

Electronic Supplementary Information

Total Synthesis of (–)-Aplaminal by Buchwald–Hartwig Cross-Coupling of an Aminoalcohol

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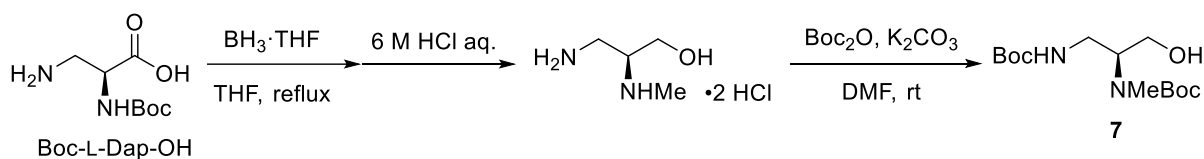
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Experimental Procedures and Spectral Data for All New Compounds.

General methods.

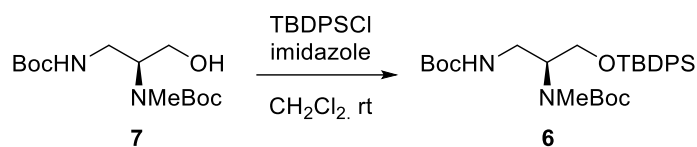
All moisture-sensitive reactions were performed under an atmosphere of argon or nitrogen, and the starting materials were azeotropically dried with benzene before use. Anhydrous benzene, CH₂Cl₂, MeOH, MeCN, DMF, THF, and toluene were used as obtained from commercial supplies. TLC analyses were conducted on E. Merck precoated silica gel 60 F₂₅₄ (0.25 mm layer thickness). Fuji Silysia silica gel BW-820MH (75–200 μm) and FL-60D (45–75 μm) were used for column chromatography. Optical rotations were measured with a JASCO DIP-370 polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 instrument, and only selected peaks are reported in wavenumbers (cm⁻¹). ¹H and ¹³C NMR spectra were recorded on a Bruker AVANCE 600, a Bruker AVANCE 400, or a Bruker DPX 400 spectrometer. The ¹H and ¹³C chemical shifts (δ) were referenced with CDCl₃ (δ_H = 7.26 (CHCl₃) and δ_C = 77.0), acetone-*d*₆ (δ_H = 2.05 (CHD₂COCD₃) and δ_C = 29.8), DMSO-*d*₆ (δ_H = 2.50 (CHD₂SOCD₃) and δ_C = 39.5), or CD₃OD (δ_H = 3.31 (CHD₂OD) and δ_C = 49.0). *J* values are given in Hz. The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. High resolution ESI/TOF mass spectra were recorded on a JEOL AccuTOFCS JMS-T100CS spectrometer. All new compounds were determined to be >95% pure by ¹H NMR unless otherwise noted.



Alcohol 7.

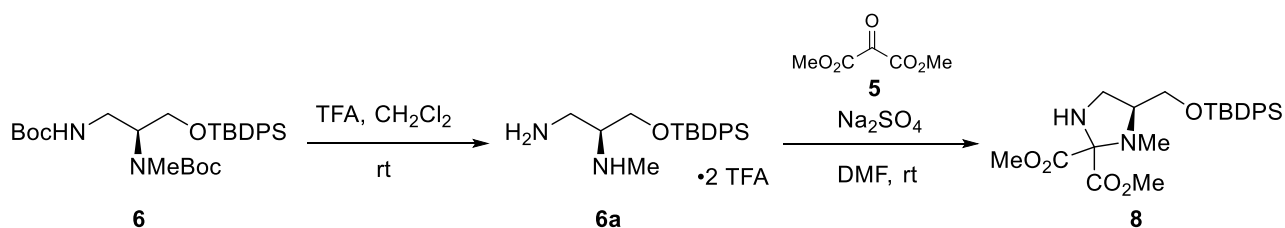
To a stirred solution of Boc-L-Dap-OH (1.04 g, 5.10 mmol) in THF (25 mL) was added BH₃·THF (1.0 M solution in THF, 25.0 mL, 25.0 mmol) at 0 °C. The mixture was stirred at reflux for 24 h, diluted with 6 M HCl aq. (15 mL), and concentrated. The crude diamine hydrochloride was used for the next reaction without further purification.

To a stirred solution of crude diamine hydrochloride in DMF (13 mL) were added K₂CO₃ (2.72 g, 20.4 mmol) and Boc₂O (3.56 mL, 15.5 mmol) at room temperature. The mixture was stirred at the same temperature for 19 h and filtered through a pad of Celite[®], which was rinsed with CHCl₃ (150 mL). The filtrate and a rinse were combined and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane–AcOEt 3:1 → 2:1 → 1:1 → 0:1) to give alcohol 7 (1.36 g, 88%) as a white solid: Mp 112.9–115.5 °C; [α]¹⁹_D –8.25 (*c* 1.33, CHCl₃); IR (CHCl₃) 3453, 2980, 2933, 1683, 1509, 1393, 1268, 1250, 1159 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1H), 4.84 (br, 1H), 3.93 (m, 1H), 3.73–3.68 (m, 2H), 3.41 (m, 1H), 3.24 (m, 1H), 2.86 (s, 3H), 1.46 (s, 9H), 1.44 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 156.8, 156.4, 79.9, 79.4, 61.3, 57.4, 38.8, 31.3, 28.3 (3C), 28.2 (3C); HRMS (ESI) *m/z* 327.1924, calcd for C₁₄H₂₈N₂NaO₅ [M+Na]⁺ 327.1896.



TBDPS ether **6**.

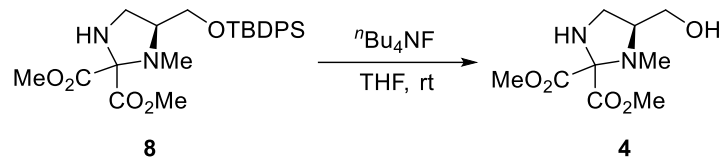
To a stirred solution of alcohol **7** (100 mg, 0.330 mmol) in CH₂Cl₂ (3.2 mL) were added imidazole (44.9 mg, 0.660 mmol) and TBDPSCl (0.11 mL, 0.43 mmol) at room temperature. The mixture was stirred at the same temperature for 30 min, diluted with brine (10 mL), and extracted with CHCl₃ (3×10 mL). The combined extracts were washed with brine (10 mL), dried (Na₂SO₄), and concentrated. The residual oil was purified by column chromatography on silica gel (5.4 g, hexane–AcOEt 10:1 → 5:1) to give TBDPS ether **6** (175 mg, 98%) as a colorless solid; Mp 74.8–76.9°C; [α]¹⁹_D –2.60 (*c* 1.03, CHCl₃); IR (CHCl₃) 3447, 3009, 2979, 2860, 1707, 1685, 1508, 1252, 1114, 998, 704 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.64–7.62 (m, 4H), 7.45–7.36 (m, 6H), 4.59 [4.71] (m, 1H), 4.29 [4.14] (m, 1H), 3.72–3.62 (m, 2H), 3.31 (m, 1H), 3.20 (m, 1H), 2.79 [2.76] (s, 3H), 1.46 [1.43] (s, 9H), 1.42 (s, 9H), 1.04 (s, 9H) (The rotamer's signals in the ratio of 1:0.9 are in brackets); ¹³C NMR (100 MHz, CDCl₃) δ 156.5 [155.8], 155.9, 135.5 (4C), 133.1 (2C), 129.7 (2C), 127.7 (4C), 79.9 [79.5], 79.3 [79.1], 63.1 [63.0], 57.5 [56.3], 39.5, 30.2 [29.6], 28.4 (3C), 28.3 (3C), 26.7 (3C), 19.3 (The rotamer's signals in the ratio of 1:0.9 are in brackets); HRMS (ESI) *m/z* 565.3068, calcd for C₃₀H₄₆N₂NaO₅Si [M+Na]⁺ 565.3074.



Aminal **8**.

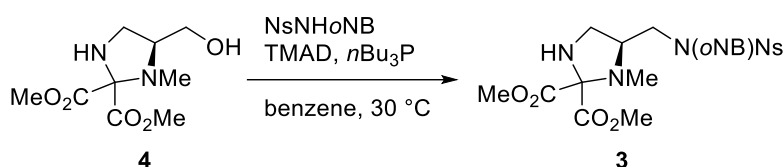
To a stirred solution of TBDPS ether **6** (1.31 g, 2.42 mmol) in CH₂Cl₂ (32 mL) was added TFA (7.0 mL, 91.5 mmol) at 0 °C. After being stirred at same temperature for 3 h, the reaction mixture was concentrated. The crude diamine TFA salt **6a** was used for the next reaction without further purification.

To a stirred solution of crude diamine TFA salt **6a** in DMF (17 mL) were added Na₂SO₄ (7.73 g, 5.12 mmol) and dimethyl 2-oxomalonate (**5**) (0.37 mL, 3.21 mmol) at room temperature. The mixture was stirred at the same temperature for 2 d, diluted with saturated aqueous NaHCO₃ (15 mL), filtered, and extracted with AcOEt (2×30 mL). The combined extracts were washed with brine (30 mL), dried (Na₂SO₄), and concentrated. The residual oil was purified by column chromatography on silica gel (70 g, hexane–acetone 6:1) to give aminal **8** (970 mg, 85%) as a colorless oil; [α]²⁴_D –0.80 (*c* 2.5, CHCl₃); IR (CHCl₃) 2955, 2858, 1736, 1472, 1227, 824, 788 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J* = 6.6 Hz, 4H), 7.45–7.36 (m, 6H), 3.78 (s, 3H), 3.77 (s, 3H), 3.67 (dd, *J* = 10.3, 4.3 Hz, 1H), 3.53 (dd, *J* = 10.3, 5.7 Hz, 1H), 3.31 (dd, *J* = 10.1, 7.7 Hz, 1H), 3.24–3.19 (m, 2H), 3.09 (dd, *J* = 10.1, 4.8 Hz, 1H), 2.56 (s, 3H), 1.07 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 169.7, 169.4, 135.6 (4C), 133.5 (2C), 129.7 (2C), 127.7 (4C), 85.4, 65.9, 65.3, 52.8, 52.2, 47.8, 35.1, 26.8 (3C), 19.2; HRMS (ESI) *m/z* 493.2135, calcd for C₂₅H₃₄N₂NaO₅Si [M+Na]⁺ 493.2142.



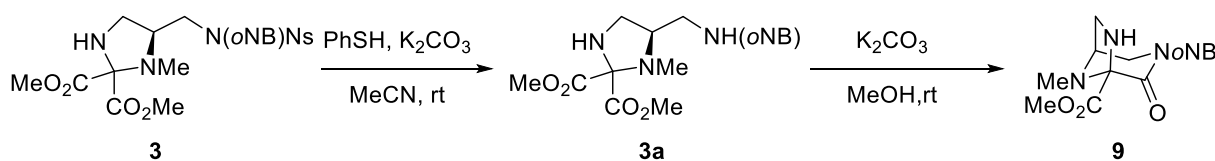
Alcohol 4.

To a stirred solution of aminal **8** (4.25 g, 9.12 mmol) in THF (150 mL) was added TBAF (1.0 M solution in THF, 12.5 mL, 12.5 mmol) at 0 °C. The mixture was stirred at room temperature for 1.5 h, diluted with AcOH (1.0 M solution in THF, 12.5 mL, 12.5 mmol), and concentrated. The residual oil was purified by column chromatography on silica gel (250 g, hexane–acetone 3:1→2:1→1:1) to give alcohol **4** (1.82 g, 86%) as a yellow oil: $[\alpha]_D^{24} +0.06$ (*c* 2.7, CHCl₃); IR (CHCl₃) 3347, 2956, 2882, 1736, 1437 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.83 (s, 3H), 3.78 (s, 3H), 3.70 (dd, *J* = 11.4, 2.8 Hz, 1H), 3.46 (d, *J* = 11.4 Hz, 1H), 3.26–3.11 (m, 3H), 2.59 (s, 3H), Signals due to two protons (NH, OH) were not observed; ¹³C NMR (100 MHz, CDCl₃) δ 169.5, 169.4, 85.2, 65.2, 60.2, 53.0, 52.3, 46.9, 34.1; HRMS (ESI) *m/z* 255.0957, calcd for C₉H₁₆N₂NaO₅ [M+Na]⁺ 255.0957.



Nosylamide 3.

To a stirred solution of alcohol **4** (43.0 mg, 185 μmol) in benzene (0.6 mL) were added NsNH_oNB (105 mg, 311 μmol), *n*Bu₃P (75 μL, 311 μmol), and TMAD (52.8 mg, 311 μmol) at 0 °C. The mixture was stirred at 30 °C for 24 h and concentrated. The residual oil was purified by column chromatography on silica gel (15 g, toluene–AcOEt 1:0→5:1) to give nosylamide **3** (32.2 mg, 32%) as a yellow oil: $[\alpha]_D^{24} -2.5$ (*c* 0.69, CHCl₃); IR (CHCl₃) 2360, 1735, 1542, 1353, 925, 853, 771 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.98 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.94 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.73–7.61 (m, 4H), 7.55 (ddd, *J* = 7.8, 6.9, 1.1 Hz, 1H), 7.41 (ddd, *J* = 8.1, 7.3, 1.0 Hz, 1H), 5.10 (d, *J* = 18.0 Hz, 1H), 5.02 (d, *J* = 18.0 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.44–3.42 (m, 2H), 3.13–3.09 (m, 2H), 2.96–2.93 (m, 2H), 2.45 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.2 (2C), 148.3, 148.0, 134.0, 133.6, 132.9, 132.0, 131.9, 130.9, 129.3, 128.6, 84.8, 63.8, 53.0, 52.3, 51.3, 50.0, 48.2, 34.8; HRMS (ESI) *m/z* 574.1220, calcd for C₂₂H₂₅N₅NaO₁₀S [M+Na]⁺ 574.1220.

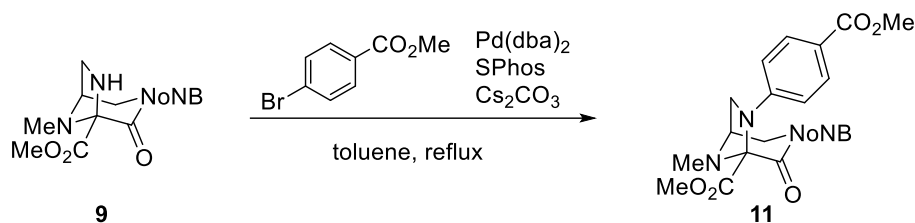


Lactam 9.

To a stirred solution of nosylamide **3** (1.01 g, 1.83 mmol) in MeCN (10 mL) were added K₂CO₃ (2.54 g, 18.3

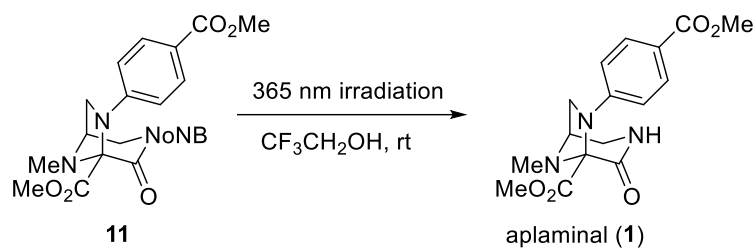
mmol) and PhSH (0.93 mL, 9.15 mmol) at 0 °C. The mixture was stirred at room temperature for 3.5 h, filtered, and concentrated. The residual oil was purified by column chromatography on silica gel (45 g, CHCl₃–MeOH 1:0 → 30:1) to give amine **3a** (contaminated with unidentified impurities).

To a stirred solution of amine **3a** in MeOH (20 mL) was added K₂CO₃ (1.26 g, 9.16 mmol) at room temperature. The mixture was stirred at the same temperature for 15 h, diluted with H₂O (10 mL), and extracted with CHCl₃ (7×15 mL). The combined extracts were washed with brine (20 mL), dried (Na₂SO₄), and concentrated. The residual oil was purified by column chromatography on silica gel (45 g, CHCl₃–MeOH 1:0 → 20:1) to give lactam **9** (592 mg, 97% in 2 steps) as a yellow solid. [α]²⁴_D +0.18 (*c* 0.48, CHCl₃); IR (CHCl₃) 3014, 2400, 1752, 1672, 1494, 1440, 1125, 669 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.99 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.63 (ddd, *J* = 7.8, 7.8, 1.0 Hz, 1H), 7.44–7.40 (m, 2H), 5.06 (d, *J* = 16.7 Hz, 1H), 4.63 (d, *J* = 16.7 Hz, 1H), 3.91 (s, 3H), 3.65 (m, 1H), 3.55–3.49 (m, 2H), 2.92 (d, *J* = 11.0 Hz, 1H), 2.89 (d, *J* = 9.6 Hz, 1H), 2.31 (s, 3H), A signal due to one proton (NH) was not observed; ¹³C NMR (100 MHz, CDCl₃) δ 167.0, 166.6, 148.7, 134.0, 132.1, 128.7, 128.2, 125.0, 87.0, 60.9, 53.2, 53.0, 46.5, 45.9, 37.0; HRMS (ESI) *m/z* 357.1175, calcd for C₁₅H₁₈N₄NaO₅ [M+Na]⁺ 357.1157.



Coupling compound **11**.

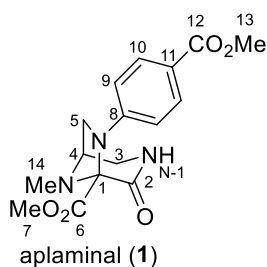
To the mixture of lactam **9** (14.4 mg, 45 μ mol), methyl 4-bromobenzoate (28.9 mg, 135 μ mol), Pd(dba)₂ (25.8 mg, 45 μ mol), SPhos (18.4 mg, 45 μ mol), and Cs₂CO₃ (87.6 mg, 269 μ mol) was added degassed toluene (0.5 mL). The mixture was stirred at reflux for 24 h, filtered through a pad of Celite[®], and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–acetone 5:1 → 1:1) to give coupling compound **11** (16.6 mg, 82%) as a yellow solid; [α]²⁴_D -13.7 (*c* 0.78, CHCl₃); IR (CHCl₃) 3019, 1759, 1704, 1675, 1606, 1527, 1287, 1192, 910, 842 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.93–7.90 (m, 3H), 7.30 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.12 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 6.89–6.84 (m, 3H), 5.12 (d, *J* = 16.6 Hz, 1H), 4.46 (d, *J* = 16.6 Hz, 1H), 4.54 (ddd, *J* = 9.2, 5.6, 1.7 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.76 (ddd, *J* = 11.3, 4.5, 1.7 Hz, 1H), 3.67 (m, 1H), 3.29 (d, *J* = 9.2 Hz, 1H), 3.06 (d, *J* = 11.3 Hz, 1H), 2.56 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.2, 165.2, 163.8, 148.7, 148.6, 133.7, 131.5, 130.5 (2C), 128.4, 128.3, 124.9, 120.1, 115.3 (2C), 86.1, 58.6, 53.2, 53.1, 52.8, 51.7, 45.9, 38.4; HRMS (ESI) *m/z* 491.1543, calcd for C₂₃H₂₄N₄NaO₇ [M+Na]⁺ 491.1577.



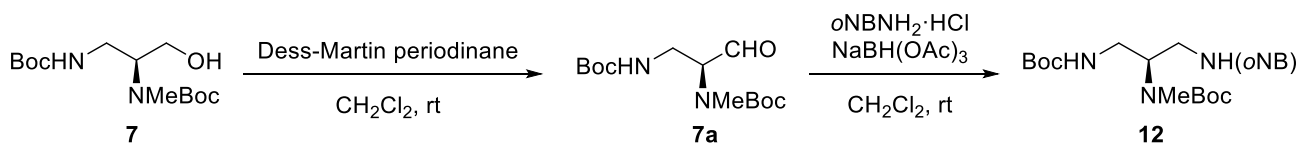
Aplaminal (1).

The solution of coupling compound **11** (16.6 mg, 35 μmol) in trifluoroethanol (12 mL) was stirred at room temperature for 24 h under 365 irradiation and concentrated. The residual oil was purified by column chromatography on silica gel (3 g, CHCl_3 –MeOH 1:0 \rightarrow 50:1) to give aplaminal (**1**) (8.6 mg, 73%) as a white solid; Mp 232–234 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{24} -107$ (*c* 0.22, MeOH); IR (MeOH) 3407, 1747, 1654, 1605, 1284, 1192, 826, 789 cm^{-1} ; ^1H NMR (600 MHz, acetone- d_6) δ 7.77 (d, $J = 8.9$ Hz, 2H), 6.86 (d, $J = 8.9$ Hz, 2H), 6.61 (brs, 1H), 4.27 (ddd, $J = 9.2, 5.8, 1.5$ Hz, 1H), 3.85–3.75 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.68 (dd, $J = 11.5, 4.3$ Hz, 1H), 3.37 (d, $J = 9.2$ Hz, 1H), 3.24 (m, 1H), 2.47 (s, 3H); ^{13}C NMR (151 MHz, acetone- d_6) δ 167.3, 166.3, 164.8, 150.7, 130.5 (2C), 119.8, 116.2 (2C), 86.9, 58.8, 53.5, 52.7, 51.6, 47.4, 38.2; HRMS (ESI) m/z 356.1222, calcd for $\text{C}_{16}\text{H}_{19}\text{N}_3\text{NaO}_5$ $[\text{M}+\text{Na}]^+$ 356.1222.

Comparison of the ^1H data of synthetic aplaminal and natural sample



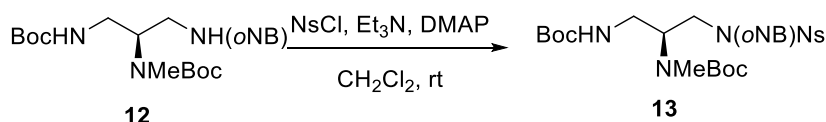
^1H in acetone- d_6	natural, δ (ppm)	synthetic, δ (ppm)
3a	3.66 (m)	3.68 (dd, $J = 11.5, 4.3$ Hz)
3b	3.23 (m)	3.24 (m)
4	3.85–3.75 (m)	3.85–3.75 (m)
5a	4.26 (ddd, $J = 9.2, 5.7, 1.4$ Hz)	4.27 (ddd, $J = 9.2, 5.8, 1.5$ Hz)
5b	3.36 (d, $J = 9.2$ Hz)	3.37 (d, $J = 9.2$ Hz)
7	3.79 (s, 3H)	3.80 (s)
9	6.85 (d, $J = 9.1$ Hz, 2H)	6.86 (d, $J = 8.9$ Hz, 2H)
10	7.76 (d, $J = 9.1$ Hz, 2H)	7.77 (d, $J = 8.9$ Hz, 2H)
13	3.78 (s)	3.79 (s)
14	2.46 (s)	2.47 (s)
N-1	6.62 (brs)	6.61 (brs)



Amine 12.

To a stirred solution of alcohol **7** (41.7 mg, 137 μmol) in CH_2Cl_2 (1.9 mL) was added Dess–Martin periodinane (116 mg, 274 μmol) at 0 °C. After being stirred at room temperature for 2 h, the mixture was diluted with saturated aqueous NaHCO_3 (1.0 mL), saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (1.0 mL), and H_2O (1.0 mL). The mixture was extracted with Et_2O (3 \times 3 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The crude aldehyde **7a** was used for the next reaction without further purification.

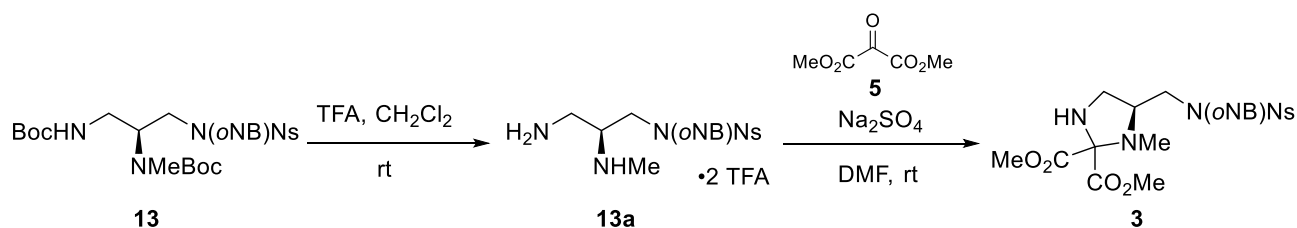
To a stirred solution of crude aldehyde **7a** in CH_2Cl_2 (1.5 mL) was added $o\text{NBNH}_2\cdot\text{HCl}$ (51.7 mg, 274 μmol) at room temperature. After the mixture was stirred at same temperature for 1 h, $\text{NaBH}(\text{OAc})_3$ (87.1 mg, 411 μmol) was added to the mixture. The mixture was stirred at same temperature for 12 h and diluted with saturated aqueous NaHCO_3 (2.0 mL). The mixture was extracted with CH_2Cl_2 (3 \times 3 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (20 g, hexane–acetone 10:1 \rightarrow 5:1) to give amine **12** (54.1 mg, 90% in 2 steps) as a colorless oil; $[\alpha]_D^{23} +4.3$ (c 1.89, CHCl_3); IR (CHCl_3) 3445, 3017, 1684, 1525, 1367, 1225, 1160, 798, 787 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.90 (d, J = 8.1 Hz, 1H), 7.71–7.64 (m, 2H), 7.49 (dd, J = 8.1, 7.8 Hz, 1H), 6.34 (brs, 1H), 4.09 (m, 1H), 3.96 (s, 2H), 3.12–2.94 (m, 2H), 2.64 (s, 3H), 2.71–2.50 (m, 2H), 1.40 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ 155.1 (2C), 148.7, 135.1, 132.4, 130.2, 127.5, 123.6, 78.7, 77.9, 77.2, 59.8, 48.7, 47.9, 38.9, 27.9 (3C), 27.7 (3C); HRMS (ESI) m/z 461.2393, calcd for $\text{C}_{21}\text{H}_{34}\text{N}_4\text{NaO}_6$ $[\text{M}+\text{Na}]^+$ 461.2376.



Nosylamide 13.

To a stirred solution of amine **12** (54.1 mg, 123 μmol) in CH_2Cl_2 (1.0 mL) were added Et_3N (34 μL , 246 μmol), NsCl (41.0 mg, 185 μmol), and DMAP (7.5 mg, 62 μmol) at room temperature. The mixture was stirred at the same temperature for 19 h, diluted with saturated aqueous NaHCO_3 (2.0 mL), and extracted with CH_2Cl_2 (3 \times 3 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (3 g, hexane–acetone 5:1 \rightarrow 3:1) to give nosylamide **13** (69.0 mg, 90%) as a yellow solid; Mp 68.0–69.0 °C; $[\alpha]_D^{23} -3.8$ (c 0.60, CHCl_3); IR (CHCl_3) 3452, 3018, 1709, 1545, 1529, 1368, 1226, 1053, 795 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.01 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 7.9 Hz, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.86 (dd, J = 8.0, 7.6 Hz, 1H), 7.76 (dd, J = 8.0, 7.6 Hz, 1H), 7.61 (dd, J = 7.9, 7.7 Hz, 1H), 7.51 (dd, J = 7.9, 7.7 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 6.45 (brs, 1H), 4.93 (s, 2H), 4.26–4.03 (m, 2H), 3.67 (dd, J = 14.2, 9.3 Hz, 1H),

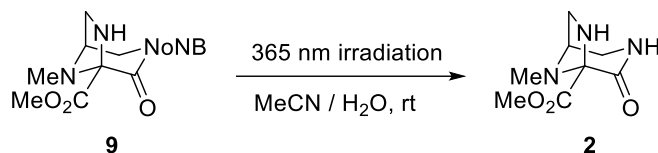
3.40 (d, $J = 15.4$ Hz, 1H), 3.04 (m, 1H), 2.54 (s, 3H), 1.35 (s, 18H); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) δ 155.8 (2C), 148.4, 147.9, 135.2, 134.0, 132.9, 132.1, 131.6, 130.7, 129.3, 129.1, 125.3, 124.9, 79.6, 79.4, 78.3, 55.2, 48.7, 48.6, 39.8, 28.6 (3C), 28.5(3C); HRMS (ESI) m/z 646.2177, calcd for $\text{C}_{27}\text{H}_{37}\text{N}_5\text{NaO}_{10}\text{S}$ $[\text{M}+\text{Na}]^+$ 646.2159.



Aminal **3**.

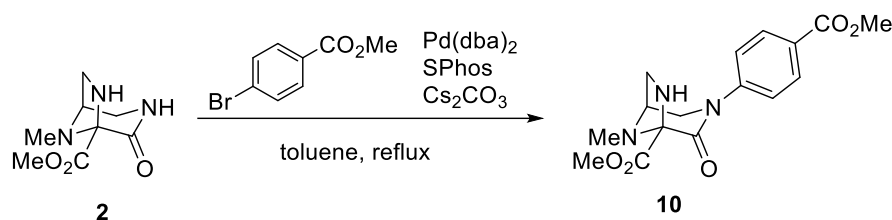
To a stirred solution of nosylamide **13** (69.0 mg, 110 μmol) in CH_2Cl_2 (2.8 mL) was added TFA (0.8 mL, 821 μmol) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was concentrated. The crude diamine TFA salt **13a** was used for the next reaction without further purification.

To a stirred solution of crude diamine TFA salt **13a** in DMF (0.8 mL) were added Na_2SO_4 (312 mg, 2.20 mmol) and dimethyl 2-oxomalonate (**5**) (16 μL , 143 μmol) at room temperature. The mixture was stirred at the same temperature for 2 d, diluted with saturated aqueous NaHCO_3 (2.0 mL), filtered, and extracted with CHCl_3 (3 \times 5 mL). The combined extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (7 g, hexane–acetone 5:1 \rightarrow 3:1) to give aminal **3** (61.0 mg, quant. in 2 steps) as a yellow oil.



Bicyclic core **2**.

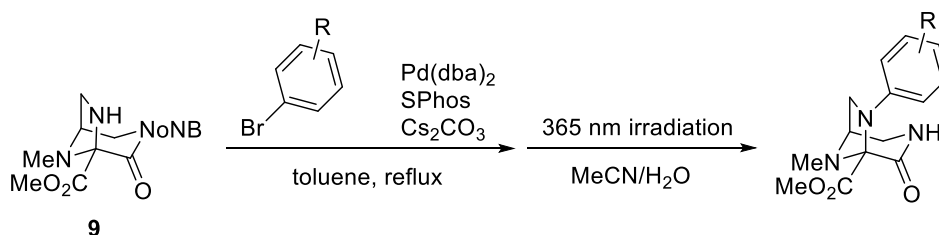
The solution of lactam **9** (20.1 mg, 60 μmol) in $\text{MeCN-H}_2\text{O}$ (4:1) (1.0 mL) was stirred at room temperature for 24 h under 365 irradiation and concentrated. The residual oil was purified by column chromatography on silica gel (3 g, $\text{CHCl}_3\text{-MeOH}$ 1:0 \rightarrow 10:1) to give bicyclic core **2** (8.8 mg, 73%) as a white solid; Mp 207.0–208.0 °C; $[\alpha]_D^{23} +30.4$ (c 0.22, CHCl_3); IR (CHCl_3) 3685, 3410, 3018, 1752, 1690, 1455, 1301, 1120 cm^{-1} ; ^1H NMR (400 MHz, CD_3OD) δ 3.85 (s, 3H), 3.59 (m, 1H), 3.52 (dd, $J = 11.5, 3.4$ Hz, 1H), 3.45 (dd, $J = 10.8, 6.4$ Hz, 1H), 3.02 (d, $J = 11.5$ Hz, 1H), 2.83 (d, $J = 10.8$ Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.4, 168.0, 88.3, 61.3, 53.2, 47.7, 47.0, 36.9; HRMS (ESI) m/z 222.0835, calcd for $\text{C}_8\text{H}_{13}\text{N}_3\text{NaO}_3$ $[\text{M}+\text{Na}]^+$ 222.0855.



Aplaminal analog 10.

To the mixture of bicyclic core **2** (8.8 mg, 44 μmol), methyl 4-bromobenzoate (33.1 mg, 154 μmol), Pd(dba)₂ (25.4 mg, 44 μmol), SPhos (18.1 mg, 44 μmol), and Cs₂CO₃ (144 mg, 440 μmol) was added degassed toluene (1.5 mL). The mixture was stirred at reflux for 24 h, filtered through a pad of Celite[®], and concentrated. The residual oil was purified by column chromatography on silica gel (2.5 g, CHCl₃-MeOH 1:0 \rightarrow 15:1) to give aplaminal analog **10** (9.6 mg, 65%) as a yellow solid; $[\alpha]_{\text{D}}^{23} +73.1$ (*c* 0.29, CHCl₃); IR (CHCl₃) 3358, 3021, 1752, 1719, 1681, 1604, 1510, 1437, 1282, 795, 760 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.04 (d, *J* = 8.9 Hz, 2H), 7.44 (d, *J* = 8.9 Hz, 2H), 4.15 (dd, *J* = 10.8, 3.7 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.68 (m, 1H), 3.58 (m, 1H), 3.36–3.33 (m, 2H), 3.08 (d, *J* = 10.3 Hz, 1H), 2.37 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.3, 166.5, 165.4, 145.1, 130.6 (2C), 128.1, 124.6 (2C), 87.7, 61.2, 55.1, 53.3, 52.3, 46.2, 37.3; HRMS (ESI) *m/z* 356.1271, calcd for C₁₆H₁₈N₃NaO₅ [M+Na]⁺ 356.1245.

General procedure for the aplaminal analogs 14, 16, and 17.



To the mixture of lactam **9** (ca. 20 μmol), bromide (3–5 eq), Pd(dba)₂ (1.0 eq), SPhos (2.0 eq), and Cs₂CO₃ (5–10 eq) was added degassed toluene (2.0 mL). The mixture was stirred at reflux for 24 h, filtered through a pad of Celite[®], and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, CHCl₃-MeOH) to give coupling compound.

The solution of crude coupling compound in MeCN/H₂O (6/1) (2.0 mL) was stirred at room temperature for 24 h under 365 irradiation and concentrated. The residual oil was purified by column chromatography on silica gel (CHCl₃-MeOH) and by HPLC (Develosil ODS-HG-5, 45% MeOH) to give aplaminal analog.

m-carbomethoxy analog 14.

¹H NMR (400 MHz, acetone-*d*₆) δ 7.48 (s, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.20 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.57 (brs, 1H), 4.29 (m, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.77 (m, 1H), 3.65 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.30 (d, *J* = 8.6 Hz, 1H), 3.22 (m, 1H), 2.47 (s, 3H); HRMS (ESI) *m/z* 356.1222, calcd for C₁₆H₁₉N₃NaO₅ [M+Na]⁺ 356.1222.

***p*-Chloro analog 16.**

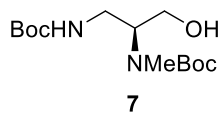
¹H NMR (400 MHz, acetone-*d*₆) δ 7.09 (dd, *J* = 9.7, 2.2 Hz, 2H), 6.83 (dd, *J* = 9.7, 2.2 Hz, 2H), 6.58 (brs, 1H), 4.23 (ddd, *J* = 8.6, 3.7, 1.4 Hz, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 3.64 (m, 1H), 3.24 (d, *J* = 8.6 Hz, 1H), 3.21 (m, 1H), 2.45 (s, 3H); HRMS (ESI) *m/z* 332.0778, calcd for C₁₄H₁₆ClN₃NaO₃ [M+Na]⁺ 332.0743.

***p*-Nitrile analog 17.**

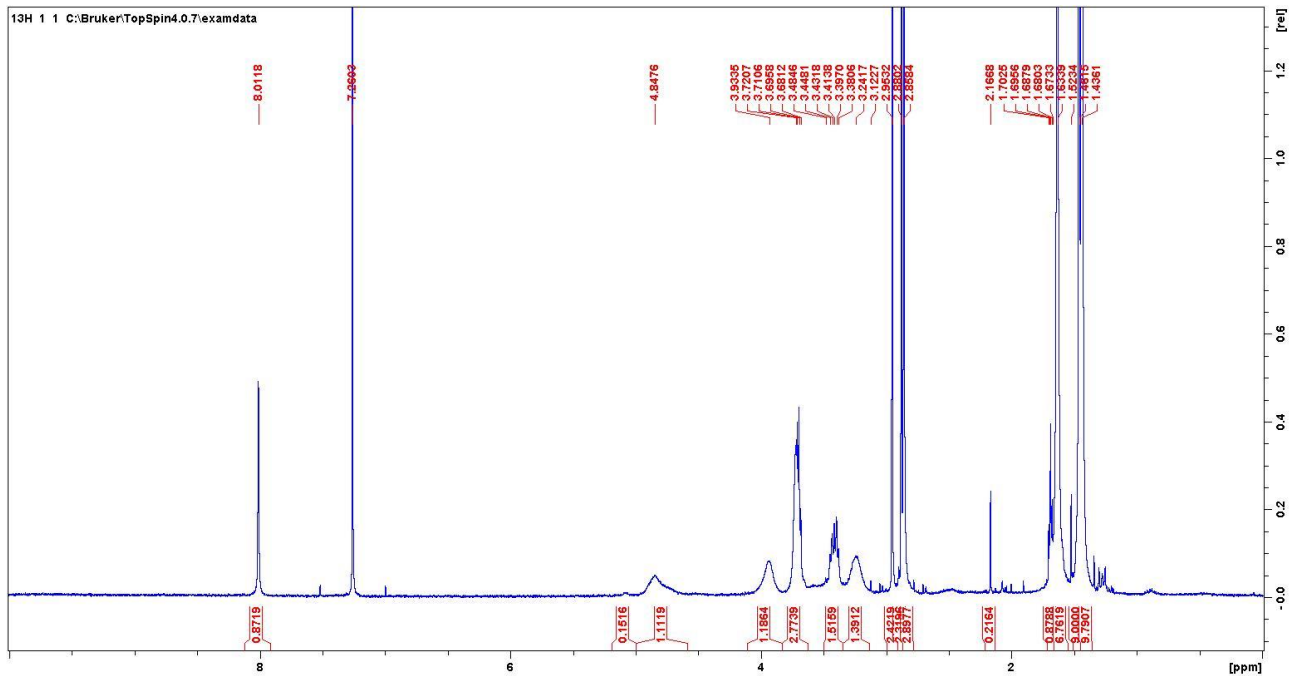
¹H NMR (400 MHz, acetone-*d*₆) δ 7.46 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8, 2H), 6.67 (brs, 1H), 4.28 (m, 1H), 3.81 (s, 3H), 3.70–3.67 (m, 2H), 3.38 (d, *J* = 9.2 Hz, 1H), 3.26 (d, *J* = 10.2 Hz, 1H), 2.46 (s, 3H); HRMS (ESI) *m/z* 323.1120, calcd for C₁₅H₁₆N₄NaO₃ [M+Na]⁺ 323.1154.

Cytotoxic activity

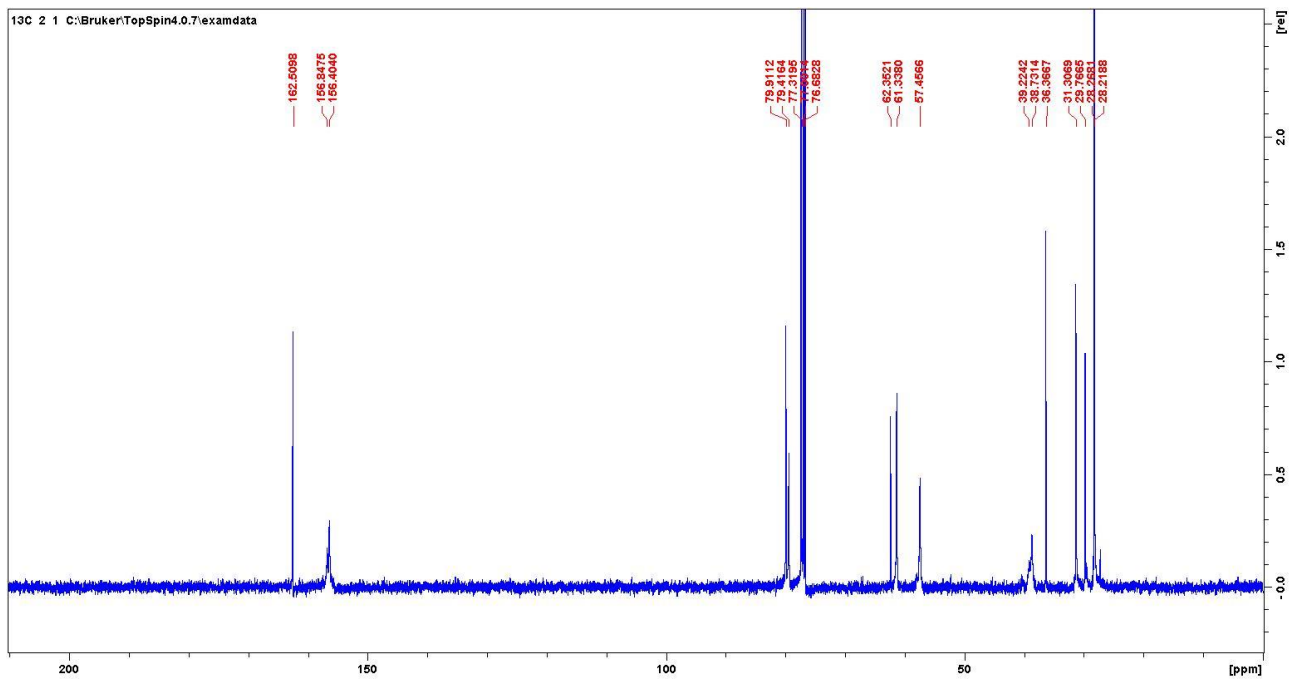
Stock cultures of HeLa S3 cells were maintained in Dulbecco's Modified Eagle Medium containing 10% fetal bovine serum, 100 µg/mL of penicillin, and 100 µg/mL streptomycin at 37 °C under 5% CO₂. For the purpose of the experiment, 5×10³ cells suspended in 100 µL of medium per well were plated in 96-well plate, and incubated at 37 °C under 5% CO₂. After incubation for 24 h, a solution of compound in DMSO (1 µL, concentration: 0.001, 0.01, 0.1, 1, 10 mM, respectively) was added to the above-mentioned well, resulting in various concentrations of the compound (0.01, 0.1, 1, 10, 100 µM) or solvent control (1% DMSO). After incubation for 96 h under the same conditions, 5 µL of WST-8 reagent solution was added to the cell culture, and the cell culture was further incubated for 2 h. Colorimetric determination of WST-8 was conducted at 450 nm with an optical reference wavelength at 595 nm using a microplate reader. The absorbance obtained upon the addition of the vehicle was considered as 100%. Data are expressed from the dose-response curve at three independent experiments. The cytotoxic effects of each compound were obtained as IC₅₀ values calculated by probit analysis using the PriProbit 1.63 software.

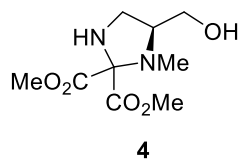


¹H NMR (400 MHz, CDCl₃)

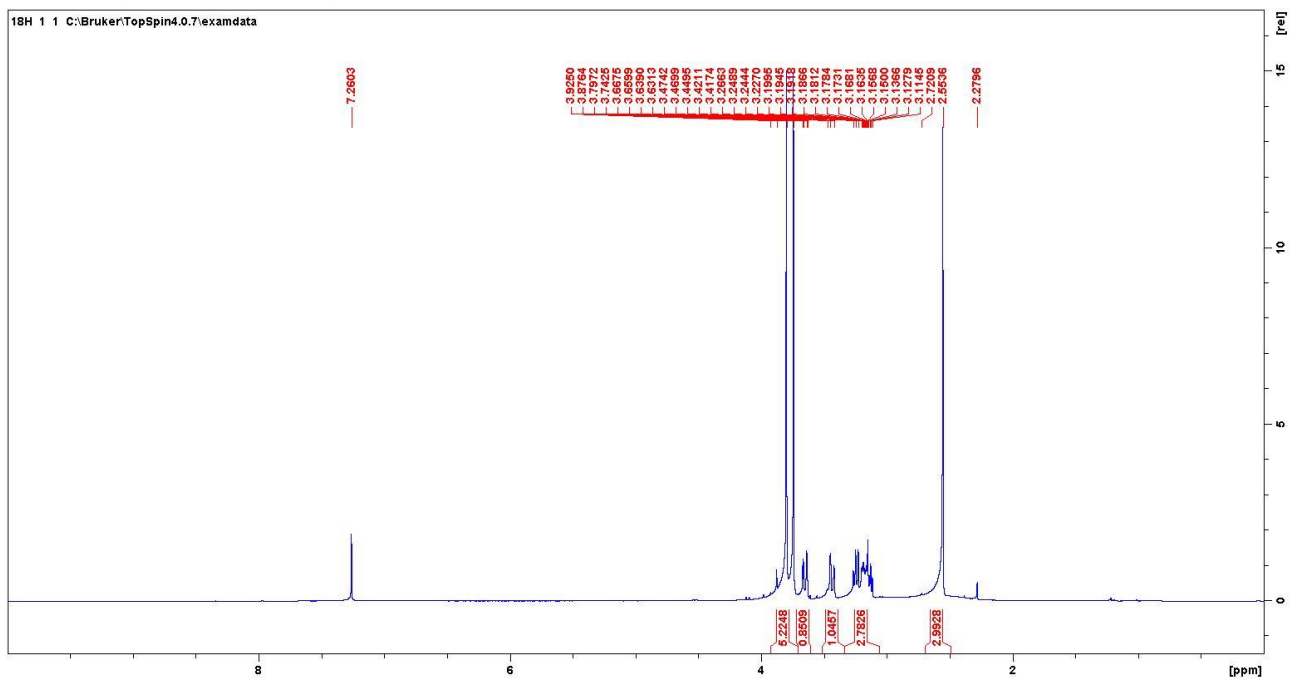


¹³C NMR (100 MHz, CDCl₃)

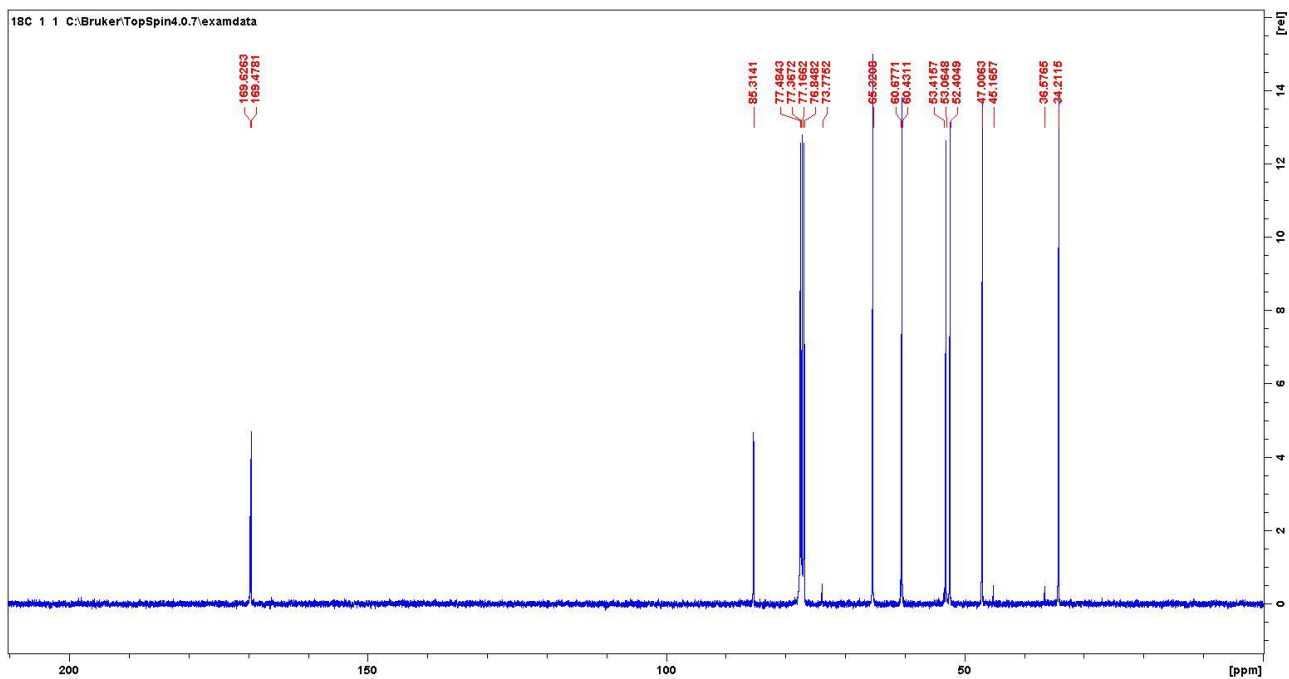


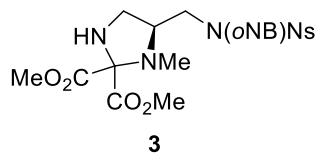


¹H NMR (400 MHz, CDCl₃)

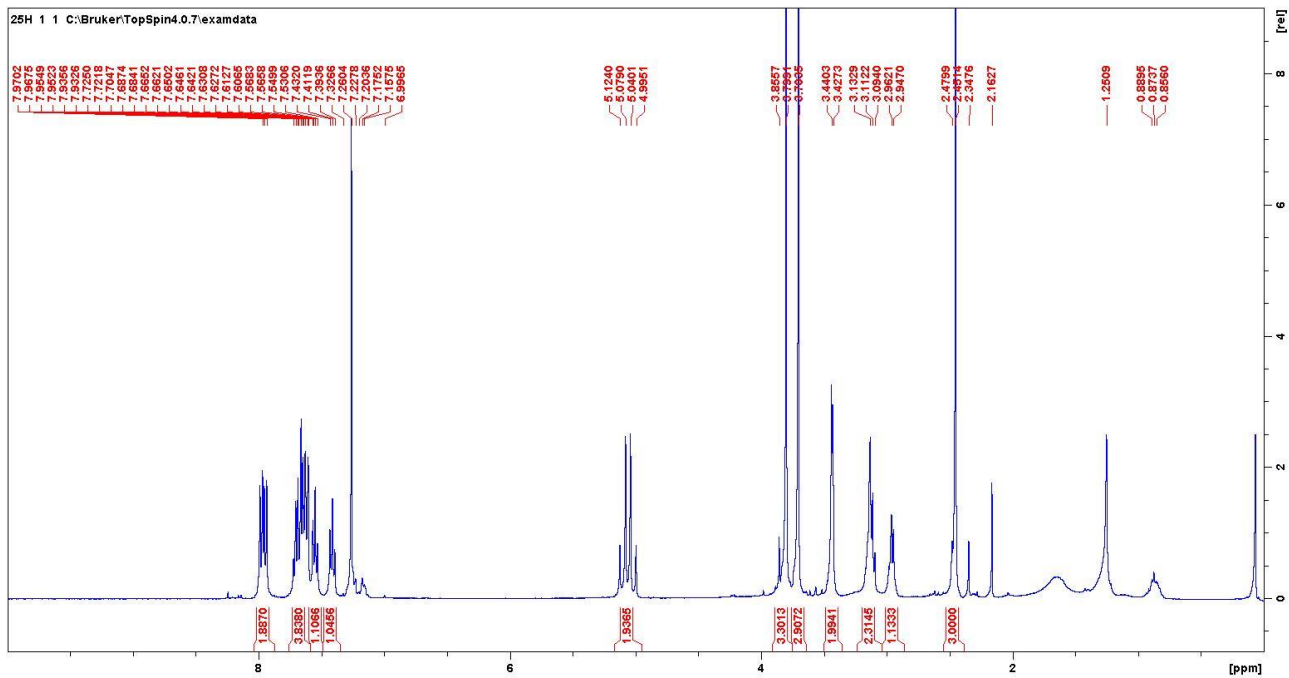


¹³C NMR (100 MHz, CDCl₃)

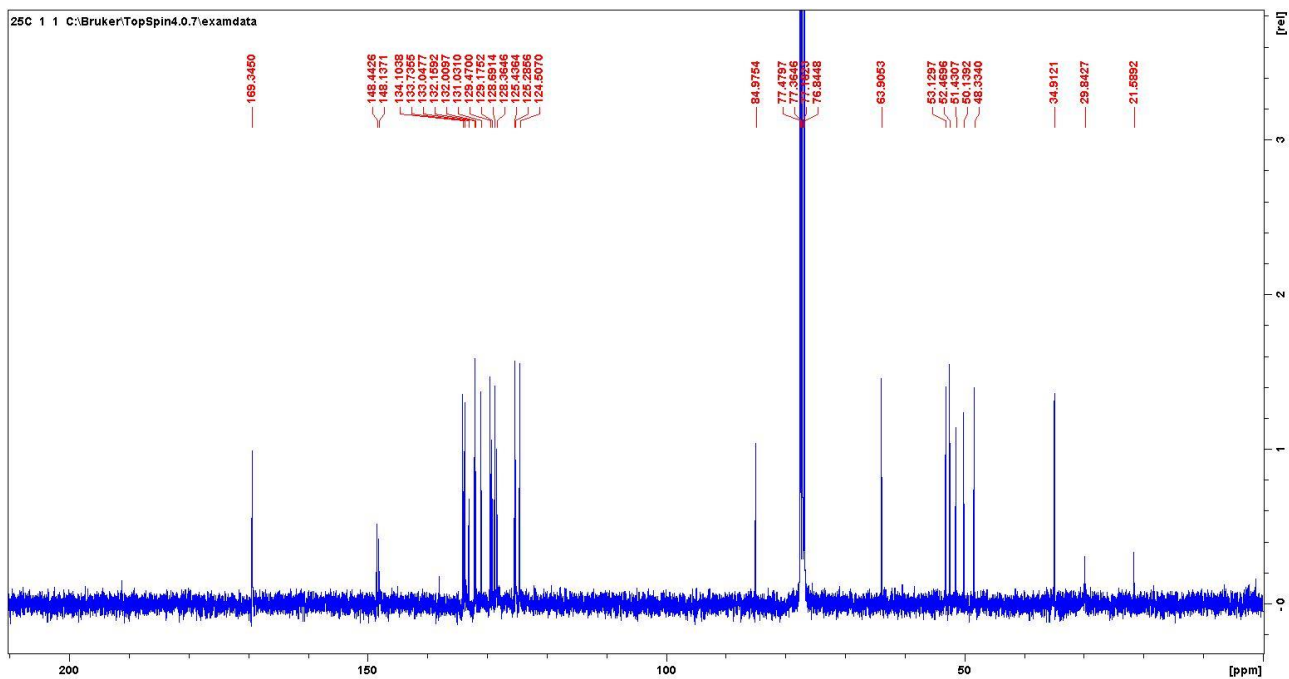


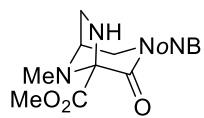


¹H NMR (400 MHz, CDCl₃)



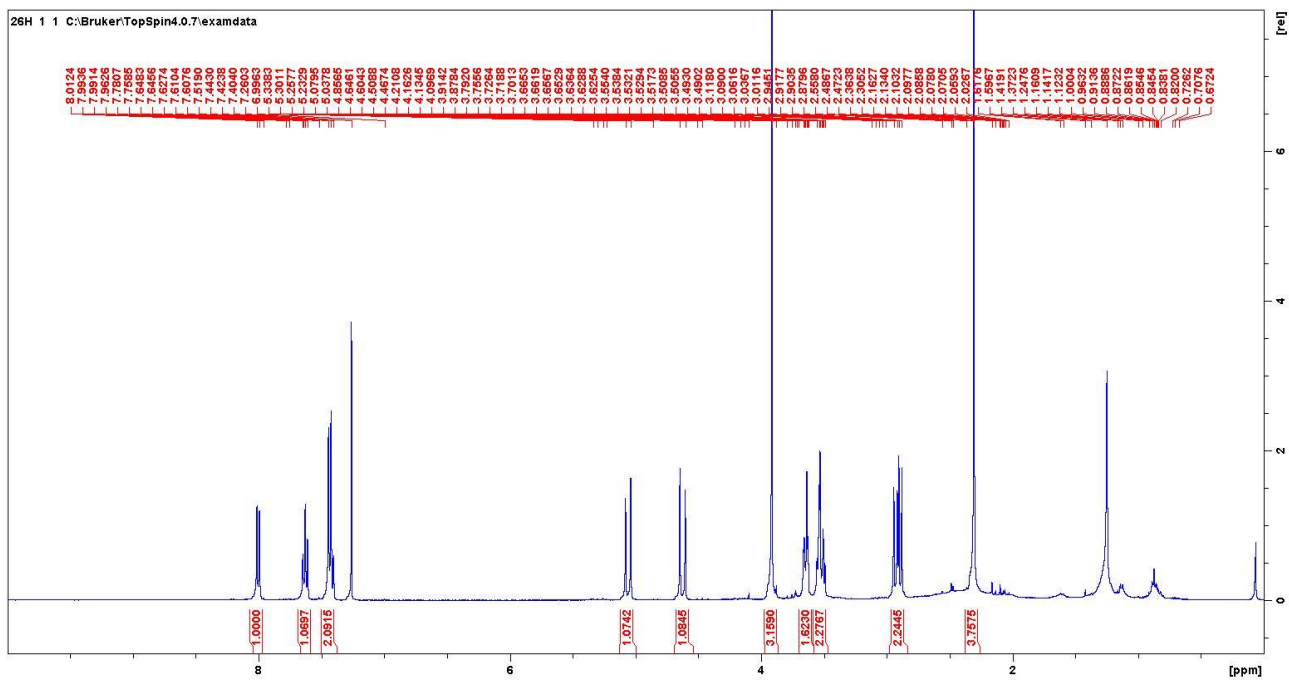
¹³C NMR (100 MHz, CDCl₃)



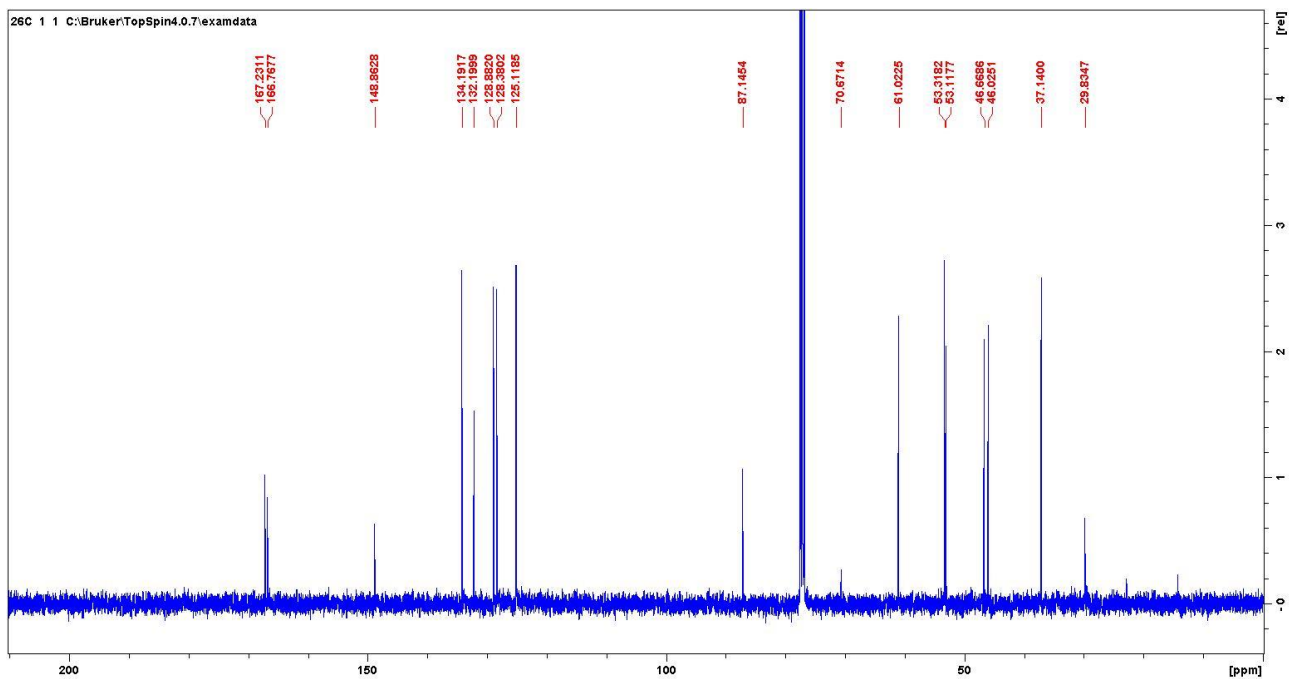


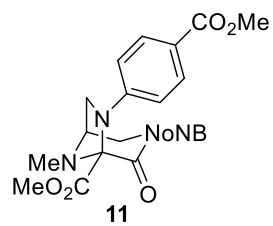
9

¹H NMR (400 MHz, CDCl₃)

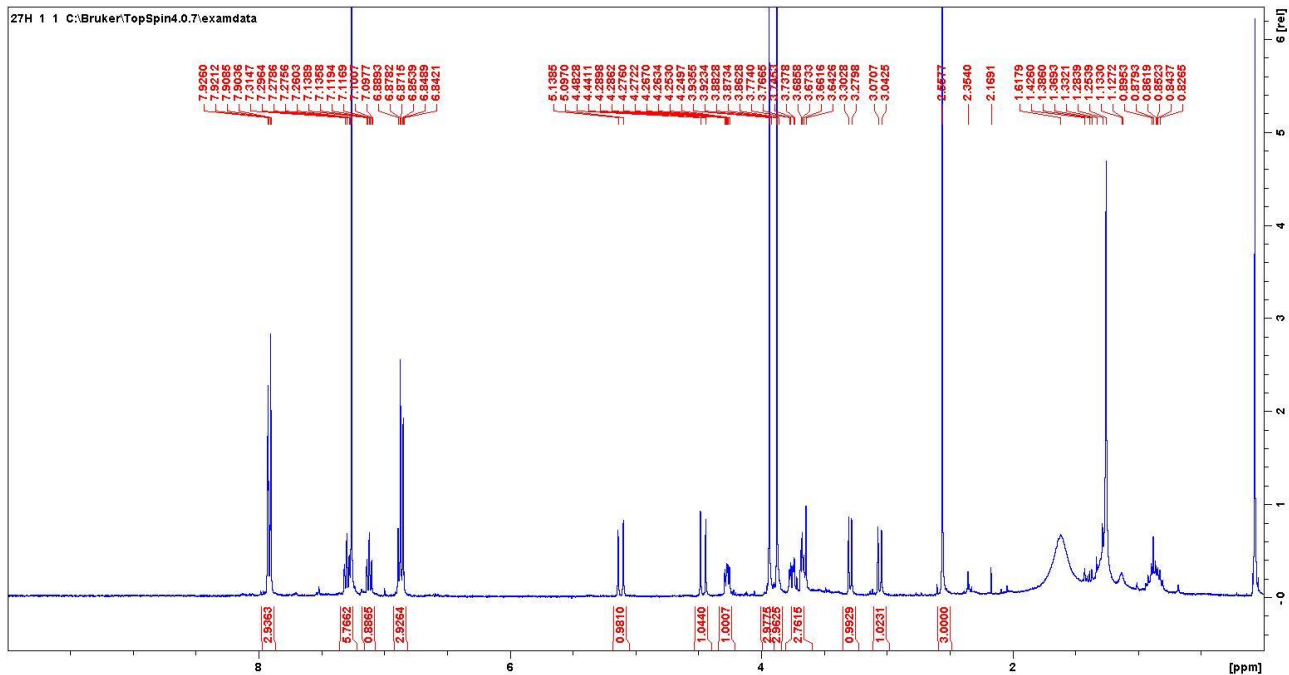


¹³C NMR (100 MHz, CDCl₃)

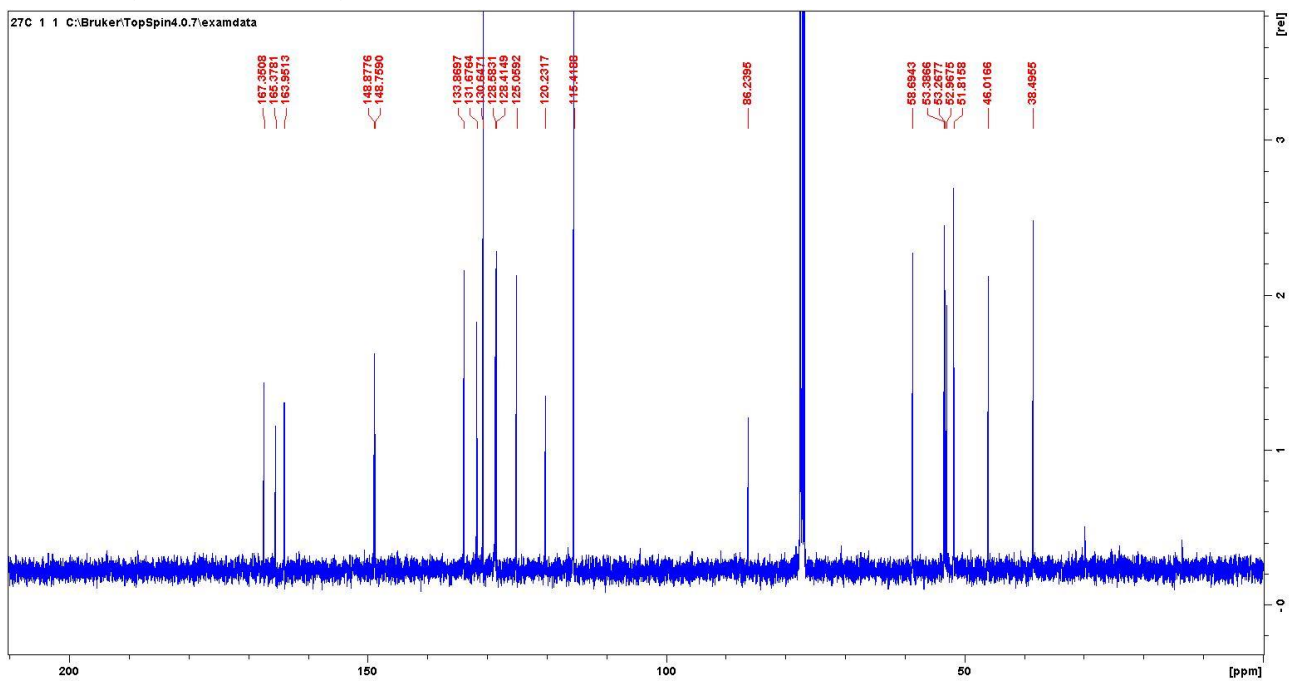


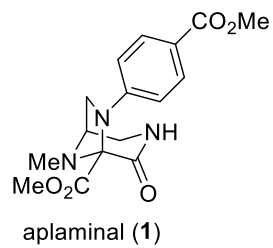


¹H NMR (400 MHz, CDCl₃)

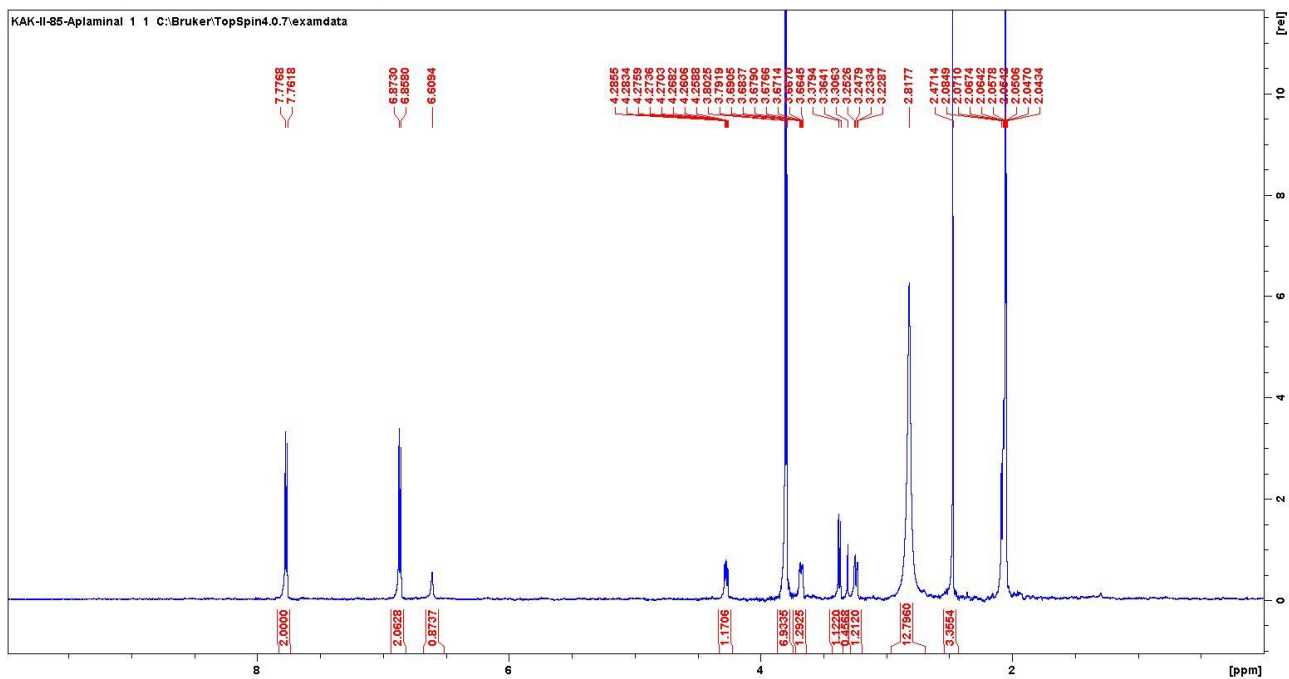


¹³C NMR (100 MHz, CDCl₃)

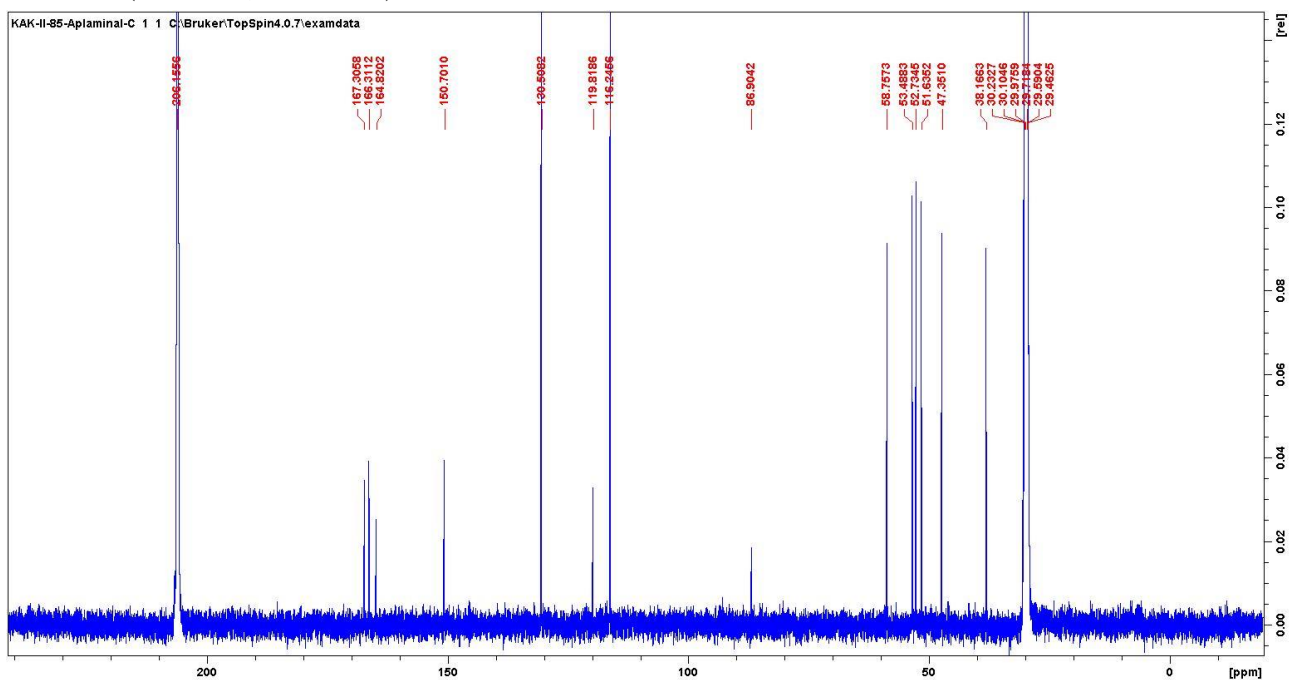


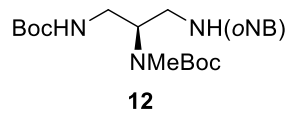


¹H NMR (600 MHz, acetone-*d*₆)

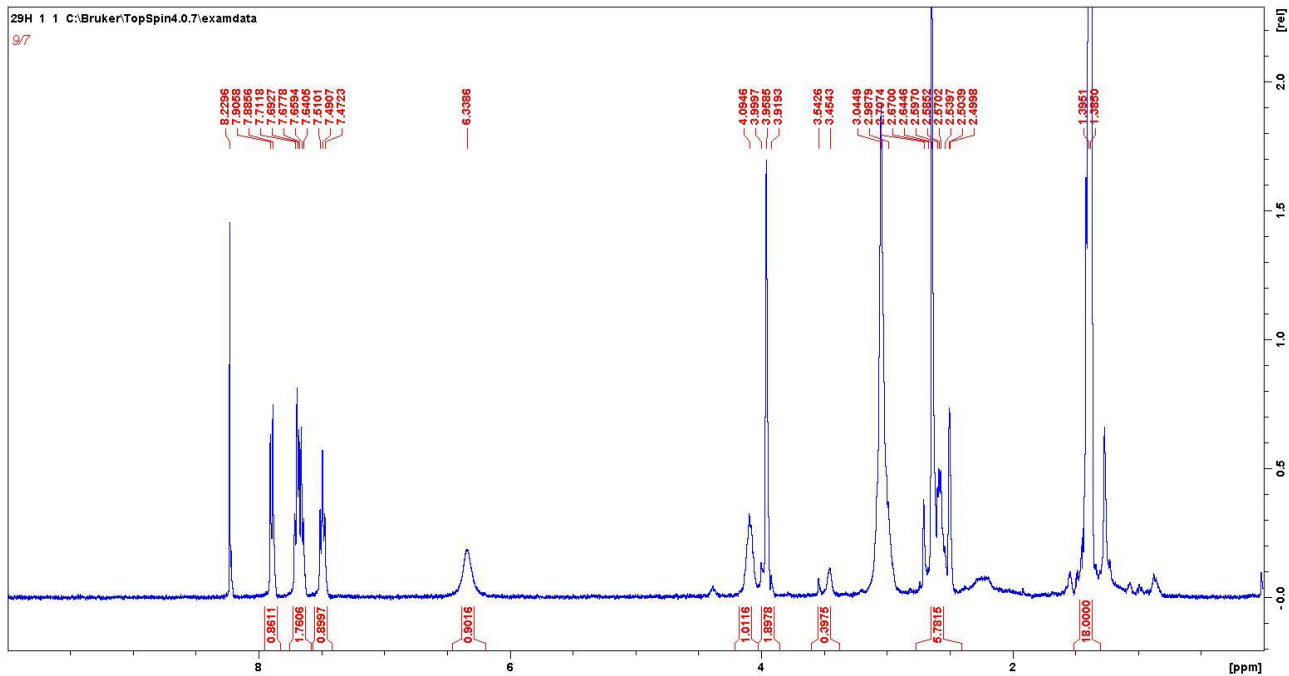


¹³C NMR (151 MHz, acetone-*d*₆)

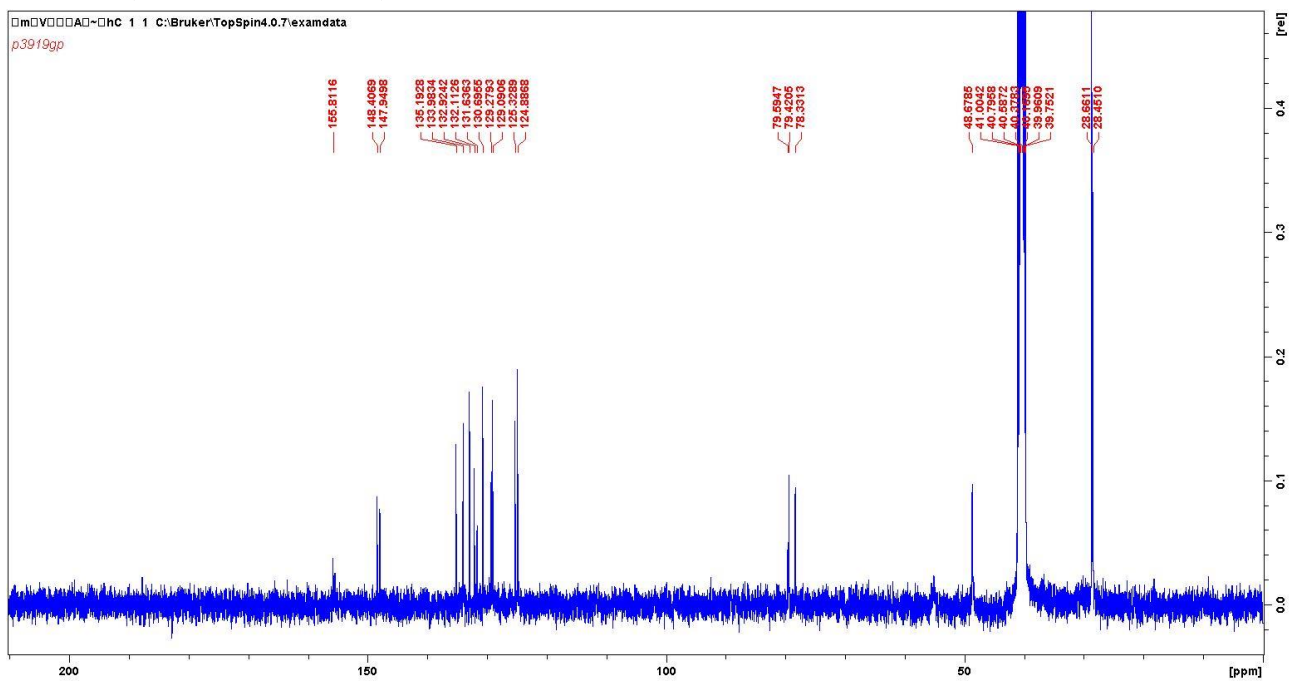


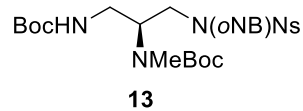


¹H NMR (400 MHz, DMSO-*d*₆)

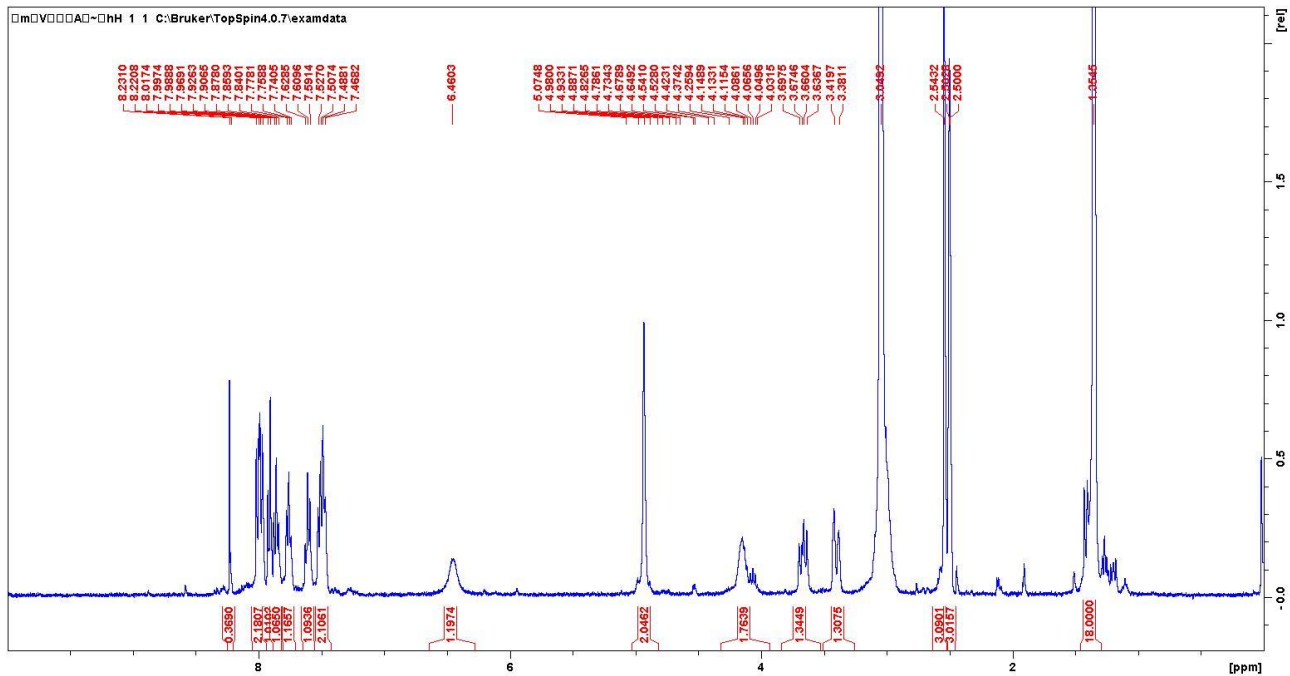


¹³C NMR (100 MHz, DMSO-*d*₆)

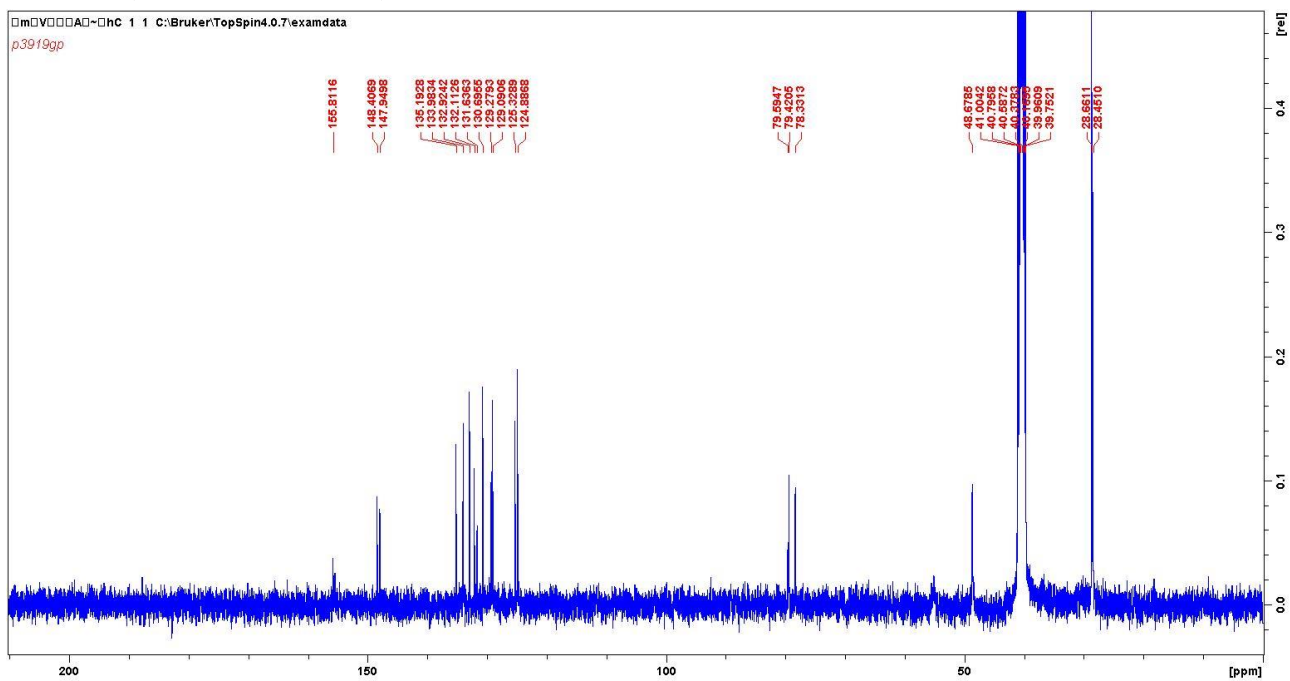


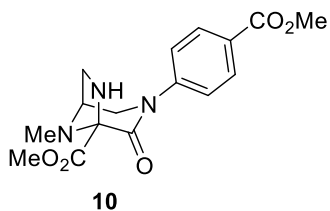


¹H NMR (400 MHz, DMSO-*d*₆)

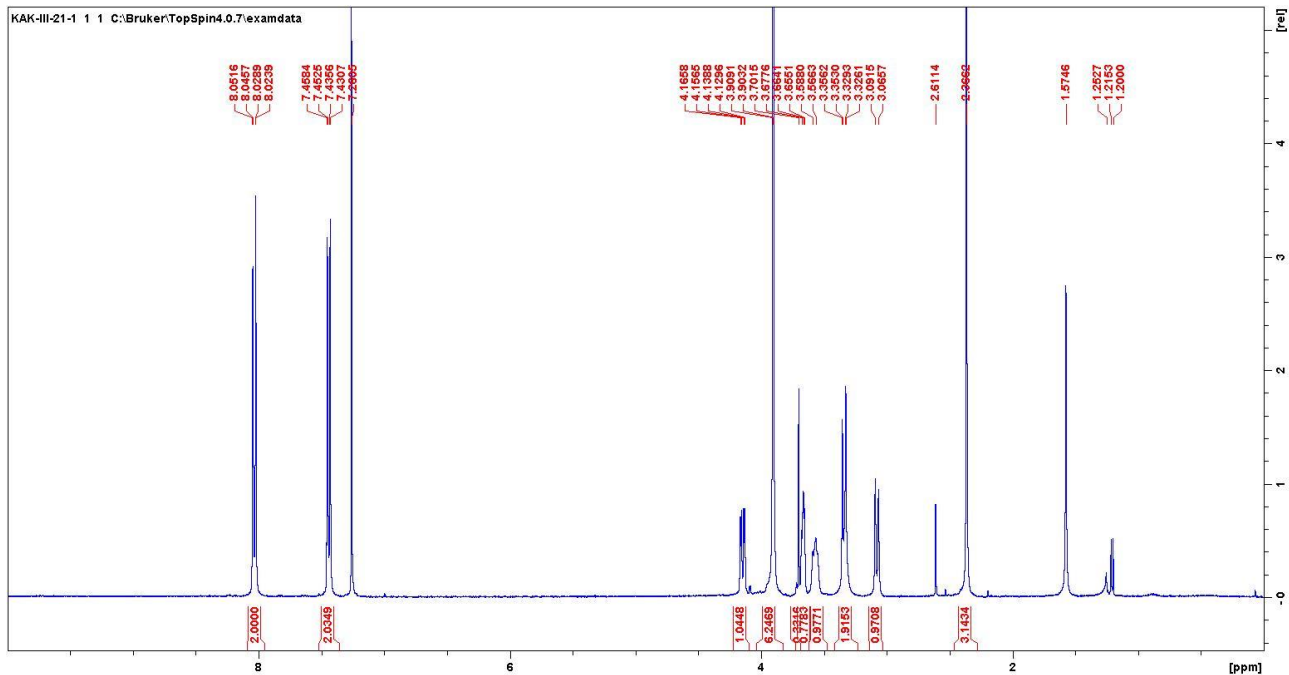


¹³C NMR (100 MHz, DMSO-*d*₆)

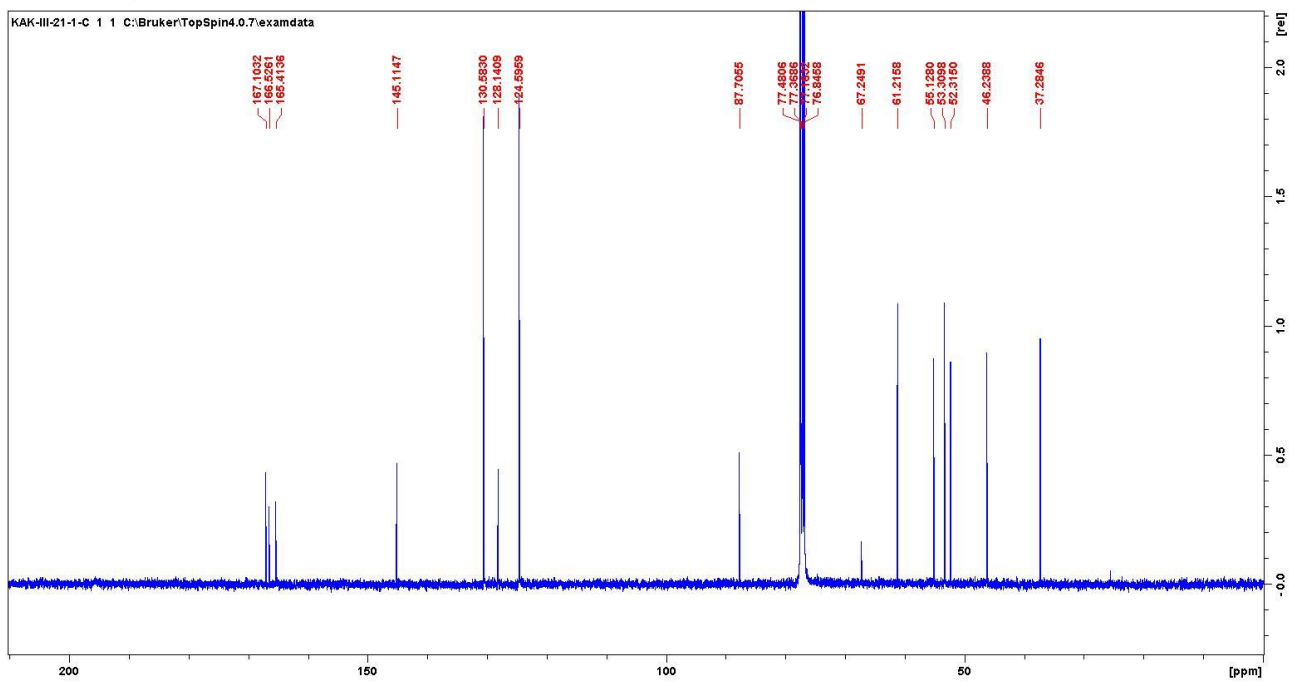


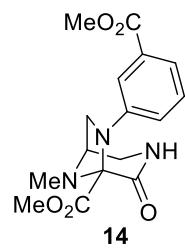


¹H NMR (400 MHz, CDCl₃)

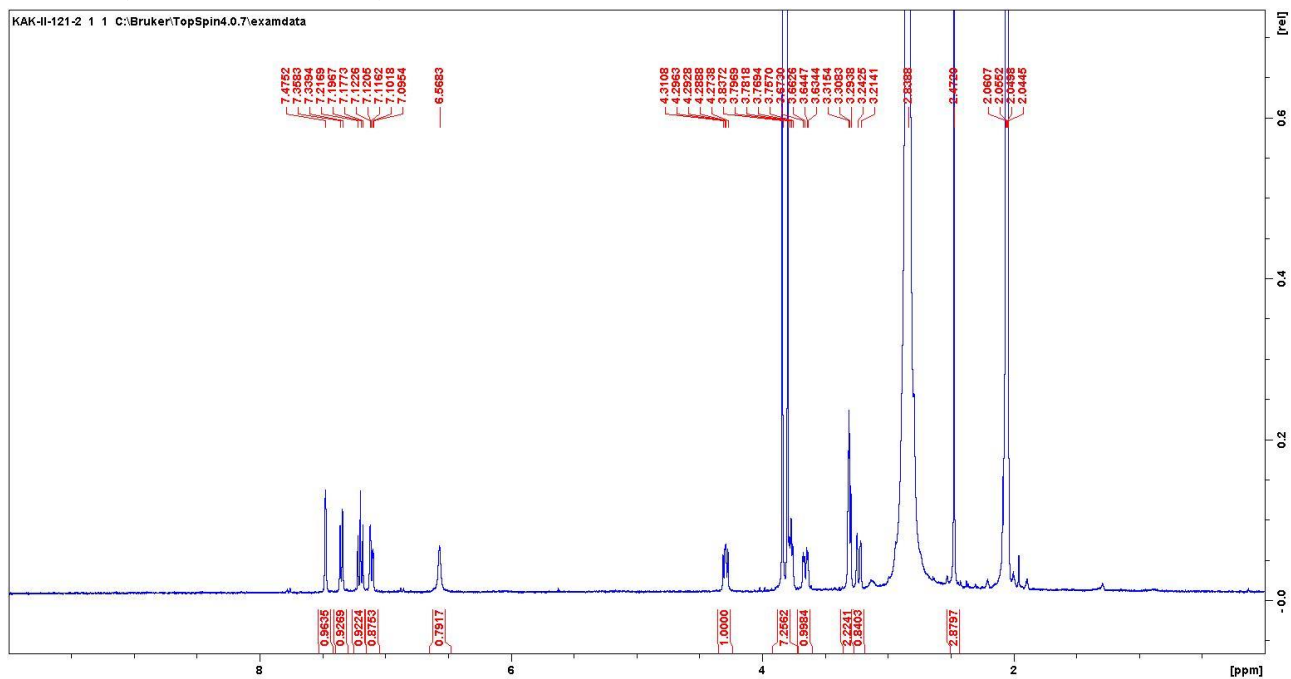


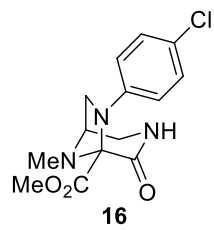
¹³C NMR (100 MHz, CDCl₃)



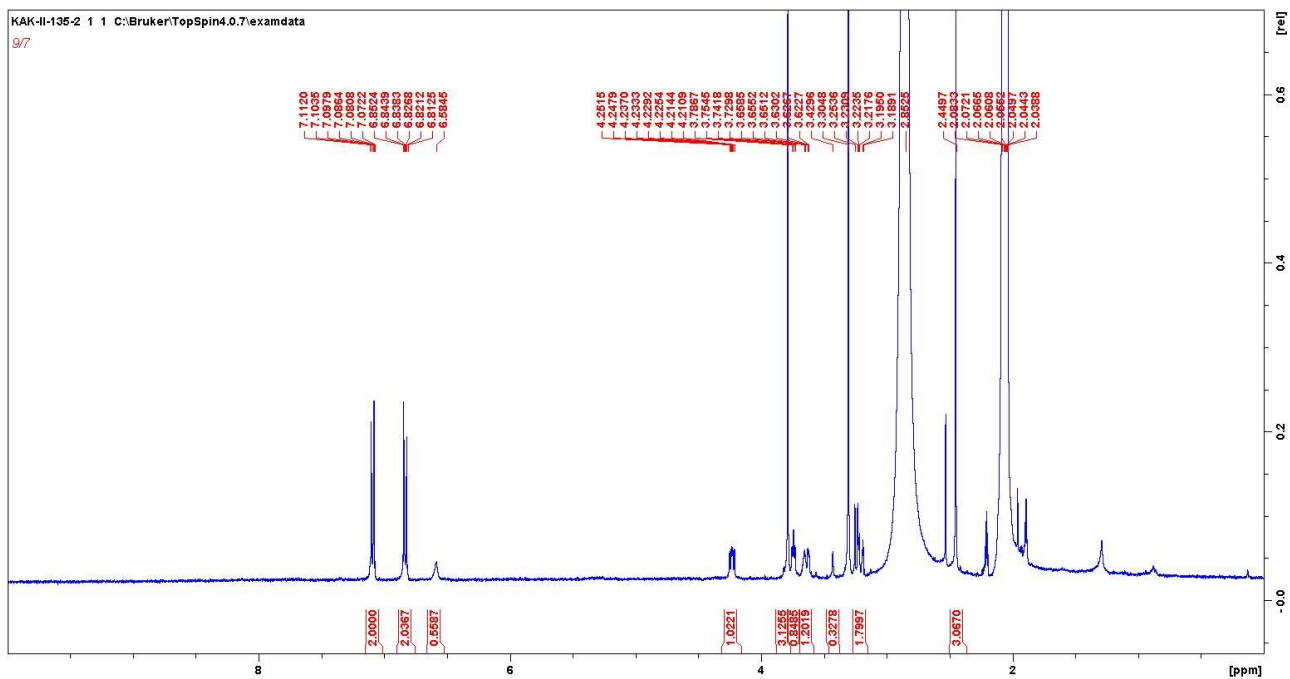


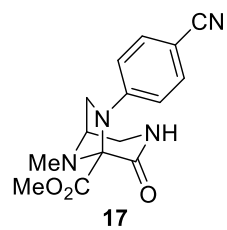
¹H NMR (400 MHz, acetone-*d*₆)





¹H NMR (400 MHz, acetone-*d*₆)





¹H NMR (400 MHz, acetone-*d*₆)

