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SUPPORTING INFORMATION

Fluorinated triazole-containing sphingosine analogues. Syntheses and *in vitro* evaluation as SPHK inhibitors.

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1. General Methods

All reagents were purchased from Sigma Aldrich, Alfa Aesar or Carbosynth chemical companies. Dichloromethane (CH_2Cl_2) was distilled from CaH_2, THF was distilled from sodium and Et_3N was stored with activated 4Å MS. 4Å MS were activated by heating under high vacuum at 260 ºC for 10 h and then were stored at 165 ºC.

^1H and ^{13}C NMR spectra were recorded on a Varian® Mercury VX 400 or on a Bruker® Avance Ultrashield (400 MHz and 100.6 MHz respectively) spectrometer. NMR signals were fully assigned by COSY, HSQC, NOESY and HMBC experiments. Coupling constants (*J*) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, bd = broad doublet, bt = broad triplet and bq = broad quartet. Infrared (IR) spectra were recorded on a JASCO FTIR-600 plus Fourier Transform Infrared Spectrophotometer. ESI MS were run on an Agilent® 1100 Series LC/MSD instrument. Melting points (m.p.) were recorded with a Reichert apparatus. Optical rotations were measured on a Perkin–Elmer® 241 polarimeter with a path length of 1.0 dm and are reported with implied units of 10^{-1} deg cm^2 g^{-1}. Concentrations (c) are given in g/100 ml.

Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck® aluminium backed sheets coated with 60 F_{254} silica gel. Visualization of the silica plates was achieved using a UV lamp (λmax = 254 nm) and/or by heating plates that were dipped in a H_2SO_4/ethanol (1:15) solution. Flash chromatography was carried out using forced flow of the indicated solvent on Fluka® or Merck® silica gel 60 (230-400 mesh).

The *in vitro* assays were performed using Adapta™ Universal Kinase assay and analysed on a BMG LABTECH's CLARIOstar® microplate reader.

2. General Procedures

General Procedure for the preparation of the phosphonium salts.

A solution of triphenylphosphine (3 equiv.) and alkyl halide (1 equiv.) in refluxing toluene was stirred for 14 h. The reaction was cooled to 0ºC and the crude solid material was filtered and washed with Et_2O to give a white solid which was dried under high vacuum prior to use.

General Procedure for Swern oxidation from primary alcohols.

A solution of oxalyl chloride (1.5 equiv.) in CH_2Cl_2 was cooled to -78 °C and a solution of dimethylsulfoxide (2.2 equiv.) in CH_2Cl_2 was added slowly. The mixture was stirred for 10 minutes and alcohol (1.0 equiv.) dissolved in CH_2Cl_2 was added with a syringe pump during 15 min. After additional stirring for 30 minutes, Et_3N (4.0 equiv.) was added and the reaction mixture was allowed to warm to room temperature over 1 h. A saturated solution of NH_4Cl was then added and the resulting mixture was extracted twice with CH_2Cl_2. The organic layer was washed twice with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude material was purified by column chromatography using mixtures of Hexanes : AcOEt to give the aldehyde.

General Procedure for the preparation of azides.

To a solution of sodium azide in H_2O was added the brominated derivative in EtOH and the mixture was warmed to 90 °C and stirred 16 h. The solution was then evaporated under reduced pressure to remove the excess of EtOH and diluted with brine. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (100% hexanes to 9:1 Hexanes:AcOEt) to yield azides.

General Procedure for the Wittig reaction in the syntheses of fluorinated azides 10b-d.

A solution of the phosphonium salt (1.3 equiv.) in THF was cooled to 0ºC and KHMDS (1.3 or 1.25 equiv.) was added slowly. The mixture changed from white to orange and it was stirred for 20 min. at rt. The mixture was then cooled to 0ºC and the aldehyde (1 equiv.) in THF was added. The mixture was stirred to 0ºC until TLC showed complete conversion of the aldehyde. A saturated solution of NH_4Cl was then added and the resulting mixture was filtered through Celite. The resulting filtrate was extracted with Et_2O and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (100% hexanes) to give the pure product as a single *Z* isomer.

General procedure of Azide-Alkyne Cycloaddition.

Terminal alkyne (1 equiv.), azide (1.1-3 equiv.), $CuSO_4 \cdot 5H_2O$ (0.3 equiv.) and sodium ascorbate (0.12 equiv.) were suspended in a mixture of CH_2Cl_2:H_2O (3:1). The reaction mixture was stirred vigorously at rt for 12–48 h. Water was then added (5 mL), extracted

with CH_2Cl_2 (3x5mL), washed with brine, desiccated over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by column chromatography (6:4 hexane: ethyl acetate) to provide 1,4-disubstituted 1,2,3-triazoles.

General procedure of reduction of carbamate.[1]

The Boc derivatives were dissolved in THF and added dropwise to a suspension of $LiAlH_4$ (3 equiv.) in THF. The resulting mixture was refluxed for 24 h and allowed to warm to room temperature. Then, a solution of 1M NaOH was added dropwise and the slurries were filtered through Celite. The resulting filtrates were extracted with AcOEt. The organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude products were purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 9:1:0.1) to give the monomethyl amines.

General procedure of deprotection of Boc- and *p*-methoxybenzyl ether.

A solution of TFA/CH_2Cl_2 (1:1, v/v) was added to the protected amine or guanidine or PMB derivatives (1 equiv.) at room temperature. After approximately 4 h, the solution was concentrated in vacuum and purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 9:1:0.1 to 9:3:0.3) to give the free desired compound.

General procedure for the hydrogenation of alkenes and the hydrogenolysis of *p*-methoxybenzyl ether.

To a flask containing the compounds **15b-d** (1.00 mmol) was added 20 % Pd/C (w/w) in MeOH (5 ml). The flask was equipped with hydrogen balloon and the misture was stirred at rt for 24-48 h. The reaction mixture was filtered through celite and washed with MeOH. The filtrate was concentrated and the residue was purified by *flash* chromatography to give **17b-d**.

General procedure of *N*,*N*-dimethylation of amines.

To a mixture of amine (1 equiv.) and *p*-formaldehyde (10 equiv.) in MeOH (3.8 ml) $NaBH_3CN$ (11 equiv.) was added at 0°C. After that, the mixture was stirred at room temperature until TLC showed that the starting material was consumed (48 h). The reaction mixture was diluted with EtOAc, washed with brine and extracted with EtOAc. The combined organic layers were filtered, dried over $MgSO_4$ and concentrated under reduced pressure. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 9:1:0.1) to give the dimethyl amine.

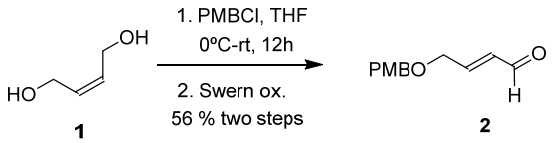
[1] O. Benson, S, H. Demirdji, R.C. Haltiwanger, T. H. Koch. *J. Am. Chem. Soc.* **1991**, *113*, 8879-8886.

General procedure of Guanidination of amine.[2]

A mixture of the free amine **19a-d** (1 equiv.), *N*-*N*'-di-Boc-1*H*-pyrazole-1-carboxiamidine (1.1 equiv.) and Et_3N (1 equiv.) in a dry mixture 3:2 v/v of dichloromethane and 1,2-dimethoxyethane was stirred at r.t. under argon atmosphere for 12 h. The solvent was removed under reduced pressure and the residue was purified by *flash* chromatography (hexanes/EtOAc 4:6 →3:7) to give Boc protected guanidines **21a-d.**

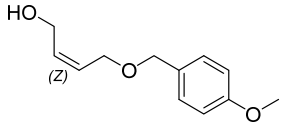
[2] R. Bittman,N.J. Pyne, S. Pyne, D. Baek, Z. Liu,H.S. Byun. *Selective inhibitors and allosteric activators of sphingosine kinase*. **Patent WO 2014118556 A3, 2014**.

3. Synthetic procedures and characterization data



Scheme 1. Synthesis of α,β-unsaturated aldehyde **2**.

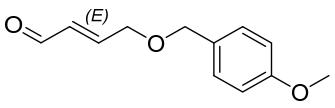
***(Z)*-4-(-(4-methoxybenzyl)oxy)but-2-en-1-ol.[3]**



To a suspension of 4.97 g (0.124 mol, 1.1 equiv.) of 60% sodium hydride dispersion in mineral oil in 300 mL of THF at 0 °C was slowly added 10 g (0.113 mol, 1 equiv.) of diol **1** *via* syringe over 20 minutes causing warming of the reaction mixture. The resulting heterogeneous mixture was stirred at rt for 3 h whereupon 4.17 g (0.0113 mol, 0.1 equiv.) of tetrabutylammonium iodide and 17.69 g of *p*-methoxybenzylchloride (15.3 ml, 0.113 mmol, 1 equiv.) were successively added. After stirring at rt for 12 h, the mixture was carefully quenched by addition of 100 mL of water, following by dilution with 200 mL of diethyl ether. The resulting clear layers were separated and the aqueous portion was extracted with diethyl ether (2x100 mL) and the combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo.* The crude was then purified by flash column chromatography (8:2 to 1:1 hexane:ethyl acetate) (R_f: 0.27 in 6:4 hexane:ethyl acetate) to give (*Z*)-4-(-(4-methoxybenzyl)oxy)but-2-en-1-ol (18.1 g, 77 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.82 – 5.74 (m, 1H), 5.73 – 5.65 (m, 1H), 4.44 (s, 2H), 4.12 (d, *J* = 6.2 Hz, 2H), 4.04 (dd, *J* = 6.2, 1.1 Hz, 2H), 3.79 (s, 3H), 2.57 (br s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 132.4, 129.9, 129.5, 128.1, 113.8, 72.1, 65.3, 58.5, 55.2. **HRMS (ESI-TOF)**: Calculated for $C_{12}H_{16}O_3Na$, $[M+Na]^+$: 231.0997, found $[M+Na]^+$: 231.0992.

(*E*)-4-((4-methoxybenzil)oxy)but-2-enal, 2.[4]

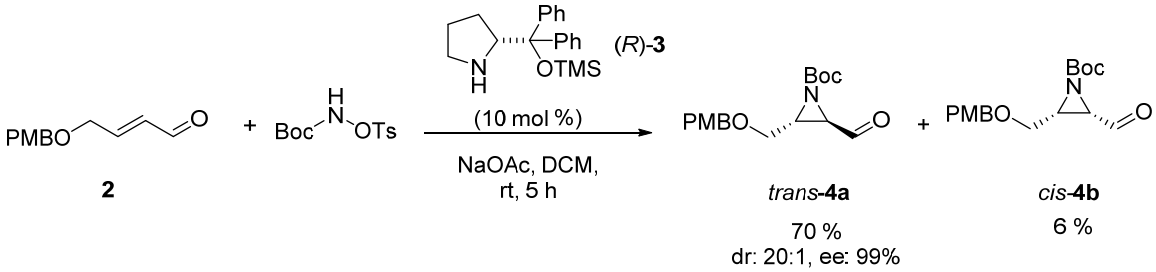


To a stirred solution of oxalyl chloride (10.8 mL, 0.128 mol, 1.5 equiv.) in CH_2Cl_2 (350 ml) was dropwise added DMSO (18.1 mL, 0.255 mol, 3 equiv.) at −78 °C. After 20 min, give (*Z*)-4-(-(4-methoxybenzyl)oxy)but-2-en-1-ol (17.75 g, 0.085 mol, 1 equiv.) in CH_2Cl_2 (100 mL) was added to the reaction mixture and stirred at −78 °C for 2 h. Then *N*,*N*-diisopropylethylamine was slowly added (44.4 mL, 0.255 mol, 3 equiv.) and warmed up to

[3] Trost, B.M.; Chisholm, J.D.; Wrobleski, S.T.; Jung. M. *J. Am. Chem. Soc.* **2002**, *124*, 12420-12421.
[4] Thirupathi, B.; Mohapatra, D.K. *Org. Biomol. Chem.* **2016**, *14*, 6212-6224.

room temperature. Then, a sol. 1 M HCl (80 mL) was added and the mixture was stirred for 30 min (isomerization was monitored by TLC). The layers were separated, and the aqueous portion was extracted with CH_2Cl_2 (100 mL) and the combined organic extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude was then purified by flash column chromatography (9:1 to 7:3 hexane:ethyl acetate) (R_f: 0.55 in 6:4 hexane:ethyl acetate) to give (*E*)-4-((4-methoxybenzil)oxy)but-2-enal **2** (12.78 g, 73 %) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 9.5 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.84 (dt, *J* = 4.2, 15.8 Hz, 1H), 6.39 (ddt, *J* = 1.9, 7.9, 15.8 Hz, 1H), 4.52 (s, 2H), 4.26 (dd, *J* = 2.0, 4.2 Hz, 2H), 3.81 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.3, 159.4, 153.3, 131.7, 129.4, 129.3, 113.8, 72.6, 68.2, 55.2. **HRMS (ESI-TOF)**: Calculated for $[M+Na]^+$: $C_{12}H_{14}O_3Na$ 229.0841, found 229.0835.



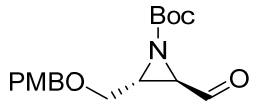
Scheme 2. Aziridination of α,β-unsaturated aldehyde **2**.

Aziridination of α,β-unsaturated aldehyde.[5]

To a stirred solution of catalyst (*R*)-**3** (1.62 g, 10 mol%) and *tert*-butyl-*N*-tosylcarbamate (17.19 g, 59.9 mmol, 1.2 equiv.) in CH_2Cl_2 (0.2 M, 250 mL) at rt was added α,β-unsaturated aldehyde **2** (10.28 g, 49.9 mmol, 1 equiv.) and NaOAc (12.27 g, 147 mmol, 3 eq.). The mixture reaction was vigorously stirred for 5 h (the progress of the reaction was monitored by TLC). Then, it was added water (8 mL) and ethyl acetate (100 mL). The layers were separated and the combined organic extracts were washed with brine (200 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude was then purified by flash column chromatography (10:0 to 4:6 hexane:diethyl eter) to give *cis*-**4b** as a minor product (1.01 g, 6 % yield) and *trans*-**4a** as a major product (11.24 g, 70 % yield), both yellow light oils. The enantiomeric excess of *trans*-**4a** was determined after Wittig reaction (with CH_3PPh_3Br) to give the corresponding vinyl aziridine **23** by HPLC analysis in comparison with authentic racemic material (OD-H column, *n*-hexane/*i*-PrOH = 95/5, λ = 230 nm, 1.0 ml/min) t_r (major enantiomer) = 8.4 min, t_r (minor enantiomer) = 7.8 min.

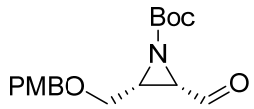
[5] Deiana, L.; Dziedzic, P.; Zhao, G.L.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.; Córdova, A. *Chem. Eur. J.* **2011**, *17*, 7904–7917.

***(2R,3R)-tert*-butyl 2-formyl-3-(((4-methoxybenzyl)oxy)methyl)aziridine-1-carboxylate, *trans*-4a.**



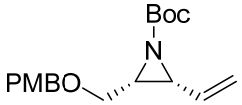
R_f = 0.33 (4:6 hexane: Et_2O). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.15 (d, *J* = 5.0 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 3.81 (s, 3H), 3.71 (dd, *J* = 3.9, 11.2 Hz, 1H), 3.65 (dd, *J* = 3.7, 11.2 Hz, 1H), 3.19 (dd, *J* = 2.7, 5.0 Hz, 1H), 3.00 (td, *J* = 2.7, 3.9 Hz, 1H), 1.45 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 195.9, 159.4, 158.2, 129.5, 129.4, 113.9, 82.5, 72.7, 66.3, 55.3, 43.89, 41.9, 28.9. **HRMS (ESI-TOF)**: Calculated for $C_{17}H_{23}NO_5Na$ $[M+Na]^+$: 344.1474, found 344.1470. **$[\alpha]^{25}_D$** + 8.22 (*c* 0.96, $CHCl_3$).

***(2S,3R)-tert*-butyl 2-formyl-3-(((4-methoxybenzyl)oxy)methyl)aziridine-1-carboxylate, 4b.**



R_f = 0.35 (4:6 hexane: Et_2O). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.30 (d, *J* = 4.7 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.47 (q, *J* = 11.7 Hz, 2H), 3.79 (s, *J* = 2.0 Hz, 3H), 3.73 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.64 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.04 (dd, *J* = 6.9, 4.7 Hz, 1H), 3.00 (ddd, *J* = 9.2, 5.8, 2.6 Hz, 1H), 1.45 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.0, 160.1, 159.3, 129.5, 129.3, 113.8, 82.7, 72.8, 66.0, 55.3, 44.9, 43.5, 27.8. **HRMS (ESI-TOF)**: calculated for $C_{17}H_{23}NO_5Na$ $[M+Na]^+$: 344.1474, found 344.1474. **$[\alpha]^{25}_D$** +6.7 (*c* 1, $CHCl_3$).

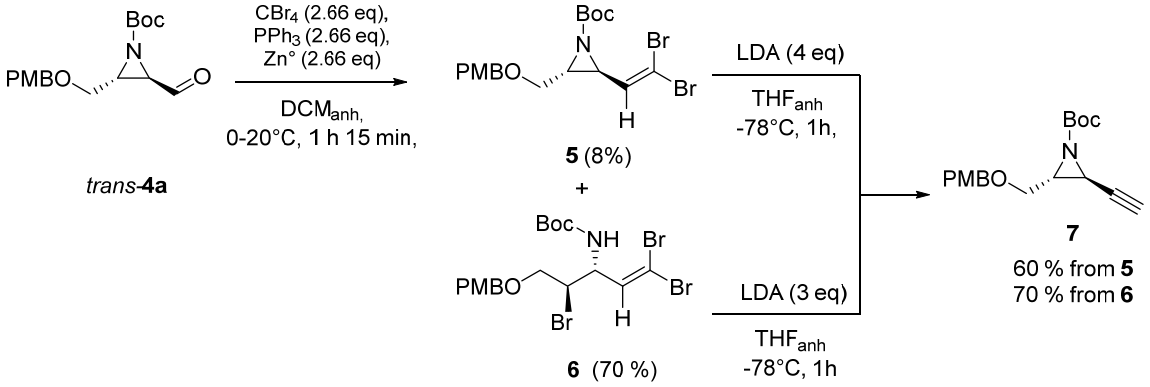
(2*R*,3*R*)-*tert*-butyl 2-(((4-methoxybenzyl)oxy)methyl)-3-vinylaziridine-1-carboxylate, 23.



In a two-neck flask with magnetic stirring and inert atmosphere, methyltriphenylphosphosphonium bromide (1.95 g, 5.47 mmol, 1.2 equiv.) was dissolved in THF (30 mL) and to this solution sodium bis(trimethylsilyl)amide (5.5 mL, 1M, 5.47 mmol, 1.2 equiv.) was added. The resulting yellow solution was stirred for 1 h at 0 ºC. A solution of *tert*-butyl 2-formyl-3-(((4-methoxybenzyl)oxy)methyl)aziridine-1-carboxylate *trans*-**4a** (1.47 g, 4.56 mmol) THF (15 mL) was then added and the solution was stirred for 12 h at room temperature. Then, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography (10:0 to 8:2 hexane:ethyl acetate) (R_f: 0.6 in 1:1 hexane:diethyl ether) to give *tert*-butyl 2-(((4-methoxybenzyl)oxy)methyl)-3-vinylaziridine-1-carboxylate **23** (0.66 g, 45%) as a yellow oil.

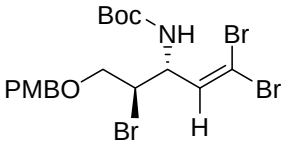
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 2H), 6.91 – 6.84 (m, 2H), 5.50 – 5.32 (m, 2H), 5.31 – 5.25 (m, 1H), 4.49 (s, 2H), 3.80 (s, *J* = 2.0 Hz, 3H), 3.66 (dd, *J* = 11.0, 4.7 Hz, 1H), 3.55 (dd, *J* = 11.0, 4.5 Hz, 1H), 2.96 (dd, *J* = 7.9, 3.1 Hz, 1H), 2.66 (td, *J* = 4.6, 3.1 Hz,

1H), 1.44 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 160.1, 159.2, 133.7, 129.9, 129.3, 119.7, 113.7, 81.3, 72.5, 68.0, 55.3, 43.1, 42.7, 28.0. **HRMS (ESI-TOF)**: Calculated for $C_{18}H_{25}NO_4Na$ $[M+Na]^+$: 342.1681, found $[M+Na]^+$: 342.1675. **$[\alpha]^{25}_D$** +7.3 (*c* 1, $CHCl_3$).



Scheme 3. Synthesis of ethynylaziridine.

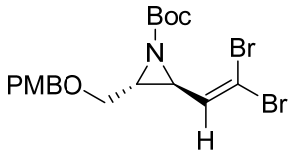
***tert*-butyl ((3*R*,4*R*)-1,1,4-tribromo-5-((4-methoxybenzyl)oxy)pent-1-en-3-yl)carbamate, 6.**



To a stirred solution of tetrabromomethane (8.15 g, 24.61 mmol, 2.66 equiv.) in anhydrous DCM (47 mL) at 0 °C, was added triphenylphosphine (6.45 g, 24.61 mmol, 2.66 equiv.) and activated zinc dust (1.6 g, 24.61 mmol, 2.66 equiv.). After 1h, a solution of *trans*-**4a** (2.97 g, 9.25 mmol, 1 equiv.) in anhydrous DCM (47 mL) was added slowly. The resulting solution was stirred at room temperature for 1 h 15 min, then the crude was filtered by vacuum, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography (95:5→90:10 hexane:ethyl acetate) to give a major product *tert*-butyl (1,1,4-tribromo-5-((4-methoxybenzyl)oxy)pent-1-en-3-yl)carbamate **6** (3.6 g, 70 %) and *tert*-butyl 2-(2,2-dibromovinyl)-3-(((4-methoxybenzyl)oxy)methyl)aziridine-1-carboxylate **5** (0.35 g, 8 %) as minor product, both as yellow oils.

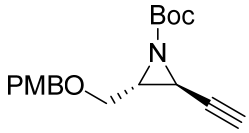
R_f: 0.7 (1:1 hexane:ethyl acetate). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 10.4 Hz, 1H), 5.11 (d, *J* = 9.5 Hz, 1H), 4.78 (dd, *J* = 10.3, 9.3 Hz, 1H), 4.48 (s, 2H), 4.06 (t, *J* = 9.4 Hz, 1H), 3.95 (dd, *J* = 1.9, 9.6 Hz, 1H), 3.81 (s, 3H), 3.54 (dd, *J* = 3.3, 9.6 Hz, 1H), 1.44 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.5, 155.2, 136.6, 129.7, 129.5, 114.0, 94.7, 80.3, 73.3, 68.8, 55.4, 54.3, 50.3, 28.4. **HRMS (ESI-TOF)**: Calculated for $C_{18}H_{24}Br_3NO_4Na$ $[M+Na]^+$: 577.9153, found $[M+Na]^+$: 577.9167. **$[\alpha]^{25}_D$** + 102.4 (*c* 1.65, $CHCl_3$).

***(2S,3R)-tert*-butyl 2-(2,2-dibromovinyl)-3-(((4-methoxybenzyl)oxy)methyl)aziridine-1-carboxylate, 5.**



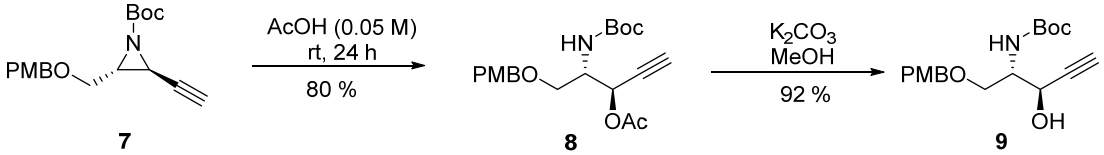
^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 1.45 (s, *J* = 5.7 Hz, 9H), 2.70 (td, *J* = 4.1, 3.1 Hz, 1H), 3.22 (dd, *J* = 8.2, 3.0 Hz, 1H), 3.64 (ddd, *J* = 42.0, 11.0, 4.1 Hz, 2H), 3.81 (s, *J* = 2.9 Hz, 3H), 4.49 (q, *J* = 11.7 Hz, 2H), 6.03 (d, *J* = 8.2 Hz, 1H), 6.91 – 6.85 (m, 2H), 7.30 – 7.21 (m, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 159.2, 134.1, 129.7, 129.2, 113.8, 93.9, 81.8, 72.6, 66.8, 55.2, 42.7, 41.4, 27.9, 27.8. **HRMS (ESI-TOF)**:, Calculated for $C_{18}H_{23}Br_2NNaO_4$ $[M+Na]^+$:497.9892, found $[M+Na]^+$: 497.9900. **$[\alpha]^{25}_D$** +95.2 (*c* 1.5, $CHCl_3$).

(2*S*,3*R*)-*tert*-butyl 2-ethynyl-3-(((4-methoxybenzyl)oxy)methyl)aziridine-1-carboxylate, 7.



To a solution of **6** (3.45 g, 6.24 mmol, 1 equiv.) in anhydrous THF (31 mL) at -78 °C was carefully added lithium diisopropylamide (prepared by adding *n*BuLi (11.73 mL, 2.5 M in hexanes, 29.34 mmol, 4.7 equiv.) to a solution of freshly distillated diisopropylamine (2.96 mL, 29.34 mmol, 4.7 equiv.) in 38 mL of THF, at 0 °C). The reaction mixture was stirred for 2 hours, while the temperature was allowed to rise to 0 °C and quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted with ethyl ether (3x50 mL), the combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo.* The crude was then purified by flash column chromatography (10:0 to 8:2 hexane:EtOAc) (R_f: 0.55 in 9:1 hexane: ethyl acetate) to give *tert*-butyl 2-ethynyl-3-(((4-methoxybenzyl)oxy)methyl)aziridine-1-carboxylate **7** (1.38 g, 70 %) as a colourless oil.

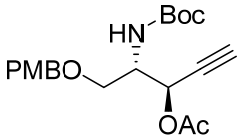
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 3.79 (s, 3H), 3.63 (dd, *J* = 4.3, 11.1 Hz, 1H), 3.53 (dd, *J* = 4.1, 11.1 Hz, 1H), 2.92 (dd, *J* = 1.9, 3.1 Hz, 1H), 2.86 (td, *J* = 3.1, 4.2 Hz, 1H), 2.22 (d, *J* = 1.9 Hz, 1H), 1.46 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 159.3, 129.8, 129.5, 113.9, 82.1, 79.0, 72.7, 71.6, 67.3, 55.4, 43.5, 29.0, 28.1. **HRMS (ESI-TOF)**: $C_{18}H_{23}NNaO_4$ calculated for $C_{18}H_{23}NNaO$ $[M+Na]^+$: 340.1525, found 340.1522. **$[\alpha]^{25}_D$** + 31.62 (*c* 0.8, $CHCl_3$).



7 **8** **9**

Scheme 4. Synthesis of intermediate **9** by ring opening of aziridine **7**.

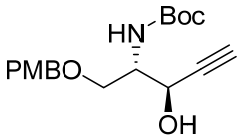
(3*R*,4*S*)-4-((*tert*-butoxycarbonyl)amino)-5-((4-methoxybenzyl)oxy)pent-1-yn-3-yl acetate, 8.



Ethynylaziridine **7** (1.04 g, 3.29 mmol) was dissolved in acetic acid (65.8 ml, 0.05 M) and the resulting solution was stirred at rt until full consumption of starting material. The reaction mixture was neutralized with saturated solution of $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3x80 mL), then combined organic were washed with brine, and dried over magnesium sulfate, filtered, and concentrated *in vacuo.* The crude was purified by flash column chromatography (hexane: EtOAc 8:2) (R_f: 0.7 in hexane: EtOAc 1:1) to give 4-((*tert*-butoxycarbonyl)amino)-5-((4-methoxybenzyl)oxy)pent-1-yn-3-yl acetate **8** (0.992 g, 80 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.60 (dd, *J* = 4.8, 2.0 Hz, 1H), 4.86 (d, *J* = 9.6 Hz, 1H), 4.44 (app q, *J* = 11.5 Hz, 2H), 4.30 – 4.17 (br, 1H), 3.79 (s, 3H), 3.54 (dd, *J* = 5.0, 9.8 Hz, 1H), 3.49 (dd, *J* = 6.7, 9.8 Hz, 1H), 2.46 (d, *J* = 2.2 Hz, 1H), 2.05 (s, 3H), 1.44 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 169.6, 159.3, 155.5, 129.8, 129.5, 113.8, 79.9, 78.1, 75.4, 72.9, 68.1, 63.9, 55.4, 51.8, 28.4, 20.9. **HRMS (ESI-TOF)**: Calculated for $C_{20}H_{27}NO_6Na$ $[M+Na]^+$: 400.1736, found 400.1724. **$[\alpha]^{25}_D$** −25.6 (*c* 1.04, $CHCl_3$).

***tert*-butyl ((2*S*,3R)-3-hydroxy-1-((4-methoxybenzyl)oxy)pent-4-yn-2-yl)carbamate, 9.**

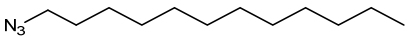


To a stirred solution of **8** (1.2 g, 3.18 mmol, 1 equiv.) in MeOH (16 mL) at rt was added K_2CO_3 (1.75 g, 12.73 mmol) and the resulting mixture was kept stirring overnight at rt. The solvent was evaporated in *vacuo*, and the residue was dissolved in ethyl acetate and H_2O. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over magnesium sulfate, filtered and evaporated in *vacuo*. The obtained residue was purified by silica gel chromatography hexane:ethyl acetate 7:3.(R_f: 0.7 in hexane:EtOAc 1:1) to give **9** (0.98 g, 92 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.27 (d, *J* = 8.3 Hz, 1H), 4.51 (ddd, *J* = 2.3, 3.3, 9.5 Hz, 1H), 4.46 (s, 2H), 4.04 – 3.96 (m, 1H), 3.91 (dd, *J* = 3.7, 8.2 Hz, 1H), 3.80 (s, 3H), 3.65 (d, *J* = 9.5 Hz, 1H), 3.61 (dd, *J* = 3.5, 9.5 Hz, 1H), 2.49 (d, *J* = 2.2 Hz, 1H), 1.44 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.5, 155.8, 129.6, 129.3, 114.0, 82.2, 80.1, 74.6, 73.5, 70.1, 64.5, 55.4, 53.7, 28.4. **HRMS (ESI-TOF)**: Calculated for $C_{18}H_{26}NO_5$ $[M+H]^+$: 336.1811, found 336.1801. **$[\alpha]^{25}_D$** −7.7 (*c* 1, $CHCl_3$).

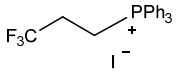
1-azidododecane, 10a.[6]

[6] Hu, J.; Zhu, T.; He, C.; Zhang, Y.; Zhang, Q.; Zou, G. *J. Mat. Chem. C.* **2017**, *5*, 5135-5142.



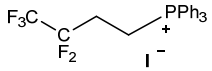
To a solution of sodium azide (3.91 g, 60.2 mmol, 5 equiv.) in 60 mL of H_2O was added 1-bromododecane (3.00 g, 12.04 mmol, 1 equiv.) in 60 mL of EtOH and it was warmed to 90 °C and stirred overnight. Then, the solution was evaporated under reduced pressure and diluted with saturated aqueous NaCl. The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography (100% hexanes) to yield 1-azidododecane as colourless oil (2.52 g, 11.93 mmol, 99%). The spectroscopic data were consistent with those previously reported. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 3.25 (t, *J* = 7.0 Hz, 2H), 1.64 - 1.54 (m, 2H), 1.41 - 1.21 (m, 18H), 0.88 (t, *J* = 6.7 Hz, 3H).

(3,3,3-trifluoropropyl)triphenylphosphonium iodide:[7]



According to the general procedure for the preparation of phosphonium salts, (3,3,3-trifluoropropyl)triphenylphosphonium iodide was prepared by refluxing 1,1,1-trifluoro-3-iodopropane (1.00 g, 4.65 mmol, 1 equiv.) with PPh_3 (3.51 g, 13.4 mmol, 3 equiv.) in 4 mL of toluene for 14 h. After the work-up, the phosphonium iodide was obtained as a white powder (1.65 g, 3.40 mmol, 73%). The spectroscopic data were consistent with those previously reported.

(3,3,4,4,4-pentafluorobutyl)triphenylphosphonium iodide:[8]

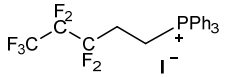


According to the general procedure for the preparation of phosphonium salts, (3,3,4,4,4-pentafluorobutyl)triphenylphosphonium iodide was prepared by refluxing 1,1,1,2,2-pentafluoro-4-iodobutane (5.00 g, 18.25 mmol, 1 equiv.) with PPh_3 (14.36 g, 54.75 mmol, 3 equiv.) in 15 mL of toluene for 14 h. After the work-up, the phosphonium iodide was obtained as a white powder (8.118 g, 15.14 mmol, 83%). The spectroscopic data were consistent with those previously reported.

[7] Liu, Z.; Kumar, K. *Synthesis* **2010**, 1905-1908.

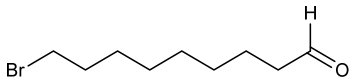
[8] Barta, T. E.; Becker, D. P.; Bedell, L. J.; Boehm, T.L.; Brown, D. L.; Carroll, J. N.; Chen, Y.; Fobian, Y.; Freskos, J. N.; Gasiecki, A. F.; Grapperhaus, M.; Heintz, R. M.; Hockerman, S. L.; Kassab, D. J.; Khanna, I. K.; Kolodziej, S. A.; Massa, M.; Mcdonald, J.; Mischke, B. V.; Mischke, D. A.; Mullins, P. B.; Nagy, M.; Norton, M. B.; Rico, J. G.; Schmidt, M. A.; Stehle, N. S.; Talley, J. J.; Vernier, W. F.; Villamill, C. I.; Wang, L. J.; Wynn, T. A. WO2003091247A3, 2003.

(3,3,4,4,5,5,5-heptafluoropentyl)triphenylphosphonium iodide:



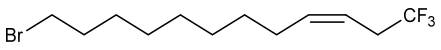
According to the general procedure for the preparation of phosphonium salts, (3,3,4,4,5,5,5-heptafluoropentyl)triphenylphosphonium iodide was prepared by refluxing 1,1,1,2,2,3,3-heptafluoro-5-iodopentane (3.24 g, 10 mmol, 1 equiv.) with PPh_3 (7.87 g, 30 mmol, 3 equiv.) in 8 mL of toluene for 14 h. After work-up, the phosphonium iodide **3.46** was obtained as a white powder (5.33 g, 9.1 mmol, 91%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ in ppm: 7.93-7.74 (m, 15H), 4.20 (m, 2H), 2.58 (m, 2H). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ in ppm: 135.8 (d, $J_{C,P}$ = 3.0 Hz), 133.8 (d, $J_{C,P}$ = 10.3 Hz), 130.9 (d, $J_{C,P}$ = 12.8 Hz), 116.6 (d, $J_{C,P}$ = 87.4 Hz), 24.3 (t, $J_{C,F}$ = 22.8 Hz), 16.1 (d, $J_{C,P}$ = 56.4 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ in ppm: -80.3 (t, $J_{F,H}$ = 9.7 Hz, 3F), -113.8 (m, 2F), -127.0 (m, 2F). **^{31}P NMR** (162 MHz, $CDCl_3$) δ in ppm: 25.7 (s)

9-bromononanal, 11:[9]



According to the general Swern oxidation procedure, 9-bromononanal was prepared as follows: A solution of oxalyl chloride (1.1 mL, 13.4 mmol, 1.5 equiv.) in 7 mL of CH_2Cl_2 was cooled to -78 °C and a solution of dimethylsulfoxide (1.4 mL, 19.7 mmol, 2.2 equiv.) in 8 mL of CH_2Cl_2 was added slowly. The mixture was stirred for 10 minutes and 9-bromononanol (2 g, 9.0 mmol, 1.0 equiv.) dissolved in 40 mL of CH_2Cl_2 was added with a syringe pump during 15 min. After additional stirring for 30 minutes, Et_3N (5 mL, 35.8 mmol, 4.0 equiv.) was added. After the work-up, the crude material was purified by column chromatography using mixtures of Hexanes : AcOEt to give the desired aldehyde as a colourless oil (1.39 g, 6.28 mmol, 70%). The spectroscopic data were consistent with those previously reported. **^{1}H NMR (401 MHz, $CDCl_3$)** δ 9.76 (t, J = 1.8 Hz, 1H), 3.40 (t, J = 6.8 Hz, 2H), 2.42 (td, J = 7.3 Hz, J = 1.8 Hz, 2H), 1.88 - 1.80 (m, 2H), 1.66 - 1.58 (m, 2H), 1.46 - 1.37 (m, 2H), 1.35 - 1.27 (m, 6H).

(*Z*)-12-bromo-1,1,1-trifluorododec-3-ene, 12:

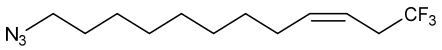


(*Z*)-12-bromo-1,1,1-trifluorododec-3-ene **12** was prepared following the general procedure for Wittig reaction. KHMDS 1M (3.1 mL, 3.1 mmol, 1.25 equiv.) was added to a solution of (3,3,3-trifluoropropyl)triphenylphosphonium iodide (1.55 g, 3.19 mmol, 1.3 equiv.) in 21 mL of THF. Aldehyde **11** (0.542 g, 2.45 mmol, 1 equiv.) was added and after the work-up, the reaction crude was purified by flash chromatography (silica gel, pure hexane) to give the desired alkene (0.551 g, 1.82 mmol, 74%) as a colourless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.50 - 5.41 (m, 1H), 5.36 – 5.27 (m, 1H), 3.40 (t, J = 6.8 Hz, 2H), 2.33 - 2.25 (m, 2H), 2.18 - 1.99 (m, 2H), 1.89 - 1.80 (m, 2H), 1.47 - 1.25 (m, 10H). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ

[9] Mayo, P.; Silk, P.; MaGee, D.; McConaghy, J. *Synth. Commun.* **2014**, *44*, 1957-1969.

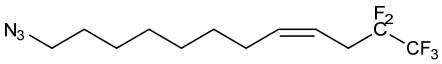
136.7, 126.3 (q, J_{CF} = 276.4 Hz), 116.9 (q, J_{CF} = 3.4 Hz), 34.1, 32.9, 32.3 (q, J_{CF} = 29.4 Hz), 29.4, 29.2, 29.2, 28.8, 28.2, 27.5. **^{19}F NMR (376.5 MHz, $CDCl_3$)** δ -66.27 (t, J_{CF} = 10.6 Hz).

(*Z*)-12-azido-1,1,1-trifluorododec-3-ene (10b):



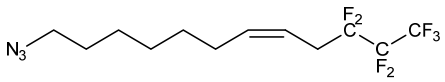
(*Z*)-12-azido-1,1,1-trifluorododec-3-ene was prepared following the general procedure for the synthesis of azides. Thus, (*Z*)-12-bromo-1,1,1-trifluorododec-3-ene **12** (0.554 g, 1.84 mmol, 1 equiv.) in 10 mL of EtOH was added to a solution of sodium azide (0.240 g, 3.7 mmol, 2 equiv.) in 10 mL of H_2O and it was warmed to 90 °C and stirred 16 h. After the work-up, the crude product was purified by column chromatography (100% hexanes to 9:1 Hexanes:AcOEt) to give azide **10b** (0.415 g, 1.575 mmol, 87%) as a colourless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.75 - 5.66 (m, 1H), 5.42 - 5.33 (m, 1H), 3.25 (t, *J* = 7.0 Hz, 2H), 2.89 - 2.78 (m, 2H), 2.05 (q, *J* = 6.7 Hz, 2H), 1.63 - 1.54 (m, 2H), 1.41 - 1.26 (m, 10H). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ 136.6, 126.2 (q, $J_{C,F}$ = 276.5 Hz), 116.7 (q, $J_{C,F}$ = 3.5 Hz), 51.4, 32.1 (q, $J_{C,F}$ = 29.5 Hz), 29.3, 29.0, 29.0, 29.0, 28.8, 27.3, 26.6. **^{19}F NMR (376.5 MHz, $CDCl_3$)** δ -66.35 (t, J_{CF} = 10.9 Hz). **MS (GCQTOF)**: $[M-H]^-$ *m*/*z* calcd for $C_{12}H_{19}F_3N_3^-$: 262.1531; found: 262.1538. **FT-IR (ATR)** ν in cm^{-1}: 3030, 2929, 2093, 1252, 1134, 1089.

(*Z*)-12-azido-1,1,1,2,2-pentafluorododec-4-ene (10c):

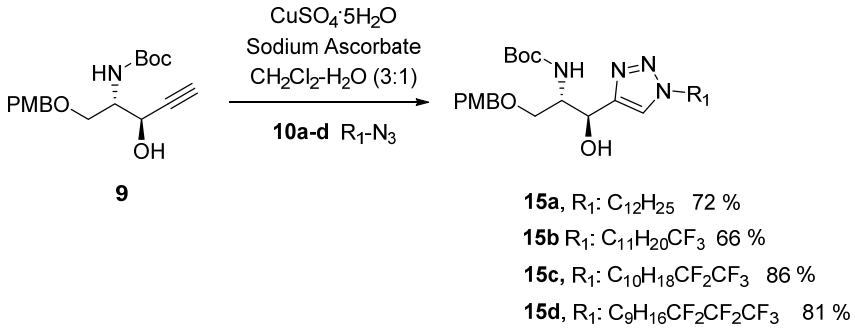


(*Z*)-12-azido-1,1,1,2,2-pentafluorododec-4-ene **10c** was prepared following the general procedure for Wittig reaction. KHMDS 0.5M (11.6 mL, 5.82 mmol, 1 equiv.) was added to a solution of (3,3,4,4,4-pentafluorobutyl)triphenylphosphonium iodide (6.24 g, 11.63 mmol, 2 equiv.) in 45 mL of THF. 8-azidononanal **13** (0.985 g, 5.817 mmol, 1 equiv.) in 30 mL of THF was then added and after the work-up, the reaction crude was purified by flash chromatography (silica gel, pure hexane). After that, the obtained mixture of the desired (*Z*)-12-azido-1,1,1,2,2-pentafluorododec-4-ene and (1*Z*, 3*Z*)-12-azido-1,1,1-trifluoro-2-fluorodoce-2,4-diene was submitted to fractional distillation at 100 ºC and 10 mmHg to give the desired azido olefine (0.783 g, 2.61 mmol, 45%) as a colourless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.78 - 5.70 (m, 1H), 5.44 - 5.36 (m, 1H), 3.26 (t, *J* = 6.9 Hz, 2H), 2.81 (td, $J_{H,F}$ = 17.8 Hz, *J* = 7.3 Hz, 2H), 2.09 - 2.00 (m, 2H), 1.64 - 1.55 (m, 2H), 1.44 - 1.27 (m, 8H). **^{13}C NMR (100.6 MHz, $CDCl_3$)** δ 137.1, 115.8 (t, $J_{C,F}$ = 4.3 Hz), 51.6, 29.3 (t, $J_{C,F}$ = 22.4 Hz), 29.1, 29.1, 28.9, 27.4, 26.8. **^{19}F NMR (376.5 MHz, $CDCl_3$)** δ -85.00 – -85.06 (m, F-1), -117.06 – -117.19 (m, F-2). **MS (GCQTOF)**: $[M-H]^-$ *m*/*z* calcd for $C_{12}H_{17}F_5N_3^-$: 298.1343; found: 298.1351. **FT-IR (ATR)** ν in cm^{-1}: 3033, 2930, 2858, 2097, 1198.

(*Z*)-12-azido-1,1,1,2,2,3,3-heptafluorododec-5-ene (10d):

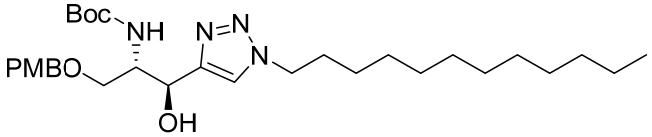


Compound **10d** was prepared following the general procedure for Wittig reaction. KHMDS 1M (4.6 mL, 4.6 mmol, 1.3 equiv.) was added to a solution of heptafluorinated phosphonium salt (2.67 g, 4.56 mmol, 1.3 equiv.) in 10 mL of THF. 7-azidoheptanal **14** (0.545 g, 3.51 mmol, 1 equiv.) was added and after the work-up, the reaction crude was purified by flash chromatography (silica gel, pure hexane) to give **10d** (0.788 g, 2.35 mmol, 67%) as a colourless oil. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 5.79 – 5.70 (m, 1H), 5.46 – 5.37 (m, 1H), 3.26 (t, *J* = 6.9 Hz, 2H), 2.84 (dt, $J_{H,F}$ = 18.5 Hz, *J* = 7.3 Hz, 2H), 2.06 (q, *J* = 6.9 Hz, 2H), 1.65 - 1.55 (m, 2H), 1.45 - 1.28 (m, 6H). **^{13}C NMR (100.6 MHz, CDCl$_3$)** δ 136.9, 115.6 (t, $J_{C,F}$ = 4.3 Hz), 51.4, 29.1 (t, $J_{C,F}$ = 22.5 Hz), 28.9, 28.7, 28.6, 27.2, 26.5. **MS (GCQTOF)**: $[M-H]^-$ *m*/*z* calcd for $C_{12}H_{15}F_7N_3^-$: 334.1154; found: 334.1152. **FT-IR (ATR)** ν in cm^{-1}: 3029, 2928, 2857, 2095, 1348, 1252, 1133, 1089.



Scheme 5. Azide-Alkyne Cycloaddition.

***tert*-butyl ((1*S*,2*S*)-1-(1-dodecyl-1*H*-1,2,3-triazol-4-yl)-1-hydroxy-3-((4-methoxybenzyl)oxy)propan-2-yl)carbamate, 15a.**

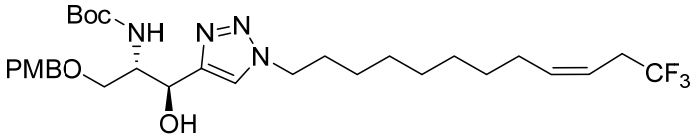


Following the general procedure of azide-alkyne cycloaddition reaction alkyne **9** (0.123 g, 0.367 mmol, 1 equiv.) was treated with azide **10a** (0.232 g, 1.101 mmol, 3 equiv.). The reaction crude was purified by flash chromatography (silica gel, hexane:ethyl acetate 7:3→1:1.(R_f: 0.42 in hexane:EtOAc 1:1) to give **15a** (0.145 g, 72 %).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 (s, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.33 (d, *J* = 8.3 Hz, 1H), 5.01 (d, *J* = 4.7 Hz, 1H), 4.41 (s, 2H), 4.27 (dd, *J* = 7.6, 6.3 Hz, 2H), 4.15 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.80 (s, 3H), 3.76 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.54 (dd, *J* = 9.6, 4.5 Hz, 1H), 1.86 (dd, *J* = 14.3, 7.1 Hz, 2H), 1.40 (s, 9H), 1.35 - 1.18 (m, 18H), 0.87 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$): δ** 159.5, 156.1, 148.8, 129.7, 129.6, 121.5,

114.0, 79.8, 73.2, 69.6, 68.9, 55.4, 54.3, 50.4, 32.0, 30.4, 29.7, 29.6, 29.5, 29.4, 29.1, 28.4, 26.6, 22.8, 14.2. **HRMS (ESI-TOF)**: for $C_{30}H_{51}N_4O_5$ calculated $[M+H]^+$: 547.3859, found: 547.3848 **$[\alpha]^{25}_D$** +2.84 (*c* 1.3, $CHCl_3$).

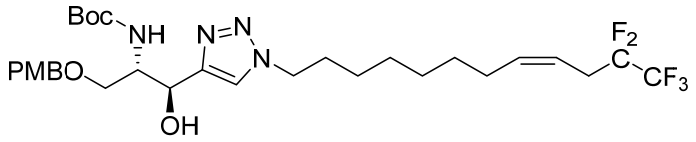
***tert*-butyl ((1*S*,2*S*)-1-hydroxy-3-((4-methoxybenzyl)oxy)-1-(1-((*Z*)-12,12,12-trifluorododec-9-en-1-yl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)carbamate, 15b.**



Following the general procedure of azide-alkyne cycloaddition reaction alkyne **9** (0.3 g, 0.895 mmol, 1 equiv.) was treated with azide **10b** (0.240 g, 0.94 mmol, 1.05 equiv.). The reaction crude was purified by flash chromatography (silica gel, hexane:ethyl acetate 8:2→4:6.(R_f: 0.38 in hexane:EtOAc 4:6) to give **15b** (0.353 g, 66 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.69 (ddd, *J* = 18.2, 7.4, 0.7 Hz, 1H), 5.41 - 5.30 (m, 1H), 5.32 (br s, 1H), 5.01 (dd, *J* = 7.2, 5.1 Hz, 1H), 4.40 (s, 2H), 4.27 (td, *J* = 7.1, 1.6 Hz, 2H), 4.19 - 4.09 (m, 1H), 4.04 (br d, *J* = 6.7 Hz, 1H), 3.79 (s, 3H), 3.75 (dd, *J* = 9.5, 4.2 Hz, 1H), 3.53 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.82 (qdd, *J* = 11.0, 7.4, 1.5 Hz, 2H), 2.03 (q, *J* = 6.7 Hz, 2H), 1.94 - 1.77 (m, 2H), 1.39 (s, 9H), 1.35 - 1.24 (m, 10H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.3, 155.9, 148.6, 136.5, 129.6, 129.5, 126.2 (app d, *J* = 276.6 Hz), 121.4, 116.7 (q, *J* = 3.7 Hz), 113.8, 79.6, 73.0, 69.4, 68.7, 55.2, 54.1, 50.2, 32.1 (q, *J* = 29.6 Hz), 30.2, 29.2, 29.0, 29.0, 28.9, 28.2, 27.3, 26.4. **^{19}F NMR (377 MHz, $CDCl_3$)** δ -66.22 (t, *J* = 10.9 Hz). **HRMS (ESI-TOF)**: Calculated for $C_{30}H_{46}F_3N_4O_5$ $[M+H]^+$: 599.3420, found, 599.3417. **$[\alpha]^{25}_D$** +3.3 (*c* 0.96, $CHCl_3$).

***tert*-butyl ((1*S*,2*S*)-1-hydroxy-3-((4-methoxybenzyl)oxy)-1-(1-((*Z*)-11,11,12,12,12-pentafluorododec-8-en-1-yl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)carbamate, 15c.**

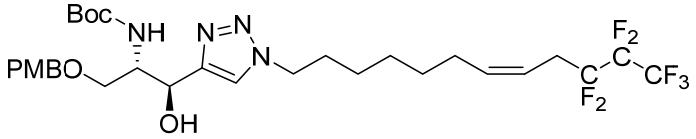


Following the general procedure of azide-alkyne cycloaddition reaction alkyne **9** (0.3 g, 0.895 mmol, 1 equiv.) was treated with azide **10c** (0.280 g, 0.94 mmol, 1.05 equiv.). The reaction crude was purified by flash chromatography (silica gel, hexane:ethyl acetate 8:2→4:6 (R_f: 0.31 in hexane:EtOAc 4:6) to give **15c** (0.487 g, 86 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.71 (dd, *J* = 17.9, 7.6 Hz, 1H), 5.44 – 5.28 (m, 2H), 5.06 – 4.95 (m, 1H), 4.40 (s, 2H), 4.25 (t, *J* = 7.2 Hz, 2H), 4.19 - 4.09 (m, *J* = 3.6 Hz, 2H), 3.78 (dd, *J* = 3.0, 1.7 Hz, 2H), 3.74 (m, 1H), 3.53 (dd, *J* = 9.3, 3.7 Hz, 1H), 2.78 (td, *J* = 17.8, 7.3 Hz, 2H), 2.02 (dd, *J* = 14.0, 7.0 Hz, 2H), 1.84 (t, *J* = 6.1 Hz, 2H), 1.38 (s, 9H), 1.36 - 1.22 (m, 8H). **^{13}C NMR (100 MHz,**

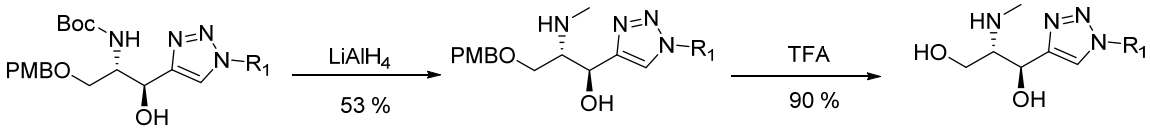
$CDCl_3$): δ 159.3, 155.9, 148.7, 136.8, 129.6, 129.5, 121.42, 120.7 (m), 115.6 (t, *J* = 4.4 Hz), 113.7, 79.61, 73.04, 69.39, 68.6, 55.2, 54.1, 50.2, 30.1, 29.1 (t, *J* = 22.3 Hz), 29.0, 28.9, 28.8, 28.3, 27.3, 26.3. **^{19}F NMR (376 MHz, $CDCl_3$):** δ -84.98 (s, *J* = 5.0 Hz), -117.09 (t, *J* = 17.8 Hz). **HRMS (ESI-TOF)**: Calculated for $C_{30}H_{44}F_5N_4O_5$ $[M+H]^+$: 635.3232, found, 635.3230. **$[\alpha]^{25}_D$** +1.8 (*c* 1, $CHCl_3$).

***tert*-butyl ((1*S*,2*S*)-1-(1-((*Z*)-10,10,11,11,12,12,12-heptafluorododec-7-en-1-yl)-1*H*-1,2,3-triazol-4-yl)-1-hydroxy-3-((4-methoxybenzyl)oxy)propan-2-yl)carbamate, 15d**.



Following the general procedure of azide-alkyne cycloaddition reaction alkyne **9** (0.245 g, 0.731 mmol, 1 equiv.) was treated with azide **10d** (0.245 g, 0.731 mmol, 1 equiv.). The reaction crude was purified by flash chromatography (silica gel, hexane:ethyl acetate 8:2→4:6.(R_f: 0.26 in hexane:EtOAc 3:7) to give **15d** (0.396 g, 81 %).

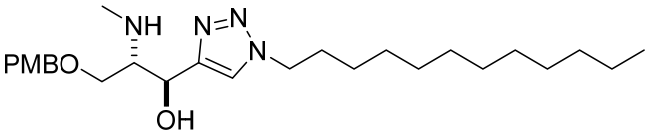
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.79 - 5.66 (m, 1H), 5.41 (dd, *J* = 18.2, 7.4 Hz, 1H), 5.32 (br d, *J* = 8.3 Hz, 1H), 5.01 (br s, 1H), 4.41 (s, 2H), 4.27 (td, *J* = 7.1, 1.7 Hz, 2H), 4.14 (tt, *J* = 11.6, 5.7 Hz, 1H), 4.01 (br s, 1H), 3.80 (s, 3H), 3.76 (dd, *J* = 9.3, 4.2 Hz, 1H), 3.54 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.83 (td, *J* = 18.4, 7.2 Hz, 2H), 2.09 - 1.99 (m, 2H), 1.93 - 1.80 (m, 2H), 1.40 (s, 9H), 1.38 -1.27 (m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 159.4, 148.8, 136.9, 129.6, 121.5, 115.8 (t, *J* = 4.4 Hz), 113.9, 79.8, 73.2, 69.5, 68.9, 55.3, 54.3, 50.3, 30.3, 29.0 (t, *J* = 17.9 Hz), 28.6, 28.4, 27.3, 26.4. **^{19}F NMR (377 MHz, $CDCl_3$)**: δ -80.61 (t, *J* = 9.7 Hz), -114.16 (m), -127.45(m). **HRMS (ESI-TOF)**: Calculated for $C_{30}H_{42}F_7N_4O_5$ $[M+H]^+$: 671.3043, found, 671.3031. **$[\alpha]^{25}_D$** +1.5 (*c* 1.1, $CHCl_3$).



15a, R_1: $C_{12}H_{25}$ **16**, R_1: $C_{12}H_{25}$ **18a**, R_1: $C_{12}H_{25}$

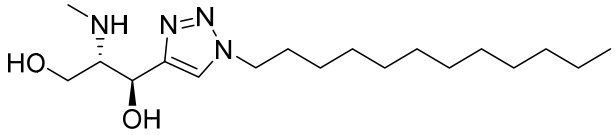
Scheme 6. Synthesis of *N*-monomethyl amino analog **18a**.

(1*S*,2*S*)-1-(1-dodecyl-1*H*-1,2,3-triazol-4-yl)-3-((4-methoxybenzyl)oxy)-2-(methylamino)propan-1-ol, 16.

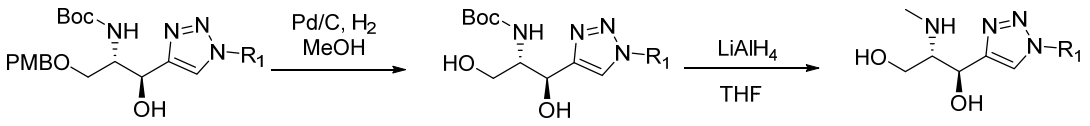


Compound **15a** (0.070 g, 0.128 mmol, 1 equiv.) was treated with $LiAlH_4$ (15 mg, 0.384 mmol, 3 equiv.) following the general procedure of reduction of carbamate. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 9:1:0.1)(R_f: 0.22 in $CHCl_3$:MeOH:NH_4OH 9:1:0.1) to give **16** (31 mg, 53 %). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 (s, 1H), 7.22 - 7.16 (m, 2H), 6.88 - 6.83 (m, 2H), 5.10 (d, *J* = 4.0 Hz, 1H), 4.38 (d, *J* = 11.3 Hz, 1H), 4.30 (d, *J* = 11.3 Hz, 1H), 4.29 - 4.23 (m, 2H), 3.79 (s, 3H), 3.50 (dd, *J* = 9.7, 6.5 Hz, 1H), 3.39 (dd, *J* = 9.7, 4.2 Hz, 1H), 3.24 - 3.16 (m, 1H), 2.51 (d, *J* = 10.3 Hz, 3H), 1.92 - 1.78 (m, 2H), 1.42 - 1.16 (m, 18H), 0.87 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.4, 149.0, 129.8, 129.6, 121.5, 113.9, 73.1, 68.7, 66.3, 62.5, 55.4, 50.4, 34.2, 32.0, 30.4, 29.7, 29.6, 29.5, 29.4, 29.1, 28.4, 26.6, 22.8, 14.2. **HRMS (ESI-TOF)**: Calculated for $C_{26}H_{45}N_4O_3$ $[M+H]^+$: 461.3492, found 461.3480. **$[\alpha]^{25}_D$** −6.0 (*c* 1.8, $CHCl_3$).

(1*S*,2*S*)-1-(1-dodecyl-1*H*-1,2,3-triazol-4-yl)-2-(methylamino)propane-1,3-diol, **18a**.



Compound **16** (0.030 g, 0.065 mmol) was treated with TFA (1 ml) following the general procedure of deprotection of *p*-methoxybenzyl group. The reaction crude was purified by *flash* chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 9:1:0.1)(R_f: 0.2 in $CHCl_3$:MeOH:NH_4OH 9:1:0.1) to give **18a** (0.020 g, 90 %). **^{1}H NMR (400 MHz, CD_3OD)** δ 7.89 (s, 1H), 5.01 (d, *J* = 4.9 Hz, 1H), 4.39 (t, *J* = 7.1 Hz, 2H), 3.62 (d, *J* = 5.2 Hz, 2H), 2.88 (q, *J* = 5.1 Hz, 1H), 2.44 (s, *J* = 2.6 Hz, 3H), 1.98 - 1.82 (m, 2H), 1.41 - 1.22 (m, 18H), 0.90 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, CD_3OD)** δ 150.5, 124.0, 67.5, 66.3, 61.0, 51.3, 34.5, 33.0, 31.3, 30,8, 30.7, 30.6, 30.6, 30.5, 30.1, 27.5, 23.7, 14.4. **HRMS (ESI-TOF)**: Calculated for $C_{18}H_{37}N_4O_2$ $[M+H]^+$: 341.2917, found: 341.2915. **$[\alpha]^{25}_D$** −3.61 (*c* 1.8, $CHCl_3$).



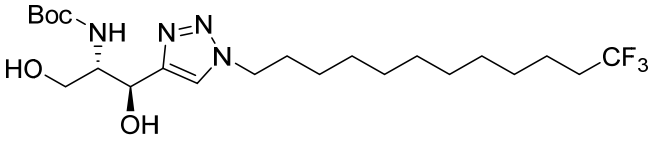
15b R_1: $C_{11}H_{20}CF_3$
15c, R_1: $C_{10}H_{18}CF_2CF_3$
15d, R_1: $C_9H_{16}CF_2CF_2CF_3$

17b R_1: $C_{11}H_{22}CF_3$ 82 %
17c, R_1: $C_{10}H_{20}CF_2CF_3$ 86 %
17d, R_1: $C_9H_{18}CF_2CF_2CF_3$ 79 %

18b R_1: $C_{11}H_{22}CF_3$ 61 %
18c, R_1: $C_{10}H_{20}CF_2CF_3$ 63 %
18d, R_1: $C_9H_{18}CF_2CF_2CF_3$ 69 %

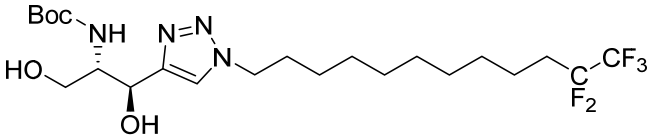
Scheme 7. Synthesis of *N*-monomethyl amino analogues **18b-d**.

***tert*-butyl ((1*S*,2*S*)-1,3-dihydroxy-1-(1-(12,12,12-trifluorododecyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)carbamate, 17b.**



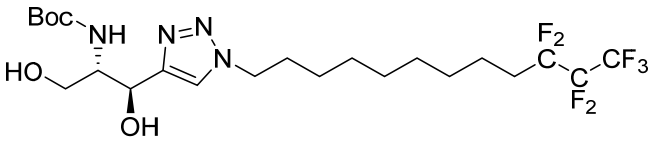
Compound **15b** (0.308 g, 0.515 mmol) was treated following the general procedure for the hydrogenation of alkenes and the deprotection of *p*-methoxybenzyl ethers. The reaction crude was purified by *flash* chromatography (silica gel, hexane: ethyl acetate 2:8)(R_f: 0.14 in hexane: ethyl acetate 2:8→0:10) to give **17b** (0.202 g, 82 %). **^{1}H NMR (400 MHz, CD_3OD)**: δ 7.86 (s, 1H), 6.34 (d, *J* = 9.3 Hz, 1H), 4.84 (d, *J* = 7.8 Hz, 1H), 4.36 (t, *J* = 7.1 Hz, 2H), 3.87 (dt, *J* = 7.9, 5.2 Hz, 1H), 3.77 (dd, *J* = 11.2, 5.5 Hz, 1H), 3.69 (dd, *J* = 11.2, 4.1 Hz, 1H), 2.21 - 2.02 (m, 2H), 1.94 - 1.81 (m, 2H), 1.60 - 1.48 (m, 2H), 1.43 - 1.21 (m, 25H). **^{13}C NMR (100 MHz, CD_3OD)** δ 156.3, 149.12, 127.4 (app d, *J* = 274.5 Hz), 122.2, 78.6, 66.3, 60.9, 56.5, 49.9, 32.9 (q, *J* = 28.2 Hz), 30.0, 29.2, 29.1, 29.0, 28.9, 28.7, 28.3, 27.3, 26.0, 21.6 (q, *J* = 2.9 Hz). **^{19}F NMR (377 MHz, CD_3OD):** δ -67.94 (t, *J* = 11.2 Hz). **HRMS (ESI-TOF)**: Calculated for $C_{22}H_{40}F_3N_4O_4$ $[M+H]^+$: 481.3002, found, 481.2998. **$[\alpha]^{25}_D$** –4.5 (*c* 0.8, $CHCl_3$).

***tert*-butyl ((1*S*,2*S*)-1,3-dihydroxy-1-(1-(11,11,12,12,12-pentafluorododecyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)carbamate, 17c**.



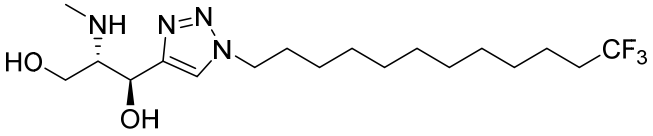
Compound **15c** (0.315 g, 0.496 mmol) was treatment following the general procedure for the hydrogenation of alkenes and the hydrogenolysis of *p*-methoxybenzyl ether. The reaction crude was purified by *flash* chromatography (silica gel, hexane: ethyl acetate 2:8→0:10)(R_f: 0.21 in hexane: ethyl acetate 2:8) to give **17c** (0.220 g, 86 %). **^{1}H NMR (400 MHz, CD_3OD)** δ δ 7.86 (s, 1H), 6.34 (d, *J* = 9.3 Hz, 1H), 4.84 (d, *J* = 7.8 Hz, 1H), 4.37 (t, *J* = 7.1 Hz, 2H), 3.95 – 3.83 (m, 1H), 3.77 (dd, *J* = 11.2, 5.5 Hz, 1H), 3.69 (dd, *J* = 11.2, 4.1 Hz, 1H), 2.18 - 1.99 (m, 2H), 1.97 - 1.82 (m, 2H), 1.64 - 1.50 (m, 2H), 1.44 - 1.25 (m, 19H). **^{13}C NMR (100 MHz, CD_3OD)** δ 156.4, 149.1, 122.3, 120.7 (app d, *J* = 179 Hz), 78.6, 66.3, 60.9, 56.5, 49.9, 30.0 (t, *J* = 21.9 Hz), 29.9, 29.7, 29.1, 29.0, 28.9, 28.6, 28.6, 27.2, 26.0, 20.0 (t, *J* = 3.4 Hz). **^{19}F NMR (376 MHz, CD_3OD)** δ -87.01 (s), -119.47 (t, *J* = 18.8 Hz). **HRMS (ESI-TOF)**: Calculated for $C_{22}H_{38}F_5N_4O_4$ $[M+H]^+$: 517.2813, found, 517.2812. **$[\alpha]^{25}_D$** –5.1 (*c* 0.8, $CHCl_3$).

***tert*-butyl ((1*S*,2*S*)-1-(1-(10,10,11,11,12,12,12-heptafluorododecyl)-1*H*-1,2,3-triazol-4-yl)-1,3-dihydroxypropan-2-yl)carbamate, 17d**.



Compound **15d** (0.221 g, 0.329 mmol) was treatment following the general procedure for the hydrogenation of alkenes and the deprotection of *p*-methoxybenzyl ethers. The reaction crude was purified by *flash* chromatography (silica gel, hexane: ethyl acetate 2:8→0:10)(R_f: 0.37 in ethyl acetate) to give **17d** (0.143 g, 79 %). **^{1}H NMR (400 MHz, CD_3OD):** δ 7.87 (s, 1H), 6.35 (d, *J* = 9.4 Hz, 1H), 4.84 (d, *J* = 7.8 Hz, 1H), 4.37 (t, *J* = 7.1 Hz, 2H), 3.93 – 3.82 (m, 1H), 3.77 (dd, *J* = 11.2, 5.4 Hz, 1H), 3.69 (dd, *J* = 11.2, 4.1 Hz, 1H), 2.10 (qt, *J* = 21.8, 10.7 Hz, 2H), 1.96 - 1.81 (m, 2H), 1.65 - 1.51 (m, 2H), 1.34 (s, 20H). **^{13}C NMR (100 MHz, CD_3OD)** δ 157.8, 150.5, 123.7, 121.3-113.9 (m), 112.1-104.2 (td, *J* = 262.4, 38.8 Hz), 80.0, 67.7, 62.3, 57.9, 51.3, 31.4, 31.3, 30.0 (t, *J* = 22.1 Hz), 29.9, 28.6, 27.4, 21.2 (t, *J* = 3.7 Hz). **^{19}F NMR (377 MHz, CD_3OD)** δ -82.23 (t, *J* = 9.9 Hz), -116.30 – -116.64 (m), -129.05 – -129.22 (m). **HRMS (ESI-TOF)**: Calculated for $C_{22}H_{36}F_7N_4O_4$ $[M+H]^+$: 553.2625, found, 553.2612. . **$[\alpha]^{25}_D$** –4.1 (*c* 0.9, $CHCl_3$).

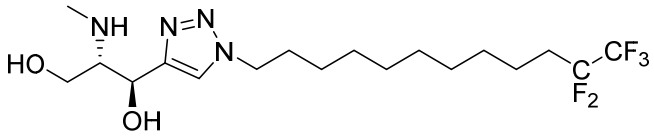
(1*S*,2*S*)-2-(methylamino)-1-(1-(12,12,12-trifluorododecyl)-1*H*-1,2,3-triazol-4-yl)propane-1,3-diol, 18b.



Compound **17b** (0.050 g, 0.104 mmol, 1 equiv.) was treated with $LiAlH_4$ (12 mg, 0.312 mmol, 3 equiv.) following the general procedure of reduction of carbamate. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 9:1:0.1)(R_f: 0.37 in $CHCl_3$:MeOH:NH_4OH 9:1:0.1) to give **18b** (25 mg, 61 %).

^{1}H NMR (400 MHz, CD_3OD): δ 7.90 (s, 1H), 5.02 (d, *J* = 5.3 Hz, 1H), 4.39 (t, *J* = 7.1 Hz, 2H), 3.62 (d, *J* = 5.2 Hz, 2H), 2.89 (q, *J* = 5.1 Hz, 1H), 2.45 (s, 3H), 2.20 - 2.02 (m, 2H), 1.98 - 1.83 (m, 2H), 1.53 (dt, *J* = 11.7, 7.4 Hz, 2H), 1.44 - 1.24 (m, 15H**). ^{13}C NMR (100 MHz, CD_3OD):** δ 150.5, 127.4 (app d, *J* = 275.3 Hz), 124.0, 67.34, 66.3, 60.9, 51.3, 32.9 (t, *J* = 14.1 Hz), 31.3, 30.5, 30.4, 30.3, 30.0, 29.7, 27.4, 21.6 (q, *J* = 2.9 Hz). **^{19}F NMR (377 MHz, CD_3OD):** δ -68.05 (t, *J* = 11.2 Hz). **HRMS (ESI-TOF)**: Calculated for $C_{18}H_{34}F_3N_4O_2$ $[M+H]^+$: 395.2634, found, 395.2634. **$[\alpha]^{25}_D$** −3.33 (c 0.9, MeOH).

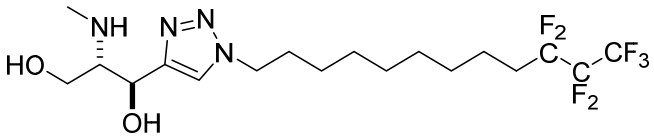
(1*S*,2*S*)-2-(methylamino)-1-(1-(11,11,12,12,12-pentafluorododecyl)-1*H*-1,2,3-triazol-4-yl)propane-1,3-diol, 18c.



Compound **17c** (0.050 g, 0.096 mmol, 1 equiv.) was treated with $LiAlH_4$ (11 mg, 0.290 mmol, 3 equiv.) following the general procedure of reduction of carbamate. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 9:1:0.1)(R_f: 0.19 in $CHCl_3$:MeOH:NH_4OH 9:1:0.1) to give **18c** (26 mg, 63 %).

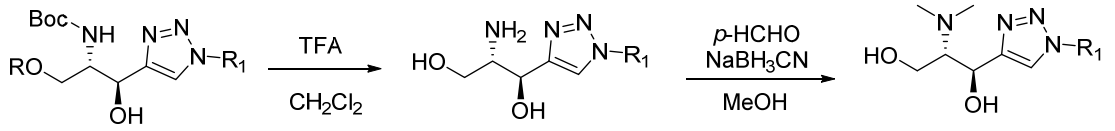
^{1}H NMR (400 MHz,CD_3OD): δ 7.89 (s, *J* = 5.7 Hz, 1H), 5.01 (d, *J* = 4.9 Hz, 1H), 4.39 (t, *J* = 7.1 Hz, 2H), 3.61 (d, *J* = 5.2 Hz, 2H), 2.88 (q, *J* = 5.1 Hz, 1H), 2.44 (s, 3H), 2.20 - 1.99 (m, 2H), 1.96 - 1.82 (m, 2H), 1.67 - 1.48 (m, 2H), 1.51 - 1.15 (m, 14H). **^{13}C NMR (100 MHz, CD_3OD):** δ 150.5, 124.0, 123.0-115.03 (m) 67.4, 66.3, 61.0, 51.3, 34.4, 31.6, 31.3 (*t*, *J* = 21.9 Hz), 30.5, 30.4, 30.3, 30.1, 30.0, 27.5, 21.4 (t, *J* = 3.5 Hz). **^{19}F NMR (376 MHz, CD_3OD)**: δ -87.06 (s, *J* = 5.0 Hz), -119.53 (t, *J* = 18.8 Hz). **HRMS (ESI-TOF)**: Calculated for $C_{18}H_{32}F_5N_4O_2$ $[M+H]^+$: 431.2445, found, 431.2446. **$[\alpha]^{25}_D$** –4.2(*c* 1, MeOH).

(1*S*,2*S*)-1-(1-(10,10,11,11,12,12,12-heptafluorododecyl)-1*H*-1,2,3-triazol-4-yl)-2-(methylamino)propane-1,3-diol, 18d.



Compound **17d** (0.050 g, 0.090 mmol, 1 equiv.) was treated with $LiAlH_4$ (10 mg, 0.271 mmol, 3 equiv.) following the general procedure of reduction of carbamate. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 9:1:0.1)(R_f: 0.26 in $CHCl_3$:MeOH:NH_4OH 9:1:0.1) to give **18d** (29 mg, 69 %).

^{1}H NMR (400 MHz, CD_3OD): δ 7.89 (s, 1H), 5.01 (d, *J* = 4.9 Hz, 1H), 4.40 (t, *J* = 7.1 Hz, 2H), 3.62 (app d, *J* = 5.1 Hz, 2H), 2.87 (q, *J* = 5.1 Hz, 1H), 2.44 (s, 3H), 2.25 - 1.99 (m, 2H), 1.97 - 1.85 (m, 2H), 1.68 -1.51 (m, 2H), 1.48 - 1.23 (m, 11H). **^{13}C NMR (100 MHz, CD_3OD):** δ 150.6, 124.0, 122.4-115.3 (m,), 112.0-108.1 (m), 67.5, 66.3, 61.0, 51.3, 34.5, 31.4 (t, *J* = 21.9 Hz), 31.3, 30.3, 30.2, 30.1, 30.0, 27.4, 21.2 (t, *J* = 3.7 Hz). **^{19}F NMR (376 MHz, CD_3OD):** δ –82.19 - –82.35 (m), –116.33-–116.70 (m), –129.01 - –129.28 (m). **HRMS (ESI-TOF)**: Calculated for $C_{18}H_{30}F_7N_4O_2$ $[M+H]^+$: 467.2257, found, 467.2255. **$[\alpha]^{25}_D$** –3.22 (*c* 0.9, MeOH).



15a, R_1:$C_{12}H_{25}$, R= PMB

17b, R_1: $C_{11}H_{22}CF_3$, R= H

17c, R_1: $C_{10}H_{20}CF_2CF_3$, R=H

17d, R_1: $C_9H_{18}CF_2CF_2CF_3$, R=H

19a, R_1: $C_{12}H_{25}$ 95 %

19b, R_1: $C_{11}H_{22}CF_3$ 68 %

19c, R_1: $C_{10}H_{20}CF_2CF_3$ 77 %

19d, R_1: $C_9H_{18}CF_2CF_2CF_3$ 90 %

20a, R_1: $C_{12}H_{25}$ 42 %

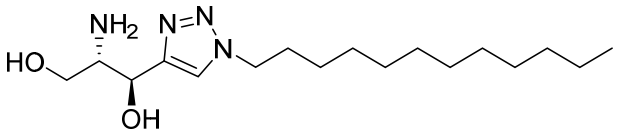
20b, R_1: $C_{11}H_{22}CF_3$ 55 %

20c, R_1: $C_{10}H_{20}CF_2CF_3$ 46 %

20d, R_1: $C_9H_{18}CF_2CF_2CF_3$ 45 %

Scheme 8. Synthesis of *N*,*N*-dimethyl amino analogues **20a-d**.

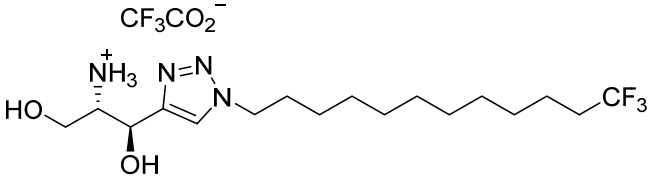
(1*S*,2*S*)-2-amino-1-(1-dodecyl-1*H*-1,2,3-triazol-4-yl)propane-1,3-diol, 19a.



Compound **15a** (0.122 g, 0.223 mmol) was treated with TFA (1 ml) following the general procedure of deprotection of Boc. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 9:1:0.1)(R_f: 0.44 in $CHCl_3$:MeOH:NH_4OH 9:1:0.1) to give **19a** (0.069 g, 95 %).

^{1}H NMR (400 MHz, CD_3OD): δ 7.90 (s, 1H), 4.81 (d, *J* = 6.1 Hz, 1H), 4.39 (t, *J* = 7.1 Hz, 2H), 3.65 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.57 (dd, *J* = 10.8, 6.7 Hz, 1H), 3.17 (br d, *J* = 4.1 Hz, 1H), 1.97 - 1.82 (m, 2H), 1.41 – 1.17 (m, 18H), 0.89 (t, *J* = 6.6 Hz, 3H).**^{13}C NMR (100 MHz, CD_3OD)** δ 150.2, 124.1, 69.2, 63.9, 58.0, 51.4, 33.0, 31.3, 30.7, 30.7, 30.6, 30.5, 30.4, 30.1, 27.5, 23.7, 14.5. **HRMS (ESI-TOF)**: Calculated for $C_{17}H_{35}N_4O_2$ $[M+H]^+$: 327.2760, found: 327.2753. **$[\alpha]^{25}_D$** +1.5 (*c* 1, MeOH).

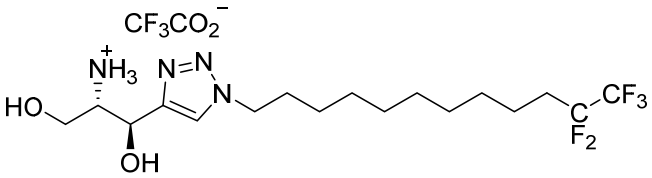
(1*S*,2*S*)-2-amino-1-(1-(12,12,12-trifluorododecyl)-1*H*-1,2,3-triazol-4-yl)propane-1,3-diol trifluoroacetate salt, 19b.



Compound **17b** (0.150 g, 0.312 mmol) was treated with TFA (1 ml) following the general procedure of deprotection of Boc. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 8:2:0.2)(R_f: 0.32 in $CHCl_3$:MeOH:NH_4OH 8:2:0.2) to give **19b** (0.104 g, 68 %). **^{1}H NMR (400 MHz, CD_3OD)**: δ 7.95 (s, 1H), 4.96 (app s, 1H),

4.40 (t, *J* = 7.1 Hz, 2H), 3.68 (dd, *J* = 11.3, 4.6 Hz, 1H), 3.64 (dd, *J* = 11.3, 7.0 Hz, 1H), 3.36 (dt, *J* = 6.8, 5.1 Hz, 1H), 2.21 - 2.04 (m, 2H), 1.97 - 1.85 (m, 2H), 1.54 (ddd, *J* = 11.7, 8.5, 6.6 Hz, 2H), 1.44 - 1.22 (m, 14H). **^{13}C NMR (100 MHz, CD_3OD)**: δ 163. 0 (app d, *J* = 34.4 Hz, $CF_3\underline{C}O_2^-$), 149.4, 128.9 (q, *J* = 275.4 Hz), 124.3, 67.5, 61.8, 58.2, 51.4, 34.4 (q, *J* = 28.1 Hz), 31.3, 30.6, 30.5, 30.4, 30.3, 30.1, 29.7, 27.5, 23.0 (q, *J* = 3.0 Hz). **^{19}F NMR (376 MHz, CD_3OD)** δ -67.97 (t, *J* = 11.2 Hz), -76.87 (s, *J* = 1.6 Hz). **HRMS (ESI-TOF)**: Calculated for $C_{17}H_{32}F_3N_4O_2$ $[M+H]^+$: 381.2477, found: 381.2478. **$[\alpha]^{25}_D$** –2.1 (*c* 1.2, MeOH).

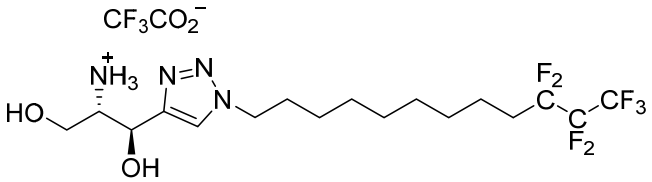
(1*S*,2*S*)-2-amino-1-(1-(11,11,12,12,12-pentafluorododecyl)-1*H*-1,2,3-triazol-4-yl)propane-1,3-diol trifluoroacetate salt, 19c.



Compound **17c** (0.171 g, 0.331 mmol) was treated with TFA (1.2 ml) following the general procedure of deprotection of Boc. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 8:2:0.2)(R_f: 0.44 in $CHCl_3$:MeOH:NH_4OH 8:2:0.2) to give **19c** (0.135 g, 77 %).

^{1}H NMR (400 MHz, CD_3OD): δ 7.97 (s, 1H), 5.05 (d, *J* = 5.1 Hz, 1H), 4.41 (t, *J* = 7.1 Hz, 2H), 3.72 (app d, *J* = 11.8 Hz, 1H), 3.67 (app d, *J* = 11.8 Hz, 1H), 3.49 (dd, *J* = 11.2, 5.6 Hz, 1H), 2.18 – 1.98 (m, 2H), 1.97 - 1.85 (m, 2H), 1.63 - 1.51 (m, 2H), 1.47 - 1.25 (m, 13H). **^{13}C NMR (101 MHz, CD_3OD):** δ 162.9 (app d, *J* = 33.9 Hz, $CF_3\underline{C}O_2^-$), 149.0, 124.3, 123.38-114.5(m), 66.6, 60.6, 58.3, 51.4, 31.4 (t, *J* = 21.9 Hz), 31.3, 30.4, 30.4, 30.3, 30.1, 30.0, 27.5, 21.4 (t, *J* = 3.5 Hz). **^{19}F NMR (376 MHz, CD_3OD)** δ -76.88 (s, *J* = 22.3 Hz), -87.01 (s), -119.49 (t, *J* = 18.8 Hz). -76.88 (s, *J* = 22.3 Hz), -86.87 (s, *J* = 16.5 Hz), -119.49 (t, *J* = 18.8 Hz). **HRMS (ESI-TOF)**: Calculated for $C_{17}H_{30}F_5N_4O_2$ $[M+H]^+$: 417.2289, found, 417.2288. **$[\alpha]^{25}_D$** –4.2(*c* 1, MeOH).

(1*S*,2*S*)-2-amino-1-(1-(10,10,11,11,12,12,12-heptafluorododecyl)-1*H*-1,2,3-triazol-4-yl)propane-1,3-diol trifluoroacetate salt, 19d.

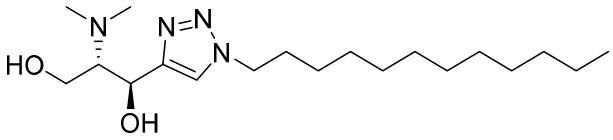


Compound **17d** (0.226 g, 0.5 mmol) was treated with TFA (1.6 ml) following the general procedure of deprotection of Boc. The reaction crude was purified by flash chromatography

(silica gel, $CHCl_3$:MeOH:NH_4OH 8:2:0.2)(R_f: 0.37 in $CHCl_3$:MeOH:NH_4OH 8:2:0.1) to give **15d** (0.255 g, 90 %).

^{1}H NMR (400 MHz, CD_3OD): δ 7.92 (d, *J* = 4.2 Hz, 1H), 4.84 (d, *J* = 6.0 Hz, 1H), 4.40 (t, *J* = 7.1 Hz, 2H), 3.66 (dd, *J* = 11.1, 4.4 Hz, 1H), 3.58 (dd, *J* = 11.0, 6.7 Hz, 1H), 3.21 (dd, *J* = 10.8, 6.2 Hz, 1H), 2.22 - 2.03 (m, 2H), 1.98 - 1.85 (m, 2H), 1.66 - 1.53 (m, 2H), 1.47 - 1.25 (m, 10H). **^{13}C NMR (100 MHz, CD_3OD):** δ 150.0, 124.2, 68.8, 63.4, 58.1, 51.3, 31.4 (t, *J* = 22.4 Hz), 31.3, 30.3, 30.2, 30.1, 30.0, 27.5, 21.2 (t, *J* = 3.6 Hz). **^{19}F NMR (376 MHz, CD_3OD)**: δ -76.92 – -76.96 (m), -82.27 (t, *J* = 9.9 Hz), -114.60 – -118.12 (m), -127.10 – -131.93 (m). **HRMS (ESI-TOF)**: Calculated for $C_{17}H_{28}F_7N_4O_2$ $[M+H]^+$: 453.2100, found: 453.2097. **$[\alpha]^{25}_D$** = −1.3 (c = 1.3, MeOH).

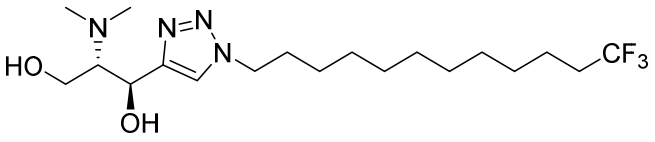
(1*S*,2*S*)-2-(dimethylamino)-1-(1-dodecyl-1*H*-1,2,3-triazol-4-yl)propane-1,3-diol, 20a.



Compound **19a** (0.029 g, 0.088 mmol) was treated with *p*-HCHO(0.026g, 0.889 mmol) and $NaBH_3CN$ (0.060 g, 0.968 mmol) following the general procedure of *N*,*N*-dimethylation of amines. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 9:1:0.1)(*R_f*: 0.45 in $CHCl_3$:MeOH:NH_4OH 9:1:0.1) to give **20a** (0.0.013 g, 42 %).

^{1}H NMR (400 MHz, CD_3OD): δ 7.88 (s, 1H), 5.11 (dd, *J* = 4.9, 0.5 Hz, 1H), 4.39 (t, *J* = 7.1 Hz, 2H), 3.83 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.79 (dd, *J* = 10.0, 3.0 Hz, 1H), 2.94 (dt, *J* = 6.6, 4.8 Hz, 1H), 2.43 (s, 6H), 1.96 – 1.84 (m, 2H), 1.40 - 1.19 (m, 18H), 0.90 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR (100 MHz, CD_3OD)** δ 152.1, 123.6, 70.5, 66.4, 59.2, 51.3, 42.4, 33.0, 31.3, 30.8, 30.7, 30.6, 30.5, 30.4, 30.1, 27.4, 23.7, 14.4. **HRMS (ESI-TOF)**: Calculated for $C_{19}H_{39}N_4O_2$ $[M+H]^+$: 355.3073, found: 355.3068. **$[\alpha]^{25}_D$** = −5.72 (c = 1.1, MeOH).

(1*S*,2*S*)-2-(dimethylamino)-1-(1-(12,12,12-trifluorododecyl)-1*H*-1,2,3-triazol-4-yl)propane-1,3-diol, 20b.

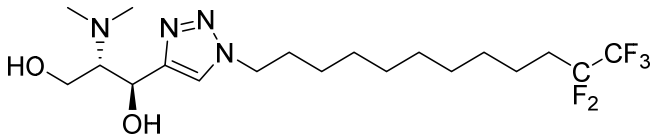


Compound **19b** (0.022 g, 0.057 mmol) was treated with *p*-HCHO(0.017 g, 0.578 mmol) and $NaBH_3CN$ (0.039 g, 0.635 mmol) following the general procedure of *N*,*N*-dimethylation of amines. The reaction crude was purified by flash chromatography (silica gel,

$CHCl_3$:MeOH:NH_4OH 9:1:0.1)(R_f: 0.5 in $CHCl_3$:MeOH:NH_4OH 9:1:0.1) to give **20b** (0.013 g, 55 %).

^{1}H NMR (400 MHz, CD_3OD): δ 7.91 (s, 1H), 5.17 (d, *J* = 4.5 Hz, 1H), 4.40 (t, *J* = 7.0 Hz, 2H), 3.86 (dd, *J* = 12.0, 7.3 Hz, 1H), 3.80 (dd, *J* = 12.0, 4.2 Hz, 1H), 3.10 - 3.03 (m, 1H), 2.54 (s, 6H), 2.20 - 2.05 (m, 2H), 1.96 – 1.85 (m, 2H), 1.54 (dt, *J* = 11.6, 7.5 Hz, 2H), 1.31 (s, 14H). ^{13}C NMR (100 MHz, CD_3OD): δ 151.7, 127.48 (app d, *J* = 275.3 Hz), 123.7, 70.7, 66.1, 58.8, 51.4, 42.4, 32.9 (q, *J* = 28.2 Hz), 31.3, 30.6, 30.5, 30.3, 30.08, 29.8, 27.5, 21.6 (q, *J* = 2.9 Hz). **^{19}F NMR (376 MHz, CD_3OD):** δ -72.11 (t, *J* = 11.2 Hz). **HRMS (ESI-TOF)**: Calculated for $C_{19}H_{36}F_3N_4O_2$ $[M+H]^+$: 409.2790, found, 409.2786. **$[\alpha]^{25}_D$** –8.4 (*c* 0.75 $CHCl_3$).

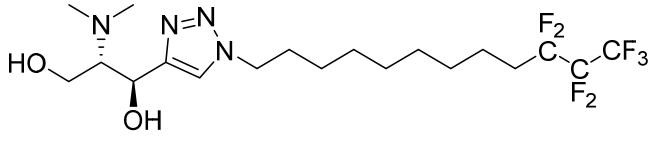
(1*S*,2*S*)-2-(dimethylamino)-1-(1-(11,11,12,12,12-pentafluorododecyl)-1*H*-1,2,3-triazol-4-yl)propane-1,3-diol, 20c.



Compound **19c** (0.035 g, 0.084 mmol) was treated with *p*-HCHO (0.025 g, 0.841 mmol) and $NaBH_3CN$ (0.057 g, 0.924 mmol) following the general procedure of *N*,*N*-dimethylation of amines. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 9:1:0.1)(*Rf*: 0.45 in $CHCl_3$:MeOH:NH_4OH 9:1:0.1) to give **20c** (0.017 g, 46 %).

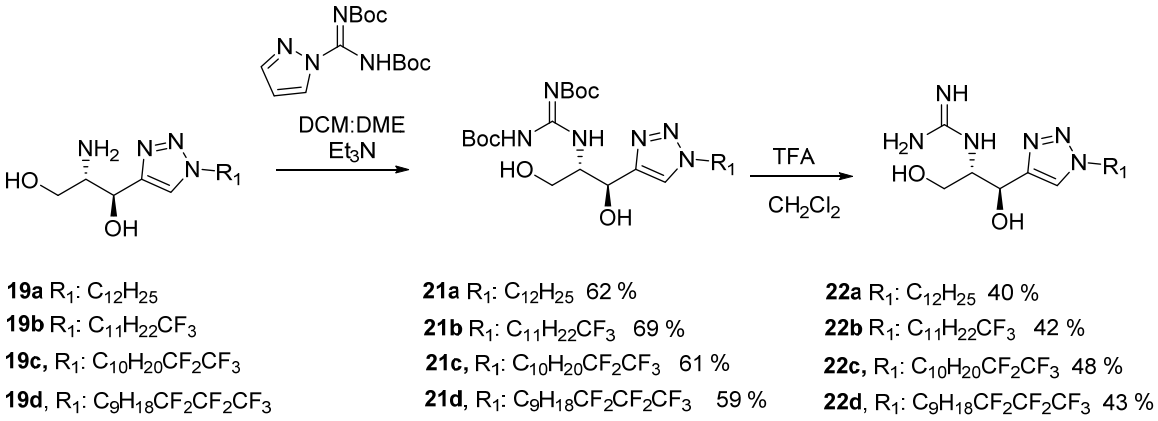
^{1}H NMR (400 MHz, CD_3OD): δ 7.96 (s, 1H), 5.32 (d, *J* = 3.5 Hz, 1H), 4.41 (t, *J* = 7.1 Hz, 2H), 3.93 (dd, *J* = 12.4, 8.0 Hz, 1H), 3.81 (dd, *J* = 12.4, 3.9 Hz, 1H), 3.35 (dt, *J* = 7.8, 3.8 Hz, 1H), 2.79 (s, 6H), 2.09 (ddd, *J* = 26.8, 18.4, 8.1 Hz, 2H), 1.98 - 1.84 (m, 2H), 1.66 - 1.50 (m, 2H), 1.48 - 1.23 (m, 12H). **^{13}C NMR (100 MHz, CD_3OD):** δ 150.5, 140.5-128.2 (m), 124.0, 121.8-108.0 (m), 71.0, 65.3, 57.6, 51.4, 42.4, 31.4 (t, *J* = 21.9 Hz), 31.3, 30.5, 30.4, 30.3, 30.1, 30.0, 27.44 (t, *J* = 3.1 Hz). **^{19}F NMR (376 MHz, CD_3OD):** δ –87.04 - –87.07 (m), –119.51 (t, *J* = 18.8 Hz). **HRMS (ESI-TOF)**: Calculated for $C_{19}H_{33}F_5N_4O_2$ $[M+H]^+$: 445.2602, found, 445.2603. **$[\alpha]^{25}_D$** –8.23 (*c* 0.85, MeOH).

(1*S*,2*S*)-2-(dimethylamino)-1-(1-(10,10,11,11,12,12,12-heptafluorododecyl)-1*H*-1,2,3-triazol-4-yl)propane-1,3-diol, 20d.



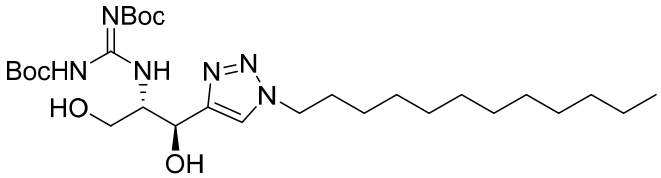
Compound **19d** (0.085 g, 0.188 mmol) was treated with *p*-HCHO (0.056 g, 1.88 mmol) and $NaBH_3CN$ (0.128 g, 2.068 mmol) following the general procedure of *N*,*N*-dimethylation of amines. The reaction crude was purified by flash chromatography (silica gel,

$CHCl_3$:MeOH:NH_4OH 9:1:0.1)(R_f: 0.28 in $CHCl_3$:MeOH:NH_4OH 9:1:0.1) to give **20d** (0.041 g, 45 %). **^{1}H NMR (400 MHz, CD_3OD)**: δ 7.88 (s, 1H), 5.11 (d, *J* = 4.8 Hz, 1H), 4.39 (t, *J* = 7.0 Hz, 2H), 3.81 (dd, *J* = 12.3, 3.3 Hz, 1H), 3.80 (dd, *J* = 10.4, 3.3 Hz, 1H), 2.94 (dt, *J* = 6.6, 4.7 Hz, 1H), 2.43 (s, *J* = 12.6 Hz, 6H), 2.12 (ddd, *J* = 28.0, 19.4, 8.3 Hz, 2H), 1.91 (td, *J* = 7.2, 2.3 Hz, 2H), 1.65 - 1.52 (m, 2H), 1.46 - 1.22 (m, 10H). **^{13}C NMR (100 MHz, CD_3OD):** δ 152.1, 124.1(app m) 123.8, 119.3 (m) 70.7, 66.0, 58.7, 51.3, 49.6, 49.4, 49.2, 49.0, 48.8, 48.6, 48.4, 42.4, 31.4 (t, *J* = 21.9 Hz), 31.3, 30.3, 30.2, 30.1, 30.0, 27.4, 21.2 (t, *J* = 3.7 Hz). **^{19}F NMR (376 MHz, CD_3OD):** δ −82.27 (t, *J* = 9.9 Hz), −116.31 - −116.61 (m), −129.08 - −129.21 (m). **HRMS (ESI-TOF)**: Calculated for $C_{19}H_{32}F_7N_4O_2$ $[M+H]^+$: 481.2413, found 481.2416**.** **$[\alpha]^{25}_D$** −5.27, (*c* 1.1, MeOH).



Scheme 9. Synthesis of *N*-guanidine analogues **22a-d**.

***N,N'*-bis(*tert*-butoxycarbonyl)-1-((1*S*,2*S*)-1-(1-dodecyl-1*H*-1,2,3-triazol-4-yl)-1,3-dihydroxypropan-2-yl)guanidine, 21a.**

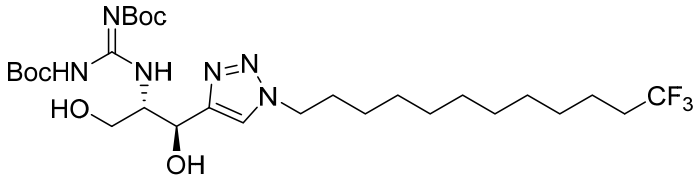


Compound **19a** (0.039 g, 0.119 mmol) was treated with *N*-*N*'-di-Boc-1*H*-pyrazole-1-carboxiamidine (0.041 g, 0.131 mmol) following the general procedure of guanidination of amines. The reaction crude was purified by flash chromatography (silica gel, hexane:ethyl acetate 4:6→2:8)(R_f: 0.5 in hexane:ethyl acetate 2:8) to give **21a** (0.042 g, 62 %) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.30 (s, 1H), 8.94 (d, *J* = 5.9 Hz, 1H), 7.58 (s, *J* = 0.6 Hz, 1H), 6.90 (br s, *J* = 37.7 Hz, 1H), 5.15 (d, *J* = 1.9 Hz, 1H), 4.86 (br s, 1H), 4.46 (tt, *J* = 5.3, 2.6 Hz, 1H), 4.40 – 4.21 (m, 2H), 4.15 (dd, *J* = 12.1, 2.7 Hz, 1H), 3.86 (dd, *J* = 12.1, 5.1 Hz, 1H), 1.88 (dd, *J* = 14.0, 7.0 Hz, 2H), 1.47 (s, 9H), 1.45 (s, 9H), 1.35 - 1.18 (m, 18H), 0.87 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 162.4, 157.5, 152.4, 149.4, 122.6, 83.7,

79.8, 72.1, 62.4, 57.8, 50.6, 32.0, 30.2, 29.7, 29.6, 29.5, 29.4, 29.0, 28.3, 28.1, 26.5, 22.8, 14.2. **HRMS (ESI-TOF)**: Calculated for $C_{28}H_{53}N_6O_6$ $[M+H]^+$: 569.4027, found: 569.4030. **$[\alpha]^{25}_D$** −6.8 (*c* 1, $CHCl_3$).

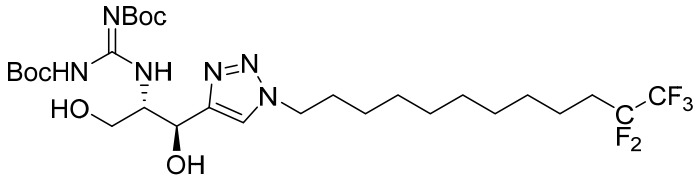
***N,N'*-bis(tert-butoxycarbonyl)-1-((1*S*,2*S*)-2-amino-1-(1-(12,12,12-trifluorododecyl)-1*H*-1,2,3-triazol-4-yl)-1,3-dihydroxypropan-2-yl)guanidine, 21b.**



Compound **19b** (0.040 g, 0.105 mmol) was treated with *N*-*N*'-di-Boc-1*H*-pyrazole-1-carboxiamidine (0.036 g, 0.115 mmol) following the general procedure of guanidination of amine. The reaction crude was purified by flash chromatography (silica gel, hexane:ethyl acetate 4:6→2:8)(R_f: 0.25 in hexane:ethyl acetate 4:6) to give **21b** (0.045 g, 69 %) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.30 (s, 1H), 8.94 (d, *J* = 5.8 Hz, 1H), 7.58 (d, *J* = 0.5 Hz, 1H), 6.95 (br s, 1H), 5.15 (d, *J* = 1.9 Hz, 1H), 4.88 (s, 1H), 4.45 (tt, *J* = 5.2, 2.5 Hz, 1H), 4.34 (dt, *J* = 10.5, 5.3 Hz, 1H), 4.27 (dd, *J* = 13.7, 7.1 Hz, 1H), 4.15 (dd, *J* = 12.2, 2.7 Hz, 1H), 3.85 (dd, *J* = 12.2, 5.2 Hz, 1H), 2.15 - 1.97 (m, 2H), 1.88 (dd, *J* = 14.0, 7.0 Hz, 2H), 1.62 - 1.48 (m, 2H), 1.46 (s, 9H), 1.44 (s, 9H), 1.39 - 1.19 (m, 16H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 162.4, 157.5, 152.4, 149.5, 125.7 (m), 125.5, 83.8, 82.5, 79.8, 72.1, 62.5, 57.8, 50.6, 33.6 (dd, *J* = 56.6, 28.4 Hz), 30.2, 29.5, 29.4, 29.3, 29.2, 29.1, 28.8, 28.3, 28.1, 26.5, 21.9 (q, *J* = 2.8 Hz). **^{19}F NMR (377 MHz, $CDCl_3$)** δ -66.42 (t, *J* = 11.0 Hz). **HRMS (ESI-TOF)**: Calculated for $C_{28}H_{50}F_3N_6O_6$ $[M+H]^+$: 623.3744, found: 623.3730. **$[\alpha]^{25}_D$** −4.8 (*c* 1, $CHCl_3$).

***N,N'*-bis(*tert*-butoxycarbonyl)-1-((1*S*,2*S*)-2-amino-1-(1-(11,11,12,12,12-pentafluorododecyl)-1*H*-1,2,3-triazol-4-yl)-1,3-dihydroxypropan-2-yl)guanidine, 21c.**

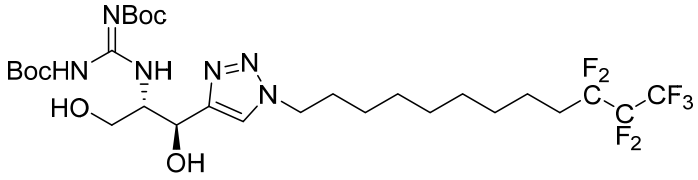


Compound **19c** (0.046 g, 0.110 mmol) was treated with *N*-*N*'-di-Boc-1*H*-pyrazole-1-carboxiamidine (0.038 g, 0.121 mmol) following the general procedure of guanidination of amine. The reaction crude was purified by flash chromatography (silica gel, hexane:ethyl acetate 4:6→2:8)(R_f: 0.14 in hexane:ethyl acetate 4:6) to give **21c** (0.047 g, 61 %) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.30 (s, 1H), 8.96 (d, *J* = 5.7 Hz, 1H), 7.58 (s, *J* = 24.3 Hz, 1H), 7.00 (br s, 1H), 5.16 (d, *J* = 1.8 Hz, 1H), 4.88 (br s, 1H), 4.46 (tt, *J* = 5.2, 2.5 Hz, 1H), 4.42 - 4.24 (m, 2H), 4.18 (dd, *J* = 12.2, 2.4 Hz, 1H), 3.87 (br d, *J* = 9.7 Hz, 1H), 2.08 - 1.92 (m, 2H), 1.92 - 1.82 (m, 2H), 1.64 - 1.49 (m, 2H), 1.47 (s, 9H), 1.45 (s, 9H), 1.40 - 1.20 (m,

14H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 157.4, 152.2, 149.4, 122.5, 83.6, 79.7, 72.1, 62.3, 57.7, 50.5, 30.6 (t, *J* = 22.0 Hz), 30.1, 29.2, 29.1, 29.0, 28.9, 28.1, 28.0, 26.4, 20.2 (t, *J* = 3.6 Hz). **^{19}F NMR (377 MHz, $CDCl_3$)** δ -85.45 (d, *J* = 5.0 Hz), -118.31 (t, *J* = 18.4 Hz). **HRMS (ESI-TOF)**: Calculated for $C_{28}H_{48}F_5N_6O_6$ $[M+H]^+$: 659.3555, found: 659.3559. **$[\alpha]^{25}_D$** −3.8 (*c* 1, $CHCl_3$).

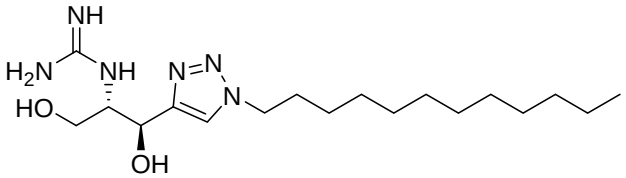
***N,N'*-bis(*tert*-butoxycarbonyl)-1-((1*S*,2*S*)-2-amino-1-(1-(10,10,11,11,12,12,12-heptafluorododecyl)-1*H*-1,2,3-triazol-4-yl)-1,3-dihydroxypropan-2-yl)guanidine, 21d.**



Compound **19d** (0.085 g, 0.188 mmol) was treated with *N*-*N*'-di-Boc-1*H*-pyrazole-1-carboxiamidine (0.064 g, 0.206 mmol) following the general procedure of guanidination of amines. The reaction crude was purified by flash chromatography (silica gel, hexane:ethyl acetate 4:6→2:8)(R_f: 0.26 in hexane:ethyl acetate 4:6) to give **21d** (0.076 g, 59 %) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.30 (s, 1H), 8.94 (d, *J* = 5.8 Hz, 1H), 7.58 (d, *J* = 0.4 Hz, 1H), 6.93 (br, 1H), 5.15 (d, *J* = 1.9 Hz, 1H), 4.85 (br, 1H), 4.46 (dq, *J* = 8.0, 2.5 Hz, 1H), 4.41 - 4.23 (m, 2H), 4.15 (dd, *J* = 12.1, 2.6 Hz, 1H), 3.86 (d, *J* = 7.9 Hz, 1H), 2.13 - 1.92 (m, 2H), 1.89 (dd, *J* = 13.8, 6.8 Hz, 2H), 1.67 - 1.50 (m, 2H), 1.47 (s, 9H), 1.45 (s, 9H), 1.39 - 1.19 (m, 12H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 162.4, 157.5, 152.4, 149.5, 122.6, 83.7, 79.9, 72.1, 62.5, 57.9, 50.6, 30.7 (t, *J* = 22.0 Hz), 30.3, 29.2, 29.1, 29.0, 28.3, 28.1, 26.5, 20.1 (t, *J* = 3.7 Hz, (t, *J* = 3.7 Hz). **^{19}F NMR (377 MHz, $CDCl_3$)** δ −80.64 (t, *J* = 9.7 Hz), −115.32 - −115.56 (m), −127.73 - −128.02 (m). **HRMS (ESI-TOF)**: Calculated for $C_{28}H_{45}F_7N_6O_6$ $[M+H]^+$: 695.3367, found 695.3366. **$[\alpha]^{25}_D$** −5.8 (*c* 1, $CHCl_3$).

1-((1*S*,2*S*)-1-(1-dodecyl-1*H*-1,2,3-triazol-4-yl)-1,3-dihydroxypropan-2-yl)guanidine, 22a.

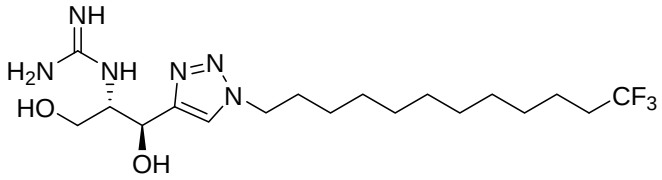


Compound **21a** (0.042 g, 0.073 mmol) was treated with TFA (0.25 ml) following the general procedure of deprotection of Boc. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 8:2:0.2)(R_f: 0.5 in $CHCl_3$:MeOH:NH_4OH 8:2:0.1) to give **22a** (0.011 g, 40 %).

^{1}H NMR (400 MHz,CD_3OD) δ 7.99 (s, 1H), 5.01 (d, *J* = 5.4 Hz, 1H), 4.40 (t, *J* = 7.1 Hz, 2H), 3.95 (dd, *J* = 11.4, 5.0 Hz, 1H), 3.78 - 3.65 (m, 2H), 1.99 - 1.83 (m, 2H), 1.40 - 1.18 (m, 18H), 0.90 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, CD_3OD)** δ 159.4, 149.3, 124.4, 67.5, 61.8, 60.2, 51.4, 33.0, 31.3, 30.8, 30.7, 30.6, 30.5, 30.4, 30.1, 27.5, 23.7, 14.5. **HRMS (ESI-**

TOF): Calculated for $C_{18}H_{37}N_6O_2$ $[M+H]^+$: 368.2978, found, 368.2978. **$[\alpha]^{25}_D$** −2.14 (*c* 0.98, MeOH).

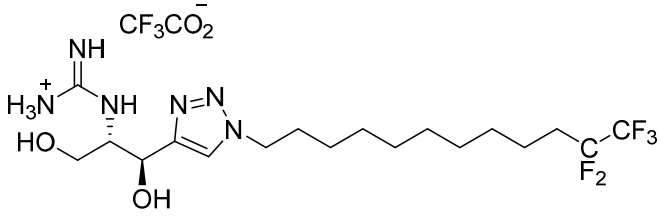
1-((1*S*,2*S*)-1,3-dihydroxy-1-(1-(12,12,12-trifluorododecyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)guanidine, 22b.



Compound **21b** (0.045 g, 0.072 mmol) was treated with TFA (0.23 ml) following the general procedure of deprotection of Boc. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 8:2:0.2) (R_f: 0.4 in $CHCl_3$:MeOH:NH_4OH 8:2:0.1) to give **22b** (0.013 g, 42 %).

^{1}H NMR (401 MHz, CD_3OD) δ 7.93 (s, 1H), 4.99 (d, *J* = 5.5 Hz, 1H), 4.40 (t, *J* = 7.1 Hz, 2H), 3.73 (dd, *J* = 10.6, 3.6 Hz, 1H), 3.69 (dd, *J* = 10.7, 5.7 Hz, 1H), 2.22 - 2.03 (m, 2H), 1.90 (dd, *J* = 14.4, 7.3 Hz, 2H), 1.62 - 1.46 (m, 2H), 1.30 (m, 14H). **^{13}C NMR (101 MHz, CD_3OD)** δ 163.3 (m, $CF_3\underline{C}O_2$-), 159.3, 149.3, 127.5 (m), 124.2, 121.3 (m, $\underline{C}F_3CO_2$-), 67.4, 61.8, 60.0, 51.4, 34.3 (q, *J* = 28.2 Hz), 31.3, 30.6, 30.5, 30.4, 30.3, 30.1, 29.8, 27.4, 23.0 (q, *J* = 3.0 Hz). **^{19}F NMR (377 MHz, CD_3OD)** δ -68.04 (t, *J* = 11.2 Hz), -75.82 – -77.93 (m) residual CF_3CO_2H. **HRMS (ESI-TOF)**: Calculated for $C_{18}H_{34}F_3N_6O_2$ $[M+H]^+$: 423.2695, found, 423.2694. **$[\alpha]^{25}_D$** −1.9 (*c* 1.3, MeOH).

1-((1*S*,2*S*)-1,3-dihydroxy-1-(1-(11,11,12,12,12-pentafluorododecyl)-1*H*-1,2,3-triazol-4-yl)propan-2-yl)guanidine, 22c.

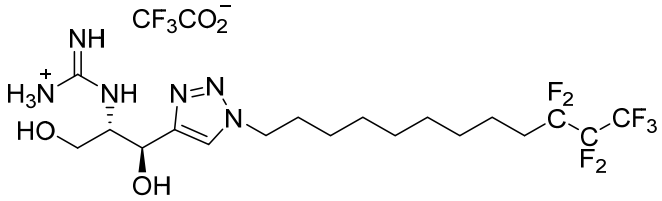


Compound **21c** (0.024 g, 0.036 mmol) was treated with TFA (0.1 ml) following the general procedure of deprotection of Boc. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 8:2:0.2)(R_f: 0.4 in $CHCl_3$:MeOH:NH_4OH 8:2:0.1) to give **22c** (0.008 g, 48 %).

^{1}H NMR (401 MHz, CD_3OD) δ 7.95 (s, 1H), 4.99 (d, *J* = 5.3 Hz, 1H), 4.40 (t, *J* = 7.1 Hz, 2H), 3.93 (dd, *J* = 10.9, 5.4 Hz, 1H), 3.72 – 3.68 (m, 2H), 2.17 - 2.00 (m, 2H), 1.95 - 1.85 (m, 2H), 1.64 - 1.52 (m, 2H), 1.45 - 1.25 (m, 12H). **^{13}C NMR (100 MHz, CD_3OD)** δ 157.9, 148.0, 122.8, 66.0, 60.3, 58.6, 49.9, 29.9, 29.4, 29.0, 28.9, 28.8, 28.7, 28.6, 26.0, 20.0. **^{19}F NMR (377 MHz, CD_3OD)** δ -87.06 (s, *J* = 12.1 Hz), -119.53 (t, *J* = 18.8 Hz). **HRMS (ESI-**

TOF): Calculated for $C_{18}H_{32}F_5N_6O_2$ $[M+H]^+$: 459.2501, found, 459.2504. **$[\alpha]^{25}_D$** −1.6 (*c* 0.8, MeOH).

1-((1*S*,2*S*)-1-(1-(10,10,11,11,12,12,12-heptafluorododecyl)-1*H*-1,2,3-triazol-4-yl)-1,3-dihydroxypropan-2-yl)guanidine, 22d.

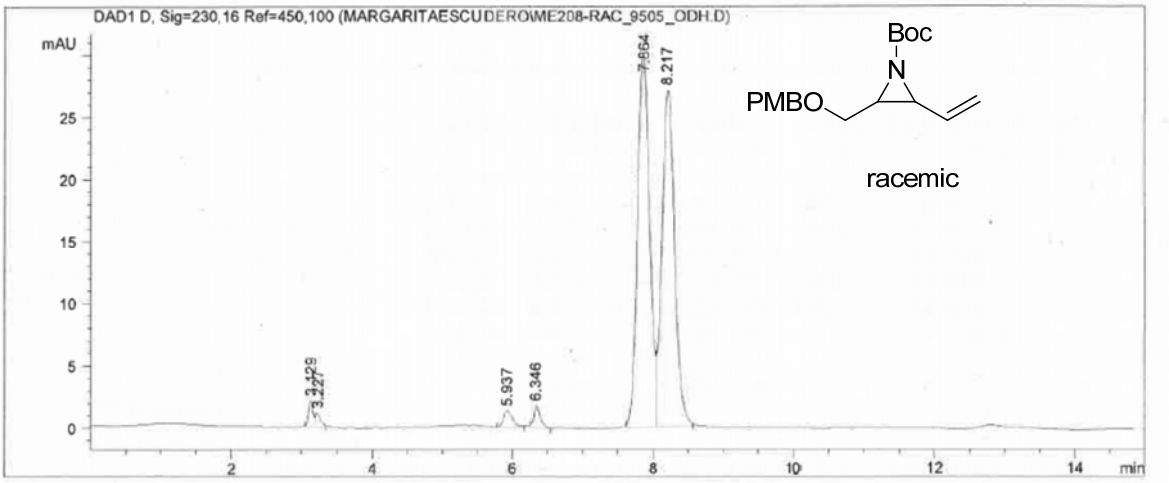


Compound **21d** (0.033 g, 0.073 mmol) was treated with TFA (0.25 ml) following the general procedure of deprotection of Boc. The reaction crude was purified by flash chromatography (silica gel, $CHCl_3$:MeOH:NH_4OH 8:2:0.2) (R_f: 0.5 in $CHCl_3$:MeOH:NH_4OH 8:2:0.1) to give **22d** (0.019 g, 43 %).

^{1}H NMR (400 MHz, CD_3OD) δ 7.93 (s, 1H), 4.99 (d, *J* = 5.4 Hz, 1H), 4.41 (t, *J* = 7.1 Hz, 2H), 3.99 - 3.87 (m, 1H), 3.72 (dd, *J* = 9.6, 2.8 Hz, 1H), 3.69 (dd, *J* = 9.7, 4.6 Hz, 1H), 2.23 - 2.03 (m, 2H), 1.97 - 1.85 (m, 2H), 1.66 - 1.53 (m, 2H), 1.48 - 1.24 (m, 10H). ^{13}C NMR (101 MHz, CD_3OD) δ 157.9, 148.0, 122.8, 66.0, 60.2, 58.5, 49.9, 30.0 (t, *J* = 22.3 Hz), 29.9, 28.9, 28.8, 28.6, 28.5, 26.0, 19.8 (t, *J* = 3.6 Hz). **^{19}F NMR (377 MHz, CD_3OD)** δ −77.00 (s), −82.28 (t, *J* = 9.9 Hz), −115.33 - −117.53 (m), −127.35 - −131.59 (m). **HRMS (ESI-TOF)**: Calculated for $C_{18}H_{30}F_7N_6O_2$ $[M+H]^+$: 495.2313, found, 495.2316. **$[\alpha]^{25}_D$** −4 (*c* 1,1, MeOH).

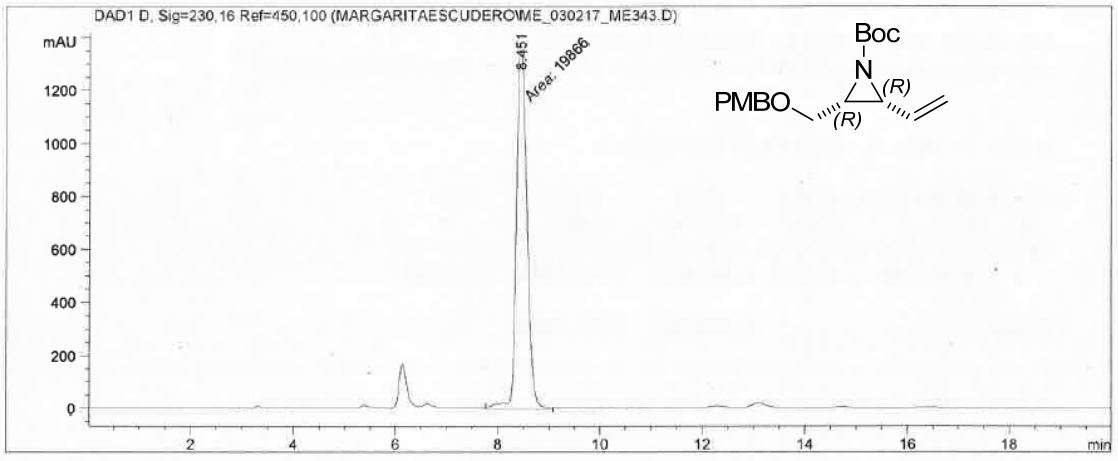
Daicel Chiralcel OD-H, *n-hexane-^{i}PrOH* 95:5, flow = 1 mL/min, detection, uv 230 nm; t_r (major enantiomer) = 8.4 min, t_r (minor enantiomer) = 7.8 min. (2*R*,3*R*)-*tert*-butyl 2-(((4-methoxybenzyl)oxy)methyl)-3-vinylaziridine-1-carboxylate, **23**.

Racemic



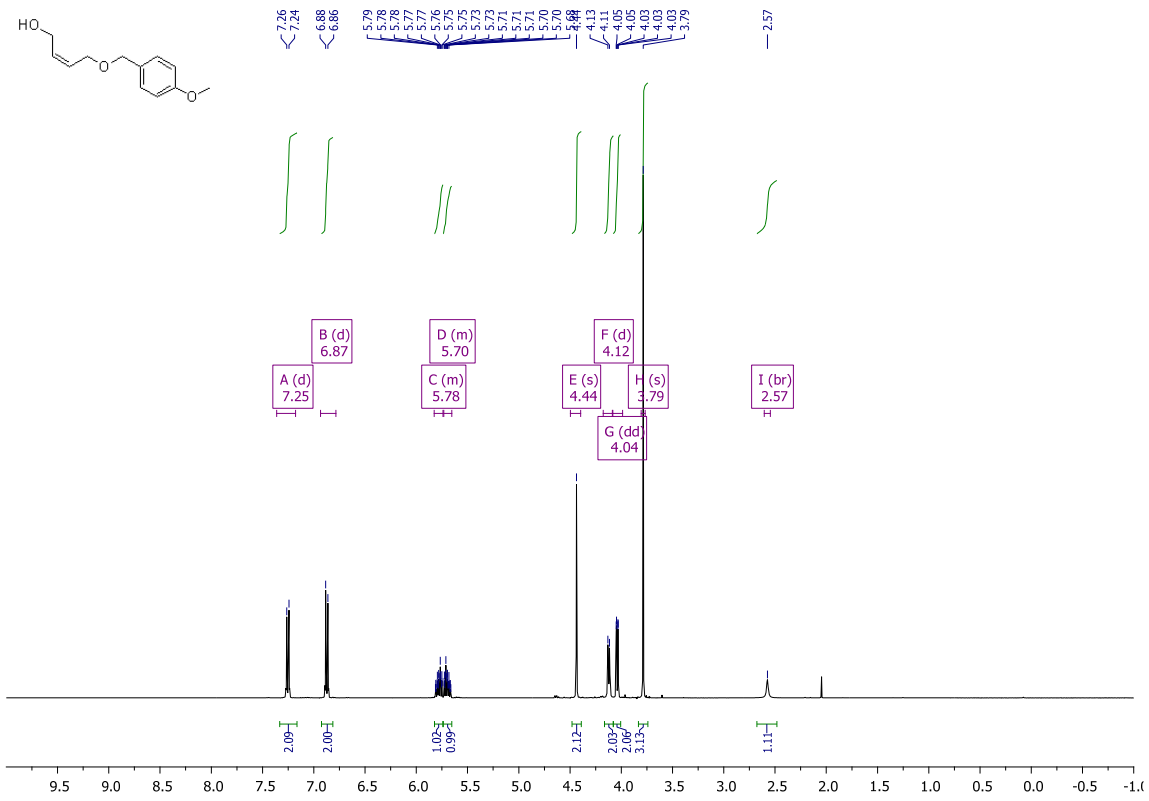
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
5	7.864	BV	0.1821	357.96536	30.23223	48.3379
6	8.217	VB	0.1936	343.25415	27.13866	46.3513

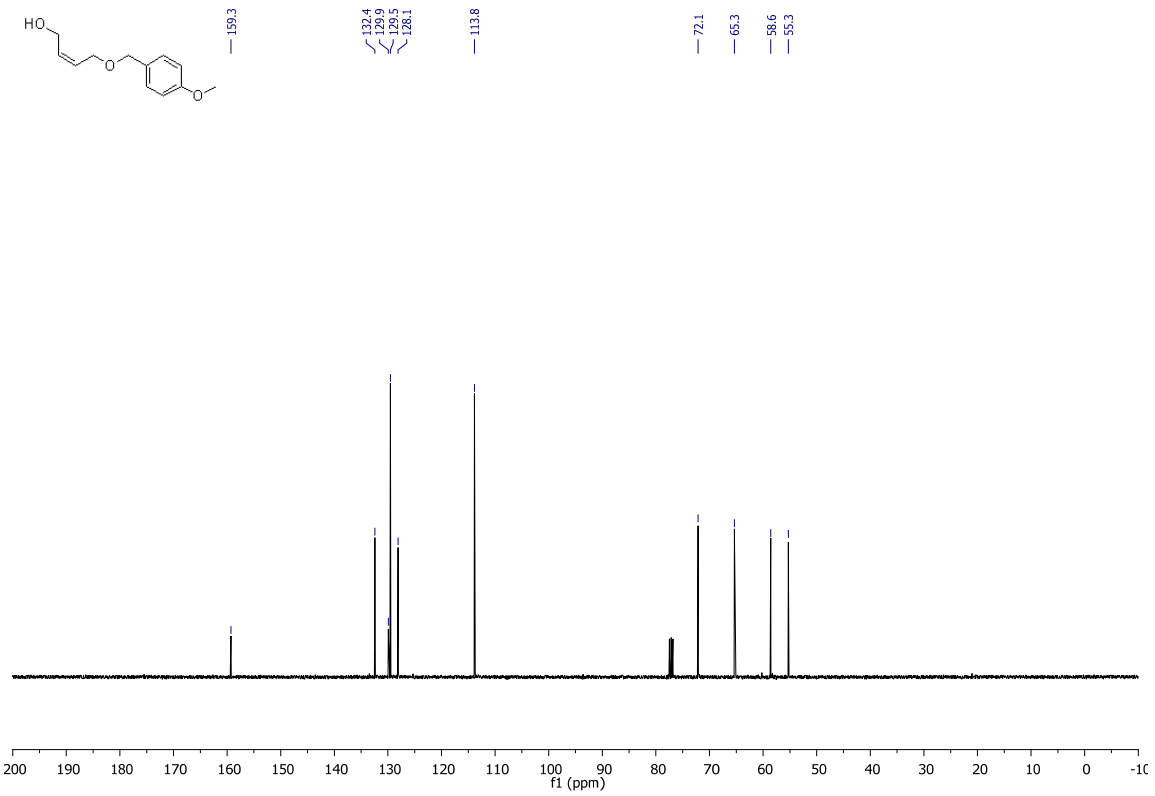
(2*R*,3*R*)-*tert*-butyl 2-(((4-methoxybenzyl)oxy)methyl)-3-vinylaziridine-1-carboxylate, **23**.

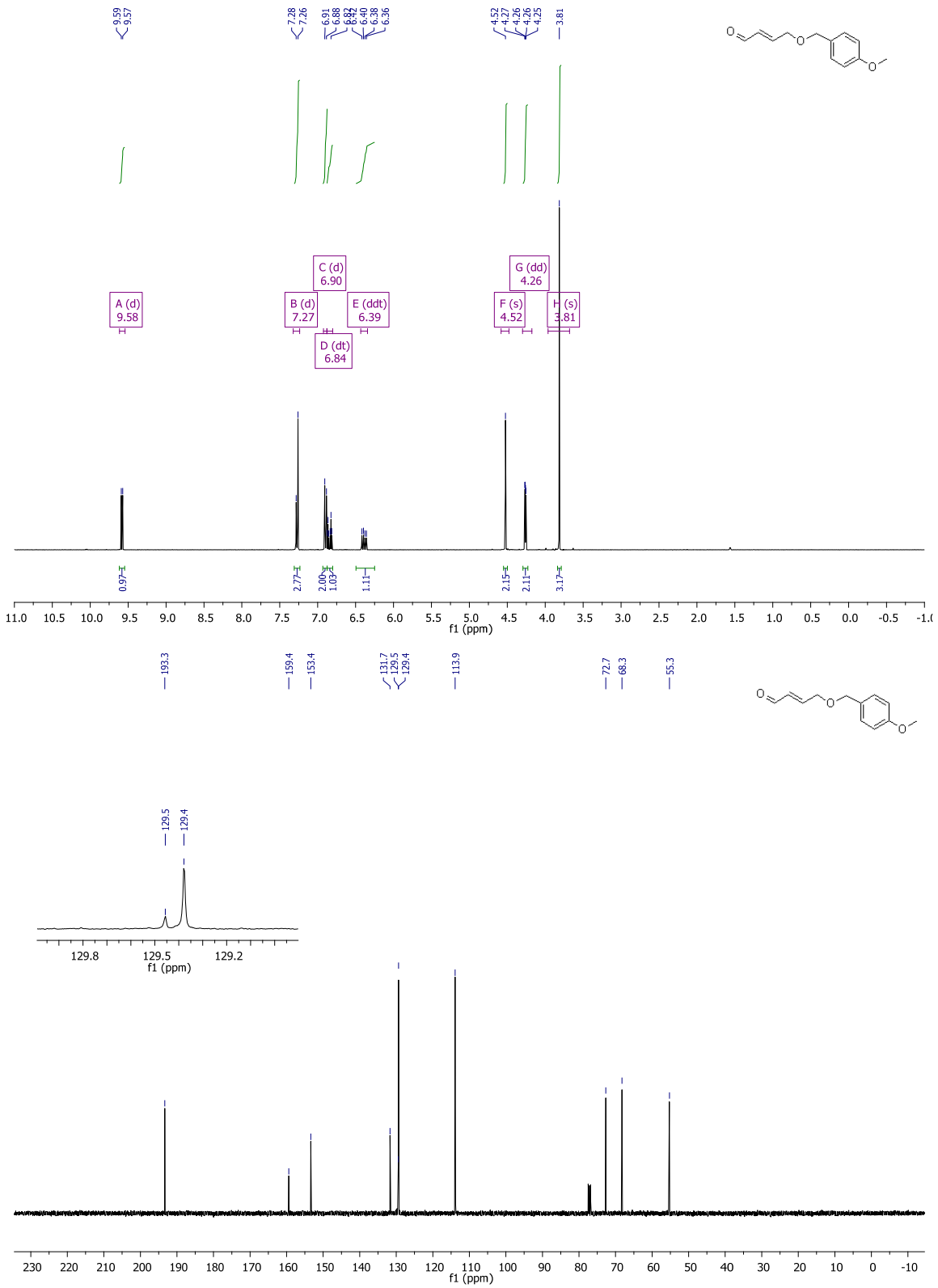


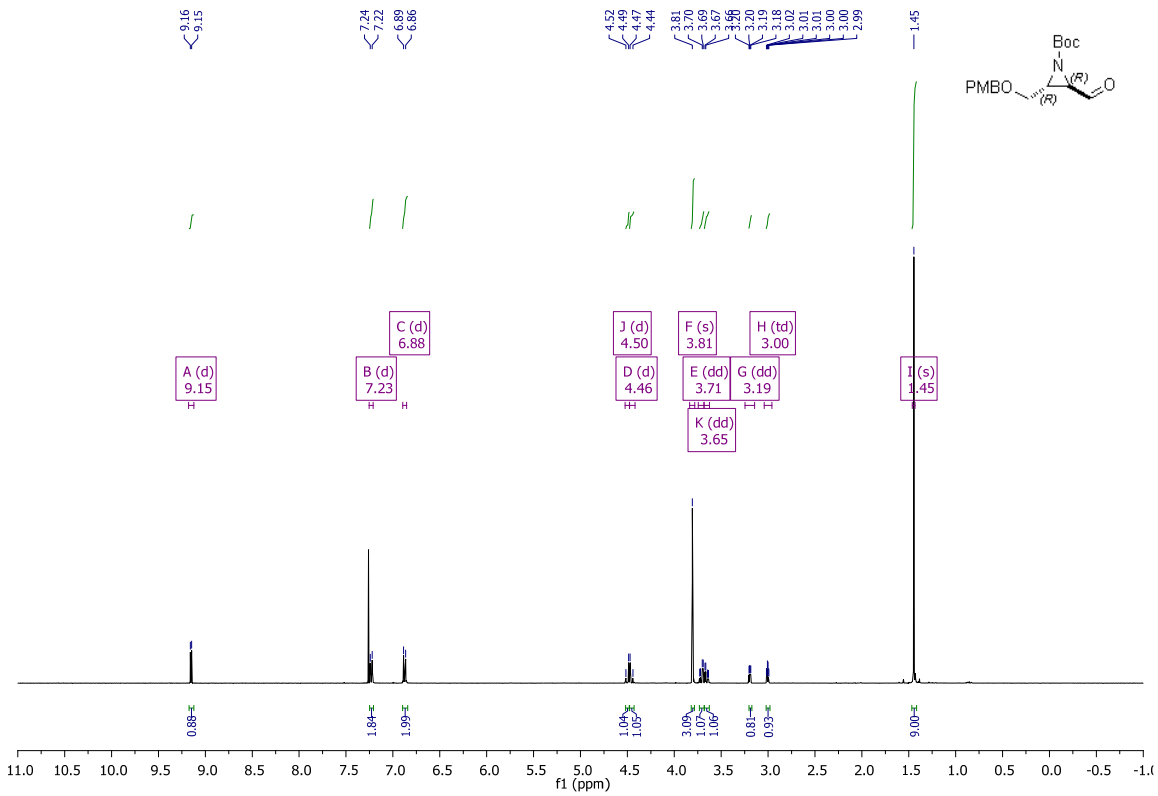
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.451	MM	0.2441	1.98660e4	1356.39868	100.0000

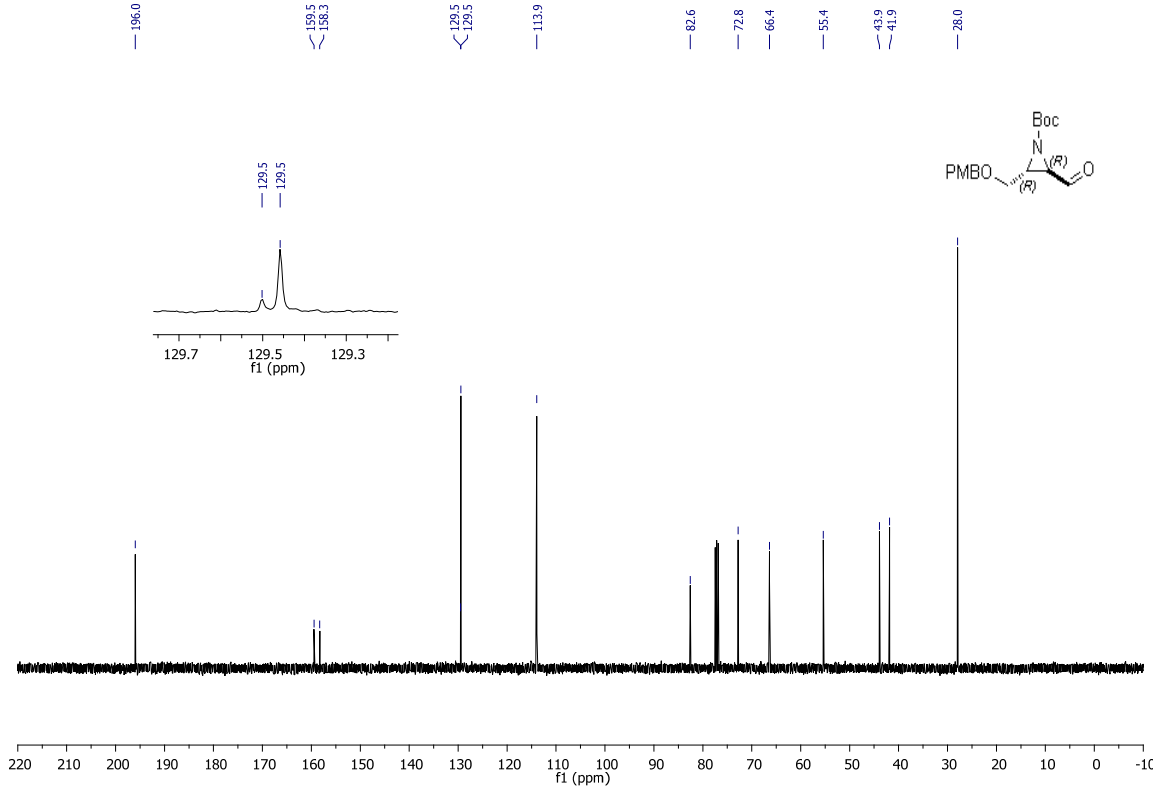
4. ^{1}H, ^{13}C and ^{19}F NMR spectra

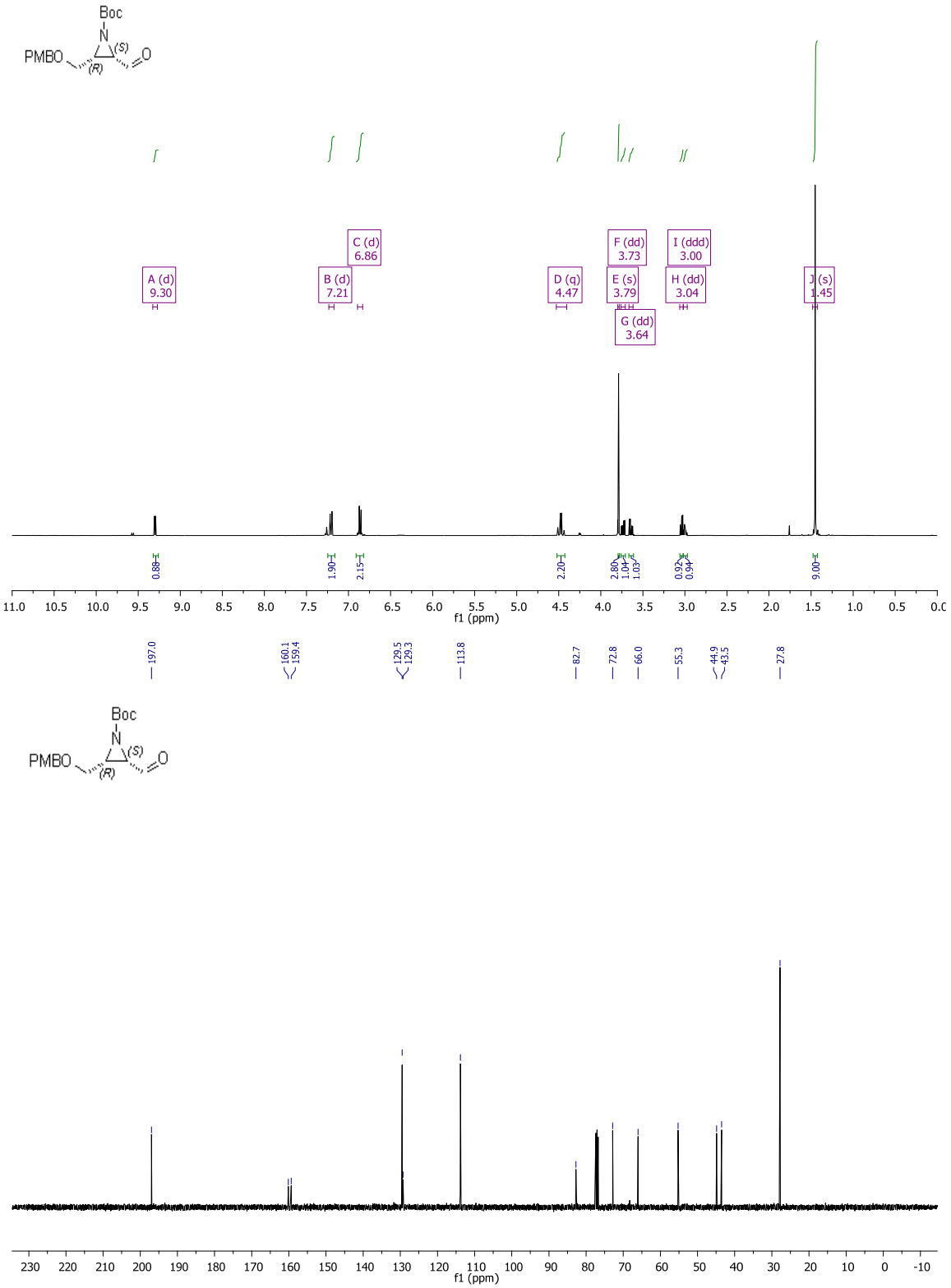

HO
O
O
7.26
7.24
6.88
6.86
5.79
5.78
5.78
5.77
5.77
5.76
5.75
5.75
5.73
5.73
5.71
5.71
5.71
5.70
5.70
4.44
4.13
4.11
4.05
4.05
4.03
4.03
4.03
3.79
2.57
A (d)
7.25
B (d)
6.87
C (m)
5.78
D (m)
5.70
E (s)
4.44
F (d)
4.12
G (dd)
4.04
H (s)
3.79
I (br)
2.57
2.09
2.00
1.02
0.99
2.12
2.03
2.06
3.13
1.11
9.5
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

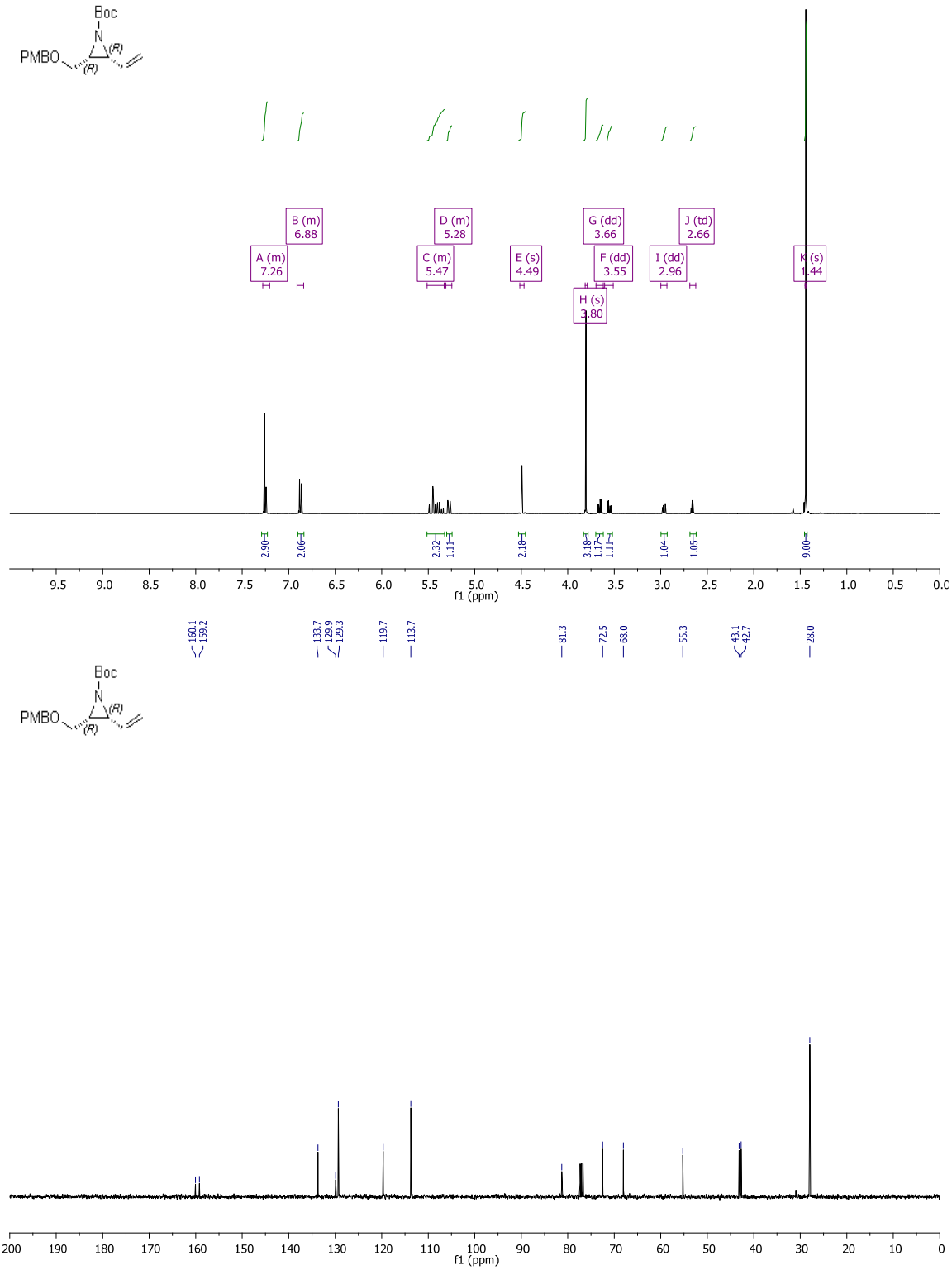

HO
O
O
159.3
132.4
129.9
129.5
128.1
113.8
72.1
65.3
58.6
55.3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

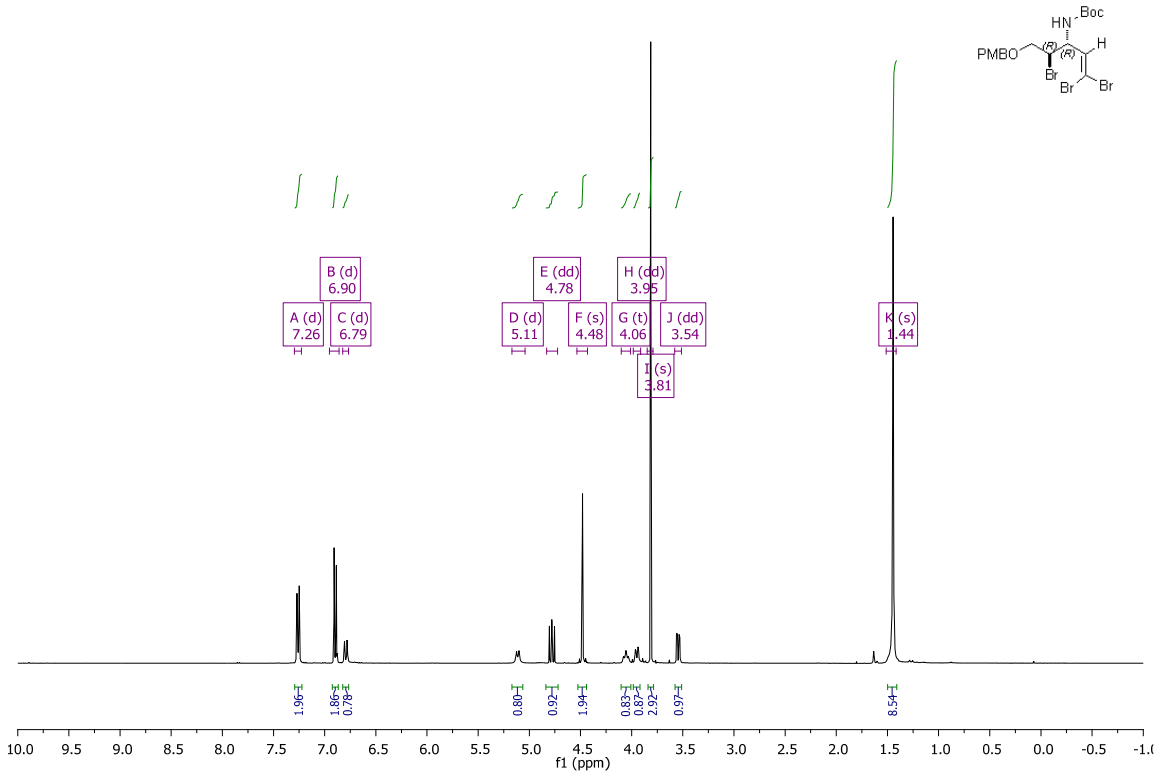

9.59
9.57
7.28
7.26
6.91
6.88
6.42
6.40
6.38
6.36
4.52
4.27
4.26
4.26
4.25
3.81
A (d)
9.58
B (d)
7.27
C (d)
6.90
D (dt)
6.84
E (ddt)
6.39
F (s)
4.52
G (dd)
4.26
H (s)
3.81
0.97
2.77
2.00
1.03
1.11
2.15
2.11
3.17
f1 (ppm)
193.3
159.4
153.4
131.7
129.5
129.4
113.9
72.7
68.3
55.3
129.5
129.4
129.8
129.5
129.2
f1 (ppm)
f1 (ppm)

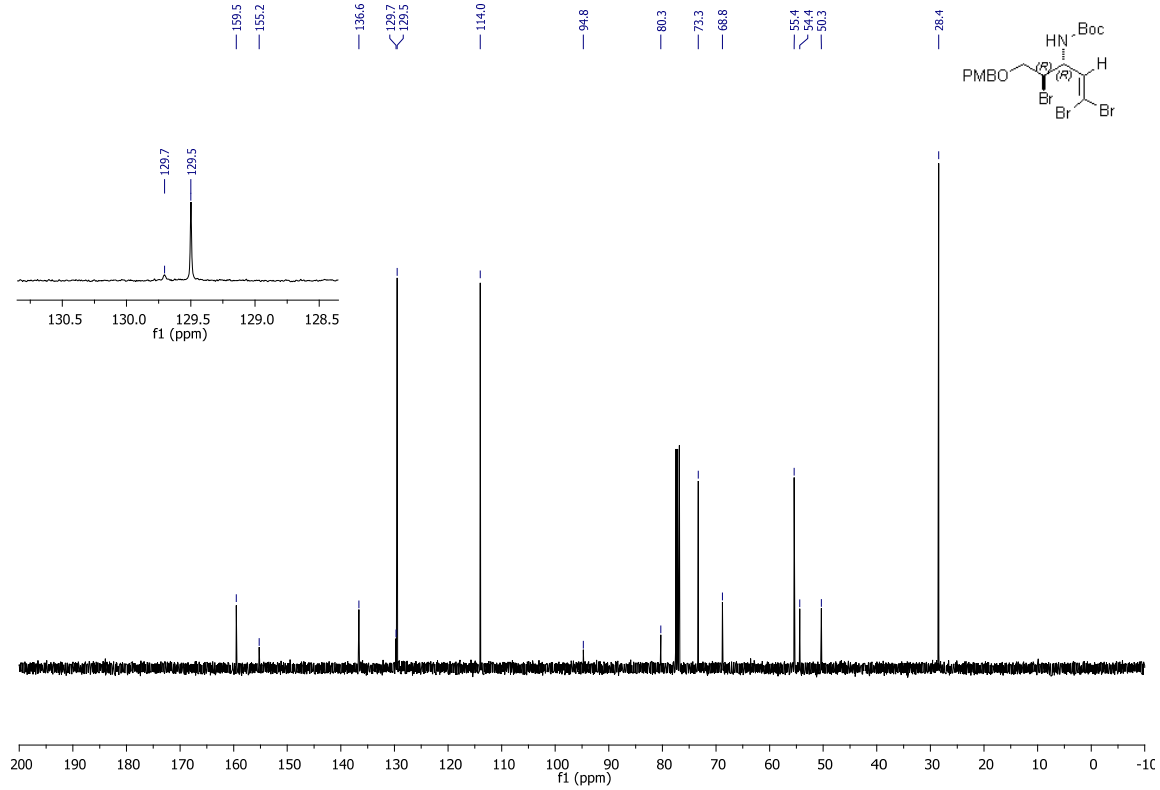

Boc
N
PMBO
(R)
(R)
O
A (d) 9.15
B (d) 7.23
C (d) 6.88
D (d) 4.46
E (dd) 3.71
F (s) 3.81
G (dd) 3.19
H (td) 3.00
I (s) 1.45
J (d) 4.50
K (dd) 3.65
f1 (ppm)

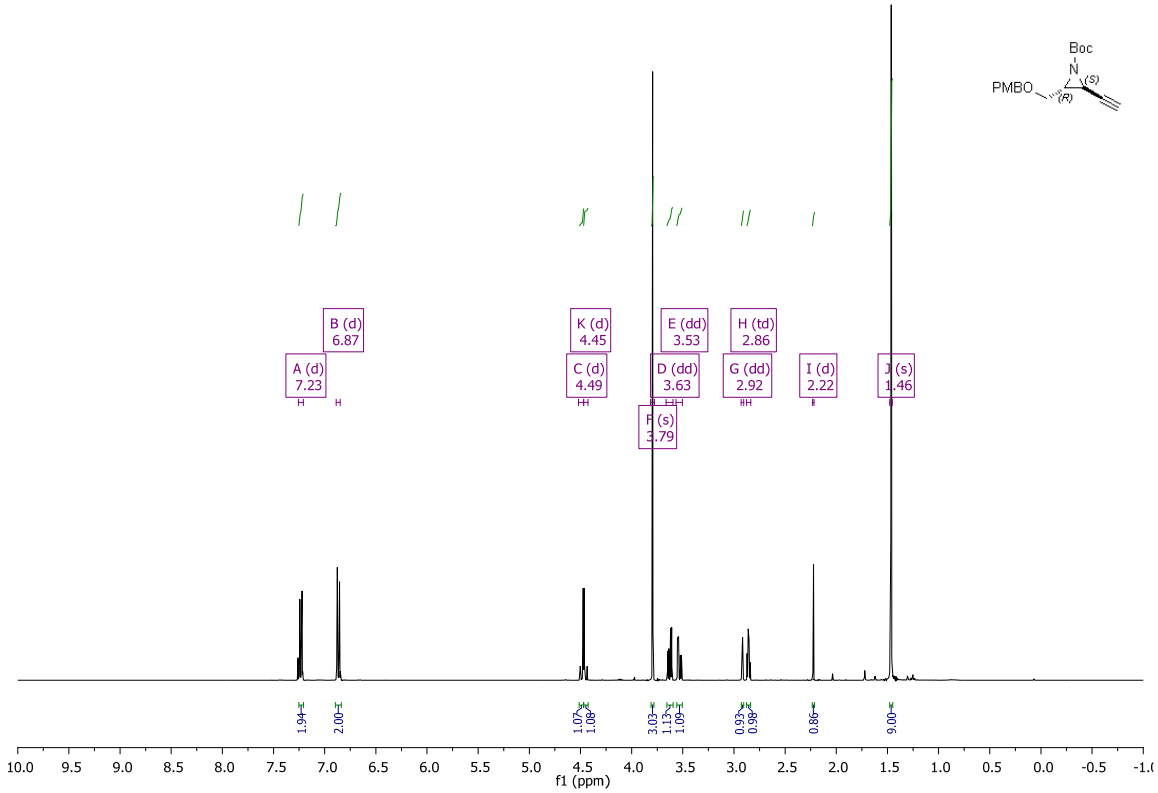

Boc
N
PMBO
(R)
(R)
O
129.7
129.5
129.3
f1 (ppm)
f1 (ppm)

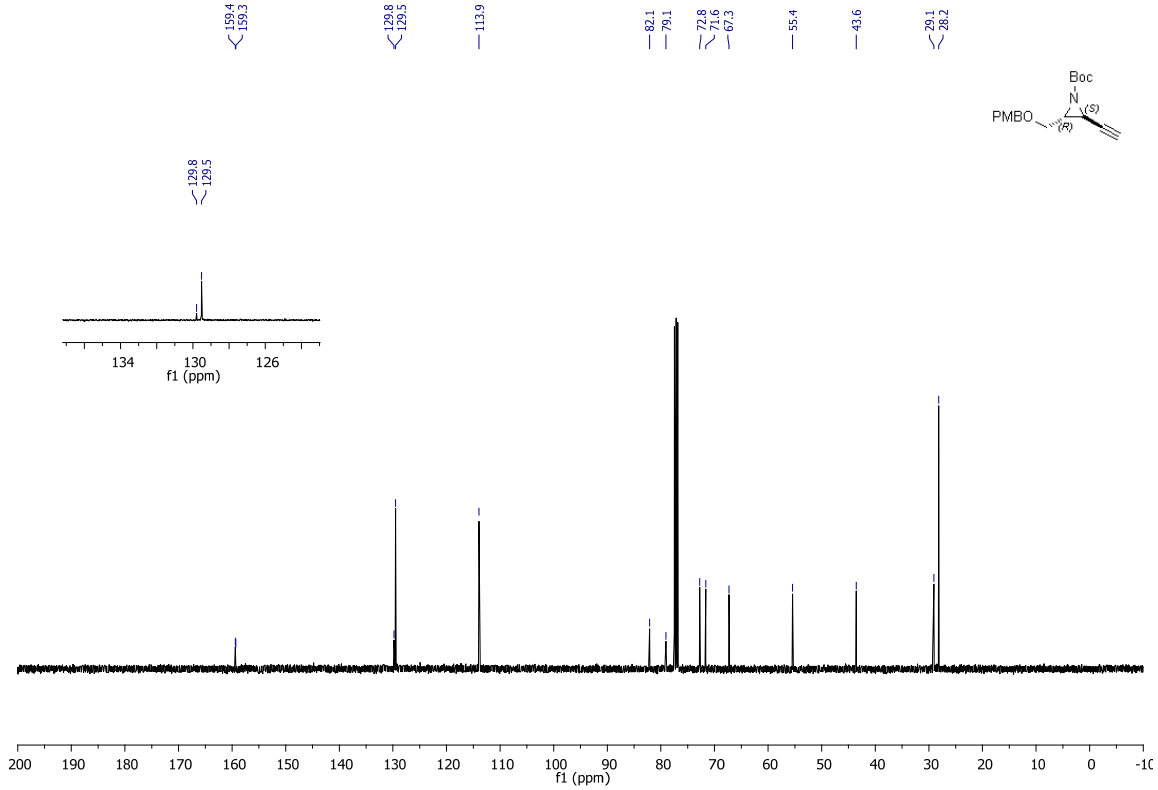

Boc
N
PMBO
(S)
(R)
O
A (d) 9.30
B (d) 7.21
C (d) 6.86
D (q) 4.47
E (s) 3.79
F (dd) 3.73
G (dd) 3.64
H (dd) 3.04
I (ddd) 3.00
J (s) 1.45
0.88
1.90
2.15
2.20
2.80
1.04
1.03
0.92
0.94
9.00
f1 (ppm)
197.0
160.1
159.4
129.5
129.3
113.8
82.7
72.8
66.0
55.3
44.9
43.5
27.8
f1 (ppm)

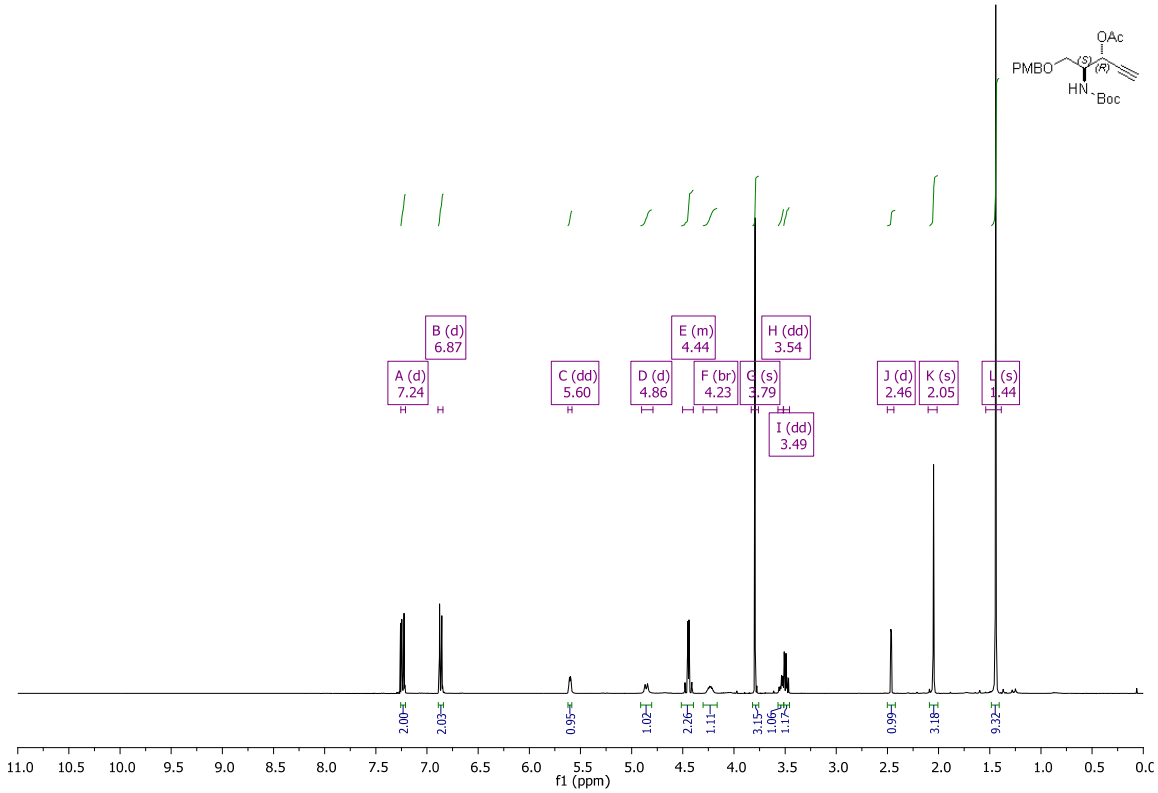

Boc
N
PMBO
(R)
(R)
A (m) 7.26
B (m) 6.88
C (m) 5.47
D (m) 5.28
E (s) 4.49
F (dd) 3.55
G (dd) 3.66
H (s) 3.80
I (dd) 2.96
J (td) 2.66
K (s) 1.44
2.90
2.06
2.32
1.11
2.18
3.18
1.17
1.11
1.04
1.05
9.00
f1 (ppm)
160.1
159.2
133.7
129.9
129.3
119.7
113.7
81.3
72.5
68.0
55.3
43.1
42.7
28.0
f1 (ppm)

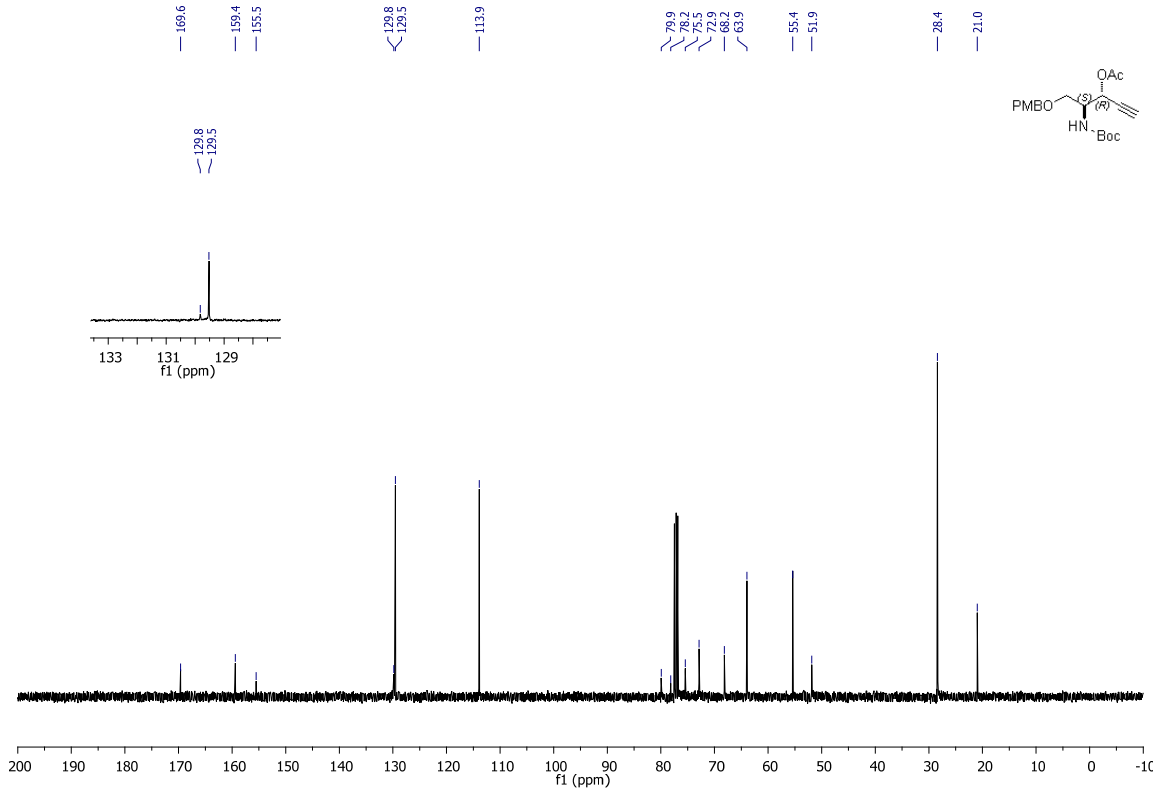

A (d) 7.26
B (d) 6.90
C (d) 6.79
D (d) 5.11
E (dd) 4.78
F (s) 4.48
G (t) 4.06
H (dd) 3.95
I (s) 3.81
J (dd) 3.54
K (s) 1.44
f1 (ppm)

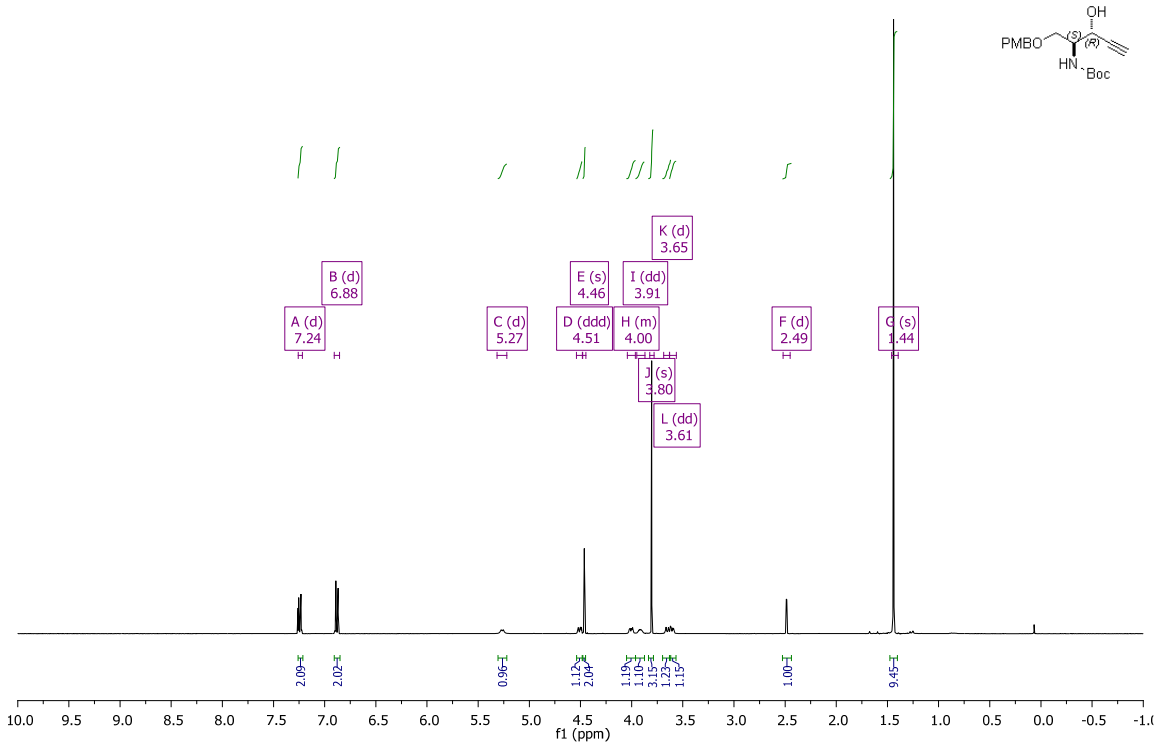

159.5
155.2
136.6
129.7
129.5
114.0
94.8
80.3
73.3
68.8
55.4
54.4
50.3
28.4
f1 (ppm)

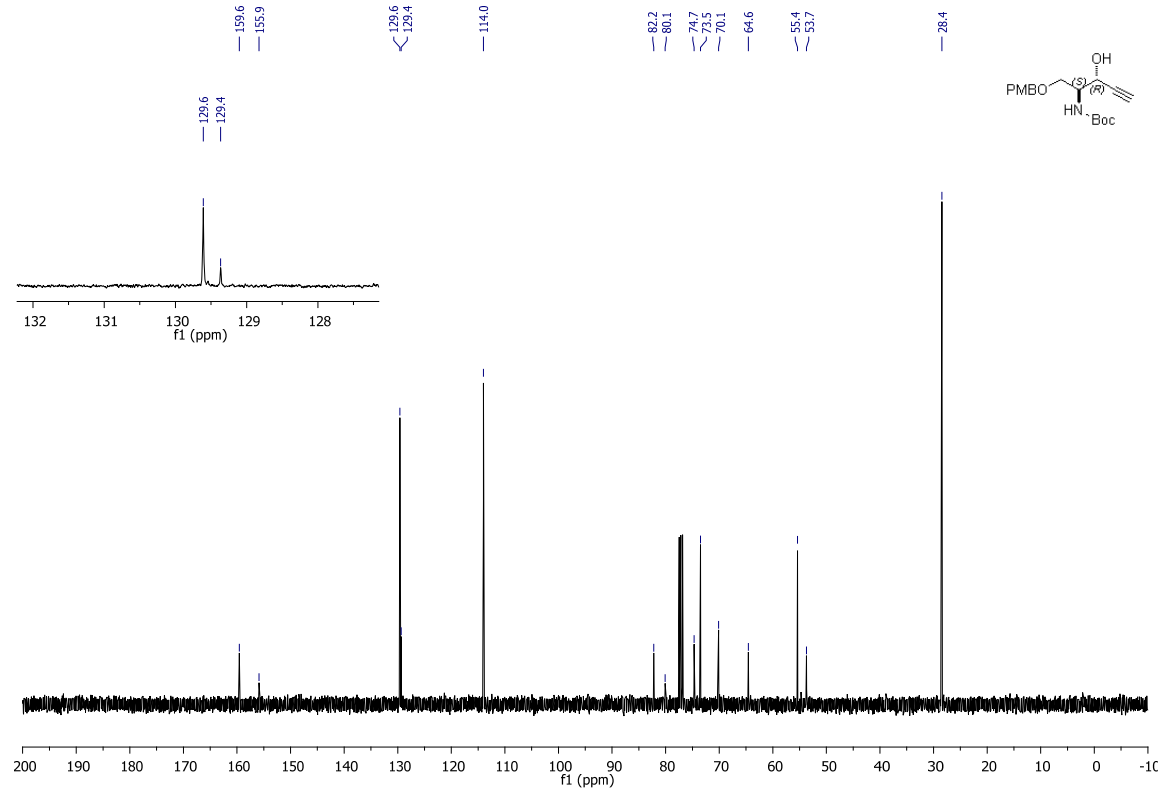

Boc
N
PMBO
(S)
(R)
A (d) 7.23
B (d) 6.87
C (d) 4.49
K (d) 4.45
D (dd) 3.63
E (dd) 3.53
F (s) 3.79
G (dd) 2.92
H (td) 2.86
I (d) 2.22
J (s) 1.46
f1 (ppm)


159.4
159.3
129.8
129.5
113.9
82.1
79.1
72.8
71.6
67.3
55.4
43.6
29.1
28.2
Boc
N
PMBO
(S)
(R)
129.8
129.5
134
130
126
f1 (ppm)
f1 (ppm)

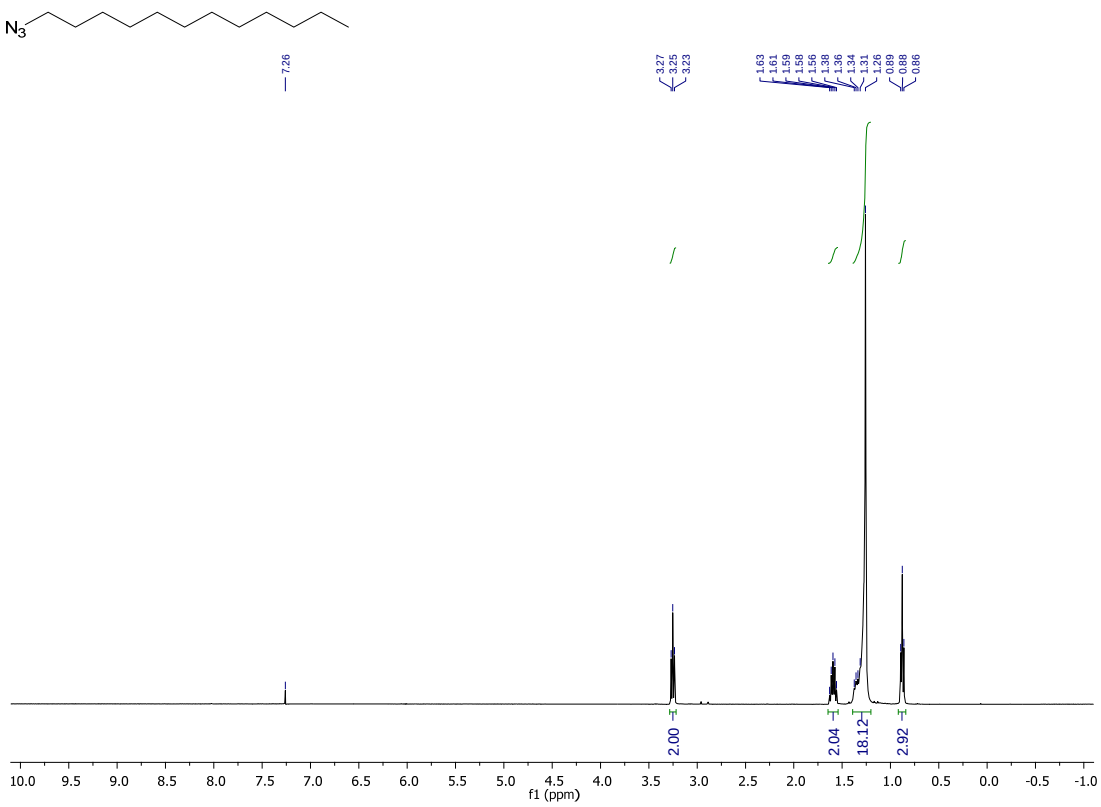

OAc
PMBO
(S)
(R)
HN
Boc
A (d) 7.24
B (d) 6.87
C (dd) 5.60
D (d) 4.86
E (m) 4.44
F (br) 4.23
G (s) 3.79
H (dd) 3.54
I (dd) 3.49
J (d) 2.46
K (s) 2.05
L (s) 1.44
2.00
2.03
0.95
1.02
2.26
1.11
3.15
1.06
1.17
0.99
3.18
9.32
f1 (ppm)


169.6
159.4
155.5
129.8
129.5
113.9
79.9
78.2
75.5
72.9
68.2
63.9
55.4
51.9
28.4
21.0
OAc
PMBO
(S)
(R)
HN
Boc
129.8
129.5
133
131
129
f1 (ppm)
f1 (ppm)

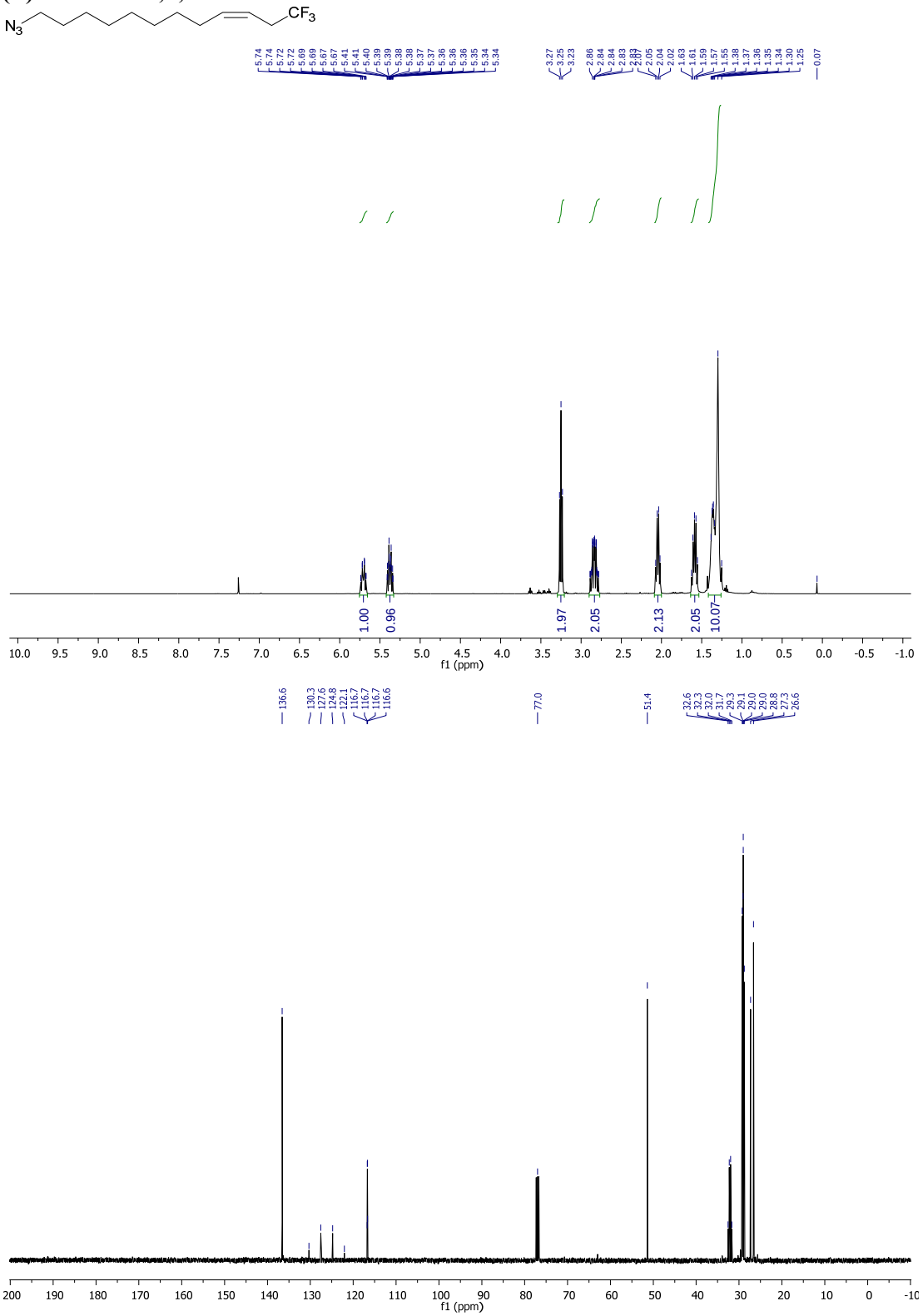

OH
PMBO
(S)
(R)
HN
Boc
A (d) 7.24
B (d) 6.88
C (d) 5.27
D (ddd) 4.51
E (s) 4.46
H (m) 4.00
I (dd) 3.91
K (d) 3.65
J (s) 3.80
L (dd) 3.61
F (d) 2.49
G (s) 1.44
f1 (ppm)

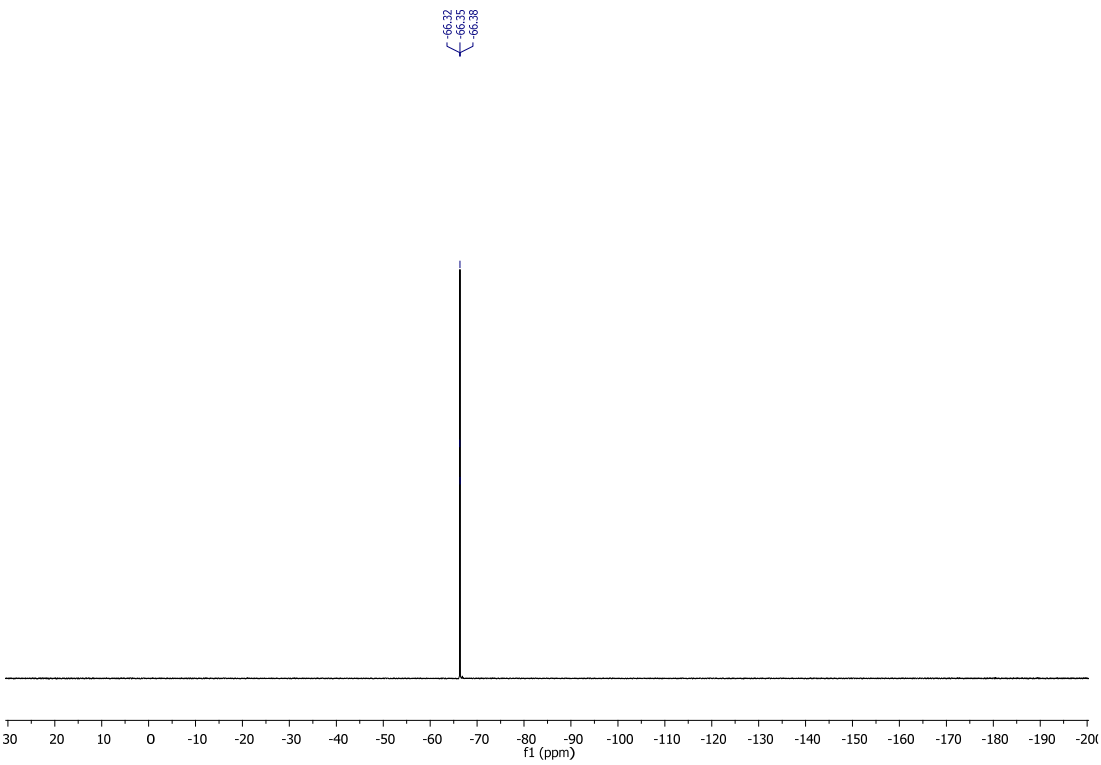

159.6
155.9
129.6
129.4
114.0
82.2
80.1
74.7
73.5
70.1
64.6
55.4
53.7
28.4
OH
PMBO
(S)
(R)
HN
Boc
f1 (ppm)
f1 (ppm)

1-azidododecane

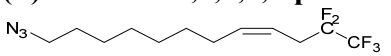


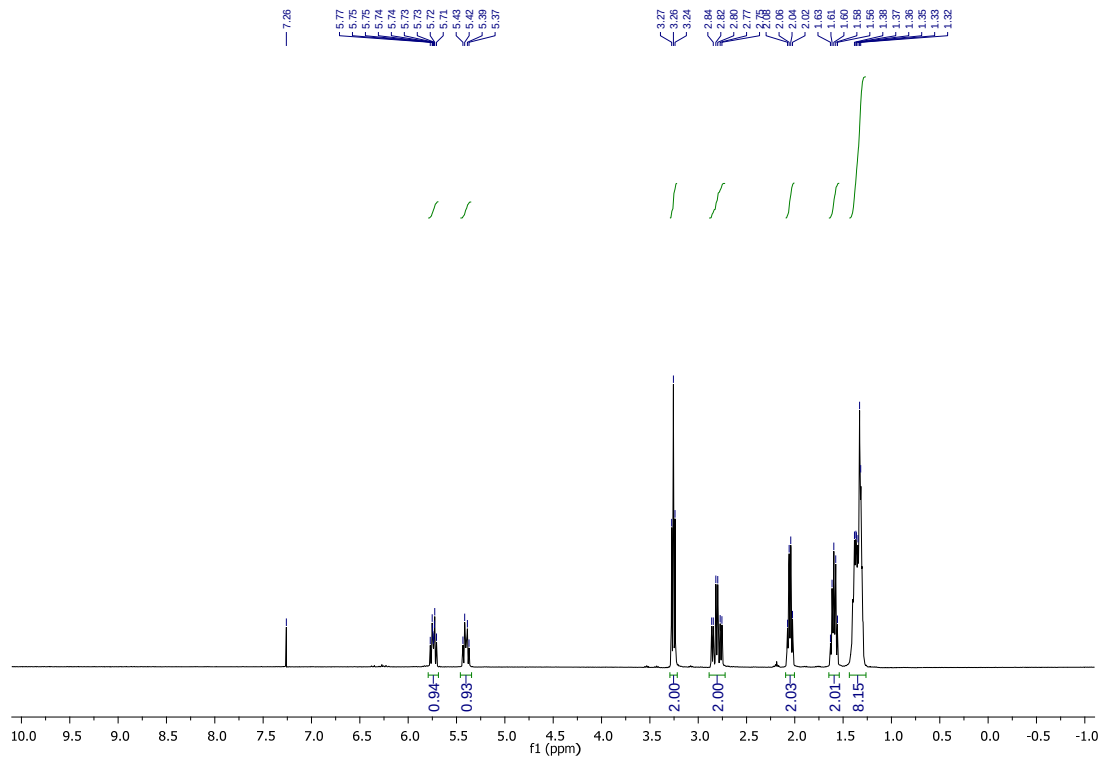
(*Z*)-12-azido-1,1,1-trifluorododec-3-ene

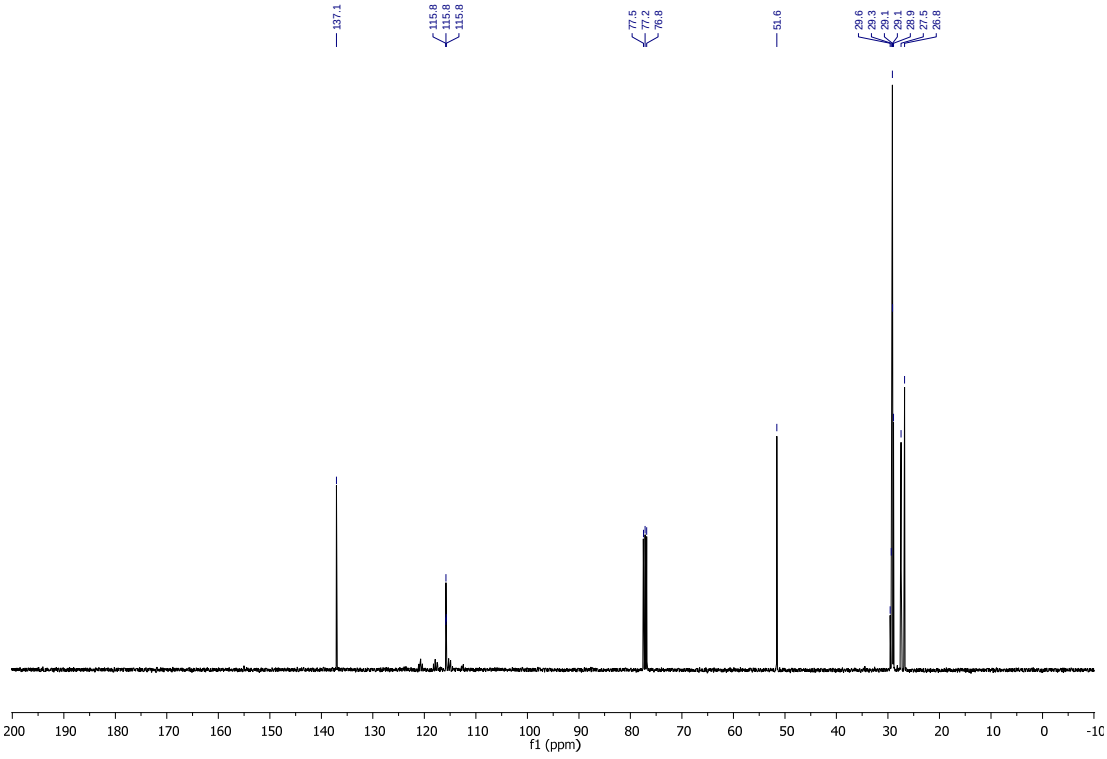


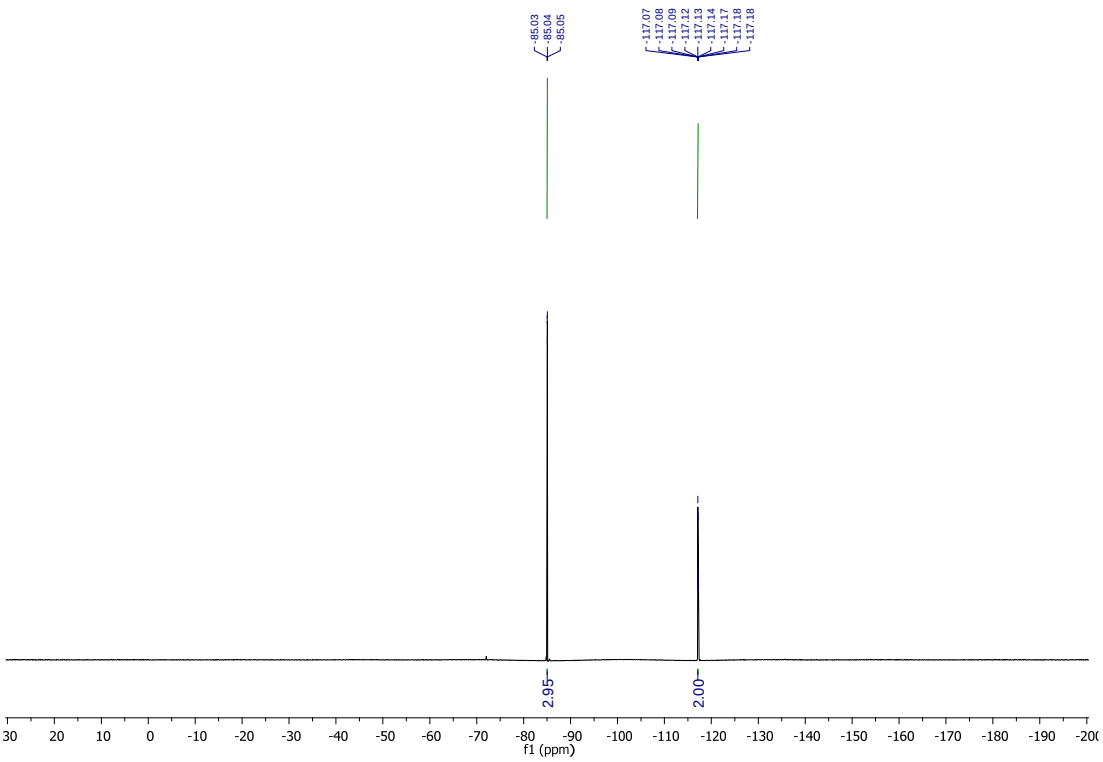

-66.32
-66.35
-66.38
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

(*Z*)-12-azido-1,1,1,2,2-pentafluorododec-4-ene

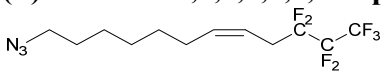


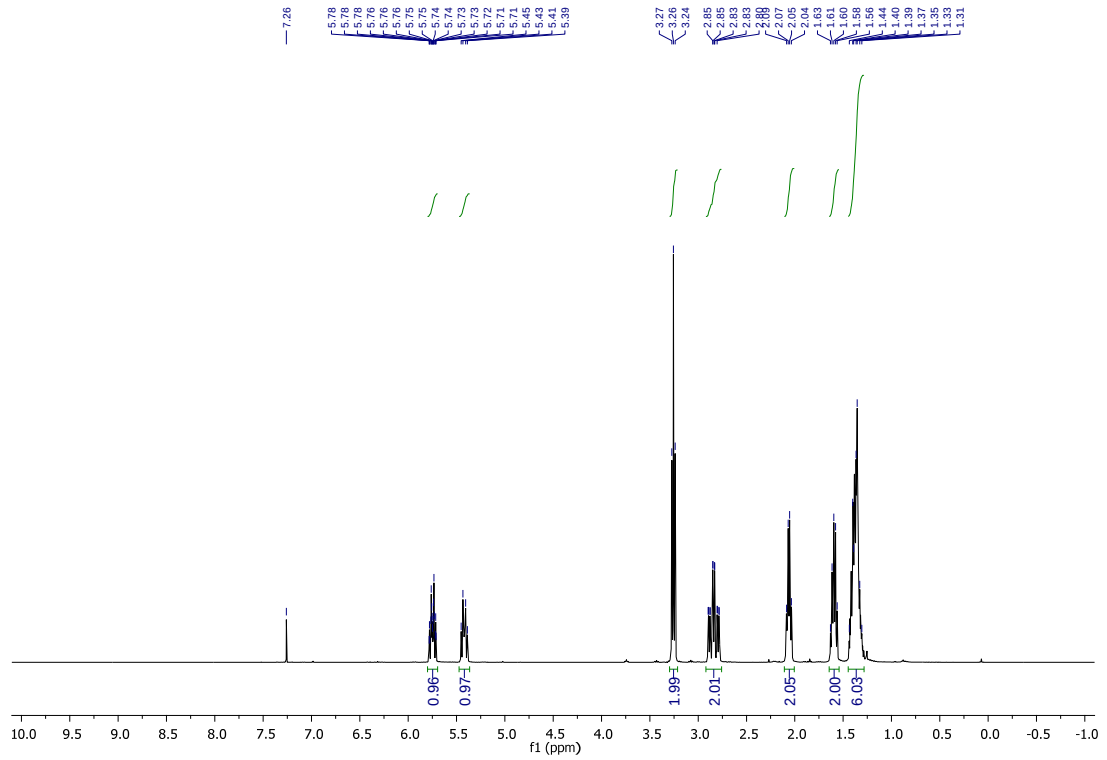


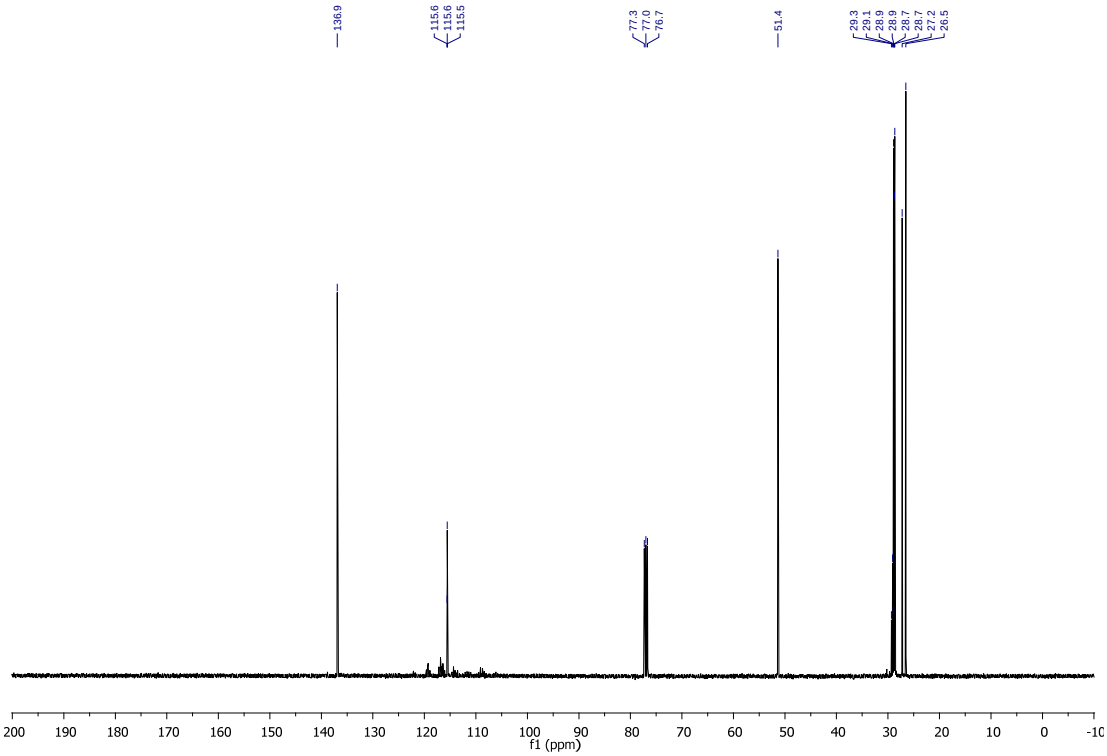



-85.03
-85.04
-85.05
-117.07
-117.08
-117.09
-117.12
-117.13
-117.14
-117.17
-117.18
-117.18
2.95
2.00
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

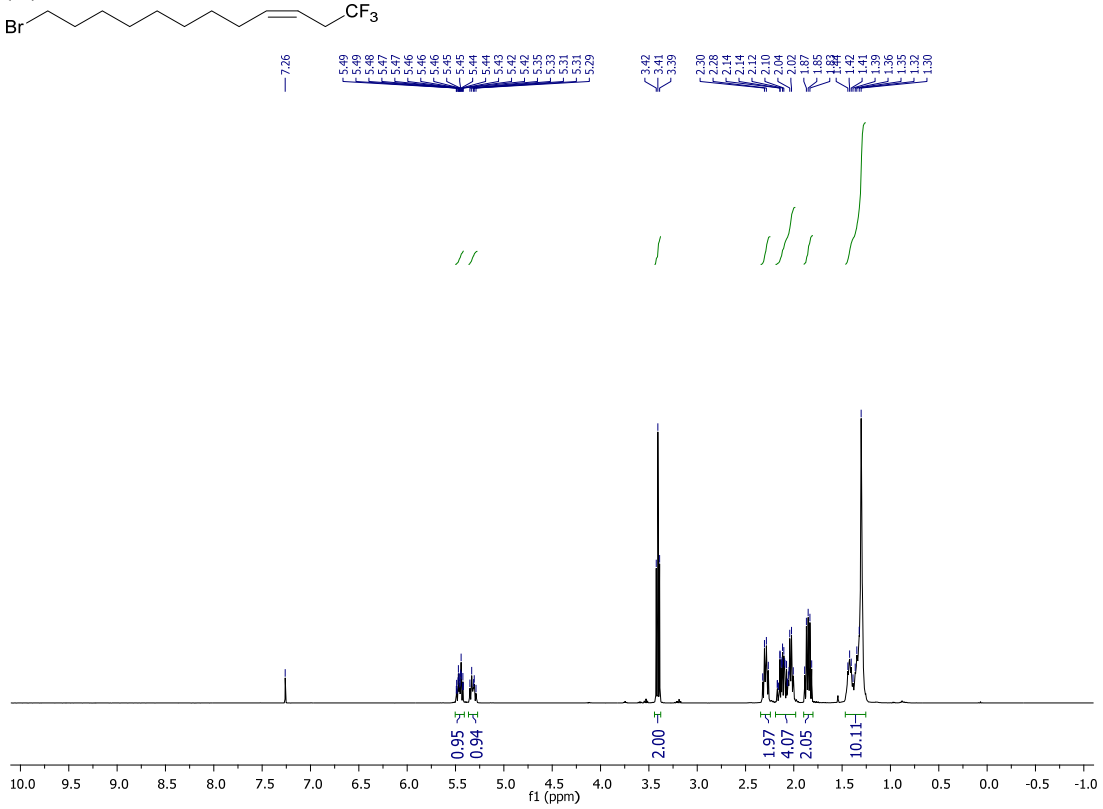
(*Z*)-12-azido-1,1,1,2,2,3,3-heptafluorododec-5-ene

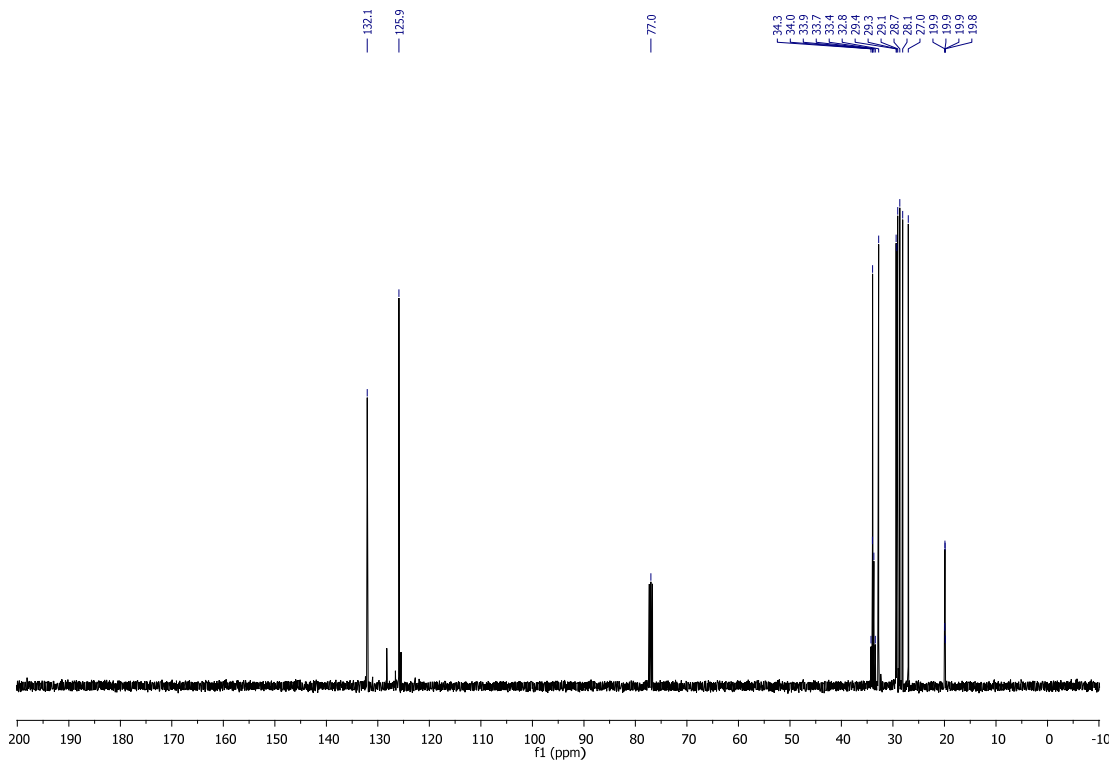


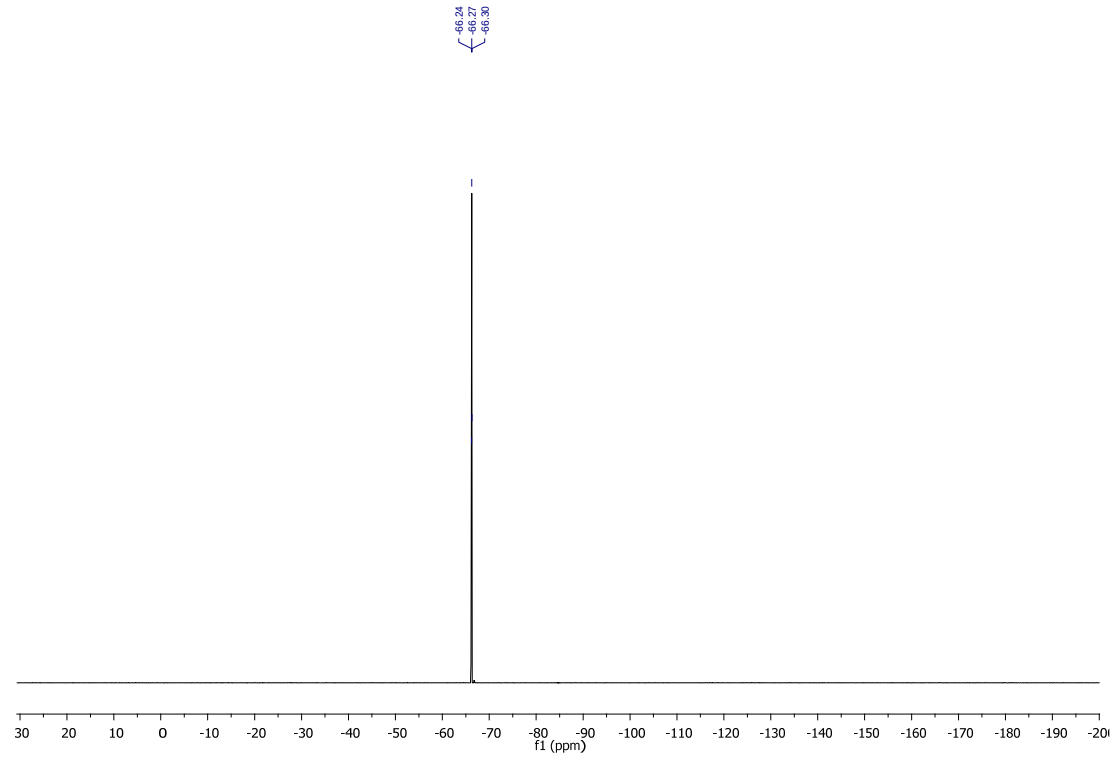


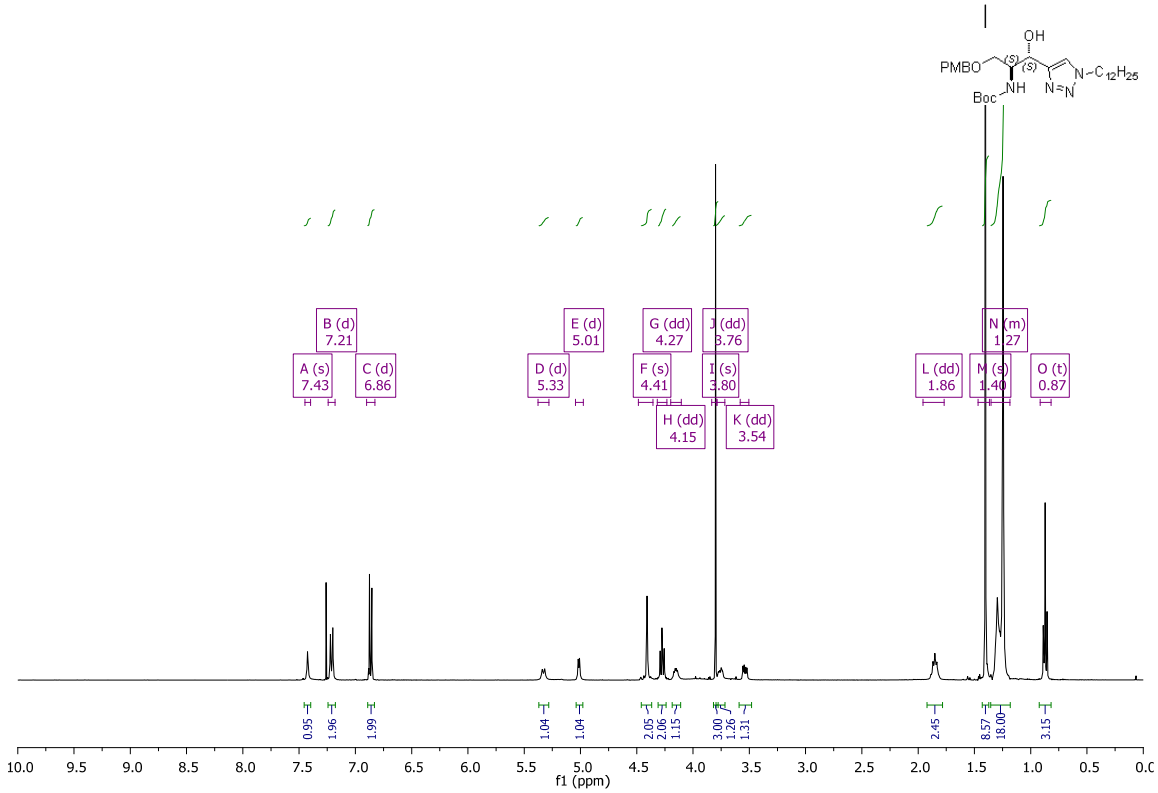


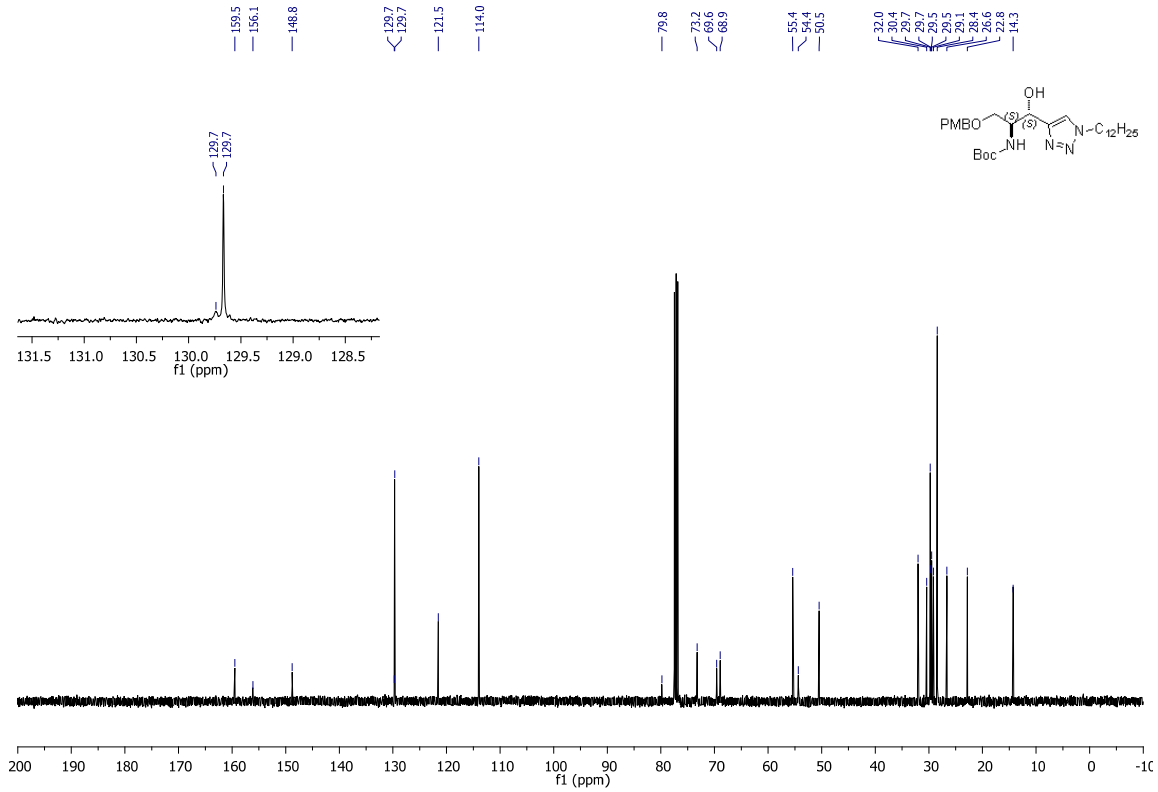
(Z)-12-bromo-1,1,1-trifluorododec-3-ene



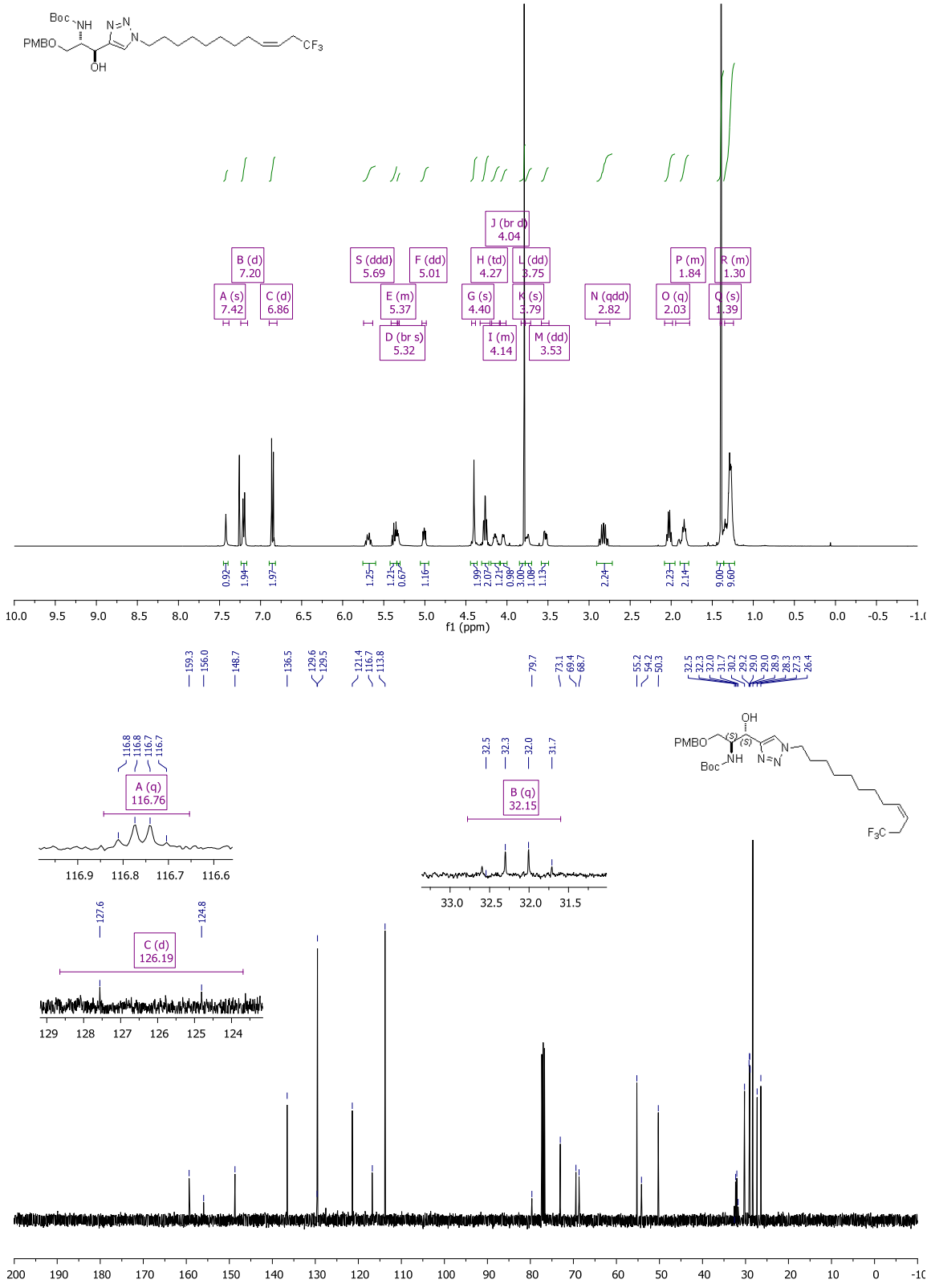

132.1
125.9
77.0
34.3
34.0
33.9
33.7
33.4
32.8
29.4
29.3
29.1
28.7
28.1
27.0
19.9
19.9
19.9
19.8
f1 (ppm)

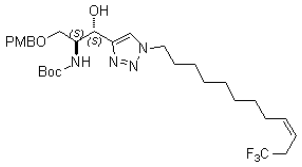

66.24
66.27
66.30
f1 (ppm)

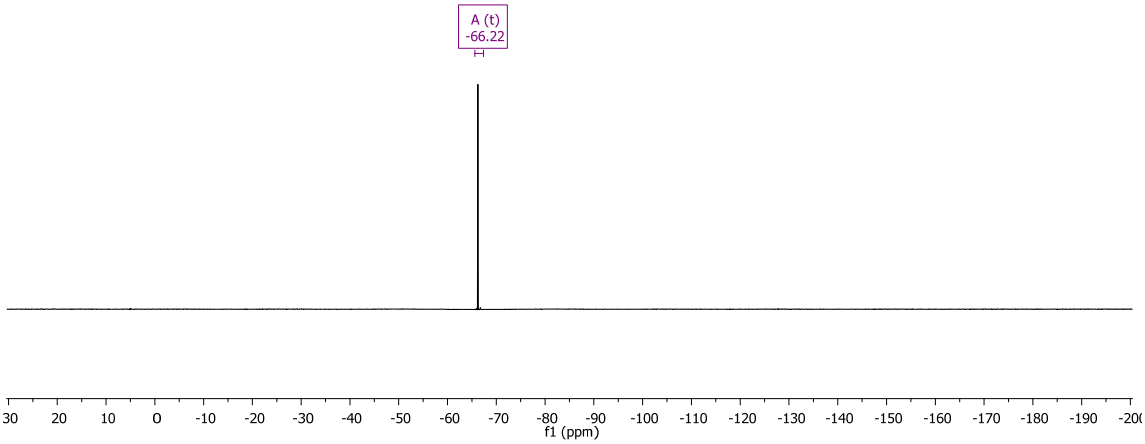

B (d) 7.21
A (s) 7.43
C (d) 6.86
E (d) 5.01
D (d) 5.33
G (dd) 4.27
F (s) 4.41
H (dd) 4.15
J (dd) 3.76
I (s) 3.80
K (dd) 3.54
N (m) 1.27
L (dd) 1.86
M (s) 1.40
O (t) 0.87
f1 (ppm)

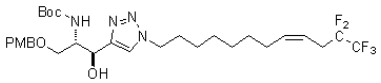

159.5
156.1
148.8
129.7
129.7
121.5
114.0
79.8
73.2
69.6
68.9
55.4
54.4
50.5
32.0
30.4
29.7
29.7
29.5
29.1
28.4
26.6
22.8
14.3
f1 (ppm)

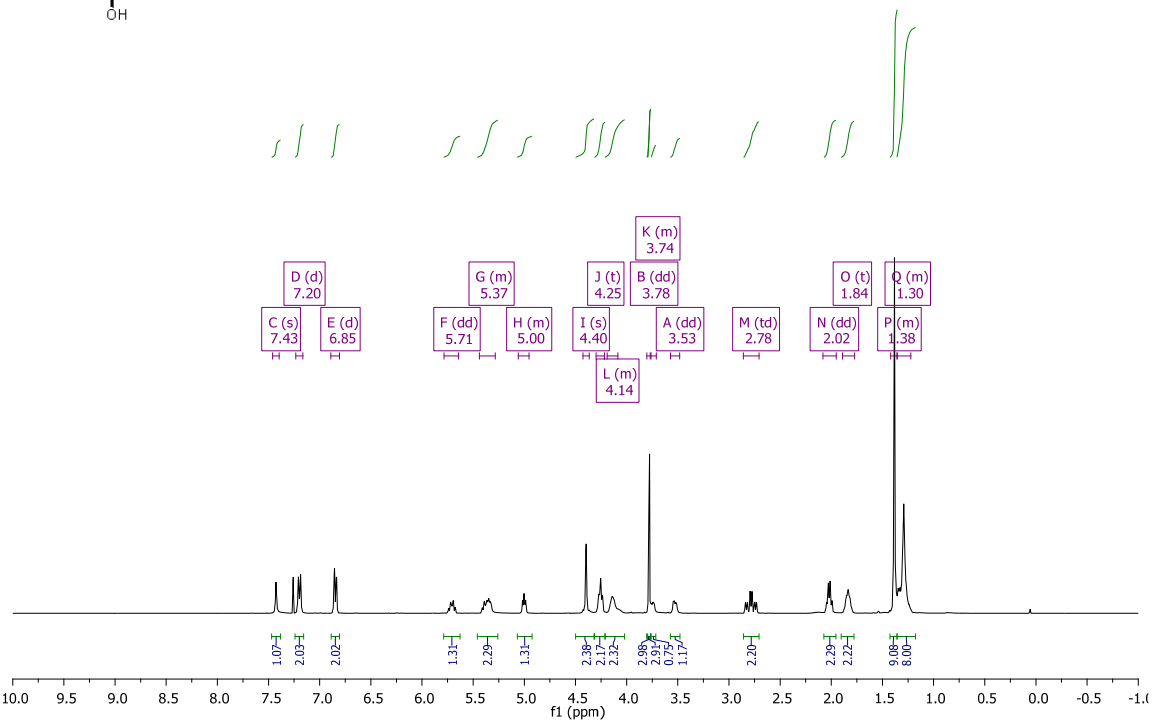
129.7
129.7
f1 (ppm)

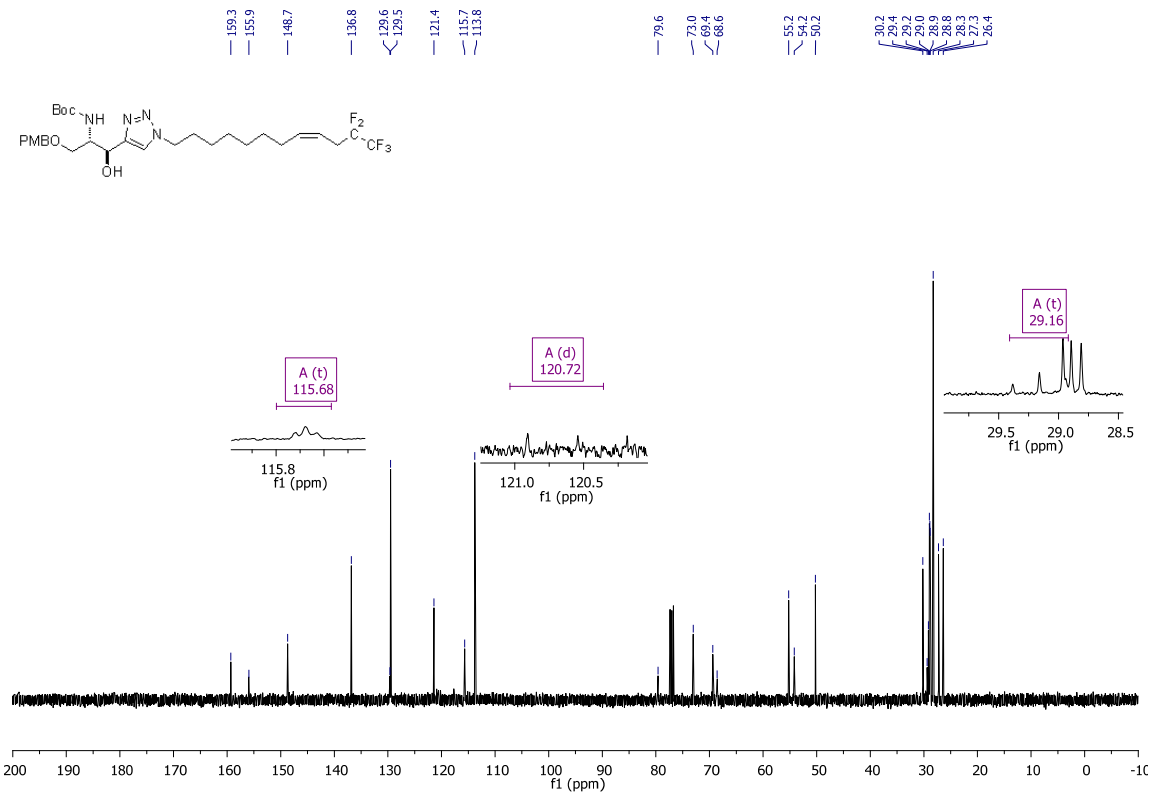

Boc
NH
N=N
PMBO
N
CF3
OH
B (d) 7.20
A (s) 7.42
C (d) 6.86
S (ddd) 5.69
F (dd) 5.01
E (m) 5.37
D (br s) 5.32
H (td) 4.27
L (dd) 3.75
J (br d) 4.04
G (s) 4.40
K (s) 3.79
I (m) 4.14
M (dd) 3.53
N (qdd) 2.82
P (m) 1.84
R (m) 1.30
O (q) 2.03
Q (s) 1.39
f1 (ppm)
159.3
156.0
148.7
136.5
129.6
129.5
121.4
116.7
113.8
79.7
73.1
69.4
68.7
55.2
54.2
50.3
32.5
32.3
32.0
31.7
30.2
29.2
29.0
29.0
28.9
28.3
27.3
26.4
A (q) 116.76
B (q) 32.15
C (d) 126.19
OH
PMBO
Boc
NH
N=N
F3C

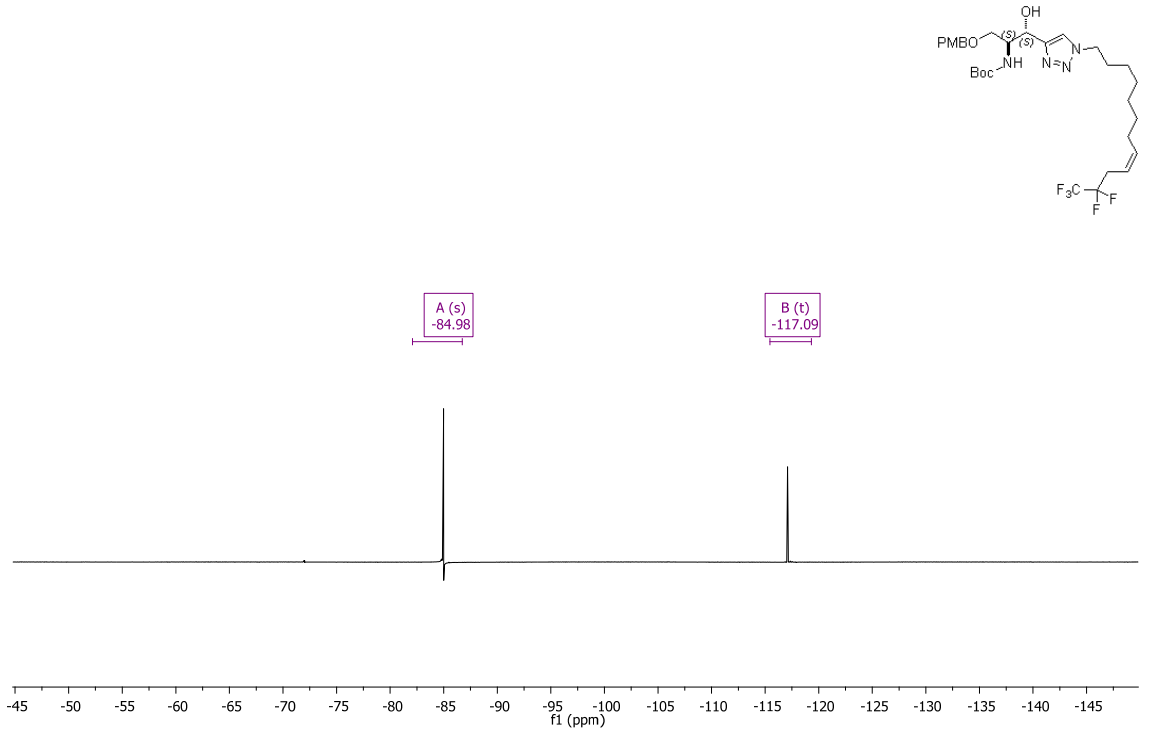

OH
PMBO
(S)
(S)
NH
Boc
N
N
F3C

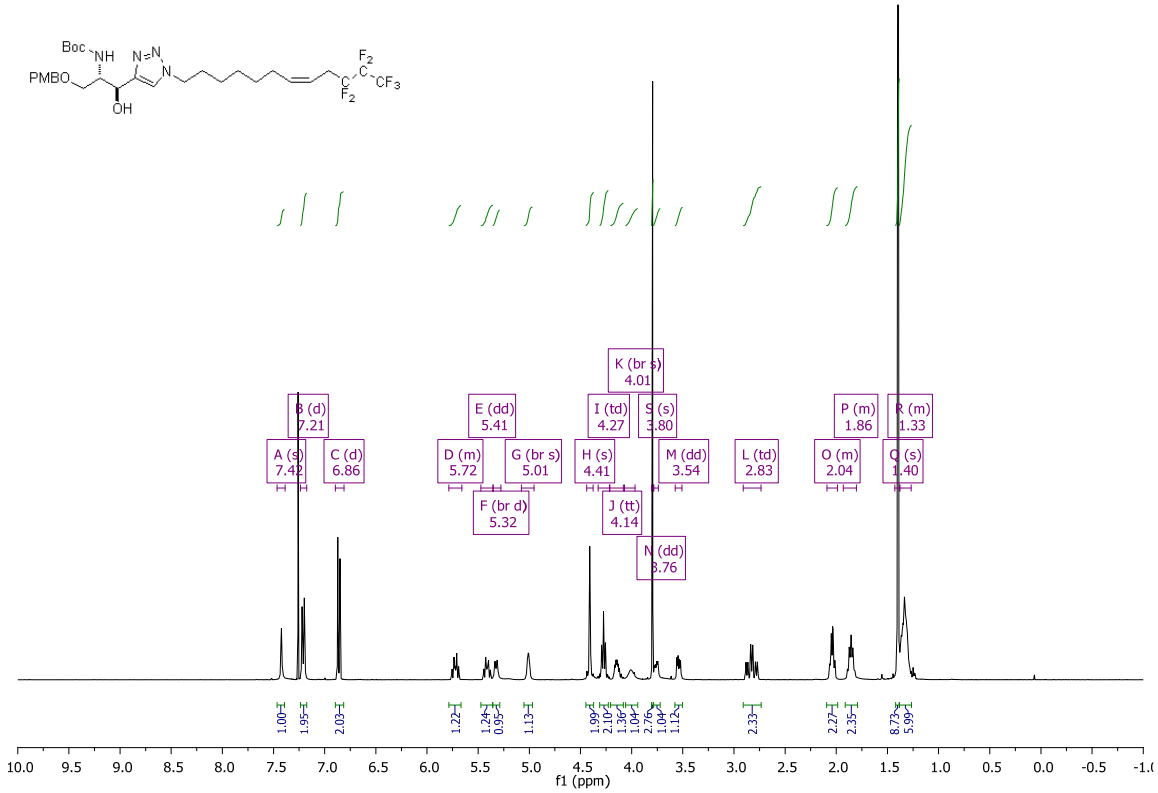

A (t)
-66.22
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

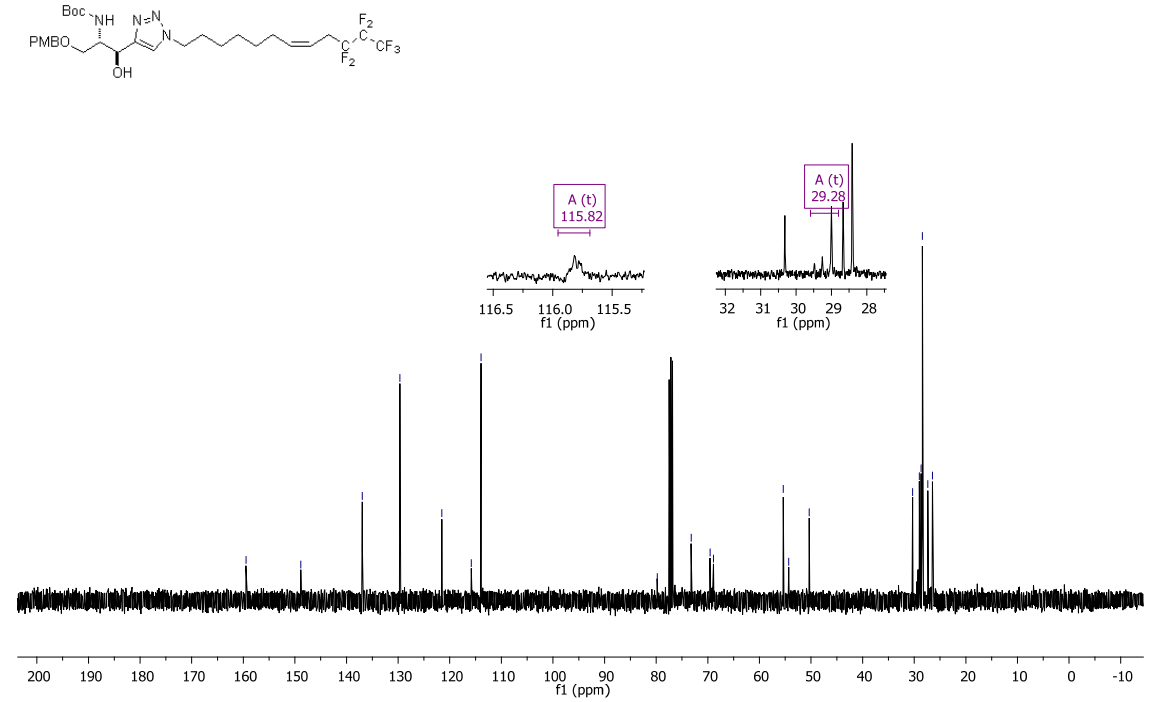

Boc
NH
N
N
PMBO
OH
F2
C
CF3

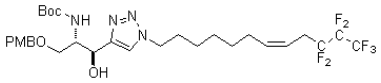

K (m)
3.74
D (d)
7.20
G (m)
5.37
J (t)
4.25
B (dd)
3.78
O (t)
1.84
Q (m)
1.30
C (s)
7.43
E (d)
6.85
F (dd)
5.71
H (m)
5.00
I (s)
4.40
A (dd)
3.53
M (td)
2.78
N (dd)
2.02
P (m)
1.38
L (m)
4.14
1.07 2.03 2.02 1.31 2.29 1.31 2.38 2.17 2.32 2.98 2.91 0.75 1.17 2.20 2.29 2.22 9.08 8.00
10.0 9.5 9.0 8.5 8.0 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)

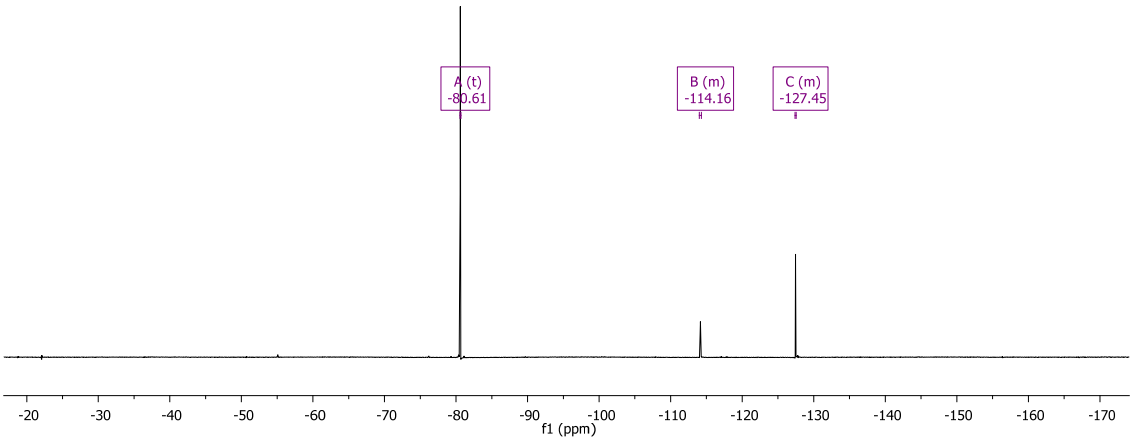

159.3
155.9
148.7
136.8
129.6
129.5
121.4
115.7
113.8
79.6
73.0
69.4
68.6
55.2
54.2
50.2
30.2
29.4
29.2
29.0
28.9
28.8
28.3
27.3
26.4
Boc
NH
N=N
N
PMBO
OH
F2
C
CF3
A (t)
115.68
115.8
f1 (ppm)
A (d)
120.72
121.0
120.5
f1 (ppm)
A (t)
29.16
29.5
29.0
28.5
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
PMBO
(S)
(S)
N
N=N
Boc
NH
F3C
F
F
A (s)
-84.98
B (t)
-117.09
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
f1 (ppm)

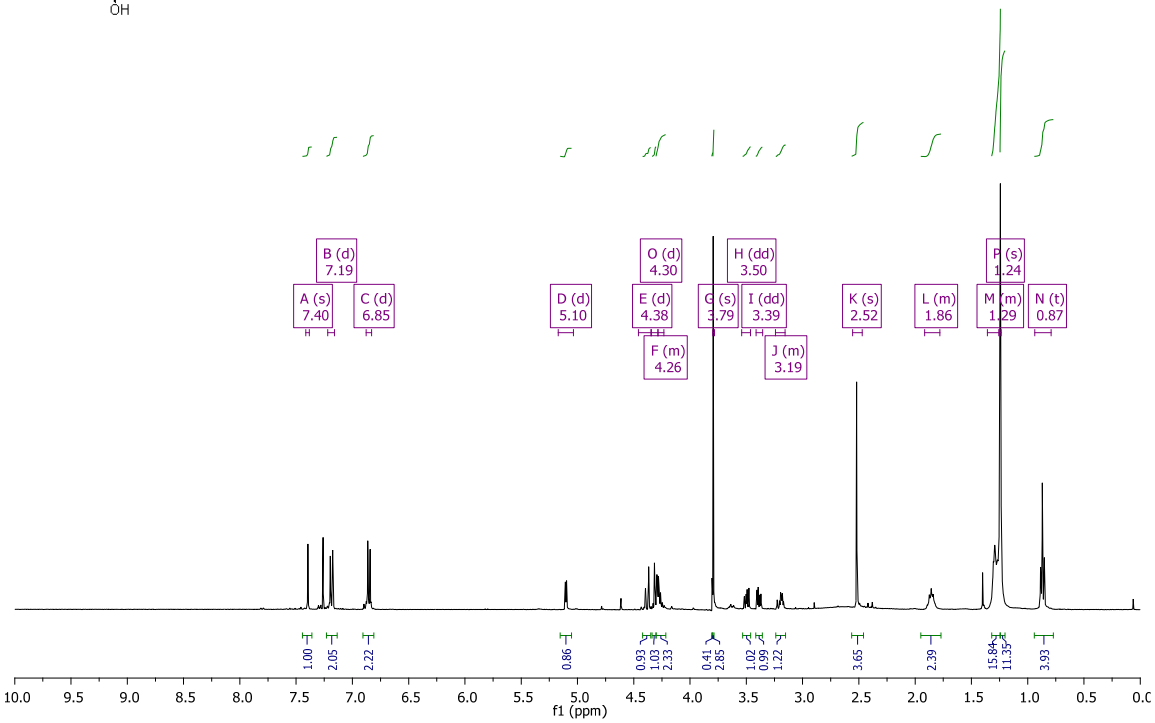

Boc
NH
N=N
PMBO
OH
F2
C
CF3
F2
B (d) 7.21
A (s) 7.42
C (d) 6.86
E (dd) 5.41
D (m) 5.72
G (br s) 5.01
F (br d) 5.32
K (br s) 4.01
I (td) 4.27
S (s) 3.80
H (s) 4.41
M (dd) 3.54
J (tt) 4.14
N (dd) 3.76
L (td) 2.83
P (m) 1.86
R (m) 1.33
O (m) 2.04
Q (s) 1.40
f1 (ppm)

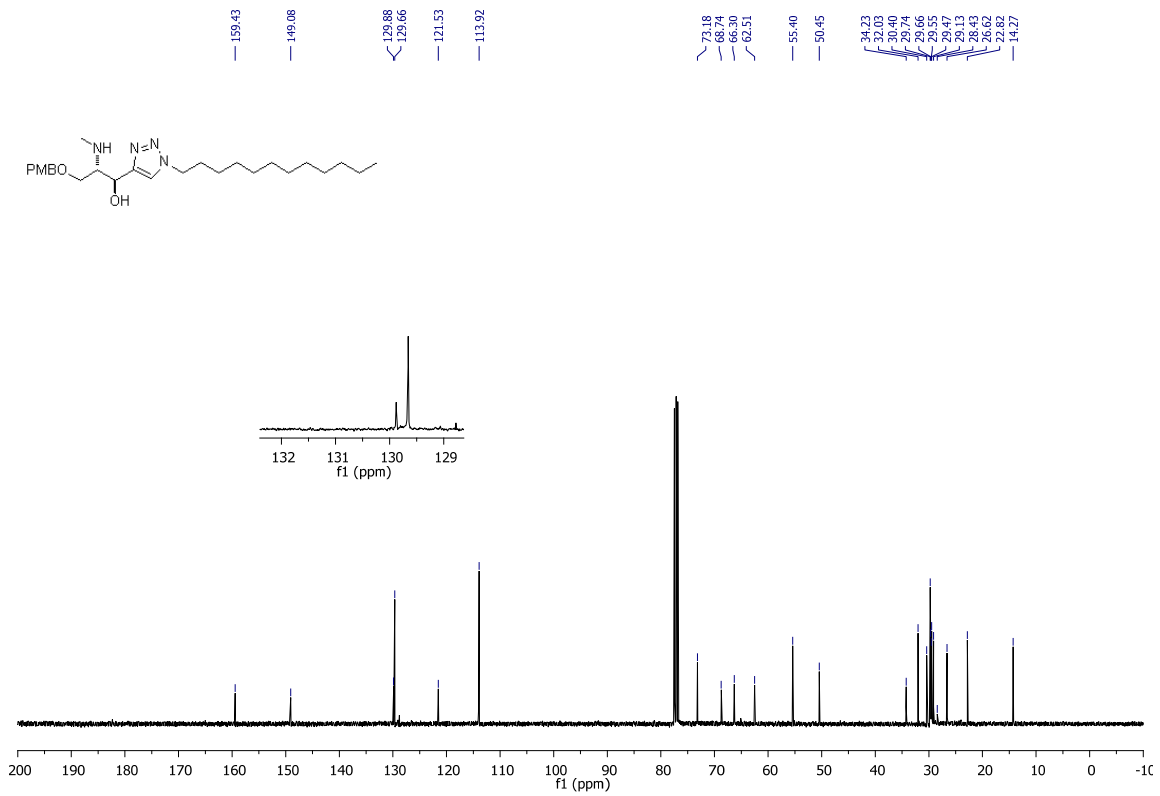

Boc
NH
N=N
PMBO
OH
F2
C
CF3
F2
A (t) 115.82
A (t) 29.28
f1 (ppm)
f1 (ppm)

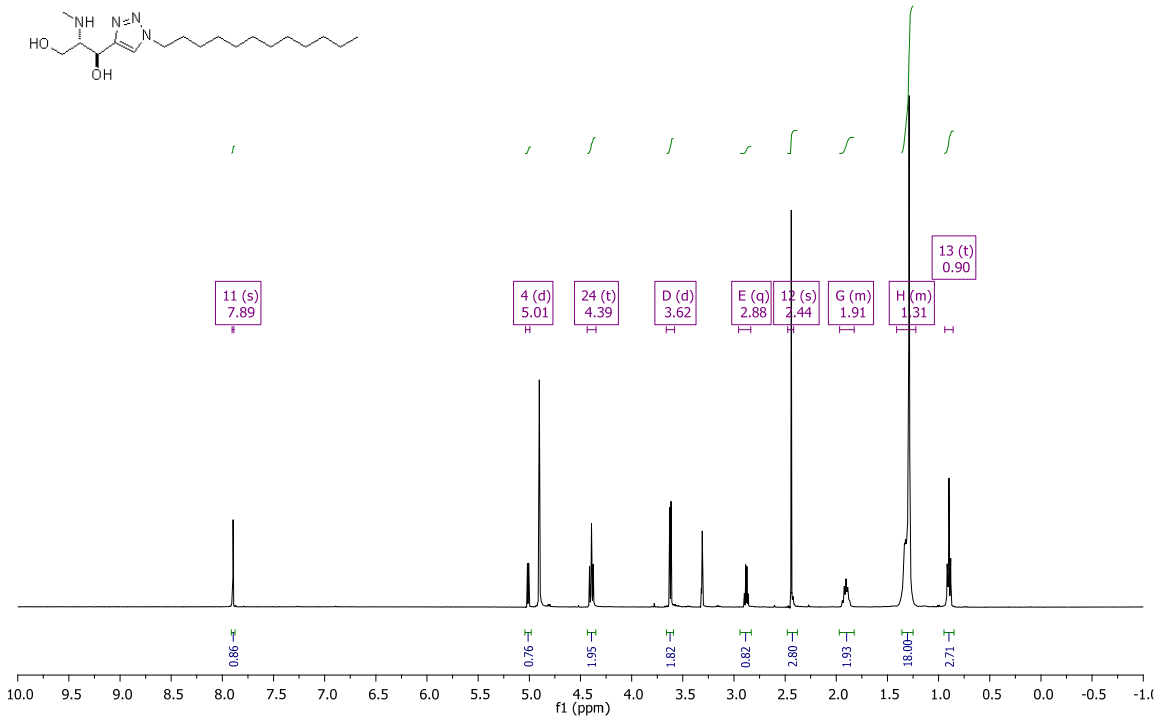

Boc
NH
N=N
PMBO
OH
F2
C
CF3
F2

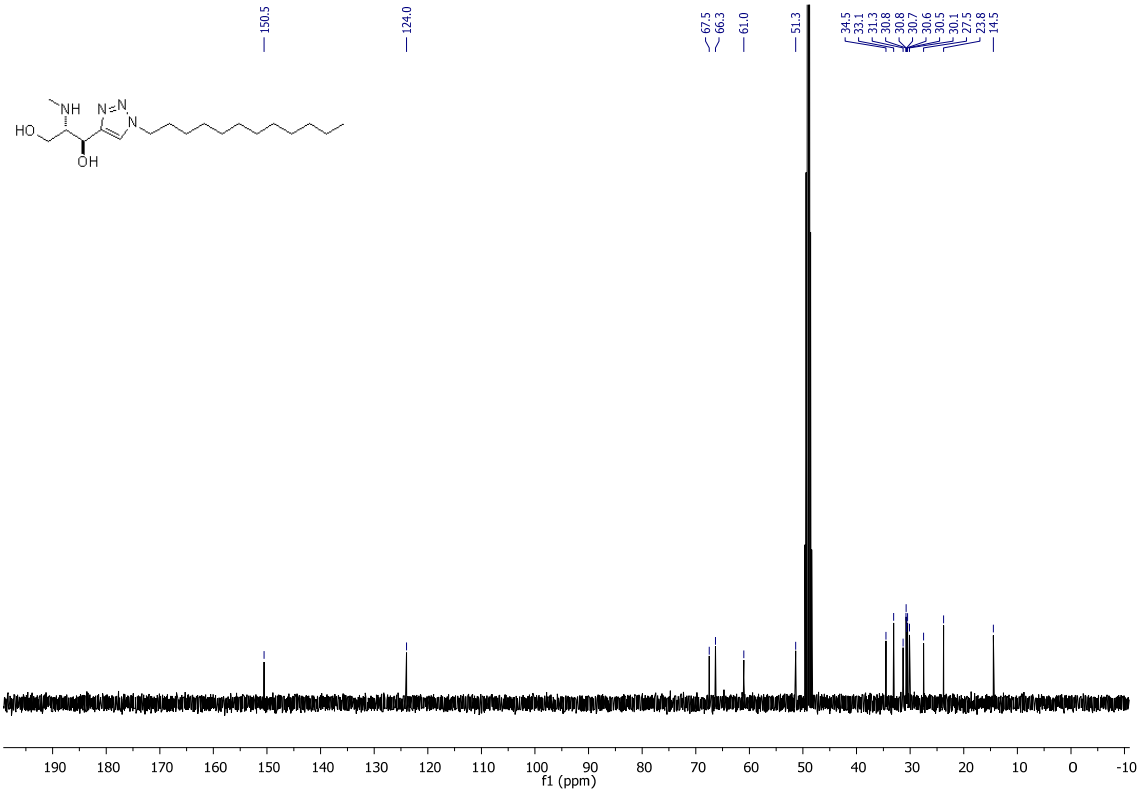

A (t)
-80.61
B (m)
-114.16
C (m)
-127.45
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
f1 (ppm)

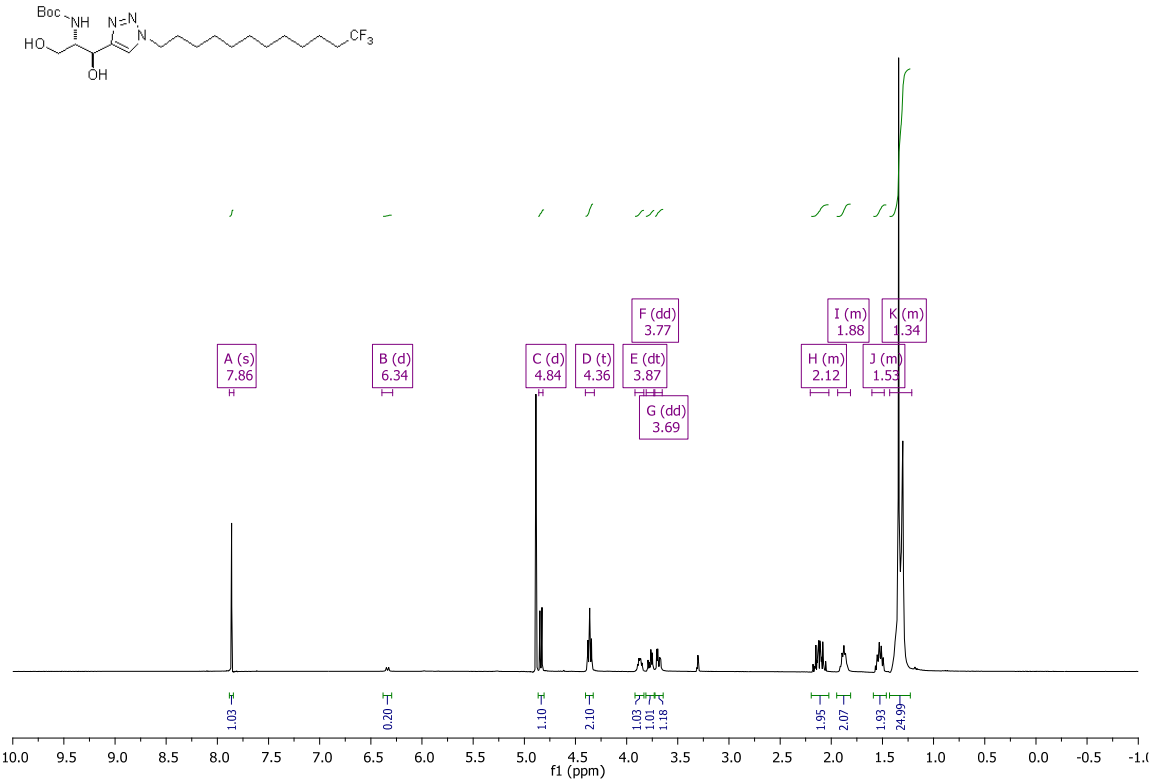

NH
N=N
PMBO
OH

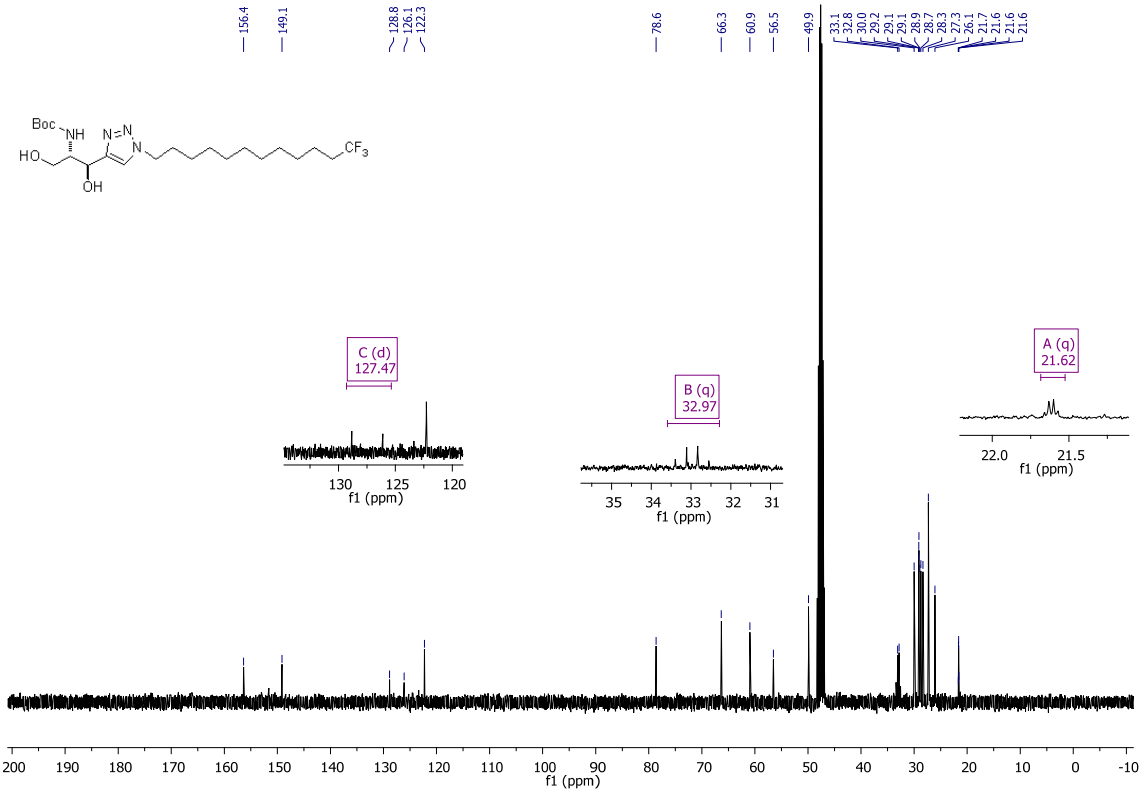

B (d)
7.19
A (s)
7.40
C (d)
6.85
D (d)
5.10
O (d)
4.30
E (d)
4.38
F (m)
4.26
G (s)
3.79
H (dd)
3.50
I (dd)
3.39
J (m)
3.19
K (s)
2.52
L (m)
1.86
P (s)
1.24
M (m)
1.29
N (t)
0.87
1.00
2.05
2.22
0.86
0.93
1.03
2.33
0.41
2.85
1.02
0.99
1.22
3.65
2.39
15.84
11.35
3.93
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


159.43
149.08
129.88
129.66
121.53
113.92
73.18
68.74
66.30
62.51
55.40
50.45
34.23
32.03
30.40
29.74
29.66
29.55
29.47
29.13
28.43
26.62
22.82
14.27
PMBO
NH
N
N
OH
132
131
130
129
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

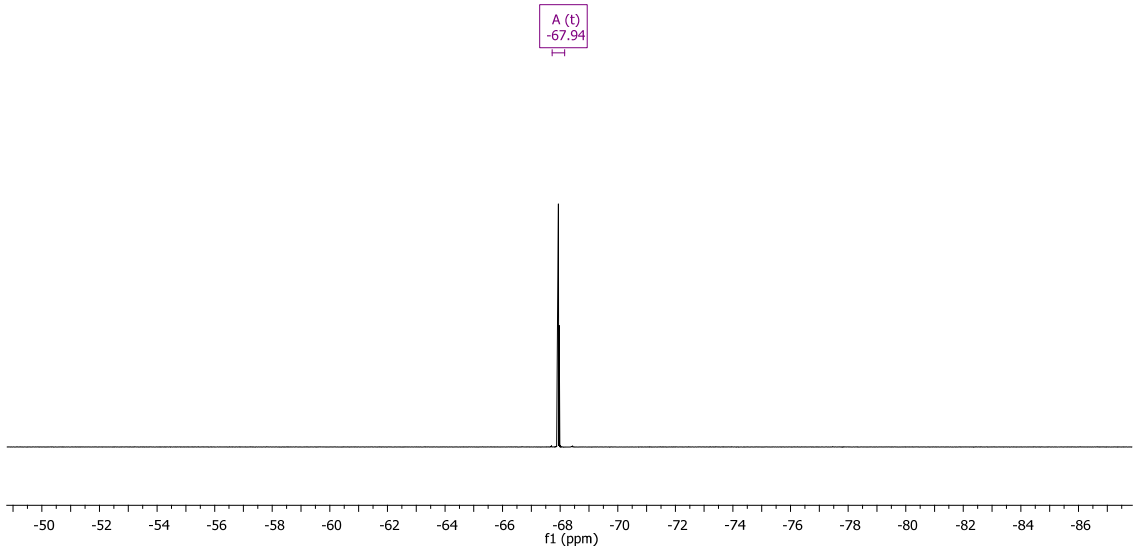

HO
NH
N
N
OH
11 (s)
7.89
4 (d)
5.01
24 (t)
4.39
D (d)
3.62
E (q)
2.88
12 (s)
2.44
G (m)
1.91
H (m)
1.31
13 (t)
0.90
0.86
0.76
1.95
1.82
0.82
2.80
1.93
18.00
2.71
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

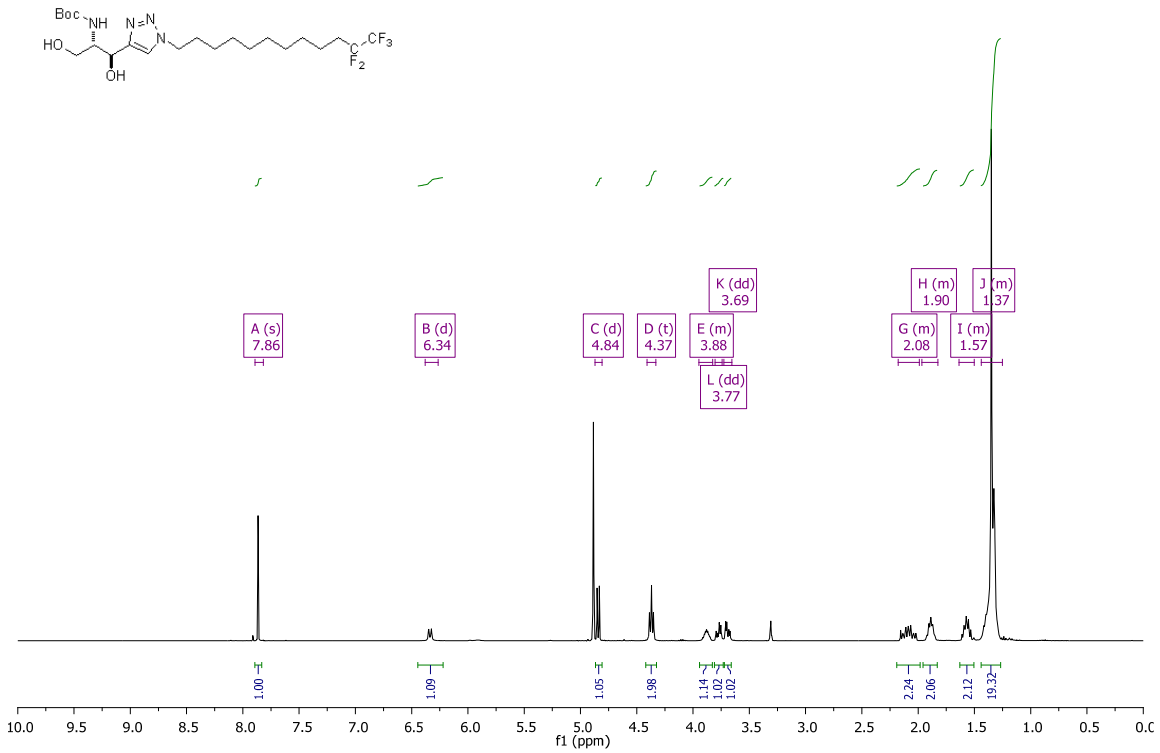

150.5
124.0
67.5
66.3
61.0
51.3
34.5
33.1
31.3
30.8
30.8
30.7
30.6
30.5
30.1
27.5
23.8
14.5
NH
N=N
N
HO
OH
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

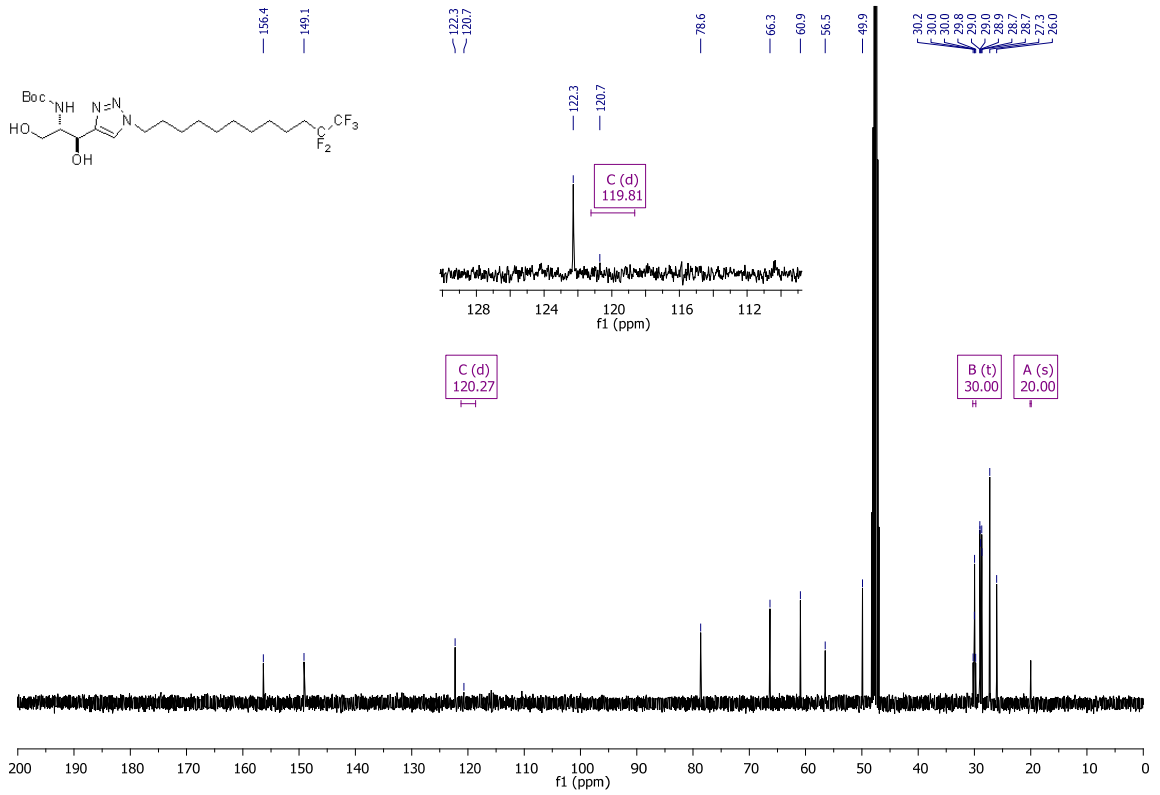

Boc
NH
N=N
N
HO
OH
CF3
A (s) 7.86
B (d) 6.34
C (d) 4.84
D (t) 4.36
E (dt) 3.87
F (dd) 3.77
G (dd) 3.69
H (m) 2.12
I (m) 1.88
J (m) 1.53
K (m) 1.34
1.03
0.20
1.10
2.10
1.03
1.01
1.18
1.95
2.07
1.93
24.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

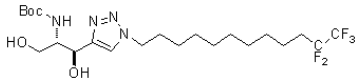

156.4
149.1
128.8
126.1
122.3
78.6
66.3
60.9
56.5
49.9
33.1
32.8
30.0
29.2
29.1
29.1
28.9
28.7
28.3
27.3
26.1
21.7
21.6
21.6
21.6
Boc
NH
HO
OH
N=N
N
CF3
C (d)
127.47
B (q)
32.97
A (q)
21.62
f1 (ppm)

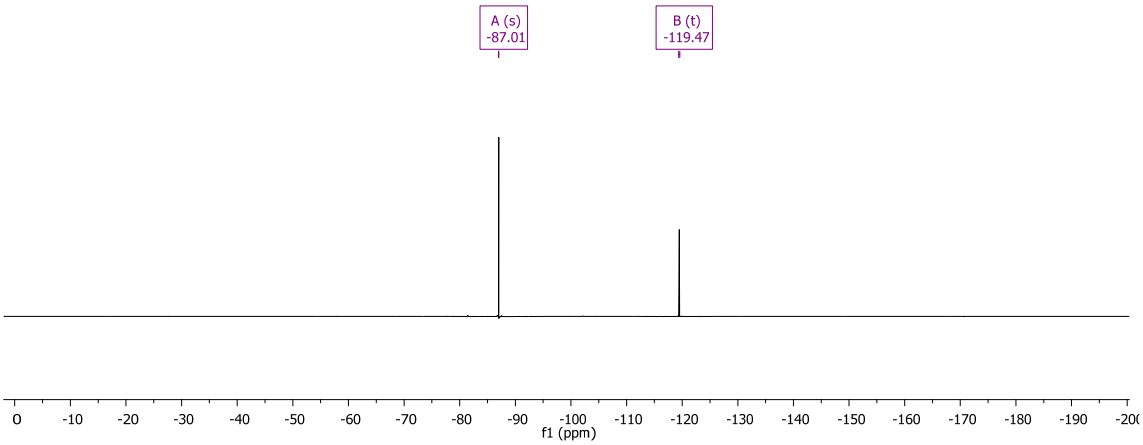

Boc
NH
HO
OH
N=N
N
CF3

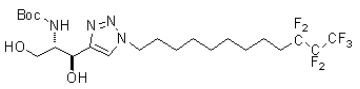

A (t)
-67.94
f1 (ppm)


A (s) 7.86
B (d) 6.34
C (d) 4.84
D (t) 4.37
E (m) 3.88
K (dd) 3.69
L (dd) 3.77
G (m) 2.08
H (m) 1.90
I (m) 1.57
J (m) 1.37
f1 (ppm)

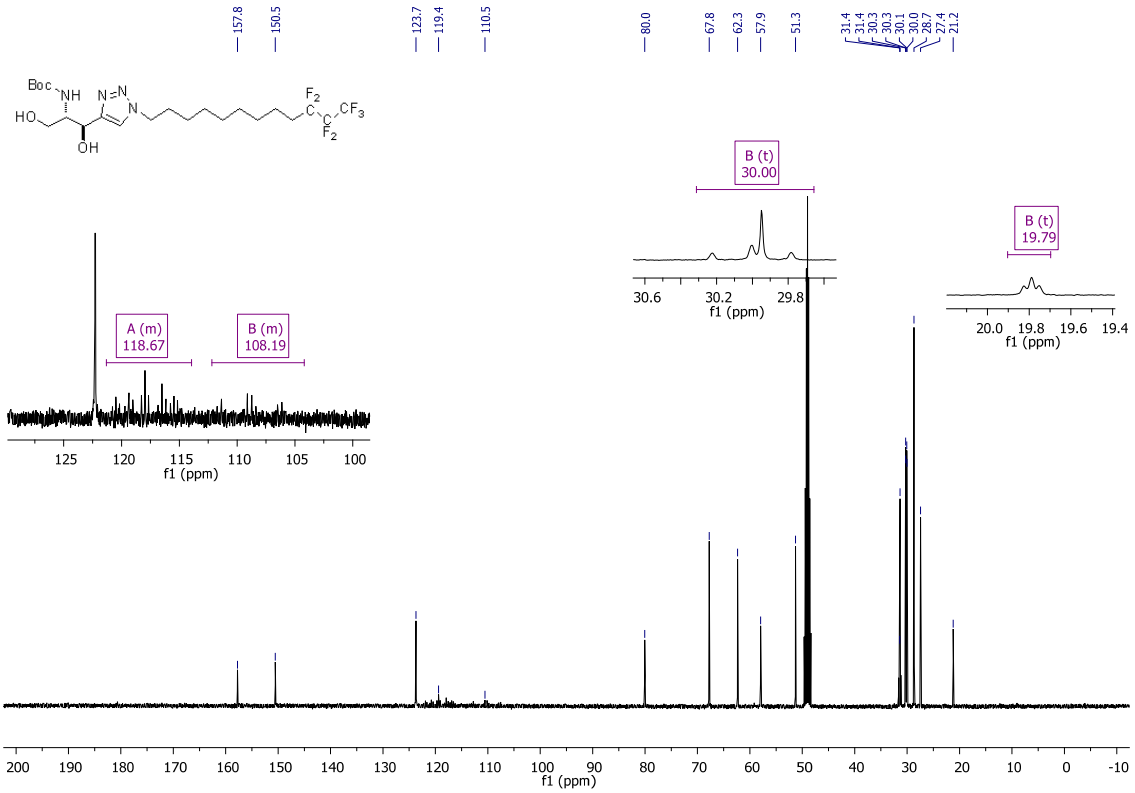

C (d) 119.81
C (d) 120.27
B (t) 30.00
A (s) 20.00
f1 (ppm)

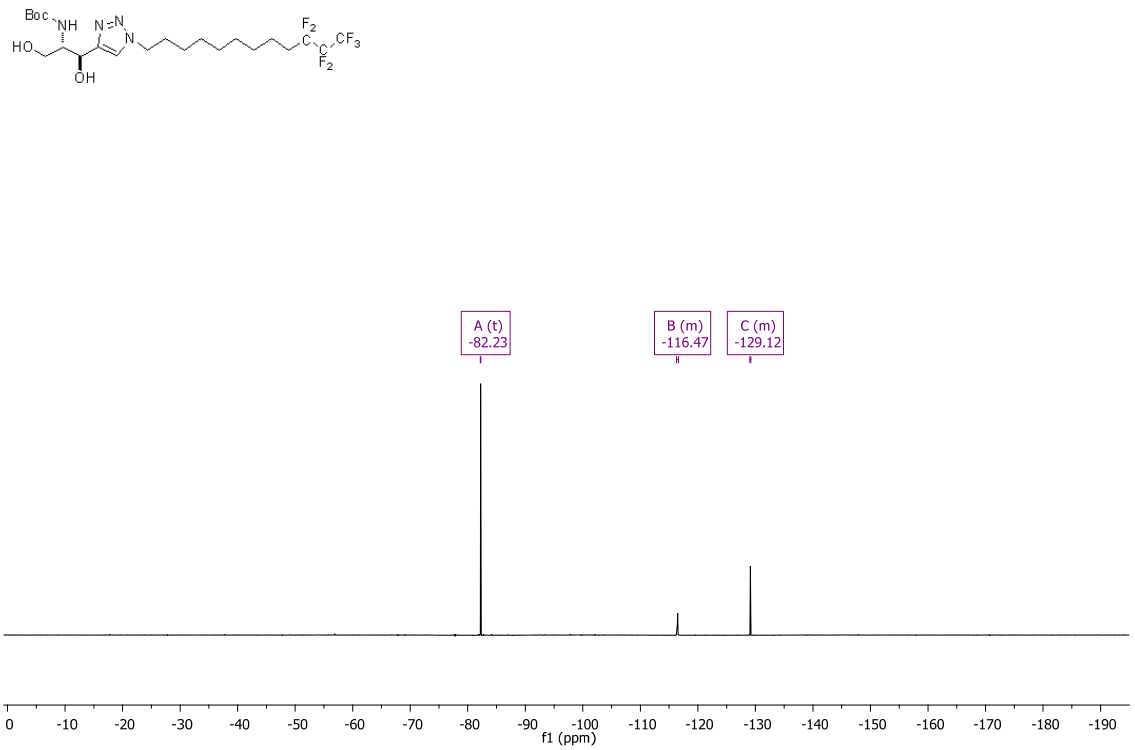

Boc
NH
N=N
HO
OH
CF3
F2

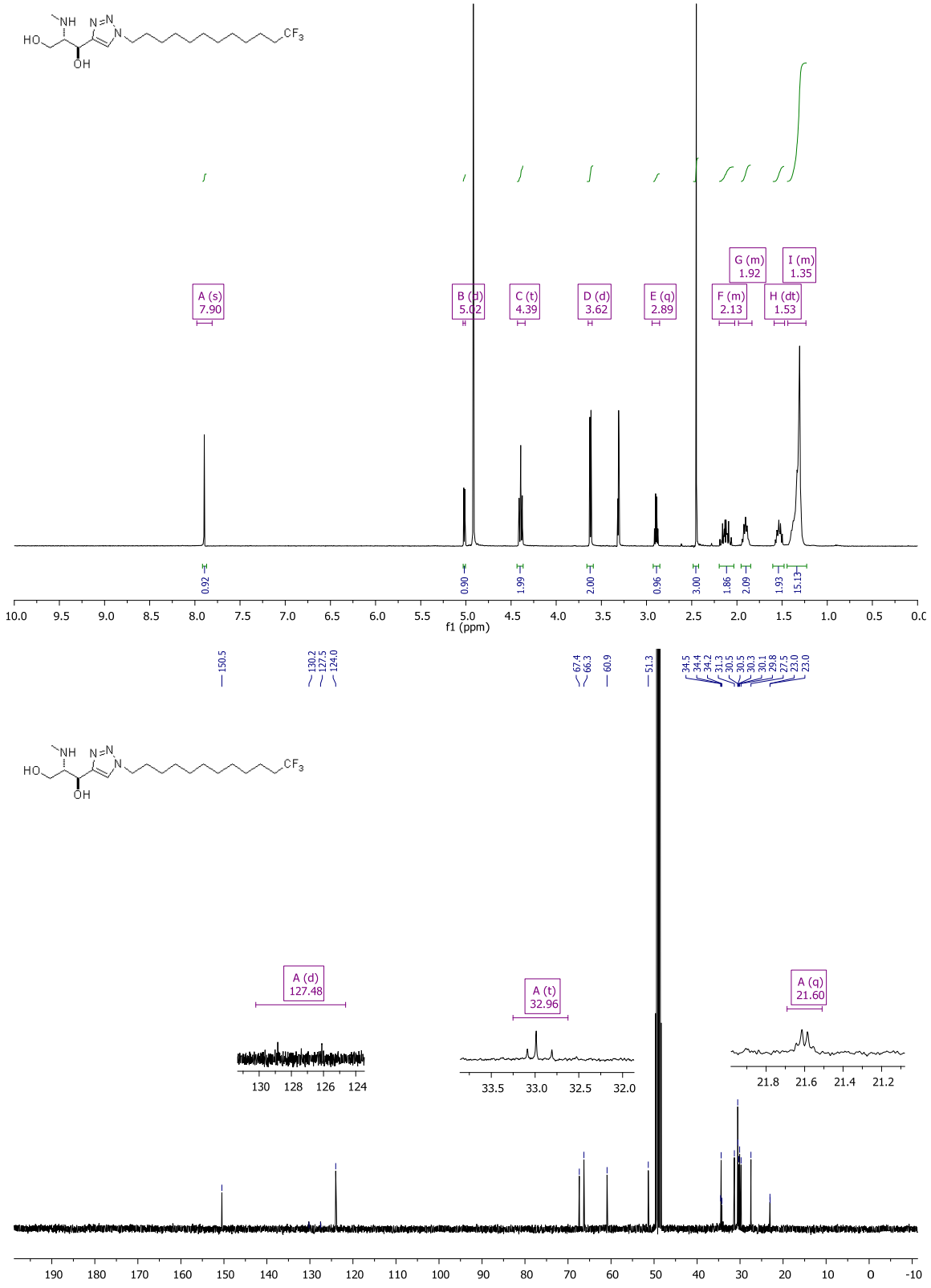

A (s)
-87.01
B (t)
-119.47
f1 (ppm)

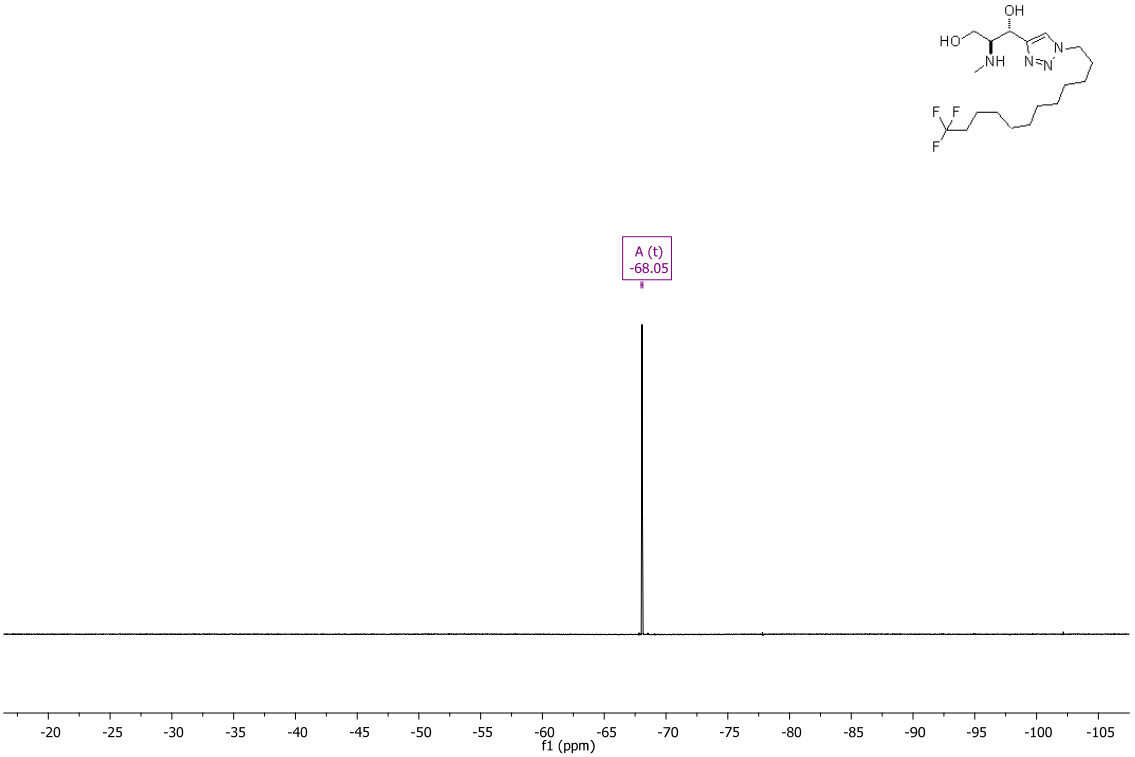

Boc
NH
N=N
HO
OH
F2
CF3
F2

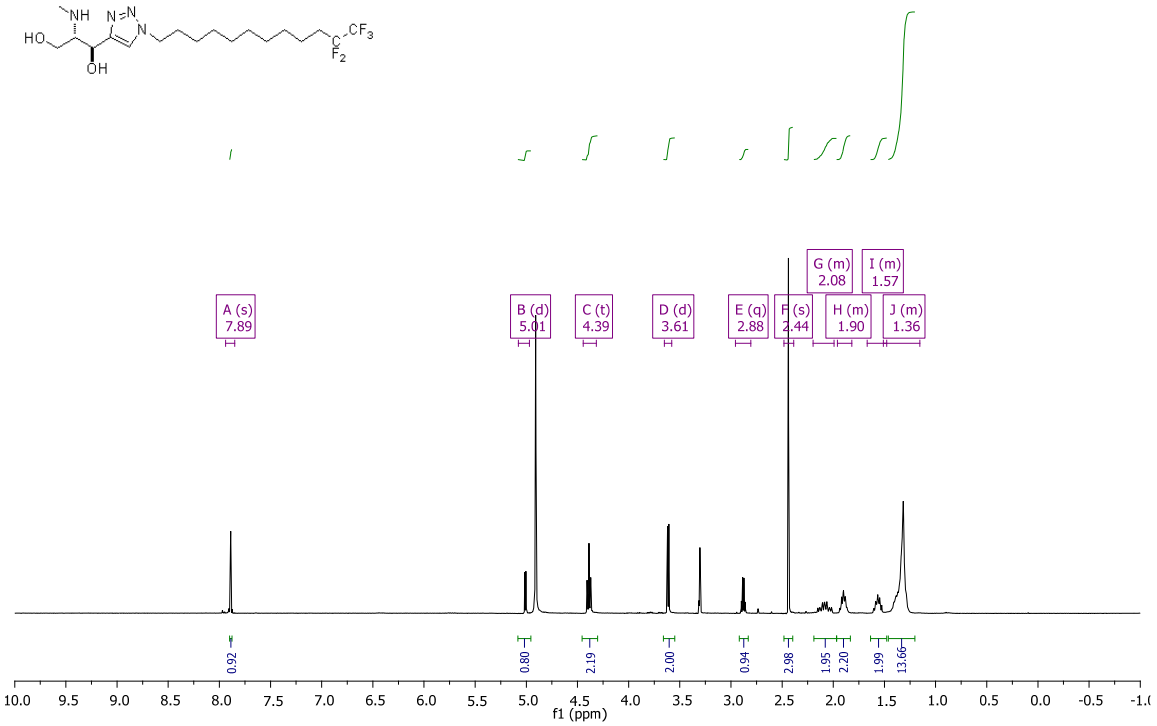
A (s)
7.87
B (d)
6.35
D (d)
4.84
E (t)
4.37
F (m)
3.87
G (dd)
3.77
H (dd)
3.69
J (qt)
2.10
K (m)
1.88
L (m)
1.58
M (s)
1.34
1.00
0.31
1.08
2.00
0.88
0.91
1.13
1.63
1.86
1.64
20.27
f1 (ppm)

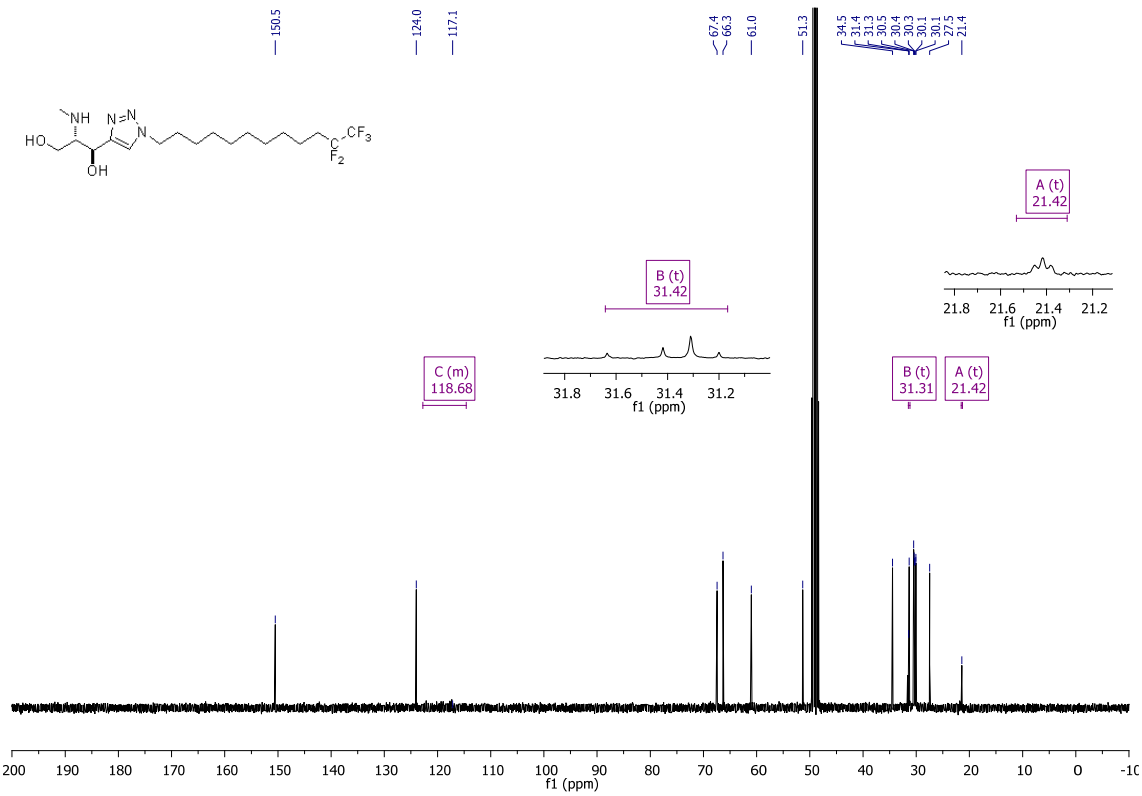

157.8
150.5
123.7
119.4
110.5
80.0
67.8
62.3
57.9
51.3
31.4
31.4
30.3
30.3
30.1
30.0
28.7
27.4
21.2
Boc
NH
HO
OH
N=N
N
F2
C
CF3
F2
A (m)
118.67
B (m)
108.19
125 120 115 110 105 100
f1 (ppm)
B (t)
30.00
30.6 30.2 29.8
f1 (ppm)
B (t)
19.79
20.0 19.8 19.6 19.4
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

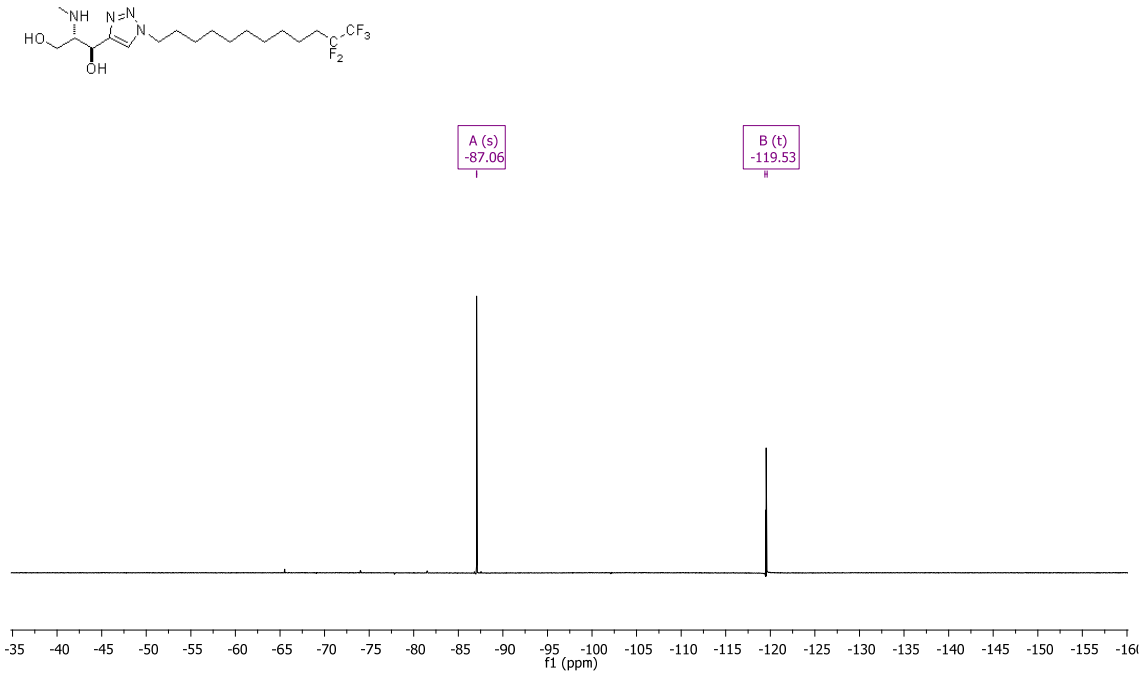

A (t)
-82.23
B (m)
-116.47
C (m)
-129.12
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

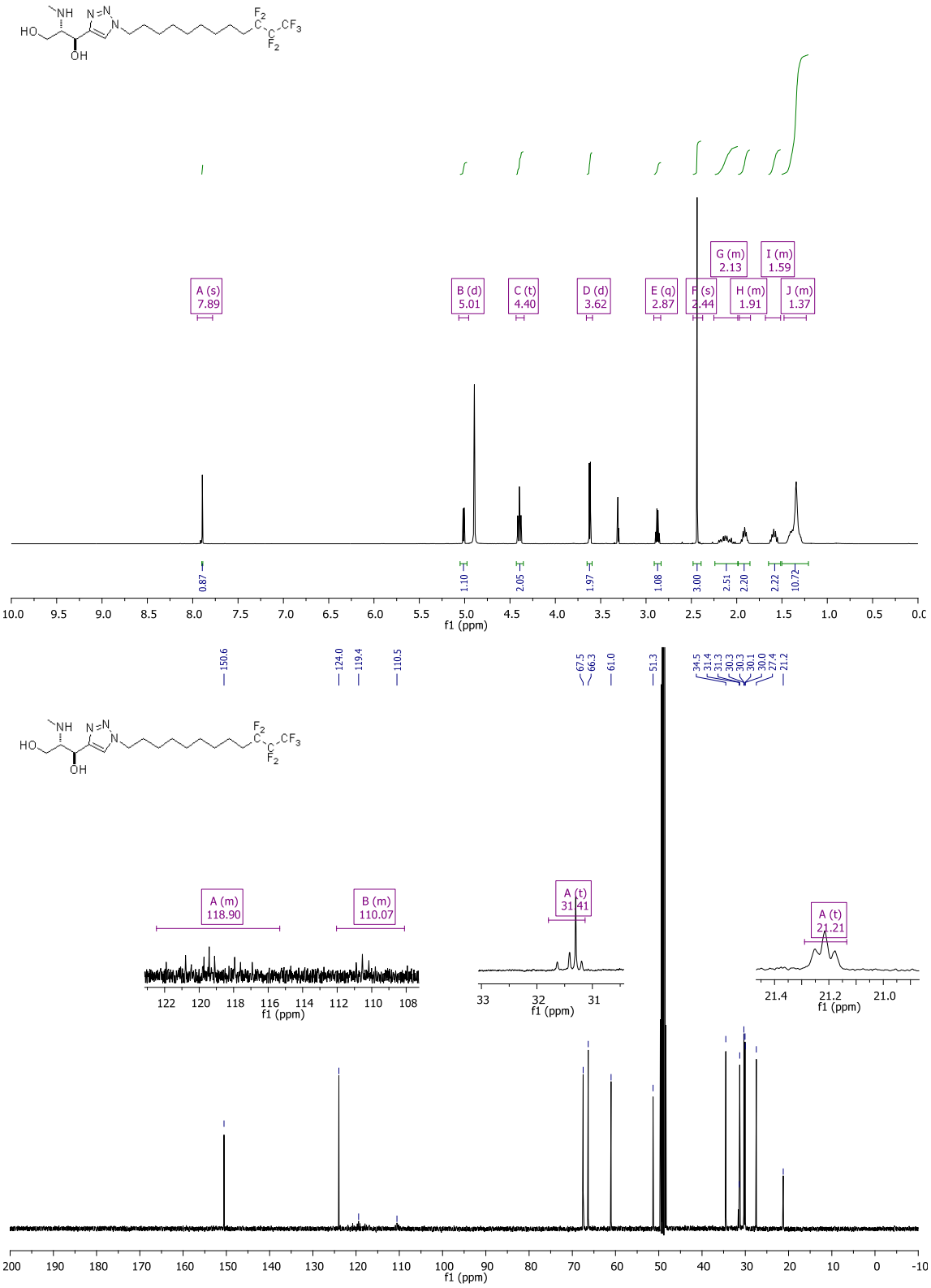

A (s) 7.90
B (d) 5.02
C (t) 4.39
D (d) 3.62
E (q) 2.89
F (m) 2.13
G (m) 1.92
H (dt) 1.53
I (m) 1.35
f1 (ppm)
A (d) 127.48
A (t) 32.96
A (q) 21.60

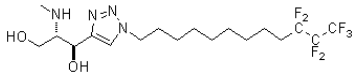

OH
HO
NH
N
N
F
F
F
A (t)
-68.05
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
f1 (ppm)

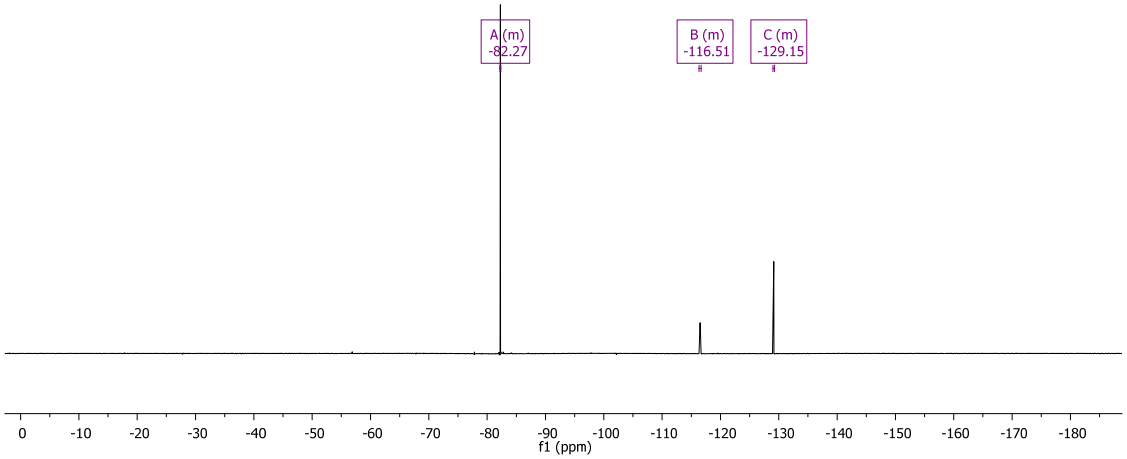

NH
N
N
HO
OH
CF3
F2
A (s)
7.89
B (d)
5.01
C (t)
4.39
D (d)
3.61
E (q)
2.88
F (s)
2.44
G (m)
2.08
H (m)
1.90
I (m)
1.57
J (m)
1.36
0.92
0.80
2.19
2.00
0.94
2.98
1.95
2.20
1.99
13.66
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

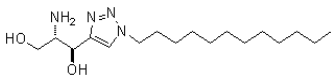

150.5
124.0
117.1
67.4
66.3
61.0
51.3
34.5
31.4
31.3
30.5
30.4
30.3
30.1
27.5
21.4
A (t)
21.42
B (t)
31.42
C (m)
118.68
B (t)
31.31
A (t)
21.42
f1 (ppm)


A (s)
-87.06
B (t)
-119.53
f1 (ppm)

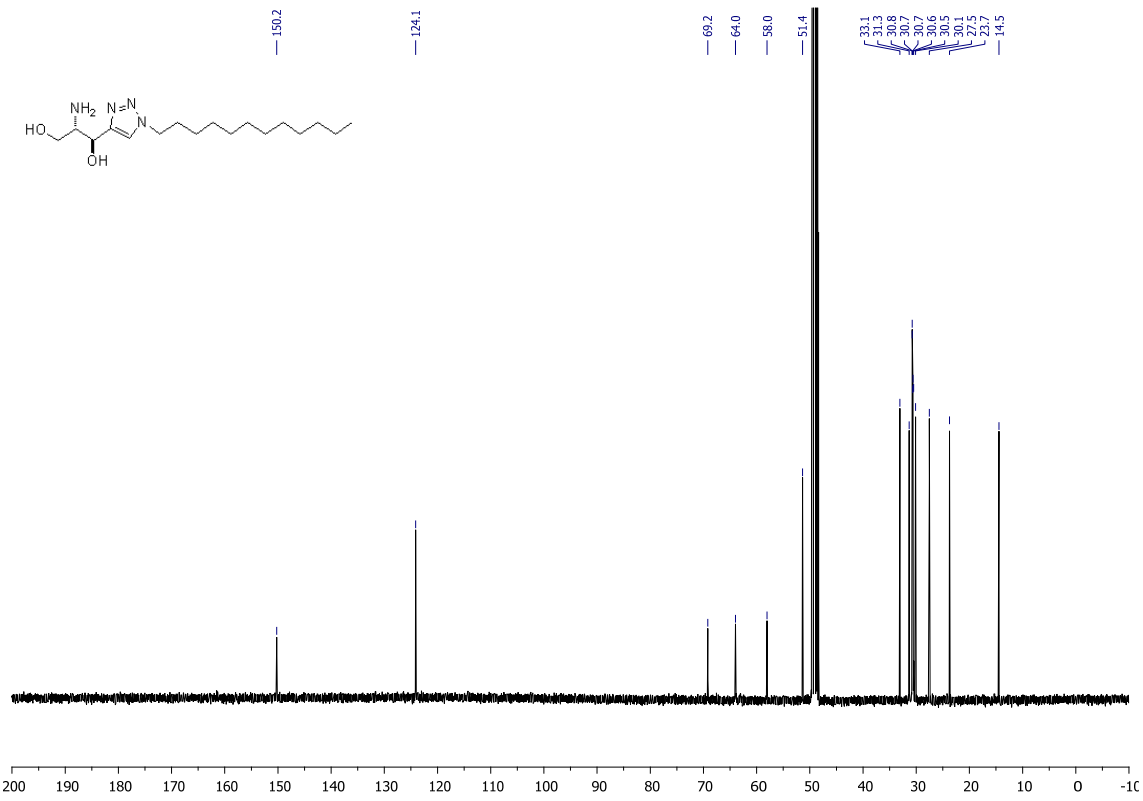

A (s) 7.89
B (d) 5.01
C (t) 4.40
D (d) 3.62
E (q) 2.87
F (s) 2.44
G (m) 2.13
H (m) 1.91
I (m) 1.59
J (m) 1.37
f1 (ppm)
150.6
124.0
119.4
110.5
67.5
66.3
61.0
51.3
34.5
31.4
31.3
30.3
30.3
30.1
30.0
27.4
21.2
A (m) 118.90
B (m) 110.07
A (t) 31.41
A (t) 21.21

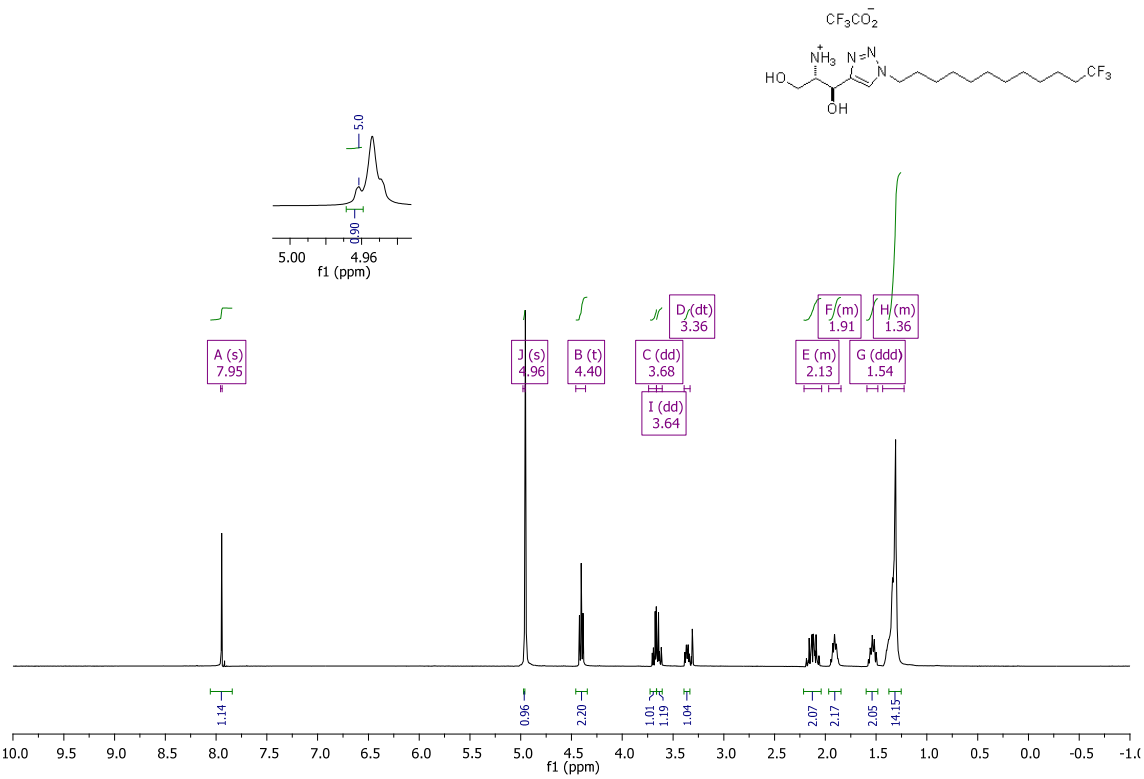


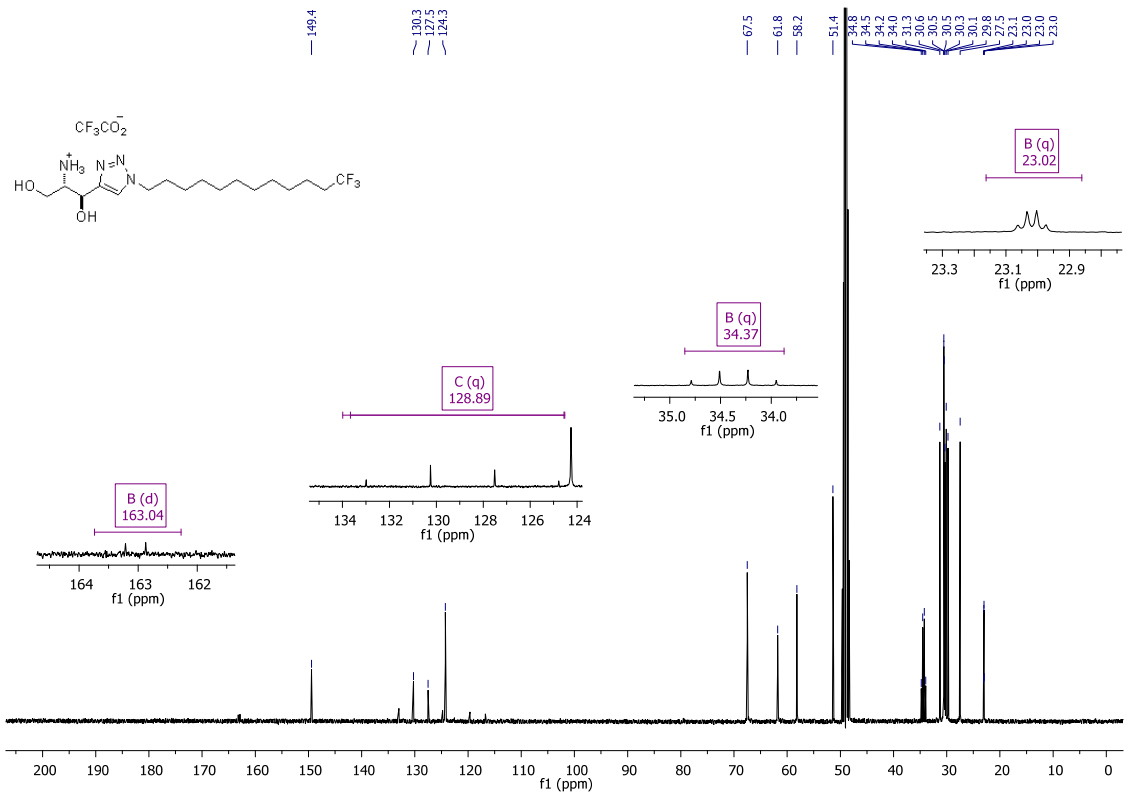

A (m)
-82.27
B (m)
-116.51
C (m)
-129.15
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180
f1 (ppm)

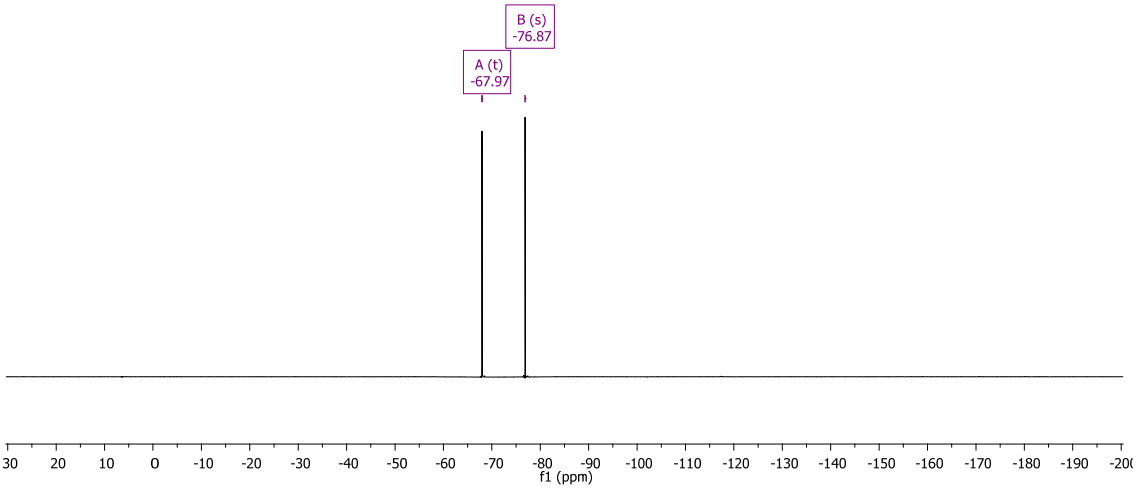


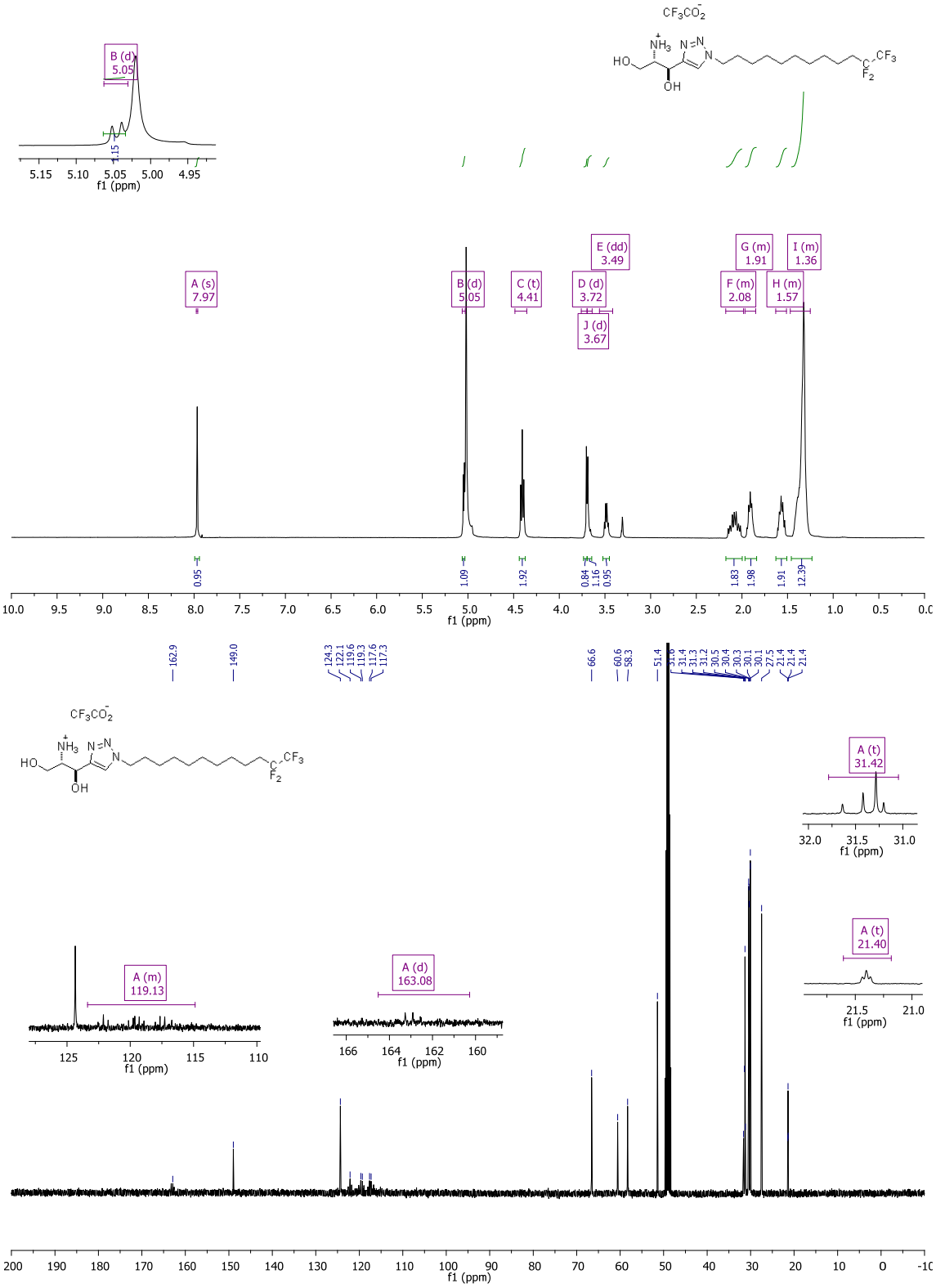
A (s)
7.90
C (d)
4.81
B (t)
4.39
E (dd)
3.57
D (dd)
3.65
G (br d)
3.17
H (m)
1.90
J (m)
1.30
I (t)
0.89
1.00
1.12
1.97
1.06
1.08
1.06
2.18
17.43
3.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

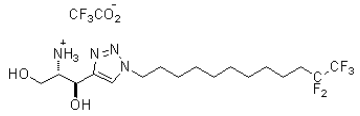

150.2
124.1
69.2
64.0
58.0
51.4
33.1
31.3
30.8
30.7
30.7
30.6
30.5
30.1
27.5
23.7
14.5
NH2
HO
OH
N
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

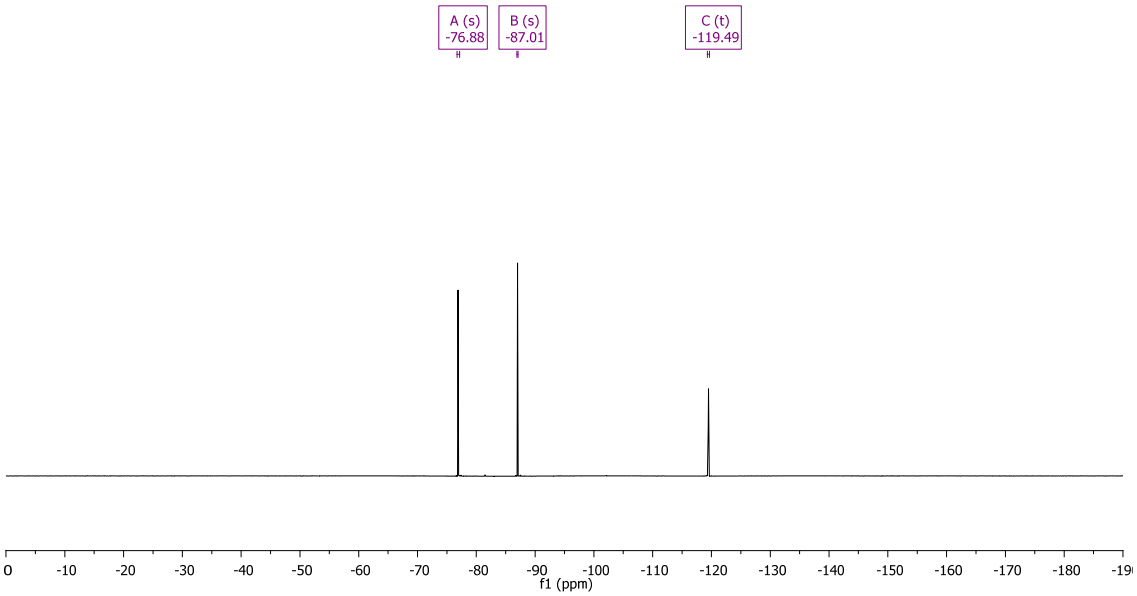

CF3CO2
NH3
HO
OH
CF3
5.0
0.90
5.00
4.96
f1 (ppm)
A (s)
7.95
J (s)
4.96
B (t)
4.40
C (dd)
3.68
D (dt)
3.36
I (dd)
3.64
E (m)
2.13
F (m)
1.91
G (ddd)
1.54
H (m)
1.36
1.14
0.96
2.20
1.01
1.19
1.04
2.07
2.17
2.05
14.15
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

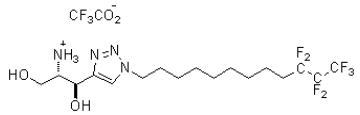

149.4
130.3
127.5
124.3
67.5
61.8
58.2
51.4
34.8
34.5
34.2
34.0
31.3
30.6
30.5
30.5
30.3
30.1
29.8
27.5
23.1
23.0
23.0
23.0
B (q)
23.02
B (q)
34.37
C (q)
128.89
B (d)
163.04
f1 (ppm)


B (s)
-76.87
A (t)
-67.97
f1 (ppm)

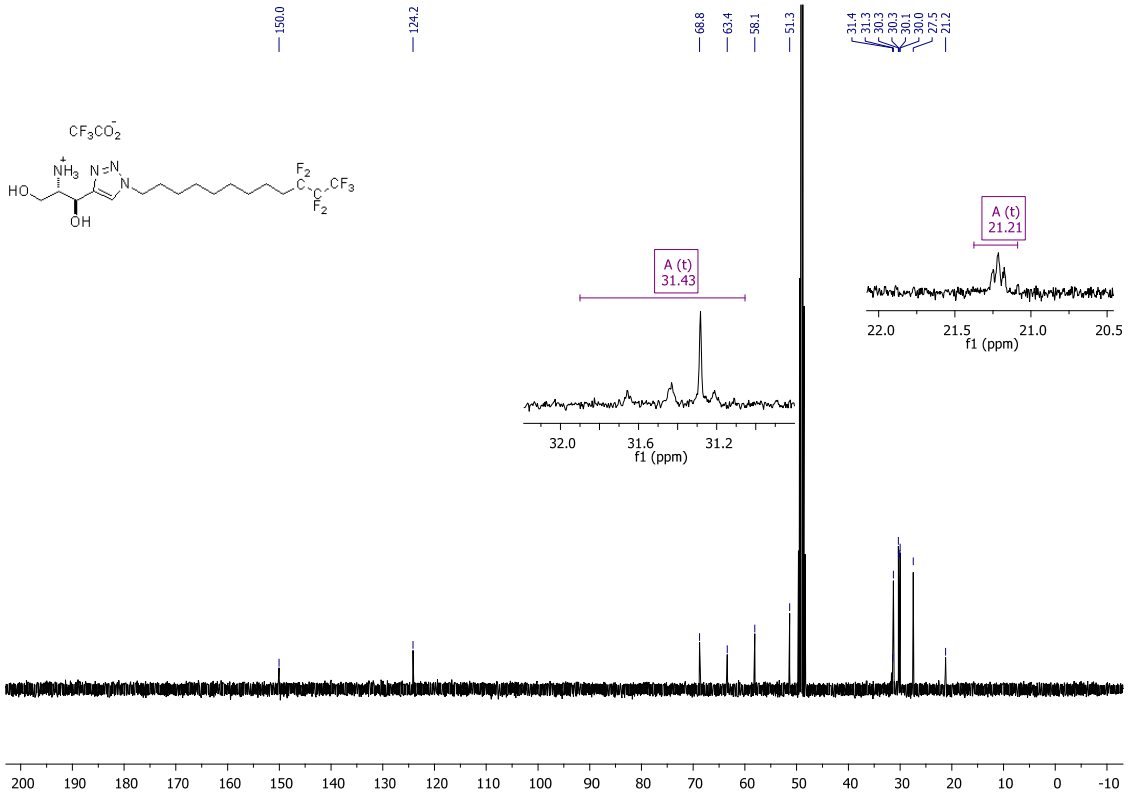

B (d) 5.05
4.15
5.15 5.10 5.05 5.00 4.95
f1 (ppm)
CF3CO2-
NH3+
N=N
HO
OH
CF3
F2
A (s) 7.97
B (d) 5.05
C (t) 4.41
D (d) 3.72
J (d) 3.67
E (dd) 3.49
F (m) 2.08
G (m) 1.91
H (m) 1.57
I (m) 1.36
0.95
1.09
1.92
0.84
1.16
0.95
1.83
1.98
1.91
12.39
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)
162.9
149.0
124.3
122.1
119.6
119.3
117.6
117.3
66.6
60.6
58.3
51.4
31.6
31.4
31.3
31.2
30.5
30.4
30.3
30.1
30.1
27.5
21.4
21.4
21.4
A (t) 31.42
32.0 31.5 31.0
f1 (ppm)
A (t) 21.40
21.5 21.0
f1 (ppm)
A (m) 119.13
125 120 115 110
f1 (ppm)
A (d) 163.08
166 164 162 160
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

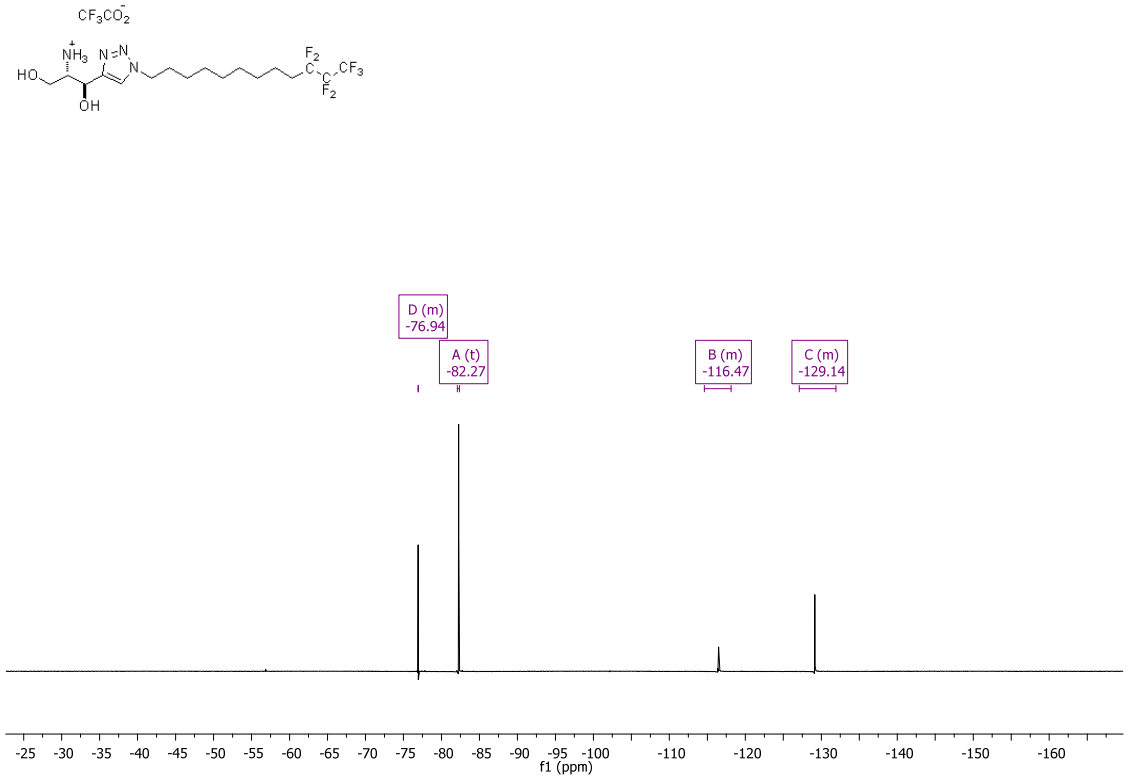


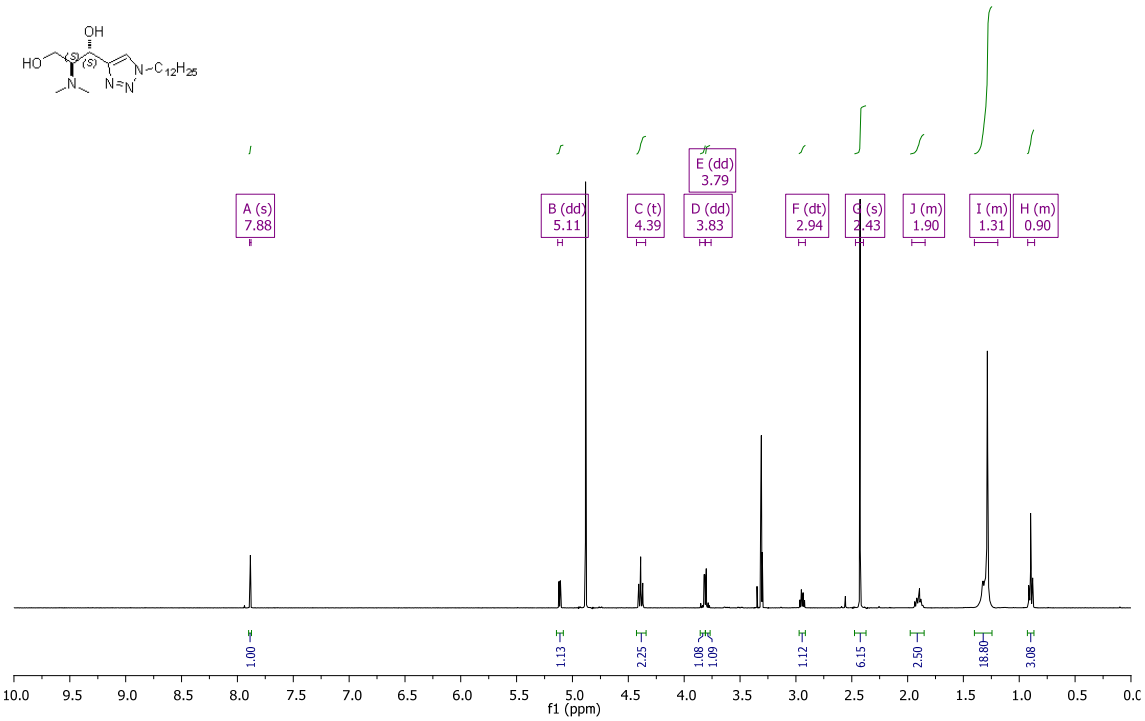

A (s)
-76.88
B (s)
-87.01
C (t)
-119.49
f1 (ppm)

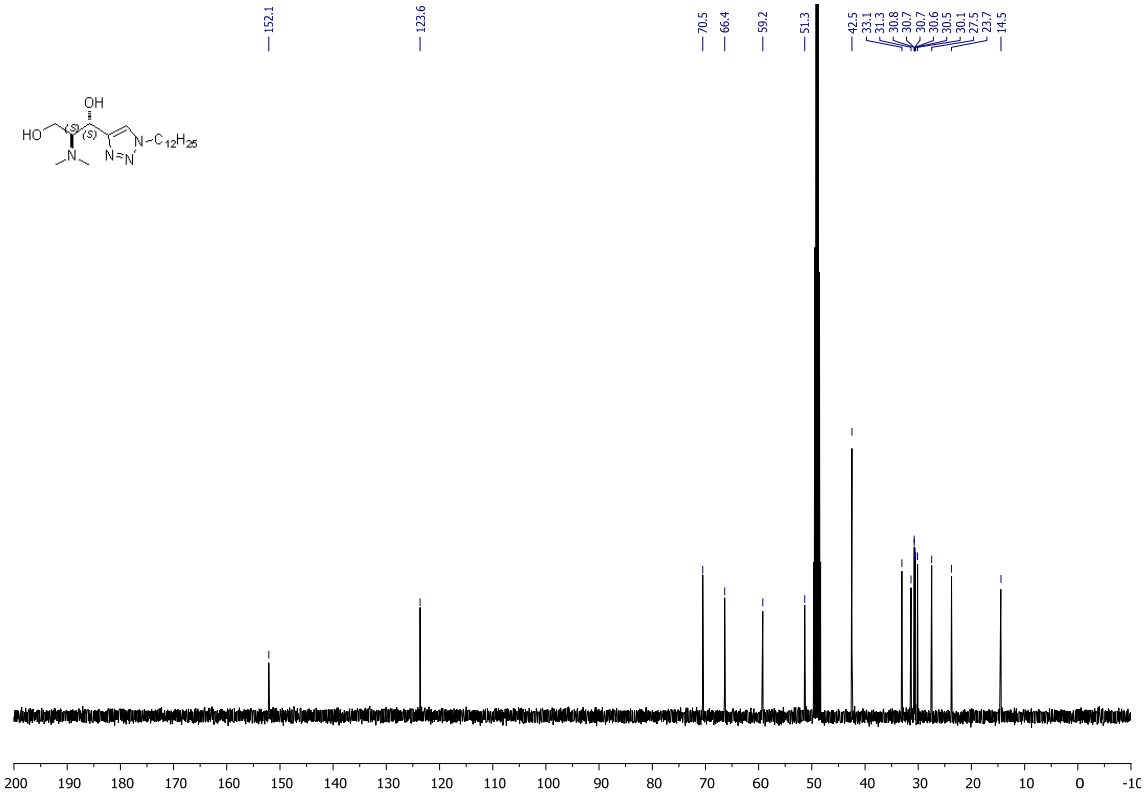


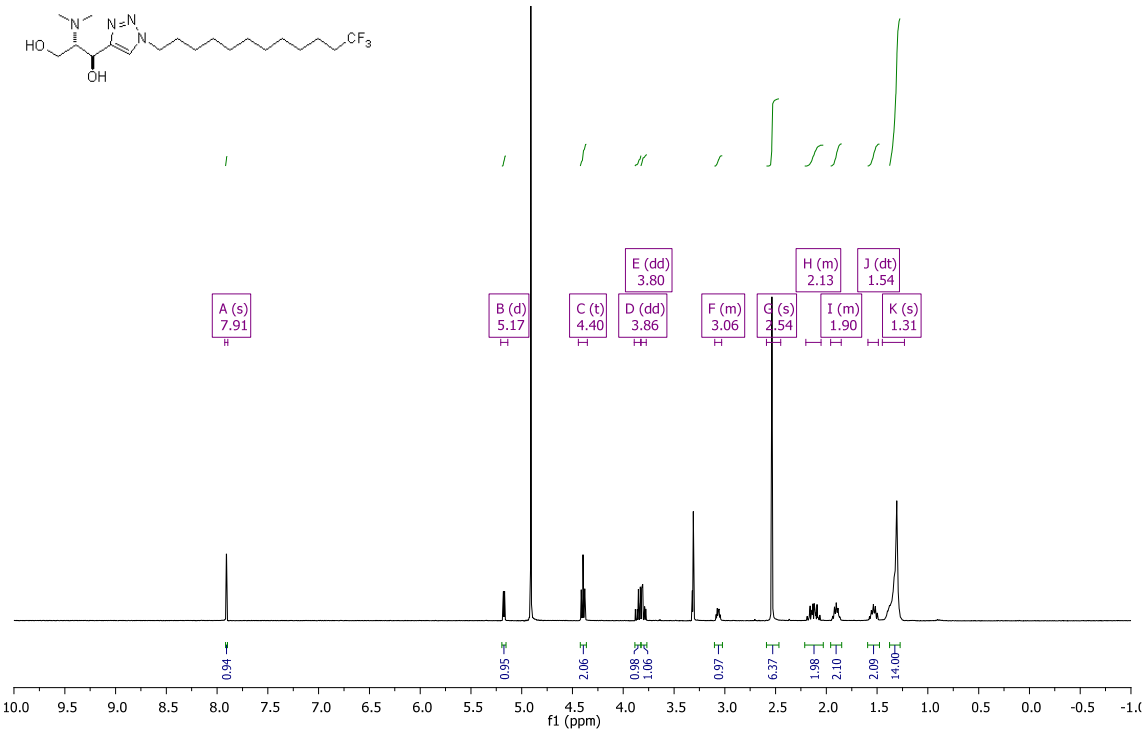
A (d)
7.92
B (d)
4.84
C (t)
4.40
D (dd)
3.66
E (dd)
3.58
F (dd)
3.21
G (m)
2.13
H (m)
1.91
I (m)
1.59
J (m)
1.36
0.90
1.15
1.97
0.90
0.97
0.91
1.91
2.09
2.06
10.00
f1 (ppm)

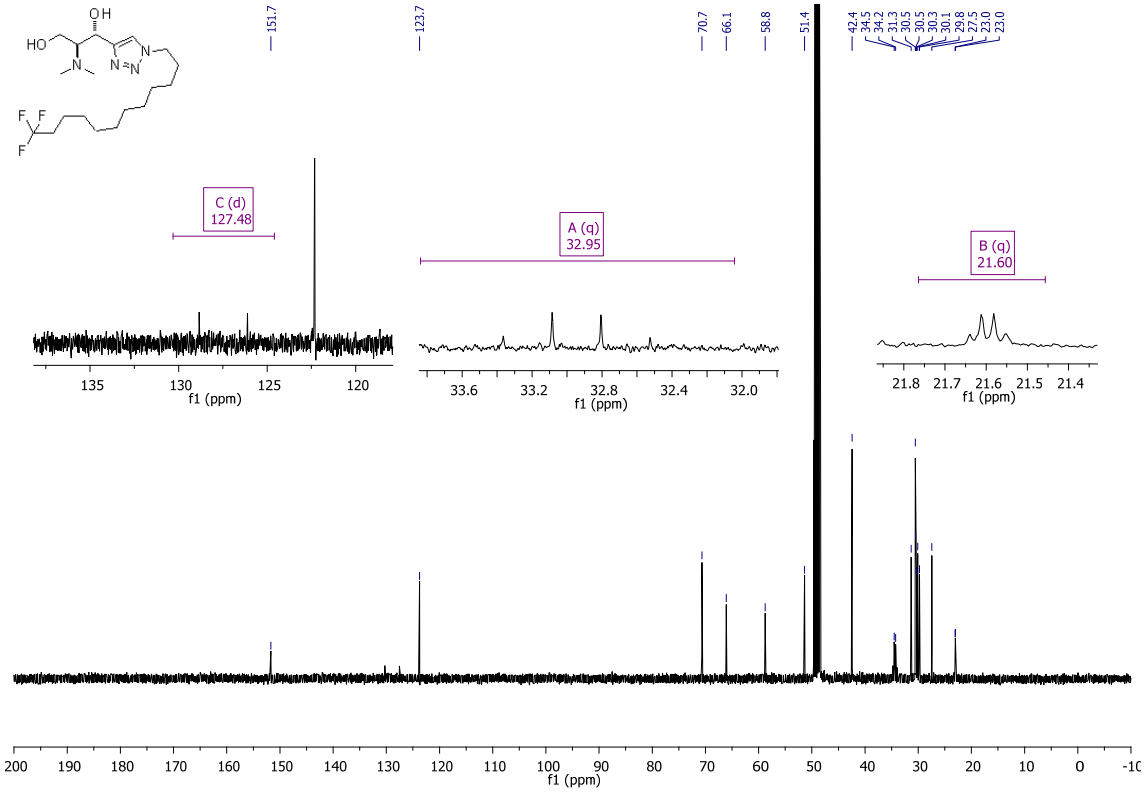

150.0
124.2
68.8
63.4
58.1
51.3
31.4
31.3
30.3
30.3
30.1
30.0
27.5
21.2
A (t)
31.43
A (t)
21.21
f1 (ppm)
f1 (ppm)

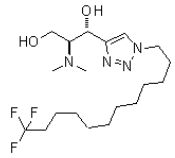

D (m)
-76.94
A (t)
-82.27
B (m)
-116.47
C (m)
-129.14
f1 (ppm)

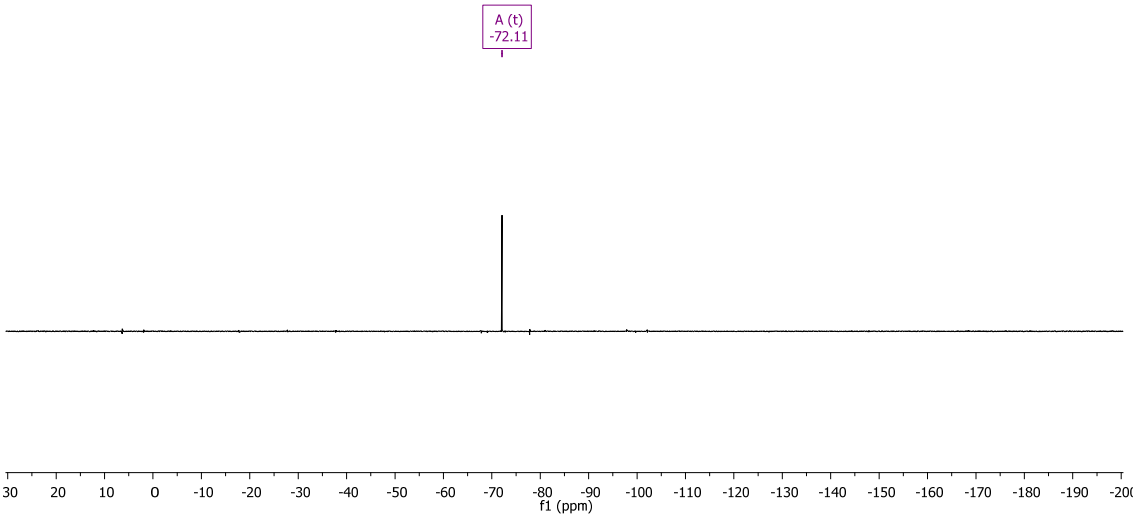

A (s) 7.88
B (dd) 5.11
C (t) 4.39
D (dd) 3.83
E (dd) 3.79
F (dt) 2.94
G (s) 2.43
J (m) 1.90
I (m) 1.31
H (m) 0.90
f1 (ppm)

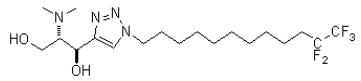

152.1
123.6
70.5
66.4
59.2
51.3
42.5
33.1
31.3
30.8
30.7
30.7
30.7
30.6
30.5
30.1
27.5
23.7
14.5


HO
OH
N
N
N
CF3
A (s) 7.91
B (d) 5.17
C (t) 4.40
D (dd) 3.86
E (dd) 3.80
F (m) 3.06
G (s) 2.54
H (m) 2.13
I (m) 1.90
J (dt) 1.54
K (s) 1.31
0.94
0.95
2.06
0.98
1.06
0.97
6.37
1.98
2.10
2.09
14.00
f1 (ppm)

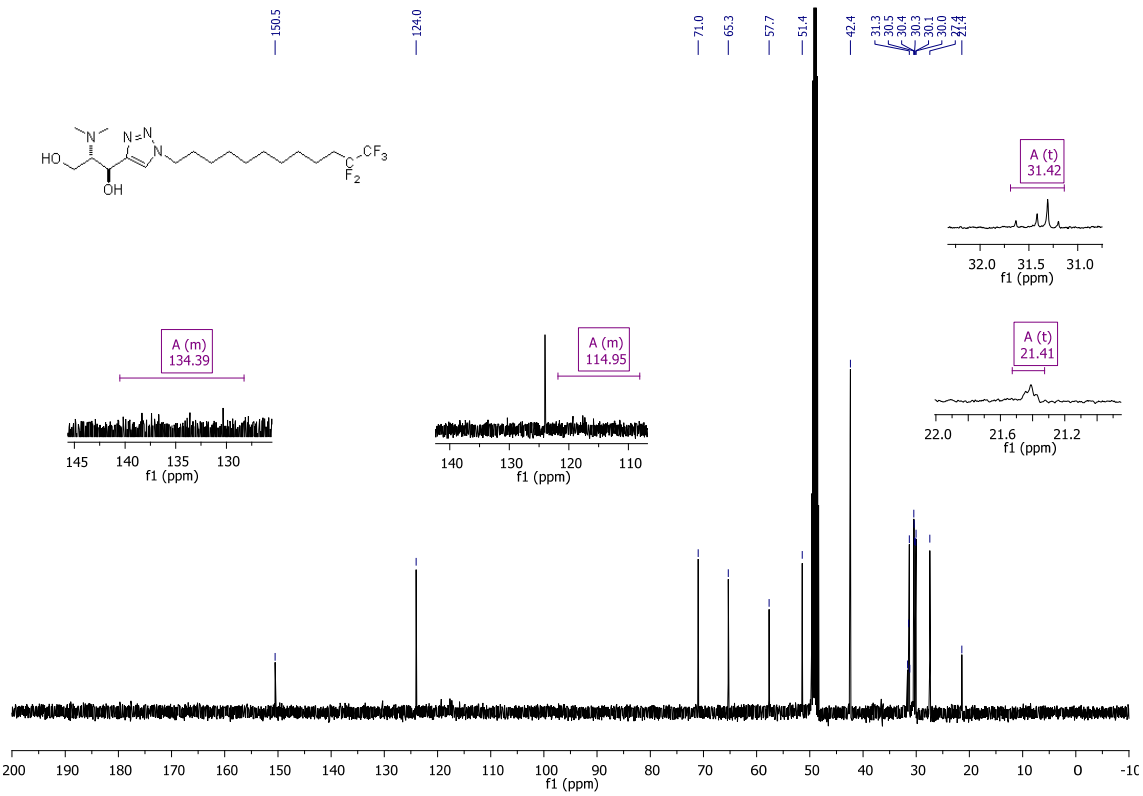

HO
OH
N
N
N
F
F
F
151.7
123.7
70.7
66.1
58.8
51.4
42.4
34.5
34.2
31.3
30.5
30.5
30.3
30.1
29.8
27.5
23.0
23.0
C (d) 127.48
A (q) 32.95
B (q) 21.60
f1 (ppm)

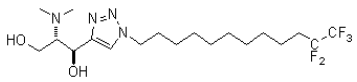


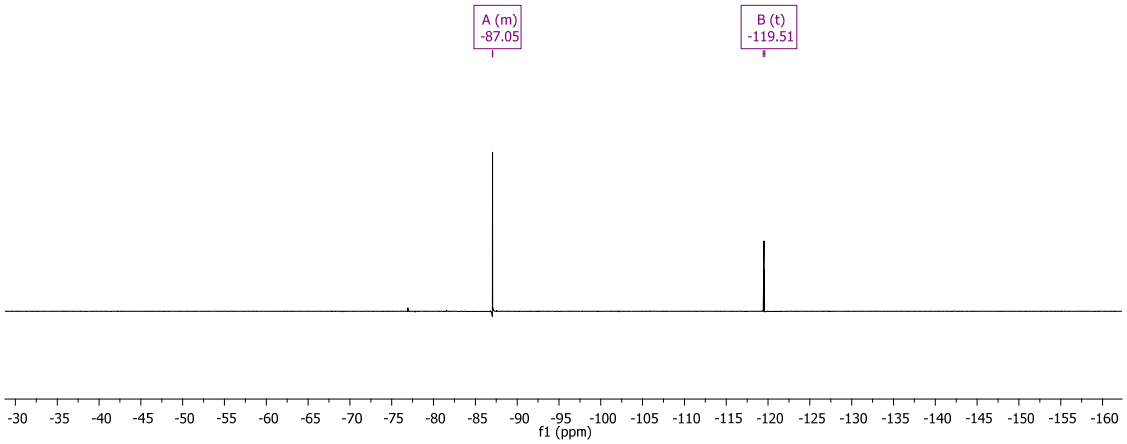

A (t)
-72.11
f1 (ppm)

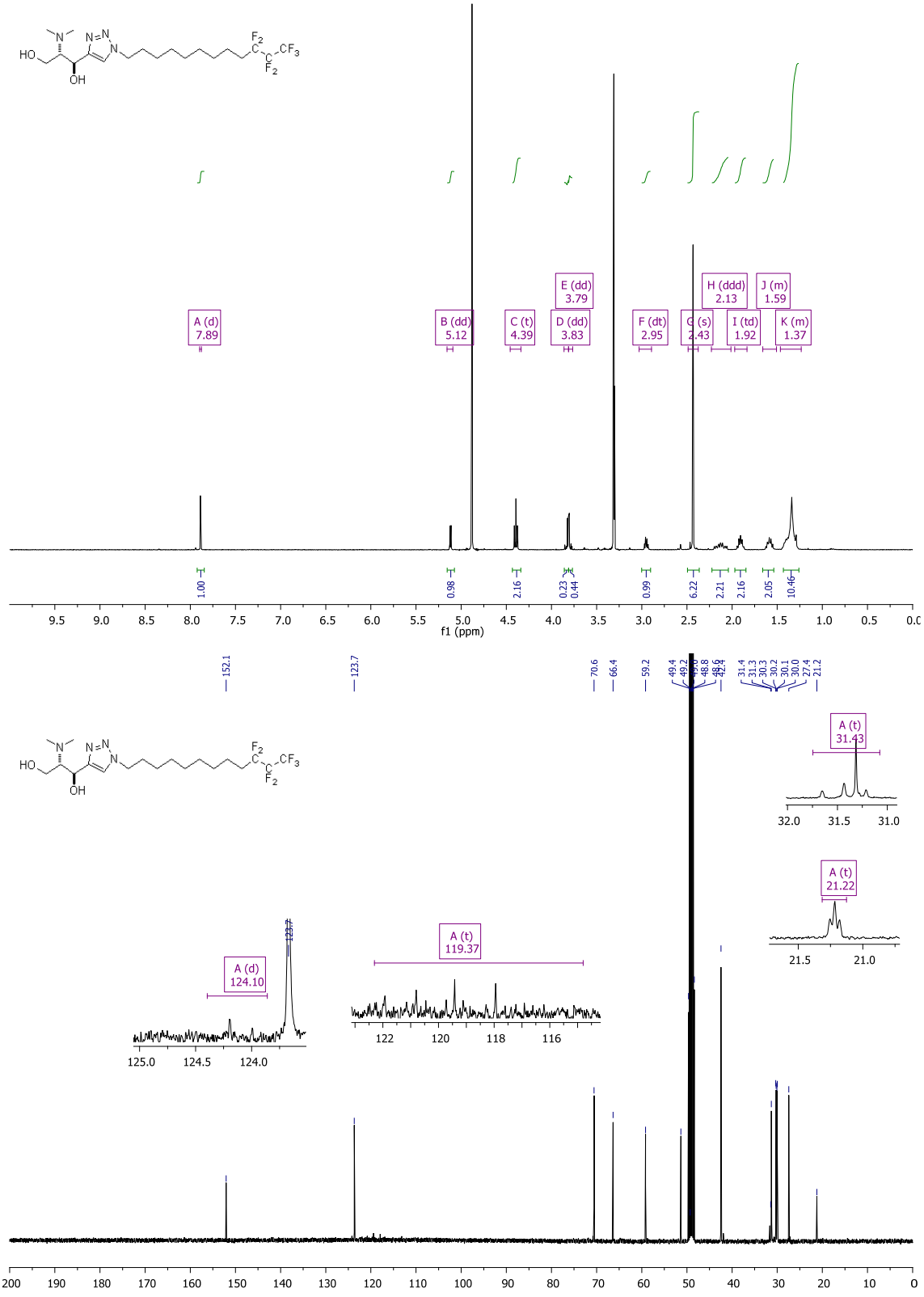


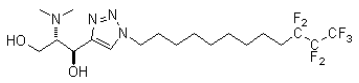
A (s)
7.96
B (d)
5.32
C (t)
4.41
D (dd)
3.93
E (dd)
3.81
F (dt)
3.35
G (s)
2.79
H (ddd)
2.09
I (m)
1.91
J (m)
1.57
K (m)
1.36
f1 (ppm)

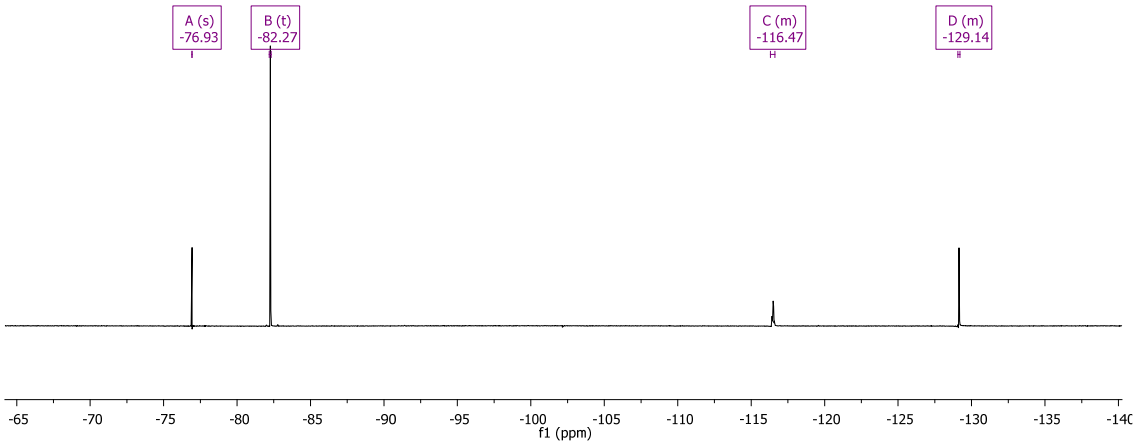

150.5
124.0
71.0
65.3
57.7
51.4
42.4
31.3
30.5
30.4
30.3
30.1
30.0
21.4
21.1
HO
OH
N
N
N
CF3
C
F2
A (t)
31.42
32.0
31.5
31.0
f1 (ppm)
A (m)
134.39
145
140
135
130
f1 (ppm)
A (m)
114.95
140
130
120
110
f1 (ppm)
A (t)
21.41
22.0
21.6
21.2
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

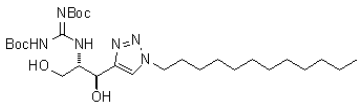

HO
OH
N
N
N
CF3
C
F2

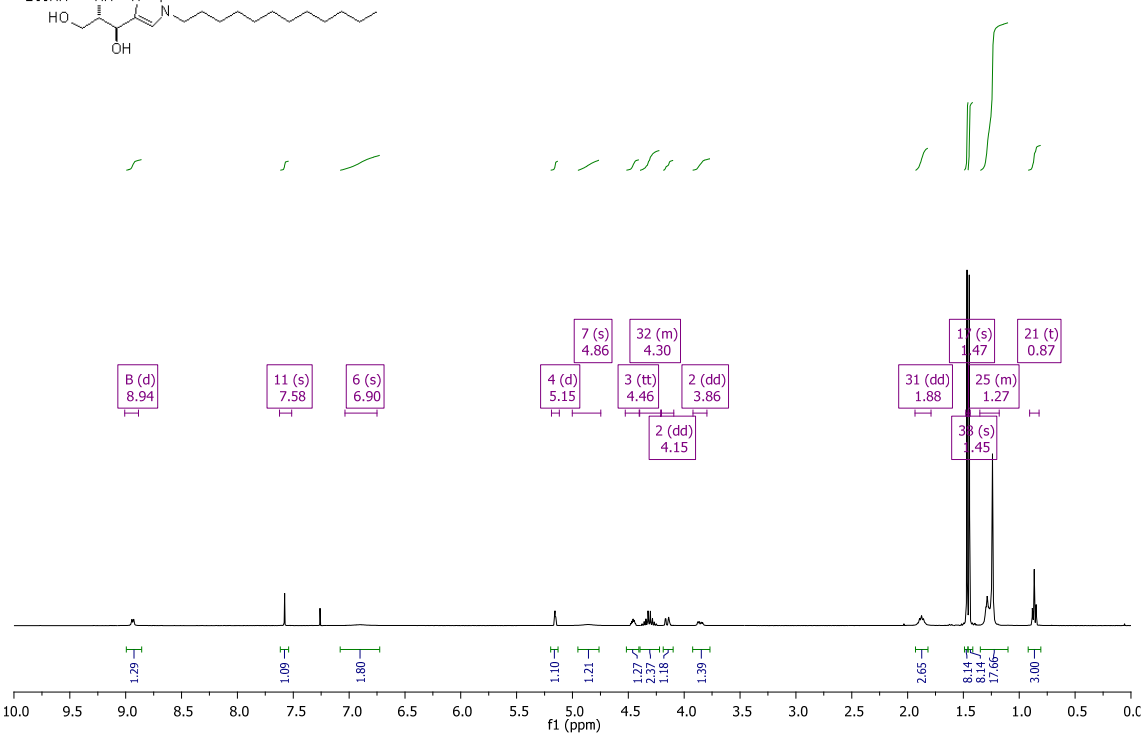

A (m)
-87.05
B (t)
-119.51
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
-125
-130
-135
-140
-145
-150
-155
-160
f1 (ppm)

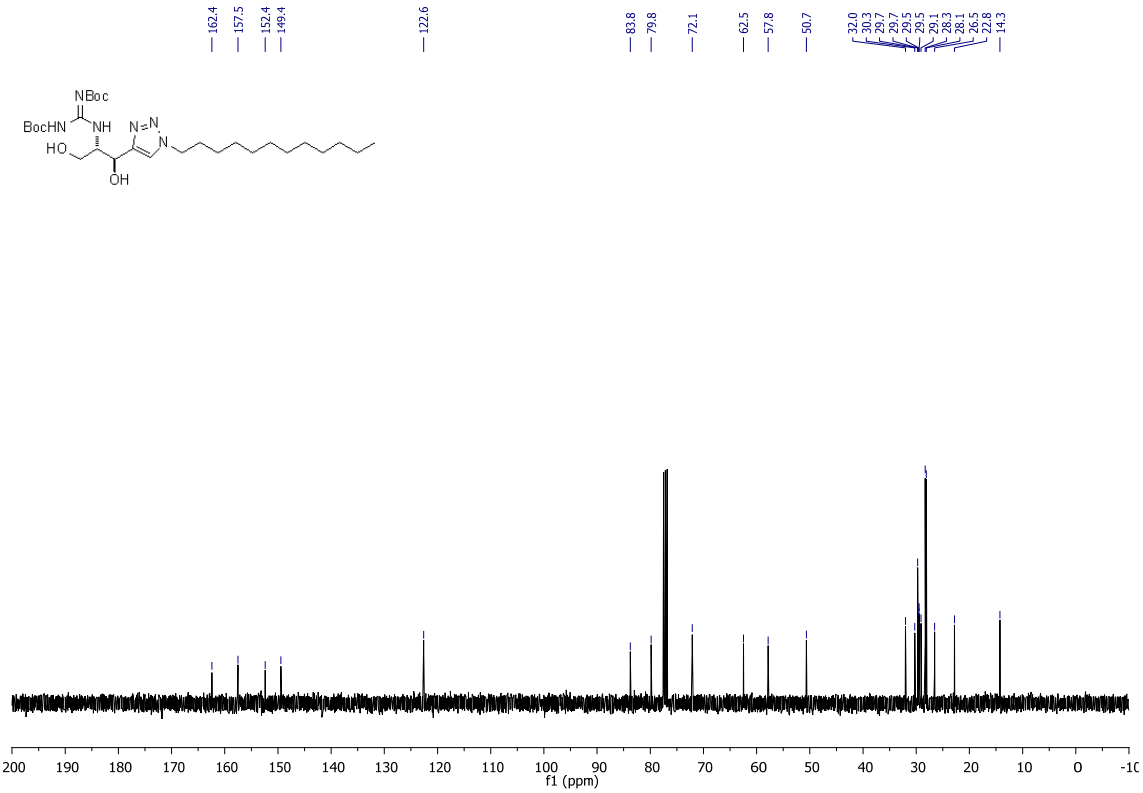

A (d) 7.89
B (dd) 5.12
C (t) 4.39
D (dd) 3.83
E (dd) 3.79
F (dt) 2.95
G (s) 2.43
H (ddd) 2.13
I (td) 1.92
J (m) 1.59
K (m) 1.37
f1 (ppm)
A (d) 124.10
A (t) 119.37
A (t) 31.43
A (t) 21.22

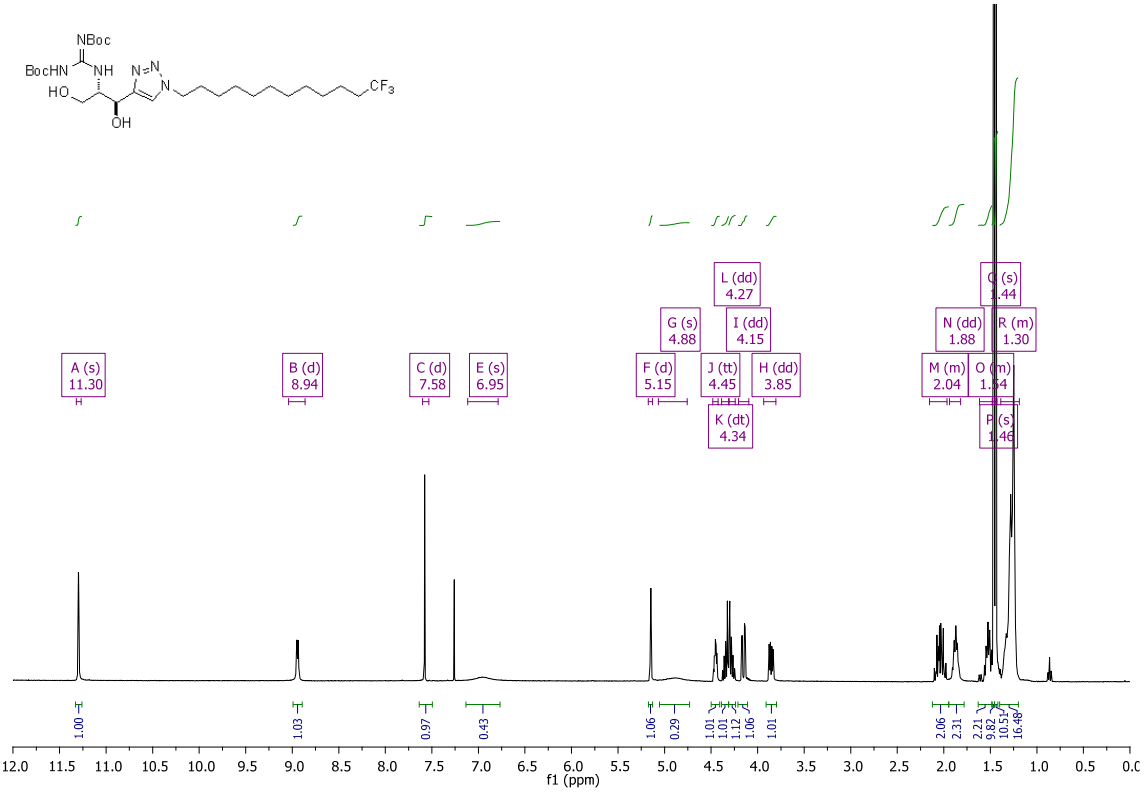


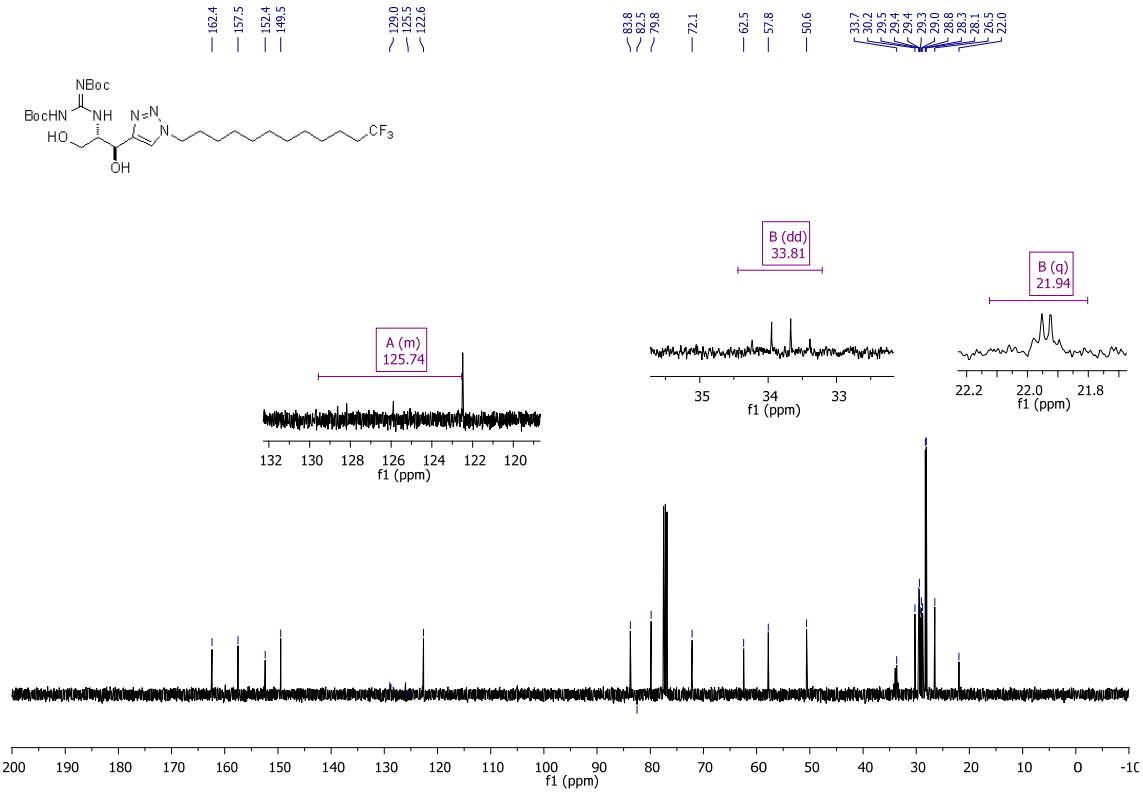

A (s)
-76.93
B (t)
-82.27
C (m)
-116.47
D (m)
-129.14
f1 (ppm)



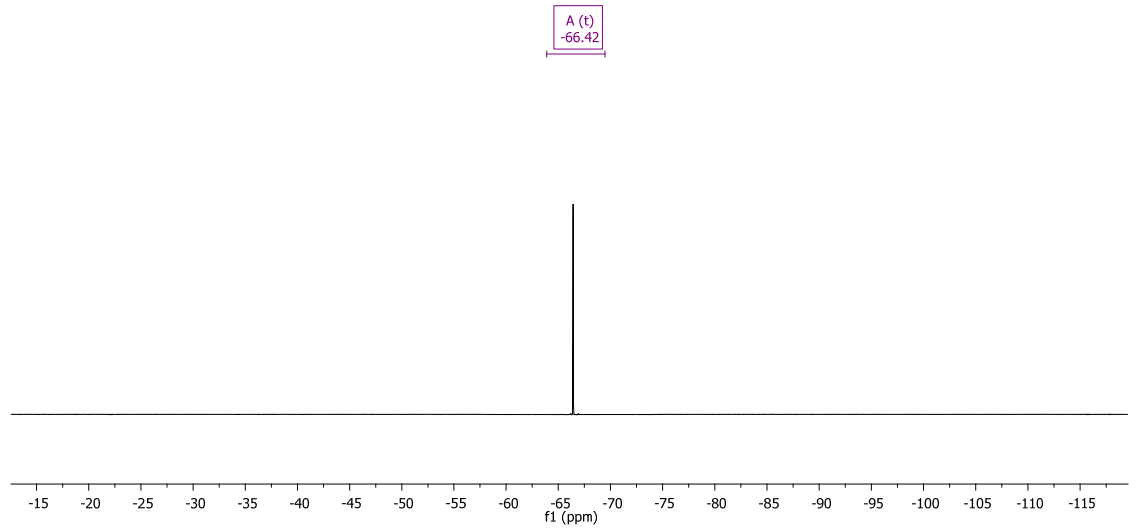

B (d)
8.94
11 (s)
7.58
6 (s)
6.90
7 (s)
4.86
4 (d)
5.15
32 (m)
4.30
3 (tt)
4.46
2 (dd)
3.86
2 (dd)
4.15
31 (dd)
1.88
25 (m)
1.27
21 (t)
0.87
f1 (ppm)

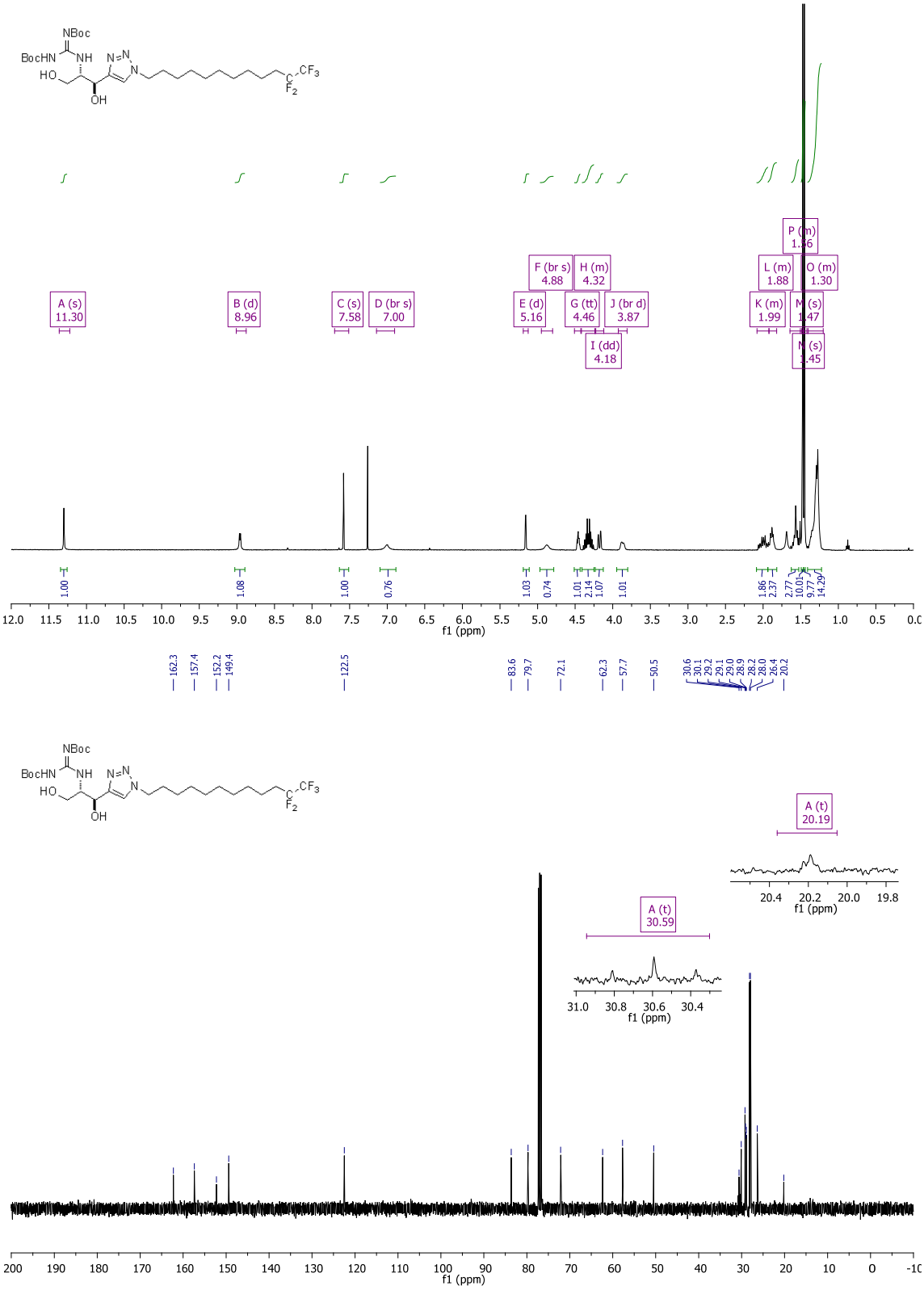

162.4
157.5
152.4
149.4
122.6
83.8
79.8
72.1
62.5
57.8
50.7
32.0
30.3
29.7
29.7
29.5
29.5
29.1
28.3
28.1
26.5
22.8
14.3
NBoc
BocHN
NH
N=N
HO
OH
f1 (ppm)

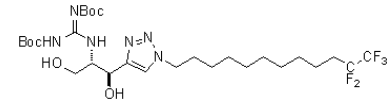

NBoc
BocHN
NH
N=N
HO
OH
CF3
A (s) 11.30
B (d) 8.94
C (d) 7.58
E (s) 6.95
F (d) 5.15
G (s) 4.88
H (dd) 3.85
I (dd) 4.15
J (tt) 4.45
K (dt) 4.34
L (dd) 4.27
M (m) 2.04
N (dd) 1.88
O (m) 1.54
P (s) 1.46
R (m) 1.30
1.00
1.03
0.97
0.43
1.06
0.29
1.01
1.01
1.12
1.06
1.01
2.06
2.31
2.21
9.82
10.51
16.48
f1 (ppm)

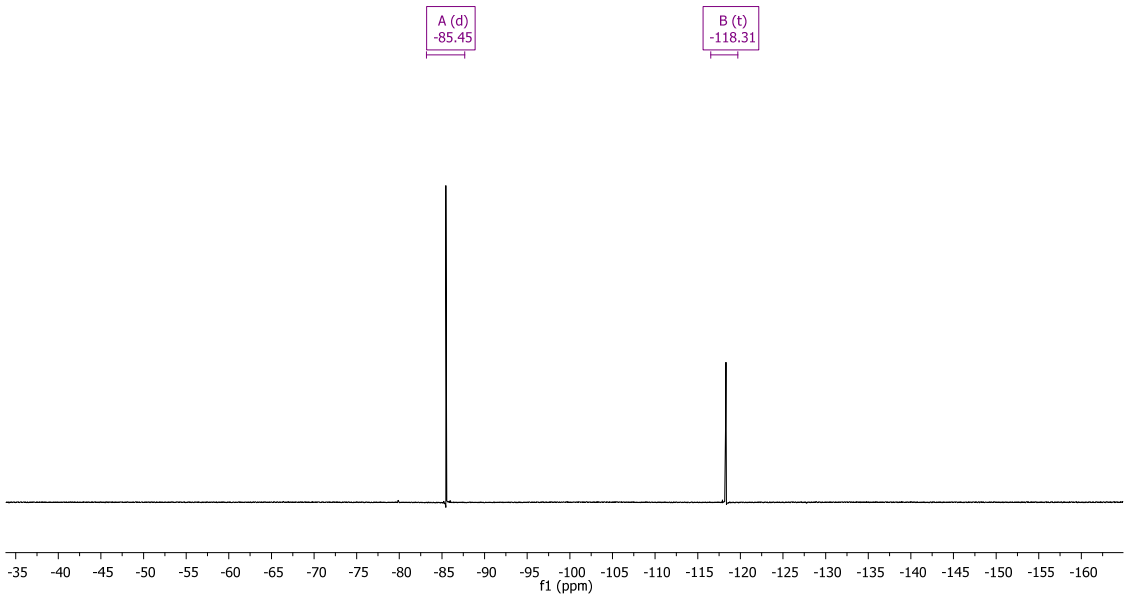

162.4
157.5
152.4
149.5
129.0
125.5
122.6
83.8
82.5
79.8
72.1
62.5
57.8
50.6
33.7
30.2
29.5
29.4
29.3
29.0
28.8
28.3
28.1
26.5
22.0
NBoc
BocHN
NH
N=N
HO
OH
CF3
A (m)
125.74
B (dd)
33.81
B (q)
21.94
f1 (ppm)

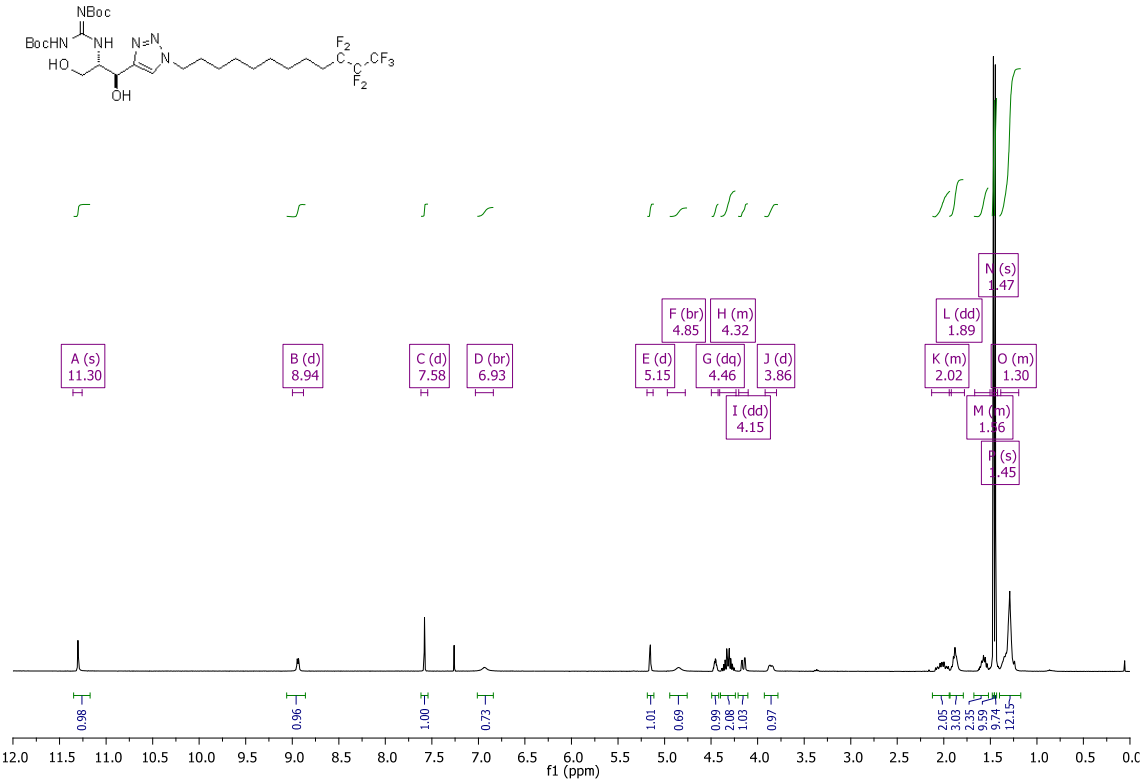

NBoc
BocHN
NH
N=N
HO
OH
CF3

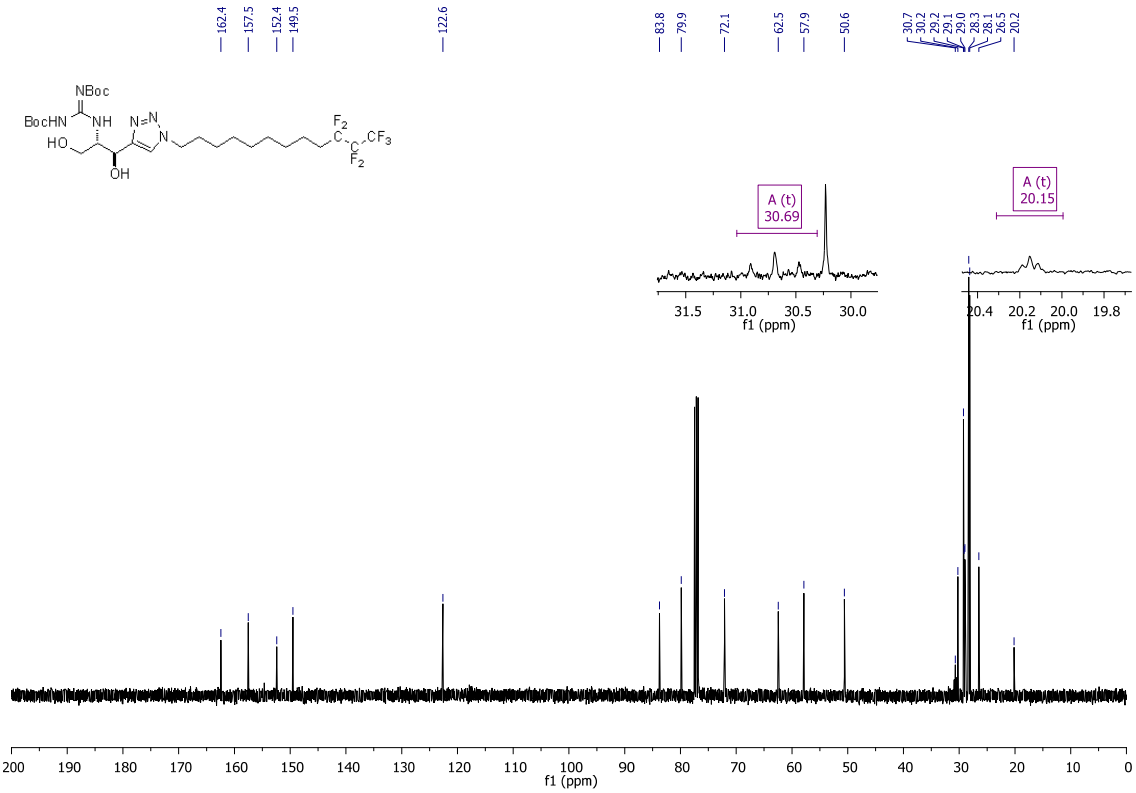

A (t)
-66.42
f1 (ppm)

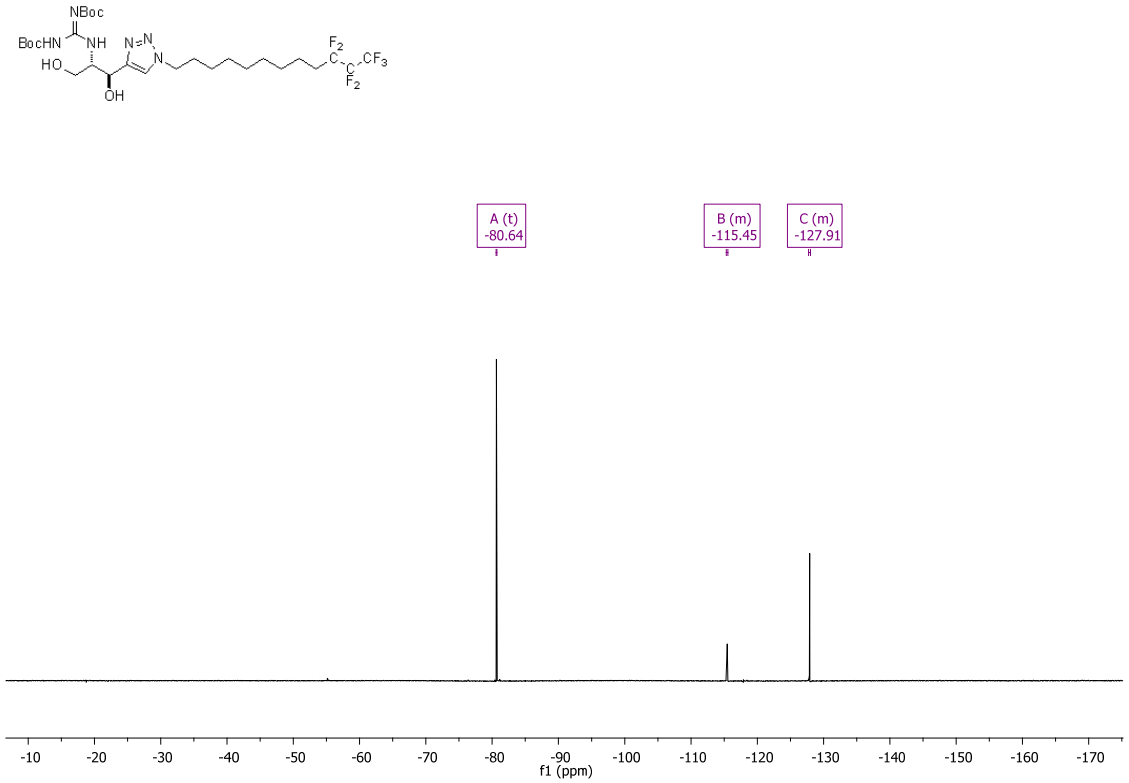

NBoc
BocHN
NH
N=N
HO
OH
CF3
F2
A (s) 11.30
B (d) 8.96
C (s) 7.58
D (br s) 7.00
E (d) 5.16
F (br s) 4.88
G (tt) 4.46
H (m) 4.32
I (dd) 4.18
J (br d) 3.87
K (m) 1.99
L (m) 1.88
M (s) 1.47
O (m) 1.30
P (m) 1.26
N (s) 1.45
f1 (ppm)
162.3
157.4
152.2
149.4
122.5
83.6
79.7
72.1
62.3
57.7
50.5
30.6
30.1
29.2
29.1
29.0
28.9
28.2
28.0
26.4
20.2
A (t) 30.59
A (t) 20.19

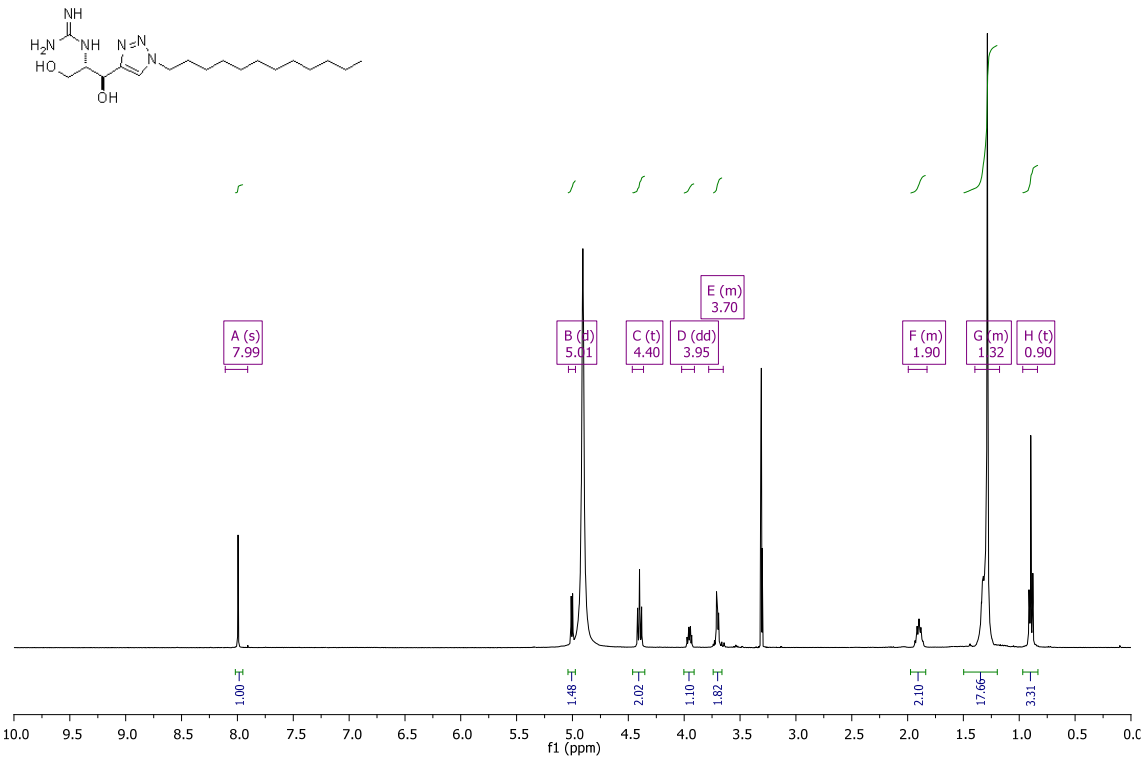

NBoc
BocHN
NH
HO
OH
N=N
N
CF3
C
F2

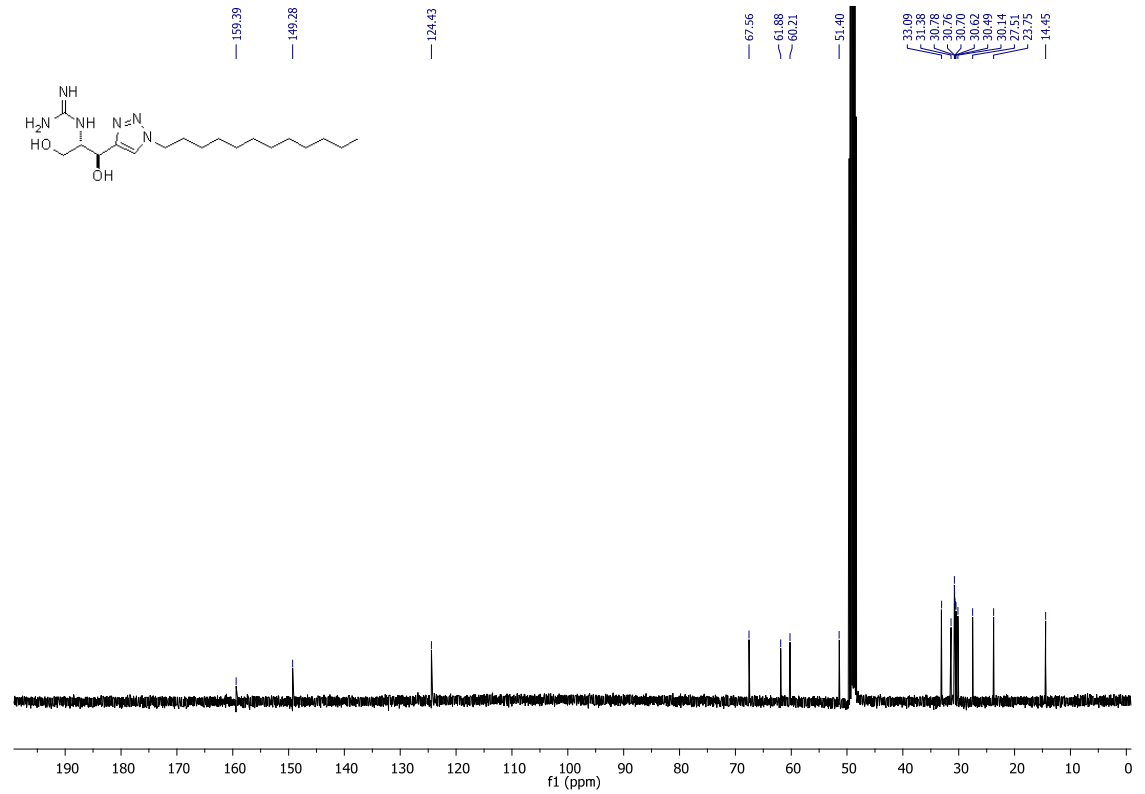

A (d)
-85.45
B (t)
-118.31
-35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160
f1 (ppm)

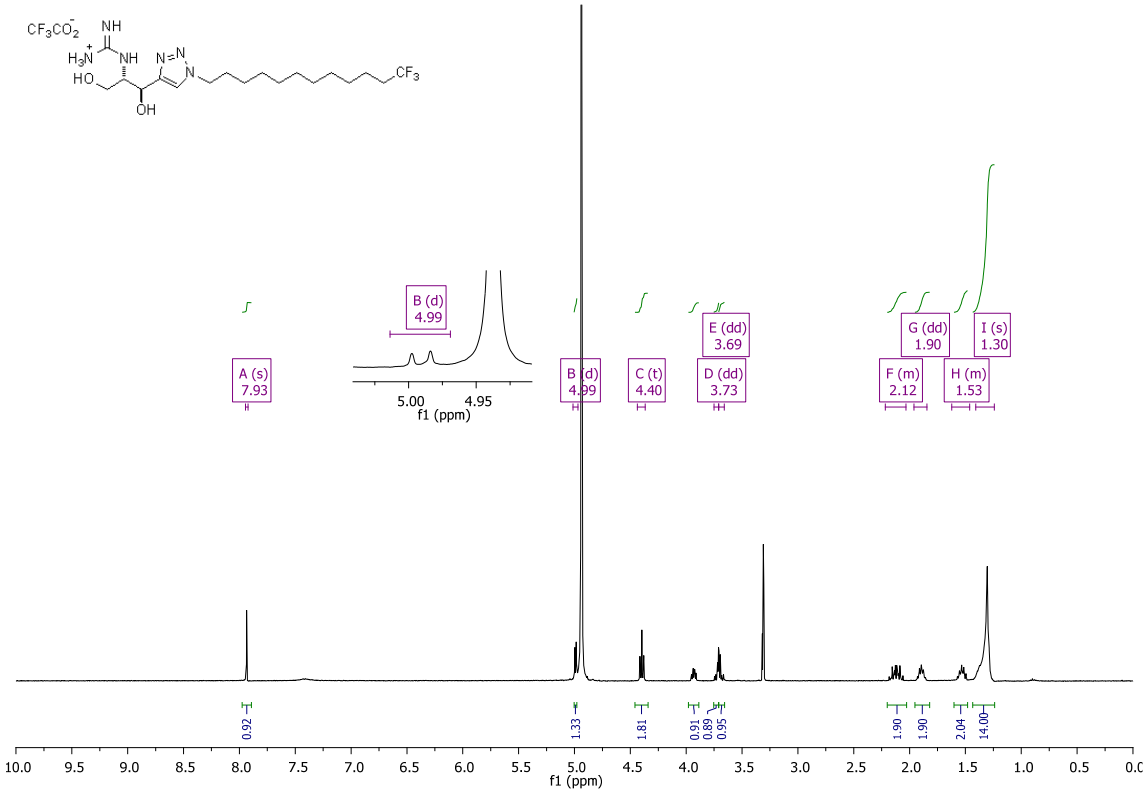

NBoc
BocHN
NH
HO
OH
N=N
N
F2
C
CF3
F2
A (s)
11.30
B (d)
8.94
C (d)
7.58
D (br)
6.93
E (d)
5.15
F (br)
4.85
G (dq)
4.46
H (m)
4.32
I (dd)
4.15
J (d)
3.86
K (m)
2.02
L (dd)
1.89
M (m)
1.86
N (s)
1.47
O (m)
1.30
P (s)
1.45
0.98
0.96
1.00
0.73
1.01
0.69
0.99
2.08
1.03
0.97
2.05
3.03
2.35
9.59
9.74
12.15
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
f1 (ppm)

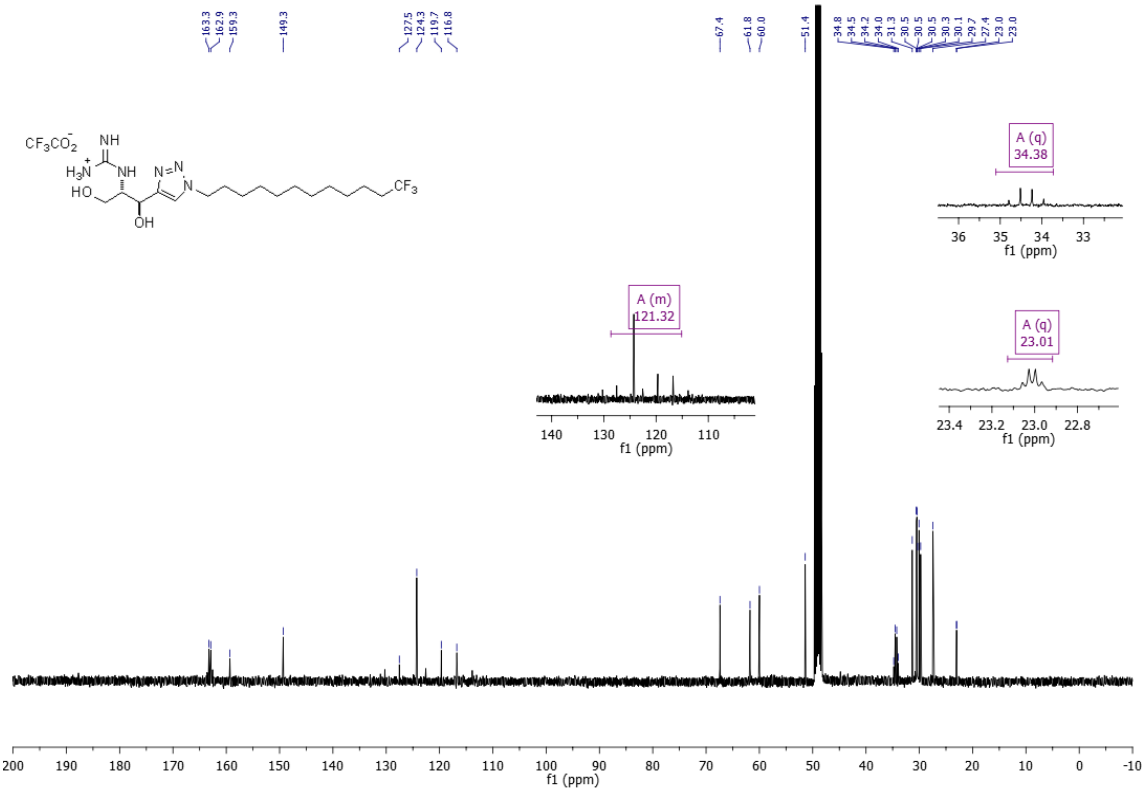

162.4
157.5
152.4
149.5
122.6
83.8
79.9
72.1
62.5
57.9
50.6
30.7
30.2
29.2
29.1
29.0
28.3
28.1
26.5
20.2
NBoc
BocHN
NH
HO
OH
N=N
N
F2
C
CF3
C
F2
A (t)
30.69
A (t)
20.15
31.5
31.0
30.5
30.0
f1 (ppm)
20.4
20.2
20.0
19.8
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

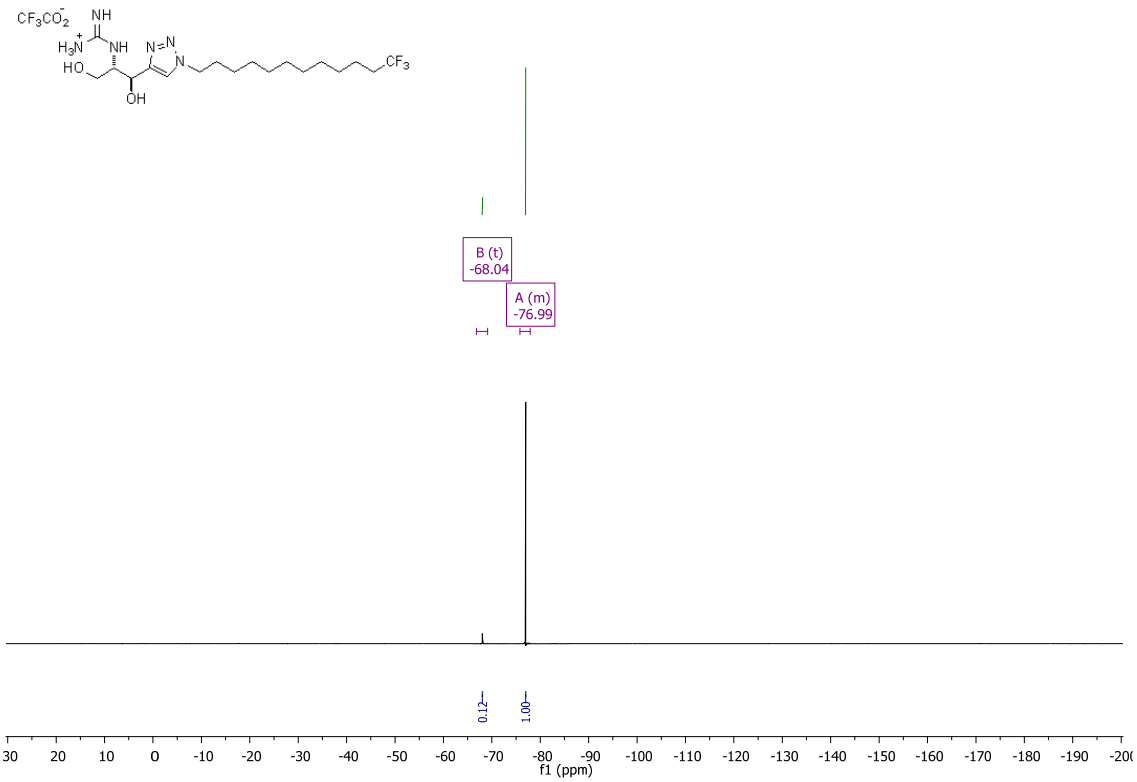

NBoc
BocHN
NH
HO
OH
N=N
N
F2
C
CF3
C
F2
A (t)
-80.64
B (m)
-115.45
C (m)
-127.91
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
f1 (ppm)

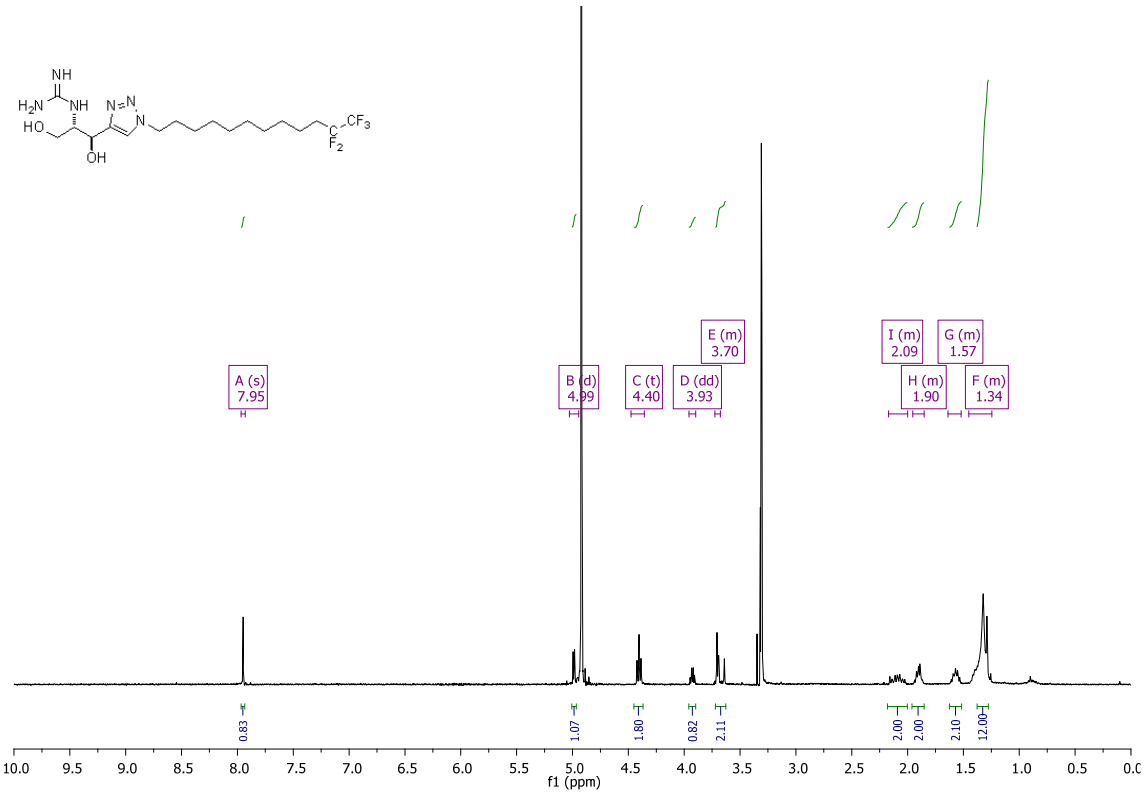

A (s) 7.99
B (d) 5.01
C (t) 4.40
D (dd) 3.95
E (m) 3.70
F (m) 1.90
G (m) 1.32
H (t) 0.90
f1 (ppm)

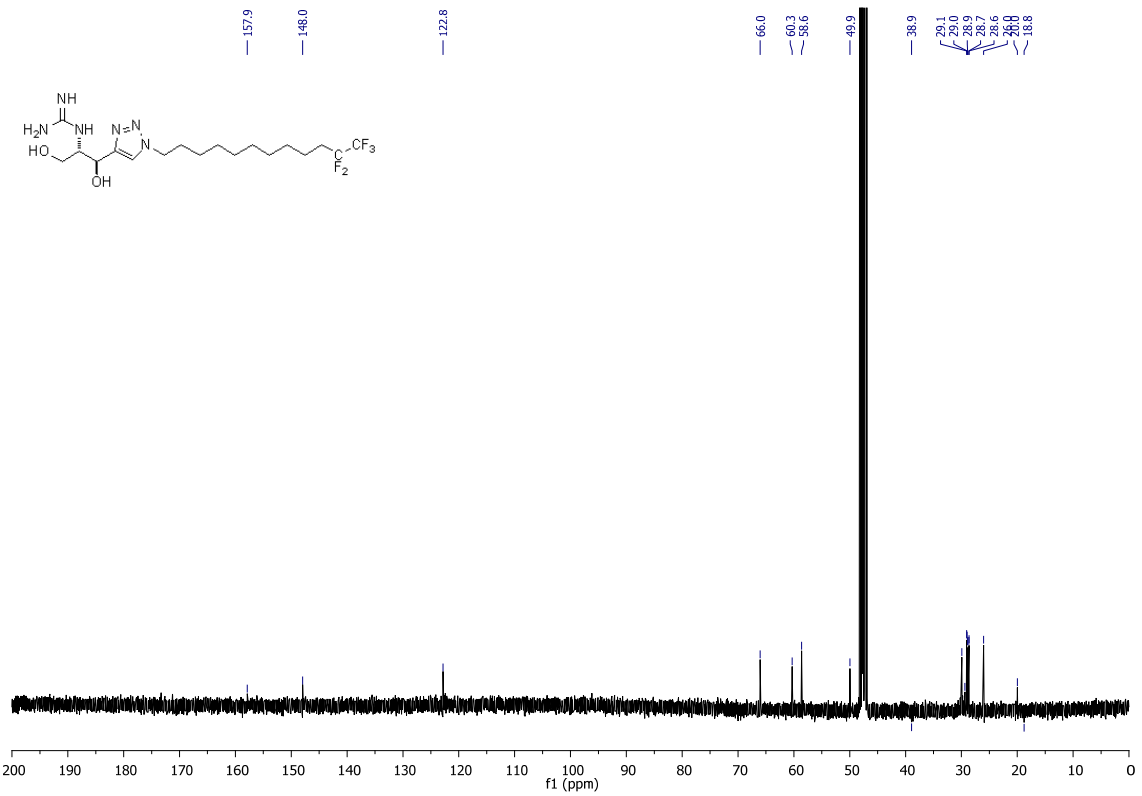

159.39
149.28
124.43
67.56
61.88
60.21
51.40
33.09
31.38
30.78
30.76
30.70
30.62
30.49
30.14
27.51
23.75
14.45
f1 (ppm)

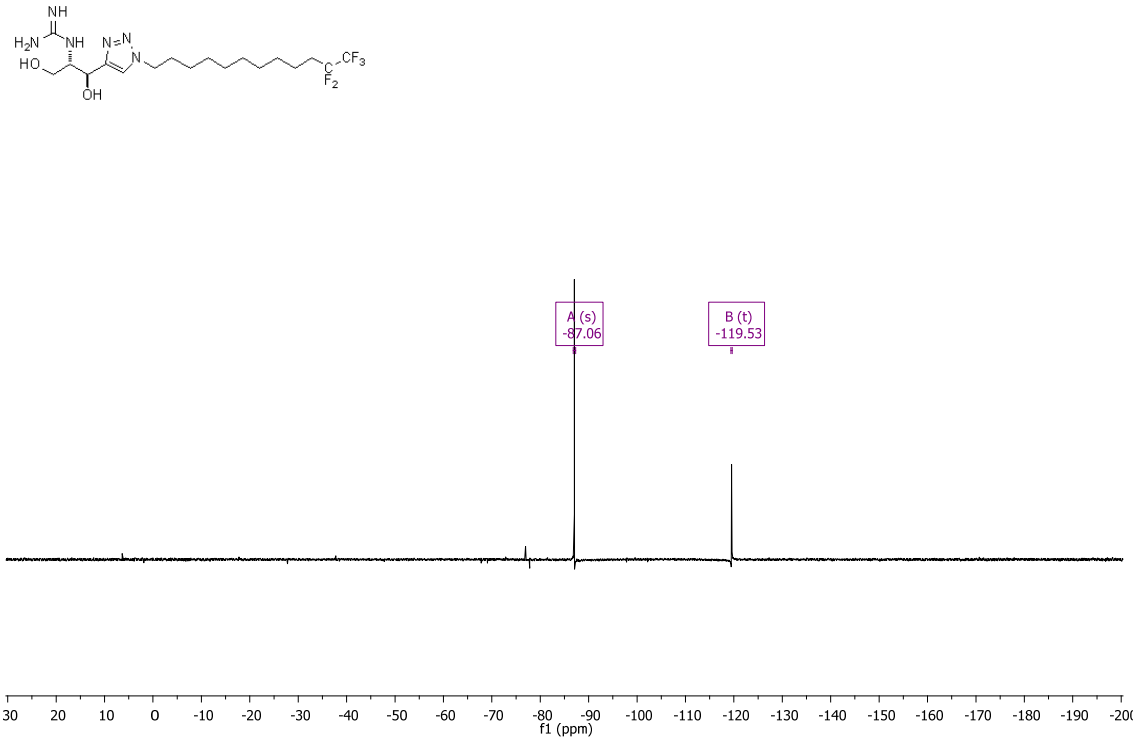

A (s)
7.93
B (d)
4.99
C (t)
4.40
D (dd)
3.73
E (dd)
3.69
F (m)
2.12
G (dd)
1.90
H (m)
1.53
I (s)
1.30
f1 (ppm)

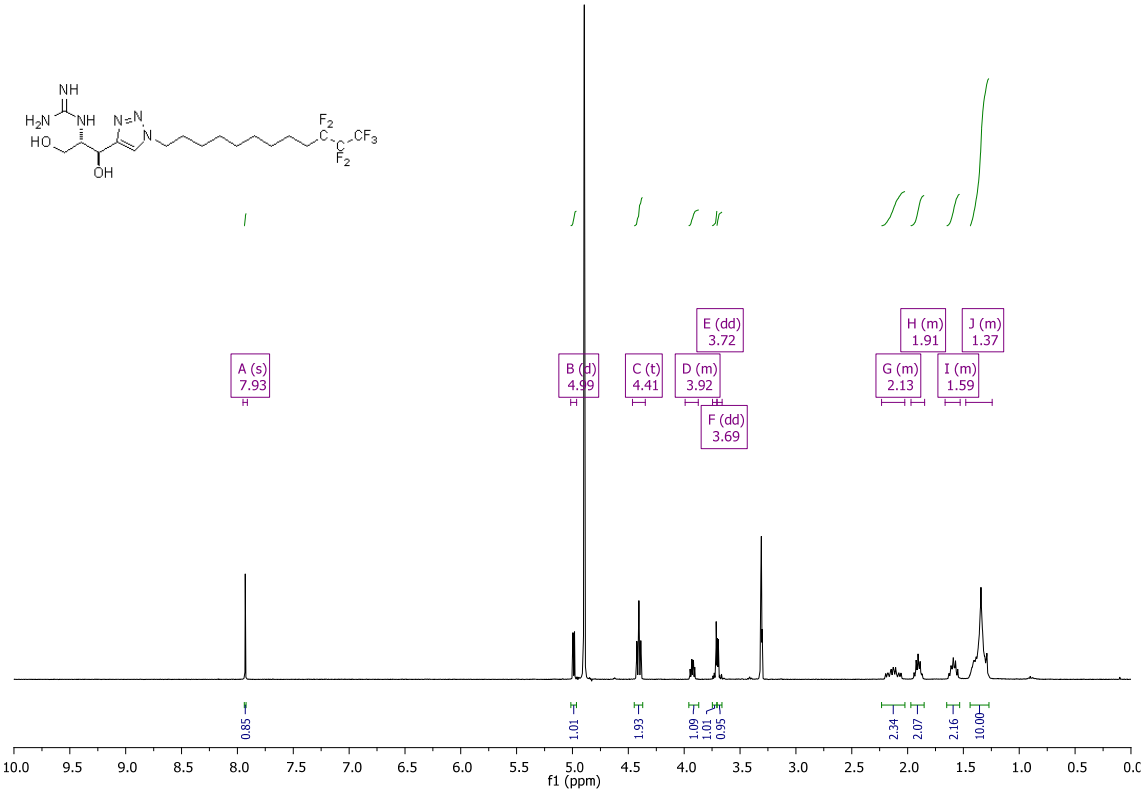

A (q)
34.38
A (m)
121.32
A (q)
23.01
f1 (ppm)

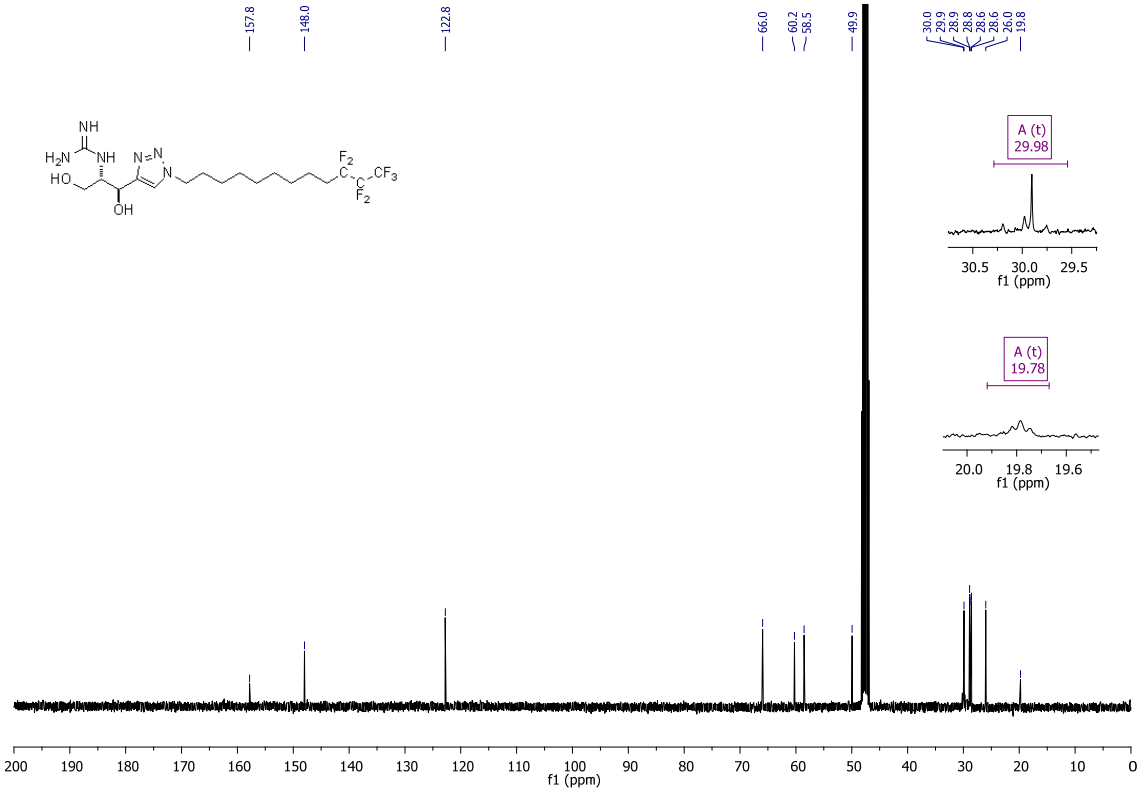

B (t)
-68.04
A (m)
-76.99
0.12
1.00
f1 (ppm)

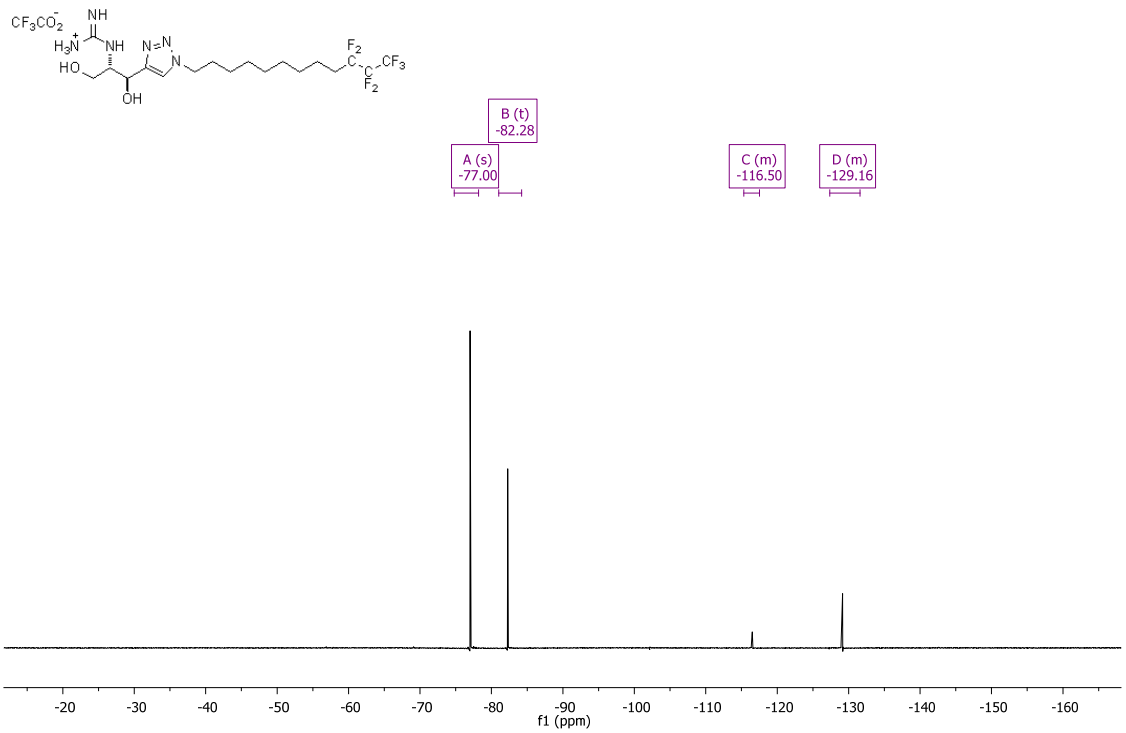

A (s)
7.95
B (d)
4.99
C (t)
4.40
D (dd)
3.93
E (m)
3.70
H (m)
1.90
I (m)
2.09
G (m)
1.57
F (m)
1.34
0.83
1.07
1.80
0.82
2.11
2.00
2.00
2.10
12.00
f1 (ppm)


157.9
148.0
122.8
66.0
60.3
58.6
49.9
38.9
29.1
29.0
28.9
28.7
28.6
26.0
18.8
NH
H2N
NH
N=N
HO
OH
CF3
CF2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


NH
H2N
NH
N=N
HO
OH
CF3
CF2
A (s)
-87.06
B (t)
-119.53
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)


A (s) 7.93
B (d) 4.99
C (t) 4.41
D (m) 3.92
E (dd) 3.72
F (dd) 3.69
G (m) 2.13
H (m) 1.91
I (m) 1.59
J (m) 1.37
f1 (ppm)


157.8
148.0
122.8
66.0
60.2
58.5
49.9
30.0
29.9
28.9
28.8
28.6
26.0
19.8
A (t) 29.98
A (t) 19.78
f1 (ppm)


CF3CO2-
NH
H2N+
NH
HO
OH
N=N
N
F2
C
C
CF3
F2
B (t)
-82.28
A (s)
-77.00
C (m)
-116.50
D (m)
-129.16
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
f1 (ppm)

5. Sphingosine kinase activity quantification.

In order to evaluate the inhibitory capacity of the synthesized compounds, the Sphingosine kinase activity in presence of these inhibitors was determined.
Adapta™ Universal Kinase Assay kit (Invitrogen, Carlsbad, CA, USA) was used following the manufacturer's protocol. Human SPHK1 and SPHK2 recombinant proteins (Thermo Fisher, Madrid, Spain) were assayed in independent experiments and each condition was analyzed in triplicate at room temperature. SPHK1 was used at final concentration of 0.025 ng/µl, SphK2 at 0.8 ng/µl and ATP and sphingosine were used at a final concentration of 1 µM and 5 µM respectively for both kinases.
Inhibitors were dissolved in 100% DMSO at an initial concentration of 50 mM. Several dilutions were performed also in DMSO, and a pre-dilution of each sample in 1X Kinase Buffer A was performed. The final concentrations assayed of each compound were 200 µM, 150 µM, 100 µM, 80 µM, 60 µM, 40 µM, 20 µM, 10 µM and 5 µM.
TR-FRET was quantified using a CLARIOstar microplate reader (BMG Labech, Biogen científica SL, Madrid, Spain) using the following parameters: Ex = 340 nm; Em1 = 620/10; Em2 = 665/10; delay = 100 µs; integration time = 200 µs; Focal height = 11 mm.
The TR-FRET ratio of each condition was calculated as EM_{665nm}/EM_{620nm} and results expressed as a percentage of inhibition using the following equation:

$$\%\ inhibition = \frac{(Ratio_{sample} - Ratio_{0\%\ inhibition})}{(Ratio_{100\%\ inhibition} - Ratio_{0\%\ inhibition})}$$

IC_{50} of each compound was calculated fitting the data to a sigmoidal dose-response curve with variable slope.

Figure 1. Inhibition curves of each compound for SPHK1

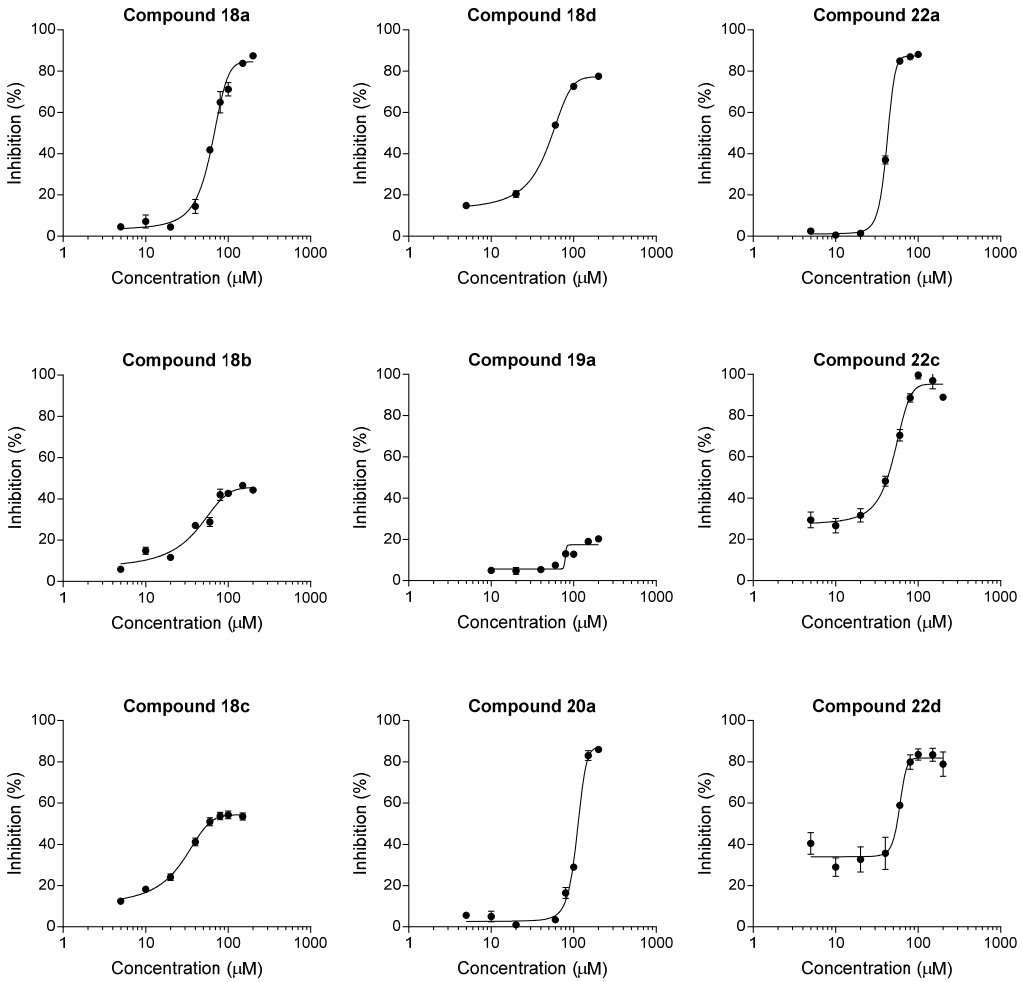


Figure 2. Inhibition curves of each compound for SPHK2: