Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Total Synthesis of (+)-Cylindradine A

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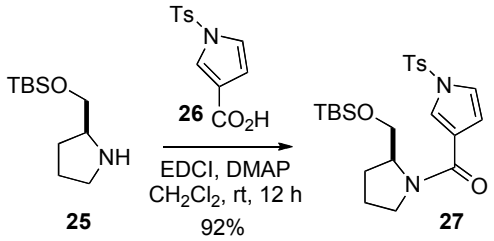
CONTENTS

1) General

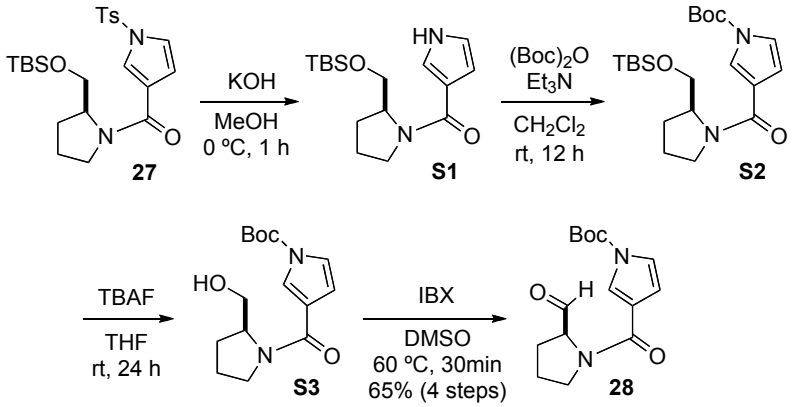
Flash chromatography was performed on Silica gel 60 (spherical, particle size 40 ~ 100 μm; Kanto) or Florisil (particle size 75 ~ 150 μm; wako) or Sephadex LH-20 (particle size 27 ~ 163 μm; General Electric Company). ^{1}H and ^{13}C NMR spectra recorded on JNM-ECX 400 and JNM-ECA 500. The spectra are referenced internally according to residual solvent signals of $CDCl_3$ (^{1}H NMR; δ = 7.26 ppm, ^{13}C NMR; δ = 77.0 ppm). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm) multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broad), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Infrared (IR) spectra were recorded on a JASCO FT/IR-420 Fourier Transform Infrared Spectrophotometer and were reported in wavenumbers (cm^{-1}). Mass spectra were recorded on a JEOL JMS-T100X spectrometer with ESI-MS mode using methanol as solvent.

2) Experimental Section



Amide **27**

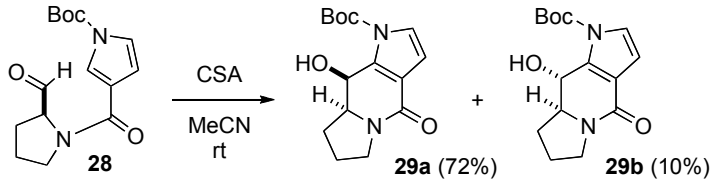
To a stirred solution of prolinol **25**[1)] (33.5 g, 155.7 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added *N*-Ts-protected pyrrole-3-carboxylic acid **26**[2)] (35.9 g, 135.4 mmol), EDCl (31.5 g, 203.1 mmol), DMAP (1.60 g, 13.5 mmol) in one portion. The reaction mixture was stirred at room temperature for 12 h then quenched with H_2O. The mixture was extracted with ethyl acetate (2 times), and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The residue was purified on silica gel column chromatography (hexane/ethyl acetate = 1:3) to give **27** as colorless oil (57.6 g, 124.6 mmol, 92%). Spectral data for **27**: $[\alpha]_D^{22}$ -60.4 (*c* 1.8, $CHCl_3$); IR (neat) 2953, 2928, 1615 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.68 (d, *J* = 8.6 Hz, 2H), 7.44 (s, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.03-7.06 (br, 1H), 6.53-6.54 (m, 1H), 4.22 (s, 1H), 3.71-3.74 (m, 2H), 3.56-3.60 (m, 1H), 3.47-3.52 (m, 1H), 2.31 (s, 3H), 1.92-1.97 (m, 2H), 1.85-1.89 (m, 1H), 1.71-1.76 (m, 1H), 0.79 (s, 9H), -0.04 (s, 3H), -0.08 (s, 3H); ^{13}C NMR (125 MHz) *δ* 162.9, 145.3, 135.1, 129.9, 126.8, 124.6, 121.9, 120.0, 113.7, 62.3, 58.9, 49.5, 26.5, 25.6, 24.7, 21.3, 17.9, -5.7; HRMS (ESI, *M*+Na^+) calcd for $C_{23}H_{34}N_2Na_1O_4S_1Si_1$ 485.1884, found 485.1906.



Aldehyde **28**

To a stirred solution of amide **27** (57.6 g, 125 mmol) in MeOH (120 mL) at 0 °C was added KOH (31.8 g, 623 mmol). The reaction mixture was stirred at 0 °C for 1 h then quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (2 times). The combined organic layer was washed with brine and dried over $MgSO_4$. The filtrates were concentrated *in vacuo* to give pyrrole **S1** (colorless oil). To a stirred solution of crude **S1** in CH_2Cl_2 (120 mL) at 0 °C was added Et_3N (105 mL, 748 mmol) and $(Boc)_2O$ (81.6 g, 374 mmol). The reaction mixture was stirred at room temperature for 12 h then quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$. The filtrates were concentrated *in vacuo* to give Boc protected pyrrole **S2** (colorless oil). To a stirred solution of crude **S2** in THF (120 mL) was added TBAF (65.2 g, 249 mmol). The reaction mixture was stirred at room temperature for 24 h then quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic layer was washed with brine and dried over $MgSO_4$. The filtrates were concentrated *in vacuo* to give alcohol **S3** (colorless oil). To a stirred solution of crude **S3** in DMSO (120 mL) was added IBX (69.8 g, 249 mmol). The reaction mixture was stirred at 60 °C for 30 min then quenched with saturated aqueous NH_4Cl and 10% aqueous $Na_2S_2O_3$ and then extracted with ethyl acetate. The combined organic layer was washed with brine and dried over $MgSO_4$. The filtrates were concentrated *in vacuo*. The residue was purified on silica gel column chromatography (hexane/ethyl acetate = 2:1) to give **28** as white amorphous (23.7 g, 81.0 mmol, 65%). Spectral data for **S1**: $[\alpha]_D^{26}$ -68.6 (*c* 1.6, $CHCl_3$); IR (neat) 3208, 2954, 2929, 1579 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.11-10.28 (br, 1H), 7.14 (s, 1H), 6.64-6.68 (br, 1H), 6.45-6.48 (br, 1H), 4.31-4.39 (br, 1H), 3.74-3.85 (m, 2H), 3.59-3.64 (m, 1H), 1.91-2.06 (m, 3H), 1.74-1.85 (m, 1H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz) δ 165.9, 122.1, 119.5, 118.2, 108.9, 62.9, 59.0, 49.8, 26.7, 25.8, 25.0, 18.1, -5.5; HRMS (ESI, M+Na^+) calcd for $C_{16}H_{28}N_2Na_1O_2Si_1$ 331.1818, found 331.1868. Spectral data for **S2**: $[\alpha]_D^{28}$ -58.0 (*c* 1.1, $CHCl_3$); IR (neat) 2954, 2930, 1751, 1619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.15-7.18 (br, 1H), 6.50-6.53 (br, 1H), 4.28-4.35 (br, 1H), 3.76-3.84 (m, 2H), 3.61-3.73 (m, 1H), 3.56-3.62 (m, 1H), 1.92-2.07 (m, 3H),

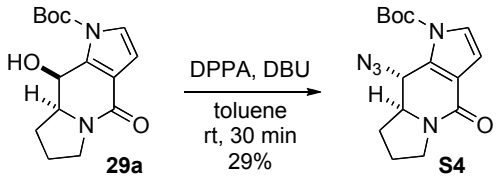
1.76-1.84 (m, 1H), 1.58 (s, 9H), 0.86 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz) δ 163.9, 148.4, 123.5, 122.1, 119.7, 112.4, 84.5, 62.7, 59.0, 49.7, 27.8, 26.7, 25.8, 25.1, 18.1, -5.5; HRMS (ESI, M+Na$^+$) calcd for $C_{21}H_{36}N_2Na_1O_4Si_1$ 431.2342, found 431.2303. Spectral data for **S3**: $[\alpha]_D^{21}$ -66.0 (*c* 1.1, $CHCl_3$); IR (neat) 3392, 2979, 1750, 1599 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.61 (br, 1H), 7.16 (dd, J = 1.7, 3.3 Hz, 1H), 6.50 (dd, J = 1.7, 3.3 Hz, 1H), 5.12-5.15 (br, 1H), 4.33-4.38 (m, 1H), 3.78-3.82 (m, 1H), 3.59-3.71 (m, 3H), 2.06 (ddd, J = 6.9, 12.6, 12.6, Hz, 1H), 1.90-1.95 (m, 1H), 1.77-1.83 (m, 1H), 1.58-1.63 (m, 1H), 1.55 (s, 9H); ^{13}C NMR (100 MHz) δ 166.3, 148.1, 122.5, 119.9, 112.2, 84.7, 67.2, 61.9, 50.0, 28.1, 27.7, 24.9; HRMS (ESI, M+Na$^+$) calcd for $C_{15}H_{22}N_2Na_1O_4$ 317.1477, found 317.1440. Spectral data for **28**: $[\alpha]_D^{21}$ -74.1 (*c* 1.2, $CHCl_3$); IR (neat) 2980, 1749, 1611 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.66 (s, 1H), 7.17 (br, 1H), 6.56 (br, 1H), 4.52 (dd, J = 5.8, 6.3 Hz, 1H), 3.78-3.81 (m, 2H), 2.06-2.11 (m, 1H), 1.91-2.01 (m, 3H), 1.55 (s, 3H); ^{13}C NMR (125 MHz) δ 199.5, 164.1, 148.1, 122.6, 121.7, 120.0, 112.2, 84.8, 65.6, 48.8, 27.7, 25.8, 25.5; HRMS (ESI, M+Na$^+$) calcd for $C_{15}H_{20}N_2Na_1O_4$ 315.1321, found 315.1296.



Alcohol **29a** and **29b**

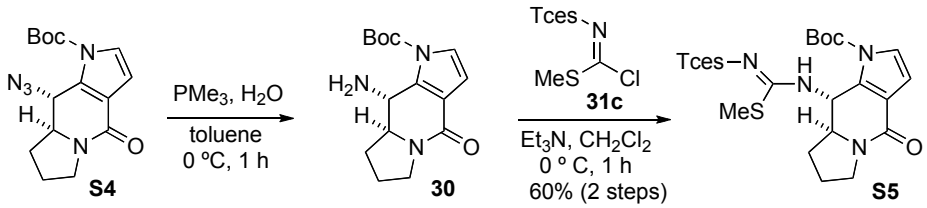
To a stirred solution of aldehide **28** (5.00 g, 17.0 mmol) in MeCN (170 mL) at 0 °C was added CSA (395 mg, 1.70 mmol). The reaction mixture was stirred at room temperature for 6 h then quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (2 times). The combined organic layer was washed with brine and dried over $MgSO_4$. The filtrates were concentrated *in vacuo*. The residue was purified on silica gel column chromatography (hexane/ethyl acetate = 2:1 to 1:1 to 1:2) to give **29a** (3.60 g, 12.3 mmol, 72%) and diastereomer **29b** as white amorphous (590 mg, 2.00 mmol, 10%). Spectral data for **29a**: $[\alpha]_D^{27}$ +85.2 (*c* 1.1, $CHCl_3$); IR (neat) 3273, 2977, 1748, 1636 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, J = 3.5 Hz, 1H), 6.22 (d, J = 3.5 Hz, 1H), 5.00 (d, J = 3.5 Hz, 1H), 3.80 (ddd, J = 3.5, 5.5, 10.0 Hz, 1H), 3.69 (ddd, J = 9.0, 10.5, 12.0 Hz, 1H), 3.48 (ddd, J = 7.5, 10.5, 11.0 Hz, 1H), 2.37 (dddd, J = 7.5, 10.0, 11.5, 12.0 Hz, 1H), 2.08-2.13 (m, 1H), 1.99-2.04 (m 1H), 1.80-1.88 (m, 1H), 1.63 (s, 9H); ^{13}C NMR (125 MHz) δ 161.2, 148.5, 137.7, 121.8, 120.6, 107.4, 84.9, 63.0, 60.8, 44.3, 27.9, 26.4, 23.5; HRMS (ESI, M+Na$^+$) calcd for $C_{15}H_{20}N_2Na_1O_4$ 315.1321, found 315.1323. Spectral data for **29b**: $[\alpha]_D^{23}$ +54.8 (*c* 2.1, $CHCl_3$); IR (neat) 3446, 2979, 1723, 1647 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, J = 3.4 Hz, 1H), 6.49 (d, J = 3.4 Hz, 1H), 5.36 (s, 1H), 4.95 (d, J = 10.3 Hz, 1H), 3.79 (ddd, J = 5.7, 10.0, 10.0 Hz, 1H), 3.64

(ddd, J = 5.7, 8.6, 9.2 Hz, 1H), 3.45 (ddd, J = 8.6, 10.0, 10.0 Hz, 1H), 2.41 (dddd, J = 5.7, 5.9, 5.9, 7.0 Hz, 1H), 1.97-2.03 (m, 1H), 1.74-1.85 (m, 2H), 1.55 (s, 9H); ^{13}C NMR (125 MHz) δ 161.1, 150.2, 138.7, 122.5, 120.5, 108.9, 86.3, 69.2, 63.8, 43.8, 31.6, 27.7, 22.9; HRMS (ESI, M+Na$^+$) calcd for $C_{15}H_{20}N_2Na_1O_4$ 315.1321, found 315.1308.



Azide **S4**

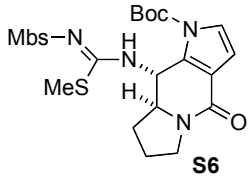
To a stirred solution of alcohol **29a** (1.93 g, 6.61 mmol) in toluene (6 mL) at 0 °C was added DPPA (4.26 mL, 19.8 mmol) and DBU (3.00 mL, 19.8 mmol). The reaction mixture was stirred at room temperature for 30 min then concentrated *in vacuo*. The residue was purified on silica gel column chromatography (hexane/ethyl acetate = 4:1 to 3:2) to give **S4** as brown amorphous (608 mg, 1.92 mmol, 29%). Spectral data for **S4**: $[\alpha]_D^{27}$ +15.8 (*c* 1.6, $CHCl_3$); IR (neat) 2977, 2110, 1750, 1652 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 2.0 Hz, 1H), 6.54 (d, J = 2.0 Hz, 1H), 4.88 (d, J = 9.5 Hz, 1H), 3.85 (ddd, J = 5.6, 9.5, 10.4, Hz, 1H), 3.66-3.71 (m, 1H), 3.53-3.58 (m, 1H), 2.42-2.47 (m, 1H), 2.06-2.12 (m, 1H), 1.81-1.94 (m, 2H), 1.61 (s, 9H); ^{13}C NMR (125 MHz) δ 161.4, 148.1, 133.0, 123.6, 121.4, 108.4, 85.6, 64.2, 61.3, 43.7, 31.5, 27.7, 22.8; HRMS (ESI, M+Na$^+$) calcd for $C_{15}H_{19}N_5Na_1O_3$ 340.1386, found 340.1388.



Tces protected thiopseudo urea **S5**

To a stirred solution of azide **S4** (572 mg, 1.80 mmol) in toluene (18 mL) at 0 °C was added PMe_3 (1.0 M in toluene, 3.61 mL, 3.61 mmol). The reaction mixture was stirred at 0 °C for 50 min and then added H_2O (1.8 mL). After 10 min, the reaction mixture was concentrated *in vacuo* to give amine **30**. To a stirred solution of crude **30** in CH_2Cl_2 (18 mL) at 0 °C was added Et_3N (759 µL, 5.40 mmol) and *S*-methyl *N*-(2,2,2-trichloroethoxysulfonyl)carbonchloroimidothioate **31c** (578 mg, 1.80 mmol). The reaction mixture was stirred at 0 °C for 1 h. The volatiles were removed under vacuum and the residue was purified on silica gel column chromatography (hexane/ethyl acetate = 1:2) to give **S5** as white amorphous (577 mg, 1.08 mmol, 60%). Spectral data for **S5**: $[\alpha]_D^{21}$ +106.3

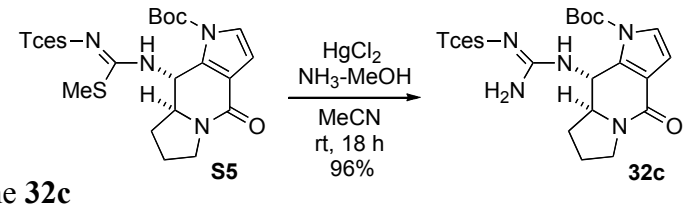
(*c* 1.8, $CHCl_3$); IR (neat) 3284, 2981, 1750, 1647, 1507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9.2 Hz, 1H), 7.16 (d, *J* = 3.2 Hz, 1H), 6.56 (d, *J* = 3.2 Hz, 1H), 5.39 (dd, *J* = 9.5, 9.8 Hz, 1H), 4.67 (s, 2H), 3.85 (m, 1H), 3.68-3.74 (m, 1H), 3.49-3.74 (m, 1H), 2.53 (s, 3H), 2.31-2.36 (m, 1H), 2.05-2.13 (m, 1H), 1.91-2.02 (m, 1H), 1.81-1.89 (m, 1H) , 1.58 (s, 9H); ^{13}C NMR (100 MHz) δ 171.9, 161.2, 147.5, 131.7, 124.3, 122.3, 108.7, 93.7, 85.8, 78.6, 64.8, 55.4, 43.8, 31.9, 27.8, 22.8, 14.9; HRMS (ESI, *M*+Na^+) calcd for $C_{19}H_{25}{}^{35}Cl_3N_4Na_1O_6S_2$ 597.0179, found 597.0134. Tces: 2,2,2-trichloroethoxysulfonyl.



S6

Mbs protected thiopseudo urea **S6**

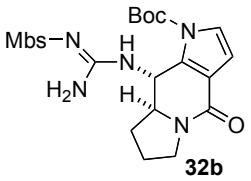
According to the procedure for **S5**, Mbs protected thiopseudo urea **S6** was synthesized from **30**. Spectral data for **S6**: $[\alpha]_D{}^{24}$ +88.7 (*c* 1.9, $CHCl_3$); IR (neat) 3275, 3011, 2979, 1755, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.2 Hz, 1H), 7.80 (d, *J* = 9.2 Hz, 2H), 7.15 (d, *J* = 3.2 Hz, 1H), 6.92 (d, *J* = 9.2 Hz, 2H), 6.55 (d, *J* = 3.2 Hz, 1H), 5.32 (t, *J* = 9.6 Hz, 1H), 3.84 (s, 3H), 3.77 (ddd, *J* = 5.6, 10.0, 10.0 Hz, 1H), 3.65-3.70 (m, 1H),3.48-3.55 (m, 1H), 2.43 (s, 3H), 2.13-2.20 (m, 1H), 2.00-2.06 (m, 1H), 1.84-1.94 (m, 1H), 1.74-1.82 (m, 1H), 1.54 (s, 9H); ^{13}C NMR (100 MHz) δ 169.2, 162.4, 161.4, 147.4, 134.3, 132.4, 128.2, 124.1, 122.1, 113.8, 108.5, 85.6, 65.2, 55.5, 54.7, 43.8, 31.6, 27.8, 22.7, 14.7; HRMS (ESI, *M*+Na^+) calcd for $C_{24}H_{30}N_4Na_1O_6S_2$ 557.1504 found 557.1471.



Tces protected guanidine **32c**

To a stirred solution of Tces protected thiopseudo urea **S5** (255 mg, 443 μmol) in MeCN (5 mL) at 0 °C was added NH_3·MeOH (2.0 M, 2.22 mL, 4.43 mmol) and $HgCl_2$ (240 mg, 886 μmol). After being stirred for 18 h at room temperature, the reaction mixture was filtered to remove solid residue. The filtrate was concentrated *in vacuo* and purified by silica gel column chromatography ($CHCl_3$/ethyl acetate = 2:1 to 1:1) to give Tces protected guanidine **32c** as white amorphous (232 mg, 0.425 mmol, 96%). Spectral data for **32c**: $[\alpha]_D{}^{21}$ +18.3 (*c* 0.76, $CHCl_3$); IR (neat) 3435, 3333, 2980, 1750, 1633, 1565 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, *J* = 3.5 Hz, 1H), 6.64 (br, 1H), 6.26

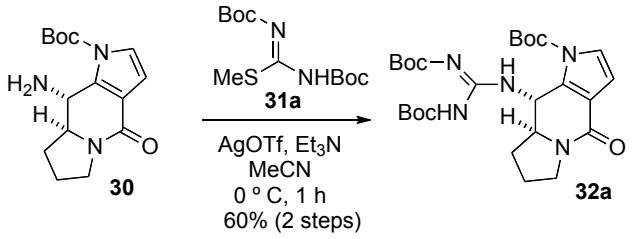
(br, 1H), 4.82 (s,1H), 4.69 (d, J = 11.0 Hz, 1H), 4.65 (d, J = 11.0 Hz, 1H), 3.69-3.73 (m, 1H), 3.39-3.46 (m, 2H), 2.34-2.37 (m, 1H), 1.92-2.04 (s, 2H), 1.76-1.79 (m, 1H), 1.56 (s, 9H); ^{13}C NMR (125 MHz) δ 162.1, 157.4, 147.6, 134.3, 123.6, 120.7, 107.9, 94.3, 93.2, 86.0, 80.5, 78.0, 65.6, 53.9, 43.9, 31.2, 27.8, 22.7; HRMS (ESI, M+Na$^+$) calcd for $C_{18}H_{24}{}^{35}Cl_3N_5Na_1O_6S_1$ 566.0411, found 566.0396.



32b

Mbs protected guanidine **32b**

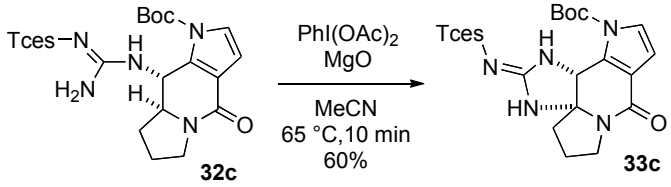
According to the procedure for **32c**, Mbs protected guanidine **32b** was obtained from **30**. Spectral data for **32b**: $[\alpha]_D^{25}$ +11.3 (c 1.2, $CHCl_3$); IR (neat) 3438, 3326, 2979, 1758, 1636, 1538 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 9.2 Hz, 2H), 6.92 (d, J = 3.6 Hz, 1H), 6.83 (d, J = 9.2 Hz, 2H), 6.60-6.65 (br, 1H), 6.20 (d, J = 3.6 Hz, 1H), 5.34 (t, J = 8.8 Hz, 1H), 3.80 (s, 3H), 3.55-3.61 (m, 1H), 3.34-3.41 (m, 1H), 3.26-3.33 (m, 1H), 2.04-2.13 (m, 1H), 1.77-1.94 (m, 2H), 1.55-1.67 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (100 MHz) δ 161.9, 161.8, 156.6, 147.3, 135.4, 134.7, 128.0, 123.3, 120.6, 113.4, 107.6, 85.2, 65.4, 55.4, 50.6, 43.7, 31.2, 27.5, 22.7; HRMS (ESI, M+Na$^+$) calcd for $C_{23}H_{29}N_5Na_1O_6S_1$ 526.1736 found 526.1758.



bis-Boc protected guanidine **32a**

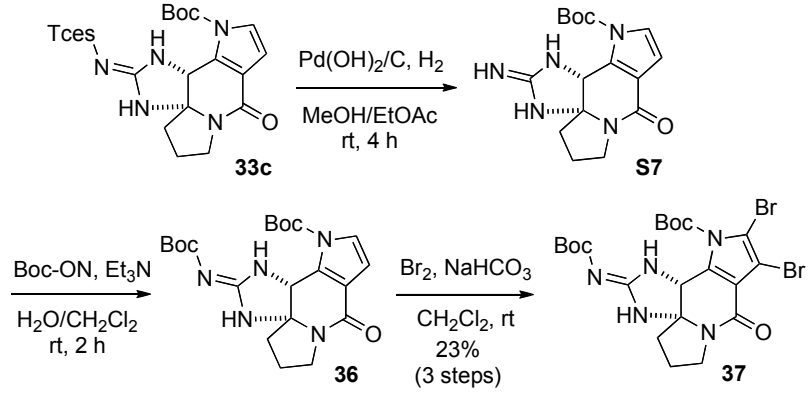
To a stirred solution of crude **30** (23.0 mg) in MeCN (1 mL) at 0 °C was added Et_3N (44 μL, 316 μmol), bis-Boc-protected pseudo thiourea **31a** (30.0 mg, 103 μmol) and AgOTf (26.0 mg, 103 μmol). After being stirred for 1 h at 0 °C, the reaction mixture was filtered to remove solid residue. The filtrate was concentrated *in vacuo* and purified by florisil column chromatography (hexane/ethyl acetate = 2:1) to give **32a** as colorless oil (25.0 mg, 47.3 μmol, 60%). Spectral data for **32a**: $[\alpha]_D^{21}$ +54.1 (c 1.0, $CHCl_3$); IR (neat) 3314, 2373, 2980, 2934, 1758, 1719, 1636 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.6 (s, 1H), 8.55 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 3.2 Hz, 1H), 6.56 (d, J = 3.2 Hz, 1H), 5.83 (dd, J = 8.4, 8.8 Hz, 1H), 3.76 (ddd, J = 5.6, 10.4, 10.4 Hz, 1H), 3.62-3.71 (m, 1H), 3.50-3.58 (m, 1H), 2.21-2.29 (m, 1H), 2.01-2.17 (m, 2H), 1.73-1.83 (m, 1H), 1.51 (s, 9H), 1.49 (s, 9H), 1.46 (s, 9H); ^{13}C NMR (100 MHz) δ 163.7, 161.7, 156.3, 153.2, 147.5, 134.3, 129.7, 123.6, 121.8, 108.5,

84.7, 83.2, 79.2, 65.5, 50.4, 43.9, 31.2, 28.3, 28.0, 27.7, 22.9; HRMS (ESI, M + K^+) calcd for $C_{26}H_{39}K_1N_5O_7$ 572.2487, found 572.2452.



Tetracyclic guanidine **33c**

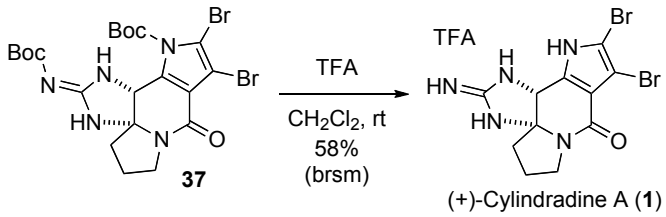
To a stirred solution of Tces protected guanidine **32c** (20.0 mg, 36.7 μmol) in MeCN (0.4 mL) at room temperature was added MgO (12.0 mg, 293 μmol) and $PhI(OAc)_2$ (47.0 mg, 147 μmol). After being stirred for 10 min at 65 °C, the reaction mixture was filtered to remove solid residue. The filtrate was concentrated *in vacuo* and purified by florisil column chromatography (hexane/ethyl acetate = 1:1) to give **33c** as white amorphous (12.0 mg, 22.0 μmol, 60%). Spectral data for **33c**: $[\alpha]_D^{20}$ +74.6 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.38 (s, 1H), 7.18 (d, J = 3.6 Hz, 1H), 6.56 (d, J = 3.6 Hz, 1H), 5.26 (s, 1H), 4.51 (d, J = 11.0 Hz, 1H), 4.42 (d, J = 11.0 Hz, 1H), 3.85-3.89 (m, 1H), 3.52-3.59 (m, 1H), 2.48-2.53 (m, 1H), 2.09-2.17 (m, 2H), 1.62 (s, 9H); ^{13}C NMR (100 MHz) δ 159.9, 157.1, 148.9, 131.1, 123.5, 119.3, 108.9, 93.9, 87.2, 82.3, 78.0, 56.2, 44.5, 40.7, 27.8, 19.9; HRMS (ESI, M + K^+) calcd for $C_{18}H_{22}{}^{35}Cl_3K_1N_5O_6S_1$ 579.9993, found 579.9998.



bis-Boc cylindradine A (**37**)

To a solution of tetracyclic guanidine **33c** (151 mg, 278 μmol) in MeOH (8 mL) and ethyl acetate (8 mL) was added 20% $Pd(OH)_2/C$ (15.1 mg) and the reaction mixture was stirred at room temperature under an atmosphere of hydrogen gas (balloon). After 4 h, the reaction mixture filtered through a

pad of celite and eluted with MeOH. The filtrate concentrated *in vacuo* to give guanidine **S7**. To a stirred solution of crude **S7** in H_2O (1.5 mL) and CH_2Cl_2 (1.5 mL) at 0 °C was added Et_3N (78.1 μL, 556 μmol) and Boc-ON (68.5 mg, 278 μmol). After being stirred for 2 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$. The filtrates were concentrated *in vacuo* to give **36**. To a stirred solution of crude **36** in CH_2Cl_2 (3 mL) at 0 °C was added $NaHCO_3$ (187 mg, 2.22 mmol) and Br_2 (57.0 μL, 1.11 mmol). After being stirred for 3 h at room temperature, the reaction mixture was quenched with 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$. The filtrates were concentrated *in vacuo* and purified by florisil column chromatography (hexane/ethyl acetate = 1:5) to give **37** as white amorphous (37.7 mg, 63.9 μmol, 23%). Spectral data for **37**: $[\alpha]_D^{24}$ +108.2 (*c* 2.3, $CHCl_3$); IR (neat) 2977, 2927, 1710, 1648, 1592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 1H), 3.75-3.83 (m, 1H), 3.57-3.64 (m, 1H), 2.42-2.45 (m, 1H), 2.09-2.12 (m, 3H), 1.66 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz) δ 159.5, 157.7, 147.8, 134.6, 116.0, 107.2, 104.8, 89.1, 82.0, 79.7, 55.8, 44.2, 40.8, 28.1, 27.6, 19.8; HRMS (ESI, $M + H^+$) calcd for $C_{21}H_{28}{}^{79}Br_1{}^{81}Br_1N_5O_5$ 590.0437, found 590.0478.



(+)-Cylindradine A (**1**)

To a stirred solution of bis-Boc cylindradine A (**37**) (125 mg, 212 μmol) in CH_2Cl_2 (2 mL) at 0 °C was added TFA (100 μL). After being stirred for 12 h at room temperature, to the reaction mixture was added toluene (500 mL).* The azeotropic mixture was concentrated *in vacuo*.** To the residue was added CH_2Cl_2,*** and the insoluble material was directly transferred to purify by Sephadex LH-20 chromatography (0.1% TFA-MeOH).**** With this purification, cylindradine A-containing fractions were collected. To the combined fractions were added water (10 mL), and the resultant was concentrated *in vacuo* with rotary evaporator to remove methanol.***** The resulting cylindradine A containing solution was freeze-dried****** to give (+)-cylindradine A (**1**) (40.0 mg, 82.7 μmol, 39%) as a white powder.

*We stopped the reaction when the decomposition of **1** was started to observe on TLC. At this stage, the starting material of **37** was still left ca. over 50% from TLC.

With this evaporation process, further decomposition of the cylindradine A (1**) was observed on TLC.

***The starting **37** was recovered at this stage as soluble material in dichloromethane (40.8 mg, 69.2 μmol, 33%). A cylindradine A (**1**) and its decomposed compounds were insoluble with dichloromethane.

****The insoluble residue was dissolved with small amount of methanol, and it was subjected to the LH-20 column chromatography.

*****Addition of the water is very important to avoid the decomposition of cylindradine A (**1**) by acid. In the evaporation of methanol, it helps to keep the low concentration of acid (TFA).

******In the freeze-dry operation, water and acid (TFA) were removed at the same time. Therefore, decomposition of **1** was minimally suppressed. In our case, unfortunately, small amount of decomposed compounds from **1** were observed by ^{1}H NMR. Please see spectra data (^{1}H and ^{13}C NMR) of **1**. Spectral data for **1**: $[\alpha]_D^{23}$ +34.4 (*c* 1.5, MeOH); IR (neat) 3160, 2949, 1678 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 5.25 (s, 1H), 3.70-3.75 (m, 1H), 3.54-3.62 (m, 1H), 2.37-2.42 (m, 1H), 2.24-2.32 (m, 1H), 2.10-2.15 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.6, 159.4, 134.6, 113.9, 107.1, 98.2, 85.8, 56.3, 46.5, 41.5, 21.2; HRMS (ESI, $M + H^+$) calcd for $C_{11}H_{12}{}^{79}Br_1{}^{81}Br_1N_5O_1$ 389.9388, found 389.9354.

Reference

1) J. Marik, R. Tykva, M. Budesinsky, J. Hlavacek, B. Bennettova, *J. Peptide Res.*, 2001, **57**, 401-408.

2) B. P. J. de Lacy Costello, P. Evans, N. Guernion, N. M. Ratcliffe, P. S. Sivanand, G.C. Teare, *Synthetic Metals,* 2000, **114**, 181-188.

Amide 27
1H NMR (500 MHz CDCl3)
TBSO
Ts
N
O
abundance
X : parts per Million : 1H
7.733
7.717
7.464
7.273
7.260
7.257
7.084
6.577
6.575
6.572
6.568
4.263
3.765
3.753
3.748
3.625
3.547
3.534
2.370
1.992
1.983
1.923
1.912
1.909
0.959
0.870
0.863
0.835
0.708
0.033
-0.002
-0.042
9.35
5.93
3.02
2.60
0.69
1.98
0.71
2.45
1.01
1.00
0.70
1.29
0.95
0.87

Amide 27
13C NMR (125 MHz CDCl3)
TBSO
Ts
N
O
x = impurity
X : parts per Million : 13C
abundance
162.874
145.304
135.117
129.890
126.800
124.625
121.906
120.046
113.732
77.258
77.200
77.000
76.742
62.340
58.896
49.463
26.485
25.588
24.749
21.325
17.862

TBSO
HN
O
N
Pyrrole **S1**
^{1}H NMR (400 MHz $CDCl_3$)
abundance
X : parts per Million : 1H
10.184
7.260
7.137
6.661
6.476
6.473
4.350
3.814
3.804
3.789
3.635
3.618
3.594
2.016
1.975
1.952
1.935
1.917
1.813
0.908
0.867
0.826
0.025
-0.005
6.56
10.24
4.48
0.71
0.91
1.01
1.00
1.06
2.48
1.11

Pyrrole S1
13C NMR (100 MHz CDCl3)
HN
O
N
TBSO
abundance
3.0
2.0
1.0
0
X : parts per Million : 13C
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
-10.0
-20.0
165.948
122.089
119.515
118.161
108.893
77.315
77.000
76.676
62.879
59.018
49.779
26.696
25.828
25.017
18.134
-5.455

Boc protected pyrrole S2
1H NMR (400 MHz CDCl3)
Boc
TBSO
N
O
abundance
X : parts per Million : 1H
9.08
4.15
9.52
6.27
1.00
0.83
0.88
0.75
0.94
7.592
7.260
7.218
7.171
6.560
6.520
6.517
6.513
4.309
3.818
3.805
3.786
3.696
3.684
3.601
3.584
2.038
2.019
2.008
1.991
1.974
1.951
1.931
1.618
1.575
1.017
0.906
0.862
0.704
0.174
0.145
0.071
0.027
-0.001
-0.122
-0.151

Boc protected pyrrole S2
13C NMR (100 MHz CDCl3)
Boc
N
O
N
TBSO
abundance
X : parts per Million : 13C
163.946
148.366
123.491
122.051
119.677
112.373
84.475
77.324
77.000
76.685
62.698
59.037
49.731
27.840
26.696
25.818
25.056
18.114
-5.455

Boc
N
O
N
HO
Alcohol S3
1H NMR (500 MHz CDCl3)
abundance
X : parts per Million : 1H
10.60
7.604
7.260
7.171
7.164
6.510
6.506
6.503
6.500
5.144
5.131
4.359
4.350
3.797
3.696
3.682
3.663
3.646
3.629
3.611
3.595
2.069
2.055
2.044
1.936
1.922
1.912
1.811
1.795
1.786
1.620
1.604
1.589
1.578
1.555
1.520
0.85
0.94
1.00
0.84
0.98
3.02
0.84
0.93
0.94
0.83

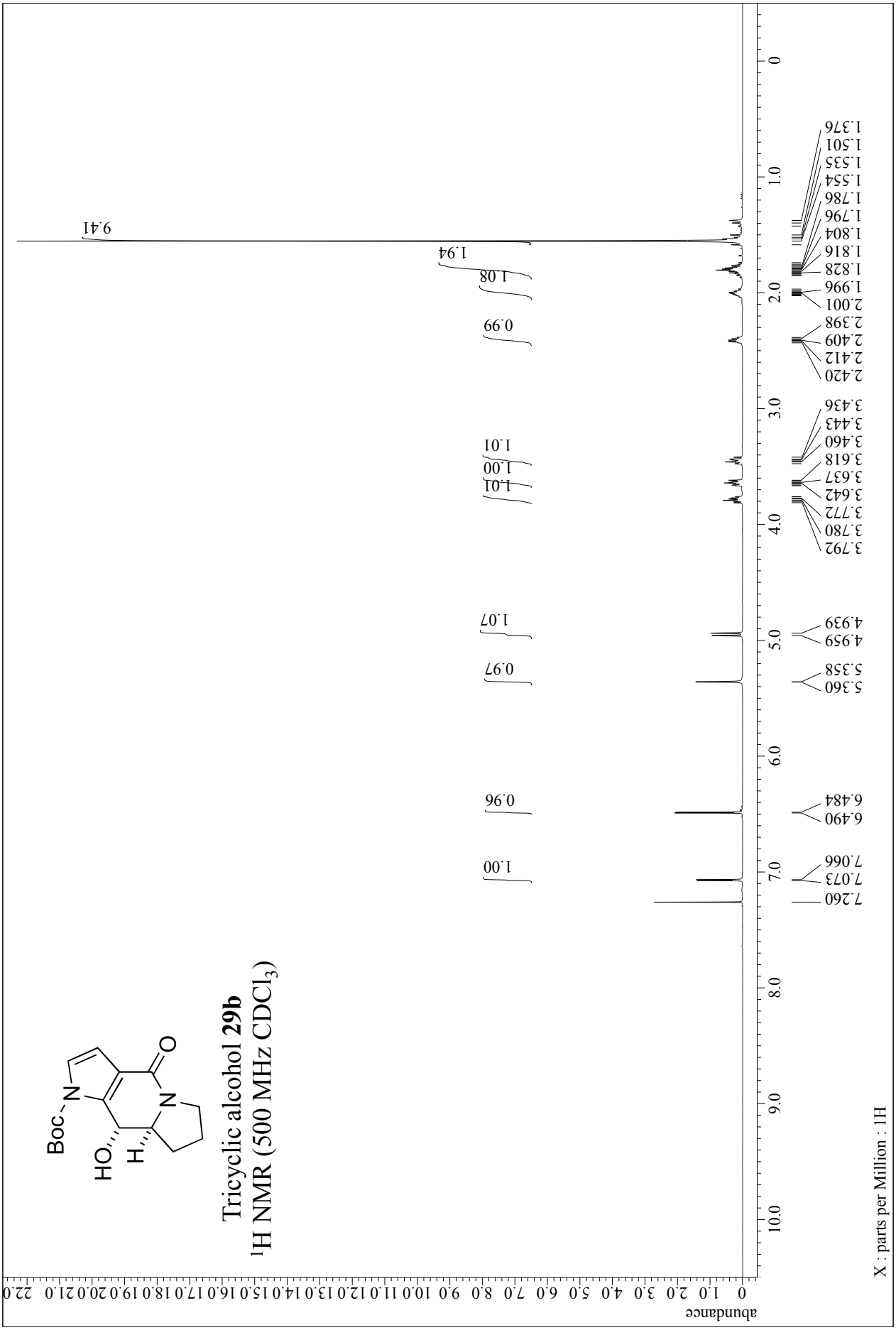
Boc
N
O
N
HO
Alcohol S3
13C NMR (125 MHz CDCl3)
abundance
X : parts per Million : 13C
166.307
148.118
122.526
122.421
119.865
112.187
84.736
77.258
77.000
76.742
67.233
61.853
50.016
28.107
27.744
24.892

Aldehyde 28
^{1}H NMR (500 MHz $CDCl_3$)
Boc
N
O
H
O
N
O
abundance
X : parts per Million : 1H
9.538
7.661
7.260
7.173
6.556
5.251
4.532
4.520
4.508
3.806
3.794
3.781
2.110
2.095
2.083
2.075
2.059
1.994
1.982
1.969
1.958
1.942
1.928
1.915
1.584
1.565
1.554
1.523
1.207
12.95
4.74
2.43
1.21
1.00
1.20
0.91
0.95

Aldehyde 28
13C NMR (100 MHz CDCl3)
Boc
N
O
H
O
N
abundance
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
0.1
0.11
0.12
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
199.557
164.213
148.204
122.776
121.841
120.115
112.287
84.895
77.315
77.000
76.676
65.702
48.940
27.840
25.923
25.570
X : parts per Million : 13C

Tricyclic alcohol 29a
1H NMR (500 MHz CDCl3)
Boc
N
O
HO
H
abundance
X : parts per Million : Proton
7.260
7.005
6.998
6.224
6.217
5.003
4.996
3.810
3.800
3.792
3.788
3.687
3.669
3.496
3.490
3.475
2.392
2.377
2.369
2.355
2.091
2.028
2.015
2.002
1.628
1.229
9.49
1.00
1.02
0.99
1.01
0.97
1.01
1.01
0.87
1.00
0.99

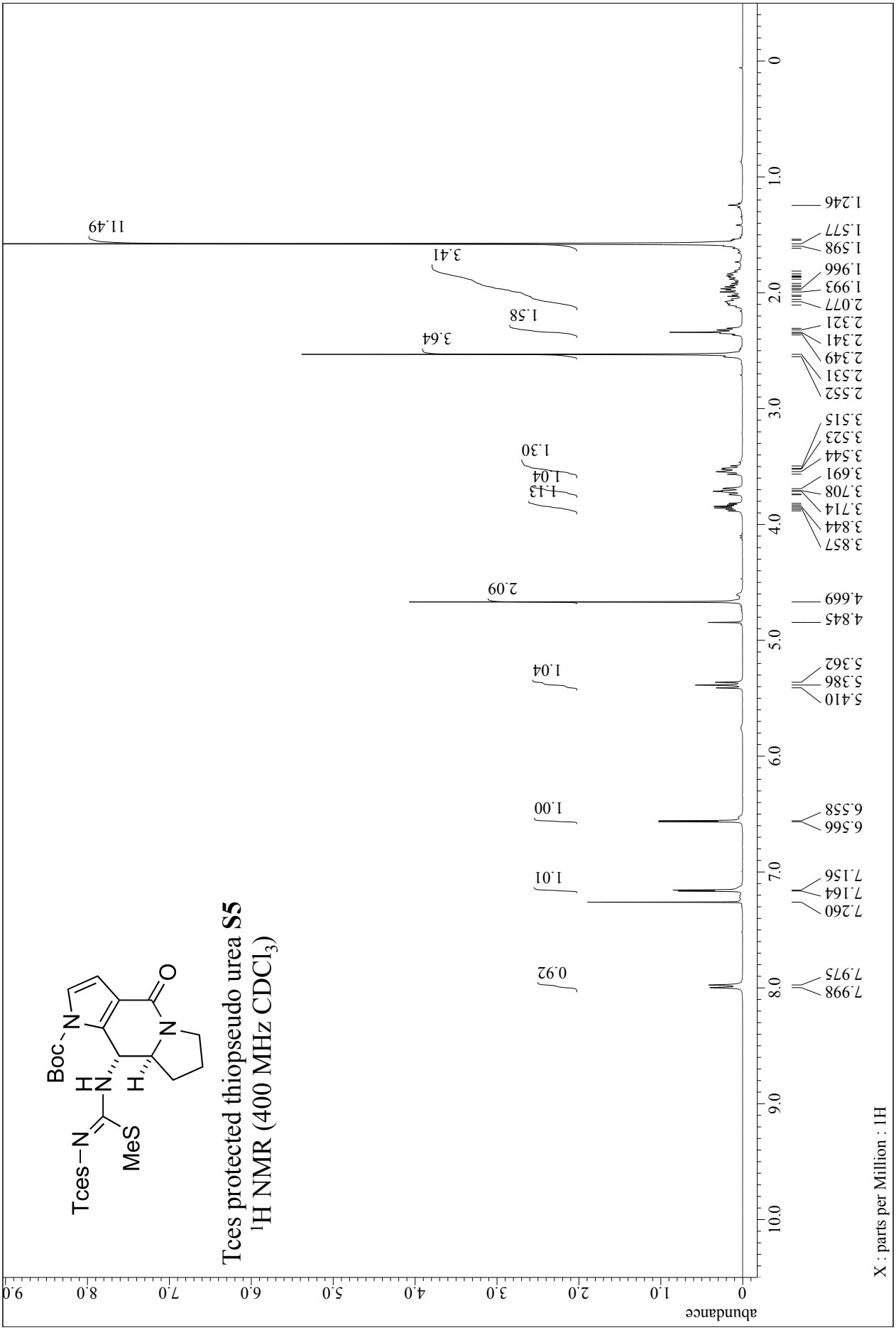
Tricyclic alcohol 29a
13C NMR (125 MHz CDCl3)
Boc
N
O
N
HO
H
abundance
X : parts per Million : Carbon13
161.185
148.480
137.673
121.821
120.619
107.351
84.945
77.258
77.000
76.752
63.007
60.794
44.303
27.963
27.897
26.371
23.461


Tricyclic alcohol 29b
1H NMR (500 MHz CDCl3)
Boc
N
HO
H
O
N
abundance
X : parts per Million : 1H
9.41
1.94
1.08
0.99
1.01
1.00
1.01
1.07
0.97
0.96
1.00
7.260
7.073
7.066
6.490
6.484
5.360
5.358
4.959
4.939
3.792
3.780
3.772
3.642
3.637
3.618
3.460
3.443
3.436
2.420
2.412
2.409
2.398
2.001
1.996
1.828
1.816
1.804
1.796
1.786
1.554
1.535
1.501
1.376

Tricyclic alcohol 29b
13C NMR (125 MHz CDCl3)
Boc
N
HO
H
O
N
abundance
0.3
0.2
0.1
0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
161.118
150.197
138.656
122.536
120.495
108.944
86.319
77.248
77.200
77.000
76.742
69.198
63.828
43.816
31.569
27.658
22.908
X : parts per Million : 13C

Boc
N
N
O
N3
H
Azide S4
1H NMR (500 MHz CDCl3)
abundance
X : parts per Million : Proton
9.58
7.285
7.260
7.152
7.148
6.545
6.539
4.887
4.868
3.843
3.831
3.682
3.677
3.665
3.658
3.566
3.543
2.455
2.447
2.443
2.432
1.879
1.872
1.865
1.611
1.589
0.72
1.00
1.01
0.99
1.01
0.91
1.01
1.96

Boc
N
N3
H
O
N
Azide S4
13C NMR (125 MHz CDCl3)
abundance
X : parts per Million : Carbon13
161.443
148.051
132.971
129.404
123.585
121.439
108.391
85.365
77.258
77.000
76.742
64.238
61.300
43.664
31.540
27.839
27.725
22.813


Tces protected thiopseudo urea S5
1H NMR (400 MHz CDCl3)
Boc
Tces
MeS
X : parts per Million : 1H
abundance
11.49
3.41
3.64
1.58
2.09
1.30
1.04
1.13
1.04
1.01
1.00
0.92

Tces protected thiopseudo urea **S5**
^{13}C NMR (100 MHz $CDCl_3$)
Tces–N
MeS
Boc
N
H
O
abundance
X : parts per Million : 13C
14.930
22.805
27.802
31.882
43.829
55.385
64.758
76.676
77.000
77.200
77.315
78.583
85.848
93.714
108.655
122.308
124.330
131.719
147.451
161.200
171.888

Mbs protected thiopseudo urea **S6**
^{1}H NMR (400 MHz $CDCl_3$)
Boc
Mbs
MeS
abundance
X : parts per Million : 1H
9.67
8.376
8.353
7.811
7.788
7.260
7.156
7.148
6.907
6.557
6.549
5.341
5.317
5.293
3.837
3.797
3.772
3.758
3.747
3.675
3.652
3.552
3.531
3.502
3.70
3.64
2.471
2.429
2.175
2.163
2.149
2.093
2.024
1.914
1.887
1.626
1.539
1.498
1.465
1.388
1.237
1.67
1.22
0.98
0.76
0.48
1.19
1.11
2.43
2.33
1.00
1.00
1.05

Mbs protected thiopseudo urea **S6**
^{13}C NMR (100 MHz $CDCl_3$)
Mbs
MeS
Boc
X : parts per Million : 13C
abundance
169.171
162.439
161.352
147.422
134.255
132.358
128.163
124.139
122.079
113.765
108.540
85.553
77.315
77.000
76.685
65.206
55.509
54.680
43.801
31.606
27.754
22.739
14.720

Tces protected guanidine 32c
1H NMR (500 MHz CDCl3)
Boc
Tces
H2N
X : parts per Million : Proton
abundance
12.07
1.04
2.56
1.30
2.52
2.77
2.57
0.77
0.79
1.00
1.84
1.01
7.260
7.150
7.063
7.056
7.005
6.636
6.261
5.515
4.856
4.820
4.696
4.674
4.659
4.638
3.759
3.725
3.714
3.455
3.439
3.409
3.386
2.541
2.505
2.370
2.360
2.347
2.001
1.982
1.959
1.773
1.646
1.629
1.620
1.606
1.587
1.562
1.424
1.249

Tces protected guanidine 32c
13C NMR (125 MHz CDCl3)
Tces
Boc
H2N
abundance
X : parts per Million : Carbon13
162.101
157.408
147.574
134.335
123.642
120.695
107.933
94.283
93.158
85.985
80.491
78.002
77.258
77.000
76.752
65.564
53.936
43.940
31.912
31.245
28.002
27.773
22.708

Mbs protected guanidine 32b
1H NMR (400 MHz CDCl3)
Boc
Mbs
H2N
X : parts per Million : 1H
abundance
8.68
7.708
7.686
7.260
6.928
6.919
6.840
6.817
6.205
6.197
5.362
5.340
5.318
3.822
3.799
3.610
3.585
3.546
3.413
3.387
3.363
3.332
3.312
3.290
3.262
2.148
2.106
2.091
2.078
1.901
1.864
1.841
1.813
1.648
1.630
1.603
1.527
1.420
1.383
1.342
1.238
2.09
0.99
1.76
1.53
1.00
1.02
3.57
1.12
2.14
1.53
2.04
1.06

Mbs protected guanidine 32b
13C NMR (100 MHz CDCl3)
Boc
Mbs
H2N
O
N
H
abundance
X : parts per Million : 13C
161.905
161.820
156.595
147.318
135.437
134.722
128.010
123.290
120.640
113.441
107.606
85.152
77.315
77.210
77.000
76.685
65.396
55.414
50.580
43.734
31.205
27.477
22.681

bis-Boc protected guanidine 32a
1H NMR (400 MHz CDCl3)
Boc
Boc–N
BocHN
H
H
N
N
N
O
abundance
X : parts per Million : 1H
11.564
8.564
8.543
7.519
7.260
7.134
6.995
6.607
6.560
6.552
5.834
5.829
5.808
5.292
4.120
4.102
3.771
3.757
3.691
3.685
3.553
2.513
2.245
2.035
1.766
1.512
1.492
1.455
1.428
0.886
0.869
0.059
27.63
0.81
0.93
0.93
1.00
0.89
3.08
0.94
1.03
2.10
1.95

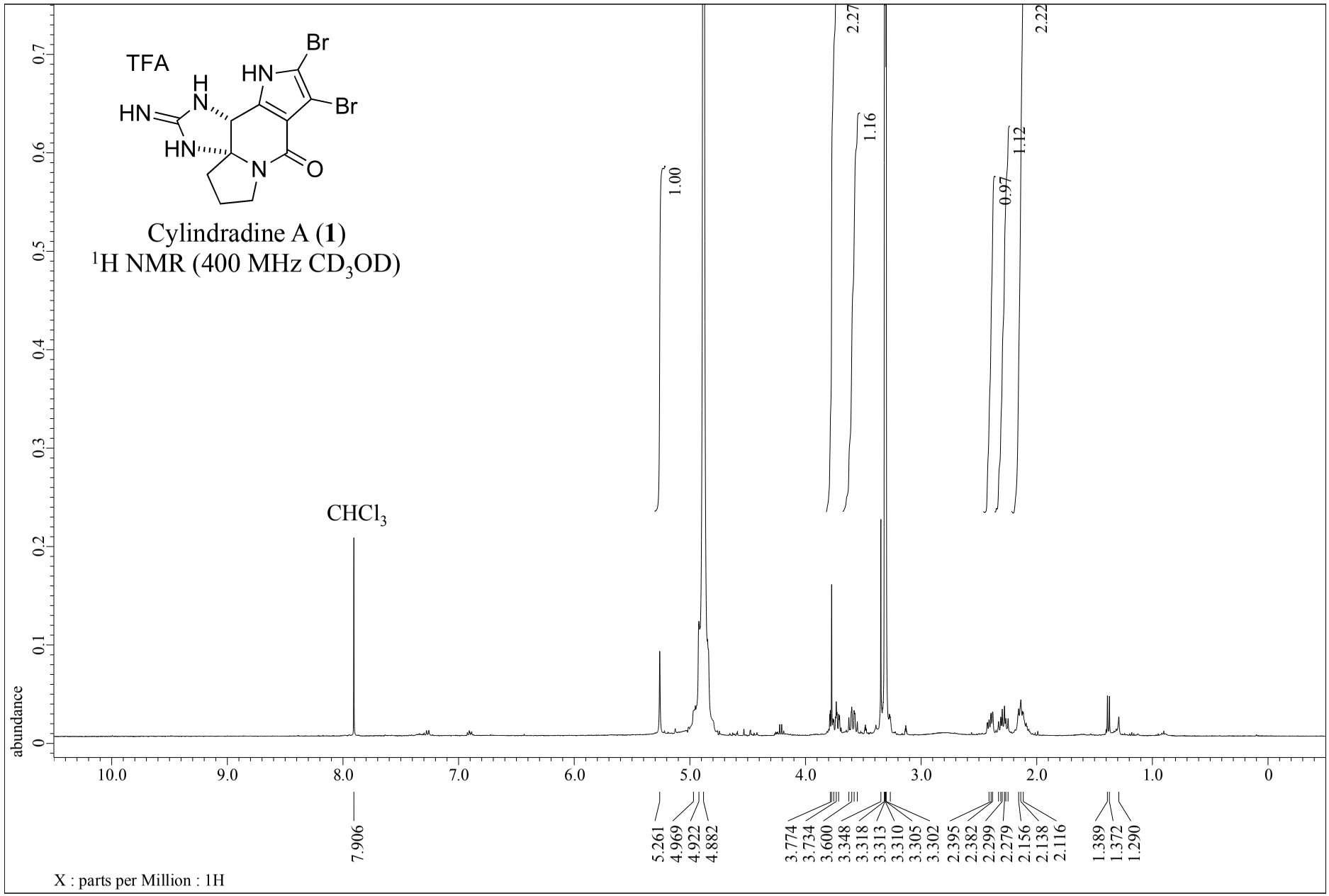
bis-Boc protected guanidine **32a**
^{13}C NMR (100 MHz $CDCl_3$)
Boc
Boc–N
BocHN
H
H
N
N
O
abundance
X : parts per Million : 13C
163.669
161.724
156.270
153.181
147.518
134.293
129.717
123.567
121.822
108.464
84.742
83.188
79.155
77.315
77.000
76.685
65.473
50.379
43.877
31.205
28.336
28.002
27.687
22.948

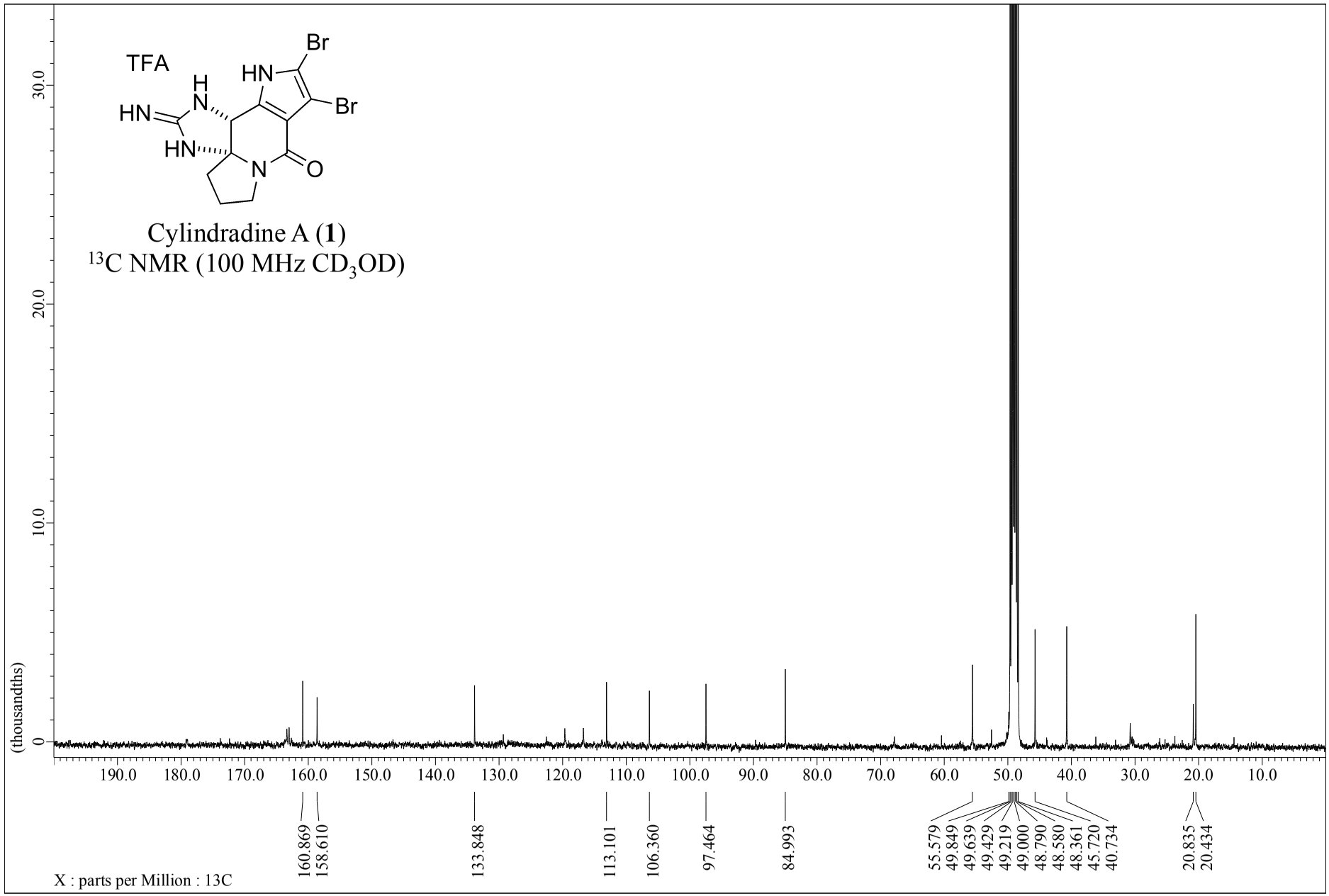
Tetracyclic guanidine 33c
1H NMR (400 MHz CDCl3)
Boc
Tces
X : parts per Million : 1H
abundance
10.79
7.463
7.376
7.260
7.186
7.176
6.562
6.553
5.259
4.523
4.496
4.440
4.412
3.880
3.869
3.588
3.566
3.539
3.517
2.504
2.496
2.483
2.157
2.144
1.903
1.663
1.652
1.625
1.580
1.496
1.331
1.247
0.062
3.73
2.41
1.19
1.15
1.05
1.04
1.00
0.86
0.83

Tetracyclic guanidine 33c
13C NMR (100 MHz CDCl3)
Boc
Tces
X : parts per Million : 13C
abundance
19.869
27.821
40.702
44.516
56.215
76.685
77.000
77.315
78.011
82.273
87.250
93.895
108.865
119.257
123.529
131.061
148.919
157.090
159.903

Bis-Boc cylindradine A (37)
1H NMR (400 MHz CDCl3)
X : parts per Million : 1H
abundance
0.061
5.150
7.260
12.75
11.86
3.91
0.95
1.31
1.25
1.00
3.812
3.798
3.783
3.754
3.643
3.618
3.599
3.591
3.569
2.454
2.443
2.121
2.108
2.094
1.987
1.656
1.554
1.482
1.467
1.436
1.245

Bis-Boc cylindradine A (37)
13C NMR (125 MHz CDCl3)
abundance
X : parts per Million : 13C
159.465
157.653
147.775
134.646
116.035
107.225
104.774
89.109
81.996
79.651
77.315
77.200
77.000
76.676
55.805
44.211
40.788
29.661
28.126
27.859
22.157
19.754


TFA
Br
HN
H
N
HN
Br
HN
N
O
Cylindradine A (1)
1H NMR (400 MHz CD3OD)
CHCl3
1.00
2.27
1.16
0.97
1.12
2.22
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
7.906
5.261
4.969
4.922
4.882
3.774
3.734
3.600
3.348
3.318
3.313
3.310
3.305
3.302
2.395
2.382
2.299
2.279
2.156
2.138
2.116
1.389
1.372
1.290
X : parts per Million : 1H


TFA
Br
HN
H
N
HN
Br
HN
N
O
Cylindradine A (1)
13C NMR (100 MHz CD3OD)
(thousandths)
30.0
20.0
10.0
0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
160.869
158.610
133.848
113.101
106.360
97.464
84.993
55.579
49.849
49.639
49.429
49.219
49.000
48.790
48.580
48.361
45.720
40.734
20.835
20.434
X : parts per Million : 13C