Application of the Rh(II)-Cyclization/Cycloaddition Cascade for the Total Synthesis of (±)-Aspidophytine

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Experimental Section

6-Iodo-2,3-dimethoxyphenylamine (14). A biphasic mixture of 220 mL of ether, 30 mL of an aqueous saturated Na_2CO_3 solution and 5.0 g (33 mmol) of dimethoxyaniline was stirred in the dark. To this mixture was added 8.8 g (54 mmol) of iodine monochloride in 36 mL of ether. The reaction mixture was stirred for 2 h, and the layers were separated. The organic layer was washed with a saturated Na_2SO_3 solution and the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 6.7 g (73%) of **14** as a yellow solid; mp 48-50 °C; IR (neat) 1601, 1481, 1458, 1291 and 1109 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.84 (s, 3H), 4.25 (brs, 2H), 6.19 (d, 1H, J = 9.0 Hz) and 7.31 (d, 1H, J = 9.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 56.0, 60.1, 74.0, 104.4, 133.3, 135.4, 141.8, and 153.2; Anal. Calcd. for $C_8H_{10}NO_2I$: C, 34.43; H, 3.61; N, 5.02. Found: C, 34.48; H, 3.52; N, 4.96.

4-(6-Iodo-2,3-dimethoxyphenylamino)-but-2-enoic Acid Methyl Ester (15). To a stirred solution of 4.5 g (16.1 mmol) of iodoaniline **14** in 60 mL of acetone/water (85:15) was added 2.5 mL (21 mmol) of methyl bromocrotonate and 5 g (60 mmol) of sodium bicarbonate. The resulting mixture was heated at reflux for 3 h and the dark reaction mixture was allowed to cool, diluted with ether and filtered through a pad of celite. The solution was added to brine and the organic layer was separated. The aqueous layer was washed twice with 250 mL of ether and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 1.7 g (38%) of starting material and 2.9 g (47%) of **15** as a clear oil; IR (neat) 1719, 1458, 1285 and 1170 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.77 (s, 3H), 3.84 (s, 3H), 3.91 (brs, 1H), 4.13 (dd, 1H, J = 5.3 and 2.0 Hz), 6.07 (dt, 1H, J = 15.6 and 2.0 Hz), 6.30 (d, 1H, J = 8.6 Hz), 7.05 (dt, 1H, J = 15.6 and 5.3 Hz) and 7.41 (d, 1H, J = 8.6Hz); ^{13}C-NMR

(100 MHz, $CDCl_3$) δ 48.4, 51.8, 56.2, 60.4, 80.7, 107.0, 121.3, 134.0, 139.6, 142.4, 146.8, 154.3 and 167.1.

(6,7-Dimethoxy-1-methyl-1*H*-indol-3-yl)-acetic Acid (16). A 3.8 g (3.4 mmol) sample of the aniline derivative **15** was dissolved in 60 mL of acetonitrile. To this solution was added 0.12 g (0.5 mmol) of palladium acetate, 3 mL (21 mmol) of triethylamine and 0.3 g (1.0 mmol) of tri-*o*-tolylphosphine. The mixture was heated at reflux for 3 h and the solvent was removed under reduced pressure. The residue was partitioned between 200 mL of ether and 50 mL of water and the layers were separated. The aqueous layer was washed twice with 200 mL of ether. The combined organic extracts were washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 2.3 g (90%) of (6,7-dimethoxy-1*H*-indol-3-yl)-acetic acid methyl ester as an oil; IR (neat) 1735, 1508, 1463, 1260 and 1127 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.75 (d, 2H, J = 1.2 Hz), 3.94 (s, 3H), 4.00 (s, 3H), 6.88 (d, 1H, J = 8.4 Hz), 7.09 (t, 1H, J = 1.2 Hz), 7.27 (d, 1H, J = 8.4 Hz) and 8.22 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 31.5, 52.2, 57.6, 61.0, 108.6, 108.9, 114.0, 122.9, 124.1, 130.9, 134.6, 147.4 and 172.6.

To a 4.9 g (20 mmol) sample of the above indole in anhydrous THF (150 mL) was added 2.6 g (39 mmol) of 85% potassium hydroxide pellets, 6.1 mL (98 mmol) of methyl iodide, 0.075 g (0.2 mmol) of tetrabutyl ammonium iodide together with 6.0 g of 4 Å molecular sieves and the mixture was stirred at rt for 2 h. The mixture was filtered over a pad of celite with THF and the solvent was removed under reduced pressure. The residue was subjected to flash silica gel chromatography to give 4.1 g (80%) of (6,7-dimethoxy-1-methyl-1*H*-indol-3-yl)-acetic acid methyl ester as an oil: IR (neat) 1735, 1508, 1463, 1260 and 1127 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 5H), 3.93 (s, 3H), 3.95 (s, 3H), 3.97 (s, 3H), 6.85 (d, 1H, J = 8.8 Hz), 6.87 (s, 1H) and 7.22 (d, 1H, J = 8.8 Hz); ^{13}C-

NMR (100 MHz, $CDCl_3$) δ 31.2, 35.5, 52.2, 57.7, 62.0, 106.8, 108.3, 114.1, 125.5, 129.0, 130.6, 136.1, 148.2 and 172.7.

A 1.0 g (3.8 mmol) sample of the above methyl ester and 0.5 g (7.6 mmol) of potassium hydroxide pellets in 40 mL of THF/water (1:1) was stirred for 2 h at rt. The THF solvent was removed under reduced pressure and 50 mL of H_2O was added. The resulting solution was washed with 50 mL of chloroform and the layers were separated and the aqueous layer was acidified to pH 2. The aqueous phase was extracted twice with 100 mL of chloroform and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 0.9 g (94%) of **16** as a clear oil: IR (neat) 1707, 1508, 1463, 1260 and 1126 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.72 (d, 2H, *J* = 0.8 Hz), 3.93 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 6.85 (d, 1H, *J* = 8.6 Hz), 6.87 (s, 1H) and 7.21 (d, 1H, *J* = 8.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 31.1, 35.5, 57.7, 62.0, 106.1, 108.5, 114.1, 125.4, 129.2, 130.6, 136.1, 148.3 and 177.6.

3-*tert*-Butoxycarbonylmethyl-2-oxo-piperidine-3-carboxylic Acid Ethyl Ester (18). To a stirred solution of 10.5 g (61 mmol) of 2-oxopiperidine-3-carboxylic acid ethyl ester (**17**) in 120 mL of THF at -78°C was added 28 mL (67 mmol) of a 2.4 M n-butyllithium solution in hexane. The resulting solution was allowed to warm to 0 °C for 10 min and was recooled to -78 °C. At this point, 11.2 g (67 mmol) of tert butyl bromoacetate were added followed by 4.5 g (13 mmol) of tetrabutyl ammonium iodide. The solution was allowed to warm up to room temperature while stirring vigorously. After stirring for 15 h the solvent was removed under reduced pressure and H_2O was added. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with a saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was recrystallized from a mixture of ethyl acetate/hexane to give 13.9 g (90%) of **18** as a white solid: mp 81-83°C; IR (neat) 1733, 1674, 1366, 1246 and 1155 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.22 (t,

3H, *J* = 7.2 Hz), 1.38 (s, 9H), 1.70-1.76 (m, 1H), 1.86-1.96 (m, 1H), 2.25 (dt, 1H, *J* = 13.6 and 3.6 Hz), 2.11-2.18 (m, 1H), 2.71 (d, 1H, *J* = 16.8 Hz), 3.01 (d, 1H, *J* = 16.8 Hz), 3.29-3.35 (m, 2H), 4.10-4.20 (m, 2H) and 6.87 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 14.1, 19.8, 28.1, 30.3, 40.8, 42.2, 51.7, 61.7, 81.0, 170.1, 170.3, and 172.0; Anal. Calcd. for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 59.03; H, 8.12; N, 4.87.

3-(3-*tert*-Butoxycarbonylmethyl-2-oxo-piperidin-3-yl)-3-oxo-propionic Acid Methyl Ester (19). A 5.4 g (19 mmol) sample of **18** and 2.4 g of lithium hydroxide (57 mmol) in THF (50 mL) and H_2O (50 mL) was stirred at rt for 12 h. The solvent was removed under reduced pressure and the residue was dissolved in water. The solution was washed with ethyl acetate and acidified to pH 2. The aqueous phase was extracted with chloroform and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 4.5 g (91%) of 3-*tert*-butoxycarbonylmethyl-2-oxo-piperidine-3-carboxylic acid as a white solid: mp 102-104°C; IR (neat) 3282, 1727, 1700, 1628, 1366, 1257 and 1155 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.78-2.10 (m, 3H), 2.30-2.38 (m, 1H), 2.68 (d, 1H, *J* = 16.4Hz), 3,12 (d, 1H, *J* = 16.4Hz), 3.32-3.46 (m, 2H) and 7.30 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.9, 28.2, 29.1, 41.8, 42.6, 51.4, 81.8, 170.0, 173.3 and 173.9; Anal. Calcd. for $C_{12}H_{19}NO_5$: C, 56.03; H, 7.44; N, 5.44. Found: C, 56.28; H, 7.44; N, 5.36.

To a 2.1 g (8.3 mmol) sample of the above carboxylic acid in methylene chloride (50 mL) was added 1.6 g (10 mmol) of 1,1'-carbonyldiimidazole and the solution was allowed to stir at rt under Ar for 12 h. The mixture was concentrated under reduced pressure and redissolved in 50 mL of THF. In the meantime, 2.6 g (17 mmol) of potassium methyl malonate, 1.6 g (17 mmol) of powdered magnesium chloride and a catalytic amount of 4-(dimethylamino)pyridine (0.1 g, 0.8 mmol) were vigorously stirred in 50 mL of THF and 25 mL of acetonitrile. After stirring for 2 h, the above lactam in THF was added dropwise to the

malonate solution together with 2.3 mL (17 mmol) of triethylamine. The solution was allowed to stir at rt for 12 h and then 80 mL of 1 N HCl was added. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 1.3 g (60%) of **19** as an off-white solid: mp 102-104°C; IR (neat) 1732, 1655, 1456, 1367, 1320 and 1156 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.75-1.90 (m, 3H), 2.42-2.49 (m, 1H), 2.69 (d, 1H, *J* = 16.4 Hz), 2.94 (d, 1H, *J* = 16.4 Hz), 3.28-3.43 (m, 2H), 3.72 (s, 1H), 3.77 (d, 1H, *J* = 16.6 Hz), 3.94 (d, 1H, *J* = 16.6 Hz) and 6.01 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.2, 28.2, 28.4, 41.9, 42.8, 45.6, 52.5, 58.1, 82.0, 168.1, 169.5, 170.7 and 200.8; Anal. Calcd. for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47. Found: C, 57.36; H, 7.40; N, 4.46.

3-(3-*tert*-Butoxycarbonylmethyl-2-oxo-piperidin-3-yl)-2-diazo-3-oxo-propionic Acid Methyl Ester (20). To a 4.8 g (15 mmol) sample of **19** in acetonitrile (125 mL) was added 1.9 g (18 mmol) of triethylamine and the solution was vigorously stirred for 30 min. To this mixture was added 3.5 g (31 mmol) of mesyl azide and the solution was stirred at rt for 10 h. The solution was concentrated under reduced pressure and recrystallized from ether which contained a trace of methylene chloride to give 5.0 g (96%) of **20** as a pale yellow solid: mp 152-154°C; IR (neat) 2124, 1725, 1669, 1480, 1437, 1321 and 1153 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.80-2.00 (m, 2H), 2.29 (dt, 1H, *J* = 12.4 and 4.0 Hz), 2.68-2.74 (m, 1H), 2.77 (d, 1H, *J* = 16.2 Hz), 2.92 (d, 1H, *J* = 16.2 Hz), 3.28-3.39 (m, 1H), 3.64 (dt, 1H, *J* = 11.2 and 4.8 Hz), 4.22 (s, 3H) and 5.65 (brs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.9, 25.7, 28.2, 38.4, 42.5, 52.4, 58.2, 80.8, 161.7, 170.4, 171.7 and 189.9; Anal. Calcd. for $C_{15}H_{21}N_3O_6$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.21; H, 6.43; N, 12.33.

3-{3-*tert*-Butoxycarbonylmethyl-1-[2-(6,7-dimethoxy-1-methyl-1*H*-indol-3-yl)-acetyl]-2-oxo-piperidin-3-yl}-2-diazo-3-oxo-propionic Acid Methyl Ester (10). A 0.9 g (3.4 mmol) sample of indole acetic acid **16** was dissolved in methylene chloride (40 mL) and 1.5 g (12 mmol) of oxalyl chloride was added dropwise. The solution was stirred overnight, concentrated under reduced pressure and the remaining solid was taken up in benzene and then immediately added to a vigorously stirred mixture containing 1.1 g (3.4 mmol) of diazo amide **20** and 8 g of 4 Å molecular sieves in benzene (30 mL). After stirring for 8 h, the mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel to give 1.8 g (92%) of **10** as a colorless oil: IR (neat) 2144, 1718, 1686, 1331 and 1154 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.65-1.77 (m, 1H), 1.82-1.92 (m, 1H), 2.14-2.30 (m, 1H), 2.19 (d, 1H, J = 15.8 Hz), 2.48 (d, 1H, J = 15.8 Hz), 2.62-2.72 (m, 1H), 3.72 (dt, 1H, J = 12.4 and 4.4 Hz), 3.78 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 4.03-4.10 (m, 1H), 4.05 (d, 1H, J = 16.8 Hz), 4.38 (d, 1H, J = 16.8 Hz), 6.78 (s, 1H), 6.80 (d, 1H, J = 8.8 Hz) and 7.14 (d, 1H, J = 8.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.5, 26.8, 28.2, 35.4, 36.1, 37.2, 44.7, 52.6, 57.6, 60.6, 61.9, 81.1, 107.5, 108.3, 114.0, 125.9, 129.9, 130.4, 136.1, 148.1, 161.7, 169.9, 173.0, 176.9 and 189.9.

3*a*-*tert*-Butoxycarbonylmethyl-5,12*b*-epoxy-7,8-dimethoxy-6-methyl-4,12-dioxo-2,3,3*a*,4,5,5*a*,6,11,12,12*b*-decahydro-1*H*-6,12*a*-diaza-indeno[7,1-*cd*]fluorene-5-carboxylic Acid Methyl Ester (11). A 1.2 g (2.2 mmol) sample of diazo amide **10** was stirred with rhodium(II) acetate (7.5 mg) and 8 g of 4 Å molecular sieves in benzene (100 mL) and the mixture was heated at reflux for 2 h. At the end of this time, the mixture was allowed to cool to rt and was filtered through a pad of celite. The solvent was removed under reduced pressure to give 1.2 g (97%) of **11** as a colorless oil: IR (neat) 1778, 1733, 1613, 1474, 1342, 1262 and 1156 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.13 (d, 1H, J = 14.6 Hz),

1.27 (s, 9H), 1.60 (d, 1H, *J* = 14.6 Hz), 1.70-1.79 (m, 2H), 1.91-2.01 (m, 1H), 2.11-2.18 (m, 1H), 2.70 (d, 1H, *J* = 17.2 Hz), 2.95 (d, 1H, *J* = 17.2 Hz), 3.04-3.12 (m, 1H), 3.11 (s, 3H), 3.60 (s, 3H), 3.74 (s, 3H), 3.80-3.86 (m, 1H), 3.82 (s, 3H), 4.27 (s, 1H), 6.23 (d, 1H, *J* = 8.6 Hz) and 6.51 (d, 1H, *J* = 8.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.3, 26.6, 28.0, 28.2, 32.9, 38.2, 39.3, 45.3, 50.4, 53.5, 56.4, 59.0, 60.3, 81.2, 82.4, 92.1, 104.0, 104.1, 118.8, 122.0, 128.5, 135.5, 145.7, 155.3, 166.3, 169.1, 176.9 and 202.4; HRMS Calcd. for [$C_{28}H_{34}N_2O_9$ + H^+]: 543.2337. Found: 543.2339.

Lewis Acid Catalyzed Ring Opening of Cycloadduct 11. A 1.2 g (2.2 mmol) sample of cycloadduct **11** was dissolved in methylene chloride (100 mL) and cooled to 0 °C. To this mixture was added 1.5 g (12 mmol) of boron trifluoride etherate in methylene chloride (10 mL). The mixture was allowed to warm to rt overnight. The solution was then added to a saturated aqueous solution of $NaHCO_3$ (200 mL), the organic layer was separated, and the aqueous layer was extracted three times with methylene chloride. The solution was dried over $MgSO_4$ and concentrated under reduced pressure. The product was recrystallized from ether to give 0.72 g (70%) of **23** as a white solid: mp 223-225 °C; IR (neat) 1798, 1727, 1608, 1493, 1262, and 1064 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.54-1.70 (m, 3H), 2.29 (d, 1H, *J* = 17.2 Hz), 2.38 (d, 1H, *J* = 17.2 Hz), 2.45-2.55 (m, 1H), 2.85-2.95 (m, 1H), 3.04 (d, 1H, *J* = 18.0 Hz), 3.13 (d, 1H, *J* = 18.0 Hz), 3.16 (s, 3H), 3.67 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 3.88-3.96 (m, 1H), 4.26 (s, 1H), 4.80 (s, 1H), 6.50 (d, 1H, *J* = 8.4 Hz) and 6.86 (d, 1H, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 18.5, 33.4, 36.6, 41.9, 43.3, 45.5, 51.6, 53.0, 53.7, 56.2, 60.1, 77.8, 82.9, 97.8, 105.5, 121.3, 123.3, 135.5, 146.7, 155.3, 166.6, 170.0, 173.7 and 204.3; Anal. Calcd. for $C_{24}H_{26}N_2O_9$: C, 59.25; H, 5.39; N, 5.76. Found: C, 59.19; H, 5.51; N, 5.56.

Magnesium Iodide Decarbomethoxylation of Hydroxy Ester 23. To a 0.9 g (1.9 mmol) sample of **23** in acetonitrile (150 mL) was added 1.1 g (4 mmol) of

magnesium iodide and the solution was heated at reflux for 4 h. The solution was allowed to cool to rt, concentrated under reduced pressure and the residue was taken up in methylene chloride (50 mL) and H_2O (50 mL). This solution was added to a saturated aqueous solution of $NaHCO_3$ (200 mL). The organic layer was separated and the aqueous layer was extracted twice with methylene chloride, dried over $MgSO_4$, and concentrated under reduced pressure to give 0.6 g (75%) of **26** as a white solid: mp 210-212 °C; IR (neat) 1794, 1720, 1609, 1494, 1263, and 1193 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.30-1.45 (m, 1H), 1.58-1.81 (m, 2H), 2.27 (d, 1H, *J* = 17.4 Hz), 2.34 (d, 1H, *J* = 17.4 Hz), 2.35-2.42 (m, 1H), 2.80 (d, 1H, *J* = 18.0 Hz), 2.93 (dt, 1H, *J* = 14.0 and 6.7 Hz), 3.14 (s, 3H), 3.27 (dd, 1H, *J* = 18.0 and 0.8 Hz), 3.68 (d, 1H, *J* = 3.6 Hz), 3.69 (s, 3H), 3.83 (s, 3H), 3.85 (d, 1H, *J* = 3.6 Hz), 4.21-4.30 (m, 1H), 4.84 (t, 1H, *J* = 3.6 Hz), 6.48 (d, 1H, *J* = 8.6 Hz) and 6.89 (d, 1H, *J* = 8.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.4, 34.1, 37.3, 40.0, 41.4, 44.7, 51.7, 53.4, 56.2, 60.4, 78.0, 98.0, 105.1, 120.4, 122.9, 135.3, 146.5, 155.5, 170.4, 172.5 and 207.8; Anal. Calcd. for $C_{22}H_{24}N_2O_7$: C, 61.67; H, 5.65; N, 6.54. Found: C, 61.18; H, 6.21; N, 5.94.

Reduction of Alcohol 26 to give Compound 27. A 0.14 g (0.3 mmol) sample of **26** was dissolved in methylene chloride (20 mL) and the mixture was cooled to 0 °C. To this mixture was added 0.16 g (1.6 mmol) of triethylamine and 0.05 g (0.64 mmol) of acetyl chloride. The solution was stirred vigorously for 2 h and was then added to a saturated aqueous solution of $NaHCO_3$ (50 mL). The organic layer was separated and the aqueous layer was extracted twice with methylene chloride, dried over $MgSO_4$, and concentrated under reduced pressure to give 0.14 g (95%) of the corresponding acetate as a white solid: mp 250-252 °C; IR (neat) 1797, 1721, 1495, 1264, 1227, and 1191 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.55-1.80 (m, 3H), 2.21-2.35 (m, 1H), 2.25 (d, 1H, *J* = 17.2 Hz), 2.27 (s, 3H), 2.33 (d, 1H, *J* = 17.2 Hz), 2.77 (d, 1H, *J* = 18.0 Hz), 2.93 (dt, 1H, *J* = 12.4 and 4.0 Hz), 3.16 (s, 3H), 3.29 (dd, 1H, *J* = 18.0 and 1.4 Hz), 3.69

(s, 3H), 3.78 (d, 1H, *J* = 2.8 Hz), 3.83 (s, 3H), 4.25-4.32 (m, 1H), 5.69 (d, 1H, *J* = 2.8 Hz), 6.48 (d, 1H, *J* = 8.4 Hz) and 6.90 (d, 1H, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.0, 20.7, 34.4, 37.7, 39.5, 40.1, 44.5, 52.9, 54.4, 56.2, 60.5, 76.2, 78.4, 98.1, 104.9, 119.9, 122.9, 135.1, 145.8, 155.6, 169.7, 170.6, 172.4 and 200.6.

A 0.18 g (0.4 mmol) sample of the above acetate was taken up in THF (35 mL) and cooled to 0 °C. The solution was stirred vigorously, while 13.5 mL (1.4 mmol) of a 0.1 M solution of samarium diiodide was added dropwise while maintaining a light blue color. When the addition was finished, the reaction mixture was diluted with ethyl acetate (20 mL) and then 20 mL of a 0.1 M solution of HCl was added to the mixture and the solution was stirred for 10 min. The solution was allowed to stir for an additional 15 min, the aqueous layer was separated and then extracted with ethyl acetate. The organic layer was washed successively with $Na_2S_2O_3$ (30 mL) and $NaHCO_3$ (30 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure to give 0.15 g (95%) of **27** as a white solid: mp 210-212 °C; IR (neat) 1791, 1716, 1652, 1471, 1266, and 1186 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.20-1.44 (m, 2H), 1.70-1.78 (m, 1H), 2.27 (d, 1H, *J* = 17.4 Hz), 2.36 (d, 1H, *J* = 17.4 Hz), 2.41-2.46 (m, 1H), 2.66 (d, 1H, *J* = 18.2 Hz), 2.80 (dd, 1H, *J* = 15.1 and 2.4 Hz), 2.90-2.96 (m, 1H), 2.99 (s, 3H), 3.04 (dd, 1H, *J* = 15.3 and 3.9 Hz), 3.28 (dd, 1H, *J* = 18.3 and 1.5 Hz), 3.62 (dd, 1H, *J* = 4.0 and 2.4 Hz), 3.71 (s, 3H), 3.84 (s, 3H), 4.24-4.30 (m, 1H), 6.46 (d, 1H, *J* = 8.4 Hz) and 6.92 (d, 1H, *J* = 8.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.8, 33.8, 35.5, 37.5, 40.6, 41.0, 44.9, 51.6, 52.2, 56.1, 60.9, 74.0, 99.0, 104.5, 120.9, 123.3, 134.7, 145.0, 155.4, 171.1, 172.8 and 206.6; HRMS Calcd. for [$C_{22}H_{24}N_2O_6$ + H^+]: 413.1707. Found: 413.1707.

Preparation of Olefinic Intermediate 28. To a 0.025 g (0.06 mmol) sample of **27** dissolved in THF (4 mL) at -78 °C was added 0.25 mL (0.072 mmol) of a 0.5

M solution of potassium bis(trimethylsilyl)amide (KHMDS) in toluene. The solution turned a deep yellow color. The reaction mixture was stirred at -78 °C for 1h, and then 0.25 mL (0.072 mmol) of a 0.29 M solution of *N*-phenyltriflimide in THF was added. The mixture was stirred at -78 °C for 30 min and the reaction was quenched with water. The resulting solution was added to a saturated aqueous solution of $NaHCO_3$ (10 mL) and methylene chloride (20 mL). The organic layer was separated and the aqueous layer was extracted with methylene chloride, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to preparative aluminum thick layer chromatography to give 0.017 g (68%) of recovered starting material and 0.01 g (30%) of the enol triflate of **27** as a clear oil; IR (neat) 1780, 1732, 1609, 1471, 1418, and 1138 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.44-1.80 (m, 3H), 2.30-2.38 (m, 1H), 2.54 (d, 1H, *J* = 16.8 Hz), 2.59 (d, 1H, *J* = 16.8 Hz), 2.76 (s, 2H), 3.27 (dt, 1H, *J* = 13.0 and 3.4 Hz), 3.16 (s, 3H), 3.76 (s, 3H), 3.83 (s, 3H), 3.85 (d, 1H, *J* = 2.8 Hz), 4.05-4.10 (m, 1H), 6.10 (d, 1H, *J* = 2.8 Hz), 6.29 (d, 1H, *J* = 8.6 Hz) and 7.01 (d, 1H, *J* = 8.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.5, 29.6, 35.7, 37.6, 44.0, 44.1, 45.1, 52.8, 56.1, 61.4, 70.7, 100.7, 103.7, 117.3, 120.6, 123.8, 129.9, 134.7, 143.3, 146.8, 155.1, 171.5 and 173.1; HRMS Calcd. for [$C_{23}H_{23}N_2O_8F_3S$ + H^+]: 545.1200. Found: 545.1199.

A 0.01 g (0.018 mmol) sample of the above enol triflate was dissolved in THF (5 mL) and to this solution was added 0.004 g (0.003 mmol) of $Pd(PPh_3)_4$ followed by 0.043 g (0.15 mmol) of *n*-tributyltin hydride. The mixture was stirred at rt for 1h and was then concentrated under reduced pressure. The resulting residue was taken up in 10 mL of acetonitrile and washed with 100 mL of hexane. The layers were separated and the acetonitrile layer was concentrated under reduced pressure. The residue was subjected to preparative aluminum thick layer chromatography to give 0.006 g of **28** as a colorless oil: IR (neat) 1797, 1777, 1719, 1609, 1465, and 1070 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ

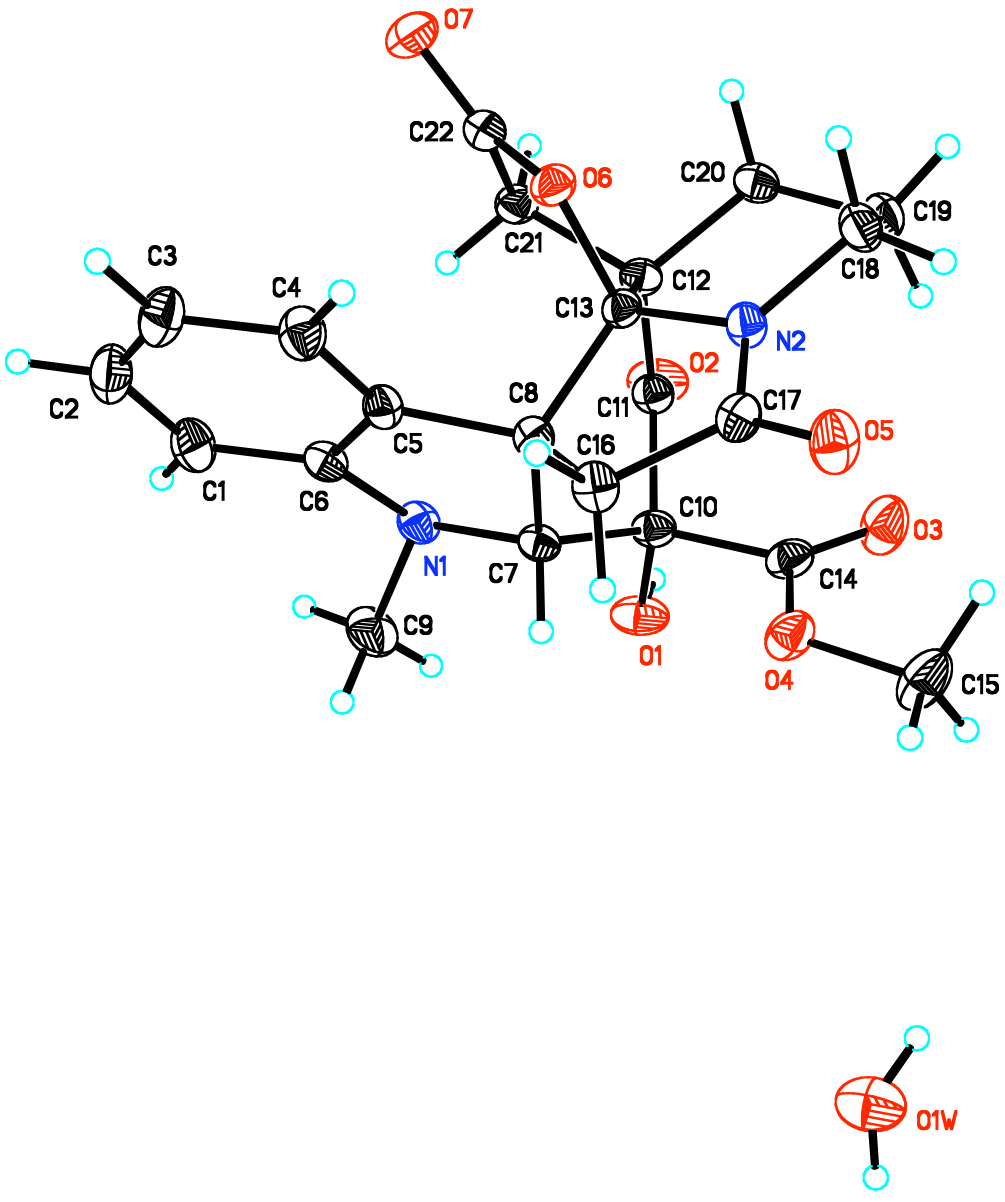
1.20-1.75 (m, 3H), 1.80-1.90 (m, 1H), 2.38 (d, 1H, *J* = 16.8 Hz), 2.43 (d, 1H, *J* = 16.8 Hz), 2.69 (d, 1H, *J* = 17.4 Hz), 2.76 (d, 1H, *J* = 17.4 Hz), 2.88 (dt, 1H, *J* = 13.2 and 3.4 Hz), 3.16 (s, 3H), 3.67 (dd, 1H, *J* = 2.8 and 1.6 Hz), 3.76 (s, 3H), 3.80 (s, 3H), 4.00-4.07 (m, 1H), 5.59 (dd, 1H, *J* = 10.4 and 1.6 Hz), 6.00 (d, 1H, *J* = 10.4 and 2.8 Hz), 6.24 (d, 1H, *J* = 8.6 Hz) and 7.01 (d, 1H, *J* = 8.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19.9, 34.7, 35.6, 37.4, 41.4, 44.8, 52.3, 56.0, 61.3, 72.4, 100.5, 102.8, 120.7, 122.0, 126.6, 129.9, 134.1, 143.7, 154.7, 173.3 and 173.8; HRMS Calcd. for [$C_{22}H_{24}N_2O_5$ + H^+]: 397.1758. Found: 397.1760.

Thiolactam Derivative of Aspidophytine 29. A 0.004 g (0.01 mmol) sample of **28** was dissolved in 10 mL of benzene, and then 0.002 g (0.006 mmol) of phosphorous pentasulfide and 0.002 g (0.016 mmol) of hexamethyldisiloxane was added. The resulting mixture was heated at reflux under Ar for 2 h. The solution was allowed to cool to rt and the solvent was removed under reduced pressure. The residue was taken up in EtOAc (containing 5% Et_3N) and filtered through a pad of florisil to give 0.004 g of **29** as a colorless oil; IR (neat) 1799, 1771, 1652, 1457 and 1070 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.50-1.60 (m, 1H), 1.73-1.90 (m, 3H), 2.45 (s, 2H), 3.01-3.07 (m, 1H), 3.13 (dd, 1H, *J* = 18.0 and 1.8 Hz), 3.16 (s, 3H), 3.32 (d, 1H, *J* = 18.0 Hz), 3.67 (dd, 1H, *J* = 2.4 and 0.8 Hz), 3.77 (s, 3H), 3.81 (s, 3H), 4.75-4.80 (m, 1H), 5.60 (dd, 1H, *J* = 10.2 and 0.8 Hz), 6.02 (d, 1H, *J* = 10.2 and 2.4 Hz), 6.24 (d, 1H, *J* = 8.7 Hz) and 6.98 (d, 1H, *J* = 8.7 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 19.8, 29.9, 34.0, 35.6, 41.9, 42.5, 46.3, 56.0, 56.4, 61.3, 71.2, 102.0, 102.9, 120.6, 121.2, 127.3, 128.8, 129.3, 131.8, 134.2, 143.8, 154.8, 172.7 and 204.8; HRMS Calcd. for [$C_{22}H_{24}N_2O_4S$ + H^+]: 413.1529. Found: 413.1533.

Aspidophytine (5). A 0.003 g (0.0073 mmol) sample of thioamide **29** in anhydrous methylene chloride (1 mL) was cooled to 0 °C and then 0.02 mL (0.02 mmol) of a 1.0 M solution of triethyloxonium tetrafluoroborate in methylene chloride was added and the mixture was stirred for 12 h. The solution was

cooled to -78 °C and 0.027 mL (0.027 mmol) of a 1.0 M solution of $LiAlH(OtBu)_3$ in THF was added to the mixture. The solution was stirred for 1 h at -78 °C and was allowed to slowly warm to rt. The solution was added to a saturated aqueous solution of $NaHCO_3$ (10 mL) and the organic layer was separated. The aqueous layer was extracted with methylene chloride, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting oil was taken up in 10 mL of benzene and 0.002 g (0.015 mmol) of AIBN and 0.1 mL (0.37 mmol) of *n*-tributyltin hydride was added. The mixture was heated at reflux for 10 h, cooled to rt and the solvent was removed under reduced pressure. The residue was dissolved in 10 mL of acetonitrile and washed with 100 mL of hexane. The layers were separated and the acetonitrile layer was concentrated under reduced pressure. The residue was taken up in methylene chloride and was then added to a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with methylene chloride, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to preparative thick layer chromatography to give 0.0017 g of aspidophytine (**5**) as a solid; IR (neat) 1733, 1609, 1494, 1463, 1457, 1265 and 1071 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 1.50-1.74 (m, 4H), 2.08 (ddd, 1H, J = 12.8, 10.5 and 6.9 Hz), 2.24 (d, 1H, J = 16.5 Hz), 2.30 (ddd, 1H, J = 12.8, 8.4 and 3.3 Hz), 2.37 (d, 1H, J = 16.5 Hz), 2.75 (br d, 1H, J = 11.4 Hz), 2.92 (td, 1H, J = 10.8 and 4.2 Hz), 3.01 (td, 1H, J = 9.6 and 3.0 Hz), 3.16 (s, 3H), 3.19 (q, 1H, J = 8.4 Hz), 3.76 (s, 1H), 3.79 (s, 3H), 5.52 (dd, 1H, J = 10.0 and 1.2 Hz), 6.02 (d, 1H, J = 10.0 and 2.4 Hz), 6.20 (d, 1H, J = 8.4 Hz) and 6.97 (d, 1H, J = 8.4 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 21.7, 34.7, 35.4, 35.5, 41.6, 43.6, 47.5, 48.0, 55.9, 57.3, 61.4, 72.0, 102.2, 120.4, 125.7, 125.8, 130.7, 133.9, 143.8, 154.1 and 176.0; HRMS Calcd. for $[(C_{22}H_{26}N_2O_4) + H]^+$: 383.19653. Found: 383.19608. This compound was identical in all respects (NMR, IR, HRMS and TLC) to a sample of aspidophytine kindly provided by Professor Fukuyama.

Ortep Drawing of Compound **24**



Ortep Drawing of Compound **25**