Concise Total Synthesis of (±)-Crinine

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SUPPORTING INFORMATION

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A. General Information.

NMR spectra were recorded with TMS as an internal standard in CDCl₃ by a Mercury-plus 300BB spectrometer (300 MHz for ¹H NMR and 75 MHz for ¹³C NMR spectra), a Brucker AM-400 spectrometer (400 MHz for ¹H NMR and 100 MHz for ¹³C NMR spectra) and a Varian Inova 600 spectrometer (600 MHz for ¹H NMR and 150 MHz for ¹³C NMR spectra). IR spectra were measured on KBr plate by using a Nicolet NEXUS 670 FTIR spectrometer. The EIMS spectra were recorded on a HP 5988A mass spectrometer, and the high-resolution mass spectra were recorded on Brucker Daltonics APEX II 49e spectrometer by means of the ESI technique. Silica gel (200–300 mesh) for column chromatography and silica GF₂₅₄ for TLC were produced by Qingdao Marine Chemical Company (P. R. China). Solvents for reaction were distilled prior to use: THF, Et₂O and toluene from Na and benzophenone, MeOH from Mg and I₂, as well as CH₂Cl₂, Et₃N, CH₃CN and DMF from CaH₂. All air- or moisture-sensitive reactions were conducted under an argon atmosphere.
B. Experimental Procedures and Analytical Data.

\[ \text{Br} \quad \text{O} \]

\textbf{5-Bromo-5-hexen-2-one (8)}

Sodium (5.75 g, 0.25 mol) was added portionwise to ethanol (100 mL), and the resulting solution reacted for 30 min at room temperature until sodium disappeared. To the resulting solution of NaOEt was added dropwise ethyl acetoacetate (35.50 mL, 0.28 mol) over 15 min. The reaction mixture was stirred for 30 min. Then 2,3-dibromopropene (25 mL, \(25 \times 10^{-2}\) mol) was added dropwise over 30 min, and it was further stirred under reflux for 1 h. After that, 10% aqueous NaOH solution (200 mL) was added and heated under reflux for 2 h. After cooling to 20 °C, the reaction mixture was acidified to pH < 3. Then the solution was heated to reflux for 2 h. The reaction mixture was cooled to room temperature and extracted with petroleum ether (30–60 °C) (3 × 100 mL). The combined organic layers were washed with saturated aqueous NaHCO\(_3\) solution (2 × 100 mL) and brine, dried with MgSO\(_4\) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (Petroleum ether (30–60 °C): Et\(_2\)O = 10: 1) to afford 8 (26.41 g, 60% yield) as a colorless liquid. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 5.54 (d, 1H, J = 1.2 \text{ Hz}), 5.32 (d, 1H, J = 1.8 \text{ Hz}), 2.63(m, 4H), 2.11 \text{ ppm (s, 3H)}\). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 206.4, 132.6, 117.3, 41.6, 35.2, 29.9 \text{ ppm}\).

\[ \text{Br} \quad \text{O} \quad \text{O} \]

\textbf{Vinyl bromide 9}

To a solution of 1,2-ethandiol (744.0 mg, 12.0 mmol) in dry benzene (75 mL) were added 8 (1.76 g, 10.00 mmol) and \(p\)-TsOH (96.0 mg, 0.5 mmol). The mixture was heated under reflux overnight with azeotropic removal of H\(_2\)O. The solution was washed with saturated aqueous NaHCO\(_3\) solution (2 × 50 mL). The organic phase was separated, and the aqueous layer was extracted with Et\(_2\)O (3 × 50 mL). The combined extracts were dried over anhydrous MgSO\(_4\). The solvent was evaporated in vacuum, and the residue was purified by flash column chromatography on silica gel (Petroleum ether: EtOAc = 4: 1) to provide 9 (2.07 g, 94% yield) as a colorless liquid. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 5.56 (d, 1H, J = 1.2 \text{ Hz}), 5.32 (d, 1H, J = 1.8 \text{ Hz}), 2.63(m, 4H), 2.11 \text{ ppm (s, 3H)}\). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 134.2, 116.2, 109.0, 64.6, 37.6, 36.0, 24.0 \text{ ppm}\). MS (70 eV, EI): \(m/z\) (%) 207 (5), 205 (4), 135 (4), 133 (4), 87 (100), 43 (78).
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The combined organic phases were dried over MgSO₄ and washed with saturated aqueous NH₄Cl solution (50 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with Et₂O (2 × 50 mL). The combined organic phases were dried over MgSO₄. After filtration and removal of solvent, the residue was purified by flash column chromatography on silica gel (Petroleum ether: EtOAc = 6:1) to give the aldehyde (2 × 50 mL). MS (70eV, EI) m/z (%) = 292 (11) [M]+, 230 (6), 215 (2), 190 (3), 173 (3), 149 (12), 87 (100), 43 (64). HRMS (ESI): m/z calcd for C₁₆H₂₀O₃Na: 315.1203 [M+Na]+; found: 315.1209.

Aldehydes 10

To a solution of allylic alcohol 6 (292.0 mg, 1.0 mmol) in acetone (10 mL) was added NBS (196.0 mg, 1.1 mmol) portionwise at room temperature. The reaction mixture was stirred for 15 min until the starting material disappeared completely as monitored by TLC. The solution was concentrated in vacuum and the residue was purified by flash column chromatography on silica gel (Petroleum ether: EtOAc = 6:1) to give the aldehyde 10 as pale yellow oil (327.0 mg, 88% yield). ¹H NMR (400 MHz, CDCl₃): δ = 9.40 (s, 1H), 6.75 (m, 3H), 5.98 (s, 1H), 3.95 (m, 4H), 3.86 (d, 1H, J = 11 Hz), 3.70 (d, 1H, J = 11 Hz), 2.13–2.25 (m, 2H), 1.66–1.46 (m, 2H), 1.33 ppm (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 199.1, 148.4, 147.4, 129.8, 121.1, 109.4, 108.6, 107.9, 101.4, 64.7, 56.9, 35.9, 32.7, 25.7, 23.8 ppm. IR (KBr): ν = 2980, 2886, 1722, 1505, 1488, 1439, 1242, 1039 cm⁻¹. MS (70eV, EI): m/z (%) = 372 (1) [M⁺ ([81]Br)]⁺, 370 (1) [M⁺ ([79]Br)]⁺, 357 (1), 355 (1), 281 (3), 279 (2), 242 (3), 240 (3), 201 (17), 87 (100), 43 (74). HRMS (ESI): m/z calcd for C₁₆H₁₅BrO₃Na: 393.0308 [M+Na]⁺; found: 393.0309.

Aldehyde 10

To a solution of vinyl bromide 9 (5.36 g, 24.35 mmol) in THF (50 mL) was added dropwise n-butyllithium (1.5 M solution in hexane, 17.86 mL) at –78 °C over a period of 30 min. The reaction mixture was stirred at –78 °C for 30 min, and then a solution of piperonal (4.38 g, 29.22 mmol) in THF (10 mL) was added dropwise over a period of 10 min. After stirred at –78 °C for additional one hour, the reaction mixture was warmed to room temperature and washed with saturated aqueous NH₄Cl solution (50 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with Et₂O (2 × 50 mL). The organic layer was stirred at –78 °C for 30 min, and then a solution of piperonal (4.38 g, 29.22 mmol) in THF (10 mL) was added dropwise over a period of 10 min. After stirred at –78 °C for additional one hour, the reaction mixture was warmed to room temperature and washed with saturated aqueous NH₄Cl solution (50 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with Et₂O (2 × 50 mL). The combined organic phases were dried over MgSO₄. After filtration and removal of solvent, the residue was purified by flash column chromatography on silica gel (Petroleum ether: EtOAc = 6:1) to give the aldehyde (2 × 50 mL). MS (70eV, EI) m/z (%) = 292 (11) [M]+, 230 (6), 215 (2), 190 (3), 173 (3), 149 (12), 87 (100), 43 (64). HRMS (ESI): m/z calcd for C₁₆H₂₀O₃Na: 315.1203 [M+Na]+; found: 315.1209.

Aldehyde 10

To a solution of piperonal (5.69 g, 80% yield). ¹H NMR (300 MHz, CDCl₃): δ = 9.40 (s, 1H), 6.75 (m, 3H), 5.98 (s, 1H), 3.95 (m, 4H), 3.86 (d, 1H, J = 11 Hz), 3.70 (d, 1H, J = 11 Hz), 2.13–2.25 (m, 2H), 1.66–1.46 (m, 2H), 1.33 ppm (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 199.1, 148.4, 147.4, 129.8, 121.1, 109.4, 108.6, 107.9, 101.4, 64.7, 56.9, 35.9, 32.7, 25.7, 23.8 ppm. IR (KBr): ν = 2980, 2886, 1722, 1505, 1488, 1439, 1242, 1039 cm⁻¹. MS (70eV, EI): m/z (%) = 372 (1) [M⁺ ([81]Br)]⁺, 370 (1) [M⁺ ([79]Br)]⁺, 357 (1), 355 (1), 281 (3), 279 (2), 242 (3), 240 (3), 201 (17), 87 (100), 43 (74). HRMS (ESI): m/z calcd for C₁₆H₁₅BrO₃Na: 393.0308 [M+Na]+; found: 393.0309.
To a solution of 10 (1.12 g, 3.00 mmol) in THF (50 mL) was added 10% of aqueous HCl solution (10 mL). After stirred at room temperature overnight, the reaction mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water, saturated aqueous NaHCO₃ solution and brine, dried (MgSO₄) and evaporated under reduced pressure. Aldehyde 5 (964.0 mg; 98% yield) was isolated by flash column chromatography on silica gel (Petroleum ether: EtOAc = 6:1) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃): δ = 9.38 (s, 1H), 6.79 (d, 1H, J = 8 Hz), 6.65 (m, 2H), 5.95 (s, 2H), 3.82 (d, 1H, J = 11 Hz), 3.68 (d, 1H, J = 11 Hz), 2.26–2.37 (m, 4H), 2.09 ppm (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 206.9, 198.8, 148.5, 147.4, 129.5, 120.8, 108.6, 107.5, 101.4, 56.5, 37.6, 35.6, 29.9, 25.5 ppm. IR (KBr): ν = 2963, 2900, 1715, 1505, 1489, 1358, 1242, 1038, 932, 814 cm⁻¹. MS (70eV, EI): m/z (%) 310 (10) [M⁺], 308 (10) [M⁺], 229 (1), 215 (100), 157 (28), 115 (66), 84 (63). HRMS (ESI): m/z calcd for C₁₄H₁₅BrO₃Na: 349.0064 [M+Na⁺]; found: 349.0049.

A solution of 5 (1.15 g, 3.50 mmol), PPTS (966.0 mg, 38.5×10⁻¹ mmol) and proline (443.0 mg, 38.5×10⁻¹ mmol) in CH₃CN (30 mL) was stirred at 40 °C for 12 h under argon. The mixture was concentrated in vacuo, the residue was diluted with EtOAc (2 × 50 mL), washed with saturated aqueous NaHCO₃ solution and brine. The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure, and the crude residue was purified by flash column chromatography on silica gel (Petroleum ether: EtOAc = 6: 1) to afford the enone 11 (977.0 mg, 90% yield). ¹H NMR (400 MHz, CDCl₃): δ = 7.08 (dd, 1H, J = 2 and 10 Hz), 6.76 (m, 3H), 6.22 (d, 1H, J = 10 Hz), 5.98 (s, 2H), 3.64 (dd, 2H, J = 10 and 24 Hz), 2.47–2.53 (m, 1H), 2.36–2.41 (m, 1H), 2.20–2.28 ppm (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 198.3, 152.9, 148.2, 147.0, 134.3, 130.5, 120.4, 108.2, 107.0, 101.3, 45.0, 42.3, 34.1, 33.7 ppm. IR (KBr): ν = 2955, 2895, 1680, 1504, 1487, 1238, 1038, 930, 813 cm⁻¹. MS (70eV, EI): m/z (%) 310 (10) [M⁺], 308 (10) [M⁺], 229 (1), 215 (100), 157 (28), 115 (66), 84 (63). HRMS (ESI): m/z calcd for C₁₄H₁₃BrO₃Na: 330.9940 [M+Na⁺]; found: 330.9946.
**Bromide 12**

A mixture of enone 11 (930.0 mg, 3.0 mmol), ethylene glycol (0.2 mL, 3.6 mmol) and PPTS (38.0 mg, 1.5x10⁻¹ mmol) in benzene (15 mL) was refluxed for 5 h. The resulting mixture was concentrated in vacuo. The residue was diluted with EtOAc, washed with saturated aqueous NaHCO₃ solution and brine. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Petroleum ether: EtOAc = 4:1) to afford the bromide 12 (977.0 mg, 92% yield). ¹H NMR (400 MHz, CDCl₃): δ = 6.80 (d, 1H, J = 1 Hz), 6.75 (d, 1H, J = 10 Hz), 5.95 (s, 2H), 5.85 (d, 2H, J = 10 Hz), 3.90–4.05 (m, 4H), 3.60 (dd, 2H, J = 16 and 26 Hz), 2.19 (m, 1H), 1.91(m, 1H), 1.64–1.74 ppm (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 147.8, 146.3, 136.4, 135.6 129.5, 120.3, 107.9, 107.2, 104.9, 101.0, 64.7, 64.4, 33.0, 30.1 ppm. IR (KBr): ν = 2955, 2885, 1681, 1503, 1487, 1436, 1237, 1136, 1040,936, 906, 813, 732 cm⁻¹. MS (70eV, EI): m/z (%) 354 (11) [M⁺Br]⁺, 352 (11) [M⁺(79Br)]⁺, 310 (2), 308 (2), 273 (4), 259 (95), 187 (100), 115 (36). HRMS (ESI): m/z calcd for C₁₆H₁₇BrO₄Na: 375.0202 [M+Na]⁺; found: 375.0205.

**Cyanide 13**

A solution of 12 (317.0 mg, 0.9 mmol), 18-crown-6 (30.0 mg, 0.9x10⁻¹ mmol), sodium cyanide (88.0 mg, 1.8 mmol) and 4Å molecular sieves (10 mg) in DMSO (15 mL) was stirred at 80 °C for 48 h under argon. After the reaction was completed as monitored by TLC, the reaction mixture was poured into water (75 mL) and extracted with Et₂O (3 x 30 mL). The combined organic phases were collected, dried over Na₂SO₄, filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (Petroleum ether: EtOAc = 5:1) to yield the cyanide 13 (206.0 mg, 76% yield). ¹H NMR (300 MHz, CDCl₃): δ = 6.77–6.83 (m, 3H), 6.05 (d, 1H, J = 10 Hz), 5.93 (t, 2H, J = 5 and 8 Hz), 5.88 (d, 2H, J = 10 Hz), 3.88–4.03 (m, 4H), 2.70 (dd, 2H, J = 5 and 20 Hz), 2.05 (m, 2H), 1.67–1.73 ppm (m, 2H). ¹³C NMR (75 MHz, CDCl₃): δ = 148.0, 146.6, 135.9, 134.5, 130.1, 119.9, 117.3, 108.1, 106.8, 104.5, 101.2, 64.7, 64.4, 41.7, 34.6, 30.6, 29.9 ppm. IR (KBr): ν = 2956, 2889, 2250, 1503, 1488, 1438, 1240, 1138, 1121, 1039, 933, 814, 732 cm⁻¹. MS (70eV, EI): m/z (%) 299 (8) [M⁺]⁺, 272 (12), 259 (32), 215 (10), 187 (37), 135 (50), 71 (53), 55 (100). HRMS (ESI): m/z calcd for C₁₃H₁₈NO₄: 300.1230 [M+H]⁺; found: 300.1234.
To a suspension of LiAlH₄ (227.0 mg, 6.0 mmol) in Et₂O (20 mL) was added a solution of 13 (598.0 mg, 2.0 mmol) in Et₂O (10 mL) at 0 °C. The solution was stirred at room temperature for 1 h. Then water (0.24 mL), aqueous NaOH solution (4 N, 0.24 mL), and water (0.72 mL) were added sequentially. The resulting mixture was filtered, and the solid residue was washed well with CHCl₃. The combined organic phases were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CHCl₃: MeOH = 10: 1) to afford the amine 4 (578.0 mg, 96% yield). ¹H NMR (400 MHz, CDCl₃): δ = 6.81 (s, 1H), 6.72 (d, 2H, J = 2 Hz), 6.03 (d, 1H, J = 10 Hz), 6.92 (s, 2H), 6.75 (d, 1H, J = 10 Hz), 3.89–4.02 (m, 4H), 2.67 (s, 1H), 2.52(s, 1H), 1.88–2.02 (m, 4H), 1.59–1.70 ppm (m, 4H). ¹³C NMR (100 MHz, CDCl₃): δ = 147.8, 145.8, 139.4, 137.5, 128.2, 120.0, 137.8, 107.2, 105.4, 100.9, 64.6, 64.4, 45.4, 42.3, 37.8, 35.3, 30.1 ppm. IR (KBr): ν = 2929, 2884, 1648, 1486, 1434, 1237, 1119, 1038, 935, 813, 731 cm⁻¹. MS (70eV, EI): m/z (%) 303 (0.2) [M⁺], 189 (0.3), 84 (100), 47 (25). HRMS (ESI): m/z calcd for C₁₇H₂₂NO₄: 304.1543 [M+H]⁺; found: 304.1546.

To a solution of the primary amine 4 (303.0 mg, 1.0 mmol) in THF (15 mL) was added 10% aqueous HCl (2.2 mL). The reaction mixture was refluxed for 2 h. After cooled to room temperature, the reaction was quenched by addition of solid NaHCO₃ until pH = 8–9. The resulting layers were separated and the aqueous layer was extracted with CHCl₃ (3 × 15 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (10 mL) followed by addition of triethylamine (0.7 mL). The resulting solution was stirred for 10 min, then (Boc)₂O (436.0 mg, 2.0 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 2 h, and then H₂O (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Petroleum ether: EtOAc = 2: 1) to give 14 (646.0 mg, 90% yield). ¹H NMR (400 MHz, CDCl₃): δ = 6.76 (m, 3H), 5.96 (s, 2H), 4.42 (br, 1H), 3.43 (br, 2H), 2.90 (m, 2H), 2.66 (br, 1H), 2.15–2.33 (m, 6H), 1.46 ppm (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ = 210.1, 154.2, 148.2, 146.3, 139.1, 118.7, 108.1, 106.6, 101.1, 80.0, 77.3, 60.4, 48.4, 44.6, 43.9, 37.2, 36.4, 33.4, 28.4 ppm. IR (KBr): ν = 2974, 2932, 2893, 1718, 1690,
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1489, 1396, 1234, 1116, 1038, 933, 810, 732 cm\(^{-1}\). MS (70eV, EI): \(m/z\) (%) 359(11) [\(M^+\)], 303 (5), 258 (6), 202 (6), 188 (11), 115 (8), 84 (28), 57 (100), 41 (30). HRMS (ESI): \(m/z\) calcd for C\(_{20}\)H\(_{26}\)NO\(_5\): 360.1805 \([M+H]^+\); found: 360.1808.

Enone 3

To a solution of diisopropylamine (0.8\(\times\)10\(^{-1}\) mL, 5.3\(\times\)10\(^{-1}\) mmol) in THF (5 mL) was added dropwise \(n\)-butyllithium (1.5 M solution in hexane, 0.37 mL) at 0 °C under argon atmosphere. The solution was stirred at 0 °C for 45 min before cooled to –78 °C and then it was treated with a solution of 14 (180.0 mg, 0.5 mmol) in THF (2 mL). After 30 min, TMSCl (0.8\(\times\)10\(^{-1}\) mL, 6.3\(\times\)10\(^{-1}\) mmol) was added. The reaction mixture was stirred at –78 °C for 30 min, slowly warmed to –20 °C, and then quenched with saturated NaHCO\(_3\) solution (2 mL) after 1 h. After diluting with ether (3 × 10 mL), the organic layer was separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed successively with saturated NaHCO\(_3\) solution and brine, dried over Na\(_2\)SO\(_4\), and concentrated in vacuum to give the crude silyl enol ether intermediate, which was used directly for the next step without further purification.

A solution of the crude silyl enol ether obtained above, Pd(OAc)\(_2\) (180.0 mg, 7.5\(\times\)10\(^{-1}\) mmol) in CH\(_3\)CN (20 mL) was stirred at room temperature overnight. The mixture was then concentrated and the brown residue was purified by flash column chromatography on silica gel (Petroleum ether: EtOAc = 4:1) to afford the enone 3 (137.0 mg, 85% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 6.79\)–6.89 (m, 3H), 6.58 (d, 1H, \(J = 10\) Hz), 6.22 (d, 1H, \(J = 10\) Hz), 5.98 (s, 2H), 4.18 (s, 0.5H), 4.06 (s, 0.5H), 3.83 (s, 0.5H), 3.72 (s, 0.5H), 3.23 (br, 1.5H), 3.04 (d, 0.5H, \(J = 9\) Hz), 2.54 (m, 2H), 2.04 (br, 1H), 1.45 ppm (s, 9H). \(^13\)C NMR (100MHz, CDCl\(_3\)): \(\delta = 197.4, 154.4, 150.7, 148.4, 147.1, 133.4, 130.0, 120.0, 108.4, 106.9, 101.3, 80.9, 80.0, 63.1, 51.7, 50.6, 45.9, 38.0, 37.2, 36.8, 36.3, 28.4 ppm. IR (KBr): \(\nu = 2776, 2892, 1690, 1504, 1487, 1393, 1364, 1243, 1170, 1121, 1039, 932, 811, 732\) cm\(^{-1}\). MS (70eV, EI): \(m/z\) (%) 357 (5) [\(M^+\)], 256 (20), 201 (17), 115 (10), 86 (31), 84 (47), 57 (100). HRMS (ESI): \(m/z\) calcd for C\(_{20}\)H\(_{27}\)N\(_2\)O\(_5\): 375.1914 \([M+NH_4]^+\); found: 375.1909.

Allylic alcohols 15b and 15a

A solution of L-Selectride (1.0 M solution in THF, 0.18 mL, 0.18 mmol) was added dropwise to a well-stirred solution of enone 3 (50.0 mg, 1.4\(\times\)10\(^{-1}\) mmol) in THF (5 mL) by
syringe at −78 ºC under argon atmosphere and the resulting solution was stirred for 15 min at this temperature. The reaction mixture was quenched by the addition of CH$_3$OH (0.6 mL) over 1 min. The resulting slurry was allowed to warm to room temperature slowly followed by addition of H$_2$O (5 mL). The aqueous layer was extracted with CHCl$_3$ (3 × 20 mL), and the combined organic layers were dried over Na$_2$SO$_4$, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (Petroleum ether: EtOAc = 10: 1 → 5: 1) afforded the separable allylic alcohols 15a and 15b (38.0 mg, 95% yield, 15a : 15b = 1 : 3).

For 15b: $^1$H NMR (400 MHz, CDCl$_3$): δ = 6.86–6.93 (m, 2H), 6.77 (d, 1H, $J$ = 8 Hz), 6.02 (d, 1H, $J$ = 10 Hz), 5.95 (s, 2 H), 5.82 (br, 1H), 5.57 (d, 1H, $J$ = 10 Hz), 4.30 (br, 1H), 3.96 (br, 0.5H), 3.85 (br, 0.5H), 3.76 (d, 0.5H, $J$ = 8 Hz), 3.63 (br, 0.5H), 3.19 (br, 1H), 2.73 (br, 0.5H), 2.32 (br, 1H), 1.81 (m, 1H), 1.67 (s, 1 H), 1.57 (m, 1H), 1.46 ppm (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ = 154.5, 147.9, 146.4, 137.0, 132.7, 120.3, 108.0, 107.5, 101.1, 79.8, 79.4, 63.6, 62.2, 50.9, 50.0, 45.6, 36.2, 31.9, 30.9, 28.5 ppm. IR (KBr): $\nu$ = 3404, 2975, 2929, 2889, 1675, 1486, 1403, 1242, 1170, 1129, 1041, 933, 811, 732 cm$^{-1}$. MS (70eV, EI): $m/z$ (%) = 359 (4) [M$^+$], 259 (5), 233 (35), 216 (11), 86 (38), 84 (63), 57(100), 41 (32). HRMS (ESI): $m/z$ calcld for C$_{20}$H$_{25}$NO$_5$Na: 382.1625 [M+Na]$^+$; found: 382.1627.

For 15a: $^1$H NMR (400 MHz, CDCl$_3$): δ = 6.74–6.08 (m, 3H), 6.06 (d, 1H, $J$ = 10 Hz), 5.95 (s, 2 H), 6.70 (dd, 1H, $J$ = 1 and 10 Hz), 4.24 (s, 1H), 3.94 (br, 1H), 3.64 (br, 1H), 3.33–3.64 (m, 1H), 2.32–2.39 (m, 1H), 2.00 (m, 2H), 1.85 (br, 1H), 1.58 (br, 2H), 1.46 ppm (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ = 154.8, 148.0, 147.8, 146.4, 145.7, 137.1, 132.7, 130.8, 119.7, 118.7, 108.0, 107.9, 107.2, 106.8, 101.1, 101.1, 100.9, 100.9, 79.8, 79.3, 66.1, 64.2, 61.6, 58.3, 50.2, 45.4, 44.0, 36.4, 35.1, 31.8, 30.6, 30.4, 29.6, 29.4, 28.5 ppm. IR (KBr): $\nu$ = 3412, 2971, 2932, 2891, 1688, 1486, 1408, 1367, 1238, 1172, 1126, 1040, 934, 914, 809, 733 cm$^{-1}$. MS (70eV, EI): $m/z$ (%) = 359 (8) [M$^+$], 305 (3), 259 (11), 233 (22), 216 (16), 149 (10), 115 (8), 57 (100), 41 (50). HRMS (ESI): $m/z$ calcld for C$_{20}$H$_{26}$NO$_5$: 360.1805 [M+H]$^+$; found: 360.1812.

(±)-Crinine 1

To a well-stirred solution of the allylic alcohol 15b (30.0 mg, 0.8×$10^{-1}$ mmol) in dry CICH$_2$CH$_2$Cl (4 mL) was added trifluoroacetic acid (1.9×$10^{-1}$ mL, 25.2×$10^{-1}$ mmol) by syringe at 0 ºC. After the mixture was stirred for 5 h at room temperature, saturated aqueous NaHCO$_3$ solution (2.0 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CHCl$_3$ (3 × 10 mL). The combined organic phases were dried over Na$_2$SO$_4$ and concentrated under reduced pressure, giving the crude amine. A solution of formalin (0.1 mL) in MeOH (0.2 mL) was added to the crude amine obtained above. After the
solution was stirred for 15 min, aqueous hydrochloric acid (6 N, 4.5 mL) was added at 0 ºC. The mixture was warmed to room temperature for 5 h, and then basified by the dropwise addition of NH₃·H₂O. The resulting mixture was extracted with CHCl₃ (5 × 10 mL), and the organic layer was dried over Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CHCl₃: MeOH = 10: 1) to afford crinine 1 (19.6 mg, 86% yield over 2 steps). ¹H NMR (600 MHz, CDCl₃): δ = 6.89 (s, 1H), 6.58 (s, 1H), 6.47 (d, 1H, J = 10 Hz), 6.08 (s, 1H), 5.98 (d, 2H, J = 6 Hz), 4.89 (d, 1H, J = 16 Hz), 4.47 (s, 1H), 4.14 (d, 1H, J = 16 Hz), 3.95 (s, 1H), 3.20 (s, 1H), 2.37 (s, 1H), 2.18 (s, 1H), 2.04 (s, 1H), 1.88 ppm (t, 1H, J = 12 Hz). ¹³C NMR (100 MHz, CDCl₃): δ = 146.3, 145.9, 137.96, 131.6, 127.8, 125.5, 106.9, 102.9, 100.8, 63.7, 63.0, 62.0, 53.4, 44.3, 43.8, 32.5 ppm. IR (KBr): ν = 3339, 2923, 2854, 1726, 1482, 1235, 1095, 1038, 936, 850, 732 cm⁻¹. MS (70eV, EI): m/z (%) = 271 (4) [M⁺], 223 (6), 205 (2), 199 (3), 187 (2), 167 (7), 149 (100), 84 (33), 71 (28), 57 (69), 43 (62). HRMS (ESI): m/z calcd for C₁₆H₁₈NO₃: 272.1281 [M+H]⁺; found: 272.1279.

(±)-epi-Crinine

The same procedure as above was subjected to the synthesis of (±)-epi-crinine, and 87% yield over two steps was obtained. ¹H NMR (600 MHz, CDCl₃): δ = 6.81 (s, 1H), 6.50 (s, 1H), 6.41(d, 1H, J = 10 Hz), 5.90 (d, 2H, J = 8 Hz), 5.79 (d, 1H, J = 10 Hz), 4.45 (d, 2H, J = 15 Hz), 3.83 (d, 1H, J = 16 Hz), 3.51 (s, 1H), 3.29 (d, 1H, J = 12 Hz), 2.97 (s, 1H), 2.23 (br, 2H), 2.13 (s, 1H), 1.61–1.65 ppm (m, 1H). ¹³C NMR (150 MHz, CDCl₃): δ = 146.4, 145.9, 138.3, 131.5, 128.7, 125.4, 107.0, 102.8, 100.9, 67.7, 66.8, 62.0, 53.2, 44.8, 44.5, 34.7 ppm. IR (KBr): ν = 3372, 2922, 2853, 1739, 1649, 1622, 1483, 1460, 1384, 1234, 1072, 1037, 934, 757, 669 cm⁻¹. MS (70eV, EI): m/z (%) = 271 (21) [M⁺], 199 (10), 187 (11), 157 (4), 128 (12), 115 (18), 69 (47), 57 (73), 55 (73), 43 (100), 41 (74). HRMS (ESI): m/z calcd for C₁₆H₁₈NO₃: 272.1281 [M+H]⁺; found: 272.1283.
C. Copies of NMR Spectra
Concise Total Synthesis of (±)-Crinine
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