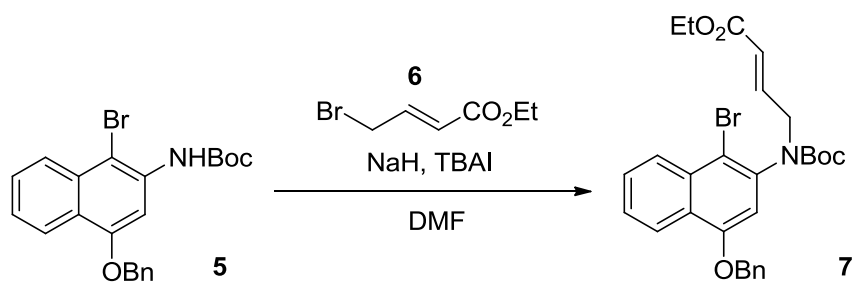


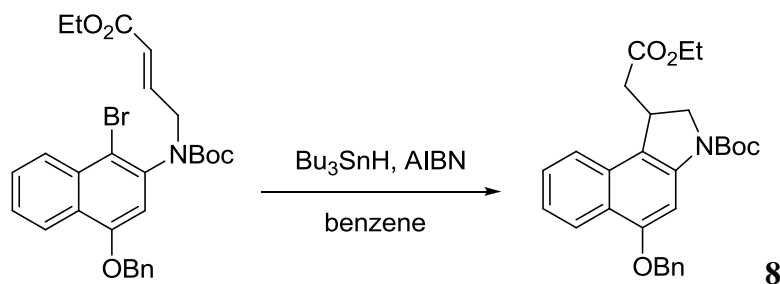
Synthesis and Characterization of a Cyclobutane Duocarmycin Derivative Incorporating the CbBI (1,2,10,11-tetrahydro-9*H*-cyclobuta[*c*]benzo[*e*]indol-4-one) Alkylation Subunit

James P. Lajiness and Dale L. Boger*

Contribution from the Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

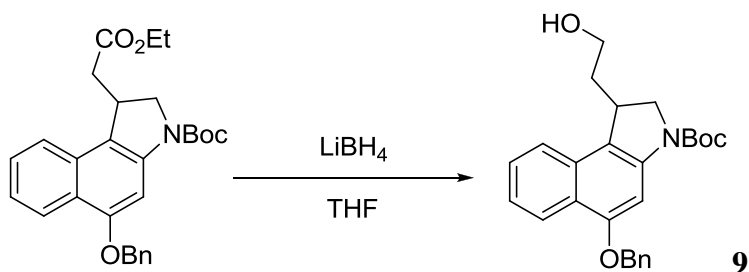


A solution of **5** (370 mg, 0.864 mmol) and tetrabutylammonium iodide (16 mg, 0.043 mmol) in DMF (3 mL) at 0 °C was treated with NaH (60% dispersion in mineral oil, 86 mg, 2.16 mmol). The reaction mixture was stirred for 30 min at 0 °C before ethyl 4-bromocrotonate (**6**, 0.36 mL, 2.59 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 2 h. Saturated aqueous NH₄Cl was added, and the mixture was diluted with ethyl acetate, washed with H₂O and saturated aqueous NaCl, and dried (MgSO₄). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (20% EtOAc/hexane) to provide **7** as a clear oil (387 mg, 83%): ¹H NMR (acetone-*d*₆, 400 MHz) δ 8.34 (d, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.64–7.58 (m, 3H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.13 (s, 1H), 5.93 (d, *J* = 19 Hz, 1H), 5.38 (s, 2H), 4.58 (dd, *J* = 16 Hz, 1.6 Hz, 1H), 4.25 (dd, *J* = 16 Hz, 2.0 Hz, 1H), 4.13 (q, *J* = 6.8 Hz, 2H), 1.30 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (acetone-*d*₆, 150 MHz) δ 167.1, 156.2, 155.3, 145.3, 141.0, 138.6, 134.5, 130.4, 130.3, 129.9, 129.4, 129.0, 128.3, 127.7, 124.8, 124.2, 115.7, 109.8, 81.8, 72.2, 61.7, 52.0, 29.3, 15.5; IR (film) ν_{max} 2976, 2926, 1701, 1659, 1619, 1589 cm⁻¹; ESI-TOF HRMS *m/z* 562.1196 (M+Na⁺, C₂₈H₃₀BrNO₅ requires 562.1199).

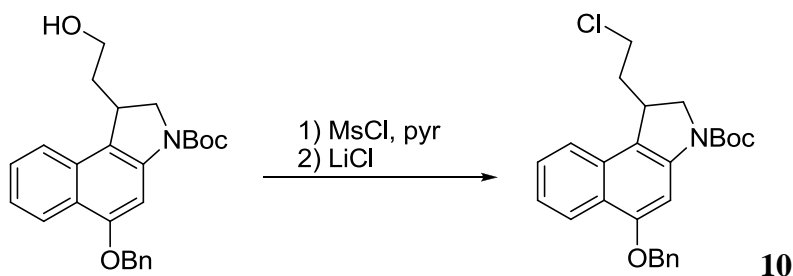


A mixture of **7** (387 mg, 0.716 mmol), tributyltin hydride (0.212 mL, 0.788 mmol), and AIBN (35.2 mg, 0.215 mmol) in benzene (10 mL) was degassed by freeze-pump-thaw three times. The solution was warmed at reflux for 14 h before the reaction mixture was cooled to room temperature and the solvent removed. The residue was purified by flash chromatography (100% CH₂Cl₂) with 10% KF doped silica to obtain **8** as a clear oil that crystallized upon standing (298 mg, 90%): ¹H NMR (acetone-*d*₆, 400 MHz) δ 8.24 (d, *J* = 8.0 Hz, 1H), 7.88 (br s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 5.30 (s, 2H), 4.18 (m, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.06 (m, 2H),

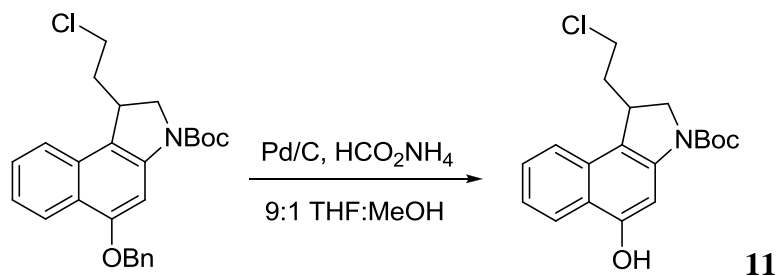
2.90 (dd, $J = 8.0, 1.6$ Hz, 1H), 2.51 (dd, $J = 8.0, 4.8$ Hz, 1H), 1.59 (s, 9H), 1.21 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (acetone- d_6 , 150 MHz) δ 173.3, 157.0, 154.0, 142.9, 139.1, 132.1, 130.3, 129.7, 129.5, 129.2, 124.9, 124.7, 124.1, 119.0, 98.5, 82.0, 71.8, 61.9, 56.5, 40.8, 36.8, 29.6, 24.0, 15.5; IR (film) ν_{max} 2979, 2905, 1726, 1692, 1624, 1581 cm^{-1} ; ESI-TOF HRMS m/z 462.2266 ($\text{M}+\text{H}^+$, $\text{C}_{28}\text{H}_{31}\text{NO}_5$ requires 462.2275).



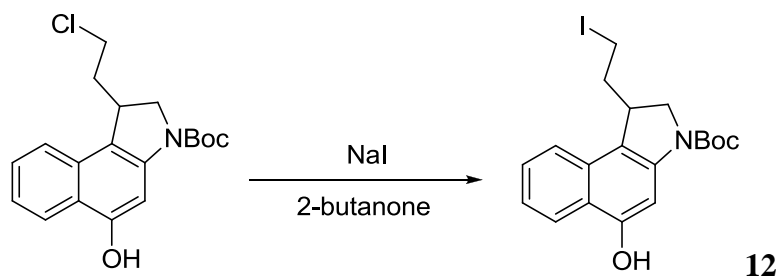
A solution of **8** (298 mg, 0.646 mmol) in THF (3 mL) at 0 °C was treated with lithium borohydride (28.1 mg, 1.29 mmol). The mixture was warmed at 40 °C and stirred for 6 h, after which it was cooled to room temperature, quenched with the addition of saturated aqueous NH_4Cl , diluted with ethyl acetate, washed with H_2O and saturated aqueous NaCl , and dried (MgSO_4). The solvent was removed under reduced pressure to yield **9** as a white foam (271 mg, 100%): ^1H NMR (acetone- d_6 , 400 MHz) δ 8.24 (d, $J = 8.4$ Hz, 1H), 7.91 (br s, 1H), 7.80 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 7.2$ Hz, 2H), 7.49 (t, $J = 8.0$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.38 (d, $J = 7.2$ Hz, 1H), 7.33 (t, $J = 7.2$ Hz, 1H), 5.30 (s, 2H), 4.09 (d, $J = 5.2$ Hz, 1H), 3.85 (m, 1H), 3.75–3.71 (m, 3H), 2.09 (m, 1H), 1.71 (m, 1H), 1.59 (s, 9H); ^{13}C NMR (acetone- d_6 , 150 MHz) δ 178.5, 156.6, 154.2, 142.4, 139.2, 132.2, 130.3, 129.7, 129.5, 128.8, 124.8, 124.6, 124.2, 121.3, 98.6, 81.8, 71.8, 61.4, 56.3, 39.9, 37.0, 29.6; IR (film) ν_{max} 3418, 2929, 1691, 1624, 1581 cm^{-1} ; ESI-TOF HRMS m/z 420.2155 ($\text{M}+\text{H}^+$, $\text{C}_{26}\text{H}_{29}\text{NO}_4$ requires 420.2169).



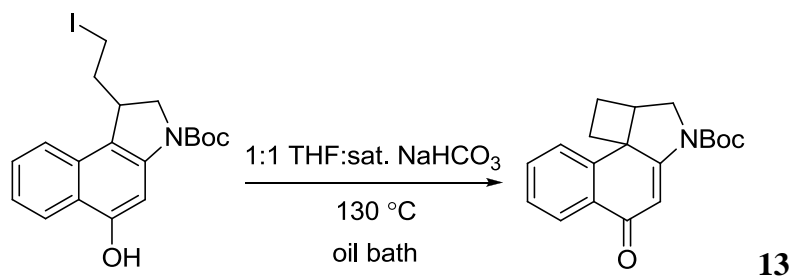
A solution of **9** (890 mg, 2.12 mmol) in pyridine (15 mL) at 0 °C was treated with methanesulfonyl chloride (0.821 mL, 10.6 mmol) dropwise. The solution was allowed to warm to room temperature. After 1 h, LiCl (450 mg, 10.6 mmol) was added. The mixture was stirred for 20 h, and then diluted with ethyl acetate, washed with H_2O and saturated aqueous NaCl , and dried (MgSO_4). The solvent was removed under reduced pressure and the residue purified by flash chromatography (30% EtOAc/hexane) to yield **10** as a white solid (607 mg, 65%): ^1H NMR (acetone- d_6 , 600 MHz) δ 8.25 (d, $J = 8.4$ Hz, 1H), 7.92 (br s, 1H), 7.78 (d, $J = 8.4$ Hz, 1H), 7.62 (d, $J = 6.6$ Hz, 2H), 7.52 (t, $J = 7.8$ Hz, 1H), 7.45 (t, $J = 7.2$ Hz, 2H), 7.38 (d, $J = 7.2$ Hz, 1H), 7.35 (t, $J = 7.8$ Hz, 1H), 5.31 (s, 2H), 4.09 (t, $J = 11$ Hz, 2H), 3.89 (m, 1H), 3.81–3.73 (m, 2H), 2.28 (m, 1H), 2.04 (m, 1H), 1.59 (s, 9H); ^{13}C NMR (acetone- d_6 , 150 MHz) δ 178.5, 157.0, 154.1, 142.7, 139.1, 132.1, 130.3, 129.7, 129.5, 129.1, 124.9, 124.8, 124.2, 119.8, 98.5, 82.0, 71.8, 55.8, 44.7, 39.6, 37.7, 29.6; IR (film) ν_{max} 2974, 1695, 1624, 1579 cm^{-1} ; ESI-TOF HRMS m/z 438.1813 ($\text{M}+\text{H}^+$, $\text{C}_{26}\text{H}_{28}\text{ClNO}_3$ requires 438.1830).



A solution of **10** (607 mg, 1.39 mmol) and ammonium formate (876 mg, 13.9 mmol) in 9:1 THF:MeOH (30 mL) was treated with 10% Pd/C (600 mg). The mixture was stirred vigorously for 1 h before being filtered through Celite to provide **11** as a white foam (480 mg, 100%): ^1H NMR (acetone- d_6 , 400 MHz) δ 9.09 (br s, 1H), 8.19 (d, $J = 8.0$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.66 (br s, 1H), 7.48 (t, $J = 7.2$ Hz, 1H), 7.30 (t, $J = 7.2$ Hz, 1H), 4.09–4.04 (m, 2H), 3.86 (m, 1H), 3.78–3.71 (m, 2H), 2.27 (m, 1H), 2.02 (m, 1H), 1.57 (s, 9H); ^{13}C NMR (acetone- d_6 , 150 MHz) δ 178.5, 155.7, 154.0, 142.5, 132.3, 128.9, 125.1, 124.1, 123.5, 119.0, 100.8, 81.9, 55.7, 44.7, 39.7, 37.8, 29.6; IR (film) ν_{max} 3367, 2976, 1699, 1628, 1581 cm^{-1} ; ESI-TOF HRMS m/z 348.1346 ($\text{M}+\text{H}^+$, $\text{C}_{19}\text{H}_{22}\text{ClNO}_3$ requires 348.1361).



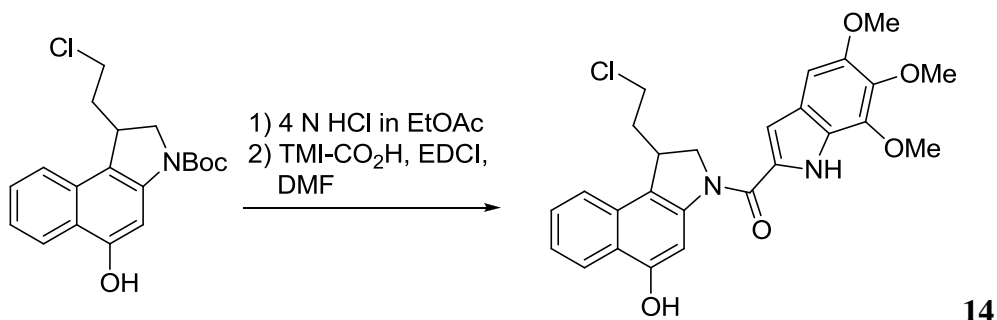
A solution of **11** (57.6 mg, 0.166 mmol) in 2-butanone (1 mL) was treated with NaI (124 mg, 0.828) and the reaction mixture was warmed at 75 $^{\circ}\text{C}$ for 3 h. The solution was diluted with ethyl acetate, washed with H_2O and saturated aqueous NaCl, and dried (MgSO_4). The solvent was removed under reduced pressure to provide **12** as a white solid (72 mg, 98%): ^1H NMR (acetone- d_6 , 400 MHz) δ 9.08 (br s, 1H), 8.19 (d, $J = 8.4$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.69 (br s, 1H), 7.48 (t, $J = 7.2$ Hz, 1H), 7.30 (t, $J = 7.6$ Hz, 1H), 4.07–4.00 (m, 2H), 3.76 (m, 1H), 3.40–3.36 (m, 2H), 2.37 (m, 1H), 2.08 (m, 1H), 1.57 (s, 9H); ^{13}C NMR (acetone- d_6 , 150 MHz) δ 178.5, 155.7, 154.0, 142.7, 132.3, 128.8, 125.1, 124.1, 123.4, 118.5, 100.7, 81.9, 55.3, 41.1, 41.0, 29.6, 5.3; IR (film) ν_{max} 3297, 2974, 1666, 1627, 1582 cm^{-1} ; ESI-TOF HRMS m/z 440.0718 ($\text{M}+\text{H}^+$, $\text{C}_{19}\text{H}_{22}\text{INO}_3$ requires 440.0717).



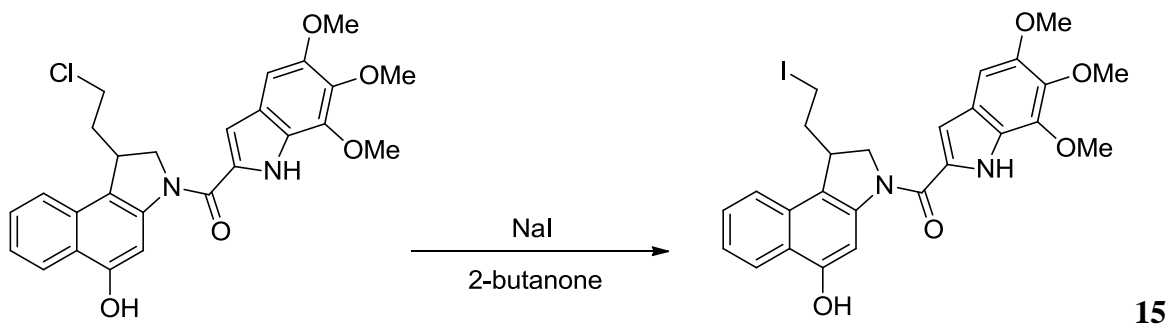
A solution of **12** (14 mg, 0.032 mmol) in 1:1 THF:saturated aqueous NaHCO_3 (1 mL) was warmed at 130 $^{\circ}\text{C}$ in an oil bath for 1 h. The solution was cooled, diluted with ethyl acetate, washed with H_2O and saturated aqueous NaCl, and dried (MgSO_4). The solvent was removed under reduced pressure and the residue purified by PTLC (5% MeOH/ CH_2Cl_2) to obtain **13** as a white solid (5.5 mg, 55%): ^1H NMR (acetone- d_6 , 600 MHz) δ 7.99 (d, $J = 7.2$ Hz, 1H), 7.85 (d, $J = 7.8$ Hz, 1H), 7.64 (t, $J = 7.8$ Hz, 1H), 7.44 (t, $J = 7.2$ Hz, 1H), 6.52 (s, 1H), 4.32 (t, $J = 10$ Hz, 1H), 4.14 (dd, $J = 11, 3.0$ Hz, 1H), 3.31 (m, 1H), 2.83 (m, 2H), 2.14 (m, 1H), 2.00 (m, 1H), 1.58 (s,

9H); ^{13}C NMR (acetone- d_6 , 150 MHz) δ 186.5, 166.4, 153.4, 145.8, 133.8, 132.5, 128.7, 127.9, 125.4, 106.2, 84.0, 61.0, 54.0, 41.2, 36.9, 29.3, 25.8; IR (film) ν_{max} 2974, 1711, 1616, 1597 cm^{-1} ; ESI-TOF HRMS m/z 312.1589 ($\text{M}+\text{H}^+$, $\text{C}_{19}\text{H}_{21}\text{NO}_3$ requires 312.1594).

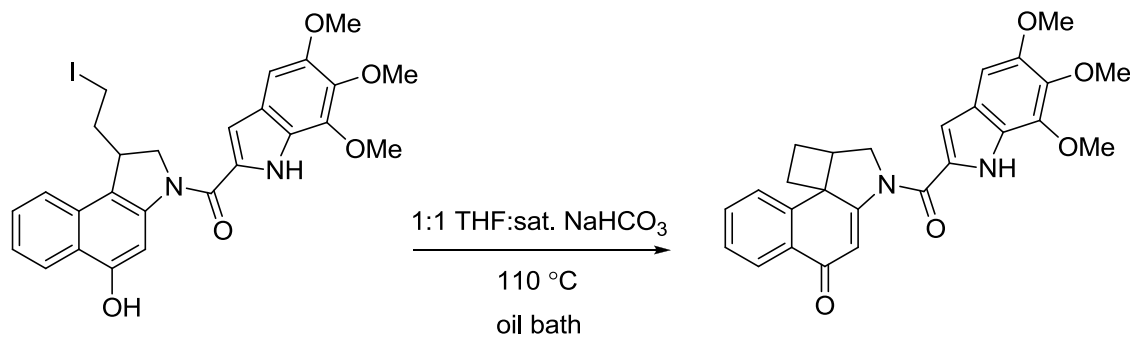
The structure of **13** was confirmed with a single-crystal X-ray analysis of a parallelepiped-shaped crystal grown from 1:4 CH_2Cl_2 :hexanes (CCDC787358).



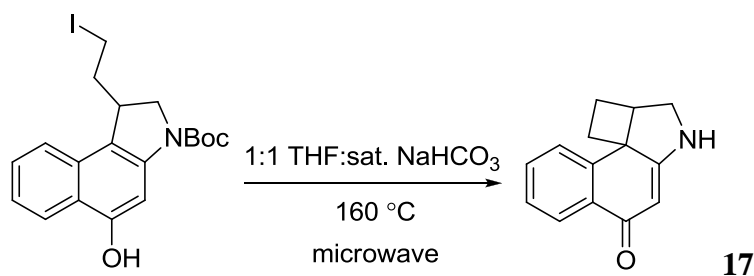
A vial containing **11** (10.2 mg, 0.0293 mmol) was treated with 4 N HCl in EtOAc (1 mL) for 30 min before the solvent was removed under a stream of N_2 . The residue was taken up in DMF (0.5 mL) and EDCI (14.3 mg, 0.0880 mmol) and 5,6,7-trimethoxyindole-2-carboxylic acid¹³ (8.1 mg, 0.032 mmol) were added. The mixture was stirred for 16 h, diluted with ethyl acetate, washed with 1 N HCl, saturated aqueous NaHCO_3 , and saturated aqueous NaCl , and dried (MgSO_4). The solvent was removed under reduced pressure and the residue purified by flash chromatography (3% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to provide **14** as a pale yellow solid (9.1 mg, 65%): ^1H NMR (DMSO- d_6 , 400 MHz) δ 11.40 (s, 1H), 10.33 (s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 7.88 (s, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.53 (t, $J = 7.6$ Hz, 1H), 7.35 (t, $J = 7.6$ Hz, 1H), 7.08 (s, 1H), 6.94 (s, 1H), 4.63 (t, $J = 8.4$ Hz, 1H), 4.38 (dd, $J = 9.6$ Hz, 1.2 Hz, 1H), 3.94 (s, 3H), 3.88–3.73 (m, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 2.15 (m, 1H), 1.99 (m, 1H); ^{13}C NMR (DMSO- d_6 , 150 MHz) δ 176.1, 160.3, 153.5, 149.1, 140.9, 139.7, 139.0, 131.0, 129.6, 127.1, 125.3, 123.2, 122.9, 122.5, 122.1, 118.3, 106.2, 100.2, 97.9, 61.1, 60.9, 56.1, 55.9, 43.4, 37.1, 36.6; IR (film) ν_{max} 3112, 2936, 1607, 1579 cm^{-1} ; ESI-TOF HRMS m/z 481.1519 ($\text{M}+\text{H}^+$, $\text{C}_{26}\text{H}_{25}\text{ClN}_2\text{O}_5$ requires 481.1525).



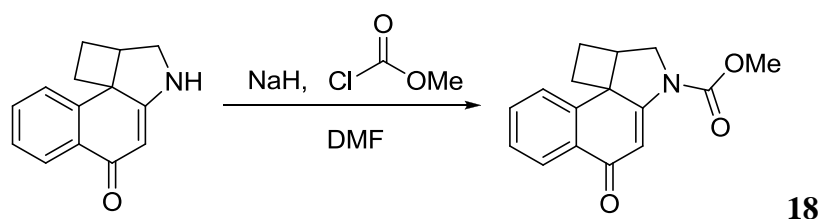
A solution of **14** (24.4 mg, 0.0507 mmol) in 2-butanone (0.8 mL) was treated with NaI (24 mg, 0.16 mmol) and the reaction mixture was warmed at 75 $^\circ\text{C}$ for 3 h. The solution was diluted with ethyl acetate, washed with H_2O and saturated aqueous NaCl , and dried (MgSO_4). The solvent was removed under reduced pressure and the residue filtered through a plug of silica gel to yield **15** as a pale yellow solid (23.6 mg, 82%): ^1H NMR (DMSO- d_6 , 600 MHz) δ 11.41 (s, 1H), 10.36 (s, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 7.90 (s, 1H), 7.79 (d, $J = 8.4$ Hz, 1H), 7.55 (t, $J = 7.2$ Hz, 1H), 7.35 (t, $J = 7.2$ Hz, 1H), 7.10 (s, 1H), 6.94 (s, 1H), 4.60 (t, $J = 9.0$ Hz, 1H), 4.36 (dd, $J = 11, 2.4$ Hz, 1H), 3.94 (s, 3H), 3.90–3.73 (m, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 2.25 (m, 1H), 2.02 (m, 1H); ^{13}C NMR (DMSO- d_6 , 150 MHz) δ 176.1, 160.2, 153.5, 149.0, 140.9, 139.7, 139.0, 131.0, 129.6, 127.0, 125.3, 123.2, 122.9, 122.5, 122.1, 118.1, 106.3, 100.1, 97.9, 61.0, 60.9, 55.9, 55.7, 34.3, 30.3, 5.6; IR (film) ν_{max} 3117, 2931, 1612, 1580 cm^{-1} ; ESI-TOF HRMS m/z 573.0885 ($\text{M}+\text{H}^+$, $\text{C}_{26}\text{H}_{25}\text{IN}_2\text{O}_5$ requires 573.0881).



A solution of **15** (20 mg, 0.035 mmol) in 1:1 THF:saturated aqueous NaHCO₃ (4 mL) was warmed at 110 °C in an oil bath for 5 h. The solution was diluted with ethyl acetate, washed with H₂O and saturated aqueous NaCl, and dried (MgSO₄). The solvent was removed under reduced pressure and the residue purified by PTLC (5% MeOH/CH₂Cl₂) to provide **16** as a white solid (2.3 mg, 15%): ¹H NMR (DMSO-*d*₆, 400 MHz) δ 11.65 (s, 1H), 7.94 (d, *J* = 7.2 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 6.95 (s, 1H), 6.56 (s, 1H), 4.65 (t, *J* = 9.2 Hz, 1H), 4.49 (dd, *J* = 9.2, 2.4 Hz, 1H), 3.93 (s, 3H), 3.81 (s, 3H), 3.81 (s, 3H), 3.38 (m, 1H), 2.89 (m, 1H), 2.79 (m, 1H), 2.15 (m, 1H), 2.04 (m, 1H); ¹³C NMR (DMSO-*d*₆, 150 MHz) δ 184.9, 165.3, 161.8, 149.3, 143.8, 140.4, 139.0, 132.5, 129.9, 129.7, 127.0, 126.1, 125.6, 124.3, 123.0, 107.9, 106.8, 98.0, 63.4, 61.1, 60.9, 60.0, 55.9, 50.9, 34.9, 23.2; IR (film) ν_{max} 2925, 2855, 1710, 1607 cm⁻¹; ESI-TOF HRMS *m/z* 445.1766 (M+H⁺, C₂₆H₂₄N₂O₅ requires 445.1758).

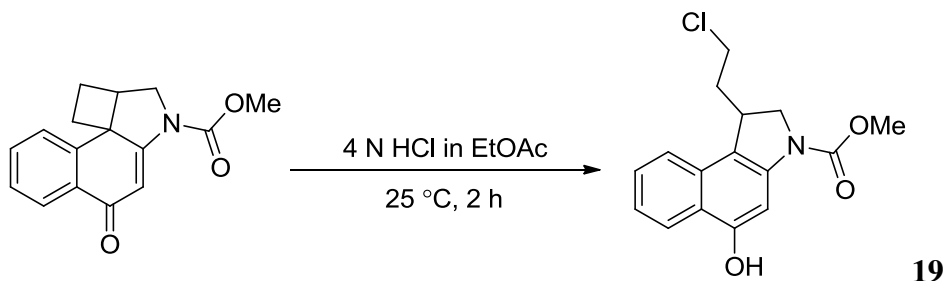


A solution of **12** (40 mg, 0.091 mmol) in 1:1 THF:saturated aqueous NaHCO₃ (4 mL) was warmed at 160 °C in a microwave reactor for 30 min. The solution was diluted with ethyl acetate, washed with H₂O and saturated aqueous NaCl, and dried (MgSO₄). The solvent was removed under reduced pressure and the residue purified by PTLC (5% MeOH/CH₂Cl₂) to provide **17** as a white solid (14.3 mg, 74%): ¹H NMR (acetone-*d*₆, 600 MHz) δ 8.00 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.17 (br s, 1H), 5.25 (s, 1H), 4.08 (t, *J* = 10 Hz, 1H), 3.79 (dd, *J* = 10, 3.2 Hz, 1H), 3.35 (m, 1H), 2.81–2.78 (m, 2H), 2.13 (m, 1H), 1.97 (m, 1H); ¹³C NMR (acetone-*d*₆, 150 MHz) δ 183.9, 176.2, 145.0, 134.1, 132.4, 128.1, 127.6, 125.0, 93.0, 58.3, 53.9, 42.3, 39.1, 26.0; IR (film) ν_{max} 3170, 3029, 2941, 2872, 1698, 1603 cm⁻¹; ESI-TOF HRMS *m/z* 212.1076 (M+H⁺, C₁₄H₁₃NO requires 212.1070).

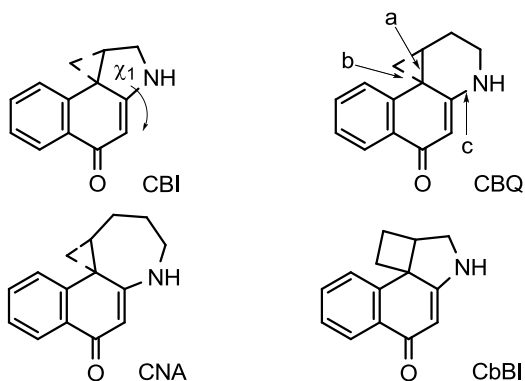


A solution of **17** (35 mg, 0.17 mmol) in DMF (1.5 mL) was cooled to 0 °C and NaH (16 mg, 0.41 mmol) was added. The solution was stirred for 30 min, and then methyl chloroformate (64 μL, 0.83 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred overnight (16 h). The solution was quenched with the addition of saturated aqueous NH₄Cl, diluted with ethyl acetate, washed with

H₂O and saturated aqueous NaCl, and dried (MgSO₄). The solvent was removed under reduced pressure and the residue purified by flash chromatography (2% MeOH/CH₂Cl₂) to provide **18** as a tan solid (43 mg, 96%): ¹H NMR (acetone-*d*₆, 400 MHz) δ 8.00 (d, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 6.54 (s, 1H), 4.32 (t, *J* = 9.6 Hz, 1H), 4.16 (dd, *J* = 11, 2.8 Hz, 1H), 3.86 (s, 3H), 3.32 (m, 1H), 2.84 (m, 2H), 2.14 (m, 1H), 2.00 (m, 1H); ¹³C NMR (acetone-*d*₆, 150 MHz) δ 186.6, 166.1, 154.9, 145.7, 133.9, 132.3, 128.7, 127.9, 125.5, 106.5, 60.7, 54.6, 41.1, 37.1, 25.7; IR (film) ν_{max} 2951, 1727, 1614, 1596 cm⁻¹; ESI-TOF HRMS *m/z* 270.1127 (M+H⁺, C₁₆H₁₅NO₃ requires 270.1125).



A vial containing **18** (5.0 mg, 0.0185 mmol) was treated with 4 N HCl in EtOAc (2 mL) and the solution stirred at room temperature for 2 h. The HCl and EtOAc were removed under a stream of nitrogen, leaving **19** as a solid residue (5.7 mg, quant.): ¹H NMR (acetone-*d*₆, 500 MHz) δ 8.20 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.71 (br s, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 4.15–4.06 (m, 2H), 3.90 (m, 1H), 3.80 (s, 3H), 3.78–3.71 (m, 2H), 2.28 (m, 1H), 2.02 (m, 1H); ¹³C NMR (acetone-*d*₆, 150 MHz) δ 155.7, 155.2, 142.5, 132.3, 128.9, 125.2, 124.3, 124.2, 123.6, 119.0, 100.4, 55.5, 53.8, 44.7, 39.6, 38.0; IR (film) ν_{max} 3271, 2954, 1679, 1629, 1583 cm⁻¹; ESI-TOF HRMS *m/z* 306.0895 (M+H⁺, C₁₆H₁₆ClNO₃ requires 306.0891).



X-ray bond lengths, Å	CbBI	CBI	CBQ	CNA
a	1.556	1.508	1.525	1.543
b	1.577	1.532	1.539	1.551
c	1.330	1.337	1.336	1.376
X-ray dihedral angles				
χ ₁	4.7°	15.7°	6.9°	50.7°
solvolysis reactivity				
t _{1/2} , (pH 3)	stable	930 h	91 h	0.62 h
t _{1/2} , (pH 7)	stable	stable	stable	563 h

Figure S1. X-ray crystal structure comparison of CbBI (**17**) with CBI analogues. Data taken from refs 17–19.