Asymmetric formal synthesis of (-)-tetrazomine

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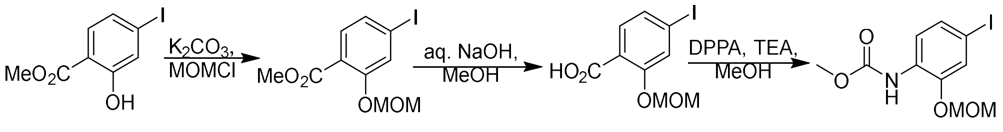
Content

1. General Information

NMR spectra were recorded on a Bruke NMR DRX–400 spectrometer operating for ^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz, using TMS as internal standard. Chemical shifts were given relative to TMS (0.00 ppm), $CDCl_3$ (7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR), CD_3OD (3.20 ppm for ^{1}H NMR, 47.63 ppm for ^{13}C NMR). The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd =doublet of doublet, m = multiplet. Coupling constants, *J*, were reported in hertz (Hz). Optical rotations were measured using a 1 mL cell with a 1 dm path length on Perkin Elmer 341 at 589 nm at 20 ^{o}C Mass spectroscopy data of the products were collected on an HRMS-TOF instrument using ESI ionization. HPLC analyses were performed on Shimadzu instrument using a chiral stationary phase column (Daicel Co.CHIRALPAK).

2. Experimental Section

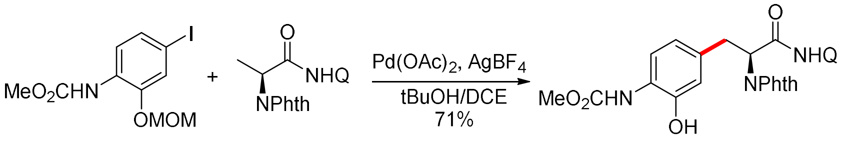


15 **S1** **S2** **16**

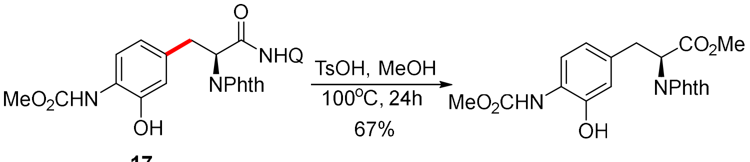
To a solution of **15** (12.0 g, 43.2 mmol) in acetone (100 mL) were added K_2CO_3 (12.0 g, 87.0 mmol) and MOMCl (6.6 mL, 87.0 mmol) at room temperature. The mixture was stirred overnight, water was added for quenching the reaction. The resultant mixture was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was used for the next step without further purification.

To a solution of the residue in MeOH (50 mL) at room temperature was added aq NaOH (3.5 g NaOH in 50 mL H_2O), After stirring at the same temperature for 7 h, the MeOH was evaporated. The pH value of the residue was adjusted to about 5 with 1 M aq HCl. The resultant mixture was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The crude acid **S2** was used for the next step without further purification.

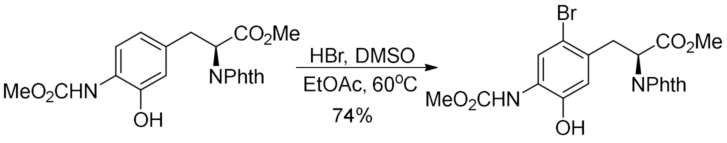
To a suspension of the crude acid **S2** in toluene (150 mL) was added Et_3N (18.2 mL, 130 mmol) and DPPA (Diphenyl Phosphorazidate, 14 mL, 65.0 mmol) at 0 °C, the mixture was then heated at 90 °C for 3 h. After cooled down to room temperature, MeOH (17.2 mL, 423 mmol) was injected. The mixture was heated at 60°C overnight, then cooled dowm, water was added. The resultant mixture was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **16** (9.42 g, 27.9 mmol, 65% for three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 1.8 Hz, 1H), 7.36 (dd, J = 8.6, 1.9 Hz, 1H), 7.22 (s, 1H), 5.22 (s, 2H), 3.82 (s, 3H), 3.51 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 153.6, 145.9, 131.4, 128.2, 122.8, 119.9, 95.3, 84.9, 56.5, 52.4; HRMS (ESI): calcd. for [$C_{10}H_{12}$ INO_4+Na]$^+$: 359.9703, found: 359.9702.


16 **11** **17**

A 250 mL flask was charged with **16** (4.05 g, 12.0 mmol), **11** (3.45 g, 10.0 mmol), $Pd(OAc)_2$ (337 mg, 1.5 mmol) and $AgBF_4$ (2.86 g, 14.7 mmol) in *t*BuOH/DCE (30 mL/15 mL). The flask was evacuated under high vacuum, backfilled with nitrogen, and capped with a Teflon septa. The flask was heated at 80 °C for 20 h, and cooled down to room temperature, Et_3N (4 mL) was added and the mixture stirred at room temperature for 2 h, the mixture was filtered through a pad of celite (eluent DCM) and the filtrate was extracted with DCM for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **17** (3.62 g, 7.1 mmol, 71%) as yellowish foam. $[\alpha]_D^{20}$ = -56.5 (c 0.375, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 10.31 (s, 1H), 8.68 (dd, *J* = 6.0, 2.8 Hz, 1H), 8.59 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.07 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.80-7.73 (m, 2H), 7.67-7.61 (m, 2H), 7.54-7.43 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.35 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.02 (s, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.76 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.41 (t, *J* = 8.3 Hz, 1H), 3.72 (s, 3H), 3.69 (d, *J* = 8.3 Hz, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ: 166.7, 155.1, 148.4, 146.3, 138.4, 136.2, 134.2, 133.7, 132.9, 131.5, 127.8, 127.2, 124.7, 123.6, 122.2, 121.6, 121.2, 120.4, 117.3, 117.0, 52.7, 34.2; HRMS (ESI): calcd. for [$C_{28}H_{22}N_4O_6$+Na]$^+$: 533.1432, found: 533.1429.

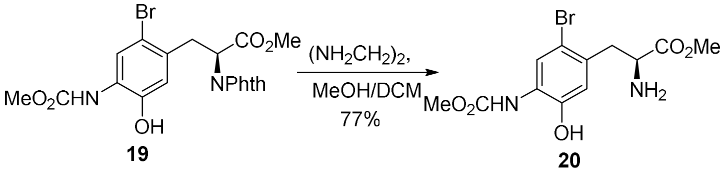

17 **18**

A 1 L flask was charged with **17** (4.12 g, 8.07mmol) and TsOH•H_2O (6.12 g, 32.2 mmol) in MeOH (100 mL). The flask was evacuated under high vacuum, backfilled with nitrogen, and closed with a Teflon septa. The flask was heated at 100 °C for 24 h, and cooled down to room temperature, saturated aq. $NaHCO_3$ was added, and MeOH was evaporated. The mixture was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **18** (2.16 g, 5.42 mmol, 67%) as white foam. $[\alpha]_D^{20}$ = -157.8 (c 0.875, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.78-7.73 (m, 2H), 7.70-7.64 (m, 2H), 7.23 (d, *J* = 8.1 Hz, 1H), 6.93 (s, 1H), 6.73 (d, *J* = 2.1 Hz, 1H), 6.65 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.12 (dd, *J* = 11.0, 5.4 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.54-3.39 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.5, 167.7, 155.4, 146.5, 134.3, 133.6, 131.6, 124.5, 123.7, 121.3, 120.8, 117.8, 53.3, 53.1, 53.0, 34.1; HRMS (ESI): calcd. for $[C_{20}H_{18}N_2O_7 + Na]^+$: 421.1006, found: 421.1008.



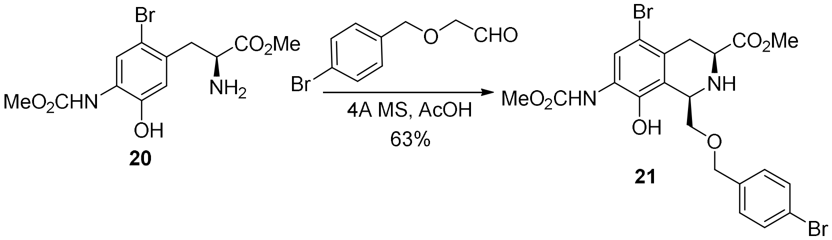
18 **19**

To a solution of **18** (6.4 g, 16.1mmol) in EtOAc (80 mL) at 60 °C were added HBr (3.12 mL, 33% w/w HBr in HOAc) and DMSO (1.26 mL, 19.2 mmol) sequentially. The mixture was stirred at 60 °C for 10h, then cooled down to room temperature. Saturated aq. $NaHCO_3$ was added, and the solution was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **19** (5.67 g, 11.9 mmol, 74%) as white solid. $[\alpha]_D^{20}$ = -174.9 (c 0.575, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.79-7.73 (m, 2H), 7.71-7.65 (m, 2H), 7.61 (s, 1H), 6.91 (s, 1H), 6.70 (s, 1H), 5.32 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.66 (dd, *J* = 14.3, 4.6 Hz, 1H), 3.48 (dd, *J* = 14.3, 11.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.4, 167.7, 155.1, 145.6, 134.4, 132.2, 131.6, 126.0, 124.3, 123.7,119.7, 114.7, 53.19, 53.17, 51.6, 34.9; HRMS (ESI): calcd. for $[C_{20}H_{17}BrN_2O_7 +Na]^+$: 499.0111, found: 499.0113.

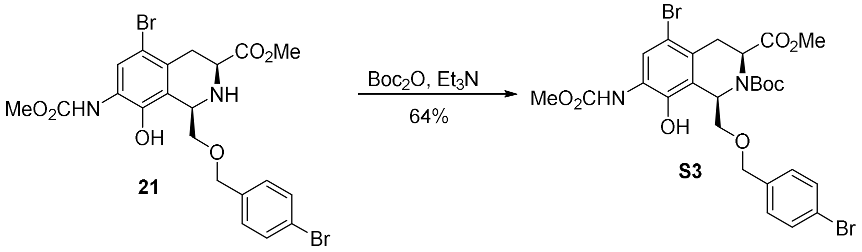


To a solution of **19** (5.6 g, 11.7 mmol) in MeOH/DCM (40mL/40mL) was added ethylenediamine (3.9 mL, 58.5 mmol). The solution was stirred at room temperature for 3h. The solvent was evaporated, and the residue was purified by silica gel column chromatography to afford **20** (3.13 g, 9.02 mmol, 77%) as yellowish foam.

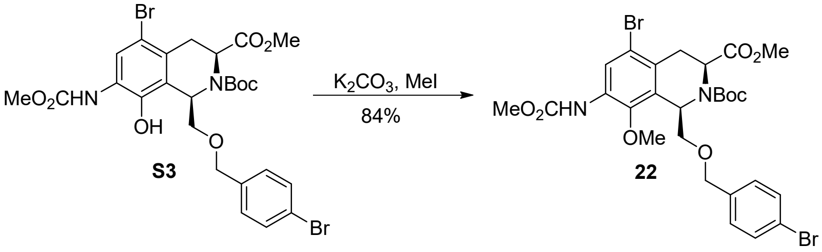
$[\alpha]_D^{20}$ = -18.7 (c 0.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.12 (s, 1H), 6.50 (s, 1H), 4.46 (brs, 3H), 3.90 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.27 (dd, *J* = 13.9, 4.2 Hz, 1H), 2.66 (dd, *J* = 13.9, 10.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 154.2, 145.3, 129.9, 127.2, 122.6, 117.5, 113.7, 53.8, 52.7, 52.6, 39.7; HRMS (ESI): calcd. for $[C_{12}H_{15}BrN_2O_5+Na]^+$: 369.0057, found: 369.0059.



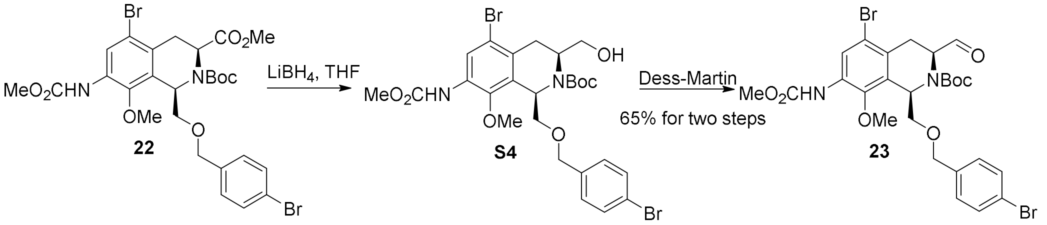
To a solution of **20** (2.75 g, 7.92 mmol) in anhydrous DCM (70 mL) were added 2-((4-bromobenzyl)oxy)acetaldehyde (2.0 g, 8.73 mmol), AcOH(0.50 mL, 8.75 mmol) and 4Å molecular sieve. The mixture was stirred at room temperature overnight. Saturated aq. $NaHCO_3$ was added, the mixture was filtered and the filtrate was extracted with DCM for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **21** (2.77 g, 4.96 mmol, 63%) as yellow solid. $[\alpha]_D^{20}$ = -22.0 (c 0.255, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 7.54-7.46 (m, 2H), 7.22 (s, 1H), 7.19 -7.12 (m, 2H), 4.65-4.45 (m, 3H), 3.81-3.66 (m, 7H), 3.64 (t, *J* = 8.8 Hz, 1H), 3.53 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.23 (dd, *J* = 16.0, 3.2 Hz, 1H), 2.60 (dd, *J* = 16.0, 3.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.0, 154.3, 142.7, 135.0, 132.0, 129.9, 129.0, 127.2, 125.9, 122.7, 121.2, 115.5, 77.1, 73.4, 54.6, 53.3, 52.7, 52.5, 33.8; HRMS (ESI): calcd. for [$C_{21}H_{22}Br_2N_2O_6$+Na]$^+$: 578.9737, found: 578.9739.



To a solution of **21** (2.40 g, 4.30 mmol) in DCM (80 mL) were added Boc_2O (1.06 mL, 4.61 mmol) and Et_3N (1.12 mL, 7.98 mmol) at room temperature. The mixture was stirred for 8h, water was added for quenching the reaction. The resultant mixture was extracted with DCM for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **S3** (1.81 g, 2.75 mmol, 64%) as white foam. $[\alpha]_D^{20}$ = +14.5 (c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: (the compound existed as a mixture of rotamers) 8.24 (brs, 1H of major rotamer), 8.20 (brs, 1H of minor rotamer), 7.70 (s, 1H of minor rotamer), 7.47(d, J = 8.3Hz, 1H of minor rotamer), 7.44 (d, *J* = 8.2 Hz, 2H of major rotamer), 7.30 (s, 1H of major rotamer), 7.22 (s, 1H of both rotamers), 7.09 (d, *J* = 8.0 Hz, 2H of minor rotamer), 7.07 (d, *J* = 8.2 Hz, 2H of major rotamer), 5.61(dd, *J* = 10.7, 3.6 Hz, 1H of major rotamer), 5.40(dd, *J* = 10.1, 3.1 Hz, 1H of minor rotamer), 4.59-4.39 (m, 2H of major rotamer, 3H of minor rotamer), 4.32 (dd, *J* = 11.7, 6.2 Hz, 1H of major rotamer), 4.10 (dd, *J* = 7.9, 3.7 Hz, 1H of major rotamer), 4.03(dd, *J* = 8.2, 3.3Hz, 1H of minor rotamer), 3.79(s, 3H of minor rotamer), 3.78 (s, 6H of major rotamer), 3.76 (s, 3H of minor rotamer), 3.63 -3.50 (m, 2H of major rotamer, 1H of minor rotamer), 3.46(dd, *J* = 8.2, 3.3Hz, 1H of minor rotamer), 2.78 (dd, *J* = 15.9, 10.0 Hz, 1H of minor rotamer), 2.63 (dd, *J* = 15.4, 11.8 Hz, 1H of major rotamer), 1.47 (s, 9H of minor rotamer), 1.41 (s, 9H of major rotamer); ^{13}C NMR (101 MHz, $CDCl_3$) (the compound existed as a mixture of rotamers and the major rotamer was assigned) δ: 173.7, 154.4, 154.0, 141.2, 135.6, 131.9, 129.6, 128.2, 125.5, 125.1, 122.4, 121.0, 114.1, 81.8, 73.9, 73.3, 55.2, 52.6, 52.5, 49.6, 29.9, 28.3; HRMS (ESI): calcd. for $[C_{26}H_{30}Br_2N_2O_8+Na]^+$: 679.0261, found: 679.0260.

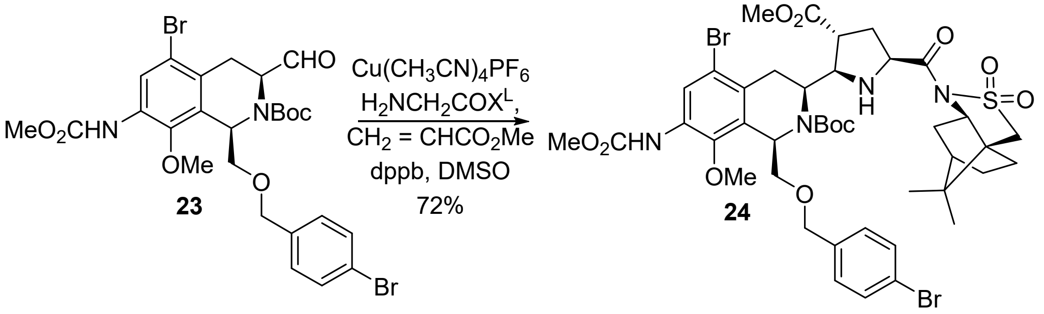


To a solution of **S3** (1.81 g, 2.75 mmol) in acetone (40 mL) were added K_2CO_3(0.57 g, 4.13 mmol) and MeI (221 μL, 3.55 mmol) at room temperature. The mixture was stirred at the same temperature for 10h, water was added for quenching the reaction. The resultant mixture was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **22** (1.55 g, 2.31 mmol, 84%) as white foam. $[\alpha]_D^{20}$ -17.8 (c 0.615, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: (the compound existed as a mixture of rotamers) 8.32(brs, 1H of both rotamers), 7.39(d, *J* = 8.0Hz, 2H of minor rotamer) 7.37(d, *J* = 8.0Hz, 2H of major rotamer), 7.04 (d, *J* = 7.8 Hz, 3H of both rotamers), 5.81(t, *J* = 6.1Hz, 1H of major rotamer), 5.63 (t, *J* = 6.3Hz, 1H of minor rotamer), 4.52-4.39(m, 2H of both rotamers), 4.36(dd, *J* = 12.6, 8.0Hz, 1H of minor rotamer), 4.28(dd, *J* = 11.9, 6.5Hz, 1H of major rotamer), 3.85-3.71(m, 10H of both rotamers), 3.67(dd, *J* = 9.8, 6.6 Hz, 1H of major rotamer), 3.61(dd, *J* = 9.6, 6.7 Hz, 1H of minor rotamer), 3.54(dd, *J* = 15.8, 6.4Hz, 1H of minor rotamer), 3.50(dd, *J* = 15.8, 6.4Hz, 1H of major rotamer), 2.84(dd, *J* = 15.7, 12.0 Hz, 1H of major rotamer), 2.83(dd, *J* = 16.2, 11.6 Hz, 1H of minor rotamer), 1.47(s, 9H of minor rotamer), 1.42(s, 9H of major rotamer); ^{13}C NMR (101 MHz, $CDCl_3$) (the compound existed as a mixture of rotamers and the major rotamer was assigned) δ: 173.4, 154.6, 153.7, 144.5, 137.3, 131.4, 131.3, 131.1, 129.2, 128.0, 121.8, 121.3, 118.4, 81.3, 72.2, 72.1, 61.8, 55.3, 52.7, 52.3, 49.1, 30.2, 28.3; HRMS (ESI): calcd. for $[C_{27}H_{32}Br_2N_2O_8+Na]^+$: 693.0418, found: 693.0422.

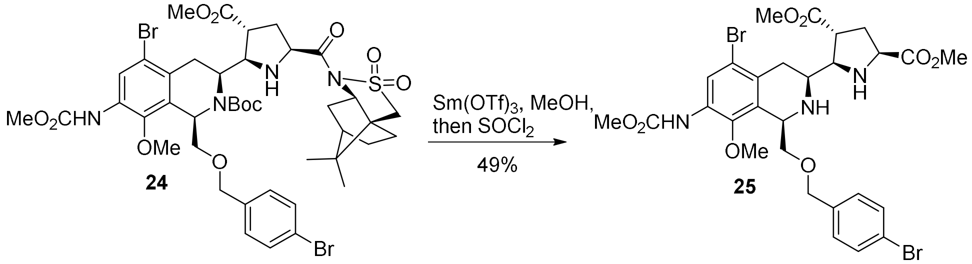


To a solution of **22** (960 mg, 1.43mmol) in THF(20 mL) at 0°C was added $LiBH_4$ (124 mg, 5.69 mmol) in batches. The mixture was warmed to 50°C and stirred for 8h. After cooled down, water was added for quenching the reaction. The resultant mixture was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The crude alcohol **S4** was used for the next step without further purification.

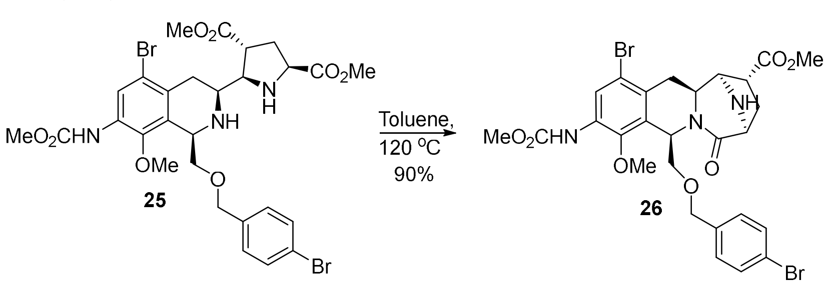
The crude alcohol **S4** was dissolved in DCM (20 mL), and cooled down to 0°C, DMP (723 mg, 1.71 mmol) was added in batches. The mixture was gradually warmed to room temperature and stirred for 1h. Saturated aq $NaHSO_3$ was added for quenching the reaction. The resultant mixture was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **23** (600 mg, 0.93 mmol, 65% for two steps) as purple foam. $[\alpha]_D^{20}$ = -58.0 (c 0.077, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: (the compound existed as a mixture of rotamers) 9.57 (brs, 1H of minor rotamer), 9.51 (d, *J* = 2.2Hz, 1H of major rotamer), 8.31 (s, 1H of both rotamers), 7.44-7.36 (m, 2H of both rotamers), 7.03-6.92 (m, 3H of both rotamers), 5.76 (t, *J* = 5.0Hz, 1H of major rotamer), 5.57 (t, *J* = 5.6Hz, 1H of minor rotamer), 4.52-4.37 (m, 1H of major rotamer, 2H of minor rotamor), 4.33 (s, 1H of major rotamer), 4.30 (s, 1H of minor rotamer), 4.22 (ddd, J = 10.0, 7.4, 2.3 Hz, 1H of major rotamer), 3.81 (s, 3H of both rotamers), 3.79-3.69 (m, 4H of major rotamer, 3H of minor rotamer), 3.61 (dd, J = 9.9, 4.4Hz, 1H of minor rotamer), 3.53 (dd, J = 10.1, 5.5Hz, 1H of major rotamer), 3.43 (dd, J = 9.9, 6.4Hz, 1H of minor rotamer), 3.29-3.16 (m, 1H of both rotamers), 3.01 (dd, J = 16.7, 8.8Hz, 1H of minor rotamer), 2.93 (dd, J = 16.2, 10.4Hz, 1H of major rotamer), 1.49 (s, 9H of minor rotamer), 1.45 (s, 9H of major rotamer); ^{13}C NMR (101 MHz, $CDCl_3$) (the compound existed as a mixture of rotamers and the major rotamer was assigned) δ: 200.3, 154.8, 153.7, 144.1, 136.7, 131.5, 131.1, 130.1, 129.4, 128.0, 122.2, 121.7, 119.1, 82.2, 72.5, 72.3, 61.7, 59.7, 52.8, 49.2, 28.3, 27.5; HRMS (ESI): calcd. for $[C_{26}H_{30}Br_2N_2O_7+Na]^+$: 663.0312, found: 663.0308.



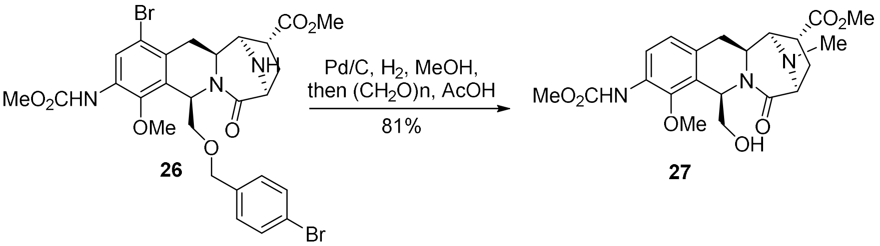
To a Schlenk flask were added $Cu(CH_3CN)_4PF_6$ (42 mg, 0.11 mmol), dppb (0.12 mmol) and anhydrous DMSO (8 mL). The mixture was stirred at room temperature for 2 h. Then a solution of **23** (600 mg, 0.93 mmol) and $NH_2CH_2COX^L$ (405 mg, 1.49 mmol) in DMSO (10 mL) was injected to this flask. The mixture was stirred for 30min, then methyl acrylate (310 µL, 2.94 mmol) was added. The mixture was stirred for further 12 h at room temperature. Saturated aq. NH_4Cl was added to quench the reaction, The resultant mixture was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **24** (0.62 g, 0.63 mmol, 71%) as white foam. $[\alpha]_D^{20}$ = -41.3 (c 0.69, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: (the compound existed as a mixture of rotamers) 8.26 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.97 (s, 1H), 5.98 (s, 1H), 4.64- 4.39 (m, 3H), 4.29 -3.97 (m, 2H), 3.92- 3.62 (m, 11H), 3.54 -3.39 (m, 3H), 3.38-3.26 (m, 1H), 3.26-3.11 (m, 1H), 3.11-3.02 (m, 1H), 2.78-2.51 (m, 2H), 2.41- 2.15 (m, 1H), 2.13- 1.98 (m, 1H), 1.97- 1.81 (m, 1H), 1.43 (s, 9H), 1.41-1.30 (m,2H), 1.14 (s, 3H), 0.97 (s, 3H); HRMS (ESI): calcd. For $[C_{42}H_{54}Br_2N_4O_{11}S +Na]^+$: 1003.1769, found: 1003.1766.



To a solution of **24** (840 mg, 0.85 mmol) in MeOH (20mL) was added Sm(OTf)$_3$ (616 mg, 1.03 mmol) at 0 °C, the mixture was stirred at room temperature for 3 h, then cooled down to 0 °C, SOCl$_2$ (0.63 mL, 8.67 mmol) was added dropwise, the mixture was gradually warm to room temperature and stirred for further 4 h, saturated aq NaHCO$_3$ was added to quench the reaction, the mixture was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na$_2$SO$_4$. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **25** (288.8 mg, 0.41 mmol, 49% over two steps) as white foam. $[\alpha]_D^{20}$ = -126.0 (c 0.04, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.25 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.98 (s, 1H), 4.49-4.34 (m, 3H), 4.07-3.93 (m, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 3.72-3.65 (m, 4H), 3.63 (s, 3H), 3.53 (t, *J* = 6.3 Hz, 1H), 3.01 (dt, *J* = 9.0, 6.7 Hz, 1H), 2.90 (dd, *J* =16.1, 2.2Hz, 1H), 2.81 (ddd, *J* = 11.1, 5.9, 3.0 Hz, 1H), 2.44-2.34 (m, 2H), 2.26- 2.19 (m, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 175.0, 174.2, 153.7, 145.0, 137.4, 131.9, 131.4, 131.0, 130.4, 129.2, 121.3, 121.1, 120.8, 72.7, 72.2, 66.7, 60.3, 59.5, 55.9, 54.7, 52.5, 52.2, 52.1, 45.4, 34.4, 34.3; HRMS (ESI): calcd. For $[C_{28}H_{33}Br_2N_3O_8+Na]^+$: 720.0527, found: 720.0525.



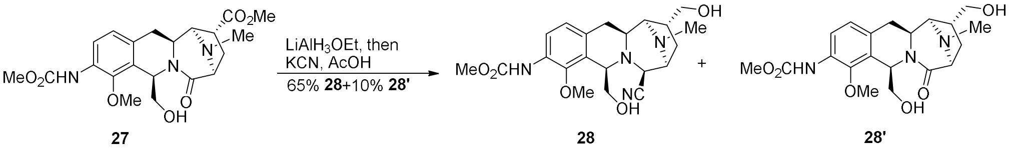
A solution of **25** (288 mg, 0.41 mmol) in toluene (20 mL) was heated at 120 °C for 36 h. The solvent was evaporated and residue was purified by silica gel column chromatography to afford **26** (248 mg, 0.37 mmol, 90%) as white foam. $[\alpha]_D^{20}$ = -92.5 (c 0.355, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.30 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.95 (s, 1H), 6.85 (d, J = 8.4 Hz, 2H), 5.35 (t, J = 2.5 Hz, 1H), 4.24 (d, J =12.0Hz, 2H), 4.15(d, J =12.0Hz, 2H), 4.10 (dd, J = 9.6, 3.6 Hz, 1H), 3.92 (d, J = 6.2 Hz, 1H), 3.84-3.82 (m, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.67 (s, 3H), 3.64(dt, J =12.4, 2.7Hz, 1H), 3.30 (dd, J = 9.6, 2.2 Hz, 1H), 3.13 (dd, J = 8.8, 6.4 Hz, 1H), 2.94 (dd, J = 15.2, 2.8 Hz, 1H), 2.80 (dd, J = 15.2, 12.4 Hz, 1H), 2.32 (dd, J = 13.2, 8.8 Hz, 1H), 2.18 (dt, J = 9.9, 3.4 Hz, 1H); ^{13}C NMR (101 MHz, CDCl$_3$) δ: 175.7, 170.0, 153.8, 144.7, 137.0, 132.0, 131.6, 131.2, 129.4, 129.3, 121.8, 121.6, 118.5, 72.5, 71.3, 62.9, 62.1, 61.4, 59.5, 52.8, 52.6, 50.2, 41.5, 38.9, 32.5; HRMS (ESI): calcd. For [C$_{27}$H$_{29}$Br$_2$N$_3$O$_7$+Na]$^+$: 688.0264, found: 688.0263.



26 **27**

To a solution of **26** (244 mg, 0.37 mmol) in 10 mL of MeOH, Pd/C (50 mg) was added at room temperature. The mixture was stirred under hydrogen (H$_2$) atmosphere at room temperature for 9 h, and then filtered through a pad of celite. The solid was washed slowly with 100 mL of methanol, and the combined filtrates were concentrated to give crude ester. Crude ester was diluted with AcOH (4 mL), paraformaldehyde (55 mg) and NaCN(BH$_3$) (108 mg, 1.72 mmol) were added at room temperature. The mixture was stirred at room temperature for 3h, and added dropwise with saturated aq NaHCO$_3$, the mixture was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na$_2$SO$_4$. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **27** (127.8 mg, 0.29 mmol, 81% for two steps) as white foam. $[\alpha]_D^{20}$ = -108.7 (c 0.355, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.94 (d, J = 8.4 Hz, 1H), 7.01 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 5.57 (dd, J = 5.6, 3.6 Hz, 1H), 3.90-3.81(m, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.69- 3.65 (m, 1H), 3.63 (d, J = 6.3Hz, 1H), 3.55 (ddd, J = 10.8, 5.8, 4.8 Hz, 1H), 3.27 (dd, J = 9.6, 6.8 Hz, 1H), 2.95-2.84 (m, 2H), 2.69 (dd, J = 13.2, 6.6 Hz, 1H), 2.63(dd, J = 14.7, 2.0 Hz, 1H), 2.46 (s, 3H), 2.37 (dd, J = 13.4, 9.6

Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.7, 172.9, 154.1, 145.7, 131.6, 130.7, 126.6, 124.2, 119.0, 68.4, 67.5, 66.7, 61.5, 56.4, 52.6, 52.4, 41.5, 37.8, 34.4, 31.8; HRMS (ESI): calcd. For $[C_{21}H_{27}N_3O_7+Na]^+$: 456.1741, found:456.1744.

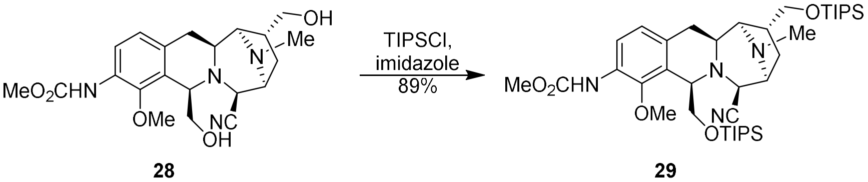


To a solution of $LiAlH_4$ (1 M solution in THF, 369 μL, 0.37 mmol) at 0 °C, anhydrous EtOAc (18 μL, 0.18 mmol) was added. This solution was allowed to stir at 0 °C for 2 hours. Then a solution of **27** (20 mg, 0.046 mmol) in THF (2 mL) was added dropwise. This solution was allowed to stir at 0°C for 45 min. AcOH (80 μL, 1.41 mmol) was added slowly followed by an aqueous solution of KCN (4.5 M, 62 μL, 0.28mmol). The resulting solution was stirred at room temperature for 16 hours. Saturated aq $NaHCO_3$ was added and the solution was extracted with 1:1 EtOAc/THF (3 x 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude material was purified by flash chromatography to yield **28** (12.6mg, 0.030 mmol, 65%, white foam) and **28'** (1.9 mg, 0.0046 mmol, 10%, white solid).

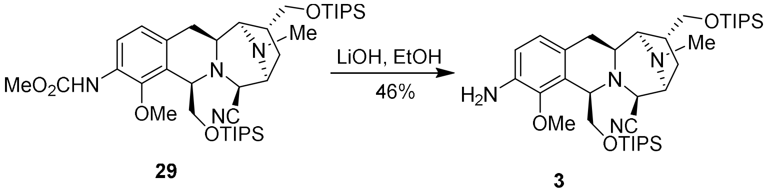
28: $[\alpha]_D^{20}$ = +56.0 (c 0.255, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (brs, 1H), 7.05 (s, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.14 (d, *J* = 4.6 Hz, 1H), 3.92 (d, *J* = 2.5 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.72-3.62 (m, 2H), 3.58 (dd, *J* = 10.1, 7.3 Hz, 1H), 3.50 (dd, *J* = 10.8, 5.2Hz, 1H), 3.48 (brs, 1H), 3.10 (d, *J* = 11.3 Hz, 1H), 2.98 (s, 1H), 2.60 (s, 3H), 2.58-2.48 (m, 2H), 2.45 (dd, *J* = 15.0, 2.6 Hz, 1H), 2.41-2.24(brs, 2H), 1.99-1.84 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 154.2, 145.6, 131.7, 129.9, 126.9, 124.3, 118.7, 67.7, 67.2, 67.0, 63.1, 61.1, 58.4, 57.0, 55.4, 52.6, 41.0, 40.1, 32.5, 31.2; HRMS (ESI): calcd. For $[C_{21}H_{28}N_4O_5+Na]^+$: 439.1952, found:439.1954.

28': $[\alpha]_D^{20}$ = -112.8 (c 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 8.1 Hz, 1H), 7.08 (s, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 5.66 (dd, *J* = 5.8, 3.6 Hz, 1H), 3.87 (dd, *J* = 9.4, 5.4 Hz, 2H), 3.84 (s, 6H), 3.78 (dd, *J* = 10.1, 4.4 Hz, 1H), 3.68-3.60 (m, 2H), 3.57 (d, *J* = 6.5 Hz, 1H), 3.28 (d, *J* = 2.9 Hz, 1H), 2.97 (t, *J* = 14.0 Hz, 1H), 2.72-2.64(m, 1H), 2.60 (s, 3H), 2.59-2.53 (m, 1H), 2.26 (dd, *J* = 13.0, 9.0 Hz, 1H), 2.12-1.98(m, 3H);

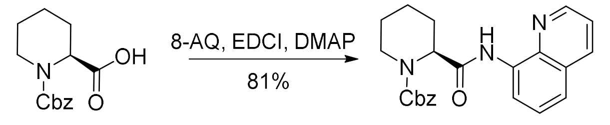
^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.3, 154.0, 145.8, 131.9, 130.5, 126.6, 124.0, 119.0, 68.5, 66.2, 66.0, 64.3, 61.4, 52.7, 52.6, 52.3, 38.5, 35.3, 34.9, 31.4; HRMS (ESI): calcd. For $[C_{20}H_{27}N_3O_6+Na]^+$:428.1792, found: 428.1793.



To a solution of **28** (47.0 mg, 0.113 mmol) in DCM (2 mL) were added TIPSCl (146 μL, 0.72 mmol) and imidazole (93 mg, 1.37 mmol) at 0 ºC, the mixture was warmed to room temperature and stirred for 12 h, another batch of TIPSCl (146 μL, 0.72 mmol) and imidazole (93 mg, 1.37 mmol) were added at 0 ºC, the mixture was stirred for further 10 h, water was added, and the mixture was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **29** (73.0 mg, 0.1 mmol, 89%) as colorless oil. $[\alpha]_D^{20}$ = +29.6 (c 0.355, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 7.8 Hz, 1H), 7.02 (s, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.33 (d, *J* = 2.8 Hz, 1H), 4.16 (dd, *J* = 8.5, 2.4 Hz, 1H), 3.82 (dd, *J* = 9.5, 2.7 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.72 (dd, *J* = 9.5, 6.9 Hz, 1H), 3.62-3.54 (m, 1H), 3.47-3.40 (m, 1H), 3.37 (d, *J* = 5.7 Hz, 1H), 3.03 (t, *J* = 10.2 Hz, 1H), 2.67-2.58 (m, 2H), 2.57 (s, 3H), 2.40 (dd, *J* = 14.9, 2.4 Hz, 1H), 2.02 (dd, *J* = 12.7, 8.9 Hz, 1H), 1.72 (dd, *J* = 12.3, 6.0 Hz, 1H), 1.19-0.94 (m, 42H); ^{13}C NMR (101 MHz, $CDCl_3$) δ:154.1, 145.5, 132.2, 129.8, 126.6, 124.2, 119.5, 71.1, 67.7, 67.5, 63.6, 61.1, 59.3, 58.9, 57.4, 52.5, 42.2, 41.3, 32.8, 29.9, 18.2, 18.1, 12.1, 12.0; HRMS (ESI): calcd. For $[C_{39}H_{68}N_4O_5Si_2+Na]^+$: 751.4620, found: 751.4619.



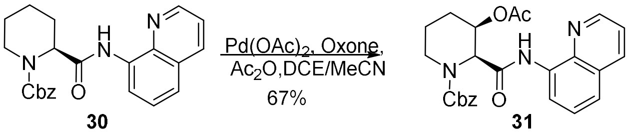
To a solution of **29** (74 mg, 0.101 mmol) in EtOH (8 mL) was added a solution of 2 M aq. LiOH (0.8 mL), the mixture was heated at 90 ^{o}C for 5 h, EtOH was removed *in vacuo* and the pH was adjusted to 7.0 with 1M HCl, the solution was extracted with DCM for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **3** (31.3 mg, 0.047 mmol, 46%) as white foam. $[\alpha]_D^{20}$ = +39.2 (c 0.485, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.66 (d, *J* = 7.9 Hz, 1H) , 6.59 (d, *J* = 7.9 Hz, 1H) , 4.37 (d, *J* = 2.6 Hz, 1H), 4.16 (dd, *J* = 8.8, 2.5 Hz, 1H) , 3.88 (dd, *J* = 9.2, 2.5 Hz, 1H), 3.79 (s, 3H) , 3.76-3.56(brs, 2H), 3.72 (dd, *J* = 9.5, 6.8 Hz, 2H), 3.61 (t, *J* = 9.5 Hz, 1H) , 3.43 (t, *J* = 9.0 Hz, 1H) , 3.37 (d, *J* = 6.2 Hz, 1H), 2.98-3.10(m, 2H), 2.57(s, 3H) , 2.52-2.68(m, 2H), 2.33 (dd, *J* = 14.8, 2.5 Hz, 1H), 2.04 (dd, *J* = 12.6, 9.0 Hz, 1H), 1.71(m, 1H) ,1.01-1.16(m, 42H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.18, 138.13, 127.37, 127.02, 123.96, 119.78, 115.07, 71.51, 67.77, 67.60, 63.69, 59.57, 59.34, 58.98, 57.52, 42.32, 41.35, 32.63, 30.01, 18.27, 18.21, 12.17, 12.04; HRMS (ESI): calcd. For $[C_{37}H_{67}N_4O_3Si_2+Na]^+$: 671.4746, found: 671.4748.



Cbz-*L*-homoPro

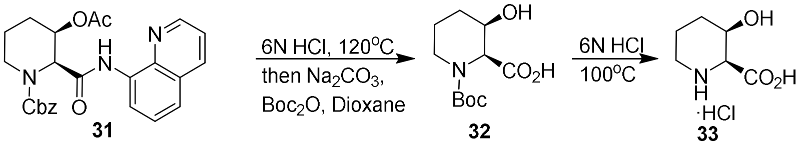
30

To a solution of Cbz-L-homoproline (10 g, 37.98 mmol) in DCM(100 mL) were added 8-aminoquinoline (5.20 g, 45.58 mmol), EDCI (9.46 g, 49.35 mmol), DMAP (464 mg, 3.80 mmol), the mixture was stirred at room temperature for 10 h, water was added, and the mixture was extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **30** (11.98 g, 30.76 mmol) as viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.43 (s, 1H), 8.76 (dd, *J* = 6.8, 2.2 Hz, 1H), 8.71 (s, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.58- 7.49 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 2H), 7.40-7.14(m, 4H), 5.42-5.04 (m, 2H), 4.29 (s, 1H), 3.15 (s, 1H), 2.50 (d, *J* = 12.8 Hz, 1H), 1.84- 1.45 (m, 6H). **30** is a known compound.[1]



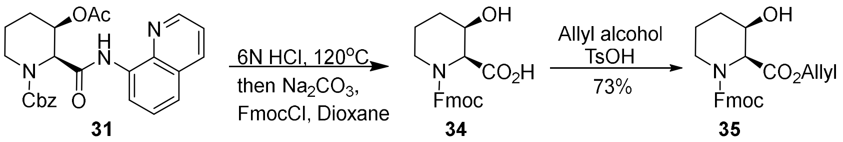
To a solution of **30** (3.0 g, 7.70 mmol) in MeCN/DCE (30 mL/30 mL) were added $Pd(OAc)_2$ (225 mg, 1 mmol), Oxone (6 g, 35.7 mmol, CAS 70693-62-8) and Ac_2O (3 mL, 31.7 mmol). The flask was evacuated under high vacuum, backfilled with nitrogen, and closed with a Teflon septa. The flask was heated at 85 °C for 16h, the mixture was filtered through a pad of celite (eluent DCM) and the filtrate was extracted with DCM for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **31** (2.32 g, 5.18 mmol, 67%). $[\alpha]_D^{20}$ = +10.0 (c 0.28, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: (the compound existed as a mixture of rotamers) 10.55 (s, 1H), 8.82 (dd, *J* = 5.9, 3.2 Hz, 1H), 8.75 (s, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.57-7.48 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.42-7.14 (m, 5H), 5.37-5.08 (m, 4H), 4.12 (s, 1H), 3.39 (s, 1H), 2.26 (s, 3H), 2.08-1.99 (m, 1H), 1.95-1.65 (m, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.82, 166.81, 148.07, 138.59, 136.41, 136.38, 134.44, 128.47, 128.01, 127.94, 127.38, 121.95, 121.67, 116.99, 70.64, 67.76, 57.78, 57.54, 40.98, 26.05, 23.47, 23.12, 21.26; HRMS (ESI): calcd. For $[C_{25}H_{25}N_3O_5+Na]^+$: 470.1686, found: 470.1686.



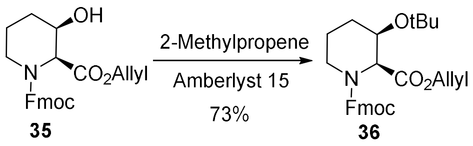
A 10 mL flask was charged with **31** (500 mg, 1.1 mmol) and 6 N HCl (6 mL). The flask was closed with a Teflon septa and heated at 120°C for 5h. After cooled down to room temperature, the solvent was removed *in vacuo*. A solution of Na_2CO_3 (0.87 g in 15 mL H_2O) was added to the residue, extracted with EtOAc for three times, the organic phase was discarded. The aqueous phase was moved to another flask, dioxane (30 mL) and Boc_2O (5 mL) were added, then the mixture was stirred at room temperature overnight. After extracted with EtOAc, the PH of the aqueous solution was adjusted to 5.0 with 1M HCl, then the aqueous solution was extracted with EtOAc, washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure to give the crude acid **32** (257.6 mg, 1.05 mmol, 95%).

A 10 mL flask was charged with **32** (30 mg, 0.122 mmol) and 6 N HCl (2 mL). The flask was closed with a Teflon septa and heated at 100°C for 20min. After cooled down to room temperature, the solvent was removed *in vacuo* to afford the amino acid **33** (21.1 mg, 0.116mmol, 95%). $[\alpha]_D^{20} = -28.9$ (c 0.735, H_2O); ^1H NMR (400 MHz, D_2O) δ: 4.48 (s, 1H), 3.93 (s, 1H), 3.39-3.32 (m, 1H), 3.00-2.89 (m, 1H), 1.97-1.81 (m, 2H), 1.78-1.60 (m, 2H); ^{13}C NMR (101 MHz, D_2O) δ: 170.5, 63.7, 60.8, 43.6, 28.3, 15.7; HRMS (ESI): calcd. For $[C_6H_{12}NO_3]^+$: 146.0812, found: 146.0812.

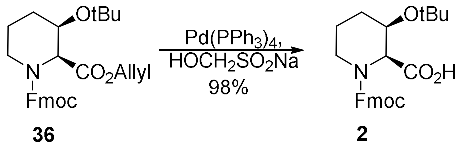


A 10 mL flask was charged with **31** (550 mg, 1.23 mmol) and 6 M HCl(6 mL). The flask was closed with a Teflon septa and heated at 120 °C for 5 h. After cooled down to room temperature, the solvent was removed *in vacuo*. A solution of Na_2CO_3 (0.87 g in 15 mL H_2O) was added to the residue, extracted with EtOAc for three times, the organic phase was discarded. The aqueous phase was moved to another flask, dioxane (30 mL) and FmocOSu (550 mg, 1.63 mmol) were added, then the mixture was stirred at room temperature overnight. After extracted with EtOAc, the PH of the aqueous solution was adjusted to 5.0 with 1M HCl, then the aqueous solution was extracted with EtOAc, washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure to give the crude acid **34** (442 mg, 1.20 mmol, 98%).

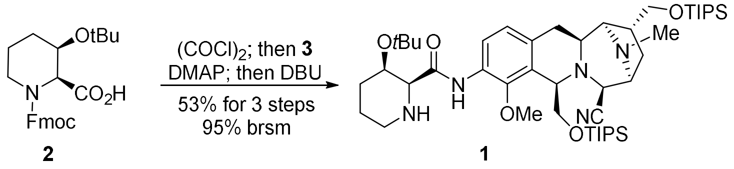
Compound **34** (440 mg, 1.20 mmol), TsOH•H2O (0.25 g, 1.31 mmol), allyl alcohol (0.82 mL, 12 mmol) were dissolved in toluene (20 mL) in a 100 mL round-bottomed flask equipped with a Dean-Stark apparatus. The mixture is heated to 130° C for 1.5 h, DCM was added, the solution was washed with aq. $NaHCO_3$ and 1M HCl. The solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **35** (354 mg, 0.87 mmol, 73%). $[\alpha]_D^{20}$ = -33.6 (c 1.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (the compound existed as a mixture of rotamers): 7.77 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.9 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.35- 7.27 (m, 2H), 5.95-5.80 (m, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.24 (dd, *J* = 10.8, 4.4 Hz, 1H), 5.15/4.95 (d, *J* = 4.8 Hz, 1H), 4.77-4.57(m, 2H), 4.55-4.36(m, 2H), 4.32-4.19(m, 1H), 4.09/3.93(d, *J* = 12.9 Hz, 1H), 3.82-3.67 (m, 1H), 2.90/2.73(t, *J* = 10.8 Hz, 1H), 2.10-1.95 (m, 1H), 1.80-1.66 (m, 1H), 1.61-1.42 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.17, 155.84, 155.26, 143.92, 143.81, 143.74, 143.68, 141.29, 131.13, 130.98, 127.73, 127.05, 124.93, 124.80, 120.01, 119.50, 119.27, 69.00, 68.73, 67.94, 67.86, 66.15, 66.04, 58.10, 57.84, 47.18, 41.15, 40.85, 30.17, 30.10, 23.70, 23.45; HRMS (ESI): calcd. For $[C_{24}H_{25}NO_5+Na]^+$: 430.1625, found: 430.1627.



To a slurry of **35** (354 mg, 0.87 mmol) in hexane (10 mL) were added 2-methylpropene (9% w/w in hexane, 20 mL) and amberlyst 15 (500 mg). The mixture was stirred at room temperature for 48h. The mixture was filtered through Celite and the filtrate was washed with hexanes. The solvent was removed *in vacuo* and the crude oil was purified via flash chromatography to afford **36** (295 mg, 0.636 mmol, 73%) as colorless oil. $[\alpha]_D^{20}$ = +5.2 (c 0.635, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (the compound existed as a mixture of rotamers): 7.76 (d, *J* = 7.6 Hz, 2H), 7.68-7.54 (m, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.35-7.27 (m, 2H), 5.99-5.85 (m, 1H), 5.35 (d, *J* = 17.3 Hz, 1H), 5.21 (d, *J* = 10.5 Hz, 1H), 4.99/4.86 (d, *J* = 6.4 Hz, 1H), 4.72-4.17 (m, 5H), 4.11-3.88 (m, 1H), 3.71-3.58(m, 1H), 3.49/3.37 (t, *J* = 12.6 Hz, 1H), 1.93 -1.42 (m, 4H), 1.22/1.21 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.63, 170.00, 156.03, 155.20, 144.04, 143.95, 143.88, 143.70, 141.29, 132.08, 127.68, 127.66, 127.04, 125.07, 124.98, 119.98, 118.16, 118.03, 74.56, 74.51, 67.75, 67.72, 67.57, 67.41, 65.26, 58.05, 57.96, 47.21, 40.31, 40.00, 28.35, 28.25, 27.97, 23.60, 23.28; HRMS (ESI): calcd. For $[C_{28}H_{33}NO_5+Na]^+$: 486.2251, found: 486.2254.



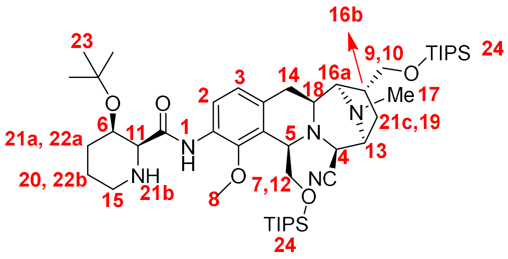
To a solution of **36** (260 mg, 0.56 mmol) in DCM (16 mL) were added $Pd(PPh_3)_4$ (53 mg, 0.046 mmol), hydroxymethanesulfinic acid sodium salt (97 mg, 0.82 mmol) in MeOH(10 mL) was then added dropwise. The mixture was stirred for 3 h at room temperature. The pH of the solution was adjusted to 2 with 1 M HCl, extracted with EtOAc for three times. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **2** (232 mg, 0.55 mmol, 98%) as white viscous oil. $[\alpha]_D^{20}$ = +14.4 (c 0.925, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (the compound existed as a mixture of rotamers): 11.07 (s, 1H), 7.78 - 7.54 (m, 4H), 7.49 -7.30 (m, 4H), 5.01/4.56 (d, *J* = 5.8 Hz, 1H), 4.55-4.38 (m, 2H), 4.29/4.24(t, *J* = 6.9Hz, 1H), 4.03/3.93(dd, *J* = 13.7, 3.5Hz,1H), 3.84-3.76/3.76-3.68(m, 1H), 2.92/2.75 (td, *J* = 13.4, 2.9Hz, 1H), 1.95-1.68(m, 2H), 1.56-1.39(m, 2H), 1.36/1.29(s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 169.19, 168.94, 156.08, 155.32, 144.04, 143.94, 143.69, 143.62, 141.36, 141.26, 141.12, 132.12, 132.02, 131.96, 131.93, 128.55, 128.43, 127.69, 127.63, 127.61, 127.17, 127.09, 127.04, 127.01, 125.12, 125.09, 124.86, 124.74, 119.95, 119.90, 78.27, 78.06, 68.42, 68.25, 67.92, 67.37, 58.00, 57.76, 47.20, 47.14, 40.39, 40.07, 30.29, 30.14, 27.86, 27.80, 23.81, 23.30. ; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{29}NO_5Na$ 446.1938; Found 446.1937.



To a solution of **2** (35.5 mg, 0.084 mmol) in anhydrous DCM (4 mL) were added oxalyl chloride (15 μL, 0.177 mmol) and DMF (2 μL). The mixture was stirred at room temperature for 2.5h, concentrated *in vacuo* and the resulting acid chloride **S5** was used for the next step directly.

The amine **3** (20.0 mg, 0.03 mmol) and DMAP (9 mg, 0.074 mmol) were dissolved in DCM (2 mL) at room temperature. Acid chloride **S5** in DCM (2 mL) was added dropwise. The mixture was stirred at room temperature for 20 h, added saturated aq $NaHCO_3$, extracted with DCM. The organic layer was washed with brine and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was redissolved in DCM (4 mL) and DBU (10 μL, 0.075 mmol) was added. After stirring at rt for 15 h, the solution was washed with $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed and the crude product was purified via flash chromatography to afford **1** (13.4 mg, 0.016 mmol, 53%, 95% based on recovered **3**). The unreacted **3** (8.9 mg, 0.0133 mmol) was recovered. $[\alpha]_D^{20} = +24.5$ (c 0.225, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ:10.06 (s, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.37 (d, *J* = 2.4 Hz, 1H), 4.17 (d, *J* = 7.9 Hz, 1H), 4.14-4.05 (m, 1H), 3.87 (dd, *J* = 9.1, 2.1 Hz, 1H), 3.80 (s, 3H), 3.73 (dd, *J* = 9.4, 6.9 Hz, 1H), 3.61 (t, *J* = 9.6 Hz, 1H), 3.53 (d, *J* = 4.2 Hz, 1H), 3.43 (t, *J* = 9.0 Hz, 1H), 3.37 (d, *J* = 5.7 Hz, 1H), 3.08-3.01 (m, 2H), 2.76-2.68 (m, 2H), 2.67-2.58 (m, 2H), 2.57 (s, 3H), 2.42 (d, *J* = 15.1 Hz, 1H), 2.03 (dd, *J* = 12.8, 9.0 Hz, 1H), 1.83-1.76 (m, 1H), 1.75-1.67(m, 3H), 1.67-1.54 (m, 2H), 1.28 (s, 9H), 1.09-1.02 (m, 42H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.41, 146.08, 132.37, 130.39, 126.40, 123.82, 119.41, 119.12, 75.63, 71.18, 68.73, 67.55, 67.36, 63.51, 62.35, 61.10, 59.23, 58.81, 57.32, 42.75, 42.14, 41.30, 32.69, 31.32, 29.74, 28.20, 24.07, 18.07, 18.00, 11.96, 11.79; HRMS (ESI): calcd. For $[C_{47}H_{83}N_5O_5Si_2+Na]^+$: 876.5825, found: 876.5823.

3. Comparison of NMR Spectroscopic Data of Published and Synthetic 1



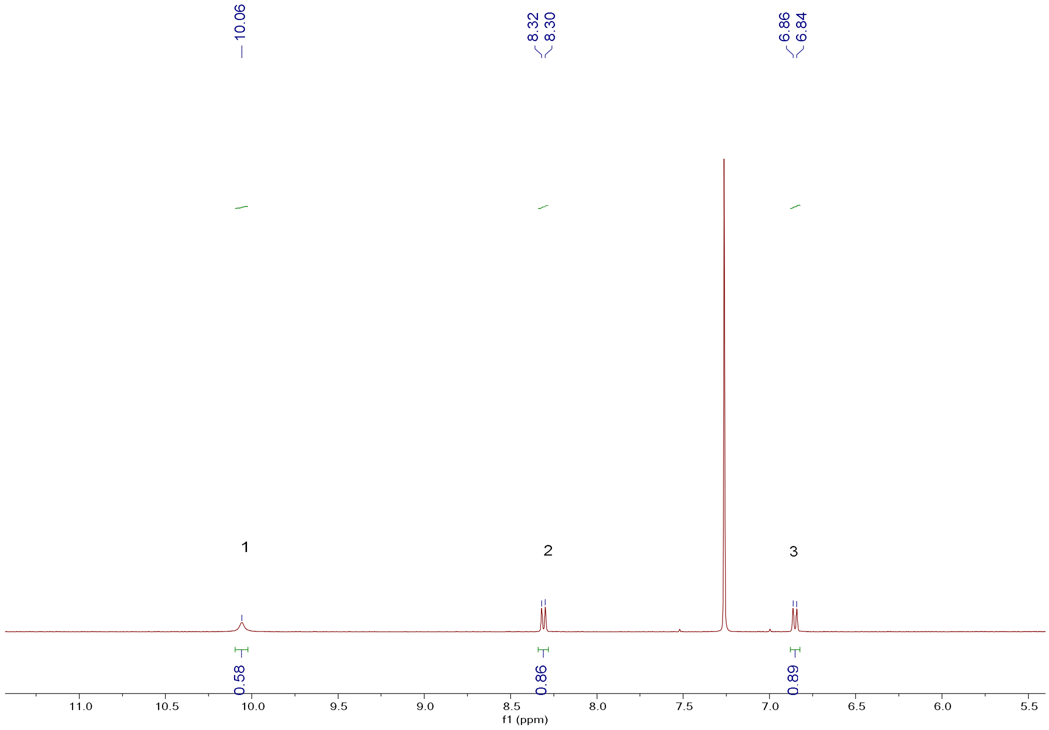
1

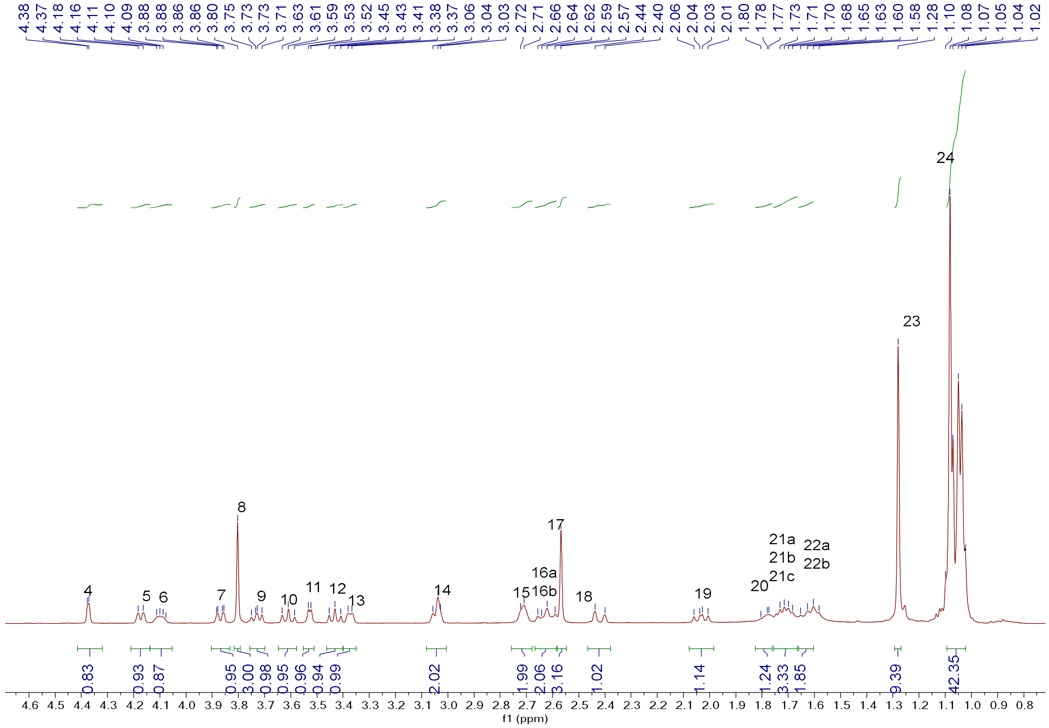
Comparison of ^{1}H NMR Spectroscopic Data of Published[2] and Synthetic 1

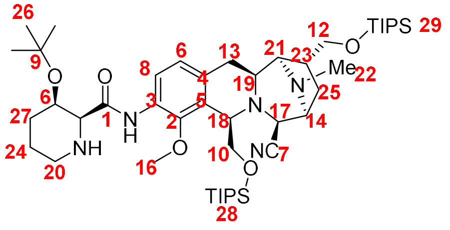
Published[a]	This work[a]	Position
10.06 (1H, s, broad)	10.06 (s, 1H)	1
8.30 (1H, d, *J* = 8.0 Hz)	8.31 (d, *J* = 8.3 Hz, 1H)	2
6.85(1H, d, *J* = 8.0 Hz)	6.85 (d, *J* = 8.3 Hz, 1H)	3
4.37 (1H, d, *J* = 2.8 Hz)	4.37 (d, *J* = 2.4 Hz, 1H)	4
4.16 (2H, m)	4.17 (d, *J* = 7.9 Hz, 1H)[b]	5
	4.14-4.05 (m, 1H)[c]	6
3.86 (1H, dd, *J* = 9.2, 1.5 Hz)	3.87 (dd, *J* = 9.1, 2.1 Hz, 1H)	7
3.80 (3H, s)	3.80 (s, 3H)	8
3.73 (1H, dd, *J* = 9.6, 5.8 Hz)	3.73 (dd, *J* = 9.4, 6.9 Hz, 1H)	9
3.61 (1H, t, *J* = 9.6 Hz)	3.61 (t, *J* = 9.6 Hz, 1H)	10
3.57 (1H, d, *J* = 4.0 Hz)	3.53 (d, *J* = 4.2 Hz, 1H)	11
3.43 (1H, t, *J* = 8.8 Hz)	3.43 (t, *J* = 9.0 Hz, 1H)	12
3.37 (1H, d, broad, *J* = 6.4 Hz)	3.37 (d, *J* = 5.7 Hz, 1H)	13
3.04 (2H, m)	3.08-3.01 (m, 2H)	14
2.74 (2H, m)	2.76-2.68 (m, 2H)	15

2.62 (1H, m)	2.67-2.58 (m, 2H)[d]	16
2.57 (3H, s)	2.57 (s, 3H)	17
2.42 (1H, d, *J* = 12.8 Hz)	2.42 (d, *J* = 15.1 Hz, 1H)	18
2.04 (1H, d, *J* = 9.2 Hz)	2.03 (dd, *J* = 12.8, 9.0 Hz, 1H)[e]	19
2.01 (1H, d, *J* = 8.0 Hz)		
1.80 (1H, m)	1.83-1.76 (m, 1H)	20
1.71 (3H, m)	1.75-1.67(m, 3H)	21
1.63 (2H, m)	1.67-1.54 (m, 2H)	22
1.28 (6H, s)	1.28 (s, 9H)	23
1.25 (3H, s)[f]		
1.07 (42H, m)	1.09-1.02 (m, 42H)	24

[a]Recorded in $CDCl_3$, measured at 400 MHz. [b]The peak at 4.17 ppm was assigned to position 5, which was confirmed by 2D NMR experiments. [c]The peak at 4.14-4.05 ppm was assigned to position 6, which was confirmed by 2D NMR experiments. [d]This peak was assigned as H16a and H16b. [e]This peak was assigned as H19. [f]This peak in previous report should be grease.







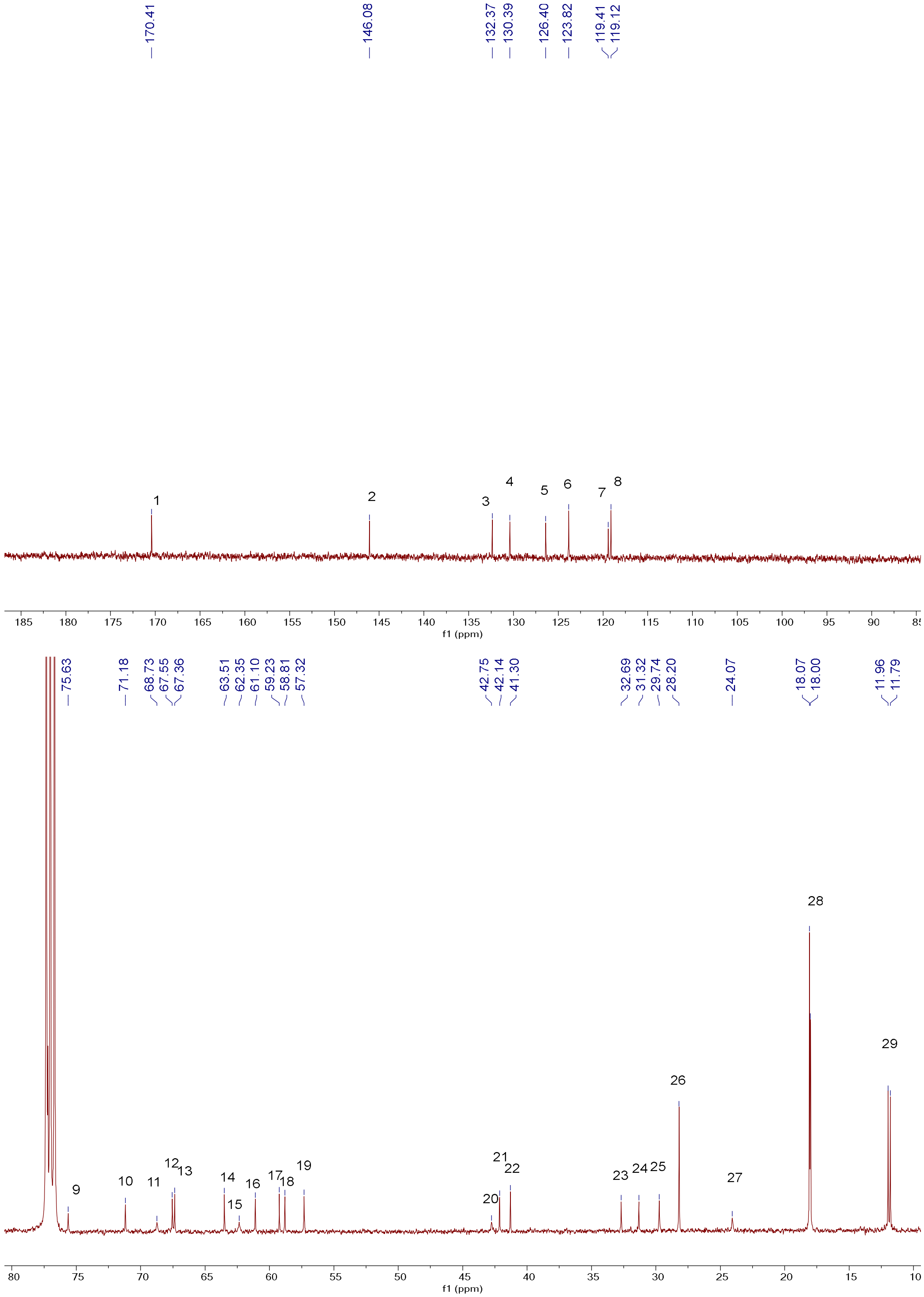
1

Comparison of ^{13}C NMR Spectroscopic Data of Published[2] and Synthetic 1

Published[a]	This work[a]	Δδ (ppm)[b]	Position
170.24	170.41	-0.17	1
146.08	146.08	0	2
132.42	132.37	0.05	3
130.36	130.39	-0.03	4
126.41	126.40	0.01	5
123.81	123.82	-0.01	6
119.39	119.41	-0.02	7
119.13	119.12	0.01	8
75.67	75.63	0.04	9
71.15	71.18	-0.03	10

68.64	68.73	-0.09	11
67.54	67.55	-0.01	12
67.35	67.36	-0.01	13
63.49	63.51	-0.02	14
62.24	62.35	-0.11	15
61.10	61.10	0	16
59.20	59.23	-0.03	17
58.81	58.81	0	18
57.28	57.32	-0.04	19
42.69	42.75	-0.06	20
42.12	42.14	-0.02	21
41.25	41.30	-0.05	22
32.68	32.69	-0.01	23
31.24	31.32	-0.08	24
29.75	29.74	0.01	25
28.17	28.20	-0.03	26
23.96	24.07	-0.11	27
18.05	18.07	-0.02	28
17.98	18.00	-0.02	28
11.95	11.96	-0.01	29
11.78	11.79	-0.01	29

[a]Recorded in $CDCl_3$, measured at 101 MHz. [b] $\Delta\delta = \delta_{(published)}-\delta_{(synthetic)}$.


170.41
146.08
132.37
130.39
126.40
123.82
119.41
119.12
1
2
3
4
5
6
7
8
185
180
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
f1 (ppm)
75.63
71.18
68.73
67.55
67.36
63.51
62.35
61.10
59.23
58.81
57.32
42.75
42.14
41.30
32.69
31.32
29.74
28.20
24.07
18.07
18.00
11.96
11.79
9
10
11
12
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14
15
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21
22
23
24
25
26
27
28
29
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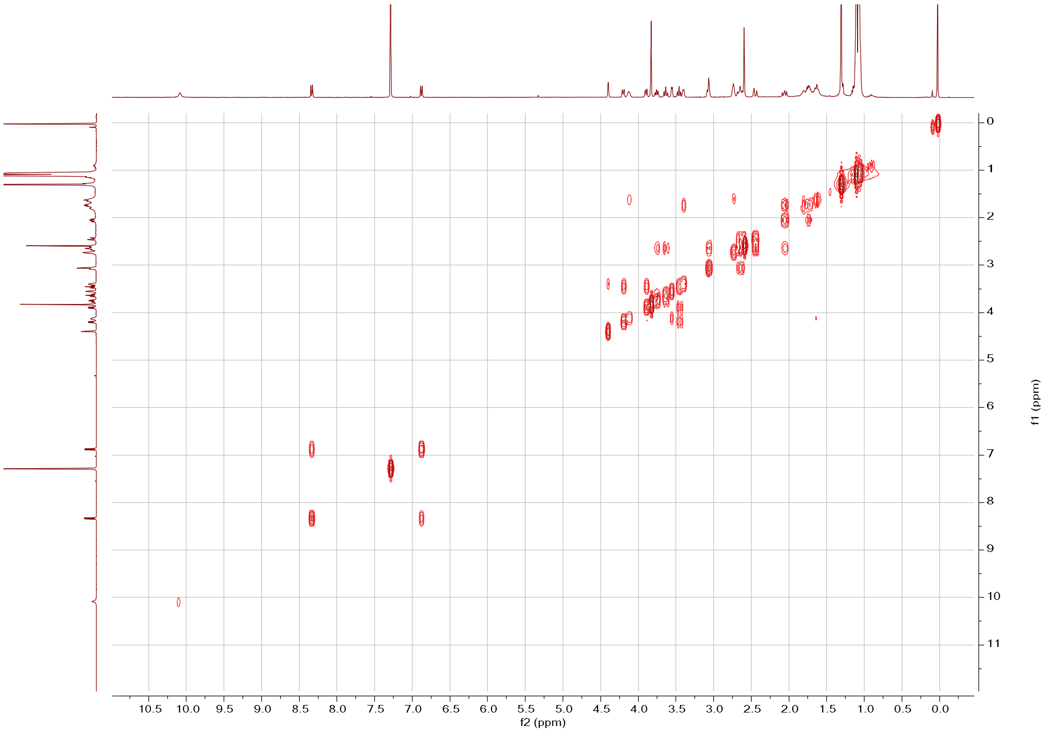
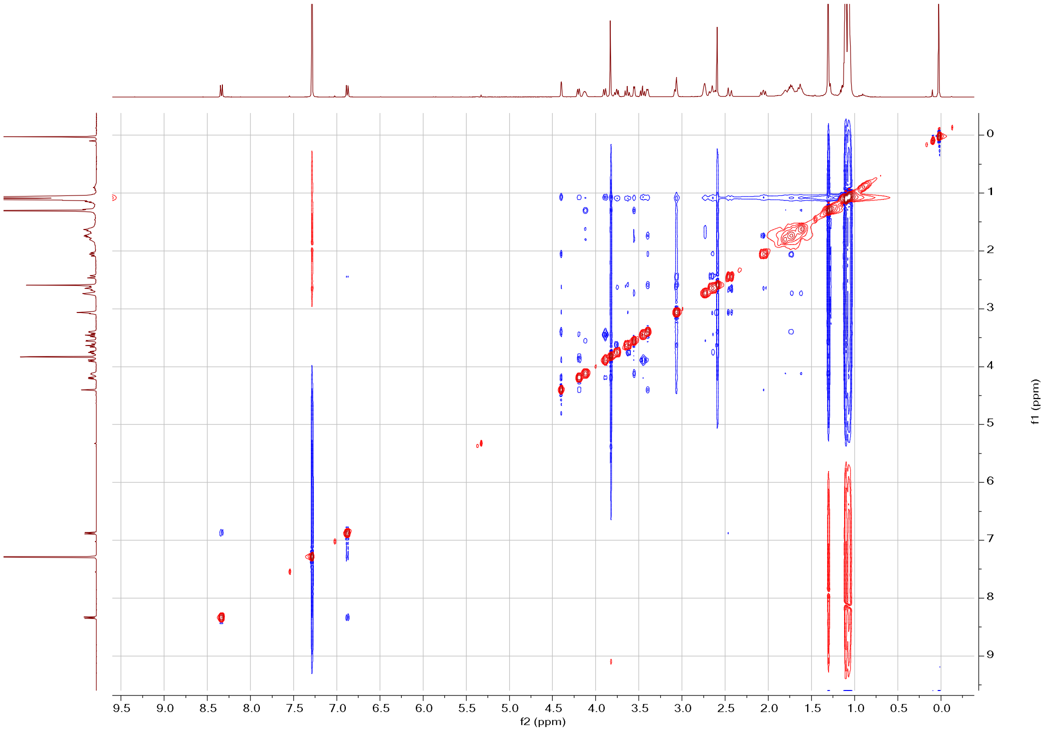
45
40
35
30
25
20
15
10
f1 (ppm)

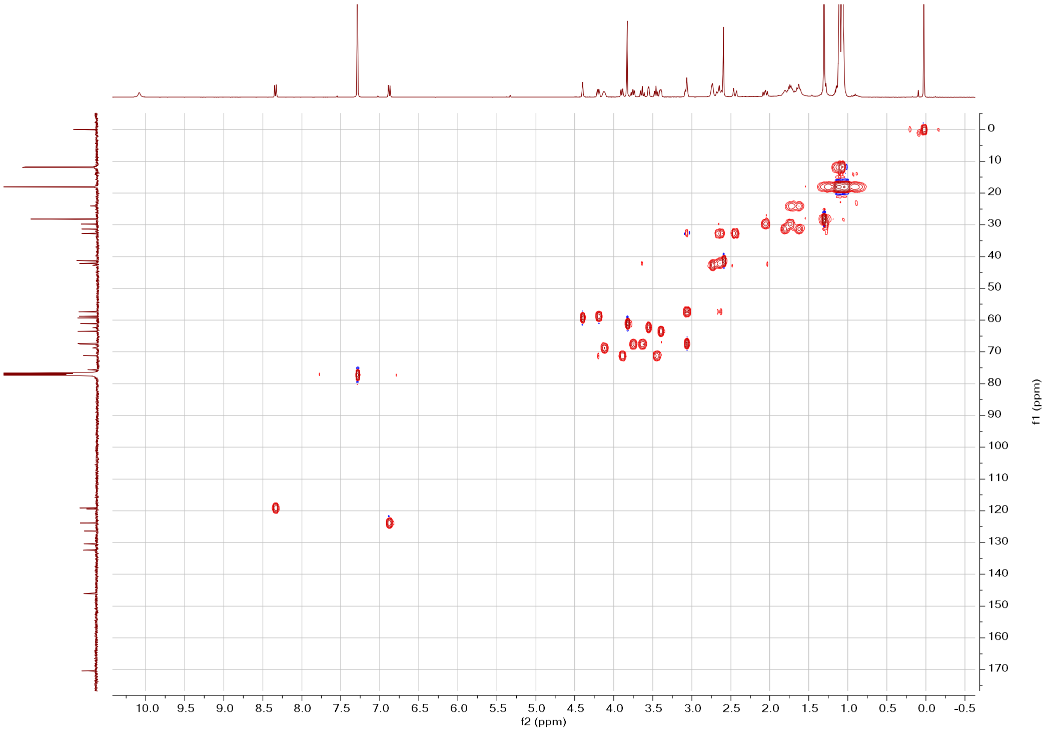
H-H COSY spectrum



NOESY



HSQC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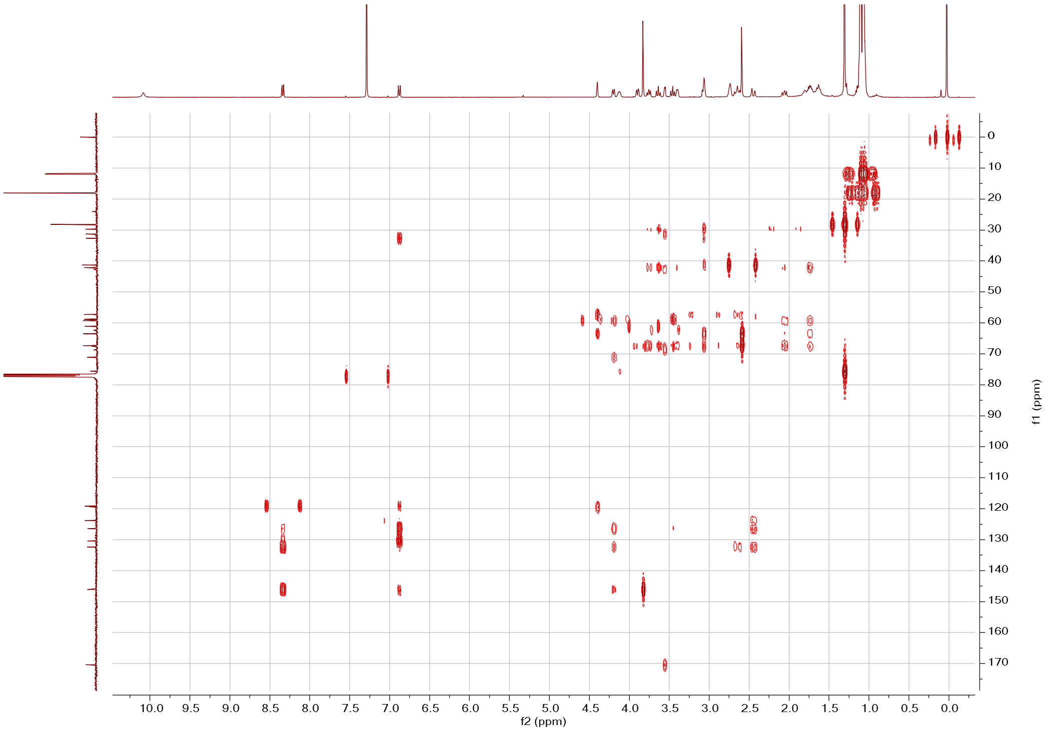
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

HMBC


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

4. X-ray crystallographic data

A single crystal of **28’** suitable for X-ray crystallography was obtained by crystallization via evaporation from its hexane/ethyl acetate solution.

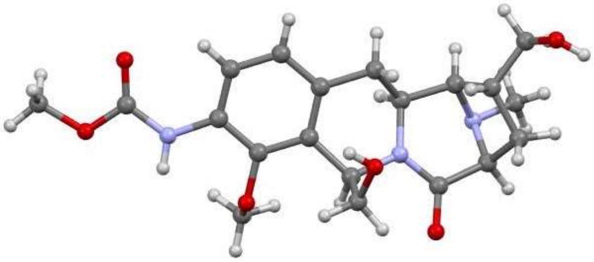


Figure S1 X-ray crystal structure of compound **28'**. The ellipsoids drawn at 30% probability level.

Crystallographic data for **28'** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC **2049198**. Copies of the data can be obtained, free of charge from https://www.ccdc.cam.ac.uk.

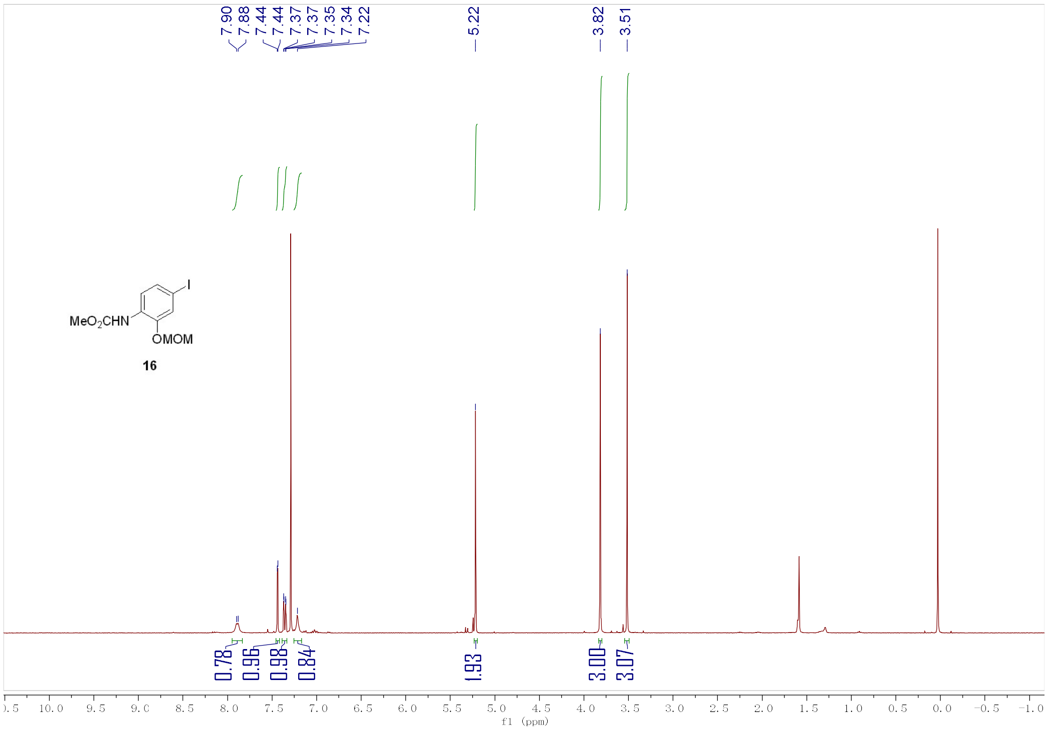
Bond precision:	C-C = 0.0020 A		Wavelength=1.54178
Cell:	a=8.2442(4)	b=13.5824(6)	c=17.5437(8)
	alpha=90	beta=90	gamma=90
Temperature:	170 K		
	Calculated	Reported	
Volume	1964.47(16)	1964.47(16)	
Space group	P 21 21 21	P 21 21 21	
Hall group	P 2ac 2ab	P 2ac 2ab	
Moiety formula	C20 H27 N3 O6	C20 H27 N3 O6	
Sum formula	C20 H27 N3 O6	C20 H27 N3 O6	
Mr	405.45	405.44	
Dx,g cm-3	1.371	1.371	
z	4	4	
Mu (mm-1)	0.847	0.847	
F000	864.0	864.0	

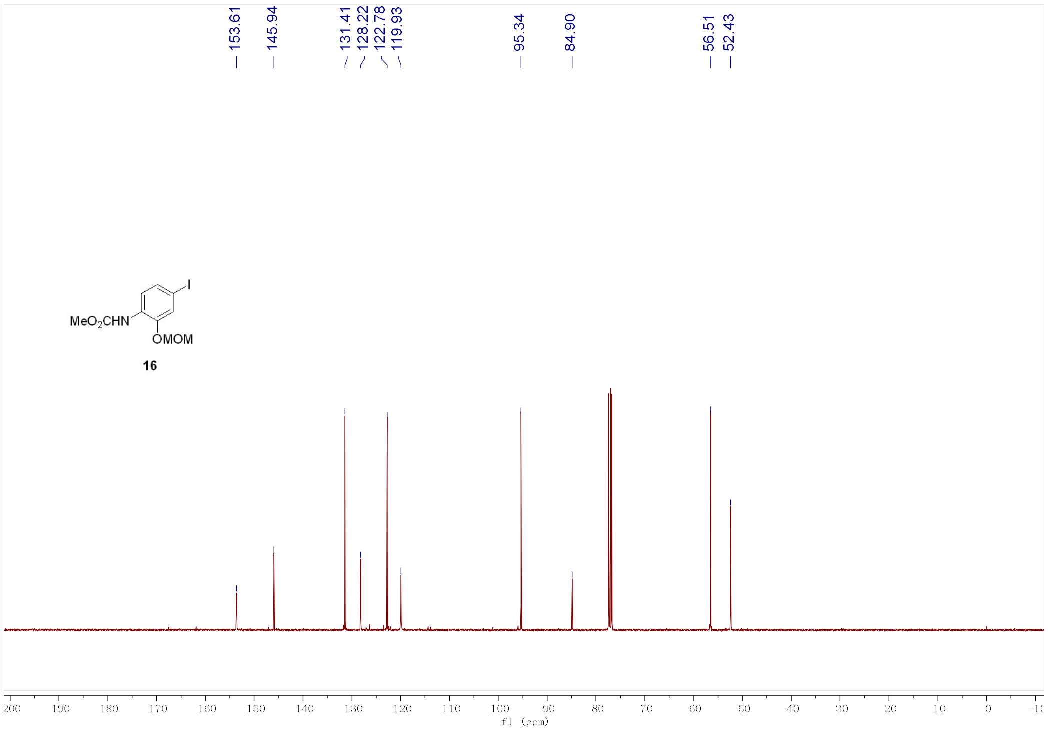
F000’	866.86		
h, k, l max	9, 16, 21	9, 16, 21	
Nref	3591[2064]	3592	
Tmin,Tmax	0.745,0.823	0.633,0.753	
Tmin’	0.725		

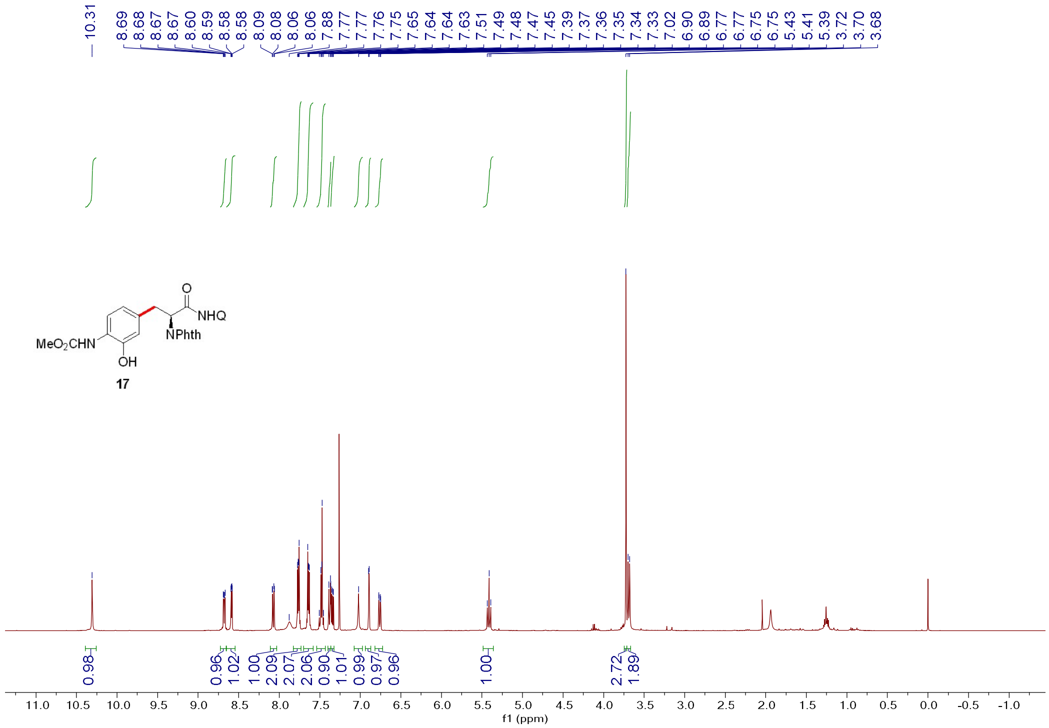
Correction method= # Reported T Limits: Tmin=0.633Tmax=0.753
AbsCorr = MULTI-SCAN			

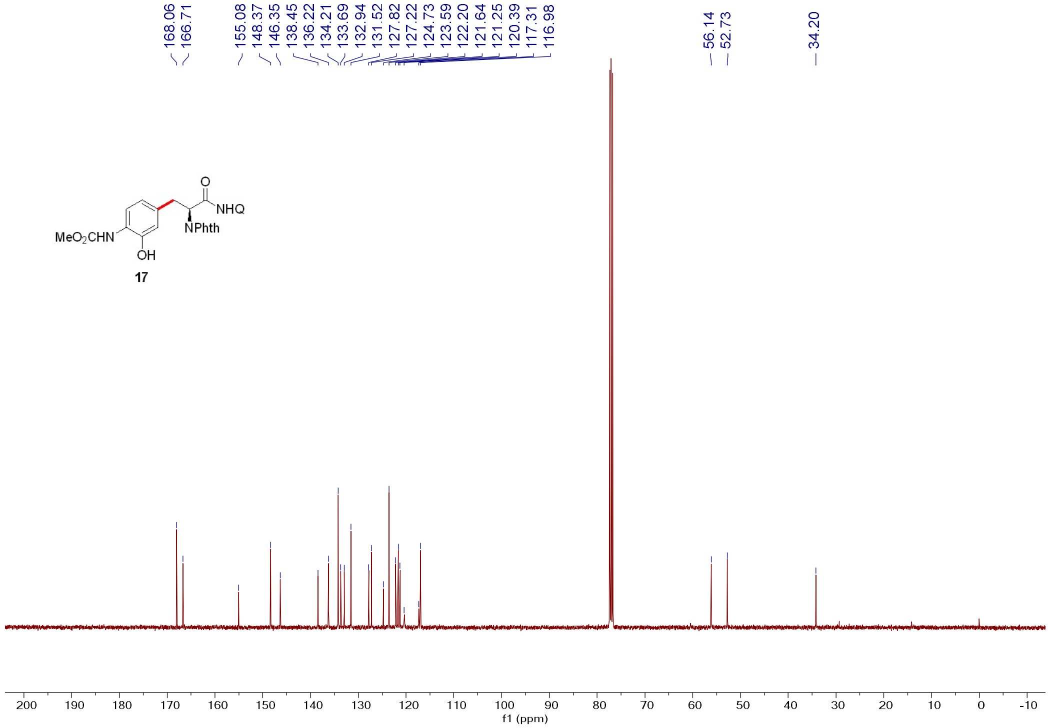
Data completeness= 1.74/1.00		Theta(max)= 68.265	
R(reflections)= 0.0265(3585)		wR2(reflections)= 0.0684(3592)	
S = 1.079		Npar= 267	

5. Copies of ^{1}H and ^{13}C NMR Spectra






10.31
8.69 8.68 8.67 8.67 8.60 8.59 8.58 8.58 8.09 8.08 8.06 8.06 7.88 7.77 7.77 7.76 7.75 7.65 7.64 7.64 7.63 7.51 7.49 7.48 7.47 7.45 7.39 7.37 7.36 7.35 7.34 7.33 7.02 6.90 6.89 6.77 6.77 6.75 6.75 5.43 5.41 5.39 3.72 3.70 3.68
MeO2CHN
OH
O
NHQ
NPhth
17
0.98 0.96 1.02 1.00 2.09 2.07 2.06 0.90 1.01 0.99 0.97 0.96 1.00 2.72 1.89
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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56.14 52.73
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OH
O
NHQ
NPhth
17
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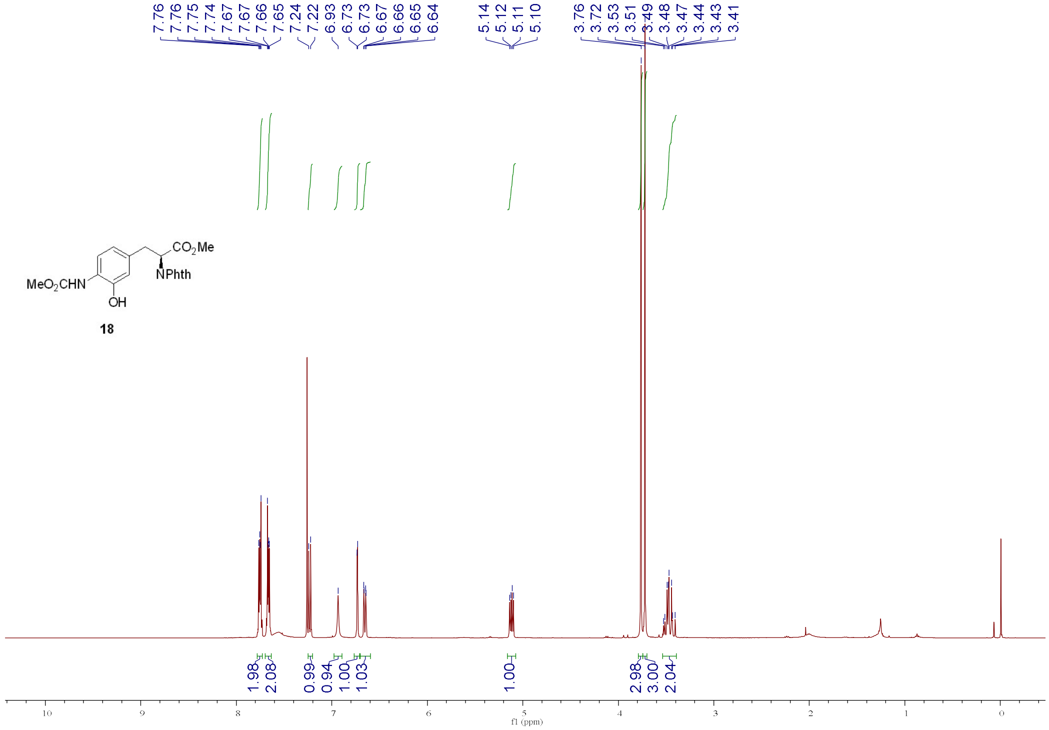
f1 (ppm)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7.65
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7.22
6.93
6.73
6.73
6.67
6.66
6.65
6.64
5.14
5.12
5.11
5.10
3.76
3.72
3.53
3.51
3.49
3.48
3.47
3.44
3.43
3.41
CO2Me
NPhth
MeO2CHN
OH
18
1.98
2.08
0.99
0.94
1.00
1.03
1.00
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3.00
2.04
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5
4
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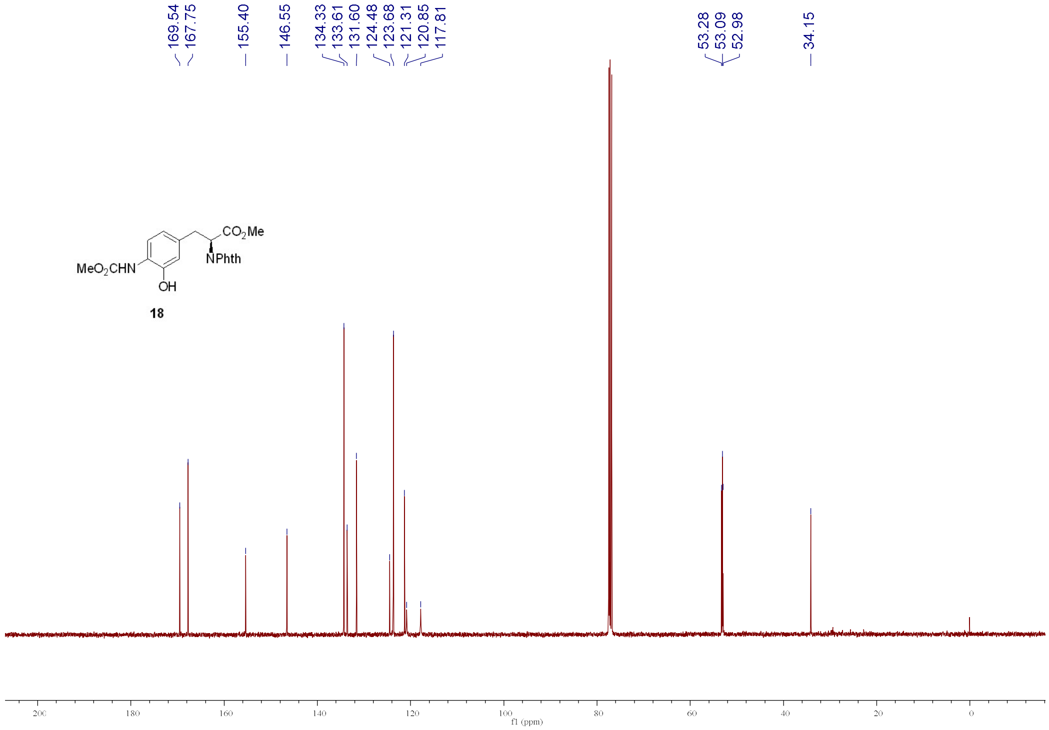
0
f1 (ppm)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53.28
53.09
52.98
34.15
CO2Me
NPhth
MeO2CHN
OH
18
200
180
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140
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100
80
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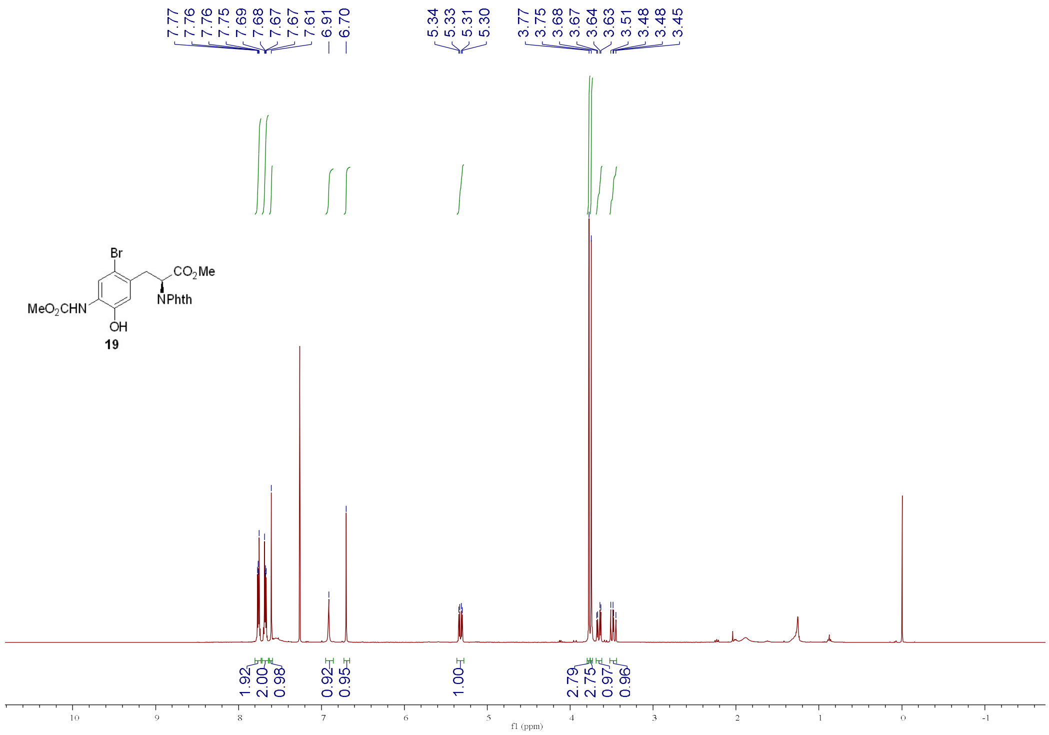
0
f1 (ppm)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5.33
5.31
5.30
3.77
3.75
3.68
3.67
3.64
3.63
3.51
3.48
3.48
3.45
Br
CO_2Me
NPhth
MeO_2CHN
OH
19
1.92
2.00
0.98
0.92
0.95
1.00
2.79
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3
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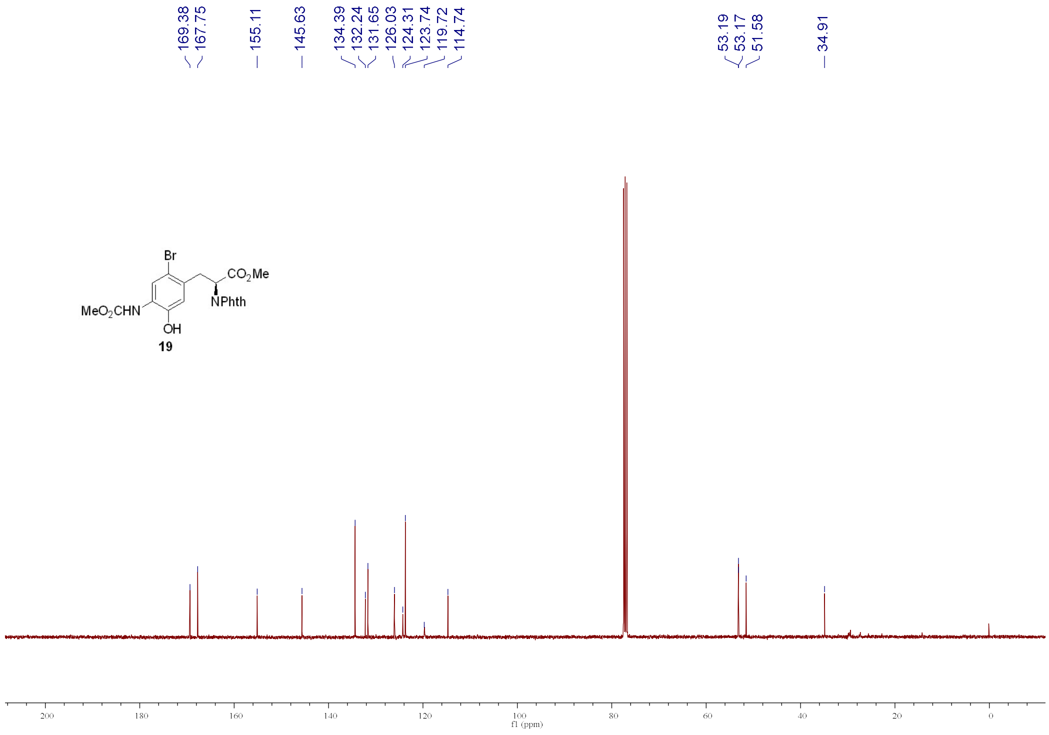
0
-1
f1 (ppm)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132.24
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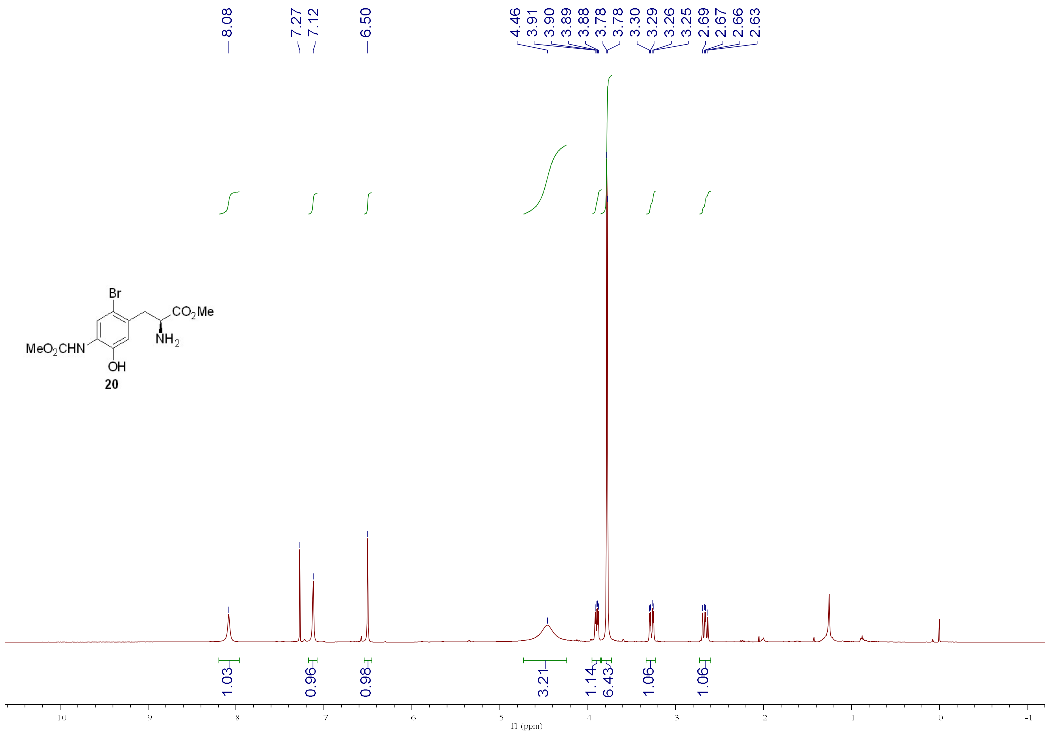
126.03
124.31
123.74
119.72
114.74
53.19
53.17
51.58
34.91
Br
CO_2Me
NPhth
MeO_2CHN
OH
19
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)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6.50
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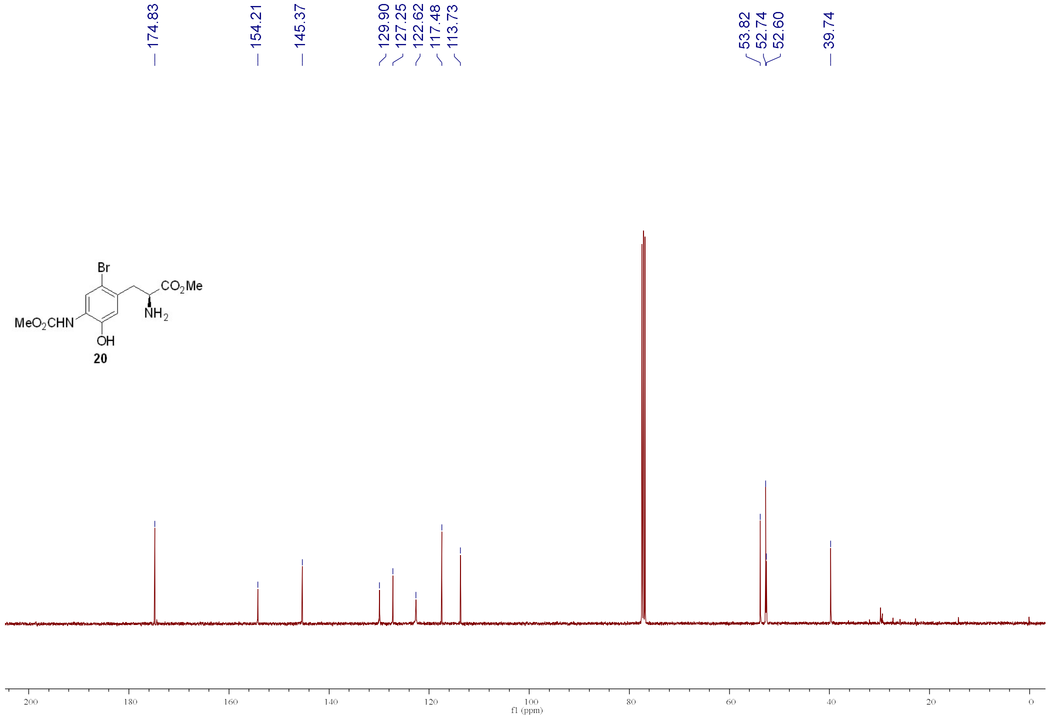
3.90
3.89
3.88
3.78
3.78
3.30
3.29
3.26
3.25
2.69
2.67
2.66
2.63
Br
CO2Me
NH2
MeO2CHN
OH
20
1.03
0.96
0.98
3.21
1.14
6.43
1.06
1.06
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

20a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154.21
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122.62
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113.73
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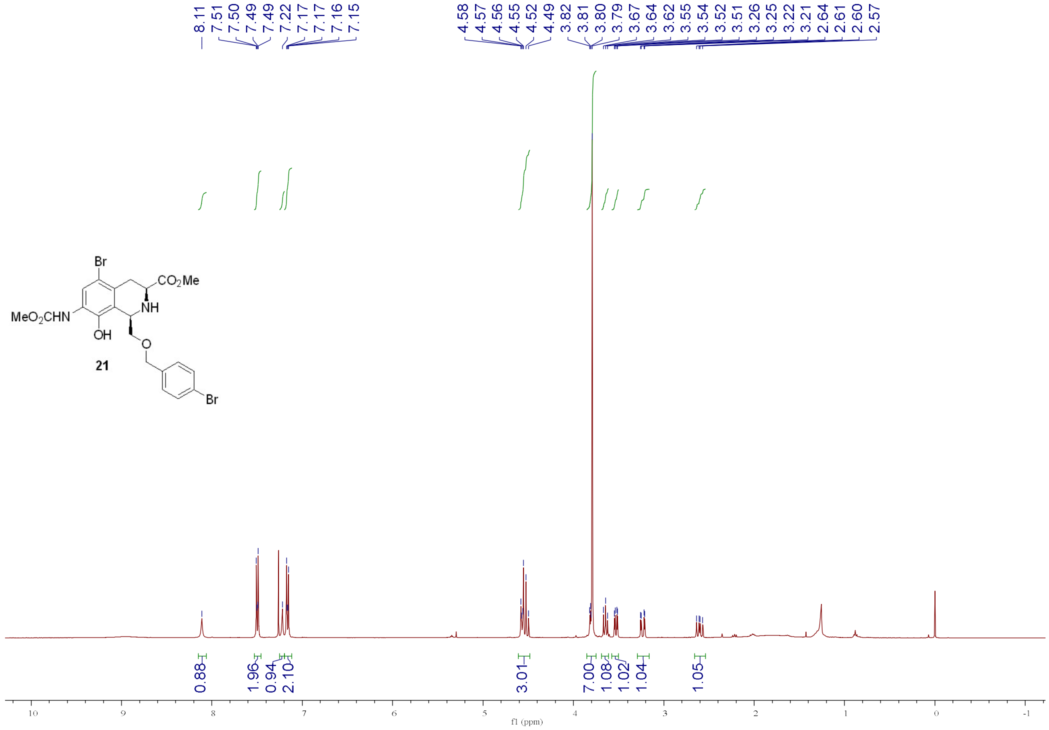
52.74
52.60
39.74
Br
CO2Me
NH2
MeO2CHN
OH
20
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)



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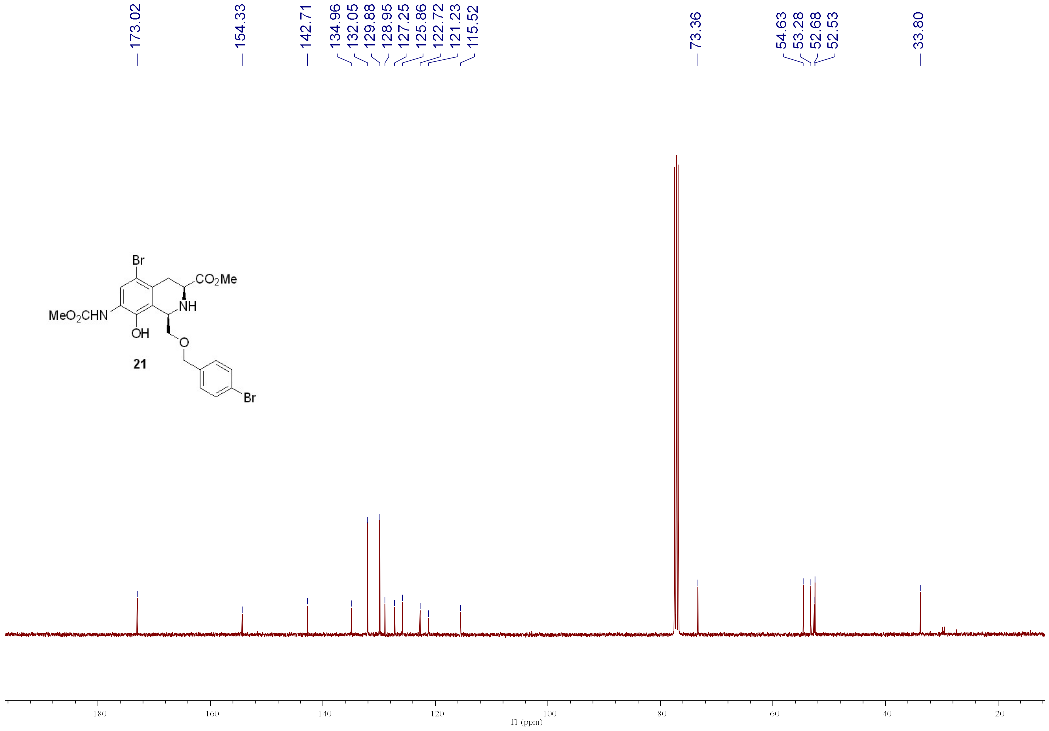
7.51
7.50
7.49
7.49
7.22
7.17
7.17
7.16
7.15
4.58
4.57
4.56
4.55
4.52
4.49
3.82
3.81
3.80
3.79
3.67
3.64
3.62
3.55
3.54
3.52
3.51
3.26
3.25
3.22
3.21
2.64
2.61
2.60
2.57
0.88
1.96
0.94
2.10
3.01
7.00
1.08
1.02
1.04
1.05
Br
CO2Me
NH
MeO2CHN
OH
O
21
Br
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)



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142.71
134.96
132.05
129.88
128.95
127.25
125.86
122.72
121.23
115.52
73.36
54.63
53.28
52.68
52.53
33.80
Br
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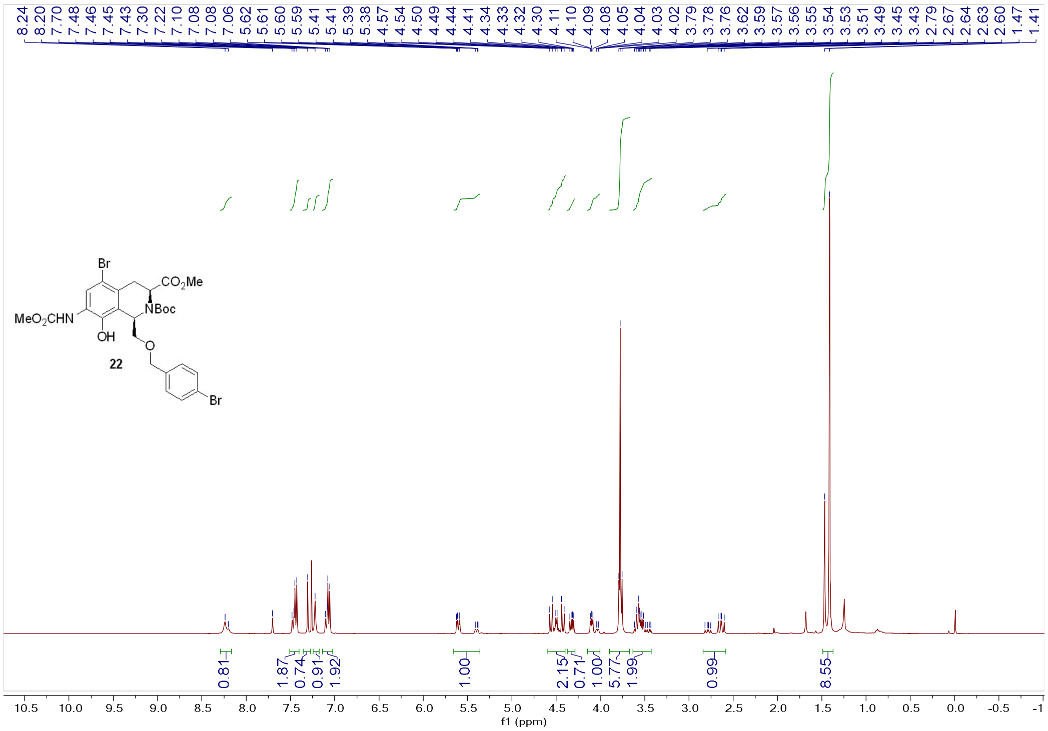
NH
MeO2CHN
OH
O
21
Br
180
160
140
120
100
80
60
40
20
f1 (ppm)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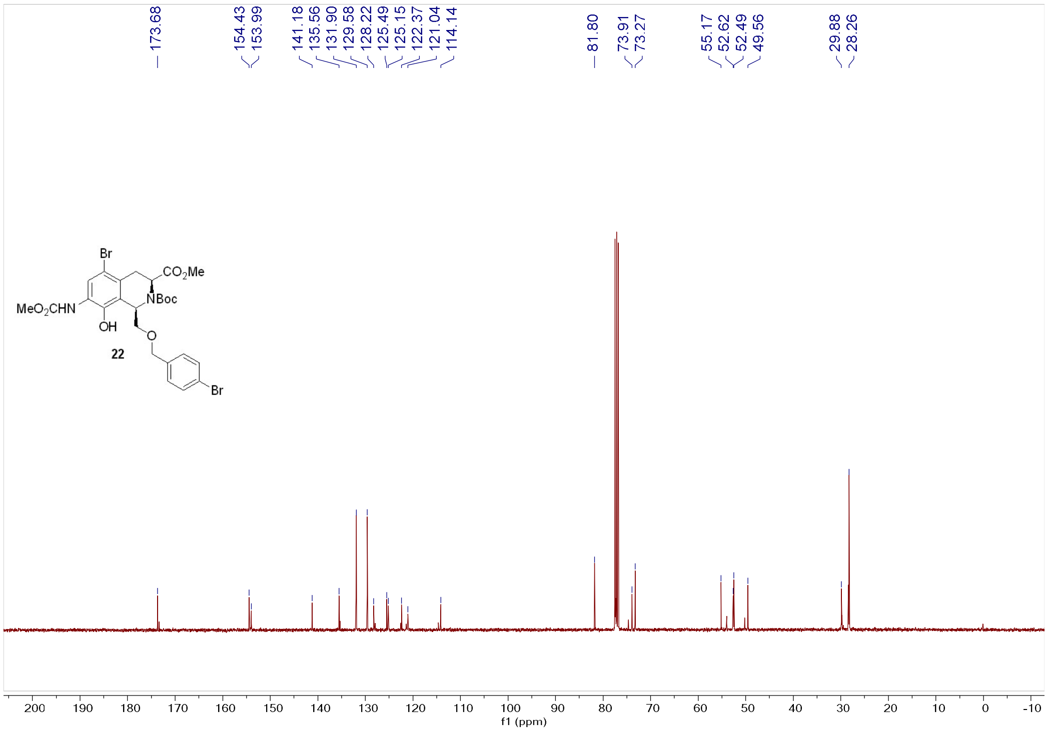
7.45
7.43
7.30
7.22
7.10
7.08
7.08
7.06
5.62
5.61
5.60
5.59
5.41
5.41
5.39
5.38
4.57
4.54
4.50
4.49
4.44
4.41
4.34
4.33
4.32
4.30
4.11
4.10
4.09
4.08
4.05
4.04
4.03
4.02
3.79
3.78
3.76
3.62
3.59
3.57
3.56
3.55
3.54
3.53
3.51
3.49
3.45
3.43
2.79
2.67
2.64
2.63
2.60
1.47
1.41
Br
CO$_2$Me
NBoc
MeO$_2$CHN
OH
O
22
Br
0.81
1.87
0.74
0.91
1.92
1.00
2.15
0.71
1.00
5.77
1.99
0.99
8.55
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)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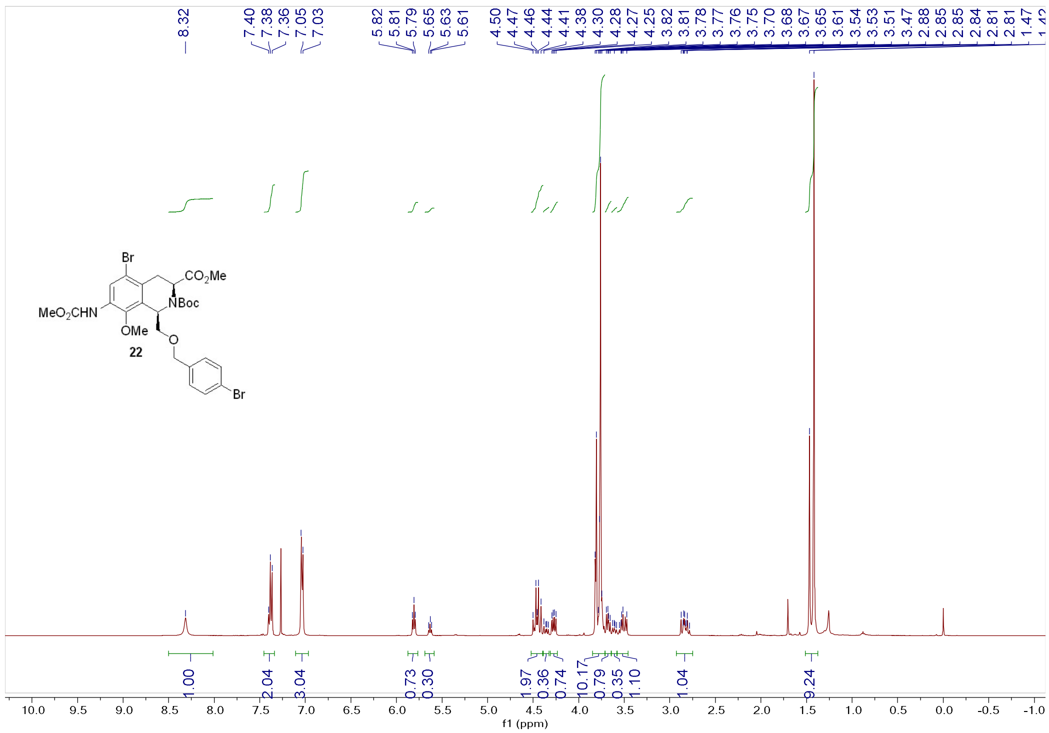
141.18
135.56
131.90
129.58
128.22
125.49
125.15
122.37
121.04
114.14
81.80
73.91
73.27
55.17
52.62
52.49
49.56
29.88
28.26
Br
CO$_2$Me
NBoc
MeO$_2$CHN
OH
O
22
Br
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.38
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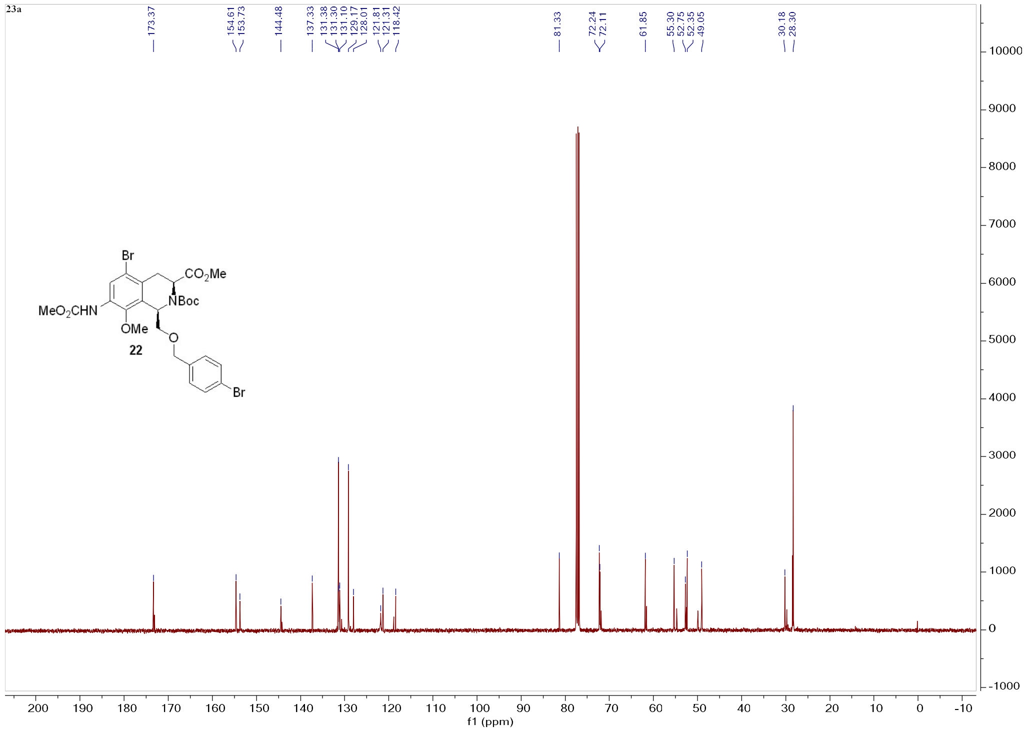
5.81
5.79
5.65
5.63
5.61
4.50
4.47
4.46
4.44
4.41
4.38
4.30
4.28
4.27
4.25
3.82
3.81
3.78
3.77
3.76
3.75
3.70
3.68
3.67
3.65
3.61
3.54
3.53
3.51
3.47
2.88
2.85
2.85
2.84
2.81
2.81
1.47
1.00
2.04
3.04
0.73
0.30
1.97
0.36
0.74
10.17
0.79
0.35
1.10
1.04
9.24
Br
CO2Me
NBoc
MeO2CHN
OMe
O
22
Br
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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131.38
131.30
131.10
129.17
128.01
121.81
121.31
118.42
81.33
72.24
72.11
61.85
55.30
52.75
52.35
49.05
30.18
28.30
Br
CO2Me
NBoc
MeO2CHN
OMe
O
22
Br
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
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60
50
40
30
20
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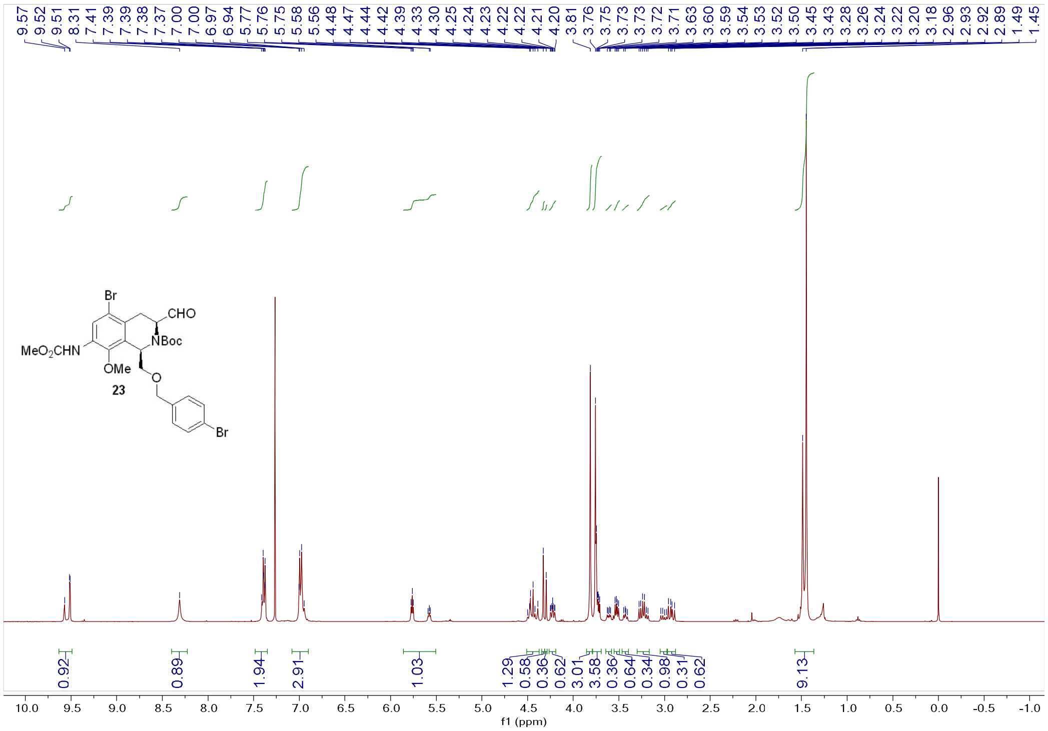
0
-10
f1 (ppm)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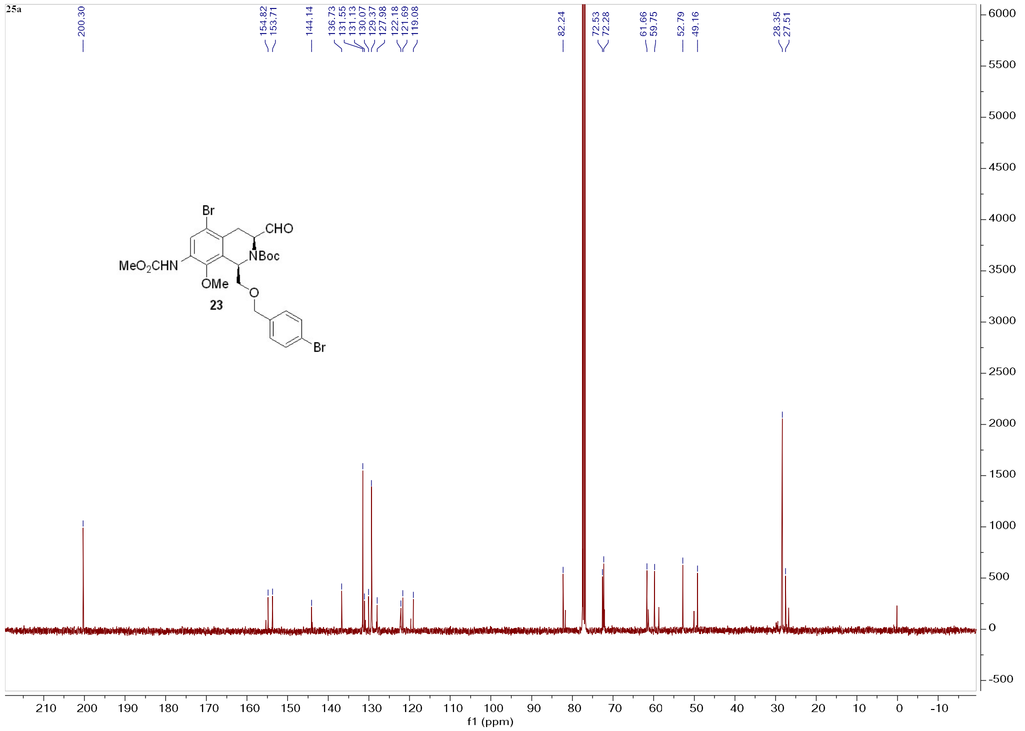
Br
CHO
NBoc
MeO2CHN
OMe
23
O
Br
0.92 0.89 1.94 2.91 1.03 1.29 0.58 0.36 0.62 3.01 3.58 0.36 0.64 0.34 0.98 0.31 0.62 9.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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144.14
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82.24
72.53 72.28
61.66 59.75
52.79 49.16
28.35 27.51
Br
CHO
NBoc
MeO2CHN
OMe
23
O
Br
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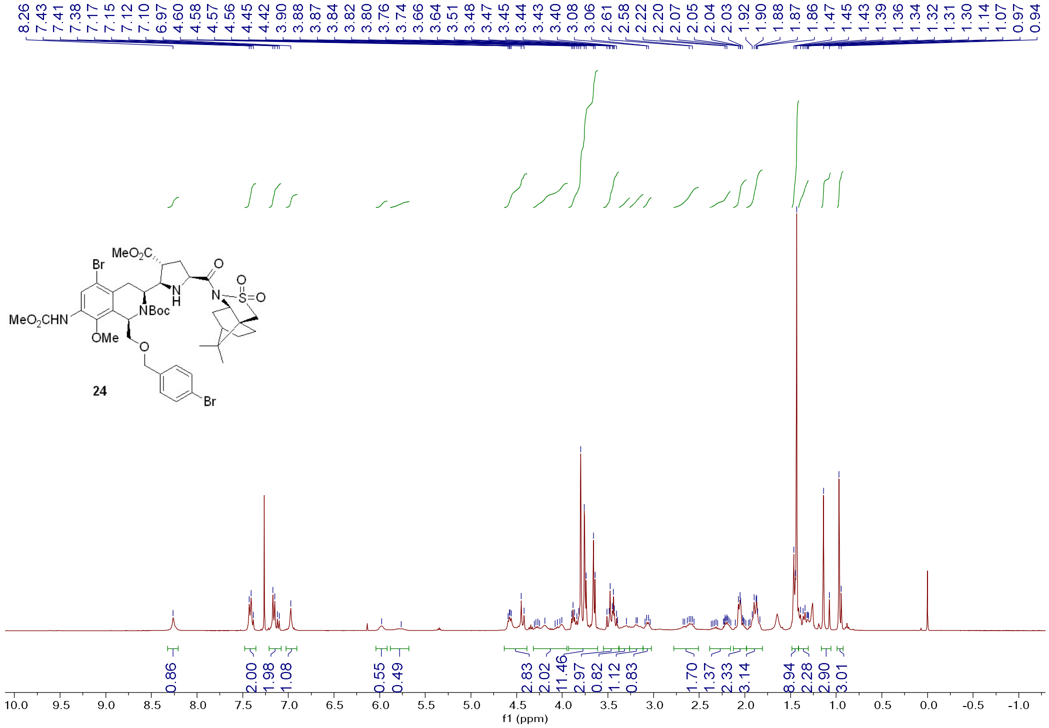
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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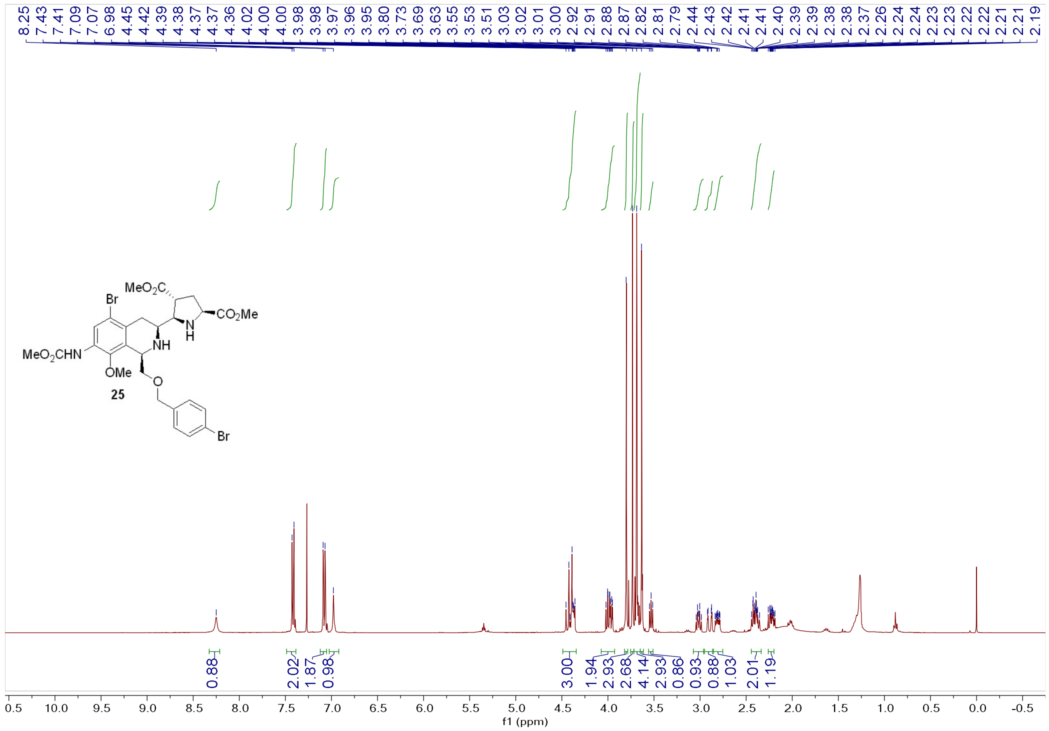
4.57
4.56
4.45
4.42
3.90
3.88
3.87
3.84
3.82
3.80
3.76
3.74
3.66
3.64
3.51
3.48
3.47
3.45
3.44
3.43
3.40
3.08
3.06
2.61
2.58
2.22
2.20
2.07
2.05
2.04
2.03
1.92
1.90
1.88
1.87
1.86
1.47
1.45
1.43
1.39
1.36
1.34
1.32
1.31
1.30
1.14
1.07
0.97
0.94
Br
MeO$_2$C
O
N
S
O
O
H
NBoc
MeO$_2$CHN
OMe
O
Br
24
0.86
2.00
1.98
1.08
0.55
0.49
2.83
2.02
11.46
2.97
0.82
1.12
0.83
1.70
1.37
2.33
3.14
8.94
2.28
2.90
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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4.45
4.42
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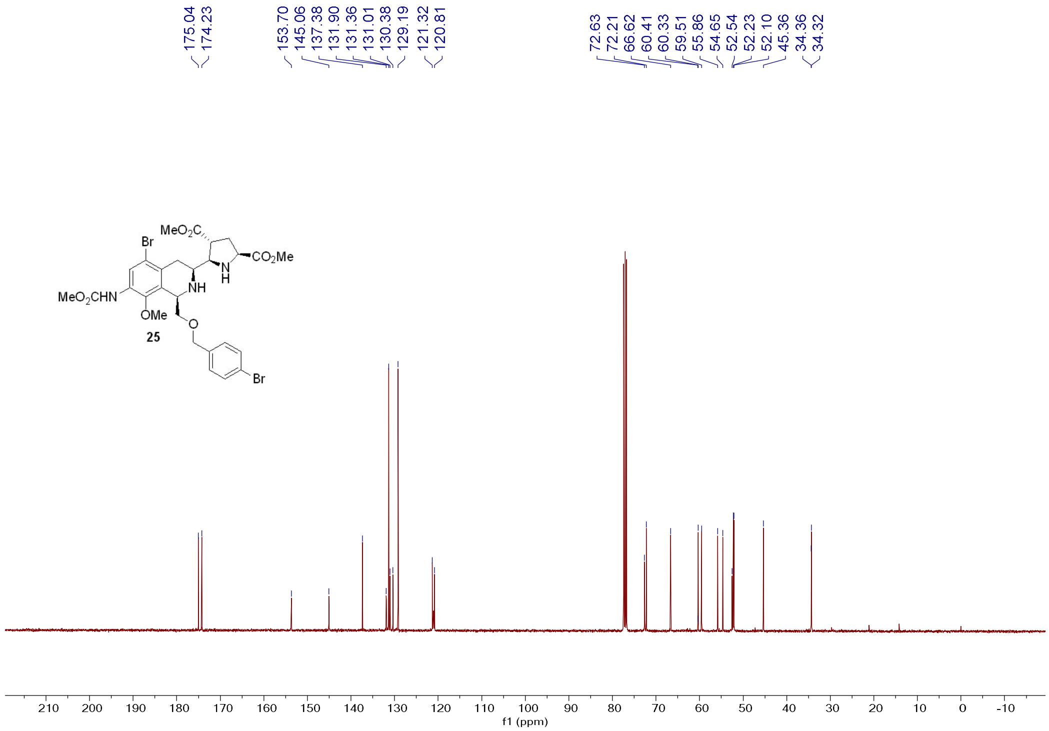
4.38
4.37
4.37
4.36
4.02
4.00
4.00
3.98
3.98
3.97
3.96
3.95
3.80
3.73
3.69
3.63
3.55
3.53
3.51
3.03
3.02
3.01
3.00
2.92
2.91
2.88
2.87
2.82
2.81
2.79
2.44
2.43
2.42
2.41
2.41
2.40
2.39
2.39
2.38
2.38
2.37
2.26
2.24
2.24
2.23
2.22
2.22
2.21
2.21
2.19
Br
MeO_2C
CO_2Me
N
H
NH
MeO_2CHN
OMe
25
O
Br
0.88
2.02
1.87
0.98
3.00
1.94
2.93
2.68
4.14
2.93
0.86
0.93
0.88
1.03
2.01
1.19
0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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131.90
131.36
131.01
130.38
129.19
121.32
120.81
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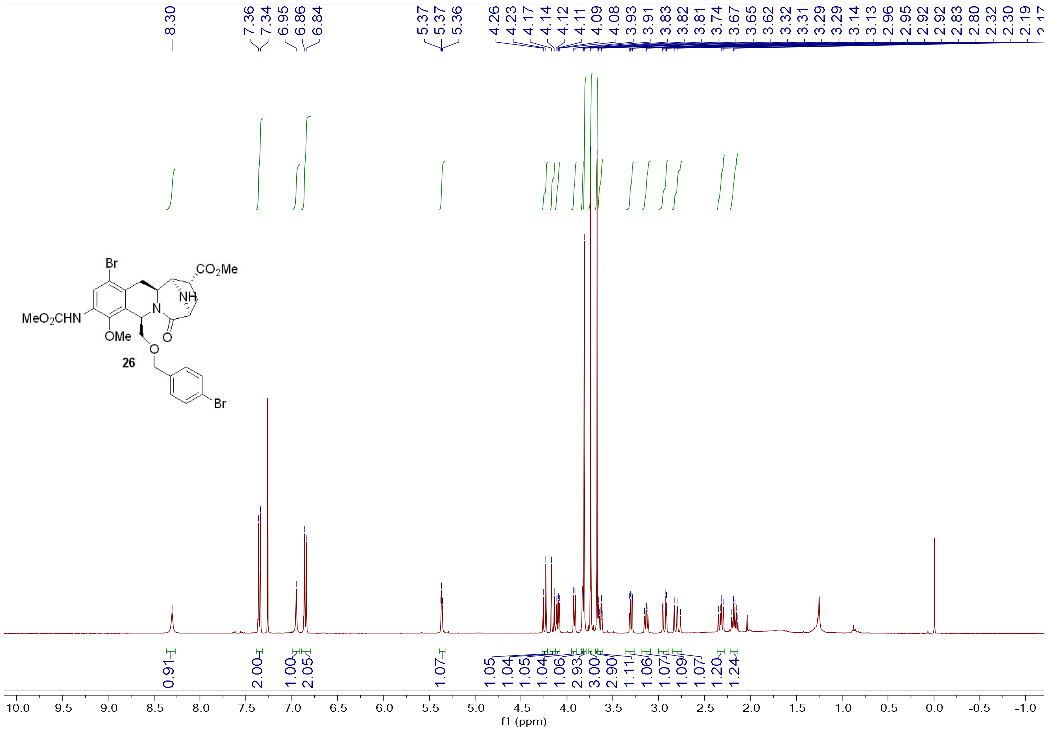
72.21
66.62
60.41
60.33
59.51
55.86
54.65
52.54
52.23
52.10
45.36
34.36
34.32
Br
MeO_2C
CO_2Me
N
H
NH
MeO_2CHN
OMe
25
O
Br
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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6.95
6.86
6.84
5.37
5.37
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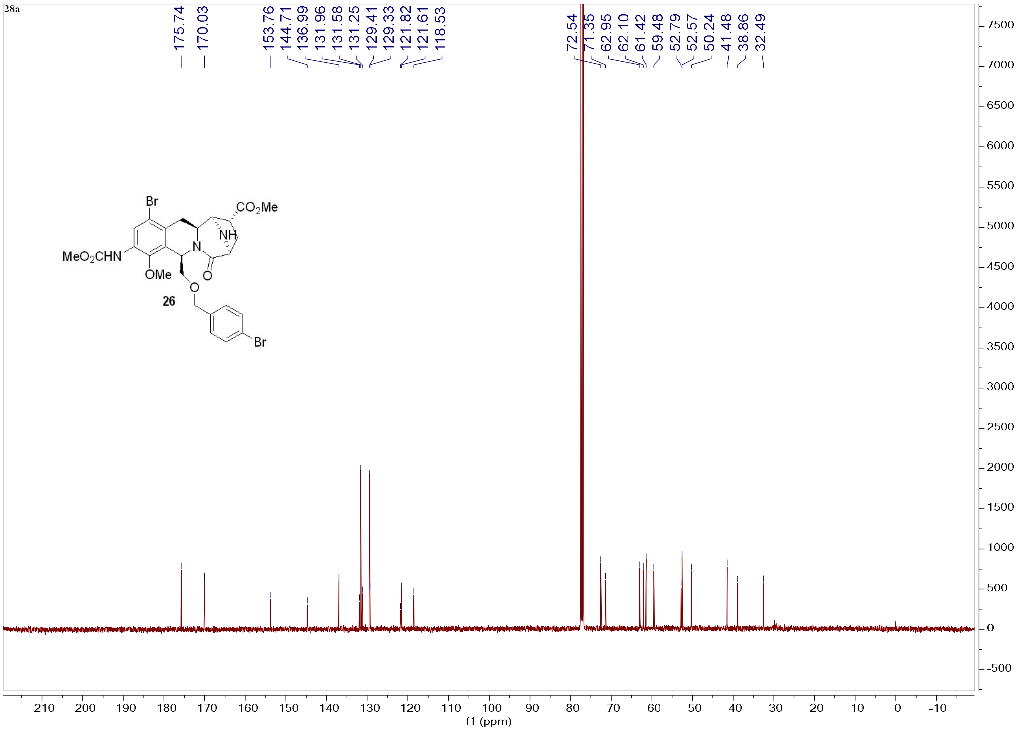
4.26
4.23
4.17
4.14
4.12
4.11
4.09
4.08
3.93
3.91
3.83
3.82
3.81
3.74
3.67
3.65
3.62
3.32
3.31
3.29
3.29
3.14
3.13
2.96
2.95
2.92
2.92
2.83
2.80
2.32
2.30
2.19
Br
CO_2Me
NH
N
MeO_2CHN
OMe
O
O
26
Br
0.91
2.00
1.00
2.05
1.07
1.05
1.04
1.05
1.04
1.06
2.93
3.00
2.90
1.11
1.06
1.07
1.09
1.07
1.20
1.24
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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129.41
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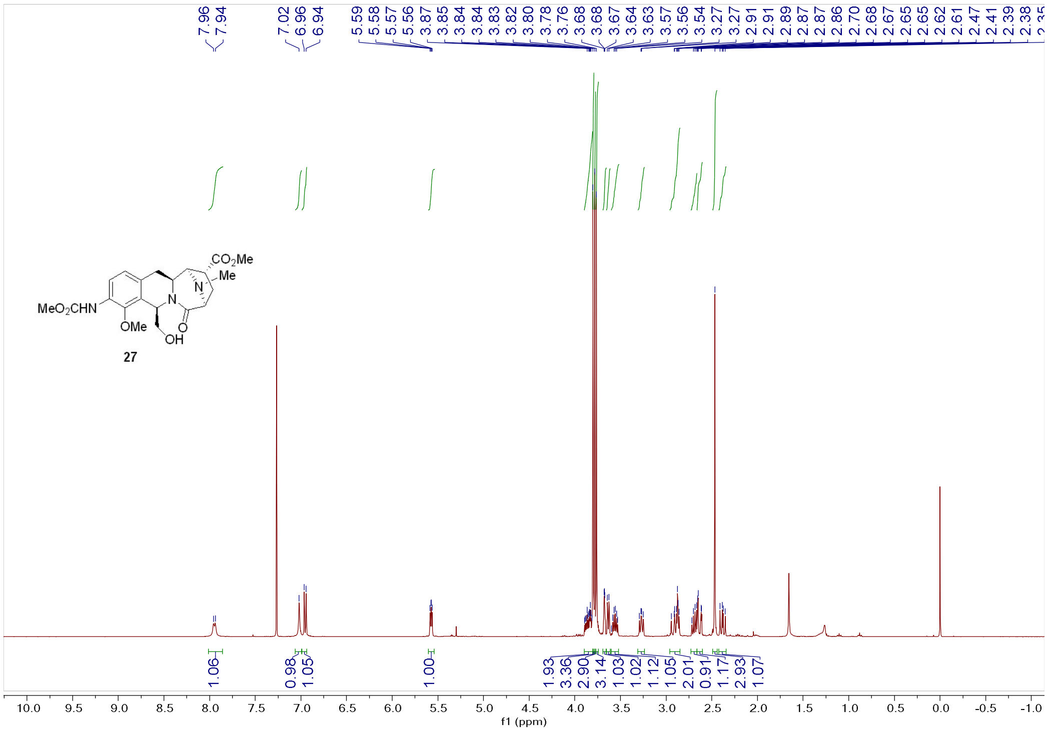
121.61
118.53
72.54
71.35
62.95
62.10
61.42
59.48
52.79
52.57
50.24
41.48
38.86
32.49
Br
CO_2Me
NH
N
MeO_2CHN
OMe
O
O
26
Br
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.96
7.94
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6.96
6.94
5.59
5.58
5.57
5.56
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3.85
3.84
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3.83
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3.76
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3.68
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3.63
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3.56
3.54
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3.27
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2.86
2.70
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2.62
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2.47
2.41
2.39
2.38
CO_2Me
Me
N
N
MeO_2CHN
OMe
O
OH
27
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1.05
1.00
1.93
3.36
2.90
3.14
1.03
1.02
1.12
1.05
2.01
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1.17
2.93
1.07
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9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
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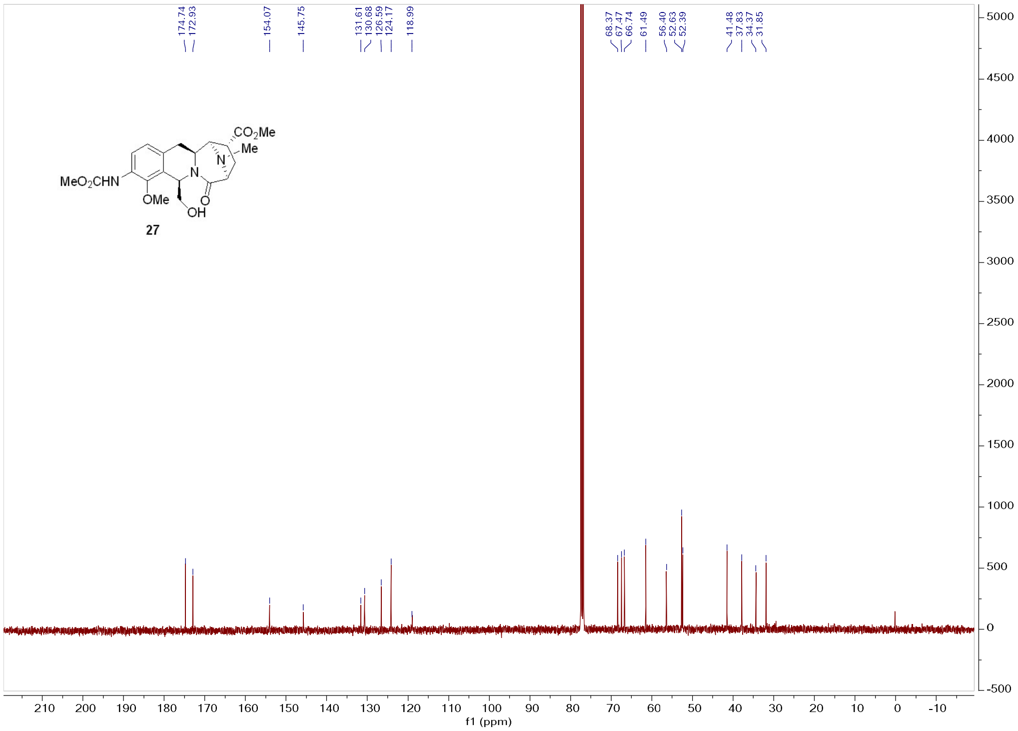
f1 (ppm)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124.17
118.99
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66.74
61.49
56.40
52.63
52.39
41.48
37.83
34.37
31.85
CO_2Me
Me
N
N
MeO_2CHN
OMe
O
OH
27
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
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140
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120
110
100
90
80
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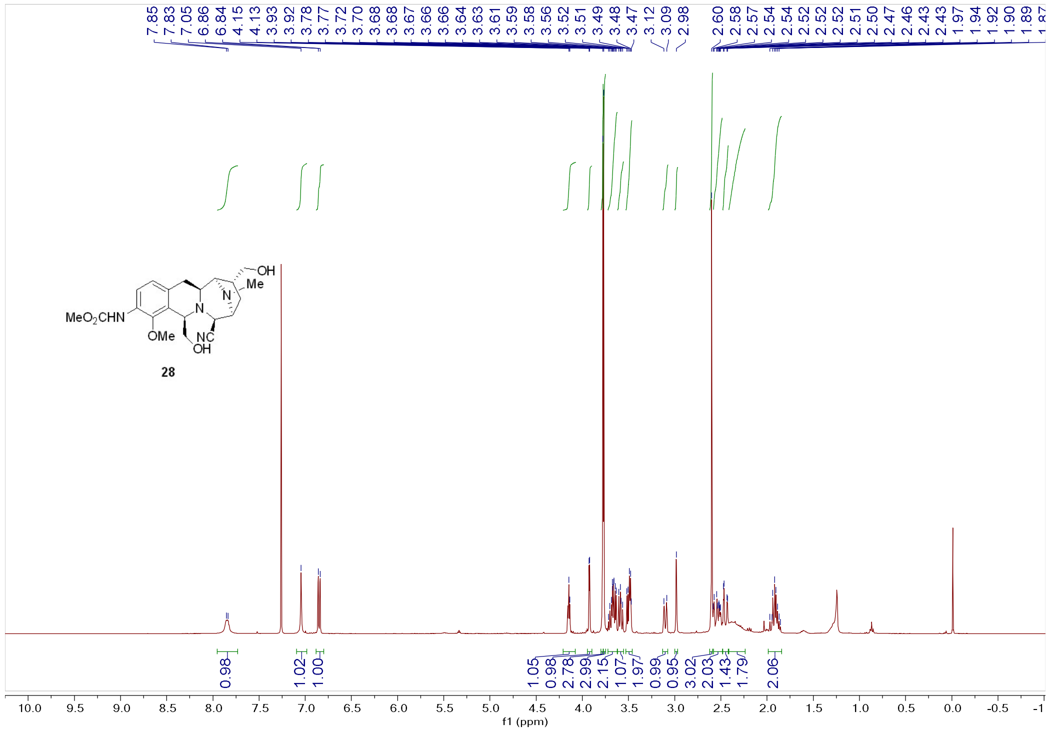
50
40
30
20
10
0
-10
f1 (ppm)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4.13
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3.92
3.78
3.77
3.72
3.70
3.68
3.68
3.67
3.66
3.66
3.64
3.63
3.61
3.59
3.58
3.56
3.52
3.51
3.49
3.48
3.47
3.12
3.09
2.98
2.60
2.58
2.57
2.54
2.54
2.52
2.52
2.52
2.51
2.50
2.47
2.46
2.43
2.43
1.97
1.94
1.92
1.90
1.89
OH
Me
N
MeO2CHN
N
OMe
NC
OH
28
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1.02
1.00
1.05
0.98
2.78
2.99
2.15
1.07
1.97
0.99
0.95
3.02
2.03
1.43
1.79
2.06
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9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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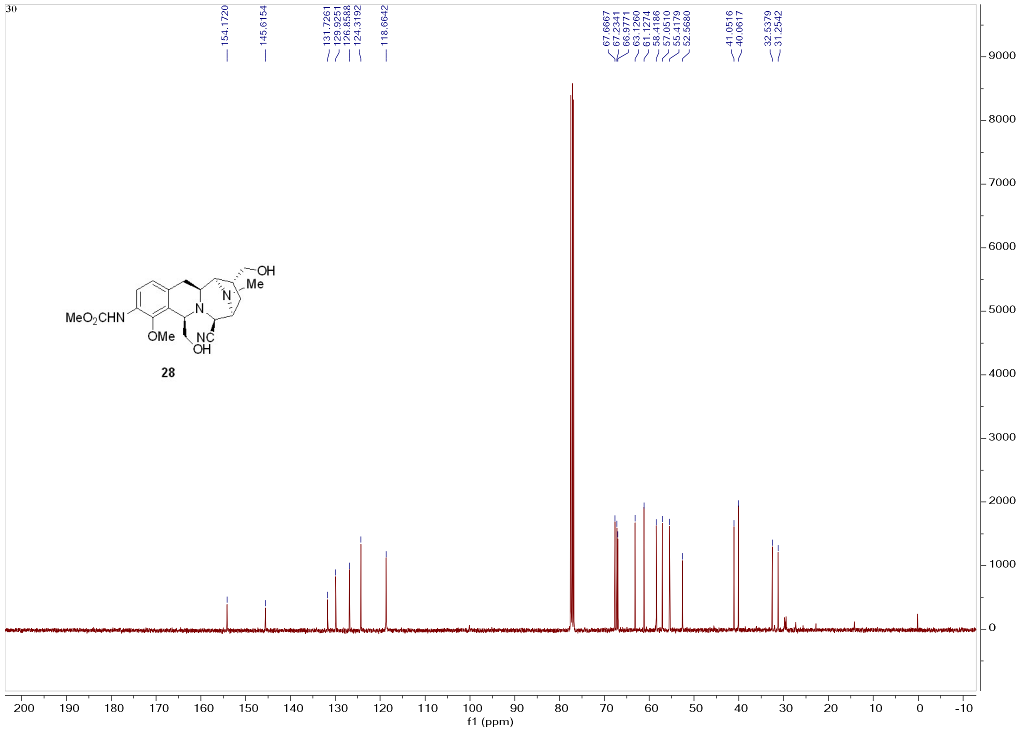
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)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66.9771
63.1260
61.1274
58.4186
57.0510
55.4179
52.5680
41.0516
40.0617
32.5379
31.2542
OH
Me
N
MeO2CHN
N
OMe
NC
OH
28
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
200
190
180
170
160
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140
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120
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100
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80
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40
30
20
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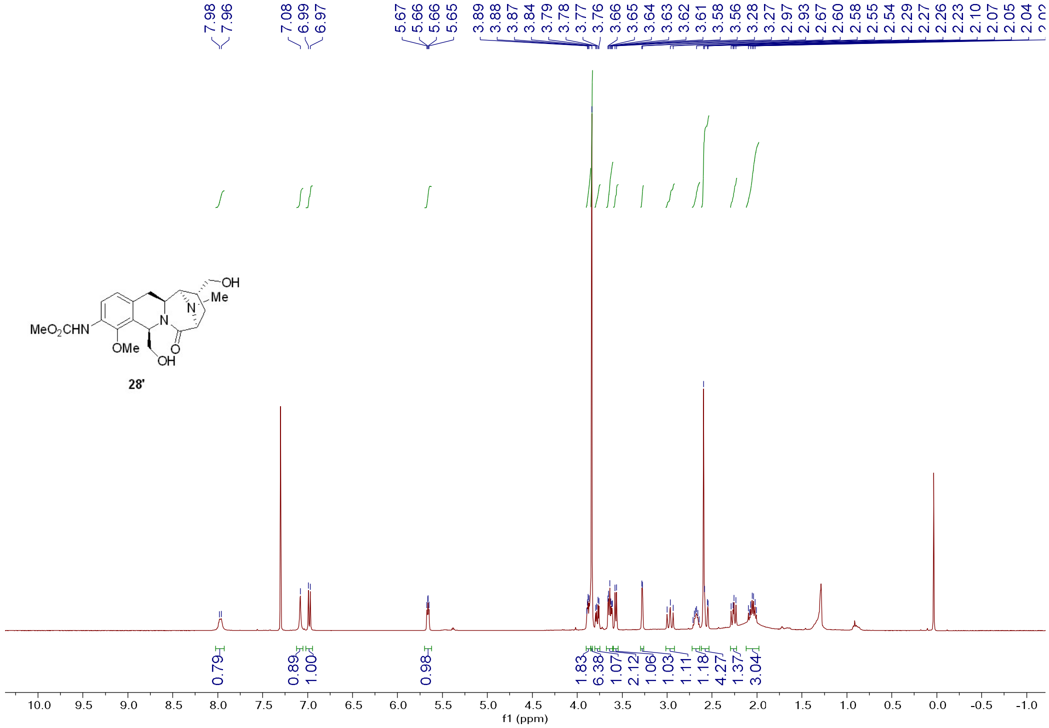
-10
f1 (ppm)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3.84
3.79
3.78
3.77
3.76
3.66
3.65
3.64
3.63
3.62
3.61
3.58
3.56
3.28
3.27
2.97
2.93
2.67
2.60
2.58
2.55
2.54
2.29
2.27
2.26
2.23
2.10
2.07
2.05
2.04
MeO2CHN
OMe
OH
N
Me
O
OH
28'
0.79
0.89
1.00
0.98
1.83
6.38
1.07
2.12
1.06
1.03
1.11
1.18
4.27
1.37
3.04
10.0
9.5
9.0
8.5
8.0
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.0
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0.0
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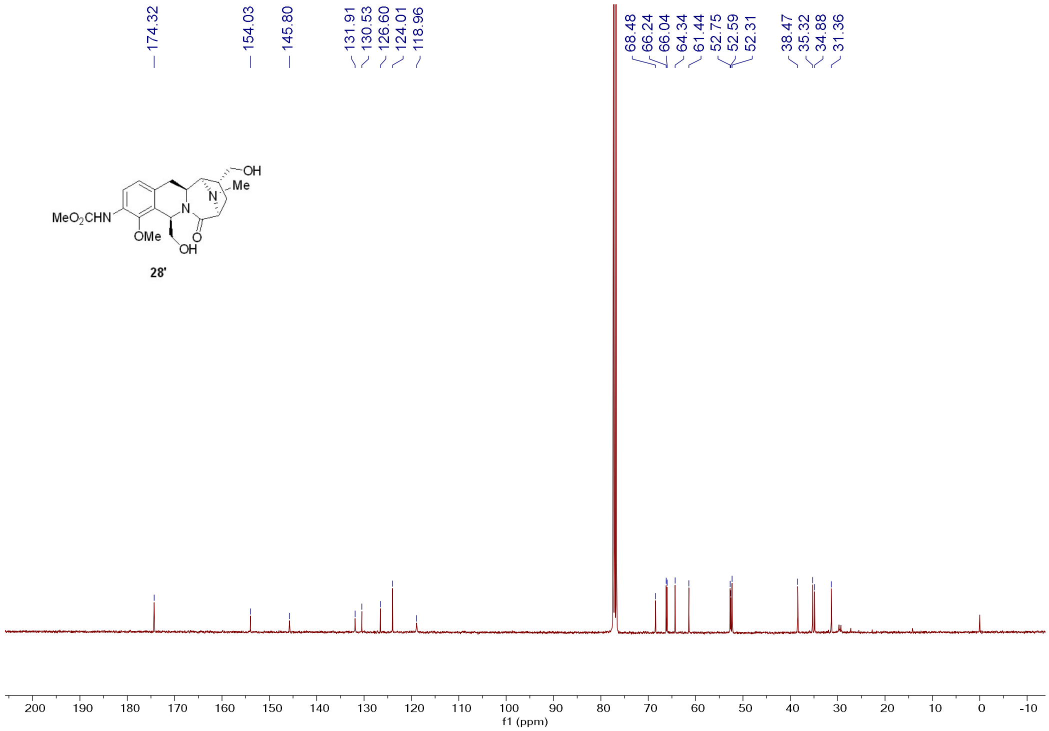
-1.0
f1 (ppm)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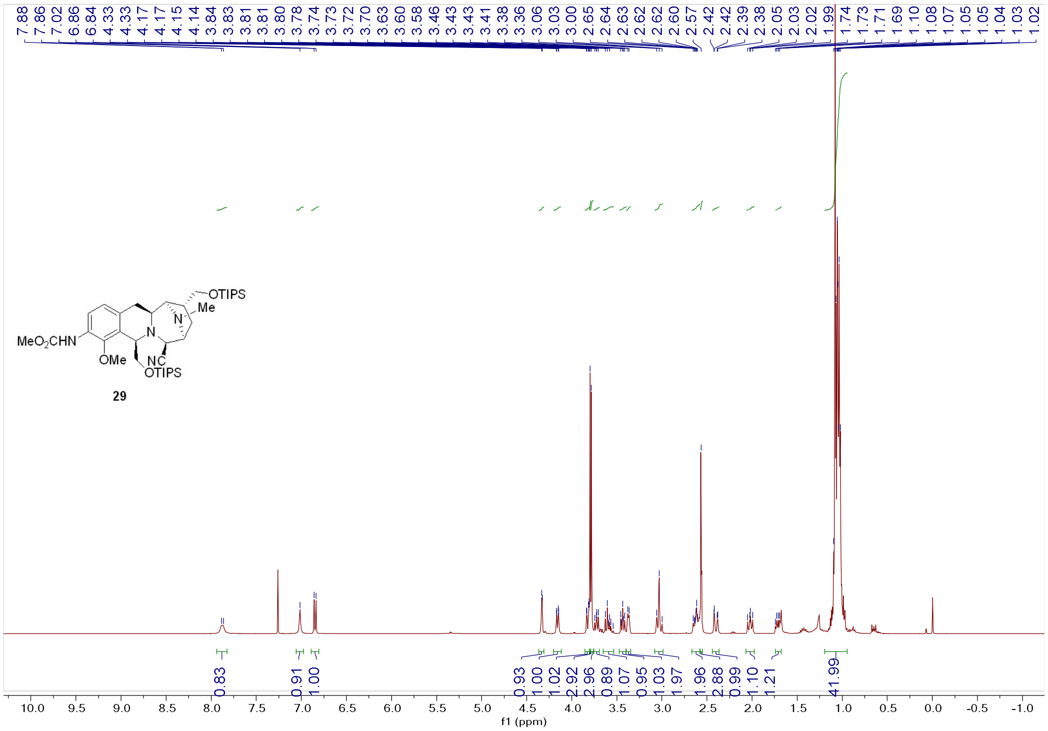
124.01
118.96
68.48
66.24
66.04
64.34
61.44
52.75
52.59
52.31
38.47
35.32
34.88
31.36
MeO2CHN
OMe
OH
N
Me
O
OH
28'
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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6.86
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4.14
3.84
3.83
3.81
3.81
3.80
3.78
3.74
3.73
3.72
3.70
3.63
3.60
3.58
3.46
3.43
3.43
3.41
3.38
3.36
3.06
3.03
3.00
2.65
2.64
2.63
2.62
2.60
2.57
2.42
2.42
2.39
2.38
2.05
2.03
2.02
1.99
1.74
1.73
1.71
1.69
1.10
1.08
1.07
1.05
1.05
1.04
1.03
1.02
OTIPS
Me
N
MeO$_2$CHN
N
OMe
NC
OTIPS
29
0.83
0.91
1.00
0.93
1.00
1.02
2.92
2.96
0.89
1.07
0.95
1.03
1.97
1.96
2.88
0.99
1.10
1.21
41.99
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.5
2.0
1.5
1.0
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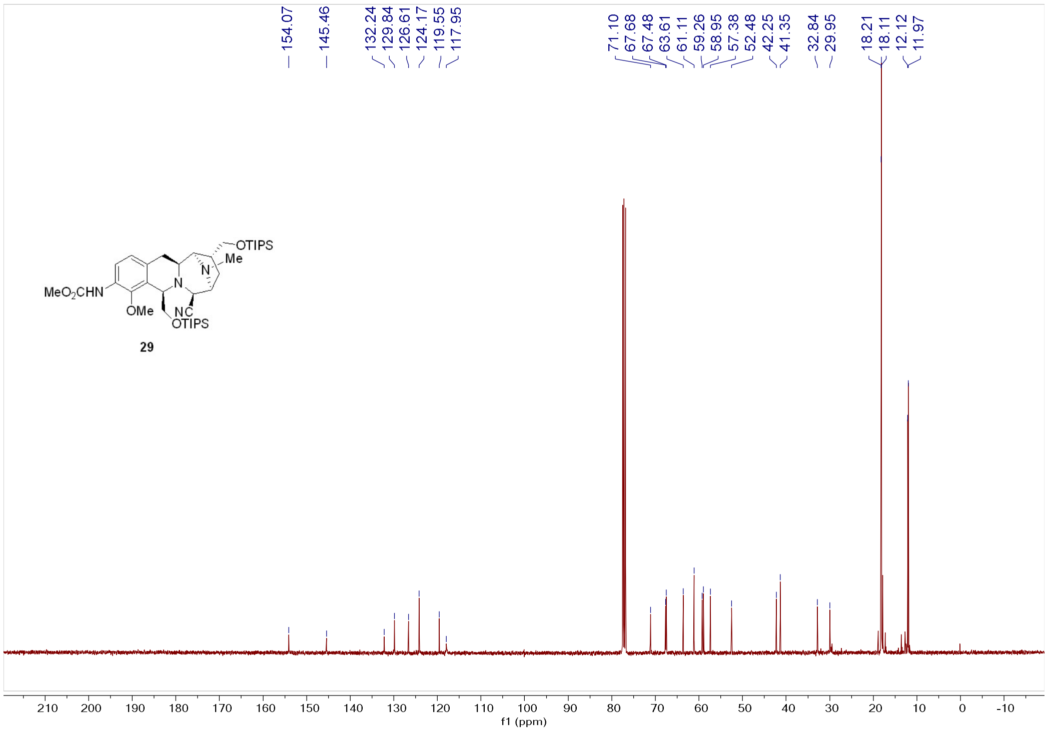
0.0
-0.5
-1.0
f1 (ppm)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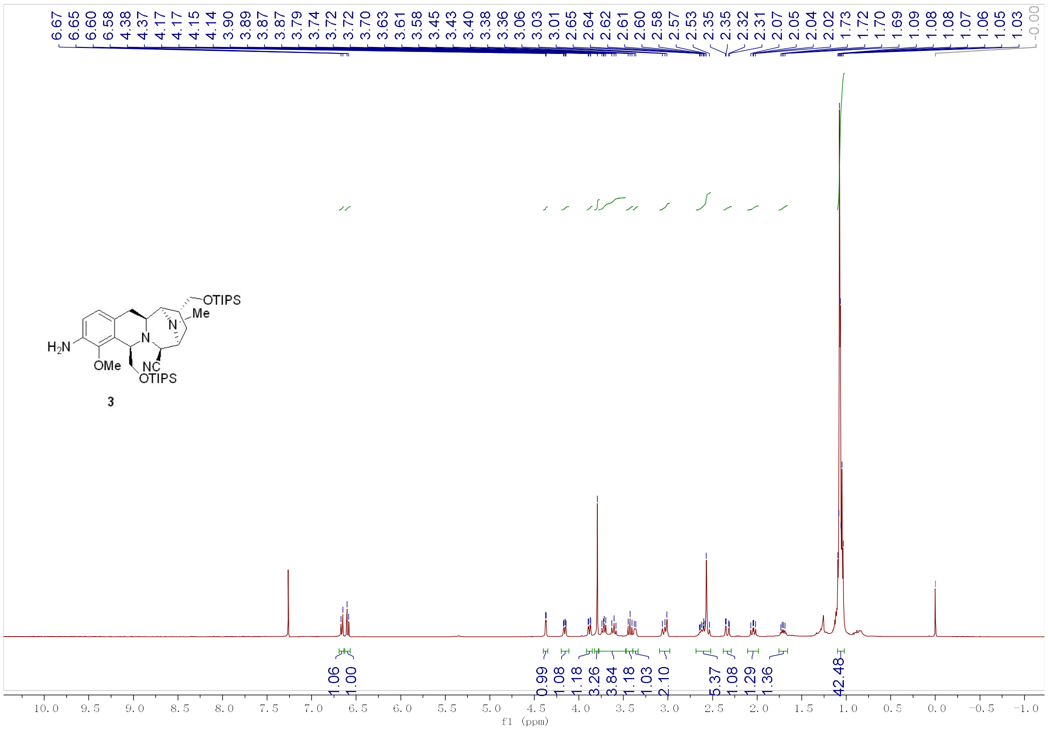
67.68
67.48
63.61
61.11
59.26
58.95
57.38
52.48
42.25
41.35
32.84
29.95
18.21
18.11
12.12
11.97
OTIPS
Me
N
MeO$_2$CHN
N
OMe
NC
OTIPS
29
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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3.87
3.87
3.79
3.74
3.72
3.72
3.70
3.63
3.61
3.58
3.45
3.43
3.40
3.38
3.36
3.06
3.03
3.01
2.65
2.64
2.62
2.61
2.60
2.58
2.57
2.53
2.35
2.35
2.32
2.31
2.07
2.05
2.04
2.02
1.73
1.72
1.70
1.69
1.09
1.08
1.07
1.06
1.05
1.03
-0.00
OTIPS
Me
N
H2N
N
OMe
NC
OTIPS
3
1.06
1.00
0.99
1.08
1.18
3.26
3.84
1.18
1.03
2.10
5.37
1.08
1.29
1.36
42.48
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.5
2.0
1.5
1.0
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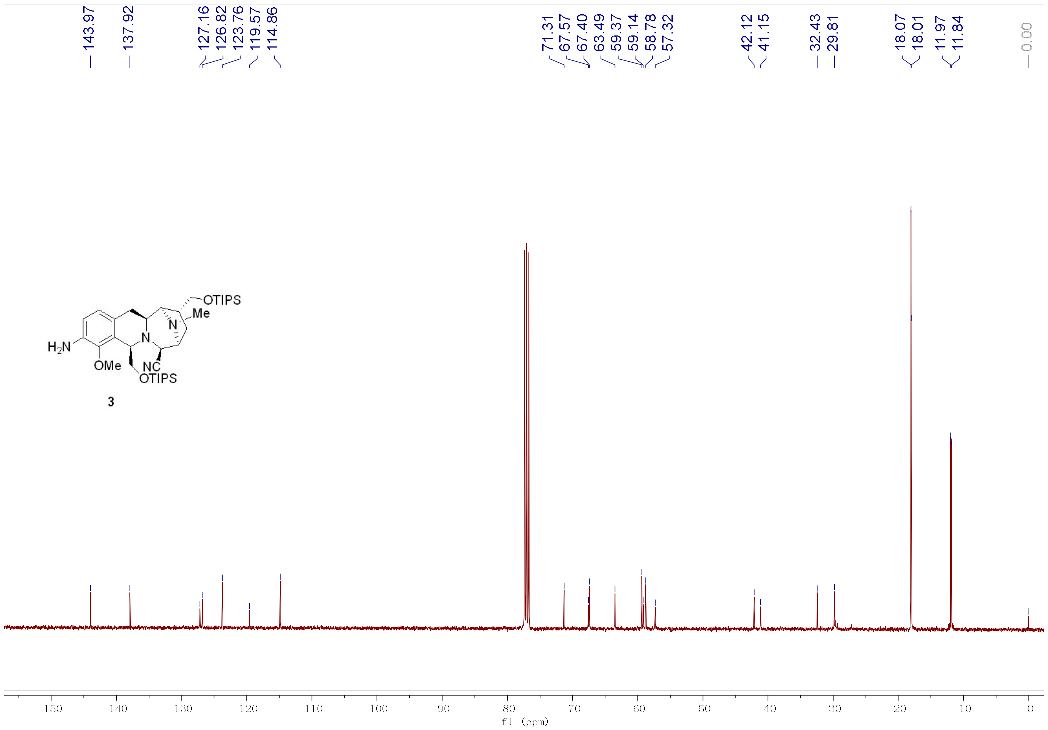
0.0
-0.5
-1.0
f1 (ppm)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67.40
63.49
59.37
59.14
58.78
57.32
42.12
41.15
32.43
29.81
18.07
18.01
11.97
11.84
0.00
OTIPS
Me
N
H2N
N
OMe
NC
OTIPS
3
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140
130
120
110
100
90
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40
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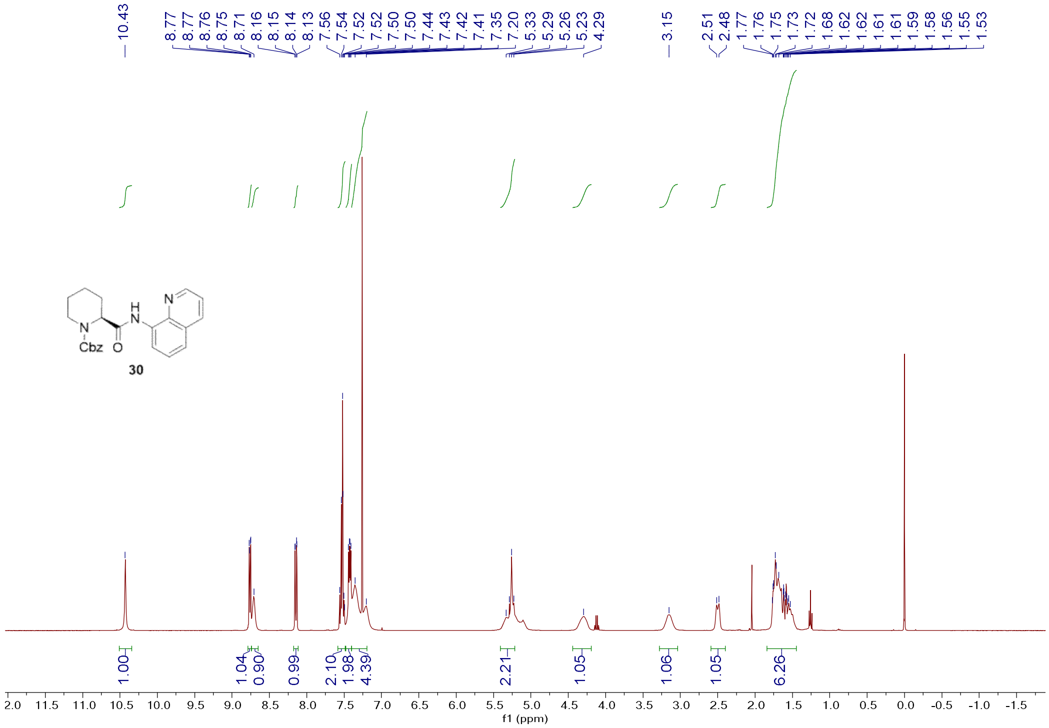
0
f1 (ppm)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7.54
7.52
7.52
7.50
7.50
7.44
7.43
7.42
7.41
7.35
7.20
5.33
5.29
5.26
5.23
4.29
3.15
2.51
2.48
1.77
1.76
1.75
1.73
1.72
1.68
1.62
1.62
1.61
1.61
1.59
1.58
1.56
1.55
1.53
N
H
N
N
Cbz
O
30
1.00
1.04
0.90
0.99
2.10
1.98
4.39
2.21
1.05
1.06
1.05
6.26
2.0
11.5
11.0
10.5
10.0
9.5
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8.5
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6.5
6.0
5.5
5.0
4.5
4.0
3.5
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2.0
1.5
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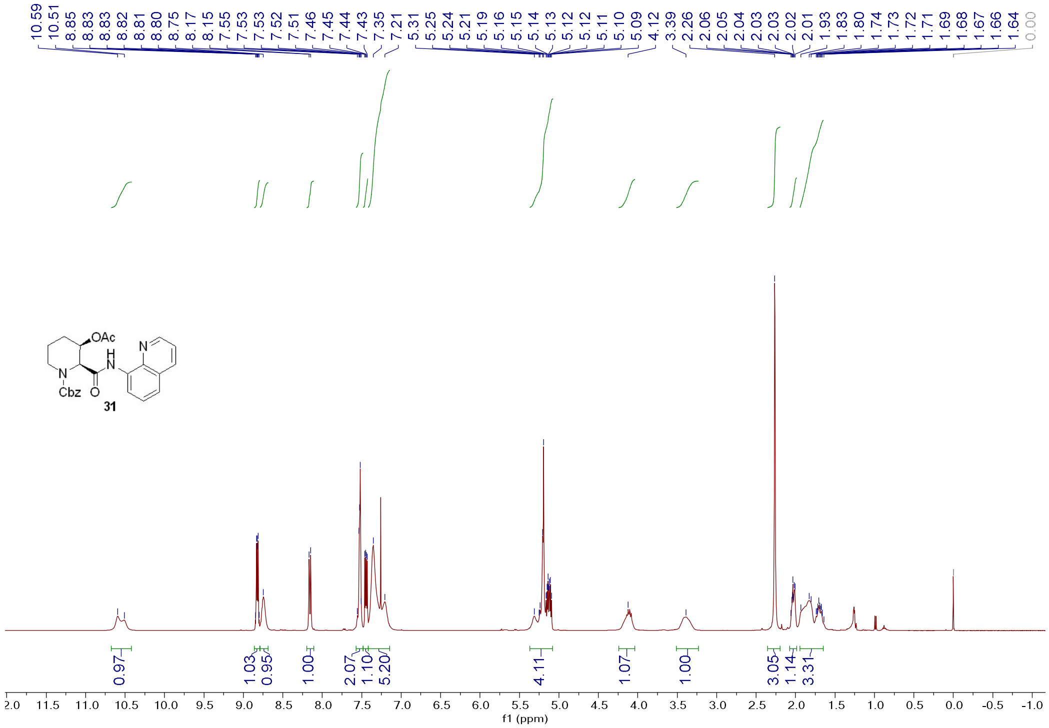
0.0
-0.5
-1.0
-1.5
f1 (ppm)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8.80
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8.15
7.55
7.53
7.53
7.52
7.51
7.46
7.45
7.44
7.43
7.35
7.21
5.31
5.25
5.24
5.21
5.19
5.16
5.15
5.14
5.13
5.12
5.12
5.11
5.10
5.09
4.12
3.39
2.26
2.06
2.05
2.04
2.03
2.03
2.02
2.01
1.93
1.83
1.80
1.74
1.73
1.73
1.72
1.71
1.69
1.68
1.67
1.66
1.64
0.00
OAc
N
H
N
N
Cbz
O
31
0.97
1.03
0.95
1.00
2.07
1.10
5.20
4.11
1.07
1.00
3.05
1.14
3.31
2.0
11.5
11.0
10.5
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9.5
9.0
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7.5
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6.5
6.0
5.5
5.0
4.5
4.0
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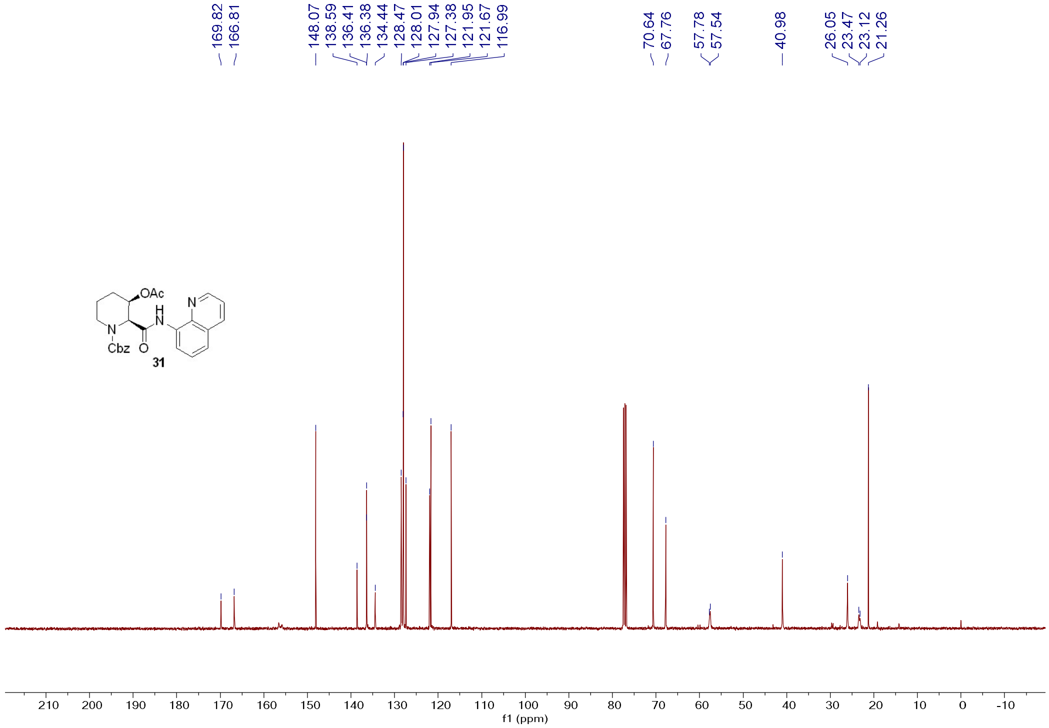
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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166.81
148.07
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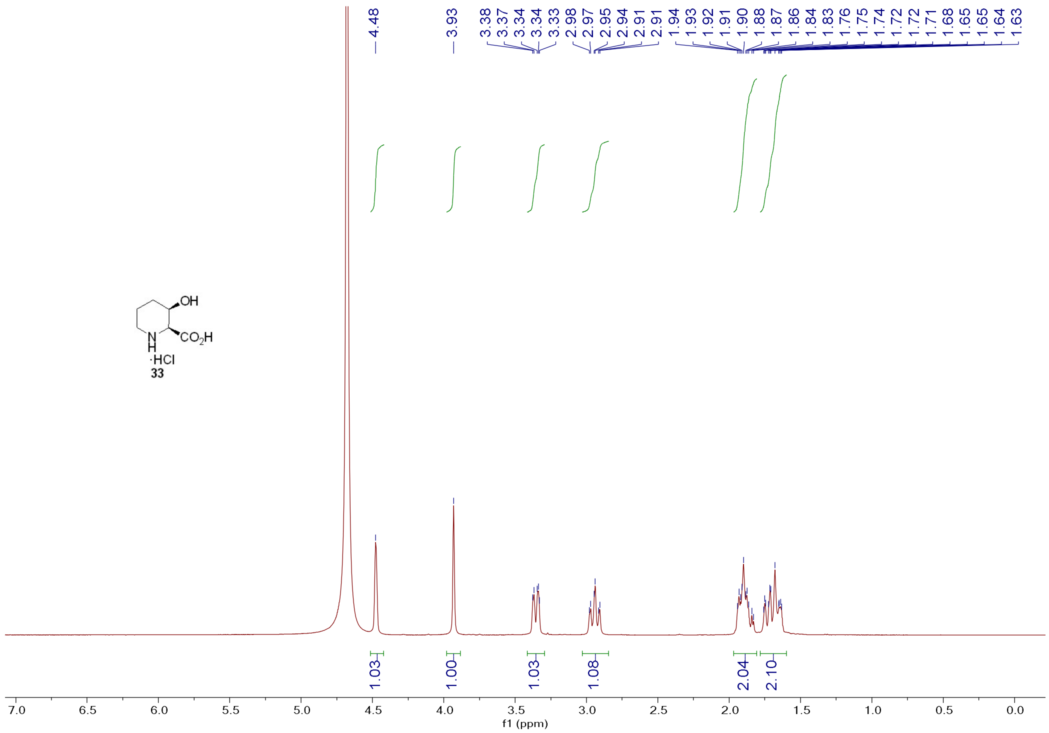
136.41
136.38
134.44
128.47
128.01
127.94
127.38
121.95
121.67
116.99
70.64
67.76
57.78
57.54
40.98
26.05
23.47
23.12
21.26
OAc
N
H
N
N
Cbz
O
31
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

OH
CO2H
N
H
·HCl

33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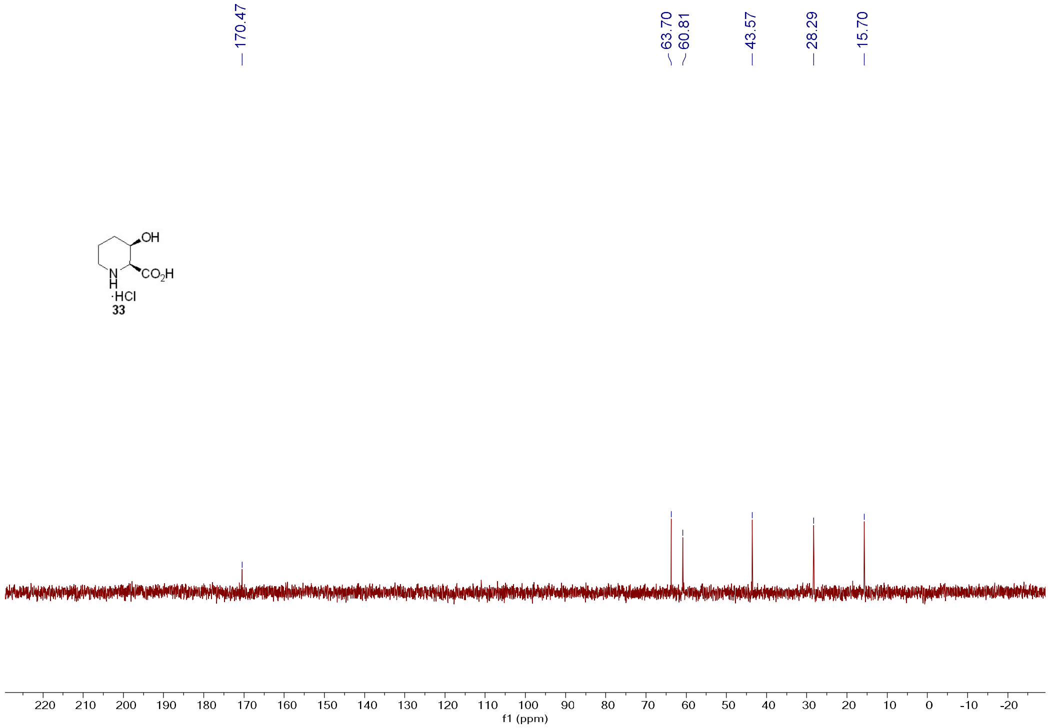
2.97
2.95
2.94
2.91
2.91
1.94
1.93
1.92
1.91
1.90
1.88
1.87
1.86
1.84
1.83
1.76
1.75
1.74
1.72
1.72
1.71
1.68
1.65
1.64
1.63
1.03
1.00
1.03
1.08
2.04
2.10
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

OH
CO2H
N
H
·HCl

33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220
210
200
190
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170
160
150
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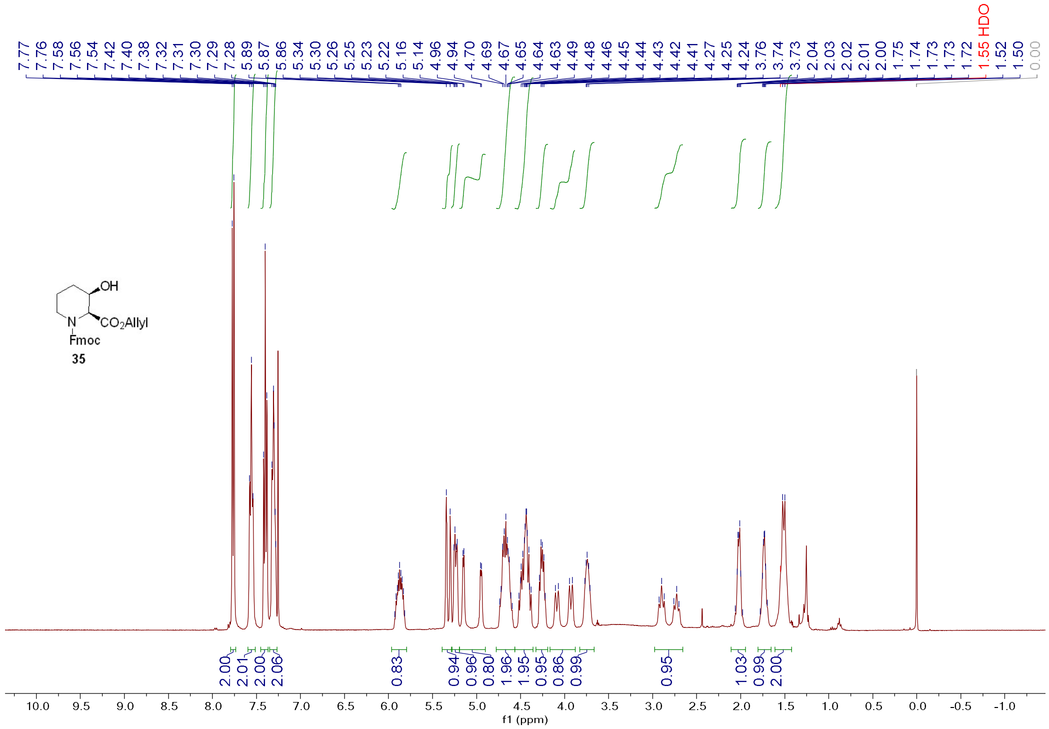
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)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7.40
7.38
7.32
7.31
7.30
7.29
7.28
5.89
5.87
5.86
5.34
5.30
5.26
5.25
5.23
5.22
5.16
5.14
4.96
4.94
4.70
4.69
4.67
4.65
4.64
4.63
4.49
4.48
4.46
4.45
4.44
4.43
4.42
4.41
4.27
4.25
4.24
3.76
3.74
3.73
2.04
2.03
2.02
2.01
2.00
1.75
1.74
1.73
1.72
1.55 HDO
1.52
1.50
0.00
OH
N
CO2Allyl
Fmoc
35
2.00
2.01
2.00
2.06
0.83
0.94
0.96
0.80
1.96
1.95
0.95
0.86
0.99
0.95
1.03
0.99
2.00
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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2.5
2.0
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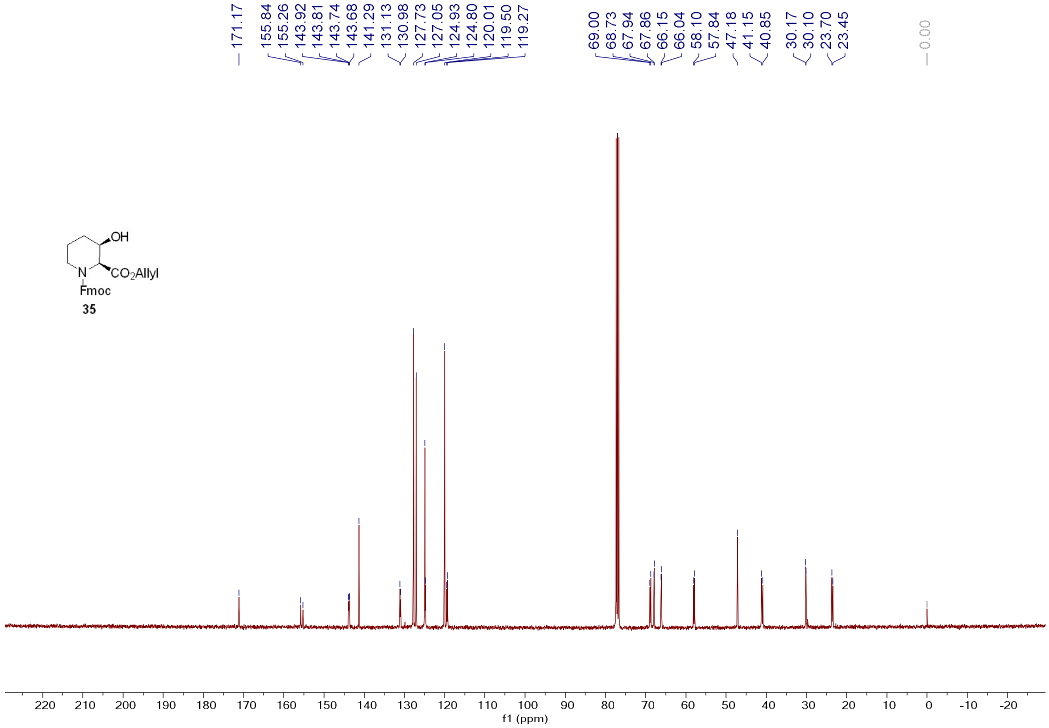
0.5
0.0
-0.5
-1.0
f1 (ppm)


171.17
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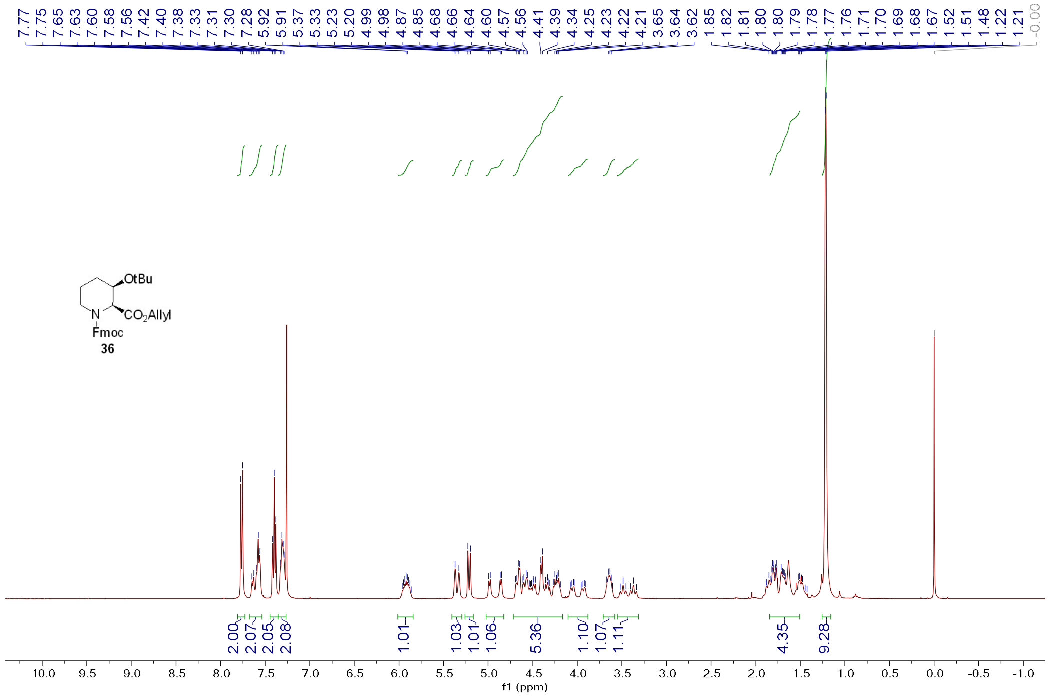
141.29
131.13
130.98
127.73
127.05
124.93
124.80
120.01
119.50
119.27
69.00
68.73
67.94
67.86
66.15
66.04
58.10
57.84
47.18
41.15
40.85
30.17
30.10
23.70
23.45
0.00
OH
N
CO2Allyl
Fmoc
35
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)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7.42
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7.38
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7.31
7.30
7.28
5.92
5.91
5.37
5.33
5.23
5.20
4.99
4.98
4.87
4.85
4.68
4.66
4.64
4.60
4.57
4.56
4.41
4.39
4.34
4.25
4.23
4.22
4.21
3.65
3.64
3.62
1.85
1.82
1.81
1.80
1.79
1.78
1.77
1.76
1.71
1.70
1.69
1.68
1.67
1.52
1.51
1.48
1.22
1.21
-0.00
OtBu
N
CO2Allyl
Fmoc
36
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2.07
2.05
2.08
1.01
1.03
1.01
1.06
5.36
1.10
1.07
1.11
4.35
9.28
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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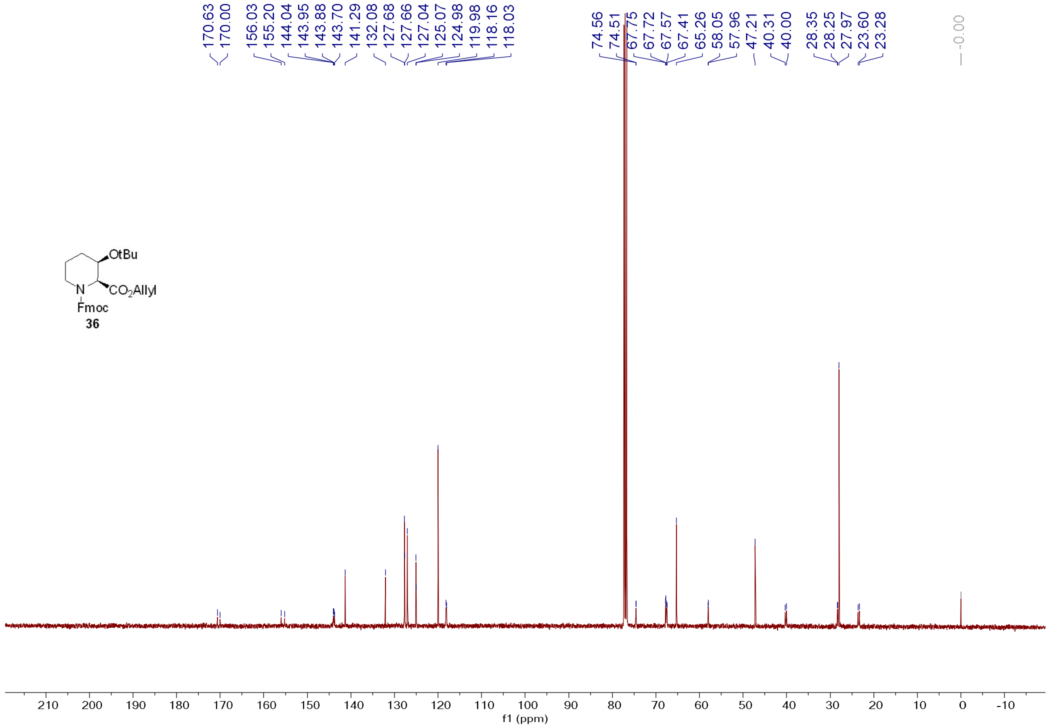
0.0
-0.5
-1.0
f1 (ppm)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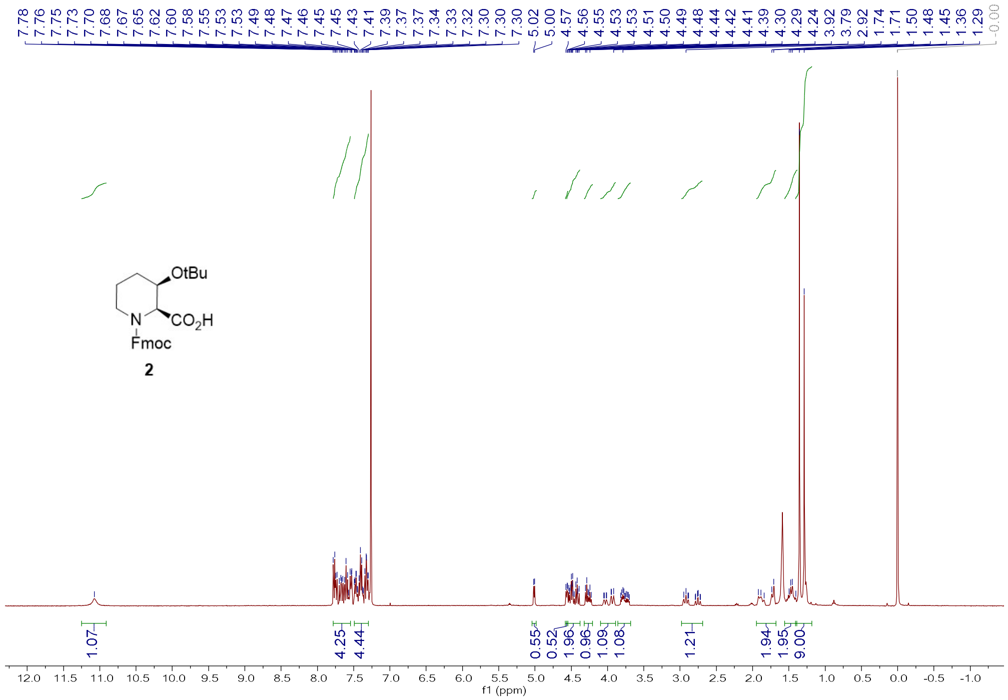
170.00
156.03
155.20
144.04
143.95
143.88
143.70
141.29
132.08
127.68
127.66
127.04
125.07
124.98
119.98
118.16
118.03
74.56
74.51
67.75
67.72
67.57
67.41
65.26
58.05
57.96
47.21
40.31
40.00
28.35
28.25
27.97
23.60
23.28
-0.00
OtBu
N
CO2Allyl
Fmoc
36
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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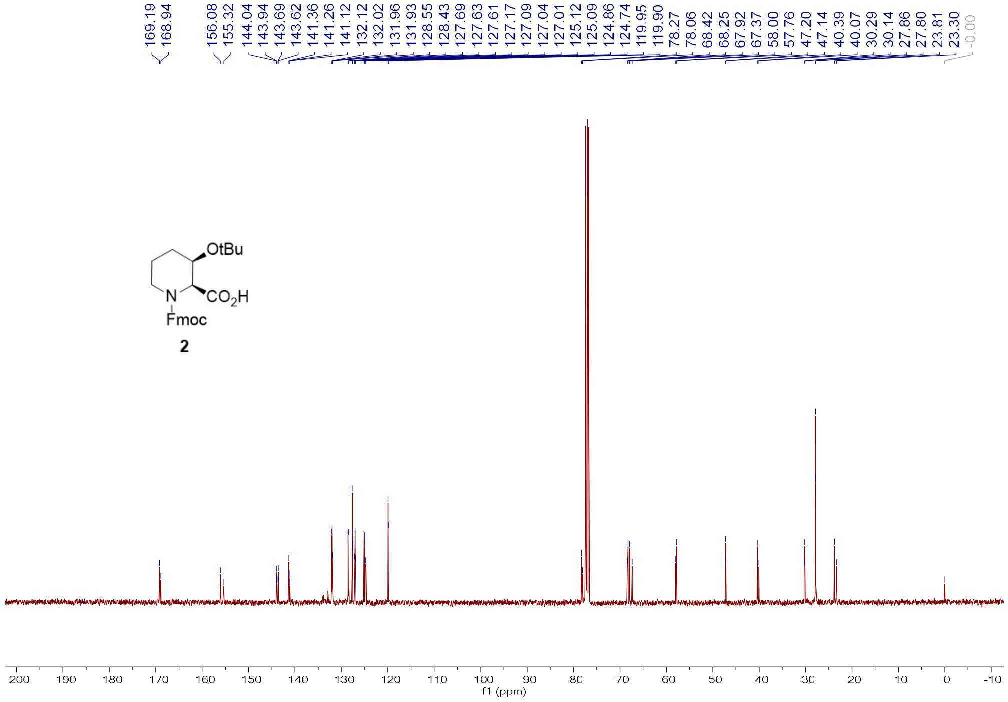
7.76
7.75
7.73
7.70
7.68
7.67
7.65
7.62
7.60
7.58
7.55
7.53
7.53
7.49
7.48
7.47
7.46
7.45
7.45
7.43
7.41
7.39
7.37
7.37
7.34
7.33
7.32
7.30
7.30
7.30
5.02
5.00
4.57
4.56
4.55
4.53
4.53
4.51
4.50
4.49
4.48
4.44
4.42
4.41
4.39
4.30
4.29
4.24
3.92
3.79
2.92
1.74
1.71
1.50
1.48
1.45
1.36
1.29
-0.00
OtBu
N
CO2H
Fmoc
2
1.07
4.25
4.44
0.55
0.52
1.96
0.96
1.09
1.08
1.21
1.94
1.95
9.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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168.94
156.08
155.32
144.04
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143.69
143.62
141.36
141.26
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132.12
132.02
131.96
131.93
128.55
128.43
127.69
127.63
127.61
127.17
127.09
127.04
127.01
125.12
125.09
124.86
124.74
119.95
119.90
78.27
78.06
68.42
68.25
67.92
67.37
58.00
57.76
47.20
47.14
40.39
40.07
30.29
30.14
27.86
27.80
23.81
23.30
-0.00
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N
CO2H
Fmoc
2
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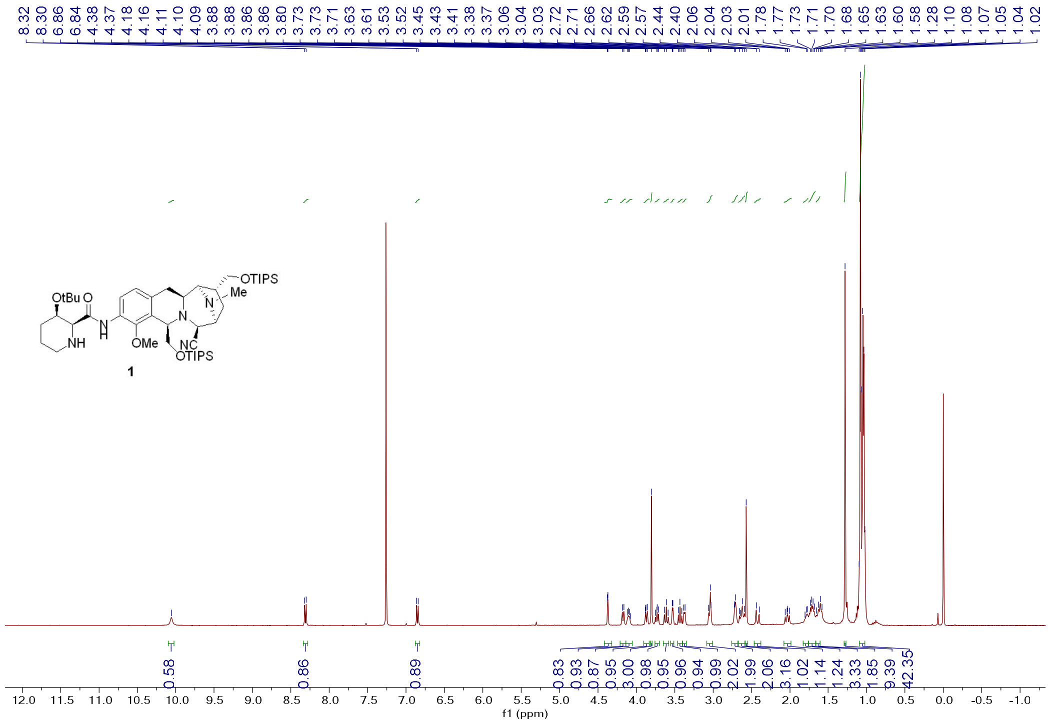
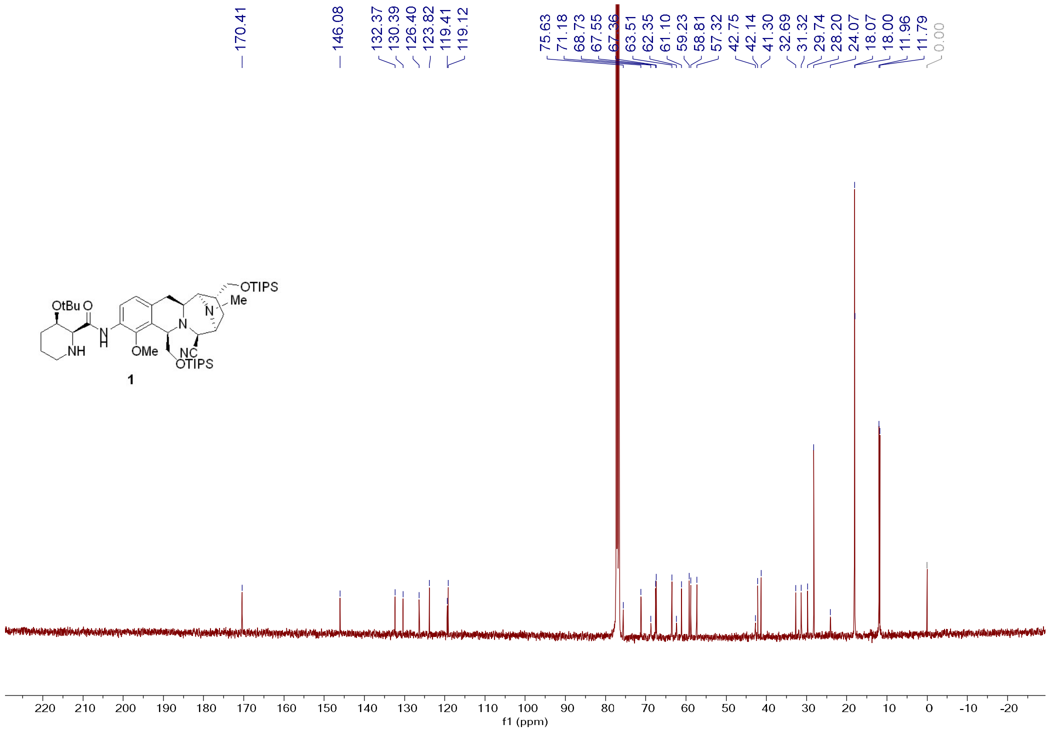
f1 (ppm)


8.32
8.30
6.86
6.84
4.38
4.37
4.18
4.16
4.11
4.10
4.09
3.88
3.88
3.86
3.80
3.73
3.73
3.71
3.63
3.61
3.53
3.52
3.45
3.43
3.41
3.38
3.37
3.06
3.04
3.03
2.72
2.71
2.66
2.62
2.59
2.57
2.44
2.40
2.06
2.04
2.03
2.01
1.78
1.77
1.73
1.71
1.70
1.68
1.65
1.63
1.60
1.58
1.28
1.10
1.08
1.07
1.05
1.04
1.02
OtBu
O
N
H
NH
OMe
NC
OTIPS
N
OTIPS
Me
1
0.58
0.86
0.89
0.83
0.93
0.87
0.95
3.00
0.98
0.95
0.96
0.94
0.99
2.02
1.99
2.06
3.16
1.02
1.14
1.24
3.33
1.85
9.39
42.35
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


170.41
146.08
132.37
130.39
126.40
123.82
119.41
119.12
75.63
71.18
68.73
67.55
67.36
63.51
62.35
61.10
59.23
58.81
57.32
42.75
42.14
41.30
32.69
31.32
29.74
28.20
24.07
18.07
18.00
11.96
11.79
0.00
OtBu
O
N
H
NH
OMe
NC
OTIPS
N
OTIPS
Me
1
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

6. Reference

1) S.-J. Zhang, W.-W. Sun, P. Cao, X.-P. Dong, J.-K. Liu and B. Wu, *J. Org. Chem.,* 2016, **81**, 956-968.

2) J. D. Scott and R. M. Williams. Total synthesis of (-)-tetrazomine. determination of the stereochemistry of tetrazomine and the synthesis and biological activity of tetrazomine analogues. *J. Am. Chem. Soc.* 2002, **124**, 2951-2956.