

Supporting information for Palladium Catalyzed Sequential Arylation and Allylic Alkylation of Highly Functionalized Ketones: A Concise Synthesis of Mesembrine

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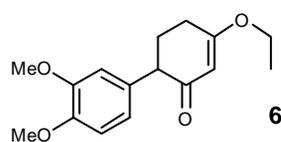
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General Experimental:

Proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz. Carbon-13 nuclear magnetic resonance ($^{13}\text{C-NMR}$) was recorded on Bruker Avance 300 spectrometer at 75 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. Starting materials and reagents used in reactions were obtained commercially from Acros, Aldrich, Fluka and were used without purification, unless otherwise indicated.

General Procedure for Palladium Catalyzed Arylations:

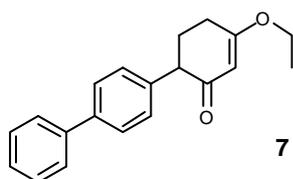
A mixture of palladium acetate (22.4 mg, 0.1 mmol, 0.1 eq.), (\pm)-BINAP (74 mg, 0.12 mmol, 0.12 eq.) and arylbromide (1.2 mmol, 1.2 eq.) in anhydrous 1,4-dioxane (10 mL) was degassed and purged with nitrogen (3 times). A solution of sodium bis(trimethylsilyl)amide (2.0 M in THF, 2.4 mmol, 2.4 eq.) was added followed by 3-ethoxy-2-cyclohexenone (140 mg, 1 mmol) in 1,4-dioxane (5 mL). The resulting mixture was then stirred at 90 °C (oil bath) under nitrogen for 20-24 hours. The reaction was monitored by thin layer chromatography (TLC). After cooling to room temperature, water (0.1 mL) was added then the solvent was removed under reduced pressure and the residue was diluted with water (25 mL) and extracted with ethyl acetate (3 \times 15 mL). The organic phases were combined and washed with brine (10 mL) and dried over anhydrous Na_2SO_4 . After removal of the solvents, the residue was chromatographed on silica gel to afford the products.



6-(3,4-Dimethoxy-phenyl)-3-ethoxy-cyclohex-2-enone

$\text{C}_{16}\text{H}_{20}\text{O}_4$ Mol. Wt.: 276.33

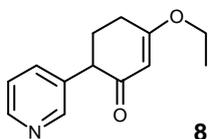
Colorless oil, $R_f = 0.45$ (EtOAc : Petroleum ether = 1:2) $^1\text{H-NMR}$ (300MHz, CDCl_3), δ (ppm): 6.83 (1H, d, $J = 8.1$ Hz), 6.72 (1H, dd, $J = 1.9, 8.2$ Hz), 6.70 (1H, d, $J = 1.9$ Hz), 5.50 (1H, s), 3.94 (2H, q, $J = 7.0$ Hz), 3.86 (6H, s), 3.47 (1H, dd, $J = 5.6, 9.4$ Hz), 2.55-2.47 (2H, m), 2.27-2.20 (2H, m), 1.39 (3H, t, $J = 7.0$ Hz). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm): 199.81 (s), 177.65 (s), 149.34 (s), 148.37 (s), 132.84 (s), 120.70 (d), 112.23 (d), 111.73 (d), 103.46 (d), 64.80 (t), 56.29 (q), 51.98 (d), 29.88 (t), 28.77 (t), 14.56 (q).



6-Biphenyl-4-yl-3-ethoxy-cyclohex-2-enone

$C_{20}H_{20}O_2$ Mol. Wt.: 292.37

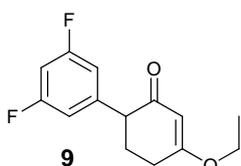
Colorless oil, $R_f = 0.56$ (EtOAc : Petroleum ether = 1:4) 1H -NMR (300MHz, $CDCl_3$), δ (ppm): 7.59-7.54 (4H, m), 7.42 (2H, t, $J = 7.1$ Hz), 7.35-7.24 (3H, m), 5.53 (1H, s), 3.95 (2H, q, $J = 7.1$ Hz), 3.57 (1H, dd, $J = 5.5, 9.9$ Hz), 2.59-2.51 (2H, m), 2.32-2.25 (2H, m), 1.39 (3H, t, $J = 7.1$ Hz). ^{13}C -NMR (75MHz, $CDCl_3$), δ (ppm): 199.33 (s), 177.45 (s), 141.09 (s), 139.86 (s), 139.10 (s), 128.86 (d), 128.79 (d), 127.40 (d), 127.19 (d), 103.23 (d), 64.53 (t), 51.81 (d), 29.50 (t), 28.46 (t), 14.27 (q).



3-Ethoxy-6-pyridin-3-yl-cyclohex-2-enone

$C_{13}H_{15}NO_2$ Mol. Wt.: 217.26

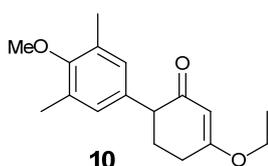
Colorless oil, $R_f = 0.55$ (EtOAc : Petroleum ether = 1:1) 1H -NMR (300MHz, $CDCl_3$), δ (ppm): 8.50 (1H, dd, $J = 1.5, 4.8$ Hz), 8.44 (1H, d, $J = 1.5$ Hz), 7.48 (1H, dt, $J = 1.9, 7.9$ Hz), 7.25 (1H, dd, $J = 4.8, 7.9$ Hz), 5.51 (1H, s), 4.00 (2H, q, $J = 7.0$ Hz), 3.53 (1H, dd, $J = 5.4, 10.4$ Hz), 2.71-2.55 (1H, m), 2.51-2.40 (1H, m), 2.28-2.22 (2H, m), 1.39 (3H, t, $J = 7.0$ Hz). ^{13}C -NMR (75MHz, $CDCl_3$), δ (ppm): 197.94 (s), 177.47 (s), 150.07 (d), 148.40 (d), 136.03 (d), 135.65 (s), 123.48 (d), 103.13 (d), 64.72 (t), 49.83 (d), 29.30 (t), 28.63 (t), 14.28 (q).



6-(3,5-Difluoro-phenyl)-3-ethoxy-cyclohex-2-enone

$C_{14}H_{14}F_2O_2$ Mol. Wt.: 252.26

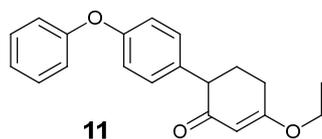
Colorless oil, $R_f = 0.45$ (EtOAc : Petroleum ether = 1:5) 1H -NMR (300MHz, $CDCl_3$), δ (ppm): 6.74-6.60 (3H, m), 5.49 (1H, s), 3.95 (2H, q, $J = 7.1$ Hz), 3.49 (1H, dd, $J = 5.1, 10.2$ Hz), 2.60-2.31 (2H, m), 2.30-2.12 (2H, m), 1.38 (3H, t, $J = 7.1$ Hz). ^{13}C -NMR (75MHz, $CDCl_3$), δ (ppm): 197.76 (s), 177.59 (s), 164.87-164.70 (s), 161.58-161.42 (s), 143.79 (s), 111.74 (d), 111.41 (d), 103.02 (d), 102.52 (d), 64.73 (t), 51.80 (d), 29.11 (t), 28.41 (t), 14.25 (q).



3-Ethoxy-6-(4-methoxy-3,5-dimethyl-phenyl)-cyclohex-2-enone

$C_{17}H_{22}O_3$ Mol. Wt.: 274.35

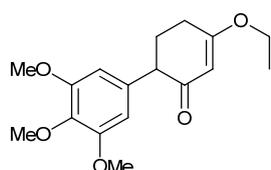
Colorless oil, $R_f = 0.52$ (EtOAc : Petroleum ether = 1:3) $^1\text{H-NMR}$ (300MHz, CDCl_3), δ (ppm): 6.79 (2H, s), 5.49 (1H, s), 3.95 (2H, q, $J = 7.1$ Hz), 3.69 (3H, s), 3.40 (1H, dd, $J = 6.0, 9.2$ Hz), 2.53-2.41 (2H, m), 2.25 (6H, s), 2.25-2.15 (2H, m), 1.38 (3H, t, $J = 7.1$ Hz). $^{13}\text{C-NMR}$ (75MHz, CDCl_3), δ (ppm): 199.66 (s), 177.30 (s), 155.73 (s), 135.22 (s), 130.75 (s), 128.70 (d), 103.12 (d), 64.37 (t), 59.58 (q), 51.51 (d), 29.63 (t), 28.39 (t), 16.18 (q), 14.20 (q).



3-Ethoxy-6-(4-phenoxy-phenyl)-cyclohex-2-enone

$\text{C}_{20}\text{H}_{20}\text{O}_3$ Mol. Wt.: 308.37

Colorless oil, $R_f = 0.50$ (EtOAc : Petroleum ether = 1:4) $^1\text{H-NMR}$ (300MHz, CDCl_3), δ (ppm): 7.39-7.27 (2H, m), 7.19-6.90 (7H, m), 5.50 (1H, s), 3.94 (2H, q, $J = 7.1$ Hz), 3.50 (1H, dd, $J = 5.2, 9.8$ Hz), 2.59-2.40 (2H, m), 2.31-2.12 (2H, m), 1.39 (3H, t, $J = 7.1$ Hz). $^{13}\text{C-NMR}$ (75MHz, CDCl_3), δ (ppm): 199.32 (s), 177.43 (s), 157.36 (s), 156.17 (s), 134.83 (s), 129.80 (d), 129.72 (d), 123.30 (d), 119.07 (d), 118.94 (d), 103.21 (d), 64.54 (t), 51.41 (d), 29.63 (t), 28.40 (t), 14.27 (q).

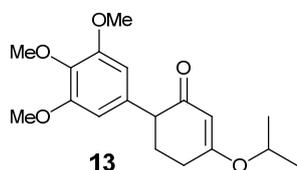


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3-Ethoxy-6-(3,4,5-trimethoxy-phenyl)-cyclohex-2-enone

$\text{C}_{17}\text{H}_{22}\text{O}_5$ Mol. Wt.: 306.35

Colorless oil, $R_f = 0.50$ (EtOAc : Petroleum ether = 1:2) $^1\text{H-NMR}$ (300MHz, CDCl_3), δ (ppm): 6.35 (2H, s), 5.90 (1H, s), 3.92 (2H, q, $J = 7.0$ Hz), 3.80 (9H, s), 3.42 (1H, dd, $J = 5.9, 9.7$ Hz), 2.54-2.45 (2H, m), 2.24-2.18 (2H, m), 1.36 (3H, t, $J = 7.0$ Hz). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ (ppm): 199.10 (s), 177.39 (s), 153.17 (s), 136.89 (s), 135.67 (s), 105.58 (d), 103.02 (d), 64.44 (t), 60.71 (q), 56.05 (q), 55.90 (q), 52.36 (d), 29.63 (t), 28.50 (t), 14.11 (q).

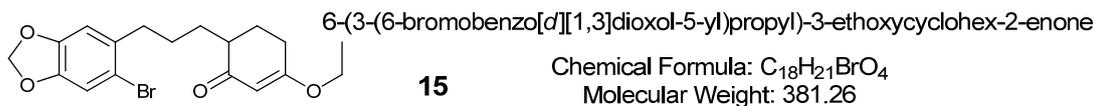


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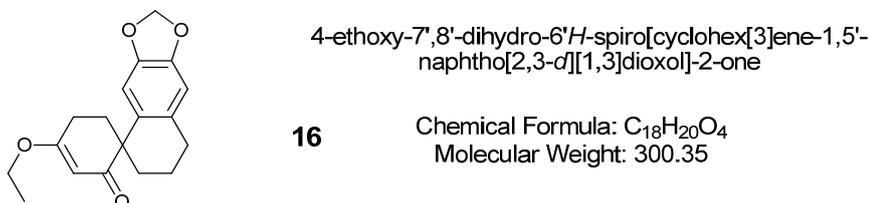
3-Isopropoxy-6-(3,4,5-trimethoxy-phenyl)-cyclohex-2-enone

$\text{C}_{18}\text{H}_{24}\text{O}_5$ Mol. Wt.: 320.38

Colorless oil, $R_f = 0.48$ (EtOAc : Petroleum ether = 1:3) $^1\text{H-NMR}$ (300MHz, CDCl_3), δ (ppm): 6.35 (2H, s), 5.46 (1H, s), 4.42 (1H, quintet, $J = 6.1$ Hz), 3.77 (9H, s), 3.41 (1H, dd, $J = 5.7, 9.7$ Hz), 3.47-2.46 (2H, m), 2.21-2.16 (2H, m), 1.30-1.24 (6H, m). $^{13}\text{C-NMR}$ (75MHz, CDCl_3), δ (ppm): 199.13 (s), 176.37 (s), 153.14 (s), 136.84 (s), 135.77 (s), 105.54 (d), 103.33 (d), 71.19 (d), 60.68 (q), 56.00 (q), 52.32 (d), 29.61 (t), 28.91 (t), 21.47 (q).

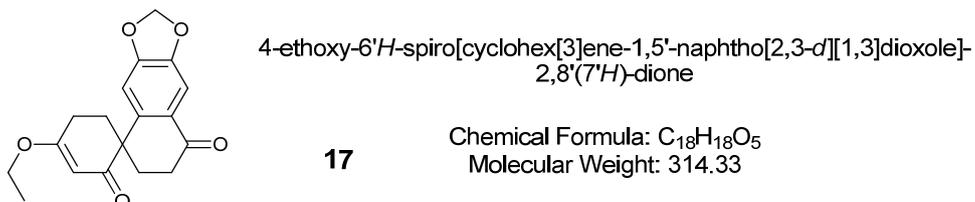


Colorless oil, $R_f = 0.51$ (EtOAc : Petroleum ether = 1:2) ¹H-NMR (300MHz, CDCl₃), δ (ppm): 6.96 (1H, s), 6.69 (1H, s), 5.92 (2H, s), 5.30 (1H, s), 3.89 (2H, q, $J = 7.0$ Hz), 2.65-2.61 (2H, m), 2.43-2.39 (2H, m), 2.30-1.50 (6H, m), 1.50-1.20 (2H, m), 1.35 (3H, t, $J = 7.0$ Hz). ¹³C-NMR (75MHz, CDCl₃), δ (ppm): 201.51 (s), 176.79 (s), 147.25 (s), 146.48 (s), 134.71 (s), 114.17 (s), 112.62 (d), 109.94 (d), 102.22 (d), 101.51 (t), 64.19 (t), 45.01 (d), 36.15 (t), 29.09 (t), 27.99 (t), 27.67 (t), 26.18 (t), 14.18 (q).



A mixture of palladium acetate (22.4 mg, 0.1 mmol, 0.1 eq.), (\pm)-BINAP (74 mg, 0.12 mmol, 0.12 eq.), cesium carbonate (652 mg, 2 mmol, 2.0 eq.) and aryl bromide (381.3 mg, 1.0 mmol) in anhydrous *m*-xylene (15 mL) was degassed and purged with nitrogen (3 times). The resulting mixture was then stirred at 130 °C (oil bath) under nitrogen for 36 hours. The reaction was monitored by thin layer chromatography (TLC). After cooling to room temperature, ethyl acetate (30 mL) was added then washed with water (10 mL) and brine (15 mL). The organic phases were dried over anhydrous Na₂SO₄. After removal of the solvents, the residue was chromatographed on silica gel to afford the products as yellow solid (213 mg, 71% yield).

Yellow solid, $R_f = 0.45$ (EtOAc : Petroleum ether = 1:2), mp: 153-155 °C (EtOAc). ¹H-NMR (300MHz, CDCl₃), δ (ppm): 6.52 (1H, s), 6.44 (1H, s), 5.86 (1H, d, $J = 1.4$ Hz), 5.83 (1H, d, $J = 1.4$ Hz), 5.43 (1H, s), 3.98-3.87 (2H, m), 2.85-2.55 (3H, m), 2.45-2.21 (2H, m), 2.12-1.72 (5H, m), 1.38 (3H, t, $J = 7.0$ Hz). ¹³C-NMR (75MHz, CDCl₃), δ (ppm): 204.15 (s), 176.20 (s), 146.46 (s), 146.18 (s), 133.20 (s), 131.30 (s), 109.06 (d), 108.53 (d), 103.01 (d), 101.06 (t), 64.73 (t), 49.40 (t), 35.27 (t), 31.24 (t), 30.49 (t), 26.54 (t), 19.40 (t), 14.61 (q).

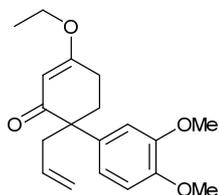


A mixture of copper iodide (CuI, 20 mg, 0.1 mmol, 0.1 eq.), *t*-butyl hydroperoxide (70 wt. % in water, 1.2 mL) and spiro-compound (301 mg, 1.0 mmol) in acetonitrile (6 mL) was stirred at 60 °C (oil bath) under nitrogen for 20-24 hours. The reaction was monitored by thin layer chromatography (TLC). After cooling to room temperature, a solution of aqueous saturated solution of sodium bicarbonate (20 mL) was added. The resulting mixture was extracted with ethyl acetate (3×10 mL). The combined organic phases were washed with brine (10 mL) and dried over anhydrous Na₂SO₄. After removal of the solvents, the residue was chromatographed on silica gel to afford the products as yellow solid (220 mg, 70% yield).

Yellow solid, R_f = 0.45 (EtOAc : Petroleum ether = 1:2), mp: 169-171 °C (EtOAc). ¹H-NMR (300MHz, CDCl₃), δ (ppm): 7.50 (1H, s), 6.60 (1H, s), 6.00 (1H, d, J = 1.3 Hz), 5.97 (1H, d, J = 1.3 Hz), 5.52 (1H, s), 4.02-3.91 (2H, m), 2.68-2.25 (6H, m), 2.17-2.05 (2H, m), 1.41 (3H, t, J = 7.0 Hz). ¹³C-NMR (75MHz, CDCl₃), δ (ppm): 200.85 (s), 195.38 (s), 176.69 (s), 152.34 (s), 147.46 (s), 143.24 (s), 128.11 (s), 107.00 (d), 106.87 (d), 102.91 (d), 101.95 (t), 64.83 (t), 48.73 (s), 33.58 (t), 32.89 (t), 30.09 (t), 26.41 (t), 14.30 (q).

General Procedure for Sequential Arylation-Allylations:

A mixture of palladium acetate (22.4 mg, 0.1 mmol, 0.1 eq.), (±)-BINAP (74 mg, 0.12 mmol, 0.12 eq.) and arylbromide (1.2 mmol, 1.2 eq.) in anhydrous 1,4-dioxane (10 mL) was degassed and purged with nitrogen (3 times). A solution of sodium bis(trimethylsilyl)amide (2.0 M in THF, 2.4 mmol, 2.4 eq.) was added followed by 3-ethoxy-2-cyclohexenone (140 mg, 1 mmol) in 1,4-dioxane (5 mL). The resulting mixture was then stirred at 90 °C (oil bath) under nitrogen for 20-24 hours. The reaction was monitored by thin layer chromatography (TLC). After cooling to room temperature, a solution of sodium bis(trimethylsilyl)amide (2.0 M in THF, 2.0 mmol, 2.0 eq.) was added followed by allyl acetate (0.32 mL, 3 mmol, 3.0 eq.). The reaction was then stirred at room temperature for 6-10 hours. Water (0.1 mL) was added then the solvent was removed under reduced pressure and the residue was diluted with water (25 mL) and extracted with ethyl acetate (3×15 mL). The organic phases were combined and washed with brine (10 mL) and dried over anhydrous Na₂SO₄. After removal of the solvents, the residue was chromatographed on silica gel to afford the products.



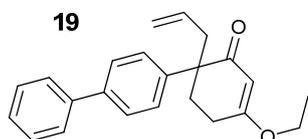
6-allyl-6-(3,4-dimethoxyphenyl)-3-ethoxycyclohex-2-enone

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Chemical Formula: C₁₉H₂₄O₄
Molecular Weight: 316.39

Colorless oil, R_f = 0.55 (EtOAc : Petroleum ether = 1:3) ¹H-NMR (300MHz, CDCl₃), δ (ppm): 6.91-6.79 (3H, m), 5.65-5.56 (1H, m), 5.38 (1H, s), 5.02-4.98 (2H, m), 3.82 (6H, s), 3.82-3.65 (2H, m), 2.65 (1H, dd, J = 9.6, 13.4 Hz), 2.48 (1H, dd, J = 7.6, 13.5 Hz), 2.42-2.06 (4H, m), 1.29 (3H, t, J = 7.1 Hz). ¹³C-NMR (75MHz, CDCl₃), δ (ppm):

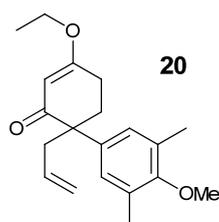
200.65 (s), 179.39 (s), 148.86 (s), 147.86 (s), 134.84 (d), 132.51 (s), 118.74 (d), 117.72 (t), 110.77 (d), 110.41 (d), 102.59 (d), 64.19 (t), 55.91 (q), 55.76 (q), 51.17 (s), 44.75 (t), 29.82 (t), 26.52 (t), 14.07 (q).



19 6-allyl-6-(biphenyl-4-yl)-3-ethoxycyclohex-2-enone

Chemical Formula: $C_{23}H_{24}O_2$
Molecular Weight: 324.44

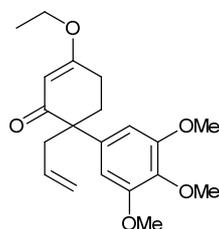
Colorless oil, $R_f = 0.58$ (EtOAc : Petroleum ether = 1:8) 1H -NMR (300MHz, $CDCl_3$), δ (ppm): 7.64-7.54 (4H, m), 7.47-7.30 (5H, m), 5.84-5.57 (1H, m), 5.43 (1H, s), 5.06-5.02 (2H, m), 3.90-3.70 (2H, m), 2.75 (1H, dd, $J = 6.9, 14.1$ Hz), 2.55-2.10 (5H, m), 1.29 (3H, t, $J = 7.0$ Hz). ^{13}C -NMR (75MHz, $CDCl_3$), δ (ppm): 200.49 (s), 176.51 (s), 140.65 (s), 139.64 (s), 139.50 (s), 134.86 (d), 128.82 (d), 127.33 (d), 127.21 (d), 127.11 (d), 127.04 (d), 117.99 (t), 102.92 (d), 64.31 (t), 51.66 (s), 44.68 (t), 29.97 (t), 26.65 (t), 14.17 (q).



20 6-allyl-3-ethoxy-6-(4-methoxy-3,5-dimethylphenyl)cyclohex-2-enone

Chemical Formula: $C_{20}H_{26}O_3$
Molecular Weight: 314.42

Colorless oil, $R_f = 0.60$ (EtOAc : Petroleum ether = 1:10) 1H -NMR (300MHz, $CDCl_3$), δ (ppm): 6.88 (2H, s), 5.65-5.56 (1H, m), 5.37 (1H, s), 5.03-4.97 (2H, m), 3.89-3.76 (2H, m), 3.69 (3H, s), 2.67 (1H, dd, $J = 6.7, 13.8$ Hz), 2.41-2.03 (5H, m), 2.24 (6H, s), 1.29 (3H, t, $J = 7.0$ Hz). ^{13}C -NMR (75MHz, $CDCl_3$), δ (ppm): 200.94 (s), 176.58 (s), 155.82 (s), 135.52 (s), 135.20 (d), 130.61 (s), 127.09 (d), 117.74 (t), 102.95 (d), 64.30 (t), 59.73 (q), 51.35 (s), 44.90 (t), 30.12 (t), 26.71 (t), 16.47 (q), 14.25 (q).

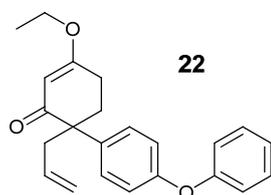


21 6-allyl-3-ethoxy-6-(3,4,5-trimethoxyphenyl)cyclohex-2-enone

Chemical Formula: $C_{20}H_{26}O_5$
Molecular Weight: 346.42

Colorless oil, $R_f = 0.55$ (EtOAc : Petroleum ether = 1:4) 1H -NMR (300MHz, $CDCl_3$), δ (ppm): 6.49 (2H, s), 5.71-5.52 (1H, m), 5.35 (1H, s), 5.00-4.96 (2H, m), 3.89-3.74 (2H, m), 3.80 (9H, s), 2.64 (1H, dd, $J = 6.9, 13.9$ Hz), 2.51-2.02 (5H, m), 1.27 (3H, t, $J = 7.0$ Hz). ^{13}C -NMR (75MHz, $CDCl_3$), δ (ppm): 200.39 (s), 176.56 (s), 153.10 (s),

137.20 (s), 135.87 (s), 134.86 (d), 117.90 (t), 104.45 (d), 102.74 (d), 64.33 (t), 60.84 (d), 56.33 (d), 51.76 (s), 44.79 (t), 30.03 (t), 26.66 (t), 14.15 (q).

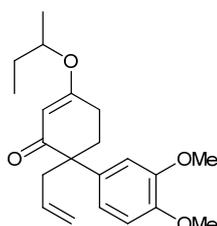


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6-allyl-3-ethoxy-6-(4-phenoxyphenyl)cyclohex-2-enone

Chemical Formula: C₂₃H₂₄O₃
Molecular Weight: 348.43

Colorless oil, $R_f = 0.55$ (EtOAc : Petroleum ether = 1:8) ¹H-NMR (300MHz, CDCl₃), δ (ppm): 7.32 (2H, dd, $J = 7.6, 8.3$ Hz), 7.26-7.22 (2H, m), 7.09 (1H, t, $J = 7.7$ Hz), 7.00 (2H, d, $J = 8.7$ Hz), 6.93 (2H, d, $J = 8.7$ Hz), 5.70-5.51 (1H, m), 5.39 (1H, s), 5.03-4.98 (2H, m), 3.88-3.80 (2H, m), 2.69 (1H, dd, $J = 6.8, 14.0$ Hz), 2.58-2.05 (5H, m), 1.30 (3H, t, $J = 7.0$ Hz). ¹³C-NMR (75MHz, CDCl₃), δ (ppm): 200.96 (s), 176.54 (s), 157.32 (s), 156.2 (s), 135.11 (s), 134.89 (d), 129.84 (d), 128.18 (d), 123.46 (d), 119.15 (d), 118.59 (d), 118.01 (t), 102.90 (d), 64.39 (t), 51.40 (s), 44.75 (t), 30.23 (t), 26.65 (t), 14.23 (q).



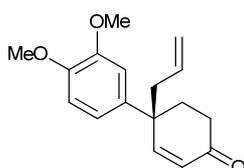
6-allyl-3-sec-butoxy-6-(3,4-dimethoxyphenyl)cyclohex-2-enone

Chemical Formula: C₂₁H₂₈O₄
Molecular Weight: 344.44

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Colorless oil, $R_f = 0.53$ (EtOAc : Petroleum ether = 1:5) ¹H-NMR (300MHz, CDCl₃), δ (ppm): 6.84-6.75 (3H, m), 5.62-5.53 (1H, m), 5.35 (1H, s), 4.99-4.95 (2H, m), 3.82 (6H, s), 3.55-3.45 (2H, m), 2.73-2.19 (7H, m), 0.92-0.83 (6H, m). ¹³C-NMR (75MHz, CDCl₃), δ (ppm): 200.72 (s), 176.72 (s), 148.91 (s), 147.90 (s), 134.99 (d), 132.57 (s), 118.79 (d), 117.84 (t), 110.75 (d), 110.41 (d), 102.68 (d), 74.79 (t), 55.98 (q), 55.85 (q), 51.24 (s), 44.93 (t), 29.90 (t), 27.77 (d), 26.52 (t), 19.14 (q).

Total Synthesis of (\pm)-Mesembrine



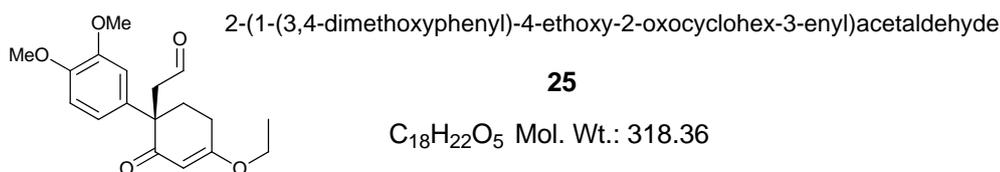
4-allyl-4-(3,4-dimethoxyphenyl)cyclohex-2-enone

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C₁₇H₂₀O₃ Mol. Wt.: 272.34

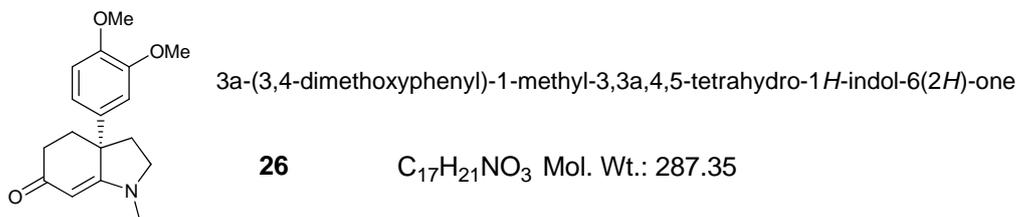
To a mixture of 3-ethoxycyclohex-2-enone derivative **18** (316 mg, 1 mmol) in THF (15 mL) was added a solution of diisobutylaluminum hydride (DIBAL-H, 1.0 M in toluene, 2.0 mL, 2.0 eq.). The resulting mixture was stirred at room temperature overnight. Aqueous NH₃-NH₄Cl solution (1 mL, PH = 8) was added and the mixture was stirred at room temperature for 30 minutes before addition of anhydrous MgSO₄ (3 g). After a further 30 minutes, the resulting mixture was filtered and washed with ethyl acetate (30 mL). After removal of the solvent, the residue was chromatographed on silica gel (Petroleum ether 60-90 °C : ethyl acetate = 4:1) to afford the product as an oil (196 mg, 72% yield).

Colorless oil, *R_f* = 0.50 (EtOAc : Petroleum ether = 1:4) ¹H-NMR (300MHz, CDCl₃), δ (ppm): 6.99 (1H, d, *J* = 10.3 Hz), 6.75 (3H, s), 6.09 (1H, d, *J* = 10.3 Hz), 5.53-5.42 (1H, m), 5.04 (1H, d, *J* = 10.7 Hz), 4.99 (1H, m), 3.80 (6H, s), 2.62 (1H, dd, *J* = 5.8, 14.1 Hz), 2.41 (1H, dd, *J* = 8.4, 14.1 Hz), 2.30-2.12 (4H, m). ¹³C-NMR (75MHz, CDCl₃), δ (ppm): 199.53 (s), 155.25 (d), 149.14 (s), 148.02 (s), 135.45 (s), 133.55 (d), 129.48 (d), 119.41 (d), 118.93 (t), 111.12 (d), 110.24 (d), 56.08 (q), 55.95 (q), 46.33 (t), 43.55 (s), 36.10 (t), 34.52 (t).



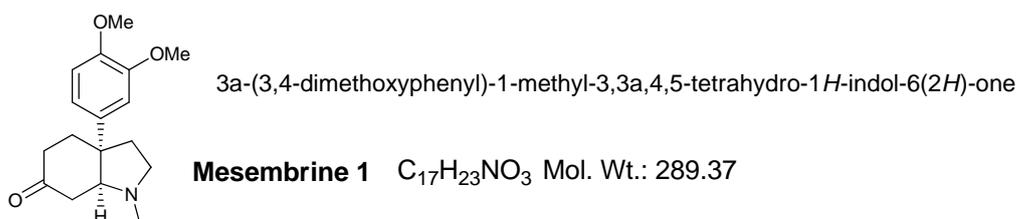
To a mixture of olefin **18** (894 mg, 2.84 mmol) in 1,4-dioxane-H₂O (32 mL, 3:1) was added osmium tetroxide (14.5 mg, 0.057 mmol, 0.02 eq.), 2,6-lutidine (0.66 mL, 5.68 mmol, 2.0 eq.) and sodium periodate (NaIO₄, 2.43 g, 11.36 mmol, 4.0 eq.). The resulting mixture was stirred at room temperature (*W. Yu, Y. Mei, Y. Kang, Z. Hua, Z. Jin, *Org. Lett.* **2004**, *6*, 3217-3219). The reaction progress was monitored by thin layer chromatography. Aqueous saturated sodium sulfite (10 mL) was added. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (5×20 mL). The organic phases were combined and washed with brine (10 mL) and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel (Petroleum ether 60-90 °C : ethyl acetate = 4:1-2.1) to afford the product as a yellow oil (811 mg, 90% yield).

Colorless oil, *R_f* = 0.45 (EtOAc : Petroleum ether = 1:2) ¹H-NMR (300MHz, CDCl₃), δ (ppm): 9.55 (1H, dd, *J* = 1.4, 2.8 Hz), 6.82 (1H, s), 6.80 (2H, d, *J* = 9.4 Hz), 5.45 (1H, s), 3.91-3.80 (2H, m), 3.85 (3H, s), 3.83 (3H, s), 2.82 (1H, dd, *J* = 1.4, 16.3 Hz), 2.64 (1H, dd, *J* = 2.8, 16.3 Hz), 2.40-2.18 (4H, m), 1.31 (3H, t, *J* = 7.0 Hz). ¹³C-NMR (75MHz, CDCl₃), δ (ppm): 201.49 (d), 200.16 (s), 177.30 (s), 149.39 (s), 148.52 (s), 131.68 (s), 119.11 (d), 111.45 (d), 110.39 (d), 102.29 (d), 64.66 (t), 56.17 (q), 56.00 (q), 52.96 (t), 50.82 (s), 32.51 (t), 26.55 (t), 14.31 (q).



To a solution of methanesulfonyl chloride (115 mg, 1 mmol) in THF (5 mL) was added water (1 mL) then aldehyde **25** (159 mg, 0.5 mmol) in THF (5 mL). The resulting mixture was stirred at 25 °C overnight. The reaction mixture was filtered through a short column of silica gel and washed with ethyl acetate (30 mL). After removal of the solvents, the residue was re-dissolved in THF (5 mL) and methylamine hydrochloride (41 mg, 0.6 mmol, 1.2 eq.) was added. The resulting mixture was stirred at room temperature for 2 hours before addition of sodium cyanoborohydride (63 mg, 1 mmol). The reaction mixture was then stirred at room temperature overnight. After removal of the solvent, the residue was chromatographed on silica gel (dichloromethane : methanol = 30:1) to afford the product (91 mg, 63%) as a white solid.

White solid, $R_f = 0.45$ (CH_2Cl_2 : $CH_3OH = 10:1$), mp: 77-78.5 °C (EtOAc). 1H -NMR (300MHz, $CDCl_3$), δ (ppm): 6.77-6.71 (3H, m), 5.20 (1H, s), 3.84 (6H, s), 3.31-3.26 (2H, m), 2.97 (3H, s), 2.59-2.35 (2H, m), 2.31-2.04 (4H, m). ^{13}C -NMR (75MHz, $CDCl_3$), δ (ppm): 196.68 (s), 171.33 (s), 149.04 (s), 148.19 (s), 133.59 (s), 119.42 (d), 110.98 (d), 110.05 (d), 93.43 (d), 56.08 (q), 55.98 (q), 53.02 (t), 52.68 (s), 39.05 (q), 35.98 (q), 33.09 (q), 32.86 (t).



To a solution of enone **26** (144 mg, 0.5 mmol) and t BuOH (74 mg, 1 mmol) in anhydrous THF (5 ml) was added a solution of liquid ammonia (50 mL) at -78 °C. A piece of metal lithium (ca. 7 mg, 1 mmol) was added and the dark-blue solution was stirred at -78 °C for 20 minutes. The excess of ammonia was then allowed to evaporate at room temperature overnight. The residue was diluted with water (15 mL) and extracted with ethyl acetate (3×10 mL). The organic phases were combined and dried over anhydrous sodium sulfate. After filtration and removal of the solvent, the residue was chromatographed on silica gel (dichloromethane : methanol = 20:1-10:1) to afford the product (117.2 mg, 81 %) as a colorless syrups.

Colorless syrups, $R_f = 0.58$ ($\text{CH}_2\text{Cl}_2 : \text{CH}_3\text{OH} = 10:1$) $^1\text{H-NMR}$ (300MHz, CDCl_3), δ (ppm): 6.92 (1H, dd, $J = 2.1, 8.3$ Hz), 6.88 (1H, d, $J = 2.1$ Hz), 6.83 (1H, d, $J = 8.3$ Hz), 3.89 (3H, s), 3.86 (3H, s), 3.18-3.06 (1H, m), 2.93 (1H, t, $J = 3.5$ Hz), 2.61-2.57 (2H, m), 2.54-2.19 (2H, m), 2.33 (3H, s), 2.21-2.02 (5H, m). $^{13}\text{C-NMR}$ (75MHz, CDCl_3), δ (ppm): 211.50 (s), 149.19 (s), 147.69 (s), 140.37 (s), 118.09 (d), 111.22 (d), 110.21 (d), 70.52 (d), 56.18 (q), 56.05 (q), 54.98 (t), 47.67 (s), 40.70 (t), 40.19 (q), 38.99 (t), 36.38 (t), 35.42 (t).