 H, br s), 8.17–7.80 (0.4 H, br s), 7.40–7.15 (5 H, m), 7.28 (1 H, t, J 7.9), 7.16 (1 H, t, J 7.7), 7.00 (2 H, br s), 6.88-6.71 (4 H, m), 6.48-6.22 (2 H, m), 5.55-4.60 (3 H, m), 3.81 (6 H, s), 3.75 (3 H, s), 3.75–3.63 (1 H, br), 3.67 (3 H, s), 3.39 (0.9 H, dd, J 8.3, 3.2), 3.22 (0.9 H, br s), 3.15 (0.1 H, br), 2.96 (0.1 H, br);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>; CDCl<sub>3</sub>) 191.5, 190.1, 161.0, 160.9, 159.9, 159.7, 159.5, 159.1, 157.9, 152.9 (br), 141.3, 141.1, 140.2, 139.6, 139.1 (br), 137.8, 137.7, 135.5, 134.9, 134.8, 129.94, 129.87, 129.82, 129.31, 129.28, 128.81, 128.76, 128.74, 128.64, 128.62, 128.3, 128.2, 122.4, 120.9, 119.1, 119.0, 114.4, 113.1, 113.0, 112.9, 112.6, 107.9, 107.4, 99.5, 97.9, 82.1 (br), 69.3, 69.2, 69.1, 57.3, 56.4, 55.6, 55.4, 55.31, 55.27, 55.1, 53.0, 42.0; IR (neat)  $v_{\text{max}}/\text{cm}^{-1}$  3067, 3004, 2939, 2836, 1724, 1665, 1599, 1580, 1489, 1453, 1432, 1413, 1390, 1308, 1282, 1262, 1236, 1205, 1162, 1136, 1084, 1010, 957, 833, 778, 757, 734, 695; FAB-MS m/z 721.0 [(M + H)<sup>+</sup>, 2%], 595.0 (3), 307.5 (20), 289.5 (15), 154.3 (100), 136.2 (70); FAB-HRMS calcd for  $C_{36}H_{35}NO_7I$  [(M + H)<sup>+</sup>] 720.1458, found 720.1476.

Vinylogous Imide solution 4. А of iodide (187)5 0.260 mmol), mg, bis(triphenylphosphine)palladium(II) dichloride (18.2 mg, 26.0 µmol), and cesium carbonate (254 mg, 0.779 mmol) in 5 mL of degassed 1,4-dioxane was stirred under a nitrogen atmosphere at 100 °C for 14 h. After the solution was cooled to room temperature, a saturated aqueous solution of ammonium chloride was added to the solution and the mixture was extracted with ether three times. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate = 90:10 to 85:15 to 80:20) on 10 g of silica gel to afford vinylogous imide 4 (115 mg, 74.9% yield) as a pale yellow syrup:  $R_f = 0.24$  (benzene/ethyl acetate = 70:30);  $\delta_H$  (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 8.07 (0.5 H, br s), 7.94 (0.5 H, br s), 7.47–7.20 (5 H, m), 7.25 (1 H, t, J 7.9), 7.18 (1 H, t, J 7.9), 7.07 (2 H, br s), 6.88–6.71 (4 H, m), 6.41 (1 H, s), 6.36 (1 H, d, J 1.7), 5.36–5.03 (3 H, m), 3.794 (3 H, s), 3.786 (3 H, s), 3.71 (3 H, s), 3.51 (3 H, s), 3.50–3.15 (1 H, m), 3.11 (1 H, dd, J 14.3, 11.1); δ<sub>C</sub> (100 MHz; CDCl<sub>3</sub>; CDCl<sub>3</sub>) 191.7, 161.4, 161.0, 159.9, 159.5, 159.4, 158.9, 152.9 (br), 143.4, 141.0, 139.0 (br), 135.6, 134.9, 129.8, 129.3, 129.1, 129.0, 128.72, 128.67, 128.2, 128.1 (br), 123.4, 121.2, 119.3, 119.0, 114.4 (br), 113.3, 112.7, 112.3, 101.0, 99.2, 69.1, 66.9, 62.5, 55.8, 55.4, 55.3, 55.1, 35.2; IR (neat)  $v_{\text{max}}/\text{cm}^{-1}$  3064, 3033, 3000, 2939, 2836, 1725, 1667, 1600, 1489, 1454, 1429, 1393, 1362, 1335, 1310, 1260, 1212, 1174, 1150, 1104, 1047, 1019, 961, 832, 781, 759, 734, 696; FAB-MS *m/z* 592.9 [(M + H)<sup>+</sup>, 25%], 307.5 (20), 282.5 (50), 266.5 (30), 154.2 (100), 136.2 (80), 91.1 (70); FAB-HRMS calcd for  $C_{36}H_{34}NO_7$  [(M + H)<sup>+</sup>] 592.2335, found 592.2333.

Indeno-Tetrahydropyridine Core 3. To a solution of vinylogous imide 4 (53.0 mg, 89.6  $\mu$ mol) in 9.0 mL of toluene were successively added *p*-toluenesulfonyl hydrazide (167 mg, 0.896 mmol) and *p*-toluenesulfonic acid monohydrate (51.1 mg, 0.269 mmol) under a nitrogen atmosphere at room temperature, and the solution was stirred under reflux for 12 h. After the solution was cooled to room temperature, a saturated aqueous solution of sodium bicarbonate was added to the solution and the mixture was extracted with dichloromethane three times. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was purified

by column chromatography (hexane/ethyl acetate = 85:15) on 5 g of silica gel to provide the indeno-tetrahydropyridine core **3** (24.0 mg, 46.4% yield) as a pale yellow syrup and recovered starting material **4** (25.0 mg, 47.2% yield).

**3**:  $R_{\rm f} = 0.43$  (hexane/ethyl acetate = 70:30);  $\delta_{\rm H}$  (400 MHz; CD<sub>3</sub>CN; CD<sub>3</sub>CN; 70 °C) 7.36–6.96 (6 H, m), 7.19 (1 H, t, *J* 7.9), 7.02 (1 H, d, *J* 7.6), 6.96 (1 H, s), 6.87 (1 H, dd, *J* 8.3, 2.4), 6.79 (2 H, dd, *J* 7.8, 2.0), 6.74 (1 H, dd, *J* 2.2, 1.7), 6.48 (1 H, s), 6.42 (1 H, s), 6.24 (1 H, s), 5.00 (1 H, t, *J* 9.0), 4.99 (2 H, br s), 4.83 (1 H, d, *J* 17.6), 4.14 (1 H, d, *J* 17.8), 3.79 (6 H, s), 3.70 (3 H, s), 3.55 (3 H, s), 3.06 (2 H, d, *J* 9.5);  $\delta_{\rm C}$  (100 MHz; CD<sub>3</sub>CN; CD<sub>3</sub>CN; 70 °C) 163.0, 161.4, 161.1, 158.3, 156.6, 149.4, 144.4, 141.8, 138.5, 133.9, 130.9, 130.2, 129.6, 128.9, 128.4, 126.1, 125.4, 120.3, 119.1, 114.6, 113.8, 112.9, 112.5, 103.5, 99.5, 67.9, 64.3, 56.5, 56.4, 56.3, 56.2, 56.1, 42.5, 34.3; IR (neat)  $v_{\rm max}/{\rm cm}^{-1}$  2934, 2837, 1697, 1595, 1486, 1455, 1432, 1336, 1287, 1248, 1203, 1149, 1103, 1049, 968, 909, 777, 730, 697; FAB-MS *m*/*z* 577.9 (M<sup>+</sup>, 5%), 442.8 (5), 307.5 (10), 282.5 (10), 154.3 (100), 136.2 (95), 91.1 (85); FAB-HRMS calcd for C<sub>36</sub>H<sub>35</sub>NO<sub>6</sub> (M<sup>+</sup>) 577.2464, found 577.2465.

**Amine 15.** To a solution of alkene **3** (7.8 mg, 13.5  $\mu$ mol) in 1.4 mL of dichloromethane was added dropwise titanium tetrachloride (15  $\mu$ L, 0.135 mmol) under a nitrogen atmosphere at 0 °C, and the solution was stirred at the same temperature for 20 min. A saturated aqueous solution of sodium bicarbonate was added to the solution, and the mixture was extracted with dichloromethane three times. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane/methanol = 99:1 to 98:2) on 0.5 g of silica gel to afford amine **15** (4.4 mg, 73.5% yield) as a pale yellow oil:  $R_f$  = 0.50 (dichloromathane/methanol = 95:5);  $\delta_H$  (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 7.25 (1 H, t, *J* 8.1), 7.17 (1 H, t, *J* 7.9), 7.04–6.98 (1 H, m), 6.94 (1 H, dd, *J* 2.2, 2.0), 6.84–6.77 (1 H, m), 6.75 (1 H, s), 6.77–6.71 (1 H, m), 6.71–6.66 (1 H, m), 6.64 (1 H, dd, *J* 2.2, 2.0), 6.47 (1 H, d, *J* 2.0), 6.35 (1 H, d, *J* 2.0), 3.82 (3 H, s), 3.81 (3 H, s), 3.81–3.77 (2 H, m), 3.73 (3 H, s), 3.68 (3 H, s), 3.60 (1 H, dd, *J* 6.5, 3.2), 3.12 (1 H, dd, *J* 16.1, 6.6), 2.80 (1 H, dd, *J* 16.1, 3.2);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>; CDCl<sub>3</sub>) 161.2, 159.7, 159.6, 158.2, 147.7, 144.4, 141.6, 135.6, 129.3, 129.1, 128.3, 124.9, 119.5, 117.7, 113.6, 112.3, 111.1, 110.7, 101.7, 97.8, 66.7, 56.1, 55.5, 55.2, 55.1, 44.5,

10

37.0, 29.7; IR (neat)  $v_{\text{max}}/\text{cm}^{-1}$  3300, 2998, 2929, 2835, 1595, 1486, 1463, 1428, 1333, 1310, 1286, 1252, 1208, 1173, 1147, 1118, 1083, 1046, 827, 779, 734, 697; FAB-MS *m/z* 444.8 [(M + H)<sup>+</sup>, 5%], 307.5 (20), 289.5 (10), 154.3 (100), 136.2 (80); FAB-HRMS calcd for C<sub>28</sub>H<sub>30</sub>NO<sub>4</sub> [(M + H)<sup>+</sup>] 444.2175, found 444.2179.

Methyl Carbamate 16. To a solution of amine 15 (7.7 mg, 17.4 µmol) in 1.7 mL of dichloromethane were added dropwise triethylamine (9.6  $\mu$ L, 69.4  $\mu$ mol) and methyl chloroformate  $(2.7 \,\mu\text{L}, 34.7 \,\mu\text{mol})$  under a nitrogen atmosphere at room temperature, and the solution was stirred at the same temperature for 35 min. Water was added to the solution, and the mixture was extracted with dichloromethane three times. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate = 90:10 to 80:20) on 0.5 g of silica gel to give methyl carbamate **16** (6.4 mg, 73.9% yield), respective spectra of which were identical with those of the synthetic intermediate reported by Trauner and Grundl,<sup>4e</sup> as a pale yellow syrup:  $R_f = 0.31$  (hexane/ethyl acetate = 70:30); δ<sub>H</sub> (400 MHz; CD<sub>3</sub>CN; CD<sub>3</sub>CN; 70 °C) 7.28 (1 H, t, *J* 8.2), 7.20 (1 H, t, *J* 7.9), 7.02 (1 H, ddd, *J* 7.8, 1.7, 1.0), 6.96 (1 H, dd, J 2.4, 1.7), 6.88 (1 H, dd, J 8.2, 2.6), 6.78 (2 H, dd, J 8.0, 2.2), 6.74 (1 H, dd, J 2.2, 2.0), 6.49 (1 H, d, J 2.2), 6.42 (1 H, d, J 2.0), 6.24 (1 H, dd, J 2.0, 1.0), 4.92 (1 H, t, J 9.3), 4.76 (1 H, d, J 18.3), 4.11 (1 H, dd, J 17.9, 1.8), 3.802 (3 H, s), 3.799 (3 H, s), 3.72 (3 H, s), 3.56 (3 H, s), 3.53 (3 H, br s), 3.07 (1 H, dd, J 15.5, 8.9), 3.02 (1 H, dd, J 15.9, 9.8); δ<sub>C</sub> (100 MHz; CD<sub>3</sub>CN; CD<sub>3</sub>CN; 70 °C) 163.1, 161.5, 161.1, 158.3, 157.5, 149.4, 144.4, 141.9, 133.9, 130.9, 130.2, 126.1, 125.5, 120.3, 119.1, 114.6, 113.9, 112.8, 112.5, 103.5, 99.5, 64.3, 56.53, 56.46, 56.3, 56.23, 56.15, 53.3, 42.6, 34.3; IR (neat)  $v_{max}$ /cm<sup>-1</sup> 3050, 2998, 2935, 2837, 1697, 1594, 1486, 1447, 1340, 1287, 1248, 1205, 1148, 1112, 1086, 1048, 996, 970, 831, 772, 734, 699; FAB-MS m/z 501.9 (M<sup>+</sup>, 2.5%), 350.6 (5), 307.6 (12), 289.5 (8), 154.3 (100), 136.2 (70); FAB-HRMS calcd for  $C_{30}H_{31}NO_6$  (M<sup>+</sup>) 501.2151, found 501.2153.







#### 14

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