Supporting Information

A stereocontrolled synthesis of (+)-saxitoxin

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1. General Experimental Considerations:

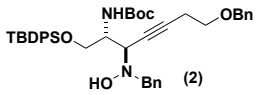
All reactions requiring anhydrous conditions were conducted in flame-dried glassware under a positive pressure of either nitrogen or argon. Commercially available reagents were used as received; otherwise, materials were purified according to *Purification of Laboratory Chemicals*.[1] Dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN) tetrahydrofuran (THF) diethyl ether (Et_2O) were degassed with nitrogen and passed through a solvent purification system (Innovative Technologies Pure Solv). Triethylamine (Et_3N) was distilled from CaH_2 immediately prior to use. Reactions were monitored by TLC and visualized by a dual short wave/long wave UV lamp and stained with aqueous solution of ceric ammonium molybdate. Flash chromatography was performed on Merck silica gel Kieselgel 60 (230-400 mesh) from EM Science with the indicated HPLC grade solvent.

Infrared spectra were obtained using Nicolet 380-FT IR spectrometer fitted with a Smart Orbit sample system. Optical rotations were obtained at ambient temperature on a Perkin Elmer Model 343 polarimeter (Na D line) using a microcell with a 1 decimeter path length. Mass spectra were determined on a Micromass Quattro II (ESI/APCI-TOF) for HRMS at the University of Utah Mass Spectrometry Facility. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively. Proton resonances were reported relative to the deuterated solvent peak: 7.27 ppm for $CDCl_3$ 7.15 ppm for C_6D_6, 3.31 ppm (center line signal) for CD_3OD and 4.80 ppm for D_2O using the following format: chemical shift (δ) (multiplicity (s= singlet, brs= broad singlet, d= doublet, dd= double of doublet, ddd= double of doublet of doublet, dddd= double of doublet of doublet of doublet, t= triplet, dtt= doublet of triplet of triplet, q= quartet, m= multiplet), coupling constant(s) *J* in Hz, integration).[2] Carbon resonances were reported as chemical shifts (δ) in parts per million, relative to the center line signal of the respective solvent peak: 77.23 ppm for $CDCl_3$, 128.0 ppm for C_6D_6 and 49.15 ppm for CD_3OD and 164.2 ppm for TFA.

[1] *Purification of Laboratory Chemicals.* 2003, 5th Ed. Armarego, W. L. F.; Chai, C. L. L.
[2] Hoye, T.R.; Hansen, P.R.; Vyvyan, J.R. *J. Org. Chem.* **1994**; *59*(15); 4096-4103.

2. Experimental Procedures:

***tert*-butyl ((2*R*,3*R*)-3-(benzyl(hydroxy)amino)-7-(benzyloxy)-1-((*tert*-butyldiphenylsilyl)oxy)hept-4-yn-2-yl)carbamate (2).** A solution of homopropargyl benzyl ether (9.62 g, 60.1 mmol) in THF (450 mL) was cooled to -15 °C (MeOH/ice). To this solution was then added a 2M solution of ^{i}PrMgCl (30.6 mL, 61.3 mmol) in THF drop wise for 15 min and the solution was stirred at the same temperature for an additional 15 minutes. The flask was then cooled to -78 °C. A precooled solution of nitrone **1** (8.01 g, 15.5 mmol) in THF (30 mL) at -78 °C was added slowly to this solution via cannula. The addition was maintained so as the internal temperature did not exceed -78 °C. The contents of the flask were stirred at the same temperature for 4 h. The reaction mixture was then quenched with an ice-cold solution of aqueous saturated NH_4Cl (100 mL) and then warmed to rt. The contents of the flask were diluted with EtOAc (500 mL) and partitioned in a separatory funnel. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield a colorless oil (dr: 9:1, based on crude ^{1}H NMR). Purification by flash column chromatography (5% EtOAc in Hexanes) gave *anti*-hydroxylamine **2** (6.88 g, 86%, based on recovery of nitrone **1**, 2.3 g) as a colorless oil.

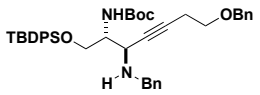


TLC R_f= 0.47 (8.5:1.5 Hexanes:EtOAc); $[\alpha]^{20}_D = -38.4°$ (c = 2.50, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz): δ 7.75- 7.71 (m, 4H), 7.53 (d, *J* = 7.3 Hz, 2H), 7.26- 7.19 (m, 9H), 7.15- 7.10 (m, 4H), 7.08- 7.05 (m, 1H), 6.79 (brs, 1H), 4.86 (d, *J* = 10.2 Hz, 1H), 4.75- 4.68 (m, 1H), 4.60 (d, *J* = 13.6 Hz, 1H), 4.20 (s, 2H), 3.95 (d, *J* = 13.6 Hz, 1H), 3.92- 3.91 (m, 1H), 3.79 (dd, *J* = 10.2, 6.3 Hz, 1H), 3.72 (dd, *J* = 10.2, 7.8 Hz, 1H), 3.14 (ddd, *J* = 15.6, 15.6, 8.7 Hz, 2H), 2.10 (m, 2H), 1.37 (s, 9H), 1.10 (s, 9H) ppm; ^{13}C NMR (C_6D_6, 125 MHz) δ 157.3, 138.9, 138.6, 136.0, 136.0, 133.7, 133.6, 130.0, 130.0, 129.5, 128.5, 128.2, 128.1, 128.0, 127.7, 127.7, 127.0, 85.4, 79.5, 76.6, 72.8, 68.3, 64.0, 61.5, 61.4, 53.2, 28.3, 27.0, 20.2, 19.4 ppm; IR (neat) 3421, 2930, 2857, 2340, 2361, 2279, 1694, 1616, 1506, 1496, 1364, 1162, 1104, 812, 738, 698, 612 cm^{-1}; HRMS (ESI) calcd for $C_{42}H_{52}N_2O_5SiNa$ (M+Na): 715.3543, found: 715.3548.

(2*R*,3*R*)-2-amino-3-(benzylamino)-7-(benzyloxy)hept-4-yn-1-ol *bis*-hydrochloride salt (3).

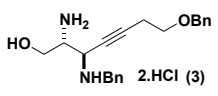
***tert*-butyl ((2*R*,3*R*)-3-(benzylamino)-7-(benzyloxy)-1((*tert*-butyldiphenylsilyl)oxy)hept-4-yn-2-yl)carbamate**

To a slurry of zinc dust (2.43 g, 37.3 mmol) in AcOH (20 mL) was added $Cu(OAc)_2$ (135 mg, 746 μmol). The vessel was sealed and contents were stirred for 15 minutes at rt. A solution of hydroxylamine **2** (5.20 g, 7.50 mmol) in AcOH (20 mL) was then added to this slurry. After sealing the flask tightly, the flask were heated at 60 °C for 2 h. The flask was then cooled to rt and solid Na_2EDTA (5.0 g) was added. This mixture was stirred vigorously for 5 minutes and the solution was basified (pH ≅10) carefully with 10% aqueous NaOH. The reaction mixture was diluted with EtOAc (200 mL) and stirred for 10 minutes. This mixture was then filtered through a pad of celite. The celite bed was washed with an additional portion of EtOAc (200 mL). The combined filtrates were then partitioned in a separatory funnel and organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford a light yellow oil which was purified by flash column chromatography (15% EtOAc in hexanes) to afford the required diamine (4.69 g, 92%) as a colorless oil.



TLC R_f= 0.52 (8:2 Hexanes:EtOAc); $[\alpha]^{20}_D = -17.2°$ (c = 3.0, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz): δ 7.73- 7.69 (m, 4H), 7.30 (d, *J* = 7.3 Hz, 2H), 7.22 (d, *J* = 7.3 Hz, 2H), 7.18- 7.16 (m, 5H), 7.14- 7.10 (m, 5H), 7.06- 7.03 (m, 2H), 5.37 (d, *J* = 9.2 Hz, 1H), 4.30- 4.24 (m, 1H), 4.26 (s, 2H), 4.03 (dd, *J* = 10.2, 9.7 Hz, 1H), 3.92 (d, *J* = 12.6 Hz, 1H), 3.81 (dd, *J* = 9.7, 5.8 Hz, 1H), 3.80- 3.76 (m, 1H), 3.72 (d, *J* = 13.1 Hz, 1H), 3.26, (ddd, *J* = 9.2, 6.3, 2.4 Hz, 2H), 2.25 (dddd, *J* = 6.8, 6.8, 1.4, 1.4 Hz, 2H), 1.42 (s, 9H), 1.03 (s, 9H) ppm; ^{13}C NMR (C_6D_6, 125 MHz) δ 155.6, 140.3, 138.7, 136.0, 136.0, 135.9, 135.9, 133.6, 133.6, 129.9, 128.7, 128.5, 128.5, 128.0, 128.0, 127.7, 127.1, 82.9, 79.9, 78.8, 72.9, 68.7, 64.3, 54.9, 51.6, 51.2, 28.4, 26.9, 20.4, 19.3 ppm; IR (neat) 2929, 2857, 2279, 1713, 1494, 1472, 1427, 1390, 1364, 1329, 1247, 1165, 1104, 1027, 812, 737, 698, 613 cm^{-1}; HRMS (ESI) calcd for $C_{42}H_{52}N_2O_4SiNa$ (M+Na): 699.3594, found: 699.3594.

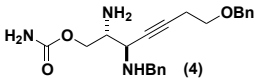
In a 50 mL sealed vessel, the diamine (0.74 g, 1.09 mmol) was dissolved in 4N HCl in MeOH (15 mL) and heated at 40 °C for 12 h. After cooling the flask to rt, decolorizing charcoal was added to the flask and the contents were heated in a open flask at 40 °C for 15 min. The contents of the flask were then filtered through a small pad of celite. The celite bed was washed with an additional 20 mL of MeOH. The combined filtrates were then evaporated under



reduced pressure to yield an off-white residue. This material was washed with ether (3 × 15 mL) to afford the diamine *bis*-hydrochloride salt **3** (398 mg, 89%) as an amorphous off white solid.

TLC R_f = 0.32 (9:1 CH_2Cl_2:MeOH); $[\alpha]^{20}_D$ = –29.1° (c = 1.65, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): δ 7.54-7.52 (m, 2H), 7.46- 7.41 (m, 3H), 7.38- 7.35 (m, 2H), 7.33- 7.29 (m, 2H), 7.28- 7.25 (m, 1H), 4.60 (s, 2H), 4.51-4.50 (bs, 1H), 4.49 (d, *J* = 13.1 Hz, 1H), 4.30 (d, *J* = 13.1 Hz, 1H), 3.87 (dd, *J* = 11.7, 5.37 Hz, 1H), 3.82 (dd, *J* = 11.7, 5.3 Hz, 1H), 3.75 (t, *J* = 6.3 Hz, 2H), 3.74 (d, *J* = 5.8 Hz, 1H), 2.75 (dt, *J* = 6.3, 2.4 Hz, 2H) ppm; ^{13}C NMR (CD_3OD, 125 MHz) δ 139.2, 131.6, 131.3, 130.8, 130.2, 129.5, 129.0, 128.9, 94.7, 74.1, 69.8, 68.7, 60.1, 54.2, 51.1, 50.8, 21.0 ppm; IR (neat) 3330, 2856, 2361, 2340, 1646, 1635, 1616, 1575, 1521, 1456, 1362, 1210, 1156, 1095, 1064, 1028, 746, 696, 607 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{27}N_2O_2$ (M+H): 339.2073, found: 339.2068.

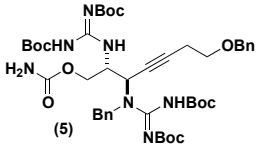
(2*R*,3*R*)-2-amino-3-(benzylamino)-7-(benzyloxy)hept-4-yn-1-yl carbamate (4). To a solution of diamine *bis*-hydrochloride **3** (1.10 g, 2.68 mmol) in CH_2Cl_2 (3 mL) was added KOCN (1.30 g, 16.0 mmol) at 0 °C. To this solution was then added Me_3SO_3H (10 mL) dropwise over a period of 10 min. The reaction mixture was stirred at the same temperature for 2 h. The contents of the flask were added carefully to crushed ice (~50 g) and basified (pH ≅10) carefully with aqueous saturated $NaHCO_3$ solution. This solution was then transferred to a separatory funnel and extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (4% MeOH in CH_2Cl_2) afforded the diaminocarbamate **4** (794 mg, 78%) as a colorless oil.



(4)

TLC R_f = 0.48 (8:1:1 EtOAc:MeOH:H_2O); $[\alpha]^{20}_D$ = +0.34° (c = 0.74, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ 7.36 (d, *J* = 7.3 Hz, 2H), 7.27 (d, *J* = 7.3 Hz, 2H), 7.19- 7.15 (m, 4H), 7.11- 7.06 (m, 2H), 4.71- 4.57 (m, 2H), 4.29 (s, 2H), 4.15 (m, 2H), 3.98 (d, *J* = 13.1 Hz, 1H), 3.79 (d, *J* = 12.6 Hz, 1H), 3.45 (m, 1H), 3.33 (td, *J* = 6.8, 0.9 Hz, 2H), 3.05 (dtt, *J* = 8.7, 4.3, 2.4 Hz, 1H), 2.31 (tt, *J* = 6.8, 1.9 Hz, 2H), 1.54 (brs, 3H) ppm; ^{13}C NMR (C_6D_6, 125 MHz) δ 156.6, 140.7, 138.8, 128.7, 128.5, 128.5, 128.2, 127.7, 127.1, 83.2, 79.4, 72.9, 68.8, 67.6, 54.2, 52.5, 51.6, 20.4 ppm. IR (neat) 3353, 3061, 3028, 2860, 2360, 2340, 1716, 1635, 1616, 1454, 1403, 1332, 1205, 1066, 1028, 911, 847, 781, 736, 697 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{28}N_3O_3$ (M+H): 382.2131, found: 382.2133.

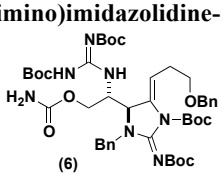
***Bis*-propargyl guanidine (5)**. To a solution of diaminocarbamate **4** (315 mg, 0.82 mmol) in CH_2Cl_2 (16 mL) was added *N*,*N*′-Di-Boc-*S*-methylisothiourea (479 mg, 1.65 mmol), NEt_3 (241 μL, 1.72 mmol) and HgO (371 mg, 1.72 mmol) at rt. The reaction mixrure was stirred at rt for 8 h. Contents of the flask were diluted with CH_2Cl_2 (5 mL) and filtered through a pad of celite. The celite bed was washed with an additional 15 mL of (CH_2Cl_2). The combined filtrates were concentrated under reduced pressure. Purification by flash column chromatography (30% EtOAc in hexanes) gave the *bis*-guanidine **5** (586 mg, 83%) as a colorless foam.



(5)

TLC R_f = 0.33 (6:4 Hexanes:EtOAc); $[\alpha]^{20}_D$ = –7.8° (c = 1.35, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz, 55 °C): 12.03 (s, 1H), 9.7 (s, 1H), 8.82 (d, *J* = 8.3 Hz, 1H), 7.27- 7.23 (m, 2H), 7.19- 7.15 (m, 4H), 7.07-7.02 (m, 3H), 6.94-6.92 (m, 1H) 6.39 (brs, 1H), 5.03- 5.02 (m, 1H), 4.99 (d, *J* =15.6 Hz, 1H), 4.90 (d, *J* = 16.5 Hz, 1H), 4.47 (dd, *J* = 11.2, 4.3 Hz, 1H), 4.42 (dd, *J* = 11.2, 5.3 Hz, 1H), 4.25 (brs, 2H), 4.19 (s, 2H), 3.20 (brs, 2H), 2.13 (brs, 2H), 1.44 (s, 9H), 1.40 (s, 9H), 1.27 (s, 9H), 1.20 (s, 9H) ppm; ^{13}C NMR (C_6D_6, 125 MHz, mixture of rotamers) 164.5, 163.1, 157.9, 156.9, 155.5, 153.6, 151.2, 139.2, 139.0, 128.9, 128.4, 128.6, 128.0, 127.4, 127.3, 82.7, 81.9, 79.3, 79.0, 76.3, 73.1, 68.6, 63.9, 54.4, 52.0, 50.6, 31.7, 28.7, 28.7, 28.3, 28.1, 28.1, 27.7, 20.6 ppm; IR (neat) 3307, 2977, 1718, 1683, 1599, 1540, 1455, 1417, 1392, 1365, 1313, 1250, 1229, 1140, 1102, 1055, 1027, 987, 807, 776, 732, 696 cm^{-1}; HRMS (ESI) calcd for $C_{44}H_{63}N_7O_{11}Na$ (M+Na): 888.4483, found: 888.4479.

(*S*,5*Z*)-*tert*-butyl 4-((*R*)-1-amino-6-((*tert*-butoxycarbonyl)amino)-10,10-dimethyl-1,8-dioxo-2,9-dioxa-5,7-diazaundec-6-en-4-yl)-3-benzyl-5-(3-(benzyloxy)propylidene)-2-((*tert*-butoxycarbonyl)imino)imidazolidine-1-carboxylate (6). To a stirred solution of *bis*-guanidine **5** (1.82 g 2.10 mmol), in CH_2Cl_2 (25 mL) was added AgOAc (34 mg, 21 μmol) at rt and the reaction was stirred for 9 h. The contents of the flask were filtered through a pad of celite and the celite bed was washed with an additional 10 mL of CH_2Cl_2. The combined filtrates were concentrated to give the ene-guanidine **6** (1.79 g, 98%) as a colorless foam which was used in the next step without any further purification.

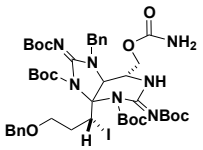


(6)

TLC R_f = 0.39 (1:1 Hexanes:EtOAc); $[\alpha]^{20}_D$ = +9.9° (c = 1.40, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz, 35 °C): δ 12.09, (s, 1H), 8.82 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 2H), 7.21- 7.18 (m, 4H), 7.13-7.08 (m, 1H), 7.05-7.01 (m, 2H), 6.98- 6.95 (m, 1H), 5.38 (d, *J* = 15.6 Hz, 1H), 4.95 (dd, *J* = 8.7, 4.8 Hz, 1H), 4.79- 4.50 (bs,

1H), 4.50 (ddd, *J* = 7.8, 7.8, 3.9 Hz, 1H), 4.35- 4.28 (m, 3H), 4.25 (d, *J* = 3.9 Hz, 1H), 4.04 (bs, 1H), 3.92 (dd, *J* = 12.2, 4.3 Hz, 1H), 3.35 (s, 2H), 3.26 (t, *J* = 6.3Hz, 2H), 2.53 (dddd, *J* =15.2, 15.2, 6.8, 6.3 Hz, 1H), 2.41 (dddd, *J* = 15.1, 11.7, 6.3, 6.3 Hz, 1H), 1.59 (s, 9H), 1.44 (s, 9H), 1.43 (s, 9H), 1.21 (s, 9H) ppm; ^{13}C NMR (C_6D_6, 35 °C, 125 MHz,) δ 164.0, 159.1, 157.0, 156.1, 153.3, 153.2, 149.6, 139.3, 136.5, 131.9, 128.9, 128.5, 128.2, 127.8, 127.5, 116.7, 83.7, 83.0, 78.9, 78.3, 72.7, 69.0, 63.2, 59.1, 53.1, 51.6, 48.9, 29.7, 28.5, 28.3, 28.0, 27.7 ppm; IR (neat) 2978, 2361, 1339, 2279, 1748, 1733, 1684, 1615, 1558, 1540,1521, 1496, 1366, 1250, 1147, 1116, 1054, 1028, 811, 699 cm^{-1}; HRMS (ESI) calcd for $C_{44}H_{63}N_7O_{11}Na$ (M+Na): 888.4483, found: 888.4480.

(4*R*,5*S*,6*S*)-di-*tert*-butyl 7-benzyl-4-((*R*)-3-(benzyloxy)-1-iodopropyl)-2,8-bis((*tert*-butoxycarbonyl)imino)-6-((carbamoyloxy)methyl)tetrahydro-1*H*-purine-3,9(2*H*,4*H*)-dicarboxylate (8).

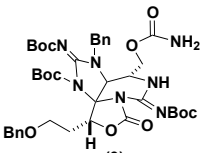


(8)

To a stirred solution of *ene*-guanidine **6** (0.93 g, 1.07 mmol) in Et_2O (15 mL) at 0 °C, was added silver acetate (214 mg, 1.28 mmol) and crushed iodine (327 mg, 1.28 mmol) and the reaction was warmed to rt and stirred for 18 h. The reaction mixture was then diluted with EtOAc (100 mL) and filtered through a small pad of celite. The combined filtrates were transferred to a separatory funnel and washed with 2N $Na_2S_2O_3$ (100 mL). The organic layer was separated and the aqueous layer was extracted with additional portions of EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (30% EtOAc in hexanes) afforded the bicyclic guanidine **8** (0.87 g, 82%) as a colorless foam.

TLC R_f = 0.38 (9.5:0.5 CH_2Cl_2:MeOH); $[\alpha]^{20}_D$ = +88.7° (c = 1.18, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz): δ 9.47 (d, *J* = 5.3 Hz, 1H), 7.49 (d, *J* = 7.3 Hz, 2H), 7.24 (d, *J* = 15.1Hz, 2H), 7.23 (d, *J* = 15.1 Hz, 2H), 7.16- 7.11 (m, 1H), 6.99- 6.91 (m, 3H), 6.48 (d, *J* = 12.6 Hz, 1H), 4.77 (d, *J* = 14.6 Hz, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 4.51- 4.46 (m, 1H), 4.47 (d, *J* = 12.6 Hz, 1H), 4.26 (t, *J* = 8.78 Hz, 1H), 4.2 (s, 1H), 3.92 (brs, 2H), 3.82 (d, *J* = 14.6 Hz, 1H), 3.54 (ddd, *J* = 9.7, 9.7, 2.9 Hz, 1H), 3.46 (m, 1H), 2.60 (m, 1H), 1.69 (s, 9H), 1.61 (s, 9H), 1.49 (s, 9H), 1.42 (s, 9H) ppm; ^{13}C NMR (C_6D_6, 125 MHz, 35 °C) δ 163.9, 159.8, 159.8, 155.6, 151.4, 150.7, 148.9, 139.2, 135.4,129.6, 128.9, 128.5, 128.2, 127.9, 127.5, 85.2, 82.6, 82.3, 78.6, 78.3, 71.7, 67.6, 64.8, 62.4, 51.0, 46.5, 39.1, 32.5, 28.7, 28.2, 28.1, 27.6 ppm; IR (neat) 3305, 2976, 2931, 2360, 1751, 1653, 1616, 1453, 1393, 1367, 1322, 1276, 1254, 1157, 1139, 1101, 845, 736, 705 cm^{-1}; HRMS (ESI) calcd for $C_{44}H_{63}N_7O_{11}I$ (M+H): 992.3630, found: 992.3631.

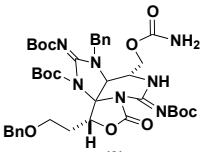
(3a*R*,4*R*,10*S*,10a*S*)-*tert*-butyl 1-benzyl-4-(2-(benzyloxy)ethyl)-2,8-bis((*tert*-butoxycarbonyl)imino)-10-((carbamoyloxy)methyl)-6-oxohexahydro-1*H*-oxazolo[3,4-*c*]purine-3(2*H*)-carboxylate (9). To a solution of iodide **8** (0.72 g, 0.72 mmol) in CH_3CN (8.0 mL) was added AgOAc (0.36 g, 2.15 mmol) and AcOH (0.50 mL) at rt and the reaction mixture was heated at 60 °C for 8 h. The reaction mixture was cooled to rt and diluted with EtOAc (10 mL). The inorganic salts were filtered through a pad of celite and the celite bed was washed with an additional 10 mL of EtOAc. The combined filtrates were concentrated under reduced pressure. Purification by flash column chromatography (50% EtOAc in hexanes) gave cyclic carbamate **9** (0.45 g, 77%) as a colorless oil.



(9)

TLC R_f = 0.49 (3:7 hexanes:EtOAc); $[\alpha]^{20}_D$ = +60.8° (c = 0.83, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz, 35 °C) δ 9.38 (brs, 1H), 7.20- 7.09 (m, 4H), 7.10 (m, 3H), 7.03- 6.95 (m, 3H), 4.68 (dd, *J* = 8.3, 5.3 Hz, 1H), 4.43(d, *J* = 15.1 Hz, 1H), 4.45- 4.39 (brs, 2H), 4.20 (d, *J* = 15.1 Hz, 1H), 4.15 (d, *J* = 11.7 Hz, 1H), 4.06 (12.2 Hz, 1H), 3.70 (s, 1H), 3.65 (d, *J* = 9.2 Hz, 1H), 3.50 (brs, 1H), 3.44 (ddd, *J* = 9.2, 9.2, 3.9 Hz, 1H), 3.31 (ddd, *J* = 10.2, 5.3, 5.3 Hz, 1H), 3.09 (bs, 1H), 2.42 (dddd, *J* = 14.1, 9.1, 4.8, 4.5 Hz, 1H), 2.23 (dddd, *J* = 14.3, 8.7, 4.8, 4.6 Hz, 1H), 1.62 (s, 9H), 1.60 (s, 9H), 1.40 (s, 9H) ppm; ^{13}C NMR (C_6D_6, 125 MHz, 35 °C) δ 159.7, 155.5, 150.6, 148.5, 138.7, 135.9, 129.2, 128.7, 128.6, 128.3, 128.2, 128.1, 127.9, 127.8, 86.2, 82.1, 79.9, 79.1, 78.7, 72.9, 65.6, 65.4, 64.1, 47.1, 30.1, 28.6, 28.1, 27.9 ppm; IR (neat) 3365, 2977, 2931, 2360, 1798, 1724, 1616, 1454, 1390, 1366, 1318, 1246, 1131, 1103, 1028, 808, 751, 703, 667 cm^{-1}; HRMS (ESI) calcd for $C_{40}H_{53}N_7O_{11}Na$ (M+Na): 830.3701, found: 830.3700.

The sequential one pot procedure for the preparation of cyclic carbamate (9). To a solution of *bis*-guanidine **5** (50 mg, 57 μmol) in CH_2Cl_2 (500 μL) was added AgOAc (10 mg, 59 μmol) at rt. The contents of the flask were stirred at rt for 1h. The reaction mixture was concentrated to dryness and the residue was dissolved in Et_2O (1.0 mL). To the reaction mixture was then added AgOAc (10 mg, 59 μmoL) and crushed iodine (15 mg, 59 μmol) and the contents were stirred at rt for 10 h. The Et_2O was evaporated under reduced pressure and the contents were diluted with CH_3CN (1.0 mL) and AcOH (16 μL, 30

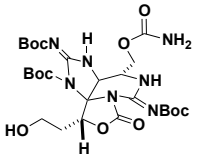


(9)

μmoL). Additional AgOAc (19 mg, 113 μmol) was added and the contents were heated at 60 °C for 8 h. The flask was cooled to rt and the contents were diluted with EtOAc (2 mL) and then filtered through a small pad of celite. The celite bed was washed with an additional portion of EtOAc (5 mL). The combined filtrates were concentrated under reduced pressure. Purification by flash column chromatography (50% EtOAc in hexanes) gave the cyclic carbamate **9** (31 mg, 67%) as a colorless oil.

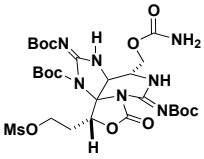
(3a*R*,4*R*,10*S*,10a*S*)-*tert*-butyl 2,8-bis((*tert*-butoxycarbonyl)imino)-10-((carbamoyloxy)methyl)-4-(2-((methyl sulfonyl)oxy)ethyl)-6-oxohexahydro-1*H*-oxazolo[3,4-*c*]purine-3(2*H*)-carboxylate (10).

In a 100 mL pressure tube, cyclic carbamate **9** (0.80 g, 0.99 mmol) was dissolved in ^{i}PrOH (20 mL). To this solution was added $Pd(OH)_2$ (120 mg) and AcOH (200 μL). The tube was evacuated and filled with hydrogen three times. Finally the hydrogen was filled to 80-psi pressure and the contents of the tube were stirred at rt behind a safety shield for 50 h. The reaction mixture was diluted with EtOAc and filtered through a small pad of celite. The celite bed was washed with an additional 20 mL of EtOAc. The combined filtrates were concentrated under reduced pressure and purified by flash column chromatography (5% MeOH in CH_2Cl_2) to yield the di-debenzylated carbamate (0.416 g, 67%) as colorless oil.



TLC R_f= 0.37 (9:1 CH_2Cl_2:MeOH); $[\alpha]^{20}_D$ = +73.3° (c = 3.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz, 35 °C) δ 9.79 (brs, 1H), 5.37 (brs, 2H), 4.92 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.51 (s, 1H), 4.27- 4.21 (m, 2H), 3.99 (brt, 1H), 3.83-3.75 (m, 3H), 2.01 (ddd, *J* = 19.0, 10.7, 4.3 Hz, 1H), 1.94 (ddd, *J* = 20.0, 7.8, 5.3 Hz, 1H), 1.57 (s, 9H), 1.49 (s, 9H), 1.48 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, 35 °C) δ 156.3, 151.5, 151.2, 149.7, 147.2, 128.1, 127.9, 127.8, 88.4, 82.5, 81.4, 80.7, 80.5, 72.0, 66.0, 58.0, 55.2, 30.9, 28.3, 28.2, 28.0 ppm; IR (neat) 3290, 2979, 2360, 1791, 1761, 1713, 1653, 1608, 1525, 1473, 1455, 1367, 1326, 1244, 1146, 1108, 1078, 907, 855, 805, 769, 726, 645 cm^{-1}; HRMS (ES^+) calcd for $C_{26}H_{41}N_7O_{11}Na$ (M+Na): 650.2762, found: 650.2762.

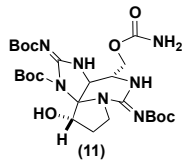
In a 10 ml round bottom flask, the free alcohol prepared above (130 mg, 207 μmol) was dissolved in CH_2Cl_2 (4.0 mL) and the flask was cooled to -35 °C (CH_3CN/dry ice). To this mixture was added NEt_3 (87 μL, 621 μmol) and DMAP (50 mg, 409 μmol). A solution of methanesulfonyl chloride (16 μL, 207 μmol) in CH_2Cl_2 (300 μL) was added drop wise to this solution. The reaction mixture was stirred at the same temperature for 2 h and then diluted with CH_2Cl_2 (5 mL) and H_2O (5 mL). The contents of the flask were partitioned in a separatory funnel and washed with 0.5% aq. HCl (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (3% MeOH in CH_2Cl_2) gave the sulfonate **10** (113 mg, 77%) as a colorless foam.



(10)

TLC R_f = 0.48 (9:1 CH_2Cl_2:MeOH); $[\alpha]^{20}_D$ = +43.5° (c = 2.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500MHz) δ 9.86– 9.41(brs, 2H), 4.97 (brs, 2H), 4.82 (dd, *J* = 8.3, 4.8 Hz, 1H), 4.46- 4.37 (m, 3H), 4.29 (dd, *J* = 11.7, 3.9Hz, 1H), 4.24 (dd, *J* = 11.7, 5.8 Hz, 1H), 4.02 (brs, 1H), 3.10 (s, 3H), 2.20 (ddd, *J* = 13.1, 9.7, 4.8 Hz, 2H), 1.59 (s, 9H), 1.51 (s, 9H), 1.49 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, 35 °C) δ 156.0, 151.1,150.4, 149.4, 146.9, 88.7, 82.6, 80.8, 80.2, 80.0, 71.9, 65.6, 65.1, 55.1, 37.6, 28.3, 28.2, 28.1, 27.9 ppm; IR (neat) 3294, 2979, 2360, 2338, 1791, 1733, 1604, 1473, 1456, 1394, 1368, 1330, 1248, 1146, 1042, 961, 915, 775, 730, 646 cm^{-1}; HRMS (ES^+) calcd for $C_{27}H_{43}N_7O_{13}SNa$ (M+Na): 728.2537, found: 728.2538.

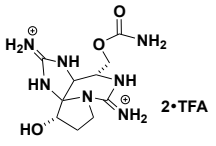
(3a*S*,4*S*,10*S*,10a*R*)-*tert*-butyl 2,6-bis((*tert*-butoxycarbonyl)imino)-4-((carbamoyloxy)methyl)-10-hydroxyoct ahydropyrrolo[1,2-*c*]purine-1(8*H*)-carboxylate (11). To a solution of sulfonate **10** (30 mg, 42 μmol) in EtOH (1.0 mL) was added Cs_2CO_3 (15 mg, 46 μmol) at 0 °C. Reaction mixture was slowly warmed to rt and stirred for 8 h. The contents of the flask were filtered through a small pad of celite and the celite bed was washed with 10 mL of EtOAc. The combined filtrates were concentrated under reduced pressure. Purification by flash column chromatography (5% MeOH in CH_2Cl_2) gave the alcohol **11** (15 mg, 61 %) as a colorless oil.



(11)

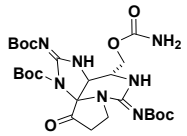
TLC R_f= 0.37 (9:1 CH_2Cl_2:MeOH), $[\alpha]^{20}_D$ = +84.6° (c = 2.80, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 500 MHz, **complex mixture of rotamers**) δ 9.6– 9.1 (brs, 1H), 5.7- 5.3 (brs, 2H), 4.46 (t, *J* = 4.1 Hz, 1H), 4.30- 4.05 (m, 3H), 3.85-3.73 (m, 2H), 3.41 (dd, *J* = 11.2, 5.8 Hz, 1H), 2.24 (dddd, *J* = 10.0, 10.0, 6.8, 7.8 Hz, 1H), 1.87 (dddd, *J* = 12.7, 8.3, 4.4, 3.9 Hz, 1H), 1.50 (s, 9H), 1.44 (s, 18H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, **complex mixture of rotamers**) δ 164.1, 163.7, 160.0, 159.4, 157.3, 157.0, 156.8, 156.6, 151.4, 149.6, 149.2, 88.4, 87.6, 85.7, 83.9, 83.1, 82.4, 81.7, 81.1, 80.8, 79.0, 78.9, 78.8, 78.7, 77.4, 76.7, 71.9, 68.2, 67.0, 64.4, 63.5, 59.6, 53.9, 53.1, 52.9, 48.8, 48.1, 43.9, 30.7, 28.6, 28.5, 28.4, 28.3, 28.3, 28.2, 27.9 ppm; IR (neat) 3285, 2978, 2360, 2339, 1717, 1635, 1584, 1558, 1473, 1393, 1367, 1317, 1248, 1147, 1094 911, 806, 756, 731 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{41}N_7O_9Na$ (M+Na): 606.2863, found: 606.2864.

β-saxitoxinol •2TFA. To the alcohol **11** (12 mg, 20 μmol) was added CH_2Cl_2: TFA (1:1, 1mL) and the reaction mixture was stirred at rt for 1 h. The contents of the flask were concentrated under reduced pressure. This residue was washed with CH_2Cl_2 several times and concentrated again under reduced pressure. The resultant residue was dissolved in 1 mL of H_2O and filtered through a 25 micron PTFE Acrodisc® syringe filter. The filter was washed with an additional 1 mL of H_2O and the filtrates were concentrated under reduced pressure to give the *bis*-TFA salt of β-saxitoxinol (9 mg, 95%) as a colorless oil.



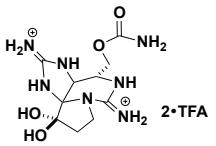
$[\alpha]^{20}_D$ = +63.0° (c = 0.13, MeOH); ^{1}H NMR (D_2O, 500 MHz) δ 4.83 (s, 1H), 4.33 (d, *J* = 4.4 Hz, 1H), 4.27 (dd, *J* = 11.7, 9.2 Hz, 1H), 4.02 (dd, *J* = 11.7, 5.3 Hz, 1H), 3.83 (ddd, *J* = 9.2, 5.3, 1.7 Hz, 1H), 3.77 (ddd, *J* =10.2, 8.3, 1.9 Hz, 1H), 3.68 (dd, *J* = 9.0, 9.0, 8.7 Hz, 1H), 2.40 (dddd, *J* = 14.1, 9.7, 9.7, 3.9 Hz, 1H), 2.23 (ddd, *J* = 14.1, 7.3, 1.2 Hz, 1H) ppm; ^{13}C NMR (D_2O, 125 MHz,) δ 159.6, 158.3, 156.4, 84.0, 75.1, 63.7, 58.3, 53.5, 44.3, 29.3 ppm; HRMS (ES^+) calcd for $C_{10}H_{18}N_7O_3$ (M+H): 284.1471, found: 284.1473.

(+)-saxitoxin •2TFA. The bis guanidine **11** (15 mg, 25 μmol) was dissolved in CH_2Cl_2 (2.5 mL) and Dess- Martin Periodinane (16 mg, 38 μmol) was added to this solution at rt. The reaction mixture was stirred for 2 h and filtered through a small pad of celite. The celite pad was washed with an additional CH_2Cl_2 (3 mL) and the combined filtrates were transferred to a separatory funnel. The organic layer was washed with 10% aqueous solution of $Na_2S_2O_3$ (5 mL). The organic layer was then separated, dried over Na_2SO_4 and concentrated under reduced pressure to yield ketone (18 mg, crude weight) as a colorless foam. This compound is unstable and hence used as such in the next step without further purification.



HRMS (ES^+) calcd for $C_{25}H_{39}N_7O_9Na$ (M+Na): 604.2692, found: 604.2707.

The crude ketone (18 mg, 30.96 μmol) was dissolved in CH_2Cl_2: TFA (1:1, 1 mL) and stirred at rt for 1 h. The contents of the flask were concentrated under reduced pressure. The resultant residue was washed with CH_2Cl_2 several times and concentrated again under reduced pressure. This semisolid was then dissolved in 1 mL of H_2O and filtered through a 25 micron PTFE Acrodisc® syringe filter. The syringe filter was washed with an additional 1 mL of H_2O. The combined filtrates were concentrated under reduced pressure to afford the bis-TFA salt of (+)-saxitoxin (11 mg, 81% over 2 steps) as a colorless oil.

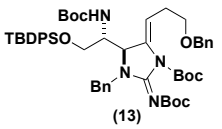


$[\alpha]^{20}_D$ = +78.1° (c = 0.3, MeOH); ^{1}H NMR (D_2O, 500 MHz) δ 4.72 (d, *J* = 0.9 Hz, 1H), 4.26 (dd, *J* = 11.2, 9.2 Hz, 1H), 3.99 (dd, *J* = 11.7, 5.3 Hz, 1H), 3.80 (ddd, *J* = 9.2, 5.3, 0.9 Hz, 1H), 3.77 (ddd, *J* = 10.2, 8.3, 1.9 Hz, 1H), 3.60- 3.53 (m, 1H), 2.40 (ddd, *J* = 14.1, 8.3, 1.9 Hz, 1H), 2.32 (ddd, *J* = 14.1, 9.7, 9.7 Hz, 1H) ppm; ^{13}C NMR (D_2O, 125 MHz,) δ 159.6, 158.4, 156.6, 99.1, 83.0, 63.7, 57.6, 53.6, 43.4, 33.5 ppm; HRMS (ES^+) calcd for $C_{10}H_{18}N_7O_4$ (M+H): 300.1420, found: 300.1431.

Propargyl guanidine (12). To a solution of diamine (151 mg, 223 μmol) in CH_2Cl_2 (2.5 mL), *N*,*N*′-Di-Boc-*S*-methylisothiourea (68 mg, 234 μmol) was added followed by HgO (49 mg, 226 μmol) and NEt_3 (47 μL, 326 μmol). The contents of the flask were stirred at rt for 8 h. The reaction mixture was then diluted with CH_2Cl_2 (5 mL) and filtered through a small pad of celite. The celite bed was washed with an additional CH_2Cl_2 (2 mL) and the combined filtrates were concentrated under reduced pressure to yield a colorless foam. Purification by flash silica gel column chromatography (10 % EtOAc in hexanes) gave the propargyl guanidine **12** (149 mg, 72%) as a colorless foam.

TLC R_f = 0.41 (8:2 Hexanes: EtOAc); $[\alpha]^{20}_D$ = –54.1° (c = 0.51, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz): δ 10.74 (s, 1H), 7.83- 7.80 (m, 4H), 7.34- 7.17 (m, 10H), 7.16- 6.97 (m, 6H), 6.29 (brs, 1H), 4.99 (d, *J* = 9.76 Hz, 1H), 4.80 (d, *J* = 16.1Hz, 1H), 4.72 (d, *J* = 16.1 Hz, 1H), 4.44- 4.20 (m, 1H), 4.19 (s, 2H), 4.13 (d, *J* = 9.2 Hz, 1H), 3.80 (dd, *J* = 10.7, 3.4 Hz, 1H), 3.23 (dt, *J* = 7.3, 5.3 Hz, 2H), 2.23 (dt, *J* = 6.8, 5.8 Hz, 2H), 1.44 (s, 9H), 1.38 (s, 9H), 1.21 (s, 9H), 1.20 (s, 9H) ppm; ^{13}C NMR (C_6D_6 125 MHz) δ 163.5, 156.5, 155.2, 152.1, 150.1, 138.9, 138.1, 136. 2, 136.1, 133.8, 133.5, 129.9, 129.8, 128.8, 128.5, 128.1, 128.0, 127.8, 127.3, 127.3, 83.0, 81.2, 78.9, 78.7, 77.9, 72.7, 68.3, 54.6, 52.3, 50.3, 28.4, 28.2, 27.8, 27.2, 20.4, 19.5 ppm; IR (neat) 2976, 2931, 2857, 2360, 2339, 1771, 1700, 1616, 1558, 1569, 1496, 1436, 1393, 1290, 1232, 1140, 1113, 824, 739, 700 cm^{-1}; HRMS (ES^+) calcd for $C_{53}H_{70}N_4O_8SiNa$ (M+Na): 941.4861, found: 941.4885.

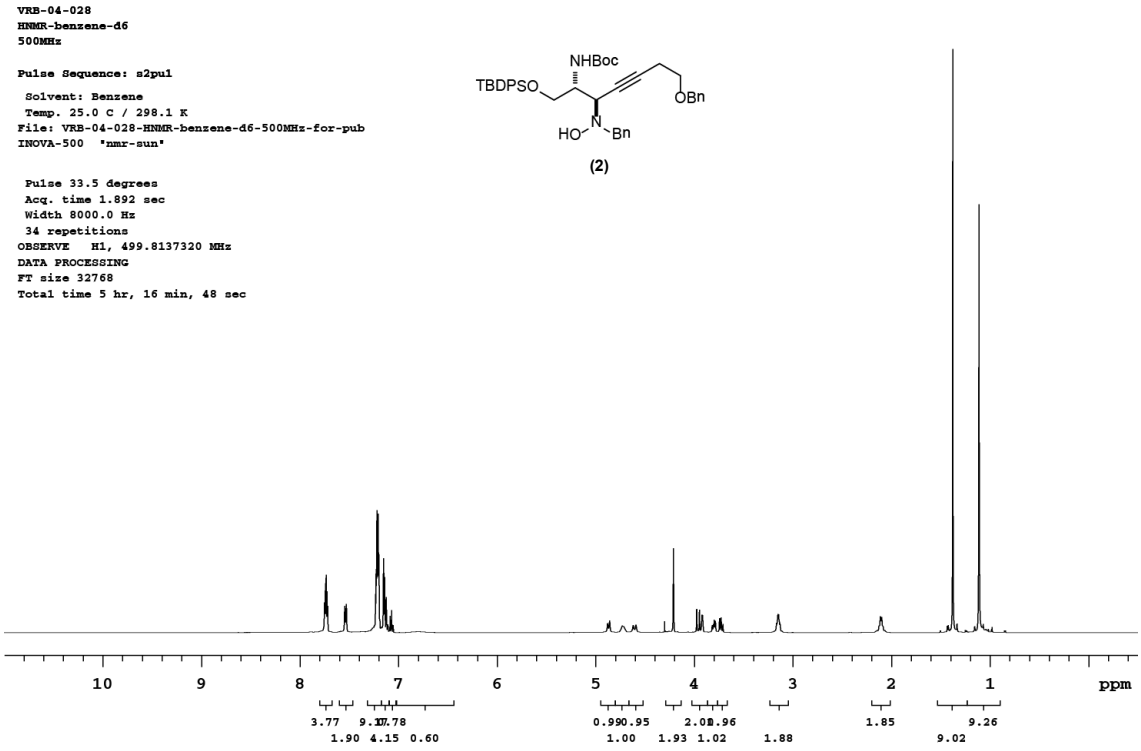
(*S*,5*Z*)-*tert*-butyl 3-benzyl-5-(3-(benzyloxy)propylidene)-2-((*tert*-butoxycarbonyl)imino)-4-((*R*)-2,2,10,10-tetramethyl-8-oxo-3,3-diphenyl-4,9-dioxa-7-aza-3-silaundecan-6-yl)imidazolidine-1-carboxylate (13). To a solution of the propargyl guanidine **12** (38 mg, 56 μmol) in CH_2Cl_2 (500 μL) was added AgOAc (1 mg, 59 μmol). The contents of the flask were stirred for 9 h and filtered through a syringe filter. The filter was washed with an additional portion of CH_2Cl_2 (1 mL) and the combined filtrates were concentrated under reduced pressure to yield ene-guanidine **13** (35 mg, 91%) as a colorless foam.

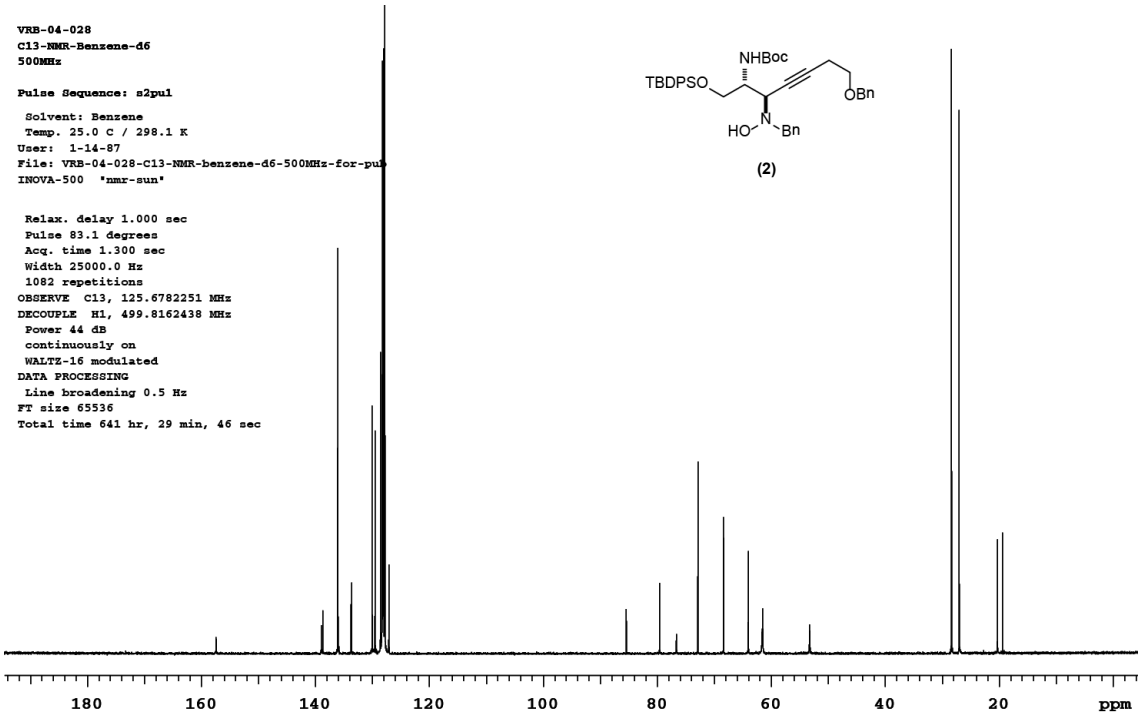


(13)

TLC R_f = 0.25 (8:2 Hexanes:EtOAc); $[\alpha]^{20}_D$ = +43.9° (c = 1.83, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz): δ 7.60– 7.5 (m, 4H), 7.26 (δ, *J* = 7.3 Hz, 2H), 7.20- 7.07 (m, 11H), 6.98- 6.93 (m, 3H), 5.36 (d, *J* = 15.6 Hz, 1H), 5.09 (dd, *J* = 8.7, 4.3 Hz, 1H), 4.42- 4.36 (m, 1H), 4.30 (d, *J* = 15.1 Hz, 1H), 4.28 (d, *J* = 12.2 Hz, 2H), 4.24 (d, *J* = 12.2 Hz, 1H), 4.16 (d, *J* = 10.2 Hz, 1H), 4.10 (s, 1H), 3.64 (dd, *J* = 10.2, 6.8 Hz, 1H), 3.43 (t, *J* = 9.7 Hz, 1H), 3.26- 3.16 (m, 2H), 2.57- 2.51 (m, 1H), 2.43- 2.39 (m, 1H), 1.65 (s, 9H), 1.45 (s, 9H), 1.42 (s, 9H), 0.99 (s, 9H) ppm; ^{13}C NMR (C_6D_6, 125 MHz) δ 159.2, 155.6, 152.0, 149.5, 139.1, 136.5, 135.9, 135.8, 133.3, 133.0, 131.0, 130.2, 130.1, 128.9, 128.5, 128.4, 128.2, 128.1, 127.8, 127.6, 127.5, 118.1, 83.3, 80.1, 77.9, 72.8, 68.8, 62.6, 58.4, 51.4, 46.5, 29.6, 28.6, 28.4, 28.2, 26.9, 19.1 ppm; IR (neat) 2974, 2930, 2857, 2360, 2339, 1751, 1717, 1699, 1684, 1646, 1635, 1521, 1506, 1472, 1419, 1365, 1293, 1249, 1147, 1112, 1027, 850, 823, 742, 701, 667, 614 cm^{-1}; HRMS (ESI) calcd for $C_{53}H_{70}N_4O_8SiNa$ (M+Na): 941.4861, found: 941.4860.

3. Representative ^{1}H NMR and ^{13}C NMR spectra

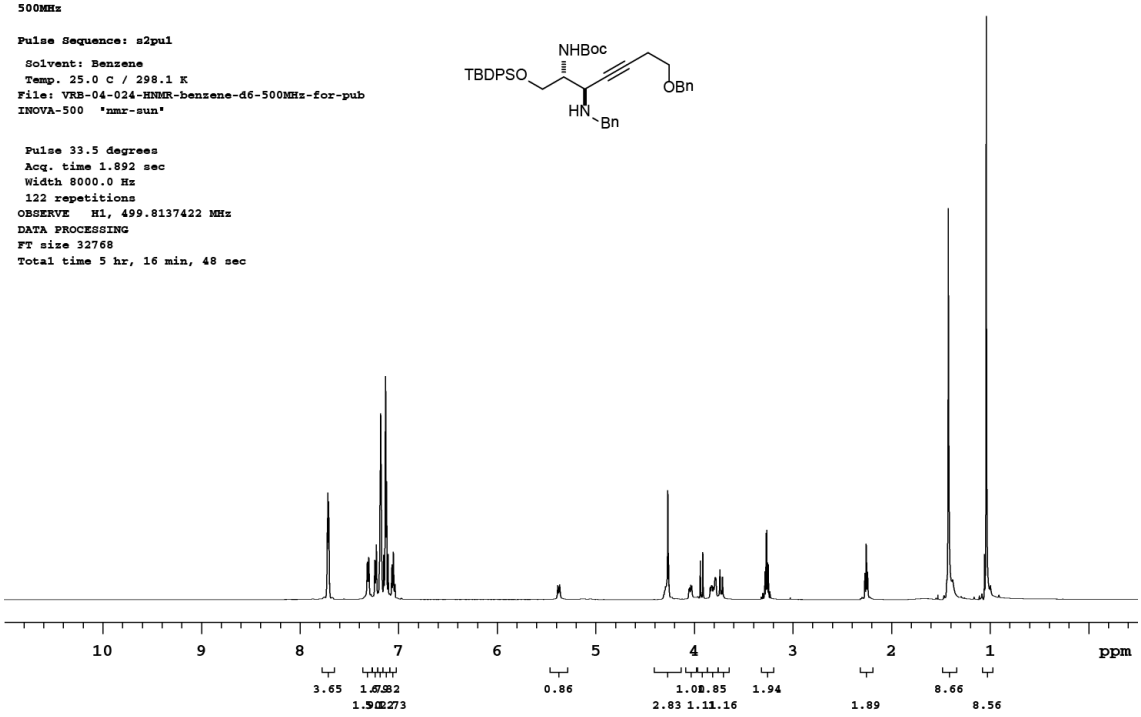




VRB-04-024
HNMR-benzene-d6
500MHz

Pulse Sequence: s2pul
Solvent: Benzene
Temp. 25.0 C / 298.1 K
File: VRB-04-024-HNMR-benzene-d6-500MHz-for-pub
INOVA-500 "nmr-sun"

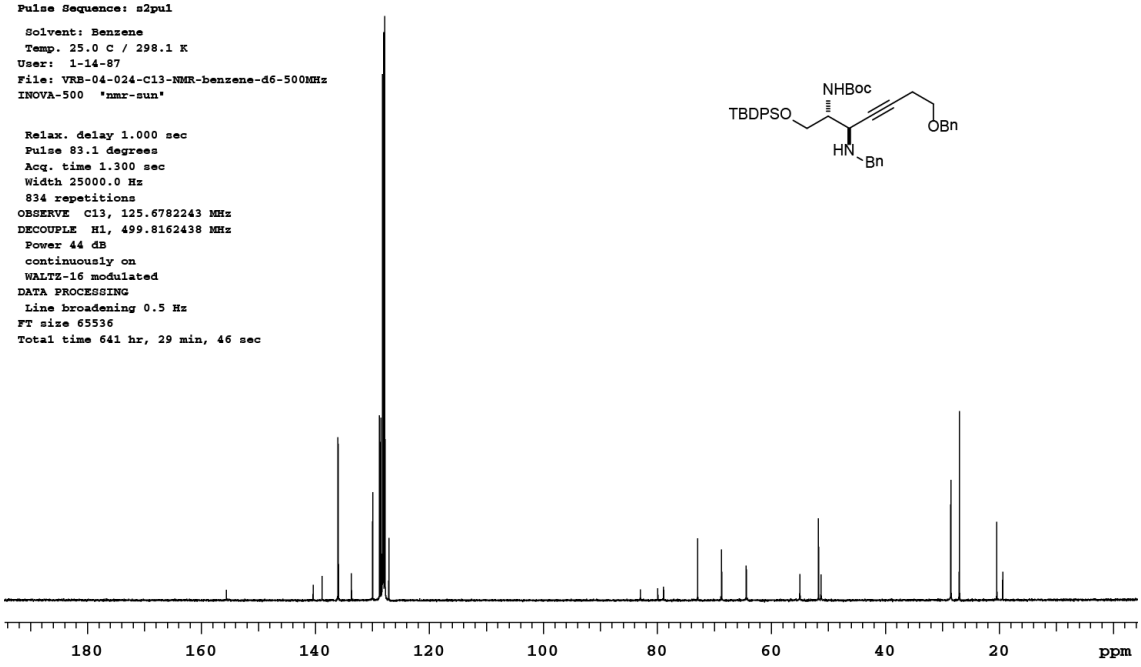
Pulse 33.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
122 repetitions
OBSERVE H1, 499.8137422 MHz
DATA PROCESSING
FT size 32768
Total time 5 hr, 16 min, 48 sec

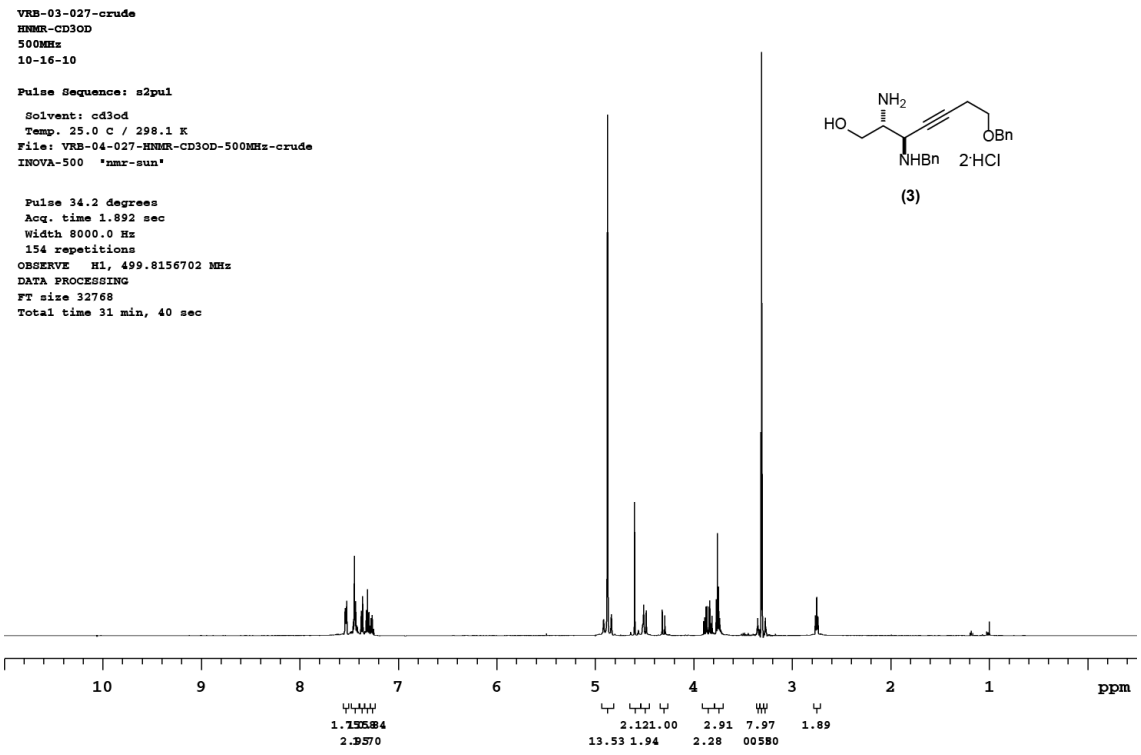


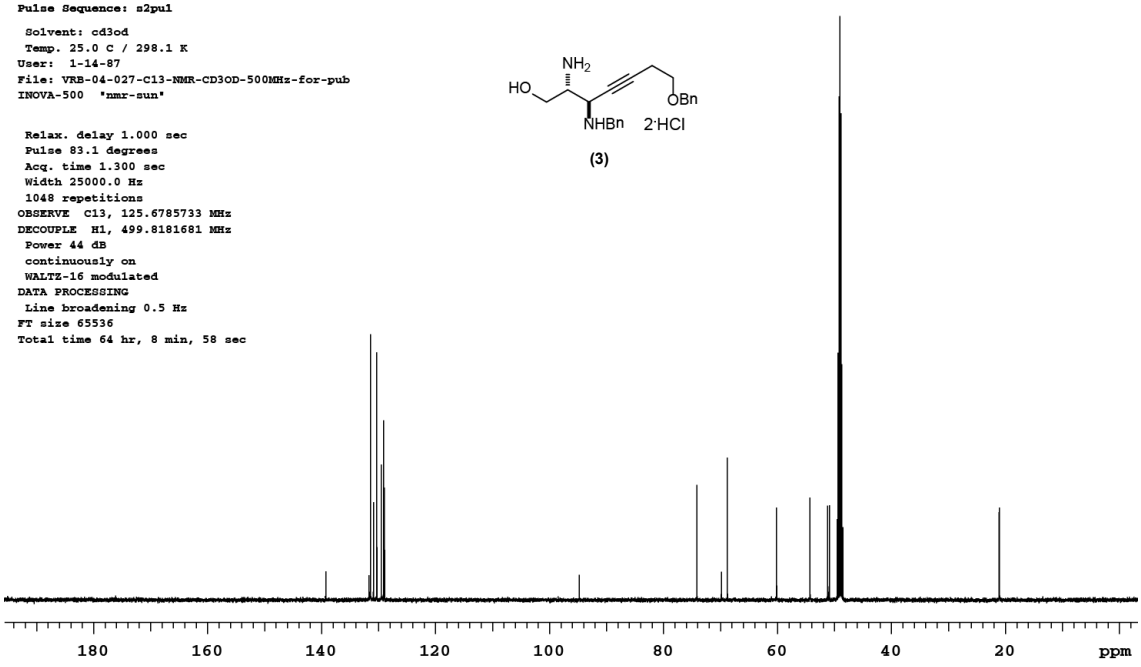
VRB-04-024//C13-NMR-benzene-d6//500MHz

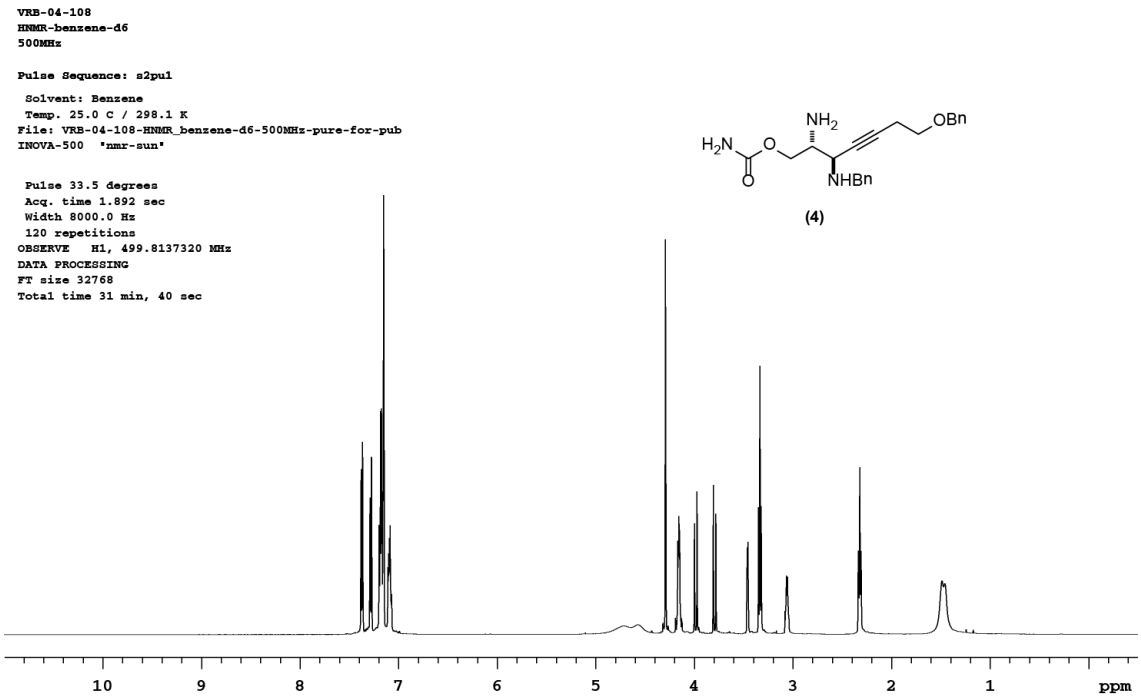
Pulse Sequence: s2pul
Solvent: Benzene
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: VRB-04-024-C13-NMR-benzene-d6-500MHz
INOVA-500 "nmr-sun"

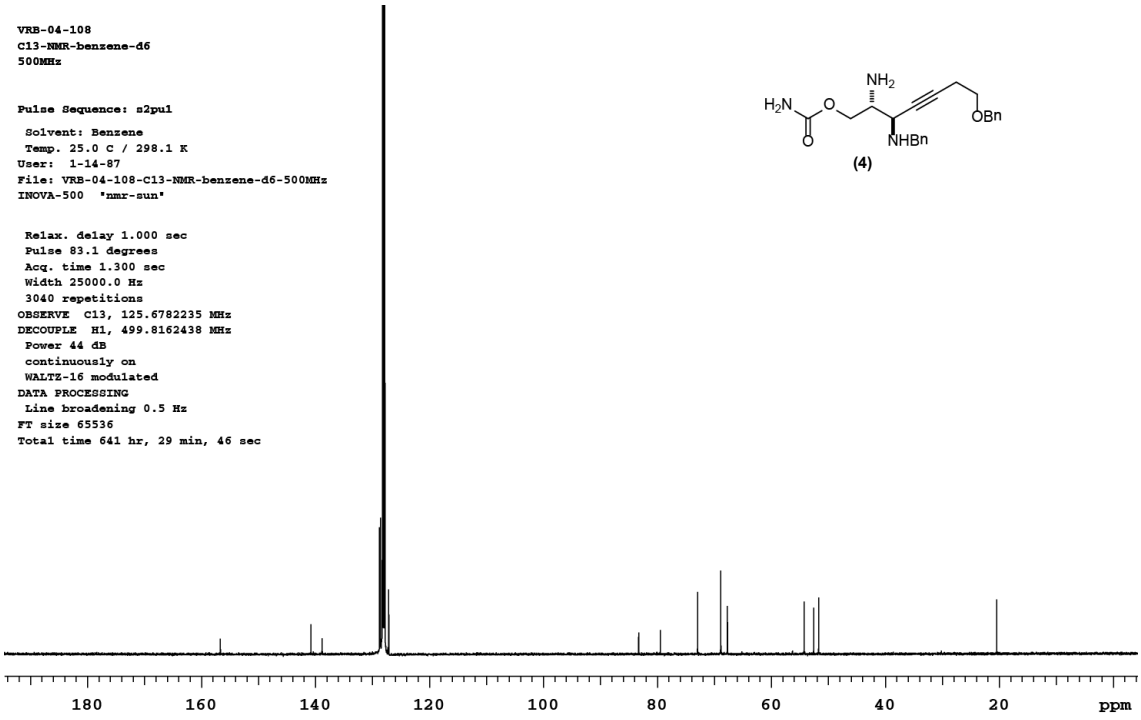
Relax. delay 1.000 sec
Pulse 83.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
834 repetitions
OBSERVE C13, 125.6782243 MHz
DECOUPLE H1, 499.8162438 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 641 hr, 29 min, 46 sec

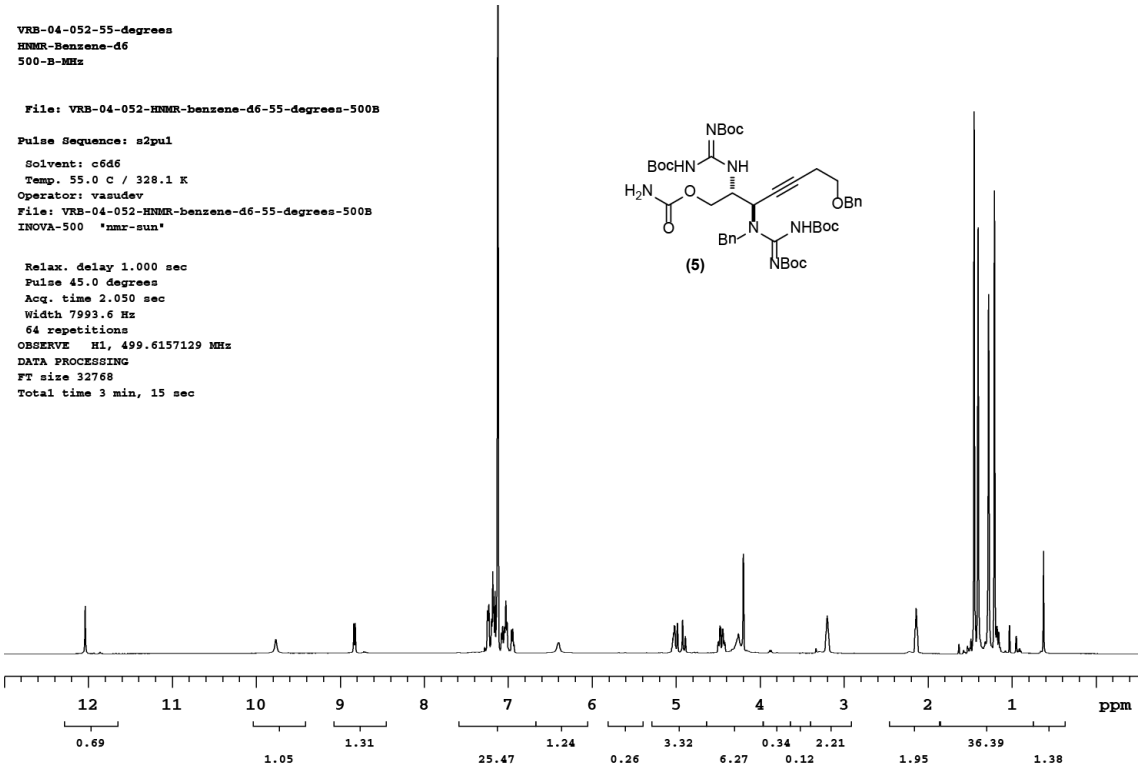


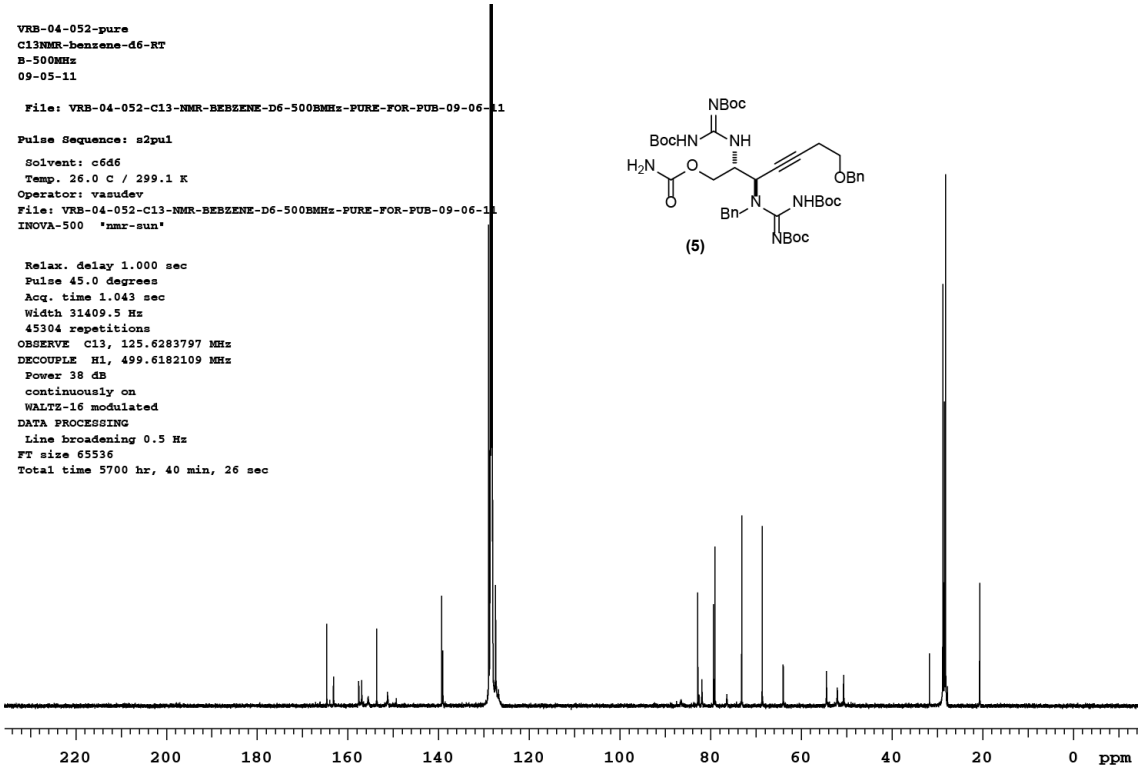

VRB-03-027-crude
HNMR-CD3OD
500MHz
10-16-10
Pulse Sequence: s2pul
Solvent: cd3od
Temp. 25.0 C / 298.1 K
File: VRB-04-027-HNMR-CD3OD-500MHz-crude
INOVA-500 "nmr-sun"
Pulse 34.2 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
154 repetitions
OBSERVE H1, 499.8156702 MHz
DATA PROCESSING
FT size 32768
Total time 31 min, 40 sec
NH2
HO
OBn
NHBn 2·HCl
(3)
10
9
8
7
6
5
4
3
2
1
ppm
2.12
1.00
2.91
7.97
1.89
13.53
1.94
2.28

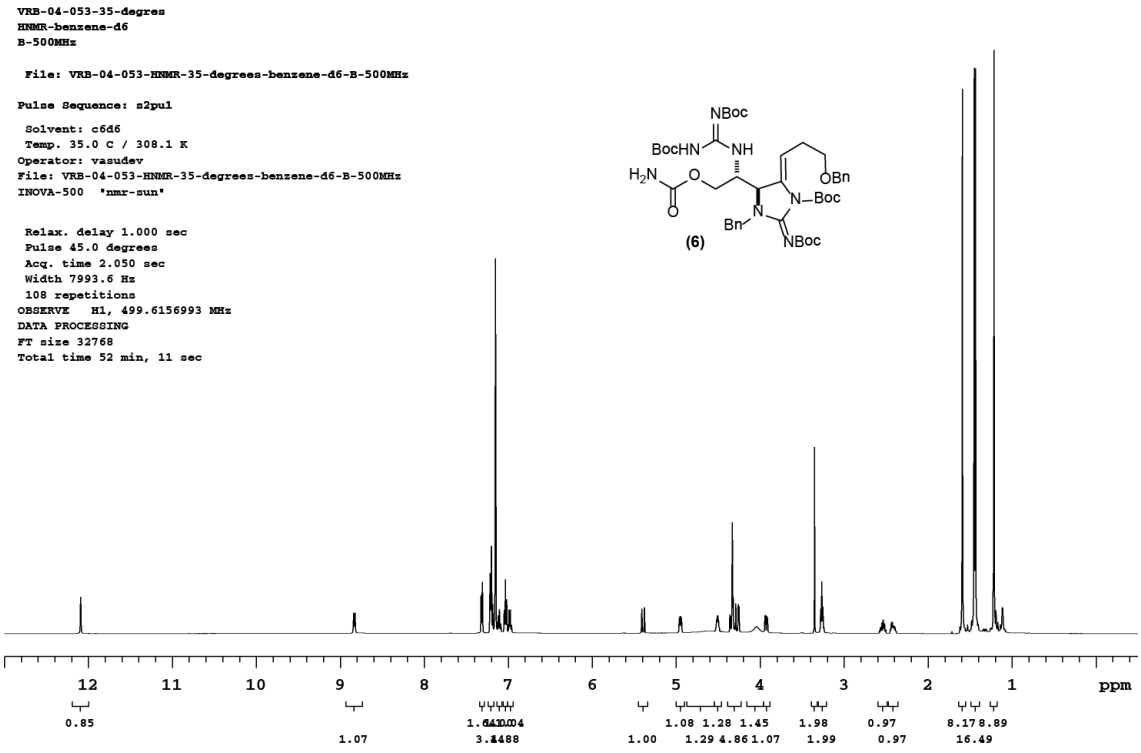

STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: cd3od
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: VRB-04-027-C13-NMR-CD3OD-500MHz-for-pub
INOVA-500 "nmr-sun"
Relax. delay 1.000 sec
Pulse 83.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
1048 repetitions
OBSERVE C13, 125.6785733 MHz
DECOUPLE H1, 499.8181681 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 64 hr, 8 min, 58 sec
NH2
HO
OBn
NHBn 2·HCl
(3)
180
160
140
120
100
80
60
40
20
ppm

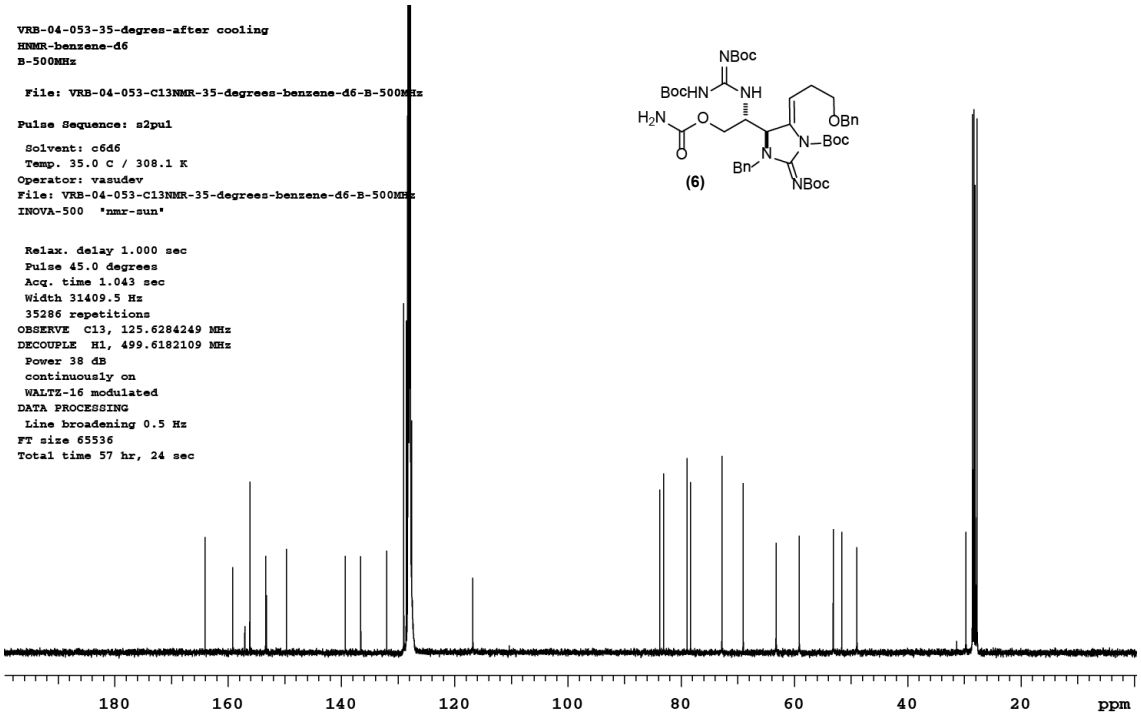

VRB-04-108
HNMR-benzene-d6
500MHz
Pulse Sequence: s2pul
Solvent: Benzene
Temp. 25.0 C / 298.1 K
File: VRB-04-108-HNMR_benzene-d6-500MHz-pure-for-pub
INOVA-500 "nmr-sun"
Pulse 33.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
120 repetitions
OBSERVE H1, 499.8137320 MHz
DATA PROCESSING
FT size 32768
Total time 31 min, 40 sec
NH2
OBn
H2N
O
NHBn
(4)
10
9
8
7
6
5
4
3
2
1
ppm

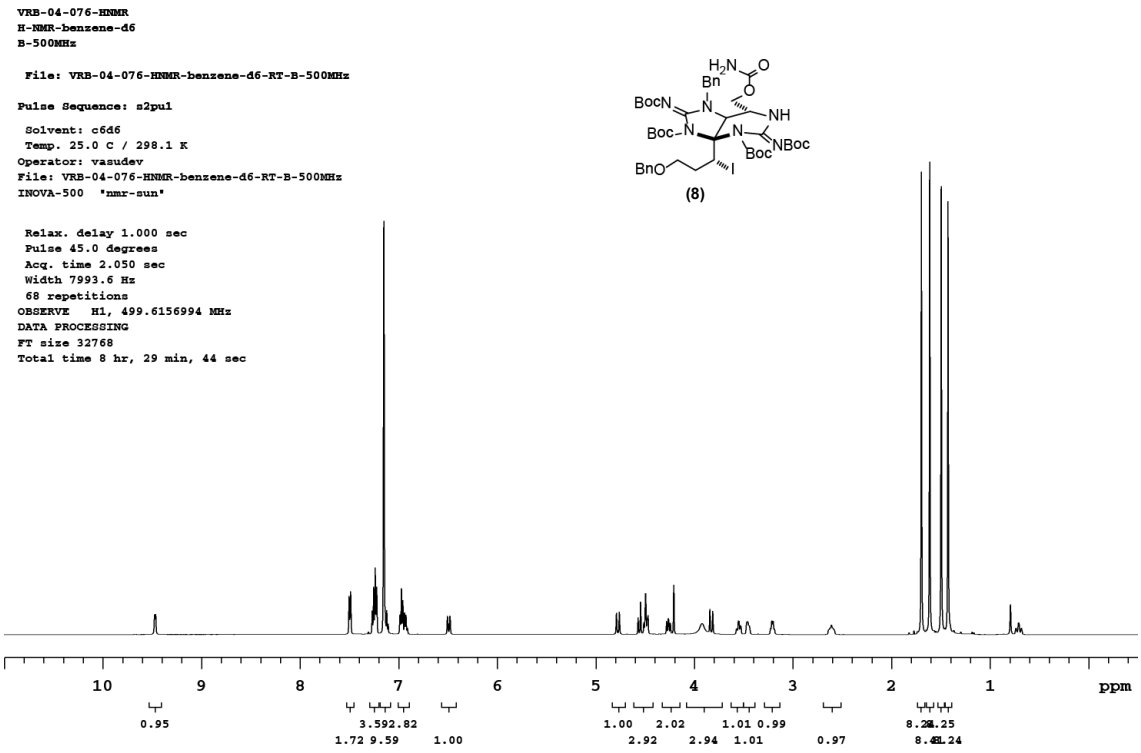

VRB-04-108
C13-NMR-benzene-d6
500MHz
Pulse Sequence: s2pul
Solvent: Benzene
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: VRB-04-108-C13-NMR-benzene-d6-500MHz
INOVA-500 "nmr-sun"
Relax. delay 1.000 sec
Pulse 83.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
3040 repetitions
OBSERVE C13, 125.6782235 MHz
DECOUPLE H1, 499.8162438 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 641 hr, 29 min, 46 sec
NH2
OBn
H2N
O
NHBn
(4)
180
160
140
120
100
80
60
40
20
ppm

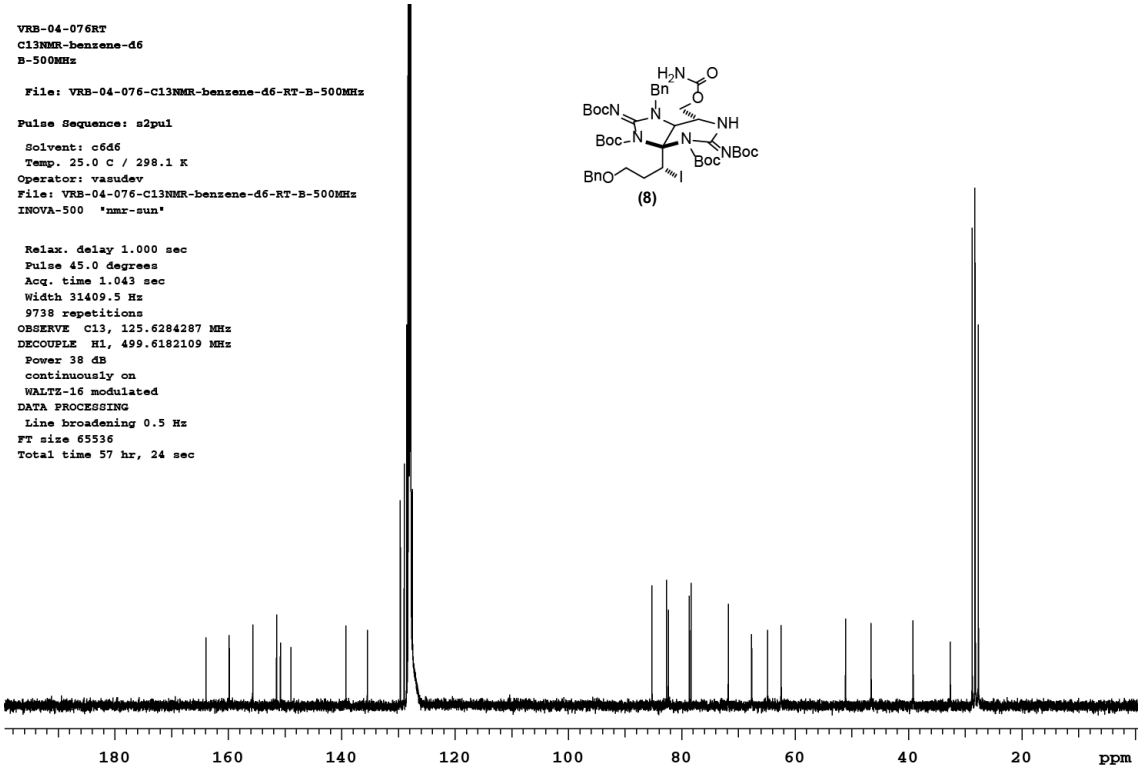

VRB-04-052-55-degrees
HNMR-Benzene-d6
500-B-MHz
File: VRB-04-052-HNMR-benzene-d6-55-degrees-500B
Pulse Sequence: s2pul
Solvent: c6d6
Temp. 55.0 C / 328.1 K
Operator: vasudev
File: VRB-04-052-HNMR-benzene-d6-55-degrees-500B
INOVA-500 "nmr-sun"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.050 sec
Width 7993.6 Hz
64 repetitions
OBSERVE H1, 499.6157129 MHz
DATA PROCESSING
FT size 32768
Total time 3 min, 15 sec
NBoc
BocHN
NH
H2N
O
OBn
Bn
N
NHBoc
NBoc
(5)
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.69
1.05
1.31
25.47
1.24
0.26
3.32
6.27
0.34
0.12
2.21
1.95
36.39
1.38

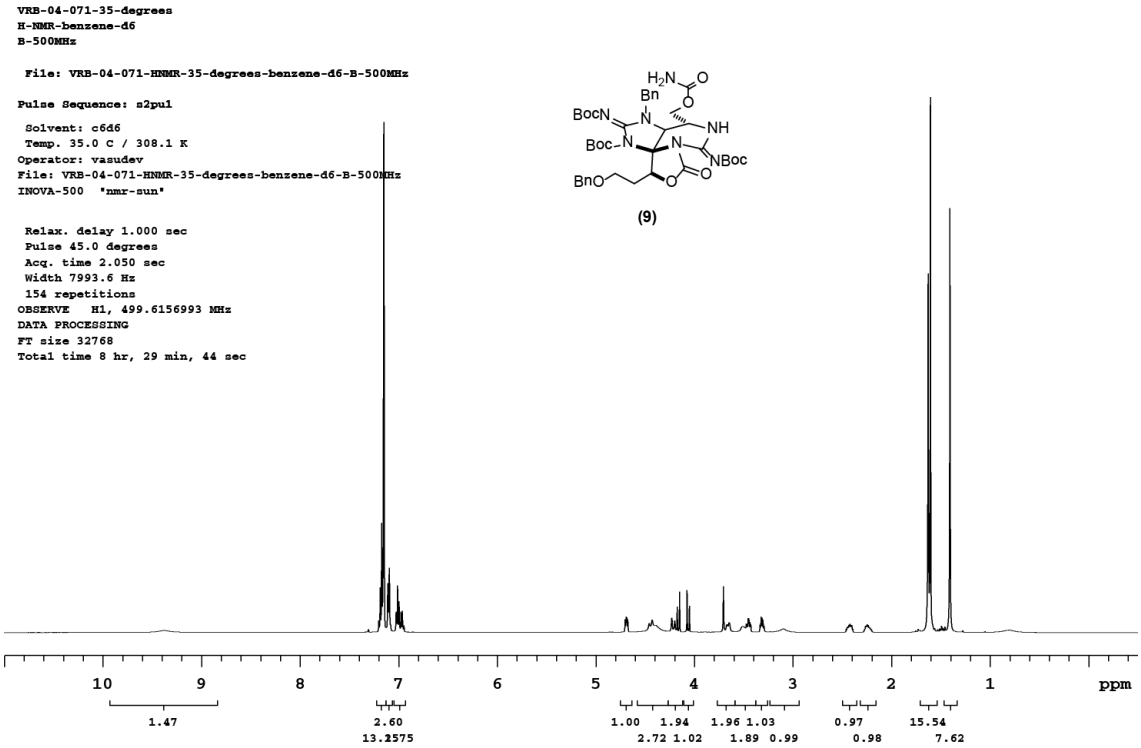

VRB-04-052-pure
C13NMR-benzene-d6-RT
B-500MHz
09-05-11
File: VRB-04-052-C13-NMR-BEBZENE-D6-500BMHz-PURE-FOR-PUB-09-06-11
Pulse Sequence: s2pul
Solvent: c6d6
Temp. 26.0 C / 299.1 K
Operator: vasudev
File: VRB-04-052-C13-NMR-BEBZENE-D6-500BMHz-PURE-FOR-PUB-09-06-11
INOVA-500 "nmr-sun"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.043 sec
Width 31409.5 Hz
45304 repetitions
OBSERVE C13, 125.6283797 MHz
DECOUPLE H1, 499.6182109 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 5700 hr, 40 min, 26 sec
NBoc
BocHN
NH
H2N
O
OBn
Bn
N
NHBoc
NBoc
(5)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

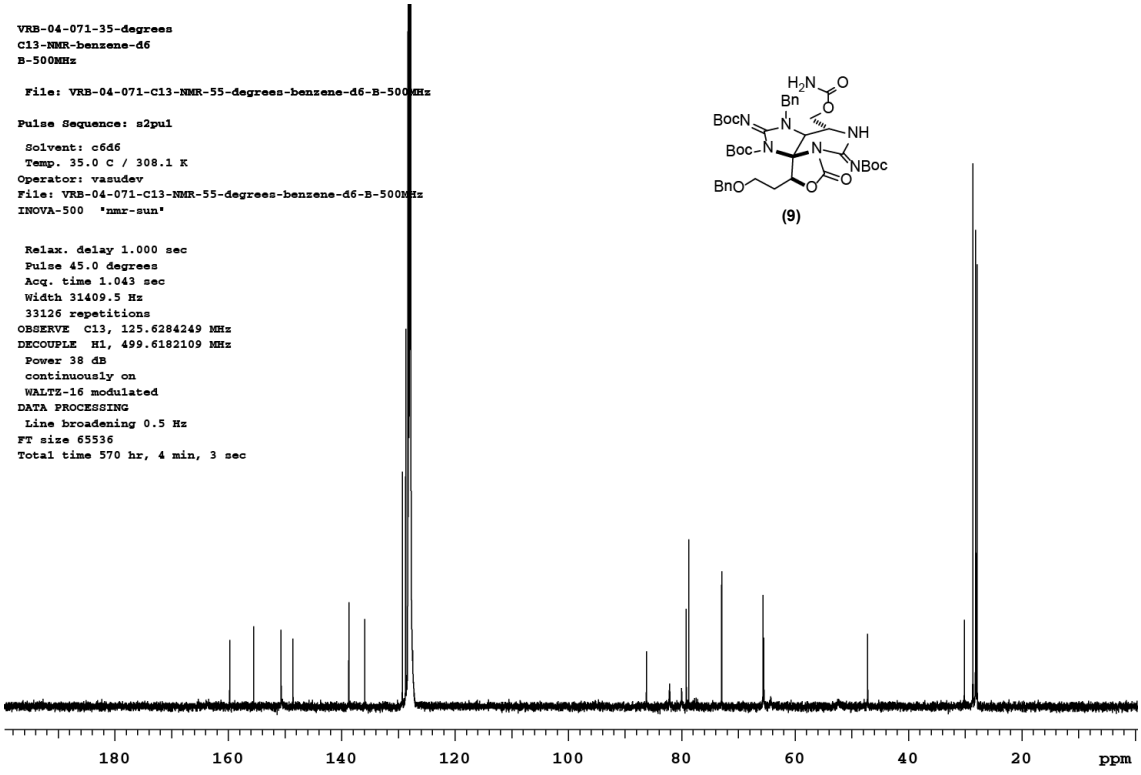

VRB-04-053-35-degres
HNMR-benzene-d6
B-500MHz
File: VRB-04-053-HNMR-35-degrees-benzene-d6-B-500MHz
Pulse Sequence: s2pul
Solvent: c6d6
Temp. 35.0 C / 308.1 K
Operator: vasudev
File: VRB-04-053-HNMR-35-degrees-benzene-d6-B-500MHz
INOVA-500 'nmr-sun'
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.050 sec
Width 7993.6 Hz
108 repetitions
OBSERVE H1, 499.6156993 MHz
DATA PROCESSING
FT size 32768
Total time 52 min, 11 sec
NBoc
BocHN
NH
H2N
O
OBn
N–Boc
N
Bn
NBoc
(6)
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.85
1.07
1.08
1.28
1.45
1.98
0.97
8.17
8.89
1.00
1.29
4.86
1.07
1.99
0.97
16.49

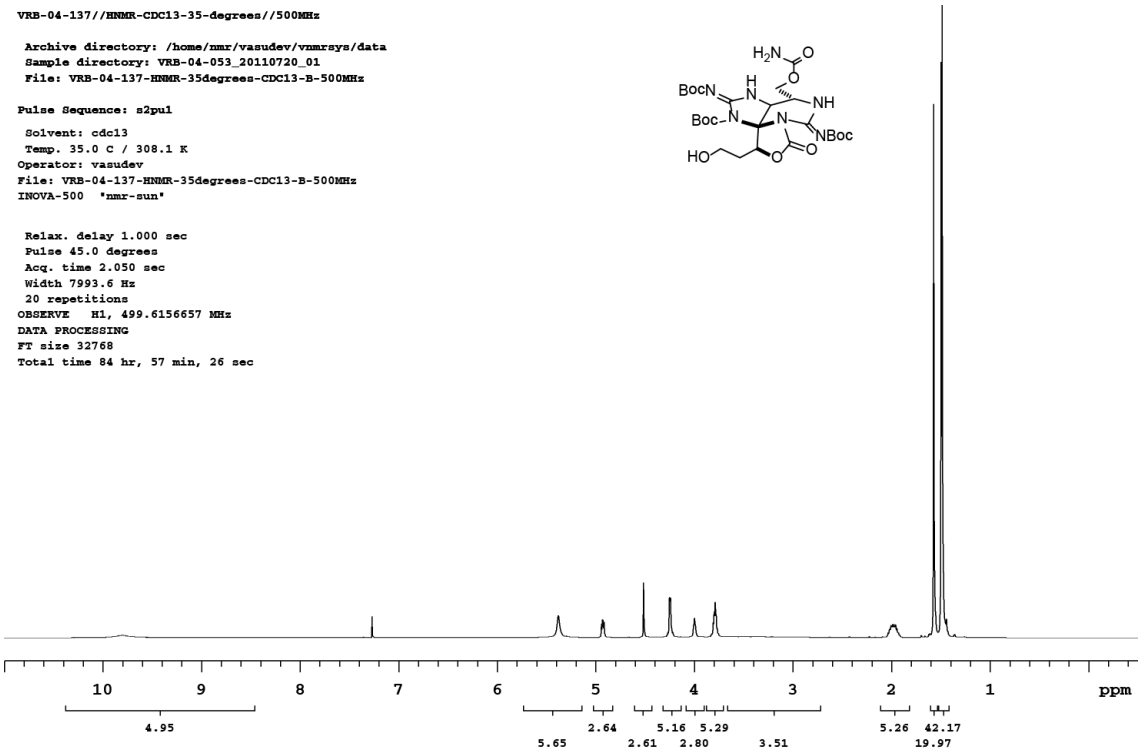

VRB-04-053-35-degres-after cooling
HNMR-benzene-d6
B-500MHz
File: VRB-04-053-C13NMR-35-degrees-benzene-d6-B-500MHz
Pulse Sequence: s2pul
Solvent: c6d6
Temp. 35.0 C / 308.1 K
Operator: vasudev
File: VRB-04-053-C13NMR-35-degrees-benzene-d6-B-500MHz
INOVA-500 'nmr-sun'
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.043 sec
Width 31409.5 Hz
35286 repetitions
OBSERVE C13, 125.6284249 MHz
DECOUPLE H1, 499.6182109 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 57 hr, 24 sec
NBoc
BocHN
NH
H2N
O
OBn
N–Boc
N
Bn
NBoc
(6)
180
160
140
120
100
80
60
40
20
ppm

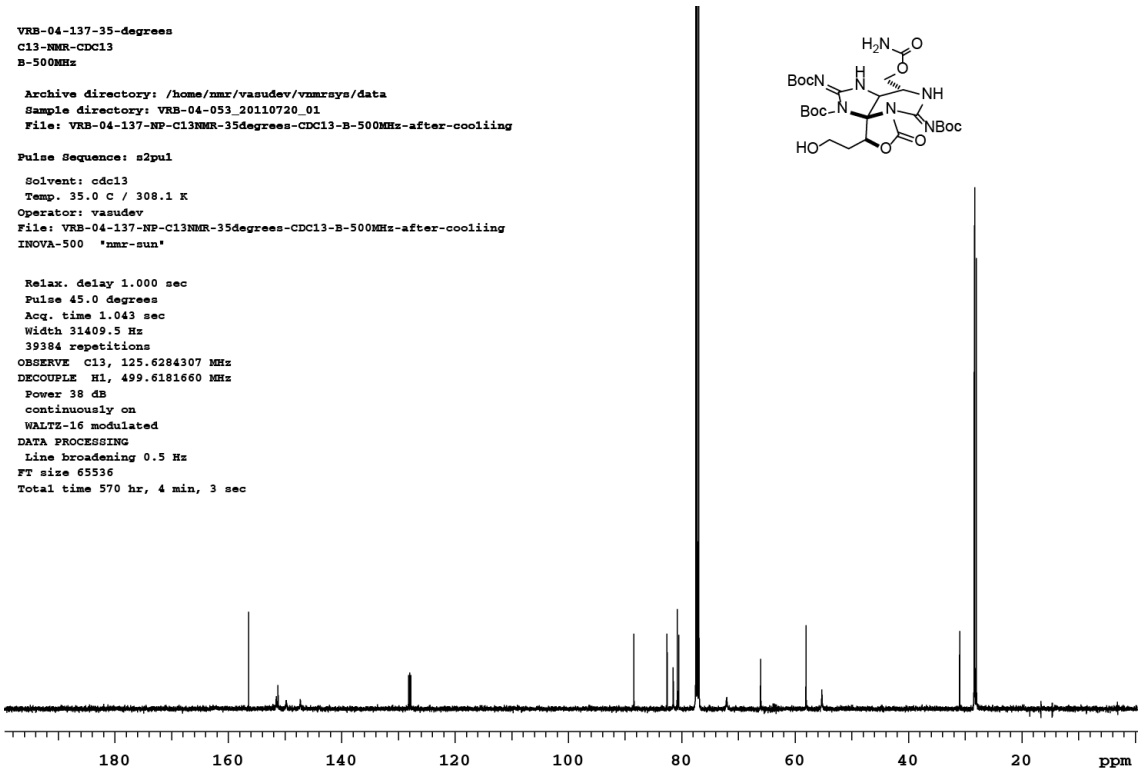

VRB-04-076-HNMR
H-NMR-benzene-d6
B-500MHz
File: VRB-04-076-HNMR-benzene-d6-RT-B-500MHz
Pulse Sequence: s2pul
Solvent: c6d6
Temp. 25.0 C / 298.1 K
Operator: vasudev
File: VRB-04-076-HNMR-benzene-d6-RT-B-500MHz
INOVA-500 "nmr-sun"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.050 sec
Width 7993.6 Hz
68 repetitions
OBSERVE H1, 499.6156994 MHz
DATA PROCESSING
FT size 32768
Total time 8 hr, 29 min, 44 sec
(8)
10
9
8
7
6
5
4
3
2
1
ppm
0.95
3.59
2.82
1.72
9.59
1.00
1.00
2.02
1.01
0.99
2.92
2.94
1.01
0.97
8.25
8.24


VRB-04-076RT
C13NMR-benzene-d6
B-500MHz
File: VRB-04-076-C13NMR-benzene-d6-RT-B-500MHz
Pulse Sequence: s2pul
Solvent: c6d6
Temp. 25.0 C / 298.1 K
Operator: vasudev
File: VRB-04-076-C13NMR-benzene-d6-RT-B-500MHz
INOVA-500 "nmr-sun"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.043 sec
Width 31409.5 Hz
9738 repetitions
OBSERVE C13, 125.6284287 MHz
DECOUPLE H1, 499.6182109 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 57 hr, 24 sec
(8)
180
160
140
120
100
80
60
40
20
ppm


VRB-04-071-35-degrees
H-NMR-benzene-d6
B-500MHz
File: VRB-04-071-HNMR-35-degrees-benzene-d6-B-500MHz
Pulse Sequence: s2pul
Solvent: c6d6
Temp. 35.0 C / 308.1 K
Operator: vasudev
File: VRB-04-071-HNMR-35-degrees-benzene-d6-B-500MHz
INOVA-500 "nmr-sun"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.050 sec
Width 7993.6 Hz
154 repetitions
OBSERVE H1, 499.6156993 MHz
DATA PROCESSING
FT size 32768
Total time 8 hr, 29 min, 44 sec
(9)
10
9
8
7
6
5
4
3
2
1
ppm
1.47
2.60
13.2575
1.00
1.94
2.72
1.02
1.96
1.03
1.89
0.99
0.97
0.98
15.54
7.62


VRB-04-071-35-degrees
C13-NMR-benzene-d6
B-500MHz
File: VRB-04-071-C13-NMR-55-degrees-benzene-d6-B-500MHz
Pulse Sequence: s2pul
Solvent: c6d6
Temp. 35.0 C / 308.1 K
Operator: vasudev
File: VRB-04-071-C13-NMR-55-degrees-benzene-d6-B-500MHz
INOVA-500 "nmr-sun"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.043 sec
Width 31409.5 Hz
33126 repetitions
OBSERVE C13, 125.6284249 MHz
DECOUPLE H1, 499.6182109 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 570 hr, 4 min, 3 sec
(9)
180
160
140
120
100
80
60
40
20
ppm


VRB-04-137//HNMR-CDC13-35-degrees//500MHz
Archive directory: /home/nmr/vasudev/vnmrsys/data
Sample directory: VRB-04-053_20110720_01
File: VRB-04-137-HNMR-35degrees-CDC13-B-500MHz
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 35.0 C / 308.1 K
Operator: vasudev
File: VRB-04-137-HNMR-35degrees-CDC13-B-500MHz
INOVA-500 "nmr-sun"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.050 sec
Width 7993.6 Hz
20 repetitions
OBSERVE H1, 499.6156657 MHz
DATA PROCESSING
FT size 32768
Total time 84 hr, 57 min, 26 sec
BocN
Boc-N
NH
NBoc
HO
10
9
8
7
6
5
4
3
2
1
ppm
4.95
5.65
2.64
2.61
5.16
2.80
5.29
3.51
5.26
19.97
42.17


VRB-04-137-35-degrees
C13-NMR-CDC13
B-500MHz
Archive directory: /home/nmr/vasudev/vnmrsys/data
Sample directory: VRB-04-053_20110720_01
File: VRB-04-137-NP-C13NMR-35degrees-CDC13-B-500MHz-after-cooliing
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 35.0 C / 308.1 K
Operator: vasudev
File: VRB-04-137-NP-C13NMR-35degrees-CDC13-B-500MHz-after-cooliing
INOVA-500 "nmr-sun"
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.043 sec
Width 31409.5 Hz
39384 repetitions
OBSERVE C13, 125.6284307 MHz
DECOUPLE H1, 499.6181660 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 570 hr, 4 min, 3 sec
BocN
Boc-N
NH
NBoc
HO
180
160
140
120
100
80
60
40
20
ppm

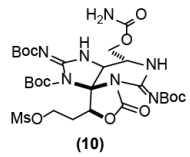
VRB-04-145-RT
HNMR-CDC13
500MHz

File: VRB-04-145-HNMNR-CDC13-RT-B-500MHz

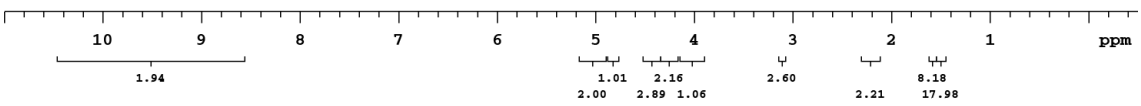
Pulse Sequence: s2pu1

Solvent: cdc13
Temp. 25.0 C / 298.1 K
Operator: vasudev
File: VRB-04-145-HNMNR-CDC13-RT-B-500MHz
INOVA-500 'nmr-sun'

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.050 sec
Width 7993.6 Hz
50 repetitions
OBSERVE H1, 499.6156662 MHz
DATA PROCESSING
FT size 32768
Total time 8 hr, 29 min, 44 sec



(10)



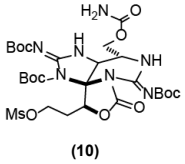
VRB-04-mesylate
C13-NMR-CDC13
B-500MHz

Archive directory: /home/nmr/vasudev/vnmrsys/data
Sample directory: VRB-04-053_20110720_01
File: VRB-04-mesylate-C13NMR-CDC13-500MHz-B-500MHz-pure-RT

Pulse Sequence: s2pu1

Solvent: cdc13
Temp. 26.0 C / 299.1 K
Operator: vasudev
File: VRB-04-mesylate-C13NMR-CDC13-500MHz-B-500MHz-pure-RT
INOVA-500 'nmr-sun'

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.043 sec
Width 31409.5 Hz
4484 repetitions
OBSERVE C13, 125.6284413 MHz
DECOUPLE H1, 499.6181660 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 570 hr, 4 min, 2 sec



(10)

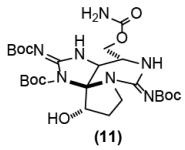
VRB-04-154-B-RT
HNMR-CDC13
500MHz

File: VRB-04-154-HNMR-CDC13-500B-rt

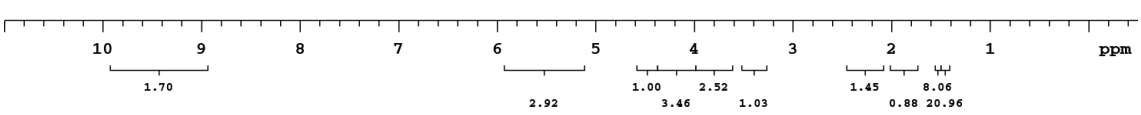
Pulse Sequence: s2pul

Solvent: cdcl3
Temp. 26.0 C / 299.1 K
Operator: vasudev
File: VRB-04-154-HNMR-CDC13-500B-rt
INOVA-500 "nmr-sun"

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.050 sec
Width 7993.6 Hz
54 repetitions
OBSERVE H1, 499.6156662 MHz
DATA PROCESSING
FT size 32768
Total time 84 hr, 57 min, 26 sec



(11)

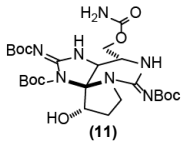


VRB-040-154//C13-NMR-CDC13//500MHz

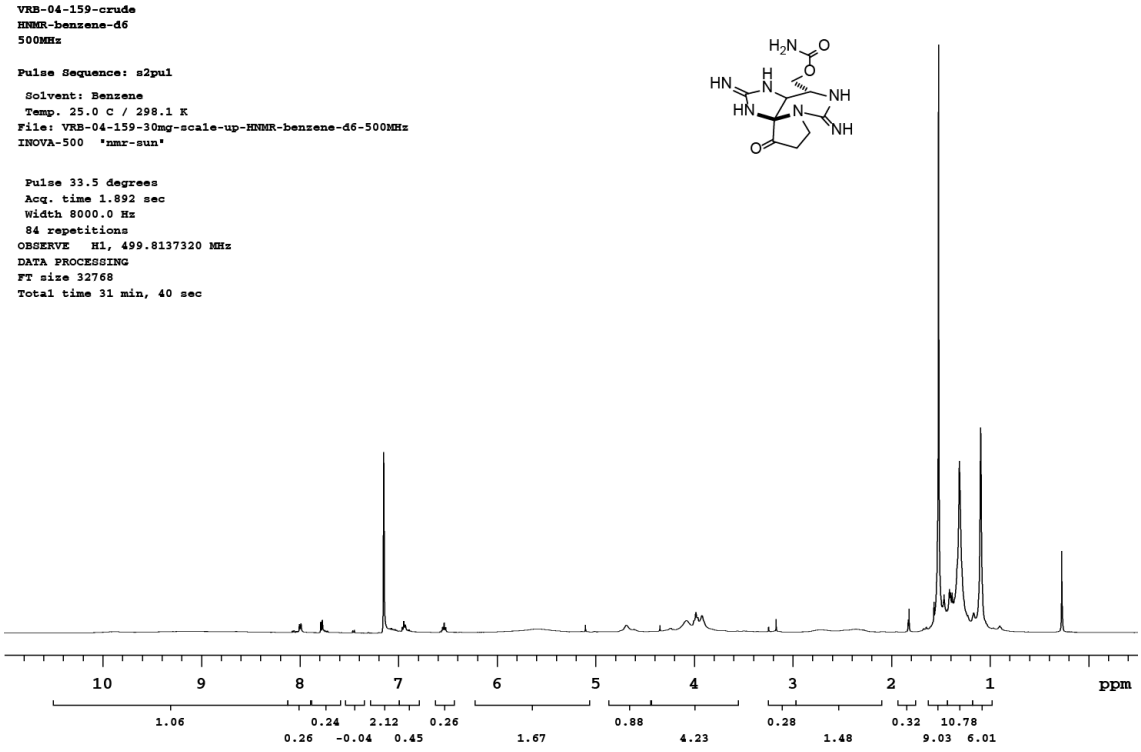
Pulse Sequence: s2pul

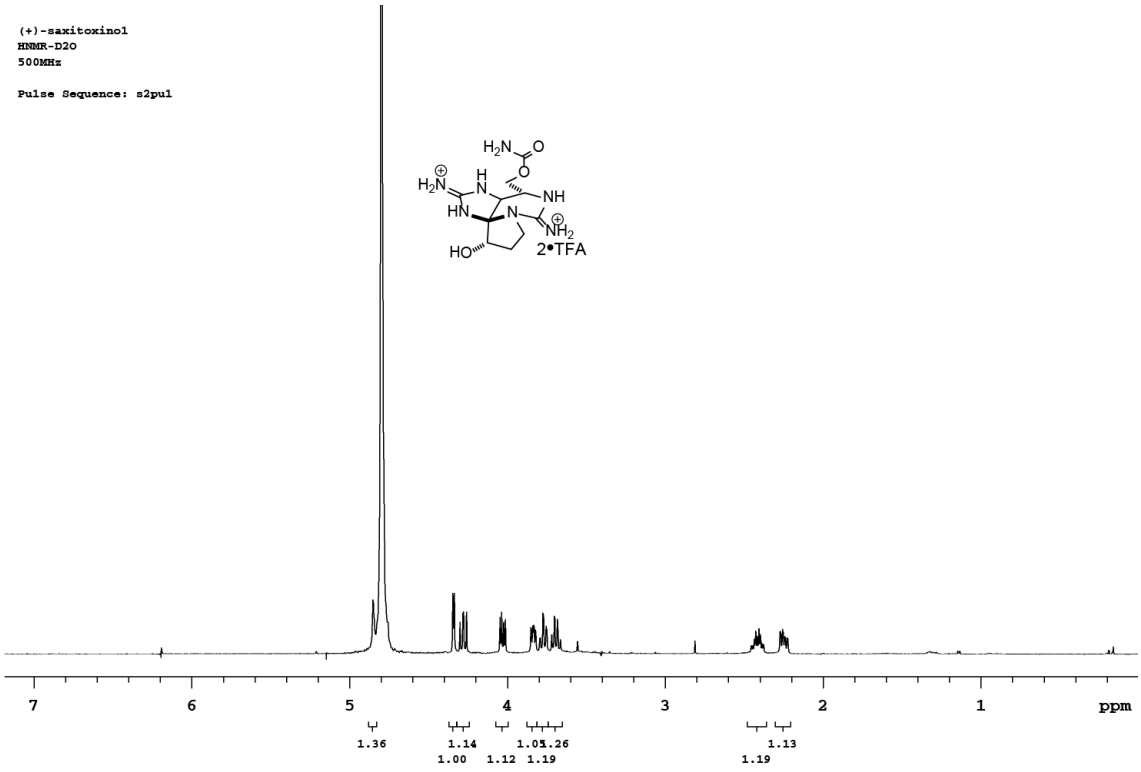
Solvent: CDC13
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: VRB-04-154-C13-NMR-CDC13-500MHz
INOVA-500 "nmr-sun"

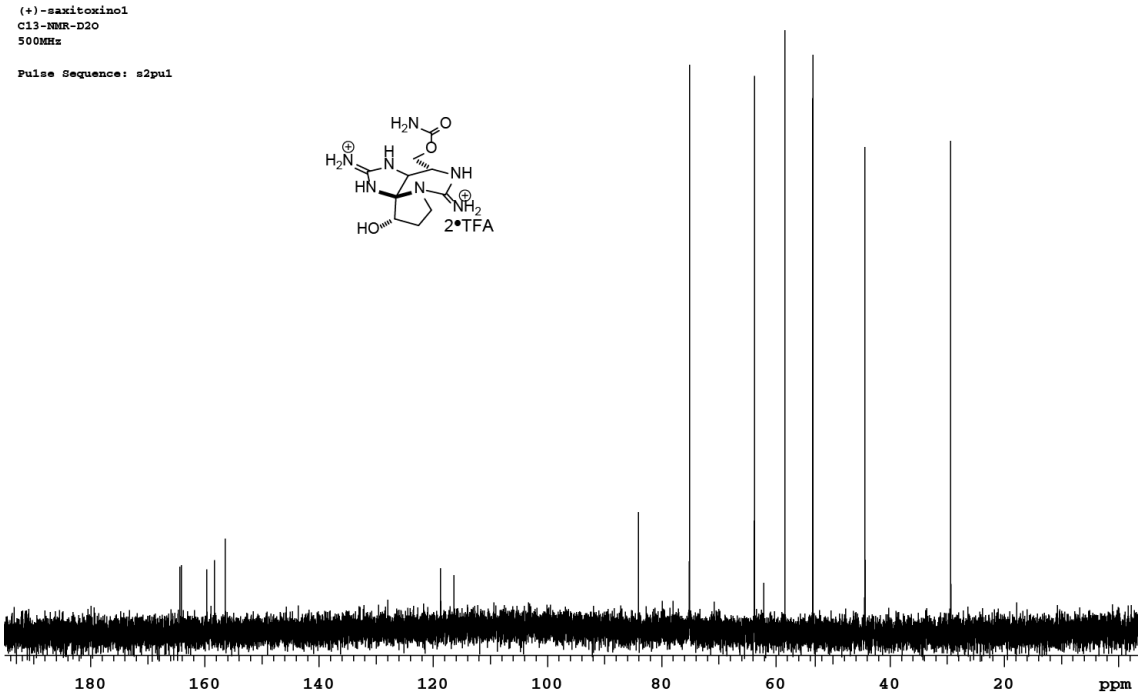
Relax. delay 1.000 sec
Pulse 83.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
24156 repetitions
OBSERVE C13, 125.6782298 MHz
DECOUPLE H1, 499.8161988 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 641 hr, 29 min, 46 sec

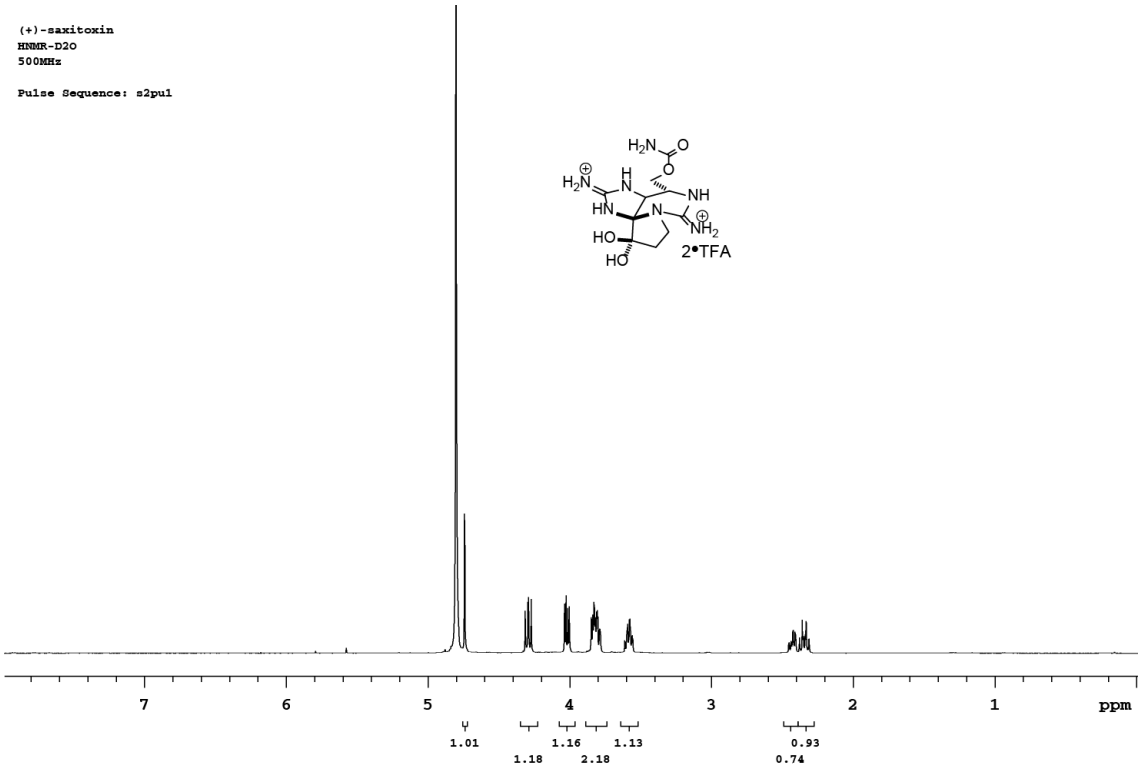


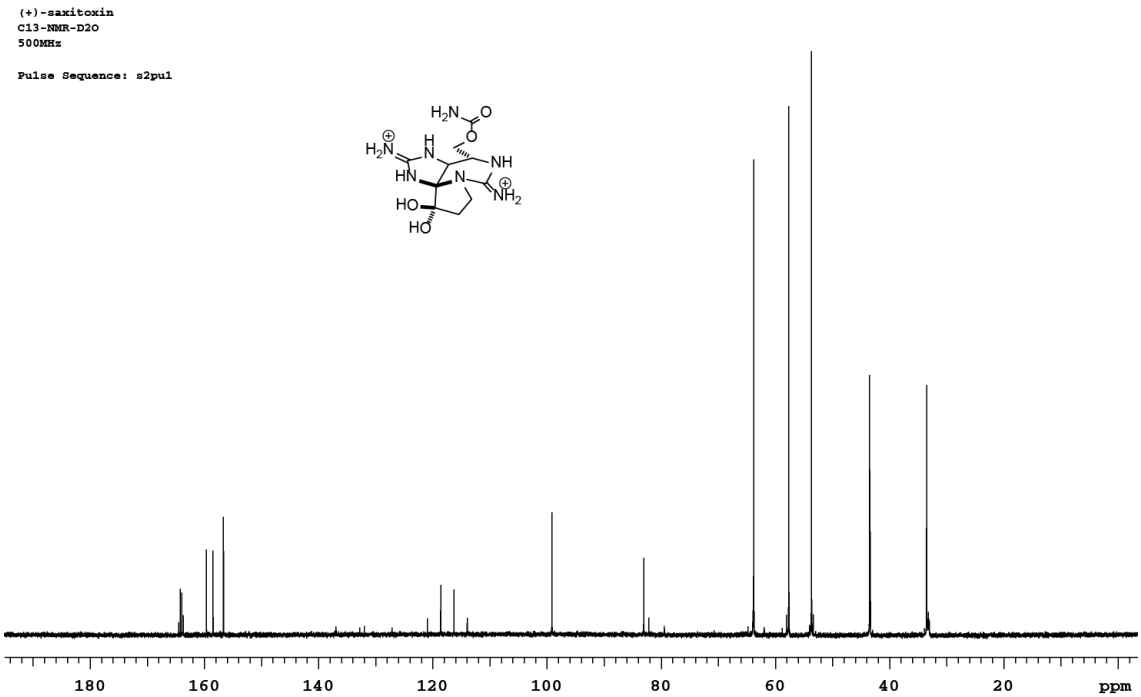
(11)

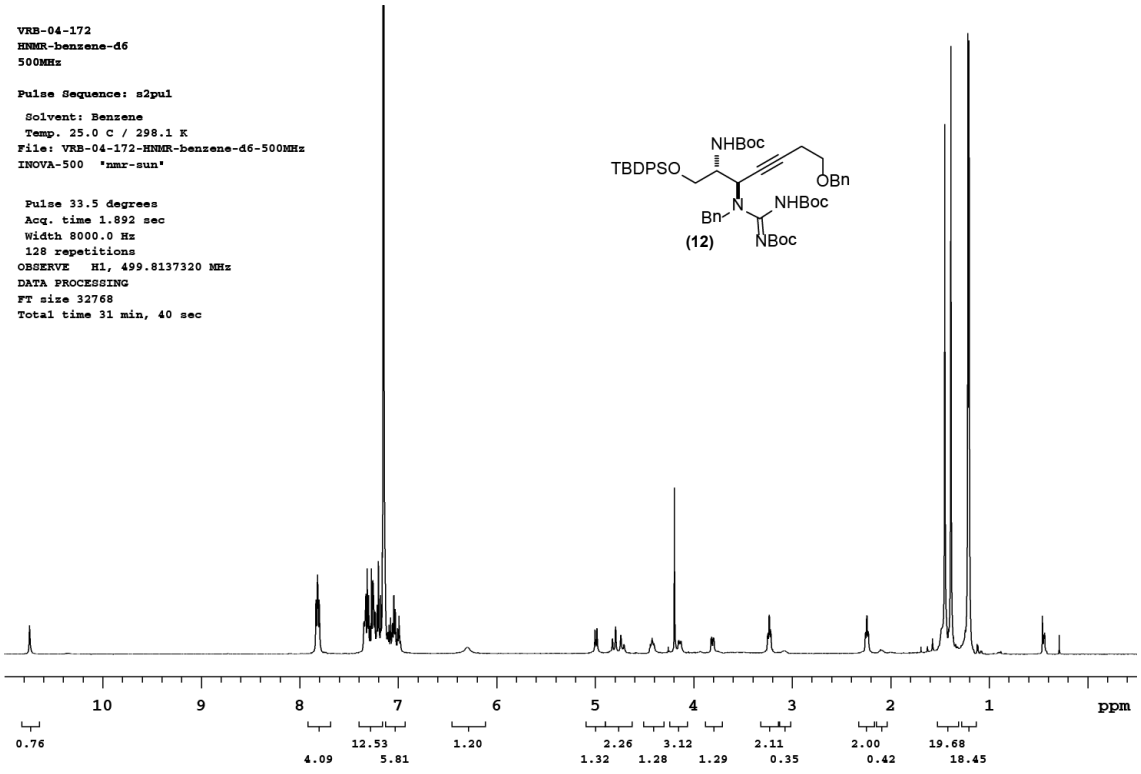

VRB-04-159-crude
HNMR-benzene-d6
500MHz
Pulse Sequence: s2pul
Solvent: Benzene
Temp. 25.0 C / 298.1 K
File: VRB-04-159-30mg-scale-up-HNMR-benzene-d6-500MHz
INOVA-500 "nmr-sun"
Pulse 33.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
84 repetitions
OBSERVE H1, 499.8137320 MHz
DATA PROCESSING
FT size 32768
Total time 31 min, 40 sec
10
9
8
7
6
5
4
3
2
1
ppm
1.06
0.24
0.26
-0.04
2.12
0.45
0.26
1.67
0.88
4.23
0.28
1.48
0.32
10.78
9.03
6.01

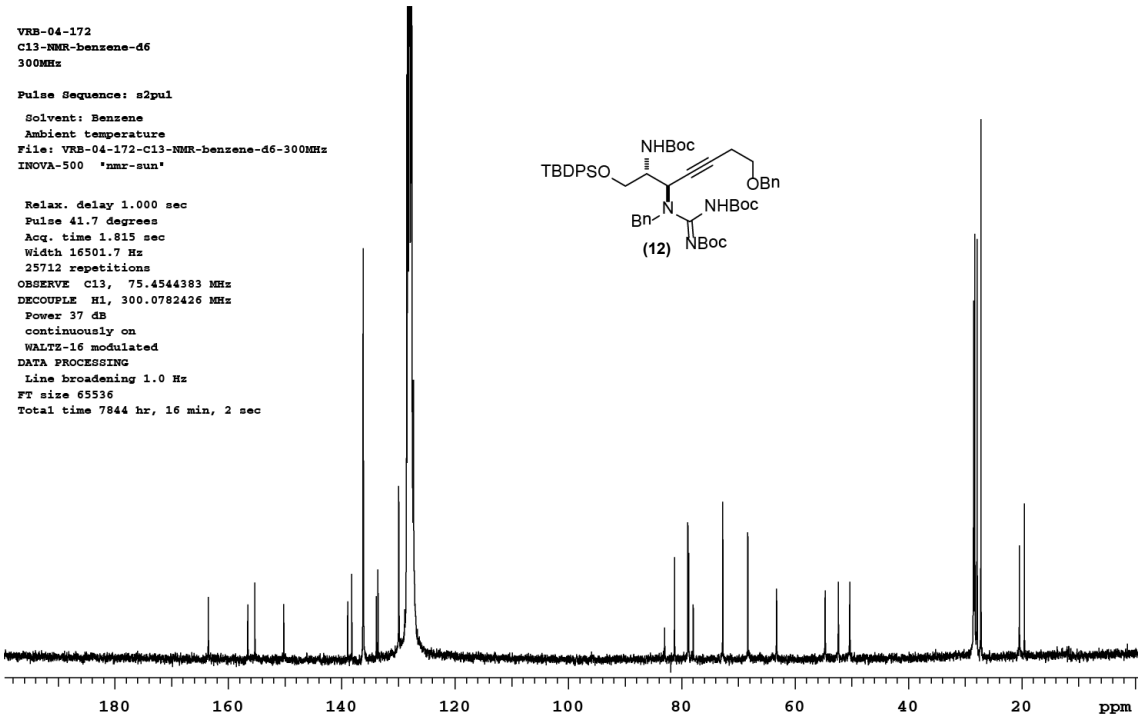

(+)-saxitoxino1
HNMR-D2O
500MHz
Pulse Sequence: s2pu1
2•TFA
7
6
5
4
3
2
1
ppm
1.36
1.14
1.00
1.12
1.05
1.26
1.19
1.19
1.13


(+)-saxitoxino1
C13-NMR-D2O
500MHz
Pulse Sequence: s2pu1
2•TFA
180
160
140
120
100
80
60
40
20
ppm

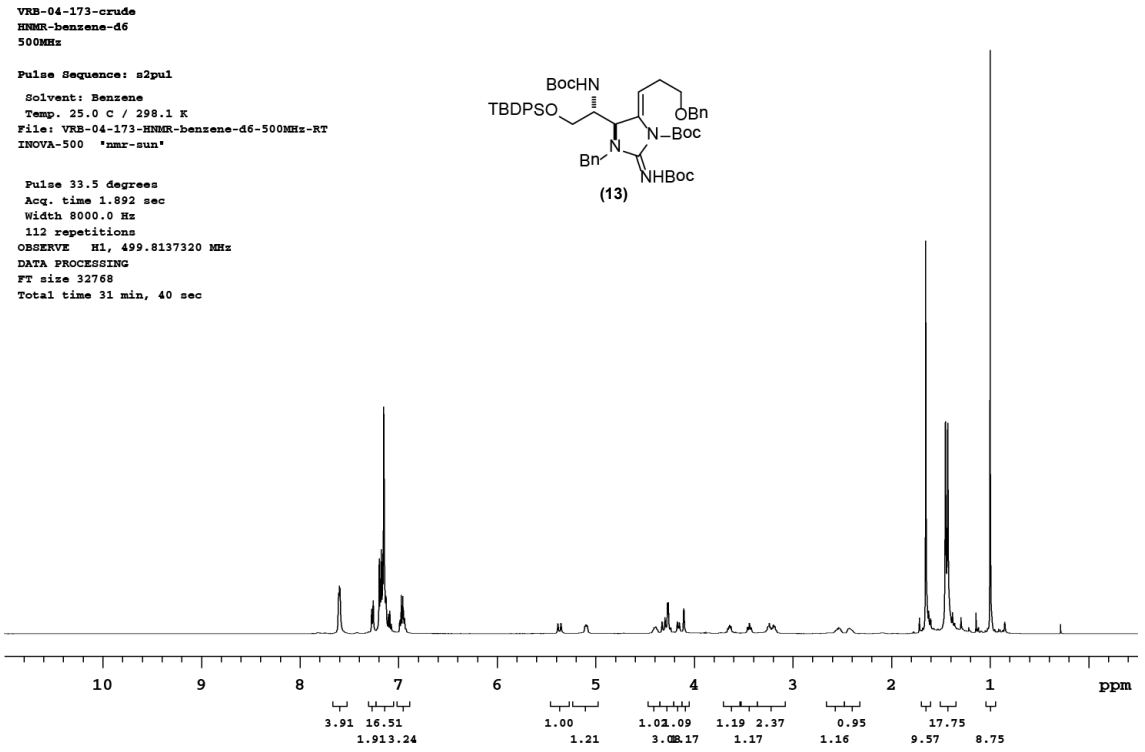

(+)-saxitoxin
HNMR-D2O
500MHz
Pulse Sequence: s2pu1
2•TFA
7
6
5
4
3
2
1
ppm
1.01
1.18
1.16
2.18
1.13
0.93
0.74

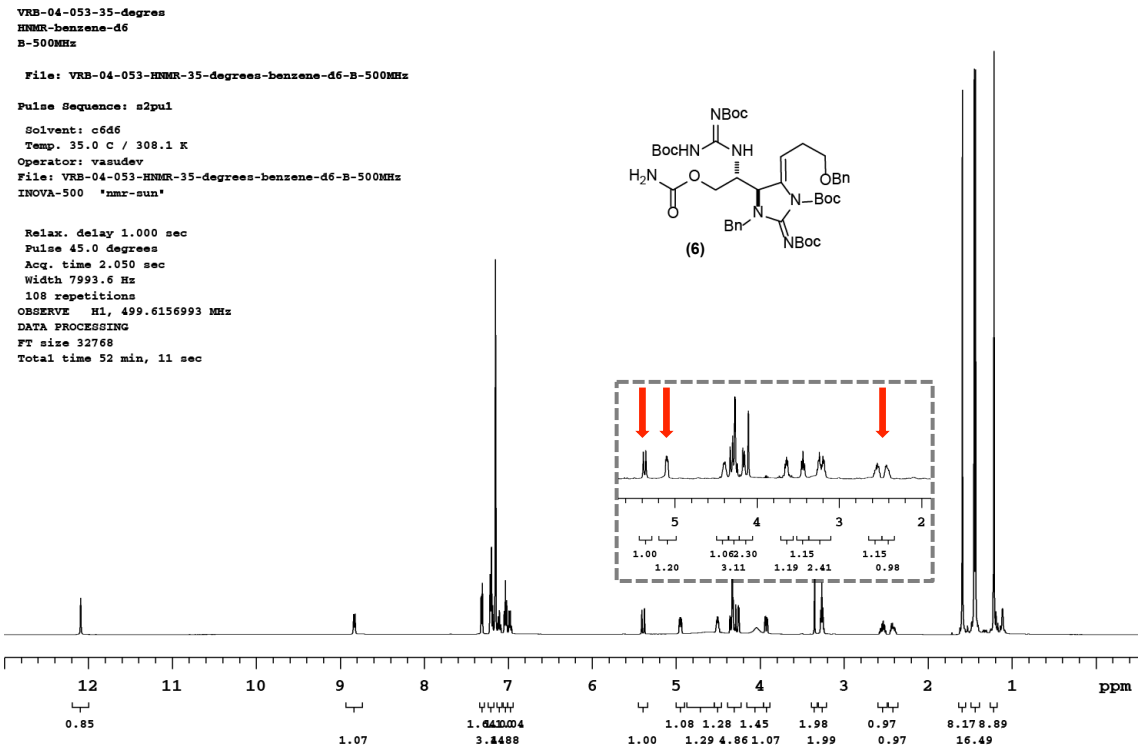

(+)-saxitoxin
C13-NMR-D2O
500MHz
Pulse Sequence: s2pu1
180
160
140
120
100
80
60
40
20
ppm

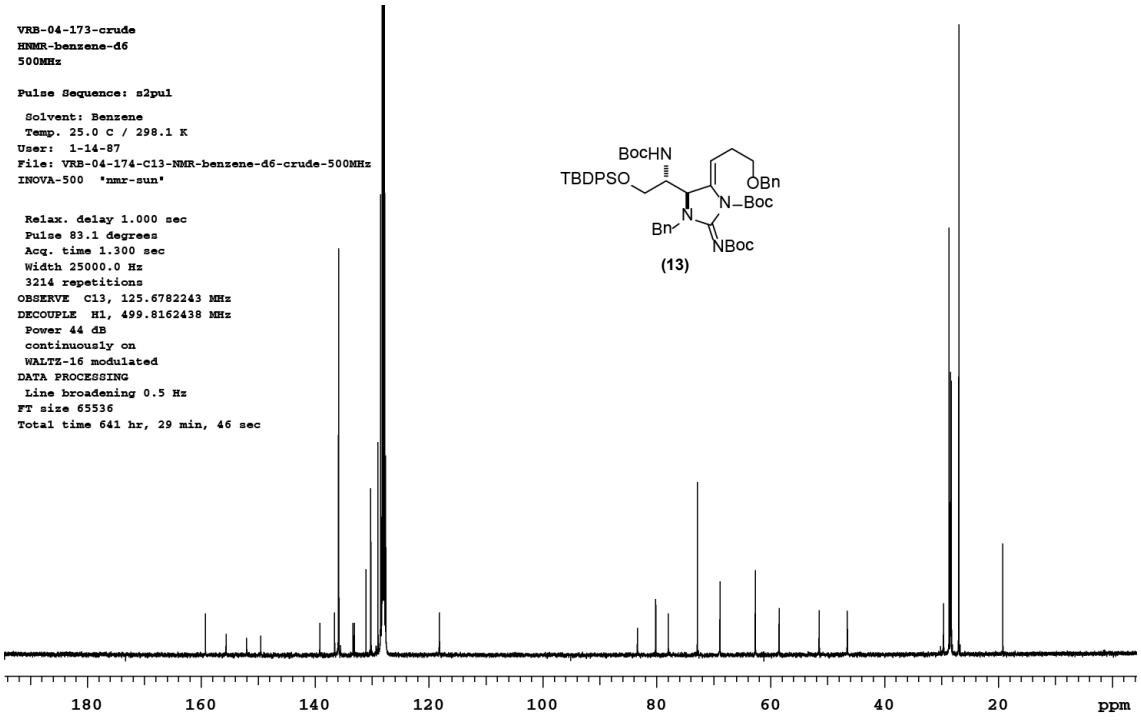

VRB-04-172
HNMR-benzene-d6
500MHz
Pulse Sequence: s2pul
Solvent: Benzene
Temp. 25.0 C / 298.1 K
File: VRB-04-172-HNMR-benzene-d6-500MHz
INOVA-500 "nmr-sun"
Pulse 33.5 degrees
Acq. time 1.892 sec
Width 8000.0 Hz
128 repetitions
OBSERVE H1, 499.8137320 MHz
DATA PROCESSING
FT size 32768
Total time 31 min, 40 sec
NHBoc
TBDPSO
OBn
N
NHBoc
Bn
NBoc
(12)
10
9
8
7
6
5
4
3
2
1
ppm
0.76
4.09
12.53
5.81
1.20
1.32
2.26
1.28
3.12
1.29
2.11
0.35
2.00
0.42
19.68
18.45


VRB-04-172
C13-NMR-benzene-d6
300MHz
Pulse Sequence: s2pul
Solvent: Benzene
Ambient temperature
File: VRB-04-172-C13-NMR-benzene-d6-300MHz
INOVA-500 "nmr-sun"
Relax. delay 1.000 sec
Pulse 41.7 degrees
Acq. time 1.815 sec
Width 16501.7 Hz
25712 repetitions
OBSERVE C13, 75.4544383 MHz
DECOUPLE H1, 300.0782426 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 7844 hr, 16 min, 2 sec
NHBoc
TBDPSO
OBn
N
NHBoc
Bn
NBoc
(12)
180
160
140
120
100
80
60
40
20
ppm

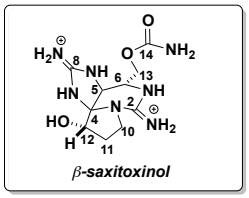
4. Aligned ^{1}HNMR spectrum of model ene-guanidine (17) with the ene-guanidine (7)






VRB-04-173-crude
HNMR-benzene-d6
500MHz
Pulse Sequence: s2pul
Solvent: Benzene
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: VRB-04-174-C13-NMR-benzene-d6-crude-500MHz
INOVA-500 "nmr-sun"
Relax. delay 1.000 sec
Pulse 83.1 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
3214 repetitions
OBSERVE C13, 125.6782243 MHz
DECOUPLE H1, 499.8162438 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 641 hr, 29 min, 46 sec
BocHN
TBDPSO
OBn
N
N–Boc
Bn
NBoc
(13)
180
160
140
120
100
80
60
40
20
ppm

Spectral comparison (^{1}H NMR and ^{13}C NMR data) of natural and synthetic β-saxitoxinol



^{1}H NMR and ^{13}C NMR data of natural β-saxitoxinol[1]

position	^{1}HNMR δ (ppm)	multiplicity	coupling constant (Hz)	^{13}C NMR δ (ppm)
2	-	-	-	156.4
4	-	-	-	80.7
5	4.33	s	-	58.4
6	3.57	m	-	53.6
8	-	-	-	158.9
10	3.35	m	-	28.2*
11	2.02 2.00	m m	- -	27.7
12	3.79	d	4.6	75.2
13	3.86 3.68	dd dd	12.0, 9.6 12.0, 5.6	63.8
14	-	-	-	159.3

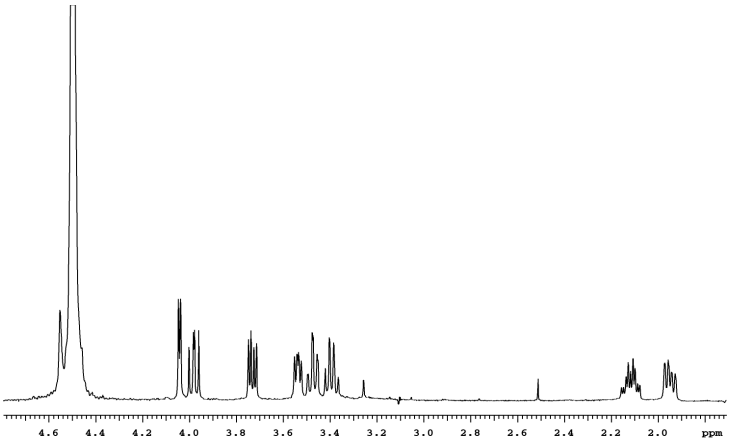
^{1}H NMR and ^{13}C NMR data of synthetic β-saxitoxinol

position	^{1}HNMR δ (ppm)	multiplicity	coupling constant (Hz)	^{13}C NMR δ (ppm)
2	-	-	-	156.4
4	-	-	-	84.0
5	4.53	brs	-	58.3
6	3.53	ddd	9.2, 5.3, 1.7	53.5
8	-	-	-	158.3
10	3.47 3.38	ddd ddd	10.2, 8.3, 1.9 9.0, 9.0, 8.7	44.3
11	2.10 1.93	ddd ddd	14.1, 9.7, 9.7, 3.9 14.1, 7.3, 1.2	29.3
12	4.03	d	4.4	75.1
13	3.93 3.72	dd dd	11.7, 9.2 11.7, 5.3	63.7
14	-	-	-	159.6

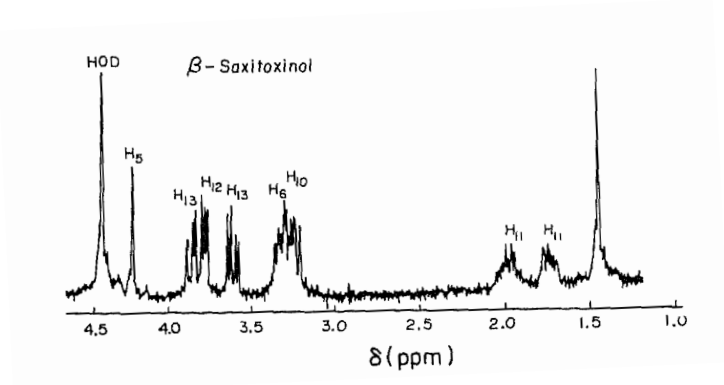
1. Koehn E. F.; Ghazarossian, E. V.; Schantz, E. J. Schnoes, H. K.; Strong F. M. *Biorganic chemistry,* **1981**, *10*, 412- 428.

* The ^{13}C NMR chemical shift value of C11 (28.2 ppm) in the natural sample appears to be incorrectly labelled. We observe this chemical shift at 44.3 ppm consistent with those reoprted by Du Bois and Nagasawa.[2]

2. (a) Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, *128*, 3926– 3927.
(b) Fleming, J. J.; McReynolds, M. D.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 9964–9975.
(c) Iwamoto, O.; Shinohara, R.; Nagasawa, K. *Chem. Asian. J.* **2009**, 4, 277- 285.

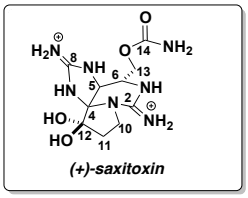


^{1}H NMR of Synthetic β-saxitoxinol
(D_2O referenced at 4.50 ppm @ 500MHz)



^{1}H NMR of Natural β-saxitoxinol
(D_2O referenced at 4.50 ppm @ 200 MHz)[1]

Spectral comparison (^{1}H NMR and ^{13}C NMR data) of natural and synthetic (+)−saxitoxin



(+)-saxitoxin

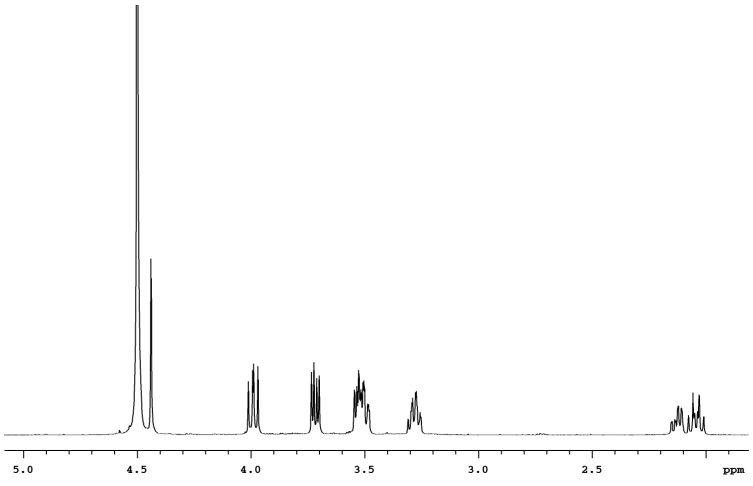
^{1}H NMR and ^{13}C NMR data of natural (+)-saxitoxin[1]

position	^{1}HNMR δ (ppm)	multiplicity	coupling constant (Hz)	^{13}C NMR δ (ppm)
2	-	-	-	156.8
4	-	-	-	83.2
5	4.33	d	1.2	57.8
6	3.47	ddd	9.0, 6.0, 1.2	53.8
8	-	-	-	158.5
10	3.40 3.18	dd ddd	10.0, 3.0 11.0, 10.0, 8.0	33.8
11	2.00 1.99	m m	- -	43.8
12	-	-	-	99.4
13	3.88 3.65	dd dd	12.0, 9.0 12.0, 6.0	64.0
14	-	-	-	159.7

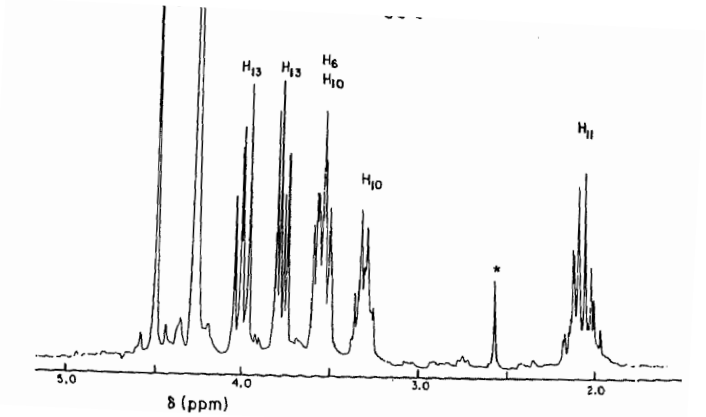
^{1}H NMR and ^{13}C NMR data of synthetic (+)-saxitoxin

position	^{1}HNMR δ (ppm)	multiplicity	coupling constant (Hz)	^{13}C NMR δ (ppm)
2	-	-	-	156.6
4	-	-	-	83.0
5	4.42	d	0.9	57.6
6	3.50	ddd	9.2, 5.3, 0.9	53.6
8	-	-	-	158.4
10	3.47 3.20- 3.23	ddd m	10.2, 8.3, 1.9 -	33.5
11	2.10 2.02	ddd ddd	14.1, 8.3, 1.9 14.1, 9.7, 9.7	43.4
12	-	-	-	99.1
13	3.96 3.69	dd dd	11.2, 9.2 12.7, 5.3	63.7
14	-	-	-	159.6

1. Koehn E. F.; Ghazarossian, E. V.; Schantz, E. J. Schnoes, H. K.; Strong F. M. *Biorganic chemistry,* **1981**, *10*, 412- 428.



^{1}H NMR spectrum of synthetic (+)-saxitoxin (D_2O referenced at 4.50ppm @ 500 MHz)



^{1}H NMR spectrum of natural (+)-saxitoxin (D_2O referenced at 4.50ppm @ 200 MHz)[1]