Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

for

Angew. Chem. Int. Ed. Z53636

69451 Weinheim, Germany

A New Total Synthesis of (-)-Galanthamine by a Novel Remote Asymmetric Induction

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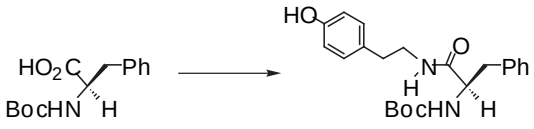
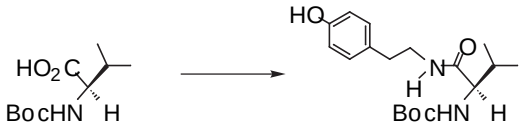
General. Melting points were taken on a micro hot-stage apparatus (Yanagimoto) and were uncorrected. Infrared (IR) spectra were recorded a Shimadzu FTIR-8300 diffraction grating infrared spectrophotometer and ^{1}H-NMR spectra were obtained on a JEOL JNM-AL300 or a Varian Unity INOVA-400 spectrometer with tetramethylsilane as an internal standard. ^{13}C-NMR spectra were obtained on a Varian Unity INOVA-400 spectrometer with $CDCl_3$ as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-SX 102A QQ or a JEOL JMS-GC-mate mass spectrometer. Combustion analysis was done on a Perkin Elmer Series II CHNS/O Analyzer 2400. Specific rotations were recorded on a Horiba SEPA-200 automatic digital polarimeter. Chiral HPLC analyses were performed with a LC-10A Liquid Chromatograph series using a Daicel chiral column (CHIRALCEL OD). Their data were recorded with Shimadzu C-R6A Chromatopac. Acetate buffer was adjusted with a Horiba pH meter F-13. Wakogel C-200 (silica gel) (100-200 mesh, Wako) was used for open column chromatography. Flash column chromatography was performed with Silica Gel 60N (Kanto Chemical Co., Inc.). Kieselgel 60 F-254 plates (Merck) were used for thin layer chromatography (TLC). Preparative TLC (PTLC) was done with Kieselgel 60 F-254 plate (0.25 mm, Merck) or Silica gel 60 F-254 plate (0.5 mm, Merck). When necessary, compounds were further purified by a recycle HPLC (JAI LC-908) on GPC column (JAIGEL 1H and 2H) after purification on silica gel.

Materials. Tetrahydrofuran (THF) and ether was distilled from sodium benzophenone ketyl, and dichloromethane was distilled from CaH_2, after ten washing with water to remove methanol contaminants. Most of the reagents were obtained from Wako pure Chemical Industries, Ltd., Nakalai Tesque, Inc., Aldrich Chemical Inc



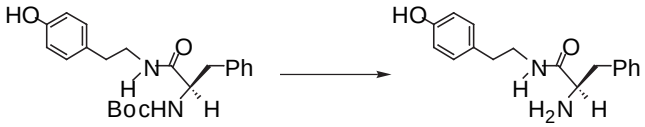
3 **13**

2-(*R*)-*tert*-Butoxycarbonylamino-*N*-[2-(4-hydroxyphenyl)ethyl]-3-phenylpropionamide (13). To a solution of (*R*)-*N*-Boc-D-phenylalanine (**3**) (5.0 g, 18.9 mmol), tyramine (3.1 g, 22.6 mmol), and HOBt (254.6 mg, 1.88 mmol) in THF (50 mL) was added EDC·HCl (4.3 g, 22.6 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature, then concentrated *in vacuo*. Water was added to the residue and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 1N HCl, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Crystallization of the residue from ether afforded **13** (6.9 g, 95%) as colorless crystals; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.18 (m, 3H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.87-6.83 (m, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 5.95 (s, 1H), 5.16 (s, 1H), 4.25 (d, 7.16 (d, *J* = 7.0 Hz, 1H), 3.42-33.5 (m, 1H), 3.29-3.22 (m, 1H), 3.00 (d, *J* = 6.2 Hz, 1H), 2.60–2.48 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 171.3, 154.9, 136.6, 129.9, 129.6, 129.4, 129.3, 128.6, 127.0, 115.5, 80.4, 56.1, 40.9, 38.8, 34.6, 28.2; IR ($CHCl_3$): 3597, 3431, 3032, 1705, 1672, 1514, 1369, 1170 cm^{-1}; FAB-MS *m*/*z*: 385 (M^++H); HRMS calcd for $C_{22}H_{29}O_4N_2$ (M^++H): 385.2127, found: 385.2120.



14 **15**

2-(*R*)-*tert*-Butoxycarbonylamino-*N*-[2-(4-hydroxyphenyl)ethyl]-3-methylbutyramide (15). To a solution of (*R*)-*N*-Boc-D-valine (**14**) (3.95 g, 18.2 mmol), tyramine (2.99 g, 21.8 mmol), and HOBt (245.88 mg, 1.82 mmol) in THF (4.5 mL) was added EDC HCl (4.18 g, 21.8 mmol) at 0 °C. The reaction mixture was stirred for 1 d at room temperature, then concentrated *in vacuo*. Water was added to the residue and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with 1N HCl, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, chlroform/methanol, 50/1) afforded **15** (3.84 mg, 63%) as colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.00 (d, *J* = 7.7 Hz, 2H), 6.75 (d, *J* = 8.3 Hz, 2H), 3.79 (dd, *J* = 8.9, 6.5 Hz, 1H), 3.57-3.39 (m, 2H), 2.71 (t, *J* = 7.0 Hz, 2H), 1.71 (t, *J* = 3.0 Hz, 1H), 1.44 (s, 9H), 0.89 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 172.0, 153.1, 155.1, 129.8, 129.6, 115.6, 80.2, 60.2, 41.0, 34.8, 30.8, 28.3, 19.2, 18.0; IR ($CHCl_3$): 3339, 2976, 1705, 1670, 1514, 1456, 1369, 1238, 1171 cm^{-1}; EI-MS *m/z*: 336 (M^+, 2), 280 (6), 263 (4), 236 (8), 217 (14), 161 (42), 120 (100), 107 (4), 72 (46), 56 (99); HRMS calcd for $C_{18}H_{28}N_2O_4$ (M^+): 336.2049, found: 336.2046.

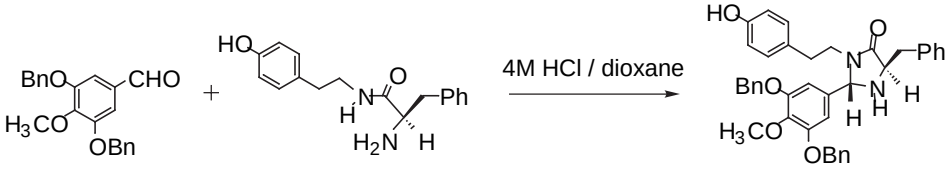


13 **4a**

2-(*R*)-Amino-*N*-[2-(4-hydroxyphenyl)ethyl]-3-phenylpropionamide (4a). To a solution of **13** (4.2 g, 10.8 mmol) in methanol (40 mL, 0.27 M) was added methanesulfonic acid (1.4 mL, 21.6 mmol) at room temperature. The reaction mixture was stirred for 3 h at 40 °C, then concentrated *in vacuo*. The residue was added chilled water and neutralized with potassium carbonate. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Crystallization of the residue from ether afforded **4a** (3.0 g, 97%) as colorless crystals; m.p. 87-88 °C; $[\alpha]_D^{26}$ = +39.5 (0.59, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.13 (m, 5H), 6.98 (d, *J* = 8.6 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 3.56 (dd, *J* = 9.2, 4.1 Hz, 1H), 3.53-3.43 (m, 2H), 3.22 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.71 (t, *J* = 7.1 Hz, 2H), 2.57 (dd, *J* = 13.7, 9.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.5, 154.8, 137.7, 130.2, 129.7, 129.3, 128.7, 126.8, 115.5, 56.4, 41.0, 40.5, 34.8; IR ($CHCl_3$): 3362, 1657, 1614, 1514, 1454, 1362, 1240, 1173, 1105 cm^{-1}; EI-MS *m/z*: 284 (M^+, 1), 193 (12), 165 (12), 136 (5), 120 (100), 107 (14), 103 (9), 91 (16), 77 (12); HRMS calcd for $C_{17}H_{20}N_2O_2$ (M^+): 284.1525, fond: 284.1522; Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. found: C, 71.78; H, 7.06; N, 9.63.

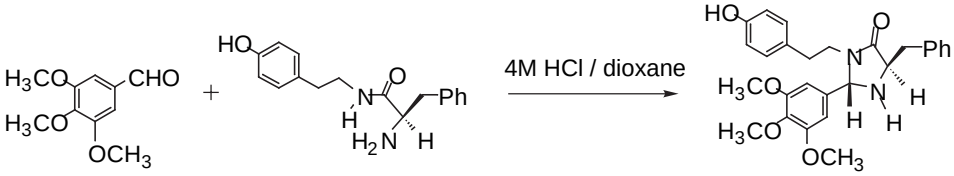
15 **4b**

2-(*R*)-Amino-*N*-[2-(4-hydroxyphenyl)ethyl]-3-methylbutyramide (4b). To a solution of **15** (3.84 g, 11.4 mmol) in methanol (32 mL, 0.36 M) was added methanesulfonic acid (1.48 mL, 22.8 mmol) at room temperature. The reaction mixture was stirred for 1 d at the same temperature, then concentrated *in vacuo*. The residue was added chilled water and neutralized with potassium carbonate. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, chlroform/methanol, 5/1) afforded **4b** (1.03 g, 38%) as colorless crystals; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.6 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 3.58-3.43 (m, 2H), 3.19 (d, *J* = 3.7 Hz, 1H), 2.75 (t, *J* = 7.0 Hz, 2H), 2.32-2.24 (m, 1H), 0.96 (d, *J* = 7.0 Hz, 1H), 0.77 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.4, 154.5, 130.7, 129.8, 115.4, 60.1, 40.3, 35.0, 19.7, 15.9; IR ($CHCl_3$): 3342, 2964, 1655, 1614, 1597, 1514, 1466, 1369, 1252, 1173, 829 cm^{-1}; EI-MS *m/*z: 236 (M^+, 1), 193 (1), 165 (3), 149 (1), 136 (2), 120 (5), 117 (7), 07 (4), 103 (1), 97 (2), 91 (3), 83 (2), 77 (5), 72 (100), 55 (21); HRMS calcd for $C_{13}H_{20}N_2O_2$ (M^+): 236.1525, found: 236.1532.



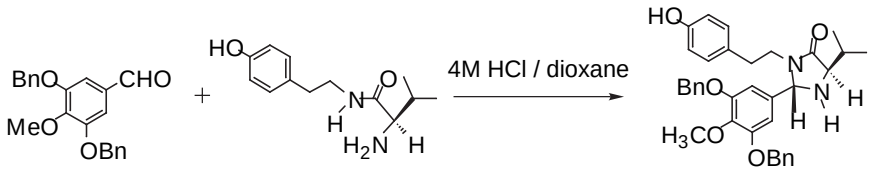
5a **4a** **6a**

(2*S*,5*R*)-5-Benzyl-2-(3,5-dibenzyloxy-4-methoxyphenyl)-3-[2-(4-hydroxyphenyl)ethyl] imidazolidin-4- one (6a). To a solution of 3, 5-dibenzyloxy-4-methoxybenzaldehyde (**5a**) (100 mg, 0.29 mmol) in dioxane (3 mL, 0.097 M) was added **4a** (97.9 mg, 0.34 mmol) at 0 °C, and the reaction mixture was stirred for 1 d at room temperature. Hydrogen chloride (4.0 M 1,4-dioxane solution, 1.5 mL) was added at 0 °C. The reaction mixture was stirred for 1d at room temperature, then concentrated *in vacuo*. The residue was poured into a saturated $NaHCO_3$ solution, the aqueous layer was extracted with ethyl acetate, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 2/1) afforded **6a** (115.4 mg, 64%) as amorphous, accompanied with the starting material **5a** (33.1 mg, 33%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.1 (m, 16H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.71 (d, *J* = 8.6Hz, 2H), 6.34 (S, 2H), 5.07 (s, 4H), 4.73 (d, *J* = 1.5 Hz, 1H), 3.88 (s, 3H, OCH_3), 3.93-3.80 (m, 1H), 3.70 (quintet, *J* = 6.9 Hz, 1H), 3.01 (dd, *J* = 13.7, 3.8 Hz, 1H), 2.77 (dd, *J* = 13.7, 7.5 Hz, 1H), 2.59 (quintet, *J* = 7.1 Hz, 1H), 2.50-2.36 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.1, 154.9, 152.8, 140.0, 137.3, 136.7, 134.3, 129.8, 129.7, 129.6, 128.6, 128.5, 128.0, 127.3, 127.0, 115.4, 106.2, 75.9, 71.1, 60.9, 59.7, 41.7, 38.1, 32.6; IR ($CHCl_3$): 3595, 3007, 1686, 1595, 1516, 1445, 1327, 1240, 1113 cm^{-1}; FAB-MS *m/z*: 615 (M^++H); HRMS calcd for $C_{39}H_{39}O_5N_2$ (M^++H): 615.2859, found: 615.2871.



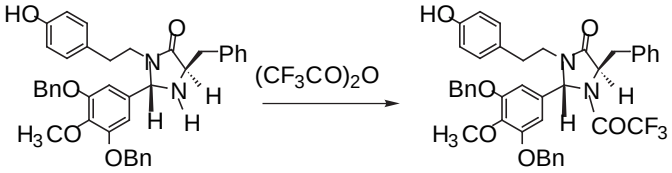
5b **4a** **6b**

(2*S*,5*R*)-5-Benzyl-3-[2-(4-hydroxyphenyl)ethyl]-2-(3,4,5-trimethoxyphenyl)imidazolidin-4-one (6b). To a solution of **4a** (2.5 g, 8.8 mmol) in dioxane (30 mL, 0.29 M) was added 3,4,5-trimethoxybenzaldehyde (**5b**) (2.6 g, 13.2 mmol) at room temperature and the reaction mixture was stirred for 12 h at room temperature. Hydrogen chloride (4.0 M 1,4-dioxane solution, 20 mL) was added at 0 °C. The reaction mixture was stirred for 12 h at room temperature, then concentrated *in vacuo*. The residue was diluted with ethyl acetate, washed with 1N HCl, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 2/1) afforded **6b** (1.75 g, 43%) as amorphous; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.22 (m, 5H), 6.86 (d, A part of AB, J_{AB} = 8.4 Hz, 1H), 6.75 (d, A part of AB, J_{AB} = 8.6 Hz, 1H), 6.34 (s, 2H), 4.85 (d, *J* = 1.5 Hz, 1H), 4.05-4.02 (m, 1H), 3.93-3.74 (m, 1H), 3.81 (s, 3H), 3.80 (s, 6H), 3.05 (dd, *J* = 13.8, 3.9 Hz, 1H), 2.88-2.73 (m, 2H), 2.61-2.48 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.35, 155.13, 153.67, 138.48, 137.14, 134.52, 129.70, 129.66, 129.62, 128.50, 126.76, 115.45, 103.51, 76.34, 60.77, 59.93, 56.13, 42.05, 38.09, 32.72; IR ($CHCl_3$): 1686, 1597, 1516, 1447, 1425, 1329, 1238, 1130 cm^{-1}; EI-MS *m/z*: 462 (M^+, 34), 371 (100), 298 (24), 251 (35), 208 (32), 193 (33), 168 (14), 148 (17), 121 (62), 91 (32); HRMS calcd for $C_{27}H_{30}N_2O_5$ (M^+): 462.2154, found: 462.2158.



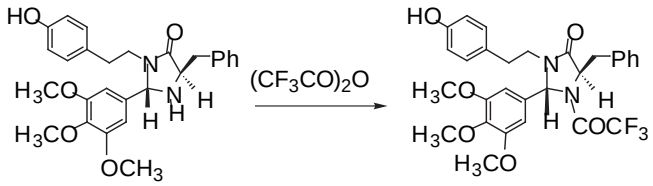
5a **4b** **6c**

(2*S*,5*R*)-2-(3,5-Dibenzyloxy-4-methoxyphenyl)-3-[2-(4-hydroxyphenyl)ethyl]-5-isopropylimidazolidin-4-one (6c). To a solution of **4b** (300 mg, 1.27 mmol) in dioxane (6 mL, 0.21 M) was added 3, 5-dibenzyloxy-4-methoxybenzaldehyde (**5a**) (653.9 mg, 1.90 mmol) at 0 °C, and the reaction mixture was stirred for 1 d at room temperature. Hydrogen chloride, (4.0 M 1,4-dioxane solution, 6 mL) was added at 0 °C. The reaction mixture was stirred for 2 d at room temperature, then concentrated *in vacuo*. The residue was poured into a saturated $NaHCO_3$ solution, the aqueous layer was extracted with chloroform. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 2/1) afforded **6c** (473.9 mg, 66%) as amorphous; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.28 (m, 10H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.43 (s, 2H), 5.11 (s, 4H), 5.04 (d, *J* = 2.0 Hz, 1H), 3.92 (s, 3H), 3.86-3.79 (m, 1H), 3.56 (dd, *J* = 3.1, 2.0 Hz, 1H), 2.68-2.46 (m, 3H), 2.10-2.03 (m, 1H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.4, 154.9, 152.9, 140.1, 136.7, 134.9, 129.7, 128.6, 128.0, 127.3, 115.4, 106.2, 76.7, 71.1, 63.6, 60.9, 41.4, 32.5, 30.8, 19.4, 16.2; IR ($CHCl_3$): 3327, 2964, 1682, 1595, 1516, 1445, 1369, 1352, 1327, 1259, 1240, 1113, 1078, 1003, 827 cm^{-1}; EI-MS *m/z*: 566 (M^+, 4), 523 (2), 475 (7), 447 (2), 402 (5), 381 (24), 369 (2), 348 (2), 312 (3), 221 (3), 151 (8), 121 (13), 97 (16), 91 (100), 55 (70); HRMS calcd for $C_{35}H_{38}N_2O_5$ (M^+): 566.2780, found: 566.2784.



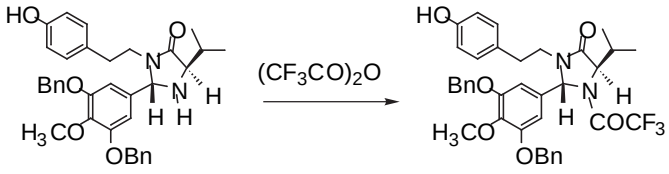
6a **7a**

(2*S*,5*R*)-5-Benzyl-2-(3,5-dibenzyloxy-4-methoxyphenyl)-3-[2-(4-hydroxyphenyl)ethyl]-1-(2,2,2-trifluoroacetyl)imidazolidin-4-one (7a). To a solution of **6a** (1.63 g, 2.64 mmol) in pyridine (10 mL, 0.264 M) was added trifluoroacetic anhydride (0.89 mL, 6.33 mmol) at 0 °C, and the reaction mixture was stirred for 15 min at the same temperature. After methanol (10 mL) was added, the reaction mixture was concentrated *in vacuo*. The residue was diluted with ethyl acetate, washed with 1N HCl, and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 2/1) afforded **7a** (1.77 g, 94%) as a colorless crystal; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 13 H), 7.20-7.18 (m, 1H), 7.13-7.11 (m, 1H), 6.64 (dd, *J* = 8.5, 6.0 Hz, 2H), 6.54 (d, *J* = 8.6 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 6.24 and 6.02 (s, 2H), 5.53 and 5.47 (br s, 1H), 5.07-4.97 (m, 4H), 4.91 and 4.85 (br s, 1H), 3.87 and 3.86 (s, 3H), 3.68 and 3.65 (d, *J* = 5.2 Hz, 1H), 3.60-3.53 (m, 1H), 3.46-3.39 (m, 1H), 3.33-3.25 (m, 1H), 2.32-2.14 (m, 1H), 2.09-1.96 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.0, 166.4, 156.1, 155.7, 155.2, 154.7, 154.6, 152.6, 141.2, 140.4, 136.6, 136.2, 134.6, 133.6, 131.2, 130.3, 130.2, 130.1, 130.0, 129.8, 129.6, 128.9, 128.6, 128.6, 128.1, 128.0, 127.9, 127.5, 127.2, 127.2, 1167.0, 116.4, 115.4, 114.1, 113.5, 107.4, 76.0, 71.3, 71.2, 61.2, 61.0, 60.9, 60.8, 41.6, 38.6, 33.2, 33.0, 32.3; IR ($CHCl_3$): 3314, 1701, 1597, 1454, 1443, 1327, 1169, 1115 cm^{-1}; FAB-MS *m/z*: 711 (M^++H); HRMS calcd for $C_{41}H_{38}O_6N_2F_3$ (M^++H): 711.2682, found: 711.2690; Anal. Calcd for $C_{41}H_{38}O_6N_2F_3$: C, 69.29; H, 5.25; N, 3.94. found: C, 69.13; H, 5.20; N, 3.82.



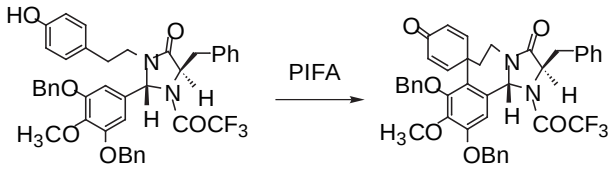
6b **7b**

(2*S*,5*R*)-5-Benzyl-3-[2-(4-hydroxyphenyl)ethyl]-1-trifluoroacetyl-2-(3,4,5-trimethoxyphenyl)imidazolidin-4-one (7b). To a solution of **6b** (311.6 mg, 0.67 mmol) in pyridine (3 mL, 0.23 M) was added trifluoroacetic anhydride (0.23 mL, 1.62 mmol) at 0 °C and the reaction mixture was stirred for 1 h at the same temperature. After methanol (3 mL) was added, the reaction mixture was concentrated *in vacuo*. The residue was diluted with ethyl acetate, washed with 1N HCl, saturated $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 1/1) afforded **7b** (358.0 mg, 95%) as colorless crystals; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.36 (m, 3H), 7.23 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.17 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 2H), 6.61 (d, *J* = 8.6 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.21 (S, 1H), 6.04 (S, 1H), 5.59 and 5.52 (br s, 1H), 5.08 (d, *J* = 3.3 Hz, 1H), 5.05-5.01 (m, 1H), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.75-3.69 (m, 1H), 3.61-3.54 and 3.36-3.32 (m, 1H), 3.46 and 3.36 (dd, *J* = 14.9, 2.3 Hz, 1H), 2.50-2.26 (m, 2H), 2.15-2.07 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.08, 166.50, 154.69, 154.58, 153.66, 153.54, 139.56, 138.91, 134.66, 133.60, 131.61, 130.42, 130.33, 130.23, 130.15, 129.83, 129.63, 128.95, 128.67, 127.93, 127.57, 115.43, 104.21, 76.26, 76.22, 61.33, 60.93, 60.81, 56.29, 56.18, 41.77, 41.71, 38.71, 33.31, 33.05, 32.50; IR ($CHCl_3$): 3323, 1701, 1597, 1516, 1466, 1425, 1350, 1329, 1240, 1169, 1130 cm^{-1}; EI-MS *m/z*: 558 (M^+, 17), 438 (100), 347 (46), 329 (10), 286 (12), 250 (15), 222 (41), 181 (20), 121 (52), 91 (33); HRMS calcd for $C_{29}H_{29}O_6N_2F_3$ (M^+): 558.1975, fond: 558.1977; Anal. Calcd for $C_{29}H_{29}O_6N_2F_3$: C, 62.36; H, 5.23; N, 5.02. found: C, 62.27; H, 5.14; N, 4.90.



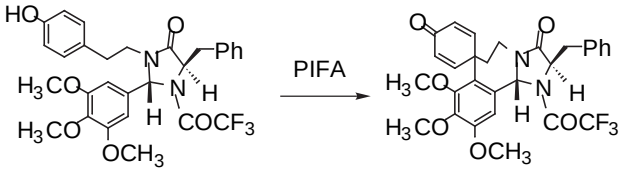
6c **7c**

(2*S*,5*R*)-2-(3,5-Dibenzyloxy-4-methoxyphenyl)-3-[2-(4-hydroxyphenyl)ethyl]-5-isopropyl-1-trifluoroacetylimidazolidin-4-one (7c). To a solution of **6c** (34.8 mg, 0.06 mmol) in pyridine (1 mL, 0.06 M) was added trifluoroacetic anhydride (0.02 mL, 0.147 mmol) at 0 °C and the reaction mixture was stirred for 3 h at the same temperature. After methanol (1 mL) was added, the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 10/1) afforded **7c** (30.5 mg, 77%) as colorless crystals; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.264 (m, 10H), 6.90 and 6.87 (d, *J* = 8.6 Hz, 2H), 6.5 and 6.72 (d, *J* = 8.5 Hz, 2H), 6.40 and 6.25 (s, 2H), 5.68 (d, *J* = 1.1 Hz, 0.5H) and 5.56 (s, 0.5H), 5.16-5.05 (m, 4H), 4.52 (d, *J* = 1.6 Hz, 0.5H) and 4.43 (br s, 0.5H), 3.92 and 3.91 (s, 3H), 3.82-3.71 (m, 1H), 2.60-2.50 (m, 1H), 2.49-2.35 (m, 2H), 2.16-2.11 (m, 1H), 1.23 and 1.19 (d, *J* = 7.1 Hz, 3H), 0.73 and 0.66 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 166.8, 166.4, 154.8, 154.8, 152.7, 141.3, 140.5, 136.6, 136.3, 131.5, 130.2, 129.8, 129.7, 129.4, 128.7, 128.6, 128.3, 128.0, 127.2, 115.5, 107.5, 76.1, 71.4, 71.1, 64.2, 63.9, 61.1, 60.9, 40.9, 40.9, 34.2, 32.8, 32.4, 28.2, 18.6, 18.1, 15.9, 14.9; IR ($CHCl_3$): 3325, 2936, 1697, 1597, 1516, 1504, 1445, 1420, 1371, 1346, 1327, 1292, 1259, 1238, 1167, 1115, 1078, 1003, 826 cm^{-1}; FAB-MS *m*/*z*: 662 (M^++H); HRMS calcd for $C_{37}H_{37}O_6N_2F_3$ (M^++H): 662.2604, found: 662.2608.



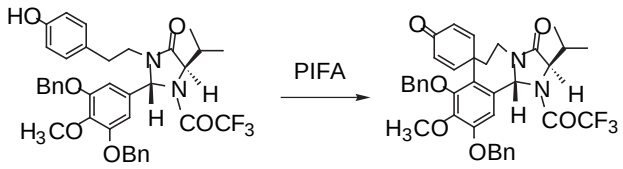
7a **8a**

An Oxidative Coupling Reaction of 7a with PIFA. To a solution of **7a** (86.8 mg, 0.12 mmol) in CF_3CH_2OH was added dropwise a solution of phenyliodine(III) bis(trifluoroacetate) (PIFA, 57.8 mg, 0.13 mmol) in CF_3CH_2OH at –40 °C, and the reaction mixture was stirred for 10 min at the same temperature. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 2/1) afforded dienone **8a** (51.8 mg, 61%) as amorphous; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.08 (m, 15H), 6.78 and 6.69 (dd, *J* = 9.9, 3.0 Hz, 1H), 6.36 and 6.29 (s, 1H), 6.145 and 6.140 (d, *J* = 9.9 Hz, 1H), 6.06 and 5.60 (s, 1H), 5.96 and 5.91 (dd, *J* = 10.1, 1.7 Hz, 1 H), 5.21 and 5.08 (d, *J* = 12.3 Hz, 1H), 5.04 and 4.99 (d, *J* = 12.1 Hz, 1H), 4.90 (br s, 0.5H) and 4.47 (d, *J* = 4.0 Hz, 0.5H), 4.89 and 4.82 (d, *J* = 10.6 Hz, 1H), 4.70 and 4.61 (d, *J* = 10.6 Hz, 1H), 3.85-3.75 (m, 1H), 3.80 and 3.76 (s, 3H), 3.60 and 3.54 (dd, *J* = 13.5, 5.0 Hz, 1H), 3.43 and 3.30 (d, *J* = 13.5 Hz, 1H), 3.36-3.28 (m, 1H), 3.15 and 2.90 (t, *J* = 13.1 Hz, 1H), 2.10 and 1.48 (t, *J* = 14.2 Hz, 1H), 1.88 and 1.75 (dd, *J* = 16.3, 5.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 184.9, 184.6, 165.5, 164.7, 157.2, 156.8, 156.3, 155.9, 153.7, 153.4, 152.6, 152.5, 150.9, 143.7, 136.4, 136.2, 136.0, 136.0, 134.1, 133.2, 130.3, 129.8, 129.6, 128.9, 128.7, 128.4, 128.3, 128.1, 128.0, 127.5, 127.4, 127.2, 127.1, 126.0, 123.4, 122.6, 121.9, 121.4, 104.5, 104.4, 77.2, 75.8, 71.0, 70.9, 70.7, 70.4, 62.8, 62.7, 60.9, 46.5, 46.1, 39.1, 37.3, 37.2, 36.7, 32.6; IR ($CHCl_3$): 1707, 1660, 1456, 1333, 1184, 1171, 1117 cm^{-1}; FAB-MS *m*/*z*: 709 (M^++H); HRMS calcd for $C_{41}H_{36}O_6N_2F_3$ (M^++H): 709.2525, found: 709.2530.



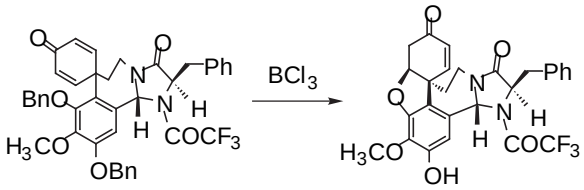
7b **8b**

An Oxidative Coupling Reaction of 7b with PIFA. To a solution of **7b** (100 mg, 0.179 mmol) in CF_3CH_2OH (3 mL, 0.06 M) was added dropwise a solution of phenyliodine(III) bis(trifluoroacetate) (84 mg, 0.197 mmol) in CF_3CH_2OH (3.5 mL) at –40 °C, and the reaction mixture was stirred for 1.5 h at the same temperature. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 1/1) afforded dienone **8b** (41 mg, 41%) as amorphous; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.04 (m, 5H), 6.74 and 6.68 (dd, *J* = 10.1, 2.7 Hz, 1H), 6.31-6.17 (m, 3H), 6.09 and 5.63 (s, 1H), 5.04 (br s, 0.5 H) and 4.86 (d, *J* = 4.2 Hz, 0.5H), 3.85-3.33 (m, 4H), 3.81 and 3.79 (s, 3H), 3.77 and 3.76 (s, 3H), 3.59 and 3.54 (s, 3H), 3.24 and 2\3.00 (t, *J* = 13.2 Hz, 1H), 2.13 (t, *J* = 13.2 Hz, 0.5H) and 1.91 (dd, *J* = 16.1, 5.1 Hz, 0.5H), 1.75 (dd, *J* = 16.3, 5.7 Hz, 0.5H) and 1.55 (t, *J* = 13.9 Hz, 0.5H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 185.08, 165.50, 164.88, 157.22, 156.67, 153.52, 153.16, 151.10, 134.14, 133.28, 130.44, 129.80, 129.60, 128.77, 128.46, 128.13, 127.61, 127.35, 127.20, 125.97, 123.47, 122.73, 102.14, 70.66, 62.99, 62.75, 60.83, 60.73, 60.63, 55.91, 55.50, 46.62, 46.30, 39.25, 37.27, 39.80, 36.47, 35.99, 32.75; IR ($CHCl_3$): 1709, 1661, 1464, 1323, 1173, 1124 cm^{-1}; EI-MS *m/z*: 556 (M^+, 82), 541 (11), 465 (39), 321 (14), 312 (23), 298 (11), 284 (49), 270 (18), 254 (22), 131 (20), 103 (19), 91 (100); HRMS calcd for $C_{29}H_{27}F_3N_2O_6$ (M^+): 556.1821, found: 556.1824.



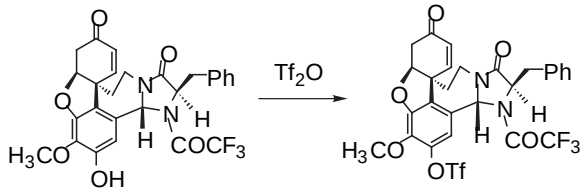
7c **8c**

An Oxidative Coupling Reaction of 7c with PIFA. To a solution of **7c** (10.0 mg, 0.015 mmol) in CF_3CH_2OH (0.5 mL, 0.03 M) was added dropwise a solution of phenyliodine(III) bis(trifluoroacetate) (7.14 mg, 0.017 mmol) in CF_3CH_2OH (0.5 mL) at –40 °C, and the reaction mixture was stirred for 15 min at the same temperature. The reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 15/1) afforded dienone **8c** (4.5 mg, 45%) as amorphous; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.20 (m, 15H), 6.90 (dd, *J*=10.0, 3.0 Hz, 1H), 6.73 (d, *J* = 17.4 Hz, 1H), 6.32 and 6.31 (s, 1H), 6.23 (td, *J* = 9.1, 1.8 Hz, 1H), 6.02 (dd, *J* = 10.1, 1.8 Hz, 1H), 5.23 and 5.10 (d, *J* = 12.3 Hz, 1H), 5.02 (t, *J* = 12.5 Hz, 1H), 4.91 (t, *J* = 10.5 Hz, 1H), 4.74 and 4.71 (d, *J* = 7.0 Hz, 1H), 4.41 (br s, 0.5 H) and 4.06 (d, *J* = 2.6 Hz, 0.5H), 3.90 (dd, *J* = 14.0, 5.4 Hz, 0.5H) and 3.74 (dd, *J* = 13.9, 5.5 Hz, 0.5H), 3.88-3.76 (m, 1H), 3.82 and 3.79 (s, 3H), 3.19 (q, *J* = 12.9 Hz, 1H), 3.00-2.93 (m, 0.5H) and 2.35-2.31 (m, 0.5H), 2.63-2.55 (m, 1H), 2.14-2.05 (m, 1H), 1.30 and 1.23 (d, *J* = 7.0 Hz, 3H), 0.94 and 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 184.9, 184.7, 165.7, 164.6, 157.2, 157.0, 153.7, 152.6, 151.4, 151.1, 143.6, 136.4, 136.3, 136.0, 135.9, 130.8, 128.9, 128.7, 128.4, 128.4, 128.3, 128.1, 128.0, 127.6, 127.5, 127.2, 127.1, 126.5, 123.4, 123.2, 122.3, 121.6, 104.6, 104.3, 75.9, 75.8, 70.9, 70.8, 70.7, 70.5, 65.8, 65.6, 61.0, 60.9, 46.7, 46.7, 37.6, 37.4, 37.3, 36.9, 34.1, 25.8, 18.4, 17.9, 15.4, 15.0; IR ($CHCl_3$): 3007, 1707, 1661, 1622, 1593, 1487, 1456, 1437, 1423, 1366, 1321, 1238, 1186, 1171, 1119, 1061, 1005, 854 cm^{-1}; EI-MS *m/z*: 660 (M^+, 53), 569 (42), 493 (3), 438 (3), 342 (6), 312 (4), 252 (5), 181 (20), 167 (7), 107 (5), 91 (100), 79 (3); HRMS calcd for $C_{37}H_{35}F_3N_2O_6$ (M^+): 660.2247, found: 660.2454.



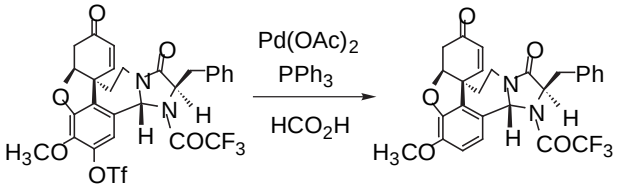
8a **9**

Debenzylation of 8a with BCl_3. To a solution of dienone **8a** (20 mg, 0.028mmol) in dichloromethane (0.5 mL, 0.056 M) was added dropwise boron trichloride (0.085 mL, 1.0 M solution in dichloromethane, 0.085 mmol) at –78 °C. After being stirred for 20 h, the reaction mixture was quenched with ice and water, continued to stir for 30 min at room temperature. The mixture was extracted with chloroform. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 10/1) afforded **9** (14.1 mg, 95 %) as amorphous; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.13 (m, 5H), 6.54 and 6.32 (d, *J* = 9.3 Hz, 0.5H), 6.20 (s, 0.5H) and 6.05-5.96 (m, 2.5H), 5.93 and 5.42 (s, 1H), 4.94 (s, 0.5H) and 4.70-4.65 (m, 1.5H), 4.00 and 3.92 (s, 3H), 4.00-3.84 (m, 1H), 3.46 (t, *J* = 11.8 Hz, 1H), 3.38 (t, *J* = 10.8 Hz, 2H), 3.07 (t, *J* = 18.0 Hz, 1H), 2.74 (t, *J* = 19.5 Hz, 1H), 2.06-2.01 (m, 1H), 1.94-1.84 and 1.37-1.26 (m, 2H),; ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.6, 167.2, 166.2, 149.5, 149.3, 144.2, 142.9, 134.3, 133.5, 132.3, 129.9, 129.7, 12837, 158.3, 127.9, 127.4, 125.7, 119.4, 103.4, 102.9, 88.0, 87.5, 77.2, 72.2, 71.3, 62.0, 61.2, 60.4, 4737, 46.8, 38.9, 37.6, 37.0, 36.5, 33.0, 32.3, 30.3; IR ($CHCl_3$): 3526, 1693, 1510, 1456, 1437, 1238, 1169 cm^{-1}; EI-MS *m/z*: 528 (M^+, 100), 459 (9), 437 (36), 431 (25), 409 (10), 397 (25), 353 (6), 339 (14), 286 (15), 216 (9), 131 (10), 103 (6), 91 (47), 77 (4); HRMS calcd for $C_{27}H_{23}O_4N_2F_3$ (M^+): 528.1514, found: 528.1508.



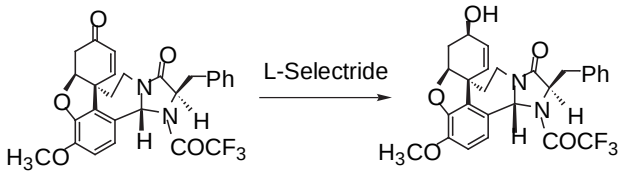
9 **16**

Triflation of 9. To a solution of **9** (343.0 mg, 0.65 mmol) in pyridine was added trifluoromethanesulfonic anhydride (0.131 mL, 0.78 mmol) at 0 °C. After being stirred for 3 h at 0 °C, the reaction mixture was added methanol (3 mL), and stirred for additional 30 min at room temperature. The mixture was concentrated *in vacuo*. The residue was added 1 N HCl, and aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, ethyl acetate) afforded triflate **16** (354.3 mg, 83%) as amorphous; ^{1}H NMR (400 MHz, CDCl3): δ 7.35-7.16 (m, 5H), 6.54-6.08 (m, 3H), 5.93 and 5.41 (s, 1H), 4.95 and 4.73 (s, 1H), 4.79 and 4.68 (s, 1H), 3.99 (brs, 3H), 3.89 (m, 1H), 3.52-3.07 (m, 4H), 2.76 (t, *J* = 15.8 Hz, 1H), 2.09 (m, 1H), 1.95 and 1.46 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 192.7, 167.0, 166.3, 150.6, 150.2, 142.6, 141.3, 133.9, 133.3, 129.9, 128.8,128.4, 128.0, 127.6, 123.4, 122.7, 120.2, 117.0, 110.3, 88.5, 88.0, 71.6, 71.0, 61.9, 61.1, 60.8, 48.2, 47.4, 39.0, 38.7, 37.7, 36.7, 36.3, 33.2, 32.4, 30.8; IR ($CHCl_3$): 1709, 1697, 1508, 1456, 1429, 1312, 1256, 1240, 1169, 1140, 1038, 1007 cm^{-1};EI-MS *m/z*: 660 (M^+, 14), 569 (18), 527 (100), 499 (5), 339 (4), 284 (5), 91 (41); HRMS calcd for $C_{28}H_{22}O_8N_2F_6S$ (M^+): 660.0996, found: 660.1000.



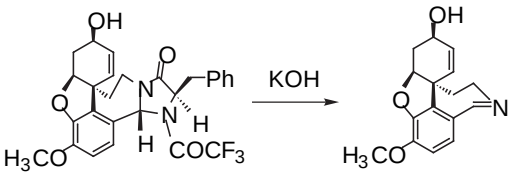
16 **10**

Detriflation of 16. To a solution of triflate **16** (114.4 mg, 0.17 mmol), palladium acetate (7.86 mg, 0.035 mmol), triphenylphosphine (18.17 mg, 0.069 mmol) in *N*,*N*- dimethylformamide (1.5 mL, 0.11 M) was added formic acid (0.064 mL, 1.7 mmol) and triethylamine (0.355 mL, 2.55 mmol). After being stirred for 3 d at 60 °C, the reaction mixture was concentrated *in vacuo*. The residue was diluted with ethyl acetate and washed with brine. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, ethyl acetate) afforded **10** (85.6 mg, 98%) as amorphous; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.14 (m, 5H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.60-6.50 (m, 0.5H) and 6.35 and 6.30 (d, *J* = 8.8 Hz, 0.5H), 6.59 and 6.53 (d, *J* = 9.3 Hz, 1H), 6.06 (d, *J*=10.4 Hz, 1H), 6.01 and 5.50 (s, 1H), 4.96 (s, 0.5H) and 4.72-4.65 (m, 1.5H), 4.02 (m, 1H), 3.95-3.83 (m, 1H), 3.86 (br s, 3H), 3.48-3.37 (m, 2H), 3.17 (d, *J* = 17.6 Hz, 1H), 2.76 (dd, *J* = 17.9, 3.4 Hz, 1H), 2.17-1.83 and 1.49-1.42 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.2, 167.1, 166.4, 156.5, 155.8, 148.0, 145.8, 145.2, 143.3, 141.9, 134.2, 133.4, 129.9, 129.7, 128.7, 128.3, 128.1, 127.9, 127.4, 126.6, 123.5, 121.2, 116.4, 112.6, 112.1, 111.3, 88.0, 87.5, 87.0, 77.2, 72.6, 71.8, 61.9, 61.1, 56.1, 55.9, 48.6, 47.7, 39.8, 38.9, 37.8, 36.8, 36.3, 35.1, 33.6, 32.3, 30.9; IR ($CHCl_3$): 2937, 1693, 1510, 1456, 1437, 1286, 1167, 1055; EI-MS *m/z*: 512 (M^+, 100), 443 (18), 421 (50), 381 (38), 323 (26), 270 (25), 200 (10), 131 (16), 91 (86); HRMS calcd for $C_{27}H_{23}O_5N_2F_3$ (M^+): 512.1559, found: 512.1553.



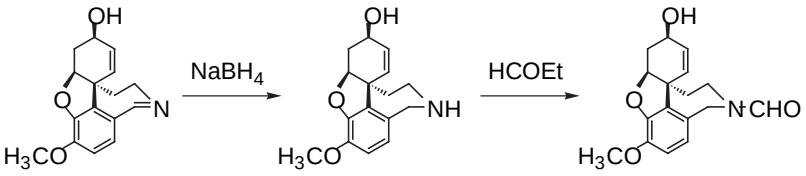
10 **17**

Reduction of 10 with L-Selectride. To a cooled (-78 °C) solution of enone **10** (200 mg, 0.39 mmol) in THF (2 mL, 0.195 M) was added dropwise lithium tri-*sec*-buthylborohydride (L-Selectride®) (0.937 mL, 1.0 M solution in THF, 0.937 mmol). After being stirred for 3 h at the same temperature, the reaction mixture was quenched saturated aqueous Na_2SO_4. The reaction mixture was extracted with chloroform, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, ethyl acetate) afforded **17** (156.3 mg, 78%) as amorphous; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.12 (m, 5H), 6.73 (d, *J* = 8.6 Hz, 1H), 6.49 and 6.26 (d, *J* = 8.2 Hz, 1H), 6.07 and 6.05 (d, *J* = 5.1 Hz, 1H), 5.99 (s, 1H), 5.73 (d, *J*=9.9 Hz, 1H), 4.93 (brs, 0.3H) and 4.63 (d, *J*=3.7 Hz, 0.7H), 4.58 and 4.51 (s, 1H), 4.16 (br s, 1H), 4.03-3.98 (m, 1H), 3.89-3.80 (m, 1H), 3.87 and 3.85 (s, 3H), 3.40 (t, *J* = 12.5 Hz, 2H), 2.67 (t, *J* = 16.7 Hz, 1H), 2.03-1.56 (m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.1, 147.0, 145.9, 134.4, 134.4, 129.9, 129.7, 129.2, 128.7, 128.3, 127.3, 126.8, 125.6, 116.3, 114.0, 111.8, 111.3, 88.1, 72.7, 72.1, 61.9, 61.5, 61.1, 60.7, 55.9, 48.1, 47.3, 38.8, 37.9, 34.6, 32.4, 29.6, 29.1; IR ($CHCl_3$): 3568, 2937, 1709, 1508, 1456, 1437, 1286, 1238, 1194, 1167, 1060; EI-MS *m/z*: 514 (M^+, 97), 496 (12), 443 (58), 423 (28), 395 (9), 383 (22), 325 (21), 313 (10), 272 (17), 200 (24), 131 (21), 103 (14), 91 (100), 65 (15), 55 (11); HRMS calcd for $C_{27}H_{25}N_2O_5F_3$ (M^+): 514.1715, found: 514.1711.



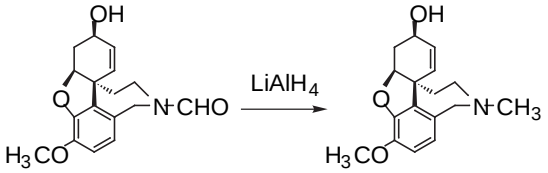
17 **11**

Hydrolysis of 17. To a mixture of **17** (93.7 mg, 0.18 mmol) and tetra-*n*-butylanmonium bromide (29.4 mg, 0.09 mmol) was added KOH (3.0 mL, 10% solution in ethanol) at room temperature. The reaction mixture was stirred for 1 d at 80 °C. The reaction mixture was cooled to room temperature, concentrated *in vacuo*. The residue was added water, and aqueous layer was extracted with chloroform. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, chlroform/methanol, 10/1) afforded **11** (46.7 mg, 96%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 （br s、1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.01 (ddd, *J* = 10.0, 5.2, 1.1 Hz, 1H), 5.59 (d, *J* = 10.1 Hz, 1H), 4.72 (br s, 1H), 4.17 (t, *J* = 4.8 Hz, 1H), 4.11-4.01 (m, 2H), 3.91 (s, 3H), 2.73-2.680 (m, 1H), 2.09-1.98 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 158.9, 146.5, 145.2, 134.6, 128.7, 127.6, 126.4, 122.6, 111.7, 88.9, 61.7, 56.0, 49.7, 47.6, 35.9, 29.5; IR ($CHCl_3$): 3564, 2930, 1620, 1506, 1454, 1437, 1406, 1286, 1173, 1090, 1063, 991; EI-MS *m/z*: 271 (M^+, 100), 254 (14), 238 (5), 212 (7), 193 (8), 181 (11), 165 (10), 155 (8), 115 (12), 91 (21), 85 (32), 83 (77); HRMS calcd for $C_{16}H_{17}NO_3$ (M^+): 271.1208, found: 271.1214.



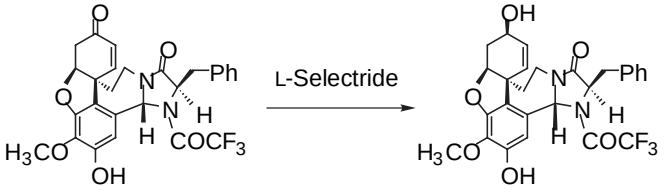
11 **18**

***N*-Formyl-*N*-norgalanthamine (18).** To a solution of **11** (40 mg, 0.147 mmol) in methanol (1.0 mL, 0.147 M) was added sodium borohydride (13.4 mg, 0.354 mmol) at 0 °C and the reaction mixture was stirred for 1 d at room temperature, concentrated *in vacuo*. Water was added to the residue and the aqueous layer was extracted with chloroform. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. A solution of the residue in ethyl formate was refluxed for 2 d, concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, chlroform/methanol, 10/1) afforded **18** (46.3 mg, quant.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 and 8.12 (s, 1H), 6.86 (d, *J* = 8.2 Hz, 0.5H) and 6.69 (d, *J* = 8.2 Hz, 0.5H), 6.74 and 6.70 (s, 1H), 6.11-5.97 (m, 2H), 5.21 (d, *J* = 15.2 Hz, 0.5H) and 4.03 (d, *J* = 15.0 Hz, 0.5H), 4.59 (br s, 1H), 4.17 (t, *J* = 4.6 Hz, 1H), 3.85 and 3.84 (s, 3H), 3.74-3.66 (m, 1H), 3.28-3.21 (m, 1H), 2.75-2.68 (m, 1H), 2.07-1.94 (m, 2H), 1.92-1.77 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 162.4, 161.8, 146.7, 146.3, 144.8, 144.6, 132.1, 132.0, 128.6, 128.4, 128.4, 127.7, 126.1, 125.8, 121.8, 120.1, 111.4, 111.3, 88.2, 88.1, 61.8, 55.9, 52.8, 48.3, 48.2, 46.8, 46.5, 41.0, 39.3, 36.0, 29.8, 29.7; IR ($CHCl_3$): 3564, 2936, 1668, 1628, 1591, 1510, 1456, 1435, 1396, 1375, 1281, 1240, 1194, 1171, 1132, 1059, 1063, 993, 966; EI-MS *m/z*: 301 (M^+, 100), 282 (5), 270 (6), 252 (4), 243 (7), 225 (19), 211 (24), 195 (9), 181 (11), 165 (9), 152 (5), 141 (8), 128 (14), 115 (20), 105 (6), 91 (12), 77 (15), 55 (24); HRMS calcd for $C_{17}H_{19}NO_4$ (M^+): 301.1314, found: 301.1317.



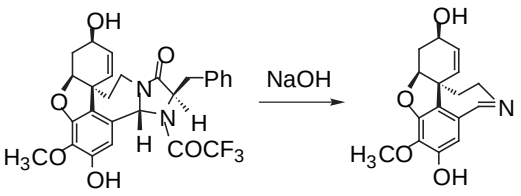
18 **(-)-Galanthamine (1)**

(-)-Galanthamine (1). To a solution of lithium aluminum hydride (3.2 mg, 0.084 mmol) in THF (1.00 mL, 0.035 M) was added **18** (10.5 mg, 0.035 mmol) at 0 °C and the reaction mixture was stirred for 7 h at room temperature. The reaction mixture was added saturated Na_2SO_4, extracted with chloroform. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, chlroform/methanol, 10/1) afforded (-)-galanthamine (**1**) (9.5 mg, 94%); $[\alpha]_D^{22}$ = -121.7 (0.30, EtOH); ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.68 (d, *J* = 8.1 Hz, 1H, H-8), 6.64 (d, *J* = 8.2 Hz, 1H, H-7), 6.06 (d, *J* = 10.3 Hz, 1H,H-4a), 6.02 (dd, *J* = 10.5, 4.1 Hz, 1H, H-4), 4.62 (br s, 1H, H-1), 4.15 (t, *J* = 4.8 Hz, 1H, H-3), 4.14 (d, *J*=15.4 Hz, 1H, H-6), 3.84 (s, 3H, OMe), 3.73 (d, *J* = 14.7 Hz, 1H, H-6), 3.32 (t, *J* = 13.0 Hz, 1H, H-12), 3.09 (d, *J* = 14.5 Hz, 1H, H-12), 2.72-2.67 (m, 1H, H-2), 2.43 (s, 3H, NMe) 2.31-2.06 (m, 1H, H-2), 2.04-1.89 (m, 1H, H-11), 1.70-1.60 (m, 1H, H-11); ^{13}C NMR (400 MHz, $CDCl_3$): δ 145.7, 144.0, 132.9, 128.9, 127.6, 126.7, 122.0, 111.1, 88.6, 61.9, 60.4, 55.8, 53.6, 48.1, 41.8, 33.6, 29.8; IR ($CHCl_3$): 3410, 2964, 2933, 1626, 1601, 1514, 1462, 1439, 1408, 1375, 1283, 1234, 1223, 1202, 1173, 1138, 1115, 1090, 1069, 1047, 1015, 988, 943, 922, 870, 826; EI-MS *m/z*: 287 (M^+, 100), 270 (13), 244 (33), 230 (16), 216 (40), 174 (19), 166 (7), 150 (9), 57 (5); HRMS calcd for $C_{17}H_{21}NO_3$ (M^+): 287.1521, found: 287.1515.



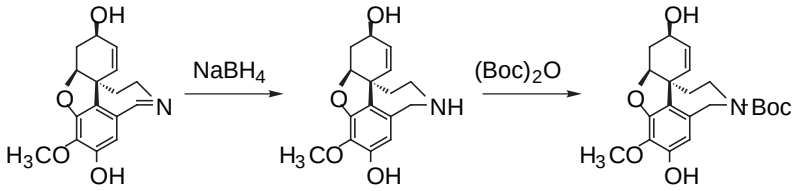
9 **19**

Reduction of 9 with L-Selectride. To a cooled (-78 °C) solution of enone **9** (141.2 mg, 0.27 mmol) in THF (2 mL, 0.135 M) was added lithium tri-*sec*-buthylborohydride (L-Selectride®) (0.64 mL, 1.0 M solution in THF, 0.64 mmol) dropwise at -78 °C. After being stirred for 1 d at the same temperature, the reaction mixture was quenched saturated aqueous Na_2SO_4. The reaction mixture was extracted with chloroform, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, chlroform/methanol, 50/1) afforded **19** (131.7 mg, 92%) as amorphous; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.13 (m, 5H), 6.17 and 5.92 (s, 1H), 6.02 (dd, *J* = 9.9, 4.8 Hz, 1H), 5.69 (d, *J* = 10.4 Hz, 1H), 5.44 (br s, 1H), 4.92 and 4.57 (br s, 1H), 4.63 (d, *J* = 3.6 Hz, 0.5H) and 4.51 (br s, 0.5H), 4.14-4.11 (m, 1H), 3.96 (s, 3H), 3.93-3.82 (m, 1H), 3.43-3.34 (m, 2H), 2.62 (t, *J* = 15.3 Hz, 1H), 2.18 (d, *J* = 10.8Hz, 1H), 2.04-1.66 (m, 3H), 1.39-1.18 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.1, 166.3, 156.0, 155.6, 148.8, 148.7, 134.3, 133.5, 132.3, 129.7, 128.7, 128.3, 127.9, 127.3, 126.5, 121.9, 116.8, 114.0, 103.2, 102.8, 88.8, 72.4, 71.6, 61.9, 61.6, 61.2, 60.4, 47.1, 46.3, 38.8, 37.7, 34.2, 32.4, 31.7, 29.7, 29.3; IR ($CHCl_3$): 3530, 2939, 1709, 1603; EI-MS *m/z*: 530 (M^+, 100), 459 (20), 433 (19), 399 (16), 341 (15), 288 (15), 268 (11), 241 (55), 227 (18), 216 (51), 209 (12), 201 (13), 181 (11), 131 (15), 103 (15), 91 (63); HRMS calcd for $C_{27}H_{25}N_2O_6F_3$ (M^+): 530.1664, found: 530.1660.



19 **20**

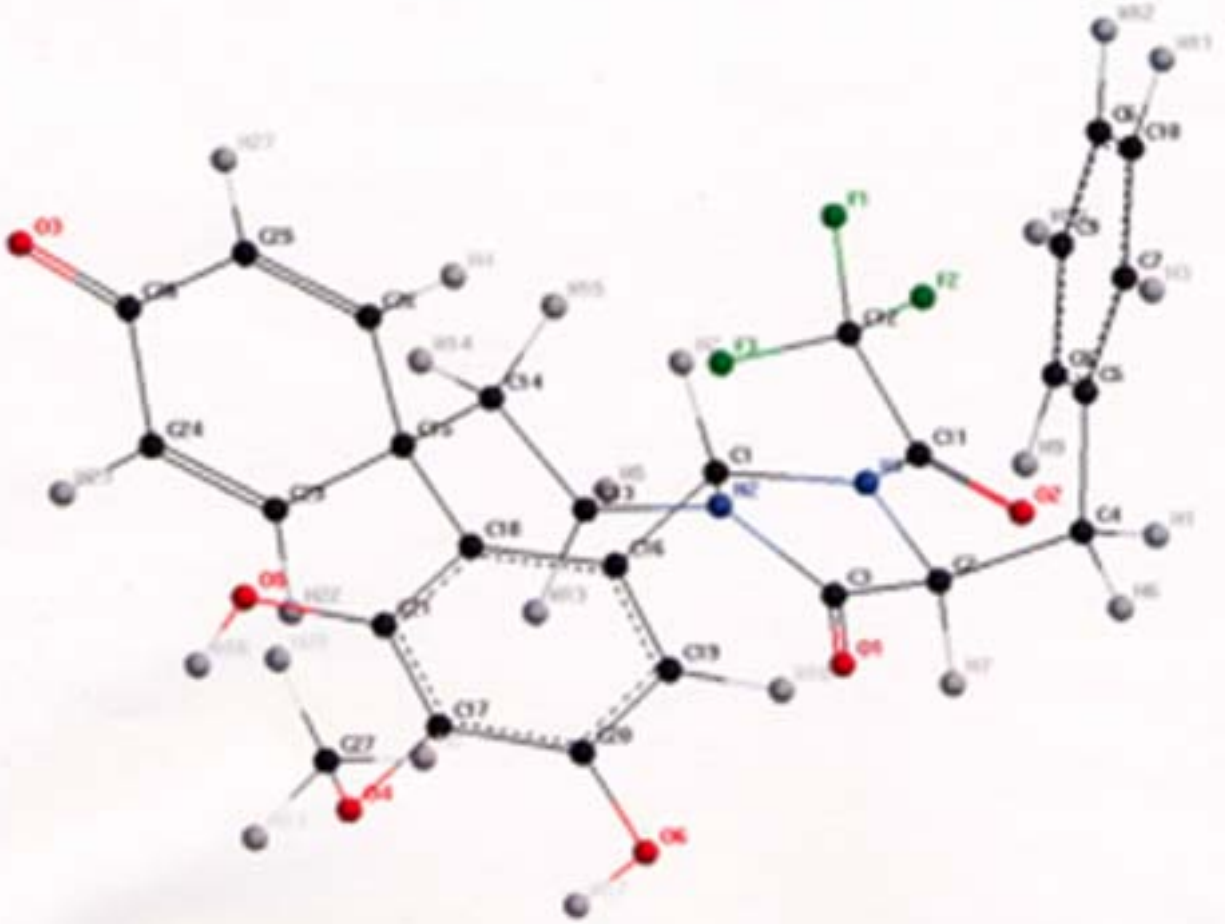
Hydrolysis of 19. To a mixture of **19** (50 mg, 0.094 mmol) in THF (0.5 mL, 0.188 M) was added NaOH (0.5 mL, 10% solution in H_2O) at room temperature. The reaction mixture was stirred for 12 h at room temperature, the reaction mixture was quenched 1N HCl. The reaction mixture was extracted with chloroform, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, chlroform/methanol, 10/1) afforded amine (40.9 mg, quant.). To a mixture of amine (20 mg, 0.046 mmol) was added NaOH (4.5 mL, 10% solution in H_2O) at room temperature. The reaction mixture was stirred for 7.5 d at room temperature, the reaction mixture was quenched 1N HCl. The reaction mixture was extracted with chloroform, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, chlroform/methanol, 5/1) afforded **20** (11.0 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 6.63 (s, 1H), 5.89 (dd, *J* = 9.9, 5.1 Hz, 1H), 5.56 (d, *J* = 9.9 Hz, 1H), 4.71 (br s, 1H), 4.17 (t, *J* = 4.7 Hz, 1H), 4.16-4.01 (m, 2H), 4.06 (s, 3H), 2.68-2.63 (m, 1H), 2.08-2.00 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 159.6, 148.8, 146.7, 133.9, 129.9, 127.7, 127.0, 111.4, 89.8, 70.7, 61.9, 60.5, 50.0, 47.0, 36.8, 29.8; IR ($CHCl_3$): 3533, 2934, 1601, 1504, 1404, 1369, 1298; EI-MS *m/z*: 287 (M^+, 100), 269 (13), 242 (42), 227 (34), 209 (34), 197 (23), 181 (23), 141 (11), 115 (24), 91 (23), 77 (25); HRMS calcd for $C_{16}H_{17}NO_4$ (M^+): 287.1157, found: 287.1151.



20 **21** **12**

***N*-Boc-7-hydroxy-*N*-norgalanthamine (12).** To a solution of **20** (8.8 mg, 0.031 mmol) in methanol (0.5 mL, 0.062 M) was added sodium borohydride (4.63 mg, 0.123 mmol) at 0 °C and the reaction mixture was stirred for 4 h at room temperature, then concentrated *in vacuo*. The residue was diluted with H_2O, extracted with chloroform, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. To a solution of residue in THF (0.5 mL) was added di-*tert*-butyl dicarbonate (21.05 mg, 0.096 mmol) at 0 °C, and the reaction mixture was stirred for 2 h at room temperature, concentrated *in vacuo*. Water was added to the residue and the aqueous layer was extracted with chloroform. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (silica gel, ethyl acetate) afforded **12** (7.0 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.45 and 6.34 (s, 1H), 5.98-5.92 (m, 2H), 4.79 (d, *J* = 15.9 Hz, 0.5H) and 4.27 (d, *J* = 14.8 Hz, 0.5H), 4.62 and 4.58 (s, 1H), 4.15 (s, 1H), 3.96 and 3.93 (s, 3H), 3.28 (t, *J* = 13.0 Hz, 1H), 2.65 (d, *J* = 15.7 Hz, 1H), 2.04 and 2.00 (dt, *J* = 15.7, 2.4 Hz, 1H), 1.90 (dt, *J* = 13.1, 3.1 Hz, 1H), 1.77-1.65 (m, 2H), 1.43 and 1.39 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 154.9, 148.2, 147.8, 132.0, 130.8, 127.5, 127.2, 127.0, 124.4, 108.2, 107.5, 89.2, 89.0, 80.0, 62.0, 60.5, 52.0, 51.4, 47.6, 46.0, 45.3, 37.3, 36.3, 30.0, 28.5, 28.3; IR ($CHCl_3$): 3531, 2937, 1686, 1601, 1508, 1462, 1441, 1416, 1367, 1251, 1169; EI-MS *m/z*: 389 (M^+, 14), 332 (100), 288 (11), 242 (9), 197 (14), 115 (6); HRMS calcd for $C_{21}H_{27}NO_6$ (M^+): 389.1838, found: 389.1836.

PM3 Calculation of the intermediate **B** (R^1 = H, R^2 = Bn, R^3 = $COCF_3$)



kodama-norbelladine_copu_OH-PM3

Molecule	Energy(kcal/mol)	Dist(C22,O5)	Dist(O5,C23)
Kodama-dienone-OH0001	-277.887771	3.15385503	2.60778392